Carbohydrate Research, 250 (1993) 249–260
Elsevier Science Publishers B.V., Amsterdam

Stereocontrol in Diels–Alder cycloaddition to unsaturated sugars: reactivities of acyclic seven-carbon *trans* dienophiles derived from aldopentoses †

Derek Horton * and Dongsoo Koh

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (USA)

(Received December 28th, 1992; accepted July 16th, 1993)

ABSTRACT

Acyclic *trans*-2,3-unsaturated aldoheptonate derivatives (**1**–**9**) obtained from D-aldopentoses by Wittig chain-extension served as dienophiles for a detailed comparative study of their asymmetric Diels–Alder cycloaddition with cyclopentadiene. Cycloaddition under uncatalyzed thermal conditions gave mixtures of the four possible stereoisomeric norbornene adducts. The *endo*:*exo* ratios and the diastereofacial selectivities in the formation of the adducts were determined by NMR spectroscopy and by chemical transformations. The quantitative distribution of adducts as a function of stereochemistry of the dienophile is discussed.

INTRODUCTION

The goal of obtaining high levels of diastereofacial selectivity is a sustained challenge in synthetic transformations[2] effected at C=C or C=O double bonds adjacent to a chiral center. Several reviews[3] have addressed the achievement of high diastereofacial selectivities in asymmetric Diels–Alder reactions employing chiral dienes, dienophiles, or catalysts. In particular, various derivatives of the inexpensive "chiral pool" provided by the sugars have been shown to be efficient chiral auxiliaries. (For general references see ref 4a; for Diels–Alder applications see refs 4b–4i.)

As part of a general program[5] on synthetic transformations of sugars having potential value for access to enantiomerically pure, polysubstituted carbocycles, we have made a systematic study of the reactions of various dienes with sugar-derived alkenes serving as dienophiles. In a preceding paper we introduced[6] a significant preparative improvement in obtaining acyclic *trans*-2,3-unsaturated aldoheptonate

† For a preliminary report, see ref 1.

* Corresponding author (present address): Department of Chemistry, The American University, 4400 Massachusetts Ave. NW, Washington, DC 20016, USA.

SSDI 0008-6215(93)E0267-5

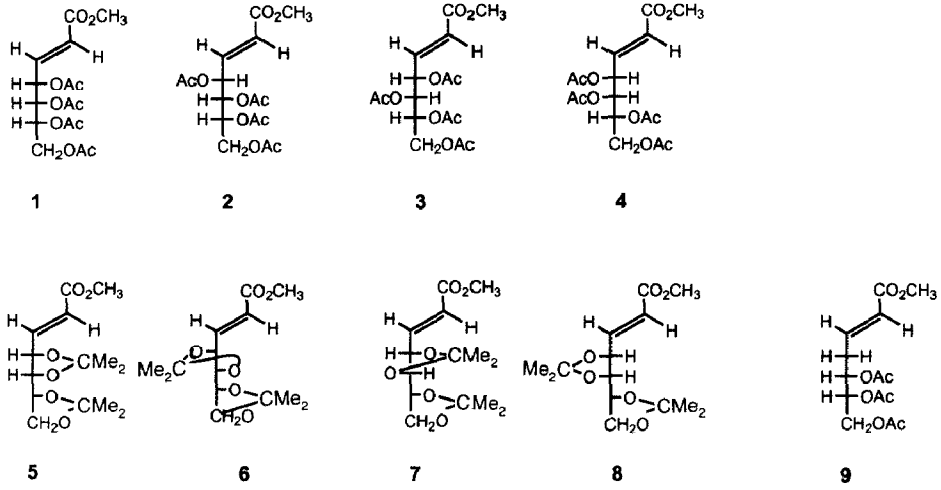
derivatives (**1–9**) by direct Wittig chain-extension from free aldopentose precursors. Here we present the results of reactions between cyclopentadiene and a complete stereoisomeric set of acyclic *trans*-2,3-unsaturated aldonic esters derived from the four D-aldopentoses. Having different configurations and conformations depending on the parent sugars and protecting groups, these unsaturated sugars offer useful potential as tools for elucidating the stereochemical pathways of asymmetric Diels–Alder reactions. The work allows predictive understanding of the steric factors dictating product distribution in the reaction. Further, it provides a methodology for utilizing readily available sugars as chiral precursors to tetra-*C*-substituted cyclopentane derivatives in enantiomerically pure forms and having functional substituents capable of differential elaboration.

RESULTS AND DISCUSSION

The dienophiles used were prepared directly from D-ribose, D-arabinose, D-xylose, or D-lyxose by reaction with Ph_3PCHCO_2Me, followed by an acetylation or acetonation step to give the corresponding 7-carbon *trans*-enonates as the tetraacetates (**1–4**, respectively) or 4,5;6,7-disopropylidene acetals (**5–8**, respectively). Use of 2-deoxy-D-*erythro*-pentose as the precusor, followed by an acetylation step, gave the 4-deoxy triacetate **9**.

