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Efficient Synthesis of Enantiomerically Pure 2-Acylaziridines: Facile Syntheses of *N*-Boc-safingol, *N*-Boc-D-*erythro*-sphinganine, and *N*-Boc-spisulosine from a Common Intermediate

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Various enantiomerically pure 2-acylaziridines were prepared efficiently from the corresponding aziridine-2-carboxylate via Weinreb's amide and the subsequent treatment of organometallic compounds. The carbonyl group of those 2-acylaziridines was stereoselectively reduced by $NaBH_4$ in the presence of $ZnCl_2$ to give *erythro*-1,2-amino alcohols with high diastereoselectivities and chemical yields. Using this methodology, we prepared (1*R*,2*S*)-*N*-Boc-norephedrine **5**, *N*-Boc-safingol **8,** *N*-Boc-D-*erythro*-sphinganine **9**, and *N*-Boc-spisulosine **10** in high yields.

1,2-Amino alcohol units with unique stereochemistry are found as essential components in many biologically active natural products and important pharmaceuticals.[1] Representative examples relevant to lipid metabolism include sphingosine and sphinganine (dihydrosphingosine), which are precursors of cerebrosides, gangliosides, sphingomyelin. These lipids are composed of three structural units: a long-chain aliphatic 2-amino-1,3-diol, a fatty acid, and a polar headgroup.[2] The inherent structural variation of fatty acids and polar headgroups in sphingolipids attracts great interest because of their diverse biological activities including cell regulation and signal transduction.[3] Safingol (L-*threo*-dihydrosphingosine), 2(*S*)-amino-1,3(*R*)-octadecanediol, is known as an inhibitor of protein kinase C (PKC)[4] and acts synergistically with anti-cancer drugs.[5] D-*erythro*-Sphinganine, 2(*S*)-amino-1,3(*S*)-octadecanediol, is an important part of symbioramide, a new type of bioactive ceramide, which is known for increasing sarcoplasmic reticulum Ca^{2+}-ATPase activity.[6] Spisulosine, 2(*S*)-amino-3(*R*)-octadecanol, was isolated from a new organism recently, *Spisula polynyma*, and was reported to promote the disassembly of actin stress fiber by inhibiting the activity of Rho protein.[7] Therefore, the asymmetric synthesis of 1,2-amino alcohols is the subject of current interest.[8]

We recently reported the preparation of *threo*-1,2-amino alcohols from highly stereoselective carbonyl group reduction of 2-acylaziridines, prepared by Swern oxidation of the corresponding secondary alcohols, using L-Selectride.[9] However, we devised a more efficient approach to prepare enantiomerically pure 2-acylaziridines from the corresponding aziridine-2-carboxylate via Weinreb's amide.[10] The reaction of *N*,*O*-dimethylhydroxylamine hydrochloride and commercially available *N*-[(*R*)-(+)-α-methylbenzyl]-2(*S*)-aziridinecarboxylic acid menthol ester **1**[11] in the presence of $AlMe_3$ in CH_2Cl_2 provides the Weinreb's amide **2** in 92% yield. The Weinreb's amide

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(11) Both 2(*S*) and 2(*R*) isomers are available from Sigma-Aldrich Co. (www.sigma-aldrich.com) and Imagene (www.imagene.co.kr).

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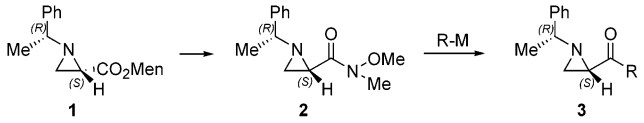
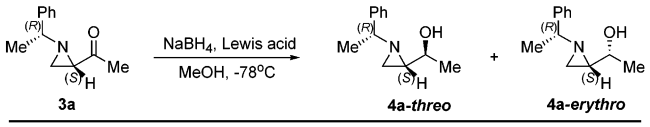
SCHEME 1. Preparation of Various Ketones from Weinreb's Amide 2[a]



Entry	R	Yield of 3 (%)
a	Methyl	92
b	*iso*-Propyl	95
c	*n*-Butyl	88
d	*t*-Butyl	87
e	Allyl	a
f	1-Pentadecynyl	99
g	Pentadecanyl	96
h	Benzyl	96
i	Phenyl	99
j	4-Methoxyphenyl	90
k	4-Chlorophenyl	90

[a] Since compound **3e** is unstable and decomposed during silica gel chromatography, the crude product was directly reduced to give **4e**.

