Stereoselection in Thermal Asymmetric Diels–Alder Reactions. Electronic vs Steric Effects

Blanda Stammen, Ulrich Berlage, Richard Kindermann, Manfred Kaiser, Barbara Günther, William S. Sheldrick, Peter Welzel,* and Wolfgang R. Roth*

Fakultät für Chemie der Ruhr-Universität, Postfach 102148, D-4630 Bochum, Germany

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Experimental evidence was found for an electronic contribution favoring the cisoid conformation of α,β-unsaturated carbonyl compounds in thermal Diels–Alder transition states.

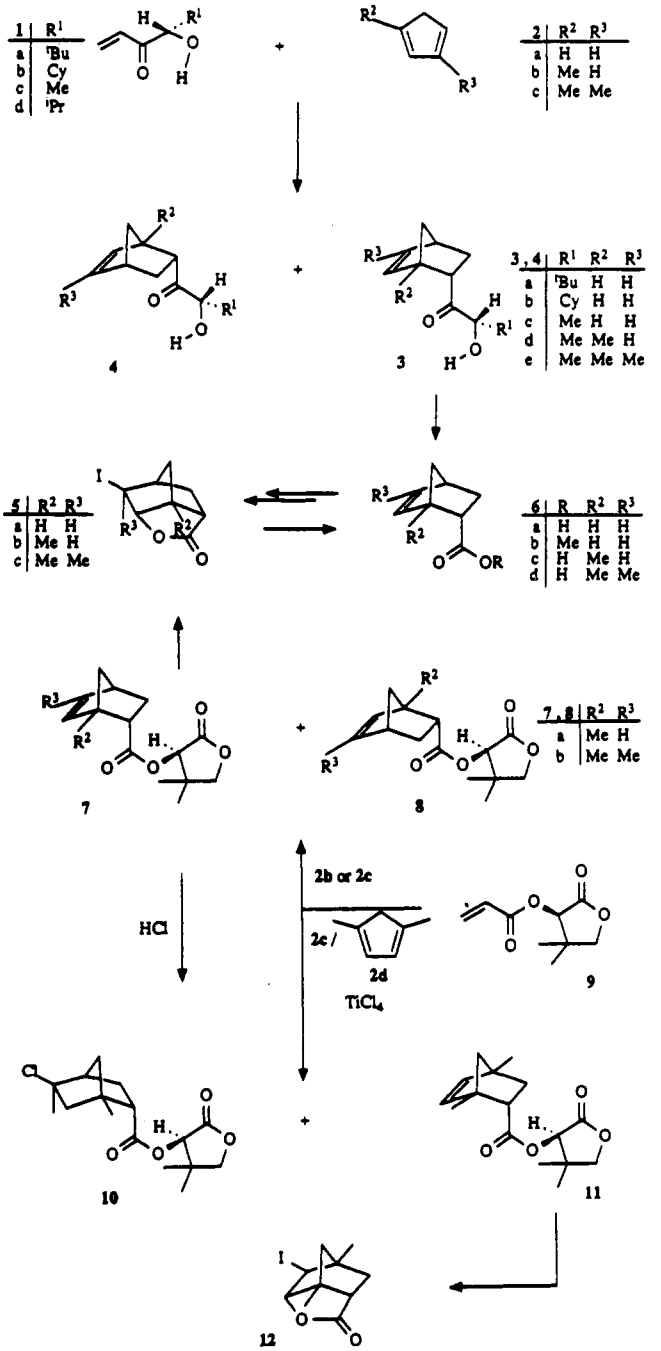
Introduction

Four transition state structures for the Diels–Alder reaction of butadiene with acrolein have been obtained by Houk and co-workers with ab initio quantum mechanical calculations, two of them with endo and two with exo orientation.[1] For the endo transition structures (only these will be discussed in the sequel) the one with the acrolein moiety in its *cisoid* conformation was shown to be 0.6 kcal/mol more stable than the endo *transoid* transition structure, although the transoid conformation of the dienophile in the ground state is preferred by 1.7 kcal/mol, according to these calculations. Thus, there is a 2.3 kcal/mol difference between the conformational preferences of the ground state and the transition structure. The formyl substituent causes the transition structures to be unsymmetrical, more in the s-cis than in the s-trans transition structure (for the endo s-cis case the difference in the forming bond lengths is 0.3 Å). The quite large relative stabilization energy of the acrolein s-cis conformation in the transition structure was reported to have several sources: (i) the lower energy of the butadiene moiety in the endo cisoid transition structure (favored by 1.0 kcal/mol) and (ii) the greater electrophilicity of the acrolein s-cis conformation and the greater secondary orbital interaction that is possible for this conformer between orbitals on the carbonyl group and on the diene.

Houk's results are not amenable to direct experimental scrutinity. Since the problems addressed in this study are, however, of eminent importance in the context of asymmetric Diels–Alder reactions we have undertaken an experimentally based investigation aimed at verifying the calculated electronic stabilization of the cisoid conformation of the dienophilic moiety in the transition state.[2]

Dienophiles of type 1 were used in this study (Scheme I). Masamune[3] has reported that **1a** and **1b** react with cyclopentadiene (**2a**) even in the absence of a Lewis acid with good endo selectivity and that the two endo cycloadducts **3** and **4** are formed, depending on the reaction temperature, in a ratio ranging from 13:1 to 28:1 for R^1 = cyclohexyl (**3b**, **4b**) and from 23:1 to >100:1 for R^1 = *tert*-butyl (**3a**, **4a**). These high diastereoselectivities were attributed to a high preference of one conformation of the enone unit and to the strong hydrogen bond between the

Scheme I. Diels–Alder Reaction of Dienophiles 1 with Cyclopentadienes 2: Product Formation and Configurational Assignments



(1) (a) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129–1134. (b) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14–23. For a review, see: Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem.* **1992**, *104*, 711–739; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682. A reviewer has directed our attention to the work of: Branchadell, V.; Orti, J.; Ortuño, R. M.; Oliva, A.; Font, J.; Bertrán, J.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 2190–2193 and earlier papers cited therein. This work describes studies on Diels–Alder reactions by means of MNDO and AM1 methods but is restricted to butenolides (s-trans enone unit) as dienophiles.

(2) Model calculations and experimental studies of thermal Diels–Alder reactions indicate that there is a slight preference for acrylates to have the s-cis conformation in the transition state: Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137–2141.

(3) (a) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137–1139. (b) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441–4444.

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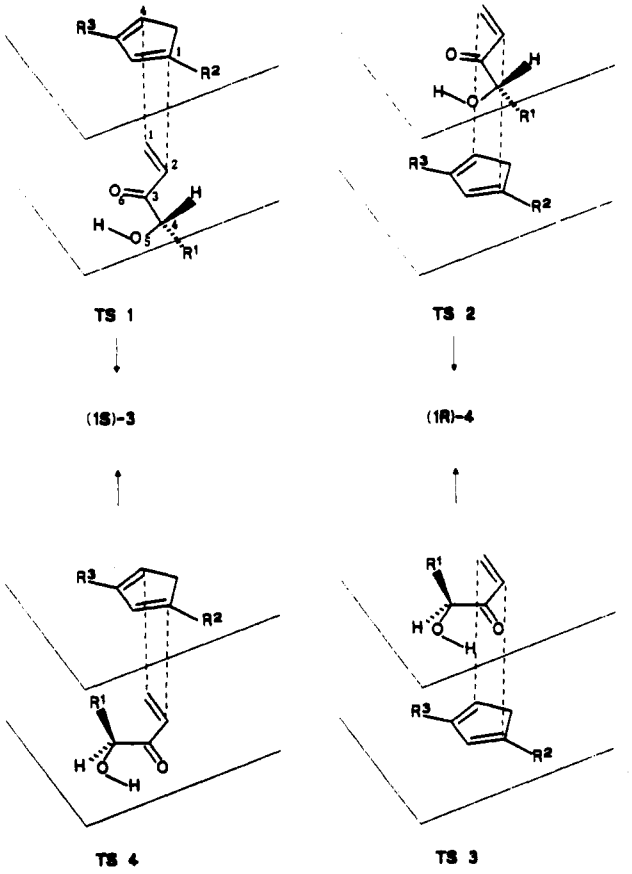
Scheme II. Four Transition States for the Diels–Alder Reaction of Dienophiles 1 with Cyclopentadienes 2

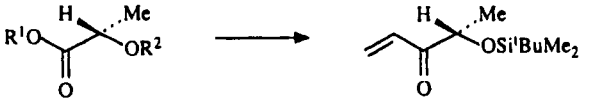


hydroxyl and the keto function freezing the rotation around the bond between C-3 and C-4, thus making the two diastereotopic faces of the enone system highly distinguishable.[3]

From the presumed favored reaction of the dienophile on the less shielded face opposite to group R^1 and the established configuration of the main cycloadduct **3** (**3a** and **3b**, respectively) it was inferred that **3** is formed via a transition state as depicted in TS1 with the dienophile in its cisoid conformation (Scheme II). According to Masamune the cisoid conformation is preferred because of a repulsive interaction between the substituent R^1 and one of the vinylic protons in the transoid conformation.[3]

For the formation of minor product **4** (in Masamune's work: **4a** and **4b**) two reaction paths can be envisaged (Scheme II), one leading via TS2 (s-cis conformation of the enone system, attack on the face shielded by group R^1), the other via TS3 (s-trans conformation of the enone system, attack on the face opposite to group R^1). In our study we used **1c** as dienophile. Replacement of the large R^1 groups present in **1a** and **1b** by the methyl group was assumed to bring the competing transition states both closer in energy and in structure and to make them more sensitive to further perturbations (vide infra). Besides cyclopentadiene (**2a**) we used 1-methylcyclopentadiene (**2b**) as diene. Introduction of the methyl group (cf. Scheme II, R^2 = Me, R^3 = H) should influence the competing transition states in a different way: TS1 and TS3 should not be affected very much whereas TS2 (and TS4) should be higher in energy than in the unsubstituted case (R^2 and R^3 = H) because of the repulsive interactions between R^1 and R^2. If the minor compound (1*R*)-**4** is exclusively formed via TS2 the ratio **3d**:**4d** should be higher than **3c**:**4c** whereas exclusive formation via TS3 should give

Scheme III. Synthesis of Dienophile 1c



13	R^1	R^2
a	Me	H
b	Me	Si^tBuMe_2
c	Li	Si^tBuMe_2

14

about the same diastereomeric ratios. The steric interactions in the various transition states were calculated by force field methods in order to evaluate, by comparing the calculated and the experimental differences in energy, any *electronic* contribution to the energy content of TS2 and TS3 relative to TS1. Included is also the same type of analysis using 1,3-dimethylcyclopentadiene (**2c**, $R^2 = R^3$ = Me in Scheme II) as diene which was expected to give results very similar to those obtained for **2b**.

