Asymmetric Synthesis of (+)-*allo*-Quercitol and (+)-*talo*-Quercitol via Free Radical Cycloisomerization of an Enantiomerically Pure Alkyne-Tethered Aldehyde Derived from a Carbohydrate[$]

J. S. Yadav,* Arup Maiti, A. Ravi Sankar,[#] and A. C. Kunwar[#]

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500007, India

yadav@iict.ap.nic.in

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We describe for the first time the free radical cyclization of enantiomerically pure alkyne-tethered aldehydes obtained from a carbohydrate (**6**, **7**). The synthesis of compounds **6** and **7** obtained from a derivative of D-ribose is reported. These radical precursors have been submitted to cyclization with tributyltin hydride plus azobisisobutyronitrile to yield, after ring closure, two carbocycles, respectively. These carbocycles have been obtained as mixtures of *E* and *Z* vinyltin isomers, but with excellent diastereoselection at the new stereocenter formed during the ring closure. After protodestannylation, only one diastereomer was detected and isolated. The absolute configuration at the new stereocenter formed during the carbocyclization has been established by detailed ^{1}H NMR analysis. The specific transformation of 7-methoxymethoxy-2,2-dimethyl-4-methylene-5-*tert*-butyldimethylsilyloxy-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxole into optically pure (+)-*allo*-quercitol and (+)-*talo*-quercitol is described. From these results, we conclude that under an appropriate choice of radical precursors and conditions, the synthesis of highly functionalized cyclohexane derivatives of biological interest is now available.

Introduction

Asymmetric syntheses of polyhydroxycyclohexane derivatives are of interest due to their versatility as synthetic intermediates, for their significant biological activity, and for the structural challenge inherent in their syntheses.[1] "Quercitols", a generic term used for cyclohexanepentols, are the largest family of diastereoisomers which can exist in 16 stereoisomeric forms, of which four are symmetric, with the other 12 being grouped in six pairs of enantiomers.[2] (+)-*Proto*,[3] (−)-*proto*,[4] and (−)-*vivo*[5] are the only optically active stereoisomeric forms found in nature. So far, 10 possible diastereomers of quercitols have been synthesized by different methods.[1c] In most of the previous reports, the naturally available cyclitols have been used as starting materials for the synthesis of quercitols. However, the limited availability of chiral sources has restricted their utility. The first synthesis of (±)-*allo*-quercitol and (+)-*talo*-quercitol was described by McCasland[6] starting from haloinositols. Recently Balci[7] et al. have synthesized (±)-*talo*-quercitol. To the best of our knowledge, no report is available on the synthesis of (+)-*allo*-quercitol.

Strategies for synthesizing such carbocycles from carbohydrates have gained importance over the past decade because of the readily available starting materials and due to the high chirality content that can be transformed into a variety of products, leading to the construction of functionalized chiral carbocyclic building blocks.[8] The transformation of carbohydrate derivatives into functionalized carbocycles has usually been achieved by multistep protocols involving the initial conversion of the carbohydrates into suitable functionalized open-chain products, followed by ring closure using different procedures.[9−12] In particular, radical carbocyclization has been recognized as a most efficient tool because it tolerates high levels of substrate functionalization.[10] In recent years, there have been numerous examples of the use of vinyl radical cyclization for the synthesis of five-membered cyclitols.[11] However, there are very few examples for the preparation of six-membered cyclitols employing radical cyclization of a vinyl radical derived from an alkyne.[12] This is possibly due to the failure of acyclic carbohydrate intermediates to yield cyclized products.[12b,c] One of the reasons attributed is the fact that

* To whom correspondence should be addressed. Telefax: +91 40 7170512.

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[#] Center for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Hyderabad-500007, India.

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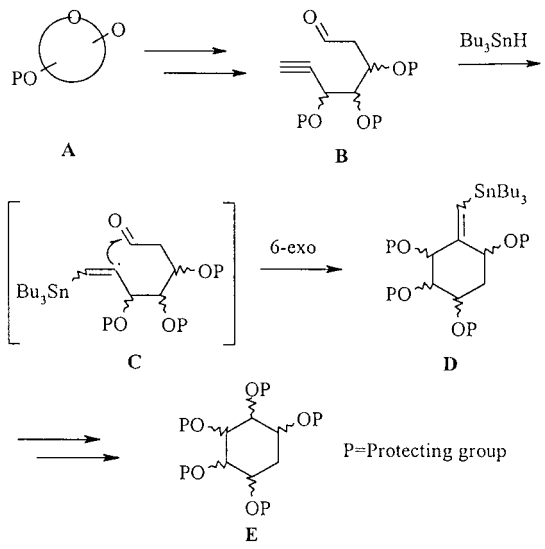
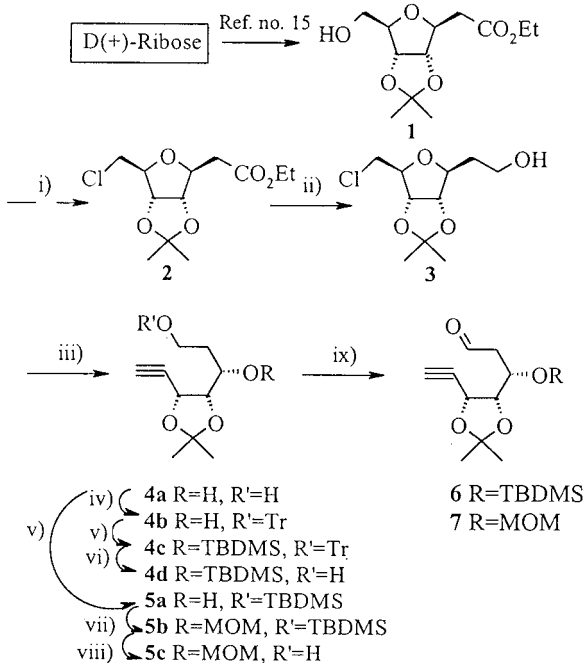
such a cyclization is about 40 times slower than that of the 5-hexenyl radical.[13] Fraser-Reid et al. have reported partial success using aldehyde functional groups as the radical acceptor in 6-exo cyclizations.[14] The efficiency may be diminished by several factors; for example, the presence of oxygen α to the aldehyde may inhibit the reaction. They concluded that care should be taken in choosing the radical precursor for cyclization.[12b] With this information in hand, we report the first examples of the 6-exo-trig radical cycloisomerization of enantiomerically pure polyoxygenated alkyne-tethered aldehydes. This strategy has resulted in a new and highly diastereoselective method for the synthesis of (+)-*allo*-quercitol (6-deoxy-D-*allo*-inositol) and (+)-*talo*-quercitol (1-deoxy-D-*neo*-inositol).

Scheme 1



Scheme 2[a]



[a] Reagents: (i) PPh_3, CCl_4, reflux; (ii) LAH, Et_2O, 0 °C to room temperature; (iii) $LiNH_2$, liquid NH_3; (iv) TrCl, Et_3N, CH_2Cl_2, room temperature; (v) TBDMSCl, imidazole, CH_2Cl_2, room temperature; (vi) HCO_2H, Et_2O, 0 °C; (vii) MOMCl, $(^iPr)_2NEt$, CH_2Cl_2, room temperature; (viii) TBAF, THF, room temperature; (ix) $(COCl)_2$, DMSO, Et_3N, −78 °C.

Results and Discussion

The synthetic approach used is described in Scheme 1. The essential aspects of this strategy include a Wittig-type reaction on aldoses **A**, followed by some functional group transformations, selective protections, and activations to afford the highly functionalized chiral, radical precursors **B**. These compounds, upon treatment with a tin hydride reagent, provide the vinyl radical,[11] species **C**, which leads to cyclitol derivatives **D**. These compounds were conveniently designed for further synthetic manipulation to **E**. We therefore chose to prepare radical precursors from D-(+)-ribose as shown in Scheme 2. Accordingly, alcohol-ester **1**, available from D-(+)-ribose,[15]

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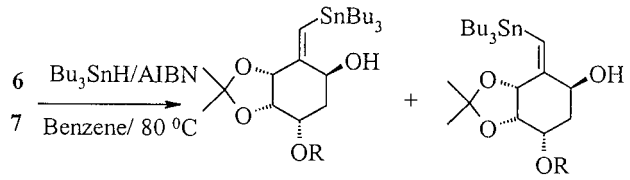
Scheme 3



