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Highly diastereoselective synthesis of two analogues of dihydrosphingosine

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Abstract

Diastereomeric analogues **8** and **9** of dihydrosphingosine **2** with a shortened alkyl chain were obtained with high diastereoselectivity via addition of *n*-hexyl magnesium bromide or dihexylzinc to a chiral aldehyde **3**, respectively. These compounds are precursors of new potentially hydrosoluble analogues of glycosphingolipides. © 1998 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

Sphingosine **1** and sphinganine (dihydrosphingosine) **2** emerged as important precursors for the synthesis of naturally occuring biological compounds such as cerebrosides or gangliosides.[1] Kitagawa et al. reported the ring opening of chiral epoxides with azide as the key step in an approach to **1**.[2] Other methods are based on the addition of chiral glycinate derivatives to an aldehyde,[3] or on the use of enantiopure starting materials like sugars.[4] Nevertheless, the most used methods reported so far are diastereoselective additions of alkynyl, alkenyl or alkyl nucleophiles centered on lithium,[5,6] magnesium,[6] or zinc[7] to chiral aldehyde **3**,[8] deriving from L-serine (Scheme 1). In our current research project, we were interested in preparing a new class of hydrosoluble glycosphingolipid analogues deriving from (2*S*,3*R*)-dihydrosphingosine **2**. One possible way to increase the hydrosolubility of such compounds without introducing new functional groups consists of shortening the long alkyl chain of natural **2**.

In this paper, we report the synthesis of two diastereomeric analogues of dihydrosphingosine, **8** and **9**, via the highly diastereoselective addition of *n*-hexylmetal derivatives to aldehyde **3**. Various reagents and experimental conditions were examined (Table 1).

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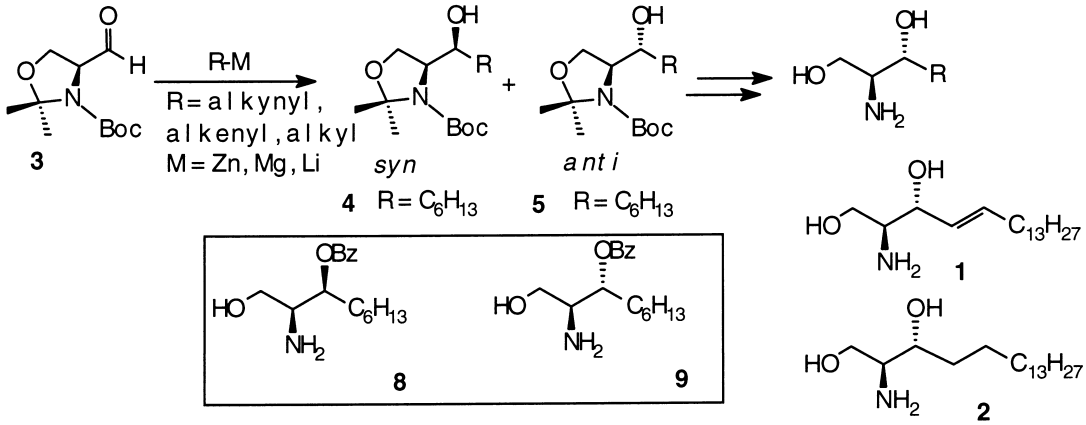


Scheme 1.

Table 1
Addition of *n*-hexylmetal reagents to aldehyde **3**

Entry	Reagent	Temperature (°C)[a]	Solvent	Additive (1 equiv.)	**4/5**[b]	Yield (%)
1	$(C_6H_{13})_2Zn$	25	toluene[c]	-	9:91	67
2	$(C_6H_{13})_2Zn$	0	toluene[c]	$ZnCl_2$	83:17	79
3	$C_6H_{13}MgBr$	25	Et_2O	-	95:5	90
4	$C_6H_{13}MgBr$	25	Et_2O	$ZnCl_2$	93:7	63
5	$C_6H_{13}MgBr$	25	THF	-	92:8	79
6	$C_6H_{13}MgBr$	25	THF	HMPA	90:10	73
7	$C_6H_{13}Li$	25	THF	-	0:100	23

[a] *n*-Hexylmetal reagents were added at -78 °C. [b] Because of overlaps of the ^1H NMR signals of **4** and **5**, the ratio could not be determined on the crude reaction mixture. It is thus indicated after careful chromatographic separation. [c] Reaction performed in the presence of *N,N*-dibutylethanolamine (2 equiv.).

