Three step synthesis of single diastereoisomers of the vicinal trifluoro motif

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Abstract
A three step route to single diastereoisomers of the vicinal trifluoromethyl motif is described. The route starts from either syn- or anti-α,β-epoxy alcohols and takes a direct approach in that each of the three steps introduces a fluorine atom in a regio- and stereospecific manner. Starting from either the syn- or the anti-α,β-epoxy alcohol, stereospecific reactions generate two separate diastereoisomeric series of this motif. The route is a significant improvement on an earlier six step strategy.

Introduction
Selective fluorination is an important strategy for the design of performance molecules in medicinal chemistry programmes and in organic materials [1,2]. To date arylfluorines have dominated this agenda. However molecules where the C–F bond is a constituent of a stereogenic centre are gaining in prominence, particularly as new reagents and more versatile asymmetric methods facilitate their syntheses [3,4]. The fluorine atom is small, with a steric impact only a little larger than hydrogen, and it is a weak hydrogen bond acceptor [4]. However the C–F bond is polar and thus interactions with nearby functional groups are largely a result of dipolar interactions rather than hydrogen bonding or steres. We have focused a recent synthetic effort on the assembly of multivinicial fluorine motifs where contiguous fluorines have been placed along alkane chains [5]. It emerges that different diastereoisomers of otherwise constitutionally identical isomers have very different properties and conformations as a consequence of the preferred alignments of the C–F bonds, and thus the specific stereogenic relationship between the vicinal fluorines alters the properties of the compounds in a very specific manner [6-10]. Earlier contributions in this area outlined a synthetic approach to the vicinal trifluoro motif as shown in Scheme 1 [11,12]. However this method had some limitations and particularly the final step was susceptible to competing elimination, resulting in poor yields. The route also required six steps to insert the three fluorine atoms, with a poor overall yield. A more practical route to this class of compounds is required if these vicinal trifluoro motifs are to be applied usefully.
A three step strategy, as illustrated in Scheme 2, starting from
diastereoisomeric syn- or anti-α,β-epoxy alcohols A was envis-
aged, each step incorporating a fluorine atom in a stereospe-
cific manner. Conversion of the free hydroxyl group to fluorine
would generate α-fluoro-epoxides B. Epoxide ring opening with
an HF source could then provide difluoroalcohols C. Insertion
of the third fluorine would reasonably be achieved by fluorina-
tion of the free hydroxyl group of C to generate D. Such a
strategy offers a three step route to the vicinal trifluoroalkane
motif and would avoid the use of TBAF, reducing the risk of
elimination reactions competing with fluorine substitution, a
problematic aspect of the last step in the earlier route shown in
Scheme 1.

Results and Discussion

The chemistry was initiated from allylic alcohol 2 which can
readily be prepared in enantiomerically pure form by hydro-
lytic kinetic resolution of vinyl epoxide 1 following Jacobsen’s
protocol [13] (Scheme 3).

Diol 2 was converted to tosyl ester 3 in a regioselective manner
following the procedure of Marinelli [14]. The tosyl ester 3 was
then submitted to two cross-metathesis reactions using the
Grubbs II catalyst and with an excess of either hexene or allyl
benzene (5 equiv) to form allylic alcohols (S)-4 and (S)-5.
Scheme 3: Synthesis approach to the requisite α,β-epoxy alcohols 6b and 7b.

respectively [15]. The excess of alkene favours the cross metathesis reaction and the products were obtained in good yields predominantly as the (E)-isomer. It was not possible to separate the minor (Z)-isomer at this stage, however isomer separation was more readily achieved after the subsequent epoxidation step. Thus (S)-4 and (S)-5 were subjected to epoxidation reactions following Sharpless’ methodology [16]. The anti-epoxy alcohols were easily generated, however it proved more difficult to prepare the syn-epoxides cleanly. Treatment with titanium isopropoxide (Ti(OiPr)4) and D-diisopropyl tartrate (D-DIPT) favoured formation of the anti-α,β-epoxy alcohols. In the case of 4, epoxide 6b was obtained in 80% yield and in 97:3 dr. For 5, the resulting epoxide 7b was generated as the only observable diastereoisomer. Epoxide (2R,3R,4R)-7b was recrystallised from diethyl ether to afford a suitable crystal for X-ray structure analysis which confirmed its relative and absolute configuration (Figure 1).

