mp 120–122 °C (lit.[7] mp 123–124 °C); R_f (3) 0.32; mass spectrum m/z 394 ($M + H^+$); ^1H NMR ($CDCl_3$) δ 7.3–7.1 (dd, 4 H, C_6H_4), 5.8–5.2 (br s, 1 H, NH), 5.5 (d, 1 H, α-CH), 3.65 (s, 2 H, SCH_2), 2.3 (s, 3 H, $C_6H_4CH_3$), 1.8–1.5 (m, 10 H, CH_2).

Registry No. 1, 67654-35-7; 2, 115797-97-2; 3, 115797-98-3; 4, 115797-99-4; 5, 105563-00-6; 4-$MeC_6H_4CH_2SH$, 4498-99-1; cyclohexanone, 108-94-1; methyl isocyanoacetate, 39687-95-1.

Diels–Alder Reactions of Cycloalkenones. 13. Reactions of 2-Cyclohexenones with (*E*)-1-Methoxy-1,3-butadiene[1]

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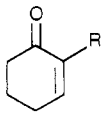
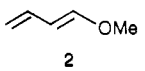
Introduction

Several years ago we undertook a broad study on the Lewis acid catalyzed Diels–Alder reaction of conjugated cycloalkenones with simple dienes such as 1,3-butadiene, isoprene and (*E*)-piperylene.[3] In the course of this investigation we analyzed the effects of specific reaction parameters on the reaction yield[4] and then examined the diastereofacial selectivity,[5] the exo–endo diastereoselectivity,[6] and the regioselectivity[7] of the reactions of these dienes with several substituted 2-cyclohexenones. In continuation of this study and in consideration of the relatively modest functionalities incorporated into the dienic framework used so far, we focused our attention on the reactions of cycloalkenones with alkoxybutadienes, a diene class interesting for its introduction of valuable functional groups into the adducts. These dienes have been used widely in cycloadditions with highly reactive dienophiles, their use being limited in reactions with poor dienophiles such as conjugated cycloalkenones.[8] In this connection we now report the Diels–Alder reaction of 2-cyclohexenone (**1a**) and 2-methyl-2-cyclohexenone (**1b**) with (*E*)-1-methoxy-1,3-butadiene (**2**).



1a, R=H
b, R=Me



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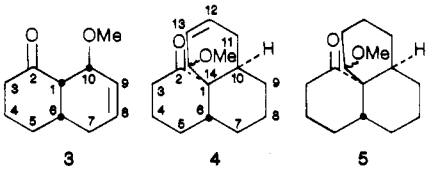
Results and Discussion

Thermal cycloaddition of 2-cyclohexenone (**1a**) with (*E*)-1-methoxy-1,3-butadiene (**2**) at 160 °C in the presence of hydroquinone affords the endo adduct **3** in moderate yield (47%). In order to improve the yield, Lewis acid catalyzed reactions were executed. Lewis acids have been known for some time to increase remarkably the rates and yields of Diels–Alder reactions.[9] On the other hand, care had to be exercised to avoid polymerization of the dienes, especially electron-rich dienes.

When 2-cyclohexenone (**1a**) and diene **2** interact in toluene solution under the influence of the most common Lewis acids ($AlCl_3$, $BF_3{\cdot}Et_2O$, $EtAlCl_2$, $SnCl_4$), resinous materials (formed by the Friedel–Crafts reaction between diene and solvent or diene polymerization) were produced, only traces of adducts being detected. The recent Danishefsky discovery[10] of the ability of certain lanthanide complexes to act as mild Lewis acid catalysts in a variety of Diels–Alder and homo-Diels–Alder reactions induced us to explore this new type of catalyst in the present case.

The reaction of (*E*)-1-methoxy-1,3-butadiene (**2**) with 2-cyclohexenone (**1a**) under $Yb(fod)_3$ catalysis[11] in toluene solution at 110 °C for 110 h afforded a 1.5:1 mixture (55%) of two compounds, neither of which was adduct **3**.

