Hz, $J_{4\text{-ax.},5\text{-eq}}$ = 3.70 Hz, 4-$H_{ax.}$), 4.68 (dd, 1 H, $J_{8,9}$ = 1.65 Hz, 8-H), 6.11 (dd, 1 H, $J_{9,10}$ = 5.75 Hz, 9-H), 6.50 (d, 1 H, 10-H); **23b** (12% diastereomer) δ 0.26 (s, 18 H, 2/3-OSiMe_3), 1.58 (s, 3 H, 3-CH_3), 4.77 (dd, 1 H, $J_{8,9}$ = 1.85 Hz, 8-H), 6.18 (dd, 1 H, $J_{9,10}$ = 5.85 Hz, 9-H), 6.34 (d, 1 H, 10-H); **23c** (12% diastereomer) δ 0.40 (s, 18 H, 2/3-OSiMe_3), 1.49 (s, 3 H, 3-CH_3), 4.65 (dd, 1 H, $J_{8,9}$ = 1.60 Hz, 8-H), 6.37 (dd, 1 H, $J_{9,10}$ = 5.75 Hz, 9-H), 6.75 (d, 1 H, 10-H); **23d–f** (10% three diastereomers) δ 0.27, 0.287, 0.295, 0.42, 0.46 (s, 18 H, 2/3-OSiMe_3), 4.75 (dd, 1 H, $J_{8,9}$ = 1.65 Hz, 1.75 Hz, 1.65 Hz, 8-H), 6.08, 6.26 (dd, 1 H, $J_{9,10}$ = 5.75 Hz, 5.75 Hz, 5.75 Hz, 9-H), 6.44, 6.45, 6.63 (d, 1 H, 10-H).

1-(2-Furyl)-2-hydroxy-2-methyl-5-hexen-1-one (24), (1*R,6*S**,8*R**)-3-Hydroxy-3-methyl-11-oxatricyclo-[6.2.1.$0^{1,6}$]-9-undecen-2-one (*exo*-25a and *exo*-25b), and (1*R**,6*R**,8*R**)-3-Hydroxy-3-methyl-11-oxatricyclo-[6.2.1.$0^{1,6}$]-9-undecen-2-one (*endo*-25).** The product mixture of **23** and **22** (1.03 g, 2.82 mmol) was treated with 954 mg (5.64 mmol) of BTAF in 6 mL of CH_2Cl_2 for 1 h. Workup similar to that for **19** yielded 445 mg (81%) of **25/24**, 90:10 (^{1}H NMR). Flash chromatography (SiO_2 Woelm 32–63 m, CH_2Cl_2, after the first two fractions acetone). Fraction 1: 36 mg (9%) of **24** (IR, ^{1}H NMR). Fraction 2: 225 mg of *exo*-**25a** (55%), colorless crystals, mp 48–49 °C. Fraction 3: 40 mg (10%) of a mixture of *exo*-**25a**, *exo*-**25b**, and *endo*-**25** (63:25:12, ^{1}H NMR, 400 MHz). *exo*-**25a**: IR (film) 3540, 3090, 1720 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.22 (AB, 1 H, $J_{7\text{-endo},7\text{-exo}}$ = 11.10 Hz, $J_{7\text{-endo},8}$ = 0 Hz, 7-H_{endo}), 1.28 (A*B*, 1 H, $J_{7\text{-exo},8}$ = 4.30 Hz, 7-H_{exo}), 1.44–1.52 (m, 2 H, 5-$H_{ax.}$, 5-H_{eq}), 1.58–1.69 (m, 1 H, $J_{6\text{-endo},7\text{-endo}}$ = 7.00 Hz, $J_{6\text{-endo},7\text{-exo}}$ = 2.65 Hz, 4-H_{eq}, 6-H_{endo}), 1.63 (s, 3 H, 3-CH_3), 1.84 (dt, 1 H, $J_{4\text{-ax.},4\text{-eq}}$ = 12.60 Hz, $J_{4\text{-ax.},5\text{-ax.}}$ = 13.85 Hz, $J_{4\text{-ax.},5\text{-eq}}$ = 3.20 Hz, 4-$H_{ax.}$), 2.07 (dd, 1 H, $J_{4\text{-eq},5\text{-ax.}}$ = 3.75 Hz, $J_{4\text{-eq},5\text{-eq}}$ = 3.0 Hz, 4-H_{eq}), 4.20 (s, 1 H, 3-O*H*), 4.77 (dd, 1 H, $J_{8,9}$ = 1.65 Hz, 8-H), 6.02 (dd, 1 H, $J_{9,10}$ = 5.85 Hz, 9-H), 6.56 (d, 1 H, 10-H); ^{13}C NMR (C_6D_6, 100 MHz) δ 23.95 (t, 3-CH_3), 28.29 (t, C-5, exchangeable for C-7), 35.79 (t, C-7), 41.87 (t, C-4), 43.08 (d, C-6), 77.25 (s, C-3), 81.04 (d, C-8), 90.50 (s, C-1), 133.21 (d, C-9), 136.81 (d, C-10), 209.45 (s, C-2).

With these data at hand, the following signals of the product mixture were assigned: ^{1}H NMR (C_6D_6, 400 MHz) *exo*-**25b** δ 1.15 (mc, 1 H, $J_{7\text{-endo},7\text{-exo}}$ = 10.95 Hz, $J_{7\text{-endo},6\text{-endo}}$ = 7.00 Hz, $J_{7\text{-endo},8}$ = 0 Hz, 7-H_{endo}), 1.58 (s, 3 H, 3-CH_3), 4.74 (dd, 1 H, $J_{8,7\text{-exo}}$ = 4.60 Hz, $J_{8,9}$ = 1.85 Hz, 8-H), 6.27 (dd, 1 H, $J_{9,10}$ = 5.70 Hz, 9-H), 6.96 (d, 1 H, 10-H); ^{13}C NMR (C_6D_6, 100 MHz) *exo*-**25b** δ 24.89 (q, 3-CH_3), 25.78, 31.50 (t, C-5, C-7), 46.05 (d, C-6), 77.13 (s, C-3), 78.55 (d, C-8), 134.11 (d, C-9), 138.31 (d, C-10); ^{1}H NMR (C_6D_6, 400 MHz) *endo*-**25** δ 1.44 (s, 3 H, 3-CH_3), 4.67 (dd, 1 H, $J_{8,7\text{-exo}}$ = 4.50 Hz, $J_{8,9}$ = 1.75 Hz, 8-H), 5.94 (dd, 1 H, $J_{9,10}$ = 5.85 Hz, 9-H), 6.59 (d, 1 H, 10-H); ^{13}C NMR (C_6D_6, 100 MHz) *endo*-**25** δ 23.05 (q, 3-CH_3), 26.47, 36.05 (t, C-5, C-7), 41.53 (t, C-4), 42.88 (d, C-6), 81.83 (d, C-8), 132.46 (d, C-9).

Formation of 24 by Cycloreversion of *exo*-25a. Compound *exo*-**25a** (110 mg, 0.57 mmol) in 0.45 mL of C_6D_6 was treated as described for *exo*-**19**, yielding 105 mg (95%) of **24**, bp 85 °C (0.01 Torr) (IR, ^{1}H NMR). Anal. Calcd for $C_{11}H_{14}O_3$ (194.2): C, 68.2; H, 7.26. Found: C, 68.04; H, 7.49.

Acknowledgment. We are indebted to Fonds der Chemischen Industrie, Frankfurt/Main, BRD, and BASF-Aktiengesellschaft, Ludwigschafen, BRD, for support of this work. We also thank Prof. M. Christl for his comments on our NMR data and Dr. E. Ciganek[3e] for a preprint of his review article.

Registry No. **8**, 73602-61-6; **10**, 40861-56-1; **11**, 5162-44-7; **12**, 1119-51-3; **13**, 106161-85-7; **14**, 106161-86-8; *exo*-**15a**, 106247-63-6; *endo*-**15a**, 106161-82-4; *exo*-**15b**, 106247-64-7; *endo*-**15b**, 106247-62-5; **17**, 59304-43-7; **18**, 106161-87-9; *exo*-**19**, 106247-65-8; *endo*-**19**, 106161-83-5; **20**, 106191-38-2; **21**, 109-49-9; **22a**, 106161-88-0; **22b**, 106161-84-6; **23**, 106161-89-1; **24**, 106161-90-4; *exo*-**25a**, 106161-91-5; *exo*-**25b**, 106247-66-9; *endo*-**25**, 106247-67-0; TMSCN, 7677-24-9; Furfural, 98-01-1.

Two Approaches to Angularly Fused Triquinanes via Intramolecular Pauson–Khand Cyclization

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The Pauson–Khand reaction has been used to form angularly fused triquinanes via the cyclization of derivatives of 1-(4-pentynyl)cyclopentene in the presence of $Co_2(CO)_8$. Precursor enynes were prepared in two ways: the key to the first method involved addition of 1,4-bis-Grignard reagents to butyrolactone, while the second utilized addition of regioselectively prepared 5-methyl-1-cyclopentenyllithium to a suitable substrate. Tri- but not tetrasubstituted alkenes could be induced to cyclize. Extensive NMR analyses of the products allowed determination of product stereochemistry and generalization of some useful spectroscopic characteristics of these compounds.

Introduction

Interest in the intramolecular Pauson–Khand reaction[1] as a route to polycyclopentanoid intermediates for natural product synthesis has increased dramatically in the past several years. Syntheses of bicyclo[3.3.0]octanes,[2] tricyclo[6.3.0.$0^{1,5}$]undecanes,[3] tricyclo[5.2.1.$0^{4,10}$]undecanes,[4] and heteroatom-containing analogues[5] using this methodology[6] have been reported. We describe herein two simple approaches toward cyclization precursors for angularly fused triquinanes (tricyclo[6.3.0.$0^{1,5}$]undecanes). The first affords the unsubstituted ring system in only four steps from

(1) General references for the Pauson–Khand reaction: (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. (b) Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2. (c) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.

(2) (a) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. (b) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. (c) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (d) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. (e) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835.

(3) Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025.

(4) Carceller, E.; Centellas, V.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Tetrahedron Lett.* **1985**, *26*, 2475.

(5) (a) Croudace, M. C.; Schore, N. E. *J. Org. Chem.* **1981**, *46*, 5357. (b) Billington, D. C.; Willison, D. *Tetrahedron Lett.* **1984**, *25*, 4041. (c) Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245; (d) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

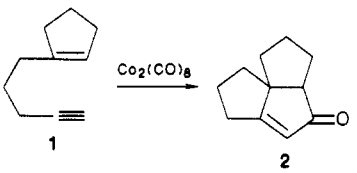
(6) The *intermolecular* Pauson–Khand reaction has also been used in syntheses of several of these systems: (a) Newton, R. F.; Pauson, P. L.; Taylor, R. G. *J. Chem. Res.* Miniprint **1980**, 3501. (b) Daalman, L.; Newton, R. F.; Pauson, P. L.; Wadsworth, A. *J. Chem. Res.* Miniprint **1984**, 3150. (c) Billington, D. C. *Tetrahedron Lett.* **1983**, *24*, 2905.

0022-3263/87/1952-0569$01.50/0

essentially acyclic precursors, and the second permits regiochemically controlled construction of more highly substituted derivatives. A preliminary account of a portion of this work has already appeared.[3]

Results and Discussion

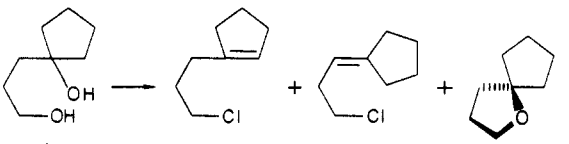
At the time we began this study syntheses of bicyclo[4.3.0]nonanes and bicyclo[3.3.0]octanes using the intramolecular variant of the Pauson–Khand cyclization process had been demonstrated.[2a,b] However, extension of this process to the synthesis of tricyclics presented several substantial additional demands on what was at the time a rather poorly understood reaction. In the model reaction in its simplest form (eq 1) the cyclization of 1-(4-pentynyl)cyclopentene (1) to tricyclic enone 2 requires that a trisubstituted alkene react to give rise to a product containing a quaternary carbon at a multiple ring fusion. Only in electronically unusual cases such as arylnorbornenes had cyclization of trisubstituted alkenes previously been demonstrated.[1b,7] Substrate 1, possessing no additional substitution, was chosen as our first target for study in the hope that the additional steric impediment of the trisubstituted double bond (relative to simple α,ω-enynes) would be partly counteracted by its increased electron density, a factor that appeared to favor cyclization reactivity.[1b,5a]



(1)

Synthesis and Cyclization of 1-(4-Pentynyl)cyclopentene. We initially envisioned an apparently straightforward preparation of 1 via addition of a protected 3-hydroxypropyl organometallic to cyclopentanone, followed by appropriate manipulation to give the required cyclization substrate. In fact, this approach fails in two ways. Neither the Grignard nor the organolithium reagents derived from the THP ethers of either 3-bromo- or 3-chloropropanol add in better than 15% yield. In addition, deprotection of the primary alcohol is difficult to achieve without substantial spiroether formation at the tertiary center. Fortunately, work of Canonne et. al.[8] provided a remarkably simple solution in the direct addition of α,ω-bis-Grignard reagents to lactones to produce hydroxyalkyl-substituted cycloalkanols. Thus, reaction of 1,4-dibromobutane with excess magnesium in tetrahydrofuran (THF), followed by slow addition of γ-butyrolactone at reflux gave 88% yields of 1-(3-hydroxypropyl)cyclopentanol (3) even on an 0.5 mol scale.

