101759-95-9; **6**, 79-83-4; **7**, 101759-90-4; **8**, 28891-35-2; **9** (isomer 1), 101759-91-5; **9** (isomer 2), 101759-92-6; **10** (isomer 1), 101759-93-7; **10** (isomer 2), 101759-94-8; **11**, 87137-59-5; **12**, 101759-96-0; **14** (isomer 1), 101759-97-1; **14** (isomer 2), 101759-98-2; *cis*-**15**, 101760-01-4; *trans*-**15**, 101760-02-5; *cis*-**16**, 101759-99-3; *trans*-**16**, 101760-00-3; *cis*-**17**, 101760-03-6; *trans*-**17**, 101760-04-7; *cis*-**18**, 101760-05-8; *trans*-**18**, 101760-06-9; *cis*-**19**, 101760-07-0; *trans*-**19**, 101760-08-1; *cis*-**21** (isomer 1), 101760-09-2; *cis*-**21** (isomer 2), 101760-10-5; *trans*-**21** (isomer 1), 101760-11-6; *trans*-**21** (isomer 2), 101760-12-7; calcium pantothenate, 137-08-6.

Cobalt-Mediated Cyclopentenone Annulation: An Approach to the Synthesis of Cyclocolorenone

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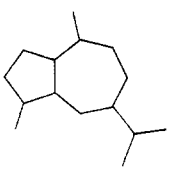
A new methodology is presented for generating the guaiane sesquiterpene skeleton as in cyclocolorenone (**4**) which features cyclopentenone annulation of a suitable cycloheptanone derivative using the sequence: propargylation by the cobalt complex $(MeC{\equiv}CCH_2)Co_2(CO)_6BF_4$ (**1a**), demetalation, regiospecific hydration to a 1,4-diketone, and base-catalyzed cyclization (Scheme I). Synthesis of the key cycloheptanone TMS enol ether **5** is foiled by the intervention of a novel cyclopropane mislocation reaction which occurs during the reaction of cycloheptadienone ketal **8** with $PhHgCBr_3$. Nonetheless, the isomeric TMS enol ether **5′** has been successfully carried through the annulation sequence of Scheme I in an efficient and highly regio- and stereoselective manner to produce the isocyclocolorenones **16′** and **16b′**. The molecular structure of the product from propargylation of **5′** by **1a** has been determined by single-crystal X-ray diffraction.

During the last several years we have been engaged in a program to explore the chemistry of (propargylium)-$Co_2(CO)_6^+$ complexes, **1**, particularly their use as electrophilic agents for carbon–carbon bond formation. Resulting from these efforts have been novel and efficient methods for the coupling of **1** with aromatics,[1] β-dicarbonyls,[2] enol derivatives,[3] allylsilanes,[4] and aluminum alkyls.[5] The propargylation of ketones (usually as their TMS ether derivatives) by **1** has been incorporated recently into a useful sequence for cyclopentenone annulation according to Scheme I.[6]

In order to further illustrate the utility of the method outlined in Scheme I, we have initiated efforts directed toward the synthesis of selected cyclopentanoid natural products. An early study using *acyclic* starting materials led to a simple, highly efficient synthesis of dihydrojasmone.[7] More challenging classes of target molecules are the guaiane (**2**) and pseudoguaiane (**3**) sesquiterpenes,



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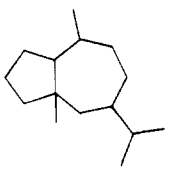

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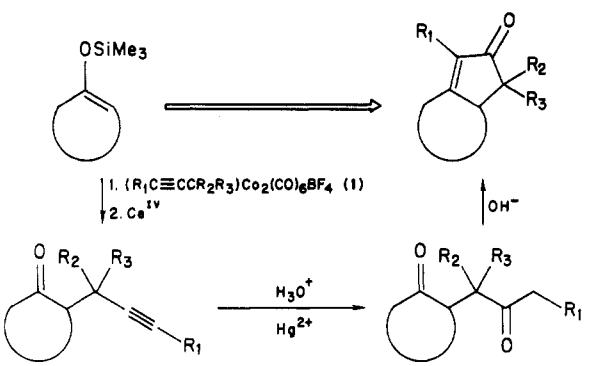
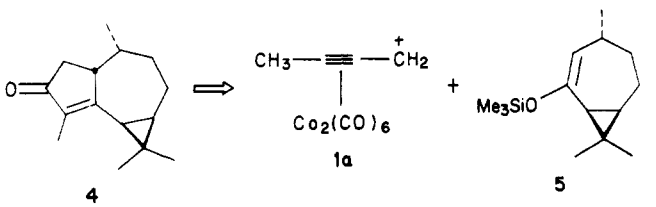
which, in addition to the characteristic[5,7] hydroazulenic skeleton, also feature several stereocenters. These compounds have been the object of intense synthetic efforts during the last ten years,[8] in part because of the significant cytotoxic and antitumor activity of several members.[9] Perusal of the syntheses reported to date reveals: (1) that most generate the azulenic skeleton by rearrangement of decalone derivatives[10] or start from natural products already possessing the bicyclo[5.3.0] framework;[11] (2) that stereochemical control remains a major challenge; and (3) that few guaianes (**2**) have been successfully synthesized.

Scheme I



Scheme II



[†] Boston College.
[‡] University of Oklahoma.

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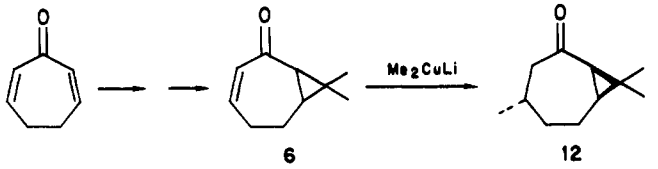
Scheme III

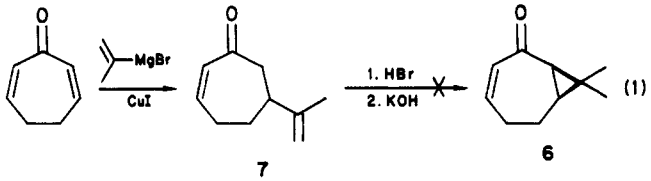


With the above limitations in mind we have sought to synthesize the guaiane cyclocolorenone (4) by applying the cobalt-based cyclopentenone annulation of Scheme I to a suitably functionalized cycloheptanone derivative, **5** (Scheme II). In our approach the relative stereochemistry of the C-7 methyl and the dimethylcyclopropane ring are fixed in the cycloheptanone species **5** while the C-8 configuration is established during the annelation. This latter feature represented a possible complication since the natural product is known to be the less stable epimer.[11] The only successful synthesis of cyclocolorenone reported to date employed photochemical rearrangement of a decalenic enone derivative to generate the requisite carbon skeleton.[12]

In this report we present some of our synthetic ventures aimed toward the deceptively simple intermediate **5**, one of which fails because of an unprecedented cyclopropane mislocation reaction. Using an isomer of **5**, however, we demonstrate here the feasibility of Scheme I for generation of the hydroazulenic skeleton. In another publication[13] the successful total synthesis of cyclocolorenone employing the cobalt-mediated annulation of TMS ether **5** (prepared by a completely different route) is described.

