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Titanium mediated asymmetric aldol reaction with α-fluoropropionimide enolates

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Dedicated to Professor Kenji Uneyama as recipient of the ACS Fluorine Chemistry Award for 2007.

Abstract

Aldol reaction utilising Evans *N*-(α-fluoropropyl)-2-oxazolidinones with $TiCl_4$ have been explored. Reactions of *N*-(α-fluoropropyl)-2-oxazolidinones with aliphatic aldehydes generated α-fluoro-β-hydroxy-aldol products with high diastereoselectivities. When (α*R*)- and (α*S*)-*N*-(α-fluoropropyl)-2-(4*S*)-oxazolidinones were explored as substrates they gave rise to identical aldol diastereoisomer products. Examination of the enolates formed in each case by ^{19}F NMR, after treatment with $TiCl_4$, indicated that both preparations gave the same predominant enolate. This was assumed to be the *E*-enolate. The α-fluoro-β-hydroxy-aldol products were removed from the auxiliary either by alcoholysis or reduction and converted to the corresponding α,β-difluoro products by treatment with Deoxofluor™.

Keywords: Asymmetric synthesis; Evans auxiliary; α-Fluoroenolates; Asymmetric aldol reactions; Stereoselective fluorination; Vicinal difluoro compounds

1. Introduction

We have a current interest in preparing vicinal difluoro aliphatic compounds in a stereospecific manner. Although the fluorine atom is the next smallest to hydrogen and has a limited steric impact, the polar nature of the C–F bond induces stereoelectronic influences which can differentially influence the properties of *erythro* and *threo* diastereoisomers of otherwise identical vicinal difluorine containing compounds [1]. We have shown this for 9,10-difluorostearic acids and small peptidic compounds derived from *erythro*- and *threo*-difluorosuccinic acids [2]. In this regard, our attention was drawn to the possibility of carrying our asymmetric aldol reaction with chiral α-fluoroenolate equivalents and aliphatic aldehydes to generate α-fluoro-β-hydroxy compounds, which could then be manipulated by stereospecific fluorination of the product alcohol to give vicinal difluoro compounds. Although there has been some discussion on the nature and utility of α-fluoroenolates they have never found a significant role in the synthesis of organofluorine compounds [3]. In terms of asymmetric aldol reactions, Pridgen et al. [4] have demonstrated the most impressive methodology in this area exploring asymmetric aldol reactions with fluoroacetamide **1**, and using a variety of base or Lewis acid catalysed enolate generation processes for condensations to aromatic aldehydes.

These reactions generated predominant *syn* aldol products **2a** as major isomer when boron, titanium or tin^{II} were employed as Lewis acids, and *anti* aldol products **2b** as major isomers in the cases of tin^{IV} and zinc (Scheme 1). In this paper, we report our results on aldol reactions using (α*R*)- and (α*S*)-*N*-(α-fluoropropyl)-2-(4*S*)-oxazolidinones **3** (Scheme 2). Unlike aldol products such as **2**, the aldol products **4** and **5** from reaction of **3** are protected from epimerisation or elimination due to the presence of the α-methyl group. In the subsequent manipulations of these more stable products, this presents a significant advantage. In this study, aldol reactions of the diastereoisomers **3a** and **3b** were explored with hexanal and benzaldehyde and these results are reported. This required a suitable preparation of each of the diastereoisomers of **3** (Scheme 3).

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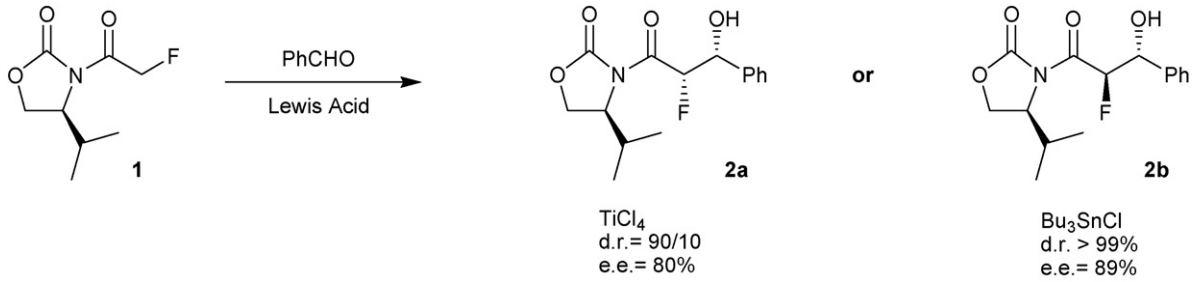
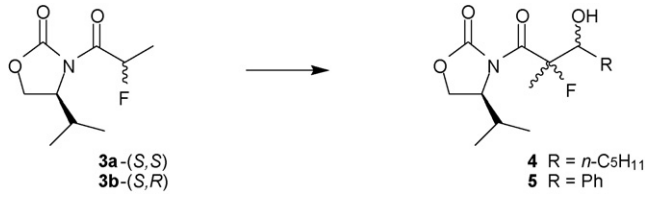
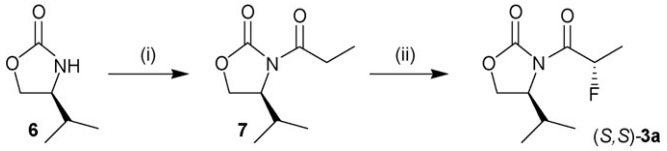


Scheme 1.



Scheme 2.



Scheme 3. *Reagents and conditions*: (i) propionyl chloride, LDA, THF, −78 °C, 80% (ii) LDA, NFSI, THF, −78 °C, 56%.

2. Results and discussion

2.1. Oxazolidinone diastereoisomers (S,S)-3a and (S,R)-3b

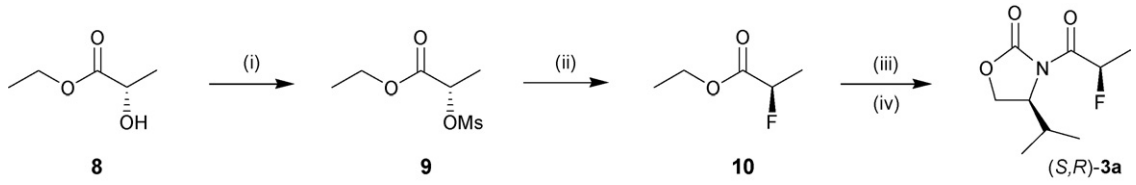
In order to explore these aldol reactions, several methods were investigated for the preparation of **3a** and **3b**. To this end the (*S*,*S*) diastereoisomer **3a** was prepared from the reaction of propionyl chloride and oxazolidinone **6** to generate **7**. An electrophilic fluorination reaction was then explored with *N*-fluorobenzene sulfonamide (NFSI) [5]. In the event, **3**-(*S*,*S*) was obtained in a moderate yield (56%) and ^{19}F NMR analysis revealed a diastereoisomeric ratio of 89:11. This ratio could be improved to 95:5 after chromatography over silica gel.

The (*S*,*R*) diastereoisomer **3b** was prepared by mesylation of ethyl (*S*)-lactate **8** (Scheme 4). The mesylate **9** was treated with potassium fluoride to generate α-fluoro ester **10** [6]. Direct treatment of **10** with phthaloyl chloride and chlorosulfonic acid gave the acid chloride as an intermediate [7], and the reaction with oxazolidinone **6** gave **3b**-(*S*,*R*) with a diastereoisomeric ratio of 97:3 and in moderate yield (59%).