In all, three two-step approaches for the conversion of 3 into 1 were investigated. Reagent systems were chosen such that elimination at the tertiary center could be achieved concomitantly with conversion of the primary alcohol into a leaving group. Recognizing that acidic conditions that would lead to cyclic ether formation had to be avoided, thionyl chloride in pyridine was initially tried, but was found to give rise to substantial amounts of ether 6. Greater success was obtained with the triphenylphosphine–carbon tetrachloride reagent, provided that a large excess of the phosphine was present. Under the best conditions approximately equal quantities of chloroalkenes 4 and 5 and ether 6 could be obtained (eq 2). Although a less than ideal situation, the ease of

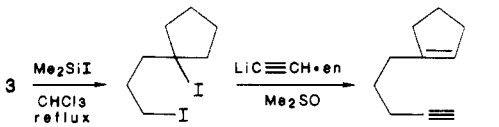


(2)

3	4	5	6
$SOCl_2$, py	20%	3%	77%
CCl_4, PPh_3	36%	5%	39%

chromatographic removal of 6 allowed the synthesis of 1 to be completed by reaction of the chloroalkene mixture with the ethylenediamine (EDA) complex of lithium acetylide in dimethyl sulfoxide (Me_2SO).

A more successful approach made use of trimethylsilyl iodide (Me_3SiI) in the first step. Addition of diol 3 to a preformed solution of Me_3SiI generated by reaction of iodine with hexamethyldisilane in chloroform[9] leads in nearly quantitative yield to a mixture containing mostly diiodide 7 together with smaller amounts of iodoalkenes from elimination at the tertiary center. This mixture was used directly in reaction with excess lithium acetylide EDA, leading directly to enyne 1 (eq 3).



(3)

Having in hand two viable routes to 1, its reactivity towards cyclization in the presence of $Co_2(CO)_8$ could be investigated. No success was obtained with the reaction conditions used in the cyclization of simple acyclic enynes[2a] (equimolar enyne/$Co_2(CO)_8$, 2,2,4-trimethylpentane solvent, 95 °C, 4 days). Since in earlier work we had found that significant changes in the product distribution of related reactions could be affected by changing the coordinating ability of the solvent,[10] we looked for improvement using either benzene or toluene. In toluene at reflux only intractable products of decomposition were obtained. Small amounts of the desired enone were obtained, however, in initial experiments using benzene. Taking care to use carefully purified solvent and moderate levels of dilution, we were able to realize reproducible yields of about 35% of enone 2 from reaction of 1 with a slight excess of $Co_2(CO)_8$ at reflux for 3–4 days. The product was characterized both spectroscopically and by the results of further transformations (vide infra). In the IR characteristic enone absorbances at 1630 and 1690 cm^{-1} were present. The high-field proton NMR displayed a characteristic signal for the enone proton at δ 5.82, a complex pattern at δ 2.59 due presumably to the allylic methylene, and a signal at δ 2.42 (d, J = 8.3 Hz) due to the methine α to the ketone.[11] This reaction therefore represents the first example of the generation of a quaternary carbon at a multiple ring fusion using the Pauson–Khand process, the first use of this methodology in an intramolecular reaction of a cyclic substrate and one of the very few examples of successful application of this reaction on a trisubstituted alkene. It is also noteworthy that the cyclization of 1 takes place under conditions as mild as those used for simple acyclic enynes and gives comparable yields.

With the entry to the triquinane system established, we directed our efforts towards transformations that might

(7) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 30.

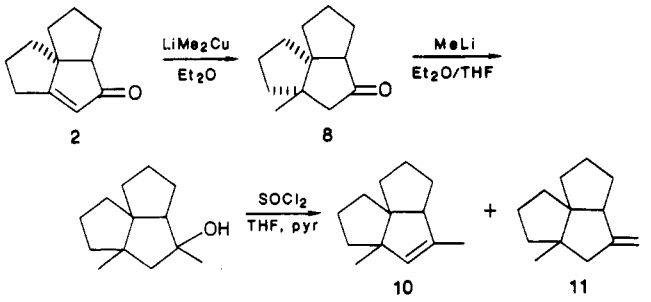
(8) Cannone, P.; Foscoles, G. P.; Bêlanger, D. *J. Org. Chem.* **1980**, *45*, 1828.

(9) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

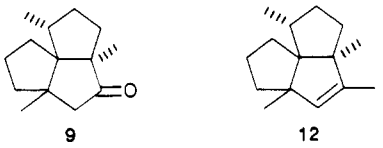
(10) Schore, N. E.; LaBelle, B. E.; Knudsen, M. J.; Hope, H.; Xu, X-J. *J. Organometal. Chem.* **1984**, 272, 435.

(11) Ketone 2 has been reported previously: Cargill, R. L.; Foster, A. M. *J. Org. Chem.* **1970**, *35*, 1971.

Scheme I



ultimately prove useful in natural product synthesis. Addition of lithium dimethylcuprate to **2** proved to be quite slow, but through the use of a 5-fold excess of the reagent an 89% yield of **8** was obtained. Characterization of **8** rests partially on spectroscopic comparisons with the known ketone **9**.[12a] Both show typical IR bands for cyclopentanones: **8** at 1735 cm^{-1} and **9** at 1730 cm^{-1}. In the NMR ketones **8** and **9** show singlets for angular methyl

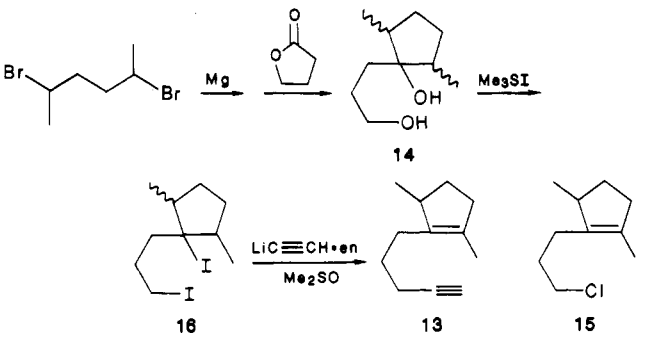


groups at δ 1.08 and 1.10, respectively. For the methylene protons α to the ketone, one observes AB patterns centered at δ 2.27 (J = 18.2 Hz) for **8** and at δ 2.28 (J = 17 Hz) for **9**. In addition, **8** displays a signal at δ 2.31 (dd, J = 4.5, 10.8 Hz) for the methine on the other side of the carbonyl.

Addition of methyllithium to **8** gave good yields of the rather sensitive tertiary alcohol (methyl signals centered about δ 1.13 and 1.68, presumably a mixture of isomers) which was best dehydrated using thionyl chloride in pyridine/THF at −45 °C,[13] affording a 93% yield of a 7:3 mixture of endo and exocyclic alkenes **10** and **11**. The NMR of **10** showed the alkene hydrogen signal at δ 4.89 (br s), two methyl singlets at δ 1.00 and 1.60, and the signal for the allylic methine at δ 2.46 (br d, J = 8.6 Hz). For comparison purposes, the alkene hydrogen and two of the methyl groups in isocomene (**12**) appear at δ 4.83, 1.03, and 1.56, respectively,[12a] and the allylic methine in pentalenene absorbs at δ 2.56 (d, J = 10 Hz).[12b] Scheme I summarizes the transformations involved in the synthesis of **10**.

Synthesis and Attempted Cyclization of 1,3-Dimethyl-2-(4-pentynyl)cyclopentene. Given the success achieved in the cyclization of **1**, the obvious next step was the synthesis of the dimethyl analogue **13**, the successful cyclization of which would open the way to an efficient synthesis of the naturally occurring sesquiterpene isocomene.[14,15] The synthesis of the cyclization precursor was in fact straightforward, and followed the general approach used to prepare **1**. Reduction of 2,5-hexanedione to the diol followed by conversion to 2,5-dibromohexane followed the literature procedures in 79% overall yield.[16]

Scheme II



Subsequent conversion to the corresponding bis(Grignard reagent) and addition to γ-butyrolactone proceeded in excellent overall yield (86%) to the dimethyl diol **14** as a mixture of stereoisomers. Since separation of the individual isomers was for our purposes unnecessary, all that was done on this mixture was purification of a small quantity of the major diastereomer, which showed in the NMR a methyl doublet at δ 0.95 (J = 7.0 Hz) and a triplet for the methylene of the primary alcohol function at δ 3.68 (J = 6.1 Hz). It is noteworthy that this represented the first application of this diol synthesis utilizing other than doubly primary (i.e., α,ω) bis(Grignard reagents).

As we found in the conversion of **3** to **1**, the conversion of diol **14** to enyne **13** required a good deal of trial-and-error experimentation. Treatment of **14** with the triphenylphosphine–carbon tetrachloride reagent led to considerable decomposition under a variety of conditions. At best we achieved only a 3% yield of chloroalkene **15**, quite an unfortunate result since the latter could be converted into the desired enyne with lithium acetylide EDA in excellent yield. As before, an acceptible alternative made use of Me_3SiI to convert **14** into diiodide **16**, which upon treatment with an excess of the acetylide gave **13** in an overall yield of 49%. Scheme II summarizes these results.

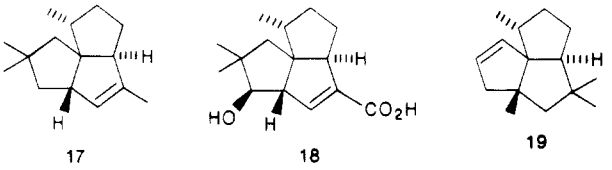
With enyne **13** in hand we were in a position to test several new points of interest. First, and most critical, was the question of compatibility of the Pauson–Khand cyclization with a tetrasubstituted alkene substrate. Even given the benefits of intramolecularity, this represented a major step beyond anything that had been attempted previously. Should the cyclization succeed, however, a useful stereochemical question would also be answered, namely the fate of the allylic methyl group. Inspection of models suggested that this methyl could exert a directing role on the cyclization, causing the alkyne–$Co_2(CO)_6$ moiety to complex predominantly to the face of the cycloalkene opposite to it. This would conveniently lead to the stereochemical outcome required for the synthesis of virtually all naturally occurring compounds with this skeleton.

In the event however, enyne **13** failed to cyclize to a useful extent under any conditions tried. Mixing of the substrate with $Co_2(CO)_8$ leads to evolution of CO and, presumably, formation of the usual alkyne complex. Heating of this material chiefly leads to alkyne trimerization, forming ill-characterized benzenoid products in moderate yield, and returning considerable amounts of unreacted alkyne complex even after several days at reflux. On a large scale small amounts of polar fractions are isolated which give evidence (NMR, IR, MS) of containing very small amounts of one or more cyclopentenones. Unfortunately all attempts at isolating the compound(s) responsible for these signals met with failure. Clearly, given the option of trimerizing a terminal alkyne, the Pauson–Khand cyclization of a tetrasubstituted alkene is

(12) (a) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (b) Paquette, L. A.; Annis, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358.
(13) Compare experiment 5 in Greene, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 5337.
(14) Isolation: Zalkow, L.; Harris, R.; Van der Veer, D.; Bertrand, J. *J. Chem. Soc., Chem. Commun.* **1977**, 456. Bohlman, F.; LeVan, N.; Pickardt, J. *Chem. Ber.* **1977**, *110*, 3777.
(15) Syntheses: Paquette, L.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014. Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493. Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445. Tobe, Y.; Yamashita, T.; Kakaiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898.
(16) Kornblum, N.; Eicher, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2259.

for all practical purposes unable to compete. The limit of tolerance for alkene substitution in the Pauson–Khand reaction is therefore defined with the cyclization of trisubstituted alkene 1.

