A Non-infringing Route for Enantioselective Synthesis of Antiepileptic Agent Lacosamide

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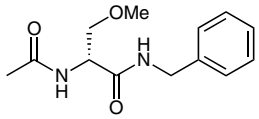
Received: 29.07.2013; Accepted: 11.09.2013

Abstract: A non-infringing route for enantioselective synthesis of lacosamide has been developed. The synthesis started from commercially available acrylic acid and was completed in eight steps using Sharpless asymmetric dihydroxylation as a key step with an overall yield of 29%. All the reactions were very clean with good yields.

Key words: antiepileptic agent, dihydroxylation, tosylation, azide, lacosamide

Epilepsy is a common neurological disorder characterized by the onset of spontaneous convulsant and nonconvulsant seizures that result from neuronal hyperexcitability and hypersynchronous neuronal firing. Epilepsy affects around 3% of the population worldwide and 2 million people in the United States alone.[1] This disorder encompasses a number of syndromes, many of which have a strong genetic component, the predominant type of seizure begins in both cerebral hemispheres. Treatment of epilepsy often imposes an exposure to various antiepileptic drugs (AEDs) and requires long-term commitment. Lacosamide (**1**, Figure 1) was recently approved as an antiepileptic drug for adjunctive therapy of partial onset seizures in the United States and European Union.[2]



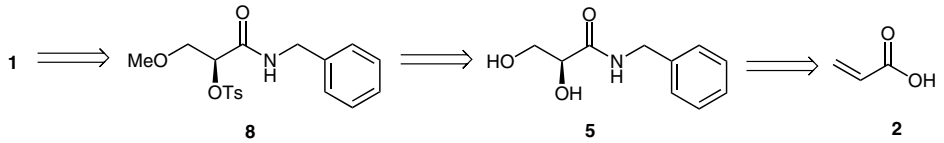
lacosamide (**1**)

Figure 1

The pharmaceutical importance of lacosamide has attracted many synthetic chemists and led to its synthesis by different routes.[3] Many reports are patents and their synthesis started from a chiral pool of unnatural amino acid D-serine and its derivatives.[4]

As part of our regular research program for the synthesis of biologically active molecules,[5] herein we report a non-infringing route for the enantioselective synthesis of lacosamide from a non-amino acid starting material. As shown in the retrosynthesis (Scheme 1), our synthetic strategy started from commercially available acrylic acid (**2**).

