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A facile stereodivergent synthesis of *threo*- and *erythro*-*N*,*N*-dibenzyl sphingosines from (*S*)-*N*,*N*-dibenzyl-*O*-TBDMS-serinal

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Abstract

The (L)-*threo*-*N*,*N*-dibenzyl sphingosine was prepared in two steps from the serinal derivative **1** by diastereoselective alkenylation with pentadec-1-enyl(ethyl)zinc and deblocking. (D)-*erythro*-*N*,*N*-Dibenzyl sphingosine was also prepared in two steps from **1** by a highly diastereoselective alkynylation with pentadecynyl magnesium bromide and subsequent stereoselective LAH reduction.

1. Introduction

The fact that sphingosines or their derivatives exert important biological activities[1] has attracted a lot of synthetic attention.[2] Some of the most interesting methods start from serine because this α-amino acid bears a part of the chiral moiety present in the final product.[3] Starting from these derivatives two stereochemical aspects must be solved: the implantation of the *trans* double bond[4] and the control of the stereochemistry at C-3.[5]

Our recent report on the stereoselective *syn*-addition of diethylzinc to α-*N*,*N*-dibenzylamino-aldehydes[6] prompted us to prepare the (*S*)-serinal derivative **1** as a starting chiron capable of giving different stereoisomers by tuning the nature of the organometallic used as the nucleophile,[7] and now we report here on the transformation of **1** into both *threo*- and *erythro*-*N*,*N*-dibenzyl sphingosines *syn*-**3** and *anti*-**3** in two steps.

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2. Results and discussion

(*S*)-*N*,*N*-Dibenzyl-*O*-TBDMS serinal **1** was prepared from (L)-*N*,*N*-dibenzyl methyl serinate in 74% overall yield. Protection of the alcohol as TBDMS ether followed by reduction of the ester with $NaBH_4$–LiCl in THF–ethanol gave the corresponding monoprotected aminodiol which was submitted to Swern oxidation affording the serinal derivative **1**.[7]

The synthesis of (2*S*,3*S*,4*E*)-2-(*N*,*N*-dibenzyl)-4-octadecene-1,3-diol (L-*threo*-sphingosine) *syn*-**3** was achieved by *syn*-addition of pentadec-1-enyl(ethyl)zinc to **1** (Scheme 1). The mixed zinc derivative was prepared as previously described[8] by transmetallation with diethylzinc of the hydroboration product of 1-pentadecyne with dicyclohexylborane. The reaction of **1** with two equivalents of the zinc derivative in toluene–heptane at 0°C for 4 h gave the protected sphingosines **2** in 57% yield as a mixture (4:1) of epimers where the major diastereomer was *syn*-**2** as demonstrated by ^{1}H NMR analysis after separation of the mixture by flash chromatography (silica gel, toluene:hexane=3:1). The final *threo*-*N*,*N*-dibenzyl sphingosine (*syn*-**3**) was obtained in 78% yield from *syn*-**2** by treatment with TBAF in THF at 0°C for 12 h.

An alternative method allowed the preparation of (D)-*erythro*-*N*,*N*-dibenzyl sphingosine (*anti*-**3**) from the serinal derivative **1**. The reaction of **1** with pentadecynyl magnesium bromide[9] at 0°C for 45 min in diethyl ether yielded *anti*-**4** as a single diastereomer in 82% yield after purification by flash chromatography.

