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Stereoselective synthesis of 2-(*S*)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(*S*)-phenyl-1,4-oxazine

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Abstract: A convenient process for the preparation of the secondary amine **6**, 2-(*S*)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(*S*)-phenyl-1,4-oxazine, is described starting from the readily available (*S*)-phenylglycine **1**. The process features efficient construction of the homochiral oxazinone intermediate **3** and stereoselective introduction of the 2-(3,5-bis(trifluoromethyl)-benzyloxy) group by L-Selectride reduction followed by *in situ* alkylation with the highly reactive 3,5-bis(trifluoromethyl)-benzyl triflate **4**. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

The secondary amine, 2-(*S*)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(*S*)-phenyl-1,4-oxazine, **6** is a key intermediate for the synthesis of a number of compounds that have been shown to be active at the NK_1 receptor and are currently undergoing pharmacological evaluation.[1] A number of synthetic routes to homochiral 3-alkyl-1,4-oxazin-2-ones have been reported,[1–6] one of which was the reaction of homochiral *N*-benzyl-amino acids with dibromoethane in the presence of a base in DMF to give substituted homochiral *N*-benzyl-1,4-oxazin-2-ones in 39–74% yield.[2] As this approach was a potential route to **3** starting from inexpensive and readily available starting materials, this was chosen to pursue our goal. This note describes the development of a convenient process for the preparation of **6** featuring efficient construction of the homochiral oxazinone intermediate **3** and stereoselective introduction of the 2-(3,5-bis(trifluoromethyl)-benzyloxy) group by L-Selectride reduction followed by *in situ* alkylation with the highly reactive triflate **4**.[1]

Results and discussion

Reductive amination of benzaldehyde with (*S*)-phenylglycine **1** in aqueous methanol/sodium hydroxide/sodium borohydride following the method of Gerlach[7] gave *N*-benzyl-(*S*)-phenylglycine **2**.

Reaction of **2** in DMF (17.5 mL/g) with 1,2-dibromoethane/*N*,*N*-diisopropylethylamine (DIPEA) at 90°C gave the chiral oxazinone **3**, 91% e.e.[8]

