**Catalytic Enantio- and Diastereoselective Aldol Reactions of Glycine-Derived
Silicon Enolate with Aldehydes: An Efficient Approach to the Asymmetric
Synthesis of *Anti*- β -Hydroxy- α -Amino Acid Derivatives**

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Discussion on the Stereoselectivity of the Aldol Reactions.

The unexpected reversion of the diastereoselectivity seems to be attributed to an interesting reactive feature of silicon enolate **2** (see Table 1). Since the reactivity of **2** is rather high, two silyl enol ether moieties, especially the one on the nitrogen bond, should be easily hydrolyzed in this catalyst system containing a proton source such as H₂O and a large amount of ⁿPrOH. (Rapid hydrolysis of the amide enolate moiety was observed by NMR analysis.) Hydrolysis of the silicon enolate is competitive with the desired reaction with an aldehyde. Therefore, when **2** is added to the reaction solution in one portion, the relative concentration of **2** becomes maximum at the beginning of the reaction and it may result in the reaction of an aldehyde with the enolate partly hydrolyzed at the trifluoroacetyl amino group. In Mukaiyama aldol reactions of enolates with aldehydes catalyzed by bulky Lewis acids, it is known that if the reaction proceeds via an open-chain transition state and the enolates have a hetero

atom-containing substituent at the α -position, *syn*-selectivity should be predominant because of the interaction between the hetero atom and the Lewis acid.^{1,2} It seems that the *syn*-adduct becomes a major product for similar reason under our initial reaction conditions since the amide oxygen of the trifluoroacetyl group of the partly hydrolyzed enolate **2** can coordinate to zirconium. This speculation is supported by the fact that the reaction of silicon enolate **5**, whose amide bond should participate in coordination to zirconium, also proceeded with high *syn*-selectivity (Table 1, entry 3). On the other hand, under the optimal reaction conditions, in which turnover of the catalyst is accelerated by increasing the amount of ⁿPrOH and the relative concentration of the enolate is decreased by slow addition, the desired reaction of the silicon dienolate might occur before hydrolysis. Steric repulsion between the bulky silyl amide enolate and the crowded zirconium center can afford *anti*-aldol adducts.³

Table 1. Catalytic Enantio- and Diastereoselective Aldol Reactions of Silicon Enolate **2** with Benzaldehyde (**1a**)^a

Entry	BINOL derivative	PrOH (mol%)	Time (h) ^b	Yield (%)	<i>anti</i> / <i>syn</i>	ee (%) (<i>anti</i>)
1 ^c	3a	80	0	71	43/57	46 ^d
2 ^e	3a	80	0	80	29/71	63 ^d
3 ^{e,f}	3a	80	0	18	17/83	93 ^d
4	3a	150	0	50	55/45	75
5	3b	150	0	74	58/42	32
6	3b	150	1	97	72/28	71
7	3b	150	4	92	75/25	77
8	3b	150	8	93	78/22	87
9	3b	300	8	92	90/10	95

X = I, Y = H: (*R*)-3,3'-I₂-BINOL (**3a**)
X = Y = I: (*R*)-3,3',6,6'-I₄-BINOL (**3b**)

2 **5**

syn-**6**

^aUnless noted otherwise, the reaction was carried out with 1.5 equiv of **2** in toluene-^tBuOMe (1:1) at -20 °C for 12 h in the presence of a chiral zirconium catalyst prepared from Zr(O^tBu)₄ (10 mol%), (*R*)-BINOL derivative **3** (12 mol%), PrOH, and H₂O (10 mol%). ^bAddition time of silicon enolate. ^cIn toluene at 0 °C. ^dEe of *syn*-isomer. ^eAt 0 °C. ^fSilicon enolate **5** was used and the major product was *syn*-**6**.

Experimental Section

General: Melting points were uncorrected. Optical rotations were recorded on a JASCO P-1010 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-610 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in CDCl_3 unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^1H NMR, and CDCl_3 was used internal standard ($\delta = 77.0$) for ^{13}C NMR. High performance liquid chromatography (HPLC) was carried out using following apparatuses: SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV-VIS detector), and SHIMADZU C-R6A or C-R8A chromatopac. Mass spectrometry was carried out using SHIMADZU GCMS-QP5050A. High-resolution mass spectrometry was carried out using JEOL JMS-SX 102. Column chromatography was performed on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. Toluene was distilled and dried over MS 4A. *tert*-Butyl methyl ether was distilled and dried over sodium. 1-Propanol was distilled in the presence of magnesium propoxide and dried over MS 4A. Zirconium tetra-*tert*-butoxide was purchased from Trichemical Laboratory Co., Ltd. Aldehydes **1a-1i** were purchased from Tokyo Kasei Kogyo Co., Ltd. and purified by distillation. BINOL derivatives **3a** and **3b** were prepared according to the previously reported methods.³ Aldehydes **1j**,⁴ **1k**,⁵ and **7**⁶ and silicon enolates **2**⁷ and **5**⁸ were prepared according to the literature procedures. All other solvents and chemical compounds were purified based on standard procedures. All reactions were carried out under argon atmosphere in well-dried glassware.