Treatment of *anti*-**4** with LAH in THF at 0°C quantitatively removed the TBDMS protecting group leading to the propargyl amino diol *anti*-**5** in 80% yield after purification. However, when a mixture of *anti*-**4** and LAH was refluxed in THF for 6 h, a concomitant deprotection and reduction of the triple bond led to a mixture of (D)-*erythro*-*N*,*N*-dibenzyl sphingosine (*anti*-**3** and *anti*-**5**). Separation by flash chromatography allowed *anti*-**3** to be isolated in 62% yield and *anti*-**5** to be recovered in 17% yield, which was available for recycling.[3c]

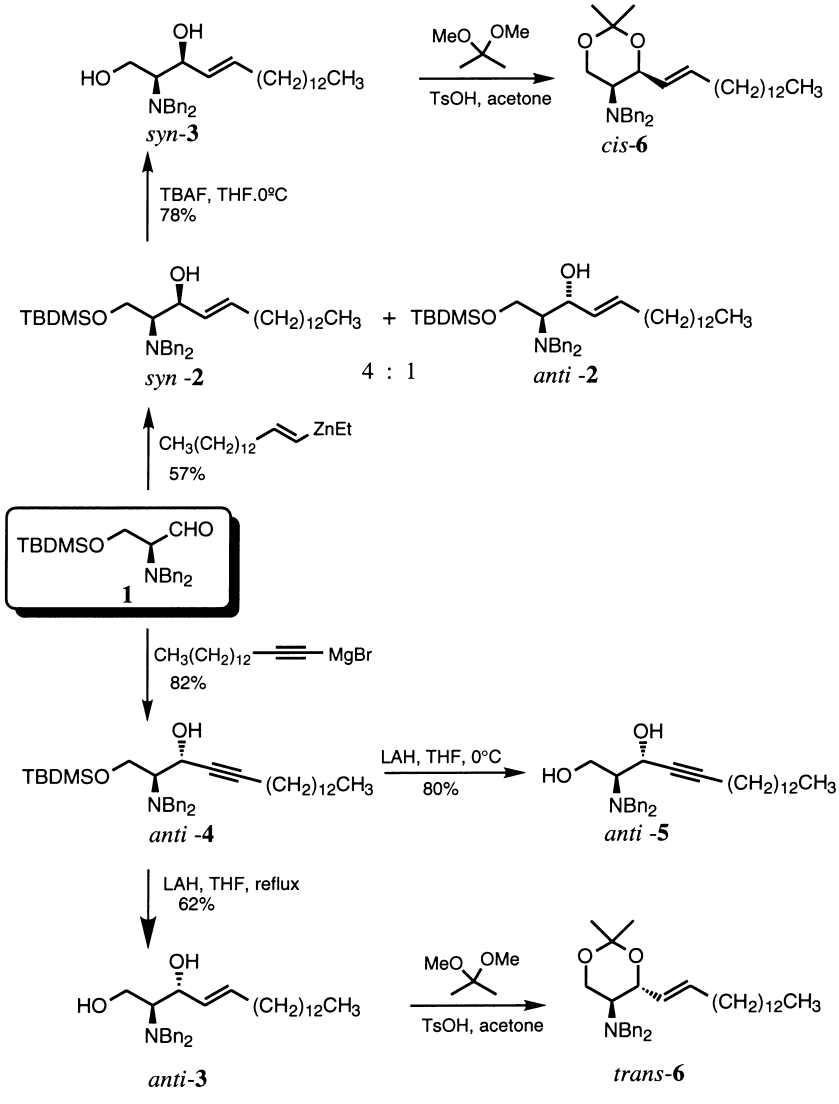
The stereochemistry of the final products, *syn*-**3** and *anti*-**3**, was determined by ^{1}H NMR spectroscopy. To this end, *syn*-**3** and *anti*-**3** were transformed into the dioxane derivatives *cis*-**6** and *trans*-**6** respectively by reaction with 2,2-dimethoxypropane (acetone, cat. TsOH, 8 h, reflux). The coupling constant[10] (^{1,3}J=4.1 Hz) between H-4 (m, δ=4.43) and H-5 (m, δ=2.39) in *cis*-**6** showed a *cis* relationship of these protons, and consequently for the substituents at C-4 and C-5. However, the *trans* relationship for H-4 (dd, δ=4.36) and H-5 (m, δ=2.82) was deduced from their coupling constant[10] (^{1,3}J=9.8 Hz) in *trans*-**6**.