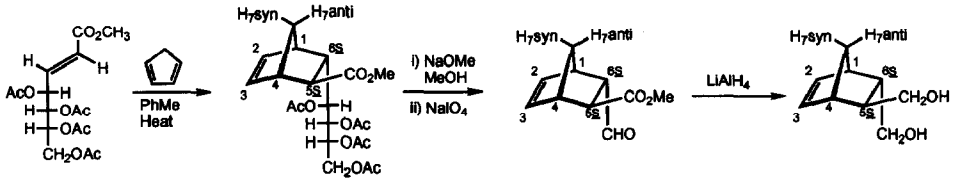
All of these nine alkenes reacted with cyclopentadiene under thermal conditions to afford a mixture of Diels–Alder adducts in high net yield.

Four stereoisomeric products are, in principle, possible in each instance, formed through transition states leading to *endo* or *exo* carboxylate norbornene products and from *si*- or *re*-face attack by the diene on the dieophile. Optimized experimental conditions for addition of cyclopentadiene to the sugar enonate **2** derived from D-arabinose were described earlier[5c] and are depicted in Scheme 1. The Diels–Al-



1 **2** **3** **4**

5 **6** **7** **8** **9**



2 **10** **(+) - 11** **(-) - 12**

Scheme 1.

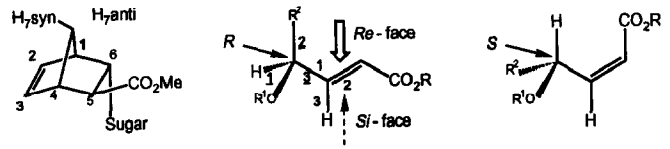
der product mixture, obtained in 92% yield, was resolved to afford 39% of the crystalline major isomer **10**, which was converted by *O*-deacetylation, followed by periodate oxidation, into the enantiomerically pure aldehydo ester **11**, $[\alpha]_D$ +89° in chloroform (lit.[5e] $[\alpha]_D$ −93° for the enantiomer of **11**). Reduction of **11** with lithium aluminum hydride afforded enantiomerically pure diol **12**, $[\alpha]_D$ −21° in chloroform (lit.[5c] $[\alpha]_D$ −23°, lit.[7] $[\alpha]_D$ −24.9°).

The Diels–Alder products are the result of a kinetically controlled process, as evidenced by the fact that the single isolated isomer **10**, when subjected to the same conditions used for the Diels–Alder reaction, was recovered unchanged.

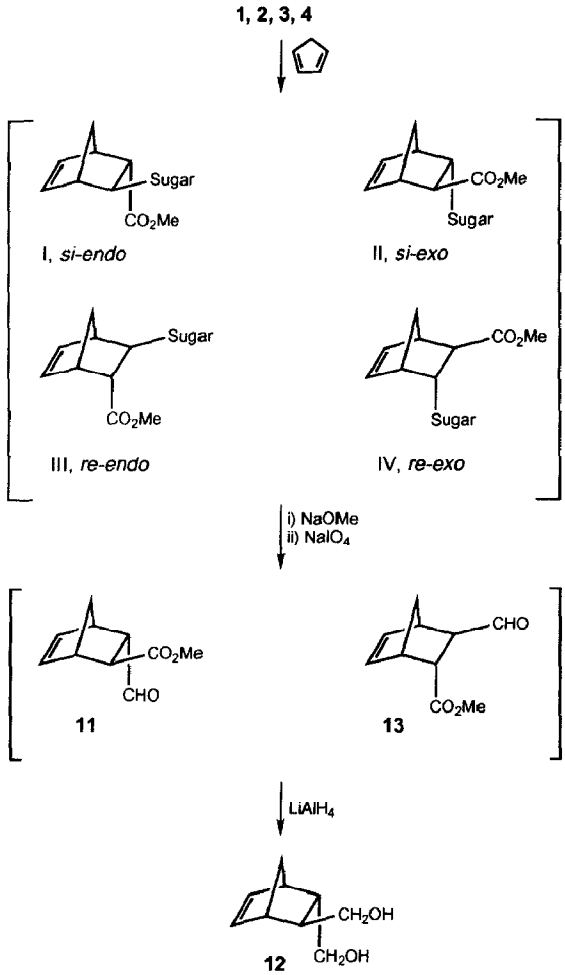
The observed products from each of the *trans* acetylated dienophiles (**1–4**) comprised mixtures of all four possible isomers. These could be detected in most instances by differences in TLC mobility and could be quantitated by NMR integration of key signals (the proton adjacent to the carboxylate group, H-5, and the methyl resonance of that ester group) *.

However, the isolative separation of each isomer out of the mixture of products was difficult, and hence a method (Scheme 2) based on chemical modification was used to determine the *endo* : *exo* ratios and the diastereofacial selectivities. For accurate quantitation of the isomer distribution in the products of cycloaddition to each of the dienophiles **1–4**, the entire mixtures of the four stereoisomeric products (**I–IV**) in each instance were first subjected to sequential *O*-deacetylation

* In the Diels–Alder products, the ring numbering assigns the carboxylate group at C-5 at and the sugar substituent at C-6 in the norbornene system (**I**). In the dienophiles, the configuration of the allylic carbon was assigned by the convention of the Cahn–Ingold–Prelog rule. For the double-bond configuration (see the bold numbers), priorities are set so that the allylic carbon is the first, and the alkene is the second. Therefore the *E*-isomer **II** has the (*β-re*, *α-re*) face forward. For convenience in this discussion, by taking the *β*-carbon as the reference carbon, both the (*β-re*, *α-re*) face in the *E*-isomer **II** and the (*β-re*, *α-si*) face in the *Z*-isomer **III** is assigned as the *re*-face.



