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Asymmetric synthesis of (*S*)-vigabatrin® and (*S*)-dihydrokavain via cobalt catalyzed hydrolytic kinetic resolution of epoxides

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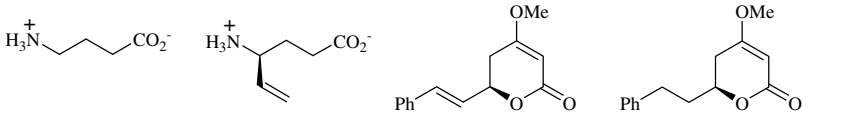
Abstract

A concise route to the asymmetric synthesis of (*S*)-vigabatrin® and (*S*)-dihydrokavain has been described using Co-catalyzed hydrolytic kinetic resolution of racemic epoxides and regiospecific opening of terminal epoxides with dimethylsulfonium methylide as the key steps.

GABA (γ-aminobutyric acid, **1**) deficiency has been associated with a variety of neurological disorders including Parkinson's disease, epilepsy and Huntington's chorea.[1] GABA-T (GABA aminotransferase), a mitochondrial enzyme found in synaptic neurons, metabolizes GABA to succinic semialdehyde thereby lowering the GABA levels in the brain.[2] One of the most effective and selective irreversible inhibitors of GABA-T is 4-amino-5-hexenoic acid (γ-vinyl GABA, vigabatrin, **2**), an important anticonvulsant drug marketed in the racemic form as Sabril.[3] It has been shown that vinyl GABA **2** inactivates GABA-T by selective reaction with the pyridoxal aldehyde moiety so that there is an increase in the levels of GABA in the central nervous system (CNS) and in the brain.[4]

(*S*)-Kavain **3** and (*S*)-dihydrokavain **4**, isolated from the kava plant (*Piper methysticum*, a Polynesial shrub of the Piperaceae family), possess lactone moieties that are responsible for the wide range of biological activities including sedatives, analgesic, anticonvulsive, antispasmodic, antimycotic, antifungal antithrombotic and central relaxing properties.[5] The kava plant has been used by the Pacific Island societies to prepare an intoxicating ceremonial beverage known for its relaxing effects and the ability to promote sociability. Although several methods have been reported for the asymmetric synthesis of (*S*)-vigabatrin[6] and (*S*)-dihydrokavain,[7] many of them have certain disadvantages such as large number of reaction steps, use of chiral building blocks and expensive catalysts coupled with low ee so that these are not amenable to scale up. In this letter, we report an efficient route to the synthesis of (*S*)-vigabatrin® **2** and (*S*)-dihydrokavain **4** via cobalt-catalyzed hydrolytic kinetic resolution (HKR)[8] of racemic epoxides coupled with regiospecific opening of terminal epoxides with dimethylsulfonium methylide[9,10] as the key reactions (Schemes 2 and 3).

Retrosynthetic analysis outlined in Scheme 1 reveals that chiral allylic alcohols **5** and **6** could be visualized as



GABA (**1**) (*S*)-Vigabatrin (**2**) (*R*)-Kavain (**3**) (*S*)-Dihydrokavain (**4**)

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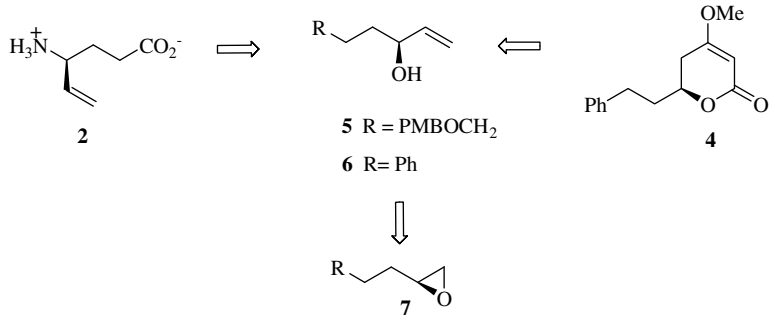