Typical experimental procedure for enantio- and diastereoselective aldol reactions using a chiral zirconium catalyst: A typical experimental procedure is described for the reaction of silicon enolate **2** with benzaldehyde (**1a**). To a suspension of (*R*)-3,3',6,6'-tetraiodo-1,1'-binaphthalene-2,2'-diol ((*R*)-3,3',6,6'-I₄BINOL (**3b**)) (0.024 mmol) in toluene (0.20 mL) was added $\text{Zr}(\text{O}^i\text{Bu})_4$ (0.020 mmol) in toluene (0.50 mL) at room temperature, and the solution was stirred for 3 h. Then a mixture of 1-propanol (0.60 mmol) and H_2O (0.020 mol) in toluene (0.30 mL) was added, and the whole was stirred for 1 h at room temperature. After cooling at

–20 °C, benzaldehyde (0.20 mmol) in *t*BuOMe (0.30 mL) was added and then silicon enolate **2** (0.30 mmol) in *t*BuOMe (0.70 mL) was slowly added over 8 h. The whole reaction mixture was stirred for 4 h, and 0.5 M aqueous KHSO₄ (10 mL) was added to quench the reaction. After addition of ethyl acetate (10 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL x 2). Combined organic extracts were washed with saturated aqueous NaHCO₃ and brine, and dried over Na₂SO₄. Filtration and concentration under reduced pressure afforded the crude material. When a silyl ether form of the product was detected by TLC analysis, the crude adduct was treated with THF-1N HCl (20:1) at 0 °C for 1h. The solution was then basicified with saturated aqueous NaHCO₃, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by silica gel chromatography (hexane/ethyl acetate) to afford the desired aldol adduct **4a**. The diastereomer ratio was determined by ¹H NMR analysis, and the optical purity was determined by HPLC analysis using a chiral column (see below).

Methyl 3-hydroxy-3-phenyl-2-(trifluoroacetyl-amino)propionate (4a): IR (neat) 3316, 1749, 1703, 1556, 1182 cm⁻¹. ¹H NMR (CDCl₃) *anti*-isomer: δ 3.12 (br s, 1H), 3.69 (s, 3H), 4.96 (dd, *J* = 3.9, 7.6 Hz, 1H), 5.22 (d, *J* = 3.9 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.26-7.30 (m, 2H), 7.31-7.40 (m, 3H). *syn*-isomer (detectable peaks): δ 3.12 (br s, 1H), 3.81 (s, 3H), 4.83 (dd, *J* = 2.7, 8.8 Hz, 1H), 5.40 (d, *J* = 2.7 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H). ¹³C NMR (CDCl₃) *anti*-isomer: δ 52.9, 58.5, 74.0, 115.5 (q, *J* = 287.4 Hz), 125.7, 128.6, 128.7, 138.0, 157.1 (q, *J* = 38.1 Hz), 168.7. *syn*-isomer (detectable peaks): δ 52.8, 58.1, 73.0, 125.4, 128.7, 138.6, 169.3. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *anti*-isomer: *t*_R = 17.5 min (major), *t*_R = 38.7 min (minor). *syn*-isomer: *t*_R = 20.2 min (major), *t*_R = 24.4 min (minor). Anal. calcd for C₁₂H₁₂F₃NO₄: C 49.49, H 4.15, N 4.81; found: C 49.26, H 4.26, N 4.77. ESI-MS (*m/z*) 314 ([M+Na]⁺).

Other analytical data of aldol adducts.

Methyl 3-hydroxy-2-methyltrifluoroacethylamino-3-phenylpropionate (6): IR (neat) 3484, 1749, 1686, 1249, 1198, 1150 cm^{-1} . ^1H NMR (CDCl_3) *syn*-isomer: δ 2.68 (q, $J = 1.4$ Hz, 3H), 3.79 (s, 3H), 4.05 (d, $J = 8.6$ Hz, 1H), 5.38 (d, $J = 8.6$ Hz, 1H), 7.26-7.41 (m, 5H). *anti*-isomer (detectable peaks): δ 3.17 (q, $J = 1.6$ Hz, 3H), 5.31 (d, $J = 5.1$ Hz, 1H), 5.55 (d, $J = 5.1$ Hz, 1H), 7.34-7.28 (m, 1H), 7.32-7.40 (m, 4H). ^{13}C NMR (CDCl_3) *syn*-isomer: δ 36.4, 52.2, 68.3, 71.2, 116.1 (q, $J = 287.7$ Hz), 126.8, 128.8, 129.0, 138.6, 157.4 (q, $J = 37.3$ Hz), 170.5. *anti*-isomer (detectable peaks): δ 52.8, 68.0, 70.9, 125.7, 128.4, 128.6, 128.9, 138.3, 167.3. HPLC (Daicel Chiralpak AD-H, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *syn*-isomer: $t_R = 11.9$ min (minor), $t_R = 15.6$ min (major). *anti*-isomer: $t_R = 16.9$ min (minor), $t_R = 20.9$ min (major). Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_4$: C 51.15, H 4.62, N 4.59; found: C 51.02, H 4.73, N 4.65. ESI-MS (m/z) 328 ($[\text{M}+\text{Na}]^+$).

Methyl 3-hydroxy-3-(4-methylphenyl)-2-(trifluoroacetylamino)propionate (4b): IR (neat) 3303, 1746, 1707, 1560, 1216, 1187, 1166 cm^{-1} . ^1H NMR (CDCl_3) *anti*-isomer: δ 2.35 (s, 3H), 2.94 (br s, 1H), 3.71 (s, 3H), 4.96 (dd, $J = 4.2, 8.3$ Hz, 1H), 5.20 (d, $J = 4.2$ Hz, 1H), 7.03 (br s, 1H), 7.11-7.22 (m, 4H). *syn*-isomer (detectable peaks): δ 2.33 (s, 3H), 3.82 (s, 3H), 4.81 (dd, $J = 2.6, 9.0$ Hz, 1H), 5.37 (d, $J = 2.6$ Hz, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 21.1, 52.8, 58.4, 74.0, 115.6 (q, $J = 287.4$ Hz), 125.6, 129.3, 134.9, 138.6, 157.3 (q, $J = 38.1$ Hz), 168.7. *syn*-isomer (detectable peaks): δ 21.1, 53.1, 58.1, 72.9, 125.4, 129.4, 135.6, 138.5, 169.3. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *anti*-isomer: $t_R = 16.8$ min (major), $t_R = 31.6$ min (minor). *syn*-isomer: $t_R = 19.2$ min (major), $t_R = 24.6$ min (minor). Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_4$: C 51.15, H 4.62, N 4.59; found: C 51.03, H 4.65, N 4.60. ESI-MS (m/z) 328 ($[\text{M}+\text{Na}]^+$).