SCHEME 2. Results of Reduction of Aziridinyl Methyl Ketone 3a



Entry	Lewis acid	Reducing reagent	Solvent	Temperature (°C)	Ratio(4a-*t* : 4a-*e*)
1	$CeCl_3$	$NaBH_4$	MeOH	0°C	3 : 1
2	$TiCl_4$	$NaBH_4$	MeOH	-78°C	1 : 1
3	$CoCl_2$	$NaBH_4$	MeOH	-78°C	1 : 3
4	$NiCl_2$	$NaBH_4$	MeOH	-78°C	1 : 5
5	$ZnCl_2$	$NaBH_4$	MeOH	-78°C	<1:>99

2 was reacted with various organometallic compounds to provide the corresponding ketones **3** in high yields which are shown in Scheme 1. Since we recently reported stereoselective reduction of the ketone carbonyl group of 2-acylaziridines to provide *threo*-1,2-amino alcohols, we envisaged stereoselective preparation of *erythro*-1,2-amino alcohols from enantiomerically pure 2-acylaziridines.[12] The aziridinyl methyl ketone **3a** was reduced by $NaBH_4$ in the presence of various Lewis acids. To achieve high erythro stereoselectivity by chelation-controlled reduction, we need a tight bidentate chelating metal ion fitting in the space provided between the aziridine nitrogen and the carbonyl oxygen atom. As a result, the reduction of the ketone **3a** using $ZnCl_2$ as a Lewis acid provided the best selectivity (>99:<1) in 97% yield while other Lewis acids gave low stereoselectivity or reversed selectivity (Scheme 2).

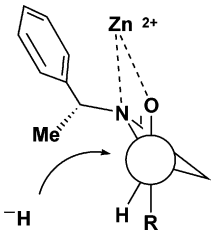


FIGURE 1. Structure of the chelated intermediate.

TABLE 1. Results of the Chelation-Controlled Reduction of Various Ketones

entry	R	diastereomer ratio erythro/threo	yield (%)
a	methyl	>99:<1	97
b	isopropoyl	>99:<1	95
c	*n*-butyl	97:3	86
d	*t*-butyl	97:3	86
e	allyl	>99:<1	96
f	1-pentadecynyl	>99:<1	99
g	pentadecanyl	94:6	84[a]
h	benzyl	>99:<1	96
i	phenyl	>99:<1	90
j	4-methoxyphenyl	>99:<1	99
k	4-chlorophenyl	98:2	90

[a] The low stereoselectivity results from high reaction temperature, −30 °C, due to the solubility of the ketone.

The excellent stereochemical control of the reaction using $ZnCl_2$ and $NaBH_4$ can be explained by hydride delivery through the "chelated intermediate" in Figure 1. The chelated structure appears to be stabilized by strong interactions of the empty d orbitals of Zn^{2+} with the lone pairs of the aziridine ring nitrogen and the carbonyl oxygen atoms.

On the basis of the above results, we prepared various *erythro*-1,2-amino alcohols through the chelation-controlled reduction by $NaBH_4$ and $ZnCl_2$ in MeOH with excellent diastereoselectivities as well as in high yields (Table 1). Therefore, these results and our previous report[9] allow us to control the stereochemistry of the secondary alcohol easily by reduction of the corresponding ketones with a suitable reducing agent: either L-Selectride only or $NaBH_4$ in the presence of $ZnCl_2$ (Scheme 3).[13] To prove the efficiency of the present method, we selected four easily accessible natural products (1*R*,2*S*)-*N*-Boc-norephedrine **5** and *N*-Boc-safingol **8**, which have *threo*-1,2-amino alcohol structural units[14] and also *N*-Boc-D-*erythro*-sphinganine **9** and *N*-Boc-spisulosine **10,** which have an *erythro*-1,2-amino alcohol unit.[15]

N-[(*R*)-(+)-α-Methylbenzyl]aziridin-2(*S*)-yl phenyl ketone **3i** was reduced with $NaBH_4$ and $ZnCl_2$ to give the corresponding *erythro*-1,2-amino alcohol **4i-*erythro*** in 90% yield. The regioselective reduction of the aziridine ring C(3)−N bond and subsequent removal of the α-methylbenzyl group on the nitrogen was achieved by catalytic hydrogenation in the presence of $(Boc)_2O$ to provide the *N*-Boc-norephedrine **5** in 85% yield. (Scheme 4)[16] We

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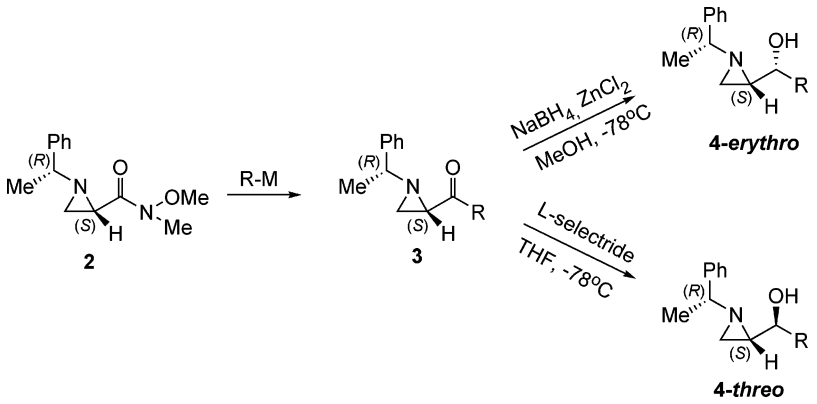
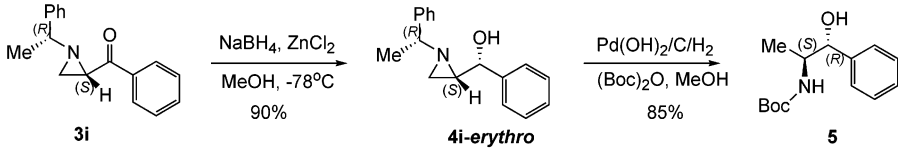
SCHEME 3. Control of Stereochemistry in the Reduction of 2-Acylaziridines



