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Stereocontrol in Diels–Alder cycloaddition to unsaturated sugars: reactivities of *cis*-dienophiles with cyclopentadiene *

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ABSTRACT

Cycloaddition of cyclopentadiene with a D-arabinose-derived *cis*-dienophile, methyl (*Z*)-4,5,6,7-tetra-*O*-acetyl-2,3-dideoxy-D-*arabino*-hept-2-enonate (**2**), under thermal conditions gave essentially a single norbornene aduct, isolated crystalline in 81% yield and identified by NMR spectroscopy and X-ray crystallography as methyl (5*R*,6*S*)-6-*endo*-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]-hept-2-ene-5-*endo*-carboxylate (**3**). The diene adds exclusively from the *si*-face of the dienophile and give only the *endo* product. The same sequence starting from L-arabinose gave the enantiomer (**7**) of **3**. In contrast, a related *cis*-dienophile (**9**) having a butenolide ring reacts with cyclopentadiene from the opposite (*re*) face giving mainly the *endo* adduct (5*S*,6*R*)-6-*endo*-(2,3,4-tri-*O*-acetyl)-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,4-lactone (**10**), isolated crystalline in 70% yield, whose structure was again established by NMR spectroscopy, and firmly consolidated by X-ray crystallography. The minor (11%) product was the *exo*(5*S*,6*R*) isomer **11**. A *cis*-enonate **14**, analogous to **2** but deoxygenated at the allylic position, showed negligible diastereofacial selectivity and reacted with cyclopentadiene to give a mixture of all four possible adducts. A 6-membered ring dienophile **16** was also subjected to the same cycloaddition for comparison with the butenolide **9**; it gave principally the two *endo* products **17** and **19** in 31 and 38% yields, respectively, accompanied by 12% of a mixture of the two *exo* products (**18** and **20**). The quantitative distribution of cycloaddition products as a function of dienophile stereochemistry is discussed. The high degree of asymmetric induction observed, especially with the readily accessible dienophiles **2** and **7**, provides a valuable route of access to enantiomerically pure tetra-*C*-substituted cycloalkanes.

INTRODUCTION

Synchronous creation of multiple asymmetric centers by the Diels–Alder reaction is one of the most powerful tools for organic synthesis[2]. Asymmetric versions of this reaction have empolyed chiral dienophiles[3], dienes[4], and catalysts[5]. However, relatively few acyclic *cis*-1,2-disubstituted chiral dienophiles have been made[3b,c]. As part of a broad program concerned with asymmetric Diels–Alder reactions[6] employing acyclic unsaturated sugars[6a–c,e] as dienophiles, we sought to

* For a preliminary report, see ref 1.

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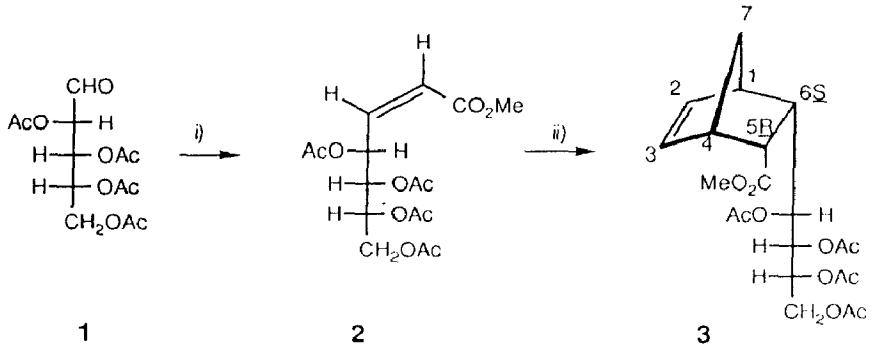


Scheme 1. (i) $(CF_3CH_2O)_2POCH_2CO_2Me$, KN $(Me_3Si)_2$, 18-crown-6, −78°C, THF. (ii) Cyclopentadiene, toluene, 130°C.

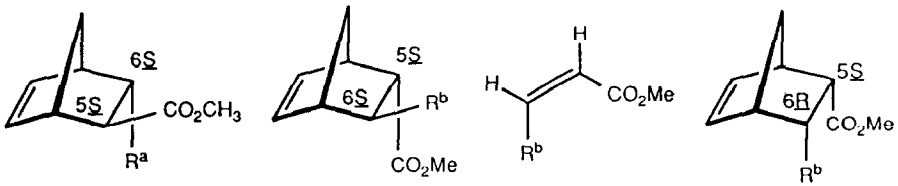
prepare and evaluate *cis*-1,2-disubstituted dienophiles in order to expand and generalize a synthetic approach[6f] to carbocycles having four functionally different carbon side chains of defined and controllable absolute stereochemistry. These results complement earlier and concurrent work[7] on analogous *trans*-dienophiles. The results presented here demonstrate the high yields may be achieved with arabinose-derived *cis*-dienophiles and excellent facial selectivity. The ready availability of both enantiomers of arabinose provides both practicality and versatility in this approach to stereochemically defined tetra-*C*-substituted cyclopentanes.

RESULTS AND DISCUSSION

Synthesis of methyl (Z)-*4,5,6,7-tetra*-O-*acetyl-2,3-dideoxy*-D-arabino-*hept-2-enonate* (**2**) *and its enantiomer* (**6**), *and their reaction with cyclopentadiene.*— Horner–Emmons alkenation of *aldehydo*-D-arabinose tetraacetate[8] (**1**) with bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate[9] gave a 91% yield of (+)-methyl (*Z*)-4,5,6,7-tetra-*O*-acetyl-2,3-dideoxy-D-*arabino*-hept-2-enonate (**2**) with high geometric stereoselectivity ($Z:E > 20:1$). The crude solid was recrystallized from 2-propanol to afford the pure *Z*-isomer **2**; mp 68°C; $[\alpha]_D$ + 16° ($CHCl_3$). The $J_{2,3}$ coupling constant of 11.6 Hz indicated that **2** was the *cis* (*Z*) product. The corresponding *trans* (*E*) product shows[6c] a $J_{2,3}$ value of 15.6 Hz (Scheme 1).

Diels–Alder reaction of **2** with an excess of cyclopentadiene under thermal conditions (30 h, 130°C) gave (+)-methyl (5*R*,6*S*)-6-*endo*-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]hept-2-eno-5*endo*-carboxylate (**3**) in 95% yield, accompanied by a very small proportion (< 5%) of another isomer. Recrystallization from ethanol gave pure **3**; yield 81%; mp 103°C; $[\alpha]_D$ +7.8° ($CHCl_3$). The relative configurations at the newly formed carbon centers C-5 and C-6 were assigned by ^1H NMR spectroscopy through comparison with the established ^1H NMR spectra[6b,c] of the known 5,6-*trans* analogues **4** (*exo* carboxylate) and **5** (*endo* carboxylate).

