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The Synthesis of (R)-γ-Phenyl-γ-(trifluoromethyl)-butyrolactone and (2R,3S)-1,1,1-Trifluoro-2-methoxy-2-phenyl-3,4-epoxybutane in Homochiral Forms.

David O'Hagan*[a], Naveed A. Zaidi[a] and R. Brian Lamont[b]

[a] The University of Durham, Department of Chemistry, Science Laboratories, South Road, Durham DH1 3LE, UK.

[b] Glaxo Group Research Limited, Greenford Road, Middlesex UB6 OHE, UK.

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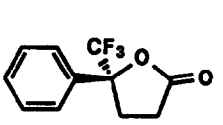
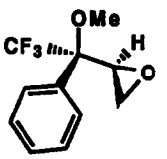
Abstract; (R)-γ-Phenyl-γ-(trifluoromethyl)-butyrolactone (1) and (2R,3S)-1,1,1-trifluoro-2-methoxy-2-phenyl-3,4-epoxybutane (2) have been prepared in high optical purity from the tertiary (S)-(3)-acetate which was resolved using the lipase from *Candida cylindracea*.

Preparative methods for the synthesis of homochiral compounds containing fluorine[1] or trifluoromethyl[2] groups are increasingly in demand both for pharmaceutical[3] and materials[4] applications. As part of a more general programme we are committed to developing methods towards homochiral fluorine containing compounds and materials. In this paper we outline synthetic routes to the γ,γ-substituted (R)-butyrolactone (1) and the (2R,3S)-epoxide (2) both of which contain a tertiary stereogenic centre carrying a trifluoromethyl group. In our case these compounds were prepared as candidate monomers for the preparation of stereoregular polymers, however they represent versatile synthetic intermediates to homochiral compounds and materials which possess a stereogenic centre bearing a trifluoromethyl group.



(1)



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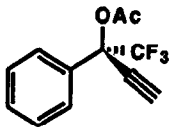
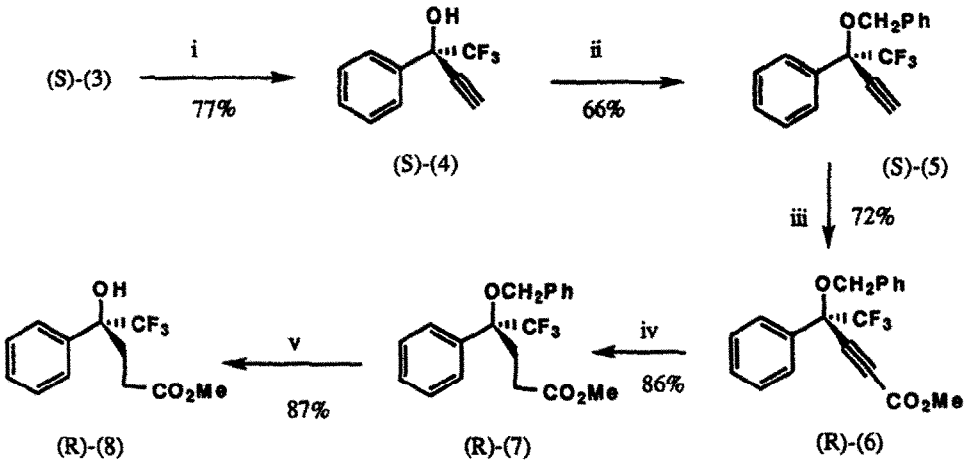


(S)-(3)

Compounds (1) and (2) have been prepared in homochiral form, from the homochiral tertiary acetate (S)-(3) which is available in gramme quantities after hydrolytic resolution of the corresponding racemic acetate with the lipase from *Candida cylindracea* [5]. Residual (S)-acetate (3) is isolated in >98%ee, 29% yield, after allowing the lipase hydrolysis to proceed to 60% conversion. The (R) enantiomer of (4) is also available directly from this biotransformation in 87%ee if the lipase resolution is stopped at 40% conversion, and therefore both enantiomeric series are accessible.