The synthesis of *N*,*N*-dibenzyl-sphingosines presented here has several advantages. The stereochemistry at C-2 is introduced directly from L-serine. This stereocenter is then used to induce the stereochemistry at C-3. All four stereoisomeric *N*,*N*-dibenzyl sphingosines can be prepared in two steps and high yield by a single synthetic strategy depending only on the choice of starting amino aldehyde (D or L) and the alkylating agent.

3. Experimental

3.1. General

The reactions were carried out in oven-dried glassware, under an argon atmosphere, and using anhydrous solvents. Diethylzinc, as a 1 M solution in heptane, and borane–methyl sulfide complex were purchased from Aldrich. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were registered on a Bruker AC 300 or Bruker AMX 300, using TMS as the internal standard. IR spectra were recorded on



Scheme 1.

a Philips PU 9706 spectrometer, as a film or by KBr dispersion. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1 dm cell.

3.2. *Reaction of **1** with pentadec-1-enyl(ethyl)zinc*

Cyclohexene (0.41 ml, 4 mmol) was added under Ar at 0°C to a stirred 1 M solution of borane–methyl sulfide complex (0.20 ml, 2 mmol) in toluene (2 ml). After 3 h at 0°C, 1-pentadecyne (417 mg, 0.53 ml, 2 mmol) was added, and the mixture was stirred at r.t. for 1 h. Then, the solution was cooled to −78°C and Et_2Zn 1 M solution in heptane (2.1 ml, 2.1 mmol) was added to it. The mixture was then placed in an ice-bath and the chiral aldehyde **1** (383 mg, 1 mmol) in toluene (4 ml) was added. The mixture was stirred for 4 h, after which it was treated with saturated aq. NH_4Cl solution (30 ml) to quench the reaction. The mixture was then extracted with ether (2×20 ml) and the combined extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by flash-

chromatography (silica gel, toluene:hexane=3:1) afforded *syn*-**2** (274 mg, 0.46 mmol; 46%) and *anti*-**2** (66 mg, 0.11 mmol; 11%).

*3.3. (2S,3S,4E)-2-(*N,N-*Dibenzylamino)-1-*O-*(*tert-*butyldimethylsilyl)-4-octadecene-1,3-diol (*syn-***2***)*

Colorless oil. $[\alpha]_D^{23}$=+45.4 (c 1.15, $CHCl_3$). IR (film): 3400, 2910, 1450, 1250, 1090, 970, 835, 750, 700 cm^{-1}. ^1H NMR δ: 0.09 and 0.11 (2s, 6H); 0.88 (t, 3H, J=7.0 Hz); 0.96 (s, 9H); 1.25 (br s, 22H); 1.98 (m, 2H); 2.63 (m, 1H); 3.68 (d, 2H, J=13.2 Hz); 3.78 (dd, 1H, J_1=11.2 Hz, J_2=6.8 Hz); 3.86 (dd, 1H, J_1=11.2 Hz, J_2=3.1 Hz); 3.97 (m, 1H); 4.00 (d, 2H, J=13.2 Hz); 4.35 (br s, 1H); 5.18 (dd, 1H, J_1=15.3 Hz, J_2=8.0 Hz); 5.68 (dt, 1H, J_1=15.3 Hz, J_2=6.8 Hz); 7.20–7.40 (m, 10H). ^{13}C NMR δ: −5.7; −5.6; 14.11; 8.1; 22.7; 25.9; 29.1; 29.2; 29.3; 29.5; 29.6; 29.7; 31.9; 32.3; 54.5; 59.6; 63.3; 68.6; 127.1; 128.4; 129.1; 129.9; 135.3; 139.2.