Results and Discussion

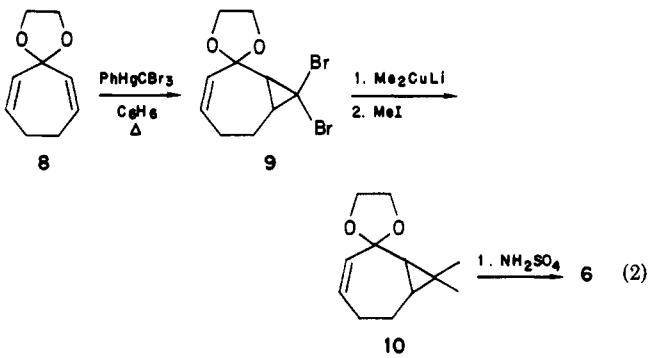
The various routes considered for the preparation of TMS ether **5** or its precursor ketone **6** differed primarily in the mode of introducing the cyclopropane ring. It was considered advantageous to incorporate first the bulky *gem*-dimethylcyclopropane group with the expectation that subsequent conjugate addition of methyl cuprate would result in the desired trans relationship with a high degree of stereochemical control (Scheme III). Preliminary evaluations of a number of direct cyclopropanation methods on readily available 2,6-cycloheptadienone were negative. Thus, treatment of this dienone with the ylides $Ph_3P^+C^-Me_2$ or $Ph_2S^+C^-Me_2$ failed to produce any characterizable products; only modest quantities of unreacted starting material were recovered. The indirect route shown in eq 1 was also briefly examined. Hydrobromination of



(1)

the known isopropenyl derivative **7**[14] gave the desired bromide (judging by ^1H NMR and IR) but its subsequent treatment with methanolic KOH produced a complex mixture of products, none of which appeared to be the cyclopropanated ketone **6**. The base sensitivity of the cycloheptenone and cycloheptadienone systems may be at the root of these failed attempts.

Reactions of electrophilic carbenoid agents with the corresponding ketal 8[22] were also examined. Of the various dibromocarbene equivalents tested ($CHBr_3/OH^-$; $CHBr_3/BzNEt_3^+Br^-/OH^-$; $PhHgCBr_3$), only Seyferth's reagent (15.1 equiv, C_6H_6 reflux, 1.5 h) afforded a single major product (65% yield) as an unstable yellow oil which, on the basis of its IR and ^1H (80 MHz) and ^{13}C NMR was formulated as the dibromocyclopropane derivative **9** (eq 2). Addition of this material to excess Me_2CuLi in ethyl



(2)

ether (−60 °C → 0 °C) followed by quenching with excess MeI led, after chromatographic workup, to a dimethylated product (δ 1.06 (s, 3 H), 1.01 (s, 3 H)), apparently ketal **10**, in excellent yield (90%). Hydrolysis of the latter (1 N H_2SO_4, 20 °C, 1 h) gave 76% of a ketone whose spectral properties were consistent with those of structure **6**.

Addition of methylcuprate to the cycloheptenone derivative believed to be **6** followed by aqueous workup produced a saturated trimethyl ketone (87%, ν(C=O) 1700 cm^{-1}) as a single isomer (based on the ^{13}C NMR spectrum). The noncoincidence of the ^1H NMR spectrum of this species with that of the known *endo*-4,8,8-trimethyl-

(10) See; e.g.: Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1968**, *90*, 1010. Suchy, M.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1964**, *29*, 1829.

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(16) The structural features of the (butynyl)$Co_2(CO)_6$ group are unexceptional, showing the characteristic lengthening of the coordinated C–C triple bond (1.325 Å vs. 1.21 Å in free alkynes) and the substantial bending from linearity of the complexed butynyl group (av = 144°). The π-interaction of the $Co_2(CO)_6$ system with the butynyl group shows the alkyne bond (C(10)–C(11)) to be perfectly perpendicular to the Co–Co bond. This bonding scheme has been observed before, initially by Sly[17] and most recently in a set of structures in which the molecular parameters were correlated with the electron-withdrawing properties of the substituents of the coordinated acetylene.[18] The results of the present structure (Table II) afford new and reliable data points for these relations and follow the previously observed trends. Also in agreement with previous observations is the bend of the trigonal prism formed by $Co_2(CO)_6$ and the interesting and significant lengthening of the four Co—C(≡O) bonds which are approximately parallel to the alkyne bond and the shortening of the two Co—C(≡O) bonds which are perpendicular to the alkyne bond (Table II).

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(21) Stork, G.; Borch, R. *J. Am. Chem. Soc.* **1964**, *86*, 935.

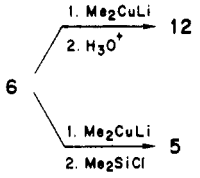
(22) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109. Spectral data for 2,6-cycloheptadienone (17) and its ethylene ketal (8) prepared as in ref 22 follow. 17: IR (cm^{-1}) 1650, 1615; ^{13}C NMR ($CDCl_3$) δ 193, 145, 133, 27. 8: IR (cm^{-1}) 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 5.8 (bm, 2 H), 5.6 (d, J = 8 Hz, 2 H), 3.8 (s, 4 H), 2.3 (bm, 4 H); ^{13}C NMR ($CDCl_3$) δ 133, 131, 108, 63, 25. These data agree with the available literature data and are indicative of the assigned structures.

(23) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912.

Table I. Properties of Isomeric Cyclocolorenones

	UV, λ_{max}, nm	mp, °C	IR, cm^{-1}	^1H NMR, δ
cyclocolorenone	262		1693, 1624	0.78 (d, 7 Hz, 3 H), 1.04 (s, 3 H), 1.23 (s, 3 H), 1.65 (d, 3 H, 2 Hz)
epicyclocolorenone	253	69–70	1696, 1628	1.02 (bs, 6 H), 1.22 (s, 3 H), 1.63 (t, 1.2 Hz, 3 H)
isocyclocolorenone (**16a**)	243	oil	1700, 1640	1.04 (s, 3 H), 1.10 (s, 3 H), 1.64 (s, 3 H)
isocyclocolorenone (**16b**)	249	oil	1700, 1648	0.80 (d, 7 Hz, 3 H), 1.00 (s, 3 H), 1.11 (s, 3 H), 1.73 (s, 3 H)

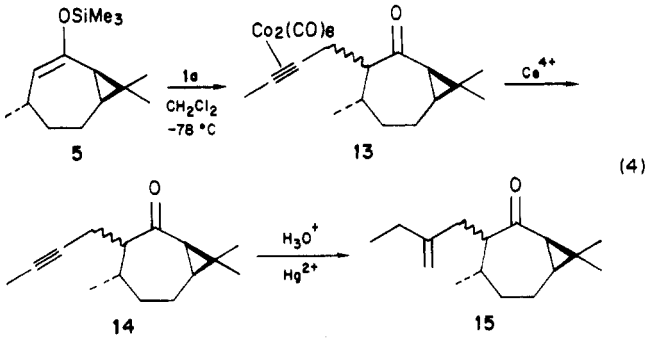
bicyclo[5.1.0]octan-3-one (**11**)[14] and the anticipated preferential approach of the cuprate reagent from the less hindered exo face of **6** supported our formulation of this product as the exo derivative **12** (eq 3). When the above



(3)

hydrolytic workup was replaced by quenching with excess Me_3SiCl, the corresponding TMS enol ether was isolated (92%) and formulated as the sought after intermediate **5** on the basis of its spectroscopic properties.