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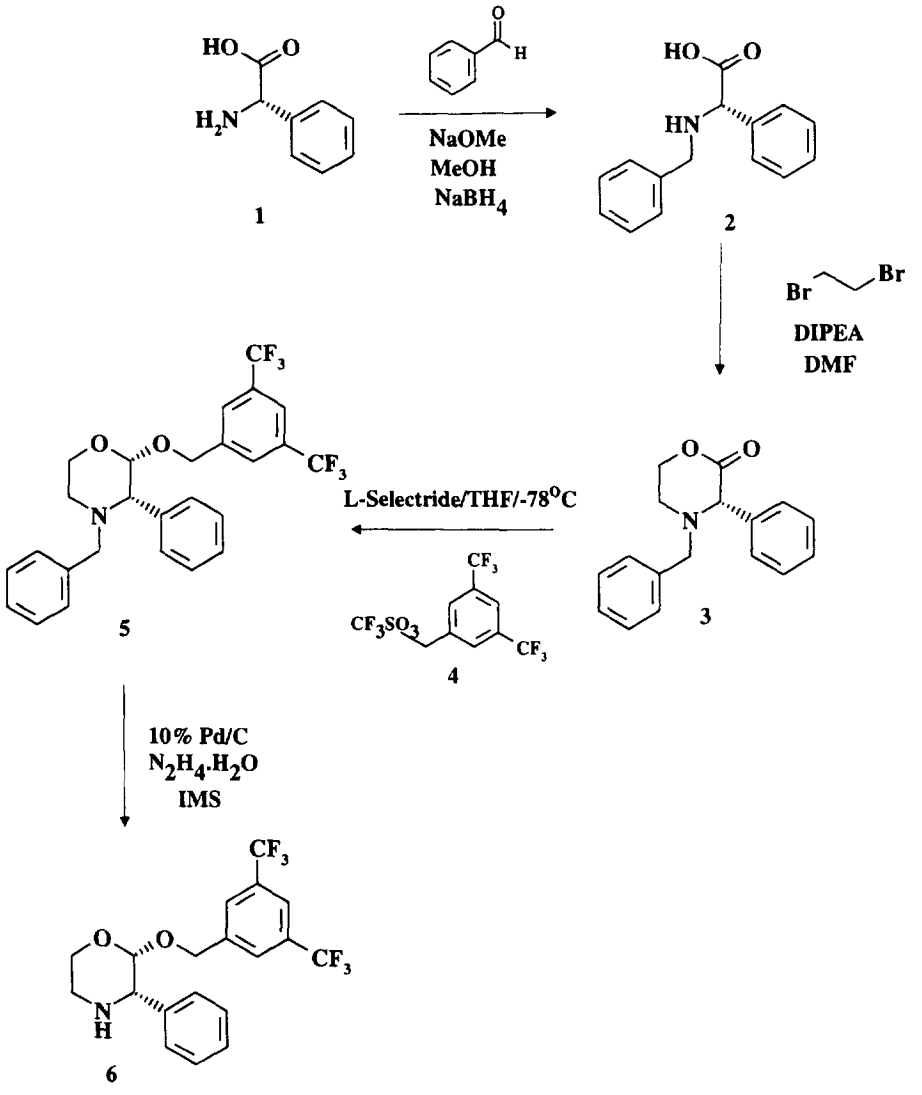
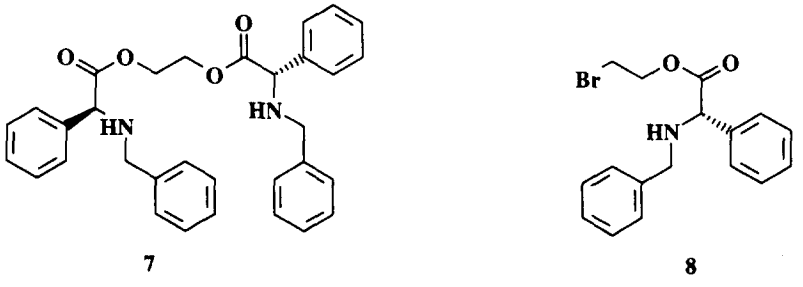
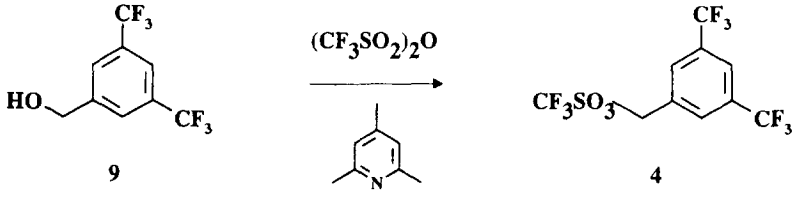


Crystallisation from tert-butyl methyl ether afforded product **3** of >99% e.e. in 57% yield. Performing the cyclisation at increased concentration led to a reduction in yield due to increased formation of the diester **7**[9] from the intermediate bromoester **8**.[9]

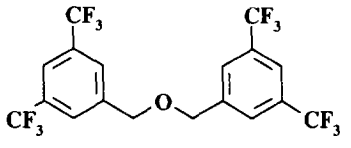


Central to the reaction sequence was the stereoselective reduction of the chiral oxazinone **3** followed by alkylation with 3,5-bis(trifluoromethyl)benzyl triflate **4**.[1] Preparation of the triflate **4** from 3,5-bis(trifluoromethyl)benzyl alcohol **9** was initially carried out using triflic anhydride and 2,6-di-tert-

butyl-4-methylpyridine[10] in carbon tetrachloride.[1] It was found that 2,4,6-collidine was effective as a replacement for 2,6-di-tert-butyl-4-methylpyridine when used in hexane. When used in more polar solvents, such as methylene chloride, the collidine triflate formed reacted with **4**. However collidine triflate salt precipitated quantitatively from the reaction mixture in hexane, leaving the benzyl triflate **4** in solution. Filtration of the collidine triflate followed by evaporation of the filtrate under reduced pressure gave the benzyl triflate **4** as a mobile oil which was used without purification. ^{1}H NMR showed that the oil was a mixture of triflate **4**:ether **10**:alcohol **9** in the ratio of 100:3:1.[11]



