Regio- and diastereoselective ring-opening of (*S*)-(−)-2-(trifluoromethyl)oxirane with chiral 2,5-disubstituted tetrahydroquinolines in hexafluoro-2-propanol

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Multi-hundred grams of (*S*)-1,1,1-trifluoro-3-{(*R*)-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)-phenyl]-3,4-dihydroquinolin-1(2H)-yl}propan-2-ol, a potent cholesteryl ester transfer protein (CETP) inhibitor, was prepared in quantitative isolated yield (>99%) with excellent chemical (>99% HPLC area%) and optical (>99% de) purities. The cornerstone to these results were achieved by regiospecific and diastereoselective ring-opening of optically pure (*S*)-(−)-2-(trifluoromethyl)-oxirane (>99% ee) with (*R*)-2-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-5-[3-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydro-quinoline (>99% ee) in hexafluoro-2-propanol at 22 °C for 24 h. This reaction did not require a rare earth metal salt ($Yb(OTf)_3$) as the catalyst nor a column chromatography for the purification. The excess (*S*)-(−)-2-(trifluoromethyl)oxirane and the solvent hexafluoro-2-propanol were recovered by distillation from the reaction and reused.

Introduction

(*S*)-1,1,1-Trifluoro-3-((*R*)-2-(3-(1,1,2,2-tetrafluoroethoxy)-phenyl)-5-(3-(trifluoromethoxy)phenyl)-3,4-dihydroquinolin-1-(2H)-yl)propan-2-ol ((*R*,*S*)-**2**), a potent cholesteryl ester transfer protein (CETP) inhibitor with IC_{50} = 39 nM in a CETP SPA assay and IC_{50} = 0.2 μM in a human plasma 3H-CE HDL *in vitro* assay,[1a,1b] was originally prepared in 29–69% chromatographically isolated yield *via* Lewis acid $Yb(OTf)_3$-catalyzed epoxide ring-opening[2] of (*S*)-(−)-2-(trifluoromethyl)oxirane ((*S*)-TFMO) with (*R*)-2-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)-5-(3-(trifluoromethoxy)-phenyl)-1,2,3,4-tetrahydroquinoline[1] ((*R*)-**1**, ≥97% ee) in dichloromethane (DCM)[1b] or 1,2-dichloroethane (DCE)[1a,1c] at 50 °C for 48 h. Because a rare earth metal salt ($Yb(OTf)_3$) and a carcinogenic solvent (DCM or DCE) were used in this last step to afford a low-to-moderate yield of the desired diastereomeric pure product (*R*,*S*)-**2** after purification by column chromatography, there was a need to find an environmental benign and more efficient method for scale up preparation of (*R*,*S*)-**2**. Herein, we report a green chemical process that is suitable for large quantity production of (*R*,*S*)-**2**.

Results and discussion

Among all physical and chemical parameters whose values determine the quality and yield of the product (*R*,*S*)-**2** from the ring-opening of (*S*)-TFMO with (*R*)-**1**, the chemical and optical purities of both starting (*R*)-**1** and (*S*)-TFMO have the most impact. Yet, (*S*)-TFMO with 75% ee (bp 25–32 °C) was the only commercially obtainable source in the early stage of this project in the beginning of 2006. Although a few stereoselective synthetic methods[3] for preparing 96% ee[3a] and ≥99% ee[3b] (*S*)-TFMO were available before 2006, optically pure (*S*)-TFMO was not commercially available until recently.[4] For the purpose of scale up, the reproducibility of $Yb(OTf)_3$-catalyzed ring-opening reaction was examined under the reported conditions,[1] where (*S*)-TFMO with 75% ee was treated with (*R*)-**1** (97% ee) in DCE at 50 °C for 48 h, HPLC analysis showed an incomplete reaction mixture that was composed of 61% of (*R*,*S*)-**2** and 11% of (*R*,*R*)-**2** along with 25% of starting (*R*)-**1** (entry 1 of Table 1). Noticeably, the (*R*,*S*)-**2** produced in this reaction mixture was 69.4% de, which was lower than the optical purity of starting (*S*)-TFMO (75% ee), indicating the epoxide ring-opening of (*S*)-TFMO under this $Yb(OTf)_3$-catalyzed conditions was not 100% stereoselective. These results contrasted with the reported ring-opening of (*S*)-2-(chloromethyl)oxirane (3–5 eq.) with 1,2,3,4-tetrahydro-1,5-naphthyridine or 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepine, where the reactions were carried out under similar conditions ($Yb(OTf)_3$ (0.2 eq.) in DCM at 60 °C for 3–5 h) but in a pressure tube to afford 53–95% isolated yields.[2a] Furthermore, the treatment of (*S*)-TFMO (96% ee) with excess diethylamine (10 eq.) in a sealed tube at 55 °C afforded a 88% isolated yield of (*S*)-1-(diethylamino)-3,3,3-trifluoro-2-propanol with retained optical purity (96% ee).[3a] This reaction demonstrated the first example for regiospecifically ring-opening of (*S*)-TFMO with a secondary amine without the aid of a Lewis acid as the catalyst. However, sealed-tube closed-system conditions[2a,3a] are not a first choice for scale up production of (*R*,*S*)-**2** in a regular chemistry lab. In addition to $Yb(OTf)_3$-catalyzed ring-opening, simple epoxides and 1-substituted-2-(trifluoromethyl)oxirane ethers were treated