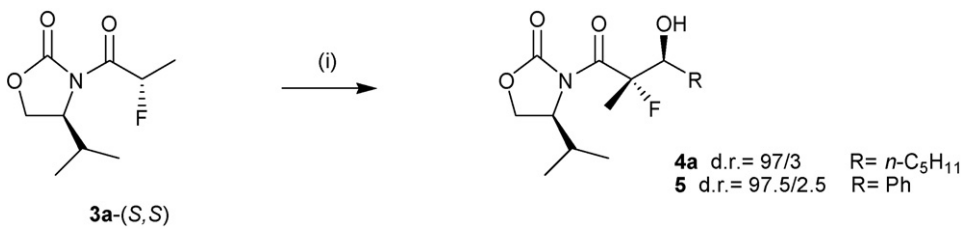
Aldol reactions with each of the diastereoisomers were then carried out [8] (Scheme 5). Thus treatment of **3a**-(*S*,*S*) with $TiCl_4$ (2 equivalents), DIEA (1 eq.) and hexanal (5 eq.) at −78 °C generated **4a** in 74% yield and as a predominant diastereoistereoisomer (d.r. 97/3 by ^{19}F NMR). A corresponding reaction with benzaldehyde (2 eq.) generated aldol product **5** in 67% yield (d.r. 97.5/2.5 by ^{19}F NMR).

X-ray structure analysis of a suitable crystal of the major aldol product **4a** (Fig. 1) revealed that the absolute and relative configuration of **4a** as shown in Scheme 5 with an *anti* relationship between the fluorine and the hydroxyl group [9]. It is notable also that in the solid state the C–F bond and the amide carbonyl are *anti* to each other, a stereoelectronic preference found more generally in α-fluoroamides [10].

When the reaction was investigated with **3b**-(*S*,*R*) the same aldol diastereoisomer was observed as the major product (as determined by ^{19}F NMR). It is clear that the nature of the starting diastereoisomer of **3a**-(*S*,*S*) or **3b**-(*S*,*R*) has no influence on the stereochemical outcome of the aldol product,



Scheme 4. *Reagents and conditions*: (i) MsCl, DMAP, Et_3N, THF, reflux, 91% (ii) KF, formamide, 70–90 °C, 87% (iii) phthaloyl chloride, HSO_3Cl, 120 °C, 63% (iv) oxazolidinone 6, BuLi, THF, −50 °C, 59%.



Scheme 5. *Reagents and conditions*: (i) $TiCl_4$ (2 eq.), DIEA (1 eq.), hexanal (5 eq.) or benzaldehyde (2 eq.), DCM, −78 °C, 74% (**4a**) and 67% (**5**).

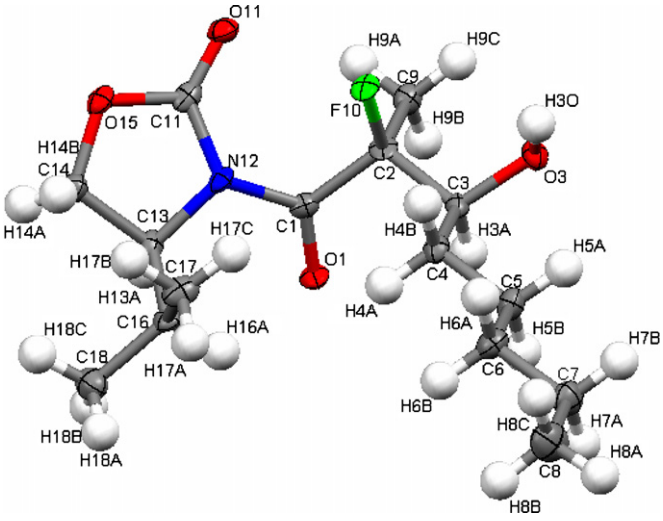


Fig. 1. X-ray structure of **4a**.

suggesting that the reactions proceed through a common thermodynamically favoured enolate (Scheme 6).

Each of the two diastereoisomers of **3a** and **3b** were separately treated with $TiCl_4$ at −78 °C in deuteriated dichloromethane ($C^2H_2Cl_2$) and enolate formation was monitored by ^{19}F NMR. Only one enolate was apparent at −150.1 ppm in $^{19}F\{^1H\}$ NMR (Fig. 2). The observation of a common, enolate resulting from each of the diastereoisomers of **3** is consistent with the experimental outcome, where each diastereoisomer gives the same product.

We assume that the *E*-enolate is the favoured enolate in solution. The *Z*-enolate would necessarily result in a steric clash of the methyl group of the propionimide moiety with the isopropyl group of the auxiliary. Also the orientation of the C–F bond *anti* to the enolate/amide C–O bond is anticipated to be stereoelectronically favoured as it will result in a dipolar relaxation.

The $^{19}F\{^1H\}$ NMR spectrum recorded at −78 °C in $C^2H_2Cl_2$ showed only one enolate (Fig. 2) but when the solution was warmed up to 0 °C a second signal appeared at −148.6 ppm (Fig. 3a). This was assumed to be the *Z*-enolate, representing around 4% of the overall enolate signal. When proton decoupling was turned off both signals became quartets in the ^{19}F NMR spectrum, as expected (Fig. 3b). The ^{19}F NMR signals of the *E*- and *Z*-enolates derived from **3b** after $TiCl_4$ treatment at 0 °C are shown in Fig. 3a and b. Treatment of **3a** under the same conditions gave similar spectra with a similar *E*/*Z* ratio.

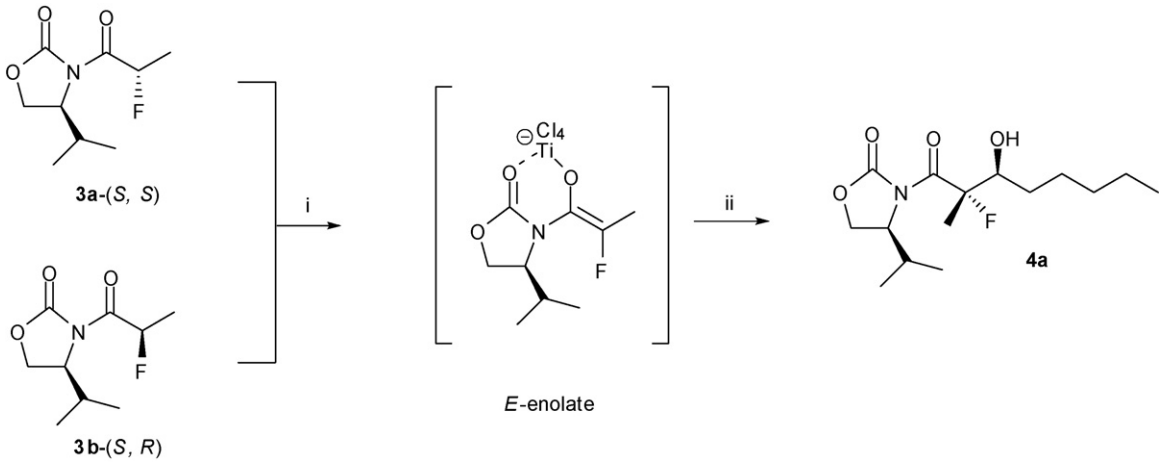
Generation of the *E*-enolate is also consistent with the stereochemical outcome as deduced by Zimmerman/Traxler intermediates as illustrated in Scheme 7. Crimmins et al. [8], have proposed that the second equivalent of $TiCl_4$ abstracts Cl^- from the complexed titanium allowing coordination of the oxazolidinone carbonyl to Ti to generate a highly ordered bicyclic enolate intermediate (Scheme 8).