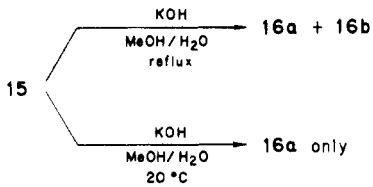
With the requisite intermediate **5** apparently in hand the annulation sequence of Scheme I was executed. Treatment of crude **5** directly with $(CH_3C{\equiv}CCH_2)Co_2(CO)_6{}^+BF_6{}^-$ (**1a**) at −78 °C in CH_2Cl_2 afforded a single dark red complex (90%) after workup as determined by TLC and ^{13}C NMR. The spectral properties were consistent with those of structure **13** with undetermined stereochemistry (eq 4). Demetalation with ceric ammonium



(4)

nitrate proceeded normally (78%) to give an acetylenic ketone, apparently **14**, (single isomer by ^{13}C NMR) which, in turn, was hydrated under standard conditions ($HgSO_4$, H_2SO_4, H_2O/MeOH, 50 °C), producing a diketone (78%) assigned structure **15**; appropriate spectral and elemental analytical data for **15** were obtained. A single diastereomer was produced here as well (^{13}C NMR).

The final cyclization step was carried out by using KOH/H_2O/MeOH under two sets of conditions: (a) reflux/1 h and (b) 20 °C/10 h. At reflux two isomeric compounds, **16a** and **16b** (*m/e* 218), were produced in a 1:2 ratio (separable by preparative TLC, 89% total yield), which had very similar IR and ^1H NMR spectra (eq 5). At



(5)

room temperature only **16a** was obtained (83%). The presence of the α-methylcyclopentenone moiety in both products was indicated by IR absorptions at 1700 and 1640 cm^{-1} (for **16a**) and 1700 and 1648 cm^{-1} (for **16b**), ^1H NMR

Table II. Dimensions of 13′ (Standard Deviation for Last Digit in Parentheses)

Bond Distance, Å			
Co(1)–Co(2)	2.4688 (9)	C(11)–C(12)	1.486 (6)
Co(1)–C(16)	1.783 (5)	C(10)–C(11)	1.325 (6)
Co(1)–C(17)	1.827 (5)	C(9)–C(10)	1.500 (7)
Co(1)–C(18)	1.830 (5)	C(4)–C(9)	1.530 (7)
Co(2)–C(19)	1.814 (6)	C(4)–C(5)	1.568 (7)
Co(2)–C(20)	1.819 (5)	C(5)–C(13)	1.528 (6)
Co(2)–C(21)	1.787 (6)	C(5)–C(6)	1.534 (7)
Co(1)–C(11)	1.981 (5)	C(6)–C(7)	1.511 (7)
Co(1)–C(10)	1.974 (5)	C(7)–C(8)	1.533 (7)
Co(2)–C(11)	1.972 (4)	C(1)–C(7)	1.522 (7)
Co(2)–C(10)	1.970 (5)	C(8)–C(14)	1.503 (8)
C(16)–O(1)	1.139 (6)	C(8)–C(15)	1.548 (7)
C(17)–O(2)	1.129 (6)	C(1)–C(8)	1.535 (7)
C(18)–O(3)	1.125 (7)	C(1)–C(2)	1.490 (7)
C(19)–O(4)	1.125 (8)	C(2)–C(3)	1.517 (8)
C(20)–O(5)	1.131 (6)	C(3)–C(4)	1.516 (6)
C(21)–O(6)	1.139 (7)	C(3)–O(7)	1.215 (6)
Bond Angle, deg			
Co(2)–Co(1)–C(16)	149.5 (2)	Co(1)–Co(2)–C(20)	99.9 (2)
Co(2)–Co(1)–C(17)	99.6 (2)	Co(1)–Co(2)–C(21)	147.4 (2)
Co(2)–Co(1)–C(18)	98.6 (2)	C(10)–C(11)–C(12)	143.9 (5)
Co(1)–Co(2)–C(19)	96.7 (2)	C(9)–C(10)–C(11)	144.5 (4)

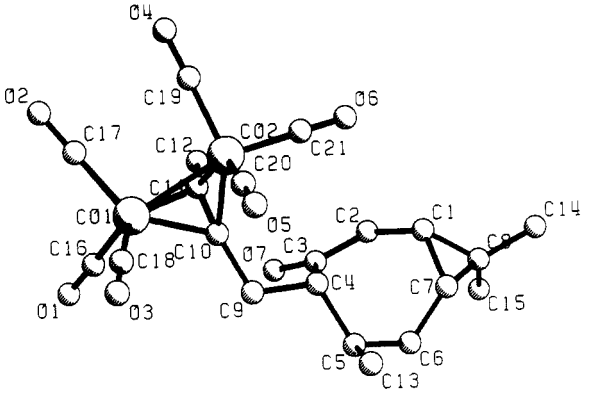


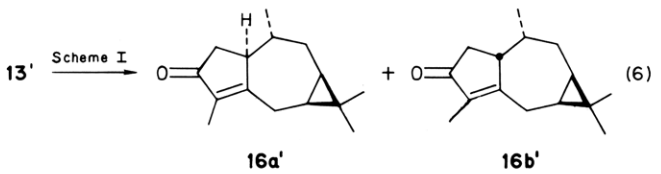
Figure 1. Molecular structure of 13′.

absorptions for the α-Me at δ 1.64 (for **16a**) and 1.73 (for **16b**), and UV λ_{max} at 243 nm (for **16a**) and 249 nm (for **16b**). At this point it was tempting to conclude that the reflux reaction had produced a mixture of cyclocolorenone and epicyclocolorenone and that at room temperature the less stable epimer, cyclocolorenone, was formed selectively. Careful comparison of the spectral properties of the products **16b** and **16a** with those reported for cyclocolorenone and its epimer, however, did not support these conclusions (see Table I). All the data taken together indicated that the products **16a** and **16b**, while possessing the basic hydroazulenone skeleton, were isomeric in some way with the natural product (and its epimer).

