Stereocontrolled Transformations of Orthoester Intermediates into Substituted Tetrahydrofurans

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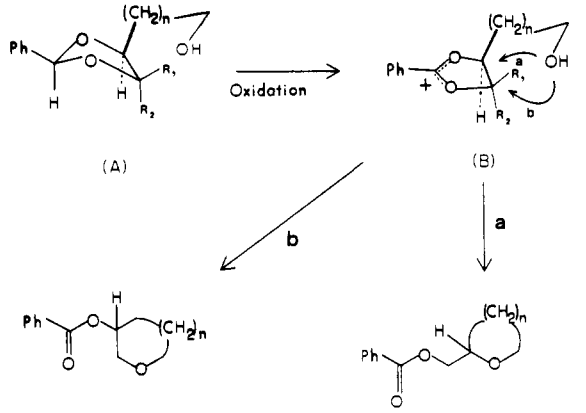
Abstract: Investigations of NBS oxidations of 1,3-dioxolane and 1,3-dioxane precursors bearing a neighboring hydroxyl have afforded the intramolecular preparation of substituted tetrahydrofurans. Stereochemical development is imposed by initial formation of orthoester intermediates folllowed by cleavage to dioxolenium cations and subsequent five-membered ring closure through a collinear backside displacement. Yields range from 45 to 80%.

Recent investigations have focused on the stereocontrolled preparation of substituted tetrahydrofurans.[2] As part of a continuing investigation of strategies of the stereocontrolled preparation of complex oxacyclic systems,[3] we have explored opportunities for synthesis of substituted tetrahydrofurans from 1,3-dioxolane and 1,3-dioxane precursors. Furthermore, to delineate the consequences of stereochemical development in these reactions, we report studies culuminating in a total synthesis of the marine natural product **1**.

As illustrated, formation of a benzylidene actal (A) with a

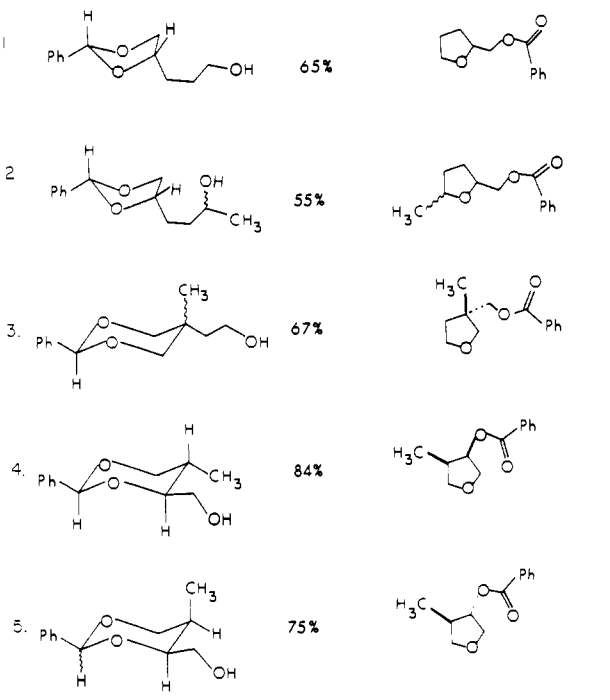


suitably positioned hydroxyl group would allow for oxidation to a highly stabilized carbocation (**B**) followed by intramolecular nucleophilic attack. Thus, ring closure via pathway **a** or pathway **b** could be expected to give rise to tetrahydrofuranyl or tetrahydropyranyl systems.

To demonstrate the feasibility of the plan, several substrates were examined as shown in Table I. Oxidations were conducted using *N*-bromosuccinimide (2 equiv) in chloroform or carbon tetrachloride at room temperature. In each case, exclusive ring closure to the tetrahydrofuran was observed. For entry 2, a mixture of diastereoisomeric alcohols (1:1) afforded an equal proportion of cis- and trans-2,5-disubstituted tetrahydrofurans. Additionally, 1,3-dioxanes, bearing appropriately positioned hydroxyl groups, are suitable precursors, even in situations where the hydroxyl appears locked in a nonparticipating equatorial conformation (entry 4).

In 1980, investigations at the Roche Research Institute of Marine Pharmacology reported isolation of a lipid diol, (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**1**) as a

Table I. NBS in $CHCl_3$ at 22 °C



component of the brown alga, *Notheia anomala*.[4] The structure was unambiguously confirmed by single-crystal X-ray analysis and thus offered an excellent target for evaluation of stereochemical features. Our plan called for oxidation of a 1,3-dioxolane with participation of a secondary hydroxyl along pathway **b** (diagramed above) with endocyclic production of a secondary benzoate and a new chiral center at C-5 (R_1 or $R_2 = C_5H_{11}$). A stereocontrolled sequence would provide 2,4,5-trisubstituted tetrahydrofurans with either backside inversion or net retention at C-5.[5] All diastereoisomers were examined with starting substrates prepared according to Scheme I. Each of the four diastereomers available from the cis series **2** were separated and individually submitted to oxidation conditions. Thus, dioxolane **2a** afforded a 78% yield of the all cis-substituted tetrahydrofuran **3**, whereas, diastereomer **2c** yielded 45% of benzoate **4**. Highly polar diol benzoates were observed as the only other products in all reactions.[6] Mass spectroscopy gave no evidence of bromide incorporation. Of course, stereochemical features at benzylic C-2 as displayed by isomers **2b** and **2d**, proved to be of no consequence.[7]

(1) Alfred P. Sloan Foundation Fellow (1983-1986).

