Fluorine-containing optically active allylic alcohols: preparation and Claisen rearrangement as a new entry to highly functionalized fluorinated amino alcohol derivatives

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The reaction of Garner aldehyde **1** with 2-bromo-3,3,3-trifluoropropene in the presence of Zn–Ag couple gave the fluorine-containing, optically active allylic alcohol **2** in 65% yield with a diastereomeric excess greater than 98%. The treatment of Garner aldehyde **1** with CF_3CFBr_2 (**3a**) and CF_3CCl_3 (**3b**) in the presence of zinc powder and catalytic $AlCl_3$ highly diastereoselectively afforded **4a** and **4b**, respectively, in moderate yield. The orthoester Claisen rearrangement of **4a**, **b** and **2** provided a new way to highly functionalized amino alcohol derivatives **6a**–**f** containing a limited number of fluorine atoms.

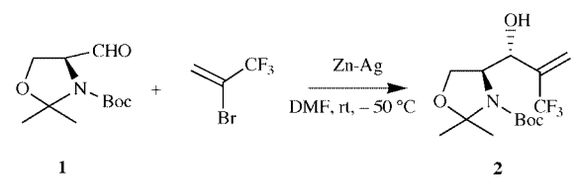
Introduction

Unnatural amino alcohol derivatives and their respective amino acids possess important actions as components of bioactive peptides, enzyme inhibitors, therapeutic agents and chiral ligands.[1] Because the introduction of fluorine into an organic molecule often leads to dramatic changes in biological activity, due to the unique properties of fluorine,[2] fluorine-containing analogs and derivatives of amino acids attract increasing attention,[3] and how to both introduce the fluorine atom and construct such compounds in a stereocontrolled manner and under mild conditions is a challenge to synthetic organic chemists.[4]

As chiral building blocks, the chiral serine aldehyde (Garner aldehyde **1**) has found numerous applications in the synthesis of a variety of amino alcohol- and amino acid-containing bioactive compounds.[5] In this respect, the most used methods reported so far are diastereoselective addition of alkynyl, alkenyl or alkyl nucleophiles centred on lithium,[6] magnesium,[6,7] or zinc[8] to Garner aldehyde **1**. However, to our knowledge, there are few reports on the diastereoselective addition of fluorine-containing organometallic reagents to Garner aldehyde.[9] We report herein the highly diastereoselective synthesis of fluorine-containing, optically active allylic alcohols through the addition of fluorine-containing organometallic reagents to Garner aldehyde, and their Claisen rearrangement as a new entry to highly functionalized fluorinated amino alcohol derivatives; a preliminary report of a portion of this work has appeared.[10]

Results and discussion

Several years ago, Hu and co-workers[11] reported that zinc-promoted Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with aromatic and aliphatic aldehydes gave CF_3-substituted allylic alcohols in good yields. As part of our continuing interest in the synthesis of trifluoromethyl-containing analogs and derivatives of amino acids, this approach stimulated us to extend Hu's procedure to chiral Garner aldehyde **1**. When Zn–Ag couple was used instead of Zn, the reaction of Garner aldehyde **1** with 2-bromo-3,3,3-trifluoropropene in DMF at 50 °C for 4 h gave the product **2** in 65% yield (Scheme 1). The Barbier-type reaction was highly

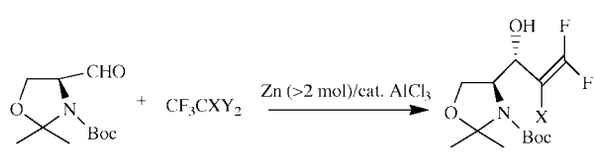


1 **2**

Scheme 1

diastereoselective, affording the *anti* product with a diastereomeric excess greater than 98%. The absolute stereochemistry of **2** was determined by X-ray analysis.[12] The facial selectivity observed here indicated the strong preference for nucleophilic approach according to the Felkin–Anh model.[13]

