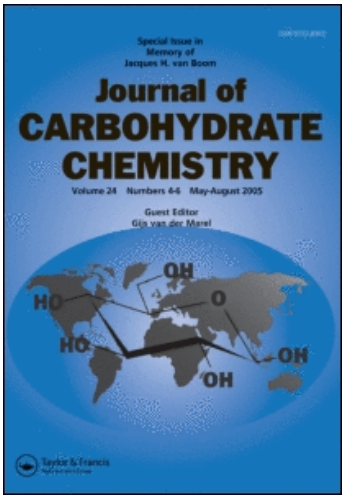

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Thermal and Catalytic Diels-Alder Reactions Between (*2E*)-4, 5,6-Tri-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro* -Hex-2-Enose and Cyclopentadiene

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THERMAL AND CATALYTIC DIELS-ALDER REACTIONS BETWEEN (2*E*)-4,5,6-TRI-*O*-ACETYL-2,3-DIDEOXY-*ALDEHYDO*-D-*ERYTHRO*-HEX-2-ENOSE AND CYCLOPENTADIENE

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ABSTRACT

Thermal and catalytic reactions between (2*E*)-4,5,6-tri-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-hex-2-enose (**1**) and cyclopentadiene led, in each case, to the four stereoisomeric 5-formyl-6-(1,2,3-tri-*O*-acetyl-D-*erythro*-triol-1-yl)bicyclo[2.2.1]hept-2-enes (**2-5**). The role of the catalysts is discussed, and the face selectivity is rationalized in terms of both steric and electrostatic arguments. Upon subsequent sodium borohydride reduction, iodination, and zinc reduction, the adducts **2-5** were converted to their respective primary alcohols **6-9**, that could be separated by column chromatography. Sequential basic deacetylation, oxidative cleavage of the sugar side-chain with sodium metaperiodate, and reduction with sodium borohydride, yielded the previously known (5*R*,6*R*)- or (5*S*,6*S*)-bis(hydroxymethyl)norbornene-diols **12** or **13**, thus establishing the C-5 and C-6 absolute configurations of their synthetic precursors.

INTRODUCTION

Although Diels-Alder cycloadditions are among the most widely-used reactions in organic synthesis,[1] there are not many examples in the carbohydrate field.[2] In our laboratory, we have recently shown that (*E*)-1-deoxy-1-nitroalkenes derived from sugars

react, as dienophiles, with cyclic or acyclic dienes, yielding mixtures of their corresponding stereoisomeric norbornene[3] or cyclohexene[4] adducts. These reactions proceeded thermally, and we did not observe for them any Lewis-acid catalytic effect. Most of the time, the same catalysts that we used in this work only produced decomposition of the reaction mixtures, with the appearance of numerous by-products. Nevertheless, a few cases of catalyzed Diels-Alder cycloadditions with sugar-derived dienophiles, mainly α,β-unsaturated esters, have been described.[5] As far as we know, a recent paper[6] from our group on cycloaddition reactions between **1** and 2,3-dimethyl-1,3-butadiene is the only example described for the use of α,β-unsaturated *aldehydo*-sugars as dienophiles in asymmetric Diels-Alder reactions.

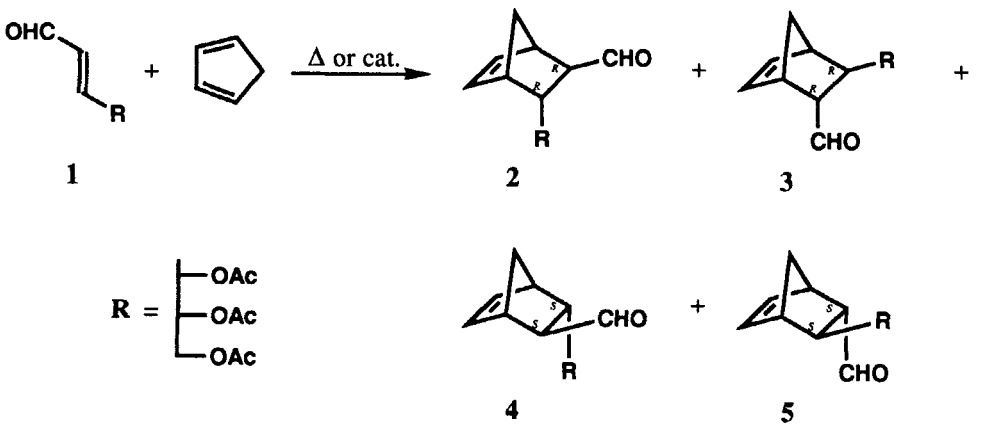
In this paper we examine the reaction of the sugar-derived α,β-unsaturated aldehyde **1** with cyclopentadiene, as well as the role played in this case by the catalysts in determining the stereochemistry and the rate of the processes. Although the observed *exo/endo* or *R,R/S,S* selectivity was rather low and mixtures of the four adducts were produced in all cases, further synthetic applications could be possible due to the facile conversion of the formyl-glyconorbornenes **2-5** into their corresponding primary alcohols. These were easily separated through an extension of the iodolactone method,[7] in a similar way to one that was used by Takano *et al.*[8] for the separation of closely related *endo* and *exo* norbornene adducts.

