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Enantiomerically pure Diels–Alder cycloadducts from aldohexose-derived dihydropyranones

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Abstract—The thermal and $Et_2O{\cdot}BF_3$-catalyzed Diels–Alder additions of 2,3-dimethylbutadiene and cyclopentadiene to (2*S*,6*S*)-6-acetoxymethyl-2-(2-propyloxy)-2*H*-pyran-3(6*H*)-one **1**, derived from D-galactose, afforded the corresponding enantiomerically pure tetrahydrobenzopyrones resulting from the addition of the diene to the α or β face of **1**. The facial and *endo–exo* selectivities in the formation of the adducts, and their yields, are influenced by the diene and the reaction conditions employed. In particular, low overall yields were obtained in the Lewis acid-promoted reactions. This was attributed to the presence of a Lewis base (an acetoxymethyl group) in the pyranone **1**. Therefore, (2*R*,6*S*)-6-methyl-2-(2-propyloxy)-2*H*-pyran-3(6*H*)-one **7**, which possesses a C-6 methyl substituent instead of an acetoxymethyl, was prepared from L-fucose and subjected to the $Et_2O{\cdot}BF_3$-catalyzed addition of cyclopentadiene. As expected, a good yield (74%) of the corresponding Diels–Alder product was obtained, with excellent β- and *endo*-diastereoselectivities.
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1. Introduction

Sugar-derived dihydropyranones have been employed for the synthesis of a variety of natural products and asymmetric molecules, which display biological activity.[1] The usefulness of the dihydropyranones as versatile building blocks relies on the reactivity of the α,β-unsaturated carbonyl system present in their molecules. In addition, the stereocenters located in the pyranones are able to induce stereocontrol in reactions applied to the conjugated carbonyl group.[1b,d] For example, Diels–Alder cycloadditions to pyranones such as 2-alkoxy-4-*O*-benzoyloxy-methyl-2*H*-pyran-3(6*H*)-ones (enolones),[2] levoglucosenone,[3] and isolevoglucosenone,[4] led stereoselectively to carbocyclic derivatives that carried a number of stereogenic centers. Similarly, we have recently described that 2-alkoxy-2*H*-pyran-3(6*H*)-ones, obtained from pentoses,[5] proved to be active dienophiles in highly *endo*- and facial-diastereoselective [4+2]-cycloadditions with butadienes[5,6] and cyclic dienes.[6,7] The 6-substituted analogues of these pyranones, synthesized from hexoses,[8] underwent addition reactions to their enone system with high stereoselectivity,[9] and have been employed as chiral templates for the enantioselective synthesis of natural products.[10] We report herein the relative reactivity and level of stereocontrol of Diels–Alder cycloadditions of 6-substituted 2-alkoxy-2*H*-pyran-3(6*H*)-ones with dienes under thermal and Lewis acid-promoted conditions.

2. Results and discussion

The dihydropyranone **1** [(2*S*,6*S*)-6-acetoxymethyl-2-(2-propyloxy)-2*H*-pyran-3(6*H*)-one] was readily synthesized from penta-*O*-acetyl-D-galactose, via the per-*O*-acetyl-2-acetoxy-D-galactal. This compound underwent a double allylic rearrangement during the glycosylation catalyzed by a Lewis acid,[8b] to afford **1**. The Diels–Alder reaction of **1** with an excess of butadiene under thermal conditions (toluene, 140 °C for 110 h) showed by TLC the formation of two products and starting material remaining (Scheme 1). The mixture was separated by flash chromatography, with the less polar adduct readily isolated and characterized as (1*S*,3*S*,4a*S*,8a*R*)-1-acetoxymethyl-6,7-dimethyl-3-(2-propyloxy)-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one **2** on the basis of its NMR data and by comparison with the spectra of the

