HETEROCYCLES, Vol. 71, No. 5, 2007, pp. 1127 - 1134. © The Japan Institute of Heterocyclic Chemistry
Received, 9th January, 2007, Accepted, 8th March, 2007, Published online, 9th March, 2007. COM-07-10994

EFFICIENT SYNTHESIS OF (±)-N-Boc-PREGABALIN VIA HETERO-DIELS-ALDER ADDITION OF METHYL 3-NITROSOACRYLATE TO ETHYL VINYL ETHER

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Abstract – A new synthetic approach towards (±)-*N*-Boc-pregabalin is reported in this paper, which involves hetero-Diels-Alder addition of 3-nitrosoacrylate to ethyl vinyl ether and subsequent reduction of the C=N double bond of adduct, alteration of the ester functionality and reductive N-O bond scission followed by oxidation of the alcohol thus produced.

INTRODUCTION

γ-Aminobutyric acid (GABA) and L-glutamic acid (Figure 1) are the two major neurotransmitters in the mammalian central nervous system,[1] the first one being the major inhibitory and the later the excitatory transmitter. An imbalance in their concentration can lead to convulsive states. When the level of GABA in the brain falls under a threshold, convulsions occur. Despite the fact that increasing the brain concentration of GABA prevents convulsive seizures, the low lipophilicity of this compound is probably responsible for its inefficiency as anticonvulsant drug. Many GABA mimetic substances such as GABA receptor agonists, GABA reuptake inhibitors and GABA metabolism inhibitors have been developed[1,2] as potent anticonvulsant agents and an number of GABA analogs such as pregabalin (Figure 1), vigabatrin and gabapentin have introduced as medicines against epilepsy, neuropathic pain and anxiety.[3]

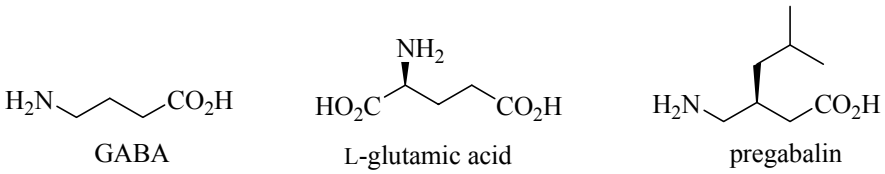


Figure 1

(*S*)-3-Isobutyl-*γ*-aminobutyric acid (pregabalin) binds with high affinity to the α_2-δ subunit of voltage-gated calcium channels in central nervous system tissues.[4] As a consequence, calcium influx is modulated at nerve terminals, which in turn reduces the release of several neurotransmitters including glutamate. It has

been postulated that pregabalin and related GABA analogs exert their therapeutic effects through the inhibition of calcium influx and the subsequent attenuation of neurotransmitter release.

In general, it is difficult to synthesize *β*-substituted-*γ*-amino acids,[5] but a number of methods for both racemic[6] and asymmetric syntheses of pregabalin have been developed. The existing asymmetric syntheses of pregabalin involve either Evans' chiral oxazolidinone alkylation chemistry[7] or enantioselective catalytic conjugate addition of cyanide to *α,β*-unsaturated imides[5] or rhodium-catalyzed asymmetric hydrogenation of an unsaturated pregabalin precursor.[8] However, the current manufacturing process for pregabalin is based on the synthesis of racemic product, followed by late-stage classical resolution with (*S*)-(+)-mandelic acid.[9] This fact makes interesting and potentially applicable any new improved racemic synthesis of pregabalin.

