Synthesis of Optically Active 2-Alkoxy-2*H*-pyran-3(6*H*)-ones. Their Use as Dienophiles in Diels−Alder Cycloadditions

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Optically active 2-alkoxy-2*H*-pyran-3(6*H*)-ones (**4a**−**d**) were synthesized in one step by the tin(IV) chloride-promoted glycosylation and rearrangement of the 2-acetoxy-3,4-di-*O*-acetyl-D-xylal (**3**) prepared from D-xylose (**1**). The absolute configuration of the new stereocenter at C-2 was determined by chemical transformation of the dihydropyranones **4a** and **4b** into the known alkyl pentopyranosides (**7a** and **7b**, respectively). Also, from ^{1}H NMR experiments using a chiral ytterbium shift reagent, the enantiomeric excesses for **4a** (>86%) and **4b** (>77%) were established. Enantiomerically pure **4c** and **4d** were obtained by reaction of **3** with chiral 2-octanol (R and S, respectively). Dihydropyranones **4a**−**d** were employed as dienophiles in Diels−Alder cycloadditions with 2,3-dimethylbutadiene and butadiene. Under thermal conditions, only moderate yields (∼50%) of cycloadducts **9a**−**c** and **10a** were respectively obtained with good diastereofacial selectivity (>80%). Optimized Lewis acid promoted cycloadditions led to **9a**−**d** and **10a**,**c** in higher yields (∼80%) and with higher diastereoselectivities (>94%). The major products were formed by approach of the dienes from the less hindered face of the dihydropyranones, and the minor products (such as **11a**) were formed by addition from the opposite side. Furthermore, cycloadduct **9a** was stable in an alkaline solution, whereas **11a** underwent epimerization under the same conditions.

Introduction

Carbohydrate-derived sugar enones have been employed for the synthesis of a variety of asymmetric molecules, and they constitute versatile building blocks for the construction of natural products.[1] Due to the highly stereoselective nature of addition reactions to the enone system of these sugar derivatives, we have employed them for the enantioselective synthesis of natural products,[2] in particular diamino tetradeoxy sugars found in antibiotics,[3] and for the preparation of modified glycosides.[4] Lichtenthaler and co-workers have described convenient procedures for the synthesis of 4-acyloxy-6-acyloxymethyl dihydropyranones[5] (enolone esters) and their use as six-carbon synthons of non-carbohydrate natural products such as (−)-palythazine[6] and (−)-bissetone.[7] We have also reported[8] a straightforward synthesis of 6-acyloxymethyl dihydropyranones by glycosylation of 2-acyloxy-hex-1-enitols in the presence of a Lewis acid. This procedure gave ready and large-scale accessibility to the 6-substituted sugar enones, which could be otherwise obtained via multistep procedures.[1,9] We report here a convenient preparation of optically active 2-alkoxy-2*H*-pyran-3(6*H*)-ones via tin(IV) chloride-promoted rearrangement of 2-acetoxy-3,4-di-*O*-acetyl-D-xylal.

The synthetic usefulness of these dihydropyranones would be considerably enlarged if they could be employed as dienophiles in Diels−Alder reactions. Structurally similar pyranoid enones such as levoglucosenone,[10] isolevoglucosenone,[11] 2-alkoxy-2*H*-pyran-5(6*H*)-ones,[12] and enolone esters[13] underwent [4+2] cycloaddition of dienes to give a variety of configurationally well-defined carbocyclic derivatives. We have now examined the Diels−Alder reactions of the dihydropyranone dienophiles, under thermal conditions and Lewis acid catalysis, and the level of stereocontrol was determined.

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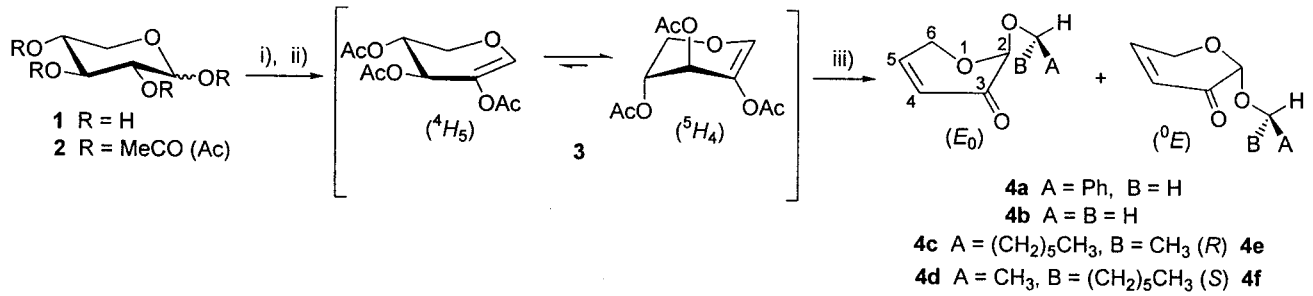
Scheme 1[a]



[a] Reagents and conditions: (i) 32% HBr, AcOH, 0 °C, 2 h; (ii) DBU, room temperature, 30 min; (iii) ABCHOH, $SnCl_4$, CH_2Cl_2, −18 °C, 20 min.

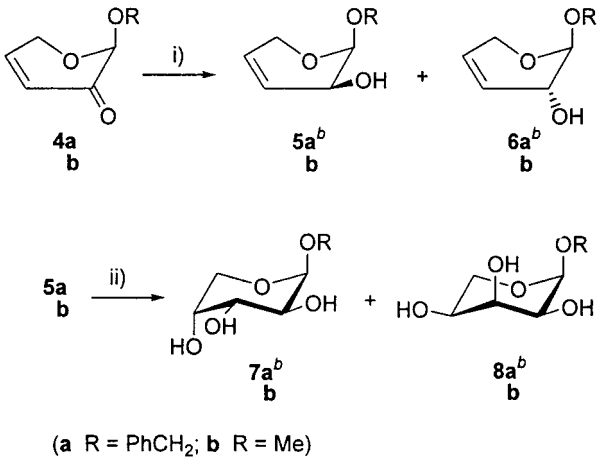
Results and Discussion

Acetylation of D-xylose (**1**) with acetic anhydride-pyridine afforded the per-*O*-acetyl derivative **2**. Treatment of **2** with 32% hydrogen bromide in acetic acid gave the corresponding glycosyl bromide, which underwent elimination of HBr on reaction with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to afford the 2-acyloxy glycal derivative **3** (Scheme 1). Crude intermediates were employed for all the steps, and compound **3** was isolated in crystalline form in 72% yield from **1**. The ^{1}H NMR spectrum of **3** showed small values for $J_{3,4}$, $J_{4,5}$, and $J_{4,5'}$, which indicated a preferred $^5H_4$(D) conformation, in agreement with the preferential conformation of its 2-unsubstituted analogue.[14,15] Such a conformation is free of 1,3-diaxial interactions between substituents, and the 3-acyloxy group is quasiaxially oriented, which is a factor that provides additional conformational stability[15] (allylic effect).

Treatment of the pent-1-enitol **3** with benzyl alcohol, in the presence of tin(IV) chloride as Lewis acid catalyst, afforded benzyl pent-3-enopyranosid-2-ulose **4a** (2-benzyloxy-2*H*-pyran-3(6*H*)-one) in 85% yield. We have reported[8] a similar $SnCl_4$-catalyzed rearrangement of 2-acyloxy-hex-1-enitols derived from hexoses to alkyl hex-3-enopyranosid-2-uloses having an α configuration for the anomeric center. In the case of **4a**, the large negative value for its optical rotation ($[\alpha]_D$ −200.6) suggested a *β*(S) configuration for the new stereocenter. The glycosylation of **3** was also performed using methyl alcohol as a nucleophile to afford the 2-methoxy-2*H*-pyran-3(6*H*)-one (**4b**) in 77% yield. Similar to its 2-benzyloxy analogue (**4a**), the 2-ulose derivative **4b** showed a large negative optical rotation value, suggesting again a *β*(R in this case) configuration at C-2.