Results

Synthesis of 1c, 2b, and 2c. Following Masamune's approach the α,β-unsaturated ketone **1c** was prepared commencing from (*S*)-methyl lactate (**13a**, Scheme III). Treatment with $^tBuMe_2SiCl$[4] furnished **13b** which was saponified to yield the lithium salt **13c**. Vinylation[5,6] with 1 equiv vinyllithium[7] gave the silylated compound **14**. Removal of the protecting group[8] afforded dienophile **1c** in 47% overall yield. Selection of the appropriate protecting group was important. The Et_3Si group did not survive the saponification step[9] whereas under the rather harsh conditions needed to cleave the $^tBuPh_2Si$ ether of **1c** considerable decomposition of the very sensitive enone **1c** was observed.[10]

For optical purity determination a reference sample of racemic ketol (*rac*-**1c**) was prepared in the same way. Capillary GC analysis using a β-cyclodextrin-derived stationary phase[11] showed the ee of the optically active compound to be >99%. 1-Methylcyclopentadiene (**2b**) was prepared by the method of Mironov et al.[12] Cyclopentadiene (**2a**) was treated with ethylmagnesium bromide in toluene–THF (3:1) to give the corresponding anion. Methylation afforded first 5-methylcyclopentadiene which rearranged by fast 1,5-H shift at low temperatures to the 1-methyl isomer **2b**. Further equilibration with 2-methylcyclopentadiene could be avoided by purifying (distillation) and keeping the diene at −20 °C (the 1- and the 2-methyl isomers equilibrate to give a roughly 1:1 mixture within 2–3 days at 20 °C). The use of THF proved necessary in the deprotonation reaction. From the mag-

(4) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975–2977.
(5) (a) Bare, T. M.; House, H. O. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. 5, pp 775–779. (b) Jorgenson, M. J. *Organic Reactions*; J. Wiley and Sons: New York, 1970; Vol. 18, pp 1–97.
(6) Floyd, J. C. *Tetrahedron Lett.* **1974**, 2877–2878. Larcheveque, M.; Petit, Y. *Synthesis* **1986**, 60–64. Seyferth, D.; Weinstein, R. M.; Wang, W.-L.; Hui, R. C.; Archer, C. M. *Isr. J. Chem.* **1984**, *24*, 167–175.
(7) (a) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785–2812. Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847–853. (b) Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583–3586.
(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(9) Stammen, B. Dissertation, Ruhr-Universität, Bochum, 1991.
(10) Berlage, U. Dissertation, Ruhr-Universität, Bochum, 1987.
(11) König, W. A. *Kontakte (Merck)* **1990**, *2*, 3–14. Schurig, V.; Nowotny, H.-P. *Angew. Chem.* **1990**, *102*, 969–986, *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939.
(12) Mironov, V. A.; Sobolev, E. V.; Elizarova, A. N. *Tetrahedron* **1963**, *19*, 1939–1958.

nesium salt of **2a** THF was then carefully removed in order to obtain **2b** completely free of THF, since it was anticipated that this ether compound would break the internal hydrogen bond in **1c**.

For the synthesis of 1,3-dimethylcyclopentadiene (**2c**) the McLean and Haynes method[13] was used to give a 4:1 mixture of **2c** and its 1,4-dimethyl isomer (**2d**).

Diels–Alder Reactions of 1c with 2a–2c. Product Analysis and Configurational Assignments. Reaction of the dienophile **1c** with a 10-fold excess of cyclopentadiene (**2a**) in toluene gave four cycloaddition products. The endo cycloadducts (**3c** and **4c**) and the corresponding exo isomers (structures not shown) were identified both by ^{13}C and ^{1}H NMR. The results of a detailed spectral analysis (using **6a** and its exo isomer as model compounds[14,15]) are collected in Tables III and IV. Especially indicative are the chemical shifts of C-6 and of C-7. The C-7 signal in the endo compounds is high-field shifted by the γ_{anti} effect of the substituent at C-2. In the exo compounds the γ_{anti} effect causes a high-field shift of the C-6 signal. In the ^{1}H NMR spectra the chemical shift difference of 5-H and 6-H is about 0.3 ppm in the endo compounds and almost zero in the exo isomers. The main endo isomer was degraded with $NaIO_4$, followed by esterification with diazomethane to give a norbornenecarboxylic acid methyl ester to which the configuration depicted in **6b** could be assigned, since its circular dichroism (CD) was enantiomorph to that of *ent*-**6b** prepared from optically pure *ent*-**5a**.[16]

The Diels–Alder reaction of 1-methylcyclopentadiene (**2b**) with dienophile **1c** was performed under the same conditions as described for **2a**. Again four stereoisomeric cycloadducts were identified. No adducts arising from the 2-methyl isomer could be detected.

The main endo product was treated with $NaIO_4$ and then KI and I_2 to give the corresponding iodo lactone which must have one of the structures **5b** or *ent*-**5b**. For comparison an uncatalyzed Diels–Alder reaction of *O*-acryloyl-D-pantolactone (**9**) with diene **2b** was performed and the resulting cycloadducts **7a** and **8a** were degraded to the iodo lactones **5b** and *ent*-**5b**. The CD curves of these two compounds (see Figure 1) are mirror images of each other. The compound showing the same Cotton effects as *ent*-**5a** (the CD curves of two different samples[16] are shown) was assigned structure *ent*-**5b**. The other enantiomer (**5b**) had the same CD curve as the degradation product obtained from the main endo cycloadduct of **2b** with **1c** which must, therefore, have structure **3d**.

The Diels–Alder reaction of **1c** with a 10-fold excess of 1,3-dimethylcyclopentadiene (4:1 mixture of **2c** and the 1,4-dimethyl isomer **2d**) yielded only the cycloadducts of **2c**. The main endo product was proven to be **3e** by degradation to the corresponding iodo lactone as described above. For this compound the (1*S*) configuration as depicted in formula **5c** was again concluded from comparison of the CD spectrum with that of *ent*-**5a**. The configuration of cycloadduct **3e** was independently proven by two other methods. One was based on the $TiCl_4$-catalyzed Diels–Alder reaction of *O*-acryloyl-D-pantolactone (**9**) with the

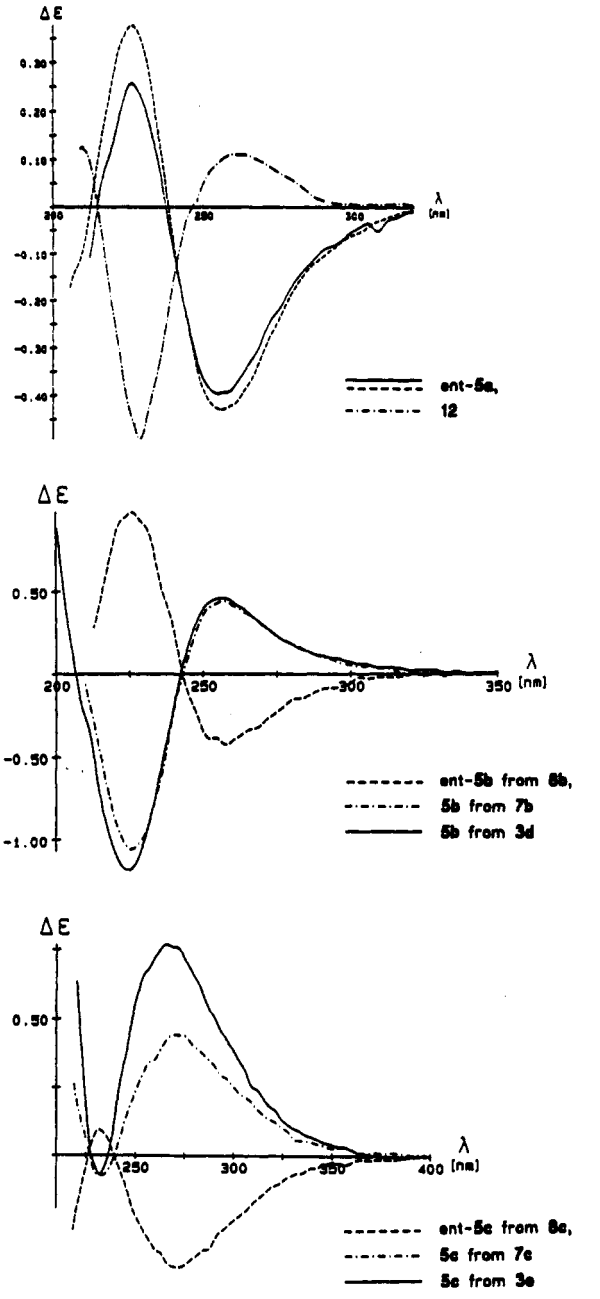


Figure 1. CD spectra of the iodo lactones.

1,3-/1,4-dimethylcyclopentadiene mixture (**2c**/**2d**)[13] which was expected to follow the stereochemistry well-established for cyclopentadiene (**2a**) by Helmchen.[17] In the event, from **9** and a 10-fold excess of the 4:1 mixture of **2c** and **2d** were obtained two products. The main component was shown to be an endo cycloadduct of 1,4-dimethylcyclopentadiene (**2c**) which was assigned structure **11** based on its degradation to iodo lactone **12** (cf. the CD curve in Figure 1). In addition, in very small amounts an HCl addition product of an endo adduct of **2c** was isolated which on the basis of Helmchen's results[17] was assigned the configuration depicted in formula **10**. At the beginning the outcome of the $TiCl_4$-catalyzed reaction was rather surprising but it finds its explanation in the very pronounced acid sensitivity of 1,3-dimethylcyclopentadiene (**2c**). Under the reaction conditions polymerization is obviously faster than cycloaddition.[18] In agreement with

(13) (a) Acheson, R. M.; Robinson, R. *J. Chem. Soc.* **1952**, 1127–1133. (b) McLean, S.; Haynes, P. *Tetrahedron* **1965**, *21*, 2313–2327.

(14) Stothers, J. B.; Tan, C. T.; Teo, K. C. *Can. J. Chem.* **1973**, *51*, 2893–2901. Brouwer, H.; Stothers, J. B.; Tan, C. T. *Org. Magn. Reson.* **1977**, *9*, 360–366.

(15) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17–22. Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 26–31.

(16) Samples obtained from Prof. Kirmse: Kirmse, W.; Siegfried, R. *J. Am. Chem. Soc.* **1983**, *105*, 950–956. Prof. Helmchen: Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *24*, 2191–2194.

(17) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095–3098.

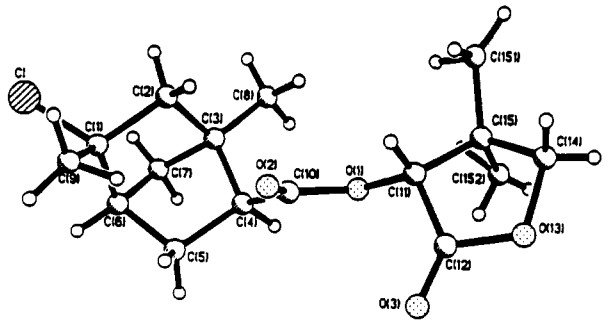


Figure 2. X-ray structure of 10.