In order to resolve this dilemma, we sought to establish unambiguously the structure of a late intermediate in the synthetic sequence by X-ray diffraction. The cobalt complex earlier assigned structure **13** proved particularly convenient for this purpose, suitable crystals being obtained from 95% ethanol at low temperature. The actual molecular structure of this compound **13′** is shown in Figure 1 (crystallographic details are given in the Experimental Section). Although all of the expected sub-

stituents—dimethylcyclopropane, 2-(butynyl)$Co_2(CO)_6$, methyl—were found to be present in **13′**, to our great surprise *the cyclopropane unit was found to be mislocated, β,γ to the carbonyl rather than α,β.* As a small consolation the expected trans relationship of the cyclopropane and C-3 methyl was present. The trans relationship of the C-3 methyl and the butynyl-$Co_2(CO)_6$ side chain at C-2 suggests that the C-3 methyl (rather than the dimethylcyclopropane group) controls the stereochemical course of alkylation of the TMS ether by **1a**. The figure also shows the conformation of the seven-membered ring to be a boat with C(6) forming the bow and C(2),C(3) the stern.[16]

Establishment of the structure of the alkylated product as **13′** combined with the spectroscopic data for the final annelated products (formerly **16a** and **16b**) brought us to conclude that the latter in fact also have the cyclopropane rings "relocated" as in **16a′** and **16b′** (eq 6). In retrospect



perhaps the most revealing data are the λ_{max} values (Table I). The observed values for **16a′** and **16b′** are in the normal range for α,β,β-substituted cyclopentenones (ca. 248 nm) whereas those of cyclocolorenone and its epimer reflect the pseudoconjugation of the cyclopropane ring at the γ,δ-position.[11] Tentatively, we assign the structures of the individual epimeric isocyclocolorenones as shown in eq 6 based on the position of the C-7 methyl ^1H NMR resonance (see Table I). In structure **16b′** as in cyclocolorenone itself[11] inspection of molecular models reveals that the most stable conformation for each places the C-7 methyl over and near to the π-system of the α,β-unsaturated carbonyl group producing the relatively high field resonances, δ 0.80 and 0.79, respectively. In **16a′** and epicyclocolorenone the C-7 methyl group is directed away from the π-system in the preferred conformations resulting in less shielded values, δ 1.04 and 1.02, respectively. Despite the unexpected cyclopropane mislocation *prior to the key coupling step* with cobalt complex **1a** (vide infra), the annulation sequence of Scheme I proved quite efficient (49% overall for four steps) for fusing the cyclopentenone unit onto the cycloheptanone ring.

Our attentions were quickly directed toward determining where in the sequence leading to the cobalt complex **13′** the cyclopropane ring had become mislocated. Neither hindsight reexamination of the 80-MHz NMR spectra of putative intermediates **5**, **6**, and **9–12** nor acquisition of their 300-MHz spectra provided a quick, easy answer since no diagnostic resonances were sufficiently well separated from the saturated proton envelope to be useful. Inspection of the ^{13}C NMR spectrum of the initial diene ketal showed only the five peaks expected for the symmetrical structure of the 2,6-isomer **8** (see also ref 22). Finally, the lanthanide-shifted ^1H NMR spectrum provided the sought-after answer. The spectrum of presumed cycloheptenone derivative **6** before and after addition of Eu(fod)$_3$ is shown in Figure 2. Also given is the simulated spectrum for the ABCC′DD′ portion of the ABCC′DD′EF system for the *cyclopropane-mislocated isomer* **6′**. That the cyclopropane ring was already mislocated at this stage (i.e., **6′** is the actual structure) was demonstrated by the near congruence of the experimental and simulated spectra. First-order analysis of the shifted spectrum assuming maximal shifts for those protons near to the Eu-coordinated carbonyl group leads to the same conclusion (see

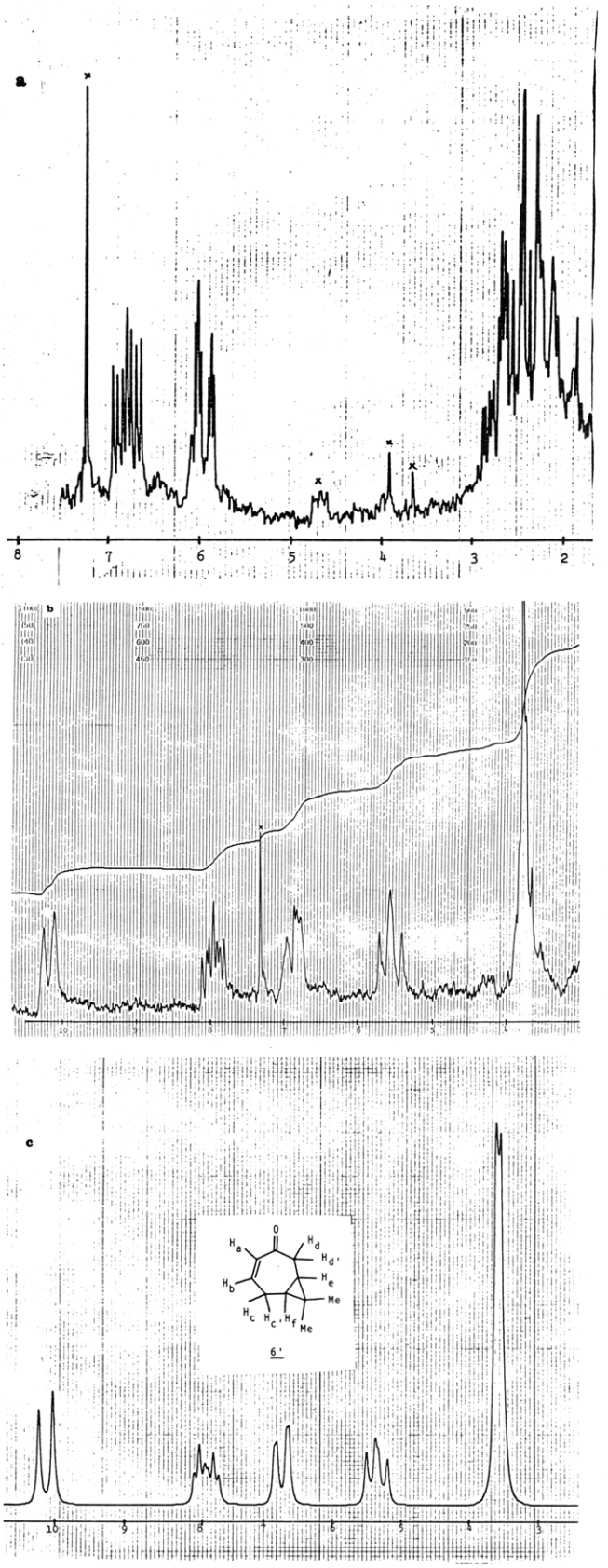
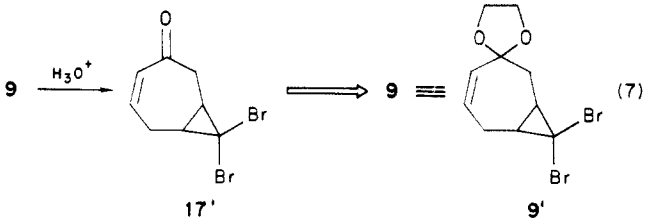


Figure 2. (a) 80-MHz ^1H NMR spectrum (partial) of putative **6**; (b) ^1H NMR spectrum of putative **6** plus added Eu(dpm)$_3$; (c) simulated ^1H NMR (expanded) of **6′**.