9 **4**



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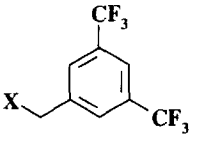
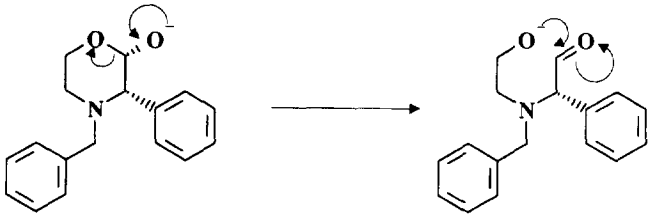
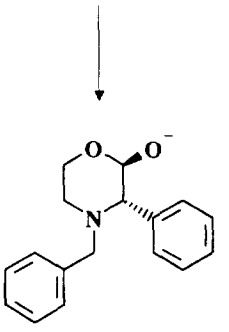


11, X=Br, I

Reduction of the oxazinone **3** with L-Selectride at −75°C in THF followed by *in situ* alkylation at −40°C with 3,5-bis(trifluoromethyl)benzyl triflate **4** gave predominately the required 2*S*,3*S*-acetal **5** [ratio 2*S*,3*S*:2*R*,3*S*=11:1],[1,12,14] the steric bulk of the reducing agent causing delivery of the hydride from the less hindered face of the oxazinone **3**.[13] The corresponding benzyl bromide or iodide (**11**; X=Br or I) reacted only at or above room temperature to give predominately the *trans* acetal **12** with only a low level of the *cis* product **5** present. After an extractive work up the 2*S*,3*S*-isomer **5** could be obtained with >98% d.e.[14] in 54% yield by crystallisation of the triflate salt.[9] Alternatively the 2*S*,3*S*- and 2*R*,3*S*-isomers **5** and **12** could be separated after debenzylation (see below).



14 **15**

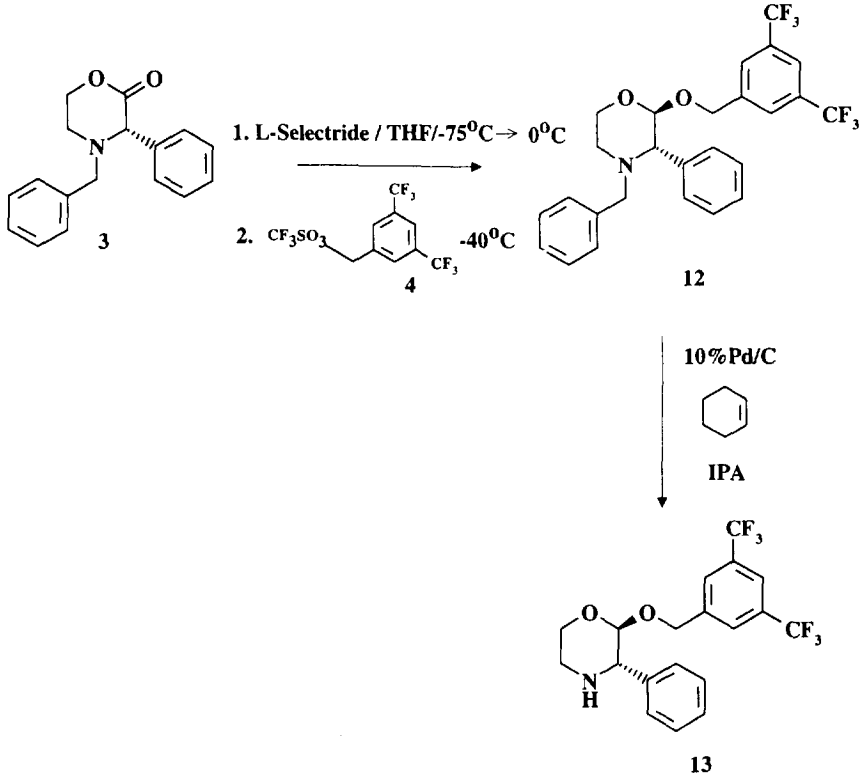


16

Transfer hydrogenation of the triflate salt **5** over Pd/C with hydrazine hydrate as the transfer agent in aqueous industrial methylated spirits (IMS) at 50°C gave the desired secondary amine **6** in quantitative yield as a single enantiomer.[15] Alternatively, hydrogenation of the crude alkylation product mixture (**5**:**12**, 11:1) afforded an 11:1 mixture of the 2*S*,3*S*-**6** and 2*R*,3*S*-diastereomers **13**. Selective crystallisation of the methanesulphonate salts from tert-butyl methyl ether gave the *cis*-secondary amine **6** of >99% d.e[14] in 65–69% yield.

