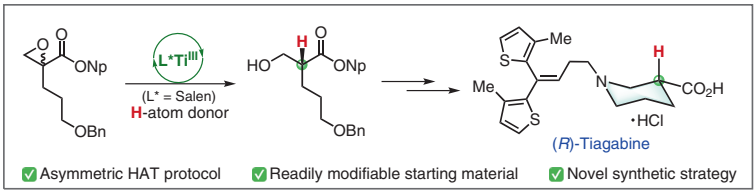
Synthesis L. Li et al. Paper

Enantioselective Synthesis of (*R*)-Tiagabine via Asymmetric Hydrogen Atom Transfer Protocol

Longfei Li
Wanjiao Chen
Zhongyun Xu
Jie Jiang*
Yong-Qiang Zhang*

School of Chemistry and Chemical Engineering, Shandong University, 27 Shanda South Road, Jinan 250100, P. R. of China
jiejiang@sdu.edu.cn
yongqzhang@sdu.edu.cn



Received: 23.10.2022
Accepted after revision: 21.02.2023
Published online: 21.02.2023 (Accepted Manuscript), 20.03.2023 (Version of Record)
DOI: 10.1055/a-2039-6180; Art ID: SS-2022-10-0495-OP

Abstract An enantioselective synthesis of tiagabine has been achieved utilizing an asymmetric hydrogen atom transfer protocol to construct its essential chiral tertiary carbon center. A cyclization reaction via double N-substitution is tactically orchestrated as the other key step to install the crucial alkaloid ring. Compared with the previous synthetic strategy, which used commercially available nicotinate as the starting material to ensure a short synthetic route, this strategy uses a readily modifiable and accessible alkyl-substituted acrylate as the starting material and thus provides a scenario for the facile synthesis of analogues and derivatives of tiagabine for further biological research.

Key words analogue synthesis, chiral tertiary center, enantioselective, hydrogen atom transfer, tiagabine, titanium catalysis

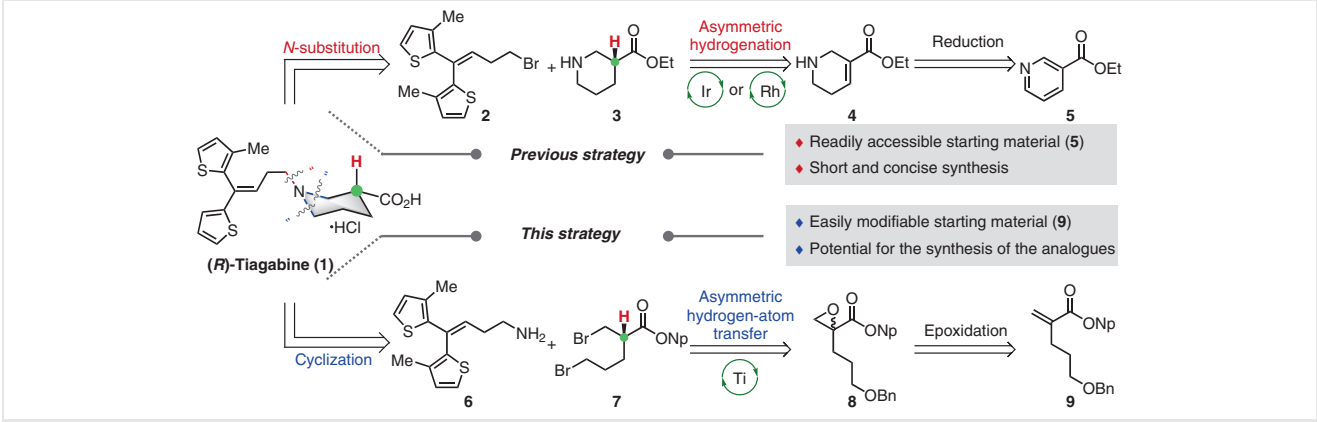
Tiagabine (**1**) is an antispasmodic drug marketed for the treatment of epilepsy.[1] Its mechanism of action is selective and novel when compared with that of other marketed AEDs, relying on its structural features with nipecotic acid moiety being the potent γ-aminobutyric acid (GABA) uptake inhibitor, and the lipophilic biaryl-appendage on the nitrogen atom ensuring the requisite blood-brain barrier transport.[2] Notably, the chirality of the sole stereocenter in the alkaloid ring is essential for its activity, with the *R*-(−)-enantiomer being four times more potent than its *S*-(+)-enantiomer.[3] Efficient construction of the chiral tertiary carbon center is therefore the key for the asymmetric synthesis of tiagabine.

