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Aziridine-2-Carboxylic Acid Mediated Asymmetric Synthesis of D-*erythro*- and L-*threo*-Sphingosine from a Common Precursor

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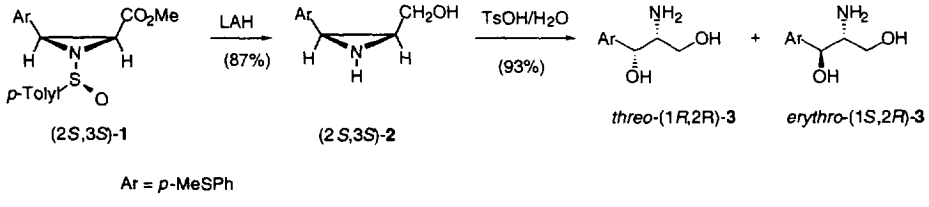
Summary: Short, two and three step asymmetric syntheses of L-*threo*- and D-*erythro*-sphingosine (–)-**6a** and (–)-**9a**, respectively, in 58 and 31 percent overall yield were accomplished via the stereo and regioselective ring opening of N-sulfinylaziridine 2-carboxylic acid **4**.

Enantiomerically pure aziridines serve as versatile intermediates for the asymmetric synthesis of biologically active materials because they undergo highly regio- and stereocontrolled ring opening reactions with nucleophiles.[1] This is particularly true for aziridine 2-carboxylic acids which afford β-substituted α-amino acids upon opening.[2] Using *cis*-*N*-(*p*-toluenesulfinyl)-2-carbomethoxyaziridine **1**, we recently described a highly efficient asymmetric synthesis of *threo*-(-)-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol (**3**), the key intermediate in the manufacture of the broad spectrum antibiotics thiamphenicol and florfenicol.[3] This procedure involved the regio- and stereospecific S_N2 ring opening of the corresponding aziridine-2-methanol **2** with TsOH/H_2O affording *threo*-**3** in 93% yield with none of the *erythro*-**3** isomer being detected (Scheme 1). A similar 2-amino-1,3-diol unit is found in sphingosine [*erythro*-(-)-2-amino-D-4(E)-octadecene-1,3-diol (**9a**)], the major constituent of the lipid backbone of the sphingolipids (e.g. ceramides, cerebrosides, sphingomyelins, gangliosides and glycosphingolipids).[4] The sphingolipids are important membrane components that play crucial roles in cell recognition events such as growth,

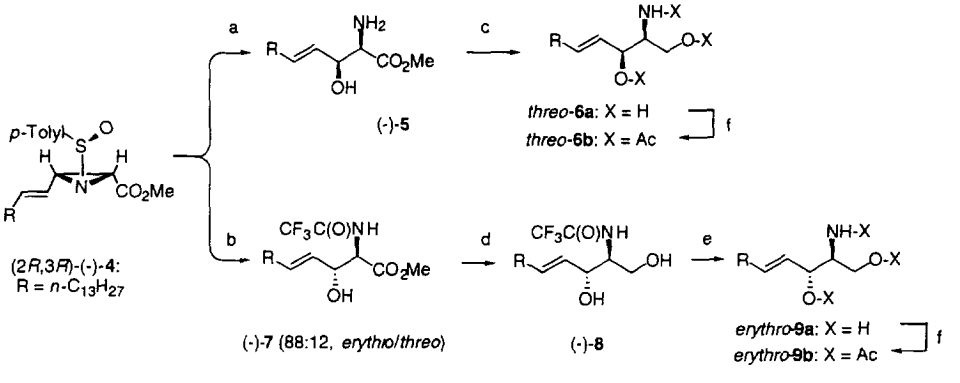
Scheme 1



differentiation, the immune response[5] and as receptors for HIV binding in cells lacking the CD4 receptor.[6] Furthermore, all of the sphingosine enantiomers are reported to be potent inhibitors of protein kinase C (PKC)[7] as well as stimulators of DNA synthesis and cell proliferation.[8] In this letter we describe the first aziridine-mediated asymmetric syntheses of L-*threo* and D-*erythro* sphingosines **6a** and **9a**, via a common intermediate and we also discoverd a new Pummerer induced rearrangement of N-sulfinyl aziridines.[9]