Table I. Endo Product Ratios of the Diels–Alder Reactions of 1b and 1c with 2a–2c. Temperature Dependence and $\Delta\Delta H^{\ddagger}$ Determined by Analysis Using Eq 1

educts	products	temperature (°C)	product ratio	$\Delta\Delta H^{\ddagger}$ (kcal/mol)
1c + 2a	3c + 4c	25	3.04:1	
		0	3.54:1	0.89 ± 0.04
		−20	3.96:1	
1c + 2b	3d + 4d	25	6.25:1	
		0	8.12:1	1.55 ± 0.08
		−20	9.98:1	
1c + 2c	3e + 4e	25	5.64:1	
		0	7.29:1	1.74 ± 0.04
		−20	9.52:1	
1b + 2a	3b + 4b	25	13:1[3]	
		−20	20:1[3]	1.24 ± 0.11[19]
		−55	28:1[3]	

this, the two cycloadducts of 1,3-dimethylcyclopentadiene (7c and 8c) were formed practically exclusively when the Diels–Alder reaction was performed in the absence of a Lewis acid. One of these cycloadducts yielded 10 on HCl addition and should, therefore,[17] have the configuration depicted in 7c. The CD curves of the iodo lactones 5c and ent-5c obtained from 7c and 8c, respectively, by saponification and treatment with KI/I_2 confirmed the correctness of the configurational assignment based on the result of the $TiCl_4$-catalyzed Diels–Alder reaction. A definite proof of the configuration came from an X-ray crystallographic analysis of 10, the result of which is shown in Figure 2.

A final comment should be made concerning the CD method used in our study for the configurational assignment of the methyl-substituted cycloadducts. The degradation to the iodo lactones 5b, ent-5b, 5c, ent-5c, and 12 is easily executed and the correctness of the assignments based on comparison with the CD spectrum of ent-5a (see Figure 1) has been confirmed by other methods.

Diels–Alder Reactions of 1c with 2a–2c. Diastereomeric Ratios of the Endo Products and Their Temperature Dependencies. The Diels–Alder reactions of 1c with 2a–2c have been performed at three temperatures (−20, 0, and 25 °C). The product ratios have been determined by capillary GC. The enthalpy differences for the formation of the endo products 3 and 4 were calculated by eq 1. The results are collected in Table I. Included also is an analysis of the results reported by Masamune for the reaction of 1b with 2a.

$$\ln (k_3/k_4) = \ln (A_3/A_4) - \Delta\Delta E_a/RT \qquad (1)$$

The results clearly show that the diastereomeric ratio increases in going from 2a to 2b and 2c, respectively, which means that transition state TS2 must be involved in the formation of the minor endo products 4. A rigorous evaluation of the kinetic results was performed using force field calculations.

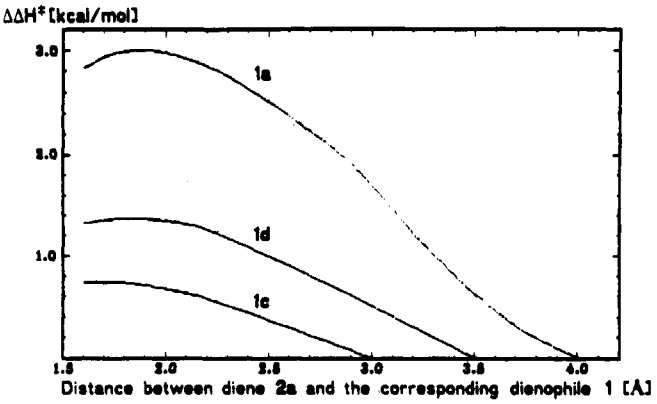


Figure 3. Calculated $\Delta\Delta H^{\ddagger}$ values for the Diels–Alder reactions of cyclopentadiene (2a) with dienophiles 1a, 1d, and 1c (for details, see text).

Molecular Mechanics Force Field Calculations. In the first trial the enthalpy differences of TS1 and TS2 for the reaction of 2a and the dienophiles 1c and 1d were calculated using the ordinary MM2ERW force field.[20] The components were taken as educt-like and were oriented in two parallel planes varying the distance between 1.6 and 4.0 Å. The torsional angle (C-2)C-3–C-4(OH) was fixed at 180°. The result is shown in Figure 3. In the range around 2 Å there is (at least as far as 1c and 1d are concerned) only a small variation in the $\Delta\Delta H^{\ddagger}$ values, and furthermore, the dependence of $\Delta\Delta H^{\ddagger}$ on the distance is practically identical (parallel curves). This means that an exact knowledge of the distance between diene and dienophile is not important for this type of treatment.

The calculated enthalpy differences (for the 1c and 1d examples) are fully in accord with experimental values. For 1c about 0.6 kcal/mol was calculated (at 2.25 Å) and 0.89 ± 0.04 kcal/mol was found. Comparison of the calculated value for the isopropyl-substituted dienophile 1d (about 1.3 kcal/mol) with the experimental result obtained for cyclohexyl-substituted 1b from Masamune's publication[3] (1.24 ± 0.11 kcal/mol) again showed the excellent agreement. This result demonstrates that the stereoselectivity in the Diels–Alder reactions of 2a with 1b and 1c, respectively, is solely governed by transition states TS1 and TS2. The enthalpy difference between these two transition states is nicely accounted for by the force field calculations.

What remained to be analyzed was the question raised in the Introduction of a possible electronic contribution favoring TS1 and TS2 versus the transition states with a transoid dienophile moiety (TS3 and TS4). Several problems needed consideration. The first was to describe correctly by force field calculations the structure of the α-hydroxy keto unit for which a strong internal hydrogen bond has been found by Masamune.[3] According to the results of X-ray analyses,[21] microwave spectra,[22] and theoretical calculations,[23] all atoms of the ketol unit should be in one plane. This geometry could not be realized as

(18) Aso, C.; Ohara, O. *Makromolek. Chem.* **1969**, *127*, 78–93.
(19) The results are taken from Masamune's publication.[3] An analysis using eq 1 gave the following expression:

$$\ln (k_{3b}/k_{4b}) = (0.50 \pm 0.22) + (1.24 \pm 0.11)\ \text{kcal}/RT\ \text{mol}$$

(20) Roth, W. R.; Adamczak, O.; Breuckmann, R.; Lennartz, H.-W.; Boese, R. *Chem. Ber.* **1991**, *124*, 2499–2521.
(21) Hünig, S.; Marschner, C.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1989**, *122*, 2131–2138.
(22) Blom, C. E.; Bauder, A. *J. Am. Chem. Soc.* **1982**, *104*, 2993–2996.
(23) (a) Newton, M. D.; Jeffrey, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 2413–2421. (b) Bursi, R.; Devlin, F. J.; Stephens, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 9430–9432.

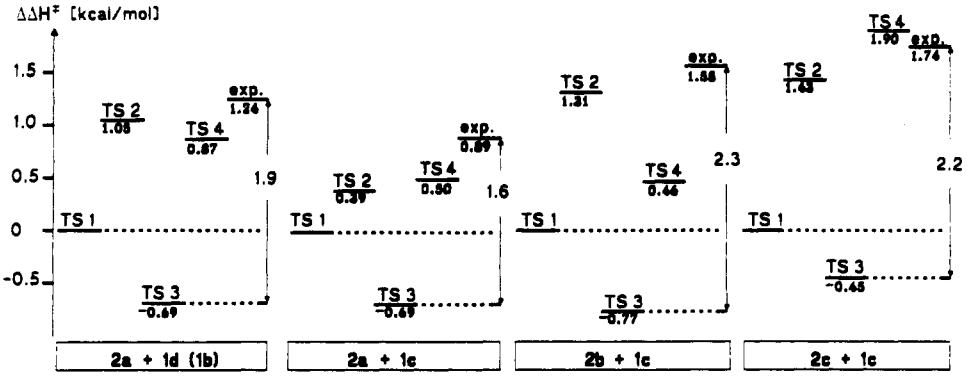


Figure 4. Calculated $\Delta\Delta H^{\ddagger}$ values for the Diels–Alder reactions of dienophiles **1b** and **1c** with dienes **2a–2c** (for details, see text).

an energy minimum using the common MM2 force field for which it is known that hydrogen bonding is accounted for only qualitatively. When the torsional angle (C-2)C-3–C-4(OH) was fixed at 180° as described above, the ketol unit formed an envelope with the hydrogen out of the plane of the other "ring" atoms, turned toward the hydrogen substituent at C-4 (torsional angle (C-3)C-4–O(H): −44°). Furthermore, in agreement with previous observations, when the calculated energy of this structure was compared with that of the structure lacking the hydrogen bond (torsional angle (C-3)C-4–O(H): 180°) the stabilizing effect of the hydrogen bond was found to be too small (about 2 kcal/mol).[24] Allinger has developed a modified version which reproduces hydrogen bonds fairly well when compared with ab initio calculations and experimental values.[25] This correction is part of MM3.[26] However, MM3 fails to describe the rotational barrier of enone moieties correctly. Therefore, the torsional potential for the torsional angle (O)C-3–C-4(O) was taken from MM3 and implemented into MM2ERW and in the same way the torsional potential of (C-2)C-3–C-4(O) was altered. Furthermore, the dipole moment of the O–H bond was increased (see Experimental Section). With these modifications MM2ERW reproduced correctly the planar structure of the α-hydroxy keto unit (without fixing any torsional angle).

For the calculation of the energies of the four transition-state geometries (TS1–TS4) the components were taken as educt-like (early transition states). Unsymmetric geometries were calculated using the bond lengths of the forming bonds (2.3 and 2.1 Å) reported by Houk for the acrolein-butadiene system. The energy differences between TS1 and the other transition state geometries are summarized in Figure 4.

Discussion

Comparison of Figure 4 with Table I shows that the modified force field nicely accounts for the observed stereoselectivities of **1c** and **1d** (the calculated value for **1d** is compared with Masamune's **1b** result) in the reaction with cyclopentadiene (**2a**) assuming that only TS1 and TS2 are involved in the product formation. This supports the result summarized in Figure 3 that product formation appears to occur only via reaction channels that pass transition-state geometries of type TS1 and TS2, i.e., with cisoid conformation of the dienophile. In agreement with this conclusion the selectivity increases in going from cyclopentadiene (**2a**) to the 1-methyl-substituted analogues **2b** and **2c**, respectively (see Introduction). The increase in selectivity is again nicely accounted for by the calculated enthalpy differences of TS1 and TS2. However, Figure 4 also shows that, if only *steric interactions* were responsible for the relative energies of the various transition states, TS3 should have the *lowest* energy. This is, of course, in contrast to the experimental results and the conclusions arrived at above which show that TS1 and TS2 are energetically below TS3. Obviously, there exists an *electronic* stabilization that *favors the cisoid geometry of the dienophile in the transition states.* This stabilization is at least in the range of 1.6–2.3 kcal/mol (see Figure 4, difference between the experimental $\Delta\Delta H^{\ddagger}$ and the enthalpy of TS3, relative to TS1), in excellent agreement with the value reported by Houk in his paper referred to above. Our results thus nicely confirm the conclusions drawn by Houk and co-workers from their calculations[1] as summarized in the Introduction.

Finally, we also calculated the relative stabilities of the cisoid and transoid ground-state conformations of the dienophiles **1a–c**. The transoid conformation was found to be more stable by about 0.2 (**1a**) and 0.7 kcal/mol (**1b** and **1c**) in contrast to the previous assumptions.[3] From this result it is obvious that the type of purely steric explanation[3] to account for the observed stereoselectivities is not adequate. Electronic effects in the transition states as discussed above play a major role in determining product ratios.