After L-Selectride reduction of the chiral oxazinone **3** significant equilibration of the *cis*-intermediate **14** to the thermodynamically favoured *trans*-intermediate **16** occurred at temperatures >−40°C via a ring opening and closing mechanism.

This afforded a method for the preparation of the 2*R*,3*S*-isomer **12**. Carrying out the reduction at −75°C, warming the solution to 0°C and cooling to −40°C before reacting with 3,5-bis(trifluoromethyl)benzyl triflate **4** led to formation of the 2*R*,3*S*-acetal **12** as the major product [ratio 2*S*,3*S*:2*R*,3*S*=1:11].[14] Debenzylation by transfer hydrogenation over Pd/C in isopropanol using cyclohexene as the hydrogen source and purification by column chromatography on silica gel gave the secondary amine **13** in 43% yield, 90% d.e.[14] from the chiral oxazinone **3**.



In conclusion this paper describes a facile synthesis of the chiral oxazine **6** starting from the inexpensive and readily available (*S*)-phenylglycine. The key step involves the stereoselective reductive alkylation of the chiral oxazinone **3** affording the *cis* acetal **5** with excellent diastereoselectivity.

Experimental

^{1}H and ^{13}C NMR spectra were obtained at 250 and 62.5 Mhz in the solvent indicated on a Brucker DPX 250 spectrometer. Specific rotations [α] were determined on a Perkin–Elmer 241 polarimeter at the sodium D line at 25°C in the solvent indicated. Melting points were obtained on a Buchi 510 melting point apparatus and are uncorrected.

N-*Benzyl-3-(S)-phenyl-1,4-oxazin-2-one* ***3***

N-Benzyl-(*S*)-phenylglycine (**2**; 10 g; 41.5 mmoles) was slurried in a mixture of DMF (175 ml), *N,N*-diisopropylethylamine (14.44 ml; 82.9 mmoles) and 1,2-dibromoethane (28.5 ml; 0.332 moles). The mixture was heated to 90°C for 4 hours, cooled to room temperature and partitioned between isopropyl acetate (150 ml) and water (150 ml). The organic layer was washed with water (100 ml), evaporated to residue and dissolved in tert-butyl methyl ether (50 ml), seeding causing the product to crystallise. The mixture was cooled in ice for two hours and filtered. The solid was washed with tert-butyl methyl ether (2×10 ml), collected and dried *in vacuo* overnight. The colourless, crystalline product (**3**; 6.4 g; 57%) was obtained as a single enantiomer,[8] mp 101–102.5°C; $[\alpha]_D$=+127.5 (c=1.0, $CHCl_3$); ^{1}H NMR (CD_2Cl_2) δ 2.56 (dt, J=3.28, 11.60 Hz, 1H), 2.88 (dm, J=11.6 Hz, 1H), 3.08 (d, J=13.5 Hz, 1H), 3.66 (d, J=13.5 Hz, 1H), 4.15 (s, 1H), 4.26 (dm, J=10.9 Hz, 1H), 4.46 (dt, J=3.08, 10.9 Hz, 1H), 7.25 (m, 10H); ^{13}C NMR δ 168.9, 138.4, 137.6, 129.4, 129.2, 129.0, 128.7, 127.8, 126.3, 71.0, 69.2, 59.0, 47.2; Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.78. Found: C, 76.12; H, 6.38; N, 5.77.

N-*Benzyl-2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-1,4-oxazine, trifluoromethane sulphonate salt* ***5***

3,5-Bis(trifluoromethyl)benzyl alcohol (**9**; 650 g; 2.66 moles) was dissolved in hexane (13.0 L) with 2,4,6-collidine (435 mL; 3.29 moles) and cooled to 10°C. Trifluoromethanesulphonic anhydride (481 ml; 2.86 moles) was added at <25°C. The mixture was stirred at 20°C for 1.5 hours and filtered. The filtrate was evaporated under reduced pressure and the product **4** used without further purification.[11]

