Synthesis of Polysubstituted Oxygenated Bicyclo Compounds

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Declaration

I, Rossella Promontorio, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in this thesis.

Abstract

Saturated (or at least sp^3-enriched) molecules have acquired an increasingly important role in medicinal and organic chemistry. The architectural complexity of three-dimensional, saturated molecules often confers greater biological activity and makes these compounds more likely to succeed as drugs. The challenge associated with their synthesis and the lower degree of toxicity compared to flat, aromatic molecules makes them very attractive synthetic targets.

Polysubstituted bicyclo compounds are found in many biologically active natural products. In particular, the bicyclo[3.3.1]nonane system constitutes the core of the PPAP (polyprenylated acylphloroglucinol) family, whose members have shown multiple beneficial medicinal properties. A main approach to the construction the bicyclo[3.3.1]nonane core involves the biomimetic dearomatisation of prenylated phloroglucinols. The initial aim of the thesis work was to use chiral epoxides to achieve the dearomatisation of these derivatives and a consequent enantiodivergent synthesis of the PPAP scaffold. Inspired by the enantioselective total synthesis of hyperforin, achieved by Shair's group through desymmetrisation of a cyclohexadiene ring, the thesis study initially focused on investigating an epoxide-mediated ring closure using more readily available 1,3-diketones. However, this approach met with little success, instead the products of O-cyclisation often being obtained.

As an alternative, the construction of functionalised bicyclo[3.n.1]alkanes by a Michael-aldol type annulation was investigated. This method has previously furnished bicyclic compounds but was limited in scope and/or stereocontrol. We thus aimed to develop a general, reliable route for the synthesis of a variety of polysubstituted bicyclo[3.3.1]nonane derivatives using a Michael-aldol annulation. A novel and effective one-pot process was achieved by the reaction of substituted 1,3-cyclohexanediones with enals. The desired bicyclic ketols were generally obtained in good to excellent yields, and often with appreciable stereocontrol. The possibility to further functionalize the bicyclo system with other electrophiles was shown to be effective for fluorine, and afforded a selection of novel fluorinated bicyclic scaffolds of relevance to medicinal chemistry.

Impact Statement

Over the past century, the discovery and development of important life-saving drugs was greatly enabled by the outstanding advances made in synthetic organic chemistry. The invention of new synthetic methods provide access to diverse, extensive regions of the chemical space containing a large array of biologically active molecules, a necessity for all drug discovery programmes. One of the key challenges in synthetic organic chemistry is the achievement of a certain degree of complexity and stereochemical diversity together with the selective construction of highly functionalized saturated scaffolds; in this context, architecturally complex molecules like bridged bicyclo compounds possess great structural diversity and a high level of saturation, which has been shown to confer higher aqueous solubility and lower toxicity when compared to the unsaturated/aromatic counterpart.

Many biologically active natural products and marketed drugs possessing multiple therapeutic effects including anti-bacterial, antidepressant, anti-viral and anti-cancer feature a bicyclic core in their chemical structure. These rigid, saturated frameworks can be decorated with multiple substituents whose orientations can cover multiple directionalities, with potential for efficient interactions with biological targets.

Following on these key concepts, we developed an annulation methodology *via* a tandem Michael-Aldol reaction to provide a diverse range of [3.3.1] and [3.2.1]bicyclo compounds in good to high yield and stereoselectivity. Having devised a method that can efficiently build a complex bicyclic scaffold in one step, we also sought a concise route to fluorinated bicyclo compounds of defined stereochemistry since the introduction of fluorine can beneficially alter physicochemical properties. As a result, we synthesized the most extensive series of monofluorobicyclo[3.3.1]nonane derivatives, achieving high stereoselectivity and chemoselective introduction of fluorine.

The shape of bicyclo compounds and the ability to control the spatial orientation of various substituents on these rigid structures is crucial in determining their chemical and biological properties. This study highlights the 3D-structure of a selection of bicyclo and fluorobicyclo compounds and paves the way for the exploration of new regions of the chemical space. The bicyclic molecules synthesized have also a great potential for use as bioisosteres and provide structural diversity suitable for use in medicinal chemistry and drug design programme.

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Lastly, my deepest gratitude goes to the person that supervised me in Singapore, Dr. Richard, JA. Since day one he infused me with his passion for organic synthesis; he trained me on how to plan a synthesis, how to think towards a synthesis and taught me consistency, method and time optimisation. Thanks to him and his immence patience and dedication I've read countless papers and completed and understood three total synthesis books, enjoying the process immensely. He pushed me when I needed to be pushed and left me without an answer when he knew I could get there on my own. He believed in me, motivated me and his chemistry knowledge and growing mindset inspires me and pushes me to be a better chemist evey single day. I could have not wish for a better supervision during my unforgettable time in Singapore.

Life is like a garden,

perfect moments can be had, but not preserved, except in memory…

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LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
AUC	Area under the curve
Boc	*tert*-Butoxycarbonyl
BzCl	Benzoyl chloride
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCCA	Dearomative conjunctive allylic annulation
DCM	Dichloromethane
DMA	Double Michael addition
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMDO	Dimethyldioxirane
DMM	Dimethoxymethane
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DOS	Diversity-Oriented-Synthesis
eq	Equivalent
Fsp^3	Number of sp^3 hybridized carbon
GSK	GlaxoSmithKline
g	Grams
h	Hours
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	High resolution mass spectrometry

IC_{50}	Concentration causing 50% inhibition of the desired activity
IBX	2-iodoxybenzoic acid
IR	Infrared
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LiTMP	Lithium tetramethylpiperidide
m-CPBA	*meta*-Chloroperoxybenzoic acid
m.p.	Melting point
MPO	4-Methoxypyridine-N-oxide hydrate
mL	Milliliters
min	Minutes
MsCl	Methanesulfonyl chloride
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorobenzensulfonimide
NHC	*N*-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
p-TsOH	*para*-Toluenesulfonic acid
PCC	Pyridinium chlorochromate
PPA	Polyphosphoric acid
PPAP	Polycyclic Polyprenylated Acylphloroglucinols
RT	Room temperature
RCM	Ring Closing Methathesis
sat.	Saturated (aqueous solution)
TBAB	Tetra-*n*-Butylammonium bromide
TBAF	Tetra-*n*-Butylammonium fluoride

TBAI	Tetra-*n*-Butylammonium iodide
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDMS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TMG	1,1,3,3,-tetramethylguanidine
$TMSCHN_2$	Trimethylsilyldiazomethane
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
THS	Tetrabutylammonium hydrogen sulfate
TLC	Thin layer chromatography
TS	Transition state

CHAPTER 1

1.1 Natural products; complexity, diversity and exploration of the chemical space

The constant demand for new specific and potent therapeutic agents and the necessity for novelty in chemical patents has made the medicinal chemistry community increasingly aware of the limitation of classical systems such as (hetero)aromatic compounds; their low-cost synthesis and structural flexibility often comes with poor solubility and toxicity, features that cannot be neglected in drug development. Thanks to the remarkable advances in synthetic organic chemistry the tendency to prepare more architecturally complex molecules has emerged and new and uncommon saturated scaffolds are now accessible and progressively considered in the drug development process.[1]

Natural products have always been an essential source of bioactive compounds. From their use by indigenous and agrarian societies to the breakthrough discovery of Penicillin in 1928 until the post-industrialised discovery of important molecules like Daunorubicin or Cephalosporin C, natural products' contribution to the progress of anti-infective and anti-tumoral agents after the second world war has been enormous. Nowadays, natural products constitute one third of the top marketed drugs worldwide, covering a variety of therapeutic application, from the immunosuppressive agent cyclosporin A, to cholesterol-lowering agents to Doxorubicin and Artemisinin for cancer and malaria treatment respectively.[2]

The remarkable chemical diversity and complexity possessed by natural products leads to the concept of chemical space, which was created to group all possible organic molecules. The majority of molecules that are able to interact with high specificity with their biological targets are however confined in only few regions of the chemical space and this number is additionally limited to those compounds possessing key features *i.e.* aqueous solubility and non-toxic metabolites.[3] The exploration of unknown regions of the chemical space is therefore becoming very important as it can lead to an increased number of molecules to choose from at the "hit" stage and consequently to a higher success rate in the later stages of drug development.[4] In this context, Diversity-Oriented-Synthesis (DOS), a concept pioneered by Schreiber in 2000, which is "aimed at the collection of many compounds having structural diversity and complexity", addresses the urgency to explore the uninvestigated regions of the chemical space by building libraries of small-molecule chemical probes with chemical complexity and diversity. In his work, Schreiber proposed the ideal synthetic plan to be an integration of complexity and diversity elements, as illustrated for the Ugi and

intramolecular Diels-Alder reactions which are able to generate complexity in one single sequence (Fig. 1.1 top). Products derived from one single transformation can be split and pooled in a collection of different scaffolds, leading to a large number of components with different complex scaffolds (Fig.1.1, bottom).[5] This strategy can be combined with a certain degree of stereochemical diversity to efficiently access a full display of chemical information in the three-dimensional space.[6]

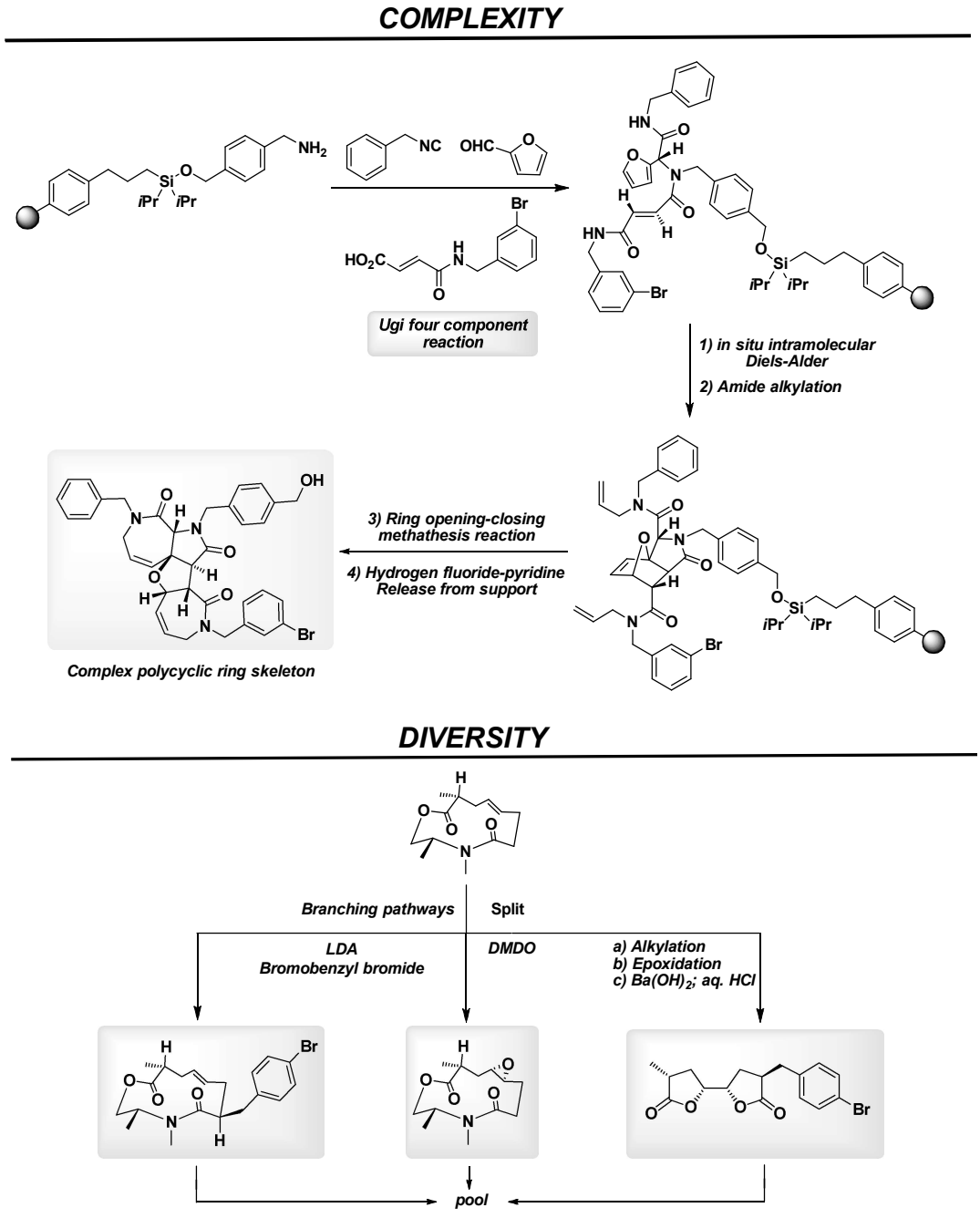


Fig.1.1: DOS ideal synthetic plans, combining complexity and diversity.[5]

1.2 The concept of saturation

In 2009, Lovering[7] introduced two central criteria for drug-likeness; the number of chiral centres and the sp^3 character, *i.e.* the carbon bond saturation. The rationale behind this selection is the effect on the molecular shape; a higher level of saturation, defined by the sp^3 hybridized carbons (Fsp^3), allows the exploration of diverse, natural product-like regions of the chemical space. The proof of concept was the discovery of the direct correlation between the various stage of drug development (with the GSK BIO database of molecules taken as a source) and the level of saturation, with a 31% increase of Fsp^3 from discovery to phase III of clinical trials. Additionally, the average saturation, chiral centres count and molecular weights were calculated for each stage of the drug discovery process and the same increase in the compound likelihood to become a drug was observed. Fsp^3 was also found to be highly correlated with solubility and can be increased without causing any significant change in the overall molecular weight, both key elements in Lipinski rule of 5.[7]

Lovering's study paves the way for a deeper investigation of saturated, architecturally complex natural products and confirms the Fsp^3 as an important factor, which does not only enhance the specificity and/or the potency of certain compounds but more importantly increase their probabilities to become a successful marketed drug.

1.3 Bridged bicyclo compounds in medicinal chemistry

In this context, bridged bicyclo compounds are highly valued as they feature key complexity descriptors, i.e. the number of sp^3 hybridized carbon atoms and the presence of chiral centres. The presence of a bridged bicyclic scaffold in particular has increased in therapeutic and biologically active natural products (Fig. 1.2). For instance, the bicyclo[2.2.1]heptane mecamylamine, being a non selective antagonist of the nicotinic acetylcholine receptor, has been shown to have some efficacy in the treatment of nicotine addiction; bicyclo[3.2.1]octane derivatives were initially synthesised for the structural similarity with the anti-cancer family of *ent*-kaurenoid diterpene mimics and indeed the amide derivative shown was found to exhibit a IC_{50} value between 1.1 and 4.3 μM in 5 cancer cell lines.[1, 8] Tricyclic pyrimidine derivative was patented instead as JAK inhibitor, highlighting the increased use of small strained ring systems like bicyclo[1.1.1]pentane or cyclobutane and azetidine as bioisosteres in medicinal chemistry.[9] Two of the most famous and important marketed drugs known to possess a bicyclic scaffold are also highlighted in Fig.1.2; Taxol, a complex natural

product able to block mitosis through stabilization of the microtubule polymer, has been successfully on the market for over 30 years as a chemotherapeutic drug; Ingenol mebutate, thanks to its antibody-dependant cellular toxicity and its rapid lesion necrosis[10], has emerged recently as the main treatment for actinic keratosis, a skin condition considered potentially precancerous.

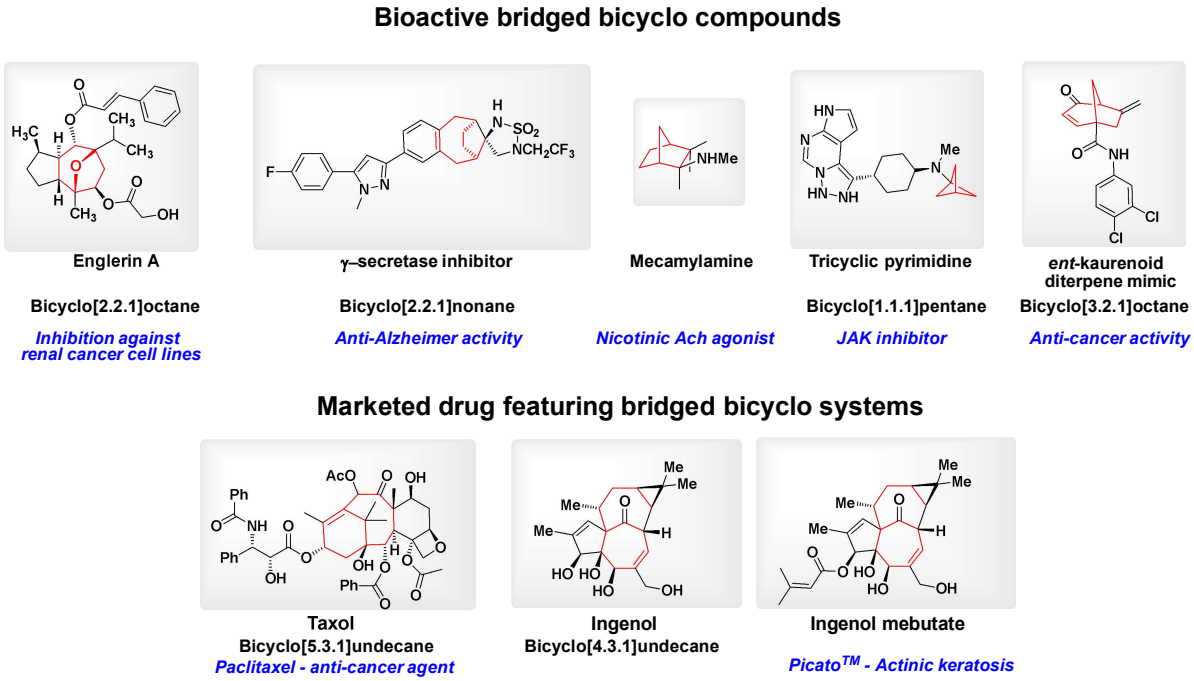


Fig.1.2: Biologically active and marketed bridged bicyclo compounds.

1.4 Biological relevance of the bicyclo[3.3.1]nonane and bicyclo[3.2.1]octane bridged scaffolds

Amongst all the different types of bridged bicyclic frameworks that can be investigated for medicinal chemistry purposes and for a better understanding of the chemical space, systems containing the bicyclo[3.3.1]nonane and the bicyclo[3.2.1]octane scaffold have drawn attention from the synthetic community, particularly because of their involvement in many sesquiterpenoids and other natural products biosynthetic pathways.[11] For instance, 3 and 3,7-substituted bicyclo[3.3.1]nonanes are potential precursors of adamantanoid compounds whose framework is very common in nature and is found in many biologically active molecules.[12] Fig. 1.3 showcases a few examples: huperzine A, an inhibitor of the central acetylcholinesterase, has been clinically evaluated as an anti-Alzheimer drug and marketed in few countries as a dietary supplement for memory loss. Hypatulin A and

Platensimycin exhibited remarkable antimicrobial and antibacterial activity, [13] respectively whereas a potent anti-influenza virus activity is shown by the diterpene Wickerol A[14] (Fig.1.3a). Densely prenylated bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione cores are also found within the family of polycyclic polyprenylated acylphloroglucinols (PPAP) natural products, considered intriguing because of their complex chemical structure and interesting biological activities. Hyperforin, the primary active constituent of the flowering plant *Hypericum perforatum* (St. John's wort) and the main representative of this class of phloroglucinol derivatives possess potent antidepressant and anxiolytic properties along with *in vitro* and *in vivo* activity against several bacterial species and cancer cell lines. Additionally, *in vivo* studies showed that Hyperforin can also have a nootropic effect, improving cognitive functions by reducing biomarkers of Alzheimer's disease.[15] The same anti-neurodegenerative, anticancer and antibacterial effect is possessed by several members of the PPAP family, including Garsubellin A, Nemorosone and Hyperibone K (Fig. 1.3c).

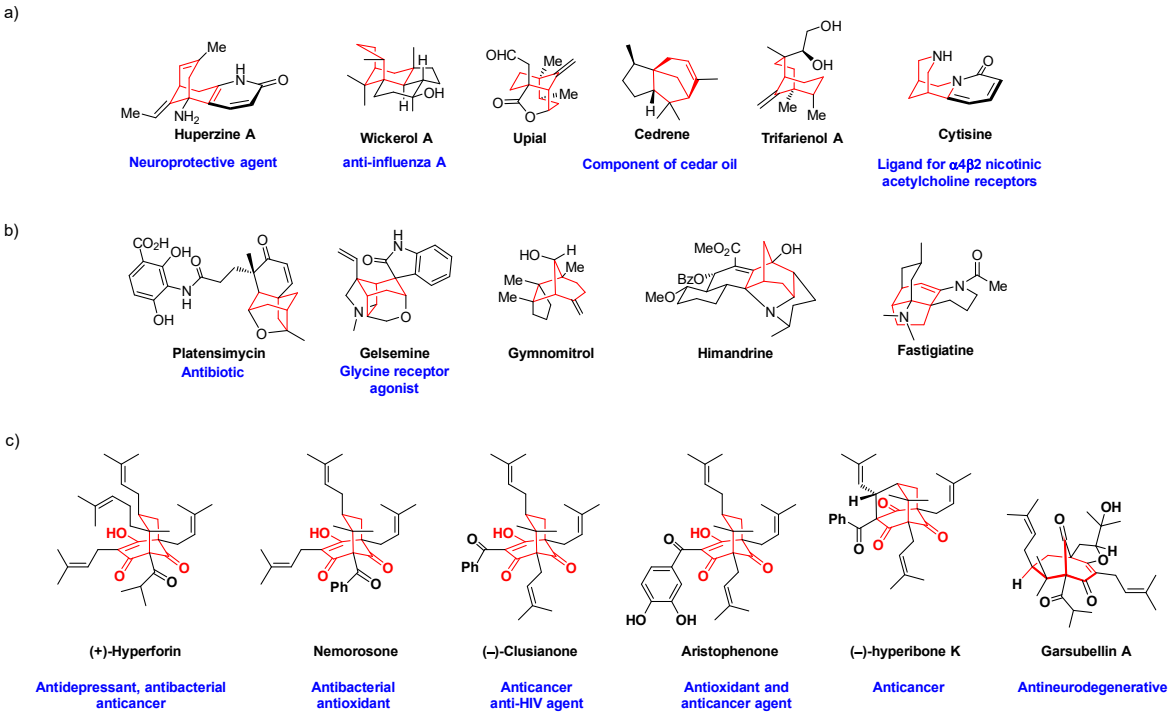


Fig. 1.3: a) Biologically active natural products featuring the bicyclo[3.3.1]nonane scaffold, b) Biologically active natural products containing the bicyclo[3.2.1]octane core, c) Representative PPAP natural products.

1.5 Synthetic strategies towards the bicyclo[3.3.1]nonane framework

This incredibly extended therapeutic range across natural products featuring the bicyclo[3.3.1]nonane scaffold encouraged the synthetic chemistry community towards the development of stereoselective routes for the synthesis of this framework. The synthetic strategies developed so far are summarized in four major reviews; the first two, reported by Peters[16]and Buktus[12] either describe general approaches towards relatively unfunctionalised bicyclo[3.3.1]nonane systems or report selective examples towards the synthesis of 3,7-substituted derivatives. The other two reviews by Njardarson[17] in 2011 and Richard[18] et *al.* in 2012 analysed the synthetic advances towards this scaffold within the context of PPAP natural products, showcasing the latest total syntheses together with the most recent synthetic approaches and their limitations. The following discussion will be divided by chemical transformation, highlighting the synthesis of functionalised and unfunctionalised bicyclo[3.3.1]nonane and [3.2.1]octane cores, mostly in the context of natural products synthesis.

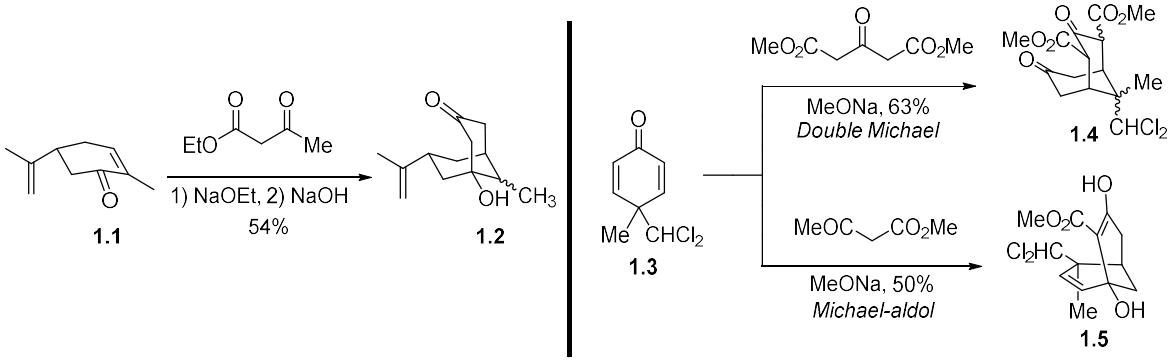
1.5.1 Annulation Strategies

1.5.1.1. Annulation of cyclohexanone derivatives featuring Michael, double Michael or Michael-aldol reactions

In their detailed analysis of all the synthetic approaches towards bicyclo[3.3.1]nonanes, Butkus and Peters cite one main reaction that has been historically used to forge the bicyclo[3.3.1] skeleton; the annulation of cyclohexanone derivatives. Most of these reactions feature Michael, double Michael or Michael-aldol mechanisms so a major focus will be given to these powerful C-C bond forging reactions.

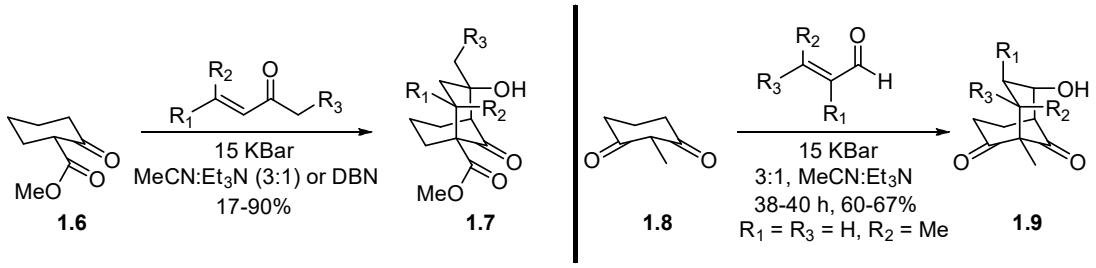
The first synthesis of a substituted bicyclo[3.3.1]nonane was reported at the beginning of the 20th century[19] and involved the annulation of terpene carvone **1.1** with ethyl acetoacetate under basic conditions (Scheme 1.4, left). The mechanism was not described but most likely involves a Michael-aldol-decarboxylation sequence to give bicyclo **1.2**. This methodology and other related reactions were successfully applied for many years for the synthesis of bicyclo[3.3.1]nonanes;[20] reaction of 6-dichloromethyl-6-methyl-3-oxo-cyclohexa-1,4-diene **1.3** for example[21] has been reported to give the bicyclo[3.3.1]nonane core albeit with two different mechanisms depending on the reagent used; bicyclo compound of type **1.4** arises

from a double Michael addition between **1.3** and dimethyl acetonedicarboxylate whereas the use of methyl acetoacetate gives rise to diene **1.5** following a Michael-aldol sequence (Scheme 1.4, right).



*Scheme 1.4: Left: First synthesis reported for the construction of bicyclo[3.3.1]nonane. Right; double Michael and Michael-aldol strategies to access bicyclo compounds **1.4** and **1.5**.*[19a, 21]

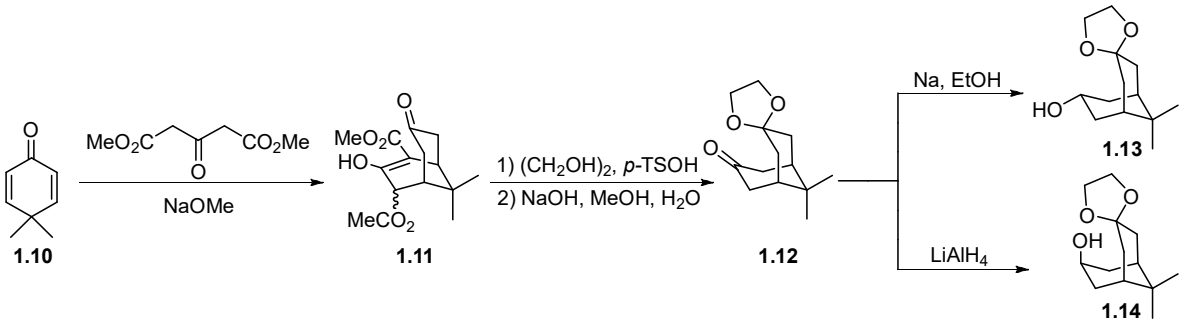
In 1986 Dauben[22] showed that cyclic β-keto ester **1.6** reacts with a variety of enones at 15 Kbar in the presence of an excess of a tertiary amine as co-solvent yielding substituted bicyclic ketols of type **1.7** (Scheme 1.5, left). Noteworthy is the extension of the methodology to various ring sizes and the use of unreactive enones such as mesityl oxide. The same reaction conditions were extended to enals like acrolein and methacrolein to give 6-hydroxy-8-methylbicyclo[3.3.1]nonane-2,9-diones of type **1.9**; importantly this constitutes to date the only example of annulation involving the use of unsaturated aldehydes with this type of 1,3-cyclohexanedione system (Scheme 1.5, right).



*Scheme 1.5: Dauben's use of high pressure in the synthesis of bicyclic ketols of type **1.7** and **1.9**.*[22]

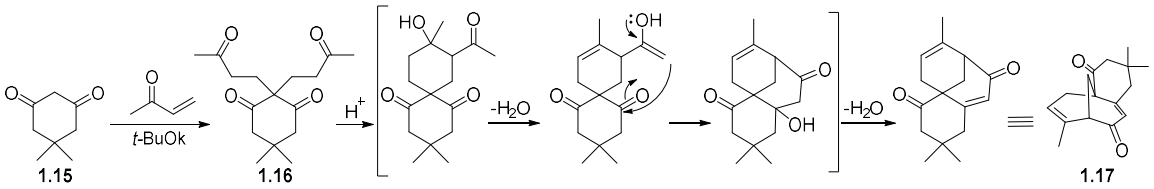
In his account for the conformational analysis of 9,9-dimethylbicyclo[3.3.1]nonane derivatives, Fetizon[23] explored a double Michael addition of 4,4-dimethylcyclohexadienone **1.10** with dimethyl acetonedicarboxylate; ketalisation of the resulting mixture of enolised stereoisomers **1.11** and subsequent decarboxylation under basic conditions gave 9,9-dimethylbicyclo[3.3.l]nonane-3,7-dione-ethylene acetal **1.12**. Noteworthy is the high stereoselectivity of both reductions; in the presence of $LiAlH_4$, because of the likely chelation

of Al to the acetal motif, the hydride is delivered on the more accessible face of the molecule, providing exclusively to the *endo*-epimer **1.14**; reduction in the presence of Na/EtOH (initially via a radical oxyanion) yields solely the thermodynamically preferred *exo*-isomer **1.13** instead (Scheme 1.16).



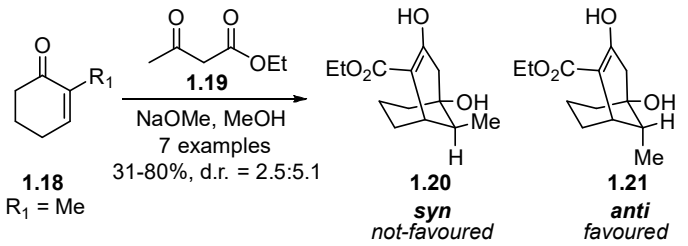
Scheme 1.6: Fetizon double Michael addition for the synthesis of 9-disubstituted bicyclo[3.3.1]nonane-3,7-diones.[23]

In the case of the synthesis developed by Pennetreau,[24] a combination of Michael addition and Robinson annulation led to a bicyclo[3.3.1]nonane skeleton fused with a 6-membered ring. Michael product **1.16** arising from reaction of 5,5-dimethyl-1,3-cyclohexane-1,3-dione **1.15** with two equivalents of methyl vinyl ketone undergoes a double Robinson annulation with elimination of two molecules of water; noteworthy is the regioselectivity of the last annulation, which gives rise only to the 6-membered ring product **1.17** rather than 5 or 4 membered ring (Scheme 1.7).



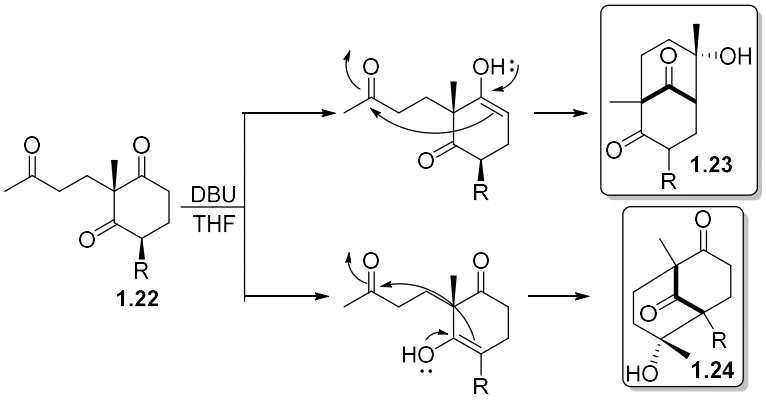
*Scheme 1.7: Michael addition-Robinson annulation for the synthesis of fused bicyclo **1.17**.*[24]

Very recently, an interesting mechanistic rationale for the diastereoselectivity observed in the base-catalysed Robinson annulation for the synthesis of bridged bicyclo[3.3.1]nonanes was proposed by Yu et al.[25] DFT calculation and a detailed analysis of the reaction energy profiles revealed in fact the *anti*-product **1.21** to be formed preferably (Scheme 1.8).



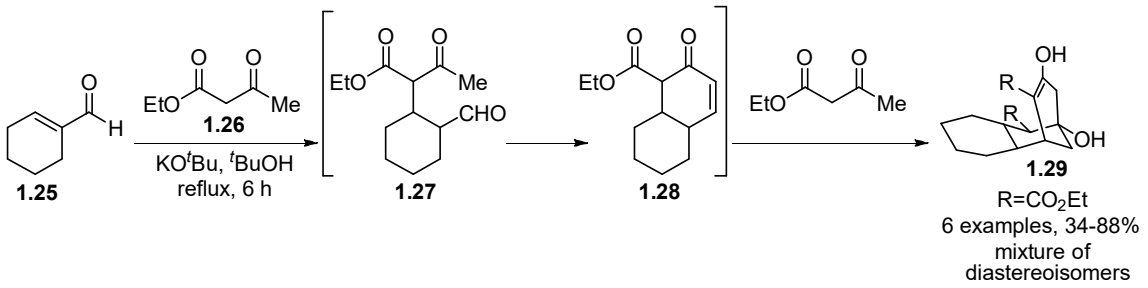
*Scheme 1.8: Base-catalysed Robinson annulation of enones of type **1.18** to give bicyclo[3.3.1]nonanes **1.21.**[25]*

Another example featuring cyclohexane-1,3-dione was showcased by Coates and co-workers.[26] During their study on the aldol cyclisation of cyclohexane-1,3-dione derivatives a similar aldol cyclisation from 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**1.22**) and its 4-methyl analogue was also observed leading to bicyclo[3.3.1]nonane derivatives. Base-catalysed cyclisation may occur on both carbonyl groups in the ring leading to two types of bridged bicyclic ketols (**1.23** and **1.24**) as a mixture of *exo* and *endo*-diastereoisomers (Scheme 1.9).



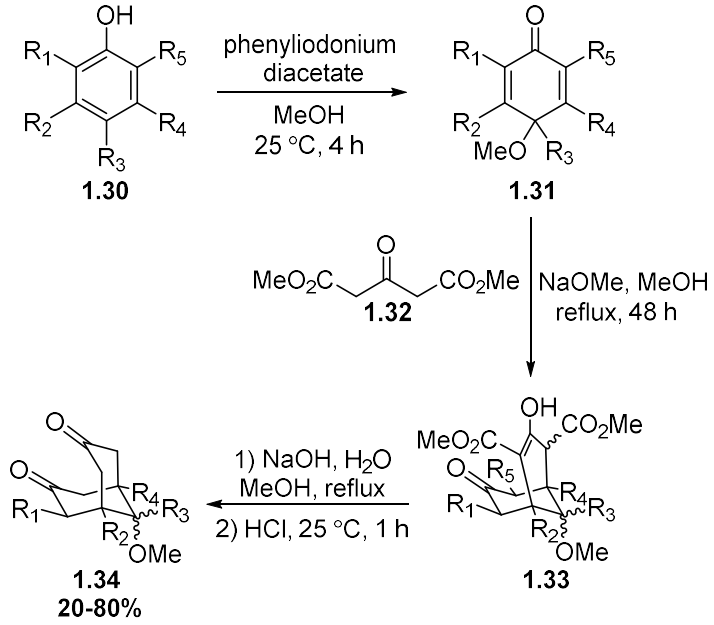
*Scheme 1.9: Coates aldol cyclisation approach and different mode of cyclisation leading to ketol **1.23** and **1.24.**[26]*

In 2000, Koo[27] et al envisioned a one-pot reaction for the construction of the [3.3.1]nonane bicyclic skeleton *en route* to cyclic steroids. Two consecutive intramolecular Michael-aldol reactions starting from aldehyde **1.25** and ethyl acetoacetate **1.26** afforded bicyclo[3.3.1]nonane scaffold **1.29** in moderate to good yields, albeit with poor diastereoselectivity (Scheme 1.10).



*Scheme 1.10: Michael-aldol sequence employed by Koo et al for the synthesis of fused ketol **1.29**.*[27]

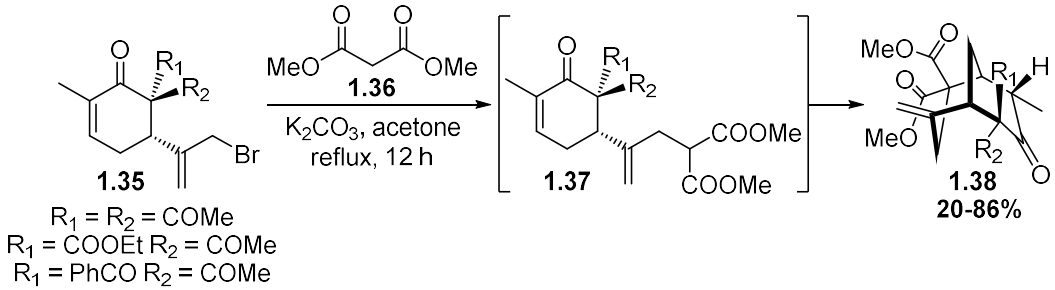
Camps et al applied a double Michael strategy for the synthesis of differently substituted bicyclo[3.3.1]nonane-3,7-diones **1.34**. Their synthetic sequence involved oxidation of polysubstituted phenols **1.30** with phenyliodonium diacetate followed by a double Michael addition of the resulting 4-alkoxy-4-alkylcyclohexa-2,5-dienones **1.31** with dimethyl 1,3-acetonedicarboxylate **1.32** under basic conditions. The bicyclo[3.3.1]nonane-3,7-diones obtained after subsequent hydrolysis and decarboxylation of **1.33** are the same, regardless of the face selectivity of the Michael addition (Scheme 1.11).[28]



Scheme 1.11: Camp's double Michael approach for the synthesis of 3,7-substituted bicyclo[3.3.1]nonanes.[28]

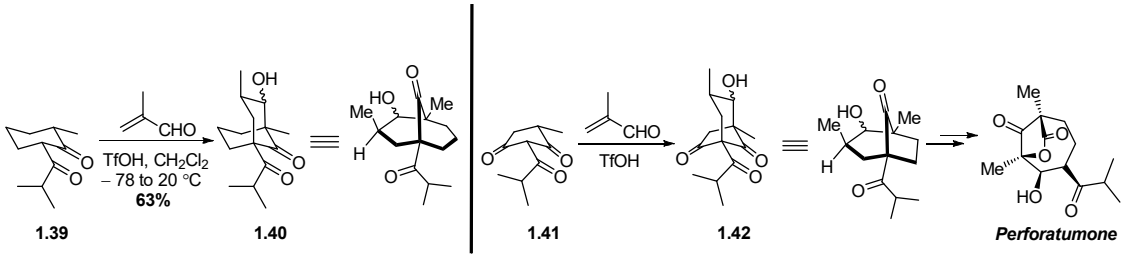
In a related manner, Reddy et al developed a simple methodology for the enantioselective synthesis of functionalised bicyclo[3.3.1]nonanes via intermolecular alkylation of Michael donors with 10-bromocarvones **1.35** and subsequent intramolecular Michael addition.[29] Although the scope of the methodology wasn't expanded further than the use of three

different Michael acceptors and only methyl substitution at position 7, the simplicity and the enantioselectivity of the approach paved the way for Porco's transformation of Clusiaphenone B into the bicyclo[3.3.1]nonane precursor of the natural product Clusianone [30] (Scheme 1.12).



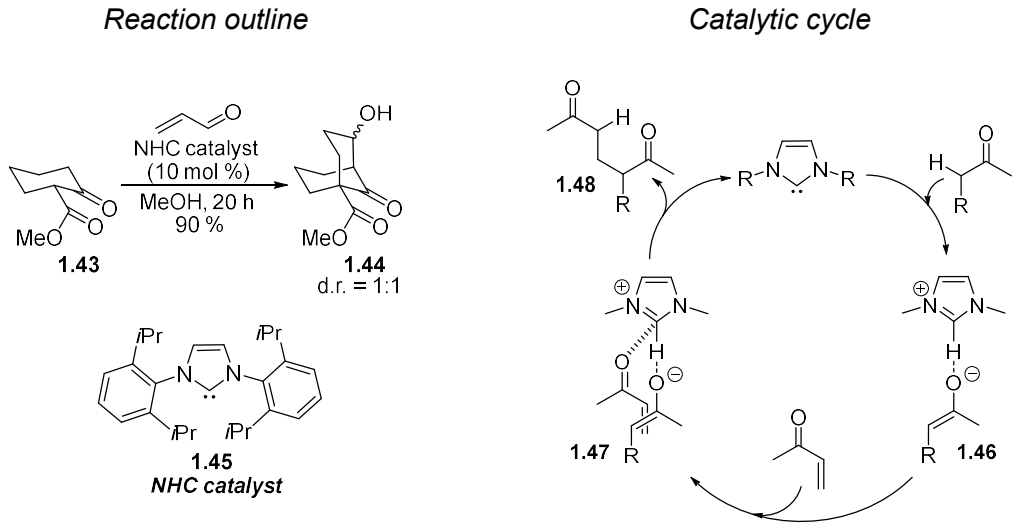
Scheme 1.12: Reddy's alkylation/intramolecular Michael addition strategy.[29]

More recently, bicyclo formation has been achieved by employing α-alkoxycarbonyl- and/or α-acyl-cycloalkanones. Two important related examples are the acid-catalysed annulation of substituted 2-acylcyclohexanone with methacrolein and the domino carbocyclization reactions of cyclic 1,3-dicarbonyl compounds with malonic acid derivatives catalyzed by N-Heterocyclic carbenes. In the former described by Nicolaou[31], addition of TfOH at –78 °C to a solution of diketone **1.39** and methacrolein in CH_2Cl_2 enabled the intermolecular 1,4-addition to the α,β-unsaturated aldehyde followed by subsequent protonation and intramolecular aldol reaction which gave rise to bicyclic hydroxyl diketone **1.40** in 63% as a 2:1 mixture of diastereoisomers. The scope was not studied and the relative configurations were not assigned, given that both stereogenic centres were destroyed in the following oxidation step, but are presumably as shown on scheme 1.13, with the 3-methyl group being assigned as *exo* to the bridgehead carbonyl group. The group subsequently applied the same strategy for the synthesis of bicyclo[3.2.1]octane scaffold in order to access the complex polycyclic skeleton of Perforatumone, a member of the PPAP family (Scheme 1.13).



Scheme 1.13: Nicolaou's Michael-aldol strategy in the synthesis of bicyclo[3.3.1]nonane and bicyclo[3.2.1]octane towards natural product perforatumone.[31]

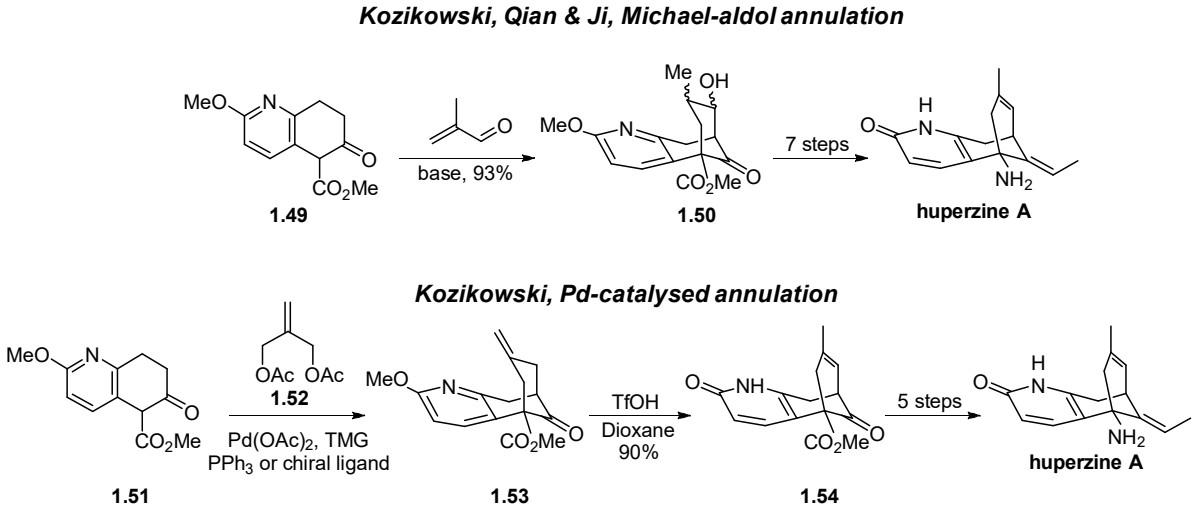
Rodriguez proved the utility of N-heterocyclic carbenes (NHC) of type **1.45** in the Michael addition of 1,3-carbonyl compounds.[32] As shown by the formation of enolate-imidazolium complex **1.46** in the catalytic cycle, the NHC catalyst has the unique role of acting as Brönsted base and Lewis acid on the same carbon atom; complex **1.47** would then activate the electrophile, acting as Lewis acid and generating Michael adduct **1.48**. This method gave access to bridged bicyclic compounds in good to excellent yields, with either cyclic or acyclic nucleophiles (such as 1,3-keto esters, 1,3-diketones, 1,3-ketoamides) in combination with methyl acrylate, acrylamide, phenyl vinyl sulfone, acrylonitrile, methyl vinyl ketone, or acrolein. However, only [3.2.1]octane bicyclic scaffold could be accessed with this method with the only example of bicyclo[3.3.1]nonanol shown on Scheme 1.14, which proceeded in good yield but poor stereoselectivity (Scheme 1.14).



Scheme 1.14: Rodriguez N-heterocyclic carbene-catalysed Michael addition of 1,3-carbonyl compounds.[32]

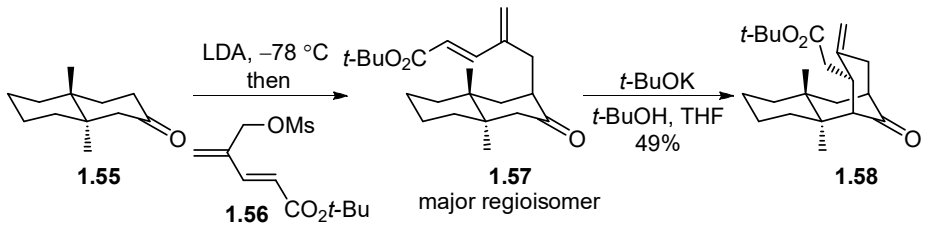
A related Michael-aldol approach starting from β-keto esters was undertaken by two different groups at the same time[33] in their effort towards the total synthesis of huperzine A. In both cases, β-keto ester **1.49** was reacted with methacrolein to furnish the bicyclic scaffold of huperzine A in 93% yield. This Michael-aldol sequence was later implemented with the use of a chiral *Cinchona* base[34] or with a quinine-derived chiral thiourea organocatalyst[35] to give the desired bicyclic scaffold in 64% and 94% *ee* respectively. Another powerful method for the construction of the bicyclo[3.3.1]nonane scaffold, which will be explored more in depth for the synthesis of PPAP natural products, is the Pd-catalysed annulation of β-keto ester; in this context, Kozikowski[36] investigated a second generation synthesis of huperzine A by reaction of β-keto ester **1.51** with 2-methylenepropane-1,3-diol diacetate **1.52**. The exocyclic

double bond at position 8 was isomerized with triflic acid and the synthesis of the natural product carried out using the same racemic sequence reported originally (Scheme 1.15).[33a]



Scheme 1.15: Access to huperzine A *via Michael-aldol and Pd-catalysed annulation approaches.*[33, 36]

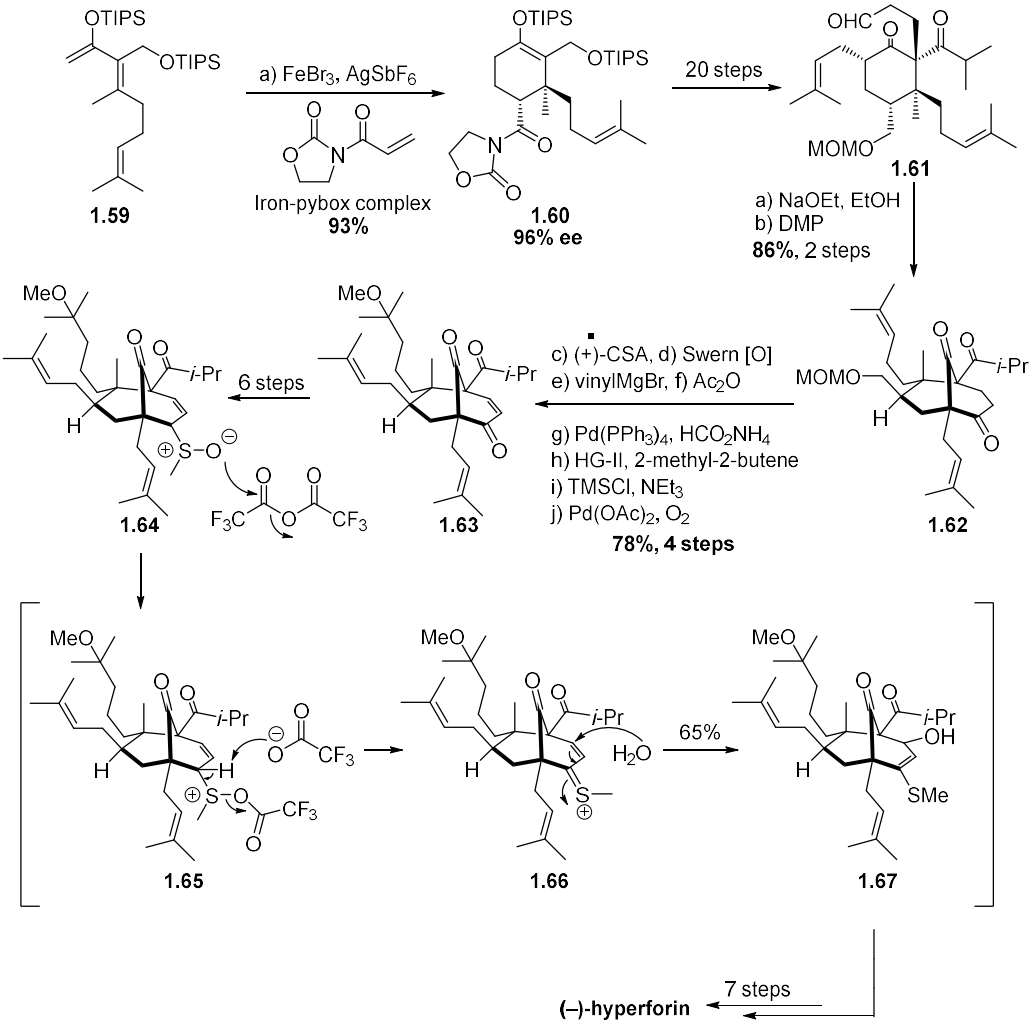
A similar bicyclic compound, featuring a cyclohexane ring fused to the bicyclo[3.3.1]nonane unit rather than the 2-pyridone ring of huperzine A was observed by Hassner et al during the development of a route for the construction of functionalized eight and seven-membered rings.[37] LDA mediated alkylation of *trans*-methyldecalone **1.55** with pentadienoic ester **1.56** followed by intramolecular Michael addition of the major isomer **1.57** with *t*-BuOK yielded exclusively *endo*-bicyclic ketol **1.58** in 49% yield (Scheme 1.16).



*Scheme 1.16: Intramolecular Michael addition for the synthesis of fused bicyclo compound **1.58.***[37]

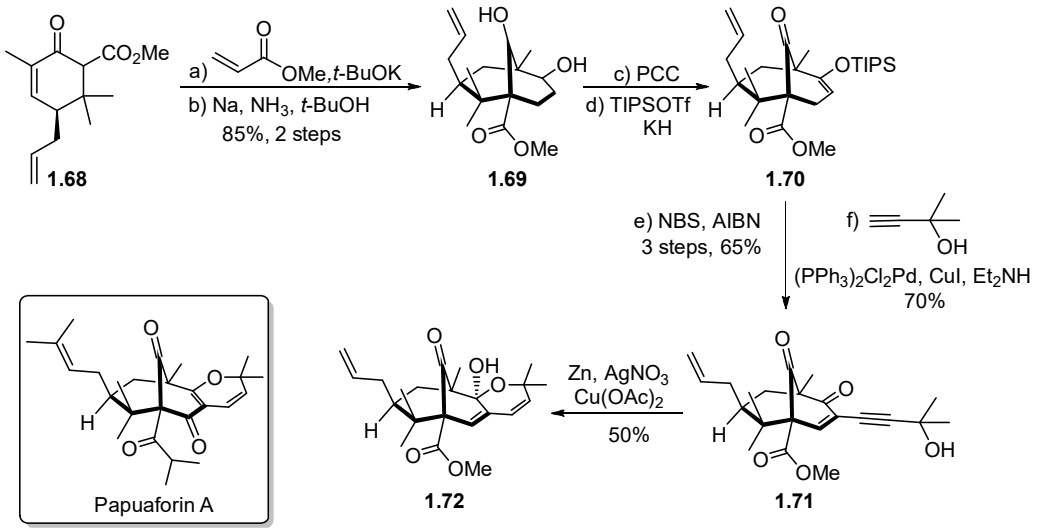
The PPAP class of natural products greatly benefited from Michael type reaction and in this context the first asymmetric total synthesis of (–)-hyperforin, reported by Shibasaki in 2010, remains a milestone in this field.[38] The synthetic sequence started with a Diels-Alder reaction pioneered by the same group[39] between diene TIPS enol ether **1.59** and dienophile oxazolidinone acrylamide; the reaction, catalysed by a cationic iron-pybox complex, cleanly afforded cyclohexene **1.60** in high yield with simultaneous installation of the two vicinal

tertiary and quaternary centres in high enantiomeric excess. A long, however, well maneuvered sequence with several functional group manipulation of the ketone moiety and installation of prenyl and isopropyl groups at C-5 and C-1 respectively gave after 20 steps aldehyde intermediate **1.61**; the latter underwent the key intramolecular aldol reaction in the presence of NaOEt furnishing the bicyclo[3.3.1]nonane scaffold to which followed DMP oxidation of the resultant alcohol. Installation of the enone moiety and of two additional prenyl substitutents *via* palladium enolate oxidation, π-allyl palladium chemistry and olefin cross-methathesis respectively was achieved in 4 steps and afforded intermediate **1.63**. Conversion to the desired 1,3-ketone moiety however proved to be extremely difficult and the Shibasaki group had to turn to an unusual vinylogous Pummerer rearrangement of allylic sulfoxide **1.64** (highlighted in brackets) in the presence of the bulky base 2,6-di-tert-butylpyridine; the resulting allylic alcohol **1.67**, obtained in 65% yield, was subjected to a few more manipulations for the installation of the remaining functionalities and within 7 steps the first total synthesis of (–)-hyperforin, the antipode of the natural occurring PPAP, was completed (Scheme 1.17).



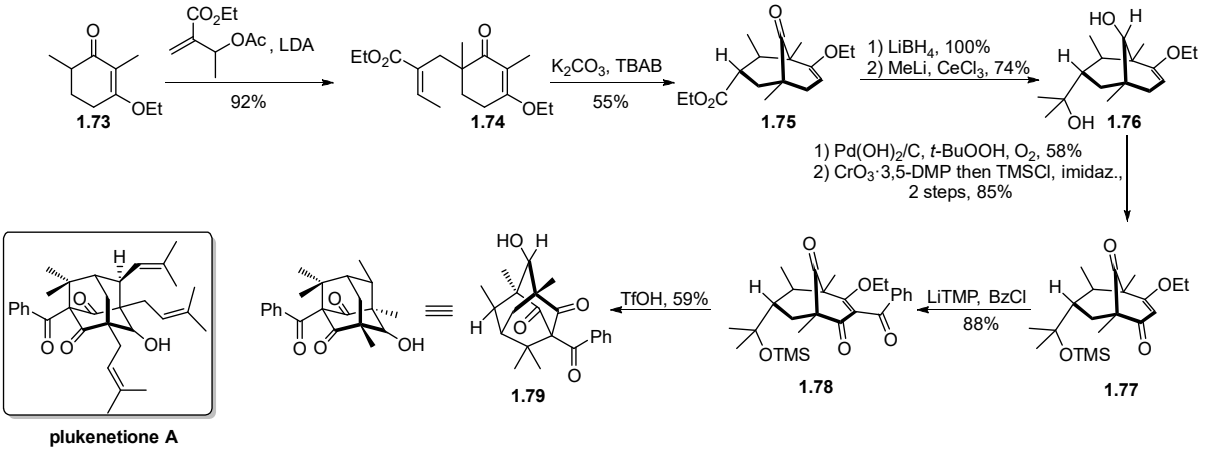
Scheme 1.17: The first total synthesis of (–)-hyperforin by Shibasaki's group.[38]

In their synthetic efforts towards Papuaforin A, a PPAP natural product featuring a *2H*-pyran ring fused to the bicyclo[3.3.1]nonane core, Kraus et al developed an eight step methodology towards **1.72**, a valuable intermediate in the synthesis of the above-mentioned natural product.[40] A notable two step sequence involving Michael addition of cyclohexanone **1.68** to methyl acrylate followed by subsequent cyclisation and Birch reduction forged the bicyclo[3.3.1]nonane scaffold **1.69** in 85% yield. The resulting diol was oxidised and transformed to the TIPS enol ether which was brominated under radical conditions to afford an α-bromoenone (not shown) which after a Sonogashira cross coupling reaction afforded tertiary alcohol **1.71**. Stereoselective reduction of **1.71** alkyne group yielded pyran hemiketal **1.72** in 35% overall yield (Scheme 1.18).



Scheme 1.18: Synthesis of Papuaforin A core via Michael addition/Birch reduction/cyclisation.[40]

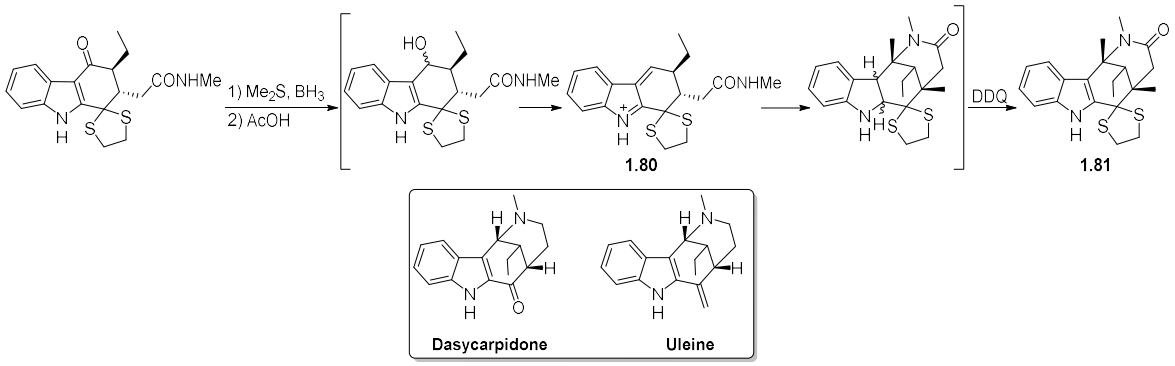
Michael addition followed by acid catalysed intramolecular cyclisation was also the strategy adopted by Takagi and co-workers towards the construction of natural product plukenetione A.[41] The complex adamantane framework was built in only eight steps starting from **1.73**. After two consecutive Michael additions to build the bicyclo[3.3.1]nonane core, $LiBH_4$ reduction of the bridge ketone and organometallic addition of two methyl groups afforded intermediate **1.76**; two sequential oxidations, protection of the tertiary alcohol and introduction of the benzoyl functionality gave triketone **1.78** which upon treatment with TfOH underwent intramolecular cyclisation to afford the highly advanced intermediate **1.79** (Scheme 1.19).



Scheme 1.19: Takagi's Michael addition/acid-catalised cyclisation strategy towards Plukenetione A.[41]

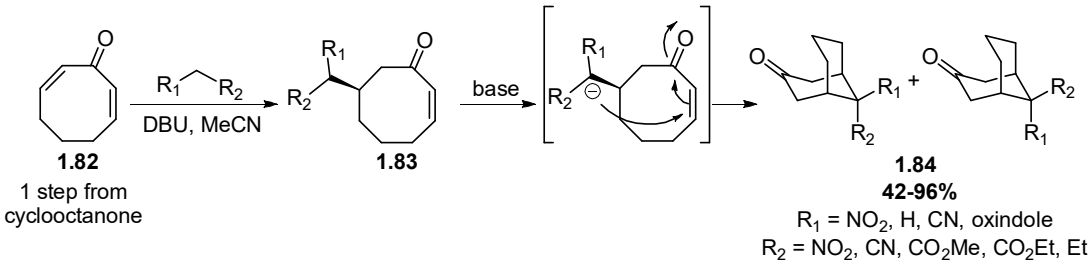
Also of interest is the effort by Patir's group towards the synthesis of Uleine and Dasycarpidone type-alkaloids.[42] The tetracyclic compound **1.81** featuring a bridged

[3.3.1]azabicyclo unit was obtained from a multi-step reaction involving a Michael-type intramolecular cycloaddition, this time on a conjugated iminium species **1.80** (Scheme 1.20).



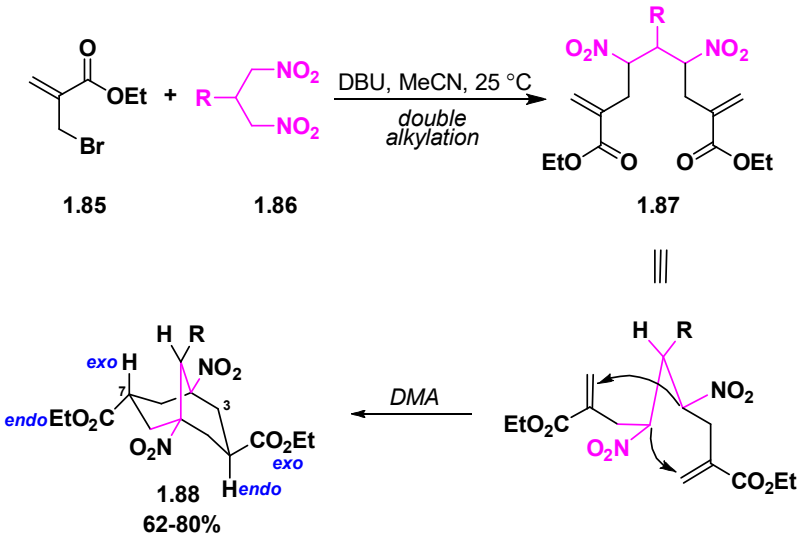
*Scheme 1.20: Patir's synthesis of intermediate **1.81**, a highly advanced intermediate in the synthesis of Uleine and Dasycarpidone alkaloids.*[42]

Lastly, a double Michael addition for the synthesis of 9-disubstituted bicyclo[3.3.1]octane-3-ones was reported in 2013 by Richard and co-workers; reaction between 2,7-cyclooctadien-1-one **1.82** with various carbon nucleophiles under basic conditions afforded a good array of substituted bicyclo[3.3.1]nonanes in 42–96% yield (Scheme 1.21).[43]



*Scheme 1.21: DMA approach for the synthesis of C-9 substituted bicyclo[3.3.1]nonanes from cyclooctadienones of type **1.82**.*[43]

In contrast, Ballini approached the synthesis of the bicyclo[3.3.1]nonane scaffold from acyclic reactants.[44] Commercially available ethyl 2-(bromomethyl)acrylate undergoes a double alkylation in the presence of 1,3-dinitroalkanes with concomitant release of two molecules of HBr to give intermediate **1.87**; the two electron-poor olefin moieties engage in a double conjugate addition to generate in one-pot and under mild basic conditions the bicyclic framework in a highly diastereoselective manner, forming the 3-*exo*-7-*endo* diastereoisomers **1.88** in 62-80% yield (Scheme 1.22).

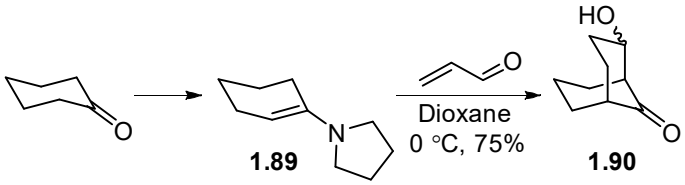


1.85 1.86 1.87 1.88

Scheme 1.22: Ballini's synthesis of highly functionalized bicyclo[3.3.1]nonanes.[44]

1.5.1.2 Annulation of enamine cyclohexanone derivatives

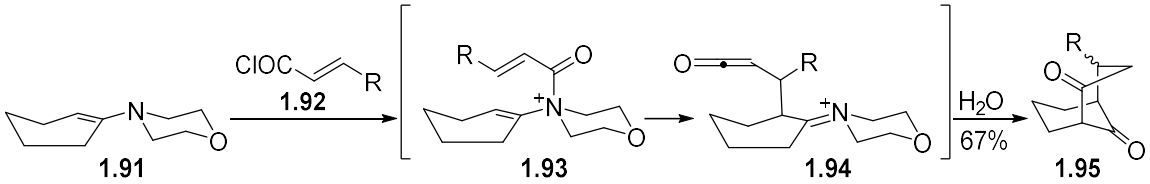
In his extensive study towards the enamine alkylation and acylation of carbonyl compounds, Stork reported for the first time the formation of bicyclo[3.3.1]nonane in the form of an hydroxyketone **1.90**, which arises from a double enamine mechanism (Scheme 1.23).[45]



1.89 1.90

Scheme 1.23: Stork first reported use of enamines in the synthesis of bicyclo[3.3.1]nonanes.[45]

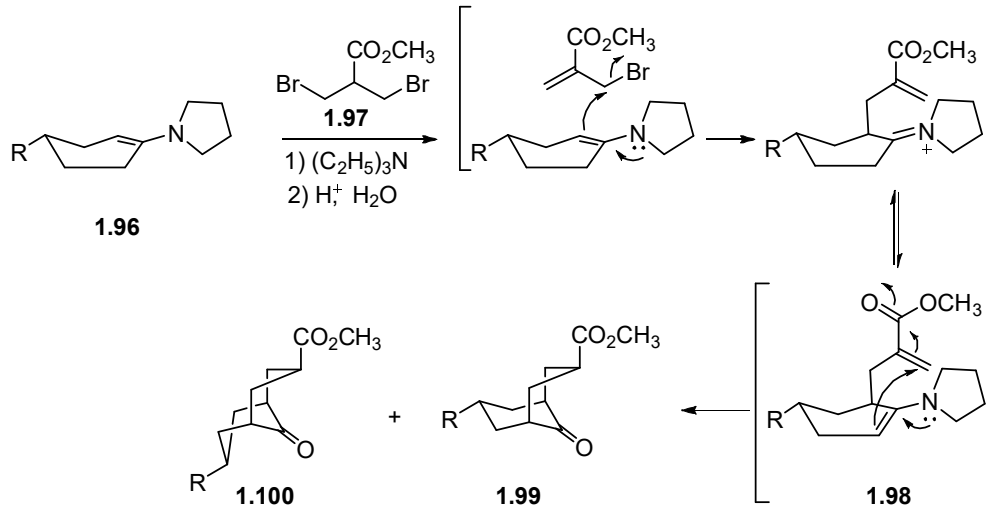
Enamines of cyclohexanone can be converted into bicyclo[3.3.1]nonane by various condensation reactions. Bicyclo[3.3.1]-2,9-diones **1.95** for example were obtained by reacting enamine **1.91** and acyl chloride **1.92**, through a sequence that has been reported[46] to involve *N*-acylation, a [3,3]-sigmatropic rearrangement and enamine-mediated ring closure (Scheme 1.24).



1.91 1.93 1.94 1.95

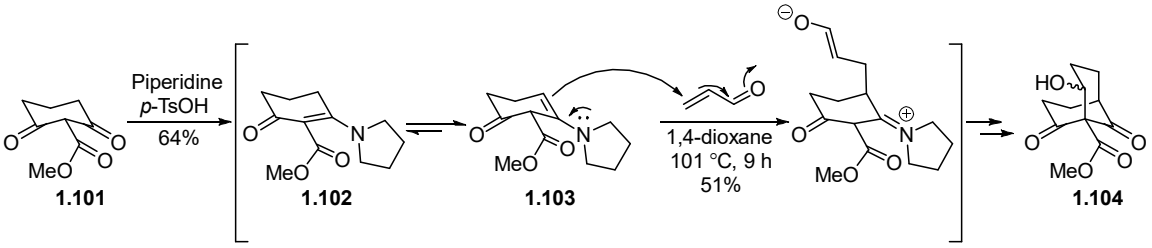
Scheme 1.24: Synthesis of bicyclo[3.3.1]-2-9-diones via enamine acylation/sigmatropic rearrangment/ring closure sequence.[46]

Synthesis of 3-substituted derivatives could be achieved by a more general annulation method between enamine **1.96** with methyl 2,3-dibromopropanoate.[47] The reaction proceeds *via* dehydrobromination of **1.97** followed by alkylation of the enamine with the latter and Michael annulation. Interestingly the less thermodynamically stable conformer **1.100** was obtained as well as the more favored one **1.99** (Scheme 1.25).



Scheme 1.25: General method for the synthesis of 3-substituted bicyclic compounds via enamine annulation with halogenated esters.[47a]

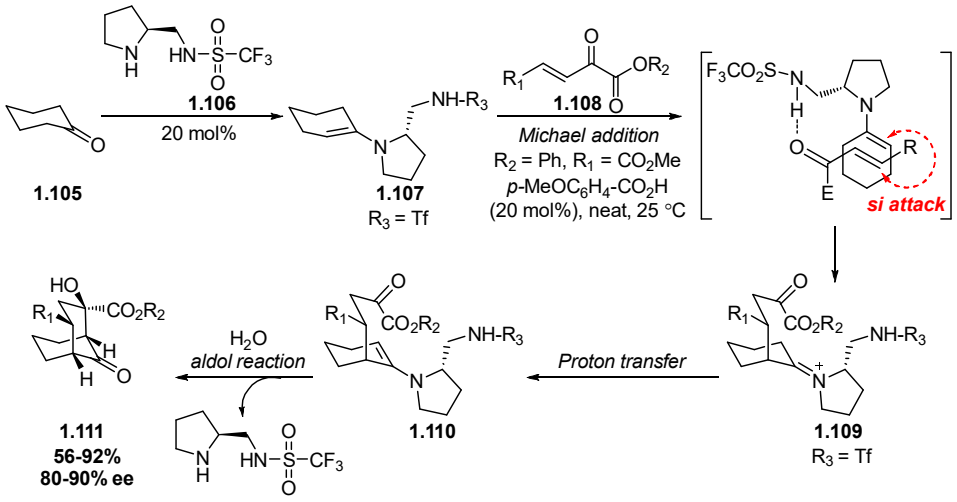
Almost 30 years later, Gravel in the process of developing a mild method for the γ-alkylation of β-keto esters, observed the formation of bicyclo[3.3.1]nonane **1.104** by reacting the enamino derivative of β-keto ester **1.103** with electrophilic olefins like acrolein and methacrolein.[48] The rationale for the inverse mode of cyclisation was based on the higher γ-reactivity of β-keto esters enamino derivatives, which was first observed by Colonna[49] and demonstrates how the enamino form **1.103** was more reactive than the vinylogous carbamate **1.102** (Scheme 1.26).



Scheme 1.26: Gravel rationale for the enamine reactivity in the synthesis of bicyclo[3.3.1]nonane.[48]

More recently, the power of enamine chemistry in the construction of bicyclo[3.3.1]nonane derivatives was elegantly demonstrated by Tang and co-workers.[50] Optically active 2-hydroxy-9-oxo-bicyclo[3.3.1]nonanes **1.111** were obtained in good to high yields and high

ee via a one-pot, formal [3+3] annulation reaction of enamines derived from cyclic ketones of type **1.105** and enones. In the presence of a catalyst like **1.106,** cyclohexanone **1.105** is converted into enamine **1.107** first, which undergoes Michael addition followed by isomerization and final aldol reaction with regeneration of the catalyst. The high enantioselectivity is explained by the selective attack of the enamine to one of the two planar faces of the prochiral sp^2-hybridized carbon of the enone, *i.e.* the *si* face, which is activated by the sulfonamide *via* hydrogen bond (Scheme 1.27).

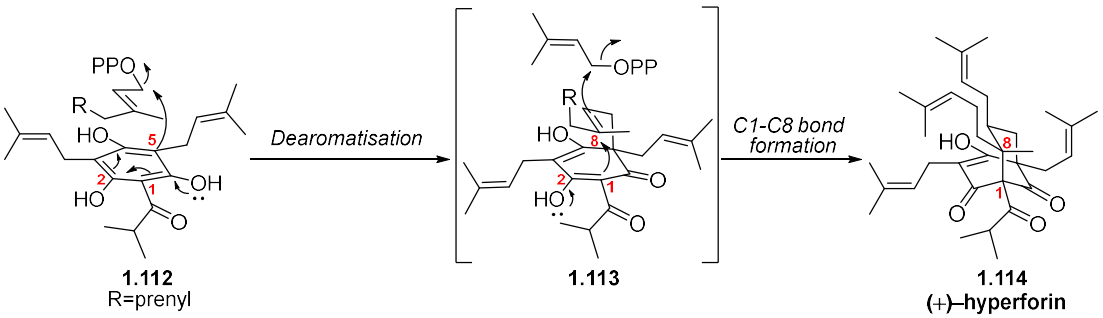


Scheme 1.27: Tang's use of enamine chemistry for the synthesis of optically active 2-hydroxy-9-oxo-bicyclo[3.3.1]nonanes.[50]

1.5.1.3 Biomimetic annulation and dearomatisation strategies

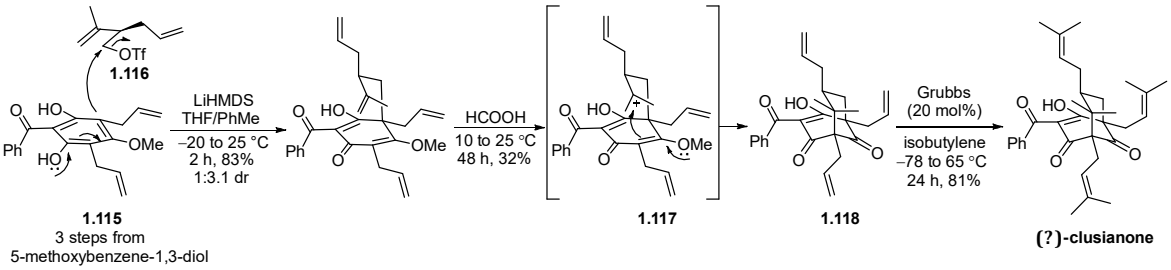
The number of dearomatisation examples carried out in nature by microorganisms, mostly oxygenase and reductase enzymes, is quite significant and surprising at the same time, considering the high resonance energy of the benzene ring. Dearomatisation of aromatic or heteroaromatic substrates is a very powerful synthetic tool for the conversion of planar, aromatic substrates into sp^3-enriched architecturally complex molecules.[51]

One of the most important and compelling dearomatisation process in nature is the putative biosynthesis of (+)-hyperforin, a PPAP natural product which features the bicyclo[3.3.1]nonane scaffold. The diprenylated ring of benzene intermediate **1.112** is suspected to be dearomatised in the presence of geranyl diphosphate, followed by a C-2 enol attack; in the same step, the C-1,C-8 bond would be made and an additional prenyl group installed at C-7, leading to (+)-hyperforin **1.114** (Scheme 1.28).[15]



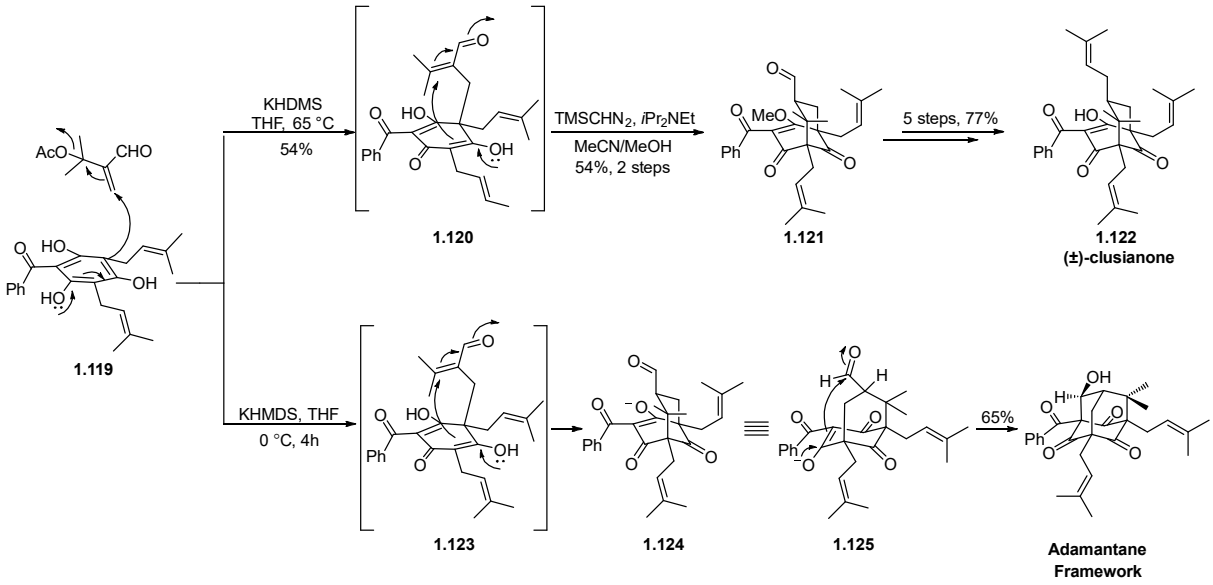
Scheme 1.28: Putative mechanism for the biosynthesis of the natural product (+)-hyperforin.[15]

In this context and inspired by (+)-hyperforin's proposed biosynthetic pathway, Porco's group pioneered most of the dearomatisation-annulation strategies known for the construction of the bicyclo[3.3.1]nonane scaffold, completing several total synthesis of PPAP natural products in the process. One important example is represented by the asymmetric total synthesis of (–)-clusianone;[52] alkylative dearomatisation of **1.115** with triflate **1.116** followed by the key formic acid-mediated cationic cyclisation (intermediate **1.117**) forged the bicyclo[3.3.1]nonane core affording intermediate **1.118**; RCM with Grubbs second generation catalysts completed the total synthesis of the natural product, yielding (–)-clusianone in 81% yield (Scheme 1.29).