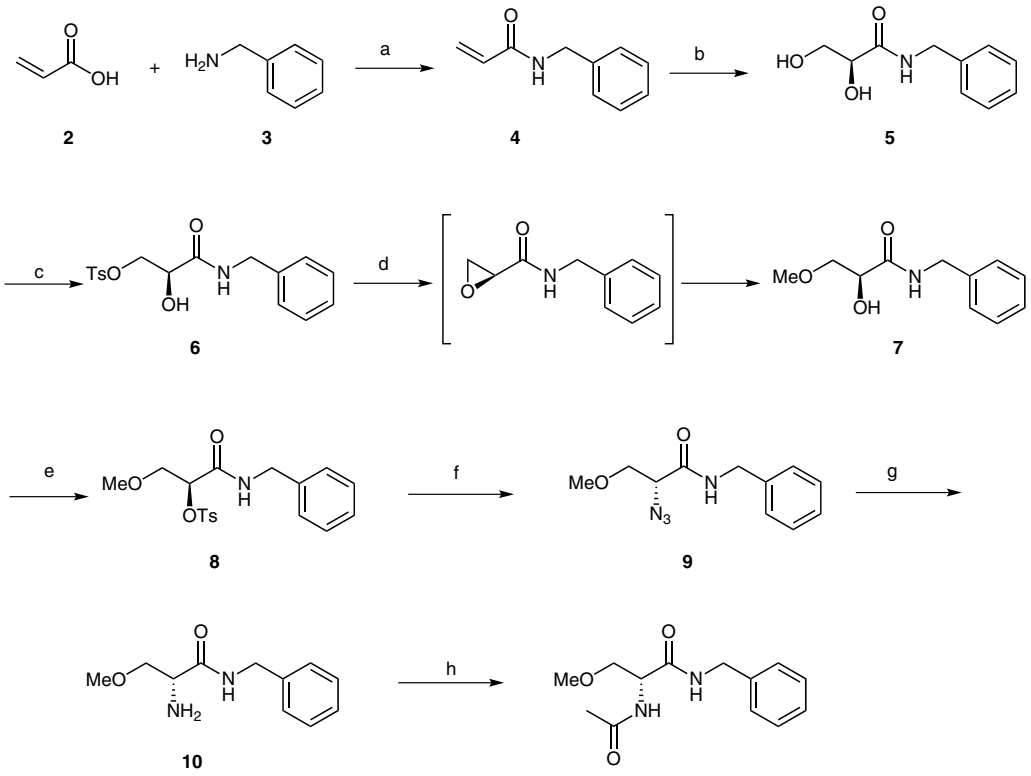
As shown in the Scheme 2, the peptide bond was formed by reacting acrylic acid (**2**) with benzylamine (**3**) in presence of 1-hydroxybenzotriazole in *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) at 0 °C to room temperature to obtain, *N*-benzylacrylamide (**4**) in 70% yield.[6] The amide compound was subjected to Sharpless asymmetric dihydroxylation with AD-mix-β and methanesulfonamide using a mixture of *tert*-butyl alcohol–water (1:1) as solvent at 0 °C to afford (*S*)-*N*-benzyl-2,3-dihydroxypropanamide (**5**) in very good yields with 93% ee.[7] The dihydroxy compound was treated with tosyl chloride and dibutyltin oxide in the presence of triethylamine at 0 °C to obtain the primary hydroxy group tosylated product, (*S*)-3-(benzylamino)-2-hydroxy-3-oxopropyl 4-toluenesulfonate (**6**) in 95% yield exclusively.[8] This tosyl compound was treated with potassium carbonate in methanol at 0 °C resulting in the in situ formation of an epoxide that was opened by methanol to give (*S*)-*N*-benzyl-2-hydroxy-3-methoxypropanamide (**7**) in 90% yield. Compound **7** was treated with tosyl chloride in the presence of 4-(dimethylamino)pyridine at 0 °C to obtain the secondary alcohol protected product, (*S*)-1-(benzylamino)-3-methoxy-1-oxopropan-2-yl 4-toluenesulfonate (**8**) in excellent yield. The tosylated compound was treated with sodium azide in *N*,*N*-dimethylformamide at 70 °C to yield (*R*)-2-azido-*N*-benzyl-3-methoxypropanamide (**9**) in 87% yield.[9]



8 **5** **2**

Scheme 1 Retrosynthesis of (*R*)-lacosamide (**1**)

SYNTHESIS 2013, 45, 3383–3386
Advanced online publication: 02.10.2013
DOI: 10.1055/s-0033-1339901; Art ID: SS-2013-Z0527-OP



Scheme 2 *Reagents and conditions:* (a) HOBt, EDCI, Et_3N, CH_2Cl_2, 0 °C–r.t., 8 h, 70%. (b) AD-mix-β, $MsNH_2$, *t*-BuOH–H_2O (1:1), 0 °C, 4 80%. (c) Bu_2SnO, TsCl (1 equiv), Et_3N, CH_2Cl_2, 0 °C, 2 h, 95%. (d) K_2CO_3, MeOH, 0 °C, 8 h, 90%. (e) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 92%. (f) NaN_3, DMF, 70 °C, 6 h, 87%. (g) Ph_3P, THF–H_2O (9:1), 50 °C, 12h, 85%. (h) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 1 h, 90%.

Reduction of azide **9** with triphenylphosphine in tetrahydrofuran–water (9:1) mixture at 50 °C to afforded (*R*)-2-amino-*N*-benzyl-3-methoxypropanamide (**10**) in very good yield.[10] The thus-obtained amine compound was treated with acetic anhydride in dichloromethane at 0 °C for one hour to afford the target molecule, (*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide (**1**), in 90% yield. All the products were characterized by their ^{1}H NMR, ^{13}C NMR, IR, HRMS, and optical rotation data compared with literature reports.[1a,3a]

In conclusion, a non-infringing route for enantioselective synthesis of (*R*)-lacosamide (**1**) has been carried out successfully. The synthesis started from a commercially available acrylic acid and was completed within eight steps with an overall yield of 29%.

