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Enantiodivergent Synthesis of D- and L-*erythro*-Sphingosines through Mannich-Type Reactions of *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitrone

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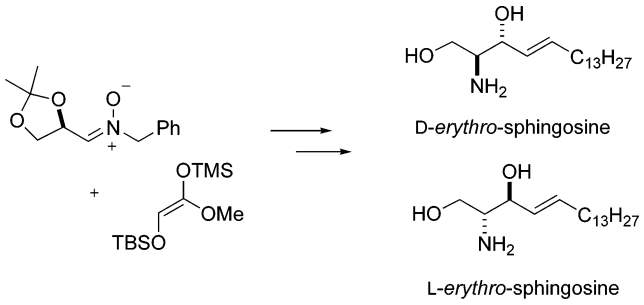
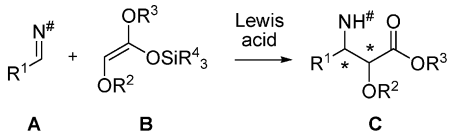


The addition of a 2-silyloxy silylketene acetal to *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (Mannich-type reaction) can be stereocontrolled to give 2*S*,3*S*,4*S* and 2*R*,3*R*,4*S* adducts as major compounds, depending on whether the reaction is activated with zinc(II) triflate or tin(IV) chloride, respectively. The corresponding major adducts were used for preparing diastereomeric polyhydroxy-β-aminoesters that were further converted into suitable orthogonally protected enantiomeric D- and L-*erythro*-sphingosines.

Stereoselective nucleophilic additions of enolates to imines and related compounds (the so-called Mannich-type reactions) are used extensively for the asymmetric synthesis of a broad range of β-amino carbonyl derivatives, which are useful as chiral auxiliaries, ligands, and building blocks for the preparation of various nitrogen-containing biologically active compounds.[1] Several examples concerning the Lewis-acid promoted addition of silylketene acetals to C═N double bonds **A**, including imines,[2] nitrones,[3] hydrazones,[4] and iminium salts,[5] have been reported during the past years. Of particular interest is the addition of 2-silyloxy silylketene acetals **B**, because two adjacent stereogenic centers are created simultaneously and α-silyloxy-β-amino acids **C** are obtained[6] (eq 1).



A **B** **C**

N#: NR^5, $N^+(O^-)R^5$, $NN(R^5)R^6$, $N^+(R^5)R^6$ (1)

Among the C═N functionalities **A** that can be used in Mannich-type reactions, nitrones offer some advantages. In addition to their high reactive C═N bond, nitrones possess a reactive oxygen atom, which allows the use of Lewis acids to modulate the reactivity. In this respect, Mannich-type reactions are rather suitable to be studied with nitrones, because those processes need to be activated by a Lewis acid. We have already reported[6] the stereocontrolled addition of unsubstituted silyl ketene acetals to D-glyceraldehyde-derived nitrone **1** en route to a new class of nucleoside analogues. Nitrone **1** has demonstrated to be an excellent equivalent of several chiral units containing both amino and oxygen functionalities.[7] On the basis of these results, we describe herein the stereocontrolled addition of a 2-silyloxy silylketene acetal to nitrone **1** en route to

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TABLE 1. Addition of Silylketene Acetal 2 to Nitrone 1[a]