Our attempts to prepare diastereoisomer **4b** in a stereoselective manner were only partially successful. When only 1 equivalent of each of $TiCl_4$ and DIEA was added, the reaction proceeded with a poor conversion and only a low stereoselectivity was observed. When DIEA was replaced by (−)-sparteine (1 eq. at 0 °C) a diastereoisomer ratio (80:20) in favour of the assumed isomer **4b** was observed. Although we could reproduce the expected stereochemical tendancy, this did not result in a satisfactory preparative method for the fluorinated aldol product **4b**.

2.2. Strategies for vicinal difluoro preparation

The overall objective of this study was to develop a novel stereoselective method for the introduction of the vicinal difluoromotif into organic molecules. Having developed a satisfactory stereoselective route to the *anti*-α-fluoro-β-hydroxy products **4a** and **5**, we then investigated different strategies for the introduction of the second fluorine substituent. Direct deoxofluorination reactions of **4a** were explored with Deoxofluor™ however these were unsuccessful giving rise to only uncharacterised products.

An alternative strategy envisaged removal of the α-fluoro-β-hydroxyacyl group from the auxiliary. This was achieved in two ways. Firstly, reaction of lithium phenylmethanolate with **4a** generated the benzyl ester **11** in 79% yield [11]. Separate



Scheme 6. *Reagents and conditions*: (i) $TiCl_4$ (1 eq.), DIEA (1 eq.), $C^2H_2Cl_2$, −78 °C (ii) $TiCl_4$ (1 eq.) hexanal.

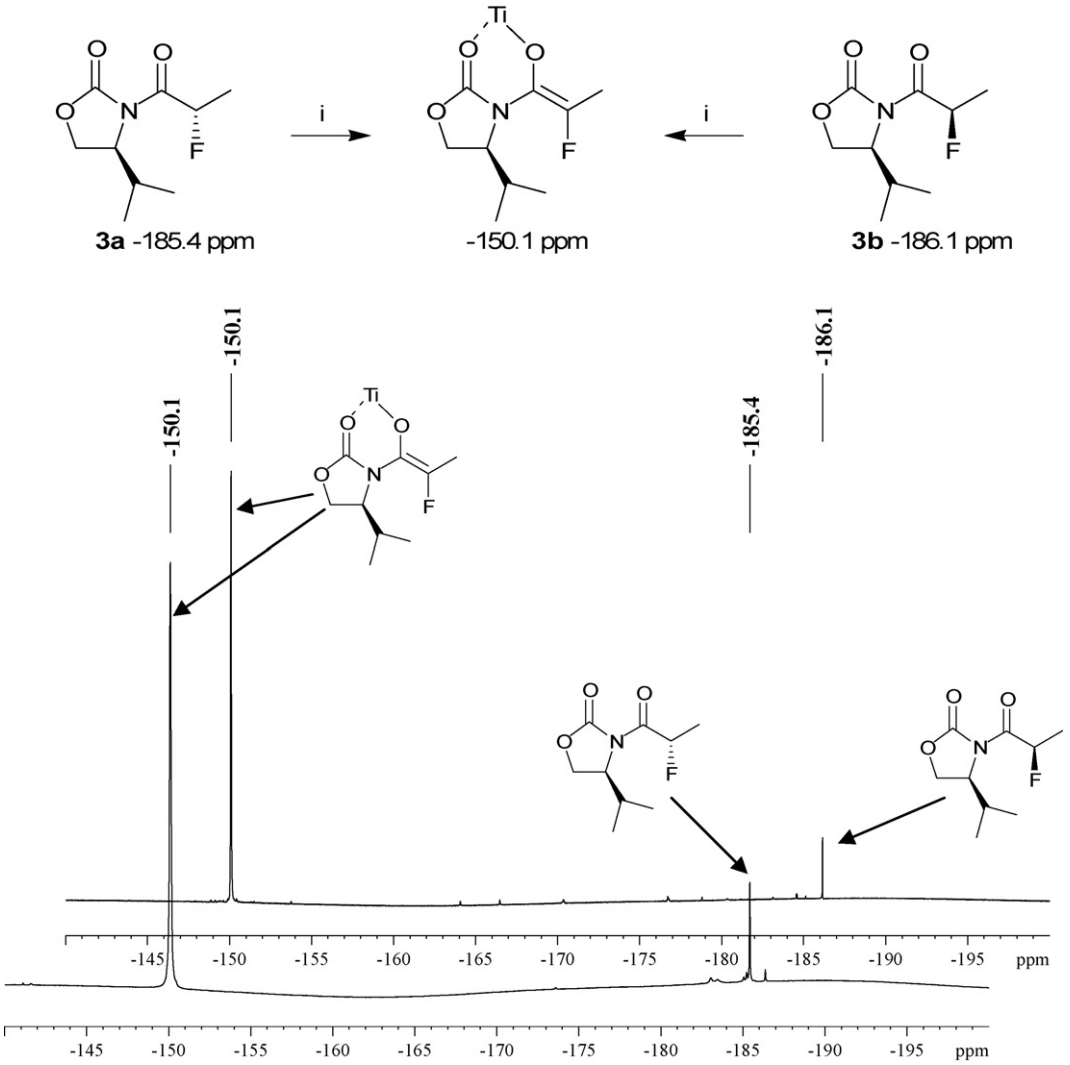


Fig. 2. Comparison of the $^{19}F\{^{1}H\}$ NMR spectra of the enolates generated from **3a** and **3b** after treatment with $TiCl_4$ (1 eq.) and DIEA in $C^2H_2Cl_2$, −78 °C.