Experimental Section

All O_2- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe. Small-scale reactions were performed in Wheaton serum bottles sealed with aluminum caps with open top and Teflon-faced septum (Aldrich). *Usual workup* means partitioning the reaction mixture between an aqueous phase and an organic solvent (given in parentheses), drying the combined organic solutions over Na_2SO_4, and removal of solvent by distillation using a rotatory evaporator (bath temperature 40 °C, if not otherwise stated). Solvents were purified by standard techniques. The following materials and methods were used for chromatographic separations: preparative gravitational liquid chromatography (LC): silica gel (ICN Biomedicals Silica 63-100); medium-pressure liquid chromatography (MPLC): 31.0-cm × 2.5-cm glass tubes, 50-μm silica gel (Amicon), Duramat pump (CfG), Thomachrom UV detector (Reichelt); analytical TLC: Merck precoated silica gel 60 F_{254} plates (0.2 mm), spots were identified under a UV lamp (Camag 29 200) and by spraying with a 2.22 mol/L H_2SO_4 solution which contained $Ce(SO_4)_2 \cdot 4H_2SO_4$ (10 g/L) and $H_3[PO_4(Mo_3O_9)_4] \cdot xH_2O$ (25 g/L) and heating at 140 °C. For NMR and MS equipment, see ref 27. The ^1H

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NMR data consist of chemical shifts and coupling constants and also of integration results (if they could be definitely identified). For CD equipment, see ref 28.

1-Methylcyclopentadiene (2b). To a solution of cyclopentadiene (**2a**, 2.0 mL, 1.6 g, 24 mmol) in toluene (10 mL) was added CH_3MgBr (1.5 M solution in toluene–THF (3:1), 20 mL, 30 mmol), and the mixture was heated to 80 °C for 2 h. THF was then evaporated at normal pressure (controlled by ^1H NMR). The residual toluene solution was treated at −20 °C with Me_2SO_4 (2.5 mL, 3.3 g, 26 mmol) for 1 h. Distillation at 400 Pa (bath temperature: −196 °C → 20 °C, temperature of the trap: −80 °C) gave a toluene solution of **2b** which was kept at −20 °C before being used in the Diels–Alder reactions. The sample was free of 2-methylcyclopentadiene as determined by GC (71.5-m × 0.278-mm glass capillary column (fractonitrile III), 50 °C, carrier gas: H_2): retention times 672 (**2a**), 743 (2-methylcyclopentadiene), 767 (**2b**), 972 (THF), 1494 s (toluene): ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (d, 3 H, CH_3-6), 2.88 (q, 2 H, CH_2-5), 6.13 (m, 1 H, 2-H), 6.23 (m, 1 H, 4-H), 6.40 (m, 1 H, 3-H); $J_{6,2}$ = 1.5 Hz, $J_{2,3}$ = 2.0 Hz, $J_{2,5}$ = 1.5 Hz, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 1.5 Hz.

Methyl (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanoate (13b). To (*S*)-methyl lactate (**13a**, 1.00 mL, 1.09 g, 10.5 mmol) were added DMF (25 mL) and a solution of imidazole (1.06 g, 15.6 mmol) in DMF (5 mL). At 0 °C the mixture was treated with a solution of *tert*-butyldimethylchlorosilane (1.97 g, 13.1 mmol) in DMF (7 mL). The mixture was allowed to warm to 20 °C and was then stirred for 3.5 h. Addition of saturated aqueous NaCl, the usual workup (Et_2O, solvent evaporation at 20 °C/2000 Pa), and LC (hexanes/acetone (30:1)) provided **13b** (2.27 g, 99%): ^1H NMR (80 MHz, $CDCl_3$) δ 0.02 and 0.06 (2 s, 6 H, OSi^tBuMe_2), 0.88 (s, 9 H, OSi^tBuMe_2), 1.36 (d, 3 H, CH_3-1), 3.68 (s, 3 H, OCH_3), 4.29 (q, 1 H, 2-H), $J_{1,2}$ = 7 Hz; IR (CCl_4) 1760, 1740 cm^{-1}; MS 203 (1.5), 161 (57), 133 (36), 103 (8), 89 (100), 73 (34), 59 (24); $[\alpha]^{20}_D$ −26.9 (*c* 1.89 in CCl_4); $C_{10}H_{22}O_3Si$ (218.4); HRMS calcd for $C_9H_{19}O_3Si$ 203.1104, found 203.1111.

Lithium (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanoate (13c). A mixture of **13b** (243.9 mg, 1.117 mmol) and $LiOH{\cdot}xH_2O$ (41.3 mg, 0.983 mmol) in H_2O (50 mL) was vigorously stirred at 20 °C for 16.5 h. After extraction with CH_2Cl_2 the aqueous layer was freeze-dried to give Li-salt **13c** (200.6 mg, 97% based on $LiOH{\cdot}xH_2O$): ^1H NMR (80 MHz, D_2O) δ 0.07 (s, 6 H, OSi^tBuMe_2), 0.85 (s, 9 H, OSi^tBuMe_2), 1.29 (d, 3 H, CH_3-1), 4.20 (q, 1 H, 2-H), $J_{1,2}$ = 7 Hz; $[C_9H_{19}O_3Si^-]Li^+$ (210.3).

(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-3-one (14). To THF (5 mL) were added vinyl bromide (0.3 mL, 0.46 g, 4.3 mmol) and pentane (5 mL) at −78 °C. The solution was cooled to −90 °C, and then ^{t}butyllithium (1.5 M solution in hexanes, 5 mL, 7.5 mmol, precooled to −78 °C) was added dropwise. After being stirred for 1.5 h at −90 °C → −78 °C, the mixture was permitted to warm to −40 °C and then treated with a solution of **13c** (446 mg, 2.12 mmol, dried overnight at 50 °C/133 Pa over P_4O_{10}) in pentane. The mixture was left for 4 h at −40 °C → 20 °C, and then aqueous NH_4Cl (30 mL) was added. Usual workup (CH_2Cl_2, solvent evaporation at 50 °C to 70 °C, normal pressure) yielded the rather volatile **14** that was purified by LC (pentane/CH_2Cl_2 (5:1)) to give the pure compound (334 mg, 73%): ^1H NMR (80 MHz, $CDCl_3$) δ 0.07 (s, 6 H, OSi^tBuMe_2), 0.90 (s, 9 H, OSi^tBuMe_2), 1.30 (d, 3 H, CH_3-5), 4.29 (q, 1 H, 4-H), 5.64–7.05 ABX system (5.64–5.82 X, 1 H, 1-H, 6.22–6.49 B, 1 H, 1-H', 6.70–7.05 A, 1 H, 2-H); $J_{4,CH3-5}$ = 5 Hz, $J_{A,B}$ = 18 Hz, $J_{A,X}$ = 10 Hz, $J_{B,X}$ = 3 Hz; IR ($CDCl_3$) 1700, 1615 cm^{-1}; MS 199 (3), 159 (27), 157 (87), 142 (3), 115 (23), 103 (10), 85 (13), 75 (44), 73 (100); $[\alpha]^{20}_D$ −3.5 (*c* 1.99 in $CHCl_3$); $C_{11}H_{22}O_2Si$ (214.4); HRMS calcd for $C_{10}H_{19}O_2Si$ 199.1154, found 199.1154.

(*S*)-4-Hydroxypent-1-en-3-one (1c). To a solution of **14** (334 mg, 1.56 mmol) in THF–H_2O (8:1, 1.5 mL) at 0 °C was added dropwise a solution of tetrabutylammonium fluoride (1 M in THF, 3.0 mL, 3.0 mmol). The mixture was left at 0 °C for 3 h, and was then allowed to warm to 20 °C. Usual workup (CH_2Cl_2, solvent evaporation at 50–70 °C, normal pressure), followed by LC (CH_2Cl_2/pentane (40:1)) gave **1c** (105 mg, 67%): ^1H NMR (80 MHz, $CDCl_3$) δ 1.39 (d, 3 H, CH_3-5), 3.50 (d, 1 H, OH), 4.34–4.68 (m, 1 H, 4-H), 5.82–5.08 (1 H, vinyl H) and 6.43–6.53 (2 H, vinyl H); $J_{4,5}$ = 7 Hz, $J_{4,OH}$ = 5 Hz; IR ($CHCl_3$) 3490, 1695 cm^{-1}; MS 100 (2.5) [M^+], 57 (12), 56 (54), 55 (34), 45 (100), 43 (37); $[\alpha]^{20}_D$ +62.0 (*c* 1.02 in $CHCl_3$); HRMS calcd for $C_5H_8O_2$ 100.0524, found 100.0526. The ee determination using *rac*-**1c** (prepared as described above) as reference sample was performed by GC (28-m × 0.25-mm glass capillary column (heptakis(2,6-di-*O*-methyl-3-*O*-trifluoroacetyl)-β-cyclodextrin in OV 1701, 90 °C, carrier gas: H_2); retention times: 5.5 ((*R*)-**1c**), 7.0 min ((S)-**1c**). The ee of (*S*)-**1c** was >99%.

Diels–Alder Reaction of Cyclopentadiene (2a) with 1c. The reaction was performed exactly as described below for the reaction of **2b** with **1c**. The product ratios were determined by GC (7-m × 0.28-mm glass capillary column (Marlophen 814), 105 °C, carrier gas: H_2); retention times: 428 (major exo isomer), 468 (minor exo isomer), 535 (**3c**), and 629 s (**4c**). The results are collected in Table II. An analysis using eq 1 gave the following expression:

$$\ln (k_{3c}/k_{4c}) = -(0.37 \pm 0.08) + (0.89 \pm 0.04)\ \text{kcal}/RT\ \text{mol}.$$

Table II. Product Ratios (in %) from the Diels–Alder Reaction of 1c with 2a

T (°C)	3c	4c	major exo isomer[a]	minor exo isomer[a]
25	63.2	20.8	11.2	4.7
0	67.3	19.0	9.8	3.8
−20	70.5	17.8	8.5	3.1

[a] The configuration was not determined.

(2*S*)-1-((1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (3c): ^1H NMR (Table V); $J_{CH(OH),CH_3}$ = 7.0 Hz; ^{13}C NMR (Table IV), IR (CCl_4) 1700 cm^{-1}; MS 166 (4) [M^+], 148 (2), 121 (27), 101 (15), 93 (28), 66 (71), 55 (100); CD λ_{max} (Δε) 279 (+1.18), 200 (<0); $C_{10}H_{14}O_2$ (166.2).

(2*S*)-1-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (4c): ^1H NMR (Table V); $J_{CH(OH),CH_3}$ = 7.0 Hz; ^{13}C NMR (Table IV), IR (CCl_4) 1700 cm^{-1}; MS 166 (3) [M^+], 148 (15), 121 (18), 93 (20) 66 (43), 55 (100); CD λ_{max} [nm] (Δε) 285 (+0.21), 200 (>0); $C_{10}H_{14}O_2$ (166.2).

(2*S*)-1-(Bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (Minor Exo Isomer, Configuration Not Determined). The minor exo isomer could not be obtained completely pure: ^1H NMR (Table V) $J_{CH(OH),CH_3}$ = 7.0 Hz; ^{13}C NMR (Table IV); IR (CCl_4) 1700 cm^{-1}; MS (from GC/MS, GC conditions as described in the product analysis of the Diels–Alder reaction) 166 (2) [M^+], 123 (4), 121 (7), 101 (19), 67 (50), 66 (100); $C_{10}H_{14}O_2$ (166.2).

(2*S*)-1-(Bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (major exo isomer, configuration not determined): ^1H NMR (Table V); $J_{CH(OH),CH_3}$ = 7.0 Hz; ^{13}C NMR (Table IV); IR (CCl_4) 1700 cm^{-1}; MS 166 (3) [M^+], 148 (2), 121 (25), 101 (25), 93 (33), 66 (76), 55 (100); $C_{10}H_{14}O_2$ (166.2).

