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STEREOSELECTIVE SYNTHESIS OF (±)-METHYL NONACTATE AND (±)-METHYL 8-*epi*-NONACTATE.

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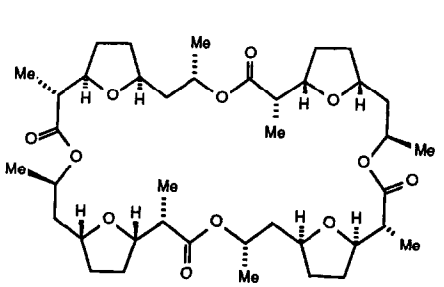
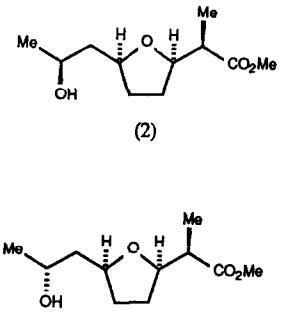
Summary: (±)-Methyl nonactate (2) and (±)-methyl 8-*epi*-nonactate (3), synthetic precursors to the antibiotic nonactin have been synthesised, employing the reaction of substituted epoxides with dianions derived from β-ketoesters as the key carbon-carbon bond-forming step.

Nonactin (1) is a S_4-symmetrical macrotetrolide antibiotic isolated from a variety of *Streptomyces* cultures and is effective in controlling mitochondrial potassium ion flux[1]. It is composed of two subunits of (-)-nonactic acid and two subunits of (+)-nonactic acid, arranged in an alternating order. Syntheses of nonactin have been achieved by coupling together derivatives of either nonactic acid [eg. (2)][2] or 8-*epi*-nonactic acid [eg. (3)][3].



(1)

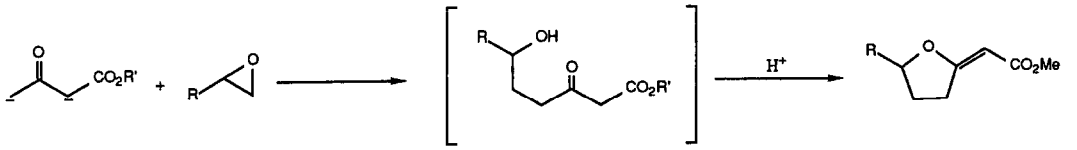


(2)

(3)

There have been many reported syntheses of nonactic acid derivatives in both optically active and racemic form[2-4], unfortunately with few exceptions, overall yields are generally not good. We report here a short and stereoselective approach to both (±)-methyl nonactate (2) and (±)-methyl 8-*epi*-nonactate (3) in yields of 30-40%.