The relatively low-field chemical shift of H-5 in **3** (δ 3.01) indicated the ester group to be *endo* (δ 2.71, H-5 in **5**, δ 1.66, H-5 in **4**), and the large $J_{5,6}$ coupling



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constant (9.3 Hz in **2**) showed that H-5 and H-6 are in the *cis* relationship ($J_{5,6}$ 4.7 Hz in the *trans* isomers **4** and **5**)[6b,c], establishing that the ester group and sugar chain are both *endo*. The absolute configurations at C-5 and C-6 were affirmed by a single-crystal X-ray structure analysis[10] in conjunction with the known D-*arabino* configuration of the sugar chain, and were assigned as (5*R*,6*S*).

The same sequence of reactions was applied to the *aldehydo*-L-arabinose tetraacetate derivative to furnish the enantiomerically pure *cis* dienophile **6** (mp 68°C; $[\alpha]_D$ −15.8°), and the Diels–Alder adduct, the L-*arabino*-(5*S*,6*R*)-norbornene **7** (mp 103.5°C; $[\alpha]_D$ −7.9°) which are enantiomers of the corresponding dienophile **2** and norbonene derivative **3**.

Having the absolute configuration of **3** firmly assigned, the stereochemical course of the Diels–Alder reaction of the *cis* dienophile **2** could be traced. The high diastereofacial selectivity observed in the reaction with **2** and **6** may be attributed to a highly favored conformation at the allylic center in these dienophiles. The bulky sugar chain and the 4-acetoxy group can be expected to constrain each dienophiles **2** and **6** to essentially a single conformer along the C-3–C-4 bond.

Thus confomer **2A** is expected to be overwhelmingly more favored than **2B**, as the latter would have severe allylic strain between the methoxycarbonyl and acetyl groups. The diene thus attacks preferentially from the *si*-face[7] of the favored conformer **2A** to give **3**. The same arguments can be made for the L-analogue, dienophile **6**. The reaction proceeds essentially in the *endo*-product mode. This excellent selectivity, giving a single isomer crystalline in high yield out of four possible products, thus offers preparative utility in the chiral synthesis of tetra-*C*-substituted cyclopentanes[6f].

Synthesis of butenolide **9** *and its reactivity with cyclopentadiene.*—In order to reinforce the preceding hypothesis concerning stereocontrol in the reaction of **2**

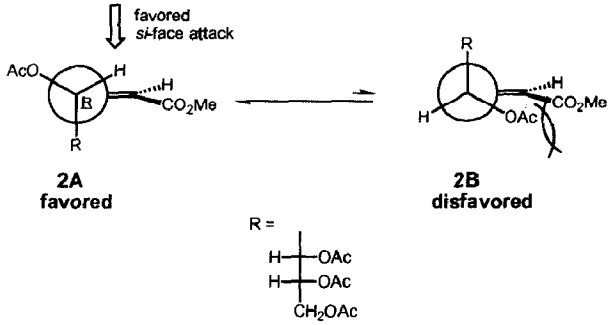
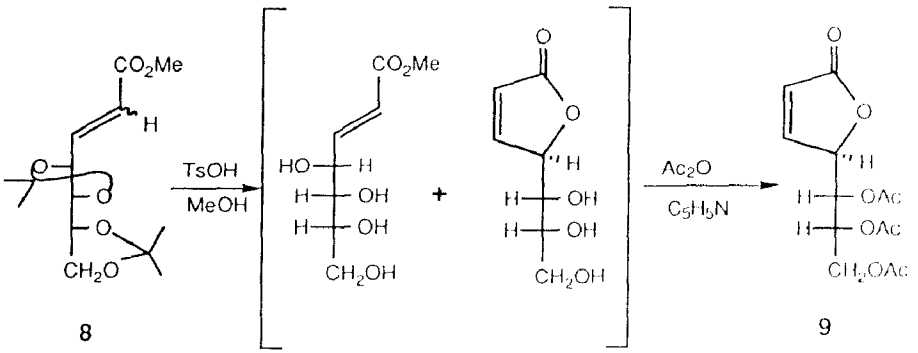


Fig. 1. Facial selectivity in cycloaddition to acyclic dienophile **2**.

with cyclopentadiene, a butenolide dienophile **9**, which has the allylic oxygen atom fixed in the plane of a 5-membered ring, was prepared. The ring in this compound constrains the molecule into a conformation that corresponds to the unfavored conformation of the acyclic dienophiles **2** and **6**. Wittig condensation of 2,3;4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[11] with methyl (triphenylphosphoranylidene)acetate under essentially kinetic conditions (methanol at 0°C) gave a 4:1 mixture of methyl (*Z*)-2,3-dideoxy-4,5;6,7-di-*O*-isopropylidene-D-*arabino*-hept-2-enonate and its (*E*)-isomer (**8**), as determined by the ^{1}H NMR spectrum. The *E*:*Z* ratio depends on the solvent and reaction temperature; the (E)-isomer may be obtained preparatively (56%) by conducting the reaction in hot benzene[6c]. Direct separation of the *E* and *Z* isomers is difficult, and consequently, the 4:1 *Z*,*E* mixture was used for preparation of butenolide **9** without further separation. The *O*-isopropylidenated alkene **8** was deacetonated and concurrently lactonized in methanol in the presence of *p*-toluenesulfonic acid, and subsequential acetylation gave 5,6,7-tri-*O*-acetyl-2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactone (**9**) in 38.5% yield (based on the *Z*-isomer of **8**), Scheme 2.

