# A Four-Step Diastereoselective Synthesis of D-*erythro*-Sphingosine by an Enantioselective Aldol Reaction Using a Titanium Enolate Derived from a Chiral Iminoglycinate

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Natural sphingosines[1] (the lipophilic portion of glycosphingolipids and ceramides) have the D-*erythro* (2*S*,3*R*) structure. Although a great deal of effort has been devoted to the synthesis of sphingosines,[2] enantioselective synthesis of *erythro*-sphingosines through an aldol condensation has not yet been accomplished. D-*erythro*-Sphingosines are usually obtained from sugars[3] in seven to ten steps, alkyl serinates[4] in four to six steps, through a Sharpless monoepoxidation of an enynol in seven steps[5] or through an aldol reaction but with inversion at carbon-3 in five steps.[6]

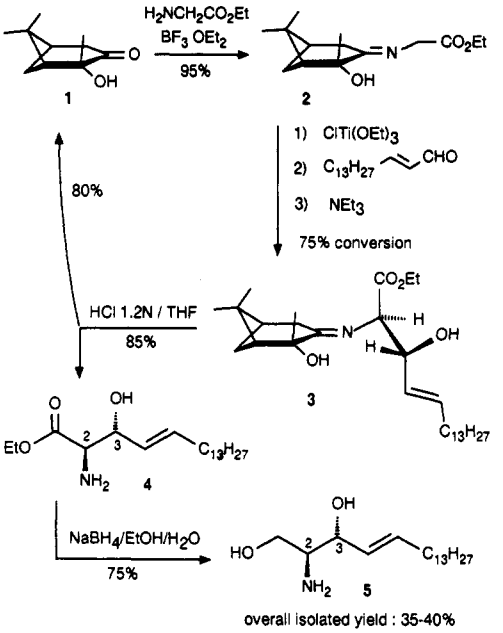
We report here a four-step *erythro*-selective and *enantio*-selective synthesis of sphingosine **5**, Scheme 1, based on an asymmetric aldol reaction using a titanium enolate directly generated from the chiral iminoglycinate **2** with $ClTi(OEt)_3/NEt_3$. In this synthesis the chiral auxiliary **1** is recovered and may, thus, be used again.

Titanium enolates are usually obtained by transmetalation of lithium enolates with $ClTi(O\text{-}i\text{-}Pr)_3$[7a,b] but the exchange is slow. High selectivity requires the use of an excess of $ClTi(O\text{-}i\text{-}Pr)_3$[7c] and low diastereoselectivity (70/30)[8] or threo selectivity[9] was obtained in similar reactions on glycinate derivatives.

We therefore decided to generate the titanium enolate directly, using $ClTi(OEt)_3/NEt_3$[10] instead of $TiCl_4/NEt_3$.[11] Only 1 equiv of the titanium reagent was used in an attempt to change the nature of the aggregate.

The iminoglycinate **2** was prepared according to a known procedure[12a–c] from (+)-(*R*,*R*,*R*)-hydroxypinanone **1**[13] and

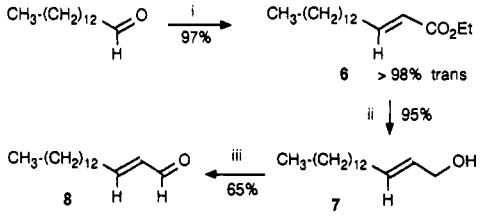
**Scheme 1**




overall isolated yield : 35-40%

the desired 2(*E*)-hexadecenal (**8**) in three steps and 60% overall yield from tetradecanal, Scheme 2. The crude product of the reaction showed, using 200-MHz $^1H$ NMR, only one diastereomer (~97%) of the desired compound **3** but as a mixture of ethyl and isopropyl esters[10] in a ~9/1 ratio. After separation from remaining starting materials **2** and **8** and hydrolysis, diastereomer **5** was obtained as a mixture of ethyl and isopropyl esters in about the same 9/1 ratio. Sodium borohydride reduction[14] then provided D-*erythro*-sphingosine **5** in 75% yield. The D-*erythro* structure is based on the known $[\alpha]_D$ and $^{13}C$ NMR of its triacetyl derivative.[4a,d,9,15]

**Scheme 2**




i : $(EtO)_2P(O)(CH_2CO_2Et)$ / NaH / THF, 0°C.
ii : DIBAL / THF, 0°C. iii : PCC / $CH_2Cl_2$, 0°C.

