HETEROCYCLES, Vol. 68, No. 10, 2006, pp. 2031 - 2036. © The Japan Institute of Heterocyclic Chemistry
Received, 5th July, 2006, Accepted, 27th July, 2006, Published online, 1st August, 2006. COM-06-10837

SYNTHESIS OF VIGABATRIN®

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Abstract – A concise synthesis of vigabatrin® has been achieved from *trans*-(2*S*,4*R*)-4-hydroxyproline via the key regioselective Baeyer-Villiger lactonization reaction.

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**), it possesses three functional groups that can be easily modified.[1] The skeleton represents the significant feature for producing a series of different carbon framework using an efficient modification technique.[2] Recently we have introduced some approaches toward anisomycin,[2l] epibatidine,[2m] pancracine,[2n] streptorubin B core,[2o] and statine[2p] employing *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) as the starting material.

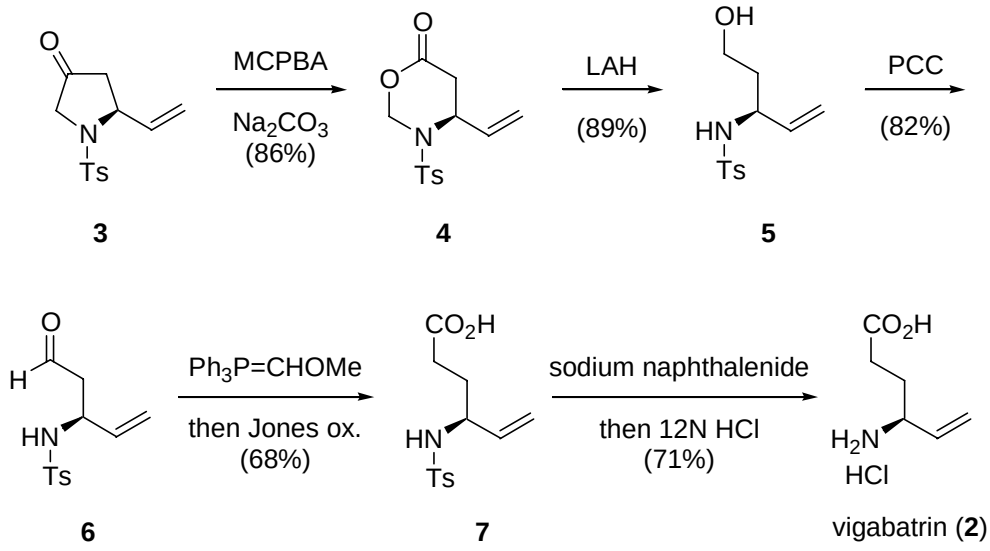
trans-(2*S*,4*R*)-4-hydroxyproline (**1**) vigabatrin (**2**)

Figure 1. Structures of *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) and vigabatrin® (**2**)

Vigabatrin® (**2**, γ-vinyl-GABA, 4-amino-5-hexenoic acid, Sabril®), which is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain,[3a-b] crosses the BBB and is used clinically primarily to control seizures refractory to other anticonvulsant drugs. Although racemic vigabatrin® is used in clinical practice, *S*-isomer is the pharmacologically active, whereas *R*-isomer is inactive. Vigabatrin® is therefore useful for treating disorders associated with depletion of GABA levels in central nervous system such as schizophrenia and epilepsy.[3c-d] Methodologies[4-5] for the synthesis of vigabatrin® (**2**) have been described so far based on thermal rearrangement,[4c-d] catalytic palladium-mediated enantioselective syntheses,[5a-d] asymmetric syntheses starting from α-amino acids[5e-j] (e.g. methionine,

glutamic acid, and pyroglutamate) and other chiral materials,[5k-l] and large scale enzyme-catalyzed resolution.[5m] The other related vigabatrin® derivatives were synthesized as the potential biological inhibitors.[6] In continuing the previous investigations and building upon these observations on *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) as the chiral material, we are interested in developing an easy approach to vigabatrin® (**2**) via the key regioselective Baeyer-Villiger lactonization reaction.