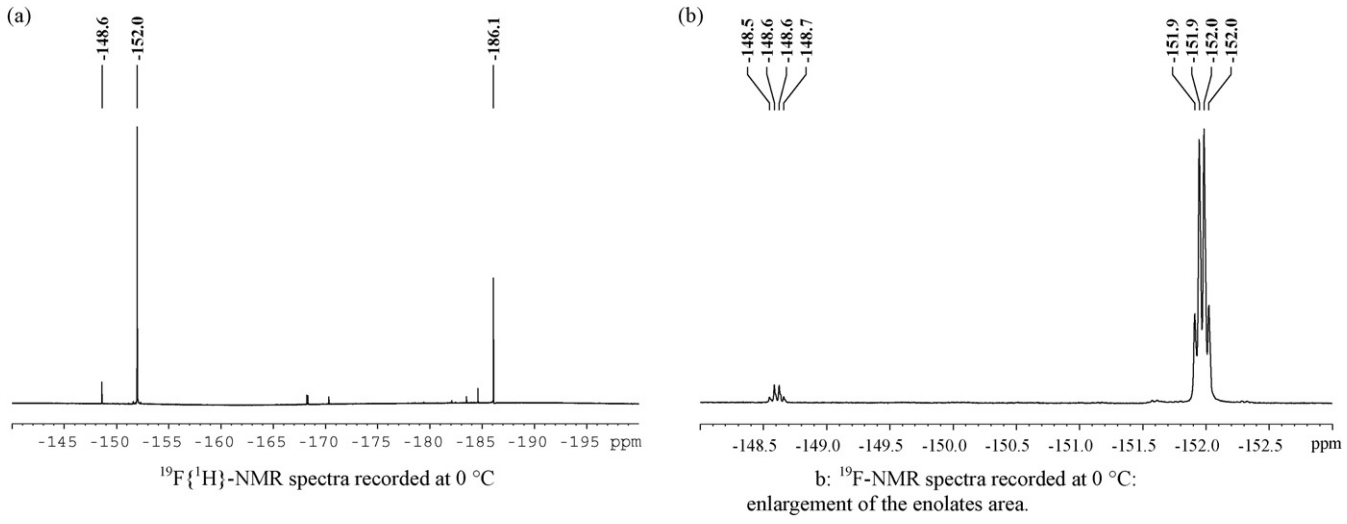
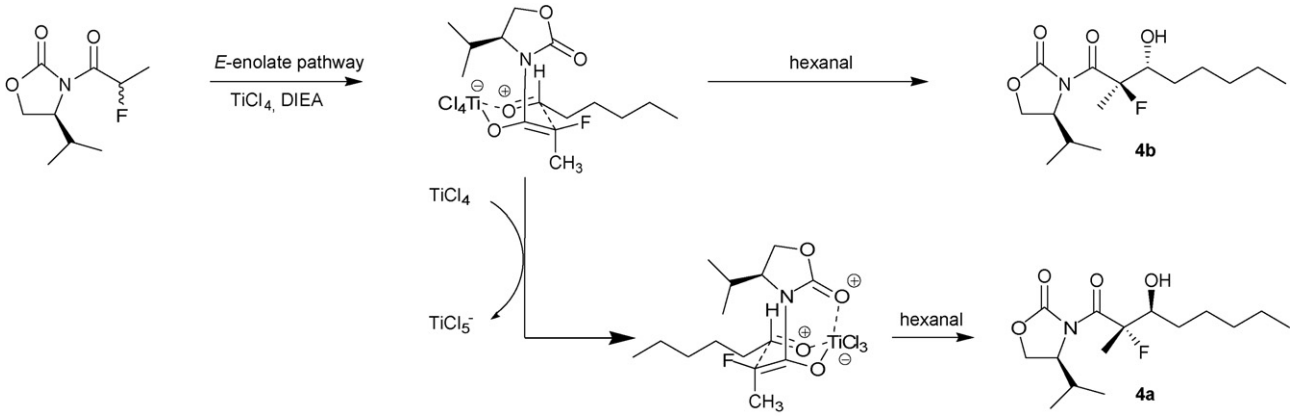
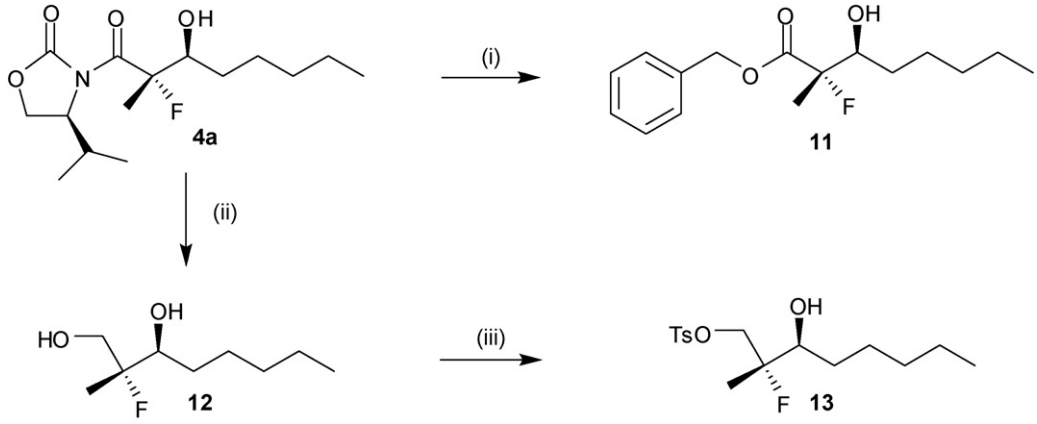


Fig. 3. (a) $^{19}F\{^{1}H\}$ NMR and (b) ^{19}F NMR spectra of the *E/Z* enolate solution after treatment of 3b with $TiCl_4$ and DIEA in DCM at 0 °C.



Scheme 7. Zimmerman/Traxler intermediates showing the different intermediates after one and two equivalents of $TiCl_4$, giving different stereochemical outcomes.



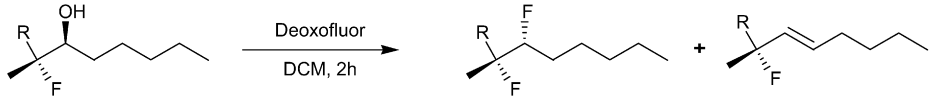
Scheme 8. *Reagents and conditions*: (i) benzyl alcohol, BuLi, THF, 0 °C, 79% (ii) $NaBH_4$, THF, MeOH, 0 °C, 66% (iii) TsCl, collidine, 1,2-dichloroethane, 60 °C, 57%.

treatment with $NaBH_4$, generated diol **12** in 66% yield. This diol was selectively protected as its monotosyl derivative **13**. Our recent experience [12] has demonstrated that tosyl groups are compatible with Deoxofluor™ deoxofluorination reactions and in the event this proved a robust protecting group.

Reaction of **11** with Deoxofluor™ in DCM resulted in complete conversion to a mixture of **14** and olefin **15**, but with poor selectivity (35:65) in favour of **15** (Table 1, Entry 1). Products **14** and **15** were purified in moderate yields, of 23% and 40%, respectively. The selectivity was improved (72:28) when the reaction was carried out at −30 °C also in favour of **14** (by ^{19}F NMR), but now with a lower conversion (55%) (Table 1, Entry 2).

When **13** was treated with Deoxofluor™ only the elimination product **17** was generated (Entry 3), and when the reaction was carried out at −30 °C no products formed at this lower temperature (Entry 5). The vicinal difluoro product

Table 1



Entry	R	Temperature	Conversion	Selectivity
1	BnO(CO)	Reflux	100%	**14/15** = 35/65
2	BnO(CO)	−30 °C	55%	**14/15** = 72/28
3	$TsOCH_2$	Reflux	100%	**16/17** = 0/100
4	$TsOCH_2$	r.t.	96%	**16/17** = 11/85
5	$TsOCH_2$	−30 °C	No reaction	

16 was generated after treatment with Deoxofluor™ at room temperature but with a poor selectivity (85:11) in favour of **17** (Entry 4). Our attempts to purify **16** were unsuccessful due to the small scale and poor selectivity of the reaction.

3. Conclusion

This study has explored enolate formation from the diastereoisomers of **3a** and **3b**, and has demonstrated that the common thermodynamic enolate results after treatment with $TiCl_4$. This was shown by $^{19}F\{^1H\}$ NMR analysis of the intermediate titanium enolates and was also manifest in the product outcome where the same α-fluoro-β-hydroxyl products **4a** and **5** were generated with high diastereoselectivity from each of **3a** or **3b**. Subsequent manipulation of **4a** to generate vicinal difluoroproducts such as **14** and **16** were only moderately successful.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under a positive pressure of nitrogen. Solvents were dried prior to use. High-resolution mass spectrometry was performed on a Waters LCT or GCT time-of-flight mass spectrometer.

NMR spectra were recorded on either Bruker AV-300 (^1H at 300.06 MHz, ^{13}C at 75.45 MHz, ^{19}F at 282.34 MHz), or Bruker AV-500 (^1H at 499.90 MHz, ^{19}F at 470.33 MHz). Chemical shifts δ are reported in parts per million (ppm) and quoted relative to internal standards (Me_4Si, $CFCl_3$). ^1H, ^{13}C and ^{19}F spectroscopic data were assigned by a combination of one- and two-dimensional experiments (COSY, HSCQ, HMBC, NOESY).

4.1.1. Preparation of the (S)-4-isopropyl-3-propionyloxazolidin-2-one 7

LDA (2 M in THF/*n*-heptane, 4.18 mL, 8.36 mmol) was added to a solution of 4-(*S*)-4-isopropyl-2-oxazolidinone **6** 98% (1 g, 7.59 mmol) in dry THF (15 mL) at −78 °C. Propionyl chloride 97% (0.82 mL, 9.11 mmol) was added after 35 min, and the solution was stirred for 1 h at −78 °C. The reaction was then quenched with a saturated solution of NH_4Cl. The product was extracted into Et_2O, washed, and dried over $MgSO_4$. Solvents were removed under reduced pressure. The product **7** was purified over silica (cyclohexane/EtOAc, 80/20) and recovered as a colourless oil (1.12 g, 80%).