Generation of the syn-α,β-epoxy alcohols Aa was more challenging. This stereoisomer will ultimately deliver the all-syn Da trifluoro motif (Scheme 1). Epoxidation of (S)-5 with L-DIPT showed poor stereoselectivity and under optimised conditions the resultant α,β-epoxy-alcohols 7a and 7b were obtained in a 3:1 ratio. Epoxidation reactions with m-CPBA and Ti(OiPr)4 gave diastereomeric ratios of between 2:1 and 3:1, thus L-DIPT showed only a modest improvement in the stereoselectivity. These diastereoisomers were not easily separated by chromatography, however the absolute and relative stereochemistry of the crystalline threo-isomer (2R,3S,4S)-7a was confirmed by X-ray structure analysis as shown in Figure 2.

Figure 1: X-ray structure (CCDC 750307) and stereochemistry of α,β-epoxy alcohol 7b.
With a strategy to access both stereoisomeric series of the allylic alcohol epoxides A in place, the fluorination reactions were then explored.

The fluorination of the anti-isomers 6b and 7b was attempted using Deoxo-Fluor® [17]. α,β-Epoxy-alcohol 7b reacted smoothly with Deoxo-Fluor® at 40 °C (Scheme 4) to give fluoroepoxide (2S,3S,4R)-8b in 83% yield and with a 97:3 dr. Epoxide ring opening of 8b was then explored with HF/pyridine and this reaction proved to be both regio- and stereo-selective [18,19]. When the reaction was carried out at 0 °C the resultant difluoro alcohol 10 was obtained in 36% yield, whereas the yield improved as the temperature was lowered (47% at −35 °C and 56% at −60 °C). Epoxide ring opening was stereospecific, and the (2S,3S,4S)-difluoro alcohol 10 was obtained as the major diastereoisomer in a 97:3 ratio. The third fluorine atom was inserted in a smooth reaction by treatment of 10 again with Deoxo-Fluor® to generate (2S,3R,4S)-11. The sequence illustrated in Scheme 4 validated the three step fluorination protocol for this diastereoisomeric series.

Reaction of α,β-epoxy alcohol 7b with Deoxo-Fluor® also proceeded smoothly generating fluoro epoxide (2S,3S,4R)-9b in 95% yield and as a single stereoisomer. However when 9b was treated with HF/pyridine [19,20] there was no evidence that the expected difluoro alcohol 12b had formed (Scheme 5). Instead the fluorinated tetrahydrofuran 14 was isolated as a crystalline product in 33% yield and its structure and stereochemistry were established by X-ray structure analysis (Scheme 5). This deviant reaction was surprising not only because there was no trace of the analogous cyclisation product after treatment of 8b with HF/pyridine, but also because cyclisation had occurred with retention of configuration at C4. One explanation for this outcome is that the reaction proceeds via a bicyclic phenoxonium intermediate 13 generated after HF promoted epoxide ring opening. Fluoride ion triggered tosyl cleavage generates a

![Figure 2: X-ray structure (CCDC 750306) and stereochemistry of α,β-epoxy alcohol 7a.](image)

![Scheme 4: Three step sequential fluorination from α,β-epoxy alcohols to eg. the vicinyltrifluoro tosylate 11.](image)
sufficiently nucleophilic oxygen, to promote cation quenching and formation of the cyclic ether. This process would involve two configurational inversions at C4 giving overall retention.

