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BIFUNCTIONAL CHIRAL SYNTHONS VIA BIOCHEMICAL METHODS. VI. C_5 ISOPRENOID UNITS.[1]

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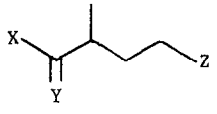
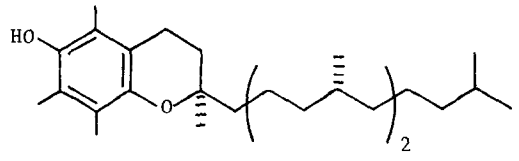
Summary: Two methods for the preparation of the isoprenoid chiron 4 have been developed using a microbial kinetic resolution of 5 and an enantiotopically selective hydrolysis of 7 catalyzed by PLE.

The utility of the isoprenoid chiron 1 for the synthesis of bioactive natural products has been demonstrated by its conversion to such important compounds as vitamin E, 2[2], and the mammalian dolichols, 3[3]. However, the difficulty in securing 1 in chiral form has limited its synthetic utility.[4]



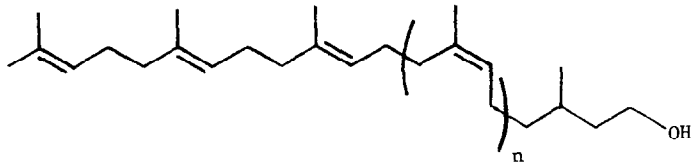


1 X = Br; Y = H,H; Z = OTHP or
X = H; Y = O; Z = Cl

4 X = H; Y = O; Z = OBzl

5 X = OCH_3; Y = O; Z = OBzl

2



3 n = 12-18

Herein, we describe two methods of obtaining aldehyde 4, of either absolute configuration, required in our polyether synthetic projects. The first method consists of a microbial kinetic resolution of 5, whereas the second entails an enantiotopically selective hydrolysis of 7. The resolution method is unique in that the chemical yield was optimized by using a combination of two esterases having opposite enantioselectivity.

A number of microorganisms were found to hydrolyze 5[5] and representative examples are listed in Table 1.[6] The optical purities, expressed as enantiomeric excess (ee)[7], of substrates (ee_s) and products (ee_p) resulting from typical incubations of 5 with microorganisms are also listed along with the extent of conversion (c) and the enantiomeric ratio (E value)[8] for each system. As shown, most microbial esterases are only moderately enantioselective (E = 5-14),

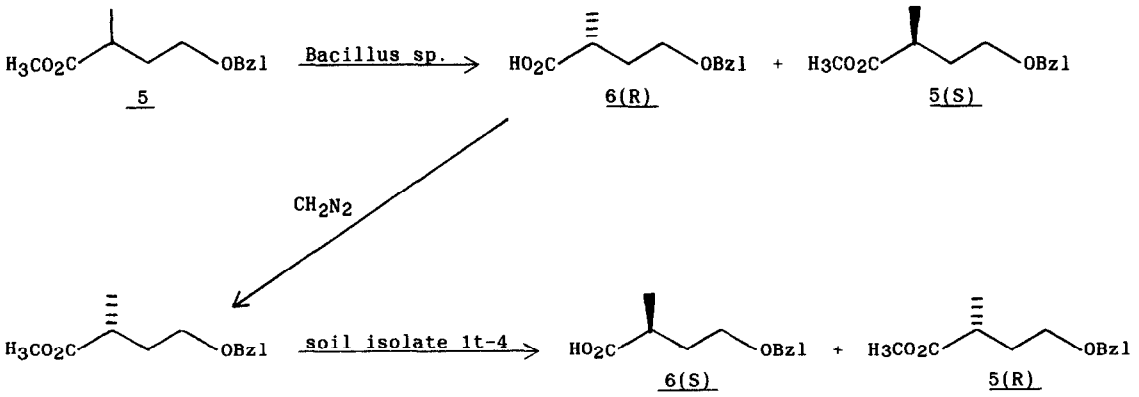
and preferentially hydrolyze the 5(R) enantiomer.[9] However, one complementary microorganism (soil isolate 1t-4) hydrolyzes the 5(S) enantiomer preferentially.

