Stereospecific Dicobalt Octacarbonyl Mediated Enyne Cyclization for the Synthesis of the Cytotoxic Sesquiterpene (±)-Quadrone

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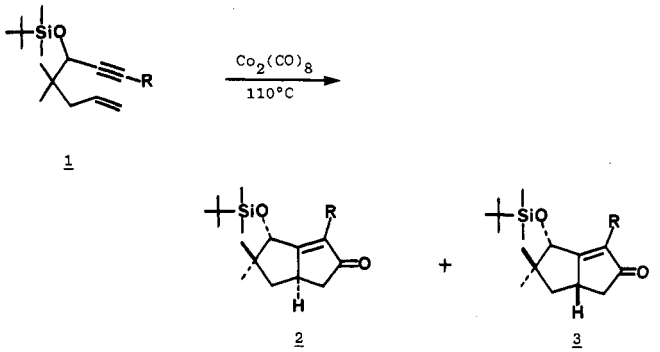
Ethyl isobutyrate was converted into the enyne **20**, through a straightforward sequence of transformations. Treatment of **20** with $Co_2(CO)_8$/CO/86 °C, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (0.1 equiv), gave the bicyclo[3.3.0] enone **25** (45%), in a completely stereospecific reaction. The stereochemistry of **25** was confirmed by converting it into **32**, which was an intermediate used in Isoe's synthesis of quadrone and terrecyclic acid. A mechanistic interpretation of the stereochemical outcome of the dicobalt octacarbonyl mediated enyne cyclization is described.

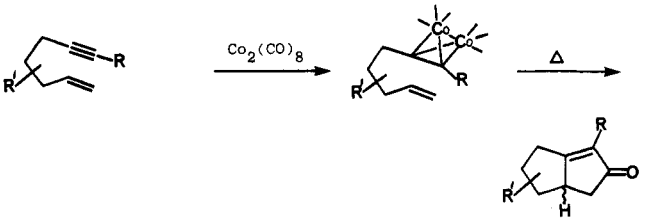
During the past several years, the synthesis of both linear and angularly fused polyquinanes has been one of the most active areas of terpene research.[1] This effort has resulted in many important and general methods that can be used for the construction of five-membered rings.[2] While our earlier studies in this area centered upon the development of organosilicon chemistry,[3] more recently, we have used the dicobalt octacarbonyl mediated cyclization of 1,5-enynes (Pausen–Khand reaction) to construct [3.3.0]oct-2-en-3-ones in a single step.[4] If this reaction (see Scheme I for a general intramolecular representation) is to be useful for the synthesis of natural products, in particular polyquinanes, it is important that a high degree of stereoselectivity be observed with respect to the newly created ring fusion and any allylic or propargylic substituents. It has been established during the course of the total synthesis of coriolin that the propargylic oxygen functionality present in **1** emerges predominantly on the exo face, cis to the ring fusion hydrogen, resulting in **2**/**3**.



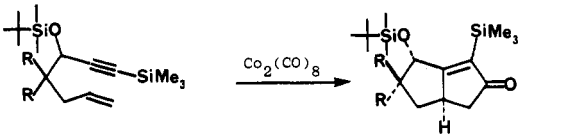
A mechanistic hypothesis has been put forward to rationalize this stereoselectivity as a function of the size of the R group on the acetylene.[5] In this study we report the stereochemical outcome of an allylic alkyl substituent with respect to the ring fusion (1,2-stereoselectivity) and its application to the synthesis of quadrone **4**.[6]

It would not be an exaggeration to say that quadrone **4** has attracted a disproportionate amount of synthetic attention relative to its modest biology. It was isolated in 1978 from *Aspergillus terreus* and found to exhibit inhibitory activity in vitro against human epidermoid carcinoma of the nasopharynx and in vivo activity against P388 lymphocytic leukemia in mice. Each one of the now substantial number of total syntheses is unique both in the overall strategy and more importantly with regard to the particular key synthetic transformation that has been melded into a completed synthesis of quadrone **4**.[7]