R=TBDMS **8E** (40%) **8Z** (8%)
R=MOM **9E** (56%) **9Z** (10%)

was converted to the corresponding chloride **2** in 88% yield by refluxing it with triphenylphosphine in carbon tetrachloride. Ester reduction using lithium aluminum hydride afforded **3** in 90% yield which, upon treatment with $LiNH_2$ in liquid NH_3,[16] produced alkynediol **4a** in 91% yield. Alkynediol **4a** was converted into alkyne-tethered aldehydes **6** and **7** by a four-step sequence in high overall yield: (a) selective protection of the primary hydroxyl group either as trityl (Tr) ether or *tert*-butyldimethylsilyl (TBDMS) ether to yield **4b** and **5a**, respectively; (b) *tert*-butyldimethylsilyl protection of the secondary alcohol in **4b** afforded **4c**, and methoxymethyl (MOM) protection of the same in **5a** gave **5b**; (c) selective deprotection of trityl ether in **4c** was effected by formic acid[17] and that of silyl ether in **5b** was effected by TBAF to afford alcohols **4d** and **5c**, respectively; (d) Swern oxidation[18] of **4d** and **5c** readily provided aldehydes **6** and **7**, respectively. First, we took stable intermediate alkyne-tethered aldehyde **6** for the investigation of radical cyclization as shown in Scheme 3. Since under the experimental conditions as described by Fraser-Reid[12b] [tri-*n*-butyltin hydride (TBTH; 1.4 equiv), azobisisobutyronitrile (AIBN; 0.1 equiv) in refluxing benzene (0.02 M) and slow addition of reagents (AIBN, TBTH) (thermodynamic conditions)] and the conditions described by Oshima[19a] (Et_3B as radical initiator[19b]) no cyclized products were obtained, we turned our attention to a change in the reaction conditions. It was observed that at higher concentrations of AIBN (0.6−0.8 equiv) and with addition of the reagents (TBTH, AIBN) together (not via syringe pump) and in high concentration (1.5 M) (kinetic conditions), the cyclization was quite facile[20] and afforded substituted cyclohexyl stannane **8** in moderate yield, which was a separable mixture of **8*E*** (40%) and **8*Z*** (8%)[21] geometrical isomers. After this initial success, we tried the reaction conditions on aldehyde **7**, and, as expected, the cyclization went smoothly in high yield (66%). This time it was a separable mixture of **9*E*** (56%) and **9*Z*** (10%)[21] geometrical isomers. Each geometrical isomer

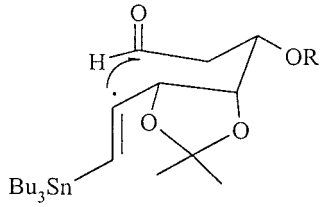


Figure 1.

(**8*E***, **8*Z*** and **9*E***, **9*Z***) was diastereomerically homogeneous at the new stereocenter (C-5), formed during the cyclization. The strongly reduced conformational flexibility of these carbocycles facilitated the stereochemical assignments by inspection of the respective ^1H NMR and 2-D NOESY spectra. The structures were obtained from the diagnostic data and derived from the measurements of interproton coupling constants, detection of specific NOEs, and by minimum energy calculations. We have carried out extensive studies on products **8*E***, **8*Z*** and **9*E***, **9*Z*** (see Experimental Section and Supporting Information). Because of the presence of an sp^2 carbon, the six-membered ring took on a distorted chair conformation in all the cases. The presence of NOE between H_{3a} and H_{4a} confirmed the *E* configuration in **8*E***. Long-range coupling of $J_{6'-7a}$ of 1.3 Hz implied a W coupling with both the protons in an equatorial-coplanar disposition. We also observed an allylic coupling between H_{4a} and H_{3a} of 1.1 Hz. Large vicinal coupling between H_6 and H_7 of 11.4 Hz, NOEs between acetonide methyl (2a) with H_{3a}, H_{7a}, and NOEs between acetonide methyl (2b) with H_5 were also consistent with the proposed structure. The absence of NOE between H_{4a} and H_{3a} supported the *Z* configuration in **8*Z***. The rest of the NOEs and couplings were consistent with the proposed conformation. These observations in combination with other couplings in the six-membered ring suggested the *S* configuration at the new stereocenter (C-5) formed during cyclization. This was further confirmed at a later stage. The energy-minimized structure also supported our experimental values (see Supporting Information). Similar trends were also observed in the other cyclized products, **9*E*** and **9*Z*** (see Supporting Information). The stereochemical outcome of the radical cyclization could be rationalized using Beckwith's guidelines,[13b] assuming that the major products came via a transition state in which the radical species adopted a chairlike conformation with most of the substituents in the preferred pseudoequatorial positions, as shown in Figure 1. The formation of the major *E* isomer was in agreement with the results shown by Oshima.[19] Both **9*E*** and **9*Z*** isomers were stirred together with dry silica gel in methylene chloride, causing protodestannylation[11b] to produce **10** in 95% yield as a single product (Scheme 4). Protection of **10** as a silyl ether afforded **11** in 82% yield. The absolute configuration at the new stereocenter (C-5) has been further confirmed as *S* (vide supra) after careful analysis of the 2-D NOESY spectrum of **11**. The ^1H NMR data of **11** suggested a distorted chair conformation. All the vicinal couplings, with the exception of $J_{6,7}$, were small, supporting the assigned absolute stereochemistry at C-5. The characteristic NOE H_5−acetonide methyl (2b), $H_{4a'}-H_5$, $H_{3a}-H_{4a''}$, and $H_{3a}-H_7$ were further support for the assigned stereochemistry and structure. The NOEs between $H_{7a}-CH_2$ of MOM and $H_{7a}-CH_3$ of the MOM group confirmed that the bulky substituent was equatorially placed. Two allylic couplings between

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(19) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (b) During the course of our studies, a similar cyclization reaction has been reported by Malacria et al. (see ref 12f). We have applied their reaction conditions even at 80 °C but end up with an unsuccessful result.
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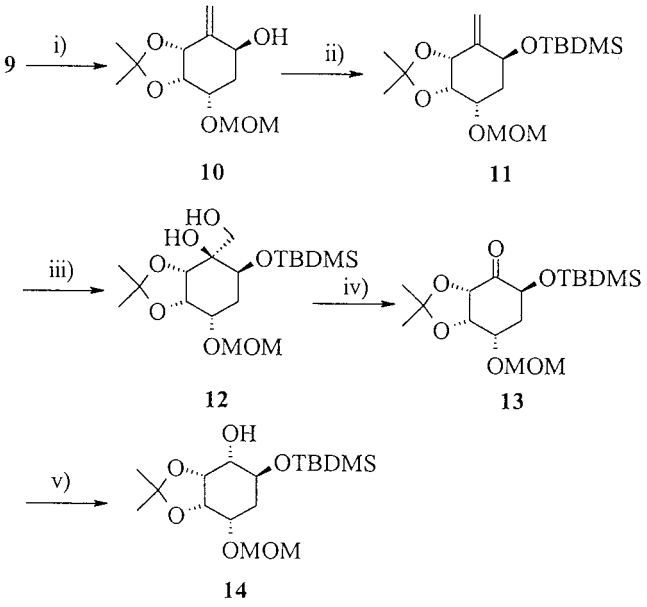
(21) We failed to get the minor isomers **8Z** and **9Z** in pure form. It always contains some impurities. Prolonged silica gel column chromatographic separation yields protodestannylation.[11b]

Scheme 4[a]



[a] Reagents: (i) silica gel, room temperature; (ii) TBDMSCl, imidazole, CH_2Cl_2, room temperature; (iii) OsO_4, NMO, aqueous acetone; (iv) $NaIO_4$, aqueus THF; (v) $NaBH_4$, MeOH, 0 °C/Dibal-H, CH_2Cl_2, −78 °C.

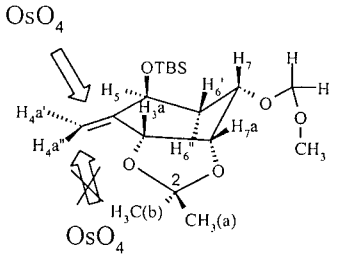


Figure 2.