To confirm the configuration of the new stereocenters in compounds **4a**,**b**, they were converted into the known benzyl and methyl pentopyranosides by a sequence that consisted of the reduction of the carbonyl function followed by dihydroxylation of the double bond (Scheme 2). In this sequence, there was a remarkable diastereoselectivity in the reduction of **4a** to **5a**, probably due to the stereocontrol exerted by the anomeric center vicinal to the carbonyl group.[3,4,16] The following osmylation[17] of **5a** occurred also by diastereoselective addition of osmium

Scheme 2[a]



[a] Reagents and conditions: (i) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, MeOH, 0 °C, 20 min; (ii) OsO_4, NMO, *tert*-butyl alcohol−H_2O, room temperature, 16 h. [b] Diastereomeric ratios: 40:1 for **5a**:**6a** and 6:1 for **7a**:**8a**.

tetroxide to the double bond from the side of the ring opposite to the allylic hydroxyl group, in agreement with Kishi's rule of osmylation of allylic alcohols.[18] The NMR spectra of the major glycoside (**7a**) isolated from **4a** were consistent with a *β*-arabinopyranoside structure,[19,20] and the largely negative optical rotation ($[\alpha]_D$ −184.0) led to the conclusion that it belonged to the D-series. However, such a value, compared with that of the pure benzyl *β*-D-arabinopyranoside[19] ($[\alpha]_D$ −217.0), indicated that **7a** was a partially racemic product. The enantiomeric excess (ee) for **7a** (ee > 84%) was estimated on the basis of these data. An analogous sequence applied to dihydropyranone **4b** led to partially racemic methyl *β*-D-arabinopyranoside (**7b**) as the main product, and an ee > 75% was calculated from the optical rotation.[21]

The foregoing syntheses confirmed that the enantiomer in excess in **4a** and **4b** had the same *β* configuration (S and R, respectively). To establish the enantiomeric composition directly from partially racemic **4a** and **4b**, NMR experiments were conducted using a chiral lanthanide shift reagent.[22,23] Thus, with ytterbium tris[3-

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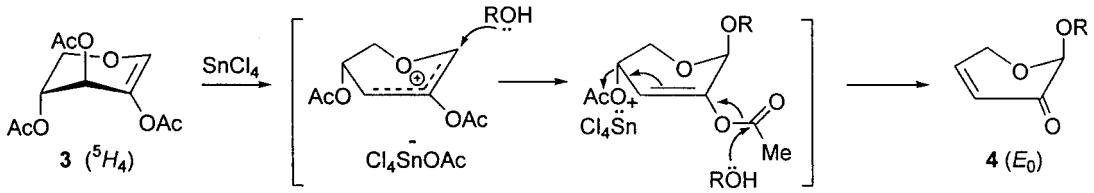
Scheme 3



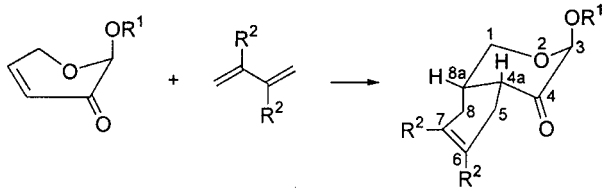
(heptafluoropropylhydroxymethylene)-(+)-camphorate], the H-2 resonance of **4a** split into two broad singlets; from the integral of these signals, the enantiomeric excess in favor of the (2S) isomer (ee > 86%) was calculated. Similarly, a satisfactory split of the methyl signal was observed upon addition of the ytterbium compound to **4b**, and an ee > 77% was established for **4b.** These ee values were in good agreement with those previously estimated from the optical rotation of **7a** and **7b**.

Enantiomerically pure dihydropyranones were prepared by the tin(IV) chloride-promoted glycosylation of **3** with a chiral alcohol ((*R*)-2-octanol). The introduction of an additional stereocenter of defined configuration led to the diastereomeric products **4c** and **4e**. The ^{1}H NMR spectrum of the crude reaction mixture showed characteristic signals for each diastereoisomer, and from the average integral of such signals, a diastereomeric excess (de) > 80% was determined for **4c**. The mixture was subjected to chromatographic purification to afford pure **4c** (de > 97%). The glycosylation of **3** was also conducted with (*S*)-(+)-2-octanol to give **4d** and 4**f**. The NMR spectra of purified **4d** (de > 96%) exactly overlapped those of **4e**, as expected for enantiomeric compounds. This fact provides additional support to all the structural assignments.

The selectivity for the β isomer in the formation of **4a**−**d** can be explained by taking into account the steric course of the glycosylation of **3**. Assuming that **3** reacts in the preferred $^5H_4$ conformation, the quasiaxial allylic acetoxy group can be readily eliminated by coordination with the Lewis acid. Simultaneous migration of the double bond (Ferrier's rearrangement[24]) generates a cation at C-1 that can be stabilized by participation of the oxygen-ring lone pair (Scheme 3). The quasiaxially oriented alkoxy group at C-4 should induce the attack of the alcohol from the opposite face to give the 2-enopyranoside having the β anomeric configuration. This intermediate undergoes a second Ferrier's rearrangement affording the dihydropyranones **4a**−**d**.

The ^{1}H NMR spectra of **4a**−**d** showed magnitudes for homoallylic couplings ($J_{4,6}$ and $J_{4,6'}$) that were consistent with a preferential E_0 conformation for such compounds. This assignment was confirmed by the characteristic long-range coupling between H-2 and H-4 (0.7 Hz) similar to that observed for levoglucosenone, in which the pyranone is constrained to the E_0 conformation because of the five-membered fused ring.[25] The E_0 conformation for **4a**−**d** is stabilized by the anomeric effect, which is probably intensified by the carbonyl function next to the anomeric center.[26] Furthermore, molecular mechanics calculations for the β isomer of 2-methoxy-4,6-disubstituted dihydropyranones showed that the conformer with an axial methoxy group (E_0) was preferred by −27 kJ/mol over its equatorial (^0E) counterpart.[13] The same conformational preference has been found in the solid state.[27]

Scheme 4



4a R^1 = $PhCH_2$
4b R^1 = Me
4c R^1 = 2-(*R*)-octyl
4d R^1 = 2-(*S*)-octyl

9a R^1 = $PhCH_2$, R^2 = Me
9b R^1 = Me, R^2 = Me
9c R^1 = 2-(*R*)-octyl, R^2 = Me
9d R^1 = 2-(*S*)-octyl, R^2 = Me
10a R^1 = $PhCH_2$, R^2 = H
10c R^1 = 2-(*R*)-octyl, R^2 = H

As far as we know, this is the first report on the synthesis of optically active pure 2,6-dihydropyran-3-ones. Previous preparations of **4b** in racemic form have been described.[28]

As compounds **4a**−**d** possess in their structures a carbonyl group conjugated with a double bond, we have explored their reactivity as dienophiles in Diels−Alder cycloadditions. Reaction of **4a**−**d** with common acyclic dienes would lead to two cycloadducts, if isomerization is excluded. However, the chiral center at C-2 of pyranones is expected to induce asymmetry, to afford a major diastereoisomer. Such facial selectivities have been reported for cyclic enones.[10−13] With these considerations in mind, we have examined the Diels−Alder reactions of **4a**−**d** toward butadienes to determine the level of stereocontrol attainable. The reactions were performed under thermal and Lewis acid catalyzed conditions (Scheme 4); selected experiments are shown in Table 1.