Methyl 3-(4-chlorophenyl)-3-hydroxy-2-(trifluoroacetylamino)propionate (4c): IR (neat) 3392, 3298, 1748, 1704, 1556, 1271, 1181 cm^{-1} . ^1H NMR (CDCl_3) *anti*-isomer: δ 3.34 (br s, 1H), 3.71 (s, 3H), 4.93 (dd, $J = 3.9, 8.3$ Hz, 1H), 5.21 (d, $J = 3.9$ Hz, 1H), 7.16 (d, $J = 8.3$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H). *syn*-isomer (detectable peaks): δ 2.95 (br s, 1H), 3.83 (s, 3H), 4.83 (dd, $J = 2.2, 9.0$ Hz, 1H), 5.39 (d, $J = 2.2$ Hz, 1H), 7.02 (br s, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 52.9, 58.5, 73.5, 115.5 (q, $J = 287.4$ Hz), 127.1, 128.8, 134.4, 136.6, 157.4 (q, $J = 38.0$ Hz),

168.4. *syn*-isomer (detectable peaks): δ 53.2, 57.9, 72.4, 126.9, 128.8, 137.1, 169.1. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *anti*-isomer: t_R = 18.3 min (major), t_R = 39.0 min (minor). *syn*-isomer: t_R = 24.4 min (major), t_R = 31.9 min (minor). Anal. calcd for C₁₂H₁₁ClF₃NO₄: C 44.26, H 3.40, N 4.30; found: C 44.02, H 3.49, N 4.30. ESI-MS (m/z) 348 ([M+Na]⁺).

Methyl 3-hydroxy-3-(3-methylphenyl)-2-(trifluoroacetylamino)propionate (4d):

IR (neat) 3428, 3347, 1710, 1549, 1292, 1202, 1176 cm⁻¹. ¹H NMR (CDCl₃) *anti*-isomer: δ 2.34 (s, 3H), 3.38 (br s, 1H), 3.68 (s, 3H), 4.93 (dd, J = 4.0, 8.2 Hz, 1H), 5.17 (d, J = 4.0 Hz, 1H), 7.04-7.27 (m, 5H). *syn*-isomer (detectable peaks): δ 2.33 (s, 3H), 3.10 (br s, 1H), 3.80 (s, 3H), 4.80 (dd, J = 2.6, 9.2 Hz, 1H), 5.34 (d, J = 2.6 Hz, 1H). ¹³C NMR (CDCl₃) *anti*-isomer: δ 21.3, 52.7, 58.5, 74.0, 115.6 (q, J = 286.7 Hz), 122.7, 126.3, 128.5, 129.4, 137.9, 138.4, 157.3 (q, J = 37.9 Hz), 168.8. *syn*-isomer (detectable peaks): δ 21.3, 53.0, 58.1, 72.9, 122.5, 126.1, 128.5, 129.3, 138.4, 138.6, 157.0 (q, J = 38.5 Hz), 169.3. HPLC (Daicel Chiralcel OD, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *anti*-isomer: t_R = 11.0 min (minor), t_R = 13.1 min (major). *syn*-isomer: t_R = 16.4 min (major), t_R = 26.7 min (minor). Anal. calcd for C₁₃H₁₄F₃NO₄: C 51.15, H 4.62, N 4.59; found: C 51.06, H 4.67, N 4.52. ESI-MS (m/z) 328 ([M+Na]⁺).

Methyl 3-(3-chlorophenyl)-3-hydroxy-2-(trifluoroacetylamino)propionate (4e):

IR (neat) 3283, 1746, 1705, 1560, 1209, 1180 cm⁻¹. ¹H NMR (CDCl₃) *anti*-isomer: δ 3.51 (br s, 1H), 3.70 (s, 3H), 4.92 (dd, J = 3.9, 8.1 Hz, 1H), 5.20 (d, J = 3.9 Hz, 1H), 7.08 (br s, 1H), 7.17-7.36 (m, 4H). *syn*-isomer (detectable peaks): δ 3.22 (br s, 1H), 3.83 (s, 3H), 4.84 (dd, J = 2.4, 9.2 Hz, 1H), 5.39 (br s, 1H). ¹³C NMR (CDCl₃) *anti*-isomer: δ 52.8, 58.5, 73.4, 115.5 (q, J = 286.5 Hz), 123.8, 126.0, 128.7, 129.8, 134.6, 140.8, 157.4 (q, J = 38.1 Hz), 168.4. *syn*-isomer (detectable peaks): δ 53.1, 57.9, 72.3, 123.7, 125.8, 129.9, 134.7, 140.8, 169.0. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min) *anti*-isomer: t_R = 28.8 min (major), t_R = 50.9 min (minor). *syn*-isomer: t_R = 33.6 min (major), t_R = 42.7 min (minor). Anal. calcd for C₁₂H₁₁ClF₃NO₄: C 44.26, H 3.40, N 4.30; found: C 44.20, H 3.55, N 4.49. ESI-MS (m/z) 348 ([M+Na]⁺).