Our group has recently applied the hetero-Diels-Alder addition reactions of ethyl 2-nitrosoacrylate to electron-rich alkenes in the development of new synthetic approaches to either hydroxylated pyrrolizidines[10] or non-proteinogenic *α*-amino acids.[11] Methyl 3-nitrosoacrylate is another reactive intermediate heterodiene, known to react with ethyl vinyl ether to give adduct **3**[12] (Scheme 1). It was thus considered that a sequence of standard manipulations, involving reduction of the C=N double bond in **3**, alteration of the ester functionality and further N-O bond scission followed by oxidation of the C-6 carbon of the oxazine skeleton, could lead to *β*-substituted-*γ*-amino acids. We now report our results towards the synthesis of (±)-pregabalin based on the above outlined scheme.

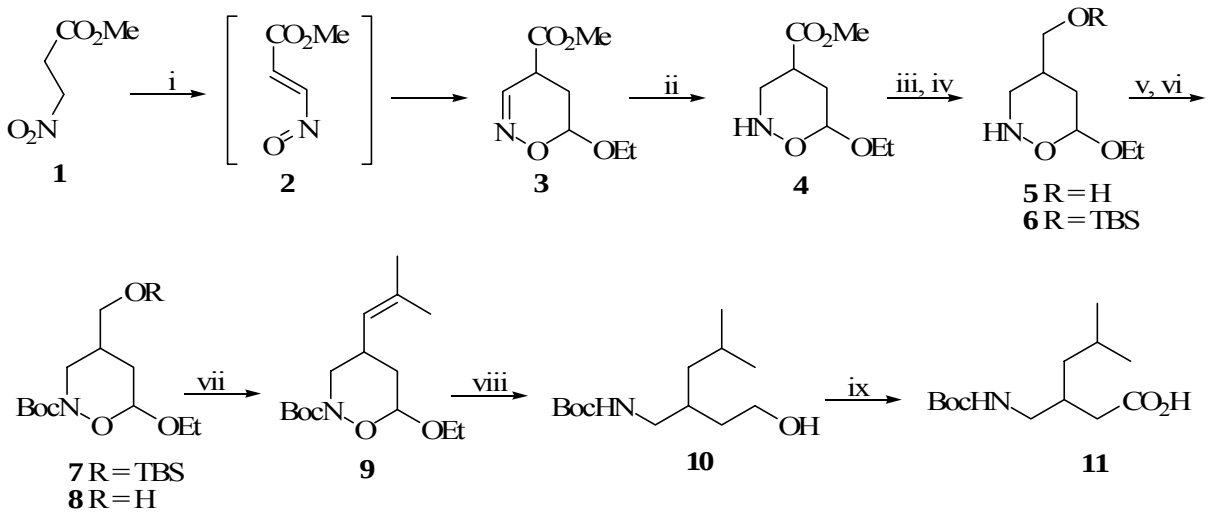
RESULTS AND DISCUSSION

Methyl 3-nitropropionate (**1**), easily accessible from the commercial 3-nitropropionic acid[12c] was the source of the highly reactive intermediate methyl 3-nitrosoacrylate **2**, which added to ethyl vinyl ether to give **3** (Scheme 1), according to the literature.[12] We found **3** quite unstable and thus, it was directly converted to oxazine (**4**) by treatment with sodium cyanoborohydride, in 50% overall yield. Compound (**4**), as well as all oxazines subsequently prepared from this (**5-9**), existed as a ca. 2:1 mixture of diastereoisomes. This, however, was not an issue for the synthesis of racemic pregabalin, since the C-6 stereocenter was going to be destroyed in a late-stage.

In the next step the ester was reduced to a hydroxymethyl group by $LiBH_4$ in 60% yield. Planning to construct the isobutyl group by a Wittig reaction, the N-H group in **5** should be protected. Because this direct protection of N-atom proceeded with low yield, the primary hydroxyl group was firstly protected by silylation to **6** in 75% yield and then the Boc group was introduced by standard procedure to give 87% yield of the fully protected oxazine (**7**). The best way for the TBS group removal in **7** was treatment with THF/AcOH/H_2O[13] to afford **8**, in high yield (96%). This method was superior and gave higher yields than those using PPTS/EtOH[14] or $CeCl_3$/NaI/MeCN[15] which were also tested.