Configurational Assignment of 3c (the Main Endo Product of 1c and 2a) by Degradation to 6b. To a solution of **1c** (25 mg, 0.16 mmol) in THF (4.50 mL) was added a solution of $NaIO_4$ (130 mg, 0.61 mmol) in H_2O (1.9 mL). The reaction mixture was stirred for 8 h at 20 °C. After filtration (SiO_2, hexanes/ethyl acetate (10:1)) and solvent evaporation the residue was dissolved in Et_2O (2.0 mL) and MeOH (2.0 mL) and then treated with diazomethane in Et_2O until a slightly yellow color persisted (15 min). Et_2O (50 mL) was added, and the organic layer was washed with saturated NaCl (3 × 30 mL). Usual workup (Et_2O) and LC (hexanes/ethyl acetate (50:1)) yielded **6b** (10 mg, 44%): ^1H NMR (Table V); ^{13}C NMR (Table IV); $[\alpha]^{20}_D$ −107 (*c* 0.19 in ethanol); CD (CH_3CN): λ_{max} [nm] (Δε) 223 (0.326).

ent-**6b** was obtained from nonracemic iodo lactone *ent*-**5a** as described by Berson et al.[29]: $[\alpha]^{20}_D$ +118 (ethanol);[30] CD (CH_3CN) λ_{max} [nm] (Δε) 220 (−0.43).

Diels–Alder Reaction of 1-Methylcyclopentadiene (2b) with 1c. A solution of **1c** (105 mg, 1.05 mmol) in toluene (6 mL)

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(30) The highest reported rotation of *ent*-**6b** is $[\alpha]_D$ +141 (in ethanol).[29]

Table III. ^{13}C NMR Spectral Data (DEPT) of 3c, 4c, the Major Exo Isomer (A),[a] the Minor Exo Isomer (B),[a] *endo*-Norbornenecarboxylic Acid (6a), *exo*-Norbornenecarboxylic Acid (C),[b] 6b, and Methyl *exo*-Norbornenecarboxylate (D)[b]

	3c	4c	A	B	6a	C	6b	D
C-1	46.5*	45.9	46.3*	45.9*	45.7	46.8	45.6	46.5
C-2	46.3*	43.6	45.5*	45.7*	43.4	43.3	43.1	42.9
C-3	27.7	30.1	31.1	29.8	29.2	30.4	29.2	30.3
C-4	42.7	42.6	41.6	41.7	42.6	41.7	42.4	41.5
C-5	138.4	137.3	138.0	138.6	137.9	138.2	137.6	137.9
C-6	130.4	132.6	135.9	135.7	132.5	135.8	132.2	135.6
C-7	50.2	49.6	46.3*	47.0	49.7	46.5	49.5	46.3
C=O	212.5	213.7	+	214.9	181.3	183.1	175.0	176.5
OCH_3							51.3	51.6
-CHOH	71.5	72.4	72.8	72.4				
$-CH(OH)CH_3$	20.5	19.7	20.1	19.9				

*Assignments (in one column) may have to be reversed. +Signal could not be identified. [a]The configuration was not determined. [b]Formula not shown in the text.

Table IV. ^1H NMR Spectral Data (δ Values, 400 MHz, $CDCl_3$, ^1H-^1H COSY) of 3c, 4c, the Major Exo Isomer (A),[a] the Minor Exo Isomer (B),[a] 6b, and Methyl *exo*-Norbornenecarboxylate (D, cf. Table III)[b]

	3c	4c	A	B[c]	6b	D	D[d]
1-H	3.20	3.23	2.96+	2.97+	3.14	3.01	2.99
2x-H	3.17	3.13			2.89		
2n-H			2.48	2.47		2.20	2.15
3x-H	1.60	1.28	1.93	1.73	1.36	1.90	1.97
3n-H	1.76	1.97	1.25	1.29	1.85	1.34	1.18
4-H	2.95	2.93	2.89+	3.00+	2.84	2.90	2.65
5-H	6.21	6.20	6.12*	6.12*	6.12	6.07	5.98
6-H	5.77	5.88	6.18*	6.18*	5.85	6.11	5.95
7a-H	1.34	1.31	1.33	1.33	1.22	1.34	1.33
7s-H	1.47	1.45	1.56	1.55	1.36	1.50	1.67
OCH_3					3.54	3.66	3.38
CHOH	4.35	4.19	4.42	4.31			
$CH(OH)CH_3$	1.42	1.41	1.38	1.45			

*,+Assignments (in one column) may have to be reversed. [a]The configuration was not determined. [b]Formula not shown in the text. [c]Obtained from the spectrum of a 1:1 mixture of A and B by subtraction of the A signals. [d]Spectrum in C_6D_6 solution.

Table V. Product Ratios (in %) from the Diels–Alder Reaction of 1c and 2b

T (°C)	3d	4d	major exo isomer[a]	minor exo isomer[a]
25	67.7	11.2	12.8	8.2
0	72.2	9.0	11.6	7.1
-20	76.1	7.7	10.0	6.2

[a]The configuration was not determined.

was divided into three equal parts which were set to different temperatures (25, 0, and -20 °C) and kept at these temperatures for 30 min. Then to each of the reaction flasks a toluene solution of freshly prepared 1-methylcyclopentadiene (**2b**, about one third of the amount prepared as described above, precooled to the reaction temperatures) was added. The reactions were stopped when 1c was completely consumed (TLC analysis). Reaction times: 12.5 h (14 h in a second experiment) at 25 °C, 43 h (38.5 h) at 0 °C, 7 d (11 d) at -20 °C. Product ratios were determined by GC (7-m × 0.28-mm glass capillary column (Marlophen 814), 88 °C, carrier gas: H_2); retention times: 600 (major exo isomer), 855 (**4d**), 905 (**3d**), 1075 s (minor exo isomer). The results are collected in Table V. An analysis using eq 1 gave the following expression:

$$\ln (k_{3d}/k_{4d}) = -(0.78 \pm 0.12) + (1.55 \pm 0.08)\ \text{kcal}/RT\ \text{mol}.$$

The combined reaction mixtures were then separated by MPLC (toluene/ethyl acetate (25:1)) to give the major exo isomer (7.5 mg), a fraction containing **4d** and an unknown compound (10.0 mg), a 91:9 mixture (GLC) of **3d** and the minor exo isomer (89.8 mg), and a fraction containing all four cycloadducts (26.8 mg). The total isolated yield of all cycloadducts was 134.1 mg, 71%. Further purification of the **4d**-containing fraction by MPLC (hexanes/toluene/ethyl acetate (15:3:1)) allowed **4d** to be enriched to 60% purity (GC).

(2*S*)-2-Hydroxy-1-(1-methylbicyclo[2.2.1]hept-5-en-2-yl)-propan-1-one (major exo isomer, configuration not determined): ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (m, 1 H, 7a-H), 1.20 (s, 3 H, 1-CH_3), 1.31 (d, 3 H, $CH(OH)CH_3$), 1.39 (ddd, 1 H, 7s-H), 1.86–1.92 (m, 2 H, 3x- und 3n-H), 2.45 (ddd, 1 H, 2n-H), 2.89 (broad s, 1 H, 4-H), 3.62 (d, 1 H, OH), 4.24–4.32 (dq, 1 H, CH(OH)), 5.84 (d, 1 H, 6-H), 6.16 (dd, 1 H, 5-H); $J_{2n,3x}$ = 4.5 Hz, $J_{2n,3n}$ = 8.5 Hz, $J_{2n,7a}$ = 1.5 Hz, $J_{5,4}$ = 3 Hz, $J_{5,6}$ = 6 Hz, $J_{CH(OH),CH_3}$ = 7 Hz, $J_{CH,OH}$ = 5 Hz; IR ($CHCl_3$) 1705 cm^{-1}; MS 180 (3) [M^+], 162 (1.5), 135 (12), 107 (10), 101 (9), 93 (20), 80 (100), 79 (37), 55 (68), 45 (44); $C_{11}H_{16}O_2$ (180.2).

(2*S*)-2-Hydroxy-1-((1*R*,2*R*,4*R*)-1-methylbicyclo[2.2.1]-hept-5-en-2-yl)propan-1-one (4d). The following ^1H NMR signals (400 MHz, $CDCl_3$) were unequivocally identified: δ 1.35 (d, $CH(OH)CH_3$), 1.38 (s, 1-CH_3), 2.39 (ddd, 3x-H), 2.81 (broad s, 1 H, 4-H, $W_{1/2}$ = 8 Hz), 2.90 (dd, 2x-H), 3.50 (d, 1 H, OH), 4.13 (m, 1 H, CH(OH)), 6.00 (d, 1 H, 6-H), 6.05 (dd, 5-H); $J_{2x,3x}$ = 7.5 Hz, $J_{2x,3n}$ = 4 Hz, $J_{3x,3n}$ = 9 Hz, $J_{3x,4}$ = 3 Hz, $J_{5,4}$ = 2.5 Hz, $J_{5,6}$ = 4 Hz, $J_{CH(OH),CH_3}$ = 5 Hz, $J_{CH,OH}$ = 3.5 Hz; GC/MS 135 (6), 107 (5), 101 (3), 93 (15), 80 (100), 55 (62), 43 (25), 40 (39); $C_{11}H_{16}O_2$ (180.2).

(2*S*)-2-Hydroxy-1-((1*S*,2*S*,4*S*)-1-methylbicyclo[2.2.1]-hept-5-en-2-yl)propan-1-one (3d): ^1H NMR (400 MHz, $CDCl_3$) δ 1.27–1.43 (3 H, 7s-, 7a-, and 3n-H), 1.35 (d, 3 H, $CH(OH)CH_3$), 1.38 (s, 3 H, 1-CH_3), 2.04 (ddd, 1 H, 3x-H), 2.85 (broad s, 1 H, 4-H, $W_{1/2}$ = 8 Hz), 2.95 (dd, 1 H, 2x-H), 3.55 (d, 1 H, OH), 4.24–4.32 (dq, 1 H, CH(OH)), 5.68 (d, 1 H, 6-H), 6.21 (dd, 1 H, 5-H); $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 5 Hz, $J_{3x,3n}$ = 11.5 Hz, $J_{3x,4}$ = 4 Hz, $J_{5,4}$ = 3 Hz, $J_{5,6}$ = 5.5 Hz, $J_{CH(OH),CH_3}$ = 7 Hz, $J_{CH,OH}$ = 5 Hz; IR ($CHCl_3$) 1705 cm^{-1}; MS 180 (16) [M^+], 162 (5), 147 (6), 135 (50), 107 (23), 101 (20), 93 (64), 80 (100), 79 (64), 55 (95), 45 (40), 27 (38); $C_{11}H_{16}O_2$ (180.2).

Uncatalyzed Diels–Alder Reaction of 1-Methylcyclopentadiene (2b) with *O*-Acryloyl-D-pantolactone (9). Solutions of **9**[17] (87.7 mg, 0.476 mmol) in toluene (2 mL) and of freshly prepared diene **2b** (2 mL of a toluene solution, vide supra) were mixed and stirred at 20 °C for 14 h. Solvent evaporation and MPLC (hexanes/ethyl acetate (10:1)) yielded **8a** (47.3 mg) and **7a** (47.7 mg) and 12.3 mg of a mixture of both compounds. Total yield: 107.3 mg (85%).