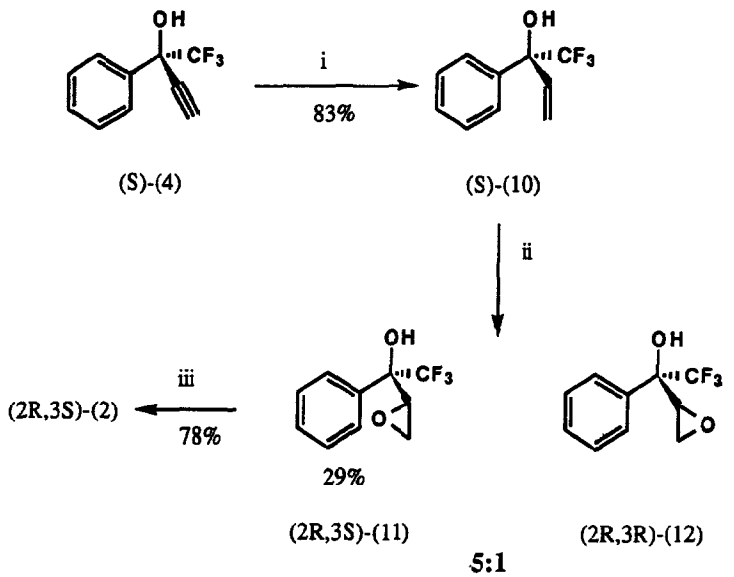


Scheme 1

i. KOH, MeOH; ii BnBr, NaH, Et_2O/DMSO; iii LDA/THF/HMPA, $NCCO_2Me$, -78°C; iv. PtO_2/H_2, MeOH, 1 atm; iv 10% Pd/C/MeOH, pTSA, 5 atm; v BuLi/THF, -78°C.

The (S)-acetate (3) was hydrolysed to the free (S)-alcohol (4) in basic methanol according to Scheme 1 and converted to the (S)-benzyl ether (5). Treatment of (S)-(5) with LDA, followed by methyl chloroformate gave unsatisfactory yields of (R)-(6), however Mander's reagent[6] proved very successful here and the (R)-carbomethoxy ester (6) was recovered in good yield. Reduction of the acetylene functionality to give (R)-(7) was achieved with Adam's catalyst in methanol under hydrogen. The (R)-alcohol (8) was then released after catalytic hydrogenolysis of the benzyl ether of (R)-(7) with palladium on charcoal in acidic methanol. Cyclisation of (R)-(8) to afford the (R)-γ,γ-butyrolactone (1) could not be achieved with sodium hydride, however more vigorous conditions using butyllithium gave (R)-(1) in moderate yield as a colourless oil ($[\alpha]_D^{20}$ = -58.6 (c=0.6, CH_2Cl_2)).

The synthesis of the (2R,3S)-epoxide (11) is detailed in Scheme 2. (S)-Alcohol (4) was reduced with Lindlar's catalyst over hydrogen to generate the (S)-allylic alcohol (10) in excellent yield. Treatment of (S)-(10) with *m*-chloroperbenzoic acid resulted in a 5:1 diastereomeric mixture of hydroxy epoxides (2R,3S)-(11) and (2R,3R)-(12). These epoxides are nice crystalline solids and after two recrystallisations the predominant diastereoisomer (2R,3S)-(11) could be recovered cleanly in 29% yield (mp 155°C). We were able to confirm the relative stereochemistry of (11) after X-ray structure analysis of a suitable crystal[7]. The structure shown in the Figure was obtained from a crystal of the opposite enantiomeric series (2S, 3R)-(11). The diastereomeric bias in favour of (11) was unexpected on steric grounds and the reaction has been subjected to a theoretical analysis evaluating stereoelectronic and electrostatic interactions[8].



Scheme 2 i. Lindlar catalyst, quinoline, H_2, 1atm; ii. mCPBA, CH_2Cl_2; iii. NaH, Et_2O, DMSO, MeI.

