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A STEREOCONTROLLED SYNTHESIS OF THE METHYL ESTER OF (±)-NONACTIC ACID

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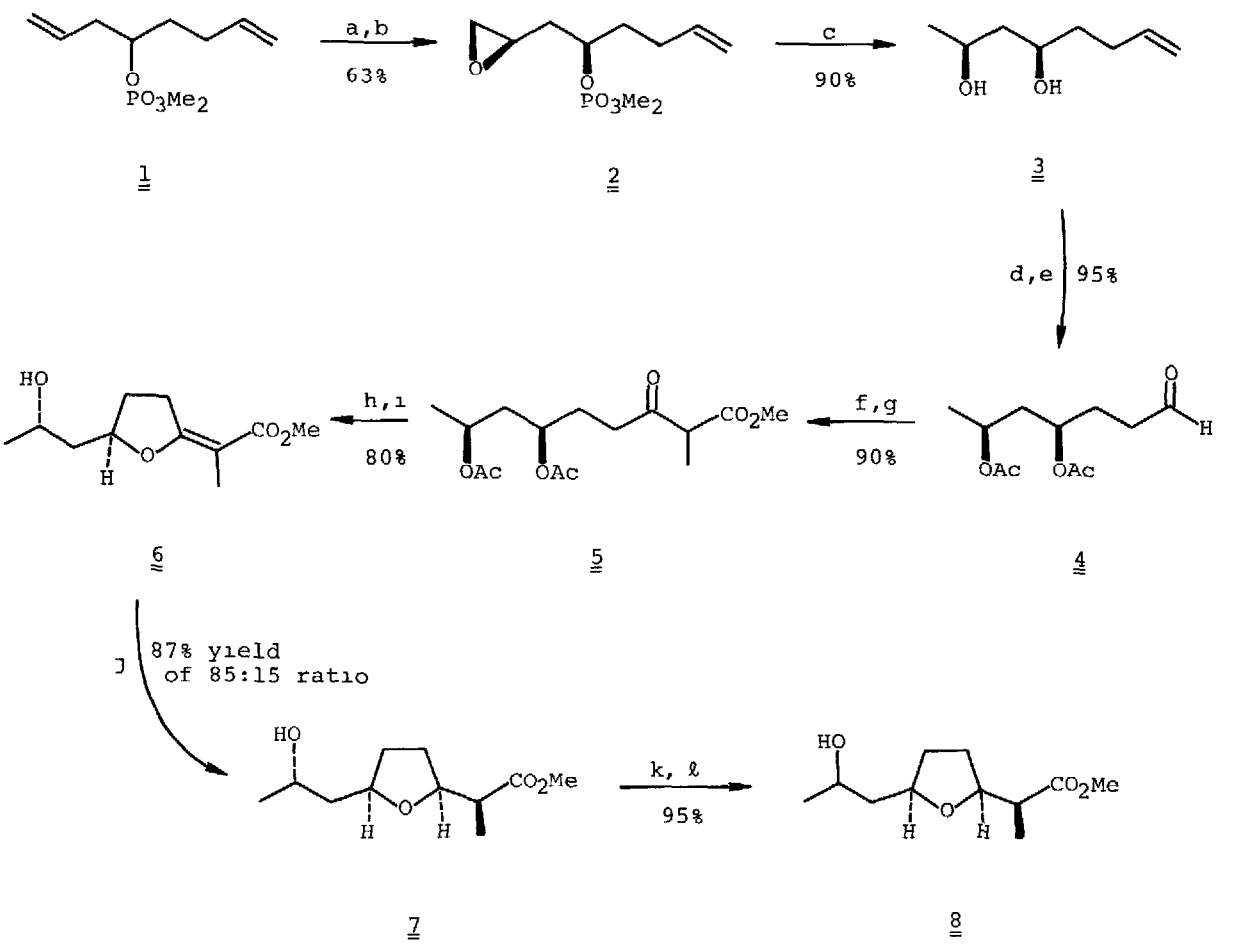
Iodine-induced cyclization of a homoallylic phosphate and hydrogenation of a 2,3-dehydrononactic acid derivative are used to introduce the chiral centers selectively in a highly efficient synthesis of methyl nonactate.

Nonactic acid, the subunit of the macrocyclic ionophore nonactin,[1] has been the target of a number of syntheses during recent years.[2] As part of a program concerned with acyclic stereocontrol,[3] we developed a stereoselective synthesis of the methyl ester of (±)-nonactic acid, 8, in which all of the chiral centers are introduced in a controlled manner.

