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Enantioselective synthesis of (*S*)-Vigabatrin®

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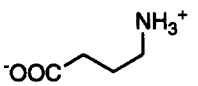
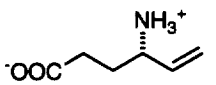
Abstract: An asymmetric synthesis of fully protected (*S*)-Vigabatrin® has been developed. The key intermediate in the sequence is enantiomerically pure *N*-Boc-5-phenyl-3-amino-1,2-diol **5a**, obtained from (*E*)-5-phenyl-2-penten-1-ol by employing a catalytic Sharpless epoxidation as the sole source of chirality. Aminodiol **5a** was converted into the target *N*-Boc-(*S*)-Vigabatrin methyl ester **3** by a five-step sequence involving the actualization of the latent carboxyl group (phenyl oxidation) and a Corey–Hopkins deoxygenative protocol of the 1,2-diol. © 1997 Elsevier Science Ltd

Several important neurological disorders such as Parkinson's disease and epilepsy have been associated[1] to a deficiency of 4-aminobutanoic acid (γ-aminobutyric acid, GABA) **1**. Although it is known that increasing the brain concentration of GABA prevents convulsions[2,3] the low lipophilicity of this compound is probably responsible for its inefficiency as an anticonvulsant when administered orally or intravenously.[4] The brain concentration of GABA can also be raised using selective inhibitors of GABA catabolism. The most important enzyme in this catabolism is GABA-aminotransferase (GABA-T) which degrades GABA to succinic semialdehyde.[5] One of the most effective and selective inhibitors of GABA-T is 4-amino-5-hexenoic acid (γ-vinyl GABA, Vigabatrin®)[3,6] **2** which is an important anticonvulsant drug marketed in racemic form as Sabril®.[2,7] Since only the *S* enantiomer is pharmacologically active[3a] the asymmetric synthesis of this compound is a matter of current interest, and several preparations of the enantiomerically pure compound, most of them starting from natural α-amino acids, have been described.[8]

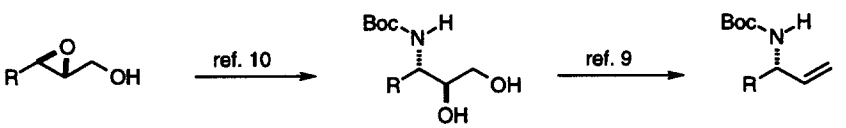


1 (GABA)



2 (*S*)-Vigabatrin

We have recently reported an efficient methodology[9] for the preparation of enantiomerically pure allylamines based on the deoxygenation of chiral, readily available[10] *N*-Boc-3-amino-1,2-diols (Scheme 1).



Scheme 1.

We wish to report now an asymmetric synthesis of fully protected, enantiomerically pure (*S*)-Vigabatrin®, where the allylamine moiety is constructed by use of our previously reported procedure. According to our retrosynthetic analysis, *N*-Boc-Vigabatrin methyl ester **3** could be obtained by deoxygenation of aminodiol **4**. We envisaged that the carboxylic acid functionality of this compound could arise from the oxidation of a phenyl group in a conveniently protected compound **5**, whereas

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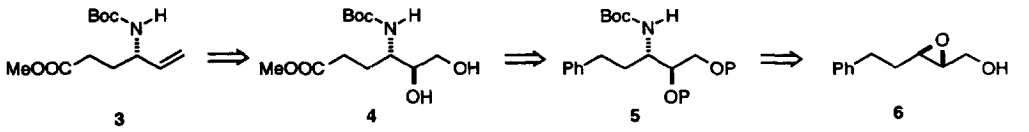
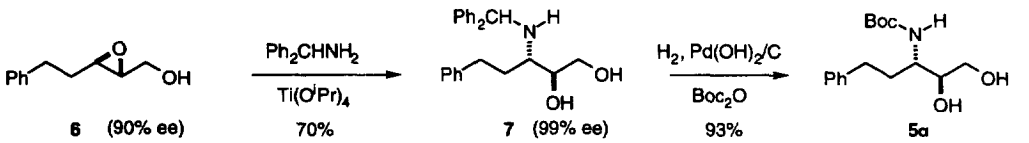
the aminodiol moiety would arise from the stereospecific and regioselective ring-opening[10] of an enantioenriched epoxy alcohol **6**, easily available by Sharpless epoxidation[11] (Scheme 2).