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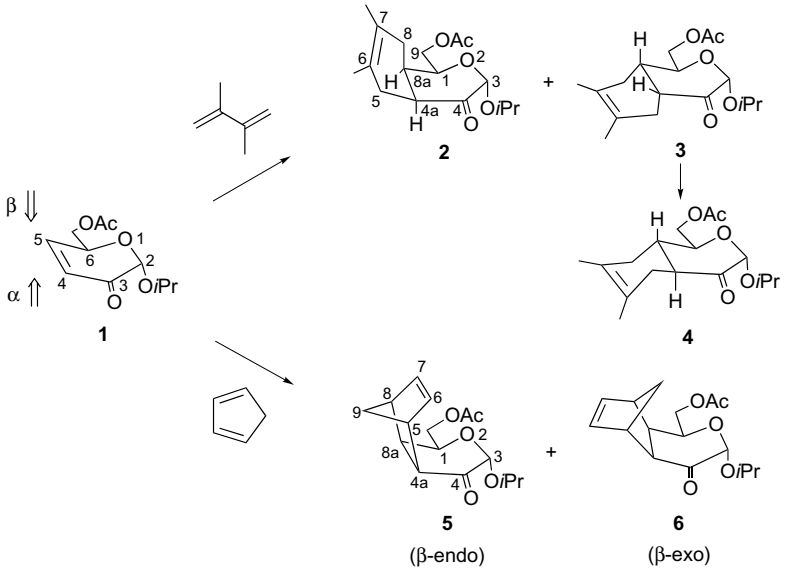


Scheme 1.

adducts of 6-unsubstituted dihydropyranones.[5] Thus, the value of the coupling constant between H-4a and H-8a ($J_{4a,8a}$ = 5.3 Hz) was consistent with a *gauche* quasiaxial–equatorial disposition for those protons, and the small value for $J_{1,8a}$ (1.8 Hz) agreed with a *gauche* axial–equatorial orientation for H-1 and H-8a. The relative configurations for the stereocenters of **2** indicated that the cyclohexene ring was *cis*-fused to the β-face of the pyranone. This arrangement results from the attack of the diene from the face[11] (opposite to the C-2 isopropyloxy group) of the dihydropyranone. The other adduct **3** could not be obtained pure since during the chromatography, it partly converted into an even more polar product. After an additional chromatographic purification this adduct was identified as **4**. The spectral data suggested that the primary adduct **3** (which showed $J_{4a,8a}$ = 5.6 Hz and $J_{1,8a}$ = 9.8 Hz) was formed by attack of the diene from the α face of the dienophile **1** and underwent further isomerization at C-4a to give **4**. The ^{1}H NMR spectrum of **4** exhibited large values for $J_{1,8a}$ (9.6 Hz) and $J_{4,8a}$ (11.3 Hz), indicative of an *anti*-diaxial disposition of H-8a with respect to H-1 and H-4a.

Furthermore, the NOESY spectra of **2** and **4** showed a cross-peak between H-1 and H-4a in agreement with their 1,3-diaxial orientation in the distorted chair conformation of the pyranone ring. This result confirms that **2** and **4** have the same configuration at C-4a.

The isomerization of **3** is probable because of the presence of a hydrogen atom (H-4a) in the carbon vicinal to the carbonyl group. Analogous isomerizations have been reported for Diels–Alder adducts of conjugated cyclohexenones[12] and of 2-alkoxy-2*H*-pyran-3(6*H*)-ones.[5] In order to confirm this result, we explored the tendency of **3** to isomerize under base-catalyzed conditions, where the keto-enol equilibrium is favorable. In fact, the isomerization of **3** to **4** was observed when **3** was treated with a 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) solution. It is noteworthy that **3** can isomerize to **4** without a substantial change of the conformation of the pyranoid ring, and that such a transformation would eliminate the 1,3-diaxial interaction between the alkoxy group at C-3 and C-5 of the cyclohexene ring present in **3**.

The thermal cycloaddition of 2,3-dimethylbutadiene to **1** gave a low isolated yield of adducts (25%) while the remaining starting pyranone (42%) was recovered (yield of cycloadducts 43%, based on unrecovered **1**). The addition took place with poor β/α facial diastereoselectivity (∼1:1) (Table 1). The same reaction promoted by $Et_2O{\cdot}BF_3$, under optimized conditions, also led to low yield of adducts (9%; or 26% based on unrecovered **1**) but in turn, the facial selectivity was higher (8:1 β/α ratio). On the other hand, the thermal promoted Diels–Alder reaction of **1** with the more reactive cyclopentadiene led to moderate yields of products (61%), whereas, the optimized $Et_2O{\cdot}BF_3$-promoted reactions afforded lower yields (36%) of adducts and large amounts (∼50%) of unreacted starting material being recovered.