TABLE 1.

Microorganism	ee_s	ee_p	c	E	Enantiomer hydrolyzed
Bacillus sp. ATCC B-15053	.72	.77	.48	14	R
Enterobacter cloacae-41	.18	.82	.18	12	R
Oospora lactis-978	.12	.68	.15	6	R
Saccharomyces cerevisiae-1015	.11	.58	.16	4	R
Soil isolate 1t-4	.25	.71	.26	8	S
Soil isolate 8t-1	.52	.72	.42	10	R

Because of the unsymmetrical nature of kinetic resolutions[8], the availability of oppositely selective enzyme systems greatly facilitated the resolution of (±)5. In principle, the unreacted substrate fraction can always be obtained in optically pure form (ee > .97) using enzymes of moderate E value and longer reaction times. On the other hand, the preparation of chiral products of high optical purity (ee > .97) is more difficult and would require enzymes of high E values.

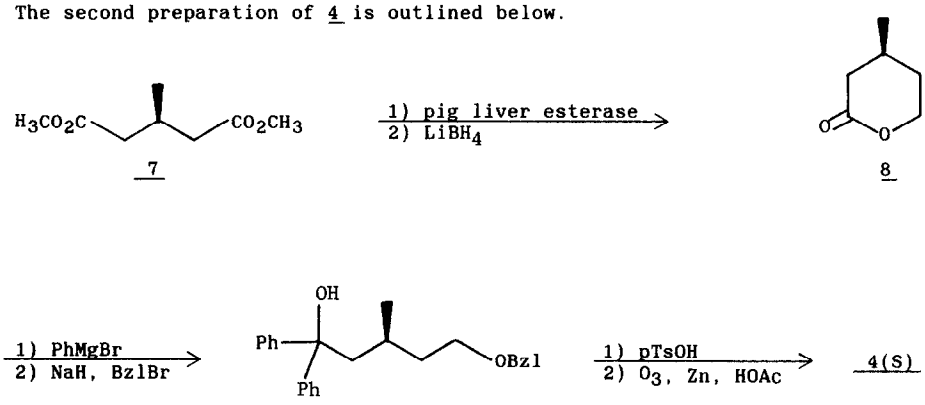
As outlined below, the first step in the kinetic resolution was to incubate (±)5 with Bacillus sp., which has the higher enantiomeric ratio, and terminate the reaction at 63% conversion.



After separation of the acid and ester fractions, the optically pure 5(S) (ee = .97) could be obtained in 31% isolated yield (of the 50% available). The partially resolved acid, 6(R) (ee = .60), could then be reesterified and incubated with the S selective soil isolate 1t-4. By

terminating this second reaction at 60% conversion, 5(R) could be obtained in 23% isolated yield (of the 50% available) and also in optically pure (ee = .97) form. In general, the sequential use of two enzymes of opposite enantioselectivity has the distinct advantage of providing both optically pure enantiomers in synthetically useful yields after only two incubations. Transformation of 5(S) or 5(R) to the desired benzyloxy aldehyde 4(S) or 4(R) could be achieved via a reduction-oxidation sequence (1. $LiAlH_4$, 2. DMSO, $(COCl)_2$).[10]

The second preparation of 4 is outlined below.