The acetylated butenolide **9**, when treated with a large excess of cyclopentadiene in the presence of a small amount of hydroquinone for 17 h in boiling toluene

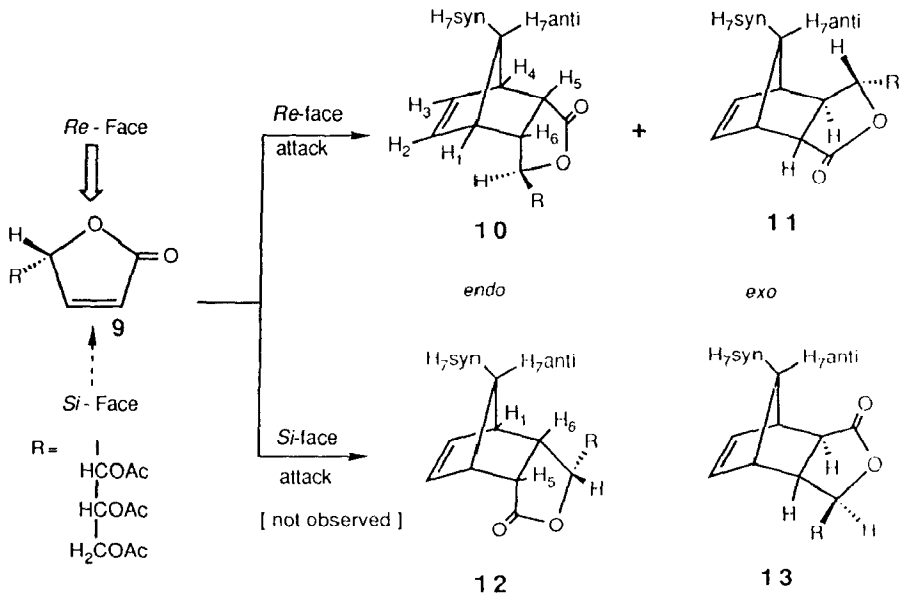


Scheme 2.

gave two products. TLC and the ^1H and ^{13}C NMR spectra of the crude adduct indicated formation of only two out of the four possible products. Careful flash chromatography (1:3 EtOAc–hexane) afforded 69.5% of the major product as crystals, mp 149°C, identified as an *endo* product (5*S*,6*R*)-6-*endo*-(2,3,4-tri-*O*-acetyl-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,4-lactone (**10**), along with 10.8% of a syrupy minor product, an *exo* derivative (5*S*,5*R*)-6-*exo*-(2,3,4-tri-*O*-acetyl-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*exo*-carboxylic acid 1,4-lactone (**11**).

The ^1H NMR spectrum of **10** showed the H-5 and H-6 protons (3.09 and 2.72 ppm, respectively, in $CDCl_3$) to have relatively low-field chemical shifts as compared with those of **11** (2.55 and 2.18 ppm, respectively, in $CDCl_3$), indicating that the relative configuration of **10** is *endo*, having two protons (H-5 and H-6) in *exo* mode, whereas the relative configuration of **11** is *exo*, having two protons (H-5 and H-6) in *endo* mode. Strong supporting evidence that **10** is an *endo* product was obtained from an NOE experiment (benzene-d_6), which showed large NOE increments at H-5 (5.4%) and H-6 (10.1%, occurring with H-1), when H-7anti in **10** was irradiated. Irradiation of H-5 in the minor product **11** caused a relatively large NOE increment for H-3 (3.3%), indicating that **11** is an *exo* product, Scheme 3.

The absolute configuration of the major Diels–Alder adduct **10**, differentiating it from the other possible *endo* isomer **12**, could also be established through NOE experiments (benzene-d_6). The *endo* adduct **10**, which may be considered to arise from attack of the diene from the *re*-face, has H-1′ on the opposite side from H-5 and H-6 in the ring plane of the 5-membered lactone. The other possible *endo*



Scheme 3.

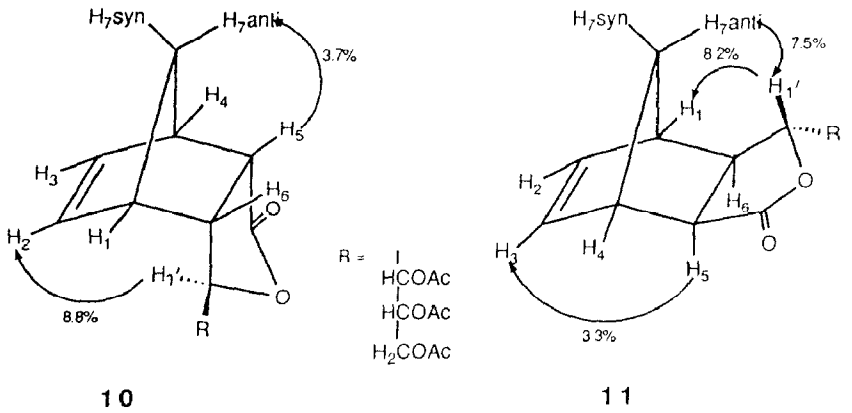


Fig. 2. NOE enhancements of compounds **10** and **11**.

isomer **12**, however, has H-1′, H-6, and H-5 on the same side of the lactone ring. No NOE enhancement in H-1′ was observed when H-5 was irradiated, whereas a large increment would have been expected had the structure been **12**. Moreover, a very large NOE increment for H-2 (8.8%) was observed when H-1′ was irradiated. This information permits assignment of the newly formed carbon centers as (5*S*,6*R*). Finally an X-ray crystal structure[10] of compound **10** showed definitely that the absolute configuration of **10** is (5*S*,6*R*). A similar discrimination between the two possible *exo* isomers **11** and **13** was made through NOE experiments (benzene-d_6). A large NOE increment in H-1′ (7.5%) when H-7anti was irradiated ruled out the possibility of structure **13**, thus permiting assignment of of the product of **11**, with the newly formed carbon centers having the (5*S*,6*R*) stereochemistry, Fig. 2.

These two assignments of absolute configuration revealed that the diene attacks the dienophile **9** exclusively from the *re*-face. Because of the γ-lactone ring, the butenolide **9** can have only one conformer, namely **9A**, which corresponds to the disfavored conformation **2B** of acyclic dienophile **2**. On steric grounds it is clear that favored attack of the diene will be from the *re*-face of the unique conformer **9A**, Fig. 3.

Two reasons may account for the very high diastereofacial selectivity (> 99% de) observed with the butenolide **9**. The first is the difference in steric bulk between R and H, which is larger than that in **2** and **6** (OAc vs. R), in the

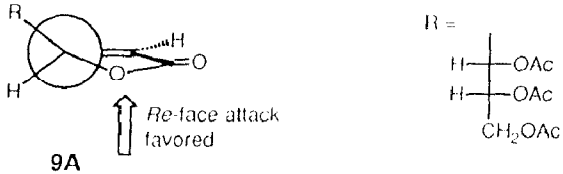
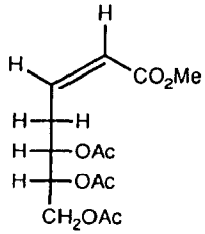


Fig. 3. Facial selectivity in cycloaddition to butenolide **9**.

conformationally restricted butenolide system. The second factor is steric congestion in the resulting products. Attack at the *si*-face could give two products (**12** and **13**), each of which would force the large R group toward the norbornene ring system and considerably augment the steric congestion in the products. The consistency in the diastereofacial selectivities observed for **2** and **9** supports the foregoing hypothesis of conformational restriction in the acyclic dienophile **2** and its analogues.