These results show that the C-6 substituted 2-alkoxy-2*H*-pyran-3(6*H*)-one **1** underwent a much smaller conversion into cycloadducts than their 6-unsubstituted analogues,[5,7] even for longer reaction times. The lower dienophilic reactivity may be attributed to the presence of the *trans*-disposed substituents at C-2 and C-6 of the ring, which would hinder the approach of the diene from both faces of the dihydropyranone. Probably for this reason the thermal cycloaddition of 2,3-dimethylbutadiene to **1** showed no facial diastereoselection, affording adducts **2** and **3** in a ∼1:1 ratio. In contrast, as observed for enolones,[2] the same reaction catalyzed by the Lewis acid was highly diastereoselective, while the addition took place from the side of the pyranone opposite to the alkoxy substituent.

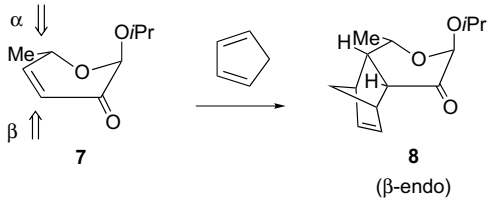
Table 1. Facial selectivities of Diels–Alder reactions of **1** and **7** with dienes under thermal and Lewis acids catalyzed conditions

Dienophile	Diene (molequiv)	Catalyst (molequiv)	Temperature (°C)	Time (h)	Yield[a] (%)	Recovered[a] **1** or **7** (%)	Dr[b] β/α	Dr[b] *endo*/*exo*
1	2,3-Dimethylbutadiene (3.6)		140	110	25[c]	42	1:1[d]	
1	2,3-Dimethylbutadiene (2.2)	$Et_2O{\cdot}BF_3$ (1.0)	−18	3	9[c]	65	8:1[d]	
1	Cyclopentadiene (4.3)		140	110	61	16	>15:1	5:1
1	Cyclopentadiene (1.9)	$Et_2O{\cdot}BF_3$ (1.0)	−18	1	36	50	β[e]	21:1
7	Cyclopentadiene (1.9)	$Et_2O{\cdot}BF_3$ (1.0)	−18	1	74	17	β[e]	>25:1

[a] Yield of adducts or starting material recovered, after flash chromatography.
[b] The diastereomeric ratio (dr) was calculated from the ^1H NMR spectrum of the crude reaction mixture.
[c] Yield of adducts **2** and **4** after treatment with DBU of the reaction mixture and isolation by flash chromatography.
[d] Calculated from the ^1H NMR signals of the crude reaction mixture previously treated with DBU.
[e] The formation of the α-adduct was negligible.

The diastereoselectivity was also influenced by the diene employed. Thus, both thermal and $Et_2O{\cdot}BF_3$-catalyzed Diels–Alder reaction of cyclopentadiene with **1** were highly diastereofacial selective, as only the β-adducts **5** and **6** could be isolated (the formation of α-adducts was negligible). The alkoxy substituent of **1**, seems to induce the approach of cyclopentadiene from the other side of the ring. Furthermore, as expected, the cycloadditions were also *endo*-diastereoselective in favor of *endo* adduct **5**, as predicted by the Alder *endo* rule.[13]