The nucleophilic addition of the zinc reagent of 2-bromo-3,3,3-trifluoropropene to Garner aldehyde **1** diastereoselectively affording the fluorinated chiral allylic alcohol inspired us to use other fluorohalogenocarbons in a similar reaction. In 1986, Hiyama reported the reaction of aldehydes with CF_3CCl_3,[14] but no such reaction has been reported for chiral aldehydes. In addition, another readily accessible bromofluorocarbon, CF_3CFBr_2, which has been widely utilized in the synthesis of trifluoromethylated heterocyclic compounds,[15] is rarely used for reaction with aldehydes. Thus the reactions of Garner aldehyde **1** with CF_3CFBr_2 **3a** and CF_3CCl_3 **3b** were investigated. We were pleased to find that the reaction of Garner aldehyde **1** with **3a** proceeded smoothly using *N,N*-dimethylacetamide (DMA) as solvent in the presence of zinc powder and catalytic $AlCl_3$ (Scheme 2). The reaction was highly



1 **3a**: X=F, Y=Br; **3b**: X=Y=Cl **4a**: X= F; **4b**: X=Cl

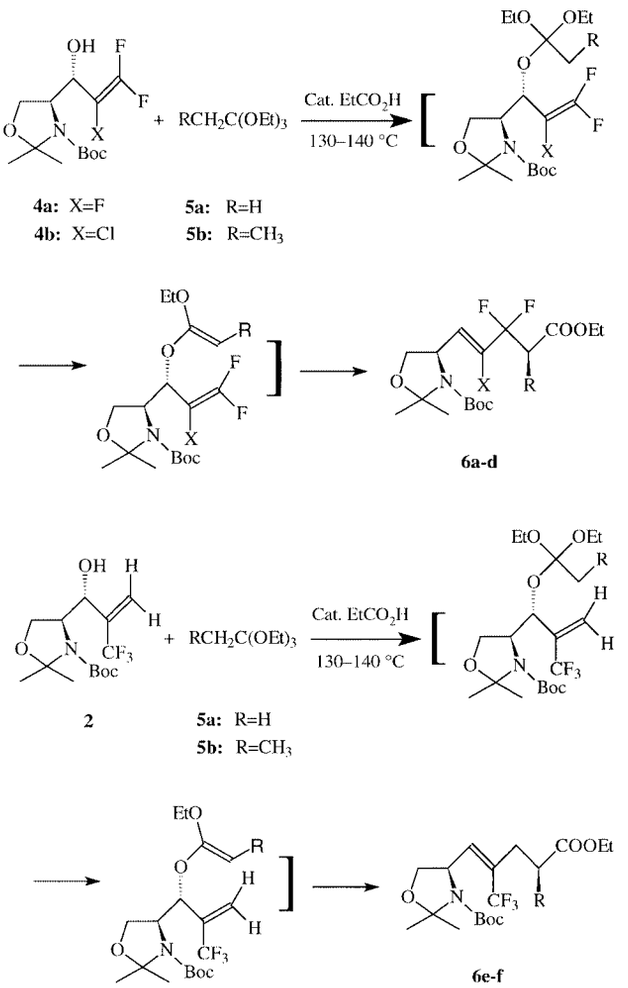
Scheme 2

diastereoselective, affording the *anti* product **4a** in 54% yield with a diastereomeric excess greater than 98% as determined by ^{19}F NMR spectroscopy. When CF_3CCl_3 was used instead of

Table 1 The Claisen rearrangement of compounds **4a**,**b**, **2**

Entry	Allyllic alcohol	Orthester	Product	Yield (%)[a]
1	**4a**	**5a**	**6a**	75
2	**4a**	**5b**	**6b**	80
3	**4b**	**5a**	**6c**	81
4	**4b**	**5b**	**6d**	85
5	**2**	**5a**	**6e**	82
6	**2**	**5b**	**6f**	86

[a] Isolated yield based on compounds **2**, **4a**, **4b**.