Scheme I

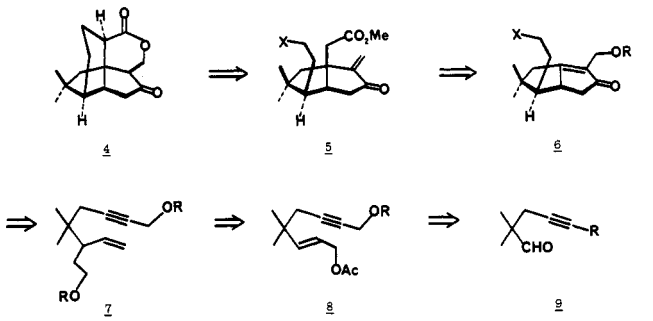


Scheme II



For R = H :yield is 14%
For R = Me:yield is 78%

Scheme III



(1) Paquette, L. A. *Recent Synthetic Developments in Polyquinane Chemistry*; Topics in Current Chemistry 119; Springer: Berlin 1984.
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(7) For references to the total synthesis of quadrone see: Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136. Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *Ibid.* **1981**, *103*, 4647. Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Oplinger, J. A.; Dike, M. S. *Ibid.* **1984**, *106*, 4558; **1982**, *104*, 872. Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *Ibid.* **1982**, *104*, 5808. Takeda, K.; Shimono, Y.; Yoshii, E. *Ibid.* **1983**, *105*, 563. Dewanckele, J. M.; Dutterman, F.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3235. Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146. Wender, P. A.; Wolanin, D. J. *Ibid.* **1985**, *50*, 4418. Smith, A. B.; Konopelski, J. P. *Ibid.* **1984**, 49, 4094. Iwata, C.; Yamashita, M.; Aoki, S.; Suzuki, K.; Takashi, I.; Arakawa, H.; Imanishi, T.; Tanaka, T. *Chem. Pharm. Bull.* **1985**, *33*, 436. Cooper, K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 799. Kon, K.; Ito, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 3739. Piers, E.; Moss, N. *Ibid.* **1985**, *26*, 2735. Paquette, L. A.; Annis, G. D.; Schostarez, M. *J. Am. Chem. Soc.* **1982**, *104*, 6646. Monti, S. A.; Dean, S. R. *J. Org. Chem.* **1982**, *47*, 2679. Funk, R. L.; Abelman, M. M., *Ibid.*, in press.

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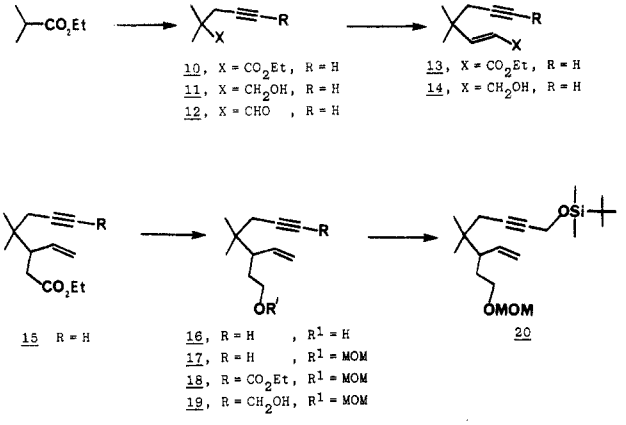
The most attractive feature of the dicobalt octacarbonyl mediated enyne cyclization, as depicted in Scheme I, is its intrinsic ability to assemble a [3.3.0]octenone in a single step from a totally acyclic precursor. With respect to its application to the synthesis of quadrone [4], two crucial questions must be addressed that not only impinge upon the specific problem presented here but are of general chemical edification. First, can one expect good stereochemical control for an allylic substituent with respect to the ring fusion stereochemistry in the resulting product, and second, are the yields in the dicobalt octacarbonyl enyne cyclization sufficiently high to be practical? In general, the yields in the dicobalt octacarbonyl enyne are modest (10–30%)[4] for unsubstituted systems, but if the alkyl chain connecting the alkene to the alkyne is substituted, particularly geminal substitution, then the yields improve (40–85%) appreciably, Scheme II. Clearly, conformationally restricted systems (Thorpe–Ingold effect) are very beneficial.[8] This is not a serious limitation, since many polyquinane terpenoid natural products possess geminal substituents. Scheme III depicts a retrosynthetic pathway for quadrone 4 based upon the above considerations.

The substrate **5** (X = OH) has been converted into quadrone **4** by Isoe[7] using a sequence of reactions that involve masking the α-methylene ketone functionality, followed by intramolecular alkylation to establish the final six-membered ring paralleling the original protocol used by Danishefsky.[7] We have established in earlier studies an efficient way for converting **6** into **5**, and this will be described later.[9] The most dramatic step in the retrosynthetic analysis is the transformation of **7** into **6**. This single step most clearly illustrates the intrinsic attractiveness of this strategy. The key substrate **7** should be available via a (Johnson)–Claisen rearrangement[10] of **8**, followed by reduction. Finally, **8** derives from **9** through straightforward transformations.