(2) Recent developments: Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. Stork, G.; Poirer, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073. Ko, S. S.; Klein, L. L.; Pfaff, K.-P.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 4415. Hanessian, S.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6243. Brokatzky-Geiger, J.; Eberbach, W. *Tetrahedron Lett.* **1982**, *23*, 4665. Schreiber, S. L.; Hoveyda, A. H.; Wu, H.-J. *J. Am. Chem. Soc.* **1983**, *105*, 660.

(3) Williams, D. R.; Phillips, J. G.; Barner, B. A. *J. Am. Chem. Soc.* **1981**, *103*, 7398. Williams, D. R.; Grote, J. *J. Org. Chem.* **1983**, *48*, 134.

(4) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891.

(5) For a study of stereochemistry in the NBS oxidation of benzylidene acetals: Seeley, D. A.; McElwee, J. *J. Org. Chem.* **1973**, *38*, 1691.

(6) Diol benzoates, presumably arising from hydrolysis of orthoester intermediates, failed to undergo cleavage with lead tetraacetate and thus are not 1,2-diols.

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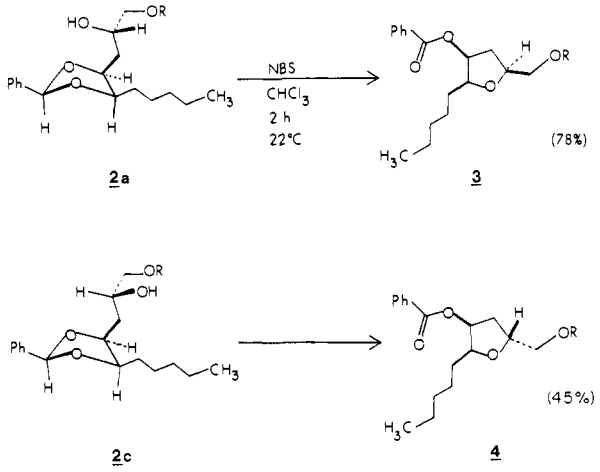
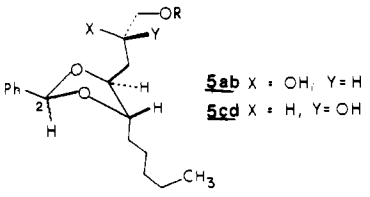
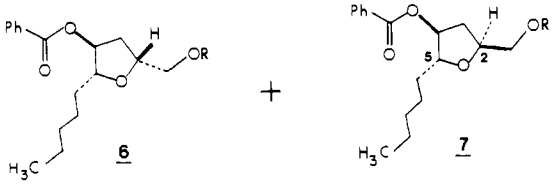


2a 3 2c 4

In the trans series **5**, chromatography afforded three fractions, two of which were pure benzylic epimers of diastereomeric secondary alcohols **5a** (least polar) and **5d** (most polar), whereas the middle component consisted of an equal mixture of **5bc**. Subsequently small amounts of **5bc** were separated by HPLC for spectroscpic characterization. Proton and carbon NMR data do not allow for unambiguous assignment of relative stereochemistry at the remote secondary alcohol for these isomers. However, the stereorelationships in the series **5a–d** have been investigated by chemical transformations. Individual oxidations (PCC, CH_2Cl_2, room temperature) of **5a** and **5d** afforded two different ketones (differing at C-2). Likewise, acetylation (Ac_2O, pyridine, 22 °C) of **5a** and **5d** followed by acetal hydrolysis ((1) $TiCl_4$, CH_2Cl_2, 22 °C, 2 h, (2) NH_4Cl, H_2O) provided two distinctive diol acetates (different configurations at the carbon bearing acetate). Similar treatment of **5bc** gave a 1:1 mixture of the same two ketones described from **5a** and **5d**, as well as, an equal proportion of the two diol acetates.[8] Regardless of substrate, oxidation of either **5a**, **5d**, or **5bc** afforded a 60:40 ratio of tetrahydrofurans **6** and **7** in yields of 68–80%, which were separated by silica gel chromatography.[9,10]



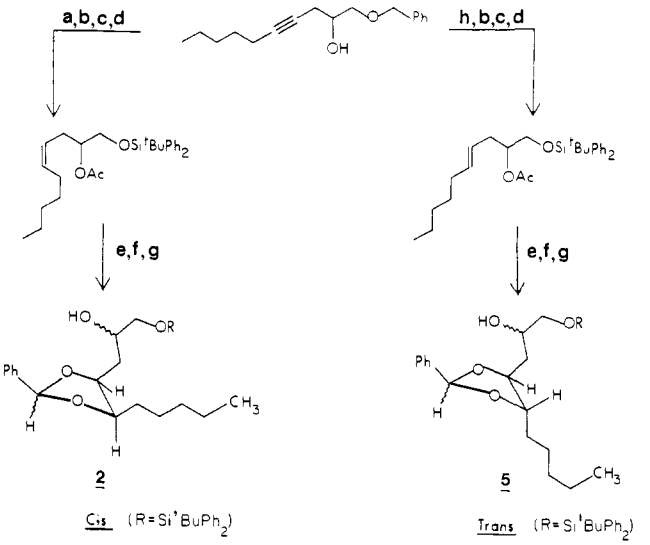
5ab X = OH, Y = H
5cd X = H, Y = OH



6 + 7

80%
ratio 60:40

Scheme I[a]



2 5

Cis (R = Si^{t}BuPh$_2$) Trans (R = Si^{t}BuPh$_2$)

[a] a, H_2/5% Pd–$BaCO_3$, EtOAc (87%); b, Na/NH_3, 2-propyl alcohol, −78 °C (98%); c, *t*-$BuPh_2SiCl$, CH_2Cl_2, pyridine, room temperature (92%); d, Ac_2O, pyridine (98%), e, catalytic OsO_4, *N*-methylmorpholine oxide, acetone, aqueous *t*-BuOH (98%); f, C_6H_5CHO, 1,2-dichloroethane, TsOH, 3-Å molecular sieves, Δ (96%); g, $NaOH_3$, CH_3OH, room temperature (89%); h, $LiAlH_4$, diglyme–THF (5:2) at 140 °C (98%).