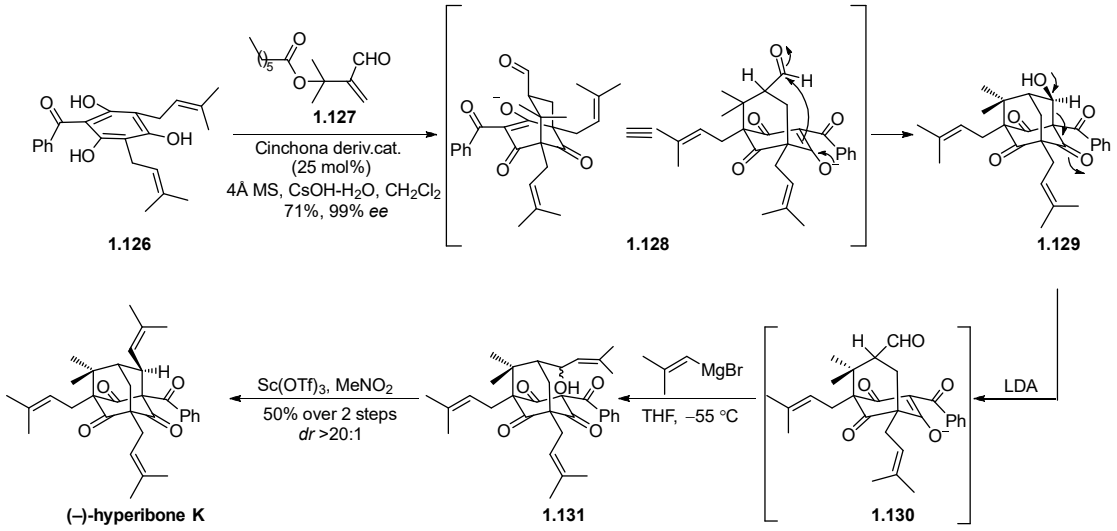
Scheme 1.29: Porco's dearomatisation approach in the enantioselective total synthesis of (–)-clusianone.[52]

A domino alkylative dearomatisation-annulation was first developed in 2007 for the synthesis of racemic (±)-clusianone;[30] as depicted in Scheme 1.30 the use of an α-acetoxy enal led to a highly diasereoselective dearomatisation-annulation of substrate **1.119**, which was followed by an intramolecular Michael reaction to give **1.121,** an important intermediate towards clusianone's synthesis. By changing the reaction conditions and cooling the reaction mixture to 0 °C the kinetic protonation product **1.124** was instead favoured and underwent an intramolecular aldol reaction giving the complex adamantane scaffold, whose structure is closely related to the PPAP natural product (–)-hyperibone K (Scheme 1.30).



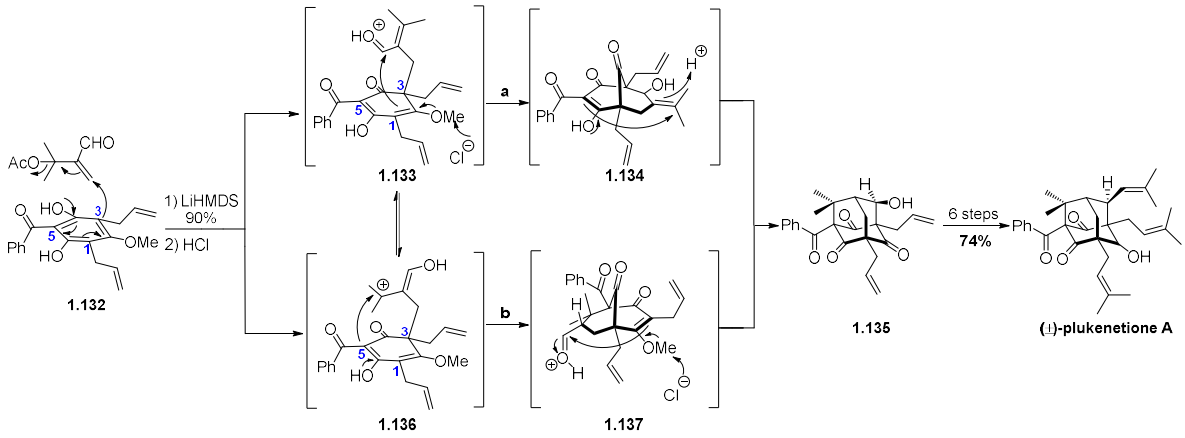
Scheme 1.30: Porco's divergent synthesis of highly functionalized intermediates in the synthesis of PPAP derivatives.[30]

Three years later, the same alkylative dearomatisation-annulation strategy was used for the enantioselective total synthesis of (–)-hyperibone K.[53] Cinchona-alkaloids-derived phase transfer catalyst mediated the key dearomatisation-annulation step between phloroglucinol derivative **1.126** and heptanoate aldehyde **1.127**, followed by a subsequent aldol reaction to give adamantane compound **1.129**. A retro-aldol step triggered by LDA followed by addition of 2-methyl propenyl magnesium bromide afforded allylic alcohol **1.131**; (–)-hyperibone K was finally obtained through an intramolecular cationic cyclisation catalised by scandium triflate (Scheme 1.31).



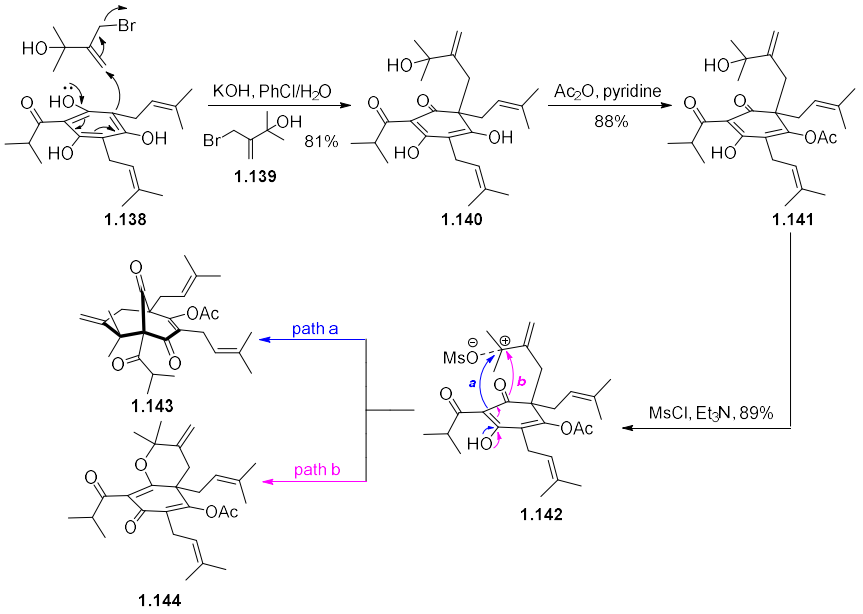
Scheme 1.31: Porco's dearomatisation/annulation strategy for the synthesis of (–)-hyperibone K.[53]

To complete their studies towards the PPAP family, Porco and co-workers ultimately managed to access the highly substituted adamantane core of (±)-plukenetione A, a C-3,C-5 regioisomer of the previously synthesised (−)-hyperibone K.[54] In this context, his group devised a synthetic route with a selective alkylative dearomatisation as the key step; treatment of **1.132** with α-acetoxy enal under strong basic conditions delivered the mono-alkylated product where dearomatisation took place as planned, exclusively at C-3. Direct access to the annulation product through a domino cascade was not possible due to a probable retro-Michael process; nevertheless, exposure to conc. HCl forged the adamantane scaffold, giving alcohol **1.135** in 75% as a single diastereoisomer. Two possible mechanistic pathways were proposed to rationalize the adamantane formation (Scheme 1.32, path **a** and **b**); in path **a** the acid mediated protonation of the aldehyde in **1.133** can promote a demethylative aldol cyclisation followed by a second protonation of the alkene and subsequent cationic cyclisation to give **1.134**; in path **b** the allylic resonance structure (**1.136**) derived from aldehyde **1.133** can undergo directly a cationic cyclisation to forge the bicyclo[3.3.1]nonane core which participates in a final aldol reaction to give the adamantane core. (±)-plukenetione A was lastly accessed from **1.135** in 6 steps and in 74% yield (Scheme 1.32).



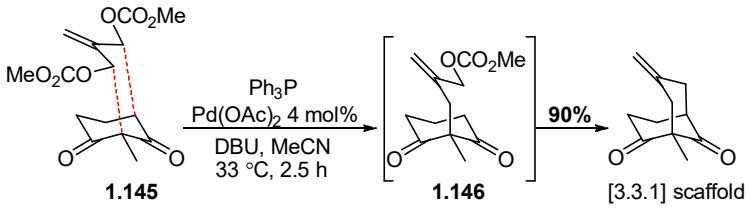
Scheme 1.32: Selective alkylative dearomatisation for the access to (±)*-plukenetione A.*[54]

In the context of biomimetic approaches, another contribution was given by Couladouros' work on the synthesis of the highly functionalised bicyclo[3.3.1]nonane framework.[55] The same alkylative dearomatisation strategy pioneered by Porco was applied to substrate **1.138** affording selective acetylated intermediate **1.141**. Conversion of the tertiary alcohol into the corresponding mesylate led to spontaneous cyclisation to bicyclo[3.3.1]nonane (**path a**) albeit with concomitant formation of the *O*-alkylation product (**path b**) in 89% combined yield (1.143:1.144 ca 1.5:1) (Scheme 1.33).



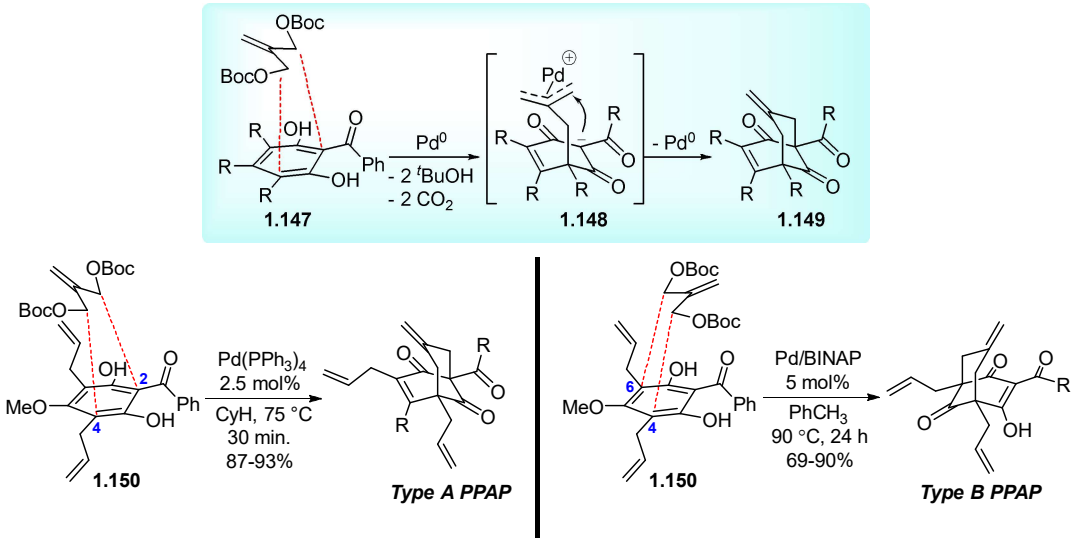
Scheme 1.33: Couladouros' alkylative dearomatisation approach for the synthesis of highly functionalized bicyclo[3.3.1] intermediates.[55]

Another well-recognized annulation method for the rapid formation of carbon-carbon bond is the reaction of various nucleophiles with allylic substrates via Pd π-allyl intermediates. The reaction between cyclic enamines and allylic alkylating reagents to afford bridged bicyclic ketones was documented by Murahashi for the first time in 1973;[56] later in 1998 Tenaglia accessed bicyclo[3.n.1]alkanones through a palladium-catalyzed *C*,*C*-dialkylative cyclisation of monoalkylated β-diketones (Scheme 1.34).[57]



Scheme 1.34: Tenaglia's palladium-catalyzed C,C-dialkylative cyclisation of monoalkylated β-diketones.[57]

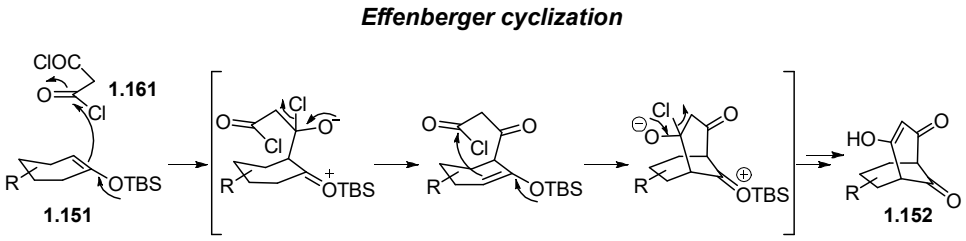
These two precedents remained little explored until very recently, with Porco's report on the Pd-catalysed dearomative conjunctive allylic annulation (DCAA) between desoxyhumulone derivative **1.147** and bis-Boc-protected-methylenepropane-1,3-diol;[58] this method represents a powerful domino strategy and depending on the mode of annulation both type A and type B PPAP analogs can be easily accessed in high yield (Scheme 1.35).



Scheme 1.35: Porco's Pd-catalysed dearomative conjunctive allylic annulation strategy to access both type A and B PPAP.[58]

1.5.1.4: Annulation of cyclohexanone derivatives featuring the Effenberger cyclisation

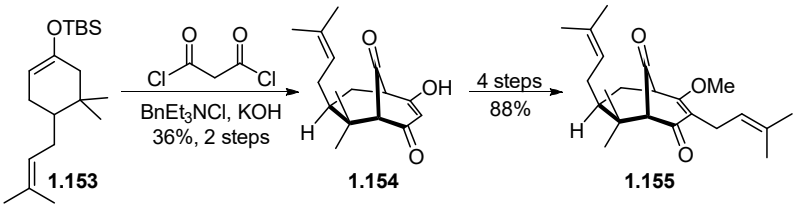
The Effenberger cyclisation[59], in which cyclohexanones derivatives **1.151** are annulated in the presence of malonyl chloride to give the bicyclo[3.3.1]nonane scaffold **1.152**, also represents a powerful annulation method (Scheme 1.36).



Scheme 1.36: Mechanism for the Effenberger annulation.

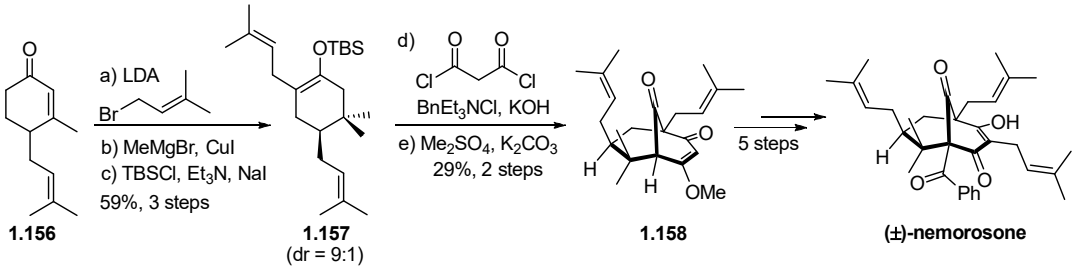
Although limited by the modest yield, the restrictive use of 2-unsubstituted malonyl derivatives and 6-membered rings, a few groups successfully applied this strategy to the synthesis of the bicyclo[3.3.1]nonane scaffold. The first application of the Effenberger annulation in the construction of this bicyclic scaffold was reported by Stoltz in 2002, who obtained bicyclo[3.3.1]nonane **1.154** via a one-pot reaction of TBS enol ether **1.153** and malonyl chloride under basic and phase-transfer conditions.[60] This protocol was particularly attractive despite the modest yield as the annulation was completely stereoselective in

respect to the prenyl group, which was found to have an *anti*-orientation relative to the 1,3-diketone moiety just formed (Scheme 1.37).



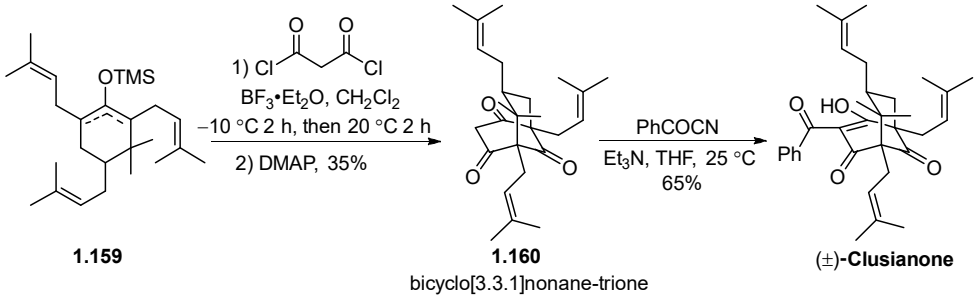
Scheme 1.37: Stoltz' application of the Effenberger annulation for the synthesis of bis-prenylated bicyclo[3.3.1]nonanes.[60]

A closely related Effenberger annulation was also used by Simpkins in his total synthesis of (±)-nemorosone in 2010.[61] Bis-prenylated silyl enol ether **1.157** generated via prenylation, cuprate mediated conjugate addition and subsequent silylation from **1.156**, was readily cyclised in the presence of malonyl chloride with *in situ* methylation of the resulting alcohol to afford intermediate **1.158**. A challenging C-3 prenylation and acylation of the C-1 bridgehead position completed the total synthesis of this PPAP natural product in 55% overall yield (Scheme 1.38).



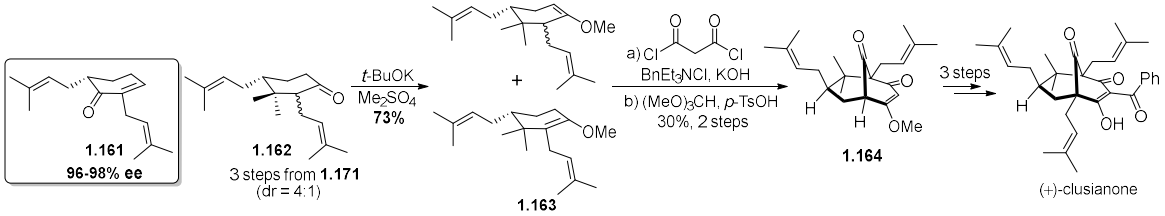
Scheme 1.38: Simpkins' total synthesis of (±)-nemorosone.[61]

Marazano's α,α-annulation of silyl enol ether **1.159** with malonyl chloride is also noteworthy and afforded the corresponding bicyclo[3.3.1]nonane-trione **1.160** in 35% yield.[62] C-acylation with benzoyl cyanide completed their total synthesis, giving (±)-clusianone in 65% yield (Scheme 1.39).



*Scheme 1.39: Marazano's α,α-annulation of **1.159** with malonyl chloride for the synthesis of (±)-clusianone.[62]*

Lastly, Coltart and co-workers devised an Effenberger annulation strategy for the asymmetric synthesis of (+)-clusianone.[63] The key optically enriched cyclohexenone intermediate **1.162**, obtained in 3 steps from **1.161** as a 4:1 epimeric mixture at C-1, was converted into its methyl enol ether **1.163.** This then underwent an Effenberger type cyclisation affording bicyclo **1.164** with concomitant methylation of the enolisable β-diketone. Introduction of the remaining prenyl and benzoyl substituents followed by demethylation gave (+)-clusianone in 71% yield (Scheme 1.40).

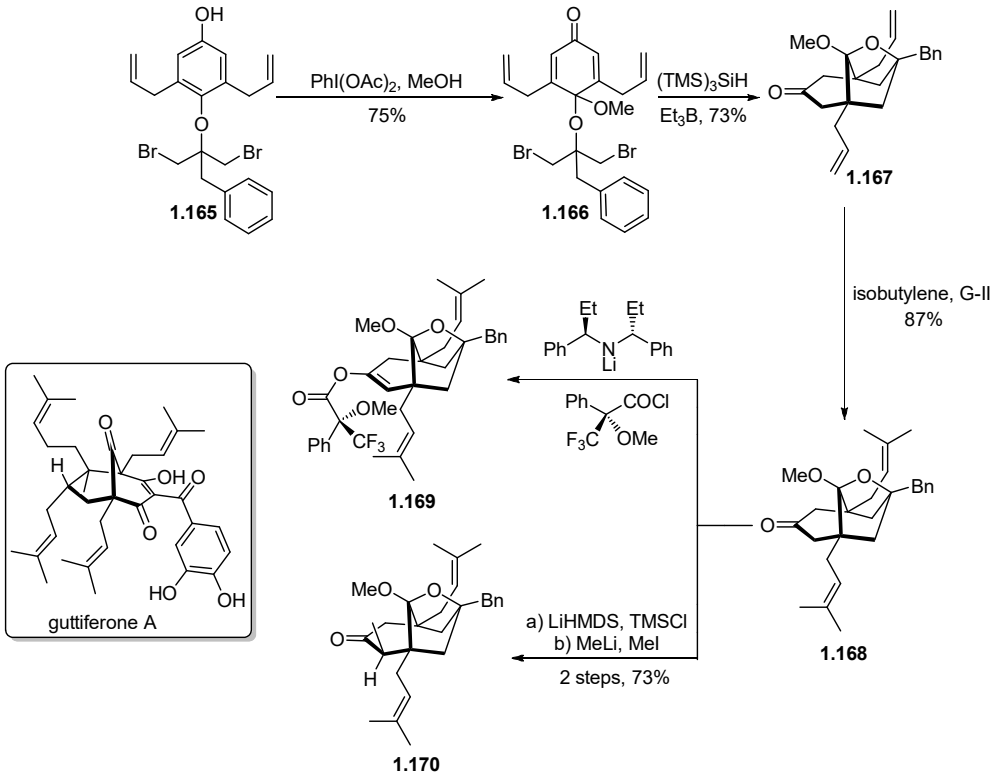


Scheme 1.40: Coltart's asymmetric synthesis of clusianone via Effenberger type annulation.[63]

1.5.2 Desymmetrisation Strategies

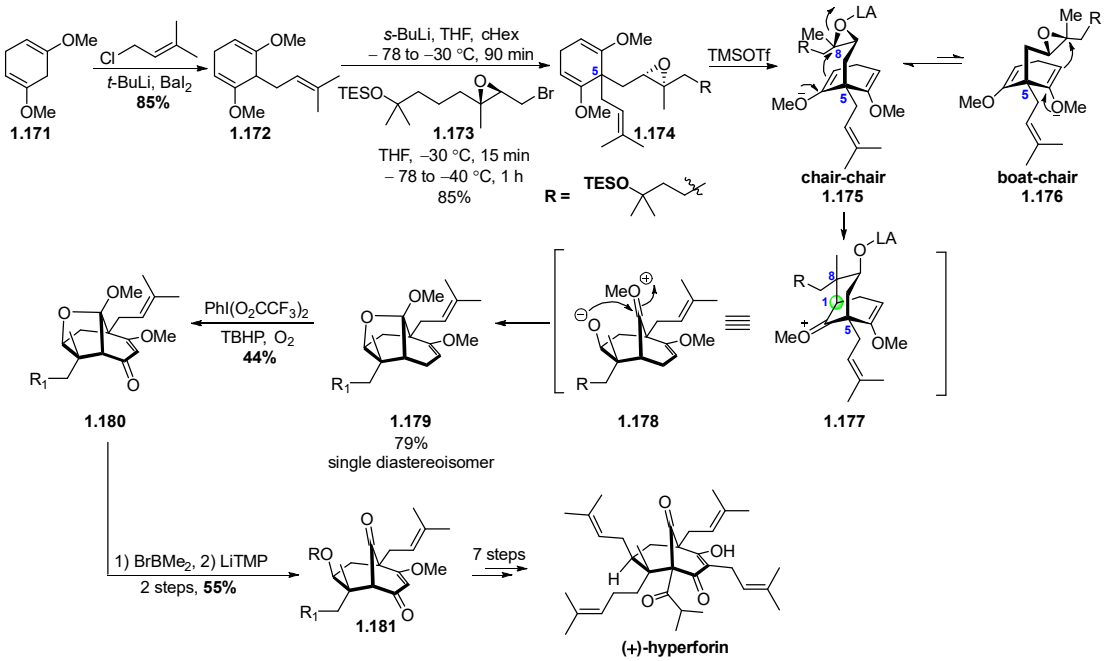
Synthetic chemistry, especially in the field of natural product total synthesis, has greatly benefited from the application of desymmetrisation strategies. Through either enantiotopic or diastereotopic group discrimination, several transformations can be in fact carried out while efficiently controlling the outcome of a particular stereocenter, guaranteeing therefore a high level of stereochemical integrity.[64]

A late-stage desymmetrisation was used by Njardarson's group in their exploration of the Guttiferone PPAP family derivatives.[65] Following dearomatisation of phenol **1.165** with (diacetoxyiodo)benzene and intramolecular radical cyclisation, the tricyclic intermediate **1.168** was successfully desymmetrised through its lithium enolate. Formation of both chiral enol ester **1.169** and α-methyl ketone **1.170** illustrated the power of this strategy in accessing optically active substrates which can be subsequently carried forward in the synthesis of PPAP derivatives (Scheme 1.41).



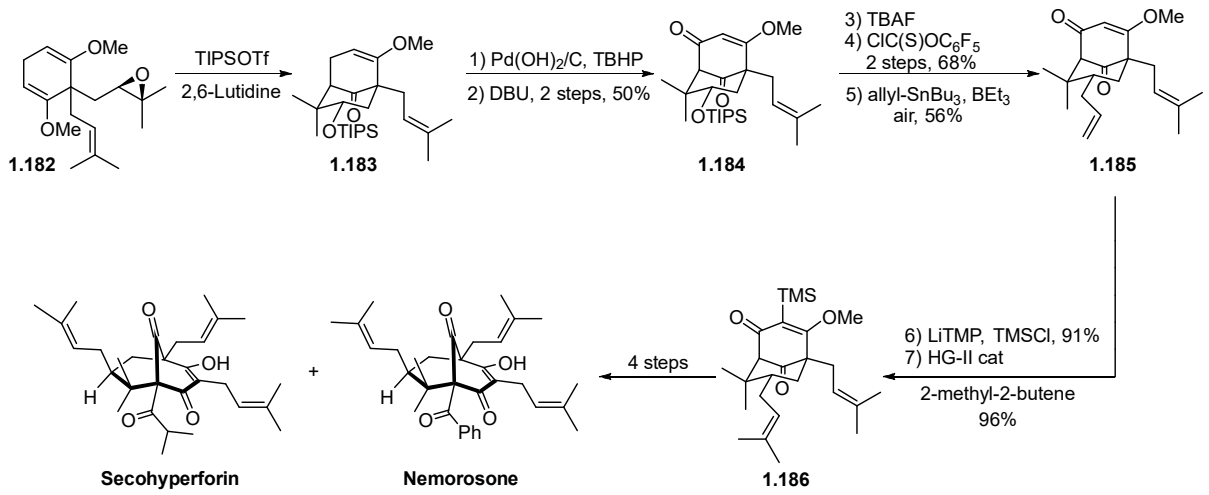
Scheme 1.41: Njardarson's desymmetrisation approach towards the synthesis of functionalized intermediates for the access to guttiferone PPAP family.[65]

Perhaps the most elegant example of desymmetrisation was demonstrated by Shair in 2013 in his enantioselective total synthesis of (+)-hyperforin.[66] The 18-step route was based around a geraniol fragment closely related to that used in nature for the biosynthesis of hyperforin. In a similar manner, deprotonation of cyclohexadiene **1.171** with *t*-BuLi and subsequent prenylation and coupling with the enantio-enriched epoxide **1.173** gave cyclisation precursor **1.174**. Exposure of the latter to the Lewis acid TMSOTf activated the epoxide towards nucleophilic attack; a careful analysis of the transition state showed how only one enol ether engaged the activated epoxide through a chair-chair transition state (**1.175**); epoxide ring-opening by the alternative enol ether would result in a boat-chair like TS (**1.176**) and in a 5-*endo*-*tet* cyclisation, both highly disfavoured. 6-(*enolendo*)-*tet* cationic cyclisation at the epoxide carbon atom via a more favourable chair-chair TS afforded an oxonium ion **1.178** that was trapped internally by the liberated oxygen atom, giving the bridged acetal **1.179** in 79% yield as single diastereoisomer**.** Vinylogous ester **1.180** was prepared via iodine(III)-mediated allylic oxidation which installed the last required carbonyl group. Final hydrolysis of the ketal and insertion of the three remaining prenyl chains yielded (+)-hyperforin (Scheme 1.42).



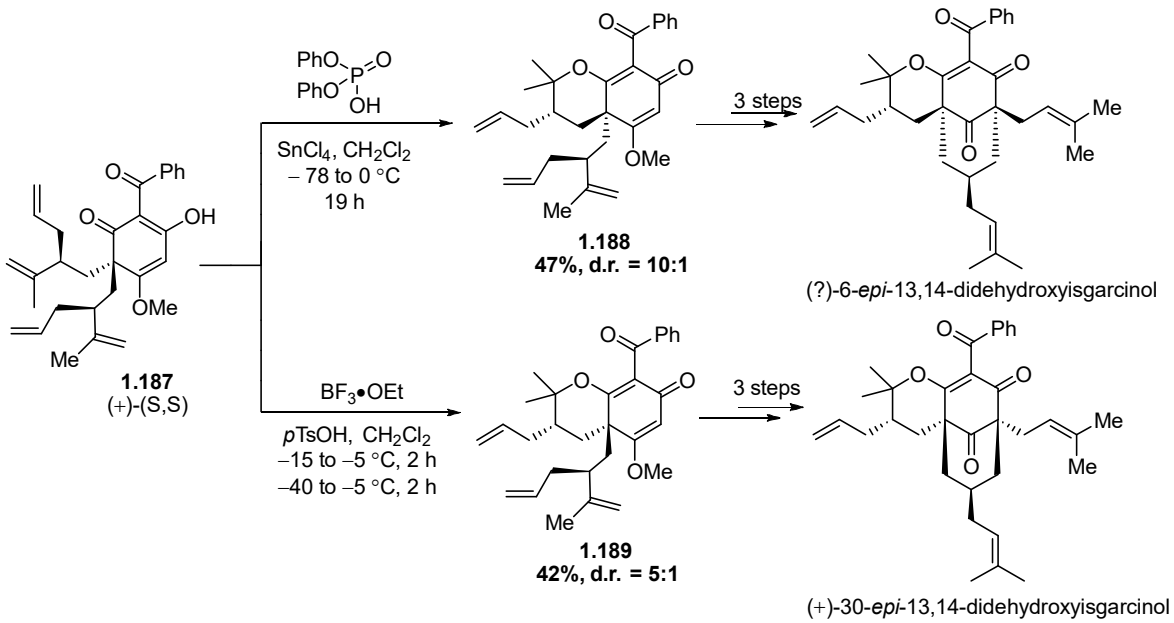
Scheme 1.42: Shair's enantioselective total synthesis of (+)-hyperforin through desymmetrisation of epoxide intermediate ***1.174.***[66]

Later in 2015, Shair and co-workers applied the same desymmetrisation strategy in the synthesis of two other members of the PPAP family, Nemorosone and Secohyperforin.[67] This time their choice fell upon a Lewis acid featuring a larger trialkylsilyl group as they postulate the latter would prevent the formation of a cyclic ketal of type **1.179** (scheme 1.42); its subsequent cleavage would in fact require the use of Me_2BBr (as previously employed in the total synthesis of (+)-hyperforin) which was considered not practical for their purposes and difficult to scale up. Thus, addition of TIPSOTf and 2,6-lutidine at −78 °C to a solution of **1.182** followed by slow warming of the mixture to room temperature afforded the TIPS-protected alcohol **1.183** in 95% yield. Allylic oxidation was rather challenging and was ultimately achieved with Pearlman's catalyst ($Pd(OH)_2/C$) and TBHP, despite the additional requirement of DBU to convert the undesired allylic peroxide also formed during the reaction (not shown). Keck allylation after thiocarbonylation of the secondary alcohol and subsequent olefin cross-metathesis afforded intermediate **1.186** that was used for the synthesis of both Nemorosone and Secohyperforin, depending on the use of benzoyl chloride or isobutyroyl chloride respectively in the bridgehead acylation step (Scheme 1.43).



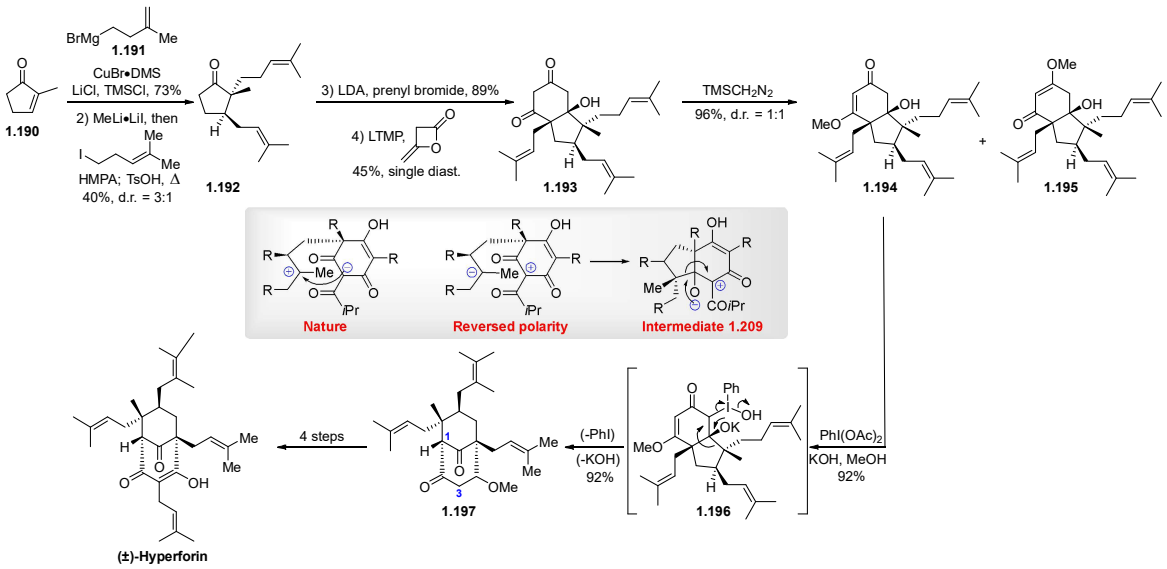
Scheme 1.43: Application of a similar desymmetrisation method for the synthesis of Secohyperforin and Nemorosone.[67]

Porco's group applied a similar diastereotopic group differentiation strategy for the synthesis of garcinol and isogarcinol derivatives, two type B members of the PPAP family.[68] Intermediate **1.187** was obtained as a single enantiopure diastereoisomer via bis-alkylation of acylphloroglucinol (not shown) and subjected to diastereoselective oxycyclisation; depending on the reaction conditions the two pyranodienone products **1.188** and **1.189** were obtained in different d.r. and yields. The diastereoselectivity was rationalised as a result of an intramolecular protonation after the formation of a hexacoordinate tin complex in the reaction using $SnCl_4$ or a tetrahedral BF_2 complex when BF_3•Et_2O was used. The same three steps sequence was then used to complete the synthesis of (–)-6-*epi*-and (+)30-*epi*-13,14-didehydroxyisogarcinol respectively (Scheme 1.44).



Scheme 1.44: Diastereoselective, Lewis acid-controlled oxycyclisation for the synthesis of (–)-6-epi-and (+)-30-epi-13,14-didehydroxyisogarcinol.[68]

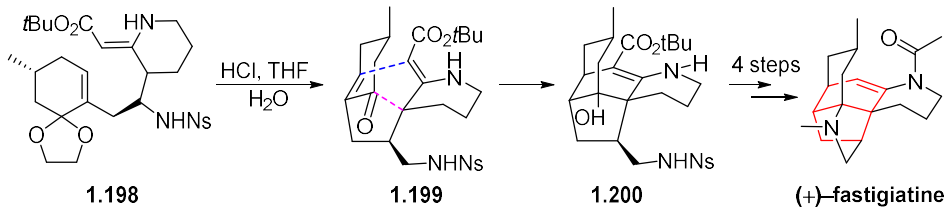
A very different approach was pursued in the remarkably short total synthesis of (±)-hyperforin by Maimone and deserves comment because it provides a very succinct access to the bicyclo[3.3.1]nonane core (Scheme 1.45).[69] Maimone and co-workers were indeed able to access the highly prenylated bicyclo[3.3.1]nonane-1,3,5-trione scaffold in only 6 steps, completing the total synthesis in a total of 10 steps. Their strategy was based upon the exploration of a polarity-reversed reactivity; as highlighted in the grey box on Scheme 1.45, whereas PPAPs in nature are presumably formed by attack of a nucleophilic enolate to a carbocationic intermediate, the reverse mode of attack will instead lead to a hypothetical carbonyl addition product which can undergo a [1,2]-alkyl rearrangement with ring expansion to give the bicyclo[3.3.1]nonane core. After copper mediated conjugate addition of **1.190** and two subsequent alkylations, LTMP mediated deprotonation gave rise to a highly hindered enolate which engages in a diketene annulation reaction to afford **1.193** as single diastereoisomer. Generation of the key cationic intermediate **1.196** was achieved after extensive experimentation with hypervalent iodine where simply stirring at room temperature in MeOH effected the desired ring expansion, affording the PPAP skeleton in 92% yield. Functionalisation of the C-1 bridgehead position and a last *C*-prenylation afforded (±)-hyperforin in 56% yield (Scheme 1.45).



Scheme 1.45: Maimone's total synthesis of (±)-hyperforin via diketene annulation/ring expansion strategy.[69]

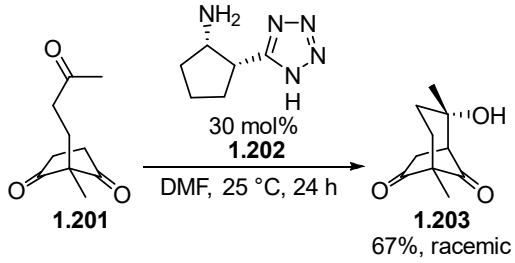
1.6 Synthetic strategies towards bicyclo[3.2.1]octane framework

Many new, stereoselective methodologies for the construction of the bicyclo[3.2.1]octane have been developed, a few being used in the total synthesis of complex natural products.[70] Shair assembled the desired bicyclic core of the natural product (+)-fastigiatine by hydrolysis of the acetal moiety in **1.198**; the corresponding ketone **1.199** underwent a diastereoselective intramolecular Michael addition followed by a transannular aldol reaction to give aldol product **1.200** from which (+)-fastigiatine was obtained in 4 steps (Scheme 1.46).[71]



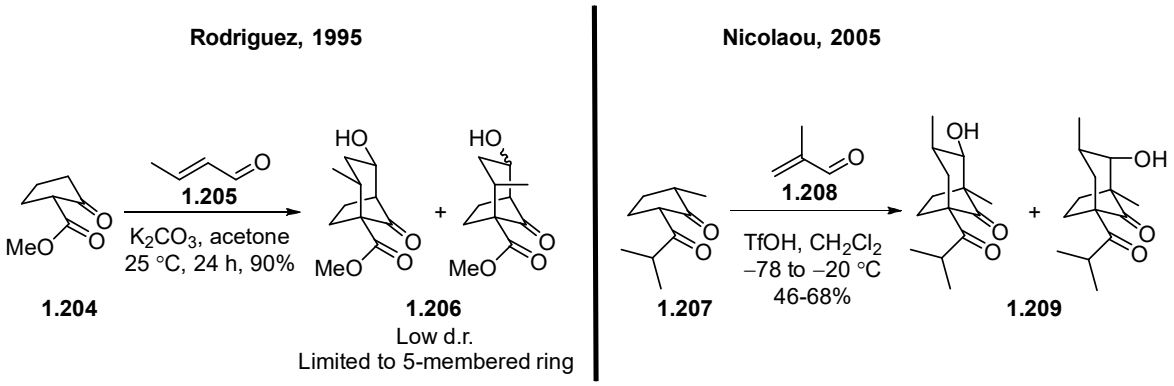
Scheme 1.46: Shair's total synthesis of (+)-fastigiatine through a Michael-transannular aldol reaction.[71]

As part of their study towards the Hajos–Parrish–Eder-Sauer-Wiechert reaction, Stephen Davies catalysed the intramolecular aldol reaction of triketone **1.201** with amine **1.202** to provide bicyclo aldol product **1.203** with high diastereoselectivity (Scheme 1.47).[72]



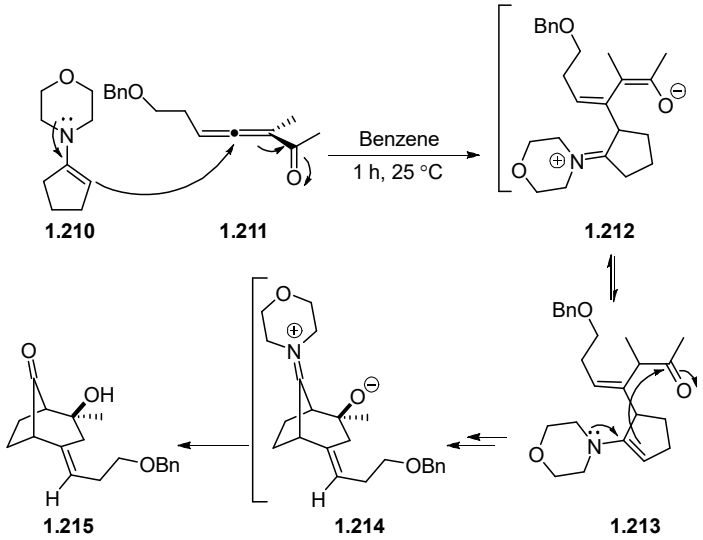
*Scheme 1.47: Davies' aldol condensation of **1.201** catalysed by cispentacin tetrazole derivative.*[72]

Michael-aldol sequences have also afforded the bicyclo[3.2.1]octane system. In 1995 Rodriguez reported the base-catalysed reaction between 2-oxocyclopentane-1-carboxylate **1.204** and crotonaldehyde **1.205**; despite the high yield obtained this sequence presented low diastereoselectivity as well as being limited to only five membered ring precursors.[73] Ten years later Nicolaou described the acid-catalysed Michael-aldol sequence between **1.207** and methacrolein **1.208** to give bicyclic diastereomeric mixture **1.209** in good yield although the diastereoselectivity was not rationalised or described as the alcohol functionality was readily oxidized in the subsequent step (Scheme 1.48).[31]



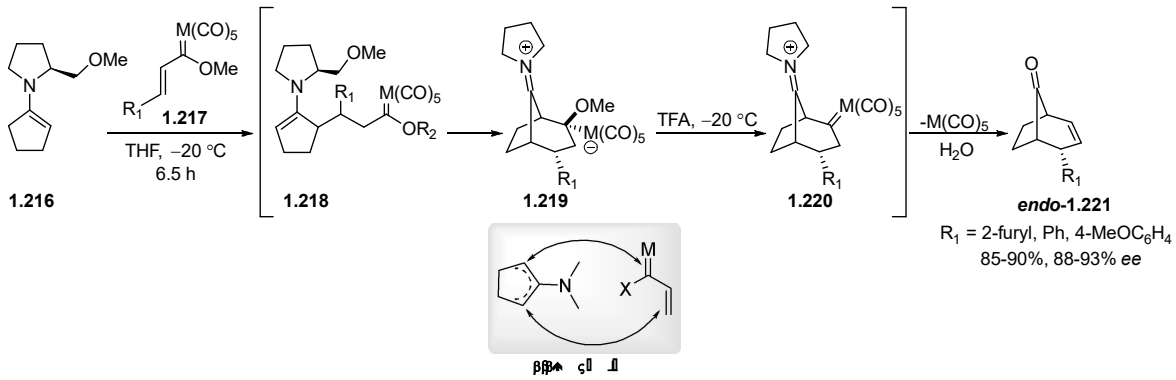
Scheme 1.48: Rodriguez' and Nicolaou's Michael-aldol approaches for the synthesis of bicyclo[3,2,1]octanes.[31, 73]

In the same year Lepore proved the synthetic utility of enamines in the stereoselective synthesis of the [3.2.1] bicyclic scaffold; reaction between morpholine derivative **1.210** and allenyl methyl ketone **1.211** afforded bicyclo[3.2.1]octane **1.215**; the *endo* mode of cyclisation observed was attributed to a better charge stabilisation in the *endo* bicyclo zwitterionic intermediate **1.214** which is also thermodynamically favoured; the (*E*)-geometry of the alkene arose from the initial Michael-Stork addition occurring at the less hindered bottom face of allene **1.211** (Scheme 1.49).[74]



*Scheme 1.49: Rationalisation for the endo-selectivity and the double bond geometry observed in the reaction between enamines and allene of type **1.211**.[74]*

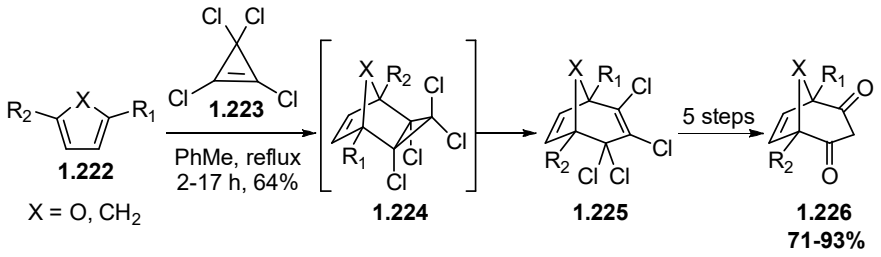
Barluenga was the first to describe the transition metal-assisted [3+3] carbocyclisation reaction of enamines with Fisher carbenes (Scheme 1.50).[75] Chiral cyclopentanone enamines **1.216** undergoes β,β'-annulation with either chromium or tungsten alkenyl carbene complexes of type **1.217** to generate bicyclic metallated intermediate **1.220** via Michael adduct **1.218**. The acid-induced elimination of methanol from **1.219** forms the stabilized carbene species **1.220** which undergoes β-elimination and reductive metal elimination to give enantiomerically enriched *endo*-cycloadduct **1.221** in very high yields and *ee*. However, the same transformation using cyclohexanone enamine gave much lower levels of diasteroselectivity and enantioselectivity (Scheme 1.50).



Scheme 1.50: Barluenga's transition metal-assisted carbocyclisation reaction to give bicyclo[3.2.1]octanes.[75]

Wright and co-workers investigated the Diels-Alder reaction of tetrahalocyclopropenes to access bicyclic skeletons of biological relevance.[76] Beaudegnies' group applied this strategy for the synthesis of bicyclo[3.2.1]octane-2,4-diones with the intent to access novel

precursors for 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors (Scheme 1.51).[77] Heating a mixture of cyclopentadiene **1.222** and tetrachlorocyclopropene **1.223** in toluene readily afforded the *exo*-adduct **1.224** which underwent a spontaneous torquoselective sigmatropic rearrangement to give bicyclic structure **1.225**. Conversion into the desired diketone product **1.226** was then achieved in 5 steps, accessing three different bicyclo[3.2.1] compounds in good to high yield (Scheme 1.51).



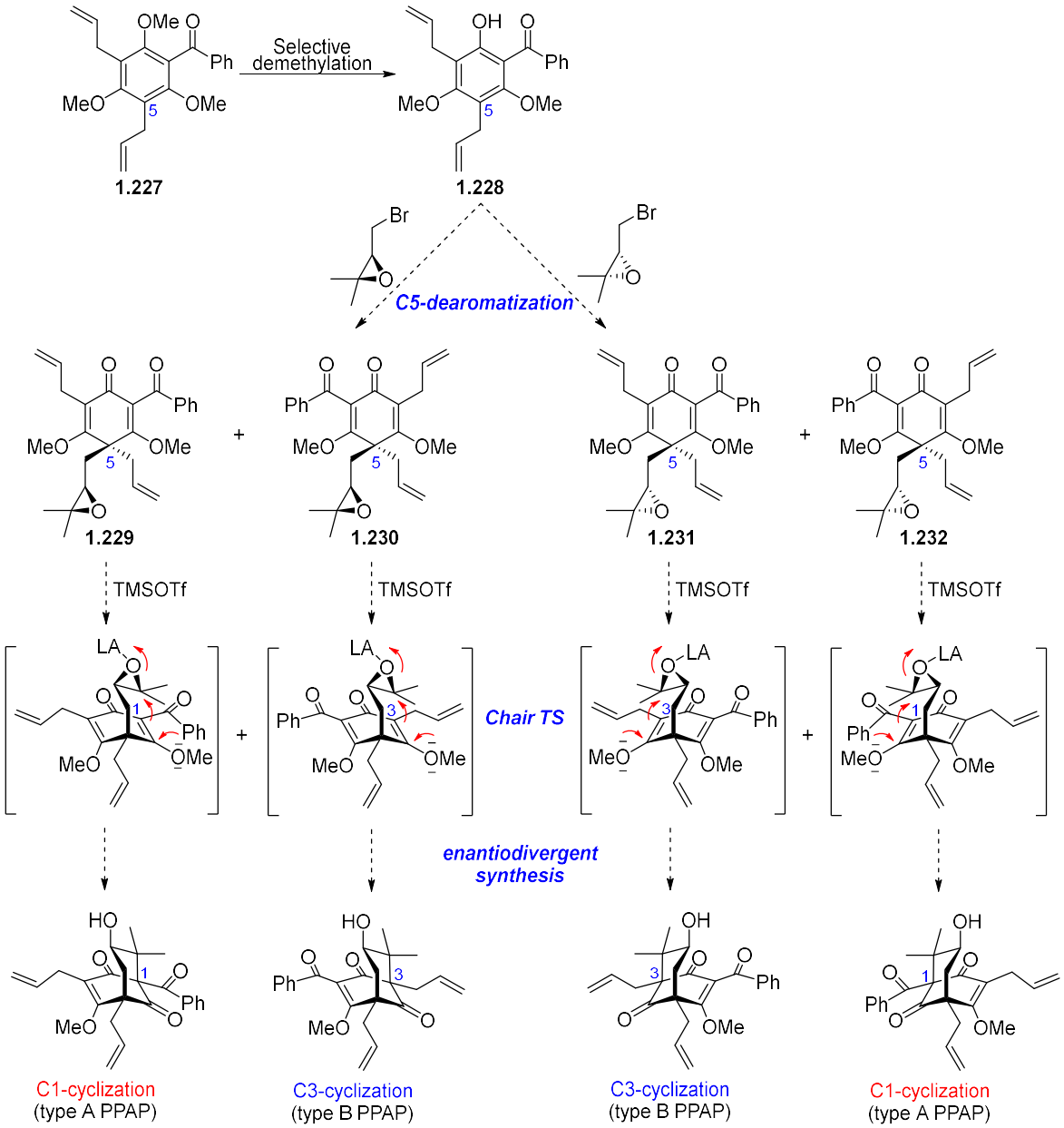
Scheme 1.51: Beaudegnies' Diels-Alder strategy for the synthesis of bicyclo[3.2.1]octane-2,4-diones.[77]

1.7 Our synthetic plan and initial aim of the project

As outlined in this chapter, the exploration of new regions of the chemical space is a priority for the discovery of new compounds with unique chemical and biological properties. In particular, saturated bridged carbobicyclo systems attracted our attention because of the recent emphasis on compounds with a higher fraction (approx. 50%) of sp^3 carbon atoms per molecule for improved physicochemical properties (better 'drug-likeness') and because of the challenge of constructing such scaffolds with specific three-dimensional direction of multiple substituents.

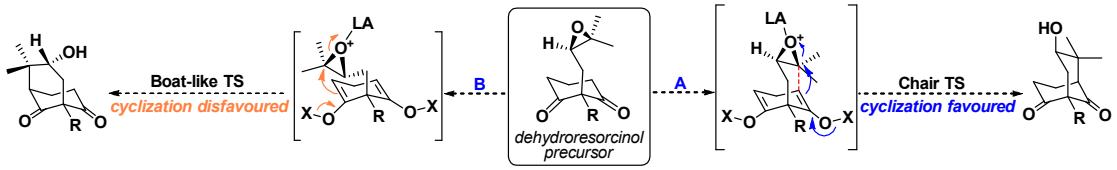
Our interest initially fell upon the class of polycyclic polyprenylated acylphloroglucinols (PPAPs), whose members display a diverse array of biological properties and whose structures feature a complex, densely prenylated bicyclo[3.3.1]nonane or [3.2.1]octane scaffold. Our first approach towards the PPAP framework investigated a dearomatisation strategy, the addition of a three-carbon chain across the carbon atoms derived from a benzene ring to create the bicyclo[3.3.1]nonane core (Scheme 1.52). The dearomatisation precursor **1.228** could be accessed from commercially available 1,3,5-trimethoxybenzene in three steps, *i.e.* Friedel-Crafts acylation, subsequent allylation and selective demethylation. The methyl ester groups at positions 4 and 6 would closely relate to Shair's intermediate **1.172** (Scheme 1.42) and would render the compound easier to handle. The key dearomatisation of **1.228** by two chiral epoxides would give a pair of diastereomers,

1.229/**1.230** or **1.231**/**1.232,** which following two possible modes of cyclisation would give the bicyclo[3.3.1]nonane skeleton of type A (C-1 cyclisation) and type B (C-3 cyclisation) PPAP. This enantiodivergent sequence has not, to our knowledge been investigated and could provide a short route to fully-substituted bicyclo[3.3.1]nonane systems (Scheme 1.52).



Scheme 1.52: Enantiodivergent synthesis of type A and B PPAP via dearomatisation and epoxide-mediated cyclisation.

The second strategy we pursued relied upon a desymmetrisation approach, starting from simpler, readily available 1,3-diketones (dihydroresorcinol derivatives); after introduction of a similar epoxide functionality and subsequent ring opening cascade *via* a chair-like transition state (path A), the desired bicyclic scaffold with desymmetrisation of the diketone precursor would be accessed in just one step (Scheme 1.53).

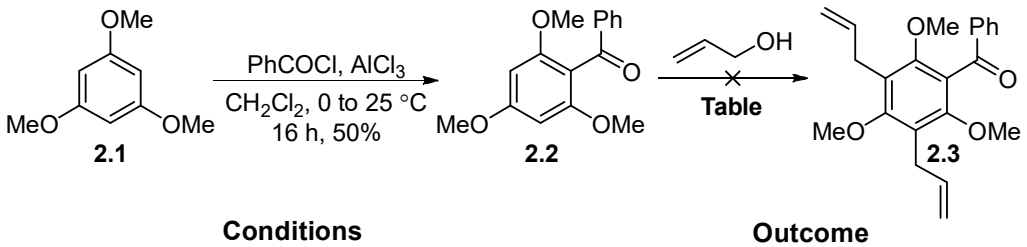


Scheme 1.53: Access to the bicyclo[3.3.1]nonane scaffold via desymmetrisation of dehydroresorcinol precursors.

CHAPTER 2: APPROACHES TOWARDS BICYCLO[3.3.1]NONANE VIA EPOXIDE CYCLISATION

2.1 Synthesis of the dearomatisation precursor 3,5-diallyl-2,4,6-trimethoxyphenyl methanone

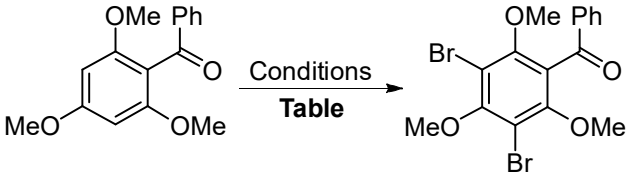
Allylated aromatic compounds constitute useful intermediates in organic synthesis and can be synthesised using palladium[80] or other transition metal catalysts.[78] Besides these methods a few Friedel Craft-type allylations have also been reported using Lewis acids although the yields of the desired allylated products are low due to side reactions or decomposition of the catalyst.[79] For instance, Fukuzawa[79] described a $Sc(OTf)_3$ Friedel-Crafts allylation where an allylic alcohol could be used directly as alkylating agent and the reaction could be run without specific dryness requirements. In this context, our investigation started with the synthesis of the unknown bis-allylated compound **2.3**. We started with the acylation of the commercially available 1,3,5-trimethoxybenzene **2.1** with benzoyl chloride which provided 2,4,6-trimethoxyphenylmethanone **2.2** in 50% yield. We then sought allylation of compound **2.2** under the conditions reported by Fukuzawa[79] and Tamaru[80] as well as using two more Lewis acids $SnCl_4$ and TfOH but unfortunately none of the conditions showed in Scheme 2.1 led to the desired product **2.3**.



Conditions	Outcome
$Pd(PPh_3)_4$, 5 mol%, Et_3B, THF, 25 °C, 16 h	No reaction
$Sc(OTf)_3$, PhMe, 100 °C, 24 h	Unidentified mixture
TfOH, 1,2–DCE, 80 °C, 16 h	Unidentified mixture
$SnCl_4$, 1,2-DCE, 80 °C, 16 h	Unidentified mixture

*Scheme 2.1: Conditions for the allylation of **2.2**.*

Given the inability to achieve Friedel-Crafts allylation, bromine groups were introduced for an alternative strategy involving a subsequent cross-coupling reaction. Reaction of **2.2** with Br_2 in CH_2Cl_2 gave **2.4** in only 12%; *N*-bromosuccinimide led to a slight improvement, giving the dibromo product in 21%. Eventually, an improved procedure was found; heating at 50 °C in glacial acetic acid afforded **2.4** in 62% (Scheme 2.2).

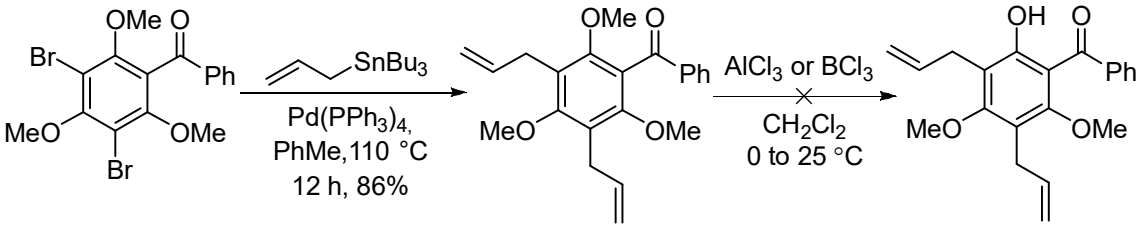


2.2 **2.4**

Conditions	(%)
Br_2, CH_2Cl_2, 25 °C	12%
NBS, CH_2Cl_2, 25 °C	21%
Br_2, glacial AcOH, 50 ?C	**62%**

*Scheme 2.2: Optimisation conditions for the bromination of **2.2.***

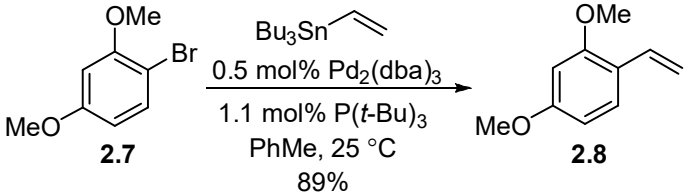
When Stille coupling conditions were applied to the trimethoxy derivative **2.4**, compound **2.5** was obtained in 86%. Unfortunately, the reaction was successful only when a stoichiometric amount of $Pd(PPh_3)_4$ was used, limiting the practicality of the reaction. Moreover, the organotin byproducts and impurities were found to be quite difficult to remove, despite purification on column chromatography using 10% w/w potassium carbonate-silica, as reported by Harrowven and co-workers.[81] Selective deprotection was attempted on coupling product **2.5**; it was hoped that the presence of the carbonyl substituent would determine the regioselectivity of the deprotection, with $AlCl_3$ chelating to the carbonyl group and directing the deprotection of the methoxy group next to it. Both $AlCl_3$ and BCl_3 are known to be efficient for the deprotection of methoxy groups[82] and were preferred over BBr_3 as they are safer to handle on large scale. What we observed instead of the mono-deprotected **2.6** was either the loss of the two allyl groups or degradation of the product if the temperature was raised above 0 °C (Scheme 2.3).



2.4 **2.5** **2.6**

Scheme 2.3: Stille coupling/selective demethylation sequence.

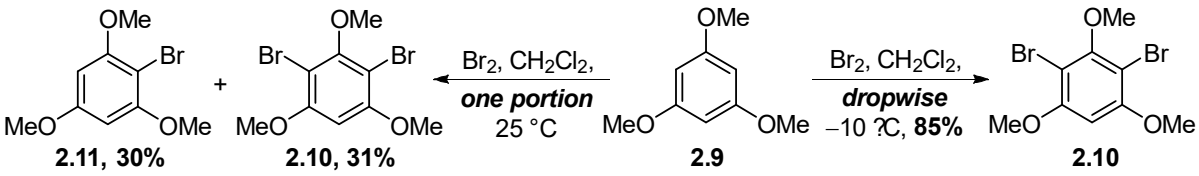
A search for alternative conditions for allylation revealed Fu's procedure[83] employing P(*t*-Bu)$_3$ as the first general method for room temperature cross-coupling of aryl bromides (Scheme 2.4).



2.7 **2.8**

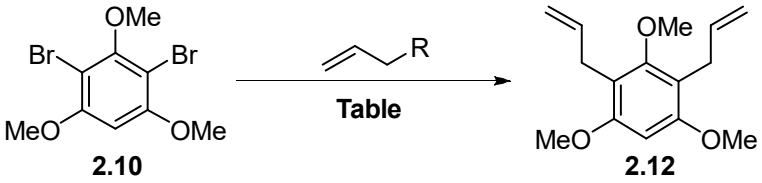
*Scheme 2.4: Fu's reported conditions for the cross coupling of aryl halides of type **2.7**.*[83]

The use of Grignard or organocopper reagents was also considered as reported by Hiyama.[84] We therefore started with direct bromination of 1,3,5-trimethoxybenzene **2.9**, which was closely related to Fu substrate **2.7** and was lacking any carbonyl group that could interfere with Grignard reagents. Controlling the temperature for this reaction was critical; at 25 °C only 31% of the desired **2.10** was isolated, along with 30% of the monobrominated product **2.11**. Instead, dropwise addition of Br_2 at –10 °C gave **2.10** in 85% yield (Scheme 2.5).



*Scheme 2.5: Bromination of 1,3,5-trimethoxybenzene **2.9**.*

As shown in Scheme 2.6, the dibrominated precursor **2.10** was completely unreactive towards Fu conditions (Table, entry 2) whereas some reactivity was observed when standard Stille conditions were used yielding however only the monoallylated product (Table, entry 1). After a few failed attempts, it was discovered that slow addition of **2.10** to a solution of dibutylcopperlithium at –48 °C and subsequent quenching with allyl bromide afforded the desired product **2.12**, but in 17% yield (entry 7). Given the low yield and the poor mass recovery, it was decided to not attempt the subsequent Friedel-Crafts acylation and put aside this strategy.

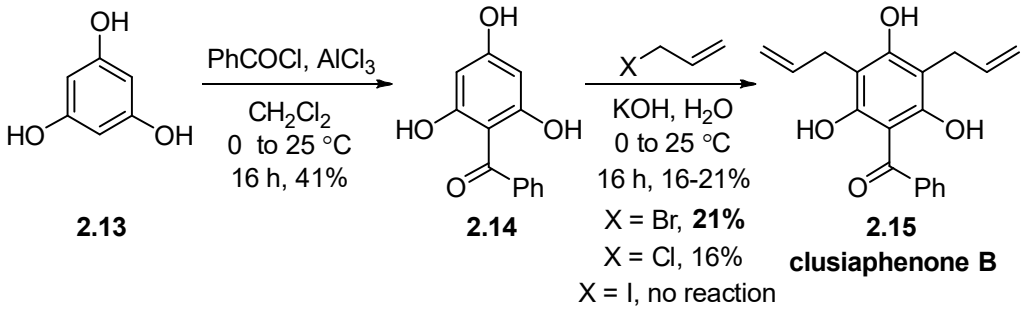


Entry	Conditions	Reagent	Outcome
1	$Pd(PPh_3)_4$, 0.5 mol%, PhMe, 110 °C, 12 h	$SnBu_3$	Mono-allyl product
2	0.5 mol% $Pd_2(dba)_3$, 1.1 mol% P(*t*-Bu)$_3$ PhMe, 25 °C	$SnBu_3$	No reaction
3	$Pd(OAc)_2$, P(*t*-Bu)$_3$, THF, 16 h	MgBr	Unidentified mixture
4	Mg, I_2, Et_2O, 45 °C, 1 h	Br	Unidentified mixture
5	Mg, LiCl, $Fe(acac)_3$, THF, 25 to 0 °C, 16 h	OAc	Unidentified mixture
6	Mg, LiCl, THF, 25 to 0 °C, 16 h	OAc	Unidentified mixture
7	*n*Bu_2CuLi, THF, –48 °C, 2 h	Br	**17%**

*Scheme 2.6: Conditions screening for the synthesis of **2.12**.*

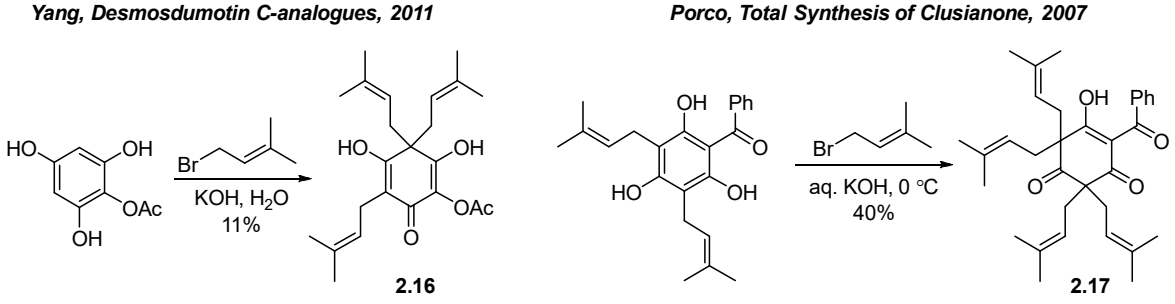
2.2 Revised Strategy: Synthesis of dearomatisation precursor Clusiaphenone B

The use of unprotected phloroglucinol itself was considered as an alternative starting point for the synthesis of the proposed allylated derivatives. Two literature procedures[58, 85] were adopted for the acylation/alkylation sequence showed on Scheme 2.7. The allylation was already reported to be low yielding[85] (22%) and indeed the best result was achieved using allyl bromide, which gave **2.15** in 21% yield. Despite the low yield, the mass recovery was considered sufficient (1.5 g starting from 5 g of **2.13**) for continuing the sequence (Scheme 2.7).



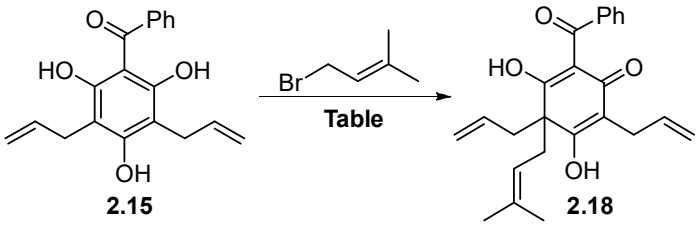
*Scheme 2.7: Synthesis of clusiaphenone B **2.15.***

Prenyl bromide was chosen as first electrophilic option for the dearomatisation of clusiaphenone B. To our surprise there were only two precedents involving dearomatisation of substrate **2.15** with prenyl bromide; the first one was reported by Yang and co-workers and involved the synthesis of various trialkylated intermediates *en route* to desmosdumotin C analogues; triprenylated adduct **2.16** was obtained in very low yield (11%) along with a mixture of diprenylated and tetraprenylated product.[86] The second one was used by Porco in his total synthesis of clusianone[30] who applied a previously reported procedure[87] for the synthesis of dearomatised intermediate **2.17** (Scheme 2.8).



*Scheme 2.8: Yang's access to triprenylated **2.16** and Porco's dearomatisation of phloroglucinol derivative.[30, 86]*

Inspired by these precedents, a few dearomatisation conditions were tested (Scheme 2.9)



2.15 **2.18**

Entry	Conditions	Temperature	Outcome
1	NaH, THF	0 °C	Rearomatisation
2	LiHMDS, THF	–20, 0 and 25 °C	No reaction
3	KOH, H_2O	0 °C	No reaction
4	NaOMe, MeOH	25 to 65 °C	Rearomatisation
5	KOH-aliquat336, PhCl	25 °C	Rearomatisation
6	K_2CO_3, DMF	25 °C	O-alkylation
7	Cs_2CO_3, DMF	0 to 25 °C	O-alkylation
8	Cs_2CO_3, THF	0 to 25 °C	**New, isolated spot**
9	KOH-TBAI, THF	25 °C	Degradation

*Scheme 2.9: Attempted dearomatisation of precursor **2.15.***

Whereas a few of these conditions gave exclusively *O*-alkylation (Table, entries 6 and 7) or no reaction at all (Table, entries 2 and 3), the pattern for entries 1, 4 and 5 was very similar; a new spot was formed on TLC and crude ^{1}H NMR always indicated the presence of the prenyl goup and a new quaternary carbon; however, after purification on silica gel only starting material **2.15** was recovered suggesting that the product had the tendency to rearomatise and/or undergo decomposition due to the acidity of the silica; the use of eluents containing 1% Et_3N did not resolve the issue. Surprisingly, when the reaction was run in the presence of cesium carbonate no decomposition or rearomatisation was observed; when the reaction was performed in DMF *O*-alkylation occurred whereas the use of THF led to the formation of a new spot on TLC, which was subsequently isolated. A comparison was then made between our crude ^{1}H NMR spectrum and the ^{1}H NMR spectrum of the isomer compound **13** isolated by George;[85] like in their case, a mixture of tautomers was expected and their carbonyl pattern was found quite similar to ours (Fig. 2.10 and 2.11).

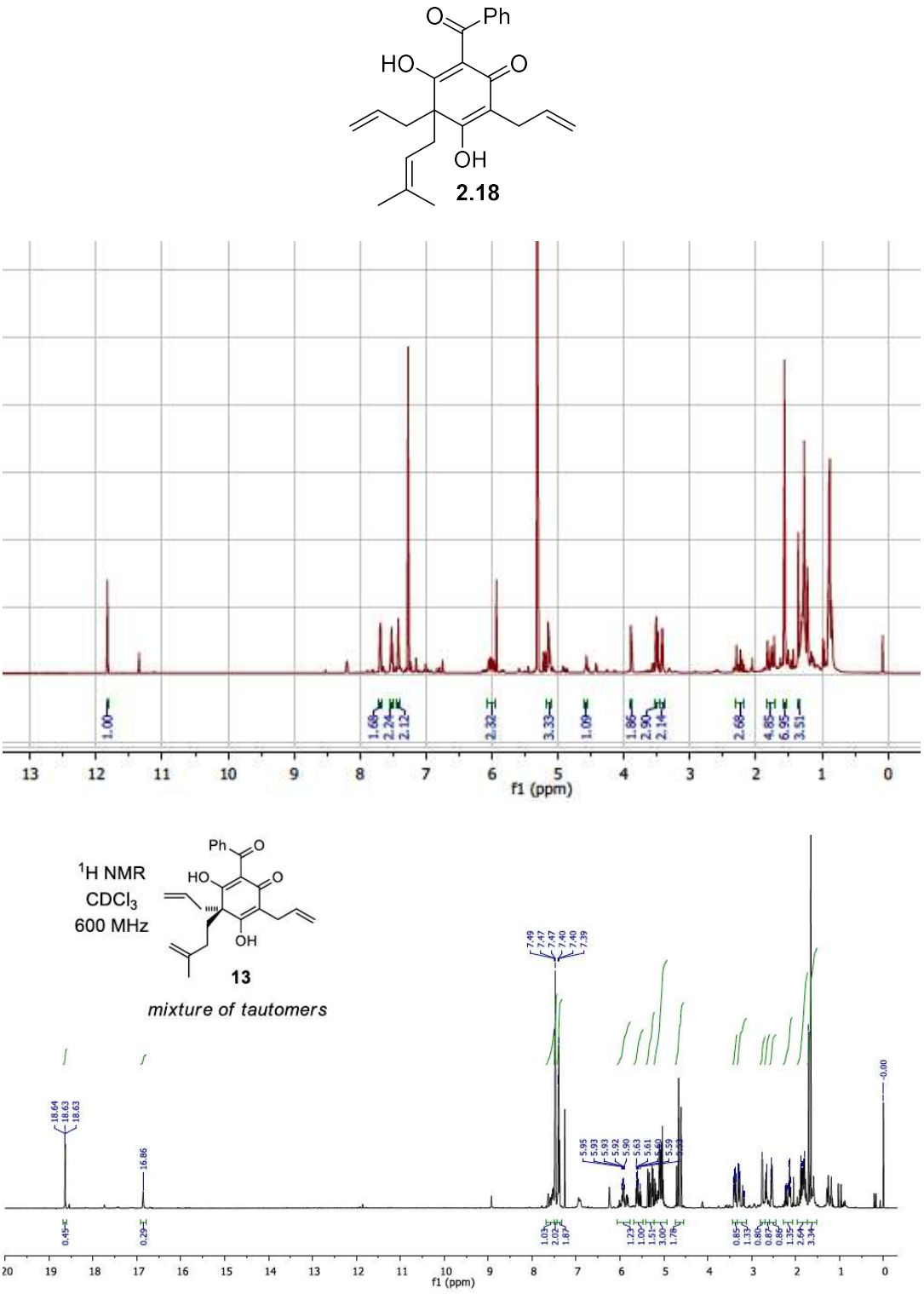


*Fig. 2.10: Comparison between the crude ^{1}H NMR spectrum of **2.18** (top) and and George's isolated compound **13** (bottom).*

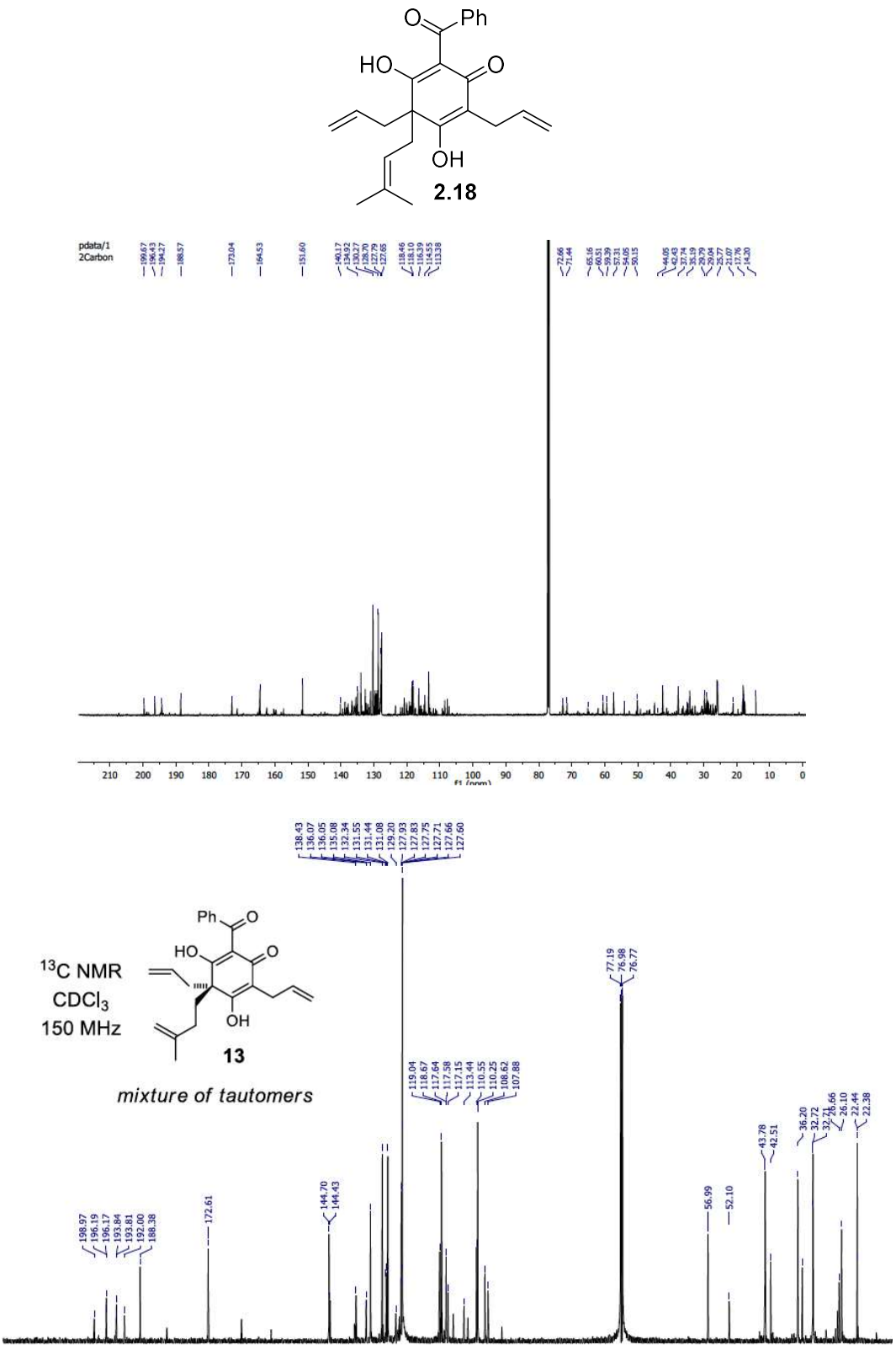
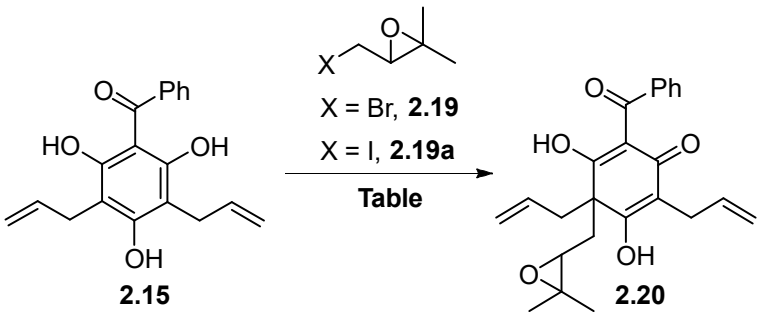


*Fig. 2.11: Comparison between crude ^{13}C NMR spectrum of **2.18** (top) and George's isolated compound **13** (bottom).*

Initial assessment of our NMR was based on a promising pattern in the carbonyl region; however, some key signals, more upfield methylenes for instance and very downfield ones (16-18 ppm) for the free OHs were missing, suggesting that the desired product was actually not present in the mixture.