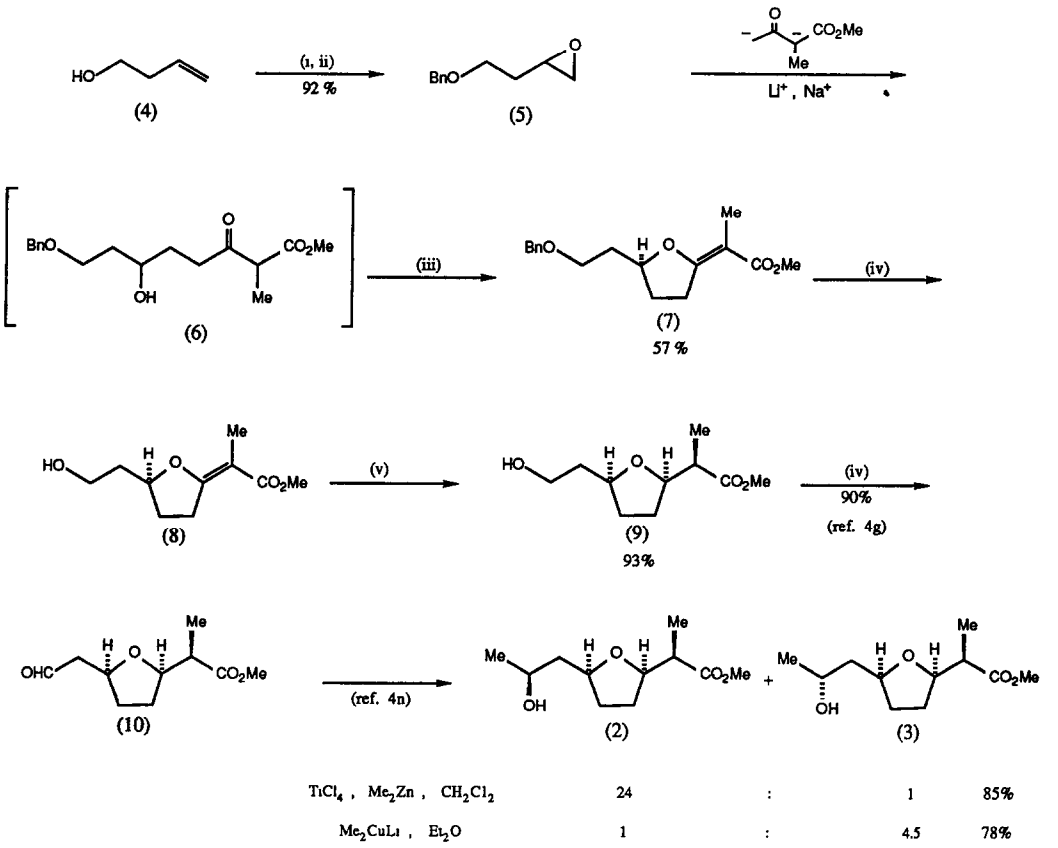
Dianions derived from β-ketoesters are known to react with substituted epoxides[5], allowing rapid access to tetrahydrofuran systems (Scheme 1). Indeed this reaction would seem ideally set up to prepare compounds such



Scheme 1

as nonactic acid. Previous attempts to utilise this approach were unsuccessful, no reaction being observed between the dianion and the requisite epoxide [R = $CH_2CH(Me)OSiMe_2{}^tBu$][4i]. The precise reason for this lack of reaction is not clear, however, there are very few examples of oxygenated epoxides participating in this condensation.

Due to an interest in preparing tetrahydrofuranyl systems related to nonactic acid, we decided to investigate whether oxygenated epoxides could be used, and if derivatives of nonactic acid could be prepared by this approach. To this end we examined the reaction between epoxide (5) and the dianion derived from methyl(2-methyl, 3-oxo)butanoate (Scheme 2).

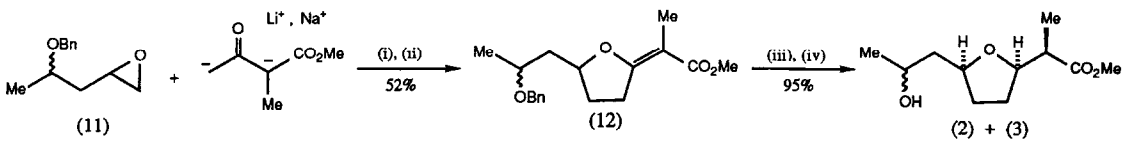


Scheme 2

Reagents: (i) NaH, THF; BnBr, (ii) *m*-CPBA, CH_2Cl_2, (iii) oxalic acid, CH_2Cl_2, reflux, (iv) 10% Pd/C, MeOH, H_2, 1atm, (v) 5% Rh/Al_2O_3, MeOH, H_2, 65psi, (vi) DMSO, $(COCl)_2$; Et_3N.