This is thus the first and short (four steps) *diastereo*- and *enantio*-selective synthesis of D-*erythro*-sphingosine, with recovery of the chiral auxiliary.

(1*R*,2*S*)-*erythro*-Chloramphenicol and (1*R*,2*R*)-allothreonine have also been obtained in good yields through this route.[16] It is worth noting that the readily available (−)-(*S*,*S*,*S*)-hydroxypinanone will provide the enantiomers of the above compounds.

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Although a *Z*-structure could be envisaged for the corresponding lithium enolate[12b,c] and besides the fact that it is known that the *E* Ti enolate of the "stabase"-protected glycine ethyl ester lead to the threo amino hydroxy ester,[7b,17] there is no evidence for a *Z*-structure in the case of the titanium enolate involved here (which was not obtained by Li–Ti exchange). The structure of this enolate is under study.

## Experimental Section

Reagent-grade MeOH, EtOH, $Et_2O$, and $CHCl_3$ from SDS were used without purification. THF was distilled under argon over Na/benzophenone prior to use. $CH_2Cl_2$ was distilled over $CaH_2$ and $NEt_3$ from KOH pellets; both were stored over molecular sieves. $Ti(OEt)_4$ was purchased from Aldrich and contains 15% of $Ti(O\text{-}i\text{-}Pr)_4$ as determined by 200-MHz $^1H$ NMR. $ClTi(OEt)_3$ was prepared from $Ti(OEt)_4$ and $CH_3COCl$ according to a known procedure.[18] (+)-(*R,R,R*)-Hydroxypinanone **1** was obtained from (−)-α-pinene[13] and ethyl iminoglycinate **2** by refluxing (+)-hydroxypinanone **1**, ethyl glycinate, and three drops of $BF_3$–$Et_2O$ in benzene according to a literature procedure.[12] Melting points are uncorrected and were taken on a Reichert microscope. IR spectra were recorded on a Perkin-Elmer 257. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC 200 and referenced to TMS. Flash chromatography was carried out using silica gel (230–400 mesh) from Merk. Microanalyses were performed in our department.

**Preparation of 2(*E*)-Hexadecenal (8). Synthesis of Ethyl 2-Hexadecenoate (6).** To a suspension of NaH (0.8 g, 33 mmol) in anhydrous THF (20 mL) was added dropwise and at 0 °C triethyl phosphonoacetate (5.3 mL, 27 mmol). After 0.5 h of stirring at 0 °C, tetradecanal (5.65 g, 27 mmol) was added in one fraction and the temperature was allowed to rise 25 °C under stirring. The workup was performed by pouring the mixture onto a saturated solution of NaCl (50 mL), and the new phase was extracted with $Et_2O$ (4 × 50 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, and concentrated under vacuum. After purification by column chromatography ($Et_2O$/hexane, 5/95), ethyl hexadecenoate (**6**) (7.27 g, 97%) was obtained and used for the next step. **Reduction to 2-Hexadecen-1-ol (7).** DIBAL-H (60 mL, 1 M in toluene, 2.4 equiv) was added dropwise at 0 °C to a solution of the above prepared ethyl hexadecenoate (7 g, 25 mmol) in anhydrous THF (20 mL), stirring was maintained at 0 °C, and the progression of the reaction was monitored by TLC. $Et_2O$ (30 mL) and a saturated solution of sodium tartrate (30 mL) were then successively added, and stirring was maintained until full separation of the two phases. The aqueous phase was extracted with $Et_2O$ (4 × 75 mL), and the joined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. After chromatography, 2-hexadecen-1-ol (**7**) (5.7 g, 24 mmol, 95%, $Et_2O$/hexane 1/1) was used for the last step. **Oxidation to (*E*)-Hexadecenal (8).** A solution of the above alcohol (5.7 g, 24 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise at 0 °C to a suspension of PCC (10.3 g, 48 mmol) in $CH_2Cl_2$ (50 mL). After 3 h at 0 °C, $Et_2O$ (30 mL) was added, the precipitate was filtered out and carefully rinsed with $Et_2O$, and the resulting solution was concentrated under vacuum. After chromatography, (2*E*)-hexadecenal (**8**) (3.7 g, 16 mmol, 65%) was isolated.