The first phase of the synthesis is concerned with a convenient method for the preparation of **7** or its equivalent. Treatment of ethyl isobutyrate with LDA/



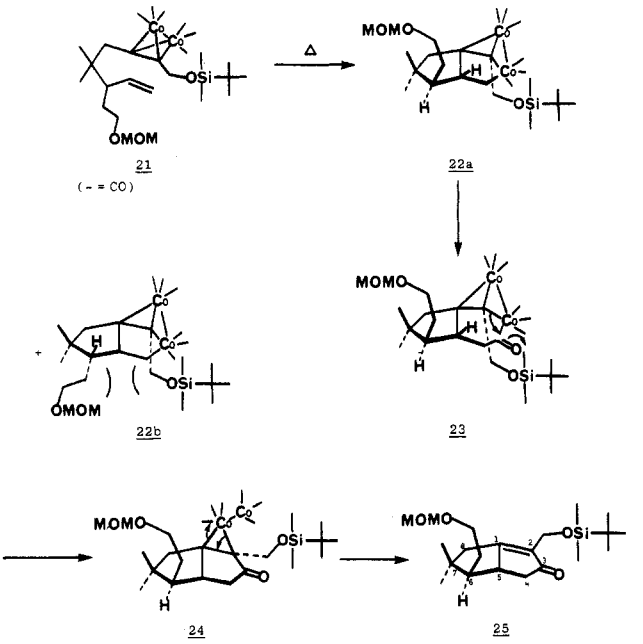
THF/propargyl bromide at −78 °C gave **10** (91%), which was reduced with $LiAlH_4$ to **11** (96%) and oxidized by using Me_2SO/oxalyl chloride/Et_3N/CH_2Cl_2 to give the aldehyde **12** (95%). Wadsworth–Emmons homologation of **12** gave **13** (84%), which was reduced by using DIBAL/THF to give the allylic alcohol **14** (95%). Exposure of **14** to $MeC(OEt)_3$/$EtCO_2H$(cat.)/140 °C resulted in the required Johnson–Claisen rearrangement to provide **15** (73%). Reduction of the ester in **15** using $LiAlH_4$/THF/0 °C gave **16** (91.5%), which was protected as its methoxymethyl ether (MOM), **17** (79%). Deprotonation of **17** using *n*-BuLi/THF/−78 °C followed by quenching with ethyl chloroformate gave **18** (86%), which was reduced with $LiAlH_4$/Et_2O/−78 °C to 0 °C to **19** (77%) and protected as its dimethyl-*tert*-butylsilyl ether **20** (86%).

Through this sequence the enyne **20** (see equivalent in Scheme III, structure **7**) is available in a reproducible manner in 11 steps, overall yield 20%.

When **20** was treated with $Co_2(CO)_8$/heptane/CO, resulting alkyne–$Co_2(CO)_6$ complex was isolated as a red oil in quantitative yield. It should be noted that the alkyne–$Co_2(CO)_6$ complex(s) is more stable than $Co_2(CO)_8$. At 50 °C $Co_2(CO)_8$ is converted into $Co_4(CO)_{12}$.

Using the mechanistic hypothesis we have advanced to predict the stereochemical outcome of bicyclo[3.3.0] enone formation,[5] Scheme IV suggests that the major product from **21** will be the desired stereoisomer **25** with a cis relationship between the 5 and 6 positions. The complex **21** can form two cobalt metallocycles, **22a** and/or **22b**, upon alkene insertion into the internal C–Co bond. The newly formed five-membered ring Co–metallocycle is presumably cis-fused, since the corresponding trans fusion is unacceptably strained. The Co–metallocycle **22a** minimizes the steric interactions between the $-CH_2CH_2OMOM$ group and $-CH_2OSiMe_2Bu$-*t*, whereas **22b** has a severe interaction between these substituents on the endo face. Subsequent CO insertion into **22a** is speculated to give the acylcobalt intermediate **23**, which undergoes C–CO migration to **24**, followed by elimination of $[Co_2(CO)_6]$ to give the desired bicyclo[3.3.0]octenone **25**. The species $[Co_2(CO)_6]$ can react with CO to regenerate $Co_2(CO)_8$ or dimerize to give $Co_4(CO)_{12}$. As a consequence, the enyne cyclizations are, at least in principle, catalytic with respect to the $Co_2(CO)_8$. This is indeed the case, although the yields of bicyclo[3.3.0]octenones fall by 50% if 1/10 mol of $Co_2(CO)_8$ is used. Since $Co_2(CO)_8$ is relatively inexpensive, it is better to use it stoichiometrically. This loss of efficiency is caused by the competitive formation of $Co_4(CO)_{12}$, which is inert toward enynes.