In order to solve the stability issues caused by the presence of the allylic position in our substrate, which renders it more prone to rearomatisation, epoxide **2.19** was chosen as electrophile instead of prenyl bromide, giving the additional advantage of a direct insertion of the desired epoxide functionality in our scaffold, and in principle, a more convergent synthesis. Accordingly, several conditions were screened (Scheme 2.11).

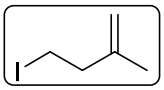


Entry	Conditions	X	Outcome
1	NaH, THF, 25 °C	Br	Unidentified mixture
2	LiHMDS, THF, 0 to 65 °C	Br	No reaction
3	Cs_2CO_3, NaI, THF, 0 to 65 °C	Br	O-alkylation
4	Cs_2CO_3, THF, 25 °C	Br	Unidentified mixture
5	NaOMe, MeOH, 25 °C	Br	No reaction
6	KOH-TBAI, THF, 25 °C	Br	Unidentified mixture
7	KOH-TBAI, PhCl, 25 °C	Br	Unidentified mixture
8	NaH, DMF, 25 °C	Br	Degradation
9	KOH 3M, aliquat-336, 25 °C	Br	O-alkylation
10	NaH, DMF, 0 °C	I	Degradation

*Scheme 2.11: Attempted dearomatisation with epoxide **2.19.***

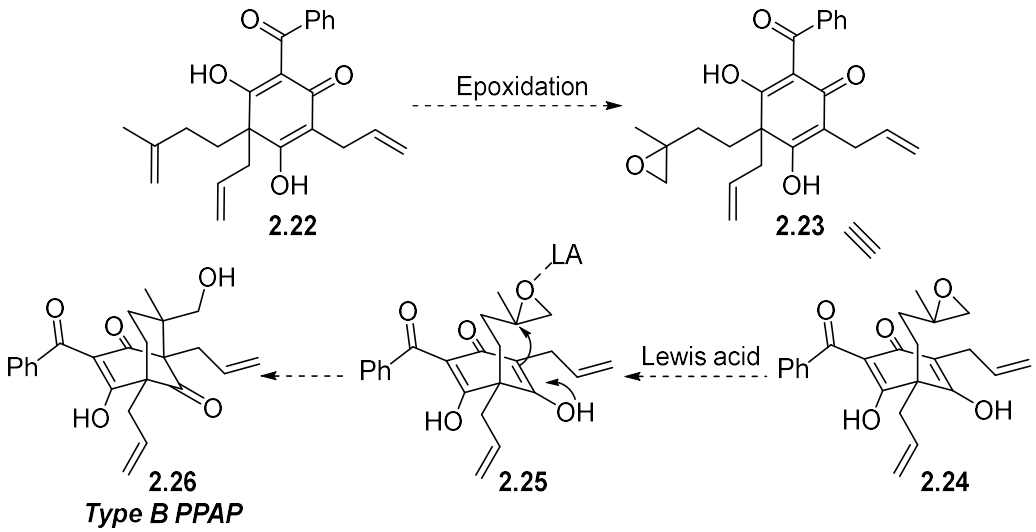
As shown in the last entry of the table, iodo derivative **2.19a** was also synthesised and used instead of the bromo one hoping for an enhanced reactivity; as seen previously with bromo epoxide **2.19**, a new spot was formed but rearomatisation occurred after column chromatography.

George described the use of homoallylic iodide **2.21** for alkylative dearomatisation, the advantage being that the product is less likely to undergo deallylation by S_N2' attack.[85]



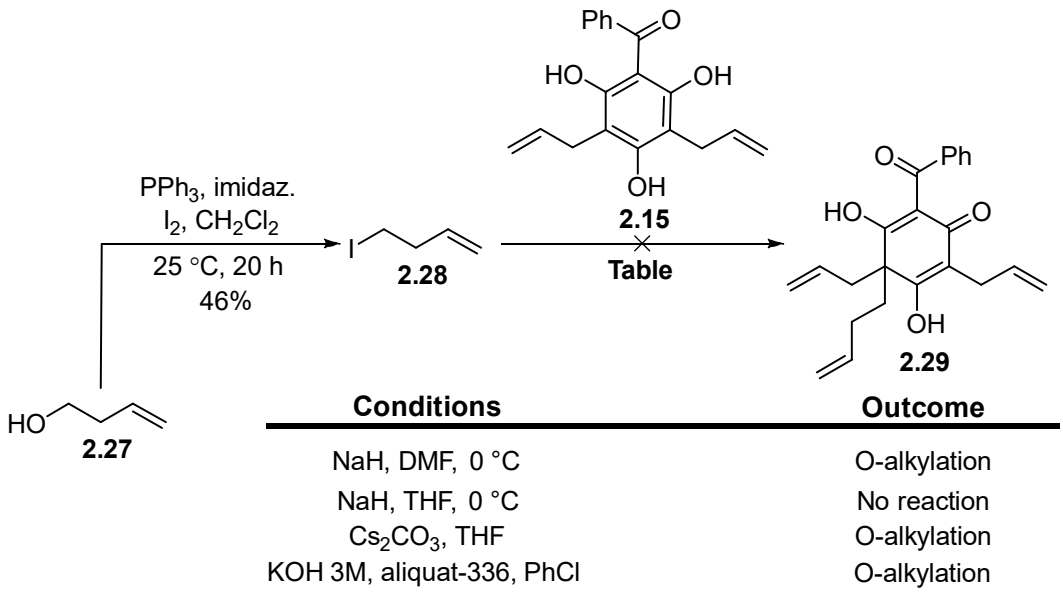
2.21

If the dearomatised precursor **2.22** could be accessed, it was envisioned that a regioselective epoxidation of the more substituted olefin and subsequent cyclisation of **2.24** would give access to the type B PPAP core **2.26** (Scheme 2.12).



Scheme 2.12: Proposed plan towards an epoxide-opening cyclisation strategy.

Iodide **2.28**, suspected to have a closer reactivity to **2.21**, was prepared *via* Appel reaction and subsequently used in an attempted dearomatisation reaction but unfortunately *O*-alkylation predominated (Scheme 2.13). A different approach to the synthesis of bicyclo[3.3.1]nonane core was then considered, and one also consistent with our efforts towards a biomimetic dearomatisation of prenylated phloroglucinols.



*Scheme 2.13: Attempted dearomatisation with iodo precursor **2.28.***

2.3 Desymmetrisation of 1,3-diketones derivatives

Over the past decade, advances in desymmetrisation strategies have delivered efficient syntheses, especially of natural products.[88] Two examples are the total synthesis of natural products lycoperine A[89] and maistemonine.[90] As shown in Fig. 2.14, the synthesis of lycoperine A commenced by reacting dione **2.30** with acrolein affording hemiacetal **2.31** which was desymmetrised with an aminoalcohol to yield vinylogous amide intermediate **2.32** (Fig.2.14, A). Similarly, a desymmetrisation strategy was used in one of the key steps of Tu's total synthesis of maistemonine; $TiCl_4$-catalysed desymmetrisation of diketone **2.33** *via* an intramolecular Schmidt reaction afforded the desymmetrised azepine intermediate **2.34** as a single diastereoisomer (Fig. 2.14, B).

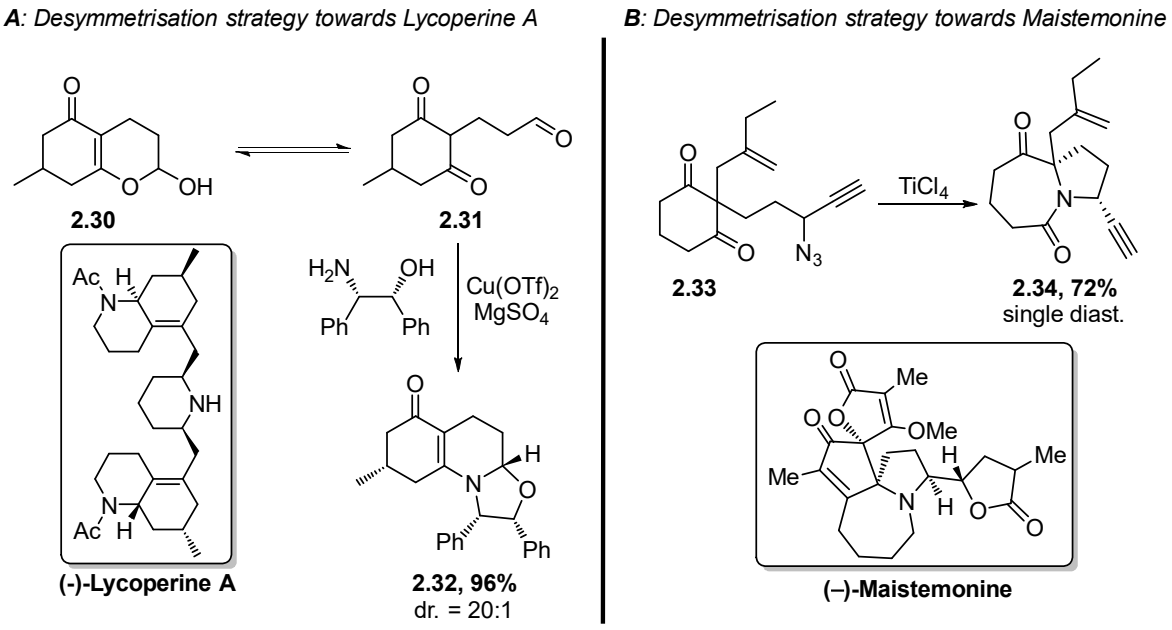
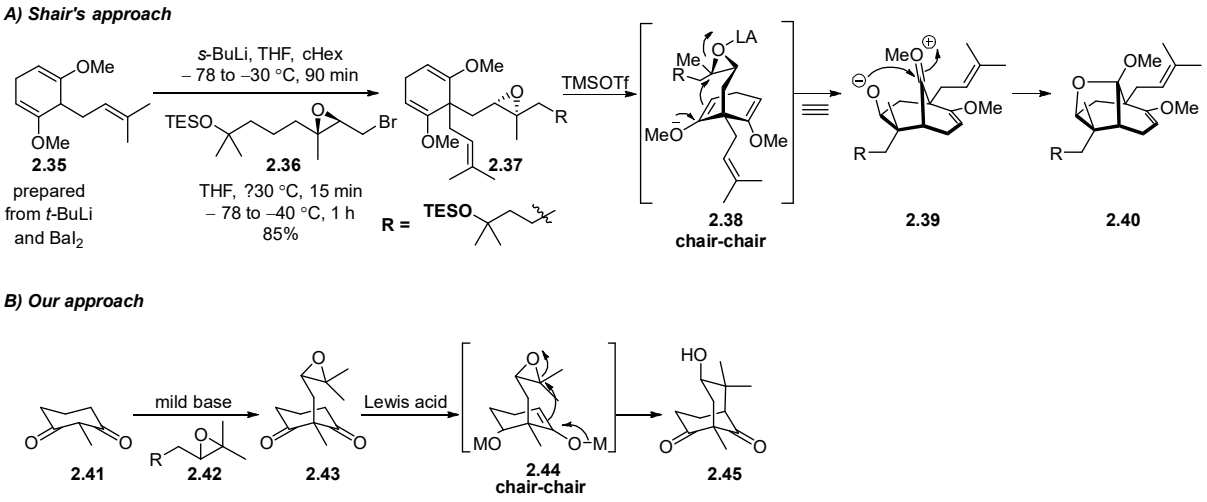


Fig 2.14: Desymmetrisation strategies in the context of natural product total synthesis.[89-90]

Another interesting example of desymmetrisation was demonstrated by Shair in his enantioselective total synthesis of (+)-hyperforin (Scheme 2.15, A).[66] As previously highlighted in chapter 1, the requirement for a chair-like transition state for **2.38** enables only one ketone to attack the epoxide at its carbon atom giving oxonium ion **2.39** which was trapped internally by the liberated oxygen atom, leading to bridged acetal **2.40**. Encouraged by Shair's approach, we sought to investigate new desymmetrisation strategies using more readily available diketones of type **2.41** (Scheme 2.15, B); a base like KHMDS, previously reported[91] to effectively convert a 2,2-disubstituted cyclohexane-1,3-dione into the ditriflate ester could be used instead of the hazardous *t*-BuLi to obtain epoxide intermediate **2.43**; if alkylation could be achieved there will be much to be gained since the same step in Shair's synthesis required BaI_2, prepared from beaten barium rod and iodine (see Chapter 1,

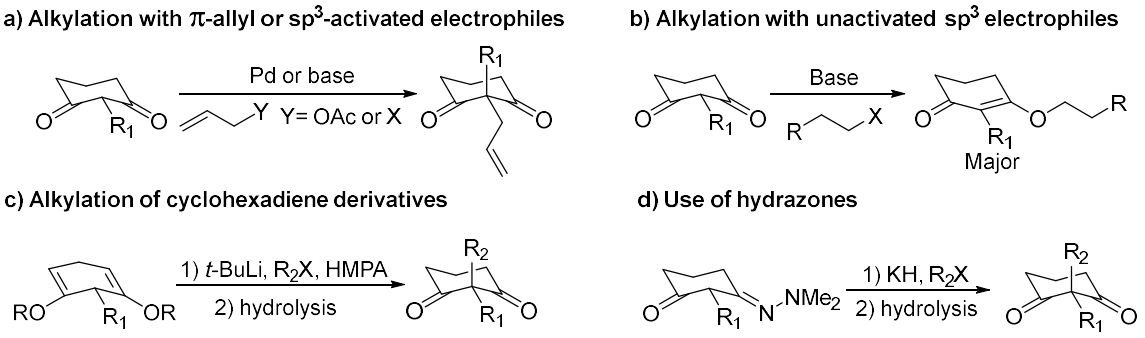
Scheme 1.42). Finally an oxophilic Lewis acid like Et_2AlCl should be sufficient to enolise the CO group as well as activating the epoxide toward cyclisation to give the [3.3.1]nonane bicyclic scaffold **2.45** (Scheme 2.15 B).



Scheme 2.15: A) Shair's desymmetrisation approach,[66] B) our proposed strategy.

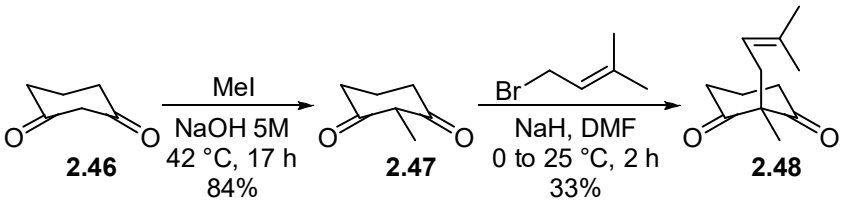
2.3.1 Preparation of 2,2-disubstituted cyclohexane-1,3-diones

The above epoxide cyclisation strategy required 2,2-disubstituted cyclohexane-1,3-diones, important building blocks in the synthesis of steroidal and terpene natural products.[92] Preparing this scaffold via alkylation has always been challenging; alkylation with activated sp^3 electrophiles or π-allyl electrophiles is the preferred method of synthesis [93] (Scheme 2.16, a), while the use of non activated sp^3 electrophiles is very limited due to the predominant formation of the *O*-alkylated product. (Scheme 2.16, line b). Methods that give selective *C*-alkylation with these types of electrophiles mostly refer to two main strategies: alkylation of cyclohexanediene derivative and subsequent hydrolysis, as reported by Piers[94] first and recently used by Shair[66] (Scheme 2.16, line c), which is limited by the hazardous nature and toxicity of *t*-BuLi and HMPA, and the use of cyclic ketohydrazones (Scheme 2.16, line d) as pioneered by Enders[95] and lately used by Johnson.[96]



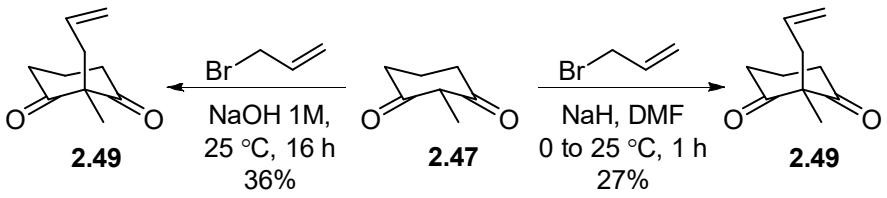
Scheme 2.16: C-alkylation strategies of 2,2-disubstituted cyclohexane-1,3-diones.[93a, 94-95]

Scheme 2.17 shows the first two steps of our initial strategy; alkylation of commercially available **2.46** with MeI following a literature method [97] gave 2-methyl-1,3-cyclohexanedione **2.47** in 84%. Its synthesis was preferred over the commercially available sample which invariably contained impurities and was prone to decomposition. Significantly, the melting point of the freshly prepared sample was 204–206 °C, very close to the literature reference of 206–208 °C, in contrast to 195–203 °C recorded for the commercial material. Subsequent alkylation with prenyl bromide gave the 2,2-dialkylated product **2.48** in 33% yield (Scheme 2.17). The moderate yield is explained by the concomitant formation of the mono and bis-*O*-alkylated products (not shown) and it drops drastically to 5% if the temperature is raised above 0 °C. The only report for this alkylation was from the *Zhurnal Obshchei Khimii* which could not be accessed; two other related procedures start from 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione (dimedone), not substituted at the 2-position, to give either the mono or the bis-prenylated derivative or a mixture of the two.[98]



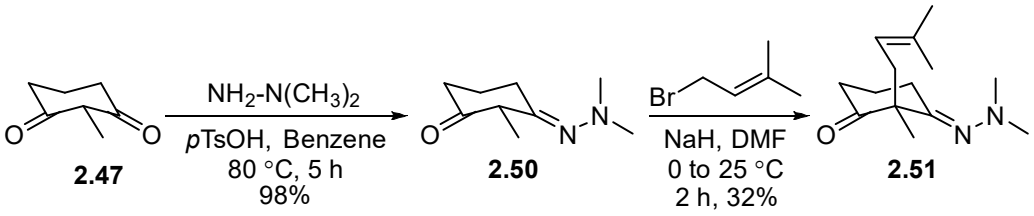
Scheme 2.17: Methylation and subsequent prenylation of 1,3-cyclohexanedione.

Allylation of 2-methyl-1,3-cyclohexanedione was instead known but the 85% yield reported[99] could not be reproduced, obtaining **2.49** in 36%. Switching to NaH in DMF even lowered the yield to 27% (Scheme 2.18).



*Scheme 2.18: Different basic conditions for the allylation of **2.47.***

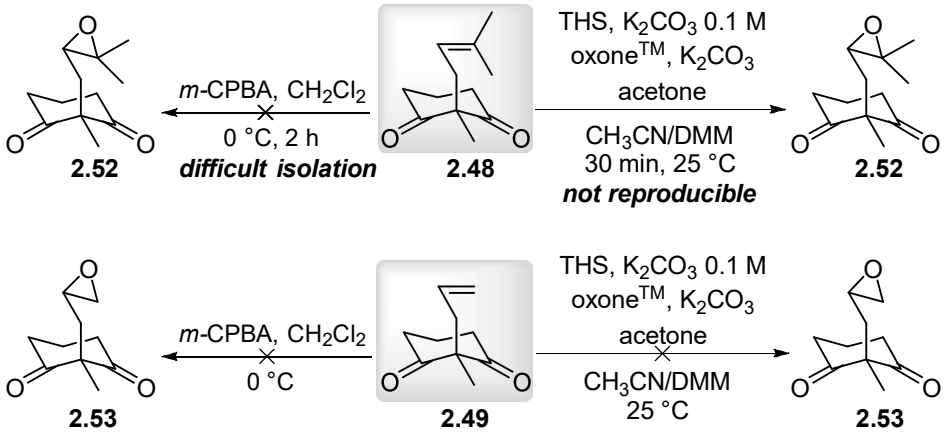
Since the first report by Enders,[95] C-2 substituted hydrazones are known to give the *C*-alkylated product regioselectively. Accordingly, monohydrazone **2.50** was synthesised and alkylation with prenyl bromide was then attempted but with no significant improvement in the yield (**2.51**, Scheme 2.19).



*Scheme 2.19: Synthesis of monohydrazone **2.50** and subsequent C-alkylation.*

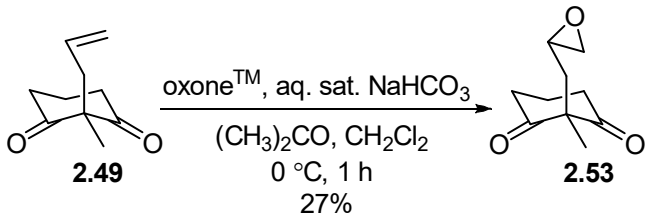
2.3.2 Epoxidation of 2-allylated and prenylated cyclohexanedione

At this point the issues surrounding *C*-alkylation were set aside and attention was turned to the epoxidation step of the alkenes previously prepared. Dimethyldioxirane (DMDO) and *m*-CPBA were the reagents selected to attempt this transformation. Shi's conditions[100] are known to work for terminal, *cis*, *trans* and tri-substituted alkene; however, this method has never been applied to 2-substituted cyclohexane-1,3-dione. A first attempt on substrate **2.48** (Scheme 2.20) afforded a crude product whose mass and ^{13}C NMR spectrum were as expected; however, subsequent attempts to repeat and/or scale up this reaction were unsuccessful, despite the accurate control of pH and the use of freshly prepared K_2CO_3 and Oxone™ solutions. The use *of m*-CPBA showed one new spot by TLC after 30 minutes but separation from benzoic acid and isolation of the pure product proved difficult. The same two conditions were repeated and tried on alkene **2.49**, unfortunately without success.



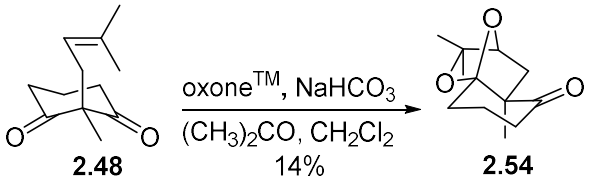
*Scheme 2.20: Attempted epoxidation of alkenes **2.48** and **2.49.***

A different way of forming DMDO in situ under biphasic conditions, as used by Dondoni[101] was then selected for a second epoxidation attempt using alkene **2.49** (Scheme 2.21).



*Scheme 2.21: Dondoni's biphasic conditions applied to alkene **2.49.***

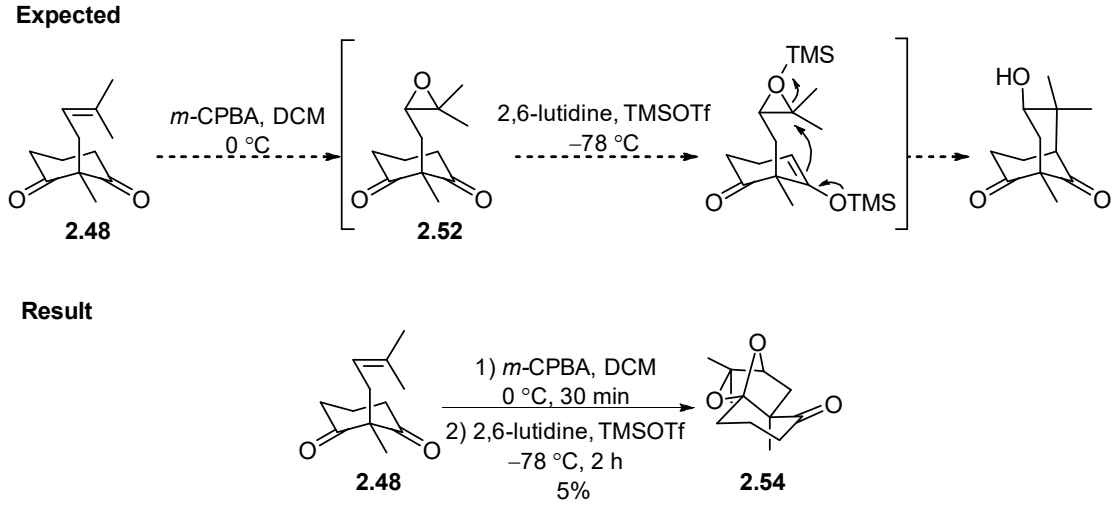
Despite four equivalents of Oxone^{TM} added, the yield obtained was modest although 30% of starting material could be recovered. The same biphasic conditions were then repeated on alkene **2.48** (Scheme 2.22); after column chromatography of the crude mixture, a new product was isolated in 14% as a crystalline solid but unexpectedly, the structure assigned was the complex acetal **2.54**.



*Scheme 2.22: Unexpected formation of complex acetal **2.54.***

When it became clear that isolation of the desired epoxide was not trivial, a tandem epoxidation cyclisation was attempted on alkene **2.48**. The starting material was completely consumed after 20 minutes stirring at 20 °C, with TLC showing a spot with the same R_f of

the epoxide previously isolated **(2.52**); at this point the reaction mixture was cooled to –78 °C and 2,6-lutidine and TMSOTf were added. Scheme 2.23 shows the expected and actual transformations.



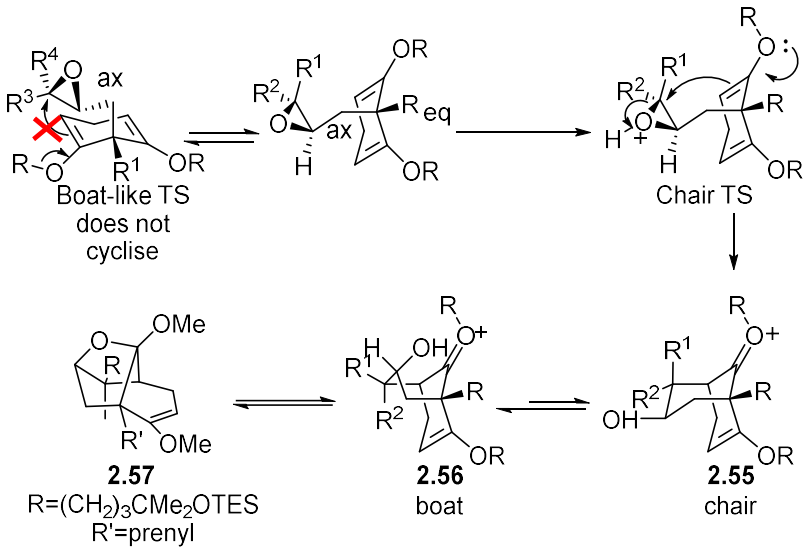
*Scheme 2.23: Expected mechanism for the tandem epoxidation-cyclisation and formation of acetal **2.54**.*

The TLC of the reaction showed three main spots which were separated; interestingly, the same complex acetal structure **2.54** previously obtained under biphasic epoxidation conditions was isolated in 5% yield.

There are three requirements for such tandem cyclisations:

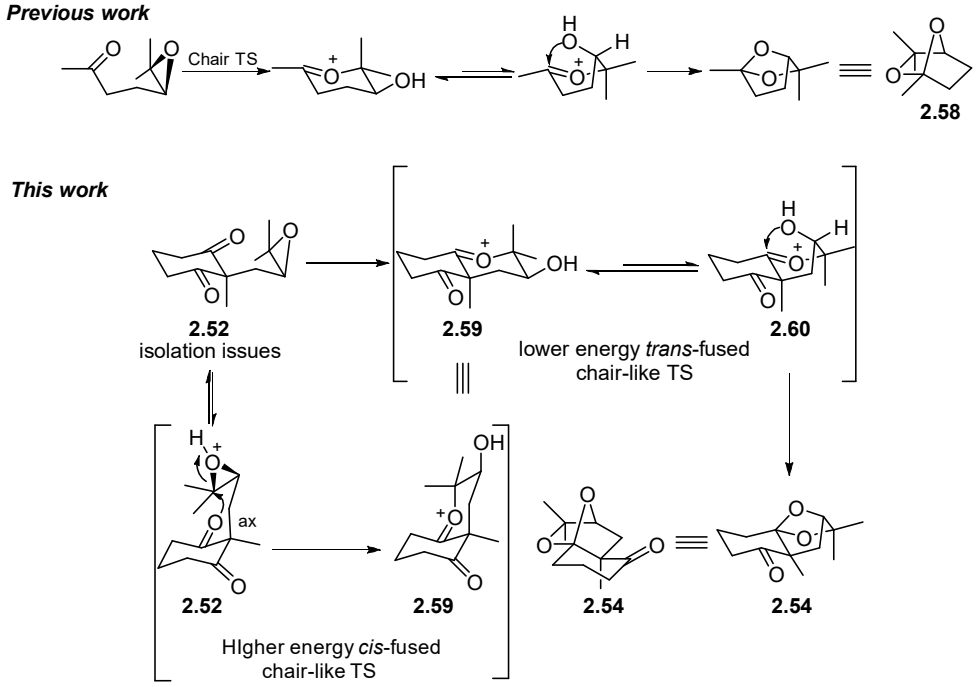
- Generation of an enolic species so that the reaction occurs on the carbon instead of the oxygen.
- Activation of the epoxide by a Lewis acid or Brönsted acid
- Reaction of epoxide and enolic species via a low-energy chair transition state.

In scheme 2.24 a new perspective is used to highlight in more detail Shair's work (see Scheme 1.42 and 2.15 for a reminder) and his use of a preformed methyl vinyl ether and a Lewis acid to activate the epoxide and enable cyclisation to the bicyclo[3.3.1]nonane core. A chair transition state enables **2.55** to align and form **2.56** which cyclises via a boat conformation to give **2.57** (Scheme 2.24).



Scheme 2.24: Analysis of Shair's epoxide mediated cyclisation.

In our case one can rationalise the formation of acetal **2.54** starting from the oxonium ion **2.59** (Scheme 2.25), the boat conformer of which (**2.60**) undergoes intramolecular attack via a low-energy *trans*-fused chair-like transition state, showing an axial interaction between the methylene and the epoxide. This mechanism has been reported before for the formation of 2,7-dioxabicyclo[2.2.1]heptane leading to type **2.58** bicyclo.[102] The acidity of the reaction mixture, due to either *m*-CPBA, the 3-chlorobenzoic acid produced after the epoxidation reaction or the silica gel, would then catalyse the ring closure that leads to **2.54**. Notably, even the disfavoured high-energy chair-like TS of a *cis*-fused decalin-type (**2.52** and **2.59** shown in brackets) will lead to the same oxonium ion **2.59**, revealing thus only one possible cyclisation product (Scheme 2.25).



*Scheme 2.25: Cyclisation analysis leading to the formation of complex acetal **2.54.***

The analysis of acetal **2.54**'s ^{13}C NMR spectrum showed the absence of a second carbonyl group, evidence that *O*-alkylation has occurred. Cyclisation when X=H would be reversible thus formation of acetal **2.62** (Fig. 2.26) could also be excluded, in contrast to Shair's intermediate **2.57**[66] which is formed after quenching the *O*-methylated oxonium ion. A thorough comparison of ^{13}C NMR chemical shift values was carried out between acetal **2.54,** compound **2.61**[103] and **2.58**[102] (whose signals have been assigned by analogy with **2.58**). The data were found to be in fair agreement with those reported in the literature, with the exception of the peak at 70.9 ppm which was assigned to the bridgehead carbon atom bonded to one oxygen atom (Fig 2.26).

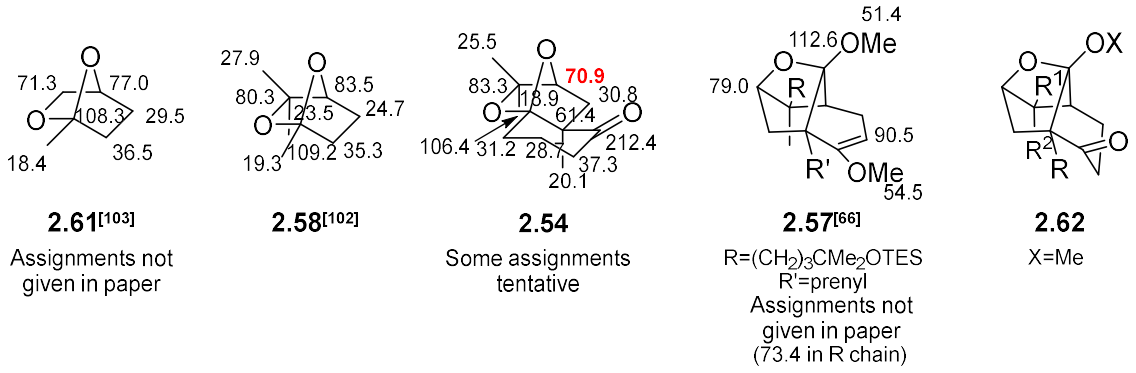
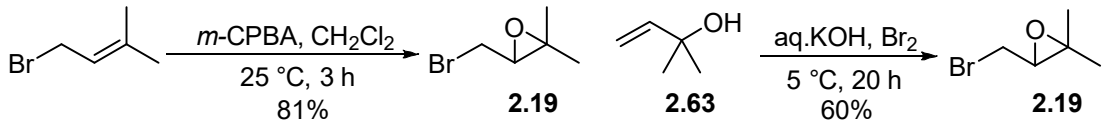


*Fig. 2.26: Comparison between ^{13}C NMR values for **2.54** with previously reported bicyclic acetal **2.58** and **2.61**.*

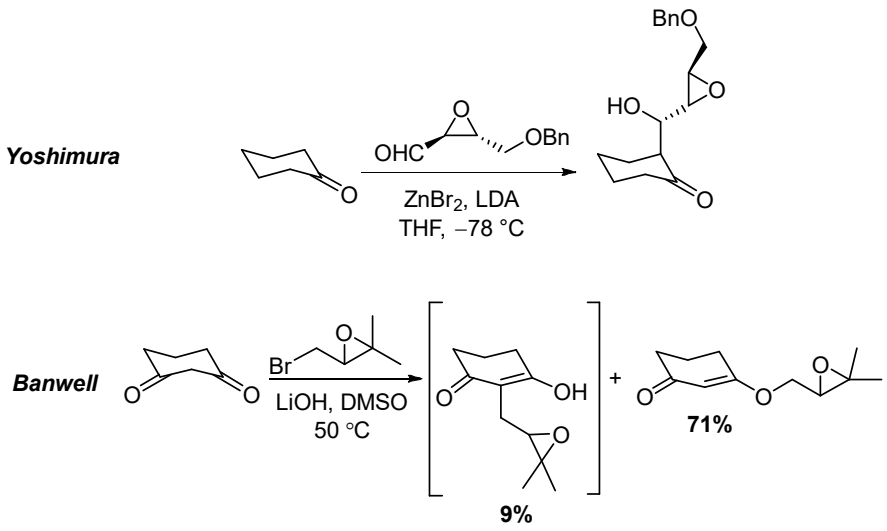
2.3.3 Direct C-alkylation with 1-bromoethyl-3,3-dimethyloxirane

As an alternative to alkene epoxidation, the direct installation of the epoxide functionality onto the cyclohexanedione ring by direct *C*-alkylation with epoxy bromide of type **2.19** was considered. Its synthesis was achieved in high yield from both prenyl bromide and commercially available 2-methyl-3-buten-2-ol **2.63** (Scheme 2.27).



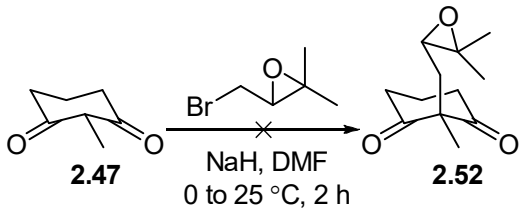
*Scheme 2.27: Synthesis of bromo epoxide **2.19.***

2-Epoxy-substituted cyclohexane-1,3-diones are not known in the literature, with the only two related examples prepared by an aldol reaction of cyclohexanone with an epoxy aldehyde as shown by Yoshimura,[104] and an attempted *C*-alkylation with epoxy bromide *en route* to the natural product angelmarin as carried out by Banwell (Scheme 2.28).[105]



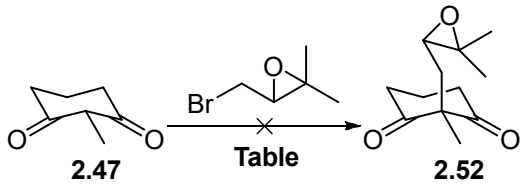
Scheme 2.28: Previous reports on the synthesis of 2-epoxy-substituted cyclohexane-1,3-ones.[104-105]

Alkylation of 2-methyl-1,3-cyclohexanedione with 1-bromoethyl-3,3-dimethyloxirane was first attempted using NaH in DMF (Scheme 2.29); TLC analysis of the crude showed two products, with NMR analysis revealing that *O*-alkylation had occurred predominantly. The *O*-alkylated product was isolated after column chromatography in 10% yield along with a 16% of a not identified second product. Although ^{13}C NMR for this second product was consistent with the structure expected for the desired C-alkylated derivative, ^{1}H NMR revealed a multiplet at 4.23 ppm which could not be assigned.



*Scheme 2.29: Attempted C-alkylation of **2.47** with bromo-epoxide.*

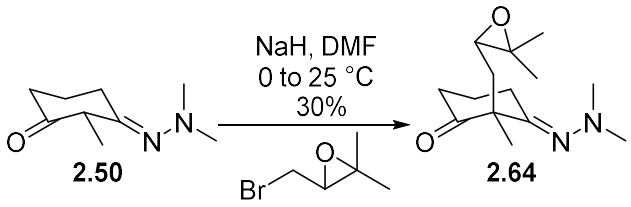
A brief screening of conditions (Scheme 2.30) did not lead to any improvement.



Conditions	Outcome
K_2CO_3, acetone, 25 °C	No reaction
NaH, $PhCH_3$, 118 °C	No reaction
t-BuOk, *t*-BuOH, 25 °C	No reaction
NaH, DMF, 155 °C	O-alkylation

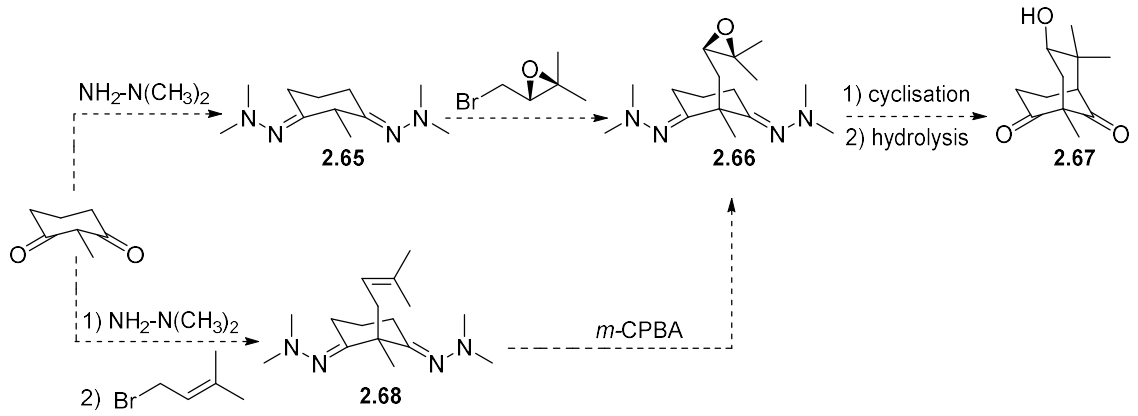
*Fig. 2.30: Attempted C-alkylation of 2-methyl-1,3-cyclohexanedione **2.47**.*

However, the monohydrazone previously synthesised (**2.50**, see scheme 2.19) could be alkylated with the bromo epoxide giving the corresponding 2,2-dialkylated hydrazone **2.64** in moderate yield (Scheme 2.31).



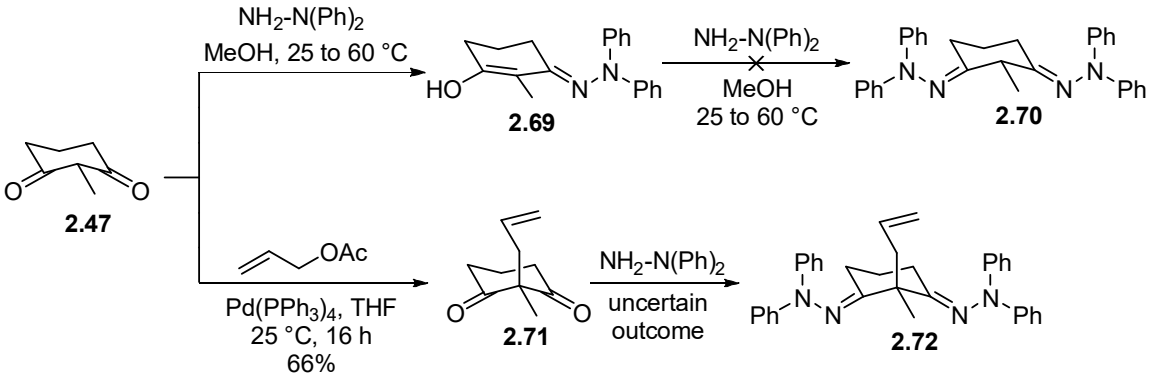
*Scheme 2.31: Successful C-alkylation of hydrazone **2.50.***

Given the encouraging result on this direct alkylation with bromo epoxide, formation of bishydrazones of type **2.65** and **2.68** could give access to the functionalized bicyclo[3.3.1]nonanone **2.67** via cyclisation of epoxide **2.66** and subsequent hydrolysis (Scheme 2.32).



*Scheme 2.32: Planned strategy for the formation of bishydrazones **2.68** and/or **2.70** and subsequent epoxide-mediated cyclisation.*

Unfortunately, *N,N*-dimethylhydrazine could not be purchased in Singapore so we decided to use *N,N*-diphenylhydrazine to access the key hydrazone intermediates. As highlighted on scheme 2.33, monohydrazone enol form **2.69** could be obtained but could not be converted to the bis-derivative **2.70** by either addition of more equivalents or increase of temperature. Similarly, blocking the 2-position with an allyl group and treating the Tsuji-Trost product **2.71** with *N,N*-diphenylhydrazine did not lead to the desired product **2.72** (Scheme 2.33). Indeed, ^{1}H NMR indicated only 10 aromatic protons and mass spectroscopy couldn't confirm the structure, despite the fact that ^{1}H and ^{13}C NMRs were as expected, showing clearly a symmetrical product and no carbonyl signal present. A possible explanation could be that the phenyl groups are too bulky for the reaction to take place.

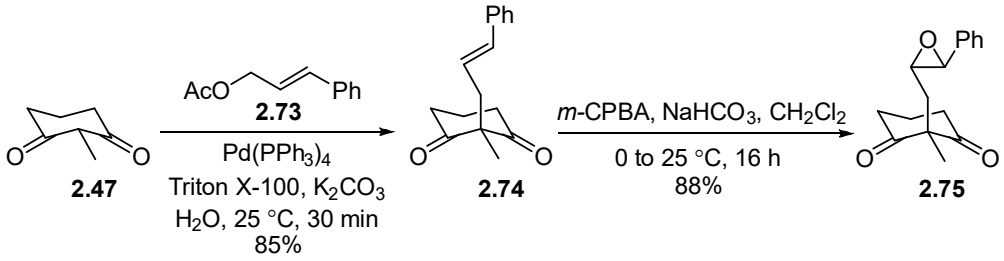


*Scheme 2.33: Attempted formation of bishydrazone **2.70** and **2.72**.*

2.3.4 6-endo-tet cyclisation strategy

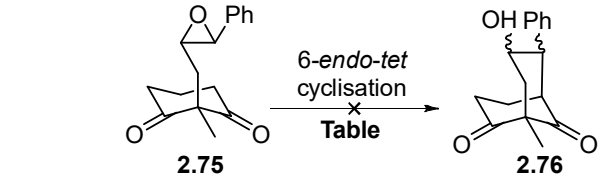
Given the simplicity and the high yield of the Tsuji-Trost reaction employed for the synthesis of compound **2.71**, we thought that this reaction could represent a valid alternative to the difficult *C*-alkylation, *en route* to a subsequent epoxidation. Cinnamyl acetate **2.73** was

tested as the first allylic electrophile, giving **2.74** in 85% yield. Triton X-100 was chosen as surfactant over CTAB, which was tried first but gave alkene **2.74** in only 47% yield. Subsequent epoxidation with *m*-CPBA proceeded smoothly affording epoxide **2.75** in 88% yield as a crude product, which needed no further purification (Scheme 2.34).



Scheme 2.34: Tsuji-Trost epoxidation sequence.

With the key precursor in hand, five different conditions were tested for the desired epoxide-mediated cyclisation (Scheme 2.35).



Conditions	Outcome
LDA, THF, −78 °C	Unidentified mixture
t-BuOK, 25 °C	Unidentified mixture
Et_3N, TMSCl, DMF, 0 to 135 °C	Unidentified mixture
LDA, TMSCl, THF, −78 °C	Unidentified mixture
2,6-lutidine, TMSOTf, DCM, −78 °C	Unidentified mixture

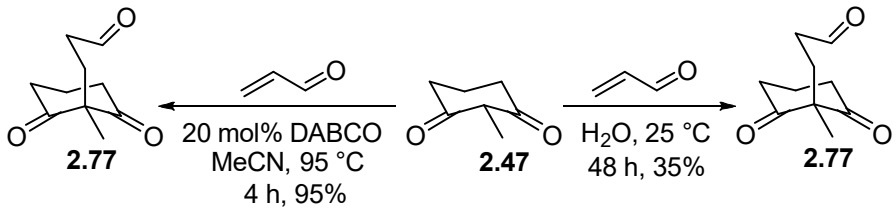
Scheme 2.35: 6-endo-tet cyclisation attempts.

Unfortunately, none of these conditions led to the formation of the desired bicyclo[3.3.1]nonane. A reasonable explanation could be that this type of ring closure is classified as a 6-*endo-tet* which is disfavoured according to Baldwin's rules.

2.3.5 6-exo-tet cyclisation strategy

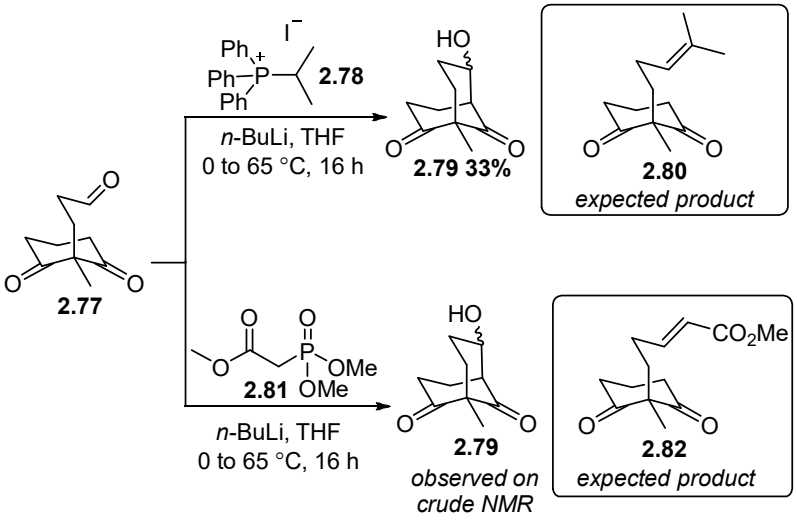
According to Baldwin's rules the 6-*endo-tet* cyclization that was tried first (Scheme 2.35) was disfavoured. Seeking a potentially more favourable 6-*exo-tet* cyclisation, addition of one more carbon atom to the side chain of our cyclohexanedione was pursued and the synthesis of aldehyde **2.77** was therefore considered. The latter was known and easily accessible via Michael additions from 2-methyl-1,3-cyclohexanedione **2.47**, with reported syntheses mostly carried out in water at room temperature.[106] Accordingly, after 48 h stirring at 25 °C pure

2.77 was isolated but in only 35% yield. A major improvement of the yield (up to 95%) resulted when the reaction was carried out in CH_3CN at reflux with the addition of 20 % mol of DABCO (Scheme 2.36).



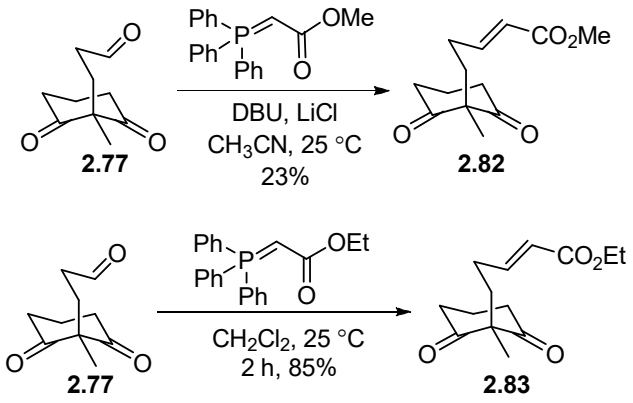
Scheme 2.36: Synthesis of 3-(1-methyl-2,6-dioxocyclohexyl)propanal ***2.77.***

A Wittig reaction between aldehyde **2.77** and phosphonium salt of type **2.78** or phosphonate of type **2.81** was then attempted. Instead of the expected alkene **2.80**, aldol product **2.79** was formed exclusively and isolated in 33% after purification when **2.78** was used. Exclusive formation of the same aldol derivative was also observed in the crude ^1H NMR when switching to phosphonate **2.81** (scheme 2.37).



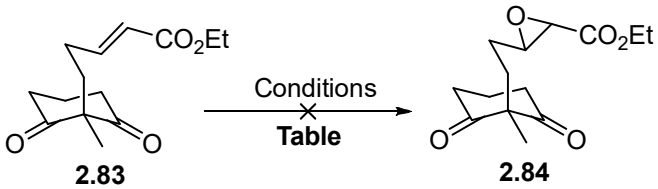
Scheme 2.37: Horner-Wadsworth-Emmons reaction on aldehyde ***2.77****.*

A milder base like DBU did lead to the desired unsaturated ester **2.82** although in low yield whereas complete elimination of the base source finally yielded compound **2.83** in 85%, as the only product of the reaction (Scheme 2.38).



Scheme 2.38: Synthesis and optimization of α,β-unsaturated ester derivatives.

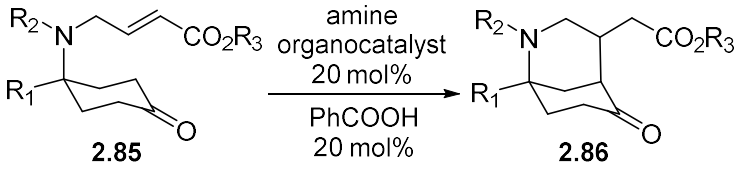
At this point, a few conditions were tested for the epoxidation of the unsaturated ester (Scheme 2.39). In all cases shown in the embedded table there was a clear formation of just one polar spot but isolation was particularly difficult. During work-up it was noticed that the TLC spot disappeared under acidic or neutral pH whereas if the solution was kept basic, decomposition probably due to fragmentation caused by H_2O_2, was observed in the form of colour change after concentration or after dissolving the crude product in deuterated solvents.



Conditions	Outcome
m-CPBA, 1,2-DCE, 25 °C	Decomposition
H_2O_2 30%, NaOH 3M, 0 °C	Decomposition
TBHP, Triton B, THF	Decomposition

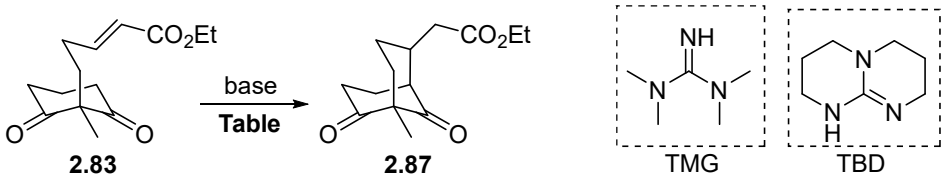
*Fig. 2.39: Attempted epoxidation of the α,β-unsaturated ester **2.83.***

Given the difficulties encountered we momentarily put aside epoxidation and thought about an alternative way to build the desired bicyclo[3.3.1]nonane scaffold. Considering the ease in which this unsaturated ester could be accessed, an intramolecular base-catalysed Michael reaction looked appealing and most importantly a catalytic asymmetric version had not yet been reported. We were particularly inspired by Dixon's report on the catalytic asymmetric desymmetrisation of prochiral cyclohexanones **2.85** leading to 2-azabicyclo[3.3.1]nonane **2.86** (Scheme 2.40).[107]



Scheme 2.40: Synthesis of 2-azabicyclo[3.3.1]nonane through catalytic asymmetric desymmetrisation of prochiral cyclohexanones.[107]

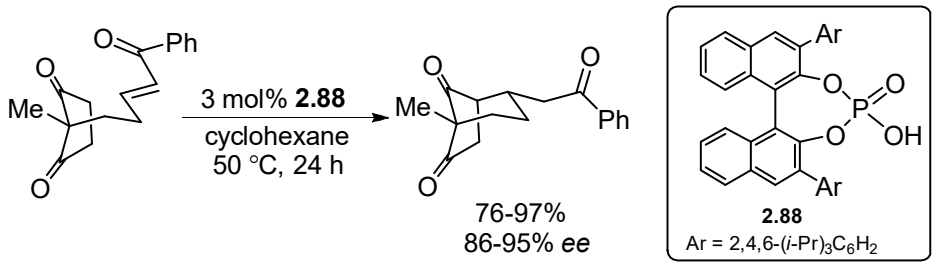
We first ran preliminary studies with the guanidine base 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (Scheme 2.41, highlighted in turquoise); in the case of a 20 mol% loading a new spot was formed within an hour on TLC; it was then decided to stop the reaction even though it had not reached completion, to identify the spot which was in fact the desired bicyclic product **2.87**. With the amount of base increased to 0.5 eq TLC showed complete consumption of starting material but crude ^{1}H NMR revealed 11% of **2.83** still present. Following these promising results, screening of a few primary and secondary amine organocatalysts was pursued (highlighted in pink); unfortunately, with all the three bases chosen, no conversion was observed, even after 5 days or the aid of additives like benzoic acid.



Base	Additive	Time	Solvent	Outcome
TBD (20 % mol)		1 h	THF	Identification
TBD (0.5 equiv.)		1 h	THF	89% NMR yield, single diast.
(S)-(-)-methylbenzylamine		5 days	CH_2Cl_2	No reaction
(S)-(-)-methylbenzylamine	PhCOOH	5 days	CH_2Cl_2	No reaction
(+/-)-trans-1,2-diaminocyclohexane		5 days	CH_2Cl_2	No reaction
(+/-)-trans-1,2-diaminocyclohexane	PhCOOH	5 days	CH_2Cl_2	No reaction
L-proline		3 days	CH_2Cl_2	No reaction
L-proline	PhCOOH	3 days	CH_2Cl_2	No reaction

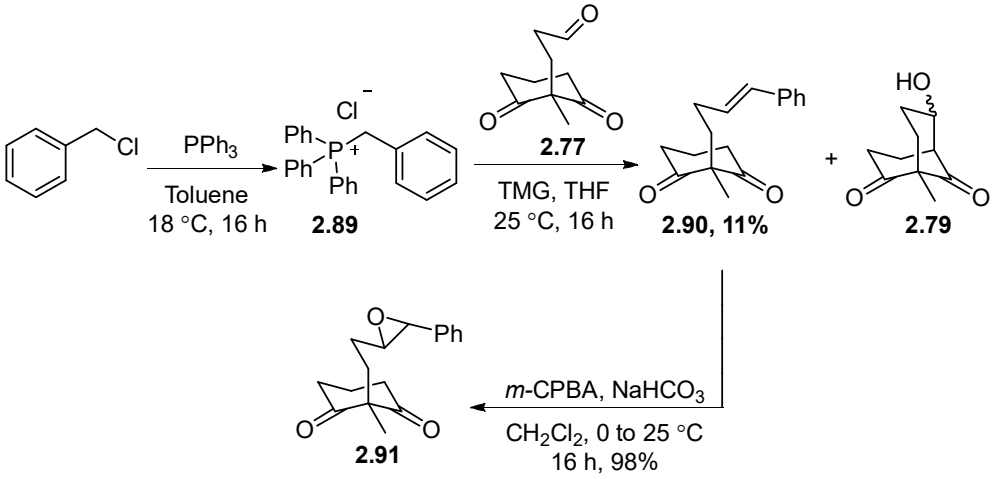
Scheme 2.41: Intramolecular Michael reaction to forge the bicyclo[3.3.1]nonane core.

Given that our first results with chiral bases were not promising and that the novelty aspect was lessened because of the publication[108] of the phosphoric acid-catalysed desymmetrising Michael cyclisation of 2,2-disubstituted-1,3-diketones (Scheme 2.42), such asymmetric desymmetrisations were not pursued further.



Scheme 2.42: Lam's desymmetrising strategy of 2,2-substituted-1,3-diketones.[108]

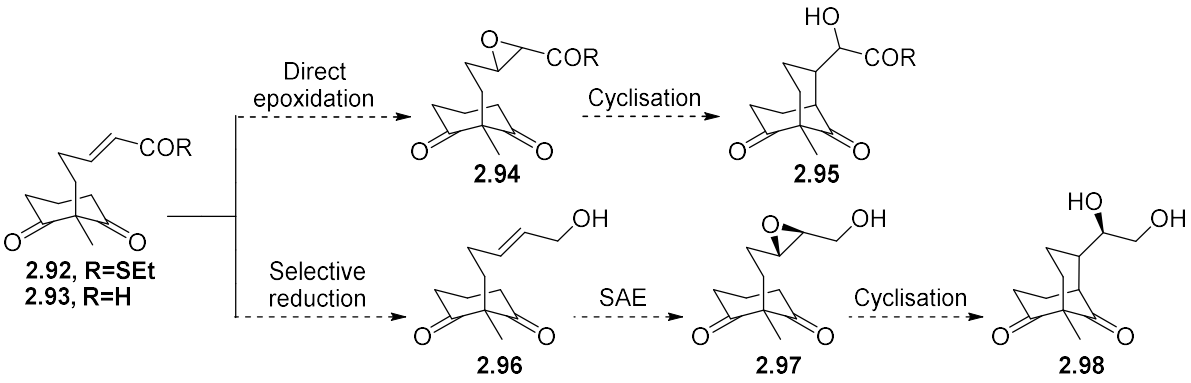
The original epoxidation strategy was revisited, this time using a pre-formed phosphonium precursor of type **2.89** for the Wittig reaction (Scheme 2.43). As previously reported, [109] guanidine bases like TBD and TMG could promote Wittig and HWE reactions on enolisable aldehydes. Despite the promising precedents, aldol product **2.79** was obtained predominantly along with 11% of the desired alkene **2.90**. Epoxidation of the latter afforded the desired epoxide **2.91** in 98% yield (Scheme 2.43). The low yield of the alkene precursor was considered not practical enough to continue the investigation of our 6-*exo-tet* cyclisation strategy; we thus turned our attention to the epoxidation of other α,β-unsaturated compounds.



*Scheme 2.43: TMG-promoted Wittig reaction and subsequent epoxidation of alkene **2.90.***

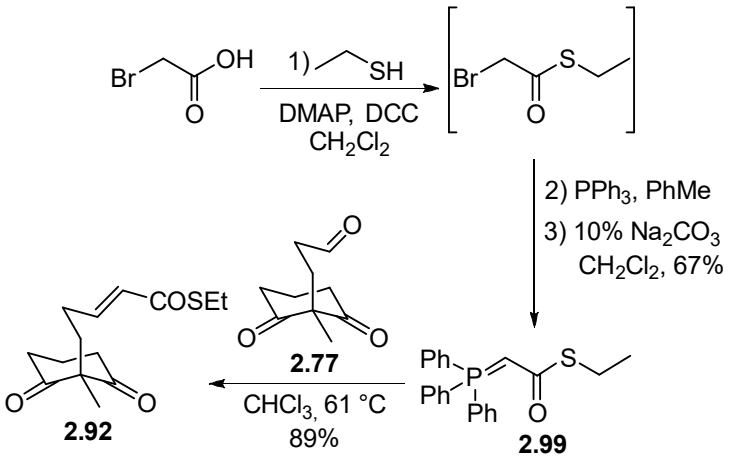
2.3.6 Synthesis and epoxidation of more α,β-unsaturated compounds

After the difficulties encountered in the synthesis of **2.90**, other α,β-unsaturated compounds were evaluated with unsaturated thioester **2.92** (R=SEt) and aldehyde **2.93** (R=H) (Scheme 2.44). These intermediates were proposed as versatile starting materials for either direct epoxidation or selective reduction to allylic alcohol **2.96**, which in turn would allow Sharpless asymmetric epoxidation.



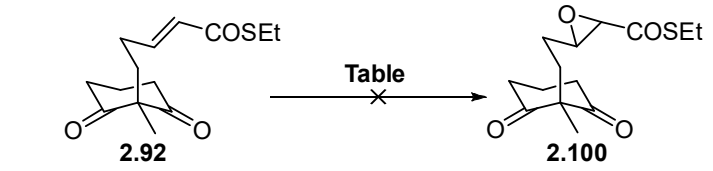
Scheme 2.44: Proposed strategy to access the bicyclic core through reduction or epoxidation of unsaturated carbonyl compounds.

For the preparation of thioester **2.92**,we started the synthesis of phosphorane precursor **2.99** which was carried out in two steps from commercially available 2-bromoacetic acid, yielding **2.99** in 67% yield. Wittig reaction with aldehyde **2.77** afforded the desired α,β-unsaturated thioester in 89% yield (2.99, scheme 2.45).



*Scheme 2.45: Synthesis of thioester **2.92.***

Attempted epoxidation of the α,β-unsaturated thioester with three different set of conditions was troublesome in much the same way as before with ester **2.83** and the pattern revealed to be the same; formation of a new polar spot which decomposes upon work-up, drying *in vacuo* or solubilisation in deuterated solvents (Scheme 2.46).

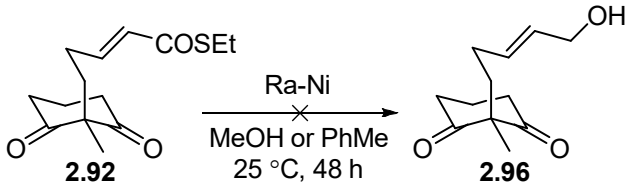


2.92 **2.100**

Conditions	Outcome
H_2O_2, NaOH, MeOH	Degradation
Oxone™, acetone sat. $NaHCO_3$, CH_2Cl_2	Degradation
m-CPBA, CH_2Cl_2, 0 °C	Degradation

*Scheme 2.46: Attempted epoxidation of thioester **2.92.***

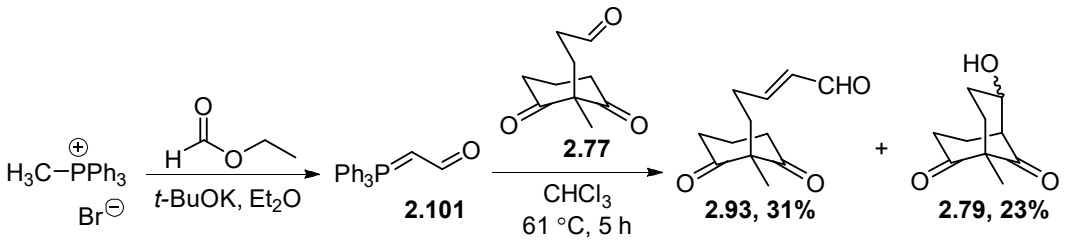
Selective reduction of the thioester over the ketones was then considered, a reaction usually achieved using Raney-Nickel.[110] Unfortunately, no reactivity was observed after treatment of thioester **2.92** with Ra-Ni, either in methanol or toluene (Scheme 2.47).



2.92 **2.96**

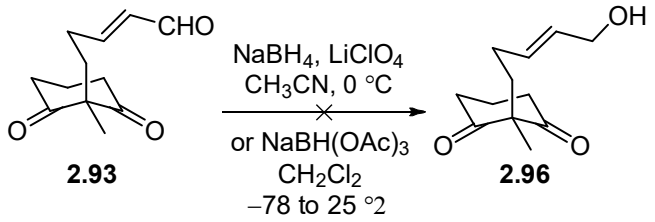
*Scheme 2.47: Attempted selective thioester reduction to allylic alcohol **2.96.***

We then turned to the synthesis of unsaturated aldehyde **2.93** which was prepared in 31% yield (Scheme 2.48). Despite the modest yield and the formation of the already observed aldol product **2.79**, the mass recovery was sufficiently good to proceed to the next step.



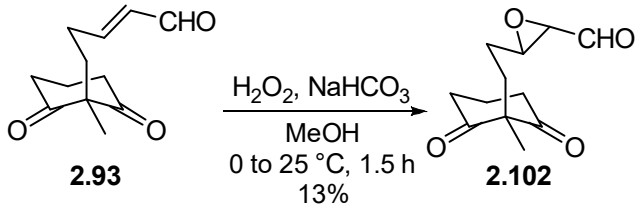
*Scheme 2.48: Synthesis of unsaturated aldehyde **2.93.***

Encouraged by a few reported chemoselective reduction of aldehydes over ketones,[111] a few reductive conditions were tried. In the case of $NaBH_4$ in the presence of $LiClO_4$, reduction of both ketones was unfortunately also observed. With $NaBH(OAc)_3$ instead only starting material was recovered, even when the reaction was subjected to the addition of more equivalents of the hydride and/or higher temperature (Scheme 2.49).



*Scheme 2.49: Attempted synthesis of allylic alcohol **2.96** via chemoselective reduction of aldehyde **2.93.***

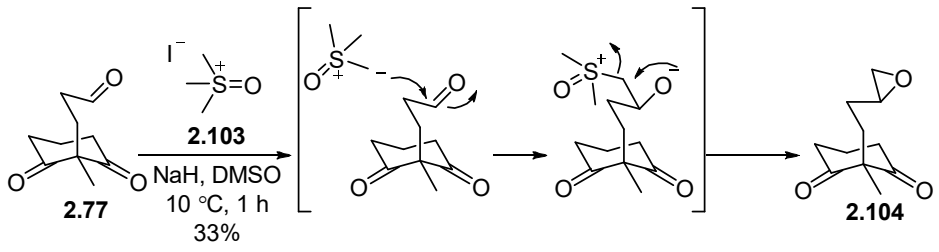
Attempted epoxidation of the same unsaturated aldehyde with hydrogen peroxide led to the desired epoxide **2.102**, albeit in low yield (13%, Scheme 2.50). In an attempt to synthesize more material and in the hope of optimising the yield, the reaction was run a second time; unfortunately, the result of the previous reaction could not be reproduced.



*Scheme 2.50: Synthesis of epoxy aldehyde **2.102.***

2.3.7 Alternative pathways towards epoxidation: the Corey-Chaykovsky reaction

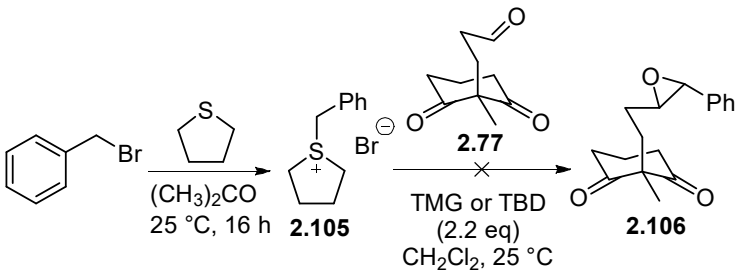
In the Corey-Chaykovsky reaction, a sulfur ylide reacts with carbonyl compounds or imines leading to the corresponding epoxides or aziridines, with high diastereoselectivity towards the *trans* product (where stereochemistry applies). Accordingly, this reaction was performed on the previously synthesised aldehyde **2.77**; generation of trimethylsulfoxonium ylide **2.103** after treatment of trimethylsulfoxonium iodide with NaH, subsequent nucleophilic addition and ring closing led to the formation of epoxide **2.104** in 33% yield (Scheme 2.51). Unfortunately, compound **2.104** decomposed after a week even if kept at –20 °C.



*Scheme 2.51: Corey-Chayvkosky reaction for the synthesis of epoxide **2.104.***

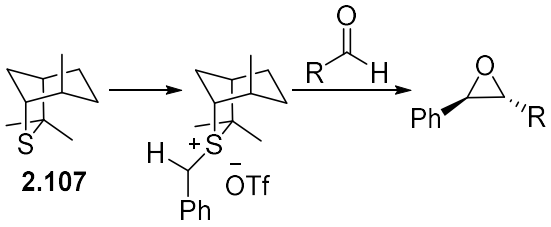
Despite the modest yield, the Corey-Chaykovsky reaction held promise, since in one step process the result is the same as a Wittig olefination followed by an epoxidation. A report by Graham described the guanidine base TBD as very effective for *in situ* generation of

sulfonium salt of the type **2.105** (Scheme 2.52).[112] The latter can then be reacted with a variety of aldehydes to give the corresponding oxiranes in high yield and *trans* stereoselectivity. This protocol is known to work for both enolisable and non enolisable aldehydes; however, the examples with aliphatic aldehydes were limited to two (80 and 36% yield respectively), as opposed to nine aromatic ones. Unfortunately, both TBD and TMG were found to be inefficient in delivering the desired epoxide **2.106** (Scheme 2.52).



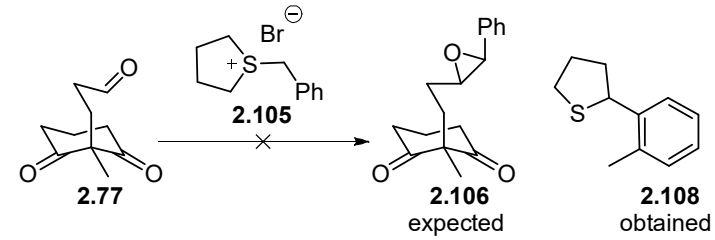
*Scheme 2.52: Guanidine base-promoted Corey-Chaykovsky for the synthesis of epoxide **2.106.***

The Aggarwal group has a long-standing interest in the asymmetric synthesis of epoxides employing chiral sulfides. In 2013, the group published an extensive study on the application of chiral isothiocineole **2.107** to the asymmetric epoxidation of aldehydes extending the study to a wide range of aliphatic and aromatic aldehydes, all obtained in high yield, d.r. and *ee* (Scheme 2.53).[113]



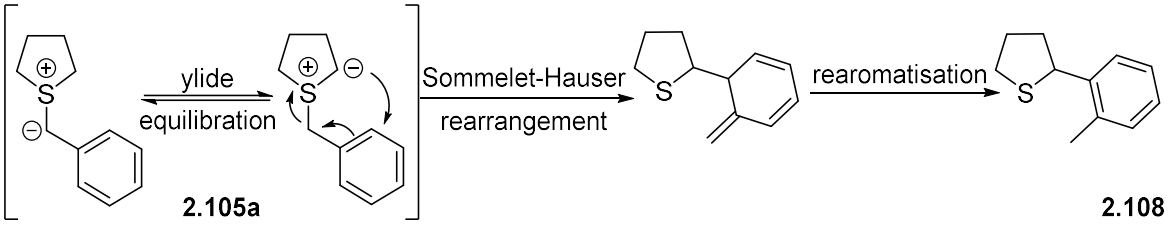
Scheme 2.53: Chiral isothiocineole for the asymmetric epoxidation of aldehydes.[113]

Tempted by the simplicity of their protocol, we sought to apply these reaction conditions to our system. In a first attempt to apply the Aggarwal protocol, we decided to keep using the sulfonium salt **2.105** as isothiocineole **2.107** was not available in our laboratory. A mixture of protic and aprotic solvents was reported to be ideal for aliphatic aldehydes and a few conditions were tried but unfortunately none of them delivered the desired oxirane **2.106** (Scheme 2.54). In two cases, the same observation as the Aggarwal group was made, namely the Sommelet-Hauser rearrangement, a 2,3-sigmatropic rearrangement of equilibrated ylide **2.105a** (Scheme 2.54).[114]



Conditions	Outcome
KOH, CH_3CN/*t*-BuOH (15:1) 0 to 25 °C, 72 h	Unidentified mixture
KOH, CH_3CN/H_2O (9:1)	Sommelet-Hauser
KHMDS, THF, −78 °C, 7 h	Unidentified mixture
NaH, DMSO, 25 °C	Sommelet-Hauser

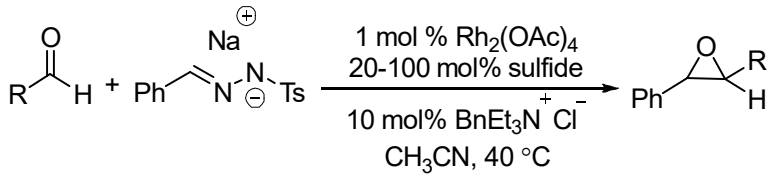
*Scheme 2.54: Attempted synthesis of epoxide **2.106.***



Scheme 2.55: Mechanistic details of the Sommelet-Hauser rearrangement.

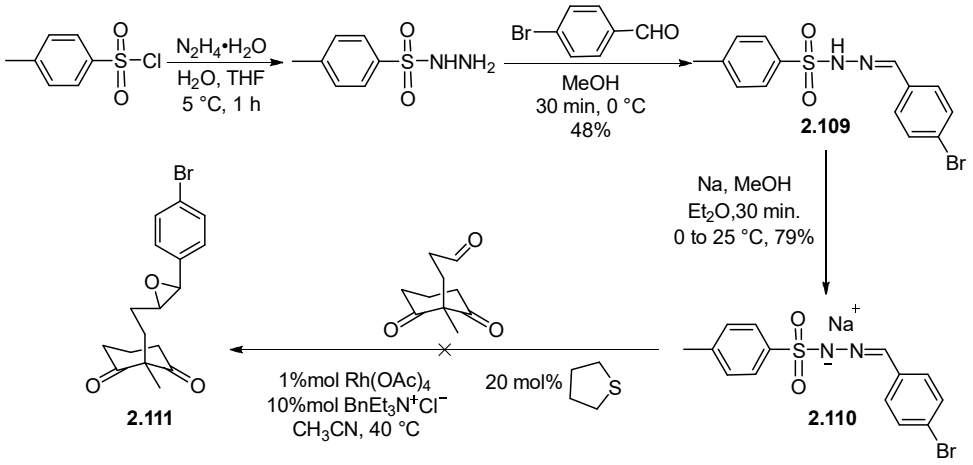
In Aggarwal's case, the product of the Sommelet-Hauser rearrangement **2.108** arises when ketones and less electrophilic aldehydes are employed in the reaction. He postulated that ylide **2.105a** has time to equilibrate because of the slow reaction rate of these carbonyl partners compared to more electrophilic substrates. He then applied Fava's studies[115] on the rate of deuterium exchange of the cyclic sulfonium salt's protons and substituted tetrahydrothiophene with its 6-membered ring homologue (pentamethylene sulfide); this resulted in an increase of the epoxide yield from 15 to 69%, as the rate of exchange of α-protons is much slower.

Since the pentamethylene sulfide was not available in our laboratory, the conditions published by Aggarwal in 2003 were used,[114] in which a variety of metalated tosylhydrazone salts derived from benzaldehyde in the presence of rhodium catalyst delivered epoxides in very good yield and d.r. (Scheme 2.56).



Scheme 2.56: Use of tosylhydrazone and rhodium catalyst for the epoxidation of aldehydes.

Formation of the tosyl hydrazone of *p*-bromobenzaldehyde **2.109** proceeded in high yield. However, the desired epoxide **2.111** was not obtained, instead a range of decomposition products were detected (Scheme 2.57). Possibly the aldehyde was insufficiently reactive; indeed, Aggarwal noted that the reaction failed with hindered aliphatic aldehydes such as pivaldehyde. The use of the 5-membered tetrahydrothiophene rather than the suggested 6-membered ring (pentamethylene sulfide) to avoid the Sommelet-Hauser rearrangements could be the solution to this reactivity problem.



*Scheme 2.57: Synthesis of the metalated tosyl hydrazone **2.110** and its use in the attempted Corey-Chaykovsky epoxidation.*

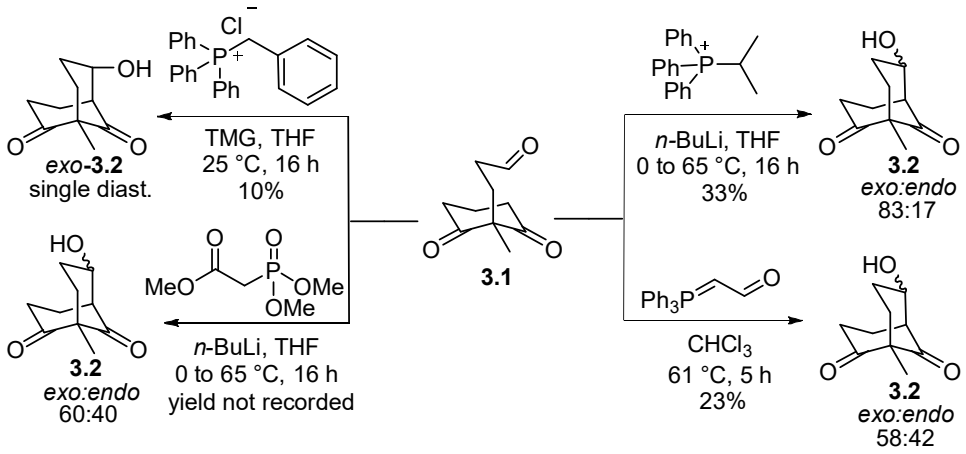
2.4 Conclusion

Unfortunately, we were not able to realize the synthetic plan presented in Scheme 1.52 for the construction of the PPAP core via a dearomatisation approach. We encountered many challenges during the dearomatisation step because of repeated rearomatisation pathways. The epoxide-mediated cyclisation of 1,3-dihydroresorcinol derivatives envisioned did afford some interesting intermediates but was limited by low product yields, epoxide decomposition and/or instability. However, observation and accurate NMR analysis of a side product deriving from a Wittig reaction prompted us to explore further another approach which will be described in details in the following chapter 3.

