SYNTHETIC STUDIES ON THE BRYOSTATIN B-RING

by

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Dedicated with love to my parents.
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ABSTRACT

A completely stereocontrolled asymmetric synthesis of an advanced B-ring synthon for the bryostatin family of antitumour agents is described in this thesis. Noteworthy features of our synthesis include the Smith-Tietze bis-alkylation reaction between 12 and 13 en route to C₂-symmetrical ketone 10, and the totally stereoselective conversion of 10 into triol 18 via a Grignard addition tactic. Triol 18 was converted to epoxide 3 in nine steps and an acid-catalysed intramolecular Williamson etherification reaction completed the synthesis of 2.
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1.0 Introduction

1.1 Isolation and Structure Elucidation of the Bryostatins 1-18

Scheme 1 The Bryostatin family of antitumour macrolides

The bryostatins are a structurally novel family of macrolides first encountered by Pettit and coworkers during their search for new anticancer drugs from the marine Bryozoan, *Bugula neritina*.1
To date eighteen bryostatins have been isolated, and all show significant antitumour activity *in vivo* (Scheme 1). The molecular structures of the bryostatins have been deduced either by X-ray crystallography or through detailed spectroscopic analysis, with several interesting structural patterns having emerged. All bryostatins possess a 20-membered macrolactone in which there are three remotely functionalised pyran rings interconnected by an \((E)\)-disubstituted alkene and a methylene bridge. All family members also contain a pair of geminal dimethyls at C(8) and C(18). Each bryostatin has a four-carbon side chain emanating from the A and C-rings, and virtually all possess an exocyclic methyl enoate unit in their B and C rings. In the majority of cases the only difference lies in the substituents at C(7) and C(20). Saying this, there are some bryostatins that do not conform to this basic structural blueprint. For example, bryostatin 3 has a butenolide appended to the C-ring rather than an exocyclic methyl enoate, and bryostatins 16 and 17 both have a glycal replacing the C(19)- and C(20)-hydroxyls. Additional differences can be found in bryostatins 17 and 18 which have opposite methyl enoate geometries in their C-rings.

1.2 Biosynthesis of Bryostatin 1

Through elegant radiolabelling and incubation studies, Kerr and coworkers\(^2\) have demonstrated that acetate, S-adenosylmethionine (SAM) and glycerol are all key building blocks involved in bryostatin 1 production. Propionate, n-butyrate, isobutyrate and succinate are not needed for bryostatin 1 biosynthesis. It has been suggested by Kerr that the geminal dimethyl groups of the bryostatins might originate from a series of SAM methylations on incorporated acetate units, as was found for the biosynthesis of lankacidin and aplasmomycin. As for the exocyclic olefin units, these probably derive from the addition of acetate to a polyketide chain followed by dehydration. Current work in Kerr's group is attempting to identify the sites at which the polyketide building blocks are incorporated, and clearly, these results are awaited with great interest.
2.0 Bryostatin Biology

2.1 The Antitumour Profile of the Bryostatins

Bryostatin 1 shows remarkable in vitro and in vivo anticancer effects against a range of mouse tumours that include P388 lymphocytic leukaemia, ovarian sarcoma, B16 melanoma, and M5076 reticulum cell sarcoma. Combinations of bryostatin 1 and auristatin PE, and bryostatin 1 and dolastatin 10 have successfully cured five out of five, and two out of five, SCID mice with human chronic lymphocytic leukaemia xenografts. Bryostatin 1 has also recently completed several phase 1 and 2 anticancer trials in man, where its most significant side effect was myalgia. The trials clearly demonstrated that bryostatin 1 has considerable potential for the treatment of ovarian and relapsed low-grade Hodgkin's lymphoma, it being effective when given alone or in combination with other anticancer drugs. To date, only one patient has had their cancer completely cured by bryostatin 1, but many partial remissions have been observed. The complete remission was seen in a 41-year old woman who had stage 4 follicular small-cell cleaved non-Hodgkin's lymphoma that had recurred at multiple sites, 5 years after she had gone into remission through combination therapy with alkylating drugs. Eight fortnightly cycles of bryostatin 1 were required to elicit this cure, each cycle corresponding to a 72 h intravenous fusion at a dose of 120 μg/Kg.

2.2 Mechanism of Antitumour Action

The antitumour effects of bryostatin 1 have been linked to its selective modulation of the functioning of individual protein kinase C (PKC) isozymes. PKCs are serine and threonine kinases that catalyse the O-phosphorylation of proteins involved in cell signal transduction. They are thought to play a critical role in the control of cell division, their over- or under-expression in some tissues having been correlated with the transition into malignancy. For example, Mushinski and coworkers observed that when nPKC-ε is overexpressed in NIH3T3 cells, it makes them highly neoplastic and tumourigenic towards nude mice. Elevated n-PKC-ε levels in rat fibroblasts also make them tumourigenic and malignant, while PKCβ overexpression renders these cells...
considerably more susceptible to undergoing transformation with the Ha-ras oncogene. The cotransfection of human small cell lung carcinoma cells with the c-myc and Ha-ras oncogenes serves to increase PKC-βIII levels, and significantly, this is correlated with the conversion of these cells into the more malignant large cell phenotype. cPKC-α levels are also raised significantly in human A549 lung cancer cells as compared with other nearby normal lung tissue. Taken together these findings lend weight to the idea that deregulated PKC activity could be contributing significantly to the onset of a range of tumours.

Since the growth inhibition of A549 human lung cancer cells by bryostatin 1 correlates very closely with the down-regulation of cPKC-α, this has led to the view that the down-regulation of certain PKC isozymes might be generally responsible for it and can actually prevent some “tumour-suppressing” PKCs from being down-regulated, most notably isoforms of the PKC-δ variety in a range of cell types. PKC-δs are now known to be intimately involved in cancer cell growth, their degree of expression frequently determining whether a cell will undergo growth arrest or proliferation. For example, PKC-δ over-expression in mouse keratinocytes results in apoptosis, which is the hallmark of efficient tumour suppression. PKC-δ will also override the effects of an over-expressed c-srcproto-oncogene in 3Y1 fibroblasts, it preventing such cells from undergoing transformation. Deliberate over-expression of PKC-δ in NIH 3T3 cells halts their proliferation, while its enforced under-expression in other tissues dramatically increases their rate of growth.

The fact that bryostatin 1 can protect PKC-δ from undergoing down-regulation in mouse keratinocytes supports the notion that bryostatin 1 might be inhibiting the growth of some tumours via a PKC-δ protecting or stabilising mechanism. Thus it appears as though bryostatin 1 acts upon the PKC isozymes of various tumours in a number of ways, and this significantly complicates the situation with regard to explaining its antitumour effects.

Because bryostatin 1 can selectively target different PKCs in a tissue-dependent manner, this has led to substantial interest in the structure determination of these complexes. Bryostatin 1 competitively binds to the phorbol ester/diacylglycerol binding sites of PKC isozymes at two highly
conserved regions known as the cysteine-rich domains 1 and 2 (PKC CRDs 1 and 2). Considerable effort has gone into mapping the three-dimensional structures of several CRDs, with the result that an NMR solution structure has recently been determined for a murine PKCα CRD2 complex,\textsuperscript{24} and a 2.2Å resolution X-ray crystal structure has been solved for a murine PKCd CRD2 complexed to phorbol 13-acetate.\textsuperscript{25} The latter work unambiguously showed that tumour-promoting phorbol esters sit in a groove that exists between two opened β-strands at the tip of the CRD. It also revealed that complexation does not induce a significant conformational change in the PKC activator-binding domain. In essence, the phorbol ester caps the polar inside of the groove and creates a long continuous hydrophobic surface that extends over roughly one-third of the complexed protein. It was suggested that the greatly increased hydrophobicity of the phosphorylated PKCd-phorbol ester complex promotes its insertion into the plasma membrane from where it can elicit its tumourigenic signalling.\textsuperscript{25} It is likely that when bryostatin 1 binds to the CRDs of various PKCs, a similar increase in PKC hydrophobicity occurs. However, with bryostatin 1, the complexation possibly elicits more a substantial conformational change in some of the PKC proteins than does the phorbol 13-acetate. It is quite reasonable to suppose that the protective action of bryostatin 1 upon PKCd from some tissues might be the result of its complexation inducing a "stabilising" conformational change in the enzyme that prevents it from inserting into the plasma membrane and/or being degraded. For other PKCs, bryostatin 1 might equally well be eliciting conformational changes that conspire to favour protein insertion into the plasma membrane and subsequent down-regulation.

Scheme 2 The hypothetical pathway of PKC synthesis and downregulation.
With regard to the latter proposal, remarkable insights have recently been garnered into the way in which bryostatin 1 down-modulates PKC-α in renal epithelial cells, and PKC-α and PKC-ε in human fibroblasts. Through an elegant series of $^{32}$P labelling studies, Bingham-Smith and coworkers have shown that for these two cell lines, the down-modulation of PKC-α and -ε occurs through the ubiquitin-proteasome pathway. They demonstrated that soon after a phosphorylated PKCα- or -ε-bryostatin 1 complex is formed, autophosphorylation occurs, with the result that the drug-protein complex is translocated from the cytosol to the plasma membrane where it then becomes embedded. Once there, the complex is apparently rendered susceptible to dephosphorylation by various membrane-bound alkaline phosphatases. Dephosphorylation yields a catalytically inactive form of the PKC protein that predisposes it to ubiquitinylation by Ub-activating (E1), -conjugating (E2), and ligating (-E3) enzymes found within the cytosol. As the ubiquitin ~26 proteasome organelle resides both in the cytoplasm and in the nucleus, it is likely that the cytoplasmic variant degrades the membrane-bound ubiquinylated PKC-α and -ε proteins, and that this is the entity responsible for the down-regulation of these two PKCs (Scheme 2).

This ability of bryostatin 1 to bind selectively to different PKC isoforms and render them susceptible or non-susceptible to undergoing degradation within cells is really quite remarkable, and probably holds the key to explaining many of the observed antitumour effects, and its future clinical use. It is easy to imagine that, for some cancers, selective downregulation of a particular upregulated PKC-isozymic pathway by bryostatin 1 might be all that is needed for correcting the aberrant mitogenic state, while for others, it could be the upregulation of a particular PKC pathway that is the critical event required for switching off the cellular proliferative machinery.

While most biological research on bryostatin 1 has focused on the study of its interactions with various PKC isozymes, it should be noted that bryostatin 1 can function as a powerful immunostimulant, and this has led some to suggest that a possible mode of antitumour action in some patients could be through it eliciting an enhanced immune response. Bryostatin 1 readily activates resting human T cells and neutrophils in vitro, and in vivo it can enhance the levels of
tumour-necrosis factor-α (TNF-α) in certain patients undergoing therapy. TNF-α is powerful tumouricide produced by the body upon immunostimulation. Bryostatin 1 also induces the rapid release of TNF-α from MONO-MAC-6 cells. Significantly, in a murine macrophage ANA-1 cell line, bryostatin 1 significantly increased TNF-α mRNA expression and production, and it synergised with IFN-γ in the production of NO\textsuperscript{2-} and in the expression of the inducible nitric oxide synthase (iNOS) gene. NOS catalyses the \textit{in vivo} production of NO from L-arginine; in turn, NO confers powerful tumouricidal effects on murine macrophages. It also induces the apoptosis of tumour cells. Such observations clearly lend support to the idea that bryostatin 1 could be exerting its antineoplastic effects through an immunostimulatory mechanism.

While bryostatins 1, 3, 8, and 9 are all capable of activating neutrophil chemiluminescence and the cytotoxic killing of K562 cells, identical actions have not so far been detected for bryostatin 13; a member of the 20-deoxy class of bryostatins, which are even more potent as antitumour drugs. Bryostatin 13 is also unable to stimulate colony formation from bone marrow progenitor cells, notwithstanding the fact that bryostatins 1, 3, 8 and 9 can all perform this task very effectively. Such data suggests that while an immunostimulatory antitumour mechanism might be significant for the C(20)-O-acyl bryostatins in some patients, a similar mode of action is probably not operative for molecules of the 20-deoxy class.

The divergent actions of the bryostatins on PKCs from different sources, coupled with the ability of some family members to function as immunostimulants, make it most unlikely that a single, all-encompassing, mechanism of antitumour action will ever be proposed for this class. Current biological data suggests that the antitumour properties of bryostatin 1 almost certainly vary from patient to patient, the observed response being contingent both on the cancer type and on the overall PKC content of the recipient’s cells. Clearly a great deal more biological evaluation will have to be done before a more complete mechanistic picture is gained of the various ways in which this class is exerting its anticancer effects.
2.3 Can Bryostatin 1 Accelerate the Growth of Some Tumours and Function as a Tumour Promoter?

Recently it has been demonstrated that PKCβ isozyme levels can markedly affect whether some cells rest or proliferate. This is significant for bryostatin 1 can selectively target PKCβIIIs in human erythroleukaemia (K562) and promyelocytic (HL60) cells. Bryostatin 1 complexation leads to these PKCs selectively translocating to the nuclear membrane, where they phosphorylate lamin B at its Ser-395 and Ser-405 residues. Lamin phosphorylation is associated with disassembly and increased solubility of the nuclear lamina network during mitosis, resulting in breakdown of the nuclear envelope. Importantly, these actions of bryostatin 1 correlate closely with an increased rate of proliferation for both cancer cell lines. Data of this sort apparently suggest that bryostatin 1 could actually worsen some tumours, and strongly point to the need for performing detailed in vitro anticancer tests of bryostatin 1 prior to commencing therapy. Preliminary in vitro screening might at least establish whether the drug will have a realistic chance of arresting or worsening tumour growth in a given patient before any clinical treatment is attempted.
3.0 Bryostatin Total Synthesis

The remarkable molecular structures of the bryostatins, coupled with their excellent antitumour properties and scarcity in nature, have educed considerable synthetic interest in this class over the past two decades. So far, only three bryostatin family members have succumbed to total chemical synthesis. Bryostatin 7 was the first family member to be synthesised by Masamune in 1990. Eight further years elapsed before Evans and coworkers crowned this monumental achievement with an equally impressive total synthesis of bryostatin 2. Two years later in 2000, Nishiyama and Yamamura reported their asymmetric pathway to the structurally most complex member of this family, bryostatin 3. In the coming sections, each of these syntheses will be discussed in detail.

3.1 Masamune's Enantioselective Total Synthesis of Bryostatin 7 (1990)


The strategic planning used by Masamune and coworkers for their total synthesis of bryostatin 7 is summarised in Scheme 3.

Scheme 3 Masamune's retrosynthetic planning for bryostatin 7
Key elements of their proposed route were a regioselective macrolactonisation of seco-acid 1 to construct the 20-membered macrolide ring, the use of a reagent-controlled acetate aldol reaction to set the C(3)-hydroxy stereocentre and concurrently install C(1) and C(2) carbons of the polyketide backbone, and a Julia olefination reaction between 3 and 4 to fashion the sterically encumbered C(16)-C(17) trans-alkene, and connect the three pyran segments together. A chemoselective oxymercuration of the less hindered olefin in diene 5 was envisioned for B-ring assembly, while a borolane mediated asymmetric aldol reaction appeared strategic for uniting the A- and B-ring sectors. The C-ring sulfone 4 appeared accessible from the protected ketone 8 which, itself, looked derivable from the addition of a vinylmetal species to the α-alkoxy aldehyde 10, when followed by appropriate functional group interconversions. The presence of a DMBO group at the α-position of aldehyde 10 could be expected to favour the emergence of the chelation controlled addition product with the correct alcohol configuration at C(20).


For methyl ketone 6 (Schemes 3 and 4), efficient installation of the masked 1,3,5-triol motif spanning carbons-3 to 7 was the main concern. Some years earlier, Masamune and Sharpless had proposed a general solution to this problem as part of their synthetic work on the antifungal agent amphotericin B. Their approach was based upon the creation of an appropriate chiral 2,3,4,5-bis-epoxy alcohol via the AE and regioselective ring-opening at C(2) and C(4) with REDAL. The substrate that would be needed for the A-ring sector was compound 14; it was prepared in nine steps from 2,2-dimethyl-propane-1,3-diol 11 as detailed in Scheme 4. Diol 11 was converted to aldehyde 12 by selective O-benzylation and oxidation. Wadsworth-Horner-Emmons (WHE) reaction, DIBAL reduction and Sharpless AE subsequently delivered the 2,3-epoxy alcohol 13 in 92% ee, while Swern oxidation secured the epoxy aldehyde. The latter underwent Wittig formylation and borohydride reduction to the allylic alcohol needed for the second AE, which enhanced the d.e. of the product 14 to 99%. As expected, 14 underwent regiospecific alkoxide-directed ring opening with REDAL, compound 15 being obtained as the sole product. Selective O-silylation and
acetalation yielded 16. O-Debenzylation via Birch reduction followed by Swern oxidation, methyllithium addition, and a second Swern oxidation completed the sequence to methyl ketone 6.

Treatment of 6 with the \((R,R)\)-borolane triflate 18 and Hunig’s base produced a chiral boron enolate 19 which readily added to the dienyl aldehyde 7 to afford β-hydroxy ketone 20 with 8:1 selectivity. Fischer glycosidation of 20 with MeOH, PPTS and trimethylorthoformate next unmasked the C(5) and C(7)-hydroxyls and instigated formation of the α-methyl glycoside 5. The B-ring was elaborated via chemoselective intramolecular alkoxymercuration, acetylation, and oxidative demercuration under free radical conditions. The end-result was a 1:1 mixture of diastereoisomeric alcohols 23 that were epimeric at C(15). In order to remedy this adverse stereochemical situation,
23 was oxidised to the 1:1 mixture of aldehyde epimers 24 and these equilibrated under mildly basic enolisation conditions to a 9:1 mixture enriched in the more stable equatorial product 3.

Scheme 5  Masamune's synthesis of the C(11)-C(16) B-ring fragment 7.

Important steps in the route (Scheme 5) to aldehyde 7 included the Corey trisubstituted olefin synthesis\(^4\) that was used to access iodo allylic alcohol 27, the protection of its OH with TBDPSCI, and the copper-catalysed cross-coupling reaction with allylmagnesium bromide. The THP group was hydrolysed from 28 with PPTS in ethanol, and a Collins oxidation used to secure 7.


Scheme 6  Masamune's route the bryostatin 7 "Southern Hemisphere".
A two-pronged strategy was devised for the C(17)-C(27) sector 4, which relied upon the preparation of fragments 9 and 10 (see Schemes 6 and 7). Vinyl iodide 9 was synthesised from L-threonine as detailed in Scheme 6. The route opened with the sequence of amine diazotisation, O-esterification, and O-isopropylidenation to acquire methyl ester 31. The latter was then reduced to the corresponding aldehyde with DIBAL and this, in turn, subjected to a Wittig olefination with methylenetriphenylphosphorane. Hydroboration and oxidation of alkene 32 furnished alcohol 33 which was further oxidised to aldehyde 34. A chelation-controlled addition of allenylzinc bromide was now effected on 34 to introduce the acetylene needed for later elaboration of the exocyclic olefin. The C(23)-hydroxy stereocentre was set with 8:1 selectivity, notwithstanding the fact that β-alkoxy aldehydes are generally not regarded as good substrates for chelation-controlled nucleophilic additions of organometallics. After protection of the predominant alcohol as a PMB ether, the alkyne terminus of 36 was homologated with t-BuLi and methyl chloroformate to obtain the alkynyl ester 37. Stannylicupration of 37 via the Piers methodology proved highly stereospecific, it depositing the requisite vinylstannane group within 38 in high yield. DIBAL reduction of the ester and protection of the resulting alcohol transformed 38 into 39, which engaged in a stereospecific substitution reaction with iodine to give 9. The lithiation of 9 yielded a vinyllithium intermediate that added readily to aldehyde 10, to afford a mixture of alcohols enriched in the chelation-controlled product 40. Protecting group manipulation and oxidation completed ketone 41. The sulfone unit was best elaborated by sulfide oxidation with MoOPH, conditions which left the trisubstituted double bond unperturbed. A DDQ-induced removal of the PMB group now followed and the mixture of hemiketals then subjected to Fischer glycosidation with Me₃SiOMe and Me₃SiOTf.
to secure 4. Compound **10**, the aldehyde coupling partner for vinyl iodide **9**, was prepared according to Scheme 7. Significant steps in the route were the Sharpless AE and intramolecular urethane/epoxide ring opening used to generate the requisite stereochemistry at C(19).

d. The Masamune Bryostatin 7 Endgame.

![Scheme 8 Masamune's synthetic route to bryostatin 7.](image)

Not only did the Julia olefination\(^{38}\) between 3 and 4 serve to connect the AB- and C-ring fragments together (Scheme 8), it also fashioned the C(16)-C(17) (E)-disubstituted olefin geometry with good stereocontrol \((E:Z = 6.2:1)\). Masamune now wanted to selectively O-acetylate the C(20)-
and C(7)-hydroxyls. Consequently, compound 2 was globally O-desilylated, and the three primary OH units reblocked with TBS groups prior to this reaction being attempted with acetic anhydride/pyridine. A second global O-desilylation with TBAF was now needed to permit selective oxidation of the allylic hydroxyls with MnO2 in THF. By adhering closely to Corey’s recommended conditions for oxidising enals to methyl enoates,47 the intermediary enals were converted to the corresponding allylic cyanohydrins with HCN, and these oxidised and methanolysed in situ to obtain the expected bis(methyl enoate). Swern oxidation of the primary OH that remained led to the acquisition of aldehyde 47. The aldol reaction between 48 and 47 next introduced the C(1)/C(2) segment with 3:1 selectivity in favour of the desired alcohol. Transketalisation of this product with MeOH/CSA unmasked the C(25)/C(26)-dihol unit, which was temporarily O-triethylsilylated along with the C(3)-OH. This transitory protection step proved necessary to permit hydrolysis of the C(1)-thioester, which liberated 1 after O-desilylation. The partially protected seco-acid 1 was now coaxed into undergoing a highly regioselective macrolactonisation reaction with DCC and PPTS in pyridine/1,2-dichloroethane.48 The reaction conditions also caused glycoside hydrolysis at C(9) but not at C(19). Presumably the electron-withdrawing O-acetate group at C(20) conferred added acid stability on this glycoside by lowering its basicity. The observation of selectivity in this cleavage was most unfortunate because hydrolysis of the C(9)- and C(19)-methyl glycosides had been the next step planned after macrolactonisation in the original synthesis. After much experimentation, it transpired that conditions could not be identified for accomplishing the C(19)-OMe hydrolysis that also did not cause damage to the remainder of the molecule. Masamune therefore detached the C(20)- and the C(7)- O-acetates with catalytic KOMe, to render the offending glycoside more acid labile; that the macrolactone ring of compound 50 survived these transesterification conditions is most noteworthy. While this tactic did actually allow the C(19)-OMe group to be hydrolysed under mild acid conditions, it still left the issue of selective silylation of O(26) to allow repositioning of the O-acetate groups at C(7) and C(20) by selective O-acetylation of 51. Fortunately, both of these rather risky steps worked successfully, and served as the prelude to O-desilylation of 52 with aq.HF to obtain bryostatin 7.
3.2 The Evans Enantioselective Total Synthesis of Bryostatin 2 (1999)


Early work by Evans on the bryostatins investigated the utility of pyran-tethered phosphonoacetates and the intramolecular Wadsworth-Horner-Emmons process for positioning the exocyclic enoate stereoselectively.

For the B-ring enoate, a six-carbon tether was considered optimal, as MM2 calculations suggested it would lead to a free-energy difference of greater than 10 kcal/mol between the geometric isomer products, with the desired 14-membered macrocycle being the lower in energy. Accordingly, when Evans and Carreira investigated the high-dilution macrocyclisation of tethered phosphonoacetate 54 (Scheme 9) with 33 equiv of lithium chloride and 30 equiv of triethylamine in acetonitrile, they were gratified to find that a very clean cyclisation took place after 36 h, with the desired enoate 53 having formed as the sole product in 60% yield. While related model studies indicated that such tethers could be cleaved successfully with K$_2$CO$_3$/MeOH without accompanying olefin isomerisation, such a cleavage was not reported on 53 to obtain the corresponding methyl enoate. Although the tethered intramolecular Wadsworth-Horner-Emmons technology was not eventually used in Evans' bryostatin 2 synthesis, it does remain a strategy worth considering for the future stereospecific introduction of exocyclic alkenic arrays in other systems.

Scheme 10  Evans' retrosynthetic analysis of bryostatin 2.

Having grappled with the bryostatin problem for quite some time, and having learnt much about the many synthetic pitfalls that lie on route to these molecules, Evans decided that it might be
strategically advantageous to postpone exocyclic olefination until late in his projected total synthesis of bryostatin 2. As a consequence, macrocyclic diketone 58 was selected as an advanced sub-target, and a Fuji asymmetric Wadsworth-Horner-Emmons reaction with 59 was selected for stereoselective installation of the B-ring enoate (Scheme 10). Evans believed that the C(21)-enoate could be readily elaborated from a C(20)-ketone intermediate by an aldol addition/dehydration tactic. The C(20)-OH stereochemistry would be set by stereoselective reduction of the resulting keto-enoate. Diketone 58 appeared accessible from the seco-acid 61 and it, in turn, looked derivable from glycal 62. It was reasoned that the more electron-rich C(19)-C(20) enol ether double bond in 62 would undergo regioselective epoxidation with a limited quantity of oxidant, and assuming that this situation prevailed, a subsequent glycosidation with methanol could be expected to anchor a methyl glycoside at C(19) and post the requisite hydroxyl at C(20) in the forward route to 58. The forward pathway would also have to address the issue of converting the C(1)-anilide to a carboxylic acid. For connecting the A, B and C fragments, a Beau-Sinay alkylative C-glycosidation was envisioned between 63 and 64, with the BC-fragment 64 being prepared by a Julia olefination between 65 and 66.

c. Synthesis of the C(1)-C(9) Glycosylsulfone 63.

The starting material for the synthesis of 63 was methallyl chloride 67; it was converted to aldehyde 72 in four straightforward steps, one of which was the acid-induced cyclopropylcarbinol rearrangement of 71 (Scheme 11). Aldehyde 72 partnered oxazolidinone 73 in an Evans asymmetric aldol reaction; the result was aldol adduct 74. A zinc-mediated dehalogenation was next effected, and the acetate aldol product 75 reduced to diol 76 with lithium borohydride. These combined tactics sculpted the C(9)-C(5) sector of the A-ring sulfone and simultaneously controlled the C(7)-hydroxyl stereochemistry with 9:1 selectivity in the desired direction. The route continued with selective blocking of the C(7)-OH as a PMB ether, a transformation accomplished by the two step procedure of O-benzylidenation and regioselective acetal reduction with DIBAL. Aldehyde 77 (derived from the primary alcohol by Swern oxidation) combined with 78 in a Lewis acid mediated acetoacetate aldol condensation that completed the C(1)-C(9)-carbon backbone. Solvent choice
Scheme 11  Evans' synthesis of the A-ring glycosyl phenylsulfone 63.

profoundly affected the diastereoselectivity of this reaction; toluene leading to 94:6 selectivity in favour of 79, and dichloromethane eroding the level of selectivity to 6:1. An Evans hydroxyl-directed reduction$^{56}$ was now implemented on β-hydroxyketooester 79 to finalise the installation of all the asymmetric centres needed in this sector. The desired anti-product 80 emerged from this reaction in good yield and with high stereoselectivity (ca. 10:1). The C(3)- and C(5)-hydroxyls were now differentially protected via a PPTS-induced lactonisation and an O-silylation, and the lactone ring of 81 opened with the aluminate formed from aniline hydrochloride and trimethylaluminium. Ozonolytic cleavage of the product 82 afforded a 1.5:1 mixture of β:α-hemiacetals (72%) along 20% of the C(9)-epoxide. The latter was suggested to arise from an end-on approach of the ozone to the
alkene, a pathway known to be facile with sterically-demanding alkenes. The two hemiacetals were converted to the O-acetates 83 without hitch. A Hanessian-Guindon thioglycosidation reaction and a buffered m-CPBA epoxidation concluded this pathway to the α-phenylsulfone 63.

d. Evans’ asymmetric route to C(10)-C(16)-B-Ring Fragment 65

In 1996, Evans, Murry and Kozlowski described a powerful new method for effecting the catalytic asymmetric acetoacetate aldol reaction in high yield and excellent ee. The chemistry appeared tailor-made for exploitation in the bryostatin arena, as it readily allowed 1,3-diol arrays to be efficiently constructed if used alongside existing technology for the stereoselective reduction of β-hydroxy ketones. Evans decided to enlist this powerful new reaction combine for his assembly of the protected bryostatin B-ring synthon 65 (Scheme 12).

