Diacetone Glucose† Derived Dienes in Diels-Alder Reactions. Products and Transformations

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Diene **2** which is readily prepared from diacetone glucose undergoes Diels-Alder reaction with maleic anhydride in a completely stereoselective manner to give compound **3** as the sole product. Subsequent hydrogenation of the double bond is also stereoselective and affords the *cis*-cyclohexanofurano ring junction. Sodium borohydride reduction of the anhydride **4** is chemoselective and lactone **7** is produced. The apparent anomalous reduction of the less-hindered carbonyl is rationalized by a chelation postulate. Diels-Alder reaction of the dienic alcohol **8a** is equally selective and the primary product, **12**, undergoes intramolecular trans acylation to afford **10a** directly. DIBAL reduction of the lactonic ester, **10b**, occurs preferentially at the lactone, and the acetal **13a** is the product. The double bond of **13a** resisted hydrogenation; however, if the rings were uncoupled with base and the hydrogenation carried out in the basic solution, the lactone **16a** was obtained in excellent yield. The lactonic ester **10b** reacts at the lactone carbonyl preferentially with Grignard reagents to give caged ketal lactones, e.g., **13b**, **13c**, and **13d**. The "cage" in these molecules can be unravelled by treatment with alkali and reduction with sodium borohydride. Experiments have been carried out for giving access to the various groups in these condensed polyfunctional systems.

We are interested in extending the scope of carbohydrate derivatives in natural product synthesis, and the development of routes to carbocyclic compounds is an obvious area to pursue in view of the abundance of these systems in nature. Of particular interest to us has been the family of sesquiterpene α-methylene lactones,[1] whose diverse and complex skeleta have exercised the imagination of synthetic organic chemists.[2] The well-known biological importance of this family of compounds[1] adds to their allure, and we therefore initiated a research program in this area.[3-7]

An examination of the literature[1] with the primary focus on the lactone residue allows division of the family into cis and trans categories as summarized by I and IV, respectively. Further retronanalysis of these substructures indicates that the absolute configuration of the ring oxygen of each, i.e., C-8 of I and C-6 of IV, is the same as that at C-4 of "diacetone glucose", 1 (Scheme I). We have already shown that the *O*-isopropylidene ring of compounds such as II and III is an effective mask for the α-methylene lactone,[3] and hence the challenge for utilizing "diacetone glucose" requires the stereocontrolled introduction of the carbon center at C-3, whereby the cis- or trans-fused annulated furanoses, II or III, can be elaborated. In this manuscript we report on some of the chemistry of the cis-fused systems related to II[4-7].

In view of our interest in the application of the Diels-Alder reaction to carbohydrate substrates,[8] it was logical to explore this route to compound II and for this approach, the dienes V, VI, and VII are plausible substrates. Notably in sugar-based Diels-Alder reactions that have been reported since our pioneering studies,[8a] it is the dienophile that had been obtained from the sugar.[9-13] In the case of V, VI, and VII, it is a diene that is to be derived from the sugar. Diene VII was chosen for our preliminary studies since its synthesis from diacetone glucose could be readily achieved.[6,14]

Formation and Reactions of Diels-Alder Adduct. The reaction of diene **2**[6,14] with a number of dienophiles was examined, and among those that failed to react under thermal conditions were crotonaldehyde, methyl crotonate, and even α-chloroacrylonitrile which is reported to be excellent for dienes substituted with vinyl ethers.[15] Lewis acid catalysts, for example, cupric tetrafluoroborate the recommended catalyst for cyano dienophiles,[16] aluminum chloride, or methyl aluminum dichloride[17] caused decomposition of **2**.

Success was had when diene **2** was treated with maleic anhydride in refluxing toluene whereby a single product was obtained after chromatography in 86% yield (Scheme

† Trivial name for 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

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(2) See for example: Wender, P. A.; Howbert, J. J., *Tetrahedron Lett.* **1983**, *24*, 5325. Wender, P. A.; Howbert, J. J. *Ibid.* **1982**, *83*, 3982. Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805. Lansbury, P. T. Vacca, J. P. *Tetrahedron* **1982**, *38*, 2797. Ando, M.; Tajima, K.; Takase, K. *J. Org. Chem.* **1983**, *48*, 1210. Jalali-Naini, M.; Guillerm, D.; and Lallemand, J. Y. *Tetrahedron* **1983**, *39*, 749. Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1983**, 729. Paquette, L. A.; Galemmo, R. A., Jr.; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 6975. Witton, J. H.; Doskotch, R. W. *J. Org. Chem.* **1983**, *48*, 4251. Ley, S. V.; Mahon, M. *J. Chem. Soc., Perkin Trans 1* **1983**, 1379.
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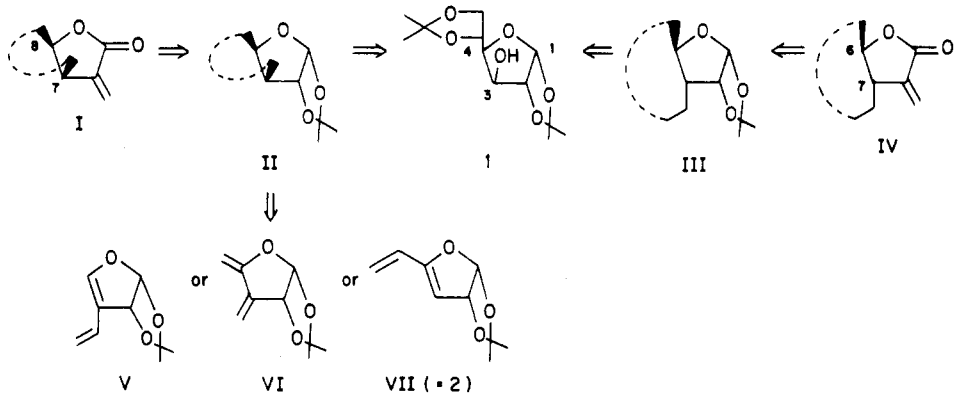
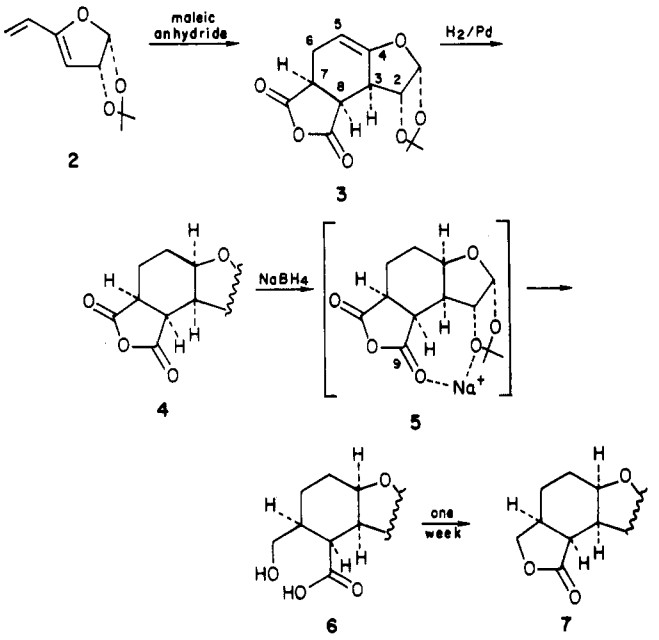
Scheme I



Scheme II



II). That the addition had occurred exclusively from the convex surface of **2** was apprarent from the value $J_{2,3}$ = 0.4 Hz which can be accomodated only by a trans relationship between H2 and H3 where the projected angle between these protons is approximately 90°.

In addition to this exclusive facial selectivity, the Diels–Alder reaction was entirely endo selective. Thus in the single isomer obtained, i.e., **3**, $J_{3,8}$ was 5.6 Hz which indicated a cis relationship between the hydrogens concerned.

The stereochemical consequence of endo addition was that the anhydride ring of **3** was effectively poised to occlude the *re-re*[β] face of the double bond. Thus, not surprisingly, hydrogenation of 3 occurred entirely from the *si-si* face to give compound **4**.