The hydroxymethyl group of the the later product was oxidized to the respective aldehyde, which without characterization was subjected to a Wittig reaction with the phosphonium ylide $Ph_3P{=}CMe_2$ to yield oxazine (**9**). Having this compound in hands, the carbon skeleton of pregabalin was ready and only the proper functional group transformation was left for the completion of the synthesis.

The N-O bond was then cleaved by Raney Ni hydrogenation[11] with concomitant reduction of the aldehyde thus generated from the acetal functionality. The double bond of the isobutenyl group, which was survived under these reaction conditions, was hydrogenated over Pd/C to give **10**, in a 68% overall yield. In the last step, the terminal hydroxymethyl group was successfully oxidized to carboxylate by potassium persulfate[16] and catalytic ruthenium trichloride, affording the desired (±)-*N*-Boc-pregabalin (**11**) in good yield (70%). The reported here results introduce a new synthetic approach to (±)-pregabalin, complementary to the existing methods and also exemplify its potential to a generalized synthesis of *β*-substituted-*γ*-amino acids. Our efforts are now focusing on the exploration of the scope and limitations of this methodology regarding the synthesis of *β*-substituted-*γ*-amino acids, both racemic and asymmetric.



Scheme 1 *Reagents and conditions*: (i) Ref. 12; (ii) $NaBH_3CN$, AcOH, 0 °C, 4 h, 50% from **1**; (iii) $LiBH_4$, THF, 0→20 °C, 12 h, 60%; (iv) TBSCl, imidazole, CH_2Cl_2, 0→20 °C, 12 h, 75%; (v) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 0→20 °C, 12 h, 87%; (vi) AcOH/H_2O/THF (13:7:3), 20 °C, 4 h, 96%; (vii) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -55→20 °C; (b) $Ph_3P^+CHMe_2Br^-$, THF, -78 °C, 90 min, 40 °C, 71%; (viii) (a) Raney Ni, H_2, H_3BO_3, MeOH/H_2O (1:1), 16 h; (b) Pd/C, H_2, MeOH, 16 h, 68% overall; (ix) $K_2S_2O_8$, $RuCl_3{\cdot}H_2O$, KOH, H_2O, *t*-BuOH, 1 h, 71%.

EXPERIMENTAL

Methyl 6-ethoxy-5,6-dihydro-4H-1,2-oxazine-4-carboxylate (3)

To a solution of methyl 3-nitropropionate (**1**, 3.26 g, 24.5 mmol) in ethyl vinyl ether (90 mL), *N,O*-bis(trimethylsilyl)acetamide (BSA, 17.8 mL) was added under external cooling with an ice-bath and

the mixture was stirred at rt for 3.5 days. MeOH (7.75 mL) and CH_2Cl_2 (4.5 mL) were then added and the resulting mixture was allowed to stir for 12 h. The volatiles were taken off in a rotavapor and the residue, with spectral data identical to those reported in the literature for **3**, was used in the next step without any further purification.

Methyl 6-ethoxy-1,2-oxazinane-4-carboxylate (4)

The above residue (~5 g) was dissolved in AcOH (25 mL), cooled with an ice-bath and then $NaBH_3CN$ (5.8 g) was slowly added. The mixture was stirred under argon atmosphere for 4 h at rt, then neutralized with saturated aqueous Na_2CO_3 and extracted three times with CH_2Cl_2 (3x50 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on a column of silica gel with hexane-EtOAc 3:1 as the eluent to give **4** (2.3 g, 50% from **1**) as a yellowish oily inseparable mixture of diastereoisomers: FT-IR (neat) 3165, 1734 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.3 Hz, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 3.14 (m, 1H), 3.3 (m, 1H), 3.6 (m, 2H), 3.72 (s, 3H), 3.96 (m, 1H), 5.11 (s, 1H), 8.52 (d, *J* = 10.4 Hz, 1H) (major isomer) and 1.23 (t, *J* = 7.3 Hz, 3H), 2.3 (m, 2H), 2.86 (m as br s, 1H), 3.35 (m, 1H), 3.58 (m, 1H), 3.7 (m, 1H), 3.72 (s, 3H), 3.85 (m, 1H), 5.01 (s, 1H), 7.66 (d, *J* = 10.1 Hz, 1H) (minor isomer); HRMS calcd for $C_8H_{15}NO_4$ 189.10011 (M^+), found 189.10009.