SCHEME 4. Preparation of (1*R*,2*S*)-*N*-Boc-norephedrine 5



compared all the physical properties of **5** with those of known data to find a good agreement.[17] Therefore, this method allows us to prepare various aryl and heteroaryl analogues of **5** in simple steps from **2**.

The stereoselective reduction of the ketone carbonyl group of 2-acylaziridine **3g** and the subsequent regioselective ring opening allows us to prepare *N*-Boc derivatives of safingol,[18] D-*erythro*-sphinganine,[19] and spisulosine[20] from the common intermediate **3g**. The aziridine ring of the 1,2-amino alcohols **4g** (both *threo* and *erythro*) was regioselectively opened with AcOH, and the acetate was hydrolyzed by KOH in ethanol to give 2-amino-1,3-ocatdecanediol **6** and **7** in 98% yield, respectively.[21] The α-methylbenzyl group of **6** and **7** was removed by successive catalytic hydrogenation with atmospheric pressure of H_2 (1 atm of H_2) in methanol in the presence of Boc_2O to provide *N*-Boc derivatives **8** (*N*-Boc-safingol) and **9** (*N*-Boc-D-*erythro*-sphinganine), respectively, as stable solids in 91% yield. Furthermore, the aziridine ring of **4g-*erythro*** was regioseletively reduced by catalytic hydrogenation in the present of Boc_2O to provide the *N*-Boc-spisulosine **10** as a white solid in 95% yield (Scheme 5). The synthesis of D-*erythro*-sphinganine from serine has been reported[19] but the present method is more efficient because the aziridine compound does not require protection−deprotection steps.

The above results show that Zn^{2+} tightly binds to the carbonyl oxygen and the aziridine ring nitrogen to provide a strong facial bias to the carbonyl group to give highly diastereoselective reduction products. Since both *erythro*- and *threo*-1,2-amino alcohols are found as important structural units in many biologically active compounds, the control of the stereochemistry in carbonyl reduction of enantiomerically pure 2-acyl aziridines provides us access to both *erythro*- and *threo*-1,2-amino alcohols very efficiently.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were obtained on 200, 300, and 500 MHz spectrometers using $CDCl_3$ as the solvent. NMR spectra were recorded in ppm (δ) related to tetramethylsilane (δ = 0.00) as an internal standard. Elemental analyses were determined by an elemental analyzer. Optical rotations were obtained on a digital polarimeter. Reagents and solvents used were reagent grade. Methylene chloride and triethylamine were dried over calcium hydride prior to use.

Preparation of the *N*-[(*R*)-(+)-α-Methylbenzyl]-2(*S*)-aziridine *N*-Methoxy-*N*-methylcarboxamide (2). To the solid of *N*,*O*-dimethylhydroxylamine·HCl (880 mg, 9.11 mmol) in 10 mL of CH_2Cl_2 was added $AlMe_3$ (2.00 M, 4.55 mL, 9.11 mmol) under nitrogen at −10 °C carefully. The solution was stirred for 30 min at room temperature, and the solution of *N*-[(*R*)-(+)-α-methylbenzyl]aziridine-2(*S*)-carboxylic acid menthol ester **(1) (**1.00 g, 3.04 mmol) in CH_2Cl_2 (5.0 mL) was added dropwisely at −10 °C. The mixture was stirred for 2 h at room temperature. The reaction was quenched carefully by water, and the organic layer was separated. After extraction with CH_2Cl_2 three times, the combined organic layer was dried, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 50:50) yielded pure **2** as an oil (655 mg, 92%): $[\alpha]^{22}_D$ = +56.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 3.13 (s, 3H), 3.12 (s, 3H), 2.57 (m, 2H), 2.42 (dd, *J* = 3.05, 1.10 Hz, 1H), 1.76 (dd, *J* = 6.35, 1.28 Hz, 1H), 1.48 (d, *J* = 6.59 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 144.3, 128.4, 127.1, 126.8, 70.6, 61.0, 35.1, 34.1, 32.4, 23.5. Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.63; H, 7.79; N, 11.96.