In order to differentiate between the two carbonyl groups of **4**, sodium borohydride reduction was examined.[18] This led to the hydroxy acid **6**, which lactonized over a period of one week to **7**. The assignment of the structure of **7** rested on the fact that double irradiation experiments revealed that H8 was coupled to two hydrogens only—H3 and H7. Concomitantly, H7, thus identified, was a complex mutliplet.

According to Bloomfield's rationalization for chemoselectivity in succinic anhydride reductions, the carbonyl that survives is the one which is chelated to sodium.[18] Models show that a sodium ion can chelate the C9 and the furanoid oxygen as depicted in **5**.

Formation and Reactions of Adduct 10. The foregoing results indicated that systems shown in Scheme II display complete stereoselectivities and we were therefore encouraged to examine substrates that would afford additional stereochemical factors. The preparation of the dienic alcohol **8a** from "diacetone glucose" has also been described previously by us,[6] and we found that the silylated derivative **8b** reacted smoothly with maleic anhydride in refluxing toluene to afford adduct **9** in 85% yield.

Our thoughts for manipulating this polyfunctional molecule, **9**, were conditioned by the observation (vide supra) that the hydroxylic acid **6** had required one week for formation of the γ-lactone ring in **7** (Scheme II). This observation implies that a five-membered ring which incorporates C7 and C8 is not very favorable. Accordingly, compound **9** was desilylated in the hope that the resulting oxy anion would uncouple the anhydride thereby differentiating between the two carboxylic groups as shown in **10**. Unfortunately, treatment of **9** with fluoride ion caused decomposition.

On the other hand, it was found that reaction of dienol **8a** with maleic anhydride at room temperature went smoothly in 30 h to give the lactonic acid **10a** directly (Scheme III). (A similar process has been observed by Woodward and Greenlee.[19]) It was most convenient to isolate the product as the ester **10b** obtained in 85% overall yield. However, the product was surprisingly labile. Thus attempts to hasten the Diels–Alder reaction by heating at 50° or by the inclusion of bases to expedite the lactonization process caused severe decomposition.

It is conceivable that the reaction of dienol **8a** with maleic anhydride proceeds by an intramolecular Diels–Alder (IMDA) pathway involving **11** and **12**. Although this possibility could not be definitively evaluated, we have determined that the free and protected dienols **8a** and **8b** reacted at approximately the same rate with maleic anhydride, and that the product from each, **10a** and **9**, respectively, was formed in comparable yields, and was of similar stereochemical purity. Furthermore subsequent studies have shown that IMDA reactions of esters derived from **8a** are much slower and the products more complex.[7]

We now desired to gain access to the various functional groups of **10b** and some of our results are summarized in Scheme III. DIBAL attacked the lactonic carbonyl in preference to the ester, the resulting product being the

(18) (a) Bloomfield, J. J.; Lee, S. *J. Org. Chem.*, **1967**, *32*, 3919. (b) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574. (c) Kayser, M. M.; Morand, P. *Tetrahedron Lett.* **1979**, 695. (d) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1978**, *56*, 1524.

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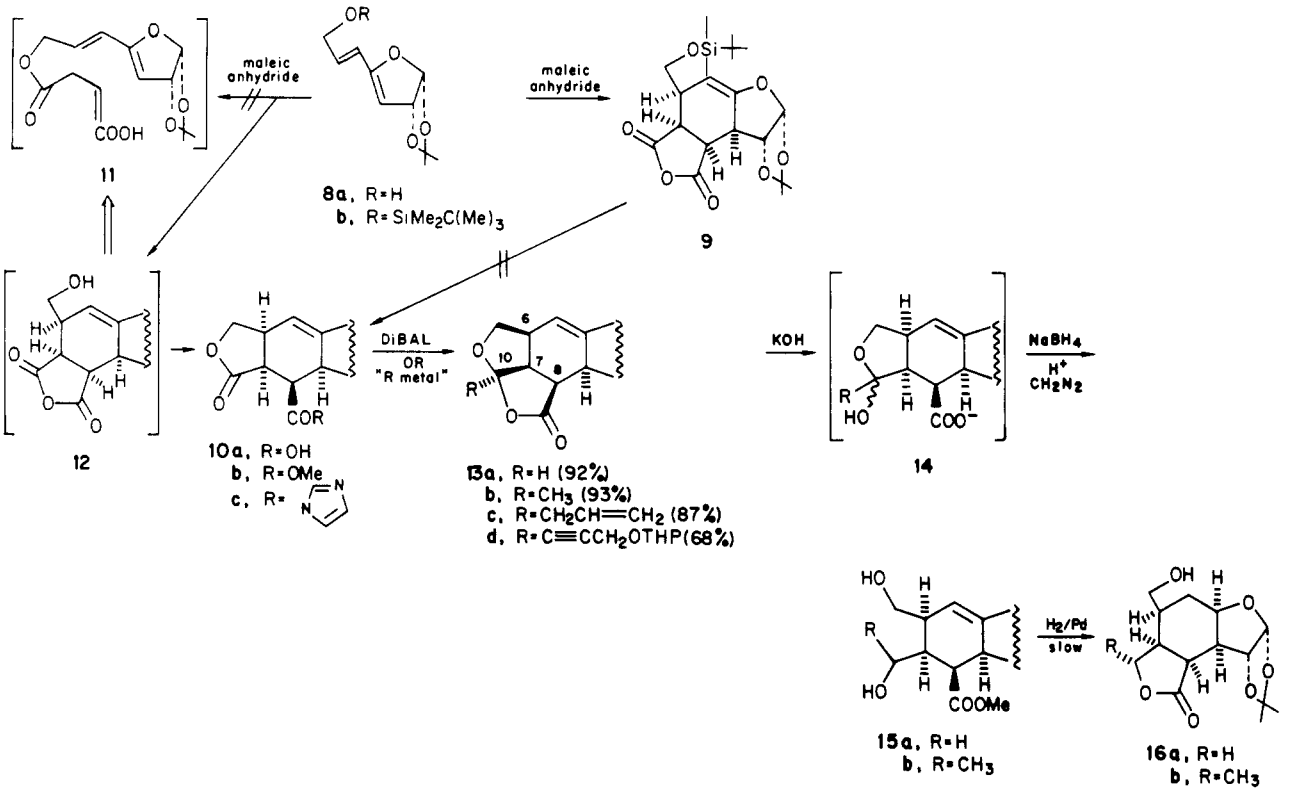
Scheme III



acetal **13a**. Reduction of the double bond of the condensed system, **13a**, proved to be much more difficult than with the simpler analogue **3**. The implication was that the additional five-membered ring at C6/C7 was responsible for the increased difficulty toward hydrogenation, and we therefore directed our efforts toward opening that ring. It transpired that sequential treatment of **13a** with warm aqueous potassium hydroxide (to give compound **14**), followed 2 h later by sodium borohydride, acidification, and finally with diazomethane, led to the ester diol **15a**, which *again showed no tendency for lactone formation.* Compound **15a** could be hydrogenated; however, extensive experimentation showed that hydrogenation of the double bond was best achieved right after the sodium borohydride reduction. Acidification followed by diazomethane esterification then led to lactone **16** directly.

It was of interest to see whether this stereoselectivity (between the carbonyl groups of **10**) would also extend to carbon nucleophiles. In the event we found that the ester **10b** reacted with methylmagnesium chloride to give the ketal lactone **13b**. Even with the imidazolide **10c**, the product with the Grignard reagent was still **13b**, there being no trace of a methyl ketone which is the expected product of the imidazolide.[20] With allylmagnesium bromide, a smooth reaction with ester **10b** occurred to give diene **13c** in 87% yield, and with the alkynyl Grignard reagent, $BrMgC{\equiv}CCH_2OTHP$, the ketal lactone **13d** was obtained in 68% yield.

As in the case of **13a**, treatment of **13b** with potassium hydroxide followed by sodium borohydride and diazomethane, gave diol ester, **15b**, which also showed no tendency to lactonize. As before, hydrogenation of the double bond was best carried out immediately after borohydride reduction whereupon the lactone **16b** was obtained in 80% yield.

