Application of D-*chiro*-Inositol as a Chiral Template for the *Diels–Alder* Reaction

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday and in recognition of his many contributions to our discipline

The *Diels–Alder* reaction can reliably provide the expected *endo*-product in the presence of secondary orbital overlap. It can be considerably more difficult to access a single enantiomer of the *exo*-product. In this paper, a D-*chiro*-inositol derivative is used as a chiral tether to facilitate the regio-, diastereo-, and enatioselective cycloaddition between cinnamic acid and hexa-3,5-dienoic acid. The *Diels–Alder* reaction between these two substrates, or their respective esters, does not occur under thermal conditions. Because of the ease of removal of the chiral tether from the resulting cyclohexene, this approach could provide a viable technique to access otherwise unavailable systems.

1. Introduction. – The use of chiral tethers connecting two reactive moieties provides an excellent solution for asymmetric induction in C–C bond-forming reactions [1]. Highly functionalized chiral cyclic systems, such as inositols, could serve as templates for such applications. An ideal reaction for the investigation of the use of inositols as chiral tethers is the *Diels–Alder* cycloaddition, in which the diene and the dienophile can combine to form up to eight potential products, and four stereogenic centers in fully substituted systems. In the *Diels–Alder* reaction, regiochemistry is often controlled through the careful tuning of the electronic nature of the substituents, and diastereoselectivity can often be controlled through secondary orbital overlap, but regiochemical control is often less than perfect even for biased systems, and selectivity is difficult to obtain in cases where one of the reagents lacks a large difference in the orbital coefficients at the terminal positions of either the diene or dienophile [2][3]. Exclusive selectivity is of great interest, as the regioisomers and diastereoisomers often have similar chemical and physical properties that complicate their isolation. The formation of enantiomers, of course, leads to even greater purification difficulties. A chiral template, such as D-*chiro*-inositol, may be ideal for conducting otherwise difficult transformations to possibly provide only a single product. D-*chiro*-Inositol has been previously used as a chiral auxiliary, but not, to the best of our knowledge, as a chiral tether [4]. In this paper, we report the results of a stereoselective *Diels–Alder* cycloaddition mediated by D-*chiro*-inositol.

2. Preparation of Cycloadduct 4a and Diol 5. – To investigate the above premise, the reaction between cinnamic acid and hexa-3,5-dienoic acid was investigated. The

Diels–Alder reaction between these two substrates or between their corresponding esters has not been reported, although more complex cinnamyl and more highly substituted $\beta,\gamma,\delta,\varepsilon$-unsaturated esters have been subjected to *Diels–Alder* reactions [5]. The resulting cycloadducts would be of considerable interest as they contain three stereogenic centers and an olefin that can be readily functionalized. However, there are eight possible products that can form (*i.e.*, **A**–**H**; *Fig. 1*). An attempt at an intermolecular *Diels–Alder* reaction between cinnamic and hexadienoic acid was unsuccessful; when the substrates were heated to 100° for 96 h in 1,2,4-trichlorobenzene, only the starting materials were recovered. At 140°, the hexadienoic acid completely decomposed, and only the cinnamic acid was quantitatively recovered. Similarly, when the methyl esters of the two substrates were subjected to reaction at 80°, no reaction was observed after 24 h, and after an additional 48 h at 140°, the methyl 3,5-hexadienoate had fully decomposed leading to a quantitative recovery of unreacted methyl cinnamoate from the reaction mixture. As neither the carboxylic acids nor their respective methyl esters led to the formation of *Diels–Alder* products under thermal conditions, D-*chiro*-inositol-derived templates were investigated to access the cycloadducts.

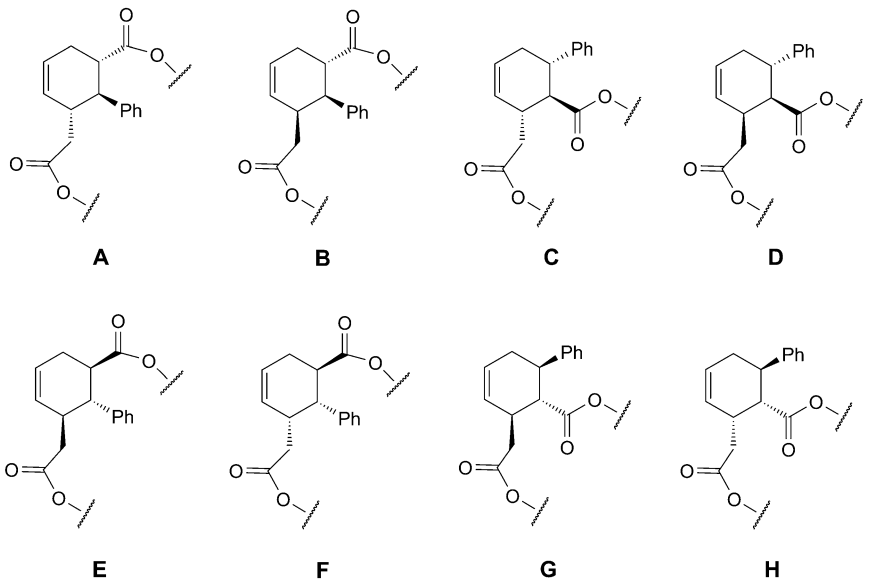
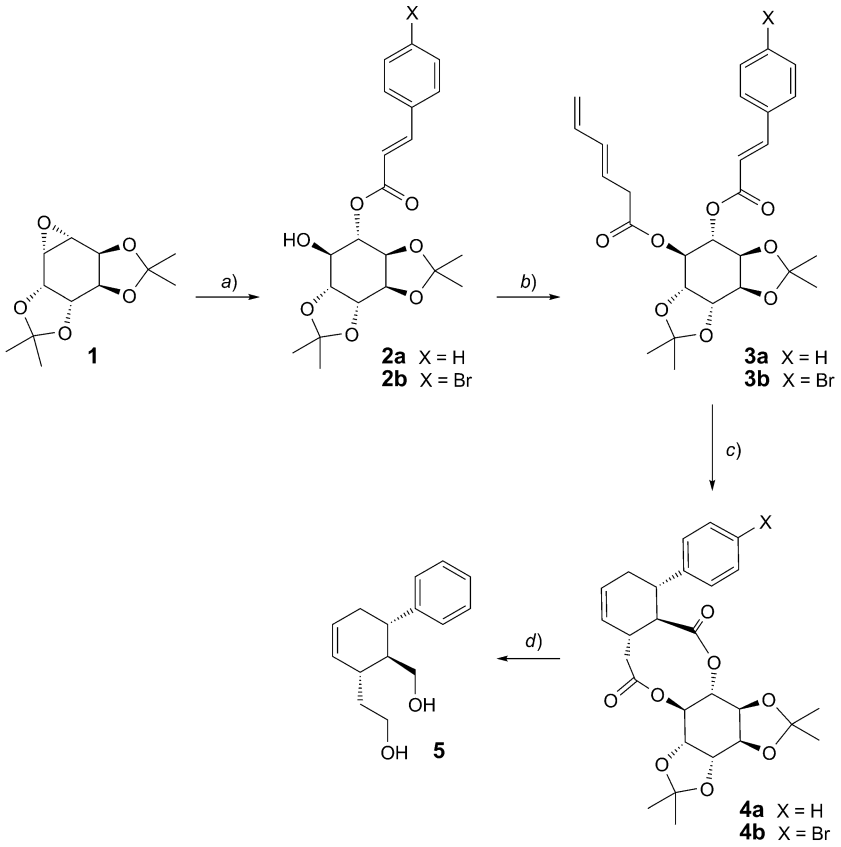


