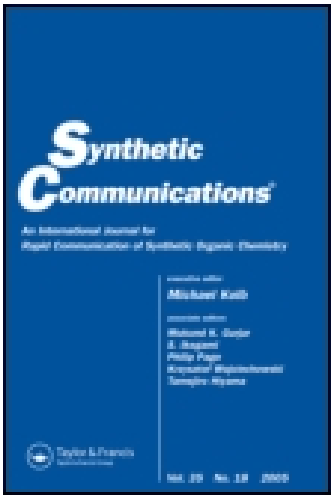

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Efficient One-Pot Synthesis of the $GABA_B$ Positive Allosteric Modulator (R,S)-5,7-Di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one

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Efficient One-Pot Synthesis of the $GABA_B$ Positive Allosteric Modulator (R,S)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-*3H*-benzofuran-2-one

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Abstract: The $GABA_B$ positive allosteric modulator (*R,S*)-5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (**1**) was synthesized in one pot from the anhydrous lithium salt of 2,4-di-*tert*-butylphenol and methyl trifluoropyruvate mediated by a stoichiometric amount of anhydrous gallium(III) chloride in 64% overall yield. The enantiomers of **1** were separated by chiral-phase HPLC (Chiralpak AD®), and the absolute configuration was determined by X-ray crystallography.

Keywords: (*R,S*)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one, $GABA_B$ positive allosteric modulator, gallium(III) chloride, one-pot synthesis

INTRODUCTION

In the course of our investigations directed at the discovery of novel $GABA_B$ positive allosteric modulators,[1] We identified (*R,S*)-5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (**1**) (Scheme 1) as a screening hit from our corporate compound collection. We set out to resynthesize lactone **1** in a larger quantity needed for enantiomer separation and derivatization. This lactone **1** was first reported in the Russian literature.[2] We have evaluated a range of methods for the synthesis of lactone **1** encompassing Lewis acid and transition-metal-catalyzed

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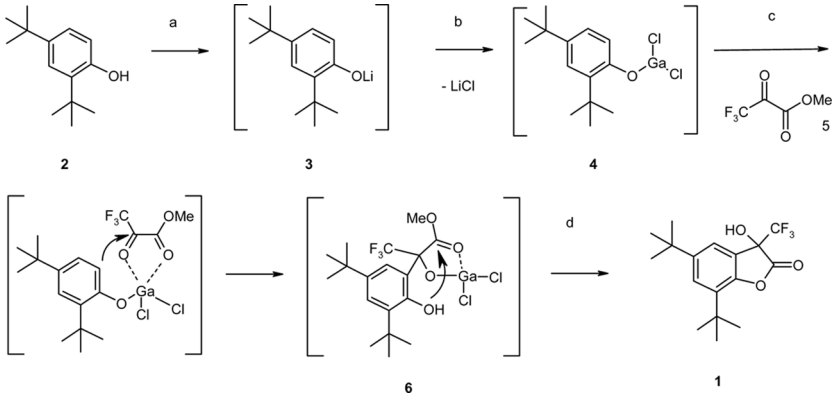
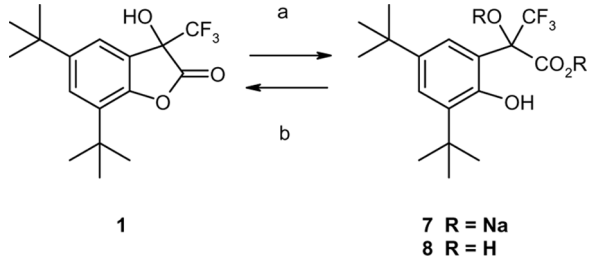


Scheme 1. (a) n-Bu Li (1 eq), THF, −70 to 20°C, distill off THF; (b) $GaCl_3$ (1 eq), DCE, −10 to 80°C, 15 min; (c) CF_3COCO_2Me (1 eq), DCE, 0–20°C; (d) DCE, 28–80°C.

protocols: $AlCl_3$,[3] $TiCl_4$,[4] (*S*)-t-Bu-BOX-Cu$(OTf)_2$,[5] Ga$(OTf)_3$,[6] In$(OTf)_3$,[7] (*S*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-$PdCl_2$, and (S)-5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxide (SEGPHOS)-$PdCl_2$.[8] Our choice fell on the Casiraghi[3] protocol, wherein we replaced $AlCl_3$ by $GaCl_3$ in analogy to the modified protocol for the Sugasawa reaction.[9,10]

