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Synthesis of (±)-Nonactic Acid[1]

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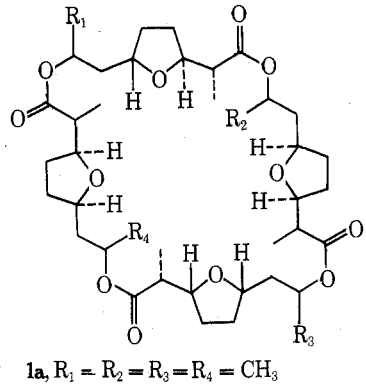
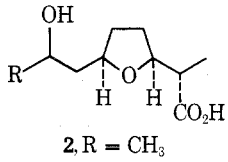
Two routes to (±)-nonactic acid (**2**) are described, both starting with furan. 2-Lithiofuran was alkylated with propylene oxide to give **4**, which underwent Friedel–Crafts reaction with acetic anhydride to keto acetate **17**. Hydrogenation of **17** over rhodium resulted in the cis fused tetrahydrofuryl alcohol **19**, and this was oxidized with Jones reagent to **22**. A Wittig reaction of **22** with methylenetriphenylphosphorane afforded **28**, which was saponified to **29**. Olefin **29** was treated with diborane, followed by basic hydrogen peroxide and then Jones reagent, to give keto acids **30** and **31** (2:1, respectively). These were converted to the corresponding methyl esters **32** and **33**, and the latter was reduced with L-selectride to methyl 8-epinonactate (**36**). Inversion of hydroxyl configuration was accomplished via benzoate **40** which, after methanolysis, gave methyl nonactate (**35**). In a second approach to **2**, the adduct **42** from furan and 2,4-dibromopentan-3-one was hydrogenated to **43**. Baeyer–Villiger oxidation of this ketone furnished lactone **44**, which underwent methanolysis to **45**. Conversion of alcohol **45** to its xanthate **53**, followed by pyrolysis, yielded the vinyltetrahydrofuran **54**. Oxidative hydroboration with disiamylborane transformed **54** to primary alcohol **55** which, after oxidation with Collins reagent, produced epimeric esters **56** and **57** (1:1). The Grignard reaction of **56** with methylmagnesium iodide gave methyl nonactate (**35**) and the 8-epi ester **36**.

The family of macrotetrolide antibiotics produced by *Streptomyces*, and known collectively as nactins, comprise a series of homologues based upon a parent 32-membered ring **1**.[2] The lowest homologue, nonactin (**1a**), is constituted of four nonactic acid (**2**) subunits, linked in alternating enantiomeric sequence (+−+−), so that the macrocycle overall possesses meso configuration. Monactin (**1b**), dinactin (**1c**), trinactin (**1d**), and tetranactin (**1e**), as well as isodinactin (**1f**) and isotrinactin (**1g**), contain the same basic macrotetrolide structure but incorporate to varying extents the homologue **3** of nonactic acid. The special feature of nonactin, and presumably other nactins, which lend them chemical interest and potential biological importance is their ability to bind alkali metal cations, particularly potassium,[3] within an ionophoric core enclosed by a lipophilic "skin". The resulting ion-transport property associated with nonactin has been shown to have a powerful influence upon mitochondrial respiration[4] and oxidative phosphorylation.[5]



1a, $R_1 = R_2 = R_3 = R_4 = CH_3$
b, $R_1 = C_2H_5$; $R_2 = R_3 = R_4 = CH_3$
c, $R_1 = R_3 = C_2H_5$; $R_2 = R_4 = CH_3$
d, $R_1 = R_2 = R_3 = C_2H_5$; $R_4 = CH_3$
e, $R_1 = R_2 = R_3 = R_4 = C_2H_5$
f, $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = CH_3$
g, $R_1 = R_2 = R_4 = C_2H_5$; $R_3 = CH_3$

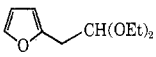
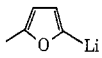
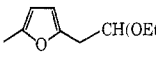
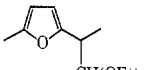
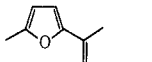
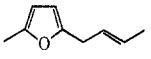
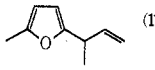
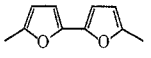


2, R = CH_3
3, R = C_2H_5

The hydrolysis of nonactin (**1a**) to nonactic acid (**2**) was a key step in the structural elucidation of this macrolide by Gerlach and Prelog.[6] Reconstitution of the macrolide thus requires synthesis of **2**, followed by successive coupling of the hydroxy acid in the proper enantiomeric sequence, and finally closure of the linear tetrolide by lactonization. We describe herein the completion of the first of these stages, the synthesis of nonactic acid in racemic form, by two independent routes.

Of the four asymmetric centers in nonactic acid, the two represented by points of attachment of the three-carbon chains to the tetrahydrofuran nucleus are the easiest to control. Earlier work by Gerlach and Huber[7] directed toward a synthesis of 8-deoxynonactic acid and, recently, syntheses of nonactic acid by Beck and Henseleit,[8] Gerlach and Wetter,[9] and Schmidt et al.,[10,11] all made use of the catalytic hydrogenation of a 2,5-disubstituted furan to produce the required

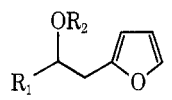
Table I. Alkylation of 2-Lithiofurans

Furan	Alkylating agent	Product(s)	Yield, %
	$BrCH_2CH(OEt)_2$	 (8)	70
	$BrCH_2CH(OEt)_2$	 (9)	45
	$CH_3CHCH(OEt)_2$ (Br)	 (10a) +  (10b)	50[a]
	$CH_2=CHCHCH_3$ (Br)	 (11a)  (11b)	59[b]
	None[c]	 (12)	24

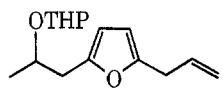
[a] Ratio 10a:10b, 2:1. [b] Ratio 11a:11b, 1:2. [c] CuBr added.

cis orientation of side chains in **2**. The first of our two approaches likewise adopted this strategy, and attention, therefore, was focused initially upon the construction of an appropriately substituted furan.

Metalation of furan with butyllithium gives the 2-lithio derivative,[12] and this intermediate reacted smoothly with propylene oxide and with 1-butene oxide to give **4** and **5**, respectively. Thus, the 2-propanol and *sec*-butyl alcohol chains of nonactic and homononactic acids can be efficiently incorporated at the outset. Unfortunately, efforts to introduce the propionic acid unit at the 5 position of **4** by a similar lithiation approach were less successful. Thus, conversion of **4** to its tetrahydropyranyl ether **6** and treatment of the latter with butyllithium, followed by ethyl α-bromopropionate, led only to recovered starting materials after hydrolytic workup. Similar results were obtained when *tert*-butyl α-bromoacetate or the diethyl acetals of α-bromoacetaldehyde and α-bromopropionaldehyde were employed as intended alkylating agents. In contrast, **6**, after metalation with butyllithium, underwent alkylation with allyl bromide to give **7** in modest yield.

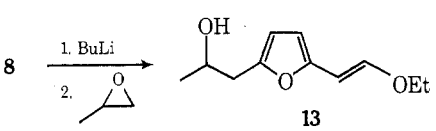


4, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = C_2H_5$; $R_2 = H$
6, $R_1 = CH_3$; $R_2 = THP$



7

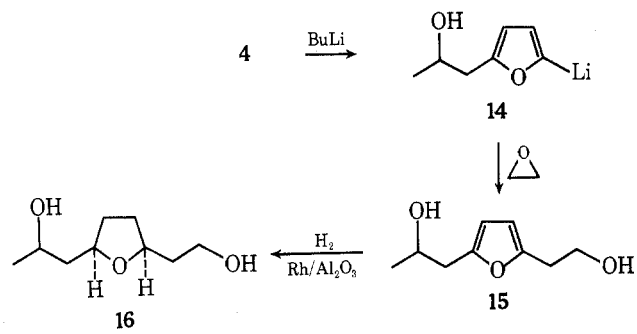
The failure of the 5-lithio derivative of **6** to undergo alkylation with α-bromo esters and acetals prompted consideration of an alternate scheme in which the sequence of attachment of propyl and isopropyl side chains to the furan is reversed. 2-Lithiofuran, in the presence of α-bromoacetaldehyde diethyl acetal, gave **8** in 70% yield, a result which encouraged us to survey a range of alkylations of this type. These are summarized in Table I. Thus, although alkylation of 2-lithiofurans and 5-lithio-2-methylfurans with α-bromo acetals can be made to proceed, yields in all cases save that of **8** were relatively poor. In one attempt to utilize lithio di(5-methylfur-2-yl)cuprate, the sole isolable product was the bifuryl **12**.[13] Lithiation of **8** with butyllithium followed by exposure to propylene oxide gave **13** (43%), in which elimination of the acetal as well as



13

alkylation had occurred. However, attempts to transform the exceptionally stable enol ether function of **13** to an aldehyde by acidic hydrolysis led only to destruction of the furan under forcing conditions.

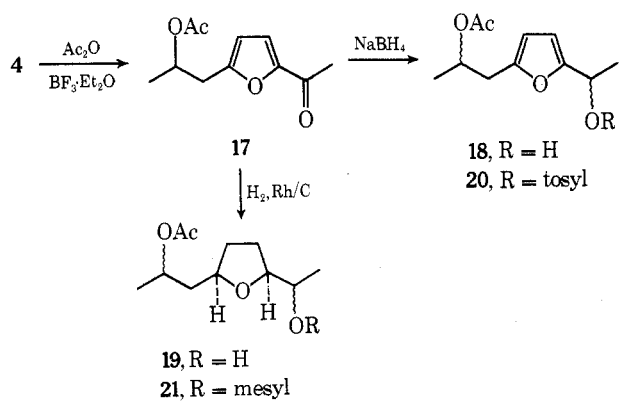
A simplification of this alkylation scheme, in which **4** was treated with an excess of butyllithium and the resulting dilithio derivative **14** was allowed to react with ethylene oxide,



14, **15**, **16**

afforded diol **15** in 80% yield. Catalytic hydrogenation of **15** over rhodium on alumina proceeded in 63% yield, giving a single stereoisomer **16**. However, although this efficient, three-step (from furan) sequence to a cis 2,5-disubstituted tetrahydrofuran appeared to offer enticingly direct access to **2**, the further transformation of **16** with a variety of oxidants gave discouragingly complex mixtures.

