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A Short Enantiodivergent Synthesis of D-*Erythro* and L-*Threo* Sphingosine

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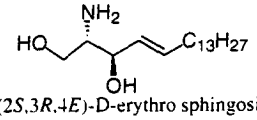
ABSTRACT: A new, short (6 steps) and efficient enantiodivergent route to both D-*erythro* and L *threo*-sphingosine **I** and **II** is disclosed. The high diastereoselection (100% de) reached in the creation of the C-3 stereocenter relies on the use of a sulfoxide as chiral controlling agent in the reduction of the common precursor β-keto sulfoxide **3**. The desired *E*-alkene of sphingosines has been constructed by the Schlosser modification of the Wittig reaction between the aldehyde **8** and the phosphoniun salt **9**. The reported methodology can easily be extended to the synthesis of a large number of optically pure *syn* and *anti* amino alcohols starting from commercially available amino acids.

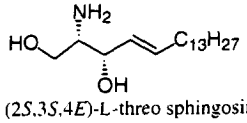
The receptor mediated enzymatic cleavage of membrane lipids to generate intracellular second messengers is a crucial biological event that has been firmly established in recent years.[1] In this connection, the generation of second messengers from inositol-containing glycolipids has been proposed as a general pathway of intracellular signal transduction.[2] The molecular basis of this new pathway of intracellular signaling remains, however, very poorly understood and quite a number of basic chemical and biological aspects have yet to be discovered. We are presently engaged in synthetic and structural studies in this area dealing with both the putative glycan mediators and the corresponding glycolipid precursors.[3] These glycolipids may contain either a diacyl glycerol moiety or a ceramide as a lipophilic region, and both of them behave in turn as an intracellular second messenger.[1,2] The long chain base component of the ceramide moiety, D-*erythro* sphingosine, has been found itself to be a potent and specific inhibitor of protein kinase C and plays therefore a pivotal role in signal transduction.[4]

As a part of our studies in this area,[3] we now report a new, short, highly diastereoselective and enantioselective synthesis of D-*erythro* and L-*threo* sphingosine. Because of its biological importance sphingosine has been a long standing synthetic target and a number of syntheses have recently appeared.[5]

Our synthetic approach to D-*erythro*, L-*threo* sphingosine starts from a common synthetic precursor and uses a sulfoxide as a chirality controlling agent for the construction of both epimers at C-3 in a predictable manner.



(2*S*,3*R*,4*E*)-D-erythro sphingosine **I**



(2*S*,3*S*,4*E*)-L-threo sphingosine **II**

Figure 1

Our synthetic approach is shown in scheme 1. Starting from L-serine, three high yielding synthetic manipulations led to the protected serine methyl ester **1**.[7] Condensation of **1** with 2 equivalents of the carbanion of (*R*)-(+)-methyl *p*-tolyl sulfoxide **2**[8] gave the common precursor β-ketosulfoxide **3** in 70% yield. The diastereoselective reduction of compound **3** by means of DIBALH or DIBALH in the presence of $ZnCl_2$[9] constitutes the key step in the synthetic sequence. A question may be raised, as to whether the chiral secondary amine protected with a bulky Boc group (α to the prochiral ketone) or the chiral sulfinyl functionality in compound **3**, will control the stereochemical outcome of the reduction reaction (the 2 factors may be expected to operate in opposite directions).[10]

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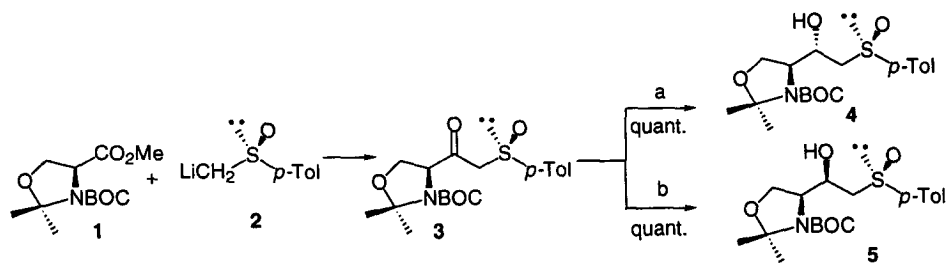