RESULTS AND DISCUSSION

Thermal and catalytic Diels-Alder reactions of α,β-unsaturated aldehyde **1** (readily available from tri-*O*-acetyl-D-glucal[9]) and cyclopentadiene led, in all cases, to mixtures of the four stereoisomeric adducts **2-5** (Scheme), from which the 5-*exo*-formyl compounds **2** and **4** could be isolated pure by preparative thin layer chromatography.

Table 1 summarizes the reaction conditions, the percentage of conversions, and the ratios of adducts (%) at the end of each time.[10] The data show that, in contrast with those observed for us in sugar-derived nitroalkenes,[3,4] the Lewis acids (entries 4-11) enhance the reaction rates, this effect being more pronounced for boron trifluoride-etherate and less for silica gel. This order may reflect not only the intrinsic catalytic activity,[11] but other factors such as the solubility of catalysts (only boron trifluoride-etherate and tin tetrachloride are

Scheme



1 2 3 4 5

soluble in toluene among those considered) and that of the complexes formed between the catalyst and the α,β-unsaturated aldehyde.[12] On the other hand, the proportion of 5-*endo*-formyl adducts is greater for catalyzed reactions, as would be expected from the FMO theory[13,14] considering the enhancement of the coefficient of the aldehydic carbon at the LUMO. The preference for 5-*exo*-formyl compounds in uncatalyzed reactions is in contrast with that observed for the cycloaddition between cyclopentadiene and acrolein.[15-17] As has been described,[16,18] however, a decrease and even inversion of the *endo* preference occurs with the introduction of substituents on the β-carbon atom of the dienophile and, particularly, when higher temperatures were used. In our case this last effect can be observed by comparing the uncatalyzed reactions at room temperature with those at reflux and, to a lesser extent, by comparing catalytic reactions at 0 °C with those at room temperature. These facts agree with previous observations[17-19] establishing the *exo* isomers as the thermodynamically favored ones. Since in our case the ratio of adducts remain invariable in each experiment, we can conclude that the reactions do not revert under our conditions; hence, these reactions are kinetically controlled, and the ratios of adducts reflect their relative rates of formation.

In water as the solvent (Table 1, entry 3), the rate of the cycloaddition as well as the stereospecificity increased moderately. According to Breslow[20,21] and Grieco,[22] in these aqueous cycloadditions the hydrophobic association of the diene with the dienophile is

Table 1. Composition of Reaction Mixtures (%) and Conditions for Cycloadditions between 1 and Cyclopentadiene.

entry	Lewis acid	A	*t* (h)	*T* (°C)	convn (%)	ratio of adducts (%) *exo*-formyl (2)	*exo*-formyl (4)	*endo*-formyl (3)	*endo*-formyl (5)	*exo:endo*	*R,R:S,S*
1	-	- : 4 : 1	336	25	90	46	15	26	13	1.56	2.57
2	-	- : 4 : 1	22	110	100	47	18	25	10	1.86	2.57
3*	-	- : 5 : 1	240	25	100	49	15	28	8	1.78	3.35
4	ZnI_2	3 : 1.4 : 1	7	0	100	20	10	45	25	0.43	1.86
5	ZnI_2	3 : 1.4 : 1	3	25	100	20	13	44	23	0.49	1.78
6	$ZnCl_2$	3 : 4 : 1	5	25	100	17	10	45	28	0.37	1.63
7	$AlCl_3$	1 : 1.4 : 1	3	0	67	20	20	23	37	0.67	0.75
8	$SnCl_4$	3 : 1.4 : 1	1.5	0	100	22	13	35	30	0.54	1.33
9	$SnCl_4$	3 : 1.4 : 1	1.5	25	100	22	15	30	33	0.59	1.08
10	$BF_3.OEt_2$	0.85 : 4 : 1	1	25	100	15	8	42	35	0.30	1.33
11**	SiO_2	- : 4 : 1	72	25	72	37	15	33	15	1.08	2.33

(A), Ratio catalyst:diene:dienophile. (*), Except for this case (water), all reactions were carried out in toluene. (**) For the quantity of SiO_2 see Experimental.