In an anomaly for which we have no rationalization, it was observed that both multiple bonds in **13d**, but NOT those in **13c**, could be hydrogenated smoothly over platinum at atmospheric pressure to give the saturated system **17**. As a result, **17** was the most accessible substrate and it was chosen for detailed examination (Scheme IV).

In view of the fact that **13d** had been formed by reaction of organometallic reagents with **10b**, it was not surprising that the C9 carbonyl of **17** was completely resistant to reaction with methylmagnesium bromide. However the rings could be opened by a three-stage, one-pot process (KOH, $NaBH_4$, CH_2N_2) which afforded **18** in 93% overall yield as a 85:15 mixture of C10 epimers. The configuration at C10 in the major isomer was determined by subjecting the mixture of diols to base-catalyzed hydrolysis followed by lactone formation with acetic anhydride and pyridine. The major product was isolated, saponified, and benzoylated to afford **19c** whose ^1H NMR (400 MHz) showed $J_{7,10}$ = 8.0 Hz consistent with trans relationship of the relevant hydrogens.

We were interested to see whether a tetrasubstituted double bond, such as that in **22**, could be introduced, this feature being found in sesquiterpenes such as eriolanin and ivangulin[1]. Diol **18** could be selectively oxidized to the hydroxy aldehyde **20a** which reacted with phenylselenenyl chloride to give a complex mixture; however, in keeping with the recent observation of Meinwald,[21] reaction with *N,N*-diethylbenzeneselenamide occurred chemoselectively at the carboxaldehyde to afford the selenide **20b**. Oxidation to the selenoxide and elimination gave a single alkene in 82% yield assignable as **21a** by virtue of the vinylic hydrogen at 7.05 ppm. The absence of the tetrasubstituted analogue[22] reflects the preference for elimination toward the less substituted carbon in selenoxide eliminations, as well as the decreased torsional strain of the double bond located in **21** (as compared to **22**), as is well-known for unsaturated hydrindane systems.[22] However for an ex-

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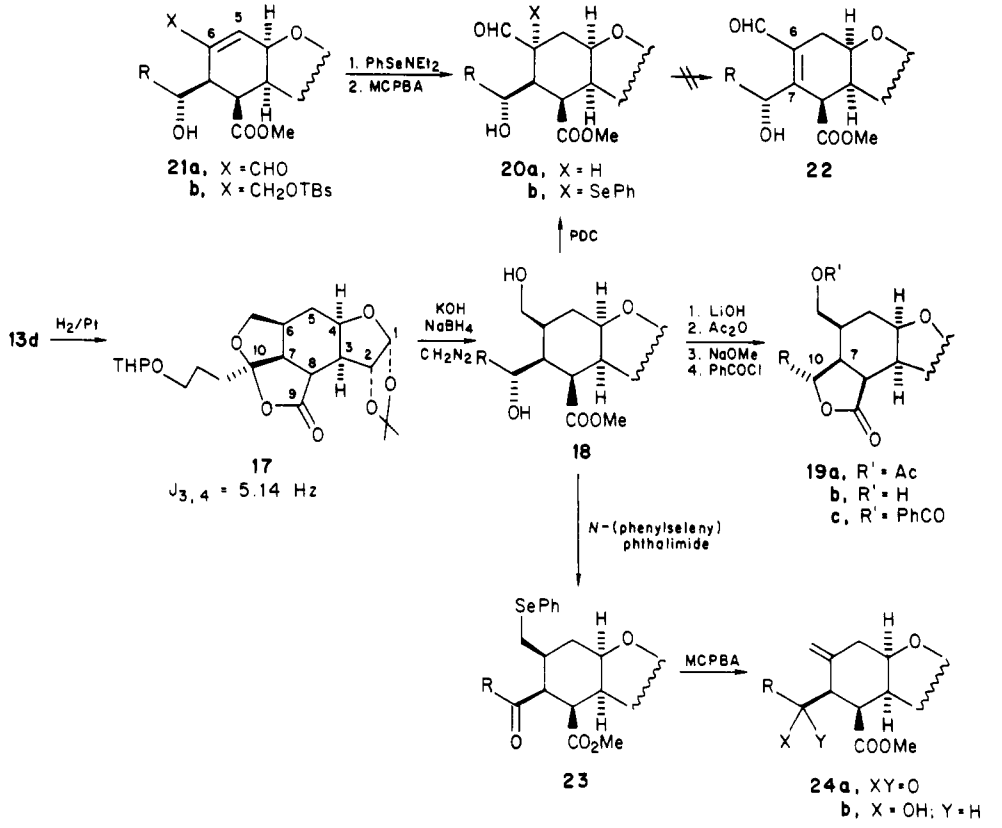
(22) Bucourt, R. In "Topics in Stereochemistry"; John Wiley and Sons: New York, 1974; Vol. 8, p 159.

Scheme IV[a]



[a] R = $CH_2CH_2CH_2OTHP$.

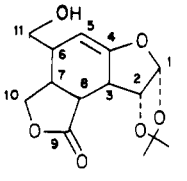
ception to this trend, see Schlessinger's synthetis of eriolanin.[23]

Further evidence for the difficulty in forming a double bond at the 6/7-position was found with compound **24a** (Scheme IV) which could not be transformed into the conjugated isomer. The formation of **24a** itself involved an anomaly. Thus treatment of **18** with *N*-(phenylseleno)phthalimide[24] brought about, not only the displacement of the primary hydroxyl as desired, but also simultaneous oxidation of the secondary hydroxyl resulting in the formation of **23**. The structure of the latter was evident since selenoxide elimination led to **24a**. It is noteworthy that sodium borohydride reduction of the latter afforded a mixture of C10 epimers of **24b** in the same 4:1 ratio as was found for the formation of **18** from **17** (vide supra).

Experimental Section

General Methods. Melting points were determined in capillary tubes in a Buchi Model SMP-20 and are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined, unless otherwise stated, in deuteriochloroform containing 1% tetramethylsilane (Me_4Si) as internal standard with either a Varian EM-360A (60 MHz), a Bruker WP-80, Varian XL 200, a Varian HR-360 spectrometer, or a 600-MHz NMR instrument. Coupling constants were obtained by measuring the spacings of spectra judged to be first order. Infrared (IR) spectra were determined with 0.1-mm sodium chloride cells and chloroform as solvent, or on sodium chloride plates. High resolution mass spectra (HRMS) were determinend on a VG 7070F. Optical rotations were determined at the sodium D line. The progress of all reactions was monitored by thin-layer chromatography (TLC) which was performed on 2.0 cm × 6.6 cm aluminum sheets precoated with silica gel 60 to a thickness of 0.25 mm. The solvent systems will be specified. The chromatograms were viewed under ultraviolet light, sprayed with concentrated sulfuric acid, and briefly heated to a temperature greater than 100 °C with a heat gun. For column chromatography, silica gel (0.063–0.20 mnm, 70–230 mesh A. S.T.M.) was used. Preparative thich-layer chromatography (PTLC) was done on glass plates (20 cm × 20 cm) coated with silica gel 60 (HF-254) to a depth of 2.0 mm.

The following solvent systems were used for TLC, PTLC, and column chromatography: A = Et_2O, B = C_6H_6/EtOAc (15:1); C = CH_2Cl_2/CH_3OH (9:1); D = EtOAc and EtOAc/petroleum ether (30–60 °C) mixtures; E = 1:4; F = 3:7; G = 3:2; H = 7:3. The numbering sequence used for reporting NMR parameters is illustrated with the structures below.



