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Enones with Strained Double Bonds. 2. The Bicyclo[4.3.1]decane System[1,2]

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When the Michael adduct (e.g., **5**) of cycloheptenone with various acetoacetic esters was heated with NaOMe in MeOH, the bicyclic bridgehead ethers **9** or **10** were formed. Several procedures (see Scheme III) have been used to convert these bridgehead ethers **9** and **10** to the enone **2** with a bridgehead carbon–carbon double bond. Although the enone **2** is a relatively reactive acceptor for the conjugate addition of nucleophiles, it is stable in the absence of nucleophiles and has shown no tendency to undergo thermally induced cyclodimerization.

Our efforts to isolate a sample of the bridgehead enone bicyclo[3.3.1]non-1-en-3-one (**1**)[2,3] have thus far been thwarted by the reactivity of this substance. When this enone **1** is generated in the presence of any reasonable nucleophile, it is rapidly converted to a Michael adduct.[2,3] Samples of the enone **1** generated in a hot tube at 400–500 °C undergo rapid thermal (or acid-catalyzed) rearrangement,[2] and samples generated at lower temperatures in the absence of nucleophiles undergo cycloaddition reactions either with more enone **1** or with added dienes.[3] To obtain a representative member of this family of strained enones that is more amenable to study under conventional conditions, we have also sought to prepare a sample of the next higher homologue, bicyclo[4.3.1]dec-6-en-8-one (**2**). This paper reports our synthesis of this enone **2** and describes our preliminary study of the chemical properties of the substance.

Our initial synthetic plan involved preparation of the intermediate ketol **3b** since the lower homologue **3a** was readily accessible via Michael addition of ethyl acetoacetate to cyclohexenone followed by hydrolysis, decarboxylation, and a base-catalyzed aldol reaction.[2,4,5] However, a variety of attempts to convert the initial Michael adduct **5** from cycloheptenone (**4**) to the ketol **3b** resulted in the isolation of the diketone **6**,[2] and all of our efforts thus far to convert the diketone **6** to the ketol **3b** have either resulted in no reaction or have led to complex mixtures. We therefore conclude that the equilibrium diketone **6** ⇌ ketol **3b** strongly favors the diketone **6**.

A possible solution to this synthetic obstacle was suggested by the report[5] that prolonged refluxing (12 h) of a solution of cycloheptenone (**4**) with ethyl acetoacetate in methanolic NaOMe resulted in the isolation of the methoxy keto ester **9**. Although the authors did not speculate on the origin of this bridgehead methyl ether **9**, our earlier experience with related systems suggested that the ether **9** was being formed from the initially formed aldol product **7** (or the corresponding ethyl ester) by base-catalyzed elimination to form the bridgehead enone **8** and subsequent addition of methanol. We repeated this reaction and were able to obtain the pure ether **9** in 55% yield. When the reaction was followed by TLC analysis, it was apparent that an initial rather polar intermediate (presumably **7** or the corresponding ethyl ester) was being formed and then slowly converted to the final product, ether **9**. Further, by use of the more hindered *tert*-butyl acetoacetate to retard ester interchange, it was possible to use the same reaction conditions to convert cycloheptenone (**4**) to the related *tert*-butyl ester **10**.

Although the conversion of the methoxy keto ester **9** to the related methoxy ketone **19** appeared to be trivial, the conventional methods involving acid-catalyzed or base-catalyzed hydrolysis were reported to fail.[5] We have confirmed these observations and found that these aqueous hydrolyses both yielded the diketone **6** (see Scheme II). Attempts to cleave the ester of **9** selectively by heating with NaCN in hexamethylphosphoramide (HMPA)[6] or by reaction with either BBr_3 or anhydrous HBr resulted in the formation of the substituted keto esters **11** and **12**. Similarly, reaction with Me_3SiI[7] formed a very unstable

(1) This research has been supported by Public Health Service Grant R01-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

(2) For the previous paper in this series, see H. O. House, W. A. Kleschick, and E. J. Zaiko, *J. Org. Chem.*, **43**, 3653 (1978).

(3) H. O. House, M. B. DeTar, and D. VanDerveer, *J. Org. Chem.*, in press.

(4) W. D. Macrosson, J. Martin, W. Parker, and A. B. Penrose, *J. Chem. Soc. C*, 2323 (1968).

(5) T. Momose and O. Muraoka, *Chem. Pharm. Bull.*, **26**, 288 (1978).

(6) For a recent review of the use of nucleophiles in dipolar aprotic solvents to cleave esters, see J. E. McMurry, *Org. React.*, **24**, 187 (1976).