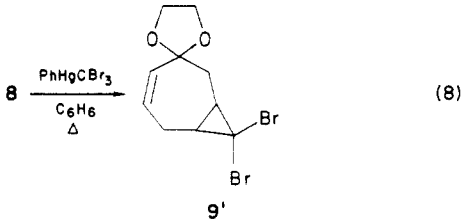
Experimental Section for assignments and simulation parameters). Proceeding back toward the starting material, the Eu-doped spectrum of the precursor to **6′** (presumed dibromo ketal **9**) showed very modest resonance

shifts which were rather uninformative. The ketone 17 resulting from hydrolysis of presumed 9 (eq 7), however,



17' 9' (7)

proved more amenable to structural elucidation. Indeed, the addition of $Eu(fod)_3$ to a solution of 17 resulted in a shifted spectrum nearly identical in the low field region with that shown above for the dimethylcyclopropane derivative 6' (data in Experimental Section). The compound earlier formulated as 9 therefore must be re-formulated as 9', also with the β,γ-cyclopropane ring. Finally then, since the precursor to isomerized dibromo ketal 9' is the "normal" diene ketal 8, we are drawn to the conclusion that the cyclopropane ring becomes mislocated in the very process of its introduction (eq 8).



9' (8)

Formation of a cyclopropane ring at other than the position of the original double bond appears to be unprecedented in the chemistry of the Seyferth reagents, $PhHgCX_3$.[15] At this point we have no positive experimental evidence regarding the mechanism of this process. Kinetic and stereochemical studies of "normal" cyclopropanations by these reagents have been interpreted in two ways: (a) rate-determining decomposition of the organomercurial to generate free singlet carbene which reacts stereospecifically with olefins,[19] and (2) a combination of pathway (a) plus a bimolecular pathway involving formation of a carbene complex by the reagent (i.e., $PhHgCBr_3 \cdot CBr_2$), which reacts with olefin stepwise (and nonstereospecifically[20]) via a diradical intermedaite. While it is easier to rationalize the cyclopropane mislocation of eq 8 by a variant of this latter, stepwise process, one must also consider the possibility of initial mercury-catalyzed double-bond isomerization (from the 2,6- to the 2,5-isomer) followed by the "normal" cyclopropanation process. An attempt to test for isomerization of the starting diene under the reaction conditions was inconclusive. Thus, when the reaction of diene 8 with $PhHgCBr_3$ was terminated after 30 min (product yield is a maximum at 90 min), no diene, original or isomerized, could be recovered—only a modest yield of product and some uncharacterizable species (intermediates?). Mechanistic information notwithstanding, we speculate that the driving force for the cyclopropane mislocation may be formation of the less hindered (more stable) tricyclic product (9' vs. 9).

Summary and Conclusions

The sequence of Scheme I—propargylation by 1, demetalation, hydration, and cyclization—has been demonstrated to be an effective method for construction of the hydroazulene skeleton as in compounds 16'. In this case the key propargylation step proceeds with complete diastereoselectivity with respect to the newly formed stereocenter. Regiospecific acetylene hydration leading to 1,4-diketone[6,21] is observed as well. The reaction of 2,6-cycloheptadiene ketal 8 with $PhHgCBr_3$ is accompanied by a novel and apparently unprecedented mislocation of the resulting dibromocyclopropane ring. Synthesis of the key bicyclic ketone 11 and its successful conversion to cyclocolorenone and epicyclocolorenone are described in a forthcoming publication.[13]

Experimental Section

General Methods. All manipulations and reactions were performed in side-arm flasks under a nitrogen atmosphere. Solvents were refluxed over drying agents for 4–5 h prior to distillation and stored over molecular sieves [CH_2Cl_2–CaH_2; ether, hydrocarbons, benzene–Na/benzophenone]. Pentane and petroleum ether (bp 30–60 °C) were distilled prior to use to remove high boiling impurities.

(2-Butynyl)dicobalt Hexacarbonyl Tetrafluoroborate (1a). A solution of 2-butyn-1-ol (1.12 g, 0.016 mol) in 20 mL of CH_2Cl_2 was treated with $Co_2(CO)_8$ (5.47 g, 0.16 mol) at room temperature. After the reaction was complete (about 3 to 4 h), the mixture was concentrated under vacuum and the residue was dissolved in 2–3 mL of propionic anhydride and cooled to −45 °C. Tetrafluoroboric acid dimethyl etherate (4.26 g, 0.032 mol) was then added to the reaction mixture. After 15–20 min a large volume of anhydrous diethyl ether (300–500 mL) was added to precipitate the dark red salt. The salt was washed with ether several times and collected by filtration under nitrogen (5.4 g, 79% overall).

Attempted Synthesis of 8,8-Dimethylbicyclo[5.1.0]oct-3-en-2-one (11). (a) Using Triphenylphosphonium Isopropylide. A suspension of isopropyltriphenylphosphonium iodide (0.40 g, 0.93 mmol) in THF (20 mL) was treated with 1 equiv of *n*-BuLi at 25 °C. The resulting deep red solution of the ylide was transferred slowly by cannula to a stirred solution of 0.12 g (0.93 mmol) of cyclohepta-2,6-dienone[22] in 5 mL of THF after 30 min. After 2 h the yellow reaction mixture was quenched with water. The water layer was extracted thoroughly with ether, and the ether layer was dried over $MgSO_4$. Solvent evaporation followed by preparative TLC (30% petroleum ether/ether) gave 0.042 g of an unidentified product with the following spectroscopic properties: ^1H NMR (CCl_4) δ 6.6 (cm, 2 H), 5.9 (m, 2 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 1.0–2.8 (c m, 4 H); IR (neat) 1650 cm^{-1} (b).

(b) Using Diphenylsulfonium Isopropylide. A solution of diphenylethylsulfonium fluoroborate (7.40 mmol)[23] and 0.66 mL of CH_2Cl_2 in 30 mL of dimethoxyethane was treated with 8.14 mmol of lithium diisopropylamide at −70 °C. The yellow green solution which resulted became cloudy after 10 min. After 30 min, the solution was treated with methyl iodide (0.56 mL, 8.14 mmol) at −70 °C and the reaction mixture was maintained at −70 °C to −50 °C for 2 h, at the end of which 8.14 mmol of LDA was again added at −70 °C. The orange yellow solution was then treated with cyclohepta-2,6-dienone (0.84 g, 7.43 mmol) at −70 °C for 2 h. The reaction mixture was poured into water and extracted with ether several times. The combined ether layer was washed with brine and dried over $MgSO_4$. After chromatographic separation by preparative TLC only starting material was recovered.

