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

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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. Its mechanism of action is selective and novel when compared with that of other marketed AEDs, relying on its structural features with nipeptic 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. 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. 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 or asymmetric hydrogenation of guvacine 4 with noble metal catalysts at elevated hydrogen pressures (Scheme 1, upper part). Nucleophilic substitution of the resulting enantioenriched 3 with homoallylic bromide 2 followed by sequential alkaline hydrolysis and acidification furnished the target tiagabine (1). Access to guvacine 4 was accomplished through hydrogenation of ethyl nicotinate (5) with Pd/C catalysis. 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.

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. 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 alkaldial 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 favorably synthesize the analogues or derivatives of tiagabine.

The synthesis began with the preparation of the thiényl homoallylic amine 6 (Scheme 2). According to the known procedure reported by Clausen and Zhou, 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.
in 70% overall yield. Azide substitution of 12 followed by Staudinger reduction\textsuperscript{10} proceeded cleanly to provide 6 in 77% yield.

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)\textsubscript{2}O) activation under basic conditions\textsuperscript{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.\textsuperscript{8} Epoxidation of 9 with m-chloroperoxybenzoic acid (mCPBA) 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\textsubscript{2} as precatalyst, zinc as reductant, (TMS)\textsubscript{3}SiH 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 \(\beta\)-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\textsuperscript{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\textsubscript{2}CO\textsubscript{3} in acetonitrile at an elevated temperature. The ex-
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 E1cb elimination/Michael addition and intramolecular substitution reaction process\(^1\) (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.

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 disobutylaluminum hydride (DIBAL-H) in toluene in 90% yield. Treatment of 18 with increased acidity 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 E1cb elimination/Michael addition and intramolecular substitution reaction process\(^1\) (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.

According to the reported procedure,\(^5\) Mg (7.92 g, 330 mmol), 2-bromo-3-methylthiophene (38.9 g, 220 mmol), and \(\gamma\)-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\(_2\)Cl (5.9 g, 77 mmol), Et\(_3\)N (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 Na\(_2\) (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\(_2\)O 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\(_3\)P (10.5 g, 40 mmol, 2.0 equiv) and H\(_2\)O (25 mL). The reaction mixture was stirred for 2 h at 50 °C. The resulting suspension was filtered. The precipitate was washed with Et\(_2\)O and the filtrate was evaporated in vacuo. The crude product 6 (4.0 g, 77%) was purified by chromatography (silica gel, CH\(_2\)Cl\(_2\)/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\(^{-1}\).

HRMS (ESI): \text{m/z [M + H]}^+ \text{ calcd for C}_{14}H_{18}NS_2: 264.0875; \text{ found: 264.0874.}
**Naphthalen-1-yl 2-(3-Benzoxyl)propyl)oxirane-2-carboxylate (8)**

To a solution of IMTS (1.87 g, 7.8 mmol), Zn (4.5 g, 55%) and freshly distilled EtOAc (10 mL) at 0 °C, (Boc)2O (3.3 g, 15 mmol), 1-naphthol (2.2 g, 14 mmol) were then added. The reaction mixture was stirred for 3 h at 3 °C and then washed with water (3 ×), dried (MgSO4), and the solvent was removed under vacuum overnight. After filtration, the solvent was removed under vacuum 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 CH2Cl2 (70 mL) was added mCPBA (85 wt%, 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 Na2S2O3 and extracted with CH2Cl2. 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):** 2857, 1754, 1596, 1285, 1139, 771 cm⁻¹.

**HRMS (ESI):** m/z [M + H]+ calcd for C16H17Br2O2: 398.9590; found: 398.9590.

**1H NMR (400 MHz, CDCl3):** δ = 7.99–7.81 (m, 2 H), 7.74 (d, J = 8.3 Hz, 1 H), 7.48 (dd, 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).

**13C NMR (100 MHz, CDCl3):** δ = 173.8, 146.5, 138.4, 134.7, 128.5, 128.0, 127.7, 126.8, 126.6, 126.5, 126.2, 125.4, 73.1, 69.8, 63.3, 47.8, 27.6, 25.5.

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$_3$): $\delta$ = 171.21, 146.39, 134.69, 128.09,
126.67, 126.59, 123.37, 121.16, 118.01, 47.65, 32.66, 31.91, 30.02, 29.98.

HRMS (ESI): $m/z$ [M + H$^+$] calcld for C$_{20}$H$_{27}$NOS$_2$: 362.1607; found:
362.1598.

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

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 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).

IR (neat): 2929, 2540, 1725, 1195, 855, 723 cm$^{-1}$.

10.2, 5.4 Hz, 1 H), 3.42 (t, $J$ = 6.9 Hz, 2 H), 2.58–2.52 (m, 1 H),
1.98–1.82 (m, 3 H), 1.61 (d, $J$ = 1.6 Hz, 1 H), 1.57 (m, 2 H).

HRMS (ESI): $m/z$ [M + H$^+$] calcld for C$_{6}$H$_{13}$Br$_2$O: 258.9328; found:
258.9331.

362.1598.

(5)-S-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 drop-
wise. 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 EtOAc and dried (Na$_2$-
SO$_4$). 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): 2926, 1715, 1382, 1268, 817 cm$^{-1}$.

1$^H$ NMR (400 MHz, CDCl$_3$): $\delta$ = 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).

IR (neat): 2929, 2540, 1725, 1195, 855, 723 cm$^{-1}$.

1$^H$ NMR (400 MHz, CDCl$_3$): $\delta$ = 6.53, 41.44, 35.58, 33.35, 30.03,
28.12.

HRMS (ESI): $m/z$ [M + H$^+$] calcld for C$_{6}$H$_{13}$Br$_2$O: 258.9328; found:
258.9331.

(R)-Tiagabine (1)
To a solution of oxalyl chloride (32 mg, 0.25 mmol) in anhyd CH$_2$Cl$_2$ (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$_2$Cl$_2$ (1 mL) was added dropwise over 5 min;
the mixture was stirred at –78 °C for 10 min. Subsequently, Et$_3$N (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$_2$Cl$_2$. 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/BuOH (1:1.8 mL)
was added 2-methylbut-2-ene (18 mg, 0.25 mmol) and a solution of
sodium chloride (24 mg, 0.19 mmol) and sodium phosphate mono-
basic (45 mg, 0.375 mmol) in H$_2$O (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$_2$-
Cl$_2$ was then added and the phases were separated. The aqueous
phase was extracted with CH$_2$Cl$_2$ (3 x), and the combined organic
phases were washed with brine (1 x), dried (MgSO$_4$), filtered, and
concentrated in vacuo to give an off-white solid. The solid was recrys-
tallized to provide (R)-tiagabine hydrochloride (20.0 mg, 40%) as a
white solid; mp 180–181 °C; [$\alpha$]$_D^{25}$ = -8.9 $\circ$ (c = 1.0, H$_2$O).

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

1$^H$ NMR (400 MHz, DMSO): $\delta$ = 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): $\delta$ = 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,

HRMS (ESI): $m/z$ [M + HCl + H]$^+$ calcld for C$_{20}$H$_{28}$Cl$_2$N$_2$: 376.1399;
found: 376.1406.

Conflict of Interest
The authors declare no conflict of interest.

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References
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(13) The formation of Int-1 was detected and confirmed by crude 1H NMR spectra, please see the experimental section for details.