The thermal Diels−Alder reactions were conducted with an excess of diene during long periods (3−4 days). In any case, a main cycloadduct was obtained in moderate yield (45−51%) and starting material was recovered. Higher concentrations of diene, higher temperatures, or longer reactions times did not improve the yield of cycloadducts and, in most cases, increased the extent of polymerization of the diene. The high total material recovery (>85%), even after extending heating, indicated that dihydropyranones **4a**−**c** and the corresponding adducts are quite stable toward heating. The main

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Table 1. Diels−Alder Reactions of Dihydropyranones 4a−d with Butadienes under Thermal and $Et_2O{\cdot}BF_3$-Catalyzed Conditions

dienophile	diene[a] (mol equiv)	mol equiv $Et_2O{\cdot}BF_3$	solv	temp (°C)	time (h)	de[b] (%)	yield of adduct[c]	dienophile	diene[a] (mol equiv)	mol equiv $Et_2O{\cdot}BF_3$	solv	temp (°C)	time (h)	de[b] (%)	yield of adduct[c]
4a	A (3.7)		PhMe	115	90	82	47	**4c**	A (1.7)	1.0	CH_2Cl_2	−18	0.25	98	80
4b	A (3.7)		PhMe	110	90	82	51	**4c**	A (2.8)	1.0	CH_3CN	−18	0.25	99	70
4c	A (3.7)		PhMe	115	90	91	46	**4c**	A (3.5)	1.0	THF	−18	0.25		
4a	B (3.7)		PhMe	125	90	85	45	**4a**	A (1.7)	1.0	PhMe	−18	0.25	96	81
4c	A (1.5)	1.0	PhMe	−18	0.25	98	81	**4b**	A (1.7)	1.0	PhMe	−18	0.25	94	80
4c	A (1.5)	0.2	PhMe	−18	0.50		32	**4d**	A (1.7)	1.0	PhMe	−18	0.25	98	81
4c	A (1.5)	1.6	PhMe	−18	0.50	98	81	**4a**	B (2.0)	1.0	PhMe	25	0.90	99	81
4c	A (1.7)	1.0	PhMe	−18	0.25	98	83	**4c**	B (2.0)	1.0	PhMe	25	0.90		80

[a] A: 2,3-dimethylbutadiene. B: butadiene. [b] Diastereomeric excess (de) was calculated from the ^1H NMR spectrum of the crude reaction mixture. [c] Yield of adducts **9a**−**d** and **10a**,**c** after isolation by flash chromatography.

products in the reaction with 2,3-dimethylbutadiene were **9a**−**c**, the adducts formed by attack of the diene from the α face of the dihydropyranones **4a**−**c**; thus, thermal cycloadditions were diastereofacially selective (de > 80%). When a preparative-scale thermal cycloaddition was conducted starting from **4a**, the minor product **11a** (formed by attack of the diene from the β face of the pyranone) could be isolated in low yield. Similar yields and selectivities were observed in the preparation of **10a** by thermal addition of butadiene to **4a**. The determination of the structure of the cycloadducts is described below.

For studying the Lewis acid mediated cycloaddition, the dihydropyranone **4c** was employed as a model dienophile. From the various Lewis acids ($AlCl_3$, $Et_2O{\cdot}BF_3$, $TiCl_4$) tested, boron trifluoride showed higher and more reproducible yields, together with low polymer formation and easy workup of the reaction mixtures. Experiments were performed in order to evaluate the effect of the concentration of boron trifluoride in the addition of 2,3-dimethylbutadiene to **4c** (Table 1). The best results were obtained when 1 molar equiv of the Lewis acid was employed. Decreasing the amount of catalyst led to lower yields, and larger amounts did not improve it. The yield of cycloaddition product was similar when the diene was added to the solution of the dihydropyranone from 4 to 5 min after addition of the catalyst. This fact suggests that the formation of enone−catalyst complex takes place rapidly, in contrast to the catalyzed cycloadditions of common cycloalkenones, in which the time of ketone−catalyst complexation dramatically influenced the product yield.[29]

The solvent effect was also evaluated; toluene and dichloromethane proved to be adequate solvents for this reaction since a small excess of diene was required for completion and, hence, low polymer formation took place. Reactions were also conducted in donor solvents such as acetonitrile and tetrahydrofuran (THF). Thus, in the case of acetonitrile, a larger amount of diene was needed, although no increase in polymer formation was detected. In THF, the cycloaddition was strongly inhibited even for large concentrations of diene. The optimized conditions established for reactions of **4c** (1 molar equiv of $Et_2O{\cdot}BF_3$, toluene, 15 min, −18 °C) with 2,3-dimethylbutadiene were applied to the cycloadditions of the other dihydropyranones **4a**,**b**,**d**. As expected, very good yields of the respective adducts **9a**,**b**,**d** were obtained. Similarly, **4a** and **4c** reacted with butadiene under the same conditions to give ∼80% yield of **10a** and **10c**, respectively. Boron trifluoride-promoted cycloadditions were also very highly diastereoselective, as the adducts **9a**−**d** and **10a**,**c** were obtained in high diastereomeric excess (>94%).

Reactions were also conducted in a preparative scale; for example, starting from **4a**, the major product **9a** was isolated in 82% yield, and the optically pure dihydropyranone **4c** afforded **9c** as a single, enantiomerically pure isomer in 79% yield. In contrast to the thermal reactions, no significant amounts of other diastereoisomers were formed. A similar trend, but a much more pronounced facial stereoselection in Lewis acid mediated cycloaddition compared to the thermal induced reaction, has been described[13] for a reactive β-methoxy-substituted pyranoid enolone ester. The high diastereoselection in cycloadditions to **4a**−**d** should result from the steric effect of the axially oriented alkoxy group at C-2, which prevents the approach of the diene to the double bond from the β face. In agreement with this explanation, the bulkyness of such a group modifies the diastereoselectivity in reactions conducted under identical conditions (compare the selectivity in the addition to octyl vs methyl derivatives **4c** and **4b** in Table 1). A similar stereocontrol has been reported in Diels−Alder reactions applied to structurally related pyranones.[10−13]

Regarding the reactivity of the dihydropyranones toward Diels−Alder reactions, it has been previously demonstrated that the location of an oxygen atom in a six-membered ring can modify the reactivity of an enone.[12b] The ring oxygen of pyranoid enolone esters makes the system much more reactive than the structurally related cyclohexanoid enolone esters, in which the ring oxygen has been formally replaced by a methylene group.[13] In the case of dihydropyranones **4a**−**d**, a similar "ring oxygen effect" seems to operate as Diels−Alder cycloadditions, mainly under Lewis acid catalysis, required much smoother reaction conditions than those described for normal cyclohexenones.[29]

The structures of cycloadducts were determined by means of NMR techniques. The enantiomerically pure adduct **9c** was employed for complete structural elucidation. The ^1H NMR spectrum (500 MHz) of this compound admitted a first-order analysis, and the assignments were confirmed by bi-dimensional (2D COSY) NMR experiments. Thus, the small J values between H-1−H-8a (2.3 Hz) and H-1′−H-8a (1.1 Hz) indicated that the C−H_{8a} bond bisects the dihedral angle of the H-1−C−H-1′ group, and the $J_{4a,8a}$ (5.3 Hz) value was compatible with a gauche axial−equatorial relationship for H-4a and H-8a. Furthermore, the coupling constants between H-4a and H-8a