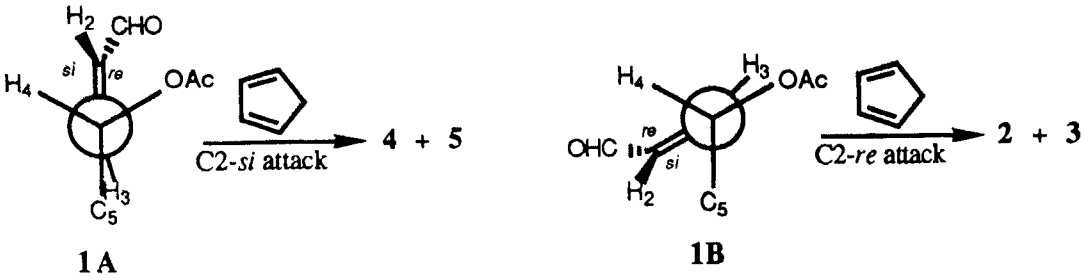


Figure 1. Preferred attack of cyclopentadiene on the conformers **1 A** and **1 B** of the dienophile.

responsible for the rate accelerations, whereas the higher stereospecificity might be explained in terms of transition state volumes, probably smaller for the *exo* isomers **2** and **3** (sugar-chain *endo*).

Concerning the facial selectivity (*i.e. R,R vs. S,S* adducts), we found that it is better for uncatalyzed reactions, the majority being the *R,R* **2** and **3** (except for the $AlCl_3$-catalyzed reaction). This result agrees with those of closely related reactions described by Horton et al.,[23] who proposed that the facial selectivity is largely controlled by the stereo center in the allylic position. In this way, the formation of the major adducts may be explained by attack of the diene at the C-2 *re*-face of the dienophile **1**, probably through its **1 B** conformer (see Figure 1), in which this approach would appear favored due to both steric and electrostatic[24] considerations. In catalytic reactions, complexation between the formyl group on the dienophile and the catalyst should additionally favor the conformer **1 A** (presumably the most stable), directing the diene, in a major degree, to the C-2 *si*-face of the α,β-unsaturated aldehyde (and therefore increasing the proportion of the *S,S* adducts).

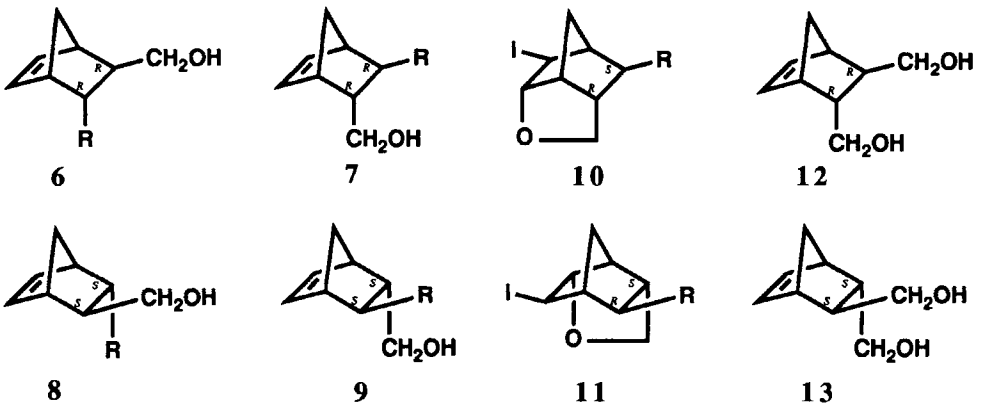
Reduction of a 47:25:18:10 mixture of the adducts **2-5** with sodium borohydride afforded quantitatively a mixture of their corresponding primary alcohols **6-9** in the same relative ratio; from this, fractions containing the 5*R*,6*R* (**6+7**) and 5*S*,6*S* (**8+9**) were separated by column chromatography on silica gel.

Upon treatment with iodine,[25] the mixture of 5*R*,6*R* alcohols **6+7** furnished the iodo-ether **10** (formed from **7**), that could be easily separated from unchanged **6**; in the same

way, the 5*S*,6*S* alcohols **8**+**9** yielded the iodo-ether **11** (from **9**) and **8**. Reductive cleavage with zinc[26] of iodo-ethers **10** and **11** led to their corresponding *endo*-alcohols **7** and **9**, respectively.

Each one of the four diastereoisomeric 5-hydroxymethyl-6-glyconorbornenes **6**-**9** was subjected to sequential basic deacetylation, oxidative cleavage of the sugar side-chain with sodium metaperiodate, and reduction with sodium borohydride, yielding their respective optically active known[23,27] diols **12** and **13**. Thus, the *exo*-**6** and *endo*-**7** alcohols (which led to **12**) must have the 5*R*,6*R* configurations, whereas the *exo*-**8** and *endo*-**9** (which yielded **13**) must be 5*S*,6*S*.

On the other hand, the configuration of aldehydes **2** (*exo*-5*R*,6*R*) and **4** (*exo*-5*S*,6*S*) follows from their respective transformation into alcohols **6** and **8**, whereas for **3** (*endo*-5*R*,6*R*) and **5** (*endo*-5*S*,6*S*) the absolute stereochemistry was achieved through correlation of their relative proportions in the **2**-**5** mixture with those of the *endo*-alcohols in the **6**-**9** mixture.



