Diels–Alder Reactions of Some Carenones[1]

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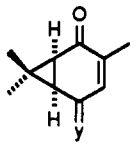
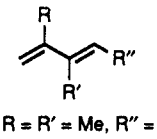
The Diels–Alder reactions of (+)-car-3-en-2-one, (+)-car-4-en-3-one, and car-3-ene-2,5-dione with 2,3-dimethyl-1,3-butadiene and (*E*)-1-methoxy-1,3-butadiene under $Yb(fod)_3$ catalysis are described, and a structure analysis of the adducts by NMR spectroscopy is presented. The effect of the *gem*-dimethylcyclopropane ring on the regioselectivity and diastereoselectivity of the reactions is discussed.

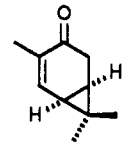
In the course of our exhaustive study of the Diels–Alder reaction of cycloalkenones under Lewis acid catalysis we have investigated a variety of substituted 2-cyclohexenones in order to acquire some insight into the effects of substituents on reactivity, regioselectivity, and diastereoselectivity.[3] It now became of interest to investigate the cycloadditions of some carenones to evaluate the effects of the *gem*-dimethylcyclopropane ring on the selectivities. For this reason we have studied the Diels–Alder reactions of (+)-car-3-en-2-one (**1a**)[4] and car-3-ene-2,5-dione (**1b**)[5] with the two electron-rich dienes 2,3-dimethyl-1,3-butadiene (**2a**) and (*E*)-1-methoxy-1,3-butadiene (**2b**).



1a, Y = H_2
b, Y = O



2a, R = R′ = Me, R″ = H
b, R = R′ = H, R″ = OMe
c, R = Me, R′ = R″ = H



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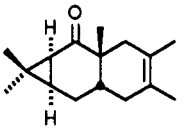
Highly reactive dienes were chosen in view of the low reactivity of the cycloalkenones[6] and the sensitivity of the carenones to acid precluding the use of strong Lewis acids as catalysts. As a consequence the cycloadditions were performed under the mild catalysis of the lanthanide complex $Yb(fod)_3$.[7] In view of the ability of the cyclopropane ring to conjugate with an adjacent double bond[8] and the presence of two methyl groups on the ring exerting steric hindrance, the *gem*-dimethylcyclopropane unit can be expected to affect the cycloaddition process by electronic as well as steric means.

Results and Discussion

The reactions were carried out in dry toluene solution under $Yb(fod)_3$ catalysis at 120 °C. The cycloadditions of (+)-car-3-en-2-one (**1a**) with dienes **2a** and **2b** afforded anti diastereoselectively adducts **4** and **5** in 60% and 64% yields, respectively.[9] Furthermore, the reaction of the latter diene was totally endo diastereoselective and regioselective. When carenedione **1b** interacted with diene **2a**, the anti addition product **6a** was obtained in 90% yield. The cycloaddition of diene **2b** with carenedione **1b** led to a 16.4:2.6:1 mixture (88%) of ketones **7a**, **7b**, and **8**, respectively. Whereas the tricyclic compounds **7** were the anti-endo and anti-exo adducts of a Diels–Alder reaction of normal electron demand, tetracycle **8**, present only as a 5% component in the reaction mixture, was not an en-



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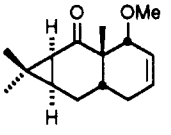

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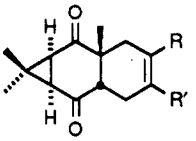
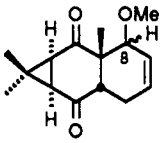
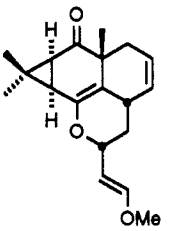


6a, R = R′ = Me
b, R = H, R′ = Me
c, R = Me, R′ = H



7a, H-8β
b, H-8α



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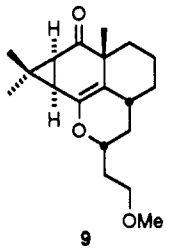

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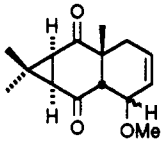

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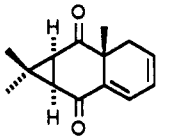

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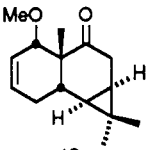

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(9) ^1H and ^{13}C NMR spectral analysis of the reaction mixtures of both cycloadditions revealed the presence of 15–20% of products of the hydrobenzosuberone type, presumably formed by the Diels–Alder reactions of dienes **2a** and **2b** with eucarvone (produced by acid-induced ring expansion of carenone **1a**). In separate experiments carenone was shown to be converted almost completely into eucarvone on heating at 140 °C for 16 h. At the reaction temperature (120 °C) the conversion occurred slowly and at 100 °C carenone was thermally stable. Thus, the reaction temperature of 120 °C was the best compromise between the competing reactions.

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edione, but a trienic ketone possessing a dihydropyran moiety as part of its structure. The overall configuration of ketone **8** suggested it to be 2:1 diene–enone adduct of a "tandem Diels–Alder reaction".[10] Presumably the first cycloaddition afforded a mixture of regioisomers **7** and **10**, the latter of which underwent acid-induced β-elimination of methanol giving dienone **11**. Interaction of this intermediate with diene **2b** in a cycloaddition of inverse electron demand[11] led endo diastereoselectively to adduct **8** (i.e., dienone **11** acting as heterodiene and ether **2b** as dienophile). The 2:1 adduct formation is reminiscent of (but not identical with) the previously observed $Yb(fod)_3$-catalyzed cycloaddition between **2b** and 2-cyclohexenone.[12]

As the **1b–2b** cycloaddition showed a decrease of regioselectivity when compared with that of the **1a–2b** reaction, the regioselectivity of the cycloaddition with isoprene (**2c**) was examined also. The reaction of diketone **1b** with diene **2c** led in 95% yield to a 2.7:1 mixture of the anti addition tricyclic regioisomers **6b** and **6c**. These results revealed a drop in regioselectivity (with slight preference for "para" regiochemistry).