Reaction of methyl (Z)-*5,6,7-tri*-O-*acetyl-2,3,4-trideoxy*-D-erythro-*hept-2-enonate* (**14**).—To assess further the influence of the allylic substituent in cycloaddition to these *cis* dienophiles, methyl (*Z*)-5,6,7-tri-*O*-acetyl-2,3,4-trideoxy-D-*erythro*-hept-2-enonate (**14**), the 4-deoxy analogue of **2**, was prepared[12] from 2-deoxy-D-*erythro*-pentose. When this allylic-deoxy (*Z*)-enonate **14** was treated with an excess of cyclopentadiene in boiling toluene, it gave a nonseparable mixture of all four possible diastereomeric Diels–Alder adducts, as detected by ^{13}C NMR spectroscopy. The diastereofacial selectivity of **14** (as determined by ^{13}C NMR spectroscopy) was negligible (1.1 : 1) and the *endo : exo* ratio (6.5 : 1) was similar to that observed with the butenolide **9**. This result demonstrates that the stereocenter at the allylic position alone controls the diastereofacial selectivity of the Diels–Alder reaction with these acyclic *cis* dienophiles.



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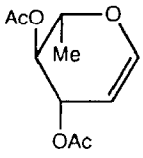

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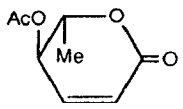

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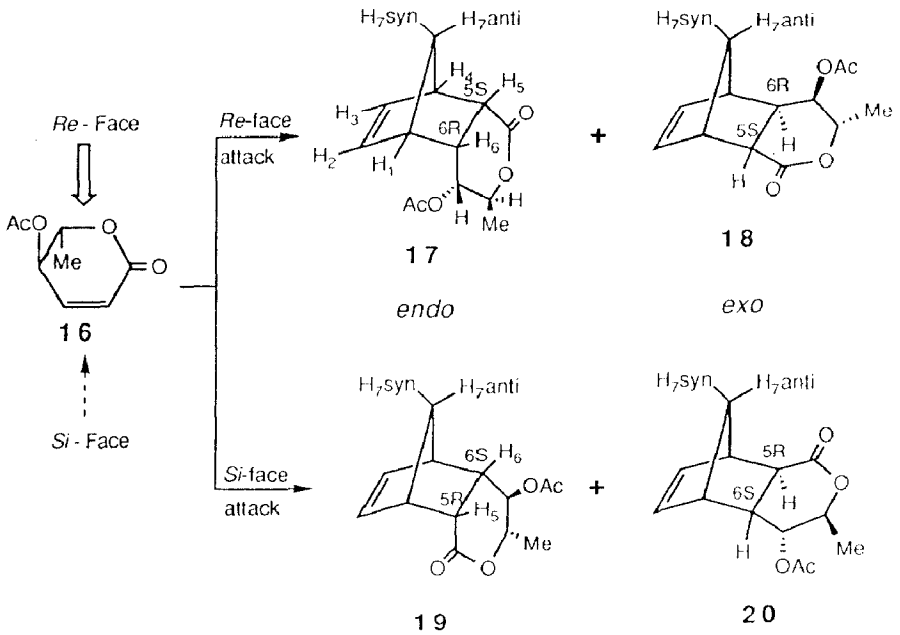
*Reaction of 4-*O-*acetyl-2,3,6-trideoxy*-L-erythro-*hex-2-enonate-1,5-lactone* (**16**).—A 6-membered ring dienophile analogue, 4-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hex-2-enonate 1,5-lactone (**16**), was prepared for comparison of its cycloaddition behavior with the 5-membered ring derivative **9**. The commercially available 3,4-di-*O*-acetyl-L-rhamnal (**15**) was oxidized[13] with pyridium chlorochromate to give the unsaturated 1,5-lactone **16**. Treatment of **16** with a large excess of cyclopentadiene for 17 h in boiling toluene, followed by separation of the mixture by column chromatography (1 : 3 EtOAc–hexanes), afforded two major products, namely (5*S*,6*R*)-6-*endo*-[(1*R*,2*S*)-1-acetoxy-2-hydroxypropyl)]bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,5-lactone (**17**, 31%) and (5*R*,6*S*)-6-endo-[(1*R*,2*S*)-1-acetoxy-2-hydroxypropyl)]bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,5-lactone (**19**, 38%), both being *endo* adducts, along with a mixture of the minor products **18** and **20** (12%); the total yield was 81%. One of the major products (**19**)



Scheme 4.

was readily assigned as an *endo* adduct by considering the relatively low-field chemical shifts of H-5 and H-6 (δ 3.09 and 2.93 ppm, respectively, in $CDCl_3$). Even though the other major product (**17**) showed relatively high field chemical shifts for H-6 (δ 2.54 ppm in $CDCl_3$), a large NOE (benzene-d_6) increase at H-5 (4.6%) and H-6 (3.5%) when H-7anti was irradiated indicated that **17** was also an *endo* product (Scheme 4).

The absolute configurations of the newly formed carbons C-5 and C-6 in the major isomers **17** and **19** were assigned by considering their NOE (benzene-d_6) enhancement with the help of the known absolute configurations of C-1′ and C-2′. Attack of the diene on the dienophile from the *re*-face of the dienophiles (called *re*-face attack) would give the product **17** having the (5*S*,6*R*) absolute configurations. In this product, the protons H-5, H-6, and H-1′ are on the same side as the ring plane of the lactone. However H-2′ is on the opposite side from these protons and is directed toward H-2. When H-2′ was irradiated, NOE enhancement was observed with H-2, thus indicating that **17** has the (5*S*,6*R*) absolute configuration. The other major isomer **19** formed by *si*-face attack, showed NOE (benzene-d_6) enhancement with H-6 when the same proton (H-2′) was irradiated. Moreover the NOE enhancement observed for H-2 when H-1′ was irradiated provided strong confirmation that **19** has the (5*R*,6*S*) absolute configuration, Fig. 4.

