BICYCLOPENTANOID SESQUITERPENES. THE SYNTHESIS OF CEDRANOID SESQUITERPENES VIA THE PHOTO-REARRANGEMENT OF BICYCLO[2.2.2]OCTENONES

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Abstract—(±) - exo - 2,6,6 - Trimethyltricyclo[5.3.1.04'8]undecane - 8,10 - dione (11) has been synthesized from dimethyl 6,6 - dimethyl - 5 - oxobicyclo[2.2.2]oct-7 - ene dicarboxylate (17). This constitutes a new synthesis of cedrol (3) since 11 has previously been converted to this compound.

Two groups of sesquiterpenes incorporate two fused 5-membered rings; both have tricyclo[5.3.1.04'8]undecane skeletons. They differ in the positioning of the four additional carbon atoms as exemplified by α-cedrene (1)2 and α-patchoulene (2).6 Our concern here is with the first group, the cedranoid sesquiterpenes. This includes in addition to 1 and the closely related cedrol, 3, a variety of more highly oxygenated compounds, such as shellelic acid (4),5 laccishellolic acid (5),6 and α-pipitzol (6).7 The first total synthesis of a cedranoid sesquiterpene was achieved by Stork and Clarke1 who synthesized cedrol (3) by a route involving formation of the bicyclo[3.3.0]octane ring A/B system (7) via an aldol condensation and subsequent closure of ring C. Their synthesis of 3 was followed by several total syntheses of 1 and 3 inspired by biogenetic considerations9 that involved formation of the spiro[4.5]decane ring A/C system (8) followed by closure of ring B10 or a related sequence.11 In a different approach Breitholle and Fallis12 have recently synthesized 3 via ring expansion of a compound with a tricyclo[3.2.1.02,7]decane system (9).13 The only more highly oxygenated cedranoids that have been synthesized are α-pipitzol (6) and its β isomer which were formed by thermal isomerization of perezone (10).7

None of these routes appears to be readily applicable to the synthesis of many of the more highly oxygenated cedranoids and we embarked on a new synthetic approach to cedrol (3) that was designed to be applicable to the eventual incorporation of oxygenated functions at C-10, C-12, C-14, and C-15. We chose as our target the β-diketone 11, a pivotal intermediate in the synthesis of Stork and Clarke,6 which they obtained by base-catalyzed cyclization of the keto ester 12. This intermediate clearly has the potential of serving as a source of cedranoids with oxygenated functions at C-10 and C-15. We describe now a synthesis of 11 that is potentially adaptable to the introduction of oxygenated functions at C-12 and C-14 also.

Our synthetic strategy had its origin in observations that we had made during an investigation of the photochemistry of bicyclo[2.2.2]octenones formed by modified Wessely oxidation of ortho-substituted phenols.13 Ketone 13, obtained by oxidation of 2,6-dimethylphenol with lead tetraacetate in the presence of excess methyl hydrogen maleate, gave on direct irradiation in ether the cyclobutanone 14 and its decarbonylation product 15,14 while on sensitized photolysis in acetone it gave the tricyclo[3.2.1.02,7]octan-3-one derivative 16 (Scheme 1). Formation of 14 involves a 1,3-acetyl migration and that of 16 a 1,2-acetyl migration (oxadi-n-methane rearrangement); such reactions are well known for related compounds15 and other types of β,γ-unsaturated ketones.16 This investigation led us to consider the utilization of the photosensitized oxo-di-α-methylene rearrangement of a suitably substituted bicyclo[2.2.2]octenone for the synthesis of the bicyclo[3.3.0]octane system of the cedranoid sesquiterpenes.17 We envisaged that homoconjugate addition to the cyclopropane ring of the tricyclo[3.2.1.02,7]octan-3-one18 would provide a route for the stereoselective introduction both of the C-12 methyl
group at C-2 in 11 and of other groups that could be converted to the functionalized substituents at this carbon in the more highly oxygenated cedranoids.

We choose 17 as our starting bicyclo[2.2.2]octenone, which we had prepared by the route shown in Scheme 2 in the course of another investigation.\textsuperscript{17} 6,6-Dimethyl-2,4-cyclohexadienone (18), obtained by thermolysis of 19, a dimer of 6,6-dimethylfulvene 5,6-epoxide (20),\textsuperscript{20} gave the adduct 21 with dimethyl acetylenedicarboxylate in boiling xylene, which on hydrogenation over platinum underwent reduction of the unconjugated ethylenic double bond only to give 17.