Representative Example of the Formation of 2-Acylaziridine. Preparation of (2*S*)-2-*N*-[(*R*)-(+)-α-Methylbenzyl]aziridinyl Methyl Ketone 3a. To the solution of **2** (100 mg, 0.43 mmol) in 2.10 mL of THF under nitrogen at −78 °C

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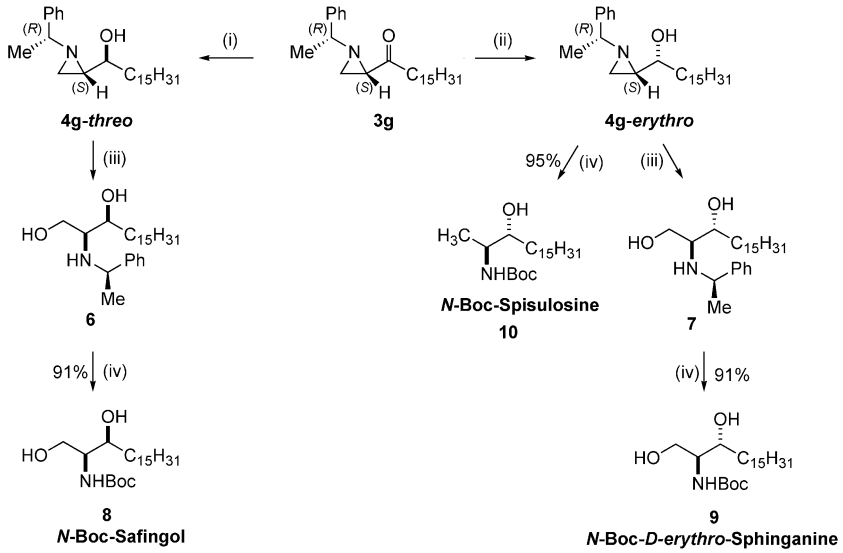
SCHEME 5. Preparation of *N*-Boc-D-*erythro*-sphinganine, *N*-Boc-safingol, and *N*-Boc-spisuosine[a]



[a] Conditions: (i) L-Selectride, THF, −70 °C (84%); (ii) $NaBH_4$, $ZnCl_2$, MeOH, −30 °C (84%); (iii) (a) AcOH, CH_2Cl_2, rt, (b) KOH, EtOH (98%); (iv) H_2 (1 atm), $Pd(OH)_2/C$, Boc_2O, MeOH.

was added MeMgBr (2.0 M, 0.32 mL, 0.64 mmol). The solution was stirred for 30 min at −78 °C. After the solution was warmed to room temperature, 2.0 mL of water was added to the solution and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 mL × 5), and the combined organic extracts were dried, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 1:4) provided **3a** as an oil (74 mg, 92%): $[\alpha]^{27}_D$ = −53.1 (*c* 1.40, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32−7.23 (m, 5H), 2.55 (q, *J* = 6.2 Hz, 1H), 2.28 (d, *J* = 2.9 Hz, 1H), 2.11 (dd, *J* = 6.6, 2.7 Hz, 1H), 2.02 (s, 3H), 1.81 (d, *J* = 6.8 Hz, 1H), 1.43(d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.4, 144.1, 128.6, 127.4, 126.6, 69.7, 44.5, 35.0, 25.3, 23.3. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.07; H, 8.04; N, 7.34.

3b: $[\alpha]^{29}_D$ = +28.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 2.63 (m, 1H), 2.54 (q, *J* = 6.59 Hz, 1H), 2.28 (dd, *J* = 1.37, 3.30 Hz, 1H), 2.18 (dd, *J* = 3.30, 6.59, 1H), 1.79 (dd, *J* = 1.37, 6.59 Hz, 1H), 1.46 (d, *J* = 6.59 Hz, 3H), 0.92 (d, *J* = 6.89 Hz, 3H), 0.85 (d, *J* = 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 143.8, 128.4, 127.3, 126.7, 70.2, 42.0, 37.9, 36.0, 23.1, 18.0, 17.8. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.39; H, 8.85; N, 6.46.

3c: $[\alpha]^{24}_D$ = −62.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−7.18 (m, 5H), 2.53 (q, *J* = 6.5 Hz, 1H), 2.31 (m, 2H), 2.25 (d, *J* = 2.6 Hz, 1H), 2.12 (dd, *J* = 6.9, 3.2 Hz, 1H), 1.78 (d, *J* = 6.6 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.38 (m, 2H), 1.21 (sextet, *J* = 7.0 Hz, 2H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.0, 144.1, 128.6, 127.4, 126.7, 69.9, 43.8, 38.1, 35.2, 25.3, 23.1, 22.0, 13.5. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.58; H, 9.37; N, 6.21.

3d: $[\alpha]^{24}_D$ = −34.5 (*c* 1.00, $CHCl_3$); mp 60−62 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.18 (m, 5H), 2.55 (q, *J* = 6.6 Hz, 1H), 2.43 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.34 (dd, *J* = 3.1, 1.7 Hz, 1H), 1.78 (dd, *J* = 6.3, 1.7 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 211.3, 144.2, 128.5, 127.4, 126.9, 70.7, 43.7, 37.9, 37.3, 25.4, 23.0. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.73; H, 9.01; N, 6.07.