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Table 1 The results of selective ring-opening of (*S*)-TFMO with (*R*)-**1** or (*S*)-**1** in HFP

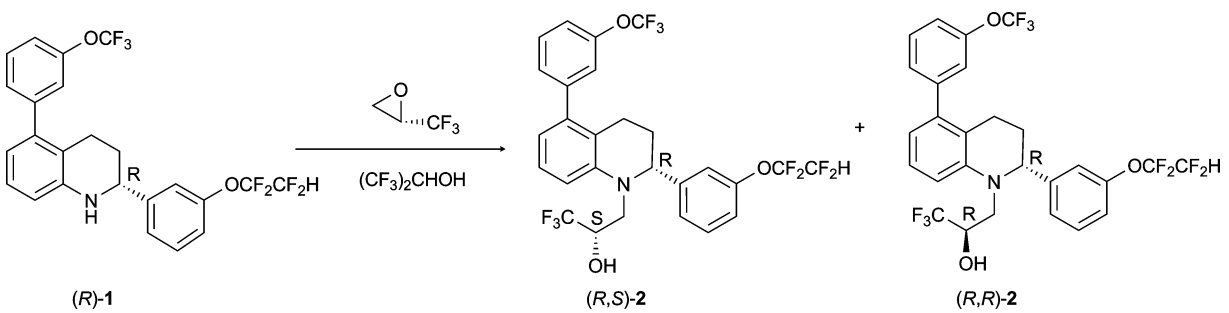
Entry	(*R*)-**1** (g/% ee)	(*S*)-TFMO (eq./% ee)	Solvent (mL or eq.)	*T*/°C	Time/h	(*R*,*S*)-**2**/(*R*,*R*)-**2**/(*R*)-**1** (HPLC, area%)	(*R*,*S*)-**2** (g/%)
1	1.0/97.0	5.0/75.0 $Yb(OTf)_3$ (0.25 eq.)	DCE (12 mL)	50	48	61%/11%/25%[b]	0.62/46.0[a]
2	1.0/97.0	5.0/75.0	DCE (12 mL)	40	24	0%/0%/97%	0/0
3	1.0/97.0	5.0/75.0	DCE/HFP (5 mL/5 eq.)	40	48	50%/7%/40%	N/I[b]
4	1.0/97.0	5.0/75.0	HFP (23 eq.)	40	6	87.7%/11.6%/0.67%	0.96/78.0[a]
5	1.0/97.0	2.3/75.0	HFP (23 eq.)	40	24–48	77%/11%/9%	N/I[b]
6	1.0/97.0	5.0/75.0	IPA (12 mL)	40	24	0%/0%/96%	N/I[b]
7	0.5/99.0	2.0/96.0	H_2O (0.2 mL)	40	48	0%/0%/99%	N/I[b]
8	30/99.0	3.6/75.0	HFP (14 eq.)	40	19	83.6%/12.4%/4%	29.5/80.0 (99.5% de)
9	1.0/99.7	3.0/99.2	HFP (9.3 eq.)	22	24	99.7%/0.0%/0.3%	1.27/103[c] (99.5% de)
10	255.3/99.5	3.0/99.2	HFP (10 eq.)	22	24	99.2%/0.0%/0.2%	294.5/99.3[d] (99.5% de)
11	0.2/99.8	8.5/75.0	HFP (11.5 eq.)	22	48	88.0%/12.0%/0.0%	N/I[b]
12	(*S*)-**1** 0.2/99.7	8.5/75.0	HFP (11.5 eq.)	22	48	(*S*,*S*)-**2**/(*S*,*R*)-**2**/(*S*)-**1** 88.0%/12.0%/0.0%	N/I[b]
13	(*S*)-**3** 223.5/85.0	2.5/99.2	HFP (9.0 eq.)	50	19	(*S*,*S*)-**4**/(*S*,*R*)-**4**/(*S*)-**3** 92.6%/7.4%/0.0%	(*S*,*S*)-**4** 162.3/61.0[e] (>98% de)