The diastereofacial selectivity (**17**/**19**) of attack on chiral 1,5-lactone **16** was very small (1.2 : 1). This very low diastereofacial selectivity may be ascribed to the competing effect of two chiral centers, the allylic oxygen atom O-4 (which would favor *si*-face attack), and the C-5 methyl group (which would favor *re*-face attack).

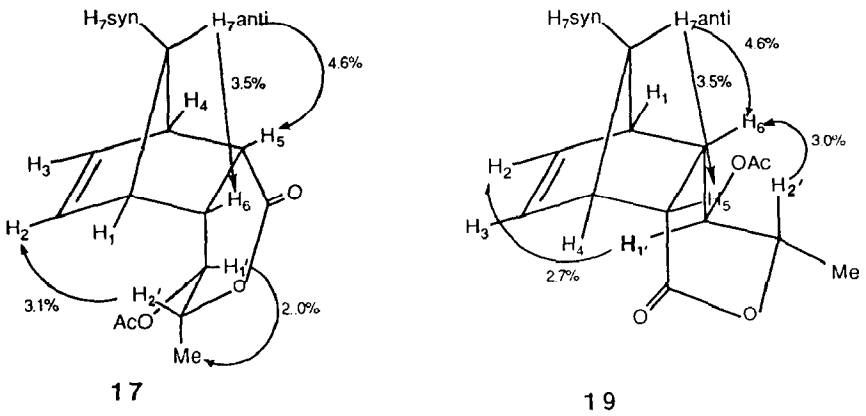


Fig. 4. NOE enhancements of compounds **17** and **19**.

In summary, the diastereofacial selectivities in cycloaddition to the *cis* dienophiles studied here are mainly controlled by the allylic stereocenter and its conformational disposition. The *cis*-dienophiles demonstrate higher diastereofacial selectivities than the corresponding *trans*-dienophiles[7], a phenomenon attributable to their allylic strain. Noteworthy for synthetic applications is the excellent stereoselectivity and high yield of crystalline product observed with the acyclic *cis* dienophiles **2** and **6** (Table I).

EXPERIMENTAL

General methods.—These were as detailed in an accompanying paper[12].

Methyl (Z)-*4,5,6,7-tetra*-O-*acetyl-2,3-dideoxy*-D-arabino-*hept-2-enonate* (**2**).—A solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (160 mg, 0.5 mmol), and 18-crown-6 (0.76 g, 2.5 mmol, 18-crown-6–CH_3CN complex) in 10 mL of anhyd THF was treated with potassium bis(trimethylsilyl)amide (1 mL, 0.5 M solution in toluene, 0.5 mmol) and stirred for 5 min at −78°C. To this solution was added 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-arabinose[8] (**1**, 159 mg, 0.05 mmol), and the mixture was stirred for 20 min at −78°C. TLC then indicated a single product having R_f 0.5 (1:1 EtOAc–hexanes). The mixture was quenched with aq NH_4Cl (8 mL), and the product was extracted with ethyl ether (3 × 15 mL). The

TABLE I

The diastereofacial selectivities (%) of *cis*-dienophiles

Dienophile	Diastereofacial selectivity (*si* : *re*)	*endo* : *exo*
2	95 > 5	95 > 5
9	1 < 99	86:14
14	~ 50:50	85:15
16	45:55	85:15

combined extracts were washed with water (30 mL), dried (Na_2SO_4), and evaporated to a liquid that was purified by flash chromatography (2:1 hexanes–EtOAc) to give a syrup (170 mg, 91%, $E:Z = 1:20$ by ^1H NMR spectroscopy), that turned into a solid after 2 days at room temperature. The crude solid was recrystallized from Pr^{i}OH to afford the pure *Z*-isomer **2**; mp 68°C; $[\alpha]_D$ +16° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz): δ 6.51 (dd, 1 H, $J_{3,4}$ 5.8 Hz, H-4), 5.88–5.94 (m, 2 H, $J_{2,3}$ 11.6 Hz, H-2, H-3), 5.58 (dd, 1 H, $J_{4,5}$ 3.1 Hz, H-5), 5.26 (ddd, 1 H, $J_{6,7}$ 2.6, $J_{6,7'}$ 5.7, $J_{5,6}$ 8.3 Hz, H-6), 4.28 (dd, 1 H, $J_{7,7'}$ 12.4 Hz, H-7), 4.16 (dd, 1 H, H-7′), 3.77 (s, 3 H, CO_2Me), 2.09, 2.08, 2.07, and 2.04 (s, 12 H, 4 OAc); ^{13}C NMR: δ 164.5 (C-1), 142.6 (C-3), 122.7 (C-2), 70.8, 68.6 (double intensity) (C-4, C-5, and C-6), 62.1 (C-7), 51.7 (OCH_3); MS: *m/z* (rel. intensity) 375 (80, M + 1), 315 (100, M + 1 − AcOH), 255 (64, 315 − AcOH), 195 (48, 255 − AcOH), 135 (42, 195 − AcOH), 85 (43). Anal. Calcd for $C_{16}H_{22}O_{10}$ (374.36): C, 51.34; H, 5.92. Found: C, 51.25; H, 5.88.

The enantiomer (**6**) of **2** was prepared by the same method; mp 67°C; $[\alpha]_D$ −17° (*c* 1, $CHCl_3$); other spectral data were the same as for **2**.