entry	Lewis acid	equiv	time (h)	**3**:**4**[b]	**4a**:**4b**:**4c**:**4d**[c]	(3*S*,4*S*)/(3*R*,4*S*)[d]	anti/syn[e]	yield[f] (%)
1	TMSOTf	1.0	3	100:0	92:1:1:6	93:7	93:7	80
2	$ZnBr_2$	1.0	3	100:0	89:2:3:6	92:8	91:9	76
3	$ZnBr_2$	0.2	3	100:0	86:2:4:8	90:10	88:12	78
4	Et_2AlCl	1.0	3	0:100	94:0:3:3	97:3	94:6	68
5	Et_2AlCl	0.2	6	0:100	90:2:5:3	90:10	92:8	35
6	$AlCl_3$	1.0	3	30:70	88:3:6:3	94:6	91:9	60
7	$SnCl_2$	1.0	3	0:100	98:0:2:0	100:0	98:2	55
8	$Cu(OTf)_2$	1.0	3	60:40	81:1:14:4	95:5	82:18	66
9	$Sc(OTf)_3$	1.0	3	100:0	81:4:10:5	91:9	85:15	80
10	$Yb(OTf)_3$	1.0	3	100:0	98:0:2:0	100:0	98:2	84
11	$Zn(OTf)_2$	1.0	3	90:10	95:1:4:0	99:1	96:4	86
12	$Zn(OTf)_2$[g]	1.0	2	100:0	97:0:3:0	100:0	97:3	89
13	$Zn(OTf)_2$[g]	0.2	2	100:0	97:0:3:0	100:0	97:3	86
14	$SnCl_4$	1.0	3	75:25	35:47:6:12	41:59	82:18	82
15	$SnCl_4$[g]	1.0	3	70:30	7:85:3:5	10:90	92:8	84
16	$SnCl_4$[g]	0.2	3	70:30	20:72:3:5	23:77	92:8	30

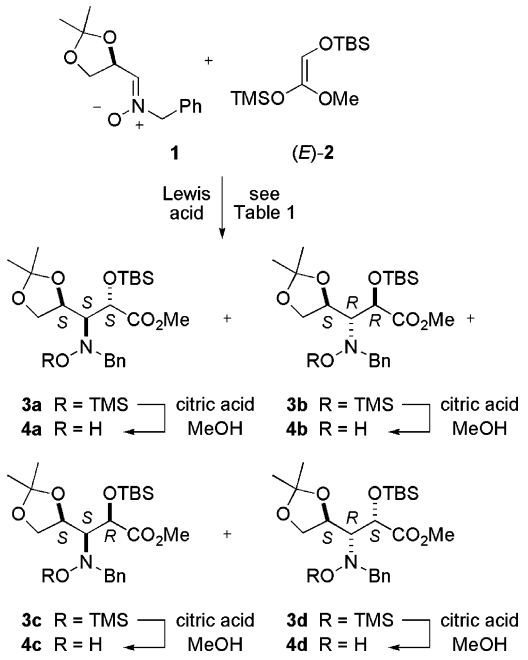
[a] The reaction was carried out in dichloromethane at −78 °C. [b] Determined by NMR of the crude reaction mixture. [c] Determined by NMR after desilylation of the reaction mixture, when necessary. [d] Referred to the diastereofacial selectivity, induced by the stereocenter at C-4. [e] Referred to the relative configuration between the two newly formed stereocenters at C-2 and C-3. [f] Referred to isolated yields of **3** + **4**. [g] The reaction was conducted in the presence of 4-Å molecular sieves.

polyhydroxy-*β*-amino acids. We further describe the use of the obtained products for the enantiodivergent synthesis of orthogonally protected D- and L-*erythro*-sphingosines.[8]

We studied the Mannich-type reaction of the readily available[9] nitrone **1** and silyl ketene acetal **2**.[10] We chose derivative **2** because it is easily synthesized from methyl glycolate, it is configurationally stable, and it bears two different silyl groups, facilitating further elaborations. The corresponding *Z*-isomer cannot be obtained with good stereoselectivity, and only an unuseful derivative with two TBS groups (which would give rise to nonorthogonally protected derivatives) can be prepared in the *Z* configuration with good yields.

In a typical experimental procedure, nitrone **1** in dichloromethane was stirred at −78 °C with silyl ketene acetal **2** and in the presence of a Lewis acid. Yields, product distribution, and Lewis acids are collected in Table 1. Depending on the Lewis acid used to promote the reaction, *O*-silyl hydroxylamines **3** and free hydroxylamines **4** were obtained. The formation of four diastereoisomers is possible on the addition of **2** to **1**. Whereas TMSOTf (entry 1) and Zn-derived Lewis acids (entries 2, 3, 9, 11−13) only afforded *O*-silyl hydroxylamines **3**, the rest of Lewis acids produced either free hydroxylamines (entries 4, 5, 7, and 10) or mixtures of compounds (entries 6, 8, 14−16). From a synthetic point of view and to analyze the stereoselectivity of the reaction, it was convenient to treat the reaction mixture with citric acid in methanol to obtain free hydroxylamines **4** (Scheme 1). Under these conditions, only