***O*-((1*S*)-1-Methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (7a):** ^1H NMR (80 MHz, $CDCl_3$) δ

1.48 (s, 3 H, 1-CH_3), 1.20–1.60 (3n-H, 7s-H, 7a-H), 2.13 (ddd, 1 H, 3x-H), 2.81 (dd, 1 H, 2x-H), broad signal at 2.83 (1 H, 4-H), 5.73 (d, 1 H, 6-H), 6.20 (dd, 1 H, 5-H), pantolactone part: 1.10 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 3.98 (s, 2 H, CH_2), 5.28 (s, 1 H, CH(OR)); $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 4 Hz, $J_{3x,3n}$ = 13 Hz, $J_{3x,4}$ = 3 Hz, $J_{5,6}$ = 8 Hz, $J_{5,4}$ = 3 Hz; IR (CCl_4) 1800, 1750 cm^{-1}; MS 264 (0.2) [M^+], 185 (1.5), 135 (1.8), 91 (4), 80 (100), 55 (30), 41 (10); $[\alpha]^{20}_D$ −34.6 (*c* 1.93 in $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_4$ (264.3): C, 68.16; H, 7.63. Found: C, 68.01; H, 7.65.

***O*-((1*R*)-1-Methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (8a)**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (m, 1 H, 7a-H), 1.36 (ddd, 1 H, 7s-H), 1.52 (s, 3 H, 1-CH_3), 1.56 (ddd, 1 H, 3n-H), 2.09 (ddd, 1 H, 3x-H), 2.77 (dd, 1 H, 2x-H), 2.85 (broad s, 1 H, 4-H), 5.87 (d, 1 H, 6-H), 6.18 (dd, 1 H, 5-H), pantolactone part: 1.10 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 3.99 and 4.04 (2d, AB system, CH_2, $J_{H,H}$ = 9 Hz), 5.31 (s; 1 H, CH(OR)); $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 4 Hz, $J_{3x,3n}$ = 12 Hz, $J_{3x,4}$ = 3.5 Hz, $J_{3n,7s}$ = 3 Hz, $J_{5,4}$ = 3 Hz, $J_{5,6}$ = 6 Hz, $J_{7s,7a}$ = 8 Hz, $J_{7s,4}$ = 1.5 Hz; IR (CCl_4) 1800, 1750 cm^{-1}; MS 264 (0.3) [M^+], 185 (1.6), 135 (1.8), 91 (5), 80 (100), 55 (35), 41 (10); $[\alpha]^{20}_D$ +42.6 (*c* 1.94 in $CHCl_3$); Anal. Calcd for $C_{15}H_{20}O_4$ (264.3): C, 68.16; H, 7.63. Found: C, 68.30; H, 7.71.

(1*S*)-6-*endo*-Hydroxy-5-*exo*-iodo-1-methylbicyclo[2.2.1]-heptane-2-*endo*-carboxylic Acid Lactone (*ent*-5b). To **8a** (45.7 mg, 0.173 mmol) was added LiOH·xH_2O (1 M in H_2O, 0.7 mL) and THF (1 mL), and the mixture was stirred for 2 days at 20 °C. Then the pH was adjusted to 4 with 1 M HCl, and the reaction mixture was treated with $NaHCO_3$ until pH 8 was reached. I_2 (47.9 mg, 0.189 mmol) and KI (180.3 mg, 1.086mmol) were added, and the mixture was left at 20 °C for 19 h. Extraction with CH_2Cl_2, followed by washing the organic layer with 10% aqueous $Na_2S_2O_3$, drying, solvent evaporation, and LC (hexanes/ethyl acetate (20:1)) afforded 25.9 mg (54%) of iodo lactone *ent*-**5b**: mp 82–83 °C (CH_2Cl_2–pentane); ^1H NMR (400 MHz, $CDCl_3$, ^1H–^{13}C COSY) δ 1.40 (s, 3 H, 1-CH_3), 1.78 (ddd, 1 H, 7a-H), 1.90 (ddd, 1 H, 3n-H), 2.15 (ddd, 1 H, 3x-H), 2.29 (ddd, 1 H, 2-H), 2.31 (ddd, 1 H, 7s-H), 2.64 (1 H, 4-H), 3.97 (d, 1 H, 5-H), 4.77 (s, 1 H, 6-H), $J_{2x,3x}$ = 11 Hz, $J_{2x,3n}$ = 1.5 Hz, $J_{3x,3n}$ = 13 Hz, $J_{3x,4}$ = 4 Hz, $J_{5,4}$ = 4 Hz, $J_{7s,7a}$ = 12 Hz, $J_{7s,4}$ = 3 Hz, $J_{7s,3n}$ = 1.5 Hz, $J_{7a,5}$ = 1.5 Hz, $J_{7a,4}$ = 2 Hz; ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT) δ 15.9 (1-CH_3), 30.7 (CH-5), 35.7 (CH_2-3), 43.3 (CH_2-7), 43.9 (CH-2), 47.2 (CH-4), 55.2 (C-1), 93.6 (CH-6), 179.1 (C=O); IR ($CHCl_3$) 1785 cm^{-1}; MS 278 (4) [M^+], 151 (30), 107 (100), 93 (45), 79 (75), 67 (18), 55 (20); $[\alpha]^{20}_D$ −72.5 (*c* 1.99 in CCl_4); CD (CH_3CN, see Figure 1) λ_{max} [nm] (Δε) 258 (−0.42), 226 (0.98). Anal. Calcd for $C_9H_{11}O_2I$ (278.1): C, 38.87; H, 3.99. Found: C, 38.90; H, 3.90.

(1*R*)-6-*endo*-Hydroxy-5-*exo*-iodo-1-methylbicyclo[2.2.1]-heptane-2-*endo*-carboxylic Acid Lactone (5b). **5b** was prepared from **7a** as described for the degradation of **8a** to *ent*-**5b**. For ^1H NMR, IR, MS, see *ent*-**5b**; $[\alpha]^{20}_D$ +75.8 (*c* 2.01 in CCl_4); CD (CH_3CN, see Figure 1) λ_{max} [nm] (Δε) 257 (0.44), 225 (−1.06). Anal. Calcd for $C_9H_{11}O_2I$ (278.1): C, 38.87; H, 3.99. Found: C, 38.88; H, 3.88.

Configurational Assignment of 3d (the Main Endo Product Obtained from 1c with 2b) by Degradation to 5b. A solution of **3d** (41.3 mg, 0.229 mmol) in THF (5 mL) was treated with $NaIO_4$ (147.3 mg, 0.689 mmol) in H_2O (3.5 mL) for 6 h at 20 °C. Then, a further portion of $NaIO_4$ (49.2 mg, 0.230 mmol) in H_2O (1 mL) was added, and the reaction mixture was stirred at 50 °C until **3d** was completely consumed (after about 7.5 h, TLC control). The mixture was allowed to cool to room temperature and was extracted with CH_2Cl_2. The solvent was removed, and H_2O (4 mL) was added. The solution was treated with $NaHCO_3$ until pH 8.5 was reached, and then KI (233.1 mg, 1.404 mmol) and I_2 (59.9 mg, 0.236 mmol), dissolved in H_2O (2 mL), were added. After 23 h at 20 °C an additional 28.4 mg (0.112 mmol) of I_2 and 114.9 mg (0.692 mmol) of KI were used to complete the reaction. The mixture was stirred for another 16 h and then extracted with CH_2Cl_2. Workup and LC were performed as described for *ent*-**5b** to give a sample of **5b**, the spectra of which (^1H NMR, IR, MS) were completely identical with those of *ent*-**5b** (vide supra): $[\alpha]^{20}_D$ +77.3 (*c* 2.01 in $CHCl_3$); CD (CH_3CN, see Figure 1) λ_{max} [nm] (Δε) 255 (0.47), 224 (−1.21); HRMS calcd for $C_9H_{11}O_2I$ 277.9804, found 277.9804.

Diels–Alder Reaction of 1,3-Dimethylcyclopentadiene (2c) with 1c. The reaction was performed as described for **2b**. The product ratios were determined by GC (25.5-m × 0.28-mm glass capillary column (Carbowax 20M), 122 °C, carrier gas: H_2); retention times: 1318 (major exo isomer), 1380 (**3e**), 1516 (**4e**), 1605 s (minor exo isomer). The results are collected in Table VI. An analysis using eq 1 gave the following expression:

$$\ln (k_{3e}/k_{4e}) = -(1.21 \pm 0.08) + (1.74 \pm 0.04)\ \text{kcal}/RT\ \text{mol}$$

Table VI. Product Ratios (in %) from the Diels–Alder Reaction of 1c with 2c

T (°C)	3e	4e	major exo isomer[a]	minor exo isomer[a]
25	65.8	11.5	15.8	6.6
0	72.7	10.0	15.0	2.3
−20	77.0	8.1	14.0	1.0

[a] The configuration was not determined.

(2*S*)-1-((1*S*,2*S*,4*S*)-1,5-Dimethylbicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (3e): ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.70 (7a-H, 3n-H), 1.32–1.36 (d, CH(OH)CH_3, s, 1-CH_3), 1.43 (ddd, 7s-H), 1.79 (d, 3 H, 5-CH_3), 1.98 (ddd, 1 H, 3x-H), 2.60 (broad s, 1 H, 4-H, $W_{1/2}$ = 8 Hz), 2.99 (dd, 1 H, 2x-H), 3.55 (d, 1 H, OH), 4.25–4.30 (dq, 1 H, C*H*(OH)), 5.16 (s, 1 H, 6-H), $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 5 Hz, $J_{3x,3n}$ = 11.5 Hz, $J_{3x,4}$ = 4 Hz, $J_{5\text{-}CH_3,6}$ = 1.5 Hz, $J_{CH(OH),CH_3}$ = 7 Hz, $J_{CH,OH}$ = 5 Hz; IR (neat) 1705 cm^{-1}; MS 194 (8) [M^+], 149 (8), 107 (10), 94 (100), 79 (38), 55 (34); $C_{12}H_{18}O_2$ (194.3).

(2*S*)-1-((1*R*,2*R*,4*R*)-1,5-Dimethylbicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (4e): ^1H NMR (400 MHz, $CDCl_3$) δ 1.10–1.40 (7s-, 7a-, 3n-H), 1.33–1.38 (d, CH(OH)CH_3, s, 1-CH_3), 1.70 (d, 3 H, 5-CH_3), 2.25 (ddd, 1 H, 3x-H), 2.55 (broad s, 1 H, 4-H, $W_{1/2}$ = 8 Hz), 2.91 (dd, 1 H, 2x-H), 3.51 (d, 1 H, OH), 4.09–4.14 (dq, 1 H, C*H*(OH)), 5.50 (s, 1 H, 6-H); $J_{2x,3x}$ = 10 Hz, $J_{2x,3n}$ = 5.5 Hz, $J_{3x,4}$ = 3 Hz, $J_{CH(OH),CH_3}$ = 7 Hz, $J_{CH,OH}$ = 5 Hz; IR (neat) 1705 cm^{-1}; MS 194 (7) [M^+], 149 (7), 107 (10), 94 (100), 79 (40), 55 (42); $C_{12}H_{18}O_2$ (194.3).