![Scheme 12 Evans' B-ring synthesis.](image)

The key aldol reaction that served to spark this sequence involved 84 and 85 and utilised the $C_2$-symmetric copper (II) complex ([Cu(R,R)-Ph-pybox]) (SbF$_6$)$_2$ 86 as the chiral catalyst. Significantly, this process proved exceedingly efficient, it affording 87 in 99% ee and 85% yield on 10 g scale. After reduction with Me$_4$NBH(OAc)$_3$, the anti-diol 88 emerged as the predominant product of the 94:6 mixture that resulted. Lactonisation and protection subsequently furnished lactone 89 in 77% yield for the two steps. The latter was reacted with $p$-methoxybenzoyloxyethylmethyl lithium to obtain a mixture of hemiketals which were subjected to ionic
reduction. Importantly, this reduction step proceeded with excellent stereocontrol it furnishing the desired product 90 in good yield and with 94:6 diastereoselectivity. Standard protecting group manipulation and oxidation finalised this brief synthesis of 65.

e. Synthesis of the C-ring sector and elaboration into the BC-segment 64

Scheme 13  Evans' synthesis of the bryostatin 2 BC-ring synthon 64.

The route to the C-ring glycal 64 commenced with a four-step preparation of 95 from 2,2-dimethyl-1,3-propanediol (Scheme 13). Aldehyde 95 combined with pentenylmagnesium bromide to create 97. Dihydroxylation and oxidative cleavage were then used to convert 97 into aldehyde 99 which was submitted to a DIP-Cl mediated Brown-Paterson asymmetric aldol reaction with 93, which proceeded with 93:7 diastereoselectivity in the desired direction. Ketone 93 was procured
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through Sharpless kinetic resolution,42 as detailed in Scheme 14. Tischenko reduction63 of 101 with Sml<sub>2</sub> not only installed the C(25)-hydroxyl, but also introduced the p-nitrobenzoate group at O(23) in 101. Protection and saponification were the next reactions implemented. Mild acid treatment finally afforded the desired phenylsulfonyl glycal 66. The Julia olefination38 between 66 and 65 proceeded with high geometric control (E:Z = 95:5), it initially affording 103, and then 64 after selective O-desilylation of the primary TBS group and O-triflation with triflic anhydride and 2,6-lutidine.

f. Completion of the bryostatin 2 synthetic venture

The fulcrum of Evans' strategy for bryostatin 2 was his use of the Beau-Sinay glycosylsulfone C-alkylation tactic51 for joining the A- and BC-segments together (Scheme 15). The reaction between 63 and 64 initially afforded a mixture of glycosyl sulfones 104, which readily underwent hydrolysis at C(9) upon exposure to silica gel. The excellent yield observed in this alkylation is noteworthy given the high degree of steric hindrance that exists around the glycosylsulfone anionic centre, and the β-oxygen functionality that is present in the triflate component 64. The synthesis proceeded with conversion of the C(1)-acyl anilide into a benzyl ester. For this, it proved necessary to ring-open hemiketal 62 by O-silylation with Et<sub>3</sub>SiCl and then install a Boc group on the anilide nitrogen. The Boc unit greatly facilitated the subsequent nucleophilic addition/elimination step with lithium benzyloxide. Selective epoxidation of the C(19)-C(20)-glycal in 106 was then attempted. Fortunately, this process proceeded with complete regiocontrol, which beautifully set the stage for acid-catalysed epoxide ring-opening with methanol to obtain methyl glycoside 107. Dess-Martin oxidation54 of 107 yielded 108 which underwent simultaneous O-desilylation and Fischer glycosidation with HF/MeOH in THF buffered with pyridine to give 109. The latter was selectively O-triethylsilylated at OH(3) and OH(13). Transfer hydrogenation55 with 1,4-cyclohexadiene on a palladium-carbon catalyst subsequently detached the benzyl ester from this product to provide 61. The emergence of the C(16)-C(17)-alkene from this
hydrogenation step is particularly noteworthy. A Yamaguchi macrolactonisation was now
effected to secure 60 which was selectively O-desilylated at O(13) and oxidised. Olefination of
ketone 58 with the Fuji chiral phosphonoacetate 59 produced a 5.5:1 mixture of enoates enriched
in the desired alkene component 57. Significantly, no addition occurred at the C(20)-ketone due to
steric hindrance from the two C(18)-substituents. The aldol-dehydration olefination tactic was now
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implemented on 57 to obtain 56, and a CBS reduction performed on the C(20)-ketone. It generally proved beneficial to trap the product alcohol as the O-methoxyacetate ester 111 to facilitate compound isolation.

With compound 111 in hand, the O(3)-TES group and the C(9)-methyl glycoside were selectively hydrolysed with PPTS in THF/H$_2$O. As found by Masamune in his bryostatin 7 synthesis, the presence of the C(20)-O-acyl substituent dissuaded the C(19)-methyl glycoside from undergoing mild acid hydrolysis. To overcome this problem, the Masamune O-deacylation tactic was mustered, whereafter the desired hydrolysis was achieved with p-TsOH in aq. acetonitrile, a set of conditions that proved fully compatible with the remainder of the molecule. The synthesis of bryostatin 2 was completed by selective esterification of OH(20) with octadienoic acid (in the presence of the C(3)-OH), and DDQ deprotection of two PMB groups.

3.3 The Nishiyama/Yamamura Total Synthesis of Bryostatin 3 (2000)

a The Nishiyama/Yamamura Retrosynthetic Plan for bryostatin 3

Scheme 16 The Nishiyama/Yamamura retrosynthetic analysis of bryostatin 3.

Bryostatin 3 is structurally the most complex member of this family by virtue of its additional C(22)-stereocentre which is buried within the pyran-butenolide framework. The flanking functionality that is present on either side of the C-ring alkene potentially makes its stereocontrolled construction an even more challenging task than that for other family members. Nishiyama and Yamamura hoped to forge this domain from the addition of a vinylithium intermediate (derived from 118) onto a-alkoxy aldehyde 119 under conditions of chelation control (Scheme 16). Such a sequence was expected to furnish an alcohol with the correct stereochemistry at C(22), which could then be
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transformed into sulfone 115. As in the Masamune\textsuperscript{35} and Evans\textsuperscript{36} syntheses, a Julia olefination\textsuperscript{38} was to be deployed for establishing the C(16)-C(17) (E)-disubstituted alkene linkage, and a Yamaguchi seco-acid macrolactonisation\textsuperscript{66} was envisaged for constructing the 20-membered macrolide ring. Like Evans, Nishiyama and Yamamura thought it prudent to postpone installation of the B-ring enoate until the final stages of the synthesis, and they too envisaged using the Fuji chiral phosphonacetate\textsuperscript{50} for effecting stereoselective olefination. However, the substrate on which they proposed to attempt olefination was considerably more fragile, adding extra risk (not to mention spice!) to the final outcome.

\textbf{b Preparation of the AB-Aldehyde Intermediate 114}

The "chiral pool" starting material, D-mannitol 120, served as the starting point for the synthesis of the advanced B-ring intermediate 116 (Scheme 17).\textsuperscript{37a} It was converted to D-glyceraldehyde acetonide 121 by standard literature procedures,\textsuperscript{67} and this then subjected to a Danishefsky hetero-Diels Alder (DA) reaction\textsuperscript{68} with 122 under zinc chloride catalysis. The DA reaction, which conforms to the predictions of the Cram model, furnished 123 as the sole product in 72\% yield. The latter readily engaged in a copper-mediated conjugate addition with vinyl magnesium bromide to give 124 with total stereocontrol. Ketone 124 was then protected as a dimethyl acetal with dimethoxypropane, a tactic which preserved the O-isopropylidene group. Ozonolysis of the double bond provided an aldehyde whose C(14)-position could be readily epimerised to the desired equatorial configuration via the aldehyde enolate. Aldehyde 125 was reduced to the alcohol, an O-benzyl ether introduced, the isopropylidene group removed, and the 1,2-diol unit oxidatively cleaved and reduced. The product 126 was then O-tosylated and subjected to iodide displacement to access the desired iodide 116.

The A-ring was elaborated from this B-ring template by a series of reactions that commenced with the alkylation of dithiane 117. Aldehyde 128, derived from this alkylation product, was then used in an aldol addition reaction to access 129. Transesterification with trimethylsilylethanol converted 129 into the β-keto ester 130 which underwent Evans reduction\textsuperscript{56} in
good yield to give the 1,3-anti-diol 131 with 24:1 selectivity. A three step sequence was now successfully implemented to access 132, involving hydrolysis of the dithiane with Hg(II) salts, Fischer glycosidation with methanol/PPTS, and silylation of the C(3)-OH. An O-allyl for O-
trimethylsilyl ethyl protecting group interchange was then effected to transform 132 into 133. O-Debenzylation and TPAP oxidation finalised the synthesis of aldehyde 114.

\[
\begin{align*}
\text{Scheme 18} & \quad \text{Route to dithiane 117.}
\end{align*}
\]

Dithiane 117 was prepared in ten steps (Scheme 18) by modifying some of the chemistry used by Masamune in his A-ring synthesis. The most notable new reaction in this sequence was 1,3-dithiane formation with 1,3-propanedithiol and magnesium bromide etherate, which proceeded in good yield without disrupting the potentially labile OTBS groups.

c  \quad \text{Synthesis of the C-Ring Sulfone 115}

A carbohydrate starting material again figured in the preparation of aldehyde 119 (Scheme 19), whose carbon framework of this fragment equated with C(27)-C(22)-sector of bryostatin 3. Commercially available diacetone D-glucose 135 was tosylated at OH(3) and an E2-elimination performed to access glycal 136.®® A stereospecific hydrogenation on the less-hindered face of 136 inverted the stereochemistry at C(4) to correctly establish the syn-relationship needed for the C(25)- and C(26)-hydroxyls of the target. However, before the C(25)-C(27) region could be completely tailored, it was necessary to selectively deprotect the exo-\(\alpha\)-isopropylidene group from this product, and deoxygenate the primary alcohol to obtain 138.®® Cleavage of the remaining \(\alpha\)-isopropylidene group, and hemiacetal
ring opening (both accomplished with 1,3-propanedithiol) subsequently furnished 139, which was transformed into aldehyde 119 by BOM-protection and thioketal hydrolysis.

(iii) PhSNa, 18-Cr-6, DMF, 90 °C (82%)
(iv) AcOH, THF, H2O
(v) SOa Py, MejSO2, CH2Cl2, B3N (83%)
(vi) (EtO)2 P (0 )CH2CO2Et, NaH, PhMe (100%)
(vii) DHQPHN (2 mol%), O2H/THF, 0 °C, 18 h (94%, 90% ee)
(viii) Me2CO(OMe)2, p-TsOH, CH2Cl2 (ca.93%)

The fragment that would partner aldehyde 119 was vinyl iodide 118. It was prepared efficiently by the pathway shown in Scheme 20. A five-step protocol secured aldehyde 141, which was olefinated and dihydroxylated with potassium osmate in the presence of the Sharpless DHQ-PHN ligand. The resulting diol 142 was then O-isopropylidened to obtain 143, the ester selectively reduced to the aldehyde with DIBAL, and a Corey-Fuchs olefination used to acquire the dibromoolefin 144. Conversion of 144 into the lithium acetylide with n-BuLi, and trapping with paraformaldehyde yielded the expected propargylic alcohol, which underwent a hydroxyl-directed hydroalumination and iodination to furnish the iodoalkene 145 after cleavage of the isopropylidene acetal. An additional set of protecting group adjustments were then made to install a TBDPS on the allylic OH and a PMB-ether group upon O(19).
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The critical union between 118 and 119 was accomplished by initially reacting 118 with MeLi and t-BuLi, and adding aldehyde 119 to the resulting lithiodianion at −90 °C; 3:1 selectivity resulted in favour of the desired alcohol, which was protected as a TBS ether. Selective oxidation of the phenylsulfide to the phenylsulfone next ensued with m-CPBA. It is noteworthy that the potentially sensitive alkene unit survived this reaction unscathed. The PMB ether was now detached from this product and the alcohol oxidised to the β,γ-unsaturated ketone 148 under Dess-Martin conditions. In yet another compelling transformation, the BOM ether was cleaved selectively from 148 by catalytic hydrogenation without perturbing the trisubstituted double bond. Presumably selectivity arises from the bulky allylic OTBDPS group preventing complexation of the catalyst with the double bond. Somewhat surprisingly, these conditions also brought about partial cleavage of the O-isopropylidene group which was restored by treatment with PPTS, dimethoxypropane and acetone. Importantly, these reprotection conditions did not move the trisubstituted alkene into conjugation with the nearby ketone, again presumably, due to the steric protective effect of the bulky C(20)-OTBS group. Formation of methyl glycoside 149 was accomplished by reacting the product ketone with TBSOTf, TMSOMe and dimethoxypropane in dichloromethane. A protecting group interchange (OTES for OTBS) finally afforded 115.

d Union of the AB- and C-Ring Intermediates 114 and 115 and completion of the bryostatin 3 synthetic venture

Application of the Julia olefination technique to fragments 114 and 115 gave a single alkene product 151 in 52% yield (Scheme 21). The TES groups at O(22) and at the C-ring allylic position were then selectively detached with TBAF/AcOH (1:1) in THF to afford the diol 152 in nearly quantitative yield. Selective allylic oxidation of 152 with TPAP/NMO now sculpted the desired butenolide system. A second exposure to TBAF/AcOH selectively deprotected the C(20)-OTES group, providing the key scaffold 154 needed for attaching the (E,E)-octadienoic acid unit; a task accomplished via the Yamaguchi mixed anhydride protocol. Transketalisation of 155 with CSA/MeOH unmasked the O(25)- and C(26)-hydroxyls without disturbing other potentially sensitive features such as the C(1)-C(3) β-hydroxy allylic ester or the (O)-7 TBS group. Triol 156 was now
selectively O-silylated with TESCI at OH(26) and OH(3). A palladium (0) mediated O-deallylation subsequently provided seco-acid 113. Macrolactonisation of 113 was again achieved by the Yamaguchi method, the desired product being isolated in a magnificent 93% yield. It was then O-desilylated with HF in aq. MeCN; conditions that concurrently brought about hydrolysis at C(13) and C(9) to furnish the keto-dilactone 157. Then in a rather risky but quite breathtaking master-stroke,
an asymmetric Wadsworth-Horner-Emmons reaction\(^5\) was performed on 157 with phosphonoacetate 95, leaving the C(26)-, the C(9)-, the C(7)- and the C(3)-hydroxyls all unprotected. Remarkably, this tactic substantially improved the stereoselectivity of olefination (relative to the Evans synthesis) to ca. 9:1 in favoured the desired alkene product. As found by Masamune and Evans in their synthetic endeavours, acid hydrolysis of the C(19)-methyl glycoside proved problematical when a C(20)-ester group was resident. Notwithstanding this, however, conditions were eventually devised for accomplishing this reaction in high yield without any need for removing the C(20)-ester grouping. Specifically, the glycoside was hydrolysed with aqueous trifluoroacetic acid for 1 h. Having successfully overcome this particular obstacle, there now remained the issue of installing the C(7)-O-acetate group. This was done by selectively silylating the C(26)-OH with TESCl to obtain 158, and selectively O-acetylation the C(7)-hydroxyl. The observed selectivity arises because the C(3)- and C(19)-hydroxyls both participate in a very stable hydrogen bonding network, which positions the C(3)-OH within the 20-membered macrolactone cavity, and makes it considerably more hindered than either the C(7)- or C(26)-OH groups. The synthesis of bryostatin 3 was completed by O-desilylation with aq. HF in MeCN. So far, the Nishiyama/Yamamura route has been able to deliver 25 mg of synthetic bryostatin 3 for testing; this really is a most noteworthy achievement and suggests that a future commercial synthesis might soon be on the horizon.

4.0 Synthetic Studies on the Bryostatins

Besides these three groups, a significant number of other teams have also been active in this area, with some having reported syntheses of various advanced synthetic intermediates \textit{en route} to bryostatins 1 and 11; their efforts will now be discussed.

4.1 Thomas' Synthetic Studies on Bryostatin 11\(^72,73\)

Thomas' work on the bryostatin 11 problem has so far resulted in the B- and C-Ring fragments 159 and 163 having been prepared; both have functionality that looks appropriate for
future manipulation into the natural product. The retrosynthetic planning they have used for these segments is shown in Scheme 22.

Thomas' Retrosynthetic Analysis of Bryostatin 11

For the B-ring synthon 159, a very bold 6-endo-trig vinyl radical cyclisation was proposed, involving the free radical intermediate 162 (Scheme 22). Thomas envisioned that such a radical would conjugatively add to the tethered enol enoate to generate a captodatively stabilised tertiary tetrahydropyranyl radical 161 which could then go on to abstract hydrogen from tributylstannane from the less-hindered α-pyran face, opposite to the bulky C(15)-CH₂OTBS group. A key element of this stratagem was the tenet that the (Z)-vinyl radical would lie in equilibrium with its (E)-counterpart (as a result of rapid vinyl radical inversion), and that the former would cyclise much more rapidly due to this addition being far less sterically crowded than that of its isomeric alternative, which would inevitably place the (E)-vinyl radical ester methoxy in close proximity to the enol enoate methylene and lead to greater steric repulsions in the transition state. Provided that the rate of (Z)-vinyl radical cyclisation was considerably faster that of the (E)-isomer, it could easily be imagined that even a rapidly equilibrating mixture of vinyl radicals might predominantly channel through to the desired alkene product. It was envisaged that the requisite vinyl radical intermediates might be
available from a vinyl iodide precursor through attack of a tributylstannyl radical, and that this iodide could in turn be derived from (S)-glycidol.

For the C-ring sulfone 163, a novel palladium (0) catalysed cross-coupling was proposed for uniting the stereodefined vinyl bromide 165 with the tributylstannyl enolate derived from 164 (Scheme 22). The fact that there were few examples of such cross-couplings ever previously being used in complex natural product synthesis made this a particularly interesting disconnection worthy of further evaluation.


![Scheme 23](image)

Scheme 23  Thomas' free radical cyclisation technology for controlling bryostatin B-ring olefin geometry.

To test out the viability of all the aforementioned planning, Thomas performed his synthesis in racemic form rather than with optically pure (S)-glycidol. Thus (RS)-glycidol was O-silylated with
TBSCI, and the resulting epoxide 166 ring-opened with the lithio-anion of methyl propiolate in the presence of Lewis acid (Scheme 23). The product alcohol 167 was converted to the alkoxymalonate 169 by carbenoid insertion with 168 in the presence of rhodium acetate. Alkylation of this malonate with Me₂N=CH₂⁺ and decarboxylative elimination subsequently fashioned the enol enoate 171. A highly chemoselective stannylcupration was now effected on the alkynyl ester in 171, notwithstanding the presence of the enol enoate, which also could have behaved as a potential Michael acceptor. ipso-substitution of the vinylstannane in 172 with iodine likewise did not cause damage to the pendant enol enoate. Vinyl iodide 173 was the key precursor needed for investigating the vinyl radical cyclisation chemistry. It transpired that when 173 was exposed to tributyltin hydride and AIBN in benzene at reflux for 45 min, a 4:1 mixture of exocyclic alkene isomers emerged, enriched in the desired product 174. Borohydride reduction of the more electrophilic ester group in this mixture and separation of the two isomeric components completed the route to the bryostatin B-ring.

Thomas and coworkers have also prepared the racemic PMB-protected vinyl iodide 178 and investigated its radical induced ring-closure (Scheme 24). The latter cyclised with a 4:1 level of (E/Z) stereocontrol, which again was comparable to that attained with 173. However, the selectivity observed in setting the C(11)-stereocentre was substantially eroded. Thomas attributed the formation of 179 to competitive internal 1,7-hydrogen-atom abstraction of the benzylic hydrogen from the PMB group, which would guarantee syn-delivery of the hydrogen to more hindered β-face of the tetrahydropyranyl radical. However, the formation of 179 can equally well be explained by the reduced steric size of C(14)-CH₂OPMB group making it much less effective than the CH₂OTBS at

\[
\text{Scheme 24 Outcome of free-radical cyclisation with a C(16)-OPMB protecting}
\]

Thomas and coworkers have also prepared the racemic PMB-protected vinyl iodide 178 and investigated its radical induced ring-closure (Scheme 24). The latter cyclised with a 4:1 level of (E/Z) stereocontrol, which again was comparable to that attained with 173. However, the selectivity observed in setting the C(11)-stereocentre was substantially eroded. Thomas attributed the formation of 179 to competitive internal 1,7-hydrogen-atom abstraction of the benzylic hydrogen from the PMB group, which would guarantee syn-delivery of the hydrogen to more hindered β-face of the tetrahydropyranyl radical. However, the formation of 179 can equally well be explained by the reduced steric size of C(14)-CH₂OPMB group making it much less effective than the CH₂OTBS at
directing the stereochemical course of H-atom abstraction from the stannane. Undoubtedly this finer mechanistic point will be resolved by labelling-work with Bu$_3$SnD.


The cardinal intermediate 186 required for Thomas' Pd(0) catalysed enolate cross-coupling strategy was prepared according to Scheme 25. β,γ- Unsaturated ester 182 (synthesised by an undisclosed route) was reduced to the homoallylic alcohol 183 with DIBAL, and protected as a TBS ether. Compound 184 was then subjected to a Sharpless AD reaction with AD-mix-β to obtain diol 185 in 85% ee (+ or −5%). Thomas transformed diol 185 into the Masamune aldehyde 34 in a further three steps; these were O-isopropylidenation, O-desilylation and Swern oxidation.
The next six steps were identical to those published by Masamune in his route to 39 (see section 3.1, Scheme 6); the only discrepancy noted was in the diastereoselectivity of the propargylation reaction with aldehyde 34, where Thomas recorded 4:1 selectivity in favour of 35, which contrasted with the 8:1 selectivity level reported by Masamune. Stannane 39 underwent an N-bromosuccinimide mediated halogen-metal exchange with retention of olefin geometry to provide 186 which willingly engaged in the Pd(0)-mediated cross-coupling process. The desired β,γ-unsaturated ketone was isolated in 73% yield. It was converted to the target sulfone 163 by chemoselective oxidation with m-CPBA which, significantly, left the trisubstituted alkene untouched.

4.1 Vandewalle’s Synthetic Studies on Bryostatin 11

Vandewalle and coworkers have been particularly active in the bryostatin arena having reported the results of several model studies, and the synthesis of various advanced intermediates; their work will now be described.

a Attempted construction of the C(1)-C(9) backbone of the bryostatins via a dithiane coupling strategy (1991)

Scheme 26 Vandewalle’s attempt at implementing a dithiane linchpin strategy for assembly of the C(1)-C(9)-sector.
Early effort in the Vandewalle laboratory focused on the use of a dithiane/epoxide coupling tactic for assembly of the C(1)-C(9)-backbone involving epoxides 194 and 197 and 1,3-dithiane as a C(5)-linchpin (Scheme 26). Epoxide 194 was prepared in five steps from (R)-pantolactone by the method of Lavallee. His route entailed reducing 191 to the ring-opened triol with lithium aluminium hydride, selectively preparing the dioxolane acetal 192 with 3-pentanone, protecting the remaining primary OH as a PMB-ether, and hydrolysing the acetal to obtain the 1,2-diol 193, which was converted to the terminal epoxide 194 by treatment with sodium hydride and N-tosylimidazole. The other epoxide 197 was derived from (S)-malic acid. Vandewalle noted that while the epoxide 194 reacted efficiently with 2-lithio-1,3-dithiane to give 196 after O-benzylation, the subsequent alkylation between 196 and 197 proceeded poorly, even when it was conducted in the presence of TMEDA and DMPU. At best, alcohol 198 was obtained in a rather meagre 13% yield, along with 4% of the elimination product 199 and recovered starting materials. In light of this setback, Vandewalle decided to change his approach to the C(1)-C(9)-segment in favour of the one shown below (Scheme 27).

Scheme 27  Vandewalle's stereocontrolled route to the C(1)-C(9) segment of the bryostatins.

\[\text{Epoxide 194 would again be mustered in this new route, which had identified compound 205 as a key intermediate. Epoxide 194 reacted readily with the Lipschutz HO vinylcyanocuprate}\]
reagent$^a$ to yield a homoallylic alcohol 203 that readily underwent dihydroxylation and oxidative cleavage. The product aldehyde 206 was then exploited in a substrate-controlled asymmetric aldol addition reaction with the lithium enolate of 207. Amazingly, excellent stereocontrol was manifest in this process which afforded the correct alcohol stereochemistry emerging at C(5) in the product 208. Some nineteen different reducing reagents were evaluated before success was attained in the hydroxyl-directed anti-reduction of 208 and, somewhat surprisingly, the normally reliable Evans reagent Me$_2$NBH(OAc)$_4$ apparently showed no selectivity in this reduction. After much effort, the combination of LiI and lithium tri-f-butoxyaluminium hydride$^b$ delivered the required result, namely, a 17.6:1 ratio in favour of the desired 1,3-diol 209, which was converted to 210 by acetal exchange. Clearly, the orthogonal arrangement of the protecting groups in this intermediate make it attractive for further elaboration into one of the bryostatins, but no additional results in this direction have yet been reported.

Model studies on the bryostatin B-ring (1991)$^{78a}$

Vandewalle's gameplan for construction of the bryostatin B-ring centred around the use of a stereoselective Michael addition to set the C(11)-stereocentre, and the creation of the appropriate enone framework by addition of a suitably elaborated C(1)-C(10) ketophosphonate to hemiacetal 217. To test out the viability of these concepts, a model study was undertaken (Scheme 28). Importantly, this revealed that total stereocontrol could be attained using such an approach; compound 220 being formed as a single product.
after application of a tandem WHE olefination/Michael addition to hemiacetal 217. Very recently, Yadav and coworkers (see section 4.10) reported the application of an even more elaborate WHE strategy for connecting bryostatin A and B-ring synthons together, and its great utility in this capacity. Other work along these lines will be awaited with interest.