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 4.39 (m, 1 H, N–C*H*); 4.23 (dd, 1H, $^2J_{H-H}$ = 9.0 Hz, $^3J_{H-H}$ = 8.1 Hz, O–C*H*H); 4.16 (dd, 1 H, $^2J_{H-H}$ = 9.0 Hz $^3J_{H-H}$ = 3.2 Hz, O–CH*H*); 2.89 (m, 2 H, CH_3–CH_2); 2.33 (m, 1 H, $(CH_3)_2$C*H*); 1.12 (*t*, 3 H, $^3J_{H-H}$ = 7.3 Hz, CH_2–CH_3); 0.87 (d, 3H, $^3J_{H-H}$ = 7.1 Hz, CH_3); 0.83 (d, 3 H, $^3J_{H-H}$ = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 174.4 (*C*O); 154.5 (*C*O); 63.8 (OC–*C*H_2); 58.8 (N–*C*H); 29.5 (O–*C*H_2); 28.7 $(CH_3)_2$*C*H); 18.3 (CH_2–*C*H_3); 15.0 (*C*H_3); 8.8 (*C*H_3). [13]

4.1.2. Preparation of the (S)-3-((S)-2-fluoropropanoyl)-4-isopropyloxazolidin-2-one 3a

LDA (2 M in THF/*n*-heptane, 5.6 mL, 11.2 mmol) was added to a solution of **7** (1.72 g, 9.29 mmol) in dry THF (30 mL) at −78 °C. After 1.5 h *N*-fluorobenzene sulfonimide 97% (4.51 g, 13.93 mmol) was added and the solution was stirred for 2 h at −78 °C. The reaction was then quenched with a saturated solution of NH_4Cl. The product was extracted into Et_2O, washed and dried over $MgSO_4$. Solvents were removed under reduced pressure. The product was purified over silica (hexane/EtOAc from 90/10 to 70/30), and recovered as a brown oil (1.05 g, 56%) with a diastereoisomeric ratio of 90:10. This selectivity was improved to 95/5 after a second purification over silica (hexane/EtOAc 95/5).

HRMS (CI) calculated for $C_9H_{15}NO_3F$ = 204.1036 found = 204.1029. ν_{max}/cm^{-1} 2962, 1777, 1713, 1388, 1201, 1133, 1044. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.01 (qd, 1 H, $^3J_{H-H}$ = 6.5 Hz, $^2J_{F-H}$ = 49.0 Hz, FC*H*); 4.42 (m, 1 H, N–C*H*); 4.34 (dd, 1 H, $^3J_{H-H}$ = 7.9 Hz, $^2J_{H-H}$ = 8.9 Hz, *H*CH); 4.27 (dd, 1 H, $^3J_{H-H}$ = 3.1 Hz, $^2J_{H-H}$ = 8.9 Hz, HC*H*); 2.47 (m, 1 H, $(CH_3)_2$C*H*); 1.58 (dd, 3 H, $^3J_{H-H}$ = 6.5 Hz, $^3J_{F-H}$ = 23.9 Hz, FHC–CH_3); 0.93 (d, 3 H, $^3J_{H-H}$ = 7.0 Hz, CH_3); 0.88 (d, 3H, $^3J_{H-H}$ = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 170.7 (d, $^2J_{F-C}$ = 22.8 Hz, O*C*–CHF); 153.9, (*C*O); 86.2 (d, $^1J_{F-C}$ = 176.5 Hz, *C*HF); 64.5 (*C*H_2); 59.0 (N–*C*H); 28.4 ($(CH_3)_2$*C*H); 18.6 (d, $^2J_{F-C}$ = 23.3 Hz, FHC–*C*H_3); 18.3 (*C*H_3); 14.8 (*C*H_3). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −184.5 (qd, $^3J_{F-H}$ = 23.9 Hz, $^2J_{F-H}$ = 49.0 Hz). $^{19}F\{^1H\}$ NMR ($CDCl_3$, 282 MHz): δ (ppm) = −184.5. MS (CI^+) *m*/*z* (rel. int.): [MH^+] 204 (100), 184 (100).

4.1.3. Preparation of the ethyl (S)-2-(methylsulfonyloxy)-propanoate 9

(*S*)-(−)-Ethyl lactate **8** 98% (10 mL, 85.78 mmol) was added to a solution of triethylamine (15 mL, 107.62 mmol), DMAP (0.2 g, 1.64 mmol) in dry THF (50 mL) at room temperature. The solution was cooled to −20 °C and methyl sulfonyl chloride (8 mL, 103.36 mmol) was added. The reaction was then warmed to 60 °C and stirred for 6 h. The solution was filtered through celite, washed with Et_2O and solvents were removed under reduced pressure. The product was recovered as a brown oil (15.4 g, 91%) and used without further purification.

$[\alpha]_D = -44.4°$ (*C* = 1.05, DCM). ^1H–NMR ($CDCl_3$, 300 MHz): δ (ppm) = 5.07 (q, 1 H, $^3J_{H-H}$ = 7.0 Hz); 4.21 (q, 2 H, $^3J_{H-H}$ = 7.1 Hz); 3.11 (s, 3 H); 1.57 (d, 3H, $^3J_{H-H}$ = 7.0 Hz); 1.27 (*t*, 3 H, $^3J_{H-H}$ = 7.1 Hz). ^{13}C–NMR ($CDCl_3$, 75 Mz): δ (ppm) = 169.81 (*C*O); 74.72 (SO_2*C*H_3); 62.46 (*C*H_2); 39.49 (O*C*H); 18.75 (CH_3); 14.44 (CH_3). [14].

4.1.4. Preparation of the ethyl 2-(R)-fluoropropanoate 10

(*S*)-Ethyl 2-(methylsulfonyloxy)-propanoate **9** (15 g, 76.44 mmol) was added to a solution of potassium fluoride (17.7 g, 305 mmol) in formamide (60 mL). The solution was heated at 90 °C for 4 h and then the product was distilled from the reaction mixture under reduced pressure. The title compound **10** was recovered as a colourless oil (8.1 g, 87%).

$[\alpha]_D$ = + 3.9 ° (*C* = 1.045, DCM). ^{1}H–NMR ($CDCl_3$, 300 MHz): δ (ppm) = 4.97 (qd, 1 H, $^3J_{H-H}$ = 6.9 Hz, $^2J_{F-H}$ = 48.7 Hz); 4.23 (q, 2 H, $^3J_{H-H}$ = 7.1 Hz); 1.55 (dd, 3H, $^3J_{H-H}$ = 6.9 Hz, $^3J_{F-H}$ = 23.6 Hz); 1.28 (*t*, 3 H, $^3J_{H-H}$ = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) = 170.4 (d, $^2J_{C-F}$ = 23.4 Hz, *C*O); 85.6 (d, $^1J_{C-F}$ = 181.4 Hz, *C*F); 61.5 (*C*H_2); 22.5 (d, $^2J_{C-F}$ = 18.3 Hz, *C*H_3); 14.11 (*C*H_3). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −185.05 (dq, $^3J_{F-H}$ = 23.6 Hz, $^2J_{F-H}$ = 48.7 Hz). [14].

