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Synthesis of Two Pairs of Enantiomeric C_{18}-Sphingosines

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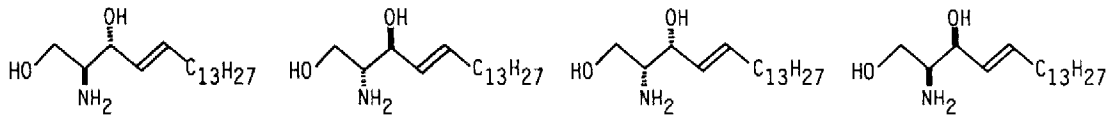
Summary: Two pairs of enantiomeric (D-erythro, L-erythro, D-threo, L-threo) C_{18}-sphingosines have been synthesized from Z-butene-1,4-diol utilizing Sharpless asymmetric epoxidation and a regiospecific ring-opening reaction of the resulting C_4-chiral epoxide with an azide anion.

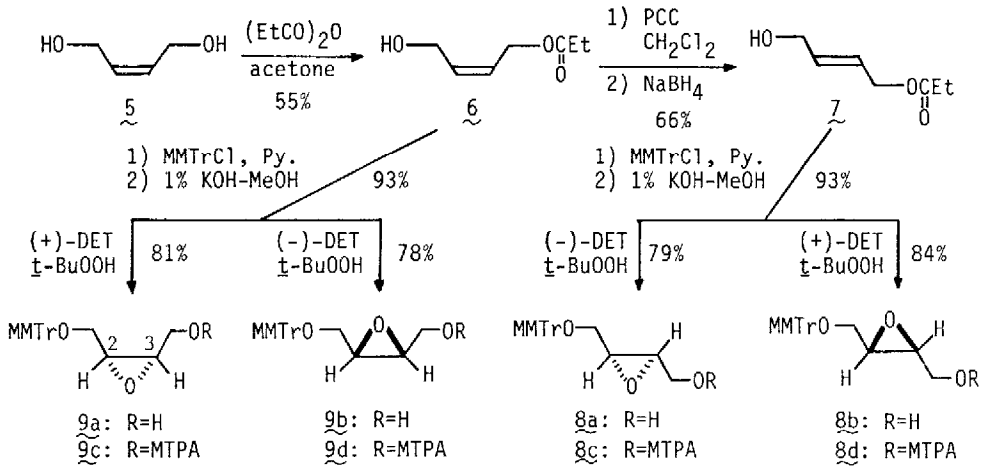
Sphingolipids, commonly possessing D-erythro-C_{18}-sphingosine as an essential component, have become of interest in recent years because of their bioactivities and biological roles.[1] Recently, Merrill et al.[2] reported that all enantioisomers of C_{18}-sphingosine showed a potent in vitro inhibitory activity against protein kinase C. We wish to report here a new synthetic method for two pairs of enantiomeric (D-erythro, L-erythro, D-threo, L-threo) C_{18}-sphingosines (1~4).[3] Our synthetic scheme involves Sharpless asymmetric epoxidation of E- and Z-C_4-allylic alcohols and a regiospecific ring-opening reaction of the resulting C_4-chiral epoxide with an azide anion.



D-erythro-sphingosine (1) L-erythro-sphingosine (2) D-threo-sphingosine (3) L-threo-sphingosine (4)

E-Diol monopropionate (7) was prepared from Z-butene-1,4-diol (5) via Z-diol monopropionate (6) by the North's procedure.[4] (2R,3R)-Epoxide (8a) and (2S,3S)-epoxide (8b) were given in the sequence of m-methoxytritylation, alkaline hydrolysis, and Sharpless asymmetric epoxidation[5] using (-)-diethyl tartrate [(-)-DET] or (+)-diethyl tartrate [(+)-DET] in 73% and 78% yields from 7, respectively. On the other hand, (2R,3S)-epoxide (9a) and (2S,3R)-epoxide (9b) were synthesized from 6 in 75% and 73% yields, respectively, in the same manner as for 8a and 8b. The values of those enantiomeric excess were determined by ^{1}H nmr analysis[5b] of their corresponding MTPA-esters (8c, 8d, 9c, 9d) to be 94%, 97%, 97%, and 93%, respectively for 8a, 8b, 9a, and 9b.