Scheme 2.

In the present instance, the known[12,13] epoxy alcohol **6** was prepared in 77% yield and 90% ee (according to ^{1}H-NMR analysis of its Mosher ester) by a catalytic Sharpless epoxidation. The ring opening of **6** by benzhydrylamine in the presence of titanium tetraisopropoxide took place with high regioselectivity (C-3/C-2: 94.5/5.5) and the crystalline aminodiol **7**[13] could be isolated in high yield (87%) as a single regioisomer by column chromatography. A single crystallization from hexane/dichloromethane afforded enantiomerically pure (according to a DSC analysis[14]) samples of **7** without significant yield losses (77%). A subsequent hydrogenolysis of the instrumental benzhydryl group with simultaneous protection (Boc_2O) led to the known *N*-Boc aminodiol **5a**[13] in high yield (Scheme 3).

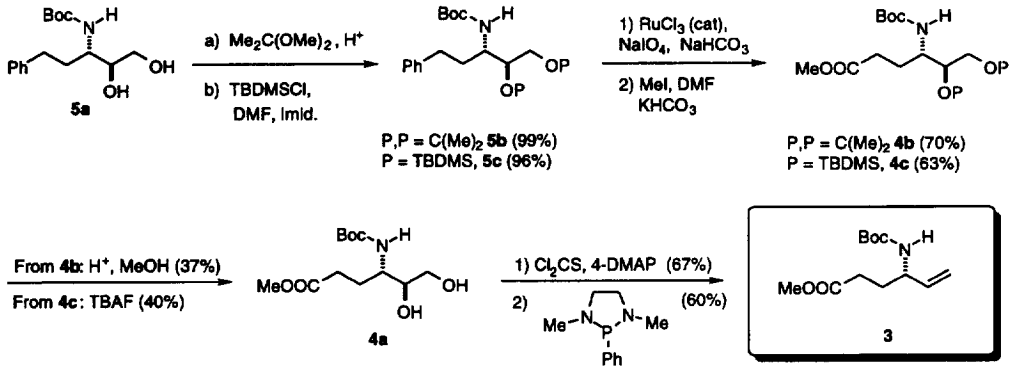


Scheme 3.

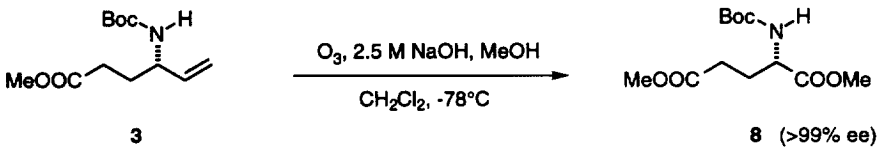
As a diol protecting group for **5a**, we first selected the acetonide, since it is stable to the oxidation conditions required for the planned conversion of the phenyl ring into a carboxy group. The formation of the acetonide **5b** was nearly quantitative using acetone dimethyl acetal and acid catalysis. The subsequent oxidation took place in good yield by the Sharpless procedure,[15] the corresponding acid being converted[16] to its methyl ester **4b** in order to facilitate the isolation of the product (Scheme 4). Unfortunately, the subsequent cleavage of the acetal protecting group[17a] proved to be very problematic leading to diol **4a** only in moderate yield, probably because of a competing lactonization of the product under acidic conditions.[18] In spite of the many alternative deprotection protocols[17] that were assayed in the hydrolysis of the isopropylidene acetal, we were not able to improve this yield. Consequently, we decided to use a different protecting group that could be deprotected under non-acidic conditions. The *tert*-butyldimethylsilyl group fulfilled these requirements and, hence, seemed appropriate to our needs. The formation of the bis-silyl ether **5c** was performed under standard conditions, affording the diprotected compound in excellent yield. The subsequent oxidation and esterification steps took place conveniently leading to the methyl ester **4c**. However, the deprotection of the silyl ethers with TBAF was plagued with the same problems as the hydrolysis of **5b** and also gave only moderate yields of **4a**. With diol **4a** in hand, the Corey–Hopkins deoxygenation protocol[19] (formation of the thionocarbonate and treatment with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine) was carried out without problems leading to the target *N*-Boc-Vigabatrin methyl ester **3** in good yields (Scheme 4).

