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Synthesis of optically active β-alkyl aspartate via [3,3] sigmatropic rearrangement of α-acyloxytrialkylsilane

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Abstract—The synthesis of four types of optically active β-carbon-substituted analogs of *threo*-β-hydroxy aspartate (THA) and a β-carbon-substituted analog of *threo*-β-benzyloxy aspartate (TBOA), which are potent blockers of excitatory amino acid transporters in the mammalian central nervous system, via the chirality-transferring ester–enolate Claisen rearrangement of α-acyloxytrialkylsilane is described.

L-Glutamate acts as an excitatory neurotransmitter in the mammalian central nervous system and is as well a potent neurotoxin.[1] For normal neurotransmission by glutamate, it is necessary to maintain the extracellular glutamate concentration below neurotoxic levels and, therefore, glutamate transporters play an important role for this purpose.[2,3] To date, five subtypes of glutamate transporters have been found in mammalian tissues.[3] For elucidation of the intrinsic properties and physiological roles of transporters, development of subtype-selective inhibitors of glutamate transporters is required. (2*S*,3*S*)-THA **1a**[4] and (2*S*,3*S*)-TBOA **1b**[5] are known as representative inhibitors; in particular, the latter exhibits potent nontransportable blocker activity to glutamate transporters (Fig. 1). Therefore, β-substituted aspartates are expected as a lead for developing useful blockers of glutamate transporters.

1a: R^1= OH, R^2= H (**THA**)
1b: R^1= $PhCH_2O$, R^2= H (**TBOA**)
1c: R^1= Me, R^2= H
1d: R^1= Me, R^2= Me
1e: R^1= $PhCH_2CH_2$, R^2= H

2c: R^1= Me, R^2= H
2d: R^1= Me, R^2= Me

Figure 1.

In a previous study, we reported the synthesis of optically active vinylsilane-containing α-amino acids via the chirality-transferring ester–enolate Claisen rearrangement of α-acyloxytrialkylsilane (Scheme 1).[6] This method is characterized by the complete transfer of the chirality that is, a carbon center attached to a *tert*-butyldimethylsilyl (TBDMS) group to both the 2- and 3-positions of the product. Conversion of the resulting amino acids to the β-substituted aspartates will be achieved by the oxidative cleavage of the C–C double bond of the vinylsilane moiety. We wish to report herein the synthesis of a β-carbon-substituted analog of THA **1c**, its α-methyl-substituted analog **1d**, their C3-epimers **2c** and **2d**, and a β-carbon-substituted analog of TBOA **1e** in optically active form. According to the previous research, the construction of each 2*S*,3*S*-*threo* configuration for **1c**–**e** and 2*S*,3*R*-*erythro* configuration for **2c**,**d** will be achieved by this method using *E*- and *Z*-(*S*)-α-acyloxysilanes, respectively.

The synthesis of THA analog **1c** was started with optically active amino acid, *syn*-(2*S*,3*R*)-**5c**, prepared from

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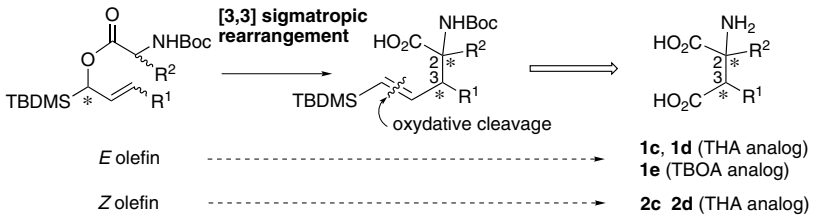
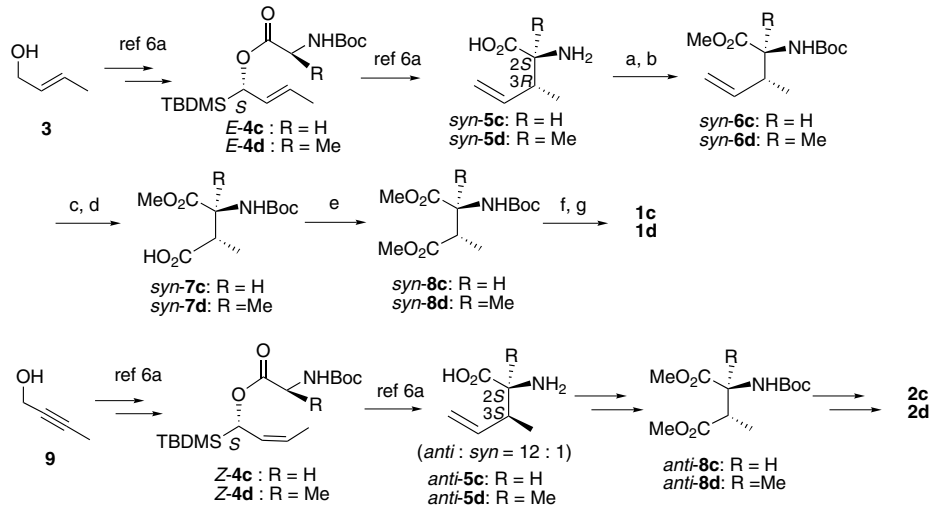


Scheme 1.