The acylation of furans, in contrast to alkylation, is a generally well-behaved, electrophilic substitution, in which attack invariably occurs at position 2.[14] This tactic therefore appeared to offer an alternative approach to the required 2,5-disubstituted furan, and our efforts along these lines met with early success. Treatment of **4** with acetic anhydride in the presence of boron trifluoride etherate gave **17** in 86% yield

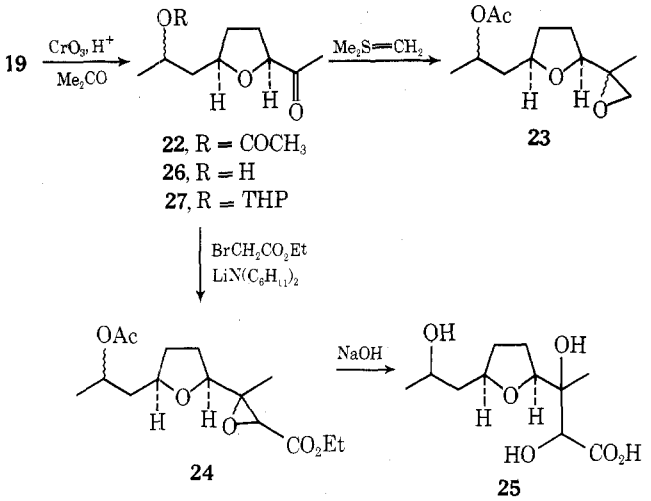


17, **18**, **19**, **20**, **21**

when the Friedel–Crafts reaction was carried out at −25 °C.[15] The presence of an acetate as well as a conjugated ketone was apparent from the infrared spectrum (1730, 1680 cm^{-1}) and was confirmed by the NMR spectrum (δ 2.0 and 2.4, both three-proton singlets), which also displayed two furan β protons (δ 6.25 and 7.12, each a one-proton doublet with $J = 3$ Hz, the latter signal reflecting a strong deshielding influence due

to conjugative electron withdrawal by the ketone carbonyl). Reduction of 17 with sodium borohydride in glyme–*tert*-butyl alcohol yielded a mixture of epimeric alcohols 18 (80%), whereas exhaustive hydrogenation of 17 over a rhodium on charcoal catalyst furnished cis-fused hydroxy acetate 19, in which reduction of the ketone had accompanied saturation of the furan moiety. Unfortunately, although both 18 and 19 could be converted to their respective sulfonate esters 20 and 21, neither ester proved amenable to displacement with cyanide (in Me_2SO), 21 being exceedingly sluggish whereas 20 was excessively reactive and underwent rapid polymerization.

Oxidation of 19 with Jones reagent afforded keto acetate



22 in 98% yield as a pair of acetoxyl epimers, and studies were then directed toward homologation from this intermediate to the requisite carboxyl function of 2. Treatment of 22 with dimethylsulfonium methylide[16] produced epoxide 23 (70%), readily identified by the appearance of a new two-proton singlet at δ 2.50 in the NMR spectrum. Likewise, 22 underwent a smooth Darzens condensation with ethyl α-bromoacetate, in the presence of lithium dicyclohexylamide,[17] to give glycidic ester 24 in 90% yield. However, attempted saponification–decarboxylation of 24 resulted in trihydroxy acid 25, whereas exposure of 23 to boron trifluoride etherate yielded a mixture which evidently included products (olefinic) resulting from a pinacol rearrangement rather than the hoped-for transformation to an aldehyde.

We turned therefore to a different plan, involving the Wittig reaction, for the transformation of 22 to nonactic acid, and this was ultimately successful. Although treatment of 22, as well as its derived tetrahydropyranyl ether 27, with methoxymethylenetriphenylphosphorane gave only traces of an enol ether, the condensation of keto acetate 22 with the Wittig reagent derived from methyltriphenylphosphonium bromide

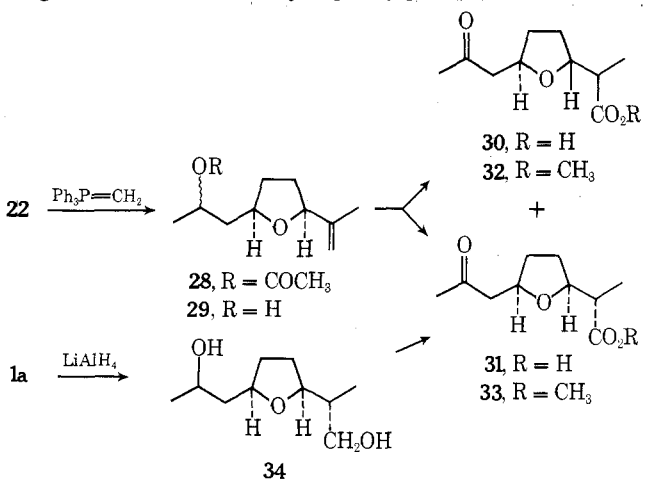
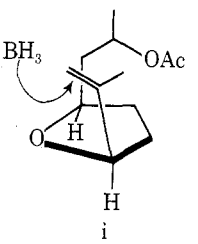


Table II. Chemical Shift of C-2 Methyl Substituent in Nonactic Acid and Derivatives

Compd	C-2 CH_3, δ, ppm
Nonactic acid (2)	1.09
Methyl nonactate (35)	1.08
Methyl 2-epinonactate (39)	1.14
Methyl 8-epinonactate (36)	1.09
8-Oxononactic acid (31)	1.08
Methyl 8-oxononactate (33)	1.09
Methyl 2-epi-8-oxononactate (32)	1.18

and sodium hydride in Me_2SO[18] afforded 28 in good yield, accompanied by a small quantity of alcohol 29. Hydroboration of 28 with diborane in THF, followed by oxidation with basic hydrogen peroxide, furnished an epimeric mixture of diols, which was oxidized with Jones reagent to keto acids 30 and 31 (2:1, respectively). Alternatively and more conveniently, saponification of 28 with 5% methanolic sodium hydroxide, followed by hydroboration and titration of the resulting alkylborane with Jones reagent, gave 30 and 31 in the same ratio. Separation of these keto acids proved to be difficult and they were therefore converted to the corresponding methyl esters 32 and 33 with methanol in the presence of boron trifluoride etherate.[19]

The configuration of these esters was established by comparison with keto ester 33 derived from nonactin.[6] Reduction of nonactin with lithium aluminum hydride gave diol 34 which was oxidized with Jones reagent. The resulting keto acid 31 was esterified as before to 33. The chemical shift (Table II) of the C-2 methyl substituent in the major keto ester 32 reveals quite clearly that it is of the unnatural series; the doublet resonance associated with this methyl group is consistently downfield (Δδ 0.06–0.09) in the 2-epi derivatives of nonactic acid as contrasted with compounds having natural configuration at C-2. Fortunately, the predominance of the wrong stereoisomer 32 at this stage was of little consequence, since it was already known that equilibration of configuration at C-2 of methyl nonactate leads to an epimeric mixture containing approximately 60% of the natural ester.[20] In the synthesis scheme, configuration at C-2 is determined at the stage of borane attack on the alkene linkage of 28 (or the derived alcohol 29), and prevalence of keto acid 33 after oxidation must reflect a preference for hydroboration in a conformation resembling i, since attack from a direction across the tetrahydrofuran ring would be prohibited by the cis disposition of alkyl side chains.



i

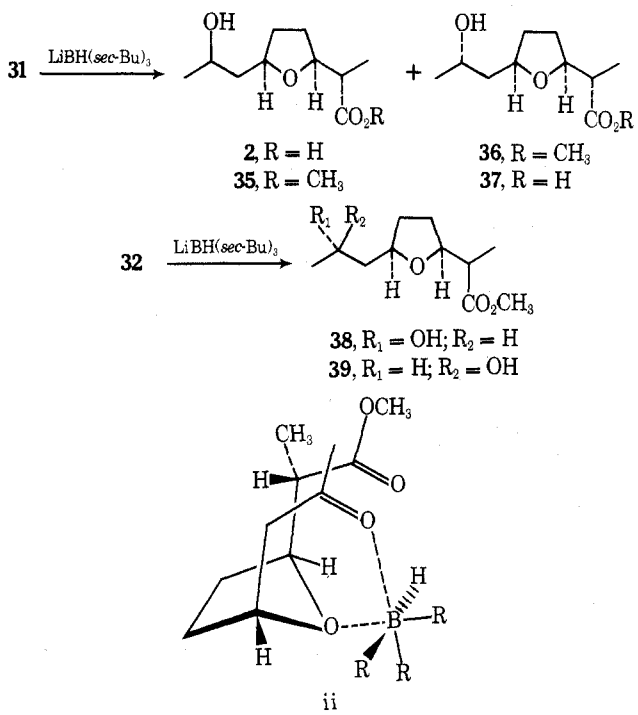
For reasons that will be discussed more fully in connection with the coupling of nonactic acid,[21] it was of importance to have available a route to 8-epinonactic acid, as well as the natural compound. Reduction of 33 with sodium borohydride in methanol gave methyl nonactate (35) and methyl 8-epinonactate (36) in the ratio of 1:3, a result which suggested that higher stereoselectivity might be realized under modified reaction conditions. As seen from Table III, the highest degree of stereocontrol was achieved in the reduction of keto acid 31 with L-selectride,[22] which gave nonactic acid (2) and its 8-epimer (37) in the ratio 1:9. Reduction of the 2-epiketo ester 32 with sodium borohydride afforded predominantly methyl 2,8-bisepinonactate (38) with <20% of 2-epi ester 39 present.

Table III. Epimer Ratios from Reduction of Ketones to Nonactic Acid Derivatives

Ketone	Reducing agent	Solvent	Product (ratio)
32	$NaBH_4$	MeOH	39 (17):38 (83)
33	$NaBH_4$	MeOH	35 (26):36 (74)
33	$LiAlH(t\text{-}BuO)_3$	THF	35 (21):36 (79)
31	$[(CH_3)_2CHCH(CH_3)]_2BH$	THF	35 (42)[a]:36 (58)[a]
31	9-BBN[b]	THF	35 (35)[a]:36 (65)[a]
31	$LiBH(sec\text{-}Bu)_3$[c]	THF	35 (10)[a]:36 (90)[a]

[a] After conversion to methyl ester. [b] 9-Borabicyclo-[3.3.1]nonane. [c] L-selectride.