Photolysis of 17 with acetophenone as both sensitizer and solvent gave the desired oxa-di-\pi-methane rearrangement product 22 in 76% yield (Scheme 3). This showed bands at 5.75 and 5.79 \mu in its IR spectrum and no vinyl proton signals in its \textsuperscript{1}H NMR spectrum excluding the possibility that it was a 1,3-acyl migration product of type 14. Interestingly, photolysis of 13 was sensitized by acetone (E_F \approx 80 \text{ kcal/mol})\textsuperscript{21} but not by acetophenone (E_F \approx 74 \text{ kcal/mol}).\textsuperscript{21} Observations on \beta,\gamma-unsaturated ketones suggest that they have triplet energies in the range 74-80 kcal/mol. The present results indicate that the triplet energies of 13 and 17 fall in this range with that of the latter being lower than that of the former; this relationship may be attributed to skeletal distortion in the former\textsuperscript{13} and/or the presence of the carbomethoxy substituents in the latter.

Reaction of 22 with lithium dimethylcuprate in ether gave the desired product 23 in 75% yield together with
two minor products 24 and 25 (Scheme 3); one of the minor products was very difficult to separate from 23 and complete purification of the latter was attended by considerable losses. However, $^1$H NMR spectroscopic analysis of the crude reaction product showed that the ratio of major to combined minor products was 14:1. The gross structure of 23 was readily assigned on the basis of spectroscopic data. Its IR spectrum showed strong bands at 6.08 and 6.20 $\mu$, and a broad shallow band at 3.0-3.5 $\mu$, consistent with the presence of an enolized $\beta$-keto ester group, together with a strong band at 5.82 $\mu$, in accord with the presence of an ester group on a quaternary carbon atom. Its $^1$H NMR spectrum included signals at $\delta$ 1.11 (6,5H) and 1.13 ppm (J = 6 Hz, 3H), attributable to the gem-dimethyl groups and the methyl group at C-8, respectively, and a one-proton singlet at $\delta$ 10.85 as expected for an enolic proton.

The relative configuration at C-8 was assigned in the expectation that addition of the methyl group to 22 would occur with inversion of configuration in analogy with related homoconjugate addition reactions of lithium cuprate reagents. This assignment was eventually verified by the successful outcome of the synthesis of 11. The $^1$C NMR spectrum of 23 showed three C-methyl signals at $\delta$ 16.1, 19.4 and 28.0 ppm; comparison of these values with the chemical shifts of the C-methyl groups of analogous compounds indicated that the C-8 methyl group gives rise to the signal at $\delta$ 16.1 ppm. This high field position is more characteristic of an endo C-8 methyl group in simple bicyclo[3.3.0]octanes, but in 23 the C-1 methyl ester group is expected to exert a large $\gamma$-shielding effect on the exo C-8 methyl group.

As in related cases, the cyclopropyl bond of 22 that undergoes cleavage to give 23 is the one best oriented to give rise to maximum overlap of the developing carbamion with both the ketone and the C-2 ester carbonyl groups. It is of interest that when the treatment of 22 with lithium dimethylcuprate was attempted in tetrahydrofuran very little reaction occurred. The use of this solvent was suggested by earlier work in which it had been found that the reaction of 26 with lithium dimethylcuprate gave improved yields of the homoconjugate addition product 27 when the solvent was changed from ether/pentane to ether/tetrahydrofuran or ether/dimethoxymethane. This type of effect has been interpreted in terms of increased nucleophilicity of the organometallic cluster resulting from improved coordination of the solvent with lithium ions. In the present case it may be suggested that reaction of 22 with lithium dimethylcuprate requires prior coordination with a lithium ion to give 28, such coordination both increasing electron withdrawal from the cyclopropane ring and maintaining an optimal orientation of the ketone and C-2 ester carbonyl groups for delocalization of the developing anion. In tetrahydrofuran improved solvation of the lithium ions could retard or inhibit the formation of 28. This observation finds analogy in the retardation of the reactions of oxiranes with lithium dimethylcuprate in tetrahydrofuran relative to ether solution. The postulated intermediacy of 28 in the reactions of 22 with lithium dimethylcuprate may also account for the observation that two equivalents of the latter reagent were required for the reaction to proceed at a practicable rate.

We return now to the assignment of the structures of the minor products 24 and 25 from the reaction of 22 with lithium dimethylcuprate. One of these, 25, was observed mixed with 23 in small amounts on chromatography of the crude reaction mixture, its presence being vouched for by peaks at $\delta$ 1.20, 1.29, and 12.11 ppm in the $^1$H NMR spectra of the chromatographic fractions. The other minor product, 24, could be cleanly separated from 23 by chromatography; its IR spectrum resembled that of 23 and its $^1$H NMR spectrum included two three-proton singlets at $\delta$ 1.13 and 1.19 ppm, two one-proton multiplets at $\delta$ 2.40 and 3.24 ppm, a one-proton triplet (J = 4 Hz) at $\delta$ 2.67 ppm, and a one-proton singlet at $\delta$ 12.15 ppm. The mass spectrum of 24 exhibited a peak at m/e 268, indicating that it was a reduction product of 22 and suggesting that it arose by reduction of the cyclopropane ring, as did its IR and $^1$H NMR spectra which indicated the presence of an enolized $\beta$-keto ester grouping.