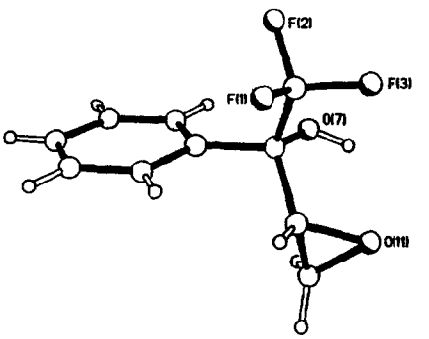


Figure The X-ray structure of (2S,3R)-(11)

The (2R,3S)-methoxyepoxide (2) was then generated from the (2R,3S)-epoxide (11) after treatment with sodium hydride and methyl iodide. We are currently investigating the polymerisation of (1) and (2) as monomers for stereochemically defined polymeric systems.

ACKNOWLEDGEMENT

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EXPERIMENTAL

All solvents were distilled and dried under standard condition before use. Chromatography was performed over silica gel (Merck Kieselgel 60) and preparative t.l.c. on (Merck Kieselgel GF_{254}). Melting points were determined on a digital melting point apparatus. Infra-red spectra were recorded on a Perkin-Elmer grating spectrometer, as thin film (neat or nujol mull) and selected values are quoted in cm^{-1}. NMR spectra were recorded on a Varian Gemini 200 (^1H; 199.98 MHz and ^{13}C; 50.29 MHz); Varian VxR 400S (^1H; 250.13 MHz, ^{13}C; 62.0 MHz and ^{19}F; 235.0 MHz). Multiplicities are reported as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m). Mass spectra were recorded on a V.G. Analytical 7070E spectrometer (EI (70 eV) and CI(NH_3)). Optical rotations were measured at 20°C on a Optical Activity Ltd. AA-10 polarimeter.

(S)-1,1,1-Trifluoro-2-phenylbut-3-yne-2-ol (4); A solution of tertiary acetate (S) (3) (1.1 g, 4.6 mmol) in 5% methanolic potassium hydroxide (20 ml) was stirred for 30 min. The mixture was dilute with water and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (100 ml), dried and the solvent evaporated *in vacuo*. Distillation gave the title compound (4) as a colourless oil (0.7 g, 77%), b.p. 36-40°C (0.1 mmHg); $[\alpha]_D^{20}$ -7.2 (c = 0.7 in CH_2Cl_2) ν_{max} (neat) 3500 (OH), 3310, 2210 (C≡CH); δ_H (400 MHz) 2.71 (1H, s, C≡CH), 3.82 (1H, s, D_2O Ex.), 7.3-7.40 (3H, m, phenyl), 7.7-7.75 (2H, m, phenyl); δ_C 72.5-73.5 (q), 76.9(s), 79.5 (s), 119.1-127.6(q), 127.3(s), 128.4(s), 129.8(s), 134.9(s); δ_F -80.1(s); Ms (m/e) EI (183 (-17), 77.4%), CI (200, 68.3%).

(S)-1,1,1-Trifluoro-2-benzyloxy-2-phenylbut-3-yne (5); Alcohol (4) (1 g, 5 mmol) was added to a solution of sodium hydride (0.17 g, 7 mmol) in dry diethyl ether (10 ml) and the mixture was heated under reflux for 15 min. A solution of benzyl bromide (0.96 g, 5.6 mmol) in dimethylsulphoxide (10 ml) was then added and the mixture was refluxed for a further 1hr, until the reaction was complete (t.l.c.). The reaction mixture was cooled diluted with water (15 ml) and diethyl ether (20 ml) added. The organic layer was washed with water (50 ml) then brine (50 ml), dried and the solvent removed *in vacuo*. Purification by chromatography over silica gel (CH_2Cl_2:petroleum 40-60°C, 2:1) gave (5) as a colourless oil (0.95 g, 66%); $[\alpha]_D^{20}$ -12.1 (c = 1.9, CH_2Cl_2); ν_{max} (neat) 3310, 2210 (C≡CH); δ_H (250 MHz), 2.97 (1H, s), 4.4-4.89 (2H, q), 7.4-7.80 (10H, m); δ_C (200 MHz), 68.23 (s), 78.35 (s), 79.94 (s), 128.14 (s), 128.40 (s), 128.77 (s), 128.96 (s), 130.42 (s), 133.57 (s), 137.59 (s); δ_F (250 MHz), -78.91 (s); Ms (m/e) EI (184 (-106), 33.2%), CI (308 (+18), 100%).