Scheme IV



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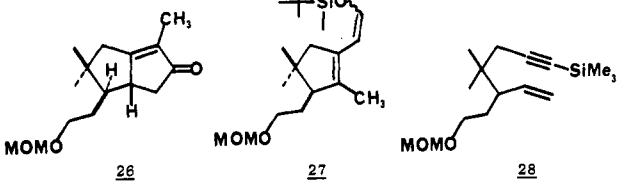
(9) Exon, C.; Nobbs, M.; Magnus, P. *Tetrahedron* **1981**, *37*, 4515.

(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. All attempts at Ireland–Claisen rearrangement of the derived acetate of **14** gave complications arising from acetylene–allene rearrangements.

In the event, treatment of **20** with $Co_2(CO)_8$ in heptane purged with CO gave **21** (ca. 100%) as a red oil. The complex **21** was heated in heptane containing 2,6-di-*tert*-butyl-4-methylpyridine (0.1 equiv) under CO, in a resealable tube, at 86 °C for 30 h. Workup by chromatography and removal of the cobalt residue by oxidation with *N*-methylmorpholine *N*-oxide gave **25** (45%). The assigned cis stereochemistry cannot be made from the ^1H NMR data but is based on its subsequent conversion into **32**. There was no evidence for any other stereoisomers of **25**; the only organic byproduct is the reduction product **26**. At higher temperatures (>95 °C) the diene **27** becomes the major product. If the enyne cyclization is carried out



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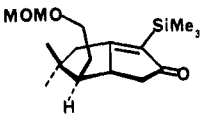

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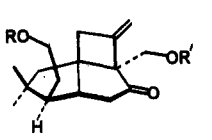
in the presence of tri-*n*-butylphosphine oxide,[11] then **26** is the major product. It should be noted that the 45% yield of **25** represents an optimized experiment. This is a reduction of 35%, compared with Scheme II (R = Me). To locate the origin of this effect, we have made **28** through entirely analogous chemistry (**10** to **19**, where R = $SiMe_3$). Treatment of **28** with $Co_2(CO)_8$/heptane/CO/115 °C/36 h gave **29** (78%). Obviously, the cause of the diminished yield of **25** is the lability of the CH_2OSiMe_2Bu-*t* to the $Co_2(CO)_8$ cyclization condition. Although **29** is available in good yield, we were unable to convert it into **25**, or derivatives thereof, using procedures that are described in the literature.[12] Consequently, while the yield of **25** from **20** is modest, this highly convergent single step assembles the central core of quadrone, with the correct relative stereochemistry and requisite functionality.

In order to proceed from **6** to **5** (Scheme III), we made use of a sequence of reactions that does not require any protection group chemistry.[13] Photolysis (450-W Hanovia lamp) of **25** in the presence of allene/hexane/THF/−78 °C[14] gave the [2 + 2]-cycloadduct **30** (84%). Acid hydrolysis (5% H_2SO_4/48% HBF_4/THF) gave the diol **31** (96%). Ozonolysis of **31** (O_3/CH_2Cl_2/MeOH), followed by reductive workup (Me_2S/MeOH), cleanly resulted in the fragmentation product **32** (90%), thus providing a correlation with Isoe[7] and substantiating the stereochemical assignments.

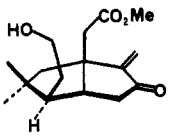
Since Isoe has converted **32** into quadrone **4** and its direct precursor, terrecyclic acid A, this constitutes a total synthesis of these sesquiterpenes.

In summary, the dicobalt octacarbonyl mediated enyne cyclization provides a stereospecific method for constructing highly substituted bicyclo[3.3.0]octenones from



30 R = MOM; $R^1 = SiMe_2Bu^t$

31 R = R^1 = H



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acyclic precursors in a single step. Its use for the synthesis of other polyquinanes is currently being investigated.

Experimental Section

The general experimental protocols used in this work have been described previously. A complete description of the preparation and characterization details for **10**, **11**, **12**, **13**, **14**, and compounds leading to **28** is available in the supplementary material.