[a] Isolated yield after chromatography. [b] The reaction mixture was not purified. [c] The compound contained traces of solvent residue HFP. [d] Isolated without chromatographic purification. [e] The isolated yield from crystallization.

with secondary aromatic amines in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP, bp 58.2 °C) without the need for a Lewis acid to afford moderate-to-high yields of the corresponding cyclic amino alcohols (68–92%)[5a,5b] and 3-trifluoromethyl indole derivatives (65–98%), respectively.[5c,5d] Interestingly, the reaction of 1-substituted 2-(trifluoromethyl)oxirane ethers with 1,2,3,4-tetrahydroquinoline in HFP resulted in high yields (90–98%) of 2-substituted 3-(trifluoromethyl)-1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-ij]quinolin-1-ols.[5c] However, regiospecific and diastereoselective ring-opening of (*S*)-TFMO with (*R*)-**1** in HFP have not yet been communicated. In order to investigate the role of HFP in this reaction, a control experiment was conducted in DCE by treating (*S*)-TFMO with (*R*)-**1** without $Yb(OTf)_3$ at 40 °C for 24 h, which gave no reaction (entry 2 of Table 1). When $Yb(OTf)_3$ was replaced with five equivalents of HFP in DCE, the formation of a diastereomeric mixture of (*R*,*S*)-**2** and (*R*,*R*)-**2** was observed along with 40% of unreacted starting (*R*)-**1** after 48 h (HPLC analysis). This result demonstrated the usefulness of HFP to selectively open (*S*)-TFMO with (*R*)-**1** (entry 3 of Table 1 and Scheme 1).

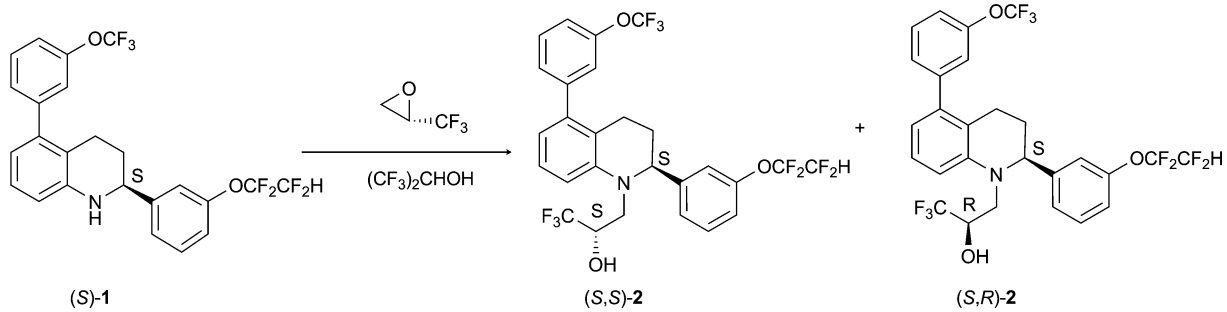
The above incomplete reaction was advanced to near 100% conversion when DCE was replaced by HFP (23 eq.) as the solvent, which achieved a diastereomeric mixture of (*R*,*S*)-**2**/(*R*,*R*)-**2** (87.7%/11.6%; HPLC area%) that retained an optical purity (75% de for (*R*,*S*)-**2**) the same as starting (*S*)-TFMO (entry 4 of Table 1 and Scheme 1). When the amount of (*S*)-TFMO was reduced to 2.3 eq., an incomplete reaction was observed with 9% of unreacted (*R*)-**1** (entry 5 of Table 1); the diastereomeric excess of (*R*,*S*)-**2** was still unchanged at 75% de. Attempts for ring-opening in other solvents, such as IPA or water, were studied and neither (*R*,*S*)-**2** nor (*R*,*R*)-**2** was observed in either reaction by HPLC analyses after 24–48 h at 40 °C (entries 6 and 7 of Table 1). In contrast, a scale up reaction using a 30 g input of (*R*)-**1** with conditions (*S*)-TFMO (75% ee; 3.6 eq.) and HFP (14 eq.) at 40 °C for 19 h resulted in an 80% of (*R*,*S*)-**2** after chromatography with excellent optical purity, which demonstrated the scalable reproducibility of this HFP-assisted ring-opening of (*S*)-TFMO (entry 8 of Table 1). Furthermore, the treatment of a small (1 g) or a large (255 g) amount of optically pure (*R*)-**1** (>99.5% ee) with (*S*)-TFMO (99.2% ee) in HFP at room temperature for 24 h afforded quantitative isolated yields of the desired (*R*,*S*)-**2** with retained optical purity (99.5% de) without chromatographic purification (entries 9 and 10 of Table 1).

