Diels–Alder Reactions of Pyranoid Enolone Esters with Cyclopentadiene under Thermal, Lewis Acid Catalysis, and High-Pressure Conditions[1]

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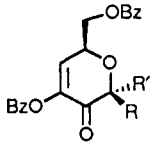
Four sugar-derived dihydropyranones with an enolone ester function and, hence, low dienophilicity, have been subjected to Diels–Alder additions of cyclopentadiene under thermal (200 °C, 48 h), Lewis acid catalyzed (−78 °C), and high-pressure (15 kbar, 25 °C) conditions. Generally most useful in terms of conversion, overall yields, and degree of stereoselection proved to be the 15-kbar pressurization, usually providing one of the four possible cycloadducts, α/β (syn/anti) and endo/exo diastereomeric, 5,8-methano-bridged tetrahydrobenzopyrones with high preference. The ground-state conformations of the individual dihydro-3-pyrone dienophiles and the steric disposition of the substituent at C-6 and the anomeric C-2 carbon provide a rationale for the π-facial selectivities such that preferential diene capture is effected from the sterically less hindered side with endo/exo selectivities of 5:1 to 9:1. The ring oxygen in the pyranoid dienophiles **1a–d** substantially enhances their Diels–Alder reactivity as is inferred from MNDO calculations, UV spectral data, and the nonreactivity of a cyclohexanoid enolone ester. The thermally induced Diels–Alder additions exhibit analogous trends in their facial stereoselection except for less pronounced selectivity margins. The Lewis acid mediated cycloadditions proceed sluggishly with low overall conversion, except for the β-methoxy-substituted dihydropyranone where $TiCl_4$ complexation of the carbonyl and methoxy functions provide a sterically and electronically ideal disposition for exclusive α-endo addition of the diene.

Introduction

Sugar-derived enantiomerically pure dihydropyranones (enolone esters) of type **1** have been subject of considerable interest in recent years. Their ready accessibility via practical, large-scale procedures[3] and the highly stereoselective nature of addition reactions[4] make them particularly versatile six-carbon synthons for the construction of non-carbohydrate natural products. Highly efficient syntheses have been developed for such varied compounds as the soft coral constituents (−)-palythazine[5] and (−)-bissetone,[6] the antibiotic spectinomycin,[7] and a cardiac glycoside-derived reductic acid,[8] all in optically pure form.

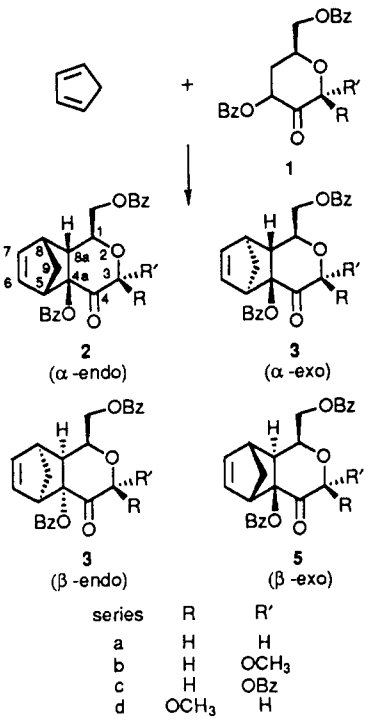


1

R = OMe; R' = H
R = H; R' = H, OMe, OBz
Bz = PhCO

The synthetic usefulness of these dihydropyranones would be considerably enlarged if they could be utilized as dienophiles in Diels–Alder reactions. However, unlike a number of structurally similar pyranoid enones (H instead of the olefinic OBz in **1**) which have led to various cycloaddition reactions,[9] the enolone esters have not been exploited in this manner and are anticipated to be rather poor dienophiles. Simple acyclic analogues, such as mono enol esters of diacetyl, react sluggishly with dienes,[10] and placing an enolone ester group into a ring would be expected to reduce their dienophilicity even further.[11] It

Scheme I



(1) Enantiomerically Pure Building Blocks from Sugars, 11. Part 10: Lichtenthaler, F. W.; Nishiyama, S.; Weimer, T. *Justus Liebigs Ann. Chem.*, in press.

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0022-3263/90/1955-2391$02.50/0

Table I. Diels-Alder Reactions of Dihydropyranones 1a–d with Cyclopentadiene in Dichlormethane under Thermal, Lewis Acid Catalyzed, and High-Pressure Conditions (See Scheme I)

		products (%, isolated by HPLC)					
dienophile	conditions	**2** (α-endo)	**3** (α-exo)	**4** (β-endo)	**5** (β-exo)	starting material recovery, %	total material recovery, %
1a	200 °C, 2 days	25	3	8	2	41	79
1b	200 °C, 2 days	5	9	16	7	55	92
1c	200 °C, 2 days	9	4	50	9	16	88
1d	150 °C, 2 days	24	9	1	<1	50	84
	200 °C, 2 days[a]	31	10	3	4	41	89[a]
	250 °C, 2 days	28	12	5	4	28	77
	200 °C, 6 days[a]	35	10	4	10	17	76[a]
1a	$SnCl_4$, −78 °C, 20 min	7	6	1	2	64	80
1b	$SnCl_4$, −78 °C, 20 min	10	13	trace	–	63	86
	$TiCl_4$, −78 °C, 20 min	8	1	7	–	32	48
1c	$SnCl_4$, −78 °C, 20 min	–	–	7	1	72	80
1d	$AlCl_3$, −78 °C, 1 h	41	trace	–	–	27	68
	$AlCl_3$, −25 °C, 18 h	42	8	trace	3	–	53
	$TiCl_4$, −78 °C, 40 min	81	1	–	–	–	82
	$SnCl_4$, −78 °C, 20 min	45	1	1	4	14	65
1a	15 kbar, 2 days, 25 °C	53	11	17	4	5	90
1b	15 kbar, 2 days, 25 °C	3	3	33	5	56	100
1c	15 kbar, 2 days, 25 °C	11	3	69	11	5	99
1d	15 kbar, 2 days, 25 °C	84	11	1	1	2	99

[a] In addition, fragmentation product **6** (1.6% after 2 days, 13% after 6 days) was isolated from the reaction mixture.

Table II. Selected ^1H NMR Spectral Data for 5,8-Methano-2-benzopyranones 2d–5d

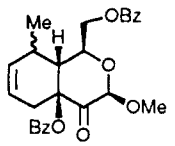
	chemical shifts, ppm					coupling constants, Hz				
cycloadduct	H-1	H-3	H-6	H-7	H-8a	$J_{1,8a}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,8a}$
2d (α-endo)	3.73	4.41	6.14	6.67	2.68	8.6	3.2	5.7	2.9	3.6
3d (α-exo)	3.96	4.81	6.48		2.03	8.2	–	–	–	2.5
4d (β-endo)	5.01	5.13	5.96	6.62	2.47	3.5	3.0	5.8	2.6	3.5
5d (β-exo)	5.10	5.22	6.53		1.81	3.6	–	–	–	2.7

was, therefore, anticipated that either forcing thermal, Lewis acid catalysis, or high-pressure conditions would have to be employed. With these considerations in mind we have examined the Diels–Alder reactions of four dienophiles of type **1** toward cyclopentadiene, to determine the level of stereocontrol attainable.

Results

The reactions of cyclopentadiene with any of the four D-glucose-derived[5,12] dihydropyranones **1a–d** can lead to four diastereomers, i.e. to the tetrahydro-5,8-methanobenzopyrones **2–5**, respectively (Scheme I). Their separation from the reaction mixtures is readily achieved by HPLC; the product distributions yields, and total material recovery, are shown in Table I.