For the $Et_2O{\cdot}BF_3$-promoted cycloadditions of 2,3-dimethylbutadiene and cyclopentadiene to **1**, it was surprising to find much lower yields of cycloadducts, when compared with those observed for the pyranones not substituted at C-6. The less favorable conversion of **1** into adducts may be attributed to the basic acetate of the acetoxymethyl group at C-6, which may compete with the C-3 carbonyl group in the coordination to the Lewis acid.[14] Such a competitive complexation would decrease the catalytic effect of the Lewis acid. To support this hypothesis, ^1H NMR experiments[14] were conducted in order to establish the coordination sites of **1**. In contrast with the behavior shown by the 6-unsubstituted analogues of **1**,[6] the chemical shifts of the signals in the ^1H NMR spectrum of this compound were just slightly affected by the presence of increasing amounts of $Et_2O{\cdot}BF_3$. The addition of other Lewis acids, such as $SnCl_4$ (~1 equiv) to a solution of **1** in $CDCl_3$, also produce a smaller effect in the deshielding of the H-5 signal (0.11 ppm), when compared with that of the 6-unsubstituted analogue (0.32 ppm). Interestingly, in this case, as expected for the coordination of the acetate carbonyl group with the Lewis acid, the signal of the methyl group of the acetyl function showed the same downfield shifting as observed for H-5. The magnitude of the deshielding of the H-β in an α,β-unsaturated complexed carbonyl is usually related to the acidity of the Lewis acid,[14] and hence with its catalytic activity.[15] However, the more acidic $SnCl_4$ (compared with $Et_2O{\cdot}BF_3$) induce competitive polymerizations precluding the formation of adducts,[15] as happened with the $SnCl_4$-promoted cycloadditions of **1**. Finally, to confirm the influence of the acetoxy group of **1** on its reactivity as dienophile, we prepared dihydropyranone **7** from L-fucose.[8b] Compared with **1**, pyranone **7** lacks the acetyloxy group located in the methyl substituent at C-6. Compound **7** was subjected to the $Et_2O{\cdot}BF_3$-promoted cycloaddition with cyclopentadiene, under identical conditions to those employed for **1** (Scheme 2). The higher yield (74%) obtained for *endo*-adduct **8** seems to confirm that the acetoxy group of the C-6 substituent of **1** is responsible for the smaller conversion into cycloadducts of this pyranone, with respect to that of **7**, under Lewis acid catalysis.



Scheme 2.

The structures of cycloadducts **5**, **6**, and **8** were determined on the basis of their NMR spectra as well as by 2D COSY and NOESY NMR experiments. The α/β and *endo*/*exo* assignments were aided by NMR data reported for the adducts of their 6-unsubstituted analogues,[5,7] 2-cyclohexenones,[16,17] and enolones.[2] For the norbornene system of such cycloadducts, the large $J_{4a,8a}$ (8.4–9.1 Hz) and the relatively small $J_{1,8a}$ (4.2–4.5 Hz) values are in agreement with the geometry resulting from the β-addition of the diene. Furthermore, compounds **5** and **8** showed larger chemical shift differences between H-6 and H-7 compared with that of **6**, while the protons of the fused rings (H-4a and H-8a) appeared more deshielded in **5** and **8** than in **6**. These spectral data are consistent with an *exo* arrangement in **6** and an *endo* in **5** and **8**, as reported for analogous systems.[2,7] The structural assignments were confirmed by means of NOESY experiments. Thus, for cycloadduct **5**, the cross-peak between H-1 and H-4a was indicative of the relative configuration of C-4a, while the cross-peaks between H-4a–H-9′ and H-8a–H-9′ were in agreement with the *endo* configuration proposed for this isomer.

3. Conclusion

In summary, 6-substituted 2-alkoxy-2*H*-pyran-3(6*H*)-ones exhibited a lower dienophilic activity than their 6-unsubstituted counterparts. The stereochemical course

of thermal and Lewis acid-promoted Diels–Alder cycloadditions of the former is influenced by the nature of the 6-substituent and the reactivity of the diene. The $Et_2O{\cdot}BF_3$-promoted cycloadditions are highly facial- and *endo*-diastereoselective and provide a straightforward access to enantiomerically pure carbocycles that possess a number of stereocenters generated under stereocontrol. In fact, enantiomerically pure Diels–Alder adducts have found applications to elegant total synthesis of many complex natural products.[18,19]

4. Experimental

4.1. General methods

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (E. Merck) aluminum-supported plates (layer thickness 0.2 mm). Visualization of the spots was effected by exposure to UV light or by charring with a solution of 5% (v/v) sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was carried out with silica gel 60 (230–400 mesh, E. Merck). Optical rotations were measured with a Perkin–Elmer 343 digital polarimeter at 25 °C. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AMX 500 or a Bruker AC 200 instruments, in $CDCl_3$ solutions (tetramethylsilane as internal standard). For full assignments, 2D COSY experiments were conducted, and for the ^{13}C NMR spectra, DEPT techniques were employed.