Epoxide (5) was prepared in 92% yield from commercially available 4-hydroxy but-1-ene, using standard methods. This was then allowed to react with the dianion obtained by treatment of methyl(2-methyl, 3-oxo)butanoate with sodium hydride followed by n-butyl lithium[6]. It was found that condensation proceeded smoothly in tetrahydrofuran solution, usually taking 12-24h at room temperature to reach completion. The resulting hydroxy β-ketoester proved difficult to purify and was therefore cyclised directly using oxalic acid[5]. The desired tetrahydrofuran (7) was obtained cleanly, in 57% overall yield, and appeared to be only one double bond isomer by ^{1}H nmr[7], this we assumed to be the more stable *E*-isomer by analogy with literature precedence[4i,5]. Debenzylation gave alcohol (8), which could then be hydrogenated at 65 psi using 5% Rh/Al_2O_3 as catalyst and methanol as solvent. Complete hydrogenation was achieved after a period of 90h, giving the known stereoisomer (9)[4g] with *ca* 8:1 selectivity, however, it should be noted that not all samples of Rh/Al_2O_3 would effect reduction[8]. The hydrogenation selectivity and variability of catalyst activity is consistant with results obtained in similar reactions[3b]. This completes the formal synthesis of both (±)-methyl nonactate (2) and (±)-methyl 8-*epi*-nonactate (3), since oxidation to the corresponding aldehyde (10)[4g], and stereoselective introduction of the C-8 methyl group[4n] are both known transformations.

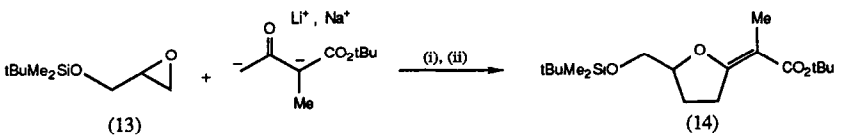
In order to test the generality of the epoxide opening reaction two other related approaches to nonactic acid were investigated. First, reaction of the dianion from methyl(2-methyl, 3-oxo)butanoate with epoxides (11) derived from 4-hydroxy pent-1-ene was examined (Scheme 3). This proceeded exactly as before, giving tetrahydrofuran (12), 52% after cyclisation. Debenzylation, followed by hydrogenation with Rh/Al_2O_3 gave a 1:1 mixture[9] of (±)-methyl nonactate (2) and (±)-methyl 8-*epi*-nonactate (3) which could be separated by silica gel chromatography. In this case it was difficult to assess the precise selectivity of hydrogenation for each isomer, although it appeared to be ≥5:1 in both cases. The overall yield for this sequence was an impressive 40%.



Scheme 3

Reagents: (i) THF, RT, (ii) oxalic acid, CH_2Cl_2, reflux, (iii) 10% Pd/C, MeOH, H_2, 1atm, (iv) 5% Rh/Al_2O_3, MeOH, H_2, 65psi.

Finally reaction of protected glycidol (13) with the dianion derived from *t*-Butyl(2-methyl, 3-oxo)butanoate was examined (Scheme 4). This proceeded in a similar fashion to the previous examples, giving after cyclisation, the known tetrahydrofuran (14)[4l]. Since this material has also been converted to a derivative of 8-*epi*-nonactic acid, this consitutes a third approach to such compounds.



Scheme 4

Reagents: (i) THF. RT, (ii) oxalic acid, CH_2Cl_2, reflux.

It appears from the results presented here that reaction of β-ketoester dianions with epoxides containing oxygenated substituents is fairly general, and can be used very effectivly to prepare nonactic acid derivatives. Further extensions of this work, and other applications to natural product synthesis are currently being investigated.

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7. ^{1}H nmr data for compound (8); ($CDCl_3$, 300MHz) δ 4.48 (1H, quintet, J = 6.5 Hz, C*H*O), 3.77 (2H, t, J = 6 Hz, CH_2OH), 3.63 (3H, s, CO_2CH_3), 3.19 (1H, m, CH_aH$_b$C=C), 2.87 (1H, dtq, J = 18, 9, and 1.5 Hz, CH$_a$$H_b$C=C), 2.24-2.12 (1H, m), 2.06 (1H, br.s, O*H*), 1.88-1.60 (3H, m), and 1.73 (3H, t, J = 1.5 Hz, CH_3).

8. Active samples of 5% Rh/Al_2O_3 were obtained from Fluka agents: Fluorochem Ltd., Glossop, Derbyshire Old samples (3 yrs) appeared to be no longer effective.

9. This mixture results from the fact that epoxide (11) used was a *ca.* 1:1 mixture of diastereoisomers.

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