*Methyl (5*R*,6*S*)-6-*endo*-(*1,2,3,4-tetra*-O-*acetyl*-D-arabino-*tetritol-1-yl)bicyclo-[2.2.1]hept-2-ene-5*-endo-*carboxylate* (**3**).—To a solution of the *Z*-alkene **2** (950 mg, 2.5 mmol) in 4 mL of toluene was added 3 mg of hydroquinone and 1 mL of cyclopentadiene (12.1 mmol, freshly distilled from dicyclopentadiene), and the mixture was boiled under reflux for 14 h. TLC showed a small proportion of starting material **2**. Additional cyclopentadiene (0.6 mL) and hydroquinone (3 mg) was added, and the mixture was refluxed for a further 16 h. The solvent was evaporated to give a residue (1.9 g) that was charged onto a column of silica gel to remove cyclopentadiene-related products (1:2 EtOAc–hexane). The eluate was evaporated to a syrup (1.05 g, 95%), which turned into a solid after 1 day at room temperature. The ^1H NMR spectrum showed the solid to be contaminated by small amounts of other Diels–Alder products (> 5%). Recrystallization from EtOH gave pure **3** (81%); mp 102–103°C; $[\alpha]_D$ +7.8° (*c* 1 $CHCl_3$); ^1H NMR (300 MHz): δ 6.11 (dd, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 6.07 (dd, 1 H, $J_{2,3}$ 5.6 Hz, H-2), 5.36 (dd, 1 H, $J_{1',2'}$ 1.5 Hz, H-1′), 5.26 (dd, 1 H, $J_{2',3'}$ 9.1 Hz, H-2′), 4.98 (ddd, 1 H, $J_{3',4a'}$ 2.6, $J_{3',4b'}$ 4.6 Hz, H-3′), 4.17 (dd, 1 H, $J_{4a',4b'}$ 12.4 Hz, H-4a′), 4.09 (dd, 1 H, H-4b′), 3.66 (s, 3 H, OCH_3), 3.13 (bs, 1 H, $J_{4,5}$ 3.5 Hz, H-4), 3.01 (dd, 1 H, $J_{5,6}$ 9.3 Hz, H-5), 2.74 (bs, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 2.33 (dd, 1 H, $J_{1',6}$ 11.2, $J_{1,6}$ 3.0 Hz, H-6), 2.12, 2.08, 2.06, and 1.99 (4 s, 12 H, 4 Ac), 1.43 (dt, 1 H, $J_{1,7anti}$ 1.8, $J_{4,7anti}$ 1.8 Hz, H-7anti), 1.28 (bd, 1 H, $J_{7syn,7anti}$ 8.5 Hz, H-7syn); ^{13}C NMR: 173.6 (C-1), 170.5, 170.2, 169.9, 169.5 (4 $COCH_3$), 135.5, 134.9 (C-2, C-3), 70.9, 70.2, 68.5 (C-1′, C-2′, C-3′), 62.1 (C-4′), 51.4 (OCH_3), 48.7 (C-7), 48.1 (double intensity), 45.9, 44.2 (C-1, C-4, C-5, C-6), 20.9, 20.8, 20.7, 20.7 (4 $COCH_3$); MS: *m/z* (rel. intensity) 441 (9.3, M + 1), 381 (100), 315 (14.2), 255 (18.9), 219 (22.5), 201 (26.7), 194 (15.6), 187 (15.0), 153 (40.7), 103 (19.2), 85 (21.8). Anal. Calcd for $C_{21}H_{28}O_{10}$ (440.45): C, 57.27; H, 6.41. Found: C, 57.36; H, 6.46.

The enantiomer (**7**) of **3** was prepared by the same method; mp 101–103°C; $[\alpha]_D$ −6.8° (*c* 1, $CHCl_3$); other spectral data were the same as for **3**.

Methyl (E) *and* (Z)*-2,3-dideoxy-4,5;6,7-di-*O*-isopropylidene-*D-arabino*-hept-2-enonate* (**8**) *by kinetic Wittig reaction in MeOH at 0°C.*—To a solution of 2,3;4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[11] (2 g, 86 mmol) in MeOH (150 mL) was added methyl (triphenylphosphoranylidene)acetate (3.46 g) at 0°C, and the mixture was stirred for 20 h at the same temperature. TLC then showed a major product spot (R_f 0.46, 1:2 EtOAc–hexanes). After evaporation of the solvent, the residue was passed through a short column of silica gel (1:2 EtOAc–hexanes). The eluent was evaporated to give **8** as a syrup (2.15 g, 86.4%). The ^{1}H NMR spectrum of the syrup showed that the product was an inseparable 4:1 mixture of (*Z*) and (*E*)-isomers. The mixture was used for further transformations.

*5,6,7-Tri-*O*-acetyl-2,3-dideoxy-*D-arabino*-hept-2-enono-1,4-lactone* (**9**).—To a solution of the isopropylidenated *E,Z*-alkene **8** (2 g, 7.0 mmol, 4:1 mixture of *Z*- and *E*-isomers) in MeOH (20 mL) was added *p*-TsOH (308 mg, 1.6 mmol), and the mixture was stirred for 3 h at 50°C. TLC (1:2 PhMe–Me_2CO) indicated two major spots (R_f 0.27 and 0.75). After evaporation to syrup, the residue was dissolved in a small volume of MeOH, and the solution was poured into cold Et_2O to afford a precipitate. Filtration of the precipitate, followed by washing with Et_2O, gave crude 2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactone as a colorless solid; yield 670 mg; R_f 0.27 (1:2 PhMe–Me_2CO). The ^{1}H NMR spectrum of the solid showed it to contain ~20% of methyl (*E*)-2,3-dideoxy-D-*arabino*-hept-2-enonate; ^{1}H NMR (Me_2SO-d_6) δ 7.68 (dd, $J_{2,3}$ 5.5, $J_{3,4}$ 1.5 Hz, H-3), 6.14 (dd, $J_{2,4}$ 2 Hz, H-2), 5.33 (m, H-4). To a solution of the crude butenolide (670 mg) in 5 mL of pyridine was added 3 mL of Ac_2O (3 mL) at 0°C, and the mixture was stirred for 2 h at room temperature. TLC (1:1 EtOAc–hexanes) then showed a major spot (R_f 0.31) and a minor spot (R_f 0.58). The solution was poured into cold water, and the resultant precipitate was filtered off and washed with water. The solid product was recrystallized from 3:7 $CHCl_3$–hexanes to give pure **9** [650 mg, 38.5% based on the (*Z*)-isomer of **8**]; mp 144°C; $[\alpha]_D$ +99° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz): δ 7.35 (dd, 1 H, $J_{2,3}$ 5.7, $J_{3,4}$ 1.7 Hz, H-3), 6.14 (dd, 1 H, $J_{2,4}$ 2.0 Hz, H-2), 5.25–5.35 (m, 3 H, H-4,5,6), 4.43 (dd, 1 H, $J_{7,7'}$; 12.8, $J_{6,7}$ 2.2 Hz, H-7), 4.23 (dd, 1 H, $J_{6,7'}$ 3.7 Hz, H-7'), 2.10, 2.05 and 2.00 (3 s, 9 H, 3 $COCH_3$); ^{13}C NMR δ 171.67 (C-1), 170.3, 169.6, 169.3 (3 $COCH_3$), 151.97 (C-3), 122.95 (C-2), 80.59 (C-4), 69.94, 67.83 (C-5,6), 61.24 (C-7), 20.74, 20.54 and 20.33 (3 $COCH_3$); MS: *m/z* (rel. intensity) 301 (33.2, M + 1), 241 (100, M + 1 − AcOH), 181 (28.7, 241-AcOH), 139 (52.4), 137 (71.1), 136 (62.0), 107 (26.5). Anal. Calcd for $C_{13}H_{16}O_8$ (300.26): C, 52.00; H, 5.37. Found: C, 52.12; H, 5.42.