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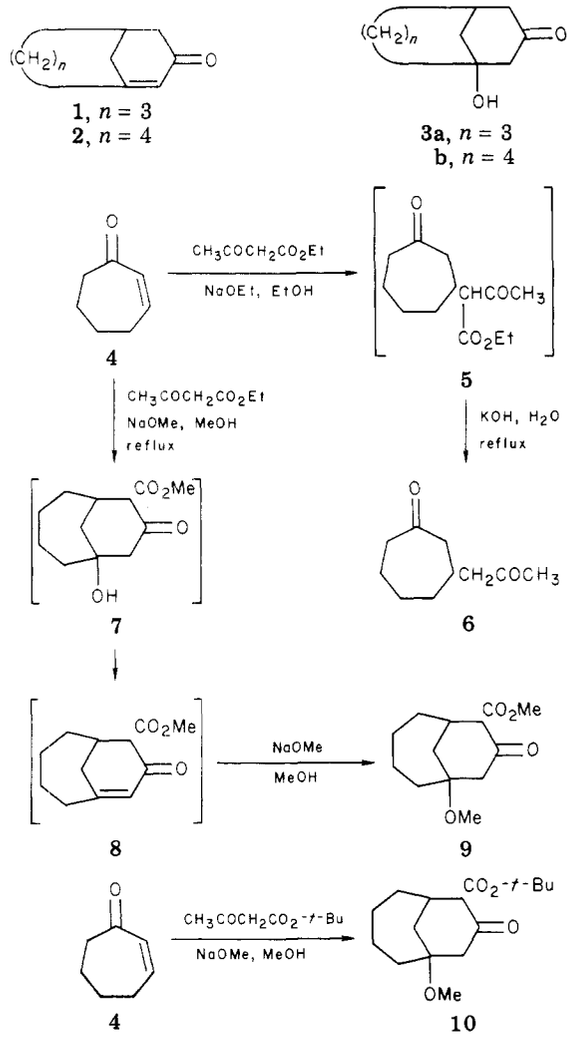
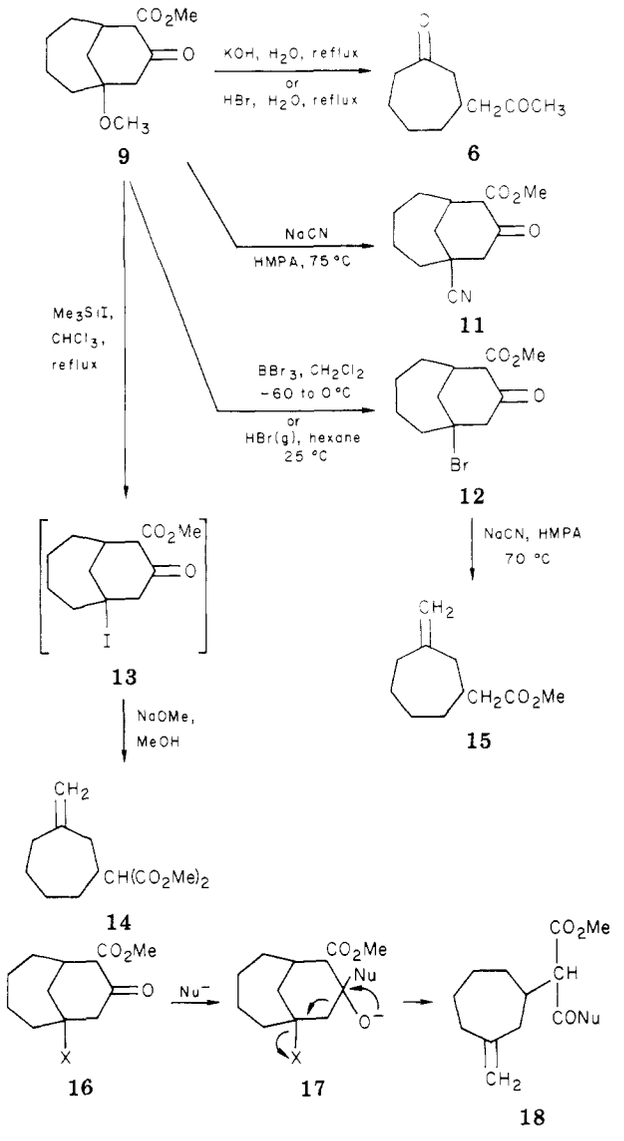
Scheme I



material believed to be the iodo keto ester **13**. We believe that each of these products arises via an acid- or base-catalyzed elimination to form the enone **8** followed by conjugate addition of HCN, HBr, or HI. Treatment of the crude iodo keto ester **13** with methanolic NaOMe yielded the olefinic diester **14** and similar treatment of the bromo compound **12** with NaCN in HMPA formed a crude product believed to be the olefinic ester **15**. In both cases, we presume that these products arise from the nucleophile-induced fragmentation illustrated in structures **16**–**18**.[8]

Since neither acidic nor basic conditions were satisfactory for cleaving the ester function of keto ester **9**, the material was heated with NaCl and a small amount of H_2O in Me_2SO (Scheme III).[6] The product of this reaction was the desired methoxy ketone **19** accompanied by variable amounts of the enone **2**. For reasons that are not understood, the proportions of the two products **2** and **19** varied from run to run although the conditions (including the acidity) of successive reactions appeared to be the same. The methoxy ketone **19** was converted to the rather unstable bromo ketone **20** by brief reaction with anhydrous HBr, and further reaction of the bromo ketone **20** either with a slurry of KO-*t*-Bu in Et_2O or with Et_3N in Et_2O yielded the enone **2**. This conversion of **19** to the enone

Scheme II



2 (70% yield) was accomplished more easily by brief warming of the methoxy ketone **19** with anhydrous *p*-TsOH in PhH.

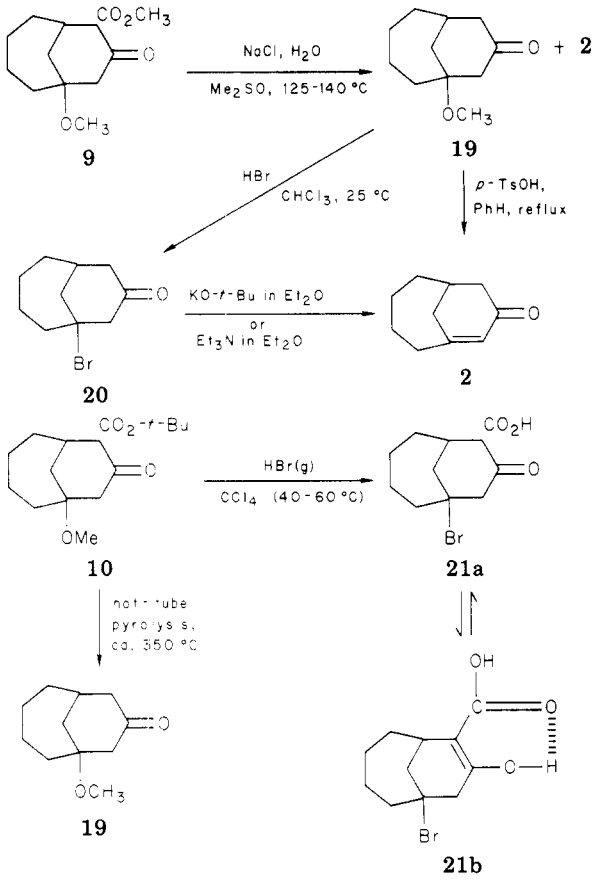
The *tert*-butyl ester **10** was converted to the bromo keto acid **21** by warming with anhydrous HBr in CCl_4. The reluctance of this keto acid **21** to undergo thermal decarboxylation appears to be attributable to the existence of the keto acid in the enol form **21b**. The most satisfactory preparative route for the enone **2** proved to be the pyrolysis of the *tert*-butyl keto ester **10** in a glass tube heated to 350–370 °C. The methyl ether **19** (56–58% yield) formed by this pyrolysis was then converted to enone **2** by the previously described acid-catalyzed elimination with *p*-TsOH in PhH. Although the enone **2** could also be formed directly by reaction of the *tert*-butyl ester **10** with *p*-TsOH in refluxing PhH, this procedure formed a complex mixture of products from which the enone **2** was isolated in 25% yield by liquid chromatography.