Scheme 3

CF_3CFBr_2 under identical reaction conditions, product **4b** was obtained in 58% yield as a single isomer. The absolute structure of **4b** was also determined by X-ray analysis.[16]

Chiral allylic alcohols containing a limited number of fluorine atoms, as a kind of versatile building block, have attracted more attention. In the last ten years, the Claisen rearrangement of fluorinated allylic alcohols has been developed widely;[17] many highly functionalized molecules containing fluorine which are difficult to prepare in the usual way were synthesized through this method. Compounds **2**, **4a** and **4b** are versatile building blocks to synthesize optically active, highly functionalized, fluorinated amino alcohol derivatives. To demonstrate the synthetic utilities of **2**, **4a** and **4b**, the elaboration of their side-chain was investigated by Claisen rearrangement, performed under Claisen–Johnson conditions.[18] Treatment of **2**, **4a** and **4b** with orthoesters **5a**,**b** containing propionic acid at 140 °C for 24 h gave the rearrangement products **6a**–**f** in good yields (Scheme 3 and Table 1). The reaction was stereoselective and gave only one isomer.

The stereochemistry of the products was examined. The

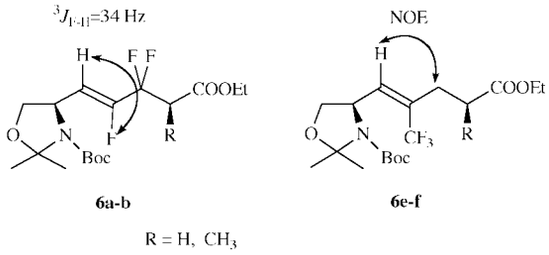


Fig. 1

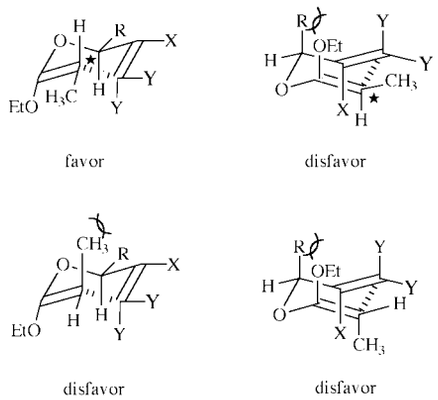
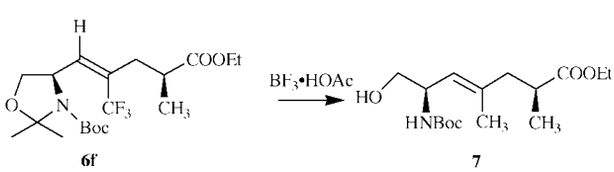


Fig. 2

olefin geometries of **6a**,**b** are assigned to be *Z*; that is, the olefinic proton and the olefinic fluorine are *trans*, since the coupling constants between them are 34.0 Hz;[19] then, the double bond configurational assignments of **6c**,**d** were deduced from this. The assignment of the double bond configuration of **6e**,**f** was confirmed by the strong correlation NOE between the vinylic proton and the allylic proton in the NOESY spectra of these compounds (Fig. 1).

From the *Z* stereochemistry of all the products, the Claisen rearrangements should follow an accepted chair-like transition state[20] as shown in Fig. 2, so we inferred the stereochemistry of the methyl group in compounds **6b**, **6d** and **6f** which were formed in the reaction of compounds **4a**,**b** and **2** with triethylorthopropionate **5b**.

Finally, we used BF_3·HOAc to selectively cleave the acetonide of compound **6f** and obtained the highly functionalized, fluorinated amino alcohol derivative **7** (Scheme 4).



Scheme 4

In conclusion, fluorinated chiral allylic alcohol synthons **2** and **4a**,**b** can be prepared by the reaction of Garner aldehyde **1** with fluorocarbons. The orthoester Claisen rearrangement of **4a**,**b** and **2** provided a new route to highly functional amino alcohol derivatives containing a limited number of fluorine atoms.

Experimental

^{1}H NMR spectra were recorded on a 300 MHz spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were obtained on a 56.4 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. IR

spectra were recorded on a Shimadzu IR-440 spectrometer. Mass spectra were obtained using EI ionization at 70 eV. All reactions were routinely monitored with the aid of TLC or ^{19}F NMR spectroscopy.