Structure analysis by IR and ^1H and ^{13}C NMR spectroscopy showed these compounds to be methoxy dienic ketone stereoisomers having a tricyclic skeleton with three fused, six-membered rings and differing from one another only in the configuration of the methoxy group. For the determination of the complete stereochemistry the hydrogen coupling characteristics in the ^1H NMR spectra were inspected but were found to leave ambiguities of interpretation for the J_{HH} values of the allylic hydrogens of the two cyclohexene moieties of each compound. Hence the dienes **4a** and **4b** were hydrogenated, yielding the saturated ketones **5a** and **5b**, respectively. On the basis of the structure analysis of the latter two substances, it was possible to assign rigorously structure **4a** with an equatorial 14β-methoxy group to the major product and structure **4b** with an axial 14α-methoxy group to the minor component of the reaction mixture. Both ring junctions of the tricycles could be shown to be cis and the carbon–carbon double bonds of the unsaturated ketones to be positioned at C(8)–C(9) and C(12)–C(13).



3 **4** **5**

a, β-OMe; **b**, α-OMe

The sequence of events leading to the tricyclic ketones **4** was examined next. When octalone **3**, prepared by the thermal cycloaddition, was treated with (*E*)-1-methoxy-1,3-butadiene (**2**) in toluene solution under $Yb(fod)_3$ catalysis at 100 °C for 13 h, there was obtained a mixture of the tricyclic ketones **4a** and **4b**, identical with that from the reaction of 2-cyclohexenone (**1a**) and (*E*)-1-methoxy-1,3-butadiene (**2**). Heating a toluene solution of octalone

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(11) $Yb(fod)_3$ is an abbreviation for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium.

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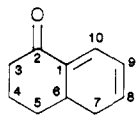
3 and $Yb(fod)_3$ at 100 °C for 7 h led to the dienone **6**[12] in 88% yield. Finally, when dienone **6** was treated with diene **2** under the conditions of the latter's reaction with octalone **3**, a 1.5:1 mixture of the Diels–Alder adducts **4a** and **4b** was obtained once again.

In summary, these experiments prove rigorously the sequence of reactions of 2-cyclohexenone (**1a**) with (*E*)-1-methoxy-1,3-butadiene (**2**) en route to the tricyclic ketones to be (i) a Diels–Alder reaction affording endo adduct **3**, (ii) an acid-induced methanol β-elimination of the latter, and (iii) a Diels–Alder reaction of the resultant dienone **6** with the starting diene **2** affording a 1.5:1 mixture of endo and exo adducts **4a** and **4b**. Furthermore, the tricyclic ketones were shown to be kinetically based Diels–Alder products on the basis of the constancy of the product ratio throughout the course of the reaction and the lack of exo–endo isomerization of the pure adducts on their exposure to the reaction conditions of the Diels–Alder reaction.

Interaction of 2-methyl-2-cyclohexenone (**1b**) with diene **2** under $Yb(fod)_3$ catalysis in a variety of experimental conditions failed, leading only to unchanged starting ketone or resinous material. On the other hand, thermal cycloaddition at 160 °C for 72 h afforded endo adduct **7** in modest yield (32%). Hydrogenation of octalone **7** gave decalone **8**. The observed low reactivity of ketone **1b** may be due to the presence of an electron-donor substituent (i.e., a methyl group) on the reacting double bond.