Fig. 1. *Eight possible cyclohexenes from the intramolecular* Diels–Alder *reaction of* **3a**

Epoxide **1** [6] was found to be chemically inert to many published ring-opening techniques including *Brønsted* and *Lewis* acid catalysis, amine catalysis, hydrolysis with KOH in DMSO, opening with cesium carboxylates, and reaction with neat carboxylic acid in a melt [7], but it was cleanly converted to cinnamate **2a** (*Scheme*) in the presence of 18-crown-6, Bu_4NI, and cinnamic acid. The reaction did not proceed significantly without all the components present. A further analysis of the conditions and results of epoxide opening under these conditions can be found in the

Scheme. *Preparation of Cyclohexene* **5** via *Cycloadducts* **4a** *and* **4b**



a) 3 Equiv. of potassium cinnamate, 3 equiv. of 18-crown-6, 1 equiv. of cinnamic acid, 0.2 equiv. of Bu_4NI, DMF, 1,2-dimethoxyethane, hexamethylphosphoric triamide, 127°, 96 h. *b*) Hexa-3,5-dienoic acid, *N*,*N*′-dicyclohexylcarbodiimide (DCC), CH_2Cl_2. *c*) 1,3,5-Trichlorobenzene, 141°, 72 h. *d*) 1. $LiAlH_4$, THF, reflux, 4 h; 2. 60% AcOH, 80°, 12 h; 3. MeONa/MeOH.

supplementary information. Standard *N*,*N*′-dicyclohaxylcarbodiimide (DCC) coupling of the resulting alcohol provided fully substituted inositol **3a** that was then subjected to thermal *Diels–Alder* conditions. The reaction was first carried out in deuterated toluene and DMSO, and monitored by NMR. Reaction mixtures were heated to 60°, and warmed by a further 10° every 4 h after NMR analysis showed no further conversion. At 130°, trace conversion was noted after 4 h, and conversion increased slowly after 12 h, providing what appeared to be a single compound. However, this reaction provided insufficient material for characterization as it contained a significant amount of decomposed material (presumably because of the instability of DMSO at higher temperatures); consequently, the solvent was changed to 1,2,4-trichlorobenzene, and, after 92 h at 140–142°, a single tricyclic compound (of the eight possibilities) was isolated in 62% yield by chromatography as the only product, with the mass balance

recovered as unreacted starting material. The relative configuration of the cyclohexene ring was assigned by NMR coupling constant analysis and is consistent with structures **C** and **G** (*Fig. 1*). However, the conformational flexibility of the nine-membered ring did not allow for an unambiguous assignment of the configuration using NOESY studies.

3. Density-Functional-Theory (DFT) Analysis of the Intramolecular *Diels–Alder* Reaction of 5a. – To better understand the origin of stereoselectivity in the above *Diels–Alder* reaction, a set of hybrid DFT calculations were performed at the B3LYP/6–31G(d) level of theory at 100°, using the IEFPCM method with the default parameters of toluene to account for solvent effects. All geometrically viable *Diels–Alder* transition states were considered; eleven transition states were located, each possessing only a single imaginary frequency. Of these, at least one transition state for each of the eight possible diastereoisomers was located. One of the most noticeable structural features of these first-order saddle points is that all eleven were highly asynchronous, yet concerted in nature, with C(3)–C(4) bond-formation preceding that of the C(1)–C(2) bond. Furthermore, in those transition states where the ester groups had their carbonyl O-atoms directed *syn* to one another, it was found that an unfavorable $O_{LP}-O_{LP}$ coulombic interaction forced the [6.9.6] ring system into a distorted geometry.