3f: $[\alpha]^{24}_D$ = −81.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.22(m, 5H), 2.61 (q, *J* = 6.6 Hz, 1H), 2.43 (dd, *J* = 2.9, 1.2 Hz, 1H), 2.35 (t, *J* = 7.1 Hz, 2H), 2.25 (dd, *J* = 6.5, 2.9 Hz, 1H), 1.86 (dd, *J* = 6.5, 1.2 Hz, 1H), 1.56 (m, 2H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.40 (m, 2H), 1.31−1.26 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 143.8, 128.4, 127.1, 126.4, 96.6, 79.3, 77.4, 77.1, 69.6, 36.2, 31.9, 29.6, 29.6, 29.6, 29.4, 29.3, 29.0, 28.8, 27.6, 23.7, 22.7, 19.1, 14.1. Anal. Calcd for $C_{26}H_{39}NO$: C, 81.84; H, 10.30; N, 3.67. Found: C, 81.83; H, 10.16; N, 3.71.

3g: $[\alpha]^{24}_D$ = −52.7 (*c* 1.0, $CHCl_3$); mp 28.9−29.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 2.53 (q, *J* = 6.50 Hz, 1H), 2.36 (m, 1H), 2.26 (d, *J* = 3.50, 1H), 2.23 (m, 1H), 2.12 (dd, *J* = 7.00, 3.00 Hz, 1H), 1.79 (d, *J* = 7.00 Hz, 1H) 1.44 (d, *J* = 6.50 Hz 3H), 1.43 (m, 2H), 1.32−1.19 (m, 26H), 0.88 (t, *J* = 7.00 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.60, 143.87, 128.39, 127.21, 126.50, 69.97, 43.94, 38.55, 35.36, 31.89, 29.66, 29.65, 29.64, 29.62, 29.57, 29.41, 29.32, 29.10, 23.38, 23.36, 22.65, 14.08; HRMS(EI) calcd for $C_{26}H_{43}NO$ 385.3345, found 385.3347.

3h: $[\alpha]^{24}_D$ = −71.0 (*c* 1.00, $CHCl_3$); mp 48−50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.20 (m, 8H), 7.06−7.04 (m, 2H), 3.61 (q, *J* = 15.6 Hz, 2H), 2.54 (q, *J* = 6.6 Hz, 1H), 2.31 (dd, *J* = 3.1, 1.0 Hz, 1H), 2.18 (dd, *J* = 6.7, 3.1 Hz, 1H), 1.80 (dd, *J* = 6.7, 1.0 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 143.7, 133.8, 129.4, 128.5, 128.4, 127.3, 126.8, 126.5, 69.9, 45.4, 43.7, 35.7, 23.4. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.42; H, 7.14; N, 5.31.

3i: $[\alpha]^{28}_D$ = −22.7 (*c* 0.55, $CHCl_3$); mp 56−57 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8,3 Hz, 2H), 7.52−7.21 (m, 8H), 2.88 (dd, *J* = 6.4, 3.1 Hz, 1H), 2.71 (q, *J* = 6.6 Hz, 1H), 2.55 (d, *J* = 3.1 Hz, 1H), 1.94 (d, *J* = 6.4 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 196.9, 144.2, 137.0, 133.2, 128.7, 128.6, 128.4, 127.4, 126.8, 70.6, 40.2, 36.8, 23.3. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.26; H, 6.85; N, 5.53.

3j: $[\alpha]^{24}_D$ = −17.8 (*c* 1.00, $CHCl_3$); mp 65−66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 2H), 7.40−7.21 (m, 5H), 6.78 (m, 2H), 3.81 (s, 3H), 2.84 (dd. *J* = 6.3, 3.2 Hz, 1H), 2.70 (q, *J* = 6.6 Hz, 1H), 2.54 (dd, *J* = 3.2, 1.3 Hz, 1H), 1.90 (dd, *J* = 6.3, 1.3 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 163.4, 144.0, 130.6, 129.9, 128.5, 127.2, 126.7, 113.5, 70.7, 55.4, 40.1, 36.6, 23.5. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.71; H, 6.92; N, 5.01.

3k: $[\alpha]^{24}_D$ = −21.8 (*c* 1.00, $CHCl_3$); mp 74−76 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68−7.18 (m, 9H), 2.82 (dd, *J* = 6.4, 3.2 Hz, 1H), 2.70 (q, *J* = 6.6 Hz, 1H), 2.57 (dd, *J* = 3.2, 1.4 Hz, 1H), 1.97 (dd, *J* = 6.4, 1.4 Hz, 1H), 1.51 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 195.5, 144.1, 138.5, 134.9, 133.1, 129.9, 128.8, 128.4, 127.6, 126.8, 126.5, 70.8, 40.2, 37.0, 23.3.

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.48; H, 5.53; N, 4.80.