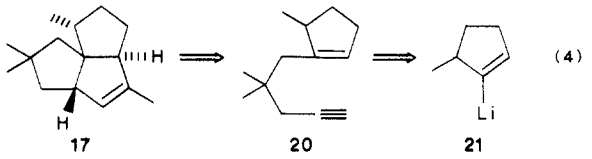
More Highly Substituted Systems. A number of natural products possessing the triquinane skeleton contain, like isocomene, a secondary methyl substituent oriented trans to the adjacent ring fusion, but lack the additional ring-fusion methyl group that rendered isocomene inaccessible via the methodology described above. These include pentalenene (**17**),[17,18] pentalenic acid (**18**),[19,20] and



17 18 19

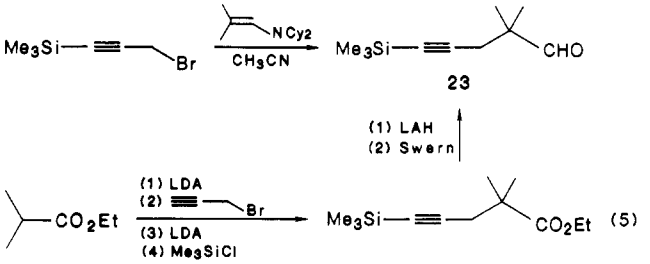
silphinene (**19**),[21,22] and they have proved to be extremely popular targets on which to test novel synthetic methodology.[23]

Syntheses of any of these systems via Pauson–Khand cyclization requires first a regioselective preparation of the precursor enyne. For pentalenene this is **20**, which we had



17 20 21 (4)

hoped to approach via reaction of the regioselectively generated vinyllithium reagent **21** with an appropriate alkynyl substrate. Vinyllithium **21** is readily prepared using a modification of the Shapiro reaction[24] that employs the triisopropylbenzenesulfonyl (trisyl) hydrazone of 2-methylcyclopentanone as a precursor.[25] Although **21** readily alkylates unhindered primary haloalkanes,[26] no success was obtained in reactions with several derivatives of 4,4-dimethyl-1-trimethylsilyl-1-pentyne, including the 5-iodide and 5-tosylate. Lacking at the time any other direct routes to **20**, we chose instead to prepare enyne alcohol **22** by reaction of **21** with 2,2-dimethyl-5-trimethylsilyl-4-pentynal (**23**). The latter was prepared in two different ways, the first involving alkylation of the dicyclohexylenamine of isobutyraldehyde with 3-bromo-1-trimethylsilylpropyne, following the procedure of Stevens et al.[27] for the synthesis of the same aldehyde lacking the trimethylsilyl group. While adequate, this route is rendered somewhat cumbersome by the need for careful fractional distillation under vacuum to remove the dicyclohexylamine. A second route, developed by Magnus,[2c,28] begins with alkylation of the enolate of ethyl isobutyrate with propargyl bromide, followed by silylation of the alkyne, reduction to the alcohol, and finally Swern oxidation (eq 5). Although the overall yields of the two

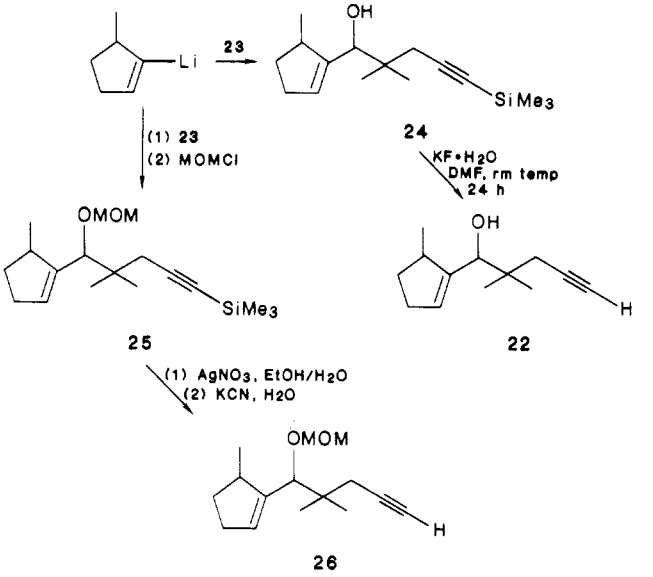


(5)

sequences are essentially identical (39% vs. 38%), the second is preferable from a practical standpoint.

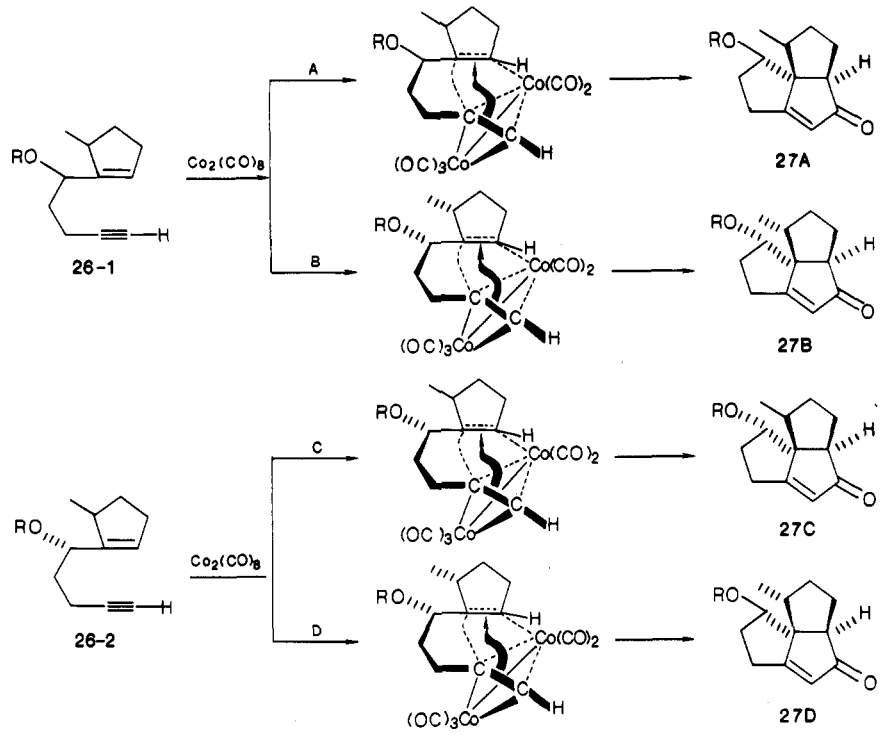
The synthesis of enyne **22** was achieved in an 86% overall yield by reaction of vinyllithium **21** with aldehyde **23** to give **24**, followed by removal of the silyl group with potassium fluoride in DMF.[29] The product was obtained as a mixture of inseparable (LC, GC) diastereomers whose ratio (NMR) varied from reaction to reaction between 55:45 and 70:30. Although several examples of Pauson–Khand cyclizations of substrates possessing free hydroxyl groups have been reported,[1c,30] enyne **22** gave no evidence of cyclization to an enone upon treatment with $Co_2(CO)_8$ under a variety of conditions. (The silylated derivative **24** was similarly unreactive.) As a result, protection of the alcohol in **24** as a methoxymethyl (MOM) ether[31] was carried out, forming **25**. In this case the subsequent de-

Scheme III



(17) Isolation: Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92.
(18) Syntheses: (a) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2869. (b) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1982**, *104*, 4504. (c) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1984**, 959. (d) Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1984**, 3021. (e) Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800. See also ref 2e for a synthesis of (+)-17 using the intramolecular Pauson–Khand cyclization of an acyclic enyne.
(19) Isolation: Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411.
(20) Syntheses: Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 355. Crimmins, M. T.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 2076.
(21) Isolation: Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, 19, 259.
(22) Syntheses: Leone-Bay, A.; Paquette, L. A. *J. Org. Chem.* **1983**, *47*, 4173. Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83. Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149. Wender, P. A. *Tetrahedron Lett.* **1985**, *26*, 2625. Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435.
(23) Reviews: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*, 1.
(24) Review: Shapiro, R. H. *Org. Reactions* **1976**, *13*, 405.
(25) Stenke, J. E.; Chamberlin, A. R.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. Chamberlin, A. R.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 154.
(26) Knudsen, M. J.; Schore, N. E., unpublished results.
(27) Stevens, R. V.; Christensen, C. G.; Edmondson, W. L.; Kaplan, M.; Reid, E. B.; Wentland, M. P. *J. Am. Chem. Soc.* **1971**, *93*, 6629.
(28) Magnus, P., personal communication. We thank Prof. Magnus for providing us with experimental details for his synthesis of **23**.
(29) Corey, E. J.; Fleet, G. W. J.; Kato, M. *Tetrahedron Lett.* **1973**, 3963.
(30) La Belle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yanuck, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215.
(31) The protecting group of choice for allylic alcohols in this reaction.[2c]

Scheme IV

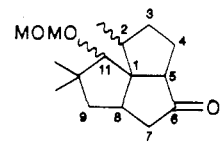


silation was found to be best achieved using silver nitrate followed by potassium cyanide.[32] Protected enyne **26** was thus obtained in 88% overall yield from **23** (Scheme III).

Since enyne **26** was obtained as an inseparable mixture of diastereomers, cyclization could in principle lead to as many as four stereoisomeric products (Scheme IV, C-10 methyls omitted). If the secondary methyl were to exert a sterically controlling influence on the course of the reaction in the desired manner (vide supra) then the major products should be enone **27B** from enyne **26-1**, and enone **27D** from enyne **26-2**, in each case the isomer with the methyl group trans to the adjacent fused ring. However, this expectation ignores the presence of the MOM ether which, also being an allylic substituent, would be expected to have some steric influence on the reaction as well.[30]

Cyclization reactions were attempted on both **25** and **26**. While no silated enones were formed from **25**, enyne **26** cyclized relatively rapidly, with no unreacted enyne–$Co_2(CO)_6$ complex remaining after about 18–22 h at 80 °C. Thus the additional substitution clearly exerts an accelerating effect on the reaction.[2b] The isolated yield of enone **27** is a somewhat disappointing 30%, and the mass balance is unusually low. Indeed, **27** is a rather sensitive compound which does not survive extended contact with the reaction conditions under which it is generated. This may be due to slow loss of the MOM protecting group due to the presence of adventitious Lewis acid in the reaction mixture,[10] followed by fragmentation of the free alcohol via a vinylogous retro-aldol pathway. The latter also explains the lack of enone products from attempted cyclization of **22**.

Typically, preparations of **27** were purified by repeated chromatography immediately after completion of the cyclization process. Due to their instability, little could be accomplished in the way of direct stereochemical analysis of the components present in **27**. Proton NMR suggested the presence of at least two, and perhaps three stereoisomers (alkene signals at δ 5.78 and 5.90, and methine signals at δ 3.61, 3.78, and 3.88), but quantification proved to be impossible due to decomposition of the enone in solution. The expected IR absorptions were observed at 1639 and 1709 cm^{-1}. Instead, detailed analysis was carried out on the mixture of saturated ketones (IR 1730 cm^{-1}) produced by lithium/ammonia reduction of crude enone preparations (yield 90%). These reduction products proved to be separable into three fractions by MPLC, two of which were pure single ketones, and the third a mixture with one major component which could not be further purified. Each fraction gave MS, NMR, and IR spectra consistent with ketone **28**, as well as correct microanalytical data. At high



28

fields (360 and 500 MHz) the proton NMR spectra showed variations attributable to stereochemical differences, but definitive assignments required the collection of additional data. This is described in the next section.

Structure Determinations for Ketones 28. A series of proton NMR experiments were carried out in an effort to assign structures to the two pure ketone fractions obtained from the reduction of enone mixture **27**. The 500 MHz spectra of the two are remarkably similar (Table I). Both show three high-field methyl signals in regions typical for angularly fused triquinanes[33] (δ 0.89–1.06) and the expected signals for the MOM group. Each spectrum shows an unexpectedly deshielded signal (ca. δ 3.0) for, presumably, the ring-fusion proton α to a ketone.[34] The main differences between the isomers were evident in two

(32) Rajagopalan, S.; Zweifel, G. *Synthesis* **1985**, 111.