A brief survey of some of the chemical properties of the enone **2** is summarized in Scheme IV. Although less reactive than the more strained enone **1**, the enone **2** is nonetheless a reactive acceptor in various conjugated addition reactions as indicated by the formation of adducts **19**, **20**, and **22**. When enone **2** was stirred with H_2O in the absence of any added catalyst, a crude, unstable product with properties expected for the ketol **3b** was formed. As

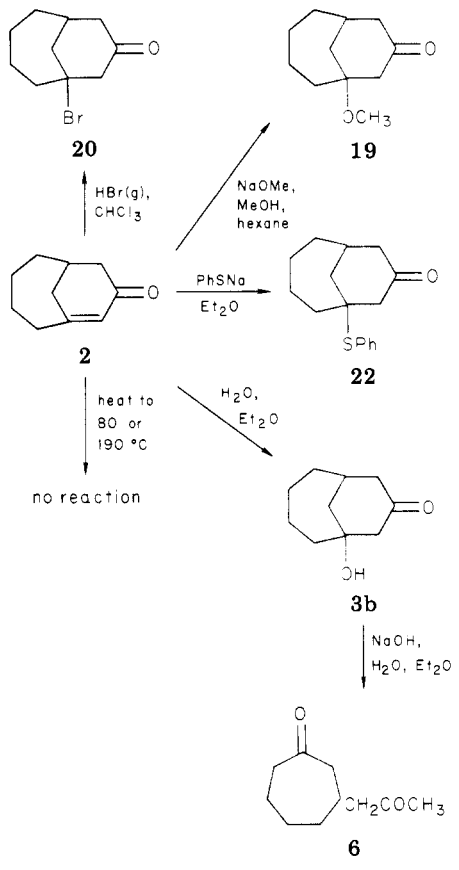
(7) For a recent review of the uses of silicon compounds including the cleavage of esters with Me_3SiI, see E. W. Colvin, *Chem. Soc. Rev.*, 7, 15 (1978).

(8) For a recent review of fragmentation reactions of this type, see C. J. M. Stirling, *Chem. Rev.*, 78, 517 (1978).

Scheme III



Scheme IV



surmised earlier in this paper, treatment of this ketol **3b** with a catalytic amount of base resulted in a retrograde aldol condensation to form the diketone **6**. The most striking difference between the two enones **1** and **2** was the lack of any indication that the enone **2** will form thermally induced cyclic dimers. By contrast, samples of the enone **1** generated in the absence of nucleophiles or other olefins dimerized rapidly at or below room temperature.[3]

Experimental Section[9]

Preparation of Cycloheptenone (4). Following a previously described procedure,[10] a stirred solution of 10.0 g (89.2 mmol) of cycloheptanone in 100 mL of $HOCH_2CH_2OH$ was treated with three drops of Br_2 and then warmed to 34 °C to initiate reaction (with loss of the yellow color). Then the solution was cooled to 15 °C and 14.2 g (89.2 mmol) of Br_2 was added, dropwise and with stirring. The resulting yellow solution was warmed to 25 °C (with loss of the yellow color) and then poured into a suspension of 25 g of anhydrous Na_2CO_3 in 150 mL of pentane. After 5 min, 100 mL of H_2O was added and the organic layer was separated, dried, and concentrated. The residual colorless liquid was distilled to separate 13.9 g (67%) of the crude ethylene ketal of 2-bromocycloheptanone; bp 85–91 °C (0.6 mm) [lit.[10] bp 79–83 °C (0.5 mm)]. This crude product contained some ketone impurity: IR (CCl_4) 1721 (weak, C=O) cm^{-1}; NMR (CCl_4) δ 3.7–4.4 (4 H, m, CH_2O), 1.0–2.35 (10 H, m, aliphatic CH).

A solution of 13.0 g (55.3 mmol) of this crude bromo ketal and 12.5 g (313 mmol) of NaOH in 50 mL of MeOH was refluxed for 72 h and then partitioned between pentane and aqueous NaCl. The organic layer was dried and concentrated. Distillation of the residual yellow liquid (6.6 g) separated 5.31 g (63%) of the ethylene ketal of 2-cycloheptenone: bp 57–59 °C (1.6 mm) [lit.[10] bp 67 °C (2.4 mm)]; n^{25}_D 1.4876; IR (CCl_4) 1653 (C=C) cm^{-1}; NMR (CCl_4) δ 5.4–6.1 (2 H, m, vinyl CH), 3.8–4.1 (4 H, m, CH_2O), 1.2–3.0 (8 H, m, aliphatic CH); mass spectrum m/e (relative intensity) 154 (M^+, 22), 126 (31), 125 (100), 99 (71), 81 (22), 55 (29), 41 (22), 39 (22).

A solution of 5.0 g (32 mmol) of the unsaturated ketal and 2 mL of concentrated H_2SO_4 in 20 mL of MeOH was stirred for 10 min and then diluted with 60 mL of Et_2O and washed with aqueous $NaHCO_3$. The organic layer was dried and concentrated and the residual yellow liquid (3.4 g) was distilled to separate 2.5 g (70%) of the enone **4** as a colorless liquid: bp 49–51 °C (2.3–2.4 mm) [lit.[10] bp 52 °C (2.4 mm) n^{25}_D 1.4879 (lit.[10] n^{20}_D 1.4950); IR (CCl_4) 1665 (conjugated C=O) cm^{-1}; NMR (CCl_4) δ 5.8–6.8 (2 H, m, vinyl CH), 0.8–3.0 (8 H, m, aliphatic CH).