4.1.5. Preparation of (S)-3-((R)-2-fluoropropanoyl)-4-isopropyloxazolidin-2-one **3b**

4.1.5.1. Preparation of (R)-2-fluoropropanoyl chloride. Chlorosulfonic acid (3.3 mL, 50 mmol) was added to a solution of phthaloyl dichloride (7.2 mL, 50 mmol) and ethyl-2-(*R*)-fluoropropanoate **10** (3 g, 25 mmol) at room temperature. The solution was heated at 120 °C for 4 h. 2-(*R*)-Fluoropropanoyl chloride was distilled from the reaction mixture under reduced pressure and recovered as a colour less oil (1.73 g, 63%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 5.15 (dq, 1 H, $^3J_{H-H}$ = 6.9 Hz, $^2J_{F-H}$ = 48.6 Hz); 1.71 (dd, 3 H, $^3J_{H-H}$ = 6.9 Hz, $^3J_{F-H}$ = 22.8 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −171.4 (dq, $^3J_{F-H}$ = 22.8 Hz, $^2J_{F-H}$ = 48.6 Hz).

*4.1.5.2. Preparation of (S)-3-((R)-2-fluoropropanoyl)-4-isopropyloxazolidin-2-one **3b**.* *n*-Butyl lithium (2.5 M in hexane, 7.5 mL, 18.7 mmol) was added to a solution of 4-(*S*)-4-isopropyl-2-oxazolidinone **6** (2.2 g, 1.7 mmol) in dry THF (20 mL) at −50 °C. After 30 min (*R*)-2-fluoropropanoyl chloride (1.7 mL, 1.5 mmol) was added, and the solution was stirred for 4 h at −50 °C. The reaction was then quenched with a saturated solution of NH_4Cl. The organic compounds were extracted into Et_2O, washed and dried over $MgSO_4$. Solvents were removed under reduced pressure. The product **3b** was purified over silica (hexane/EtOAc, 80/20), and recovered as a brown oil (1.85 g, 59%) with a diastereoisomeric ratio of 97:3 (in ^{19}F NMR).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.0 (qd, 1 H, $^3J_{H-H}$ = 6.7 Hz, $^2J_{F-H}$ = 49.5 Hz, FC*H*); 4.5 (m, 1 H, N–C*H*); 4.4 (dd, 1H, $^3J_{H-H}$ = 8.4 Hz, $^2J_{H-H}$ = 9.2 Hz, *H*CH); 4.3 (dd, 1 H, $^3J_{H-H}$ = 3.2 Hz, $^2J_{H-H}$ = 9.2 Hz, HC*H*); 2.35 (m, 1 H, $(CH_3)_2$C*H*); 1.64 (dd, 3 H, $^3J_{H-H}$ = 6.7 Hz, $^3J_{F-H}$ = 23.6 Hz, FHC–C*H*$_3$); 0.92 (d, 3 H, $^3J_{H-H}$ = 7.0 Hz, C*H*$_3$); 0.87 (d, 3 H, $^3J_{H-H}$ = 6.9 Hz, C*H*$_3$). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −186.2 (qd, $^3J_{F-H}$ = 23.6 Hz, $^2J_{F-H}$ = 49.5 Hz). MS (CI^+) *m*/*z* (rel. int.): [MH^+] 204 (100), 184 (100).

4.1.6. Preparation of the aldol product **4a**:

$TiCl_4$ (1 M in DCM, 1.5 mL, 1.5 mmol) was added to a solution of **3a** (0.3 g, 1.48 mmol) in dry DCM (5 mL) at −78 °C. After 5 min, diisopropylethyl amine 99.5% (310 μL, 1.77 mmol) was added and the solution was stirred for 2 h at −78 °C. Then $TiCl_4$ (1 M in DCM, 3 mL, 3 mmol) was added, and then after 5 min hexanal 96% (0.9 mL, 7.5 mmol) was added. The solution was stirred for 4 h at −78 °C and the reaction was then quenched with a saturated solution of NH_4Cl. The organic products were extracted into Et_2O, washed and dried over $MgSO_4$. Solvents were removed under reduced pressure and the product was purified over silica (hexane/ethyl acetate, 80/20). The title compound **4a** was recovered as a white solid (0.332 g, 74%).

HRMS (CI) calc for $C_{15}H_{27}NO_4F$ = 304.1924, found = 304.1929. mp = 122 °C. $[\alpha]_D$ = +45° (*C* = 0.82, DCM). ν_{max}/cm^{-1} 3329, 2953, 1803, 1692, 1365, 1208, 1150, 1125. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 4.46 (m, 1 H, N–C*H*); 4.32 (dd, 1 H, $^2J_{H-H}$ = 9.0 Hz $^3J_{H-H}$ = 8.0 Hz, *O*–C*H*H); 4.23 (dd, 1 H, $^3J_{H-H}$ = 3.6 Hz, $^2J_{H-H}$ = 9.0 Hz, O–CH*H*); 4.1 (m, 1 H, HOC*H*); 3.26 (1 H, $^3J_{H-H}$ = 5.3 Hz, *H*OCH); 2.38 (m, 1 H, $(CH_3)_2$C*H*); 1.7 (d, 3 H, $^3J_{F-H}$ = 22.2 Hz, FC–C*H*$_3$); 1.47–1.29 (m, 8 H, 4× CH_2); 0.90 (m, 9 H, 3× C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 172.8 (d, $^2J_{C-F}$ = 27.9 Hz, O*C*–CF); 153.0 (*C*O); 101.7 (d, $^1J_{C-F}$ = 190.2 Hz, *C*F); 75.2 (d, $^2J_{C-F}$ = 23.5 Hz, HO*C*H); 64.1 (O–*C*H_2); 60.8 (N–*C*H); 32.0 (*C*H_2); 31.5 (d, $^3J_{C-}$ = 4.5 Hz, *C*H_2); 28.7 $(CH_3)_2$*C*H); 26.0 (*C*H_2); 22.9 (*C*H_2); 19.6 (d, $^2J_{C,F}$ = 23.6 Hz, FC–*C*H_3); 18.4 (*C*H_3); 15.1 (*C*H_3); 14.4 (*C*H_3). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −158.3 (qd, $^3J_{H-F}$ = 22.2 and 15.5 Hz). ^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −158.3.

4.1.7. Preparation of the aldol product **5**

$TiCl_4$ (1 M in DCM, 0.5 mL, 0.5 mmol) was added to a solution of **3a** (0.1 g, 0.45 mmol) in dry DCM (2 mL) at −78 °C. After 5 min, diisopropylethyl amine 99.5% (105 μL, 0.59 mmol) was added and the solution was stirred for 2 h at −78 °C, and then $TiCl_4$ (1 M in DCM, 0.5 mL, 0.5 mmol) was added. After 5 min, benzaldehyde 99.5% (90 μL, 0.9 mmol) was added and the solution was stirred for 4 h at −78 °C. Then the reaction was quenched with a saturated solution of NH_4Cl. The products were extracted into Et_2O, washed and dried over $MgSO_4$. Solvents were removed under reduced pressure and the product was purified over silica (hexane/ethyl acetate, 70/30). The aldol product **5** was recovered as a white solid (0.093 g, 67%).