(33) Paquette, L. A.; Galemmo, R. A., Jr.; Caille, J.-C.; Valpey, R. S. *J. Org. Chem.* **1986**, *51*, 686.

(34) This is ca. 0.5 ppm downfield of the typical position for these protons. Compare δ values of 2.42 for **2**, 2.31 for **8**, and 2.51 for the ketone derived from hydroboration/oxidation/oxidation of pentalenene: Cane, D. E.; Abell, C.; Tillman, A. M. *Bioorg. Chem.* **1984**, *12*, 312.

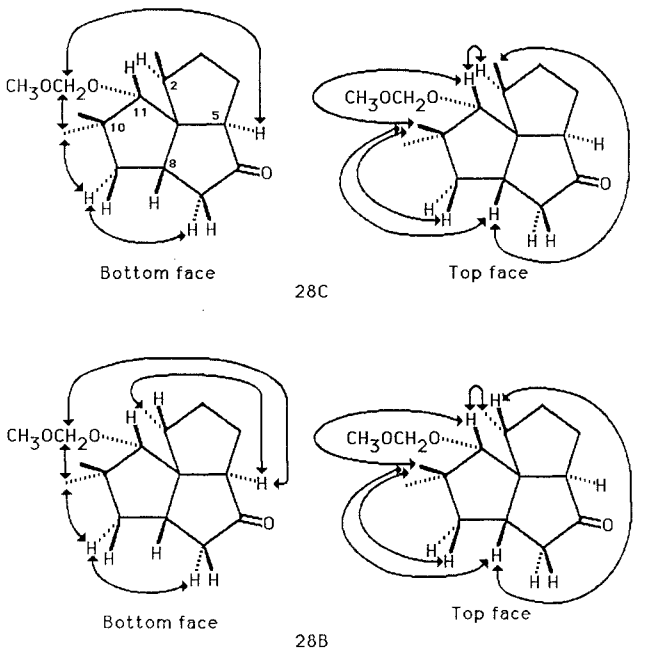


Figure 1. NOE interactions in the ^1H NMR spectra of ketones **28C** and **28B**.

signals: the methine hydrogen at the ether carbon is deshielded by 0.2 ppm in the more polar of the compounds (δ 3.66 vs. 3.45), while an apparent ring-fusion methine hydrogen is deshielded by 0.2 ppm in the less polar isomer (δ 2.47 vs. 2.24).

In order to interpret this data, we recorded two-dimensional proton–proton correlated spectra for identification of both coupled protons (COSY) and proximal protons (NOESY) in both compounds. The results not only allowed structural assignment with a high degree of certainty, they provided information concerning chemical shift and coupling constant patterns that appears to be generally applicable to both di- and triquinanes. The COSY experiments allowed assignment of chemical shifts to all protons on all but carbons 3 and 4 (see numbering[35] on structure above). Based on simple molecular models, it was anticipated that the NOESY data would be extremely useful for stereochemical assignment, since the structures possess numerous 1,2- and 1,3-interactions which should be observable without ambiguity due to the limited flexibility of the tricyclic system.

The keys to the analyses lay in NOE's associated with the methylene of the C-11 MOM group and with the C-11 methine. In both ketones the MOM methylene shows a major NOE with the high-field C-10 methyl, suggesting a cis relationship between the two. The C-11 methine in the more polar isomer exhibits strong NOE's with the low-field C-10 methyl and the C-2 methyl. The C-11 methine in the less polar isomer also shows a strong NOE with the low-field C-10 methyl, but only a weak NOE with the methyl at C-2. Instead, the C-11 methine shows strong enhancement with the methine at C-2 (well-resolved at δ 2.04). These observations suggest that the ketones are epimeric at least at the secondary methyl center (C-2). Confirmation of this and establishment of the rest of the relative stereochemistry in each involved relaying NOE's across both faces of the molecules. Thus in both compounds the C-8 methine shows an NOE with the C-10 methyl at low-field, but in *only* the less polar isomer, there is an additional NOE between the C-8 methine and the secondary methyl at C-2. These and other internally consistent observations allowed the assignments of structure **28C** to the less polar ketone and structure **28B** to the more polar isomer (Figure 1). The aforementioned chemical shift differences between the methines at C-8 and C-11 are therefore the expected[36a] results of a deshielding 1,3-pseudodiaxial interaction of the C-2 methyl with the C-8 proton in **28C** and with the C-11 methine in **28B**. In addition, the low-field shift for the C-5 proton is explained by its proximity to the MOM group.[36b]

Table I. Proton NMR Data for Ketones 28[a]

	28A	28B	28C
Me-2	(β) 1.02	(α) 1.03	(β) 1.03
H-2	(α) 2.38	(β) 1.7	(α) 2.04
H-3α	*b*	1.39	0.95[c]
H-3β	1.81[c]	1.7	1.72[c]
H-4α	*b*	1.95	1.76[c]
H-4β	*b*	1.7	1.90[c]
H-5(α)	2.68	3.04	2.99
H-7α	2.13	2.15	2.17
H-7β	2.31	2.50	2.38
H-8(β)	2.50	2.24	2.47
H-9α	1.03[b]	1.31	1.32
H-9β	1.73	1.7	1.72
Me-10α	0.94[c]	1.00	0.89
Me-10β	1.08[c]	1.05	1.06
H-11	(α) 3.55	(β) 3.66	(β) 3.45
$-OCH_2O-$	4.60, 4.65	4.58, 4.62	4.64, 4.66
MeO–	3.40	3.37	3.37

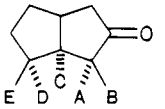
[a] 360 or 500 MHz, $CDCl_3$. [b] Location uncertain due to presence of impurities. [c] Stereochemical assignment uncertain.

The third saturated ketone, obtained only in impure form from the most polar of the LC fractions isolated, has been tentatively identified as **28A** (from enone **27A**; see Scheme IV for structure) on the basis of the following considerations. The simple NMR spectrum resembles in many ways that of **28C** (Table I). A COSY experiment allows identification of the resonances for the five-proton system associated with carbons 7, 8, and 9, the chemical shifts of which compare well in the two isomers. The position of the C-8 methine, δ 2.50, suggests the same configuration for the C-2 methyl in both compounds. On the other hand, the proton at the C-5 ring fusion is now in a more normal position (δ 2.68), while the C-2 methine is strongly deshielded (δ 2.38). This may be readily explained by postulating the opposite configuration at C-11, placing the MOM group in very close proximity to the proton at C-2, and removing its interaction with the C-5 methine. In spite of the somewhat incomplete NMR data for this compound, it seems reasonable to conclude that the only difference between it and **28C** is the configuration at C-11. Thus three of the four possible stereoisomers (**27A**, **27B**, and **27C**) appear to form in the cyclization process. The absence of **27D** is not at all surprising as models clearly indicate a severe steric interaction between the C-2 methyl and the C-11 ether, a result of the geometric constraints imposed by the spiro linkage at C-1. The presence of the MOM group has therefore at the least obscured any desirable stereochemical control that may be displayed by the C-2 methyl group on the cyclization process.[37] Several routes to the structurally simpler enyne

(35) We are no more thrilled by the plethora of numbering systems in use for these compounds than is anyone else. We have chosen to use what we hope is a correct application of the von Baeyer system in the text. The corresponding Chemical Abstracts names are referenced in the experimental section.

(36) (a) Jackman, L. M.; Sternhell, S. In *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Barton, D. H. R., Doering, W., Eds.; International Series of Monographs in Organic Chemistry; Pergamon: Oxford, 1969; Vol. 5, pp 78–80; (b) pp 80–81.

Table II. Proton Chemical Shifts in Bicyclo[3.3.0]octan-3-ones[a]



	A	B	C	D	E
28A	2.31	2.13	2.50	1.73	1.03[b]
28B	2.50	2.15	2.25	1.70	1.31
28C	2.37	2.17	2.47	1.72	1.33
8	2.36	2.18	(Me)	*b*	*b*
29	2.60	2.04	2.88	2.18	1.17
30	2.62	2.27	3.15	(MOMO)	3.27

[a] 360 or 500 MHz, $CDCl_3$. [b] Location uncertain.

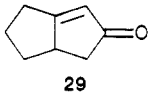
Table III. Coupling Constants in Bicyclo[3.3.0]octan-3-ones[a]

	ab	ac	bc	cd	ce	de
28A	18.7	8.6	1.8	7.2	*b*	12.8
28B	19.2	8.9	2.0	≈9	9.4	13.1
28C	19.2	10.2	3.3	≈9	5.0	13.5
8	18.2	–	–	–	*b*	*b*
29	17.8	6.5	3.3	7.0	8.6	11.8
30	17.5	6.4	3.8	–	10.3	–

[a] For proton labeling, see structure, Table II. [b] Could not be extracted from spectrum.

20 are currently under investigation, and we hope to be able to provide an answer to this question and, therefore, an assessment of this particular approach to stereocontrol in natural product synthesis in the near future.[38]

Characteristic Proton NMR Patterns in Di- and Triquinanes. Certain aspects of the NMR spectra of bicyclo[3.3.0]octanones seem to be characteristic of the structural type and may be useful in solving stereo- and regiochemical questions. Certainly, the ongoing studies regarding the structure of the sesquiterpene senoxydene[33] amply illustrate the potentially deceptive nature of NMR in this area. A summary of 360 and 500 MHz spectral data for four tricyclic and two bicyclic ketones (**29**[2a,39] and **30**[2c,40])



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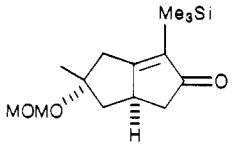

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is presented in Tables II and III. Assignments have been made on the basis of decoupling experiments and by analogy with the results of the two-dimensional data obtained for ketones **28B** and **28C**.

The data consistently suggest that protons located within the concave fold of a bicyclo[3.3.0]octane fragment are shielded relative to protons on the convex face. This is in accord with most observations of methyl group chemical shifts in these systems as well.[23,33,41] The relatively high-field shift for the proton in position 'E' (which is especially noticeable in the spectrum of **29**) is typical. One consistently sees $J_{cis} > J_{trans}$ for coupling between ring-fusion protons and protons α to a ketone, but this unfortunately does not appear to be general for α-methylated derivatives.[42] Clearly care must be exercised in inferring structural information concerning these systems from spectroscopic data; nonetheless, these results illustrate several correlations of a reasonably reliable nature that should be of general use in the study of these compounds.

Experimental Section

General. Solvents. For procedures carried out under anhydrous conditions, tetrahydrofuran (THF), hexane, benzene, and toluene were vacuum distilled from sodium benzophenone ketyl and stored over 4-Å molecular sieves under argon. Isooctane, dioxane, pyridine, dimethylformamide (DMF), acetonitrile, and dimethyl sulfoxide (Me_2SO) were distilled from calcium hydride before use. Carbon tetrachloride, chloroform, and dichloromethane were dried over 4-Å molecular sieves. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was distilled from sodium metal and stored over 4-Å molecular sieves.

Reagents. Thionyl chloride was purified by distillation. Triphenylphosphine was dried for use by dissolving the reagent in the reaction solvent, drying the resultant solution over anhydrous sodium sulfate, and filtering the solution into the reaction vessel. Propargyl bromide, triethylamine, and dicyclohexylamine were distilled before use. Following literature procedures, 2,5-dibromohexane was prepared from 2,5-hexanedione,[16] 3-bromo-1-trimethylsilyl-1-propyne was prepared from propargyl alcohol,[43] and the dicyclohexyl enamine of isobutyraldehyde was prepared in the usual way.[44] Unless otherwise noted, other reagents were obtained commercially and used without further purification. All reactions were carried out under an atmosphere of dried argon or nitrogen.

Separation and Purification. Neutral alumina (Mallinckrodt), silica gel (Baker), and Florisil (Sigma) for column chromatography were used as received. Commercially prepared silica gel columns (LiChroprep Si60, EM Reagents) were used for medium-pressure liquid chromatography (MPLC) with a Waters Differential Refractometer detection system (Model R403). Other chromatographic separations were carried out on a Chromatotron (Harrison Research) using silica gel with calcium binder (E. Merck). Analytic thin-layer chromatography was done on

(37) Ratio of **28A**(impure):**28B**:**28C** is 6:3:1. However, the relative rates of decomposition of the enones **27A–C** are not known; neither are the relative reactivities of the diastereomeric precursor enynes **26-1** and **26-2** towards cyclization. Thus using the ketone ratio to derive information concerning the detailed course of the reaction is suspect.

