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Late-stage fluorination of bridged scaffolds: Chemoselective generation of a CHF group at three positions of the bicyclo[3.3.1]nonane system

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ABSTRACT

Monofluorobicyclo[3.3.1]nonane derivatives were prepared by late-stage fluorination, often proceeding with control of stereochemistry. Introduction of fluorine at the 3-, 6- or 7-position was achieved chemoselectively, the bicyclo system being constructed by a tandem one-pot Michael-aldol annulation. The major conformer was deduced for each of the fluorobicyclo compounds prepared, each possessing a unique C—F orientation on a common rigid bridged scaffold that can be polysubstituted.

Introduction

The importance of organofluorine compounds in pharmaceuticals[1–6] and the recent applications of bicyclo compounds in medicinal chemistry[7–11] suggest the value of developing versatile protocols for the synthesis of fluorinated bicyclo compounds. While the fluorination of aromatic compounds has been extensively studied, the introduction of fluorine into alicyclic systems is more challenging and for most bicyclo systems little studied. Ideally, the set would comprise diversity in the orientation of the C—F bond since a contemporary objective is the selective generation of a sp^3-CHF unit[12] in which the single fluorine atom can alter the physicochemical and biological properties of a molecule. For example, the single replacement of methyl by fluoromethyl usually lowers the lipophilicity more than methyl to trifluoromethyl.[13] Other benefits of introducing fluorine into a scaffold include an increased ligand-protein binding which is commonly used to block undesirable drug metabolism.

Polysubstituted bridged compounds[14–17] have become increasingly important in medicinal chemistry (*e.g.* Fig. S1, Supplementary data).[8,18–21] Many bridged systems are highly saturated and contain chiral centres, two essential criteria for drug-likeness proposed by Lovering and co-workers.[18] A bicyclo compound may provide structural novelty,[22] act as a bioisostere of an aromatic ring,[23] or improve physicochemical properties, as in the bicyclo core of ledipasvir compared to the simpler piperidine analog.[24] Overall, bridged systems often exhibit superior pharmaceutical properties, including appreciable aqueous solubility, low toxicity, and structural diversity including stereochemistry.[8,18]

Bridged systems such as hyperforin, a member of the polyprenylated acylphloroglucinol (PPAP) family, can possess multiple therapeutic effects including anti-bacterial, anti-depressant, anti-viral and anti-cancer properties.[25–27] Inspired by the biosynthetic annulation of phloroglucinol derivatives, we examined their more saturated analogues, dihydroresorcinol derivatives, and reported their use in a tandem Michael-aldol annulation process that delivers densely-substituted bridged scaffolds (eq. i, Scheme 1).[28] Herein we report that highly substituted bridged fluoro compounds can be accessed *via* the late-stage fluorination[29,30] of bicyclo compounds, usually from only two one-pot processes.

Results and discussion

Introduction of fluorine into bridged compounds has often typically involved perfluorination with elemental fluorine.[31] In contrast, few monofluorobicyclo compounds are known, being mainly fluoroadamantane derivatives. A single example of γ-fluorination directed by an α-keto group on a bicyclo[2.2.1]pen-

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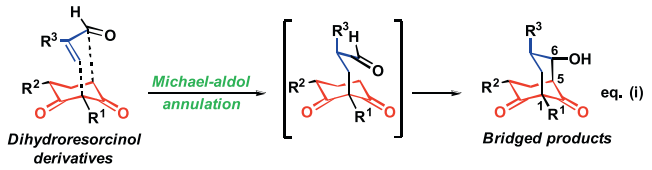
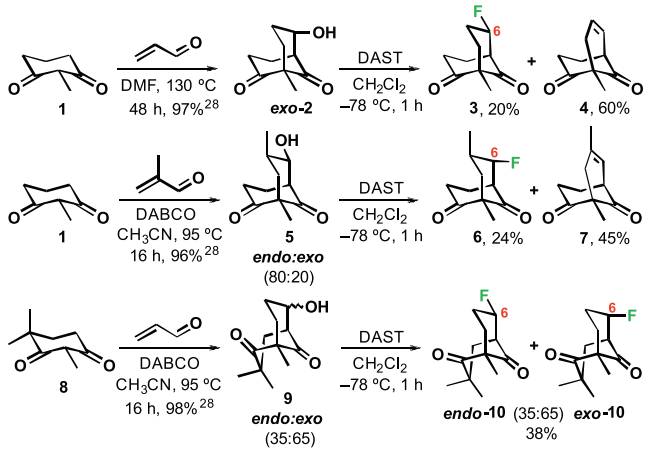


