A facile approach to the synthesis of chiral 2-substituted benzofurans

Lidia De Luca, Giampaolo Giacomelli, and Giammario Nieddu.*

Dipartimento di Chimica, Università degli Studi di Sassari, via Vienna 2,
I-07100, Italy.

Supporting Information

Table of Contents:

General Methods page S2

Preparation of:

ethyl benzofuran-2-carboxylate 3a page S2

2-Phenyl benzofuran 3b page S2

2-tert-Butylbenzofuran 3c page S2

Spectroscopic data of compounds:

2-Methoxymethylbenzofuran 3d page S3

(S)-2-sec-Butylbenzofuran 3f page S3

2-((R)-2,2,2-trifluoro-1-methoxy-1-phenylethyl)-benzofuran 3g page S3

(S)-tert-Butyl-1-(benzofuran-2-yl)-3-methylbutylcarbamate 3h page S3

Preparation of:

(S)-1-(Benzofuran-2-yl)-3-methylbutan-1-amine 4h page S4

Spectroscopic data of compounds:

(S)-tert-Butyl-1-(benzofuran-2-yl)-2-phenylethylcarbamate 3i page S4

(S)-1(benzofuran-2-yl)-2-phenylethanamine 4i page S5

(S)-tert-Butyl-1-(benzofuran-2-yl)ethylcarbamate 3j page S5

(S)-1-(Benzofuran-2-yl)ethanamine 4j page S5

(S)-tert-Butyl-2-(benzofuran-2-yl)pyrrolidine-1-carboxylate 3k page S6

(S)-2-(Benzofuran-2-yl)pyrrolidine 4k page S6

(S)-tert-Butyl-2-(1-(benzofuran-2-yl)-3-methylbutylamino)-2-oxoethylcarbamate 3l page S6

(S)-2-Amino-N-(1-(benzofuran-2-yl)-3-methylbutyl)acetamide 4l page S7

tert-Butyl-(S)-1-[(S)-1-(benzofuran-2-yl)-2-methylpropylamino)-1-oxo-3-phenyl-propan-2-ylcarbamate 3m page S7

General Methods. All solvents and reagents were used as obtained from commercial source. The *N*-Boc derivatives of the α -amino acids were prepared according standard methods,¹ purified before use and their purity was established before utilization by melting point and optical rotations. Cyanuric chloride (TCT) was purified by crystallization before use. Standard ¹H-NMR, ¹³C-NMR and ¹⁹F-NMR were recorded at 300, 75.4 and 282 MHz, from CDCl₃ solutions. Analytical HPLC analysis was performed with a Water 1525 analytical instrument, equipped with an automated injector system and UV dual l absorbance detector. Grade quality solvents for HPLC (Merck) were employed.

Preparation of:

Preparation of ethyl benzofuran-2-carboxylate² 3a. (2-Hydroxybenzyl) triphenylphosphonium bromide (0.82 g, 1.83 mmol) and NEt₃ (0.76 mL, 5.94 mmol) were added to a solution of ethyl chlorooxacetate (0.20 ml, 1.83 mmol) in toluene (20 ml). The open flask was irradiated at 110°C for two cycles of 30 min in a self-tuning single mode CEM DiscoverTM Focused Synthesizer. The solution was cooled rapidly at room temperature by passing compressed air through the microwave cavity for 3 min. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure to give an oil. The crude product was purified by silica gel column chromatography (AcOEt:hexane = 1:9) to afford **3a** as a white oil (Yield: 74%).

2-Phenyl benzofuran³ 3b: (Yield: 79%)

2-tert-Butylbenzofuran⁴ 3c: (Yield: 75%)

Spectroscopic data of compounds:

2-Methoxymethylbenzofuran⁵ 3d: Yield: 78%, ¹H NMR: δ = 7.55 (d, J =7.3 Hz, 1 H); 7.48 (d, J =7.5 Hz, 1 H); 7.25 (m, 2 H); 6.68 (s, 1 H); 4.55 (s, 2 H), 3.43 (s, 3 H) ppm. ¹³C NMR: δ = 155.1; 154.0; 128.0; 124.3; 122.7; 121.0; 111.3; 105.7; 66.9, 58.2 ppm.