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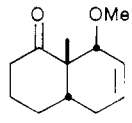

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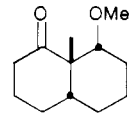

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The thermal reactions of cyclohexenones **1a** and **1b** with diene **2** are highly regioselective and endo-diastereoselective. The reactions of both dienophiles with (*E*)-1-methyl-1,3-butadiene[3b] are also highly regioselective, but show a different diastereoselectivity. Whereas the reaction of **1a** is highly endo-diastereoselective, the one of **1b** is poorly endo-diastereoselective (a 2.2:1 endo–exo ratio). The difference of degree of endo-diastereoselectivity of the reactions of 2-methyl-2-cyclohexenone (**1b**) with the two dienes may be due to secondary orbital interactions.[13]

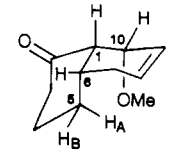
The Diels–Alder reaction of dienone **6** with (*E*)-1-methoxy-1,3-butadiene (**2**) is highly regioselective but poorly endo-diastereoselective (1.5:1 endo–exo ratio). The low endo preference may be the consequence of both endo and exo transition states incorporting comparably stabilizing, secondary orbital interactions. Moreover, the reaction is highly site-selective, no cycloadducts from involvement of the γ,δ-olefinic bond[14] being detected. The α,β double bond is more reactive, being more polarized because of its proximity to the carbonyl group. The value of the carbonyl stretching vibration (1680 cm^{-1}) seems to support the hypothesis of only modest involvement of the γ,δ double bond in conjugation with the keto group.

Finally, the reaction is totally facial-diastereoselective, i.e., the reaction being a syn addition with respect to the pseudoaxial bridgehead H-6. The facial diastereoisomerism may be rationalized on the basis of the cycloaddition taking place in a concerted manner with an unsymmetrical, nonsynchronous transition state in which σ-bond formation with the dienophile β-carbon atom is in advance of that at the α-carbon site.[5] In this event the expected transition state has the incipiently fused cyclohexene ring in half-chair conformation for syn addition and half-boat conformation for anti addition. Moreover, the latter transition state involves also three nonbonded, 1,3-diaxial interactions of the developing carbon–carbon bond at the α-carbon site with hydrogens at carbons 3, 5, and 7. Thus the transition state for syn addition is preferred strongly.

Structure Analysis

The structures of the bicyclic and tricyclic ketones[16] were assigned by analysis of their high-field ^1H and ^{13}C NMR spectra. The ^1H and ^{13}C chemical shift values are reported in the Experimental Section.

(a) Bicyclic Ketones. The structure of octalone **3** follows from both the values of the carbon chemical shifts and their multiplicities and the interproton coupling values. The coupling constant of the bridgehead protons ($^3J_{1,6}$ = 5.0 Hz) assures a cis junction of the fused ring system, while the coupling constants $^3J_{5A,6}$ = 8.0 Hz and $^3J_{5B,6}$ = 3.8 Hz indicate an axial H-6 orientation with respect to the ketonic ring and therefore conformation **9** for



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octalone **3**. Furthermore, the coupling value $^3J_{1,10}$ = 5.0 Hz shows the methoxy group to be antiperiplanar to H-1.

Comparison of the carbon chemical shifts of octalones **3** and **7** reveals the latter ketone with a 1 ppm upfield shift of C-7 due to a γ-effect by the angular methyl group and deshielding of C-5 caused by δ-syn–diaxial interaction of the methoxy group. These observations support conformation **9** for octalone **7**. Moreover, the COSY analysis of ketone **7** shows scalar coupling between the methoxy group and H-5, indicating an α-configuration for the methoxy group.

The structure of dienone **6** is supported by its carbon shift values and their multiplicities as well as by the values of the proton shifts. Selective decoupling experiments have shown the most deshielded proton, H-10 at 7.67 ppm, not to be correlated with the most deshielded carbon, C-8. Furthermore, the structure of dienone **6** is based also on chemical correlations: (i) being derived from octalone **3** by acid-catalyzed β-elimination of methanol and (ii) being converted into the tricyclic ketones **4a** and **4b**.