Finally, in order to gain more information on the parameters controlling the regioselectivity, the reaction of (*E*)-1-methoxy-1,3-butadiene (**2b**) with (+)-car-2-en-4-one (**3**),[4] an enone whose cyclopropane ring was disposed differently (from both an electronic and steric point of view) toward its reaction site than the carenones **1**, was examined. The reaction of carenone **3** with diene **2b** at 110 °C led in 80% yield to the anti-endo addition compound **12** as the sole reaction adduct. The reaction was totally regioselective and endo diastereoselective, as had been the case with carenone **1a**.

The strong preference for anti diastereoselectivity in the cycloadditions of carenones **1** and **3** may be ascribed to the steric hindrance of the cyclopropane methyl group overhanging the cyclohexenone ring. The severe nonbonded interactions between this substituent and the diene destabilizes strongly the transition state for syn addition, thus favoring that of anti addition. Furthermore, the reaction of (*E*)-1-methoxy-1,3-butadiene (**2b**) with carenones **1a** and **3** is totally regioselective, but the one with car-3-ene-2,5-dione (**1b**) is less regioselective. In the case of the reaction of dione **1b** with isoprene (**2c**) this drop of regioselectivity is even more evident. Comparison of the results of the **1b–2c** reaction with those reported for the cycloaddition of isoprene (**2c**) with 2,5-dimethylbenzoquinone[13] —a regiounselective reaction—shows the slight difference of behavior of a 1,2-diacylcyclopropane from that of a 1,2-diacyl olefin.

The cycloadditions of the chiral carenones **1a** and **3**, both prepared from carvone, represent a new approach to optically active substances in view of the ready availability of carvone in each of its enantiomeric forms and the facile conversion of the *gem*-dimethylcyclopropane ring into a variety substituents.

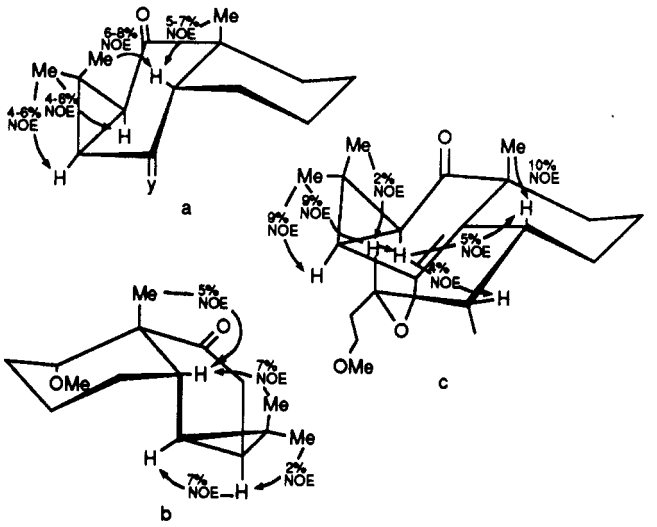
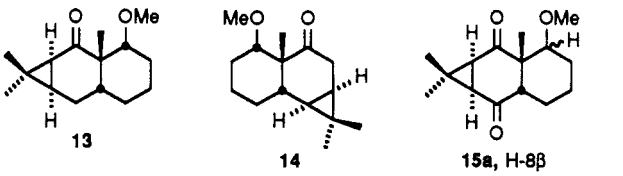


Figure 1.

Structure Analysis.[14] The structure and stereochemistry of the Diels–Alder products were inferred from the analysis of their high-field ^1H and ^{13}C NMR spectra. The pertinent data are collated in the Experimental Section.

(a) Tricyclic Ketones. The experimental data show that all tricyclic compounds possess cis stereochemistry at the B/C ring junction, while the cyclopropane ring assumes a syn orientation with respect to the angular methyl group. These conclusions follow from the values of the $^3J_{HH}$ coupling constants of H-4a, indicating its *equatorial* orientation with respect to ring C, as well as from the NOE enhancements observed on irradiation of the methyl hydrogen resonances. Thus, the H-4a signal height was enhanced on selective preirradiation of the angular methyl hydrogen resonance (5–6%) as well as the resonance of the C-10 hydrogens (5–10%). Saturation of the resonance of the C-11 hydrogens resulted in signal enhancement of H-2 and H-3. These data agree with a conformation in which the angular methyl group assumes an axial orientation with respect to ring C and bridgehead hydrogen 4a an equatorial disposition (Figure 1a,b). The relative configuration of the methoxy group for ethers **5**, **12**, and **7** was inferred from the vicinal $^3J_{HH}$ values of H-8 of the dihydro derivatives **13–15**, respectively (prepared by catalytic hydrogenation[15]



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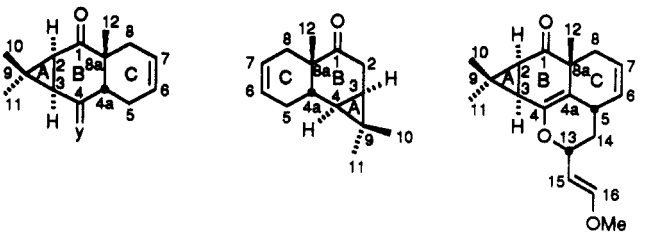
(14) Formulas **1** and **3–15** represent the absolute configurations of the optically active compounds. The tricyclic and tetracyclic compounds are named according to the following numbering system. The letters A and B are used to distinguish sterically different hydrogens of the methylene groups.



of the olefins). Inspection of the pertinent coupling data revealed 1.5–3-Hz $^3J_{7A,8}$ and $^3J_{7B,8}$ values for ketones **13**, **14**, and **15a**, corresponding to an orientation of the methoxy group trans to the angular methyl function. By contrast, the same vicinal couplings for ketone **15b** assumed the values of 4.5 and 11 Hz, indicating the opposite methoxy group configuration.