To date, there have been only a few strategies to achieve the essential chiral stereocenter relying on either resolution of racemate ethyl nipecotate (*rac*-**3**) with L-tartaric acid[4] or asymmetric hydrogenation of guvacine **4** with noble metal catalysts at elevated hydrogen pressures (Scheme 1, upper part).[5] Nucleophilic substitution of the resulting enantioenriched **3** with homoallylic bromide **2** followed by sequential alkaline hydrolysis and acidification furnished the target tiagabine (**1**).[5c] Access to guvacine **4** was accomplished through hydrogenation of ethyl nicotinate (**5**) with Pd/C catalysis.[5b] In particular, the abundance and commercial accessibility of the starting material **5** renders this synthetic route concise. On the other hand, due to the well-structurally defined nature of the starting material nicotinate, it can be difficult to employ this strategy to access analogues of tiagabine such as isosteres, positional isomers, and distinct ring systems in the alkaloid moiety, which can be otherwise significant in drug development and research.[6,7]

We recently reported a catalytic asymmetric hydrogen atom transfer (HAT) reaction that proceeded via a radical approach to the chiral tertiary carbon center, as part of our program directed toward the development of catalytic enantioselective radical reactions.[8] The reaction enantioconvergently transforms racemic glycidic ester **8** into an enantioenriched β-hydroxy ester featuring an α-tertiary carbon center, which we envisioned can be readily transformed to the dibromo intermediate **7** to construct the alkaloid ring of tiagabine via a di-N-substitution cyclization reaction with homoallylic amine **6** (Scheme 1, lower part). The glycidic ester **8** can be accessed via epoxidation of acrylate **9**. Compared with the previous synthetic strategy, the modular accessible and readily modifiable starting material **9** enables this strategy to favorable synthesize the analogues or derivatives of tiagabine.

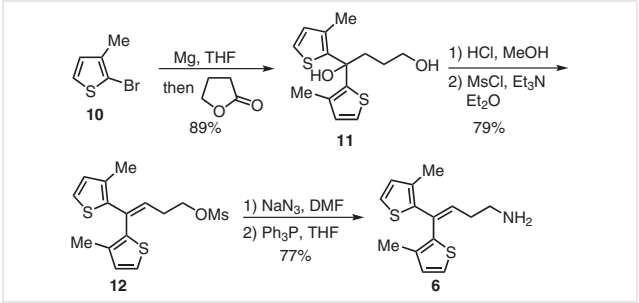
The synthesis began with the preparation of the bithienyl homoallylic amine **6** (Scheme 2). According to the known procedure reported by Clausen and Zhou,[5a,9] commercially available brominated thiophene **10** was treated with magnesium, followed by nucleophilic addition of the resultant Grignard reagent with γ-butyrolactone to give **11**, which underwent elimination and sulfonation to afford **12**

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 Comparison of the strategies for the synthesis of (*R*)-tiagabine

in 70% overall yield. Azide substitution of **12** followed by Staudinger reduction[10] proceeded cleanly to provide **6** in 77% yield.

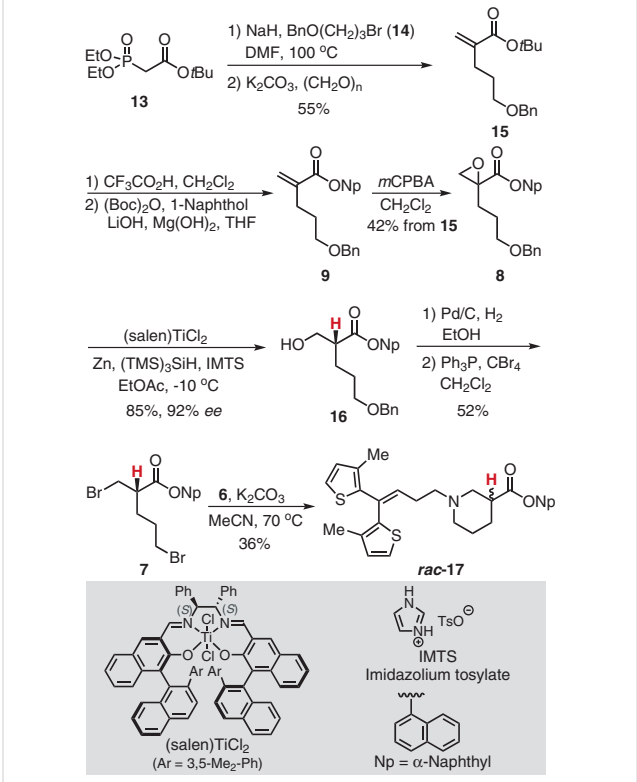


Scheme 2 Synthesis of dithiophenyl homoallylic amine **6**

Having obtained building block **6** in hand, we then focused our attention on the construction of its substitution counterpart **7** which bears a multiple-functionalized chiral tertiary carbon center (Scheme 3). Commercially available phosphonate ester **13** was treated with commercially available bromide **14**, followed by olefination with paraformaldehyde to afford *tert*-butyl acrylate **15** in 55% overall yield. Sequential removal of the *tert*-butyl group of **15** with trifluoroacetic acid and esterification of the resulting acid with 1-naphthol by di-*tert*-butyl dicarbonate ($(Boc)_2O$) activation under basic conditions[11] provided naphthyl acrylate **9**, which was used directly for the next step without further purification. The naphthyl ester is better suited to the HAT reaction in terms of enantioselectivity.[8] Epoxidation of **9** with *m*-chloroperoxybenzoic acid (*m*CPBA) generated glycidic ester **8** in an overall 39% yield for two steps.