Thermal Cycloadditions. Appropriate conditions were determined with **1d** as a model dihydropyranone being allowed to react in dichloromethane with a 10-fold excess of cyclopentadiene for 2–6 days at temperatures varying from 150 to 250 °C. In each case, all four cycloadducts **2d–5d** were invariably produced. The total recovery of material was very good, even on extended heating (6 days 200 °C), indicating the enolone ester **1d** to be quite stable toward the thermal conditions. The cycloadducts, in fact, appear to be thermally less stable, since a fifth product was additionally obtained from **1d** (1.6% after 2 days 13% after 6 days at 200 °C), which on the basis of ^1H and ^{13}C NMR data is tentatively assigned structure **6**, it seems to be generated by homolytic fragmentation of the 5,8-methano bridge in one of the α-cycloadducts. Accordingly, the most favorable conditions with respect to material recovery, diastereoselectivity attainable and low production of fragmentation products are considered to be 2 days at 200 °C, to which dihydropyranones **1a**, **1b**, and **1c** were exosed with the results listed in Table I.



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Lewis Acid Mediated Cycloadditions. Of the various Lewis acids tried with dihydropyranone **1d**, ferric nitrate on clay,[13] silica gel, and boron trifluoride met with no success, but aluminum trichloride (20 °C and −78 °C), tin tetrachloride (−78 °C), and titanium tetrachloride (−78 °C) were reasonably effective (Table I). Some polymeric material invariably formed, complicating the workup. An increase of the amount of cyclopentadiene to more than 2 molar equiv increased polymer formation without improving yields, as did longer reaction times. The most notable example is the high yield of the α-endo adduct **2d** (81%) on $TiCl_4$ catalysis at −78 °C, with only minute amounts of the α-exo isomer **3d** being formed. Unfortunately, the other enolone esters, when subjected to these conditions with either $TiCl_4$ or $SnCl_4$ as the catalyst, gave distinctly inferior results, mostly due to sluggish reactions and low conversion.

High-Pressure Conditions. Trial runs at 15 kbar with a 1:7 ratio of **1d** and cyclopentadiene in dichloromethane indicated essentially complete conversion into its cycloadducts when allowed to react for 2 days at room temperature. Similar results were obtained with **1a** and **1c** (Table I), while **1b** appeared to be less reactive on the basis of the low conversion observed.

Configurational Assignments. The structure and configurations of the individual cycloadducts **2–5** are convincingly derived from ^1H NMR spectral data, the availability of the four possible Diels-Alder products fa-

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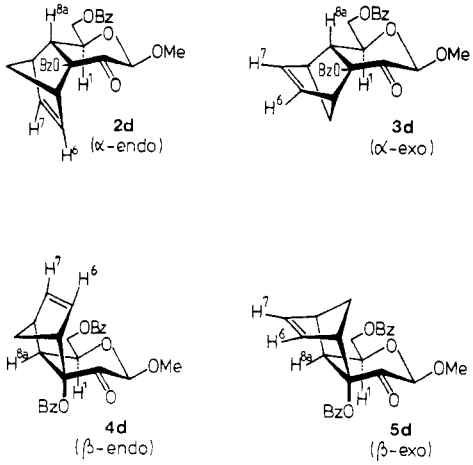
cilitating unequivocal assignments. This is exemplified by the configurationally relevant data for the **1d**-derived products **2d–5d**, listed in Table II.



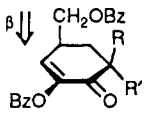
The α- or β-facial annullation of the carbocyclic protion onto the pyranoid ring is most clearly revealed by the chemical shift of H-1 and its coupling constant to the vicinal H-8a. In two of the isomers, H-1 appears at comparatively high field as a doublet with a $J_{1,8a}$ value of 8.2 and 8.6 Hz, respectively, which unequivocally indicates a diaxial orientation of H-1 and H-8a, and, hence, the presence of α-adducts **2d** and **3d**. In contrast, the other two isomers exhibit H-1 at distinctly lower field with a smaller $J_{1,8a}$ coupling of 3.5 and 3.6 Hz, respectively, that proves a cis relationship of the two protons, as required for the β-adducts **4d** and **5d**.

The endo/exo assignments rest on the following evidence: (i) the olefinic protons H-6 and H-7 have identical chemical shifts in **3d** and **5d**, their magnetic equivalence being only reconcilable with the absence of any shielding effects exerted by the pyranoid ring or its substituents, which, in turn, is only conceivable for exo adducts; (ii) the other two isomers, **2d** and **4d**, correspondingly show distinct shift differences of 0.53 and 0.66 ppm for H-6 and H-7 (cf. Table II), the substantial shielding of the former being possible only in the endo orientation that brings H-6 close to the carbonyl function; (iii) H-8a in the exo isomers **3d** and **5d** is shifted upfield by 0.65 ppm from the corresponding endo compounds, obviously due to shielding from the olefinic double bond. These assignments are substantiated by numerous minor differences between endo and exo isomers. For example, the coupling constants $J_{5,6}$, $J_{7,8}$, and $J_{8,8a}$ (Table II) are essentially the same for the endo adducts, and, in turn, for the exo isomers as well.

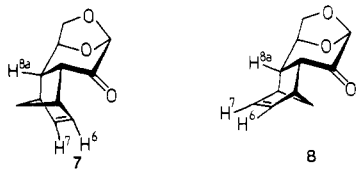
The α- or β-facial orientation of the adducts can also be determined based on the chemical shift of H-1 and H-3. In the β-isomers **4d** and **5d**, H-1 is in a 1,3-diaxial disposition to the C-5a benzoyloxy group, the strong deshielding effect of the latter causing the large down field shift of over 1 ppm relative to the α-isomers **2d** and **3d**, where an equatorially oriented benzoyloxy group cannot influence the H-1 proton. The same, if in a less pronounced form, applies to the chemical shifts of H-3 (Table II).

Additional confirmation for these assignments is provided by the NMR spectral characteristics of cycloadducts **7** and **8** prepared via thermal Diels-Alder reaction from levoglucosenone with cyclopentadiene.[9c,d] The configuration of the major adduct **7** was conclusively established by X-ray analyses of transformation products:[9d,14] the chemical shift differences between H-6 and H-7 are less pronounced (0.22 ppm for the endo adduct **7** versus 0.09 ppm for **8**), yet H-8a in **8** is substantially shielded (0.72 ppm) by the contiguous olefinic double bond over that in **7**.

Table III. Approximate Diastereofacial and Endo/Exo Selectivities in Diels–Alder Reactions of Dihydropyranones 1a–d (α/β) with Cyclopentadiene



		conditions	ratio of cycloadducts α:β	α endo:exo	β endo:exo
1a	R = H	Δ	3:1	8:1	5:1
	R′ = H	$TiCl_4$	4:1	1.2:1	1:1.3
		15 kbar	3:1	5:1	4.3:1
1b	R = H	Δ	1:1.7	1:1.7	2.5:1
	R′ = OMe	$SnCl_4$	α	1:1.3	–
		15 kbar	1:6	1:1	7:1
1c	R = H	Δ	1:5	2.3:1	6:1
	R′ = OBz	$SnCl_4$	β	–	9:1
		15 kbar	1:6	4:1	6.5:1
1d	R = OMe	Δ	6:1	3:1	1:1
	R′ = H	$TiCl_4$	α	100:1	–
		15 kbar	40:1	8:1	1:1



The chemical shift features and coupling patterns found for **2d–5d** are practically identical in the other sets of cycloadducts derived from dihydropyranones **1a–c**, allowing analogous rationalizations and configurational assignments.

Discussion

Although the data in Table I are purely preparative and encumbered in some cases by low overall conversion and insufficient material recovery, they nevertheless provide a fairly comprehensive picture of the reactivities of the four dihydropyranone dienophiles as well as the distereofacial and endo/exo selectivities (cf. Table III). Throughout these cycloadditions an intrinsic preference for endo addition of the cyclopentadiene is observed, the ratios of 3:1 to 9:1 being in line with similar preferences in a variety of conjugated cyclohexenones[15] as well as levoglucosenone.[9c,d]

In order to rationalize the diastereofacial selectivities given by the dihydropyranones, i.e. their below-/above-plane or (in sugar nomenclature) α/β-preference for diene addition (Table III), we next consider the respective ground-state conformations.