Methyl 3-hydroxy-3-(3-methoxyphenyl)-2-(trifluoroacetylaminopropionate (4f):

IR (neat) 3432, 3319, 1731, 1708, 1558, 1277, 1201, 1180, 1162 cm^{-1} . ^1H NMR (CDCl_3) *anti*-isomer: δ 3.70 (br s, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 4.96 (dd, $J = 4.1$, 8.3 Hz, 1H), 5.19 (d, $J = 4.1$ Hz, 1H), 6.82-6.90 (m, 3H), 7.12 (d, $J = 8.3$ Hz, 1H), 7.24-7.29 (m, 1H). *syn*-isomer (detectable peaks): δ 3.70 (s, 3H), 3.81 (s, 3H), 4.83 (dd, $J = 2.4$, 9.0 Hz, 1H), 5.36 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 52.8, 55.1, 58.4, 73.9, 111.1, 114.3, 115.6 (q, $J = 287.4$ Hz), 117.9, 129.7, 139.9, 157.3 (q, $J = 38.0$ Hz), 159.8, 168.7. *syn*-isomer (detectable peaks): δ 53.1, 55.1, 58.1, 72.8, 114.0, 117.7, 129.7, 140.3, 169.3. HPLC (Daicel Chiralpak AS, hexane/*i*PrOH = 9/1, flow rate = 0.5 mL/min) *anti*-isomer: $t_R = 23.1$ min (minor), $t_R = 34.0$ min (major). *syn*-isomer: $t_R = 17.4$ min (major), $t_R = 29.8$ min (minor). Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_5$: C 48.60, H 4.39, N 4.36; found: C 48.48, H 4.46, N 4.34. ESI-MS (m/z) 344 ($[\text{M}+\text{Na}]^+$).

Methyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(trifluoroacetylaminopropionate (4g):

IR (KBr) 3311, 2966, 1743, 1702, 1603, 1180, 1066 cm^{-1} . ^1H NMR (CDCl_3) *anti*-isomer: δ 3.74 (s, 3H), 3.77 (s, 6H), 4.98 (dd, $J = 4.0$, 8.2 Hz, 1H), 5.19 (d, $J = 4.0$ Hz, 1H), 6.40-6.43 (m, 3H), 7.01 (d, $J = 8.2$ Hz, 1H). *syn*-isomer (detectable peaks): δ 3.76 (s, 6H), 3.84 (s, 3H), 4.83 (dd, $J = 2.4$, 9.1 Hz, 1H), 5.33 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 52.9, 55.3, 58.4, 74.1, 100.6, 103.6, 115.6 (q, $J = 287.5$ Hz), 140.3, 157.4 (q, $J = 38.0$ Hz), 161.1, 168.5. *syn*-isomer (detectable peaks): δ 53.1, 57.9, 73.0, 100.3, 103.2, 141.0. HPLC (Daicel Chiralpak AD-H, hexane/*i*PrOH = 9/1, flow rate = 0.5 mL/min) *anti*-isomer: $t_R = 27.8$ min (major), $t_R = 32.3$ min (minor). *syn*-isomer: $t_R = 22.4$ min (minor), $t_R = 26.2$ min (major). Anal. calcd for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}_6$: C 47.87, H 4.59, N 3.99; found: C 47.65, H 4.74, N 3.99. FAB-MS (m/z) 352 ($[\text{M}+\text{H}]^+$).

Methyl 3-hydroxy-3-(2-naphthyl)-2-(trifluoroacetylaminopropionate (4h):

IR (neat) 3411, 1718, 1552, 1441, 1217, 1169 cm^{-1} . ^1H NMR (CDCl_3) *anti*-isomer: δ 3.61 (s, 3H), 5.02 (dd, $J = 4.0$, 8.2 Hz, 1H), 5.33 (d, $J = 4.0$ Hz, 1H), 7.30 (d, $J = 8.2$ Hz, 1H), 7.35 (dd, $J = 1.7$, 8.5 Hz, 1H), 7.46-7.51 (m, 2H), 7.74-7.84 (m, 4H). *syn*-isomer (detectable peaks): δ 3.78 (s, 3H), 4.92 (dd, $J = 2.6$, 9.0 Hz, 1H), 5.52 (d, $J = 2.6$ Hz, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 52.7, 58.5, 74.0, 115.6 (q, $J = 287.0$

Hz), 123.2, 124.9, 126.4, 126.5, 127.7, 127.9, 128.4, 133.0, 133.2, 135.5, 157.4 (q, $J = 38.0$ Hz), 168.7. *syn*-isomer (detectable peaks): δ 53.0, 58.1, 73.0, 123.0, 124.7, 126.3, 127.9, 128.5, 133.1, 136.2, 169.3. HPLC (Daicel Chiralpak AD-H, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *anti*-isomer: $t_R = 21.8$ min (major), $t_R = 48.0$ min (minor). *syn*-isomer: $t_R = 26.8$ min (major), $t_R = 31.5$ min (minor). ESI-HRMS (m/z) calcd for $C_{16}H_{14}F_3NO_4Na$: 364.0773 ($[M+Na]^+$); found 364.0779.