(6-Ethoxy-1,2-oxazinan-4-yl)methanol (5)

To a solution of **4** (2.046 g, 10.83 mmol) in dry THF (120 mL) was slowly added $LiBH_4$ (840 mg, 37.9 mmol) under external cooling with an ice-bath and the mixture was stirred at rt for 12 h under argon atmosphere. CH_2Cl_2 (10 mL) was then added and the mixture was neutralized with 10% aqueous H_3PO_4. The organic layer was washed with saturated aqueous Na_2CO_3 and brine. The aqueous layer was extracted twice with CH_2Cl_2 (2x20 mL) and EtOAc (2x20 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a column of silica gel with hexane-EtOAc 1:1 as the eluent to give **5** (1.046 g, 60%) as a colorless oily inseparable mixture of diastereoisomers: FT-IR (neat) 3500, 3162 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.3 Hz, 3H), 1.7 (m, 2H), 2.4 (m, 1H), 2.90 (ddd as q, *J* = 12.2 Hz, 1H), 3.5 (m, 2H), 3.6 (m, 2H), 3.85 (m, 2H), 5.06 (s, 1H), 7.22 (d, *J* = 9.8 Hz, 1H) (major isomer) and 1.30 (t, *J* = 7.3 Hz, 3H), 1.7 (m, 2H), 2.3 (m, 1H), 3.1 (br s, 1H), 3.38 (m, 1H), 3.5 (m, 1H), 3.6 (m, 2H), 3.85 (m, 2H), 5.05 (d, *J* = 4.3 Hz, 1H), 7.61 (d, *J* = 9.8 Hz, 1H) (minor isomer); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.8, 29.5, 30.9, 56.3, 64.1, 64.9, 100.0 (major isomer) and 14.7, 28.9, 29.7, 55.1, 65.1, 65.8, 98.8 (minor isomer); HRMS calcd for $C_7H_{15}NO_3$ 161.10519 (M^+), found 161.1052.

4-((*tert*-Butyldimethylsilyloxy)methyl)-6-ethoxy-1,2-oxazinane (6)

To a solution of **5** (0.777 g, 4.83 mmol) in dry CH_2Cl_2 (50 mL) was firstly added imidazole (2,039 g, 13.52 mmol) and then slowly TBS-Cl (0.855 g, 12.56 mmol), while the temperature was kept at 0 °C. The mixture was stirred at rt overnight under argon atmosphere, water (50 mL) was then added, the organic layer was

separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a column of silica gel with hexane-EtOAc 9:1 as the eluent to give **6** (0.996 g, 75%) as a yellowish oily inseparable mixture of diastereoisomers: FT-IR (neat) 3158 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.85 (s, 9H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.7 (m, 2H), 2.3 (m, 1H), 2.90 (ddd as q, *J* = 12.2 Hz, 1H), 3.39 (m, 2H), 3.58 (m, 2H), 3.85 (m, 1H), 5.04 (s, 1H), 7.12 (d, *J* = 10.4 Hz, 1H) (major isomer); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -0.2, 14.8, 18.0, 25.7, 29.4, 31.0, 53.7, 64.4, 64.8, 100.0 (major isomer); HRMS calcd for $C_{13}H_{29}NO_3SiNa$ 312.21453 (M^++Na), found 312.21426.