Conformation of Dienophiles. The conformations adopted by these dihydropyranones are either envelope (E) forms with the ring oxygen above (^{O}E) or below (E_O) a plane formed by the five ring carbon atoms, or, alternately, either of the two half-chair conformations $^{2}H_O$ or $^{O}H_2$.[16] In the case of dihydropyranone **1a**, lacking an anomeric substituent, PIMM molecular mechanics calcu-

(14) Stevenson, T. T.; Essig, M. G.; Shafizadeh, F.; Jensen, L. H.; Stenkamp, R. E. *Carbohydr. Res.* **1983**, *118*, 261.

(15) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642 and literature cited there.

(16) The conformational descriptors used for the pyranoid rings are those recommended by the IUPAC–IUB Joint Commission on Nomenclature; cf. *J. Chem. Soc., Chem. Commun.* **1973**, 505; *Eur. J. Biochem.* **1980**, *111*, 295.

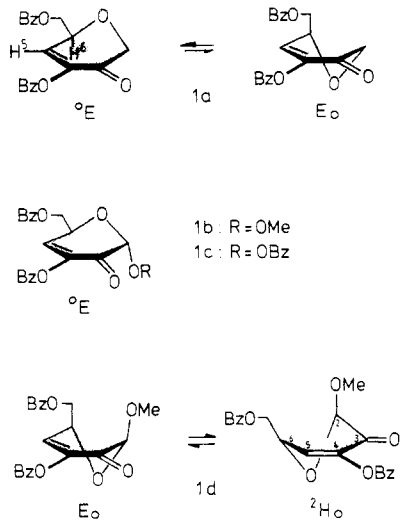


Figure 1. Preferred envelope conformations[16] for dihydro-3-pyrones **1a–d** as inferred from molecular mechanics calculations, ^1H NMR data, and, in the case of **1a**, from X-ray structural data.

lations[17] predict a near equivalence of the enthalpies of the two conformers, as evidenced by 11 local minima for the ^0E form in the range of −855 to −864 kJ/mol versus five for E_0 conformations between −856 and −862 kJ/mol.[18] For dihydropyrones **1b** and **1c**, both carring α-OR substituents at the anomeric carbon, calculations reveal the ^0E form to be favored by 21 kJ/mol,[19] a conformational preference to be expected, by operation of the anomeric effect.[20] The carbonyl function next to the anomeric center probably intensifies this effect, since it is known that 2-alkoxytetrahydropyranones show a substantially enhanced axial preference of the 2-alkoxy group when adjacent to both a carbonyl group and a ring oxygen.[21] For the same stereoelectronic reasons, a β-oriented oxygen substituent, as in **1d**, shifts the ring oxygen to the other (α) side (Figure 1). PIMM[17] calculations for **1d**, for example, show the conformer with an axial methoxy group to be preferred by −27 kJ/mol over its equatorial OMe counterpart, resulting in torsional angles for the lowest enthalpy conformer that are best described by an E_0 conformation somewhat distorted toward the $^2H_0$ form.[19]

These molecular mechanics derived conformational preferences also appear to prevail in the *crystalline state*, as well as in *solution*. An X-ray crystal structure determination of **1a**, for example, exhibits four conformational species in the crystal lattice: two are best approximated by ^0E forms with slightly differing molecular geometries, while the other two, occupying about 20% of the lattice positions, clearly reveal E_0 characteristics.[18] This clear predominance of the ^0E form for **1a** in the solid state is also found in $CDCl_3$ and acetone solutions as indicated by

Table IV. Conformationally Relevant Coupling Constants (300 MHz, $CDCl_3$) and UV Spectral Data (CH_3OH) of Dihydropyranones 1a–d and a Cyclohexanoid Analogue 10

dihydro-pyranone	$J_{5,6}$, Hz ($CDCl_3$)	preferred conformation[16]	λ_{max}, nm (ε)	n→π*, nm (ε)
1a	2.0[a]	^0E	231 (42562)	330 (39.4)
1b	2.0	^0E	231 (49793)	336 (54.5)
1c	1.8	^0E	232 (40621)	334 (81.6)
1d	3.5	$E_0(\rightarrow{}^2H_0)$	232 (31008)	336 (43.0)
10	–	–	232 (23941)	316 (44.6)

[a] A long-range coupling of 0.9 Hz ($J_{2,6}$) is also observed.

small $J_{5,6}$ values of 2.0 Hz (cf. Table IV).[22] The ^1H NMR coupling constant between H-5 and H-6 provides a suitable means for distinguishing between H-6 in a quasi-axial orientation, i.e. perpendicular to the plane of the ^0E envelope ($J_{5,6}$ values of 1.8–2.0 Hz[12,18]), and a quasi-equatorial arrangement in the ring oxygen inverted E_0 form ($J_{5,6}$ range 3.0–3.5 Hz for 11 compounds of type **1d**[12,19]). On the basis of the $J_{5,6}$ values found experimentally (Table IV) **1a** and the two α-alkoxy compounds **1b** and **1c** obviously have a quasi-axial H-6 proton and, hence, adopt the ^0E form with high preference in chloroform. In contrast, the larger $J_{5,6}$ value of the β-methoxy compound **1d** indicates a quasi-equatorial H-6 and, accordingly, a pronounced predominance of the E_0 conformation, whereby the 1,2-syn-diaxial interactions between 2-methoxy and 6-(benzoyloxy)methyl groups probably induce some distortion toward the $^2H_0$ half-chair.

π-Facial Selectivities. For rationalization of α/β-preferences for diene addition (cf. Table III), it appears reasonable to utilize the individual conformations identified above, i.e. ^0E forms for **1a–c**, and somewhat distorted E_0 conformation for **1d**, with the respective substituent at C-2 and C-6 in either quasi-axial or equatorial disposition. Considering first the *high-pressure cycloadditions*, the steric bias of approach of the cyclopentadiene to the α-side (below plane) or β-side of the dihydropyrones is guided by the C-6 benzoyloxymethyl and the C-2 anomeric substituent. For **1a**, the quasi-equatorial β-CH_2OBz at C-6 apparently provides some steric resistance to approach from the β-face, which results in a 3:1 preference for diene addition from the α-side (Table III). In the case of **1e**, the quasi-axial oxygen substituent at C-2 (cf. Figure 1) induces complete facial selectivity for α-adducts **2c** and **3c**. Similarly high (40:1) is the preference for α-addition of cyclopentadiene onto dienophile **1d**, both ring substituents encumbering the β-face (Figure 1) approach of the diene from this side. The opposite 6:1 preference for β-addition given by the dihydropyrones **1b** and **1c** is in line with the π-facial rationalizations made so far under the plausible premise, that a quasi-axial α-methoxy or α-benzoyloxy group exerts more steric hindrance against diene addition from the same side, than a β-benzoyloxy group (cf. formula in Figure 1) does for diene c apture from the β-face.

Another interesting feature clearly evident from the high-pressure selectivities listed in Table III is the comparatively high endo selectivity on the favored side of attack (5:1 to 9:1 endo/exo ratios for **1a–d**), compared to attack from the other, sterically more hindered side (1:1 ratio each for the anomeric pair **1b** and **1c**).

The correlation between conformation and steric substitution pattern in the dienophile and π-facial preference for diene addition is also borne out in the *thermally induced Diels–Alder reactions*, despite the considerably

(17) The PIMM program (for π-SCF Molecular Mechanics) used comprises an improved version of the π-SCF–LCAO force field methodology developed for the calculation of molecular geometrics: Lindner, H. J. *Tetrahedron* **1974**, *30*, 1127. Smith, A. E. Ph.D. Dissertation, Technische Hochschule Darmstasdt, 1989. This version with the accompanying graphics routine was run on an IBM-AT microcomputer.

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(19) Köhler, Ph.D. Dissertation, Technische Hochschule Darmstadt, 1986.