[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(4*S*,5*R*)-4,5-dicarboxycyclohexene-4,5-anhydide, 3. 3,5,6-Trideoxy-1,2-*O*-isopropylidene-α-D-*glycero*-hexa-3,5-dienofuranose, **2**[6] (2.5 g, 14.9 mmol) and maleic anhydride (1.5 g, 15.3 mmol) were dissolved in toluene (50 mL) and the solution was refluxed for 10 h. The solvent was then removed and the crude residue was chromatographed (A) to give **3** as a white solid (3.4 g, 86%) which showed the following characteristics: mp 170 °C dec; TLC R_f 0.48 (A); $[\alpha]^{20}_D$ +21.34° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 1855, 1785 (anhydride), 1685 (vinyl ether) cm^{-1}; ^1H NMR (360 MHz) δ 1.46 (s, 3, $OCCH_3$), 1.50 (s, 3, $OCCH_3$), 2.33 (dddd, 1, $J_{6',3}$ = 3.0 Hz, $J_{6',5}$ = 7.2 Hz, $J_{6,6'}$ = 15.7 Hz, $J_{6'7}$ = 1.2 Hz, H6'), 2.85 (ddd, 1, $J_{6,5}$ = 1.3 Hz, $J_{6,7}$ = 7.2 Hz, H6), 2.87 (m, 1, H3), 3.40 (ddd, 1, $J_{7,8}$ = 9.3 Hz, H7), 3.73 (dd, $J_{8,3}$ = 5.6 Hz, H8), 4.95 (ddd, 1, $J_{5,3}$ = 3.0 Hz, H5), 5.46 (dd, $J_{2,3}$ = 0.4 Hz, H_2), 5.95(d, 1, $J_{1,2}$ = 4.0 Hz, H1); MS, *m/e* 266 (M^+), 251 ($M^+ - CH_3$), 237, 208; HRMS calcd for $C_{13}H_{14}O_6$ 266.0790, found 266.0791.

(23) Roberts, M. R., Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724.

(24) Grieco, P. A.; Jan, J. Y.; Glaremon, D. A.; Nicolaou, K. C. *J. Org. Chem.* **1981**, *46*, 1215.

[1,2-*O*-Isopropylidene-α-D-*xylo*-pentofurano]-[3,4-*f*]-(4*S*,5*R*)-4,5-dicarboxycyclohexane-4,5-anhydride, 4. The above described olefin **3** (150 mg, 0.56 mmol), was dissolved in anhydrous diethyl ether (200 mL) and hydrogenated over palladium (5% on barium sulfate) under atmosphere pressure until hydrogen uptake ceased. Filtration through Celite followed by evaporation gave crystalline **4** (124 mg, 83%): mp 159 °C; TLC R_f 0.38 (A); $[\alpha]^{20}_D$ +10.27° (*c* 1.46, $CHCl_3$); IR ($CHCl_3$) 1865, 1785 (anhydride) cm^{-1}; ^1H NMR (80 MHz) δ 1.35 (s, 3, $OCCH_3$), 1.51 (s, 3, $OCCH_3$), 1.59–2.30 (m, 5, 2 H5, 2 H6), 2.41 (dd, 1, $J_{3,4}$ = 5.0 Hz, $J_{3,8}$ = 6.8 Hz, H3), 3.09–3.50 (m, 2, H7, H8), 4.47 (dt, 1, $J_{4,5}$ = 5.0 Hz, $J_{4,5'}$ = 6.7 Hz, H4), 5.22 (d, 1, $J_{2,1}$ = 3.9 Hz, H2), 5.92 (d, 1, H1). Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.43. Found: C, 58.10; H, 6.00.

[1,2-*O*-Isopropylidene-α-D-*xylo*-pentofurano]-[3,4-*f*]-(4*S*,5*R*)-5-carboxy-4-(hydroxymethyl)cyclohexane 4,5-Lactone, 7. To a solution of sodium borohydride (10 mg) in dry tetrahydrofuran (100 mL) at 0 °C, the anhydride **4** (50 mg, 0.19 mmole in dry tetrahydrofuran (2 mL) was added. The reaction solution was allowed to warm up to room temperature and stirred until no more starting material was left (TLC). Dilute hydrochloric acid (1%) was added slowly to make the solution to slightly acidic (pH ~4) and stirring was continued for another 0.5 h before the mixture was poured into water (100 mL). The aqueous layer was extracted by methylene chloride (4 × 50 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and condensed to give **6** (41 mg, 82%). Lactonization to **7** in chloroform occurred slowly (~ one week). Compound **7** showed the following characteristics: TLC R_f 0.37 (A); $[\alpha]^{20}_D$ +1.96° (*c* 0.92, $CHCl_3$); IR ($CHCl_3$) 1775 (lactone) cm^{-1}; ^1H NMR (360 MHz) δ 1.36 (s, 3, $OCCH_3$), 1.51 (s, 3, $OCCH_3$), 1.55–1.65 (m, 3, H5, 2 H6), 2.14 (m, 1, H5′), 2.36 (dd, 1, $J_{3,4}$ = 4.0 Hz, $J_{3,8}$ = 8.6 Hz, H3), 2.40 (m, 1, H7), 2.77 (dd, 1, $J_{7,8}$ = 6.4 Hz, H8), 4.00 (d, 1, $J_{7,10}$ = 5.0 Hz, H10), 4.20 (dd, 1, $J_{10,10'}$ = 9.0 Hz, H10′), 4.29 (dd, 1, $J_{4,5}$ = $J_{4,5'}$ = 4.0 Hz, H4), 5.42 (d, 1, $J_{1,2}$ = 4.0 Hz, H2), 5.91 (d, 1, H1); MS, *m/e* 254 (M^+), 239 ($M^+ - CH_3$).

[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*S*,4*S*,5*R*)-3-[(*tert*-butyldimethylsiloxy)methyl]-4,5-dicarboxycyclohexene-4,5-anhydride, 9. The alcohol **8a**[6] (0.75 g, 3.8 mmol) was dissolved in dry dimethylformamide (25 mL), and imidazole (0.44 g, 6.47 mmol) and *tert*-butyldimethylsilyl chloride (0.75 g, 4.95 mmol) were added. The reaction was complete in 15 min and the mixture was processed in the usual way. A portion of the resulting diene, **8b**, (0.75 g, 2.8 mmol) and maleic anhydride (0.25 g, 2.5 mmol) were dissolved in dry toluene (25 mL). The solution was refluxed for 2 h by which time the reaction was shown to be complete by TLC (B). The solvent was removed and the crude product was chromatographed (B) to give pure **9** (0.86 g, 86%): TLC R_f 0.39 (B); $[\alpha]^{20}_D$ +25.2° (*c* 11.1, $CHCl_3$); IR ($CHCl_3$) 1857, 1780 (anhydride), 1680 (vinyl ether) cm^{-1}; ^1H NMR (60 MHz) δ 0.13 (s, 6, $Si(CH_3)_2$), 0.95 (s, 9, $SiC(CH_3)_3$, 1.47 (s, 3, $OCCH_3$), 1.51 (s, 3, $OCCH_3$), 2.45–2.70 (m, 1, H6), 2.87 (bd, 1, $J_{3,8}$ = 5.0 Hz, H3), 3.39–4.20 (m, 4, H7, H8, 2 H11), 4.70 (m, 1, H5), 5.40 (d, 1, $J_{1,2}$ = 4.0 Hz, H2), 5.94 (d, 1, H1); MS, *m/e* 410 (M^+).

Methyl [1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*S*,4*S*,5*R*)-4-carboxy-3-(hydroxymethyl)cyclohexene-5-carboxylate 3,4-Lactone, 10b. A solution containing 7-*O*-(*tert*-butyldimethylsilyl)-3,5,6-trideoxy-3,5(*E*)-dieno-1,2-*O*-isopropylidene-α-D-*glycero*-heptofuanose, **8a**, (5 g, 25.3 mmol) and maleic anhydride (2.5 g, 25.5 mmol) in dry diethyl ether (250 mL) was stirred at room temperature for 30 h. The solvent was removed under reduced pressure to give crude **10a**. The resultant residue was redissolved in dry tetrahydrofuran (250 mL), excess diazomethane was added, and the solution was stirred until it stopped bubbling upon the addition of more diazomethane. The excess diazomethane was then destroyed by the careful addition of glacial acetic acid. The residue obtained after removing the solvent was recrystallized from methylene chloride–petroleum ether (30–60 °C) to give the ester **10b** (6.7 g, 85%). Compound **10b** showed the following characteristics: mp 180.5–182 °C; TLC R_f 0.53 (A), 0.64 (G); $[\alpha]^{20}_D$ +18.25° (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 1775 (lactone), 1740 (ester), 1698 (vinyl ether) cm^{-1}; ^1H NMR (600 MHz) δ 1.44 (s, 3, $OCCH_3$), 1.51 (s, 3, $OCCH_3$), 2.96 (dddd, 1, $J_{2,3}$ = 2.1 $H_{3,5}$ = $J_{3,6}$ = 2.0 Hz, $J_{3,8}$ = 3.9 Hz, H3), 2.99 (dd, 1, $J_{6,7}$ = 10.4 Hz, $J_{7,8}$ = 5.7 Hz, H7), 3.38 (m, 1, $J_{6,5}$ = 2.6 Hz, $J_{6,11}$ = 9.0 Hz, $J_{6,11'}$ = 10.6 Hz, H6), 3.64 (dd, 1, H8), 3.70 (s, 3, CO_2CH_3), 3.72 (dd, 1, $J_{11,11'}$ = 9.0 Hz, H11′), 4.51 (t, 1, H11), 4.78 (dt, 1, $J_{2,5}$ = 0.77 Hz, H5), 5.13 (ddd, 1, $J_{1,2}$ = 4.44 Hz, H2), 6.05 (d, 1, H1); MS, *m/e* 310 (M^+), 295 ($M^+ - CH_3$). Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.81. Found: C, 57.73; H, 5.99.