(b) Tricyclic Ketones. An examination of the data shows compounds **4a** and **4b** to have a skeleton consisting of three, doubly fused, six-membered rings, differing from

(12) Dienone **6** was obtained also from octalone **3** under different experimental conditions: (i) 0.1 M toluene solution of octalone in a heating tube (degassed and sealed under vacuum) heated at 160 °C for 90 h, 16% yield (GLC); (ii) octalone (1 mmol), $BF_3{\cdot}Et_2O$ (0.25 mmol) in toluene solution, room temperature, 3 h, 90% yield (GLC); (iii) octalone (100 mg), 2% aqueous, ethanolic sodium hydroxide solution (30 mL), 0 °C, 24 h, 90% yield (GLC).

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(14) In the catalyzed Diels–Alder reaction of methyl sorbate with 1,3-butadiene and 2,3-dimethyl-1,3-butadiene, the γ,δ carbon–carbon bond is involved in cycloaddition.[15]

(15) Garratt, P. J.; Wyatt, M. *J. Chem. Soc., Chem. Commun.* **1974**, 251.

(16) The pictorialization of the racemic bicyclic and tricyclic compounds is based on an arbitrary choice of absolute configurations.

each other only in the configuration of the methoxy group, in view of the $^3J_{13,14}$ values (3.0 and 4.0 Hz, respectively) and the characteristic differences in the H-14 coupling patterns. As detailed stereochemical information for these ketones cannot be obtained on the basis of their NMR data owing to ambiguities of stereochemical conclusions inferred from interproton couplings involving allylic protons in unsaturated, six-membered ring systems, the ketones were converted into their tetrahydro derivatives **5a** and **5b**. Analysis of the coupling characteristics of the hydrogens on carbons 5, 6, and 7 in the ketones **5a** ($^3J_{5A,6}$ = 4.0, $^3J_{5B,6}$ = 3.5, $^3J_{6,7A}$ = 12, and $^3J_{6,7B}$ = 3.5 Hz) and **5b** ($^3J_{5A,6}$ = 4.5, $^3J_{5B,6}$ = 2.5, $^3J_{6,7A}$ and $^3J_{6,7B}$ = 16.0 Hz) shows H-6 to be equatorial with respect to the cyclohexanone ring in both ketones. A similar analysis of the J values of the hydrogens attached to carbons 9, 10, and 11 in the ketones **5a** ($^3J_{9A,10}$ and $^3J_{9B,10}$ = 6.5, $^3J_{10,11A}$ = 13.0 and $^3J_{10,11B}$ = 4.0 Hz) and **5b** ($^3J_{9B,10}$ = 2.0, $^3J_{10,11A}$ = 12.5, and $^3J_{10,11B}$ = 4.5 Hz) reveals H-10 to be axial with respect to the methoxy-containing ring in both ketones. These data indicate both ring junctions of the tricyclic skeleton to be cis. Moreover, the coupling values of the methylene hydrogens indicate each of the three, six-membered rings of both ketones to adopt a chair conformation. The $^3J_{13B,14}$ value (6.0 Hz) of ketone **5b** accounts for an equatorial H-14 and hence a methoxy group with an α-axial configuration.

Carbon chemical shift data confirm the configuration assignment. The 10 ppm difference in the C-14 shifts of ketones **5a** and **5b** reflects the change in the orientation of the methoxy group from an equatorial (89.5 ppm) to an axial (79.0 ppm) orientation, respectively. The C-5 shift is higher (28.8 ppm) for ketone **4a** than **4b** (26.1 ppm) because of the presence of a δ-effect between C-5 and the methoxy group. The C-13 shift (25.3 ppm) increase of ketone **5a** over **5b** (22.7 ppm) can be attributed to the β-effect of the methoxy group, a shift contributor larger for an equatorial than for an axial substituent. The strong upfield shifts of the C-10 and C-12 resonances of ketone **4b** is due to the γ-effect exerted on the carbons by the axial methoxy group.