*3.4. (2S,3R,4E)-2-(*N,N-*Dibenzylamino)-1-*O-*(*tert-*butyldimethylsilyl)-4-octadecene-1,3-diol (*anti-***2***)*

Colorless oil. $[\alpha]_D^{23}$=−5.8 (c 0.65, $CHCl_3$). IR (film): 3400, 2910, 2840, 1450, 1250, 1070, 830, 740, 690 cm^{-1}. ^1H NMR δ: 0.09 and 0.11 (2s, 6H); 0.88 (t, 3H, J=7.0 Hz); 0.92 (s, 9H); 1.25 (br s, 22H); 2.05 (m, 2H); 2.85 (m, 1H); 3.66 (d, 2H, J=13.6 Hz); 3.88 (d, 2H, J=13.6 Hz); 3.90 (dd, 1H, J_1=10.4 Hz, J_2=6.1 Hz); 4.00 (dd, 1H, J_1=10.4 Hz, J_2=5.8 Hz); 4.26 (m, 1H); 5.48 (dd, 1H, J_1=15.3 Hz, J_2=6.8 Hz); 5.72 (dt, 1H, J_1=15.3 Hz, J_2=6.6 Hz); 7.20–7.40 (m, 10H). ^{13}C NMR δ: −5.6; 14.1; 18.1; 22.7; 25.9; 27.5; 29.2; 29.4; 29.7; 31.9; 32.4; 55.3; 61.7; 72.3; 127.0; 128.2; 128.9; 131.3; 132.4; 140.0. MS (m/z, %): 593.75 (M^+, 0.63), 430 (33), 354 (100), 262 (15), 222 (17), 181 (34), 132 (29), 91 (77).

*3.5. (2S,3S,4E)-2-(*N,N-*Dibenzylamino)-4-octadecene-1,3-diol (*syn-***3***)*

Tetrabutylammonium fluoride (142 mg, 0.45 mmol) in THF (0.5 ml) was slowly added to a solution of *syn*-**2** (178 mg, 0.3 mmol) in THF (3 ml) at 0°C. The mixture was stirred overnight at 0°C, and the reaction was quenched by the addition of water (3 ml). The aqueous phase was extracted with ether (3×10 ml), and the combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and flash-chromatographed (ethyl acetate:hexane=1:2) to yield *syn*-**3** (112 mg, 0.23 mmol; 78%) as a pure compound.

Colorless solid, m.p. 60–61°C (from hexane). $[\alpha]_D^{23}$=+19.4 (c 1, $CHCl_3$). IR (film): 3370, 2900, 2830, 1440, 955, 750, 690 cm^{-1}. ^1H NMR δ: 0.88 (t, 3H, J=7.0 Hz); 1.24 (br s, 22H); 1.99 (m, 2H); 2.73 (m, 1H); 3.48 (br s, 2H); 3.70 (m, 2H); 3.72 (d, 2H, J=13.1 Hz); 3.95 (d, 2H, J=13.1 Hz); 4.07 (m, 1H); 5.30 (dd, 1H, J_1=15.3 Hz, J_2=8.1 Hz); 5.73 (dt, 1H, J_1=15.3 Hz, J_2=6.8 Hz); 7.20–7.35 (m, 10H). ^{13}C NMR δ: 14.1; 22.6; 29.0; 29.2; 29.3; 29.4; 29.5; 29.6; 31.9; 32.2; 54.2; 59.2; 63.2; 71.0; 127.2; 128.4; 129.2; 130.2; 135.4; 139.0. MS (m/z, %): 479.75 (M^+, 0.79), 240 (100), 181 (43), 148 (14), 91 (80), 70 (20). Anal. calcd for $C_{32}H_{49}NO_2$: C, 80.11; H, 10.29; N, 2.92. Found: C, 80.06; H, 10.18; N, 3.25.

