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Authors: Gorakhnath R. Jachak and D Srinivasa Reddy

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Full Paper

Scalable Synthesis of Both Enantiomers of Vigabatrin, an Antiepileptic Drug

Gorakhnath R. Jachak[a, b] and Dr. D. Srinivasa Reddy*[a, b]

Abstract: Vigabatrin is a potent inhibitor of gamma-aminobutyric acid (GABA) catabolism used for the treatment of epilepsy. Here we have synthesized both enantiomers of the drug vigabatrin in five steps from known intermediates using Wittig olefination and pyrolytic elimination as key steps. The target compounds are synthesized in gram scale with >98% enantiopurity.

Introduction

Epilepsy is estimated to universally affect one percent of the entire population.[1] Though the biochemical mechanisms responsible for epilepsy, are not fully understood, it is known that GABA is a major inhibitory neurotransmitter present in the mammalian central nervous system (CNS) that prevents seizures.[2] Indeed, convulsions occur when GABA level diminishes below a specific threshold in the brain, so increase in the brain concentration of GABA prevents the same.[3] The low lipophilicity of this compound is probably responsible for its inefficiency as an anticonvulsant when administered orally or intravenously. The brain concentration of GABA can also beraised using selective inhibitors of GABA catabolism such as Gabapentin, Pregabalin, and Pivagabine. The most important enzyme in this catabolic process is GABA-aminotransferase (GABA-T) which degrades GABA to succinic semialdehyde. One of the most effective and selective inhibitors of GABA-T is 4-amino-5-hexenoic acid known as vigabatrin which is an important anticonvulsant drug marketed as Sabril (**Figure 1**).[4] The pharmacological properties of vigabatrin have been studied extensively which demonstrate its absolute configuration to be highly crucial for the concerned biological activity of the drug. Although racemic vigabatrin is used in clinical practice, (*S*)-vigabatrin is the pharmacologically active enantiomer.[5] Since stereochemistry is a key important facet in the efficacy and safety of a drug molecule, synthesis of chirally pure drugs is presently an area of major interest in the domain of medicinal chemistry and drug discovery.[6] Hence the asymmetric synthesis of vigabatrin holds a critical standpoint in this context. Several methods for the racemic as well as asymmetric synthesis of this anti-convulsive drug have been reported in the literature,[7] some of them having certain disadvantages like more number of reaction sequences and expensive catalysts coupled with low enantiomeric purity. In this letter, we report an efficient and scalable route, which can furnish both the enantiomers of vigabatrin with impressive enantiopurity. A route by Knaus to prepare vigabatrin is worth mentioning here, which also uses methionine as the starting material.[7d, e]

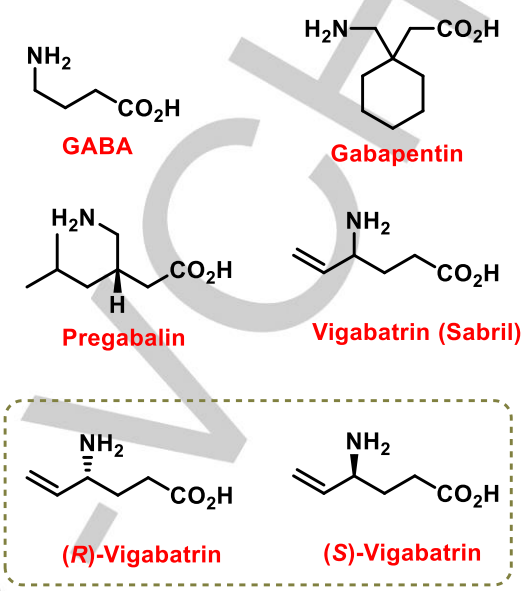

Figure 1: Structure of GABA and their analogues.