Stereochemical assignments based upon NMR considerations were only certain after completion of the total synthesis of **1**, and by careful comparisons of all four tetrahydrofurans.[11] However, valuable information was obtained by benzoate saponification (LiOH, aqueous MeOH, 22 °C) and oxidation (PCC, CH_2Cl_2, 22 °C). Thus, benzoate pairs **3**,**6** and **4**,**7** individually produced cis- and trans-2,5-disubstituted tetrahydrofuranyl ketones **8** and **9**. Lithium selectride reductions (THF, −78 °C) gave only the

8 9

alcohol of **3** from **8**, whereas ketone **9** yielded a separable mixture (3:1 ratio) of alcohols corresponding to **4** and **7**, respectively.

These results suggest a mechanistic scheme featuring backside displacement with inversion of configuration at C-5, although reasons for the loss of stereointegrity in formation of **6** and **7** are presently unclear. Finally, total synthesis of the marine lipid diol **1** has been achieved by silyl ether deprotection (*n*-$Bu_4N^+F^-$, THF, 22 °C, 12 h) of **4** and Swern oxidation (−50 °C) to aldehyde **10** (90%). Addition of excess Grignard reagent **11** in ether occurred predominantly with chelation-controlled attack affording the racemic diol **1** (78% yield), which was spectroscopically confirmed

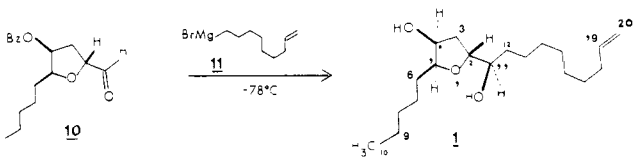
(7) Stereochemical features of *cis*-1,3-dioxolanes **2a–d** are assigned by ^1H ^{13}C NMR and by chemical transformations as described for trans series **5a–d**. See: Willy, N. E.; Binsch, G.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 5394. Eliel, E. L.; Ko, K.-Y., *Tetrahedron Lett.* **1983**, *24*, 3547 and references therein.

(8) Our hydrolysis results were found to be internally consistent when checked against the pair of diastereomeric diol acetates prepared in Scheme I (step e). Thus, no migration of the acetyl group has occurred (^1H NMR δ 2.07 (s, 3, $COCH_3$, **2a**), 2.01 (s, 3, $COCH_3$, **2d**), and ^{13}C NMR δ 210.0 (C=O), 100.4 (C-2) and 207.4 (C=O), 102.7 (C-2)).

(9) Tetrahydrofuran **6** is formed at a faster rate than isomer **7**. Results suggest two reaction pathways and a common intermediate from **5a** and **5d**. No conditions could be found for the conversion of **6** into **7**.

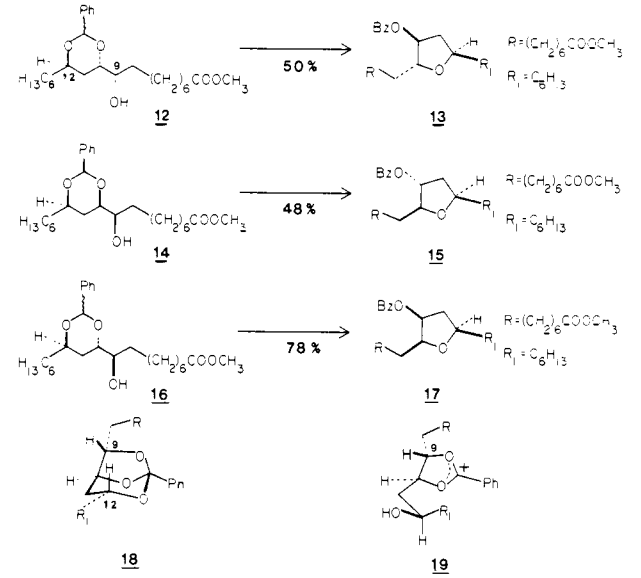
(10) Mechanistically, our racemic products cannot distinguish reaction pathways which provide scrambling of stereochemistry at the starting secondary alcohol versus possibilities of a pathway allowing coordinated inversions at C-4 and C-5. We have noted that 1-acetoxy-3,4-epoxypentanes isomerize to 2-methyl-3-acetoxytetrahydrofurans under acid conditions (Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H., *J. Org. Chem.* **1974**, *39*, 1142). However, the incorporation of quantities of (1*R**,3*S**,4*R**)-1-[(*tert*-Butyldiphenylsiloxy)methyl]-3,4-epoxy-1-nonanol benzoate into oxidations of **5a** failed to yield additional **6** or **7**.