The scope of this HFP-assisted selective opening of (*S*)-TFMO was extended to prepare diastereomeric mixture pairs of (*R*,*S*)-**2**/(*R*,*R*)-**2** and (*S*,*S*)-**2**/(*S*,*R*)-**2** for qualitative controls on (*R*,*S*)-**2** production. The resulting diastereomeric pairs,

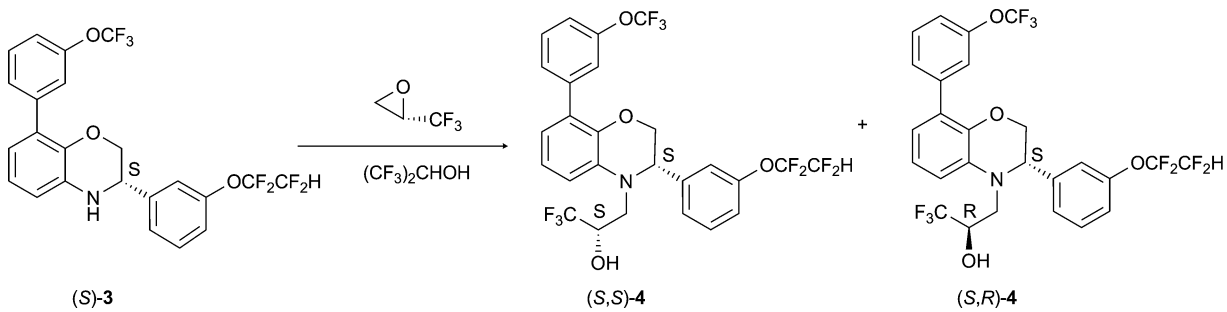


(*R*)-**1** (*R*,*S*)-**2** (*R*,*R*)-**2**

Scheme 1



Scheme 2



Scheme 3

(*R*,*S*)-**2**/(*R*,*R*)-**2** or (*S*,*S*)-**2**/(*S*,*R*)-**2,** were prepared in quantitative yield using (*S*)-enriched TFMO (75% ee) with optically pure (*R*)-**1** (99.8% ee) or (*S*)-**1** (99.7%% ee), respectively (entries 11 and 12 of Table 1 and Scheme 2). Moreover, this HFP-assisted method was also successfully used in the scale up production of (*S*,*S*)-**4** (Scheme 3), another known potent CETP compound, in 61% isolated yield with high chemical and optical purities (entry 13 of Table 1).[6]

In summary, an efficient synthetic method has been developed for the preparation of multi-hundred gram quantities of potent CETP inhibitor (*R*,*S*)-**2** in a quantitative isolated yield with excellent chemical (>99% HPLC area%) and optical (>99% de) purities, by regiospecific and diastereoselective ring-opening of (*S*)-TFMO (99.2% ee) using optically pure *R*-**1** (99.5% ee) in HFP at 22 °C for 24 h. Excess reagent (*S*)-TFMO and the solvent HFP were easily recycled after distillation. This process does not require special equipment nor conditions and generates a minimal amount of chemical waste, which provided a green process for scale-up production of (*R*,*S*)-**2** as well as (*S*,*S*)-**4**.