Meanwhile *N*-benzyl-3-(*S*)-phenyl-1,4-oxazin-2-one (**3**; 435 g; 1.62 moles) was dissolved in THF (4.35 L) at −75°C. L-Selectride (1.0 M in THF; 1.63 L; 1.63 moles) was added <−60°C and the mixture was stirred at −70°C for 30 minutes. The triflate oil was added to the reaction mixture at <−60°C. The solution was warmed to −40°C and stirred at this temperature for 2.5 hours. The reaction mixture was stirred with 1N aqueous methane sulphonic acid at 25°C for 20 minutes and extracted into ethyl acetate (6.35 L). The organic layer was washed with brine (2.0 L) and the ethyl acetate exchanged for isopropyl acetate under reduced pressure, giving a final volume of 4 litres. The mixture was cooled to 14°C for 1 hour before filtering. The solid was washed with cold isopropyl acetate (2×500 mL) and dried *in vacuo* to give the product triflate salt (**5**; 567 g; 54%) as a highly crystalline, colourless solid,[8] d.e. 98.8%[14]; mp 175.5–8°C (dec); $[\alpha]_D$=+155.0 (c=0.53, CH_3OH); ^{1}H NMR (CD_2Cl_2) δ 3.19 (m, 1H), 3.70 (d, J=12.12 Hz,1H), 3.87 (dd, J=13.31, 4.08 Hz, 1H), 4.14 (dd, J=10.24, 2.48 Hz, 1H), 4.26 (dd, J=13.52, 3.08 Hz, 1H), 4.40 (dd, J=13.52, 2.38 Hz, 1H), 4.55 (d, J=13.31 Hz, 1H), 4.62 (dt, J=13.02, 2.38 Hz, 1H), 4.83 (d, J=2.38 Hz, 1H), 4.97 (d, J=13.31 Hz, 1H), 7.19 (d, J=8.25 Hz, 2H), 7.36–7.63 (m, 10H), 7.75 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 132.7, 131.5, 131.2, 130.9, 130.1, 129.7, 129.4, 128.0, 125.9, 95.9, 67.8, 67.7, 58.0, 56.3, 51.3: Anal. Calcd for $C_{27}H_{24}F_9NO_5S.H_2O$: C, 48.87; H, 3.95; F, 25.76; N, 2.11; S, 4.83. Found: C, 49.10; H, 3.97; F, 25.68; N, 2.17; S, 4.98.

2-(S)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-1,4-oxazine ***6***

10% Palladium on charcoal (272 g) was slurried with water (730 mL) and IMS (13.0 L). 4-Benzyl-2-(*S*)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(*S*)-phenyl-1,4-oxazine triflic acid salt (**5**; 2.72 kg; 4.21 moles) was added and the mixture heated to 50°C. Hydrazine hydrate (55% w/w solution in water; 736 g; 12.627 moles) was added over 15 minutes. The mixture was heated at 50°C for 4 hours, filtered hot, and the catalyst was washed with warm IMS (1.0 L). The filtrate was evaporated to residue and partitioned between isopropyl acetate (10.9 L) and 10% aqueous sodium carbonate solution (5.4 L). The organic layer was washed with water (5.0 L), filtered and evaporated to residue, to give the product (**6**; 1.62 kg; 100%) as a colourless oil,[8] e.e. >99.0%.[15]; $[\alpha]_D$=+125.3 (c=1.4, $CHCl_3$); ^{1}H NMR (CD_2Cl_2) δ 1.92 (br s, 1H), 3.41 (dt, J=4.0, 12.5 Hz, 1H), 3.58 (bd, J=12.5 Hz, 1H), 3.892 (dd, J=4.0, 13.0 Hz, 1H), 4.41 (dt, J=3.0, 12.5 Hz,1H), 4.54 (d, J=2.0 Hz, 1H), 4.59 (d, J=13.5 Hz, 1H), 4.97 (dd, J=5.0, 7.5 Hz, 2H), 7.38–7.57 (m, 5H), 7.66 (s, 2H), 7.80 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 141.5,

140.0, 131.8, 128.5, 127.8, 127.4, 121.6, 98.1, 67.7, 62.8, 59.9, 46.7. Anal Calcd for $C_{19}H_{17}F_6NO_2$: C, 56.30; H, 4.23; F, 28.12; N, 3.46. Found: C, 56.20; H, 4.29; F, 27.94; N, 3.34.