Results and Discussion

We planned to access Vigabatrin starting from methionine which is readily available in both enantiomeric forms. Two carbon homologation was planned using Wittig olefination followed by hydrogenation, which is in turn prepared from methionine. Vinyl moiety was planned through pyrolytic elimination of corresponding sulfoxide (**Figure 2**). Accordingly, the synthesis of (*S*)-vigabatrin **1a** commenced with a known D-methionine aldehyde **3a**[8] which on two carbon Wittig olefination reaction with ethyl 2-(triphenyl-l5-phosphaneylidene) acetate in CH_2Cl_2 gave the desired α, β-unsaturated ester **4a** in 81% yield.[9] To our delight, compound **4a** upon hydrogenation using catalytic amount of 10% Pd/C in ethanol under 60 psi pressure of H_2 gave saturated ester **2a** with quantitative yield. It was reported in the literature that reduction of α, β-unsaturated ester having methylthio group is difficult because of its interference in catalytic hydrogenation

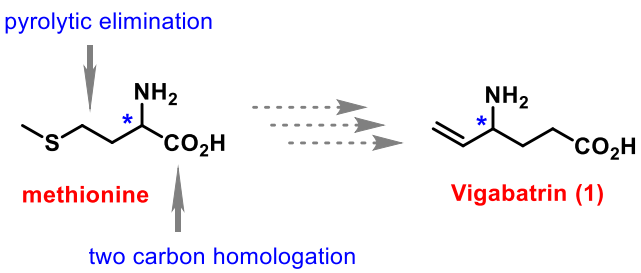

Figure 2: Synthetic plan towards vigabatrin

[a] Organic Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India
E-mail: ds.reddy@ncl.res.in (D. S. Reddy)
http://academic.ncl.res.in/ds.reddy
[b] Academy of Scientific and Innovative Research (AcSIR), New Delhi, 110 025, India
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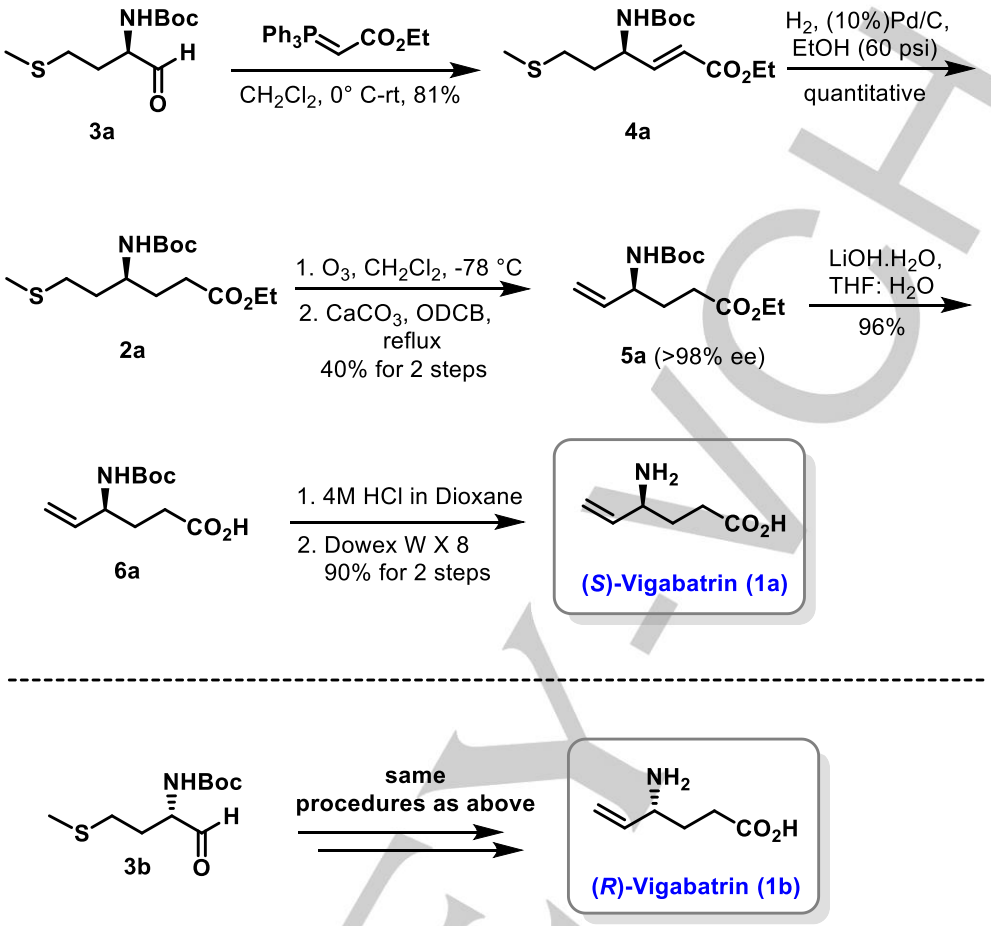