CHAPTER 3: MICHAEL-ALDOL TANDEM ANNULATION

3.1 Introduction

During the investigation of Wittig and HWE conditions in order to access various alkene intermediates, the persistent formation of bicyclo ketols **3.2** was observed (see also Scheme 2.37 in Chapter 2), the product of an intramolecular aldol reaction of aldehyde **3.1**.



*Scheme 3.1: Bicyclic epimers **3.2** arising as side product of Wittig and HWE reactions on aldehyde **3.1**.*

Given that this unexpected intramolecular reaction afforded the desired bicyclo[3.3.1]nonane scaffold, this process was studied in more detail for three main reasons:

- The aldol product was readily formed under mild conditions
- The diastereoselectivities observed were promising given that the reaction had not been optimised
- An intramolecular aldol was not very well studied for cyclic 1,3-diketones

Our main goal was to develop a short and efficient route towards the bicyclo[3.3.1]nonane scaffold. Having regard to various, mostly biomimetic, domino annulations that have been used in the synthesis of the PPAP bicyclic core, we proposed to develop a one-pot annulation process to functionalised bicyclo ketols. Accordingly, a Michael addition prior to the cyclisation observed above was considered.

A detailed account of all the strategies used so far for the synthesis of bicyclo[3.3.1]nonane core, with their application in natural product total synthesis and their limitations, was given in Chapter 1 and is summarized in Fig.3.2.

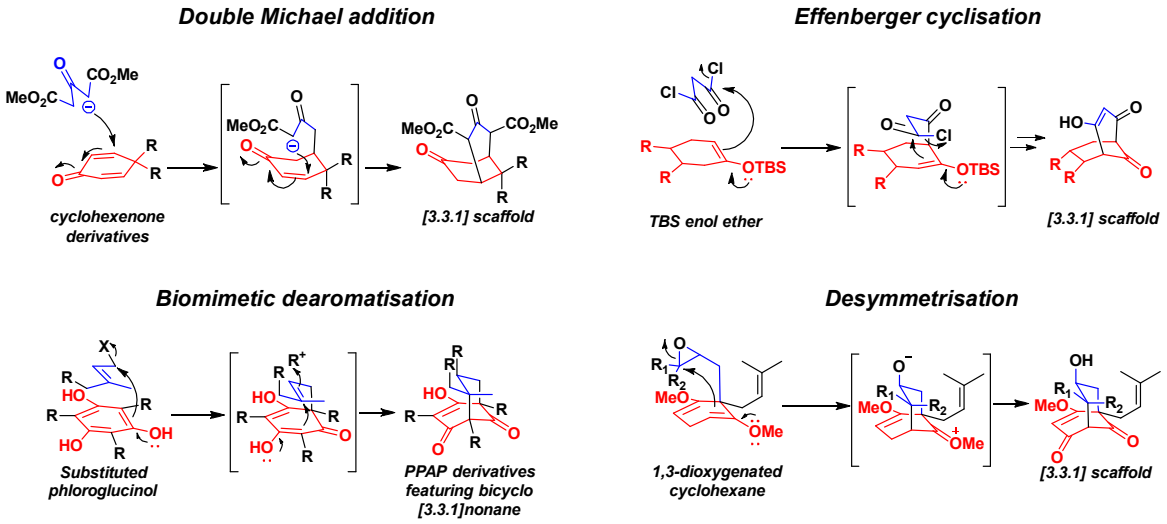
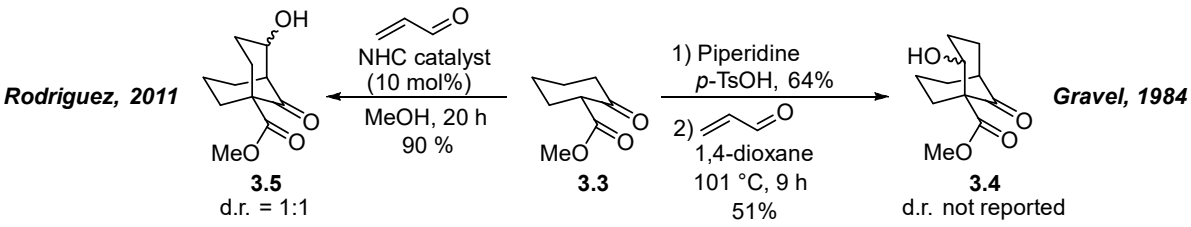


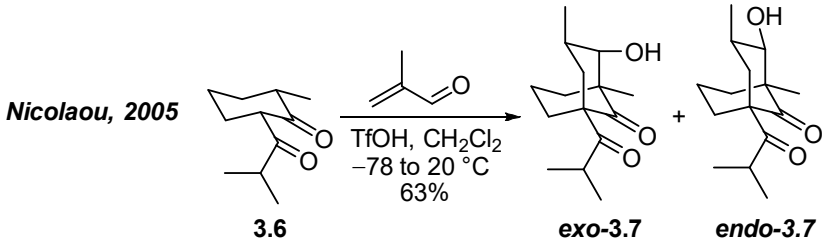
Fig. 3.2: Summary of the main synthetic strategies to access the bicyclo[3.3.1]nonane scaffold.

Given our first preliminary results on the construction of the [3.3.1]nonane scaffold via an intramolecular aldol (see Scheme 3.1) and inspired by domino-type annulations we considered the development of a Michael-aldol annulation reaction starting from readily available 2-methylcyclohexane-1,3-dione. Shair's enantioselective total synthesis of (+)-hyperforin had already established the importance of dihydroresorcinol derivatives as key precursors for the formation of the bicyclo[3.3.1]nonane scaffold[66-67] and we were intrigued by the very few annulation reports that used them as starting material. Bicyclic ketol formation has been achieved using mainly α-alkoxycarbonyl or acyl-cycloalkanones which bear an electron withdrawing group at the α-position of the cyclic ketone. For instance, Gravel reported that β-keto esters of type **3.3** can undergo Michael-aldol annulations via enamine formation at the less hindered carbon, thus positioning the resulting alcohol next to the β-keto ester unit (Scheme 3.3, **3.4**).[48] The yield achieved was moderate and the diastereoselectivity of the reaction was not examined. More recently, Rodriguez reported the same type of annulation in the presence of a NHC catalyst which gave bicyclo ketol **3.5** in high yield but poor d.r.(Scheme 3.3).[32]



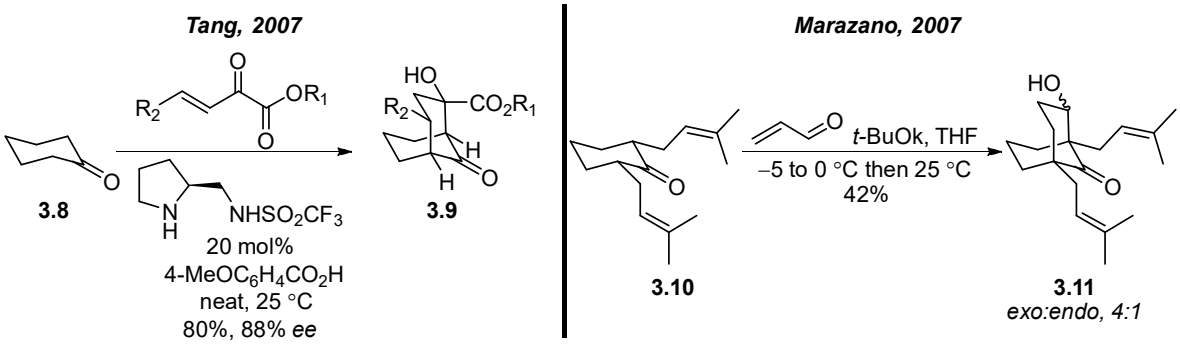
*Scheme 3.3: Michael-aldol annulation sequence from β-keto ester **3.3**.*

A similar strategy was reported by Nicolaou in 2005;[31] acid-catalysed annulation of 2-acylcyclohexanone **3.6** with methacrolein afforded a 2:1 mixture of *exo* and *endo*-ketols **3.7** in which the relative configurations were not assigned but the methyl group is presumably as drawn in the scheme below, *i.e. exo* to the bridgehead carbonyl group (Scheme 3.4).



*Scheme 3.4: Nicolaou's annulation of acylcyclohexanone **3.6**.[31]*

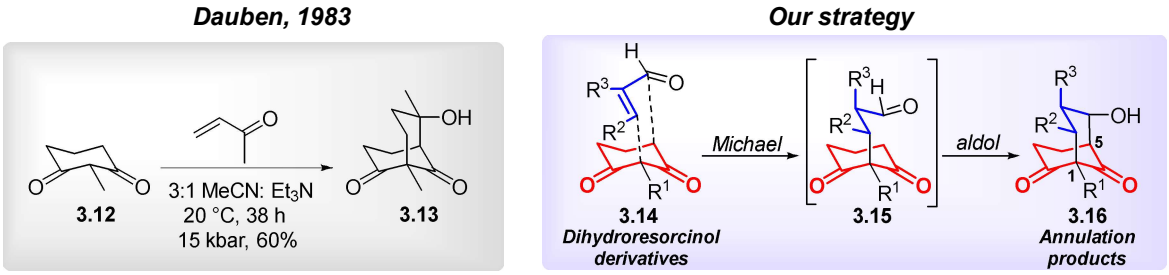
Only two cases of annulations where the cyclohexanone derivative lacks an electron withdrawing group at the α or β-position have been described (Scheme 3.5). While Tang[50] managed to react cyclic ketone **3.8** with various enones in the presence of pyrrolidine-sulfonamide-derived catalyst to obtain the desired bicyclic scaffold **3.9** in good yields and *ee*, Marazano's use of enals[62] afforded the diprenylated bicyclic compound **3.1** in moderate yields and d.r. (Scheme 3.5).



Scheme 3.5: Two Michael-aldol annulation approaches to the bicyclo[3.3.1] none scaffold.[50, 62]

These few examples highlighted the limitations in scope and mainly in stereocontrol for the annulation of α-alkoxycarbonyl and acyl-cycloalkanones. To date, the only example of annulation involving 2-substituted-cyclohexane-1,3-diones of type **3.12** was reported by Dauben in 1983;[22] a mixture of unassigned diastereoisomers of bicyclo ketol **3.13** was formed after 2 days reaction at high pressure (Scheme 3.6, left). With these considerations in mind, we sought a succinct and efficient method that could build the bicyclo[3.3.1]nonane scaffold **3.16** in just one step from dihydroresorcinol derivatives **3.14** and substituted enals; ideally this strategy would be flexible enough so that a diverse range of substituents could

be incorporated with high stereocontrol into the bicyclic scaffold, generating the maximum number of stereogenic centres at once, without being limited by the ring size (Scheme 3.6, right).



Scheme 3.6: Left: only example of Michael-aldol annulation featuring a 2-substituted-1,3-cyclohexanedione.[22] *Right: our proposed annulation strategy.*

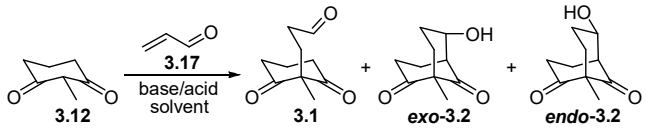
3.2 Synthesis of bicyclo[3.3.1]nonanes through a domino Michael-aldol annulation of cycloalkane 1,3-diones with α,β-unsaturated aldehydes

3.2.1 Optimisation of the annulation conditions

Our study began with the investigation of the reaction between 2-methyl-1,3-cyclohexanedione **3.12** and acrolein **3.17** (Table 3.7).

With inorganic bases like NaH or NaOMe (entries 1-4) the desired bicyclo ketol was never observed. The use of Et_3N in THF did not lead to any promising results but the Michael adduct **3.1** was obtained in 62% when the reaction was run in acetonitrile (entry 6). A catalytic amount of the same base afforded mainly the aldol products in good diastereoselectivity (entry 7). The same outcome was observed when a base like DIPEA was employed; stochiometric amount afforded exclusively **3.1** whereas catalytic amount drove the equilibrium slightly towards the aldol products, which were detected in appreciable diastereoselectivity and yields (entries 9 and 10). Imidazole and pyridine both afforded only aldehyde **3.1** whereas a stronger base such as DBU led to a mixture of Michael and aldol products in a 1:1 ratio when used in stochiometric and catalytic amount (entries 11 and 13). The use of DABCO in dichloromethane provided the bicyclo ketols in very low yield but promising diastereoselectivity; switching to acetonitrile dramatically improved the yield, and complete conversion into the desired bicyclic products was observed (entry 19). Although a 10 mol% loading of DABCO appeared to be too low, giving a 1:1 mixture of Michael and aldol adducts, 20 mol% led instead to the exclusive formation of the aldol products in 65% isolated yield and a 1:1 ratio between the two epimers (entry 21). Given the promising results with DABCO, a solvent screening was performed in the hope of improving the

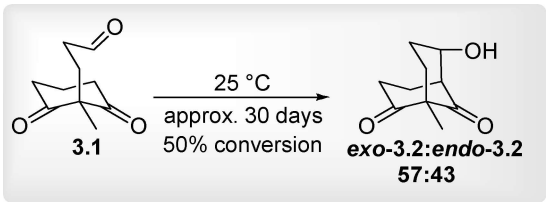
diastereoselectivity; the use of a more polar solvent such as ethanol or dimethyl sulfoxide (entries 22 and 25) gave either exclusively **3.1** or a mixture of **3.1** with bicyclo compound(s) **3.2**. Conducting the reaction in toluene or THF gave high yields but with no improvement of the diastereoselectivity and aldehyde **3.1** could be detected in 7% yield (entries 26 and 27); the quantitative conversion into a 66:34 ratio of epimers was achieved when the reaction was heated at reflux in acetonitrile (entry 28). Prolonging the reaction time (48 h) led to high diastereoselectivity and quantitative yields (entry 29). A stochiometric amount of DABCO under the same conditions led to exclusive formation of the *exo*-adduct **3.2**, the best result that could be achieved (Table 3.7)



entry	Base	Solvent	T (° C)	Time (h)	3.01 (%)	*exo*-3.02 (%):*endo*-3.02 (%)
1	NaH	THF	25	16	-	-
2	*t*-BuOK	*t*-BuOH	25	16	-	-
3	NaOH (4%)	EtOH	25	16	-	-
4	NaOMe	MeOH	25	16	-	-
5	Et_3N (1 eq.)	THF	25	16	-	-
6	Et_3N (1 eq.)	MeCN	25	16	62	-
7	Et_3N (0.2 eq.)	MeCN	25	16	30	80 : 20 (70)
8	Et_3N (0.2 eq.)	MeCN	65	16	20	70 : 30 (80)
9	DIPEA (0.2 eq.)	MeCN	25	32	42	66 : 33 (58)
10	DIPEA (1 eq.)	MeCN	25	16	62	-
11	DBU (0.2 eq.)	MeCN	25	16	40	53 : 47 (60)
12	DBU (0.2 eq.)	THF	25	32	traces	-
13	DBU (1 eq.)	MeCN	25	32	50	50 : 50 (50)
14	Imidazole (1 eq.)	MeCN	25	16	83	-
15	Pyridine (1 eq.)	MeCN	25	32	83	-
16	Pyrroldine (1 eq.)	MeCN	25	16	-	-
17	DMAP (1 eq.)	MeCN	25	16	traces	70 : 30 (95)
18	DABCO (1 eq.)	CH_2Cl_2	25	16	-	70 : 30 (12)
19	DABCO (1 eq.)	MeCN	25	16	-	50 : 50 (100)
20	DABCO (0.1 eq.)	MeCN	25	16	50	50 : 50 (100)
21	DABCO (0.2 eq.)	MeCN	25	16	-	50 : 50 (65)
22	DABCO (0.2 eq.)	EtOH	25	16	62	traces
23	DABCO (0.2 eq.)	CH_2Cl_2	25	16	83	-
24	DABCO (0.2 eq.)	DMF	25	16	95	traces
25	DABCO (0.2 eq.)	DMSO	25	16	50	50 : 50 (50)
26	DABCO (0.2 eq.)	THF	25	16	7	68 : 32 (93)
27	DABCO (0.2 eq.)	$PhCH_3$	25	16	7	86 : 14 (93)
28	DABCO (0.2 eq.)	MeCN	95	16	-	66 : 34 (100)
29	DABCO (0.2 eq.)	MeCN	95	48	-	90 : 10 (100)
30	DABCO (1 eq.)	MeCN	95	48	-	100 : 0 (100)
31	-	MeCN	95	72	-	100 : 0 (70)
32	-	DMF	135	24	-	100 : 0 (100)

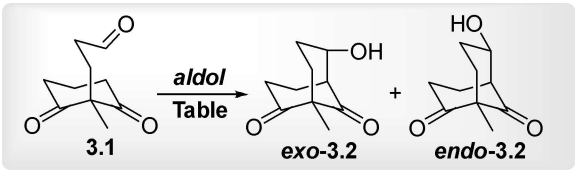
Table 3.7: Optimisation of the annulation reaction conditions.

We later discovered that approximately 50% of pure isolated Michael product **3.1**, if not stored at low temperature, spontaneously converts to the aldol product in almost a 1:1 mixture of epimers (Scheme 3.8) over a 30-day period.

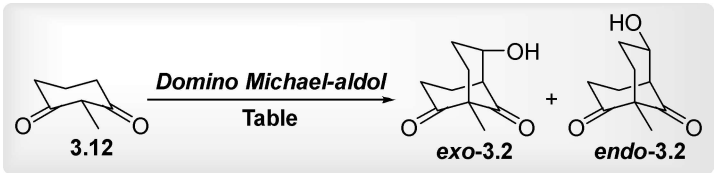


Scheme 3.8: Spontaneous intramolecular aldol reaction at room temperature.

Accordingly, we tested the hypothesis that no base was needed for the aldol reaction to occur. Scheme 3.9 highlights a short screening of solvent, temperature and time for both aldol and domino Michael-aldol reactions. For the aldol reaction, after careful monitoring of the reaction at fixed intervals of time, 72 h was found to be the ideal time to reach complete selectivity towards *exo*-**3.2**, which could be isolated in quantitative yield (entry 1). Although quantitative yields were also achieved using DMF, complete stereocontrol was never achieved (entry 2 to 4). In contrast, for the domino reaction the use of DMF gave a better outcome as the reaction time could be shortened to 24 h and the desired bicyclo compound could be isolated in quantitative yield exclusively as *exo*-adduct **3.2** (entry 8).



entry	Reagent	Solvent	T (° C)	Time (h)	yield 3.2(%)	*exo*-3.2(%) : *endo*-3.2(%)
1	-	MeCN	95	72	100	100 : 0
2	-	DMF	130	18	100	78 : 22
3	-	DMF	130	32	100	81 : 19
4	-	DMF	130	64	100	81 : 19

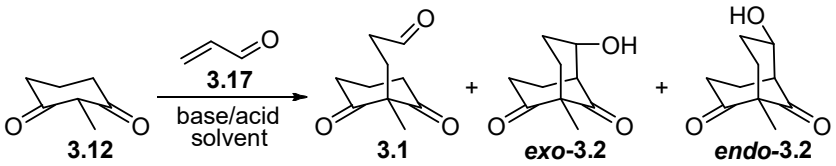


entry	Base	Solvent	T (° C)	Time (h)	yield 3.2(%)	*exo*-3.2(%) : *endo*-3.2(%)
5	-	MeCN	95	72	70	100 : 0
6	-	DMSO	140	24	80	100 : 0
7	-	DMF	155	24	100	100 : 0
8	-	DMF	130	24	100	100 : 0

Scheme 3.9: Solvent and temperature optimisation for the Michael-aldol annulation reaction.

Although the above results were satisfactory, a few acidic conditions were also tested. Literature[31] conditions using TfOH for cyclisations involving 2-methylcyclohexane-1,3-dione

with acrolein were unsuccessful (entry 1). In the same way, the use of TFA at ambient temperature was ineffective to deliver the desired aldol adduct (entry 2) although at 95 °C *exo*-**3.2** could be isolated but in low yield (Scheme 3.10, entry 3).

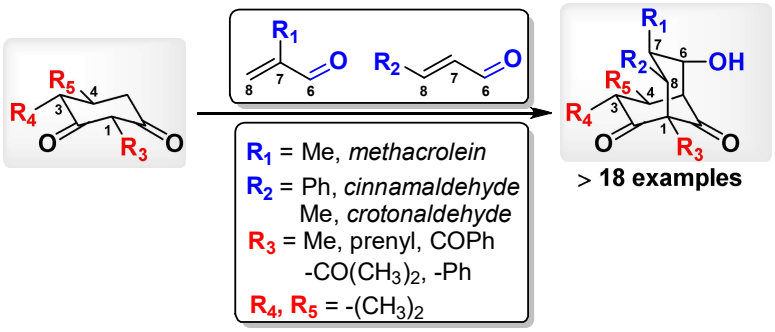


entry	Acid	Solvent	T (° C)	Time (h)	3.1 (%)	*exo*-3.2 (%) : *endo*-3.2 (%)
1	TfOH	CH_2Cl_2	–78 to 25	16	-	-
2	TFA	MeCN	25	16	80	-
3	TFA	MeCN	95	16	-	100 : 0 (36)

Scheme 3.10: Initial screening of the Michael-aldol annulation reaction using acidic conditions.

3.2.2 Scope of the reaction

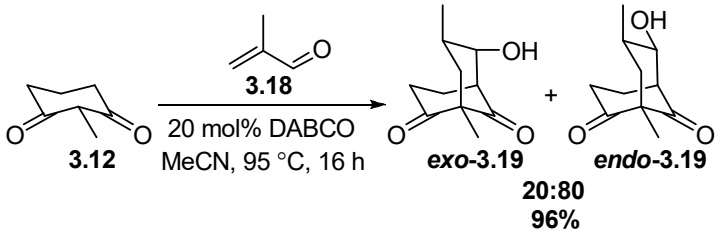
After the optimum conditions for the annulation were established the scope of the reaction was examined. Our approach relied on the incorporation of substituents at two of the three carbon atoms in the annulating unit, *i.e.* position-7 and -8, through reaction with commercially available substituted enals, and on the modification of the dihydroresorcinol scaffold to diversify position -1, -3 and -4. Reaction of each substituted dione with each of the enals selected would in principle give three analogs per substituent (Scheme 3.11).



Scheme 3.11: Determination of the scope for the Michael-aldol annulation.

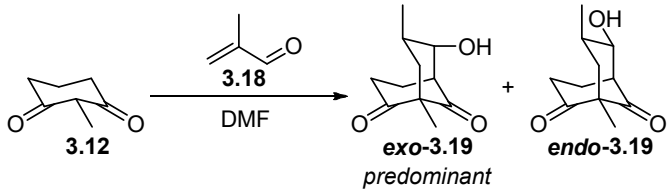
3.2.2.1 Substitution at position -6,-7 and -8

Our investigation of the scope of the reaction started with the use of methacrolein **3.18**; heating in acetonitrile overnight with 20 mol% loading of DABCO gave predominantly the *endo*-isomer **3.19** in almost quantitative yield. Extending the reaction time to 48 h led to a lower diastereomeric ratio (65:35) instead (Scheme 3.12).



Scheme 3.12: Synthesis of 6-hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione.

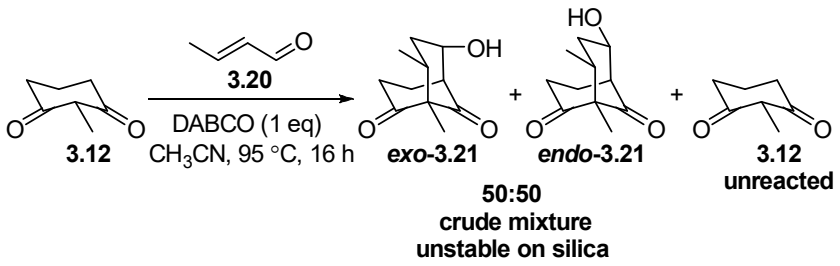
Neutral conditions were then tested to see if stereocontrol could be further enhanced. Surprisingly, heating for 72 h in DMF led to the predominant formation of *exo*-**3.19** although in very low isolated yield. Several conditions in DMF were then tested and the formation of the *exo*-**3.19** was predominant in all cases, with its exclusive formation when the reaction was heated for 48 h with 1 eq of DABCO (Scheme 3.1). Unfortunately, the crude product contained several other unidentified impurities; the reaction always required purification and *exo*-**3.19** was never obtained in satisfactory yield (Scheme 3.13).



Conditions	Outcome
95 °C, 72 h	*exo* : *endo*, 80:20 6% of pure *exo* recovered
130 °C, 16 h	*exo* : *endo*, 75:25
20 mol% DABCO,130 °C, 16 h	*exo* : *endo*, 63:37
DABCO (1 eq), 130 °C, 24 h	*exo* : *endo*, 70:30 32% of pure *exo* recovered
DABCO (1 eq), 130 °C, 48 h	*exo*-3.19 32% NMR yield

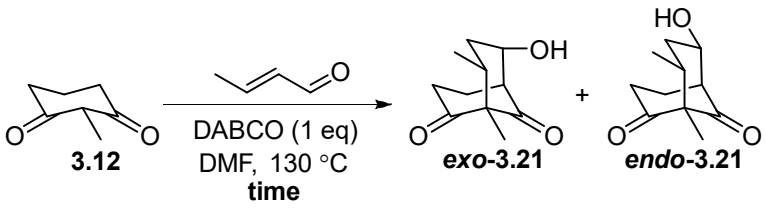
*Scheme 3.13: Optimisation of the reaction conditions for exo-isomer **3.19**.*

After installing the methyl group at the 7-position, substitution at position -8 was examined using crotonaldehyde **3.20**. Whereas 20 mol% loading of DABCO failed to deliver any annulation product, treatment of **3.12** with 1 eq of DABCO led to the desired *exo* and *endo*-**3.21** adducts in a 50:50 diastereomeric ratio. Together with the aldol products, a significant amount of unreacted 2-methylcyclohexane-1,3-dione was also present in the crude mixture; unfortunately, any attempt to separate it from the desired mixture of aldol isomers was not successful and the crude mixture seemed to degrade during column chromatography on silica gel (Scheme 3.14).



Scheme 3.14: Synthesis of 6-hydroxy-1,8-dimethylbicyclo[3.3.1]nonane-2,9-dione and its attempted isolation.

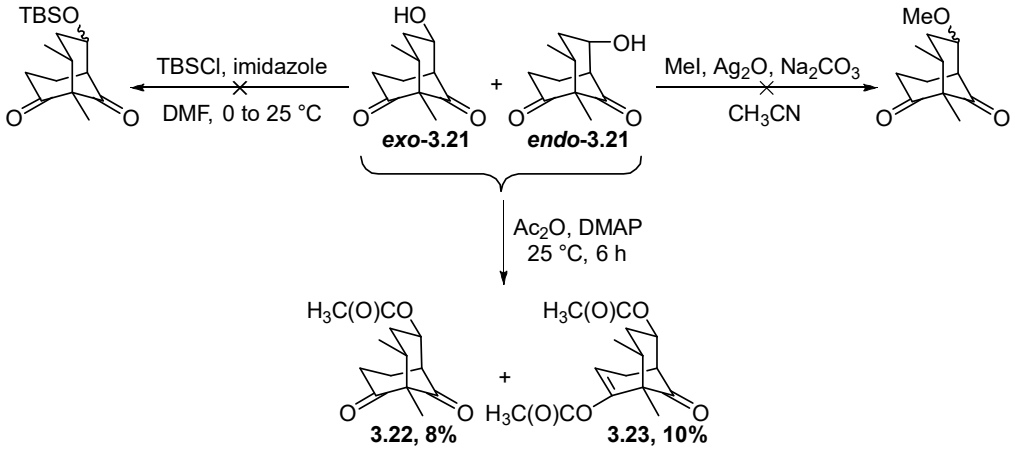
As shown in scheme 3.15, prolonging the reaction time and using DMF as solvent seemed to lead to better results in terms of NMR yield and diastereoselectivity. However, unreacted dione **3.12** was still present in the crude mixture and, as described before, purification was not possible.



Solvent	T (° C)	Time (h)	*exo*-**3.21**:*endo*-**3.21**	NMR yield (%)	recovered. **3.12**
DMF	130	**16**	42:53	60	40
DMF	130	**30**	58:42	38	62

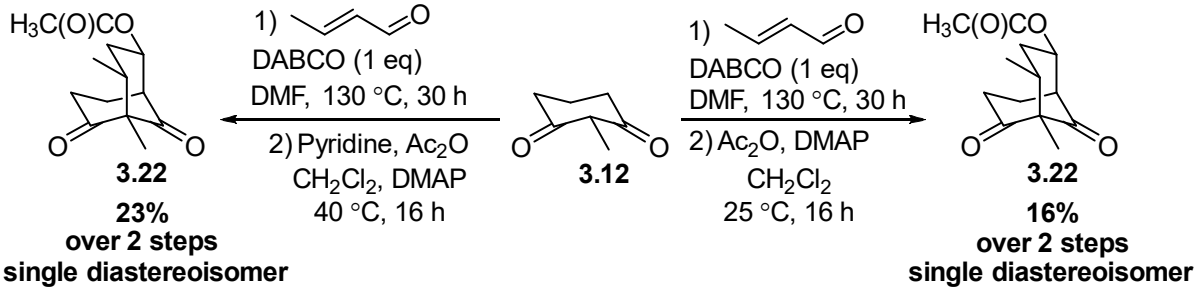
Scheme 3.15: Attempted optimisation of the synthesis of 6-hydroxy-1,8-dimethylbicyclo[3.3.1]nonane-2,9-dione.

We therefore decided to derivatise the mixture of the free alcohols as the acetate ester or methyl ether in order to avoid a possible retro-aldol process, most likely catalysed by the acidity of silica. As shown on scheme 3.16, attempted derivatisation as either the TBS ether or the methyl ether failed. In both cases no reaction occurred and a mixture of *exo* and *endo*-**3.21** was recovered. Reaction with acetic anhydride and DMAP however afforded, after separation on column chromatography, two products, the desired **3.22** and the dimethyl ester **3.23**, both as single diastereoisomers but unfortunately in very low yield (Scheme 3.16).



*Scheme 3.16: Derivatisation of bicyclo ketol mixture as methyl ester **3.22.***

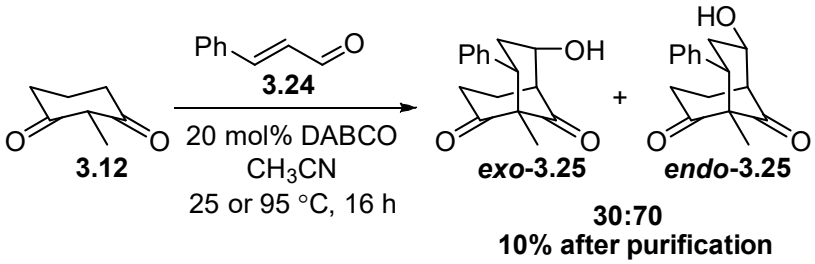
A one-pot strategy was then devised to improve the efficiency of the derivatisation and the yield of **3.22**. The Michael-aldol annulation was first run under the conditions that gave the best results in terms of diastereoselectivity and starting material *vs* product ratio (see Scheme 3.15). When TLC showed that the annulation reaction was completed, DMF was evaporated at reduced pressure, the crude mixture redissolved in dichloromethane and acetic anhydride and DMAP were added. This strategy slightly improved the yield (8% to 16%), probably owing to a more efficient work-up; however, the best result was obtained when the reaction was heated at reflux in the presence of pyridine and the crude product chromatographed on neutral alumina, giving 3.22 in 23% yield. Interestingly, only the major *endo*-isomer of the crude product could be recovered to give the desired product as a single diastereomer (Scheme 3.17).



*Scheme 3.17: One-pot strategy for the synthesis and isolation of the derivatised bicyclo **3.22**.*

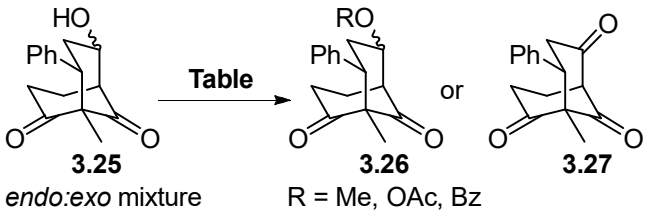
The substitution of position -8 was further explored using cinnamaldehyde **3.24**. No reaction was observed with a catalytic amount of DABCO whereas the use of stochiometric quantities drove the reaction to completion, with 95% conversion observed by crude ^{1}H NMR and satisfactory d.r. (*exo*:*endo*, 37:63). Unfortunately, the crude product could not be freed from cinnamaldehyde impurities, either by evaporation or distillation. In the attempt to separate

the desired aldol adducts from the aldehyde residues on column chromatography it was observed that the products were also unstable on silica even when the solvent was neutralised or neutral Al_2O_3 was used instead, and at best only 10% of a mixture of the *exo* and *endo*-**3.25** products could be isolated (Scheme 3.18).



Scheme 3.18: Synthesis and difficult isolation of 6-hydroxy-1-methyl-8-phenylbicyclo[3.3.1]nonane-2,9-dione.

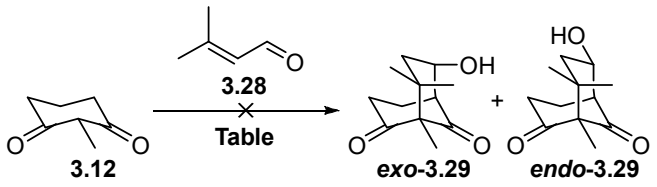
Derivatisation was again attempted but the esterification that was successful for bicyclo **3.21** could not be achieved. Scheme 3.19 shows how only reaction with benzoyl chloride and triethylamine led to a pure adduct (**3.26**, R = Bz) as a single diastereoisomer, although in only 5% yield. Oxidation of the alcohol was considered as a means of making the bicyclo system more stable but unfortunately all oxidation attempts were unsuccessful (Scheme 3.19).



Conditions	Outcome
NaH, MeI, THF	Degradation
Py, Ac_2O, DMAP, CH_2Cl_2, 40 °C, 16 h	No reaction
Et_3N, BzCl, CH_2Cl_2, 25 °C, 16 h	R = Bz **3.26**, 5%
DMP, $NaHCO_3$, CH_2Cl_2, 25 °C, 16 h	No reaction
PCC, CH_2Cl_2, 25 °C, 16 h	Promising crude, unstable on silica
IBX, EtOAc	Degradation

*Scheme 3.19: Derivatisation to ester analogue **3.26** and attempted oxidation to triketone **3.27**.*

Limitations to install an 8-substituent was shown when **3.12** was reacted with 3-methyl-2-butenal **3.28** using the same conditions previously employed for crotonaldehyde. No bicyclo product was observed, only no reaction or degradation (Scheme 3.20).

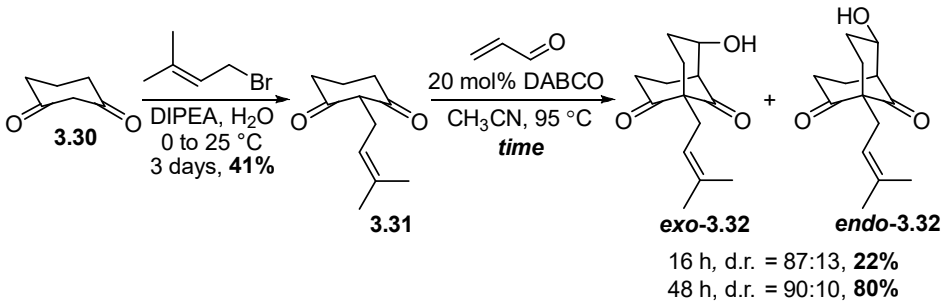


Conditions	Outcome
DMF, 130 °C, 16 h	Degradation
DABCO (1 eq), DMF, 130 °C, 16 h	No reaction
DABCO (1 eq), CH_3CN, 95 °C, 16 h	No reaction

Scheme 3.20: Limitation on substitution at the 8-position.

3.2.2.2 Substitution at position -1,-3 and -4

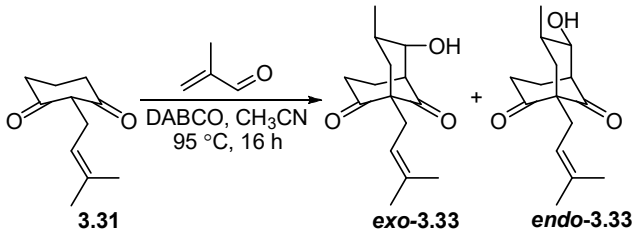
With the idea of synthesizing a bicyclo compound that more closely resembled the PPAP scaffold, replacement of the methyl group at the C-1 bridgehead position by a prenyl group was attempted. 2-prenyl-1,3-cyclohexanedione **3.31** was obtained by alkylation of 1,3-cyclohexanedione **3.30** with prenyl bromide in water (Scheme 3.21).[62] Reaction of this precursor with a catalytic amount of DABCO under optimal conditions (acetonitrile, 95 °C) yielded the desired bicyclic adducts **3.32** in high d.r. but only in 22% yield. Simply increasing the reaction time to 48 h dramatically improved the efficiency of the reaction (80% yield) and the diastereomeric mixture (d.r. = 90:10). Surprisingly, only traces of the aldol product could be detected if the same reaction was run in DMF under neutral conditions.



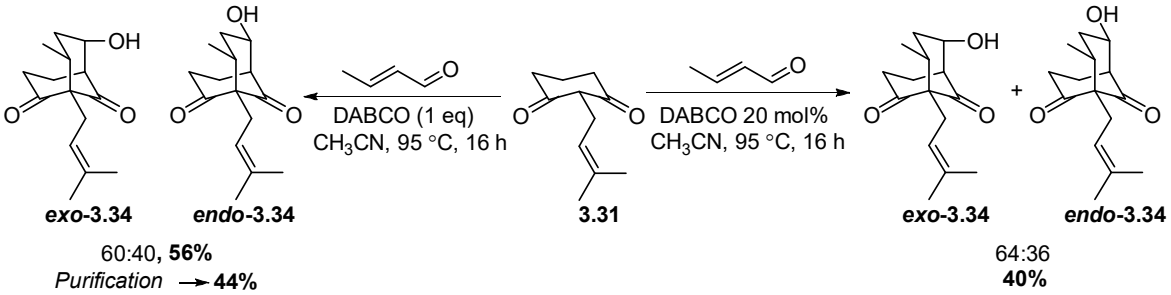
Scheme 3.21: Reaction sequence for the synthesis of 6-hydroxy-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione.

With precursor **3.31** in hand, its reaction with methacrolein and with crotonaldehyde was then tested. In both cases catalytic loading of base afforded unsatisfactory yields; however, use of a stochiometric amount of DABCO led to good to high isolated yields and satisfactory d.r. For bicyclo **3.34** the crude product was not pure enough and column chromatography had to be performed, affording the pure compound in 44% yield (Scheme 3.22). Reaction with cinnamaldehyde was not attempted given the instability issues encountered with the methylated precursor **3.12**.

Reaction with methacrolein

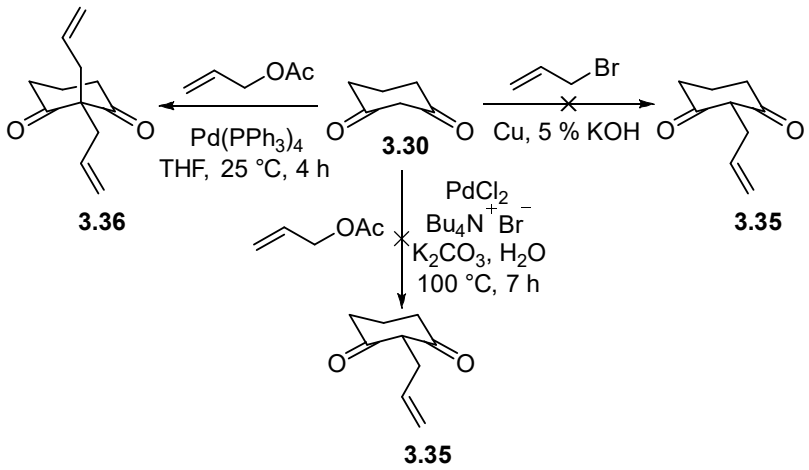


Reaction with crotonaldehyde



Scheme 3.22: Michael-aldol annulation of 2-prenyl-1,3-cyclohexanedione with methacrolein and crotonaldehyde.

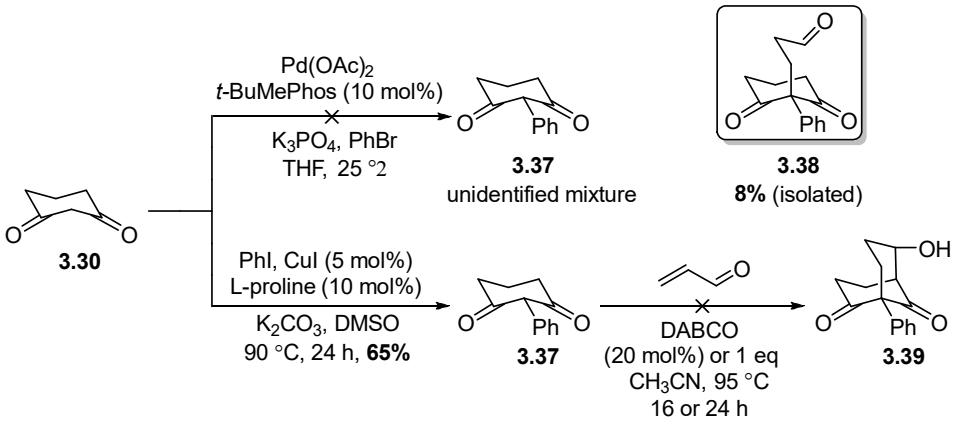
A simple variant to the prenyl precursor **3.31** was the synthesis of 2-allyl-1,3-cyclohexanedione **3.35** for use in the Michael-aldol annulation. Reported allylation conditions in aq. KOH in the presence of Cu [116] could not be repeated while a Tsuji-Trost reaction under standard or modified[117] conditions both provided the diallylated adduct **3.36** instead of the desired monoallylated product **3.35** (Scheme 3.23).



*Scheme 3.23: Attempted monoallylation of 1,3-cyclohexanedione **3.30.***

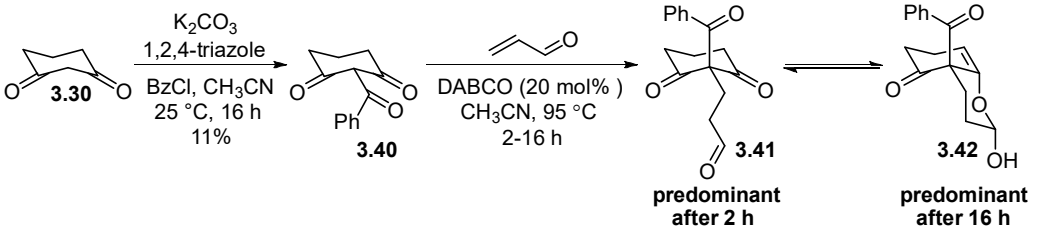
Determined to install more functional groups at position-1 of **3.30** and expand the scope behind the prenyl group, the possibility of installing an acyl group or an aromatic ring at this

position was considered. The preparation of 2-phenyl-1,3-cyclohexanedione (**3.37**) has been previously described;[118] after an initial unsuccessful attempted synthesis through a palladium-mediated arylation, reaction of 1,3-cyclohexanedione with iodobenzene in the presence of CuI and L-proline[119] gave dione **3.37** in 65% yield. The crude product was not stable on silica for purification but was found to be sufficiently pure to attempt the cyclisation step. Treatment of **3.37** with 20 mol% of DABCO in acetonitrile over the course of 16 or 24 h both led to a complex mixture from which only 8% of Michael adduct **3.38** could be isolated (Scheme 3.24). The outcome was the same when a stochiometric amount of DABCO was used so this route was abandoned.



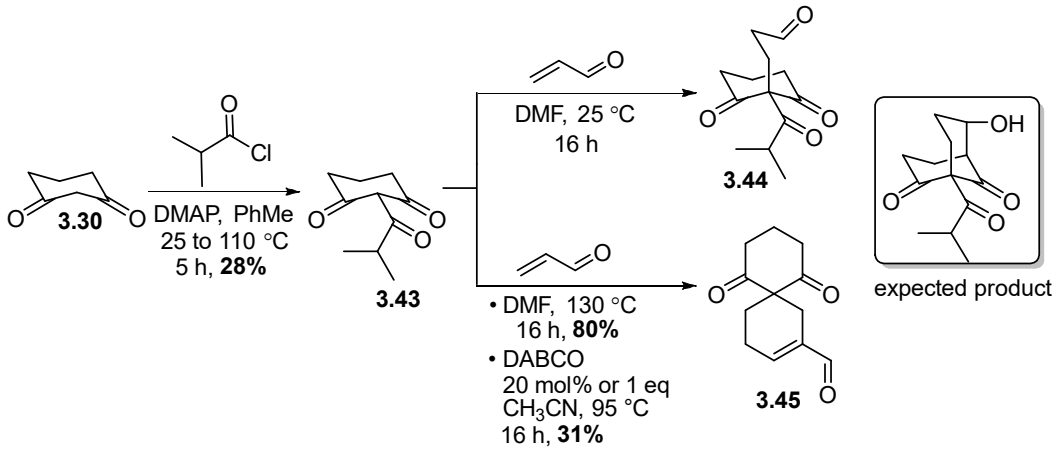
*Scheme 3.24: Synthesis of 2-phenyl-1,3-cyclohexanedione **3.37** and its use in the Michael-aldol annulation.*

Attention was then turned to preparing a 1-acyl precursor. The synthesis of the monoacylated 1,3-dione has been scarcely described, and the best procedure[120] afforded the key precursor **3.40** in 11% yield. Treatment of **3.40** under the optimum onditions led to the equilibrium depicted on Scheme 3.25. As the reaction was monitored by crude ^{1}H NMR at regular intervals of two hours it was observed that Michael adduct **3.41** was the major product after 2 h and then gradually decreased at the expense of the formation of hemiacetal **3.42** which after 16 h was almost the sole identified product. The products were well distinguished on NMR but unfortunately they co-eluted on column chromatography and could not be separated (Scheme 3.25).



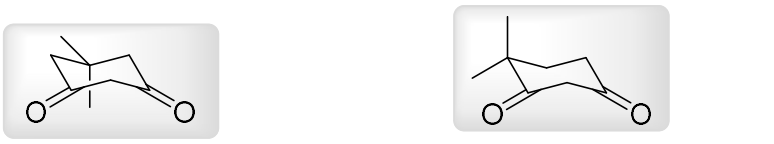
*Scheme 3.25: Aldehyde-hemiacetal equilibrium for the annulation of 2-acyl-cyclohexanedione **3.40.***

In case the steric hindrance caused by the phenyl group at position -1 was preventing cyclisation of the Michael product, the cyclisation of 2-isobutyrylcyclohexane-1,3-dione (**3.43**) was examined. Following a patent application[121] cyclohexane-1,3-dione was heated at reflux with 2-methylpropionyl chloride in toluene in the presence of DMAP to give trione **3.43** in 28% yield. Reaction of the latter with acrolein under neutral reaction conditions at room temperature afforded an inseparable mixture of starting material and aldehyde **3.44**, whereas heating at 130 °C led unexpectedly to the formation of spiro compound **3.45** in high yield and as the only product of the reaction. However, in the presence of DABCO the yield was only 31%. To the best of our knowledge, such unsaturated spirocyclic diones have not been previously described and a detailed account of its formation will be given in chapter 4 (Scheme 3.26).



*Scheme 3.26: Synthesis of 2-isobutyrylcyclohexane-1,3-dione and unexpected formation of enal **3.45.***

Moving to the functionalization of position -4 and -5, we considered two commercially available diones, 5,5-dimethyl-1,3-cyclohexanedione **3.46** and 4,4-dimethyl-1,3-cyclohexanedione **3.47** respectively (Fig. 3.27).



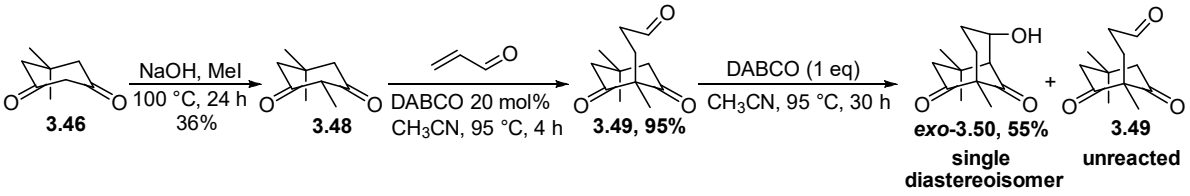
3.46
5,5-dimethyl-1,3-cyclohexanedione

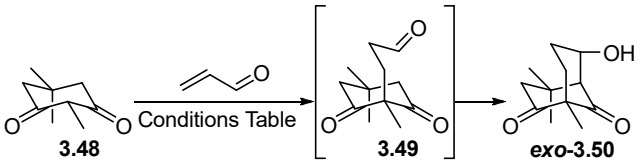
3.47
4,4-dimethyl-1,3-cyclohexandione

Fig. 3.27: Structure of gem-dimethyl 1,3-cyclohexanediones.

Starting from the 5,5-dimethylated precursor **3.46**, methylation[97] with MeI in a freshly prepared 3M solution of NaOH yielded **3.48** in 36% yield. Treatment of the latter with acrolein and a catalytic amount of DABCO gave aldehyde **3.49** in nearly quantitative yield. The

desired bicyclo compound *exo*-**3.50** could be obtained as a single diastereoisomer from isolated Michael adduct **3.49** in 55% yield upon heating in acetonitrile in the presence of DABCO for 30 h. Unfortunately, most of the attempts to trigger the domino Michael-aldol sequence by either prolonging the reaction time or changing the reaction conditions were unsuccessful and *exo*-**3.50** was obtained only in the presence of 2 eq of DABCO in an unsatisfactory yield of 12% (Scheme 3.28).

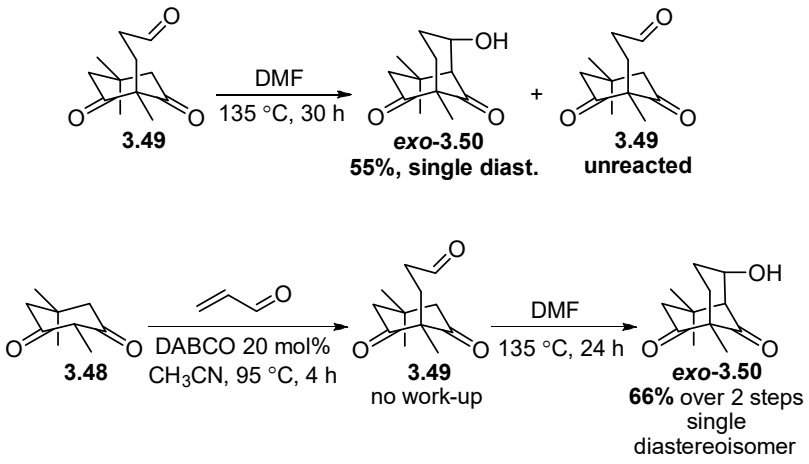




Conditions	Outcome
DMF, 130 °C, 24 h	Unidentified mixture
DABCO (20 mol%) CH_3CN, 95 °C, 16 h	**3.49** + unidentified product
DABCO (1 eq) CH_3CN, 95 °C, 16 h	Unidentified mixture
DABCO (2 eq) CH_3CN, 95 °C, 16 h	***exo*-3.50, 12%**

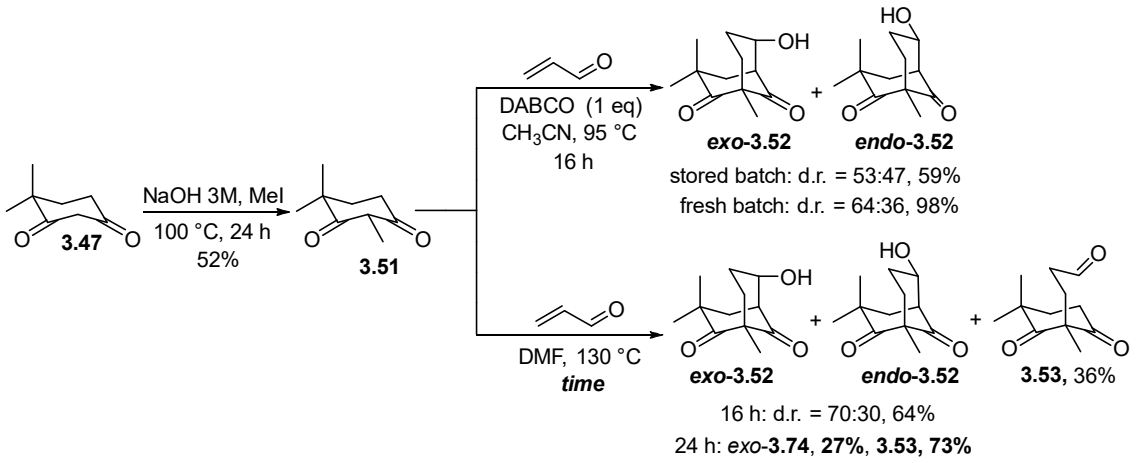
*Scheme 3.28: Stepwise access to bicyclo compound **3.50** and attempted optimisation of domino Michael-aldol from 5,5-dimethyl-1,3-cyclohexanedione.*

Interestingly, heating in DMF at 135 °C led to a faster conversion of the Michael adduct to the desired bicyclo product, in the exact same yield and diastereoselectivity as before. A one-pot strategy was then devised; once **3.49** was formed from the reaction in acetonitrile, the solvent was evaporated at reduced pressure and replaced with DMF; the resulting mixture was heated at 135 °C for 24 h which allowed the intramolecular aldol to take place giving *exo*-**3.50** in an improved yield of 66% over 2 steps (Scheme 3.29).



*Scheme 3.29: Improved stepwise sequence for the synthesis of **exo-3.50** in which no work-up is required.*

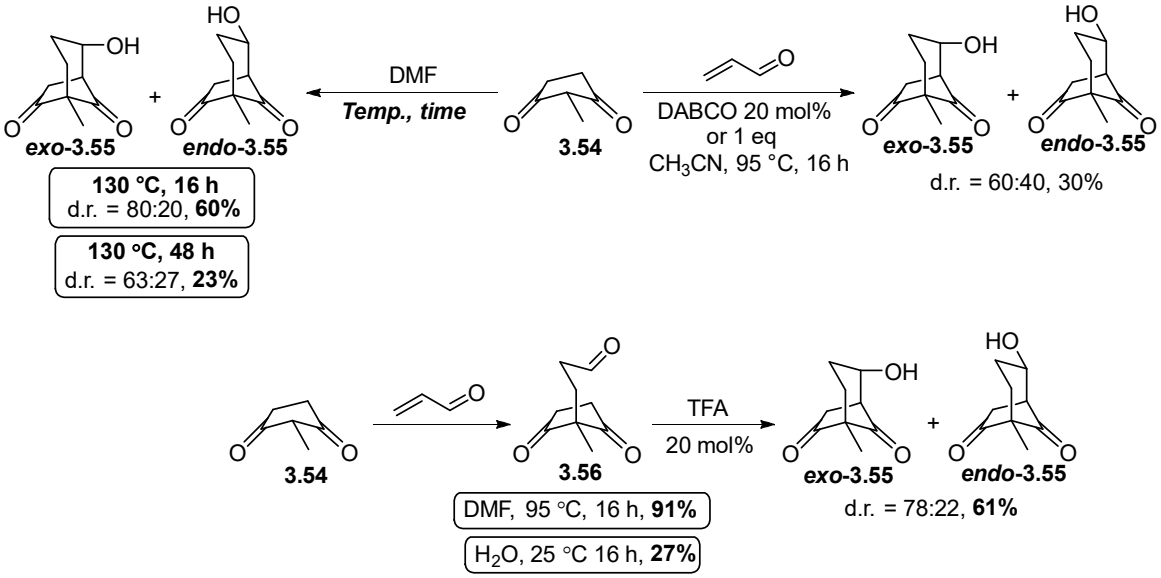
With 4,4-dimethyl-1,3-cyclohexanedione **3.47** as starting material instead, addition of 1 equivalent of DABCO to a solution of **3.51** and acrolein in acetonitrile led to the formation of the desired mixture of bicyclic products **3.52** in nearly quantitative yield and satisfying d.r. (Scheme 3.30). The reaction could not be driven to completion when dione **3.51** was heated in DMF, affording a mixture of aldol **3.52** and Michael product **3.53;** the aldol products were predominant in case of overnight heating (16 h) whereas the Michael adduct was favoured when the reaction time was prolonged to 24 h (Scheme 3.31). It is worth noting that the purity of dione **3.51**, synthesised from **3.47** via methylation in aq. NaOH, was critical; being highly unstable at room temperature (although it can be stored at -20 °C for several weeks) it was crucial to use it as soon as it was prepared; the use of the stored sample, even after few days, made the yield of the annulation drop significantly (from 98 to 59%) (Scheme 3.30).



*Scheme 3.30: Michael-aldol annulation for the synthesis of bicyclo **3.52** bearing a gem-dimethyl group at the 4-position.*

3.3 Domino Michael-aldol annulation of cycloalkane 1,3-dione with α,β-unsaturated aldehydes to give bicyclo[3.2.1]octanes derivatives

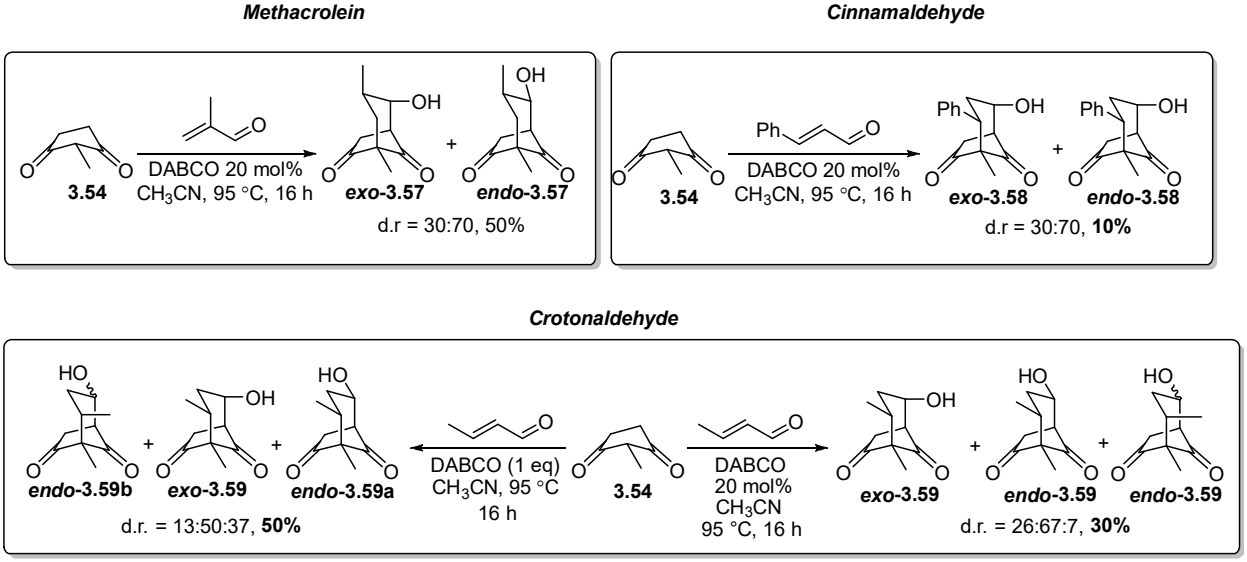
At this point it was reasoned that the same methodology adopted for the construction of the bicyclo[3.3.1]nonane core could be applied to the synthesis of bicyclo[3.2.1]octane by employing **3.54**, the 5-membered ring analogue of 2-methyl-1,3-cyclohexanedione. To test our hypothesis, the reaction between commercially available dione **3.54** and acrolein with both catalytic and stochiomentric amount of DABCO was carried out and delivered the desired annulation products *exo*- and *endo*-**3.55**, albeit in only 30% yield. Both d.r. and yield of the domino Michael-aldol were improved under neutral conditions (DMF at 130 °C), although a prolonged reaction time was detrimental for the yield. Interestingly, by reducing the temperature to 95 °C Michael product was obtained exclusively in 91% yield (Scheme 3.31). Isolation of the Michael product **3.56** was also achieved after overnight stirring of a solution of **3.54** and acrolein in water. Subsequent cyclisation of **3.56** to the desired bicyclo compound was surprisingly successful under acidic conditions, affording **3.55** in 61% yield with the *exo*-isomer favored over the *end*o (Scheme 3.31).



Scheme 3.31: Application of our methodology to 2-methyl-1,3-cyclopentanedione for the construction of the [3.2.1]bicyclic scaffold.

As highlighted in scheme 3.32, the extension of the methodology to methacrolein delivered the desired bicyclic ketols in 50% yield and good d.r.. Similarly to the bicyclo[3.3.1]nonane scaffold, isolation of bicyclo compounds *exo*- and *endo*-**3.58** arising from the reaction with cinnamaldehyde was particularly difficult. Even if crude ^{1}H NMR showed 95% conversion and only residual amounts of cinnamaldehyde, the product was found unstable on silica gel

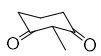
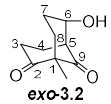
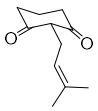
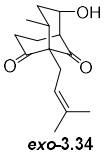
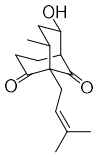
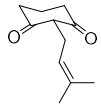
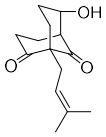
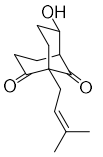
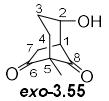
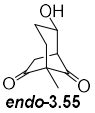
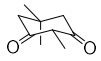
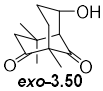
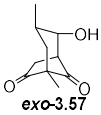
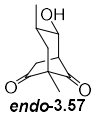
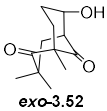
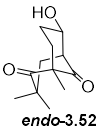
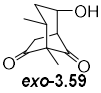
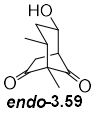
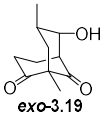
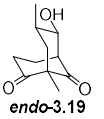
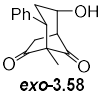
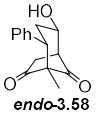
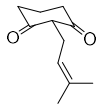
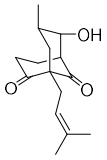
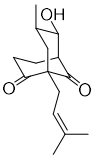
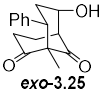
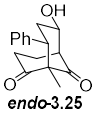
and could be isolated in only 10% yield (Scheme 3.32). The mixture resulting from the reaction with crotonaldehyde was isolated as a mixture of three diastereoisomers, the third one being most likely *endo*-**3.59b**, bearing the methyl group in axial position at C-8, a trend already observed for the reaction with 2,4,4-trimethylcyclohexanedione (Scheme 3.32).



Scheme 3.32: Annulation reaction with methacrolein, cinnamaldehyde and crotonaldehyde.

3.4 Trends in the mode of cyclisation and stereochemical assignment

A summary of bicyclo ketols synthesised with our Michael-aldol annulation is depicted on Table 3.33

Entry	1,3-dione	Bicyclic ketols and yields	Entry	1,3-dione	Bicyclo ketols and yields
1		 97% ***exo*-3.2**	7		 60:40 44%  ***exo*-3.34** ***endo*-3.34**
2		 90:10 80%  ***exo*-3.32** ***endo*-3.32**	8		 80:20 60%  ***exo*-3.55** ***endo*-3.55**
3		 55% ***exo*-3.50**	9		 28:72 50%  ***exo*-3.57** ***endo*-3.57**
4		 64:36 98%  ***exo*-3.52** ***endo*-3.52**	10		 50:37* 61%  ***exo*-3.59** ***endo*-3.59**
5		 20:80 96%  ***exo*-3.19** ***endo*-3.19**	11		 30:70 10%  ***exo*-3.58** ***endo*-3.58**
6		 70:30 86%  ***exo*-3.33** ***endo*-3.33**	12		 30:70 10%  ***exo*-3.25** ***endo*-3.25**

*13% of an additional isomer was also detected by ^{1}H NMR

Table 3.33: Summary of bicyclo[3.3.1]nonanes and [3.2.1]octanes synthesised, with yields and diastereoselectivity.

Since the beginning of our investigation, it became clear how the configuration of the alcohol at the 6-position could be controlled through modification of the reaction conditions or the type of substituent present in the annulating unit and in the cycloalkane dione. For instance, the use of neutral conditions with DMF as solvent was found to be optimal in terms of yield only for annulations involving acrolein; in terms of diastereoselectivity, it seemed that the absence of substituents in the enals (*i.e.* acrolein) led to the formation of the *exo*-adduct predominantly (entries 2, 4 and 8) or exclusively (entries 1 and 3) in both the bicyclo[3.3.1]nonane and [3.2.1]octane series. As previously mentioned, whereas neutral conditions gave the best results only for unsubstituted bicyclo ketols **3.2** and **3.55**, the use of stoichiometric amount of DABCO in acetonitrile was found to be ideal for all other bicyclo

compounds, with the successful use of catalytic amount of base only for entries 2 and 5. The use of α-methyl substituted enals led to the predominant formation of the *endo*-adduct; this can be rationalised by the substituent effect on the Michael adduct conformation and consequently on the mode of cyclisation; in case of an α-methyl group, the *endo*-mode of cyclisation would in fact be preferred because of one less synclinal interaction, compared to when the *exo*-adduct is formed (Scheme 3.34).

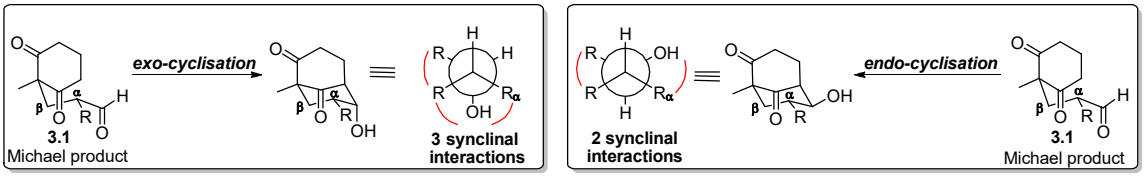


Fig.3.34: Michael adducts containing α-substitutents.

An exception to this is represented by the annulation involving 2-prenyl derivatives, where the *exo*-ketol is formed predominantly where both α and β-substitutents are present. At the same time, a β-methyl or phenyl group present on the annulating unit does not exert the same effect as an α-group, although preference for the exclusive formation of the *exo*-adduct is smaller (entries 7, 10, 11 and 12).

Substituents on the cyclohexane-1,3-dione system also have a profound effect on the Michael adduct conformation and therefore on the stereochemical outcome. The placement of the *gem*-dimethyl group at position -3 (entry 4) causes the dione ring to adopt a boat conformation, a peculiarity that will be discussed in detail in paragraph 3.5, rather than a chair-chair; in this way, the non-bonding interactions with the aldehyde carbonyl group are minimized leading mostly to the formation of the *endo*-isomer. When the *gem*-dimethyl group is located at position-4, the 1,3-diaxial interaction between the carbonyl and the equatorial methyl group completely suppress the *endo* mode of cyclisation, giving exclusively the *exo*-isomer (entry 3). A detailed assignment of the first bicyclo ketol obtained, *exo*-**3.2**, revealed two small coupling constants (3.1 and 2.6 Hz) for δ 4.28, assigned as the H-6 proton; these couplings make this in theory a doublet of triplets, with the 2:1 and 1:2 regions close but not superimposed (which would give 1:3:3:1), with the peak height found to be about 1:2.5:2.5:1, consistent with partial overlap of the 2 and 1 regions. Importantly, the values of the coupling constant suggested that the H-6 adopted an equatorial position, the C-OH being in an axial orientation. Additional proof for this assignment came from the ^{1}H NMR analyses of the *endo*-**3.2** ketol (never isolated pure but whose crude ^{1}H NMR was clear enough to allow stereochemical assignment) which showed a big, *trans*-diaxial coupling constant of 11.5 Hz for its H-6 proton. HMQC and HMBC established the location of all the other peaks in the ^{1}H NMR where general trends were observed; for instance the multiplets at δ 2.32 and 2.60

cleanly coupled with the peak at 38.2 in ^{13}C NMR, identified through HMBC correlation and DEPT as the 3-CH_2; *J* values for the multiplet at δ 2.32 was found to be 9.4 Hz indicating a *trans*-diaxial coupling, identifying therefore that multiplet as the 3-Hax and the higher δ 2.60 as the 3-Heq. This chemical shift trend for the axial/equatorial protons was generally found throughout the bicyclo series and was used to assign axial/equatorial 3-CH_2 in other chair-chair structures (Fig. 3.35).

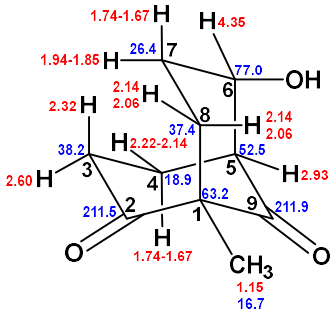


*Fig. 3.35: Details of the NMR assignment of ketol **3.2***

The stereochemical assignment was unequivocally confirmed by the X-ray crystal structure obtained for the 3,5-dinitrobenzoyl derivative of *exo*-**3.2**, previously assigned by NMR, which showed the C-OH moiety occupying the axial position (Fig.3.36).

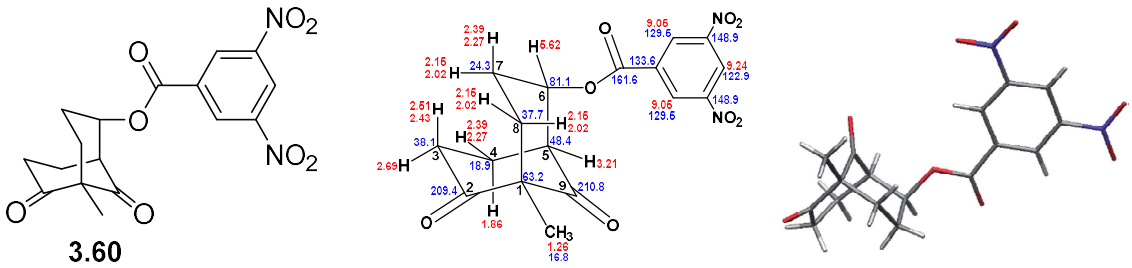


*Fig.3.36: NMR assignment and X-ray crystal structure of the ester derivative of bicyclo **3.60**.*

Assignment of **3.19** was based on a few key observations; the value for the H-6 coupling constant was found to be at 10.5 Hz, clearly indicating a *trans*-diaxial relationship with H-7, positioning at the same time the C-7 methyl group in equatorial position. The second coupling constant for H-6 matched with the same value found for H-5 (4.8 Hz), confirming the axial-equatorial relationship between H-6 and the bridgehead proton. Although assignment for the H-6 of the *exo*-isomer was troublesome as the ^{1}H NMR showed only complex multiplets, its synthesis and isolation confirmed the presence of two distinct

diastereoisomers rather than equilibrating conformers. Noteworthy is the chemical shift for C-8 at 44.5 ppm and C-3 at 38.4 ppm; the effect of the 7-C-Me group is in fact to deshield C-8 by about 10 ppm, which is consistent with the effect seen on cyclohexanone and its 4-Me derivatives (Fig. 3.37, left).

In the prenylated series it is interesting to highlight that the 7-CH_2 signals are found to be the most shielded, which was almost always the case for the H-4 protons in other bicyclo compounds. It was also noticed that there was little separation in chemical shift between axial and equatorial protons as shown for instance in ketol **3.32** by the region at δ 2.2-2.0, which contains 4 and 8-CH_2, both equatorial and axial, as well as the 3-Hax; those separations were usually bigger in non-prenyl analogs. The presence of a prenyl chain was confirmed by the presence of the olefinic peak at δ 5.05, which featured an allyl/vinyl coupling constant of 5.0 Hz and a multiplicity of a triplet of septets, consistent with its coupling to the neighbouring -CH_3 and -CH_2. Stereochemical assignment of H-6 was confirmed by the coupling constant of the *endo*-isomer, whose values (11.5 and 4.6 Hz) clearly indicated a *trans*-diaxial coupling with H-7 (Fig. 3.37, right). Assignment for *exo,endo*-**3.33** and *exo,endo*-**3.34**, containing a methyl group at the 7 and 8-position respectively, was complicated by unclear integration and unresolved couplings in some regions of the ^{1}H NMR, which sometimes contained 4 or 5 protons all together. However, some trends were noticed; whereas increase in the chemical shift values were expected for the carbon directly substituted with the methyl group, as clearly shown by comparison of C-7 for *exo*-**3.2** and *endo*-**3.19**, a difference in the chemical shift value of the vicinal 6-CH-OH was also observed, showing an increase of about 3 ppm when the Me groups was located at position -7 and a decrease of about the same range when C-8 was substituted instead. The same difference was also observed in the bicyclo[3.2.1]octane series.

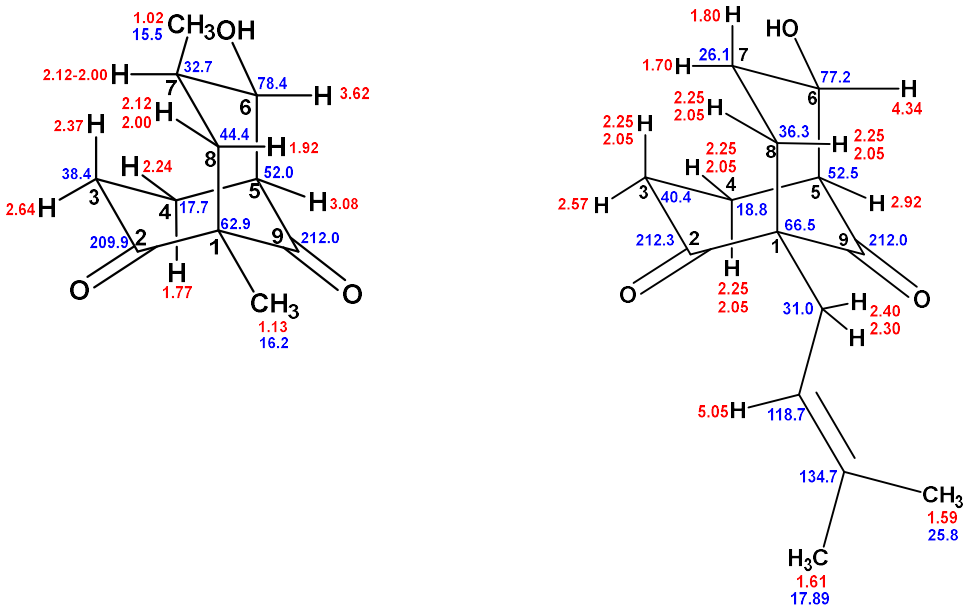


*Fig.3.37: Details of the NMR assignments of ketol **3.19** and **3.32***

Relatively to the bicyclo[3.2.1]octane series, HMBC and HMQC confirmed the consistency observed for all the other bicyclic compounds relative to carbon 3 and 4, having values of 26.5 ppm and 40 ppm respectively. A coupling constant of 5.4 Hz was found for the bridgehead proton at C-1 of *exo*-**3.55** and it was especially puzzling, given the fact that there was no evidence for a –O-H-O=C hydrogen bond and it was too large for a W coupling. However, this value could be explained on the basis of the dihedral angles being different, and giving rise to unequal *J* values.

Additionally, the cyclopentane-1,3-dione ring is much flatter than a cyclohexane-1,3-dione ring with models showing the (pseudo) axial 7-CH being at 90 ° to the bridgehead 1-CH so that *J* = 0; this information was particularly useful in the interpretation of *exo,endo*-**3.57** as it explains why only *J*-geminals of 19 Hz are seen for the 7-CHax, and at δ 2.9; however there is also a vicinal coupling for 7-CHeq, so that a doublet of doublets at δ 2.5 is also observed. A straightforward distinction was also made for the 2-CH multiplet, which showed a *J* of 9.6 Hz for the major *endo*-isomer and a W-coupling of 2.3 Hz for *exo*-**3.57**. As mentioned before, trends in the chemical shift adopted by the substituted carbon were also particularly noticeable in this series (Fig. 3.38).

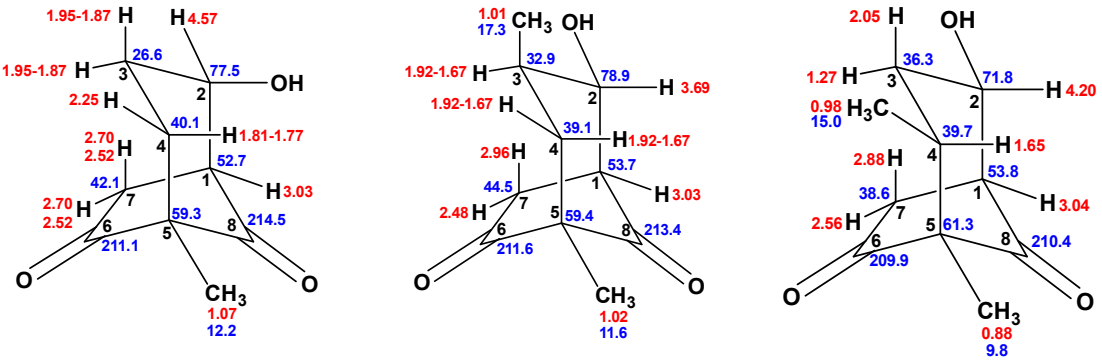


*Fig.3.38: Details of the NMR assignments of bicyclo[3.2.1] ketols **3.55** (left), **3.57** (centre) and **3.59** (right).*

For *exo*-**3.50**, the carbon at position -4 bears two methyl groups so 3-CH_2 was unambiguously identified as at δ 52.6; coupling with 3-Hax (δ 2.45) and 3-Heq (δ 2.72), both having a *gem*-coupling of 18 Hz, was subsequently confirmed by HMQC. A small coupling was also noticed in the COSY NMR between the 3-Heq at δ 2.72 and the methyl group at δ 0.91, which could have supported the equatorial assignment, but no splitting was seen on this signal. Conversely, a small splitting was also seen on the δ 2.45 signal belonging to 3-Hax, but it was negligible as a W conformation is not generally adopted for some 4- or 5-bond couplings. Chemical shift values for C-8 and C-7 were also found to match previous values of the bicyclo series (Fig. 3.39). As will be discussed extensively in the next paragraph, the position of the *gem*-dimethyl group in *exo,endo*-**3.52** forces the molecule to adopt an unusual boat-chair conformation. This is confirmed in the chemical shift values of 4-CHax which are much more shielded (δ 1.48 in *exo*-**3.52** and δ 1.70 in *endo*-**3.55**) compared to the rest of the series. Additionally, the delta value for 8-Hax is much lower (δ 1.41-1-26) in the *endo* isomer compared to *exo*-**3.52** (δ 2.12-2.00) since the latter experiences a severe 1,3-diaxial interaction with the axial OH group (which is also strongly deshielding). The carbon pattern is however unchanged, although actual delta values slightly differ (Fig. 3.39).