**6**: colorless oil. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.28; H, 12.04. $R_f$ = 0.24 ($Et_2O$/hexane, 5/95). IR (neat): 1720, 1650 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) δ: 0.87 (t, 3H, $CH_3$), 1.25 (br, 20H), 1.28 (t, 3H, $CH_3$); 1.44 (m, 2H, $CH_2$); 2.18 (qd, 2H, $CH_2$, $^3J$ = 6.5 Hz, $^4J$ = 1.5 Hz); 4.18 (q, 2H, $CH_2$), 5.80 (dt, 1H, $^3J$ = 15.5 Hz, $^4J$ = 1.5 Hz); 6.96 (dt, 1H, $^3J$ = 15.5 Hz, $^3J$ = 6.5 Hz). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ: 13.8 ($CH_3$), 14.0 ($CH_3$); 22.5 ($CH_2$), 27.8 ($CH_2$); 28.9–29.5 ($8CH_2$); 31.7 ($CH_2$); 31.9 ($CH_2$); 59.7 ($CH_2$ ester); 121.0 (CH); 148.9 (CH); 166.2 (C=O).

**7**: white wax; mp = 36–37 °C. Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 80.11; H, 13.39. $R_f$ = 0.31 ($Et_2O$/hexane, 1/1). $^1H$ NMR (200 MHz, $CDCl_3$) δ: 0.87 (t, 3H, $CH_3$); 1.25 (br, 22H); 2.03 (q, 2H, $CH_2$, $^3J$ = 6 Hz); 4.09 (d, 1H, $^3J$ = 5 Hz); 5.66 (m, 2H). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ: 14.1 ($CH_3$); 22.7 ($CH_2$), 29.1–29.7 ($9CH_2$); 31.9 ($CH_2$); 32.2 ($CH_2$), 63.9 ($CH_2$); 128.7 (CH); 133.7 (CH).

**8**: white wax. Anal. Calcd for $C_{16}H_{30}O$: C, 80.60; H, 12.68. Found: C, 80.81; H, 12.83. $R_f$ = 0.14 ($Et_2O$/hexane, 5/95). IR (KBr): 1700, 1675, 1625 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $CH_3$); 1.26 (br, 20H); 1.50 (m, 2H, $CH_2$); 2.35 (qd, 2H, $3J$ = 7 Hz, $^4J$ = 1.5 Hz); 6.1 (ddt, 1H, $^3J$ = 15.5 Hz, $^3J$ = 8 Hz, $^4J$ = 1.5 Hz); 6.85 (td, 1H, $^3J$ = 15.5 Hz, $^3J$ = 7 Hz); 9.5 (d, 1H, $^3J$ = 8 Hz). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ: 14.1 ($CH_3$), 22.6 ($CH_2$), 27.8 ($CH_2$), 29.1–29.6 ($8CH_2$); 31.8 ($CH_2$); 32.7 ($CH_2$); 132.9 (CH), 159.0 (CH); 194.0 (C=O).