(2*S*)-1-(1,5-Dimethylbicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (major exo isomer, configuration not determined): ^1H NMR (400 MHz, $CDCl_3$) δ 1.10–1.95 (7a-, 7s-, 3n-, 3x-H), 1.18 (s, 1-CH_3), 1.30 (d, CH(OH)CH_3), 1.73 (d, 5-CH_3), 2.50 (ddd, 1 H, 2n-H), 2.62 (broad s, 1 H, 4-H, $W_{1/2}$ = 8 Hz), 3.60 (d, 1 H, OH), 4.22–4.30 (dq, 1 H, C*H*(OH)), 5.48 (s, 1 H, 6-H); $J_{2n,3x}$ = 4.5 Hz, $J_{2n,3n}$ = 8.5 Hz, $J_{2n,7s}$ = 1.5 Hz, $J_{5\text{-}CH_3,6}$ = 1.5 Hz, $J_{CH(OH),CH_3}$ = 7 Hz, $J_{CH,OH}$ = 5 Hz; IR (neat) 1705 cm^{-1}; MS 194 (7) [M^+], 149 (8), 107 (12), 94 (100), 79 (40), 55 (42); $C_{12}H_{18}O_2$ (194.3).

$TiCl_4$-Catalyzed Diels–Alder Reaction of a Mixture of Dimethylcyclopentadiene 2c/2d with Acrylate 9. To a solution of **9** (413.6 mg, 2.245 mmol) in CH_2Cl_2 (14 mL) and hexanes (2 mL) was added a solution of $TiCl_4$ (1 M in hexanes, 2.1 mL, 2.1 mmol) at 0 °C. The reaction mixture was stirred for 1 h, and then **2c/2d** (2.06 g, 21.9 mmol) were added. After 4 h at 0 °C the reaction was quenched with saturated aqueous Na_2CO_3. Usual workup (CH_2Cl_2) followed by MPLC (hexanes/*tert*-butyl methyl ether (3:1)) afforded **10** (61.1 mg, 9%) and **11** (120.8 mg, 17%). **10** decomposed on the TLC plates but furnished three characteristic spots.

***O*-((1*S*)-1,4-Dimethylbicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (11)**: ^1H NMR (400 MHz, $CDCl_3$, ^1H–^1H COSY) δ 1.2–1.4 (m, 2 H, 7s-H and 7a-H), 1.27 (s, 3 H, 5-CH_3), 1.43 (s, 3 H, 1-CH_3), 1.62 (ddd, 1 H, 3n-H), 1.88 (dd, 1 H, 3x-H), 2.92 (dd, 1 H, 2x-H), 5.71 (d, 1 H, 5-H), 5.98 (d, 1 H, 6-H), pantolactone part: 1.10 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 3.98 and 4.02 (2 H, AB system, CH_2, $J_{H,H}$ = 9 Hz), 5.30 (s, 1 H, CH(OR)); $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 4 Hz, $J_{3x,3n}$ = 12 Hz, $J_{3n,7s}$ = 2.5 Hz, $J_{5,6}$ = 6 Hz, $J_{7s,7a}$ = 8 Hz; IR (CCl_4) 1810, 1750 cm^{-1}; MS 278 (0.2) [M^+], 185 (0.5), 149 (3.1), 121 (2.1), 105 (3), 94 (100), 79 (24), 55 (21); $[\alpha]^{20}_D$ −52.2 (*c* 1.00 in CCl_4); Anal. Calcd for $C_{16}H_{22}O_4$ (278.3): C, 69.04; H, 7.97. Found: C, 69.03; H, 7.90.

***O*-((1*S*)-5-*exo*-Chloro-1,5-*endo*-dimethylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (10)**: mp 118–119 °C (CH_2Cl_2–pentane); ^1H NMR (400 MHz, $CDCl_3$, ^1H–^1H COSY, ^1H–^{13}C COSY, NOE) δ 1.30 (s, 3 H, 1-CH_3), 1.50 (ddd, 1 H, 7a-H), 1.78 (s, 3 H, 5-CH_3), 1.90 (m, 1 H, 3x-H), 1.90 (dd, 1 H, 6n-H), 2.02 (dd, 1 H, 6x-H), 2.10 (ddd, 1 H, 3n-H), 2.25 (ddd, 1 H, 7s-H),

Table VII. Torsional Parameters (kcal/mol) and Dipole Parameters (D) Implemented into MM2ERW

	torsional parameters		
atom types	V_1	V_2	V_3
6-1-3-7	-0.5	2.5	0.5
6-1-3-2	0	2.5	0.5
atom types	dipole parameters		
6-21	-3.000		

2.40 (d, 1 H, 4-H), 2.69 (ddd, 1 H, 2x-H), pantolactone part: 1.11 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 4.02 and 4.07 (2 H, AB system, CH_2, J = 9 Hz), 5.39 (s, 1 H, CH(OR)); $J_{2x,3x}$ = 12 Hz, $J_{2x,3n}$ = 5 Hz, $J_{2x,6x}$ = 2 Hz, $J_{3x,3n}$ = 14 Hz, $J_{3x,4}$ = 5 Hz, $J_{3n,7a}$ = 3 Hz, $J_{6x,6n}$ = 14 Hz, $J_{7s,7a}$ = 10.5 Hz, $J_{7s,4}$ = 1.5 Hz, $J_{7a,6n}$ = 3 Hz, $J_{7a,4}$ = 1.5 Hz; ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT, ^1H ^{13}C COSY) δ 20.36 (5-CH_3), 27.91 (1-CH_3), 29.18 (CH_2-3), 47.91 (CH_2-7), 49.22 (CH-2), 49.85 (C-1), 50.38 (CH_2-6), 52.01 (CH-4), 78.04 (C-5), 172.18, 172.80 (C=O and C=O pantolactone), pantolactone part: 20.28 (CH_3), 22.93 (CH_3), 40.06 ($C(CH_3)_2$), 75.27 (CH(OR)), 76.09 (CH_2); IR (CCl_4) 1805, 1740 cm^{-1}; MS 278 (0.5) [M^+ - HCl], 185 (5.3), 165 (1.6), 157 (3.8), 149 (3.6), 121 (8), 107 (6), 94 (100), 79 (32), 77 (10), 55 (28), 41 (16); $[\alpha]^{20}_D$ +13.9 (*c* 0.92 in CCl_4). Anal. Calcd for $C_{16}H_{23}O_4Cl$ (314.8): C, 61.04; H, 7.36. Found: C, 61.07; H, 7.42.

Conversion of 11 to (1*S*)-1,4-Dimethyl-6-*endo*-hydroxy-5-*exo*-iodobicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone (12). The reaction was performed as described for the preparation of *ent*-**5b** from **8a**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3 H, 4-CH_3), 1.32 (s, 3 H, 1-CH_3), 1.58 (dd, 1 H, 7a-H), 1.87 (ddd, 1 H, 3n-H), 2.11 (dd, 1 H, 7s-H), 2.31-2.45 (2 m, 2 H, 2x-H, 3x-H), 3.98 (d, 1 H, 5-H), 4.92 (broad s, $W_{1/2}$ = 2 Hz, 1 H, 6-H), $J_{7a,7s}$ = 11 Hz, $J_{7a,5}$ = 3 Hz, $J_{3n,7s}$ = 2.5 Hz, $J_{3n,3x}$ = 13 Hz, $J_{3n,2x}$ = 1.5 Hz; IR ($CHCl_3$) 1780 cm^{-1}; MS 292 (1), 165 (100), 136 (36), 121 (34), 109 (64), 93 (82); CD (CH_3CN, see Figure 1); λ_{max} [nm] ($\Delta\epsilon$) 264 (0.15), 229 (-0.5), 210 (0.1); $C_{10}H_{13}O_2I$ (292.1).

Uncatalyzed Diels-Alder Reaction of Dimethylcyclopentadienes 2c/2d with 9. The reaction was performed as described for **2b**. Freshly distilled acrylate **9** (349.0 mg, 1.895 mmol) in CH_2Cl_2 (10 mL) was treated dropwise with diene **2c/2d** (875.1 mg, 9.300 mmol). Purification by MPLC (hexanes/ethyl acetate (10:1)).

***O*-((1*R*)-1,5-Dimethylbicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (8b):** ^1H NMR (400 MHz, $CDCl_3$, ^1H-^1H COSY) δ 1.23 (broad d, 1 H, 7a-H), 1.36 (ddd, 1 H, 7s-H), 1.44 (s, 3 H, 1-CH_3), 1.55 (ddd, 1 H, 3n-H), 1.74 (d, 3 H, 5-CH_3), 2.04 (ddd, 1 H, 3x-H), 2.58 (broad d, 1 H, 4-H, $W_{1/2}$ = 7 Hz), 2.77 (dd, 1 H, 2x-H), 5.36 (broad s, 1 H, 6-H, $W_{1/2}$ = 5 Hz), pantolactone part: 1.07 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 3.97 and 4.01 (2 H, AB system, CH_2, $J_{H,H}$ = 9 Hz), 5.30 (s, 1 H, CH(OR)); $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 4 Hz, $J_{3x,3n}$ = 12 Hz, $J_{3x,4}$ = 3 Hz, $J_{7s,7a}$ = 8 Hz, $J_{7s,3n}$ = 3 Hz, $J_{7s,4}$ = 2 Hz, $J_{5\text{-}CH_3,6}$ = 2 Hz; IR (CCl_4) 1805, 1745 cm^{-1}; MS 278 (0.1) [M^+], 165 (0.1), 149 (2.6), 121 (1), 94 (100), 79 (26), 55 (15); $[\alpha]^{20}_D$ +61.4 (*c* 2.00 in CCl_4); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1526.

***O*-((1*S*)-1,5-Dimethylbicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (7b):** ^1H NMR (400 MHz, $CDCl_3$, ^1H-^1H COSY) δ 1.25 (broad d, 1 H, 7a-H), 1.36 (dd, 7s-H), 1.41 (s, 3 H, 1-CH_3), 1.54 (ddd, 1 H, 3n-H), 1.74 (d, 3 H, 5-CH_3), 2.07 (ddd, 1 H, 3x-H), 2.59 (broad d, 1 H, 4-H, $W_{1/2}$ = 7 Hz), 2.81 (dd, 1 H, 2x-H), 5.26 (broad s, 1 H, 6-H, $W_{1/2}$ = 4 Hz), pantolactone part: 1.11 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 3.98 and 4.02 (2 H, AB system, CH_2, $J_{H,H}$ = 9 Hz), 5.30 (s, 1 H, CH(OR)); $J_{2x,3x}$ = 9 Hz, $J_{2x,3n}$ = 4 Hz, $J_{3x,3n}$ = 12 Hz, $J_{3x,4}$ = 4 Hz, $J_{7s,7a}$ = 8 Hz, $J_{7s,3n}$ = 3 Hz, $J_{7a,4}$ = 1.5 Hz, $J_{5\text{-}CH_3,6}$ = 1.5 Hz; IR (CCl_4) 1805, 1750 cm^{-1}; MS 278 (0.05) [M^+], 165 (0.3), 149 (2.8), 121 (1.2), 94 (100), 79 (26), 55 (16); $[\alpha]^{20}_D$ -59.9 (*c* 2.01 in CCl_4). Anal. Calcd for $C_{16}H_{22}O_4$ (278.3): C, 69.04; H, 7.97. Found: C, 69.12; H, 8.03.