***tert*-Butyl 4-((*tert*-butyldimethylsilyloxy)methyl)-6-ethoxy-1,2-oxazinane-2-carboxylate (7)**

To a solution of **6** (0.829, 3.02 mmol) and Et_3N (0.66 mL, 4.77 mmol) in dry CH_2Cl_2 (40 mL) was added $(Boc)_2O$ (2.629 g, 12.06 mmol) at 0 °C, followed by addition of catalytic amount of DMAP and the mixture was stirred at rt overnight under argon atmosphere. Aqueous $NaHCO_3$ was then added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over Na_2SO_4, the solvent was then evaporated and the residue was chromatographed on a column of silica gel with hexane-EtOAc 15:1 as the eluent to give **7** (0.985 g, 87%) as a yellowish oily inseparable mixture of diastereoisomers: FT-IR (neat) 1695 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.49 (s, 9H), 1.63 (m, 1H), 1.73 (m, 1H), 2.24 (m, 1H), 3.00 (dd, *J* = 13.4 and 10.4 Hz, 1H), 3.40 (dd, *J* = 10.4 and 7.3 Hz, 1H), 3.55 (m, 2H), 4.10 (m, 1H), 4.93 (s, 1H) (major isomer); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -0.2, 14.8, 18.2, 25.8, 28.4, 31.5, 47.5, 64.4, 64.9, 80.6, 99.8, 154.2 (major isomer); HRMS calcd for $(C_{18}H_{37}NO_5Si)_2Na$ 773.47797 ($2M^+$+Na), found 773.47197.

***tert*-Butyl 6-ethoxy-4-(hydroxymethyl)-1,2-oxazinane-2-carboxylate (8)**

A solution of **7** (0.852 g, 2.272 mmol) in a 3:13:7 mixture of THF/AcOH/H_2O (70 mL) was allowed to stand at rt for 4 h, then neutralized with saturated aqueous Na_2CO_3 and extracted four times with CH_2Cl_2 (4x50 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on a column of silica gel with hexane-EtOAc 1:1 as the eluent to give **9** (0.569 g, 96%) as a yellowish oily inseparable mixture of diastereoisomers: FT-IR (neat) 3449, 1698 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.5 Hz, 3H), 1.50 (s, 9H), 1.6 (m, 1H), 1.7 (br s, 1H), 1.8 (m, 1H), 2.26 (m, 1H), 3.15 (dd, *J* = 13.2 and 9.3 Hz, 1H), 3.55 (m, 3H), 4.08 (m, 2H), 4.92 (dd as t, *J* = 3.1 Hz, 1H) (major isomer) and 1.25 (t, *J* = 7.5 Hz, 3H), 1.50 (s, 9H), 1.6 (m, 1H), 1.7 (br s, 1H), 1.8 (m, 1H), 2.0 (m, 1H), 3.27 (dd, *J* = 13.4 and 6.8 Hz, 1H), 3.55 (m, 3H), 3.89 (dd, *J* = 13.4 and 4.9 Hz, 1H), 4.08 (m, 1H), 4.72 (dd, *J* = 7.3 and 3.0 Hz, 1H) (minor isomer); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.9, 28.4, 31.7, 32.1, 35.4, 46.9, 64.5, 81.0, 99.8, 154.6 (major isomer) and 15.1, 28.4, 31.7, 32.1, 35.4, 46.9, 64.3, 81.3, 102.1, 155.1 (minor isomer); HRMS calcd for $C_{12}H_{23}NO_5Na$ 284.14684 (M^++Na), found 284.14685.