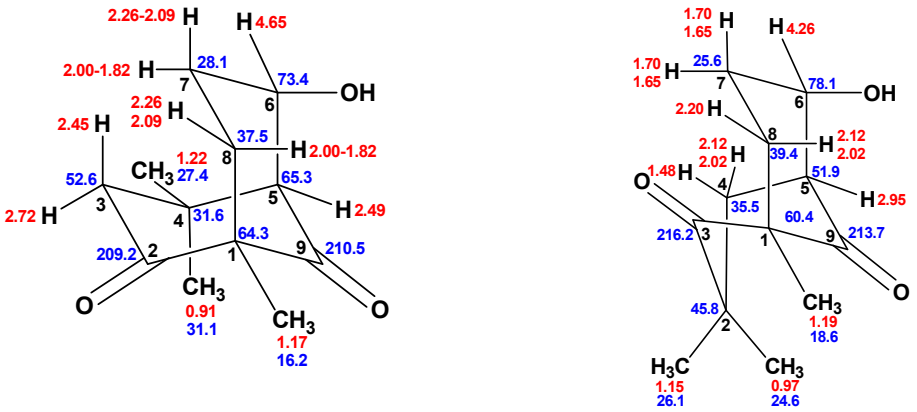
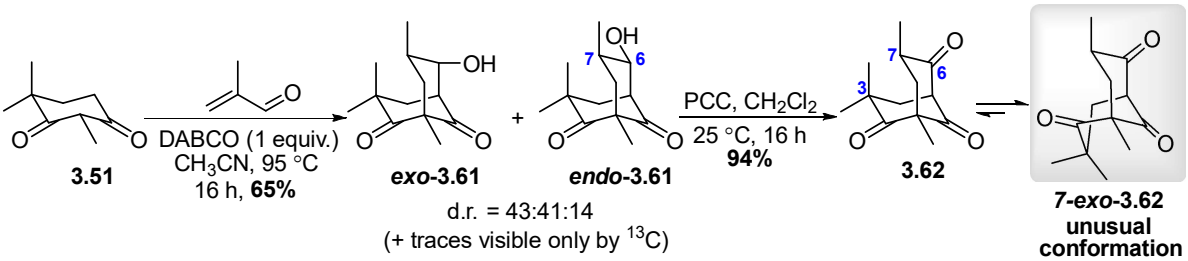


*Fig.3.39: Details of the NMR assignment of bicyclo **3.50** (left) and **3.52** (right).*

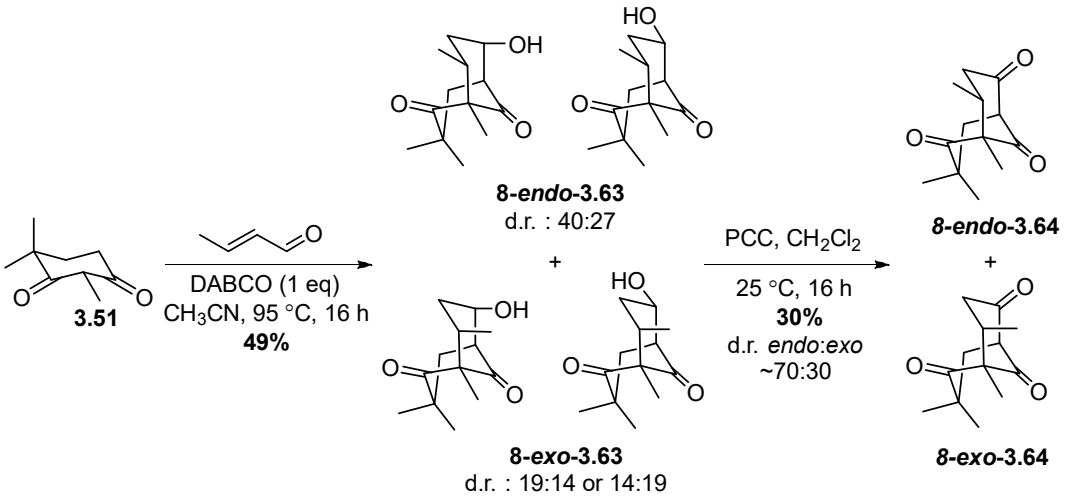
3.5 Oxidation product and conformational studies

Given that the annulation methodology was found to be particularly effective using the *gem*-dimethylsubstituted cyclohexane-1,3-diones, their reaction with methacrolein was studied, the expected epimers *exo*- and *endo*-**3.61** being obtained in almost the same amount (Scheme 3.40). A small amount of what looked like a third and a fourth diastereoisomer was also observed by ^{13}C NMR. Oxidation with pyridinium chlorochromate converted the complex ketol mixture into trione **3.62**. It was however noticed that a second product was formed in 15% yield; the epimer at C-7 could be excluded as it would suffer severe non-bonding Me-Me interaction between the *gem*-dimethyl group at C-3 and the axial methyl group at C-7. The 85:15 ratio observed could have been an evidence that trione 7-*exo*-**3.62** existed as chair and boat form and that in reality we were observing conformers, not diastereisomers. Molecular models indeed suggested that the steric hindrance brought by the presence of the *gem*-dimethyl would result in an alternative boat-chair conformation compared to the usually observed chair-chair conformation of bicyclo[3.3.1]nonanes (Scheme 3.40).



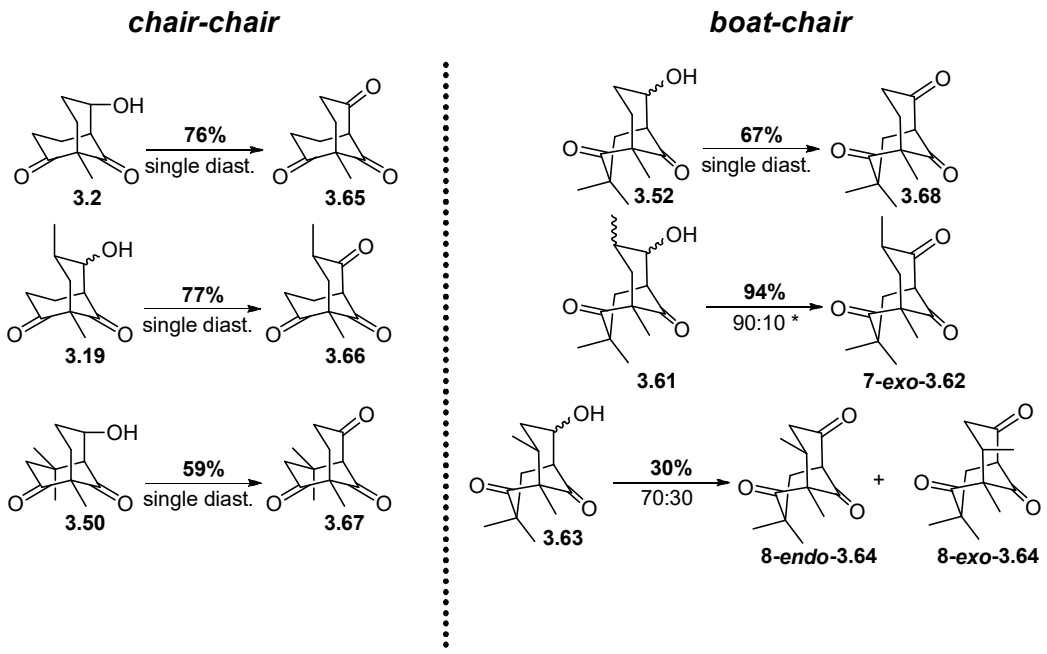
*Scheme 3.40: Michael-aldol annulation for the synthesis of **3.61**, oxidation to **3.62** and observation of an unusual boat-chair conformation.*

At this point we wanted to test whether the placement of other substitutents in different position of the scaffold would exert this same conformational effect; **3.51** was thus reacted with crotonaldehyde under the same reaction conditions giving a complex mixture of four diastereoisomers (Scheme 3.41). Despite the complex spectrum, the fact that the chemical shift for the major diastereoisomer peak was comparable with previously assigned *exo*-isomers (4.25 ppm), the identification of a coupling constant of 4.3 Hz and the absence of any *trans*-diaxial coupling, suggested that also in this case the major isomer possessed an *exo*-configuration (at carbon 6). The mixture was then readily oxidized yielding approximately a 70:30 mixture of 8-*endo*-**3.64**:8-*exo*-**3.64**. 8-H was assigned *via* COSY and HMQC but being a complex multiplet no *J* could be deduced from it; however, 7-Hax, assigned as a doublet of doublet, showed a big coupling constant of 15.5 Hz with 8-Hax, suggesting a *trans*-diaxial interaction and establishing that 8-CH_3 was equatorial. Moreover, the multiplicity observed for the peak at 3.71 ppm, assigned to the bridgehead H-5, is a doublet of triplets, as expected given the presence of the W-coupling from 5-CH to 7-CHeq; this is in contrast to 7-*exo*-**3.61**, where the 7-Me group is present, in which the peak for H-5 (found at 3.69 ppm) is only a doublet of doublet because no W-coupling is possible.



*Scheme 3.41: Michael-aldol annulation for the synthesis of ketols **3.63** and subsequent oxidation reactions.*

The same oxidation reactions were also performed on all the previous ketol derivatives with very good results, as summarized on scheme 3.42.



*Scheme 3.42: Left: chair-chair triketone derivatives, Right: boat-chair triketone derivatives synthesised. *On standing for 2 weeks 7-exo-**3.62** was converted into a single diastereomer.*

With a series of triketone derivatives in hand, computational experiments using the Schrödinger software package were performed on all the triketones containing the *gem*-dimethyl group at C-3 as well as the annulation product **3.52**. Minimization and conformational analyses using the OPLS3 force field showed that the boat-chair was always the more stable conformation adopted (Table 3.43). The values are energy penalties from the zero value (which indicates the most stable conformer) for adopting a less than optimum conformation. Less favourable chair-boat, twistboat–twistboat and boat–boat conformations could be detected but never the usual chair–chair conformation. The results obtained in Table 3.44 were confirmed by quantum mechanics calculations using Jaguar and the B3LYP 6-31g** hybrid functional (see Table 3.44) which gives the same lowest energy conformer as OPLS3- GB/SA.

Compound	*7-exo-* **3.62**	*8-endo-* ***3.64***	**3.68**	***endo*-3.52**	***exo*-3.52**
Boat-Chair	0	0	0	0	0
Chair-Boat	16.2	-	10.0	35.6	28.4
Twistboat-Twistboat	23.9	27.7	19.2	34.2	33.1
Boat-Boat	27.4	-	21.0	-	-
Twistboat-Twistboat2	-	-	-	41.3	-
Chair-Chair	-	-	-	-	-

- Conformation not found during conformational search

Fig.3.43: Conformational energies (kJ mol^{-1}) of C3-gem-dimethyl-bicyclo compounds (relative to boat-chair conformer).

Compound	*7-endo-* ***3.62***	*8-endo-* **3.64**	**3.68**	***endo*-3.52**	***exo*-3.52**
Boat-Chair	0	0	0	0	0
Chair-Boat	20.1	15.0‡	12.3	32.6	29.1
Twistboat-Twistboat	20.7	18.8	13.7	23.0	29.4
Boat-Boat	*	*	*	*	*
Twistboat-Twistboat2	17.1	13.4	9.7	21.4	19.2
Chair-Chair	-	-	-	-	-

* Conformation minimized to Twistboat-Twistboat2, ‡ Conformation minimized to Twistchair-Twistboat

Fig.3.44: Gas-phase conformational energies (kJ mol^{-1}) of C3-gem-dimethyl-bicyclo compounds (relative to boat-chair conformer).
*The assistance of Dr. Anders Poulsen (Experimental Therapeutic Centre (ETC), A*STAR, Singapore in performing computational calculations is gratefully acknowledged.*

The unusual boat-chair conformation predicted by the above calculations was confirmed by a single crystal X-ray structure of 7-*endo*-**3.62**. The commonplace chair-chair conformation is excluded because of the severe non-bonding interactions that would arise between the C-3 axial methyl group with the 7-methylene unit. Additionally, the bridging carbonyl group (as distinct from an sp^3 carbon atom) is able to accommodate a boat structure, the ring containing the *gem*-dimethyl group not suffering any significant flagpole interactions (Fig. 3.45). In cases where such a non-bonding interaction is absent, as for triones **3.65**, **3.66** and **3.67**, the usual chair-chair conformation for saturated, substituted bicyclo[3.3.1]nonanes is preferred (Scheme 3.42).

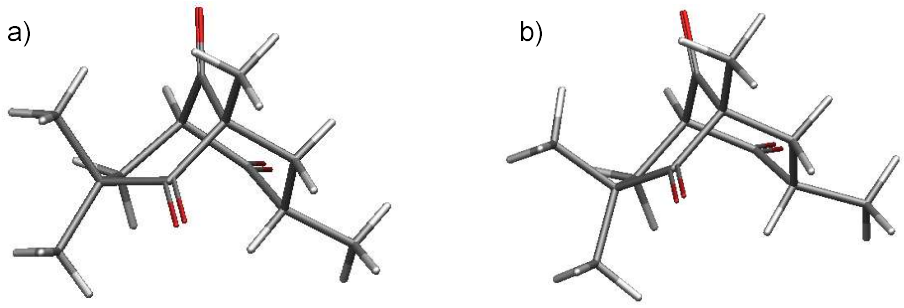
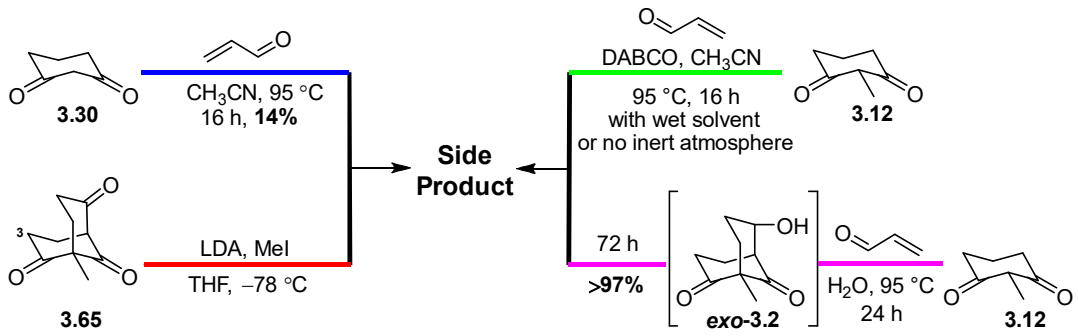


*Fig. 3.45: a) X-ray crystal structure of trione 7-exo-**3.62**, b) representation of the lowest energy conformer obtained by using OPLS3-GB/SA force field.*

3.6 Additional Reactions

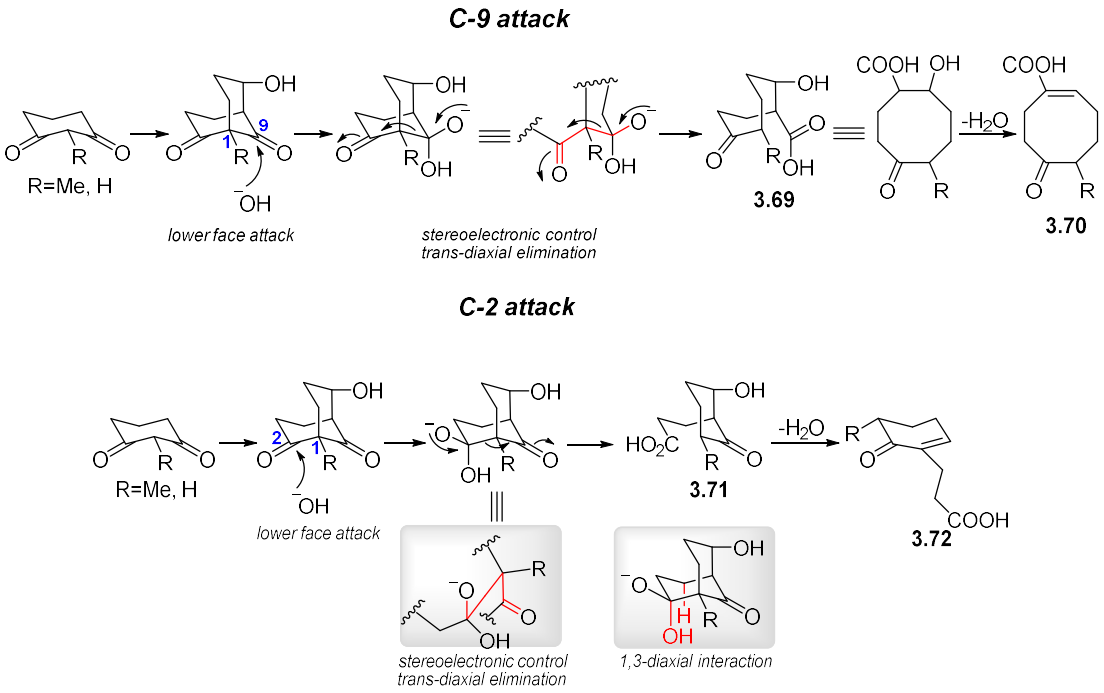
3.6.1 Formation of enone derivatives

While investigating the Michael-aldol annulation, a side product was observed at the expense of the bicyclo ketol, particularly when the reaction solvent was not dry, or without an inert atmosphere. This compound was also detected when 1,3-cyclohexanedione **3.30** was used instead of the 2-methyl derivative (Scheme 3.46, blue) and during attempted methylation of the 3-position (Scheme 3.46, red) but it was obtained exclusively and isolated in near-quantitative yield when the reaction was heated in water (Scheme 3.46, magenta).



Scheme 3.46: Highlight of a few reactions leading to a common side product.

The product displayed both a carboxylic acid and a ketone function, as shown by the ^{13}C NMR (202.0 ppm and 177.9 ppm) and by the IR spectrum (1600 cm^{-1}). It could only have been formed by attack either at the bridge carbonyl group (C-9) giving cycloctanone of type **3.70,** or at the C-3 carbonyl group, leading to cyclohexenone of type **3.72** (Scheme 3.47); however, which reverse Claisen reaction had occurred was not clear. Dehydration was observed which might be expected in the six-membered ring, rather than the more conformationally flexible eight-membered ring.



Scheme 3.47: Mechanistic hypothesis for the formation of the carboxylic acid product observed.

Selected ^{13}C chemical shift data[26, 122] were then collected which showed that the ketone signal at 202.0 ppm was in agreement with other related cyclohexenone derivatives, but did not fit with cycloctanone related structures (Fig. 3.48).

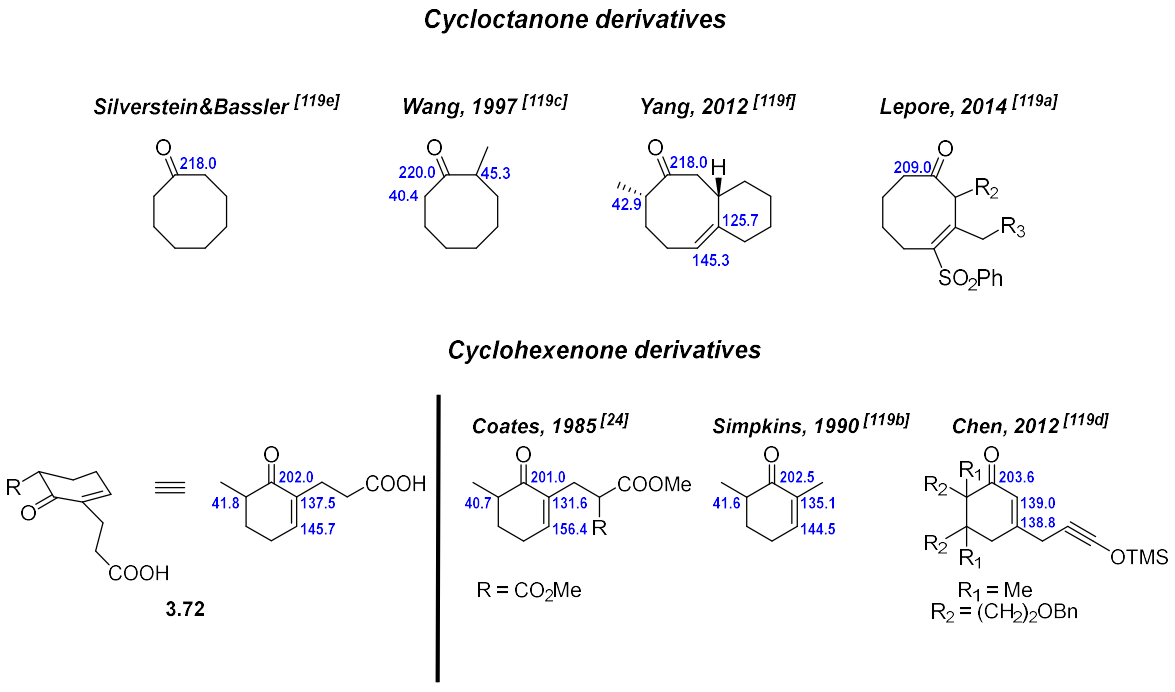


Fig. 3.48: A few reported literature values for the chemical shift of cycloctanone and cyclohexanone derivatives.[26, 122]

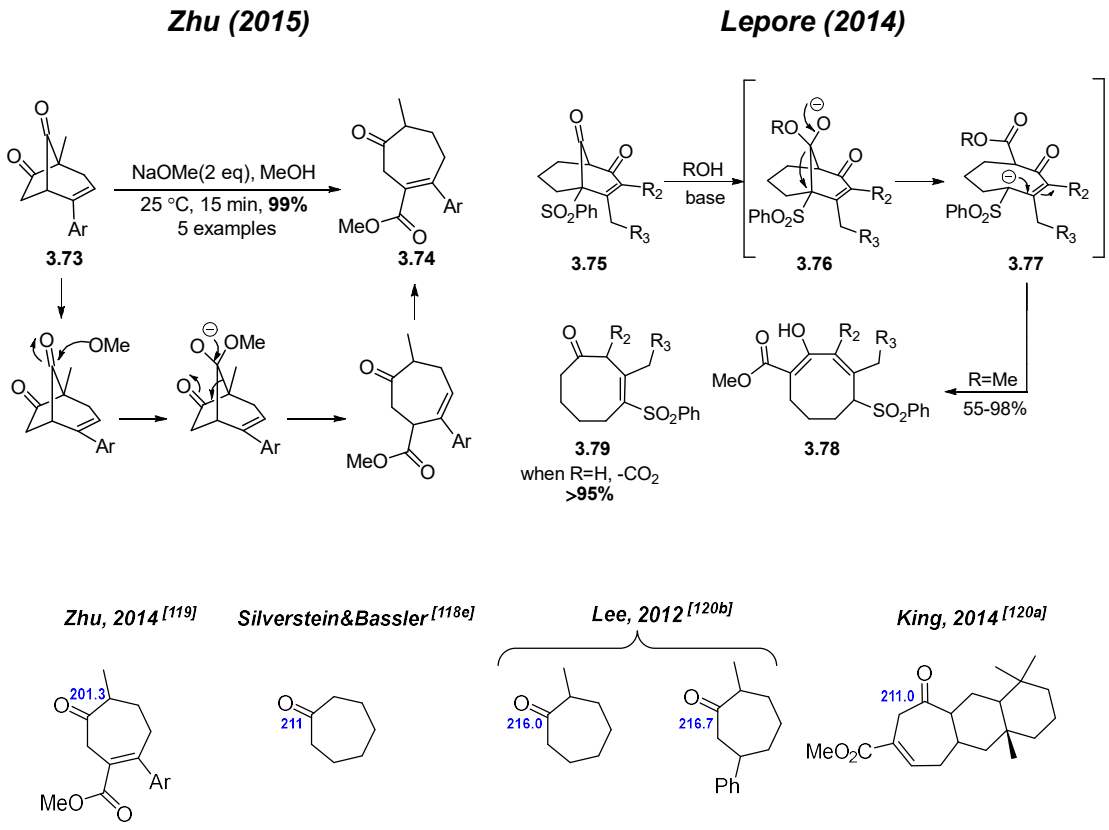
The above tentative assignment was unambiguosly confirmed by HMBC analysis of **3.72** which showed no correlation between the olefinic proton and the carboxylic acid signal whose shift is instead correlated with the linear side chain, confirming the formation of cyclohexenone **3.72** over cycloctanone **3.70**.

There are examples of attack on bicyclo[3.3.1]octane-2,9-diones by oxygen nucleophiles in the literature. Initially, it was thought that the cycloctanone derivative **3.70** might have been formed, on the basis that the bridging carbonyl group could have been more prone to nucleophilic attack than the carbonyl at position-2. This reasoning was used to account for a 7-membered ring being formed as a result of a metal/proton-catalyzed Conia–ene reaction, as recently reported by Zhu.[123] However, while 1,2-addition at the 9-CO group could be faster, because more angle strain is relieved, the major consideration may be the relief of diaxial interactions during the fragmentation. As previously shown on scheme 3.47, both reverse Claisen processes go through stereoelectronically favoured *trans*-diaxial eliminations, but the breaking of the 1,2-bond, as shown in Scheme 3.47, removes the severe 1,2-/4,5-diaxial interaction, providing a driving force that is not present in case of C-9 attack because the breaking 1,9-bond is not in a 1,3-diaxial configuration. Additionally, the H/OH being 1,3-diaxial might render the attack at C-2 even slower than at C-9 (Scheme 3.47).

While the above is only a partial analysis, it led us to reconsider the literature data. As mentioned above, Zhu recently reported the formation of differently substituted cycloheptanones derivatives arising from nucleophilic attack on the bridged carbonyl group of bicyclo[3.2.1] **3.73**, which led, after ring opening and isomerization, to the more stable unsaturated methyl ester **3.74** (Scheme 3.49).[123]
Given the higher chemical shift value for the ketone 7-membered ring reported in the literature (Fig. 3.48), the value of 201.3 ppm reported by Zhu was not consistent. He suggested that bicyclo[3.2.1]octanes possess a higher ring strain and therefore are more prone to ring-open at the bridgehead position; however, this line of reasoning was simply adopted from an earlier paper [57] in which no further literature reference or justification was given. Overall, few comments and little analysis of such reverse Claisen reactions in bicyclo systems, especially bicyclo[3.3.1]octanediones, have been given.

Noteworthy is the recent report by Lepore who documented a Grob-type fragmentation of bicyclo[3.3.1]nonane of type **3.75** to give highly functionalized 8 and 9-membered rings.[122a] Attack of the nucleophile on the carbonyl bridge gives a tetrahedral intermediate **3.76**;

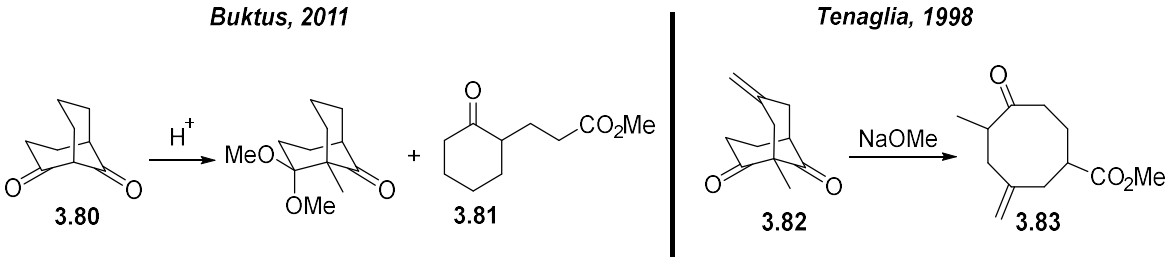
subsequent breaking of the C2-C9 bond forms carbanion **3.77**, which is stabilised by the sulfone group and rapidly protonates to give the desired monocyclic products **3.78** and **3.79**, notable for the keto groups being at 209.0 ppm (as depicted in Fig. 3.48). However, the presence of the sulfone group is a special case, enabling anion stabilisation, so conclusions concerning bicyclo[3.2.1]octanediones and/or bicyclo[3.3.1]octanediones cannot readily be drawn from this study. Interestingly, when the reaction is run in the presence of TBAF·3H_2O instead of methanol, decarboxylation is followed by a double bond shift to give the more stable, conjugated vinyl sulfone **3.79** (Scheme 3.49).



Scheme 3.49: Zhu's and Lepore's approaches to diversely substituted cycloalkanones and a few reported literature values for cycloheptanone derivatives.[118a, 118e, 119,124]

To our knowledge, there is no precedent for bicyclo[3.2.1]octane ring-opening. However, for bicyclo[3.3.1]nonane, a reliable account by Butkus describes the acid-mediated ring opening of bicyclo of type **3.80** leading to cyclohexanone of type **3.81**.[125] Perhaps the only precedent for a bridgehead nucleophilic attack on bicyclo of type **3.82** is that of Tenaglia[57] but no ^{13}C NMR data were given in support of the structure of cycloctanone **3.83** (Scheme 3.50). These weak precedents together with our detailed NMR analysis suggest that a deeper investigation of the ring opening of bicyclo[3.3.1]nonanes and [3.2.1]octanes would be

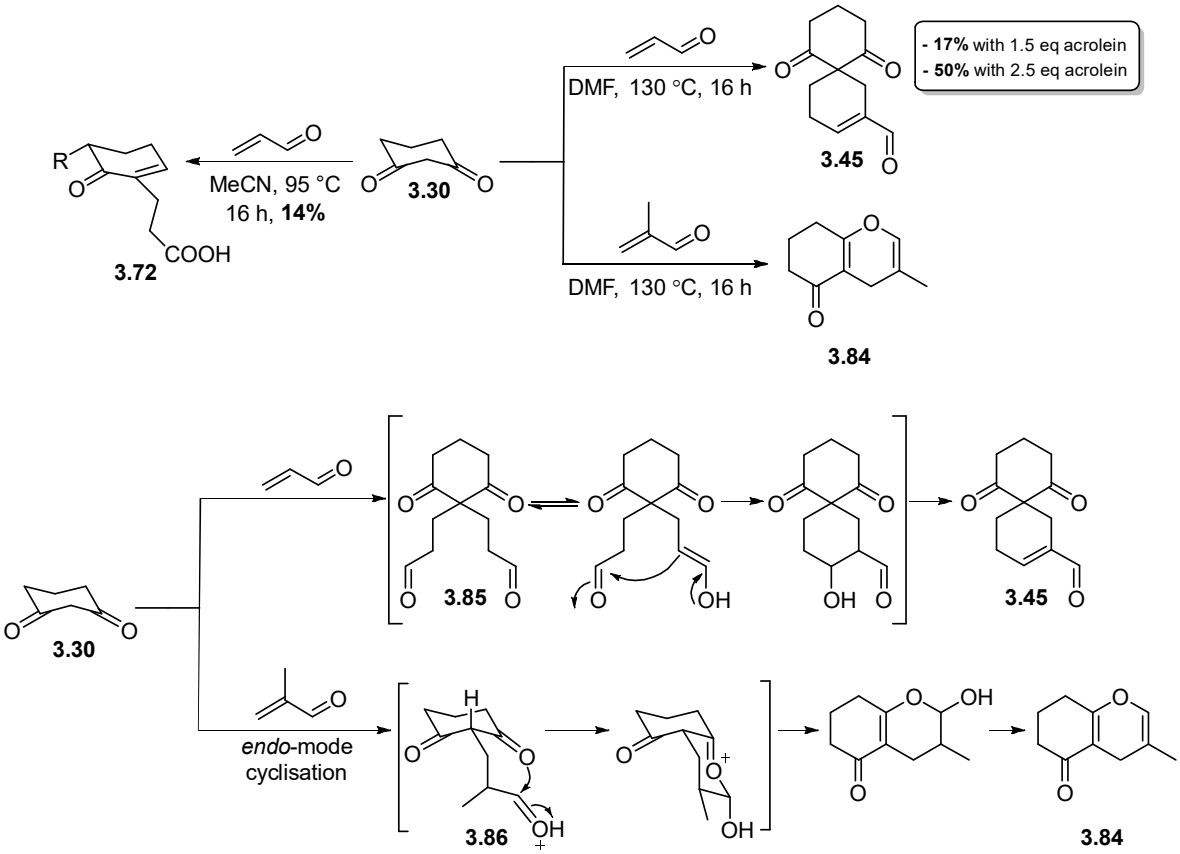
desirable.



Scheme 3.50: Butkus' and Tenaglia's reports on bicyclo[3.3.1]nonane ring opening.[57, 125]

3.6.2 Reaction of 1,3-cyclohexanedione

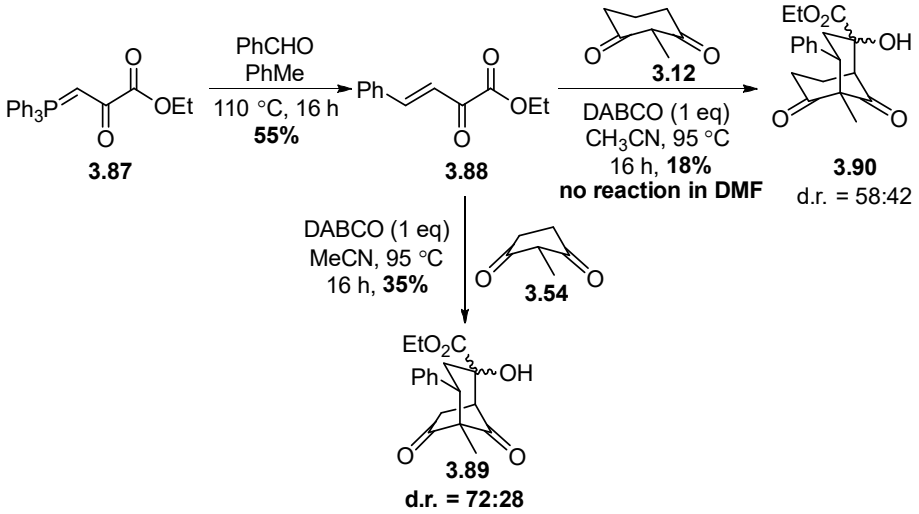
Whereas heating **3.30** with acrolein in acetonitrile afforded cyclohexenone derivative **3.72** as depicted in scheme 3.51, heating at 130 °C using DMF as solvent led to spiro compound **3.45** when acrolein was used as electrophile and to fused bicyclic compound **3.84** when methacrolein was used instead. This set of results can be rationalized by the absence of the methyl group at the 2-position (Scheme 3.51). The alkyl chain added during the Michael reaction of a 2-substituted cycloalkane-1,3-dione adopts an axial position about 50% of the time (leading to the bicyclo ketols) in contrast to a > 95% adopting the equatorial position when position 2 is not further substituted, the axial hydrogen having only small 1,3-diaxial interactions compared to a methyl or a chain when axial. Since an equatorial mode of cyclisation (**3.86**) is kinetically faster than a small concentration of axial chain cyclising to the bicyclo ketol, the fused bicyclo of type **3.84** is formed. Enal formation instead is the result of axial attack to give the dialkylated derivative **3.85**. The rate of cyclisation of an aldehyde enolate is faster than a ketone enolate as it lacks the inductively-deactivating effect of a second alkyl group attached to the C=O carbon atom so that one aldehyde group is attacked by the other aldehyde enolate to give the spiro system. Cyclisation to the desired bicyclo is possible but evidently much slower than the alternative aldol involving the aldehyde enolate. In this case, compared to when the same enal was obtained from reaction of 2-acyl-cyclohexanedione **3.43** with acrolein, and isolated in 80% yield (paragraph 3.2.2.2, Scheme 3.26), a lower yield was observed and the efficiency of the reaction seems to be dependent on the amount of acrolein added.



Scheme 3.51: Cyclisation of cycloalkane-1,3-diones and some mechanistic rationales.

3.6.3 Construction of more stereogenic centres

In the attempt to extend the scope of the reaction to electrophiles other than unsaturated enals, the unsaturated pyruvate **3.88** was prepared by Wittig reaction of the phosphonate **3.87** with benzaldehyde. Following addition of cyclopentane-1,3-dione **3.54** and a stochiometric amount of DABCO to a stirring solution of **3.88**, a mixture of bicyclo ketols **3.89** was obtained in modest yield, the d.r. favouring the larger ester group being equatorial. However, in the reaction with 6-membered ring **3.12** the desired **3.90** could only be detected in the ^{1}H NMR to the extent of 18% conversion, traces being isolated (Scheme 3.52). Attempts to optimize the formation of the bicyclo[3.2.1]octane dione **3.89** using various combinations of base and solvents were not promising, although triethylamine increased the extent of conversion (by ^{1}H NMR spectroscopy) to 33% (Scheme 3.52). Although these highly functionalised scaffolds obtained were of interest, the poor yields could not be improved and so no further work using the pyruvate acceptors was undertaken.



Optimisation conditions: 25 °C, 7 days

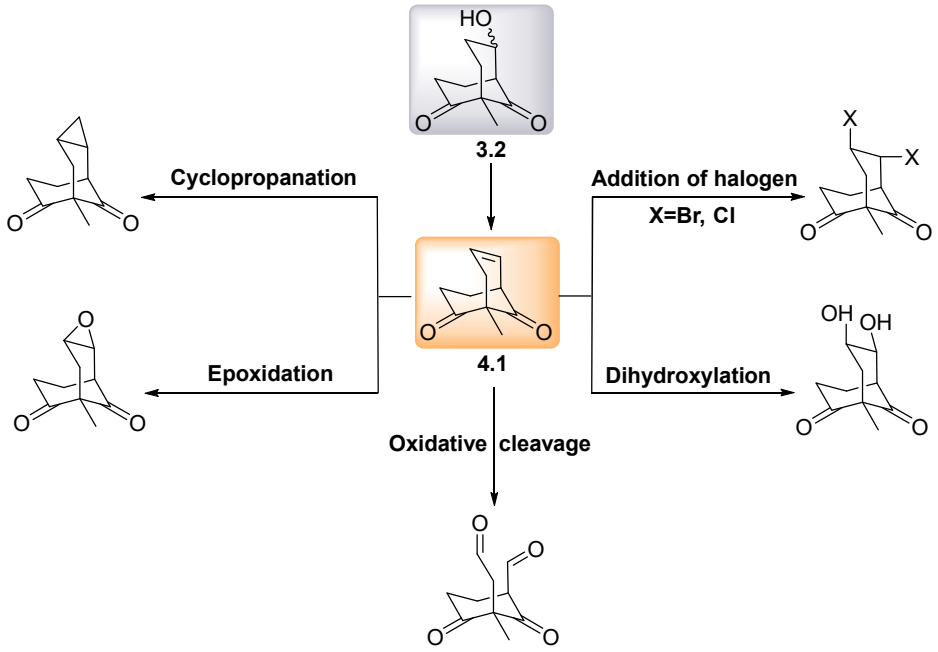
Base (20 mol%)	Outcome
CH_3CN, 95 °C	no reaction
DBU, CH_2Cl_2	Unidentified mixture
Et_3N, CH_2Cl_2	33% conversion
Quinine, CH_3CN	Unidentified mixture
TBD, CH_2Cl_2	Unidentified mixture

Scheme 3.52: Michael-aldol annulation with an unsaturated pyruvate.

CHAPTER 4: Scaffold functionalization and synthesis of new fluorinated substituted bicyclo compounds

4.1 Synthesis of alkene **4.1** and its reactions

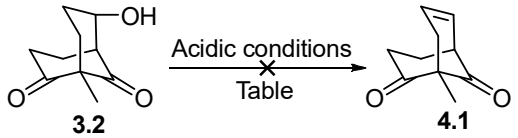
Having demonstrated the efficiency of the domino annulation to access quickly and stereoselectively bicyclo[3.3.1]nonane and [3.2.1]octane cores, their further functionalisation by halogenation was investigated. Halogens can be used in increasing diversity by displacements. Additionally, fluorinated scaffolds often show improved physicochemical properties and are often key compounds in medicinal chemistry programmes. The secondary alcohol at position-6 in bicyclo[3.3.1]nonanones, e.g. **3.2**, could in principle be dehydrated to the corresponding alkene (e.g. **4.1**) which could be transformed into a variety of functionalised derivatives, a selection of which is shown in Scheme 4.1.



*Scheme 4.1: Dehydration of the alcohol functionality in bicyclo **3.2** leads to alkene intermediate **4.1**, which can undergo a variety of different transformations.*

We therefore sought to access alkene **4.1** first to then proceed with the desired scaffold functionalization. Dehydration of the simplest bicyclo ketol **3.2** proved to be challenging, either with traditional methods or more harsh conditions. Various acid-catalysed conditions (Scheme 4.2) were unsuccessful. Polyphosphoric acid (PPA) gave some reaction, but the

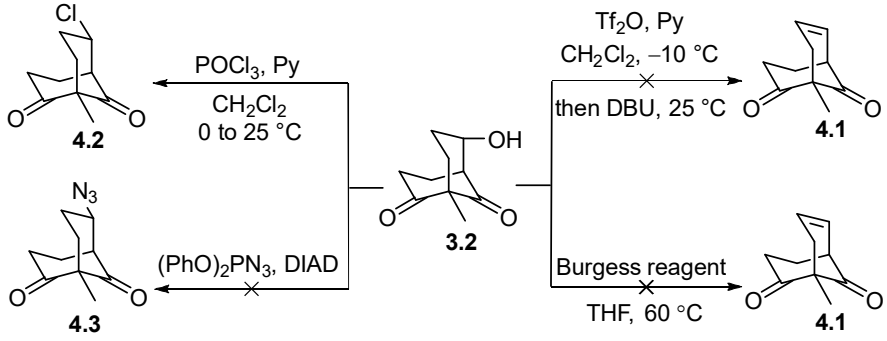
NMR spectra were inconclusive, and indicated that product(s) other than the alkene had been formed.



Conditions	Outcome
HBr, AcOH, 25 °C	No reaction
10% H_2SO_4, AcOH, 25 °C	No reaction
TsOH, 25 °C	No reaction
PPA, 70 °C	New spot, NMR inconclusive

*Scheme 4.2: Attempted dehydration of alcohol **3.2** under acidic conditions.*

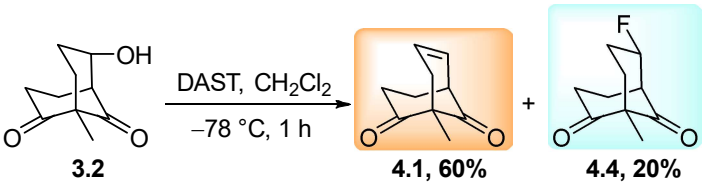
Non-acidic methods were then examined. Reaction of ketol **3.2** with phosphoryl chloride using an excess of pyridine afforded three products, of which only the chloro derivative **4.2** could be isolated and identified, although characterisation was not possible as it rapidly underwent a retro-aldol reaction followed by ring opening. Triflates are known to undergo rapid elimination in the presence of a base hence ketol **3.2** was reacted with triflic anhydride and the crude triflate subjected to dehydration with DBU; unfortunately, no elimination reaction was observed at both room and reflux temperature. Burgess' reagent, a mild and selective *N*-(triethylammoniumsulfonyl)carbamate known to work well for secondary alcohols[126] was also found to be ineffective. Lastly, a Mitsunobu reaction to install an azide (**4.3**) and hence obtain the corresponding amine by reduction, also failed (Scheme 4.3).



Scheme 4.3: Attempted dehydration and Mitsunobu reaction.

Given the above difficulties in achieving elimination of the alcohol group, this problem was temporarily put aside and other functionalisations were explored, in particular fluorination. Fluoro compounds are of paramount importance today in drug design. Some 20-25% of pharmaceuticals contain at least one fluorine atom.[127] The electronegativity and the size of

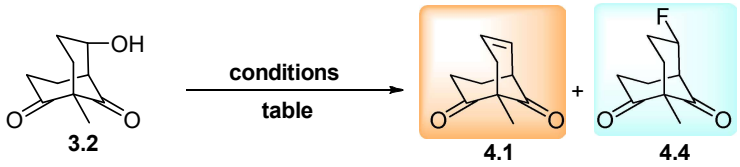
fluorine usually enhance lipophilicity and metabolic stability but fluorination can also lead to a different preferred conformation.[128] However, because of the reactivity and hazards of elemental fluorine and hydrogen fluoride, introduction of fluorine into organic molecules presents particular challenges and has led to the development of specialised fluorination technologies and reagents. Amongst them, diethylaminosulfur trifluoride (DAST), a reagent derived from sulfur tetrafluoride, is convenient to handle and quite selective, being especially useful for the conversion of alcohols into alkyl fluorides, carboxylic acids to acyl fluorides, and carbonyl compounds to *gem*-difluorides.[129] Treatment of alcohol **3.2** with DAST at –78 °C did afford the fluorinated bicyclo compound **4.4** but also a surprisingly high yield of the previously sought alkene **4.1** (Scheme 4.4).



3.2 **4.1, 60%** **4.4, 20%**

*Scheme 4.4: Reaction of bicyclo ketol **3.2** with DAST to afford alkene **4.1** and fluorinated bicyclo **4.44.***

Complete conversion of alcohol **3.2** was only observed using 5 equivalents of DAST, making this reaction hardly practical. Attempted optimisations involved using polar aprotic solvents like DMF and THF which in theory should favor S_N2 substitution over E2 elimination but in fact afforded a mixture of unidentified products. The best results were obtained in dichloromethane, however, the yield of isolated alkene was quite inconsistent and variable (Scheme 4.5).

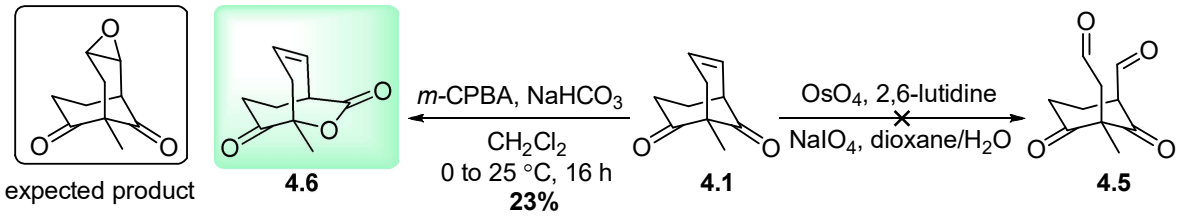


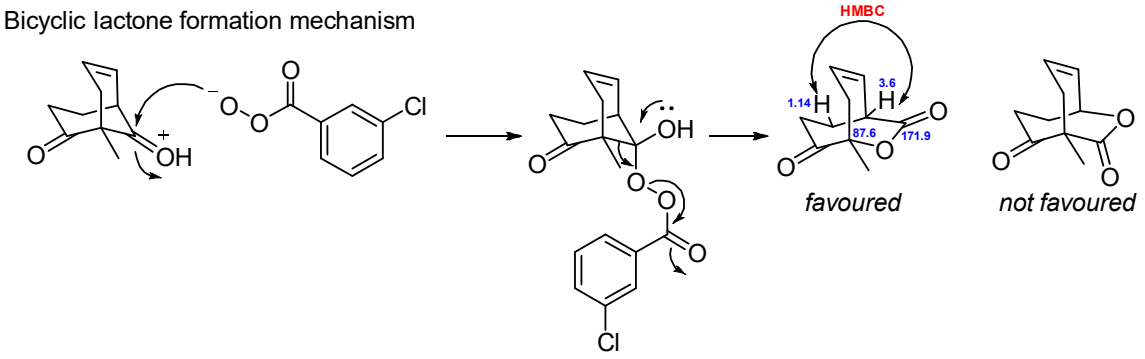
3.2 **4.1** **4.4**

Conditions	% conversion 4.1	% conversion 4.4
DAST (1.2 eq), CH_2Cl_2, –78 °C	15	16
DAST (2.5 eq), CH_2Cl_2, –78 °C	50	50
DAST (5 eq), CH_2Cl_2, –78 to 25 °C	-	-
DAST (5 eq), DMF, –78 °C	53	47
DAST (5 eq), THF, –78 °C	-	-

*Scheme 4.5: Optimization of the yield of fluoro and unsaturated bicyclo compounds **4.1** and **4.4.***

Dihydroxylation/oxidative cleavage and epoxidation were then attempted on the small amount of material prepared. An improved procedure reported by Jin[130] using 2,6-lutidine to suppress unwanted side reactions did not afford the desired dialdehyde **4.5**. Epoxidation using *m*-CPBA instead led to the formation of a new compound (single spot by TLC) which was isolated and identified as the bicyclic lactone **4.6**, arising from a Baeyer-Villiger oxidation. As expected, migration of the C1-C9 bond was favored and the structure confirmed by HMBC, which clearly correlates the carbonyl lactone signal at 171.9 ppm with both the C-H bridgehead and the CH_2 next to it. Moreover, the quaternary carbon was identified at 87.6 ppm; this high shift was considered consistent with the expected value for a carbon next to an oxygen as in **4.6**, and unlikely for a carbon placed next to a carbonyl group, as would be in the not favoured structure (Scheme 4.6). Surprisingly the desired epoxide was never detected nor could an oxidative cleavage be achieved (Scheme 4.6).





*Scheme 4.6: Attempted oxidation cleavage on alkene **4.1** and synthesis of a novel bicyclic lactone **4.6**.*

4.2 Selective fluorination and further scaffold functionalization

As an alternative to the nucleophilic fluorine source DAST, the electrophilic Selectfluor was considered because of its ability to fluorinate silyl enol ethers.[131] For their formation, triketone **3.62** and **3.68** were immediately considered. Indeed, stereocontrol by approach on the face opposite the hindered *gem*-dimethyl ring could have been expected and bridgehead protons are notoriously hard to abstract[132] leading, in theory, to the formation of only one silyl enol ether (Fig. 4.7).

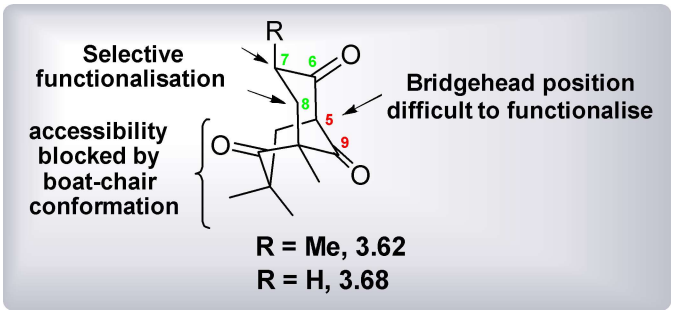
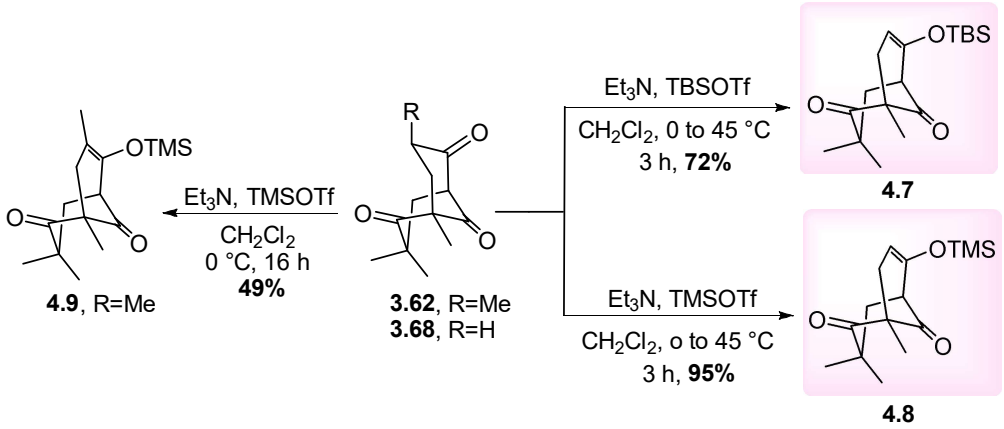


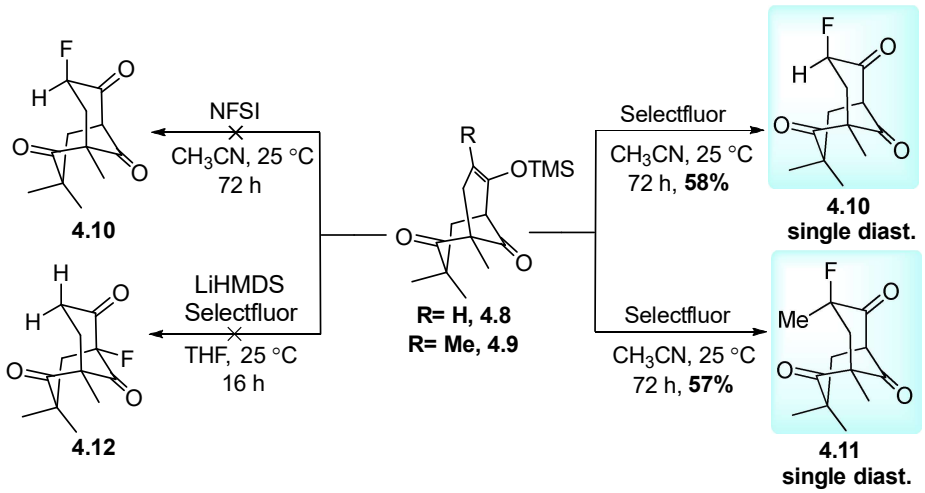
*Fig. 4.7: Rationale for the selective functionalisation of triketones **3.62 and 3.68.***

Addition of 3.6 eq of Et_3N at 0 °C to a stirring solution of trione **3.68** in dry dichloromethane followed by quenching after 5 minutes with either TMS or TBS triflate cleanly afforded **4.7** and **4.8** (Scheme 4.8). For derivatives **4.7** and **4.8**, with no 7-substituent, the yields were higher (72% for the TBS derivative and 95% for the TMS derivative) whereas the yield of derivative **4.9**, obtained from reaction of trione **3.62**, was lower (49%).



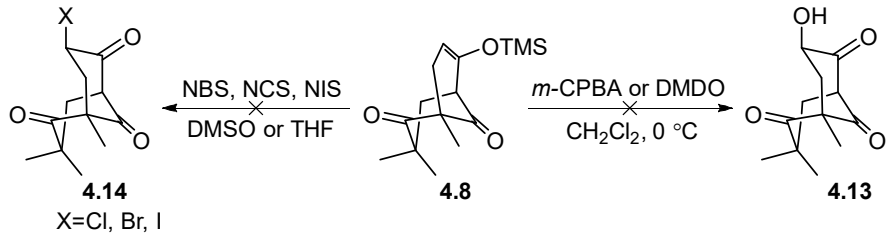
*Scheme 4.8: Synthesis of the TBS and TMS silyl enol ethers derived from triketones **3.62** and **3.68**.*

Reaction of both TMS derivatives **4.8** and **4.9** with Selectfluor afforded the expected fluoro compounds **4.10** and **4.11** in 57% and 58% yield respectively, and both as single diastereoisomers (Scheme 4.9). Analysis of the coupling constants revealed that the fluorine atom was placed on the axial position; the *J* value of 12.4 Hz for one of the H-7 coupling constants conclusively established a *trans*-diaxial interaction of H-7 with H-8ax, which was confirmed by the value of *J* = 7.6 Hz for H-7 (axial) with equatorial H-8. Interestingly, the use of NFSI did not lead to **4.10**, nor could the bridgehead hydrogen atom be removed to give **4.12** with a strong base such as LiHMDS (Scheme 4.9).



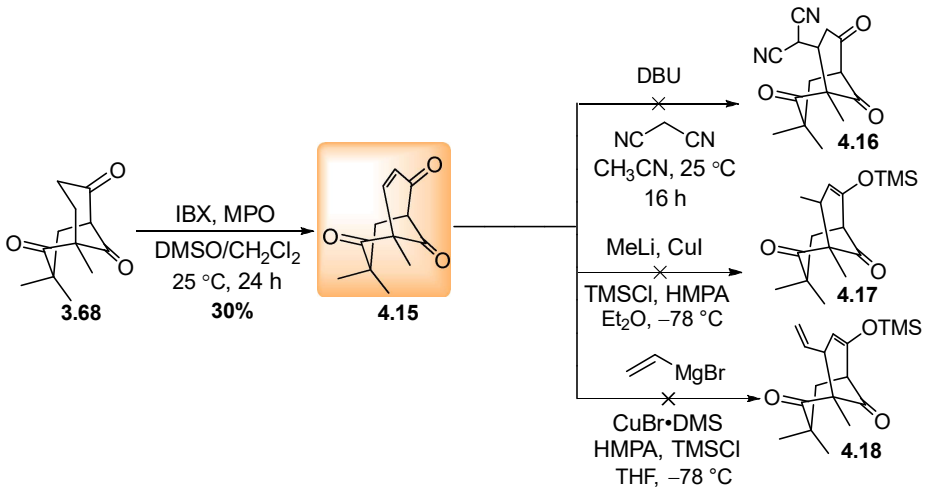
*Scheme 4.9: Synthesis of fluorinated bicyclo compounds **4.10** and **4.11.***

Having successfully introduced the fluoro functionality into the scaffold *via* silyl enol ethers, it was hoped to introduce other halogen atoms and to achieve oxidations. However, reaction of **4.8** with *N*-bromosuccinimide or peroxidants (Rubottom oxidation) did not lead to the desired functionalised products (Scheme 4.10).



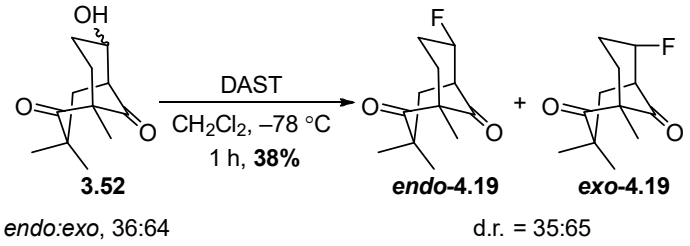
*Scheme 4.10: Attempted Rubottom oxidation and halogenation of TMS-silyl enol ether **4.8**.*

Formal dehydrogenation of trione **3.68** to enone **4.15** could be a powerful way of functionalising position 8 by means of Michael additions. IBX oxidation afforded enone **4.15** in modest yield, which however was found to be unreactive towards all the standard Michael additions attempted (Scheme 4.11). In order to improve the yield of the oxidation step, Saegusa oxidation of silyl enol ether **4.8** was also tried, but without success (not shown).



*Scheme 4.11: Preparation of enone **4.15** and attempted Michael addition.*

Analogous to ketol **3.2**, the epimeric mixture of ketols **3.52** also underwent fluorodehydroxylation upon treatment with DAST at –78 °C to give *exo*- and *endo*-**4.19** in 38% yield (Scheme 4.12).



*Scheme 4.12: Fluorodehydroxylation of the mixture of ketols **3.52** to give fluoro derivatives **4.19**.*

Triketone **3.67** had been selected as the first compound to be studied for functionalisation because of the *gem*-dimethyl group blocking the reaction at position-3, thereby simplifying the number of potential products. Having established several efficient functionalisation reactions, it proved timely to investigate the transformation of trione **3.65**, for which reaction at position-3 was an additional possibility. The relatively accessible chair-chair conformation gave the possibility of functionalisation at positions-3 and -7, and, via additions to the corresponding enone, also at positions-4 and -8 (Fig. 4.13). Moreover, Michael addition on **4.15** could have been difficult due to the particular boat-chair conformation, a difficulty that might not apply to **3.65**.

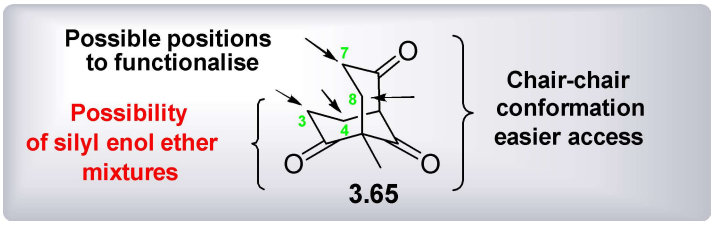
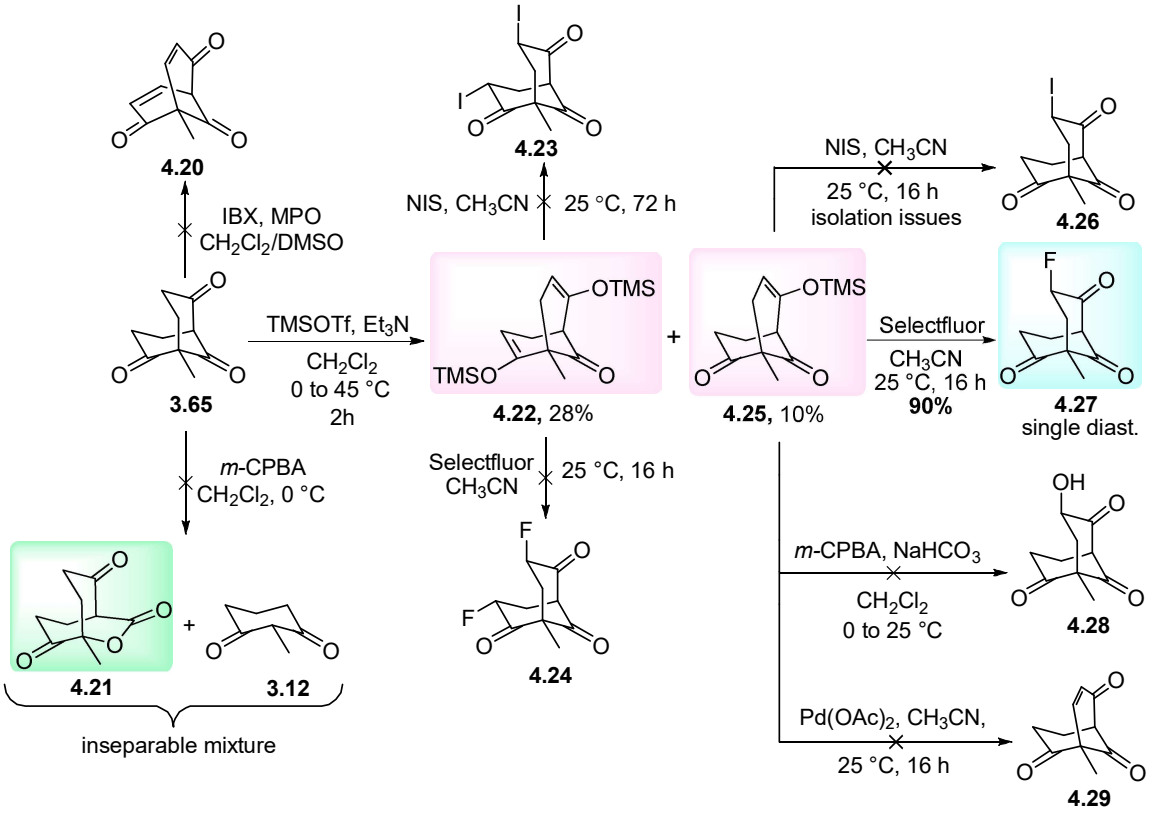


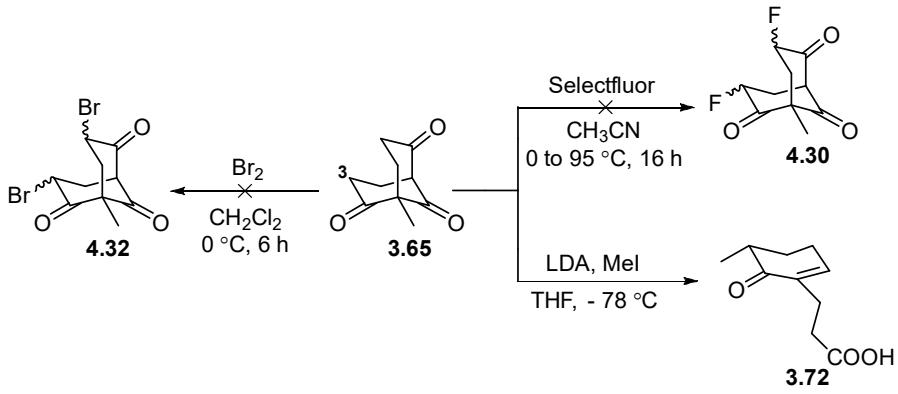
*Fig.4.13: Rationale for the functionalization of bicyclo **3.65.***

Most of the reactions performed on scaffold **3.65** are shown in scheme 4.14. A mixture of the bis (**4.22**) and mono (**4.25**) silyl enol ethers was formed; separation by column chromatography afforded both derivatives in low yield but sufficient mass recovery to proceed with the desired subsequent transformations. Dihalogenation of the bis-silyl enol ether was not possible, and reaction with either Selectfluor or NIS led to complex mixtures of unidentified products. However, fluorination of the mono silyl enol ether **4.25** gave the fluorinated 7β-fluorotrione **4.27** as a single diastereoisomer in 90% yield. The mono iodinated product **4.26**, arising from reaction with NIS, was identified in the crude ^{1}H NMR spectrum but it could not be isolated pure. Rubottom and/or Saegusa oxidation were likewise unsuccessful. Whereas oxidation of triketone **3.68** with IBX had afforded the corresponding enone, the desired **4.20** could not be obtained using the same procedure. Treatment of **3.65** with *m*-CPBA gave bicyclic lactone **4.21** through Baeyer-Villiger oxidation, although it could not be separated by column chromatography from the 2-methyl-1,3-cyclohexanedione starting material (Scheme 4.14).



*Scheme 4.14: Summary of the halogenation and oxidation reactions attempted on triketone **3.65.***

Fluorination and bromination were also tried on triketone **3.65** without success. Interestingly, in an early attempt to add a 3-methyl group to the scaffold, the use of the strong base LDA afforded cyclohexenone **3.72**, which was also obtained from other reactions as highlighted on Scheme 3.47 in paragraph 3.6.1 (Scheme 4.15).



Scheme 4.15: Initial attempts to synthesise α-halogenated and methylated ketones.

With the introduction of fluorine at position-7 in both the chair-chair and boat-chair conformers, our attention was turned to the functionalisation of the 3- and 4-positions. One

way to achieve selectivity was to block the 7-β-position; scaffold **3.66**, previously prepared in 77% yield, was used to test our hypothesis (Fig. 4.16).

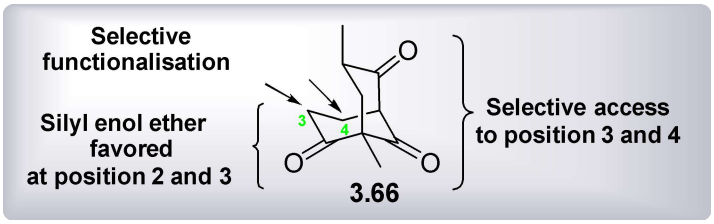
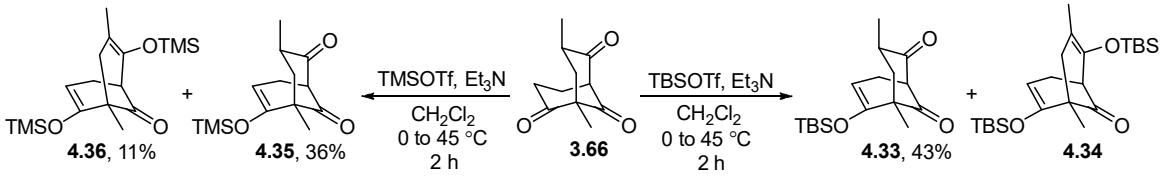


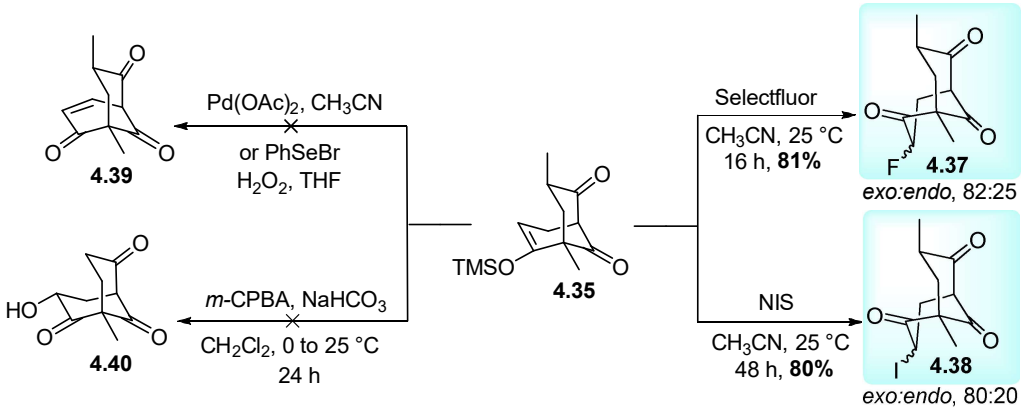
Fig. 4.16: Strategy for the selective access to positions-3 and -4 of the bicyclic scaffold.

Silylation was unselective, as small amount of the disilyl-derivatives **4.34** and **4.36** were obtained. TBS derivative **4.33** was obtained in higher yields (43% c.w. 36% of the TMS derivative) although it did not react with the chosen electrophiles (Selectfluor and NIS) thus **4.35** was used instead (Scheme 4.17).



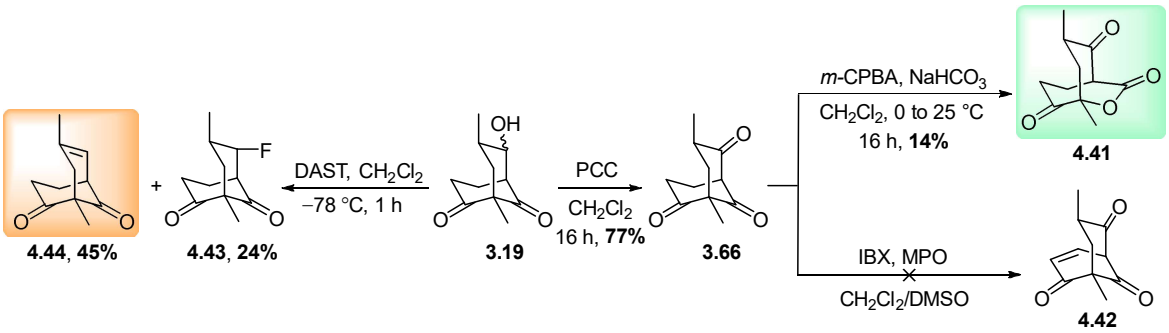
*Scheme 4.17: Silylation of triketone **3.66.***

Reaction of silyl enol ether **4.35** with selectfluor gave a mixture of the 3-fluoro epimers **4.37** in 81% yield, the major isomer having fluorine in axial position. To our delight, reaction with NIS afforded iodo-derivative **4.38** and in excellent yield. Unfortunately, neither a Rubottom reaction, nor a Saegusa oxidation, nor reaction of triketone **3.66** with IBX (not shown) gave the respective desired products (Scheme 4.18).



Scheme 4.18: Preparation of a 3-fluoro- and a 3-iodo-bicyclo compound, and their attempted transformations.

As we were intrigued by the formation of bicyclic lactone **4.6** and **4.21** previously formed, triketone **3.66** was reacted with *m*-CPBA; indeed, the desired complex lactone **4.41** was obtained but in low yield. A brief attempt at optimization was made (not shown) using other peroxides (*t*-BuOOH) and oxidants (Oxone) or with the aid of Lewis acids (BF_3•Et_2O) but it gave no improvements. Through reaction of ketol **3.19** with DAST in dichloromethane at –78 °C alkene **4.44** and the 6-β-fluoro derivative **4.43** were additionally obtained (Scheme 4.19).



*Scheme 4.19: Synthesis of bicyclic lactone **4.41** and fluorinated and unsaturated derivatives **4.43** and **4.44.***

Lastly, functionalisation of dimedone derivative **3.67** attracted our attention in the same way as the boat-chair conformer did, for the possibility of selective functionalisation at the 8-position via conjugate addition to the corresponding enone. (Fig. 4.20).

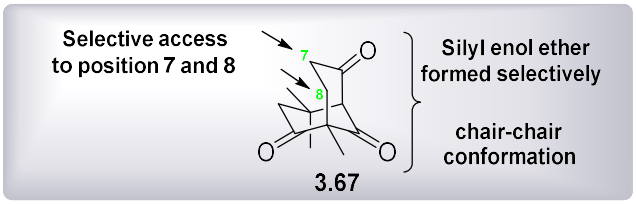
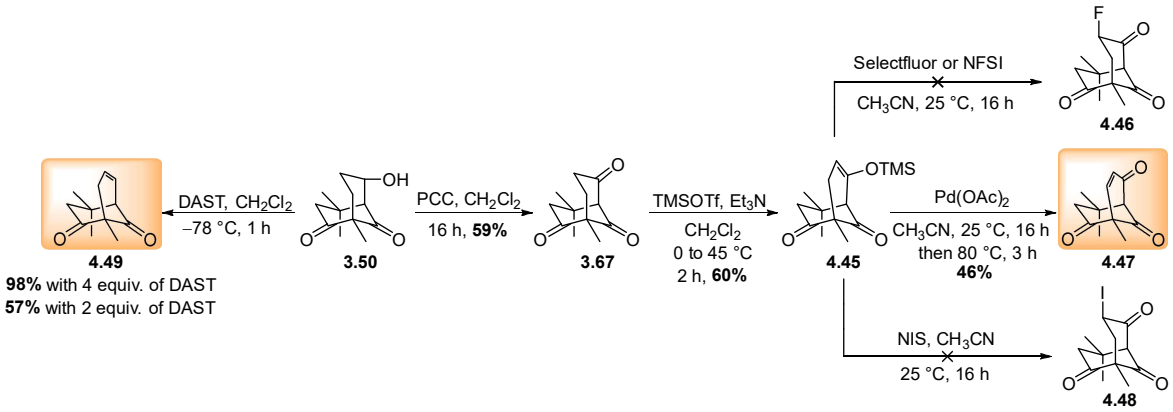


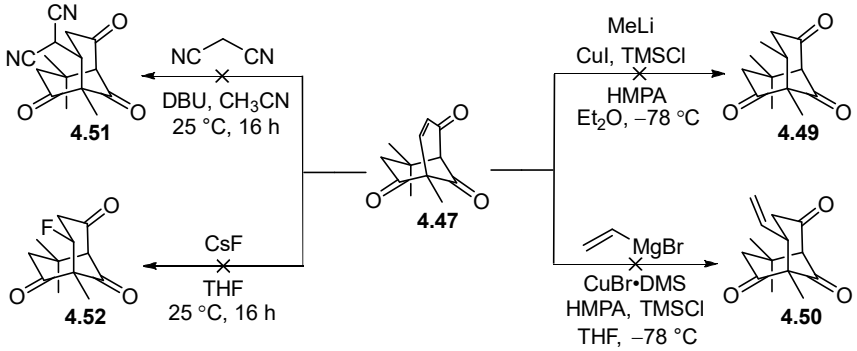
*Fig. 4.20: Strategy for the C-7 and C-8 functionalization of scaffold **3.67***

Unlike all other scaffolds investigated, reaction of bicyclo ketol **3.50** with DAST afforded no fluorination products, but instead alkene **4.49** in nearly quantitative yield, nor did iodination occurred with NIS. Silyl enol ether derivative **4.45** was obtained from trione **3.67** in 60% but no reaction was observed when reacted with either Selectfluor or NFSI. In contrast, Saegusa oxidation applied to the silyl enol ether **4.45** afforded enone **4.47** in 46% yield (Scheme 4.21).



*Scheme 4.21: Attempted fluorination of silyl enol ether **4.45** and synthesis of enone **4.47** and alkene **4.49.***

The same conjugate addition reactions previously attempted on the boat-chair enone **4.15** were applied to enone **4.47** but unfortunately here also no reactions occurred (Scheme 4.22)



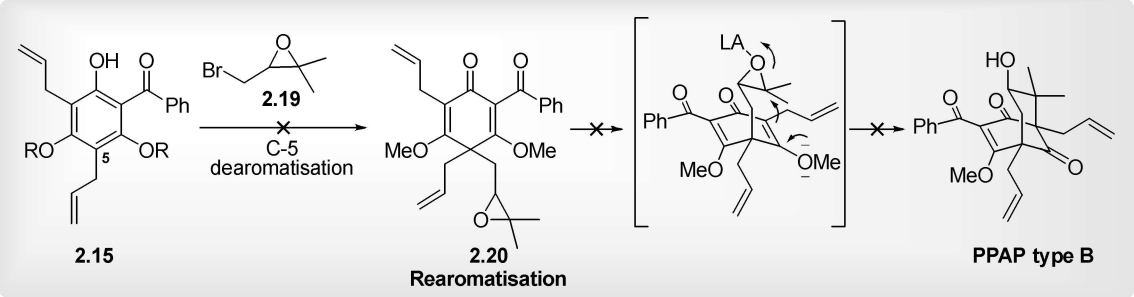
*Scheme 4.22: Attempted conjugate addition reactions on enone **4.47.***

4.3 Conclusions, summary and future work

The aim of this project was to develop new synthetic methodologies towards the synthesis of nearly saturated bicyclic compounds. The construction of architecturally complex caged sp^3-enriched molecules is synthetically challenging and new methods are needed in order to access these promising scaffolds and explore new regions of chemical space.