(11) Two diagnostic features, which seem especially noteworthy for recognition of stereochemical relationships, became apparent in NMR spectra of our trisubstituted tetrahydrofuran benzoates. The four possible diastereoisomers are recognized as two sets of pairs. Trans relationships at the 2 and 3-substituents result in shielding of the benzoate methine proton (H_A δ 5.3) by the C-2 aliphatic side chain compared to a cis 2,3-substitution (H_A δ 5.6). Nonequivalent methylene protons (H_D, H_E) at C-4 are indicative of the 1,3-relative asymmetry at C-3 and C-5. For the isomer pair bearing syn 3,5-stereochemistry, chemical shift patterns reveal $\Delta\nu_{DE}$ is 0.4 ppm or larger, and for anti 3,5-isomers, $\Delta\nu_{DE}$ is 0.2 ppm or smaller. (See supplementary materials for NMR analysis.)



by comparison with a sample of the natural product.[12]

Further investigations have revealed elegant and important distinctions for mechanistic tranformations of 1,3-dioxanes (such as entries **4** and **5**) into their corresponding tetrahydrofuranyl ethers. Evidence was provided following preparation of the six-membered benzylidene acetal **12** from optically active triol with subsequent NBS oxidation affording cyclic ether **13**. Likewise acetals **14** and **16** gave **15** and **17**, respectively, with complete stereospecificity and inversion at C-9.



Initial carbocation capture by the neighboring hydroxyl at C-9 of **12** leads to orthoester **18**. Opening of the six-membered ring forms dioxolenium cation **19**, which then suffers internal nucleophilic attack at C-9 providing the observed tetrahydrofuran **13**. Although each of the oxygens of orthoester **18** are suitable leaving groups, these results demonstrate that ring closure is feasible only in cases where two or three bridging methylenes separate a nucleophilic hydroxyl from its cationic partner, thus achieving an intramolecular backside collinear displacement. Consequently, hydroxy groups located on a single methylene bridge (as seen in entries **4** and **5** and compounds **12**, **14**, and **16**) fail to participate in ether formation, but instead are incorporated as carbonyls of the benzoate products.[13]

Experimental Section[14]

Preparations of Benzylidene Acetals. A round-bottom flask, containing the starting diol, freshly distilled benzaldehyde (1.5 equiv), and one crystal of *p*-toluenesulfonic acid monohydrate in 1,2-dichloroethane, was equipped with a distilling column packed with dry 3-Å molecular sieves topped by a condenser and drying tube. Reactions were generally complete after heating at reflux for 20 min, and products were isolated by silica gel chromatography. Acetals **12**, **14**, and **16** were formed at 22 °C without use of sieves for removal of water.

(**αS*,2R*,4S*,5R***)-α-[(***tert*-Butyldiphenylsiloxy)methyl]-5-pentyl-2-phenyl-1,3-dioxolane-4-ethanol (**2a**): ^{1}H NMR δ 7.67 (d, 4, *J* = 7.0 Hz), 7.48 (m, 11), 5.78 (s, 1), 4.48 (dd, 1, *J* = 13.0, 5.0 Hz), 4.15 (m, 1), 4.04 (br s, 1, OH), 3.69 (dd, 1, *J* = 10.0, 3.0 Hz), 3.53 (dd, 1, *J* = 10.0, 7.5 Hz), 2.66 (d, 1, *J* = 3.0 Hz), 1.70–1.22 (m, 10), 1.04 (s, 9), 0.88 (t, 3, *J* = 7.0 Hz); IR (film) 3580, 3460, 1589, 1456, 1421, 1105, 700 cm^{-1}; MS (70 eV), *m/z* 532 (0.5), 291 (54), 241 (27), 199 (67), 181 (60), 163 (76), 139 (84), 135 (60), 123 (18), 107 (58), 105 (100), 79 (58), 78 (49), 77 (49).

(**αS*,2S*,4S*,5R***)-α-[(***tert*-Butyldiphenylsiloxy)methyl]-5-pentyl-2-phenyl-1,3-dioxolane-4-ethanol (**2b**): ^{1}H NMR δ 7.68 (d, 4, *J* = 7.0 Hz), 7.37 (m, 11), 5.96 (s, 1), 4.52 (ddd, after D_2O ex *J* = 10.0, 5.5, 3.5 Hz), 4.18 (m, 1), 4.05 (br, 1), 3.73 (dd, 1, *J* = 10.0, 4.0 Hz), 3.57 (dd, 1, *J* = 10.0, 7.5 Hz), 2.68 (br d, 1, *J* = 3.5 Hz, OH), 1.78–1.25 (m, 10), 1.05 (s, 9), 0.88 (t, 3, *J* = 7.0 Hz); IR (film) 3564, 3464, 1588, 1458, 1424, 1104, 700 cm^{-1}; MS (70 eV), *m/z* 532 (M$^+$, 0.2), 291 (52.7), 241 (25.2), 207 (19.0), 199 (65.8), 181 (60.1), 165 (21.9), 163 (74.8), 139 (79.9), 135 (58.8), 123 (22.6), 121 (19.1), 117 (19.9), 107 (62.4), 105 (100), 79 (59.5), 78 (50.9), 77 (52.8), 57 (50.2), 43 (88.1).

(**αR*,2S*,4S*,5R***)-α-[(***tert*-Butyldiphenylsiloxy)methyl]-5-pentyl-2-phenyl-1,3-dioxolane-4-ethanol (**2c**): ^{1}H NMR δ 7.71 (d, 4, *J* = 7 Hz), 7.52–7.34 (m, 11), 5.59 (s, 1), 4.02 (dt, 1, *J* = 5.5, 15.0 Hz), 3.87 (dd, 1, *J* = 10.5, 5.5 Hz), 3.82 (m, 2), 3.72 (dd, 1, *J* = 10.5, 5.5 Hz), 2.08 (br s, 1, OH), 1.75–1.22 (m, 10), 1.05 (s, 9), 0.90 (t, 3, *J* = 7.0 Hz); IR (film) 3577, 3470, 1586, 1455, 701 cm^{-1}; MS (70 eV), *m/z* 532 (0.8), 291 (58), 199 (68), 181 (59), 163 (73), 139 (79), 107 (64), 105 (100).