(a) DIBALH, THF, -78°C; (b) DIBALH / $ZnCl_2$, THF, -78°C

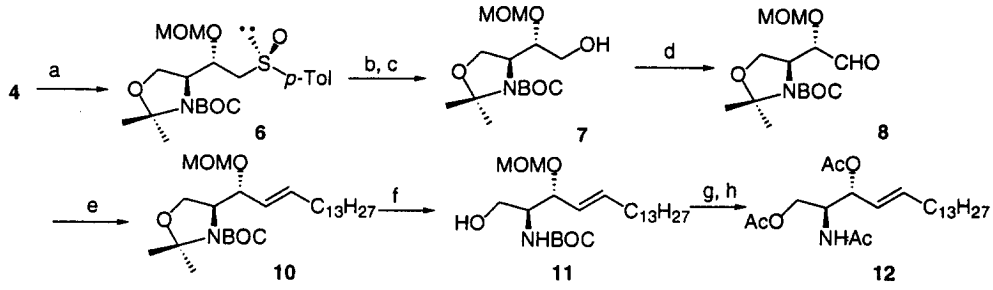
Scheme 1

Treatment of **3** with 1.1 equivalent of DIBALH at -78 C gave β-hydroxysulfoxide **4** in quantitative yield as a single isomer as shown by ^1H NMR and ^{13}C NMR of the crude product.[11] In contrast, the same reaction using DIBALH in the presence of 1 equivalent of $ZnCl_2$ gave the β-hydroxysulfoxide **5** epimer of **4** at the newly created chiral center in quantitative yield and also as a single isomer. The absolute configuration at C-3 (sphingosine numbering) in compounds **4** and **5** was determined from the proton NMR data. Table 1 shows the significant coupling constants J_{anti} and J_{gauche} and the chemical shift data for the methylene protons α to the sulfinyl group in both compounds. The value ΔJ (J anti - J gauche) is higher for compound **4** (9.6 Hz), than for compound **5** (4.6 Hz), and additionally Δν is also higher for compound **4** (111.4 Hz) than for compound **5** (15.65 Hz). Based on previous studies with related systems[12] these data are indicative of an (R_S, 2*S*) relative configuration in **4** and (R_S, 2*R*) relative configuration in **5**.

Table 1: Vicinal coupling constants and chemical shifts data for the methylene protons α to the sulfinyl group in **4** and **5**.

Compound	J_{anti}	J_{gauche}	J_{anti}-J_{gauche}	$\Delta\nu=\delta_A-\delta_B$
4	9.66 Hz	<1 Hz	~9.0 Hz	111.4 Hz
5	8.35 Hz	3.75 Hz	4.6 Hz	15.65Hz

Treatment of the secondary alcohol **4** with methoxymethyl chloride in THF at 0°C using sodium hydride as base gave the fully protected sulfinyl derivative **6** in 90 % yield (scheme 2).[12] One pot Pummerer rearrangement using trifluoroacetic anhydride at 0 °C and sodium borohydride reduction led to the optically pure primary alcohol **7** in 80% yield.[13] Swern oxidation of **7** gave the highly functionalized aldehyde **8** which was used in the next step without further purification. Wittig coupling of the aldehyde **8** and tetradecyltriphenyphosphonium bromide **9** gave the desired adduct in variable yield and stereoselectivity depending on the experimental conditions performed. The *Z* alkene ($J_{4,5}$ = 9.2 Hz) was the major product under most conditions, as expected for a non-stabilized phosphonium salt ylide and all attempts to isomerize this *Z* alkene to the *E*-isomer failed. The *E* alkene ($J_{4,5}$ = 15 Hz) could, nevertheless, be obtained as the only isomer using the Schlosser modification of the Wittig reaction under controlled experimental conditions. It is worth noting that attempts to perform this olefination by means of a Julia-Lythgoe coupling afforded **10** in a rather low yield and low selectivity. The acetal group was removed by treatment with 80% aqueous acetic acid at 80 °C to give the free primary alcohol **11** in 90 % yield.