[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*R*,9*S*)-5-carboxy-3-hydroxy-1,3,4,5,6,9-hexahydroisobenzofuran 5,3-Lactone, 13a. To a solution containing the ester **10b** (1.5 g, 5.4 mmol) in dry tetrahydrofuran (250 mL) cooled to −70 °C by a dry ice–acetone bath, diisobutylaluminum hydride was added slowly, under argon atmosphere, and the reaction was followed closely by TLC (H). After all the starting material had reacted, saturated ammonium chloride solution (2 mL) was added. After stirring for 10 min, anhydrous sodium sulfate was added and the solution was stirred further for 1 h and then filtered. The filtrate, after concentration gave **13a** (1.25 g, 92%). Compound **13a** showed the following characteristics: mp 173–173.5 °C; TLC R_f 0.32 (H); $[\alpha]^{20}_D$ +45.01° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 1770 (lactone), 1700 (vinyl ether) cm^{-1}; ^1H NMR (60 MHz) δ 1.42 (s, 3, $OCCH_3$), 1.49 (s, 3, $OCCH_3$), 2.90–3.93 (m, 5, H3, H6, H7, H8, H11), 4.40 (t, 1, $J_{11,11'}$ = $J_{11',6}$ = 8.0 Hz, H11′), 4.82 (bs, 1, H5), 5.48 (dd, 1, $J_{1,2}$ = 4.2 Hz, $J_{2,3}$ = 2.0 Hz, H2), 5.97 (d, 1, H1), 6.01 (d, 1, $J_{10,7}$ = 4.0 Hz, H10); MS, *m/e* 280 (M^+), 265 ($M^+ - CH_3OH$). Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.70. Found: C, 60.03; H, 5.87.

Methyl [1,2-*O*-Isopropylidene-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*S*)-3,4-bis(hydroxymethyl)cyclohexene-5-carboxylate, 15a. Compound **13a** (326 mg, 1.16 mmol) was dissolved in methanol. Water (5 mL) and potassium hydroxide (6 N, 2 mL) were added. The reaction mixture was warmed to 60 °C for 2 h by which time no more starting material was left as evidenced by TLC. The solution was then cooled to 0 °C and sodium borohydride (80 mg, 2.1 mmol) was added. After stirring for 15 min, enough glacial acetic acid was added to destroy the excess sodium borohydride. The solution was made slightly acidic by 1% hydrochloric acid. Excess diazomethane was added until the esterification was complete (TLC). The solution was poured into water (15 mL) and extracted by methylene chloride (4 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporation of the solvent gave **15a** (347 mg, 95%). Compound **15a** showed the following characteristics: TLC R_f 0.33 (C); IR ($CHCl_3$) 3400 (hydroxyl), 1725 (ester) cm^{-1}; ^1H NMR (60 MHz) δ 1.40 (s, 3, $OCCH_3$), 1.50 (s, 3, $OCCH_3$), 1.80–3.65 (m, 10, H3, H6, H7, H8, 2 H10, 2 H11, 2 OH), 3.64 (s, 3, CO_2CH_3), 4.63 (t, 1, $J_{3,5}$ = $J_{6,5}$ = 2.8 Hz, H5), 4.88 (dd, 1, $J_{1,2}$ = 4.7 Hz, $J_{2,3}$ = 2.8 Hz, H2), 5.97 (d, 1, H1).

[1,2-*O*-Isopropylidene-α-D-*xylo*-pentofurano]-[3,4-*f*]-(3*R*,4*S*,5*S*)-5-carboxy-3,4-bis(hydroxymethyl)cyclohexane 4,5-Lactone, 16a. A solution containing **13a** (430 mg, 1.54 mmol), methanol (30 mL), water (5 mL), and potassium hydroxide (6 N, 4 mL), was warmed to 60 °C for 2 h. It was then cooled to 0 °C and sodium borohydride (110 mg, 2.9 mmol) was added. After stirring for 15 min at 0 °C, enough glacial acetic acid was added to destroy the excess sodium borohydride. The solution was brought to pH ~11 by the addition of dilute potassium hydroxide solution. The solution was transferred to a hydrogenation bottle, 0.5 g of 5% palladium was added and the reaction mixture was placed under 60 psi of hydrogen for four days. The solution was then suction filtered through Celite. The filtrate was condensed, and the residue was redissolved in methanol (20 mL) and made slightly acidic by 1% methanolic hydrochloric acid. Diazomethane was added to excess and after 10 min, the excess was then destroyed by glacial acetic acid. After removal of the solvent, the residue was extracted with methylene chloride. Evaporation of the methylene chloride yielded **16a** (344 mg, 80%) as a syrup. Compound **16a** showed the following characteristics: TLC R_f 0.57 (C); IR ($CHCl_3$) 3460 (hydroxyl), 1765 (lactone) cm^{-1}; ^1H NMR (60 MHz) δ 1.32 (s, 3, $OCCH_3$), 1.50 (s, 3, $OCCH_3$), 1.75–2.30 (m, 6, H3, 2H5, H6, H7, H8), 2.75 (bs, 2, 2 OH), 3.33–3.72 (m, 2, 2 H11), 4.00 (t, 1, $J_{7,10}$ = $J_{10,10'}$ = 9 Hz, H10), 4.40–4.75 (m, 2, H4, H10′), 5.00 (d, 1, $J_{1,2}$ = 4.0 Hz, H2), 5.87 (d, 1, H1).

[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*S*,4*S*,5*R*)-4-carboxy-3-(hydroxymethyl)-5-(1-imidazolylcarbonyl)cyclohexene 3,4-Lactone, 10c. The acid **10a** (200 mg)[1] was dissolved in dry tetrahydrofuran (50 mL) and carbonylbis(imidazole) (0.32 g, 2 mmol) was added. The reaction mixture

was stirred at room temperature for 5 h. The solvent was then removed and the crude product was purified by silica gel chromatography (G). The imidazolide **10c** (0.28 g, 81%) thus obtained showed the following characteristics: mp 141–141.5 °C; TLC R_f 0.23 (D), 0.58 (C); $[\alpha]^{20}_D$ +62.55° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 1755 (lactone), 1728 (amide) cm^{-1}; ^1H NMR (60 MHz) δ 1.37 (s, 3, $OCCH_3$), 1.52 (s, 3, $OCCH_3$), 3.01–3.80 (m, 3, H3, H6, H7), 3.90–4.64 (m, 4, H2, H8, 2 H11), 4.95 (t, 1, $J_{3,5} = J_{5,6} = 2.0$ Hz, H5), 5.73 (d, 1, $J_{1,2} = 4.8$ Hz, H1), 7.10–8.21 (m, 3, CO-Im); mass spectrum, *m/e* 346 (M^+), 331 ($M^+ - CH_3$), 316 ($M^+ - nCH_3)_2$). Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.20; N, 8.09. Found: C, 58.88; H, 5.18; N, 7.72.