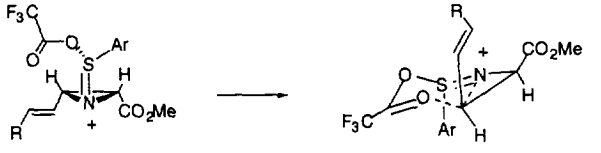
Synthesis of the less common L-*threo* sphingosine **6a** by the protocol outlined in Scheme 1 requires aziridine (2*R*,3*R*)-(-)-**4**[13] and would appear to be straightforward (Scheme 2). However, model studies with aziridine *rac*-**4** (R = *n*-C_3H_7) quickly demonstrated the problematic nature of this approach. Reduction to the aziridine methanol with lithium aluminum hydride (LAH) and other reducing reagents (DIBAL, $NaBH_4$) gave the alcohol in low yield (ca 30%) and hydrolysis ($TsOH/H_2O$) gave an inseparable mixture of stereo- and regioisomeric aminodiols. On the other hand, treatment of (-)-**4** in acetone/TFA/H_2O gave β-hydroxy-α-amino acid (-)-**5** as a single isomer in 72% yield following flash chromatography. This hydrolysis proved to be very sensitive to the reaction conditions with higher temperatures and other solvents (MeCN, THF) giving multiple, unidentified products, and up to 10% of the *erythro*-isomer. Reduction of (-)-**5** with $LiBH_4$ gave L-(-)-*threo* sphingosine (**6a**) in 80% yield. This was quantitatively acetylated to the more stable triacetate (+)-**6b**. Both materials had spectral properties identical with literature values.[12a]

Scheme 2



(a) 50% aqueous TFA/acetone, 0 °C, 24 h, 72%; (b) TFAA/CH_2Cl_2, 35 °C, 15 min., radial chromatography, 59%; (c) $LiBH_4$/MeOH, rt. , 30 min. 80%; (d) $LiBH_4$/MeOH, rt., 1 h, 71%; (e) K_2CO_3/EtOH, 50 °C, 5 h, 75%; (f) Ac_2O/pyr. 100%.

Selectivity in aziridine ring-opening depends on the ring substituents, the activating group on nitrogen and the reaction conditions because competitive S_N1 and S_N2 process are involved. Since anti selectivity generally predominates, it would appear impossible to obtain the naturally occurring D-(-)-*erythro*-sphingosine **9a** as the major isomer from cis-aziridine (-)-**4**. Remarkably, treatment of (-)-**4** with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at 35 °C resulted in an 88:12 mixture of *erythro*- and *threo*-**7** which were separated by radial chromatography (ether:*n*-pentane) to give the major isomer in 59% yield. Formation of *erythro*-**7** from cis-**4** requires the highly unusual attack of the nucleophile from the same side as the departing amino group. While details of this transfromation are at present unclear, we suggest that activated sulfoxide complex **10**, well precedented in the Pummerer rearrangement of sulfoxides,[14] undergoes a stereospecific [3,3]-sigmatropic rearrangement of the trifluoromethyl acetoxy group to a developing carbocation or ion pair **11**. The aziridine N-activating group which promotes this type of ring-opening is the amino-sulfonium salt.



10 **11**

Despite literature to the contrary,[15] all attempts to remove the *N*-trifluoroacetyl group in *erythro*-(-)-**7** by reaction with aqueous K_2CO_3/EtOH failed, affording instead the retro-aldol aldehyde (*E*)-hexadecenal in 50% yield.[16] This problem was solved by reduction of (-)-**7** with $LiBH_4$ to give (-)-**8** in 80% and then by hydrolysis with aqueous K_2CO_3/EtOH at 50 °C for 5 h. *erythro*-(-)-Sphingosine **9a** was isolated by flash chromatography in 71% yield and was identical in all respects with an authentic sample.[12a]

In summary, short two and three step asymmetric syntheses of *threo* and *erythro* sphingosine (-)-**6a** and (-)-**9a**, respectively, in 58 and 31 % overall yield from the N-sulfinylaziridine 2-carboxylic acid **4** are described. Significantly, the discovery of a novel Pummerer induced rearrangement of N-sulfinylaziridines makes it possible for the first time to prepare both *erythro* and *threo* β-hydroxy-α-amino acid derivatives from a single precursor.

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