The enantiomeric purity of *N*-Boc-Vigabatrin methyl ester **3** was checked by chiral HPLC analysis[20] (Chiralcel®-ODR) of *N*-Boc-glutamic acid dimethyl ester **8**, prepared from **3** by Marshall's ozonolysis[21] (Scheme 5).

In summary, we have developed a new stereoselective synthesis of enantiomerically pure *N*-Boc-Vigabatrin methyl ester **3** starting from enantiomerically enriched epoxy alcohol **6**, easily available by catalytic Sharpless epoxidation. The synthesis is based on the preparation of enantiomerically



Scheme 4.



Scheme 5.

pure *N*-Boc-5-phenyl-3-amino-1,2-diol **5**, which was converted into **3** through a five steps procedure involving the oxidation of the phenyl group to a carboxylic ester and the deoxygenation of the diol fragment using the Corey–Hopkins protocol.[19]

Experimental section

General methods

Optical rotations were measured at room temperature (23°C) on a Perkin–Elmer 241 MC automatic polarimeter (Concentration in g/100 mL). Melting points were determined on a Reichert–Thermovar Köfler apparatus and have not been corrected. Infrared spectra were recorded on a Perkin–Elmer 681, or on a Nicolet 510 FT-IR instrument using NaCl film or KBr pellet techniques. NMR spectra were acquired on Varian XL-200 or Varian-Unity-300 instruments. ^{1}H-NMR were obtained at 200, 300 or 500 MHz (s=singlet, d=doublet, t=triplet, q=quartet, dt=double triplet, m=multiplet, b=broad and bd=broad doublet). ^{13}C-NMR were obtained at 50.3 MHz or 75.4 MHz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra were recorded on a Hewlett–Packard 5890 instrument. Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". DSC measurements were performed on a Mettler DSC30 instrument at the "Servei de Calorimetria de Reacció i Anàlisi Tèrmica, Divisió III, Universitat de Barcelona". Methylene chloride was distilled from CaH_2 under nitrogen prior to use. Chromatographic separations were carried out using NEt_3 pre-treated (2.5% v/v) SiO_2 (70–230 mesh). Chromatographic analyses were performed on a Hewlett–Packard 1050 HPLC instrument equipped with a Chiralcel® ODR (25 cm) column.

(2R,3R)-5-Phenyl-2,3-epoxypentanol ***6***

Into a 100 mL flask were introduced dry powdered 4 Å molecular sieves (1.2 g) and anhydrous dichloromethane (26 mL) under nitrogen. After cooling to −20°C (CO_2/CCl_4 bath) the following reagents were introduced sequentially *via cannula* under stirring: D-(−)-diisopropyl tartrate (172 mg, 0.74 mmol) in dichloromethane (4 mL), titanium tetraisopropoxide (0.17 mL, 0.6 mmol) and, slowly, a solution of (*E*)-5-phenyl-2-penten-1-ol (2 g, 12.3 mmol) (previously distilled and stored 24 h over