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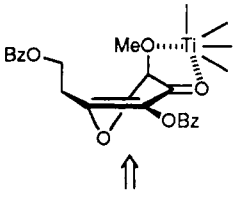
(22) The temperature dependence of the $J_{5,6}$ values has been proved for **1a** in acetone, decreasing from 2.0 Hz at 25 °C to 1.7 at −20 °C, and to 1.6 Hz at −80 °C.[19]

harsher conditions (2 days, 200 °C): for both thermal and high-pressure reactions, the anomerically unsubstituted **1a** gives a 3:1 α preference and its α-benzoyloxy analogue gives a 5:1 β preference. Thus, the preferred conformations at 200 °C appear to be essentially the same as at room temperature. Even in the conformationally more flexible 2-methoxy-substituted cases, **1b** and **1d**, π-facial preferences are in the same direction although less pronounced, decreasing from 1:6 (15 kbar) to 1:1.7 (Δ) for **1b**, and from 40:1 to 5:1 in the latter case (**1c**).

As for the *Lewis acid mediated cycloadditions*, the most salient features are the low reactivity of dihydropyranones **1a–c** and the different diastereofacial selectivities of the two α-anomeric dienophiles, the methoxy compound **1b** yielding α-cycloadducts, the benzoyloxy analogue **1c** β-cycloadducts, yet due to the low overall conversion (cf. Table II), this switch in selectivities may not bear much significance. The ease of reaction and remarkable stereoselectivity, however, with which the β-methoxy compound **1d** adds cyclopentadiene in the presence of $TiCl_4$ or $SnCl_4$ is striking and is conceivably attributed to a specific complex such as **9**, which has the metal bound to



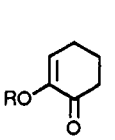
9

the methoxy and carbonyl oxygen, for which there are cyclohexanoid precedents.[23] For a complex of this type the $E_0 \rightarrow {}^2H_0$ distortion in **1a** apparently provides the sterically as well as electronically ideal disposition for diene addition from the α-face, a bias, which cannot be provided by the other dihydropyranones.

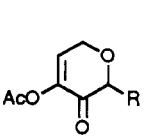
Dienophile Reactivity of Dihydro-3-pyrones. It has been previously demonstrated that an oxygen suitably disposed in a six-membered ring can significantly change the reactivity of an enone.[24] In order to evaluate the possible effect of the ring oxygen on the reactivity of dihydropyranones **1a–d**, the cyclohexanoid enolone ester **10**, in which the ring oxygen is formally replaced with a methylene group, was subjected to Diels–Alder reactions with cyclopentadiene, with the unexpected result that all conditions attempted, i.e. high pressure, thermal, and Lewis acid catalysis, failed to produce any cycloadducts. Therefore, it seems reasonable that a "ring oxygen effect" makes the pyranoid enolone esters considerably more reactive than their carbocyclic analogue **10**.

Some further evidence for an electronic interaction between the ring oxygen and the enolone π-system is derivable from the UV spectra of **1a–d** and **10** (Table IV). While the $\pi \rightarrow \pi^*$ transition overlapped the benzoyloxy absorptions, the $n \rightarrow \pi^*$ transition was clearly discerned in all of the compounds, showing a bathochromic shift of 14–20 nm for the pyranoid **1a–c** relative to carbocyclic **10**.

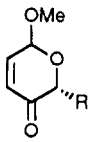
Since the Diels–Alder reactivity-enhancing effect of the ring oxygen on the enone system may be inferred from LUMO energies, we have performed such semiempirical calculations on cyclohexenone **11** and the dihydropyranones **12** and **13** using the standard protocol.[25] The respective LUMO energies obtained are distinctly less negative for the cyclohexanoid **10** (−8.6 kcal/mol) than for the pyranoid counterparts **12** and **13** (−14.4 and −13.7, respectively). Accordingly, the ring oxygen significantly lowers the LUMO of the proximate enone π-system, accounting at least partially for the enhanced dienophilicity of the pyranoid systems **1a–d** over the carbocyclic analogue **10**. However, the overall picture of the "ring oxygen effect" in pyranoid systems appears to be more complex than can be rationalized by LUMO energies only. For example, a series of dihydropyranones of type **14** have MNDO-calculated LUMO energies between −10.5 and −11 kcal/mol, yet exhibit high reactivity in thermal Diels–Alder reactions.[24] Hence, lowering of the LUMO by the ring oxygen is but one factor contributing to the extreme differences in reactivity; another may be that the ring oxygen causes an asymmetric distribution of the π-electron density via π-σ hybridization, thus enhancing dienophilicity.



10: R = Bz
11: R = Ac



12: R = H
13: R = OMe



14: R = H, CH_3, CH_2OR

Concluding Remarks

The results show that cyclopentadiene addition onto modestly dienophilic dihydropyranones is readily effected under high pressure and under thermal conditions, while Lewis acid mediated reactions are limited to sterically or electronically propitious cases. The methodology constitutes a short route to enantiomerically pure tetrahydrobenzopyrones that carry a multitude of stereogenic centers installed in a predictable way and have significant synthetic potential for the construction of complex natural products. Currently under study is the possibility of elaborating cyclopentanoid systems via oxidative cleavage of the olefinic double bond and opening of the pyranoid ring as a potentially useful route to prostaglandinoids.

Experimental Section

General. Dichloromethane was distilled from P_2O_5. Tin tetrachloride was distilled from P_2O_5 and stored in septum sealed glass containers. Cyclopentadiene was obtained by thermal treatment of dicyclopentadiene in a distillation apparatus and used immediately. All other reagents were obtained from commercial suppliers and used without further purification. Reactions involving Lewis acids were conducted under a nitrogen atmosphere in a septum sealed round-bottomed flask. Melting points were taken in Pyrex capillary and are uncorrected. IR spectra were measured in CCl_4, ^{13}C NMR spectra were determined at 50.78 MHz. The HPLC was conducted on a Whatman M-9 column with 10/50 Partisil packing at 4.0 mL/min. The HPLC eluent refractive index was followed to determine when fractions were to be collected. The high-pressure apparatus has been previously described.[26] The purity of all title compounds was judged to be ≥90% by analytical HPLC and ^1H NMR spectroscopy.

Preparation of Pyranone Starting Materials. Dihydropyranones **1a–d** are readily accessible from D-glucose via the perbenzoylated hydroxyglucal (2,3,4,6-tetra-*O*-benzoyl-D-*arabino*-hex-1-enitol[27]), which by a chlorination → hydrolysis → elimination procedure is converted into **1c**[12] while another

(23) The $TiCl_4$-induced cycloaddition of butadiene to 2-methoxycyclohex-2-enone has been shown by ^1H NMR spectroscopy to involve complexation at the carbonyl and ether oxygen (Blackburn, C.; Childs, R. F.; Kennedy, R. A. *Can. J. Chem.* **1983**, *61*, 1981).

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three-step sequence comprising hydroxylaminolysis, deoximination, and elimination[28] provided **1a**.[5,6] In both cases, the three consecutive steps were performed as a one-pot operation, furnishing yields (based on D-glucose) of well over 60 %. The (*S,S*)-dihydropyranone **1b** and its 2-epimer **1d** were readily prepared from the 2-benzoyloxy analogue **1c** via treatment with HBr and ensuing α-[29] or β-selective methanolysis.[12] 2-(Benzoyloxy)cyclohex-2-enone (**10**) was prepared by benzoylation of commercially available cyclohexane-1,2-dione, in benzene solution, with benzoyl chloride/pyridine, providing a product of mp 85–87 °C (lit.[30] mp 86.5–87 °C).

General Thermal Cycloaddition Procedure. Freshly distilled cyclopentadiene (0.38 g, 5.8 mmol) and a solution of the respective dihydropyranone **1** (0.58 mmol) in dichloromethane (4 mL) were placed in a thick-walled glass tube (total volume 45 mL). The glass tube was sealed using a gas/oxygen torch and buried in a sand bath which was heated to 150, 200, or 250 °C (see Table I) by a hot plate. The internal sand bath temperature was determined using a temperature probe next to the sealed glass tube, which allowed maintenance of the temperature (±10 °C) throughout the reaction time. After the appropriate reaction time (see Table I), the glass tube was cooled and opened, and the reaction mixture was concentrated under reduced pressure. The residue was filtered through silica gel (3 × 10 cm column) with 30% ethyl acetate in hexanes as the eluent. The solvents were removed under reduced pressure, and the residue was purified by HPLC using 20% ethyl acetate in hexanes as the eluent.