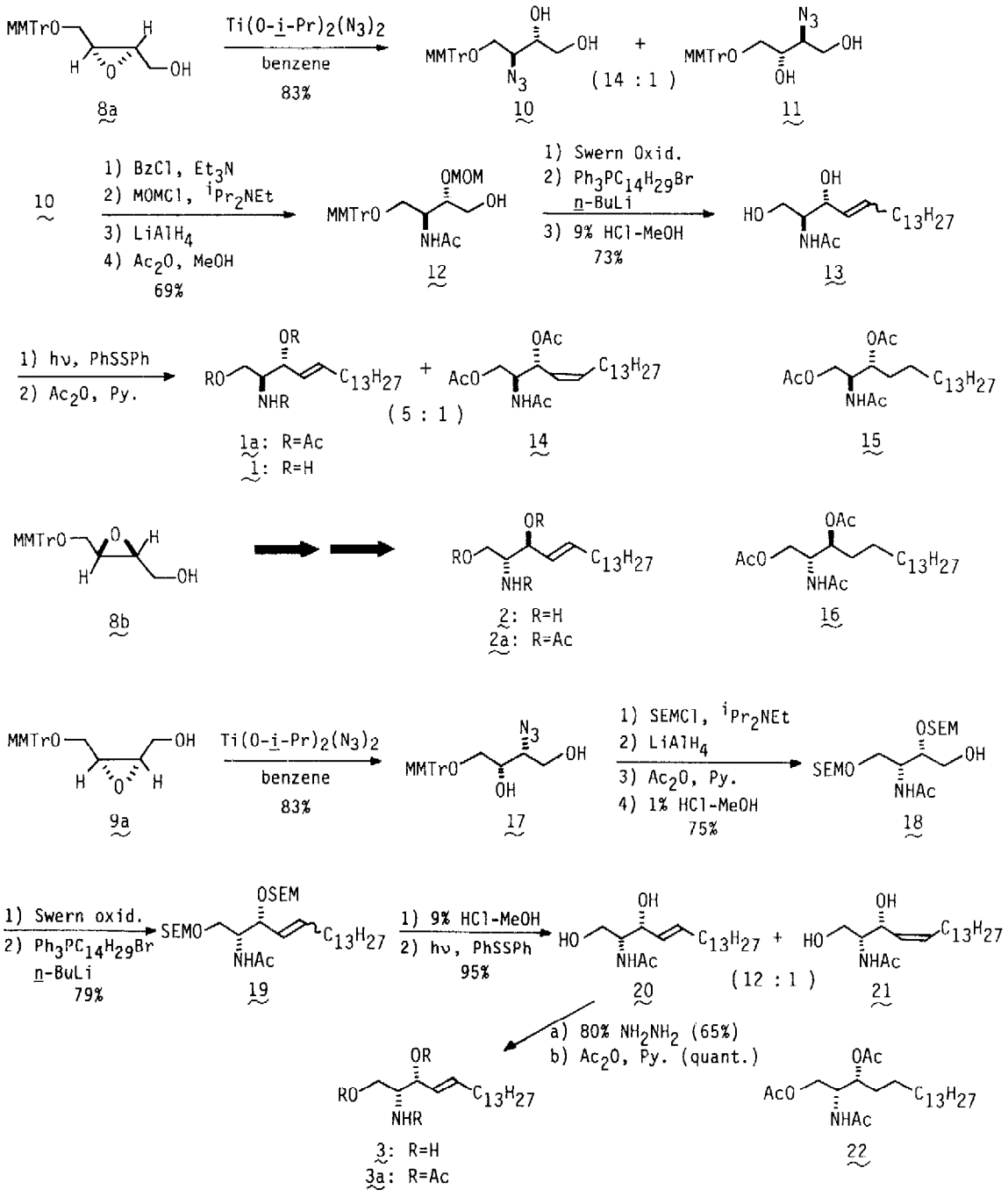
(2R,3R)-Epoxide (8a) was transformed into 1,2-diol (10) and 1,3-diol (11) in a ratio of 14:1 by treatment with $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$[6] in a good yield. The major 1,2-diol (10) was then converted to hydroxy-amide (12) through successive reactions: benzoylation ($BzCl\text{-}Et_3N$, 0°C), methoxymethylation ($MOMCl\text{-}^iPr_2EtN$), reduction ($LiAlH_4$ in THF), and acetylation (Ac_2O in MeOH), in a satisfactory yield. C_{18}-compound (13, E:Z=1:2) was synthesized from 12 by Swern oxidation,[7] Wittig reaction ($Ph_3PC_{14}H_{29}Br$, n-BuLi, in THF, -78° to 0°C) and acidic hydrolysis in 73% yield. Photoisomerization of 13 in the presence of PhSSPh[8] [500 W high pressure mercury lamp, Pyrex filter, in cyclohexane-dioxane (4:1), 6 h] followed by



acetylation, gave a product mixture which was subjected to HPLC (ZORBAX-SIL, n-hexane-EtOAc=2:3) to provide triacetyl-D-erythro-sphingosine [1a, mp. 101-102°C, $[\alpha]_D^{24}$ -11.4° ($CHCl_3$), δc 32.3 (C-6 in $CDCl_3$): lit.[9] mp. 101-102°C, $[\alpha]_D^{25}$ -11.7° ($CHCl_3$)] and its Z-isomer [14, δc 28.1 (C-6 in $CDCl_3$)] in a ratio of 5:1. Finally, D-erythro-sphingosine [1, mp. 81-82°C, $[\alpha]_D^{24}$ -2.8° ($CHCl_3$): lit.[3j] mp. 79-82°C, $[\alpha]_D^{22}$ -2.5° ($CHCl_3$)] was afforded from 1a by alkaline hydrolysis (1% KOH-MeOH) and subsequent treatment with hydrazine hydrate in 60% yield. Further, triacetyl-D-erythro-dihydrosphingosine [15, mp. 95-96°C, $[\alpha]_D^{24}$ +16° ($CHCl_3$): lit.[10] mp. 97-98°C, $[\alpha]_D^{19}$ +17.4° ($CHCl_3$): lit.[11] mp. 98-100°C, $[\alpha]_D^{22}$ +19.2° ($CHCl_3$)] was prepared quantitatively from 13 by catalytic hydrogenation and acetylation.