II **III**



Scheme 2.

and periodate oxidation to afford a mixture of two aldehydo esters **11** and **13**, which upon reduction with lithium aluminum hydride afford *trans*-2-norbornene-5,6-dimethanol (**12**) as an unequal mixture of the two enantiomers (only the 5*S*,6*S* enantiomer is shown).

NMR spectral analysis of the mixture of **11** and **13** showed distinctive resonances for the CH_3O and CHO groups in both the *exo* and *endo* orientations, permitting accurate determination of the *endo* : *exo* ratio of the products in the mixture. The observed specific rotation of the diol **12**, in comparison with that determined[5c] for the enantiomerically pure 5*S*,6*S* diol **12** (−23°C), provided a quantitative measure of the *si*, *re* diastereofacial selectivity.

For comparative studies, the dienophile **9** deoxygenated at the allylic position was also used in the Diels–Alder reaction. However the foregoing method of chemical modification for determination of the *endo* : *exo* ratio and the diastereo-

TABLE I

Stereoselectivity in the reaction of acetylated dienophiles **1–4** and **9** with cyclopentadiene

Dienophile configuration	Yield [a]	*endo*:*exo* (%)	*si*:*re* (%)
1 (D-*ribo*)	86	31:69	30:70
2 (D-*arabino*)	92	31:69	64:36
3 (D-*xylo*)	72	29:71	38:62
4 (D-*lyxo*)	97	37:63	60:40
9 [b] (2-deoxy-D-*erythro*)	93	41:59	53:47

[a] After removal of cyclopentadiene-related material. [b] By ^{1}H NMR spectral integration.

facial selectivity was not applicable. The product ratio from dienophile **9** was determined by ^{1}H NMR integration of the singlet methyl peaks of the methoxycarbonyl group in the product mixture. The four singlets had almost the same integrals in the ^{1}H NMR spectrum. The *exo* products (**II** and **IV**) showed[5c,e] their methoxy signals at lower field (3.60 and 3.58 ppm) than the *endo* products (**I** and **III**; 3.52 and 3.50 ppm), affording the *endo* : *exo* ratio. A general trend established[5e] in work from this laboratory has shown that the *si*-face products (**II** or **I**) show $MeCO_2$ resonances at slightly lower field than the *re*-face products (**IV** or **III**), which permits the diastereofacial selectivity to be determined.

The results for the four dienophiles **1–4**, together with that for the 2-deoxy-D-*erythro*-pentose-derived dienophile **9**, are shown In Table I.

It is evident from these results that the thermal reaction favors the *exo* carboxylate products throughout. As regards diastereofacial selectivity, the two dienophiles (**1** and **3**) that have the same *S* configuration at the allylic center show the same tendency for favored attack at the *re* face (see footnote on p 251). In contrast, the other two dienophiles (**2** and **4**, *R* configuration at the allylic center) show favored *si*-face attack. The dienophile **9**, having no chiral group at the allylic position, showed negligible facial selectivity.

The relatively low diastereofacial selectivities exhibited by the acyclic sugar-chain enonates **1–4** may be attributed to the conformational mobility of the chain. These chains are depicted in their Fischer projections rather than as conformational representations because the planar zigzag orientation of the chain is clearly favored only in those chains having the *arabino* stereochemistry[8]. For the other configurations, the conformational preference is for non-extended conformations, and these may be conformational mixtures interconverting through low-energy barriers. It is clearly naive to depict exact molecular orientations for putative transition states in such reactions. Nevertheless, the model depicted here for interpreting the course of the reaction, which is in accord with the general model proposed by Trost and Mignani[9] for diastereofacial selectivity in additions to alkenes having an adjacent asymmetric center, has predictive utility in these reactions. The Trost–Mignani model satisfactorily correlates with the observed

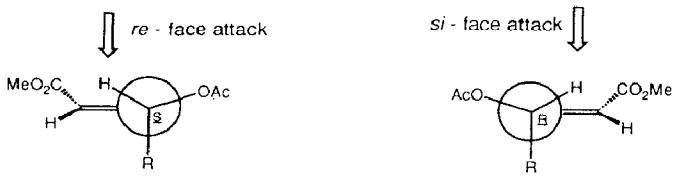


Fig. 1. Facial attack mode for the acetylated dienophiles.