4.2. Adducts of (2*S*,6*S*)-6-acetoxymethyl-2-(2-propyloxy)-2*H*-pyran-3(6*H*)-one 1 with 2,3-dimethylbutadiene: synthesis of (1*S*,3*S*,4a*S*,8a*R*)-1-acetoxymethyl-6,7-dimethyl-3-(2-propyloxy)-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one 2 and (1*S*,3*S*,4a*S*,8a*S*)-1-acetoxymethyl-6,7-dimethyl-3-(2-propyloxy)-4a,5,8,8a-tetrahydro-1*H*-2-benzopyran-4(3*H*)-one 4

4.2.1. Thermal cycloaddition procedure. A mixture of **1** (312 mg, 1.37 mmol), hydroquinone (4 mg) and toluene (0.2 mL), was placed in a thick-walled glass tube and 2,3-dimethylbutadiene (402 mg, 4.89 mmol) added. The glass tube was flushed with dry argon, sealed, and heated to 140 °C for 110 h. The reaction mixture showed by TLC (3:1 hexane–EtOAc) three main spots having R_f values 0.44, 0.42, and 0.33. The faster moving component (R_f 0.44) was readily isolated by flash chromatography (17:1 hexane–EtOAc), but the other two products could not be separated. Therefore, the procedure described above was repeated and the reaction mixture thus obtained after heating was concentrated and treated with 1,8-diazabycyclo[5.4.0]undec-7-ene (DBU, two drops) in anhydrous CH_2Cl_2 (4 mL) over molecular sieves beads (3 Å), as it was proven that **3** isomerizes to **4** under these conditions (see below). After stirring at room temperature for 40 min, the mixture was neutralized with glacial acetic acid and concentrated. The residue was purified by flash chromatography (17:1 hexane–EtOAc) to afford the faster moving product (R_f 0.44) identified as **2** (50.5 mg, 11.9%); mp 47 °C; $[\alpha]_D = -9.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.71 (br s, 1H, H-3), 4.69 (ddd, 1H, $J_{1,8a} = 1.8$, $J_{1,9} = 5.6$, $J_{1,9'} = 7.3$ Hz, H-1), 4.18 (dd, 1H, $J_{9,9'} = 11.4$ Hz, H-9), 4.15 (dd, 1H, H-9′), 4.00 (septet, 1H, $J = 6.2$ Hz, $(CH_3)_2CHO$), 3.24 (br dd, 1H, $J_{4a,5} < 1.0$, $J_{4a,5'} = 6.3$, $J_{4a,8a} = 5.3$ Hz, H-4a), 2.47 (br d, 1H, $J_{5,5'} = 17.4$ Hz, H-5), 2.42 (dddd, 1H, $J_{8,8a} = 11.3$, $J_{8',8a} = 5.7$ Hz, H-8a), 2.08 (s, 3, CH_3CO overlapped with br t, 1H, H-8), 1.97 (br d, 1H, H-5′), 1.73 (br dd, 1H, $J_{8,8'} = 17.2$ Hz, H-8′), 1.64, 1.57 (2br s, 6H, $2CH_3$), 1.29, 1.17 (2d, 6H, $J = 6.2$ Hz, $(CH_3)_2CHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9 (C-4), 170.7 (CH_3CO), 123.4, 122.5 (C-6,7), 98.3 (C-3), 71.3 ($(CH_3)_2CHO$), 69.5 (C-1), 64.1 (C-9), 43.5 (C-4a), 39.2 (C-8a), 28.4 (C-5), 27.2 (C-8), 23.4, 21.9 ($(CH_3)_2CHO$), 20.8 (CH_3CO), 19.3, 18.8 (2 CH_3). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 66.07; H, 8.47.