Since insufficient material was available for full characterization of these minor products, we undertook a study of the reduction of 22 with lithium in liquid ammonia. This gave a ~1:1 mixture of two products whose spectra were identical to those of the minor products from the reaction of 22 with lithium dimethylcuprate; these were separated and individually characterized. Their IR and $^1$H NMR spectra confirmed that both incorporate an enolized $\beta$-keto ester grouping, and the multiplicities of the signals in their SFORD $^1$C NMR spectra showed that they both arise by reductive cleavage of the C-2-C-8 bond of 22 to give a bicyclo[3.2.1]octane system rather than by cleavage of the C-1-C-2 bond to give a bicyclo[3.3.0]octane system. It was concluded that these products are epimers at the C-8 position of compounds with gross structures corresponding to 24 and 25. The individual structural assignments were made on the basis of an analysis of their $^1$H NMR spectra (Table I). Inspection of a molecular model of 24 shows that the dihedral angle between the (C-1)-H and (C-8)-H bonds is ~45°, as is that between the (C-5)-H and (C-8)-H bonds; this would result in the splitting of the C-8 proton signal into a triplet with J = 4 Hz. Thus the reduction product whose spectrum included a one-proton triplet (J = 4 Hz) at $\delta$ 2.67 ppm was assigned this structure. On the other hand, a model of 25 indicated that the corresponding dihedral angles are ~90°, which would be expected to result in negligible coupling between the C-8 proton signal and the C-1 and C-5 protons. Accordingly, the signal at $\delta$ 2.8 ppm assigned to the C-8 proton in the spectrum of the other reduction product is a singlet, and this product is assigned structure 25. That 24 and 25 are epimers was confirmed by the conversion of 24 to a mixture of 24 and 25 on treatment with methanolic sodium methoxide.

It has previously been reported that reduction of the parent tricyclo[3.2.1.0²⁷]octan-3-one (29) with lithium in liquid ammonia gives bicyclo[3.3.0]octan-3-one (30) as...
the major product (95%) and only a minor amount (5%) of bicyclo[3.2.1]octan-3-one (31) (Scheme 4). This was interpreted in terms of preferential cleavage of the cyclopropyl bond that has greater overlap with the π-orbital of the ketonic group. That reduction of 22 gives only bicyclo[3.2.1]octane derivatives, contrary to the case of 29, is accountable to the presence of the C-8 ester bond; this must favor C-2-C-8 bond cleavage because of stabilization of the anion radical 32 (Scheme 5).

The formation of 24 and 25 in the reaction of 22 with lithium dimethylcuprate was an unexpected, but interesting, nuisance. To our knowledge there is no previous report of the reduction of an activated cyclopropane with a lithium organocuprate reagent. Reduction of α,β-unsaturated ketones and oxiranes in reactions with the thermally unstable cuprates prepared from s- and t-butyllithium have been attributed to unidentified copper hydride species formed by decomposition of the cuprates, probably involving transfer of a β-hydrogen to the copper atom and elimination of an alkene. However, there is no evidence that lithium dimethylcuprate in ether solution is unstable under the conditions (0°) of its reaction with 22, and indeed its stability has been attributed to the absence of β-hydrogen atoms. Furthermore, lowering the reaction temperature to −15° did not change the amounts of 24 and 25 formed. A more likely interpretation of the formation of these products can be advanced on the basis of the extensive investigation of the reactions of α,β-unsaturated carbonyl compounds with lithium organocuprates, which has established that these reactions proceed via electron transfer. α,β-Unsaturated carbonyl compounds whose reduction potentials are more negative than −2.35 V do not undergo conjugate addition with lithium dimethylcuprate, and they either do not react or undergo enolization or slow 1,2-addition to the carbonyl group. Activated cyclopropanes that undergo homoconjugate addition with lithium organocuprates, such as 33 and 34, have reduction potentials that are too low to permit reaction via an initial electron transfer (E_red −2.93 and −2.98 V, respectively). and House has proposed that in the case of such cyclopropane derivatives, unlike those of α,β-unsaturated carbonyl compounds, homoconjugate addition occurs by nucleophilic displacement rather than by initial electron addition. In the present case, although the reduction potential of 22 is not known, it may be anticipated that the ketonic group and C-8 ester group will increase this potential relative to 34 and raise it close enough to −2.35 V to permit a small amount of electron transfer from lithium dimethylcuprate. The resulting anion radical, 32, must then undergo further reduction competitively with rebonding or methyl transfer.

Revenons à nos moutons. We now discuss the elaboration of compound 23 to the β-diketone 11 by the construction of ring C. The carbomethoxy group at C-2, having served its purpose in activating and directing homoconjugative addition to the cyclopropane ring of 22, was first removed. Decarbomethoxylation was effected by the Krapcho procedure, involving treatment with sodium chloride in hot, aqueous dimethyl sulfoxide. This gave the keto ester 35 in 74% yield (Scheme 6), whose 'H NMR spectrum clearly showed the C-2 methylene proton signals as an AB doublet of doublets with J = 20 Hz, as expected for the geminal coupling of protons adjacent to a carbonyl group.