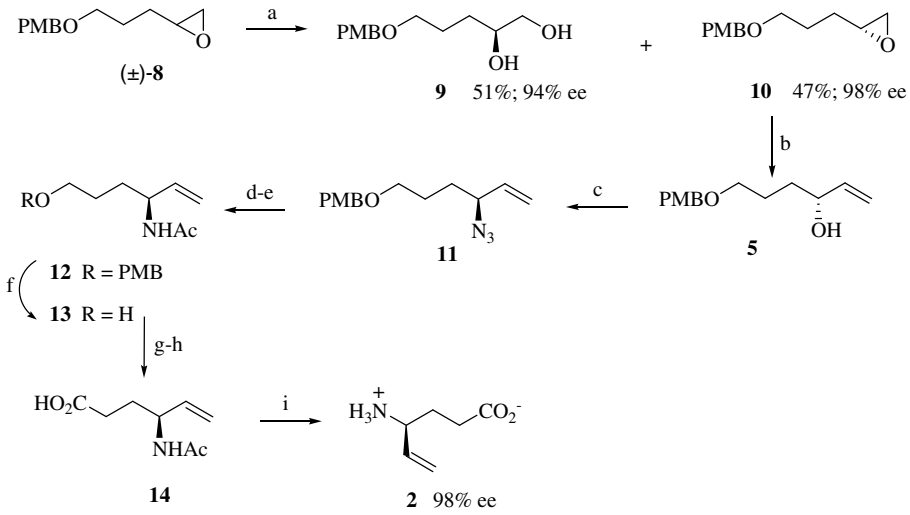
Scheme 1. Retrosynthesis of (*S*)-vigabatrin® (**2**) and (*S*)-dihydrokavain (**4**).

the key intermediates for the synthesis of both (*S*)-vigabatrin® (**2**) and (*S*)-dihydrokavain (**4**), respectively. Allylic alcohols **5** and **6** in turn could be readily obtained by the regiospecific ring opening of chiral epoxide **7** with dimethylsulfonium methylide.

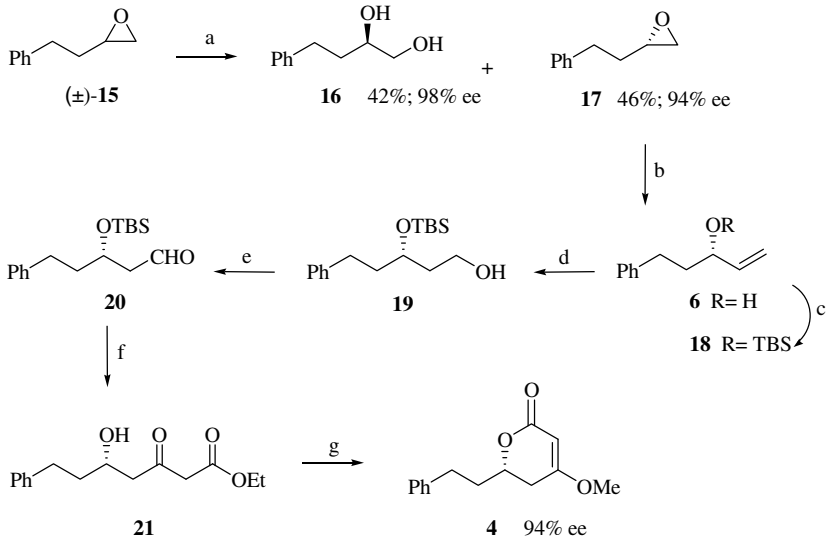
Our synthesis of (*S*)-vigabatrin (**2**) started with Co-catalyzed hydrolytic kinetic resolution of racemic epoxide **8**, which furnished chiral epoxide **10** (47% yield; 98% ee) and chiral diol **9** (51% yield; 94% ee). Compounds **9** and **10** were readily separated by column chromatographic purification. Regiospecific ring opening of epoxide **10** with dimethylsulfonium methylide (formed in situ by the treatment of $(CH_3)_3S^+I^-$ with *n*-BuLi at −10 °C) gave allyl alcohol **5**[11] in 89% yield. Direct nucleophilic displacement of alcohol in **5** with azide anion gave azide **11**, which was smoothly reduced to amine (Ph_3P, THF, H_2O) and subsequently protected (Ac_2O, Py) as *N*-acetate **12** in 97% yield. At this stage, the PMB group was selectively deprotected with DDQ to give the corresponding alcohol **13**, which was further subjected to oxidations (IBX and $NaClO_2$) to give carboxylic acid **14** in 77% yield. Finally, the *N*-acetyl moiety was deprotected on reduction with hydrazine hydrate to afford (*S*)-vigabatrin **2** in 87% yield and 98% ee (Scheme 2).