(**αR*,2S*,4S*,5R***)-α-[(***tert*-Butyldiphenylsiloxy)methyl]-5-phenyl-2-phenyl-1,3-dioxolane-4-ethanol (**2d**): ^{1}H NMR δ 7.68 (dd, 4, *J* = 7.0, 10.0 Hz), 7.41 (m, 11), 5.75 (s, 1), 4.28 (m, 1), 4.14 (m, 1), 3.98 (m, 1), 3.72 (dd, 1, *J* = 10.0, 5.5 Hz), 3.64 (dd, 1, *J* = 10.0, 5.5 Hz), 3.05 (br d, 1, *J* = 2 Hz, OH), 1.89–1.27 (m, 10), 1.05 (s, 9), 0.90 (t, 3, *J* = 7.0 Hz); IR (film) 3565, 3460, 1585, 1451, 700 cm^{-1}; MS (70 eV), *m/z* 532 (0.2), 291 (50), 199 (62), 181 (55), 163 (71), 139 (79), 107 (61), 105 (100).

Dioxolanes of the Trans Series. Isomer 5a: ^{1}H NMR δ 7.65 (d, 4, *J* = 6.9 Hz), 7.39 (m, 11), 5.83 (s, 1), 4.05 (m, 2), 3.76 (dd, 1, *J* = 7.2, 4.9 Hz), 3.72 (dd, 1, *J* = 10.1, 4.3 Hz), 3.58 (dd, 1, *J* = 10.1, 7.1 Hz), 2.72 (br s, 1, OH), 1.67–1.40 (m, 6), 1.31 (m, 4), 1.06 (s, 9), 0.89 (t, 3, *J* = 6.9 Hz); ^{13}C NMR δ 138.2, 135.5, 133.1, 129.8, 129.1, 128.3, 127.8, 128.9, 102.6 (C-2), 83.1, 78.2, 69.5, 68.0, 36.0, 32.5, 31.8, 26.9, 25.7, 22.5, 19.3, 14.0; IR (film) 3567, 3475, 1589, 1463, 1428, 1112, 700 cm^{-1}; MS (70 eV), *m/z* 532 (M$^+$, 0.5), 291 (49), 199 (61), 181 (42), 163 (68), 139 (72), 107 (59), 105 (100).

Isomer 5b: ^{1}H NMR δ 7.68 (d, 4, *J* = 6.5 Hz), 7.37 (m, 11), 5.55 (s, 1), 4.01 (m, 1), 3.87 (dd, 1, *J* = 10.5, 5.4 Hz), 3.71 (m, 2), 3.55 (m, 1), 2.42 (d, 1, *J* = 3.6 Hz, OH), 1.66 (dt, 1, *J* = 13.0, 2.5 Hz), 1.51 (m, 5), 1.33 (m, 4), 1.06 (s, 9), 0.91 (t, 3, *J* = 6.7 Hz); IR (film) 3565, 3475, 1588, 1455, 1425, 1108, 698 cm^{-1}; MS (70 eV), *m/z* 532 (M$^+$. 0.2), 291 (53), 199 (69), 181 (52), 163 (78), 139 (79), 107 (65), 105 (100).

Isomer 5c: ^{1}H NMR δ 7.65 (d, 4, *J* = 6.5 Hz), 7.38 (m, 11), 5.88 (s, 1), 4.06 (m, 2), 3.76 (dt, 1, *J* = 4.0, 7.5 Hz), 3.69 (dd, 1, *J* = 10.1, 4.0 Hz), 3.54 (dd, 1, *J* = 10.1, 7.0 Hz), 2.67 (d, 1, *J* = 3.8 Hz, OH), 1.80–1.70 (m, 2), 1.68 (m, 2), 1.62–1.32 (m, 6), 1.06 (s, 9), 0.89 (t, 3, *J* = 6.9 Hz); IR (film) 3565, 3465, 1590, 1460, 1428, 1115, 703 cm^{-1}; MS (70 eV),*m/z* 532 (M$^+$, 0.3), 291 (58), 199 (69), 181 (68), 163 (81), 139 (89), 107 (65), 105 (100); ^{13}C NMR (mixture of **5bc**) δ 138.35, 138.28, 135.59, 135.49, 133.45, 133.07, 129.77, 129.62, 129.05, 128.74, 128.24, 128.09, 127.72, 127.59, 126.55, 126.16, 102.66 (C-2), 100.57 (C-2), 81.68, 79.69, 79.55, 76.87, 73.80, 69.25, 67.96, 66.78, 36.05, 32.65, 32.12, 31.87, 29.49, 26.84, 25.62, 25.01, 22.59, 22.52, 19.24, 14.05.