*(5*S*,6*R*)-6-*endo*-(2,3,4-Tri-*O*-acetyl-*D*-arabino-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,4-lactone* (**10**) *and (5*S*,6*R*)-6-*exo*-(2,3,4-tri-*O*-acetyl-*D*-arabino-tetritol-1-yl)bicyclo[2.2.1]hept-2-ene-5-*exo*-carboxylic acid 1,4-lactone* (**11**).—To a susupension of butenolide **9** (175 mg, 0.58 mmol) in 3 mL of toluene was added cyclopentadiene (0.8 mL, 0.99 mmol, freshly distilled from dicyclopentadiene), and hydroquinone (1 mg), and the mixture was heated (125°C) in a closed vessel overnight (17 h). TLC then showed one major product (R_f 0.44), one minor

product (R_f 0.54), and small amount of starting material (R_f 0.31, 1:1 EtOAc–hexanes). The solvent was evaporated to give a solid (205 mg). ^{1}H NMR and ^{13}C NMR spectroscopy of the crude solid showed two Diels–Alder products and starting material in the ratio of 5.6:1:0.2. Purification by column chromatography on silica gel (3:1 hexanes–EtOAc) gave pure **11** (23 mg, 10.8%) and **10** (148 mg, 69.5%) in 80.3% total yield (*endo:exo* 6.4:1). The major *endo* isomer **10** had mp 148–149°C (EtOH); $[\alpha]_D$ +39.7° (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz): δ 6.23 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 6.19 (dd, 1 H, $J_{2,3}$ 5.7 Hz, H-2), 5.23 (dd, 1 H, $J_{1',2'}$ 2.7 Hz, H-2′), 5.10 (ddd, 1 H, $J_{2',3'}$ 6.6 Hz, H-3′), 4.30 (dd, 1 H, $J_{3',4a'}$ 2.7 Hz, $J_{3',4b'}$ 5.3 Hz, H-4a′), 4.08 (dd, 1 H, $J_{4a',4b'}$ 12.6 Hz, H-4b′), 4.04 (t, 1 H, $J_{1',6}$ 2.9 Hz, H-8), 3.24 (m, 1 H, $J_{4,5}$ 4.6 Hz, H-4), 3.09 (dd, 1 H, $J_{5,6}$ 9.1 Hz, H-5), 3.09 (bs, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 2.72 (ddd, 1 H, $J_{1,6}$ 3.0 Hz, H-6), 2.06, 2.02, and 1.99 (3 s, 9H, 3 Ac), 1.57 (dt, 1 H, $J_{1,7anti}$ 1.7 Hz, $J_{4,7anti}$ 1.7 Hz, H-7anti), 1.28 (bd, 1 H, $J_{7syn,7anti}$ 8.7 Hz, H-7syn); ^{13}C NMR: 176.61 (C-1), 170.32, 169.77, 169.56 (3 $COCH_3$), 135.98 (C-2), 134.14 (C-3), 79.13 (C-1′), 72.87, 69.83 (C-2′, C-3′), 61.25 (C-4′), 51.46 (C-7), 47.68 (C-5), 45.78 (C-1), 45.60 (C-4), 43.01 (C-6), 20.71, 20.57, 20.53 (3 $COCH_3$); MS: *m/z* (rel. intensity) 367 (42.4, M + 1), 325 (20.6), 307 (100, M + 1 − AcOH), 265 (19.1, 241 (25.5), 181 (20.4), 154 (70.3), 136 (85.2), 107 (40.3), 77 (43.8). Anal. Calcd for $C_{18}H_{22}O_8$ (366.37): C, 59.01; H, 6.05. Found: C, 58.94; H, 6.10.

The minor *exo* isomer **11** was a syrup; $[\alpha]_D$ +52.0° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz): δ 6.21 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 6.14 (dd, 1 H, $J_{2,3}$ 5.6 Hz, H-2), 5.31 (dd, 1 H, $J_{1',2'}$ 2.4 Hz, H-2′), 5.21 (ddd, 1 H, $J_{2',3'}$ 7.0 Hz, H-3′), 4.39 (dd, 1 H, $J_{3',4a'}$ 2.5, $J_{3',4b'}$ 5.0 Hz, H-4a′), 4.34 (t, 1 H, $J_{1',6}$ 2.7 Hz, H-1′), 4.15 (dd, 1 H, $J_{4a',4b'}$ 12.7 Hz, H-4b′), 3.26 (bs, 1 H, $J_{4,5}$ 0 Hz, H-4), 2.96 (bs, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 2.55 (dd, 1 H, $J_{5,6}$ 8.2 Hz, H-5), 2.18 (dd, 1 H, H-6), 2.10, 2.09, and 2.05 (3 s, 9 H, 3 Ac), 1.53 (dt, 1 H, $J_{1,7anti}$ 1.7, $J_{4,7anti}$ 1.4 Hz, H-7anti), 1.44 (bd, 1 H, $J_{7syn,7anti}$ 9.7 Hz, H-7syn); ^{13}C NMR: 176.31 (C-1), 170.49, 169.86, 169.68 (3 $COCH_3$), 137.73, 137.51 (C-2, C-3), 80.44 (C-1′), 71.80, 69.94 (C-2′, C-3′), 61.39 (C-4′), 48.10, 47.60, 46.67, 44.80, 43.41 (C-1, C-4, C-5, C-6, C-7), 20.86, 20.65 (double intensity), (3 $COCH_3$). Anal. Calcd for $C_{18}H_{22}O_8$ (366.37): C, 59.01; H, 6.05. Found: C, 59.16; H, 6.14.

*Diels–Alder reaction of cyclopentadiene with (+)-methyl(Z)-5,6,7-tri-*O*-acetyl-2,3,4-trideoxy-*D-erythro-*hept-2-enonate* (**14**).—The same Diels–Alder reaction was conducted as just described in the synthesis of **10** and **11**, but starting from the dienophile **14**. After removal of cyclopentadiene-related material, an inseparable product mixture was obtained in good yield (89%). The ^{13}C NMR spectrum of the mixture showed CO_2Me signals of four possible products: δ_c 175.4 and 175.1 (~1:1 *exo* isomers), and 173.6 and 173.4 (~1:1 *endo* isomers). Further identification was not made.