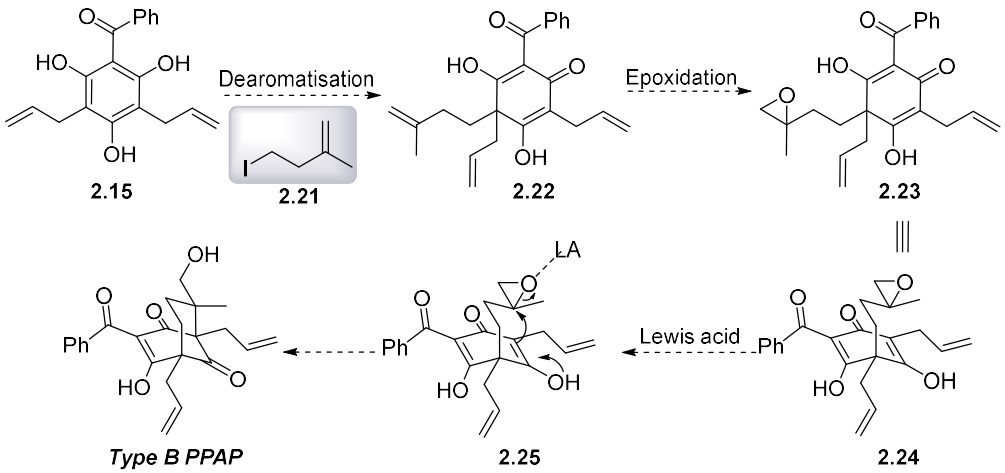
Our interest initially fell on a specific class of molecules, the polycyclic polyprenylated acylphloroglucinols (PPAPs) because of their remarkable range of biological activity. Although other groups have recently made considerable progress in their synthesis, difficulties remain in the efficient construction of such highly congested scaffolds, which

require densely prenylated bicyclo[3.3.1]nonanes. The first approach towards a new synthetic route for the construction of the PPAP core was based on the dearomatisation of a phloroglucinol with an epoxide moiety, in the hope of triggering a ring-opening reaction to give the [3.3.1] bicyclic skeleton. This strategy, as shown on chapter 2 (Scheme 2.11) faced many difficulties due to the challenge of the dearomatisation step and the tendency of the C-alkylated precursor **2.20** to undergo rearomatisation (Scheme 4.30).



Scheme 4.30: Difficulties encountered in the epoxide-mediated dearomatisation-cyclisation of phloroglucinols derivatives

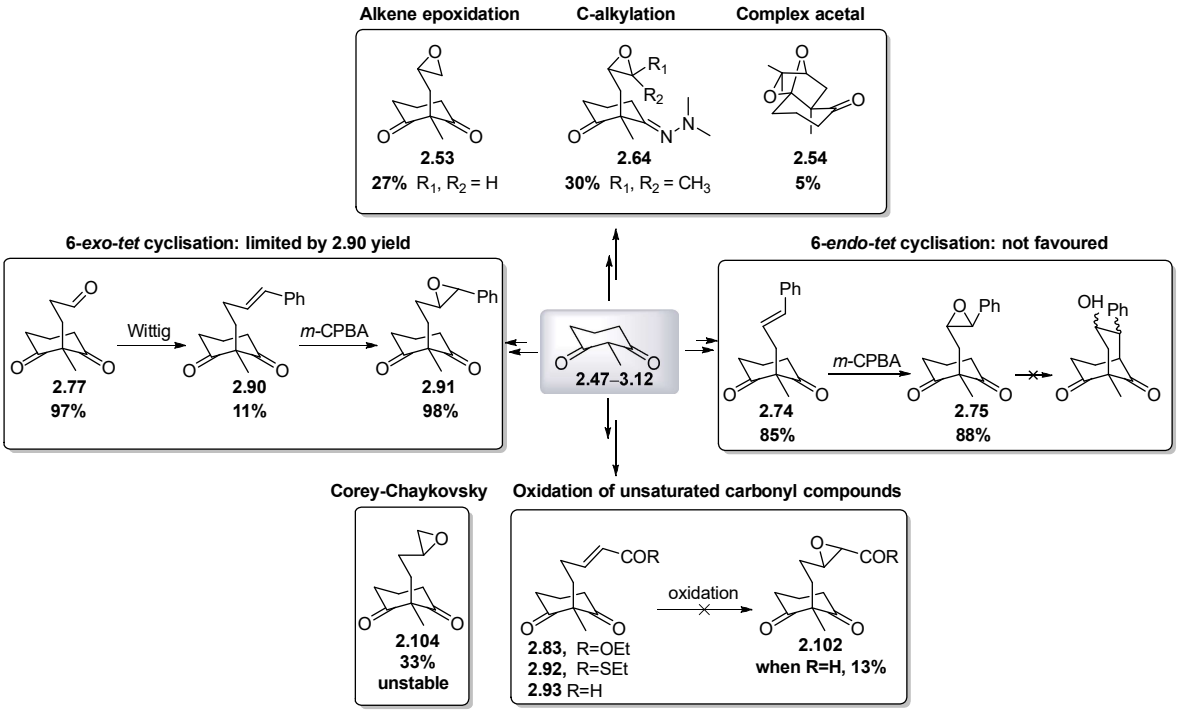
A possible alternative was depicted on Chapter 2 (Scheme 2.12) and could be represented by the use of iodo derivative **2.21**, which was used successfully by George[85] for the dearomatisation of our same substrate **2.15**. If the dearomatised precursor **2.22** could be obtained, and a chemoselective epoxidation of the most electron-rich, terminal olefin achieved, then a subsequent cyclisation of epoxide **2.24** would give access to the type B PPAP core (Scheme 4.31).



Scheme 4.31: Proposed alternative pathway towards the synthesis of PPAP-like bicyclic compounds.

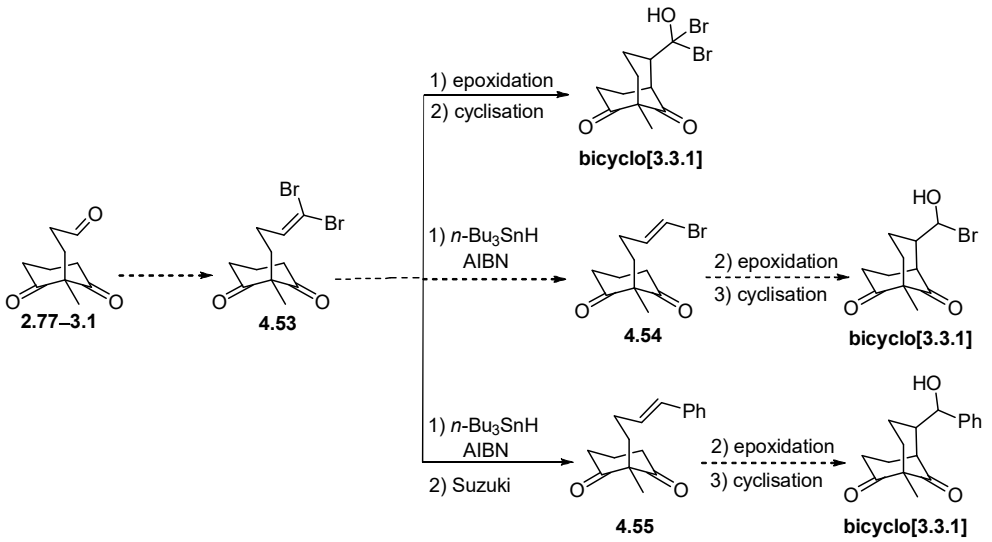
The second strategy pursued was intended to use the same epoxide functionality for the desymmetrisation of more readily available 1,3-diketone dihydroresorcinol derivatives **2.47**-

3.12. Scheme 4.32 summarizes the pathways explored and highlights the alkene and epoxides intermediates synthesised, although an epoxide-mediated ring closure to the desired [3.3.1] bicyclic scaffold was never achieved.



*Scheme 4.32: Summary of epoxide intermediates obtained from 2-methylcyclohexane-1,3-dione **3.12**.*

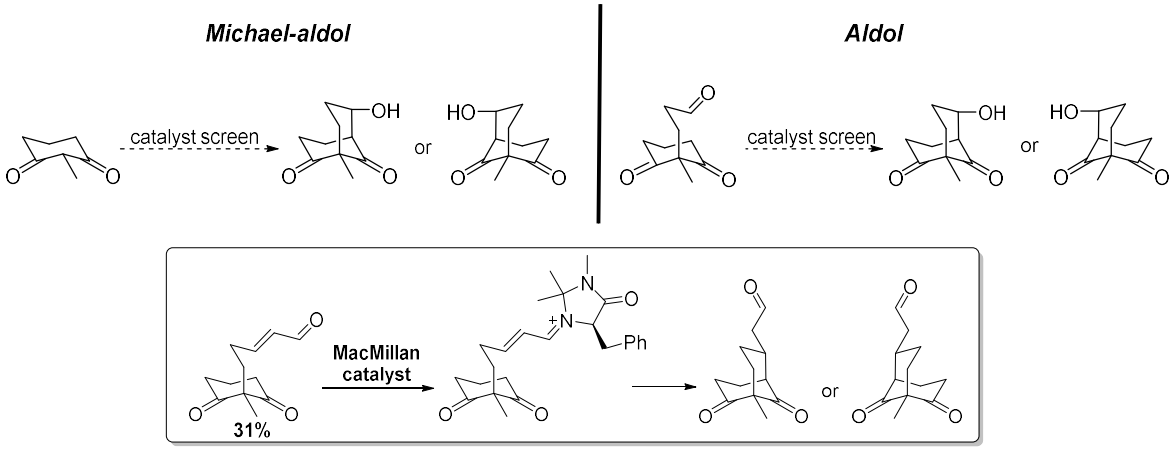
Of these pathways, exploration of the 6-*exo-tet* cyclisation seemed the more promising owing to the high accessibility of the epoxide **2.91**; however, the poor yield of the alkene precursor **2.90** was a synthetic bottleneck. Alternative precursors could be obtained by synthesis of dibromoalkene **4.53** from which substituted [3.3.1] bicyclic scaffolds might be obtained (Scheme 4.33).



*Scheme 4.33: Proposed alternative synthesis of dibromo intermediate **4.53** as versatile intermediate to access [3.3.1] bicyclic scaffolds.*

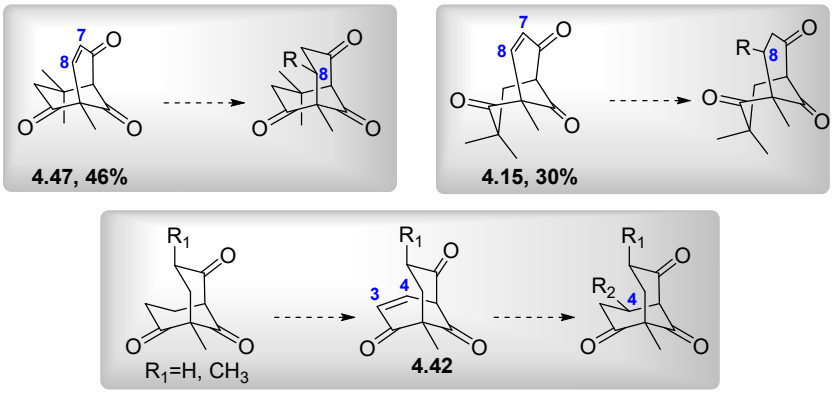
During the exploration of our desymmetrisation strategy we noticed that under Wittig and Horner-Wadsworth-Emmons conditions the formation of the desired olefination product was in most cases prevented by the formation of the product of an intramolecular aldol reaction on aldehyde **2.77-3.1**, which featured the desired [3.3.1] bicyclic scaffold (see chapter 3, Scheme 3.1). Exploration of this side reaction led us to a third strategy and to the development of a general method for the synthesis of 6-hydroxybicyclo[3.3.1]nonane-2,9-diones and 2-hydroxybicyclo[3.2.1]octane-6,8-diones. This one-pot Michael-aldol annulation enables stereoselective incorporation of different substituents at three positions, in which the relative configurations can be partly controlled through appropriate choice of solvent, temperature and reagent. The scope of the reaction was explored and oxidation of the annulation products to the corresponding bicyclo triketones led to the discovery of an unusual boat-chair conformation adopted by 2,4,4-trimethylcyclohexane-1,3-dione derivatives (see chapter 3, Table 3.33 and Fig. 3.45).

An enantioselective cyclisation, with the aid of *Cinchona* alkaloids or MacMillan catalysts would be a natural evolution of this promising study (Scheme 4.34).



Scheme 4.34: Proposed enantioselective Michael-aldol annulation.

Preliminary fluorination and derivatisation studies were performed on the bicyclic scaffolds synthesised in order to access unique aliphatic fluorinated bicyclo compounds. Optimisation of the reaction conditions to access enones of type **4.15** and **4.47** and synthesis of enone of type **4.42** would permit functionalisation of positions-8 and -4 respectively, allowing the study of facial selectivity toward addition reactions and providing access to other fluorinated and functionalised bicyclo compounds (Scheme 4.35).



Scheme 4.35: Synthesis of additionally functionalised bicyclo compounds via enone formation and conjugate addition.

The bicyclic compounds synthesised in this study (Fig. 4.36), with their high level of saturation and complexity, have good potential for use in medicinal chemistry and in drug-design programmes. The structural diversity provided by the different configurations and conformations adopted and the specific directionalities of the various substituents pave the way for a more extensive exploration of bicyclo chemical space.

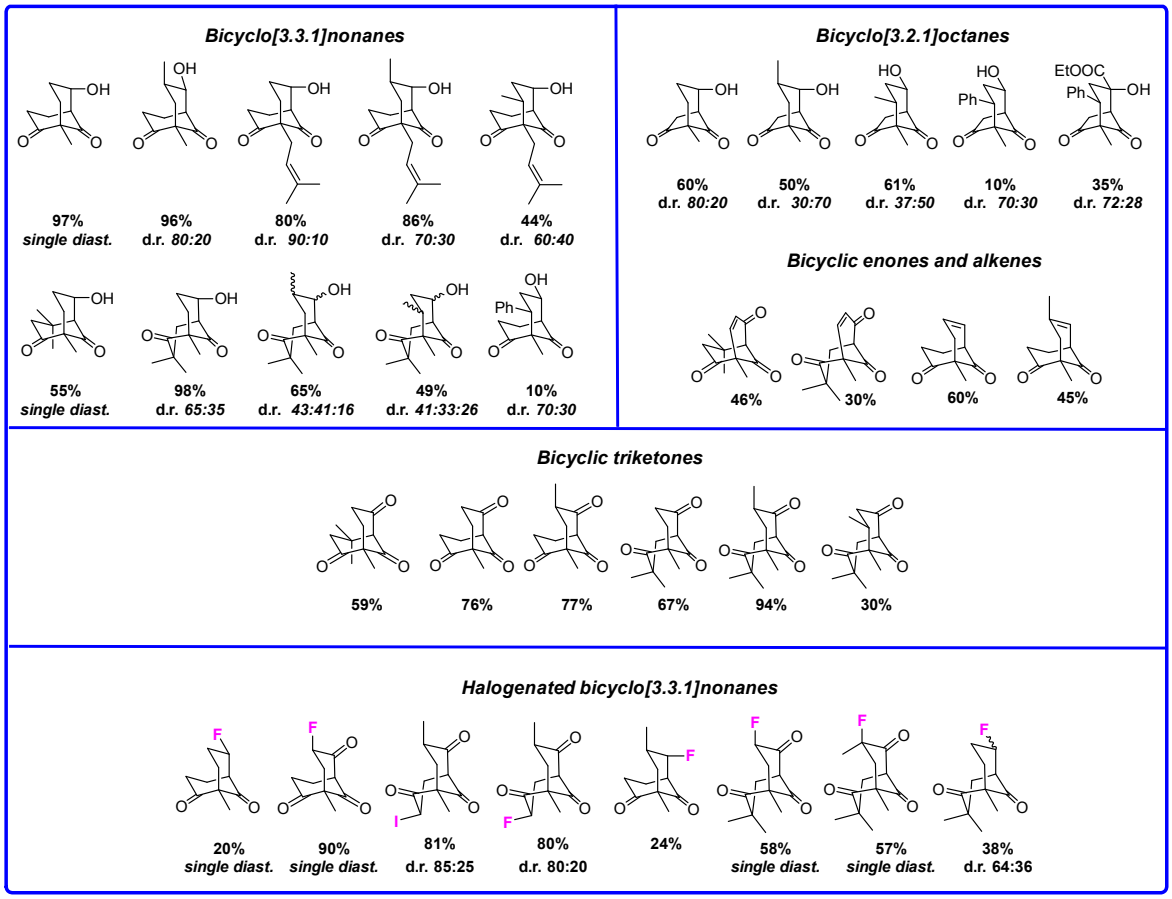
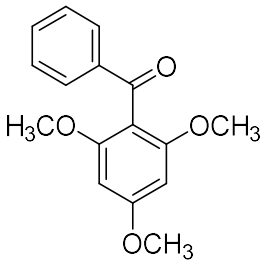


Fig. 4.36: Summary of all the bicyclic compounds synthesised.

CHAPTER 5: EXPERIMENTAL

General. All moisture-sensitive reactions were performed under an atmosphere of argon and using glassware pre-dried in an oven (100 °C). Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualised by UV (254 nm) or by staining with potassium permanganate with subsequent heating. Flash column chromatography was performed using Merck 0.040-0.063 mm, 230-400 mesh silica gel. Evaporation refers to the removal of solvent under reduced pressure. Melting points were determined using a Büchi B-540 apparatus. Infrared (IR) spectra were recorded on a Perkin−Elmer Spectrum One FT-IR spectrometer; absorptions are quoted in wavenumbers. ^{1}H and ^{13}C NMR spectra were recorded respectively at 300 MHz/75 MHz on a Bruker AMX-300 spectrometer, at 400 MHz/100 MHz on a DRX-400 spectrometer, at 500 MHz/125 MHz on a Bruker Advance 500 spectrometer and at 600 MHz/151 MHz on a Bruker Advance 600 spectrometer and calibrated using residual undeuterated solvent as an internal reference; chemical shifts are in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). High-resolution mass spectra (HRMS) were obtained using either an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage, or using a VG7070H mass spectrometer with Finigan Incos II data system at University College London.

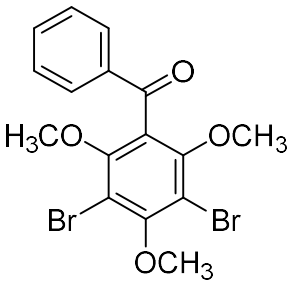
Phenyl(2,4,6-trimethoxyphenyl)methanone (2.2)



2.2

A literature procedure was adapted.[133] To an ice-cooled stirring mixture of $AlCl_3$ (5.95 g, 44.6 mmol, 1.5 eq) in dichloromethane (60 mL) benzoyl chloride (3.45 mL, 29.7 mmol, 1 eq) was added dropwise at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was slowly poured into a stirring solution of 1,3,5-trimethoxybenzene (5.00 g, 29.7 mmol, 1 eq) in dichloromethane (50 mL) at 0 ºC. The reaction was then allowed to warm to 25 ºC over the course of the night and stirred at the same temperature for further 12 h. The resulting suspension was then quenched with ice water and conc. HCl was added until a clear solution was formed. The organic layer was diluted with dichloromethane, washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether:ethyl acetate, 80:20) afforded phenyl (2,4,6-trimethoxyphenyl)methanone **2.2** (4.00 g, **50%**) as white solid, m.p. 110–116 °C (lit.[133] m.p 108–111 °C); IR (film): 3707, 3681, 2973, 2865, 1597, 1455, 1054, 1012, 750 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ ppm 7.79–7.74 (2H, m, aryl), 7.58 (1H, tt, *J* = 7.2, 1.6 Hz, aryl), 7.46 (2H, dd, *J* = 8.4, 7.1 Hz, aryl), 6.34 (2H, s, aryl), 3.89 (3H, s, -OCH_3), 3.68 (6H, s, 2xOCH_3).^{13}C NMR (101 MHz, Acetone-d_6) δ ppm 194.7 (Ph-CO), 164.0 (*C*-OCH_3), 160.1 (*C*-OCH_3), 140.0 (aryl), 134.0 (aryl), 130.2 (aryl), 129.8 (aryl), 112.3 (aryl), 92.3 (aryl), 56.7 (1xO-*C*H_3), 56.4 (2xO-*C*H_3).

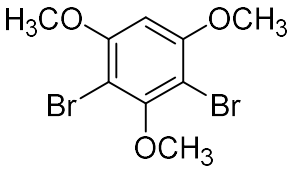
(3,5-Dibromo-2,4,6-trimethoxyphenyl)(phenyl)methanone (2.4)



2.4

To a stirred solution of phenyl (2,4,6-trimethoxyphenyl)methanone **2.2** (0.200 g, 0.72 mmol, 1 eq) in glacial acetic acid (5 mL), bromine (0.23 g, 1.44 mmol, 70 µL, 2 eq) was added dropwise at 25 ºC. The reaction mixture was heated at 50 ºC for one hour and then quenched with a 5% $Na_2S_2O_3$ solution. The aqueous phase was extracted with dichloromethane (3x30mL), the combined organic layers washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography (petroleum ether:ethyl acetate, 95:5) afforded 3,5-dibromo-2,4,6-trimethoxyphenyl)(phenyl)methanone **2.4** (0.19 g, **62%**) as white crystalline solid, m.p 135–139 °C, R_f = 0.44 (hexanes:ethyl acetate, 80:20); IR (film): 3707, 2981, 2973, 1275, 1260, 1054, 1033, 764, 750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 7.85−7.80 (2H, m, aryl), 7.60 (1H, t, *J* = 6.4 Hz, aryl), 7.50−7.45 (2H, t, *J* = 6.4 Hz, aryl), 3.97 (3H, s, O-C*H*$_3$), 3.74 (6H, s, 2xOC*H*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 192.7 (Ph-*C*O), 156.6 (*C*-OCH_3), 154.6 (*C*-OCH_3), 136.8 (aryl), 134.0 (aryl), 129.6 (aryl), 128.7 (aryl), 126.8 (aryl), 109.4 (aryl), 62.4 (2xO*C*H_3), 60.8 (-O*C*H_3); HRMS (ESI-TOF) $[M+H]^+$ $C_{16}H_{15}Br_2O_4$ calcd. 428.9332, found 428.9344.

2,4-Dibromo-1,3,5-trimethoxybenzene (2.10)

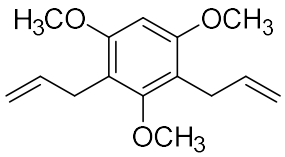


2.10

A literature procedure was adapted.[134] A solution of bromine (17.8 mmol, 0.92 mL, 3 eq) in dichloromethane (20 mL) was added dropwise to a stirred solution of 1,3,5-trimethoxybenzene (1.00 g, 5.9 mmol, 1 eq) in dichloromethane (20 mL) at –10 ºC. After one hour stirring at this temperature, the reaction mixture was quenched with a 5% $Na_2S_2O_3$

solution, the organic layers separated, washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Recrystallization from dichloromethane afforded 2,4-dibromo-1,3,5-trimethoxybenzene **2.10** (1.65 g, **85%**) as white crystalline solid, m.p. 128−131 °C (lit m.p. 129−130 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 6.36 (1H, s, aryl), 3.92 (6H, s, 2xOC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 156.6 (2 x -*C*-OCH_3), 155.7 (*C*-OCH_3), 99.0 (*C*-Br), 93.2 (-*C*-H), 60.5 (-O*C*H_3), 56.6 (2xO*C*H_3).

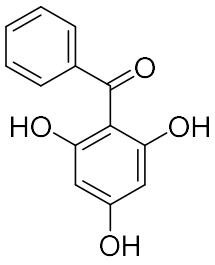
2,4-Diallyl-1,3,5-trimethoxybenzene (2.12)



2.12

A literature procedure was adapted.[84] n-Butyllithium (7.2 mL, 5.6 mmol, 8 eq) was slowly added under an atmosphere of argon over a period of 10 minutes to a suspension of copper(I) iodide (1.13 g, 6.0 mmol, 8.5 eq) in tetrahydrofuran (20 mL) at –48 ºC. After 10 minutes, 2,4-dibromo-1,3,5-trimethoxybenzene (0.250 g, 0.70 mmol, 1 eq.) was dissolved in tetrahydrofuran (5 mL) and cannulated into the lithium dibutylcopper solution. The resulting mixture was stirred for further 30 minutes and then treated with an excess of allyl bromide (5.6 mmol, 0.48 mL, 8 eq). After 30 minutes stirring at −48 ºC, the reaction mixture was quenched with methanol (1 mL), diluted with sat. NH_4Cl and the aqueous phase extracted with Et_2O (2x20 mL). The combined organic layers were washed with sat. NH_4Cl and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (petroleum ether:ethyl acetate, 95:5) afforded 2,4-diallyl-1,3,5-trimethoxybenzene **2.12** (0.034 g, **18%**) as colorless oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 6.32 (1H, s, aryl), 6.05–5.94 (2H, m, C*H*$_2$=CH), 4.99 (1H, m, CH_2=C*H*), 4.97–4.93 (4H, m, C*H*$_2$=CH, CH_2=C*H*), 3.82 (-OC*H*$_3$) 3.72 (3H, s, -OC*H*$_3$), 3.37 (4H, dt, *J* = 6.0, 1.6 Hz, CH_2=CH-C*H*$_2$). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 158.0 (=*C*-OCH_3), 157.4 (2x=*C*-OCH_3), 137.9 (2x*C*H=CH_2), 114.2 (2X=C-CH_2-CH=*C*H_2), 114.0 (2X=*C*-CH_2-CH=CH_2), 92.0 (=*C*-H), 62.2 (-O*C*H_3), 55.9 (2xO*C*H_3), 28.2 (2x*C*H_2-CH=CH_2).

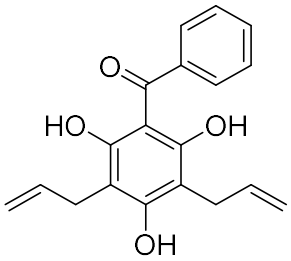
Phenyl(2,4,6-trihydroxyphenyl)methanone (2.14)



2.14

A literature procedure was adapted.[85] A 25-mL flame-dried round-bottom flask was charged with phloroglucinol (dried for two nights in the oven at 200 °C) (0.500 g, 3.96 mmol, 1 eq) and $AlCl_3$ (1.00 g, 7.5 mmol, 2 eq) under an atmosphere of argon. Dichloromethane (7.2 mL) was added and the reaction vessel was submerged in an ice bath. Once at 0 °C, benzoyl chloride (0.55 g, 0.46 mL, 1 eq) was added dropwise over a period of 2 min. The syringe was rinsed with dichloromethane (5 mL) and the reaction was left to slowly warm to room temperature overnight. After the allotted reaction time, crushed ice was added and the quenched reaction mixture was then transferred to a separatory funnel containing ethyl acetate (50 mL) and extracted with 1M HCl (2x20 mL) followed by brine (1x20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by flash chromatography (petroleum ether:ethyl acetate, 80:20 → 70:30) to give **2.14** (0.38 g, 41%) as a yellow solid, m.p. 158–166 °C, (lit. m.p. 164–167 ºC); R_f 0.1 (petroleum ether:ethyl acetate, 70:30); ^{1}H NMR (500 MHz, Acetone-d_6) δ ppm 9.76–10.11 (3H, br. s, O*H*), 7.60–7.56 (2H, m, aryl), 7.45 (1H, tt, *J* = 7.4, 2.2 Hz, aryl) 7.37 (2H, t, *J* = 7.6 Hz, aryl), 5.85 ppm (2H, s, aryl); ^{13}C NMR (DMSO-d_6,125 MHz) δ ppm 199.8 (Ph-*C*O), 165.5 (3x*C*-OH), 142.8 (aryl), 131.7 (aryl), 129.0 (aryl), 128.3 (aryl), 105.3 (aryl), 96.0 (aryl).

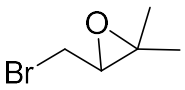
(3,5-Diallyl-2,4,6-trihydroxyphenyl)(phenyl)methanone (2.15)



2.15

A literature procedure was adapted.[85] To a solution of phenyl(2,4,6-trihydroxyphenyl)methanone **2.14** (0.140 g, 0.60 mmol, 1 eq) in H_2O (2 mL), was added potassium hydroxide (0.07 g, 1.20 mmol, 1.2 eq) at 0 ºC. Allyl bromide (1.2 mmol, 0.140 mL) was then added dropwise over a period of 5 minutes. The reaction mixture was allowed to slowly warm to room temperature over 16 h. The mixture was then quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate, 90:10 → 75:25 → 65:55) to give **2.15** (0.036 g, **21%**) as yellow oil, IR (film); 3497, 1742, 1601, 1450, 1257, 1128, 1062, 706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 8.94 (1H, s, O*H*), 7.67–7.63 (2H, m, aryl), 7.58 (1H, tt, *J* = 0.8, 4.8 Hz, aryl), 7.51 (2H, m, aryl), 5.96 (2H, ddt, *J* = 13.6, 6.8, 4.0 Hz, CH=CH_2), 5.17 (1H, q, *J* = 1.2 Hz, C*H*=CH_2), 5.13 (3H, app ddt, *J* = 6.8, 2.4, 1.2 Hz, CH=CH_2, C*H*=CH_2), 3.41 (4H, m, CH_2-CH=CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 198.1 (Ph-*C*O), 160.9 (*C*-OH), 158.2 (*C*-OH), 140.1 (aryl), 136.2 (CH_2=*C*H), 132.4 (aryl), 129.3 (aryl), 128.0 (aryl), 115.9 (*C*H_2=CH), 104.8 (aryl), 104.7 (aryl), 27.1 (CH_2=CH-*C*H_2).

1-Bromoethyl-3,3-dimethyloxirane (2.19)

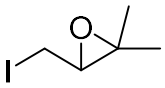


2.19

A literature procedure was adapted.[135] To a stirred solution of aqueous potassium hydroxide (14.5 g, 258 mmol, 4,4 eq) was added bromine (14.0 g, 4.5 mL, 87 mmol, 1.5 mmol) via syringe pump at 5 ˚C. The mixture was kept stirring at 5 °C for 15 min. and 2-methyl-3-buten-2-ol **2.63** (5.00 g, 6.0 mL, 58 mmol, 1 eq.) was then added. The mixture was stirred for 5 h at 5 °C. The mixture was extracted with hexane (3x30 mL), the organic layers separated,

dried over $MgSO_4$ and evaporated to give **2.19** as colorless liquid (5.60 g, 60%), which was used in the next step without further purification, IR (film): 2965, 1379, 1218, 1127 883, 648, 495 cm[1]; [1]H NMR (600 MHz, $CDCl_3$) δ ppm 3.47 (1H, dd, *J* = 7.2, 4.0 Hz, C*H*$_2$-CO, C*H*-O), 3.22 (1H, dd, *J* = 6.8, 4.8 Hz, C*H*$_2$-CO, C*H*-O), 3.04 (1H, dd, *J* = 5.0, 4.4 Hz, C*H*$_2$-CO, C*H*-O), 1.27 (3H, s, -C*H*$_3$), 1.13 (3H, s, -C*H*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 61.6 (-*C*$(CH_3)_2$), 60.0 (CH_2-*C*O), 29.7 (*C*H_2-CO), 24.0 (-C(*C*$H_3)_2$), 17.8 (-C(*C*$H_3)_2$).

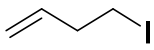
3-(Iodomethyl)-2,2-dimethyloxirane (2.19a)



2.19a

A literature procedure was adapted.[136] To a solution of bromo epoxide **2.19** (0.100 g, 0.6 mmol, 1 eq) in dry acetone (5 mL) NaI (0.13 g, 0.9 mmol, 1.5 eq) was added and the reaction heated at 80 °C for 1 h. The solution was then allowed to cool to room temperature and the organic portion extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give 3-(iodomethyl)-2,2-dimethyloxirane **2.19a** as brownish oil (0.050 g, 40%) which was used in the next step without any further purification, [1]H NMR (400 MHz, $CDCl_3$) δ ppm 3.32 (1H, dd, *J* = 10.0, 6.0 Hz, C*H*$_2$-CO), 3.09 (1H, dd, *J* = 8.4, 5.6 Hz, C*H*-O), 2.99 (1H, dd, *J* = 10.0, 8.4 Hz, C*H*$_2$-CO), 1.34 (3H, s, C*H*$_3$), 1.29 (3H, s, -C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 63.4 (CH_2-*C*O), 61.8 (-*C*$(CH_3)_2$), 24.5 (-C(*C*$H_3)_2$), 18.0 (-C(*C*$H_3)_2$), 2.5 (*C*H_2-CO).

4-Iodobut-1-ene (2.28)

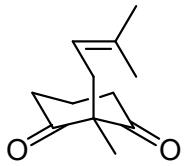


2.28

A literature procedure was adapted.[137] PPh_3 (3.81 g, 14.5 mmol, 1.05 eq) and imidazole (0.990 g, 14.5 mmol, 1.05 eq) were stirred for 5 minutes in dry dichloromethane at 25 °C. The reaction was then brought to 0 °C and I_2 (3.60 g, 14.5 mmol, 1.05 eq) was added in 4 portions. After stirring at the same temperature for 15 minutes, 3-buten-1-ol (1.17 mL, 13.8 mmol, 1 eq) was added dropwise. The solution was left stirring overnight at 25 °C. The solvent was then evaporated under carefully controlled reduced pressure (800 mbar, the

product is extremely volatile). The residue was dissolved in pentane and filtered through a pad of celite. Pentane was then evaporated at 40 °C and 850 mbar to afford 4-iodobut-1-ene **2.28** (1.70 g, **46%**) as colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* = 12.8, 10.8, 6.4 Hz, CH_2=C*H*), 5.14−5.09 (2H, m, C*H*$_2$=CH), 3.18 (2H, t, *J* = 7.2 Hz, C*H*$_2$-I), 2.62 (2H, qt, *J* = 7.2, 1.3 Hz, =CH-C*H*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0 (CH_2=*C*H), 117.1 (*C*H_2=CH), 37.8 (=CH-*C*H_2), 4.6 (*C*H_2-I).

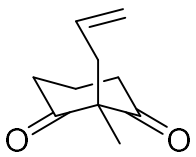
2-Methyl-2-(3-methylbut-2-enyl) cyclohexane-1,3-dione (2.48)



2.48

Sodium hydride (60% dispersion in mineral oil, 0.100 g, 2.5 mmol, 4.3 eq) and dry dimethylformamide (6 mL) were placed in a dry flask under an atmosphere of argon and stirred at 20 °C for 5 min. 2-Methyl-1,3-cyclohexanedione **2.47** (0.200 g, 1.6 mmol, 1 eq) was added and the mixture was stirred at 20 °C for 30 min. The solution was then cooled to 0 ˚C and prenyl bromide (0.4 mL, 3 mmol, 1.5 eq) was added dropwise *via* a syringe pump over 25 min. The cold bath was removed and the mixture stirred at 20 °C for 2 h. Water (10 mL) was then added at 0 °C and the mixture extracted with diethyl ether (3x20 mL). The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered and evaporated to give a crude colorless oil (1.20 g). TLC (hexane:ethyl acetate, 60:40), revealed 4 spots with R_f 0.7, 0.4, 0.3, 0.2 respectively. Column chromatography (hexane:ethyl acetate, 90:10→ 80:20 → 70:30) afforded **2.48** (0.100 g , **33%**), R_f 0.14 (hexane:ethyl acetate, 80:20); IR (film): 2966, 2914, 1724, 1452, 1381, 1025 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.83 (1H, m, C*H*=C$(CH_3)_2$), 2.63 (2H, ddd, *J* = 16.0, 10.2, 5.7 Hz, CO-C*H*$_2$), 2.54 (2H, ddd, *J* = 16.0, 6.3, 5.0 Hz, CO-C*H*$_2$), 2.45 (2H, d, *J* = 6.0 Hz, C*H*$_2$-CH=) 2.04–1.95 (1H, m, CO-CH_2-C*H*$_2$), 1.85–1.75 (1H, m, CO-CH_2-C*H*$_2$), 1.62 (3H, s, -C*H*$_3$), 1.55 (3H, s, -C*H*$_3$), 1.16 (3H, s, C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 210.3 (*C*O), 135.8 (CH=*C*$(CH_3)_2$), 117.6 (CH=*C*$(CH_3)_2$), 65.4 (*C*-CH_3), 38.0 (2 x CO-*C*H_2), 36.5 (*C*H_2-CH=) 25.8 (C(*C*$H_3)_2$), 18.5 (C-*C*H_3) 17.5 (C(*C*$H_3)_2$), 17.2 (C(*C*$H_3)_2$) ; HRMS (ESI-TOF) [M$^+$] calcd. for $C_{12}H_{18}O_2$ 194.1307, found 194.1302.

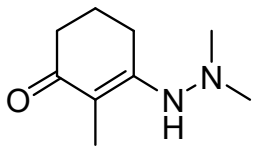
2-Methyl-2-(3-propenyl)-1,3-cyclohexanedione (2.49)



2.49

A literature procedure was adapted.[99] To a solution of 2-methyl-1,3-cyclohexanedione **2.47** (1.00 g, 8 mmol, 1 eq) in aqueous sodium hydroxide (1M, 8 mL) was added 3-bromopropene (1.90 g, 1.4 mL, 16 mmol, 2 eq). The mixture was stirred for 16 h, and then extracted with dichloromethane (3x10 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over $MgSO_4$, filtered and evaporated to give a crude yellow liquid (1.10 g). Column chromatography (hexane:ethyl acetate, 80:20) afforded 2-allyl-2-methylcyclohexane-1,3-dione **2.49** (0.390 g, **29%**) as colourless liquid. The same compound was also obtained via Tsuji Trost reaction, procedure follows: to a solution of 2-methyl-1,3-cyclohexanedione **2.47** (0.501 g, 4.36 mmol, 1 eq) in dry THF (10 mL) was added $Pd(PPh_3)_4$ (0.050 g, 0.43 mmol) and allyl acetate (0.75 mL, 1.5 eq). The solution was stirred at 25 °C for 30 minutes. After this time the solvent was removed under reduced pressure to afford crude 2-allyl-2-methylcyclohexane-1,3-dione **2.49** (0.560 g, **66%**) which was used in the subsequent step without any further purification, R_f 0.5 (hexane:ethyl acetate, 50:50); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 5.52 (1H, ddt, *J* = 14.4, 9.6, 7.2 Hz, C*H*=CH_2), 4.95−4.93 (2H, m, CH=C*H*$_2$), 2.62−2.56 (3H, m, CO-C*H*$_2$), 2.49−2.45 (2H, dt, *J* = 7.2, 1.2 Hz, C*H*$_2$-CH=CH_2), 2.01−1.92 (1H, m, 1xCO-CH_2-C*H*$_2$), 1.89−1.78 (1H, m, 1xCO-CH_2-C*H*$_2$), 1.18 (3H, s, -C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 209.6 (2x*C*O), 131.9 (*C*H=CH_2), 118.9 (CH=*C*H_2), 64.9 (-*C*-CH_3), 41.0 (2xCO-*C*H_2), 37.8 (*C*H_2-CH=CH_2), 19.1 (C-*C*H_3), 17.2 (CO-CH_2-*C*H_2).

2-Methylcyclohexane-1,3-dione dimethylhydrazone (2.50)

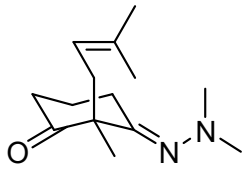


2.50

A literature procedure was adapted.[95] A solution of 2 methyl-cyclohexane-1,3-dione **2.47** (1.26 g, 10 mmol, 1 eq), *N*,*N*-dimethylhydrazine (0.720 g, 0.9 mL, 12 mmol, 1.2 eq) and *p*-

TsOH (0.100 g, 0.52 mmol) in benzene (50 mL) was heated at reflux for 5 h while water was removed with a Dean-Stark apparatus. The solvent was then evaporated to give a crude orange oil (1.75 g) which was recrystallized from hexane, to give **2.50** (1.55 g, **98%**) as yellow needles, m.p. 105–109°C (lit.[95] m. p. 112–114 °C); R_f 0.57 (ethyl acetate); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 5.05 (1H, s, -N*H*), 2.65 (2H, t, *J* = 4.0 Hz, N-C-C*H*$_2$), 2.53 (6H, s, -N(C*H*$_3$)$_2$), 2.34 (2H, t, *J* = 4.0 Hz, CO-C*H*$_2$), 1.91 (2H, m, CO-CH$_2$-C*H*$_2$), 1.66 (3H, s, -C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 195.5 (*CO*), 160.8 ((CH$_3$)C=*C*-NH), 128.6 ((CH$_3$)*C*=C-NH), 48.9 (-N(*C*H$_3$)$_2$), 31.6 (*C*H$_2$-C(N)=C(CH$_3$)), 24.7 (CO-*C*H$_2$), 21.3 (CO-CH$_2$-*C*H$_2$), 7.4 (-C(*C*H$_3$)).

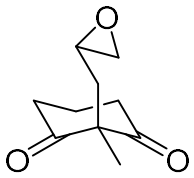
2-Methyl-2-(3-methylbut-2-enyl)-cyclohexane-1,3-dione dimethylhydrazone (2.51)



2.51

To a stirring solution of 2-methylcyclohexane-1,3-dione-dimethylhydrazone **2.50 (**0.090 g, 0.53 mmol, 1 eq) in dry dimethylformamide, sodium hydride (60% dispersion in mineral oil, 0.04 g, 1.00 mmol, 5.2 eq) was added under an atmosphere of argon. Upon addition of sodium hydride the solution turned red-brown. Prenyl bromide (0.13 mL, 1 mmol, 2 eq) was then added dropwise at 0 ˚C. After stirring the solution for 4 h, saturated ammonium chloride (10 mL) was added and the aqueous phase was extracted with ethyl acetate (2x30 mL). The combined organic layers were washed twice with brine, dried over $MgSO_4$ and evaporated to give a crude yellow oil (0.090 g). Column chromatography (hexane:ethyl acetate, 50:50) afforded **2.51** (40 mg, **32%**) as yellow oil which was found very unstable and used immediately for the subsequent step, R_f 0.57 (ethyl acetate); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.92 (1H, t, *J* = 4.8 Hz, C*H*=C(CH$_3$)$_2$), 3.11 (1H, dt, *J* = 10.4, 3.6 Hz, 1xN=C-C*H*$_2$), 2.57−2.51 (1H, m, 1xN=C-C*H*$_2$), 2.46−2.39 (10H, m, -N(C*H*$_3$)$_2$, 2xCO-C*H*$_2$), 1.93 (1H, dtd, *J* = 15.2, 7.6, 3.6 Hz, CO-CH$_2$-C*H*$_2$eq), 1.75−1.68 (1H, dtd, *J* = 15.2, 6.8, 3.6 Hz, CO-CH$_2$-C*H*$_2$ax), 1.64 (3H, s, -C*H*$_3$), 1.59 (3H, s, -C*H*$_3$), 1.24 (3H, s, -C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 212.8 (CO), 169 (*C*=N), 134.4 (CH=*C*(CH$_3$)$_2$), 118.8 (*C*H=C(CH$_3$)$_2$), 57.9 (-*C*-CH$_3$), 47.3 (N(*C*H$_3$)$_2$), 38.5 (N=C-*C*H$_2$), 37.8 (CO-*C*H$_2$), 25.9 ((CH$_3$)$_2$C=CH-*C*H$_2$), 24.9 (CO-CH$_2$-*C*H$_2$), 20.5 (-*C*H$_3$), 20.0 (-*C*H$_3$), 18.0 (-*C*H$_3$).

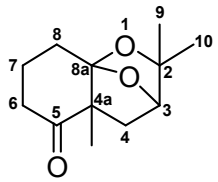
2-Methyl-2-(oxiran-2-ylmethyl)cyclohexanone-1,3-dione (2.53)



2.53

To a stirred solution of 2-methyl-2-(3-propenyl)-cyclohexane-1,3-dione **2.49** (0.200 g, 1.2 mmol, 1 eq) in dichloromethane (10 mL), acetone (1 mL) and saturated aqueous sodium hydrogen carbonate (5 mL) was added dropwise a solution of oxone™ (0.700 g, 2.4 mmol, 2 eq) in water (6.0 mL) over a period of 10 min at 0 °C. After stirring for 1 additional hour, additional Oxone™ (0.700 g, 2.4 mmol, 2 eq) was added over a period of 10 min. The mixture was extracted with dichloromethane (3x10 mL), the organic layers washed with brine, filtered and evaporated to give **2.53** (0.070 mg, 27%) as colourless liquid, R_f 0.7 (hexane:ethyl acetate, 80:20); IR (film): 2952, 1695, 1455, 1242, 1007 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 2.92–2.88 (1H, m, CH_2-C*H*-O), 2.74−2.67 (5H, m, 2xC*H*$_2$, 1xC*H*$_2$-O) 2.46 (1H, dd, *J* = 3.2, 1.6 Hz, 1xC*H*$_2$-O), 2.17–2.10 (2H, m, -C*H*$_2$), 2.08−1.97 (2H, m, -C*H*$_2$), 1.31 (3H, s, C-C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 210.5 (*C*O), 210.1 (*C*O), 67.2, 63.0, 48.9, 48.4, 38.0, 37.8, 37.2, 22.4, 17.8; HRMS (ESI-TOF) [M^+] $C_{10}H_{15}O_3$ calcd. 183.1021, found 183.1020.

2,2,4a-Trimethylhexahydro-3,8a-epoxychromen-5(6*H*)-one (2.54)

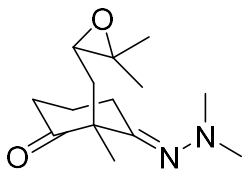


2.54

In a flame-dried round-bottom flask, under an atmposphere of argon, alkene **2.48** (0.200 g, 1.0 mmol, 1 eq) was dissolved in dry dichloromethane (2.5 mL) and stirred at 20 °C for 5 min. After this period, *m*-CPBA (0.300 g, 2 mmol, 2 eq) was added. A white precipitate was observed almost immediately. After 30 min. starting material was absent and TLC showed a new spot with 0.42 R_f (hexane:ethyl acetate, 50:50). The mixture was then brought to −78 °C and 2,6-lutidine (0.750 g, 0.81 mL, 7 mmol, 7 eq) and TMSOTf (0.72 mL, 4 mmol, 4 eq)

were added. Upon disappearance of the TLC spot at R_f 0.42 (and formation of two new spots at R_f 0.89 and 0.54 respectively) after approximately 1 h, sat $NaHCO_3$ (1 mL) was added and the temperature was slowly raised to 20 °C. The mixture was extracted with ethyl acetate (3x10 mL) and the combined organic layers washed sequentially with an aqueous solution of hydrochloric acid (2M, 10 mL), saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a crude yellow oil (0.060 g). Column chromatography (hexane:ethyl acetate, 90:10→ 70:30) afforded **2.54** (10 mg, **5%**) as white crystalline microprisms, R_f 0.54 (hexane:ethyl acetate, 50:50); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 3.72 (1H, dd, *J* = 9, 7.2 Hz, 3-H), 2.73 (1H, dd, *J* = 8.4, 4.8 Hz, 8-H), 2.53 (1H, td, *J* = 9.6, 4.4 Hz, 6-H), 2.30 (1H, app d, *J* = 9.2 Hz, 6-H), 2.11 (1H, app d, *J* = 9.6 Hz, 4-H), 2.00 (1H, td, *J* = 9.2, 3.2 Hz, 4-H), 1.85−1.67 (3H, m, 8-H, 2x7-H), 1.31 (3H, s, -C*H*$_3$), 1.26 (3H, s, -C*H*$_3$), 1.13 (3H, s, -C*H*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 212.3 (C-5), 171.5, 106.4 (C-8a), 83.1 (C-2), 70.9 (C-3), 60.4 (C-4a), 37.2 (C-6), 30.7 (C-8), 28.8 (-*C*H$_3$), 25.4 (-*C*H$_3$), 19.9 (*C*-4), 18.8 (-*C*H$_3$); HRMS (ESI-TOF) [M$^+$] $C_{12}H_{18}O_3$ calcd. 211.1334, found 211.1333.

3-(2,2-Dimethylhydrazono)-2-((3,3-dimethyloxiran-2-yl)methyl)-2-methylcyclohexanone (2.64)

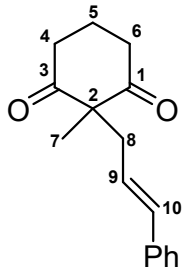


2.64

Sodium hydride (60% dispersion in mineral oil, 0.04 g, 1.00 mmol, 2 eq) and dry dimethylformamide (5 mL) were placed in a dry flask under an atmosphere of argon and stirred at 20 °C for 5 min. 2-Methylcyclohexane-1,3-dione dimethylhydrazone **2.50** (0.100 g, 0.6 mmol, 1 eq) was added to the mixture and stirred at 20 °C for 30 min. Then 1-bromoethyl-3,3-dimethyloxirane **2.19** (0.200 g, 1.2 mmol, 2 eq) was added dropwise via a syringe pump, over a period of 10 min. The reaction was stirred at 20 °C for 2 h. Slow addition of water at 0 ˚C (5 mL) gave a mixture that was extracted with diethyl ether (3x20 mL). The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered and evaporated. Column chromatography (hexane:ethyl acetate, 70:30) afforded **2.64** (0.045 g , **30%**) as a yellow oil, R_f 0.25 (100% ethyl acetate); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 3.97 (2H, dd, *J* = 6.0, 3.2 Hz, CH_2-C*H*O), 3.50 (1H, dd, *J* = 6.8, 4.0 Hz, CH_2-C*H*O), 3.24 (1H, dd, *J* = 6.8, 4.8

Hz, CH_2-C*H*O), 2.63−2.56 (2H, m, -N=C-C*H*$_2$), 2.51−2.46 (6H, s, -N-(C*H*$_3$)$_2$), 2.44−2.31 (2H, m, CO-C*H*$_2$), 1.84 (3H, s, C-C*H*$_3$), 1.83−1.80 (2H, m, CO-CH_2-C*H*$_2$), 1.37 (3H, s, -C*H*$_3$), 1.32 (3H, s, -C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 207.1 (*C*O), 158.0 (*C*-N), 66.7 (-*C*-CH_3), 61.7 (*C*H-O), 58.1 (-*C*-(CH_3)$_2$), 47.4 (2xN-(*C*H_3)$_2$), 30.9 (CO-*C*H_2), 25.6 (*C*H_2-CH(O)), 24.6 (-C(*C*H_3)$_2$), 21.4 (-N=C-*C*H_2), 18.9 (C-*C*H_3), 9.6 (CO-CH_2-*C*H_2); HRMS (ESI-TOF) $[M]^+$ $C_{14}H_{24}N_2O_2$ calcd. 252.1838, found 252.1833.

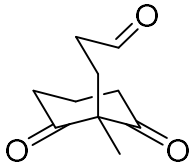
2-Cinnamyl-2-methylcyclohexane-1,3-dione (2.74)



2.74

To a round bottom flask containing $Pd(PPh_3)_4$ (0.010 mg, 5 mol%) was added an aqueous solution of Triton X-100 (0.010 mg, 9 µL in 3.2 mL H_2O) at ambient temperature. Cinnamyl acetate (0.253 g, 1.44 mmol, 239 µL, 1 eq) was then introduced in the same flask and the resulting solution stirred for 15 minutes. After this time 2-methyl-1,3-cyclohexanedione **2.47** (0.200 g, 1.58 mmol, 1.1 eq) was added at 30 ºC followed by an aqueous solution of K_2CO_3 (0.200 g, 1.44 mmol in 1.6 mL of H_2O, 1.1 eq). After stirring for 10 minutes the reaction was quenched with sat. NH_4Cl and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (petroleum ether:ethyl acetate, 85:15) afforded 2-cinnamyl-2-methylcyclohexane-1,3-dione **2.74** (0.330 g, **85%**) as yellow oil, R_f 0.31 (petroleum ether:ethyl acetate, 85:15); IR (film) 2940, 1725, 1694, 1494, 1450, 1319, 1270, 1192, 1026, 969, 827, 734, 644, 636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34−7.20 (5H, m, aryl), 6.43 (1H, d, *J* = 15.9 Hz, 10-H) 6.07−5.92 (1H, dt, *J* $H_{9\text{-}10}$ = 15.9, *J* $H_{8\text{-}9}$ = 7.2 Hz, 9-H), 2.77−2.61 (6H, m, H-4,H-6, 8-H), 2.07−1.86 (2H, m, 5-H), 1.31 (3H, s, 2-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 210.0 (C-1,3), 136.9 (C-9), 134.1 (C-10), 128.5 (aryl), 127.5 (aryl), 126.2 (aryl), 123.8 (aryl), 65.3 (C-2), 40.3 (C-4,6), 38.3 (C-8), 20.3 (C-2-*C*H_3), 17.4 (C-5); HRMS (ESI-TOF) $[M+H]^+$ $C_{16}H_{19}O_2$ calcd. 243.1380, found 243.1389.

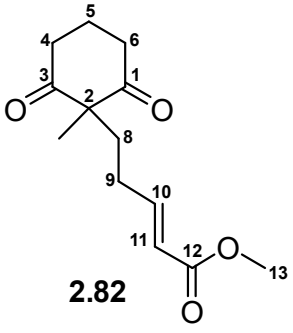
3-(1-Methyl-2,6-dioxocyclohexyl)propanal (2.77/3.1)



2.77 / 3.1

To a solution of 2-methyl-1,3-cyclohexanedione **2.47** (0.080 g, 0.64 mmol, 1 eq) in dry CH_3CN (6 mL) were added acrolein (64 μL, 0.96 mmol, 1.5 eq) and DABCO (0.014 g, 0.13 mmol) at 25 °C under an atmosphere of argon. The resulting solution was heated at 95 °C for 6 h. After this time the reaction was allowed to cool to 25 °C and quenched with water (6 mL). Dichloromethane was then added and the aqueous phase was extracted three times (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 3-(1-methyl-2,6-dioxocyclohexyl)propanal **2.77/3.1** (0.130 g, **97%**) as a yellow oil, which was used in the subsequent step without further purification, IR (film): 3427, 2932, 2870, 1719, 1691, 1452, 1372, 1238, 1047, 956; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 9.69 (1H, t, *J* = 0.8 Hz, C*H*-O), 2.74−2.64 (4H, m, 2xCO-CH_2), 2.35 (2H, app t, *J* = 4.8 Hz, CH_2-CHO), 2.12 (2H, t, *J* = 5.2 Hz, CH_2-CH_2-CHO), 2.03−1.91 (2H, m, CO-CH_2-CH_2), 1.29 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.9 (*C*O), 201.1 (*C*HO), 64.5 (*C*-CH_3), 39.5 (*C*H_2-CHO), 37.9 (CO-*C*H_2), 27.3 (*C*H_2-CH_2-CHO), 21.7 (C-*C*H_3), 17.6 (CO-CH_2-*C*H_2)**.** HRMS (ESI-TOF) $[M+Na]^+$ $C_{10}H_{14}NaO_3$ calcd. 205.0835, found 205.0842.

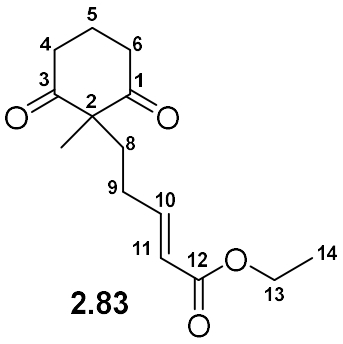
Methyl-5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enoate (2.82)



2.82

A literature procedure was adapted.[106b] LiCl (0.030 g, 0.63 mmol, 1.2 eq) was placed in a 25 mL round bottom flask and flame dried under vacuum at 400 ºC for 5 minutes. Trimethyl phosphonoacetate (0.120 g, 0.65 mmol, 1.2 eq), DBU (0.090 g, 0.6 mmol, 1.1 eq) and dry CH_3CN (6 mL) were subsequently added to the flask under an atmosphere of argon. A solution of 3-(1-methyl-2,4-dioxocyclohexyl) propanal **2.77** (0.100 g, 0.54 mmol, 1 eq) dissolved in dry CH_3CN (5 mL) was then added dropwise to the mixture. The solution was stirred for 3 h at 25 °C and then quenched with sat. NH_4Cl. The aqueous phase was extracted with ethyl acetate (3x30 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Column chromatography (petroleum ether:ethyl acetate, 60:40) afforded 5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enoate **2.82** (0.030 g, **23%**) as colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.86 (1H, dt, *J* H_{10-11} = 15.6, *J* H_{9-10} = 6.7 Hz, 10-H), 5.79 (1H, dt, *J* H_{10-11} = 15.6, *J* H_{9-11} = 1.5 Hz, 11-H), 3.71 (3H, s, O-C*H*$_3$), 2.79−2.55 (4H, m, 4-H, 6-H), 2.12−1.89 (6H, m, 5-H, 8-H, 9-H), 1.28 (3H, s, 2-C-C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.8 (C-1,3), 166.7 (C-12), 147.7 (C-10), 121.5 (C-11), 64.8 (C-2), 51.4 (C-13), 37.9 (C-4.6), 34.0 (C-8), 27.5 (C-9), 21.3 (C-2-*C*H_3), 17.5 (C-5).

Ethyl-5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enoate (2.83)

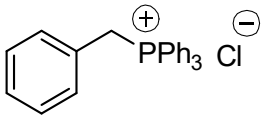


2.83

A literature procedure was adapted.[106b] To a solution of carbethoxymethylene triphenyl phosphorane (0.570 g, 1.64 mmol, 1.2 eq) in dry dichloromethane (4 mL) was added a solution of 3-(1-methyl-2,4-dioxocyclohexyl) propanal (**2.77**, 0.250 g, 1.37 mmol, 1 eq) dissolved in dry dichloromethane (2 mL). The solution was stirred at 25 °C over the course of the night. The aqueous phase was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude mixture was purified by flash column chromatography (petroleum ether:ethyl acetate, 80:20) to afford ethyl 5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enoate **2.83** (0.25 g, **85%**) as colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.85 (1H, dt, *J* H_{10-11} = 15.7, *J* H_{9-10} = 6.6, *J*

$H_{9\text{-}10}$ = 6.6 Hz, 10-H), 5.78 (1H, dt, *J* $H_{10\text{-}11}$ = 15.7, *J* $H_{9\text{-}11}$ = 1.8, $H_{9\text{-}9}$ = 1.8 Hz, 11-H), 4.14 (2H, q, *J* = 7.1 Hz, 13-H), 2.73−2.59 (4H, m, 4-H, 6-H), 2.08−1.91 (6H, m, 5-H, 8-H, 9-H), 1.27 (6H, dt, *J* = 7.1, 3.7 Hz, 14-H, 2-C-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.7 (C-1,3), 166.3 (C-12), 147.3 (C-10), 121.9 (C-11), 64.8 (C-13), 60.2 (C-2), 37.9 (C-4,6), 34.1 (C-8), 27.4 (C-9), 21.1 (C-14), 17.5 (C-5), 14.2 (C-2-*C*H_3).

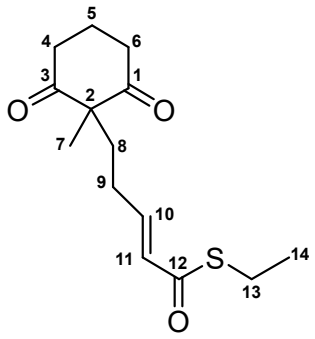
Benzyltriphenylphosphonium chloride (2.89)



2.89

A literature procedure was adapted.[138] Benzyl chloride (1.08 g, 8.6 mmol, 2.25 eq) was added to a stirring solution of PPh_3 (1g, 3.81 mmol, 1 eq) in toluene (12 mL) at room temperature. The reaction was heated at 110 ºC for 6 hours. The white solid formed was collected through filtration, washed with warm toluene and dried to give benzyl triphenylphosponium chloride **2.89** as a white solid (370 mg, **11%**), m.p. 270−275 ºC (lit.[138] m.p. >300 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80−7.57 (15H, m, aryl) 7.24−7.06 (5H, m, aryl), 5.53 (2H, d, *J* = 14.5 Hz, C*H*$_2$-PPh_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 134.6 (d, *J* = 9.8 Hz, aryl), 131.7 (d, *J* = 5.6 Hz, aryl), 130.3 (d, *J* = 12.5 Hz, aryl), 128.9 (d, *J* = 3.4 Hz, aryl), 128.4 (d, *J* = 4.0 Hz, aryl), 127.5 (d, *J* = 8.5 Hz, aryl), 118.7 (aryl), 117.9 (aryl), 31.1 (d, *J* = 46.5 Hz, *C*H_2-PPh_3).

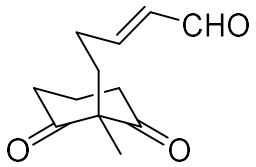
Ethyl-5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enethioate (2.92)



2.92

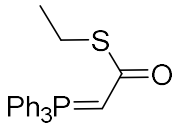
A literature procedure was adapted.[141] To a solution of 3-(1-Methyl-2,6-dioxocyclohexyl)propanal **2.77** (0.200 g, 1.09 mmol, 1 eq) in $CHCl_3$ (20 mL) was added ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate (0.520 g, 1.42 mmol, 1.3 eq.) in one portion at 25 °C and the reaction heated at reflux for 2 hours. After this time the mixture was allowed to cool to 25 °C and the solvent evaporated under reduced pressure. The crude residue was purified by flash column chromatography (hexane:ethyl acetate, 80:20) to afford ethyl-5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enethioate **2.92** (0.260 g, **89%**) as a 80:20 mixture of isomers, R_f 0.29 (hexane:ethyl acetate, 60:40), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.77−6.68 (m, 1H, 10-H), 6.02 (1H, m, 11-H), 2.93–2.84 (2H, m, 13-H), 2.67−2.58 (4H, m, 4-H, 6-H), 2.01–1.96 (2H, m, 9-H), 1.95−1.88 (4H, m, 5-H, 8-H), 1.24 (6H, m, 2x*C*H_3); Major isomer ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.8 (C-1,3), 189.9 (C-12), 143.5 (C-10), 129.3 (C-11), 64.8 (C-2), 38.0 (C-4,6), 34.0 (C-8), 27.6 (C-9), 23.1 (C-7), 21.6 (C-13), 17.6 (C-5), 14.8 (C-14); Minor isomer ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 189.4, 144.5, 127.2, 65.2, 35.7, 25.5, 23.3, 19.9, 17.7, 14.8.

5-(1-Methyl-2,6-dioxocyclohexyl)pent-2-enal (2.93)



A literature procedure was adapted.[139]To a stirring solution of 3-(1-Methyl-2,6-dioxocyclohexyl)propanal **2.77** (0.260 g, 1.42 mmol, 1 eq) in dry $CHCl_3$ (12 mL) was added 2-(triphenyl-λ^5-phosphanylidene)acetaldehyde (0.430 g, 1.42 mmol, 1 eq) in one portion at 25 °C and the reaction heated at reflux for 5 h. After this time the solvent was evaporated under reduced pressure and the crude residue purified by flash column chromatography (dichloromethane:ethyl acetate, 95:5) to afford 5-(1-methyl-2,6-dioxocyclohexyl)pent-2-enal **2.93** (0.092 g, **31%**) as 6.6:3.6 mixture; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 9.62 (1H, s, C*H*O) 9.43 (1H, d, *J* = 5.2 Hz, C*H*O), 6.73 (1H, dt, *J* = 10.4, 4.4 Hz, C*H*-CHO), 6.02 (1H, m, CH_2-C*H*=), 2.73−2.52 (8H, m, -CH_2), 2.30 (1H, t, *J* = 5.6 Hz, -CH_2), 2.15−2.08 (2H, m, -CH_2), 2.06 (1H, t, *J* = 5.2 Hz, -CH_2), 1.99–1.82 (8H, m, CH_2) 1.27 (3H, s, -CH_3), 1.23 (3H, s, -CH_3). Major isomer ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 209.9 (*C*O), 201.0 (*C*O), 193.8 (*C*HO), 157.2 (CH_2-*C*H=), 133.1 (=*C*H-CHO), 64.7 (*C*-CH_3), 37.8 (CO-*C*H_2), 33.1 (*C*H_2-CH=), 28.3 (CH_2-CH_2-CH=CH), 22.6 (C-*C*H_3), 17.5 (CO-CH_2-*C*H_2). Minor isomer ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.9, 201.0, 193.8, 157.0, 132.9, 64.4, 39.3, 37.8, 27.2, 21.6, 17.5.

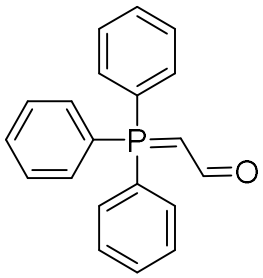
Ethyl 2-(triphenyl-phosphanylidene)ethanethioate (2.99)



2.99

A literature procedure was adapted.[140] To a solution of bromoacetic acid (5.26 g, 37.6 mmol, 1 eq) in dry dichloromethane (170 mL) was added ethanethiol (48.9 mmol, 3.62 mL, 1.3 eq) and DMAP (0.450 g, 3.76 mmol) and the resulting mixture brought to 0 °C. DCC (8.15 g, 39.5 mmol, 1.05 eq) was then added in 3 portions. The reaction was allowed to warm to room temperature over the course of the night and the cloudy white solution filtered through celite. The resulting cake was washed twice with cold dichloromethane, the filtrate transferred in a separating funnel and washed with sat. $NaHCO_3$ and water. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give ethyl 2-bromoethanethioate as a yellowish solid (4.6 g, 67%). The latter was stirred in dry toluene (40 mL) at 25 °C in the presence of PPh_3 (6.20 g, 23.7 mmol, 1 eq) for 2 days. The white solid obtained was filtered and washed twice with toluene. The resulting crystals were dissolved in dichloromethane (40 mL) and stirred for 30 minutes in the presence in a 10% solution of Na_2CO_3 (30 mL). The aqueous phase was extracted with dichloromethane three times, and the combined organics were partially concentrated under reduced pressure, diluted with pentane and filtered twice to afford ethyl 2-(triphenyl-phosphanylidene)ethanethioate **2.99** (2.00 g, **15%** over 2 steps) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.67−7.53 (9H, m, aryl), 7.46 (6H, tdd, *J* = 8.2, 2.5, 0.8 Hz, aryl), 3.65 (1H, s, P=C*H*), 2.84 (2H, q, *J* = 7.3 Hz, S-C*H*$_2$), 1.25 (3H, t, *J* = 7.4 Hz, S-CH_2-C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 180.7 (*C*O), 133.2 (aryl), 133.1 (aryl), 132.3 (aryl), 129.0 (aryl), 127.5 (aryl), 126.6 (aryl), 46.5 (P=CH), 23.3 (S-*C*H_2), 16.5 (S-CH_2-*C*H_3).

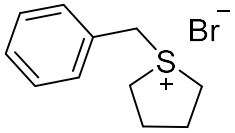
2-(Triphenylphosphanylidene)acetaldehyde (2.101)



2.101

A literature procedure was adapted.[142]To a solution of methyl triphenylphosphonium bromide (7.40 g, 20 mmol, 1 eq) in dry Et_2O (40mL) was added *t*-BuOK (2.70 g, 24.0 mmol, 1.2 eq) and the resulting bright yellow solution stirred for 30 minutes at 25 °C. The latter was then poured dropwise into a stirring solution of ethyl formate (2.25 mL, 28.0 mmol, 1.4 eq) in dry Et_2O (40 mL) and the resulting cloudy solution was stirred for 2 h at the same temperature. After this time the reaction mixture was cooled down to 0 °C and cold aqueous HCl first (0.1 M, 100 mL) then (1M, 12 mL) were subsequently added. The solution was washed with aqueous HCl (0.1 M, 3x15mL) and the combined aqueous layers were basified with aqueous NaOH (2 M) until pH 10. Over the course of the night a precipitate formed which was washed with water and Et_2O to afford 2-(triphenylphosphanylidene)acetaldehyde **2.101** as yellow solid (60:40 mixture of trans/cis isomer, 1.50 g, **25%**), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.97 (1H, d, *J* = 38.2 Hz, C*H*O-*trans*), 8.25 (1H, dd, *J* = 10.7, 3.5 Hz, C*H*O-*cis*), 7.72−7.43 (30H, m, aryl), 4.07 (1H, dd, *J* = 19.4, 10.8 Hz, P=C*H*-*trans*), 3.75−3.56 (1H, m, P=C*H*-*cis*). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 181.8 (*C*HO), 181.7 (*C*HO), 133.4 (aryl), 133.3 (aryl), 133.3(aryl), 133.1(aryl), 132.8 (aryl), 132.4 (aryl), 129.2 (aryl), 129.1 (aryl), 127.1 (aryl), 126.2 (aryl), 55.3 (P=*C*H), 54.3 (P=*C*H).

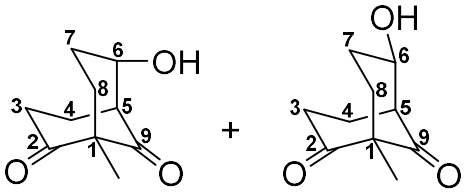
1-Benzyltetrahydrothiophenium bromide (2.105)



2.105

A literature procedure was adapted.[143] To a solution of tetrahydrothiophene (3.57 g, 40.6 mmol, 1 eq) in dry acetone (20 mL) benzyl bromide was added (6.94 g, 40.6 mmol, 1 eq) at 25 °C. After overnight stirring the resulting white solid was filtered and washed twice with acetone to afford 1-benzyltetrahydrothiophene **2.105** (4.27 g, **23%**) as a white solid, m.p. 122–124 °C, ^{1}H NMR (600 MHz, D_2O) δ ppm 7.57−7.50 (5H, m, aryl), 4.54 (2H, s, S-C*H*$_2$), 3.56−3.40 (4H, m, 2xC*H*$_2$), 2.37−2.22 (4H, m, 2xC*H*$_2$). ^{13}C NMR (101 MHz, D_2O) δ ppm 130.4 (aryl), 130.1 (aryl), 129.7 (aryl), 128.4 (aryl), 45.7 (SH-*C*H$_2$), 42.4 (2xSH-*C*H$_2$), 28.2 (2x*C*H$_2$).

6-Hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (3.2)

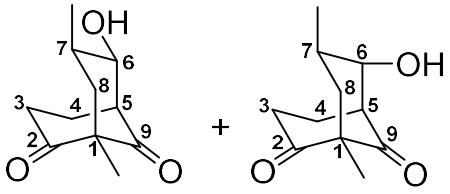


***exo*-3.2** ***endo*-3.2**

To a stirred solution of 2-methyl-1,3-cyclohexanedione (0.100 g, 0.79 mmol, 1 eq) in dimethylformamide (4 mL) was added acrolein (81 µL, 1.18 mmol, 1.5 eq) at 25 °C. The solution was then heated at 130 °C for 24 h. After allowing the mixture to cool the solvent was evaporated. The residue was washed with chloroform (2x3 mL) to give *exo*-ketol **3.2** (0.142 g, **97%**) as a colorless oil, R_f 0.3 (dichloromethane:ethyl acetate, 60:40); IR (film): 3405, 2936, 1727, 1697, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, dt, *J* = 3.1, 2.6 Hz, 6-H), 2.93 (1H, dm, *J* = 9.7 Hz, 5-H), 2.60 (1H, m, 3-Heq), 2.32 (1H, dt, *J* = 16.5, 9.5 Hz, 3-Hax), 2.22–2.14 (1H, m, 4-Heq), 2.14–2.06 (2H, m, 8-H), 1.84 (1H, m, 7-Heq), 1.74–1.67 (2H, m, 4-Hax, 7-Hax), 1.15 (3H, s, 1-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9 (C-9), 211.5 (C-2), 77.0 (C-6), 63.2 (C-1), 52.2 (C-5), 38.2 (C-3), 37.4 (C-8), 26.4 (C-7), 18.9 (C-4), 16.7 (1-C-*C*H$_3$); HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{15}O_3$ calcd. 183.1016, found 183.1018. From the above reaction conducted in the presence of DABCO (0.2 eq) in acetonitrile at 20 °C was obtained a 1:1 mixture of epimers at position-6. For *endo*-ketol **3.2**: R_f 0.28

(dichloromethane:ethyl acetate, 60:40), ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (1H, dt, *J* = 11.5, 5.0 Hz, 6-H), 3.10 (1H, m, 5-H), 2.50-2.45 (2H, m, 3-H), 2.29-2.14 (4H, m, 4-Heq, 7-Heq and 8-H), 1.65-1.56 (1H, m, 4-Hax), 1.47-1.38 (1H, m, 7-Hax), 1.14 (3H, s, 1-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (C-9), 209.3 (C-2), 73.2 (C-6), 61.8 (C-1), 52.5 (C-5), 38.8 (C-3), 35.6 (C-8), 27.8 (C-7), 16.3 (C-4) 15.0 (1-C-*C*H$_3$).

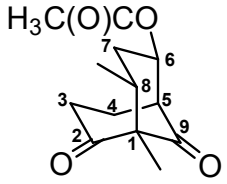
6-Hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione (**3.19**)



***endo*-3.19** ***exo*-3.19**

To a solution of 2-methyl-1,3-cyclohexanedione (0.100 g, 0.8 mmol, 1 eq) in acetonitrile (6 mL) were added methacrolein (98 µL, 1.19 mmol, 1.5 eq) and DABCO (0.018 g, 0.16 mmol, 20 mol%) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (5 mL) was added and the mixture extracted with dichloromethane (3x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give ketol **3.19** (0.150 g, **96%**) as an 80:20 mixture of ***endo*-3.19**:***exo*-3.19**, IR (film): 3455, 2936, 1728, 1697 cm^{-1}. ***endo*-3.19,** R_f 0.45 (dichloromethane:ethyl acetate, 60:40) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.62 (1H, dd, *J* = 10.5, 4.8 Hz, 6-H), 3.08 (1H, ddd, *J* = 8.9, 4.8, 2.1 Hz, 5-H), 2.64 (1H, m, 3-Heq), 2.37 (1H, m, 3-Hax), 2.24 (1H, m, 4-Heq), 2.12–2.00 (2H, m, 7-H, 8-Heq), 1.92 (1H, m, 8-Hax), 1.77 (1H, m, 4-Hax), 1.13 (3H, s, 1-C-C*H*$_3$), 1.02 (3H, d, *J* = 6.3 Hz, 7-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 212.0 (C-9), 209.9 (C-2), 78.4 (C-6), 62.9 (C-1), 52.0 (C-5), 44.4 (C-8), 38.4 (C-3), 32.7 (C-7), 17.7 (C-4), 16.2 (1-C*C*H$_3$), 15.5 (7-C*C*H$_3$); ***exo*-3.19** was isolated pure in 6% yield under neutral conditions (DMF, 95 °C, 72 h), R_f 0.48 (dichloromethane:ethyl acetate, 60:40) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.96 (1H, m, 6-H), 2.96 (1H, ddd, *J* = 10.2, 4.2, 2.0 Hz, 5-H), 2.62 (1H, ddd, *J* = 16.2, 7.4, 3.4 Hz, 3-Heq), 2.34 (1H, m, 3-Hax), 2.20 (1H, m, 4-H), 2.10 (1H, m, 7-H), 2.01 (1H, m, 8-Heq), 1.82 (1H, dd, *J* = 12.9, 4.5 Hz, 8-Hax), 1.70 (1H, m, 4-Hax), 1.14 (3H, s, 1-C-C*H*$_3$), 1.00 (3H, d, *J* = 6.6 Hz, 7-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 212.5 (C-9), 211.8 (C-2), 80.4 (C-6), 62.5 (C-1), 52.1 (C-5), 44.5 (C-8), 38.4 (C-3), 29.9 (C-7), 18.6 (C-4), 16.8 (1-CH*C*H$_3$), 16.7 (7-C*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{17}O_3$ calcd. 197.1172, found 197.1170.

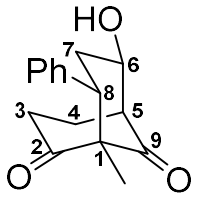
endo-1,8-Dimethyl-6-acetoxy-bicyclo[3.3.1]nonane-2,9-dione (3.22)



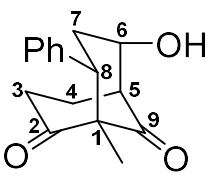
***endo*-3.22**

To a solution of 6-hydroxy-1,8-dimethylbicyclo[3.3.1]nonane-2,9-dione (crude mixture, 0.082 g, 0.41 mmol, 1 eq) in dry dichloromethane (4 mL) were added acetic anhydride (1.64 mmol, 155 μL, 4 eq), DMAP (0.050 g, 0.41 mmol, 1 eq) and pyridine (1.23 mmol, 100 μL, 3 eq) at 25 °C under an atmosphere of argon. The resulting solution was stirred at the same temperature for 1 h, then at 45 °C for 2 days. After this time water (10 mL) was added to the reaction and the aqueous phase was extracted three times with dichloromethane (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash column chromatography on neutral Al_2O_3 (petroleum ether:ethyl acetate, 90:10) to give **3.22** (0.031 g, **23%** over 2 steps) as a single diastereoisomer, IR (film, cm^{-1}): 2989, 2946, 1734, 1697, 1456, 1347, 1238, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.29 (1H, dd, $J_{eq\text{-}ax}$ = 5.6, $J_{eq\text{-}eq}$ = 3.2 Hz, 6-H), 2.95–2.90 (1H, m, 5-H), 2.56 (2H, ddd, $J_{eq\text{-}ax}$ = 8.9, $J_{eq\text{-}ax}$ 6.8, $J_{eq\text{-}eq}$ 2.1 Hz, 3-H), 2.29–2.18 (1H, sept, $J_{ax\text{-}ax}$ = 12.7, $J_{ax\text{-}eq}$ = 5.8 Hz, 8-H), 2.05 (3H, s, -OCOCH_3), 2.04–1.82 (4H, m, 4H, 7-H), 1.22 (3H, s, 1-C-CH_3), 0.98 (3H, d, J = 6.8 Hz, 8-CH-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.1 (C-9), 208.4 (C-2), 170.1 (6-O*C*OCH$_3$), 76.8 (C-6), 69.2 (C-1), 48.4 (C-5), 41.5 (C-8), 38.4 (C-3), 34.5 (C-7), 21.3 (6-OCO*C*H$_3$), 19.9 (C-4), 16.2 (8-CH-*C*H$_3$), 14.0 (1-C-*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{13}H_{18}O_4$ calcd. 239.1205, found 239.1283.