Isomer 5d: ^{1}H NMR δ 7.66 (d, 4, *J* = 7.6 Hz), 7.38 (m, 11), 5.87 (s, 1), 3.98 (m, 1), 3.90 (ddd, 1, *J* = 8.5, 7.4, 3.8 Hz), 3.81 (dt, 1, *J* = 4.7, 7.4 Hz), 3.69 (dd, 1, *J* = 10.1, 5.8 Hz), 3.65 (dd, 1, *J* = 10.1, 5.4 Hz), 2.99 (d, 1, *J* = 2.7 Hz, OH), 1.85 (dt, 1, *J* = 14.2, 3.8 Hz), 1.78 (dt, 1, *J* = 14.2, 8.5 Hz), 1.64 (m, 2), 1.53 (m, 1), 1.46 (m, 1), 1.32 (m, 4), 1.07 (s, 9), 0.90 (t, 3, *J* = 6.9 Hz); ^{13}C NMR δ 138.0, 135.5, 133.2, 129.8, 129.2, 128.3, 127.7, 126.6, 102.8 (C-2), 83.1, 79.9, 70.5, 67.4, 36.1, 32.5, 31.8, 26.9, 25.7, 22.5, 19.3, 14.0; IR (film) 3560, 3470, 1588, 1458, 1425, 1110, 700 cm^{-1}; MS (70 eV), *m/z* 532 (M$^+$, 0.3), 291 (51), 199 (62), 181 (45), 163 (70), 139 (78), 107 (52), 105 (100).

Oxidations Using *N*-Bromosuccinimide. To a stirred solution of benzylidene acetal in chloroform was added 2 equiv of freshly recrystallized *N*-bromosuccinimide all at once with continued stirring at room temperature under an inert atmosphere. Although rates were faster in chloroform than in carbon tetrachloride, all cases displayed an initial

(12) Grignard addition also gave 13% of the epimeric C-11 alcohol of **1**. Likewise, the 19,20-dihydro derivative of **1** was prepared by Grignard addition and was also identical with the authentic materials generously supplied by Dr. Robert Wells.

(13) By collaboration with Dr. Edward Mihelich (Proctor and Gamble) we have obtained and transformed chiral samples of known fatty acid triols into dioxanes **12**, **14**, and **16**. These results have demonstrated that our tetrahydrofurans **13**, **15**, and **17** are also enantiomeric to those produced by direct dehydration of the series of triols as observed by Dr. Mihelich. Dehydration results, featuring selective C-12 inversion, will be reported separately (E. Mihelich). For recognition of the stereochemical features of **13**, **15**, and **17**, see footnote 11 and supplementary material. Recently we have purified and characterized small samples of orthoesters from **12** and **14** by ^{1}H NMR and infrared techniques.

(14) Proton magnetic resonance spectra were recorded on a Nicolet NT-360 instrument in $CDCl_3$ (0.1% Me_4Si), and carbon-13 spectra were determined at 90.8 MHz with proton decoupling. All coupling constants are reported in Hertz. Silica gel 60 from E. Merck (0.063-0.2 mm) and precoated glass plates (60F-254) were employed throughout.

induction period (15–25 min) before onset. Reactions proceeded at similar rates in light or in the dark, but could be initiated (in CCl_4) by addition of benzoyl peroxide. After onset, solutions became deep red-orange in color, then gradually fading to a pale yellow-orange. In most cases, experiments were complete after 2 h, whereby the reaction mixtures were directly submitted for flash column chromatography or applied to plates for preparative thin-layer separation. The use of olefins to trap bromine or various bases to neutralize HBr failed to alter the course of reactions, but generally lowered yields. Tetrahydrofuran products are characterized by spectral and other data as described below.

(2*R,3*R**,5*R**)-5-[(*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-2-pentyl-3-furanyl Benzoate (3)**: ^{1}H NMR δ 7.92 (dd, 2, J = 1.2, J = 8.2), 7.67 (m, 4), 7.54 (t, 1, J = 7.4), 7.36 (m, 6), 7.27 (t, 2, J = 7.4), 5.48 (ddd, 1, J = 6.07, J = 3.66, J = 1.61), 4.16 (dddd, 1, J = 8.35, J = 5.95, J = 5.66, 5.31), 3.90 (ddd, 1, J = 7.67, J = 5.6, J = 3.66), 3.76 (AB of ABX, 2, $\Delta\nu$ 59.7, J = 10.24, J = 5.95, J = 5.66), 2.50 (ddd, 1, J = 14.49, J = 8.35, J = 6.07), 2.02 (ddd, 1, J = 14.49, J = 5.31, J = 1.61), 1.68 (m, 2), 1.46 (m, 1), 1.2–1.4 (m, 5), 1.015 (s, 9), 0.836 (t, 3, J = 6.9); ^{13}C NMR δ 165.88, 135.62, 135.53, 133.57, 132.91, 130.08, 129.54, 128.33, 127.54, 82.31, 77.87, 75.13, 66.58, 35.81, 31.90, 29.26, 26.79, 26.04, 22.52, 19.25, 13.98; IR (neat) 3067, 3044, 1718, 1600, 1586, 1426, 1264, 1115, 705, 696 cm^{-1}. Anal. Calcd for $C_{33}H_{42}O_4Si$: C, 74.67; H, 7.98. Found: C, 74.54; H, 7.94. R_f 0.41, Et_2O–hexane (25:75).