Garner aldehyde **1**,[21] 2-bromo-3,3,3-trifluoropropene,[22] CF_3CCl_3 **3b**[23] and CF_3CFBr_2 **3a**[24] were prepared according to published procedures. DMF and DMA were freshly distilled from calcium hydride under reduced pressure. 'Petroleum ether' refers to the fraction with distillation range 60–90 °C.

tert-Butyl (4*S*,1′*S*)-4-[1′-hydroxy-2′-(trifluoromethyl)allyl]-2,2-dimethyloxazolidine-3-carboxylate 2

A mixture of Garner aldehyde **1** (3.0 g, 13.2 mmol), 2-bromo-3,3,3-trifluoropropene (3.5 g, 19.6 mmol), Zn–Ag couple (1.74 g, 26.8 mmol) and anhydrous DMF (50 ml) in a Schlenck tube was stirred at room temperature for 2 h. The reaction mixture was then stirred for 2 h at 50 °C. The mixture was poured into 2 M aq. HCl (45 ml), and the mixture was extracted with ethyl acetate (3 × 40 ml). The combined organic extracts were washed successively with water and brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography, using 10% ethyl acetate–petroleum ether as eluent, to give title compound **2** as a white solid (2.7 g, 65%); $[\alpha]_D$ −35.0 ($CHCl_3$, c = 3.9); ^1H NMR (CD_3COCD_3; 300 MHz) δ 5.99–5.90 (2H, m), 4.81 (1H, m), 4.10–3.85 (4H, m), 1.56–1.44 (15H, m); ^{19}F NMR (CD_3COCD_3; 56.4 MHz) δ −12.0 (s); IR (cm^{-1}) ν_{max} 3458, 2983, 1702, 1479, 1458, 1172, 962, 854; MS (*m*/*z*) 326 (M^+ + 1, 4.33%), 252 (16.17), 210 (25.83), 144 (21.67), 100 (100), 57 (95) (Calc. for $C_{14}H_{22}F_3NO_4$: C, 51.69; H, 6.77; N, 4.31. Found: C, 51.48; H, 7.06; N, 4.14%).

tert-Butyl(4*S*,1′*S*)-2,2-dimethyl-4-(2′,3′,3′-trifluoro-1′-hydroxyallyl)oxazolidine-3-carboxylate 4a

Under nitrogen atmosphere at 0 °C, zinc powder (0.86 g, 13.2 mmol) and anhydrous $AlCl_3$ (175 mg, 1.3 mmol) were added to a solution of aldehyde **1** (1.0 g, 4.4 mmol) and CF_3CFBr_2 **3a** (1.7 g, 6.5 mmol) in DMA (15 ml). The reaction mixture was then stirred for 8 h at 50 °C. The mixture was poured into 2 M aq. HCl (10 ml), and the mixture was extracted with ethyl acetate (3 × 15 ml). The combined organic extracts were washed successively with water and brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography, using 10% ethyl acetate–petroleum ether as eluent, to give title compound **4a** as an oil (740 mg, 54%), $[\alpha]_D^{20}$ −8.63 ($CHCl_3$, c = 3.1); ^1H NMR ($CDCl_3$; 300 MHz) δ 5.10–5.07 (1H, m), 4.44–3.87 (3H, m), 2.95 (1H, br), 1.57–1.48 (15H, m); ^{19}F NMR (CCl_4; 56.4 MHz) δ 29.0 (1F, dd, *J* 90 and 32 Hz), 47.6 (1F, dd, *J* 122 and 90 Hz), 118.0 (1F, ddd, *J* 122, 32 and 32 Hz); IR (cm^{-1}) ν_{max} 3437, 2984, 1791, 1704, 1678, 1040; MS (*m*/*z*) 312 (M^+ + 1, 17.87%), 256 (52.60), 174 (26.50), 144 (17.21), 100 (44.96), 57 (100) (Calc. for $C_{13}H_{20}F_3NO_4$: C, 50.16; H, 6.43; N, 4.50. Found: C, 49.84; H, 6.89; N, 4.10%).