$H_{3a}-H_{4a'}$ and $H_{3a}-H_{4a''}$ of 1.6 Hz were also observed. The observation of W coupling between H_6' and H_{7a} further corroborated the structure which was also consistent with the energy-minimized structure (see Supporting Information). Treatment of **11** with OsO_4, NMO in 80% aqueous acetone produced exclusively cyclohexitol **12** (85%). The flagpole−flagpole interaction between H_7 and C_4-OH in the 2-D NOESY spectrum suggested that **12** took a boat conformation with an *R* configuration at the C_4 stereocenter. The vicinal couplings $J_{6,7} = 10.0$ Hz and $J_{3a,7a} = 7.3$ Hz were also consistent with the boat conformation. The long-range coupling of 1.0 Hz between H_6' and H_{7a} suggested the equatorial-coplanar disposition of these protons. The NOE between the acetonide methyl (2b) and H_5 further supported the boat conformation. The observed stereochemical outcome of the dihydroxylation reaction can be rationalized on the basis of the preferred conformation of **11** (Figures 2 and 3) derived by a minimum energy calculation (see Supporting Information) in which the OsO_4 attack took place from the less-hindered exo face of the exocyclic double bond. Treatment with $NaIO_4$ in aqueous THF produced inosose **13** in 80% yield. The final correlation between **13** and the quercitols was carried out by stereoselective reduction of **13**. As expected, reduction of inosose **13** with $NaBH_4$ in methanol or with Dibal-H in CH_2Cl_2 was exo face-selective giving exclusively (+)-*allo*-quercitol derivative **14** in 93−

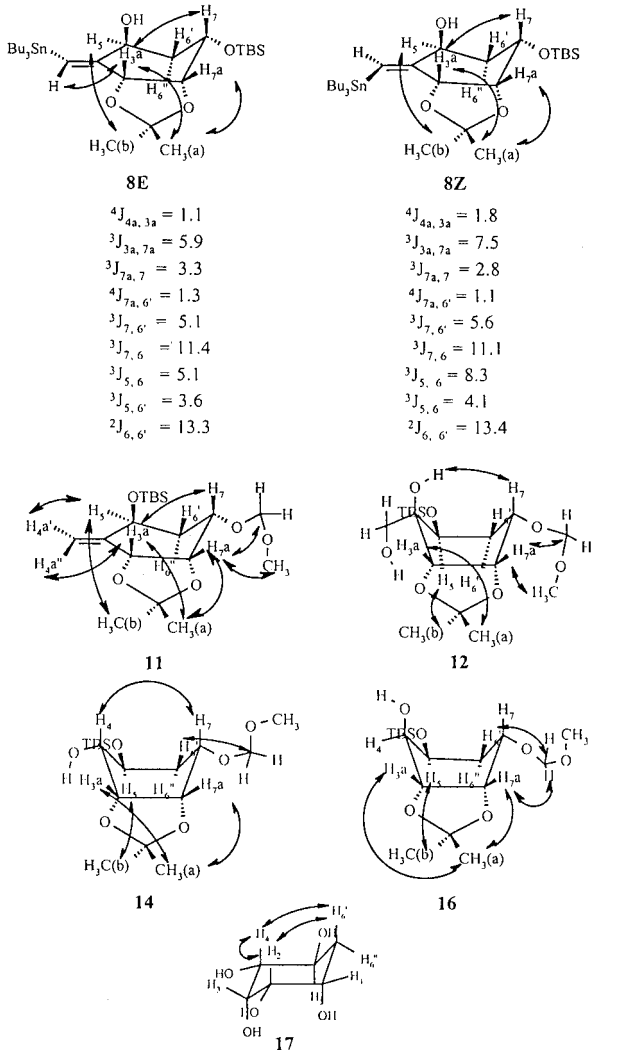
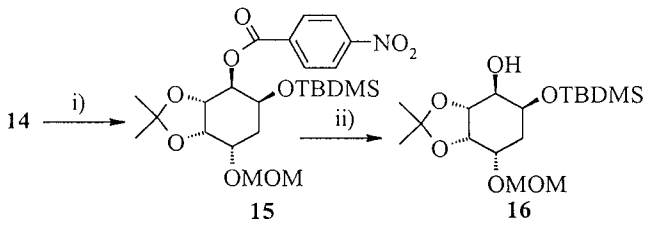


Figure 3. Preferred conformation for a few compounds, with the most significant NOEs observed in the 2-D NOESY spectrum.

Scheme 5[a]

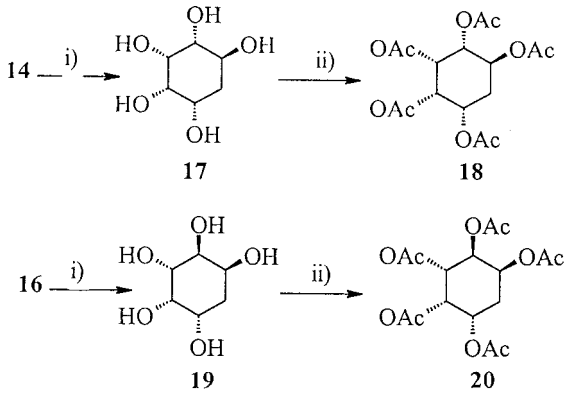


[a] Reagents: (i) DEAD, PPh_3, *p*-nitrobenzoic acid, THF, room temperature; (ii) NaOMe, MeOH.

95% isolated yield. The compound **14** was converted into benzoate derivative **15** in 35% yield under Mitsunobu conditions[22] as shown in Scheme 5. Base treatment of benzoate derivative **15** produced (+)-*talo*-quercitol derivative **16** in 88% yield. These two derivatives of quercitols **14** and **16** were characterized by NMR spectroscopy. To accommodate the bulky TBDMS group in the equatorial position, the ring adopted boat conformations in both the cases. In **14**, the flagpole−flagpole NOE of H_4-H_7 confirms the *S* absolute configuration at the

(22) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme 6[a]



[a] Reagent: (i) 6 M HCl, MeOH, reflux; (ii) Ac_2O, pyridine.

C-4 stereocenter. The couplings ($J_{4,5}$, $J_{5,6'}$, $J_{6',7}$), the NOEs between H_5−acetonide methyl (2b) and between $H_{6'}$−CH_2 of MOM and H_{7a}−CH_3 of the MOM group, further supported the boat conformation. In **16**, despite not observing the characteristic flagpole−flagpole NOE between the C_4−OH and H_7, NOE peaks between H_5−acetonide methyl (2b) and H_{7a}−CH_2 of the MOM group suggested a boat conformation with the *R* configuration at the C-4 stereocenter. Removal of protecting groups from compounds **14** and **16** produced (+)-*allo*-quercitol **17**[6b] and (+)-*talo*-quercitol **19**,[6b] respectively, in high yields as shown in Scheme 6. These were acetylated to get the pentaacetate derivative of the respective quercitols **18** and **20**; the spectral data for these compounds were in agreement with those reported earlier.[6b]

Conclusion

We have described a new protocol for the preparation of a highly functionalized cyclohexane derivative from carbohydrates, which features the tri-*n*-butyltin hydride mediated 6-exo-trig radical cycloisomerization of polyoxygenated, enantiomerically pure alkyne-tethered aldehyde. Carbocyclization is possible in good yield using AIBN as the radical initiator. This procedure gives chiral, highly functionalized vinyltin[23] derivatives with large potential synthetic applications, and the correct selection of the radical precursor allows very high diastereoselection. In summary, the present method is to be very useful for the synthesis of (+)-*allo*-quercitol and (+)-*talo*-quercitol.

Experimental Section

General. Melting points were recorded on a Buchi R-535 apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer Infrared 683 spectrophotometer with NaCl optics. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on Varian Gemini-200, Varian Unity-400, and Varian Inova-500 NMR spectrometers in deuteriochloroform unless otherwise stated. In the ^{1}H NMR spectra, tetramethysilane (TMS) (δ 0 ppm) was used as an internal reference, whereas for the ^{13}C NMR spectra, $CDCl_3$ (δ 77.0 ppm) was used as an internal reference. Chemical shifts were reported in ppm downfield from TMS and were given on the δ scale. The multiplicity, coupling constants (hertz), and number of protons were indicated in parentheses and were specified as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet for unresolved lines), br (broad), etc. ^{13}C spectra were obtained with proton decoupling. The assignments were carried out with the help of Nuclear Overhauser Effect Spectroscopy (NOESY). Mass measurements were carried out on either a Finnigan-MAT1020B or a MicroMass VG70−70H mass spectrometer operating at 70 eV using the direct inlet system and were given in mass units (*m*/*z*). The energy minimization was performed using the Steepest descent method with tripos force field default parameters in the SYBYL 6.7 program on an O_2 workstation. Minimization was carried out for a maximum of 1000 iterations or with the gradient criterion of less than 0.05 kcal/mol between successive iterations, whichever was earlier. This locates a local minimum close to the starting configuration. The configurations were further minimized with MOPAC software, for geometrical normalization. This structure was taken as input for a MD run in search of a much bigger conformational space. The protocol followed is described below. A single interval of the 100 ps dynamics run at 300 °K was carried out with a 1 fs time step. The results of the dynamics run were saved after every 1 ps, resulting in 100 conformers. All these conformers were again minimized as mentioned earlier. The SYBYL program selects unique conformations (for structures see Supporting Information). For tin-substituted compounds, the minimization was carried out with the help of PCMODEL.[24] Compound names were given according to IUPAC nomenclature.