(R)-Methyl 5,5,5-trifluoro-4-benzyloxy-4-phenylpent-2-yneoate (6); Diisopropylamine (0.43 g, 4.3 mmol) was added to a solution of butyllithium (0.3 g, 4.6 mmol) in THF (5 ml) at room temperature. The LDA formed was cooled to -78°C and a solution of acetylene (5), (1 g, 3.5 mmol) in THF (10 ml) was added and the reaction mixture left to stir and warm to room temperature over 1 hr. The reaction was then cooled to -78°C and HMPA (0.68 g, 3.8 mmol) followed by methyl cyanoformate (0.42 g, 5 mmol) was added. The mixture was further stirred for 10 mins and then poured onto ice and extracted into diethyl ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml) then brine (50 ml), dried and the solvent removed *in vacuo*. Purification by preparative t.l.c. (CH_2Cl_2) gave the title compound (6) as a colourless oil (0.86 g, 72%); $[\alpha]_D^{20}$ +30.2 (c = 0.86, CH_2Cl_2); ν_{max} (neat) 2220 (C≡C), 1745 (C=O), 1245 (C-O); δ_H (200 MHz) 3.9 (3H, s), 4.5-4.92 (2H, q), 7.4-7.52 (10H, m); δ_C 53.19 (s), 68.23 (s), 78.72 (s), 79.35 (m), 81.33 (s), 114-

130.2 (q), 127.67 (s), 130.99 (s), 131.86 (s), 136.42 (s), 152.66 (s); δ_F (250 MHz) -78.26 (s); Ms (m/e) F$^+$ (M^+ 1,349, 9.5%), CI (366 (+18), 100%).

(R)-Methyl 5,5,5-trifluoro-4-benzyloxy-4-phenylpentanoate (7); Adam's catalyst (PtO_2) (0.05 g, 0.2 mmol) was added to a solution of ester (6) (0.8 g, 2.3 mmol) in methanol (10 ml) and the mixture was placed under hydrogen at 1 atm until the consumption of hydrogen had ceased. The crude mixture was filtered and the methanol removed *in vacuo*. Purification by preparative t.l.c. (CH_2Cl_2) gave ester (7) as a colourless oil (0.7 g, 86%); $[\alpha]_D^{20}$ -5.6 (c = 0.9, CH_2Cl_2); ν_{max} (neat) 1740, 1250 (ester); δ_H (250 MHz) 2.3-2.8 (4H, m), 3.67 (3H, s), 4.62 (2H, s), 7.3-7.6 (10H, m); δ_C (200 MHz) 28.32 (s), 28.96 (s), 52.26 (s), 66.7 (s), 81.3 (m), 119-133.3 (q), 127.6 (s), 129.3 (s), 135.89 (s), 138.1 (s), 173.75 (s); δ_F (250 MHz) -72.9 (s); Ms (m/e) EI (M+1, 353, 0.6%), CI (370 (+18), 43%).

(R)-Methyl 5,5,5-trifluoro-4-hydroxy-4-phenylpentanoate (8); To a solution of ester (7) (0.7 g, 2 mmol) in methanol (10 ml) and a catalytic amount of p-toluenesulphonic acid (0.04 g, 2 mmol) was added 10% Pd on charcoal (0.15 g, 14 mmol) and the mixture placed under hydrogen at 5 atm for 12hr. The crude mixture was filtered and the methanol removed *in vacuo*. Purification by preparative t.l.c. (CH_2Cl_2) gave ester (8) as a colourless oil (0.45 g, 87%); $[\alpha]_D^{20}$ -83.3 (c = 0.3, CH_2Cl_2); ν_{max} (neat) 3420 (OH), 1725, 1260 (ester); δ_H (200 MHz) 2.3-2.53 (2H, m), 3.65 (3H, s), 4.40 (1H, s, D_2O Ex), 7.3-7.60 (5H, m); δ_C 28.34 (s), 30.06 (s), 52.79 (s), 76.9-78.3 (m), 127.1 (s), 128.9 (s), 129.1 (s), 136.6 (s), 175.9 (s); δ_F (250 MHz) -80.6; Ms (m/e) EI (M+1, 263, 7%), CI (280 (+18), 6.6%).