tert-Butyl (4*S*,1′*S*)-4-(2′-chloro-3′,3′-difluoro-1′-hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylate 4b

Treatment of aldehyde **1** (1.0 g, 4.4 mmol) with CF_3CCl_3 **3b** (0.19 ml, 6.5 mmol) as described above yielded title compound **4b** as a white solid (835 mg, 58%), $[\alpha]_D^{20}$ −15.40 ($CHCl_3$, c = 5.0); ^1H NMR ($CDCl_3$; 300 MHz) δ 4.58–4.56 (1H, m), 4.27–4.23 (1H, m), 4.04–4.02 (2H, m), 1.49–1.44 (15H, m); ^{19}F NMR (CCl_4; 56.4 MHz) δ 8.7 (1F, d, *J* 40 Hz), 13.4 (1F, d, *J* 40 Hz); IR (cm^{-1}) ν_{max} 3435, 2983, 1743, 1672, 1407, 1278; MS (*m*/*z*) 254 (M^+ − 73, 10.83%), 200 (26.67), 144 (25.83), 127 (15.0), 100 (96.67), 57 (100) (Calc. for $C_{13}H_{20}ClF_2NO_4$: C, 47.63; H, 6.11; N, 4.27; F, 11.60. Found: C, 47.78; H, 6.31; N, 4.21; F, 11.59%).

General procedure for the Claisen rearrangement reactions

A mixture of an allylic alcohol **2**, **4a**,**b** (0.5 mmol), orthoester **5a**,**b** (3.5 mmol), and propionic acid (4 mg, 0.05 mmol) were heated in an oil-bath at 140 °C for 24 h, the excess of reagent was removed under vacuum, and the resulting oil was purified by flash column chromatography, using 4% ethyl acetate–petroleum ether as eluent, to afford product **6**. Yields are reported above in Table 1.

***tert*-Butyl (4*S*)-4-(4′-ethoxycarbonyl-2′,3′,3′-trifluorobut-1′-enyl)-2,2-dimethyloxazolidine-3-carboxylate 6a.** Oil, $[\alpha]_D^{20}$ +12.60 ($CHCl_3$, c = 0.9); ^1H NMR ($CDCl_3$; 300 MHz) δ 5.47 (1H, dd, *J* 34.1 and 9.5 Hz), 4.78–4.76 (1H, m), 4.19 (2H, q, *J* 7.1 Hz), 4.10 (1H, dd, *J* 9.0 and 6.0 Hz), 3.78–3.75 (1H, m), 3.15–3.04 (2H, m), 1.62–1.43 (15H, m), 1.27 (3H, t, *J* 7.1 Hz); ^{19}F NMR (CCl_4; 56.4 MHz) δ 30.3–31.0 (2F, m), 52.0–53.0 (1F, m); IR (cm^{-1}) ν_{max} 2984, 1749, 1702, 1258, 1175, 1089; MS (*m*/*z*) 381 (M^+, 7.23%), 366 (M^+ − 15, 42.55), 326 (22.55), 308 (16.17), 266 (100), 57 (17.87) (HRMS for $C_{17}H_{26}F_3NO_5$: Calc. *M*, 381.1764. Found: M^+, 381.1735).

***tert*-Butyl (4*S*,4′*R*)-4-(4′-ethoxycarbonyl-2′,3′,3′-trifluoropent-1′-enyl)-2,2-dimethyloxazolidine-3-carboxylate 6b.** Oil, $[\alpha]_D^{20}$ −3.77 ($CHCl_3$, c = 1.1); ^1H NMR ($CDCl_3$; 300 MHz) δ 5.44 (1H, dd, *J* 34.3 and 9.2 Hz), 4.78–4.77 (1H, m), 4.19 (2H, q, *J* 7.1 Hz), 4.10 (1H, dd, *J* 9.0 and 6.0 Hz), 3.75–3.73 (1H, m), 3.20–3.14 (1H, m), 1.62–1.43 (15H, m), 1.27 (3H, t, *J* 7.1 Hz), 1.21–1.16 (3H, m); ^{19}F NMR (CCl_4; 56.4 MHz) δ 22.6–24.0 (2F, m), 53.0–54.0 (1F, m); IR (cm^{-1}) ν_{max} 2984, 1745, 1702, 1459, 1386, 1259; MS (*m*/*z*) 395 (M^+, 0.09%), 380 (3.83), 322 (0.2), 281 (10), 280 (100), 57 (27.83) (Calc. for $C_{18}H_{28}F_3NO_5$: C, 54.68; H, 7.09; N, 3.54. Found: C, 54.50; H, 7.37; N, 3.48%).