Our next aim was to add a two-carbon chain at C-3 in 35 that would permit the closure of ring C. Our initial attempts sought to use Wittig-type reactions for this purpose. Pursuing a contemporaneous preliminary report, we investigated the applicability of the lithio derivative of 36, whose addition to aldehydes was described. Model studies with benzophenone did on one occasion give a ~20% yield of 1,1-diphenylacetone but on others returned only starting materials. Reactions with 35 were not successful even to this meager extent, uniformly returning starting materials. When the reaction was attempted in tetrahydrofuran at −75° addition of 35 to the deep red solution of the anion of 36 immediately discharged the color, and we therefore conclude that enolate ion formation preempts addition. When the reaction was attempted at −95° the color of the anion persisted for several hours; subsequent warming of the reaction mixture to −80° led to rapid disappearance of the color,
but workup again gave only starting materials. We were equally unsuccessful in inducing the lithio derivatives of the α-chloroalkylsilanes \( \text{P} \) and \( \text{Q} \) to react with \( \text{R} \); here the difficulties were probably due to steric hindrance, since lithiated \( \text{R} \) adds readily to cyclopentanone but gives only poor yields with camphor.

With a view to minimizing steric difficulties we turned to a more classical approach to the introduction of a functionalized two-carbon substituent, via reaction with lithium acetylide at \(-78^\circ\) in tetrahydrofuran. Here success finally attended our efforts and we obtained a 61\% yield of the desired propargylic alcohol \( \text{S} \) (Scheme 7); the \( ^1\text{H} \) NMR spectrum of the crude reaction product showed that \(-30\%\) of \( \text{R} \) was unreacted, presumably as a result of competitive enolate ion formation, since attempts to force complete conversion of \( \text{R} \) to \( \text{S} \) by use of the lithium acetylide-ethylenediamine complex or by using a mixture of pentane and tetrahydrofuran as solvent were unsuccessful. The presence of hydroxyl and terminal acetylenic groups in the product was evidenced by its IR spectrum, which showed peaks at 3.03 \( \mu\) (m, \( \text{OH} \) stretch) and 2.79 \( \mu\) (m, \( \text{CH} \) stretch), although the \( \text{C}==\text{CH} \) stretching band was too weak to be identified unambiguously. Its \( ^1\text{H} \) NMR spectrum, like that of \( \text{R} \), showed the \( \text{C}-2 \) methylene proton signals as an AB system, but the geminal coupling constant is reduced from 20 to 14 Hz in the absence of the adjacent ketonic group. Its SFORD \( ^{13}\text{C} \) NMR spectrum includes doublets at \( \delta 73.0 \) and \( 85.3 \) ppm that are assigned to the terminal and non-terminal acetylenic carbons, respectively; the residual coupling shown by the former signal is 72 Hz, attributable to the very large \( ^3\text{J} \) \( \text{C}==\text{CH} \) coupling constant for acetylenic carbon \( \sim 250 \) Hz, and that shown by the latter signal is 14 Hz, attributable to the unusually large \( ^3\text{J} \) \( \text{C}==\text{CH} \) coupling constant for the non-terminal carbon in the \( \text{C}==\text{CH} \) group \( \sim 50 \) Hz. The acetylic group in \( \text{S} \) is assigned the \( \text{exo} \) configuration in the expectation that attack of the acetylide ion occurs on the less hindered side of \( \text{R} \).

Having successfully introduced a two-carbon substituent at \( \text{C}-3 \), we now sought to convert this to an acetyl group for the construction of ring \( \text{C} \) of \( \text{N} \), and to remove the extraneous hydroxyl group at \( \text{C}-3 \). To this end \( \text{S} \) was treated with hot 92\% formic acid containing a small amount of concentrated sulfuric acid in order to convert it to \( \text{T} \) by a Rupe rearrangement (Scheme 7). This gave a mixture of two products in a \( \sim 1:2 \) ratio. The elemental composition and spectra of the former product, \( \text{C}_{10}\text{H}_{16}\text{O}_{2} \), showed it to be \( \text{T} \). Its IR spectrum showed bands at 6.00 (s), 6.20 (w), and 7.37 \( \mu\) (m) in accord with the presence of an \( \alpha,\beta\)-unsaturated methyl ketone grouping. Its \( ^1\text{H} \) NMR spectrum includes signals at \( \delta 2.29 \) (s, 3\( \text{H} \)) and 6.56 (s, 1\( \text{H} \)) as expected for the methyl group of a methyl ketone and the \( \beta \) proton of an \( \alpha,\beta\)-unsaturated ketone, respectively. Its \( ^{13}\text{C} \) NMR spectrum showed a signal at \( \delta 197.3 \) ppm, confirming the presence of an \( \alpha,\beta\)-unsaturated ketonic group, together with signals at \( \delta 144.0 \) and 149.2 ppm, attributable to the ethylenic carbons of this group.