10 from *O*-((1*S*)-1,5-Dimethylbicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (7b) by HCl Addition. To **7b** (32.7 mg, 0.117 mmol) was added a solution of HCl in $CHCl_3$ (saturated at -50 °C, 5 mL). The mixture was allowed to warm to 20 °C within 2 h and then concentrated to give 54.3 mg of **10**, identical with the sample obtained from the $TiCl_4$-catalyzed Diels-Alder reaction.

HCl Addition to *O*-((1*R*)-1,5-Dimethylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carbonyl)-D-pantolactone (8b). The reaction was performed as described in the preceding procedure. On the TLC plate the HCl adduct decomposed to yield four characteristic spots. ^1H NMR of an impure specimen of the HCl adduct: (400 MHz, $CDCl_3$) δ 1.31 (s, 3 H, 1-CH_3), 1.48 (d, 1 H, 7a-H), 1.77 (s, 3 H, 5-CH_3), 1.85 (ddd, 1 H, 3x-H), 2.02 (s, 2 H, CH_2-6), 2.08 (ddd, 1 H, 3n-H), 2.23 (ddd, 1 H, 7s-H), 2.37 (d, 1 H, 4-H), 2.60 (m, 1 H, 2x-H), pantolactone part: 1.09 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 4.05 and 4.01 (2 d, AB system, CH_2, $J_{H,H}$ = 9 Hz), 5.37 (s, 1 H, CH(OR)); $J_{2x,3x}$ = 11 Hz, $J_{2x,3n}$ = 5 Hz, $J_{3x,3n}$ = 14 Hz, $J_{3x,4}$ = 5 Hz, $J_{3n,7s}$ = 3 Hz, $J_{7s,7a}$ = 10 Hz, $J_{7a,4}$ = 1.5 Hz.

(1*S*)-1,5-Dimethyl-6-*endo*-hydroxy-5-*exo*-iodobicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone (*ent*-5c). The iodo lactone *ent*-**5c** was prepared from **8b** as described for *ent*-**5b**. Purification (LC, hexanes/ethyl acetate (20:1)) of the crude material afforded *ent*-**5c** (14%), which was very sensitive and decomposed rapidly: ^1H NMR (400 MHz, $CDCl_3$, ^1H-^1H COSY) δ 1.40 (s, 3 H, 1-CH_3), 1.79-1.88 (3x-H, 7a-H), 2.01-2.08 (ddd, 1 H, 3n-H), 2.06 (s, 3 H, 5-CH_3), 2.22 (ddd, 1 H, 2x-H), 2.48 (ddd, 1 H, 7s-H), 2.64 (broad d, 1 H, 4-H, $W_{1/2}$ = 8 Hz), 4.99 (s, 1 H, 6-H), $J_{2x,3x}$ = 11.5 Hz, $J_{2x,3n}$ = 1.5 Hz, $J_{2x,6}$ = 1.5 Hz, $J_{3x,3n}$ = 11.5 Hz, $J_{3x,4}$ = 1.5 Hz, $J_{3n,7s}$ = 2.5 Hz, $J_{7s,7a}$ = 11.5 Hz, $J_{7a,4}$ = 1.5 Hz; IR ($CHCl_3$) 1780 cm^{-1}; MS 165 (40) [M^+ - I], 121 (100), 107 (38), 93 (95), 79 (33); $[\alpha]^{20}_D$ -97.4 (*c* 1.00 in CCl_4); CD (CH_3CN, see Figure 1) λ_{max} [nm] ($\Delta\epsilon$) 231 (0.10), 272 (-0.41); $C_{10}H_{13}O_2I$ (292.1).

(1*R*)-1,5-Dimethyl-6-*endo*-hydroxy-5-*exo*-iodobicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone (5c). Iodo lactone **5c** was prepared from **7b** as described above: $[\alpha]^{20}_D$ +101.5 (*c* 1.00 in CCl_4); CD (CH_3CN, see Figure 1) λ_{max} [nm] ($\Delta\epsilon$) 233 (-0.07), 274 (0.44); $C_{10}H_{13}O_2I$ (292.1).

Configurational Assignment of 3e (the Main Endo Product Obtained from 1c and 1,3-Dimethylcyclopentadiene (2c)) by Degradation to 5c. The reaction was performed as described for **3d**. Purification as described for *ent*-**5c**: The spectroscopic data are in agreement with those of the enantiomer *ent*-**5c**; $[\alpha]^{20}_D$ +98.3 (*c* 0.95 in CCl_4); CD (CH_3CN, see Figure 1) λ_{max} [nm] ($\Delta\epsilon$) 232 (-0.07), 267 (0.77).

X-ray Structural Analysis of 10. **10**, $C_{16}H_{23}O_4Cl$, crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 6.992 (4) Å, b = 10.502 (5) Å, c = 23.203(7) Å, V = 1703.8 (14) Å^3, M = 314.8, Z = 4, D_x = 1.23 g cm^{-3}, $F(000)$ = 672. Intensity data (+h, +k, +l) were collected on a Siemens P4 diffractometer with Cu Kα radiation (λ = 1.541 84 Å) using an ω-scan for the 2θ-range 3 ≤ 2θ ≤ 115°. A total of 1343 independent reflections were collected of which 1123 with $F_o^2 > 2\sigma(F_o^2)$ were used for the subsequent refinement. An empirical absorption correction based on ψ-scan data was applied to the reflections (maximum transmission 0.86; minimum transmission 0.15, μ = 21.0 cm^{-1}). The structure was solved by direct methods and refined by least-squares analysis to R = 0.078, $wR = [\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}$ = 0.085 with weights given by $w^{-1} = \sigma^2(F_o) + 0.0001F_o^2$. The quality of the analysis was limited as a result of the wide mosaic spread of the investigated crystal. Anisotropic temperature factors were introduced for the non-hydrogen atoms; the latter were included at geometrically calculated positions. The assignment of the absolute configuration was performed by use of the Roger's η factor, which refined to 1.01 (17). A final difference Fourier map showed a largest peak at 0.58 e Å^{-3} and a largest hole of -0.23 e Å^{-3}. The structure solution and refinement were performed with the SHELXTL system of programs (Siemens Analytical X-Ray Instruments 1990). Tables 1-5 of the supplementary material contain atom positional and thermal parameters and bond lengths and angles.

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Supplementary Material Available: ^{1}H NMR spectra for compounds **2b**, **13b**, **13c**, **14**, **1c**, (2*S*)-2-hydroxy-1-(1-methylbicyclo[2.2.1]hept-5-en-2-yl)propan-1-one (major exo isomer), **4d**, **3d**, **3c**, **4c**, (2*S*)-1-(bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (minor exo isomer), (2*S*)-1-(bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (major exo isomer), **6b**, **3e**, **4e**, (2*S*)-1-(1,5-dimethylbicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxypropan-1-one (major exo isomer), **8c**, **8c**·HCl (impure specimen), **5c**, and *ent*-**5c**, and X-ray crystallographic data for **10** (34 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Thermolysis of 2-Benzylidenebenzocyclobutenols†

Jean-Claude Bradley,‡ Tony Durst,* and A. J. Williams

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 6Y7

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The thermolysis of a series of 2-benzylidenebenzocyclobuten-1-ols has been studied. Whenever comparisons can be made, the rate of opening of the benzocyclobutene ring was slower for these compounds than the corresponding 2-ones. The intermediate vinylallenes underwent a variety of electrocyclization reactions which depended on the nature of the additional substituent at C-1. 10-Benzylideneanthrone and 4-benzylidene-1-tetralones, respectively, were obtained when this substituent was phenyl or vinyl. 1-(Alkynylphenyl)-2-benzylidenebenzocylobuten-1-ols were converted to mixtures of 4-benzylidene-1,4-naphthoquinonemethides, 2,3-dibenzylidene-1-indanones, and 10-phenylbenzo[b]fluoroeneone.

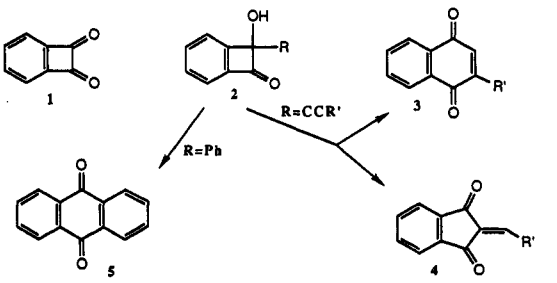
Introduction

Cyclobutene-1,2-diones and their derivatives have gained much attention during the past decade as versatile intermediates in organic synthesis mainly due to the work of Moore and Liebeskind.[1,2] Somewhat less attention has been paid to the benzocyclobutenedione analogs **1**. Nevertheless, these compounds have been used effectively as precursors to naphthoquinones, anthraquinones, and 2-alkylidene-1,2-indandiones. For example, as shown in Scheme I, thermolysis of adducts **2**, formed from **1** and alkynyl or aryl anions, respectively, proceeds readily to yield **3**, **4**, and **5**.[1] Ring expansion of **1** to naphthoquinones via metal carbonyl complexes has also been reported.[2]

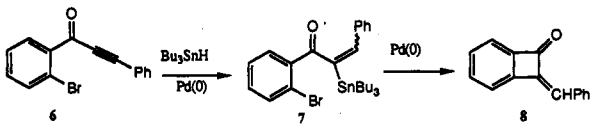
Recently, we have reported a convenient one-pot preparation of benzylidenecyclobutenones **8** starting with alkynones **6**.[3] Palladium-mediated regioselective addition of tributyltin hydride to **6** followed by intramolecular Stille coupling of the intermediate arylbromide–vinylstannane **7** gave **8** as a mixture of *E*/*Z* isomers about the exocyclic double bond in approximately 50% isolated yield. (Scheme II). Furthermore, this methodology enabled us to prepare derivatives of **8** with predictable substitution patterns in the aromatic ring. Methylenebenzocyclobutenones, of which **8** is a representative, have proven surprisingly difficult to prepare. For example, 2-methylenebenzocyclobutene has been prepared in low yield by Trahanovsky[4a] via flash vacuum pyrolysis of 3-[(benzoyloxy)methyl]benzofuran and 2-(carbethoxyethylidene)benzocyclobutenone was obtained by Cava[4b] from the dione and (carbethoxymethylene)triphenylphosphorane; Wittig reactions did not yield the simple alkylidene analogues.

In view of the work summarized in Scheme I, it became apparent that our compounds could lead to a regiospecific entry into similar ring systems if the benzylidene moiety could be shown to function as a masked carbonyl functionality. Thus, Scheme III was considered as a potential

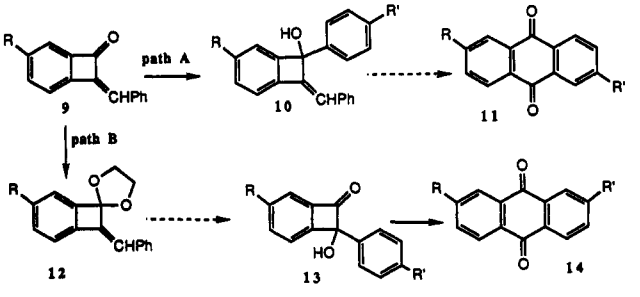
Scheme I



Scheme II



Scheme III



route to a set of regioisomeric anthraquinones. In path A, reaction of **9** with an aryllithium would yield the car-

† This paper is dedicated to the memory of our colleague Jean-Louis Roustan.

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