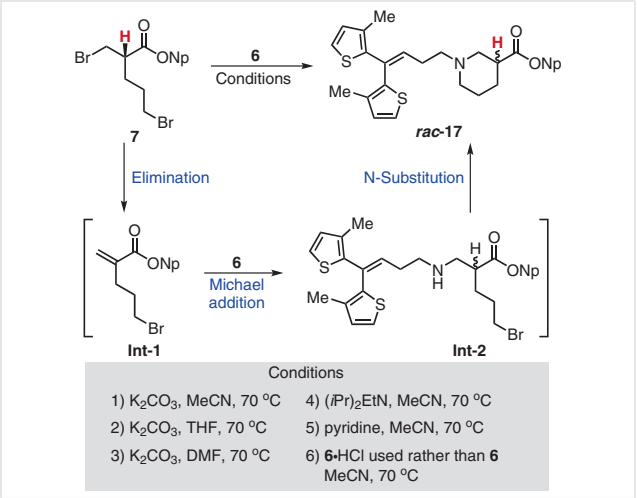
Next, **8** was subjected to our standard catalytic asymmetric HAT reaction, with (salen)$TiCl_2$ as precatalyst, zinc as reductant, $(TMS)_3SiH$ as hydrogen atom donor, and imidazolium tosylate (IMTS) as acid to furnish the catalytic cycle. The reaction went through a cascade regioselective homolytic epoxide opening and an enantioselective hydrogen atom transfer to the resulting tertiary carbon radical to provide the β-hydroxy ester **16** with 85% yield and 92% *ee*. Removal of the benzyl group of **16** under catalytic hydrogenation conditions followed by bromination of the resulting diol by the Appel reaction[12] furnished the dibromo compound **7** in 52% yield.

With **7** in hand, we then conducted the planned cyclization reaction with primary amine **6** in the presence of K_2CO_3 in acetonitrile at an elevated temperature. The ex-



Scheme 3 Synthesis of racemic alkaloid ring structure of tiagabine

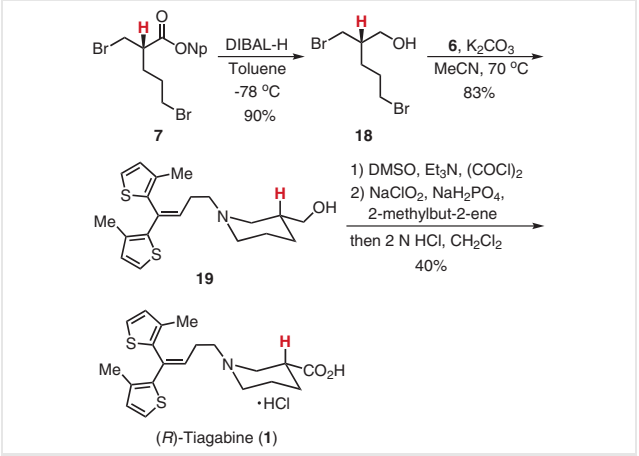
pected piperidine structure was readily formed within 2 hours in a yield of 36%, however, detection of its enantiopurity on HPLC indicated that racemic product *rac*-**17** was generated without any enantiomeric excess value. The unexpected formation of racemic cyclization product can be rationalized by a sequential $E1_{cb}$ elimination/Michael addition and intramolecular substitution reaction process[13] (Scheme 4). Therein, the loss of the essential chiral stereocenter arises from the enolization of **7** due to the relatively high acidity of the H atom adjacent to the ester group under basic conditions. Extensive screening of the bases and solvents led to racemic cyclization products as well.



Scheme 4 Investigation of the racemization process in the cyclization reaction

Moving forward, we continue toward the final stage of the construction of the alkaloid ring while retaining the chiral stereocenter. Given that the ester group readily initiated the unexpected elimination reaction, we assumed that a reduction of the ester to the alcohol before the cyclization reaction would inhibit the elimination reaction and therefore maintain the chiral carbon center. Oxidation of the primary alcohol to the acid after ring closure would then furnish the target molecular. As shown in Scheme 5, the reduction of **7** to alcohol **18** was effected with diisobutylaluminum hydride (DIBAL-H) in toluene in 90% yield. Treatment of **18** with **6** in the presence of K_2CO_3 at 70 °C furnished the alkaloid ring **19** in a nice yield without any loss of enantioselectivity. Finally, a decent sequential Swern[14] and Pinnick oxidation[15] followed by acidification with HCl provided the target molecular (*R*)-tiagabine (**1**).