(38) Not unexpectedly, the highly hindered (doubly neopentyl) C-11 oxygen in **28** has proved to be most resistant to removal.

(39) The *J* values reported in ref 2a are in error. The correct values: δ 1.17 (dddd, *J* = 8.6, ca. 11.8 × 3) and 2.18 (ddd, *J* = 7.0, 7.0, 11.8).

(40) MacWhorter, S., unpublished results from these laboratories.

(41) Moinet, G.; Brocard, J.; Conia, J. M. *Tetrahedron Lett.* **1972**, 4461.

(42) Contrast data for compounds **15** and **31** in ref 33 with data for compound **28** in ref 18e.

(43) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.

(44) Opitz, G. *Justus Liebigs Ann. Chem.* **1961**, 650, 122.

fluorescent indicating silica gel sheets (Merck). Iodine was used to visualize nonchromophoric bands.

Analysis. Analytical samples were purified by chromatotron or MPLC and followed by GC using a 10-ft preparatory column packed with 7% FFAP liquid phase on Chromosorb W (General, 40/60 mesh) solid support. Nuclear magnetic resonance spectra (^{1}H) were recorded on a Varian EM-390 (90 MHz) spectrometer. High-field NMR spectra were recorded on Nicolet NT-1180 or NT-1280 360 and 500 MHz FT-NMR spectrometers. Chemical shifts are expressed in parts per million relative to tetramethylsilane (δ 0.00) or residual chloroform in deuterochloroform (δ 7.26 relative to Me_4Si). Listed NMR data are given in the order: number of protons (by integrated intensity), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), and coupling constants. IR spectra were recorded on a Beckman IR-8, Perkin-Elmer 180, or IBM FT-IR 900 spectrophotometers. High resolution mass spectral data were determined at the Facility for Advanced Instrumentation (FAI) at the University of California, Davis. Microanalyses were performed at the microanalytical laboratory facility at the University of California, Berkeley.

1-(3-Hydroxypropyl)-1-cyclopentanol (3). The procedure that follows was adopted and scaled up from that in the literature.[8] To 180 g (7.40 mol) of dry Mg turnings was vacuum transferred 200 mL of THF. To the mixture was added dropwise a solution of 62.0 mL (0.51 mol) of 1,4-dibromobutane and 60 mL of THF at such a rate as to insure mild refluxing of the solution over about 4 h. The solution was refluxed for an additional 1 h, allowed to cool to room temperature, and then transferred from the unreacted Mg to another reaction vessel. A solution of 44.0 mL (0.577 mole) of γ-butyrolactone and 75 mL of THF was added dropwise over 2.5 h to the reaction solution at reflux, and the mixture was allowed to cool to room temperature and stirred for 6 h. The product mixture was poured into saturated aqueous ammonium chloride (200 mL) and extracted with ether (4 × 150 mL), and the combined ether extracts were washed with saturated aqueous ammonium chloride (100 mL) and saturated aqueous sodium chloride (100 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed (neutral alumina) and eluted with ether to give upon solvent removal 64.80 g (88%) of **3**: mp 32–33 °C; NMR (360 MHz, $CDCl_3$) δ 3.68 (2 H, t, J = 6.0 Hz), 2.20 (2 H, s), 1.54–1.87 (12 H, m); IR (CCl_4) 3320, 1065 cm^{-1}. Data are in agreement with that in the literature.[8]

1-(3-Chloropropyl)cyclopentene (4). To a solution of 2.00 g (13.9 mmol) of **3** in 100 mL of carbon tetrachloride was added 9.12 g (34.8 mmol) of triphenylphosphine. The solution was heated to reflux for 1.5 h during which time a white precipitate of triphenylphosphine oxide formed. The solution was diluted with n-hexane and gravity filtered. The filtrate was distilled at high vacuum (25 °C, ca. 0.005 mmHg) into a receiver cooled with liquid nitrogen. The distillate was warmed to room temperature and concentrated. Chromatography (neutral alumina) gave two fractions eluting with n-hexane. The first fraction after solvent removal yielded 0.823 g (41%) of a mixture of the desired product **4** (36%) and its isomer **5** (5%). For further preparative work the isomers were not separated; however, for characterization purposes they were separated by GC into two bands, the first being pure **4** and the second **5**. The second chromatography fraction gave after solvent removal 0.782 g (39%) of spiro ether **6**.

For **4**: NMR ($CDCl_3$, 360 MHz) δ 5.37 (1 H, m), 3.54 (2 H, t, J = 6.9 Hz), 2.17–2.28 (4 H, m), 2.10 (2 H, m), 1.51–1.97 (4 H, m); IR (film) 1645 (w), 3060 (w) cm^{-1}. Anal. Calcd for $C_8H_{13}Cl$: C, 66.43; H, 9.06. Found: C, 66.63; H, 8.96.

For **5**: NMR ($CDCl_3$, 360 MHz) δ 5.26 (1 H, m), 3.51 (2 H, t, J = 6.9 Hz), 2.45 (2 H, m), 2.17–2.28 (4 H, m), 1.57–1.73 (4 H, m).

For **6**: NMR ($CDCl_3$, 360 MHz) δ 3.80 (2 H, t, J = 6.8 Hz), 1.85 (4 H, m), 1.65 (8 H, m); IR (film) (neat) 1045 cm^{-1}. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.04; H, 11.08.

1-(4-Pentynyl)cyclopentene (1) via 4. To a solution of 0.170 g (95%, 1.75 mmol) of lithium acetylide EDA in 20 mL of Me_2SO and 5 mL of THF at 0 °C was added dropwise 0.116 g (0.80 mmol) of **4** in 5 mL of THF over 10 min. The solution was stirred at 0 °C for 30 min and allowed to warm to room temperature for 10 h. The reaction was quenched with 10 mL of 3 N hydrochloric acid, extracted with ether, and the ether extracts were combined, washed with saturated aqueous sodium chloride (100 mL), and dried (Na_2SO_4). After removal of solvent, the crude mixture was chromatographed (neutral alumina). Elution with n-hexane yielded 0.082 g (76%) of **1** as a colorless liquid: NMR ($CDCl_3$, 360 MHz) δ 5.35 (1 H, m), 2.29 (2 H, m), 2.18 (6 H, m), 1.95 (1 H, t, J = 2.6 Hz), 1.85 (2 H, m), 1.68 (2 H, m); IR (film) 1650, 2140, 3320 cm^{-1}. Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.66; H, 10.37.

In a typical application of the above procedure on a mixture of chloroalkenes **4** and **5**, reaction of 0.703 g (4.86 mmol) of the mixture with 1.136 g (11.72 mmol) of lithium acetylide EDA yielded 0.423 g (65%) of a mixture of **1** and its exocyclic isomer, which could be used directly in subsequent reactions.

1-(4-Pentynyl)cyclopentene (1) via 7. To a solution of 22.9 g (90.2 mmol) of iodine in 75 mL of chloroform cooled to 0 °C was added dropwise 9.63 mL (95%, 44.7 mmol) of hexamethyldisilane over 90 min. The solution was stirred at 0 °C for an additional 20 min after which a solution of 3.22 g (22.4 mmol) of diol **3** in 20 mL of chloroform was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature and heated at 62 °C (mild reflux) for 120 min. The resultant solution was washed with saturated aqueous sodium thiosulfate solution until no change in color was observed (4 × 100 mL). The individual aqueous fractions were each extracted with ether (3 × 100 mL) and these combined with the organic phase. The combined organic solution was washed with 50 mL of water and then saturated aqueous sodium chloride (2 × 50 mL) and dried (Na_2SO_4). The solution was concentrated and chromatographed (florisil) eluting with hexane to give a 7.95 g (98%) yield as a mixture of 1-(3-iodopropyl)-1-iodocyclopentane **7** and the two deiodohydrogenated isomers (1-(3-iodopropyl)cyclopentene and (3-iodopropylidene)cyclopentane in an NMR ratio of 3.26:1.00:1.05, respectively. The mixture was subjected to further reaction without purification: NMR ($CDCl_3$, 90 MHz) δ 5.32 (s), 4.60 (s, br), 3.18 (br t, J = 6.2 Hz), 1.65–2.83 (series of multiplets). A solution of the mixture of the iodinated products (7.84 g, ca. 24.9 mmol.) in 10 mL of Me_2SO and 10 mL of THF was added dropwise to a mixture of 5.42 g (95%, 56.0 mmol) of lithium acetylide EDA, 20 mL of Me_2SO, and 20 mL of THF at 0° over 2 h. After addition the solution was stirred an additional 60 min and allowed to warm to room temperature over 10 h. The reaction was quenched with 75 mL of 3 N hydrochloric acid and poured into a separatory funnel containing 100 mL of water. The solution was extracted with ether (4 × 75 mL) and the combined ether extracts washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and saturated aqueous sodium chloride (1 × 75 mL) and dried (Na_2SO_4). The dried solution was concentrated and chromatographed (neutral alumina), eluting with hexane 1.43 g (43%) of a mixture of **1** and its exocyclic alkene isomer, containing 89% **1**. The calculated yield of **1** therefore is 38%. For analytical purposes the mixture was subjected to GC separation to give both pure isomers.

Tricyclo[6.3.0.0^{1,5}]undec-7-en-6-one (2).[45] Under a nitrogen atmosphere, 1.20 g (8.96 mmol) of enyne **1** (as the isomer mixture described above) was dissolved in 150 mL of benzene. To this solution was added 3.77 g (11.0 mmol, 1.2 equiv) of dicobalt octacarbonyl. Bubbling ensued immediately, indicating the formation of the cobalt–acetylene complex. The solution was blanketed with a carbon monoxide atmosphere and stirred at room temperature for 4 h and then heated to reflux and allowed to stir for 4 days. The crude reaction mixture was concentrated onto neutral alumina and placed on top of a neutral alumina column. Elution with hexane removed nonpolar organometallic species. Elution with ether gave 0.59 g of crude product containing small amounts of cobalt species. Chromatotron purification of this material gave upon elution with ether 0.51 g (35%) of product **2**. For analytical purposes, the enone was purified by GC: NMR ($CDCl_3$, 500 MHz) δ 5.82 (1 H, t, J = 2.0 Hz), 2.65 (1 H, dddd, J = 2.0, 3.8, 11.0, 18.4 Hz), 2.54 (1 H, br dt, J_d = 18.4, J_t = 7.0 Hz), 2.42 (1 H, br d, J = 8.3 Hz), 1.93–2.16 (3 H, m), 1.86 (1 H,

(45) *CA* names: 1,2,3,3a,7,8-hexahydrocyclopenta[*c*]pentalen-4(6*H*)-one (**2**); octahydro-5a-methylcyclopenta[c]pentalen-4(5*H*)-one (**8**); 1,2,3,3a,5a,6,7,8-octahydro-3a,5-dimethylcyclopenta[*c*]pentalene (**10**); 1,2,3,3a,7,8-hexahydro-1,7,7-trimethyl-8-(methoxymethoxy)cyclopenta-[*c*]pentalen-4(6*H*)-one (**27**); octahydro-1,7,7-trimethyl-8-(methoxymethoxy)cyclopenta[*c*]pentalen-4(5*H*)-one (**28**).

dd, J = 6.5, 11.3 Hz), 1.76 (1 H, dd, J = 4.8, 6.5 Hz), 1.59–1.72 (3 H, m), 1.40 (1 H, dt, J_d = 5.6, J_t = 12.3 Hz), 1.30 (1 H, septet, J = 6.1 Hz); IR (CCl_4) 1630, 1690 cm^{-1}; high-resolution mass spectrum, calcd for $C_{11}H_{14}O$ 162.1045, found 162.1099. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.29; H, 8.52.