From next fractions of the column was isolated the cycloadduct having R_f 0.42, which was characterized as **4** (47.1 mg, 11.1%); $[\alpha]_D = +179.7$ (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 1H, H-3), 4.32 (dd, 1H, $J_{1,9} = 2.0$, $J_{9,9'} = 11.7$ Hz, H-9), 4.22 (ddd, 1H, $J_{1,9'} = 5.7$, $J_{1,8a} = 9.6$ Hz, H-1), 4.16 (dd, 1H, H-9′), 4.01 (septet, 1H, $J = 6.2$ Hz, $(CH_3)_2CHO$), 2.78 (td, 1H, $J_{4a,5'} = 5.0$, $J_{4a,5} \sim J_{4a,8a} = 11.3$ Hz, H-4a), 2.23-1.90 (m, 5H, H-5,5′,8,8′,8a), 2.09 (s, 3H, CH_3CO), 1.65, 1.61 (2s, 6H, $2CH_3$), 1.28, 1.18 (2d, 6H, $(CH_3)_2CHO$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.1 (C-4), 171.0 (CH_3CO), 124.7, 123.1 (C-6,7), 98.4 (C-3), 71.4, 71.3 (C-1, $(CH_3)_2CHO$), 63.8 (C-9), 44.4, 41.6 (C-4a,8a), 34.4, 29.4 (C-5,8), 23.3, 21.8 ($(CH_3)_2CHO$), 20.8 (CH_3CO), 19.0, 18.7 ($2CH_3$). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.39; H, 8.57.

4.2.2. $Et_2O{\cdot}BF_3$-promoted cycloaddition. A solution of **1** (409 mg, 1.79 mmol) in dry toluene (4.5 mL) was cooled to −18 °C and $Et_2O{\cdot}BF_3$ (230 μL, 1.83 mmol) added under argon. The vial was sealed and the mixture stirred at −18 °C for 15 min, after which 2,3-dimethylbutadiene (317 mg, 3.86 mmol) dissolved in toluene (2.5 mL) was injected. The stirring was continued at the same temperature for 2.5 h, and then the mixture diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was treated with DBU as described for the thermal procedure, and purified by flash chromatography to afford **2** (44.5 mg, 8.0%) and **4** (5.6 mg, 1.0%). Compounds **2** and **4** showed the same spectral data as the respective products obtained in the thermal cycloaddition.

4.2.3. Isomerization of 3 to 4. Compound **3** (210 mg, 0.68 mmol, somewhat contaminated with **4**) was dissolved in chloroform (3 mL) and treated with DBU (0.1 mL) at room temperature. Monitoring of the reaction mixture by TLC showed the gradual disappearance of **3** and intensification of the spot having the same mobility as **4** (complete conversion after 0.5 h). The pattern of signals in the ^{13}C NMR spectrum of the crude reaction mixture exactly overlapped with that of **4**.

4.2.4. Complexation of 1 with Lewis acids: ^{1}H NMR experiments. An NMR tube containing a solution of compound **1** (~10 mg) in $CDCl_3$ (0.6 mL) was cooled to −78 °C and an increasing amount of the Lewis acid added (molar ratio of Lewis acid: **1** from 0.1:1 to 1:1). After the addition, the ^{1}H NMR spectrum was immediately recorded. Dihydropyranone **1** proved to be stable in the solution with the Lewis acid for longer times than those required for the acquisition of the spectrum.

4.3. Adducts of 1 with cyclopentadiene: synthesis of (1*S*,3*S*,4a*S*,5*R*,8*S*,8a*R*)-1-acetoxymethyl-3-(2-propyloxy)-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)-one 5 and (1*S*,3*S*,4a*S*,5*S*,8*R*,8a*R*)-1-acetoxymethyl-3-(2-propyloxy)-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)-one 6

4.3.1. Thermal cycloaddition procedure. A mixture of **1** (166.4 mg, 0.73 mmol), hydroquinone (4 mg), and toluene (0.1 mL), was placed in a thick walled glass tube and cyclopentadiene (208 mg, 3.15 mmol), freshly distilled from the commercial dimer,[20] added. The glass tube was flushed with dry argon, sealed and heated at 140 °C for 110 h. The reaction mixture was then concentrated and subjected to chromatography (17:1 hexane–EtOAc). The less polar adduct (R_f 0.48, 2.5:1 hexane–EtOAc) was spectroscopically characterized as **6** (22 mg, 10%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (br t, 2H, $J_{5,6} \sim J_{7,8} = 1.8$ Hz, H-6,7), 4.75 (br s, 1H, H-3), 4.65 (ddd, 1H, $J_{1,8a} = 4.2$, $J_{1,10} = 4.4$, $J_{1,10'} = 7.7$ Hz, H-1), 4.37 (dd, 1H, $J_{10,10'} = 11.6$ Hz, H-10), 4.35 (dd, 1H, H-10′), 4.04 (septet, 1H, $J = 6.2$ Hz, $(CH_3)_2CHO$), 3.20, 2.93 (2m, 2H, H-5,8), 2.36 (br d, 1H, $J_{4a,8a} = 8.4$ Hz, H-4a), 2.11 (s, 3H, CH_3CO), 1.79 (ddd, 1H, $J_{8,8a} = 1.7$ Hz, H-8a), 1.67 (br d, 1H, $J_{9,9'} = 9.1$ Hz, H-9), 1.55 (br d, 1H, H-9′), 1.27, 1.23 (2 d, 6H, $(CH_3)_2CHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9 (C-4), 170.8 (CH_3CO), 139.2, 137.3 (C-6,7), 95.9 (C-3), 70.6 ($(CH_3)_2CHO$), 67.1, 65.2 (C-1,10), 49.3, 47.7, 45.0, 42.5, 38.2 (C-4a,5,8,8a,9), 23.1, 21.3, 20.8 ($3CH_3$).