*4-*O*-Acetyl-2,3,6-trideoxy-*L-erythro-*hex-2-enono-1,5-lactone*[13] (**16**).—A mixture of 3,4-di-*O*-acetyl-L-rhamnal (**15**, 4.28 g, 20 mmol) and 8.62 g of pyridinium chlorochromate (40 mmol) in 80 mL of CH_2Cl_2 was stirred overnight at 80°C. TLC (2:3 EtOAc–hexanes) then indicated conversion of the glycal (R_f 0.69) into a single product (R_f 0.47). The mixture was cooled and poured onto a column of

silica gel prepared in hexane and eluted with 2:3 EtOAc–hexanes. Evaporation of the eluate yielded a pale-yellow syrup that was distilled in vacuo to afford 2.3 g (74%) of **16**; bp 67–69°C/0.02 mmHg; $[\alpha]_D$ – 177°C (*c* 1, $CHCl_3$); lit.[14] bp 110°C/0.5 mmHg, lit.[15] 73°C/0.01 mmHg; lit.[14] $[\alpha]_D$ – 179°C (*c* 1, $CHCl_3$); ^1H NMR (300 MHz) δ 6.67 (dd, 1 H, $J_{2,3}$ 9.9, $J_{3,4}$ 3.3 Hz H-3), 5.96 (dd, 1 H, $J_{2,4}$ 1.5 Hz, H-2), 5.13 (ddd, 1 H, $J_{4,5}$ 5.9 Hz, H-4), 4.45 (qt, 1 H, $J_{5,Me}$, 6.6 Hz, H-5), 2.01 (s, 3 H, $COCH_3$), 1.29 (d, 3 H, CH_3); ^{13}C NMR (75 MHz) δ 169.76 (C-1), 161.87 ($COCH_3$), 142.76 (C-3), 122.64 (C-2), 70.29 (C-4), 67.61 (C-5), 20.60 ($COCH_3$), 18.19 (CH_3); MS: *m/z* (rel. intensity) 171 (43.9, M + 1), 137 (10.6), 111 (100, M + 1 – AcOH); IR (neat) 2988, 1732 (C=O, 1,5-lactone), 1634, 1378, 1234, 1114, 1052 and 970 cm^{-1}.

*(5S,6R)-6-*endo*-[(1R,2S)-1-Acetoxy-2-hydroxypropyl)]bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,5-lactone* (**17**) *and (5R,6S)-6-*endo*-[(1R,2S)-1-acetoxy-2-hydroxypropyl)]bicyclo[2.2.1]hept-2-ene-5-*endo*-carboxylic acid 1,5-lactone* (**19**).—To a solution of the 1,5-lactone **16** (600 mg, 3.53 mmol) in 3 mL of toluene was added cyclopentadiene (1 mL, freshly distilled from dicyclopentadiene), and the mixture was heated (125°C) in a closed vessel for 17 h. TLC then showed one minor spot (R_f 0.66) and a major one (R_f 0.58, 1:1 EtOAc–hexanes). The solvent was evaporated to give a syrup. Careful flash chromatography (1:3 EtOAc–hexanes) afforded two principal products, **17** (a syrup; R_f 0.44, 1:3 EtOAc–hexanes; 260 mg, 31.3%) and **19** (crystalline; R_f 0.33; 315 mg; 37.9%), and a mixture (11.6%) of minor products **18** and **20** (R_f 0.54; 96 mg; 1:2 EtOAc–hexanes). The total yield was 80.8%.

Compound **19** had mp 109°C; $[\alpha]_D$ –63.1° (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 6.17 (dd, 1 H, $J_{3,4}$ 2.9 Hz, H-3), 6.12 (dd, 1 H, $J_{2,3}$ 5.7 Hz, H-2), 4.96 (t, 1 H, $J_{1',6}$ 7.1 Hz, H-1'), 4.31 qt, 1 H, $J_{1',2'}$ 7.0 Hz, H-2'), 3.29 (bs, 1 H, $J_{4,5}$ 4.2 Hz, H-4), 3.09 (dd, 1 H, $J_{5,6}$ 9.8 Hz, H-5), 2.93 (m, 2 H, $J_{1,2}$ 2.2 Hz, H-1,6), 2.03 (s, 3 H, $COCH_3$), 1.45 (d, 1 H, H-7anti), 1.30 (bd, 1 H, $J_{7syn,7anti}$ 8.7 Hz, H-7syn), 1.18 (d, 3 H, J_{2',CH_3} 6.5 Hz, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 171.64 (C-1), 169.85 ($COCH_3$), 136.82 (C-2), 135.36 (C-3), 73.76 (C-1'), 71.20 (C-2'), 50.36 (C-7), 46.89, 45.35, 43.11, 39.40 (C-1, C-4, C-5, C-6), 20.89 ($COCH_3$), 18.26 (CH_3); MS: *m/z* (rel. intensity) 237 (100, M + 1), 177 (21.9, M + 1 – AcOH), 154 (38.7), 136 (42.7), 111 (44.3), 91 (24.7). Anal. Calcd. for $C_{14}H_{20}O_8$ (316.31): C, 66.08; H, 6.83. Found: C, 65.86; H, 6.81.

Compound **17** was a syrup; $[\alpha]_D$ – 134° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 6.26 (dd, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 6.22 (dd, 1 H, $J_{2,3}$ 5.6 Hz, H-2), 4.16–4.32 (m, 2 H, H-1', 2'), 3.32 (bs, 1 H, $J_{4,5}$ 3.9 Hz, H-4), 3.16 (dd, 1 H, $J_{5,6}$ 10.6 Hz, H-5), 2.89 (bs, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 2.54 (ddd, 1 H, $J_{1',6}$ 9.2, $J_{1,6}$ 3.4 Hz, H-6), 2.08 (s, 3 H, $COCH_3$), 1.49 (d, 1 H, $J_{1,7anti}$ 1.7, $J_{4,7anti}$ 1.7 Hz, H-7anti), 1.28 (bd, 1 H, $J_{7syn,7anti}$ 8.8 Hz, H-7syn), 1.20 (d, 3 H, J_{2',CH_3} 5.7 Hz, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 172.49 (C-1), 169.75 ($COCH_3$), 137.82 (C-2), 135.94 (C-3), 75.01 (C-1'), 73.41 (C-2'), 47.70 (C-7), 45.56, 44.71, 44.30, 44.13 (C-1, C-4, C-5, C-6),

20.77 ($COCH_3$), 16.93 (CH_3); MS: *m/z* (rel. intensity) 237 (100, M + 1), 177 (27.3, M + 1 − AcOH), 154 (20.7), 136 (29.2), 111 (70.6), 91 (22.1).

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