The synthesis of (*S*)-dihydrokavain **4** was started with the HKR of racemic epoxide **15** using (*S*,*S*)-Co(III)-salen·OAc as catalyst, which resulted in chiral epoxide **17** (46% yield; 94% ee) and diol **16** (42% yield; 98% ee). Compounds **16** and **17** were readily separated by column chromatographic purification. Regiospecific opening of epoxide **17** with dimethylsulfonium methylide gave allylic alcohol **6**[12] in 82% yield. Allylic alcohol **6** was protected with TBSCl to afford **18**, which on hydroboration–oxidation ($Me_2S{\cdot}BH_3$, 3 N NaOH and 30% H_2O_2) gave the primary alcohol **19** in 73% yield. The IBX oxidation of **19** gave the corresponding aldehyde **20**, which on reaction with ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$ gave the β-keto ester **21** in 77% yield. It may be noted that the silyl group in **20** was also deprotected during the reaction. Lactonization of **21** under basic conditions (K_2CO_3, MeOH) followed by the methylation of its enol with dimethyl sulfate was smoothly accomplished to afford (*S*)-dihydrokavain **4** in 81% yield and 94% ee (Scheme 3).

In conclusion, the asymmetric synthesis of (*S*)-vigabatrin® (**2**) with an overall yield of 17.8% and (*S*)-dihydrokavain (**4**) with an overall yield of 15.9% has been achieved using Co-catalyzed hydrolytic kinetic resolution of racemic



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-Co(III)-salen·OAc (0.5 mol %), H_2O (0.55 equiv), 25 °C; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, −10 °C, 89%; (c) NaN_3, PPh_3, DMF, CCl_4, 60 °C, 79%; (d) PPh_3, THF, H_2O, 89%; (e) Ac_2O, CH_2Cl_2, pyridine, 97%; (f) DDQ, CH_2Cl_2, 25 °C, 93%; (g) IBX, DMSO, 25 °C; (h) $NaClO_2$, NaH_2PO_4, DMSO, 77%; (i) $N_2H_4{\cdot}H_2O$, THF, MeOH, 87%.



Scheme 3. Reagents and conditions: (a) (*S*,*S*)-Co(III)-salen·OAc (0.5 mol %), H_2O (0.55 equiv), 25 °C; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, −10 °C, 82%; (c) TBSCl, imidazole, CH_2Cl_2, 97%; (d) (i) $Me_2S{\cdot}BH_3$, THF, (ii) 3 N NaOH, 30% H_2O_2,73%; (e) IBX, DMSO, 0 °C, 96%; (f) $BF_3{\cdot}OEt_2$, N_2CHCO_2Et, CH_2Cl_2, −10 °C, 77%; (g) (i) K_2CO_3, MeOH, (ii) $(CH_3)_2SO_4$, acetone, 81%.

epoxides **8** and **15**, respectively. Hydrolytic kinetic resolution coupled with regiospecific ring opening of chiral epoxides with dimethylsulfonium methylide constituted the key steps. Good yields, simple and ready availability of starting materials and less number of steps are some of the salient features of this approach.

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11. *Spectral data for* **5**: Colorless oil; IR (KBr): 669, 859, 1032, 1215, 1473, 1590, 3019 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.57–1.70 (m, 4H), 3.42–3.48 (t, $J = 5.4$ Hz, 2H), 3.78 (s, 3H), 4.05–4.11 (m, 1H), 4.42 (s, 2H), 5.03–5.23 (m, 2H), 5.75–5.91 (m, 1H), 6.82–6.86 (d, $J = 8.7$ Hz, 2H), 7.20–7.24 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.7, 34.3, 55.0, 69.9, 72.4, 72.5, 113.7, 114.2, 129.2, 130.1, 141.1, 159.1. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.27; H, 8.73.
12. *Spectral data for* **17**: $[\alpha]_D^{25}$ −4.65 (*c* 1, $CHCl_3$); 94% ee [Chiral OD-H column; hexane/*i*-PrOH (98:2 v/v); flow rate 1.0 mL/min; UV −210 nm; column temperature 25 °C; retention time: 13.295 min (*R*-isomer) and 14.450 min (*S*-isomer)]; colorless liquid; IR (KBr): 821, 1035, 1247, 1514, 1614, 2339, 2856 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.84–1.88 (m, 2H), 2.46–2.50 (m, 1H), 2.73–2.81 (m, 4H), 7.19–7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.3, 34.3, 47.0, 51.5, 126.0, 128.3, 128.4, 141.1. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.07; H, 8.13.