The position of the olefinic methyl group in adducts **6b** and **6c** was deduced on the basis of selective 2D INEPT experiments. With the frequency of the "soft" proton pulses centered on the H-7 resonance of compound **6b**, the 2D map contained two cross peaks separated by 5.3 Hz at the C-8a frequency, indicative of the latter carbon being separated by three chemical bonds from the site of irradiation. Similar experiments performed on isomeric adduct **6c** confirmed the assigned regiochemistry.

(b) Tetracyclic Ketones. The structure of product **8** was inferred from a series of selective NOE experiments and values of the relevant proton–proton couplings. Irradiation of the angular methyl protons gave an enhancement (8%) of the H-5 signal, suggesting a cis spatial relationship between the two proton groupings. In a similar manner, saturation of the H-13 resonance gave rise to signal enhancement (4%) of H-5, revealing spatial proximity of these hydrogens. The 12.7-Hz splitting of H-15 and H-16 indicated the side-chain olefinic protons to be in a trans relationship to each other.[15] Further support for the structure of ketone **8** was obtained from the NMR analysis of its tetrahydro derivative **9**. Irradiation of the C-10 hydrogen resonance resulted in a 2% enhancement of the H-13 resonance, and preirradiation of the C-11 hydrogen resonance gave a 9% enhancement of the H-2 and H-3 resonances. These data show a cis relationship of the cyclopropane ring and the angular methyl group. Furthermore, the coupling constants of the hydrogens at C-5 ($^3J_{5,6A}$ = 11.9, $^3J_{5,6B}$ = 4.5, $^3J_{5,14A}$ = 9.9, $^3J_{5,14B}$ = 7.6 Hz) and C-13 ($^3J_{13,14A}$ = 11.5, $^3J_{13,14B}$ = 1.7 Hz) confirm the axial H-5 orientation with respect to ring C, its pseudoaxial disposition with respect to the heterocyclic ring and an axial H-13 orientation with respect to the latter. Hence, the conformation portrayed in Figure 1c represents structure **9** in solution.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared spectra of $CHCl_3$ solutions were recorded on a Perkin-Elmer 257 spectrophotometer and mass spectra on a Hewlett-Packard 5970 GC–MS instrument, calibrated with perfluorotributylamine for 70-eV operations. All starting mixtures for the Diels–Alder reactions were prepared in a drybox, and the cycloadditions were carried out in rigorously degassed (oxygen-free) solutions. GC analyses were performed on Carlo Erba HRGC-5160 (with an on-column injection system on an 0.32-mm-diameter, 30-m SP-2340 fused silica capillary column) and Hewlett-Packard 5880A (with an on-column injection system on an 0.25-mm diameter, 30-m SPB-5 capillary column) chromatographs (internal standards *m*-methoxy- and *p*-methoxyacetophenone). Absorption chromatography was carried out on Merck silica gel (0.040–0.063 mm, 230–240 mesh ASTM). All extracts were dried over anhydrous Na_2SO_4. Optical rotations were measured in chloroform solution on a Jasco DIP 360 polarimeter.

All NMR spectra were run on dilute deuteriochloroform solutions (internal Me_4Si) at ambient temperature, using a Varian Associates VXR-400 multinuclear instrument. The assignment of resonances in terms of ^1H and ^{13}C chemical shifts, ^{13}C multiplicities, and interproton coupling constants was performed by standard one- and two-dimensional FT NMR techniques. ^1H 2D chemical shift correlation (COSY) experiments[16] were run to establish proton–proton connectivities via J_{HH} couplings. These were followed by ^{13}C multiplicity selection (via APT)[17] and carbon–proton heteronuclear chemical shift correlations mediated by one-bond J_{CH} couplings. Assignment of carbon–carbon connectivities involving quaternary carbon atoms was made by means of selective 2D INEPT experiments.[18] Proton–proton coupling constants were inferred from 1D spectra. Homonuclear selective $^1H\{^1H\}$ NOE data were obtained by the difference method[19] using the frequency cycling techniques[20] for selective preirradiation. Standard pulse programs were used in obtaining the 2D spectra.

Table I. Reaction Conditions of the Diels–Alder Reactions of Carenones 1 and 3 and Dienes 2[a]

reactants	Yb(fod)$_3$/ketone[b]	diene/ketone[b]	reactn temp, °C	reactn time, h	yield,[c] %
1a–2a	0.5	9	120	95	60
1a–2b	0.5	6	120	80	64
1b–2a	0.25	6	120	48	90
1b–2b	0.25	6	120	48	88
1b–2c	0.25	6	120	48	95
3–2b	0.5	9	110	38	80

[a] Complexation time, 40 min; complexation temperature, 22 °C;[3a] ketone concentration, 0.2 M. [b] Ratio of equivalents. [c] GC-based yields (isolated product yields 10–20% lower).

General Procedure for the Diels–Alder Reactions. The following discussion of the **3–2b** reaction is a typical procedure used for all cycloadditions. Details are listed in Table I.