Unless otherwise stated, all nonaqueous reactions were performed under an atmosphere of nitrogen in flame-dried glassware equipped with a stir bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture-sensitive reagents. Reactions were monitored by analytical thin-layer chromatography (TLC) using 0.25 mm E.Merk precoated silica gel plates ($60F_{254}$). The spots were detected using UV light (254 nm), blowing I_2, or by dipping into anisaldehyde/sulfuric acid (A) or β-naphthol/sulfuric acid (B) solution followed by charring on a hot plate. Product purification by flash column chromatography (FCC)[25] and dry flash column chromatography (DFC)[26] were performed using silica gel (100−200 mesh). Solutions in organic solvents were dried over anhydrous sodium sulfate, and solvents were evaporated with a Buchi rotary evaporator connected to a water aspirator. Trace solvent was removed on a vacuum pump. All compounds were stored at −5 °C in vials flushed with nitrogen.

Pyridine and triethylamine (Et_3N) were dried over KOH. Solvents were dried and purified in the following fashion: toluene and benzene were distilled over P_2O_5, Et_2O and THF were distilled from sodium benzophenone ketyl, dichloromethane (CH_2Cl_2) and dimethyl sulfoxide (DMSO) were distilled from calcium hydride, and methanol was distilled from magnesium methoxide.

Ethyl-2-[6-chloromethyl-2,2-dimethyl-(3a*S*,4*S*,6*S*,6a*S*)-perhydrofuro[3,4-*d*][1,3]dioxol-4-yl] Acetate (2). To a stirred solution of alcohol ester **1**[15] (10.0 g, 38.4 mmol) in dry CCl_4 (150 mL) was added triphenylphosphine (12.1 g, 46.2 mmol), and the reaction mixture was heated under reflux with exclusion of moisture. Triphenylphosphine oxide commenced to separate from the mixture after 15 min, and after 6 h, 2 g of $PdCO_3$ was added. The cooled solution was filtered, concentrated, and strongly cooled. A further portion of triphenylphosphine oxide that deposited was filtered, and the residue was washed several times with ice-cold ether. The solution was then concentrated, and the residue was charged on a silica gel column and eluted with ether/hexane (5/95 to 20/80) to afford chloro derivative **2** (9.4 g, 88%) as a colorless oil. R_f = 0.49 (25% ether/hexane, A: black). $[\alpha]^{25}_D$ −11.06 (*c* 1.01, $CHCl_3$). IR γ_{max} (film): 1730 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, J = 7.0 Hz, 3H), 1.35 (s, 3H), 1.55 (s, 3H), 2.66 (d(ABq), J = 5.6, 15.8, 6.8 Hz, 2H), 3.62 (d(ABq), J = 4.5, 11.5, 5.3 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.20 (ddd, J = 4.1,

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(24) PCMODEL. Gilbert, K. E.; Gajewski, J. J. Senna Software, Box 4076, Bloomington, IN 47402.

(25) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(26) Harwood, L. M. *Aldrichimica Acta* **1985**, *18*, 25.

11.5, 5.3 Hz, 1H), 4.33 (ddd, J = 4.5, 6.8, 10.1 Hz, 1H), 4.56 (dd, J = 4.4, 6.6 Hz, 1H), 4.65 (dd, J = 4.1, 6.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.01, 25.34, 27.22, 38.29, 44.38, 60.54, 80.97, 82.75, 83.38, 84.07, 114.50, 170.10. MS m/z (assignment, relative intensity): 265 ($M^+ + 2 - CH_3$, 20), 263 ($M^+ - CH_3$, 60), 235 ($M^+ - C_3H_7$, 20), 43 (100). Anal. Calcd for $C_{12}H_{19}ClO_5$: C, 51.71; H, 6.87. Found: C, 51.59; H, 6.52.

2-[6-Chloromethyl-2,2-dimethyl-(3a*S*,4*S*,6*S*,6a*S*)-perhydrofuro[3,4-*d*][1,3]dioxol-4-yl]-1-ethanol (3). A suspension of $LiAlH_4$ (1.1 g, 28.9 mmol) in dry ether (100 mL) was cooled to 0 °C, and a solution of chloroester **2** (8.0 g, 28.8 mmol) in ether was added slowly and allowed to attain room temperature. The reaction mixture was stirred further for 30 min, after which the reaction mixture was quenched with saturated Na_2SO_4. The solution was filtered through a Celite pad and washed thoroughly with hot chloroform, concentrated, and purified by chromatography to give compound **3** (6.1 g, 90%) as a colorless oil. R_f = 0.5 (50% EtOAc/hexane, A: green). $[\alpha]^{25}_D$ −18.95 (*c* 1.02, $CHCl_3$). IR γ_{max} (film): 3300−3450 (br s, OH) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.55 (s, 3H), 1.91 (m, 2H), 2.11 (t, J = 5.7 Hz, 1H), 3.66 (d(ABq), J = 11.6, 4.3, 15.2 Hz, 2H), 3.81 (q, J = 5.7 Hz, 2H), 4.06 (dt, J = 5.2, 7.9, 13.0 Hz, 1H), 4.18 (q, J = 4.6, 9.0 Hz, 1H), 4.40 (dd, J = 5.3, 6.7 Hz, 1H), 4.63 (dd, J = 3.9, 6.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.25, 27.13, 35.62, 44.38, 59.53, 82.45, 82.86, 83.13, 84.49, 114.62. MS m/z (assignment, relative intensity): 223 ($M^+ + 2 - CH_3$, 19), 221 ($M^+ - CH_3$, 58), 263 (13), 161 (40), 43 (100). Anal. Calcd for $C_{10}H_{17}ClO_4$: C, 50.74; H, 7.24. Found: C, 50.44; H, 7.03.

1-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-(1*S*)-propane-1,3-diol (4a). To a stirred suspension of lithium amide (prepared from 1.1 g, 0.157 g atom of Li) in liquid NH_3 (70 mL) was added compound **3** (6.0 g, 25.4 mmol) in dry THF (10 mL) over a period of 2 min. After being stirred for 1 h, the reaction mixture was quenched with solid NH_4Cl (2.0 g), and ammonia was allowed to evaporate. The residue portion was filtered and washed with hot chloroform. The filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography to give compound **4a** (4.63 g, 91%) as a colorless crystalline solid. R_f = 0.35 (80% EtOAc/hexane, A: green). mp 78 °C. $[\alpha]^{25}_D$ +30.16 (*c* 1.2, $CHCl_3$). IR γ_{max} (KBr): 3230−3450 (br s, OH's), 3310 (s, C≡C−H), 2105 (w, C≡C) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.52 (s, 3H), 1.84 (dddd, J = 8.7, 14.7, 4.2, 8.2 Hz, 1H), 2.05 (dddd, J = 3.1, 14.7, 6.8, 3.2 Hz, 1H), 2.25 (br s, 1H), 2.64 (d, J = 2.2 Hz, 1H), 2.92 (br s, 1H), 3.93 (m, 2H), 4.00 (dd, J = 5.9, 8.7 Hz, 1H), 4.19 (dt, J = 3.1, 8.7 Hz, 1H), 4.92 (dd, J = 2.2, 5.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.86, 27.41, 35.47, 60.80, 68.14, 71.00, 76.29, 80.08, 110.73. MS m/z (assignment, relative intensity): 185 ($M^+ - CH_3$, 13), 149 (12), 43 (100). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.55; H, 7.89.

1-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-3-triphenylmethyloxy-(1*S*)-propane-1-ol (4b). To a stirred solution of alkynediol **4a** (0.8 g, 4 mmol) in dry CH_2Cl_2 (12 mL) was added dropwise Et_3N (0.57 mL, 6 mmol) at 0 °C. TrCl (1.2 g, 4.3 mmol) was added portionwise to this reaction mixture. The reaction mixture was stirred at room temperature for 1 h. Then 10 mL of water was added to the mixture and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by dry column chromatography to provide **4b** (1.67 g, 90%) as a colorless semisolid. R_f = 0.35 (25% EtOAc/hexane, A: blue). $[\alpha]^{25}_D$ +14.18 (*c* 1.1, $CHCl_3$). IR γ_{max} (film): 3370 (br s, OH) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.49 (s, 3H), 1.87 (dddd, J = 4.4, 7.1, 8.3, 14.7 Hz, 1H), 2.14 (dddd, J = 2.6, 6.9, 4.7, 14.7 Hz, 1H), 2.55 (d, J = 2.3 Hz, 1H), 3.26 (d, J = 4.2 Hz, 1H), 3.41 (m, 2H), 3.83 (dd, J = 5.6, 8.6 Hz, 1H), 4.11 (ddt, J = 2.6, 4.2, 8.5 Hz, 1H), 4.87 (dd, J = 2.3, 5.6 Hz, 1H), 7.24 (m, 3H), 7.30 (m, 6H), 7.43 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.00, 27.51, 33.29, 62.16, 68.47, 70.86, 75.73, 79.82, 80.31, 87.50, 110.59, 127.13, 127.93, 128.58, 143.74. MS m/z (assignment, relative intensity): 442 (M^+, <1), 243 (CPh_3, 100), 183 (12), 165 (30).