4 Å molecular sieves) in dichloromethane (4 mL). The mixture was stirred for 1 hour at −30°C (CO_2/anisole bath) and a 3 M solution of *tert*-butyl hydroperoxide in isooctane (8 mL, 24.6 mmol) was added dropwise. After 25 hours of stirring at the same temperature, the reaction mixture was allowed to warm to 0°C and was then slowly poured into a beaker containing a freshly prepared ferrous sulfate solution (4 g of $FeSO_4 \cdot 7H_2O$, 1.2 g of citric acid monohydrate in 12.5 mL of water) at 0°C. The two-phase mixture was stirred for 5–10 min, the phases were separated and the aqueous phase was extracted with ether. The combined organic layers were treated with a precooled (0°C) solution of 30% NaOH (1.5 mL) in saturated brine. The mixture was stirred vigorously for 1 h at 0°C and then diluted with water (6 mL). The phases were separated and the aqueous phase was extracted with ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude reaction product was then purified by flash chromatography eluting with hexanes/ethyl acetate mixtures yielding 1.7 g of **6** (77% yield). The enantiomeric excess was determined to be 90% by ^{1}H-NMR analysis of the Mosher ester. $[\alpha]_D$ +45.4 (*c* 2.8, $CHCl_3$). IR (film) ν 3440, 3040, 2880, 1750, 1610, 1500, 1460, 1100, 1040, 1010, 880, 750, 700 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (m, 5H), 3.83 (m, 1H), 3.55 (m, 1H), 3.0 (dt, J=6 Hz, J=2 Hz, 2H), 2.9–2.6 (m, 2H), 2–1.8 (m, 2H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 145.1 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 61.5 (CH_2), 58.7 (CH), 55.2 (CH), 33.1 (CH_2), 31.9 (CH_2) ppm. MS (EI) m/e 178 (M^+, 0.4%), 118 (32%), 105 (30%), 104 (39%), 91 (100%).

(2S,3S)-3-Diphenylmethylamino-5-phenyl-1,2-pentanediol **7**

To a solution of **6** (3 g, 16.7 mmol) in dichloromethane (121 mL) was added titanium tetraisopropoxide (15 mL, 50 mmol). The mixture was stirred for several minutes and a solution of freshly distilled benzhydrylamine (6.1 g, 34 mmol) in dichloromethane (41 mL) was added *via cannula*. After 72 hours of reflux the mixture was cooled to 25°C and quenched with 10% NaOH solution saturated with NaCl (50 mL). The mixture was stirred 15 hours, filtered through a short Celite® pad and washed thoroughly with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organic phases were dried ($MgSO_4$) and evaporated. Solid CO_2 was added to the ethereal solution and the precipitated benzhydrylamine carbonate was filtered off and washed with ether saturated with CO_2. The solvent was evaporated and the reaction crude was purified by flash chromatography eluting with hexanes/ethyl acetate mixtures to afford 5.2 g of **7** (87% yield) and 0.3 g of (2*S*,3*R*)-2-diphenylmethylamino-5-phenyl-1,3-pentanediol (5%). Compound **7** that was recrystallized from hexane/dichloromethane to afford 4.2 g of a white solid (99% ee by DSC). m.p. 76.5–77.6°C. $[\alpha]_D$ +45.0 (*c*=1, $CHCl_3$). IR (film) 3400 (broad), 3060, 3030, 2930, 1600, 1500, 1460, 1180, 1040, 750, 700 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.5–7 (m, 15H), 4.99 (s, 1H), 3.8–3.6 (m, 3H), 2.9–2.5 (m, 6H), 2–1.7 (m, 2H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 144.5 (C), 143.6 (C), 142.4 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 126.5 (CH), 71.8 (CH), 64.8 (CH_2), 64.7 (CH), 57.4 (CH), 32.3 (CH_2), 32.1 (CH_2) ppm. MS (EI) m/e 362 (M+1, 1%), 300 (15%), 167 (100%). Anal. Calcd for: $C_{24}H_{27}NO_2$: C, 79.74%; H, 7.53%; N, 3.87%. Found: C, 79.77%; H, 7.52%; N, 3.63%.