Experimental

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H-NMR spectra were recorded at 300 MHz on a Bruker Avance-300 instrument. Mass spectra were recorded on an Agilent Series 180 LC/MS instrument (positive/negative modes). The diastereomeric excess of (*R*,*S*)-**2**/(*R*,*R*)-**2** and (*S*,*S*)-**2**/(*S*,*R*)-**2** were determined with an Agilent Series 1100 system at UVmax = 210, 254, using a Chiralcel OJ column (4.6 mm ID × 250 mm, 10 micron) at 20 °C with a flow rate of 0.5 mL min^{-1} and run time of 50.0 min. Solvents: A heptane, B IPA; Gradient: isocratic with 10% IPA. While the chemical purity of (*R*,*S*)-**2** was determined with an Agilent Series 1100 system at UVmax = 210, 240, and 280 nm, using a Agilent Zorbax SB–C_{18} column (4.6 mm ID × 250 mm, 3.5 micron) at 35 °C with flow rate of 1.0 mL min^{-1} and run time of 20 min. Solvents: A H_2O + 0.05% TFA, B CH_3CN; Gradient: B 10%/0 min, B 50%/6 min, B 90%/12 min, B 50%/18 min, B 10%/20 min. The diastereomeric excess of (*S*,*S*)-**4**/(*S*,*R*)-**4** were determined with an Agilent Series 1100 system at UVmax = 210, 254, and 280 nm, using a Chiralcel OD column (4.6 mm ID × 150 mm, 10 micron) at 35 °C with flow rate of 1.0 mL min^{-1} and run time of 30.0 min. Solvents: A hexane, B EtOH, and C MeOH; Gradient: isocratic with 2% of EtOH and 2% of MeOH. While The chemical purity of (*S*,*S*)-**4** was determined with an Agilent Series 1100 system at UVmax = 310 (220–400 nm), using a Waters Sunfire C_{18} column (0.3 mm ID × 150 mm, 3.5 micron) at 45 °C with flow rate of 0.6 mL min^{-1} and run time of 40 min. Solvents: A H_2O + 0.1% formic acid + 0.01% TFA, B CH_3CN + 0.1% formic acid + 0.01% TFA; Gradient: B 25%/0 min, B 25%/3 min, B 95%/30 min, B 95%/35 min, B 25%/35.1 min, B 25%/40 min. All reactions were conducted in a 4-neck round bottom flask equipped with a thermocouple controller, a mechanical stirrer, a pressure-equalization dropping funnel, a cooling condenser, and a nitrogen inlet/outlet adapter.

A general procedure for the preparation of (*S*)-1,1,1-trifluoro-3-{(*R*)-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-3,4-dihydroqui-nolin-1-(2*H*)-yl}propan-2-ol ((*R*,*S*)-2)

A 2 L 4-neck round bottom flask equipped with a thermocouple, a mechanic stirrer, a dry ice-cooled condenser, and a nitrogen inlet/outlet adapter was charged with (*R*)-**1** (255.3 g, 0.487 mol), 1,1,1,3,3,3-hexafluoro-2-propanol (511 mL, 4.866 mol), and cold 3,3,3-trifluoro-1,2-epoxypropane (165 g, 1.473 mol) from 4 °C freezer. The flask was wrapped with aluminium foil and

the mixture was stirred at 20–30 °C for 24 h. The progress of the reaction was monitored by HPLC and LC-MS. The solvent HFP was recovered *in vacuo* at 40 °C to afford an oil, which was dissolved in EtOH (500 mL; 200 proof), polish filtered through a M-sintered glass filtration funnel, and concentrated *in vacuo* at 50 °C. The resulting material was dissolved in EtOH (500 mL; 200 proof) and concentrated again *in vacuo* at 50 °C, dried at 50 °C under high vacuum (<6 mmHg) for 24 h to afford the desired (*R*,*S*)-**2** (294.45 g, 99.3% yield; 99.4% HPLC area% with 99.5% de) as a very viscous golden oil. (Found: C, 54.4; H, 3.65; N, 2.33; F, 31.4%. $C_{27}H_{21}F_{10}NO_3$ requires C, 54.28; H, 3.55; N, 2.34; F, 31.8.%; Ash < 0.1). $[\alpha]_D^{22}$ −125.5°, (C 1.0 in $CHCl_3$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 7.38 (d, J = 7.6 Hz, 1 H), 7.33 (d, J = 7.5 Hz, 1 H), 7.23 (d, J = 8.3 Hz, 1 H), 7.20–7.10 (m, 5 H), 7.04 (s, 1 H), 6.73 (d, J = 8.3 Hz, 1 H), 6.67 (d, J = 7.3 Hz, 1 H), 5.89 (tt, J = 53.0, 2.8 Hz, 1 H), 4.90 (t, J = 4.5 Hz, 1 H), 4.45–4.36 (m, 1 H), 3.91 (d, J = 15.6 Hz, 1 H), 3.30 (dd, J = 15.6, 9.7 Hz, 1 H), 2.51 (d, J = 4.5 Hz, 1 H), 2.47–2.31 (m, 2 H), 2.18–2.09 (m, 1 H), 2.00–1.91 (m, 1 H).). LC-MS m/z 598 [MH^+] (100), 1216 [2M + Na]$^+$ (36).