[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*R*,9*S*)-5-carboxy-3-methyl-3-hydroxy-1,3,4,5,6,9-hexahydroisobenzofuran 5,3-Lactone, 13b. (a) The imidazolide **10c** (50 mg, 0.14 mmol) was dissolved in dry tetrahydrofuran (10 mL) and the solution was cooled to −50 °C and placed under argon atmosphere. Methylmagnesium chloride was added slowly and the reaction was followed by TLC (G). After the reaction was complete, the mixture was poured into water (10 mL) and extracted with methylene chloride (4 × 30 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The removal of solvent yielded **13b** (39.5 mg, 93%). Compound **13b** showed the following characteristics: mp 172 °C; TLC R_f 0.60 (G); $[\alpha]^{20}_D$ 180.61° (*c* 0.327 $CHCl_3$); IR ($CHCl_3$) 1770 (lactone), 1700 (vinyl ether) cm^{-1}; ^1H NMR (360 MHz) δ 1.43 (s, 3, $OCCH_3$), 1.52 (s, 3, $OCCH_3$), 1.69 (s, 3, 3 H12), 2.92 (dd, 1, $J_{6,7} = 10.0$ Hz, $J_{7,8} = 7.8$ Hz, H7), 2.99 (m, 1, H3), 3.11 (m, 1, H6), 3.45 (dd, 1, $J_{3,8} = 4.7$ Hz, H8), 3.61 (t, 1, $J_{11,11'} = J_{6,11} = 8.4$ Hz, H11), 4.34 (t, 1, $J_{6,11'} = 8.4$ Hz, H11′), 4.78 (t, 1, $J_{5,6} = J_{5,3} = 2.1$ Hz, H5), 5.45 (dd, 1, $J_{2,3} = 2.4$ Hz, $J_{1,2} = 4.3$ Hz, H2), 5.94 (d, 1, H1); MS, *m/e* 294 (M^+), 279 ($M^+ - CH_3$). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.20; H, 6.22. Found: C, 60.75; H, 6.22.

(b) When ester **10b** was treated under the same conditions described in part a for the imidazolide **10c**, compound **13b** was obtained in 91% yield.

[1,2-*O*-Isopropylidene-β-L-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*R*,9*S*)-3-allyl-5-carboxy-3-hydroxy-1,3,4,5,6,9-hexahydroisobenzofuran 5,3-Lactone, 13c. A solution of ester **10b** (230 mg, 0.74 mmol) in dry tetrahydrofuran (25 mL) was cooled to −50 °C under argon atmosphere. Allylmagnesium bromide in diethyl ether (prepared from allyl bromide and magnesium in diethyl ether at room temperature) was added and the reaction was followed closely by TLC (B). When the reaction was complete, the mixture was poured into water (25 mL) and extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with brine, and dried over anhydrous sodium sulfate. The solvent was then removed to give **13c** (206 mg, 87%) as a white solid. Compound **13c** showed the following characteristics: mp 167 °C; TLC R_f 0.61 (B); $[\alpha]^{20}_D$ +155.7° (*c* 0.893, $CHCl_3$); IR ($CHCl_3$); 1765 (lactone), 1700 (vinyl ether) cm^{-1}; ^1H NMR (60 MHz) δ 1.41 (s, 3, $OCCH_3$), 1.49 (s, 3, $OCCH_3$), 2.68 (d, 2, $J_{12,13} = 6.2$ Hz, 2 H12), 2.80–4.05 (m, 5, H3, H7, H8, H11), 4.18–4.50 (m, 1, H11), 4.81 (bs, 1, H5), 5.05–5.82 (m, 4, H2, H13, 2 H14), 5.88 (d, 1, $J_{1,2} = 4.2$ Hz, H1); mass spectrum, *m/e* 320 (M^+), 305 ($M^+ - CH_3$). Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.25. Found: C, 63.46; H, 6.44.

Methyl [1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*S*,1′*R*)-4-(1′-hydroxyethyl)-3-(hydroxymethyl)cyclohexene-5-carboxylate, 15b. Compound **13b** (450 mg, 1.53 mmol) was dissolved in methanol. Water (5 mL) and potassium hydroxide (6 N, 2 mL) were added. The reaction mixture was warmed to 60 °C for 2 h by which time no more starting material was left as evidenced by TLC. The solution was then cooled to 0 °C and sodium borohydride (80 mg, 2.1 mmol) was added. After stirring for 15 min, enough glacial acetic acid was added to destroy the excess sodium borohydride. The solution was made slightly acidic by 1% hydrochloric acid. Excess diazomethane was added until the esterification was complete (TLC). The solution was poured into water (15 mL) and extracted by methylene chloride (4 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporation of the solvent gave **15b** (472 mg, 94%). Compound **15b** showed the following characteristics: TLC R_f 0.57 (C); $[\alpha]^{20}_D$ +3.57° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) 3650 (hydroxyl groups), 1725 (ester), 1700 (vinyl ether) cm^{-1}; ^1H NMR (60 MHz) δ 1.28 (d, 3, $J_{10,11} = 7.5$ Hz, 3 H11), 1.41 (s, 3, $OCCH_3$), 1.50 (s, 3, $OCCH_3$), 1.90–2.41 (bs, 5, H3, H7, H8, 2-OH), 2.71–2.92 (m, 1, H6), 3.35 (d, 2, $J_{6,12} = 6.0$ Hz, 2 H12), 3.50–3.70 (m, 1, H10), 3.63 (s, 3, CO_2CH_3), 4.62 (t, 1, $J_{3,5} = J_{5,6} = 1.6$ Hz, H5), 4.83 (dd, $J_{1,2} = 4.2$ Hz, $J_{2,3} = 2.2$ Hz, H2), 5.95 (d, 1, H1); MS, *m/e* 328 (M^+).

[1,2-*O*-Isopropylidene-α-D-*xylo*-pentofurano]-[3,4-*f*]-(3*R*,4*S*,5*S*,1′*S*)-5-carboxy-4-(1′-hydroxyethyl)-3-(hydroxymethyl)cyclohexane 4,5-Lactone, 16b. A solution containing **13b** (500 mg, 1.7 mmol), methanol (30 mL), water (5 mL), and potassium hydroxide (6 N, 4 mL) was warmed to 60 °C for 2 h. It was then cooled to 0 °C and sodium borohydride (110 mg, 2.9 mmol) was added. After stirring for 15 min at 0 °C, enough glacial acetic acid was added to destroy the excess sodium borohydride. The solution was brought to pH ~11 by the addition of dilute potassium hydroxide solution. The solution was transferred to a hydrogenation bottle, 0.5 g of 5% palladium on carbon was added, and the reaction mixture was placed under 60 psi of hydrogen for 4 days. The solution was then suction filtered through Celite. The filtrate was condensed, and the residue was redissolved in methanol (20 mL) and made slightly acidic by 1% methanolic hydrochloric acid. Diazomethane was added to excess and after 10 min, the excess was then destroyed by glacial acetic acid. After removal of the solvent, the residue was extracted with methylene chloride. Evaporation of the methylene chloride gave **16b** (402 mg, 80%) as a syrup. Compound **16b** showed the following characteristics: TLC R_f 0.60 (B); $[\alpha]^{20}_D$ −19.5° (*c* 3.95, $CHCl_3$); IR ($CHCl_3$) 3460 (hydroxyl), 1765 (lactone) cm^{-1}; ^1H NMR (600 MHz) δ 1.32 (s, 3, $OCCH_3$), 1.47 (d, 3, $J_{10,12} = 6.1$ Hz, 3 H12), 1.51 (s, 3, $OCCH_3$), 1.63 (ddd, 1, $J_{4,5} = 5.3$ Hz, $_{5,6} = 8.1$ Hz, $J_{5,5'} = 1.42$ Hz, H5), 1.65 (m, 1, H6), 2.08 (ddd, 1, $J_{4,5'} = 6.7$ Hz, $J_{5',6} = 4.2$ Hz, H5′), 2.24–2.32 (m, 3, H3, H7, H8), 2.80 (bs, 1, OH), 3.54–3.60 (m, 1, H11), 3.65 (dd, 1, $J_{6,11} = 4.6$ Hz, $J_{11,11'} = 11.0$ Hz, H11′, 4.42 (dq, 1, $J_{7,10} = 8.9$ Hz, $J_{10,12} = 6.0$ Hz, H10), 4.55 (ddd, 1, $J_{3,4} = 3.9$ Hz, $J_{4,5} = 5.3$ Hz, $J_{4,5'} = 6.7$ Hz, H4), 4.98 (d, 1, $J_{1,2} = 3.7$ Hz, H2), 5.88 (d, 1, H1); MS, *m/e* 298 (M^+), 297 ($M^+ - 1$), 283 ($M^+ - CH_3$), 268 ($M^+ - C_2H_6$), 265 ($M^+ - CH_3 - H_2O$), 253 ($M^+ - (CH_3)_3$).