Scheme 1. Versatile route to polysubstituted bridged scaffolds *via* Michael-aldol annulation.[28]

tane has recently been reported.[12] The paucity of monofluorinated bridged compounds can be attributed in part to the polar repulsive forces and steric hindrance that often develop in attempts at the introduction of fluorine *via* a S_N2 transition state. The scope and limitations were summarised in the Richardson-Hough rules[32] formulated for the viability of S_N2 displacements of sulfonated derivatives of carbohydrates, which were recently further analysed by Hale and co-workers.[33,34] To the best of our knowledge, almost no fluorobicyclo[3.3.1]nonane derivatives with fluorine at any of the 2-, 4-, 6- or 8-positions (adjacent to a bridgehead position) or at the 3- or 7-positions have been described.[35]

Initially, reaction with DAST was chosen to assess whether displacement of an activated hydroxyl group in sterically encumbered bicyclo[3.3.1]nonane derivatives was feasible (Scheme 2). Chemoselectivity of the introduction of fluorine was also a potential issue, since DAST can react with adamantanone derivatives to give the corresponding *gem*-difluoroadamantanes.[36] However, for the ketols **2**, **5** and **9** derived from the annulation protocol, none of the products isolated corresponded to reaction at a carbonyl group; from the least substituted system, pure *exo*-**2**, the only fluoride isolated being the 6-*endo* isomer **3** (fluorine *endo* w.r.t. the C-9 carbonyl group), as implied by the *trans*-diaxial coupling (11.2 Hz) of 6-H with 7-Hax which also supports a chair conformation for the fluorinated cyclohexane ring, and hence a chair, chair conformation for **3**. In contrast, from a mixture of the epimers **5**, the only fluoride isolated was the 6-*exo* isomer **6**; its 6-H at δ 4.75 (J_{HF} = 47.8 Hz) exhibited additional couplings of $J_{6\text{-Heq},7\text{-Hax}}$ = 4.0 Hz and $J_{5\text{-Heq},6\text{-Heq}}$ = 2.0 Hz, implying an axial fluoro substituent and excluding the equatorial epimer which would have a large *trans*-diaxial coupling constant. Fluorine was introduced *via* inversion to give **3**, as is also likely for **6**. Reaction of **9** with DAST gave both 6-fluoro epimers, but given the low mass balance and the epimeric mixture of **9** unequivocal mechanistic inferences as to their formation is not currently possible.



Scheme 2. Synthesis of 6-fluoro-1-methylbicyclo[3.3.1]nonane derivatives *via* a tandem Michael-aldol annulation-fluorodehydroxylation protocol.

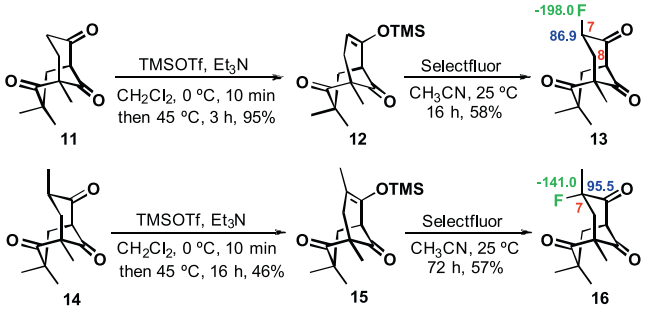
In both reactions, formal dehydration gave significant quantities of the corresponding alkenes **4** and **7**, albeit useful compounds since those alkenes could not be prepared by standard methods for the dehydration of alcohols, including phosphoric acid, $POCl_3$-pyridine, $(CF_3CO)_2O$ and DBU in pyridine, or Burgess' reagent. The 6,7-unsaturation of alkene **4** was confirmed by coupling of the 5-H bridgehead signal to the signal at δ 5.77 (H-6) and by analysis of the COSY spectrum.