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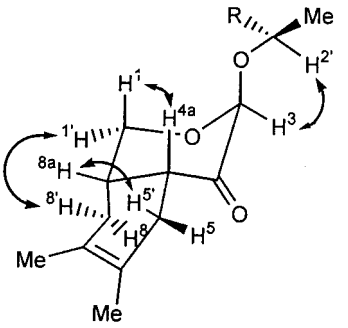
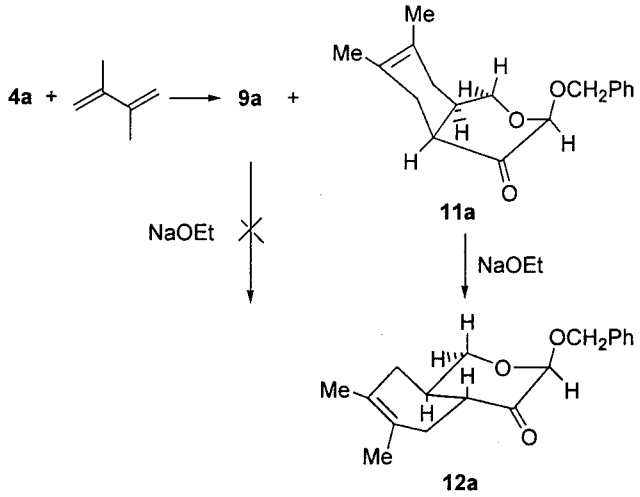


Figure 1. Important correlations observed in the ROESY spectrum of **9c**.

Scheme 5



with the vicinal methylene protons (at C-5 and C-8, respectively) were consistent with a half chair conformation ($^{4a}H_{8a}$) for the cyclohexene ring. The structure of **9c** was further confirmed by means of ^{1}H,^{1}H-ROESY experiments;[30] the cross-peaks observed are indicated in Figure 1. In particular, the cross-peak between H-1 and H-4a protons confirmed their 1,3-diaxial orientation in the distorted chair conformation of the pyranone ring. The structure of the other adducts **9a**,**b**,**d** was established by comparison of their spectra to those of **9c**.

The minor product isolated in the thermal cycloaddition of **4a** with 2,3-dimethyl-1,3-butadiene was identified as **11a**, the diastereoisomer of **9a** that had the opposite configuration at C-4a and C-8a (Scheme 5). The ^{1}H NMR spectrum of **11a** showed relatively large coupling constant values between H-8a−H-1 and H-8a−H-1′ (7.8 and 4.3 Hz, respectively) compared to those of **9a**, indicating an axial disposition for H-8a. The $J_{4a,8a}$ (6.2 Hz) value was consistent with an equatorial−axial disposition for H-4a and H-8a.

The cis octalones, obtained by Lewis acid induced Diels−Alder reaction of butadienes with conjugated cyclohexenones, equilibrate to the trans isomeric adduct.[29] In contrast, the analogous cis octalones **9a** and **11a** were stable and did not isomerize when treated with solutions of $Et_2O{\cdot}BF_3$ during long periods. Similarly, the hydrobenzosuberones derived from 2-cycloheptenone underwent a very slow acid-induced isomerization during the cycloaddition process.[29b] However, such adducts have a strong tendency to isomerize under base-catalyzed conditions. To determine the stability of **9a** and **11a** to alkali, they were treated with a solution of sodium ethoxide in ethanol. The cycloadduct **9a** was recovered unchanged, whereas **11a** underwent rapid conversion into the trans tetrahydrobenzopyranone **12a**. The stereochemistry of **12a** was readily deduced from its ^{1}H NMR spectrum, which showed large J values (11.0 Hz) for the coupling of H-8a with H-1 and H-4a, consistent with a trans diaxial disposition for the pyranone-ring-coupled protons. It is noteworthy that **11a** can isomerize without substantial change of the conformation of the pyranoid ring, whereas a shifting to the conformer having the benzyloxy substituent in an equatorial orientation is required for the isomerization of **9a**.

(30) Kessler, H.; Gehrke, M.; Griesinger, C. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 490.

Conclusions

A short route is described for the direct conversion of the acetoxy groups of 2-acetoxy-3,4-di-*O*-acetyl-D-xylal into an enone system of a dihydropyranone derivative. These compounds may be otherwise synthesized by multistep procedures that require protection−deprotection, oxidation, and elimination of hydroxyl groups in a monosaccharide. The resulting optically active dihydropyranones proved to be excellent dienophiles in Diels−Alder cycloadditions under Lewis acid catalyzed conditions. Their reactivity is probably enhanced by the ring-oxygen atom. The high diastereofacial selectivity in the cycloaddition provides straightforward access to optically active tetrahydrobenzopyranones that carry a number of stereogenic centers installed in a predictable way. Such bicyclic compounds have significant synthetic potential as chiral building blocks for the construction of complex natural products.

Experimental Section

General Methods. Melting points are uncorrected. Optical rotations were measured at 25 °C. Column chromatographic separations were performed with silica gel 60, 240−400 mesh. Analytical TLC was performed on silica gel 60 F_{254} precoated plates (0.2 mm). Visualization of the spots was effected by exposure to UV light or charring with a solution of 5% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Solvents were reagent grade and, in most cases, were dried and distilled prior to use according to standard procedures.

1,5-Anhydro-2,3,4-tri-*O*-acetyl-D-*threo*-pent-1-enitol (2-Acetoxy-3,4-di-*O*-acetyl-D-xylal, 3). To a mixture of anhydrous pyridine (40 mL) and acetic anhydride (32 mL) at 0 °C was added D-xylose (**1**, 5.00 g, 33.30 mmol), and the mixture was stirred overnight at room temperature. To this solution was slowly added methanol (70 mL) at 0 °C, and after 1 h of stirring at 0 °C and 1 h at room temperature, the mixture was concentrated. Pyridine was removed by successive evaporations with toluene. The resulting syrup, which was homogeneous by TLC (R_f = 0.51, hexane/EtOAc 1.6:1), was dissolved in anhydrous 1,2-dichloroethane (14 mL) and cooled to 0 °C, and 32% HBr in glacial acetic acid (12.2 mL) was added dropwise in the dark. After 2 h, TLC showed a main spot (R_f = 0.62). The solution was evaporated in a vacuum (20 °C), and successive dissolutions followed by evaporation with toluene and ethyl ether afforded a partly crystalline product, which was dissolved in 1,2-dichloroethane (20 mL). The solution was cooled to −18 °C, and 1,8-diazabycyclo[5.4.0]undec-7-ene (DBU, 5.6 mL) was added dropwise in the dark. After stirring for 30 min at room temperature, TLC showed a main spot having an R_f = 0.55. The mixture was diluted with CH_2Cl_2 and washed with 10% aqueous HCl, saturated (satd) aqueous (aq) $NaHCO_3$

and satd aq NaCl. The organic extract was dried ($MgSO_4$) and concentrated to afford a partly crystalline product. Upon purification by flash chromatography (hexane/EtOAc 7:1), crystalline **3** was obtained (6.22 g, 72% from **1**): mp 80−81 °C; $[\alpha]_D$ −272.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.73 (s, 1, H-1), 5.34 (dd, 1, $J_{3,4}$ = 2.2 Hz, $J_{3,5}$ = 1.8 Hz, H-3), 4.95 (ddd, 1, $J_{4,5}$ = 2.2 Hz, $J_{4,5'}$ = 1 Hz, H-4), 4.23 (ddd, 1, $J_{5,5'}$ = 12.4 Hz, H-5), 3.95 (dd, 1, H-5′), 2.11, 2.10, 2.07 (3 s, 9, 3 CH_3CO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 169.9, 169.8 (×2), 141.3, 127.5, 67.4, 64.3, 63.7, 20.9, 20.8, 20.6. Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.17; H, 5.46. Found: C, 51.12; H, 5.48.