Scheme 1. Gram scale synthesis of vigabatrin enantiomers

reaction or poisoning of catalyst.[10] In this context it is worth mentioning that we have performed hydrogenation on a gram scale in single batch operation without any complicacies. The next task was to install olefin by converting it to sulfoxide followed by elimination. One possible way to make sulfoxide is by the use of sodium metaperiodate, however, it generates a considerable amount of solid waste. But here we have utilized ozonolysis reaction to convert sulphur to sulphoxide in CH_2Cl_2 at -78˚C which also makes it a greener approach.[11] Crude sulphoxide thus obtained was subjected for pyrolytic elimination in the presence of calcium carbonate in ODCB (*o*-dichloro benzene) as solvent under reflux condition to result in compound **5a** with an overall yield of 40% over two steps.[12] The product was characterized by all the spectral data and it is in agreement with the depicted structure as **5a**. Essentially following the same sequence, we have prepared corresponding enantiomer starting from **3b**. The enantiomeric excess of compound **5a** and its enantiomer was determined by using chiral HPLC method which came out to be >98%.[13] The next task was to hydrolyze the ethyl ester which was achieved using LiOH.H_2O in THF:H_2O mixture which gave N-Boc protected (*S*)-vigabatrin **6a** with a 96% yield in gram scale. Finally Boc deprotection using 4M HCl in dioxane followed by passing through Dowex resin resulted in (*S*)-vigabatrin (**1a**) with a yield of 90%. After the successful synthesis of **1a**, we turned our attention to its enantiomer **1b**. The gram scale synthesis of (*R*)-vigabatrin (**1b**) was achieved by repeating essentially the same scheme used for **1a** (**Scheme 1**). Both the enantiomers of vigabatrin are well characterized using spectroscopic techniques, which are in well accordance with the literature data.[7]

Conclusions

In conclusion, we have developed a novel enantiospecific route to access both the *R* and *S* isomers of an antiepileptic drug vigabatrin from known intermediates which in turn was prepared from methionines. A two carbon homologation through Wittig olefination and hydrogenation followed by pyrolytic elimination are key features of the synthesis. The developed route discussed herein is simple and amenable to scale up to access the enantiopure drugs in a gram scale. Although this synthesis is not the best one, it can be an alternate synthetic route to access vigabatrin and related compounds. During the course of synthesis, Wittig olefination reaction furnished chiral γ-amino-α, β-unsaturated ester which can be a useful building block for the synthesis of biologically important compounds, as peptide isosteres or peptide mimics.

Experimental Section

General Information: All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), para-anisaldehyde, 2,4-DNP, $KMnO_4$ solution or Iodine adsorbed on silica gel followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Melting points (mp) were determined using a Bruker capillary melting point apparatus. Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 400 MHz or 500 MHz spectrometer. Coupling constants were measured in Hertz. Chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet. HRMS (ESI) were recorded on ORBITRAP mass analyser (Thermo Scientific, Q Exactive). Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

Ethyl (*R*,*E*)-4-((tert-butoxycarbonyl)amino)-6-(methylthio)hex-2-enoate (4a):