Representative Example of the Stereoselective Reduction to 1,2-*erythro*-Amino Alcohols. Preparation of 4a-*erythro*. To the solution of **3a** (74 mg, 0.39 mmol) in 2.0 mL of MeOH at −78 °C was added $ZnCl_2$ (80.0 mg, 0.59 mmol). The solution was stirred for 30 min, and $NaBH_4$ (29.6 mg, 0.78 mmol) was added at −78 °C. The mixture was stirred for 30 min, and 2.0 mL of water was added. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 mL × 5), and the combined organic extracts were dried, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 3:7) provided **4a** as a white solid (73 mg, 97%): $[\alpha]^{24}_D = +38.1$ (*c* 0.81, $CHCl_3$); mp 64−66 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 3.69 (m, 1H), 2.59 (q, *J* = 6.6 Hz, 1H), 1.95 (d, *J* = 3.4 Hz, 1H), 1.55 (m, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 1,39 (d, *J* = 6.9 Hz, 1H), 1.00 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.7, 128.5, 127.3, 126.7, 69.2, 64.5, 42.7, 29.1, 22.9, 19.6. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.17; H, 8.67; N, 7.03.

4b: $[\alpha]^{25}_D = +61.1$ (*c* 1.00, $CHCl_3$); mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 3.31 (dd, *J* = 3.02, 3.30 Hz, 1H), 2.68 (bs, OH), 2.62 (q, *J* = 6.59 Hz, 1H), 1.97 (d, *J* = 3.57 Hz, 1H), 1.62 (m, 1H), 1.56 (m, 2H), 1.42 (d, *J* = 6.59 Hz, 3H), 0.85 (d, *J* = 6.87 Hz, 6H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 144.47, 128.38, 127.06, 126.48, 72.26, 69.17, 39.95, 32.37, 29.29, 23.37, 18.25, 17.92. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.65; H, 9.66; N, 6.38.

4c: $[\alpha]^{27}_D = +25.0$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−7.20 (m, 5H), 3.55 (m, 1H), 2.58 (q, *J* = 6.5 Hz, 1H), 2.45 (s, 1H), 1.95 (d, *J* = 3.5 Hz, 1H), 1.57 (duint, *J* = 3.5 Hz, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.40 (m, 2H), 1.30 (m, 5H), 0.85(m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.8, 128.4, 127.1, 126.9, 69.4, 68.5, 42.0, 34.4, 29.4, 27.4, 23.1, 22.8, 13.9. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.28; H, 10.16; N, 6.21.

4d: $[\alpha]^{24}_D = +0.2$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 3.31 (d, *J* = 2.2 Hz, 1H), 2.64 (q, *J* = 6.5 Hz, 1H), 2.03 (d, *J* = 3.6 Hz, 1H), 1.59 (m, 1H), 1.43 (d, *J* = 6.3, Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.8, 128.5, 127.1, 126.6, 74.0, 69.0, 38.1, 34.2, 29.3, 25.6, 23.3. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H,9.93; N, 6.00. Found: C, 77.24; H, 9.73; N, 5.94.

4e: $[\alpha]^{24}_D = +35.9$ (*c* 1.00, $CHCl_3$); mp 51−53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 5.71 (m, 1H), 5.01 (m, 1H), 4.99 (m, 1H), 3.54 (m, 1H), 2.57 (q, *J* = 6.6 Hz, 1H), 2.06 (m, 2H), 1.97 (m, 1H), 1.59 (m, 1H), 1.42 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.4, 134.3, 128.4, 127.2, 126.6, 117.4, 69.3, 68.2, 41.4, 39.2, 29.9, 23.1. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 7.36; N, 6.45. Found: C, 77.38; H, 7.47; N, 6.41.

4f: $[\alpha]^{25}_D = +37.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.30 (t, *J* = 1,71 Hz, 1H), 2.62 (q, *J* = 6.4 Hz, 1H), 2.54 (brs, 1H), 2.12 (m, 3H), 1.82 (m, 1H), 1.50 (d, *J* = 6.4 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.20−1.34 (m, 22H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 128.4, 127.2, 126.6, 86.0, 78.3, 69.1, 60.3, 41.8, 31.9, 30.2, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 29.1, 28.8, 28.5, 23.1, 22.7, 18.7, 14.1. Anal. Calcd for $C_{26}H_{41}NO$: C, 81.41; H, 10.77; N, 3.65. Found: C, 81.38; H, 10.99; N, 3.66.

4g: $[\alpha]^{24}_D = +19.04$ (*c* 1.00, $CHCl_3$); mp 49.8−51.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 3.53 (m, 1H), 2.59 (q, *J* = 6.50 Hz, 1H), 2.46 (br, 1H), 1.95 (d, *J* = 3.50 Hz, 1H), 1.57 (m, 1H), 1.42 (d, *J* = 6.50, 3H), 1.38 (d, *J* = 6.00, Hz, 1H), 1.37−1.19 (m, 28H), 0.88 (t, *J* = 7.00 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.48, 128.38, 127.09, 126.57, 69.26, 68.33, 41.85, 34.64, 31.91, 29.72, 29.68, 29.65, 29.64, 29.56, 29.50, 29.39, 29.34, 25.21, 23.20, 22.67, 14.05; HRMS-(EI) calcd for $C_{26}H_{45}NO$ 387.3501, found 387.3501.