4-[1-*tert*-Butyldimethylsilyloxy-3-triphenylmethyloxy-(1*S*)-propyl]-5-(1-ethynyl-2,2-dimethyl-(4*R*,5*R*)-1,3-dioxolane (4c). TBDMSCl (0.62 g, 4.1 mmol) was added portionwise over 10 min to a stirred solution of **4b** (1.5 g, 3.4 mmol) and imidazole (1.4 g, 20.5 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 48 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with water. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent EtOAc:hexane 2:98) to give compound **4c** (1.1 g, 56%) as a colorless oil. R_f = 0.35 (25% EtOAc/hexane, A: greenish blue). $[\alpha]^{25}_D$ +26.81 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.88 (s, 9H), 1.36 (s, 3H), 1.60 (s, 3H), 2.17 (m, 2H), 2.59 (d, J = 2.2 Hz, 1H), 3.26 (dt, J = 6.3, 8.4 Hz, 1H), 3.39 (dt, J = 6.5, 8.4 Hz, 1H), 3.95 (dd, J = 5.2, 8.2 Hz, 1H), 4.31 (td, J = 4.6, 8.2 Hz, 1H), 4.78 (dd, J = 2.2, 5.2 Hz, 1H), 7.24 (m, 3H), 7.30 (m, 6H), 7.43 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.51, −4.13, 17.94, 25.82, 26.24, 27.54, 34.68, 59.73, 68.89, 69.42, 76.17, 80.32, 81.10, 86.61, 110.31, 126.79, 127.66, 128.74, 144.40. MS m/z (assignment, relative intensity): 556 (M^+, <1), 243 (100), 165 (35), 73 (78).

3-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-3-*tert*-butyldimethylsilyloxy-1-propanol (4d). To a solution of **4c** (1.0 g, 1.8 mmol) in Et_2O was added a mixture of HCO_2H (2 mL)/Et_2O (2 mL) at 0 °C, and after 1 min, 20 mL of Et_2O was added. The reaction mixture was washed successively with brine and $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography to yield **4d** (0.37 g, 66%) as a colorless oil. R_f = 0.48 (25% EtOAc/hexane, A: green). $[\alpha]^{25}_D$ +15.9 (*c* 1.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 1.36 (s, 3H), 1.54 (s, 3H), 1.98 (m, 2H), 2.55 (d, J = 2.1 Hz, 1H), 3.83 (t, J = 5.9 Hz, 2H), 4.04 (dd, J = 8.5, 5.1 Hz, 1H), 4.27 (ddd, J = 4.1, 5.1, 8.5 Hz, 1H), 4.79 (dd, J = 2.1, 5.1 Hz, 1H). ^{13}C NMR (125 Hz, $CDCl_3$): δ −4.47, −3.89, 17.97, 25.82, 26.31, 27.50, 37.60, 59.01, 69.14, 70.48, 76.44, 80.08, 80.90, 110.66.

1-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-3-*tert*-butyldimethylsilyloxy-(1*S*)-propane-1-ol (5a). TBDMSCl (2.9 g, 19.5 mmol) was added portionwise over 10 min to a stirred solution of alkynediol **4a** (3.8 g, 19.0 mmol) and imidazole (1.94 g, 28.5 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 4 h. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with water. The organic layer was dried (Na_2SO_4), filtered, and concentrated giving a residue which was purified by chromatography. Elution with EtOAc/hexane (5/95 to 10/90) gave compound **5a** (4.75 g, 80%) as a colorless liquid. R_f = 0.64 (25% EtOAc/hexane, A: bluish green). $[\alpha]^{25}_D$ +38.03 (*c* 1.0, $CHCl_3$). IR γ_{max} (film): 3330−3450 (br s, OH), 3310 (s, C≡C−H), 2108 (w, C≡C) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.90 (s, 9H), 1.35 (s, 3H), 1.53 (s, 3H), 1.78 (dddd, J = 4.1, 8.7, 14.5, 8.5 Hz, 1H), 2.03 (dddd, J = 2.4, 3.8, 6.1, 14.5 Hz, 1H), 2.58 (d, J = 2.10 Hz, 1H), 3.64 (d, J = 3.3 Hz, 1H), 3.91 (ddd, J = 3.8, 8.1, 4.1 Hz, 1H), 3.97 (m, 2H), 4.19 (ddt, J = 2.4, 3.3, 8.6 Hz, 1H), 4.92 (dd, J = 2.1, 5.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.59, 18.06, 25.80, 26.06, 27.50, 35.14, 62.16, 68.49, 71.38, 75.69, 80.00, 80.33, 110.50. MS m/z (assignment, relative intensity): 299 ($M^+ - CH_3$, 4), 131 (100), 75 (60). Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.61. Found: C, 61.05; H, 9.67.

4-(1-Ethynyl)-5-(1-methoxymethoxy-3-*tert*-butyldimethylsilyloxy-(1*S*)-propyl)-2,2-dimethyl-(4*R*,5*S*)-1,3-dioxolane (5b). (^{i}Pr)$_2$NEt (12.5 mL, 71.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **5a** (4.5 g, 14.3 mmol) in CH_2Cl_2 (50 mL). After 15 min, methoxymethylene chloride (MOMCl) (3.25 mL, 57.2 mmol) was added dropwise over a period of 10 min, and stirring was continued for 1 h. The cold bath was removed, and stirring was continued for 12 h. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (eluent EtOAc:hexane 4:96) gave compound **5b** (3.8 g, 75%) as a colorless liquid. R_f = 0.85 (10% EtOAc/hexane, A: green).

$[\alpha]^{25}_D$ +22.35 (*c* 1.04, $CHCl_3$). IR γ_{max} (film): 3320 (s, C≡C−H), 2120 (w, C≡C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.062 (s, 3H), 0.90 (s, 9H), 1.35 (s, 3H), 1.53 (s, 3H), 1.87 (qd, J = 6.3, 12.5, 14.2 Hz, 1H), 2.06 (ddt, J = 3.9, 7.5, 14.2 Hz, 1H), 2.54 (d, J = 2.3 Hz, 1H), 3.39 (s, 3H), 3.80 (m, 1H), 4.06 (dd, J = 3.9, 6.3 Hz, 1H), 4.10 (ABq, J = 7.5, 12.9 Hz, 2H), 4.73 (ABq, J = 6.6, 17.3 Hz, 2H), 4.87 (dd, J = 2.3, 5.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.38, −5.35, 18.23 25.91, 27.28, 35.03, 55.90, 59.13, 68.47, 75.04, 76.04, 79.47, 80.47, 96.95, 110.21. MS *m*/*z* (assignment, relative intensity): 343 ($M^+ - CH_3$, 5), 131 (100), 45 (90). Anal. Calcd for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.69. Found: C, 60.39; H, 9.60.

3-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-3-methoxymethoxy-1-propanol (5c). To a solution of **5b** (3.5 g, 9.77 mmol) in dry THF (20 mL) was added Bu_4NF (1.0 M solution in dry THF, 12.7 mL, 1.3 mmol) at 0 °C, and the resulting solution was allowed to warm to room temperature. The mixture was stirred for 3 h. Saturated NH_4Cl solution (5 mL) was added, and the reaction mixture was stirred for few minutes. It was then diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated under reduced pressure. The crude product was purified by flash chromatography; elution with EtOAc/hexane (10/90 to 40/60) gave **5c** (2.27 g, 95%) as a colorless oil. R_f = 0.43 (50% EtOAc/hexane; A, green; B, brown). $[\alpha]^{25}_D$ +6.48 (*c* 1.1, $CHCl_3$). IR γ_{max} (film): 3200−3450 (br s, OH), 3310 (s, C≡C−H), 2106 (w, C≡C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.54 (s, 3H), 1.95 (m, 1H), 2.11 (m, 1H), 2.38 (br s, 1H), 2.58 (d, J = 2.2 Hz, 1H), 3.39 (s, 3H), 3.83 (m, 2H), 4.12 (m, 2H), 4.76 (ABq, J = 6.6 Hz, 2H), 4.89 (dd, J = 2.2, 5.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.84, 27.20, 34.81, 55.95, 58.95, 68.36, 76.34, 76.38, 79.08, 80.33, 97.12, 110.39. MS *m*/*z* (assignment, relative intensity): 229 ($M^+ - CH_3$, 8), 125 (60), 45 (100), 43 (100). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.89; H, 8.12.