Methyl 3-(2-furyl)-3-hydroxy-2-(trifluoroacetylamino)propionate (4i): IR (neat) 3300, 1749, 1708, 1559, 1214, 1182 cm^{-1} . 1H NMR ($CDCl_3$) *anti*-isomer: δ 3.40 (br s, 1H), 3.75 (s, 3H), 5.05 (dd, $J = 4.2, 8.3$ Hz, 1H), 5.24 (d, $J = 4.2$ Hz, 1H), 6.35 (dd, $J = 1.0, 3.4$ Hz, 1H), 6.36 (dd, $J = 1.7, 3.4$ Hz, 1H), 7.21 (d, $J = 8.3$ Hz, 1H), 7.40 (dd, $J = 1.0, 1.7$ Hz, 1H). *syn*-isomer (detectable peaks): δ 3.10 (br s, 1H), 3.83 (s, 3H), 4.97 (dd, $J = 2.4, 9.0$ Hz, 1H), 5.37 (d, $J = 2.4$ Hz, 1H), 7.38 (dd, $J = 1.0, 2.0$ Hz, 1H). ^{13}C NMR ($CDCl_3$) *anti*-isomer: δ 53.1, 57.0, 68.4, 108.3, 110.5, 115.6 (q, $J = 287.4$ Hz), 143.1, 151.0, 157.6 (q, $J = 38.1$ Hz), 168.4. *syn*-isomer (detectable peaks): δ 53.2, 55.9, 67.6, 107.8, 110.7, 143.0, 151.3, 168.8. HPLC (Daicel Chiralcel OD-H (double), hexane/*i*PrOH = 9/1, flow rate = 0.5 mL/min) *anti*-isomer: $t_R = 31.0$ min (minor), $t_R = 32.7$ min (major). *syn*-isomer: $t_R = 26.8$ min (major), $t_R = 41.0$ min (minor). Anal. calcd for $C_{10}H_{10}F_3NO_5$: C 42.71, H 3.58, N 4.98; found: C 42.72, H 3.68, N 4.98. ESI-MS (m/z) 304 ($[M+Na]^+$).

Methyl 3-hydroxy-8-phenyl-2-trifluoroacetylamino-4-octynoate (4j): IR (neat) 3281, 1754, 1710, 1560, 1181 cm^{-1} . 1H NMR ($CDCl_3$) *anti*-isomer: δ 1.82 (tt, $J = 7.1, 7.6$ Hz, 2H), 2.22 (dt, $J = 1.5, 7.1$ Hz, 2H), 2.68 (t, $J = 7.6$ Hz, 2H), 3.17 (br s, 1H), 3.81 (s, 3H), 4.85-4.91 (m, 2H), 7.13 (br s, 1H), 7.14-7.24 (m, 3H), 7.24-7.32 (m, 2H). *syn*-isomer (detectable peaks): δ 2.19 (dt, $J = 2.0, 7.1$ Hz, 2H), 3.81 (s, 3H), 4.83-4.85 (m, 1H), 4.93-4.96 (m, 1H). ^{13}C NMR ($CDCl_3$) *anti*-isomer: δ 17.9, 29.7, 53.2, 57.6, 63.0, 75.5, 81.9, 89.0, 115.6 (q, $J = 286.6$ Hz), 126.0, 128.4, 128.4, 141.1, 157.6 (q, $J = 38.0$ Hz), 168.0. *syn*-isomer (detectable peaks): δ 17.8, 29.6, 53.1, 57.1, 62.5, 76.3, 88.2, 125.9, 128.3, 141.2, 168.3. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH = 19/1, flow rate = 1.0 mL/min) *anti*-isomer: $t_R = 33.6$ min (minor), $t_R = 53.2$ min (major). *syn*-isomer: $t_R = 21.2$ min (major), $t_R = 23.8$ min (minor). ESI-HRMS (m/z) calcd for $C_{17}H_{19}F_3NO_4$: 358.1266 ($[M+H]^+$); found 358.1272.

Methyl 6-*tert*-butyldiphenylsiloxy-3-hydroxy-2-trifluoroacetylamino-4-hexynoate (4k): IR (neat) 3413, 2940, 2858, 1729, 1546, 1429, 1172, 1113 cm^{-1} . ^1H NMR (CDCl_3) *anti*-isomer: δ 1.05 (s, 9H), 3.78 (s, 3H), 4.34 (d, $J = 1.4$ Hz, 2H), 4.82-4.87 (m, 2H), 7.15 (br s, 1H), 7.37-7.47 (m, 6H), 7.65-7.72 (m, 4H). *syn*-isomer (detectable peaks): δ 1.05 (s, 9H), 3.79 (s, 3H), 4.32 (d, $J = 1.7$ Hz, 2H), 4.78 (dd, $J = 2.7, 9.0$ Hz, 1H), 4.88-4.91 (m, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 19.0, 26.6, 52.3, 53.2, 57.2, 62.8, 79.7, 86.8, 115.6 (q, $J = 287.4$ Hz), 127.8, 129.9, 132.7, 135.5, 157.6 (q, $J = 38.0$ Hz), 167.7. *syn*-isomer (detectable peaks): δ 19.0, 26.6, 52.3, 52.9, 56.6, 62.3, 80.6, 86.0, 127.7, 130.0, 132.8, 135.6, 168.7. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min) *anti*-isomer: $t_R = 35.1$ min (major), $t_R = 43.1$ min (minor). *syn*-isomer: $t_R = 26.5$ min (major), $t_R = 33.3$ min (minor). ESI-HRMS (m/z) calcd for $\text{C}_{25}\text{H}_{32}\text{F}_3\text{N}_2\text{O}_5\text{Si}$: 525.2033 ($[\text{M}+\text{NH}_4]^+$); found 525.2037.

Determination of relative and absolute configuration of aldol adduct 4a.