8-Methyltricyclo[6.3.0.0^{1,5}]undecan-6-one (8).[45] To a mixture of 0.65 g (3.4 mmol) of cuprous iodide (dried under high vacuum at 120 °C) in 15 mL of ether cooled to 0 °C was added dropwise under Ar 3.8 mL (2 M in ether, 7.6 mmol) of methyllithium. To this solution 0.119 g (0.740 mmol) of enone **2** was added dropwise over 30 min. The solution was stirred 2 h, allowed to warm to room temperature (22 °C), and then poured into 100 mL of 1.2 N hydrochloric acid and extracted with ether (4 × 100 mL). The combined ether extracts were dried (Na_2SO_4) and upon solvent removal yielded 0.117 g (89%) of **8**. The product was clean enough to use for the next reaction. For characterization purposes it was purified by GC: NMR ($CDCl_3$, 360 MHz) δ 2.36 (1 H, dd, J = 1.6, 18.2 Hz), 2.31 (1 H, br dd, J = 4.5, 10.8 Hz), 2.18 (1 H, d, J = 18.2 Hz), 1.94 (1 H, m), 1.43–1.87 (11 H, m), 1.08 (3 H, s); IR (neat, film) 1735 cm^{-1}; high-resolution mass spectrum, calcd for $C_{12}H_{18}O$ 178.1357, found 178.1328. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.74; H, 10.33.

5,7-Dimethyltricyclo[6.3.0.0^{1,5}]undec-6-ene (10).[45] To a stirred solution of 2.0 mL (2 M in ether, 4.0 mmol) of methyllithium and 20 mL of THF at −78 °C was added 0.163 g (0.916 mmol) of tricyclic methyl ketone **8** in 3 mL of THF over 45 min. The resulting solution was stirred for an additional 2.5 h. The solution was transferred to a separatory funnel containing ca. 100 mL of ice. Ether extraction (4 × 50 mL) of the mixture, drying (Na_2SO_4) of the combined ether extracts, and solvent removal yielded 0.162 g (91%) of tertiary alcohol. No starting material was observed in the IR or NMR spectrum. This sensitive substance was used without further purification for the next reaction: NMR ($CDCl_3$, 90 MHz) δ 1.0–2.0 (all signals, m, br); the product mixture showed new methyl singlets (br) centered at δ 1.68 in addition to the original methyl singlets (br) centered at δ 1.13; IR (film) 3505 cm^{-1}. A solution of 0.067 g (0.34 mmol) of this alcohol mixture in 5 mL of THF was cooled to −45 °C (chlorobenzene/liquid nitrogen slush bath). A solution of 0.5 mL of THF, 0.5 mL of pyridine, and 0.5 mL (6.96 mmol) of freshly distilled thionyl chloride cooled to −45 °C was added dropwise and the resultant solution stirred an additional 15 min and allowed to warm to room temperature. The solution was poured into water (100 mL) and extracted with ether (4 × 50 mL), and the combined ether extracts were washed with saturated aqueous sodium chloride (2 × 20 mL) and dried (Na_2SO_4). After removal of solvent, the crude product was chromatographed and eluted with hexane after solvent removal to yield 0.056 g (93%) of a mixture of endocyclic alkene **10** and its exo methylene isomer **11** in a ratio of 7:3, respectively. For **10**: NMR ($CDCl_3$, 360 MHz) δ 4.89 (1 H, br s), 2.46 (1 H, br d, J = 8.6 Hz), 1.78 (1 H, m), 1.60 (3 H, apparent t, J = 1.2 Hz), 1.24–1.67 (11 H, m), 1.00 (3 H, s); IR (neat, film) 1680, 3015 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O$: C, 88.57; H, 11.43. Found: C, 88.40; H, 11.38.

2,5-Dimethyl-1-(3-hydroxypropyl)-1-cyclopentanol (14). Onto 64.1 g (2.64 mol) of dry magnesium turnings was vacuum transferred 200 mL of THF. To the mixture was added dropwise a solution of 60.5 g (0.248 mol) of 2,5-dibromohexane and 60 mL of THF at such a rate as to insure mild refluxing of the reaction solution over about 4 h. The mixture was refluxed an additional 1 h, allowed to cool to room temperature, and transferred from unreacted magnesium to another reaction vessel (cannula). A solution of 18.6 mL (0.244 mol) of γ-butyrolactone and 75 mL of THF was added dropwise over 2.5 h to the reaction solution at reflux, allowed to cool to room temperature, and stirred for 6 h. The product mixture was poured into saturated aqueous ammonium chloride (200 mL) and extracted with ether, and the combined ether extracts were washed with saturated aqueous ammonium chloride (100 mL) and saturated aqueous sodium chloride (50 mL), dried (Na_2SO_4), and concentrated. The crude product was chromatographed (neutral alumina) and eluted with ether to give upon solvent removal 36.2 g (86%) of **14**: NMR ($CDCl_3$, 360 MHz, major diastereomer) δ 3.68 (2 H, t, J = 6.1 Hz), 2.01 (2 H, m), 1.76 (2 H, m), 1.72 (2 H, m), 1.59 (4 H, m), 1.31 (2 H, m), 0.95 (6 H, d, J = 7.0 Hz); IR (CCl_4) 3450 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.08; H, 11.92.

2-(3-Chloropropyl)-1,3-dimethylcyclopentene (15). To a solution of 5.41 g (31.4 mmol) of diol **14** in 750 mL of carbon tetrachloride was added 45.3 g (0.173 mol) of triphenylphosphine. The solution was stirred at room temperature 1 h and heated to reflux for 2 h during which time a white precipitate of triphenylphosphine oxide formed. The solution was diluted with *n*-hexane, and the combined extracts were gravity filtered. The filtrate was vacuum transferred (25 °C, ca. 0.005 mmHg) into a receiver cooled with liquid nitrogen. The distillate was warmed to room temperature and concentrated. The residue was chromatographed (neutral alumina) and eluted with hexane/ether (2:1) affording **15** after solvent removal (0.168 g, 3% yield): NMR ($CDCl_3$, 360 MHz) δ 3.52 (2 H, t, J = 6.8 Hz), 2.61 (1 H, m), 1.67–2.35 (7 H, series of overlapping m), 1.63 (3 H, br s), 1.30 (1 H, m), 0.97 (3 H, d, J = 6.8 Hz); IR (neat, film) 1635 cm^{-1} (vw). Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.55; H, 9.92. Found: C, 69.71; H, 9.85.

1,3-Dimethyl-2-(4-pentynyl)cyclopentene (13) via 15. A solution of 1.82 g (10.6 mmol) of chloroalkene **15** in 30 mL of Me_2SO was added dropwise to a mixture of 2.27 g (24.7 mmol) of lithium acetylide EDA in 30 mL of Me_2SO cooled to 15 °C over 60 min. After the addition the solution was allowed to warm to room temperature over 8 h. The solution was transferred to a separatory funnel along with ether washings of the reaction flask (3 × 50 mL) containing 20 mL of 4 N hydrochloric acid. The acid layer was separated and extracted with ether (3 × 75 mL). The combined ether fractions were washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and saturated aqueous sodium chloride (100 mL) and dried (Na_2SO_4). The dried solution was concentrated and chromatographed, eluting with hexane 1.44 g (84%) of **13**: NMR ($CDCl_3$, 360 MHz) δ 2.62 (1 H, m), 1.65–2.35 (10 H, series of m), 1.63 (3 H, br s), 1.31 (1 H, m), 0.98 (3 H, d, J = 6.8 Hz); IR (neat, film) 3340, 2140, 1640 (vw) cm^{-1}(s); high-resolution mass spectrum, calcd for $C_{12}H_{18}$ 162.1408, found 162.1421.

1,3-Dimethyl-2-(4-pentynyl)cyclopentene (13) via 16. To a solution of 22.9 g (90.2 mmol) of iodine in 150 mL of chloroform cooled to 0 °C and stirred 30 min was added dropwise 9.6 mL (95%, 45 mmol) of hexamethyldisilane over 90 min. The solution was stirred at 0 °C for an additional 30 min, after which a solution of 4.35 g (25.3 mmol) of diol **14** in 25 mL of chloroform was added dropwise over a period of 30 min. The solution was allowed to warm to room temperature over 6 h and heated at 62 °C (mild reflux) for 60 min. The resultant solution was poured into a separatory funnel containing 150 mL of saturated aqueous sodium thiosulfate solution and 100 mL of ether, the resulting bilayer was thoroughly mixed, and the layers were separated. The organic phase was washed with additional thiosulfate until no change in color was observed (2 × 150 mL). The successive separate aqueous fractions were each extracted with ether (3 × 100 mL) and these combined with the organic phase. The combined ether extracts and organic solution were washed with saturated aqueous sodium bicarbonate (2 × 50 mL), the washes extracted successively with ether (2 × 50 mL), and these combined with the organic mixture. This solution was washed with saturated aqueous sodium chloride (2 × 50 mL) and dried (Na_2SO_4). The dried solution was concentrated and chromatographed (florisil) eluting with hexane a clean product fraction (**16**, 7.41 g, 75%) of sufficient purity for further reaction. The product proved to be relatively unstable and was used directly in the next step: NMR (90 MHz, $CDCl_3$) δ 3.21 (2 H, br t, J = ca. 6), 0.6–2.2 (16 H, series of overlapping signals); IR (film, neat) 1170 (m) cm^{-1}; no alcohol absorbance visible.

A solution of 2.17 g (5.54 mmol) of iodide **16** in 10 mL of Me_2SO and 5 mL of THF was added dropwise over 2 h to a mixture of 1.63 g (95%, 16.8 mmol) of lithium acetylide EDA in 20 mL of Me_2SO and 10 mL of THF cooled to 0 °C. After the addition the solution was allowed to warm to room temperature over 10 h. The solution was transferred to a separatory funnel along with ether washings of the reaction flask (3 × 20 mL) containing 75 mL of 0.6 N hydrochloric acid. The acid layer was separated and extracted with ether (4 × 50 mL). The combined organic/ether fractions were washed with saturated aqueous sodium bicarbonate (2 × 100 mL) and saturated aqueous sodium chloride (50 mL) and dried (Na_2SO_4). The dried solution was concentrated and chromatographed (florisil) eluting with hexane 0.583 g (65%) of

product **13** sufficiently pure to use in subsequent reactions: NMR, IR, and MS were identical with the sample prepared as described above.

Attempted Cyclization of 13. A large number of attempted dicobalt octacarbonyl cyclizations of enyne **13** were unsuccessful. A single reaction performed on a relatively large scale gave trace amounts of, apparently, the desired enone product. To a solution containing 0.75 g (4.64 mmol) of enyne **13** in 300 mL of benzene was added under nitrogen 1.89 g (5.54 mmol) of dicobalt octacarbonyl. The resulting solution was flushed with carbon monoxide and the stirred at room temperature for 6 h under a carbon monoxide atmosphere. The mixture was brought to reflux and stirred for 4 days. The reaction mixture was concentrated onto neutral alumina and the powdery material placed at the top of an alumina column. Elution with hexane removed nonpolar organometallic impurities, and then elution with ether gave a crude mixture of organic compounds (0.222 g) containing trace impurities of cobalt materials. The ether fraction was rechromatographed (neutral alumina, ether eluant) and further separated on the chromatotron, eluting with ether a fraction containing a mixture of organic material. IR and NMR analysis of the mixture showed weak signals consistent with the desired structure, together with signals characteristic of both starting material and large amounts of benzenoid side products. No further purification of the trace enone product was attempted. Data for impure product: NMR ($CDCl_3$, 90 MHz) δ 5.86 (br, w); IR (CCl_4, liquid cell) 1700 (m), 1663 (w) cm^{-1}; low-resolution mass spectrum, m/e 190.

2,2-Dimethyl-5-(trimethylsilyl)-4-pentynal (23). A stirred solution of 10.0 g (42.4 mmol) of 1-(*N*,*N*-dicyclohexylamino)-2-methyl-1-propene, 8.55 g (44.7 mmol) of 3-bromo-1-(trimethylsilyl)-1-propyne, and 20 mL of acetonitrile was warmed at 45 °C for 3 days. The resulting mixture was cooled, the solvent removed, and 100 mL of 10% potassium hydroxide poured into the residue remaining in the reaction flask. The mixture was stirred vigorously for 2 h at room temperature and poured into a separatory funnel. The layers were separated, the aqueous layer was extracted with ether (3 × 100 mL), and the combined ether extracts and organic layer were washed with water and saturated aqueous sodium chloride and dried (Na_2SO_4). The dried solution was concentrated and found to be composed of mainly product and dicyclohexylamine. NMR analysis revealed the product to have formed in a 76% crude yield. Chromatography (Florisil) of the mixture gave a product mixture still containing the amine but in lower proportions. Attempts at vacuum distilling the mixture gave clean product but in low yield and mass recovery. Alternatively, the product was more satisfactorily purified with MPLC, eluting with hexane/ether (97:3), giving **23** in yields between 42 and 45%: NMR (360 MHz, $CDCl_3$) δ 9.50 (1 H, s), 2.33 (2 H, s), 1.12 (6 H, s), 0.11 (9 H, s); IR (neat, film) 2830, 2730, 2190, 1730 cm^{-1}. Anal. Calcd for $C_{10}H_{18}OSi$: C, 65.80; H, 9.95. Found: C, 65.50; H, 10.00.