6-Hydroxy-1-methyl-8-phenylbicyclo[3.3.1]nonane-2,9-dione (**3.25**)



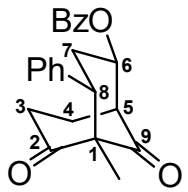
***endo*-3.25**



***exo*-3.25**

To a solution of 2-methyl-1,3-cyclohexanedione **3.12** (0.100 g, 0.8 mmol, 1 eq) in CH_3CN (6 mL) at 25 °C were added cinnamaldehyde (150 μL, 1.1 mmol, 1 eq) and DABCO (0.089 g, 0.8 mmol, 1 eq). The solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4x10 mL). The combined organic layers were washed with water (3x15 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (dichloromethane:ethyl acetate, 90:10) gave **3.25** (0.022 g, **10%**) as a yellow oil, a 70:30 mixture of ***endo*-3.25**:***exo*-3.25**; R_f 0.41 (ethyl acetate:dichloromethane, 40 : 60) IR (film): 3443, 2927, 1725, 1691, 1496, 1041 cm^{-1}. ***endo*-3.25**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32–7.26 (3H, m, aryl), 7.03–6.97 (2H, m, aryl), 4.34 (1H, dt, *J* = 11.0, 5.5 Hz, 6-H), 3.09 (1H, app. t, *J* = 5.5 Hz, 5-H), 2.75 (1H, m, 3-Heq), 2.81–2.70 (2H, m, 3-Hax, 8-H), 2.58 (1H, m, 4-Heq), 2.44–2.25 (2H, m, 7-H), 1.82 (1H, m, 4-Hax), 0.95 (3H, s, 1-C-C*H₃*); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 208.5 (C-9), 208.0 (C-2), 138.2 (*ipso*-Aryl), 128.7 (Aryl), 128.6 (Aryl), 128.5 (Aryl), 71.2 (C-6), 68.9 (C-1), 52.8 (C-5), 51.2 (C-8), 40.2 (C-3), 37.0 (C-7), 17.2 (C-4), 15.0 (1-C-*C*H_3); ***exo*-3.25**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32–7.26 (3H, m, Aryl), 7.03-6.97 (2H, m, Aryl), 4.52 (1H, dd, *J* = 2.5, 2.2 Hz, 6-H), 3.45 (1H, dd, *J* = 13.9, 4.7 Hz, 5-H), 2.96 (1H, m, 3-Heq), 2.81–2.70 (2H, m, 3-Hax, 8-H), 2.65–2.62 (1H, m, 4-Heq), 2.44–2.45 (2H, m, 7-H), 2.11 (1H, m, 4-Hax), 1.00 (3H, s, 1-C-C*H₃*); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 209.2 (C-9), 207.8 (C-2), 138.5 (*ipso*-Aryl), 128.7 (Aryl), 128.6 (Aryl), 128.5 (Aryl), 75.0 (C-6), 70.4 (C-1), 53.0 (C-5), 52.2 (C-8), 39.0 (C-3), 36.0 (C-7), 20.7 (C-4), 15.1 (1-C-*C*H_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{16}H_{18}O_3$ calcd. 259.1329, found 259.1328.

***endo*-6-Benzyloxy-1-methyl-4-phenylbicyclo[3.3.1]nonane-2,9-dione (3.26)**

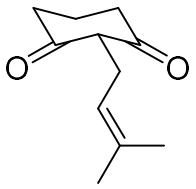


***endo*-3.26**

To a solution of 6-hydroxy-1-methyl-8-phenylbicyclo[3.3.1]nonane-2,9-dione (crude mixture, 0.100 g, 0.38 mmol, 1 eq) in dry Et_3N (522 μL), was slowly added benzoyl chloride (0.058 g, 0.42 mmol, 50 μL, 1,1 eq) at 25 °C under an atmosphere of argon. The resulting dark

solution was left stirring at the same temperature for 6 h. After this time the reaction was quenched with water (5 mL). Dichloromethane was then added and the aqueous phase extracted three times (3 x 8 mL). The combined organic layers were washed twice with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give ***endo*-3.26** (0.007 g**, 5%** over 2 steps) as a single diastereoisomer, IR (film, cm^{-1}): 2393, 1721, 1697, 1495, 1451, 1269, 1176, 1113, 767, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.09–8.05 (2H, m, Aryl), 7.64–7.57 (1H, m, aryl), 7.51–7.45 (2H, m, aryl), 7.32–7.27 (3H, m, aryl), 7.04–6.98 (2H, m, aryl), 5.57 (1H, td, $J_{ax\text{-}ax}$ = 8.6, $J_{ax\text{-}eq}$ = 5.4, $J_{ax\text{-}eq}$ = 3.1 Hz, 6-H), 3.39 (1H, appt t, $J_{eq\text{-}ax}$ = 5.8 Hz, 5-H), 3.08–2.97 (1H, ddd, J_{gem} = 18.2, $J_{ax\text{-}ax}$ =11.2, $J_{ax\text{-}eq}$ = 9.3 Hz, 1H, 3-Hax), 2.90–2.79 (2H, m, $J_{ax\text{-}ax}$ = 10.2, $J_{ax\text{-}ax}$ = 8.6, $J_{ax\text{-}eq}$ = 2.36 Hz, 3-Heq, 8-H), 2.64–2.47 (3H, m, 7-H, 4-Heq), 2.01-1.89 (1H, dddd, J_{gem} = 14.4, $J_{ax\text{-}ax}$ = 11.5, $J_{ax\text{-}eq}$ = 8.4, $J_{ax\text{-}eq}$ = 5.8 Hz, 4-Hax), 1.03 (3H, s, 1-C-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 207.42 (C-9), 206.72 (C-2), 165.25 (6-O-*C*OPh), 137.83 (aryl), 133.63 (aryl), 130.73 (aryl), 129.83 (aryl), 129.03 (aryl), 128.72 (aryl), 128.63 (aryl), 128.10 (aryl), 72.61 (C-6), 69.44 (C-1), 50.90 (C-8), 49.57 (C-5), 40.16 (C-3), 34.12 (C-7), 18.64 (C-4), 14.95 (1-C-*C*H_3).

2-(3-Methylbut-2-en-1-yl)cyclohexane-1,3-dione (3.31)

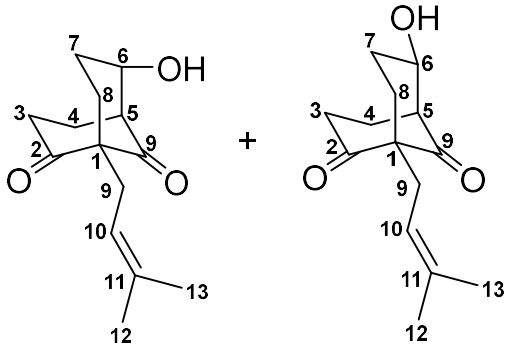


3.31

A literature procedure was adapted.[144] To a cool solution of cyclohexane-1,3-dione **3.30** (3.00 g, 26.7 mmol, 1 eq) in water (45 mL) DIPEA was added (32.1 mmol, 5.58 mL, 1.2 eq) and the resulting solution stirred for 5 minutes at 25 °C. After this time prenyl bromide was added dropwise (26.7 mmol, 3 mL, 1 eq) over a period of 15 minutes. The ice bath was removed and the reaction was stirred at 25 °C for 3 days. NaOH (1 M aqueous solution, 20 mL) was then added to the mixture and the aqueous phase washed twice with hexane (2x40 mL) and acidified with acetic acid until a precipitate was formed. The solid was collected and the filtrate extracted with ethyl acetate (2x 40 mL). Flash column chromatography (petroleum ether:ethyl acetate, 80:20) afforded pure 3-hydroxy-2-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one **3.31** (2.00 g, **41%**) as a white solid, IR (film) 2944, 2254, 1634, 1443, 1375, 1270, 1039, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.20 (1H, t, *J* = 4.4 Hz, C*H*=C$(CH_3)_2$), 3.07 (2H, d, *J* = 4.8 Hz, CH_2-CH=C$(CH_3)_2$), 2.40 (4H, t, *J* = 4.0 Hz, CO-CH_2), 1.95 (2H, m, CO-CH_2-CH_2), 1.75 (3H, s, CH_3), 1.74 (3H, s, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 205.0

(*C*O), 136.2 (*C*H=C(CH_3)$_2$), 122.0 (CH=*C*(CH_3)$_2$), 113.8 (C=*C*(OH)), 68.0 (*C*-CH_3), 39.9 (CO-*C*H_2), 25.9 (*C*H_2-CH=C(CH_3)$_2$), 21.3 (CH=C(*C*H_3)$_2$), 20.7 (CH=C(*C*H_3)$_2$), 17.9 (CO-CH_2-*C*H_2).

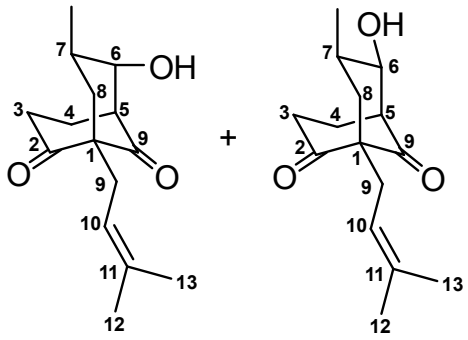
6-Hydroxy-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (3.32)



***exo*-3.32** **$endo$-3.32**

To a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **3.31** (0.200 g, 1.1 mmol, 1 eq) in dry acetonitrile (12 mL) were added acrolein (111 µL, 1.65 mmol, 1.5 eq) and DABCO (0.025 g, 0.22 mmol, 20 mol %) at 25 °C. The solution was then heated at 95 °C for 48 h. After allowing to cool, water (20 mL) was added, and the mixture extracted with dichloromethane (4x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give 6-hydroxy-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (0.200 g, **80%**) as a 90:10 mixture of ***exo*-3.32**: ***endo*-3.32**, IR (film): 3416, 2917, 1701, 1450 cm^{-1}; ***exo*-3.32**: R_f 0.5 (dichloromethane:ethyl acetate, 60:40); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 5.05 (1H, tsept., *J* = 5.0, 1.0 Hz, 10-H), 4.34 (1H, m, 6-H), 2.92 (1H, dm, *J* = 6.8 Hz, 5-H), 2.57 (1H, m, 3-Heq), 2.40–2.30 (2H, m, 9-H), 2.25–2.05 (5H, m, 3-Hax, 4-H, 8-H), 1.80 (1H, m, 7-Heq), 1.70 (1H, m, 7-Hax), 1.61 (3H, s, 12-H), 1.59 (3H, s, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 212.0 (C-9), 212.3 (C-2), 134.7 (C-11), 118.7 (C-10), 77.2 (C-6), 66.5 (C-1), 52.5 (C-5), 40.4 (C-3), 36.3 (C-8), 31.0 (C-9), 26.1 (C-7), 25.8 (C-12), 18.8 (C-4), 17.9 (C-13). ***endo*-3.32**: : R_f 0.47 (dichloromethane:ethyl acetate, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.05 (1H, m, 10-H), 4.06 (1H, dt, *J* = 11.5, 4.9 Hz, 6-H), 3.11 (1H, m, 5-H), 2.55 (1H, m, 3-Heq), 2.40–2.30 (2H, m, 9-H), 2.26–2.15 (3H, m, 3-Hax, 4-H), 2.11–2.05 (2H, m, 8-H), 1.80 (1H, m, 7-Heq), 1.70 (1H, m, 7-Hax), 1.58 (6H, m, 12,13-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 212.3 (C-9), 210.3 (C-2), 135.0 (C-11), 118.6 (C-10), 73.7 (C-6), 65.2 (C-1), 52.8 (C-5), 40.6 (C-3), 34.2 (C-8), 30.6 (C-9), 27.2 (C-7), 26.1 (C-12), 18.8 (C-4), 14.6 (C-13). HRMS (ESI-TOF) $[M+H]^+$ $C_{14}H_{21}O_3$ calcd. 237.1485, found 237.1481.

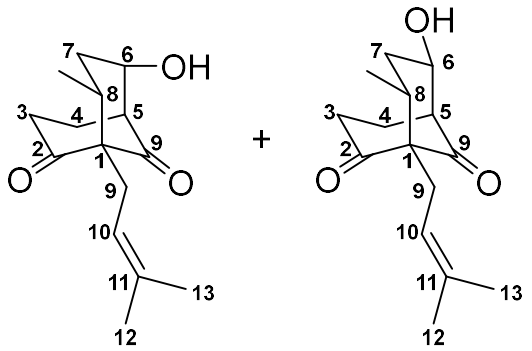
6-Hydroxy-7-methyl-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (**3.33**)



***exo*-3.33** ***endo*-3.33**

To a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **3.31** (0.100 g, 0.55 mmol, 1 eq) in dry acetonitrile (6 mL) were added methacrolein (68 µL, 0.82 mmol, 1.5 eq) and DABCO (0.062 g, 0.55 mmol, 1 eq) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (10 mL) was added and the mixture extracted with dichloromethane (4x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give ketol **3.33** (0.118 g, **86%**) as a 70:30 mixture of ***exo*-3.33**:***endo*-3.33**, IR (film): 3416, 2918, 1700, 1456 cm^{-1}; ***exo*-3.33,** R_f 0.53 (dichloromethane:ethyl acetate, 60:40) ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 5.05 (1H, m, 10-H), 3.98 (1H, m, 6-H), 2.92 (1H, m, 5-H), 2.62–2.51 (1H, m, 3-Heq), 2.39–2.27 (3H, m, 9-H, 3-Hax) 2.24–2.13 (m, 2H, 4-H), 1.98 (1H, m, 7-H), 1.97–1.74 (2H, m, 8-H), 1.61 (3H, s, 1-C-*cis*-C*H*$_3$), 1.58 (3H, s, 1-C-*trans*-C*H*$_3$), 0.97 (3H, d, *J* = 7.0 Hz, 7-CH-C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 212.4 (C-9), 210.3 (C-2), 134.8 (C-11), 118.6 (C-10), 80.6 (C-6), 65.8 (C-1), 52.2 (C-5), 43.3 (C-8), 40.5 (C-3), 31.0 (C-9), 29.4 (C-7), 26.0 (1-C-*cis*-*C*H$_3$), 18.5 (C-4), 17.9 (1-C-*trans*-*C*H$_3$), 16.6 (7-CH-*C*H$_3$); ***endo*-3.33,** R_f 0.50 (dichloromethane:ethyl acetate, 60:40) ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 5.05 (1H, m, 10-H), 3.55 (1H, dd, *J* = 7.0, 4.8 Hz, 6-H), 3.07 (1H, ddd, *J* = 6.5, 3.2, 1.4 Hz, 5-H), 2.62–2.51 (2H, m, 3-H), 2.39–2.27 (2H, m, 9-H), 2.13–2.06 (2H, m, 4-H), 1.98 (1H, m, 7-H), 1.87–1.74 (2H, m, 8-H), 1.65 (3H, s, 1-C-*cis*-C*H*$_3$), 1.60 (3H, s, 1-C-*trans*-C*H*$_3$), 1.00 (3H, d, *J* = 7.0 Hz, 7-CH-C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 212.7 (C-9), 212.5 (C-2), 135.0 (C-11), 118.5 (C-10), 78.8 (C-6), 66.1 (C-1), 52.2 (C-5), 43.0 (C-8), 40.3 (C-3), 32.1 (C-7), 30.6 (C-9), 26.0 (1-C-*cis*-*C*H$_3$), 17.6 (1-C-*trans*-*C*H$_3$), 16.6 (7-CH-*C*H$_3$), 15.1 (C-4); HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{23}O_3$ calcd. 251.1642, found 251.1639.

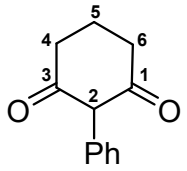
6-Hydroxy-8-methyl-1-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]nonane-2,9-dione (**3.34**)



***exo*-3.34** ***endo*-3.34**

To a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **3.31** (0.100 g, 0.55 mmol, 1 eq) in dry acetonitrile (6 mL) were added crotonaldehyde (68 µL, 0.82 mmol, 1.5 eq) and DABCO (0.062 g, 0.55 mmol, 1 eq) at 25 °C. The solution was heated at 95 °C for 60 h. After allowing to cool, water (10 mL) was added, and the mixture extracted with dichloromethane (4x10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Column chromatography (dichloromethane:ethyl acetate, 80:20) of the residue gave ketol **3.34** (0.061 g, **44%**) as 60:40 mixture of ***exo*-3.34**: ***endo*-3.34**, IR (film): 3432, 2971, 2992, 1728, 1697 cm^{-1}. Repeated column chromatography of a small fraction enabled the *exo*-isomer to be isolated, and hence NMR data for the *endo*-isomer to be deduced: ***exo*-3.34**, R_f 0.53 (silica gel, EtOAc/CH_2Cl_2, 4 : 6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 ppm (1H, tsept., *J* = 7.1, 1.4 Hz, 10-H), 4.27 (1H, dt, *J* = 3.0, 2.5 Hz, 6-H), 2.87 (1H, dm, *J* = 8.7 Hz, 5-H), 2.60–2.33 (5H, m, 9-H, 3-H), 2.15–2.03 (2H, m, 4-H), 1.89–1.74 (2H, m, 7-H), 1.64 (6H, s, 1-C-*cis*-C*H*$_3$ and 1-C-*trans*-C*H*$_3$), 0.99 (3H, d, *J* = 6.8 Hz, 8-CH-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 210.6 (C-9), 209.5 (C-2), 134.2 (C-11), 119.4 (C-10) 75.5 (C-6), 71.7 (C-1), 52.6 (C-5), 39.6 (C-3), 38.3 (C-8), 36.3 (C-7), 27.1 (C-9), 26.1 (1-C-*cis*-*C*H_3), 19.7 (C-4), 18.0 (1-C-*trans*-*C*H_3), 15.8 (8-CH-*C*H_3); ***endo*-3.34**, R_f 0.51 (dichloromethane:ethyl acetate, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.98 (1H, m, 10-H), 4.10 (1H, dt, *J* = 11.1, 5.4 Hz, 6-H), 2.99 (1H, app. t, *J* = 6.0 Hz, 5-H), 2.58–2.43 (5H, m, 9-H, 8-H, 3-H), 2.15–2.03 (2H, m, 4-H) 1.83–1.71 (2H, m, 7-H), 1.64 (6H, s, 1-C-*cis*-C*H*$_3$ and 1-C-*trans*-C*H*$_3$), 0.96 (3H, d, *J* = 6.8 Hz, 8-CH-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 212.6 (C-9), 211.6 (C-2), 135.0 (C-11), 118.5 (C-10), 71.3 (C-6), 70.2 (C-1), 52.4 (C-5), 40.2 (C-3), 37.5 (C-8), 37.4 (C-7), 29.8 (C-9), 26.0 (1-C-*cis*-*C*H_3), 18.0 (C-4), 17.8 (1-C-*trans*-*C*H_3), 15.7 (8-CH-*C*H_3). Traces of a third diastereoisomer were detected by ^{13}C NMR spectroscopy. HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{23}O_3$ calcd. 251.1642, found 251.1640.

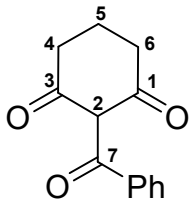
2-Phenylcyclohexane-1,3-dione (3.37)



3.37

Literature procedure was followed.[118] PhI (0.70 g, 3.47 mmol, 1 eq) was added to a solution of CuI (0.033 g, 0.17 mmol), L-proline (0.040 g, 0.34 mmol) K_2CO_3 (1.91 g, 13.81 mmol, 4 eq) and 1,3-cyclohexanedione (1.16 g, 10.3 mmol, 3 eq) in dry DMSO (6 mL). The reaction was stirred at 90 °C for 24 h after which time the cooled solution was slowly transferred in a flask containing aqueous HCl (45 mL). The aqueous phase was extracted with ethyl acetate (3x50 mL) and the combined organics washed twice with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give crude 2-phenylcyclohexane-1,3-dione **3.37** (1.30 g, **65%**) as redish oil, which was used in the subsequent step without any further purification, IR (film) 2952, 1583, 1404, 1345, 1232, 1184, 838, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 7.71−7.68 (2H, m, aryl), 7.44−7.27 (1H, m, aryl), 7.24−7.07 (1H, m, aryl), 5.48 (1H, s, 2-H), 2.63−2.56 (2H, m, 6-H), 2.38 (2H, m, 4-H), 2.03−1.95 (2H, m, 5-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 199.6 (C-1,3), 134.2 (aryl), 130.3 (aryl), 128.8 (aryl), 118.0 (aryl), 36.9 (C-2), 28.6 (C-4,6), 21.5 (C-5); HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{13}O_2$ calcd. 189.0910, found 189.0910.

2-Benzoylcyclohexane-1,3-dione (3.40)

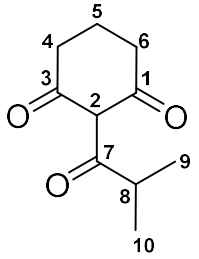


3.40

A literature procedure was adapted.[120] To a stirring solution of 1,3-cyclohexanedione (2.30 g, 20 mmol, 1 eq) in dry CH_3CN (20 mL) was added K_2CO_3 (1.50 g, 10.8 mmol, 0.5 eq) and the resulting orange suspension was stirred at 35 °C for 3 h. After this time benzoyl chloride (1.50 g, 1.2 mL, 0.5 eq) was added dropwise and a color change from orange to light yellow was observed. After 30 minutes of stirring at the same temperature more K_2CO_3 (2.00 g)

and 1,2,4-triazole (0.035 g, 0.025 mmol) were added. The resulting pink suspension was stirred for 5 h at the same temperature and overnight at 25 °C. The solvent was then removed under reduced pressure and the residue partitioned between water and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (2x50 mL), the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether:ethyl acetate, 80:20) to give 2-benzoylcyclohexane-1,3-dione **3.40** (0.560 g, **11%**) as red oil, IR (film) 3067, 2954, 1741, 1676, 1644, 1601, 1452, 1369, 1247, 1238, 1123, 1060, 1021, 879, 707, 581 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ ppm 8.10−8.06 (2H, m, aryl), 7.64 (1H, ddt, *J* = 8.8, 7.3, 1.3 Hz, aryl), 7.53−7.47 (2H, m, aryl), 6.04 (1H, s, 2-H), 2.68 (2H, td, *J* = 6.2, 1.3 Hz, 6-H), 2.46 (2H, dd, *J* = 7.4, 6.0 Hz, 4-H), 2.13 (2H, dq, *J* = 7.6, 6.3 Hz, 5-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 199.5 (C-1, C-3), 199.1 (C-7), 134.1 (aryl), 130.2 (aryl), 128.7 (aryl), 118 (C-2), 36.8 (C-6), 28.4 (C-4), 21.3 (C-5); HRMS (ESI-TOF) $[M+H]^+$ $C_{13}H_{13}O_3$ calcd. 217.0859, found 217.0855.

2-Isobutyrylcyclohexane-1,3-dione (3.43)

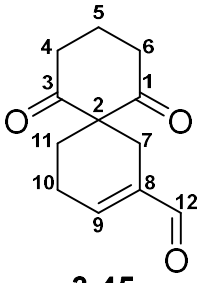


3.43

A literature procedure was adapted.[121] Cyclohexane-1,3-dione **3.30** (1.00 g, 8.65 mmol, 1 eq), 2-methyl propionyl chloride (1.03 mL, 11.6 mmol, 1.3 eq) and DMAP (0.180 g, 1.60 mmol, 18 mol %) were stirred in anhydrous toluene (30 mL) for 30 min at 25 °C and refluxed for 1 h. The cooled reaction mixture was then washed 3 times with water and once with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was taken up in anhydrous toluene (50 mL), combined with DMAP (0.150 g, 1.12 mmol) and refluxed for 3 h. The cooled reaction mixture was washed three times with water and once with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (petroleum ether:ethyl acetate, 60:40) to afford pure 2-isobutyrylcyclohexane-1,3-dione **3.43** as an orange oil (0.420 g, **28%**), IR (film) 2979, 1760, 1676, 1470, 1366, 1343, 1327, 1275, 1260, 1120, 1083, 967, 922, 881,

764, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.84 (1H, t, *J* = 1.3 Hz, 2-H), 2.71−2.60 (1H, m, 8-H), 2.49 (2H, t, *J* = 6.2 Hz, 4-H), 2.36 (2H, dd, *J* = 7.4, 6.0 Hz, 6-H), 2.06−1.97 (2H, m, 5-H), 1.23 (3H, s, C*H*$_3$), 1.21 (3H, s, C*H*$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 199.4 (C-3), 173.7 (C-7) 170.1 (C-1), 117.5 (C-2), 36.8 (C-6), 34.3 (C-8), 28.3 (C-4), 21.3 (C-5), 18.7 (C-9,10).

1,3-Dioxospiro[5.5]undec-8-ene-8-carbaldehyde (3.45)



3.45

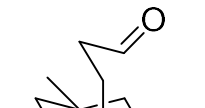
To a solution of 2-isobutyrylcyclohexane-1,3-dione **3.43** (0.100 g, 0.54 mmol, 1 eq) in dry DMF (4 mL) was added acrolein (54 µL, 0.81 mmol, 1.5 eq) at 25 °C. The resulting orange solution was stirred at 130 °C for 16 h. After this time, the reaction was allowed to cool and quenched with H_2O (6 mL). The aqueous phase was extracted three times with dichloromethane (3x15 mL), the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated. Column chromatography (hexane:ethyl acetate, 80:20 → 70:30 → 50:50) afforded 1,3-dioxospiro[5.5]undec-8-ene-8-carbaldehyde **3.45** (0.092 g, **80%**) as yellow oil, IR (film) 2957, 1726, 1694, 1426, 1382, 1277, 1221, 1174, 1182, 1021, 911, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.43 (1H, s, 12-H), 6.71 (1H, tt, *J* = 3.8, 1.7 Hz, 9-H), 2.80–2.65 (4H, m, 4-H, 6-H), 2.62 (2H, m, 11-H), 2.47–2.40 (2H, m, 10-H), 2.05 (2H, t, *J* = 6.3 Hz, 7-H), 2.02–1.83 (2H, m, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 207.71 (C-1,3), 193.11 (C-12), 148.02 (C-8), 138.94 (C-9), 64.76 (C-1), 37.12 (C-4,6)), 28.28 (C-7), 24.69 (C-10), 24.14 (C-11), 18.26 (C-5); HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{14}O_3$ calcd. 207.1016, found 207.1020.

3-Hydroxy-2,5,5-trimethylcyclohex-2-en-1-one (3.48)

3.48

A literature procedure was adapted.[145] To a cooled solution of aqueous NaOH (3 M, 12.5 mL) dimedone (**3.46**, 5.00 g, 35.6 mmol, 1 eq) was added in one portion. Iodomethane (4.5 mL, 72.3 mmol, 2 eq) was then added dropwise and the mixture heated at 100 °C for 25 h. The reaction mixture was allowed to cool at 25 °C and water and ethyl acetate were added. The aqueous phase was extracted with ethyl acetate (3x25 mL), the combined organic layers dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether:ethyl acetate, 80:20) to afford 3-hydroxy-2,5,5-trimethylcyclohex-2-en-1-one **3.48** (2.00 g, **36%**) as white solid, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.28 (4H, s, 2xC*H*$_2$), 1.65 (3H, s, -C*H*$_3$), 1.01 (6H, br s, 2xC*H*$_3$). ^{13}C NMR (101 MHz, MeOD) δ ppm 208.9 (*C*O), 110.6 (*C*(OH)=*C*(CH_3)), 47.5 (-*C*(CH_3)$_2$), 32.8 (2 x *C*H$_2$), 28.5 (-C(*C*H$_3$)$_2$), 6.9 (=C(*C*H$_3$)).

3-(1,4,4-Trimethyl-2,6-dioxocyclohexyl)propanal (3.49)

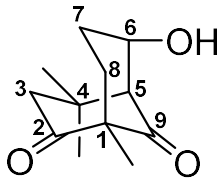


3.49

A literature procedure was adapted.[146]To a solution of 3-hydroxy-2,5,5-trimethylcyclohex-2-en-1-one **3.48** (0.080 g, 0.64 mmol, 1 eq) in dry CH_3CN (4 mL) was added acrolein (0.96 mmol, 64 µL, 1.5 eq) and DABCO (0.014 g, 0.12 mmol) at 25 °C and the reaction was heated at reflux for 4 h. The reaction mixture was allowed to cool at 25 °C and water and dichloromethane were added. The aqueous phase was extracted with dichloromethane (3x15 mL), the combined organic layers dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford pure 3-(1,4,4-trimethyl-2,6-dioxocyclohexyl)propanal **3.49** (0.130 g, **97%**) as a yellow oil, which was used in the subsequent step without any further purification, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.71 (1H, t, *J* = 1.1 Hz, C*H*O), 2.61 (4H, s,

2xCO-C*H*$_2$), 2.38 (2H, ddd, *J* = 7.9, 6.8, 1.1 Hz, C*H*$_2$-CHO), 2.07 (2H, dd, *J* = 8.3, 6.8 Hz, C*H*$_2$-CH$_2$-CHO), 1.28 (3H, s, C-C*H*$_3$), 0.99 (3H, s, C-(C*H*$_3$)$_2$), 0.98 (3H, s, C-(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.7 (*C*O), 200.8 (*C*HO), 63.5 (*C*-CH$_3$), 51.3 (-*C*(CH$_3$)$_2$), 39.3 (2 x CO-*C*H$_2$), 30.8 (*C*H$_2$-CHO), 28.8 (*C*H$_2$-CH$_2$-CHO), 28.4 (-C(*C*H$_3$)$_2$), 27.3 (-C(*C*H$_3$)$_2$), 21.0 (C-*C*H$_3$).

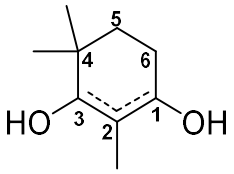
6-*exo*-Hydroxy-1,4,4-trimethylbicyclo[3.3.1]nonane-2,9-dione (3.50)



***exo*-3.50**

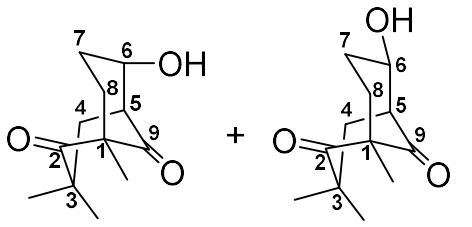
To a stirred solution of 2,5,5-trimethyl-1,3-cyclohexanedione **3.48** (1.00 g, 6.5 mmol, 1 eq) in dry acetonitrile (25 mL) were added acrolein (650 µL, 9.72 mmol, 1.5 eq) and DABCO (0.145 g, 1.3 mmol, 20 mol %) at 25 °C. The mixture was heated at 95 °C for 4 h. After allowing to cool, crude aldehyde 3-(1,4,4-trimethyl-2,6-dioxocyclohexyl)propanal **3.49** was dissolved in dry DMF (20 mL) and the reaction heated at 135 °C for 24 h. After allowing to cool, the solvent was evaporated and the residue washed with chloroform (2x5 mL) to give ketol **3.50** (0.90 g, **66%** over 2 steps) as a single diastereoisomer, R_f 0.42 (dichloromethane:ethyl acetate, 60:40) IR (film): 3455, 2958, 1728, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.65 (1H, m, 6-H), 2.72 (1H, d, *J* = 18.0 Hz, 3-Heq), 2.49 (1H, m, 5-H), 2.45 (1H, m, 3-Hax), 2.26–2.09 (2H, m, 7-Heq, 8-Heq), 2.00–1.82 (2H, m, 7-Hax, 8-Hax), 1.22 (3H, s, 4-C(C*H*$_3$)CH$_3$), 1.17 (3H, s, 1-CC*H*$_3$), 0.91 (3H, s, 4-C(CH$_3$)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 210.5 (C-9) 209.2 (C-2), 73.4 (C-6), 65.3 (C-5), 64.3 (C-1), 52.6 (C-3), 37.5 (C-8), 31.6 (C-4), 31.1 (4-*C*CH$_3$eq), 28.1 (C-7), 27.4 (4-C*C*H$_3$ax), 16.2 (1-C*C*H$_3$). HRMS (ESI-TOF) [M+H]$^+$ $C_{12}H_{19}O_3$ calcd. 211.1329, found 211.1338.

2,4,4-Trimethylcyclohexane-1,3-dione (3.51)



To a solution of 4,4-dimethyl-1,3-cyclohexanedione **3.47** (5.00 g, 35.6 mmol, 1 eq) in aqueous sodium hydroxide (3 M, 12.5 mL) at 0 °C was added iodomethane (4.43 mL, 71.3 mmol, 1 eq), dropwise over 30 min. The ice-bath was then removed and the mixture heated at 100 °C for 24 h. After cooling, the mixture was extracted with dichloromethane (3x30 mL), and the combined organic layers washed with water (2x20 mL) dried over $MgSO_4$, filtered and evaporated. Flash column chromatography (ethyl acetate;petroleum ether, 30:70) of the residue gave 2,4,4-trimethylcyclohexane-1,3-dione **3.51** (2.84 g, **52%**) as a white solid, stable for several weeks when stored at –20 °C; m.p. 163–165 °C, IR (film): 3005, 2988, 1711, 1458 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ ppm 2.48 (2H, td, *J* = 6.5, 1.3 Hz, 6-H), 1.79 (2H, t, *J* = 6.5 Hz, 5-H), 1.63 (3H, t, *J* = 1.3 Hz, 2-C-C*H*$_3$), 1.08 (6H, s, 4-C-(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, CD_3OD) δ ppm 110.0 (C-1,2,3), 40.1 (C-4), 35.8 (C-5), 28.0 (C-6), 25.4 (4-C-(*C*H_3)$_2$), 7.7 (2-C-*C*H_3); HRMS (ESI-TOF) $[M+H]^+$ $C_9H_{15}O_2$ calcd. 155.1067, found 155.1065.

6-Hydroxy-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (**3.52)**

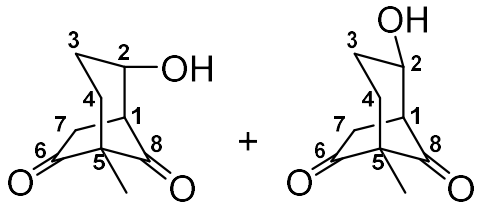


***exo*-3.52** ***endo*-3.52**

To a solution of 2,4,4-trimethylcyclohexane-1,3-dione **3.51** (0.200 g, 1.28 mmol, 1 eq) in dry acetonitrile (12 mL) were added acrolein (128 µL, 1.98 mmol, 1.5 eq) and DABCO (0.143 g, 1.28 mmol, 1 eq) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (20 mL) was added. The mixture was extracted with dichloromethane (3x20 mL) and the combined organic layers washed three times with water, dried over Na_2SO_4, filtered and evaporated to give ketol **3.52** (0.264 g, **98%**), as a 65:35 mixture of ***exo*-3.52**:***endo*-3.52**, IR (film): 3417, 2936, 1729, 1697, 1469 cm^{-1}. Column chromatography (ethyl acetate:

dichloromethane, 40:60) afforded ***exo*-3.52**: R_f 0.57 (dichloromethane:ethyl acetate, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.26 (1H, dq, *J* = 4.5, 2.4 Hz, 6-H), 2.95 (1H, m, 5-H), 2.20 (1H, m, 8-Heq), 2.12–2.00 (2H, m, 4-Heq, 8-Hax), 1.70–1.65 (2H, m, 7-H), 1.48 (1H, dm, *J* = 14.4 Hz, 4-Hax), 1.19 (3H, s, 1-C-CH_3), 1.15 (3H, s, 1x3-C(CH_3)$_2$), 0.97 (3H, s, 1x3-C(CH_3)$_2$; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 216.2 (C-2), 213.7 (C-9), 78.1 (C-6), 60.4 (C-1), 51.9 (C-5), 45.8 (C-3), 39.4 (C-8), 35.5 (C-4), 26.1 (3-C*C*H$_3$eq), 25.6 (C-7), 24.6 (3-C*C*H$_3$ax), 18.7 (1-C*C*H$_3$) and ***endo*-3.52**, R_f 0.55 (dichloromethane:ethyl acetate, 60:40), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.02 (1H, dt, *J* = 11.0, 4.5 Hz, 6-H), 3.15 (1H, m, 5-H), 2.17 (1H, m, 8-Heq), 2.05 (1H, dd, *J* = 14.7, 2.0 Hz, 4-Heq), 1.80–1.70 (2H, m, 4-Hax, 7-Heq), 1.41–1.26 (2H, m, 7-Hax, 8-Hax), 1.22 (3H, 1-C-CH_3), 1.20 (3H, 3-C(CH_3)$_2$), 0.97 (3H, s, 3-C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 216.1 (C-2), 211.9 (C-9), 74.3 (C-6), 58.9 (C-1), 52.5 (C-5), 45.7 (C-3), 37.0 (C-8), 30.9 (C-4), 27.1 (C-7), 26.0 (3-C*C*H$_3$eq), 24.1 (3-C*C*H$_3$ax), 18.3 (1-C*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{19}O_3$ calcd. 211.1329, found 211.1333.

2-Hydroxy-5-methylbicyclo[3.2.1]octane-6,8-dione (**3.55**)

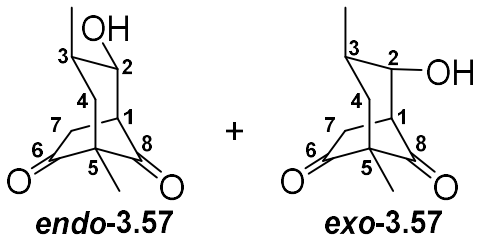


***exo*-3.55** ***endo*-3.55**

To a solution of 2-methyl-1,3-cyclopentanedione **3.54 (**0.100 g, 0.89 mmol, 1 eq) in dry DMF (4 mL) was added acrolein (90 µL, 1.3 mmol, 1 eq) at 25 °C. The solution was heated at reflux at 130 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture was extracted with dichloromethane (4x15 mL). The combined organic layers were washed with water (3x15 mL), dried over Na_2SO_4, filtered and evaporated to give ketol **3.55** (0.090 g, **60%**) as an 80:20 mixture of ***exo*-3.55**:***endo*-3.55**, R_f 0.4 (dichloromethane:ethyl acetate, 60:40) IR (film): 3450, 2933, 1765, 1723, 1453 cm^{-1}; ***exo*-3.55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.57 (1H, m, 2-H), 3.03 (1H, app. t, *J* = 5.4 Hz, 1-H), 2.70–2.52 (2H, m, 7-H), 2.25 (1H, m, 4-Heq), 1.95–1.87 (2H, m, 3-H), 1.81–1.77 (1H, m, 4-Hax), 1.07 (3H, s, 5-CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 214.5 (C-8), 211.1 (C-6), 77.5 (C-2), 59.3 (C-5), 52.7 (C-1), 42.1 (C-7), 40.1 (C-4), 26.6 (C-3), 12.2 (5-C*C*H$_3$); ***endo*-3.55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.25 (1H, m, 2-H), 3.08 (1H, dd, *J* = 7.5, 3.3 Hz, 1-H), 2.50-2.43 (2H, m, 7-H), 2.25

(1H, m, 4-Heq), 1.95–1.75 (3H, m, 3-H, 4-Hax), 1.06 (3H, s, 5-CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 213.5 (C-8), 211.6 (C-6), 73.6 (C-2), 58.3 (C-5), 54.4 (C-1), 38.7 (C-7), 35.9 (C-4), 27.1 (C-3), 11.6 (5-C*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_9H_{13}O_3$ calcd. 169.0859, found 169.0861.

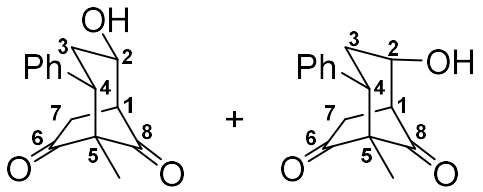
2-Hydroxy-3,5-dimethylbicyclo[3.2.1]octane-6,8-dione (**3.57**)



***endo*-3.57** ***exo*-3.57**

To a solution of 2-methyl-1,3-cyclopentanedione **3.54** (0.100 g, 0.9 mmol, 1 eq) in dry acetonitrile (6 mL) were added methacrolein (73 µL, 1.3 mmol, 1.5 eq) and DABCO (0.020 g, 0.18 mmol, 20 mol %) at 25 °C. The solution was heated at reflux at 130 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4x15 mL). The combined organic layers were washed with water (3x15 mL), dried over Na_2SO_4, filtered and evaporated to give ketol **3.57** (0.080 g, **50%**) as a 70:30 mixture of ***endo*-3.57**: ***exo*-3.57**, R_f 0.53 (dichloromethane:ethyl acetate, 60:40) IR (film): 3499, 2933, 1767, 1724, 1455 cm^{-1}; ***endo*-3.57**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.69 (1H, dd, *J* = 9.6, 3.2 Hz, 2-H), 3.03 (1H, dd, *J* = 7.5, 3.3 Hz, 1-H), 2.96 (1H, d, *J* = 19.4 Hz, 7-Hax), 2.48 (1H, dd, *J* = 19.4, 7.5 Hz, 7-Heq), 1.92–1.67 (3H, m, 3-H, 4-H), 1.02 (3H, s, 5-CC*H*$_3$), 1.01 (3H, d, *J* = 6.6 Hz, 3-CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 213.4 (C-8), 211.6 (C-6), 78.9 (C-2), 59.4 (C-5), 53.7 (C-1), 44.5 (C-7), 39.1 (C-4), 32.9 (C-3), 17.3 (3-CH-*C*H$_3$), 11.6 (5-C*C*H$_3$) (400 MHz, $CDCl_3$); ***exo*-3.57**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.25 (1H, ddd, *J* = 5.1, 3.4, 2.3 Hz, 2-H), 3.01 (1H, m, 1-H), 2.60–2.58 (2H, m, 7-H), 2.08 (1H, m, 3-Heq), 1.92–1.67 (2H, m, 3-Hax, 4-Hax), 1.03 (3H, s, 5-CC*H*$_3$), 0.97 (3H, d, *J* = 6.7 Hz, 3-CH-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 215.1 (C-8), 211.4 (C-6), 79.6 (C-2), 58.8 (C-5), 52.5 (C-1), 46.7 (C-7), 41.8 (C-4), 30.2 (C-3), 15.4 (3-CH-*C*H$_3$), 12.0 (5-C-*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{15}O_3$ calcd. 183.1016, found 183.1014.

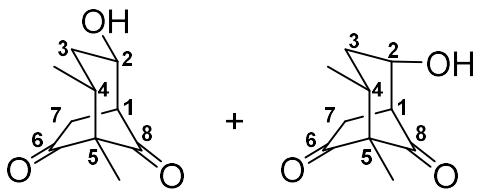
2-Hydroxy-5-methyl-4-phenylbicyclo[3.2.1]octane-6,8-dione (**3.58**)



***endo*-3.58** ***exo*-3.58**

To a solution of 2-methyl-1,3-cyclopentanedione **3.54** (0.100 g, 0.9 mmol, 1 eq) in dry acetonitrile (6 mL) were added cinnamaldehyde (168 µL, 1.3 mmol, 1.5 eq) and DABCO (0.101 g, 0.9 mmol, 1 eq) at 25 °C. The solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4x15 mL). The combined organic layers were washed with water (3x15 mL), dried over $MgSO_4$, filtered and evaporated. Column chromatography (dichloromethane:ethyl acetate, 80:20) gave ketol **16** (0.020 g, **10%**) as a 60:40 mixture of mixture of ***endo*-3.58**:***exo*-3.58**; R_f 0.3 (silica gel, EtOAc/CH_2Cl_2, 2 : 8, v/v) IR (film): 3488, 2988, 1763, 1721, 1455, 1046 cm^{-1}; ***endo*-3.58**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34–7.26 (3H, m, *m*- and *p*-aryl), 7.03 (2H, dd, *J* = 7.8, 2.4 Hz, *o*-aryl), 4.38 (1H, ddd, *J* = 10.4, 5.9, 3.5 Hz, 2-H), 3.19 (1H, dd, *J* = 7.5, 3.5 Hz, 1-H), 3.16 (1H, d, *J* = 19.0 Hz, 7-Hax), 2.65 (1H, dd, *J* = 14.0, 4.8 Hz, 4-H), 2.60 (1H, dd, *J* = 19.0, 7.5 Hz, 7-Heq), 2.29–2.23 (1H, m, 3-Heq), 2.05 (1H, m, 3-Hax), 0.77 (3H, s, 5-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 212.5 (C-6), 210.3 (C-8), 137.6 (*ipso*-aryl), 128.7 (aryl), 128.6 (aryl), 128.1 (aryl), 71.7 (C-2), 61.7 (C-5), 54.3 (C-1), 50.6 (C-4), 38.8 (C-7), 35.3 (C-3), 10.7 (5-C*C*H$_3$); ***exo*-3.58**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34–7.26 (3H, m, *m*- and *p*-aryl), 7.07 (2H, dd, *J* = 7.8, 2.4 Hz, *o*-aryl), 4.63 (1H, ddd, *J* = 5.2, 3.5, 1.7 Hz, 2-H), 3.41 (1H, dd, *J* = 13.7, 4.8 Hz, 4-H), 3.13 (1H, dd, *J* = 8.0, 4.5 Hz, 1-H), 2.68–2.56 (2H, m, 7-H), 2.26 (1H, m, 3-Heq), 2.04 (1H, m, 3-Hax), 0.79 (3H, s, 5-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 213.1 (C-8), 212.5 (C-6), 138.0 (*ipso*-aryl), 128.7 (aryl), 128.6 (aryl), 128.1 (aryl), 75.1 (C-2), 62.7 (C-5), 54.1 (C-1), 52.6 (C-4), 42.0 (C-7), 34.8 (C-3), 11.0 (5-C-*C*H$_3$); HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{17}O_3$ calcd. 245.1172, found 245.1172.

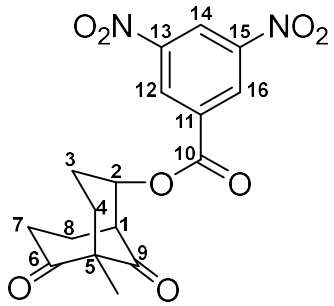
2-Hydroxy-4,5-dimethylbicyclo[3.2.1]octane-6,8-dione (**3.59**)



***endo*-3.59** ***exo*-3.59**

To a solution of 2-methyl-1,3-cyclopentanedione **3.54** (0.100 g, 0.9 mmol, 1 eq) in dry acetonitrile (6 mL) were added crotonaldehyde (73 µL, 1.3 mmol, 1.5 eq) and DABCO (0.101 g, 0.9 mmol, 1 eq) at 25 °C. The resulting solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4x15 mL). The combined organic layers were washed with water (3x15 mL), dried over $MgSO_4$, filtered and evaporated to give ketol **3.59** (0.109 g, **61%**) as a 37:50 mixture of mixture of ***endo*-3.59**: ***exo*-3.59**, R_f 0.46 (dichloromethane:ethyl acetate, 60:40), IR (film): 3441, 2936, 1763, 1719, 1455, 1041 cm^{-1}; ***endo*-3.59**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.20 (1H, ddd, *J* = 11.1, 5.9, 3.4 Hz, 2-H), 3.04 (1H, dd, *J* = 7.0, 3.4 Hz, 1-H), 2.88 (1H, d, *J* = 19.5 Hz, 7-Hax), 2.56 (1H, dd, *J* = 19.5, 7.0 Hz, 7-Heq), 2.05 (1H, dt, *J* = 14.4, 5.5 Hz, 3-Heq), 1.65 (1H, m, 4-H), 1.27 (1H, m, 3-Hax), 0.98 (3H, d, *J* = 5.0 Hz, 4-CH-C*H*$_3$), 0.88 (3H, s, 5-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 210.4 (C-8), 209.9 (C-6), 71.8 (C-2), 61.3 (C-5), 53.8 (C-1), 39.7 (C-4), 38.6 (C-7), 36.3 (C-3), 15.0 (4-CH-*C*H_3), 9.79 (5-C-*C*H_3); ***exo*-3.59**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.48 (1H, ddd, *J* = 5.1, 4.1, 1.6 Hz, 2-H), 2.98 (1H, m, 1-H), 2.55–2.45 (2H, m, 7-H), 2.36 (1H, m, 4-H), 1.82 (1H, ddt, *J* = 15.8, 5.6, 1.3 Hz, 3-Heq), 1.55 (1H, ddd, *J* = 15.8, 13.1, 3.9 Hz, 3-Hax), 0.99 (3H, d, *J* = 5.0 Hz, 4-CH-C*H*$_3$), 0.90 (3H, s, 5-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 215.5 (C-8), 214.3 (C-6), 75.8 (C-2), 62.4 (C-5), 52.1 (C-1), 44.0 (C-4), 42.0 (C-7), 35.6 (C-3), 15.1 (4-CH-*C*H_3), 10.0 (5-C-*C*H_3). The ^1H NMR spectrum showed the presence of third diastereoisomer (13%). HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{15}O_3$ calcd. 183.1016, found 183.1012.

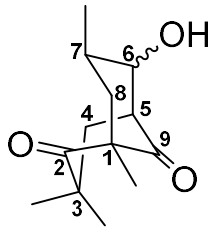
5-exo-Methyl-6,9-dioxobicyclo[3.3.1]nonan-2-yl 3,5-dinitrobenzoate (3.60)



To a solution of 6-*exo*-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione ***exo*-3.2** (0.170 g, 0.93 mmol, 1 eq) in dry dichloromethane were added triethylamine (400 µL, 2.79 mmol, 3 eq) and 3,5-dinitrobenzoyl chloride (0.235 g, 1.02 mmol, 1.1 eq) at 25 °C. The mixture was then stirred at 25 °C for 16 h. Water (20 mL) was then added, and the mixture extracted with dichloromethane (4x20 mL). The combined organic layers were washed with water (3x10

mL), dried over $MgSO_4$, filtered and evaporated. Flash column chromatography (dichloromethane:ethyl acetate, 80:20) of the residue gave **3.60** (0.030 g, **8%**) which was recrystallized by slow diffusion of hexane into a nearly sat. solution in dichloromethane, R_f 0.3 (ethyl acetate:petroleum ether, 30:70), IR (film): 2936, 1731, 1704, 1629, 1545, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.24 (1H, t, *J* = 2.1 Hz, 14-aryl), 9.05 (2H, d, *J* = 2.1 Hz, 12,16-aryl), 5.62 (1H, m, 2-H), 3.21 (1H, m, 1-H), 2.69 (1H, ddd, *J* = 16.5, 7.5, 4.5 Hz, 7-Heq), 2.47 (1H, dt, *J* = 16.5, 9.5 Hz, 7-Hax), 2.39–2.27 (2H, m, 3-Heq, 8-Heq), 2.15-2.02 (3H, m, 3-Hax, 4-H), 1.86 (1H, m, 8-Hax), 1.26 (3H, s, -5-C-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 210.8 (C-9), 209.4 (C-6), 161.6 (C-10), 148.9 (C-13,15), 133.6 (C-11), 129.5 (C-12,16), 122.9 (C-14), 81.1 (C-2), 63.2 (C-5), 48.4 (C-1), 38.1 (C-7), 37.7 (C-4), 24.4 (C-3), 18.9 (C-8), 16.8 (5-C-*C*H_3); *m/z* (EI^+, %) 395 (20), 394 (M^+, 100), 364 (17); HRMS (ESI-TOF) $[M+H]^+$ $C_{17}H_{17}N_2O_8$ calcd. 377.0979, found 377.0981.

6-Hydroxy-1,3,3,7-tetramethylbicyclo[3.3.1]nonane-2,9-dione (**3.61**)

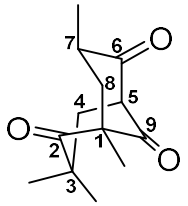


3.61

To a solution of 2,4,4-trimethylcyclohexane-1,3-dione **3.51** (0.200 g, 1.28 mmol, 1 eq) in dry acetonitrile (10 mL) were added methacrolein (160 µL, 1.92 mmol, 1.5 eq) and DABCO (0.143 g, 1.28 mmol, 1 eq) at 25 °C. The solution was heated at 95 °C for 16 h. After this time the reaction was allowed to cool to 25 °C then evaporated. Water (15 mL) was then added and the mixture extracted with dichloromethane (2x15 mL). The combined organic layers were washed with water (2x15 mL) and then with brine, dried over Na_2SO_4, filtered and evaporated to give ketol **3.61** (0.186 g, **65%**) as a colourless oil (mixture of diastereoisomers approx. 43:41:14:2 and confirmed by oxidation to **3.62**); R_f 0.7 (dichloromethane:ethyl acetate, 60:40); IR (film): 3405, 2972, 2937, 1726, 1694, 1496, 1061, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.93 and 3.78 (1H, m, 6-H), 3.50 (1H, dd, *J* = 10.5, 4.5 Hz, 5-H), 3.15–2.63 (2H, m), 2.40–0.90 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 216.4, 216.1, 215.2, 213.8, 213.40, 212.1, 211.7, 207.5, 83.9, 83.1, 81.2, 79.3, 77.4, 59.9, 59.8, 59.3, 53.0, 51.9, 51.7, 46.2, 45.8, 45.72, 45.4, 45.3, 44.1, 43.4, 37.1, 35.3, 33.4, 31.9, 31.5, 31.4, 29.4, 27.4, 26.3, 26.1, 26.1, 25.8, 25.5, 25.3, 24.6, 24.1, 19.2, 18.6, 18.5, 18.3, 17.2, 16.5; *m/z* (EI^+, %) 225 (3), 224 (M^+, 17), 196 (6), 138 (52), 123 (100); HRMS

(ESI-TOF) [M+] $C_{13}H_{20}O_3$ calcd. 224.1407, found 224.1408.

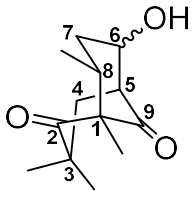
1,3,3,7-*exo*-Tetramethylbicyclo[3.3.1]nonane-2,6,9-trione (**3.62**)



3.62

To a solution of 6-hydroxy-1,3,3,7-tetramethylbicyclo[3.3.1]nonane-2,9-dione **3.61** (0.200 g, 0.90 mmol, 1 eq) in dry dichloromethane (10 mL) was added pyridinium chlorochromate (0.230 g, 1.08 mmol, 1.2 eq) and the resulting dark solution was stirred at 25 °C for 16 h. After allowing to cool, the solution was filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate, the mixture filtered through a pad of silica, and the filtrate evaporated to give an 85:15 mixture of epimers. On standing for 2 weeks, the mixture afforded trione **3.62** (0.191 g, **94%**) as pale green needles, R_f 0.73 (petroleum ether:ethyl acetate, 70:30), m.p. 94–95 °C; IR (film): 2262, 1716, 1699, 1270, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ ppm 3.69 (dd, *J* = 10.8, 1.7 Hz, 5-H), 2.51 (1H, m, 7-H), 2.31 (1H, dd, *J* = 14.5, 10.8 Hz, 4-Heq), 2.32–2.22 (2H, m, 8-H), 1.75 (1H, d (br), *J* = 14.5 Hz, 4-Hax), 1.25 (3H, s, 3-C-C*H*$_3$eq), 1.13 (3H, s, 1-C-C*H*$_3$), 1.00 (3H, s, 3-C-C*H*$_3$ax), 0.98 (3H, d, *J* = 6.3 Hz 7-CH-C*H*$_3$); ^{13}C NMR (100 MHz, CD_3CN) δ ppm 215.6 (C-2), 206.7 (C-9), 205.4 (C-6), 64.8 (C-5), 60.6 (C-1), 45.6 (C-3), 41.7 (C-8), 38.9 (7-*C*H-CH_3), 36.4 (C-4), 26.3 (2-C-*C*H$_3$*eq*), 24.3 (2-C-*C*H$_3$*ax*), 18.7 (1-C-*C*H$_3$), 13.7 (7-CH-*C*H$_3$); *m/z* (EI+, %) 223 (9), 222 (M^+, 66), 194 (36), 138 (100), 123 (97); HRMS (ESI-TOF) [M+] $C_{13}H_{18}O_3$ calcd. 222.1251, found 222.1251.

6-Hydroxy-1,3,3,8-tetramethylbicyclo[3.3.1]nonane-2,9-dione (**3.63**)

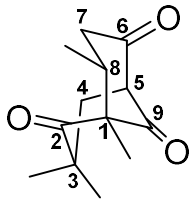


3.63

To a solution of 2,4,4-trimethylcyclohexane-1,3-dione **3.51** (0.100 g, 0.64 mmol, 1 eq) in dry

acetonitrile (6 mL) were added crotonaldehyde (80 µL, 0.96 mmol, 1.5 eq) and DABCO (0.072 g, 0.64 mmol, 1 eq) at 25 °C. The resulting solution was heated at 95 °C for 16 h. After allowing to cool, water (15 mL) was added and the mixture extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (3x10 mL), dried over $MgSO_4$, filtered and evaporated to give **3.63** (71 mg, **49%)** as a pale yellow oil, (mixture of 4 diastereoisomers approx. 40:27:19:14 and confirmed by oxidation to **3.63**); R_f 0.6 (dichloromethane:ethyl acetate, 60:40) ; IR (film): 3405, 2972, 2937, 1726, 1694, 1496, 1061, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.25 and 4.00 (1H, m, 6-H), 3.20 and 2.90 (1H, m, 5-H), 2.70–1.20 (m, 5H), 1.25–0.80 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 216.9, 216.8, 214.9, 214.0, 213.6, 212.5, 211.5, 80.9, 76.3, 72.6, 70.6, 63.8, 63.6, 62.5, 61.9, 52.4, 52.2, 51.7, 51.2, 46.0, 45.7, 45.6, 45.4, 45.3, 42.6, 41.1, 39.8, 36.2, 36.1, 36.0, 34.6, 34.2, 31.9, 30.9, 30.7, 27.3, 27.1, 26.6, 26.5, 24.7, 24.6, 24.3, 24.1, 17.1, 17.0 (2 lines), 16.9, 16.4, 15.7, 15.6, 14.6; *m/z* (EI^+, %) 225 (8), 224 (M^+, 58), 196 (14), 178 (22), 138 (88), 123 (100); HRMS (ESI-TOF) $[M]^+$ calcd. 224.1407, found 224.1408.

1,3,3,8-Tetramethylbicyclo[3.3.1]nonane-2,6,9-trione (**3.64**)

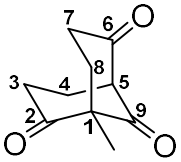


3.64

To a solution of 6-hydroxy-1,3,3,8-tetramethylbicyclo[3.3.1]nonane-2,9-dione **3.63** (0.050 g, 0.2 mmol, 1 eq) in dry dichloromethane (3 mL) was added pyridinium chlorochromate (0.057 g, 0.26 mmol, 1.2 eq) and the mixture was stirred at 25 °C for 16 h. The mixture was then filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate, filtered through a pad of silica and the filtrate evaporated. The residue was purified by flash column chromatography (dichloromethane:ethyl acetate, 90:10) to give trione **3.64** (0.015 g, 30%) as a 70:30 mixture of **8-*endo*-3.64**:**8-*exo*-3.64**; R_f 0.66 (silica gel, EtOAc/petroleum ether, 3 : 7, v/v); IR (film): 2975, 1741, 1716, 1698, 1455 cm^{-1}; **8-*endo*-3.64**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.71 (1H, dt, *J* = 10.7, 1.5 Hz, 5-H), 2.57 (1H, dd, *J* = 15.5, 6.3 Hz, 7-Hax), 2.47 (1H, m, 8-H), 2.35–2.21 (2H, m, 7-Heq, 4-Heq), 1.68 (1H, m, 4-Hax), 1.31 (3H, s, 3-C-CH_3eq), 1.18 (3H, s, 1-C-CH_3), 1.08 (3H, s, 3-C-CH_3ax), 0.82 (3H, d, *J* = 7.2 Hz, 8-CH-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 215.2 (C-2), 205.0 (C-9), 204.2 (C-6), 64.4 (C-5), 63.0 (C-1), 45.2 (C-3), 42.6 (C-7), 37.4 (C-8), 36.9 (C-4), 27.0 (3-C-

*C*H$_3$eq), 24.8 (3-C-*C*H$_3$ax), 16.6 (1-C-*C*H$_3$), 15.3 (8-CH-*C*H$_3$); **8-*exo*-3-64**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 3.73 (1H, dt, *J* = 10.8, 1.8 Hz, 5-H), 2.41 (1H, dd, *J* = 4.7, 1.8 Hz, 7-Heq), 2.32–2.05 (3H, m, 7-Hax, 4-Heq, 8-H), 1.75 (1H, m, 4-Hax), 1.36 (3H, s, 3-C-C*H$_3$*eq), 1.22 (3H, d, *J* = 6.7 Hz, 8-CH-C*H$_3$*), 1.17 (3H, s, 1-C-C*H$_3$*), 1.02 (3H, s, 3-C-C*H$_3$*ax); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm 213.6 (C-2), 205.5 (C-9), 203.8 (C-6), 63.1 (C-5), 62.0 (C-1), 45.1 (C-3), 43.8 (C-7), 37.2 (C-4), 35.8 (C-8), 27.4 (3-C-*C*H$_3$eq), 24.7 (3-C-*C*H$_3$ax), 17.3 (1-C-*C*H$_3$), 15.1 (8-CH*C*H$_3$); ***m/z*** (EI$^+$, %) 223 (7), 222 (M$^+$, 49), 194 (19), 179 (62); HRMS (ESI-TOF) [M$^+$] C$_{13}$H$_{18}$O$_3$ calcd. 222.1251, found 222.1251.

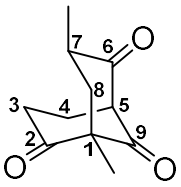
1-Methylbicyclo[3.3.1]nonane-2,6,9-trione (**3.65**)



3.65

To a solution of 6-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione **3.2** (0.040 g, 0.22 mmol, 1 eq) in dry dichloromethane was added pyridinium chlorochromate (0.056 g, 0.26 mmol, 1.2 eq) in one portion at 25 °C and stirred for 16 h. The mixture was then filtered through a pad of Celite® and evaporated. The residue was dissolved in ethyl acetate, the solution passed through a pad of silica and the filtrate evaporated to give trione **3.65** (0.030 g, **76%**) as a pale green powder, R$_f$ 0.58 (petroleum ether:ethyl acetate 70:30), m.p. 97–99 °C. IR (film): 1711, 1453, 1246, 1036, 1029 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$CN) δ ppm 3.45 (1H, t, *J* = 5.0 Hz, 5-H), 2.70–2.55 (4H, m, 7-H, 8-H), 2.53 (1H, m, 3-Heq), 2.12–2.03 (2H, m, 4-H), 1.75 (1H, m, 3-Hax), 1.22 (3H, s, -C*H$_3$*); ^{13}C NMR (100 MHz, CD$_3$CN) δ ppm 209.9 (C-9), 208.0 (C-2), 204.6 (C-6), 64.5 (C-5), 63.9 (C-1), 37.9 (C-3), 37.5 (C-7), 32.1 (C-8), 23.4 (C-4), 16.5 (1-C-CH$_3$); HRMS (ESI-TOF) [M+H]$^+$ C$_{10}$H$_{13}$O$_3$ calcd. 181.0859, found 181.0857.

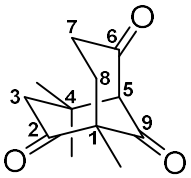
1,7-*exo*-Dimethylbicyclo[3.3.1]nonane-2,6,9-trione (**3.66**)



3.66

To a solution of 6-hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione **3.19** (0.050 g, 0.25 mmol, 1 eq) in dry dichloromethane was added pyridinium chlorochromate (0.066 g, 0.30 mmol, 1.2 eq) in one portion at 25 °C, and the mixture was stirred for 16 h. The mixture was then filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate and the solution passed through a pad of silica. The filtrate was evaporated to give trione **3.66** (0.037 g, **77%**) as a light green oil; R_f 0.23 (petroleum ether:ethyl acetate 70:30); IR (film): 2983, 2988, 1740, 1709, 1457, 1038 cm $^{-1}$; ^{1}H NMR (400 MHz, CD_3CN) δ ppm 3.54 (1H, dd, *J* = 7.2, 2.6 Hz, 5-H), 2.75-2.52 (3H, m, 7-H, 3-H), 2.25–2.15 (3H, m, 8-H, 4-Heq) 2.04 (1H, m, 4-Hax), 1.20 (3H, s, 1-C-C*H*$_3$), 1.04 (3H, d, *J* = 6.3 Hz, 7-CH-C*H*$_3$); ^{13}C NMR (100 MHz, CD_3CN) δ ppm 210.7 (C-9), 208.1 (C-2), 204.2 (C-6), 64.8 (C-5), 64.6 (C-1), 41.6 (C-7), 41.1 (C-8), 37.6 (C-3), 22.5 (C-4), 16.5 (1-C-*C*H$_3$), 14.5 (7-CH-*C*H$_3$); *m/z* (EI$^+$, %) 194 (M$^+$, 34), 166 (19), 152 (20), 140 (30), 69 (100); HRMS (ESI-TOF) [M$^+$] $C_{11}H_{14}O_3$ calcd. 194.0937, found 194.0938.

1,4,4-Trimethylbicyclo[3.3.1]nonane-2,6,9-trione (3.67)

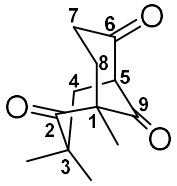


3.67

To a solution of 6-*exo*-hydroxy-1,4,4-trimethylbicyclo[3.3.1]nonane-2,9-dione **3.50** (0.500 g, 2.37 mmol, 1 eq) in dry dichloromethane was added pyridinium chlorochromate (0.610 g, 2.85 mmol, 1.2 eq) in one portion at 25 °C and stirred for 16 h. The mixture was then filtered through a pad of Celite® and evaporated. The residue was dissolved in ethyl acetate, the solution passed through a pad of silica and the filtrate evaporated to give trione **3.67** (0.290 g, **59%**), R_f 0.23 (petroleum ether:ethyl acetate, 80:20). IR (film): 2955, 2023, 2851, 1734, 1709, 1697, 1453, 1375, 1265, 1236, 1158, 1095, 1010, 736, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.27 (1H, s, 5-H), 2.73 (1H, ddt, J_{gem} = 18.5, $J_{eq\text{-}ax}$ = 7.6, $J_{eq\text{-}eq}$ = 1.7 Hz, 7-

Heq), 2.64–2.51 (1H, m, 7-Hax), 2.56 (s, 2H, 3-H), 2.09–2.01 (1H, m, 8-Heq), 1.72 (1H, ddd, J_{gem} = 14.0, $J_{ax\text{-}ax}$ = 12.3, $J_{ax\text{-}eq}$ = 7.7 Hz, 8-Hax), 1.30 (3H, s, 1-C-CH_3), 1.12 (3H, s, 4-C-CH_3)$_2$), 0.95 (3H, s, 4-C-CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 207.4 (C-9), 205.3 (C-6), 203.2 (C-2), 76.5 (C-5), 62.4 (C-1), 52.2 (C-3), 38.1 (C-7), 33.9 (C-4), 31.4 (C-8), 29.5 (4-C-CH$_3$)$_2$), 27.4(4-C-CH$_3$)$_2$), 15.9 (1-C-CH$_3$). HRMS (ESI-TOF) [M+H]$^+$ $C_{12}H_{17}O_3$ calcd. 209.1172, found 209.1179.

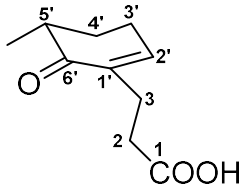
1,3,3-Trimethylbicyclo[3.3.1]nonane-2,6,9-trione (**3.68**)



3.68

To a solution of 6-hydroxy-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione **3.52** (0.075 g, 0.36 mmol, 1 eq) in dry dichloromethane (3 mL) was added pyridinium chlorochromate (0.092 g, 0.43 mmol, 1 eq) and the dark solution was stirred at 25 °C for 16 h. The mixture was then filtered through a pad of Celite® and the filtrate was evaporated. The residue was dissolved in ethyl acetate, the solution filtered through a pad of silica and the filtrate was evaporated to give trione **3.68** (0.050 g, **67%**) as a white solid, R_f 0.31 (petroleum ether:ethyl acetate, 70:30), m.p. 99–104 °C; IR (film) 2977, 2934, 1742, 1715, 1694, 1470, 1373, 1276, 1087, 1045, 764, 740 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ ppm 3.65 (1H, d, J = 10.8 Hz, 5-H), 2.45 (1H, m, 7-Heq), 2.37–2.25 (2H, m, 4-Heq, 7-Hax), 2.21 (1H, app. dd, J = 13.3, 7.6 Hz, 8-Heq), 1.72 (1H, m, 4-Hax), 1.47 (1H, td, J = 13.3, 5.3 Hz, 8-Hax), 1.26 (3H, s, 3-C-CH_3eq), 1.13 (3H, s, 1-C-CH_3), 1.01 (3H, s, 3-C-CH_3ax); ^{13}C NMR (100 MHz, CD_3CN) δ ppm 215.5 (C-2), 206.0 (C-9), 205.8 (C-6), 65.1 (C-5), 59.8 (C-1), 45.7 (C-3), 36.3 (C-7), 35.3 (C-4), 33.1 (C-8), 26.2 (3-C-CH$_3$), 24.4 (3-C-CH$_3$), 18.9 (1-C-CH$_3$); *m/z* (EI$^+$, %) 209 (8), 208 (M$^+$, 62), 180 (53), 138 (68), 123 (100), 110 (52); HRMS (ESI-TOF) [M$^+$] $C_{12}H_{16}O_3$ calcd. 208.1094, found 208.1094.

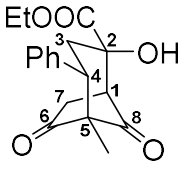
3-(5-Methyl-6-oxocyclohex-1-en-1-yl)propanoic acid (3.72)



3.72

To a solution of 2-methyl-1,3-cyclohexanedione **2.47** (0.100 g, 0.8 mmol, 1 eq) in water (13 mL) was added acrolein (80 µL, 1.2 mmol, 1.5 eq) at 25 °C. The resulting solution was stirred at 95 °C for 72 h. After this time, the reaction was allowed to cool and the aqueous phase was extracted three times in dichloromethane (3x15 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to give **3.72** (0.142 g, **97%**) as colorless oil, IR (film) 2933, 1710, 1668, 1381, 1197, 911, 732, 646, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.74 (1H, t, *J* = 3.7 Hz, 2'-H), 2.49 (4H, m, 2-C*H*$_2$, 3-C*H*$_2$), 2.41–2.34 (3H, m, 3'-H, 5'-H), 2.08–1.99 (1H, dqd, *J* = 13.5, 4.6, 1.1 Hz, 4'-Heq), 1.77–1.65 (1H, dddd, *J* = 13.2, 11.8, 8.6, 6.5 Hz, 4'-Hax), 1.14 (3H, d, *J* = 6.8 Hz, 5'-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 202.0 (C-6'), 177.9 (C-1), 145.7 (C-2'), 137.5 (C-1'), 41.8 (C-5'), 33.1 (C-2), 31.0 (C-4'), 25.6 (C-3), 25.5 (C-3'), 15.2 (5'-CH_3); HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{14}O_3$ calcd. 183.0999, found 183.1021.

Ethyl-2-hydroxy-5-methyl-6,8-dioxo-4-phenylbicyclo[3.2.1]octane-2-carboxylate (3.89)



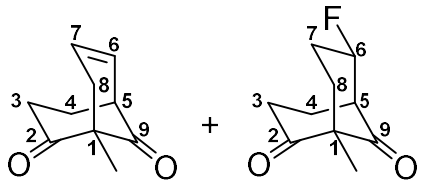
3.89

To a solution of 2-methyl-1,3-cyclopentanedione **3.54** (0.100 g, 0.9 mmol, 1 eq) in dry acetonitrile (6 mL) were added ethyl 2-oxo-4-phenylbut-3-enoate **3.88** (0.181 g, 0.9 mmol, 1 eq) and DABCO (0.099 g, 0.9 mmol, 1 eq) at 25 °C. The resulting solution was heated at 95 °C for 16 h. After allowing to cool down to room temperature, water (15 mL) was added and the mixture extracted with dichloromethane (4 x 20 mL). The combined organic layers were

washed with water, dried over $MgSO_4$, filtered and evaporated. Column chromatography (petroleum ether:ethyl acetate, 85 : 15 → 75 : 25 → 70 : 30) afforded **3.89** (0.050 g, **35%**) as a 57:43 mixture of diastereoisomers, IR (film): 3450, 2931, 1770, 1731, 1455, 1258, 1217, 1084, 1055, 758, 701 cm^{-1}; Major diastereoisomer ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32–7.28 (3H, m, Aryl), 7.10 (2H, dd, *J* = 7.5, 2.1 Hz, Aryl), 4.35–4.29 (2H, m, -OC*H*$_2$CH$_3$), 3.36–3.30 (1H, dd, $J_{ax\text{-}ax}$ = 13.7, $J_{ax\text{-}eq}$ = 4.7 Hz, 4-H), 3.23–3.15 (1H, m, 7-Hax), 3.07 (1H, d, $J_{eq\text{-}ax}$ = 7.9 Hz, 1-H), 2.72–2.56 (2H, m, 7-Heq, 3-Hax), 2.09–2.04 (1H, m, 3-Heq), 1.36 (3H, t, *J* = 7.2 Hz, -OCH$_2$C*H*$_3$), 0.82 (3H, s, 5-C-C*H*$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.7 (C-8), 209.4 (C-6), 172.57 (-*C*O$_2$Et), 137.6 (Aryl), 128.8 (Aryl), 128.7 (Aryl), 128.3 (Aryl), 79.7 (C-2), 63.3 (-O*C*H$_2$CH$_3$), 62.4 (C-5), 54.4 (C-1), 51.7 (C-4), 42.1 (C-7), 36.31 (C-3), 14.40 (-OCH$_2$*C*H$_3$), 11.10 (5-C-*C*H$_3$) Minor diastereoisomer; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32–7.28 (3H, m, aryl), 7.06 (2H, dd, *J* = 7.4, 2.1 Hz, 2H, Aryl), 4.35–4.29 (2H, m, -OC*H*$_2$CH$_3$), 3.36–3.30 (1H, m, 7-Hax) 3.23–3.15 (1H, m, 4-H), 2.72–2.56 (2H, m, 7-Heq, 3-Hax), 2.35–2.19 (1H, m, 3-Heq), 1.36 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 0.81 (3H, 5-C-C*H*$_3$).^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.7 (C-8), 209.0 (C-6), 173.8 (*C*O$_2$Et), 137.6 (Aryl), 128.8 (Aryl), 128.6 (Aryl), 128.2(Aryl), 78.0 (C-2), 61.2 (-O*C*H$_2$CH$_3$), 60.5 (C-5), 55.6 (C-1), 50.2 (C-4), 40.9 (C-7), 36.7 (C-3), 14.2 (-OCH$_2$*C*H$_3$), 10.9 (5-C-*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{18}H_{21}O_5$ calcd. 317.1384, found 317.1375.

1-Methylbicyclo[3.3.1]non-6-ene-2,9-dione (4.1)

6-Fluoro-1-methylbicyclo[3.3.1]nonane-2,9-dione (4.4)

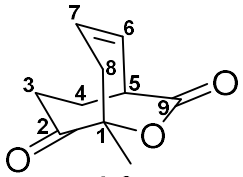


4.1 **4.4**

To a stirring solution of 6-*exo*-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (**3.2**) (0.073 g, 0.40 mmol) in dry dichloromethane (6 mL) at -78 °C DAST (0.322 g, 2.0 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 h then quenched with water (5 mL); the aqueous phase was extracted with dichloromethane (3x20 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (95:5 then 93:7 hexane:ethyl acetate) of the residue gave **4.1** (0.036 g, 60%) as a colourless oil; IR (film) ν_{max} 3005, 2989, 1733, 1691, 1455, 1376, 1350, 1275, 1260, 1195, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, ddd, *J* = 9.2, 3.6, 2.5, 7-H),

5.77 (1H, dm, *J* = 9.2 Hz, 6-H), 3.23–3.18 (1H, m, 5-H), 2.88–2.77 (1H, m, 3-Heq), 2.69 (1H, dd, $^{2}J_{HH}$ = 18.0 Hz, *J* = 4.0 Hz, 1x8-C*H*$_2$), 2.57–2.49 (2H, m, 3-Hax, 1x8-C*H*$_2$), 2.02–1.94 (1H, m, 4-Heq), 1.89–1.79 (1H, m, 4-Hax), 1.22 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6 (C-9), 208.5 (C-2), 128.4 (C-6), 127.7 (C-7), 64.6 (C-1), 46.5 (C-5), 44.8 (C-8), 34.9 (C-3), 24.6 (C-4), 15.8 (CH_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{13}O_2$ calcd. 165.0910, found 165.0913; and **4.4** (0.015 g, 20%) as a colourless oil; IR (film) ν_{max} 3000, 2968, 2925, 1720, 1700, 1275, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, ddt, *J* = 48.3, $J_{ax\text{-}ax}$ = 11.2, $J_{ax\text{-}eq}$ = 5.6 Hz, 6-H), 3.42–3.33 (1H, m, 5-H), 2.62 (1H, ddd, $^{2}J_{HH}$ = 16.3, $J_{ax\text{-}ax}$ = 7.5, $J_{ax\text{-}eq}$ = 4.6 Hz, 3-Heq) 2.37 (1H, dtm, $^{2}J_{HH}$ = 16.3, $J_{ax\text{-}ax}$ = 9.5 Hz, 3-Hax), 2.21–2.09 (3H, m, 7-Heq, 4-Heq, 8-Hax), 2.04–1.94 (1H, m, 4-Hax), 1.85–1.69 (1H, m, 7-Hax), 1.37 (1H, tdm, $^{2}J_{HH}$ = 14.0, *J* = 4.8 Hz, 8-Heq), 1.15 (3H, s, 1-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211. 2 (C-2), 207.7 (d, $^{3}J_{CF}$ = 10.6 Hz, (C-9), 92.2 (d, J_{CF} = 188.2 Hz, C-6), 61.9 (C-1), 50.8 (d, $^{2}J_{CF}$ = 19.4 Hz, C-5), 38.5 (C-3), 33.5 (d, $^{3}J_{CF}$ = 11.6 Hz, C-8), 25.7 (d, $^{2}J_{CF}$ = 19.8 Hz, C-7), 16.2 (1-*C*H_3), 15.3 (d, $^{3}J_{CF}$ = 4.3 Hz, C-4). ^{19}F NMR (565 MHz, $CDCl_3$) δ -176.3. HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{14}FO_2$ calcd. 185.0972, found 185.0967.