(S)-2-sec-Butylbenzofuran 3f: {from (*S*)-2-methylbutanoic acid [α]_D²⁰ +19.0 (neat)⁶} Yield: 75%), ¹H NMR: δ = 7.48 (m, 1 H), 7.41 (m, 1 H), 7.19 (m, 1 H), 7.17 (m, 1H), 6.36 (s, 1 H), 2.86 (m, 1 H), 1.80 (m, 1H), 1.64 (m, 1H), 1.32 (d, J =6.9 Hz, 3 H), 0.92 (t, J =7.4 Hz, 3 H) ppm. ¹³C NMR: δ = 163.7, 154.5, 128.8, 122.9, 122.3, 120.2, 110.7, 100.7, 35.1, 28.2, 18.4, 11.5 ppm. [α]_D²⁰ +18.7 (*c* 0.67, DCM). Anal. Calcd for C₁₂H₁₄O (174.24) C, 82.72; H, 8.10. Found: C, 82.71; H, 8.13.

2-((*R*)-2,2,2-trifluoro-1-methoxy-1-phenylethyl)benzofuran 3g: {from (*R*)- α -methoxy- α -trifluoromethylphenylacetic acid, [α]_D²⁰ +72.0 (*c* 1.6, MeOH)} Yield: 73%, ¹H NMR: δ = 7.65 (m, 1H), 7.48 (m, 1H), 7.33 (m, 7 H), 7.09 (s, 1 H), 3.39 (s, 3 H) ppm. ¹³C NMR: δ = 155.0, 150.3, 134.5, 129.2, 128.1, 127.1, 126.0, 125.5, 124.7, 123.3, 121.7, 116.5, 111.9, 110.5, 54.2 ppm. [α]_D²⁰ +22.0 (*c* 0.31, DCM). Anal. Calcd for C₁₇H₁₃F₃O₂ (306.28) C, 66.67; H, 4.28; F, 18.61. Found: C, 66.68; H, 4.25; F, 18.6.

(S)-tert-Butyl-1-(benzofuran-2-yl)-3-methylbutylcarbamate 3h: {from Boc-Leu-OH, [α]_D²⁰ -25.3 (*c* 1.6, AcOH)} Yield: 63%, ¹H NMR: δ = 7.51 (d, J =6.9 Hz, 1 H), 7.43 (d, 1 H), 7.22 (m, 2 H), 6.56 (s, 1 H), 4.94 (s, 1H, NH), 3.56 (m, 1 H), 1.72 (m, 3 H), 1.44 (s, 9 H), 0.95 (t, J =7.3 Hz, 6 H) ppm. ¹³C NMR: δ = 156.1, 155.1, 154.7, 128.2, 123.8, 122.6, 120.8, 111.1, 102.5, 79.6, 47.4, 28.3, 27.9, 24.8, 22.4 ppm. [α]_D²⁰ -73.0 (*c* 0.45, DCM). Anal. Calcd for C₁₈H₂₅NO₃ (303.40) C, 71.26; H, 8.31; N, 4.62. Found: C, 71.30; H, 8.31; N, 4.64.

Preparation of:

(S)-1-(Benzofuran-2-yl)-3-methylbutan-1-amine 4h: The procedure is representative for all cases of deprotection of *N*-Boc-2-benzofuranmethanamine. Trifluoro acetic acid (0.88 ml, 11.5 mmol) was added to a solution of **3h** (0.35 g, 1.15 mmol) in DCM (10 ml) at room temperature. After 2 h, TLC analysis showed the complete absence of the starting material and the reaction mixture was extracted with 5% HCl aqueous solution. The 5% HCl aqueous solution was then added with saturated solution of NaHCO₃ until pH 8 at 0°C. The aqueous solution was extracted with DCM. The DCM solution was dried over anhydrous Na₂SO₄. The solvent was evaporated to dryness under reduced pressure to give pure (*S*)-1-(benzofuran-2-yl)-3-methylbutan-1-amine. Yield: 94%, ¹H NMR: δ = 7.51 (m, 1 H), 7.44 (m, 1 H), 7.23 (m, 2 H), 6.5 (s, 1 H), 4.09 (t, *J*=7.1 Hz, 1 H), 1.88 (s, 2 H, NH₂), 1.73 (m, 3 H), 0.95 (t, *J*=6.3 Hz, 6 H) ppm. ¹³C NMR: δ = 155.2, 154.6, 128.4, 123.6, 120.7, 116.5, 111.1, 101.1, 63.6, 48.2, 24.9, 22.4 ppm. $[\alpha]_D^{20}$ -3.69 (*c* 1.12, DCM). Anal. Calcd for C₁₃H₁₇NO (203.28) C, 76.81; H, 8.43; N, 6.89. Found: C, 76.83; H, 8.42; N, 6.88.