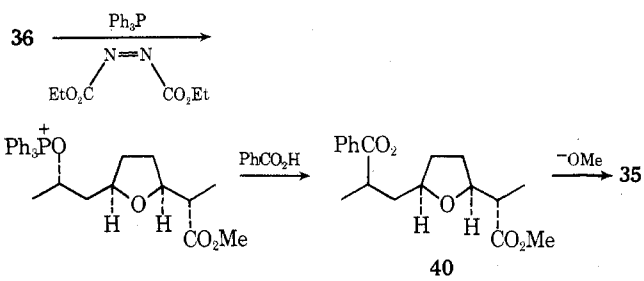
Thus, in both the natural and 2-epi series, hydride attack at the C-8 carbonyl occurs preferentially from the direction which is expected if complexation of the reducing agent with other oxygens in the substrate, particularly that of the tetrahydrofuran, is assumed.[23] The representation ii depicts such a complex, and also explains why improved stereoselectivity is observed with the bulkier hydride reagent where R groups



ii

(*sec*-butyl) are excluded from the congested region shown occupied by the hydride ligand.

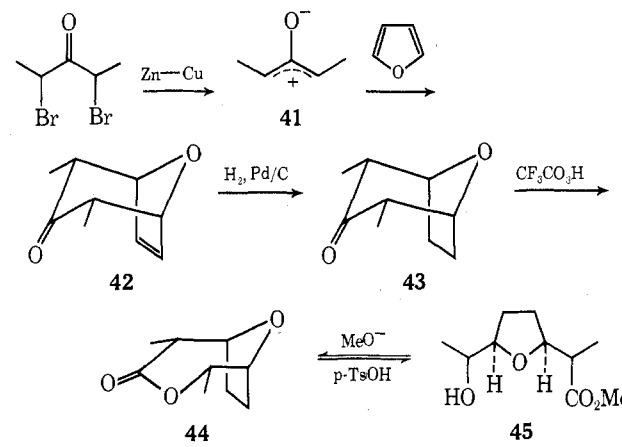
Inversion of configuration at the C-8 hydroxyl group in **36** was accomplished by treatment with triphenylphosphine, diethyl azodicarboxylate, and benzoic acid,[24] a protocol which has been notably successful in the inversion of sterols.[25] In the present case, a 90% yield of the inverted benzoate **40** was ob-



tained. This diester was rigorously purified by chromatography on Florisil, and then subjected to methanolysis to give methyl nonactate (**35**), identical by comparison of infrared, nuclear magnetic resonance, and mass spectra, as well as chromatographic behavior, with authentic material derived by methanolysis of nonactin. It may be noted that ^1H NMR spectroscopy conveniently distinguishes all four stereoisomers of methyl nonactate differing with respect to centers at carbons 2 and 8, although the mass spectra are virtually identical. Saponification of **35** has been previously shown to give nonactic acid (**2**).[9]

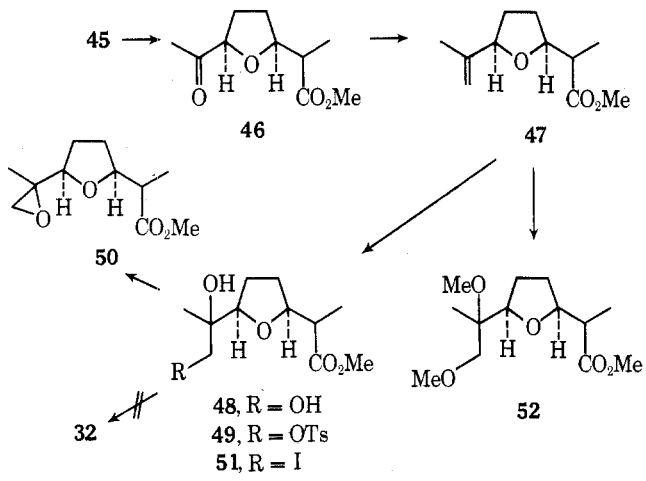
An alternative approach to the 2,5-disubstituted tetrahydrofuran skeleton of nonactic acid, which was suggested by the work of Noyori,[26] entails cycloaddition of an oxoallyl cation, generated from an α,α'-dibromo ketone with diiron nonacarbonyl, with furan to produce an 8-oxabicyclo[3.2.1]octane system.[27] This reaction, which, along with related cycloadditions, has been extensively studied by Hoffmann,[28] appeared ideally adapted to our purpose, since it establishes at the outset the cis relationship of side chains, and also provides functionality well suited to elaboration of the nonactic acid structure.

In our scheme, the oxoallyl intermediate **41** from 2,4-dibromo-3-pentanone was produced by means of the LeGoff zinc–copper couple.[29] In the presence of furan, **41** gave cy-



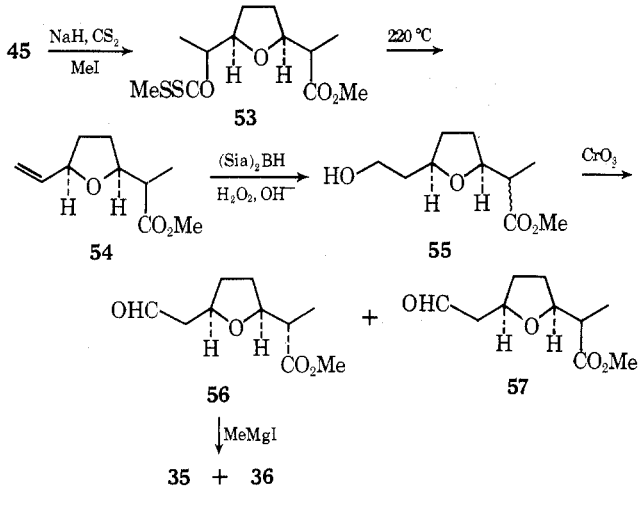
cloadduct **42**, in admixture with minor quantities of the two adducts epimeric with respect to the methyl-bearing centers, as previously described.[30] Hydrogenation over 10% palladium on carbon proceeded quantitatively to give **43**, which then underwent Baeyer–Villiger oxidation with trifluoroperacetic acid in dichloromethane buffered with disodium hydrogen phosphate. The resulting lactone **44**, obtained crystalline in 94% yield, conveniently served as a stage for removing traces of epimeric impurities carried through with **42**. The configuration of **44** is based upon well-established precedent for retention in Baeyer–Villiger oxidation,[31] in conjunction with the careful study by Hoffmann,[30] which showed that cycloaddition of the oxoallyl cation to furan takes place stereospecifically in the W conformation via a preferred boatlike (endo) transition state. Methanolysis of lactone **44** produced a single hydroxy ester **45**, from which **44** could be regenerated in virtually quantitative yield upon treatment with *p*-toluenesulfonic acid in benzene. This result confirmed that no epimerization had occurred during methanolysis, even though the configuration at C-2 of **45** corresponds to the 2-epinonactate series and, hence, is presumably the less stable of the epimeric pair (vide supra). The equilibration of configuration of the ester group of **45** is evidently more difficult than the analogous process in **39**. A possible explanation may be that, while epimerization of **39** can occur via a kinetically favorable, *intramolecular*, α-proton abstraction by alkoxide, a similar pathway for **45**, with a shorter side chain, is sterically prohibited.

It now remained to find a method for homologation of the ethyl chain of **45** to the hydroxypropyl grouping of **2**. Initially, efforts toward this end were channelled through ketone **46**, readily obtained by oxidation of **45** with Collins reagent.[32]



Olefin **47**, prepared by the Wittig reaction of **46** with methylenetriphenylphosphorane in 65% yield, appeared to be a suitable precursor from which to develop the functionality needed for a 1,2 transposition of the tetrahydrofuryl moiety. Hydroxylation of **47** with potassium chlorate and a catalytic quantity of osmium tetroxide[33] furnished diol **48**, which was converted to tosylate **49** with *p*-toluenesulfonyl chloride in pyridine. Attempted pinacolic rearrangement[34] of **49** afforded no trace of the 2-epi-8-keto ester **32**[35] but instead, epoxide **50** was produced. A modification of this approach, in which **48** was converted to iodohydrin **51** and the latter treated with silver nitrate,[36] similarly yielded **50**. An alternate scheme, based upon work by Taylor and McKillop,[37] in which terminal olefins were shown to undergo oxidative rearrangement to methyl ketones in the presence of thallium(III) nitrate and methanol,[38] gave only the dimethoxy derivative **52** when applied to **47**.

Thwarted in our efforts to extend the synthesis from **47**, we returned to alcohol **45**, with the hope of transferring functionality from the site of the hydroxyl group to the adjacent terminus of the ethyl chain. Thus, **45** was converted to xanthate **53** with sodium hydride, carbon disulfide, and methyl iodide in 94% yield. Slow pyrolysis of **53** over the range 150–220 °C, with continuous, distillative removal of product, gave **54** as the sole alkene in 50% yield after chromatography on silica.[39] The terminal double bond of **54** underwent hydroboration with disiamylborane with high regioselectivity[40] to give, after oxidative workup with alkaline, 30% hydrogen peroxide, the primary alcohol **55**. Oxidation of **55** by Collins reagent[32] yielded an easily separable mixture of epimeric aldehydes **56** and **57** in the ratio 1:1, the NMR spectra of which displayed signals for the C-2 methyl groups (δ 1.06 and 1.19, respectively) in close agreement with the corresponding methyl shifts observed previously in the natural and 2-epi-



nonactates. Loss of configurational fidelity at C-2 along this route must have occurred subsequent to the stereochemically homogeneous ester **45**, and the hydroxide-promoted oxidation of the alkylborane from **54** affords the most likely opportunity for this event. Treatment of **56** with methylmagnesium iodide produced methyl nonactate (**35**) and methyl 8-epinonactate (**36**) without stereoselectivity.