Epoxide ring opening of the *threo* isomer 9b was eventually achieved, however this required much more forcing conditions using 3HF·Et$_3$N in toluene at 120 °C, and generated three products 12b, 15 and 16, two of which arose by fluoride ion displacement of the tosyl group to generate a fluoromethyl group (Scheme 6). Interestingly there was no evidence for the formation of 14 with this less acidic reagent. Compounds 12b and 16 were isolated in 23% and 25% yields respectively, and the stereochemistry of each was established by X-ray structure analysis. Epoxide ring opening occurred in each case in a regio- and stereo-selective manner with the expected inversion of configuration, and thus there was no evidence for the involvement of an intermediate phenoxonium ion under

![Scheme 5](image-url)

**Scheme 5:** Unexpected cyclisation of 9b to furan 14 with HF·pyridine. An X-ray structure of 14 (CCDC 750309) reveals that the cyclisation proceeds with a retention of configuration.

![Scheme 6](image-url)

**Scheme 6:** Epoxide ring opening of 9b with 3HF·Et$_3$N required forcing conditions. The structure and stereochemistry 12b (CCDC 750308) and 16 (CCDC 750310) was established by X-ray analysis.
these conditions. The ring opening reaction of 9b was explored under a variety of conditions and the best conversion and selectivity was obtained using chloroform at 100 °C in a sealed autoclave with a Teflon inner layer (12b 58%, 15 2% and 16 4%). For the final step of the sequence shown in Scheme 7, difluoro alcohol 12b reacted smoothly with Deoxo-Fluor® to generate trifluoroalkane 17b which could be isolated in 78% yield.

Fluorination of epoxy alcohol 7b by the three step protocol (44% overall yield), illustrates a second substrate of this diastereoisomeric series, and demonstrates a reasonably efficient protocol to the vicinal trifluoro motif, much improved over the original six step sequence [11,12].

Fluorination of the threo-α,β-epoxy alcohol 7a proved more challenging because of a propensity to give isomeric fluorination products. Due to the difficulty in purifying the diastereomerically pure epoxide a deshydroxyfluorination reaction on a 1:1 mixture of 7a : 7b was explored. Grée and co-workers have also noticed that erythro-epoxy alcohols react relatively smoothly but that threo-epoxy alcohols are prone to rearrangement [21,22]. Thus the mixture of 7a and 7b was treated with Deoxo-Fluor® or DAST under a variety of conditions and the outcomes are summarised in Table 1.

With this inseparable mixture of 9a and 9b (1:1.3 ratio) in hand, a reaction to explore the introduction of the second fluorine was carried out as illustrated in Scheme 8. Accordingly the mixture was treated with 3HF-Et3N in chloroform at 100 °C and this generated 12a among other products.

Separation of (2S,3R,4R)-12a was achieved from the product mixture by chromatography (preparative TLC) in 33%. Finally, treatment of 12a with Deoxo-Fluor® gave the desired all-syn-trifluoro alkane (2S,3S,4R)-17a as a single enantiomer in moderate 57% yield. In general the vicinal trifluoro compounds were stable and showed no tendency to degrade over time.

![Scheme 7: Three step sequential fluorination from α,β-epoxy alcohol 7b to vicinal trifluoro tosylate 17b.](image)