**Vandewalle's synthetic strategy for the C-Ring region of bryostatins 1 and 11 (1994)**

Vandewalle has disclosed a unified synthetic strategy to the advanced C-ring intermediates 235 and 237 which look applicable to a future bryostatin synthesis. The main features of his route are presented in Schemes 29 and 30. Commercially available D-isobutyl lactate 221 was selected
as a starting material for the C(21)-C(27) sector primarily because there was a chirality match between it and the C(26)-hydroxyl of the bryostatins, and also because it was cheap. Protection and reduction of 221 yielded 222 which underwent Swern oxidation and Keck allylation\(^3\) to provide 223 with high stereocontrol (97% de) (Scheme 29). \(\rho\)-Methoxybenzylolation\(^4\) of this alcohol and two-stage oxidative cleavage of the double bond subsequently furnished aldehyde 224 which participated in a second, highly diastereoselective, Keck allylation\(^5\) with allyltributylstannane (97% de). Dimethoxybenzylolation of 225 and oxidative degradation of the alkene appropriated aldehyde 227 which was alkynylated with the Seyferth-Gilbert reagent 228\(^6\) and then homologated with \(n\)-butyllithium and methylchloroformate. Strategically the remainder of the route to 235 mirrored that of Masamune’s C-ring synthesis\(^7\) (see Scheme 6) except for the fact that a TBS-protecting group was present in aldehyde 234 and the latter had opposite absolute stereochemistry to the aldehyde used by Masamune (see compound 10 in Scheme 6). The primary effect of making these two changes was to substantially erode the stereoselectivity observed in the vinyl anion addition step. It will be recalled that Masamune obtained 8:1 selectivity in his chelation-controlled addition, whereas Vandewalle observed only 2:1 stereoselectivity in their addition.

It should also be noted that Vandewalle investigated the opening of epoxide 236 with the HO vinylthienylcuprate derived from iodide 233. The latter reaction only proceeded in 29% yield and gave ketone 237 after oxidation. The more recently reported Thomas enolate cross-coupling
strategy to 163 consequently represents a significant improvement over this prior methodology for constructing the C(20)-C(21) bond in the bryostatin 11 venture.

e. Vandewalle's use of (R)-carvone for synthesis of the Masamune C(27)-C(34)-alkyne fragment (1997)

![Diagram of Vandewalle's alternative route to the Masamune bryostatin 7 alkyne intermediate 36 from (R)-carvone.]

Before departing completely from Vandewalle's synthetic efforts on the bryostatin C-ring, it is worthwhile discussing his alternate routes to the Masamune C(27)-C(34) alkyne fragment 36 and to 253 both of which commence from (R)-carvone (Schemes 31 and 32). (R)-Carvone was stereospecifically epoxidised with basic hydrogen peroxide, and an organoselenium-mediated reductive ring-opening used to regioselectively deoxygenate α- to the ketone without damaging this potentially sensitive group. A 4:1 level of selectivity in favour of 246 was recorded for this reduction, which served as the prelude to protection and oxidative cleavage to access 247. A double Baeyer-Villiger oxidation was executed on 247 for installing the remaining masked OH with stereochemistry appropriate for the target fragment, the C(25)-hydroxyl having been introduced at
the epoxidation stage. The outcome was the seven-membered β-acetoxy lactone 248 which was reduced to 249 and selectively protected to obtain 250. O-Desilylation and oxidation of 250 furnished an aldehyde that willingly participated in a Seyferth/Gilbert alkynylation reaction. Although Vandewalle’s synthesis of this fragment is four steps longer than Masamune’s, his route does commence from a chiral starting material that lacks any hydroxy asymmetric centres; extra length was therefore somewhat expected.

4.3 R.W. Hoffmann’s Route to the C(1)-C(9) Segment 267 (1995)\textsuperscript{87}

A diastereocountrolled, racemic, route to an advanced A-ring synthon 267 has been disclosed by Hoffmann and Stiasny\textsuperscript{87} which capitalises on Matteson haloboronate displacement technology\textsuperscript{88} for backbone assembly (Scheme 33). The central intermediate in this novel pathway was the geminal dibromide 258 which was available from nucleophilic displacement of the cyclic sulfate 257 with 1,1-dibromomethyl lithium and protection with TBSCI. Treatment of 258 with \( n \)-BuLi in the Trapp-solvent mixture at \(-110 ^\circ C \) generated a mixture of carbenoids 259 and 260 in which the former species
predominated with 3:1 selectivity. While carbenoid 260 spontaneously cyclised to 261 when electrophiles were absent, carbenoid 259 showed little tendency to do this, so long as the temperature was kept at \(-110^\circ C\), this intermediate having a greater lifetime at this temperature. As a consequence, it proved possible to intercept this species with the cyclic boronate 262 in a reasonably efficient fashion. The \(\alpha\)-bromo-boronate 263 so formed was then combined with the dienolate 264 and the product 265 subjected to trimethylamine-N-oxide oxidation. The overall yield of alcohol 266 from 258 was 35%. Evans reduction of 266 and protection finally afforded the protected intermediate 267.

4.4 The Kalesse Route to the C(1)-C(9)-Segment 257 (1996)

Kalesse has reported a C(1)-C(9) segment synthesis (Scheme 34) which exploits a biotransformation as the key asymmetry-inducing step. His route to 275 opened with an acetoacetate aldol reaction between 268 and 269 to obtain 270 which was protected and C-desilylated to obtain the racemic keto-alkyne 271. A stereoselective reduction/kinetic resolution was now performed on 271 with Baker's yeast in the presence of water and sucrose. Alcohol 272 was isolated with 84% ee and 82% de, and taken forward to alkene 273 as shown. Hydroboration and oxidation converted 273 into the desired aldehyde which was used in a Sakurai reaction with allyltrimethylsilane; the end-result was an inseparable 6:1 mixture of alcohols enriched in 275.
4.5 The Kiyooka Reagent-Controlled Asymmetric Aldol Route to the C(1)-C(9) Segment of the Bryostatins (1997)\(^9\)

In a most stunning display of reagent-controlled asymmetric aldol technology, Kiyooka\(^9\) has reported the application of valine-derived sulfonamido-boranes 278 and 281 for efficient construction of the C(1)-C(9) intermediate 285. The strategy, which is outlined in full in Scheme 35, is based upon the iterative application of the mixed silylketene thioacetal 276 as a nucleophile in a series of boron-mediated aldol reactions with aldehydes 277 and 280 respectively. A nickel-boride mediated desulfurisation was used to liberate the desired acetate add product on each occasion. The final aldol addition between 283 and 284 generated 285 as a single isomer. The synthesis really is quite noteworthy as it proceeds with excellent stereocontrol and requires only nine steps.

4.6 Roy’s Synthetic Studies on Bryostatin 1\(^9\)

Roy has reported synthetic pathways to the A- and C-ring synthons 296, 298 and 307 which are attractive for their brevity. The unified route to 296 and 298 relies upon a biotransformation for asymmetric induction (Scheme 36), while that to 307 exploits the chiral pool starting material, D-galactono-1,4-lactone 299 (Scheme 37).
Roy's Synthetic Path to the C(1)-C(9) Fragment of Bryostatin 1 (1990)

Commercially available dimethyl 3-ketoglutarate 286 was reduced with sodium borohydride and the product protected as the MOM ether 287 (Scheme 36). An enzymatic hydrolysis of the pro-S methyl ester in 287 with α-chymotrypsin next secured the acid 288 in 94% ee; the latter was reduced to the primary alcohol 289 via a mixed anhydride. After oxidation with PCC, the resulting aldehyde was deployed for a substrate-controlled Mukaiyama aldol reaction with the enol ether 291. Considerable effort was put into modulating the stereochemical outcome of this reaction in favour the desired anti-product 293. After much experimentation, boron trifluoride etherate was identified as the best Lewis acid for this purpose, it affording a 1.9:1 mixture of epimers at C(5) enriched in 293. An almost totally stereoselective Evans reduction now followed for introduction of the C(7)-
hydroxyl. Separation of the diastereomeric mixture was best effected at the O-isopropylidenation stage. Whilst one can readily envisage using 298 in a future bryostatin synthesis, Evans' later work would suggest that lactone 296 (obtained from 295) might be an equally valuable synthon for a future venture in this direction.

b Roy's Enantiospecific route to a C(21)-C(27)-Synthon 307

Starting from the inexpensive but rarely used D-galactono-1,4-lactone 299, Roy has prepared the dithiane intermediate 307 in only nine steps (Scheme 37). He equated the six-carbon backbone of this hexose with the C(21)-C(27) sector of bryostatin 1, after having stereochemically matched the C(25)- and C(26)-hydroxys of 307 with the C(4)- and C(5)-hydroxys of 299. Clearly deoxygenation would be a necessity at both C(3) and C(6) for successful implementation of this approach, but this did not look problematical.

Scheme 37 Roy's synthesis of a C(21)-C(27)-dithiane intermediate for the bryostatins. Accordingly, 299 was brominatively O-acetylated under strongly acidic conditions and the product 300 hydrogenated in the presence of base. The latter facilitated β-elimination of the C(3)-acetate to give the enol acetate 301 which then underwent alkene reduction from the less-hindered β-side, in addition to reductive dehalogenation to provide 302. Thus, in only two steps the requisite carbon framework and stereochemical arrangement of the masked hydroxys had been hewed with complete control. The remainder of the synthesis focussed differential protecting the tetraol 303 derived from 302 by lithium borohydride reduction. For this, bis-acetalation was required followed by regioselective hydrolysis of the least hindered acetal. The latter was accomplished with either p-TsOH/MeOH or 1% iodine in MeOH. Selective O-tosylation of 305 was next attempted, and the
product tosylate converted to epoxide 306 with mild base. Opening of 306 with 2-lithio-1,3-dithiane followed by protection finally provided the C(21)-C(27) segment 307.

4.7 The H.M.R. Hoffmann Route to the C(1)-C(16) AB Segment 308 (2000)

a. The H.M.R. Hoffman Retrosynthetic Analysis of the C(1)-C(16) Fragment 308

The presence of a 1,3-dithiane protecting group at C(9) in this sub-target structure primes the adjacent C(9)-C(10)-bond for retrosynthetic disjunction, and resulted in Hoffmann selecting triflate 309 and dithiane 310 as possible progenitors (Scheme 38). Hoffmann was attracted to the idea of controlling the B-ring olefin geometry by means of a protecting group-directed Wadsworth-Horner-Emmons (WHE) reaction between 312 and an appropriately protected phosphonoalkanoate. He envisioned that the C(11)-trityloxymethyl would effectively shield the upper face of the ketone and favour stereospecific phosphine oxide formation and elimination. Accordingly 313 was selected as the precursor of 312, and ozonolysis and reduction were proposed as key
steps in the forward sequence. With regard to the critical issue of asymmetric induction, Hoffmann recognised that such a pathway would create a *meso*-diol from 313, and he proposed obtaining optically-pure product via O-acylation of both hydroxyls and enzymatic desymmetrisation with an appropriate lipase. Further retrosynthetic reasoning suggested that pyran 313 might be available from a cationic [4+2]-cycloaddition between 315 and furan, a reaction invented by Hoffmann in the early 1970s, and later refined into a more general and synthetically useful process by the groups of Noyori and Fohlisch. A similar cycloaddition between 314 and 324 was envisioned for creating the racemic pyranones 321 and 322, one of which would be developed into the A-ring partner 310 by a series of very elaborate reactions. Now the issue was to identify a suitable asymmetric reaction that could effect the efficient kinetic resolution of 321 and 322. Hoffmann believed that a Brown asymmetric hydroboration might suffice in this capacity. He reasoned that this might proceed under electronic control, which would lead to the more electron rich alkene carbon bonding to the boron of the hydroborating agent. A double oxidation could then be used to introduce a ketone on the carbon closest to the geminal dimethyl group, which would pave the way for a Baeyer-Villiger oxidation being used to access 320. With this as background, we will now discuss the Hoffmann synthesis of 308 in more detail.

**b. Synthesis of the C(1)-C(9) Dithiane 310**

Following the experimental procedure of Fohlisch, which was published in 1982, Hoffmann and coworkers reacted the α-chloromethyketone 324 with furan and lithium perchlorate in a mixture of ether and triethylamine (Scheme 39). An oxyallyl cation is formed under these conditions which then undergoes a [4+3]-cycloaddition with furan to generate a racemic mixture of the ketones 321 and 322. The latter were then reduced stereoselectively with L-selectride and protected as O-benzyl ethers. Asymmetric hydroboration of 325 and 326 with (-)-Ipc₂BH was not regioselective, but this was of little consequence, for oxidative work up and subsequent oxidation with PDC produced a mixture of two regioisomeric ketones which underwent regioselective Baeyer-Villiger oxidation to give 320 and 327. Being diastereoisomers, it proved possible to separate these
intermediates by flash chromatography. Transesterification converted 320 into a mixture of the hemiacetals 319 which were taken forward to dithiane 317. Compound 317 was homologated by Claisen condensation with an excess of the enolate of t-butyl acetate. This created a β-keto ester 316 with the requisite C(1)-C(9)-backbone, which then underwent reduction to the anti-1,3-diol 328 with the Evans reagent. Protection and ester reduction were now used to obtain 329. The next deprotection was particularly noteworthy, as it entailed reductively removing the C(7)-O-benzyl group from 329 with lithium di-t-butylbiphenyl\(^{100}\) in the presence of the potentially labile 1,3-dithiane; significantly, this reaction proceeded in excellent yield (98%). A series of silylations on diol 330 completed the synthesis of 310.
The best procedure currently available for the preparation of meso-ketone 313 is that of Noyori and coworkers. They observed that heating a mixture of tetrabromoacetone, diiron nonancarbonyl and furan at reflux for two days brought about a reasonably facile [4+3]-cycloaddition reaction.
between the intermediary dibromoallyloxy cation and the furan to produce a 9:1 mixture of the two isomeric bromopyranones 332 and 333, which could be reductively dehalogenated with zinc/copper couple to give 313 in 63% overall yield (Scheme 40). Anticipating problems in the sodium borohydride reduction step, if ozonolysis and reduction were to be attempted on 313, Hoffmann elected to protect its carbonyl as an acetal. Ozonolysis of 334 and reduction with NaBH₄ now proceeded smoothly to generate 335 in high overall yield after O-acetylation. This was the key intermediate needed for the enzymatic desymmetrisation step. The latter was accomplished with lipase PS at pH7 and provided 336 in 96% yield and > 98% ee. The carbonyl group was now regenerated under Pd (II) catalysis, the primary OH O-tritylated, and an O-deacetylation performed to access the partially-protected ketone 338. A range of phosphonates were investigated in the WHE reaction with ketone 338; it transpired that the best results were attained with more sterically demanding phosphonoacetates at low reaction temperatures over prolonged reaction times. The optimal conditions employed isopropyl diisopropoxyphosphonoacetate in toluene at -8 °C for 7 days, and provided 339 in 99% yield and with 49:1 (E/Z) selectivity. O-Silylation of 339 and enoate reduction with DIBAL transformed it into 340 which was protected as a triphenylsilyl ether. Now, another very noteworthy deprotection was accomplished, namely, the zinc bromide mediated cleavage of the O-trityl ether in the presence of the potentially labile allylic TPS ether. As can be seen, this deprotection proceeded cleanly delivering 342 in 94% yield.

The requisite triflate 309 for coupling to 310 was best prepared using the very hindered base, 2,6-di-tert-butyly pyridine, to prevent quaternisation of the resulting primary O-triflate ester. The latter is often a problem when other less hindered bases such as pyridine are used in such triflations. Compound 309 coupled smoothly with the lithio-anion derived from 310, this reaction furnishing 343 in 63% yield. Hoffmann drew attention to the observation that different protecting groups on O(7) quite dramatically affect the coupling yield; the best results were obtained when a TBS protecting group was positioned at this site. The final two steps in his route to 308 involved a selective manipulation of the silyl protecting groups.

Hoffmann’s route to 308 is clearly very good, and should permit a future bryostatin total synthesis; further results are awaited eagerly.
4.8 Hale's Synthetic Work on the Bryostatins

a Hale's Retrosynthetic Planning for Bryostatin 1

Hale's most recent retrosynthetic analysis of bryostatin 1 is summarised in Schemes 41 and 42. A biogenetically-modelled macrolactonisation on 344 is planned for assembly of the 20-membered macrolide, and a Julia olefination will be used for connecting the AB- and C-ring segments (345 and 346) together and setting the C(16)-C(17)-(E)-disubstituted alkene (Scheme 41).

Scheme 41 Hale's retrosynthetic analysis of bryostatin 1.

The collective past precedents of Masamune, Evans and Nishiyama suggest that good (E)-selectivity should be observed in this reaction. A Julia olefination is also proposed for linking 347 with 348 (Scheme 42). If successful, the latter should afford to an exocyclic glycal that could potentially be converted to the methyl glycoside by treatment with methanol under mild acid catalysis. After selective removal of the primary PMB group, alcohol oxidation should create aldehyde 345.

Scheme 42 Hale's retrosynthetic planning for the "Northern Hemisphere" of bryostatin 1.

For the C-ring of bryostatin 1, the bicyclic lactone 349 was identified as a key sub-target, and a stereospecific Wittig olefination was planned for fashioning its exocyclic enoate (Scheme 43).
In this instance, the flanking functionality at C(20) was expected to have a beneficial effect on the stereochemical outcome of olefination. Further unravelling of the bicyclic array in 349 next allowed the β-keto ester 350 to be selected as a sub-target; its most logical site for retroynthetic cleavage was across its C(18)-C(19)-bond via retro-Claisen condensation. The latter operation yielded ester 352 as a target intermediate. All its stereocentres appeared installable through a series of Sharpless catalytic AD reactions\textsuperscript{39} on appropriate alkene precursors. With this as background, progress on this pathway will now described.

Turning attention now to the C-ring chemistry that has so far been developed.\textsuperscript{10b} At first Hale set about introducing the O(26), the O(25)- and the O(23)-hydroxy stereocentres of the O-ring sub-sector through a Sharpless AD reaction\textsuperscript{70,102,103} on (E)-1,4-hexadiene 353 with excess AD-mix-β (Scheme 44). Whilst this reaction did successfully install the O(25) and O(26)-hydroxyls with high stereocontrol, the second AD process on the terminal alkene proceeded without control, it affording an inseparable 1:1 mixture of epimers at the O(23)-position. Attention was therefore focussed upon the selective dihydroxylation of 353 with a limited quantity of AD-mix-β (0.6 equiv), as described by Sharpless et al.\textsuperscript{110} Typically this provided the volatile diol 356 in 45-59% yield and 94% ee. It was then envisaged that installation of the O(23)-stereocentre could be achieved via a Sharpless asymmetric epoxidation reaction.\textsuperscript{42} After blocking the hydroxyls in 356 with TBSCI, the double bond of 357 was oxidatively degraded with cat. OsO₄ and NaIO₄, and the product aldehyde 358 taken forward to the requisite allylic alcohol 360 by Wittig reaction and DIBAL reduction. The Sharpless AE on 360 proceeded smoothly, and enhanced the optical purity of the product to 96% ee.
Regioselective epoxide ring opening of 361 was then effected with REDAL; this led to the 1,3-diol 362 in good yield. Next, it was necessary to selectively position a PMB group on the C(23)-OH, oxidise the C(21)-hydroxyl to the aldehyde, and implement a Wittig reaction on 365 with
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Ph₃P=CHCO₂Et. All these reactions proceeded efficiently, producing the desired enolate 366 as a single geometrical isomer in 89% overall yield from 364. A Sharpless AD reaction on 366 with AD-mix-β was now relied upon for introducing the C(20)-hydroxy stereocentre; it furnished diol 367 as essentially a single diastereoisomer. To successfully implement the aforementioned Claisen condensation, this diol had to be protected. An O-isopropylidene group performed well in this capacity, it allowing the desired β-keto ester Claisen condensation product 350 to be obtained in 81% yield from 352. The synthesis proceeded with removal of the O-isopropylidene group using acidic methanol, and in situ butyrolactonisation upon the C(20)-hydroxyl. It was felt that this would allow the C(20)- and C(21)-hydroxyl groups to be readily differentiated, and would set the stage for a tandem Fischer glycosidation at C(19). Reasoning that installation of an electron withdrawing ester group at C(20) would almost certainly necessitate the use of fairly forcing acidic conditions to bring about the desired glycosidation, it was accepted that it would be necessary to replace both the TBS groups in 350 with much more acid-stable O-pivaloyl esters. The PMB ether was then detached from 369 with DDQ to access 370. Treatment of 370 with methanolic HCl led to the expected methyl glycoside 371 in 58% yield. A Sharpless oxidation with RuCl₃/NalO₄ subsequently afforded ketone 372, which reacted with Ph₃P=CHCO₂Me to furnish a 1:1 mixture of exocyclic alkenes, which were only readily separable by preparative TLC. Wadsworth-Horner-Emmons reaction with MeO₂CCH₂P(O)(OMe)₂ gave similar results. Clearly, the butyrolactone unit was insufficiently bulky to direct the stereochemical course of olefination in favour of the desired product. Given this impasse, Hale decided to investigate the effect of increasing the steric size of the ester component in our phosphorus ylide. To his delight, changing the ester alkoxy from OMe to OBU-t improved the stereoselectivity of olefination to 3:1 in favour of the desired isomer 349 (Scheme 44). Given this encouraging result, Hale is currently modifying his synthetic route to obtain an α-alkoxy ketone with a bulkier protecting group on the C(20)-oxygen (e.g. a TES or TBS or PMB ether). Hopefully, these combined tactics will ultimately allow for a completely stereocontrolled introduction of the C-ring exocyclic olefin via this approach. Isomerisation tactics might also prove useful here in the event of a mixture still being obtained. All of these studies will eagerly awaited in future reports.
Janda has recently reported a solution-phase polymer-supported pathway to the orthogonally protected alcohol 383 (Scheme 45) in which an intermolecular nitrile oxide cycloaddition reaction between 374 and methyl vinyl ketone is used as a key step. A racemic product mixture 375 was generated which underwent stereoselective reduction to 376 and 377 with L-Selectride. This mixture of enantiomers was then enzymatically resolved through an acetylation reaction with the polymer-supported enzyme Novozyme 435. While only a 40% conversion was achieved, the ee of the desired product 378 was high (99%). Separation of the mixture was accomplished after the products (379 and 380) were cleaved from the support with aq. HF. The primary alcohol in 380 was selectively O-silylated with TBSCI, and 381 was converted to the
β-hydroxyketone by treatment with Raney nickel. An Evans reduction then afforded diol 382 with 89% diastereoselectivity. The more hindered, but also more nucleophilic, hydroxyl in 382 was thenselectively triethylsilylated. While it is difficult to envision using this piece in an actual bryostatin synthesis, with due protecting group adjustment, it might prove possible to exploit this chemistry in this capacity.

\[
\begin{align*}
\text{Bryostatin 1} & \Rightarrow \text{MOMO} 384 & \Rightarrow \text{OCH}_3 \text{CHO}_3 \text{Me} 385 & \Rightarrow \text{CHO} \text{MeO} \text{O} \text{O} 386 + 387
\end{align*}
\]

Scheme 46  Yadav's retrosynthetic planning for the bryostatin "Northern Hemisphere".

4.10  Yadav's Synthesis of the Bryostatin “Northern Hemisphere”\textsuperscript{107}

Building upon Vandewalle's earlier ideas for connecting appropriately tailored A- and B-segments via the Wittig-Horner-Emmons reaction, and closing the B-ring pyran via intramolecular Michael addition, Yadav and coworkers proposed the retrosynthetic strategy shown in Scheme 46 for assembly of the bryostatin "Northern Hemisphere".\textsuperscript{107} In their second generation approach, β-ketophosphonate 387 would be condensed with aldehyde 386 to obtain enone 385, and the B-ring pyran formed by O-desilylation with fluoride ion. A Fischer glycosidation was then envisaged for establishing the A-ring of 384.

a.  Yadav's asymmetric synthesis of the ketophosphonate 387.

A Jacobsen Salen-mediated kinetic hydrolytic resolution\textsuperscript{108} was used to secure the key chiral epoxide 390 needed for the synthesis of 387 (Scheme 47). Epoxide 390 was converted into the propargylic alcohol 391 by standard literature protocols, and this reduced to the (E)-allylic alcohol to allow a Sharpless AE to be used to introduce the C(5)-stereocentre with high diastereoocontrol. Given that the latter reaction placed a surplus oxygen atom in the carbon-chain of 392, a reductive ring-opening sequence was now implemented on 392. This deoxygenation was
accomplished in two steps by iodination and zinc-mediated dehalogenative elimination; after silylation with TIPSOTf the desired product 393 was isolated in good yield. Hydroboration and oxidation converted the terminal alkene of 393 into a primary alcohol which was oxidised. An aldol addition was then used to complete the C(1)-C(9) backbone. Unfortunately, this reaction was not especially selective, it affording a separable 2:3 mixture of diastereomeric alcohols enriched in 396. O-Desilylation and O-isopropylidenation were now effected, along with phosphonate anion condensation to obtain the key β-ketophosphonate 387.

**Completion of the AB-Intermediate 384**

A fifteen-step sequence was devised by Jadav and coworkers for assembling the aldehyde fragment 386 (Scheme 48). Its lone asymmetric centre (which corresponded to the O(15) stereocentre of bryostatin 1) was successfully installed through a combined Sharpless AE/reductive
dehalogenation tactic. The key union between 386 with 387 was effected with lithium
diisopropylamide as the base and proceeded with complete stereocontrol. As might be expected

Scheme 48  Yadav's synthetic route to the bryostatin 1 "Northern Hemisphere".

from Vandewalle's earlier model studies (see Scheme 28), the critical intramolecular Michael
addition on 385 sculpted the B-ring pyran with excellent stereocontrol. Fischer glycosidation of 404
with PPTS and methanol finalised this interesting route to the advanced AB-fragment 384, which
looks suitably protected for future elaboration into a naturally-occurring bryostatin.

4.11  Wender's Analogue Work
The encouraging clinical trials and great natural scarcity of bryostatin 1 have collectively ignited interest in the synthesis of simplified analogue structures. The identification of a substantially simplified analogue with an enhanced antitumour profile remains a major goal of many research teams active in the area. Realistically, such an analogue will probably need to be synthesised in less than twenty steps if there is going to be a genuine prospect of preparing it on industrial scale. Notwithstanding the large amount of synthetic effort that has been expended on the bryostatin synthetic problem over the past two decades, only Wender's group has made significant progress on the analogue front, and in the coming paragraphs we will detail their efforts in this regard.

**Scheme 49** Some examples of Wender's PKC-binding bryostatin analogues and their antitumour properties.

Early PKC binding studies on the bryostatins by Pettit, Blumberg and Wender indicated that structural changes to the A- and B-rings were often not that detrimental to binding activity, but changes to the C-ring were usually found to erode affinity for the enzyme quite substantially. Consequently, Wender decided to retain as much of the C(19)-C(27) domain as was possible in his target analogue structures, confining most of his simplifying changes to the A- and B-regions. Molecular modelling proved especially valuable for guiding his design process, it being used to ensure that there was substantial structural congruence between prospective target structures and the natural products prior to attempting their synthesis. By following this design strategy, Wender and associates were able to make some major simplifying changes to the bryostatin structure.
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without causing a significant loss in PKC-binding and antitumour activity. Indeed, some of the structures they have prepared have a PKC binding affinity in the nanomolar range. Some also displayed powerful in vitro antitumour activity against several human cancer cell lines. The most promising results are shown in Scheme 49.