N-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-1,4-oxazine ***12***

3,5-Bis(trifluoromethyl)benzyl alcohol (**9**; 4 g; 16.4 mmoles) was dissolved in hexane (80 ml) with 2,4,6-collidine (2.68 ml; 20.2 mmoles) at room temperature and cooled to 10°C. Trifluoromethanesulphonic anhydride (2.96 ml; 17.6 mmoles) was added at <25°C. The mixture was stirred at 20°C for 1.5 hours and filtered. The filtrate was evaporated under reduced pressure to residue and the product **4** used without further purification.

Meanwhile *N*-benzyl-3-(*S*)-phenyl-1,4-oxazin-2-one (**3**; 2.92 g; 10.9 mmoles) was dissolved in THF (60 ml) and cooled to −75°C. L-Selectride (1.0 M in THF; 10.9 ml; 10.9 mmoles) was added at <−60°C and the mixture was stirred at −70°C for 30 minutes, warmed to 0°C and immediately cooled to −75°C. The triflate oil was added to the reaction mixture at <−60°C. The solution was warmed to −40°C and stirred at this temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate (140 ml) and saturated aqueous sodium bicarbonate solution (140 ml). The organic layer was washed with brine (50 ml) and dried over sodium sulphate before evaporating to an orange oil. This was purified by column chromatography on silica gel to give the 2*R*,3*S* product (**12**; 3.15 g; 56%) as a colourless oil, 82% d.e.[14]; $[\alpha]_D=-53.4$ (c=1.4, $CHCl_3$); ^1H NMR (CD_2Cl_2) δ 2.34 (dt, J=3.60, 11.63 Hz, 1H), 2.75 (dt, J=2.88, 11.53 Hz, 1H), 2.97 (d, J=13.41 Hz, 1H), 3.27 (d, J=7.35 Hz, 1H), 3.85 (m, 2H), 3.98 (m, 1H), 4.50 (d, J=11.92 Hz, 1H), 4.52 (d, J=7.35 Hz, 1H), 4.88 (d, J=13.32 Hz, 1H), 7.50 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 141.2, 139.2, 139.0, 129.2, 129.1, 128.8, 128.5, 128.3, 127.5, 127.3, 126.3, 121.6, 103.8, 71.7, 69.2, 64.9, 59.0, 51.1; Anal. Calcd for $C_{26}H_{23}F_6NO_2$: C, 63.03; H, 4.68; F, 23.01; N, 2.83. Found: C, 63.13; H, 4.76; F, 23.20; N, 2.75.

2-(R)-(3,5-Bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-1,4-oxazine ***13***

10% Palladium on charcoal (0.87 g) was slurried with isopropanol (30 ml). 4-Benzyl-2-(*R*)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(*S*)-phenyl-1,4-oxazine (**12**; 2.50 g; 4.9 mmol) in isopropanol (26 ml) was added to the slurry with cyclohexene (2.60 ml; 25.7 mmol). The reaction was heated at reflux temperature for 9 hours, the mixture was filtered hot and the catalyst washed with warm isopropanol (20 ml). The filtrate was evaporated to residue under reduced pressure and the colourless oil purified by column chromatography on silica gel. The product **13** was obtained as a colourless oil (1.51 g; 76%), 90% d.e.[14] An analytical sample of **13** was prepared after column chromatography on silica gel (ethyl acetate/hexane 1:1)and crystallisation of the product from hexane: mp 80–82°C; $[\alpha]_D=-58.7$ (c=1.3, $CHCl_3$); ^1H NMR (C_3D_6O) δ 2.90 (m, 2H), 3.65 (d, J=7.5 Hz, 1H), 3.80 (dt, J=3.0, 10.0 Hz, 1H), 3.95 (d, J=10.0 Hz, 1H), 4.45 (d, J=7.5 Hz, 1H), 4.65 (d, J=13.5 Hz, 1H), 4.95 (d, J=13.5 Hz, 1H), 7.5 (m, 8H); ^{13}C NMR (C_3D_6O) δ 143.1, 141.5, 131.5, 129.1, 128.8, 128.3, 128.1, 128.0, 126.6, 121.7, 121.6, 121.5, 104.6, 68.9, 66.9, 65.4, 46.3; Anal. Calcd for $C_{19}H_{17}F_6NO_2$: C, 56.30; H, 4.23; F, 28.12; N, 3.46. Found: C, 56.30; H, 4.29; F, 27.92; N, 3.44.