The computed *Gibbs* free-energy values indicated that (*R*,*S*,*S*)-TS-**C** (*Fig. 2*) was energetically favored. The only other transition state within 4 kcal/mol was (*S*,*S*,*S*)-TS-**D**, which was higher in energy by 1.4 kcal/mol. To further substantiate these results, single-point MP2/6-31G(d) calculations were performed on the optimized transition state structures. Again, (*R*,*S*,*S*)-TS-**C** was preferred over (*S*,*S*,*S*)-TS-**D** by 1.9 kcal/mol, and all other transition states were higher in energy by at least 4 kcal/mol. It is noteworthy that the predicted stereochemical outcome of this reaction was not only consistent with experiment, but was also made in advance of the stereochemical assignment of the observed product. However, it is granted that the computed energetic difference between (*R*,*S*,*S*)-TS-**C** and (*S*,*S*,*S*)-TS-**D** is slightly underestimated. In terms

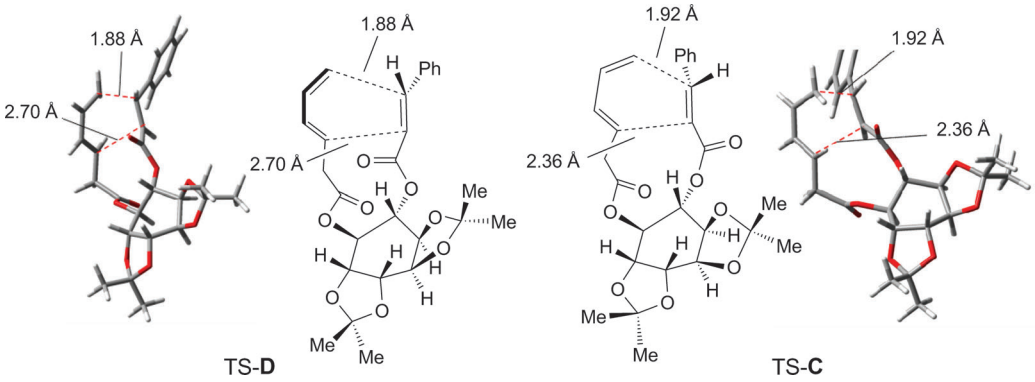


Fig. 2. *Calculated lowest-energy transition-state structures for the formation of diastereoisomer* **D** (TS-**D**), *and diastereoisomer* **C** (TS-**C**) *at B3LYP/6-31G(d) level of theory with toluene as solvent*

of the key metrics of both (*R,S,S*)-TS-**C** and (*S,S,S*)-TS-**D**, the ester carbonyl O-atoms were aligned *anti* to one another, minimizing the aforementioned distortion in the [6.9.6] ring system. Following the Intrinsic Reaction Coordinate (IRC), one observes that the C(1)–C(2) bond actually begins to form after the transition state. It is likely that this asynchronicity arises primarily from steric constraints imposed by the chiral, sugar based tether, as opposed to electronic effects. As such, those tethered transition states which allow C(1) and C(2) to lie closer together, with minimal steric repulsion, will be favored. The calculated transition-state structures show that geometrical constraints imposed by the tether affect the allowed C(1)···C(2) interatomic distance in (*S,S,S*)-TS-**D** more so than in (*R,S,S*)-TS-**C**. In (*S,S,S*)-TS-**D**, there exists an unfavorable steric contact between H(40) of the diene and H(60) of the dienophile (2.54 Å). The result is an elongated C(1)···C(2) interatomic distance (2.70 Å), beyond that of an optimal bond-forming distance. As such, C(1)–C(2) bond formation is driven by the preceding C(3)–C(4) bond-forming event, which subsequently forces C(1) and C(2) into closer proximity. Conversely, due to the orientation of the diene in (*R,S,S*)-TS-**C**, this steric contact does not exist. The closest contact with H(40) becomes O(38) at 2.62 Å, which still allows C(1) and C(2) to remain at a much closer distance of 2.36 Å.

To confirm the predictions made by the molecular calculation, an X-ray crystal structure was required. Unfortunately, neither **4a** nor any derivative thereof formed a crystal suitable for analysis under any of the recrystallization conditions tested. However, when bromine derivative **4b** was prepared using the same sequence as used for **4a** with *para*-bromocinnamic acid instead of cinnamic acid for the epoxide ring opening, a crystalline solid suitable for x-ray analysis was obtained (*Fig. 3*)[1]). The absolute configuration determined for this derivative demonstrates that the *Diels–Alder* reaction does definitely occur through the predicted *exo*-transition state to provide a cyclohexene with configuration of **C** (*Fig. 3*). This product would not be expected from the intermolecular reaction between the corresponding esters, which should lead to a racemic mixture consisting mostly of the *endo*-cycloadduct due to the stabilization provided by the secondary orbital overlap. Consequently, this intramolecular methodology using D-*chiro*-inositol as a chiral tether provides access to a cycloadduct that would be very difficult to obtain through other means.

This chiral tether is removed in several ways: reductive cleavage of the ester functionalities of **4a** with $LiAlH_4$ provides cyclohexene derivative **5**. Similarly, hydrolysis of the esters can provide the dicarboxylate derivative. Consequently, this methodology could provide access to substituted cyclohexenes in various oxidation states, compounds that could serve as important building blocks for organic synthesis.

4. Remarks and Conclusions. – A stereoselective *Diels–Alder* cycloaddition was performed by utilizing D-*chiro*-inositol as a reaction tether. The results of this cycloaddition, which would not have been possible without the tether, matched the prediction made by computational methods. Furthermore, it appears that not only this, but no cycloadduct is not obtainable using either the parent carboxylic acids or their

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[1]) CCDC-885508 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