**General Procedure for the Aldol Condensation.** To a solution of iminoglycinate **2** (2.53 g, 10 mmol) in $CH_2Cl_2$ (6 mL) were added, dropwise and at 0 °C, a solution of $ClTi(OEt)_3$ (2.18 g, 1 equiv) in $CH_2Cl_2$ (10 mL), a solution of 2(*E*)-hexadecenal (**8**) (2.38 g, 1.1 equiv) in $CH_2Cl_2$ (5 mL), and anhydrous triethylamine (2.8 mL, 2 equiv). After 4 h of stirring at 0 °C, workup was performed by pouring the mixture into a cold saturated solution of NaCl. The aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated under vacuum. The crude product, analyzed by NMR prior to purification, is a 20% **2**/20% 8/60% **3** mixture, indicating a 75% conversion. After chromatography, compound **3** (2.8 g) was isolated as a mixture of ethyl and isopropyl esters in a 9/1 ratio. The yield, taking into account the isopropyl ester present, was 60%. This 9/1 mixture was used without further purification for the last step because the isopropyl ester has the same *R,R,R,R* absolute configuration[19] as the ethyl ester.

**3**-(*R,R,R,R*)-(+): pale yellow oil, 9/1 mixture of ethyl and isopropyl esters. Anal. Calcd for the mixture [$0.9(C_{30}H_{53}NO_4)$ + $0.1(C_{31}H_{55}NO_4)$]: C, 73.32; H, 10.87; N, 2.84. Found: C, 73.19; H, 11.00; N, 2.73. $R_f$ = 0.34 ($Et_2O$/hexane, 7.3). $[\alpha]_D$ = +36 (*c* = 1, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): ethyl ester, δ 0.85 (t, 3H, $CH_3$); 0.88 (s, 3H, $CH_3$); 1.25 (br m, 25H, $CH_3$ + $11CH_2$); 1.33 (s, 3H, $CH_3$); 1.50 (s, 3H, $CH_3$); 1.52 (m, 1H, CH); 2.0 (m, 4H, 2CH + $CH_2C$=); 2.32 (m, 1H, CH); 2.52 (br, 2H, $CH_2$); 4.18 (m, 3H, $CH_2$ + CH); 4.55 (t, 1H, *J* = 7 Hz, CH); 5.45 (dd, A part of an ABX, 1H, $^3J$ = 15 Hz, $^3J$ = 7 Hz, CH=); 5.77 (dt, B part of ABX, 1H, $^3J$ = 15 Hz, $^3J$ = 6.5 Hz). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ: 14.1 ($CH_3$-18, $CH_3$ ester); 22.7 ($CH_2$-17); 22.8 ($CH_3$); 27.2 ($CH_3$); 27.8 ($CH_2$); 28.3 ($CH_3$); 29.0–29.7 ($CH_2$-7 to 15); 31.9 ($CH_2$); 32.3 ($CH_2$); 34.2 ($CH_2$); 38.4 (CH); 38.6 (C); 50.0 (CH); 61.1 ($CH_2$ ester); 67.1 (CH); 73.7 (CH); 76.7 (C); 127.8 (CH); 134.7 (CH); 170.3 (C=N); 180.5 (C=O).

**3** (isopropyl ester). $^1H$ NMR: the only signal which does not overlap with the major ethyl ester is 5.05 (sept, 1H, $CH(Me)_2$, $^3J$ = 6.5 Hz).

**Hydrolysis.** The above mixture of imino ester **3** (1.46 g, 2.96 mmol), 1.2 N HCl (20 mL), and THF (5 mL) was stirred at 25 °C for 3 days. After concentration under vacuum the residue was purified by chromatography ($Et_2O$/MeOH, 96/4). Hydroxypinanone **1** (0.35 g, 2.08 mmol) was recovered and 2-amino-3-hydroxy-4-octadecenoate **4** was isolated as a mixture of ethyl and isopropyl esters in the same 9/1 ratio (0.832 g).