The two routes to nonactic acid (**2**) described above are readily extensible to homononactic acid (**3**) and its derivatives. Thus, the Grignard reaction of **56** with ethylmagnesium bromide would give methyl homononactate and the 8-epi ester. Alternatively, the furan alkylation route, beginning from **5**, could be extrapolated via homologues of **17**, **22**, **29**, and **33** to afford a stereoselective route to 8-epihomonactic acid. These pathways are of potential value in connection with total synthesis of the unsymmetrical macrotetrolides **1b–g**.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are corrected; boiling points are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on Varian Associates EM-360 and HA-100 spectrometers. Peak positions are given in parts per million (δ) downfield from the internal standard Me_4Si. The abbreviations s, d, t, q, p, and m refer to singlet, doublet, triplet, quartet, quintet, and multiplet, respectively. The coupling constant (*J*) is measured in hertz. Mass spectra (MS), including high-resolution data, were determined using a CEC-103B spectrometer. The abbreviation M^+ refers to the molecular ion. Thin layer chromatograms (TLC) were made on Merck silica gel GF-254 or on alumina. Merck silica gel (0.05–20 mm) and Fisher Florisil (100–200 mesh) were used for column chromatography. Analytical VPC was performed on a Varian Aerograph Model 700 gas chromatograph using a 5 ft × 0.25 in. SE-30 (20% on Chromosorb G) column.

2-(2-Hydroxypropyl)furan (4). A solution of *n*-butyllithium in tetrahydrofuran (50 ml) was prepared from *n*-butyl chloride (5.42 g, 60 mmol) and finely cut lithium metal (0.875 g, 125 mmol) at −25 °C. Furan (4.1 g, 60 mmol) was added at −15 °C and the solution was stirred for 6.5 h. Propylene oxide (3.48 g, 60 mmol) in tetrahydrofuran (15 ml) was added. The solution was stirred at −15 °C for 2 h and then allowed to warm to room temperature while stirring was continued overnight. The solution was poured over ice and sodium chloride was added. The aqueous layer was extracted repeatedly with ether. The extracts were combined with the original organic layer, washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and distilled, affording 7.7 g (58 mmol, 98%) of **4**: bp 47–50 °C (0.3 mm); ir (film) 3500, 1600, 1500, 1150, 1080, 1010, 950, 890, 740 cm^{-1} (br); NMR ($CDCl_3$) 1.20 (d, 3 H, J = 6 Hz), 2.76 (d, 2 H, J = 6 Hz), 2.12 (s, br, 1 H), 4.08 (m, 1 H), 6.1 (d, 1 H, J = 3 Hz), 6.3 (d of d, 1 H, J = 3, 1 Hz), 7.36 (d, 1 H, J = 1 Hz); *m/e* 126.068 (M^+, calcd for $C_7H_{10}O_2$, 126.068).

2-(2-Hydroxybutyl)furan (5). A solution of *n*-butyllithium in tetrahydrofuran (80 ml) was prepared from *n*-butyl chloride (12.1 g, 130 mmol) and finely cut lithium metal (2.0 g, 285 mmol) at −25 °C. Furan (8.9 g, 130 mmol) was added at −15 °C, the resulting solution was stirred for 6.5 h, and 1-butene oxide (9.4 g, 130 mmol) in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred at −15 °C for 2 h, then overnight at room temperature, and was worked up as described for **4**. Distillation yielded 15.5 g (111 mmol, 85%) of **5**, bp 46 °C (0.4 mm), *m/e* 140.084 (M^+, calcd for $C_8H_{12}O_2$, 140.083).

2-(2-Tetrahydropyranyloxypropyl)furan (6). A solution of 5.2 g (41 mmol) of **4** in 10 ml of benzene was added to 7 ml of freshly distilled dihydropyran. A few crystals of *p*-toluenesulfonic acid were added and the mixture was stirred for 1 h. Potassium carbonate (2 g) was added to the cooled mixture, which was allowed to stand overnight. The reaction mixture was filtered, evaporated in vacuo at room temperature, and distilled at reduced pressure, yielding 7.2 g (36 mmol, 89%) of diastereomeric ethers **6**: bp 62–65 °C (0.3 mm); ir (film) 3200, 3000, 1580, 1495, 1120, 1080, 1040, 875, 735 cm^{-1}; NMR ($CDCl_3$) 1.20 and 1.30 (d, 3 H, J = 6 Hz), 1.45–1.95 (br, 6 H), 2.80 and 2.86 (d, 2 H, J = 6 Hz), 3.54 (m, 1 H), 4.1 (m, 2 H), 4.5 and 4.8 (m, 1 H), 6.12 and 6.16 (d, 1 H, J = 3 Hz), 6.31 (t, 1 H, J = 3 Hz), 7.34 (s, 1 H); *m/e* 210.126 (M^+, calcd for $C_{12}H_{18}O$, 210.123).

2-Allyl-5-(2-tetrahydropyranyloxypropyl)furan (7). A solution of *n*-butyllithium in tetrahydrofuran (20 ml) was prepared from *n*-butyl chloride (0.92 g, 10 mmol) and lithium shavings (0.15 g, 22

mmol) at −35 °C. Tetrahydropyranyl ether **6** (2.1 g, 10 mmol) was added, and the mixture was stirred for 4 h at −15 °C. A solution of allyl bromide (1.21 g, 10 mmol) in 1 ml of tetrahydrofuran was added and the mixture was stirred for 1 h at −15 °C and overnight at room temperature. The mixture was poured onto ice, and sodium chloride was added. The aqueous layer was extracted three times with ether. The organic layer was combined with the extracts and dried ($MgSO_4$), and solvent was evaporated. The residual oil was distilled, affording 0.92 g (37%) of **7**, bp 85–88 °C (0.25 mm). A pure sample of **7** was obtained by preparative gas chromatography: ir (film) 3150, 3000, 1560, 1130, 1020, 995, 910, 785 cm^{-1}; NMR ($CDCl_3$) δ 6.1–5.8 (m, 3 H), 5.0–5.2 (m, 2 H), 4.2–3.9 (m, 2 H), 3.6–3.3 (m, 4 H), 2.7 (d of d, 2 H, J = 7 Hz), 1.8–1.3 (m, 6 H), 1.10 and 1.20 (d of d, 3 H, J = 7 Hz); m/e 250 (M^+).

2-Furylacetaldehyde Diethyl Acetal (8). A solution of n-butyllithium in tetrahydrofuran (200 ml) was prepared from n-butyl chloride (13.8 g, 150 mmol) and finely cut lithium metal (2.27 g, 320 mmol) at −25 °C. Furan (10.2 g, 150 mmol) was added and the solution was stirred at −15 °C for 6 h. α-Bromoacetaldehyde diethyl acetal (29.6 g, 150 mmol) was added and the solution was stirred overnight at room temperature. The mixture was poured over ice and sodium chloride was added. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were combined with the organic layer, dried ($MgSO_4$), and evaporated. Vacuum distillation afforded 19.3 g (105 mmol, 70%) of **8**: ir (film) 3120, 3000, 2920, 1580, 1120, 1050, 720 cm^{-1}; NMR ($CDCl_3$) 7.32 (d, 1 H, J = 1 Hz), 6.3 (d of d, 1 H, J = 3, 1 Hz), 4.8 (t, 1 H, J = 6 Hz), 3.8–3.3 (d of q, 4 H, J = 6 Hz), 2.96 (d, 2 H, J = 6 Hz), 1.16 (t, 3 H, J = 6 Hz).

2-(5-Methylfuryl)acetaldehyde Diethyl Acetal (9). A solution of n-butyllithium in tetrahydrofuran (15 ml) was prepared from n-butyl chloride (1.84 g, 20 mmol) and lithium shavings (0.29 g, 42 mmol) at −25 °C. 2-Methylfuran (1.68 g, 20 mmol) in tetrahydrofuran (4 ml) was added, and the solution was stirred at −15 °C for 6 h. α-Bromoacetaldehyde diethyl acetal (3.9 g, 20 mmol) was added, and the solution was stirred overnight at room temperature. The mixture was poured into cold water and was saturated with sodium chloride. The organic layer was retained, and the aqueous layer was extracted with ether (150 ml). The organic layers were combined, dried ($MgSO_4$), and evaporated. Distillation through a spinning-band column afforded 1.8 g (45%) of **9**: bp 44–46 °C (0.4 mm); ir (film) 3000, 1500, 1120, 1060, 780 cm^{-1}; NMR ($CDCl_3$) δ 6.96 (d, 1 H, J = 3 Hz), 6.84 (d, 1 H, J = 3 Hz), 4.8–4.3 (d of q, 4 H, J = 7 Hz), 2.88 (d, 2 H, J = 6 Hz), 2.20 (s, 3 H), 1.14 (t, 3 H, J = 7 Hz).

2-(5-Methyl-2-furyl)propionaldehyde Diethyl Acetal (10a). 2-Lithio-5-methylfuran, prepared from 4.92 g (60 mmol) of 2-methylfuran, 0.91 g (130 mmol) of lithium, and 8.22 g (60 mmol) of n-butyl bromide, was allowed to react with α-bromopropionaldehyde diethyl acetal (2.71 g, 128 mmol) as described for the preparation of **9**. Workup in the usual way, followed by distillation, gave 6.36 g (50%) of a mixture of **10a** and **10b** (ca. 2:1). Attempted gas chromatographic separation resulted in further elimination of **10a** to give **10b**, as indicated by a pair of doublets (J = 2 Hz) at δ 6.17 and 6.36 (*E* and *Z* isomers of **10b**).