General Lewis Acid Catalyzed Cycloaddition Procedure. The respective dihydropyranone **1** (0.54 mmol) was weighed into a 25-mL, round-bottomed flask equipped with a magnetic stirrer and septum seal. The flask was thoroughly flushed with dry nitrogen and left under positive nitrogen pressure. In a separate flask, a solution of freshly distilled cyclopentadiene (0.145 g) in 4 mL of dichloromethane was made, and 2 mL (1.1 mmol) of this solution was injected into the round-bottomed flask. The flask was stirred to dissolve the enolone ester and cooled to −78 °C in a dry ice/acetone bath. Into a separate nitrogen flushed flask equipped with a septum seal was charged tin tetrachloride (0.318 g) and 2 mL of dichloromethane. This solution was cooled to −78 °C, and 1 mL (0.61 mmol) of the solution was injected into the cooled dihydropyranone/cyclopentadiene solution. The reaction mixture turned yellow, was stirred for the desired reaction time, and was poured into 10 mL of 2 M hydrochloric acid and 5 mL of dichloromethane. The mixture was shaken and the organic layer was separated. The acid layer was extracted with 10 mL of dichloromethane, and the combined organic layers were washed with 10 mL of saturated aqueous sodium bicarbonate and 10 mL of saturated aqueous sodium chloride. The aqueous washes were extracted with 10 mL of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated using a rotary evaporator, and the residue was filtered through silica gel (1.5 × 4 cm column) with 40% ethyl acetate in hexanes as the eluent. The eluate was taken to dryness and the residue was purified by HPLC using 20% ethyl acetate in hexanes.

General High-Pressure Procedure. Into an 8 × 1 cm Teflon tube (wall thickness 0.038 cm), clamped at one end, was charged dihydropyranone **1** (0.64 mmol), freshly distilled cyclopentadiene (0.283 g, 4.3 mmol), and dichloromethane (2 mL). The open end of the tube was clamped shut. The sealed tube was transferred to the high-pressure apparatus and pressurized to 15 kbar of hydrostatic pressure for 48 at room temperature. The sealed tube was removed from the depressurized high pressure apparatus, opened, and concentrated using a rotary evaporator. The residue was filtered through silica gel (3 × 10 cm column) with 30% ethyl acetate in hexanes as the eluent. The filtrate was concentrated under reduced pressure. The residue was purified by HPLC using 20% ethyl acetate in hexanes as the eluent.

Cyclopentadiene Adducts with Dihydropyranone 1a: 4a-(Benzoyloxy)-1-((benzoyloxy)methyl)-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)-ones, 2a (α-Endo-Adduct, [1*S*-(1α,4aα,5α,8α,8aα)]-Isomer), 3a (α-Exo, [1*S*-(1α,4aα,5β,8β,8aα)]), 4a (β-Endo, [1*S*-(1α,4aβ,5β,8β,8aβ)]), and 5a (β-Exo, [1*S*-(1α,4aβ,5α,8α,8aβ)]). The first HPLC fraction, with a retention time of 11.5 min, was concentrated to give β-exo adduct **5a** as a clear oil: $[\alpha]_D$ −20° (*c* 0.4, $CHCl_3$); IR 1730 (br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.52 (d (br), 1, H-9, $J_{9,9}$ = 9.7 Hz), 1.83 (dd, 1, H-8a, $J_{8a,1}$ = 3.0 Hz, $J_{8,8a}$ = 3.0 Hz), 2.21 (d (br), 1, H-9, $J_{9,9}$ = 9.7 Hz), 3.17 (s (br), 1, H-5), 3.27 (s (br), 1, H-8), 4.33 (d, 1, H-3, $J_{3,3}$ = 18.3 Hz), 4.46–4.66 (m, 2, H-10,10), 4.54 (d, 1, H-3, $J_{3,3}$ = 18.3 Hz), 5.00–5.06 (m, 1, H-1), 6.54 (s (br), 2, H-6,7), 7.29–7.63 (m, 6, H-*m,p*-aromatic), 7.93–8.10 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{25}H_{22}O_6$ 418.1417, found 418.1423.

The second HPLC fraction, with a retention time of 12.0 min, was concentrated to give β-endo adduct **4a** as a clear oil: $[\alpha]_D$ +16.8° (*c* 0.7, $CHCl_3$); IR 1730 (br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.82 (d (br), 1, H-9, $J_{9,9}$ = 8.9 Hz), 2.01 (d (br), 1, H-9, $J_{9,9}$ = 8.9 Hz), 2.47 (dd, 1, H-8a, $J_{1,8a}$ = 3.4 Hz, $J_{8,8a}$ = 3.4 Hz), 3.13 (s (br), 1, H-5), 3.34 (s (br), 1, H-8), 3.90 (d, 1, H-3, $J_{3,3}$ = 18.4 Hz), 4.35 (d, 1, H-3, $J_{3,3}$ = 18.4 Hz), 4.43–4.46 (m, 2, H-10,10), 4.92–4.95 (m, 1, H-1), 5.93 (dd, 1, H-6, $J_{6,7}$ = 5.6 Hz, $J_{5,6}$ = 3.1 Hz), 6.60 (dd, 1, H-7, $J_{6,7}$ = 5.6 Hz, $J_{7,8}$ = 2.7 Hz), 7.42–7.63 (m, 6, H-*m,p*-aromatic), 8.02–8.08 (m, 4, H-*o*-aromatic). Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.48; H, 5.27.

The third HPLC fraction, with a retention time of 17.0 min, upon three recycles through the column gave fractions A and B. Fraction A was concentrated to give α-exo adduct **3a** as a clear oil: $[\alpha]_D$ −34.6° (*c* 0.67, $CHCl_3$); IR 1730 (br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.64 (d (br), 1, H-9, $J_{9,9}$ = 10.1 Hz), 1.72 (d (br), 1, H-9, $J_{9,9}$ = 10.1 Hz), 1.95 (dd, 1, H-8a, $J_{8,8a}$ = 2.1 Hz, $J_{1,8a}$ = 8.9 Hz), 2.94 (s (br), 1, H-5), 3.49 (s (br), 1, H-8), 3.75–3.83 (m, 1 H-1), 4.02 (d, 1, H-3, $J_{3,3}$ = 7.8 Hz), 4.51–4.66 (m, 2, H-10,10), 4.76 (d, 1, H-3, $J_{3,3}$ = 7.8 Hz), 6.48 (s (br), 2, H-6,7), 7.35–7.60 (m, 6, H-*m,p*-aromatic), 7.92–8.06 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{25}H_{22}O_6$ 418.1417, found 418.1434.

Fraction B was concentrated to give α-endo adduct **2a** as a clear oil: $[\alpha]_D$ −102.9° (*c* 1.6, $CHCl_3$); IR 1730 (br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.85 (d (br), 1, H-9, $J_{9,9}$ = 8.6 Hz), 2.15 (d (br), 1, H-9, $J_{9,9}$ = 8.6 Hz), 2.63 (dd, 1, H-8a, $J_{8,8a}$ = 3.4 Hz, $J_{1,8a}$ = 9.4 Hz), 3.07 (s (br), 1, H-5), 3.51 (s (br), 2, H-1,8), 3.62 (d, 1, H-3, $J_{3,3}$ = 7.4 Hz), 4.44–4.61 (m, 3, H-3,10,10), 6.12 (dd, 1, H-6, $J_{6,7}$ = 5.1 Hz, $J_{5,6}$ = 3.2 Hz), 6.59 (dd, 1, H-7, $J_{7,8}$ = 2.5 Hz, $J_{6,7}$ = 5.1 Hz), 7.32–7.63 (m, 6, H-*m,p*-aromatic), 8.01–8.05 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{25}H_{22}O_6$ 418.1417, found 418.1414.