*(2S,3S)-3-(*tert*-Butoxycarbonylamino)-5-phenyl-1,2-pentanediol* **5a**

A suspension of 10% $Pd(OH)_2$ on carbon (88 mg) in ethyl acetate (1.1 mL) was stirred at room temperature under a hydrogen atmosphere for 10 minutes, whereupon a solution of di-*tert*-butyl dicarbonate (687 mg, 3.15 mmol) and the aminodiol **3** (875 mg, 2.42 mmol) in ethyl acetate (4.3 mL) was added. The resulting mixture was hydrogenated at room temperature until disappearance of **3** (monitored by TLC). To the reaction mixture was added Celite® and the mixture was filtered through a Celite® pad to separate the catalyst. The filtrate was concentrated *in vacuo* and the crude product purified by flash chromatography eluting with hexanes/ethyl acetate mixtures and recrystallized (hexane/dichloromethane) yielding 664 mg of **5a** (93%) as a white solid. m.p. 129–130°C; $[\alpha]_D$ −13.5 (*c* 1, $CHCl_3$). IR (KBr) ν_{max} 3450, 2960, 2930, 1680, 1520, 1170, 1040, 750, 700 cm^{-1}. ^{1}H-NMR

(200 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H), 4.55 (broad d, J=11 Hz, 1H), 3.7–3.5 (m, 3H), 3.3 (broad, 1H), 2.9–2.5 (m, 2H), 2.3–2.1 (m, 2H), 1.7 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 157.1 (C), 141.3 (C), 128.4 (CH), 129.3 (CH), 125.9 (CH), 80.3 (C), 74.5 (CH), 63.0 (CH_2), 52.1 (CH), 32.8 (CH_2), 32.4 (CH_2), 28.3 (CH_3) ppm. MS (EI) m/e 295 (M^+, 0.1%), 234 (6%), 178 (16%), 117 (44%), 57 (100%). Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06%; H, 8.53%; N, 4.74%. Found: C, 64.59%; H, 8.40%; N, 4.63%.

*(1S,4′S)-N-*tert*-Butoxycarbonyl-1-2′2′-dimethyl[1′,3′]dioxolan-4′-yl-3-phenylpropylamine* ***5b***

To a solution of **5a** (200 mg, 0.68 mmol), in acetone (8.2 mL) were added acetone dimethyl acetal (125 µL, 1 mmol) and *p*-toluenesulfonic acid (6 mg, 5% molar ratio). After 1 hour, the solution was washed with 10% NaOH, and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to yield 225 mg of **5b** (99% yield) as a white solid. m.p. 105–107°C. $[\alpha]_D$ −22.3 (*c* 1, $CHCl_3$). IR (KBr) ν_{max} 3348, 2983, 2931, 1686, 1534, 1446, 1368, 1173, 1057, 862, 758, 700 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 5H), 4.5 (d broad, 1H), 4.1–3.95 (m, 2H), 3.8–3.6 (m, 2H), 2.7 (m, 2H), 2.1–1.5 (m, 2H), 1.46 (s, 9H), 1.38 (s, 3H), 1.32 (s, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 155.6 (C), 141.6 (C), 128.3 (CH), 126.0 (CH), 125.9 (CH), 109.4 (C), 79.4 (C), 78.3 (CH), 66.6 (CH_2), 52.5 (CH), 32.5 (CH_2), 32.1 (CH_2), 28.3 (CH_3), 26.3 (CH_3), 25.1 (CH_3) ppm. MS (EI) m/e 335 (M^+, 0.1%), 279 (3%), 234 (9%), 178 (22%), 134 (59%), 117 (54%), 91 (49%), 57 (100%). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03%; H, 8.71%; N, 4.18%. Found: C, 68.06%; H, 8.79%; N, 4.22%.