***trans*-2-Methyl-5-(but-2-enyl)furan (11a) and 2-Methyl-5-(2-but-3-enyl)furan (11b).** Tetrahydrofuran (10 ml) was placed in a three-necked flask fitted with a mechanical stirrer, a condenser, and a pressure-equalized addition funnel. The air was swept out of the flask with dry nitrogen and a steady flow of the gas was maintained throughout the reaction. Lithium metal, finely cut (0.315 g, 45 mmol), was introduced, and the suspension was cooled to −25 °C. A solution of n-butyl chloride (1.84 g, 20 mmol) in tetrahydrofuran (10 ml) was placed in the addition funnel, and a small quantity was added to the stirred suspension to start the reaction. When the reaction had started, as indicated by the appearance of cloudiness, the remaining chloride solution was added while the cooling bath was maintained at −35 °C. 2-Methylfuran (1.64 g, 20 mmol) was added neat. The mixture was stirred for 1 h at −25 °C and for 4 h at −15 °C. 3-Bromo-1-butene (2.7 g, 20 mmol) in tetrahydrofuran (4 ml) was then added slowly. Stirring was continued for 1 h at −15 °C, and then the cooling bath was removed while the mixture was stirred for an additional 3 h. The mixture was poured over crushed ice and the two layers were separated. The aqueous layer was extracted with ether, and the ether extracts were added to the tetrahydrofuran layer. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled in a Kugelrohr apparatus (oven temperature 77 °C at 0.2 mm), yielding 1.6 g (60%) of a mixture of **11a** and **11b**. These were separated by VPC (ratio 1:2) to give **11a** [ir (film) 3150, 1650, 1560, 920, 780 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, 3 H, J = 7 Hz), 2.22 (s, 3 H), 3.46 (m, 1 H), 5.08 (d, 1 H, J = 17 Hz), 5.04 (d, 1 H, J = 9 Hz), 5.85 (s, 2 H), 5.94 (m, 1 H); m/e 136 (M^+)] and **11b** [ir (film) 3100, 1580, 1020, 970, 780 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (d, 3 H, J = 4 Hz), 2.22 (s, 3 H), 3.30 (m, 2 H), 5.56 (m, 2 H), 5.84 (s, 2 H); m/e 136 (M^+)].

5,5′-Dimethyl-2,2′-difuryl (12). n-Butyllithium (60 mmol) in ether was prepared according to the method of Gilman. 2-Methylfuran (4.8 g, 60 mmol) was added at −20 °C, and the mixture was warmed to room temperature and then refluxed for 4 h. The solution was cooled to 0 °C, and 3.5 g (24 mmol) of cuprous bromide was added. After stirring for 5 min, the solution was refluxed for 72 h while air was swept through the reaction flask. The mixture was quenched with aqueous ammonium chloride and the organic layer was separated. The aqueous phase was washed with ether. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled under vacuum, yielding 1.0 g (6.1 mmol, 25%) of **12**: bp 41–43 °C (2.8 mm); ir (film) 3000, 1600, 1500, 1150, 890, 730 cm^{-1}; NMR ($CDCl_3$) 2.28 (s, 3 H), 5.98 (d, 1 H, J = 3 Hz), 6.36 (d, 1 H, J = 3 Hz); m/e 162.067 (M^+, calcd for $C_{10}H_{10}O_2$, 162.068).

2-(2-Hydroxypropyl)-5-(2-ethoxyvinyl)furan (13). A solution of n-butyllithium in tetrahydrofuran (10 ml) was prepared from n-butyl chloride (4.14 g, 45 mmol) and lithium shavings (0.665 g, 95 mmol) at −25 °C. Compound **8** (2.76 g, 15 mmol) was added neat and the solution was stirred at −15 °C for 6 h. Propylene oxide (0.87 g, 15 mmol) in tetrahydrofuran (1 ml) was added and the solution was allowed to warm to room temperature while stirring was continued overnight. The flask contents were poured over crushed ice and the two layers were separated. The aqueous layer, after saturation with sodium chloride, was extracted with ether and the ether extracts were added to the tetrahydrofuran layer. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled in a Kugelrohr apparatus in vacuo affording 1.1 g (37%) of **13**: ir (film) 3500, 3180, 3000, 1640, 1580, 1200, 1100, 1050, 930, 790 cm^{-1}; NMR ($CDCl_3$)δ 6.9 (d, 1 H, J = 14 Hz), 6.0 (d, 1 H, J = 3 Hz), 5.8 (d, 1 H, J = 3 Hz), 5.6 (d, 1 H, J = 14 Hz), 4.1 (m, 1 H), 3.8 (q, 2 H, J = 6 Hz), 2.7 (d, 2 H, J = 6 Hz), 2.3 (s, 1 H), 1.26 (t, 3 H, J = 6 Hz), 1.16 (d, 3 H, J = 6 Hz).

2-(2-Hydroxyethyl)-5-(2-hydroxypropyl)furan (15). A solution of n-butyllithium in tetrahydrofuran (180 ml) was prepared from n-butyl chloride (16.5 g, 180 mmol) and lithium metal (2.62 g, 375 mmol) at −25 °C. Compound **4** (7.5 g, 59 mmol) was added and the solution was stirred at −15 °C for 6 h. Ethylene oxide (7.9 g, 180 mmol) in tetrahydrofuran (10 ml) was added and the solution was stirred at −15 °C for 2 h. The flask contents were allowed to warm to room temperature while stirring was continued overnight. The mixture was quenched with ice and the two layers were separated. The aqueous phase was extracted with ether, and the extracts were combined with the tetrahydrofuran layer. The combined extracts were dried ($MgSO_4$), evaporated, and distilled, affording 8.1 g (80%) of **15**: ir (film) 3600–3400, 2950, 1560, 1050, 950, 790 cm^{-1}; NMR ($CDCl_3$) δ 5.96 (s, 2 H), 4.05 (p, 1 H), 3.75 (t, 2 H, J = 6 Hz), 3.06 (s, 2 H), 2.75 (t, 2 H, J = 6 Hz), 2.65 (d, 2 H, J = 6 Hz), 1.16 (d, 3 H, J = 6 Hz); m/e 170 (M^+).

***cis*-2-(2-Hydroxyethyl)-5-(2-hydroxypropyl)tetrahydrofuran (16).** Diol **15** (2.7 g, 15.8 mmol), in 50 ml of anhydrous methanol, was hydrogenated over rhodium on alumina at atmospheric pressure for 4 h. The catalyst was filtered and the filtrate was evaporated to a clear liquid which, upon distillation, afforded 1.7 g (63%) of **16**: bp 86–89 °C (0.15 mm); ir (film) 3500, 3000, 1160–1060, 950 cm^{-1}; NMR ($CDCl_3$) δ 4.0 (m, 3 H), 3.75 (t, 2 H, J = 6 Hz), 3.5 (br s, 2 H), 1.7 (m, 8 H), 1.16 (d, 3 H, J = 6 Hz); m/e 174 (M^+).

2-Acetyl-5-(2-acetoxypropyl)furan (17). Alcohol **4** (10.05 g, 79 mmol) and acetic anhydride (16.5 g, 175 mmol) were placed in a flask equipped with a side arm fitted with a rubber septum. The reaction vessel was cooled to −25 °C with stirring and 2.4 g of boron trifluoride etherate was added at once by means of a syringe. The cold bath was removed after 5 min and stirring was continued for 20 min. The mixture was quenched with 6 ml of water and the contents of the flask were extracted with ether. The ether extracts were washed with saturated sodium carbonate, dried ($MgSO_4$), and concentrated. The residual oil was distilled in an air bath, yielding 0.87 g (83%) of **17**: bp 92–93 °C (0.1 mm); ir (film) 3120, 1730, 1680, 1580, 1500, 1250 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (d, 1 H, J = 3 Hz), 6.25 (d, 1 H, J = 3 Hz), 5.2 (p, 1 H), 2.96 (d, 2 H, J = 6 Hz), 2.4 (s, 3 H), 2.0 (s, 3 H), 1.22 (d, 3 H, J = 6 Hz); m/e 167.072 (M^+ − 43, calcd for $C_9H_{11}O_3$, 167.071).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.71. Found: C, 63.16; H, 6.67.

2-(1-Hydroxyethyl)-5-(2-acetoxypropyl)furan (18). To a slurry of sodium borohydride (0.54 g, 14 mmol) in 20 ml of a 1:1 mixture of glyme and *tert*-butyl alcohol at 0 °C was added, with stirring, 1.99 g (9.5 mmol) of **17** in 10 ml of *tert*-butyl alcohol. After stirring for 3 h at room temperature, the flask contents were poured into iced water. The mixture was extracted with ether, dried ($MgSO_4$), and distilled, giving 1.6 g (80%) of alcohol **18**: bp 92–93 °C (0.15 mm); ir (film) 3500, 1740, 1560, 1360, 1250 cm^{-1}; NMR ($CDCl_3$) δ 6.1 (d, 1 H, J = 3 Hz),

5.98 (d, 1 H, J = 3 Hz), 5.15 (m, 1 H), 4.8 (m, 1 H), 2.82 (d, 2 H, J = 6 Hz), 2.3 (s, 1 H), 1.98 (s, 3 H), 1.46 (d, 3 H, J = 6 Hz), 1.20 (d, 3 H, J = 6 Hz); m/e 212 (M^+).

***cis*-2-(1-Hydroxyethyl)-5-(2-acetoxypropyl)tetrahydrofuran (19).** Ketone **17** (420 mg, 2 mmol) in ethyl acetate (5 ml) was hydrogenated over 20 mg of rhodium on charcoal for 24 h. After the catalyst was filtered, removal of the solvent left a colorless oil. Distillation in an air bath afforded 415 mg (96%) of alcohol **19:** ir (film) 3500, 1740, 1380, 1250, 1050 cm^{-1} (br); NMR ($CDCl_3$) δ 5.0 (m, 1 H), 3.7 (m, 3 H), 1.96 (s, 3 H), 1.8–1.4 (m, 6 H), 1.2 (d, 3 H, J = 6 Hz), 1.0 (d, 3 H, J = 6 Hz); m/e 171.101 ($M^+ - 43$, calcd for $C_9H_{15}O_3$, 171.102).

2-(2-Acetoxypropyl)-5-(1-*p*-toluenesulfonyloxyethyl)furan (20). Alcohol **18** (212 mg, 1 mmol) was dissolved in dry pyridine (3 ml) at −20 °C and *p*-toluenesulfonyl chloride (380 mg, 2 mmol) was added. The cold bath was removed and stirring was continued overnight. The flask contents were poured into iced water and the mixture was extracted with ether. The extracts were washed with aqueous copper sulfate, aqueous sodium bicarbonate, and brine, and then dried ($MgSO_4$) and concentrated under vacuum at room temperature. The residual oil was shown to be a mixture of two compounds by thin layer chromatography. The major component, which was unstable and resisted purification, was assigned structure **20** based on its infrared spectrum: 1725, 1580, 1380, 1180–1150, 890 cm^{-1}.