R = D-*erythro*-$(CHOAc)_2$-CH_2OAc

^1H and ^{13}C NMR data of compounds **2**-**11** are in agreement with their proposed structures. For each of these substances, the relative chemical shifts for protons on *exo* or *endo* carbons provides the information needed to determine their orientation, because it is known that *endo* substituents are more shielded than those *exo*.[18,28] Concerning the absolute stereochemistry at C-5 and C-6, we have observed that H-1 is always at lower field for (5*S*,6*S*) **4**, **5**, **8** and **9** than for (5*R*,6*R*) **2**, **3**, **6** and **7** compounds, the reverse being true for H-5.

Table 2. ^{1}H NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) of Compounds 2-5 and 6-9.

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-7s	H-7a	H-1′	H-2′	H-3′	H-3′′	OCOCH_3	CHO (CH_2OH)
2	2.87	6.32	6.04	3.18	2.25	2.75	1.45	1.30	4.66	4.92	4.41	4.20	2.12, 2.04, 2.00	9.83
3	2.68	6.22	6.08	3.35	2.90	2.06	1.62	1.44	5.13	5.06	4.38	4.26	2.14, 2.12, 2.04	9.54
4	3.06	← 6.31 →		3.10	2.06	2.66	1.54	1.43	4.74	5.21	4.53	4.16	2.08, 2.04, 2.02	9.73
5	2.94	6.30	6.04	3.18	2.69	2.10	1.60	1.50	← 5.20 →		4.41	4.16	2.09, 2.07, 2.04	9.41
6	2.75	5.92	6.27	2.75	1.42	1.90	← 1.42 →		4.68	5.19	4.51	4.12	2.05, 2.02, 2.00	(3.69, 3.61)
7	2.55	6.16	6.08	2.95	2.08	1.21	1.39	1.52	5.13	5.35	4.41	4.18	2.17, 2.08, 2.05	(3.44, 3.37)
8	2.87	6.16	6.22	2.70	1.22	1.74	← 1.44 →		4.68	5.16	4.44	4.11	2.04, 2.02, 1.99	(3.59, 3.45)
9	2.80	6.20	6.11	2.91	1.91	1.18	← 1.53 →		5.16	5.24	4.39	4.15	2.10, 2.08, 2.06	(3.34, 3.23)

Compound	$J_{1,2}$	$J_{1,6}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{7s,7a}$	$J_{1',6}$	$J_{1',2'}$	$J_{2',3'}$	$J_{2',3''}$	$J_{3',3''}$	$J_{5,CHO}$	$J_{5,CHaHbOH}$	$J_{a,b}$
2	2.9	4.1	5.6	2.7	<1	4.1	8.9	11.5	1.8	2.9	8.5	12.1	1.1	–	–
3	3.2	<1	5.6	2.7	4.0	4.0	9.0	10.9	2.8	2.7	7.9	11.8	1.1	–	–
4	--	3.5	–	–	<1	4.2	8.8	10.7	2.7	2.8	8.5	12.2	2.0	–	–
5	2.9	<1	5.6	2.8	4.0	4.0	9.9	–	–	2.8	8.5	12.2	2.3	–	–
6	2.7	4.0	5.6	3.1	<1	4.0	–	11.3	2.0	2.1	8.7	12.1	--	7.2, 7.4	10.4
7	3.0	<1	5.6	2.6	--	4.2	9.0	10.6	2.0	2.2	8.7	12.1	–	7.6, 7.4	12.0
8	2.6	3.9	5.6	2.8	<1	3.9	–	11.0	2.6	2.8	8.6	12.1	–	6.5, 8.4	10.7
9	2.7	<1	5.7	2.9	–	4.4	–	11.0	2.9	2.7	8.6	12.3	–	6.8, 8.2	10.6

The values of the coupling constants $J_{1',2'}$ and $J_{2',3'}$ of the protons on the sugar side-chains are similar (2-3 Hz), indicating a *gauche* relationship for H-1′--H-2′ and H-2′--H-3′, and establishing a sickle conformation ($^1G_+$). This would result from the zig-zag extended planar conformation (*P*), by clockwise rotation by 120° of O-2′ along the C-1′--C-2′ bond[29] (the $^1G_-$ form would generate an interaction between C-1 of the norbornene ring and C-3′ of the sugar-chain). This conformational homogeneity in the adducts contrasts with that observed[9] for the starting aldehyde **1**, whose analogous coupling constants ($J_{4,5}$, $J_{5,6}$, and $J_{5,6'}$) showed intermediate values (4.2-6.1 Hz).