*(2S,3S)-3-(*tert*-Butoxycarbonylamino)-5-phenyl-1,2-bis(*tert*-butyldimethylsilyloxy) pentane* ***5c***

To a solution of **5a** (413 mg, 1.4 mmol) in dimethylformamide (3.3 mL) were added *tert*-butyldimethylsilyl chloride (633 mg, 4.2 mmol) and imidazole (571 mg, 8.4 mmol). The mixture was stirred at 35°C for 16 hours. Then the mixture was cooled to room temperature and diluted with water (8.4 mL) and ether (9.8 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$ and the solvents were evaporated *in vacuo*. The crude product was purified by chromatography eluting with hexanes/ethyl acetate (8:2) to afford 704 mg of **5c** (96% yield) as a colorless oil. $[\alpha]_D$ −12.0 (*c*=2.1, $CHCl_3$). IR (film) ν_{max} 3348, 3280, 2956, 2931, 2860, 1706, 1497, 1472, 1366, 1256, 1175, 1090, 835, 778, 698 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.2 (m, 5H), 5 (d broad, 1H), 3.8–3.5 (m, 4H), 2.7 (m, 2H), 1.8–1.3 (m, 2H), 1.45 (s, 9H), 0.89 (s, 18H), 0.05 (m, 12H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 155.7 (C), 142.3 (C), 128.3 (CH), 125.7 (CH), 78.5 (C), 74.1 (CH), 65.0 (CH_2), 52.9 (CH), 32.6 (CH_2), 31.8 (CH_2), 28.4 (CH_3), 25.8 (CH_3, ^{t}Bu), 18.2 (C), 18.0 (C), −4.5 (CH_3), −5.0 (CH_3), −5.5(CH_3), −5.6 (CH_3) ppm. MS (CI−NH_3) m/e 541 (M+18, 8%), 524 (M+1, 100%), 424 (8%), 269 (3%).

*(4S,4′S)-4-(*tert*-Butoxycarbonylamino)-4-2′2′-dimethyl-[1′,3′]dioxolan-4′-ylbutyric acid methyl ester* ***4b***

To a mixture of **5b** (300 mg, 0.9 mmol), carbon tetrachloride (6.3 mL), acetonitrile (6.3 mL), water (12.6 mL) and $NaHCO_3$ (1.3 g, 15.3 mmol) were added slowly sodium metaperdiodate (3.5 g, 16.2 mmol) and ruthenium trichloride hydrate (20 mg, 0.09 mmol). The mixture was stirred vigorously at 25°C for 4 days, after which it was diluted with water (24 mL) and ethyl acetate (25 mL) and filtered through a short Celite® pad. The filtrate was separated and the aqueous layer was extracted with ethyl acetate (4×25 mL). The aqueous layer was cooled at 0°C, acidified with 4 M HCl to pH=2–3 and extracted with precooled (0°C) ethyl ether (4×25 mL), The combined organic extracts were dried over $MgSO_4$, and concentrated to give 224 mg of a crude product [(4*S*,4′*S*)-4-(*tert*-butoxycarbonylamino)-4-2′2′-dimethyl[1′,3′]dioxolan-4′-ylbutyric acid]. To a solution of this crude in dimethylformamide (1.1 mL) were added under nitrogen $KHCO_3$ (1.49 mg, 1.48 mmol) and methyl iodide (74 µL, 1.2 mmol). The mixture was stirred for 16 h at room temperature and then quenched by addition of water (4 mL). The product was extracted with 1:1 benzene/ethyl acetate mixtures. The combined organic phases were washed with water, 5% Na_2SO_3 and brine, dried over $MgSO_4$ and evaporated yielding

198 mg of **4b** (70% yield) as a white solid. m.p. 79–80°C. $[\alpha]_D$ −16.0 (*c* 1, $CHCl_3$). IR (film) ν_{max} 3359, 2983, 1750, 1715, 1522, 1455, 1370, 1171, 1054, 853 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.55 (d broad, 1H), 4.1–3.6 (m, 4H), 3.68 (s, 3H), 2.4 (t, J=7.4 Hz, 2 H), 2.1 (m, 2H), 1.43 (s, 12H), 1.33 (s, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 174 (C), 155.6 (C), 109.6 (C), 79.5 (C), 78.2 (CH), 66.7 (CH_2), 52.6 (CH), 51.6 (CH_3), 30.5 (CH_2), 28.3 (CH_3), 26.3 (CH_3), 25.9 (CH_2), 25.1 (CH_3) ppm. MS (CI−NH_3) m/e 335 (M+18, 100%), 318 (M+1, 78%), 279 (38%).