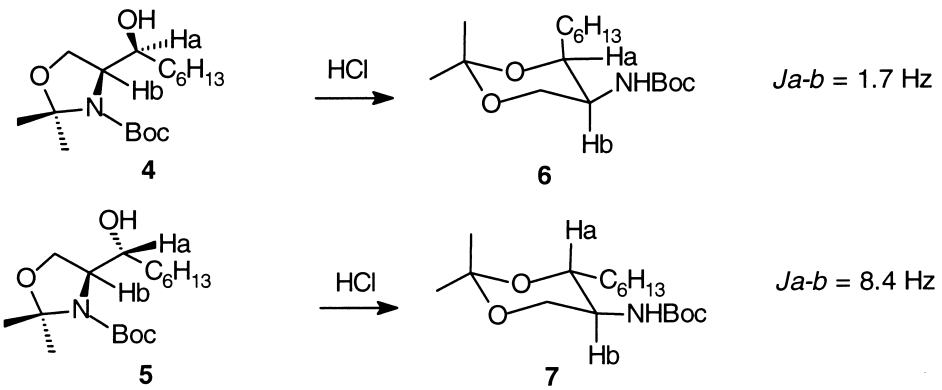
2. Results and discussion

Seebach et al. reported the in situ preparation of dialkylzinc compounds from Grignard reagents in diethyl ether and zinc chloride on a 20 mmol scale.[9] To obtain multigram quantities of analogues **8** and **9**, we adapted this method to a larger scale and we isolated pure dihexylzinc after distillation ($bp_{0.01}$ 46°C).[11] This procedure avoids the presence in the reaction medium of residual $MgCl_2$ or $ZnCl_2$ that can play the role of Lewis acid and affect diastereoselectivity.

It appears that condensation of dihexylzinc in toluene leads preferentially to the formation of the *anti* diastereomer **5**, as predicted by the Felkin–Ahn model (entry 1).[5] As expected, addition of a stoichiometric amount of zinc chloride inversed the selectivity in favour of the *syn* diastereomer **4**, which can be rationalized in terms of a chelated Cram model (entry 2).[5] In contrast with dihexylzinc, hexylmagnesium bromide in diethyl ether afforded **4** with excellent diastereoselectivity (de 90%) and high yield (entry 3). The Grignard reagent should thus behave as a chelating Lewis acid. However, addition of one equivalent of zinc chloride did not increase either the diastereoselectivity in favour of **4** or the yield of the reaction (entry 4). Conversely, neither inversion nor notable decrease of diastereoselectivity were observed in more coordinating solvents such as THF, or in the presence of

one equivalent of HMPA, as would be expected (entries 5 and 6). Remarkably, the use of hexyllithium in THF led to total *anti* diastereoselectivity, but a low yield (entry 7). Thus, depending on the *n*-hexylmetal reagent used, we could obtain either **4** or **5** in good yield and with high diastereoselectivity.

The relative configuration of diastereomers **4** and **5** was clearly established by the ^{1}H NMR spectra of the corresponding 1,3-dioxanes **6** and **7**, respectively, that result from rearrangement of the former under catalytic acidic conditions according to the procedure described by Hafner et al. (Scheme 2).[10] The Ha–Hb coupling constant was 1.7 Hz for the *syn* diastereomer **6**, versus 8.6 Hz for the *anti* one **7**.



Scheme 2.