(c) By Hydrobromination/Dehydrobromination of 6-Isopropenylcyclohept-2-enone. To a saturated solution of HBr in HOAc (10 mL) at 0 °C was added slowly 0.56 g (3.7 mmol) of 6-isopropenylcycloheptenone (14) in 1 mL of HOAc. The resulting mixture was stirred for an hour at 0 °C and then poured into an ice water mixture. The mixture was extracted thoroughly with ether and the ether layer was washed with $NaHCO_3$ and brine and then dried over $MgSO_4$. Evaporation of the solvent gave 0.81 g (96%) of 6-(1-bromopropyl)cyclohept-2-enone 7 as a crude, dark red oil which was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 6.65 (m, 1 H), 6.15 (m, 1 H), 1.95 (s, 6 H), 2.60–1.20 (m, 7 H); IR (neat) 1700, 1655 cm^{-1}.

To a solution of the crude bromide 7 (0.24 g, 1.8 mmol) in 10 mL of MeOH was added 8 equiv of KOH (0.55 g). The resulting mixture was refluxed for 1 h (monitored by TLC). The cooled reaction mixture was poured into ice water and extracted with ether. The ether layer was washed with $NaHCO_3$ and brine and dried over $MgSO_4$. Following evaporation of the ether, the crude product was subjected to preparative TLC from which several unidentified products were isolated, none of which gave NMR

spectra consistent with the desired enone **6**.

8,8-Dibromobicyclo[5.1.0]oct-4-en-3-one Ethylene Ketal (9′). A solution of 2,6-cycloheptadienone ethylene ketal (**8**) (6.85 g, 44.7 mmol, 22) in benzene (700 mL) was mixed with 17.8 g (32.9 mmol) of $PhHgCBr_3$.[15] The mixture was refluxed for 1.5 h (appearance of solid at the end). The reaction mixture was cooled to room temperature and filtered to remove the precipitated phenylmercuric bromide. The filtrate was concentrated to 50 mL under reduced pressure and filtered again. Saturated ethanolic sodium borohydride was added dropwise to the filtrate until the vigorous reaction ceased. The mixture was then poured into water and the product was isolated by extraction with ether. The ether layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave the crude product as a yellow oil. The pure product **9′** was isolated as a yellow oil (low melting solid on long term refrigeration) in 65% yield (9.59 g) by column chromatography over silica gel (elution with 10% ether/petroleum ether): ^1H NMR ($CDCl_3$) (300 MHz) δ 5.9 (m, 1 H), 5.8 (m, 1 H), 3.9 (s, 4 H), 2.6 (m, 4 H), 2.4–1.9 (m, 2 H); IR (CCl_4) 2954, 1620, 1745, 950 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 127.62, 127.30, 64.81, 64.36, 39.89, 36.05, 34.36, 28.66, 25.97.

8,8-Dimethylbicyclo[5.1.0]oct-4-en-2-one Ethylene Ketal (10′). A lithium dimethylcuprate solution was prepared at 0 °C by adding 18.7 mL of 1.4 M MeLi in ether (26.2 mmol) to a stirring suspension of 2.47 g (13.0 mmol) of cuprous iodide in 250 mL of dry ether. After being stirred at 0 °C for 10 min, the solution was cooled to −60 °C. The dibromocarbene adduct **9′** (1.42 g, 4.40 mmol) in ether (10 mL) was added slowly to the Me_2CuLi solution at −60 °C. The solution turned yellow-orange immediately. The reaction mixture was stirred overnight (12 h) at −60 °C and then for 3 h at 0 °C. Methyl iodide (5 mL) was added at 0 °C and the bright yellow solution was stirred at room temperature for 1.5 h. The reaction mixture was then poured into 150 mL of rapidly stirred saturated ammonium chloride solution. A few milliliters of concentrated ammonia were added to facilitate dissolution of copper salts. The phases were separated, and the organic phase was washed with dilute ammonium hydroxide and then saturated sodium chloride solution. After drying over $MgSO_4$ the solvent was evaporated in vacuo to furnish a yellow oil which was purified by column chromatography on silica gel using 20% ether/petroleum ether solvent mixture to afford 0.59 g (90%) of 8,8-dimethylbicyclo[5.1.0]oct-4-en-2-one ethylene ketal (**10′**): ^1H NMR ($CDCl_3$) δ 5.70 (cm, 1 H), 5.35 (dt, 1 H, J = 12 Hz), 3.95 (2, 4 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 2.50–0.95 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 116.4, 114.99, 49.3, 49.1, 29.6, 19.4, 17.4, 13.1, 11.0.

8,8-Dimethylbicyclo[5.1.0]oct-4-en-2-one (6′). To a stirred solution of **10′** (0.593 g, 2.80 mmol) in THF (10 mL) was added 10 mL of 1 N H_2SO_4. The mixture was stirred at room temperature for 1 h and then saturated with sodium chloride. The mixture was then extracted thoroughly with diethyl ether. The ether layer was washed with $NaHCO_3$ and evaporated to give a yellow oil which on chromatography (silica gel) using 25% petroleum ether/ether gave 0.322 g (75%) of pure enone **6′**: IR (CCl_4) 1650, 1380, 1366, 890, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (m, 1 H), 5.90 (bd, J = 12 Hz, 1 H), 1.15 (s, 3 H), 1.05 (s, 3 H), 2.90–0.80 (cm, 6 H); IR (CCl_4) 1945, 1665 (b), 1390, 1370 cm^{-1}.

***exo*-4,8,8-Trimethylbicyclo[5.1.0]octan-3-one (12′).** A Me_2CuLi solution was prepared at 0 °C by adding 0.72 mL of 1.3 M methyllithium in ether (0.91 mmol) to a stirring suspension of 0.091 g (0.47 mmol) of cuprous iodide in 10 mL of dry ether. The enone (**11′**) (0.068 g, 0.45 mmol) in 1 mL of ether was added slowly over a 5-min period. After an additional 40 min at 0 °C, the reaction mixture was slowly poured into 15 mL of saturated NH_4Cl solution. The phases were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with dilute NH_3 and then brine and dried over $MgSO_4$. After evaporation and chromatography on silica gel, 0.065 g (87%) of pure **12′** was obtained: ^1H NMR (CCl_4) δ 1.14 and 1.0 (9 H, apparent d), 2.70–0.73 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 213.0, 50.9, 39.1, 30.3, 28.7, 28.4, 22.3, 20.2, 20.1, 19.8, 15.0; IR (neat) 2945, 1700 cm^{-1}.