*(4S,5S)-4-(*tert*-Butoxycarbonylamino)-5,6-bis(*tert*-butyldimethylsilyloxy)hexanoic acid methyl ester* ***4c***

To a mixture of **5c** (400 mg, 0.76 mmol), carbon tetrachloride (5.3 mL), acetonitrile (5.3 mL), water (10.6 mL) and $NaHCO_3$ (1.1 g, 12.9 mmol) were added slowly sodium metaperdiodate (2.9 g, 13.7 mmol) and ruthenium trichloride hydrate (17 mmg, 0.076 mmol). The mixture was stirred vigorously at 25°C for 4 days, and then, it was diluted with water (21 mL) and ethyl acetate (21 mL) and filtered through a short Celite® pad. The filtrate was separated and the aqueous layer was extracted with ethyl acetate (4×21 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated to give 343 mg of a crude product ((4*S*,5*S*)-4-(*tert*-butoxycarbonylamino)-5,6-bis(*tert*-butyldimethylsilyloxy)hexanoic acid). To a solution of this crude in dimethylformamide (1.1 mL) were added under nitrogen $KHCO_3$ (140 mg, 1.4 mmol) and methyl iodide (61 μL, 1.1 mmol). The mixture was stirred for 16 h at room temperature and then quenched by addition of water (4 mL). The product was extracted with 1:1 benzene/ethyl acetate mixtures. The combined organic phases were washed with water, 5% Na_2SO_3 and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography eluting with hexanes/ethyl acetate (98:2) to afford 245 mg of **4c** (63% yield). $[\alpha]_D$ −14.9 (*c* 2.1, $CHCl_3$). IR (film) ν_{max} 3440, 2931, 2860, 1750, 1719, 1501, 1474, 1366, 1256, 1173, 837, 778 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.0 (broad d, 1H), 3.8–3.4 (m, 4H), 3.69 (s, 3H), 2.4 (m, 2H), 1.8 (m, 2H), 1.44 (s, 9H), 0.91 (s, 18H), 0.08 (s, 12H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ 174 (C), 155.7 (C), 78.7 (C), 74.1 (CH), 65.1 (CH_2), 52.8 (CH), 51.5 (CH_3), 31.0 (CH_2), 28.4 (CH_3), 25.9 (CH_3), 25.8(CH_3), 24.9 (CH_2), 18.1 (C), −4.4, −5.0 (CH_3), −5.5 (CH_3), −5.6 (CH_3) ppm. MS (CI−NH_3) m/e 523 (M+18, 2%), 506 (M+1, 100%), 492 (45%), 392 (16%).

*(4S,5S)-4-(*tert*-Butoxycarbonylamino)-5,6-dihydroxyhexanoic acid methyl ester* ***4a***

From **4b**: To a solution of **4b** (50 mg, 0.16 mmol) in MeOH (2.1 mL) was added *p*-toluenesulfonic acid (4 mg, 0.022 mmol). After 30 minutes, a saturated $NaHCO_3$ aqueous solution (7 mL) was added and the solution was extracted with ethyl acetate. The combined organic phases were washed with a saturated NaCl aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 16 mg of **4a** (37% yield) as an oil.