1-Methyl-9-oxabicyclo[3.3.2]decane-2,6,10-trione (4.6)

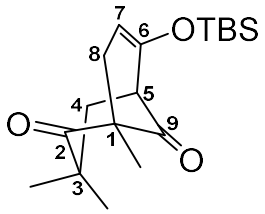


4.6

To a stirring solution of 1-methylbicyclo[3.3.1]non-6-ene-2,9-dione **4.1** (0.020 g, 0.12 mmol, 1 eq) in dry dichloromethane (3 mL) *m*-CPBA (0.042 g, 0.24 mmol, 2 eq) and $NaHCO_3$ (0.020 g, 0.24 mmol, 2 eq) were added in one portion at 0 °C. The reaction was kept at 0 °C for 1 hour, the ice bath removed and stir for additional 16 h. After this time, the reaction was quenched with H_2O (5 mL) and the aqueous phase extracted three times in dichloromethane (3x20 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated. Column chromatography (hexane:ethyl acetate, 85:15) afforded **4.6** (0.0050 g, **23%**), IR (film): 3009, 2978, 1445, 1270, 1263, 760, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.70 (1H, ddd, *J* = 11.4, 6.4, 1.9 Hz, 7-H), 5.60–5.50 (1H, m, 6-H), 3.71 (1H, t, *J* = 8.3 Hz, 5-H), 3.06 (1H, td, J_{gem} = 12.1, 9.3 Hz, 3-Heq), 2.85 (1H, dd, J_{gem} = 18.5, 6.5 Hz, 8-Heq), 2.53–2.37 (3H, m, 8-Hax, 3-Hax, 4-Heq), 1.87–1.77 (1H, m, 4-Hax), 1.26 (3H,

s, 1-C-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 203.9 (C-2), 171.0 (C-9), 128 (C-7), 124.0 (C-6), 87.6 (C-1), 44.0 (C-5), 37.0 (C-8), 35.0 (C-3), 26.0 (1-C-CH$_3$), 25.0 (C-4).

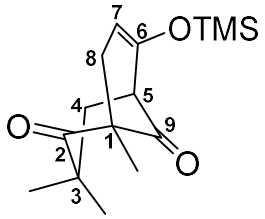
6-(*tert*-Butyldimethylsilyl)oxy)-1,3,3-trimethylbicyclo[3.3.1]non-6-ene-2,9-dione (4.7)



4.7

A stirring solution of 1,3,3-trimethylbicyclo[3.3.1]nonane-2,6,9-trione **3.68** (0.045 g, 0.21 mmol, 1 eq) in dry dichloromethane (6 mL) was brought to 0 °C. Et_3N (132.0 µL, 0.095 g, 0.94 mmol, 4.5 eq) was then added and the mixture stirred for 5 minutes. TBSOTf (0.199 g, 173.7 µL, 0.75 mmol, 3.6 eq) was added at last and the reaction kept at 0 °C for 10 minutes. After this time, the ice bath was removed, the mixture was slowly warmed up to room temperature and then heated at 45 °C for 1 hour. After allowing to cool down to room temperature the solution was quenched with sat. $NaHCO_3$ (5 ml) and the aqueous phase extracted three times with dichloromethane (3x15 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to afford **4.7** (0.051 g**, 72%**) as colorless oil, IR (film): 2933, 1741, 1705, 1662, 1471, 1254, 1194, 870, 839, 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.72 (1H, dd *J* = 5.5, 1.8 Hz, 7-H), 3.04 (1H, dt, *J* = 7.4, 1.4 Hz, 5-H), 2.71 (1H, dd, J_{gem} = 16.0, *J* = 5.5 Hz, 8-Hax), 2.11–2.04 (2H, m, 8-Heq, 4-Hax), 1.96 (1H, dd, J_{gem} = 13.5, 7.5 Hz, 4-Heq), 1.24 (3H, s, 1-C-CH_3), 1.17 (3H, s, 3-C-(CH_3)$_2$), 1.03 (3H, s, 3-C-(CH_3)$_2$), 0.90 (9H, s, Si(CH$_3$)$_2$-C(CH_3)$_3$), 0.14 (3H, s, Si(CH_3)$_2$-C(CH$_3$)$_3$), 0.12 (3H, s, Si(CH_3)$_2$-C(CH$_3$)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 216.8 (C-2), 209.3 (C-9), 150.6 (C-6), 101.2 (C-7), 59.1 (C-1), 51.7 (C-5), 44.4 (C-3), 39.1 (C-4), 38.0 (C-8), 28.7 (3-C-(CH$_3$)$_2$), 26.5 (3-C(CH$_3$)$_2$), 25.6 (Si(CH$_3$)$_2$-C(CH$_3$)$_3$), 18.1 (Si(CH$_3$)$_2$-C(CH$_3$)$_3$), 17.7 (1-C-CH$_3$), -4.4 (Si(CH$_3$)$_2$-C(CH$_3$)$_3$), -4.6 (Si(CH$_3$)$_2$-C(CH$_3$)$_3$). HRMS (ESI-TOF) [M+H]$^+$ $C_{18}H_{31}O_3Si$ calcd. 324.2063, found 324.2036.

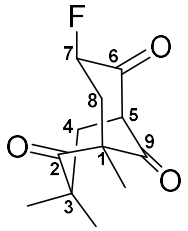
1,3,3-Trimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (4.8)



4.8

To a stirring solution of 1,3,3-trimethylbicyclo[3.3.1]nonane-2,6,9-trione **3.68** (0.050 g, 0.24 mmol) in dry dichloromethane (6 mL) at 0 °C was added Et_3N (0.109 g, 1.08 mmol). The mixture was stirred for 5 min, then TMSOTf (0.192 g, 0.86 mmol) was added and the mixture was stirred at 0 °C for a further 10 min. The ice-bath was then removed, and the mixture was allowed to warm to 20 °C, then heated at 45 °C for 3 h. After allowing to cool to 20 °C a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the aqueous layer extracted with dichloromethane (3x15 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **4.8** (0.064 g, 95%) as colourless oil; IR (film) ν_{max} 2965, 2925, 1706, 1470, 1277, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, dd, *J* = 5.5, 2.0 Hz, 7-H), 3.03 (1H, d, *J* = 7.5 Hz, 5-H), 2.72 (1H, dd, *J* = 16.0, 5.6 Hz, 8-Heq/ax), 2.11–2.03 (2H, m, 8-Hax/eq, 4-Hax), 1.96 (1H, dd, *J* = 13.5, 7.5 Hz, 4-Heq), 1.26 (3H, s, 1-C*H*$_3$), 1.18 (3H, s, 3-C*H*$_3$), 1.04 (3H, s, 3-C*H*$_3$), 0.20 (9H, s, OSi(C*H*$_3$)$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{15}H_{25}O_3Si$ calcd. 281.1567, found 281.1567.

7-Fluoro-1,3,3-trimethylbicyclo[3.3.1]nonane-2,6,9-trione (4.10)

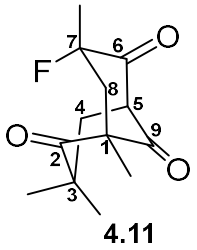


4.10

To a stirring solution of 1,3,3-trimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **4.8** (0.037 g, 0.13 mmol) in dry acetonitrile (2 mL) was added selectfluor in one portion (0.093 g, 0.26 mmol) at 25 °C. After stirring the mixture for 16 h, water (2 mL) was added and the aqueous phase extracted with dichloromethane (3x10 mL). The combined organic

layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **4.10** (0.018 g, 58%) as a colourless oil; IR (film) ν_{max} 2918, 1850, 1729, 1703, 1462, 1270, 1239, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, ddd, J_{HF} = 46.5, $J_{ax\text{-}ax}$ = 12.4, $J_{ax\text{-}eq}$ = 7.6 Hz, 7-H), 3.92 (1H, ddd, J = 11.0, 4.5, 1.2 Hz, 5-H), 2.75 (1H, ddd, $^2J_{HH}$ = 12.4, $^3J_{HF}$ = 7.6, $J_{eq\text{-}ax}$ = 2.5 Hz, 8-Heq), 2.33 (1H, dd, $^2J_{HH}$ = 15.2, $J_{eq\text{-}eq}$ = 11.0 Hz, 4-Heq), 1.76 (1H, m, 4-Hax), 1.63 (1H, apparent q, $^2J_{HH}$ = $J_{ax\text{-}ax}$ = $^3J_{HF}$ = 12.4 Hz, 8-Hax), 1.39 (3H, s, 1-CH_3), 1.20 (3H, s, 3-CH_3), 1.08 (3H, s, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0 (C-2), 201.9 (C-9), 198.0 (d, $^2J_{FC}$ = 15.0 Hz, C-6), 86.9 (d, J_{FC} = 195.4 Hz, C-7), 62.0 (C-5), 58.5 ($^3J_{FC}$ = 8.5 Hz, C-1), 45.1 (C-3), 37.9 (d, $^3J_{FC}$ = 20.5 Hz, C-8), 35.5 (C-4), 26.1 (3-CH_3), 24.6 (3-CH_3), 18.6 (1-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -198.0. HRMS (ESI-TOF) $[M]^+$ $C_{12}H_{15}FO_3$ calcd. 226.1005, found 226.1007.

7-Fluoro-1,3,3,7-tetramethylbicyclo[3.3.1]nonane-2,6,9-trione (4.11)

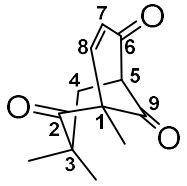


4.11

To a stirring solution of 1,3,3-trimethylbicyclo[3.3.1]non-6-ene-2,6,9-trione **(3.62)** (0.050 g, 0.22 mmol) in dry dichloromethane (3 mL) at 0 °C was added Et_3N (0.101 g, 1.0 mmol, 4.54 eq). The mixture was stirred for 5 min, then TMSOTf (0.177 g, 0.80 mmol, 3.63 eq) was added and the mixture was stirred at 0 °C for a further 10 min. The ice-bath was then removed and the mixture allowed to warm to 20 °C, then heated at 45 °C for 16 h. After allowing to cool to 20 °C, sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer extracted with dichloromethane (3x15 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (petroleum ether then 97:3 petroleum ether:ethyl acetate) of the residue gave 1,3,3,7-tetramethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **4.9** (0.030 g, 46%) as a colourless oil of which 0.025 g (0.08 mmol) were immediately placed in a flame-dried round-bottom flask containing dry acetonitrile (3 mL) to which Selectfluor (0.060 g, 0.16 mmol, 2 eq) was added at 25 °C. The resulting solution was stirred at 25 °C for 3 days after which water (2 mL) was added and the aqueous layer extracted with dichloromethane (3x10 mL).

The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **4.11** (0.011 g, 57%) as a colourless oil; IR (film) ν_{max} 2925, 2845, 1732, 1707, 1455, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (1H, dt, $J_{eq\text{-}eq}$ = 8.4, $J_{eq\text{-}eq}$ = 2.4 Hz, 5-H), 2.60–2.45 (1H, dm, $^3J_{HF}$ = 36.0, J = 14.8 Hz, 8-Heq), 2.44–2.38 (1H, dd, J = 13.6 Hz, 1.6 Hz, 4-Hax), 2.14–2.03 (2H, m, 4-Heq, 8-Hax), 1.46 (3H, d, $^3J_{HF}$ = 22.1 Hz, 7-C*H*$_3$), 1.35 (3H, s, 1-C*H*$_3$), 1.12 (3H, s, 3-C*H*$_3$), 1.09 (3H, s, 3-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.3 (C-2), 204.2 (C-9), 202.3 (d, $^2J_{FC}$ = 25.8 Hz, C-6), 95.5 (d, J_{FC} = 170.8 Hz, C-7), 60.0 (C-1), 57.5 (C-5), 45.9 (C-3), 45.6 (d, $^2J_{FC}$ = 3.7 Hz, C-8), 36.6 (C-4), 28.5 (3-*C*H$_3$), 26.6 (3-*C*H$_3$), 20.1 (1-*C*H$_3$), 19.7 (d, J_{FC} = 23.4 Hz, 7-*C*H$_3$); ^{19}F NMR (565 MHz, $CDCl_3$) δ -141.0.

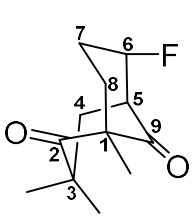
5,7,7-Trimethylbicyclo[3.3.1]non-3-ene-2,6,9-trione (4.15)



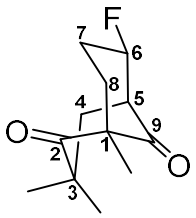
4.15

To a mixture of DMSO and dichloromethane (2:1 by volume, 1 mL) were added IBX (0.201 g, 0.72 mmol, 3 eq) and MPO hydrate (0.090 g, 0.72 mmol, 3 eq). The resulting cloudy solution was stirred at 25 °C for 90 min, the colour becoming yellow. 1,3,3-Trimethylbicyclo[3.3.1]nonane-2,6,9-trione **3.68** (0.050 g, 0.24 mmol, 1 eq) was then added and the mixture stirred at 25 °C overnight. 5% aqueous $NaHCO_3$ (10 mL) was then added and the mixture was extracted with diethyl ether (3x10 mL). The combined organic layers were filtered through a pad of celite. The filtrate was washed with 5% aqueous $NaHCO_3$ (10 mL), then with water (10 mL) and lastly with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to give **4.15** (0.015 g, 30%) as a colourless oil; IR (film) ν_{max} 2928, 1748, 1718, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, d, J = 9.6 Hz, 8-H), 6.21 (1H, d, J = 9.6, 7-H), 3.76 (1H, dd, J = 7.6, 4.0 Hz, 5-H), 2.24–2.13 (2H, m, 4-H), 1.50 (3H, s, 1-C*H*$_3$), 1.25 (3H, s, 3-C*H*$_3$), 1.10 (3H, s, 3-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1 (C-2), 201.9 (C-9), 197.6 (C-6), 150.4 (C-8), 128.9 (C-7), 65.5 (C-1), 60.5 (C-5), 45.9 (C-3), 38.6 (C-4), 29.3 (3-*C*H$_3$), 28.1 (3-*C*H$_3$), 15.3 (1-*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{15}O_3$ calcd. 207.1016, found 207.1025.

6-Fluoro-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (4.19)



***exo*-4.19**

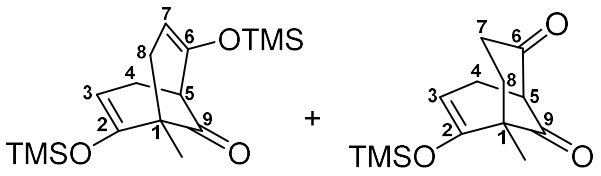


***endo*-4.19**

To a stirring solution of 6-hydroxy-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (**3.52**) (0.030 g, 0.14 mmol, 1 eq) in dry dichloromethane (4 mL) at -78 °C DAST (0.115 g, 0.71 mmol, 5 eq) was added dropwise. The mixture was stirred at -78 °C for 1 h then quenched with water (5 mL) and the aqueous phase extracted with dichloromethane (3x15 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (95:5 then 93:7 hexane:ethyl acetate) of the residue gave **4.19** (0.011 g, 38%) as a 65:35 mixture of *exo*-**4.19**:endo-**4.19;** IR (film) ν_{max} 3018, 1643, 1603, 1379, 1275, 1260, 1226, 1187 cm^{-1}; *exo*-**4.19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (1H, ddq, $^2J_{HF}$ = 47.4, $J_{eq\text{-}ax}$ = 4.5, $J_{eq\text{-}eq}$ = 1.6 Hz, 6-H), 3.25–3.17 (1H, m, 5-H), 2.25–2.18 (1H, m, 7-Heq), 2.11–1.91 (3H, m, 4-Heq, 7-Hax, 8Heq), 1.65–1.45 (1H, m, 4-Hax), 1.29–1.24 (1H, m, 8-Hax), 1.22 (3H, s, 3-CH_3), 1.15 (3H, s, 3-CH_3), 0.99 (3H, s, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7 (C-2), 210.9 (C-9), 97.6 (d, J_{CF} = 177.7 Hz, C-6), 60.2 (C-1), 49.1 (d, $^2J_{CF}$ = 22.7 Hz, C-5), 45.5 (C-3), 38.4 (C-7), 34.1 (d, $^3J_{CF}$ = 9.4 Hz, C-8), 26.2 (3-*C*H_3), 24.7 (3-*C*H_3), 24.65 (C-4), 18.7 (1-*C*H_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -174.9; *endo*-**4.19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (1H, dm, J_{HF} = 58.0 Hz, 6-H), 3.33–3.30 (1H, m, 5-H), 2.25–2.18 (1H, m, 7-Heq), 2.11–1.91 (3H, m, 4-Heq, 7-Hax, 8-Heq), 1.91–1.85 (1H, m, 4-Hax), 1.22 (3H, s, 3-C*H*$_3$), 1.15 (3H, s, 3-C*H*$_3$), 0.99 (3H, s, 1-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, part assignments) δ 215.7 (C-2), 210.9 (C-9), 97.6 (d, J_{CF} = 177.7 Hz, C-6), ^{19}F NMR (565 MHz, $CDCl_3$) δ -163.8. HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{18}FO_2$ calcd. 213.1285, found 213.1288.

5-Methyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (4.25)

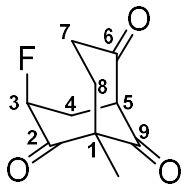
1-Methyl-2,6-bis((trimethylsilyl)oxy)bicyclo[3.3.1]nona-2,6-dien-9-one (4.22)



4.22 **4.25**

To a stirring solution of 1-methylbicyclo[3.3.1]nonane-2,6,9-trione **3.65** (0.040 g, 0.22 mmol, 1 eq) in dry dichloromethane (3 mL) at 0 °C was added Et_3N (0.066 g, 0.66 mmol, 3 eq) was then added. The mixture was stirred for 5 min, then TMSOTf (0.120 g, 0.54 mmol, 2.4 eq) was added and the mixture was stirred at 0 °C for a further 10 min. The ice-bath was then removed, and the mixture was allowed to warm to 20 °C, then heated at 45 °C for 2 h. After allowing to cool to 20 °C, sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer extracted with dichloromethane (3x12 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography of the residue (hexane then 95:5 hexane:ethyl acetate) gave **4.22** (0.020 g, 28%) as an oil; IR (film) ν_{max} 2959, 1734, 1658, 1253, 1181, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81–4.77 (2H, m, 3-H, 7-H), 2.80 (1H, d, *J* = 4.8 Hz, 5-H), 2.50–2.41 (2H, m, 4-Heq, 8-Heq), 2.35 (1H, dm, *J* = 16.4 Hz, 4-Hax), 2.00 (1H, m, 8-Hax), 1.53 (3H, s, 1-C*H*$_3$), 0.18 (9H, OSi(C*H*$_3$)$_3$), 0.17 (9H, OSi(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C-9), 152.4 (C-2), 150.2 (C-6), 101.7 (C-3/C-7), 99.8 (C-7/C-3), 51.3 (C-5), 50.5 (C-1), 36.4 (C-8), 28.2 (C-4), 16.3 (1-*C*H_3), 0.38 (OSi(*C*H_3)$_3$), 0.35 (OSi(*C*H_3)$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{16}H_{29}O_3Si_2$ calcd. 325.1650, found 325.1658; and **4.25** (0.005 g, 10%) as an oil; IR (film) ν_{max} 3003, 2978, 1709, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (1H, dd, *J* = 5.2, 2.4 Hz, 3-H), 3.38 (apparent d, $J_{eq\text{-}ax}$ = 6.4 Hz, 5-H), 2.69–2.61 (2H, m, 4-Heq, 7-Heq), 2.51 (1H, ddt, $^2J_{HH}$ = 17.0 Hz, $J_{ax\text{-}eq}$ = 5.6, $J_{eq\text{-}eq}$ = 1.6 Hz, 7-Hax), 2.39 (1H, ddd, $^2J_{HH}$ = 17.1, $J_{ax\text{-}ax}$ = 5.1, $J_{ax\text{-}eq}$ = 1.6 Hz, 4-Hax), 2.10 (1H, ddd, $^2J_{HH}$ = 13.7, $J_{ax\text{-}ax}$ = 8.0 Hz, *J* =1.7 Hz, 8-Hax), 1.47 (1H, m, 8-Heq), 1.24 (3H, s, 1-C*H*$_3$), 0.24 (9H, s, (OSi(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8 (C-9), 205.3 (C-6), 150.7 (C-2), 100.2 (C-3), 63.6 (C-5), 51.0 (C-1), 36.8 (C-7), 30.4 (C-8), 29.4 (C-4), 16.5 (1-*C*H_3), 0.32 (OSi(*C*H_3)$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{13}H_{21}O_3Si$ calcd. 253.1254, found 253.1259.

3-Fluoro-1-methylbicyclo[3.3.1]nonane-2,6,9-trione (4.27)

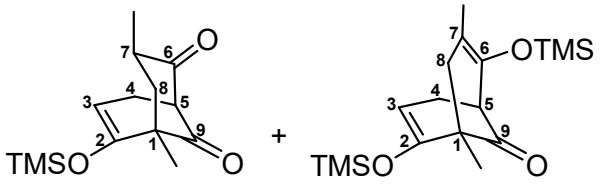


4.27

To a stirring solution of 5-methyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **4.25** (0.005 g, 0.02 mmol, 1 eq) in dry acetonitrile (2 mL) was added selectfluor (0.014 g, 0.04 mmol, 2 eq) at 25 °C. After stirring the mixture for 16 h water (3 mL) was added and the aqueous layer extracted with dichloromethane (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give **4.27** (0.0035 g, 90%) as a colourless oil; IR (film) ν_{max} 2919, 1719, 1456, 1270, 1109, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (1H, dtd, J_{HF} = 47.7, $J_{ax\text{-}eq}$ = 7.5, ^4J = 1.6 Hz, 3-H), 3.64 (1H, dd, J = 6.8, 3.3 Hz, 5-H), 2.64–2.50 (2H, m, 7-CH_2), 2.46–2.36 (2H, m, 4-CH_2), 2.25 (1H, ddd, $^2J_{HH}$ = 14.0 Hz, $J_{ax\text{-}eq}$ = 7.3, $J_{eq\text{-}eq}$ = 5.0 Hz, 8-Heq), 1.74 (1H, ddd, $^2J_{HH}$ = 13.9, $J_{ax\text{-}ax}$ = 9.7, $J_{ax\text{-}eq}$ = 7.7 Hz, 8-Hax), 1.40 (3H, s, 1-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8 (C-6), 202.5 (d, $^2J_{CF}$ = 17.6 Hz, C-2), 200.9 (C-9), 89.0 (d, J_{CF} = 184.5 Hz, C-3), 61.5 (C-1), 60.9 (d, $^3J_{CF}$ = 4.6 Hz, C-5), 36.4 (C-7), 30.2 (C-8), 29.0 (d, $^2J_{CF}$ = 22.5 Hz, C-4), 16.9 (1-*C*H_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -187.13. HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{11}FO_3$ calcd. 199.0765, found 199.0771.

1,7-Dimethyl-2-((trimethylsilyl)oxy)bicyclo[3.3.1]non-2-ene-6,9-dione (4.35)

1,7-Dimethyl-2,6-bis((trimethylsilyl)oxy)bicyclo[3.3.1]nona-2,6-dien-9-one (4.36)

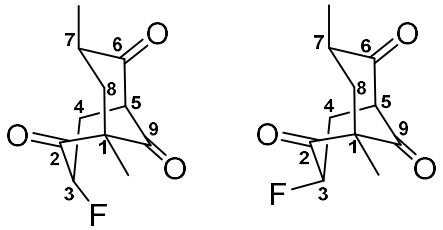


4.35 **4.36**

To a stirring solution of 1,7-*exo*-dimethylbicyclo[3.3.1]nonane-2,6,9-trione **3.66** (0.090 g, 0.46 mmol, 1 eq) in dry dichloromethane (5 mL) at 0 °C was added Et_3N (0.140 g, 1.38 mmol, 3 eq). The mixture was stirred for 5 min, then TMSOTf (0.245 g, 1.1 mmol, 2.4 eq) was added and the mixture was stirred at 0 °C for a further 10 min. Then the ice-bath was

then removed and the mixture heated at 45 °C for 3 h. After allowing to cool to 20 °C, sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer was extracted with dichloromethane (3x20 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (petroleum ether then 95:5 petroleum ether:ethyl acetate) of the residue gave 1,7-dimethyl-2-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **4.35** (0.045 g, 36%) as a colourless oil; R_f 0.6 (petroleum ether:ethyl acetate, 80:20); IR (film) ν_{max} 2955, 2931, 2849, 1728, 1702, 1653, 1452, 1252, 1225, 1048, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (1H, dd, J = 4.8, 2.4 Hz, 3-H), 3.47 (1H, apparent d, $J_{eq\text{-}endo}$ = 6.4 Hz, 5-H), 2.80–2.72 (1H, m, 7-CH), 2.71–2.62 (1H, ddd, $^2J_{HH}$ = 17.2, $J_{ax\text{-}eq}$ = 6.8, $J_{eq\text{-}eq}$ = 2.0 Hz, 4-Hax), 2.53–2.40 (1H, m, 8-Heq), 2.34 (1H, ddd, $^2J_{HH}$ = 17.2, $J_{eq\text{-}eq}$ = 4.8, $J_{eq\text{-}eq}$ = 0.8 Hz, 4-Heq), 2.20 (1H, dd, $^2J_{HH}$ = 13.2, $J_{ax\text{-}eq}$ = 7.2 Hz, 8-Hax), 1.20 (3H, s, 1-CH_3), 1.12 (3H, d, J = 6.8 Hz, 7-CH_3), 0.24 (9H, s, $OSi(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C-9), 204.8 (C-6), 151.3 (C-2), 100.0 (C-3), 63.5 (C-5), 51.7 (C-1), 40.6 (C-7), 39.9 (C-8), 29.1 (C-4), 16.4 (1-CH_3), 13.4 (7-CH_3), 0.3 ($OSi(CH_3)_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{14}H_{23}O_3Si$ calcd. 267.1411, found 267.1413; and 1,7-dimethyl-2,6-bis((trimethylsilyl)oxy)bicyclo[3.3.1]nona-2,6-dien-9-one **4.36** (0.018 g, 11%) as a colourless oil; R_f 0.76 (petroleum ether:ethyl acetate, 80:20); IR (film) ν_{max} 1723, 1420, 1262, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, dd, J = 5.6, 2.0 Hz, 3-H), 2.83 (1H, d, $J_{eq\text{-}ax}$ = 4.8 Hz, 5-H), 2.47 (1H, ddd, $^2J_{HH}$ = 16.4, $J_{ax\text{-}eq}$ = 5.2, $J_{ax\text{-}eq}$ = 1.6 Hz, 4-Heq), 2.41–2.34 (2H, m, 4-Hax, 8-Heq), 2.01 (1H, dd, $^2J_{HH}$ = 16.4, $J_{eq\text{-}eq}$ = 1.2, 8-Hax), 1.56 (3H, s, 7-CH_3), 1.12 (3H, s, 1-CH_3), 0.18 (18H, s, 2x$OSi(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C-9), 152.4 (C-2), 141.9 (C-6), 111.5 (C-7), 99.5 (C-3), 64.2 (C-1), 50.9 (C-5), 42.8 (C-8), 28.2 (C-4), 16.2 (1-CH_3), 15.7 (7-CH_3), 0.8 ($OSi(CH_3)_3$), 0.3 ($OSi(CH_3)_3$); HRMS (ESI-TOF) $[M+H]^+$ $C_{17}H_{31}O_3Si_2$ calcd. 339.1806, found 339.1807.

3-Fluoro-1,7-dimethylbicyclo[3.3.1]nonane-2,6,9-trione (4.37)

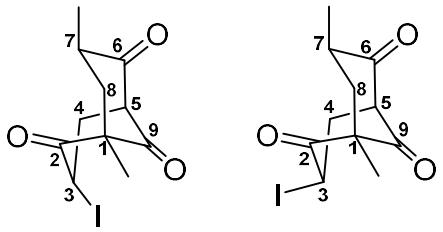


exo-4.37 *endo*-4.37

To a stirring solution of 3,5-dimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (**4.36**) (0.020 g, 0.08 mmol, 1 eq) in dry acetonitrile (2 mL) was added Selectfluor in one portion (0.056 g, 0.16 mmol, 2 eq) at 25 °C. After stirring the mixture for 16 h water (2 mL)

was added and the aqueous layer extracted with dichloromethane (3x10 mL). The combined organic layers were washed with water (3 x10 mL), dried over Na_2SO_4, filtered and evaporated to give **24** (0.013 g, 81%) as a 75:25 mixture of ***exo*-4.37**:***endo*-4.37**, R_f 0.23 (petroleum ether: ethyl acetate, 80:20); IR (film) ν_{max} 2916, 1721, 1642, 1452, 1218, 1022, 995 cm^{-1}; ***exo*-4.37**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (1H, dt, J_{HF} = 48.4, $J_{eq\text{-}eq}$ = 4.8 Hz, 3-H), 3.74 (1H, td, J = 9.2, 2.0 Hz, 5-H), 2.70–2.50 (2H, m, 8-CH_2), 2.51–2.36 (2H, m, 4-CH_2), 2.35–2.25 (1H, m, 7-H), 1.38 (3H, s, 1-CH_3), 1.13 (3H, d, J = 6.5 Hz, 7-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0 (C-9), 203.9 (d, $^2J_{FC}$ = 19.7 Hz, C-2), 200.2 (C-6), 89.7 (d, J_{FC} = 180.4 Hz, C-3), 63.3 (C-1), 61.4 (C-5), 40.4 (C-7), 39.6 (d, $^2J_{FC}$ = 4.6 Hz, C-4), 37.2 (C-8), 17.1 (1-CH_3), 14.2 (7-*C*H_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -183.0; ***endo*-4.37**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, ddd, J_{HF} = 46.7, $J_{ax\text{-}ax}$ = 11.8, $J_{ax\text{-}eq}$ = 7.6 Hz, 3-H), 3.70 (1H, m, 5-H), 2.51–2.36 (2H, m, 4-CH_2), 2.35-2.25 (1H, m, 7-H), 2.18 (1H, tdd, J_{gem} = 17.2, $J_{ax\text{-}ax}$ = 6.8, $J_{ax\text{-}eq}$ = 2.0 Hz, 8-Heq), 2.05-1.96 (1H, m, 8-Hax), (3H, s, 1-CH_3), 1.11 (3H, d, J = 6.8 Hz, 7-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8 (C-9), 206.8 (C-2), 203.4 (C-6), 87.1 (d, J_{FC} = 192.2 Hz, C-3), 77.4 (C-1), 63.4 (d, $^3J_{FC}$ = 26.8 Hz, C-5), 40.6 (C-7), 28.7 (d, $^2J_{FC}$ = 22.8 Hz, C-4), 21.6 (C-8), 16.3 (1-*C*H_3), 14.4 (7-*C*H_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -195.8; HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{14}FO_3$ calcd. 213.0921, found 213.0930.

3-Iodo-1,7-dimethylbicyclo[3.3.1]nonane-2,6,9-trione (4.38)



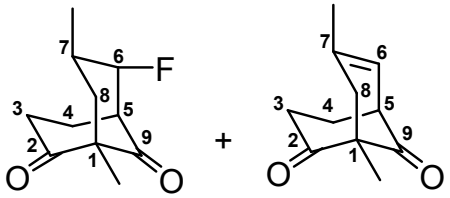
exo-4.38 *endo*-4.38

To a stirring solution of 3,5-dimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (**4.36**) (0.018 g, 0.06 mmol, 1 eq) in dry acetonitrile (2 mL) was added *N*-iodosuccinimide in one portion (0.022 g, 0.10 mmol, 1.6 eq) at 25 °C, and the mixture stirred at 25 °C for 48 h. Then, sat. aqueous NH_4Cl (5 mL) was added and the aqueous layer extracted with dichloromethane (3x10 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **4.36** (0.015 g, 80%) as a 80:20 mixture of ***endo*-4.36**:***exo*-4.36**; IR (film) ν_{max} 2939, 1715, 1452, 1230, 1108 cm^{-1}; ***endo*-4.36**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, dd, $J_{eq\text{-}ax}$ = 6.3, $J_{eq\text{-}eq}$ = 2.2 Hz, 3-H), 3.87 (1H, dd, $J_{eq\text{-}ax}$

= 10.2, $J_{eq\text{-}eq}$ = 2.0 Hz, 1H, 5-H), 2.85 (1H, dd, J_{gem} = 16.8, $J_{ax\text{-}eq}$ = 10.2 Hz, 4-Hax), 2.66 (1H, ddd, J_{gem} = 16.8, $J_{eq\text{-}ax}$ = 6.3, $J_{eq\text{-}eq}$ = 2.0 Hz, 4-Heq), 2.56–2.45 (2H, m, 7-H), 2.40 (1H, dd, J_{gem} = 13.1, $J_{eq\text{-}ax}$ = 7.0 Hz, 8-Heq), 1.61 (3H, s, 1-C*H*$_3$), 1.33–1.22 (1H, m, 8-Hax), 1.07 (3H, d, J = 6.4 Hz, 7-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (C-2), 204.2 (C-6), 201.0 (C-9), 62.0 (C-5), 61.2 (C-1), 41.0 (C-8), 38.6 (C-7), 31.5 (C-4), 21.8 (C-3), 21.2 (1-*C*H$_3$), 13.7 (7-*C*H$_3$); ***exo*-4.36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, dd, $J_{eq\text{-}ax}$ = 12.0, $J_{eq\text{-}eq}$ = 3.6 Hz, 3-H), 3.73 (1H, dd, $J_{eq\text{-}ax}$ = 8.4, $J_{eq\text{-}eq}$ = 2.0 Hz, 1H, 5-H).

(1S,5R,6R,7R)-6-Fluoro-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione (4.43)

1,7-dimethylbicyclo[3.3.1]non-6-ene-2,9-dione (4.44)

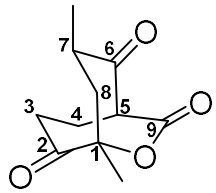


4.43 **4.44**

A stirring solution of 6-hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione **3.19** (0.050 g, 0.25 mmol, 1 eq) in dry dichloromethane (4 mL) was brought to –78 °C and DAST (0.080 g, 0.5 mmol, 70 µL, 2 eq) was added dropwise. The reaction was kept at –78 °C for 3 hours until completion. After this time, the reaction was quenched with H_2O (5 mL) and the aqueous phase extracted three times in dichloromethane (3x20 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated. Column chromatography (hexane:ethyl acetate, 90:10) afforded **4.43** (0.012 g, **24%**) and **4.44** (0.020 g, **45%**) as colorless oils; **4.43:** IR (film):1733, 1705, 1451, 1263, 1043, 845, 732, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.75 (1H, ddd, $^1J_{HF\text{-}gem}$ = 47.8, $J_{eq\text{-}ax}$ = 4.0, $J_{eq\text{-}eq}$ = 2.0 Hz, 6-H), 3.18 (1H, m, 5-H), 2.60 (1H, dddd, J_{gem} = 16.4, $J_{eq\text{-}ax}$ = 7.5, $J_{eq\text{-}eq}$ = 3.9, ^wJ = 1.3 Hz, 3-Heq), 2.38 (1H, dt, J_{gem} = 16.4, $J_{ax\text{-}ax}$ = 9.6, $J_{ax\text{-}ax}$ = 6.8 Hz, 3-Hax), 2.25–1.99 (4H, m, 4-Heq, 7-H, 8-H), 1.67 (1H, m, 4-Hax), 1.15 (3H, s, 1-C-C*H*$_3$), 1.06 (3H, d, J = 6.6 Hz, 7-CH-C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 211.6 (C-2), 209.3 (C-9), 99.8 (d, J_{CF} = 178.7 Hz, C-6), 62.1 (C-1), 48.9 (d, $^2J_{FC}$ = 24.0 Hz, C-5), 43.7 (C-8), 37.6, (C-3), 29.7 (d, $^3J_{CF}$ = 20.1 Hz, C-7), 17.4 (d, $^3J_{FC}$ = 11.0 Hz, C-4), 16.5 (1-C-*C*H$_3$), 15.9 (d, J = 5.1 Hz, 7-*C*H$_3$). ^{19}F NMR (376 MHz, $CDCl_3$) δ -189.01. HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{16}FO_2$ calcd. 199.1129, found 199.1123. **4.44**: IR (film): 1732, 1693, 1444, 1232, 1193, 1085, 1017, 847, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.47 (1H, d, J = 6.0 Hz, 6-H), 3.11 (1H, m, 5-H), 2.80 (1H, m, 3-Heq), 2.59–2.42 (3H, m, 3-Hax, 8-H), 1.95 (1H, m, 4-Heq), 1.86–1.75 (1H, m, 4-Hax), 1.72

(3H, s, 7-C*H*$_3$), 1.20 (3H, s, 1-C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.7 (C-2), 209.3 (C-9), 135.7 (C-7), 123.0 (C-6), 63.9 (C-1), 49.0 (C-8), 46.0 (C-5), 34.9 (C-3), 25.2 (C-4), 21.7 (7-*C*H$_3$), 15.7 (1-C-*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{15}O_2$ calcd.179.1067, found 179.1058.

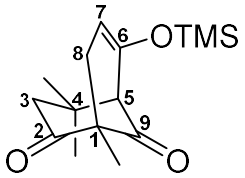
1,7-Dimethyl-9-oxabicyclo[3.3.2]decane-2,6,10-trione (4.41)



4.41

To a stirring solution of 1,7-*exo*-dimethylbicyclo[3.3.1]nonane-2,6,9-trione **3.66** (0.040 g, 0.5 mmol, 1 eq) in dry dichloromethane (2 mL) were added *m*-CPBA (0.070 g, 0.4 mmol, 2 eq) and $NaHCO_3$ (0.034 g, 0.4 mmol, 2 eq) in one portion at 0 °C. The reaction was kept at 0 °C for 6 h, the ice bath removed and stir for additional 16 h. After this time, the reaction was quenched with H_2O (5 mL) and the aqueous phase extracted with dichloromethane (3x20 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated. Column chromatography (hexane:ethyl acetate, 90:10) afforded **4.41** (0.006 g, **14%**), IR (film): 2923, 1717, 1698, 1277, 760, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.79–4.70 (1H, sext., $J_{ax\text{-}ax}$ = 12.2, $J_{ax\text{-}eq}$ = 6.2 Hz, 7-H), 4.16–4.09 (1H, m, 5-H), 2.76–2.69 (1H, m, CO-3-Hax), 2.69–2.58 (m, 1H, 4-Hax), 2.43–2.28 (3H, m, 3-Heq, 4-Heq, 8-Heq), 1.90 (1H, dd, J_{gem} = 14.9, $J_{ax\text{-}ax}$ = 11.0 Hz, 8-Hax), 1.36 (3H, d, J = 6.1 Hz, 7-CH-C*H*$_3$), 1.25 (3H, s, 1-C-C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.63 (C-6), 202.68 (C-2), 166.37 (C-9), 73.84 (C-7), 62.53 (C-1), 56.38 (C-5), 47.63 (C-8), 38.58 (C-3), 23.44 (C-7-*C*H$_3$), 19.01 (1-C-*C*H$_3$), 18.90 (C-4). HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{15}O_4$ calcd. 211.0965, found 211.0969.

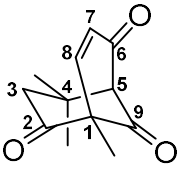
1,4,4-Trimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (4.45)



4.45

To a stirring solution of 1,4,4-trimethylbicyclo[3.3.1]nonane-2,6,9-trione **3.67** (0.050 g, 0.24 mmol, 1 eq) in dry dichloromethane (4 mL) at 0 °C was added Et_3N (0.036 g, 0.36 mmol, 1.38 eq). The mixture was stirred for 5 min, then TMSOTf (0.064 g, 0.29 mmol, 5.8 eq) was added and the mixture was stirred at 0 °C for a further 10 min. Then the ice bath was then removed and the mixture heated at 45 °C for 2 h. After allowing to cool to 20 °C, sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer was extracted with dichloromethane (3x15 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **4.45** (0.043 g, 60%); IR (film) ν_{max} 1731, 1701, 1449, 1249, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, t, J = 3.2 Hz, 7-H), 2.92 (1H, m, 3-Heq), 2.68 (1H, s, 5-H), 2.39 (1H, dd, J_{gem} = 17.6, $J_{eq\text{-}ax}$ = 3.6 Hz, 8-Heq), 2.30–2.22 (2H, m, 8-Hax, 3-Hax), 1.21 (3H, s, 1-CH_3), 1.17 (3H, s, 4-CH_3), 0.85 (3H, s, 4-CH_3), 0.23 (9H, s, O(SiCH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (C-2), 205.9 (C-9), 149.1 (C-6), 102.4 (C-7), 63.6 (C-5), 61.8 (C-1), 49.6 (C-3), 37.9 (C-8), 35.7 (C-4), 27.7 (4-CH$_3$), 27.4 (4-CH$_3$), 15.3 (1-CH$_3$), 0.3 O(SiCH$_3$)$_3$); HRMS (ESI-TOF) [M+H]+ $C_{15}H_{25}O_3Si$ calcd. 281.1567, found 281.1566.

5,8,8-Trimethylbicyclo[3.3.1]non-3-ene-2,6,9-trione (4.47)

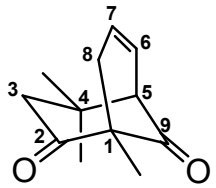


4.47

To a stirring solution of 1,4,4-trimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **4.45 (**0.043 g, 0.15 mmol, 1 eq) in dry acetonitrile (4 mL) was added $Pd(OAc)_2$ in one portion (0.124 g, 0.18 mmol, 1.2 eq) at 25 °C. The mixture was stirred at 25 °C for 16 h, then at 80 °C for 3 h. After allowing to cool, water (2 mL) was added and the aqueous layer extracted with diethyl ether (3x10 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **4.47** (0.014 g, 46%) as a

colourless oil; IR (film) ν_{max} 1710, 1678, 1447, 1374, 1250, 1218, 1174, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (1H, d, *J* = 6.4 Hz, 7-H), 6.42 (1H, d, *J* = 6.4 Hz, 8-H), 3.35 (1H, s, 5-H), 3.06 (1H, d, J_{gem}= 9.6 Hz, 3-Heq), 2.25 (1H, d, J_{gem}= 10.4, 3-Hax), 1.43 (3H, s, 1-C*H*$_3$) 1.18 (3H, s, 4-C*H*$_3$), 0.95 (3H, s, 4-C*H*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.1 (C-9), 200.2 (C-6), 196.4 (C-2), 151.4 (C-7), 131.8 (C-8), 73.3 (C-5), 69.3 (C-1), 46.5 (C-3), 33.9 (C-4), 28.5 (4-C-*C*H$_3$eq), 27.1 (4-C-*C*H$_3$ax), 13.2 (1-C-*C*H$_3$); HRMS (ESI-TOF) [M+H]+ $C_{12}H_{15}O_3$ calcd. 207.1016, found 207.1009.

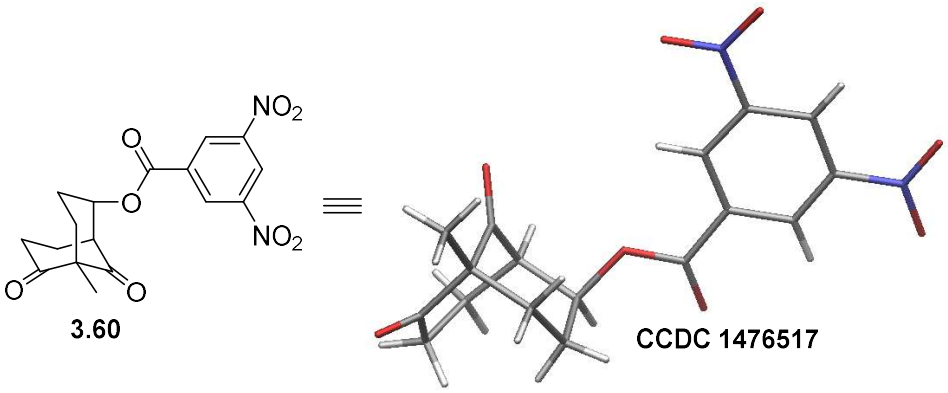
1,4,4-Trimethylbicyclo[3.3.1]non-7-ene-2,9-dione (4.49)



4.49

A stirring solution of 6-*exo*-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione **3.50** (0.100 g, 0.55 mmol, 1 eq) in dry dichloromethane was brought to –78 °C and DAST (0.354 g, 2.2 mmol, 295 µL, 4 eq) was added dropwise. The reaction was kept at the same temperature and stirred for 1 hour. After this time, the reaction was quenched with H_2O (5 mL) and the aqueous phase extracted with dichloromethane (3x20 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to afford **4.49** (0.103 g, **98%**) as colorless oil, IR (film): 2961, 1927, 1734, 1700, 1452, 1275, 1260, 764, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.94–5.84 (2H, m, 6-H, 7-H), 2.83 (1H, dd, J_{gem} = 15.4, *J* = 1.1 Hz, 3-Heq), 2.77–2.74 (1H, m, 5-H), 2.63 (1H, dd, $J_{eq\text{-}eq}$ = 3.5, *J* = 1.0 Hz, 8-Heq), 2.50 (1H, ddt, J_{gem} = 18.5, *J* = 2.6, 1.4 Hz, 8-Hax), 2.24 (1H, dd, J_{gem} = 15.4, *J* = 1.5 Hz, 3-Hax), 1.20 (3H, s, 1-C-C*H*$_3$), 1.10 (3H, s, 4-C-(C*H*$_3$)$_2$), 0.86 (3H, s, 4-C-(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 209.0 (C-9), 208.9 (C-2-), 128.3 (C-6), 128.1 (C-7), 62.9 (C-1), 57.8 (C-5), 49.2 (C-3), 44.9 (C-8), 35.7 (C-4), 27.3 (4-C(*C*H$_3$)$_2$), 26.2 (4-C(*C*H$_3$)$_2$), 15.6 (1-C-*C*H$_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{17}O_2$ calcd. 193.1223, found 193.1227.

X-ray crystallographic data



An X-ray quality crystal was obtained by slow diffusion of hexane into a nearly sat. solution in dichloromethane.

A colorless block-like specimen of $C_{17}H_{16}N_2O_8$, approximate dimensions 0.220 mm x 0.400 mm x 0.420 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 1.02 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 24863 reflections to a maximum θ angle of 36.39° (0.60 Å resolution), of which 7597 were independent (average redundancy 3.273, completeness = 99.8%, R_{int} = 4.59%, R_{sig} = 4.71%) and 6529 (85.94%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.6964(11) Å, b = 25.365(3) Å, c = 6.2244(6) Å, volume = 1688.8(3) $Å^3$, are based upon the refinement of the XYZ-centroids of 4917 reflections above 20 σ(I) with 4.981° < 2θ < 67.90°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.861. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9520 and 0.9740.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P n a 21, with Z = 4 for the formula unit, $C_{17}H_{16}N_2O_8$. The final anisotropic full-matrix least-squares refinement on F^2 with 245 variables converged at R1 = 4.46%, for the observed data and wR2 = 10.94% for all data. The goodness-of-fit was 1.009. The largest peak in the final difference electron density synthesis was 0.453 $e^-/Å^3$ and the largest hole was -0.241 $e^-/Å^3$ with an RMS deviation of 0.058 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.480 g/cm^3 and F(000), 784 e^-.

Crystal data, data collection and structure refinement.

Identification code	ices15
Chemical formula	$C_{17}H_{16}N_2O_8$
Formula weight	376.32 g/mol
Temperature	103(2) K
Wavelength	0.71073 Å

Crystal size	0.220 x 0.400 x 0.420 mm	
Crystal habit	colorless block	
Crystal system	orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 10.6964(11) Å	α = 90°
	b = 25.365(3) Å	β = 90°
	c = 6.2244(6) Å	γ = 90°
Volume	1688.8(3) $Å^3$	
Z	4	
Density (calculated)	1.480 g/cm^3	
Absorption coefficient	0.120 mm^{-1}	
F(000)	784	
Theta range for data collection	2.49 to 36.39°	
Index ranges	-17<=h<=17, -42<=k<=40, -10<=l<=9	
Reflections collected	24863	
Independent reflections	7597 [R(int) = 0.0459]	
Coverage of independent reflections	99.8%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9740 and 0.9520	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/4	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	7597 / 1 / 245	
Goodness-of-fit on F2	1.009	

Final R indices	6529 data; I>2σ(I)	R1 = 0.0446, wR2 = 0.1037
	all data	R1 = 0.0542, wR2 = 0.1094
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0599P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.453 and -0.241 $eÅ^{-3}$	
R.M.S. deviation from mean	0.058 $eÅ^{-3}$	

Table S1. Bond lengths (Å).

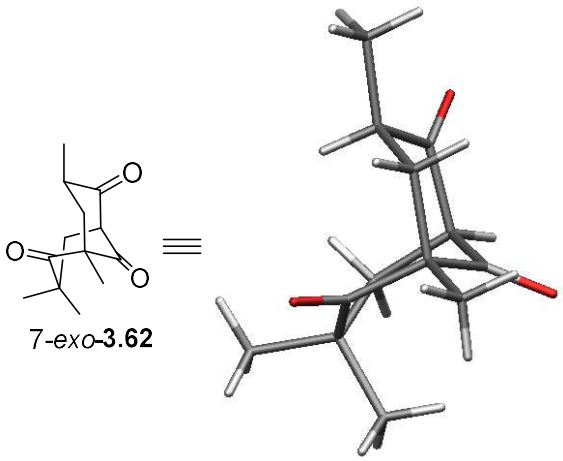
C1-C2	1.3913(19)	C1-C6	1.392(2)
C2-C3	1.382(2)	C2-N1	1.477(2)
C3-C4	1.387(2)	C4-C5	1.3846(19)
C4-N2	1.471(2)	C5-C6	1.396(2)
C6-C7	1.4942(18)	C7-O5	1.2117(17)
C7-O6	1.3371(18)	C8-O6	1.4717(17)
C8-C14	1.522(2)	C8-C9	1.524(2)
C9-C10	1.513(2)	C9-C15	1.545(2)
C10-O7	1.2156(18)	C10-C11	1.525(2)
C11-C12	1.523(2)	C11-C17	1.545(2)
C11-C13	1.559(3)	C13-C14	1.529(2)
C15-C16	1.539(2)	C16-C17	1.512(2)
C17-O8	1.2144(19)	N1-O1	1.224(2)
N1-O2	1.2250(18)	N2-O4	1.2288(19)
N2-O3	1.2325(16)		

Table S2. Bond angles (°).

C2-C1-C6	118.14(14)	C3-C2-C1	123.37(14)
C3-C2-N1	118.36(13)	C1-C2-N1	118.27(15)
C2-C3-C4	116.32(13)	C5-C4-C3	123.15(15)
C5-C4-N2	118.34(14)	C3-C4-N2	118.51(12)
C4-C5-C6	118.44(14)	C1-C6-C5	120.57(12)
C1-C6-C7	121.53(13)	C5-C6-C7	117.89(12)
O5-C7-O6	125.12(13)	O5-C7-C6	123.28(14)
O6-C7-C6	111.60(12)	O6-C8-C14	107.96(12)
O6-C8-C9	104.62(12)	C14-C8-C9	113.86(12)
C10-C9-C8	109.63(13)	C10-C9-C15	108.87(12)
C8-C9-C15	113.04(12)	O7-C10-C9	123.62(13)
O7-C10-C11	122.72(13)	C9-C10-C11	113.65(12)
C12-C11-C10	112.20(13)	C12-C11-C17	110.79(13)
C10-C11-C17	108.69(13)	C12-C11-C13	109.74(15)
C10-C11-C13	106.98(13)	C17-C11-C13	108.29(13)
C14-C13-C11	114.75(14)	C8-C14-C13	112.22(13)
C16-C15-C9	115.38(12)	C17-C16-C15	117.49(12)
O8-C17-C16	120.78(14)	O8-C17-C11	119.44(14)
C16-C17-C11	119.65(12)	O1-N1-O2	124.56(14)
O1-N1-C2	117.86(13)	O2-N1-C2	117.58(15)

O4-N2-O3	123.93(15)	O4-N2-C4	117.75(12)
O3-N2-C4	118.33(13)	C7-O6-C8	116.95(11)

X-ray crystallographic data



7-*exo*-**3.62**

CCDC 1485262

An X-ray quality crystal was obtained by slow diffusion of hexane into a nearly sat. solution of 7-*exo*-**20** in dichloromethane.

A colorless block-like specimen of $C_{13}H_{18}O_3$, approximate dimensions 0.100 mm x 0.220 mm x 0.420 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

The total exposure time was 0.99 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 21935 reflections to a maximum θ angle of 29.70° (0.72 Å resolution), of which 6533 were independent (average redundancy 3.358, completeness = 99.2%, R_{int} = 8.68%, R_{sig} = 9.08%) and 4743 (72.60%) were greater than $2\sigma(F^2)$. The final cell constants of a = 12.6185(16) Å, b = 6.4539(8) Å, c = 28.975(4) Å, β = 100.150(2)°, volume = 2322.8(5) $Å^3$, are based upon the refinement of the XYZ-centroids of 4832 reflections above 20 σ(I) with 5.713° < 2θ < 59.23°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.815. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9640 and 0.9910.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/n 1, with Z = 8 for the formula unit, $C_{13}H_{18}O_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 297 variables converged at R1 = 6.23%, for the observed data and wR2 = 17.86% for all data. The goodness-of-fit was 1.029. The largest peak in the final difference electron density synthesis was 0.447 $e^-/Å^3$ and the largest

hole was -0.329 $e^-/Å^3$ with an RMS deviation of 0.073 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.271 g/cm^3 and F(000), 960 e^-.

Crystal data, data collection and structure refinement for 7-*exo*-**20**:

Identification code	ices7
Chemical formula	$C_{13}H_{18}O_3$
Formula weight	222.27 g/mol
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal size	0.100 x 0.220 x 0.420 mm
Crystal habit	colorless block
Crystal system	monoclinic
Space group	P 1 21/n 1
Unit cell dimensions	a = 12.6185(16) Å α = 90°
	b = 6.4539(8) Å β = 100.150(2)°
	c = 28.975(4) Å γ = 90°
Volume	2322.8(5) $Å^3$
Z	8
Density (calculated)	1.271 g/cm^3
Absorption coefficient	0.089 mm^{-1}
F(000)	960
Theta range for data collection	1.43 to 29.70°
Index ranges	-17<=h<=13, -8<=k<=8, -40<=l<=40

Reflections collected	21935	
Independent reflections	6533 [R(int) = 0.0868]	
Coverage of independent reflections	99.2%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9910 and 0.9640	
Structure solution technique	direct methods	
Structure solution program	XS, VERSION 2013/1	
Refinement method	Full-matrix least-squares on F2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6533 / 0 / 297	
Goodness-of-fit on F2	1.029	
Δ/σmax	0.001	
Final R indices	4743 data; I>2σ(I)	R1 = 0.0623, wR2 = 0.1622
	all data	R1 = 0.0846, wR2 = 0.1786
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0843P)^2+0.3771P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.447 and -0.329 eÅ^{-3}	

R.M.S. deviation from mean	0.073 eÅ^{-3}

Table S3. Bond lengths (Å).

C1-O1	1.2128(16)	C1-C2	1.523(2)
C1-C8	1.5468(19)	C2-C11	1.530(2)
C2-C10	1.543(2)	C2-C3	1.5487(18)
C3-C4	1.5669(19)	C4-C9	1.5140(19)
C4-C5	1.5314(19)	C5-O2	1.2099(16)
C5-C6	1.5146(19)	C6-C12	1.522(2)
C6-C7	1.5395(19)	C7-C8	1.5506(19)
C8-C9	1.5187(19)	C8-C13	1.5267(19)
C9-O3	1.2113(17)	C14-O4	1.2083(17)
C14-C15	1.525(2)	C14-C21	1.547(2)
C15-C24	1.526(2)	C15-C23	1.546(2)
C15-C16	1.5481(19)	C16-C17	1.5617(19)
C17-C22	1.5122(18)	C17-C18	1.5314(19)
C18-O5	1.2106(16)	C18-C19	1.5158(19)
C19-C25	1.523(2)	C19-C20	1.5367(19)
C20-C21	1.5529(19)	C21-C22	1.5145(19)
C21-C26	1.5277(19)	C22-O6	1.2121(17)

Table S4. Bond angles (°).

O1-C1-C2	123.11(13)	O1-C1-C8	119.31(13)
C2-C1-C8	117.56(11)	C1-C2-C11	111.24(12)
C1-C2-C10	106.98(11)	C11-C2-C10	109.45(12)

C1-C2-C3	109.71(11)	C11-C2-C3	108.84(12)
C10-C2-C3	110.61(11)	C2-C3-C4	115.91(11)
C9-C4-C5	109.28(11)	C9-C4-C3	110.18(10)
C5-C4-C3	108.76(11)	O2-C5-C6	124.09(13)
O2-C5-C4	120.25(12)	C6-C5-C4	115.65(11)
C5-C6-C12	112.53(11)	C5-C6-C7	109.74(11)
C12-C6-C7	112.36(12)	C6-C7-C8	113.88(11)
C9-C8-C13	112.28(12)	C9-C8-C1	110.24(11)
C13-C8-C1	110.30(11)	C9-C8-C7	105.43(10)
C13-C8-C7	110.70(12)	C1-C8-C7	107.69(11)
O3-C9-C4	123.46(13)	O3-C9-C8	124.35(13)
C4-C9-C8	112.15(11)	O4-C14-C15	122.52(13)
O4-C14-C21	119.45(13)	C15-C14-C21	117.98(11)
C14-C15-C24	110.86(12)	C14-C15-C23	106.69(12)
C24-C15-C23	109.59(12)	C14-C15-C16	110.95(11)
C24-C15-C16	108.53(12)	C23-C15-C16	110.22(11)
C15-C16-C17	116.38(11)	C22-C17-C18	109.57(11)
C22-C17-C16	110.16(11)	C18-C17-C16	108.54(11)
O5-C18-C19	123.96(13)	O5-C18-C17	120.39(12)
C19-C18-C17	115.61(11)	C18-C19-C25	112.58(11)
C18-C19-C20	109.54(11)	C25-C19-C20	112.40(12)
C19-C20-C21	113.93(11)	C22-C21-C26	112.48(12)
C22-C21-C14	110.29(11)	C26-C21-C14	110.51(11)
C22-C21-C20	105.63(10)	C26-C21-C20	110.30(12)
C14-C21-C20	107.39(11)	O6-C22-C17	123.41(13)
O6-C22-C21	124.10(13)	C17-C22-C21	112.47(11)

REFERENCES

(1) Marson, C. M. *Chem. Soc. Rev.* **2011,** *40*, 5514–5533.
(2) (a) Koehn, F. E.; Carter, G. T. *Nat. Rev. Drug. Discov.* **2005,** *4*, 206–220; (b) Strohl, W. R. *Drug Discovery Today* **2000,** *5*, 39–41.
(3) Tan, D. S. *Nat. Chem. Biol.* **2005,** *1*, 74–84.
(4) Reymond, J.-L.; Awale, M. *ACS Chem. Neurosci.* **2012,** *3*, 649–657.
(5) Schreiber, S. L. *Science* **2000,** *287*, 1964–1969.
(6) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004,** *43*, 46–58.
(7) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009,** *52*, 6752–6756.
(8) Zhang, H.; Ryono, D. E.; Devasthale, P.; Wang, W.; O'Malley, K.; Farrelly, D.; Gu, L.; Harrity, T.; Cap, M.; Chu, C.; Locke, K.; Zhang, L.; Lippy, J.; Kunselman, L.; Morgan, N.; Flynn, N.; Moore, L.; Hosagrahara, V.; Zhang, L.; Kadiyala, P.; Xu, C.; Doweyko, A. M.; Bell, A.; Chang, C.; Muckelbauer, J.; Zahler, R.; Hariharan, N.; Cheng, P. T. W. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 1451–1456.
(9) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *Science* **2016,** *351*, 241-246.
(10) Rosen, R. H.; Gupta, A. K.; Tyring, S. K. *J. Am. Acad. Dermatol.* **2012,** *66*, 486-493.
(11) Aleu, J.; Hernandez-Galan, R.; R. Hanson, J.; B. Hitchcock, P.; G. Collado, I. *J. Chem. Soc., Perkin Trans. 1* **1999,** 727–730.
(12) Butkus, E. *Synlett* **2001,** *2001*, 1827–1835.
(13) (a) Tanaka, N.; Yano, Y.; Tatano, Y.; Kashiwada, Y. *Org. Lett.* **2016,** *18*, 5360–5363; (b) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basilio, Á.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006,** *441*, 358–361.
(14) Yamamoto, T.; Izumi, N.; Ui, H.; Sueki, A.; Masuma, R.; Nonaka, K.; Hirose, T.; Sunazuka, T.; Nagai, T.; Yamada, H.; Ōmura, S.; Shiomi, K. *Tetrahedron* **2012,** *68*, 9267–9271.
(15) Richard, J.-A. *Eur. J. Org. Chem.* **2014,** *2014*, 273–299.
(16) Peters, J. A. *Synthesis* **1979,** *1979*, 321–336.
(17) Njardarson, J. T. *Tetrahedron* **2011,** *67*, 7631–7666.
(18) Richard, J.-A.; Pouwer, R. H.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2012,** *51*, 4536–4561.
(19) (a) Rabe, P. *Ber. Dtsch. Chem. Ges.* **1903,** *36*, 225–227; (b) Rabe, P. W., K. *Ber. Dtsch. Chem. Ges.* **1904,** *37*, 1667.
(20) (a) Rabe P. *Ber. Dtsch. Chem. Ges.* **1904,** *37*, 1671; (b) Theobald, D. W. *Tetrahedron* **1969,** *25*, 3139.
(21) Stetter, H. M., J. *Angew. Chem.* **1959,** *71*, 430–436.
(22) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983,** *48*, 4642–4648.
(23) Aranda, G.; Bernassau, J. M.; Fetizon, M.; Hanna, I. *J. Org. Chem.* **1985,** *50*, 1156–1161.
(24) Houbrechts, Y.; Laszlo, P.; Pennetreau, P. *Tetrahedron Lett.* **1986,** *27*, 705–706.
(25) Wang, D.; Miao, L.; Feng, L.; Yao, Q.; Mkrtchyan, G.; Crowe, W. E.; Nesterov, E. E.; Wang, Y.; Zhang, X.; Yu, P. *J. Phys. Org. Chem.* **2017,** *30*, e3595.
(26) Muskopf, J. W.; Coates, R. M. *J. Org. Chem.* **1985,** *50*, 69–76.
(27) Yang, J.-D.; Kim, M.-S.; Lee, M.; Baik, W.; Koo, S. *Synthesis* **2000,** *2000*, 801–804.

(28) Camps, P.; González, A.; Muñoz-Torrero, D.; Simon, M.; Zúñiga, A.; Martins, M. A.; Font-Bardia, M.; Solans, X. *Tetrahedron* **2000,** *56*, 8141–8151.
(29) Srikrishna, A. P. K., P.; Reddy, T. J. *Arkivoc* **2003,** 55–66.
(30) Qi, J.; Porco, J. A. *J. Am. Chem. Soc.* **2007,** *129*, 12682–12683.
(31) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem. Int. Ed.* **2005,** *44*, 3895–3899.
(32) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2011,** *17*, 2266–2271.
(33) (a) Qian, L.; Ji, R. *Tetrahedron Lett.* **1989,** *30*, 2089–2090; (b) Xia, Y.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1989,** *111*, 4116–4117.
(34) Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron* **1998,** *54*, 5471–5484.
(35) Ding, X.-H.; Li, X.; Liu, D.; Cui, W.-C.; Ju, X.; Wang, S.; Yao, Z.-J. *Tetrahedron* **2012,** *68*, 6240–6248.
(36) (a) Campiani, G.; Sun, L. Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M. *J. Org. Chem.* **1993,** *58*, 7660–7669; (b) Kozikowski, A. P.; Campiani, G.; Aagaard, P.; McKinney, M. *J. Chem. Soc., Chem. Commun.* **1993,** 860–862.
(37) Ramesh, N. G.; Hassner, A. *Synlett* **2004,** *2004*, 975–978.
(38) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010,** *49*, 1103–1106.
(39) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004,** *6*, 4387–4390.
(40) Kraus, G. A.; Jeon, I. *Tetrahedron Lett.* **2008,** *49*, 286–288.
(41) Takagi, R.; Inoue, Y.; Ohkata, K. *J. Org. Chem.* **2008,** *73*, 9320–9325.
(42) Patir, S.; Uludag, N. *Tetrahedron* **2009,** *65*, 115–118.
(43) Moulia, A.; Teo, J.; Johannes, C. W.; Richard, J.-A. *RSC Adv.* **2013,** *3*, 22882–22886.
(44) Barboni, L.; Gabrielli, S.; Palmieri, A.; Femoni, C.; Ballini, R. *Chem Eur. J.* **2009,** *15*, 7867–7870.
(45) Stork, G. L., H. K. *J. Am. Chem. Soc.* **1965,** *78*, 5129–5130.
(46) Hickmott, P. W.; Hargreaves, J. R. *Tetrahedron* **1967,** *23*, 3151–3159.
(47) (a) McEuen, J. M.; Nelson, R. P.; Lawton, R. G. *J. Org. Chem.* **1970,** *35*, 690–696; (b) Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron* **1974,** *30*, 633–640.
(48) Gravel, D.; Labelle, M. *Can. J. Chem.* **1985,** *63*, 1874–1883.
(49) Colonna, F. P.; Pitacco, G.; Valentin, E. *Tetrahedron* **1971,** *27*, 5481–5494.
(50) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007,** *9*, 4151–4154.
(51) Roche, S. P.; Porco, J. A. *Angew. Chem. Int. Ed.* **2011,** *50*, 4068–4093.
(52) Boyce, J. H.; Porco, J. A. *Angew. Chem. Int. Ed.* **2014,** *53*, 7832–7837.
(53) Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. J. A. *J. Am. Chem. Soc.* **2010,** *132*, 13642–13644.
(54) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A. *J. Am. Chem. Soc.* **2010,** *132*, 14212–14215.
(55) Couladouros, E. A.; Dakanali, M.; Demadis, K. D.; Vidali, V. P. *Org. Lett.* **2009,** *11*, 4430–4433.
(56) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973,** *14*, 121–124.
(57) Buono, F.; Tenaglia, A. *Synlett* **1998,** *1998*, 1153–1155.
(58) Grenning, A. J.; Boyce, J. H.; Porco, J. A. *J. Am. Chem. Soc.* **2014,** *136*, 11799–11804.
(59) K.-H. Schönwälder, P. K., J. J. Stezowski, F. Effenberger *Chem. Ber.* **1984,** *117*, 3280–3296.
(60) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002,** *4*, 1943–1946.
(61) Simpkins, N. S.; Taylor, J. D.; Weller, M. D.; Hayes, C. J. *Synlett* **2010,** *2010*, 639–643.
(62) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007,** *9*, 287–289.
(63) Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010,** *12*, 5234–5237.
(64) Horwitz, M. A.; Johnson, J. S. *Eur. J. Org. Chem.* **2017,** *2017*, 1381–1390.

(65) McGrath, N. A.; Binner, J. R.; Markopoulos, G.; Brichacek, M.; Njardarson, J. T. *Chem. Commun.* **2011,** *47*, 209–211.
(66) Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013,** *135*, 644–647.
(67) Sparling, B. A.; Tucker, J. K.; Moebius, D. C.; Shair, M. D. *Org. Lett.* **2015,** *17*, 3398–3401.
(68) Boyce, J. H.; Eschenbrenner-Lux, V.; Porco, J. A. *J. Am. Chem. Soc.* **2016,** *138*, 14789–14797.
(69) Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* **2015,** *137*, 10516–10519.
(70) (a) Liebman, J. F. G. *Chem. Rev.* **1976,** *61*, 8456; (b) Presset, M.; Coquerel, Y.; Rodriguez, J. *Chem. Rev.* **2013,** *113*, 525–595; (c) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999,** *99*, 27–76.
(71) Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010,** *132*, 9594–9595.
(72) Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005,** 3802–3804.
(73) Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995,** *60*, 6872–6882.
(74) Silvestri, M. A.; Bromfield, D. C.; Lepore, S. D. *J. Org. Chem.* **2005,** *70*, 8239–8241.
(75) Barluenga, J.; Ballesteros, A.; Bernardo de la Rúa, R.; Santamaría, J.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc.* **2003,** *125*, 1834–1842.
(76) Oblak, E. Z.; Wright, D. L. *Org. Lett.* **2011,** *13*, 2263–2265.
(77) Baalouch, M.; De Mesmaeker, A.; Beaudegnies, R. *Tetrahedron Lett.* **2013,** *54*, 557–561.
(78) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem* **2010,** *6*, 6.
(79) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-i. *Synlett* **1996,** *1996*, 557–559.
(80) Kimura, M.; Fukasaka, M.; Tamaru, Y. *Synthesis* **2006,** *2006*, 3611-3616.
(81) Harrowven, D. C.; Curran, D. P.; Kostiuk, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010,** *46*, 6335–6337.
(82) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980,** *45*, 4275–4277.
(83) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002,** *124*, 6343–6348.
(84) Hiyama, T.; Yamamoto, H.; Nishio, K.; Kitatani, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979,** *52*, 3632–3637.
(85) Pepper, H. P.; Tulip, S. J.; Nakano, Y.; George, J. H. *J. Org. Chem.* **2014,** *79*, 2564–2573.
(86) Nakagawa-Goto, K.; Wu, P.-C.; Bastow, K. F.; Yang, S.-C.; Yu, S.-L.; Chen, H.-Y.; Lin, J.-C.; Goto, M.; Morris-Natschke, S. L.; Yang, P.-C.; Lee, K.-H. *Bioorg. Med. Chem.* **2011,** *19*, 1816–1822.
(87) Monache, F. D.; Monache, G. D.; Gacs-Baitz, E. *Phytochemistry* **1991,** *30*, 2003–2005.
(88) Wang, M.; Feng, M.; Tang, B.; Jiang, X. *Tetrahedron Lett.* **2014,** *55*, 7147–7155.
(89) Nakamura, Y.; Burke, A. M.; Kotani, S.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett.* **2010,** *12*, 72–75.
(90) Chen, Z.-H.; Chen, Z.-M.; Zhang, Y.-Q.; Tu, Y.-Q.; Zhang, F.-M. *J. Org. Chem.* **2011,** *76*, 10173–10186.
(91) Willis, M. C.; Claverie, C. K. *Tetrahedron Lett.* **2001,** *42*, 5105–5107.
(92) (a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990,** *112*, 6429–6431; (b) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994,** *367*, 630–634.
(93) (a) Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Fuji, K. *Synthesis* **1995,** *1995*, 1069–1070; (b) Rajamannar, T.; Palani, N.; Balasubramanian, K. K. *Synth. Commun.* **1993,** *23*, 3095–3108.
(94) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977,** *42*, 3755–3757.
(95) Demir, A. S.; Enders, D. *Journal für Praktische Chemie/Chemiker-Zeitung* **1997,** *339*, 553–563.

(96) Sharpe, R. J.; Portillo, M.; Vélez, R. A.; Johnson, J. S. *Synlett* **2015,** *26*, 2293–2295.
(97) Barrack, S. A.; Okamura, W. H. *J. Org. Chem.* **1986,** *51*, 3201–3206.
(98) (a) Narender, T.; Sarkar, S.; Venkateswarlu, K.; Kumar, J. K. *Tetrahedron Lett.* **2010,** *51*, 6576–6579; (b) Nickl, J. *Chem. Ber.* **1958,** *91*, 553–565.
(99) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987,** *52*, 3223–3232.
(100) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998,** *63*, 6425–6426.
(101) Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydr. Res.* **2006,** *341*, 2714–2716.
(102) He, J.-F.; Wu, Y.-L. *Synth. Commun.* **1985,** *15*, 95–99.
(103) Whiting, B. T.; Coates, G. W. *J. Am. Chem. Soc.* **2013,** *135*, 10974–10977.
(104) Yoshimura, F.; Kowata, A.; Tanino, K. *Org. Biomol. Chem.* **2012,** *10*, 5431–5442.
(105) Harris, E. B. J.; Banwell, M. G.; Willis, A. C. *Tetrahedron Lett.* **2011,** *52*, 6887–6889.
(106) (a) Deschamp, J.; Hermant, T.; Riant, O. *Tetrahedron* **2012,** *68*, 3457–3467; (b) Deschamp, J.; Riant, O. *Org. Lett.* **2009,** *11*, 1217–1220.
(107) Gammack Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2015,** *54*, 4899–4903.
(108) Burns, A. R.; Madec, A. G. E.; Low, D. W.; Roy, I. D.; Lam, H. W. *Chem. Sci.* **2015,** *6*, 3550–3555.
(109) Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F. P. *Org. Lett.* **2000,** *2*, 3765–3768.
(110) (a) Liu, H.-J.; Lai, H. K. *Can. J. Chem.* **1979,** *57*, 2522–2525; (b) Liu, H.-J.; Oppong, I. V. *Can. J. Chem.* **1982,** *60*, 94–96.
(111) (a) Halimjani, A. Z.; Saidi, M. R. *Synth. Commun.* **2005,** *35*, 2271–2276; (b) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Synth. Commun.* **2005,** *35*, 867–872.
(112) Phillips, D. J.; Kean, J. L.; Graham, A. E. *Tetrahedron* **2013,** *69*, 6196–6202.
(113) Illa, O.; Namutebi, M.; Saha, C.; Ostovar, M.; Chen, C. C.; Haddow, M. F.; Nocquet-Thibault, S.; Lusi, M.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013,** *135*, 11951–11966.
(114) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003,** *125*, 10926–10940.
(115) Barbarella, G.; Garbesi, A.; Fava, A. *Helv. Chim. Acta* **1971,** *54*, 2297–2307.
(116) Gao, J.; Orso Simon, J.; Rodrigo, R.; Assoud, A. *J. Org. Chem.* **2013,** *78*, 48–58.
(117) Ranu, B. C.; Chattopadhyay, K.; Adak, L. *Org. Lett.* **2007,** *9*, 4595–4598.
(118) Anderson, E. PCT Int. Appl. WO 2015/112792 A1, 2015
(119) Kong, C.; Jana, N.; Jones, C.; Driver, T. G. *J. Am. Chem. Soc.* **2016,** *138*, 13271–13280.
(120) Shen, Q.; Huang, W.; Wang, J.; Zhou, X. *Org. Lett.* **2007,** *9*, 4491–4494.
(121) Treu, M. PCT Int Appl. WO 2012010704 A1, 2012
(122) (a) Bhat, B. A.; Maki, S. L.; St.Germain, E. J.; Maity, P.; Lepore, S. D. *J. Org. Chem.* **2014,** *79*, 9402–9407; (b) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990,** *46*, 523–544; (c) Liu, H.-J.; Wang, D.-X.; Kim, J. B.; Browne, E. N. C.; Wang, Y. *Can. J. Chem.* **1997,** *75*, 899–912; (d) Richard, J.-A.; Chen, D. Y. K. *Eur. J. Org. Chem.* **2012,** *2012*, 484–487; (e) Silverstein, R. M., Bassler, G. C., Morrill, T. C., *Spectrometric identification of organic compounds*. Wiley: New York, 1991; (f) Sun, T.-W.; Ren, W.-W.; Xiao, Q.; Tang, Y.-F.; Zhang, Y.-D.; Li, Y.; Meng, F.-K.; Liu, Y.-F.; Zhao, M.-Z.; Xu, L.-M.; Chen, J.-H.; Yang, Z. *Chem. Asian. J.* **2012,** *7*, 2321–2333.
(123) Zhu, S.; Zhang, Q.; Chen, K.; Jiang, H. *Angew. Chem. Int. Ed.* **2015,** *54*, 9414–9418.
(124) (a) King, K. C., R. G. PCT Int. Appl. WO 350100 A1, 2014; (b) Liu, H.; Sun, C.; Lee, N.-K.; Henry, R. F.; Lee, D. *Chem. Eur. J.* **2012,** *18*, 11889–11893.
(125) Kubilius, R.; Bagdžiūnas, G.; Butkus, E. *Tetrahedron Lett.* **2011,** *52*, 346–348.

(126) (a) Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem. Eur. J.* **2004,** *10*, 5581–5606; (b) Sultane, P. R.; Bielawski, C. W. *J. Org. Chem.* **2017,** *82*, 1046–1052.
(127) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008,** *37*, 320–330.
(128) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem.* **2004,** *5*, 637–643.
(129) Ferreira, S. B. *Synlett* **2006,** *2006*, 1130–1131.
(130) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004,** *6*, 3217–3219.
(131) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005,** *44*, 192–212.
(132) Hayes, C. J.; Simpkins, N. S. *Org. Biomol. Chem.* **2013,** *11*, 8458–8462.
(133) Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007,** *72*, 2068–2076.
(134) Kiehlmann, E.; Lauener, R. W. *Can. J. Chem.* **1989,** *67*, 335–344.
(135) Shimizu, H.; Shimizu, K.; Kubodera, N.; Mikami, T.; Tsuzaki, K.; Suwa, H.; Harada, K.; Hiraide, A.; Shimizu, M.; Koyama, K.; Ichikawa, Y.; Hirasawa, D.; Kito, Y.; Kobayashi, M.; Kigawa, M.; Kato, M.; Kozono, T.; Tanaka, H.; Tanabe, M.; Iguchi, M.; Yoshida, M. *Org. Process Res. Dev.* **2005,** *9*, 278–287.
(136) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988,** *1988*, 862–868.
(137) Helmboldt, H.; Köhler, D.; Hiersemann, M. *Org. Lett.* **2006,** *8*, 1573–1576.
(138) Porcal, W.; Merlino, A.; Boiani, M.; Gerpe, A.; González, M.; Cerecetto, H. *Org. Process Res. Dev.* **2008,** *12*, 156-162.
(139) Koech, P. K.; Krische, M. J. *Org. Lett.* **2004,** *6*, 691–694.
(140) Gramain, J. C.; Remuson, R.; Vallee, D. *J. Org. Chem.* **1985,** *50*, 710–712.
(141) Ou, J.; Wong, W.-T.; Chiu, P. *Org. Biomol. Chem.* **2012,** *10*, 5971–5978.
(142) Schmidt, A.; Hilt, G. *Org. Lett.* **2013,** *15*, 2708–2711.
(143) Phillips, D. J.; Graham, A. E. *Synlett* **2010,** *2010*, 769–773.
(144) Yu, B.; Jiang, T.; Quan, W.; Li, J.; Pan, X.; She, X. *Org. Lett.* **2009,** *11*, 629–632.
(145) Schröder, S. P.; Taylor, N. J.; Jackson, P.; Franckevičius, V. *Org. Lett.* **2013,** *15*, 3778–3781.
(146) Mahajan, J. R.; Resck, I. S. *Synthesis* **1980,** *1980*, 998–999.