# Asymmetric Reduction of 3-Oxo-octadecanoic Acid with Fermenting Baker's Yeast. An Easy Synthesis of Optically Pure (+)-(2*R*,3*R*)-Corynomycolic Acid

**Masanori Utaka,* Hiroshi Higashi, and Akira Takeda**

*Department of Synthetic Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700, Japan*

Optically pure (+)-corynomycolic acid has been synthesised from methyl acetoacetate by a route including asymmetric reduction of 3-oxo-octadecanoic acid with baker's yeast as a key step.

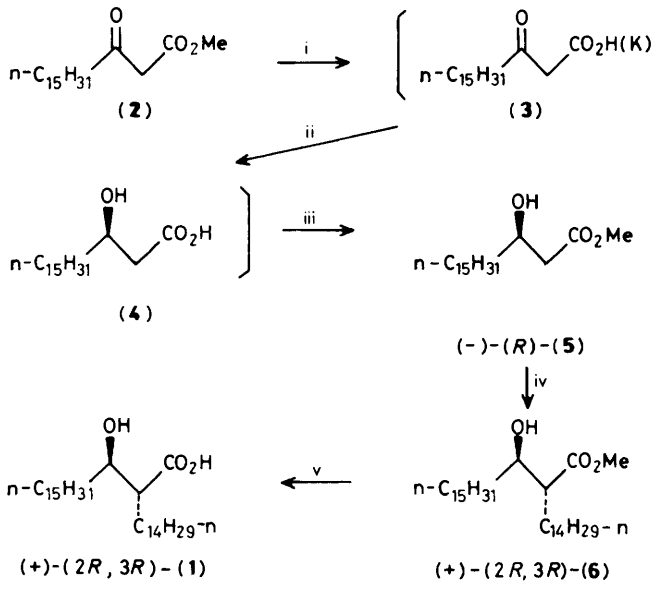
(+)-Corynomycolic acid (**1**) is an acid constituent of trehalose diesters, which can be isolated from the cell walls of corynebacteria or related organisms and show interesting biological activities.[1] The acid (**1**) possesses a long palmitic acid carbon chain substituted with an n-tetradecyl group at the α-position and a hydroxy group at the β-position; both α- and β-centres are of *R*-configuration.[2] The racemic acid (**1**) has been prepared previously by a condensation reaction of methyl palmitate,[3] and by an aldol reaction of alkyl ketones or aryl palmitates with palmitaldehyde.[4] Recently, optically active (**1**) has been synthesised from an optically active epoxide.[5] We considered that the key α-alkyl β-hydroxy acid unit could be constructed effectively by asymmetric reduction of a β-oxo acid followed by α-alkylation of the resulting optically active β-hydroxy acid.

This paper reports an easy, short, asymmetric synthesis of the acid (+)-(2*R*,3*R*)-(**1**) which includes a completely enantioselective reduction of 3-oxo-octadecanoic acid (**3**) by fermenting baker's yeast (Scheme 1). Such a long-chain β-oxo acid or ester has never been reported to undergo the reduction by yeast, although β-oxo acids or esters of short to moderate chain length have been studied extensively.[6]

In a mixture of ethanol (15 ml) and M-KOH (7 ml), methyl 3-oxo-octadecanoate (**2**)† (600 mg, 1.9 mmol) was dissolved, and the solution was stirred overnight at room temperature. Then the ethanol was removed under reduced pressure and the residue was added with water (30 ml) to a vigorously fermenting baker's yeast suspension‡ at 28—29 °C. The

† Prepared from methyl acetoacetate and n-tetradecyl iodide in 79% yield.

‡ Fresh baker's yeast (Oriental Yeast Co.; 12 g), glucose (6 g), $MgSO_4$ (15 mg), and 0.1 M-citric acid (3 ml) in water (36 ml).




**Scheme 1.** *Reagents:* i, aq. KOH/EtOH; ii, baker's yeast, 48 h; iii, $CH_2N_2$, 40% based on (**2**); iv, $LiNPr^i_2$, n-$C_{14}H_{29}I$, $PO(NMe_2)_3$, 50%; v, aq. KOH/EtOH, 85%.