General Procedure for Oxidation of Alkyne-Tethered Alcohols. To a solution of oxalyl chloride (1.5 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added DMSO (1.6 mmol) in CH_2Cl_2 (1 mL) over 1 min, and the mixture was stirred for 20 min. A solution of alcohol (1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 1 min. After 1 h of stirring at −78 °C, Et_3N (6.0 mmol) was added, and the resulting white slurry was stirred further for 20 min and allowed to warm slowly to room temperature. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed several times with water, dried, and concentrated under reduced pressure at very low temperature. Rapid flash chromatography of the residue gave aldehyde in good yield.

3-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-3-*tert*-butyldimethylsilyloxy-1-propanal (6). A solution of alcohol **4d** (0.35 g, 1.1 mmol) was oxidized using the general procedure to give aldehyde **6** (0.3 g, 89%) as a colorless oil. R_f = 0.55 (25% EtOAc/hexane, A: violet). $[\alpha]^{25}_D$ +38.6 (*c* 2.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.11 (s, 3H), 0.8 (s, 9H), 1.38 (s, 3H), 1.42 (s, 3H), 2.58 (d, J = 2.1 Hz, 1H), 2.74 (m, 2H), 4.03 (dd, J = 5.2, 7.8 Hz, 1H), 4.56 (dt, J = 5.3, 7.8 Hz, 1H), 4.79 (dd, J = 5.3, 2.1 Hz, 1H), 9.82 (t, J = 2.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.53, −4.20, 17.89, 25.69, 26.08, 27.27, 48.87, 67.89, 68.55, 76.71, 80.42, 110.59, 200.44.

3-[5-(1-Ethynyl)-2,2-dimethyl-(4*S*,5*R*)-1,3-dioxolan-4-yl]-3-methoxymethoxy-1-propanal (7). A solution of alcohol **5c** (2.0 g, 8.19 mmol) was oxidized using the general procedure to give aldehyde **7** (1.78 g, 90%) as a colorless oil which decomposes on standing. So it was immediately used for the next step. R_f = 0.43 (25% EtOAc/hexane; A, violet; B, green). $[\alpha]^{25}_D$ +2.2 (*c* 2.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.50 (s, 3H), 2.58 (d, J = 3.0 Hz, 1H), 2.76 (ddd, J = 2.7, 7.0, 16.9 Hz, 1H), 2.86 (ddd, J = 4.2, 1.6, 16.9 Hz, 1H), 3.31 (s, 3H), 4.17 (dd, J = 6.1, 7.3 Hz, 1H), 4.42 (dt, J = 4.2, 7.0, 7.3 Hz, 1H), 4.71 (ABq, J = 6.9 Hz, 2H), 4.89 (dd, J = 6.1, 3.0 Hz, 1H), 9.79 (dd, J = 1.6, 2.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.66, 27.09, 46.70, 55.77, 68.13, 73.92, 76.57, 78.74, 79.82, 97.26, 110.62, 200.19.

General Procedure for Radical Cyclization. A solution of AIBN (1.0 mmol) and tributyltin hydride (3.0 mmol) in dry degassed benzene (2 mL) was added to a degassed solution of alkyne-tethered aldehyde (1.5 mmol) in dry degassed benzene (1.5 M) at reflux under nitrogen. After being heated at reflux for 2 h (monitored by TLC), the solution was concentrated at reduced pressure. The resulting residue was diluted with acetonitrile, and the acetonitrile phase was washed with hexane and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography eluting with EtOAc/hexane (0/100 to 20/80) gave the cyclized products. Yields were shown in Scheme 3.

4-[1-Tributyltinstannyl-(*Z*)-methylidene]-7-*tert*-butyldimethylsilyloxy-2,2-dimethyl-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-5-ol (8*Z*). 4-[1-Tributyltinstannyl-(*E*)-methylidene]-7-*tert*-butyldimethylsilyl-oxy-2,2-dimethyl-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-5-ol (8*E*). 8*Z*. R_f = 0.55 (25% EtOAc/ hexane, B: brown). ^1H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.88 (t, J = 7.2 Hz, 9H), 0.90 (s, 9H), 1.30 (m, 9H), 1.34 (s, 3H), 1.45 (s, 3H), 1.50 (m, 9H), 2.08 (dddd, J = 4.1, 5.6, 1.1, 13.4 Hz, 1H), 2.40 (ddd, J = 11.1, 8.3, 13.4, 1H), 3.78 (ddd, J = 2.8, 5.6, 11.1 Hz, 1H), 4.25 (ddd, J = 2.8, 7.5, J = 1.1 Hz, 1H), 4.47 (dd, J = 7.5, 1.8 Hz, 1H), 4.58 (dt, J = 8.3, 4.1 Hz, 1H), 6.16 (d, J = 1.8 Hz, 1H).

***8E*.** R_f = 0.6 (25% EtOAc/hexane, B: brown). ^1H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90 (t, J = 7.1 Hz, 9H), 0.91 (s, 9H), 1.30 (m, 9H), 1.35 (s, 3H), 1.44 (s, 3H), 1.46 (m, 9H), 1.78 (ddt, J = 5.1, 3.6, 13.3 Hz, 1H), 2.19 (ddd, J = 11.4, 5.1, 13.3 Hz, 1H), 4.18 (ddd, J = 5.1, 11.4, 3.3 Hz, 1H), 4.25 (ddd, J = 3.3, 5.9, 1.3 Hz, 1H), 4.44 (dt, J = 5.1, 3.6 Hz, 1H), 4.63 (dd, J = 5.9, 1.1 Hz, 1H), 6.18 (d, J = 1.1 Hz, 1H).

4-[1-Tributyltinstannyl-(*Z*)-methylidene]-7-methoxymethoxy-2,2-dimethyl-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-5-ol (9*Z*). 4-[1-Tributyltinstannyl-(*E*)-methylidene]-7-methoxymethoxy-2,2-dimethyl-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-5-ol (9*E*). 9*Z*. R_f = 0.51 (25% EtOAc/hexane, B: brown). $[\alpha]^{25}_D$ +51.4 (*c* 1.01, $CHCl_3$). IR γ_{max} (film): 3350−3450 (br s, OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.4 Hz, 9H), 1.28 (m, 9H), 1.3 (m, 9H), 1.41 (s, 3H), 1.54 (s, 3H), 1.79 (dddd, J = 3.3, 5.3, 13.6, 1.0 Hz, 1H), 2.47 (ddd, J = 11.3, 8.1, 13.6 Hz, 1H), 3.38 (s, 3H), 3.74 (ddd, J = 3.3, 5.5, 11.3 Hz, 1H), 4.49 (ddd, J = 7.6, 3.3, 1.0 Hz, 1H), 4.59 (d, J = 7.6 Hz, 1H), 4.66 (m, 1H), 4.70 (ABq, J = 6.8 Hz, 2H), 6.27 (d, J = 1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.60, 13.62, 27.27, 27.30, 29.09, 29.12, 33.80, 55.39, 67.24, 71.32, 76.63, 79.49, 95.12, 109.62, 128.52, 153.01.

***9E*.** R_f = 0.48 (25% EtOAc/hexane, B: brown). $[\alpha]^{25}_D$ −2.92 (*c* 1.09, $CHCl_3$). IR γ_{max} (film): 3350−3450 (br s, OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.4 Hz, 9H), 1.28 (m, 9H), 1.3 (m, 9H), 1.41 (s, 3H), 1.54 (s, 3H), 2.02 (dddd, J = 1.03, 3.6, 4.4, 13.4 Hz, 1H), 2.18 (dt, J = 4.3, 2.2, 13.4 Hz, 1H), 3.41 (s, 3H), 4.18 (ddd, J = 3.6, 5.0, 12.2 Hz, 1H), 4.47 (ddd, J = 5.0, 5.7, 1.0 Hz, 1H), 4.49 (dt, J = 4.3, 4.4, 1.0 Hz, 1H), 4.73 (dd, J = 1.48, 5.7 Hz, 1H), 4.75 (ABq, J = 6.8, 10.8 Hz, 2H), 6.28 (d, J = 1.48 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.97, 13.64, 25.74, 27.20, 27.28, 29.20, 29.28, 33.56, 55.44, 70.45, 71.72, 76.31, 78.02, 95.62, 109.62, 130.96, 152.79. MS *m*/*z* (assignment, relative intensity): 533 (M^+, 7), 515 ($M - H_2O$, 20), 177 (100). Anal. Calcd for $C_{24}H_{46}O_5Sn$: C, 54.06; H, 8.69. Found: C, 54.27; H, 8.59.