RESULTS AND DISCUSSIONS

Lithium phenolate **3** (Scheme 1) was prepared in tetrahydrofuran (THF) at low temperature by treatment of 2,4-di-*tert*-butylphenol (**2**) with n-butyl lithium. THF was replaced with 1,2-dichloroethane (DCE) before addition of a stoichiometric amount of anhydrous gallium(III) chloride at −10°C. Brief heating under reflux led to the precipitation of LiCl with concomitant formation of the gallium phenolate **4**. Addition of the highly electrophilic methyl trifluoropyruvate (**5**) led to gallium-directed regiospecific ortho-alkylation of the phenolate **4** to afford the aldol-type intermediate **6**, which cyclized in situ upon heating to afford lactone **1** in 74% isolated yield. The use of DCE as solvent was essential because the reaction failed in toluene, the solvent originally used by Casiraghi, due to transfer of the *tert*-butyl groups from the substrate **2** to toluene, a well-known process.[11] $GaCl_3$ was superior to $AlCl_3$ in promoting this one-pot process. We have attempted to eliminate the need to switch solvent after generation of the lithium phenolate **3** by using sodium

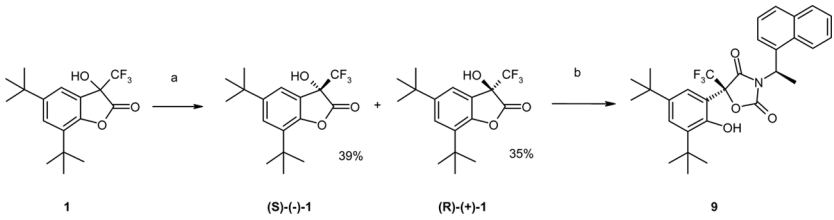


Scheme 2. (a) 1 N NaOH (2 eq), dioxane, 0–20 °C, 16 h; (b) 1 N HCl, AcOEt, 0° C, upon extraction.

trimethylsilanolate (NaOTMS), which had been previously used for mild ester hydrolysis in DCE under non aqueous conditions.[12] However, the yield was less then 30%.

Hydrolysis of lactone **1** (Scheme 2) occurred readily with 2 equivalents of 1 N NaOH in dioxane at 20 °C, and a highly lipophilic sodium salt **7** could be extracted with hot toluene. Interestingly, acidification of the sodium salt **7** with 1 equivalent of 1 N HCl gave lactone **1** again and only trace amounts of the expected hydroxyl acid **8**. Thus the ring closure of the hydroxy acid **8** to lactone **1** occurred rapidly under acidic conditions, probably as a consequence of the Thorpe–Ingold effect.[13]

Separation of the enantiomers of racemic lactone **1** was carried out (Scheme 3) by chiral-phase medium-pressure chromatography on a Chirapak AD® column with heptane/2-propanol 97:3 as the eluent. To determine the absolute configuration, we prepared a derivative of the (+)-enantiomer of **1** with (*R*)-(−)-1-(naphthyl)ethyl isocyanate. Unexpectedly, we obtained the oxazolidine-2,4-dione **9**, which became evident only after X-ray crystal analysis (Fig. 1). From these data, the (*R*)-configuration could be assigned to the (+)-enantiomer of **1**. (CCDC 643853 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk or by contacting



Scheme 3. (a)Chromatography on Chiralpack AD, heptane/2-propanol 97:3; (b) (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (1 eq), cat. DMAP, toluene, reflux, 1 h.

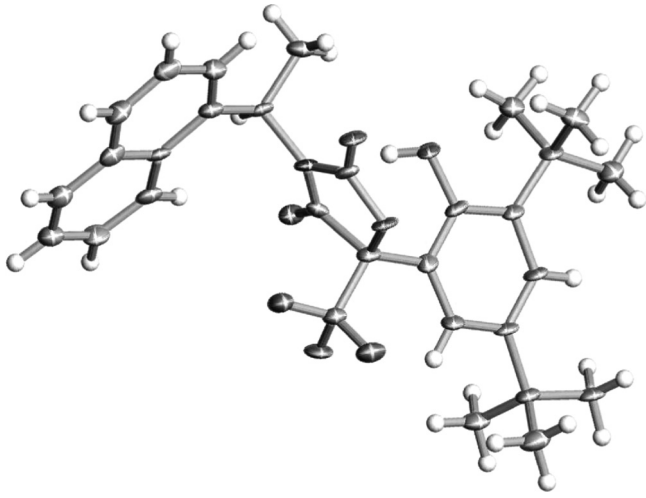


Figure 1. ORTEP plot of the X-ray structure of **9**.

the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

CONCLUSIONS

In summary we have developed an efficient one-pot synthesis of racemic 5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one, separated the enantiomers by chromatography on a chiral stationary phase, and determined the absolute configuration via X-ray crystal analysis of a suitable derivative.