To a solution of compound **3a** (15.0 g, 64.29 mmol) in anhydrous dichloromethane (250 mL) at 0 °C under the nitrogen atmosphere (ethyl 2-(triphenyl-l5-phosphaneylidene)propanoate) Wittig ylide (40.31 g, 115.72 mmol) was added in portion wise. The progress of reaction was monitored by TLC. After the completion of reaction (8 h) CH_2Cl_2 was evaporated and product was purified by column chromatography (silica gel 230-400 mesh 8% ethyl acetate - pet ether) to afford compound **4a** as an oily liquid (15.7 g, 81% yield). $[\alpha]_D^{22}$ + 5.23 (*c* 0.6, $CHCl_3$); IR $_{umax}$(film): cm^{-1} 3345, 2978, 2918, 1690, 1515, 1366; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (dd, *J* = 4.9, 15.9 Hz, 1H), 5.89 (d, *J* = 15.3 Hz, 1H), 4.87 (brs, 1H), 4.39 (brs, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 2.54 - 2.49 (m, 2H), 2.05 (s, 3H), 1.84 - 1.74 (m, 2H), 1.39 (s, 9H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 166.1, 155.0, 147.5, 121.0, 79.7, 60.5, 60.4, 50.7, 33.8, 30.2, 28.2, 15.4, 14.1; HRMS calculated for $C_{14}H_{26}O_4NS$ [M+H]+ : 304.1577, found 304.1571.

Ethyl (*S*)-4-((tert-butoxycarbonyl)amino)-6-(methylthio)hexanoate (2a):

To a solution of compound **4a** (15.5 g, 51.08 mmol) in ethanol (70 mL), 10% Pd/C (~ 300 mg) was added and stirred in reactor with 60 psi pressure of H_2 atmosphere for 8 h. The reaction mixture was then filtered through a pad of celite, concentrated to afford saturated ester compound **2a** as a colorless liquid with quantitative yield. $[\alpha]_D^{22}$ + 16.18 (*c* 0.67, $CHCl_3$); IR $_{umax}$(film): cm^{-1} 3351, 2977, 2919, 1711, 1687, 1516, 1447; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (d, *J* = 8.5 Hz, 1H), 4.12 (q, *J* = 6.7 Hz, 2H), 3.72 - 3.66 (m, 1H), 2.56 - 2.48 (m, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.09 (s, 3H), 1.87 - 1.81 (m, 1H), 1.78 - 1.73 (m, 1H), 1.68 - 1.65 (m, 2H), 1.42 (brs, 9H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 155.6, 79.2, 60.5, 49.9, 35.4, 31.0, 30.6, 30.3, 28.3, 15.6, 14.2; HRMS calculated for $C_{14}H_{28}O_4NS$ [M+H]+ : 306.1734, found 306.1721.

Ethyl (*S*)-4-((tert-butoxycarbonyl)amino)hex-5-enoate (5a):

To a solution of compound **2a** (15.3 g, 50.09 mmol) in CH_2Cl_2 (250 mL) ozone was bubbled at -78 °C until the color becames blue, once the blue color appeared oxygen was bubbled to remove excess ozone, then reaction mixture was allowed to warm to room temperature and stirred for 1 h. After concentration under vacuocrude sulfoxide compound was taken in 1,2 dichloro benzene (500 mL), followed by addition of $CaCO_3$ (5 g, 50.09 mmol) and refluxed for 6 h. The crude reaction mixture was purified by column chromatography (silica gel 230-400 mesh 10% ethyl acetate – pet ether) to afford **5a** as a colorless powder (5.20 g, 40% yield). Mp = 61 - 63 °C; $[\alpha]_D^{22}$ **+** 13.5 (*c* 0.95, $CHCl_3$); IR $_{umax}$(film): cm^{-1} 3557, 2979, 2933, 1711, 1692, 1513, 1366; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.74 (ddd, *J* = 5.7, 10.6, 16.9 Hz, 1H), 5.19 - 5.10 (m, 2H), 4.56 (brs, 1H), 4.13 (q, *J* = 7.0 Hz, 3H), 2.36 (t, *J* = 7.6 Hz, 2H), 1.91 - 1.87 (m, 1H), 1.80 - 1.76 (m, 1H), 1.43 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 173.3, 155.3, 138.2, 115.0, 79.4, 60.5, 52.4, 30.8, 29.9, 28.3, 14.2; HRMS calculated for $C_{13}H_{23}O_4NNa$ [M+H]+ : 280.1519, found 280.1513.