(R)-γ-Phenyl-γ-(trifluoromethyl)butyrolactone (1); Butyllithium (0.07 g, 1.1 mmol) was added to a solution of ester (8) (0.28 g, 1.1 mmol) in THF (7 ml) at -78°C and the solution stirred for 2 hr. The mixture was then diluted with water (10ml) and extracted into diethyl ether (50 ml). The ether layer was washed with water (2 x 20 ml) then brine (20ml), dried and the solvent removed *in vacuo*. Purification using preparative t.l.c. gave lactone (1) as the colourless oil (0.08 g, 33%) which solidified on standing to afford an amorphous white solid (mp. 67.5-69.3°C); $[\alpha]_D^{20}$ -58.6 (c = 0.6, CH_2Cl_2); ν_{max} (neat) 1810 (lactone); δ_H (250 MHz) 2.6-3.02 (4H, m), 7.4-7.53 (5H, m); δ_C (200 MHz) 27.5 (s), 29.6 (s), 82.83.3 (m), 116-132.4 (q, J_{C-F} (270 Hz)), 126.2 (s), 128.6 (s), 129.6 (s), 134.8 (s), 174.2 (s); δ_F (250 MHz) -80.47; Ms (m/e) EI (230, 4.5%), CI (248 (+18), 28%), (Found: C57.16, H4.02, Calc for $C_{11}H_9F_3O_2$: C57.44, H3.91%).

(S)-1,1,1-Trifluoro-2-phenylbut-3-ene-2-ol (10); To a solution of (4) (0.8 g, 4 mmol) in pentane (10 ml) and quinoline (0.1 g, 0.8 mmol) was added Lindlar's catalyst (0.1 g). The mixture was evacuated and flushed three times with hydrogen. The mixture was then stirred under an atmosphere of hydrogen, until the consumption of hydrogen had ceased. The crude mixture was filtered and the solvent removed *in vacuo*. Purification by distillation gave alcohol (10) as a colourless oil (0.67 g, 83%), b.p. 36-39°C (0.1 mm Hg); $[\alpha]_D^{20}$ -63.2 (c = 0.9, CH_2Cl_2); ν_{max} (neat) 3500 (OH); δ_H (400 MHz) 2.82 (1H, s, D_2O Ex), 5.5-5.6 (2H, dd, J = 10.8, 17.2 Hz), 6.4 (1H, dd, J = 10.8 Hz), 7.35-7.43 (3H, m), 7.58-7.62 (3H, m); δ_C (250 MHz), 78.36 (m), 118.2 (s), 120.2-128.8 (q), 126.2 (s), 128 (s), 128.4 (s), 135 (s), 136.8 (s); δ_F (400 MHz), -78.34 (s); Ms (m/e) EI (185 (-17), 30.7%), CI (220 (+18), 0.4%), (Found: C59.83, H4.75. Calc. for $C_{10}H_9F_3O$: C59.43, H4.45%).