4h: $[\alpha]^{25}_D = +27.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.12 (m, 10H), 3.73 (m, 1H), 2.58 (m, 3H), 1.98 (d, *J* = 3.5 Hz, 1H), 1.58 (m, 1H), 1.44 (d, *J* = 6.3 Hz 1H), 1.42 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 138.0, 129.4, 128.4, 128.3, 127.2, 126.6, 126.3, 69.6, 69.2, 41.4, 41.2, 29.7, 23.2; HRMS(EI) calcd for $C_{18}H_{21}NO$ 267.1623, found 267.1623. Anal. Calcd for $C_{26}H_{41}NO$: C, 81.41; H, 10.77; N, 3.65. Found: C, 81.38; H, 10.99; N, 3.66.

4i: $[\alpha]^{26}_D = +58.7$ (*c* 0.95, $CHCl_3$); mp 88−90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31−7.26 (m, 10H), 4.66 (d, *J* = 3.2 Hz, 1H), 2.67 (q, *J* = 6.5 Hz, 1H), 2.12 (d, *J* = 3.4 Hz, 1H), 1.84(m, 1H), 1.43 (d, *J* = 6.5 Hz,3H), 1.41 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.4, 141.8, 128.5, 128.3, 128.0, 127.8, 127.5, 127.2, 126.6, 126.1, 70.1, 69.1, 43.0, 29.4, 23.3. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.42; H, 7.80; N, 5.56.

4j: $[\alpha]^{29}_D = +6.2$ (*c* 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.32 (m, 5H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.61 (d, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 2.65 (q, *J* = 6.4 Hz, 1H), 2.14 (d, *J* = 3.9 Hz, 1H), 1.79 (m, 1H), 1.59 (m, 1H), 1.43 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 144.3, 133.7, 128.4, 127.4, 127.3, 127.1, 126.5, 113.7, 69.7, 69.0, 55.2, 42.9, 29.4, 23.3. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.10; H, 7.37; N, 4.96.

4k: $[\alpha]^{23}_D = +60.0$ (*c* 0.23, $CHCl_3$); mp 98−100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45−7.00 (m, 9H), 4.60 (d, *J* = 3.6 Hz, 1H), 2.66 (q, *J* = 6.6 Hz, 1H), 2.07 (d, *J* = 3.6 Hz, 1H), 1.79 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.3, 140.3, 133.4, 128.6, 128.5, 127.5, 127.3, 126.6, 69.5, 69.0, 42.5, 29.2, 23.0. Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 70.89; H, 6.30; N, 4.73.

Preparation of 4g-*threo*. To the solution of **3g** (139 mg, 0.36 mmol) in 2.0 mL of THF under nitrogen at −78 °C was added L-Selectride (1.0 M, 0.72 mL, 0.72 mmol) in THF. The mixture was stirred for 30 min at −70 °C and warmed to room temperature. The reaction mixture was treated with 10% aqueous NaOH solution, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 mL × 5), and the combined organic extracts were dried, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 3:7) provided **4g-*threo*** as a white solid (118 mg, 84%): $[\alpha]^{24}_D = +38.2$ (*c* 1.0, $CHCl_3$); mp 31.5−32.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 3.15 (m, 1H), 2.46 (q, *J* = 6.50 Hz, 1H), 1.89 (d, *J* = 3.00 Hz, 1H), 1.66 (d, *J* = 5.00, 1H), 1.50 (m, 3H), 1.44 (d, *J* = 6.50 Hz, 1H), 1.30−1.13 (m, 26H), 0.88 (t, *J* = 7.00 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.54, 128.62, 127.52, 126.89, 71.48, 69.73, 42.89, 35.40, 31.91, 31.76, 29.68, 29.65, 29.63, 29.57, 29.53, 29.46, 29.35, 25.36, 22.68, 22.51, 14.11; HRMS(EI) calcd for $C_{26}H_{45}NO$ 387.3501, found 387.3528.

Preparation of 2(*S*)-[1(*R*)-Phenylethylamino]octadecane-1,3-diol 6 and 7. To the solution of **4g-*threo*** (227 mg, 0.590 mmol) in 2.90 mL of methylene chloride was added 0.17 mL (2.93 mmol) of acetic acid. The mixture was stirred for 14 h and then quenched by 1 mL of saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (4 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated, and 2.90 mL of EtOH was added. To the solution was added KOH (67 mg, 1.18 mmol), and the reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo and then was treated with 1.0 mL of water and 1.0 mL of methylene chloride. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 mL × 4). The combined organic extracts were washed with 1.0 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Short silica gel chromatography provided 235 mg (98%) of **6** as a white solid. **6:** $[\alpha]^{24}_D = +30.0$ (*c* 1.00, $CHCl_3$); mp 57.4−59.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 3.91 (q, *J* = 6.50 Hz, 1H), 3.81 (dd, *J* = 10.5, 3.00 Hz, 1H), 3.56 (m, 2H), 2.61 (br, 2H), 2.29 (m, 1H), 1.39 (d, *J* = 6.50 Hz, 3H), 1.32−1.22 (m, 28H), 0.88 (t, *J* = 7.00 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.03, 128.47, 127.11, 126.77, 72.82, 61.32, 58.52, 55.30,

