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ASYMMETRIC SYNTHESIS OF THREO- AND ERYTHRO-SPHINGOSINES BY ASYMMETRIC ALDOL REACTION OF α-ISOCYANOACETATE CATALYZED BY A CHIRAL FERROCENYLPHOSPHINE-GOLD(I) COMPLEX

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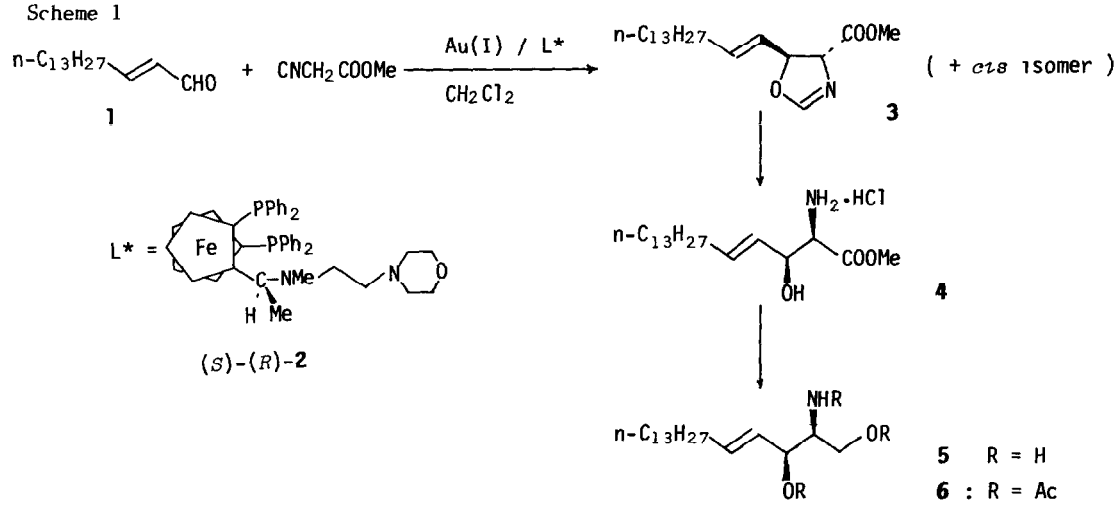
Summary: Asymmetric aldol reaction of methyl α-isocyanoacetate with (E)-2-hexadecenal in the presence of 1 mol% of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) complex gave optically active trans-4-(methoxycarbonyl)-5-((E)-1-pentadecenyl)-2-oxazoline (93% ee) which was readily converted into D-threo- and erythro-sphingosines.

The sphingolipid bases, D-erythro- and threo-sphingosines are the target molecules which have been synthesized to demonstrate the efficiency of a new methodology to control both absolute and relative configurations in acyclic systems.[1] Here we wish to report a new short step synthesis of D-sphingosines which has been attained by using the gold(I)-catalyzed asymmetric aldol reaction of aldehydes with isocyanoacetate[2,3] as a key step.

Asymmetric aldol reaction of (E)-2-hexadecenal[4] (1) with methyl α-isocyanoacetate was carried out in the presence of 1 mol% of the gold catalyst prepared in situ by mixing bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate and (S)-N-methyl-N-[2-(morpholino)ethyl]-1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine[3] [(S)-(R)-**2**] in dichloromethane at 25 °C for 35 h (Scheme 1). Treatment of the reaction mixture with short Florisil column (dichloromethane) gave a quantitative yield of methyl 5-((E)-1-pentadecenyl)-2-oxazoline-4-carboxylate (3) consisting of trans and cis isomers[5] in a ratio of 89/11, whose enantiomeric purities were determined to be 93% and 20%, respectively, by ^{1}H NMR spectra using Eu(dcm)$_3$. The trans isomer ($[\alpha]_D^{20}$ -173° (c 1.2 THF)), which was isolated by silica gel MPLC (hexane/ethyl acetate = 1/1) in 80% yield, was treated with conc HCl in methanol at 55 °C for 2 hr to give a quantitative yield of β-hydroxyamino acid methyl ester hydrochloride 4[6] ($[\alpha]_D^{20}$ -23° (c 1.1,