(2R,3S) and (2R,3R) -1,1,1-Trifluoro-2-phenyl-3,4-epoxybutane-2-ols (11 and 12); To a solution of allylic alcohol (10) (0.8 g, 4 mmol) in dry CH_2Cl_2 (50 ml) at 0°C was added m-chloroperbenzoic acid (1.5 g, 8.7 mmol) and the mixture left to stir at room temperature for 24hr. The reaction was diluted with CH_2Cl_2 (50 ml) and washed sequentially with 10% sodium sulphite (50 ml), 10% sodium bicarbonate (50), water (50), and finally brine. The organic layer was dried and the solvent removed *in vacuo*. Purification by chromatography over silica gel gave a product which was recrystallised from petroleum ether (40-60°C) to give the major epoxide (11) (0.25 g, 29%) as colourless crystals (m.p. 152-155°C); $[\alpha]_D^{20}$ -48.8 (c = 1.6, CH_2Cl_2); ν_{max} (Nujol) 3400 (OH), 890 (epoxide); δ_H (250 MHz), 2.6-2.7 (1H, m), 2.73-2.8 (1H, m), 3.26 (1H, s, D_2O Ex), 3.8-3.86 (1H, m), 7.4-7.46 (3H, m), 7.6-7.62 (2H, m); δ_C (200 MHz), 42.2 (s), 52.1 (s), 72-73.7 (q), 116.4-133.6 (q), 125.7 (s), 128.4 (s), 129.1 (s), 134.5 (s); δ_F (250 MHz), -79.75 (s); Ms (m/e) EI (201 (-17), 27.1%), CI (236, 16.3%) (Found: C55.28, H4.10: Calc. for $C_{10}H_9F_3O_2$: C55.10, H4.13%). The minor epoxide (12) (5%) was not fully characterised, δ_H (250 MHz), 2.75 (1H, s, D_2O Ex), 2.97-3.0 (1H, m), 3.13-3.16 (1H, m), 3.78-3.80 (1H, m), 7.4-7.47 (3H, m), 7.68-7.69 (2H, m).

(2R,3S)-1,1,1-Trifluoro-2-methoxy-2-phenyl-3,4-epoxybutane (2); Sodium hydride (0.07 g, 2.9mmol) was added to a solution of alcohol (11) (0.06 g, 2.8 mmol) in diethyl ether (10ml) and the reaction was heated uner reflux for 15min. MeI (0.06 g, 0.4 mmol) was then added, and refluxing was continued for a further 1hr. The reaction was worked up following the procedure for (5) above. Purification by preparative t.l.c. gave the epoxide (2) as a colourless oil (0.05 g, 78%); $[\alpha]_D^{20}$ -80 (c = 0.44, CH_2Cl_2); ν_{max} (neat) 1265, 890 (epoxide); δ_H (200 MHz), 2.69-2.77 (2H, m), 3.33-3.4 (4H, m), 7.4-7.55 (5H, m); δ_C (400 MHz), 42.7 (s), 53.99 (s), 80.5-81.52 (q), 120.92-129.61 (q), 127.68 (s), 127.7 (s), 128.53 (s), 129.21 (s), 131.75 (s); δ_F (250 MHz), -68.79; Ms (m/e) EI (189 (-43), 100%), CI (232, 0.6%) (189, 100%), (Found: C56.58, H4.89. Calc. for $C_{11}H_{11}F_3O_2$: C56.95, H4.74%).

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7. Crystal data for (2S,3R)(11): $C_{10}H_9F_3O_2$, M = 218.17, monoclinic, C2, a = 16.959(17), b = 5.804(5), c = 13.066(14)Å, β = 129.8(2)°, V = 988(5)Å^3, λ = 1.54178Å, z = 4, D_c =1.47g cm^{-3}, F(000) = 448, μ(Cu-Kα) = 11.9cm^{-1}.Siemens R3m/V diffractometer, 1271 independent reflections measured ($3 < 2\theta < 115°$) of which 908 reflections had $I > 3.0\ \sigma(I)$. The structure was solved using direct methods in the chiral space group C2. Hydrogen atoms with the exception of H(7A) bonded to oxygen were refined in riding mode but with individual isotropic temperature factors. Individual weights were applied according to the scheme $w = [\sigma^2 (F_o) + 0.0012\ |F|^2]^{-1}$, refinement converged at R 0.049, R_w 0.054, goodness-of-fit = 1.32. Full details have been deposited at the Cambridge Data Centre.
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