References

1. Hale, J. J. *et al. J. Med. Chem.* **1996**, *39*, 1760–1762.
2. Kashima, C.; Harada, K. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1521–1526.
3. Jankowski, K.; Berse, C. *Can. J. Chem.* **1968**, *46*, 1939–1942.
4. Chang, C.-J.; Fang, J.-M.; Lee, G.-H.; Wang, Y. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3587–3593.
5. Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47 (25)*, 4343–4354.
6. Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547–1557.
7. Gerlach, H. *Helv. Chim. Acta* **1966**, *49*, 2481–2489.
8. HPLC System: 250×4.6 mm covalently bonded D-phenylglycine, 4% isopropanol 96% hexane, 210 nm, 1.0 ml/min. Retention times: R-enantiomer 28.0 min, S-enantiomer 29.3 min
9. All new compounds were characterised by ^1H NMR, ^{13}C NMR and elemental analysis. Selective data (^1H NMR at 250 MHz, ^{13}C NMR at 62.5 Mhz): Diester **7**: mp 204–6°C (HCl salt);

$[\alpha]_D$=+170.9 (c=0.31, CH_3OH); ^1H NMR (CD_2Cl_2) δ 2.32 (br s, 2H), 3.72 (s, 4H), 4.30 (m, 6H), 7.36 (m, 20H); ^{13}C NMR (CD_2Cl_2) δ 173.0, 140.3, 138.5, 129.0, 128.7, 128.6, 128.4, 127.9, 127.5, 64.8, 62.9, 51.7; Anal. Calcd for $C_{32}H_{34}Cl_2N_2O_4$ (HCl salt): C, 66.09; H, 5.89; Cl, 12.19; N, 4.82. Found: C, 65.91; H, 5.98; Cl, 11.97; N, 4.74. Bromoester **8**: mp 168–71°C (HCl salt); $[\alpha]_D$=+94.9 (c=0.66, CH_3OH); ^1H NMR (CD_2Cl_2) δ 2.23 (br s, 1H), 3.46 (dt, J=5.96, 1.00 Hz, 2H), 3.74 (d, J=1.00 Hz, 2H), 4.39 (m, 3H), 7.31 (m, 10H); ^{13}C NMR (CD_2Cl_2) δ 172.9, 140.1, 138.4, 129.0, 128.7, 128.5, 127.9, 127.5, 64.8, 64.7, 51.8, 29.1; Anal. Calcd for $C_{17}H_{19}ClBrNO_2$ (HCl salt): C, 53.08; H, 4.98; Cl, 9.22; Br, 20.77; N, 3.64. Found: C, 53.13; H, 5.05; Cl, 8.95; Br, 20.71; N, 3.65.

10. Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

11. ^1H NMR (250 MHz in CD_2Cl_2) of the triflate **4** gave the following δ (ppm) for the benzylic protons:

5.54	triflate **4**	(singlet)
5.34	alcohol **9**	(doublet, J=5.1 Hz)
4.68	ether **11**	(singlet)

12. Other reducing agents such as Dibal-H or Red-Al were effective in reducing the oxazinone **3** but the resulting alkoxide did not alkylate with the triflate.
13. Brown, H. C.; Krishnamurthy, S. *J. Org. Chem.* **1972**, *94*, 7159–7161.

14. HPLC system: 250×4.6 mm YMC AQ-ODS; mobile phase: A=0.001 M Na_2HPO_4, 0.005 M KH_2PO_4, 0.01 M sodium hexanesulphonate, B=CH_3CN, 1.5 mL/min, 220 nm.

Time/min	%A	%B
0	60	40
20	10	90
30	10	90

Retention times: (2*S*,3*S*; **5**) 24.76 min, (2*R*,3*S*; **12**) 25.12 min, (2*S*,3*S*; **6**) 15.88 min, (2*R*,3*S*; **13**) 16.53 min.

15. e.e. Determined as the (−)FLEC derivatives on HPLC. HPLC system: 250×4.6 mm YMC AQ-ODS; mobile phase: 20% 0.001 M Na_2HPO_4, 0.005 M KH_2PO_4 , 0.01 M sodium hexanesulphonate, 80% CH_3CN, 1.5 mL/min, 220 nm. Retention times: (2*S*,3*S*; **6**) 15.8 min, (2*R*,3*R*) 17.4 min.

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