Experimental Section

All operations involving the preparations of the starting reaction mixtures for both thermal and catalyzed Diels–Alder reactions were executed in a drybox. All cycloadditions were carried out in rigorously degassed[17] (oxygen-free) solutions or neat liquids in heating tubes sealed under vacuum. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra of carbon tetrachloride solutions were measured on a Perkin-Elmer 257 spectrometer. GC analyses were executed on Carlo Erba HRGC-5160 (with an "on column" injection system, 30-m SP-2340 fused silica capillary column, 0.32-mm diameter) and Hewlett-Packard 5880A (with an "on column" injection system, 30-m SPB-5 capillary column, 0.25-mm diameter) chromatographs (internal standards: *m*-methoxy- and *p*-methoxyacetophenone). Absorption chromatography was carried out on Merk silica gel (0.040–0.063 mm, 230–400-mesh ASTM). All extracts were dried over anhydrous Na_2SO_4.

The spectra of $CDCl_3$ solutions were recorded on a Varian-XL-400 spectrometer for proton spectra, with the use of tetramethylsilane as internal standard. Standard pulse programs were used in obtaining the 2D spectra. The assignments of proton and carbon chemical shifts, ^{13}C multiplicities, and interproton coupling constants (J_{HH}) were performed by means of one- and two-dimensional FT NMR techniques. Firstly proton–proton connectivities via J_{HH} couplings were established by COSY experiments.[19] These were followed by ^{13}C multiplicity selection (DEPT)[20,21] and carbon–proton heteronuclear chemical shift correlation experiments mediated by one-bond J_{CH} couplings. Proton–proton coupling constants were inferred from individual traces of the phase-sensitive COSY data matrices[22] and/or determined by means of conventional double resonance techniques. The routine spectra were recorded on a Brucker WP 80 SY spectrometer.[23]

(1β,6β)-10α-Methoxybicyclo[4.4.0]dec-8-en-2-one (3). A mixture of 1.25 g (13 mmol) of 2-cyclohexenone (**1a**), 20 mg of hydroquinone, and 3.28 g (39 mmol) of (*E*)-1-methoxy-1,3-butadiene (**2**) was degassed, sealed in vacuo in a glass ampule, and heated at 160 °C for 24 h. Then the reaction mixture was purified by column chromatography on 130 g of silica gel (elution with 9:1 ethyl acetate–pentane) to afford 1.10 g (47%) of octalone **3**: IR 3030 (m, olefinic CH), 1705 (s, C=O), 1655 (w, C=C), 1080–1095 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.66 (H-5B), 1.81 (H-4B), 1.91 (H-5A), 2.00 (H-4A, H-7B), 2.13 (H-7A), 2.31 (H-6), 2.40 (H-3B), 2.46 (H-3A), 2.92 (H-1), 3.34 (OMe), 3.80 (H-10), 5.76 (H-8A, H-8B), 5.93 (H-9A, H-9B); ^{13}C NMR δ 24.5 (C-4), 28.0 (C-5), 28.4 (C-7), 35.1 (C-6), 42.0 (C-3), 52.1 (C-1), 57.3 (OMe), 74.6 (C-10), 125.2 (C-9), 127.3 (C-8), 211.4 (C-2). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.21; H, 8.85.