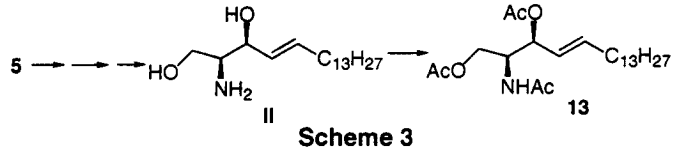


(a) NaH, MOMCl, THF, 0°C; (b) $(CF_3CO)_2O$, CH_3CN, Collidine, 0°C; (c) $NaBH_4$, H_2O; (d) $(COCl)_2$, DMSO, NEt_3; (e) $CH_3(CH_2)_{12}CH_2PPh_3Br$ (**9**), PhLi, LiBr, Et_2O/toluene , -30°C to rt; (f) Aq. AcOH(80%); (g) CF_3CO_2H, H_2O; (h) Ac_2O, Pyridine, DMAP (cat.)

Scheme 2

Alcohol **11** is a valuable building block that can be readily connected to inositol derivatives through a phosphodiester linkage or directly glycosylated with a suitable glycosyl donor. Further deprotection of **11** with trifluoroacetic acid-water followed by acetylation of the crude material afforded the known triacetyl C-18 D-*erythro* sphingosine **12**, whose spectroscopic and physical data are in excellent accord with the reported literature values.[5a,c,14]

The same reaction sequence, conducted on the β-hydroxysulfoxide **5**, yielded optically pure *threo* sphingosine **II**. Conversion to the known triacetate **13** having spectroscopic data identical to that reported in the literature confirmed the structure of **II** (scheme 3).[5a,c,14]



Scheme 3

The above results permit the unequivocal confirmation of the structural assignment of the precursors **4** and **5** and demonstrates that the sulfinyl group controls the stereochemical course of the reduction of the β-ketosulfoxide **3**. To the best of our knowledge this is the first time that it has been shown clearly that the sulfinyl sulfur controls the diastereoselective reduction of a ketone α to a bulky N-Boc group.Thus the method reported here permits the synthesis of a large number of biologically important *syn* and *anti* amino alcohols in a predictable manner. Moreover, starting from commercially available D-serine and using the same strategy will permit the synthesis of L-*erythro* and D-*threo* sphingosines.

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(10) The bisprotected amino ketone **3** is expected to give *syn* amino alcohol by assuming external hydride delivery to the less hindred face of the carbonyl of **3** existing in a non chelated conformation (Felkin-Ahn model). In contrast, the keto sulfoxide **3** is expected to give the *anti* amino alcohol, assuming hydride delivery from the same side as the sulfinyl oxygen previously chelated to DIBAL.

(11) **4**: To a solution of β-ketosulfoxide **3** (2.4 g , 6.3mmol) in tetrahydrofuran (50 mL) was added at -78°C DIBALH (1M solution in toluene, 7 mL, 7 mmol, 1.1equ.) dropwise. After 30 min, the reaction mixture was treated with methanol (30 mL), and evaporated to dryness. The residue was dissolved in a 5% aqueous solution of HCl (50 mL), and extracted with dichloromethane (4 x 50mL) dried over magnesium sulfate, filtered and evaporated under vacuum to obtain β-hydroxy sulfoxide **4** (2.4 g,100%) as a colorless oil. $[\alpha]^{23}_D$ = +59 (*c* 2, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$, 50°C) δ. 7.4 (AA'BB'system, J_{AB}= 8.3 Hz, 4H, Δν = 52.83, 4H), 4.5 (br, 1H), 4.1 (m, 1H), 4 (m. 1H), 3.9 (ABX system, J_{AB} = 9.10 Hz, J_{AX} = 5.6 Hz, J_{BX} = 0.9 Hz, Δν = 59.97 Hz, 2H), 3.29 (ABX system, J_{AB} = 13.7 Hz, J_{AX} = 9.66 Hz, J_{BX} <1 Hz, Δν = 111.4 Hz, 2H), 2.36 (s, 3H), 1,4 (br s, 12H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, 50°C, $CDCl_3$) δ 21.1, 23.7, 26.7, 28.1, 59.1, 61.0, 64.5, 68.2, 80.8, 94.1, 124.0, 1329.9, 141.3; *Anal.* Calcd. for $C_{19}H_{29}NO_5S$: C, 59.50; H, 7.61; N, 3.65; S, 8.36. Found: C, 59.57; H, 7.85; N, 3.68; S, 8.15.

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