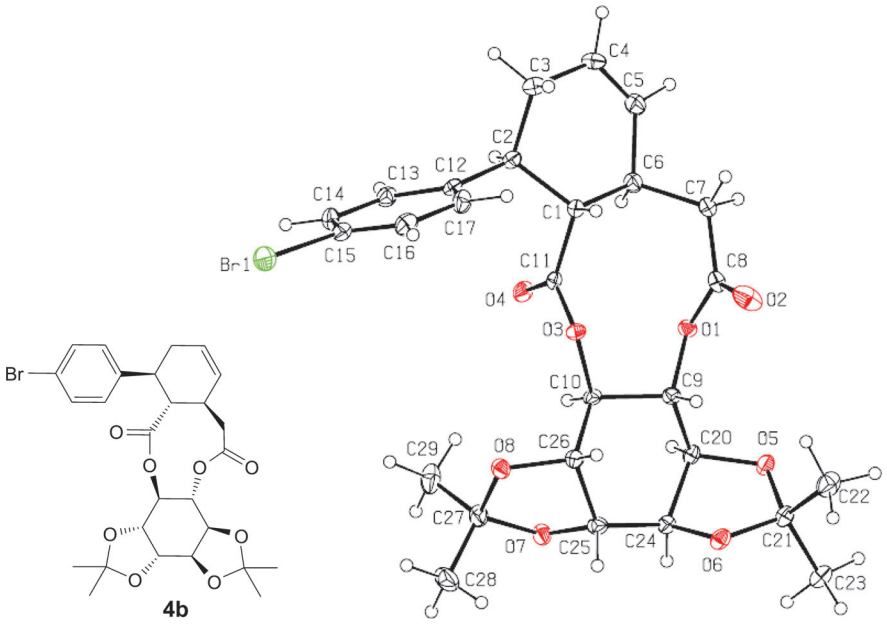

Fig. 3. *X-Ray structure obtained for bromo-aryl derivative* **4b** *corresponding to TS-***C**

respective methyl esters under thermal conditions. Consequently, D-*chiro*-inositol-derived tethers can provide selective access to novel cycloadducts that are difficult to obtain by other means.

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Experimental Part

1. *General.* Reactions were carried out under Ar in flame-dried glassware unless otherwise stated. Solvents were distilled: CH_2Cl_2, DMF, Et_3N, 1,2,4-trichlorobenzene, *ortho*-xylene, and pyridine from CaH_2; THF and 1,2-dimethoxyethane from Na/benzophenone. Other reagents were used from commercial sources (*Sigma-Aldrich*, *Alfa Aesar*, *Acros Organics*, *Oakwood Products, Inc.*) without further purification. Qual. TLC was conducted with pre-coated silica gel aluminum sheets (*EMD* silica gel *60* F_{254}), detection by UV, or by spraying with *Hanessian*'s stain, vanillin, or aq. $KMnO_4$ soln. followed by heating. M.p.: uncorrected. Flash chromatography (FC): silica gel *SiliaFlash P60* from *Silicycle* (40–66 μm). Optical rotation: 1-dm cell at 20–25° and 589 nm with a *Perkin-Elmer 341* polarimeter, concentration (*c*): in g/100 ml. IR Spectra: in a KBr cell in soln. with a *Perkin-Elmer Spectrum One* instrument; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: at 300 or 600 MHz, and 75 or 150 MHz, resp. on *Bruker AVANCE* spectrometers; calibrated on the solvent residual peak or TMS signal ($CDCl_3$: 7.26 ppm); the chemical shifts in ppm, *J* in Hz. MS: *Concept 1S* spectrometer (Dr. *Tim Jones*, Brock University) or on a *Micromass GCT* spectrometer (Dr. *Kirk Green*, McMaster University); *m*/*z* (rel. %). Elemental analysis (C and H): carried out by *Atlantic Microlab, Inc.*, 6180 Atlantic Blvd. Suite M, Norcross, GA 30071.

2. *Syntheses.* 2.1. *(1*R,*2*R,*3*S,*4*S,*5*S,*6*R*)-5-Cinnamoyloxy-6-hydroxy-1,2;3,4-di(isopropylidenedioxy)-cyclohexane (=*(3a*S,*4*S,*5*R,*5a*R,*8a*R,*8b*S*)*-Hexahydro-5-hydroxy-2,2,7,7-tetramethylbenzo[1,2-d:3,4-d'*]bis[1,3]*dioxol-4-yl *(2*E*)*-3-Phenylprop-2-enoate*; **2a**). Epoxide **1** (600 mg, 2.47 mmol) [6], potassium cinnamate (1.60 g, 8.60 mmol), freshly recrystallized 18-crown-6 (2.40 g, 9.00 mmol) [8], cinnamic acid (366 mg, 2.47 mmol), Bu_4NI (200 mg, 0.54 mmol), DMF (6 ml), 1,2-dimethoxyethane (6 ml), and HMPA (2 ml) were mixed in a pressure tube, sealed under Ar, and heated to 127° for 84 h with vigorous stirring. Reaction progress was monitored by TLC (hexanes/AcOEt 2:1; ceric ammonium molybdate (*Hannesian*'s stain)/UV). After final cooling, the reaction mixture was diluted with H_2O and CH_2Cl_2, and the phases were separated. The aq. phase was twice extracted with additional CH_2Cl_2, and the combined org. phases were washed twice with sat. Na_2CO_3 and with brine. Following drying and concentration in the usual fashion, the reaction vessel was sealed and stored at 4° for 12 h. FC of the crude material (hexanes/AcOEt (0.1% Et_3N on Et_3N-neutralized silica) 8:1 (5 column volumes) to 4:1 (5 column volumes) to 3.5:1 (2 column volumes)) provided **2a** (830 mg) in 87% isolated yield. White solid. R_f (hexanes/AcOEt 2:1) 0.29. M.p. 73–77° (precipitated from Et_2O/heptanes). $[\alpha]_D^{20} = 96.5$ (c = 1.0, $CHCl_3$). IR ($CHCl_3$, c = 26 mM): 3606, 2992, 2938, 1716, 1637, 1450, 1385, 1308, 1163, 1060, 859, 754. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.75 (*d*, *J* = 16.0, 1 H); 7.55–7.46 (*m*, 2 H); 7.41–7.35 (*m*, 3 H); 6.50 (*d*, *J* = 16.0, 1 H); 5.09 (*dd*, *J* = 11.4, 8.2, 1 H); 4.55–4.40 (*m*, 2 H); 4.35 (*dd*, *J* = 8.0, 5.9, 1 H); 4.27 (*dd*, *J* = 7.9, 6.0, 1 H); 3.68 (*dd*, *J* = 10.8, 8.3, 1 H); 2.47 (br. *s*, OH); 1.53 (*s*, 3 H); 1.52 (*s*, 3 H); 1.38 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.9; 146.1; 134.2; 130.5; 128.9; 128.2; 117.3; 109.7; 109.6; 79.0 77.5; 77.0; 76.6; 76.4; 75.6; 75.4; 73.5; 71.8; 27.8; 27.6; 25.6; 25.4. EI-MS: 375 (16.5), 317 (3.5), 227 (7.3), 142 (72.7), 131 (100). HR-EI-MS: 375.1437 ($[M-15]^+$, $C_{20}H_{23}O_7^+$; calc. 375.1444). Anal. calc. for $C_{20}H_{23}O_7$: C 64.6, H 6.7; found: C 64.2, H 6.8.