Preparation of the Keto Ester 9. Following a previously described procedure,[5] a solution of NaOMe, from 0.50 g (20 mg-atoms) of Na and 50 mL of MeOH, was treated with a solution of 2.80 g (21.5 mmol) of $CH_3COCH_2CO_2Et$ in 5 mL of MeOH. Then a solution of 2.00 g (18.2 mmol) of the enone **4** in 5 mL of MeOH was added and the resulting yellow solution was refluxed for 12 h. Aliquots were removed periodically for TLC analysis (silica gel coating with an Et_2O–hexane eluent, 1:4 (v/v)). After 30 min three components were present corresponding to the product **9** (R_f 0.65), the enone **4** (R_f 0.52), and a component believed to be the ketol **7** (R_f 0.35). After a reaction period of 4 h none of the enone **4** was detected (TLC) and after 12 h none of the component believed to be **7** was detected (TLC). The mixture was partitioned between dilute aqueous HCl and PhH, and the organic layer was dried and concentrated. Distillation of the residual brown liquid (3.9 g) separated 2.5 g of yellow liquid: bp 105–106 °C (0.02 mm) [lit.[5] bp 140 °C (0.02 mm)]; n^{25}_D 1.4995. This sample was chromatographed on silica gel with an Et-

(9) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian Model T-60A NMR spectrometer, and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with either Hitachi Perkin-Elmer Model RMU-7 or a Varian MAT Model 112S mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(10) E. W. Garbisch, *J. Org. Chem.*, **30**, 2109 (1965).

OAc–hexane eluent (1:19 (v/v)) to separate 1.07 g (25%) of the pure keto ether **9** as a colorless liquid: n^{25}_D 1.5038; IR (CCl_4) 1720, 1650, 1615 (keto and enol forms of a β-keto ester) cm^{-1}; ^1H NMR (CCl_4) δ 12.26 (1 H, s, enol OH), 3.75 (3 H, s, CO_2CH_3), 3.16 (3 H, s, OCH_3), 1.1–3.1 (13 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 240 (M^+, 13), 184 (13), 183 (100), 177 (12), 176 (13), 152 (14), 151 (96), 125 (12), 85 (10), 43 (14), 41 (10); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 172.0 (s), 171.0 (s), 99.7 (s), 75.1 (s), 51.1 (q), 48.5 (q), 43.0 (t), 39.1 (t), 36.4 (t), 33.4 (t), 30.8 (d), 26.9 (t), 23.4 (t) ppm.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.87; H, 8.42.

In a subsequent reaction employing 45.5 mmol of the enone **4** and 54.5 mmol of $CH_3COCH_2CO_2Et$, the crude product was chromatographed without prior distillation to separate 5.92 g (55%) of the keto ether **9**; n^{25}_D 1.5050.

Preparation of the Cyano Ketone 11. A solution of 275 mg (5.6 mmol) of NaCN and 750 mg (3.1 mmol) of the keto ester **9** in 5 mL of HMPA was heated at 75 °C, with stirring and under an N_2 atmosphere, for 1 h.[6] The resulting solution was partitioned between Et_2O and aqueous 2 M HCl, and the organic layer was dried and concentrated. The residual liquid (1.0 g, contains HMPA) was chromatographed on silica gel with an EtOAc–hexane eluent (2:23 (v/v)) to separate 0.40 g (55%) of the cyano compound **11** as a colorless solid; mp 103–109 °C. Recrystallization from a hexane–$CHCl_3$ mixture separated 0.33 g (45%) of the nitrile **11** as colorless plates: mp 110.5–113 °C; IR (CCl_4) 2240 (C≡N), 1690 (sh), 1655, 1610 (enolic β-keto ester) cm^{-1}; NMR (CCl_4) δ 12.56 (1 H, s, enol OH), 3.85 (3 H, s, CO_2CH_3), 1.0–3.2 (13 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 235 (M^+, 8), 178 (62), 167 (100), 165 (22), 153 (23), 147 (28), 146 (83), 134 (28), 121 (30), 91 (22), 79 (20), 53 (27).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.22; H, 7.28; N, 5.93.

In another attempt to hydrolyze and decarboxylate the β-keto ester **9**, we refluxed a mixture of 0.500 g (2.08 mmol) of the ester **9**, 10 mL of 48% aqueous HBr, and 10 mL of H_2O for 2 h. The crude neutral organic product (331 mg of yellow liquid) was separated and chromatographed on silica gel with an EtOAc–hexane eluent (3:7 (v/v)) to afford 78 mg (22%) of the diketone **6**, n^{25}_D 1.4750 (lit.[2] n^{25}_D 1.4751), that was identified with an authentic sample by comparison of IR and NMR spectra.

A solution of 0.44 g (1.8 mmol) of the keto ester **9** and 0.64 g (3.2 mmol) of Me_3SiI[7] in 3 mL of $CHCl_3$ was refluxed for 23 h and then cooled and neutralized by the addition of 3.7 mmol of NaOMe in 8 mL of MeOH. After the resulting mixture had been partitioned between H_2O and Et_2O, the organic layer was dried and concentrated. Chromatography of the residual liquid on silica gel with an EtOAc–hexane (1:9 (v/v)) eluent separated 0.25 g (57%) of the olefinic ester **14**[8] as a colorless liquid: n^{25}_D 1.4845; IR (CCl_4) 1760, 1740 (ester C=O), 1642 (weak, C=C), 895 (C=CH_2) cm^{-1}; NMR (CCl_4) δ 4.71 (2 H, broad, vinyl CH), 3.71 (6 H, s, OCH_3), 3.1–3.3 [1 H, m, $CH(CO_2R)_2$], 1.1–2.4 (11 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 240 (M^+, 1), 133 (23), 121 (49), 119 (100), 117 (100), 108 (36), 93 (41), 84 (25), 82 (45), 80 (30), 56 (21), 54 (23), 47 (42), 43 (23), 41 (35).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.86; H, 8.41.