The minor product from the treatment of \( \text{S} \) with formic and sulfuric acids is assigned structure \( \text{U} \) (Scheme 7) on the basis of its elemental composition, \( \text{C}_{10}\text{H}_{16}\text{O}_{2} \), and spectra. Its IR spectrum, with bands at 3.13 (m) and 4.78 (vw) \( \mu\), showed that it retained the terminal acetylenic group. Its \( ^1\text{H} \) NMR spectrum includes signals at \( \delta 1.75 \) (d, \( J=1.5 \) Hz, 3\( \text{H} \)) and 2.27 (s, 1\( \text{H} \)), attributable to a vinyl methyl group and an acetylenic proton, respectively. The formation of \( \text{U} \) can readily be interpreted in terms of the postulated mechanism for the Rupe rearrangement (Scheme 8). The cationic intermediate \( \text{V} \) can either lose a proton to give \( \text{W} \), which on acid-catalyzed hydration gives \( \text{X} \), or can undergo a 1,2 migration of a methyl group to give \( \text{Y} \), which on loss of a proton gives \( \text{Z} \). It was subsequently found that with anhydrous formic acid and increased concentrations of sulfuric acid the formation of \( \text{Y} \) could be suppressed, but this was at the expense of increased polymerization and the yield of \( \text{X} \) remained low.

Because of this low yield we investigated an alternative reaction sequence in which \( \text{S} \) was converted to the \( \alpha\)-ketol \( \text{A} \) and the corresponding acetate \( \text{B} \) (Scheme 9). However, it was not found possible to bring about reductive cleavage of either the hydroxyl or acetoxy group under a variety of conditions.
The synthesis was therefore continued via 40. Hydrogenation of this over platinum gave a dihydro compound whose IR and \(^1\)H NMR spectra (\(\lambda_{max} 5.83 \mu \) (br); \(\delta 2.14 (s, 3H), no vinyl proton signal) showed that it had a gross structure corresponding to 47 (Scheme 10). The acetyl group in 47 is assigned the endo configuration in the expectation that delivery of hydrogen occurs from the less hindered side of 40, and 47 is thus considered to be the C-3 epimer of 12, the intermediate that Stork and Clarke\(^*\) cyclized to give 11. We anticipated that 47 would also cyclize to 11 via epimerization at C-3 under the strongly basic reaction conditions and were happy to find this indeed was the case. Treatment with potassium t-butoxide in t-butyl alcohol gave (\(+\)-)11 in good yield with solution IR \(^1\)H NMR, and \(^13\)C NMR spectra identical with those of a sample of optically active 11 obtained previously.\(^{8,22}\) The IR spectrum (CHCl\(_3\)) shows a strong band at 5.88 \(\mu \) with a shoulder at 5.81 \(\mu \), typical of unenolized 1,3-cyclohexanediones;\(^3\) the \(^1\)H NMR spectrum, with a two-proton singlet attributable to the protons at C-9, also shows that 11 is not significantly enolized in chloroform solution. The PND \(^13\)C NMR spectrum of 11 was recorded in NaOH-D\(_2\)O and showed thirteen sharp lines and a broadened signal at \(\delta 103.9 \)ppm in the spectrum of 1,3-cyclohexanediene in NaOH/D\(_2\)O.

The synthesis of 11 from 17 completes the formal synthesis of cedrol and paves the way for an assault on the more highly oxygenated cedrarroids. Our preliminary results\(^1\) on the introduction of functionalized substituents at C-1 in 22 suggest that this approach is not without promise.

**EXPERIMENTAL**

M.ps were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were taken in CHCl\(_3\) solution and the \(^1\)H and \(^13\)C NMR spectra in CDCl\(_3\) solution. Analytical thin layer chromatography was carried out on 0.25 \(\times\) 20 cm plates coated with 0.5 mm, 1 mm or 2 mm silica gel layers (Merck Kieselgel 60 PF254 containing gypsum). Medium pressure liquid chromatography was carried out on a Merck Silica gel 60 Pre-packed column (Size B) operated at a pressure of \(-5\) psi. Unless otherwise stated, solutions were dried over magnesium sulfate and concentrated on a Büchi Rotovapor R rotary evaporator under water aspirator pressure. Solvents used for workups and chromatography were either distilled or were ACS Reagent grade quality. Unless otherwise stated, photolyses were carried out in a Rayonet Srinivasan-Griffith Photochemical Reactor equipped with eleven low pressure RPR lamps. Photolysis solutions were

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<thead>
<tr>
<th>H</th>
<th>(^1)H NMR spectra of 24 and 25*</th>
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<tr>
<td>1</td>
<td>3.24 (m) 3.30 (m)</td>
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<tr>
<td>5</td>
<td>2.40 (m) 2.53 (m)</td>
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<td>6,7</td>
<td>1.4-2.1 (m) 1.6-2.1 (m)</td>
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<td>8</td>
<td>2.67 (t, J = 4 Hz) 2.66 (s)</td>
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<td>COH</td>
<td>1.13 (s), 1.19 (s) 1.20 (s), 1.29 (s)</td>
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<tr>
<td>OCH(_3)</td>
<td>3.64 (s), 3.81 (s) 3.71 (s), 3.78 (s)</td>
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<tr>
<td>OH</td>
<td>12.15 (s) 12.11 (s)</td>
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*The relative intensities of the signals were in accord with the assignments.
flushed with a stream of dry nitrogen for 0.5-3 hr prior to irradiation. Solvents for photolysis were distilled prior to use.