The boat, chair conformation of **9** is consistent with the same conformation as previously found for **14** which was established by X-ray crystallography. OPLS3-GB/SA conformational search calculations also confirmed the boat, chair to be the lowest energy conformer for both compounds.[28]

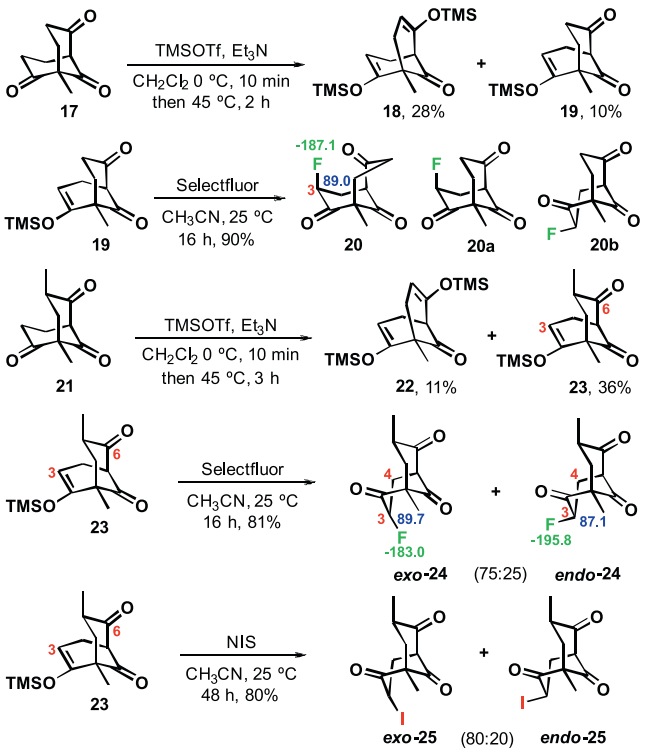
With some success in preparing 6-fluorobicyclo[3.3.1]nonane derivatives, attention was turned to functionalisation *alpha* to one of the carbonyl groups. Fluorination of silyl enol ethers using Selectfluor is known to be effective in cyclic and acyclic ketones.[31] In order to avoid participation of the unprotected 6-hydroxy group and the attendant complication of epimers, the bicyclo[3.3.1]nonanetriones **11**, **14**, **17** and **21** were prepared by oxidation of the corresponding ketols using PCC.[28] Their conversion into silyl enol ethers was achieved by reaction with TMSOTf in the presence of Et_3N (Schemes 3 and 4).[37]

The *gem*-dimethyltriones **11** and **14** were initially selected for study on the basis that the non-enolisable 2-keto group would be inert to attack. That proved to be the case, the corresponding 7-fluorotriones **13** and **16** being the only products isolated from the fluorination of the respective silyl enol ethers **12** and **15** using Selectfluor (Scheme 3). The unusually large vicinal coupling (11.0 Hz) of the bridgehead 5-H with 4-Heq in **13** confirms the boat conformation of the cyclohexane-1,3-dione ring, the corresponding value for compounds with chair, chair conformations being much lower, and typically 5–7 Hz, as found without exception in our previous study.[28] Additionally, the large H-7,H-8 *trans*-diaxial coupling constant (12.4 Hz) established the 3-*exo* configuration of the 7-fluoro substituent in **13**. The formation of **16** from **15** implies attack from the *endo*-face (without the possibility of forming a neutral fluoro silyl enol ether), resulting in fluorine in the *axial* position. The formation of **13** could also be accounted for by axial attack, followed by enolisation to give the fluoro substituent in the *equatorial* position. Such late-stage fluorinations are notable, being achieved in the presence of ketones, themselves capable of a wide range of transformations.