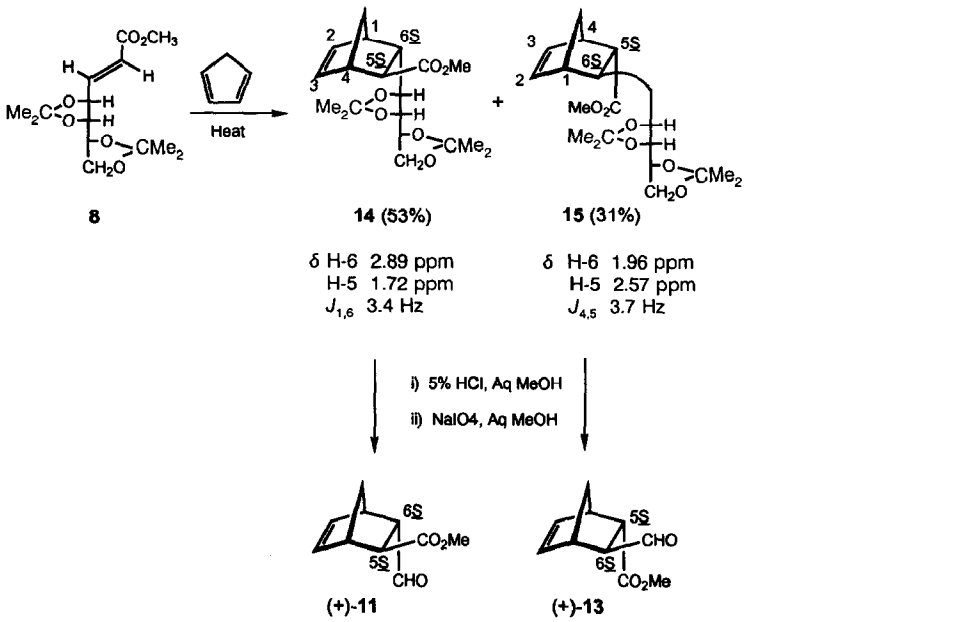
diastereofacial selectivity. Considering the predicted most stable conformation * as shown in Fig. 1, the two dienophiles possessing the *S* configuration at the allylic position favor *re*-face attack, and the other dienophiles possessing the *R* configuration favor *si*-face attack.

Because the diastereofacial selectivities were relatively low with the acetylated dienophiles, another group of dienophiles (di-*O*-isopropylidenated enonates, **5–8**) were also examined in the Diels–Alder reaction. This group of enonates has less conformational freedom than the corresponding acetylated enonates and thus might be expected to show higher diastereofacial selectivities in the Diels–Alder reaction. Enonate **8**, having the D-*lyxo* configuration, gave a readily separable mixture of products under thermal Diels–Alder reaction conditions. Two major products were separated by flash chromatography (1:7 EtOAc–hexanes). The principal isomer obtained (53%) was the *si-exo* product **14**, mp 88–9°C, $[\alpha]_D$ +33.6°. The resonance of H-6 (2.89 ppm, ddd) observed at lower field than that of H-5 (1.72 ppm, dd) indicating that **14** was an *exo* product. Compound **14** was deprotected with 5% aqueous hydrochloric acid at room temperature with subsequent chain degradation with sodium metaperiodate, to give the known aldehydo ester (+)-**11**, $[\alpha]_D$ +89° in chloroform, thus establishing that **14** has the 5*S*,6*S* absolute configuration.

The second major norbornene adduct (**15**) was obtained as a syrup, $[\alpha]_D$ +40.7° in 31% yield. The ^{1}H NMR spectrum of **15** showed the chemical shift of H-5 (2.57 ppm) at lower field than that of H-6 (1.95 ppm), indicating that **15** was and *endo* product. The deacetonation–glycol cleavage sequence gave the *endo* aldehydo ester **13**, ($[\alpha]_D$ −86°; $[\alpha]_D$ −93° for the enantiomer of **13**, lit.[5e]), and thus the absolute configuration of **15** could be assigned as 5*S*,6*S*.

The *endo* : *exo* ratio of **15**: ~ **14** thus determined by direct isolation was 36:64. The ratio determined by ^{13}C NMR integration of the carbonyl carbon (C=O) resonances of the crude product was 40:60 and was thus in good agreement. The diastereofacial selectivity for **8** was 92:18 (*si* : *re*) in favor of *si*-face attack. This ratio as determined by ^{13}C NMR was 86:14.

* Another model was proposed by Stock and Kahn[10] accounting for different diastereofacial selectivity. For a general review see ref 11.



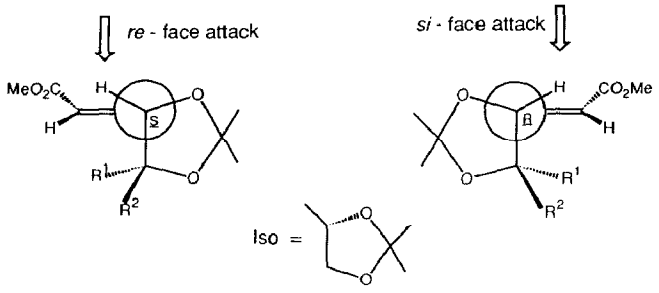
Scheme 3.

For the other di-*O*-isopropylidenated dienophiles (**5–7**), the separation of each product mixture was sufficiently difficult that ^{13}C NMR alone was used for quantitative determination of stereoselectivity. After conducting the Diels–Alder reaction as before, each mixture of products was analyzed by ^{13}C NMR spectroscopy. Each mixture showed separate peaks for the four possible isomers. In particular the carbonyl carbon peaks are well separated, with good resolution. Integrations of these peaks were thus used as a reliable basis for determination of the product ratio in the Diels–Alder reaction. The carbonyl peaks for the two *exo* products (**II** and **IV** in Scheme 2) resonate at lower field than those of the *endo* products (**I** and **III**). Furthermore, products resulting from *si*-face attack (**I** and **II**) show shifts at relatively low field in comparison with products of *re*-face attack (**III** and **IV**)[5e]. The overall results of the stereoselectivity studies are summarized in Table II.