**Table 1**: Reaction of α,β-epoxy alcohol 7a and 7b under various fluorination conditions. Ratios determined by 19F NMR.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>9a</th>
<th>9b-(R,S,R)</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoxo-Fluor®, DCM</td>
<td>1</td>
<td>1.43</td>
<td>0.56</td>
</tr>
<tr>
<td>Deoxo-Fluor®, toluene</td>
<td>1</td>
<td>1.41</td>
<td>0.53</td>
</tr>
<tr>
<td>DAST, DCM</td>
<td>1</td>
<td>1.54</td>
<td>0.66</td>
</tr>
<tr>
<td>Deoxo-Fluor®, THF</td>
<td>1</td>
<td>1.29</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Conclusion
In summary a direct three step route has been developed from α,β-epoxy alcohols for the synthesis of the vicinal trifluoro motif where a fluorne atom is introduced in each step. Two different diastereoisomeric series (a and b) of the trifluoro motif were explored. The diastereoisomeric series Db (Scheme 2) could be prepared in a relatively straightforward manner, however the diastereoisomeric series Da (Scheme 2), where all three fluorines are syn with respect to an extended alkyl chain, proved to be more challenging. This is due to a greater difficulty in obtaining diastereoisomerically pure syn-α,β-epoxy alcohols, and also a greater propensity to side product formation during the first two fluorination reactions. Nonetheless the methods provide a direct route to this largely unexplored motif, and in the cases exemplified the synthesis delivers a product carrying a terminal tosyl ester, which should allow the vicinal trifluoro motif to be incorporated into larger molecular architectures.

Experimental
Selected experimental data is presented. Full details are in Supporting Information.

(2S,3R,4S)-2,3,4-Trifluoro-5-phenylpentyl 4-methylbenzenesulfonate (17b)
Deoxo-Fluor® (50% in THF, 175 μL, 0.47 mmol) was added to a solution of 12b (58 mg, 0.16 mmol) in DCM (3 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h, and the reaction was quenched by the addition of silica gel. Solvents were removed under reduced pressure, and the product was purified over silica (hexane 5/DCM 3/EtOAc 2). The title compound was recovered as a colourless oil (45 mg, 78%).

[$\alpha$]D{sub 20} = −2.7 (c = 1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 7.81 (d, 2 H, J = 8.3 Hz, CH ar); 7.76 (d, 2 H, J = 8.3 Hz, CH ar); 4.86 (m, 1 H, J = 45.5 Hz, FC'H); 4.74–4.37 (m, 3H, 2 × FCH + O₂SOCH₂Hb); 4.27 (dd, J = 2.6, 4.2, 11.9, 29.6 Hz, O₂SOCH₂Hb); 2.46 (s, 3 H, CH₃); 1.94–1.84 (m, 1 H, CHaHb); 1.70–1.58 (m, 1 H, CHaHb); 1.49–1.33 (m, 1 H, CH₂); 0.92 (t, 3 H, J = 7.4 Hz, CH₃). ¹³C NMR (CDCl₃, 100 MHz): 145.3 (C ar); 132.3 (C ar); 130.0 (CH ar); 128.0 (CH ar); 89.8 (dd, J = 178.3, 18.7, 1.9 Hz, CF); 88.3 (dd, J = 181.7, 18.6, 29.1 Hz, CF); 85.7 (dd, J = 179.0, 30.4, 5.6 Hz, CF); 67.4 (d, J = 19.8 Hz, C-CH₂); 29.6 (dd, J = 21.1, 4.6 Hz, CH₂); 27.0 (d, J = 5.0 Hz, CH₂); 22.3 (d, J = 13.8 Hz, CH₂). ¹⁹F NMR (CDCl₃, 376 MHz): −199.82 to −200.12 (m, 1 F); −201.04 to −201.38 (m, 1 F), −214.61 to −214.89 (m, 1 F). ¹⁹F {¹H} NMR (CDCl₃, 376 MHz): −199.9 (dd, 1 F, J = 15.9, 32 Hz); −201.2 (dd, 1 F, J = 19.5, 3.2 Hz); −214.7 (dd, 1 F, J = 9.5, 15.9 Hz). νmax/cm⁻¹ 1363, 1275, 1179, 897, 758, 749. m/z (ES⁺) = 361.01 (MNa⁺, 100%); HRMS (ES⁻) found 361.1047 for C₁₅H₂₂F₂NaO₃S, requires 361.1061.

[Supporting Information. Selected experimental data is presented. Full details are in Supporting Information.]