**4** (ethyl ester)-(2*R*,3*R*)-(+): $R_f$ = 0.25 ($Et_2O$/MeOH/$NH_4OH$ 33%, 100/2/1). Anal. Calcd for $C_{24}H_{39}NO_3$: C, 70.33; H, 11.51; N, 4.10. Found: C, 70.34; H, 11.57; N, 4.13. Mp = 51–52 °C. $[\alpha]_D$ = +11 (*c* = 1, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $CH_3$); 1.25 (br, 22H); 1.29 (t, 3H, $CH_3$ ester); 2.0 (q, 2H, $^3J$ = 6.5 Hz, $CH_2$-6); 3.62 (d, 1H, $^3J$ = 5 Hz, CH-2); 4.20 (q, 2H, $^3J$ = 7 Hz, $CH_2O$); 4.35 (t, 1H, $^3J$ = 5 Hz, CH-3); 5.36 (dd, 1H, $^3J$ = 15 Hz, $^3J$ = 5 Hz, CH-4); 4.68 (dt, 1H, $^3J$ = 15 Hz, $^3J$ = 6.5 Hz, CH-5). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ: 14.0 (Me-18); 14.2 (Me ester); 22.6 ($CH_2$-17); 29.1–29.6 ($CH_2$-7 to 15); 32.3 ($CH_2$-6 and $CH_2$-16); 58.5 (CHN); 61.1 ($CH_2$ ester); 73.0 (CHO); 126.9 (CH); 134.7 (CH); 173.5 (C=O).

**Reduction.** To a solution of compound **4** (0.204 g, 0.6 mmol) in a 75/25 mixture of EtOH/$H_2O$ (5 mL) cooled at 0 °C was added in one fraction $NaBH_4$ (0.090 g). After stirring at 0 °C for 4 days, the mixture was extracted with $CH_2Cl_2$ (4 × 5 mL). The combined

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(19) Isolated in high yield when $ClTi(O\text{-}i\text{-}Pr)_3$ was used, this iminoester **3(iPr)** lead to the sphingosine **5** having the same spectral characteristics.

organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. The crude compound (0.140 g) was purified by chromatography ($CHCl_3$/MeOH/$H_2O$, 13/6/1) and afforded D-*erythro*-sphingosine (0.135 g, 75%).

5-(2*S*,3*R*)-(−): mp = 76–77 °C (lit. mp 72–75 °C[4b] and 75–80 °C[9]). $R_f$ = 0.45 ($CHCl_3$/MeOH/$H_2O$, 65/30/5). $[\alpha]_D$ = −7 (*c* = 0.8, $CHCl_3$). $^1H$ NMR (200 MHz, $CD_3OD$) δ: 0.89 (t, 3H, $CH_3$-18); 1.28 (br, 22H); 2.07 (q, 2H, $^3J$ = 6 Hz, $CH_2$-6); 2.76 (td, 1H, $^3J$ = 6.5 Hz, $^3J$ = 4 Hz, CH-2); 3.48 (dd, 1H, $^3J$ = 11 Hz, $^3J$ = 6.5 Hz, $CH_2$-1); 3.66 (dd, 1H, $^3J$ = 11 Hz, $^3J$ = 4 Hz, $CH_2$-1); 3.97 (t, 1H, $^3J$ = 6.5 Hz, CH-3); 5.48 (dd, 1H, $^3J$ = 15 Hz, $^3J$ = 6.5 Hz, CH-4); 5.70 (dt, 1H, $^3J$ = 15 Hz, $^3J$ = 6 Hz, CH-5). $^{13}C$ NMR (50 MHz, $CD_3OD$) δ: 14.5 (Me-18); 23.8 ($CH_2$-17); 30.4–30.9 ($CH_2$-7 to 15); 33.2 and 33.5 ($CH_2$-6, $CH_2$-16); 58.1 (CHN); 64.2 ($CH_2$-1); 75.0 (CHO); 130.8 (CH); 135.4 (CH).