The fourth HPLC fraction, with a retention time of 27.0 min, proved to be starting material.

Cyclopentadiene Adducts with Dihydropyranone 1b: [1*S*-(1α,3β,4aα,5α,8α,8aα)]-, [1*S*-(1α,3β,4aα,5β,8β,8aα)]-, [1*S*-(1α,3β,4aβ,5β,8β,8aβ)]-, and [1*S*-(1α,3β,4aβ,5α,8α,8aβ)]-4a-(Benzoyloxy)-1-((benzoyloxy)methyl)-3-methoxy-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)-ones (2b–5b). The first fraction, with a retention time of 13 min, was concentrated to give α-exo adduct **3b** as a clear oil: $[\alpha]_D$ −19.8° (*c* 0.53, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.62 (dm, 1, H-9, $J_{9,9}$ = 10.0 Hz), 1.89 (dm, 1, H-9, $J_{9,9}$ = 10.0 Hz), 1.98 (dd, 1, H-8a, $J_{8,8a}$ = 2.8 Hz, $J_{1,8a}$ = 10.4 Hz), 2.89 (s (br), 1, H-5), 3.50 (s (br), 1, H-8), 3.53 (s, 3, H-OMe), 4.09 (m, 1, H-1), 4.48 (dd, 1, H-10, $J_{1,10}$ = <0.5 Hz, $J_{10,10}$ = 11.6 Hz), 4.65 (dd, 1, H-10, $J_{1,10}$ = 2.5 Hz, $J_{10,0}$ = 11.6 Hz), 5.18 (s, 1, H-3), 6.46 (m, 2, H-6,7), 7.34–7.61 (m, 6, H-*m,p*-aromatic), 7.90–8.09 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{26}H_{24}O_7$ − CO 420.1573, found 420.1579.

The second fraction, with a retention time of 16 min, was recycled to give fractions A and B. Fraction A was concentrated to give α-endo adduct **2b** as a clear oil: $[\alpha]_D$ −53.6° (*c* 0.28, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.86 (dm, 1, H-9, $J_{9,9}$ = 9.2 Hz), 2.14 (dm, 1, H-9, $J_{9,9}$ = 9.2 Hz), 2.64 (dd, 1, H-8a, $J_{8,8a}$ = 3.6 Hz, $J_{1,8a}$ = 10.8 Hz), 3.04 (s (br), 1, H-5), 3.44 (s, 3, H-OMe), 3.51 (s (br), 1, H-8), 3.73 (m, 1, H-1), 4.45 (dd, 1, H-10, $J_{1,10}$ = 6.7 Hz, $J_{10,10}$ = 11.8 Hz), 4.61 (dd, 1, H-10, $J_{1,10}$ = 3.2 Hz, $J_{10,10}$ = 11.8 Hz), 5.10 (s, 1, H-3), 6.14 (dd, 1, H-6, $J_{5,6}$ = 3.3 Hz, $J_{6,7}$ = 5.6 H), 6.49 (dd, 1, H-7, $J_{7,8}$ = 2.8 Hz, $J_{6,7}$ = 5.6 Hz), 7.35–7.64 (m, 6, H-*m,p*-aromatic), 7.97–8.08 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{26}H_{24}O_7$ 448.1522, found 448.1512.

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Fraction B was concentrated to give β-exo adduct **5b** as a clear oil: $[\alpha]_D$ −0.8° (*c* 0.49, $CHCl_3$); $[\alpha]_{436}$ +22.7° (*c* 0.49, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.53 (d (br), 1, H-9, $J_{9,9}$ = 9.8 Hz), 1.85 (dd, 1, H-8a, $J_{8,8a}$ = 2.7 Hz, $J_{1,8a}$ = 2.8 Hz), 2.25 (d (br), 1, H-9, $J_{9,9}$ = 9.8 Hz), 3.18 (s (br), 1, H-5), 3.23 (s (br), 1, H-8), 3.60 (s, 3, H-OMe), 4.47 (dd, 1, H-10, $J_{1,10}$ = 3.4 Hz, $J_{10,10}$ = 11.6 Hz), 4.69 (dd, 1, H-10, $J_{1,10}$ = 8.6 Hz, $J_{10,10}$ = 11.6 Hz), 4.83 (s, 1, H-3), 5.47 (m, 1, H-1), 6.54 (m, 2, H-6,7), 7.39–7.62 (m, 6, H-*m*,*p*-aromatic), 7.96–8.11 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{26}H_{24}O_7$ 448.1522, found 448.1546.

The third fraction, with a retention time of 23 min, was concentrated to give β-endo adduct **4b** as a clear oil: $[\alpha]_D$ +33.3° (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.84 (d (br), 1, H-9, $J_{9,9}$ = 9.0 Hz), 2.03 (d (br), 1, H-9, $J_{9,9}$ = 9.0 Hz), 2.50 (dd, 1, H-8a, $J_{8,8a}$ = 3.3 Hz, $J_{1,8a}$ = 6.6 Hz), 3.16 (s (br), 1, H-5), 3.32 (m, 1, H-8), 3.52 (s, 3, H-OMe), 4.40 (s, 1, H-3), 4.47 (dd, 2, H-10,10, $J_{1,10}$ = 2.5 Hz, $J_{10,10}$ = 6.1 Hz), 5.34 (m, 1, H-1), 5.91 (dd, 1, H-6, $J_{5,6}$ = 3.1 Hz, $J_{6,7}$ = 5.6 Hz), 6.61 (dd, 1, H-7, $J_{7,8}$ = 2.8 Hz, $J_{6,7}$ = 5.6 Hz), 7.42–7.63 (m, 6, H-*m*,*p*-atomatic), 8.06–8.10 (m, 4, H-*o*-aromatic); ^{13}C NMR (δ (50.78 MHz, $CDCl_3$) δ 44.29, 49.11, 49.63, 53.11, 56.16, 64.72, 67.88, 85.17, 98.14, 127.16, 128.36, 128.71, 128.94, 129.56, 129.64, 130.01, 133.13, 133.55, 141.97, 166.01, 166.24, 200.99. Anal. Calcd for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39. Found C, 69.34; H, 5.43.

The fourth fraction, with a retention time of 28 min, was concentrated to give starting dihydropyranone **1b**.

Cyclopentadiene Adducts with Dihydropyranone 1c: [1*S*-(1α,3β,4aα,5α,8α,8aα)]-, [1*S*-(1α,3β,4aα,5β,8β,8aβ)]-, [1*S*-(1α,3β,4aβ,5β,8β,8aβ)]-, and [1*S*-(1α,3β,4aβ,5α,8α,8aβ)]-3,4a-Bis(benzoyloxy)-1-((benzoyloxy)methyl)-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)-ones (2c–5c). The first fraction, with a retention time of 17 min, was recycled twice into four fractions A–D. Fraction A was concentrated to give β-exo adduct **5c** as a clear oil: $[\alpha]_D$ +3.6° (0.14, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.61 (d (br), 1, H-9, $J_{9,9}$ = 10.3 Hz), 1.95 (dd, 1, H-8a, $J_{1,8a}$ = 2.7 Hz, $J_{8,8a}$ = 2.7 Hz), 2.34 (d (br), 1, H-9, $J_{9,9}$ = 10.3 Hz), 3.19 (s (br), 1, H-5), 3.32 (s (br), 1, H-8), 4.50–4.58 (m, 2, H-10,10), 5.63–5.69 (m, 1, H-1), 6.51 (s, 1, H-3), 6.59 (s (br), 2, H-6,7), 7.40–7.68 (m, 9, H-*m*,*p*-aromatic), 7.76–8.26 (m, 6, H-*o*-aromatic); HRMS calcd for $C_{32}H_{26}O_8$ − CO 510.1679, found 510.1663.