From the next fractions of the column (R_f 0.41, 2.5:1 hexane–EtOAc) was isolated **5** (109 mg, 51%); $[\alpha]_D = +58.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19, 5.98 (2 dd, 2H, $J_{5,6} = J_{7,8} = 2.8$, $J_{6,7} = 5.7$ Hz, H-6,7), 4.57 (ddd, 1H, $J_{1,8a} = 4.3$, $J_{1,10} = 4.0$, $J_{1,10'} = 8.4$ Hz, H-1), 4.41 (s, 1H, H-3), 4.34 (dd, 1H, $J_{10,10'} = 11.6$ Hz, H-10), 4.17 (dd, 1H, H-10′), 3.93 (septet, 1H, $J = 6.2$ Hz, $(CH_3)_2CHO$), 3.35 (m, 1H, $J_{4a,5} = 4.5$, $J_{5,9} \sim 1.8$ Hz, H-5), 3.05 (ddd, 1H, $J_{4a,8a} = 9.1$ Hz, H-4a), 3.02 (br s, 1H, H-8), 2.54 (ddd, 1H, $J_{8,8a} = 3.2$ Hz, H-8a), 2.10 (s, 3H, CH_3CO), 1.48 (dt, 1, $J_{5,9} \sim J_{8,9} \sim 1.0$, $J_{9,9'} = 8.5$ Hz, H-9), 1.32 (br d, 1H, H-9′), 1.23, 1.18 (2d, 6H, $(CH_3)_2CHO$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.8 (C-4), 170.8 (CH_3CO), 135.6, 134.1 (C-6,7), 95.7 (C-3), 70.4 ($(CH_3)_2CHO$), 65.3 (C-1), 65.0 (C-10), 49.8 (C-9), 47.8 (×2) (C-4a,8a), 44.2, 38.6 (C-5,8), 23.1, 21.3, 20.8 ($3CH_3$). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.50; H, 7.63.

4.3.2. $Et_2O{\cdot}BF_3$-promoted cycloaddition. A solution of **1** (271 mg, 1.19 mmol) in dry toluene (4 mL) was cooled to −18 °C and $Et_2O{\cdot}BF_3$ (190 μL, 1.19 mmol) then added under argon. The vial was sealed and the mixture stirred at −18 °C for 15 min, after which freshly distilled cyclopentadiene[20] (146 mg, 2.21 mmol) dissolved in toluene (1 mL) was injected. After stirring at −18 °C for 1 h, the mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography to afford **5** (120.1 mg, 34.4%) and **6** (5.7 mg, 1.6%).

4.4. Cycloaddition of (2*R*,6*S*)-6-methyl-2-(2-propyloxy)-2*H*-pyran-3(6*H*)-one 7 with cyclopentadiene: synthesis of (1*S*,3*R*,4a*R*,5*S*,8*R*,8a*S*)-1-methyl-3-(2-propyloxy)-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)- one 8