(6β,10α)-14β-Methoxytricyclo[8.4.0.0^{1,10}]tetradeca-8,12-dien-2-one (4a) and (6β,10α)-14α-Methoxytricyclo[8.4.0.0^{1,10}]tetradeca-8,12-dien-2-one (4b). A solution of 0.29 g (3 mmol) of 2-cyclohexenone (**1a**) in 10 mL of dry toluene was added to a solution of 0.79 g (0.75 mmol) of Yb(fod)$_3$ in 10 mL of dry toluene in a heating tube. The solution was stirred under nitrogen at room temperature for 40 min. Then 0.76 g (9 mmol) of the diene **2** and enough solvent to form a 30-mL volume of the final solution were added. The heating tube was degassed, sealed in vacuo, and heated at 100 °C on a heating bath for 110 h. The reaction mixture was cooled, poured into ice–water, and extracted with ether. The extract was washed with 10% sodium bicarbonate solution, dried, and evaporated under vacuum. Chromatography of the residue on 90 g of silica gel and gradient elution with 20:1 to 1:1 pentane–ether mixtures led to 0.23 g (33%) of ketone **4a**: IR 3030 (m, olefinic CH), 1703 (s, C=O), 1655 (w, C=C), 1097 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.76 (H-4B), 1.78 (H-7B), 1.80 (H-11B), 1.90 (H-5B), 1.94 (H-11A), 1.95 (H-5A), 1.98 (H-4A), 2.39 (H-6), 2.41 (H-3B), 2.59 (H-7A), 2.60 (H-3A), 2.81 (H-10), 3.38 (OMe), 4.14 (H-14), 5.55 (H-8A, H-8B), 5.71 (H-12A, H-12B), 5.74 (H-9A, H-9B), 5.88 (H-13A, H-13B); ^{13}C NMR δ 24.1 (C-4), 28.8 (C-5), 30.3 (C-11), 31.0 (C-7), 31.8 (C-10), 35.6 (C-6), 39.5 (C-3), 55.9 (C-1), 58.9 (OMe), 79.1 (C-14), 125.6 (C-13), 126.9 (C-8), 127.7 (C-12), 128.9 (C-9), 214.5 (C-2). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.65; H, 8.70.

Further elution gave 0.15 g (22%) of ketone **4b**: IR 3030 (m, olefinic CH), 1722 (s, C=O), 1660 (w, C=C), 1090 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.52 (H-5B), 1.74 (H-11B), 1.86 (H-4B), 1.88 (H-7B), 1.93 (H-5A), 1.97 (H-4A), 2.15 (H-7A), 2.28 (H-11A), 2.33 (H-3B), 2.36 (H-6), 2.38 (H-3A), 2.77 (H-10), 3.30 (OMe), 4.04 (H-14), 5.44 (H-8A, H-8B), 5.72 (H-12A, H-12B), 5.74 (H-9A, H-9B), 5.92 (H-13A, H-13B); ^{13}C NMR δ 23.5 (C-4), 26.1 (C-5), 28.3 (C-7), 29.4 (C-10), 31.0 (C-11), 33.5 (C-6), 38.3 (C-3), 54.4 (C-1), 57.2 (OMe), 75.1 (C-14), 123.4 (C-8), 123.7 (C-13), 128.6 (C-9), 131.3 (C-12), 209.9 (C-2). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.50; H, 8.58.

A solution of 0.054 g (0.3 mmol) of octalone **3** in 0.5 mL of dry toluene was added to a solution of 0.080 g (0.076 mmol) of Yb(fod)$_3$ in 1 mL of dry toluene in a glass ampule. The solution was stirred under nitrogen for 40 min. Then 0.076 g (0.90 mmol) of diene **2** and enough solvent to form a 3-mL volume of the final solution were added. The glass ampule was degassed, sealed in vacuo, and heated at 100 °C in a heating bath for 13 h. The reaction mixture

(17) Experiments carried out without degassing the glass ampule with helium and sealing it under vacuum gave systematically 10–25% lower product yields. The same observation has been reported by others.[18]

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was worked up as usual. The residue was a 1.5:1 mixture of ketones **4a** and **4b**, as shown by GLC analysis.

The catalyzed Diels–Alder reaction of dienone **6** with diene **2** and its workup followed the procedure of the **2–3** reaction. A 1.5:1 mixture of the ketones **4a** and **4b** was obtained, as shown by GLC analysis.