(2S,3R,4S)-2,3,4-Trifluoro-5-phenylpentyl 4-methylbenzenesulfonate (17b)
HRMS (ES+) found 395.0903 for C$_{11}$H$_{11}$46, 983, 910, 740. + m/z/cm (dd, 1 F, J$_{19}$F = 10.8 Hz); −201.29 (dd, 1 F, J$_{19}$F = 19.7 Hz, CH$_2$); 363 (dd, J = 22.5, 5.2 Hz, CH$_2$); 21.7 (CH$_3$). 19F NMR (CDCl$_3$, 376 MHz): −198.80 to −199.23 (m, 1 F); −200.27 to −200.69 (m, 1 F), −215.48 to −215.78 (m, 1 F). 19F {1H} NMR (CDCl$_3$, 376 MHz): −198.61 (dd, 1 F, J = 9.6, 2.8 Hz); −200.03 (dd, 1 F, J = 15.4, 2.8 Hz); −215.18 (dd, 1 F, J = 9.6, 15.4 Hz). v$_{\text{max}}$/cm$^{-1}$: 1365, 1261, 1267, 1208, 1190, 1177, 1151, 749. m/z (ES$^+$) 394.95 (MNa$^+$, 100%); HRMS (ES$^+$) found 395.0906 for C$_{18}$H$_{19}$F$_3$NaO$_3$S, requires 395.0905.

(2S,3S,4R)-2,3,4-Trifluoro-5-phenylpentyl 4-methylbenzenesulfonate (17a)

Deoxo-Fluor® (50% in THF, 15 µL, 0.05 mmol) was added to a solution of 12a (7 mg, 0.02 mmol) in DCM (1 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h and the reaction was quenched by the addition of silica gel. Solvents were removed under reduced pressure and 17a was purified by preparative TLC (hexane:Et$_2$O 3) and recovered as a colourless oil (4 mg, 57%).

[a]$_D^{20}$ = +1.75 (c = 0.4, CDCl$_3$). 1H NMR (CDCl$_3$, 300 MHz): δ (ppm) 7.74 (d, 2 H, J = 8.3 Hz, H ar); 7.37–7.22 (m, 7 H, H ar); 5.06–4.43 (m, 3 H, 3 × HCF); 4.73–4.38 (m, 2 H, 2 × HCF); 4.35 (brd, 1 H, J = 3.8 Hz, SO$_2$CH$_2$Hb); 4.27 (brd, 1 H, J = 3.8 Hz, SO$_2$CH$_2$Hb); 3.15–2.97 (m, 2 H, CH$_2$Ph); 2.45 (s, 3 H, CH$_3$). 13C NMR (CDCl$_3$, 75 MHz): 130.1 (CH ar); 129.3 (CH ar); 128.9 (CH ar); 127.3 (CH ar); 21.7 (CH$_3$). Quaternary carbons and carbons coupled bound to fluorine were not observed, even with an extended number of scans (12000 scans). 19F NMR (CDCl$_3$, 376 MHz): −195.84 to −196.29 (m, 1 F); −201.07 to −201.51 (m, 1 F), −212.23 to −212.63 (m, 1 F). 19F {1H} NMR (CDCl$_3$, 376 MHz): −196.1 (d, 1 F, J = 10.8 Hz); −201.29 (d, 1 F, J = 13.6 Hz); −212.43 (dd, 1 F, J = 10.8, 13.6 Hz). v$_{\text{max}}$/cm$^{-1}$: 1360, 1269, 1208, 1190, 1146, 983, 910, 740. m/z (ES$^+$) 394.96 (MNa$^+$, 100%); HRMS (ES$^+$) found 395.0903 for C$_{18}$H$_{19}$F$_3$NaO$_3$S, requires 395.0905.

References

Supporting Information
Supporting Information File 1
Experimental methods and full characterisation and spectral data of all prepared compounds. [http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-5-61-S1.doc]

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