A solution of 0.75 g (5 mmol) of ketone **3** in 10 mL of dry toluene was added to a solution of 2.65 g (2.5 mmol) of Yb(fod)$_3$ in 10 mL of dry toluene in an ampule and the mixture stirred at room temperature for 40 min. Then 3.78 g (45 mmol) of (*E*)-1-methoxybutadiene (**2b**) was added to the reaction mixture, the ampule sealed under vacuum, and the mixture warmed at 110 °C for 38 h. It then was cooled, poured into ice–water, and extracted with ether. The extract was washed with sodium bicarbonate solution, dried (Na_2SO_4), and evaporated under reduced pressure, giving in 80% yield (GLC) crude adduct **12**, which was chromatographed and eluted with 9:1 hexane–ethyl acetate.

Tricyclic ketone 12: mp 47–48 °C (*n*-hexane); IR 1705 (s, C=O), 1657 (w, C=C) cm^{-1}; ^1H NMR δ 0.77 (m, 1, H-4), 0.78 (dd, 1, $J_{3,4}$ = 7.6 Hz, $J_{3,2B}$ = 9.2 Hz, H-3), 1.01 (s, 3, C-12 Hs), 1.03 (s, 3, C-10 Hs), 1.10 (s, 3, C-11 Hs), 1.50 (dd, 1, $J_{4a,4}$ = 7 Hz, $J_{4a,5B}$ = 2.7 Hz, H-4a), 1.82 (dd, 1, $J_{2A,3}$ = 6.7 Hz, H-2A), 2.15 (dd, 1, $J_{5B,6}$ = 5.3 Hz, H-5B), 2.35 (dm, 1, $J_{5a,4a}$ = 6.3 Hz, H-5a), 2.53 (dd, 1, H-2B), 3.27 (s, 3, OMe), 3.42 (br d, 1, $J_{7,8}$ = 4.3 Hz, H-8), 5.87 (m, 1, $J_{6,7}$ = 10.5 Hz, $J_{6,5A}$ = 2.4 Hz, H-6), 5.97 (m, 1, H-7); ^{13}C NMR δ 14.35 (C-10), 20.22 (C-3), 20.34 (C-9), 20.86 (C-12), 25.51 (C-4), 28.16 (C-11), 28.35 (C-5), 32.05 (C-4a), 35.67 (C-2), 46.92 (C-8a), 58.45 (OMe), 79.33 (C-8), 123.97 (C-7), 127.44 (C-6), 217.05 (C-1); MS, *m/e* (rel intens) 234 (M$^+$, 7), 155 (66), 91 (97), 77 (76), 69 (65), 45 (base); $[\alpha]^{21}_D$ = −0.4° (*c* = 6.51). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.95; H, 9.45.

Tricyclic ketone 4: colorless liquid (elution with 9:1 hexane–ethyl acetate); IR 1680 (s, C=O) cm^{-1}; ^1H NMR δ 1.02 (s, 3, C-12 Hs), 1.10 (s, 3, C-10 Hs), 1.12 (s, 3, C-11 Hs), 1.16 (m, 1, $J_{3,4A}$ = 4.5 Hz, $J_{3,4B}$ = 3.5 Hz, H-3), 1.38 (br d, 1, H-8B), 1.42 (d, 1, $J_{2,3}$ = 7.5 Hz, H-2), 1.54 (m, 1, H-5B), 1.60 (s, 3, 6-Me), 1.62 (s, 3, 7-Me), 1.75 (m, 1, $J_{4a,4A}$ = 11.5 Hz, $J_{4a,5a}$ = $J_{4a,5B}$ = 6 Hz, $J_{4a,4B}$ = 1.7 Hz, H-4a), 1.83–1.85 (m, 2, H-4A, H-4B), 2.15 (dm, 1, H-5A), 2.35 (br d, 1, H-8A); ^{13}C NMR δ 17.69 (C-10), 17.85 (C-12), 19.00 (C-6 and C-7 methyls), 23.44 (C-4), 23.97 (C-9), 24.07 (C-3), 30.02 (C-11), 31.39 (C-2), 33.09 (C-4a), 34.85 (C-5), 36.48 (C-8), 45.76 (C-8a), 121.42 (C-7), 121.60 (C-6), 213.01 (C-1); MS, *m/e* (rel intens) 232 (M$^+$, 7), 150 (66), 121 (41), 107 (base), 91 (55); $[\alpha]^{21}_D$ = −234° (*c* = 1.71). Anal. Calcd for $C_{16}H_{24}O$: C, 82.71;

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H, 10.41. Found: C, 82.90; H, 10.40.

Tricyclic ketone 5: colorless liquid (elution with 95:5 hexane–ethyl acetate); IR 1670 (s, C=O) cm^{-1}; ^1H NMR δ 1.04 (s, 3, C-12 Hs), 1.13 (s, 3, C-11 Hs), 1.20 (ddd, 1, $J_{3,2}$ = 8.1 Hz, $J_{3,4B}$ = 6 Hz, $J_{3,4A}$ = 5.4 Hz, H-3), 1.20 (s, 3, C-10 Hs), 1.61 (d, 1, H-2), 1.86 (ddd, 1, $J_{4B,4a}$ = 1.2 Hz, H-4B), 1.87 (m, 1, $J_{5B,4a}$ = 6.5 Hz, $J_{5B,6}$ = 5.3 Hz, H-5B), 1.98 (m, 1, $J_{4a,4A}$ = 13.5 Hz, $J_{4a,5A}$ = 6 Hz, H-4A), 2.25 (ddd, 1, H-4A), 2.28 (m, 1, $J_{5A,6}$ = 2.3 Hz, H-5A), 3.24 (m, 1, $J_{8,7}$ = 1.5 Hz, H-8), 3.26 (s, 3, OMe), 5.78 (m, 1, $J_{6,7}$ = 10.2 Hz, H-6), 5.88 (m, 1, H-7); ^{13}C NMR δ 18.67 (C-10), 19.18 (C-12), 24.77 (C-9), 25.05 (C-4), 26.29 (C-3), 28.75 (C-5), 30.83 (C-11), 31.14 (C-4a), 37.08 (C-2), 47.23 (C-8a), 58.14 (OMe), 80.47 (C-8), 122.99 (C-7), 127.11 (C-6), 213.47 (C-1); MS, *m/e* (rel intens) 234 (M^+, 16), 93 (92), 91 (83), 84 (72), 83 (79), 82 (base), 67 (74); $[\alpha]^{21}_D$ = −323° (*c* = 0.88). Anal. Calcd for: $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.99; H, 9.45.