[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*S*,4*S*,5*R*,9*S*)-3-[3-[(tetrahydropyranyl)oxy]prop-1-ynyl]-5-carboxy-3-hydroxy-1,3,4,5,6,9-hexahydroisobenzofuran 5,3-Lactone, 13d. Ethylmagnesium bromide (20 mmol) was prepared in diethyl ether (30 mL) from magnesium turnings (0.46 g) and ethyl bromide (ca. 15 mL) added until the metal had dissolved. The solution was refluxed for 20 min and then stirred at room temperature. Propargyl alcohol–THP ether (2.7 mL) was added dropwise in THF (10 mL) and after stirring briefly the reaction was cooled to 0 °C. A solution of the lactone ester **10b** (1.0 g, 3.2 mmol) in THF (ca. 30 mL) was added dropwise with stirring. Additional THF (10–20 mL) was added and the reaction mixture was kept overnight in a freezer (0–2 °C). TLC (F) showed that the starting material was consumed and the mixture was poured onto ice–ammonium chloride, and extracted with ether. The combined ether extracts (300 mL) were washed with water and brine, and dried over sodium sulfate. Evaporation left a brown syrup which was purified by flash chromatography (F) to give 0.92 g (68%) of crystalline product, mp 105–108 °C. Two crystallizations from chloroform–petroleum ether gave analytically pure **13d**: mp 118–119 °C; $[\alpha]^{27}_D$ +124.3 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3050 cm^{-1}, 2950, 2250, 1775, 1710, 1450, 1440, 1385, 1375; ^1H NMR ($CDCl_3$) 200 MHz δ 5.95 (d, 1, H-1, $J_{1,2} = 4.5$ Hz), 5.44 (dd, 1, H-2, $J_{2,3} = 2.25$ Hz), 4.76 (m, 2, H5, THP-H 1′, $J_{3,5} = 2$ Hz), 4.44 (t, 1, H11 or H11′, $J_{11,11'} = 9$ Hz), 4.35 (s, 1, H14), 4.31 (s, 1, H14), 3.91 (m, 4, H11′, H8, THP group), 3.32 (dd, 1, H7, $J_{7,8} = 8$ Hz), 3.16 (m, 1, H-6, $J_{5,6} = 3$ Hz, $J_{6,7} = 10.4$ Hz, $J_{6,11} = 7$ Hz), 2.97 (dd, 1, H3, $J_{3,8} = 4.5$ Hz), 1.81–1.51 (m, 6, THP), 1.48 (s, 3, CH_3), 1.42 (s, 3, CH_3). Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 62.87; H, 6.20.

[1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*R*,9*S*)-3-[3-[(tetrahydropyranyl)oxy]propyl]-5-carboxy-3-hydroxy-1,3,4,5,6,9-hexahydroisobenzofuran 5,3-Lactone, 17. A mixture of ketal lactone **13d** (0.5 g, 1.2 mmol), platinum oxide (25 mg), absolute methanol (20 mL), and THF (6 mL) was hydrogenated at atmospheric pressure (balloon) for 5 h. TLC (G) showed that the major product was a low running spot which charred only after considerable heating. A side product of higher R_f was also observed. The catalyst was removed by

filtration through florisil and the solvent was evaporated to afford crystalline product which was purified by flash chromatography (G) to obtain 390 mg (77%) of the desired product, **17**, as white crystals, mp 139–140 °C. Crystallization from chloroform–petroleum ether gave pure compound: mp 140.5–141.5 °C; $[\alpha]^{27}_D$ +4.52° (*c*, 1.0, $CHCl_3$); IR ($CHCl_3$) 3100 cm^{-1} 2970, 1770, 1385, 1375; ^1H NMR 200 MHz ($CDCl_3$) δ 5.92 (d, 1, H1, $J_{1,2}$ = 4 Hz), 5.33 (d, 1, H2, $J_{2,3}$ = 0 Hz), 4.56 (m, 1, THP-H 1′), 4.45 (dd, 1, H4, $J_{4,5}$ = 6 Hz), 4.04 (dd, 1, H11 or H11′), 3.92–3.72 (m, 3, H11 or H11′, THP), 3.56–3.4 (m, 2, THP), 3.02 (dd, H8, $J_{3,8}$ = 6 Hz, $J_{7,8}$ = 8.5 Hz), 2.86 (t, 1 H7, $J_{6,7}$ = 8.5 Hz), 2.38 (m, 1, H3), 2.34 (m, 1, H6, $J_{6,7}$ = 10 Hz, $J_{6,11'}$ = 6 Hz), 2.2–1.9 (m, 2, H-5, H-5′), 1.85–1.50 (m), 1.5 (s, 3, CH_3), 1.36 (s, 3, CH_3). From the 600 MHz spectrum, $J_{3,4}$ = 5.14 Hz. Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.59. Found: C, 62.30; H, 7.74.

Methyl [1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,1′*R*)-4-[4-[(tetrahydropyranyl)oxy]-1-hydroxybutyl]-3-(hydroxymethyl)cyclohexane-5-carboxylate, 18. A mixture of ketal lactone **17** (0.51 g, 1.2 mmol), potassium hydroxide (0.34 g, 5 equiv), methanol (35 mL), and water (7 mL) was refluxed on a steam bath for 1.5 h and followed by TLC (G). The solution was then cooled to 0 °C and sodium borohydride (90 mg, 2 equiv) was added. The reaction was stirred 1.5 h and then carefully neutralized with methanolic HCl (saturated solution) to pH 7. Removal of the solvent left a solid which was dried under vacuum and then suspended in tetrahydrofuran. Excess diazomethane in diethyl ether was added at 0 °C, after 1 h (TLC) a few drops of glacial acetic acid were added, and the solvent was removed. The residue was extracted thoroughly with dichloromethane to give a yellow solution which was washed with dilute sodium bicarbonate solution, water, and brine. Drying over sodium sulfate and evaporation left 0.514 g (93%) of a pale yellow syrup containing only traces of impurities. Purification of flash chromatography (G) gave **18** as a colorless syrup: $[\alpha]^{29}_D$ +6.5° (*c* 1.2, $CHCl_3$); IR (thin film) 3450 cm^{-1}, 3020, 2960, 1740, 1460, 1390, 1380; ^1H NMR 60 MHz ($CDCl_3$) δ 5.72 (m, 1), 5.6 (d, 1, H1, $J_{1,2}$ = 4 Hz), 4.97 (d, 1, H2), 4.65–4.4 (m, 3), 3.73 (s, 3, OCH_3), 3.9–3.3 (m, 7), 3.05–2.62 (m, 4), 2.25–1.5 (m, 12), 1.48 (s, 3, CH_3), 1.31 (s, 3, CH_3). Anal. Calcd for $C_{23}H_{38}O_9$: C, 60.24; H, 8.35. Found: C, 59.96; H, 8.09.