Fraction B was concentrated to give β-endo adduct **4c** as colorless crystals: mp 182–183 °C; $[\alpha]_D$ +36.9° (*c* 1.3, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.88 (d (br), 1, H-9, $J_{9,9}$ = 9.0 Hz), 2.06 (d (br), 1, H-9, $J_{9,9}$ = 9.0 Hz), 2.59 (dd, 1, H-8a, $J_{1,8a}$ = 3.3 Hz, $J_{8,8a}$ = 3.3 Hz), 3.17 (s (br), 1, H-5), 3.38 (s (br), 1, H-8), 4.33–4.51 (m, 2, H-10,10), 5.49–5.52 (m, 1, H-1), 6.01 (dd, 1, H-6, $J_{5,6}$ = 3.1 Hz, $J_{6,7}$ = 5.6 Hz), 6.06 (s, 1, H-3), 6.66 (dd, 1, H-7, $J_{7,8}$ = 2.8 Hz, $J_{6,7}$ = 5.6 Hz), 7.41–7.65 (m, 9, H-*m*,*p*-aromatic), 7.75–8.26 (m, 6, H-*o*-aromatic); ^{13}C NMR (50.78 MHz, $CDCl_3$) δ 44.28, 49.20, 49.73, 53.07, 64.34, 69.99, 85.27, 90.01, 127.31, 128.16, 128.43, 128.76, 129.33, 129.46, 129.97, 130.21, 132.94, 133.45, 133.67, 142.15, 165.12, 166.11, 200.01. Anal. Calcd for $C_{32}H_{26}O_8$: C, 71.37; H, 4.87. Found C, 71.21; H, 5.00.

Fraction C was concentrated to give α-exo adduct **3c** as a clear oil: $[\alpha]_D$ −17.6° (*c* 0.54, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.78 (d (br), 1, H-9, $J_{9,9}$ = 11.3 Hz), 1.89 (d (br), 1, H-9, $J_{9,9}$ = 11.3 Hz), 2.20 (dd, 1, H-8a, $J_{8,8a}$ = 3.0 Hz, $J_{1,8a}$ = 10.4 Hz), 2.94 (s (br), 1, H-5), 3.72 (s (br), 1, H-8), 4.17–4.25 (m, 1, H-1), 4.45 (dd, 1, H-10, $J_{1,10}$ = 6.1 Hz, $J_{10,10}$ = 12.1 Hz), 4.63 (dd, 1, H-10, $J_{1,10}$ = 2.7 Hz, $J_{10,10}$ = 12.1 Hz), 6.45 (dd, 1, H-6, $J_{5,6}$ = 3.4 Hz, $J_{6,7}$ = 5.2 Hz), 6.53 (dd, 1, H-7, $J_{7,8}$ = 3.1 Hz, $J_{6,7}$ = 5.2 Hz), 6.86 (s, 1, H-3), 7.21–7.68 (m, 9, H-*m*,*p*-aromatic), 7.81–8.23 (m, 6, H-*o*-aromatic); HRMS calcd for $C_{32}H_{26}O_8$ − CO 510.1679, found 510.1659.

Fraction D was concentrated to give α-endo adduct **2c** as a clear oil: $[\alpha]_D$ −67.0° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.92 (d (br), 1, H-9, $J_{9,9}$ = 9.0 Hz), 2.18 (d (br), 1, H-9, $J_{9,9}$ = 9.0 Hz), 2.78 (dd, 1, H-8a, $J_{8,8a}$ = 3.5 Hz, $J_{1,8a}$ = 10.8 Hz), 3.09 (s (br), 1, H-5), 3.59 (s (br), 1, H-8), 3.83–3.92 (m, 1, H-1), 4.42 (dd, 1, H-10, $J_{1,10}$ = 6.0 Hz, $J_{10,10}$ = 11.9 Hz), 4.56 (dd, 1, H-10, $J_{1,10}$ = 3.4 Hz, $J_{10,10}$ = 11.9 Hz), 6.31 (dd, 1, H-6, $J_{5,6}$ = 3.1 Hz, $J_{6,7}$ = 5.6 Hz), 6.60 (dd, 1, H-7, $J_{7,8}$ = 2.7 Hz, $J_{6,7}$ = 5.6 Hz), 6.73 (s, 1, H-3), 7.20–7.65 (m, 9, H-*m*,*p*-aromatic), 7.84–8.05 (m, 6, H-*o*-aromatic); ^{13}C NMR (50.78 MHz, $CDCl_3$) δ 44.27, 44.76, 51.76, 52.40, 65.33, 72.91, 82.44, 90.06, 128.27, 128.48, 128.55, 129.27, 129.47, 129.56, 129.79, 130.04, 133.06, 133.48, 133.79, 133.89, 140.55, 164.43, 165.26, 166.31, 198.76; HRMS calcd for $C_{32}H_{26}O_8$ − CO 510.1679, found 510.1680.

The second fraction, with a retention time of 22 min, was concentrated to give educt.

Cyclopentadiene Adducts with Dihydropyranone 1d: [1*S*-(1α,3α,4aα,5α,8α,8aα)]-, [1*S*-(1α,3α,4aα,5β,8β,8aα)]-, [1*S*-(1α,3α,4aβ,5β,8β,8aβ)]-, [1*S*-(1α,3α,4aβ,5α,8α,8aβ)]-4a-(Benzoyloxy)-1-((benzoyloxy)methyl)-3-methoxy-4a,5,8,8a-tetrahydro-5,8-methano-1*H*-2-benzopyran-4(3*H*)-ones (2d–5d), and Rearrangement Adduct (6). The first fraction, with a retention time of 11.5 min, was concentrated to rearrangement adduct **6** as a solid: mp 51–53 °C; $[\alpha]_D$ −42.9° (*c* 0.59, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (d, 3, H-Me, J_{Me5or8} = 7.8 Hz), 2.09–2.44 (m, 3, H-8a,5,5 or -8,8), 2.80 (s (br), 1, H-8 or -8a), 3.65 (s, 3, H-OMe), 4.25–4.35 (m, 1, H-1), 4.47–4.58 (m, 2, H-10,10), 4.81 (s, 1, H-3), 5.71–5.79 (dm, 1, H-6, $J_{6,7}$ = 8 Hz), 5.80–5.89 (dm, 1, H-7, $J_{6,7}$ = 8 Hz), 7.38–7.63 (m, 6, H-*m*,*p*-aromatic), 7.99–8.14 (m, 4, H-*o*-aromatic); ^{13}C NMR (50.78 MHz, $CDCl_3$) δ 17.33 (CH_3, H-9), 22.65 (CH_2, C-5 or -8), 29.86 (CH, C-5 or -8), 37.26 (CH, C-8a), 57.13 (CH_3, C-OMe), 68.14 (CH_2, C-10), 73.61 (CH, C-1), 81.48 (C, C-4a), 101.52 (CH, C-3), 121.63, 128.37, 128.43, 129.33, 129.48, 129.75, 129.87, 133.20, 133.37, 164.49 (C, ester), 199.60 (C, ketone). Anal. Calcd for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82. Found: C, 69.54; H, 6.02.

The second fraction, with a retention time of 12 min, was concentrated to β-exo adduct **5d** as a clear oil: $[\alpha]_D$ −23.5° (*c* 1.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.50 (d (br), 1, H-9, $J_{9,9}$ = 9.9 Hz), 1.81 (dd, 1, H-8a, $J_{1,8a}$ = 3.0, $J_{8,8a}$ = 3.0 Hz), 2.25 (d (br), 1, H-9, $J_{9,9}$ = 9.9 Hz), 3.17 (s (br), 1, H-5), 3.31 (s (br), 1, H-8), 3.65 (s, 3, H-OMe), 4.49–4.70 (m, 2, H-10,10), 5.07–5.13 (m, 1, H-1), 5.22 (s, 1, H-3), 6.49–6.56 (m, 2, H-6,7), 7.37–7.65 (m, 6, H-*m*,*p*-aromatic), 7.90–8.12 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{26}H_{24}O_7$ − CO 420.1573, found 420.1576.