HRMS (ES) calculated for $C_{16}H_{20}NO_4FNa$ = 332.1274, found = 332.1280. mp = 102–104 °C. $[\alpha]_D$ = +43.5° (*C* = 1, DCM). ν_{max}/cm^{-1} 3490, 2965, 1787, 1701, 1454, 1387, 1366, 1305, 1201, 1112, 1054, 704. NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.38 (m, 2 H, Ar); 7.30 (m, 3 H, Ar); 5.35 (d, 1 H, $^3J_{F-H}$ = 15.9 Hz, *H*C–OH); 4.29 (m, 1 H, N–C*H*); 4.17 (m, 2 H, O–CH_2); 3.70 (br s, 1 H, O*H*); 2.16 (m, 1 H, $(CH_3)_2$C*H*); 1.67 (d, 3H, $^3J_{F-H}$ = 22.3 Hz, FC–C*H*$_3$); 0.85 (d, 3 H, $^3J_{H-H}$ = 7.0 Hz, $(CH_3)_2$CH); 0.75 (d, 3 H, $^3J_{H-H}$ = 6.9 Hz, $(CH_3)_2$CH). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 171.5 (d, $^2J_{C-F}$ = 27.5 Hz, O*C*–CF); 152.7 (*C*O); 138.1 (Ar); 128.5 (Ar); 128.2 (Ar); 127.8 (Ar); 99.4 (d, $^1J_{C-F}$ = 194.0 Hz, *C*F); 76.3 (d, $^2J_{C-F}$ = 23.1 Hz, HO*C*H); 63.7 (O–*C*H_2); 60.3 (N–*C*H); 28.4 $(CH_3)_2$*C*H); 19.6 (d, $^2J_{C,F}$ = 23.3 Hz, FC–*C*H_3); 17.9 (*C*H_3); 14.5 (*C*H_3). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −159.2 (dq, $^3J_{H-F}$ = 22.3 Hz and 15.9 Hz). ^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −159.2.

4.1.8. Preparation of (2S,3S)-benzyl 2-fluoro-3-hydroxy-2-methyloctanoate **11**

n-Butyl lithium (0.2 mL, 0.49 mmol) was added to benzyl alcohol (70 μL, 0.66 mmol) in THF (2 mL) at 0 °C. After

30 min, a solution of **4a** (0.1 g, 0.33 mmol) in THF (2 mL) (previously cooled down to 0 °C) was added and the solution stirred at 0 °C for 2 h. The reaction was then quenched with a saturated solution of NH_4Cl. Organic residues were extracted into Et_2O and the organic layer was washed and dried over $MgSO_4$. Solvents were removed under reduced pressure. The title compound **11** was purified over silica (hexane/EtOAc, 80/20), and recovered as a white solid (73 mg, 79%).

HRMS (ES) calculated for $C_{16}H_{23}O_3FNa$ = 305.1529, found = 305.1534. mp = 36–38 °C. $[\alpha]_D = -25.4^\circ$ (*C* = 1.1, DCM); ν_{max}/cm^{-1} 3443, 2954, 2859, 1739, 1456, 1283, 1114, 1082, 956, 751, 697 ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.36 (br s, 5 H); 5.23 (AB system, 2 H, PhC*H*$_2$); 3.77 (ddd, 1 H, $^3J_{H-H}$ = 2.3 Hz, $^3J_{H-H}$ = 10.0 Hz $^3J_{F-H}$ = 17.8 Hz, HOC*H*); 2.05 (br s, 1 H, O*H*), 1.60 (d, 3 H, $^3J_{F-H}$ = 22.1 Hz, FCC*H*$_3$); 1.53–1.12 (br m, 8 H, 4× C*H*$_2$); 0.87 (*t*, 3 H, $^3J_{H-H}$ = 6.8 Hz, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 171.2 (d, $^2J_{C-F}$ = 25.0 Hz, CO); 144.4 (*C* ar); 129.1 (*C* ar); 129.0 (*C* ar); 128.8 (*C* ar); 97.3 (d, $^1J_{C-F}$ = 187.3 Hz, CF); 75.0 (d, $^2J_{C-F}$ = 22.7 Hz, COH); 67.7 (ph*C*H$_2$); 31.9 (*C*H$_2$); 31.5 (d, $^3J_{C-F}$ = 3.4 Hz, *C*H$_2$); 26.0 (*C*H$_2$); 22.9 (*C*H$_2$); 20.2 ($^2J_{C-F}$ = 23.9 Hz, *C*H$_3$CF); 14.4 (*C*H$_3$). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −167.4 (dq, $^3J_{F-H}$ = 17.8 Hz, $^3J_{F-H}$ = 22.1 Hz).

4.1.9. Preparation of vicinal difluoro compound *14*

Deoxofluor™ (50% in THF, 200 μL, 0.53 mmol) was added to **11** (30 mg, 0.11 mmol) in DCM (2 mL) at room temperature. The solution was then heated under reflux for 2 h and then the reaction mixture was cooled to room temperature and quenched by passing through a pad of silica. ^{19}F NMR analysis indicated complete conversion of the starting material to products **14** and **15** with a ratio 35/65. These two products were purified over silica (hexane/ethyl acetate, 95/5) and recovered as colour less oils (**14**, 7 mg, 23%) (**15**, 11 mg, 40%).

4.1.10. Difluoro compound *14*

HRMS (ES) calculated for $C_{16}H_{22}O_2F_2Na$ = 307.1486, found = 307.1479. $[\alpha]_D = +5.0^\circ$ (*C* = 0.7, $CDCl_3$). ν_{max}/cm^{-1} 2958, 1768, 1652, 1456, 1381, 1282, 1136, 1104. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.4–7.3 (m, 5 H, Ar); 5.2 (2× d, 2 H, $^2J_{H-H}$ = 12.2 Hz, PhCH$_2$); 4.6 (dddd, 1 H, $^3J_{H-H}$ = 1.9 Hz, $^3J_{H-H}$ = 10.0 Hz $^3J_{F-H}$ = 19.8 Hz, $^2J_{F-H}$ = 46.5 Hz, FC–CF*H*); 1.7–1.8 (m, 1 H, FC–C*H*H); 1.6–1.5 (m, 1 H, FC–CH*H*); 1.5 (dd, 3 H, $^3J_{F-H}$ = 21.2 Hz, $^4J_{F-H}$ = 1.2 Hz, C*H*$_3$–CF–CF); 1.4–1.2 (m, 6 H, 3CH$_2$); 7.0 (*t*, 3 H, $^3J_{H-H}$ = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 128.6 (Ar); 128.5 (Ar); 128.2 (Ar); 94.7 (dd, $^1J_{C-F}$ = 179.5 Hz, $^2J_{C-F}$ = 23.4 Hz, HC*F*); 67.5 (Ph*C*H$_2$); 31.4 (*C*H$_2$); 28.2 (dd, $^2J_{C-F}$ = 21.5 Hz, $^3J_{C-F}$ = 3.5 Hz, FC*C*H$_2$); 24.8 (*C*H$_2$); 22.4 (*C*H$_2$); 19.5 (dd, $^2J_{C-F}$ = 24.0 Hz, $^3J_{C-F}$ = 5.1 Hz, FC*C*H$_3$); 14.0 (CH$_3$). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −170.2 (m, 1 F); −191.2 (m, 1 F). ^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz): δ (ppm) = −170.2 (d, $^3J_{F-F}$ = 11.1 Hz, CH$_3$–C*F*); −191.2 (d, $^3J_{F-F}$ = 11.1 Hz, HC*F*).