In summary, we have achieved the enantioselective synthesis of tiagabine utilizing a catalytic asymmetric HAT strategy to construct its essential tertiary carbon center. Given that a readily modifiable glycidic ester is used as the crucial starting material, this work will serve as a basis for the asymmetric synthesis of analogues and derivatives of tiagabine to facilitate further biological studies.



Scheme 5 Synthesis of (*R*)-tiagabine

^{1}H and ^{13}C NMR spectra were measured on Bruker 400 MHz spectrometers. ^{1}H NMR spectra were calibrated by using the residual undeuterated solvent as internal reference ($CDCl_3$ δ = 7.26, DMSO-d_6 δ = 2.50). ^{13}C NMR spectra used the solvent peak as internal reference ($CDCl_3$ δ = 77.0, DMSO-d_6 δ = 39.5). IR spectra were measured on an ATR-IR-Spectrometer Nicolet TM 380 instrument as a neat film. HRMS analysis data were obtained on a Thermoquest MAT 95 XL instrument. Chiral HPLC analysis was performed with a Shimadzu HPLC instrument.

4,4-Bis(3-methylthiophen-2-yl)but-3-en-1-amine (6)

According to the reported procedure,[5a,9] Mg (7.92 g, 330 mmol), 2-bromo-3-methylthiophene (38.9 g, 220 mmol), and γ-butyrolactone (4.8 mL, 79.2 mmol) yielded the crude product **11** (19.7 g, 89%), which was used directly without further purification with HCl (4N, 50 mL) and MeOH (250 mL), and then $MeSO_2Cl$ (5.9 g, 77 mmol), Et_3N (13.6 mL, 98 mmol, 1.4 equiv) to afford **12** (19 g, 79%) as a yellow oil.

A mixture of compound **12** (6.84 g, 20 mmol, 1.0 equiv) and NaN_3 (6.5 g, 100 mmol, 5.0 equiv) in DMF (80 mL) was stirred at 80 °C for 3 h. Then, the reaction mixture was treated with a mixture of Et_2O and water, the ether extract was dried ($MgSO_4$), and the ether was removed under reduced pressure to give a yellow oil. To a solution of this oil in THF (75 mL) was added Ph_3P (10.5 g, 40 mmol, 2.0 equiv) and H_2O (25 mL). The reaction mixture was stirred for 2 h at 50 °C. The resulting suspension was filtered. The precipitate was washed with Et_2O and the filtrate was evaporated in vacuo. The residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 9:1) to afford the crude product **6** (4.0 g, 77%) as a yellow oil.

IR (neat): 2922, 1450, 844, 724, 456 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 5.1 Hz, 1 H), 7.05 (d, *J* = 5.1 Hz, 1 H), 6.84 (d, *J* = 5.1 Hz, 1 H), 6.76 (d, *J* = 5.1 Hz, 1 H), 6.05 (t, *J* = 7.5 Hz, 1 H), 2.81 (t, *J* = 6.9 Hz, 2 H), 2.30 (q, *J* = 7.1 Hz, 2 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.73 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 135.4, 135.2, 133.7, 132.6, 131.2, 129.6, 129.3, 124.4, 122.8, 41.9, 34.1, 14.9, 14.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NS_2$: 264.0875; found: 264.0874.

***tert*-Butyl 5-(Benzyloxy)-2-methylenepentanoate (15)**

To a solution of NaH (1.3 g, 33 mmol, 60% in mineral oil) in DMF (120 mL), *tert*-butyl diethylphosphonoacetate (7 mL, 30 mmol) was added dropwise at r.t. After stirring at r.t. for 30 min, ((3-bromopropoxy)methyl)benzene (**14**; 5.8 mL, 33 mmol) was added. The mixture was heated at 100 °C for 16 h and then cooled to r.t. K_2CO_3 (12.0 g, 90 mmol) and paraformaldehyde (5.4 g, 60 mmol) were then added, and the mixture was stirred at 100 °C for 6 h. After cooling down to r.t., the mixture was extracted with EtOAc, washed with brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane/EtOAc 9:1) to give **15** (4.5 g, 55%) as a colorless oil.

IR (neat): 2977, 2858, 1631, 1453, 1252, 738, 638 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.19 (m, 5 H), 6.05 (d, *J* = 1.6 Hz, 1 H), 5.44 (d, *J* = 1.5 Hz, 1 H), 4.49 (s, 2 H), 3.48 (t, *J* = 6.4 Hz, 2 H), 2.43–2.28 (m, 2 H), 1.87–1.73 (m, 2 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 141.8, 138.6, 128.4, 127.6, 127.5, 123.8, 80.4, 72.9, 69.6, 28.7, 28.6, 28.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{25}O_3$: 277.1798; found: 277.1804.