A sample of **4h** (1.3 mmol) and distilled (+)-MPTACl (1.55 mmol) were mixed with DCM (1.1 mL) and dry pyridine (1.1 mL) and allowed to stand for 12h. Water was added and the mixture extracted with Et₂O. The ethereal phase was washed successively with sat. Na₂CO₃, H₂O and dried (Na₂SO₄). After removal of the solvent at reduced pressure, the residual crude (*R*)-*N*-[(*S*)-1-(benzofuran-2-yl)-3-methylbutyl]-4,4,4-trifluoro-3-methoxy-3-phenylbutanamide was analyzed by ¹H NMR: δ = 7.38 (m, 9 H), 6.58 (s, 1 H), 5.32 (m, 1 H), 3.37 (s, 3H), 1.84 (m, 2 H), 1.66 (m, 1 H), 0.97 (m, 6 H) ppm and by ¹⁹F-NMR: δ = 72.49 (0.02), 72.42 (0.98).⁷

Spectroscopic data of compounds:

(S)-tert-Butyl-1-(benzofuran-2-yl)-2-phenylethylcarbamate 3i: {from Boc-Phe-OH, $[\alpha]_D^{20}$ +25.2 (*c* 1.0, EtOH)} Yield: 58%, ¹H NMR: δ = 7.52 (d, *J*=7.9 Hz, 1 H), 7.42

(d, $J=7.8$ Hz, 1 H), 7.15 (m, 7 H), 6.43 (s, 1H), 5.43 (m, 1 H), 3.01 (m, 2 H), 1.4 (s, 9 H) ppm. ^{13}C NMR: δ = 159.6, 156.1, 154.7, 136.7, 129.3, 128.3, 126.6, 124.5, 123.9, 122.7, 120.9, 111.1, 105.1, 87.6, 60.3, 40.1, 28.2 ppm. $[\alpha]_{\text{D}}^{20}$ -23.9 (c 0.19, DCM). Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_3$ (337.41) C, 74.75; H 6.87; N, 4.15. Found: C, 74.74; H 6.86; N, 4.15.

(S)-1-(benzofuran-2-yl)-2-phenylethanamine 4i: Yield: 95% ^1H NMR: δ = 7.51 (m, 2 H), 7.23 (m, 7 H), 6.48 (s, 1 H), 4.33 (m, 1 H), 3.27 (dd, $J_1=5.4$ Hz, $J_2=2.9$ Hz, 1 H), 2.98 (dd, $J_1=5.5$ Hz, $J_2=2.9$ Hz 1 H), 1.89 (s, 2 H) ppm. ^{13}C NMR: δ = 159.6, 154.9, 138.2, 129.6, 128.8, 128.6, 126.9, 124.0, 122.9, 121.1, 112.3, 102.5, 59.8, 43.1 ppm. $[\alpha]_{\text{D}}^{20}$ +1.50 (c 0.46, DCM). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}$ (237.30) C, 80.98; H, 6.37; N, 5.90. Found: C, 80.97; H, 6.37; N, 5.87. Crude (*R*)-*N*-[(*S*)-1-(benzofuran-2-yl)-2-phenylethyl]-3,3,3-trifluoro-2-methoxy-2-phenylbutanamide from a sample of **4i** was analyzed by ^1H NMR: δ = 7.46 (m, 14 H), 6.52 (s, 1 H), 5.61 (m, 1 H), 3.40 (s, 3H), 3.24 (dd, $J_1=1.5$ Hz, $J_2=13.8$ Hz, 2 H) ppm and by ^{19}F -NMR: δ = 72.55 (100).⁷