Bicyclo[4.4.0]-8,10-dien-2-one (6). A solution of 0.18 g (1 mmol) of octalone **3** in 2 mL of dry toluene was added to a solution of 0.265 g (0.25 mmol) of $Yb(fod)_3$ in 5 mL of dry toluene in a glass ampule. Then enough solvent to form 10 mL of the final solution was added. The ampule was degassed, sealed in vacuo, and heated at 100 °C for 7 h in a heating bath. After the usual workup, the resulting oil was purified by column chromatography on 12 g of silica gel (elution with pentane) to yield 130 mg (88%) of colorless, oily ketone **6**: IR 3040 (m, olefinic CH), 1680 (s, C=O), 1620 (s, C=C) cm^{-1}; ^1H NMR δ 1.0–3.4 (m, 9, methylenes, CH), 6.28 (m, 2, H-8, H-9), 7.67 (m, 1, H-10); ^{13}C NMR δ 21.4 (C-4), 30.1 (C-5), 30.9 (C-7), 34.0 (C-6), 40.0 (C-3), 124.7 (C-9), 130.9 (C-10), 134.6 (C-8), 135.3 (C-1), 200.3 (C-2). Anal. Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.11. Found: C, 81.20; H, 8.05.

Diels–Alder Adduct 7. A mixture of 1.5 g (13.6 mmol) of ketone **1b**, 6.90 g (82 mmol) of diene **2**, and 20 mg of hydroquinone was heated in a degassed, sealed tube at 160 °C for 72 h. The volatile materials were removed under vacuum and the crude residue was chromatographed on 110 g of silica gel. Elution with 9:1 pentane–ether afforded 0.85 g (32%) of octalone **7**: IR 3030 (m, olefinic CH), 1702 (s, C=O), 1655 (w, C=C), 1085 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.12 (Me), 1.51 (H-7B), 1.78 (H-4A), 1.82 (H-4B), 1.87 (H-6), 2.07 (H-5B), 2.12 (H-7A), 2.29 (H-5A), 2.53 (H-3A, H-3B), 3.24 (H-10), 3.26 (OMe), 5.80 (H-8A, H-8B), 5.87 (H-9A, H-9B); ^{13}C NMR δ 21.0 (Me), 23.8 (C-4), 27.4 (C-7), 28.9 (C-5), 39.0 (C-6), 41.1 (C-3), 50.9 (C-1), 57.7 (OMe), 79.4 (C-10), 123.1 (C-9), 127.5 (C-8), 214.4 (C-2). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.22; H, 9.28. Found: C, 74.53; H, 9.40.

Catalytic Hydrogenations. The reductions of olefinic ketones **4** and **7** were carried out according to the following procedure. Platinum oxide (30 mg) in 8 mL of dry ethanol was stirred under a hydrogen atmosphere until cessation of hydrogen absorption. A solution of 0.77 mmol of the ketone in 5 mL of dry ethanol was added and the reaction carried out at room temperature and atmospheric pressure. It was terminated at the stage of consumption of the required amount of hydrogen. The workup followed the normal procedure.

(6β,10α)-14β-Methoxytricyclo[8.4.0.0^{1,10}]tetradecan-2-one (5a): mp 71–72 °C (pentane); IR 1700 (s, C=O), 1093, 1082 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.26 (H-9B), 1.29 (H-11B), 1.34 (H-7A, H-7B or H-8A, H-8B), 1.37 (H-5B), 1.44 (H-13B), 1.46 (H-12B), 1.47 (H-8A, H-8B or H-7A, H-7B), 1.54 (H-12A), 1.58 (H-11A), 1.88 (H-9A), 1.89 (H-4B), 1.96 (H-4A), 2.00 (H-13A), 2.11 (H-5A), 2.23 (H-3B), 2.27 (H-6), 2.36 (H-10), 2.54 (H-3A), 3.24 (OMe), 4.03 (H-14); ^{13}C NMR δ 19.2 (C-12), 20.8 (C-8), 22.0 (C-4), 22.7 (C-13), 26.1 (C-5), 26.7 (C-11), 28.6 (C-9), 29.4 (C-7), 30.1 (C-10), 35.9 (C-6), 37.9 (C-3), 56.2 (OMe), 57.0 (C-1), 79.0 (C-14), 213.0 (C-2). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.28; H, 10.35.