***tert*-Butyl (4*S*)-4-(2′-chloro-4′-ethoxycarbonyl-3′,3′-difluorobut-1′-enyl)-2,2-dimethyloxazolidine-3-carboxylate 6c.** Oil, $[\alpha]_D^{20}$ +23.45 ($CHCl_3$, c = 0.5); ^1H NMR (CD_3COCD_3; 300 MHz) δ 6.39 (1H, d, *J* 8.3 Hz), 4.84–4.79 (1H, m), 4.26–4.16 (3H, m), 3.79 (1H, dd, *J* 9.2 and 2.6 Hz), 3.31 (2H, t, *J* 14.3 Hz), 1.59 (3H, s), 1.48 (3H, s), 1.44 (9H, s), 1.26 (3H, t, *J* 7.1 Hz); ^{19}F NMR (CCl_4; 56.4 MHz) δ 18.5 (t, *J* 14.3 Hz); IR (cm^{-1}) ν_{max} 2983, 1749, 1704, 1459, 1379, 1257; MS (*m*/*z*) 398 (M^+, 0.09%), 342 (22.31), 324 (13.76), 298 (38.01), 282 (100), 57 (60.03); ^{13}C (CD_3COCD_3; 75 MHz) δ 167.0, 155.0, 133.8, 127.5, 119.0, 95.5, 81.7, 68.4, 62.1, 56.7, 41.5, 30.2, 28.8, 14.6 (HRMS for $C_{17}H_{26}Cl^{35}F_2NO_5$: Calc. *M*, 397.1469. Found: M^+ 397.1512).

***tert*-Butyl (4*S*,4′*R*)-4-(2′-chloro-4′-ethoxycarbonyl-3′,3′-difluoropent-1′-enyl)-2,2-dimethyloxazolidine-3-carboxylate 6d.** Oil, $[\alpha]_D^{20}$ +32.80 ($CHCl_3$, c = 4.5); ^1H NMR ($CDCl_3$; 300 MHz) δ 6.29 (1H, d, *J* 8.3 Hz), 4.82–4.77 (1H, m), 4.23–4.12 (3H, m), 3.76–3.73 (1H, m), 3.38–3.29 (1H, m), 1.63–1.43 (15H, m), 1.33 (3H, m), 1.28 (3H, t, *J* 7.0 Hz); ^{19}F NMR (CCl_4; 56.4 MHz) δ 26.3–27.0 (2F, m); IR (cm^{-1}) ν_{max} 2984, 1745, 1704, 1461, 1379, 1257; MS (*m*/*z*) 396 (M^+ − 15, 3.33%), 338 (1.21), 296 (100), 254 (6.14), 188 (4.26), 57 (74.75) (Calc. for $C_{18}H_{28}F_2ClNO_5$: C, 52.49; H, 6.80; N, 3.40. Found: C, 52.18; H, 7.04; N, 3.19%.