***tert*-Butyl 6-ethoxy-4-(2-methylprop-1-enyl)-1,2-oxazinane-2-carboxylate (9)**

A solution of dry DMSO (1.5 mL, 20 mmol) in dry CH_2Cl_2 (5 mL) was added to a solution of $(COCl)_2$ (0.94 mL, 10 mmol) in dry CH_2Cl_2 (10 mL) which had been cooled to -55 ˚C, under argon atmosphere. The resulting mixture was further stirred at the same temperature for another 2 min before a solution of **8** (0.522 g, 2 mmol) in dry CH_2Cl_2 (20 mL) was added carefully during the period of 5 min, while the temperature was kept below –50 ˚C. The stirring was continued for 15 min and then dry Et_3N (6 mL) was added at the same temperature. After another 15 min stirring at low temperature the mixture was allowed to warm to rt, CH_2Cl_2 (50 mL) was subsequently added and the solution was washed with saturated NaCl (3×50 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated give the respected aldehyde, which was further used without purification.

To a stirred solution of $Ph_3P^+CHMe_2Br^-$ (3.21 g, 9.25 mmol) in dry THF (15 mL), 2.3 M of *n*-BuLi solution in pentane (4.2 mL, 9.62 mmol) was added dropwise at –78 ºC and the mixture was allowed to stir at this temperature for 90 min. The above prepared aldehyde, dissolved in dry THF (15 mL), was then added to this solution at temperature not exceeding –40 ºC, the mixture was allowed to obtain the rt, then quenched by adding saturated aqueous NH_4Cl (60 mL) and H_2O (60 mL) and extracted with CH_2Cl_2 (3x90 mL). The organic layer was dried over $MgSO_4$, the solvent was then evaporated and the residue was chromatographed on silica gel with hexane/EtOAc 30:1 as the eluent to give **9** (0.4 g, 71%) as a yellowish oily inseparable mixture of diastereoisomers: FT-IR (neat) 1695 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.3 Hz, 3H), 1.50 (s, 9H), 1.6 (m, 1H), 1.68 (s, 3H), 1.70 (s, 3H), 1.8 (m, 1H), 2.87 (m, 2H), 3.57 (m, 1H), 3.95 (d, *J* = 8.5 Hz, 1H), 4.07 (m, 1H), 4.81 (d, *J* = 6.7 Hz, 1H), 4,91 (s, 1H) (major isomer) and 1.26 (t, *J* = 7.3 Hz, 3H), 1.51 (s, 9H), 1.6 (m, 1H), 1.66 (s, 3H), 1.70 (s, 3H), 1.8 (m, 1H), 2.65 (m, 1H), 2.80 (m, 1H), 3.72 (m, 1H), 3.85 (dd, *J* = 13.4 and 4.3 Hz, 1H), 4.07 (m, 1H), 4.65 (dd, *J* = 9.7 and 1.8 Hz, 1H), 4,85 (d, *J* = 8.5 Hz,1H) (minor isomer); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.7, 17.9, 25.5, 28.2, 35.3, 36.3, 49.2, 64.4, 80.4, 99.7, 124.5, 134.2, 154.0 (major isomer) and 15.1, 17.8, 25.5, 28.1, 35.3, 36.3, 49.2, 65.3, 81.0, 102.4, 123.7, 134.3, 154.6 (minor isomer); HRMS calcd for $C_{15}H_{27}NO_4Na$ 308.18323 (M^++Na), found 308.18324.

tert-Butyl 2-(2-hydroxyethyl)-4-methylpentylcarbamate (10)

To a solution of **9** (0.13 g, 0.456 mmol) and boric acid (0.563 g, 9.16 mmol) in an 1:1 mixture of MeOH/H_2O (12 ml) was added Raney Ni (catalytic) and the mixture was stirred at rt under 1 atm H_2 for 16 h. The solids were filtered off and the solution was then neutralized with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (50 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on a column of silica gel with hexane-EtOAc (4:1) as the eluent to give *tert*-butyl 2-(2-hydroxyethyl)-4-methylpent-3-enylcarbamate (0.083 g, 75%) as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.44 (m, 1H), 1.62 (m, 1H), 1.65 (s, 3H), 1.73 (s, 3H), 2.32 (br s, 1H), 2.60 (m, 1H), 2.79 (m, 1H), 3.23 (m, 1H), 3.60 (m, 2H), 4.68 (br s, 1H), 4.84 (d, *J* = 9.7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.2, 25.9, 28.4, 35.7, 35.8, 45.2, 60.8, 79.1, 126.2, 134.7, 156.1.