Direct photolysis of 13: formation of 14 and 15-
(a) Compound 13 (59 mg, 0.24 mmol) was dissolved with stirring in ether (25 ml) in a Pyrex tube. The solution was degassed with nitrogen for 2 hr, and was then irradiated at 300 nm for 3.5 hr to give a mixture of 14 and 15. The solution was cooled to 0°, when 14 crystallized. Two recrystallizations by solution of the crystals in large volumes of ether, reduction of the volume without heating and cooling gave 14 (17 mg, 0.068 mmol, 28%) m.p. 148-153°; \( \delta_{1H} \) 1.16, 5.67, 7.12 \( \mu \); \( \delta_{13C} \) NMR: 8 16.4 (q), 22.8 (q), 34.6 (d), 40.1 (d), 42.3 (d), 52.1 (q), 55.8 (d), 96.9 (s), 117.2 (d), 133.4 (s), 170.7 (s), 174.7 (s), 201.6 (s); m/e 251 (M+1, 12%). Calc. for \( \text{C}_{12} \text{H}_{10} \text{O}_{2} \): C, 63.15; H, 6.81; found: C, 63.08; H, 6.898.

(b) Continued irradiation of a mixture of 14 and 15 as described above for irradiation of 13 (170 mg, 0.68 mmol) in tert-butyl alcohol (21 ml) with a Hanovia 450W medium-pressure mercury arc lamp to the exclusive formation of 14 (17 mg, 0.068 mmol, 28%)

Crystallization from ethyl acetate/pentanes (1:1 i/v) gave 14, m.p. 76-78°; \( \delta_{1H} \) NMR: 8 1.14-2.33 (m, 2H), 1.68 (s, 3H), 1.98 (s, 3H), 3.40-3.83 (m, 3H), 2.79 (s, 3H), 5.61 (m, 1H); \( \delta_{13C} \) NMR: 8 18.5 (q), 20.3 (q), 22.2 (d), 42.4 (d), 44.4 (d), 51.9 (q), 68.1 (s), 118.7 (d), 134.9 (s), 170.7 (s), 176.3 (s); m/e 251 (M+1, 12%). Calc. for \( \text{C}_{12} \text{H}_{10} \text{O}_{2} \): C, 63.15; H, 6.81; found: C, 63.17; H, 6.896.

Dimerization also occurred on standing at room temperature, and therefore this material was used immediately.

5.6. Dicarbomethoxy-3,3-dimethylcyclohexene (18). Compound 19 (30.0 g, 0.123 mol) was dissolved in reduced pressure (60 mm) through a hot (380°) Pyrex tube (length 25 cm, inner diameter 1.5 cm) packed with glass beads (diameter 3 mm). The product was distilled at reduced pressure (60 mm) to give 16 (395 mg, 1.58 mmol, 4%) as hard, white crystals, m.p. 150.5-152°; \( \delta_{1H} \) NMR: 8 0.93 (s, 3H), 1.22 (s, 3H), 1.25-2.5 (m, 4H), 2.85-3.30 (m, 2H), 3.70 (s, 3H), 3.72 (s, 3H); \( \delta_{13C} \) NMR: 8 17.1 (q), 25.2 (q), 26.8 (q), 34.6 (t), 41.6 (d), 51.4 (d), 52.4 (d), 52.7 (d), 52.8 (q), 54.1 (s), 55.4 (s), 163.7 (s), 169.9 (s), 210.5 (s); m/e 267 (M+1, 76%), 266 (3%). Calc. for \( \text{C}_{12} \text{H}_{10} \text{O}_{2} \): C, 63.15; H, 6.81; found: C, 63.17; H, 6.896.