The triacetylated sphingosine was prepared as in ref 9. Anal. Calcd for $C_{24}H_{43}NO_5$: C, 67.73; H, 10.18; N, 3.29. Found: C, 67.50; H, 10.08; N, 3.20. Mp = 102–103 °C (lit. mp 104–105 °C[4d] and 101 °C[5]). $R_f$ = 0.18 (AcOEt/hexane, 60/40). The $^1H$ and $^{13}C$ NMR spectra are identical to those of the literature (refs 4a,d and 15).

# *Additions and Corrections*

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**Neal O. Brace.** Amides as Nucleophiles: Reaction of Alkyl Halides with Amides or with Amides and Water. A New Look at an Old Reaction.

Page 1804. **Caution!** Toxicity of **1-iodo-2-(*F*-hexyl)ethane.** The author has been informed by responsible persons at Hoechst Aktiengeschellschaft and at E. I. du Pont de Nemours and Co. that toxicity measurements of **1-iodo-2-(*F*-hexyl)ethane (1)** are as follows. *Acute Oral* $Ld_{50}$ (female rats, in mg/kg): 3868. *Acute Vapor Inhalation* (not for dusts or aerosols) female rats, 4 h, *LC 50*: >1182 ppm; 4 h, aerosol inhalation: *LC 50*, 537 ppm. These levels of response are considered to show only slight or borderline toxicity. Samples of **1** used in the published paper contained only traces of the lower homologue, **2-(*F*-ethyl)-1-iodoethane**, which has high toxicity ($Ld_{50}$ 100–500 ppm/vol; same conditions as for **1**); contact with this homologue must be carefully avoided in any case.

**Stephen Hanessian,* Arthur Gomtsyan, Andrew Payne, Yolande Hervé, and Serge Beaudoin.** Asymmetric Conjugate Additions of Chiral Allyl- and Crotylphosponamide Anions to α,β-Unsaturated Carbonyl Compounds: Highly Stereocontrolled Access to Vicinally Substituted Carbon Centers and Chemically Asymmetrized Chirons.

Page 5033, column 2, line 7. *si* face should be *re* face.

Page 5034, Figure 1. The designations *si* face and *re* face should be interchanged.

Page 5034, ref 14, should read *Chim. Script.* **1985**, *25*, 5.

**Jilles J. H. Edema, Jan Buter, Franck S. Schoonbeek, Auke Meetsma, Fre van Bolhuis, and Richard M. Kellogg*.** Cesium Dithiolate Based Syntheses of Keto-Functionalized Thio-Crown Ethers Employing the Novel Building Block 1,3-Dimercaptoacetone. Molecular Structures of 2,5,9,12-Tetrathia-7-oxo-(13)-*m*-benzenophane and 1,4,7,10,13-Pentathiacyclohexadecan-15-one.

Pages 5625 and 5626. Sulfur atoms should be inserted at position 3 in the structure of 1,5-di-X-pentane in eq 2 and at position 3 in **10**, at positions 3 and 6 in **11**, at positions 3 and 7 in **12**, at positions 4 and 9 in **13**, at the two benzylic carbons in **14**, and at positions 3, 6, and 9 in **15** (Scheme II).

**Iwao Hachiya and Shu Kobayashi*.** Aqueous Reactions with a Lewis Acid and an Organometallic Reagent. The Scandium Trifluoromethanesulfonate-Catalyzed Allylation Reaction of Carbonyl Compounds with Tetraallyltin.

Page 6959, Table I. References for entry 9 should read 81[b,c], 89[b,d], and 93[b,e]; entry 10 should read 89[b,f]; and entry 11 should read 88[b,f].

References *c–f* should read as follows: [c] Syn/anti = 72/28. [d] *Syn*/anti = 73/27. [e] *Syn*/anti = 74/26. [f] *Diastereomer* ratio = 50/50.