Ethyl 2,2-Dimethyl-5-(trimethylsilyl)-4-pentynoate.[28] Lithium diisopropylamide (LDA) was prepared in the quantity needed by adding dropwise *n*-butyllithium to a slight excess of diisopropylamine in hexane at −78 °C followed by vacuum filtration of the resultant product under a nitrogen atmosphere. To a solution of 55.5 g (0.518 mol) of LDA in 200 mL of THF at −78 °C was added dropwise a solution of 54.0 mL (0.404 mol) of ethyl isobutyrate in 175 mL of THF over 2.5 h. The solution was stirred an additional 20 min, a solution of 56 mL (80%, 0.52 mol) of 3-bromopropyne and 150 mL of THF added dropwise over 3 h, and the mixture allowed to stir an additional 3 h. The solution was warmed to 0 °C, stirred 1 h, and allowed to slowly warm to room temperature over 3 h.

Without any workup, the resulting solution was cooled to −78 °C and stirred for 30 min. To the cold solution was added dropwise a solution of 51.1 g (0.477 mole) of LDA in 400 mL of THF over a period of 3.5 h. The solution was stirred 1 h and to the resulting mixture a solution of 70.0 mL (0.551 mol) of trimethylsilylchloride in 400 mL of THF was added dropwise over 3 h. The solution was allowed to stir for 30 min, slowly warmed to room temperature (8 h), and poured into 200 mL of saturated aqueous ammonium chloride. The layers were separated, the aqueous layer was extracted with ether (3 × 75 mL), and the combined ether extracts and organic layer were concentrated to a total solution volume of 200 mL. The concentrated solution was washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and sodium chloride (75 mL) and dried (Na_2SO_4). The dried solution was concentrated, the residue flushed through a florisil column with ether, and the concentrate of the fraction distilled yielding 58.5 g (64%) product. Spectral data for the product were identical with the reference values.[28]

2,2-Dimethyl-5-(trimethylsilyl)-4-pentyn-1-ol.[28] To a solution of 18.2 g (95%, 0.480 mol) of lithium aluminum hydride in 200 mL of diethyl ether at 0 °C was added dropwise 58.5 g (0.259 mol) of ethyl 2,2-dimethyl-5-(trimethylsilyl)-4-pentynoate in 200 mL of ether over 2 h. The solution was stirred an additional 30 min and warmed to room temperature over 2 h. The solution was recooled to 0 °C and the reaction quenched by the addition in succession 18.2 mL of water, 18.2 mL of 10% aqueous sodium hydroxide, and 55 mL of water. The mixture was poured into a separatory funnel along with ether washings, the aqueous layer was separated and extracted with ether (3 × 100 mL), and the combined ether extracts and organic layer were washed with saturated aqueous sodium chloride (100 mL) and dried ($MgSO_4$). The dried solution was concentrated and chromatographed (florisil), eluting with ether 66.30 g (75%) of alcohol. Spectral data for the product were identical with the reference values.[28]

2,2-Dimethyl-5-(trimethylsilyl)-4-pentynal (23). To a solution of 36.6 mL (0.419 mol) of oxalyl chloride in 500 mL of methylene chloride cooled to −60 °C was added dropwise a solution of 62 mL (0.874 mol) of Me_2SO in 200 mL of methylene chloride over 2 h. The mixture was stirred an additional 30 min and a solution of 66.3 g (0.360 mol) of 2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-1-ol in 200 mL of methylene chloride added dropwise over 2.5 h. The resulting solution was stirred an additional 40 min, whereupon 251 mL (1.81 mol) of triethylamine was added dropwise over 1 h, and the solution was stirred for an additional 45 min and finally allowed to warm to room temperature. The reaction mixture was quenched with 400 mL of water, the aqueous layer was separated and extracted with methylene chloride (3 × 75 mL), and the combined extracts and the organic layer were washed with 1 N hydrochloric acid (3 × 200 mL) and water. The separate washes were successively extracted with methylene chloride (3 × 50 mL) and the combined wash extracts and product solution washed with saturated aqueous sodium chloride and dried ($MgSO_4$). The dried solution was concentrated and flushed through a florisil column with 10% ether in hexane and the solvent removed. The crude product was vacuum transferred at room temperature to give fairly clean material. Small scale (2–4 g) MPLC purification of this material, eluted using 3% ether in hexane afforded clean **23** in 80% calculated yield. Spectral data for the product were identical with those found previously as well as the reference values.[28]

2-Methylcyclopentanone 2,4,6-Triisopropylbenzenesulfonylhydrazone. To a solution of 9.75 g (32.7 mmol) of 2,4,6-triisopropylbenzenesulfonyl hydrazide in 50 mL of methanol was added 3.55 mL (33.1 mmol) of freshly distilled 2-methylcyclopentanone over 15 min. The solution was stirred for 20 min, 0.33 mL of concentrated hydrochloric acid added, the solution stirred 10 min, and the reaction mixture chilled in a freezer for 12 h. The material was removed from the freezer and immediately vacuum filtered. The solid product was washed with freezer-chilled methanol (2 × 50 mL) and dried (P_2O_5 drying pistol) at room temperature under high vacuum (0.02 mmHg) to yield 9.80 g (79%) of hydrazone: mp 124.0–124.5 °C dec.; NMR (90 MHz, $CDCl_3$) δ 7.25 (3 H, 2 overlapping s), 4.26 (2 H, septet, J = 7 Hz), 2.90 (1 H, septet, J = 7 Hz), 0.5–2.8 (28 H, complex series of m, includes δ 1.25, presume 18 H, d, J = 7 Hz and δ 1.00, presume 3 H, d, J = 7 Hz); IR (CCl_4) 3240, 1640, 1600, 1165, 1100, 1010 cm^{-1}.

3-Methyl-2-(5-(trimethylsilyl)-2,2-dimethyl-1-hydroxy-4-pentynyl)-1-cyclopentene (24). To a solution of 1.08 g (2.84 mmol) of 2-methylcyclopentanone trisylhydrazone in 100 mL of hexane and 13 mL of TMEDA at −78 °C was added dropwise 3.95 mL (1.6 M in hexanes, 6.32 mmol) of *n*-butyllithium over 15 min. The solution was stirred for 25 min, warmed to 0 °C, stirred 25 min, and recooled to −78 °C. A solution of 0.498 g (2.73 mmol) of aldehyde **23** in 5 mL of TMEDA, along with three 3 mL of TMEDA washes of the aldehyde container, were added to the recooled reaction mixture over 20 min, and the resulting solution was stirred for 2 h, slowly warmed to room temperature, and stirred for 8 h. The reaction mixture, along with water and ether

washes, was poured into a separatory funnel containing 75 mL of water and 100 mL of ether and thoroughly mixed. The layers were separated, and the organic layer was washed with water (2 × 50 mL) and saturated aqueous sodium chloride (2 × 50 mL). The separated aqueous layer and washes were consecutively extracted with ether (4 × 75 mL) and the combined ether extracts and organic fraction dried (Na_2SO_4). Concentration of the dried solution and MPLC of the resulting crude product gave upon eluting with 10% ether in hexane 0.82 g (83%) of product **24** as a mixture of diastereomers. All attempts at separating the isomers were unsuccessful: NMR (360 MHz, $CDCl_3$) δ 5.70 and 5.62 (1 H, two sets of m), 4.25 and 4.13 (1 H, two br s), 2.82 and 2.64 (1 H, two sets of multiplets), 2.0–2.4 (4 H, complex series of multiplets including two sets of apparent AB quartets with d at δ 2.32, 2.31, 2.15, and 2.14, presume 2 H, J = 16.8 and 16.7 Hz, respectively), 1.1–1.6 (2 H, complex series of multiplets), 1.14 and 1.07 (presume 3 H, two sets of d, J = 6.9, 6.8 Hz), 0.94–1.05 (6 H, unresolved set of s), and 0.15 (9 H, s). The added complexity of the NMR spectrum appeared to be due to the presence of consistently matched signals from two diastereomers. The major one (55 to 70%) had olefin and carbinol hydrogen signals at δ 5.62 and 4.25 and the minor (45 to 30%) at δ 5.70 and 4.13; IR (neat, film) 3501, 2173 cm^{-1}. Anal. Calcd for $C_{16}H_{28}SiO$: C, 72.66; H, 10.67. Found: C, 72.34; H, 10.77.

3-Methyl-2-(2,2-dimethyl-1-hydroxy-4-pentynyl)-1-cyclopentene (22). To a solution of 0.641 g (6.81 mmol) of potassium fluoride dihydrate in 20 mL of DMF at room temperature was added 0.282 g (1.07 mmol) of trimethylsilylalcohol **24** in 10 mL of DMF. The reaction was stirred at room temperature for 32 h and the reaction mixture transferred to a separatory funnel along with ether and water washes. The aqueous layer was removed and the organic layer washed with 1 N aqueous hydrochloric acid (7 × 50 mL), water (2 × 20 mL), saturated aqueous sodium bicarbonate (2 × 20 mL), water (20 mL), and saturated aqueous sodium chloride (20 mL). The aqueous washes were further extracted with ether (3 × 50 mL), these were combined with the above organic layer, and the entire mixture was dried (Na_2SO_4). The combined material was flushed through a florisil column, concentrated, and then subjected to MPLC to elute with 10% ether in hexane one main fraction yielding 0.162 g (79%) of **22**: NMR (90 MHz, $CDCl_3$) δ 5.40–5.80 (1 H, two sets of overlapping m), 3.97–4.26 (1 H, series of overlapping m), 2.5–2.9 (1 H, series of overlapping m), 0.5–2.5 (17 H, series of overlapping m)); IR (neat, film) 3480 (s, br), 3330 (m), 3090 (w), 2140 (w), 1650 (w) cm^{-1}. Anal. Calcd for $C_{13}H_{20}O$: C, 81.02; H, 10.48. Found: C, 80.90; H, 10.55.

2-[2,2-Dimethyl-1-(methoxymethoxy)-5-(trimethylsilyl)-4-pentynyl]-3-methyl-1-cyclopentene (25). To a solution of 6.44 g (17.0 mmol) of 2-methylcyclopentanone trisylhydrazone in 130 mL of hexane and 8 mL of TMEDA at −78 °C was added dropwise 23.4 mL (1.6 M in hexanes, 37.4 mmol) of *n*-butyllithium over 1.5 h. The solution was stirred for an additional 40 min, warmed to 0 °C, stirred for 25 min (nitrogen gas bubbling was observed), recooled to −78 °C, and stirred for 30 min. To the recooled reaction solution was added dropwise by means of a cannula 3.10 g (17.0 mmol) of aldehyde **23** over 25 min followed by washes of the aldehyde container with TMEDA (3 × 2 mL). The solution was stirred 6 h at −78 °C and allowed to slowly warm to room temperature over 4 h. To the reaction mixture, recooled to 0 °C, was added dropwise 7.4 mL (101 mmol) of chloromethyl methyl ether (MOMCl) over 30 min. The solution was allowed to come to room temperature, stirred for 3 h, and heated at reflux for 1 h. The mixture was cooled to 0 °C and quenched by adding 30 mL of 2% aqueous sodium bicarbonate. The entire mixture was transferred along with ether and water washes to a separatory funnel containing 50 mL of water. After mixing, the layers were separated, the aqueous layer extracted with ether (3 × 50 mL), and the combined extracts and organic layer washed with water (3 × 50 mL). The combined aqueous washes were reextracted with ether (3 × 30 mL) and these extracts combined, washed with water (20 mL), and added to the organic mixture. The mixture was dried (Na_2SO_4) and concentrated. The crude product was loaded onto a column (neutral alumina), eluting with hexane a 5.16 g fraction. This was subjected to MPLC in portions, the product fraction eluting with 10% ether in hexane. In a typical MPLC purification, 0.61 g of this material was purified by MPLC to yield 0.56 g (91%) of pure product as a mixture of diastereomers. Attempts at separating the diastereomeric product mixture were unsuccessful. The NMR spectra of the products obtained had a diastereomeric ratio identical with the range found for the corresponding alcohol products **24**: NMR (360 MHz, $CDCl_3$) δ 5.67 and 5.57 (1 H, two sets of m), 4.66, 4.58, 4.428, and 4.432 (2 H, four sets of d, J = 6.6 Hz for all four), 4.16 and 4.08 (1 H, two br s), 3.48 (3 H, br s), 2.79 and 2.58 (1 H, two sets of m), 2.0–2.4 (4 H, series of m including two sets of AB quartets with d at δ 2.35, 2.34, 2.18, and 2.16, 2 H, J = 16.7 and 16.6 Hz respectively), 1.15–1.55 (2 H, complex series of overlapping m), 1.06 and 1.03 (3 H, two sets of d, J = 6.9 Hz for both), 0.993, 0.986, 0.969, and 0.963 (6 H, series of s), 0.16 (9 H, s); IR (neat, film) 3090 (w), 2140 (w), 1650 (w) cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45. Found: C, 70.06; H, 10.51.