Tricyclic ketone 6a: elution with 4:1 hexane–ethyl acetate; mp 94–95 °C (*n*-hexane); IR 1688 (s, C=O) cm^{-1}; ^1H NMR δ 1.16 (s, 3, C-12 Hs), 1.28 (s, 6, C-10 and C-11 Hs), 1.50 (br d, 1, H-8B), 1.56 (br s, 3, 7-Me), 1.67 (br s, 3, 6-Me), 1.93 (br d, 1, H-5A), 2.06 (d, 1, $J_{2,3}$ = 6.9 Hz, H-3), 2.20 (d, 1, H-2), 2.34 (dd, 1, $J_{4a,5A}$ = 6.4 Hz, $J_{4a,5B}$ = 1.7 Hz, H-4a), 2.41 (br d, 1, H-8A), 2.76 (br d, 1, H-5B); ^{13}C NMR δ 18.29 (C-10), 18.75 (6-Me), 19.03 (7-Me), 19.13 (C-12), 26.39 (C-5), 28.84 (C-9), 29.35 (C-11), 37.61 (C-8), 38.52 (C-3), 40.25 (C-2), 48.67 (C-4a), 49.73 (C-8a), 120.79 (C-7), 123.24 (C-6), 204.12 (C-4), 208.11 (C-1); MS, *m/e* (rel intens) 246 (M^+, 38), 164 (base), 121 (69), 107 (74), 96 (59), 91 (68). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.95; H, 9.03.

Tricyclic Ketones 6b and 6c. Gradient elution with 97:3 to 60:40 hexane–ethyl acetate furnished most of the adduct **6b** and some fractions enriched in isomer **6c**. These fractions were combined and evaporated, giving adduct **6c** by crystallization of the residue from n-hexane.

Tricyclic ketone 6b: mp 115–116 °C (*n*-hexane); IR 1690 (s, C=O) cm^{-1}; ^1H NMR δ 1.18 (s, 3, C-12 Hs), 1.28 (s, 3, C-11 Hs), 1.29 (s, 3, C-10 Hs), 1.65 (m, 1, H-8B), 1.71 (s, 3, 6-Me), 1.88 (br d, 1, H-5A), 2.06 (d, 1, $J_{2,3}$ = 6.9 Hz, H-3), 2.20 (d, 1, H-2), 2.40 (dd, 1, $J_{4a,5A}$ = 6.3 Hz, $J_{4a,5B}$ = 1.7 Hz, H-4a), 2.43 (br d, 1, H-8A), 2.77 (br d, 1, H-5B), 5.25 (m, 1, H-7); ^{13}C NMR δ 18.31 (C-10), 19.08 (C-12), 23.38 (6-Me), 24.89 (C-5), 28.91 (C-9), 29.36 (C-11), 31.88 (C-8), 38.45 (C-3), 40.32 (C-2), 48.63 (C-4a), 48.90 (C-8a), 116.16 (C-7), 131.71 (C-6), 203.97 (C-4), 208.44 (C-1); MS, *m/e* (rel intens) 232 (M^+, 32), 164 (75), 96 (base), 91 (90), 77 (62), 67 (66), 53 (75). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.50, H, 8.70.

Tricyclic ketone 6c: mp 100–101 °C (*n*-hexane); IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 1.18 (s, 3, C-12 Hs), 1.28 (s, 3, C-11 Hs), 1.29 (s, 3, C-10 Hs), 1.51 (br d, 1, H-8B), 1.61 (s, 3, 7-Me), 1.95 (dm, 1, H-5A), 2.08 (d, 1, $J_{2,3}$ = 7 Hz, H-3), 2.22 (d, 1, H-2), 2.34 (dd, 1, $J_{4a,5A}$ = 6.5 Hz, $J_{4a,5B}$ = 1.7 Hz, H-4a), 2.36 (m, 1, H-8A), 2.89 (dm, 1, H-5B), 5.37 (m, 1, $J_{6,5B}$ = 5.3 Hz, $J_{6,5A}$ = 2.3 Hz, H-6); ^{13}C NMR δ 18.33 (C-10), 19.16 (C-12), 20.56 (C-5), 23.69 (7-Me), 28.98 (C-9), 29.36 (C-11), 36.03 (C-8), 38.44 (C-3), 40.37 (C-2), 47.76 (C-4a), 49.66 (C-8a), 118.44 (C-6), 129.30 (C-7), 204.17 (C-4), 208.01 (C-1); MS, *m/e* (rel intens) 232 (M^+, 46), 164 (91), 107 (70), 96 (base), 91 (85). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.40; H, 8.65.

Ketones 7a, 7b, and 8. Elution with 9:1 petroleum ether–ethyl acetate furnished adduct **7a**. Fractions containing mixtures of compounds **7b** and **8** were combined and chromatographed on a Merck Lichoprep Si60 prepacked column. Elution with 9:1 petroleum ether–ethyl acetate gave ketone **7b**. Further elution with 4:1 petroleum ether–ethyl acetate gave tetracyclic compound **8**.