34.12, 31.89, 29.67, 29.65, 29.63, 29.58, 29.56, 29.33, 25.71, 24.96, 22.65, 14.08. Anal. Calcd for $C_{26}H_{47}NO_2$: C, 76.98; H, 11.68; N, 3.45. Found: C, 76.92; H, 11.50; N, 3.59. The same reaction with **4g-*erythro*** gave **7** in comparable yield. **7:** $[\alpha]^{24}_D = +28.6$ (*c* 1.0, $CHCl_3$); mp 42.8−44.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 5H), 3.90 (q, $J = 6.50$ Hz, 1H), 3.71 (d, $J = 4.50$ Hz, 2H), 3.51 (m, 1H), 2.44 (q, $J = 4.00$, Hz, 1H), 2.38 (br, 2H), 1.38 (d, $J = 6.00$ 3H), 1.37−1.22 (m, 28H), 0.88 (t, $J = 7.00$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.52, 128.54, 127.14, 126.57, 73.51, 60.22, 58.91, 55.91, 33.75, 31.91, 29.68, 29.66, 29.64, 29.63, 29.58, 29.53, 29.50, 29.35, 26.06, 24.49, 22.67, 14.10. Anal. Calcd for $C_{26}H_{47}NO_2$: C, 76.98; H, 11.68; N, 3.45. Found: C, 76.92; H, 11.50; N, 3.59.

Preparation of *N*-Boc-safingol and *N*-Boc-D-*erythro*-sphinganine 8 and 9. To the solution of **6** (167 mg, 0.41 mmol) in 21.0 mL of MeOH were added $(Boc)_2O$ (180 mg, 0.82 mmol) and 16.7 mg of $Pd(OH)_2$. The reaction mixture was stirred at room temperature with 1 atm of H_2 for 15 h, and then the catalyst was filtered and concentrated in vacuo. Purification by silica gel flash chromatography ($MeOH/CH_2Cl_2$, 5:95) provided 151 mg (91%) of **8** as a white solid. **8:** $[\alpha]^{21}_D = +19.8$ (*c* 1.00, $CHCl_3$); mp 80.0−81.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (d, $J = 8.00$ Hz, 1H), 3.90 (m, 1H), 3.79 (d, $J = 3.50$ Hz, 2H), 3.58 (m, 1H), 2.76 (br, 2H), 1.48−1.37 (m, 4H), 1.44 (s, 9H), 1.28−1.22 (m, 24H), 0.87 (t, $J = 7.00$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.50, 79.61, 73.04, 65.41, 54.25, 34.21, 31.92, 29.68, 29.66, 29.64, 29.59, 29.54, 29.34, 28.35, 25.55, 22.67, 14.09. Anal. Calcd for $C_{23}H_{47}NO_4$: C, 68.78; H, 11.80; N, 3.49. Found: C, 68.64; H, 11.99; N, 3.38. The same reaction with **7** gave **9** in comparable yield. **9:** $[\alpha]^{24}_D = +8.20$ (*c* 1.0, $CHCl_3$); mp 70.0−71.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (d, $J = 6.50$ Hz, 1H), 3.98 (dd, $J = 11.5$, 3.5 Hz, 1H), 3.77 (m, 1H), 3.75 (dd-like, 1H), 3.52 (m, 1H), 2.55 (br, 1H), 1.56−1.42 (m, 4H), 1.45 (s, 9H), 1.29−1.23 (m, 24H), 0.88 (t, $J = 7.00$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.06, 79.71, 74.41, 62.64, 54.72, 34.45, 31.91, 29.68, 29.66, 29.64, 29.58, 29.54, 29.34, 28.38, 25.94, 22.67, 14.10. Anal. Calcd for $C_{23}H_{47}NO_4$: C, 68.78; H, 11.80; N, 3.49. Found: C, 68.80; H, 11.73; N, 3.35.

Preparation of *N*-Boc-spisulosine 10. To a solution of **4g-*erythro*** (97.0 mg, 0.25 mmol) in 2.50 mL of MeOH were added $(Boc)_2O$ (60.0 mg, 0.28 mmol) and 9.70 mg of $Pd(OH)_2$. The reaction mixture was stirred at room temperature with 1 atm of H_2 for 15 h, the catalyst was filtered, and the filtrate was concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 1:9) provided 92.0 mg (95%) of the product **10** as a white solid: $[\alpha]^{24}_D = +15.2$ (*c* 1.00, $CHCl_3$); mp 82.9−84.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (m, 1H), 3.69 (m, 1H), 3.63 (m, 1H), 1.45 (s, 9H), 1.40−1.37 (m, 3H), 1.26 (m, 25H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.06, 79.63, 74.68, 50.78, 33.65, 32.12, 29.88, 29.86, 29.85, 29.78, 29.76, 29.55, 29.60, 27.17, 26.23, 22.88, 14.56, 14.31. Anal. Calcd for $C_{23}H_{47}NO_3$: C, 71.64; H, 12.28; N, 3.63. Found: C, 71.63; H, 12.26; N, 3.54.

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