As shown in Scheme 1, we studied the approach to vigabatrin® (**2**) from 1-tosyl-2-vinylpyrrolidin-4-one (**3**), which was prepared from *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) by our preliminary report.[2m] Regioselective Baeyer-Villiger lactonization[2p,7] of ketone (**3**) was treated with *m*-chloroperoxybenzoic acid and sodium carbonate to afford sole tetrahydro-1,3-oxazin-6-one (**4**). During the lactonization process, the other ring-expanded framework was not observed. While poring over the related literature of Baeyer-Villiger ring expansion reaction, we found that Young and co-workers had developed copper(II) acetate-mediated ring expansion of 4-ketoprolines with *m*-chloroperoxybenzoic acid in modest yield. The most likely explanation would be that it is controlled by involvement of the nitrogen lone pair on substituted pyrrolidin-4-one.[7] Reduction of the regioisomer (**4**) with lithium aluminum hydride was provided 1,3-aminoalcohol (**5**). Treatment of alcohol (**5**) with pyridinium chlorochromate was yielded aldehyde (**6**). One-carbon elongation of compound (**6**) was achieved via Wittig olefination of compound (**6**) and followed by Jones oxidation of the resulting enol ether to give an acid (**7**). Finally, synthesis of vigabatrin® (**2**) was accomplished via desulfonation[8] and acidification.[9]



Scheme 1. Synthesis of vigabatrin® (**2**)

In summary, we succeeded in accomplishing the synthesis of vigabatrin® (**2**) from the chiral starting material *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) via the key regioselective Baeyer-Villiger lactonization reaction. Currently studies are in progress in this direction.

ACKNOWLEDGEMENTS

The authors would like to thank the National Science Council (NSC-95-2113-M-390-003-MY2) of the Republic of China for financial support.

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9. For experimental details: **General.** Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous $MgSO_4$ before concentration *in vacuo*. Crude product was purified using column chromatography on SiO_2 (MN Kieselgel 60, 70~230 mesh).

3-(4-Methylphenylsulfonyl)-4-vinyl-[1,3]oxazinan-6-one (4).

A solution of *m*-chloroperoxybenzoic acid (600 mg, 75%, 2.6 mmol) in CH_2Cl_2 (10 mL) was added a solution of ketone (**3**) (265 mg, 1.0 mmol) and Na_2CO_3 (420 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC. The reaction mixture was stirred at rt for 40 h. Saturated aqueous Na_2CO_3 (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 4/1~2/1) afforded compound (**4**) (242 mg, 86%). $[\alpha]^{31.4}_D$ -174.31^o (*c* 0.025, $CHCl_3$); HRMS (ESI, M^++1) calcd for $C_{13}H_{16}NO_4S$ 282.0800, found 282.0803; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.83 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1H), 5.77 (dd, *J* = 1.0, 11.5 Hz, 1H),

5.29 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.25 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.12 (d, *J* = 11.5 Hz, 1H), 4.35-4.31 (m, 1H), 2.58 (dd, *J* = 7.5, 16.5 Hz, 1H), 2.50 (dd, *J* = 9.0, 16.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.57, 144.72, 135.07, 134.79, 129.91 (2x), 127.58 (2x), 117.18, 74.00, 52.50, 33.72, 21.36; Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.69; H, 5.60; N, 5.12.

***N*-[1-(2-Hydroxyethyl)allyl]-4-methylbenzenesulfonamide (5).**

A solution of compound (**4**) (200 mg, 0.71 mmol) in THF (10 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) in THF (20 mL) at 0 ^{o}C. The reaction mixture was stirred at rt for 2 h. Aqueous NH_4Cl solution (15%, 2 mL) was added to the reaction mixture and filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/EtOAc = 2/1) afforded aminoalcohol (**5**) (162 mg, 89%). $[\alpha]^{31.2}_{D}$ +22.94^{o} (*c* 0.017, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{18}NO_3S$ (M^++1) 256.1007 found 256.1010; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.57 (ddd, *J* = 6.0, 9.5, 16.5 Hz, 1H), 5.24 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.95 (d, *J* = 9.5 Hz, 1H), 3.99 (br s, 1H), 3.86 (dt, *J* = 3.5, 12.5 Hz, 1H), 3.69-3.65 (m, 1H), 2.42 (s, 3H), 2.37 (br s, 1H), 1.84-1.78 (m, 1H), 1.61-1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.39, 137.61, 137.22, 129.58 (2x), 127.12 (2x), 115.78, 58.82, 53.48, 37.22, 21.50; Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.59; H, 6.54.; N, 5.85.