***tert*-Butyl (4*S*)-4-[4′-ethoxycarbonyl-2′-(trifluoromethyl)but-1′-enyl]-2,2-dimethyloxazolidine-3-carboxylate 6e.** Oil, $[\alpha]_D^{20}$ −39.85 ($CHCl_3$, c = 0.6); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.81 (1H, d, *J* 8.6 Hz), 4.75–4.73 (1H, m), 4.18–4.09 (3H, m), 3.70 (1H, dd, *J* 9.0 and 3.0 Hz), 2.57–2.45 (4H, m), 1.63–1.41 (15H, m), 1.26 (3H, t, *J* 7.1 Hz); ^{19}F NMR (CCl_4; 56.4 MHz) δ −17.6 (s); IR (cm^{-1}) ν_{max} 2983, 1739, 1704, 1458, 1380, 1249; MS (*m*/*z*) 396 (M^+ + 1, 0.85%), 380 (26.92), 356 (11.09), 322 (22.22), 294 (6.41), 280 (100) (Calc. for $C_{18}H_{28}F_3NO_5$: C, 54.68; H, 7.09; N, 3.54. Found: C, 54.55; H, 7.16; N, 3.29%).

***tert*-Butyl (4*S*,4′*S*)-4-[4′-ethoxycarbonyl-2′-(trifluoromethyl)-pent-1′-enyl]-2,2-dimethyloxazolidine-3-carboxylate 6f.** Oil, $[\alpha]_D^{20}$ −27.38 ($CHCl_3$, $c = 2.4$); ^{1}H NMR ($CDCl_3$; 300 MHz) δ 5.80 (1H, d, J 8.7 Hz), 4.76–4.74 (1H, m), 4.19–4.08 (3H, m), 3.70 (1H, dd, J 9.0 and 2.9 Hz), 2.68–2.60 (2H, m), 2.27–2.17 (1H, m), 1.63–1.42 (15H, m), 1.25 (3H, t, J 7.1 Hz), 1.21–1.17 (3H, m); ^{19}F NMR (CCl_4; 56.4 MHz) δ −17.6 (s); IR (cm^{-1}) ν_{max} 2983, 1739, 1704, 1458, 1380, 1249; MS (*m*/*z*): 409 (M^+, 4.27%), 394 ($M^+ - 15$, 5.98), 308 (11.54), 294 (100), 248 (22.22), 208 (11.11) (Calc. for $C_{19}H_{30}F_3NO_5$: C, 55.75; H, 7.33; N, 3.42. Found: C, 55.84; H, 7.53; N, 3.18%.

Ethyl (2*S*,6*S*)-6-*tert*-butoxycarbonylamino-7-hydroxy-2-methyl-4-(trifluoromethyl)hept-4-enoate 7

A mixture of compound **6f** (50 mg, 0.13 mmol) and boron trifluoride–acetic acid (0.26 ml, 1.87 mmol) in CH_3OH (2 ml) was stirred at 0 °C for 3 h. Saturated aq. Na_2CO_3 (5 ml) was added, and the mixture was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were washed successively with water and brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography, using 20% ethyl acetate–petroleum ether as eluent, to give title compound **7** as a white solid (36 mg, 82%), $[\alpha]_D^{20}$ −13.02 ($CHCl_3$, $c = 0.7$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78–5.73 (1H, m), 5.11 (1H, br), 4.60 (1H, m), 4.12 (2H, q, J 7.1 Hz), 3.74–3.60 (2H, m), 2.70–2.53 (2H, m), 2.30–2.24 (1H, m), 1.84 (1H, br), 1.43 (9H, s), 1.25 (3H, t, J 7.1 Hz), 1.19–1.16 (3H, m); ^{19}F NMR (CCl_4; 56.4 MHz) δ −18.0 (s); ^{13}C ($CDCl_3$; 75 MHz) δ 175.56, 155.70, 137.69, 128.39, 123.79, 80.50, 65.55, 60.73, 51.16, 38.67, 36.33, 28.37, 16.94, 14.21; IR (cm^{-1}) ν_{max} 3378, 2980, 1720, 1702, 1518, 1369; MS (*m*/*z*) 337 ($M^+ - 30$, 0.80%), 296 (1.14), 263 (18.72), 238 (59.99), 164 (50), 57 (100) [HRMS for $C_{15}H_{23}F_3NO_4$ ($M^+ - 31$): Calc. *m*/*z* 338.1580. Found: *m*/*z* 338.1571].

Acknowledgements

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