3.6. Reaction of ***1*** *with pentadec-1-ynyl magnesium bromide*

1-Pentadecyne (375 mg, 1.8 mmol) was dissolved in 2 ml of ether and added to a previously prepared solution of 1 M EtMgBr in ether (2 ml, 2 mmol) after which the solution was refluxed for 2.5 h. Then, the reagent was placed in an ice-bath and aminoaldehyde **1** (517 mg, 1.35 mmol) in ether (6 ml) was added dropwise. After 45 min at 0°C, the reaction was complete and was quenched with saturated NH_4Cl solution (10 ml). The mixture was extracted with ether (2×10 ml), the combined organic layers were

washed with brine, dried over anhydrous Na_2SO_4 and the solvents evaporated under vacuum. After flash-chromatography (silica gel, hexane:ethyl acetate=15:1) *anti*-**4** (657 mg, 1.11 mmol; 82%) was obtained as a pure compound.

*3.7. (2*S,*3*R*)-2-(*N,N-*Dibenzylamino)-1-*O-*(*tert-*butyldimethylsilyl)-4-octadecyne-1,3-diol (*anti-***4***)*

Colorless oil. $[\alpha]_D^{23}$=+5.3 (c 1.1, $CHCl_3$). IR (film): 3420, 2920, 2840, 2220 (weak), 1450, 1250, 1090, 830, 770, 740, 690 cm^{-1}. ^1H NMR δ: 0.11 and 0.12 (2s, 6H); 0.88 (t, 3H, J=6.9 Hz); 0.95 (s, 9H); 1.25 (br s, 20H); 1.43 (m, 2H); 2.17 (td, 2H, J_1=6.9 Hz, J_2=2.0 Hz); 3.04 (m, 1H); 3.68 (d, 2H, J=13.1 Hz); 3.83 (dd, 1H, J_1=10.4 Hz, J_2=6.4 Hz); 3.90 (m, 1H); 4.11 (dd, 1H, J_1=10.4 Hz, J_2=6.9 Hz); 4.20 (d, 2H, J=13.1 Hz); 4.35 (brs, 1H); 7.20–7.35 (m, 10H). ^{13}C NMR δ: −5.51; 14.1; 18.1; 18.8; 22.7; 25.9; 28.5; 28.9; 29.1; 29.3; 29.5; 29.6; 31.9; 55.3; 60.2; 61.3; 80.0; 86.6; 127.1; 128.3; 129.2; 139.6. MS (m/z, %): 591.30 (M^+, 0.09), 416 (7), 354 (100), 91 (45). Anal. calcd for $C_{38}H_{61}NO_2Si$: C, 77.10; H, 10.39; N, 2.37. Found: C, 76.54; H, 10.18; N, 2.58.

3.8. LAH reduction of anti-***4***

To a stirred solution of 93 mg (2.45 mmol, 3.5 equiv.) of $LiAlH_4$ in 6 ml of THF at 0°C was added 415 mg (0.7 mmol, 1 equiv.) of *anti*-**4** in 4 ml of THF. After refluxing for 6 h, the reaction was cooled and quenched with 0.1 ml of H_2O, 0.1 ml of 15% NaOH and 0.3 ml of H_2O. The solids were removed by filtration and washed with ether. The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to yield 334 mg of crude product (a 77:23 mixture of *anti*-**3** and *anti*-**5** by ^1H NMR analysis). Flash-chromatography (silica gel, hexane:ethyl acetate=4:1) gave 206 mg of *anti*-**3** (62%) and 53 mg of *anti*-**5** (17%).

*3.9. (2*S,*3*R*)-2-(*N,N-*Dibenzylamino)-4-octadecyne-1,3-diol (*anti-***5***)*

Colorless oil. $[\alpha]_D^{23}$=−38.1 (c 1, $CHCl_3$). IR (film): 3350, 2890, 2830, 2220, 1450, 1020, 900, 730, 690 cm^{-1}. ^1H NMR δ: 0.89 (t, 3H, J=7.0 Hz); 1.25 (m, 20H); 1.48 (m, 2H); 2.22 (td, 2H, J_1=7.1 Hz, J_2=2.0 Hz); 3.04 (m, 1H); 3.79 (d, 2H, J=13.3 Hz); 3.85 (dd, 1H, J_1=11.0 Hz, J_2=6.0 Hz); 3.94 (dd, 1H, J_1=11.0 Hz, J_2=7.7 Hz); 4.02 (d, 2H, J=13.3 Hz); 4.52 (dt, 1H, J_1=6.0 Hz, J_2=2.0 Hz); 7.20–7.40 (m, 10H). ^{13}C NMR δ: 14.1; 18.8; 22.6; 28.5; 29.0; 29.1; 29.3; 29.5; 29.6; 31.9; 54.6; 59.6; 60.6; 62.0; 79.9; 87.4; 127.2; 128.4; 129.1; 139.2. MS (m/z, %): 477.30 (M^+, 0.50), 446 (2), 282 (2), 240 (100), 181 (6), 91 (99).