The absolute stereochemistry of aldol adduct **4a** was determined after converting to the known β -hydroxy- α -amino acid derivative (Scheme 1). Acid hydrolysis of *anti*-**4a** followed by methyl esterification again and protection of the amino group as the Boc group gave *anti*-**7a** in 81% yield. The absolute configuration of *anti*-**7a** was determined to be 2*S*,3*S* by comparison of the NMR data and the optical rotation with those in the literature.⁹ The stereochemistry of *syn*-**4a** was also determined to be 2*R*,3*S* in the same way.

Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonyl)amino-3-hydroxy-3-phenylpropionate

(*anti*): Aldol adduct *anti*-**4a** (purified by recrystallization, *anti*/*syn* = 97/3, *anti* = 96% ee, 60.0 mg, 0.21 mmol) was treated with 6 M HCl (4.0 mL) and refluxed for 3 h. After concentrated under reduced pressure, a saturated HCl methanolic solution (3.0

mL) was added to the residue at room temperature. The mixture was stirred at room temperature for 12 h, concentrated under reduced pressure, and the crude product was dissolved in 1,4-dioxane (1.0 mL) and H₂O (1.0 mL). To the solution were added NaHCO₃ (87.0 mg, 1.04 mmol) and Boc₂O (67.4 mg, 0.31 mmol) at room temperature. The mixture was stirred at room temperature for 5 h, quenched with saturated aqueous NaHCO₃, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/ethyl acetate) to afford *anti*-**7a** (49.0 mg, 3 steps, 81%) as a pure *anti*-isomer. $[\alpha]_{\text{D}}^{24} +79.0$ (*c* 0.98, CHCl₃) (lit.⁹: $[\alpha]_{\text{D}}^{20} +83.3$ (*c* 1.05, CHCl₃)). Mp 100-101 °C (lit.⁹: 101-102 °C). IR (neat) 3367, 3062, 2965, 1428 cm⁻¹. ¹H NMR (CDCl₃) δ 1.43 (s, 9H), 3.69 (s, 3H), 3.96 (br s, 1H), 4.77 (dd, *J* = 3.4, 6.8 Hz, 1H), 5.18 (br s, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 7.25-7.36 (m, 5H). ¹³C NMR (CDCl₃) δ 28.2, 52.4, 59.7, 75.1, 80.7, 126.0, 128.0, 128.3, 139.2, 156.3, 170.2. ESI-MS (*m/z*) 318 ([M+Na]⁺).

Methyl (2*R*,3*S*)-2-(*tert*-butoxycarbonyl)amino-3-hydroxy-3-phenylpropionate

(*syn*): According to the same procedure from *anti*-**4a** to *anti*-**7a**, aldol adduct *syn*-**4a** (purified by recrystallization, *anti/syn* = 2/98, *syn* = 98% ee, 47.0 mg, 0.16 mmol) was converted to *syn*-**7a** (39.8 mg, 3 steps, 84%) as a pure *syn*-isomer. $[\alpha]_{\text{D}}^{22} +14.6$ (*c* 0.80, CHCl₃) (lit.⁹: $[\alpha]_{\text{D}}^{20} -15.1$ (*c* 1.05, CHCl₃), (2*S*,3*R*)-form). Mp 100-101 °C (lit.⁹: 101-102 °C). IR (neat) 3367, 3062, 2965, 1428 cm⁻¹. ¹H NMR (CDCl₃) δ 1.33 (s, 9H), 2.96 (br s, 1H), 3.75 (s, 3H), 4.53 (m, 1H), 5.22 (br s, 1H), 5.35 (d, *J* = 6.6 Hz, 1H), 7.26-7.38 (m, 5H). ¹³C NMR (CDCl₃) δ 28.1, 52.5, 59.4, 73.9, 80.0, 126.0, 128.0, 128.3, 139.7, 155.6, 171.4. ESI-MS (*m/z*) 318 ([M+Na]⁺).

Asymmetric synthesis of L-erythro-sphingosine.

Methyl 6-*tert*-butyldiphenylsiloxy-3-hydroxy-2-trifluoroacetyl-amino-4-hexenoate

(**8**): IR (neat) 3420, 3332, 2956, 2857, 1724, 1546, 1213, 1174, 1113 cm⁻¹. ¹H NMR (CDCl₃) δ 1.07 (s, 9H), 2.60 (br s, 1H), 3.76 (s, 3H), 4.23 (dd, *J* = 1.3, 3.0 Hz, 2H), 4.61 (dd, *J* = 3.7, 5.4 Hz, 1H), 4.76 (dd, *J* = 3.7, 8.0 Hz, 1H), 5.87 (ddt, *J* = 1.3, 5.4, 15.3 Hz, 1H), 5.92 (dt, *J* = 3.0, 15.3 Hz, 1H), 7.19 (br s, 1H), 7.39 (dd, *J* = 7.1, 7.6 Hz, 4H), 7.42 (tt, *J* = 1.7, 7.1 Hz, 2H), 7.66 (dd, *J* = 1.7, 7.6 Hz, 4H). *syn*-isomer