2-[2,2-Dimethyl-1-(methoxymethoxy)-4-pentynyl]-3-methyl-1-cyclopentene (26). To a solution of 0.758 g (2.46 mmol) of **25** in 5.0 mL of absolute ethanol at 0 °C, was added slowly over 25 min a solution of 0.660 g (3.89 mmol) of silver nitrate dissolved in 4.5 mL of absolute ethanol and 1.5 mL of water. The solution was stirred an additional 20 min, whereupon 3 mL (6.14 M, 18.4 mmol) of aqueous potassium cyanide was added dropwise over 15 min. The solution was stirred vigorously 30 min, slowly warmed to room temperature, stirred 30 min, and transferred to a separatory funnel along with ether and water washes, and the resulting mixture was thoroughly mixed. The layers were separated, and the organic layer was washed with water (2 × 20 mL) and saturated sodium chloride. The aqueous layer and separated aqueous washes were successively extracted with ether (4 × 50 mL) and the combined extracts and organic layer dried (Na_2SO_4). The dried solution was concentrated and eluted through a florisil column with ether. The material obtained was subjected to MPLC, and eluted with 10% ether in hexane was 0.563 g (97%) of **26** as a mixture of diastereomers. No difference in diastereomeric ratio was detected in the NMR spectra of the product as compared to starting material: NMR (360 MHz, $CDCl_3$) δ 5.69 and 5.58 (1 H, two sets of m), 4.67, 4.57, 4.427, and 4.424 (2 H, four sets of d, two sets of AB quartets, J = 6.6 Hz for all), 4.15 and 4.02 (1 H, two br s), 3.38 (3 H, m), 2.78 and 2.57 (1 H, two sets of multiplets), 2.0–2.4 (4 H, complex series of multiplets including four prominent sets of multiplets at δ 2.32, 2.27, 2.19, and 2.14; presume 2 H), 1.97 (1 H, m), 1.1–1.6 (2 H, complex series of multiplets), 1.06 and 1.02 (presume 3 H, two sets of d, J = 6.9 Hz for both), and 0.96–0.99 (6 H, unresolved set of s); IR (liquid cell, CCl_4) 3314 (s), 2105 (w), 1653 (w) cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.27; H, 10.37.

2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]undec-7-en-6-one (27).[45] To a solution of 0.558 g (2.36 mmol) of **26** in 150 mL of benzene was added under nitrogen 0.903 g (2.64 mmol) of dicobaltoctacarbonyl. The resulting solution was flushed with anhydrous carbon monoxide and stirred under a carbon monoxide filled balloon for 8 h at room temperature to allow formation of the cobalt–acetylene complex. The mixture under an atmosphere of carbon monoxide was heated to reflux for 22 h. The mixture was cooled to room temperature, a 20 mL volume of florisil was added to the solution, and the mixture was taken to dryness by rotary evaporation. The powdery solids that remained were loaded atop a florisil column, prepared using hexane as the packing solvent. The nonpolar starting materials and organometallic materials were removed by eluting with 600 mL of hexane. The products were collected in a second fraction by eluting with ether, ca. 500 mL. This ether fraction, after removing solvent, gave 0.537 g of crude product. This material was rechromatographed (chromatotron); eluted with a 100% hexane to 100% ether solvent gradient was 0.203 g of product as a second band behind one containing less polar organometallic impurities. However, this fraction also contained trace amounts of organometallic impurities. For ensuing work, the product of the cobalt cyclization was used at this stage without further purification. For analytical purposes, the product of this particular reaction was repurified (chromatotron) and eluted using the same solvent system to yield 0.184 g (30%) of cyclopentenone **27**. This cobalt cyclization using substrate **26** gave no observable benzenoid side-products by IR and NMR. Due to the instability of **27**, no attempt was made to separate its diastereomeric stereoisomers: NMR (90 MHz, $CDCl_3$) δ 5.90 and 5.78 (1 H, two br s), 4.6–4.8

(2 H, m), 3.61, 3.78, and 3.88 (1 H, three s), 3.4 (3 H, m), 2.8–3.0 (1 H, m), 2.0–2.6 (2 H, series of m), 1.4–2.0 (5 H, series of m), 0.9–1.1 (9 H, m); IR (liquid, CCl_4) 1709, 1636 cm^{-1}; high-resolution mass spectrum, calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1735.

2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo-[6.3.0.0^{1,5}]undecan-6-one (28).[45] Anhydrous ammonia gas (ca. 45 mL) was condensed (dry ice/acetone bath) into a flask containing pieces of sodium metal. The solution was stirred for 15 min and allowed to warm slowly by removing the cooling bath. The dry ammonia liquid was distilled into the reaction flask equipped with a solvent vapor cooling/condensor tower. Approximately 2 cm of lithium wire (ca. 50 mg/cm, 100 mg, 14.4 mmol.), containing 2% sodium, was cut into small pieces and added piecemeal to the stirring liquid cooled at −78 °. The reaction mixture was stirred 30 min whereupon a solution of 0.365 g (1.38 mmol) of enone **27** in 20 mL of ether was added dropwise over 25 min by means of a cannula. Methanol (51 μL, 1.38 mmol) was added and the solution left at the liquid ammonia solution reflux temperature for 5 h. The mixture was recooled to −78 °C, stirred for 1 h, and slowly warmed to room temperature over 7 h. The solution was cooled to 0 °C, 50 mL of saturated ammonium chloride added, and the resulting mixture stirred for 4 h and warmed to room temperature over 4 h. The mixture along with ether and water washes were poured into a separatory funnel containing ca. 100 mL of saturated aqueous ammonium chloride. After mixing, the layers were separated, the aqueous layer was extracted with ether (4 × 100 mL), and the combined ether extracts and organic layer were washed with saturated aqueous sodium chloride (2 × 100 mL) and dried (Na_2SO_4). After solvent removal the crude product was chromatographed eluting with ether a product fraction which was purified by MPLC to give 0.330 g (90%) of ketone **28** as a mixture of diastereomers by using 10% ether in hexane as solvent. For this mixture: IR (liquid, CCl_4) 1730 cm^{-1}; high-resolution mass spectrum, calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1886. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.95. By use of MPLC the mixtures of diastereomers of **28** could be partially resolved into three fractions, two of which were pure diastereomers and the third a mixture containing a major component. One medium and two small MPLC columns were placed in series. Samples of the ketone mixture were chromatographed, eluting with 20% ether in hexane to give three main fractions.

The first of these was found by NMR analysis to be the diastereomer depicted as **28C**: **(±)-(1*R**,2*R**,5*S**,8*R**,11*R**)-2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]-undecan-6-one (28C).** NMR (500 MHz, $CDCl_3$) δ 4.66 (1 H, d, J = 6.8 Hz), 4.64 (1 H, d, J = 6.8 Hz), 3.453 (1 H, s), 3.369 (3 H, s), 2.994 (1 H, d, J = 10.0 Hz), 2.466 (1 H, m), 2.376 (1 H, dd, J = 10.2, 19.2 Hz), 2.172 (1 H, ddd, J = 1.8, 3.3, 19.1 Hz), 2.040 (1 H, dd, J = 5.5, 6.5 Hz), 1.90 (1 H, d, J = 10.0 Hz), 1.76 (1 H, d, J = 10.0 Hz), 1.72 (2 H, m, 2 J's observable = 8.9, 13.5 Hz), 1.322 (1 H, dd, J = 5.0, 13.5 Hz), 1.059 (3 H, s), 1.029 (3 H, d, J = 6.9 Hz), 0.95 (1 H, m), and 0.894 (3 H, s).

The second was determined to be diastereomer **28B**: **(±)-(1*R**,2*S**,5*S**,8*R**,11*R**)-2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]undecan-6-one (28B).** NMR (500 MHz, $CDCl_3$) δ 4.62 (1 H, d, J = 6.7 Hz), 4.58 (1 H, d, J = 6.7 Hz), 3.658 (1 H, s), 3.366 (3 H, s), 3.036 (1 H, dd, J = 2.0, 10.0 Hz), 2.501 (1 H, dd, J = 8.9, 19.2 Hz), 2.242 (1 H, dq, J_d = 2.4, J_q = 8.9 Hz), 2.151 (1 H, dt, J_d = 19.2, J_t = 2.0 Hz), 1.95 (1 H, m), 1.7 (4 H, m), 1.39 (1 H, m), 1.313 (1 H, dd, J = 9.4, 13.1 Hz), 1.045 (3 H, s), 1.030 (3 H, d, J = 6.7 Hz), and 0.997 (3 H, s) ppm.

The third fraction was an inseparable mixture whose major component appeared to be diastereomer **28A**: **(±)-(1*R**,2*S**,5*S**,8*R**,11*S**)-2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]undecan-6-one (28A).** NMR (360 and 500 MHz, $CDCl_3$) see text and Table I.

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Registry No. **1**, 93474-41-0; (±)-**2**, 106211-46-5; **3**, 73057-71-3; **4**, 93474-50-1; **5**, 106211-47-6; **6**, 176-10-3; **7**, 93474-47-6; (±)-**8**, 106211-48-7; **8** (alcohol), 106211-49-8; (±)-**10**, 106211-50-1; (±)-**11**, 85431-51-2; (±)-**13**, 106211-51-2; **14**, 93474-40-9; (±)-**15**, 106211-52-3; **16**, 106211-53-4; **22**, 106211-56-7; **23**, 106211-57-8; **23** (ethyl ester), 106211-54-5; **23** (alcohol), 106211-55-6; **24**, 106211-58-9; **25**, 106211-59-0; **26**, 106211-60-3; **27**, 106211-61-4; **28**, 106211-62-5; (±)-**28A**, 106292-64-2; (±)-**28B**, 106292-63-1; (±)-**28C**, 106292-62-0; 2,4,6-$(Me_2CH)_3C_6H_2SO_2NHNH_2$, 39085-59-1; $Br(CH_2)_4Br$, 110-52-1; LiC≡CH, 1111-64-4; $MeCHBr(CH_2)_2CHBrMe$, 24774-58-1; $TMSC{\equiv}CCH_2Br$, 38002-45-8; Me_2CHCO_2Et, 97-62-1; $BrCH_2C{\equiv}CH$, 106-96-7; 2-methyl-cyclopentanone-(±), 32854-37-8; 2-methylcyclopentanone [(2,4,6-triisopropylphenyl)sulfonyl]-hydrazone-(±), 106230-66-4; 1-(3-iodopropyl)cyclopentene, 106211-63-6; γ-butylrolactone, 96-48-0; (3-iodopropylidene)-cyclopentane, 93474-49-8; 1-(*N*,*N*-dicyclohexylamino)-2-methyl-1-propene, 88592-10-3.

1,2-Carbonyl Migrations in Organic Synthesis. An Approach to the Perhydroindanones

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The facile Lewis acid catalyzed acyl migration of several bicyclic α,β-epoxy ketones affords a practical route to both *cis*- and *trans*-8-formyl-1-hydrindanones and a variety of related perhydroindanone derivatives. The synthetic utility of 1,2-carbonyl migrations in organic synthesis and some of its limitations are discussed.

One of the challenging problems in steroid synthesis remains the construction of the trans-fused CD ring system that is present in most steroids.[1] A variety of methods have recently been described that address the construction of the basic ring system and the stereochemistry of the ring fusion. For example, Stork and Mook[2] have reported that the preparation of cis-fused 8-methyl-1-hydrindanone can

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