Ethyl 4,4-Dimethyl-3-vinylhept-6-ynoate (15). The alcohol **14** (2.65 g, 19 mM), triethyl orthoacetate (10.0 g, 62 mM), and propanoic acid (70 mg, 0.94 mM) were heated together at 140 °C with stirring and provision for the removal of volatile byproducts. Aliquots of propanoic acid (ca. 70 mg) were added every 2 h and heating continued for a total of 15 h. The mixture was cooled to 20 °C, diluted with ether (50 mL), washed with 10% aqueous $NaHCO_3$ (15 mL), dried ($MgSO_4$), and evaporated in vacuo. Purification of the residue by chromatography over silica gel, eluting with petroleum ether/EtOAc (19:1), gave the ester **15** (2.93 g, 74%) as a colorless liquid: IR (CH_2Cl_2) 3300, 3070, 2970, 2120, 1730, 1640, 1460 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.65 (1 H, m), 5.10 (2 H, m), 4.15 (2 H, q, J = 7 Hz), 2.60 (1 H, m), 2.50 (1 H, m), 2.20 (1 H, m), 2.15 (2 H, d, J = 2 Hz), 2.01 (1 H, t, J = 2 Hz), 1.24 (3 H, t, J = 7 Hz), 1.00 (3 H, s), 0.93 (3 H, s); MS, m/e calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1447.

4,4-Dimethyl-3-vinylhept-6-yn-1-ol (16) and Its Methoxymethyl Ether 17. To a suspension of $LiAlH_4$ (1.2 g, 32 mM) in THF (100 mL) at 0 °C was added a solution of the ester **15** (4.8 g, 23 mM) in THF (50 mL). Conventional workup and purification by chromatography over silica gel, eluting with petroleum ether/EtOAc (9:1), followed by petroleum ether/EtOAc (1:1), gave the alcohol **16** (3,5 g, 91.5%): IR (thin film) 3600–3150, 3320, 3080, 2970, 2120, 1640, 1470, 1420, 1390, and 1370 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.60 (1 H, m), 5.10 (2 H, m), 3.65 (1 H, m), 3.54 (1 H, m), 2.02–2.18 (2 H, m), 1.97 (1 H, t, J = 3 Hz), 1.76 (1 H, m), 1.40 (1 H, m), 0.96 (3 H, s), 0.91 (3 H, s); MS, m/e calcd for $C_{11}H_{18}O$ 166, found 166.

Conversion of **16** into its MOM ether by using standard methods gave **17** (79%): IR (thin film) 3300, 3080, 2970, 1640, 1450, 1380, and 1370 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.55 (1 H, m), 5.10 (2 H, m), 4.60 (2 H, AB q, J = 5 Hz), 3.35 (3 H, s), 2.1 (3 H, m), 1.98 (1 H, t), 1.85 (1 H, m), 1.40 (1 H, m), 0.99 (3 H, s), 0.92 (3 H, s).

Ethyl 5,5-Dimethyl-6-vinyl-8-[(methoxymethyl)oxy]oct-2-ynoate (18). To the enyne **17** (3.2 g, 15.2 mM) in dry THF (50 mL) at −78 °C under dry argon was added *n*-BuLi (6.1 mL of a 2.5 M hexane solution, 1.0 equiv) dropwise over 5 min. After stirring the mixture for 1 h at −78 °C, ethyl chloroformate (2.2 g, 20 mM) in THF (2 mL) was added dropwise, and the solution was warmed to 20 °C over a period of 150 min. The mixture was quenched with 50% saturated aqueous NH_4Cl (20 mL), and the organic layer washed with 5% aqueous $NaHCO_3$ solution and water. The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by chromotography over silica gel, eluting with petroleum ether/EtOAc (9:1) to give **18** (3.82 g, 89%) as a mobile liquid: IR (thin film) 2970, 2230, 1710, 1640, 1470, 1390, and 1370 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.55 (1 H, m), 5.10 (1 H, m), 4.58 (2 H, AB q, J = 7 Hz), 4.22 (2 H, q, J = 7 Hz), 3.5 (2 H, m), 3.35 (3 H, s), 2.25 (2 H, s), 2.05 (1 H, m), 1.85 (1 H, m), 1.40 (1 H, m), 1.30 (3 H, t, J = 7 Hz), 1.02 (3 H, s), 0.94 (3 H, s); MS, m/e calcd for $C_{16}H_{26}O_4$ 282, found 282.