Scheme 50  Wender's asymmetric synthesis of the simplified hynstatin analogue 474
Several interesting facts have so far emerged from all Wender's analogue studies: (1) the twenty-membered macrolactone framework is a requirement for good PKC binding activity; (2) the C(3)-hydroxyl is another essential feature needed for effective PKC binding; (3) (R)-stereochemistry for the C(3)-OH is important for potent binding to PKC; (4) having a free hydroxyl at C(26) is essential for an effective interaction with the PKC enzyme, and; (5) the B-ring exocyclic olefin and the A-ring can be dispensed with totally without seriously reducing the affinity of such analogues for the enzyme.\textsuperscript{3,116}

The core fragment used in most of Wender's analogue work is the α,β-unsaturated aldehyde 429,\textsuperscript{116} which he refers to as the "recognition domain". Its use in the synthesis of analogue 406 is shown in Scheme 50; this is the most biologically potent simplified bryostatin analogue so far prepared. Wender's route to 406 sets off with a Ag(l)-promoted O-benzylation of methyl D-lactate (Scheme 50); compound 409 was then partially reduced with DIBAL and aldehyde 410 subjected to a Sakurai reaction. After protection with PMBCl, ozonolysis of alkene 411 furnished aldehyde 412 which condensed non-stereoselectively with the dienolate derived from 416; a separable 1:1 mixture of the pyranones 417 resulted after acid-catalysed cyclodehydration. The enone with correct stereochemistry at C(23) was stereoselectively reduced from its less hindered β-face with the Luche reagent (NaBH₄/CeCl₃),\textsuperscript{108} and the resulting allylic alcohol used to dictate the stereochemical course of glycal epoxidation with m-CPBA in basic methanol. Under these conditions, the intermediary glycal epoxide selectively underwent ring-opening at the anomeric position to produce the methyl glycoside 418 in 71% yield for the two steps. Selective benzylation and Dess-Martin oxidation transformed 418 into the C(20)-ketone 419, whose α-benzoyloxy group was reductively deoxygenated with samarium diiodide. A pioneering tactic for exocyclic olefin construction in the C-ring was now implemented by Wender; ketone 420 was converted to its lithium enolate and this reacted with methyl glyoxalate to obtain a mixture of aldols that smoothly dehydrated when O-mesylated and treated with DBU. Keto-enoate 421, the sole product of this reaction, was then reduced stereoselectively to the desired C(20)-axial alcohol 422 under Luche conditions. The latter was unstable and so was protected as the O-octanoate ester via Yamaguchi methodology.\textsuperscript{66} A TBS deprotection/alcohol oxidation sequence now secured aldehyde 424 which was allylborated and acetylated. The terminal alkene in 425 was oxidatively degraded.
and β-elimination induced by base. The end-result was enal 427; its PMB group was removed with DDQ prior to hydrolysis of the C(19) methyl glycoside. Significantly this could be accomplished with aq. HF in acetonitrile even though there was an electron-withdrawing ester group at C(20). Compound 429 not only served as the precursor for 406, but all the analogues shown in Scheme 49. The conversion of 429 into 406 required a further 4 steps. Yamaguchi esterification yielded 431, while O-desilylation unmasked the C(3)-OH; intramolecular acetal exchange provided 432 with the 20-membered macrocycle established. The final step to obtain 406 was a highly chemoselective hydrogenolysis of the O-benzyl group at O(26) in the presence of the exocyclic enoate, which proceeded in high yield.

Key transformations in the pathway devised to acid 430 were the asymmetric hetero-Diels Alder reaction used to sculpt the A-ring framework, the Claisen rearrangement to set the C(5) stereocentre, and the Brown asymmetric allylboration to control the C(3)-OH (Scheme 51).

The synthesis of 406 proceeds in 43 steps in total, and has a longest linear sequence of 31 steps. While the route to 406 is considerably less arduous than the synthesis of a natural bryostatin, it is still far too lengthy to make this or related molecules viable candidates for commercialisation. Undoubtedly future work will focus on making even more sweeping adjustments to the bryostatin framework, given that the essential structural domains needed for PKC binding have now been clearly identified. Clearly, Wender's efforts in the bryostatin analogue area have highlighted what potentially can be achieved in the area of simplified analogue design, and hopefully his and other groups' work in the future will yield a good antitumour drug that is selective and effective in man.
5.0 Results and Discussion.

5.1 Background: The Bryostatin Synthetic Challenge.

a. Fully Stereocontrolled Synthetic Strategy for the Bryostatin B-Ring.

The potent anticancer and immunostimulatory properties of the bryostatins, coupled with their extremely low natural abundance, have made these molecules important targets for total synthesis. The supply issues, in particular, have overshadowed their clinical testing, and have dramatically affected their development as antitumour drugs. Novel synthetic routes to these molecules that are capable of delivering tens of gram quantities annually are of the utmost importance, if the bryostatins are ever to enter the clinic. Bryostatin 1 is the prototypical member of this family of macrolides, all of which contain a formidable array of functionality that includes two exocyclic $\alpha,\beta$-unsaturated esters, nine remote asymmetric centres, and a twenty-membered macrolactone ring. From a synthetic standpoint, the two $\alpha,\beta$-unsaturated esters found at C(13) and C(21) are especially challenging features for stereocontrolled synthesis. Moreover, once installed they may highly prove susceptible to undergoing either $E,Z$ or endocyclic isomerisation. They would also be susceptible to nucleophilic attack and reduction. The sterically encumbered nature of the C(16)-C(17) trans-olefinic linkage will likewise severely restrict the range of chemistry that can be used for its construction. Formation of the large macrocycle could further be complicated by the range of functionality that is present in the target molecule. The correct choice of protecting groups will also be critical to success in any synthetic venture. To avoid compromising the integrity of the target molecule, it will be important to select protecting groups that will be capable of being removed at the end under very mild conditions. Taking all these issues into consideration, our retrosynthetic analysis of bryostatin 1 is shown in Scheme 52.

Our disconnective strategy has cleaved its macrolactone bond to obtain the seco-acid 344. A biomimetic, macrolactonisation strategy is envisaged for the ring closure of 344 which, it will be noted, is distinctly lacking in protecting groups. Further disconnection of 344 at its C(16)-C(17) olefinic bond led us to phenylsulfone 346 and aldehyde 345, and a Julia-Lythgoe reaction is envisaged for their stereospecific unification. Disconnection of the northern hemisphere fragment
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Scheme 52 Our retrosynthetic analysis of bryostatin 1

345 across its C(9)-C(10) bond furnished the A and B-ring synthons 347 and 348 respectively. Reunification, again via a Julia Lythgoe olefination procedure, would yield an exocyclic glycal that could potentially be converted to the methyl glycoside by treatment with PPTS and methanol. A synthesis of the advanced C-ring precursor 349 has already been reported by the Hale group and was discussed in Chapter 1.

Scheme 53 Our retrosynthetic plan for completely controlling the B-ring geometry of the bryostatins.

Our retrosynthetic analysis of aldehyde 347 led us to select alcohol 440 as a possible precursor (Scheme 53). The primary effect of retrosynthetically positioning a hydroxymethyl group immediately adjacent to the pyranyl ether bond in 440 was to actuate the latter bond for retrosynthetic disassembly via the Williamson etherification transform, which yielded epoxy
alcohol 441 as a possible cyclisation precursor. Further analysis of 441 revealed that it might be
derivable from enoate 442, disconnection of which yielded the $C_2$-symmetrical ketone 444.
Conceptually, a Wittig or Peterson olefination reaction on such a $C_2$-symmetrical substrate would
offer the possibility of completely controlling the remote exocyclic olefin geometry of the bryostatin
B-ring, if successful. Ketone 444 itself looked accessible from a Smith-Tietze TBS-dithiane coupling
tactic.\textsuperscript{111}

\textbf{b. Efforts Towards the Synthesis of $C_2$-Symmetric Ketone 444.}

Building on some earlier work by Tietze and co-workers\textsuperscript{112}, Smith and Boldi\textsuperscript{113} observed that
when 2-(tert-butylimethylsilyl)-1,3-dithiane 446 was treated with t-BuLi in 10% HMPA/THF
and 2.5 equivalents of epoxide 448, a smooth bis-alkylation reaction occurred to produce the
bis-alkylated dithiane derivative 449 in good yield (scheme 54). In the presence of HMPA,
both the initial alkylation of 446 and the subsequent Brook rearrangement occurred within minutes
at $-78 \, ^\circ\text{C}$.

It was our belief that the bis-alkylated dithiane 453 (Scheme 55) required for our synthesis of
the B-ring synthon could be prepared from a slightly modified Smith-Tietze bis-alkylation reaction,

\textbf{Scheme 55 Mechanistic pathway of bis-alkylation and solvent controlled Brook rearrangement
incorporating trapping with TBSCI.}
where *in situ* trapping would be attempted with TBS-Cl. In the event, our modified linchpin coupling worked extremely well; the desired $C_2$-symmetric alklylation product 453 being isolated in good yield. It should be mentioned that our initial attempts at trapping the intermediary alkoxide 452 with tert-butylidimethylsilyl chloride gave irreproducible results. However, we found that this was because our reaction was extremely sensitive to moisture. So sensitive, in fact, that if the tert-butylidimethylsilyl chloride was weighed out in the air, it absorbed sufficient moisture to practically quench the reaction, even if the weighing was done quickly. To overcome this problem, the tert-butylidimethylsilyl chloride was weighed into a Schlenk flask inside a glove bag under an inert atmosphere of nitrogen, and eventually transferred into the reaction mixture (as a solid) in one portion against a counter-flow of $N_2$ from both vessels. The 500 MHz $^1$H-NMR spectrum of 453 in C$_6$D$_6$ revealed the presence of an 18 proton singlet at $\delta$ 0.84 and two 6 proton singlets at $\delta$ 0.07 and $\delta$ 0.02 respectively, which indicated that the two $O$-tert-butylidimethylsilyl protecting groups were in an identical magnetic environment. Similarly, the 6 proton singlet at $\delta$ 3.78 which corresponded to the two $O$-PMB groups and the three dithianyl double doublets at $\delta$ 2.68 ($J = 4.1, 15.3$ Hz), $\delta$ 2.47 ($J = 5.6, 5.6$ Hz) and $\delta$ 2.3 ($J = 5.4, 15.3$ Hz) indicated that dithiane 453 was $C_2$-symmetric. The lack of a broad OH absorption in the IR spectrum proved that there was no free hydroxyl present in 453. Also the presence of an (M+Na)$^+$ peak at $m/z$ 759.3566 in the high resolution mass spectrum indicated that 453 had an empirical formula of C$_{98}$H$_{64}$O$_6$Si$_2$.

The next step in our synthesis was liberation of the $C_2$-symmetric ketone 444 from 453 by treatment with mercury (II) perchlorate hydrate in aqueous THF in the presence of calcium carbonate. This deprotection worked well, it furnishing 444 as a single product after only 30
minutes; the latter was isolated in 75-86% yield. Infra red analysis of the product now revealed an intense absorption at 1715 cm\(^{-1}\) which confirmed the presence of the ketone carbonyl group. Furthermore, the simple appearance of the \(^1\)H-NMR spectrum for ketone 444 again indicated that we were dealing with a \(C_2\)-symmetrical molecule.

c. First Attempts to Olefination of Ketone 444.

Initially the olefination of ketone 444 was attempted using trimethyl phosphonoacetate under a range of conditions (Scheme 57) (shown in table 1).

<table>
<thead>
<tr>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOBu(^1) (2 eq)</td>
<td>DMF (0.3 M)</td>
<td>(MeO(_2)P(O)CH(_2)CO(_2)Me (2.5 eq), r.t. 18 hr.</td>
<td>0</td>
<td>Complete degradation of starting material/product</td>
</tr>
<tr>
<td>KOBu(^1) (5 eq)</td>
<td>DMF (0.3 M)</td>
<td>(MeO(_2)P(O)CH(_2)CO(_2)Me (6 eq), r.t. 1 hr, 30-55 °C over 2 hr.</td>
<td>0</td>
<td>Complete degradation of starting material/product</td>
</tr>
<tr>
<td>LiCl (2 eq), (^\prime)Pr(_2)Net (5 eq)</td>
<td>MeCN (0.3 M)</td>
<td>(MeO(_2)P(O)CH(_2)CO(_2)Me (1.5 eq), 80 °C. 15hr.</td>
<td>0</td>
<td>No reaction</td>
</tr>
<tr>
<td>(^\prime)BuLi (1.1 eq)</td>
<td>THF (0.16 M)</td>
<td>(MeO(_2)P(O)CH(_2)CO(_2)Me (2.5 eq), 0 °C. to r.t, 12 hr.</td>
<td>0</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Unfortunately, however, none of the desired product 442 was observed at any time. We thought that our olefination strategy was unsuccessful due to substantial steric over-crowding around the carbonyl centre caused by the bulky O- tert-butyldimethylsilyl groups flanking the ketone at both \(\beta\)-positions. The propensity for ketone 444 to undergo enolisation under the basic conditions required for ylide formation might also be a contributing factor towards the failure of this
method to olefinate successfully. However, when we observed no reaction with \( \text{Ph}_3=\text{CHCO}_2\text{Me} \), which is not especially basic, we reasoned that steric hindrance from the two TBS-groups was the

more likely origin of this lack of reactivity. A more forcing olefination strategy therefore was sought, that exploited a less sterically-demanding reagent. A Peterson olefination tactic appeared ideal (Scheme 58). The smaller size of the \( \alpha \)-silyl carbanion compared with the triphenylphosphoryl ylide frequently means that the Peterson reaction is more effective for the olefination of sterically hindered ketones than the corresponding Wittig or WHE process. Addition of the \( C_2 \)-symmetric ketone 444 to a solution of anion 456 at \(-78^\circ \text{C} \) followed by warming to \(-25^\circ \text{C} \) over 1 hour, and then to room temperature, unfortunately caused extensive degradation of the ketone.

Given that direct olefination tactics were unyielding when applied to ketone 444, an alternative strategy was sought. Encouraged by the report of Johnson and Christianson on the use of a Reformatsky/dehydration sequence for the creation of an exocyclic enoate in their synthesis of Estrone (Scheme 59), we decided to adopt this approach for the formation of enoate 442 from 444 (Scheme 60). Scheme 59: Reformatsky/dehydration strategy for olefination of Estrone

Unfortunately, the initial nucleophilic addition of the zinc enolate would not take place under any of the conditions examined. Yet again, steric congestion around the ketone carbonyl appeared to be the source of our problems. We reasoned, therefore, that an intra-molecular olefination strategy might overcome some of the problems associated with steric overcrowding. With this in mind, we
formulated the alternative approach shown in scheme 61, involving tethered β-keto phosphonate ester intermediate 465. Significantly, this substrate now lacked one TBS-group in the β-position to the ketone, and the nucleophile also lay much closer to this carbonyl. Olefination via this approach, would lead directly to lactone 464 which would now allow us to channel into our original synthetic endgame for the bryostatin B-ring synthon 347. Previous work by Regan et al.\textsuperscript{116} during their synthesis of the C(1)-C(9) fragment of rhizoxin suggested that our plan would have a good chance of succeeding (Scheme 62).

Trapping our Smith-Tietze alkoxide with diethylphosphonoacetyl chloride rather than TBS-Cl gave 469 (scheme 63). Unmasking of the dithiane moiety was achieved as previously with mercury (II) perchlorate. A range of bases and conditions were evaluated for the cyclisation of β-keto-phosphonate ester 466 with varying results as shown in table 2.
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(i) i-BuLi (1 eq), HMPA (4 eq), THF (0.3 M), -78 °C, 0.5 h; (f eq) \( \text{OPM} \)

at -78 °C, warm to 0°C, stir 1.5 h; cool to -30 °C, add \((\text{EtO})_2\text{P}^+\text{Cl}^-

warm to rt 12 hr (53%)

(ii) \( \text{Hg} \) (2 eq), \( \text{CaCO}_3 \) (4 eq). THF/H$_2$O (4:1) (0.06 M). 0°C, 3 h (81%)

Disappointingly only the action of sodium hydride afforded the desired cyclisation product 465, but it was formed only in low yield with the elimination product 467 predominating. Although our intramolecular Wadsworth-Horner-Emmons approach was largely unsuccessful, it did nevertheless show us that intramolecular olefination was indeed possible. In light of this we decided to investigate an intramolecular Reformatsky/dehydration sequence for obtaining lactone 465 (Scheme 64).

Since such reactions were not especially basic, we thought that such a tactic might potentially side-step the \( \beta \)-elimination problems associated with the cyclisation of phosphonoacetate 466.

<table>
<thead>
<tr>
<th>Base</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>KF</td>
<td>MeCN, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>KN(SiMe$_3$)$_2$</td>
<td>THF/PhMe, 0 °C</td>
<td>Destroyed substrate</td>
</tr>
<tr>
<td>KO'Bu</td>
<td>DMF, r.t.</td>
<td>( \beta )-elimination &amp; degradation only</td>
</tr>
<tr>
<td>NaH</td>
<td>THF, r.t.</td>
<td>( \beta )-elimination + 16 % lactone 465</td>
</tr>
</tbody>
</table>

Table 2
A Smith-Tietze bis-alkylation reaction would again feature in the synthesis of the requisite bromoacetate 468 selected for implementation of the intramolecular Reformatsky/dehydration tactic. Compound 468 was best prepared according to the route shown in Scheme 65. The sequence opened with the preparation of alcohol 470 in 80-90% yield. Deprotection of the dithiane functionality then generated $\beta$-hydroxy ketone 471 which reacted with bromoacetyl bromide in the presence of pyridine to give the labile bromoacetate 468. Formation of the samarium enolate was attempted by treating bromoacetate 468 with SmI$_2$ in THF at $-78^\circ$C and allowing the reaction mixture to warm to room temperature. However, no observable reaction took place until zinc dust was added, and the mixture brought to reflux. TLC analysis after 10 mins, revealed that approximately half of the starting material had been consumed and that a single, faster moving product had formed. After 60 mins all the starting material had been consumed and the aforementioned single product had formed exclusively. $^1$H-NMR analysis revealed that an intramolecular reaction had not taken place; instead only acetate 472 had formed. This result suggested that enolate formation had taken place, but that intramolecular nucleophilic attack upon the ketone had simply not occurred. In view of this, we decided to investigate alternative methods for olefination.

d. Attempted Takeda Desulfurative Titanocarbenation Strategies for Olefination of Dithiane 453.
In 1985 Takeda and coworkers described a method for converting thioacetals into titanium alkylidenes. Takeda showed that such intermediates could be used directly for olefinating a range of carbonyl compounds. Given our knowledge of this report, it occurred to us that we might be able to apply this transformation to our 1,3-dithiane substrate, to generate the titanium alkylidene (Scheme 66). We thought that we could then trap this organometallic with ethyl glyoxalate to obtain enolate. Unfortunately however, when this reaction was attempted it proved unsuccessful.

Later work by Takeda demonstrated the possibilities for using such titanium alkylidenes for tandem ring closing metathesis reactions with pendant alkenes. It was shown that this methodology constituted a most effective means of preparing carbocycles or cyclic ethers. The general mechanism proposed by Takeda for this tandem process is outlined in Scheme 67. It will be noted, however, that this is only a tentative mechanistic postulate and that Takeda et al have no firm experimental evidence for the intermediacy of a titanium-carbene complex. This interesting piece of work alerted us to the possibility of forming our desired lactone via the retrosynthetic plan shown.
scheme 68. We reasoned that the two allylic ethers present in dithiane adduct 485 would serve not only as protecting groups but also provide the double bonds required for metathesis. The $C_2$-symmetrical nature of the molecule would again lead to the formation of only one geometrical isomer upon ring-closing-metathesis. Allylic oxidation of dihydropyran 483 would then serve the dual purpose of forming the $\alpha,\beta$-unsaturated lactone 482 and converting the superfluous allylic ether into an acrylate. Again, if successful, this approach would funnel back into our original synthetic plan.

With this revised plan in place, we set off towards the bis-O-allyl ether 485 (Scheme 69). The Smith-Tietze adduct 453 was our starting point. It was O-desilylated with tetrabutylammonium fluoride in THF to obtain diol 486 in 85% yield. The $^1$H-NMR spectrum of 486 confirmed that both $O$-tert-butyldimethylsilyl ethers had been removed, as did the IR spectrum which now contained a new and very broad absorption at 3361 cm$^{-1}$ confirming the presence of free hydroxyl groups. $O$-Allylation of the two free hydroxyls was then accomplished by treating of diol 486 with sodium hydride and allylbromide; the bis-O-allyl ether 485 was isolated in 45% yield. It transpired that TLC analysis of the reaction mixture revealed that 485 was not the only product in the reaction. A more
polar co-product was also observable by TLC with an Rf of 0.3. Analysis of the $^1$H-NMR spectrum for the more polar product revealed it to be the mono-O-allylated analogue of 485, with the bis-O-allylated product predominating. Although the yield for allylation was low, it should be noted that this reaction was unoptimised. The low valent titanium species [Cp$_2$Ti(P(OEt)$_3$)$_2$] 488 used by Takeda for his desulfurative titanocarbenations is formed *in situ* by reducing titanocene dichloride with magnesium in the presence of triethyl phosphite.$^{110}$ Formation of the reactive Ti (II) 14-electron intermediate coincides with a distinct colour change for the reaction, it turning dark green and then dark brown with a slight evolution of heat. Stirring at room temperature for 3 hours is generally sufficient for the active species 488 to form (Scheme 70). Even after addition of bis-O-allyl ether 485 to this solution, the dark brown colour persisted, and no reaction appeared to take place even after a further two hours stirring at room temperature. At this point, the reaction mixture was heated to reflux whereupon a single product (observable by TLC) began to form. Continued heating saw complete consumption of the starting dithiane 485 and its replacement by a single more polar product. After work-up and purification, NMR analysis indicated that the product was not the...
desired cyclic ether 483, but rather the diol 489. The absence of olefinic signals in the \(^1\text{H}-\text{NMR}\) spectrum confirmed that metathesis had not taken place and that \(O\)-deallylation had also occurred alongside desulfurisation. LRMS data supported this structural assignment.

Although this result was most unexpected, it is nonetheless of some potential interest, as it appears we have discovered an efficient new method for desulfurisation and/or de-allylation that is compatible with \(O\)-4-methoxybenzyl ethers. Our mechanistic interpretation of the deallylation is presented in Scheme 71, although it will be noted that we have no evidence to support our hypothesis. In our opinion, coordination of the low-valent titanium species to the oxygen atoms helps bring the titanium complex in an appropriate position to allow for insertion into the allylic ether bond. Moreover, the final outcome of our reaction suggests that the rate of C-O insertion is considerably faster than the rate for C-S insertion and alkylidene formation. In our view the covalent titanium species must insert into the allyl ether bonds before desulfurative titanocarbenation takes place. Clearly, the titanium alkylidene 491 would be unable to undergo ring-closing-metathesis and as such it would remain in the reaction until aqueous work-up, whereupon diol 489 would be formed by nucleophilic attack of water upon the titanium centres.

e. An Effective Solution to the Problem of Olefination C\(_2\)-Symmetric Ketone 444.

![Scheme 72. Our revised retrosynthetic strategy incorporating a Grignard addition tactic.](image)

In view of these unforeseen events, we elected to abandon this approach and focus on more conventional methodology for alkene installation. In a last ditch attempt at providing a solution to this problem, we decided to pursue a Grignard addition tactic. Our new synthetic plan centered
around the Grignard addition/dehydration strategy shown in Scheme 72. In this retrosynthetic plan, the \( \alpha,\beta \)-unsaturated lactone 482 would be derived from the oxidation/lactonisation of triol 493 which in turn could be potentially accessible from enal 494. Compound 494 appeared derivable from the homoallylic alcohol 495 by oxidative degradation of the terminal alkene and dehydration of the resulting aldol. Compound 495 could in turn emanate from the addition of allylmagnesium bromide to the \( \text{C}_2 \)-symmetric ketone 444 which would again be derivable from the Smith-Tietze bis-alkylation process. With this in mind, we opened our synthetic campaign on \( \alpha,\beta \)-unsaturated lactone 482, with the addition of allylmagnesium bromide to 444 to access allylic alcohol 495. When monitored by

\[
\text{TLC, the product allylic alcohol has the same Rf as the starting ketone and so it is difficult to judge whether the reaction is complete. It is only after multiple-elution TLC analysis has been carried out that the extent of reaction can be readily discerned. To our delight, we found that the addition was generally complete within 20 minutes at 0 °C (Scheme 73). IR analysis of 495 revealed that the strong carbonyl absorbance previously seen at 1715 cm\(^{-1}\) was now, no longer, present. The 500 MHz \(^1\text{H-NMR spectrum of 495 in } \text{C}_6\text{D}_6 \text{ also showed the presence of a multiplet at } \delta \text{ 6.02-6.16 and a pair of doublets at } \delta \text{ 5.13 and 5.09 which corresponded to the terminal olefin hydrogens. Analysis of the } ^{13}\text{C and DEPT NMR spectra also showed the absence of a quaternary carbonyl carbon at low-field. Finally the observation of an } (\text{M+Na})^+ \text{ ion in the HRMS at } m/z \text{ 711.4091 which corresponded to the molecular ion } C_{38}H_{64}O_{17}Si_{12}Na \text{ further reinforced our structural assignment.}
\]

The oxidative cleavage of alkene 495 was best effected with osmium tetroxide and sodium periodate \(^{125}\) and delivered the aldol 496 in 76% yield when stirred overnight. The 500 MHz \(^1\text{H NMR of } \beta\text{-hydroxy aldehyde 496 in } \text{C}_6\text{D}_6 \text{ contained a triplet at } \delta \text{ 9.89 (J = 2.6 Hz) which integrated to one proton, in the region characteristic for an aldehydic resonance. The IR spectrum also contained a}
hydroxyl absorption at 3482 cm\(^{-1}\) and a strong C=O absorption at 1720 cm\(^{-1}\). Finally the 125 MHz \(^{13}\)C-NMR spectrum in C\(_6\)D\(_6\) contained an aldehydic C=O resonance at \(\delta 201.6\) while the mass spectrum showed an (M+Na\(^+\)) ion at \(m/z 713.3862\) which further strengthened our structural assignment. Our plan for the dehydration of aldol 496 initially used phosphorous oxychloride as the dehydrating agent in combination with pyridine as base. Initially the reaction was performed at room temperature for a prolonged period of time, whereupon no reaction took place. By way of contrast, there was rapid and substantial degradation, when it was heated to 50 °C. Our next attempt at dehydration treated 496 with methanesulfonyl chloride, triethylamine and catalytic 4-(dimethylamino)-pyridine in CH\(_2\)Cl\(_2\). Again, when the reaction was conducted at 0 °C no reaction occurred, but when the reaction mixture was warmed to warm to room temperature, rapid degradation took place with multiple products being formed. A similar decomposition was observed when trifluoromethanesulfonic anhydride was used for dehydration (Scheme 74). Ultimately, success was attained with trifluoroacetic anhydride, triethylamine, and catalytic 4-(dimethylamino)-pyridine (Scheme 75). It was found that by conducting the reaction at 45 °C, slow formation of the

**Scheme 74** Attempts for the dehydration of aldol adduct 496.

**Scheme 75** Successful dehydration strategy for the formation of enal 494 from aldol 496.
trifluoroacetate occurred, but this was accompanied by a spontaneous β-elimination, to give 494 as the sole product without isomeric alternatives. It should be noted that this reaction is extremely sensitive to moisture and needs to be kept sealed at all times. Indeed, when even the smallest quantities of moisture enter the reaction vessel, a distinct colour change takes place, from mild yellow to dark orange/red and copious clouds of thick white fumes are observed. The preservation of the straw colour proved to be a good indicator of the success of the reaction; successful dehydrations remaining yellow throughout. Typically, enal 494 was isolated in 80% yield. Analysis of its IR spectrum revealed a shift in the carbonyl absorption from 1720 cm\(^{-1}\) to 1673 cm\(^{-1}\), indicative of α,β-unsaturation; additionally, the lack of a hydroxyl absorption band reinforced the structural assignment of 494. Inspection of the 500 MHz \(^1\)H/\(^1\)H COSY NMR spectrum of 494 in C\(_6\)D\(_6\) showed that the expected aldehydic doublet \(δ 10.15\) \((J = 7.8\) Hz\) was now coupled to the olefinic doublet \((J = 7.8\) Hz\) at \(δ 6.6\) thus confirming α,β-unsaturation had been achieved. The high resolution mass spectrum of 494 also revealed an \((M+Na)^+\) ion at \(m/z\) 695.3765 confirming that the molecule had an empirical formula of C\(_{37}\)H\(_{46}\)O\(_2\)Si\(_2\). We had finally proven that the C\(_2\)-symmetry breaking tactic for olefination was indeed viable for completely controlling alkene geometry in a bryostatin B-ring precursor. However, we now had to address the issue of stereocontrolled pyran formation and installation of orthogonal protecting groups.