General Procedure for 2-Alkoxy-2*H*-pyran-3(6*H*)-ones (4a−d). A solution of **3** (1.00 g, 3.87 mmol) and the alcohol (7.45 mmol) in anhydrous CH_2Cl_2 (45 mL) was cooled to −18 °C, and tin(IV) chloride (0.58 mL, 4.92 mmol) was added. When TLC (hexane/EtOAc 2:1) revealed complete consumption (∼20 min) of the starting **3**, the mixture was diluted with CH_2Cl_2. This solution was washed with satd aq $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography to afford dihydropyranones **4a**−**d** as colorless oils.

The absolute configuration at C-2 of **4a** and **4b** was established by their conversion into the partially racemic pentopyranosides (next section). The enantiomeric composition was also determined directly from **4a** and **4b** by ^{1}H NMR in the presence of a chiral shift reagent.

(2*S*)-2-Benzyloxy-2*H*-pyran-3(6*H*)-one (4a): 85% yield (0.67 g). The enantiomeric excess (ee) for **4a** was determined by ^{1}H NMR using ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as a chiral resolving reagent. To a solution of **4a** (0.05 mmol) in carbon tetrachloride containing 1% benzene-d_6 (0.5 mL) was added the shift reagent. Upon addition of 0.6 molar equiv, the ^{1}H NMR spectrum showed a splitting of the H-2 signal into two broad singlets (enantiomeric shift difference[23] $\Delta\Delta\delta$ = 0.14). From the integral of these signals (14:1 ratio), the enantiomeric composition (ee > 86%) was established for **4a**. This compound had $[\alpha]_D$ −200.6 (*c* 1.1, $CHCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (bs, 5, H-aromatic), 7.05 (ddd, 1, $J_{4,5}$ = 10.6 Hz, $J_{5,6}$ = 1.8 Hz, $J_{5,6'}$ = 3.8 Hz, H-5), 6.15 (dddd, 1, $J_{2,4}$ = 0.7 Hz, $J_{4,6}$ = 2.5 Hz, $J_{4,6'}$ = 1.8 Hz, H-4), 4.96 (bs, 1, H-2), 4.85, 4.73 (2 d, 2, J = 11.8 Hz, PhCH_2O), 4.56 (ddd, 1, $J_{6,6'}$ = 19.0 Hz, H-6), 4.27 (ddd, 1, H-6′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 188.6 (C-3), 147.9 (C-5), 136.8, 128.6, 128.1 (C-aromatic), 124.9 (C-4), 97.1 (C-2), 70.8 (Ph*C*H$_2$O), 59.8 (C-6). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.28; H, 5.92.

(2*R*)-2-Methoxy-2*H*-pyran-3(6*H*)-one (4b): 77% yield (0.38 g). As for **4a**, the ee of **4b** was established from the ^{1}H NMR spectra recorded in the presence of 0.40 molar equiv of the Yb resolving agent, which caused a splitting of the methyl group resonance. Compound **4b** (ee > 77%) had $[\alpha]_D$ −160.5 (*c* 1.2, $CHCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.04 (ddd, 1, $J_{4,5}$ = 10.6 Hz, $J_{5,6}$ = 1.8 Hz, $J_{5,6'}$ = 3.7 Hz, H-5), 6.10 (dddd, 1, $J_{2,4}$ = 0.7 Hz, $J_{4,6}$ = 2.4 Hz, $J_{4,6'}$ = 1.8 Hz, H-4), 4.72 (bs, 1, H-2), 4.53 (ddd, 1, $J_{6,6'}$ = 19.0 Hz, H-6), 4.27 (ddd, 1, H-6′), 3.52 (s, 3, OCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 188.7 (C-3), 148.0, 124.7 (C-vinylic), 98.9 (C-2), 59.6 (C-6), 56.7 (*C*H$_3$O). Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 55.90; H, 6.62.

(2*S*)-[(*R*)-2′-Octyloxy]-2*H*-pyran-3(6*H*)-one (4c) and (2*R*)-[(*R*)-2′-Octyloxy]-2*H*-pyran-3(6*H*)-one (4e). The mixture of **4c** and **4e** (9.5:1 ratio from ^{1}H NMR) was obtained in 84% yield (0.74 g). Two successive purifications by column chromatography with hexane/EtOAc 35:1 afforded the less polar enuloside **4c** (0.60 g, 68%; de > 97%), $[\alpha]_D$ −183.6 (*c* 1.0, $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (ddd, 1, $J_{4,5}$ = 10.5 Hz, $J_{5,6}$ = 1.8 Hz, $J_{5,6'}$ = 4.0 Hz, H-5), 6.13 (dddd, 1, $J_{2,4}$ = 0.5 Hz, $J_{4,6}$ = 2.5 Hz, $J_{4,6'}$ = 1.6 Hz, H-4), 4.93 (bs, 1, H-2), 4.58 (ddd, 1, $J_{6,6'}$ = 18.9 Hz, H-6), 4.27 (ddd, 1, H-6′), 3.87 (sextet, 1, *H*CO octyl), 1.64−1.22 (m, 10, CH_2 octyl), 1.20 (d, 3, J = 6.5 Hz, CH_3O octyl), 0.89 (t, 3, J = 6.6 Hz, CH_3 octyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 189.1 (C-3), 147.9, 125.0 (C-vinylic), 95.7 (C-2), 74.6 (H*C*O octyl), 59.7 (C-6), 37.2, 31.8, 29.3, 25.8, 22.6, 19.4, 14.1 (*C*-octyl). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.30; H, 10.08.

Further fractions from the column were enriched in **4e**. The ^{1}H and ^{13}C NMR spectra showed a pattern of signals for **4e** that was identical to that of its enantiomer **4d** (see below).

(2*S*)-[(*S*)-2′-Octyloxy]-2*H*-pyran-3(6*H*)-one (4d) and (2*R*)-[(*S*)-2′-Octyloxy]-2*H*-pyran-3(6*H*)-one (4f). The mixture of **4d** and **4f** was obtained in 82% yield (0.72 g, de > 80%), and it was processed as described for **4c**,**e**. The more polar diastereoisomer **4d** (0.61 g, 70%; de > 96%) gave $[\alpha]_D$ −152.6 (*c* 1.2, $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (ddd, 1, $J_{4,5}$ = 10.4 Hz, $J_{5,6}$ = 1.8 Hz, $J_{5,6'}$ = 4.0 Hz, H-5), 6.12 (dddd, 1, $J_{2,4}$ = 0.7 Hz, $J_{4,6}$ = 2.6 Hz, $J_{4,6'}$ = 1.5 Hz, H-4), 4.92 (bs, 1, H-2), 4.58 (ddd, 1, $J_{6,6'}$ = 18.9 Hz, H-6), 4.27 (ddd, 1, H-6′), 3.82 (sextet, 1, *H*CO octyl), 1.62−1.25 (m, 10, CH_2 octyl), 1.27 (d, 3, J = 6.4 Hz, CH_3CO octyl), 0.88 (t, 3, J = 6.7 Hz, CH_3 octyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 188.9 (C-3), 147.9, 125.0 (C-vinylic), 97.7 (C-2), 76.7 (H*C*O octyl), 59.7 (C-6), 36.5, 31.8, 29.3, 25.2, 22.6, 21.2, 14.1 (*C*-octyl). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.09; H, 9.84.

The first fractions of the column were enriched in **4f**, which showed spectra identical to those of its enantiomer **4c**.