2.2. *5-Cinnamoyloxy-6-(hexa-3,5-dienyloxy)-2,2,7,7-tetramethylhexahydrobenzo[1,2-d;3,4-d'] bis[1,3]dioxol-4-ol* (=*(3a*S,*4*R,*5*R,*5a*S,*8a*S,*8b*S*)*-Hexahydro-2,2,7,7-tetramethyl-5-{[*(2*E*)*-3-phenylprop-2-enoyl]oxy}benzo[1,2-d:3,4-d'*]bis[1,3]dioxol-4-yl (3*E*)*-Hexa-3,5-dienoate*; **3a**). Compound **2a** (1.50 g, 3.83 mmol) was dissolved in freshly distilled CH_2Cl_2 (20 ml) along with hexa-3,5-dienoic acid (785 mg, 7.66 mmol) and cat. 4-(dimethylamino)pyridine (DMAP; 10 mg), and the yellow soln. was cooled to 0° under stirring. DCC (1.50 g, 7.27 mmol) was added, and the mixture was stirred for 3 h. The mixture turned slightly orange and formed insoluble material. TLC showed completion of the reaction, and the mixture was diluted with Et_2O and filtered through a *Celite* plug. Solvent was removed under reduced pressure, and FC (hexanes/AcOEt 8:1, 0.1% Et_3N on Et_3N-neutralized silica) of the crude product provided **3a** (1.41 g, 78%). White semi-solid. R_f (2:1 hexanes/AcOEt) 0.63. $[\alpha]_D^{20} = 30.5$ (c = 1.0, $CHCl_3$). IR ($CHCl_3$, c = 21 mM): 3941, 3052, 2987, 1744, 1718, 1265, 1163, 908, 749. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.66 (*d*, *J* = 16.0, 1 H); 7.52–7.47 (*m*, 2 H); 7.41–7.35 (*m*, 3 H); 6.38 (*d*, *J* = 16.0, 1 H); 6.13 (*ddd*, *J* = 16.6, 10.1, 10.1, 1 H); 5.99 (*dd*, *J* = 14.9, 10.5, 1 H); 5.62 (*ddd*, *J* = 14.7, 7.2, 7.2, 1 H); 5.16 (*dd*, *J* = 19.4, 8.1, 1 H); 5.19 (*dd*, *J* = 19.6, 8.0, 1 H); 5.01–4.86 (*m*, 2 H); 4.60–4.53 (*m*, 2 H); 4.44–4.34 (*m*, 2 H); 3.07 (*d*, *J* = 7.3, 2 H); 1.55 (*s*, 3 H); 1.54 (*s*, 3 H); 1.38 (*s*, 3 H); 1.37 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.6; 165.8; 146.0; 136.2; 134.7; 130.5; 128.9; 128.3; 124.8; 117.1; 117.0; 109.75; 109.71; 77.2; 76.3; 76.2; 74.9; 71.4; 71.0; 37.9; 27.6; 25.8. EI-MS: 469 (6.5), 426 (12.5), 131 (100). HR-EI-MS: 469.1868 ($[M-15]^+$, $C_{27}H_{32}O_8^+$; 469.1862). Anal. calc. for $C_{27}H_{32}O_8$: C 66.9, H 6.7; found: C 66.2, H 6.6.

2.3. *(1*S,*2*S,*3*S,*4*S,*4a*R,*6a*S,*7*S,*10a*R,*13a*R*)-1,2;3,4-Di(isopropylidenedioxy)-7-phenyl-2,3,4,4a,6a,7,10a,11-octahydro-1*H*-dibenzo[*b,f*][1,4]dioxonine-6,12(10*H,*13a*H*)-dione* (=*(3a*S,*3b*S,*6a*S,*6b*R,*8a*S,*9*S,*12a*R,*15a*R,*15b*S*)*-3a,3b,6a,6b,9,10,12a,13,15a,15b-Decahydro-2,2,5,5-tetramethyl-9-phenyl-8*H*-benzo[f]bis[1,3]dioxolo[3,4:5,6]benzo[1,2-b][1,4]dioxonine-8,14(8a*H*)-dione*; **4a**). Compound **3a** (320 mg, 0.68 mmol) was dissolved in 15 ml of 1,2,4-trichlorobenzene, and the soln. was stirred under vacuum, at r.t. for 1 h. The vessel was then isolated and sealed under vacuum, and then heated to 141° for 92 h. The ratio of product/starting material was monitored by NMR until it reached 73:27. Following cooling to r.t. the solvent was removed under high-vacuum distillation, and the residue was purified by FC (50 ml Et_3N-neutralized silica, 21-cm column height, hexanes/AcOEt 7.5:1, 0.1% Et_3N on Et_3N-neutralized silica) to provide 203 mg (62%) of **4a** as the only isolable cycloadduct. White solid. R_f (hexanes/AcOEt 6:1) 0.33. M.p. 174–176° ($CDCl_3$). $[\alpha]_D^{20} = 73.5$ (c = 0.14, $CHCl_3$). IR ($CHCl_3$, c = 3.0 mM): 3051, 2987, 1743, 1387, 1376, 1265, 1217, 1210, 1153, 783. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.27 (*m*, 2 H); 7.26–7.20 (*m*, 3 H); 5.91 (*tdd*, *J* = 9.5, 5.4, 1.9, 1.9, 1 H); 5.53 (*m*, 1 H); 5.06 (*dd*, *J* = 11.6, 8.0, 1 H); 4.86 (*dd*, *J* = 11.6, 8.6,