In conclusion, we describe here the use of an easily available α,β-unsaturated aldehyde as dienophile, from which a series of stereochemically pure bicyclo[2.2.1]-heptane derivatives have been obtained. These compounds could be useful as synthetic intermediates for a variety of natural products.[30]

EXPERIMENTAL

General Procedures. Solvents were evaporated under reduced pressure below 40 °C bath temperature. Optical rotations were obtained at 20±2 °C with a Perkin-Elmer 241 polarimeter. ^{1}H NMR (200.13 MHz) and ^{13}C NMR (50.33 MHz) were obtained on a Bruker AC 200 E instrument with tetramethylsilane as the internal reference and deuteriochloroform as the solvent. NMR assignments were facilitated by addition of deuterium oxide and selective decoupling methods. TLC was performed on silica gel 60 GF_{254} (Merck) and PTLC on silica gel 60 PF_{254} 1 mm thick (Merck) with visualization of spots by UV light or iodine vapor; solvents were: a) ethyl acetate-hexane, 1:1; b) benzene-methanol, 3:1; c) benzene-methanol-petroleum ether, 3:1:8.

Diels-Alder Cycloadditions of 1 with Cyclopentadiene to give (5*R*,6*R*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*exo*-formyl-bicyclo[2.2.1]hept-2-en-6-*endo*-yl)-D-*erythro*-triol (2), (5*R*,6*R*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*endo*-formyl-bicyclo-[2.2.1]hept-2-en-6-*exo*-yl)-D-*erythro*-triol (3), (5*S*,6*S*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*exo*-formyl-bicyclo[2.2.1]hept-2-en-6-*endo*-yl)-D-*erythro*-triol (4), and (5*S*,6*S*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*endo*-formyl-bicyclo[2.2.1]hept-2-en-6-*exo*-yl)-D-*erythro*-triol (5). (A) In Toluene without a Catalyst (Table 1, entries 1 and 2). To a solution of the α,β-unsaturated

aldehyde **1** (3.5 g, 12.8 mmol) in dry toluene (35 mL) were added hydroquinone (10 mg) and cyclopentadiene (freshly distilled from dicyclopentadiene; 4.2 mL, 51.8 mmol). After the appropriate time at the reaction temperature (Table 1), the solvent was evaporated under diminished pressure, and the oily residue (R_F 0.25-0.35, solvent *c*) was analyzed by ^1H and ^{13}C NMR spectroscopy. Pure samples of oily stereoisomers **2** and **4** could be isolated by preparative thin layer chromatography (solvent *c*, four elutions), whereas **3** and **5** were always obtained as mixed fractions in which each one of the stereoisomers was clearly preponderant. ^1H NMR data for **2-5** are given in Table 2; ^{13}C NMR (**2**) δ 201.2 (CHO), 170.6, 170.5, 170.1 ($OCOCH_3$), 136.8, 135.6 (C-2,3), 74.8 (C-1´), 72.0 (C-2´), 61.5 (C-3´), 55.1 (C-5), 45.7 (C-7), 44.2, 44.0 (C-4,6), 40.9 (C-1), 20.7, 20.6 ($OCOCH_3$). ^{13}C NMR (**3**) δ 201.2 (CHO), 170.0, 169.8, 169.4 ($OCOCH_3$), 136.4, 135.1 (C-2,3), 74.2 (C-1´), 71.6 (C-2´), 60.8 (C-3´), 54.5 (C-5), 45.2 (C-7), 44.0, 43.5 (C-4,6), 40.5 (C-1), 20.1, 19.9 ($OCOCH_3$). ^{13}C NMR (**4**) δ 201.7 (CHO), 170.7, 170.3, 170.2 ($OCOCH_3$), 137.2, 135.0 (C-2,3), 75.6 (C-1´), 71.6 (C-2´), 61.5 (C-3´), 56.4 (C-5), 47.0 (C-7), 44.4, 44.2 (C-4,6), 42.6 (C-1), 20.9, 20.8 ($OCOCH_3$). ^{13}C NMR (**5**) δ 202.5 (CHO), 170.7, 170.2, 170.1 ($OCOCH_3$), 138.3, 133.6 (C-2,3), 73.5 (C-1´), 71.5 (C-2´), 61.6 (C-3´), 55.8 (C-5), 45.9 (C-7), 44.6, 44.3 (C-4,6), 42.0 (C-1), 20.8, 20.7 ($OCOCH_3$).

B) In Water (Table 1, entry 3). A mixture of the α,β-unsaturated aldehyde **1** (0.5 g, 1.8 mmol) and freshly distilled cyclopentadiene (0.73 mL, 9.0 mmol) in water (5 mL) was stirred at 25 °C for ten days. Then, this mixture was extracted with chloroform (3x10 mL) and the combined extracts were concentrated and analyzed by ^1H and ^{13}C NMR spectroscopy.

