Asymmetric Hydrolysis of 3-Acetylthiocycloheptene and 3-Acetoxycycloheptene with a Microbial Lipase[1]

By SHINOBU IRIUCHIJIMA* and NATSUKO KOJIMA
(*Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa, 229, Japan*)

Summary With a lipase from *Candida cylindracea* (±)-3-acetylthiocycloheptene was hydrolysed with greater stereoselectivity than (±)-3-acetoxycycloheptene, in both esters the (+)-isomers being preferentially hydrolysed.

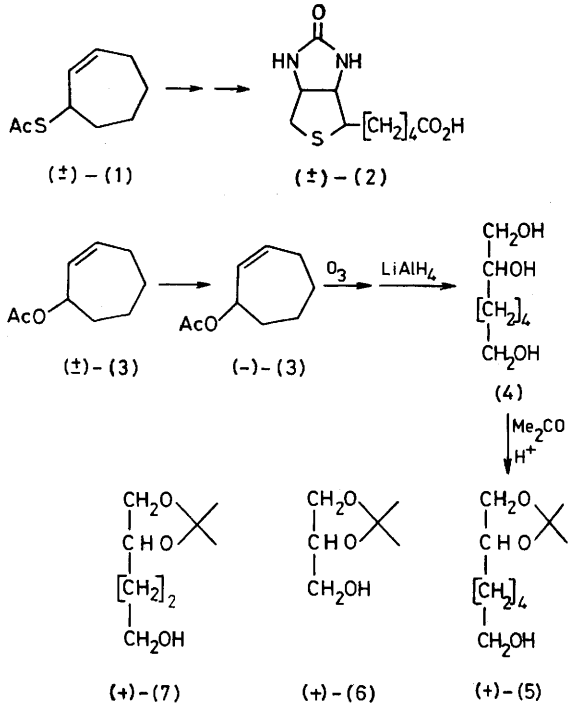
ALTHOUGH it is well known that esters are asymmetrically hydrolysed with enzymes or micro-organisms,[2] the asymmetric hydrolysis of thioesters is not known. Confalone *et al.*[3] reported the total synthesis of (±)-biotin (**2**) from (±)-3-acetylthiocycloheptene (**1**), and we thought that optically active biotin would be produced from the optically active thioester (**1**). We have studied the asymmetric hydrolysis of (±)-(**1**) with enzymes in an attempt to obtain optically active (**1**) and compared it with that of (±)-3-acetoxycycloheptene (**3**). A lipase† from *Candida cylindracea* hydrolyses the thioester (**1**) more stereoselectively than the ester (**3**).

A mixture of the thioester (**1**) (600 mg) and *Candida cylindracea* lipase MY (200 mg) in 0·2 M potassium phosphate buffer (pH 6·5; 30 ml) was stirred at room temperature overnight. The mixture was extracted with dichloromethane, and the extract dried, concentrated, and chromatographed on silica gel with hexane. Elution with hexane–dichloromethane (100:1—2) gave the optically active thioester (**1**) (108 mg, 18%) having $[\alpha]_D^{20}$ −184° (*c* 1·08, hexane). The 90 MHz n.m.r. spectrum of the product measured in the presence of tris(trifluorocamphorato)europium [Eu(tfc)$_3$] (0·2 mol. equiv.) in $CDCl_3$ showed a ratio of (+)-(**1**) to (−)-(**1**) of *ca.* 2:8.

A similar experiment using (±)-3-acetoxycycloheptene (**3**) afforded the optically active ester (**3**) having $[\alpha]_D^{20}$ −15·1° (*c* 1·18, hexane). The n.m.r. spectrum of the product in the presence of Eu(tfc)$_3$ (0·2 mol. equiv.) in $CDCl_3$ showed a ratio of (+)-(**3**) to (−)-(**3**) of *ca.* 4:6.

It is interesting that the thio-ester (**1**) is hydrolysed with greater stereoselectivity than the ester (**3**), for both esters the (+)-isomers being preferentially hydrolysed. Our result suggests that the biochemical resolution of thioesters should also be possible, as is that of esters.[2]

The absolute configuration of (−)-(**3**) was assumed to be (*S*) on the basis of the following experiments. The ester (**3**) ($[\alpha]_D$ −10°) was ozonised in cyclohexane–hexane (2:1) and the ozonide was reduced with excess of lithium aluminium hydride in tetrahydrofuran. The reduced product, heptane-1,2,7-triol (**4**), was dissolved in acetone and the solution was stirred with a catalytic amount of conc. sulphuric acid overnight. The product was chromatographed with dichloromethane–ethyl acetate (100:2—3) to produce the acetonide (**5**) having $[\alpha]_D^{25}$ + 2·5° (*c* 0·6, MeOH). The absolute configuration of (+)-(**5**) and hence of (−)-(**3**) was deduced to be (*S*) since the (*S*)-acetonides (**6**) and (**7**) derived from D-mannitol[4] and from L-glutamic acid,[5] respectively, have $[\alpha]_D^{25}$ +11·3° (*c* 5·175, MeOH) and $[\alpha]_D^{25}$ + 8·28° (*c* 0·64, MeOH). On this basis, *Candida cylindracea* lipase MY hydrolyses preferentially the (*R*)-(+)-isomer of (±)-(**3**) to leave (**3**) with the (*S*)-(−)-isomer predominating.



An attempt to convert 3-hydroxycycloheptene into the thioester (**1**) *via* the mesylate *etc.* for the determination of the absolute configuration of (**1**) was unsuccessful.

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† The lipase is available from Meito Sangyo Co. or Sigma Chemical Co., and we used lipase MY from the former company.

[1] For Part 1 of the series Asymmetric Hydrolysis of Esters with Biochemical Methods, see S. Iriuchijima and A. Keiyu, *Agric. Biol. Chem.*, in the press.
[2] For example, W. J. Marsheck and M. Miyano, *Biochim. Biophys. Acta*, 1973, **316**, 363; T. Oritani and K. Yamashita, *Agric. Biol. Chem.*, 1974, **38**, 1965; Y. Yamaguchi, A. Komatsu, and T. Moroe, *J. Agric. Chem. Soc. Japan*, 1976, **50**, 619.
[3] P. N. Confalone, E. D. Lollar, G. Pizzolato, and M. R. Uskoković, *J. Am. Chem. Soc.*, 1978, **100**, 6291.
[4] J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure, *J. Org. Chem.*, 1978, **43**, 4876.
[5] O. Červinka and L. Hub, *Coll. Czech. Chem. Commun.*, 1968, **33**, 2927.