***cis*-2-(2-Acetoxypropyl)-5-(1-methanesulfonyloxyethyl)tetrahydrofuran (21).** Alcohol **19** (320 mg, 1.47 mmol) in pyridine (3 ml) was cooled to −20 °C. Methanesulfonyl chloride (340 mg, 3 mmol) was added, and the solution was stirred for 16 h. The flask contents were poured into 5 ml of iced water, and the mixture was extracted with ether. The ether extracts were washed with aqueous copper sulfate and brine, dried ($MgSO_4$), and concentrated under vacuum to give 430 mg (99%) of mesylate **21,** which showed a single spot on thin layer chromatography (silica, ethyl acetate): ir (film) 1740, 1350, 1250, 1175 cm^{-1}; NMR ($CDCl_3$) δ 5.1–4.4 (m, 2 H), 4.2–3.7 (m, 2 H), 3.03 and 3.06 (s, 3 H), 2.0 (s, 3 H), 1.3 (d, 3 H, J = 7 Hz), 1.15 (d, 3 H, J = 7 Hz).

***cis*-2-Acetyl-5-(2-acetoxypropyl)tetrahydrofuran (22).** Jones reagent (8 N) was added dropwise to a solution of **19** (391 mg, 1.8 mmol) in 15 ml of acetone at 0 °C until the orange end point persisted. The reaction mixture was stirred for an additional 20 min and excess oxidant was destroyed by addition of isopropyl alcohol. The solution was filtered and the chromium salts were dissolved in water. The aqueous phase was saturated with sodium chloride and was extracted three times with ether. The filtrate was combined with the ether extracts and the organic layer was washed once with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. The remaining liquid was distilled, yielding 381 mg (98%) of ketone **22:** ir (film) 1735, 1710, 1240 cm^{-1}; NMR ($CDCl_3$) δ 5.0 (m, 1 H), 4.1 (m, 2 H), 2.1 (s, 3 H), 1.95 (s, 3 H), 1.23 (d, 3 H, J = 6 Hz); m/e 214.121 (M^+, calcd for $C_{11}H_{18}O_4$, 214.115).

***cis*-2-(2-Acetoxypropyl)-5-(1,2-oxidoprop-2-yl)tetrahydrofuran (23).** A 2.0 M solution of methylsulfinyl carbanion was prepared from 421 mg of sodium hydride (10 mmol, 57% dispersion in mineral oil) in 5 ml of dimethyl sulfoxide (distilled from calcium hydride) by heating to 70–75 °C with stirring until evolution of hydrogen ceased. The solution was cooled to room temperature, diluted with 5 ml of dry tetrahydrofuran, and then cooled in a salt–ice bath. With stirring, a solution of trimethylsulfonium iodide (2.0 g, 10 mmol) in dimethyl sulfoxide (10 ml) was added over a period of about 3 min. After the addition of the salt was complete, the mixture was stirred for 1 min. Ketone **22** (1.08 g, 5 mmol) in dimethyl sulfoxide (2 ml) was added at a rapid rate. Stirring was continued at salt–ice bath temperature for 10 min, and then for 60 min with the bath removed. The reaction mixture was diluted with 15 ml of distilled water and was extracted repeatedly with ether. The combined ether extract was washed with water, dried (K_2CO_3), and concentrated under vacuum to give a yellow oil. Distillation at reduced pressure afforded 800 mg (70%) of **23:** ir (film) 1740, 1250, 1100–1000 cm^{-1}; NMR (CCl_4) 5.0 (br, 1 H), 3.8 (br, 3 H), 2.5 (s, 2 H), 1.95 (s, 3 H), 1.25 (s, 3 H); m/e 228 (M^+).

***cis*-2-(2-Acetoxypropyl)-5-(1-carboethoxy-1,2-oxidoprop-2-yl)tetrahydrofuran (24).** A well-stirred solution of ethyl bromoacetate (1.79 g, 94% pure, 10 mmol) and ketone **22** (1.05 g, 5 mmol) in dry tetrahydrofuran (10 ml) was cooled to −78 °C and was treated with lithium dicyclohexylamide (10 mmol), prepared from dicyclohexylamine (1.81 g, 10 mmol) in dry tetrahydrofuran (10 ml) with *n*-butyllithium (10 mmol, 4.1 ml, 2.4 M hexane solution) at 0 °C, dropwise over a period of 5 min. The mixture was allowed to stand for 1 h at −78 °C. Water was added, and the mixture was extracted with ether. The ether layer was washed with aqueous copper sulfate (until the blue color persisted) and brine, dried ($MgSO_4$), and concentrated. The residue was distilled under vacuum to give 1.4 g (90%) of **24:** NMR (CCl_4) δ 5.0 (m, 1 H), 4.1 (q, 2 H, J = 6 Hz), 3.7 (s, 1 H), 2.0 (s, 3 H), 1.3 (s, 3 H); m/e 300 (M^+).

***cis*-2-Acetyl-5-(2-hydroxypropyl)tetrahydrofuran (26).** Ester **22** (216 mg, 1 mmol) was stirred in 10 ml of 5% methanolic potassium hydroxide at room temperature for 20 h. The solution was diluted to 50 ml with distilled water, saturated with sodium chloride, and extracted with ether. The ether extracts were dried ($MgSO_4$), evaporated, and distilled under vacuum to yield 105 mg (61%) of **26:** ir (film) 3600, 3000, 1725, 1360, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.1 (m, 3 H), 3.4 (s, 1 H), 2.14 (s, 3 H), 1.15 (d, 3 H, J = 6 Hz); m/e 172.109 (M^+, calcd for $C_9H_{16}O_3$, 172.109).

***cis*-2-(2-Tetrahydropyranyloxypropyl)-5-acetyltetrahydrofuran (27).** A solution of **26** (1.03 g, 5.66 mmol), dihydropyran (1.43 g, 17 mmol), and phosphorus oxychloride (0.1 ml) in methylene chloride (60 ml) was stirred for 3.5 h in an ice bath. The solution was washed with 10% aqueous sodium carbonate, water, and brine. Evaporation of the solvent left an oil which was distilled under vacuum, yielding 1.2 g (83%) of **27:** ir (film) 1725, 1070, 1030 cm^{-1}; NMR (CCl_4) δ 4.55 (br, 1 H), 4.2–3.2 (br, 5 H), 2.02 (s, 3 H), 1.6–1.25 (br, 6 H); m/e 256 (M^+).

***cis*-2-(2-Acetoxypropyl)-5-(2-propenyl)tetrahydrofuran (28).** Sodium hydride (1.2 mmol as a 50% dispersion in mineral oil) in a 50-ml, three-necked flask was washed with several portions of pentane to remove the mineral oil. The system was flushed with dry nitrogen while being warmed gently. Dimethyl sulfoxide (5 ml, freshly distilled from calcium hydride) was introduced via a syringe, and the mixture was heated at 70–75 °C until the evolution of hydrogen ceased. The resulting solution was cooled in an ice–water bath, and 430 mg of methyltriphenylphosphonium bromide in 5 ml of dimethyl sulfoxide was added. This mixture was stirred at room temperature for 10 min, and a solution of ketone **22** (214 mg, 1 mmol) in 5 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added. After standing at room temperature for 24 h, the solution was poured into 20 ml of water, and the product was extracted several times with pentane. The extracts were combined, washed with 50 ml of a 1:1 water–dimethyl sulfoxide solution and then with 50 ml of water, dried ($MgSO_4$), and chromatographed on silica gel. Elution with dichloromethane afforded 110 mg (52%) of **28:** ir (film) 3200, 1735, 1250, 990, 870 cm^{-1}; NMR (CCl_4) δ 5.0 (s, 1 H), 4.8 (s, 1 H), 4.3–3.5 (m, 2 H), 2.1 (s, 3 H), 1.8 (s, 3 H), 1.25 (d, 3 H, J = 6 Hz); m/e 212.141 (M^+, calcd for $C_{12}H_{20}O_3$, 212.142). In addition, 39 mg (22%) of **29,** identical with material prepared as described below, was eluted (9:1 dichloromethane–ethyl acetate).

***cis*-2-(2-Hydroxypropyl)-5-(2-propenyl)tetrahydrofuran (29).** Acetate **28** (110 mg, 0.52 mmol) was stirred at room temperature overnight with 10 ml of a 5% methanolic solution of sodium hydroxide. Water (10 ml) was added, and the resulting solution was extracted with ether. The ether extracts were combined, washed with 50% aqueous sodium chloride, and dried ($MgSO_4$). Distillation afforded 89 mg (100%) of **29:** ir (film) 3600, 3180, 1080, 890 cm^{-1}; NMR (CCl_4) δ 5.0 (s, 1 H), 4.8 (s, 1 H), 4.3 (m, 1 H), 4.15 (m, 1 H), 1.8 (s, 3 H), 1.2 (d, 3 H, J = 6 Hz); m/e 170.131 (M^+, calcd for $C_{10}H_{18}O_2$, 170.134).

***cis*-2-(5-Acetonyltetrahydrofur-2-yl)propionic Acids (30 and 31).** A solution of 120 mg (0.7 mmol) of **29** in 5 ml of tetrahydrofuran was added dropwise to an ice-cold, 1 M solution of diborane (3 ml) in tetrahydrofuran. The reaction mixture was stirred for 1 h at 0 °C, then for 2 h at room temperature. Jones reagent was added dropwise with caution until the solution remained orange. The reaction mixture was stirred for 30 min and excess oxidant was destroyed by the addition of isopropyl alcohol. The mixture was concentrated under vacuum, filtered through Celite, and the filter cake rinsed with 15 ml of chloroform. The filtrate was washed with 50% aqueous brine and dried ($MgSO_4$). Evaporation of the solvent left 121 mg (89%) of a mixture of **30** and **31.** These acids, without purification, were converted to the corresponding esters, **32** and **33,** as described below.

Methyl *cis*-2-(5-Acetonyltetrahydrofur-2-yl)propionates (32 and 33). The mixture of keto acids **30** and **31** (121 mg, 0.62 mmol) in 10 ml of dry methanol and 0.4 ml of boron trifluoride etherate was stirred at room temperature for 16 h. The reaction mixture was poured into 20 ml of water, saturated with sodium chloride, and extracted with 50 ml of chloroform. The extracts were washed with dilute sodium bicarbonate and 50% brine, and dried ($MgSO_4$). Vacuum distillation at 110 °C afforded 131 mg (99%) of a 2:1 mixture of **32** and **33:** ir 3000, 1730, 1710, 1100, 1050 cm^{-1}; NMR (CCl_4) δ 4.1 (m, 3 H), 3.64 (s, 3 H), 2.5 (m, 2 H), 2.11 (s, 3 H), 1.20 and 1.10 (d, 3 H, J = 6 Hz); m/e 214.108 (M^+, calcd for $C_{11}H_{18}O_4$, 214.106).