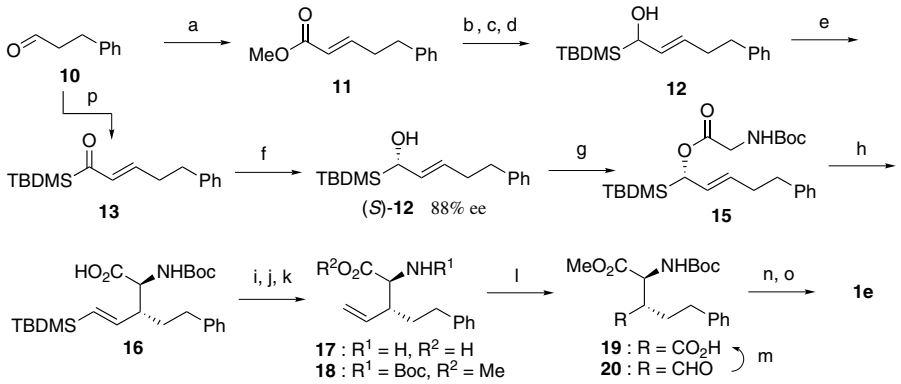


Scheme 2. Reagents and conditions: (a) Boc_2O, Na_2CO_3, H_2O–dioxane (1:2), rt, 2 h (for **5c**), 72 h (for **5d**); (b) CH_2N_2, Et_2O, 0 °C, 30 min (67–94%, two steps); (c) O_3, AcOEt, −78 °C, 10 min, then Me_2S, rt, 1 h; (d) Jones oxidation (47–57%, two steps); (e) CH_2N_2, Et_2O, 0 °C, 15 min (quant); (f) 1 M NaOH, THF, rt, 16 h; (g) TFA (50 equiv), CH_2Cl_2, 0 °C, 3 h (94–99%, two steps).

crotyl alcohol (**3**) via the ester–enolate Claisen rearrangement of α-acyloxysilane *E*-**4c** as reported (Scheme 2).[6a] Prior to carrying out an oxidative degradation of the terminal olefin, the amino, and the carboxyl groups of *syn*-**5c** were protected with a Boc group and a methyl ester, respectively (94%, two steps). Ozonolysis of the protected *syn*-**6c** followed by Jones oxidation of the resulting mixture afforded carboxylic acid *syn*-**7c** in 47% yield for two steps, which, upon treatment with CH_2N_2, gave diester *syn*-**8c** in quantitative yield. Deprotection of *syn*-**8c** was performed by the following sequence of reactions: (1) 1 M NaOH in THF and (2) TFA (50 equiv) in CH_2Cl_2. The desired **1c** was obtained in 94% yield from *syn*-**8c**. α-Methyl-substituted analog **1d** of THA was synthesized by the use of *syn*-**5d**[6a] in the same manner as for **1c**.

The 3*S*-epimers of the THA analog **2c** and **2d** were synthesized by the use of *anti*-(2*S*,3*S*)-**5c**[7] and **5d**, which were prepared from 2-butyn-1-ol (**9**) via the ester–enolate Claisen rearrangement of optically active α-acyloxysilane *Z*-**4**, in the same manner as that of the 3*R*-isomers, respectively.[6a] Thus, four types of the β-carbon-substituted analogs of THA **1c**, **1d**, **2c**, and **2d** were synthesized.[8]

According to our synthetic plan in Scheme 1, the synthesis of TBOA analog **1e** was started with 3-phenylpropanal (**10**) (Scheme 3). The Wittig olefination of **10** with methyl (triphenylphosphoranylidene)acetate gave ester **11** in 87% yield ($E : Z = 19 : 1$). After separation of the E/Z mixture, the pure *E*-**11** was reduced with DIBAL and the resulting allylic alcohol was converted to TBDMS ether (94% from *E*-**11**). The reverse-Brook rearrangement of the resulting silyl ether afforded α-hydroxysilane **12** in 80% yield,[9] which, upon Jones oxidation, gave acylsilane **13** in quantitative yield. Alternatively, this was prepared from **10** by the Horner–Wadsworth–Emmons reaction with (α-phosphonoacyl)-silane (**14**) in 75% yield.[10] Enantioselective reduction of **13** with (+)-*B*-chloro diisopinocamphenylborane (DIP-Cl)[11] under reflux in THF afforded optically active **12**, whose optical purity and absolute configuration were determined to be 88% ee and *S* by the modified Mosher method using ^1H NMR,[12] respectively. Condensation of (*S*)-**12** with *N*-Boc-Gly gave α-acyloxysilane **15** (92% from **13**). According to Kazmaier's[13] and our protocol,[6] α-acyloxysilane **15** was treated with LDA, $ZnCl_2$ in THF at −78 °C to room temperature to produce a rearrangement product **16** in 86% yield as the sole diastereomer. On treatment of **16** with 42% HBF_4 (100 equiv) in 1,4-dioxane at 65 °C for 24 h, spontaneous desilylation and removal of the Boc group proceeded to give amino acid **17** in 68% yield. According to the method for the synthesis of the THA analog, protection of both the amino and the carboxyl groups gave **18**