***N*-[1-(2-Oxoethyl)allyl]-4-methylbenzenesulfonamide (6).**

A solution of compound (**5**) (130 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) was added to a stirred mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in CH_2Cl_2 (20 mL). After being stirred at rt for 20 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/EtOAc = 5/1) afforded compound (**6**) (106 mg, 82%). $[\alpha]^{30.9}_{D}$ +31.37^{o} (*c* 0.005, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}NO_3S$ (M^++1) 254.0851, found 254.0852; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.66 (ddd, *J* = 6.0, 10.5, 17.5 Hz, 1H), 5.28 (d, *J* = 8.5 Hz, 1H), 5.02 (dd, *J* = 1.0, 17.5 Hz, 1H), 5.01 (dd, *J* = 1.0, 10.5 Hz, 1H), 4.25-4.19 (m, 1H), 2.79-2.70 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.93, 143.58, 137.50, 135.97, 129.65 (2x), 127.13 (2x), 116.84, 51.43, 48.46, 21.50.

4-Aminohex-5-enoic acid (Vigabatrin®, 2).

n-Butyllithium (1.0 mL, 1.6 M in hexane, 1.6 mmol) was added to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (686 mg, 2.0 mmol) in THF (20 mL) at –78 ^{o}C. The orange red colored mixture was stirred at –78 ^{o}C for 1 h. A solution of aldehyde (**6**) (100 mg,

0.4 mmol) in THF (5 mL) was added to the reaction mixture at –78 ^{o}C *via* a syringe and further stirred at –78 ^{o}C for 2 h. The reaction was quenched with aqueous NH_4Cl (15%, 10 mL) and the mixture was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated to yield the crude product. Excess Jones reagent (2 mL) was added to a solution of the resulting compound in acetone (10 mL) at rt. The mixture was stirred for 20 min and treated with 2-propanol (1 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water (5 mL) and extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 1/1~1/2) afforded product (**7**) (76 mg, 68% of two steps). HRMS (ESI) *m*/*z* calcd for $C_{13}H_{18}NO_4S$ (M^++1) 284.0957, found 284.0961; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 5.82-5.70 (m, 1H), 5.44-5.20 (m, 3H), 3.72-3.65 (m, 1H), 3.20 (br s, 1H), 2.45 (s, 3H), 2.28-2.10 (m, 2H), 2.00-1.82 (m, 2H).

A freshly prepared solution of sodium naphthalenide (1.0 M in THF, 2 mL, 2.0 mmol) was added to a solution of compound (**7**) (140 mg, 0.5 mmol) in THF (20 mL) at 0 ^{o}C for 2h. Water (5 mL) was poured into the reaction mixture and evaporated to afford the residue. Water (10 mL) was poured into the residue and extracted with Et_2O (3 x 20 mL). Hydrochloric acid (12N, 5 mL) was added to the water layer at rt. Then the water was evaporated under reduced pressure to give the crude hydrochloride. The crude salt was purified by ion exchange chromatography to give the vigabatrin® (**2**) (58 mg, 71%). $[\alpha]^{28.2}_{D}$ +12.02^{o} (*c* 0.026, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 5.75-5.63 (m, 1H), 5.32-5.26 (m, 2H), 3.69-3.61 (m, 1H), 2.21-2.07 (m, 2H), 1.94-1.71 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 181.46, 132.92, 121.18, 54.06, 33.41, 28.94. The NMR spectral data were in accordance with those reported in the literature.[5e]