SCHEME 1. Mannich-Type Reaction between 1 and 2



trimethylsilyl groups are removed. The addition reaction was carried out with 1.0 equiv of Lewis acid, although catalytic amounts can be used in those cases in which *O*-silylated hydroxylamines are obtained (entries 3 and 13). On the other hand, in those cases in which compounds **4** were the main products of the reaction, the yield dropped considerably under catalytic conditions (entries 5 and 16), presumably because the Lewis acid promotes the desilylation and, consequently, the catalyst is eliminated from the reaction mixture.

The diastereoselectivities are reasonably good, with the 2*S*,3*S*,4*S* isomer **4a** being the major product after desilylation. Excellent diastereofacial inductions exerted by the dioxolane ring (corresponding to a (**4a** + **4c**)/(**4b** + **4d**) ratio) were obtained with $SnCl_2$ (entry 7), $Yb(OTf)_3$ (entry 10), and $Zn(OTf)_2$ (entry 11). In the last case, better results were obtained when the reaction was conducted in the presence of molecular sieves (entry 12). Moreover, the use of 20 mol % of Lewis acid (entry 12) did not lead to loss of selectivity or chemical yield.

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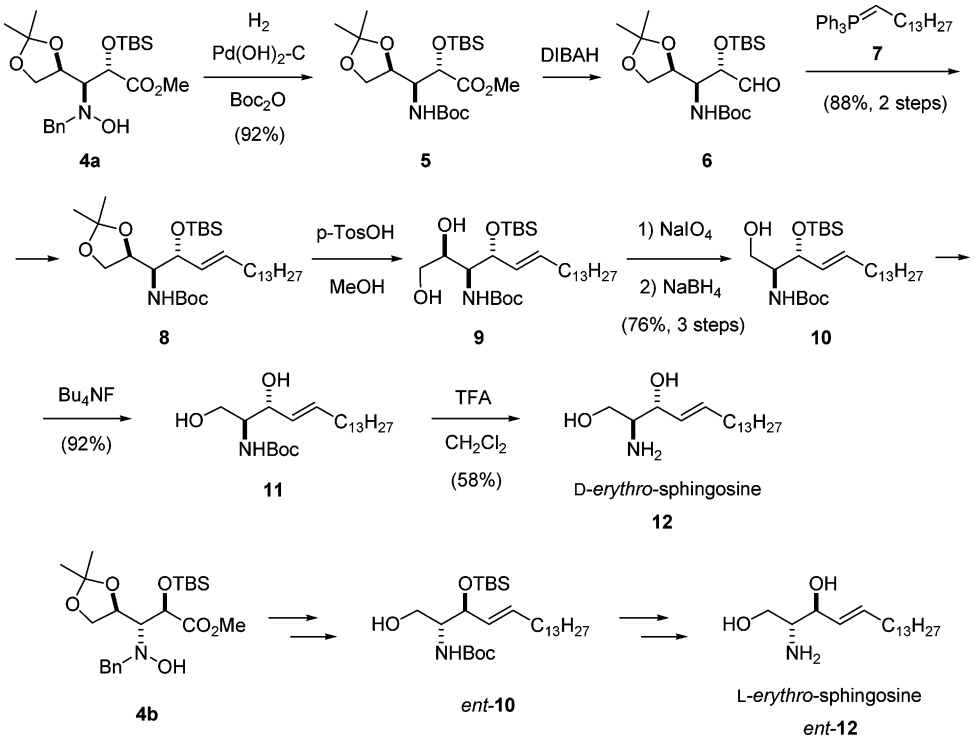
SCHEME 2. Synthesis of Sphingosines