Preparation of the Bromo Keto Ester 12. To a cold (−55 °C) solution of 0.75 g (3.1 mmol) of the ester **9** in 8 mL of CH_2Cl_2 was added, dropwise and with stirring, a solution of 4.72 g (18.7 mmol) of BBr_3 in 5 mL of CH_2Cl_2. After the resulting yellow solution had been stirred at −60 °C for 1 h and then warmed to 0 °C during 30 min, it was partitioned between H_2O and CH_2Cl_2. The organic layer was dried and concentrated to leave 0.70 g of yellow solid; mp 63–67 °C. Chromatography on silica gel with an EtOAc–hexane eluent (4:96 (v/v)) separated 0.41 g (46%) of the bromo ester **12**; mp 66–67 °C. Recrystallization from a $CHCl_3$–hexane mixture afforded 0.35 g (40%) of the pure bromo ester **12** as colorless plates: mp 73–75 °C; IR (CCl_4) 1720, 1660, 1610 (enolic β-keto ester) cm^{-1}; NMR (CCl_4) δ 12.28 (1 H, s, OH), 3.76 (3 H, s, OCH_3), 1.2–3.4 (13 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 290 (M^+, 9), 288 (M^+, 9), 259 (13), 257 (14), 209 (61), 172 (100), 121 (18), 109 (18), 67 (12).

Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.92; Br, 27.63. Found: C, 49.78; H, 5.94; Br, 27.61.

In an alternative, more efficient preparation, anhydrous HBr was passed through a solution of 325 mg (1.3 mmol) of the ester **9** in 10 mL of hexane for 5 min. The resulting yellow solution was concentrated and the residual solid (0.39 g) was recrystallized from $CHCl_3$–hexane to separate 0.31 g (80%) of the bromo keto ester **12**; mp 73–75.5 °C. In an attempt to cleave the ester function in the product **12**, we heated a solution of 40 mg (0.81 mmol) of NaCN and 188.5 mg (0.65 mmol) of the bromo keto ester **12** in 6 mL of HMPA[6] to 70 °C for 1 h and then partitioned the solution between Et_2O and aqueous 2 M HCl. The crude liquid organic product was chromatographed on silica gel with an EtOAc–hexane eluent (5:95 (v/v)) to separate 70 mg (60%) of a crude product, believed to be the unsaturated ester **15**,[8] as a colorless liquid: n^{25}_D 1.4135; IR (CCl_4) 1740 (ester C=O) cm^{-1}; NMR (CCl_4) δ 4.70 (2 H, s, vinyl CH), 3.60 (3 H, s, OCH_3), 0.7–2.6 (14 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 182 (M^+, 3), 122 (26), 109 (78), 108 (100), 93 (80), 91 (26), 81 (32), 79 (51), 74 (36), 67 (58), 55 (29), 41 (51), 39 (41).

Preparation of the Keto Ester 10. A solution of 21.7 mmol of NaOMe, 3.44 g (21.5 mmol) of *tert*-butyl acetoacetate, and 2.00 g (18.2 mmol) of cycloheptenone (**4**) in 50 mL of MeOH was refluxed for 12 h and then cooled and partitioned between H_2O and PhH. After the organic phase had been dried and concentrated, the residual yellow liquid (4.0 g) was chromatographed on silica gel with an EtOAc–hexane eluent (3:97 (v/v)) to separate 2.1 g (40%) of the *tert*-butyl keto ester **10** as a colorless liquid: n^{25}_D 1.4842; IR (CCl_4) 1645, 1610 (enolic β-keto ester) cm^{-1}; NMR (CCl_4) δ 12.33 (1 H, s, OH), 3.13 (3 H, s, OCH_3), 0.8–3.0 (22 H, m, aliphatic CH including a *t*-Bu singlet at 1.50); mass spectrum *m/e* (relative intensity) 182 (2), 125 (28), 121 (28), 119 (98), 117 (100), 82 (25), 59 (26), 47 (24).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.06; H, 9.28.

Anhydrous HBr was passed through a warm (40–60 °C) solution of 0.39 g (1.3 mmol) of the keto ester **10** in 25 mL of CCl_4 for 90 min. Then the solution was cooled, flushed with N_2 (to remove HBr), and concentrated to leave 0.30 g (97%) of the crude bromo acid **21**; mp 118–112 °C dec. Recrystallization from a CCl_4–hexane mixture separated 0.22 g (71%) of the bromo acid **21** as colorless needles: mp 126–127 °C dec; IR (CCl_4) 2850–3200 (broad, associated OH), 1740 (sh), 1652, 1590 (enolic β-keto acid) cm^{-1}; NMR (CCl_4) δ 12.33 (1 H, s, OH), 1.0–3.3 (13 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 232 (3), 230 (3), 177 (41), 122 (61), 119 (44), 117 (44), 109 (77), 108 (28), 107 (28), 95 (56), 93 (51), 91 (25), 82 (89), 81 (42), 80 (24), 79 (57), 77 (36), 67 (83), 55 (30), 53 (28), 44 (90), 41 (23), 39 (39).

Anal. Calcd for $C_{11}H_{15}BrO_3$: C, 48.01; H, 5.49; Br, 29.04. Found: C, 48.01; H, 5.59; Br, 28.97.

After a solution of 239 mg (0.84 mmol) of the keto ester **10** and 16 mg (0.084 mmol) of *p*-TsOH in 15 mL of anhydrous PhH had been refluxed for 48 h under an N_2 atmosphere, the resulting solution was washed rapidly with aqueous $NaHCO_3$ and then dried and concentrated. The residual liquid, 131 mg containing (TLC) a number of components, was chromatographed on silica gel with an EtOAc–hexane eluent (1:9 (v/v)) to separate 31 mg (25%) of the enone **2** as a colorless liquid, n^{25}_D 1.5272, that was identified with a subsequently described sample by comparison of NMR spectra.

Preparation of the Methoxy Ketone 19. A. From the Methyl Ester 9. A solution of 2.90 g (12.1 mmol) of the keto ester **9**, 1.77 g (30.2 mmol) of NaCl, and 2.0 mL of H_2O in 50 mL of Me_2SO[7] was heated to 125–130 °C under a N_2 atmosphere for 5 h and then cooled and partitioned between H_2O and hexane. After the organic layer had been dried and concentrated, the residual yellow liquid (3.3 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:4 (v/v)) to separate 1.30 g (60%) of the methoxy ketone **19** as a colorless liquid: n^{25}_D 1.4984; IR (CCl_4) 1715 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 3.23 (3 H, s, OCH_3), 1.9–3.0 (5 H, m, CH and CH_2CO), 0.8–1.9 (10 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 182 (M^+, 10), 126 (29), 125 (100), 97 (56), 93 (27), 91 (20), 43 (29), 41 (60); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 209.6 (s), 79.6 (s), 53.3 (t), 48.5 (q), 47.1 (t), 38.3 (t), 36.5 (t), 34.0 (t), 29.8 (d), 24.9 (t), 23.5 (t) ppm.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.65; H, 10.00.