7-Methoxymethoxy-2,2-dimethyl-4-methylene-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-5-ol (10). The mixture of compounds **9*Z*** and **9*E*** (2 g, 3.75 mmol) was stirred together with silica gel (150 g) in CH_2Cl_2 (300 mL) for 48 h. The reaction mixture was filtered, washed with CH_2Cl_2, concentrated, and purified by flash chromatography to yield compound **7** (0.85 g, 95%) as a colorless oil. R_f = 0.35 (50% EtOAc/hexane, B: brown). $[\alpha]^{25}_D$ +44.03 (*c* 1.01, $CHCl_3$). IR γ_{max} (film): 3330−3450 (br, OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.50 (s, 3H), 1.97 (dddd, J = 1.2, 4.0, 5.4, 13.5 Hz, 1H), 2.22 (ddd, J = 5.3, 11.8, 13.5 Hz, 1H), 3.41 (s, 3H), 4.08 (ddd, J = 3.4, 5.4, 11.8 Hz, 1H), 4.50 (ddd, J = 1.2, 3.4, 6.0 Hz, 1H), 4.60 (dd, J = 5.3, 4.0 Hz, 1H), 4.74 (ABq, J = 6.9, 12.4 Hz, 2H), 4.744 (dt, J = 1.4, 6.0 Hz, 1H), 5.28 (dt,

J = 1.4, 2.7 Hz, 1H), 5.31 (dt, J = 1.4, 2.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.40, 26.97, 33.31, 55.45, 69.10, 70.59, 76.08, 76.24, 95.51, 109.86, 114.63, 146.16. MS *m/z* (assignment, relative intensity): 229 ($M^+ - CH_3$, 20), 95 (15), 45 (100). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.95; H, 8.31.

7-Methoxymethoxy-2,2-dimethyl-4-methylene-5-*tert*-butyldimethylsilyloxy-(3a*R*,5*S*,7*S*,7a*S*)-perhydrobenzo-[*d*][1,3]dioxole (11). To a stirred solution of **10** (0.5 g, 2.05 mmol) and imidazole (0.82 g, 12 mmol) in 10 mL of CH_2Cl_2 was added TBDMSCl (0.36 g, 2.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The mixture was then diluted with CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography to give **10** (0.6 g, 82%) as a colorless oil. R_f = 0.51 (10% EtOAc/hexane, B: red). $[\alpha]^{25}_D$ +44.48 (*c* 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.40 (s, 3H), 1.50 (s, 3H), 1.92 (dddd, J = 1.2, 4.3, 5.4, 12.7 Hz, 1H), 2.10 (ddd, J = 4.8, 11.5, 12.7 Hz, 1H), 3.40 (s, 3H), 4.12 (ddd, J = 3.4, 5.4, 11.5 Hz, 1H), 4.49 (ddd, J = 1.2, 5.9, 3.4 Hz, 1H), 4.53 (dd, J = 4.3, 4.8 Hz, 1H), 4.69 (dt, J = 1.6, 5.9 Hz, 1H), 4.74 (s, 2H), 5.12 (s, 1H), 5.17 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.21, −5.01, 17.98, 25.50, 25.62, 27.08, 29.56, 34.88, 55.21, 69.93, 70.86, 76.03, 76.12, 95.47, 109.58, 113.13, 146.32. MS *m/z* (assignment, relative intensity): 359 (M^+ + 1, 1), 244 ($M^+ + 1 - Si(CH_3)_2C(CH_3)_3$, 15). Anal. Calcd for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56. Found: C, 59.95; H, 9.44.

4-Hydroxy-4-hydroxymethyl-7-methoxymethoxy-2,2-dimethyl-5-*tert*-butyldimethylsilyloxy-(3a*S*,4*S*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-4-ol (12). A solution of osmium tetroxide in toluene (0.05 M, 0.56 mL, 0.28 mmol) and NMO (0.558 g, 4.13 mmol) was added to a stirred solution of compound **11** (0.5 g, 1.39 mmol) in acetone (16 mL)/water (4 mL). The reaction mixture was stirred at room temperature in the dark for 24 h. Sodium bisulfite (0.5 g) was added, and the reaction mixture was stirred for another 1 h, dried over Na_2SO_4, filtered through a Celite pad, and concentrated under reduced pressure. The diol was purified by flash chromatography. Elution with EtOAc/hexane (15/85 to 40/60) gave **12** (0.45 g, 85%) as a colorless oil. R_f = 0.48 (50% EtOAc/hexane, B: brown). $[\alpha]^{25}_D$ +33.67 (*c* 0.59, $CHCl_3$). IR γ_{max} (film): 3320−3450 (br, OH's) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 1.29 (s, 3H), 1.43 (s, 3H), 1.72 (dddd, J = 1.0, 4.9, 6.4, 13.5 Hz, 1H), 2.09 (ddd, J = 8.1, 10.0, 13.5 Hz, 1H), 2.33 (d, J = 10.0 Hz, 1H), 2.79 (s, 1H), 3.32 (s, 3H), 3.47 (dd, J = 10.0, 11.5 Hz, 1H), 3.58 (d, J = 11.5 Hz, 1H), 4.13 (dd, J = 4.9, 8.1 Hz, 1H), 4.24 (d, J = 7.3 Hz, 1H), 4.26 (ddd, J = 3.2, 6.4, 10.0 Hz, 1H), 4.44 (ddd, J = 1.0, 7.3, 3.2 Hz, 1H), 4.64 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.01, −4.25, 17.89, 24.04, 25.77, 26.24, 32.91, 55.33, 66.41, 67.03, 70.43, 72.58, 74.66, 77.64, 95.73, 109.44. MS *m/z* (assignment, relative intensity): 394 (M^+ + 1), 377 ($M^+ + 1 - CH_3$, 5), 245 (40), 75 (55), 45 (100). Anal. Calcd for $C_{18}H_{36}O_7Si$: C, 55.07; H, 9.24. Found: C, 55.75; H, 9.65.

7-Methoxymethoxy-2,2-dimethyl-5-*tert*-butyldimethylsilyloxy-(3a*S*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-4-one (13). To a stirred solution of the diol **12** (0.4 g, 1.02 mmol) in THF (2 mL)/water (2 mL) was added sodium periodate (0.32 g, 1.5 mmol) portionwise. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was extracted with EtOAc, concentrated under reduced pressure, and purified by flash chromatography to provide inosose **13** (0.3 g, 80%). R_f = 0.72 (25% EtOAc/hexane, B: reddish brown). $[\alpha]^{25}_D$ +64.45 (*c* 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.42 (s, 3H), 1.48 (s, 3H), 2.21 (m, 2H), 3.42 (s, 3H), 4.18 (dd, J = 2.8, 4.0 Hz, 1H), 4.52 (ddd, J = 3.1, 6.4, 9.8 Hz, 1H), 4.71 (m, 2H), 4.77 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.24, −5.12, 17.97, 25.55, 25.93, 26.91, 29.63, 34.29, 55.49, 69.39, 74.11, 76.37, 78.17, 96.19, 110.83, 205.24. MS *m/z* (assignment, relative intensity): 360 (M^+ + 2), 242 (20), 184 (30), 46 (100). Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found: C, 56.57; H, 8.55.

7-Methoxymethoxy-2,2-dimethyl-5-*tert*-butyldimethylsilyloxy-(3a*R*,4*R*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-4-ol (14). Method A. $NaBH_4$ (16.5 mg, 0.45 mmol) was added to a solution of inosose **13** (150 mg, 0.41 mmol) in methanol (2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 45 min at 0 °C before quenching with a few drops of saturated Na_2SO_4 solution. The solvent was evaporated under reduced pressure and directly charged over a dry silica gel column for purification to give **14** (0.14 g, 93%) as a colorless oil.

Method B. To a stirred solution of **13** (150 mg, 0.41 mmol) in CH_2Cl_2 was added Dibal-H (0.33 mL, 1.5 M solution in toluene, 0.49 mmol) at −78 °C. After 30 min, the reaction mixture was quenched with a few drops of water and stirred for a few minutes. Then the mixture was filtered through a Celite pad, concentrated under reduced pressure, and purified by silica gel column chromatography to give **14** (143 mg, 95%). R_f = 0.45 (25% EtOAc/hexane, B: red). $[\alpha]^{25}_D$ +45.56 (*c* 0.98, $CHCl_3$). IR γ_{max} (film): 3380 (br s, OH) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.90 (s, 9H), 1.39 (s, 3H), 1.55 (s, 3H), 1.79 (dddd, J = 1.0, 6.1, 4.4, 13.5 Hz, 1H), 2.26 (ddd, J = 10.9, 7.1, 13.5 Hz, 1H), 2.36 (d, J = 4.2 Hz, 1H), 3.40 (s, 3H), 3.56 (dt, J = 4.05, 4.2, 7.8 Hz, 1H), 4.02 (ddd, J = 3.3, 6.1, 10.9 Hz, 1H), 4.07 (dt, J = 4.1, 7.8, 4.4, 7.1 Hz, 1H), 4.45 (dd, J = 4.1, 7.3 Hz, 1H), 4.54 (ddd, J = 3.3, 7.3, 1.0 Hz, 1H), 4.71 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.81, −4.61, 17.97, 24.22, 25.76, 25.91, 32.39, 55.43, 69.07, 69.46, 70.77, 74.56, 75.09, 95.38, 109.65. MS *m/z* (assignment, relative intensity): 363 (M^+ + 1, 1), 276 (6), 273 (8), 215 (10), 91 (90), 45 (100). Anal. Calcd for $C_{17}H_{34}O_6Si$: C, 56.32; H, 9.45. Found: C, 56.44; H, 9.32.