Scheme 3. Reagents and Conditions: (a) $Ph_3P{=}CHCO_2Me$ (1.5 equiv), benzene, reflux, 16 h (87%, $E : Z = 19 : 1$, separable); (b) DIBAL (2.5 equiv), CH_2Cl_2, −78 °C to rt, 1 h; (c) TBDMSCI (1.5 equiv), imidazole (1.5 equiv), CH_2Cl_2, −78 °C to rt, 1 h (94%, two steps); (d) *sec*-BuLi (4 equiv), TMEDA (4.5 equiv), THF, −78 °C to rt, 1 h (80%); (e) Jones oxidation (quant); (f) (+)-DIP-CI (3 equiv), THF, reflux, 2 h; (g) *N*-Boc-Gly (2 equiv), EDCI (2 equiv), DMAP (10 mol%), CH_2Cl_2, 0 °C, 2 h (92%, two steps); (h) LDA (3.0 equiv), $ZnCl_2$ (1.2 equiv), THF, −78 °C to rt (86%); (i) 42% HBF_4 (100 equiv), 1,4-dioxane, 65 °C, 24 h (68%); (j) Boc_2O (1 equiv), Na_2CO_3 (2 equiv), H_2O–1,4-dioxane (1:2), rt; (k) CH_2N_2, Et_2O (80%, two steps); (l) OsO_4 (0.01 equiv), $NaIO_4$ (4 equiv), H_2O–acetone (2:1), 0 °C to rt, 24 h; (m) Jones oxidation (96%, two steps); (n) 1 M NaOH (4 equiv), THF, rt, 18 h; (o) TFA (50 equiv), CH_2Cl_2, 0 °C, 4 h, then recrystallization from EtOH (50% from **19**); (p) $(MeO)_2POCH_2COTBDMS$ (**14**, 1.2 equiv), NaH (1 equiv), THF, 0 °C, 1 h (75%).

(80%, two steps). An attempt to cleave the terminal olefin by ozonolysis was not satisfactory and the desired carboxylic acid **19** was afforded in 37% yield together with trace amounts of aldehyde **20**. The yield was much improved (80%) when **18** was treated with OsO_4 (0.01 equiv) and $NaIO_4$ (4 equiv) in H_2O–acetone (2:1) at room temperature for 24 h. The by-produced **20** (18%) was converted to **19** by Jones oxidation in quantitative yield. Finally, after deprotection of **19** in two steps [(i) 1 M NaOH, (ii) TFA], recrystallization of the crude mixture from EtOH gave the TBOA analog **1e**[14] with >95% ee (50% yield from **19**). The relative and absolute configurations of **1e** were determined to be 2*S*,3*S* by the following experiments: (1) Each *J* value between H^a and H^b of the γ-butyrolactone **21** or its C2-epimer **22**, which was prepared from **20** as shown in Scheme 4, was 9.8 and 6.8 Hz, respectively. These results indicate that **21** possesses 2,3-*trans* configuration. (2) The absolute configuration of the C2-position of **1e** was determined to be *S* by comparison of the ^1H NMR spectral data of its (*R*)- and (*S*)-MTPA-amide.[15]

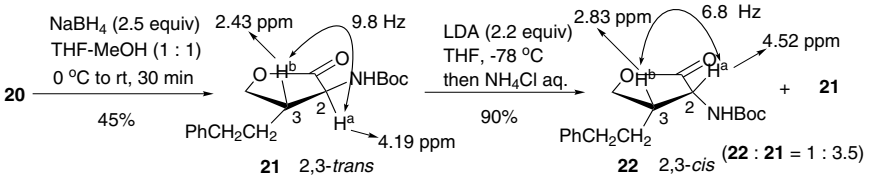
Inhibition of glutamate uptake by the synthetic aspartate derivatives was preliminarily assessed in MDCK cells stably expressing EAAT2 (glial transporter) or EAAT3 (neuronal transporter).[5b,16] The values of 50% inhibitory concentration (IC_{50}) are shown in Table 1. The activity of **1e** was about one-tenth of that of TBOA, and activities of both **1c** and **2c** were about a half of that