In a second, seemingly comparable, experiment a solution of 1.99 g (8.29 mmol) of the keto ester **9**, 0.60 g (10 mmol) of NaCl, and 2 mL of H_2O in 50 mL of Me_2SO was heated to 125–140 °C under a N_2 atmosphere for 3.5 h and then subjected to the previously described isolation procedure. The early chromatographic fractions contained 0.27 g (18%) of the methoxy ketone **19**, n^{25}_D 1.4984, that was identified with the previously described sample by comparison of IR and NMR spectra. However, later chromatographic fractions afforded, after distillation, 0.15 g (18%) of the enone **2** as a colorless liquid: bp 85–89 °C (0.075 mm); n^{25}_D 1.5272; IR (CCl_4) 1680, 1667 (conjugated C=O), 1626 (C=C) cm^{-1}; UV λ_{max} (CH_3CN) 250 (ϵ 5070), 345 (ϵ 92) nm; ^1H NMR (CCl_4) δ 5.53 (1 H, s, vinyl CH), 0.9–2.8 (13 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 150 (M^+, 4), 121 (30), 119 (91), 117 (100), 84 (22), 82 (35), 47 (30), 41 (17); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 198.8 (s), 164.1 (s), 122.7 (d), 45.6 (t), 37.4 (t), 35.4 (t), 32.2 (t), 29.4 (d), 28.6 (t), 24.1 (t) ppm.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.86; H, 9.43.

When a solution of 0.50 g (2.1 mmol) of the keto ester **9** and 0.5 mL of H_2O (but no NaCl) in 10 mL of Me_2SO was heated to 125–135 °C for 3.5 h, the crude product (0.25 g of yellow liquid) was estimated (NMR analysis) to contain ca. 73% of the enone **2**, ca. 10% of the methoxy ketone **19**, and ca. 17% of the starting keto ester **9**. In several additional experiments utilizing 2.5 mol equiv of NaCl and 8 mol equiv of H_2O/mol of keto ester **9** in Me_2SO with a reaction time of 4 h at 125–135 °C, mixtures containing (IR and NMR analyses) about equal amounts of the methoxy ketone **19** and the enone **2** were obtained. Separation of a typical mixture by liquid chromatography (with some attendant loss of the enone **2**) afforded the methoxy ketone **19** in 31% yield and the enone **2** in 18% yield.

B. From the *tert*-Butyl Ester 10. A solution of 120 mg (0.40 mmol) of the ester **10** in 15 mL of anhydrous pentane was added dropwise, during 1 h, to the top of a vertical 30-cm glass column packed with glass beads and heated with an oven held at 350–370 °C. The pyrolysis products were swept from the column into a trap, cooled to −78 °C, with a stream of nitrogen. The crude pyrolysate, 110 mg of brown liquid, was distilled in a short-path still [88–95 °C (0.05 mm)] to separate 45 mg (58%) of the pure methoxy ketone **19** as a colorless liquid, n^{25}_D 1.4985, that was identified with the previously described sample by comparison of IR and NMR spectra. Repetition of this reaction with a solution of 1.01 g (3.5 mmol) of the ester **10** in 20 mL of pentane that was added to the pyrolysis apparatus during 2 h yielded 0.36 g (56%) of the methoxy ketone **19**; bp 90 °C (0.05 mm); n^{25}_D 1.4984.

Preparation of the Bromo Ketone 20. A stream of anhydrous HBr was passed through a solution of 5.40 g (29.6 mmol) of the methoxy ketone **19** in 125 mL of $CHCl_3$ for 6 min. The resulting orange solution was swept with a stream of N_2 (to remove excess HBr) for 5 min and then washed successively with aqueous $Na_2S_2O_3$ and with H_2O. After the resulting organic solution had been dried and concentrated, the residual yellow liquid (6.6 g) was chromatographed on silica gel with an EtOAc–hexane eluent (2:1 (v/v)). The early fractions were collected and distilled to separate a sample of the bromo ketone **20** as a pale yellow liquid: bp 110–115 °C (0.2 mm); n^{25}_D 1.5240. The material crystallized from hexane as white plates; mp 34–37 °C. Recrystallization from hexane afforded the pure bromo ketone **20** as colorless plates: mp 35.5–37 °C; IR (CCl_4) 1722 (C=O) cm^{-1}; NMR (CCl_4) δ 3.12 (2 H, broad s, CH_2CO), 2.72 (2 H, broad s, CH_2CO), 0.9–2.7 (11 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 151 (3), 150 (4), 121 (40), 119 (100), 117 (99), 84 (23), 82 (23), 47 (17).

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.54; Br, 34.57. Found: C, 51.96; H, 6.57; Br, 34.60.

Subsequent fractions from the chromatography contained 0.66 g (18%) of the previously described enone **2**, n^{25}_D 1.5273.

Conversion of the Bromo Ketone 20 to the Enone 2. A. With KO-*t*-Bu. A solution of 0.16 g (0.64 mmol) of the bromo ketone **20** in 5 mL of Et_2O was added, slowly and with stirring, to a cold (0 °C) slurry of 138 mg (1.23 mmol) of KO-*t*-Bu in 10 mL of Et_2O. The resulting orange suspension was stirred at 0–3 °C for 15 min and then filtered through a bed of Celite and concentrated. The residual colorless liquid (66 mg) was distilled in a short-path still to separate 35 mg (35%) of the enone **2** as a colorless liquid (bp 85–89 °C (0.08 mm), n^{25}_D 1.5265), that was identified with the previously described sample by comparison of IR and NMR spectra.

B. With Et_3N. A solution of 0.83 g (3.6 mmol) of the bromo ketone **20** in 15 mL of anhydrous Et_2O was added, dropwise and with stirring, to a solution of 0.53 g (5.3 mmol) of Et_3N (freshly distilled) in 10 mL of anhydrous Et_2O. The mixture, from which a white flocculent precipitate separated, was stirred at 23 °C for 30 min and then filtered and concentrated. The residual pale yellow oil (0.47 g, n^{25}_D 1.5280) contained (IR and NMR analyses) a mixture of ca. 90% of the enone **2** and ca. 10% of the starting bromo ketone **23**.