Naphthalen-1-yl 2-(3-(Benzyloxy)propyl)oxirane-2-carboxylate (8)

Compound **15** (4.1 g, 15 mmol) was dissolved in a mixed solution of CF_3CO_2H (15 mL) and CH_2Cl_2 (30 mL). The mixture was stirred for 30 min at r.t., and then it was washed with water (3 ×), dried ($MgSO_4$), filtered, and evaporated to dryness. To a solution of the crude product in THF (50 mL) were added $(Boc)_2O$ (3.3 g, 15 mmol), 1-naphthol (2.2 g, 15 mmol), LiOH (29 mg, 1.2 mmol), and $Mg(OH)_2$ (17 mg, 0.3 mmol). The mixture was stirred for 3 h at 75 °C and then quenched with water and extracted with EtOAc. The combined layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give the crude product **9** which was used directly for the next without further purification.

To a solution of the crude product **9** in CH_2Cl_2 (70 mL) was added *m*CPBA (85 wt%, 6 g, 30 mmol). The mixture was stirred at reflux for 48 h, then cooled down to 0 °C. The precipitated 3-chlorobenzoic acid was removed by vacuum filtration. The resultant reaction mixture was washed with sat. aq $Na_2S_2O_3$ and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane/EtOAc 9:1) to give **8** (2.3 g, 42% overall yield from **15**) as a yellow oil.

IR (neat): 2858, 1599, 1453, 1225, 798, 678 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, *J* = 6.5, 2.9 Hz, 2 H), 7.64 (d, *J* = 8.3 Hz, 1 H), 7.45–7.38 (m, 2 H), 7.35 (t, *J* = 7.9 Hz, 1 H), 7.29–7.20 (m, 4 H), 7.17 (t, *J* = 4.9 Hz, 2 H), 4.43 (s, 2 H), 3.49 (dd, *J* = 8.7, 3.6 Hz, 2 H), 3.31 (d, *J* = 5.8 Hz, 1 H), 2.90 (d, *J* = 5.8 Hz, 1 H), 2.26 (dd, *J* = 7.9, 6.3 Hz, 1 H), 2.02–1.93 (m, 1 H), 1.92–1.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 146.3, 138.5, 134.7, 128.5, 128.2, 127.8, 127.7, 126.8, 126.6, 126.6, 126.4, 125.4, 121.0, 117.9, 72.9, 69.7, 57.1, 52.3, 28.4, 25.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}O_4$: 363.1591; found: 363.1596.

Naphthalen-2-yl (*R*)-5-(Benzyloxy)-2-(hydroxymethyl)pentanoate (16)

To a heat-dried Schlenk tube were added IMTS (1.87 g, 7.8 mmol), Zn (680 mg, 10.4 mmol), (Salen)$TiCl_2$ (567 mg, 0.52 mmol), and freshly distilled EtOAc (10 mL) under an argon atmosphere subsequently, the mixture was stirred for 2 h at the indicated temperature, $(TMS)_3SiH$ (1.95 g, 7.8 mmol) was then added, followed by addition of **8** (1.9 g, 5.2 mmol) after 1 h. The mixture was stirred at the indicated temperature for 72 h, quenched with sat. aq $NaHCO_3$ solution, diluted with EtOAc, washed with brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane/EtOAc 4:1) to give **16** (1.6 g, 85%) as a yellow oil, 92% *ee* [Daicel Chiral OD-H (0.46 cm × 25 cm), *n*-hexane/*i*-PrOH 90:10, flow rate (v) = 1.0 mL·min^{-1}, λ = 221 nm: t_R = 25.21 (major), 28.75 min (minor)].

IR (neat): 2857, 1758, 1692, 832, 790, 560 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.81 (m, 2 H), 7.74 (d, *J* = 8.3 Hz, 1 H), 7.48 (ddd, *J* = 18.7, 10.7, 5.0 Hz, 3 H), 7.40–7.30 (m, 4 H), 7.31–7.25 (m, 1 H), 7.25–7.18 (m, 1 H), 4.54 (s, 2 H), 4.07–3.88 (m, 2 H), 3.59 (dd, *J* = 8.8, 3.0 Hz, 2 H), 3.04 (dd, *J* = 11.9, 6.2 Hz, 1 H), 2.25 (td, *J* = 6.1, 2.6 Hz, 1 H), 2.07–1.93 (m, 1 H), 1.94–1.76 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 146.5, 138.4, 134.7, 128.5, 128.0, 127.7, 127.7, 126.8, 126.6, 126.5, 126.2, 125.4, 73.1, 69.8, 63.3, 47.8, 27.6, 25.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}O_4$: 365.1747; found: 365.1742.