5.7. - Dimethylbicarbomethoxy-4,4-dimethylcyclohexene (19). A solution of methyl lithium (12 ml, 0.24 mol) in ether (100 ml) was added over 1 hr to a cold (0-5°), stirred slurry of cuprous iodide (8.65 g, 45 mmol) in ether (80 ml) under argon. After a further 2 hr a solution of 22 (6.00 g, 22.5 mmol) in ether (70 ml) was added over a period of 1 hr. The reaction mixture was stirred at 0° for 12 hr and was then siphoned into cold 10% hydrochloric acid (200 ml). The resulting mixture was filtered through Celite. The filtrate was separated and the aqueous phase was extracted with ether (4 x 25 ml). The organic phases were combined and washed with saturated aq. sodium bicarbonate (25 ml). 1M aq. sodium thiosulphate (25 ml), and saturated aq. sodium chloride (25 ml). The ethereal solution was dried and concentrated to give a yellow oil (5.6 g) containing 23, 24, and 25. The \( \delta_{1H} \) NMR spectrum of this oil indicated that the ratio of 23 to 24 and 25 combined was 1:1. Repeated crystallization of this oil from pentane containing 10% ethyl acetate gave 23 as a yellow solid (1.60 g) which was sublimed at 70°, 0.03 mm) to give 23 as a white solid. Further recrystallization from pentane and sublimation gave pure 23, m.p. 76.5-78.5°; \( \delta_{1H} \) 8 5.82, 6.08, 6.20; \( \delta_{13C} \) NMR: 8 1.11 (s, 6H), 1.13 (d, J = 6 Hz, 3H), 1.2-3.3 (m, 3H), 2.5-2.9 (m, 3H), 3.68 (s, 3H), 3.81 (s, 3H), 10.85 (s, 1H); \( \delta_{13C} \) NMR: 8 16.1 (q), 19.4 (q), 28.0 (q), 29.1 (t), 36.2 (t), 44.0 (q), 54.5 (s), 51.0 (s), 128.6 (s), 136.7 (s), 169.9 (s), 173.4 (s), 175.7 (s); m/e 268 (22%). Calc. for \( \text{C}_{12} \text{H}_{10} \text{O}_{2} \): C, 63.81; H, 7.85; found: C, 63.75; H, 7.80. Compound 23 could be separated in similar yield for 24 and 25 by medium pressure liquid chromatography using 9:1 hexanes/ethyl acetate (v/v) as eluent.

- 2 - syn - 8 - Dicarbomethoxy - 4,4 - dimethylcyclohexene (21) - octa- 2 - 3 - octene (3). A mixture of 24 and 25, Separation by medium pressure liquid chromatography using hexanes/ethyl acetate (9:1 v/v) as eluent. Saturated aq. ammonium chloride (10 ml) was added, followed by sufficient water to dissolve all the salts. The layers were separated and the aqueous phase was extracted with ether (3 x 10 ml). The combined organic layers were dried and concentrated to give a colorless oil (321 mg) containing a 1:1 mixture of 24 and 25. Separation by medium pressure liquid chromatography using hexanes/ethyl acetate (9:1 v/v) as eluent, gave 25 (108 mg, 0.40 mmol, 22%) and 24 (97 mg, 0.36 mmol, 19%).

Crystallization of 24 from a mixture of pentanes and ethyl acetate gave white crystals, m.p. 113-114°; \( \delta_{1H} \) NMR: 8 1.13 (s, 3H), 1.15 (s, 3H), 1.38-2.14 (m, 4H), 2.40 (m, 2H), 3.68 (s, 3H), 3.81 (s, 3H), 12.15 (s), 16.9 (s); \( \delta_{13C} \) NMR: 8 23.7 (d), 24.1 (t), 27.4 (d), 32.7 (s), 121.2 (s), 141.8 (s), 147.5 (s), 164.7 (s), 166.6 (s), 213.5 (s); m/e 266 (100%). Calc. for \( \text{C}_{12} \text{H}_{10} \text{O}_{2} \): C, 62.67; H, 7.51; found: C, 62.73; H, 7.49. Similarly, crystallization of 25 from a mixture of pentanes and ethyl acetate gave...
silica gel plate eluted with CH2Cl2. Compounde 40 (21 mg,ay 0.08 mmol) was found at a band at Rf 0.35, while 41 (16 mg,ay 0.07 mmol) was found at Rf 0.6. Molecular distillation (50°C, 1 mm Hg) gave 42 (80 mg),a colorless oil; 43 (7.3 mg,ay 48%) 5.82 m; H NMR: δ 0.90 (d, J = 7.6 Hz, 3H), 1.28 (s, 3H), 1.15-2.5 (m, 6H), 1.75 (d, J = 1.5 Hz, 3H), 2.27 (s, 1H), 2.93 (m, 1H), 3.70 (s, 3H); m/e 232 (25%). Calc. for C16H24O2: MW 232.1463; found: m/e 232.1452.