The $Et_2O{\cdot}BF_3$-promoted cycloaddition of cyclopentadiene to **7** (200 mg, 0.85 mmol) under the conditions described above, afforded **8** (206 mg, 74%); $[\alpha]_D = -86.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 6.22, 5.95 (2dd, 2H, $J_{5,6} \sim J_{7,8} \sim 2.9$, $J_{6,7} = 5.6$ Hz, H-6,7), 4.46 (dq, 1H, $J_{1,8a} = 4.5$, $J_{1,10} = 6.5$ Hz, H-1), 4.35 (s, 1H, H-3), 3.89 (septet, 1H, $J = 6.1$ Hz, $(CH_3)_2CHO$), 3.33 (m, 1H, H-5), 3.09 (br s, 1H, H-8), 3.00 (ddd, 1H, $J_{4a,5} = 4.6$, $J_{4a,8a} = 9.0$, $J = 1.1$ Hz, H-4a), 2.46 (ddd, 1H, $J_{8,8a} = 3.2$ Hz, H-8a), 1.44 (dt, 1H, $J_{5,9} \sim J_{8,9} \sim 2.9$, $J_{9,9'} = 8.5$ Hz, H-9), 1.31 (d, 3H, H-10), 1.30 (m, 1H, H-9′), 1.20, 1.16 (2d, 6H, $(CH_3)_2CHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8 (C-4), 136.0, 133.7 (C-6,7), 96.2 (C-3), 70.3 ($(CH_3)_2CHO$), 63.1 (C-1), 49.5, 48.2, 47.9, 44.2, 42.4 (C-4a,5,8,8a,9), 23.3, 21.5, 18.8 ($3CH_3$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.35; H, 8.80.

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References

1. (a) Lichtenthaler, F. W. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: Weinheim/New York, 1992; Vol. 6, pp 273–376; (b) Lichtenthaler, F. W. In *Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Springer: New York, 1986; pp 227–254; (c) Lichtenthaler, F. W. *Acc. Chem. Res.* **2002**, *35*, 728–737; (d) Holder, N. L. *Chem. Rev.* **1982**, *82*, 287–332; (e) Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57–66.
2. Dauben, W. G.; Kowalczyk, B. A.; Lichtenthaler, F. W. *J. Org. Chem.* **1990**, *55*, 2391–2398.
3. (a) Ward, D. D.; Shafizadeh, F. *Carbohydr. Res.* **1981**, *95*, 155–176; (b) Bhaté, P.; Horton, D. *Carbohydr. Res.* **1983**, *122*, 189–199.
4. (a) Horton, D.; Roski, J. P.; Norris, P. *J. Org. Chem.* **1996**, *61*, 3783–3793; (b) Horton, D.; Roski, J. P. *J. Chem. Soc., Chem. Commun.* **1992**, 759–760.

5. Iriarte Capaccio, C. A.; Varela, O. *J. Org. Chem.* **2001**, *66*, 8859–8866.
6. Iriarte Capaccio, C. A.; Varela, O. *Tetrahedron Lett.* **2003**, *44*, 4023–4026.
7. Iriarte Capaccio, C. A.; Varela, O. *J. Org. Chem.* **2002**, *67*, 7839–7846.
8. (a) Varela, O.; De Fina, G. M.; Lederkremer, R. M. *Carbohydr. Res.* **1987**, *167*, 187–196; (b) De Fina, G. M.; Varela, O.; Lederkremer, R. M. *Synthesis* **1988**, 891–893.
9. (a) Varela, O.; De Fina, G. M.; Lederkremer, R. M. *Carbohydr. Res.* **1993**, *246*, 371–376; (b) Paulsen, H.; Koebernick, H. *Tetrahedron Lett.* **1976**, *17*, 2297–2300.
10. (a) Iriarte Capaccio, C. A.; Varela, O. *Tetrahedron: Asymmetry* **2000**, *11*, 4945–4954; (b) Zunszain, P. A.; Varela, O. *Tetrahedron: Asymmetry* **1998**, *9*, 1269–1276.
11. The α and β descriptors were employed to indicate that the addition of the diene to the dihydropyranone ring took place from the same (α) or the opposite side (β) respect to the 2-alkoxy substituent.
12. Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056–5065.
13. Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510–519.
14. Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801–808.
15. Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Hersh, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6070–6081.
16. Fringuelli, F.; Guo, M.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 710–712.
17. Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325–4328.
18. Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
19. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.
20. Moffett, R. B. *Org. Synth. Coll.* **1963**, *4*, 238–241.