Conversion of the Methoxy Ketone 19 to the Enone 2. A solution of 0.18 g (0.90 mmol) of the methoxy ketone **19** and 19 mg (0.090 mmol) of TsOH in 15 mL of anhydrous PhH was refluxed for 30 min and then cooled. After the solution had been washed rapidly with aqueous $NaHCO_3$ and then dried over $MgSO_4$, concentration left 0.12 g of the crude liquid enone **2**. Distillation under reduced pressure in a short-path still separated 104 mg (70%) of the pure enone **2** as a colorless liquid, n^{25}_D 1.5272, that was identified with the previously described sample by comparison of IR and NMR spectra.

Reactions of the Enone 2. A. With HBr. A stream of anhydrous HBr gas was passed through a solution of 2.70 g (18.0 mmol) of the enone **2** in 100 mL of $CHCl_3$ for 6 min. The resulting yellow solution was flushed with a stream of N_2 gas for 5 min and then washed with aqueous $Na_2S_2O_3$, dried, and concentrated. The residual yellow liquid (3.3 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:9 (v/v)) to separate 2.0 g (54%) of the bromo ketone **20** as a colorless liquid, n^{25}_D 1.5239, that was identified with the previously described sample by comparison of IR and NMR spectra.

B. With MeOH. A solution of 0.30 g (1.6 mmol) of the enone **2** in 1 mL of hexane was added, dropwise and with stirring, to a solution of 3.2 mmol of NaOMe in 2 mL of MeOH. After the resulting yellow solution had been stirred at 25 °C for 1 h, it was partitioned between Et_2O and H_2O. The organic layer was dried and concentrated and the residual liquid (0.32 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:9 (v/v)) to separate 0.25 g (70%) of the methoxy ketone **19**, n^{25}_D 1.4984, that was identified with the previously described sample by comparison of IR and NMR spectra.

C. With PhSH. A solution of 0.40 g (1.7 mmol) of the bromo ketone **20** in 3 mL of Et_2O was added, dropwise and with stirring, to a slurry of 0.54 g (4.0 mmol) of PhSNa in 15 mL of Et_2O. After the resulting yellow suspension had been stirred at 25 °C for 1.5 h, it was filtered through Celite and then concentrated. The residual liquid (1.2 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:9 (v/v)) to separate 0.19 g (44%) of the thioether **22** as a colorless liquid; n^{25}_D 1.5554. The sample crystallized on standing as white prisms; mp 43–45 °C. Recrystallization from an Et_2O–hexane mixture afforded the pure thioether **22**: mp 43.5–45 °C; IR (CCl_4) 1712 (C=O) cm^{-1}; NMR (CCl_4) 7.2–7.7 (5 H, m, aryl CH), 1.1–2.8 (15 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 260 (M^+, 8), 151 (100), 133 (26), 109 (62), 81 (27), 67 (25).

Anal. Calcd for $C_{15}H_{20}OS$: C, 73.80; H, 7.74; S, 12.31. Found: C, 73.75; H, 7.75; S, 12.27.

D. With H_2O. A mixture of 88 mg (0.6 mmol) of the enone **2**, 2 mL of Et_2O, and 1 mL of H_2O was stirred at 25 °C for 24 h and then extracted with Et_2O. After the organic layer had been dried and concentrated, 92 mg (94%) of the crude ketol **3b** remained as a pale yellow liquid: n^{25}_D 1.5149; IR (CCl_4) 3615, 3460 (broad, OH), 1720 (nonconjugated C=O) cm^{-1}; NMR (CCl_4) δ 3.30 (1 H, broad, OH, exchanged with D_2O), 0.9–3.0 (15 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 168 (M^+, 3), 111 (35), 55 (25), 45 (44), 44 (27), 43 (100), 41 (21). Attempts to purify the crude ketol **3b** by short-path distillation resulted in decomposition of the sample.

A solution of 250 mg (1.48 mmol) of this crude ketol **3b** in 3 mL of Et_2O was stirred (N_2 atmosphere) at 25 °C for 24 h with a solution of 59 mg (0.15 mmol) of NaOH in 3 mL of H_2O. The resulting mixture was extracted with Et_2O and the organic extract was dried and concentrated. The residual liquid (235 mg) was chromatographed on silica gel with an EtOAc–hexane eluent (1:3 (v/v)) to separate 0.15 g (60%) of the pure diketone **6**, n^{25}_D 1.4751,

that was identified with a previously described sample by comparison of IR and NMR spectra.

E. Thermal Stability. After a solution of 170 mg (1.12 mmol) of the enone **2** in 10 mL of anhydrous PhH had been refluxed under a N_2 atmosphere for 10 days, the solution was concentrated to leave 165 mg (97%) of the unchanged enone **2**, $n^{25}D$ 1.5272, that was identified with an authentic sample by comparison of IR and NMR spectra. Similarly, a solution of 160 mg (1.0 mmol) of the enone in 5 mL of decalin (bp ~190 °C) was refluxed under a N_2 atmosphere for 48 h. After the mixture had been chromatographed on a short silica gel column with an EtOAc–hexane eluent (1:1 (v/v)), distillation of the later fractions separated 104 mg (65%) of the unchanged enone **2**, $n^{25}D$ 1.5272, that was identified with an authentic sample by comparison of IR spectra. Examination of the recovered decalin and the distillation residue failed to indicate the presence of any other product such as a nonconjugated ketone formed by cycloaddition.