C) In Toluene with a Catalyst. (Table 1, entries 4-11). To a solution of the α,β-unsaturated aldehyde **1** (0.5 g, 1.84 mmol) in dry toluene (5 mL) were added freshly distilled cyclopentadiene and the catalyst. After being stirred for the appropriate time at the reaction temperature (Table 1), the mixture was diluted with ethyl acetate (15 mL) and washed with 0.1 *N* sodium hydrogensulfite (3x15 mL), and water. The organic layer was dried over anhydrous sodium sulfate, and concentrated to an oil that was analyzed by ^1H and ^{13}C NMR.

In entry 11 (Table 1), silica gel 60 (Merck, 230-400 mesh) was the catalyst. We use *ca.* 1.3 g of silica gel for 0.5 g of **1** in 3 mL of dry toluene. After 72 h at room temperature, the reaction mixture was filtered and analyzed.

Reduction of the Formyl Group of Cycloadducts (2-5) to prepare 5-Hydroxymethyl-6-glyconorbornenes (6-9). Sodium borohydride (0.15 g, 4.0 mmol) was added to a stirred solution of a mixture of the adducts (**2-5**; relative ratio 47:25:18:10; 1.37 g, 4.0 mmol) in methanol (5 mL) at 0 °C. After 15 min, TLC (solvent *a*) showed the complete absence of starting material (R_F 0.7) and the presence of two spots with R_F 0.30 and 0.24. The solution was diluted with dichloromethane (20 mL), then was washed successively with saturated aqueous $NaHCO_3$ and water, dried with magnesium sulfate, and concentrated, yielding an oil (1.30 g, 95%) that was shown to be (^{13}C NMR) a mixture of 5-hydroxymethyl-6-glyconorbornenes **6-9** in the same ratio as the starting aldehydes. After flash column chromatography on silica gel (gradient solvent *a*: 1:4 to 1:1) fractions with R_F 0.30 and 0.24 were separately concentrated; the former (0.71 g) was shown to be a 2:1 mixture of **6** and **7**, whereas the second fraction (0.29 g) was a 1.7:1 mixture of **8** and **9**.

(5*R*,6*R*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*exo*-hydroxymethylbicyclo[2.2.1]-hept-2-en-6-*endo*-yl)-D-*erythro*-triol (6) and (1*S*, 2*S*, 4*S*, 5*R*)-4-*exo*-(1′,2′,3′-Tri-*O*-acetyl-D-*erythro*-triol-1′-yl)-2-*exo*-iodotricyclo[3.2.1.1^{3,8}]-7-oxa-nonane (10). A solution of iodine (0.071 g, 0.27 mmol) in 95% ethanol (3 mL) was added dropwise to a solution of a 2:1 mixture of **6** and **7** (0.3 g, 0.88 mmol) in 95% ethanol (3 mL). After stirring for 8 h at room temperature, TLC (solvent *a*) showed two spots at R_F 0.62 and 0.30. The reaction mixture was diluted with water (20 mL), extracted with chloroform (3x20 mL), and the combined organic phases were washed successively with 5% $Na_2S_2O_3$ and water, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to leave an oily residue that was chromatographed through a dry flash-column of silica gel (gradient solvent *a*: 1:5 to 4:1) to give pure **10**; (oil, 0.096 g, 70% from **7**); R_F 0.62; $[\alpha]_D$ +68.0°, $[\alpha]_{578}$ +71.0°, $[\alpha]_{546}$ +76.0°, $[\alpha]_{436}$ +131.0°, $[\alpha]_{365}$ +212.0° (*c* 0.5, chloroform); ^1H NMR δ 5.12 (td, 1H, H-2′), 5.06 (dd, 1H, $J_{1',4}$ = 10.8, $J_{1',2'}$ = 2.3 Hz, H-1′), 4.70 (d, 1H, $J_{1,8}$ = 4.8 Hz, H-1), 4.46 (dd, 1H, $J_{2',3'}$ = 2.6, $J_{3',3''}$ = 12.1 Hz, H-3′), 4.07 (dd, 1H, $J_{2',3''}$ = 8.0 Hz, H-3′′), 3.79 (d, 1H, $J_{5,6a}$ < 1 Hz, $J_{6a,6b}$ = 9.0 Hz, CH_2O-), 3.74 (dd, 1H, $J_{5,6b}$ = 3.2 Hz, CH_2O-), 3.57 (d, 1H, $J_{2,3}$ = 2.2 Hz, H-2), 2.65 (dd, 1H, $J_{5,8}$ = 4.4 Hz, H-8), 2.34 (m, 1H, H-5), 2.11 (m, 1H, H-3), 2.10 (s, 3H, 1 OAc), 2.06 (m, 1H, H-9s), 2.04 (s, 3H, 1 OAc),

2.03 (s, 3H, 1 OAc), 1.94 (br d, 1H, $J_{9s,9a}$ = 11.4 Hz, H-9a), 1.65 (br d, 1H, H-4); ^{13}C NMR δ 170.6, 170.4, 170.0 ($OCOCH_3$), 88.8 (C-1), 73.1 (C-1'), 73.0 (C-6), 70.8 (C-2'), 61.5 (C-3'), 49.6 (C-4), 46.8 (C-3), 45.8 (C-8), 41.9 (C-5), 36.1 (C-2), 34.5 (C-9), 20.8, 20.7 ($OCOCH_3$).