![Chemoselective differentiation of two near identical 1,2-diol units.](image)

Scheme 76 Chemoselective differentiation of two near identical 1,2-diol units.

Given the potential susceptibility of enal 494, to nucleophilic addition we had to nullify its aldehyde group by diisobutylaluminium hydride reduction (Scheme 76). Accordingly, we treated
enal 494 with diisobutylaluminium hydride in CH₂Cl₂ at -78 °C to obtain allyl alcohol 497 in 95% yield. Analysis of the IR spectrum for 497 revealed the absence of the aldehydic carbonyl absorption and the presence of a strong O-H absorption at 3451 cm⁻¹. The 500 MHz ¹H-NMR spectrum of 497 in C₆D₆ also confirmed that reduction had been successful as it now lacked an aldehydic signal at δ 10.15, and the olefinic proton had shifted to δ 5.72, it now appearing as a triplet (J = 6.9 Hz).

Complete desilylation of allyl alcohol 497 was now effected by treating it with tetrabutylammonium fluoride in THF. Triol 493 was isolated in 77% yield after SiO₂ flash chromatography. In the 500 MHz ¹H-NMR spectrum of triol 493 in C₆D₆, the region between δ 1.00 and -1.00 was now devoid of signals indicating that desilylation had been successful. Other evidence for the formation of 493 was provided by its IR spectrum which showed a massive –OH absorption due to the newly formed hydroxyl groups at 3482 cm⁻¹. The high resolution mass spectrum of 493 also showed a peak at m/z 469.2221 which corresponded to the (M+Na)⁺ ion, indicating that the triol had the empirical formula C₂₅H₃₄O₇. A chemoselective oxidation of the allylic hydroxyl in 493 was performed with activated manganese dioxide in chloroform. Initially, this reaction afforded the enal with complete selectivity. Hemi-acetal formation then ensued, allowing a second chemoselective oxidation to occur to fashion the desired α,β-unsaturated lactone in one pot. The product was purified by simply filtering the reaction through a thin CELITE™ pad and removing the reaction solvent in vacuo to give a mild amber oil, after SiO₂ flash chromatography, that corresponded to pure ene-lactone 482. The 500 MHz ¹H-NMR spectrum for 482 in C₆D₆ clearly showed a single, sharp olefinic singlet at δ 5.84 which corresponded to the uncoupled proton at the α-position to the carbonyl. Added evidence for lactonisation was obtained from the IR spectrum, which contained a strong C=O stretch absorption at 1713 cm⁻¹ and the C=C stretch at 1639 cm⁻¹ indicative of an ene-lactone. Finally, the high resolution mass spectrum showed a peak at m/z 465.1870 attributable to an (M+Na)⁺ ion which confirmed that our molecule had an empirical formula of C₂₅H₃₀O₇. Efforts were now focussed upon the global debenzylation of α,β-unsaturated lactone 482. Conventional methods for PMB removal such as DDQ, CAN or silver picolinate caused
decomposition of the substrate. Eventually this was achieved with trifluoroacetic acid and anisole.\textsuperscript{122} The anisole acts to quench out the reactive benzyl cation, preventing its further attack upon the substrate and starting material. A possible mechanism for this deprotection is outlined in scheme 77. Provided the reaction temperature was maintained at $-15^\circ$C, it was possible to completely remove the terminal protecting groups after 8 hours whilst preserving the integrity of the product lactone 503. Due to the highly polar nature of the product, a non-aqueous work-up was deemed desirable. The reagents and solvent were removed by evaporation \textit{in vacuo} to leave a thick oily residue that was then purified by SiO$_2$ flash column chromatography to give analytically pure 503 in 72\% yield. The 500 MHz $^1$H-NMR spectrum of 503 in CD$_3$OD showed the absence of any aromatic protons and indicated that both the lactone linkage and olefin had remained intact; the latter was apparent from the lone singlet $\delta$ 5.81 which corresponded to the single olefinic proton in 503. The IR spectrum further corroborated this finding with both a carbonyl C=O absorption at 1704 cm$^{-1}$ and an alkene absorption at 1681 cm$^{-1}$. In addition the high resolution mass spectrum showed an (M+Na)$^+$ peak at $m/z$ 225.0739 indicating that 503 had the empirical formula C$_9$H$_{14}$O$_5$. Regioselective O-isopropylidenation of the 1,2-diol unit was next attempted with catalytic iodine in acetone to obtain compound 505 as an oil (Scheme 78). Although the isopropylidenation worked reasonably well on small scale, considerable problems were encountered on scale up, where wildly
different yields were observed while adhering to identical reaction conditions. Inexplicably, no reaction took place at all on some occasions, whist on others significant decomposition was observed. Given this capriciousness, we investigated the use of a cyclohexylidene acetal for protecting the terminal 1,2-diol grouping of triol 503. To our delight, this ketalisation worked reproducibly on large scale, giving cyclohexylidene acetal 506 routinely in 80-90% yield (scheme 79). Evidence for the cyclohexylidene acetal moiety was provided by the 500 MHz $^1$H-NMR spectrum of 506 in CDCl$_3$ where there were three broad singlets at δ 1.31, δ 1.48 and δ 1.52. Furthermore, the high resolution mass spectrum of 506 showed that an (M+Na)$^+$ peak was present at m/z 305.1379, which further confirmed that 506 had an empirical formula C$_{15}$H$_{22}$O$_5$. Given the base-lability of 506, the remaining hydroxyl was protected as a 4-methoxybenzyl ether with p-methoxybenzyldichloroacetimidate$^{123}$ and catalytic p-toluenesulfonic acid in dichloromethane (Scheme 79). The IR spectrum for 507 showed absorptions at 1514, 1585 and 1612 cm$^{-1}$, indicative of aromatic functionality. Also, the absence of a hydroxyl absorption suggested that O-benzylation had been successful. In addition, the 500 MHz $^1$H-NMR spectrum of 507 in CDCl$_3$ showed an –OMe singlet at δ 3.78 and two sets of aromatic signals at δ 7.23 and δ 6.85 which acted to support our structural determination of O-benzyl ether 507.

Our next objective was to selectively reduce the lactone moiety to obtain diol 508. This was accomplished with sodium borohydride and cerium trichloride in methanol under Luche conditions.$^{124}$ This set of reagents avoided unwanted 1,4 reduction and worked well in our system to give the desired diol 508 as the sole product, so long as the temperature was maintained at 0 °C.
(Scheme 80). Inspection of the 500 MHz, $^1$H-NMR spectrum of 508 in CDCl$_3$ revealed a triplet $\delta$ 5.75 ($J = 7.4$ Hz) which indicated that the olefin was still intact and its multiplicity was appropriate for the proposed structure. The presence of a broad singlet at $\delta$ 2.90 that integrated to 2 protons was further in agreement with the formation of a diol. The IR spectrum also showed the absence of a carbonyl absorption band, while the high resolution mass spectrum showed a peak at $m/z$ 429.2260 corresponding to the (M+Na)$^+$ ion which indicated that 508 had an empirical formula of C$_{23}$H$_{34}$O$_6$. The less sterically hindered allylic hydroxyl of diol 508 was now selectively protected as an O-TBDPS ether. The selectivity of protection was enhanced by the use of this large and bulky protecting group. Silyl ether 509 was typically isolated in 95% yield. Conventional mild acid hydrolysis of the O-cyclohexylidene acetal could not be achieved under a range of conditions (eg p-toluenesulfonic acid in methanol, ZnBr$_2$ in methanol, F$_3$CCO$_2$H in CH$_2$Cl$_2$ or camphorsulfonic acid in methanol) without also removing the other protecting groups. After considerable experimentation, we eventually found that the combination of 1,3-propanedithiol and catalytic BF$_3$ etherate at low temperature accomplished the desired transformation in 81% yield (scheme 81). It was important to carefully monitor the course of this deprotection by TLC to ensure that O-desilylation did not occur. The 500 MHz $^1$H-NMR spectrum of 510 in CDCl$_3$ showed that the cyclohexylidene signal was no longer present, and the IR spectrum for 510 showed a strong $-\text{OH}$ absorption at 3389 cm$^{-1}$ corroborating this finding. The $^1$H-NMR spectrum further confirmed that the silyl and PMB protecting groups had survived this step untouched. The presence of aromatic protons at $\delta$ 7.65 (d, $J = 6.0$ Hz) and $\delta$ 7.34-7.42 (m) and the
Chapter 2: Discussion

large singlet at $\delta$ 1.01 suggested that the two phenyl groups and t-butyl group attached to silicon were intact, while the PMB OMe was apparent at $\delta$ 3.78 as a singlet, the high resolution mass spectrum for 510 showed a peak at $m/z$ 587.2822 corresponding to the (M+Na)$^+$ ion which indicated that the empirical formula for triol 510 was C$_{23}$H$_{44}$O$_8$Si.

By synthesising triol 510 we had formed a compound in which the C(16) hydroxyl was selectively protected and the C(10)-C(11) diol unit was unmasked and available for direct manipulation. Our aim was to convert this terminal diol unit into the corresponding epoxide with retention of stereochemistry at C(9). In order to do this we hoped to selectively convert the C(10) hydroxyl into a better leaving group which would then allow epoxide formation via a classical Williamson etherification. Several methods were evaluated for the selective O-sulfonylation of triol 510. However, the methanesulfonyl chloride-collidine system of O'Donnell and Burke$^{125}$ gave the best results (Scheme 82). The steric bulk of the base was primarily responsible for the selective outcome of mesylation, the formation of a collidinium sulphonate intermediate 513 ensuring that only hydroxyls that are not too sterically demanding will react. In this case the primary hydroxyl is clearly in a less encumbered environment and thus is capable of more readily combining with 513 than the secondary hydroxyls. The optimum conditions for selective mesylation employed a 0.01 M solution of the triol in dichloromethane and added ten equivalents of 2,6-collidine followed by 1.1 equivalents of methanesulfonyl chloride. By following this protocol and maintaining the internal reaction temperature at 0 °C we were routinely able to isolate mono-mesylate 514 in 81% yield. It was apparent from the 500 MHz $^1$H-NMR spectrum of sulfonyl ester 514 in CDCl$_3$ that mono-
mesylation had taken place, by virtue of the new O-Ms methyl singlet that was observed at δ 3.03. The IR spectrum also showed sharp absorbances at 1427 cm⁻¹ and 1174 cm⁻¹ which were indicative of a sulfonyl ester. The high resolution mass spectrum of 514 further corroborated these findings by showing a peak at m/z 665.2560 attributable to an (M+Na)⁺ with empirical formula C₃₅H₄₅O₉SSiNa.

We had hoped to convert methanesulfonyl ester 514 directly into pyran 440 by treatment with two equivalents of sodium hydride and imidazole in THF as shown in scheme 83. However, no matter how great an excess of base was added, the only product formed was epoxide 441. The 500 MHz ¹H-NMR spectrum of 441 in CDCl₃ showed distinctive oxiranyl protons at δ 2.74 (dd, J = 8.9, 4.9 Hz), δ 3.45 (dd, J = 5.0, 2.7 Hz), and δ 2.09 (dd, J = 13.8, 4.8 Hz). The absence of a mesyl singlet further suggested that epoxide formation had been successful. The IR spectrum showed the characteristic epoxide absorption bands at 3047, 1249, and 823 cm⁻¹ and high resolution mass spectral analysis further elucidated the structure of 441. The peak at m/z 569.2703 in the HRMS was diagnostic of an (M+Na)⁺ ion of empirical formula C₃₃H₄₂O₅SiNa.

Based on this information we assigned the structure 441 to this epoxy alcohol.

Scheme 83 Base-induced epoxidation of hydroxymesylate 514 and attempted in-situ formation of pyran 440.

Scheme 84 Example of an intramolecular epoxide ring opening/cyclisation for the synthesis of (+)-Castospermine.
Chapter 2: Discussion

The time had now come to effect pyran-ring closure with 441. Work by Ganem on the total synthesis of (+)-castanospermine\(^\text{127}\) revealed that 7-endo-tet and 6-exo-tet ring closure could compete effectively with one another, in the ring closure of 518; the piperidine 519 and azepin 520 being isolated in a ratio of 9:11 (Scheme 84). However, later work by Kishi on the synthesis of 1,4-linked carbon disaccharides\(^\text{128}\) showed that pyran formation could occur exclusively from the epoxy alcohol similar in structure to 441 (see scheme 85). In order to bring about the desired 6-exo-tet-ring closure\(^\text{129}\) epoxide 441 was treated with a catalytic quantity of camphorsulfonic acid in dichloromethane\(^\text{130}\) (Scheme 86).

After 40 mins at room temperature only a single product was observable by TLC. The high resolution mass spectrum confirmed its identity, it showing a peak at m/z 569.2683 for the (M+Na)\(^+\) ion which corresponded to an empirical formula of C\(_{33}\)H\(_{42}\)O\(_3\)SiNa. The 500 MHz \(^1\)H-NMR spectrum of 440 in CDCl\(_3\) showed the absence of epoxide protons.

To verify that we had in fact fashioned the desired pyran with the correct exocyclic olefin geometry an nOe NMR experiment was performed upon a clean sample of pyran 440. If our C2-symmetry breaking tactic had been successful we should be able to follow nOe interactions along one side of the molecule. The PMB ether protecting group located C10 lies on the same side of the molecule as the exocyclic vinylic protons where a series of through space interactions should be traceable from PMB ether to TBDPS silyl ether.

The nOesy spectrum for pyran 440 shows the benzylic protons attached OPMB protecting group at \(\delta = 4.45\) (s) interacting with the C16 methylene protons which are part of a multiplet observable at \(\delta = 3.23-3.45\) (m). In turn, these protons show a distinct nOe interaction with the C14 axial and equatorial methylene protons seen at \(\delta = 2.21\) (d, \(J = 13.6\) Hz) and \(\delta = 1.64\) (t, 12 Hz). With this in mind it can also be seen that the C14 equatorial proton observed at \(\delta = 2.21\) (d, \(J = 13.6\) Hz)
Hz) are clearly interacting through space with the allylic methylene proton attached to the exocyclic olefin which is fixed in a cis-orientation relative to it. The only other NOE interactions observable for the exocyclic allylic protons are with the bulky TBDPS protecting group (tertbutyl group δ = 1.02 (s), and phenyl protons δ = 7.65 (d, J = 7.8 Hz)) and the lone exocyclic vinylic proton δ = 5.45 (t, J = 6.4 Hz). Clearly, based on this evidence we have shown that the orientation of the exocyclic olefin present in the target molecule is cis- with respect to the pendant PMB protecting group present in 440.

In conclusion, we have prepared an advanced bryostatin B-ring synthon whose structure incorporates carbons 10 to 16 of the bryostatin skeleton. Moreover, we have generated a suitably protected form to allow it to be used in a future bryostatin synthesis. The concept of using a C2-symmetry breaking tactic to control B-ring exocyclic olefin geometry has thus been demonstrated. We have also shown that our approach to olefination is versatile enough to provide the enantiomer of 440 by using (R)-4-methoxybenzyl glycidyl ether as the chiral starting material.
6.1 EXPERIMENTAL

Materials and Methods.

Reactions were carried out under a nitrogen atmosphere with freshly distilled solvents unless otherwise noted. Hexanes refers to the distillate fraction of petroleum spirit that is collected at 40-60 °C and are distilled prior to use. All solvents were reagent grade. Dichloromethane, toluene, benzene and acetonitrile were distilled from calcium hydride under nitrogen. Diethyl ether and THF were distilled from sodium under nitrogen. All other reagents were used 'as supplied' from manufacturer unless otherwise stated. Flash column chromatography was carried out according to Still et al.\textsuperscript{130} with Kieselgel 60 40/60A (220-240 mesh) silica gel. Precoated silica gel plates (250 μm) with a fluorescent indicator (E. Merck) were used for analytical thin layer chromatography. The plates were initially examined under UV light and then developed with either a sulfuric acid stain [EtOH:H₂SO₄:p-MeOC₆H₄CHO (95:4:1)] or iodine unless otherwise stated. Evaporation refers to the removal of solvents at ≤ 40 °C on a Büchi rotary evaporator. \(^1\)H NMR spectra were acquired at 500 MHz with a Brucker DRX 500 and \(^{13}\)C NMR spectra were acquired at 125 MHz with a Brucker DRX 500. 2-D NMR spectra were also recorded on a Brucker DRX 500. Chemical shifts are reported in δ-values relative to tetramethylsilane (\(^1\)H and \(^{13}\)C) and all NMR spectra were recorded in deuterated solvent solutions. All infrared spectra were recorded on a Perkin-Elmer 1605 FT-IR spectrophotometer. Optical rotations were measured on an Optical Activity, Polaar 2000 automatic polarimeter. High resolution mass spectra were measured at the London School of Pharmacy on a V.G. 7070H or VG-ZAB instrument with a Finnigan Incons II data system.
(S)-(−)-glycidyl-4-methoxybenzyl ether 447

VII-MH-1-COL

To a cooled (0 °C) solution of (S)-(−)-glycidol (50 g, 647.94 mmol) in dry DMF (500 mL, 1.3 M), was added NaH (60% dispersion in mineral oil, 27g, 675 mmol) in 5 g portions over 30 mins to avoid excessive foaming. The light grey solution was stirred at this temperature for a further 30 mins whereupon the reaction formed a very thick slurry. Bu₄NI (12.47 g, 33.76 mmol) was added in a single portion before addition of 4-methoxybenzyl chloride (100.67 mL, 742.44 mmol) in a slow stream via syringe. Stirring continued at 0 °C thereafter for 4 hrs, whereupon it was transferred to a refrigerator (4 °C) and left to stand overnight. The reaction was quenched by dropwise addition of methanol (5-10 mL) while stirring at 0 °C and then poured carefully into H₂O (2000 mL). The aqueous phase was extracted with diethyl ether (3 X 500 mL). The combined organic phases were then washed with H₂O (1000 mL), dried (MgSO₄), filtered and concentrated in vacuo to yield a sweet smelling amber oil. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (15:1, then 11:1) as eluent gave 90.92 g (74%) of (S)-(−)-glycidyl-4-methoxybenzyl ether 447 as a very mild amber oil.

IR (neat film): 3017 (w), 2999 (m), 2908 (m), 2860 (m), 2837 (m), 1612 (s), 1585 (m), 1514 (s), 1463 (m), 1443 (w), 1419 (w), 1398 (w), 1365 (w), 1335 (w), 1302 (m), 1248 (s), 1209 (w), 1175 (s), 1091 (s), 1033 (s), 957 (w), 901 (m), 822 (s), 768 (m), 710 (w), 637 (w), 583 (w), 519 (w) cm⁻¹.

¹H-NMR (500 MHz, in CDCl₃): δ 7.25 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.52 (D, J = 11.5 Hz, 1H), 4.46 (d, J = 11.5 Hz, 2H), 3.78 (s, 3H), 3.70 (dd, J = 3.1, 11.4 Hz, 1H), 3.38 (dd, J = 5.9, 11.4 Hz, 1H), 3.14-3.16 (m, 1H), 2.77 (dd, J = 4.3, 4.3, 1H), 2.59 (dd, J = 2.7, 3.9, 1H)ppm.
Chapter 3: Experimental

$^{13}$C-NMR (125 MHz in CDCl$_3$): $\delta$ 159, 129.9, 129.4, 113.8, 72.9, 70.4, 55.2, 50.8, 44.3 ppm.

HRMS: (FAB, MNOBA matrix) for C$_{11}$H$_{14}$O$_3$Na (M+Na)$^+$, Calcd: 194.2298, Found 194.0943.
VII-MH-1-COL
IN CDCL3
VII-MH-1-COL
IN CDCL3

PMBO
VII-MH-1-COL
IN CDCL3

PMBO

ppm
β-Hydroxy-Ketone 471

![Chemical Structure](image)

III-KH-169-COL

To a cooled (0 °C) solution of dithiane 470 (0.5 g, 0.80 mmol) in THF (4 mL), was added H₂O (2 mL) and CaCO₃ (0.32 g, 3.21 mmol). Hg(ClO₄)₂·xH₂O was then added in a single portion and stirred for a further 30 mins at 0 °C. Upon completion, CELITE™ was added to the reaction mixture and stirred before it was filtered through a CELITE™ pad. The filter cake was washed with Et₂O (1 X 100 mL) and the filtrate transferred to a separatory funnel and washed with H₂O (100 mL). The organic layer was separated, dried (MgSO₄), filtered and concentrated in vacuo to give an oily residue which was purified by flash chromatography (SiO₂) with hexanes-ethyl acetate (5:1, then 3:1) as eluent to furnish 0.382 g (89%) of β-Hydroxy-Ketone 471 as a mild amber oil.

[α]D: +51.3 ° (c 1, MeOH).

IR (neat film): 3458 (broad, m), 2999 (w), 2927 (s), 2855 (s), 1713 (s), 1612 (s), 1585 (m), 1514 (s), 1464 (m), 1442 (m), 1362 (m), 1302 (m), 1250 (s), 1209 (w), 1175 (m), 1099 (s), 1036 (s), 1007 (m), 974 (w), 939 (w), 835 (s), 779 (s), 758 (w), 772 (w), 665 (s), 638 (w), 582 (w), 515 (w) cm⁻¹.

¹H-NMR (500 MHz in CDCl₃): δ 7.26-7.22 (m, 4H), 6.89-6.86 (m, 4H), 4.47 (s, 2H), 4.44 (s, 2H), 4.43 (s, 2H), 4.35-4.30 (m, 1H), 4.25-4.20 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.45-3.38 (m, 3H), 3.31 (dd, J = 6.0, 9.6 Hz, 1H), 2.97 (d, J = 3.8 Hz, 1H), 2.70-2.59 (m, 3H), 0.84 (s, 9H), 0.05 (s, 3H) ppm.

91
\(^{13}\)C-NMR (125 MHz in CDCl\(_3\)): \(\delta\) 209.2, 159.3, 159.2, 130.1, 130.0, 129.4, 129.3, 113.8, 113.7, 73.7, 73.0, 72.9, 67.9, 66.6, 55.2, 48.7, 47.4, 25.8, 18.0, -4.6, -5.0 ppm.

HRMS (FAB, MNOBA matrix) for \(\text{C}_{19}\text{H}_{40}\text{O}_{2}\text{SiNa (M+Na)}^+\), Calcd: 555.2727, Found: 555.2754.
1H III-KH-169(A) in CDCl3

COSY
To a cooled (0 °C) solution of β-hydroxy ketone 471 (105.1 mg, 0.20 mmol) in pyridine (0.16 mL, 2.0 mmol) and dichloromethane (3 mL) was added a stock solution of bromoacetyl bromide (79.6 mg, 3.95 mmol in 0.3 mL CH₂Cl₂) over 2 minutes. The mixture was stirred at 0 °C for 50 minutes. Excess bromoacetyl bromide was then added (79.6 mg, 3.95 mmol in 0.3 mL CH₂Cl₂) over 1 minute, followed by addition of pyridine (0.16 mL, 2.0 mmol). After stirring the at 0 °C for a further 5 minutes the mixture was quenched by pouring into CH₂Cl₂ and adding 10% HCl (aq) solution. The organic layer was removed and the aqueous layer extracted further with CH₂Cl₂ (2 X 5 mL). The combined organic layers were then dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was then purified by flash chromatography (SiO₂) using hexanes/EtOAc as eluent (8:1 to 6:1) to give 84 mg (65%) of bromoacetate 468. Due to the extremely labile nature of this compound we were unable to obtain analytical data, instead using the compound directly for the next step.

To a cooled (-78 °C) solution of bromoacetate 468 (84 mg, 0.13 mmol) in dry THF (1 mL), was added 2.56 mL of a Sml₂ solution (0.1 M in THF). The reaction was stirred at -78 °C for 10 minutes before the cooling bath was removed and the reaction allowed to warm to room temperature over 1 hour. After stirring at room temperature for a further 30 minutes, zinc dust (214 mg) was added to the reaction mixture and the reaction temperature raised to reflux for 1 hour, whereupon it was cooled and allowed to stir at room temperature overnight. The reaction was diluted with Et₂O, filtered through a thin pad of CELITE™ and the filtrant concentrated in vacuo to
yield an oily residue that was purified using flash chromatography (SiO₂) with hexanes/ethyl acetate (5:1) to furnish 48.7 mg (66%) of acetate 472 and an amber oil.

\[ [\alpha]_0 \text{D} = -25.0^\circ (c 1, \text{MeOH}) \].

\textbf{IR (neat film):} 2992 (s), 2929 (s), 2865 (s), 1742 (s), 1739 (s), 1720 (s), 1715 (s), 1613 (s), 1514 (s), 1471 (m), 1464 (m), 1442 (m), 1373 (m), 1302 (m), 1247 (s), 1173 (m), 1097 (s), 1036 (s), 836 (m), 779 (m) cm⁻¹.

\textbf{¹H-NMR (in CDCl₃):} \delta 7.20 (d, J = 8.6 Hz, 4H), 6.84 (d, J = 8.6 Hz, 4H), 5.37-5.33 (m, 1H), 4.44 (d, J = 11.7 Hz, 2H), 4.39 (d, J = 11.2 Hz, 2H), 4.38-4.26 (m, 1H), 3.78 (s, 6H), 3.50 (d, J = 4.7 Hz, 2H), 3.37 (dd, J = 5.1, 9.7 Hz, 1H), 2.28 (dd, J = 6.0, 9.7 Hz, 1H), 2.79 (dd, J = 7.0, 17.3 Hz, 1H), 2.72 (dd, J = 5.7, 17.3 Hz, 1H), 1.99, (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H) ppm.

\textbf{¹³C-NMR (125 MHz in CDCl₃):} \delta 205.7, 170.2, 159.3, 159.2, 130.2, 129.9, 129.3, 129.2, 113.8, 113.7, 73.7, 72.9, 72.8, 70.1, 68.6, 67.8, 55.2, 48.3, 44.9, 25.8, 21.1, 18.0, -4.6, -5.0 ppm.