Interestingly, when $SnCl_4$ was used as Lewis acid (entry 14), a dramatic change on the products distribution was observed, with a slight reversal of the diastereofacial selectivity being found. Moreover, such a reversal increased considerably by the addition of molecular sieves to the reaction mixture (entry 15). Under these conditions, the 3*R*,4*S* isomers were obtained preferentially, with the stereofacial selectivity being 90:10. Unfortunately, $SnCl_4$ could not be used in a catalytic amount, due to the reasons given above. In all cases, the two newly formed stereogenic centers adopted an anti relative configuration corresponding to 2*R*,3*R* and 2*S*,3*S* isomers **4a** and **4b**, respectively. Because of it, only those major compounds were fully characterized and further used in the synthesis of sphingosines. The configurational assignment of compounds **4a** and **4b** was established by converting them into derivatives of known absolute configurations, as will be subsequently discussed. The stereochemical course of the reaction can be explained on the basis of alternative mechanisms, as we have previously reported.[11] According to these findings, the reaction promoted by Lewis acids such as $Zn(OTf)_2$ is better described as a nucleophilic addition stepwise process. On the other hand, the reaction promoted by Lewis acids forming more covalent interactions with the nitrone oxygen (such as $SnCl_4$) could be assigned to a polar concerted 1,3-dipolar cycloaddition.[12]

Compound **4a** was readily transformed into protected β-amino-α-hydroxy ester **5** in a very efficient way by catalytic hydrogenation in the presence of Boc_2O. Compound **5** was reduced to aldehyde **6**, which was used in the next step without further purification. A Schlosser modification of the Wittig condensation between **6** and phosphorane **7** afforded alkene **8** in 88% isolated yield and as an only *E*-isomer. The well-known two-step transformation of the dioxolane ring into a hydroxymethyl group[13] afforded the orthogonally protected D-*erythro*-sphingosine **10** (61.5% overall yield from **4a**, 6 steps). The configurational assignment of compound **10** was made by its conversion to *N*-Boc-D-*erythro*-sphingosine **11** and by a comparison of the obtained product with that described in the literature,[8c] as well as by deprotecting **11** to D-*erythro*-sphingosine **12** and comparison of the obtained compound with an authentic sample. In both cases, the physical and spectroscopic properties of the obtained compounds were fully consistent with those reported.

Following the same reaction sequence illustrated in Scheme 2, the major compound **4b**, obtained when $SnCl_4$ was used as a promoter, was transformed into the enantiomeric protected L-*erythro*-sphingosine *ent*-**10** (see Supporting Information). Complete deprotection of this compound afforded pure L-*erythro*-sphingosine *ent*-**12**, which served to further confirm the configurational assignments previously made.

In conclusion, we have achieved a stereodivergent Mannich-type reaction between nitrone **1** and α-alkoxysilyl ketene acetal **2**, which provided efficient routes to enantiomerically pure polyhydroxy-β-amino acids. In addition, further elaboration of these compounds allowed us to apply that diastereodivergent approach to the enantiodivergent preparation of orthogonally protected D- and L-*erythro*-sphingosines **10** and *ent*-**10** in 53.1 and 40.5% overall yields (7 steps from nitrone **1**), respectively, thus showing a high efficiency relative to prior syntheses.[8] Compounds **10** and *ent*-**10** are of synthetic utility for the preparation of more complex compounds such as ceramides,[8a,14] glycosphingolipids,[8h,15] or phosphorylated derivatives.[8b,d] At

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(12) Recent studies based on NMR data of the corresponding complexes have demonstrated that nitrones act as monodentate ligands with Lewis acids: Merino, P.; Tejero, T. Unpublished results. See also ref 7.

(13) For examples of the equivalence between the dioxolane ring and the hydroxymethyl group, see: Chiacchio, U.; Borrello, L.; Iannazzo, D.; Merino, P.; Piperno, A.; Rescifina, A.; Richichi, B.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2419−2425 and references therein.

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present, we are studying Mannich-type reactions of 2-silyloxy silyl ketene acetals with other chiral nonracemic nitrones.