The fractions of R_F 0.30 gave pure **6** (oil, 0.13 g); $[\alpha]_D$ -1.0°, $[\alpha]_{578}$ -2.0°, $[\alpha]_{546}$ -2.0°, $[\alpha]_{436}$ -4.0°, $[\alpha]_{365}$ -8.0° (*c* 0.54, chloroform); ^1H NMR data are given in Table 2; ^{13}C NMR δ 170.9, 170.4, 169.9 ($OCOCH_3$), 138.2, 134.1 (C-2,3), 76.1 (C-1'), 72.6 (C-2'), 66.5 (CH_2OH), 61.9 (C-3'), 45.6 (C-7), 45.0, 44.9, 44.5, 44.4 (C-1,4,5,6), 20.9, 20.8 ($OCOCH_3$).

Compound **6** was also obtained (quantitative yield) by treatment of **2** with $NaBH_4$, as described above.

(5*R*,6*R*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*endo*-hydroxymethylbicyclo[2.2.1]-hept-2-en-6-*exo*-yl)-D-*erythro*-triol (7). A suspension of the iodo-ether **10** (0.135 g, 0.29 mmol) and unactivated zinc powder (0.155 g, 2.37 matom) in 90% ethanol (3.3 mL) was heated for 18 h at 70 °C. The reaction mixture was cooled, filtered, diluted with water (10 mL) and extracted with chloroform (3x10 mL). The extracts were dried over magnesium sulfate and concentrated to an oil that was chromatographed through a dry flash-column of silica gel (solvent *a*) to afford oily compound **7** (0.036 g, 36%); $[\alpha]_D$ +14.0°, $[\alpha]_{578}$ +15.0°, $[\alpha]_{546}$ +17.0°, $[\alpha]_{436}$ +28.0°, $[\alpha]_{365}$ +43.0° (*c* 0.56, chloroform); ^1H NMR data are given in Table 2; ^{13}C NMR δ 171.0, 170.6, 170.3 ($OCOCH_3$), 136.8, 135.1 (C-2,3), 75.8 (C-1'), 72.3 (C-2'), 65.8 (CH_2OH), 61.8 (C-3'), 46.0 (C-7), 44.5, 44.4, 43.9, 43.9 (C-1,4,5,6), 21.0, 20.8 ($OCOCH_3$).

(5*R*,6*R*)-Bis(hydroxymethyl)bicyclo[2.2.1]hept-2-ene (12). To a solution of **6** (0.125 g, 0.36 mmol) in 90% methanol (5 mL) was added potassium carbonate (0.064 g, 0.46 mmol). After the mixture was stirred for 50 min at room temperature, the starting material (R_F 0.71, solvent *b*) disappeared, and the reaction mixture was neutralized with Amberlite IR-120 (H^+) resin and the solvent evaporated. The resulting oil (0.068 g; R_F 0.36) was stirred for 15 min at 0 °C with an aqueous solution (5 mL) of sodium metaperiodate (0.12 g, 0.56 mmol), then extracted with chloroform (4x20 mL), washed with water, dried over magnesium sulfate, and concentrated to a syrup (0.043 g; R_F 0.53). Treatment of the syrup with sodium borohydride (0.010 g, 0.25 mmol) in methanol, as described above, yielded chromatographically pure **12** as an oil

(0.030 g, 59%); R_F 0.47; $[\alpha]_D$ -45.0° (*c* 0.77, ethanol); Lit.[27] $[\alpha]_D$ -56.8° (ethanol); $[\alpha]_D$ +21.0° (*c* 0.6, chloroform); Lit.[23] $[\alpha]_D$ +23° (*c* 0.6, chloroform). Spectral data are identical in all respects with the reported ones.[23]

By using the same procedure described above, compound **12** (70% yield) was also prepared from **7**.