Conversion of 4a into Partially Racemic Benzyl Pentopyranosides 7a and 8a. To a solution of **4a** (131 mg, 0.64 mmol) in dry MeOH (13 mL) was added cerium(III) chloride heptahydrate (64 mg, 0.17 mmol).[31] The solution was stirred for 10 min at room temperature and then cooled to 0 °C. Sodium borohydride (25 mg, 0.66 mmol) was added, and the stirring was maintained for 20 min, when TLC (hexane/EtOAc 2:1) showed two spots having R_f = 0.44 (major) and 0.26, and no starting material (R_f = 0.50) remaining. The mixture (which showed by NMR a 40:1 diastereomeric ratio) was diluted with a large excess of ethyl ether, washed with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue with hexane/EtOAc 10:1 gave the main product (116 mg, 88%), which was spectroscopically characterized[32] as **5a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (bs, 5, H-aromatic), 5.82, 5.73 (2 bd, 2, $J_{3,4}$ = 11.3 Hz, H-3,4), 4.96 (d, 1, $J_{1,2}$ = 4.0 Hz, H-1), 4.85, 4.63 (2 d, 2, J = 11.8 Hz, PhCH_2O), 4.69 (bs, 1, *H*O), 4.18 (m, 2, H-2,5), 4.03 (bd, 1, $J_{5,5'}$ = 17.2 Hz, H-5′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.4, 128.6, 128.0 (C-aromatic), 127.1, 126.2 (C-3,4), 96.0 (C-1), 70.0 (Ph*C*H$_2$O), 64.3 (C-2), 60.3 (C-5).

Upon elution of the column with hexane/EtOAc 9:1, the minor product was isolated (4 mg, 3%) and identified as **6a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (bs, 5, H-aromatic), 5.91 (m, 2, H-3,4), 4.84, 4.61 (d, 2, J = 12.0 Hz, PhCH_2O), 4.79 (d, 1, $J_{1,2}$ = 2.5 Hz, H-1), 4.70 (bs, 1, *H*O), 4.27 (bd, 1, $J_{5,5'}$ = 16.8 Hz, H-5), 4.12 (bd, 1, H-5′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.5, 128.6, 128.1 (C-aromatic), 129.0, 124.7 (C-3,4), 100.0 (C-1), 70.2 (Ph*C*H$_2$O), 65.0 (C-2), 61.0 (C-5).

Compound **5a** (75 mg, 0.36 mmol) was dissolved in *tert*-butyl alcohol (1.5 mL)−water (0.15 mL), and to this solution was added *N*-methylmorpholine *N*-oxide (70 mg, 0.60 mmol). The mixture was cooled to 0 °C and treated with a 2% (w/v) solution (38 μL) of osmium tetroxide in *tert*-butyl alcohol. The mixture was stirred at room temperature for 16 h, when TLC (EtOAc) showed complete conversion of **5a** (R_f = 0.80) into two products having R_f = 0.25 and 0.18 (1:6 ratio from ^{1}H NMR). The solution was diluted with *tert*-butyl alcohol (4 mL), stirred with solid sodium hydrogen sulfite (0.3 g), and filtered. The residue was washed with an excess of *tert*-butyl alcohol, and the filtrate and the washing liquids were pooled and concentrated. The resulting syrup was purified by flash chromatography (EtOAc/hexane 10:1) to afford crystalline, partially racemic benzyl β-D-arabinopyranoside (**7a**, 72 mg, 82%): mp 168−169 °C (lit.[19] 167−169 °C); $[\alpha]_D$ −184.0 (*c* 0.6, H_2O); $[\alpha]_D$ −217.0, for the optically pure glycoside; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.34 (m, 5, H-aromatic), 4.75 (bs, 1, H-1), 4.64, 4.44 (2 d, 2, J = 12.4 Hz, PhCH_2O), 3.70−3.62 (m, 5), 3.45 (dd, 1, $J_{4,5'}$ = 2.7 Hz, $J_{5,5'}$ = 12.0 Hz, H-5′); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 138.3, 128.4 (×2), 127.8 (×2), 127.6 (C-aromatic), 99.0 (C-1), 69.1, 68.7, 68.4 (C-2,3,4), 68.8 (Ph*C*H$_2$O), 63.4 (C-5).

(31) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(32) Haque, E. M.; Kikuchi, T.; Kanemitsu, K.; Yoshisuke, T. *Chem. Pharm. Bull.* **1987**, *35*, 1016.

The presence of the minor component of the mixture was detected in the first fractions of the column, and its structure was assigned as benzyl α-L-ribopyranoside[20] (**8a**) by NMR spectroscopy: ^{13}C NMR (50.3 MHz, DMSO-d_6) sugar ring carbons δ 98.7 (C-1), 70.3, 69.5, 67.3 (C-2,3,4), 60.9 (C-5).

Conversion of 4b into Partially Racemic Methyl Pentopyranosides 7b and 8b. Compound **4b** (0.394 g, 3.08 mmol) dissolved in dry MeOH (65 mL) was reduced with $NaBH_4$ (0.15 g, 3.97 mmol) in the presence of $CeCl_3 \cdot 7H_2O$ (0.31 g, 0.83 mmol) as described for **4a**. After the workup, the crude syrup, which showed a main product by TLC (R_f = 0.33, hexane/EtOAc 2:1), was dissolved in a mixture of *tert*-butyl alcohol (10 mL) and water (1 mL) and *N*-methylmorpholine *N*-oxide was added (0.60 g, 5.12 mmol). The resulting solution, cooled to 0 °C, was treated with 2% (w/v) OsO_4 in *tert*-butyl alcohol (0.34 mL). After stirring at room temperature for 16 h, the mixture was processed as described for **7a**, and purified by flash chromatography (EtOAc/MeOH 10:1) to afford crystalline, partially racemic methyl β-D-arabinopyranoside (**7b**, 0.365 g, 72% from **4b**). Recrystallization from ethanol gave: mp 162−164 °C (lit.[21] 167−168 °C); $[\alpha]_D$ −180.9 (*c* 1.1, H_2O); $[\alpha]_D$ −240.6, for the optically pure glycoside.

The minor component of the mixture (**8b**) was detected in the following fractions of the column, and its ^{13}C NMR spectrum was identical to that reported[20] for its enantiomer (methyl α-D-ribopyranoside).

(4a*R*,8a*S*)-6,7-Dimethyl-3-alkoxy-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-ones (9a−d) and (4a*R*,8a*S*)-3-Alkoxy-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-ones (10a,c).

Thermal Cycloaddition General Procedure. The respective dienophile **4a**−**c** (0.25 mmol) and dry toluene (0.02 mL) were placed in a thick-walled glass tube, and hydroquinone (1 mg) was added. Argon was bubbled through the solution, and upon addition of the diene, the glass tube was sealed and heated in a sand bath at a temperature and for the time indicated in Table 1. The reaction mixture was then concentrated and purified by flash chromatography (1−2% EtOAc in hexane) to afford adducts **9a**−**c** and **10a**.

Lewis Acid Catalyzed Cycloaddition General Procedure. The respective dihydropyranone **4a**−**d** (0.24 mmol) was weighed into a vial equipped with a magnetic stirrer and septum seal. The anhydrous solvent (0.5 mL) was added, and the vial was flushed with dry argon and sealed. The mixture was cooled to −18 °C, and the Lewis acid catalyst was added. The mixture was stirred at −18 °C for 5 min, and the flask was placed in a bath at the temperature desired for the cycloaddition. A solution of the diene in the dry solvent (0.6 mL) was then slowly injected, and the temperature was maintained for the time indicated in Table 1. The reaction mixture was diluted with ethyl ether (30 mL), except for the reaction in CH_2Cl_2 in which case the same solvent was used for the dilution. The resulting solution was washed with satd aq $NaHCO_3$, satd aq NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (1−2% EtOAc in hexane) to afford the corresponding cycloadducts **9a**−**d** and **10a**,**c**. The yields are reported in Table 1.