With a viable synthesis of 7-fluorobicyclo[3.3.1]nonane-2,6,9-triones in hand, the parent trione **17** was then investigated, a mono(silyl enol ether) assigned as **19** being obtained in addition to the bis(silyl enol ether) **18** (Scheme 4). Silyl enol ether **19** efficiently afforded the corresponding 3-fluoro derivative **20**. From the 7-methyltrione **21** was isolated enol ether **23** as the major epimer which was converted into predominantly the 3-*exo*-fluoro epimer **24**. Overall, conversion of the silyl enol ethers into the



Scheme 3. Preparation of 7-fluorobicyclo[3.3.1]nonane-2,6,9-triones.



Scheme 4. Preparation of 3-fluorobicyclo[3.3.1]nonane-2,6,9-triones.

corresponding α-fluoroketones was achieved in good to excellent yields (57–91%). Electrophilic attack on silyl enol ether **22** was also probed using NIS, when introduction of the larger iodo group gave predominantly the 3-*exo*-iodo isomer **25**, together with some 3-*exo* isomer, the same pattern observed for the corresponding fluoro epimers **24**. In contrast, the bis(silyl enol ethers) **18** and **22** afforded unstable mixtures of compounds in which introduction of fluorine at the 3- and/or 7-positions probably occurred.

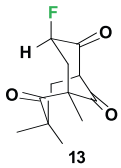
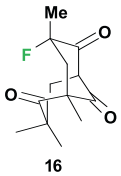
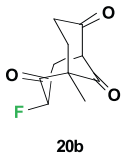
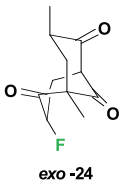
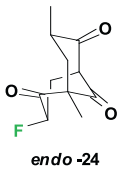
NMR analysis permitted the regioselectivity and configuration of the newly-formed bicyclo compounds to be determined. The monoenolised product could be assigned as **23**, given the presence of an olefinic signal at δ 4.92 (assigned as H-3) and a doublet methyl signal at δ 1.11, C-7 remaining sp^3-hybridised. The 7.1 Hz vicinal coupling found for the bridgehead 5-H coupling to 4-Heq is consistent with conformation **20**, but inconsistent with **20a** because the chair, chair conformation in such bicyclo compounds shows a large coupling ($J_{H4,H5}$ ~11.0 Hz).[28] The value of J_{CF} (184.5 Hz) is also consistent with the 3-*endo*-fluoro (axial) conformation of **20** rather than the boat conformer **20b**, for which a value of approximately 195 Hz would be expected (*vide infra*). Additionally, the dtd coupling for 3-H (J^3eq-eq = J^3eq-ax = 7.5 Hz) implies similar dihedral angles, consistent with the fluorinated ring adopting a chair conformation. Lastly, the smallest coupling of 3-H in fluoroketone **20** (J = 1.6 Hz), assigned to W-coupling to 5-H, suggests a chair conformation for the 3-fluorocyclohexane-1,3-dione ring. Taking those data together, this NMR analysis indicates the chair (F-ring), boat conformer **20**. Interestingly, computational calculations (*vide infra*) predict a slightly more energetically stable boat (F-ring), chair **20b**.

Variations in the one-bond C—F coupling constant reflect different torsional bond angles for F—C—C=O, which are consistent with the configurations and conformations of the α-fluoroketones shown in Schemes 3 and 4: the greatest values (J_{CF} = 195 Hz in **13** and J_{CF} = 192.2 Hz in *endo*-**24**) are found where the C-F bond is nearly coplanar with the C=O bond; smaller for compounds **20** (J_{CF} = 184.5 Hz) and *exo*-**24** (J_{CF} = 180.4 Hz) having a torsional angle of approximately 15°; and smaller still for compound **16** (J_{CF} = 170 Hz) with a torsional angle of approximately 120°.