1 H); 4.47–4.36 (*m*, 3 H); 4.31 (*dd*, *J* = 8.5, 6.1, 1 H); 3.22 (*dt*, *J* = 11.8, 11.7, 5.0, 1 H); 3.15–3.02 (*m*, 1 H); 2.96 (*dd*, *J* = 14.3, 6.4, 1 H); 2.80 (*dd*, *J* = 12.0, 8.9, 1 H); 2.33 (*dd*, *J* = 14.3, 11.6, 1 H); 2.32–2.08 (*m*, 2 H); 1.54 (*s*, 3 H); 1.42 (*s*, 3 H); 1.36 (*s*, 3 H); 1.29 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.4; 171.8; 142.8; 128.6; 128.2; 127.4; 126.9; 126.8; 1110.5; 110.2; 76.7; 74.9; 74.7; 728; 51.0; 42.5; 41.4; 39.4; 32.2; 27.5; 27.4; 25.3; 25.2. HR-EI-MS: 469.1867 ([*M* − 15]$^+$, $C_{27}H_{32}O_8^+$; calc. 469.1862). Anal. calc. for $C_{27}H_{32}O_8$: C 66.9, H 6.7; found: C 67.1, H 6.9.

2.4. *(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*)-5-(4-Bromocinnamoyloxy)-6-hydroxy-1,2;3,4-di(isopropylidenedioxy)cyclohexane* (= *(3a*S*,4*S*,5*R*,5a*R*,8a*R*,8b*S*)-Hexahydro-5-hydroxy-2,2,7,7-tetramethylbenzo[1,2*-d:*3,4*-d′*]bis[1,3]dioxol-4-yl (2*E*)-3-(4-Bromophenyl)prop-2-enoate*; **2b**). Epoxide **1** (600 mg, 2.47 mmol) [6], potassium *para*-bromocinnamate (2.40 g, 8.60 mmol), freshly recrystallized 18-crown-6 (2.40 g, 9.00 mmol) [8], *para*-bromocinnamic acid (576 mg, 2.47 mmol), Bu_4NI (200 mg, 0.54 mmol), DMF (6 ml), 1,2-dimethoxyethane (6 ml), and HMPA (2 ml) were mixed in a pressure tube, sealed under Ar, and heated to 127° for 115 h under vigorous stirring. Reaction progress was monitored by TLC (hexanes/AcOEt 2:1, CAM/UV). After final cooling, the mixture was diluted with H_2O and Et_2O, and the phases were separated. The aq. phase was twice extracted with additional Et_2O, and the combined org. phases were washed twice with sat. Na_2CO_3 and with brine. Following drying and concentration in the usual fashion, the residue was purified by FC (hexanes/AcOEt 4:1, 0.1% Et_3N on Et_3N-neutralized silica) to provide 103 mg of the undesired diastereoisomer in the first fraction and 487 mg of the desired isomer, **2b**, in the second fraction, in addition to 421 mg of material in a mixed fraction. The mixed fraction was repurified in the same manner to obtain an additional 303 mg of **2b**, for a total of 790 mg in 68% yield. Colorless amorphous gel. R_f (hexanes/AcOEt 2:1) 0.29. $[\alpha]_D^{20} = 161.5$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3554, 3022, 2995, 2937, 171, 1638, 1488, 1385, 1312, 1167, 1072, 1041, 1010, 900, 860, 803, 734. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.61 (*d*, *J* = 16.0, 1 H); 7.45 (*pseudo-d*, *J* = 8.4, 2 H); 7.30 (*pseudo-d*, *J* = 8.5, 2 H); 6.43 (*d*, *J* = 16.0, 1 H); 5.06 (*dd*, *J* = 11.4, 8.3, 1 H); 4.45 (*dd*, *J* = 6.2, 3.2, 1 H); 4.42 (*dd*, *J* = 6.2, 3.2, 1 H); 4.30 (*dd*, *J* = 8.1, 5.9, 1 H); 4.23 (*dd*, *J* = 7.9, 6.1, 1 H); 3.64 (*dd*, *J* = 11.2, 8.2, 1 H); 2.90 (br. *s*, 1 H); 1.49 (*s*, 3 H); 1.48 (*s*, 3 H); 1.34 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.4; 144.3; 133.0; 132.0; 129.4; 124.6; 118.0; 109.5; 109.4; 78.9; 76.2; 75.5; 75.2; 73.5; 71.4; 27.7; 27.4; 25.4; 25.3. HR-EI-MS: 468.0794 (M^+, $C_{21}H_{25}BrO_7^+$; 468.0784). Anal. calc. for $C_{21}H_{25}BrO_7$: C 53.74, H 5.37; found: C 53.73, H 5.47.