(5*S*,6*S*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*exo*-hydroxymethyl-bicyclo[2.2.1]-hept-2-en-6-*endo*-yl)-D-*erythro*-triol (8) and (1*R*, 2*R*, 4*R*, 5*S*)-4-*exo*-(1′,2′,3′-Tri-*O*-acetyl-D-*erythro*-triol-1′-yl)-2-*exo*-iodo-tricyclo[3.2.1.1^{3,8}]-7-oxa-nonane (11). A solution of iodine (0.144 g, 0.56 mmol) in 95% ethanol (5 mL) was treated with a 1.7:1 mixture of **8** and **9** (0.385 g, 1.13 mmol), as described above. After work-up and column chromatography, 0.1 g (52%) of pure **11** were obtained; oil, R_F 0.59 (solvent *a*); $[\alpha]_D$ -15.0°, $[\alpha]_{578}$ -16.0°, $[\alpha]_{546}$ -18.0°, $[\alpha]_{436}$ -29.0°, $[\alpha]_{365}$ -44.0° (*c* 0.59, chloroform); ^{1}H NMR δ 5.11 (m, 2H, H-1′,2′), 4.64 (d, 1H, $J_{1,8}$ = 4.8 Hz, H-1), 4.28 (dd, 1H, $J_{2',3'}$ = 3.0, $J_{3',3''}$ = 12.0 Hz, H-3′), 4.11 (dd, 1H, $J_{2',3''}$ = 7.0 Hz, H-3′′), 3.65 (dd, 1H, $J_{5,6a}$ = 3.8, $J_{6a,6b}$ = 8.2 Hz, C*H*$_2$O-), 3.55 (d, 1H, $J_{5,6b}$ < 1 Hz, C*H*$_2$O-), 3.54 (d, 1H, $J_{2,3}$ = 2.2 Hz, H-2), 2.58 (dd, 1H, $J_{5,8}$ = 3.8 Hz, H-8), 2.39 (m, 1H, H-3), 2.10 (br d, 1H, H-9s), 2.06 (m, 4H, H-5 and 1 OAc), 2.04 (s, 3H, 1 OAc), 2.01 (s, 3H, 1 OAc), 1.91 (br d, 1H, $J_{9s,9a}$ = 11.2 Hz, H-9a), 1.58 (br d, 1H, $J_{1',4}$ = 8.6, $J_{4,5}$ = 1, $J_{4,9s}$ = 1 Hz, H-4); ^{13}C NMR δ 170.4, 170.1, 169.9 (OCOCH$_3$), 88.7 (C-1), 73.3 (C-6), 73.0 (C-1′), 71.1 (C-2′), 61.3 (C-3′), 49.8 (C-4), 46.7, 46.3 (C-3,8), 41.9 (C-5), 35.8 (C-2), 35.2 (C-9), 20.7, 20.6 (OCOCH$_3$).

The fractions of R_F 0.24 gave pure **8** (oil, 0.2 g); $[\alpha]_D$ +72.0°, $[\alpha]_{578}$ +75.0°, $[\alpha]_{546}$ +85.0°, $[\alpha]_{436}$ +147.0°, $[\alpha]_{365}$ +236.0° (*c* 0.51, chloroform); ^{1}H NMR data are given in Table 2; ^{13}C NMR δ 170.9, 170.3, 169.9 (OCOCH$_3$), 138.3, 133.1 (C-2,3), 76.4 (C-1′), 71.6 (C-2′), 66.6 (CH$_2$OH), 61.4 (C-3′) 46.2 (C-7), 46.8, 44.7, 44.2, 43.8 (C-1,4,5,6), 20.8, 20.7 (OCOCH$_3$).

Compound **8** was also obtained (quantitative yield) by treatment of **4** with $NaBH_4$, as described above.

(5*S*,6*S*)-1,2,3-Tri-*O*-acetyl-1-*C*-(5-*endo*-hydroxymethyl-bicyclo-[2.2.1]hept-2-en-6-*exo*-yl)-D-*erythro*-triol (9). Following the procedure described for the synthesis of **7**, compound **11** (0.1 g, 0.21 mmol) led to oily **9** (0.03 g, 41%); $[\alpha]_D$ +40.0°, $[\alpha]_{578}$ +42.0°, $[\alpha]_{546}$ +48.0°, $[\alpha]_{436}$ +86.0°, $[\alpha]_{365}$ +133.0° (*c* 0.6,

chloroform); ^{1}H NMR data are given in Table 2; ^{13}C NMR δ 170.8, 170.3, 170.1 ($OCOCH_3$), 137.0, 134.9 (C-2,3), 75.5 (C-1'), 72.0 (C-2'), 66.1 (CH_2OH), 61.6 (C-3'), 46.7 (C-7), 44.8, 44.0, 43.8 (C-1,4,5,6), 20.9, 20.7 ($OCOCH_3$).

(5*S*,6*S*)-Bis(hydroxymethyl)bicyclo[2.2.1]hept-2-ene (13). Using the same procedure as for the preparation of **12**, compound **8** (0.085 g, 0.24 mmol) led to **13** as a chromatographically pure colourless oil (0.018 g, 53%); R_F 0.47 (solvent *b*); $[\alpha]_D$ +42.0° (*c* 0.77, ethanol); Lit.[27] $[\alpha]_D$ +57.3° (ethanol); $[\alpha]_D$ -22.0° (*c* 0.84, chloroform); Lit.[23] $[\alpha]_D$ -23° (*c* 0.8, chloroform). Spectral data are identical in all respects with the reported ones.[23]

Compound **13** was also prepared (66% yield) from **9**, as described for **12**.

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