Experimental Section

General Methods. For general experimental information see, ref 16. Nitrone **1**[9] and silyl ketene acetal **2**[10] were prepared as described.

Reaction between Nitrone 1 and Silyl Ketene Acetal 2. A 50-mL round-bottomed flask was charged, under an argon atmosphere, with 3-Å activated molecular sieves (200 mg), nitrone **1** (0.587 g, 2.5 mmol), and anhydrous dichloromethane (15 mL). The resulting mixture was cooled to 0 °C, and then a solution of the corresponding Lewis acid (see Table 1) in anhydrous dichloromethane (5 mL) was added dropwise. After 10 min of stirring, the mixture was cooled to −78 °C, and a solution of silyl ketene acetal 2 (1.39 g, 5 mmol) in dichloromethane (5 mL) was added slowly over 10 min. When the reaction was finished (see Table 1), aq saturated $NaHCO_3$ (10 mL) was added under vigorous stirring, and the reaction mixture was allowed to reach room temperature. The organic phase was separated, and the aqueous one was extracted with EtOAc (2 × 15 mL). The combined organic extracts were filtered through a pad of Celite, washed with brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/EtOAc, 95:5) to yield the pure products (data for compounds **3** and **4**: see Supporting Information).

***tert*-Butyl (2*S*,3*S*,4*R*,*E*)-2-(*tert*-Butyldimethylsiloxy)-1,2-dihydroxynonadec-4-en-2-ylcarbamate 9.** A solution of alkene **8** (0.4 g, 0.69 mmol) in MeOH (30 mL) was treated with *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol), and the resulting solution was heated at 50 °C for 4 h, at which time saturated aq $NaHCO_3$ (39 mL) was added. The resulting mixture was extracted with ethyl acetate (2 × 30 mL); the combined organic extracts were dried ($MgSO_4$), filtered, washed with brine (25 mL), and evaporated under reduced pressure. The obtained crude diol **9** was pure enough to be used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.08 (s, 6H), 0.82−0.94 (m, 12H), 1.16−1.41 (m, 22H), 1.44 (s, 9H), 1.99−2.13 (m, 2H), 3.03 (br s, 1H), 3.30 (br s, 1H), 3.53−3.71 (m, 2H), 3.76 (dd, 1H, J = 3.1, 7.6 Hz), 3.84−3.94 (m, 1H), 4.13−4.21 (m, 1H), 4.94 (d, 1H, J = 6.3 Hz), 5.46 (dd, 1H, J = 6.3, 14.7 Hz), 5.81 (dt, 1H, J = 6.6, 14.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −4.0, 15.2, 19.2, 23.9, 26.6, 29.5 (2C), 30.2, 30.3, 30.4(2C), 30.5, 30.6 (2C), 30.7, 32.4, 33.0, 33.3, 56.6, 64.3, 72.8, 74.5, 81.5, 132.3, 135.0, 156.7.