Tricyclic ketone 7a: mp 92–93 °C (*n*-hexane); IR 1687 (s, C=O) cm^{-1}; ^1H NMR δ 1.16 (s, 3, C-12 Hs), 1.26 (s, 3, C-11 Hs), 1.39 (s, 3, C-10 Hs), 1.95 (ddd, 1, $J_{5A,4a}$ = 7.4 Hz, $J_{5A,6}$ = 2.4 Hz, H-5A), 2.11 (d, 1, $J_{3,2}$ = 7.5 Hz, H-3), 2.32 (d, 1, H-2), 2.56 (dd, 1, $J_{4a,5B}$ = 1.5 Hz, H-4a), 3.13 (br d, 1, $J_{5B,6}$ = 4.5 Hz, H-5B), 3.19 (s, 3, OMe), 3.36 (d, 1, $J_{8,7}$ = 4.8 Hz, H-8), 5.87 (m, 1, $J_{7,6}$ = 10.2 Hz, H-7), 5.93 (m, 1, H-6); ^{13}C NMR δ 19.07 (C-10), 19.79 (C-12), 20.15 (C-5), 29.38 (C-9), 29.87 (C-11), 40.32 (C-3), 44.95 (C-4a), 46.65 (C-2), 52.68 (C-8a), 56.71 (OMe), 79.54 (C-8), 122.38 (C-7), 129.74 (C-6), 203.66 (C-4), 209.36 (C-1); MS, *m/e* (rel intens) 248 (M^+, 5), 96 (base), 84 (50), 81 (45), 53 (42). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12. Found: C, 72.67; H, 8.08.

Tricyclic ketone 7b: mp 99–100 °C (*n*-hexane); IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 1.16 (s, 3, C-12 Hs), 1.26 (s, 3, C-10 Hs), 1.30 (s, 3, C-11 Hs), 1.96 (dm, 1, H-5A), 2.14 (d, 1, $J_{3,2}$ = 6.9 Hz, H-3), 2.23 (d, 1, H-2), 2.44 (dd, 1, $J_{4a,5A}$ = 5.4 Hz, $J_{4a,5B}$ = 2.2 Hz, H-4a), 2.89 (dm, 1, H-5B), 3.33 (s, 3, OMe), 4.20 (m, 1, $J_{8,7}$ = 1.7 Hz, H-8), 5.66 (m, 1, $J_{7,6}$ = 10.3 Hz, H-7), 5.73 (m, 1, $J_{6,5A}$ = 2.5 Hz, $J_{6,5B}$ = 4.4 Hz, H-6); ^{13}C NMR δ 13.43 (C-12), 18.38 (C-10), 20.46 (C-5), 28.85 (C-9), 29.92 (C-11), 36.61 (C-2), 38.22 (C-3), 50.32 (C-4a), 54.15 (C-8a), 57.87 (OMe), 76.55 (C-3), 124.62 (C-7), 126.63 (C-6), 203.42 (C-4), 205.96 (C-1); MS, *m/e* (rel intens) 248 (M^+, 0.1), 123 (9), 91 (8), 84 (base), 77 (8), 69 (21), 53 (10). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12. Found: C, 72.50; H, 8.12.

Tetracyclic ketone 8: IR 1685 (s, C=O) cm^{-1}; ^1H NMR δ 1.15 (s, 3, C-10 Hs), 1.22 (s, 3, C-12 Hs), 1.25 (s, 3, C-11 Hs), 1.48 (dd, 1, $J_{14A,5}$ = 11.6 Hz, $J_{14A,13}$ = 11.0 Hz, H-14A), 1.78 (d, 1, $J_{2,3}$ = 7.3 Hz, H-2), 1.82 (d, 1, H-3), 2.06 (m, 1, H-8B), 2.07 (m, 1, H-14B), 2.08 (m, 1, H-8A), 2.93 (m, 1, $J_{5,14B}$ = 6.5 Hz, $J_{5,6}$ = 2.4 Hz, H-5), 3.59 (s, 3, OMe), 4.22 (ddd, 1, $J_{13,15}$ = 8.6 Hz, $J_{13,14B}$ = 1.7 Hz, H-13), 4.88 (m, 1, $J_{15,16}$ = 12.7 Hz, H-15), 5.56 (m, 1, $J_{6,7}$ = 10.3 Hz, H-6), 5.62 (m, 1, H-7), 6.68 (d, 1, H-16); ^{13}C NMR δ 16.66 (C-10), 19.31 (C-12), 27.42 (C-9), 27.79 (C-11), 31.27 (C-3, C-5), 35.57 (C-2), 36.57 (C-14), 38.69 (C-8), 44.34 (C-8a), 55.92 (OMe), 73.50 (C-13), 102.66 (C-15), 107.87 (C-4a), 124.20 (C-7), 128.89 (C-6), 141.78 (C-4), 151.01 (C-16), 211.52 (C-1); MS, *m/e* (rel intens) 300 (M^+, 6), 176 (21), 132 (80), 96 (17), 84 (base), 69 (18), 44 (17). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.80; H, 8.07.