References

1 (*a*) T. A. Rano, E. Sieber-McMaster, P. D. Pelton, M. Yang, K. T. Demarest and G.-H. Kuo, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2456–2460; (*b*) G.-H. Kuo, T. Rano, P. Pelton, K. T. Demarest, A. C. Gibbs, W. V. Murray, B. P. Damiano and M. A. Connelly, *J. Med. Chem.*, 2009, **52**, 1768–1772; (*c*) T. Rano, G.-H. Kuo, E. Sieber-McMaster, K. T. Demarest, P. Pelton and A. Wang, *U.S. Patent*, US 2007265304 A1, 2007.

2 (*a*) G. H. C. Woo, A. B. Beeler and J. K. Snyder, *Tetrahedron*, 2007, **63**, 5649–5665; (*b*) M. Beaton and D. Gani, *Tetrahedron Lett.*, 1998, **39**, 8549–8552; (*c*) C. Fu, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 2001, **84**, 3319–3334; (*d*) J. Picione, S. J. Mahmood, A. Gill, M. Hilliard and M. M. Hossain, *Tetrahedron Lett.*, 1998, **39**, 2681–2684; (*e*) A. E. Vougioukas and H. B. Kagan, *Tetrahedron Lett.*, 1987, **28**, 6065–6068; (*f*) S. Ishida, S. Suzuki, T. Hayano, H. Furuno and J. Inanaga, *J. Alloys Compd.*, 2006, **408–412**, 441–443.

3 (*a*) P. V. Ramachandran, B. Gong and H. C. Brown, *J. Org. Chem.*, 1995, **60**, 41–46; (*b*) C. Von dem Bussche-Huennefeld, C. Cescato and D. Seebach, *Chem. Ber.*, 1992, **125**, 2795–2802; (*c*) P. V. Ramachandran and K. J. Padiya, *J. Fluorine Chem.*, 2007, **128**, 1255–1259; (*d*) E. T. McBee and T. M. Burton, *J. Am. Chem. Soc.*, 1952, **74**, 3022–3023.

4 (*S*)-TFMO with 75% ee was purchased from TCI America, Inc before 2006. Sigma-Aldrich added (*S*)-TFMO with 96% ee to the market in 2006 while Tyger Scientific, Inc. supplied (*S*)-TFMO with >99% ee in 2007.

5 (*a*) U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon and J.-P. Bégué, *J. Org. Chem.*, 2000, **65**, 6749–67518; (*b*) V. Kesavan, D. Bonnet-Delpon and J.-P. Bégué, *Tetrahedron Lett.*, 2000, **41**, 2895–2898; (*c*) I. Rodrigues, D. Bonnet-Delpon and J.-P. Bégué, *J. Org. Chem.*, 2001, **66**, 2098–2103; (*d*) J. Iskra, D. Bonnet-Delpon and J.-P. Bégué, *Eur. J. Org. Chem.*, 2002, 3402–3410.

6 (*a*) K. L. Sorgi, F. Liu, Y. Chen, H. Chen, M. N. Patel, X. Li, A. Wang, S. A. Ballentine, D. A. Beauchamp, J.-M. T. J. L. Rammeloo and T. J. Vanhoegaerden, *International Patent*, WO 2008141077 A1, 2008; (*b*) A. Wang, C. P. Prouty, P. D. Pelton, M. Yang, K. T. Demarest, W. V. Murray and G.-H. Kuo, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1432–1435.