L-erythro-Sphingosine [2, mp. 81-82°C, $[\alpha]_D^{24}$ +2.8° ($CHCl_3$)], triacetyl-L-erythro-sphingosine [2a, mp. 101-102°C, $[\alpha]_D^{24}$ +12.1° ($CHCl_3$)] and triacetyl-L-erythro-dihydro-sphingosine [16, mp. 96-97°C, $[\alpha]_D^{24}$ -16.5° ($CHCl_3$): lit.[11] mp. 98-100°C, $[\alpha]_D^{22}$ -19.35° ($CHCl_3$)], were synthesized from (2S,3S)-epoxide (8b) in similar yields through the same reaction procedure as for D-erythro-derivatives (1, 1a, 15).

Treatment of (2R,3S)-epoxide (9a) with $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ gave predominantly 1,3-diol (17) in 85% yield, which was in different fashion from the above-described epoxide-ring opening of 8a and 8b. 1,3-Diol (17) was transformed into hydroxy-amide (18) by successive treatment of trimethylsilylethoxymethylation (SEMCl-$^iPr_2EtN$, 40°C), reduction ($LiAlH_4$ in THF), acetylation (Ac_2O-MeOH), and acidic hydrolysis (1% HCl-MeOH), in a moderate yield. Swern oxidation of 18 followed by Wittig reaction provided C_{18}-compound (19, E:Z=1:4) in 79% yield. 19 was hydrolyzed with 9% HCl-MeOH and photoisomerized in the presence of PhSSPh to furnish a mixture, which was subjected to HPLC (Cosmosil $5C_{18}$, MeOH-H_2O=8:1) to give N-acetyl-D-threo-sphingosine [20, δc 32.7 (C-6 in d_5-pyridine)] and its Z-isomer [21, δc 28.2 (C-6 in d_5-pyridine)] in a ratio of 12:1. Finally, D-threo-sphingosine [3, mp. 84-85°C, $[\alpha]_D^{24}$ +2.8° ($CHCl_3$)] and triacetyl-D-threo-sphingosine [3a, mp. 41-42°C, $[\alpha]_D^{24}$ -8.9° ($CHCl_3$)] were obtained respectively from 20 by treatment with hydrazine hydrate or by acetylation. Triacetyl-D-threo-dihydrosphingosine [22, mp. 44-45°C, $[\alpha]_{546}^{26}$ +13.2° (pentane): lit.[12] mp. 46°C, $[\alpha]_{546}^{28}$ +8.0° (pentane)] was prepared from 20 by catalytic


MMTrO
OH
8a
Ti(O-i-Pr)2(N3)2
benzene
83%
OH
N3
10
(14 : 1)
11
1) BzCl, Et3N
2) MOMCl, iPr2NEt
3) LiAlH4
4) Ac2O, MeOH
69%
OMOM
NHAc
12
1) Swern Oxid.
2) Ph3PC14H29Br
n-BuLi
3) 9% HCl-MeOH
73%
HO
C13H27
13
1) hν, PhSSPh
2) Ac2O, Py.
OR
RO
NHR
OAc
AcO
1a: R=Ac
1: R=H
(5 : 1)
14
15
8b
2: R=H
2a: R=Ac
16
9a
17
1) SEMCl, iPr2NEt
2) LiAlH4
3) Ac2O, Py.
4) 1% HCl-MeOH
75%
OSEM
SEMO
18
1) Swern oxid.
2) Ph3PC14H29Br
n-BuLi
79%
19
1) 9% HCl-MeOH
2) hν, PhSSPh
95%
20
(12 : 1)
21
a) 80% NH2NH2 (65%)
b) Ac2O, Py. (quant.)
3: R=H
3a: R=Ac
22
9b
4: R=H
4a: R=Ac
23

hydrogenation and acetylation in 93% yield.

L-threo-Sphingosine [4, mp. 84-85°C, $[\alpha]_D^{24}$ -2.7° ($CHCl_3$): lit.[3m] mp. 86-87°C, $[\alpha]_D$ -2.65° ($CHCl_3$)], triacetyl-L-threo-sphingosine [4a, mp. 41-42°C, $[\alpha]_D^{24}$ +8.5° ($CHCl_3$): lit.[3m] mp. 42-44°C, $[\alpha]_D$ +7.02° ($CHCl_3$)] and triacetyl-L-threo-dihydrosphingosine [23, mp. 44-45°C, $[\alpha]_{546}^{26}$ -13.2° (pentane): lit.[12] mp. 46°C, $[\alpha]_{546}^{28}$ -8.0° (pentane)], were synthesized from (2R,3S)-epoxide (9b) through the same reaction steps in similar yields as in the cases of D-threo-derivatives (3, 3a, 22).

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