Pergamon

Tetrahedron Letters 40 (1999) 9063–9064

TETRAHEDRON LETTERS

An alternative synthesis of D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine

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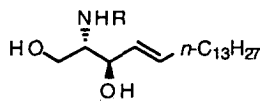
Received 27 August 1999; revised 20 September 1999; accepted 1 October 1999

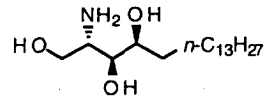
Abstract

Chiral β-lactam **1** obtained from D-(−)-tartaric acid was converted to a D-*erythro*-sphingosine equivalent **7** in 35% yield, without yielding a 4*Z*-geometrical isomer, and L-*lyxo*-phytosphingosine **8** in 45% yield, respectively.

D-*erythro*-Sphingosine, which exhibits potent inhibitory activity against protein kinase C, is a lipophilic component of glycosphingolipids and ceramides. Sphingosines and ceramides have been shown to play a role in intracellular signaling along with other secondary messenger molecules. Because of the importance of these compounds, even though a great deal of effort has been devoted to the synthesis of the chiral sphingosines, various synthetic routes are still being investigated to produce them more effectively. Here we report an alternative route for the synthesis of D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine.



D-*erythro*-sphingosine; R = H
ceramide; R = $CO(CH_2)_{14\text{-}22}Me$



L-*lyxo*-phytosphingosine

The starting β-lactam **1** ($[\alpha]_D^{24}$ −29.5, *c* 1.2, $CHCl_3$), obtained from D-(−)-tartaric acid according to a previously reported method,[1] was converted to alcohol **2** by sodium borohydride reduction (Scheme 1). The alcohol **2** was treated with triisopropylsilyl chloride using imidazole as a base, and successively treated with di-*tert*-butyl dicarbonate and triethylamine to give **3**. Treatment of **3** with *n*-tetradecyl *p*-toluenesulfonate and *n*-butyllithium yielded a mixture of diastereomers **4**.[2] The *p*-toluenesulfonyl moiety of **4** was eliminated with lithium naphthalenide[3] to give **5**. Deprotonation of **5** with potassium bis(trimethylsilyl)amide and successive sulfonylation with *N*-phenyltrifluoromethanesulfonimide[4] gave

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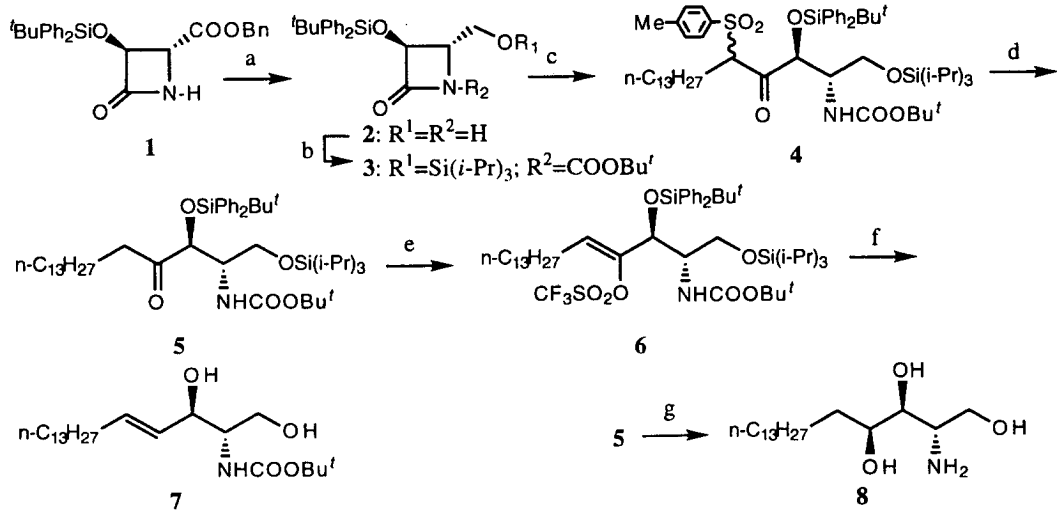
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01906-1

Z-enoltriflate **6**, exclusively. At this stage, the geometry of **6** was not yet clear. However, compound **7** obtained in the next stage was *trans*-olefin. Compound **6** was concluded to be Z-enolate, because the reductive elimination of the trifluoromethanesulfonate group from the vinyltriflates, by formic acid and triethylamine using bis(acetato)bis(triphenylphosphine)palladium(II) as a catalyst, demonstrated retention of the geometry.[5] Successive deprotection of the two silyl groups from the obtained *trans*-olefin with tetra-*n*-butylammonium fluoride in THF yielded *E*-olefin **7**.



Scheme 1. Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 1 h, 73%; (b) (1) $(i\text{-Pr})_3SiCl$, imidazole, DMF, rt, 4 h, 95%; (2) $(^tBuOC{=}O)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, rt, 1 h, quantitative; (c) $n\text{-}C_{13}H_{27}CH_2SO_2C_6H_4Me$, *n*-BuLi, THF, −78°C, 1 h, 86%; (d) Li naphthalenide, THF, −78°C, 20 min, 93%; (e) $KN(SiMe_3)_2$, $(CF_3SO_2)_2NPh$, THF, −23°C, 20 min, 99%; (f) (1) HCOOH, Et_3N, cat. $Pd(OAc)_2(PPh_3)_2$, DMF, 60°C, 7 h; (2) *n*-Bu_4NF, THF, rt, 2 h, two steps 63%; (g) (1) $LiEt_3BH$, THF, −78°C, 2 h; (2) *n*-Bu_4NF, THF, rt, 2 h; (3) 10% HCl in MeOH (w/v), 40°C, 9 h, three steps 82%

On the other hand, the ketone **5** gave (4*S*)-*epi*-phytosphingosine **8** (L-*lyxo*-phytosphingosine) without detection of a (4*R*)-isomer in the following three steps: (1) reduction of **5** using lithium triethylborohydride; (2) treatment of the resulting alcohol with *n*-Bu_4NF; and (3) successive treatment of the resulting *N*-protected triol with HCl in MeOH. Compound **8** thus obtained was identical with the reported data with respect to ^1H NMR, IR and $[\alpha]_D$.[6–8]

Compound **7** has already been converted into D-*erythro*-sphingosine by deprotection, or to the corresponding ceramides by acylation and successive deprotection of the *tert*-butoxycarbonyl group according to known methods. Thus, we have accomplished an alternative synthesis of ceramides and L-*lyxo*-phytosphingosine from a chiral β-lactam easily derived from D-(−)-tartaric acid.

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