Reduction of **18** (4.6 g) in Et_2O (50 mL) at −78 °C with a solution of $LiAlH_4$ (17 mL, 1 M solution), followed by standard workup, gave **19** (3.38 g, 86%): IR (thin film) 3700–3150, 3070, 2970, 2220, 1640, 1465, 1390, and 1370 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.55 (1 H, m), 5.05 (2 H, m), 4.59 (2 H, AB q, J = 7 Hz),

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(12) Cohen, T.; Kosorych, Z.; Suzuki, K.; Yu, L.-C. *J. Org. Chem.* **1985**, *50*, 2965. Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 1809. Burn, D.; Petrow, V. *J. Chem. Soc.* **1962**, 1223.
(13) The procedures used in the literature, ref 7, for similar overall transformations require the carbonyl group to be protected.
(14) Eaton, P. E. *Tetrahedron Lett.* **1964**, 3695. Wiesner, K. *Tetrahedron* **1975**, *31*, 1655.

4.24 (2 H, br s), 3.50 (2 H, m), 3.36 (3 H, s), 2.15 (3 H, m), 1.85 (1 H, m), 1.35 (1 H, m), 0.95 (3 H, s), 0.91 (3 H, s); MS, m/e calcd for $C_{14}H_{24}O_3$ (M^+ - OMe) 209.1542, found 209.1521.

The alcohol **19** (808 mg, 3.36 mM) in dry Et_3N (550 mg, 5.45 mM) and CH_2Cl_2 (20 mL) at 0 °C was treated with *t*-$BuMe_2SiCl$ (608 mg, 4.0 mM), and the mixture was maintained at 4 °C for 15 h. Workup in the standard manner gave **20** (960 mg, 81%) after purification by chromatography over silica gel, eluting with petroleum ether/EtOAc (19:1): IR (thin film) 3080, 2970, 2230, 1640, 1465, 1375, and 1250 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.52 (1 H, m), 5.05 (2 H, m), 4.60 (2 H, q, J = 6 Hz), 4.31 (2 H, t, J = 2 Hz), 3.45 (2 H, m), 3.34 (3 H, s), 2.0–2.15 (3 H, m), 1.83 (1 H, m), 1.40 (1 H, m), 0.96 (3 H, s), 0.90 (12 H, s), 0.11 (6 H, s); ^{13}C NMR (ref $CDCl_3$ centered at 77.0 ppm) ^1H coupled spectrum 138.5 (d), 117.4 (t), 96.5 (t), 83.2 (s), 80.5 (s), 66.7 (t), 55.1 (q), 52.0 (t), 49.0 (d), 35.7 (s), 31.2 (t), 28.4 (t), 25.6 (q), 24.6 (q), 18.3 (s), -5.1 (q). Anal. Calcd for $C_{20}H_{38}O_3Si$: C, 67.74; H, 10.80. Found: C, 67.82; H, 10.78.