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Bruker-300 MHz, spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

***N*-Benzylacrylamide (4)**

A solution of acrylic acid (**2**, 0.95 mL, 13.8 mmol), HOBt (2.06 g, 15.2 mmol), and EDCI (2.92 g, 15.2 mmol) in anhyd CH_2Cl_2 (20 mL) was stirred at 0 °C under a N_2 atmosphere for 15 min. This mixture was treated with benzylamine (**3**, 1.73 mL, 16.6 mmol) and Et_3N (3.8 mL, 27.7 mmol) and stirred for an additional 8 h. The mixture was quenched with sat. NH_4Cl soln (20 mL) and after 10 min, extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with H_2O (20 mL), $NaHCO_3$ soln (20 mL), and brine (25 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The obtained residue was purified by column chromatography (60–120 mesh silica gel, EtOAc–hexane, 2:8) to afford pure **4** (1.56 g, 70%) as a solid; mp 58–59 °C.

IR (KBr): 3285, 2930, 2851, 1654, 1623, 1536, 1453, 1240, 956, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.40 (m, 5 H), 6.33 (dd, *J* = 15.6, 1.5 Hz, 1 H), 6.11 (dd, *J* = 16.9, 10.2 Hz, 1 H), 5.89 (br s, 1 H), 5.67 (dd, *J* = 10.4, 1.3 Hz, 1 H), 4.53 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 137.9, 130.6, 128.6, 127.3, 127.5, 126.7, 43.6.

MS (ESI): *m*/*z* = 162 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{12}NO$: 162.09078; found: 162.09134.

(*S*)-*N*-Benzyl-2,3-dihydroxypropanamide (5)

To a 250-mL round-bottomed flask were added *t*-BuOH (40 mL), H_2O (40 mL), and AD-mix-β (10 g, 1.4 g/mmol), and $MsNH_2$ (0.68 g, 0.09 g/mmol). The mixture was stirred at r.t. for ~15 min, and then cooled to 0 °C. To this cooled solution was added **4** (1.4 g, 7.1 mmol) and the mixture was stirred for 48 h at 0 °C. The mixture was quenched with solid Na_2SO_3 (10.7 g) at r.t. The mixture was diluted with EtOAc (50 mL) and, after separation of the layers, the aqueous layer was further extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (50 mL) and dried (anhyd Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, EtOAc–hexane, 6:4) to give **5** (1.35 g, 80%) as a white solid; mp 81–82 °C (Lit.[3g] 83–84 °C); 93% ee [chiral HPLC analysis: (Chiralcel OD-H, 0.46 nm i.d. × 25 cm, *n*-hexane–*i*-PrOH, 9:1; flow rate 0.5 mL/min; UV detector: 254 nm): t_R = 6.08 (minor, *R*-isomer), 8.31 min (major, *S*-isomer)].

$[\alpha]_D^{25}$ –34.3 (*c* 0.1, MeOH) {Lit.[3g] $[\alpha]_D^{25}$ –35.1 (*c* 0.1, MeOH)}.

IR (KBr): 3406, 3296, 2924, 1629, 1536, 1427, 1243, 1071, 695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.37 (m, 5 H), 7.11 (br s, 1 H), 4.48 (d, *J* = 6.0 Hz, 2 H), 4.18–4.25 (m, 1 H), 3.82–3.98 (m, 2 H), 3.40–3.48 (m, 1 H), 2.63 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 137.6, 128.7, 127.6, 72.2, 64.1, 43.2.

MS (ESI): *m*/*z* = 196 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}NO_3$: 196.09616; found: 196.09682.

(*S*)-3-(Benzylamino)-2-hydroxy-3-oxopropyl 4-Toluenesulfonate (6)

To a stirred solution of diol **5** (1.2 g, 6.1 mmol) in CH_2Cl_2 (10 mL) were added Bu_2SnO (0.30 g, 1.23 mmol), TsCl (1.17 g, 6.1 mmol), and Et_3N (1.0 mL, 7.38 mmol) at 0 °C. The mixture was stirred until TLC indicated complete consumption of the starting material. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed sequentially with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford pure **6** (2.04 g, 95%) as a viscous liquid.