(S)-tert-Butyl-1-(benzofuran-2-yl)ethylcarbamate 3j : {from Boc-Ala-OH, $[\alpha]_{\text{D}}^{20}$ -25.0 (c 2.0, AcOH)} Yield: 66%, ^1H NMR: δ = 7.52 (d, $J=7.5$ Hz, 1 H), 7.43 (d, $J=7.7$ Hz, 1 H), 7.22 (m, 2 H), 6.55 (s, 1 H), 5.02 (q, $J = 1.6$ Hz, 1 H), 1.5 (d, $J = 1.6$ Hz, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR: δ = 158.8, 154.9, 154.1, 128.2, 124.9, 122.7, 120.9, 111.1, 101.9, 79.8, 44.1, 28.3, 20.1 ppm. $[\alpha]_{\text{D}}^{20}$ -79.4 (c 0.34, DCM). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ (261.32) C, 68.94; H, 7.33; N, 5.36. Found: C, 68.95; H, 7.31; N, 5.34.

(S)-1-(Benzofuran-2-yl)ethanamine 4j: Yield: 92%, ^1H NMR: δ = 7.51 (m, 1 H), 7.43 (m, 1 H), 7.21 (m, 2 H), 6.49 (s, 1 H), 4.21 (q, $J = 6.7$ Hz, 1 H), 2.29 (s, 2 H, NH_2), 1.52 (d, $J = 6.7$ Hz, 3 H) ppm. ^{13}C NMR: δ = 162.6, 154.6, 128.4, 123.7, 122.6, 120.7, 110.9, 100.4, 45.4, 21.7 ppm. $[\alpha]_{\text{D}}^{20}$ -12.8 (c 0.42, DCM). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}$ (161.20) C, 74.51; H, 6.88; N, 8.69. Found: C, 74.48; H, 6.88; N, 8.69.

(S)-tert-Butyl-2-(benzofuran-2-yl)pyrrolidine-1-carboxylate 3k: {from Boc-Pro-OH, $[\alpha]_D^{20}$ -61.5 (*c* 1.8, AcOH)} Yield: 74%, ^1H NMR: δ = 7.49 (d, *J*=7.5 Hz, 1 H), 7.41 (d, *J*=7.8 Hz, 1 H), 7.19 (m, 2 H), 6.47 (m, 1 H), 5.03 (m, 1 H), 3.55 (m, 2 H), 2.05 (m, 4 H), 1.32 (s, 9 H) ppm. ^{13}C NMR: δ = 159.4, 158.8, 154.3, 128.4, 123.4, 122.5, 120.6, 110.9, 101.9, 79.5, 55.1, 46.2, 32.0, 28.2, 23.1 ppm. $[\alpha]_D^{20}$ -96.6 (*c* 1.29, DCM). Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_3$ (287.35) C, 71.06; H, 7.37; N, 4.87. Found: C, 71.08; H, 7.35; N, 4.88.

(S)-2-(benzofuran-2-yl)pyrrolidine 4k: Yield: 93%, ^1H NMR: δ = 7.47 (d, *J*=7.1 Hz, 2 H), 7.22 (m, 2 H), 6.53 (s, 1 H), 4.34 (m, 1 H), 3.07 (m, 2 H), 2.45 (s, 1 H), 2.15 (m, 1 H), 1.95 (m, 3 H) ppm. ^{13}C NMR: δ = 160.2, 154.7, 128.3, 123.5, 122.4, 120.5, 110.9, 101.8, 55.9, 46.6, 30.8, 25.3 ppm. $[\alpha]_D^{20}$ -13.4 (*c* 0.58, DCM). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$ (187.24) C, 76.98; H, 7.00; N, 7.48. Found: C, 76.97; H, 7.03; N, 7.45.