Naphthalen-1-yl (*S*)-5-Bromo-2-(bromomethyl)pentanoate (7)

To a solution of **16** (980 mg, 2.7 mmol) in EtOH was added Pd/C (wet, 100 mg), and the resulting mixture was stirred at r.t. under a H_2 balloon overnight. After filtration, the solvent was removed under vacuum to give the crude product. Then the crude product was dissolved in dry CH_2Cl_2 (30 mL) at 0 °C, Ph_3P (1.8 g, 7 mmol) and CBr_4 (2.3 g, 7 mmol) were then added. The ice bath was removed, and the reaction was allowed to stir for 0.5 h. The reaction mixture was then concentrated and purified directly with chromatography (silica gel, hexane/EtOAc 9:1) to give pure dibromide **7** (560 mg, 52%); 90% *ee* [Daicel Chiral OD-H (0.46 cm × 25 cm), *n*-hexane/*i*-PrOH 95:5, flow rate (v) = 1.0 mL·min^{-1}, λ = 221 nm: t_R = 13.76 (minor), 17.22 min (major)].

IR (neat): 3326, 1754, 1596, 1285, 1139, 771 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.92 (m, 1 H), 7.91–7.83 (m, 1 H), 7.76 (d, *J* = 8.3 Hz, 1 H), 7.58–7.42 (m, 3 H), 7.28–7.22 (m, 1 H), 3.77 (ddd, *J* = 15.3, 10.3, 6.5 Hz, 2 H), 3.60–3.44 (m, 2 H), 3.33–3.21 (m, 1 H), 2.22–1.97 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.46, 146.56, 139.54, 135.32, 134.67, 133.71, 131.21, 129.68, 128.04, 126.85, 126.47, 125.95, 125.41, 124.40, 122.83, 121.18, 118.05, 58.07, 55.25, 53.42, 41.83, 27.32, 27.03, 24.26, 14.86, 14.45.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}Br_2O_2$: 398.9590; found: 398.9599.

(*rac*)-Tiagabine (17)

Compound **6** (130 mg, 0.5 mmol) was mixed with **7** (200 mg, 0.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in MeCN (5 mL). The mixture was heated at 70 °C for 2 h. After cooling, the solution was concentrated. The residue was purified by flash column chromatography (hexane/EtOAc 3:1) to afford **17** (90 mg, 36%) as a brown oil; 2% *ee* [Daicel Chiral OD-H (0.46 cm × 25 cm), *n*-hexane/*i*-PrOH 95:5, flow rate (v) = 1.0 mL·min^{-1}, λ = 221 nm: t_R = 11.26 (minor), 13.21 min (major)].

IR (neat): 2921, 1754, 1452, 1261, 1121, 800 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (t, *J* = 5.8 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.52–7.40 (m, 3 H), 7.21–7.17 (m, 2 H), 7.05 (d, *J* = 5.1 Hz, 1 H), 6.83 (d, *J* = 5.0 Hz, 1 H), 6.76 (d, *J* = 5.1 Hz, 1 H), 3.27–3.19 (m, 1 H),

3.09 (s, 1 H), 2.82 (s, 1 H), 2.62 (d, *J* = 6.9 Hz, 2 H), 2.58–2.52 (m, 1 H), 2.47–2.40 (m, 2 H), 2.21 (s, 2 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.89–1.82 (m, 1 H), 1.78–1.70 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.21, 146.39, 134.69, 128.09, 126.67, 126.59, 126.37, 125.37, 121.16, 118.01, 47.65, 32.66, 31.91, 30.02, 29.98.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{31}NO_2S_2$: 502.1869; found: 502.1872.

The formation of **Int-1** can be detected by TLC and confirmed by crude NMR spectra:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 1 H), 7.78–7.74 (m, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H), 7.46–7.37 (m, 3 H), 7.20 (t, *J* = 3.3 Hz, 1 H), 6.57 (s, 1 H), 5.86 (s, 1 H), 3.47–3.39 (m, 2 H), 2.63–2.57 (m, 2 H), 2.11 (dt, *J* = 13.5, 6.6 Hz, 2 H).

(*S*)-5-Bromo-2-(bromomethyl)pentan-1-ol (18)

A solution of **7** (258 mg, 0.65 mmol) in dry toluene (1 mL) was cooled to –78 °C and DIBAL-H (1 M in toluene, 0.7 mmol) was added dropwise. After stirred at –78 °C for 1 h, the mixture was then allowed to warm to r.t. slowly and stirred overnight. The reaction was quenched with sat. Rochelle salt solution, extracted with Et_2O, and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane/EtOAc 4:1) to afford the alcohol **18** (150 mg, 90%) as a brown oil.