Registry No. **2**, 70562-48-0; **3b**, 70562-49-1; **4**, 1121-66-0; **6**, 66921-76-4; **7**, 70562-50-4; **9**, 66077-95-0; **10**, 70562-51-5; **11**, 70562-52-6; **12**, 70562-53-7; **14**, 70562-54-8; **15**, 70562-55-9; **19**, 70576-36-2; **20**, 70576-35-1; **21a**, 70562-56-0; **21b**, 70562-57-1; **22**, 70562-58-2; methyl 1-methoxy-8-hydroxybicyclo[4.3.1]dec-7-ene-7-carboxylate, 70562-59-3; methyl 1-cyano-8-hydroxybicyclo[4.3.1]dec-7-ene-7-carboxylate, 70562-60-6; methyl 1-bromo-8-hydroxybicyclo[4.3.1]dec-7-ene-7-carboxylate, 70562-61-7; *tert*-butyl 1-methoxy-8-hydroxybicyclo-[4.3.1]dec-7-ene-7-carboxylate, 70562-62-8; cycloheptanone, 502-42-1; $HOCH_2CH_2OH$, 107-21-1; 2-bromocycloheptanone ethylene ketal, 70562-63-9; 2-cycloheptanone ethylene II ketal, 184-26-9; ethyl acetoacetate, 141-97-9; *tert*-butyl acetoacetate, 1694-31-1.

Peristylenones and Norperistylenones: Highly Reactive Intermediates. Synthesis of Dodecahedrane Precursors. 2[1f,g]

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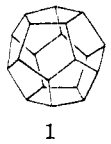
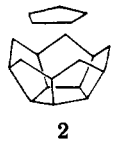
The synthesis of substituted, functionalized peristylanes (hexacyclo[7.5.1.$0^{3,13}$.$0^{5,12}$.$0^{7,11}$.$0^{10,14}$]pentadecane) and norperistylanes (hexacyclo[6.6.0.0^{2,6}.$0^{3,13}$.$0^{4,12}$.$0^{10,14}$]tetradecane) designed as dodecahedrane precursors is described. Included are pentafunctional peristylanes, e.g., 4,8,15-tris(diethylamino)peristylane-2,6-dione, tetrafunctional norperistylanes, e.g., norperistylane-5,7,9,11-tetrone, and norperistylanes and peristylanes carrying carbon substituents, e.g., 7,9-dicarbomethoxynorperistylane-5,11-dione and 4-(2,5-dioxocyclopent-1-yl)peristylane-2,6-dione, the last containing all of the 20 carbons needed for dodecahedrane. These compounds were prepared by way of Michael additions to peristylenones and norperistylenones. In turn, these α,β-unsaturated ketones were made from the saturated systems reported earlier by elimination of $H_\alpha X_\beta$ or by decomposition of phenyl selenoxide derivatives. Peristylenones and norperistylenones are shown to be exceptionally reactive compounds, forming Diels–Alder adducts with furan at room temperature. This is accounted for by recognizing that the π system in these compounds must be twisted from planarity, away from full p-orbital overlap, by the geometric demands of the molecular skeleton. Some spectroscopic evidence to this point is given. The synthesis of a peristylane bearing a bulky endo carbon substituent is described. The NMR spectrum of this compound is compared to that of the less hindered exo isomer to obtain an idea of the conformational preferences of the endo substituent in the congested peristylane cavity. Useful procedures are described for the oxidative degradation of a β-alkyl-substituted acetylacetone to the alkyl carboxylic acid and for the hydrolysis and decarboxylation of a methyl nitroacetate. A new method is given to trap phenylselenenic acid, a product of phenyl selenoxide eliminations, before it consumes the desired olefin product in unwanted side reactions.

Introduction

Dodecahedrane (1), the organic chemist's transliteration



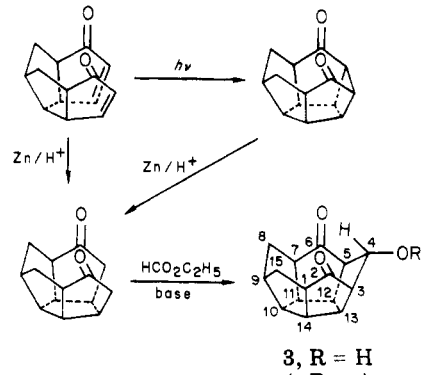
1



2

of the twelve-faced Platonic solid, presents a significant challenge. A number of interestingly different approaches to its synthesis have been devised, and reports of progress are increasingly frequent.[1] This paper is concerned with a portion of our own continuing efforts, in particular, with the chemistry of the peristylane system.[1f,g] As is evident from the drawing, peristylane (2) differs (conceptually) from dodecahedrane only by a well-placed cyclopentane ring. Clearly, adding this ring correctly requires proper site preparation, i.e., the introduction of useful functionality on each of the methylene groups of peristylane.

Chart I



3, R = H
4, R = Ac

The synthesis of the peristylane system,[1g] the last steps of which are given in Chart I, is such that first entry occurs

(1) (a) R. B. Woodward, T. Fukunaga, and R. C. Kelley, *J. Am. Chem. Soc.*, **86**, 3162 (1964); (b) I. T. Jacobson, *Acta Chem. Scand.*, **21**, 2235 (1967); (c) N. J. Jones, W. D. Deadman, and E. LeGoff, *Tetrahedron Lett.*, 2087 (1973); (d) D. McNeil, B. R. Vogt, J. J. Sudol, S. Theodoropulos, and E. Hedaya, *J. Am. Chem. Soc.*, **96**, 4673 (1974); (e) L. A. Paquette, S. V. Ley, and W. B. Farnham, *J. Am. Chem. Soc.*, **96**, 311 (1974); L. A. Paquette, W. B. Farnham, and S. V. Ley, *ibid.*, **97**, 7273 (1975); L. A. Paquette, I. Itoh, and W. B. Farnham, *ibid.*, **97**, 7280 (1975); L. A. Paquette, M. J. Wyvratt, O. Schualler, D. F. Schneider, W. J. Begley, and R. M. Blankenship, *ibid.*, **98**, 6744 (1976); L. A. Paquette, I. Itoh, and K. B. Lipkowitz, *J. Org. Chem.*, **41**, 3524 (1976); L. A. Paquette, R. A. Snow, J. L. Muthard, and T. Cynkowski, *J. Am. Chem. Soc.*, **100**, 1600 (1978); (f) P. E. Eaton and R. H. Mueller, *ibid.*, **94**, 1014 (1972); (g) P. E. Eaton, R. H. Mueller, G. R. Carlson, D. A. Cullison, G. F. Cooper, T.-C. Chou, and E.-P. Krebs, *ibid.*, **99**, 2751 (1977). For a review of various efforts, see P. E. Eaton, *Tetrahedron*, in press.

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