(S)-tert-Butyl-2-(1-(benzofuran-2-yl)-3-methylbutylamino)-2-oxoethylcarbamate 3l: {from (*S*)-2-(2-(*tert*-butoxycarbonylamino)acetamido)-4-methylpentanoic acid⁸} Yield: 72%, ^1H NMR: δ = 7.64 (d, *J*=7.1 Hz, 1 H), 7.53 (d, *J*=7.9 Hz, 1 H), 7.38 (m, 2 H), 6.55 (s, 1 H), 5.35 (m, 1 H), 3.41 (s, 2 H), 1.68 (m, 3 H), 1.45 (s, 9 H), 0.94 (d, *J*=5.8 Hz, 6 H) ppm. ^{13}C NMR: δ = 168.9, 157.3, 156.1, 154.5, 127.9, 123.7, 122.5, 120.7, 110.9, 102.7, 79.8, 53.3, 45.6, 42.3, 28.1, 22.4, 21.9 ppm. $[\alpha]_D^{20}$ -1.83 (*c* 1.69, DCM). Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4$ (360.45) C, 66.64; H, 7.83; N, 7.77. Found: C, 66.63; H, 7.83; N, 7.75.

(S)-2-Amino-N-(1-(benzofuran-2-yl)-3-methylbutyl)acetamide 4l: Yield: 89%, ¹H NMR: δ = 7.63 (s, 1 H), 7.50 (d, *J*=7.3 Hz, 1 H), 7.43 (d, *J*=7.8 Hz, 1 H), 7.22 (m, 2 H), 6.58 (s, 1 H), 5.32 (m, 1 H), 3.37 (s, 2 H), 1.77 (m, 2 H), 1.58 (m, 1 H), 0.95 (t, *J*=6.7 Hz, 6 H) ppm. ¹³C NMR: δ = 171.6, 157.4, 154.6, 128.1, 123.9, 123.6, 120.9, 111.1, 102.9, 52.9, 45.3, 42.7, 24.9, 22.3 ppm. [α]_D²⁰ 4.98 (c 0.91, DCM). Anal. Calcd for C₁₅H₂₀N₂O₂ (260.33) C, 69.20; H, 7.74; N, 10.76. Found: C, 69.18; H, 7.73; N, 10.78.

tert-Butyl-(S)-1-[(S)-1-(benzofuran-2-yl)-2-methylpropylamino]-1-oxo-3-phenylpropan-2-ylcarbamate 3m: {from (R)-2-[(S)-2-(tert-butoxycarbonylamino)-3-phenylpropanamido]-3-methylbutanoic acid⁸} Yield: 69%, ¹H NMR: δ = 7.46 (td, *J*₁=6.5, *J*₂=2.2 Hz, 1 H), 7.36 (d, *J*=7.6 Hz, 1 H), 7.13 (m, 7 H), 6.78 (s, 1 H), 4.98 (m, 1 H), 4.47 (m, 1H), 3.02 (dd, *J*₁=18.5, *J*₂=7.2 Hz, 2 H), 2.13 (m, 1 H), 1.39 (d, 9 H), 0.82 (m, 6 H) ppm. ¹³C NMR: δ = 171.0, 156.1, 155.5, 154.5, 136.4, 128.9, 128.6, 128.4, 126.9, 123.6, 122.5, 120.7, 110.92, 103.4, 79.8, 53.3, 52.7, 37.5, 31.9, 27.5, 18.9, 17.8 ppm. [α]_D²⁰ -13.77 (c 0.69, DCM). HPLC analysis: >99% MWI.⁹ Anal. Calcd for C₂₆H₃₂N₂O₄ (436.54) C, 71.53; H, 7.39; N, 6.42. Found: C, 71.53; H, 7.35; N, 6.45.

¹ Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer Lab. Manual: Berlin, 1994.

² Bogdal, D.; Warzala, M. *Tetrahedron*. **2000**, *44*, 8769-8774.

³ Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron*. **2005**, *46*, 10958-10964.

⁴ Lattanti, A.; Senatore, A.; Massa, A.; Scettri, A. *J. Org. Chem.* **2003**, *68*, 3691-3694.

⁵ Caruana, P.; Frontier, A. J. *Tetrahedron*. **2004**, *48*, 10921-10926.

⁶ Lardicci, L.; Botteghi, C.; Belgodere, E. *Gazz. Chim. Ital.* **1967**, *97*, 610-622.

⁷ Luzzio, F. A.; Duveau, D. Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1173-1180.

⁸ The dipetide was prepared according to Anderson, G. W.; Zimmermann, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1967**, *89*, 5012-5017.

⁹ HPLC conditions. Column: symmetry C18 3.5 μm, 4.6 x 75 mm, eluent: A (MeOH) and B (H₂O) UV absorption at 254 nm.