Phosphonate ester 469

![Phosphonate ester 469](image)

III-KJH-172-COL

To a cooled (-78 °C) stirred solution of 2-tert-(butyldimethylsilyl)-1,3-dithiane 446 (1.4 g, 4.68 mmol) and hexamethylphosphoric triamide (3.3 mL 18.72 mmol) in dry THF (15.5 mL 0.3 M) was added 'BuLi (Aldrich, 1.7M in hexanes, 3.10 mL, 5.27 mol) in a slow stream over 2 mins. The amber solution was stirred at this temperature for 30 minutes before the addition of (S)-(−)-glycidyl-4-methoxybenzyl ether 447 (in 2.5 mL THF, 2.0 g 5.15 mmol). The mixture was stirred at −78 °C for 15 mins and then allowed to warm to 0 °C over 60 min and stirred at this temperature for a further 30 mins. The reaction was cooled −30 °C and a chilled solution of diethylphosphonoacetyl chloride (0.41 M in THF, 16.7 mL, 7.01 mmol) added in a steady stream over 1 min. The reaction was allowed to warm to room temperature and stirred overnight. On completion, the mixture was diluted with diethyl ether (100 mL) and washed with saturated sodium bicarbonate solution (100 mL). The aqueous layer was then extracted further with diethyl ether (2 X 100 mL). The combined organic layers were combined, washed with water (1 X 100 mL), separated, dried with MgSO₄, filtered and concentrated in vacuo. Purification using flash chromatography (SiO₂) with hexanes/ethyl acetate as eluent then furnished 1.96 g (51%) of phosphonate ester 469 as an amber oil.

[α]D: +90.0 ° (c 1, MeOH).

IR (neat film): 2953 (s), 2930 (s), 2906 (s), 2855 (s), 1742 (s), 1739 (s), 1733 (s), 1729 (s), 1612 (m), 1514 (s), 1512 (s), 1471 (m), 1463 (m), 1302 (m), 1249 (s), 1173 (m), 1100 (m), 1031 (s), 972 (m), 836 (m), 812 (m), 778 (m), 778 (m) cm⁻¹.
$^1$H-NMR (500 MHz in CDCl$_3$): δ 7.24-7.20 (m, 4H), 6.85-6.80 (m, 4H), 5.44 (m, 1H), 4.45-4.39 (m, 4H), 4.16-4.08 (m, 5H), 3.77 (s, 3H), 3.76 (s, 3H), 3.48 (dd, $J = 4.9$, 10.5 Hz, 1H), 3.43 (dd, $J = 5.2$, 10.5 Hz, 1H), 3.38 (dd, $J = 4.9$, 9.5 Hz, 1H), 3.31 (dd, $J = 6.2$, 9.3 Hz, 1H), 2.91, (ddd, $J = 14.6$, 21.2, 28.5 Hz, 2H), 2.80-2.64 (m, 4H), 2.39 (dd, $J = 3.4$, 15.3 Hz, 1H), 2.34 (dd, $J = 2.7$, 15.9 Hz, 1H), 2.22 (dd, $J = 7.3$, 15.9 Hz, 1H), 1.93 (dd, $J = 5.7$, 15.3 (Hz, 1H), 1.86-1.81 (m, 2H), 1.32-1.25 (m, 6H), 0.82 (s, 9H), 0.54 (s, 3H), 0.01 (s, 3H) ppm.

$^{13}$C-NMR (125 MHz in CDCl$_3$): δ 165.0, 164.9, 159.1, 159.0, 130.3, 130.1, 129.3, 129.2, 113.6, 74.5, 72.8, 72.6, 71.0, 70.97, 70.92, 69.1, 62.60, 62.58, 62.55, 62.53, 55.2, 51.5, 44.9, 40.9, 35.0, 33.9, 26.2, 26.1, 26.0, 24.6, 18.0, 16.3, 16.2, -39, -4.2 ppm.

HRMS (FAB, MNOBA matrix): for C$_{35}$H$_{50}$O$_{10}$S$_2$SiPNa (M+Na)$^+$, Calcd: 823.3094, Found: 823.3111.
Chapter 3: Experimental

β-Keto-phosphonate ester 466

\[
\begin{align*}
\text{(EtO)}_2\text{P} & \quad \text{O} \\
\text{PMB} & \quad \text{O} \\
\text{OPMB} & \quad \text{OPMB}
\end{align*}
\]

To a cooled (0 °C) solution of 469 (1.96 g, 2.44 mmol) in THF (26 mL) was added H₂O (13 mL) and then CaCO₃ (1.38 g, 13.78 mmol) and finally Hg(ClO₄)₂·xH₂O (2.20 g, 5.51 mmol). The reaction was stirred at 0 °C for a further 30 mins. Upon completion, the reaction was diluted with ice cold diethyl ether (100 mL) and filtered through a thin CELITE™ pad. The reaction was filtered this way twice and the filtrate washed with H₂O (2 x 50 mL). The organic extracts were dried (MgSO₄), filtered, and concentrated \textit{in vacuo}. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (2:1, then 1:1, then 3:2, then 2:1) as eluent gave 1.41 g (81 %) 466 as an amber oil.

\[ [\alpha]_D^2 +17.2 ^\circ \text{ (c 1, MeOH)} \].

\textbf{IR (neat film):} 3465 (broad, m), 2954 (s), 2930 (s), 2856 (s), 1740 (s), 1737 (s), 1719 (s), 1716 (s), 1612 (s), 1472 (m), 1463 (m), 1443 (w), 1388 (m), 1384 (m), 1368 (m), 1302 (s), 1250 (s), 1210 (m), 1173 (s), 1100 (s), 1031 (s), 837 (s), 779 (s) cm⁻¹.

\textbf{¹H-NMR (500 MHz in CDCl₃):} δ 7.19 (d, \(J = 7.7\) Hz, 4H), 6.85-6.81 (m, 4H), 5.42-5.38 (m, 1H), 4.45 (d, \(J = 11.6\) Hz, 2H), 4.38 (d, \(J = 11.6\) Hz, 2H), 4.30-4.25 (m, 1H), 4.11 (dt, \(J = 7.1\), 15.3 Hz, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 3.54 (dd, \(J = 4.8\), 10.7 Hz, 1H), 3.50 (dd, \(J = 4.1\), 10.7 Hz, 1H), 3.36 (dd, \(J = 5.1\), 9.6 Hz, 1H), 3.27 (dd, \(J = 6.0\), 9.6 Hz, 1H), 2.29 (s, 1H), 2.88 (s, 1H), 2.81 (dd, \(J = 6.6, 17.6\) Hz, 1H), 2.76 (dd, \(J = 6.3, 17.6\) Hz, 1H), 2.62 (dd, \(J = 4.9, 15.9\) Hz, 1H), 2.56 (dd, \(J = 7.2, 15.9\) Hz, 1H), 1.28 (dt, \(J = 7.1, 2.3\) Hz, 6H), 0.8 (s, 9H), 0.01 (s, 3H), -0.2 (s, 3H) ppm.
$^{13}$C-NMR (125 MHz in CDCl$_3$): $\delta$ 205.3, 165.0, 159.2, 159.1, 130.2, 12909, 129.3, 129.2, 113.72, 113.70, 73.6, 72.9, 72.8, 69.9, 67.8, 62.69, 62.67, 62.64, 62.62, 55.2, 48.3, 44.6, 34.8, 33.7, 25.8, 18.0, 16.3, 16.2, -4.6, -5.0 ppm.

HRMS (FAB, MNOBA matrix) for C$_{36}$H$_{55}$O$_{10}$SiPNa (M+Na)$^+$, Calcd: 733.3176, Found: 733.3149.
To a cooled (0 °C) solution of β-keto phosphonate ester 466 (60.6 mg, 0.082 mmol) in THF (1 mL) was added NaH (60% dispersion in mineral oil, 3.4 mg, 0.082 mmol) in one portion. The reaction was allowed to warm to room temperature over the period of 1 hour and stirred at room temperature for a further two hours. The reaction was quenched by dropwise addition of methanol (approx 1 mL) and then the reaction was poured into a separating funnel containing H2O (2 mL). The aqueous was extracted with Et2O (3 X 5 mL) and the organic extracts combined, dried (MgSO4), filtered and concentrated in vacuo to yield a mild amber oil. The crude residue was purified using flash chromatography (SiO2) using hexanes-ethyl acetate (6:1, then 5:1, then 4:1) to yield 0.0076 mg (16%) of lactone 465.

\[ \alpha \text{0: } +72.9^\circ \text{ (c 1, MeOH).} \]

**IR (neat film):** 2999 (w), 2930 (s), 2901 (s), 2856 (s), 2709 (w), 1714 (s), 1614 (s), 1585 (m), 1514 (s), 1464 (s), 1443 (m), 1421 (m), 1389 (m), 1302 (m), 1248 (s), 1209 (w), 1173 (m), 1101 (s), 1036 (s), 1007 (m), 939 (w), 837 (s), 777 (s), 712 (w), 665 (w), 637 (w), 581 (m), 517 (m) cm\(^{-1}\).

**\(^1\)H-NMR (500 MHz in CDCl\(_3\)):** \(\delta 7.23, (d, J = 8.7 \text{ Hz}, 2H)\), \(7.21 (d, J = 8.6 \text{ Hz}, 2H)\), \(6.85 (d, J = 8.3 \text{ Hz}, 4H)\), \(5.80 (s, 1H)\), \(4.52-4.36 (m, 5H)\), \(4.00-3.97 (m, 1H)\), \(3.78 (s, 6H)\), \(3.61 (dd, J = 4.6, 10.4 \text{ Hz}, 1H)\), \(3.58 (dd, J = 5.1, 10.4 \text{ Hz}, 1H)\), \(3.37 (dd, J = 5.0, 9.4 \text{ Hz}, 1H)\), \(3.24 (dd, J = 6.9, 9.4 \text{ Hz}, 1H)\), \(3.37 (dd, J = 5.0, 9.4 \text{ Hz}, 1H)\), \(3.24 (dd, J = 6.9, 9.4 \text{ Hz}, 1H)\), \(3.24 (dd, J = 6.9, 9.4 \text{ Hz}, 1H)\),
2.55 (ddd, $J = 2.2, 12.1, 18.1$ Hz, 1H), 2.48 (dd, $J = 4.5, 13.6$ Hz, 1H), 2.39 (dd, $J = 6.6, 13.6$ Hz, 1H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm.

$^{13}$C-NMR (125 MHz in CDCl$_3$): $\delta$ 164.4, 159.3, 159.2, 157.8, 129.9, 129.8, 129.4, 117.9, 113.8, 76.2, 73.2, 73.1, 70.6, 69.5, 55.3, 42.2, 31.3, 25.7, 18.0, -4.5, -4.8 ppm.

HRMS (FAB, MNOBA matrix): for C$_{31}$H$_{46}$O$_4$SiNa (M+Na)$^+$, Calcd: 579.2754, Found: 579.2754.
To a cooled (0 °C) solution of dithiane 453 (1.00g, 1.35 mmol) in THF (4 mL), was added tetrabutylammonium fluoride (1 M in THF, 2.71 mL, 2.71 mmol). The reaction was allowed to warm to room temperature gradually over 1 hour and stirring was maintained at this temperature for a further 21 hours. The solvents were removed in vacuo to furnish a dark arange residue that was purified directly using silica (SiO₂) flash chromatography with hexanes-ethyl acetate (3:1, then 2:1, then 1:1, then 100% ethyl acetate) as eluent to give 0.59 g (85%) of diol 486 as a mild amber oil.

IR (neat film): 3361 (broad, s), 2999 (w), 2958 (s), 2858 (s), 2835 (s), 2454 (w), 2488 (w), 2422 (w), 2057 (w), 1806 (w), 1612 (s), 1585 (s), 1514 (s), 1464 (m), 1441 (m), 1421 (m), 1364 (m), 1302 (s), 1248 (s), 1211 (m), 1175 (s), 1103 (s), 1034 (s), 951 (w), 908 (m), 874 (w), 820 (w), 758 (m), 708 (w), 637 (w) cm⁻¹.

¹H-NMR (500 MHz in CDCl₃): δ 7.24 (d, J = 8.4 Hz, 4H), 6.85 (d, J = 8.6 Hz, 4H), 4.47 (s, 4H), 4.16-4.45 (m, 2H), 3.78 (s, 6H), 3.34-3.39 (m, 4H), 2.74-2.95 (m, 2H), 2.74 (t, J = 5.6 Hz, 4H), 2.25 (dd, J = 8.14, 15.4 Hz, 2H), 2.18 (d, J = 14.1 Hz, 2H), 1.91 (m, 2H) ppm.

¹³C-NMR (125 MHz in CDCl₃): δ 159.2, 130.0, 129.4, 113.8, 74.2, 72.9, 66.9, 55.2, 51.1, 41.4, 26.0, 25.1 ppm.

HRMS (FAB, MNOBA matrix): from C₂₆H₃₆O₇S₄Na (M+Na)⁺, Calcd: 531.1851, Found: 531.1867.
Desilylation of 2 X TBS groups.
12-07-00.

PROTON
IV-GBpd-175 col.
FINAL COMPOUND

COSY

[Chemical structure diagram]

[Graph with ppm axis from 7.0 to 2.0]
Bis-O-Allyl Ether 485

To a cooled (0 °C) solution of diol 486 (270.40 mg, 0.53 mmol) in THF (6 mL) was added NaH (60% dispersion in mineral oil, 43 mg, 1.06 mmol). The reaction was stirred at 0 °C for 30 mins until gas evolution had ceased then allyl bromide (129 mg, 1.06 mmol) added dropwise over two mins. The reaction was allowed to warm to room temperature and stirred overnight. Imidazole was added (36.04 mg, 0.53 mmol) and the reaction stirred at room temperature for 72 hrs, whereupon the reaction was diluted with EtOAc (10 mL) and washed with saturated NaCl solution (1 X 10 mL). The aqueous layer was extracted further with EtOAc (2 X 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to yield an oily amber residue. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (6:1) as eluent then furnished 145 mg of bis-allyl ether 485 in (45%) yield.

¹H-NMR (500 MHz in CDCl₃): δ 7.24 (d, J = 7.3 Hz, 4H), 6.84 (d, J = 8.4 Hz, 4H), 5.87-8.92 (d, J = 7.3 Hz, 2H), 5.22 (d, J = 17.2 Hz, 2H), 5.07 (d, J = 10.3 Hz, 2H), 4.45 (s, 6H), 4.02-4.14 (m, 2H), 3.82-3.77 (m, 2H), 3.77 (s, 6H), 3.47 (dd, J = 5.2, 10.0 Hz, 2H), 1.41 (dd, J = 5.2, 9.8 Hz, 2H), 2.81-2.72 (m, 4H), 2.18 (dd, J = 2.4, 15.5 Hz, 2H), 2.11 (dd, J = 6.3, 15.4 Hz, 2H), 1.87 (t, J = 5.5 Hz, 2H) ppm.

¹³C-NMR (125 MHz in CDCl₃): δ 159.1, 135.4, 130.4, 129.3, 129.2, 129.0, 116.4, 113.7, 113.6, 75.8, 72.8, 72.1, 71.5, 71.0, 70.9, 55.3, 55.2, 52.2, 42.9, 26.3, 24.9 ppm.

HRMS (MNOBA matrix): for C₃₂H₄₄O₆S₂Na (M+Na)⁺, Calcd: 611.2477, Found: 611.2492
**PROTON**

**Current Data Parameters**
- **NAME**: 1V-G9pd77col
- **EXPNO**: 1
- **PROCNO**: 1

**F2 - Acquisition Parameters**
- **Date**: 20000717
- **Time**: 12:09
- **INSTRUM**: ORV500
- **PROBNO**: 5 mm Multino
- **PULPROG**: zg30
- **TD**: 82642
- **SOLVENT**: CDC13
- **NS**: 32
- **DS**: 2
- **SNH**: 10338.578 Hz
- **PI**: 0.125004 Hz
- **AG**: 3.9999228 msec
- **RG**: 574.7
- **DW**: 48.400 ussec
- **DE**: 5.000 ussec
- **TE**: 300.0 K
- **DI**: 1.00000000000 sec

**F0 - Processing parameters**
- **SI**: 131072
- **SF**: 500.130026 MHz
- **SSB**: 0
- **LB**: 0.30 Hz
- **GB**: 0
- **PC**: 1.00

**1D NMR plot parameters**
- **CX**: 32.00 cm
- **FD**: 10.000 ppm
- **F1**: 5001.30 Hz
- **F2**: -500.13 Hz
- **PPMCM**: 0.36667 ppm/cm
- **HzCM**: 183.38101 Hz/cm
**Current Data Parameters**

**NAME**
IV-GBp177col

**EXPNO**
2

**PHCNO**
1

**F2 - Acquisition Parameters**

- **Date**: 20000717
- **Time**: 12.19
- **INSTRUM**: dr500
- **PROBID**: 5 mm Multinu
- **PULP1D**: 280930
- **TD**: 69536
- **SOLVENT**: CDCl3
- **NS**: 886
- **DS**: 0
- **SW**: 31446.51 Hz
- **FIDRES**: 0.479036 Hz
- **AG**: 1.0420724 sec
- **RG**: 2048
- **DM**: 15.900 ussec
- **DE**: 6.00 ussec
- **TE**: 300.0 K
- **D1**: 2.00000000 sec
- **d11**: 0.03000000 sec
- **d12**: 0.00000000 sec

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**************** CHANNEL 11 **************

- **NUC1**: 13C
- **PL1**: 11.75 usec
- **PL1**: 0.00 dB
- **SF01**: 125.7215719 MHz

---

**************** CHANNEL 12 **************

- **CFOPPG2**: walt216
- **NUC2**: 1H
- **PCPG2**: 100.00 usec
- **PL2**: 0.00 dB
- **PL12**: 22.00 dB
- **PL13**: 22.00 dB
- **SF02**: 500.1320005 MHz

**F2 - Processing parameters**

- **S1**: 32768
- **SF**: 125.7579955 MHz
- **WOM**: EM
- **SSR**: 0
- **LB**: 2.00 Hz
- **SG**: 0
- **PC**: 1.40

**1D NMR plot parameters**

- **C1**: 30.00 cm
- **F1P**: 220.000 ppm
- **F1**: 27666.71 Hz
- **F2P**: -10.000 ppm
- **F2**: 125.75 Hz
- **PMDDM**: 7.66657 ppm/cm
- **HZDM**: 964.14313 Hz/cm
Chapter 3: Experimental

Diol 489

![Structure of Diol 489](image)

Powdered 4A molecular sieves (35 mg), magnesium turnings (7 mg, 0.28 mmol), and Cp₂TiCl₂ (63 mg, 0.25 mmol) were placed in a round bottomed flask and evacuated with heating. After cooling to room temperature, a stir bar was added to the reaction vessel and dry THF (1.0 mL) added via syringe. P(EtO)₃ (85 mg, 0.59 mmol in 0.5 mL THF) was then added to the reaction via syringe and the reaction maintained at room temperature with stirring for 3 hours. During this time, the reaction colour changed from red to dark green and then dark brown/black. Bis-allyl ether 485 (50 mg, 0.0849 mmol, in 1 mL THF) was then added to the reaction and stirred at room temperature for 16 hours. The reaction temperature was then elevated to reflux and stirred at this temperature for 75 minutes, whereupon it was allowed to cool to room temperature. The reaction was quenched by addition of NaOH (aq) solution (1 mL, 1 M) and stirred vigorously for 25 minutes. The reaction was then filtered through a thin pad of silica, which was washed exhaustively with Et₂O. The filtrate was transferred to a separating funnel and washed with saturated brine. The separated organic layer was then dried (Na₂SO₄), filtered and concentrated in vacuo to yield a red oil. Flash chromatography (SiO₂) of the crude residue (solvent gradient 3:1 to 2:1 Hexanes: Ethyl acetate) led to the isolation of 21.3 mg of diol 489 as a mild amber oil.

¹H-NMR (500 MHz in CDCl₃): δ 7.22 (d, J = 9.1 Hz, 4H), 6.85 (d, J = 8.6 Hz, 4H), 4.47 (s, 4H), 4.15-4.25 (m, 2H), 3.78 (s, 6H), 3.37 (dd, J = 5.0, 9.6 Hz, 2H), 3.35 (dd, J = 6.8, 9.6 Hz, 2H), 2.74 (t, J = 5.6 Hz, 4H), 2.24 (dd, J = 8.4, 15.3 Hz, 2H), 2.83 (dd, J = 1.7, 15.3 Hz, 2H), 1.90-1.95 (m, 2H) ppm.
Chapter 3: Experimental

$^{13}$C-NMR (125 MHz in CDCl$_3$): $\delta$ 159.2, 130.1, 129.4, 113.8, 74.2, 72.9, 67.0, 63.6, 63.5, 55.3, 51.1, 41.5, 26.0, 25.1, 16.1 ppm.

LRMS (FAB): (M+Na)$^+$, Calcd: 404, Found: 399.
PROTON

\[
\begin{align*}
\text{PMBO} & \quad \text{HO} \\
\quad & \quad \text{OH} \\
\quad & \quad \text{OPMB}
\end{align*}
\]

Current Data Parameters

- **NAME**: IV-GP6-179-CD
- **EXPNO**: 10
- **PROCNO**: 1

F2 - Acquisition Parameters

- **Date**: 2000071B
- **Time**: 17:45
- **INSTRUM**: dx500
- **PROBHO**: 5 mm Multinu
- **PULPROG**: zg30
- **TO**: 0.6036
- **SOLVENT**: CDCl3
- **NS**: 2
- **DS**: 2
- **SW**: 10350.578 Hz
- **FIDRES**: 0.157632 Hz
- **AQ**: 3.1719923 sec
- **RG**: 322.5
- **DW**: 48.400 usec
- **DE**: 6.00 usec
- **TE**: 300.0 K
- **D1**: 1.0000000 sec

********** CHANNEL f1 **********

- **MUC**: H
- **P1**: 11.50 usec
- **PL1**: 0.00 dB
- **SF01**: 500.1330885 MHz

F2 - Processing parameters

- **SI**: 32768
- **SF**: 500.1300234 MHz
- **WDM**: no
- **SSB**: 0
- **LB**: 0.00 Hz
- **GB**: 0
- **PC**: 1.00

1D NMR plot parameters

- **CX**: 30.00 cm
- **F1P**: -9000 ppm
- **F1**: 4501.17 Hz
- **F2P**: -1000 ppm
- **F2**: 500.13 Hz
- **PPCM**: 0.33333 ppm/cm
- **HZCM**: 156.31001 Hz/cm
Bis-Alkylated Dithiane Adduct 453

VII-MH-3-COL

To a cooled (-78 °C) and stirred solution of 2-tert-(butyldimethylsilyl)-1,3-dithiane 446 (52.43 g, 215 mmol) and hexamethylphosphoritriamide (164.73 mL, 861 mmol) in dry THF (718 mL, 0.3M) was added 'BuLi (Aldrich 1.7M in hexanes, 139.30 mL, 237 mmol) dropwise over 45 min which caused the solution to turn ox-blood red in colour. Stirring was continued at this temperature for an additional 30 min, before addition of (S)-(−)-glycidyl-4-methoxybenzyl ether 447 (in 50 mL THF, 92.00g, 474 mmol) over 10 min. The reaction mixture was stirred and allowed to warm slowly to −45 °C over 1hr before cooling to −78 °C and adding tert-butyldimethylsilyl chloride in a single portion against a counter flow of nitrogen from the reaction vessel. Note - tert-butyldimethylsilyl chloride was handled in a glove bag and weighed into a Schlenk tube under an inert atmosphere of nitrogen. The reaction was then warmed to 20 °C and stirred at this temperature for 50 mins before addition of NaHCO₃ (approx 15 g) followed addition of saturated NaHCO₃ (300 mL). The aqueous phase was extracted with diethyl ether (4 X 400 mL). The combined organic phases were then dried (MgSO₄), filtered and concentrated in vacuo to yield a foul smelling amber oil. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (50:1, then 15:1) as eluent gave 118.28 g (75 %) of Bis-alkylated dithiane 453 as an amber oil.

[α]D: +4.70° (c 1, MeOH).

IR (neat film): 2931 (s), 2855 (s), 2790 (w), 2064 (w), 1880 (w), 1767 (w), 1612 (m), 1587 (m), 1513 (m), 1464 (m), 1420 (m), 1363 (m), 1300 (w), 1249 (s), 1175 (m), 1101 (s), 1038 (s), 909 (w), 832 (s), 776 (m) cm⁻¹
Chapter 3: Experimental

$^1$H NMR (500 MHz, in CD$_2$D$_2$): $\delta$ 7.24 (d, $J = 8.6$ Hz, 4H), 6.80 (d, $J = 8.6$ Hz, 4H), 4.59 (m, 2H), 4.42 (d, $J = 11.7$ Hz, 2H), 3.55 (dd, $J = 2.6$, 5.6 Hz, 2H), 3.29 (s, 6H), 2.68 (dd, $J = 4.1$, 15.3, 4H), 2.47 (dd, $J = 5.6$, 5.6 Hz, 4H), 2.30 (dd, $J = 5.4$, 15.3 Hz, 2H), 1.46 (m, 2H), 1.05 (s, 18H), 0.33 (s, 6H), 0.21 (s, 6H) ppm.

$^{13}$C NMR (125 MHz, CD$_2$D$_2$): $\delta$ 159.0, 130.6, 129.2, 113.6, 74.9, 72.7, 69.2, 55.3, 52.1, 45.3, 26.3, 24.9, 18.1, -3.9, -4.2 ppm.

HRMS (FAB, MNOBA matrix): for C$_{38}$H$_{64}$O$_8$S$_2$Si$_2$Na (M + Na)$^+$, Calcd: 759.3581, Found: 759.3566.
V-MH-80-COL (IN C6D6)
PROTON

PROTON

TBSO
PMBO

A-X

7 ppm
00/01/05 10:01
SCAN: 3 scans, 16.0cm⁻¹
C\textsubscript{2}-Symmetric Ketone 444

\[
\begin{array}{c}
\text{TBSO} \\
\text{PMB} \\
\text{O} \\
\text{OPMB}
\end{array}
\]

VII-MH-6-COL

To a cooled solution of dithiane 453 (50 g, 67.8 mmol) in THF (683.75 mL) was added distilled water (341.87 mL) and CaCO\textsubscript{3} (27.62 g, 271 mmol). The reaction was cooled to 0 °C and Hg(ClO\textsubscript{4})\textsubscript{2} XH\textsubscript{2}O (54.16 g, 136 mmol) added in a single portion. The reaction was maintained at 0 °C for 30 min with vigorous stirring before addition of ice cold diethyl ether (1 L). The reaction was filtered through a thin CELITE\textsuperscript{TM} pad (X 2) and the filtrate washed with H\textsubscript{2}O (2 x 300 mL). The organic extracts were dried (MgSO\textsubscript{4}), filtered, and concentrated \textit{in vacuo}. Purification using flash chromatography (Si\textsubscript{0}2) with hexanes-ethyl acetate (20:1, then 15:1) as eluent gave 38.28 g (87\%) of C\textsubscript{2}-symmetric ketone 444 as an amber oil.

\([\alpha]_D: +19.70^\circ \ (c 1, \text{MeOH}).\]

\textbf{IR (neat film):} 2932 (s), 2857 (s), 2064 (w), 1881 (w), 1715 (s), 1613 (m), 1513 (s), 1465 (m), 1364 (m), 1301 (m), 1250 (s), 1176 (m), 1108 (s), 1037 (s), 833 (m), 778 (m), 711 (w), 665 (w) cm\textsuperscript{-1}.