IR (neat): 2929, 1715, 1382, 1268, 817 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76–3.63 (m, 2 H), 3.61 (dd, *J* = 10.3, 4.3 Hz, 1 H), 3.50 (dd, *J* = 10.2, 5.4 Hz, 1 H), 3.42 (t, *J* = 6.7 Hz, 2 H), 1.98–1.82 (m, 3 H), 1.61 (d, *J* = 1.6 Hz, 1 H), 1.57 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.43, 41.44, 35.58, 33.35, 30.03, 28.12.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{13}Br_2O$: 258.9328; found: 258.9331.

(*R*)-(1-(4,4-Bis(3-methylthiophen-2-yl)but-3-en-1-yl)piperidin-3-yl)methanol (19)

Compound **6** (92 mg, 0.35 mmol) was mixed with **18** (90 mg, 0.35 mmol) and K_2CO_3 (140 mg, 1 mmol) in MeCN (5 mL). The mixture was heated at 70 °C for 2 h. After cooling, the solution was concentrated, and the crude product was purified by flash column chromatography (silica gel, hexane/EtOH 5:1) to afford **19** (105 mg, 83%) as a brown oil; 92% *ee* [Daicel Chiral IC (0.46 cm × 25 cm), *n*-hexane/*i*-PrOH 95:5, flow rate (v) = 1.0 mL·min^{-1}, λ = 257 nm: t_R = 11.92 (minor), 15.15 min (major)].

IR (neat): 2926, 2762, 1442, 1263, 1034, 805 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 5.1 Hz, 1 H), 6.97 (d, *J* = 5.1 Hz, 1 H), 6.77 (d, *J* = 5.1 Hz, 1 H), 6.68 (d, *J* = 5.1 Hz, 1 H), 5.96 (t, *J* = 7.3 Hz, 1 H), 3.48 (ddd, *J* = 16.8, 10.6, 5.7 Hz, 2 H), 2.74 (d, *J* = 9.0 Hz, 1 H), 2.59–2.52 (m, 1 H), 2.41 (m, 4 H), 2.35–2.23 (m, 2 H), 2.10–2.03 (m, 1 H), 1.97 (s, 3 H), 1.94 (s, 3 H), 1.74–1.66 (m, 2 H), 1.59 (m, 1 H), 1.51 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.53, 134.38, 134.18, 132.58, 132.10, 130.13, 128.59, 127.38, 123.29, 121.71, 65.95, 57.30, 56.20, 52.98, 36.81, 26.41, 26.28, 23.45, 13.77, 13.38.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}NOS_2$: 362.1607; found: 362.1598.

(*R*)-Tiagabine (1)

To a solution of oxalyl chloride (32 mg, 0.25 mmol) in anhyd CH_2Cl_2 (5 mL) was added dropwise DMSO (20 mg, 0.25 mmol) at –78 °C. The mixture was stirred for 10 min and a solution of alcohol **19** (45 mg, 0.125 mmol) in anhyd CH_2Cl_2 (1 mL) was added dropwise over 5 min; the mixture was stirred at –78 °C for 10 min. Subsequently, Et_3N (101 mg, 1 mmol) was added dropwise to the reaction mixture at –78 °C over 2 min. The mixture was warmed to r.t. for 0.5 h and then poured into water. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the crude product. To a solution of the crude product in a mixture of THF/^{t}BuOH (1:1.8 mL) was added 2-methylbut-2-ene (18 mg, 0.25 mmol) and a solution of sodium chlorite (24 mg, 0.19 mmol) and sodium phosphate monobasic (45 mg, 0.375 mmol) in H_2O (2 mL). The mixture was stirred for 0.5 h. Aq 1 M HCl was added to the mixture until it reached pH 1. CH_2Cl_2 was then added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 ×), and the combined organic phases were washed with brine (1 ×), dried ($MgSO_4$), filtered, and concentrated in vacuo to give an off-white solid. The solid was recrystallized to provide (*R*)-tiagabine hydrochloride (20.0 mg, 40%) as a white solid; mp 180–181 °C; $[\alpha]_D^{25}$ –8.9 (*c* = 1.0, H_2O).

IR (neat): 2939, 2540, 1725, 1195, 855, 723 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 12.79 (s, 1 H), 11.01 (s, 1 H), 7.52 (d, *J* = 4.9 Hz, 1 H), 7.33 (d, *J* = 4.9 Hz, 1 H), 6.96 (d, *J* = 4.9 Hz, 1 H), 6.85 (d, *J* = 4.9 Hz, 1 H), 6.00 (t, *J* = 7.0 Hz, 1 H), 3.47 (s, 2 H), 3.17 (d, *J* = 7.3 Hz, 2 H), 2.94 (d, *J* = 6.0 Hz, 2 H), 2.81 (s, 1 H), 2.56 (m, 2 H), 2.00 (d, *J* = 19.8 Hz, 7 H), 1.82 (s, 2 H), 1.47 (s, 1 H).