For the preparation of **9c**,**d** and **10c**, the optically pure dihydropyranones **4c** and **4d** have been employed. The enantiomeric composition of **9a**,**b** and **10a** was established by ^{1}H NMR experiments with ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

(3*S*,4a*R*,8a*S*)-6,7-Dimethyl-3-benzyloxy-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (9a). The adduct **9a** (ee > 86%) gave $[\alpha]_D$ −49.7 (*c* 1.1, $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (bs, 5, H-aromatic), 4.81, 4.57 (2 d, 2, J = 11.5 Hz, PhCH_2), 4.71 (bs, 1, H-3), 4.40 (dd, 1, $J_{1,8a}$ = 2.2 Hz, $J_{1,1'}$ = 11.2 Hz, H-1), 3.53 (dd, 1, $J_{1',8a}$ = 1.1 Hz, H-1′), 3.30 (ddd, 1, $J_{4a,5}$ < 1 Hz, $J_{4a,5'}$ = 6.5 Hz, $J_{4a,8a}$ = 5.6 Hz, H-4a), 2.48 (bd, 1, $J_{5,5'}$ = 17.4 Hz, H-5), 2.37 (m, 1, H-8a), 2.24 (bdd, 1, $J_{8a,8}$ = 11.5 Hz, $J_{8,8'}$ = 17.2 Hz, H-8), 1.96 (bd, 1, H-5′), 1.81 (bdd, 1, H-8′), 1.64, 1.58 (2 bs, 6, 2 CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2 (C-4), 137.0, 128.5, 128.1 (C-aromatic), 123.4, 123.0 (C-6,7), 99.4 (C-3), 69.7 (PhCH_2O), 63.7 (C-1), 43.2 (C-4a), 38.2 (C-8a), 31.2, 28.6 (C-5,8), 19.2, 18.7 (2 CH_3). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.18; H, 8.06.

(3*R*,4a*R*,8a*S*)-6,7-Dimethyl-3-methoxy-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (9b). Cycloadduct **9b** (ee > 75%) gave $[\alpha]_D$ +20.4 (*c* 1.1, $CHCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (bs, 1, H-3), 4.33 (dd, 1, $J_{1,8a}$ = 2.3 Hz, $J_{1,1'}$ = 11.3 Hz, H-1), 3.51 (dd, 1, $J_{1',8a}$ = 1.2 Hz, H-1′), 3.46 (s, 3, CH_3O), 3.24 (ddd, 1, $J_{4a,5}$ < 1 Hz, $J_{4a,5'}$ = 6.4 Hz, $J_{4a,8a}$ = 5.4 Hz, H-4a), 2.48 (bd, 1, $J_{5,5'}$ = 17.5 Hz, H-5), 2.37 (m, 1, H-8a), 2.23 (bdd, 1, $J_{8a,8}$ = 12.0 Hz, $J_{8,8'}$ = 16.3 Hz, H-8), 1.97 (bd, 1, H-5′), 1.81 (bdd, 1, $J_{8a,8'}$ = 6.4 Hz, H-8′), 1.68 (2 bs, 6, 2 CH_3), 1.65; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.4 (C-4), 123.3, 122.8 (C-6,7), 101.0 (C-3), 63.3 (C-1), 43.2 (C-4a), 38.1 (C-8a), 31.1, 28.5 (C-5,8), 19.1, 18.6 (2 CH_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.21; H, 8.92.

(3*S*,4a*R*,8a*S*)-6,7-Dimethyl-3-[(*R*)-2′-octyloxy]-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (9c): $[\alpha]_D$ −39.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (bs, 1, H-3), 4.40 (dd, 1, $J_{1,8a}$ = 2.3 Hz, $J_{1,1'}$ = 11.4 Hz, H-1), 3.84 (sextet, 1, J = 6.3 Hz, H-2 octyl), 3.50 (dd, 1, $J_{1',8a}$ = 1.1 Hz, H-1′), 3.27 (ddd, 1, $J_{4a,5}$ ∼ 1 Hz, $J_{4a,5'}$ = 6.1 Hz, $J_{4a,8a}$ = 5.3 Hz, H-4a), 2.49 (bd, 1, $J_{5,5'}$ = 17.6 Hz, H-5), 2.38 (m, 1, $J_{8a,8}$ = 11.8 Hz, $J_{8a,8'}$ = 4.6 Hz, H-8a), 2.25 (bdd, 1, $J_{8,8'}$ = 16.5 Hz, H-8), 1.98 (bd, 1, H-5′), 1.81 (bdd, 1, H-8′), 1.65, 1.59 (2 bs, 6, 2 CH_3), 1.62−1.25 (m, 10, CH_2 octyl), 1.14 (d, 3, J = 6.3 Hz, CH_3-1 octyl), 0.90 (t, 3, J = 6.0 Hz, CH_3-8 octyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6 (C-4), 123.4, 123.0 (C-6,7), 97.6 (C-3), 73.3 (C-2′), 63.6 (C-1), 43.3 (C-4a), 38.2 (C-8a), 37.3, 31.9, 31.2, 29.3, 28.7, 25.8, 22.7 (C-5,8 and 5 CH_2 octyl), 19.2, 19.1, 18.7, 14.1 (4 CH_3). Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.65; H, 10.78.

(3*S*,4a*R*,8a*S*)-6,7-Dimethyl-3-[(*S*)-2′-octyloxy]-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (9d): $[\alpha]_D$ −14.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (bs, 1, H-3), 4.42 (dd, 1, $J_{1,8a}$ = 2.2 Hz, $J_{1,1'}$ = 11.3 Hz, H-1), 3.77 (sextet, 1, J = 6.2 Hz, H-2 octyl), 3.49 (dd, 1, $J_{1',8a}$ = 1.2 Hz, H-1′), 3.27 (ddd, 1, $J_{4a,5}$ < 1 Hz, $J_{4a,5'}$ = 6.3 Hz, $J_{4a,8a}$ = 5.4 Hz, H-4a), 2.49 (bd, 1, $J_{5,5'}$ = 17.5 Hz, H-5), 2.37 (m, 1, $J_{8a,8}$ = 11.8 Hz, $J_{8a,8'}$ = 4.4 Hz, H-8a), 2.24 (bdd, 1, $J_{8,8'}$ = 17.2 Hz, H-8), 1.98 (bd, 1, H-5′), 1.80 (bdd, 1, H-8′), 1.65, 1.59 (2 bs, 6, 2 CH_3), 1.63−1.24 (m, 10, CH_2 octyl), 1.27 (d, 3, J = 6.2 Hz, CH_3-1 octyl), 0.88 (t, 3, J = 6 Hz, CH_3-8 octyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.5 (C-4), 123.5, 123.0 (C-6,7), 99.7 (C-3), 75.7 (C-2′), 63.6 (C-1), 43.2 (C-4a), 38.3 (C-8a), 36.5, 31.8, 31.2, 29.4, 28.7, 25.2, 22.6 (C-5,8 and 5 CH_2 octyl), 21.4, 19.2, 18.8, 14.1 (4 CH_3). Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.82; H, 10.57.

(3*S*,4a*R*,8a*S*)-3-Benzyloxy-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (10a). Cycloadduct **10a** (ee > 86%) had $[\alpha]_D$ −83.8 (*c* 1.0, $CHCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (bs, 5, H-aromatic), 5.62 (m, 2, H-6,7), 4.82, 4.57 (2 d, 2, J = 11.7 Hz, PhCH_2), 4.74 (bs, 1, H-3), 4.40 (dd, 1, $J_{1,8a}$ = 2.2 Hz, $J_{1,1'}$ = 11.3 Hz, H-1), 3.53 (dd, 1, $J_{1',8a}$ = 0.8 Hz, H-1′), 3.37 (bt, 1, J ∼ 5.7 Hz, H-4a), 2.62 (bd, 1, $J_{5,5'}$ = 17.5 Hz, H-5), 2.41 (m, 1, H-8a), 2.26 (m, 1, H-8), 2.00 (m, 2, H-5′,8′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.0 (C-4), 136.9, 128.5, 128.1 (C-aromatic), 124.9, 124.3 (C-6,7), 99.4 (C-3), 69.7 (PhCH_2O), 63.9 (C-1), 42.7 (C-4a), 37.7 (C-8a), 24.7, 22.3 (C-5,8). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.57; H, 7.21.