\textbf{\textsuperscript{1}H NMR (500 MHz in C\textsubscript{6}D\textsubscript{6}):} \delta 7.20 (d, J = 8.6 Hz, 4H), 6.80 (d, J = 8.6 Hz, 4H), 4.52 (Quin, J = 5.7 Hz, 2H), 4.34 (D, 11.6 Hz, 2H), 3.31 (d, J = 11.6 Hz, 2H), 3.41 (dd, J = 9.5, 5.7 Hz, 2H), 3.30-3.42 (m, 8H), 0.96 (s, 18H), 0.16 (s, 6H), 0.15 (s, 6H) ppm.
\(^{13}\)C NMR (125 MHz, \(\text{C}_6\text{D}_6\)): \(\delta 206.2, 159.8, 130.8, 129.5, 128.5, 114.1, 74.4, 73.1, 68.3, 54.7, 49.4, 26.2, 18.3, -4.3, -4.6\) ppm.

HRMS (FAB, MNIOBA matrix): for \(\text{C}_{39}\text{H}_{58}\text{O}_7\text{Si}_2\text{Na}\) (M + Na\(^+\)), Calcd: 669.3619, Found: 669.3604.
V-MH-99-COL (IN C6D6)
DEPT135

[Chemical structure image]

[10 ppm to 210 ppm scale]
V-MH-85-Coll
HMOC C6D6 v kjh 1
To a cooled solution of $C_2$-symmetric ketone 444 (38.00 g, 58.7 mmol) in dry THF (195.77 mL) under a nitrogen atmosphere was added allylmagnesium bromide (Aldrich 1.0 M solution in THF, 70.48 mL, 70.5 mmol) in a slow stream over 10 min. The reaction was maintained at 0 °C for a further 10 min before the dropwise addition of saturated NH$_4$Cl solution. The reaction was extracted with diethyl ether (4 X 200 mL). The combined organic extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification using flash chromatography (SiO$_2$) with hexanes-ethyl acetate (27:1, then 15:1, the 10:1) as eluent gave 34.13 g (84 %) of allylic alcohol 495 as a clear oil.

$[\alpha]_D^\circ: +8.56^\circ (c 1, \text{MeOH}).$

**IR (neat film):** 3497 (m), 3071 (w), 2932 (s), 2857 (s), 2064 (w), 1881 (w), 1316 (m), 1513 (s), 1465 (m), 1363 (m), 1301 (m), 1250 (s), 1174 (m), 1103 (s), 1037 (m), 955 (m), 915 (w), 833 (s), 777 (m), 712 (w), 663 (w) cm$^{-1}$.

$^1$H NMR (500 MHz, in CD$_2$Cl$_2$): $\delta$ 7.21 (d, $J = 8.6$Hz, 2H), 7.18 (d, $J = 8.56$ Hz, 2H), 6.78 (d, $J = 7.9$ Hz, 4H), 6.02-6.16 (m, 1H), 5.13 (d, $J = 17.16$ Hz, 1H), 5.09 (d, $J = 10.26$ Hz, 1H), 4.48-4.45 (m, 1H), 4.34-4.38 (m 1H), 4.34 (s, 2H), 4.29 (d, $J = 11.6$ Hz, 1H), 4.26 (d, $J = 11.6$ Hz, 2H), 4.14 (s, 1H), 3.57 (dd, $J = 9.6, 5.0$ Hz, 1H), 3.51 (dd, $J = 9.6, 5.9$ Hz, 1H), 3.39 (dd, $J = 9.5, 5.7$ Hz, 1H), 3.31 (dd, $J = 9.5, 5.1$ Hz, 1H), 3.30 (s, 6H), 2.88 (dd, $J = 13.9, 6.7$ Hz, 1H), 2.50 (dd, $J = 13.9, 7.9$ Hz,
Chapter 3 : Experimental

$^1$H NMR (500 MHz in CDCl$_3$): $\delta$ 1.86-2.01 (m, 4H), 1.02 (s, 9H), 0.98 (s, 9H), 0.23 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), 0.13 (s, 3H) ppm.

$^{13}$C NMR (125 MHz in CD$_2$Cl$_2$): $\delta$ 160.2, 160.1, 136.0, 131.6, 131.3, 130.9, 130.0, 129.9, 128.9, 117.9, 114.5, 114.4, 96.8, 76.3, 75.9, 73.5, 73.4, 73.3, 70.8, 69.9, 55.2, 55.2, 45.7, 45.6, 45.0, 44.9, 26.7, 26.6, 18.8, 18.7, -3.1, -3.3, -3.7, -3.9, -4.1 ppm.

HRMS (FAB, MNOBA matrix): for C$_{36}$H$_{64}$O$_7$Si$_2$Na (M + Na)$^+$, Calcd: 711.4088, Found: 711.4091.
00/01/06 10:36 ft
SCAN: 16 scans, 16.0cm⁻¹
To a cooled (0 °C) solution of allylic alcohol 495 (0.10 g, 0.145 mmol) in THF (1 mL) was added OsO₄ (0.04 M solution in H₂O, 0.049 g, 2.10 x 10⁻³ mmol). The reaction was maintained at 0 °C for 10 min before addition of NaIO₄ (0.19 g, 0.087 mmol). The reaction was allowed to warm to 20 °C over 12 hr, whereupon distilled water (1 mL) was added and the reaction extracted using diethyl ether (4 X 2 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated in vacuo. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (10:1) as eluent gave 0.0687 g (68%) of aldol 496 as a clear oil.

[α]₀: +12.60 ° (c 1, MeOH).

IR (neat film): 3482 (m), 2932 (s), 2857 (s), 2063 (w), 1720 (s), 1612 (m), 1514 (s), 1466 (m), 1410 (m), 1365 (w), 1301 (w), 1250 (s), 1175 (m), 1107 (s), 1037 (m), 955 (m), 833 (s), 778 (s), 712 (w) cm⁻¹.

¹H NMR (500 MHz in CD₃OD): δ 0.09 (s, 3H), 0.13 (s, 3H), 0.14 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H), 0.98 (s, 9H), 1.90-1.97 (m, 2H), 2.00-2.05 (m, 2H), 2.64 (dd, J=2.9, 15.5, 1H), 2.83 (dd, J = 1.9, 15.5, 1H), 3.24-3.28 (m, 1H), 3.30 (s, 6H), 3.34-3.40 (m, 3H), 4.21-4.25 (m, 1H), 4.26 (s, 2H), 4.30 (s, 2H), 4.32-4.43 (m, 1H), 4.50 (s, 1H), 6.90 (d, J = 8.6 Hz, 4H), 7.17-7.31 (m, 4H), 9.89 (t, J = 2.6 Hz, 1H) ppm.
\textbf{Chapter 3 : Experimental}

\begin{equation}
\begin{align*}
\text{\textsuperscript{13}C NMR (125 MHz in C}_4\text{D}_2):} & \quad \delta 201.6, 159.9, 159.8, 130.6, 130.3, 129.7, 129.6, 128.5, 114.1, 114.0, \\
& \quad 75.1, 73.1, 72.4, 70.3, 69.4, 54.7, 54.6, 53.5, 45.5, 45.2, 26.2, 26.1, 18.3, -3.7, -3.8, -4.3, -4.5 \text{ ppm.}
\end{align*}
\end{equation}

HRMS (FAB, MNOBA matrix): for C\textsubscript{33}H\textsubscript{64}O\textsubscript{8}Si\textsubscript{6}Na (M + Na)\textsuperscript{+}, Calcd: 713.3881, Found: 713.3862.
To a cooled (0 °C) solution of aldol 496 (33.77 g, 48.9 mmol) in dry CH₂Cl₂ (405.40 mL) was added Et₃N (340.54 mL, 2.44 mol) and 4-dimethylaminopyridine (0.60 g, 4.89 mmol). Trifluoroacetic anhydride (69.02 mL, 489 mmol) was added dropwise (CAUTION EXOTHERM), with particular attention paid to the exclusion of air from the reaction. The reaction was heated to 45 °C for 72 hr whereupon it was cooled to room temperature. Diethyl ether (200 mL) was added followed by NaHCO₃ (40 g) and saturated NaHCO₃ solution (300 mL) added slowly and the reaction was then stirred for 90 min. The aqueous layer was separated and extracted with diethyl ether (4 X 500 mL). The combined organic layers were washed with water (2 X 400 mL), dried (MgSO₄), filtered, and concentrated in vacuo to yield a dark orange oil. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (12:1, then 8:1) as eluent gave 27.13 g (82%) of enal 494.

[α]D: −15.10° (c 1, MeOH).

IR (neat film): 2932 (s), 2894 (s), 2858 (s), 2062 (w), 1673 (s), 1613 (m), 1513 (m), 1465 (m), 1403 (w), 1363 (m), 1301 (w), 1250 (s), 1175 (m), 1106 (s), 1038 (m), 1007 (m), 833 (s), 777 (m) cm⁻¹.
Chapter 3: Experimental

$^1$H NMR (500 MHz in C$_6$D$_6$): $\delta$ 10.15 (d, $J = 7.8$ Hz, 1H), 7.21 (d, $J = 4.2$ Hz, 2H), 7.19 (d, 4.2 Hz, 2H), 6.80 (d, $J = 8.1$ Hz, 4H), 6.16 (d, $J = 7.8$ Hz, 1H), 4.30 (d, $J = 10.9$ Hz, 2H), 4.26 (d, $J = 11.6$ Hz, 2H), 3.99-4.03 (m, 2H), 3.37 (dd, $J = 9.4$, 5.1 Hz, 1H), 3.33 (dd $J = 9.4$, 5.5, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 3.26 (dd, $J = 6.2$, 3.7 Hz, 1H), 3.24 (dd, $J = 5.7$, 3.3 Hz 1H), 2.89 (dd, $J = 13.1$, 8.4 Hz, 1H), 2.68 (dd, $J = 13.1$, 3.7 Hz, 1H), 2.54 (dd, $J = 13.2$, 4.0, 1H), 2.29 (dd, $J = 13.3$, 7.8, 1H), 0.94 (s, 9H), 0.92 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H) ppm.

$^{13}$C NMR (125 MHz in C$_6$D$_6$): $\delta$ 190.4, 159.9, 159.8, 158.4, 133.2, 130.6, 130.5, 129.7, 129.6, 128.5, 128.3, 114.2, 114.1, 74.3, 74.2, 73.3, 73.2, 70.8, 70.7, 54.8, 43.9, 36.7, 26.1, 26.0, 18.3, 18.2, -4.3, -4.5, -4.6 ppm.

HRMS (FAB, MNOBA matrix): for C$_{33}$H$_{60}$O$_7$Si$_2$Na (M + Na)$^+$, Calcd: 695.3775, Found: 695.3765.
00/01/06 11:18 ft
SCAN: 64 scans, 16.0 cm⁻¹, flat
 Allylic alcohol 497

To a cooled (-78 °C) solution of enal 494 (22.18 g, 33.0 mmol) in dry CH₂Cl₂ was added DIBAL-H (1.5 M in toluene, 24.19 mL, 36.2 mmol) dropwise. The reaction was maintained at -78 °C for a further 75 min before it was quenched by dropwise addition of an aqueous solution of Rochelle salt (10% w/v, 300 mL). The reaction was allowed to warm to 20 °C and stirred vigorously until the organic and aqueous phases were easily separable. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (4 X 300 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo to yield an orange oil. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (12:1, then 8:1) as eluent gave 21.04 g (95 %) of allyl alcohol 497 as an orange oil.

\[ \alpha \]₀: +6.87 ° (c 1, MeOH).

**IR (neat film):** 3451 (m, broad), 2932 (s), 2857 (s), 2710 (w), 2548 (w), 2064 (w), 1880 (w), 1613 (s), 1588 (m), 1513 (s), 1465 (s), 1363 (m), 1301 (m), 1249 (s), 1175 (m), 1107 (s), 1037 (s), 832 (s), 777 (m), 667 (w) cm⁻¹.
$^1$H NMR (500 MHz, in $C_6D_6$): $\delta$ 7.23 (d, $J = 6.0$ Hz, 4H), 6.81 (d, $J = 6.5$ Hz, 4H), 5.72 (t, 6.9 Hz, 1H), 4.34 (d, $J = 11.6$ Hz, 2H), 4.31 (d, 11.6 Hz, 2H), 4.04-4.18 (m, 4H), 3.35-3.41 (m, 3H), 3.31 (d, $J = 9.6$, 5.2 Hz, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.43-2.55 (m, 3H), 2.26 (dd, $J = 13.6$, 7.6 Hz, 1H), 1.75 (broad t, 1H), 1.00 (s, 9H), 0.98 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H) ppm.

$^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$ 159.8, 159.7, 136.6, 131.0, 130.9, 130.7, 129.6, 129.5, 128.5, 128.3, 114.1, 114.0, 74.7, 74.6, 73.3, 73.1, 70.9, 70.7, 58.9, 54.7, 42.6, 35.9, 26.2, 26.1, 18.4, -4.1, -4.3, -4.4, -4.5 ppm.

HRMS (FAB, MNOBA matrix): for $C_{37}H_{62}O_{13}Si_2Na$ (M + Na)$^+$, Calcd: 697.3932, Found: 697.3928.
V-MH-97-COL (IN C6D6)
CARBON
V-MH-97-COL (IN C6D6)
COSY

TBSO

OH

OTBS

OPMB

ppm

0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

ppm

0 1 2 3 4 5 6 7
To a solution of allylic alcohol 497 (11.60g, 17.2 mmol) in THF (57.28 mL) at room temperature, was added TBAF (1.0 M in THF, 41.25 mL, 41.2 mmol) in a single portion. The reaction was stirred at 20 °C for 24 hrs, whereupon solvents were removed in vacuo. The resultant thick orange crude residue was silicated and purified using flash chromatography (SiO$_2$) with hexanes-ethyl acetate (1.5:1, then neat ethyl acetate) as eluent to give 5.97 g (77 %) of triol 493 as an orange oil.

$[\alpha]_D^0: +1.29^\circ$ (c 1, MeOH).

IR (neat film): 3383 (s, broad), 3001 (w), 2908 (s), 2863 (s), 2059 (w), 1887 (w), 1612 (s), 1513 (s), 1459 (m), 1361 (m), 1301 (m), 1247 (s), 1176 (m), 1098 (s), 1034 (s), 821 (m), 758 (w) cm$^{-1}$.

$^1$H NMR (500 MHz in C$_6$D$_6$): $\delta$ 7.20 (d, $J = 8.6$ Hz, 4H), 6.81 (d, $J = 8.6$ Hz, 2H), 5.83 (t, $J = 7.2$ Hz, 1H), 3.31 (s, 4H), 4.21 (dd, $J = 7.9$, 12.0 Hz, 1H), 3.93-4.05 (m, 4H), 3.62 (broad s, 1H), 3.51 (broad s, 1H), 3.27-3.35 (m, 4H), 3.30 (s, 6H), 2.43 (dd, $J = 9.9$, 13.7 Hz, 1H), 2.22 (dd, $J = 2.4$, 14.6 Hz, 1H), 2.09 (dd, $J = 9.5$, 14.6, 1H), 2.05 (dd, $J = 2.6$, 11.0 Hz, 1H) ppm.
$^{13}$C NMR (125 MHz in C$_6$D$_6$): 159.8, 137.3, 130.8, 130.7, 129.7, 129.6, 128.3, 114.1, 74.6, 74.5, 73.2, 73.1, 69.1, 68.1, 58.1, 54.8, 41.0, 35.3 ppm.

HRMS (FAB, MNOBA matrix): for C$_{25}$H$_{30}$O$_2$Na (M + Na)$^+$, Calcd: 469.2202, Found: 469.2221.
V-MH-99-COL (IN C6D6)
HMOC

OH
HO OH

PMBO

PMBO
To a solution of triol 493 (8.76 g, 19.6 mmol) in dry CHCl₃ (146 ml) at room temperature, was added activated MnO₂ (50.58g, 589 mmol) in a single portion. The black solution was stirred under a nitrogen atmosphere for 48 hr before the reaction was filtered through a thin CELITE™ pad. The cake was washed with CH₂Cl₂ (3 X 100 mL) and the filtrates combined. Solvents were removed in vacuo to yield a mild amber oil. Purification using flash chromatography (SiO₂) with hexanes-ethyl acetate (1:1) as eluent gave 7.71 g (89 %) α,β-unsaturated lactone 482 as mild amber oil.

\[ \alpha \beta \text{-Unsaturated lactone 482} \]

\[
\begin{array}{c}
\text{PMBO} \quad \text{HO} \\
\quad \quad \quad \text{OPMB}
\end{array}
\]

VII-MH-28-COL

\[ \text{IR (neat film): } 3430 \text{ (m, broad), } 3064 \text{ (w), } 3033 \text{ (w), } 3000 \text{ (m), } 2934 \text{ (m), } 2908 \text{ (m), } 2862 \text{ (m), } 2837 \text{ (m), } 2122 \text{ (w), } 2057 \text{ (w), } 1888 \text{ (w), } 1713 \text{ (s), } 1639 \text{ (w), } 1612 \text{ (m), } 1585 \text{ (w), } 1514 \text{ (s), } 1464 \text{ (m), } 1421 \text{ (w), } 1389 \text{ (w), } 1366 \text{ (m), } 1302 \text{ (m), } 1248 \text{ (s), } 1175 \text{ (m), } 1094 \text{ (s), } 1033 \text{ (s), } 935 \text{ (w), } 820 \text{ (m), } 758 \text{ (w), } 734 \text{ (w) } \text{cm}^{-1}. \]

\[ \text{H NMR (500 Mhz in } \text{C}_6\text{D}_6): \delta 7.71 \text{ (d, } J = 8.7 \text{ Hz, } 2\text{H), } 7.15 \text{ (d, } J = 8.5 \text{ Hz, } 2\text{H), } 6.81 \text{ (d, } J = 8.6 \text{ Hz, } 2\text{H), } 6.79 \text{ (d, } 8.6 \text{ Hz, } 2\text{H), } 5.84 \text{ (s, } 1\text{H), } 4.32 \text{ (d, } J = 11.6 \text{ Hz, } 2\text{H), } 4.27 \text{ (d, } J = 11.6 \text{ Hz, } 2\text{H), } 4.23 \text{ (s,}
\]

\[ \text{]} \]
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2H), 4.14-4.16 (m, 1H), 3.64-3.79 (m, 1H), 3.35 (dd, J = 4.9, 1.8 Hz, 2H), 3.33 (s, 3H), 3.31 (s, 3H), 3.10-3.11 (m, 1H), 2.38 (d, J = 4.3 Hz, 1H), 2.17 (dd, 13.4, 10.1 Hz, 1H), 1.82-1.95 (m, 3H) ppm.

\(^{13}\text{C NMR (125 MHz in C}_2\text{D}_6\)): \(\delta\) 163.8, 160.0, 159.9, 157.0, 130.5, 130.4, 129.7, 129.6, 128.3, 127.9, 118.0, 114.2, 114.1, 76.0, 73.8, 73.3, 73.2, 71.0, 68.3, 54.9, 54.8, 40.6, 30.5 ppm.

V-MH-100-COL (IN C6D6)
HMOC

{Chemical shift diagram with peaks and labels from 7.5 to 160 ppm on the x-axis and from 0 to 30 ppm on the y-axis. Figure includes a molecular structure diagram in the upper right corner.}
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Triol 503

![Triol 503 structure](VII-MH-40-COL)

To a cooled (-15 °C) solution of α,β-unsaturated lactone 482 (3.89 g, 9.41 mmol) in dry CH₂Cl₂ was added anisole (44.84 mL, 301 mmol) then trifluoroacetic acid (28.81 mL, 376 mmol) in a steady stream. The amber solution was stirred at -15 °C for 4 hr. On completion, solvents were removed in vacuo to yield a purple liquid containing the desired product and anisole. The crude liquid was azeotroped from toluene (4 X 10 mL) under reduced pressure to remove excess anisole. Purification using flash chromatography (SiO₂) with neat ethyl acetate then dichloromethane-methanol (6:1) as eluent gave 1.33 g (70 %) α,β-unsaturated lactone 503 as mild amber oil.

[α]₀: +115.05 ° (c 1, MeOH).

IR (neat film): 3372 (s, broad), 2931, (m), 2886 (m), 1704 (s), 1682 (s), 1439 (m), 1402 (m), 1393 (m), 1263 (s), 1181 (w), 1154 (w), 1091 (s), 1031 (s), 986 (w), 926 (w), 874 (w), 829 (w), 739 (w), 702 (w) cm⁻¹.

¹H NMR (500 MHz in CD₃OD): δ 5.81 (s, 1H), 4.39-4.45 (m, 1H), 3.76-3.82 (m, 1H), 3.71 (dd, J = 12.2, 3.8 Hz, 1H), 3.64 (dd, J = 12.2, 4.9 Hz, 1H), 3.45 (ddd, J = 18.8, 13.0, 5.4 Hz, 2H), 2.48-2.59 (m, 2H), 2.34 (dd, J = 18.8, 3.9 Hz, 1H), 2.29 (dd, J = 14.4, 9.3 Hz, 1H) ppm.
$^{13}$C NMR (125 MHz in CD$_3$OD): $\delta$ 167.5, 161.9, 117.4, 79.8, 70.7, 67.1, 64.2, 41.8, 30.5 ppm.

To a cooled (0 °C) solution of triol 503 (0.61 g, 3.01 mmol) in acetone (8.35 mL, 0.36 M) was added 1% w/v iodine in acetone solution via syringe (1 mL). The reaction was allowed to warm to room temperature over 1 hr and stirred for 3 hours at this temperature. The reaction was quenched by dropwise addition of a saturated, aqueous solution of sodium thiosulfate while stirring vigorously, until no iodine colour persisted and the reaction was clear. The reaction was then extracted with Et₂O (4 X 20 mL) and the organic extracts combined, dried (MgSO₄), filtered and concentrated in vacuo to yield a mild amber oil. The crude residue was then purified using flash chromatography (SiO₂) with hexanes-ethyl acetate (1:1) then neat ethyl acetate as eluent to give 0.55 g (75%) of isopropylidene acetal 505 as a mild amber oil.

**IR (neat film):** 3393 (s, broad), 2986 (m), 2936 (m), 2882 (m), 1707 (s), 1641 (m), 1455 (w), 1420 (m), 1381 (s), 1371 (s), 1255 (s), 1155 (m), 1062 (s), 982 (m), 927 (w), 850 (m), 821 (m), 789 (w), 738 (w), 628 (w), 515 (w) cm⁻¹.

**¹H-NMR (500 MHz in CDCl₃):** δ 5.82 (s, 1H), 4.51 (ddd, J = 3.7, 8.4, 11.9 Hz, 1H), 4.26 (dt, J = 6.2, 12.2 Hz, 1H), 4.09 (dd, J = 6.0, 8.2 Hz, 1H), 3.87 (d, J = 11.9 Hz, 1H), 3.71 (d, J = 11.5 Hz, 1H), 3.57 (dd, J = 6.6, 8.2 Hz, 1H), 2.64 (dd, J = 12.3, 17.9 Hz, 1H), 2.48 (s, 1H), 2.46 (s, 1H), 2.27 (dd, J = 3.9, 17.9 Hz, 1H), 1.67 (broad s, 1H), 1.39 (s, 3H), 1.32 (s, 3H) ppm.
\(^{13}\)C-NMR (125 MHz in CDCl\(_3\)): \(\delta\) 164.4, 157.2, 148.1, 117.1, 109.8, 77.7, 77.2, 73.2, 69.1, 63.8, 40.7, 29.4, 29.9, 25.5 ppm.

HRMS (MNOBA matrix): for C\(_{18}\)H\(_{26}\)O\(_3\)Na (M+Na), Calcd: 243.1232, found 243.1240.
Current Data Parameters
NAME Oct26-1999
EXPND 10
PROCNO 1

F2 - Acquisition Parameters
DATE_ 991026
TIME 17.55
INSTRUM铵300
Proben 5 мм QNP III
PULPROG 2q30
TD 65536
SOLVENT CDC13
RD 20
NS 128
DS 0
SW1 6250.000 Hz
FIDRES 0.095367 Hz
AG 5.2429299 sec
RG 1024
OM 0.000000 sec
DE 114.29 Hz
TR 300.00 sec
TL 1 dB
SI 2.000000 sec
P1 7.25 usec
SFO1 299.8751747 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 32760
SF 299.8727995 MHz
DE 0
SSB 0
LB 0.30 Hz
SB 0
PC 1.00
SR 2799.56 Hz

1D NMR plot parameters
CX 30.00 cm
FPM 9.000 ppm
F1 2698.86 Hz
F2 1.000 ppm
F2 -299.87 Hz
PPCM 0.33333 ppm/cm
HZCM 29.9562 Hz/cm
V-MH-40-COL
ISOPROPYLIDINE ACETAL????
gradcosy.ucl CDCl3 v k Jh 56

Current Data Parameters
NAME: Oct26-1999
EXPN: 12
PROCJ: 1

F2 - Acquisition Parameters
Data: 990/25
Time: 26.12
INSHRM: 90000
FREQNO: 5 kHz QFF, 360 MHz QFF
FIELD: 29.485
SOLVNT: CDCl3
NO: 2
US: 16
SNR: 2232.14 Hz
FIQSES: 10009.13 Hz
AQ: 0.0000000 sec
NS: 512
DV: 2200.000 usec
DE: 127.14 usec
EC: 306.6 Hz
P1: 1000.000 usec
L21: 100
H1: 0.0000000 sec
P2: 72.75 usec
D: 0.0000000 sec
P3: 72.75 usec
L13: 0.0000000 sec
SFO: 293.8400000 MHz
WS: 1.0024147 Hz
M0: 0.0000000 sec

F1 - Acquisition parameters
NS: 127
SC: 298.074 MHz
F1QSES: 17.4305 Hz
ST: 1.444 ppm

F2 - Processing parameters
SI: 1024
SI: 298.072739 MHz
SM: 512
SB: 0
LB: 0.00 Hz
GB: 1.46
SR: 273.91 Hz

F1 - Processing parameters
SI: 1024
MC: 0
ST: 298.072739 MHz
MO: 512
SB: 0
LB: 0.00 Hz
GB: 0

2D NMR plot parameters
C3: 20.00 cc
C2: 20.00 cc
F2P: 20.00 cc
F2L: 239.520 ppm
F1P: 0.495 ppm
F1L: 148.70 Hz
F1D: 920 ppm
F2D: 239.520 ppm
F1H: 0.495 ppm
F1H: 148.70 Hz
F1NH: 0.3723 ppm/cm
F1NHC: 111.3958 Hz/cm
F1NH: 0.3723 ppm/cm
DEFAULT.IRS:
Date: 07/02/01  Time: 13:59:49  NScans: 16
Type: HYPER IR  User: A20923500085 Shimadz  Detector: standard
Abscissa: 1/cm  Ordinate: %T  Apodization: Happ
Min: 400.20  Max: 3999.61  Range: 1/cm
Ndp: 7466  Data Interval: 0.48217  Resolution: 1.0
Gain: auto  Aperture: auto  Mirror Speed: 2.8(low)
To a solution of triol 503 (1.73 g, 8.56 mmol) in dry ethyl acetate (30 mL) was added cyclohexanone (8.87 mL, 85.6 mmol) in a steady stream. Finally, p-toluenesulfonic acid (0.16 g, 0.86 mmol) was added in a single portion and the reaction stirred at room temperature for 6 hrs. The reaction was quenched by dropwise addition of saturated NaHCO₃ solution (20 mL) and then extracted using ethyl acetate (4 X 30 mL). The combined organic phases were then dried (MgSO₄), filtered and concentrated in vacuo to yield an amber liquid. The crude reaction mixture was azeotroped from toluene (4 X 10 mL) to remove majority of cyclohexanone. Purification using flash chromatography (SiO₂) with neat hexanes, then hexanes-ethyl acetate (1:1) then neat ethyl acetate as eluent gave 2.41 g (100 %) of cyclohexylidene acetal 506 as a mild amber oil.

\[ \alpha \] : +100.00° (c 1, MeOH).