2.5. *5-(4-Bromocinnamoyloxy)-6-(hexa-3,5-dienyloxy)-2,2,7,7-tetramethylhexahydrobenzo[1,2-*d*;3,4-*d′*]bis[1,3]dioxol-4-ol* (= *(3a*S*,4*R*,5*R*,5a*S*,8a*S*,8b*S*)-5-{[(2*E*)-3-(4-Bromophenyl)prop-2-enoyl]oxy}-hexahydro-2,2,7,7-tetramethylbenzo[1,2-*d*:3,4-*d′*]bis[1,3]dioxol-4-yl (3*E*)-Hexa-3,5-dienoate*; **3b**). Compound **2b** (460 g, 1.0 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 ml) along with hexa-3,5-dienoic acid (224 mg, 2.0 mmol) and cat. DMAP (10 mg), and the yellow soln. was cooled to 0° under stirring. DCC (391 mg, 1.9 mmol) was added, and the mixture was stirred for 4 h. The mixture immediately turned slightly orange and formed insoluble material. TLC showed completion of the reaction, and the mixture was diluted with Et_2O and filtered through a *Celite* plug. Solvent was removed under reduced pressure, and FC (hexanes/AcOEt 8:1, 0.1% Et_3N on Et_3N-neutralized silica) of the crude mixture provided 450 mg (80%) of **3b**. Colorless gel. R_f (hexanes/AcOEt 4:1) 0.59. $[\alpha]_D^{20} = 35.3$ ($c = 0.50$, $CHCl_3$). IR ($CHCl_3$, $c = 5$ mg/ml): 3027, 2992, 2935, 1740, 1721, 1637, 1488, 1385, 1309, 1209, 1165, 1073, 1008, 909, 855, 820, 782, 743, 679. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.53 (*d*, *J* = 16.0, 1 H); 7.45 (*pseudo-d*, *J* = 8.3, 2 H); 7.29 (*pseudo-d*, *J* = 8.4, 2 H); 6.31 (*d*, *J* = 16.0, 1 H); 6.07 (*ddd*, *J* = 16.6, 10.1, 10.1, 1 H); 5.93 (*dd*, *J* = 14.8, 10.7, 1 H); 5.56 (*ddd*, *J* = 14.7, 7.2, 7.2, 1 H); 5.20–5.05 (*m*, 2 H); 4.90 (*d*, *J* = 16.4, 1 H); 4.84 (*d*, *J* = 9.8, 1 H); 4.55–4.49 (*m*, 2 H); 4.38–4.28 (*m*, 2 H); 3.02 (*d*, *J* = 7.2, 2 H); 1.50 (*s*, 3 H); 1.48 (*s*, 3 H); 1.32 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 1703; 165.3; 144.3; 136.0; 134.4; 132.9; 131.9 (2 × CH); 129.4 (2 × CH); 124.7; 124.6; 117.6; 116.8; 109.51; 109.46; 76.1; 75.9; 74.7 (2 × CHC_2OR); 71.2; 71.0; 37.8; 27.42; 27.39; 25.6; 25.6. HR-EI-MS: 562.1198 (M^+, $C_{27}H_{31}BrO_8^+$; calc. 562.1202). Anal. calc. for $C_{27}H_{31}BrO_8$: C 57.56, H 5.55; found: C 57.41, H 5.65.

2.6. *(1*S*,2*S*,3*S*,4*S*,4a*R*,6a*S*,7*S*,10a*R*,13a*R*)-7-(4-Bromophenyl)-1,2;3,4-di(isopropylidenedioxy)-2,3,4,4a,6a,7,10a,11-octahydro-1*H*-dibenzo[b,f][1,4]dioxonine-6,12(10*H*,13a*H*)-dione* (= *(3a*S*,3b*S*,6a*S*,6b*R*,8a*S*,9*S*,12a*R*,15a*R*,15b*S*)-9-(Bromophenyl)-3a,3b,6a,6b,9,10,12a,13,15a,15b-decahydro-2,2,5,5-tetramethyl-8*H*-benzo[f]bis[1,3]dioxolo[3,4:5,6]benzo[1,2-*b*][1,4]dioxonine-8,14(8a*H*)-dione*; **4b**). Compound **3b** (400 mg, 0.71 mmol) was dissolved in 90 ml of 1,2,4-trichlorobenzene, and the soln. was

stirred under vacuum at r.t. for 1 h. The vessel was then sealed under vacuum and then heated to 141° for 120 h. Following cooling to r.t., the solvent was removed under high-vacuum destillation, and the residue was purified by FC (hexanes/AcOEt 8:1, 0.1% Et_3N on Et_3N-neutralized silica) to provide 20 mg of material in the first fraction, which although co-spotting with the starting material, was thoroughly decomposed, and 320 mg of **4b** in 80% yield as the only isolable cycloadduct in the second fraction. Additionally 10 mg of mixed fractions were obtained but were discarded. A portion of **4b** was recrystallized from a mixture of benzene/abs. EtOH (initially 4:1) and a drop of H_2O through slow evaporation over three weeks to obtain crystals suitable for X-ray analysis. White crystalline solid. R_f (hexanes/AcOEt 4:1, UV/$KMnO_4$) 0.52. M.p. 212° (dec., CH_2Cl_2). $[\alpha]_D^{20} = 83.8$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$, $c = 10$ mg/ml): 3023, 2992, 2963, 1743, 1711, 1490, 1385, 1376, 1262, 1260, 1153, 1126, 1075, 1056, 1009, 909, 856, 803, 712. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37 (*pseudo-d*, $J = 8.4$, 2 H); 7.05 (*pseudo-d*, $J = 8.4$, 2 H); 5.85 (*tdd*, $J = 9.8$, 5.8, 1.8, 1.8, 1 H); 5.48 (*m*, 1 H); 5.03 (*dd*, $J = 11.6$, 8.4, 1 H); 4.82 (*dd*, $J = 11.6$, 8.6, 1 H); 4.45–4.25 (*m*, 3 H); 4.29 (*dd*, $J = 8.6$, 6.0, 1 H); 3.15 (*dt*, $J = 11.8$, 11.7, 4.8, 1 H); 3.10–2.98 (*m*, 1 H); 2.91 (*dd*, $J = 14.3$, 6.3, 1 H); 2.72 (*dd*, $J = 12.0$, 8.8, 1 H); 2.28 (*dd*, $J = 14.3$, 11.7, 1 H); 2.20 (*td*, $J = 17.7$, 5.1, 5.1, 1 H); 2.09 (*ddd*, $J = 11.7$, 5.0, 2.8, 1 H); 1.50 (*s*, 3 H); 1.40 (*s*, 3 H); 1.33 (*s*, 3 H); 1.27 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.0; 171.5; 141.8; 131.6; 129.0; 128.1; 126.3; 120.5; 110.2; 110.1; 76.6; 76.5; 75.1; 74.7; 74.5; 72.6; 50.6; 41.9; 41.2; 39.3; 32.0; 27.35; 27.30; 25.14; 25.10. HR-EI-MS: 547.0986 ($[M-15]^+$, $C_{27}H_{31}BrO_8^+$; calc. 547.0981). Anal. calc. for $C_{27}H_{31}BrO_8$: C 57.56, H 5.55; found: C 57.30, H 5.55.