Enantiomeric purity (e.e.>98%) of alcohols **4** and **5** was assessed using the method of Brunel et al., by ^{31}P NMR of the corresponding phosphite derivatives with diisopropyltartrate which inhibits a single signal at 177.0 and 218.2 ppm respectively.[11]

Treatment of pure alcohols **4** and **5** with benzoyl chloride (2 equiv.) in pyridine (rt, 12 h), followed by an acidic hydrolysis with 5 N HCl in refluxing dioxane, led to the 3-*O*-benzoyl diastereomeric aminoalcohols (2*S*,3*S*)-**8** and (2*S*,3*R*)-**9** in 71% and 59% overall yield, respectively.

These two protected dihydrosphingosine analogues constitute key building blocks for a subsequent synthesis of unnatural ceramide and glycosphingolipide species.

3. Experimental

Toluene was distilled over sodium, and THF and diethyl ether from potassium benzophenone ketyl. ^{1}H NMR and ^{13}C NMR spectra were recorded in C_6D_6 and $CDCl_3$ solution as indicated, at 200 and 50.36 MHz, respectively (the usual abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet) and the ^{31}P NMR spectra were recorded at 40.54 Hz. ^{1}H and ^{13}C NMR spectra of compounds **6** and **7** were recorded at 400 and 100.72 MHz respectively. The following abbrevations are used: C^{I}=primary carbon; C^{II}=secondary carbon; C^{III}=tertiary carbon and C^{IV}=quaternary carbon. The positive chemical shift values are given in ppm and the coupling constants in hertz. Infrared spectra were recorded as thin films for liquids and KBr disks for solids (Perkin–Elmer 298 FT-IR). Optical rotations were taken on a Perkin–Elmer 241 MC polarimeter.

3.1. Preparation of dihexylzinc

Slow addition of anhydrous zinc chloride (10.0 g, 73 mmol, 1 equiv.) in THF (30 mL) to a 4 M solution of hexylmagnesium bromide in THF (36.7 mL, 146 mmol, 2 equiv.) led, after heating for 2 hours at reflux,

to a white suspension. The mixture was cooled to room temperature and anhydrous dioxane (31.0 mL, 365 mmol, 5 equiv.) was added. After 1 hour, the reaction mixture was filtered under an inert atmosphere and concentrated under reduced pressure. Distillation of the crude product afforded dihexylzinc as a colorless oil ($bp_{0.01}$ 46°C) in 69% yield (11.9 g, 50 mmol). ^{1}H NMR (C_6D_6) δ: 0.29 (t, *J*=7.5 Hz, 2H), 0.90 (t, *J*=6.0 Hz, 3H), 1.27–1.53 (m, 8H); ^{13}C NMR (C_6D_6) δ: 14.4 (C^I); 16.3 (C^{II}), 23.2 (C^{II}), 26.8 (C^{II}), 32.3 (C^{II}), 36.7 (C^{II}).

*3.2. 4(*S*)-(1(*S*)-Hydroxyheptyl)-2,2-dimethyloxazolidine-3-carboxylic acid* tert*-butyl ester **4** and 4(*S*)-(1(*R*)-hydroxyheptyl)-2,2-dimethyloxazolidine-3-carboxylic acid* tert*-butyl ester **5***

Under an inert atmosphere, a 5 M solution of dihexylzinc in toluene (5.2 mL, 25.9 mmol, 3 equiv.) was slowly added to 2,2-dimethylpropionic acid 4(*S*)-formyl-2,2-dimethyloxazolidin-3-yl ester **3**[8] (2.0 g, 8.6 mmol, 1 equiv.) and zinc chloride (1.1 g, 8.6 mmol, 1 equiv.) in 50 mL of dry toluene at −78°C. The reaction was stirred until the starting material had been completely consumed, as judged by thin layer chromatography (3 hours). Ethyl acetate (50 mL) was added and the mixture was poured into a saturated ammonium chloride solution (30 mL). The organic layer was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. We obtained, after silica gel column chromatography (AcOEt:petroleum ether=1:3), 1.8 g (5.6 mmol) 4(*S*)-(1(*S*)-hydroxyheptyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester **4** and 0.4 g (1.1 mmol) of 4(*S*)-(1(*R*)-hydroxyheptyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester **5**, in 79% cumulated yield.