The preference for formation of *exo* products is again evident throughout. As for the diastereofacial selectivity, the pattern shown with the acetylated dienophiles **1–4** was again evident, with favored *re*-face attack for those compounds (**5** and **7**) having the *S* configuration at the allylic center and *si*-face attack for those (**6** and **8**) having the *R* configuration at the allylic center. However, these *O*-isopropylidenated dienophiles showed much higher diastereofacial selectivity than the acetylated analogues, especially in the D-*ribo* derivative **5** and D-*lyxo* derivative **8**, a significant factor in any proposed application in chiral synthesis.

These results again accord with preditions based on the Trost–Mignani model,

and the following schematic illustration (Fig. 2) satisfactorily interprets the observed behavior of compounds **5–8**.



5 R^1=Iso, R^2=H (D-*ribo*) **6** R^1=H, R^2=Iso (D-*arabino*)
7 R^1=H, R^2=Iso (D-*xylo*) **8** R^1=Iso, R^2=H (D-*lyxo*)

Fig. 2. Facial attack mode for the *O*-isopropylidenated dienophiles.

For preparative access to specific 5,6-disubstituted norbornenes, the D-*lyxo* precursor **8** offers the highest yield route to the 5*S*,6*S*-*exo* ester **11**. D-Lyxose is less available than D-arabinose, and hence D-arabinose may be the more convenient preparative precursor for **11**. The readily available L-arabinose allows access to the enantiomer (5*R*,6*R*) of **11**, a compound accessible with optimal selectivity, however, from the D-*ribo* precursor **5** (Table II).

It should be noted that the D-*arabino* dienophile **2** reacts[5a–c] with cyclopentadiene under Lewis acid catalysis with reversal of both the *endo* : *exo* ratio and the facial preference. Parallel trends may be expected with the other dienophiles (**1**, **3**, and **4–9**), but this remains to be verified by experiment.

Comparative results with analogous *cis* dienophiles will be reported separately[12].

EXPERIMENTAL

For general methods, see the preceding paper[6].

Typical Diels–Alder reaction of acyclic sugar enonates. Preparation of methyl

TABLE II

Stereoselectivity in the reaction of isopropylidenated dienophiles **5–8** with cyclopentadiene

Dienophile (configuration)	Yield (%)	*endo*:*exo* (%)	*si*:*re* (%)
5 (D-*ribo*)	86	31:69	18:82
6 (D-*arabino*)	98	35:65	62:38
			64:36 (lit.[5e])
7 (D-*xylo*)	96	43:57	32:68
8 (D-*lyxo*)	90	40:60 [a]	86:14 [a]
		36:64 [b]	92:8 [b]

[a] Determined by ^{13}C NMR spectroscopy. [b] Determined by separation and chemical modification.

*(5S,6S)-6-*endo-*(1,2,3,4-tetra-*O*-acetyl-*D*-arabino-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*exo-*carboxylate* (**10**).—The original procedure[5c] was slightly modified for convenience in small-scale operation. To a mixture of methyl (*E*)-4,5,6,7-tetra-*O*-acetyl-2,3-dideoxy-D-*arabino*-hept-2-enonate (**2**) (500 mg, 1.34 mmol) in toluene (5 mL) was added hydroquinone (3 mg, 0.027 mmol) and cyclopentadiene (freshly distilled from dicyclopentadiene, 0.55 mL, 6.65 mmol), and the mixture was boiled under reflux for 4 h. TLC showed two product spots (R_f 0.38 and 0.31, 1:2 EtOAc–hexanes) and a large proportion of starting material **2** (R_f 0.25). Additional cyclopentadiene (0.9 mL, 11 mmol) and hydroquinone (4 mg, 0.036 mmol) were added to the mixture in two portions, with monitoring of the reaction by TLC. After 22 h, TLC showed that the starting material was absent. Solvent was distilled off to give a brown syrup that was dissolved in hot EtOH (2 mL). From this solution, crystals of crude **10** were obtained (176 mg). The crystals were, however, contaminated by the isomeric norbornene products. The mother liquors and the crystals were combined and evaporated to a syrup. This crude product was charged onto a column of silica gel that was eluted with 1:2 EtOAc–hexanes. The first fractions afforded pure compound **10** (232 mg, 39%); mp 104°C; $[\alpha]_D$ +71° (*c* 2, $CHCl_3$); lit.[5c] mp 103.5–104.5°C, $[\alpha]_D$ +73° (*c* 0.7 $CHCl_3$); the ^1H NMR spectrum was identical to that reported earlier[5c]; ^{13}C NMR (125 MHz) δ 174.8 (CO_2Me), 170.5, 170.2, 169.9, 169.5 (4 $COCH_3$), 136.5, 136.7 (C-2, C-3), 73.2, 69.5, 68.4 (C-1′, C-2′, C-3′), 62.1 (C-4′), 51.9 (OCH_3), 48.6 (C-7), 46.5, 46.1, 44.1, 43.7 (C-1, C-4, C-5, C-6), 20.78, 20.76, 20.68, 20.59 (4 $COCH_3$).