(2*R,3*R**,5*S**)-5-[(-*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-2-pentyl-3-furanyl Benzoate (4)**: ^{1}H NMR δ 8.08 (dd, 2, J = 1, J = 8), 7.72 (m, 4), 7.59 (t, 1, J = 7.5), 7.45 (t, 2, J = 7.4), 7.41 (m, 6), 5.57 (ddd, 1, J = 0.5, J = 3, J = 5.1), 4.39 (dddd, 1, J = 3.70, J = 3.91, J = 6.94, J = 8.7), 4.12 (ddd, 1, J = 3, J = 5.3, J = 7.9), 3.74 (AB of ABX, 2, $\Delta\nu$ 57.3, J = 10.76, J = 3.91, J = 3.70), 2.42 (ddd, 1, J = 13.95, J = 5.1, J = 8.7), 2.18 (dd, 1, J = 13.95, J = 6.94), 1.68 (m, 1), 1.50 (m, 1), 1.29 (m, 6), 1.061 (s, 9), 0.843 (t, 3, J = 6.8).

Decoupling experiments. Irradiation at δ 4.39, 2.42 (dd, $J \simeq$ 5, 13.8), δ 2.18 (d, $J \simeq$ 13.8), 3.74 (AB q, $J \simeq$ 10.7); irradiation at δ 2.42, 5.57 (d, $J \simeq$ 3); irradiation at δ 2.18, 5.57 (dd, $J \simeq$ 3, 5); ^{13}C NMR δ 165.97, 135.59, 133.46, 133.42, 133.04, 130.21, 129.63, 128.37, 127.64, 81.94, 77.57, 76.40, 66.05, 35.11, 31.90, 29.52, 26.84, 26.20, 22.57, 19.26, 14.00; IR (neat) 3067, 3043, 1719, 1600, 1587, 1270, 1115, 708, 698 cm^{-1}; R_f 0.52, Et_2O–hexane (25:75).

(2*R,3*S**,5*R**)-5-[(*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-2-pentyl-3-furanyl Benzoate (6)**: ^{1}H NMR δ 8.04 (dd, 2, J = 1.2, J = 8.2), 7.71 (dt, 4, J = 1.2, J = 8), 7.58 (t, 1, J = 7.4), 7.48 (t, 2, J = 7.4), 7.40 (m, 6), 5.23 (ddd, 1, J = 2.37, J = 1.70, J = 6.12), 4.30 (dddd, 1, J = 9.78, J = 5.66, J = 3.96, J = 4.05), 4.07 (ddd, 1, J = 2.37, J = 6.4, J = 6.7), 3.77 (AB of ABX, 2, $\Delta\nu$ 27.47, J_{AB} = 10.86, J = 3.96, J = 4.05), 2.29 (ddd, 1, J = 13.64, J = 9.78, J = 6.12), 2.07 (ddd, 1, J = 13.64, J = 5.66, J = 1.70), 1.6 (m, 2), 1.45 (m, 2), 1.29 (m, 4), 1.067 (s, 9), 0.873 (t, 3, J = 6.8); ^{13}C NMR δ 166.06, 135.61, 133.48, 133.41, 133.01, 130.16, 129.58, 128.33, 127.61, 84.33, 79.35, 78.88, 65.45, 34.42, 34.15, 31.77, 26.82, 25.44, 22.58, 19.26, 14.04; IR (neat) 3065, 3044, 1717, 1601, 1588, 1425, 1270, 1110, 705 cm^{-1}; MS (70 eV), m/z 473 (49, $M^+ - C_4H_9$), 369 (13), 292 (13), 291 (50), 241 (75), 199 (46), 181 (14), 163 (23), 161 (16), 153 (12), 139 (23), 135 (18), 105 (100). Anal. Calcd for $C_{33}H_{42}O_4Si$: C, 74.67; H, 7.98. Found: C, 74.66; H, 8.10. R_f 0.54, Et_2O–hexane (25:75).

(2*R,3*S**,5*S**)-5-[(*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-2-pentyl-3-furanyl Benzoate(7)**: ^{1}H NMR δ 7.93 (dd, 2, J = 1, J = 8), 7.67 (m, 4), 7.55 (t, 1, J = 7.5), 7.37 (m, 8), 5.18 (ddd, 1, J = 7, J = 3.5, J = 4), 4.29 (dddd, 1, J = 7.9, J = 6.0, J = 5.3, J = 5.4), 4.10 (ddd, 1, J = 3.5, J = 5.6, J = 7.2), 3.76 (AB of ABX, 2, $\Delta\nu$ 27.2, J = 10.27, J = 6.0, J = 5.3), 2.52 (ddd, 1, J = 13.92, J = 7.9, J = 7), 2.11 (ddd, 1, J = 13.92, J = 5.4, J = 4), 1.6–1.25 (m, 8), 1.048 (s, 9), 0.88 (t, 3, J = 6.9); ^{13}C NMR δ 166.09, 135.55, 133.59, 133.47, 132.95, 130.00, 129.55, 128.30, 127.59, 83.28, 78.77, 77.98, 66.39, 33.82, 33.34, 31.76, 26.82, 25.47, 22.58, 19.26, 14.02; IR (neat) 3067, 3042, 1717, 1600, 1585, 1424, 1270, 1115, 704, 697 cm^{-1}; MS (70 eV), m/z 473 (2, $M^+ - C_4H_9$), 241 (2), 199 (24), 157 (2), 139 (2), 122 (53), 105 (100). Anal. Calcd for $C_{33}H_{42}O_4Si$: C, 74.67; H, 7.98. Found: C, 74.48; H, 8.07. R_f 0.48, Et_2O-hexane (25:75).

