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STEREOCONTROL OF A TERTIARY HYDROXYL GROUP VIA MICROBIAL EPOXIDATION. A FACILE SYNTHESIS OF PROSTAGLANDIN ω-CHAINS

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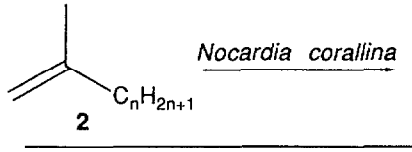
Summary; Optically active 1,2-epoxy-2-methylalkanes(**1**), useful precursors of tertiary alcohols, were prepared by microbial oxidation and converted to prostaglandin ω-chains.

Tertiary hydroxyl groups are frequently encountered in natural products and also important in drug design. Their stereocontrol, which had been difficult to access by the conventional methods,[1] got to be facilitated by the Sharpless oxidation.[2] However, processes with the Sharpless' step require multi-step FGIs in several cases. Now we wish to report another approach, thus a microbial production of optically active 1,2-epoxy-2-methylalkanes(**1**) as useful precursors of tertiary alcohols. Their short-step conversions to unnatural prostaglandin ω-chains are also described.

A mixture of 2-methyl-1-alkene **2** (200 g), *n*-tetradecane (10 l), and a cell suspension of *Nocardia corallina* B-276 (15 g cell/l, 10 l)[3] was stirred (600 rpm) at 30 °C with aeration(0.5 l/min).[4] The organic layer, separated through centrifugation, was fractionally distilled to give the corresponding epoxide **1** in optically active form.



2

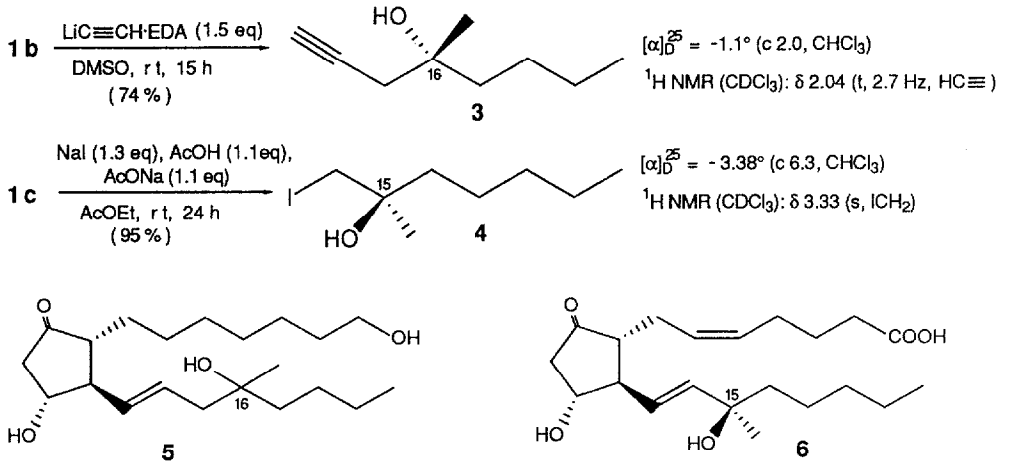
1a: n=3
1b: n=4
1c: n=5

Epoxide	Time	% Yield[a]	$[\alpha]_D^{25}$ (neat)	% ee[b]	Config.
1a	48 h	32	-8.83°	76	*R*[c]
1b	72 h	55	-9.28°	90	*R*[d]
1c	72 h	56	-7.39°	88	*R*[c]

a: See note 4. b: Determined by ^{1}H NMR analysis (270 MHz) using Eu(hfc)$_3$ as a chiral shift reagent (r/s=0.1). c: Asigned based on the similarity of the specific rotation with that of **1b**. d: Determined through a hydroxylation reaction (NaOH in aqueous DMSO) which gave (*R*)-(+)-2-methylhexane-1,2-diol (89 %ee). See note 5.

Then **1b** was reacted with lithium acetylide ethylenediamine complex in DMSO to afford acetylenic alcohol **3**, the precursor of 16-OH prostaglandins such as Rioprostil (**5**).[6] On the other hand, **1c** was reacted with sodium iodide in the presence of acetic acid[7] to give iodohydrin **4**.[8] The resulted **4** would be convertible into 15-OH prostaglandins such as Arbaprostil (**6**)[9] via β-oxide ylide.[10] In each ring-opening reaction, no detectable amount of regio-isomer was formed.[8]

Our microbial oxidation, which can be utilized for less functionalized alkenes[3] than the Sharpless' one, would give shorter synthetic routes in several cases. Further investigation on stereocontrol of tertiary asymmetric centers is now in progress.



References and notes

1. For example: G. Solladié, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Vol 2 (1983), p 157.
2. For reviews: B. E. Rossiter, *ibid*, Vol 5 (1985), p 193; M. G. Finn and K. B. Sharpless, *ibid*., Vol 5 (1985), p 247.
3. K. Furuhashi, M. Shintani, and M. Takagi, *Appl. Microbiol. Biotechnol.*, **23**, 218 (1986).
4. A better yield would be obtained through an efficient trap of the vapor of **2** lost by aeration.
5. $[\alpha]_D^{25}$=+3.60° (c 3.4, $CHCl_3$). The literature value: +4.03°: P. F. Corey, Patent, US 4,633,025. *Cf. idem.,Tetrahedron Lett.*, **28**, 2801 (1987).
6. H. C. Kluender, W. D. Woessner, and W. G. Biddlecom, Patent, US 4,132,738.
7. *Cf.* J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, **1959**, 112; R. C. Cookson and J. M. Coxon, *J. Chem. Soc. (C)*, **1971**, 1446.
8. Treatment of **4** with powdered NaOH in ether gave the starting epoxide (**1c**) with complete retention of stereochemistry. It proves that racemization caused by non-stereospecific iodination at C2 and recyclization during the ring-opening process was not occured.
9. E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974).
10. E. J. Corey, U. Koelliker, and J. Neuffer, *J. Am. Chem. Soc.*, **93**, 1490 (1971).

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