Tetracyclic ketone 9: IR 1670 (s, C=O) cm^{-1}; ^1H NMR δ 0.92 (m, 1, H-6A), 1.15 (s, 3, C-10 Hs), 1.16 (s, 3, C-12 Hs), 1.20 (m, 1, $J_{14A,5}$ = 9.9 Hz, $J_{14A,13}$ = 11.5 Hz, H-14a), 1.24 (s, 3, C-11 Hs), 1.31 (m, 1, H-8B), 1.62 (m, 2, H-7A, H-7B), 1.71 (m, 1, H-8A), 1.75 (d, 1, $J_{2,3}$ = 7.3 Hz, H-2), 1.79 (m, 1, H-15A), 1.82 (d, 1, H-3), 1.91 (m, 2, H-6B, H-15B), 2.07 (ddd, 1, $J_{14B,5}$ = 7.6 Hz, $J_{14B,13}$ = 1.7 Hz, H-14B), 2.30 (m, 1, $J_{5,6A}$ = 11.9 Hz, $J_{5,6B}$ = 4.5 Hz, H-5), 3.36 (s, 3, OMe), 3.54 (m, 2, H-16A, H-16B), 3.71 (m, 1, H-13); ^{13}C NMR δ 17.33 (C-10), 19.21 (C-12), 20.79 (C-7), 28.08 (C-9, C-11), 29.83 (C-5), 32.20 (C-3), 35.30 (C-6, C-15), 36.06 (C-2), 37.80 (C-8), 38.15 (C-14), 45.66 (C-8a), 58.76 (OMe), 69.02 (C-16), 72.34 (C-13), 112.68 (C-4a), 142.53 (C-4), 212.45 (C-1); MS, *m/e* (rel intens) 304 (M^+, 21), 276 (47), 175 (43), 147 (62), 91 (34), 45 (base). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 75.03; H, 9.30.

Tricyclic ketone 13: mp 61–62 °C (*n*-hexane); IR 1670 (s, C=O) cm^{-1}; ^1H NMR δ 1.04 (s, 3, C-12 Hs), 1.13 (s, 3, C-11 Hs), 1.19 (s, 3, C-10 Hs), 1.26 (m, 1, H-6B), 1.32 (ddd, 1, $J_{3,2}$ = 8.0 Hz, $J_{3,4B}$ = 5.6 Hz, $J_{3,4A}$ = 6.2 Hz, H-3), 1.37 (m, 1, H-5B), 1.41 (m, 1, H-7A), 1.61 (d, 1, H-2), 1.67 (m, 1, H-5A), 1.73 (m, 1, H-6A), 1.78 (ddd, 1, $J_{4B,4a}$ = 2.0 Hz, H-4B), 1.80 (m, 1, H-7B), 1.90 (m, 1, $J_{4a,4A}$ = 13.5 Hz, $J_{4a,5A}$ = $J_{4a,5B}$ = 6.0 Hz, H-4a), 2.41 (ddd, 1, H-4A), 3.14 (s, 3, OMe), 3.23 (dd, 1, $J_{8,7A}$ = 2.7 Hz, $J_{8,7B}$ = 2.8 Hz, H-8); ^{13}C NMR δ 14.39 (C-6), 18.64 (C-10), 20.01 (C-12), 23.62 (C-7), 24.20 (C-4), 25.81 (C-9), 26.84 (C-5), 27.60 (C-3), 30.74 (C-11), 33.74 (C-4a), 37.11 (C-2), 47.64 (C-8a), 57.07 (OMe), 85.83 (C-8), 216.04 (C-1); MS, *m/e* (rel intens) 236 (M^+, 24), 95 (73), 82 (75), 67 (base), 55 (54); $[\alpha]^{21}_D$ = −155° (*c* = 0.547). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.48; H, 10.20.

Tricyclic ketone 14: mp 51–52 °C (*n*-hexane); IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 0.79 (ddd, 1, $J_{3,4}$ = 9.5 Hz, $J_{3,2B}$ = 7.9 Hz, $J_{3,2A}$ = 7.6 Hz, H-3), 0.96 (dd, 1, $J_{4,4a}$ = 9.0 Hz, H-4), 0.99 (s, 3, C-12 Hs), 1.02 (s, 3, C-10 Hs), 1.11 (s, 3, C-11 Hs), 1.35 (m, 1, H-6B), 1.45 (m, 2, H-4a, H-7A), 1.55 (m, 1, $J_{4a,5B}$ = 2.5 Hz, H-5B), 1.74 (m, 1, $J_{5A,4a}$ = 5.2 Hz, H-5A), 1.80 (dd, 1, H-2A), 1.82 (m, 1, H-6A), 1.88 (m, 1, H-7B), 2.43 (m, 1, H-2B), 3.17 (s, 3, OMe), 3.50 (dd, 1, $J_{7B,8}$ = 3 Hz, $J_{7A,8}$ = 1.5 Hz, H-8); ^{13}C NMR δ 14.20 (C-10), 14.98 (C-7), 19.73 (C-9), 19.96 (C-3), 22.00 (C-12), 22.99 (C-7), 25.02 (C-4), 26.28 (C-5), 28.40 (C-11), 34.87 (C-4a), 35.19 (C-2), 47.65 (C-8a), 57.31 (OMe), 82.22 (C-8), 218.33 (C-1); MS, *m/e* (rel intens) 236 (M^+, 63), 161 (78), 95 (80), 79 (78), 67 (base), 55 (75); $[\alpha]^{21}_D$ = −93° (*c* = 3.47). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.55; H, 10.30.

Tricyclic ketone 15a: mp 90–91 °C (*n*-hexane); IR 1690 (s, C=O) cm^{-1}; ^1H NMR δ 1.21 (s, 3, C-12 Hs), 1.25 (s, 3, C-11 Hs), 1.30 (m, 1, H-6B), 1.34 (s, 3, C-10 Hs), 1.39 (m, 1, H-5A), 1.45 (m, 1, H-7A), 1.64 (m, 1, H-6A), 1.85 (m, 1, H-7B), 2.11 (d, 1, $J_{2,3}$ = 7.4 Hz, H-3), 2.29 (d, 1, H-2), 2.33 (dd, 1, $J_{4a,5A}$ = 4.9 Hz, $J_{4a,5B}$ = 2.4 Hz, H-4a), 2.38 (m, 1, H-5B), 3.12 (s, 3, OMe), 3.25 (dd, 1, $J_{8,7B}$ = 3.6 Hz, $J_{8,7A}$ = 2.0 Hz, H-8); ^{13}C NMR δ 15.54 (C-6), 18.83 (C-10), 19.72 (C-5), 19.87 (C-12), 22.75 (C-7), 29.01 (C-9), 29.69

(C-11), 40.57 (C-3), 46.25 (C-2), 47.20 (C-4a), 53.46 (C-8a), 56.18 (OMe), 84.82 (C-8), 204.39 (C-4), 211.26 (C-1); MS, *m/e* (rel intens) 250 (M^+, 24), 96 (base), 81 (56), 67 (76), 53 (61). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.10; H, 8.90.