Table 1. Inhibition of glutamate uptake in MDCK cells

	IC_{50} (M)	
	EAAT2	EAAT3
1a (THA)	19 ± 0.7	7.3 ± 0.37
1b (TBOA)	2.6 ± 0.16	1.4 ± 0.11
1c	28 ± 2.0	16 ± 1.0
1d	[a]	[a]
1e	35 ± 2.7	15 ± 1.2
2c	79 ± 5.1	16 ± 0.7
2d	[a]	[a]

[a] No inhibitory activity was observed at 100 μM.

of THA. On the other hand, **1d** and **2d** did not show any inhibitory activity at 100 μM. These results suggest that the oxygen function at the β-position of aspartate would be one of the important factors for the inhibition of glutamate transporters. In the previous studies on the inhibitors of glutamate transporter, the active conformations of both aspartate and TBOA were proposed to be HO_2C–C–C–CO_2H *anti* (conformer **A**) (Fig. 2).[5b,17] In this study, the small *J* value between H^c and H^d of **1e** (3.2 Hz) as well as that of TBOA (2.5 Hz) showed that the H^c–C–C–H^d *gauche* conformers (**A** and/or **C**) are predominant over the conformer **B**. Taking the *gauche* effect[18] between the NH_2 group and the OR group and the electrostatic effects into consideration, the conformer **A** of TBOA would have the advantage over the conformer **C**. The slightly larger *J* value of **1e** compared



Scheme 4.

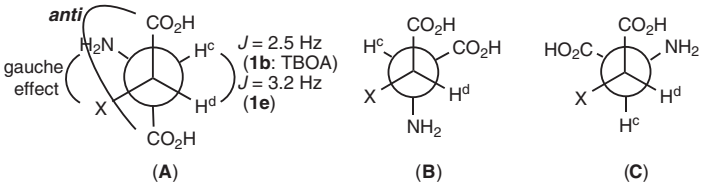


Figure 2.

to that of TBOA suggested that the loss of *gauche* effect by exchange of an oxygen atom to a carbon atom in the X group decreased the contribution of the conformer **A** in **1e**, which would result in a decrease of the inhibitory activity. Therefore, our present results supported the hypothesis that the active conformation is conformer **A**. Further studies regarding the structure–activity relationship of glutamate transporters of the synthetic **1c**, **1d**, **2c**, **2d**, and **1e** are in progress in our laboratories.

Acknowledgements

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7. The starting *anti*-**5c** was obtained as a diastereomeric mixture (*anti*:*syn* = 12:1). The minor isomer was removed as the diester **8c** by silica-gel column chromatography.
8. **1c** (90% ee): mp 268 °C (decomposition); $[\alpha]_D^{20}$ +9.8 (*c* 2.03, 5 M HCl); ^{1}H NMR (400 MHz, D_2O): δ 4.00 (d, J = 2.1 Hz, 1H), 2.94 (dq, J = 2.1, 7.1 Hz, 1H), 1.13 (d, J = 7.1 Hz, 3H). **1d** (90% ee): mp 268 °C (decomposition); $[\alpha]_D^{22}$ +11.9 (*c* 0.91, 5 M HCl); ^{1}H NMR (400 MHz, D_2O): δ 2.75 (q, J = 7.4 Hz, 1H), 1.48 (s, 3H), 1.13 (d, J = 7.4 Hz, 3H). **2c** (>95% ee): mp 268 °C (decomposition); $[\alpha]_D^{21}$ +34.3 (*c* 2.05, 5 M HCl); ^{1}H NMR (400 MHz, D_2O): δ 3.68 (d, J = 5.3 Hz, 1H), 2.90 (dq, J = 5.3, 7.5 Hz, 1H), 1.25 (d, J = 7.5 Hz, 3H). **2d** (>95% ee): mp 126 °C; $[\alpha]_D^{22}$ +28.0 (*c* 1.06, 5 M HCl); ^{1}H NMR (400 MHz, D_2O): δ 2.87 (q, J = 7.6 Hz, 1H), 1.39 (s, 3H), 1.20 (d, J = 7.6 Hz, 3H).
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14. **1e** (>95% ee): mp 194 °C; $[\alpha]_D^{30}$ +5.3 (*c* 0.95, 5 M HCl); ^{1}H NMR (400 MHz, D_2O): δ 7.41–7.36 (2H), 7.32–7.27 (3H), 3.96 (d, J = 3.2 Hz, 1H), 2.86 (dt, J = 11.2, 3.2 Hz, 1H), 2.75 (ddd, J = 14.5, 9.9, 5.1 Hz, 1H), 2.65 (ddd, J = 13.7, 9.9, 7.1 Hz, 1H), 1.90 (m, 1H), 1.70 (m, 1H).
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