2.7. *2-[(1*R*,5*S*,6*S*)-6-(Hydroxymethyl)-5-phenylcyclohex-2-en-1-yl]ethanol* (**5**). Cycloadduct **4a** (34 mg, 0.070 mmol) was dissolved in anh. THF (2 ml) under Ar. $LiAlH_4$ (22 mg, 0.562 mmol) was added at 0° in one portion, and the mixture was heated to reflux. After 2 h, the reaction was quenched through successive addition of 100 µl of H_2O, 200 µl of 15% NaOH, and 400 µl of H_2O. The suspension was then filtered through *Celite* with AcOEt, then dried ($MgSO_4$), filtered and concentrated. The crude mixture was immediately dissolved in 60% AcOH and heated to 80° for 12 h. Solvent was removed under reduced pressure, and the residue was treated with cat. MeONa in MeOH at r.t. for 2 h, followed by treatment with *Dowex-50X* resin. The resin was removed by filtration, the solvent was removed under reduced pressure, and the residue was purified by FC (AcOEt/hexanes 2:1) to provide **5** (9 mg, 58%). Clear oil. R_f (hexanes/AcOEt 1:1) 0.07. $[\alpha]_D^{20} = -47.0$ ($c = 1.0$, MeOH). IR ($CDCl_3$): 3624, 2253, 1816, 1793, 1466, 1381, 1095, 905. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.42–7.17 (*m*, 5 H); 5.87–5.77 (*m*, 1 H); 5.73 (*ddd*, $J = 10.0$, 3.6, 2.1, 1 H); 3.87–3.75 (*m*, 2 H); 3.64 (*dd*, $J = 11.5$, 3.2, 1 H); 3.38 (*dd*, $J = 11.4$, 3.1, 1 H); 2.86 (*td*, $J = 11.1$, 8.2, 8.2, 1 H); 2.53 (br. *s*, 1 H); 2.34–2.23 (*m*, 2 H); 2.02–1.86 (*m*, 1 H); 1.81–1.45 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 145.0; 130.9; 128.7; 127.7; 126.4; 126.2; 61.8; 60.6 45.7; 42.9; 36.2; 34.2; 34.1. HR-EI-MS: 214.1362 ($[M-H_2O]^+$, $C_{15}H_{20}O_2^+$; calc. 214.1358).

3. *X-Ray Analysis of* **4b**. 3.1. *General.* All measurements were made by means of a *Bruker Kappa APEX DUO CCD* area-detector diffractometer with graphite monochromated CuK_α radiation (λ 1.54178 Å) using a *Bruker ImuS* radiation source. Data reduction was performed with SAINT (*Bruker*, 2007). All calculations were performed with the SHELXL97 program [9], and the crystallographic diagrams were drawn with PLATON [10].

3.2. *Determination of Structure of* **4b**. The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 38907 reflections in the range $3.61° < 2\theta < 66.54°$. A total of 5875 frames were collected by using φ and ω scans with κ offsets. Equivalent reflections were merged.

Data Collection and Refinement Parameters. Crystallized from benzene/EtOH/H_2O; $C_{27}H_{31}BrO_8$; M_r 563.4342 g/mol; crystal dimensions, 0.19 mm × 0.14 mm × 0.01 mm; colorless plates; monoclinic; space group *P*21: unit cell parameters: $a = 12.7006(6)$, $b = 5.7739(3)$, $c = 23.6378(14)$ Å, $\alpha = 90$, $\beta = 105.522(3)°$, $\gamma = 90$; $V = 1670.19(15)$ Å^3; $Z = 2$; $F(000)$, 668.0; T 147 K; $D_x = 1.276$ g/cm^3; wavelength, 1.54178 Å; μ(CuK_α) = 2.062; scan type, φ and ω; $2\theta_{(max)} = 66.54$; 2θ range for cell determination, 3.61–66.54°; reflections for cell determination, 38907; transmission factors (min; max), 0.661, 0.7538; absorption correction, semi-empirical from equivalents; total reflections measured, 5875; symmetry-independent reflections, 3261; $R_{int} = 0.0373$; reflections with $I > 2\sigma(I)$, 5510; reflections used in refinement, 5657; parameters refined, 383; refinement method, full-matrix least-squares on F^2; final

$R(F)$ ($I > 2\sigma(I)$ reflections), 0.0260 (5510); final $wR(F^2)$ (all data), 0.0668 (5657); goodness-of-fit, 1.018; $\Delta\varrho$ (max; min) = 0.195; −0.229 e Å^{-3}.

Highly disordered solvent molecules were identified as being present in the crystal cell and could not be modeled. These pockets are assumed to contain disordered H_2O/EtOH. The 24-electron contribution of these molecules was removed during the refinement process as carried out previously [11]. A view of the molecule is shown in *Fig. 3*.

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