1. Carbomethoxy - exo 3 - (1-oxoethyl) - 44 - exo - 8 - trimethyl - cis - bicyclo[3.3.0]octan - 3 - ol (45). A solution of propargylic alcohol 81 (169 mg, 0.66 mmol) and mercuric sulfate (232 mg, 1 mmol) was stirred and heated at reflux for 2 h under nitrogen in 95% ethanol (20 ml) containing concentrated sulfuric acid (2 drops). After cooling to room temperature, a spuitola tip of sodium bicarbonate was added and the mixture was evaporated to dryness. Magnesium sulfate was added and the residual solids were washed thoroughly with chloroform. The washings were stripped of solvent and the residue was sublimed (95/0.01 mm) to give 45 (131 mg, 0.49 mmol, 72%). Thin layer chromatography with cyclohexanone/ethyl acetate as eluent (1:1 v/v) gave 45 in a band at Rf 0.51. Sublimation (75/0.15 mm) gave 45, m.p. 89-91: δ 2.94 (m, 5.85, 5.90 (sh), 7.41 (m) (4); H NMR: δ 0.90 (d, J = 7.6 Hz, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.45-2.5 (m, 5H), 1.82 (d, J = 14.5 Hz, 1H), 2.27 (t, 2.66 (t, J = 9 Hz, 3H), 1.34 (d, J = 14.5 Hz, 1H, J = 1.5 Hz, 3.38 (d, J = 1.5 Hz, 1H), 3.70 (s, 3H); 14C NMR: δ 14.5 (q, 17.7), 28 (q), 28.7 (q), 29.2 (q), 31.5 (q), 42.3 (q), 47.6 (q), 48.8 (q), 51.5 (q), 51.6 (q), 61.5 (q), 61.9 (q), 91.6 (q), 178 (s), 211 (s); m/e 286 (2%). Calc. for C23H34O2: 417.58; 417.4; 417.9; m/e 286 (2%).

1. Carbomethox - exo - 3 - Aceity - 1 - oxoethyl - bicyclo[3.3.0]octane (46). Acetic anhydride (140 mg, 1.51, 1.48 mmol) was added to a stirred solution of 45 (99 mg, 0.37 mmol) and 4-N,N-dimethylamino- pyridine (181 mg, 1.48 mmol) in dichloromethane (1.0 mm) under nitrogen. After being stirred at room temperature for 14 h, the pale yellow reaction solution was diluted with ether (20 ml). The resulting solution was washed with 10% hydrochloric acid (10 ml), saturated sodium bicarbonate (10 ml), and saturated sodium chloride (10 ml), dried, and concentrated to give 46 (110 mg, 0.35 mmol, 95%). Preparative thin layer chromatography with 2:1 cyclohexanone/ethyl acetate (v/v) as eluent gave 46 in a band at Rf 0.51; molecular distillation (80/0.02 mm) gave 46 as a colorless, viscous oil; 5:5; H NMR: δ 8.25 (s, 3H), 42 (J = 6.5 Hz, 3H), 1.6 (6.5 Hz, 3H), 1.4-2.2 (5H, 2.11 (s, 6H), 2.16 (d, J = 1.6 Hz, 3H), 3.41 (d, J = 1.6 Hz, 3H), 3.71 (3H), m/e 311 (M + 1, 29%). Calc. for C23H34O2: C, 76.78; H, 8.44; found: C, 76.54; H, 8.386.

1. Carbomethox - endo - 3 - (1-oxoethyl) - 44 - exo - 8 - trimethyl - cis - bicyclo[3.3.0]octane (47). Compound 40 (25 mg, 0.10 mmol) was hydrogenated at atmospheric pressure in ethyl acetate (5 ml) over platinum (formed from platinum oxide in situ) for 25 mg for 6 h. The catalyst was filtered and the filtrate was concentrated to give 47 (21 mg, 0.06 mmol, 80%) as a colorless, mobile oil. Purification was accomplished by thin layer chromatography with cyclohexanone/ethyl acetate (2:1 v/v) as eluent (Rf 0.55) and molecular distillation (70°/0.01 mm): 5:5, 5.83, 7.27 (m); H NMR: δ 0.80 (s, 3H, 0.92, (J = 6.5 Hz, 3H), 1.12 (3H), 1.0-2.2 (5H, 2.14 (s, 3H), 2.35-2.85 (m, 3H, 3.69 (3H); m/e 250 (21%). Calc. for C23H34O2: C, 71.39; H, 8.99; found: C, 71.63; H, 9.57.

1. Carbomethox - (c) - exo - 2.6 - 6 - Trimethylbicyclo[3.3.0]octane (48). Compound 47 (21 mg, 0.08 mmol) was added to a solution prepared by heating potassium (54 mg, 0.38 mg-atm) in boiling tert-butyl alcohol (1.5 ml), and the mixture was boiled under reflux for 1.5 h. The solution was then cooled to room temperature, diluted with water (10 ml), and washed with ether (4×5 ml). The aqueous solution was made strongly acidic by the addition of concentrated hydrochloric acid (1 ml), producing a fine white precipitate. The residue was extracted with chloroform (3×10 ml), which slowly removed the precipitate. The chloroform extracts were combined, dried, and concentrated to give 11 (18 mg, 0.08 mmol, ~100%) as an off-white solid. Recrystallization from a mixture of dioxane and pentane gave 11 (8 mg) as white crystals, m.p. 177.5-179.5; Amax 5.81 (sh), 5.85;
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This experiment was conducted under rigorously anhydrous conditions under a positive pressure of argon or nitrogen.


The multiplicities of the signals in the 13C NMR spectrum are those determined from the SFORD spectrum of an optically active sample of 11.22

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