(3*S*,4a*R*,8a*S*)-3-[(*R*)-2′-Octyloxy]-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (10c): $[\alpha]_D$ −63.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (m, 2, H-6,7), 4.73 (bs, 1, H-3), 4.42 (dd, 1, $J_{1,8a}$ = 2.2 Hz, $J_{1,1'}$ = 11.3 Hz, H-1), 3.85 (sextet, 1, J = 6.0 Hz, H-2 octyl), 3.49 (dd, 1, $J_{1',8a}$ = 1.3 Hz, H-1′), 3.34 (bt, 1, $J_{4a,8a}$ ∼ $J_{4a,5'}$ = 5.6 Hz, H-4a), 2.64 (bd, 1, $J_{5,5'}$ = 17.5 Hz, H-5), 2.42 (m, 1, $J_{8a,8}$ = 11.2 Hz, H-8a), 2.27 (m, 1, $J_{8,8'}$ = 16.8 Hz, H-8), 2.00 (m, 2, H-5′,8′), 1.62−1.32 (m, 10, CH_2 octyl), 1.14 (d, 3, J = 6.0 Hz, CH_3-1 octyl), 0.91 (t, 3, J = 6.0 Hz, CH_3-8 octyl); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.5 (C-4), 124.9, 124.3 (C-6,7), 97.6 (C-3), 73.3 (C-2′), 63.9 (C-1), 42.7 (C-4a), 37.7 (C-8a), 37.3, 31.9, 29.3, 25.8, 24.7, 22.7, 22.3 (C-5,8 and 5 CH_2 octyl), 19.3, 14.2 (2 CH_3 octyl). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.09; H, 10.25.

Preparative Synthesis of 9a under Thermal Conditions. Isolation of Isomeric (3*S*,4a*S*,8a*R*)-6,7-Dimethyl-

3-benzyloxy-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one (11a). The general procedure for thermal cycloadditions was followed starting from **4a** (0.94 g, 4.60 mmol), hydroquinone (18 mg), and dry toluene (0.37 mL). After addition of 2,3-dimethyl-1,3-butadiene (1.42 g, 17.3 mmol), the mixture was heated in a sealed tube, under argon, at 120 °C for 168 h. The resulting mixture was concentrated and the residue flash chromatographed with 1.5% EtOAc in hexane. From fractions containing the product of $R_f = 0.68$ (hexane/EtOAc 6:1) was isolated the cycloadduct **9a** (0.67 g, 51%).

From further fractions of the column was isolated a second cycloaddition product, having $R_f = 0.52$. It was characterized as **11a** (26.6 mg, 2%): $[\alpha]_D$ −11.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (bs, 5, H-aromatic), 4.82, 4.61 (2 d, 2, J = 12.1 Hz, PhCH_2), 4.76 (bs, 1, H-3), 4.02 (dd, 1, $J_{1,8a} = 7.8$ Hz, $J_{1,1'} = 11.4$ Hz, H-1), 3.69 (dd, 1, $J_{1',8a} = 4.3$ Hz, H-1′), 2.83 (dd, 1, $J_{4a,5} \sim J_{4a,8a} = 6.2$ Hz, $J_{4a,5'} \sim 6.0$ Hz, H-4a), 2.73 (bdd, 1, $J_{5,5'} = 16.5$ Hz, H-5), 2.51 (m, 1, H-8a), 2.08 (bdd, 1, $J_{8,8a} = 5.1$ Hz, $J_{8,8'} = 17.4$ Hz, H-8), 1.93 (m, 2, H-5′,8′), 1.62, 1.58 (2 bs, 6, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 204.0 (C-4), 137.1, 128.5, 127.9, 122.9 (C-aromatic, C-6,7), 98.9 (C-3), 69.9 (Ph*C*H_2O), 63.3 (C-1), 45.7 (C-4a), 35.6 (C-8a), 32.0, 28.4 (C-5,8), 19.0, 18.8 (2 *C*H_3). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.20; H, 8.09.

Preparative Synthesis of 9a and 9c under Catalysis with $Et_2O{\cdot}BF_3$. To a solution of **4a** (0.95 g, 4.65 mmol) in dry toluene (10 mL) cooled to −18 °C was added $Et_2O{\cdot}BF_3$ (584 μL, 4.65 mmol) under argon. The flask was sealed with a septum, and after 5 min, a solution of 2,3-dimethy-1,3-butadiene (1.14 g, 13.9 mmol) in dry toluene (10 mL) was slowly injected. The mixture was stirred at −18 °C for 15 min, and then it was processed as described in the general procedure and flash chromatographed with 1.5% EtOAc in hexane, affording the cycloadduct **9a** (1.09 g, 82%).

Under the same conditions, enantiomerically pure **4c** (0.42 g, 1.86 mmol) afforded **9c** (0.45 g, 79%) after chromatographic purification. Compounds **9a** and **9c** showed the same properties as the respective products isolated in small-scale syntheses.

Epimerization of 11a. Compound **11a** (20 mg) was dissolved in 0.05 M sodium ethoxide in ethanol (2 mL) and the solution stirred at room temperature for 30 min. Monitoring of the mixture by TLC (hexane/EtOAc 6:1) showed complete conversion of **11a** ($R_f = 0.52$) into a less polar product (R_f = 0.69). The solution was neutralized with acetic acid in ethanol and concentrated. Flash chromatography with 1.5% EtOAc in hexane afforded **12a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (bs, 5H-aromatic), 4.81, 4.58 (2 d, 2, J = 11.7 Hz, PhCH_2O), 4.76 (bs, 1, H-3), 3.94 (t, 1, $J_{1,1'} = 11.3$ Hz, $J_{1,8a} \sim 11.0$ Hz, H-1), 3.69 (dd, 1, $J_{1',8a} = 4.5$ Hz, H-1′), 2.78 (ddd, 1, $J_{4a,5} = 12.4$ Hz, $J_{4a,5'} = 5.1$ Hz, $J_{4a,8a} = 11.0$ Hz, H-4a), 2.21 (bt, 1, $J_{5,5'} = 17.7$ Hz, H-5), 2.16 (ddddd, 1, $J_{8a,8} = 11.0$ Hz, $J_{8a,8'} = 8.2$ Hz, H-8a), 2.03 (bdd, 1, H-5′), 1.88 (bd, 2, H-8,8′), 1.64, 1.60 (2 bs, 6, 2 CH_3); ^{13}C (50.3 MHz) δ 203.6 (C-4), 137.0, 128.6, 128.0 (C-aromatic), 124.7, 123.2 (C-6,7), 99.3 (C-3), 69.6 (Ph*C*H_2O), 64.2 (C-1), 45.8 (C-4a), 41.4 (C-8a), 33.8, 29.2 (C-5,8), 19.1, 18.8 (2 *C*H_3).

Compound **9a** was subjected to the same treatment, but it was isolated from the reaction mixture without any change (identical R_f and spectral data).

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Supporting Information Available: ^{1}H NMR spectra for **4a**, **9a**, **9c**; ^{13}C and DEPT NMR spectra for **9a**; 2D COSY and ROESY NMR spectra for **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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