(6β,10α)-14α-Methoxytricyclo[8.4.0.0^{1,10}]tetradecan-2-one (5b): mp 151–153 °C (pentane); IR 1718 (s, C=O), 1100, 1088 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.26 (H-9B), 1.29 (H-11B), 1.34 (H-7A, H-7B or H-8A, H-8B), 1.37 (H-5B), 1.44 (H-13B), 1.46 (H-12B), 1.47 (H-8A, H-8B or H-7A, H-7B), 1.54 (H-12A), 1.58 (H-11A), 1.88 (H-9A), 1.89 (H-4B), 1.96 (H-4A), 2.00 (H-13A), 2.11 (H-5A), 2.23 (H-3B), 2.27 (H-6), 2.36 (H-10), 2.54 (H-3A), 3.24 (OMe), 4.03 (H-14); ^{13}C NMR δ 19.2 (C-12), 20.8 (C-8), 22.0 (C-4), 22.7 (C-13), 26.1 (C-5), 26.7 (C-11), 28.6 (C-9), 29.4 (C-7), 30.1 (C-10), 35.9 (C-6), 37.9 (C-3), 56.2 (OMe), 57.0 (C-1), 79.0 (C-14), 213.0 (C-2). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.50; H, 10.15.

10α-Methoxy-1β-methyl-6β-bicyclo[4.4.0]decan-2-one (8): IR 1700 (s, C=O), 1100, 1072 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.22 (s, 3, Me), 3.22 (s, 3, OMe); ^{13}C NMR δ 21.8 (Me), 23.3 (C-8), 24.1 (C-4), 27.1 (C-7), 27.7 (C-9), 29.5 (C-5), 40.7 (C-3), 42.7 (C-6), 52.0 (C-1), 57.1 (OMe), 85.0 (C-10), 215.4 (C-2). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.20; H, 10.25.

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Absolute Configuration of CC-1065 by X-ray Crystallography on a Derivatized Chiral Fragment (CPI) from the Natural Antibiotic

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CC-1065, **1**, a novel, potent antitumor antibiotic isolated from *Streptomyces zelensis*, displayed remarkable cytotoxic and in vivo antitumor activity.[1] Spectral and crystallographic analyses yielded the structure of **1** but did not establish the absolute configuration of its two asymmetric centers.[2] The chirality of the antibiotic has been inferred from modeling studies of CC-1065–DNA interactions and the CC-1065–(*N*-3-adenine)–DNA adduct.[3] These studies indicated that the adduct could only be accommodated if the spirocyclopropyl group extends below the plane of the page as drawn (**1**). Recent developments have allowed us to rigorously confirm the indicated stereochemistry by single-crystal analysis of a heavy atom derivative of the chiral fragment, CPI (**3**), prepared from natural CC-1065.

Before successful crystallization and X-ray crystallography on CC-1065 allowed assignment of its structure, efforts to prepare a crystalline heavy-atom derivative were precluded by an apparent degradation of the antibiotic under acidic and basic conditions.[4] Further studies revealed a fragmentation under alkaline conditions and the addition of acid across the spirocyclopropylcyclohexadienyl system under acidic conditions.[5] The availability of the chiral cyclopropapyrroloindole CPI (**3**) from alkaline fragmentation of natural CC-1065 allowed the attempted preparation of crystalline heavy-atom derivatives having the potential to rigorously establish the absolute configuration by X-ray crystallography. Efforts on derivatizing CPI were part of the extensive synthetic studies prompted by the structural novelty and antitumor potency of CC-1065.[6] The toxicity[7] of CC-1065 precluded its development as an antitumor drug, but synthetic analogues that are *N*-acyl derivatives of the vinylogous amide of CPI displayed improved antitumor potency and efficacy without the unusual toxicity of the antibiotic itself.[8] The obser-

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