The above compound was dissolved in MeOH (7 mL), 10% Pd/C (catalytic) was added and the mixture was stirred at rt under 1 atm H_2 for 16 h. The solids were filtered off, the solvent evaporated and the residue was chromatographed on silica gel using hexane-EtOAc 2:1 as the eluent to give compound (**10**) as an oil (0.076 g, 91%, overall 68%); FT-IR (neat) 3351, 1690 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 1.12 (m, 2H), 1.44 (s, 9H), 1.5 (m, 2H), 1.7 (m, 2H), 2.1 (br s, 1H), 3.10 (dd as t, *J* = 6.5 Hz, 2H), 3.69 (m, 2H), 4.81 (dd as br t, *J* = 6.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.6, 22.8, 25.2, 28.4, 33.6, 34.7, 42.0, 44.0, 60.7, 79.2, 156.5; HRMS calcd for $C_{13}H_{27}NO_3Na$ 268.18831 (M^++Na), found 268.18831.

3-((*tert*-Butoxycarbonylamino)methyl)-5-methylhexanoic acid (11)

To a solution of KOH (80.2 mg, 1.43 mmol) and $K_2S_2O_8$ (88.7 mg, 0.328 mmol) in H_2O (10 mL) was added $RuCl_3 \cdot 3H_2O$ (2.15 mg, 0.0082 mmol) and after 15 min the deep green color was changed to light orange. To this mixture, a solution of compound (**10**) (20 mg, 0.082 mmol) in *t*-BuOH (2 mL) was then added during a period of 2 min and the color of solution was turned to green-brown. Another amount of $RuCl_3 \cdot 3H_2O$ (0.5 mg, 0.0019 mmol) was added and within 30 min the solution obtained light orange color. After stirring for an additional 30 min at rt, the solution was neutralized with 3M H_2SO_4 under external cooling with an ice-bath to pH = 7-8, the solids were taken off and the aqueous solution was extracted firstly with EtOAc (20 mL) and then with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the product was isolated with a preparative plate chromatography, using hexane-EtOAc 3:1 as the solvent to give the *N*-Boc-pregabaline (**11**) as an oil (15 mg, 71%); FT-IR (neat) 3333, 3269, 2583, 1712, cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6 Hz, 3H), 0.91 (d, *J* = 6 Hz, 3H), 1.17 (t, *J* = 7 Hz, 2H), 1.44 (s, 9H), 1.66 (m, 1H), 2.07 (m, 1H), 2.32 (d, *J* = 5.7 Hz, 2H), 3.02 (dd, *J* = 14 and 7 Hz, 1H), 3.18 (dd, *J* = 14 and 4.8 Hz, 1H), 4.79 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.6, 22.7, 25.1, 28.3, 33.9, 37.1, 41.4, 43.8, 79.8, 156.8, 176.7; HRMS calcd for $C_{13}H_{25}NO_4Na$ 282.16758 (M^++Na), found 282.16786.

REFERENCES

1. Z. Lin and P. K. Kadaba, *Med. Res. Rev.*, 1997, **17**, 537.
2. (a) G. Gatti, I. Bonomi, G. Jannuzzi, and E. Perucca, *Curr. Pharm. Design*, 2000, **6**, 839. (b) J. M. Lopes Lima, *Curr. Pharm. Design*, 2000, **6**, 873.
3. J. S. Bryans and D. J. Wustrow, *Med. Res. Rev.*, 1999, **19**, 149.
4. (a) T. R. Belliotti, T. Capiris, V. Ekhato, J. J. Kinsora, M. J. Field, T. G. Heffner, L. T. Meltzer, J. B. Schwart, C. P. Taylor, A. J. Thorpe, M. G. Vartanian, L. D. Wise, T. Z. Su, M. L. Weber, and D. J. Wustrow, *J. Med. Chem.*, 2005, **48**, 2294. (b) J. B. Schwart, S. E. Gibbons, S. R. Graham, N. L. Colbry, P. R. Guzzo, V.-D. Le, M. G. Vartanian, J. J. Kinsora, S. M. Lotarski, Z. Li, M. R. Dickerson, T. Z. Su,