The third fraction, with a retention time of 14 min, was concentrated to β-endo adduct **4d** as a clear oil: $[\alpha]_D$ −20.8° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.80 (d (br), 1, H-9, $J_{9,9}$ = 9.1 Hz), 1.98 (d (br), 1, H-9, $J_{9,9}$ = 9.1 Hz), 2.47 (dd, 1, H-8a, $J_{1,8a}$ = 3.5 Hz, $J_{8,8a}$ = 3.5 Hz), 3.17 (s (br), 1, H-5), 3.44 (s (br), 1, H-8), 3.57 (s, 3, H-OMe), 4.48 (s (br), 1, H-10), 4.51 (d, 1, H-10, $J_{1,10}$ = 1.8 Hz), 5.01 (m, 1, H-1), 5.13 (s, 1, H-3), 5.96 (dd, 1, H-6, $J_{5,6}$ = 3.0 Hz, $J_{6,7}$ = 5.8 Hz), 6.62 (dd, 1, H-7, $J_{7,8}$ = 2.6 Hz, $J_{6,7}$ = 5.8 Hz), 7.40–7.66 (m, 6, H-*m*,*p*-aromatic), 8.01–8.14 (m, 4, H-*o*-aromatic); HRMS calcd for $C_{26}H_{24}O_7$ − CO 420.1573, found 420.1575.

The fourth fraction, with a retention time of 23 min, proved to be educt.

The fifth fraction, with a retention time of 25 min, was concentrated to α-exo adduct **3d** as a clear oil: $[\alpha]_D$ −17.4° (*c* 0.34, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (dd, 1, H-9, $J_{8,9}$ = 0.7 Hz, $J_{9,9}$ = 10.1 Hz), 1.79 (d, 1, H-9, $J_{9,9}$ = 10.1 Hz), 2.03 (dd, 1, H-8a, $J_{8,8a}$ = 2.5 Hz, $J_{1,8a}$ = 8.2 Hz), 2.95 (s (br), 1, H-5), 3.44 (m, 1, H-8), 3.69 (s, 3, H-OMe), 3.96 (m, 1, H-1), 4.66 (m, 2, H-10,10), 4.81 (s, 1, H-3), 6.48 (m, 2, H-6,7), 7.37–7.60 (m, 6, H-*m*,*p*-aromatic), 7.93–8.08 (m, 4, H-*o*-aromatic); ^{13}C NMR (50.78 MHz, $CDCl_3$) δ 44.81, 48.04, 51.16, 51.36, 57.48, 66.46, 76.08, 77.21, 85.91, 101.31, 128.29, 128.38, 129.64, 129.69, 129.97, 133.15, 133.40, 135.54, 137.99, 165.07, 166.40, 200.17; HRMS calcd for $C_{26}H_{24}O_7$ − CO 420.1573, found 420.1574.

The sixth fraction, with a retention time of 28 min, was concentrated to α-endo adduct **2d** as a clear oil: $[\alpha]_D$ −93.9° (*c* 2.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.88 (d (br), 1, H-9, $J_{9,9}$ = 9.1 Hz), 2.18 (d (br), 1, H-9, $J_{9,9}$ = 9.1 Hz), 2.68 (dd, 1, H-8a, $J_{8,8a}$ = 3.6 Hz, $J_{1,8a}$ = 8.6 Hz), 3.06 (s (br), 1, H-5), 3.46 (s (br), 1, H-8), 3.62 (s, 3, H-OMe), 3.73 (m, 1, H-1), 4.41 (s, 1, H-3), 4.60 (m, 2, H-10,10), 6.14 (dd, 1, H-6, $J_{5,6}$ = 3.2 Hz, $J_{6,7}$ = 5.7 Hz), 6.67 (dd, 1, H-7, $J_{7,8}$ = 2.9 Hz, $J_{6,7}$ = 5.7 Hz), 7.34–7.62 (m, 6, H-*m*,*p*-aromatic), 8.02–8.07 (m, 4, H-*o*-aromatic); ^{13}C NMR (50.78 MHz, $CDCl_3$) δ 45.47, 48.81, 49.09, 53.20, 53.27, 57.33, 63.67, 66.32, 85.22, 101.58, 128.37, 128.84, 129.62, 129.69, 130.02, 132.81, 133.12, 133.47, 142.07, 164.89, 166.35, 199.27; HRMS calcd for $C_{26}H_{24}O_7$ − CO 420.1573, found 420.1572.

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Registry No. **1a**, 75414-38-9; **1b**, 13007-49-3; **1c**, 52080-38-3; **1d**, 52152-86-0; **2a**, 111718-45-7; **2b**, 125302-92-3; **2c**, 125302-93-4; **2d**, 125409-16-7; **3a**, 111819-59-1; **3b**, 125409-10-1; **3c**, 125409-13-4; **3d**, 125409-17-8; **4a**, 125409-08-7; **4b**, 125409-11-2; **4c**, 125409-14-5; **4d**, 125409-18-9; **5a**, 125409-09-8; **5b**, 125409-12-3; **5c**, 125409-15-6; **5d**, 125409-19-0; **6**, 125302-94-5; cyclopentadiene, 542-92-7.

Supplementary Material Available: The ^1H NMR spectra of all the Diels–Alder adducts (19 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of a Nonracemic Hydronaphthalene Subunit of Kijanolide

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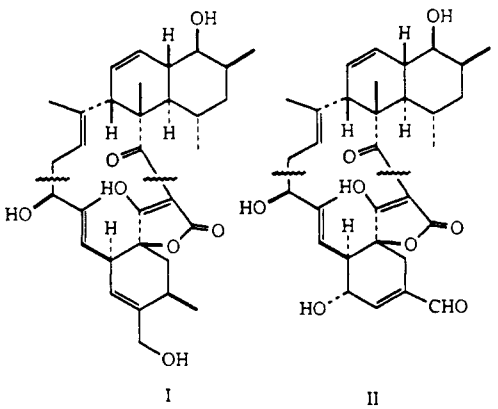
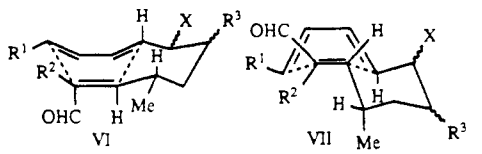
Lewis acid catalyzed Diels–Alder cyclization of the tetraenal **15** affords the endo product, hydronaphthalene **16**, with high diastereoselectivity. Nonracemic **15** is prepared by addition of dienyne **5** to resolved (2*S*,4*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2,4-dimethylpentanal followed by oxidation to ketone **7**, reduction first with *ent*-Chirald–LAH and then with Red-Al (Aldrich) and homologation of the derived aldehyde **12** by a Horner–Emmons protocol. Hydronaphthalene **16** is a subunit of the antitumor antibiotic natural products kijanimicin and tetrocarin A.

The novel macrocyclic compounds kijanolide (I) and tetronolide (II) are the aglycons of the antitumor antibiotics kijanimicin and tetrocarcin A.[1,2] To date only three representatives of this family have been identified.[3] Nonetheless these structures have elicited a great deal of interest as targets of synthesis.[4] Several years ago we showed that (*all-E*)-2,8,10-undecatrienals with a methyl substituent at C-4 (III) undergo facile Diels–Alder cyclization to endo products of type IV rather than the diastereomers V (eq 1).[5] The observed diastereoselectivity

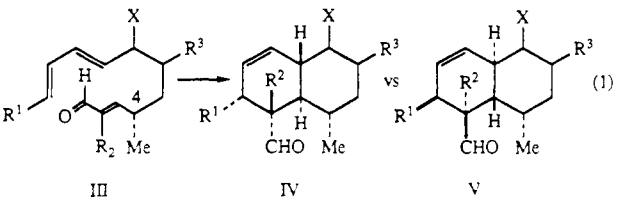


I II



VI VII

Figure 1. Endo chair cyclization pathways for 4-methyl-2,8,10-undecatrienals.



III IV V (1)

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