3-(Trimethylsiloxy)-*exo*-4,8,8-trimethylbicyclo[5.1.0]oct-3-ene (5′). A Me_2CuLi solution was made at 0 °C by adding 2.1 mL of 1.4 M MeLi in ether (0.29 mmol) to a stirring suspension of 0.30 g (1.6 mmol) of cuprous iodide in 20 mL of dry ether. The enone **11′** (0.235 g, 0.96 mmol) in 1 mL of ether was added to it and the resulting mixture was stirred for 40 min at 0 °C, and 0.32 mL (2.3 mmol) of chlorotrimethylsilane, 0.45 mL (12.9 mmol) of triethylamine, and 0.24 mL (1.1 mmol) of HMPA were added. The reaction mixture was stirred at room temperature for 1.5 h after which time it was diluted with an equal volume of pentane. The resulting mixture was washed successively with two 10-mL portions each of 5% HCl and 5% $NaHCO_3$ and dried over $MgSO_4$. Solvent removal yielded 0.164 g (92%) of crude **5′** which was used for the next step without further purification: ^1H NMR (CCl_4) δ 4.41 (br d, J = 4 Hz, 1 H), 0.12 (s, 9 H), 1.05 (br m, 9 H); IR (CCl_4) 1660 cm^{-1}.

[*trans*-5,8,8-Trimethyl-*trans*-1,4,5,7-tetrahydro-*cis*-4-(2-butynyl)bicyclo[5.1.0]octan-3-one]dicobalt Hexacarbonyl (13′). To a stirred suspension of (2-butynyl)dicobalt hexacarbonyl tetrafluoroborate (**1a**) (0.91 g, 2.2 mmol) in 10 mL of CH_2Cl_2 was added 0.43 g (2.2 mmol) of TMS enol ether **5′** in 2 mL of CH_2Cl_2 at −78 °C. The mixture was stirred for 1 h and then warmed to room temperature and filtered through Celite using dry ether. The filtrate was washed with $NaHCO_3$ and water and dried over $MgSO_4$. After solvent evaporation and separation by column chromatography over silica gel (5% ether/petroleum ether) pure **13′** was obtained as a red oil [0.97 g, 90%]. The oil was crystallized by dissolving in 95% ethanol and slowly cooling to −78 °C. Pure single crystals obtained in this way were subjected to X-ray crystallography: ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H), 1.19 (d, 3 H, J = 7 Hz), 1.10 (s, 3 H), 0.96 (s, 3 H), 3.40–0.81 (cm, 10 H); ^{13}C NMR ($CDCl_3$) δ 217.50, 57.14, 39.95, 36.67, 33.23, 28.78, 28.52, 28.23, 28.07, 26.98, 21.94, 20.65; IR (CCl_4) 2100, 2060, 2020, 1710 cm^{-1}; Anal. Calcd for $C_{21}H_{22}O_7Co_2$: C, 50.04; H, 4.36; Found: C, 50.32; H, 4.34.

5,8,8-Trimethyl-4-(2-butynyl)bicyclo[5.1.0]octan-3-one (14′). To a stirred solution of **13′** (0.24 g, 0.48 mmol) in 10 mL of acetone at −78 °C was added 0.80 g of ceric ammonium nitrate portionwise (until CO evolution ceased). The reaction mixture was stirred for 1 h at −78 °C and then poured in to 20 mL of saturated NaCl solution and extracted thoroughly with ether. The ether layer was washed with brine, dried over $MgSO_4$ and then evaporated to give a yellow oil. The yellow oil was passed through a bed of silica gel and Celite by eluting with 5% petroleum ether/ether solvent mixture. The product **14′** (yellow oil) obtained by this treatment was spectroscopically pure (0.081 g, 78%) and was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 1.75 (bs, 5 H), 1.09 and 0.90 (6 H, s, and 3 H, d overlapping), 3.10–0.75 (cm, 8 H); ^{13}C NMR ($CDCl_3$) δ 193.62, 60.17, 55.69, 39.53, 36.00, 33.24, 28.71, 28.39, 27.76, 22.25, 19.47, 19.18, 19.06, 15.07; IR (neat) 1705 cm^{-1}.

4-(2-Oxobutyl)-5,8,8-trimethylbicyclo[5.1.0]octan-3-one (15′). A mixture containing 0.31 g (1.4 mmol) of **14′**, 0.092 g (0.31 mmol) of $HgSO_4$, and 0.5 mL of H_2SO_4 in 20 mL of 10% aqueous methanol was heated for 1.5 h at 50 °C. After cooling, the mixture was poured into a saturated solution of sodium chloride and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent, the resulting residue was purified by preparative TLC on silica gel (20% ether/petroleum ether) to afford 0.28 g (78%) pure **15′** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.01 (s, 3 H), 0.91 (d, 3 H overlap with 6 H, s), 3.45–0.80 (cm, 15 H); ^{13}C NMR ($CDCl_3$) δ 218.54, 210.65, 48.83, 42.79, 39.80, 35.74, 35.24, 28.74, 28.33, 21.87, 19.58, 19.06, 15.03, 7.67; IR (neat) 1710–1708 (broad band) cm^{-1}; MS, m/e 236 (M^+), 179, 165, 149, 137, 121, 109, 96, 81, 69, 57 (base peak), 41. Anal. Calcd for $C_{15}H_{24}$: C, 76.27; H, 10.16. Found: C, 76.48; H, 10.32.

Isocyclocoloreneones 16a′ and 16b′. Method A. The diketone **15′** (0.074 g, 0.31 mmol) dissolved in 2 mL of EtOH was refluxed with 20 mL of aqueous KOH (10%) for 1 h. After cooling, the mixture was saturated with NaCl and extracted several times with ether. The combined ether extracts were washed with brine and then dried over $MgSO_4$. Solvent evaporation followed by preparative TLC (15% petroleum ether/ethyl acetate, repeated elution) gave the pure products **16a′** and **16b′** which were isolated in increasing R_f value in 33:67 isomeric ratio (overall 89% yield).

16a′: ^1H NMR ($CDCl_3$) δ 1.64 (bs, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 3.01–0.76 (cm, 15 H, diffuse); IR (neat) 1700, 1640 cm^{-1}; UV (EtOH) λ_{max} 243 nm; MS, m/e 218 (M^+), 109 (base peak).

16b′: ^1H NMR ($CDCl_3$) δ 1.73 (bs, 3 H), 1.11 (s, 3 H), 1.00 (s, 3 H), 0.80 (d, 3 H, J = 7 Hz), 3.21–0.59 (12 H, cm); IR (neat) 1700,

Table III. Crystal Data for 13′

mol form	$C_{15}H_{22}O{\cdot}Co_2(CO)_6$
mol wt	504.03 g/mol
linear absorptn coeff	14.7 cm^{-1}
space group	$P2_1/n$
cell dimensns	
a	18.184 (4) Å
b	7.564 (2) Å
c	17.00 (5) Å
β	108.80 (2)°
volume	2213.5 $Å^3$
Z	4
density (calculated)	1.51 g/cm^3
cell determinatn	40 reflections used
data collectn range	$0 < 2\theta < 53.0°$
radiatn	Mo K_α
standards	3 remeasured after every 200 reflections
temp of data collectn	138 ± 2 K
no. of reflns obsd [$I > 2\sigma(I)$]	3527
no. of reflns measd	4568
structure refinement	full matrix least squares (Shelx) (ref 24)
maximum density in final diff Fourier	0.68e·$Å^{-3}$
Final R	0.0418
R_w	0.0408

1648 cm^{-1}; UV (EtOH) λ_{max} 249 nm; MS, m/e 218 (base peak).