(detectable peaks): δ 1.05 (s, 9H), 3.80 (s, 3H), 4.20 (dd, $J = 1.4, 2.9$ Hz, 2H), 4.69 (dd, $J = 2.4, 5.8$ Hz, 1H), 4.78-4.80 (m, 1H), 5.80 (ddt, $J = 1.4, 5.8, 15.3$ Hz, 1H), 5.90 (dt, $J = 2.9, 15.3$ Hz, 1H), 7.25 (br s, 1H), 7.34-7.45 (m, 6H), 7.62-7.68 (m, 4H). ^{13}C NMR (CDCl_3) δ 19.2, 26.7, 52.9, 57.3, 63.1, 72.4, 115.6 (q, $J = 287.4$ Hz), 125.5, 127.7, 129.8, 133.3, 133.6, 135.4, 157.3 (q, $J = 38.1$ Hz), 168.8. *syn*-isomer (detectable peaks): δ 19.1, 26.7, 53.0, 56.5, 71.4, 126.2, 127.7, 129.7, 133.2, 135.4, 169.2. HPLC (Daicel Chiralpak AD (double), hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min) *anti*-isomer: $t_R = 26.1$ min (major), $t_R = 73.5$ min (minor). *syn*-isomer: $t_R = 27.8$ min (major), $t_R = 33.0$ min (minor). Anal. calcd for $\text{C}_{25}\text{H}_{30}\text{F}_3\text{NO}_5\text{Si}$: C 58.92, H 5.93, N 2.75; found: C 58.82, H 6.01, N 2.72. ESI-MS (m/z) 532 ($[\text{M}+\text{Na}]^+$).

6-*tert*-Butyldiphenylsiloxy-2-(trifluoroacetylamino)hex-4-ene-1,3-diol: ^1H NMR (CDCl_3) *anti*-isomer: δ 1.08 (s, 9H), 2.87 (br s, 1H), 2.93 (br s, 1H), 3.71 (dd, $J = 3.0, 11.3$ Hz, 1H), 3.91-3.96 (m, 1H), 3.98-4.00 (m, 1H), 4.26 (d, $J = 3.9$ Hz, 2H), 4.45 (br s, 1H), 5.83-5.95 (m, 2H), 7.30 (d, $J = 7.8$ Hz, 1H), 7.36-7.46 (m, 6H), 7.65-7.68 (m, 4H). *syn*-isomer (detectable peaks): δ 1.06 (s, 9H), 3.82-3.89 (m, 2H), 4.00-4.02 (m, 1H), 4.21 (d, $J = 2.4$ Hz, 2H), 4.55 (br s, 1H), 5.76-5.87 (m, 2H), 7.04 (d, $J = 8.5$ Hz, 1H). ^{13}C NMR (CDCl_3) *anti*-isomer: δ 19.2, 26.8, 54.0, 61.0, 63.4, 73.4, 115.8 (q, $J = 287.5$ Hz), 127.5, 127.7, 129.8, 132.5, 133.4, 135.4, 157.2 (q, $J = 37.2$ Hz). *syn*-isomer (detectable peaks): δ 19.1, 26.7, 54.3, 63.1, 63.3, 71.7, 127.7, 129.7, 132.3, 133.3, 157.6 (q, $J = 37.2$ Hz).

(4*S*,5*R*,1'*E*)-4-[3'-(*tert*-Butyldiphenylsiloxy)pent-1'-enyl]-2-(4''-methoxyphenyl)-5-trifluoroacetylamino-[1,3]dioxane (9): ^1H NMR (CDCl_3) δ 1.09 (s, 9H), 3.77 (dd, $J = 10.2, 10.9$ Hz, 1H), 3.82 (s, 3H), 4.09 (dddd, $J = 5.0, 9.4, 9.7, 10.2$ Hz, 1H), 4.24 (d, $J = 3.4$ Hz, 2H), 4.28 (dd, $J = 6.3, 9.7$ Hz, 1H), 4.39 (dd, $J = 5.0, 10.9$ Hz, 1H), 5.55 (s, 1H), 5.93 (dd, $J = 6.3, 15.5$ Hz, 1H), 5.99 (dt, $J = 3.4, 15.5$ Hz, 1H), 6.42 (br s, 1H), 6.93 (d, $J = 9.0$ Hz, 2H), 7.38-7.48 (m, 8H), 7.67-7.70 (m, 4H). ^{13}C NMR (CDCl_3) δ 19.1, 26.7, 47.7, 55.2, 63.1, 68.2, 79.8, 101.2, 113.6, 115.6 (q, $J = 287.8$ Hz), 124.4, 127.5, 127.7, 129.6, 129.7, 133.3, 134.7, 135.4, 157.1 (q, $J = 37.5$ Hz), 160.2.

(4*S*,5*R*,1'*E*)-4-(3'-Acetoxypent-1'-enyl)-2-(4''-methoxyphenyl)-5-trifluoroacetylamino-[1,3]dioxane (10): ^1H NMR (CD_3CN) δ 1.95 (s, 3H), 3.71-

3.77 (m, 1H), 3.74 (s, 3H), 3.91 (ddd, $J = 4.9, 9.9, 10.7$ Hz, 1H), 4.15 (dd, $J = 4.9, 10.7$ Hz, 1H), 4.29 (ddd, $J = 0.73, 6.8, 9.9$ Hz, 1H), 4.45-4.48 (m, 2H), 5.52 (s, 1H), 5.72 (ddt, $J = 1.3, 6.8, 15.6$ Hz, 1H), 5.88 (ddt, $J = 0.73, 5.6, 15.6$ Hz, 1H), 6.85-6.91 (m, 2H), 7.33-7.37 (m, 2H). ^{13}C NMR (CD_3CN) δ 20.8, 48.0, 55.8, 64.2, 68.6, 79.9, 101.6, 114.3, 116.8 (q, $J = 287.2$ Hz), 128.4, 129.8, 130.2, 131.2, 157.8 (q, $J = 37.1$ Hz), 161.0, 171.2.