M. L. Weber, A. El-Kattan, A. J. Thorpe, S. D. Donevan, C. P. Taylor, and D. J. Wustrow, *J. Med. Chem.*, 2005, **48**, 3026.

5. G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442.
6. (a) R. Andruszkiewicz and R. B. Silverman, *Synthesis,* 1989, 953. (b) L. Serfass and P. J. Casara, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2599.
7. (a) P.-W. Yuen, G. D. Kanter, C. P. Taylor, and M. G. Vartanian, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 823. (b) M. Brenner and D. Seebach, *Helv. Chim. Acta*, 1999, **82**, 2365.
8. (a) G. Hoge, *J. Am. Chem. Soc.*, 2003, **125**, 10219. (b) M. J. Burk, P. D. de Koning, T. M. Grote, M. S. Hoekstra, G. Hoge, R. A. Jennings, W. S. Kissel, T. V. Le, I. C. Lennon, T. A. Mulhern, J. A. Ramsden, and R. A. Wade, *J. Org. Chem.*, 2003, **68**, 5731.
9. M. S. Hoekstra, D. M. Sobieray, M. A. Schwindt, T. A. Mulhern, T. M. Grote, B. K. Huckabee, V. S. Hendrickson, L. C. Franklin, E. J. Granger, and G. L. Karrick, *Org. Process Res. Dev.*, 1999, **1**, 26.
10. (a) J. K. Gallos, V. C. Sarli, T. V. Koftis, and E. Coutouli-Argyropoulou, *Tetrahedron Lett.*, 2000, **41**, 4819. (b) J. K. Gallos, V. C. Sarli, C. I. Stathakis, T. V. Koftis, V. R. Nachmia, and E. Coutouli-Argyropoulou, *Tetrahedron*, 2002, **58**, 9351.
11. (a) J. K. Gallos, V. C. Sarli, A. C. Varvogli, C. Z. Papadoyanni, S. D. Papaspyrou, and N. G. Argyropoulos, *Tetrahedron Lett.*, 2003, **44**, 3905. (b) J. K. Gallos, V. C. Sarli, Z. S. Massen, A. C. Varvogli, C. Z. Papadoyanni, S. D. Papaspyrou, and N. G. Argyropoulos, *Tetrahedron*, 2005, **61**, 565.
12. (a) S. L. Ioffe, I. M. Lyapkalo, A. A. Tishkov, V. M. Danilenko, Y. A. Strelenko, and V. A. Tartakovsky, *Tetrahedron*, 1997, **53**, 13085. (b) A. A. Tishkov, I. M. Lyapkalo, S. L. Ioffe, Y. A. Strelenko, and V. A. Tartakovsky, *Org. Lett.*, 2000, **2**, 1323. (c) A. A. Tishkov, H.-U. Reissig, and S. L. Ioffe, *Synlett*, 2002, 863.
13. A. Kawai, O. Hara, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, 1988, **29**, 6331.
14. C. Prakash, S. Saleh, and I. A. Blair, *Tetrahedron Lett.*, 1989, **30**, 19.
15. G. Bartoli, M. Bosco, E. Marcantoni, L. Sambri, and E. Torregiani, *Synlett*, 1998, 209.
16. D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, and T. J. Stout, *J. Am. Chem. Soc.*, 1990, **112**, 7001.