(2*R,4*S**,5*S**)-Tetrahydro-4--hydroxy-5-pentyl-2-furaldehyde Benzoate (10)**. To a magnetically stirred solution of oxalyl chloride (0.030 mmol) in methylene chloride (1.0 mL), cooled to −75 °C under argon, was added 0.027 mL (0.380 mmol) of dry Me_2SO. The resulting reagent was stirred at −75 °C for 0.5 h. A solution of the tetrahydrofuranyl alcohol (10.1 mg, 0.0345 mmol) in methylene chloride (0.5 mL) was added dropwise. After stirring at −75 °C for 1 h, triethylamine (0.110 mL, 0.79 mmol) was added. The reaction was maintained at −75 °C for 0.5 h and then was allowed to slowly reach ambient temperature. The mixture was filtered through a small plug of silica gel, concentrated, and applied to a preparative thin-layer plate (ether–hexane, 1:1). The product band was quickly removed and extracted (EtOAc) to furnish pure aldehyde **14**: R_f 0.15 ether–hexane (1:1); ^{1}H NMR δ 9.76 (d, 1, J = 1.4), 8.05 (dd, 2, J = 1, J = 8), 7.60 (t, 1, J = 7.4), 7.47 (t, 2, J = 7.8), 5.58 (q, 1, J = 3.1), 4.57 (dt, 1, J = 1.4, J = 8.2), 4.05 (ddd, 1, J = 7.6, J = 6.0, J = 3.1), 2.40 (dd, 2, J = 8.2, J = 3.1), 1.8–1.55 (m, 2), 1.5–1.15 (m, 6), 0.851 (t, 3, J = 6.9; IR (neat) 1720, 1600, 1585, 1270, 1115, 725 cm^{-1}. Note: Aldehyde **14** could not be stored without decomposition. Generally **14** was purified by preparative thin-layer chromatography (silica gel) and used immediately in Grignard reactions.

(α*R,2*R**,4*S**,5*S**)-Tetrahydro-4-hydroxy-α-8-nonenyl-5-pentylfurfuryl Alcohol (1)**. Magnesium turnings (0.94 g, 38.7 mmol) were dried at 100 °C, cooled in vacuo, and then blanketed with argon. A solution of 1,2-dibromoethane (0.025 mL) in ether (2.0 mL) was added slowly, heated at reflux for 2 h, and then allowed to cool. The ether layer was removed, and a solution of 9-bromo-1-nonene (69 mg, 0.34 mmol) in 3.0 mL of ether was added. The mixture was stirred 1 h, heated at reflux for 3 h, and then was allowed to cool. Ethereal Grignard reagent was added dropwise to a magnetically stirred solution of **14** (9.1 mg, 0.031 mmol) in ether (0.5 mL) at −75 °C under argon. The reaction was allowed to warm slowly to 0 °C, then ethanol was added dropwise. The mixture was applied to two 10 × 20 cm, 0.25 mm TLC plates which were developed five times with ether–hexane (25:75). Extraction (EtOAc) gave 7.9 mg (0.024 mmol, 78%) which proved to be tetrahydrofuran **1**: R_f 0.11 ether–hexane (1:1); mp 53–54 °C; ^{1}H NMR δ 5.81 (ddt, 1, J = 17, J = 10.2, J = 6.7), 4.98 (br d, 1, J = 17), 4.92 (br dd, 1, J = 10.2, J = 0.74), 4.24 (m, 1), 4.02 (dt, 1, J = 8.5, J = 6.7), 3.75 (dt, 1, J = 2.45, J = 6.85), 3.37 (m, 1), 2.34 (br s, 1, OH), 2.02 (m, 3), 1.87 (ddd, 1, J = 13.45, J = 9.0, J = 4.5), 1.62 (m, 2), 1.55 (m, 2), 1.45–1.2 (m, 14), 0.895 (t, 3, J = 6.6); IR (neat) 3430, 3260, 3078, 1641, 1090, 995, 910 cm^{-1}; MS (70 eV), m/z 312 (2, M^+), 294 (2), 157 (100), 139 (16), 121 (25), 113 (62); MS, m/e calcd for $C_{19}H_{36}O_3$, M^+ 312.266; found, 312.263. Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.0; H, 11.5. Found: C, 73.12; H, 11.68.

Additionally, 1.7 mg (0.004 mmol, 13%) of the corresponding C-11 epimer **1a** was isolated as its C-4 benzoate: R_f 0.44 ether–hexane (1:1); ^{1}H NMR δ 8.06 (dd, 2, J = 1.2, J = 7.8), 7.59 (tt, 1, J = 1.2, J = 7.4), 7.46 (t, 2, J = 7.8), 5.80 (ddt, 1, J = 17.0, J = 10.2, J = 6.7), 5.58 (br dd, 1, J = 3.3, J = 4.3), 4.98 (dm, 1, J = 17.0), 4.92 (dm, 18 J = 10.2), 4.21 (ddd, 1, J = 3.7, J = 6.1, J = 10.0), 4.11 (ddd, 1, J = 3.3, J = 6.4, J = 7.3), 3.90 (m, 1), 2.32 (ddd, 1, J = 4.3, J = 10.0, J = 14), 2.03 (br q, 2, J = 6.7, and obscured m, 1), 1.98 (d, 1, J = 2.7, OH), 1.75–1.6 (m, 2), 1.55–1.4 (m, 2), 1.4–1.15 (m, 16), 0.838 (t, 3, J = 6.9).

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Supplementary Material Available: A listing of ^{1}H NMR, infrared, and mass spectral data and experimental notes for Scheme I, data for oxidations and reductions of tetrahydrofuran diastereoisomers (Scheme II), and reproductions of ^{1}H NMR (360 MHz) spectra for benzoates **3**, **4**, **6**, and **7**, with critical proton assignments (δ 1.99–5.77) (12 pages). Ordering information is given on any current masthead page.