(4S,5R,1'E)-2-(4''-Methoxyphenyl)-4-(pentadec-1'-enyl)-5-trifluoroacetylamino-[1,3]dioxane (11): ^1H NMR (CDCl_3) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.25-1.35 (m, 22H), 2.02-2.07 (m, 2H), 3.71 (dd, $J = 10.5, 10.7$ Hz, 1H), 3.80 (s, 3H), 4.03 (dddd, $J = 4.7, 7.3, 9.8, 10.5$ Hz, 1H), 4.10 (dd, $J = 7.4, 9.8$ Hz, 1H), 4.39 (dd, $J = 4.7, 10.7$ Hz, 1H), 5.49 (dd, $J = 7.4, 15.4$ Hz, 1H), 5.50 (s, 1H), 5.84 (dt, $J = 6.8, 15.4$ Hz, 1H), 6.12 (d, $J = 7.3$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (CDCl_3) δ 14.1, 22.7, 28.8, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.6, 31.9, 32.3, 47.4, 55.3, 68.4, 81.3, 101.4, 113.7, 115.6 (q, $J = 287.8$ Hz), 125.4, 127.5, 129.7, 138.2, 157.1 (q, $J = 37.2$ Hz), 160.2.

(4S,5R,1'E)-5-Amino-2-(4''-methoxyphenyl)-4-(pentadec-1'-enyl)-[1,3]dioxane: ^1H NMR (CDCl_3) δ 0.88 (t, $J = 6.7$ Hz, 3H), 1.25-1.40 (m, 22H), 2.09 (dt, $J = 6.8, 7.1$ Hz, 2H), 2.85 (ddd, $J = 4.9, 9.8, 10.7$ Hz, 1H), 3.50 (dd, $J = 10.7, 11.0$ Hz, 1H), 3.79 (s, 3H), 3.80 (dd, $J = 8.1, 9.8$ Hz, 1H), 4.27 (dd, $J = 4.9, 11.0$ Hz, 1H), 5.48 (s, 1H), 5.51 (dd, $J = 8.1, 15.4$ Hz, 1H), 5.88 (dt, $J = 6.8, 15.4$ Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (CDCl_3) δ 14.1, 22.7, 29.0, 29.2, 29.3, 29.4, 29.6, 29.6, 29.6, 29.6, 29.6, 31.9, 32.4, 48.5, 55.2, 72.4, 85.5, 101.0, 113.6, 126.8, 127.5, 130.6, 137.0, 159.9.

(2R,3S,4E)-2-Aminooctadec-4-ene-1,3-diol (L-erythro-Sphingosine): ^1H NMR (CDCl_3) δ 0.87 (t, $J = 6.6$ Hz, 3H), 1.25-1.37 (m, 22H), 2.05 (dt, $J = 6.6, 7.0$ Hz, 2H), 2.09 (br s, 4H), 2.80-2.89 (m, 1H), 3.60-3.69 (m, 2H), 4.03 (dd, $J = 6.1, 7.2$ Hz, 1H), 5.47 (dd, $J = 7.2, 15.2$ Hz, 1H), 5.75 (dt, $J = 7.0, 15.2$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 14.1, 22.7, 29.1, 29.2, 29.3, 29.5, 29.6, 29.6, 29.7, 29.7, 29.7, 31.9, 32.3, 56.1, 64.2, 75.6, 129.3, 134.8.

(2R,3S,4E)-2-Acetyl amino-1,3-diacetoxyoctadec-4-ene (1-O,2-N,3-O-Triacetyl-L-erythro-sphingosine): $[\alpha]_{\text{D}}^{26} +13.3$ (c 0.60, CHCl_3) (lit.¹⁰: $[\alpha]_{\text{D}}^{24} +12.1$ (CHCl_3),

lit.¹¹: $[\alpha]_{\text{D}}^{27} +11.9$ (c 0.85, CHCl_3). ^1H NMR (CDCl_3) δ 0.86 (t, $J = 6.7$ Hz, 3H), 1.24-1.35 (m, 22H), 1.97 (s, 3H), 1.99-2.04 (m, 2H), 2.05 (s, 3H), 2.06 (s, 3H), 4.03 (dd, $J = 3.9, 11.5$ Hz, 1H), 4.28 (dd, $J = 6.0, 11.5$ Hz, 1H), 4.39-4.45 (m, 1H), 5.26 (dd, $J = 6.3, 7.3$ Hz, 1H), 5.34 (dd, $J = 7.3, 15.4$ Hz, 1H), 5.71 (d, $J = 9.0$ Hz, 1H), 5.77 (dt, $J = 6.8, 15.4$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 14.1, 20.8, 21.1, 22.6, 23.3, 28.8, 29.1, 29.3, 29.4, 29.6, 29.6, 29.6, 29.6, 31.9, 32.2, 50.6, 62.6, 73.8, 124.1, 137.4, 169.6, 169.9, 170.9.

References

- (1) Yamashita, Y; Saito, S; Ishitani, H; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793.
- (2) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.
- (3) Yamashita, Y; Ishitani, H; Shimizu, H; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.
- (4) Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564.
- (5) Branch, C. L.; Pearson, M. J. *J. Chem. Soc., Perkin Trans 1* **1986**, 1077.
- (6) Quimpere, M.; Ruest, L.; Deslongchamps, P. *Synthesis* **1992**, 132.
- (7) Oesterle, T.; Simchen, G. *Liebigs Ann. Chem.* **1987**, 687.
- (8) Simchen, G.; Schulz, D.; Seethaler, T. *Synthesis* **1988**, 127.
- (9) Lago, M. A.; Samanen, J.; Elliott, J. D. *J. Org. Chem.* **1992**, *57*, 3493.
- (10) Shibuya, H.; Kawashima, K.; Ikeda, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 7205.
- (11) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 820.