Methyl [1,2-*O*-Isopropylidene-β-L-*threo*-tetrofurano]-[3,4-*f*]-(3*R*,4*S*,5*S*,1′*R*)-4-[1-hydroxy-4-[(tetrahydropyranyl)oxy]butyl]-3-formylcyclohexane-5-carboxylate, 20a. To a mixture of diol **18** (160 mg, 0.35 mmol), Celite (50 mg), and dry dichloromethane (10 mL) at 0 °C was added pyridinium dichromate (PDC) (130 mg, 1 equiv). The reaction was allowed to warm to room temperature and was stirred overnight. Additional PDC was added and oxidation was complete after a total of 48 h. The mixture was diluted with diethyl ether (30 mL) and filtered through a pad of florisil and the filtrate evaporated to leave 159 mg of aldehyde **20a** as a colorless syrup, sufficiently pure for the selenation reaction. The product could be purified by column chromatography (30% ethyl acetate–petroleum ether) to give pure aldehyde (recovery = 50–60%): $[\alpha]^{27}_D$ −10.0° (*c*, 1.0 $CHCl_3$); IR (thin film) 3500 cm^{-1}, 3000–2900, 2710, 1730, 1500, 1440, 1370, 1360; ^1H NMR 60 MHz ($CDCl_3$) δ 9.5 (s, 1, CHO), 5.48 (d, 1, H1), 4.8–4.2 (m, 2), 4.45 (m, 1, THP-H1′), 4.32 (d, 1, H2), 4.2–3.1 (m, 5), 3.65 (s, 3, OCH_3), 2.90–2.55 (m, 3), 2.4–2.2 (m, 2), 1.90–1.42 (m, 12), 1.49 (s, 3, CH_3), 1.22 (s, 3, CH_3); HRMS calcd for $C_{23}H_{36}O_9$ 456.2359, found 456.2341.

Compound 21b. To a solution of aldehyde **20a** (80 mg) in dry dichloromethane (3 mL) at room temperature was added *N,N*-diethylbenzeneselenamide[21] (40 mg, 1 equiv) and the solution was stirred for 2 h. Another equivalent of $PhSeNEt_2$ was added and the reaction was stirred overnight. Flash chromatography (B) on silica afforded 50 mg (44%) of selenide **20b** which was used immediately in the oxidation step. To the selenide (50 mg) in dry dichloromethane at −70 °C was added *m*-chloroperoxybenzoic acid (25 mg, 1.5 equiv assuming 80% strength). After stirring 1.5 h, TLC (B) showed that the reaction was complete. The solvent was evaporated and the residue purified by column chromatography (A) to give 30 mg (82%) of α,β-unsaturated aldehyde, **21a**. ^1H NMR 60 MHz ($CDCl_3$) δ 9.68 (s, 1 H, CHO). The material was dissolved in dry ether (8 mL) at −70 °C and added to lithium aluminum hydride (2.5 mg, 1 equiv). Reduction was complete in ~1 h after which sodium sulfate hydrate was added and the reaction was allowed to warm to room temperature, filtered, and dried over sodium sulfate. Evaporation of the solvent left 23 mg of syrup which was dried under vacuum and treated with *tert*-butyldimethylsilyl chloride (10 mg, 1.2 equiv), in dichloromethane and trimethylamine (0.01 mL). (Dimethylamino)pyridine was added and reaction was complete after stirring overnight. The reaction was diluted with ether, extracted with water and brine, and dried over sodium sulfate. Evaporation of the solvent left 30 mg (80%) of the silyl ether **21b**: $[\alpha]^{29}_D$ +8.6 (*c* 1.2, $CHCl_3$); ^1H NMR 60 MHz ($CDCl_3$) 6.0 (m, 1, vinyl H), 5.75 (d, 1, H1), 5.98 (d, 1, H2), 4.70–4.45 (m, 3), 4.15 (m, 2, allylic CH_2OR), 3.9–2.0 (m, 4), 3.57 (s, 3, OCH_3), 3.1–2.5 (m, 4,), 2.0–1.5 (m, 10), 1.45 (s, 3, CH_3), 1.24 (s, 3, CH_3), 0.9 (s, 9), 0.0 (s, 6); HRMS calcd for $C_{29}H_{49}SiO_9$ (M^{+1}) 569.3145, found 569.3053.

Ketone 24a. To a solution of diol **18** (140 mg, 0.306 mmol) in dry THF (15 mL) at 0 °C was added *N*-(phenylseleno)-phthalimide[24] (200 mg, 2.2 eq) followed by tri-*n*-butylphosphine (0.16 mL, 2.2 equiv). After 4 h, a few drops of methanol were added and the mixture was evaporated. Column chromatography (B) afforded 120 mg (65%) of the keto selenide **23** which, without further purification, was treated at −70 °C in dichloromethane with *m*-chloroperoxybenzoic acid (54 mg, 1.2 equiv). Oxidation was complete in 1.5 h, TLC (B) showed only baseline material, and the reaction was warmed to −25 °C. Diisopropylamine (0.06 mL, 2 equiv), was added and the reaction was stirred overnight at room temperature. Solvent was evaporated and the residue was purified by column chromatography (A) to give 60 mg of olefin **24a** (44% from 18): $[\alpha]^{28}_D$ +46.0° (*c* 1.4, $CHCl_3$); IR (thin film) 3000–2820 cm^{-1}, 1740, 1710, 1640, 1440, 1380, 1360; ^1H NMR 200 MHz ($CDCl_3$) δ 5.78 (d, 1, H1), 5.09 (broad s, 1, vinyl H), 5.05 (broad s, 1, vinyl H), 4.65 (dd, 1, H2), 4.52 (m, 2, H4, THP, H1′), 3.68 (s, 3, OCH_3), 3.90–3.63 (m, 3, H13, H8), 3.53–3.30 (m, 3, H9, THP), 2.95–2.55 (m, 3 H), 2.48–2.20 (m, 2, H5, H5′), 1.9–1.5 (m, 8), 1.5 (s, 3, CH_3), 1.32 (s, 3, CH_3); HRMS calcd for $C_{23}H_{34}O_8$ (M + 1) 439.2331, found 439.2334.

Alcohol 24b. Reduction of ketone **24a** (30 mg) was conducted in methanol (5 mL) at 0 °C by using sodium borohydride (6 mg). The reaction was complete in 15 min and a drop of glacial acetic acid was added. Sodium bicarbonate solution was added and the solvent was evaporated to leave a residue which was extracted with dichloromethane. The extract was dried over sodium sulfate and evaporated to give 26 mg (87%) of the alcohol **24b** as a syrup: $[\alpha]^{28}_D$ +81.1° (*c* 1.2, $CHCl_3$); IR (thin film) 3460 cm^{-1} 1740, 1650, 1440, 1385, 1375; ^1H NMR 200 MHz ($CDCl_3$) δ 5.80 (d, 1, H1), 5.12 (broad s, vinyl HO, 4.90 (broad s, 1, vinyl H), 4.73 (m, 2, H2, H4), 4.57 (m, 1, THP-H1′), 3.90-3.74 (m, 3, H13, H10), 3.71 (s, 3, OCH_3), 3.64–3.35 (m, 3, H9, THP group), 298 (dd, 1, H8), 2.75 (m, 2), 2.40 (m, 2), 1.85–1.50 (m, 10), 1.48 (s, 3, CH_3), 1.33 (s, 3, CH_3); HRMS calcd for $C_{23}H_{36}O_8$ (M + 1) 441.2487, found 441.2491.

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Registry No. **2**, 79507-09-8; **3**, 79507-10-1; **4**, 79507-11-2; **6**, 98050-34-1; **7**, 80243-87-4; **8a**, 81049-53-8; **8b**, 98167-20-5; **9**, 79507-15-6; **10a**, 98050-35-2; **10b**, 98050-36-3; **10c**, 98050-40-9; **13a**, 98050-37-4; **13b**, 98050-41-0; **13c**, 98050-42-1; **13d**, 98050-44-3; **15a**, 98050-38-5; **15b**, 98064-07-4; **16a**, 98050-39-6; **16b**, 98050-43-2; **17**, 98050-45-4; **18**, 98050-46-5; **19a**, 98050-54-5; **19b**, 98050-55-6; **19c**, 98050-56-7; **20a**, 98050-47-6; **20b**, 98050-48-7; **21a**, 98050-49-8; **21b**, 98050-50-1; **23**, 98050-51-2; **24a**, 98050-52-3; **24b** (isomer 1), 98050-53-4; **24b** (isomer 2), 98103-50-5; maleic anhydride, 108-31-6; carbonylbis(imidazole), 530-62-1; methyl chloride, 74-87-3; allyl bromide, 106-95-6; ethyl bromide, 74-96-4; propargyl alcohol–THP ether, 6089-04-9; *N,N*-diethylbenzeneselenamide, 57584-86-8; *N*-(phenylselenyl)phthalimide, 71098-88-9.