EXPERIMENTAL

(*R,S*)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (1)

2,4-Di-*tert*-butylphenol (**2**) (28 g, 28.5 mmol) was dissolved in THF (250 mL) under argon and cooled to −70 °C. A 1.6 M solution of n-butyllithium in hexane (85 mL, 135.7 mmol) was added, and the solution was allowed to reach 20°C. THF was distilled off and replaced by DCE (250 mL), which was distilled off again and replaced with DCE (250 mL). After cooling in ice/MeOH, a fresh ampoule of gallium(III) chloride (25 g, 142.5 mmol) was added (exothermic, 5°C). The resulting solution was heated under reflux for 15 min, affording a white precipitate of LiCl. The suspension was cooled

in ice, then methyl trifluoropyruvate (14.5 mL, 142.5 mmol) dissolved in DCE (20 mL) was added, and stirring continued for 13 h at 20°C. The reaction was driven to completion by heating under reflux for 3.5 h. After cooling, the suspension was extracted with DCM (2 ×), cold 1 M HCl (2 ×), and NaCl (1 ×). The crude product was purified by chromatography on silica gel in heptane/DCM 2:1. The purified product (37 g) was recrystallized from cold heptane (150 mL), and dried at 50°C/1 mbar for 5 h to afford 28.9 g (64%) of white crystals. From mixed fractions and the mother liquor, another 4.4 g (10%) of white crystals were isolated. Mp 83 °C. ^{1}HNMR (400 MHz, DMSO-d_6) $\delta = 1.31$ (s, 9 H, t-Bu), 1.37 (s, 9 H, t-Bu), 7.40 (s, 1 H, ArH), 7.47 (s, 1 H, ArH), 8.26 (s, 1 H, OH). IR (nujol) 3401 (s, OH), 3350 (s, OH), 2956 (s), 2854 (s), 1812 (s, CO), 1621 (w), 1608 (w), 1483 (s), 1463 (s), 1111 (s, CF_3), 1086 (s, OH). MS (EI): m/z = 330 (20, M), 315 (95, M-CH_3), 287 (100, M-CH_3CO); HRMS (FT-ICR): calcd. for $C_{19}H_{24}F_3O_5$ $(M - H + CH_3COOH)^-$ 389.158143; found 389.15797.

(*R,S*)-2-(3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-3,3,3-trifluoro-2-hydroxy-propionic Acid, Disodium Salt (7)

(*R,S*)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (**1**) (7.69 g, 23.3 mmol) was dissolved in dioxane (50 mL), cooled in ice, treated with 1 N NaOH (51.2 mL, 51.2 mmol), and stirred for 16 h at 20°C. The yellow solution was evaporated to dryness. The residue was heated to 100 °C in toluene (100 mL), and the hot solution was filtered to remove residual solids. The filtrate was evaporated to dryness, and the resulting white solid was heated to 80°C in heptane (100 mL). The slurry was allowed to cool to 20°C and then stirred in ice for 15 min. The white solid was filtered off and washed with heptane to afford 8.87 g (97%) of white solid. ^{1}HNMR (400 MHz, DMSO-d_6) $\delta = 1.14$ (s, 9 H, t-Bu), 1.31 (s, 9 H, t-Bu), 6.78 (s, 1 H, ArH), 7.50 (s, 1 H, ArH), 17.4 (s, 1 H, OH). MS (EI): m/z = 347 (M − H)); HRMS (FT-ICR): calcd. for $C_{17}H_{22}F_3O_4$ $(M + H - 2\ Na)^-$ 347.14757; found 347.14752.

(*R,S*)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (1) and (*R,S*)-2-(3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-3,3,3-trifluoro-2-hydroxy-propionic Acid (8) via Acidification of Disodium Salt 7

Lactone **1** (10 g, 30.2 mmol) was dissolved in dioxane (60 mL) and treated with 1 N NaOH (66.6 mL, 66.6 mmol) for 2 h (slightly exothermic upon mixing, 30°C). The reaction was followed by high pressure liquid chromatography (HPLC) and thin layer chromatography (TLC) in heptane/ethyl acetate 1:1, which indicated at least 95% conversion. The mixture