***tert*-Butyl (2*S*,3*R*,*E*)-2-(*tert*-Butyldimethylsiloxy)-1-hydroxyoctadec-4-en-2-ylcarbamate 10.** The diol **9** (obtained from **8**, as described above) was dissolved in CH_2Cl_2 (20 mL) and added to a vigorously stirred suspension, previously formed with chromatographic grade silica gel (1.5 g), aq solution of 0.65 M $NaIO_4$ (1.5 mL), and CH_2Cl_2 (15 mL). The reaction mixture was stirred for 45 min and filtered. The silica gel was washed with CH_2Cl_2 (2 × 10 mL), and the filtrate was evaporated under reduced pressure to afford the crude aldehyde (0.05 (s, 6H), 0.81−0.95 (m, 12H), 1.16−1.43 (m, 22H), 1.45 (s, 9H), 2.03−2.15 (m, 2H), 4.19−4.30 (m, 1H), 4.42−4.49 (m, 1H), 5.29−5.48 (m, 2H), 5.88−6.02 (m, 1H), 9.57 (d, 1H, J = 2.9 Hz)) which was taken up in MeOH (15 mL), cooled to 0 °C, and treated with $NaBH_4$ (56 mg, 1.5 mmol). After stirring at 0 °C for 1 h, the reaction mixture was treated with saturated aq $NaHCO_3$ (25 mL) and EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, washed with brine (25 mL), and evaporated under reduced pressure. The crude product was purified by radial chromatography (hexane/EtOAc, 75:25) to give pure **10** (0.269 g, 76% from **8**) as an oil: $[\alpha]^{22}_D$ −7.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.08 (s, 6H), 0.79−0.96 (m, 12H), 1.17−1.41 (m, 22H), 1.44 (s, 9H), 2.01−2.14 (m, 2H), 2.77 (br s, 1H), 3.57−3.70 (m, 1H), 3.77 (dd, 1H, J = 5.7, 11.0 Hz), 3.96 (dd, 1H, J = 1.1, 11.0 Hz), 4.40 (d, 1H, J = 6.1 Hz), 4.90 (d, 1H, J = 8.1 Hz), 5.48 (m, 1H), 5.73−5.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −4.1, 14.3, 18.0, 22.9, 25.0, 28.6, 29.2, 29.3, 29.3, 29.7, 29.7, 30.4, 31.1, 32.7, 56.8, 64.9, 72.9, 76.6, 77.0, 77.4, 80.9, 131.1, 133.5, 156.4. Anal. Calcd for $C_{29}H_{59}NO_4Si$: C, 67.78; H, 11.57; N, 2.73. Found: C, 67.89; H, 11.77; N, 2.53.

***tert*-Butyl (2*S*,3*R*,*E*)-1,3-Dihydroxyoctadec-4-en-2-ylcarbamate 11.** A solution of **10** (50 mg, 0.1 mmol) in THF (5 mL) was treated with a 1.0 M anhydrous solution of Bu_4NF in THF (0.15 mL, 0.15 mmol) at ambient temperature. After 1 h of stirring, the reaction mixture was diluted with saturated aq $NaHCO_3$ (15 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a crude product that was purified by radial chromatography (hexane/EtOAc, 80:20) to give pure **11** (36 mg, 92%) as a white solid: mp 64−66 °C; $[\alpha]^{25}_D$ −1 (*c* 0.12, $CHCl_3$) [lit.[10g] $[\alpha]^{24}_D$ −1.4 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.90 (t, 3H, J = 6.6 Hz), 1.12−1.42 (m, 22H), 1.46 (s, 9H), 2.00−2.15 (m, 2H), 2.60 (br s, 2H), 3.56−3.63 (m, 2H), 3.78 (dd, 1H, J = 11.0, 3.6 Hz), 4.30 (t, 1H, J = 4.2 Hz), 5.26 (br s, 1H), 5.50 (ddt, 1H, J = 0.9, 5.2, 15.8 Hz), 5.80 (dd, 1H, J = 5.4, 15.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.0, 22.9, 28.5, 29.1, 29.2, 29.3, 29.4, 29.6(2C), 32.0, 32.3,55.9, 62.6, 75.0, 79.8, 128.9, 134.0,156.5. Anal. Calcd for $C_{23}H_{45}NO_4$: C, 69.13; H, 11.35; N, 3.51. Found: C, 69.27; H, 11.18; N, 3.39.

(2*S*,3*R*,*E*)-2-Amino-1,3-dihydroxy-4-octadecene (D-*erythro*-sphingosine) 12. A solution of **11** (25 mg, 0.063 mmol) in TFA/H_2O (3:1 v/v, 2 mL) was stirred at ambient temperature for 12 h, at which time 33% aq ammonia was added until pH = 8−9, and the resulting reaction mixture was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a residue that was recrystallized from $CHCl_3$/Et_2O/hexane 1:1:4 to afford pure D-*erythro*-sphingosine **12** (11 mg, 58%) as a white solid. The physical and spectroscopic data of this material were identical to both the literature data[10e] and those obtained from an authentic sample.

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Supporting Information Available: Experimental procedures for the preparation of *ent*-**10** and L-*erythro*-sphingosine from **4b**, characterization of the intermediate products, and ^{1}H and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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