*Methyl (5S,6S)-6-*endo-*formylbicyclo[2.2.1]-hept-2-ene-5-*exo-*carboxylate* (**11**).—To a suspension of compound **10** (290 mg, 0.66 mmol) in dry MeOH (4 mL) was added a solution of NaOMe in MeOH (28%, 0.08 mL), and the mixture was stirred for 20 min at room temperature. TLC (5:1 $CHCl_3$–MeOH) then indicated conversion into a single product having R_f 0.5. The resultant solution was made neutral with Amberlite IR-120 (H^+) resin and evaporated to a solid (129 mg, 72%). To a solution of the foregoing solid (270 mg, 1 mmol) in 50% aq MeOH (30 mL) was added $NaIO_4$ (920 mg, 4.3 mmol), and the mixture was stirred for 3 h at room temperature. The solid that formed was filtered off, and the filtrate was concentrated to low volume (~ 15 mL). This was extracted with CH_2Cl_2 (3 × 30 mL), and the extract was washed with water (~ 10 mL), dried (Na_2SO_4), and evaporated (< 35°C) to give pure **11** as a liquid; yield 172 mg (96%); $[\alpha]_D$ +89° (*c* 1.2, $CHCl_3$); lit.[5e] for the enantiomer of **11** $[\alpha]_D$ −93.5° (*c* 1.5 $CHCl_3$); ^1H and ^{13}C NMR spectra were identical to those of the previously reported enantiomer[5e].

Preparation of (5S,6S)-bis(hydroxymethyl)bicyclo[2.2.1]-hept-2-ene (**12**).—A solution of **11** (60 mg) in dry THF (1 mL) was slowly added to a M solution of $LiAlH_4$ in THF (1.2 mL), and the mixture was stirred for 1 h at room temperature. TLC showed a major product (R_f 0.14, 1:1 EtOAc–hexanes), together with a small proportion of a byproduct (R_f 0.45). Saturated aq NH_4Cl was slowly added to the mixture in an ice bath, and inorganic material was filtered off. The filtrate was evaporated to a syrup that was dissolved in CH_2Cl_2, and the solution washed

once with a small volume of cold water, dried (Na_2SO_4), and evaporated to a syrup. The syrup was charged onto a column of silica gel, and eluted with 2:1 EtOAc–hexanes. The second fraction gave pure compound **12** as a syrup; yield 25 mg (54%); $[\alpha]_D$ −21° (*c* 0.9, $CHCl_3$); lit.[5c] mp 39–40°C; $[\alpha]_D$ −23° (*c* 0.8 $CHCl_3$); ^1H NMR and ^{13}C NMR spectra were identical to those previously reported[5c].

Diels–Alder addition of cyclopentadiene to acyclic acetylated sugar enonates **1**, **3**, *and* **4** *and transformations of Diels–Alder product to diol* **12**.—The same Diels–Alder reactions were conducted as just described, but starting from the dienophiles **1**, **3**, and **4**. After removal of cyclopentadiene-related material, the same chemical transformation of the four possible Diels–Alder products into aldehydo-esters **11** and **13** was made in each instance. The *endo* : *exo* ratio was determined by integration of the ^1H NMR [for the *endo* ester; 3.64 ppm (CO_2Me), 9.84 ppm (C*H*O), for the *exo* ester; 3.71 ppm (CO_2Me), 9.55 ppm (C*H*O)]. The mixture of the aldehydo-esters was converted in to the optically active diol **12** as described in the formation of the enantiomerically pure norbornene diols **12**. From **1**, the diol **12** had $[\alpha]_D$ +8.4° (*c* 0.8, $CHCl_3$). From **3**, the diol **12** had $[\alpha]_D$ +4.6° (*c* 0.8, $CHCl_3$). From **4**, the diol **12** had $[\alpha]_D$ −4.2° (*c* 0.8, $CHCl_3$).

Diels–Alder addition of cyclopentadiene to methyl (E)*-2,3,4-trideoxy-5,6,7-tri-*O*-acetyl-*D-erythro*-hept-2-enonate* (**9**).—The same reaction procedure was performed as described for preparation of **10**, but with enonate **9** as the starting material. After chromatography (1:5 EtOAc–hexanes) for removal of cyclopentadiene-related material, a mixture of product was obtained in 93% yield. The ^1H NMR spectrum of the mixture showed four methoxy singlets that had almost the same integrals at lower field (3.60 and 3.58 ppm, *exo* products) and at higher field (3.52 and 3.50 ppm, *endo* products).

Diels–Alder addition of cyclopentadiene to methyl (E)*-2,3-dideoxy-4,5;6,7-di-*O*-isopropylidene-*D-lyxo*-hept-2-enonate* (**8**), *methyl* (5S,6S)*-6-*endo*-(1,2;3,4-di-*O*-isopropylidene-*D-lyxo*-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*exo*-carboxylate* (**14**), *and methyl* (5S,6S)*-6-*exo*(1,2;3,4-di-*O*-isopropylidene-*D-lyxo*-tetritol-1-yl)bicyclo-[2.2.1]hept-2-ene-5-*endo*-carboxylate* (**15**).—The same procedure was performed as described for preparation of **10**, but with enonate **8** as the starting material. Careful chromatographpy (1:7 EtOAc–hexanes) of the crude mixture gave the pure crystalline *exo* ester **14** (43.7%), the *endo* ester **15** as a syrup (12.2%), and a mixture of four isomers (34.5%). The ^{13}C NMR spectrum of the mixture revealed four products in the ratio of 8 (**15**):4 (**14**):2:1 (two minor products). The total yield was 90.4%.