4.1.11. Elimination product *15*

HRMS (ES) calculated for $C_{16}H_{21}O_2FNa$ = 287.1423, found = 287.1426. $[\alpha]_D = -15.7^\circ$ (*C* = 1.1, $CDCl_3$); ν_{max}/cm^{-1} 2958, 2930, 2873, 1761, 1740, 1456, 1378, 1269, 1118, 971, 696. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.35 (m, 5 H, Ar); 5.8 (ddt, 1 H, $^3J_{H-H}$ = 6.9 Hz, $^3J_{H-H}$ = 15.7 Hz $^4J_{F-H}$ = 1.7 Hz, FC–CH = C*H*); 5.6 (ddt, 1 H, $^4J_{H-H}$ = 1.4 Hz, $^3J_{H-H}$ = 15.7 Hz $^3J_{F-H}$ = 15.9 Hz, FC–C*H* = CH); 5.2 (s, 2 H, PhC*H*$_2$); 2.0 (m, 2 H, CH = CH–C*H*$_2$); 1.6 (d, 3 H, $^3J_{F-H}$ = 21.4 Hz, FCC*H*$_3$); 1.3 (m, 4 H, C*H*$_2$ ×2); 0.9 (*t*, 3 H, $^3J_{H-H}$ = 7.1 Hz, C*H*$_3$). ^{13}C–NMR ($CDCl_3$, 75 Mz): δ (ppm) = 171.0 (d, $^2J_{C-F}$ = 27.1 Hz, CO); 135.3 (*C* ar); 133.4 (d, $^3J_{C-F}$ = 9.8 Hz (FC–C = *C*); 128.6 (*C* ar); 128.4 (*C* ar); 128.1 (*C* ar); 127.1 (d, $^2J_{C-F}$ = 21.1 Hz, (FC–*C* = C); 92.3 (d, $^1J_{C-F}$ = 183.9 Hz, *C*F); 67.1 (ph*C*H$_2$); 31.8 (*C*H$_2$); 30.8 (*C*H$_2$); 26.0 (*C*H$_2$); 23.9 (d, $^2J_{C-F}$ = 25.4 Hz, *C*H$_3$CF); 22.1 (*C*H$_2$); 13.9 (*C*H$_3$). ^{19}F NMR ($CDCl_3$, 282MHz): δ (ppm) = −150.6 (dq, $^3J_{F-H}$ = 15.9 Hz, $^3J_{F-H}$ = 21.4 Hz).

4.1.12. Preparation of (2R,3S)-2-fluoro-2-methyloctane-1,3-diol *12*

$NaBH_4$ (70 mg, 1.84 mmol) was added portion wise to a solution of **11** (138 mg, 0.455 mmol) in a mix of THF (4 mL) and methanol (0.5 mL) at 0 °C. The solution was stirred for 2.5 h at that temperature and then HCl 2N was added till pH 3–4. Water was added and the organic product was extracted into EtOAc. Organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The title compound **12** was purified over silica (cyclohexane/EtOAc, 60/40) and recovered as a white solid (53 mg, 66%).

HRMS (ES) calc for $C_9H_{19}O_2FNa$ = 201.1267 found = 201.1276. $[\alpha]_D = -28^\circ$ (*C* = 0.98, DCM). ν_{max}/cm^{-1} 3320, 2923, 2853, 1463, 1378, 1057. mp = 58–59 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 3.83 (dd, 1 H,, $^3J_{H-H}$ = 12.4 Hz $^3J_{F-H}$ = 25.1 Hz, *Ha*Hb); 3.79 (m, 1 H, *H*COH); 3.65 (dd, 1 H,, $^3J_{H-H}$ = 12.4 Hz $^3J_{F-H}$ = 17.5 Hz, Ha*Hb*); 2.96 (br s, 2 H, O*H*); 1.61–1.23 (m, 8 H, 4× CH$_2$); 1.24 (d, 3H, $^3J_{F-H}$ = 22.4 Hz, C*H*$_3$); 0.89 (*t*, 3H, $^3J_{H-H}$ = 6.6 Hz, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 97.6 (d, $^1J_{C-F}$ = 170.1 Hz, *C*F); 74.0 (d, $^2J_{C-F}$ = 26.3 Hz, H*C*OH); 66.1 (d, $^2J_{C-F}$ = 23.6 Hz, H$_2$*C*OH); 31.7 (*C*H$_2$); 30.8 (d, $^3J_{C-F}$ = 2.8 Hz, *C*H$_2$); 26.0 (*C*H$_2$); 22.5 (*C*H$_2$); 17.4 (d, $^2J_{C-F}$ = 23.2 Hz, *C*H$_3$); 14.0 (*C*H$_3$). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −162.1 (dddq, $^3J_{F-H}$ = 25.1, 22.4, 17.5 and 7.7 Hz).

4.1.13. Preparation of (2R,3S)-2-fluoro-3-hydroxy-2-methyloctyl 4-methylbenzenesulfonate *13*

Tosyl chloride 98% (65 mg, 0.33 mmol) was added to a solution of **12** (49 mg, 0.275 mmol) and 2,4,6-trimethyl pyridine (73 μL, 0.55 mmol) in dichloroethane (3 mL). The solution was heated at 60 °C for 3 days and then EtOAc was added and the reaction mixture was washed with a saturated solution of $CuSO_4$ and thus water. The organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure. The product **13** was purified over silica (cyclohexane/EtOAc, 80/20) and recovered as a colour less oil (52 mg, 57%).

HRMS (CI) calc for $C_{16}H_{26}O_4SF = 333.1536$ found = 333.1528. $[\alpha]_D = -10.4\ ^\circ$ ($C = 0.8$, DCM). ν_{max}/cm^{-1} 2360, 117, 799, 668. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.80 (d, 2 H, $^3J_{H-H} = 8.3$ Hz, H ar); 7.35 (d, 2 H, $^3J_{H-H} = 8.3$ Hz, H ar); 4.25 (dd, 1 H, $^3J_{H-H} = 11.1$ Hz $^3J_{F-H} = 21.0$ Hz, *Ha*Hb); 4.03 (dd, 1 H, $^3J_{H-H} = 11.1$ Hz $^3J_{F-H} = 20.4$ Hz, Ha*Hb*); 3.78–3.70 (m, 1 H, HOC*H*); 2.45 (s, 3 H, CH_3 ar); 2.18 (d, 1 H, $^3J_{H-H} = 5.04$ Hz, O*H*); 1.56–1.23 (m, 8 H, 4× CH_2); 1.27 (d, 3 H, $^3J_{F-H} = 22.0$ Hz, CH_3); 0.88 (*t*, 3 H, $^3J_{H-H} = 6.7$ Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 Mz): δ (ppm) = 145.6 (*C* ar); 132.9 (*C* ar); 130.3 (*C* ar); 128.4 (*C* ar); 96.5 (d, $^1J_{C-F} = 175.8$ Hz, *C*F); 73.0 (d, $^2J_{C-F} = 26.3$ Hz, HO*C*HCF); 71.6 (d, $^2J_{C-F} = 24.1$ Hz, *C*H_2CF); 32.1 (*C*H_2); 30.7 (d, $^3J_{C-F} = 2.2$ Hz, *C*H_2); 26.4 (*C*H_2); 23.0 (*C*H_2); 22.1 (*C*H_3); 17.2 (d, $^2J_{C-F} = 23.2$ Hz, *C*H_3CF); 14.4 (*C*H_3). ^{19}F NMR ($CDCl_3$, 282 MHz): δ (ppm) = −160.7 (dddq, $^3J_{F-H}$ = (21.5 Hz) × 3 and 7.8 Hz).

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[9] Crystal structure data for **4a**: X-ray diffraction studies on a colourless crystal were performed at 93 K using a Rigaku MM007 high brilliance generator, confocal optics with Mo–Kα radiation (λ = 0.71073 Å) and a Mercury CCD. The structure was solved by direct methods. C15H26FNO4, M = 303.37, crystallization from hexane/diethyl ether, monoclinic, space group P2(1), $a = 12.609(3)$, $b = 5.1419(12)$, $c = 13.677(4)$ Å, $\beta = 113.707(10)^\circ$, $U = 811.9(4)$ Å3, $Z = 2$, $D_c = 1.241$ mg m^{-}3, $\mu = 0.096$ mm^{-1}, $F_{000} = 328$, crystal size = 0.28 × 0.10 × 0.01 mm^3, The absolute structure could not be determined, Flack parameter = 0.9(9). Of 4763 measured data, 2604 were unique ($R_{int} = 0.0340$) to give $R_1 = 0.0422$ and $wR^2 = 0.0998$ for 2406 observed reflections. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC.

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