5βH-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6β-[2-(methoxymethoxy)ethyl]-7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one (25). To a solution of the enyne **20** (410 mg, 1.16 mM) in dry heptane (4 mL) purged with CO for 2 h was added $Co_2(CO)_8$ (435 mg, 1.28 mM, 1.1 equiv), and the CO purging was continued for 3 h at 20 °C to ensure complete formation of the $Co_2(CO)_6$–yne complex **21**. The heptane solution was directly chromatographed over Florisil, eluting with petroleum ether to remove nonpolar impurities, followed by elution with petroleum ether/EtOAc (19:1) to give **21** (748 mg, ca. 100%) as a red viscous oil. The $Co_2(CO)_6$–yne complex **21** was dissolved in dry heptane (4 mL) containing 2,6-di-*tert*-butyl-4-methylpyridine (22 mg, 0.1 equiv), the solution was purged with CO for 2 h in a resealable tube, and the tube was sealed and heated at 86 °C (over trichloroethylene heated at reflux) for 30 h. The tube was cooled to 20 °C, and the contents were chromatographed over Florisil eluting with 2% ether/petroleum ether, followed by petroleum ether/EtOAc (9:1), then 4:1, to give crude **25** (220 mg). The crude product was dissolved in CH_2Cl_2 (30 mL) and *N*-methylmorpholine *N*-oxide (60 mg) added. The mixture was stirred for 15 min, quenched with brine (2 × 10 mL), and extracted with CH_2Cl_2 (10 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated. The residue was filtered through a short column of Florisil, eluting with petroleum ether/EtOAc (4:1) to give **25** (200 mg, 45%) as a pale yellow oil: IR (thin film) 2950, 1710, 1670, 1470, 1400, and 1260 cm^{-1}; UV λ_{max} ($CHCl_3$) 241 nm (ϵ, 2200); NMR (300 MHz, $CDCl_3$) δ 4.37 (2 H, AB q, J = 16 Hz), 4.61 (2 H, s) 3.55 (2 H, m), 3.36 (3 H, s), 2.75 (1 H, m), 2.63 (1 H, dd, J = 16 Hz and 4 Hz), 2.60 (2 Hz, AB q, J = 17 Hz), 2.17 (1 H, dd, J = 17 Hz and 4 Hz), 1.85 (1 H, m), 1.60 (1 H, m), 1.12 (3 H, s), 1.03 (3 H, s), 0.90 (9 H, s), 0.70 (6 H, s); ^{13}C NMR (ref $CDCl_3$ centered at 77.0 ppm) ^1H coupled spectrum 208.2 (s), 183.2 (s), 135.0 (s), 96.5 (t), 66.7 (t), 57.5 (t), 55.3 (q), 50.9 (d), 49.1 (d), 43.4 (t), 42.9 (s), 42.4 (t), 29.5 (t), 29.2 (q), 25.9 (q), 18.3 (s), 0.96 (q), -5.5 (q); MS, m/e calcd for $C_{17}H_{29}O_4Si$ 382.2456, found 382.2409. Conducting the above experiment in the presence of tri-*n*-butylphosphine oxide, the reduction product **26** becomes the major product (31%): IR ($CHCl_3$) 2970, 1710, 1670, 1470, 1390, and 1370 cm^{-1}; UV λ_{max} (MeOH) 239 nm (ϵ, 7700); NMR (300 MHz, $CDCl_3$) δ 4.60 (2 H, s), 3.60 (2 H, m), 3.35 (3 H, s), 2.70 (1 H, m), 2.65 (1 H, dd, J = 15.5 Hz and 4.5 Hz), 2.42 (2 H, AB q, J = 19 Hz), 2.09 (1 H, dd, J = 15.5 Hz and 2 Hz), 1.84 (1 H, m), 1.65 (3 H, s), 1.55 (1 H, m), 1.25 (1 H, m), 1.10 (3 H, s), 1.00 (3 H, s).

Conducting the above experiment at 110 °C, followed by the same workup used for **25**, gave the diene **27** (29%): IR (thin film) 2970, 1650, 1605, 1460, 1380, 1360, and 1250 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 6.13 (1 H, d, J = 6.5 Hz), 5.10 (1 H, d, J = 6.5 Hz), 4.60 (2 H, s), 3.65 (2 H, t, J = 7 Hz), 3.35 (3 H, s), 2.5 (1 H, m), 2.05 (1 H, m), 1.65 (5 H, m), 1.05 (3 H, s), 0.95 (3 H, s), 0.90 (9 H, s), 0.10 (6 H, s).

Photoadduct 30. A solution of **25** (287 mg, 0.75 mM) in dry hexane (15 mL) and dry THF (3 mL) was purged with N_2 for 1 h in a resealable tube. Allene (ca. 1 mL) was condensed into the tube at -78 °C, and the tube was sealed and irradiated (450-W Hanovia lamp) for 5 h at 0 °C. The tube was opened and the excess allene allowed to evaporate. The remaining liquid was evaporated under reduced pressure to afford **30**, as a pale yellow liquid. Purification of **30** by chromatography over Florisil, eluting with petroleum ether/EtOAc (9:1) gave **30** (267 mg, 84%) as a colorless oil: IR (thin film) 2970–2860, 1740, 1670, 1390, 1370, and 1250 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 4.91 (1 H, t, J = 2 Hz), 4.83 (1 H, t, J = 2 Hz), 4.59 (2 H, s), 3.80 (2 H, AB q, J = 10 Hz), 3.25 (2 H, m), 3.35 (3 H, s), 2.94–2.80 (2 H, m), 2.63 (1 H, m), 2.20 (3 H, m), 1.80 (1 H, m), 1.47 (1 H, m), 1.58 (1 H, AB q, J = 15 Hz), 1.34 (1 H, dt, J = 9.6 and 4.3 Hz), 0.99 (3 H, s), 0.85 (12 H, s), 0.03 (3 H, s), 0.02 (3 H, s); MS, m/e calcd for $C_{24}H_{42}O_4Si$ 422.2852, found 422.2816.