mixture was adjusted to pH 5.3—6.0 and stirred for 48 h.§ It was then stirred with Celite (24 g) for 6 h and filtered. The filtrate was adjusted to pH 2 and extracted with EtOAc. The Celite was washed with acetone. The combined extracts and washings were dried ($MgSO_4$), filtered, and evaporated. The residue was treated with $CH_2N_2$ to give a crude solid (1.4 g). This was purified by passing through a silica gel column (hexane–EtOAc 20 : 1 → 15 : 1) to afford the ester (**5**) (244 mg, 40%, yield), m.p. 55.6—56.0 °C; $[\alpha]_D$ −13.2° (*c* 1.89, $CHCl_3$). The optical purity was determined to be >98% (enantiomeric excess) by measuring the $^1H$ n.m.r. spectra in the presence of the shift reagent Eu(hfc)$_3$.¶ The configuration was determined to be *R* by measuring the $[\alpha]_D$ value of (**4**).** We have examined various conditions for the fermentation to improve the yield, and find that the pH of the culture solution is very important. Thus, the yield was 6% at pH 4.0—4.1, 10% at pH 4.4—4.7, 39% at pH 4.8—5.1, 40% at pH 5.3—6.0, 29% at pH 6.4—7.0, and 7% at pH 7.8—8.1.

α-Alkylation of (**5**) was achieved by using $LiNPr^i_2$/n-$C_{14}H_{29}I$/$PO(NMe_2)_3$[8] to afford (**6**) in 50% yield (purified by liquid chromatography); m.p. 59.2—62.5 °C, $[\alpha]_D$ +5.74° (*c* 1.08, $CHCl_3$) [lit.,[9] m.p. 61°, $[\alpha]_D$ +5.7° (*c* 1.22, $CHCl_3$)]. The $^1H$ n.m.r. spectrum measured in the presence of Eu(hfc)$_3$ indicated that (**6**) was diastereo- and enantio-merically pure.¶ Finally (**6**) was hydrolysed by dissolving in a mixture of aq. KOH and ethanol at 40 °C for 20 h and the product was purified by passing through a silica gel column to give (**1**) in 85% yield; m.p. 77.8—79.2 °C; $[\alpha]_D^{21}$ +7.78° (*c* 1.26, $CHCl_3$) [lit.,[9] m.p. 69—70 °C; $[\alpha]_D$ +7.5° (*c* 1.64, $CHCl_3$)]. The optical purity was again confirmed to be >98% by measuring $^1H$ n.m.r. spectra in the presence of Eu(hfc)$_3$ after conversion into (**6**) with $CH_2N_2$.¶

*Received, 9th April 1987; Com. 470*

## References

1 E. Lederer, A. Adam, R. Ciorbaru, J.-F. Petit, and J. Wietzerbin, *Mol. Cell. Biochem.*, 1975, **7**, 87; E. Lederer, *J. Med. Chem.*, 1980, **23**, 819.
2 C. Asselineau, G. Tocanne, and J.-F. Tocanne, *Bull. Soc. Chim. Fr.*, 1970, 1455.
3 J. Polonsky and E. Lederer, *Bull. Soc. Chim. Fr.*, 1954, 504.
4 C. H. Heathcock and J. Lampe, *J. Org. Chem.*, 1983, **48**, 4330; M. Utaka, M. Hojo, and A. Takeda, *Chem. Lett.*, 1985, 1471.
5 Y. Kobayashi, Y. Kitano, Y. Takeda, and F. Sato, *Tetrahedron*, 1986, **42**, 2937.
6 G. Fräter, *Helv. Chim. Acta*, 1979, **62**, 2829; M. Hirama, M. Shimizu, and M. Iwashita, *J. Chem. Soc., Chem. Commun.*, 1983, 599; M. Hirama, T. Nakamine, and S. Ito, *Chem. Lett.*, 1986, 1381; *Tetrahedron Lett.*, 1986, **27**, 5281.
7 See M. Nakahata, M. Imaida, H. Ozaki, T. Harada, and A. Tai, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2186.
8 G. Fräter, *Helv. Chim. Acta*, 1979, **62**, 2825.
9 E. Lederer and J. Pudles, *Bull. Soc. Chim. Biol.*, 1951, **31**, 1003.

§ The pH was adjusted by addition of 0.1 M-citric acid or 1 M-KOH. As the glucose was consumed, 54 g of glucose was added in nine 6 g portions.

¶ The signal of the methoxy group was used for the determination. The racemic methyl ester was used as a reference compound.

** 3-Hydroxyoctadecanoic acid (**4**) from (**5**); $[\alpha]_D^{21}$ −12.0° (*c* 1.05, $CHCl_3$); *cf.* $[\alpha]_D^{20}$ −13.8° (*c* 1.0, $CHCl_3$) for (*R*)-3-hydroxyhexadecanoic acid.[7]