7 8 9

Commercially available pig liver esterase catalyzes the enantiotopically-selective hydrolysis of 7 and the resulting half-ester was selectively reduced to give (-)3S-methyl valerolactone 8 (ee = 0.90).[8,11] A modified Barbier-Wieland degradation was then employed to transform 8 into the desired 4. After treating 8 with excess phenylmagnesium bromide, followed by selective protection of the primary alcohol, 9 was obtained as a white solid. At this stage, crystallization of 9 gave a sample (hexane, mp 68.5°, $[\alpha]_D^{24}$ -10.4°, c = 2.1, $CHCl_3$) of high optical purity (ee > 0.97). Dehydration of 9 afforded the olefin, which was then ozonized to give the desired aldehyde 4(S) $[\alpha]_D^{24}$ +15.8°, c = 3.01, $CHCl_3$) in 42% overall yield from 8.[12]

In conclusion, these two methods provide ready access to the optically pure aldehyde 4 of either absolute configuration, which provides useful chirons for isoprenoid homologation. Application of the chiral benzyloxy aldehyde 4 to the field of polyether synthesis will be reported in due course.

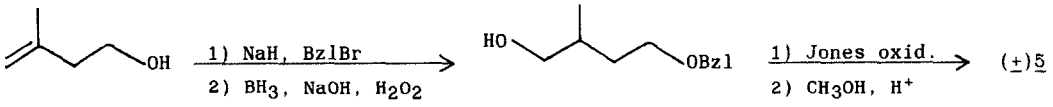
References and Notes

1. For part V in this series, see: A. Gopalan and C. J. Sih, Tet. Lett., in press (1984).
2. H. G. W. Leuenberger, W. Bogath, R. Barner, M. Schmidt, R. Zell, Helv. Chim. Acta, 62, 455, 464, 474 (1979).

3. S. Suzuki, F. Mori, T. Takigawa, K. Ibuta, Y. Ninagawa, T. Nishida, M. Mizuno, Y. Tanaka, Tet. Lett., 24, 5103 (1983).

4. Other chiral isoprenoid synthons have been reported, but were not applicable to the preparation of aldehyde 4.
   a) T. Kaneko, K. Wakabayashi and Katsura, Bull. Chem. Soc. Japan, 1149 (1962).
   b) A. I. Meyers, E. D. Mihelich, J.O.C., 40, 1186 (1975).
   c) T. Mukaiyama, K. Fujimoto, T. Hirose, T. Takeda, Chem. Lett., 635 (1980).
   d) C. Bodekar, E. R. de Waard, H. O. Husman, Tetrahedron, 1233 (1982).
   e) K. Mori, Tetrahedron, 3107 (1983).

5. Racemic ester 5 was synthesized in molar quantities by the following 4 step sequence in 52% overall yield.



6. For a detailed description of the procedures used for the evaluation of microorganisms, see: C. J. Sih, C. S. Chen, G. Girdaukas, B. N. Zhou in "The Biological Basis of New Developments in Biotechnology"; A. Hollaender, A. Laskin and P. Rogers, Eds., Plenum Press, New York, 1982.

7. Optical purities were determined by ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$.

8. The enantiomeric ratio (E value) is calculated from: $E = \frac{\ln[(1 - c)(1 - ee_s)]}{\ln[(1 - c)(1 + ee_s)]}$, where $c = ee_s/(ee_s + ee_p)$. For a comprehensive treatment of the principles involved in kinetic resolutions, see: C. S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, JACS, 104, 7294 (1982).

9. The absolute configuration of 6(S) was determined by conversion of a sample (ee = .60) to 2(S)-methylbutyrolactone ($[\alpha]_D^{24}$ = -13.0°, c = 1.6, EtOH; lit.[4a] $[\alpha]_D^{24}$ -21.5°, c = 5.5, EtOH) via hydrogenation followed by acid treatment.

10. Oxidation with pyridinium chlorochromate caused extensive racemization.

11. P. Mohr, M. Tori, P. Grossen, P. Herold, and C. Tamm, Helv. Chim. Acta, 65, 1412 (1982).

12. The 4(R) enantiomer could be obtained by the same sequence of reactions by substituting an acid selective BH_3 reduction for the ester selective $LiBH_4$ reduction as exemplified in a) F. C. Huang, L. F. H. Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, and C. R. Eck, JACS, 103, 2405 (1975), and b) C. J. Francis and J. B. Jones, J.C.S. Chem. Comm., 579 (1984).

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