^{13}C NMR (100 MHz, DMSO): δ = 173.33, 138.79, 135.97, 134.38, 134.28, 131.88, 130.41, 129.91, 129.80, 126.06, 124.44, 55.44, 52.41, 51.62, 25.36, 24.77, 22.17, 21.25, 15.05, 14.69.

HRMS (ESI): *m*/*z* [M – HCl + H]$^+$calcd for $C_{20}H_{26}ClNO_2S_2$: 376.1399; found: 376.1406.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

We thank the National Natural Science Foundation of China (NSFC, No. 21901143), the Taishan Scholar Program of Shandong Province (No. tsqn201909006), the Young Scholars Program of Shandong University (11190089964157) and the Natural Science Foundation of Shandong Province (ZR2021QB118).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2039-6180.

References

(1) (a) Luer, M. S.; Rhoney, D. H. *Ann. Pharmacother.* **1998**, *32*, 1173. (b) Andersen, K. E.; Braestrup, C.; Gronwald, F. C.; Jørgensen, A. S.; Nielsen, E. B.; Sonnewald, U.; Sørensen, P. O.; Suzdak, P. D.; Knutsen, L. J. S. *J. Med. Chem.* **1993**, *36*, 1716. (c) Wang, H.; Hussain, A. A.; Wedlund, P. J. *Pharm. Res.* **2005**, *22*, 556.

(2) (a) Takahashi, K.-I.; Miyoshi, S.; Kaneko, A.; Copenhagen, D. R. *Jpn. J. Physiol.* **1995**, *45*, 457. (b) Suzdak, P. D.; Jansen, J. A. *Epilepsia* **1995**, *36*, 612. (c) Fink-Jensen, A.; Suzdak, P. D.; Swedberg, M. D.; Judge, M. E.; Hansen, L.; Nielsen, P. G. *Eur. J. Pharmacol.* **1992**, *220*, 197.
(3) Shinnar, S. *Semin. Pediatr. Neurol.* **1997**, *4*, 24.
(4) Moher, E. D.; Tripp, A. E.; Creemer, L. C.; Vicenzi, J. T. *Org. Process Res. Dev.* **2004**, *8*, 593.
(5) (a) Song, S.; Zhu, S.-F.; Pu, L.-Y.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 6072. (b) Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem.* **2006**, 4343. (c) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265. (d) Schleich, S.; Helmchen, G. *Eur. J. Org. Chem.* **1999**, 2515.
(6) (a) Zdrazil, B.; Jurik, A.; Sitte, H. H.; Ecker, G. F. *J. Cheminf.* **2013**, *5*, 01 32. (b) Jurik, A.; Reicherstorfer, R.; Zdrazil, B.; Ecker, G. F. *Mol. Inf.* **2013**, *32*, 415. (c) Chorghadea, M. S.; Ellegaard, P.; Lee, E. C.; Petersen, H.; Sørensen, P. O. *Heterocycles* **1994**, *37*, 783. (d) Chorghade, M. S.; Petersen, H.; Lee, E. C.; Bain, S. *Appl. Chem.* **1996**, *68*, 761.
(7) (a) Dangi, M.; Khichi, A.; Jakhar, R.; Chhillar, A. K. *Curr. Pharm. Biotechnol.* **2021**, *22*, 1030. (b) Wermuth, C. G. *Drug Discovery Today* **2006**, *11*, 348.
(8) Xu, Z.; Shen, J.; Li, L.; Chen, W.; Li, S.; Jiang, J.; Zhang, Y.-Q. *Angew. Chem. Int. Ed.* **2022**, *61*, e2022141.
(9) (a) Clausen, R. P.; Moltzen, E. K.; Perregaard, J.; Lenz, S. M.; Sanchez, C.; Falch, E.; Frolund, B.; Bolvig, T.; Sarup, A.; Larsson, O. M.; Schousboe, A.; Krogsgaard-Larsen, P. *Bioorg. Med. Chem.* **2005**, *13*, 895. (b) Vogensen, S. B.; Jorgensen, L.; Madsen, K. K.; Jurik, A.; Borkar, N.; Rosatelli, E.; Nielsen, B.; Ecker, G. F.; Schousboe, A.; Clausen, R. P. *Bioorg. Med. Chem.* **2015**, *23*, 2480.
(10) (a) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Tian, W. Q.; Wang, Y. A. *J. Org. Chem.* **2004**, *69*, 4299.
(11) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Marcantoni, E.; Melchiorre, P.; Sambria, L. *Synthesis* **2007**, 3489.
(12) Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801.
(13) The formation of **Int-1** was detected and confirmed by crude ^{1}H NMR spectra, please see the experimental section for details.
(14) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(15) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.