Acyclic Stereoselection using 1,2-Asymmetric Induction. The First Total Synthesis of (+)-Corynomycolic Acid

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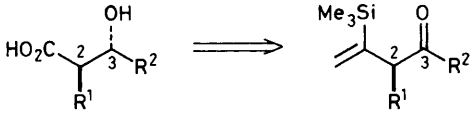
The first total synthesis of (+)-corynomycolic acid (**1**), which includes as the key step, diastereoselective reduction of the optically active carbonyl compounds (**8**) is described.

Mycolic acids, mostly found in nature as their ester with carbohydrates, are high molecular weight fatty acids having 28 to 90 carbon atoms and have the basic structure $R^2CH(OH)CH(R^1)CO_2H$.[1] The stereochemistry of the mycolic acids so far examined has been shown to be 2*R*,3*R* as shown in formula (**1**).[2] Although these acids have interesting biological properties,[1] only a few syntheses of the racemic form of (**1**) have been reported where 2,3-*anti* stereochemistry was achieved with rather low stereoselectivity.[3] Furthermore, these methods do not seem to be applicable to the synthesis of enantiomerically pure (**1**). In this communication, we report a general synthetic method for the preparation of optically active (**1**). The key feature of our approach to the synthesis of (**1**) is based on our earlier work and involves the stereoselective reduction of optically active (**2**) with a metal hydride reagent to achieve the required stereochemistry at C-3 by 1,2-asymmetric induction relative to the pre-existing C-2 chiral centre.[4,5] In this synthesis, two alkyl chains R^1 and R^2 are incorporated individually at different stages. The effectiveness of our method is demonstrated by synthesising (+)-corynomycolic acid {(**1**) $R^1 = [CH_2]_{13}Me$, $R^2 = [CH_2]_{14}Me$}, one of the mycolic acids produced by *Corynebacteria*.[2,6]

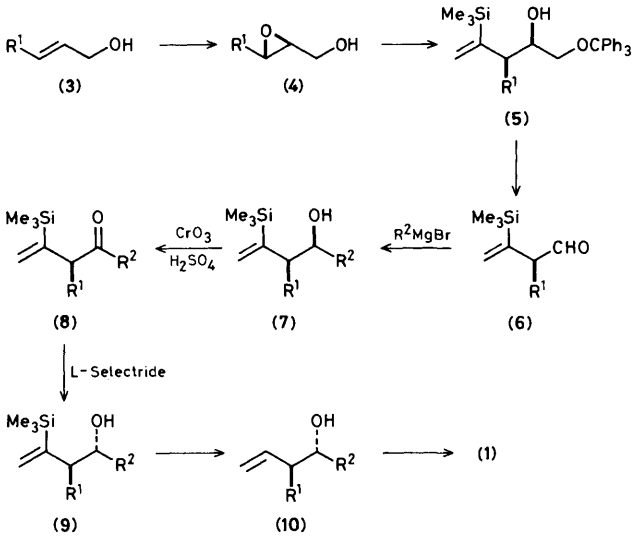
Sharpless asymmetric epoxidation[7] of the (*E*)-heptadec-2-en-1-ol (**3**), obtained from but-2-yn-1-ol and n-tetradecyl iodide,[8] using L-(+)-di-isopropyl tartrate produced the epoxide (**4**)† {$[\alpha]_D^{25}$ −27.0° (*c* 0.869, C_6H_6)} in 77% yield. Protection of the hydroxy group of (**4**) as a trityl ether (Ph_3CCl, 4-*N*,*N*-dimethylaminopyridine, NEt_3) and subsequent regioselective epoxide ring opening with 1-trimethylsilylvinylmagnesium bromide afforded (**5**) as the sole product. Compound (**5**) was converted into the aldehyde (**6**) {$[\alpha]_D^{25}$ −13.3° (*c* 0.900, $CHCl_3$)} by successive treatments with aqueous Cl_2CHCO_2H and $NaIO_4$.[8] The yield of (**6**) from (**4**) was 47%. The reaction of n-pentadecylmagnesium bromide with (**6**) gave (**7**)‡ exclusively {$[\alpha]_D^{25}$ −0.78° (*c* 1.025,



(**1**) (**2**)

† Since asymmetric epoxidation of this type of (*E*)-alk-2-en-1-ols is known to proceed with high enantiomeric excess (over 95%), the optical purities of (**4**) and other intermediates used here were not confirmed.

‡ ^{13}C N.m.r. ($CDCl_3$) (**7**) δ 73.4, 125.6, and 153.9; (**9**) δ 73.7, 127.9, and 153.9.



$R^1 = [CH_2]_{13}Me$, $R^2 = [CH_2]_{14}Me$

$CHCl_3$)} in 90% yield.[4] Jones oxidation of (**7**) followed by reduction with L-Selectride gave (**9**) (84%) as the sole product[4] {$[\alpha]_D^{25}$ +9.25° (*c* 1.06, $CHCl_3$)}: the stereoisomer (**7**) was not detected by ^{13}C n.m.r. spectroscopy. Protodesilylation of (**9**) (NaH, hexamethylphosphoramide)[9] gave the alcohol (**10**) in 86% yield. Finally (**10**) was transformed into (+)-(**1**) in 90% yield through the following sequence of reactions: conversion of (**10**) into its correponding benzyl ether ($PhCH_2Br$, KH, tetrahydrofuran), ozonolysis, Me_2S work up, oxidation (CrO_3, H_2SO_4), and debenzylation (H_2, Pd–C). The physical data {$[\alpha]_D^{25}$ +7.34° (*c* 1.90, $CHCl_3$); m.p. 70.0—71.5 °C} of (+)-(**1**) thus prepared were in good agreement with the literature values reported by Pudles *et al.* {$[\alpha]_D$ +7.5° (*c* 1.64, $CHCl_3$); m.p. 70.0 °C}.[6a] This is the first total synthesis of (+)-corynomycolic acid achieved in a stereo- and enantio-selective manner and it is clear that this method provides a general synthetic method for various mycolic acids.

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