Tricyclic ketone 15b: mp 102–103 °C (*n*-hexane); IR 1700 (s, C=O) cm^{-1}; ^1H NMR δ 1.13 (s, 3, C-10 Hs), 1.19 (s, 3, C-12 Hs), 1.29 (s, 3, C-11 Hs), 1.34 (m, 1, H-7A), 1.38 (m, 1, H-6B), 1.40 (m, 1, H-5A), 1.68 (m, 1, H-6A), 2.00 (m, 1, H-7B), 2.10 (d, 1, $J_{2,3}$ = 6.8 Hz, H-2), 2.15 (d, 1, H-3), 2.22 (m, 1, $J_{4a,5A}$ = 4.5 Hz, $J_{4a,5B}$ = 3.4 Hz, H-4a), 2.32 (m, 1, H-5B), 3.27 (s, 3, OMe), 3.62 (dd, 1, $J_{8,7A}$ = 11.0 Hz, $J_{8,7B}$ = 4.5 Hz, H-8); ^{13}C NMR δ 13.25 (C-12), 18.30 (C-10), 20.27 (C-5), 20.57 (C-6), 24.59 (C-4a), 27.55 (C-9), 28.67 (C-11), 37.88 (C-3), 38.13 (C-2), 53.10 (C-4a), 55.52 (C-8a), 56.98 (OMe), 79.56 (C-8), 204.86 (C-4), 206.17 (C-1); MS, *m/e* (rel intens) 250 (M^+, 16), 96 (base), 8 (81), 67 (60), 55 (57). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.80; H, 8.82.

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Regiochemical Control of the Ring-Opening of 1,2-Epoxides by Means of Chelating Processes. Synthesis and Reactions of the *cis*- and *trans*-Oxides Derived from 4-(Benzyloxy)cyclohexene

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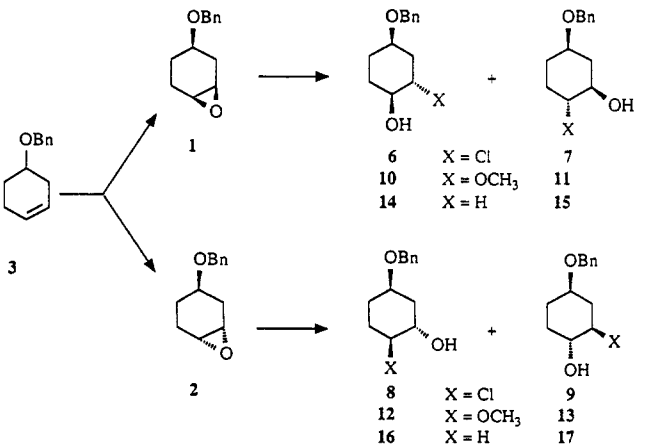
The synthesis and reactions of diastereomeric epoxides *cis*-**1** and *trans*-**2** with heteronucleophiles were carried out in order to probe the effect of remote polar functionality on the regioselectivity of nucleophilic addition to the epoxide ring. The reaction of *cis*-epoxide **1** with $TiCl_4$ in CH_2Cl_2 gave exclusively the chlorohydrin **7**, whereas the regioisomeric chlorohydrin **6** was obtained as the main product from the reaction of **1** with HCl in $CHCl_3$. The same reactions with epoxide **2** yielded chlorohydrins **8** and **9**, the main product being **8** in both cases. Chlorohydroxylation of olefin **3** via Sharpless conditions ($TiCl_4$ and TBHP) gave **7**, **8**, and **9** in a 96:6:2 ratio. The regiochemical outcome of ring-opening addition reactions with epoxide **2** is necessarily independent of any bidentate chelation effects; however, in some of the comparable nucleophilic reactions of epoxide **1**, chelation of the counterion by the oxirane oxygen and the remote benzyloxy group can substantially alter the regioselectivity of addition. Thus, the **10**:**11** regioisomeric ratio (85:15) obtained from the H^+-catalyzed methanolysis of **1** was completely inverted (2:98) when the solvolysis was carried out with concentrated methanolic $LiClO_4$. The ring-opening of **1** with $LiAlH_4$ afforded **14** and **15** in a 2:98 ratio; however, reaction of **1** with premixed $LiAlH_4$/12-crown-4 gave the opposite result, **14**:**15** = 82:18. In all of the addition reactions of **1** and **2** the ring-opened products were consistent with the well-known preference for diaxial nucleophilic ring-opening in cyclohexene oxides derivatives; our results are further interpreted as evidence for chelation control in some of the addition reactions of **1**.

Introduction

The ring-opening addition reactions of oxiranes proceed through mechanistic pathways that can range from S_N1 to S_N2 reactivity. The former is an electrophile-promoted event, followed by attack of the nucleophile, while the latter process is a nucleophilic displacement reaction that may be assisted by a proton, metal ion, or other electrophile.[3-5] The regiochemical outcome of the ring-opening process may span a range of Markovnikov to contra-Markovnikov type of cleavage, and the stereochemical course of the reaction can range from complete inversion to complete retention of configuration depending on the solvent, nucleophile, electrophilic catalyst, temperature, and the structure, configuration, and conformation of the epoxide.[3-6]

Scheme I



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