(*S*)-4-((tert-Butoxycarbonyl)amino)hex-5-enoic acid (6a):

To a solution of compound **5a** (4.00 g, 15.54 mmol) in ethanol (30 mL) was added $LiOH.H_2O$ (1.27 g, 31.08 mmol) in H_2O (30 mL) drop wise at 0 °C and stirred for 5 h at room temperature. Reaction mass was evaporated to dryness, diluted with H_2O (50 mL), washed with diethyl ether (50 mL), acidified with citric acid (20% solution). The suspension thus formed was extracted with EtOAc (3 x 70 mL), washed with H_2O (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **6a** as a yellow solid (3.36 g, 96% yield). IR $_{umax}$(film): cm^{-1} 3325, 2979, 2932, 1702, 1512, 1393; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.99 (brs, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 5.71 (ddd, *J* = 6.1, 10.4, 17.1 Hz, 1H), 5.07- 4.99 (m, 2H), 3.91 (brs, 1 H), 2.19 (t, *J* = 7.3 Hz, 2H), 1.69 - 1.56 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): 174.1, 155.1, 139.3, 114.1, 77.6, 51.9, 30.3, 29.4, 28.2; HRMS calculated for $C_{13}H_{24}O_4N$ [M+H]+ : 130.0861, found 130.0863.

(*S*)-4-Aminohex-5-enoic acid (1a):

To a solution of compound **6a** (300 mg, 1.31 mmol), 4M HCl in dioxane (5 mL) was added and stirred at room temperature for 2 h. The solvent was then removed in vacuo, and the residue was washed with diethyl ether (10 mL) to give a yellow colorled solid, which happened to be the hydrochloride salt. ^{1}H NMR (200 MHz, D_2O): δ = 5.80 (m, 1H), 5.47 - 5.36 (m, 2H), 3.82 (m, 1H), 2.46 (m, 2H), 2.08 (m, 1H), 1.94 (m, 1H). The compound was introduced in water (1 mL) solution was passed through a column of Dowex 50WX8 ion exchange resin (4 g, 200–400 mesh, H^+ form). The column was eluted with H_2O until the eluent pH was neutral. Further elution with 2N aq. NH_4OH, and removal of the latter in vacuo, afforded (*S*)-vigabatrin (**1a**) (151 mg, 90%) as a colorless solid. The spectroscopic data for this compound was in full agreement with that reported. Observed Mp = 173 - 175 °C, Literature[7e] Mp = 164 - 165 °C; Observed $[\alpha]_D^{22}$ + 14.23 (*c* 0.94, H_2O), Literature[7e] $[\alpha]_D^{25}$ +12.00 (*c* 2.5, H_2O).

Ethyl (*S*,*E*)-4-((tert-butoxycarbonyl)amino)-6-(methylthio)hex-2-enoate (4b):

Compound **4b** was synthesized from **3b** by following similar procedure for the synthesis of compound 4a. $[\alpha]_D^{22}$ - 6.03 (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (dd, *J* = 4.9, 15.9 Hz, 1H), 5.89 (d, *J* = 15.3 Hz, 1H), 4.87 (brs, 1H), 4.39 (brs, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 2.54 - 2.49 (m, 2H), 2.05 (s, 3H), 1.84 - 1.74 (m, 2H), 1.39 (s, 9H), 1.24 (t, *J* = 7.0 Hz, 3H)

Ethyl (*R*)-4-((tert-butoxycarbonyl)amino)-6-(methylthio)hexanoate (2b):