was evaporated to dryness at 50 °C/1 mbar, yielding the sodium salt **7** as a white solid. This solid was extracted with ethyl acetate (2 ×), cold 1 N HCl (1 ×), and sat. NaCl (1 ×). During this process, the sodium salt reverted almost quantitatively to the corresponding lactone. The crude product was purified by chromatography on silica gel with a gradient of ethyl acetate in heptane from 0 to 100%. The lactone was eluted first (UV active), followed by a small amount of hydroxy acid (not UV active). The lactone fraction was crystallized from cold heptane (50 mL) by seeding with authentic material to afford 7.09 g (71%) of the lactone **1** as white crystals, 1.4 g of the mother liquor, which was discarded, and 722 mg (7%) of hydroxy acid **8** as a gum. Compound **1**: ^{1}HNMR (400 MHz, DMSO-d_6) $\delta = 1.31$ (s, 9 H, t-Bu), 1.37 (s, 9 H, t-Bu), 7.40 (s, 1 H, ArH), 7.47 (s, 1 H, ArH), 8.26 (s, 1 H, OH). MS (EI): m/z = 330 (20, M), 315 (95, M-CH_3), 287 (100, M-CH_3CO). compound **8**: ^{1}HNMR (400 MHz, d_6-DMSO) d = 1.22 (s, 9 H, tBu), 1.35 (s, 9 H, t-Bu), 6.0–6.3 (s, br, 1 H, OH), 7.12 (s, 1 H, ArH), 7.60 (s, 1 H, ArH), 8.25 (s, 1 H, OH), 13.4 (s, br, 1 H, COOH). MS (ISP): m/z = 347 (M −H); HRMS (FT-ICR): calcd. for $C_{17}H_{22}F_3O_4$ $(M-H)^-$ 347.14757; found: 347.14748.

Separation of the Enantiomers (*R*)-(+)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one and (*S*)-(−)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one

(*R,S*)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (**1**) (1.5 g, 4.5 mmol) was separated on Chiralpak AD® with heptane/2-propanol 97:3. The (+)-enantiomer (534 mg, 35%) was eluted first and gave white crystals, MS (EI): m/z = 330 (M). $[\alpha]_D^{20} = +33.47$ ($CHCl_3$, c = 0.765)); HRMS (FT-ICR): calcd. for $C_{19}H_{24}F_3O_5$ $(M-H+CH_3COOH)^-$ 389.158143; found: 389.15797. The (−)-enantiomer (580 mg, 39%) was eluted last and gave white crystals, MS (EI): m/z = 330 330 (M). $[\alpha]_D^{20} = -33.27$ ($CHCl_3$, c = 0.679). ^{1}HNMR (400 MHz, DMSO-d_6) d = 1.31 (s, 9 H, t-Bu), 1.37 (s, 9 H, t-Bu), 7.40 (s, 1 H, PhH), 7.47 (s, 1 H, PhH), 8.27 (s, 1 H, OH); HRMS (FT-ICR): calcd. for $C_{19}H_{24}F_3O_5$ $(M-H+CH_3COOH)^-$ 389.158143; found: 389.15799.

Determination of the Absolute Configuration of (*R*)-(+)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one via X-ray Analysis of (*R*)-5-(3,5-Di-*tert*-butyl-2-hydroxy-phenyl)-3-((*R*)-1-naphthalen-1-yl-ethyl)-5-trifluoromethyl-oxazolidine-2,4-dione (9)

(*R*)-(+)-5,7-Di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one (100 mg, 0.3 mmol), (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.058

mL, 0.33 mmol), and 4-dimethylaminopyridine (3.7 mg, 0.03 mmol) were heated under reflux in toluene (1 mL) for 1 h under nitrogen. The resulting solution was evaporated to dryness, and the residue was purified by chromatography on silica gel with a gradient of ethyl acetate in heptane from 0 to 100% in 20 min and then with heptane/DCM 3:1 to afford 60 mg (37%) of white crystals. Crystals suitable for X-ray analysis were obtained by slow evaporation of a standing DCM solution at ambient temperature. ^{1}HNMR (400 MHz, $CDCl_3$) $\delta = 1.27$ (s, 9 H, t-Bu), 1.38 (s, 9 H, t-Bu), 1.97 (d, 3 H, $J = 8$ Hz, Me), 6.16 (q, 1 H, $J = 8$ Hz, C*H*Me), 7.27 (m, 1 H, ArH), 7.52 (s, 1 H, ArH), 7.57 (m, 3 H, ArH), 7.83 (dd, 1 H, ArH), 8.0 (m, 3 H, ArH), 8.6 (s, 1 H, OH); MS (ISP): $m/z = 545$ $(M + NH_4)^+$; HRMS (FT-ICR): calcd. for $C_{30}H_{36}F_3N_2O_4$ $(M + NH_4)^+$ 545.26217; found: 545.26227.

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