Diol 31. The photoadduct **30** (250 mg, 0.59 mM) dissolved in 5% aqueous H_2SO_4/THF/48% aqueous HBF_4 (49:49:2) (30 mL) was heated at 65 °C for 6 h. After being cooled to 20 °C, the mixture was diluted with EtOAc (20 mL), and the organic layer was washed with 10% aqueous $NaHCO_3$ solution. The aqueous fractions were extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed over silica gel, eluting with petroleum ether/EtOAc (9:1) followed by EtOAc to give the diol **31** (150 mg, 96%); IR (CH_2Cl_2) 3700–3100, 2970, 1720, 1665 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 4.92 (1 H, br s), 4.86 (1 H, br s), 3.80 (2 H, AB q, J = 11 Hz), 3.60 (2 H, m), 2.90 (2 H, m), 2.65 (1 H, m), 2.2 (2 H, m), 1.78 (2 H, AB q, J = 15 Hz), 1.70 (1 H, m), 1.45 (1 H, m), 1.28 (1 H, dt, J = 9.7 and 4.8 Hz), 0.95 (3 H, s), 0.88 (3 H, s); MS, m/e calcd for $C_{16}H_{24}O_3$ (E.I.) M^+ + 1 265.1803, found 265.1755.

7,7-Dimethyl-6-(2-hydroxyethyl)-1-(methoxycarbonyl)-2-methylenebicyclo[3.3.0]octan-3-one (32). A solution of the diol **31** (30 mg, 0.11 mM) in CH_2Cl_2 (6 mL) and MeOH (6 mL) containing molecular sieves (type 4 Å) was treated with ozone at -78 °C for 2 min (solution became pale blue). Ozonolysis was continued for a further 5 min, and the mixture was purged with oxygen and then nitrogen to remove excess ozone. Dimethyl sulfide (1 mL) was added, and the mixture was brought to 20 °C overnight (ca. 19 h). The mixture was extracted with CH_2Cl_2 (15 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude enone **32** (34 mg, ca. 100%) as a yellow oil. Purification by chromatography over Florisil, eluting with petroleum ether/EtOAc (1:1), gave **32** (27 mg, 88%): IR (CH_2Cl_2) 3700–3200, 2970, 1740, 1725, 1640, and 1260 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 6.01 (1 H, s), 5.24 (1 H, s), 3.63 (2 H, t, J = 6 Hz), 3.55 (3 H, s), 2.65 (3 H, m), 2.30 (2 H, m), 1.80 (2 H, AB q, J = 17 Hz), 1.70 1 H, m), 1.48 (1 H, m), 1.28 (1 H, m), 0.93 (3 H, s), 0.90 (3 H, s); MS, m/e calcd for $C_{16}H_{24}O_4$ (E.I.) M^+ + 1 280.1674, found 280.1652.

5βH-2-(Trimethylsilyl)-6β-[2-(methoxymethoxy)ethyl]-7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one (29). To a solution of the enyne **28** (166 mg, 0.59 mM) in dry heptane (4 mL), purged with CO for 2 h, was added $Co_2(CO)_8$ (230 mg, 0.67 mM), and the CO purging was continued for 3 h at 20 °C in a resealable tube. The tube was then sealed and heated at 115 °C for 36 h. The contents were evaporated in vacuo and chromatographed over Florisil, eluting with 2% ether/petroleum ether, followed by petroleum ether/EtOAc (9:1), and finally with petroleum ether/EtOAc (4:1) to afford **29** (143 mg, 78%) as a mobile, slightly yellow liquid: IR (thin film) 2960, 1680, 1600, 1450, 1370, and 1240 cm^{-1}; UV (MeOH) 237.5 nm (ϵ, 11 000); NMR (300 MHz, $CDCl_3$) δ 4.60 (2 H, s), 3.61 (1 H, m), 3.51 (1 H, m), 3.35 (3 H, m), 2.80 (1 H, m), 2.53 (1 H, dd, J = 16.5 and 4 Hz), 2.50 (2 H, AB q, J = 18 Hz), 1.85 (1 H, m), 1.55 (1 H, m), 1.32 (1 H, td, J = 12 and 3 Hz), 1.11 (3 H, s), 1.02 (3 H, s) 0.16 (9 H, s); MS, m/e calcd for $C_{17}H_{30}O_3Si$ (C.I.) M^+ - 1 309.1841, found 309.1812.

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Supplementary Material Available: Preparation and characterization of **10–14** and compounds leading to **28** (3 pages). Ordering information is given on any current masthead page.