Compound **2b** was synthesized from **4b** by following similar procedure for the synthesis of compound **2a**. $[\alpha]_D^{22}$ - 15.37 (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40 (d, *J* = 8.8 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.72 - 3.59 (m, 1H), 2.54 - 2.49 (m, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.09 (s, 3H), 1.87 - 1.83 (m, 1H), 1.78 - 1.74 (m, 1H), 1.69 - 1.65 (m, 2H), 1.42 (s, 9H), 1.27 - 1.20 (m, 3H)

Ethyl (*R*)-4-((tert-butoxycarbonyl)amino)hex-5-enoate (5b):

Compound **5b** was synthesized from **2b** by following similar procedure for the synthesis of compound **5a**. $[\alpha]_D^{22}$ +12.6 (*c* 0.82, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.74 (ddd, *J* = 5.7, 10.6, 16.9 Hz, 1H), 5.22 - 5.09 (m, 2H), 4.52 (brs, 1H), 4.13 (q, *J* = 7.0 Hz, 3H), 2.37 (t, *J* = 7.6 Hz, 2H), 1.91 - 1.87 (m, 1H), 1.80 - 1.76 (m, 1H), 1.44 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H).

(*R*)-4-((tert-Butoxycarbonyl)amino)hex-5-enoic acid (6b):

Compound **6b** was synthesized from **5b** by following similar procedure for the synthesis of compound **6a**. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 12.0 (brs, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 5.71 (ddd, *J* = 6.1, 10.4, 17.1 Hz, 1H), 5.09 - 4.98 (m, 2H), 3.91 (brs, 1H), 2.20 (t, *J* = 7.3 Hz, 2H), 1.69 - 1.52 (m, 2H), 1.38 (s, 9H).

(*R*)-4-Aminohex-5-enoic acid (1b):

Compound **1b** was synthesized from **6b** by following similar procedure for the synthesis of compound **1a**. Mp = 170 - 173 °C; $[\alpha]_D^{22}$ -12.81 (*c* 0.56, H_2O); ^{1}H NMR (200 MHz, D_2O): δ = 5.80 (m, 1H), 5.47 - 5.36 (m, 2H), 3.82 (m, 1H), 2.46 (m, 2H), 2.08 (m, 1H), 1.94 (m, 1H).

Supporting Information (see footnote on the first page of this article): ^{1}HNMR, ^{13}C NMR spectra and HPLC chromatograms.

Conflict of Interest The authors declare no conflict of interest.

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Keywords: Vigabatrin • Epilepsy • Wittig reactions • Hydrogenation • Elimination.

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(13) HPLC performed on Daicel Chiralpak AD-H column, n-hexane/2-propanol (95:5), flow rate = 0.6 mL/min, 210 nm UV detector, tR = 15.5 for Ethyl (*S*)-4-((tert-butoxycarbonyl)amino)hex-5-enoate (**5a**) and tR = 19.4 min for Ethyl (*R*)-4-((tert-butoxycarbonyl)amino)hex-5-enoate (**5b**).

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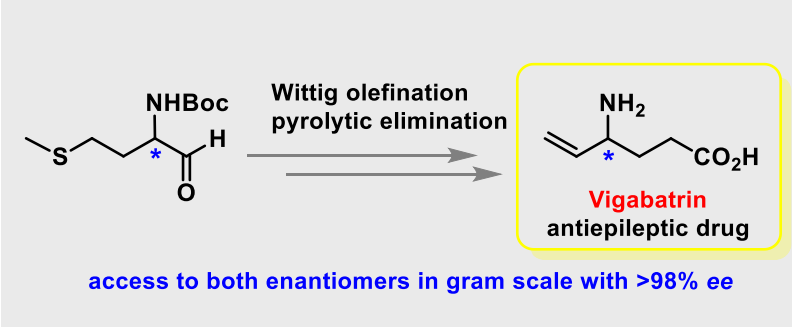
Layout 2:



*Scalable synthesis of drug vigabatrin

Key Topic*

Gorakhnath R. Jachak,[a,b] and Dr. D. Srinivasa Reddy[a,b]*

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Scalable Synthesis of Both Enantiomers of Vigabatrin, an Antiepileptic Drug