$[\alpha]_D^{25}$ –3.86 (*c* 0.5, $CHCl_3$).

IR (neat): 3392, 2928, 1660, 1538, 1359, 1175, 972, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.5 Hz, 2 H), 7.22–7.39 (m, 7 H), 7.08 (br s, 1 H), 4.36–4.48 (m, 4 H), 4.22–4.30 (m, 1 H), 3.44 (d, *J* = 4.5 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 145.4, 137.4, 132.0, 130.2, 130.0, 128.7, 128.0, 127.9, 127.6, 127.6, 127.5.

MS (ESI): *m*/*z* = 350 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}NO_5S$: 350.10431; found: 350.10567.

(*S*)-*N*-Benzyl-2-hydroxy-3-methoxypropanamide (7)

To a stirred solution of **6** (1.8 g, 5.1 mmol) in MeOH (20 mL) was slowly added powdered K_2CO_3 (1.7 g, 12.9 mmol) at 10 °C and the mixture was stirred at 0 °C for 8 h until TLC indicated complete consumption of the starting material. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (25 mL), washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane, 3:7) to afford pure **7** (0.97 g, 90%) as a viscous liquid.

$[\alpha]_D^{25}$ +1.66 (*c* 0.5, $CHCl_3$).

IR (neat): 3399, 2925, 1655, 1535, 2454, 1247, 1103, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.37 (m, 5 H), 7.079 (br s, 1 H), 4.49 (d, *J* = 5.9, Hz, 2 H), 4.26 (dd, *J* = 9.9, 5.2 Hz, 1 H), 3.68 (dd, *J* = 5.6, 2.6 Hz, 1 H), 3.41 (s, 3 H), 3.25 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 137.8, 128.7, 127.6, 127.5, 73.4, 70.4, 59.1, 43.2.

MS (ESI): *m*/*z* = 210 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{16}NO_3$: 210.11190; found: 210.11247.

(*S*)-1-(Benzylamino)-3-methoxy-1-oxopropan-2-yl 4-Toluenesulfonate (8)

To a stirred solution of **7** (0.9 g, 4.3 mmol) in CH_2Cl_2 (10 mL) were added sequentially Et_3N (0.7 mL, 5.1 mmol), TsCl (0.9 g, 4.7 mmol), and catalytic amount of DMAP at 0 °C. The mixture was stirred for 2 h until TLC indicated complete consumption of the starting material. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed sequentially with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 3:7) to afford pure **8** (1.5 g, 92%) as a white solid; mp 77–78 °C.

$[\alpha]_D^{25}$ +0.80 (*c* 0.5, $CHCl_3$).

IR (KBr): 3424, 2925, 2855, 1744, 1686, 1538, 1454, 1364, 1174, 670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.5 Hz, 2 H), 7.17–7.37 (m, 7 H), 6.69 (br s, 1 H), 5.00 (dd, *J* = 4.3, 2.6 Hz, 1 H), 4.40–4.46 (m, 2 H), 3.80 (dd, *J* = 11.1, 4.3 Hz, 1 H), 3.64 (dd, *J* = 11.1, 2.6 Hz, 1 H), 3.25 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 145.5, 137.2, 132.8, 129.9, 128.6, 127.9, 127.5, 127.5, 79.2, 71.7, 59.2, 43.3, 21.7.

MS (ESI): *m*/*z* = 364 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_5S$: 364.12004; found: 364.12132.

(*R*)-2-Azido-*N*-benzyl-3-methoxypropanamide (9)

To a stirred solution of **8** (1.4 g, 3.8 mmol) in anhyd DMF (15 mL) at 70 °C under a N_2 atmosphere was added NaN_3 (1.25 g, 19.3 mmol). The mixture was then allowed to stir at 70 °C for 6 h, and then quenched with cool H_2O (15 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with cool H_2O (20 mL) and brine (20 mL), dried (anhyd Na_2SO_4), and concentrated to give the crude product, which was purified by flash column chromatography (silica gel, EtOAc–hexane, 2:8) to give azide **9** (0.78 g, 87%) as a pale yellow liquid.