Compound **14** had mp 88–9°C; $[\alpha]_D$ +33.6° (*c* 1.9, CH_2Cl_2); R_f 0.49, 1:3 EtOAc–hexanes; ^1H NMR (300 MHz): δ 6.21 (m, 2 H, H-2, 3), 3.67–3.89 (m, 4 H, H-2′, H-3′, H-4a′, H-4b′), 3.70 (s, 3 H, OCH_3), 3.50 (dd, 1 H, $J_{1',2'}$ 5.6, $J_{1',6}$ 10.9 Hz, H-1′), 3.20 (dt, 1 H, $J_{1,6}$ 3.4 Hz, H-1), 2.99 (m, 1 H, $J_{4,7anti,} = J_{4,7syn} =$ 1.5 Hz, H-4), 2.89 (ddd, 1 H, H-6), 1.73 (m, 1 H, $J_{1,7anti}$ 1.7 Hz, H-7anti), 1.72 (dd, 1 H, $J_{5,7syn,}$ 1.3 Hz, H-5), 1.42 (m, 1 H, $J_{1,7syn}$ 1.7 Hz, H-7syn), 1.53, 1.44, 1.34, and 1.31 (4s, 12 H, 4 CH_3); ^{13}C NMR (75 MHz) δ 175.4 (CO), 109.7, 108.4 (2 O_2CMe_2,

acetal), 136.7, 1.36.1 (C-2, C-3), 80.8, 76.0, 74.7 (C-1′, C-2′, C-3′), 66.3 (C-4′), 51.9 (OCH_3), 49.1 (C-5), 46.9 (C-6), 45.7 (C-7), 45.6 (C-4), 42.8 (C-1), 26.9, 26.6, 26.5(d) (4 CH_3). Anal Calcd for $C_{19}H_{28}O_6$ (354.43): C, 64.75; H, 8.01. Found: C, 64.66; H, 7.98.

Compound **15** had $[\alpha]_D$ +40.7° (*c* 2, CH_2Cl_2); R_f 0.39, 1:3 EtOAc–hexanes; ^1H NMR (300 MHz): δ 6.30 (dd, 1 H, $J_{2,3}$ 5.6, $J_{1,2}$ 3.2 Hz, H-2), 5.96 (dd, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 4.17 (dd, 1 H, $J_{1',6} = J_{1',2'} = 6.4$ Hz, H-1′), 4.14 (m, 1 H, H-3′), 4.07 (dd, 1 H, $J_{2',3'}$ 5.0 Hz, H-2′), 3.95 (dd, 1 H, $J_{3',4a'}$ 6.1, $J_{3',4b'}$ 7.7 Hz, H-4a′), 3.69 (dd, 1 H, $J_{4a',4b'}$ 7.6 Hz, H-4b′), 3.61 (s, 3 H, OCH_3), 3.14 (bs, 1 H, $J_{4,5}$ 3.7 Hz, H-4), 3.06 (bs, 1 H, H-1), 2.57 (dd, 1 H, $J_{5,6}$ 4.8 Hz, H-5), 1.95 (m, 1 H, $J_{6,7syn}$ 1.4 Hz, H-6), 1.72 (d, 1 H, H-7anti), 1.40 (m, 1 H, $J_{7syn,7anti}$ 8.6 Hz, H-7syn), 1.51, 1.41, 1.35, 1.34 (4, 12 H, 4CH_3); ^{13}C NMR (75 MHz): δ 174.31 (CO), 138.50, 133.96 (C-2, C-3), 109.74, 108.84 ($2O_2CMe$), 79.73, 77.50, 74.47 (C-1′, C-2′, C-3′), 66.13 (C-4′), 51.64 (OCH_3), 48.20, 46.64, 46.26, 45.31, 42.80 (C-1, C-4, C-5, C-6, C-7), 26.58, 26.51, 25.36 (d) (CH_3); MS: *m/z* (rel. intensity) 353 (5.9, M + 1), 337 (23.6 M − CH_3), 277 (6.3), 237 (9.5), 219 (12.1), 187 (16.5), 159 (18.1), 131 (24.5), 115 (27.9), 101 (100), 96 (35.9), 79 (29), 59 (73). Anal. Calcd for $C_{19}H_{28}O_6$ (354.43): C, 64.75; H, 8.01. Found: C, 64.82; H, 8.13.