*3.10. (2*S,*3*R,*4*E*)-2-(*N,N-*Dibenzylamino)-4-octadecene-1,3-diol (*anti-***3***)*

Colorless oil. $[\alpha]_D^{23}$=−47.0 (c 1.1, $CHCl_3$). IR (film): 3360, 2920, 2850, 1450, 1025, 970, 745, 695 cm^{-1}. ^1H NMR δ: 0.88 (t, 3H, J=6.9 Hz); 1.26 (m, 22H); 2.50 (br s, 2H); 2.79 (m, 1H); 3.71 (d, 2H, J=13.5 Hz); 3.76 (m, 1H); 3.78 (d, 2H, J=13.5 Hz); 3.87 (dd, 1H, J_1=11.0 Hz, J_2=7.0 Hz); 4.37 (t, 1H, J=6.8 Hz); 5.48 (dd, 1H, J_1=15.4 Hz, J_2=7.2 Hz); 5.71 (dt, 1H, J_1=15.4 Hz, J_2=6.6 Hz); 7.20–7.40 (m, 10H). ^{13}C NMR δ: 29.1; 29.3; 29.5; 29.7; 31.9; 32.3; 54.4; 59.2; 62.3; 72.3; 127.1; 128.3; 128.9; 131.8 (C-5); 133.2; 139.5.

*3.11. (2*S,*3*S,*4*E*)-2-(*N,N-*Dibenzylamino)-1,3-*O*-isopropylidene-4-octadecene-1,3-diol (*cis-**6**)*

Colorless oil. ^{1}H NMR δ: 0.81 (t, 3H, J=6.2 Hz); 1.19 (m, 22H); 1.35 (s, 3H); 1.38 (s, 3H); 2.11 (m, 2H); 2.39 (m, 1H); 3.55 (d, 2H, J=14.4 Hz); 3.85 (dd, 1H, J_1=12.8 Hz, J_2=3.7 Hz); 4.22 (m, 3H); 4.43 (m, 1H); 5.61 (dt, 1H, J_1=15.5 Hz, J_2=6.5 Hz); 5.83 (dd, 1H, J=15.5 Hz, J=6.4 Hz); 7.10–7.40 (m, 10H).

*3.12. (2*S,*3*R,*4*E*)-2-(*N,N-*Dibenzylamino)-1,3-*O*-isopropylidene-4-octadecene-1,3-diol (*trans-**6**)*

Colorless oil. ^{1}H NMR δ: 0.89 (t, 3H, J=6.9 Hz); 1.28 (m, 22H); 1.35 (s, 3H); 1.46 (s, 3H); 2.15 (m, 2H); 2.82 (m, 1H); 3.64 (d, 2H, J=13.9 Hz); 3.86 (dd, 1H, J_1=11.8 Hz, J_2=5.7 Hz); 3.89 (d, 2H, J=13.9 Hz); 3.96 (dd, 1H, J_1=11.8 Hz, J_2=8.3 Hz); 4.36 (dd, 1H, J_1=9.8 Hz, J_2=7.8 Hz); 5.41 (dd, 1H, J_1=15.4 Hz, J_2=7.8 Hz); 5.87 (dt, 1H, J_1=15.4 Hz, J_2=6.6 Hz); 7.20–7.40 (m, 10H).

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