

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

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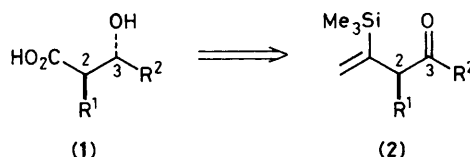
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The first total synthesis of (+)-corynomycolic acid (**1**), which includes as the key step, diastereoselective reduction of the optically active carbonyl compounds (**8**) is described.

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  $R^2CH(OH)CH(R^1)CO_2H$ .<sup>1</sup> The stereochemistry of the mycolic acids so far examined has been shown to be 2*R*,3*R* as shown in formula (**1**).<sup>2</sup> Although these acids have interesting biological properties,<sup>1</sup> only a few syntheses of the racemic form of (**1**) have been reported where 2,3-*anti* stereochemistry was achieved with rather low stereoselectivity.<sup>3</sup> 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.<sup>4,5</sup> 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*.<sup>2,6</sup>

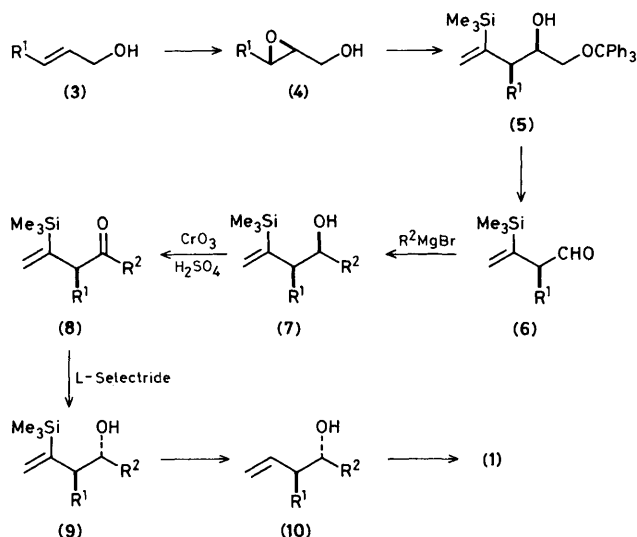
Sharpless asymmetric epoxidation<sup>7</sup> of the (*E*)-heptadec-2-en-1-ol (**3**), obtained from but-2-yn-1-ol and *n*-tetradecyl iodide,<sup>8</sup> using L-(+)-di-isopropyl tartrate produced the epox-

ide (**4**)<sup>†</sup>  $\{[\alpha]_D^{25} -27.0^\circ$  (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**)  $\{[\alpha]_D^{25} -13.3^\circ$  (c 0.900,  $CHCl_3$ ) $\}$  by successive treatments with aqueous  $Cl_2CHCO_2H$  and  $NaIO_4$ .<sup>8</sup> The yield of (**6**) from (**4**) was 47%. The reaction of *n*-pentadecylmagnesium bromide with (**6**) gave (**7**)<sup>‡</sup> exclusively  $\{[\alpha]_D^{25} -0.78^\circ$  (c 1.025,



<sup>†</sup> 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.

<sup>‡</sup> <sup>13</sup>C N.m.r. ( $CDCl_3$ ) (**7**)  $\delta$  73.4, 125.6, and 153.9; (**9**)  $\delta$  73.7, 127.9, and 153.9.



$CHCl_3$ ) in 90% yield.<sup>4</sup> Jones oxidation of (7) followed by reduction with L-Selectride gave (9) (84%) as the sole product<sup>4</sup>  $\{[\alpha]_D^{25} +9.25^\circ$  ( $c$  1.06,  $CHCl_3$ ) $\}$ : the stereoisomer (7) was not detected by  $^{13}C$  n.m.r. spectroscopy. Protodesilylation of (9) (NaH, hexamethylphosphoramide)<sup>9</sup> 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 corresponding 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  $\{[\alpha]_D^{25} +7.34^\circ$  ( $c$  1.90,  $CHCl_3$ ); m.p.  $70.0\text{--}71.5^\circ C\}$  of (+)-(1) thus prepared were in good agreement with the literature values reported by Pudles *et al.*  $\{[\alpha]_D +7.5^\circ$  ( $c$  1.64,  $CHCl_3$ ); m.p.  $70.0^\circ C\}$ .<sup>6a</sup> 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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## References

- 1 For reviews see, E. Lederer, A. Adam, R. Ciorbaru, J.-F. Petit, and J. Wietzerbin, *Mol. Cell. Biochem.*, 1975, **7**, 87; E. Lederer, *Chem. Phys. Lipids*, 1976, **16**, 91.
- 2 J.-F. Toccanne and C. Asselineau, *Bull. Soc. Chim. Fr.*, 1968, 4519; C. Asselineau, G. Toccanne, and J.-F. Toccanne, *ibid.*, 1970, 1455.
- 3 E. Lederer, V. Portelance, and K. Serck-Hanssen, *Bull. Soc. Chim. Fr.*, 1952, 413; M. J. Polonsky and E. Lederer, *ibid.*, 1954, 504; C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron*, 1981, **37**, 4087; C. H. Heathcock and J. Lampe, *J. Org. Chem.*, 1983, **48**, 4330.
- 4 F. Sato, M. Kusakabe, and Y. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1984, 1130.
- 5 Preparation of optically active (2,  $R^1 = Me$ ) was reported: Y. Kobayashi, Y. Kitano, and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1984, 1329.
- 6 (a) A. Diara and J. Pudles, *Bull. Soc. Chim. Biol.*, 1959, **41**, 481; (b) T. Itoneda, M. Lenz, and J. Pudles, *Biochem. Biophys. Res. Commun.*, 1963, **13**, 110.
- 7 B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 464.
- 8 D. E. Ames, A. N. Covell, and T. G. Goodburn, *J. Chem. Soc.*, 1963, 5889.
- 9 F. Sato, Y. Tanaka, and M. Sato, *J. Chem. Soc., Chem. Commun.*, 1983, 165.