Conversion of Diels–Alder adduct ***14*** *into methyl (5S,6S)-6-*endo*-formylbicyclo-[2.2.1]-hept-2-ene-5-*exo*-carboxylate* (**11**).—To a solution of **14** (200 mg, 0.57 mmol) in MeOH (4 mL) was added 5% aq HCl (1.5 mL) at 0°C and the mixture was stirred for 3 h at room temperature. TLC then showed a single product spot (R_f 0.58, 1:5 MeOH–$CHCl_3$). The mixture was brought to pH 8 with satd $NaHCO_3$ (4 mL). To this neutralized mixture was added $NaIO_4$ (550 mg, 2.57 mmol, 4.5 eq), and the mixture was stirred for 10 min at room temperature to give a suspension. TLC showed a single product spot (R_f 0.5, CH_2Cl_2). An inorganic precipitate was filtered off, and the filtrate was extracted with CH_2Cl_2 (3 × 20 mL). The combined extract was washed with satd NaCl, water, and dried ($MgSO_4$). Filtration and evaporation (< 35°C) gave the aldehydo-ester **11** (94 mg, 91.6%); $[\alpha]_D$ +89° (*c* 1.2 $CHCl_3$); lit.[5e] for enantiomer of **11** $[\alpha]_D$ −93.5° (*c* 1.5 $CHCl_3$). The ^1H NMR and ^{13}C NMR spectra were identical to those of the previously reported enantiomer[5e].

Conversion of Diels–Alder adduct **15** *into methyl (5S,6S)-6-*exo*-formylbicyclo-[2.2.1]-hept-2-ene-5-*endo*-carboxylate* (**13**).—The same procedures as just described was used, but starting from compound **15**, to give **13** in 84% yield; $[\alpha]_D$ +86° (*c* 0.7 $CHCl_3$); lit.[5e] for the enantiomer of **13** $[\alpha]_D$ −93° (*c* 1.5 $CHCl_3$). The ^1H NMR and ^{13}C NMR spectra were identical to those of the previously reported enantiomer[5e].

ACKNOWLEDGMENT

Supported, in part, by NIH grant NIGMS-11976.

REFERENCES

1 D. Horton, D. Koh, Y. Takagi, and T. Usui, *ACS Symp. Ser.*, 494 (1992) 66–80.
2 E.L. Eliel, in J.D. Morrison Ed., *Asymmetric Synthesis*, Vol 2, Academic Press, New York, 1983, p 125.
3 (a) G. Helmchen, R. Karge, and J. Weetman, in R. Scheffold (Ed.), *Modern Synthetic Methods*, Vol. 4, Springer–Verlag, Berlin, 1986; (b) W. Oppolzer, *Angew. Chem. Int. Ed.*, 23 (1984) 876–889; (c) S. Masamume, W. Choy, J.S. Petersen, and L.R. Sita, *Angew. Chem. Int. Ed.*, 24 (1985) 1–30.
4 (a) S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, 1983; (b) C. Burnouf, J.C. López, F.G. Calvoflores, M.A. Loborde, A. Olesker, and G. Lukacs, *J. Chem. Soc., Chem. Commun.*, (1990) 823–825; (c) C. Marazano, S. Yannic, Y. Genisson, M. Mehmandoust, and B.C. Das, *Tetrahedron Lett.*, 31 (1990) 1995–1998; (d) P. Herczgh, M. Zsély, L. Szilágyi, G. Batta, I. Bajza, and R. Bognár, *Tetrahedron*, 45 (1989) 2793–2802; (e) J.A. Serrano and E. Román, *J. Org. Chem.*, 54 (1989) 6114–6116; (f) A Lubineau, and Y. Queneau, *ibid.*, 52 (1987) 1001–1007; (g) R.M. Giuliano, and J.H. Buzby, *Carbohydr. Res.*, 158 (1986) c1–c4; (h) R.W. Franck, S. Argade, C.S. Subramaniam, and D.M. Fréchet, *Tetrahedron Lett.*, 26 (1985) 3187–3190; (i) R.W. Franck, T.V. John, and K. Olejniczak, *J. Am. Chem. Soc.*, 104 (1982) 1106–1107.
5 (a) D. Horton and T. Machinami, *J. Chem. Soc., Chem., Commun.*, (1981) 88–90; (b) D. Horton, T. Machinami, Y. Takagi, C. Bergmann, and G.G. Christoph, *ibid.*, (1983) 1164–1166; (c) D. Horton, T. Machinami, and Y. Takagi, *Carbohydr. Res.*, 121 (1983) 135–161; (d) P. Bhaté and D. Horton, *ibid.*, 122 (1983) 189–199; (e) D. Horton and T. Usui, *ibid.*, 216 (1991) 33–49; *ibid.*, 51–59.
6 D. Horton and D. Koh, *Carbohydr. Res.*, 250 (1993) 231–247, preceding paper.
7 S. Takano and A. Kurotaki, *Synthesis*, (1987) 1075–1078.
8 D. Horton and J.D. Wander, *J. Org. Chem.*, 39 (1974) 1859–1863; M. Blanc-Muesser, J. Defaye, and D. Horton, *Carbohydr. Res.*, 87 (1980) 71–86, and references therein.
9 B.M. Trost and S.M. Mignani, *Tetrahedron Lett.*, 27 (1986) 4137–4140.
10 G. Stock and M. Kahn, *Tetrahedron Lett.*, 24 (1983) 3951–3954.
11 A. Krief, W. Dumont, P. Pasau, and P. Lecomte, *Tetrahedron*, 45 (1989) 3039–3052.
12 D. Horton, D. Koh and Y. Takagi, *Carbohydr. Res.*, 250 (1993) 261–274, following paper.