***cis*-2-(2-Hydroxypropyl)-5-(1-hydroxyprop-2-yl)tetrahydrofuran (34). A. From 29.** A solution of 89 mg (0.5 mmol) of **29** in 3 ml of tetrahydrofuran was added dropwise to a cooled 1 M solution of diborane (2 ml) in tetrahydrofuran. The reaction mixture was

stirred for 1 h at 0 °C, and for 2 h at room temperature and excess diborane was decomposed by dropwise addition of water (1 ml). A 3 M solution of sodium hydroxide (3 ml) was added, followed by dropwise addition of 30% hydrogen peroxide (3 ml). The reaction mixture was stirred for 1 h at room temperature and then potassium carbonate was added. The layers were separated, the aqueous solution was extracted three times with 25 ml of ether, and the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated. Distillation afforded 75 mg (80%) of **34**, bp 82–84 °C (0.01 mm) [lit.[6] bp 80 °C (0.01 mm)], as a mixture of C-2 and C-8 epimers. One of these isomers was indistinguishable chromatographically from **34** prepared by reduction of nonactin.

B. From Nonactin (1a). Lithium aluminum hydride (204 mg, 5.38 mmol) was added in dry form to a solution of nonactin (**1a**, 1.01 g, 1.38 mmol) in 50 ml of dry ether and the mixture was stirred for 3 h at room temperature. The reaction was quenched by addition of a saturated, aqueous solution of sodium potassium tartrate, and the solids were filtered. The filtrate was washed with 10 ml of saturated brine and dried ($MgSO_4$), and the solvent was removed in vacuo to leave 1.00 g (100%) of pure **34**: ir (film) 3378, 1100 (br), 950 cm^{-1}; NMR (CCl_4) δ 0.84 (d, 3 H, J = 6 Hz), 1.14 (d, 3 H, J = 6 Hz), 1.25 (m, 2 H), 1.6 (m, 4 H), 2.0 (m, 1 H), 3.7 (m, 2 H), 4.1 (m, 5 H, collapses to m, 3 H with D_2O added).

Methyl 8-Epinonactate (36). A solution of **31** (75 mg, 0.37 mmol) in 10 ml of dry tetrahydrofuran was cooled in an ice bath, and lithium tri-*sec*-butylborohydride (800 μl of a 1 M solution, 0.80 mmol) was added. After 6 h at 0 °C the mixture was quenched with 5 ml of water, acidified with 5% aqueous hydrochloric acid, and extracted with three 10-ml portions of ether. The ether extracts were dried ($MgSO_4$), filtered, and concentrated. A solution of the residue in 5 ml of methanol was treated with 4 drops of boron trifluoride etherate, and the solution was stirred overnight at room temperature. Concentration of the methanol solution gave a residue which was dissolved in 15 ml of methylene chloride and washed once with water, dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica gel with 2:1 pentane–ethyl acetate as eluent gave 30.2 mg (41%) of **36**: ir (film) 3509, 1739 cm^{-1}; NMR (CCl_4) δ 3.98 (3 H, m), 3.66 (3 H, s), 2.94 (1 H, broad s), 2.52 (1 H, p), 2.02 (2 H, m), 1.56 (4 H, m), 1.10 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz); m/e 216 (M^+). A small quantity (3.5 mg, 4.8%) of methyl nonactate (**35**), identical with material prepared by esterification of nonactic acid derived from nonactin,[6] was eluted subsequent to **36**.

Methyl 2-Epinonactate (39) and Methyl 2,8-Bisepinonactate (38). A solution of **32** (31.4 mg, 0.15 mmol) in 8 ml of methanol was stirred with sodium borohydride (12.3 mg, 0.32 mmol) at room temperature. After 45 min the mixture was diluted with 20 ml of water, acidified with 5% aqueous hydrochloric acid, and extracted with three portions of ether. The combined extracts were dried ($MgSO_4$), concentrated, and chromatographed on 7 g of Florisil. Elution with pentane–ether (2:1) gave 15 mg (47%) of **38**: ir (CCl_4) 3509, 1736 cm^{-1}; NMR (CCl_4) δ 1.09 (d, 3 H, J = 7 Hz), 1.11 (d, 3 H, J = 7 Hz), 1.6 (m, 4 H), 2.0 (m, 2 H), 2.50 (m, 1 H), 2.7 (broad s, 1 H), 3.36 (s, 3 H), 3.93 (m, 3 H); m/e 216 (M^+).

Further elution afforded 3 mg (9%) of **39**: ir (CCl_4) 3509, 1736 cm^{-1}; NMR (CCl_4) δ 1.12 (d, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 1.6 (m, 4 H), 2.0 (m, 2 H), 2.50 (m, 2 H) 3.62 (s, 3 H), 4.0 (m, 3 H); m/e 216 (M^+). Epimers **38** (R_f 0.57) and **39** (R_f 0.45) were readily distinguishable by TLC on silica (cyclohexane–ethyl acetate, 2:1). Compound **39** was identical in all respects with methyl 2-epinonactate, prepared by methanolysis of nonactin as described below.

Methyl 8-Benzoyloxynonactate (40). A solution of methyl 8-epinonactate **36** (36.7 mg, 0.17 mmol) in 2 ml of dry tetrahydrofuran was stirred under nitrogen with triphenyphosphine (91.9 mg, 0.351 mmol) and benzoic acid (46.0 mg, 0.37 mmol). Diethyl azodicarboxylate (59.2 mg, 0.34 mmol) was slowly added to the solution. After stirring overnight, the solution was concentrated and the residue was chromatographed on Florisil (10 g). Elution with benzene gave benzoate ester **40** (89.5%): ir (CCl_4) 1739, 1718 cm^{-1}; NMR (CCl_4) δ 7.97 (m, 2 H), 7.40 (m, 3 H), 5.17 (sext, 1 H, J = 6 Hz), 4.0 (m, 2 H), 3.62 (s, 3 H), 2.46 (p, 1 H, J = 7 Hz), 1.9 (m, 4 H), 1.6 (m, 2 H), 1.36 (d, 3 H, J = 7 Hz), 1.07 (d, 3 H, J = 7 Hz); m/e 320 (M^+).

Methyl Nonactate (35). A. Methanolysis of 40. Benzoate ester **40** (48.7 mg, 0.15 mmol) was stirred in 10 ml of dry methanol containing sodium methoxide (0.87 mmol). After 18 h at room temperature, the solution was concentrated, mixed with water, and acidified with 5% aqueous hydrochloric acid. The mixture was extracted with three portions of methylene chloride, and the combined extracts were dried ($MgSO_4$), filtered, and concentrated to give 32.0 mg (100%) of methyl nonactate **35**: ir (CCl_4) 3509, 1736 cm^{-1}; NMR (CCl_4) δ 3.97 (m, 3 H), 3.63 (s, 3 H), 2.59 (s, 1 H), 2.49 (p, 1 H), 1.99 (m, 2 H), 1.59 (m, 4 H), 1.12 (d, 3 H, J = 7 Hz), 1.09 (d, 3 H, J = 7 Hz); identical in all respects with material obtained by methanolysis of nonactin.

B. Methanolysis of Nonactin (1a). Nonactin (324 mg, 0.44 mmol) was added to a solution of sodium methoxide, prepared from sodium (172 mg, 7.5 mmol) in 20 ml of dry methanol, and the mixture was heated under reflux for 19 h. The reaction mixture was poured into 10 ml of 5% aqueous hydrochloric acid and extracted with three portions of ether. The combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residual, oily mixture was chromatographed on silica (40 g) and eluted with pentane–ethyl acetate (2:1) to yield 161 mg (46%) of **35**. Earlier fractions from the chromatogram contained methyl 2-epinonactate (**39**), which was obtained in pure form by preparative TLC on silica (cyclohexane–ethyl acetate, 2:1), and shown to be identical with material obtained on reduction of **32**, as described above.

***cis*-2,4-Dimethyl-3-keto-8-oxabicyclo[3.2.1]octane (43).** A solution of **42** (3.00 g, 19.5 mmol) in 15 ml of 95% ethanol was hydrogenated at atmospheric pressure over 10% palladium on carbon. A total volume of 450 ml of hydrogen was taken up, after which the catalyst was filtered, and the solvent removed in vacuo to leave 2.95 g (98%) of **43**. An analytical sample was prepared by preparative layer chromatography: ir (film) 1715, 1155, and 952 cm^{-1}; NMR (CCl_4) δ 0.86 (d, 6 H, J = 6 Hz), 1.5–1.9 (m, 4 H), 2.68 (d of q, 2 H, J = 6, 6 Hz), 4.2–4.5 (m, 2 H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.03; H, 9.32.

Lactone 44. Pertrifluoroacetic acid, prepared by dropwise addition of trifluoroacetic anhydride (7.1 ml, 50 mmol) to a stirred, ice-cold solution of 90% hydrogen peroxide (0.96 ml, 40 mmol) in 10 ml of dichloromethane (dried over $MgSO_4$ and distilled), was added dropwise to a stirred, ice-cold mixture of finely ground disodium hydrogen phosphate (17.0 g, 120 mmol) in 25 ml of dichloromethane containing ketone **43** (2.95 g, 20 mmol). After the reaction mixture had become too viscous for effective stirring (at approximately half addition of the peracid), the cooling bath was removed and the exothermic reaction was continued. The mixture was stirred for 2 h at room temperature and then brought slowly to reflux for 15 min. The cooled mixture was filtered and the solids were washed thoroughly with dichloromethane. The combined filtrates were washed with water, 3% aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated to give an oil which crystallized upon standing. Recrystallization from petroleum ether (bp 30–60 °C) afforded 3.2 g (94%) of **44** as colorless needles: mp 57–59 °C; ir (CCl_4) 1740 and 1180 cm^{-1}; NMR (CCl_4) δ 1.07 (d, 3 H, J = 7 Hz), 1.23 (d, 3 H, J = 7 Hz), 1.90 (m, 4 H), 2.93 (q, 1 H, J = 7 Hz), 4.08 (m, 2 H), 4.64 (q, 1 H, J = 7 Hz).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.34; H, 8.23.