From **4c**: To a solution of **4c** (105 mg, 0.2 mmol) in THF (0.5 mL) at 0°C was added a solution of tetrabutylammonium fluoride (144 mg, 0.46 mmol) in THF (1.8 mL). After 5 minutes, the solution was diluted with dichloromethane, the organic layer was washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 23 mg of **4a** (40% yield) as an oil. $[\alpha]_D$ −1.5 (*c*=0.76, $CHCl_3$). IR (film) ν_{max} 3369, 2979, 1708, 1686, 1526, 1455, 1368, 1252, 1171, 1048, 874 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.9 (d broad, 1H), 3.8–3.3 (m, 4H), 3.69 (s, 3H), 2.45 (t, J=6.6 Hz, 2H), 2.1–1.8 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 174.3 (C), 157.1 (C), 80.3 (C), 74.5 (CH), 62.9 (CH_2), 52.2 (CH), 51.8 (CH_3), 31.0 (CH_2), 28.3 (CH_3), 26.0 (CH_2) ppm. MS (CI−NH_3) m/e 295 (M+18, 70%), 278 (M+1, 51%), 263 (77%), 239 (18%), 221 (21%), 91 (100%).

*(4S)-4-*tert*-Butoxycarbonylamino-5-hexenoic acid methyl ester* (N-*Boc-(S)-Vigabatrin methyl ester)* ***3***

To a stirred solution of **4a** (95 mg, 0.34 mmol) and 4-DMAP (101 mg, 0.82 mmol) in dry dichloromethane (1.4 mL) at 0°C was added 95% thiophosgene (33 μL, 0.41 mmol) under nitrogen. The mixture was stirred for 1 h at 0°C. Then, silica gel (0.7 g) was added and the mixture was allowed to warm to 25°C. After removal of the dichloromethane *in vacuo*, the remaining solid was loaded onto

a column of 2.0 g of silica gel and eluted with hexanes/ethyl acetate (8:2) to afford 73 mg of (4*S*,4′*S*)-4-(*tert*-butoxycarbonylamino)-4-2′-thioxo-[1′,3′]dioxolan-4′-ylbutyric acid methyl ester, **9** (67% yield) as a white solid. m.p. 133–136°C. $[\alpha]_D$ −33.5 (*c* 1.8, $CHCl_3$). IR (film) ν_{max} 3350, 2979, 1702, 1522, 1368, 1295, 1165, 982 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5–4.6 (m, 4H), 3.8 (m, 1H), 3.7 (s, 3H), 2.47 (t, J=6.6Hz, 2H), 2.2–2 (m, 2H), 1.43 (s, 9H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 191 (C), 173 (C), 155 (C), 83.3 (CH), 80 (C), 71.3 (CH_2), 52.3 (CH), 51.9 (CH_3), 29.9 (CH_2), 28.2 (CH_3), 24.2 (CH_2) ppm. EM (CI−NH_3) m/e 337 (M+18, 100%), 321 (M+2, 39%), 281 (58%).

A suspension of thionocarbonate **9** (41 mg, 0.13 mmol) in 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (75 μL, 0.38 mmol) was stirred under argon at 45°C for 20 h. After cooling to room temperature, the crude was directly purified by chromatography on a preparative TLC plate eluting with dichloromethane/ether (97:3) (twice) to afford 19 mg (61% yield) of **3** as an oil. $[\alpha]_D$ +11.4 (*c*=1, $CHCl_3$). IR (film) ν_{max} 3365, 2929, 2856, 1740, 1717, 1517, 1437, 1391, 1366, 1258, 1171, 1065, 1023, 920, 884, 799 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.74 (ddd, J=17 Hz, J=10.5 Hz, J=6 Hz, 1H), 5.22–5.1 (*pseudo* t, 2H), 4.5 (broad, 1H), 4.15 (m, 1H), 3.68 (s, 3H), 2.38 (t, J=6 Hz, 2H), 2–1.7 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 173.8 (C), 155.3 (C), 138.2 (CH), 115.1 (CH_2), 79.5 (C), 52.4 (CH), 51.7 (CH_3), 30.6 (CH_2), 30.0 (CH_2), 28.4 (CH_3) ppm. MS (CI−NH_3) m/e 261 (M+18, 9%), 244 (M+1, 90%), 205 (84%), 188 (100%), 144 (52%).

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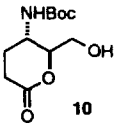

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