Method B. The diketone 15′ (0.014 g, 0.059 mmol) dissolved in 1 mL of EtOH was stirred with 10% aqueous KOH (5 mL) for 10 h. The workup was carried out as in method A. After purification by preparative TLC as before, pure **16b** (**16b′**) was isolated as an oil (0.011 g, 83%).

Shift Reagent Study of 8,8-Dimethylbicyclo[5.1.0]oct-4-en-3-one (6′). Compound 6′ (10 mg) was dissolved in 0.5 mL of $CDCl_3$ (0.2% TMS) and its ^1H NMR spectrum was recorded. $Eu(dpm)_3$ was added portionwise and spectra were taken continuously at 30-min intervals. Assignments of the protons were made on the basis of observed proton/proton couplings and from the data on the response curve of plotted chemical shift vs. portion of shift reagent added. Spectra simulations were done for ABCC′ and DD′EF systems separately (see Figure 2 for labeling) and then summed using the following parameters: J_{AB} = 16 Hz, J_{AC} = 0, J_{BC} = 8, $J_{CC'}$ = −13, $J_{DD'}$ = −14, $J_{D'E}$ = 10, $J_{D'F}$ = 0, J_{DF} = 0, and chemicals shifts from the experimental spectrum.

Hydrolysis of Dibromo Ketal 9′. Shift Reagent Study of 8,8-Dibromobicyclo[5.1.0]oct-3-en-2-one (17′). To a stirred solution of ketal 9′ (1.5 g, 4.7 mmol) in 30 mL of 97% ethanol was added 30 mL of 2% H_2SO_4. The reaction mixture was stirred for 6–7 h at room temperature and then saturated with sodium chloride, and the aqueous solution was thoroughly extracted with ether. The combined ether extracts were washed with $NaHCO_3$ and brine and dried over $MgSO_4$. Solvent evaporation followed by column chromatography using ether/petroleum ether (1:2) gave 0.71 g (82%) of the pure product 17′ as a pale yellow liquid which gave a positive Beilstein test: ^1H NMR ($CDCl_3$) δ 5.8 (bm, 2 H), 3.8–1.2 (cm, 6 H); IR (neat) 1700, 1665 cm^{-1}.

Sequential addition of small portions of $Eu(fod)_3$ to a $CDCl_3$ solution of 17′ eventually resulted in the following lanthanide-shifted ^1H NMR spectrum: δ 10.19 (1 H, d, H_A), 7.95 1 H, m, H_B), 6.84 (1 H, bd, H_D), 5.53 (1 H, bm, $H_{D'}$), 4.10 (2 H, bt, H_c, $H_{c'}$); same labeling as in Figure 2.

X-ray Analysis of 13′. Crystals of 13′ suitable for X-ray analysis were obtained by cooling a saturated 95% ethanol solution to −45 °C. A red, plate-like crystal, which measured 0.17 × 0.3 × 0.06 mm was mounted, and preliminary investigations indicated the crystal system was monoclinic. Observation of reflection conditions ($h0l$; $h + l = 2n$; $0k0$; $k = 2n$) uniquely determined the space group $P2_1/n$. Unit cell dimensions were refined by a least-squares fit of the $\pm 2\theta$ values of 40 reflections distributed throughout reciprocal space (Table III). Lattice parameters and intensity data were collected on an Enraf-Nonius CAD-4 automatic X-ray diffractometer fitted with a liquid N_2 low temperature device, using molybdenum K_α radiation (λ = 0.71069 Å).

The position of the cobalt atoms was determined by a Patterson synthesis. The rest of the structure was determined by difference Fourier syntheses and refined by a full-matrix least-squares routine using anisotropic thermal parameters for the non-hydrogen atoms. All the hydrogen atoms were located from a difference Fourier map and were refined isotropically. Scattering factors were obtained from ref 24. The refinement converged to a final R ($R = \sum||F_o| - |F_c||/\sum|F_o|$) of 0.0418 for 3527 observed reflections.[25]

Final positional parameters are listed in Table IV. The hydrogen atom parameters, vibrational parameters, and bond angles are available as supplementary material.

Table IV. Atomic Positional Parameters

atom	X	Y	Z
Co(1)	0.15869 (4)	−0.09062 (9)	−0.00323 (4)
Co(2)	0.19585 (4)	0.20013 (9)	0.06378 (4)
O(1)	0.1887 (2)	−0.3849 (6)	−0.1000 (2)
O(2)	−0.0002 (2)	−0.0077 (6)	−0.1125 (2)
O(3)	0.1452 (3)	−0.2854 (7)	0.1421 (3)
O(4)	0.0503 (3)	0.3814 (7)	−0.0268 (3)
O(5)	0.1943 (3)	0.1129 (8)	0.2323 (3)
O(6)	0.3040 (2)	0.4974 (6)	0.0907 (3)
O(7)	0.4095 (2)	0.0343 (6)	−0.0164 (2)
C(1)	0.5024 (3)	0.3876 (8)	0.1295 (4)
C(2)	0.4706 (4)	0.2959 (9)	0.0480 (4)
C(3)	0.4269 (2)	0.1234 (7)	0.0461 (3)
C(4)	0.4067 (3)	0.0647 (7)	0.1218 (3)
C(5)	0.4798 (3)	−0.0181 (7)	0.1879 (3)
C(6)	0.5545 (3)	0.0856 (7)	0.1966 (3)
C(7)	0.5452 (3)	0.2819 (8)	0.2069 (3)
C(8)	0.5896 (3)	0.4181 (8)	0.1728 (4)
C(9)	0.3391 (3)	−0.0666 (7)	0.0973 (3)
C(10)	0.2634 (2)	0.0122 (6)	0.0451 (3)
C(11)	0.2271 (3)	0.0922 (7)	−0.0262 (3)
C(12)	0.2372 (3)	0.1641 (8)	−0.1034 (3)
C(13)	0.4668 (4)	−0.040 (1)	0.2718 (4)
C(14)	0.6104 (4)	0.5910 (9)	0.2181 (5)
C(15)	0.6515 (4)	0.3616 (9)	0.1331 (4)
C(16)	0.1781 (3)	−0.2703 (7)	−0.0615 (3)
C(17)	0.0602 (3)	−0.0396 (7)	−0.0701 (3)
C(18)	0.1486 (3)	−0.2118 (8)	0.0859 (4)
C(19)	0.1057 (4)	0.3129 (8)	0.0096 (4)
C(20)	0.1940 (4)	0.1495 (9)	0.1677 (4)
C(21)	0.2609 (3)	0.3841 (8)	0.0823 (3)

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Supplementary Material Available: Tables of thermal parameters, hydrogen atomic parameters, and bond angles for 13′ (3 pages). Ordering information is given on any current masthead page.

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