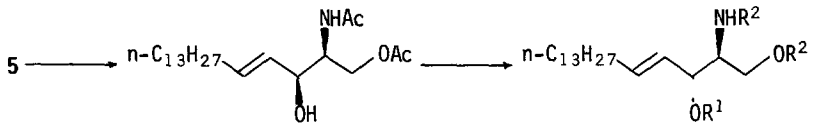
Scheme 1



chloroform)). Reduction of **4** with $LiAlH_4$ in THF gave 85% yield of D-threo-sphingosine (**5**), which was characterized by conversion (Ac_2O, Et_3N, DMAP, THF) into the known triacetate **6** ($[\alpha]_D^{24}$ +8.78° (c 1.2, chloroform)).[7]

The D-erythro-sphingosine was readily accessible from the threo isomer **5** by inversion of configuration at C-3 carbon (Scheme 2). Thus, **5** was diacetylated on amino and terminal hydroxyl groups with 2 eq of acetic anhydride and triethylamine in THF at 0 °C to give diacetate **7**[8] ($[\alpha]_D^{25}$ -20.3° (c 1.1, (chloroform)) in 53% yield. Subjecting the diacetate **7** to Mitsunobu reaction[9] (DEAD, PPh_3, PhCOOH, THF) followed by alkaline hydrolysis (2N KOH, EtOH, reflux) gave 61% yield of D-erythro-sphingosine (**9**). The structure of **9** was confirmed by conversion into the triacetate **10** ($[\alpha]_D^{24}$ -12.2° (c 1.0, chloroform), mp 103 °C).[10]

Scheme 2



8 · R^1= PhCHO, R^2= Ac
9 R^1= R^2= H
10 R^1= R^2= Ac

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4 The aldehyde **1** was prepared by oxidation (py·SO_3, DMSO) of (E)-2-hexadecenol which was obtained by hydroalumination ($HAl(i\text{-}Bu)_2$) of 1-pentadecyne followed by hydroxymethylation of the resulting alkenylalane (1. MeLi. 2. $(CH_2O)_n$).

5 ^1H NMR ($CDCl_3$) for trans-**3**. δ 0.7-1.0 (m, 3H), 1.0-1.8 (broad s, 22H), 1.8-2.3 (m, 2H), 3.72 (s, 3H), 4.30 (dd, J = 7 and 2 Hz, 1H), 5.00 (t, J = 7 Hz, 1H), 5.38 (dd, J = 15 and 7 Hz, 1H), 5.78 (dt, J = 15 and 7 Hz, 1H), 6.79 (d, J = 2 Hz, 1H). ^1H NMR ($CDCl_3$) for cis-**3**: δ 0.7-1.0 (m, 3H), 1.0-1.7 (broad s, 22H), 1.7-2.2 (m, 2H), 3.62 (s, 3H), 4.71 (dd, J = 8 and 2 Hz, 1H), 5.01 (dd, J = 9 and 8 Hz, 1H), 5.31 (dd, J = 15 and 9 Hz, 1H), 5.73 (dt, J = 15 and 7 Hz, 1H), 6.89 (d, J = 2 Hz, 1H).

6 ^1H NMR ($CDCl_3$) for **4**. δ 0.7-1.05 (m, 3H), 1.05-1.8 (broad s, 22H), 1.8-2.3 (m, 2H), 3.82 (s, 3H), 3.96 (d, J = 5 Hz, 1H), 4.56 (broad t, 1H), 5.51 (dd, J = 15 and 6 Hz, 1H), 5.90 (dt, J = 15 and 7 Hz, 1H).

7 Isolated by preparative TLC on silica gel. Reported value for **6**. $[\alpha]_D^{24}$ +8.43° (chloroform) (ref 1a).

8 ^1H NMR ($CDCl_3$) for **7** δ 0.7-1.05 (m, 3H), 1.05-1.8 (broad s, 22H), 1.8-2.2 (m, 2H), 2.00 (s, 3H), 2.08 (s, 3H), 2.95 (broad s, 1H), 4.0-4.4 (m, 4H), 5.43 (dd, J = 15 and 5 Hz, 1H), 5.76 (dt, J = 15 and 7 Hz, 1H), 6.07 (broad d, 1H). Mp 89.5-91.0 °C.

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10 Isolated (70% yield) by recrystallization from hexane. Reported value for **10**. $[\alpha]_D^{24}$ -12.9° (chloroform); mp 103.5-104.5 °C (ref 1a). $[\alpha]_D^{24}$ -12.8° (c 1, chloroform), mp 101-102 °C (ref 1b).

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