Methyl *cis*-2-(5-Hydroxyethyltetrahydrofur-2-yl)propionate (45). To a solution of sodium methoxide, prepared from sodium (190 mg, 8.2 mmol) and 25 ml of methanol (dried over magnesium and distilled), was added lactone **44** (1.40 g, 8.2 mmol) in 10 ml of dry methanol. The mixture was stirred at room temperature for 4 h and poured into 150 ml of brine containing 0.5 ml of 6 N hydrochloric acid. The mixture was extracted with chloroform, and the extract was washed with brine, dried ($MgSO_4$), and concentrated to give 1.20 g (75%) of **45** as an oil. An analytical sample was obtained by preparative layer chromatography: ir (film) 3460, 1735, 1065 cm^{-1}; NMR (CCl_4) δ 1.05 (d, 3 H, J = 7 Hz), 1.18 (d, 3 H, J = 7 Hz), 1.5–2.1 (m, 4 H), 2.54 (d of q, 1 H, J = 7, 7 Hz), 2.64 (s, 1 H), 3.4–4.1 (m, 3 H), 3.62 (s, 3 H); m/e 184 ($M^+ - 18$).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.22; H, 9.19.

Xanthate 53. A solution of **45** (1.20 g, 6 mmol) in 10 ml of dry ether was added to a stirred suspension of sodium hydride (580 mg, 12 mmol, as 50% dispersion in mineral oil which was washed with pentane) in 25 ml of ether under nitrogen. The mixture was heated at reflux for 3 h and cooled, and carbon disulfide (0.7 ml, 12 mmol) was added. The resulting pasty mixture was heated at reflux for 3 h and cooled, and methyl iodide (8 ml, 12 mmol) was added, after which the mixture was allowed to reflux for a further 2 h. The mixture was diluted with water and then ether, the layers were separated, and the organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated to leave 1.64 g (94%) of **53** as a yellow oil: ir (film) 1740, 1215, 1060 cm^{-1}; NMR (CCl_4) δ 1.20 (d, 3 H, J = 7 Hz), 1.34 (d, 3 H, J = 6 Hz), 1.5–2.2 (m, 4 H), 2.51 (d of q, 1 H, J = 7, 7 Hz), 2.54 (s, 3 H), 3.3–3.7 (m, 1 H), 3.62 (s, 3 H), 3.8–4.2 (m, 1 H), 5.61 (d of q, 1 H, J = 6, 7 Hz).

Methyl *cis*-2-(2-Vinyltetrahydrofur-5-yl)propionate (54). Xanthate **53** (460 mg, 1.58 mmol) was pyrolyzed in several batches by slow distillation over a free flame. Alkene **54** began to distill at ca. 150 °C, and distillation was continued until the temperature at the stillhead reached 220 °C. Preparative layer chromatography of the crude distillate on silica, with petroleum ether–ethyl acetate (4:1) as

eluent, afforded 130 mg (45%) of **54**: ir (film) 1745, 988, 925 cm^{-1}; NMR (CCl_4) δ 1.08 (d, 3 H, J = 7 Hz), 1.4–1.8 (m, 2 H), 1.8–2.2 (m, 2 H), 2.50 (d of q, 1 H, J = 7 Hz), 3.65 (s, 3 H), 3.8–4.5 (m, 2 H), 5.02 (d, 1 H, J = 12 Hz), 5.25 (d, 1 H, J = 18 Hz), 5.6–6.0 (m, 1 H); m/e 184.114 (M^+, calcd for $C_{10}H_{16}O_3$, 184.110).

Methyl *cis*-2-(2-Hydroxyethyltetrahydrofur-5-yl)propionate (55). To a solution of disiamylborane, prepared from 1.5 ml of 1 M borane–tetrahydrofuran (1.5 mmol of BH_3) and 2-methylbut-2-ene (0.25 g, 4.5 mmol) in 7 ml of tetrahydrofuran at 0 °C was added alkene **54** (120 mg, 0.65 mmol) in 2 ml of tetrahydrofuran. The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. A small quantity of a mixture of 30% hydrogen peroxide and sodium hydroxide was added, and the solution was extracted with ether. The ether extract was washed with water and saturated brine, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica, with gradient elution from chloroform to ethyl acetate, and gave 60 mg (46%) of **55** as a colorless, viscous oil: ir (film) 3480, 1740 cm^{-1}; NMR (CCl_4) δ 1.07 (d, 3 H, J = 7 Hz), 1.3–1.8 (m, 4 H), 1.8–2.2 (m, 2 H), 2.2–2.8 (m, 2 H), 3.6–3.8 (m, 2 H), 3.62 (s, 3 H), 3.8–4.2 (m, 2 H); m/e 170 ($M^+ - CH_3OH$).

Aldehydes 56 and 57. To a red solution of Collins reagent, prepared from rigorously dry chromium trioxide (198 mg, 2.1 mmol) and dry pyridine (0.33 ml, 3.9 mmol), in 6 ml of dry methylene chloride, was added alcohol **55** (60 mg, 0.30 mmol) in 2 ml of methylene chloride. After stirring for 15 min, the mixture was diluted with methylene chloride and washed several times with a saturated, aqueous copper sulfate solution and with brine. The methylene chloride solution was dried ($MgSO_4$) and the solvent removed in vacuo to leave 57 mg (95%) of a mixture of **56** and **57** as a straw-colored oil: ir (film) 2740, 1745, 1725 cm^{-1}. Separation of the two aldehydes was carried out (with some losses due to oxidation) by preparative layer chromatography on silica, using petroleum ether–ethyl acetate (4:1) as eluent. This gave 17 mg of **56**: NMR (CCl_4) δ 1.06 (d of q, 3 H, J = 2, 6 Hz), 1.4–1.9 (m, 2 H), 1.9–2.3 (m, 2 H), 2.3–2.8 (m, 3 H), 3.61 (s, 3 H), 3.8–4.5 (m, 2 H), 9.69 (t, 1 H); m/e 200.107 (M^+, calcd for $C_{10}H_{16}O_4$, 200.105). In addition, there was obtained 13 mg of epimeric aldehyde **57**: NMR (CCl_4) δ 1.19 (d, 3 H, J = 7 Hz), 1.4–2.3 (m, 4 H), 2.3–2.8 (m, 3 H), 3.62 (s, 3 H), 3.7–4.1 (m, 1 H), 4.24 (t of t, J = 1, 6 Hz), 9.70 (t, 1 H, J = 1 Hz).

Grignard Reaction of Aldehyde 56. Methyl Nonactate (35). A solution of methylmagnesium iodide was prepared from magnesium (24 mg, 1.0 mmol) and methyl iodide (0.07 ml, 1.1 mmol) in 10 ml of anhydrous ether, and a 0.7-ml (0.07 mmol) portion of Grignard reagent was added to **56** (14 mg, 0.07 mmol) in 1 ml of ether. After stirring at room temperature for 10 min, the reaction mixture was quenched with a 10% solution of aqueous acetic acid and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated to leave a pale yellow oil (9 mg) which, according to its NMR spectrum, consisted of methyl nonactate (**35**) and methyl 8-epinonactate (**36**) in the ratio 1:1. The two esters were separated by preparative layer chromatography on silica in chloroform, affording **35**, identical in all respects with material obtained by methanolysis of nonactin. Epimer **36** was similarly identified by comparison with the compound obtained previously as the major reduction product from **33** with sodium borohydride.

Grignard Reaction of Aldehyde 57. Methyl 2-Epinonactate (39) and Methyl 2,8-Bisepinonactate (38). A portion (0.6 ml, 0.06 mmol) of the solution of methylmagnesium iodide, prepared as described above, was added to **57** (13 mg, 0.065 mmol) and the mixture was stirred for 10 min. The reaction mixture was quenched with a 10% aqueous solution of acetic acid and worked up as described for **56** to give 9 mg (65%) of a 1:1 mixture of **38** and **39**. These epimers were identical by chromatographic and NMR comparison with the two substances previously obtained by reduction of **32** with sodium borohydride, but they were not separated.

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Registry No.—**1a**, 6833-84-7; **2**, 55220-86-5; **4**, 58769-06-5; **5**, 58703-42-7; **6** isomer A, 58703-43-8; **6** isomer B, 58703-44-9; **7**, 58703-45-0; **8**, 58703-46-1; **9**, 58703-47-2; *trans*-**10b**, 58703-48-3; *cis*-**10b**, 58703-49-4; **11a**, 58703-50-7; **11b**, 58703-51-8; **12**, 17490-66-3; **13**, 58703-52-9; **15**, 58703-53-0; **16**, 58703-54-1; **17**, 58703-55-2; **18**, 58703-56-3; **19**, 58703-57-4; **20**, 58703-58-5; **21**, 58703-59-6; **22**, 58703-60-9; **23**, 58703-61-0; **24**, 58703-62-1; **26**, 58703-63-2; **27**, 58703-64-3; **28**, 58703-65-4; **29**, 58703-66-5; **30**, 56761-08-1; **31**, 56717-16-9; **32**, 58769-07-6; **33**, 58769-08-7; **34**, 58703-67-6; **35**, 56761-10-5; **36**, 58769-09-8; **38**, 58769-10-1; **39**, 56761-11-6; **40**, 58703-68-7; **42**, 37081-58-6; **43**, 58703-69-8; **44**, 58703-70-1; **45**, 58703-71-2; **53**, 58703-72-3; **54**, 58703-73-4; **55**, 58703-74-5; **56**, 58769-67-8; **57**, 58703-75-6; butyllithium, 109-72-8; furan, 110-00-9; propylene oxide, 75-56-9; 1-butene oxide, 106-88-7; dihydropyran, 289-66-7; allyl bromide, 106-95-6; α-bromoacetaldehyde diethyl acetal, 2032-35-1; 2-methylfuran, 534-22-5; 2-lithio-5-methylfuran, 54783-53-8; α-bromopropionaldehyde diethyl acetal, 3400-55-3; 3-bromo-1-butene, 22037-73-6; ethylene oxide, 75-21-8; *p*-toluenesulfonyl chloride, 98-59-9; methanesulfonyl chloride, 124-63-0; ethyl bromoacetate, 105-36-2; benzoic acid, 65-85-0; methyl iodide, 74-88-4.

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