Dimethyl 1,7-octadien-4-yl phosphate (1)[4,5] is epoxidized stereo- and regiospecifically in 63% yield by our two-step phosphate cyclization process.[3a] ^{13}C-NMR analysis of the epoxy phosphate 2[5] showed it to be contaminated with less than 5% of isomeric material. Both the epoxide and phosphate moieties react cleanly with $LiAlH_4$ in ether to provide the *erythro* diol 3.[5] The cyclic iodophosphate intermediate in the epoxidation sequence[3a] can also be cleaved with $LiAlH_4$, furnishing the diol 3 directly. However, this reaction is accompanied by significant reductive elimination, returning up to 50% of 1,7-octadien-4-ol, and the two-step process via the epoxide is preferred. The *erythro* diol 3 is converted to the aldehyde diacetate 4 using the acetylation and ozonolysis steps reported by Gerlach and Wetter[2b] for the *threo* series.

A titanium tetrachloride-catalyzed aldol condensation[6] and subsequent Jones oxidation convert the aldehyde 4 to the β-ketoester 5.[5] With the complete carbon skeleton of nonactic acid assembled, the tetrahydrofuran ring is generated by acetate cleavage and dehydration with oxalic acid in refluxing methylene chloride, affording methyl E-epi-2,3-dehydrononactate 6.[5] From this dehydration reaction a



a: 2.2 eq. I_2, MeCN, 25°C, 24 hr, b: 1.1 eq. NaOMe, THF, 0°C, 7 hr;

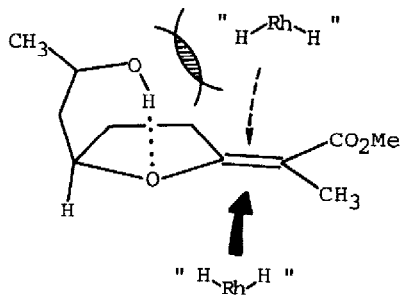
c: 3 eq. $LiAlH_4$, ether, 0°C, 1 hr; d: Ac_2O, pyridine, 25°C, 12 hr;

e: O_3, CH_2Cl_2, -78°C, 30 min; f: $MeCH{=}C(OMe)OSiMe_3$, $TiCl_4$, CH_2Cl_2, -78 → 0°C, 12 hr;

g: CrO_3, H_2SO_4, acetone/water, 0°C, 30 min; h: K_2CO_3, MeOH, 25°C, 2 hr;

i: HO_2CCO_2H, CH_2Cl_2, Δ, 2 hr; j: 3.5 atm H_2, Rh/Al_2O_3, MeOH, 25°C, 60 hr;

k EtO_2CNNCO_2Et, Ph_3P, $PhCO_2H$, THF, 25°C, 12 hr, ℓ: NaOMe, MeOH, 25°C, 18 hr



9

single isomer is isolated, to which we assign the E geometry based on precedent[7] and subsequent elaboration.

The remaining two chiral centers are introduced by hydrogenation of the double bond, using 5% rhodium on alumina as catalyst. As desired, the catalyst delivers the hydrogen to the least encumbered face of the π-system (as in 9), establishing the desired configurations at C-2 and C-3.

180-MHz ^{1}H-NMR analysis of the product from this reduction confirmed the identity of the major isomer as the methyl ester of 8-epinonactic acid (7),[5,8] and demonstrated that the stereoselectivity of the hydrogenation is better than 85:15.[9] Inversion of the hydroxyl configuration at C-8 using the same procedure described by White[2d] completes the synthesis of methyl (±)-nonactate (8) in better than 25% overall yield from 1,7-octadien-4-ol.

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4. Prepared from the alcohol (S.E. Wilson, Tetrahedron Lett., 4651 (1975)) in 98% yield using KH and $ClPO_3Me_2$.
5. Satisfactory combustion analysis and spectra were obtained for this compound.
6. K. Saigo, M. Osaki, and T. Mukaiyama, Chem. Lett., 989 (1975).
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8. Comparison was made with a ^{1}H-NMR spectrum and authentic sample which were kindly supplied by Professor J.D. White.
9. The most diagnostic resonances indicating the presence of the minor isomer, methyl 6-epinonactate, are those of the methyl groups (dilute solutions in $CDCl_3$ (1% TMS)): for the 8-epi ester, 7: δ 1.12 (J=7.1 Hz), 1.17 (J=6.4 Hz), 3.70 (MeO); for the 6-epi ester: δ 1.18 (J=6.2 Hz), 1.22 (J=7.0 Hz), 3.68 (MeO). Under the same conditions, methyl nonactate 8 shows resonances at δ 1.31 (J=7.0 Hz), 1.20 (J=6.3 Hz), 3.69 (MeO), and methyl 6,8-diepinonactate shows resonances at δ 1.21 (J=6 3 Hz), 1.22 (J=6.9 Hz), 3.68 (MeO).

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