$[\alpha]_D^{25}$ +0.60 (*c* 0.5, $CHCl_3$).

IR (neat): 3325, 2927, 2106, 1659, 1532, 1454, 1262, 1120, 678 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.40 (m, 5 H), 6.78 (br s, 1 H), 4.46 (d, *J* = 5.9 Hz, 2 H), 4.25 (dd, *J* = 6.8, 3.4 Hz, 1 H), 3.95 (dd, *J* = 10.2, 3.4 Hz, 1 H), 3.78 (dd, *J* = 10.0, 6.9 Hz, 1 H), 3.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 137.4, 128.7, 127.6, 72.9, 63.2, 59.1, 43.5.

MS (ESI): *m*/*z* = 235 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{15}N_4O_2$: 235.11815; found: 235.11895.

(*R*)-2-Amino-*N*-benzyl-3-methoxypropanamide (10)

A solution of **9** (0.6 g, 2.5 mmol) and Ph_3P (0.73 g, 2.8 mmol) in THF–H_2O (9:1, 20 mL) was stirred for 12 h at 50 °C under a N_2 atmosphere. The mixture was then diluted with EtOAc (30 mL) and acidified with 5% HCl (20 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 0.2:9.8) to give pure **10** (0.45 g, 85%) as a viscous oil.

$[\alpha]_D^{25}$ –2.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3450, 3448, 2924, 1671, 1450, 1115, 769, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.80 (br s, 1 H), 7.22–7.37 (m, 5 H), 4.39–4.52 (m, 2 H), 3.57–3.70 (m, 2 H), 3.39–3.42 (m, 1 H), 3.37 (s, 3 H), 2.38 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 137.4, 128.7, 127.6, 72.9, 59.1, 53.4, 43.5.

MS (ESI): *m*/*z* = 209 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{17}N_2O_2$: 209.12800; found: 209.12845.

(*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide (Lacosamide, 1)

To a stirred solution of **10** (0.3 g, 1.4 mmol) in anhyd CH_2Cl_2 (5 mL) was slowly added Ac_2O (0.20 mL, 2.1 mmol) dissolved in anhyd CH_2Cl_2 (1 mL) and catalytic amount of DMAP. The resulting solution was stirred at r.t. for 1 h. The solvent was removed under re-

duced pressure and the residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 0.1:9.9) to afford pure **1** (0.32 g, 90%) as a white solid; mp 140–141 °C (Lit.[1a] 143–144 °C); 95% ee [chiral HPLC analysis: (Chiralcel OD-H, 0.46 nm i.d. × 25 cm, *n*-hexane–*i*-PrOH–TFA, 60:40:1; flow rate 0.5 mL/min; UV detector: 220 nm): t_R = 10.40 (*R*-isomer), 11.6 min (*S*-isomer).

$[\alpha]_D^{25}$ +16.2 (*c* 1, MeOH) {Lit.[1a] $[\alpha]_D^{25}$ +16.4 (*c* 1, MeOH)}.

IR (KBr): 3288, 3067, 2923, 2854, 1636, 1547, 1453, 1384, 1121, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.40 (m, 5 H), 6.78 (br s, 1 H), 6.48 (br s, 1 H), 4.51–4.60 (m, 1 H), 4.48 (d, *J* = 5.7 Hz, 2 H), 3.81 (dd, *J* = 9.5, 4.2 Hz, 1 H), 3.40–3.48 (m, 1 H), 3.38 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 169.9, 137.8, 128.7, 127.5, 71.6, 59.1, 52.4, 43.6, 23.2.

MS (ESI): *m*/*z* = 251 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_3$: 251.13818; found: 251.13902.

Acknowledgement

S.B.W. is thankful to CSIR-New Delhi and CSIR-IICT Hyderabad for providing a fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Choi, D.; Stables, J. P.; Kohn, H. *J. Med. Chem.* **1996**, *39*, 1907. (b) Duncan, J. S.; Sander, J. W.; Sisodia, S. M.; Walker, M. C. *Lancet* **2006**, *367*, 1087. (c) Perucca, E.; Yasothan, U.; Clincke, C.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2008**, *7*, 973. (d) Morieux, P.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **2008**, *16*, 8968. (e) Hen, N.; Bialer, M.; Yagen, B. *J. Med. Chem.* **2012**, *55*, 2835.