4: Yellow oil; $[\alpha]_D^{20}=-17$ (*c*=2.23, $CHCl_3$); R_f=0.41 (AcOEt:petroleum ether=1:3); IR (cm^{-1}): 3500, 2950, 2894, 2820, 1710; ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, *J*=6.6 Hz, 3H), 1.28–1.60 (m, 25H), 3.55–4.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 14.0 (C^I), 22.6 (C^{II}), 25.4 (C^{II}), 26.4 (C^I), 28.4 (C^I), 29.3 (C^{II}), 29.6 (C^{II}), 31.9 (C^{II}), 61.9 (C^{III}), 62.8 (C^{III}), 64.8 (C^{II}), 81.1 (C^{IV}), 94.0 (C^{IV}), 156.0 (C^{IV}).

5: Orange oil; $[\alpha]_D^{20}=-38$ (*c*=1.17, $CHCl_3$); R_f=0.33 (AcOEt:petroleum ether=1:3); IR (cm^{-1}): 3500, 2950, 2894, 2820, 1710; ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, *J*=6.6 Hz, 3H), 1.28–1.60 (m, 25H), 3.61–4.03 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 14.1 (C^I), 22.6 (C^{II}), 25.4 (C^{II}), 26.4 (C^I), 28.2 (C^I), 29.2 (C^{II}), 29.6 (C^{II}), 31.8 (C^{II}), 61.9 (C^{III}), 63.0 (C^{III}), 64.8 (C^{II}), 81.0 (C^{IV}), 93.9 (C^{IV}), 154.3 (C^{IV}).

*3.3. (*S*)-(4(*S*)-Hexyl-2,2-dimethyl-[1,3]dioxan-5-yl)-carbamic acid* tert*-butyl ester **6***

^{1}H NMR ($CDCl_3$) δ: 0.87 (t, *J*=6.8 Hz, 3H), 1.20–1.28 (m, 10H), 1.40 (s, 3H), 1.48 (s, 9H), 1.50 (s, 3H), 3.50 (dddd, *J*=9.9 Hz, *J*=1.9 Hz, *J*=1.8 Hz, *J*=1.7 Hz, 1H), 3.76 (dd, *J*=11.9 Hz, *J*=1.8 Hz, 1H), 3.91 (dt, *J*=6.7 Hz, *J*=1.7 Hz, 1H), 4.05 (dd, *J*=11.9 Hz, *J*=1.9 Hz, 2H), 5.30 (d, *J*=9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0 (C^I), 22.6 (C^{II}), 24.1 (C^{II}), 28.4 (C^I), 29.2 (C^I), 29.7 (C^{II}), 30.9 (C^I), 31.6 (C^{II}), 31.7 (C^{II}), 46.9 (C^{III}), 62.9 (C^{II}), 71.5 (C^{III}), 79.3 (C^{IV}), 99.0 (C^{IV}), 155.8 (C^{IV}).

*3.4. (*S*)-(4(*R*)-Hexyl-2,2-dimethyl-[1,3]dioxan-5-yl)-carbamic acid* tert*-butyl ester **7***