7-Methoxymethoxy-2,2-dimethyl-4-(4-nitrophenylcarbonyloxy)-5-*tert*-butyldimethylsilyloxy-(3a*S*,4*S*,5*S*,7*S*,-7a*S*)-perhydrobenzo[*d*][1,3]dioxol (15). Diethylazodicarboxylate (DEAD) (0.09 mL, 0.56 mmol) was added dropwise to a solution of **14** (0.1 g, 0.28 mmol), triphenylphosphine (0.15 g, 0.56 mmol), and *p*-nitrobenzoic acid (0.094 g, 0.56 mmol) in THF (1.5 mL) at room temperature. After stirring for 24 h at room temperature, the solvent was removed under reduced pressure. The residue was taken up in ether and washed successively with saturated aqueous $NaHCO_3$ and brine. After drying and evaporation, the residue was purified by flash chromatography yielding benzoate ester **15** (0.048 g, 35%) as a colorless oil. R_f = 0.32 (15% EtOAc/hexane, B: brown). $[\alpha]^{25}_D$ +39.26 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.003 (s, 6H), 0.87 (s, 9H), 1.41 (s, 3H), 1.58 (s, 3H), 1.65 (m, 1H), 2.02 (m, 1H), 3.43 (s, 3H), 3.59 (m, 1H), 4.34 (m, 2H), 4.48 (dd, J = 4.9, 7.92 Hz, 1H), 4.59 (dt, J = 1.0, 4.39 Hz, 1H), 4.77 (ABq, J = 7.0, 12.5 Hz, 2H), 8.22−8.32 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.09, 25.57, 26.31, 28.10, 29.69, 32.56, 39.02, 55.6, 68.18, 69.97, 76.25, 77.60, 96.07, 123.53, 130.91, 139.50, 179.91. Anal. Calcd for $C_{24}H_{37}NO_9Si$: C, 56.34; H, 7.29; N, 2.74. Found: C, 56.15; H, 7.05; N, 2.67.

7-Methoxymethoxy-2,2-dimethyl-5-*tert*-butyldimethylsilyloxy-(3a*R*,4*S*,5*S*,7*S*,7a*S*)-perhydrobenzo[*d*][1,3]dioxol-4-ol (16). To a stirred solution of **15** (0.048 g, 0.094 mmol) in 0.5 mL of methanol was added sodium methoxide (30% solution in MeOH, 0.1 mL). The mixture was stirred for 30 min and then quenched with water. The solvent was evaporated under reduced pressure and directly charged over a dry silica gel column for purification. Elution with EtOAc/hexane (5/95 to 20/80) gave 0.03 g of **16** as a colorless oil. R_f = 0.42 (25% EtOAc/hexane, B: red). $[\alpha]^{25}_D$ +38.87 (*c* 0.48, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.39 (s, 3H), 1.55 (s, 3H), 1.94 (dddd, J = 1.0, 6.1, 4.8, 13.5 Hz, 1H), 2.00 (ddd, J = 4.2, 10.5, 13.5 Hz, 1H), 2.12 (br s, 1H), 3.40 (s, 3H), 3.62 (dd, J = 3.1, 5.7 Hz, 1H), 4.13 (t, J = 5.7 Hz, 1H), 4.14 (ddd, J = 4.8, 4.4, 3.1 Hz, 1H), 4.28 (ddd, J = 3.6, 6.1, 10.5 Hz, 1H), 4.46 (ddd, J = 5.7, 3.6, 1.0 Hz, 1H), 4.73 (s, 2H). Anal. Calcd for $C_{17}H_{34}O_6Si$: C, 56.32; H, 9.45. Found: C, 56.34; H, 9.49.

(1a,2a,3a,4a,5b)-Pentahydroxycyclohexane [(+)-*allo*-Quercitol] (17). To a stirred solution of **14** (0.15 g, 0.42 mmol) in methanol (2 mL) was added a 6 M HCl solution (1 mL), and it was heated to 60 °C. After 4 h, all the solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (35% $CHCl_3$−IPA)

to afford **17** (0.645 g, 95%) as a colorless solid. R_f = 0.5 (50% $CHCl_3$−IPA). mp >200 °C (lit.[6a] 262 °C for DL isomer). $[\alpha]^{25}_D$ +23.3 (*c* 0.36, water). ^{1}H NMR (500 MHz, D_2O): δ 1.52 (ddd, *J* = 3.1, 9.4, 13.9 Hz, 1H), 2.05 (ddd, *J* = 4.4, 5.9, 13.9 Hz, 1H), 3.49 (dd, *J* = 2.9, 8.2 Hz, 1H), 3.73 (t, *J* = 3.1 Hz, 1H), 3.93 (dd, *J* = 2.9, 3.1 Hz, 1H), 3.97 (ddd, *J* = 8.2, 9.3, 4.4 Hz, 1H), 3.99 (ddd, *J* = 5.9, 3.1, 3.2 Hz, 1H). ^{13}C NMR (500 MHz, D_2O): δ 34.21, 63.69, 67.12, 70.20, 71.34, 73.02. Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.73. Found: C, 43.79; H, 7.33.

(1a,2a,3a,4a,5b)-Pentaacetoxycyclohexane [(+)-*allo*-Quercitol Pentaacetate] (18). To a stirred solution of **17** (0.05 g, 0.3 mmol) in 0.5 mL of pyridine was added acetic anhydride (0.1 mL). The reaction mixture was stirred at room temperature for 8 h and cooled to 0 °C. After addition of 5 mL of water, the water phase was extracted with ether (4 × 5 mL). The combined organic extract was washed with $NaHCO_3$ solution (1 mL) and water and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography to afford **18** (0.1 g, 90%) as a colorless solid. R_f = 0.5 (50% EtOAc/hexane, B: brown). mp 114 °C (lit.[6a] mp 94 °C for DL isomer). IR γ_{max} (KBr): 1238, 1369, 1739, 2925, 3467 cm^{-1}. $[\alpha]^{25}_D$ +11.6 (*c* 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (dddd, *J* = 3.5, 7.4, *J* = 1.5, 14.3 Hz, 1H), 2.070 (s, 6H), 2.073 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.30 (ddd, *J* = 4.1, 7.6, 14.3 Hz, 1H), 5.12 (dd, *J* = 3.4, 7.6 Hz, 1H), 5.30 (m, 3H), 5.40 (t, *J* = 3.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.60, 20.79, 20.89, 66.70, 67.17, 67.93, 68.34, 68.97, 169.43, 169.6, 169.72, 169.75, 169.78.

(1a,2a,3a,4b,5b)-Pentahydroxycyclohexane [(+)-*talo*-Quercitol] (19). Compound **16** (30 mg) was treated with acid to remove protecting groups as described above to give (+)-*talo*-quercitol **19** (14 mg, 97%) as a colorless solid. R_f = 0.45 (50% $CHCl_3$−IPA). mp >200 °C (lit.[6a] mp 246−248 °C dec). $[\alpha]^{25}_D$ +56.4 (*c* 0.2, water) [lit.[6a] +62 (*c* 0.5, water)]. Further data are in accord with the literature.[7]

(1a,2a,3a,4b,5b)-Pentaacetoxycyclohexane [(+)-*talo*-Quercitol Pentaacetate] (20). (+)-*talo*-Quercitol **19** (10 mg) was submitted to acetylation as described above to give (+)-*talo*-quercitol pentaacetate **20** (19.8 mg, 90%) as a colorless solid. R_f = 0.6 (50% EtOAc/hexane). $[\alpha]^{25}_D$ +24 (*c* 0.2, $CHCl_3$) [lit.[6a] +28 (*c* 1, $CHCl_3$)]. mp 172−178 °C dec (lit.[6a] mp 182−183 °C). Further data are in accord with the literature.[7]

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Supporting Information Available: Energy-minimized structures of compounds **8*E***, **8*Z***, **9*E***, **9*Z***, **11**, **12**, **14**, **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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