(2) (a) Steve, S. C. *Eur. Neurol. J.* **2009**, *1*, 1. (b) Beyreuther, B. K.; Freitag, J.; Heers, C.; Krebsfanger, N.; Scharfenecker, U.; Stohr, T. *CNS Drug Rev.* **2007**, *13*, 21. (c) Abou-Khalil, B. W. *Epilepsy Curr.* **2009**, *9*, 133. (d) Halasz, P.; Kalviaien, R.; Beldzinska, M. M.; Rosenow, F.; Doty, P.; Hebert, D.; Sullivan, T. *Epilepsia* **2009**, *50*, 443.

(3) (a) Muthukrishnan, M.; Mujahid, M.; Sasikumar, M.; Mujumdar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1353. (b) Bialer, M.; White, H. S. *Nat. Rev. Drug Discovery* **2010**, *9*, 68. (c) Mcintyre, J. A.; Castaner, J.; Martin, L. *Drugs Future* **2004**, *29*, 992. (d) Park, K. D.; Stables, J. P.; Liu, R.; Kohn, H. *Org. Biomol. Chem.* **2010**, *8*, 2803. (e) Salome, C.; GrosJean, E. S.; Park, K. D.; Morieux, P.; Wsendiman, R.; DeMarco, E.; Stable, J. P.; Kohn, H. *J. Med. Chem.* **2010**, *53*, 1288. (f) Morieux, P.; Salome, C.; Park, K. D.; Stables, J. P.; Kohn, H. *J. Med. Chem.* **2010**, *53*, 5716. (g) Andurkar, S. V.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1999**, *7*, 2381.

(4) (a) Riedner, J.; Ennis, C. EP 1,642,889, **2006**; *Chem. Abstr.* **2006**, *144*, 331695 (b) Pandey, B.; Shah, K. WO 2011,039,781, **2011**; *Chem. Abstr.* **2011**, *154*, 410331 (c) Vrbanec, C.; Harca, M.; Sucec, A.; Sahnic, D.; Avdagic, A. WO 2010,107,993, **2010**; *Chem. Abstr.* **2010**, *153*, 431066 (d) Bouvy, D.; Merschaert, A.; Pinilla, V.; Hamann, J.; Kanzler, R.; Thomas, A. WO 2010,052,011, **2010**; *Chem. Abstr.* **2010**, *152*, 526141 (e) Madhra, M. K.; Singh, P. K.; Khanduri, C. H. US 2009,143,472, **2009**; *Chem. Abstr.* **2009**, *151*, 8933

(5) (a) Wadavrao, S. B.; Ghogare, R. S.; Narsaiah, A. V. *Tetrahedron Lett.* **2012**, *53*, 3955. (b) Narsaiah, A. V.; Narsimha, P. *Med. Chem. Res.* **2012**, *21*, 538. (c) Narsaiah, A. V.; Nagaiah, B.; Karuna Devi, B. *J. Heterocycl. Chem.* **2012**, *49*, 829. (d) Narsaiah, A. V.; Kumar, J. K. *Synth. Commun.* **2011**, *41*, 1603. (e) Narsaiah, A. V.; Ghogare, R. S. *Synthesis* **2011**, 3271. (f) Narsaiah, A. V.; Kumar, J. K. *Int. J. Ind. Chem.* **2011**, *3*, 154.

(6) (a) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (b) Sharma, G. V.M.; Yadav, T. A.; Choudhary, M.; Kunwar, A. C. *J. Org. Chem.* **2012**, *77*, 6834.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(8) (a) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447. (b) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrl, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 3578.

(9) (a) Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812. (b) Rao, J. M.; Kumar, R. S. C.; Eppakayala, S.; Reddy, G. V.; Babu, K. S. *Tetrahedron: Asymmetry* **2009**, *20*, 1160.

(10) (a) Tian, Q. W.; Wang, Y. A. *J. Org. Chem.* **2004**, *69*, 4299. (b) Cossy, J.; Wills, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982.