^{1}H NMR ($CDCl_3$) δ: 0.87 (t, *J*=6.8 Hz, 3H), 1.22–1.28 (m, 10H), 1.42 (s, 3H), 1.49 (s, 9H), 1.51 (s, 3H), 3.48 (dddd, *J*=9.9 Hz, *J*=8.4 Hz, *J*=1.9 Hz, *J*=1.8 Hz, 1H), 3.79 (dd, *J*=11.9 Hz, *J*=1.8 Hz, 1H), 3.89 (dt, *J*=6.7 Hz, *J*=8.4 Hz, 1H), 4.10 (dd, *J*=11.9 Hz, *J*=1.9 Hz, 2H), 5.30 (d, *J*=9.9 Hz, 1H); ^{13}C ($CDCl_3$) δ: 14.0 (C^I), 22.6 (C^{II}), 24.1 (C^{II}), 28.4 (C^I), 29.2 (C^I), 29.7 (C^{II}), 30.9 (C^I), 31.6 (C^{II}), 31.7 (C^{II}), 46.8 (C^{III}), 62.9 (C^{II}), 71.4 (C^{III}), 79.3 (C^{IV}), 99.0 (C^{IV}), 155.8 (C^{IV}).

*3.5. Benzoic acid 1-(1(*S*)-amino-2(*S*)-hydroxyethyl)-heptyl ester **8** and benzoic acid 1-(1(*S*)-amino-2(*R*)-hydroxyethyl)-heptyl ester **9***

Benzoyl chloride (1.24 g, 8.8 mmol, 2 equiv.) was slowly added to a solution of 2,2-dimethylpropionic acid 4(*S*)-[1(*S*)-hydroxyheptyl]-2,2-dimethyloxazolidin-3-yl ester **4** (1.40 g, 4.4 mmol, 1 equiv.) and DMAP (0.04 g, 0.4 mmol, 0.1 equiv.) in a mixture of 30 mL of toluene:pyridine (4:1). After 5 hours of stirring at room temperature, the reaction mixture was filtered and evaporated under reduced pressure. The crude product was dissolved in 50 mL of dioxane and 25 mL of a 5 N solution of hydrochloric acid. After heating at reflux for 45 minutes, the reaction was cooled to room temperature and basified to pH=8 with a 1 N solution of sodium hydroxide. Then 100 mL of dichloromethane were added and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. We obtained, after silica gel column chromatography (AcOEt:petroleum ether=1:1), 0.92 g (3.1 mmol, 71% yield) of benzoic acid 1-(1(*S*)-amino-2(*S*)-hydroxyethyl)-heptyl ester **8**.

8: White solid; $[\alpha]_D^{20}$=+15 (*c*=1.03, $CHCl_3$); mp=34°C; IR (cm^{-1}): 3400, 3050, 3010, 2993, 2877, 1640; ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, *J*=6.6 Hz, 3H); 1.53–1.25 (m, 10H); 3.22 (m, 1H); 3.90–3.92 (d, *J*=4.2 Hz, 2H); 4.04–4.17 (m, 2H); 7.01 (d, *J*=8.2 Hz, 2H); 7.47 (m, 3H); 7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 13.9 (C^I), 22.5 (C^{II}), 25.6 (C^{II}), 29.1 (C^{II}), 31.6 (C^{II}), 34.3 (C^{II}), 54.0 (C^{III}), 64.3 (C^{II}), 72.0 (C^{III}), 127.03 (C^{III}), 128.5 (C^{III}), 131.6 (C^{III}), 134.0 (C^{IV}), 168.2 (C^{IV}).

9: Pale yellow solid; $[\alpha]_D^{20}$=+9 (*c*=0.91, $CHCl_3$); mp=113°C; IR (cm^{-1}): 3400, 3200, 3086, 2947, 2857, 1648; ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, *J*=6.6 Hz, 3H); 1.27 (m, 8H); 1.55 (m, 2H); 3.63 (m, 1H); 3.85 (m, 2H); 4.05 (d, *J*=4.2 Hz, 2H); 7.44 (m, 5H); 7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 14.0 (C^I), 22.5 (C^{II}), 25.9 (C^{II}), 29.2 (C^{II}), 31.7 (C^{II}), 34.3 (C^{II}), 54.6 (C^{III}), 62.0 (C^{II}), 73.5 (C^{III}), 127.1 (C^{III}), 128.4 (C^{III}), 131.6 (C^{III}), 134.0 (C^{IV}), 167.9 (C^{IV}).

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