IR (neat film): 3428 (s, broad), 2936 (s), 2861 (s), 1713 (s), 1694 (s), 1641 (m), 1425 (w), 1388 (m), 1362 (m), 1335 (w), 1282 (m), 1256 (m), 1182 (w), 1166 (m), 1145 (w), 1102 (s), 1039 (m), 981 (w), 937 (m), 926 (m), 908 (w), 876 (w), 850 (m), 826 (w), 773 (w), 732 (w) cm⁻¹.

\(^1\)H NMR (500 MHz in CDCl₃): δ 5.8 (s, 1H), 4.41-4.45 (m, 1H), 4.21 (quin, 1H), 4.02 (dd, \( J = 8.1, 6.0 \) Hz, 1H), 3.77 (dd, \( J = 12.3, 3.5 \) Hz, 1H), 3.66 (dd, \( J = 12.3, 4.9 \) Hz, 1H), 3.51 (dd, \( J = 8.0, 6.7 \) Hz, 1H), 3.20 (s, 1H), 2.55 (dd, \( J = 13.2, 17.7 \) Hz, 1H), 2.37-2.45 (m, 2H), 2.26 (dd, \( J = 17.9, 3.9 \) Hz, 1.52 (s, 4H), 1.48 (s, 4H), 1.31 (m, 2H) ppm.
\(^{13}\)C NMR (125 MHz in CDCl\(_3\)): \(\delta\) 164.6, 157.6, 116.8, 110.1, 77.8, 72.8, 68.6, 68.5, 63.4, 40.7, 36.4, 34.7, 29.3, 24.8, 23.7, 23.6 ppm.

HRMS (FAB, MNOBA matrix): for C\(_{19}\)H\(_{28}\)O\(_3\)Na (M + Na)\(^+\), Calcd: 305.1365, Found: 305.1379.
To a stirred solution of cyclohexylidene acetal 506 (2.41 g, 8.56 mmol) in dry CH₂Cl₂ (33 mL) was added p-methoxybenzyl trichloroacetimidate (4.82 g, 71.1 mmol) and pyridinium p-toluenesulfonate (1.07 g, 4.27 mmol). After 8 hr at 20 °C the reaction was quenched by dropwise addition of saturated NaHCO₃ solution (20 mL) and extracted using ethyl acetate (4 X 50 mL). The organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo to yield amber slurry. Flash chromatography (SiO₂) of the crude residue (solvent gradient 6:1 to 1:1 hexanes: ethyl acetate) led to 3.42 g (99%) of 507 as a mild amber oil.

[α]₀: +82.29° (c 1, MeOH).

IR (neat film): 2935 (s), 2860 (s), 1716 (s), 1699 (s), 1641 (w), 1613 (m), 1586 (w), 1514 (s), 1463 (w), 1422 (w), 1389 (w), 1365 (m), 1331 (w), 1302 (w), 1173 (m), 1163 (m), 1101 (s), 938 (m), 910 (w), 848 (m), 822 (m), 775 (w), 733 (w), 670 (w) cm⁻¹

¹H NMR (500MHz, CDCl₃): 7.23 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.85 (s, 1H), 4.50-4.55 (m, 1H), 4.50 (d, J = 3.2 Hz, 2H), 4.21-4.26 (m, 1H), 4.06 (dd, J = 6, 8.1 Hz, 1H), 3.78 (s, 3H), 3.62-3.66 (m, 2H), 3.54 (dd, J = 6.6, 8.1, 1H), 2.35-2.58 (m, 4H), 1.58 (s, 4H), 1.54 (s, 4H), 1.37 (broad s, 2H) ppm.
"\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 164.3, 159.4, 157.0, 129.7, 129.4, 117.3, 113.8, 110.3, 76.0, 73.3, 73.0, 70.4, 68.8, 55.3, 40.8, 36.7, 35.0, 30.5, 25.0, 24.0, 23.8 ppm.

HRMS (FAB, MNOBA matrix): for C\(_{23}\)H\(_{30}\)O\(_4\)Na (M + Na)\(^+\), Calcd: 425.1940, Found: 425.1929."
V-MH-123-COL (IN CDCL3)
PROTON
V-MH-123-COL (IN CDCL3)
CARBON
V-MH-123-COL (IN CDCL3)  
DEPT135
V-MH-123-COL (IN CDCL3)
COSY
V-MH-123-COL (IN CDCL3)

HMOC

ppm

20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

OPMB

ppm
PERKIN ELMER

76.49-%T

OPMB

00/03/02 16:43 ft
SCAN: 15 scans, 2.0cm⁻¹, apod weak, flat
To a stirred solution of p-methoxybenzyl ether 507 (3.42 g, 8.49 mmol) in methanol (69 mL) was added CeCl₃·7H₂O (15.83 g, 42.5 mmol). The reaction was stirred for 40 min or until all of the solid had dissolved and a further 45 min thereafter. The reaction mixture was cooled to −20 °C and NaBH₄ added portionwise over 20 min and allowed to warm to 0 °C over 90 min. The reaction was quenched by dropwise addition of H₂O and stirred until gas evolution had ceased and extracted using ethyl acetate (4 × 100 mL). The combined organic extracts were dried using MgSO₄, filtered and concentrated in vacuo to give a clear oil. The crude residue was purified by SiO₂ flash chromatography (solvent gradient 2:1 , hexanes:ethyl acetate to neat ethyl acetate) to give diol 508 (3.34 g, 97 %) as a mild amber oil.

[α]₀: +10.75 ° (c 1, MeOH)

IR (neat film): 3395 (s, broad), 3070 (w), 3035 (w), 2994 (w), 2932 (s), 2863 (s), 2085 (w), 2003 (w), 1886 (w), 1740 (w), 1657 (w), 1616 (m), 1587 (w), 1512 (s), 1463 (m), 1428 (w), 1366 (m), 1331 (w), 1283 (w), 1248 (s), 1207 (w), 1172 (m), 1165 (m), 1103 (s), 1034 (s), 1010 (m), 934 (m), 844 (w), 823 (m), 774 (w), 764 (w), 740 (w), 706 (w) cm⁻¹.

¹H NMR (500 MHz in CDCl₃): δ 7.23 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.75 (t, J = 7.4 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.20-4.22 (m, 2H), 4.13 (dd, J = 8.1, 12.0 Hz, 1H), 4.02 (dd, J = 6.0, 8.0 Hz, 1H), 3.93 (dd, J = 7.0, 12.1 Hz, 1H), 3.87-4.01 (m, 1H), 3.79 (s,
3H), 3.51 (t, 7.8 Hz, 1H), 3.45 (dd, \( J = 3.7, 9.4 \) Hz, 1H), 3.35 (dd, \( J = 7.5, 9.3 \) Hz, 1H), 2.90 (broad s, 2H), 2.26-2.39 (m, 2H), 2.10 (dd, \( J = 3.0, 13.7 \) Hz, 1H), 1.58 (s, 4H), 1.54 (s, 4H), 1.52 (m, 2H) ppm.

\(^{13}\text{C} \) NMR (125 MHz in CDCl\(_3\)): \( \delta 195.4, 137.2, 129.8, 129.4, 129.3, 113.9, 109.7, 74.5, 74.0, 68.8, 67.8, 57.7, 55.3, 41.1, 36.6, 35.1, 34.5, 25.1, 24.0, 23.8 \) ppm.

HRMS (FAB, MNOBA matrix): for \( \text{C}_{23}\text{H}_{34}\text{O}_8\text{Na} \) (M + Na), Calcd: 429.2253, Found: 429.2260.
V-MH-126-COL (IN CDCl3)
PROTON

[Chemical structure image]

[Graph and chemical structure diagram]
00/03/15 13:43 ft
SCAN: 16 scans, 2.0cm⁻¹, apod weak, flat
Chapter 3: Experimental

 tert-Butyldiphenylsilyl ether 509

To a stirred solution of diol 508 (1.45g, 3.57 mmol) in dry DMF (24 mL) at 0 °C was added imidazole (0.36 g, 5.35 mmol) and TBDPSCI (0.93 mL, 3.57 mmol) which was added dropwise over 35 min. The reaction was maintained at 0 °C for a further 30 min, before dropwise addition of saturated NaHCO₃ solution. The reaction mixture was extracted four times with diethyl ether and the organic extracts combined, dried (MgSO₄), filtered and concentrated in vacuo to yield an amber oil. Purification of the residue by SiO₂ flash chromatography (solvent gradient 8:1 to 2:1 hexanes:ethyl acetate) gave 2.17 g (94 %) of silyl ether 509 as a mild amber oil.

[α]₀: +10.89 ° (c 1, MeOH).

IR (neat film): 3464 (m, broad), 3068 (w), 3047 (w), 3013 (w), 2999 (w), 2936 (s), 2894 (s), 2860 (s), 1966 (w), 1890 (w), 1827 (w), 1779 (w), 1661 (w), 1613 (m), 1585 (w), 1514 (s), 1471 (m), 1463 (m), 1389 (w), 1363 (m), 1331 (w), 1302 (w), 1282 (w), 1249 (s), 1164 (m), 1112 (s), 1038 (m), 998 (w), 937 (m), 846 (w), 823 (m), 776 (w), 703 (s), 689 (m), 613 (w) cm⁻¹.

¹H NMR (500 Mhz in CDCl₃): 7.37 (d, J = 6.9 Hz, 2H), 7.35-7.43 (m, 6H), 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5, 2H), 5.58 (t, 6.4 Hz, 1H), 4.41 (s, 2H), 4.16-4.26 (m, 3H), 4.00 (dd, J = 6.0, 7.9 Hz, 1H), 3.79-3.82 (m, 1H), 3.78 (s, 3H), 3.52 (t, 7.54 Hz, 1H), 3.34 (dd, J = 4.1, 9.5, 1H), 3.28 (dd, J = 6.4, 9.4, 1H), 2.71 (broad s, 1H), 2.37 (dd, J = 7.1, 14.3, 1H), 2.15-2.23 (m, 2H), 2.10 (dd, J = 4.9, 13.8, 1H), 1.60 (s, 4H), 1.57 (s, 4H), 1.38 (broad s, 2H), 1.04 (s, 9H) ppm.
$^{13}$C NMR (125 MHz in CDCl$_3$): 159.2, 135.5, 135.0, 133.7, 133.6, 130.1, 129.6, 129.4, 129.3, 127.8, 127.7, 127.6, 113.7, 109.5, 109.4, 74.3, 73.6, 72.9, 68.8, 68.7, 60.3, 55.2, 41.2, 36.6, 35.1, 26.7, 25.1, 23.9, 23.8, 19.1 ppm.

HRMS (FAB, MNOBA matrix): for C$_{39}$H$_{62}$O$_6$SiNa (M + Na)$^+$, Calcd: 667.3431, Found: 667.3440.
V-MH-128-COL (IN CDCL3)
PROTON

OTBDPS
OH
OPMB

8 7 6 5 4 3 2 1 0 ppm
V-MH-128-COL (IN CDCL3)
DEPT135
V-MH-128-COL (IN CDCL3)
COSY

[Chemical structure diagram]

[Graph with ppm scale]
V-MH-128-COL (IN CDCL3)
HMOC

OTBDPS

OH

OPMB
00/03/15 14:14 ft
SCAN: 64 scans, 2.0cm⁻¹, apod weak
Triol 510

To a stirred solution of silyl ether 509 (2.35 g, 3.64 mmol) in dry CH₂Cl₂ (24 mL) at -78 °C was added 1,3-propanedithiol (6.09 mL, 36.4 mmol). BF₃·Et₂O (approx 48% w/v in Et₂O, 0.14 mL, 0.364 mmol) was added to the reaction in a dropwise manner and the reaction was allowed to warm slowly to -10 °C over 65 min. TLC analysis of the reaction was carried out every five minutes to ensure the product was not degraded. The reaction was quenched by addition of solid NaHCO₃ (approx 2 g) followed by saturated NaHCO₃ (20 mL) solution and extracted with EtOAc (4 X 40 mL). The combined organic extracts were then dried (MgSO₄), filtered and concentrated in vacuo to give a foul smelling liquid. The crude product was purified by SiO₂ flash chromatography (solvent gradient 4:1 hexanes:EtOAc to 2:1 Et₂O:EtOAc) to give 1.76 g (86%) of triol 510.

\[\alpha\]D: +10.59° (c 1, MeOH).

IR (neat film): 3388 (s, broad), 3071 (w), 3015 (w), 3001 (w), 2956 (s), 2934 (s), 2890 (s), 2853 (s), 2103 (w), 2059 (w), 1964 (w), 1890 (w), 1831 (w), 1780 (w), 1662 (w), 1611 (m), 1589 (w), 1515 (m), 1471 (m), 1436 (m), 1427 (m), 1390 (w), 1381 (w), 1302 (w), 1250 (m), 1111 (s), 1089 (s), 1037 (m), 942 (w), 824 (m), 780 (w), 743 (m), 706 (s), 610 (w) cm⁻¹.

¹H NMR (500 MHz in CDCl₃): 7.65 (d, \(J = 6.0\) Hz, 4H), 7.34-7.42 (m, 6H), 7.18 (d, \(J = 8.6\) Hz, 2H), 6.84 (d, \(J = 8.6\) Hz, 2H), 5.61 (t, \(J = 7\) Hz, 1H), 4.40 (s, 2H), 4.18 (ddd, \(J = 6.5, 12.6, 21.3\) Hz, 2H), 3.90 (s, 3H), 3.80 (s, 2H), 3.70 (s, 2H), 3.60 (s, 3H), 3.50 (s, 3H), 3.40 (s, 3H), 3.30 (s, 3H), 3.20 (s, 3H), 3.10 (s, 3H), 3.00 (s, 3H), 2.90 (s, 3H), 2.80 (s, 3H), 2.70 (s, 3H), 2.60 (s, 3H), 2.50 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.80 (s, 3H), 0.70 (s, 3H), 0.60 (s, 3H), 0.50 (s, 3H), 0.40 (s, 3H), 0.30 (s, 3H), 0.20 (s, 3H), 0.10 (s, 3H), 0.00 (s, 3H).
3.73-3.82 (m, 2H), 3.78 (s, 3H), 3.58 (dd, $J = 3.2$, 11.1 Hz, 1H), 3.43 (dd, $J = 4.0$, 7.0 Hz, 1H) 3.31 (dd, $J = 4.0$, 9.5 Hz, 1H), 3.23 (dd, $J = 2.4$, 7.0 Hz, 1H), 1.99-2.19 (m, 4H), 1.01 (s, 9H) ppm.

$^{13}$C-NMR (125 MHz, CDCl$_3$): 159.3, 135.6, 135.1, 133.6, 130.2, 129.9, 129.7, 129.6, 129.3, 127.7, 113.8, 73.7, 73.0, 70.0, 69.1, 66.4, 60.3, 55.3, 41.3, 34.3, 26.8, 19.1 ppm.

HRMS (FAB, MNOBA matrix): for C$_{33}$H$_{44}$O$_2$SiNa (M + Na)$^+$, Calcd: 587.2805, Found: 587.2822.
V-MH-157-COL (IN CDCL3)
COSY

- OTBDPS
- OH
- OH
- OPMB

ppm

- 1.0
- 1.5
- 2.0
- 2.5
- 3.0
- 3.5
- 4.0
- 4.5
- 5.0
- 5.5
- 6.0
- 6.5
- 7.0
- 7.5
- 8.0

8 7 6 5 ppm
V-MH-157-COL (IN CDCL3)

HMOC

OTBDPS

OH OH

HO OPMB
00/03/15 13:14 ft
SCAN: 16 scans, 2.0cm⁻¹, apod weak, flat, smooth
Hydroxymesylate 514

To a cooled (0 °C) solution of triol 510 (2.24 g, 3.97 mmol) and collidine (3.21 mL, 39.7 mmol) in dry CH₂Cl₂ (79 mL) was added methanesulfonyl chloride (0.34 mL, 4.36 mmol) in a slow stream. The reaction was maintained at 0 °C for 9 hr before addition of H₂O (30 mL) and separation of the organic layer and extraction of the aqueous layer with CH₂Cl₂ (4 X 20 mL). The organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo to yield a mild amber oil. The crude residue was azeotroped from toluene (2 X 10 mL) to remove collidine and purified by SiO₂ flash chromatography to give 2.11 g (83 %) of hydroxymesylate 514 as a mild amber oil.

[α]₀: +3.18° (c 1, MeOH).

IR (neat film): 3389 (s, broad), 3070 (w), 3046 (w), 3011 (w), 2933 (s), 2884 (m), 2857 (s), 1692 (w), 1612 (m), 1635 (w), 1514 (s), 1465 (m), 1428 (m), 1381 (w), 1353 (s), 1309 (w), 1249 (s), 1174 (s), 1111 (s), 1034 (m), 926 (m), 994 (m), 964 (m), 823 (m), 742 (w), 705 (s) cm⁻¹.

¹H NMR (500 MHz in CDCl₃): δ 7.65 (d, J = 6.5 Hz, 4H), 7.33-7.46 (m, 6H), 7.18 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.63 (t, J = 6.4 Hz, 1H), 4.40 (s, 2H), 4.00-4.05 (m, 1H), 3.78 (s, 3H), 3.73-3.78 (m, 1H), 3.31 (dd, J = 3.7, 9.4 Hz, 1H), 3.21 (dd, J = 7.2, 9.4, 1H), 3.03 (s, 3H), 2.81 (broad s, 2H), 2.25 (dd, J = 2.9, 14.0 Hz, 1H), 2.17 (dd, J = 9.4, 14.0, 1H), 3.98-2.09 (m, 2H), 1.02 (s, 9H) ppm.
$^{13}$C NMR (125 MHz in CDCl$_3$): $\delta$ 159.3, 135.6, 134.0, 133.5, 131.0, 129.8, 129.7, 129.4, 127.7, 113.8, 96.1, 73.5, 73.1, 73.0, 68.0, 67.6, 60.2, 55.2, 41.4, 37.5, 34.2, 26.8, 19.1 ppm.

HRMS (FAB, MNOBA matrix): for C$_{34}$H$_{46}$O$_6$SSiNa (M + Na)$^+$, Calcd: 665.2580, Found: 665.2560.
V-MH-159-COL (IN CDCL3)
PROTON

![Chemical Structure](image)

ppm
00/03/15 10:54 ft
SCAN: 64 scans, 2.0cm⁻¹, apod weak, flat, smooth
To a cooled (0 °C) solution of hydroxymesylate 514 (1.00 g, 1.56 mmol) and imidazole (0.01 g, 0.16 mmol) in dry THF (20 mL) was added NaH (60% suspension in mineral oil, 0.12 g, 3.11 mmol) portionwise. The reaction was maintained at 0 °C with stirring for 12 min and then quenched by dropwise addition of NH₄Cl solution (1% w/v in H₂O, 20 mL) and then Et₂O (40 mL). The organic layer was separated and the aqueous phase multiply extracted with Et₂O (4 X 20 mL). The combined organic layers were washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes:ethyl acetate) to give 0.84 g (99 %) of epoxy alcohol 441 as a clear oil.

[α]₀: +10.50 ° (c 1, MeOH).

IR (neat film): 3452 (m, broad), 3070 (w), 3047 (w), 2998 (w), 2961 (s), 2931 (s), 2881 (s), 2857 (s), 1661 (w), 1613 (m), 1587 (w), 1514 (s), 1472 (m), 1428 (s), 1390 (w), 1361 (m), 1249 (s), 1173 (m), 1112 (s), 1037 (s), 998 (m), 938 (w), 823 (s), 789 (w), 741 (m), 704 (s), 689 (m), 613 (w) cm⁻¹.

¹H NMR (500 MHz in CDCl₃): δ 7.66 (d, J = 7.8 Hz, 4H), 7.34-7.39 (m, 6H), 7.18 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz), 5.64 (t, J = 6.6 Hz, 1H), 4.40 (s, 2H), 4.23 (dd, J = 12.7, 6.6 Hz, 1H), 4.16 (dd,
\[ J = 12.7, 6.6 \text{ Hz, 1H}, 3.78 \text{ (s, 3H), } 3.76-3.78 \text{ (m, 1H), } 3.33 \text{ (dd, } J = 9.5, 4.1 \text{ Hz, 1H), } 3.26 \text{ (dd, } J = 9.4, 6.5 \text{ Hz, 1H), } 2.94-2.98 \text{ (m, 1H), } 2.74 \text{ (dd, } J = 8.9, 4.9 \text{ Hz, 1H), } 2.56 \text{ (s, 3H), } 3.45 \text{ (dd, } J = 5.0, 2.7 \text{ Hz, 1H), } 2.17-2.30 \text{ (m, 3H), } 2.09 \text{ (dd, } J = 13.8, 4.8 \text{ Hz, 1H), } 1.02 \text{ (s, 9H) ppm.}

^{13}C \text{ NMR (125 MHz in CDCl}_3): \delta 159.2, 135.6, 135.0, 133.6, 133.5, 130.1, 129.6, 129.3, 129.1, 127.7, 113.8, 73.7, 73.0, 68.8, 60.3, 55.3, 51.2, 46.9, 40.0, 35.2, 26.8, 19.1 \text{ ppm.}

HRMS (FAB, MNOBA matrix): for C_{30}H_{42}O_2SiNa (M + Na)^+, Calcd: 569.2699, Found: 569.2703.
V-MH-160-COL (IN CDCL3)
CARBON
00/03/02 16:17 ft
SCAN: 16 scans, 2.0cm⁻¹, apod weak, flat, smooth
To a stirred solution of δ-hydroxy epoxide, 441 (1.76 g, 3.22 mmol) in dry CH₂Cl₂ (52 mL) was added camphorsulfonic acid (0.08 g, 0.322 mmol) in a single portion. The reaction was stirred at room temperature for 40 min before being quenched by addition of saturated NaHCO₃ solution (20 mL). The organic layer was separated and the aqueous phase extracted further with Et₂O (4 X 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. Purification of the crude residue by SiO₂ flash chromatography (solvent gradient 3:1 to 2:1 Hexanes:Et₂O) gave 1.73 g (98%) of pyran 440 as a clear oil.

[α]ₐ₀: +6.20° (c 1, MeOH).

IR (neat film): 3445 (s, broad), 3070 (m), 3047 (w), 2993 (w), 2956 (s), 2934 (s), 2890 (s), 2853 (s), 2059 (w), 1963 (w), 1890 (w), 1831 (w), 1779 (w), 1670 (w), 1611 (m), 1589 (m), 1515 (s), 1471 (m), 1463 (m), 1427 (m), 1390 (w), 1360 (m), 1324 (w), 1302 (m), 1250 (s), 1177 (m), 1111 (s), 1088 (s), 1067 (s), 1037 (s), 942 (w), 846 (w), 824 (m), 780 (m), 743 (m), 690 (s), 611 (m) cm⁻¹.

^{1}H NMR (500 MHz in CDCl₃): δ 7.65 (d, J = 7.8 Hz, 4H, Arom), 7.32-7.41 (m, 6H, Arom), 7.21 (d, J = 8.6 Hz, 2H, Arom), 6.84 (d, J = 8.6 Hz, 2H, Arom), 5.45 (t, J = 6.4 Hz, 1H, C=CH⁻), 4.45 (s, 2H, c-C-CH₂-C bezylic ), 4.16-4.24 (m, 2H, C=CH-CH₂-OTBDPS), 3.78 (s, 3H, Arom-O-CH₃), 3.62 (dd, J =
Chapter 3: Experimental

11.4, 3.0 Hz, 1H, HO-C(H)H-C), 3.53 (dd, J = 11.4, 6.6 Hz, 1H, HO-CH(H)-C), 3.23-3.45 (m, 4H, PMBO-CH$_2$, -O-CH(CH$_2$OPMB)CH$_2$), C=C(CH$_3$)CH$_2$, 2.21 (d, J = 13.6 Hz, 1H, C=CC(H)H-), 1.98-2.03 (m, 2H, C=C(CH$_3$)CH$_2$), 1.64 (t, 12 Hz, 1H, C=CCH(H/-)), 1.02 (s, 9H, C-(CH$_3$)$_3$), ppm.

$^{13}$C NMR (125 MHz in CDCl$_3$): $\delta$ 159.2, 135.6, 135.5, 135.1, 133.8, 130.2, 129.6, 129.5, 129.3, 127.7, 127.6, 123.9, 113.8, 78.8, 78.5, 76.5, 73.0, 72.7, 65.8, 60.0 4, 55.3, 37.2, 31.3, 26.8, 19.1 ppm.

HRMS (FAB, MNOBA matrix): for C$_{33}$H$_{42}$O$_2$SiNa (M + Na)$^+$, Calcd: 569.2699, Found: 569.2683.
V-MH-165-COL (IN CDCL3)
CARBON

[Chemical structure diagram]

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
00/03/15 10:20 ft
SCAN: 16 scans, 2.0cm⁻¹, apod weak, flat


34. (a) For a valuable review of synthetic endeavours on the bryostatins prior to 1995 see: R.D. Norcross and I. Paterson, *Chem. Rev.*, **1995**, 95, 2041; (b) For a selective review of some later synthetic work, see Ref 4.


some later efforts in the glycosyl sulfone area, see: (d) S.V. Ley, B. Lygo, F. Sternfeld, and A. Wonnacott, Tetrahedron, 1986, 42, 4333; (e) C. Greck, P. Grice, S.V. Ley, and A. Wonnacott, Tetrahedron Lett., 1986, 27, 5277.


76. The first group to show the potential of the Sharpless AD for introducing the C(25) and C(26)-hydroxyls of the bryostatins was that of Hale (see section xx, Scheme yy).


# Abbreviations

Common Abbreviations Used in the Text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AD</td>
<td>Asymmetric dihydroxylation</td>
</tr>
<tr>
<td>AE</td>
<td>Asymmetric epoxidation</td>
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<tr>
<td>AIBN</td>
<td>α,α'-Azoisobutyronitrile</td>
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<td>All</td>
<td>Allyl</td>
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<tr>
<td>Alloc</td>
<td>Allyloxycarbonyl</td>
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<tr>
<td>9-BBN</td>
<td>9-Borabicyclononane</td>
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<td>BMS</td>
<td>Borane-methylsulphide complex</td>
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<td>BINAP</td>
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<td>tert-Butyloxycarbonyl</td>
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<td>BOM</td>
<td>Benzylolymethyl</td>
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<tr>
<td>BOP-Cl</td>
<td>Bis(2-oxo-3-oxazolidinyl)phosphinic chloride</td>
</tr>
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<td>Bn</td>
<td>Benzyl</td>
</tr>
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<td>Bz</td>
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<td>meta-Chloroperoxybenzoic acid</td>
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<td>Lithium diisopropylamide</td>
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<td>N-Methylmorpholine-N-oxide</td>
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<td>PTSA</td>
<td>p-Toluenesulfonic acid</td>
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<td>Sodium bis(2-methoxyethoxy)aluminium hydride</td>
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