The 3-*endo* epimer **24** was readily assigned by the chemical shift of 3-F, and by the presence of a *trans*-diaxial coupling (J = 11.8 Hz) that in the ^{1}H NMR spectrum of the *3-exo* epimer **24** is 4.8 Hz. The difference in facial selectivity of fluorination to give **20** and *exo*-**24** can be accounted for by the greater conformational rigidity present in **23**, the equatorial 7-methyl group providing a conformational restriction of the cyclohexane-1,3-dione ring that hinders electrophilic approach at the *si*-face of the enol ether, resulting in *exo*-**24** as the predominant product. In contrast, the more flexible conformation of **19**, as evidenced by the preferred conformation of **20**, permits *si*-face attack.

Using molecular mechanics (MMFF) and DFT M06-2X 6-31+G* calculations,[38] conformational searches for all of the compounds **13**, **16**, *exo*-**24** and *endo*-**24** clearly identified the chair (F)-boat conformation as that of lowest energy, as had been inferred by conformational analysis of the NMR data (Table 1). In several cases, other less favourable conformers could be detected (twist-boat, twist-boat and twist-chair, twist-chair) but in no case the chair, chair conformation, precluded by the non-bonding interactions that would arise between the axial C-3 group with C-7 and its axial substituent. For compound **20**, both the chair (F)-boat (**20**) and the boat (F)-chair (**20b**) conformations are significantly populated, and in this case only was the computation in disagreement with assignments by NMR spectroscopy, since **20b** was calculated to be slightly lower in energy (2.0 kJ/mol in the gas phase) than **20**.

Table 1
M06-2X 6-31+G* gas phase relative conformational energies (kJ/mol^{-1}) of some fluorobicyclo[3.3.1]nonane-2,6,9-triones[a,b]

	 13	 16	 20b	 exo -24	 endo -24
Chair (F), boat[c]	0(83)	0(99.6)	2.0(29)	9.8(2)	6.2(7)
Boat (F), chair[c]	10.74	16.3	0(64)	0(95)	0(89)
Twist-boat, twist-boat	4.1(16)	15.4	11.5	–[d]	–[d]
Twist-boat, twist-boat 2	–[d]	18.6	–[d]	–[d]	–[d]
Twist-chair, twist-chair	–[d]	–[d]	5.66(7)	8.9(3)	7.5(4)

[a] Energies quoted are relative to the most stable conformation whose energy is assigned to zero.
[b] Values in parenthesis refer to the Boltzmann weights (*i.e.* the percentage that the conformer contributes to the total distribution).
[c] (F) refers to the position of fluorine atom.
[d] Not found during the conformational search.

Conclusion

Despite the increasing importance of polysubstituted bridged compounds in medicinal chemistry, few fluorinated bicyclo compounds are known, and even fewer of defined stereochemistry. The present study demonstrates the power of a tandem Michael-aldol annulation followed by late-stage fluorination for rapid access to polysubstituted monofluorobicyclo[3.3.1]nonanones, and should also apply to bicyclo[3.2.1]octanone derivatives.[28] These late-stage introductions of fluorine have shown chemoselectivity, and with Selectfluor usually also stereoselectivity. Bicyclo [3.3.1]nonane derivatives with up to eight substituents have been synthesised in only two laboratory steps, and the major conformer for each of the fluorobicyclo compounds was deduced. This approach is complementary to the photocatalytic β- and γ-fluorination of ketones,[12] and when combined with that could deliver CHF fluorination at most positions of suitably substituted bicyclo ketones.[28] This study demonstrates rapid access to a rigid scaffold with multiple substituents of predictable directionality, especially C—F bonds, features of interest in probes of biological targets and in medicinal chemistry programmes.

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Conflicts of interest

There are no conflicts to declare.

Supplementary data

Supplementary data (experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, **6**, **7**, **10**, **12-13**, **16**, **18-20** and **23–25**) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.02.038.

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