do not involve polarity or phase discontinuities can influence strongly the diffusion of benzyl radicals. A model for analyzing their fates in more than one phase (including a liquid-crystalline one) of a solvent has been devised. From it, we conclude that variations in viscosity, alone, cannot account for changes in the recombination probability.

The nature of the processes leading to products appears very complex and, in *n*-butyl stearate especially, merits further attention.

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Registry No. 1a, 35730-02-0; **1b**, 102-04-5; benzyl radical, 2154-56-5.

Synthesis of *dl*-Pentalenolactones E and F

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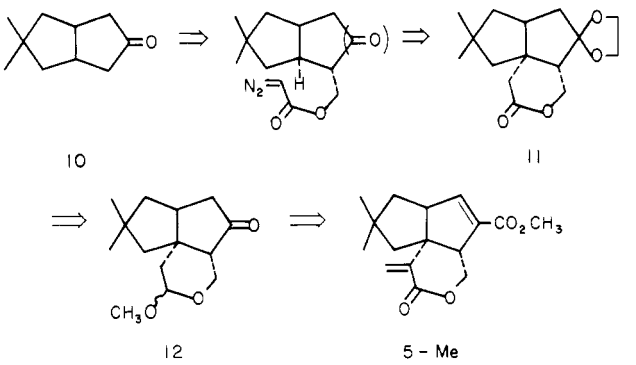
Abstract: The methyl esters of (±)-pentalenolactone E (**5**-Me) and F (**6**-Me) have been synthesized by a route based on the intramolecular insertion of an α-acylcarbene into an unactivated C–H bond to effect closure of the key fused δ-lactone ring system. Thus 7,7-dimethylbicyclo[3.3.0]octan-3-one (**10**) was assembled in seven steps from dimethyl 3,3-dimethylglutarate (**13**). The requisite (diazoacetoxy)methyl side chain was appended to **10** by a sequence of carbomethoxylation, ketalization, side-chain reduction, acylation with glyoxalyl chloride tosylhydrazone, and base-catalyzed elimination of *p*-toluenesulfinate. Ring closure to the desired δ-lactone **31** was effected in 43–47% yield by using $Rh_2(OAc)_4$ catalyst in refluxing Freon TF. Lactone reduction, deketalization, and selective acetalization of the derived lactol provided **34** as a mixture of epimers. By use of the method previously described by Paquette, **34** was converted to pentalenolactone E methyl ester (**5**-Me). Stereoselective epoxidation of the exomethylene double bond of **5**-Me provided pentalenolactone F methyl ester (**6**-Me). The use of α-diazo β-keto esters for the elaboration of bicyclo[3.3.0]octanones was also explored as an approach to the synthesis of pentalenolactone (**1**) itself. Thus exposure of **38** to $Rh_2(OAc)_4$ in refluxing Freon TF gave a 3:2 mixture of the corresponding bicyclo-[3.3.0]octan-3-one **39** and the spirocyclobutanone **40**. When **53** was subjected to the identical cyclization conditions, however, only the spirocyclobutanone adduct **54** was formed, without any evidence for the generation of the desired bicyclo[3.3.0]octan-3-one **55**.

Since the initial isolation and identification of the *Streptomyces* antibiotic pentalenolactone (**1**),[2] members of the pentalenane family of sesquiterpenes have continued to attract the attention of synthetic and bioorganic chemists. Over the last several years additional representives of this group of novel metabolites have been reported, including pentalenolactones G (**7**),[3] H (**8**),[4] and P (**9**),[5] pentalenic acid (**4**),[4] deoxypentalenic acid glucuronide (**3**),[5] and the parent hydrocarbon itself, pentalenene (**2**) (Chart I).[6] Our own group has reported the isolation and structure determination of two further metabolites, pentalenolactones E (**5**)[7] and F (**6**).[8] Many of these latter substances are believed to be intermediates or shunt metabolites in the biosynthesis of pentalenolactone. In biosynthetic investigations already reported from this laboratory we have established the mevalonoid origin of the pentalenolactones,[9] demonstrated that pentalenene is a precursor of **4**, **5**, **6**, and **8**,[10] and isolated a cell-free enzyme preparation which catalyzes the conversion of farnesyl pyrophosphate to pentalenene.[10]

Scheme I



At the same time, the considerable synthetic challenge presented by these novel polyquinane systems has inspired a number of interesting synthetic approaches. In an extensive investigation of biomimetic cyclizations of humulene and its derivatives, Matsumoto and Shirahama have prepared several members of the pentalenane family of metabolites. These studies, which are of considerable theoretical importance, have resulted in the total synthesis of pentalenene[11] and, by an extension of the basic ring-forming methodology, more oxidized derivatives such as

(1) National Institutes of Health Research Career Development Award, 1978–1983.

(2) (a) Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1970**, 4901. (b) Duchamp, D. J.; Chidester, C. G. *Acta Crystallogr., Sect. B* **1972**, *B28*, 173. (c) Takeuchi, S.; Ogawa, Y.; Yonehara, H. *Tetrahedron Lett.* **1969**, 2737. (d) Koe, B. K.; Sobin, B. A.; Celmer, W. D. *Antibiot. Annu.* **1957**, 672. (e) Hartmann, S.; Neeff, J.; Heer, U.; Mieke, D. *FEBS Lett.* **1978**, *93*, 339.

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(5) Takahashi, S.; Takeuchi, M.; Arai, M.; Seto, H.; Otake, N. *J. Antibiot.* **1983**, *36*, 226.

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(7) Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973.

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(10) Cane, D. E.; Tillman, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 122.

(11) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2869.

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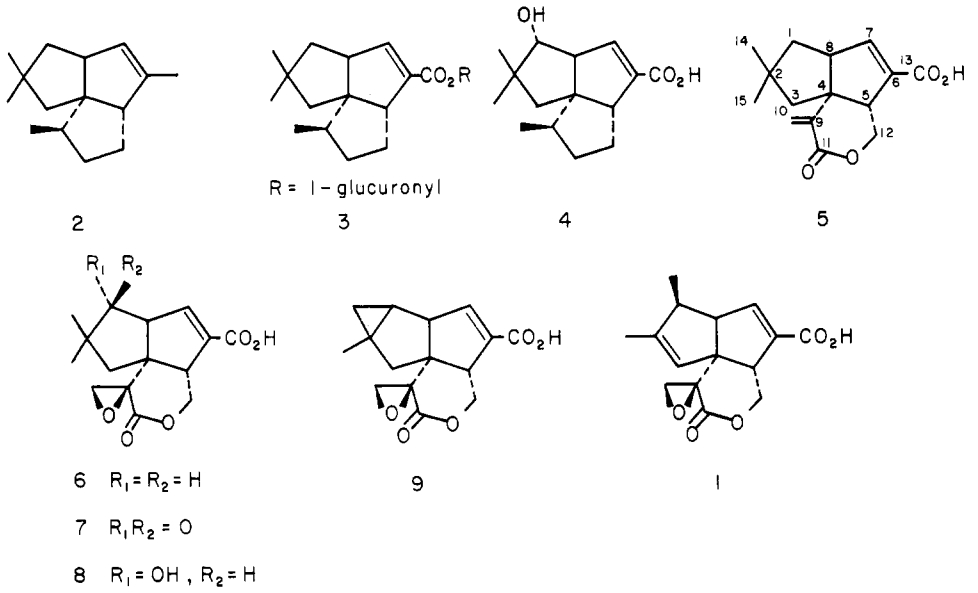
Chart I



2 3 4 5 9 1

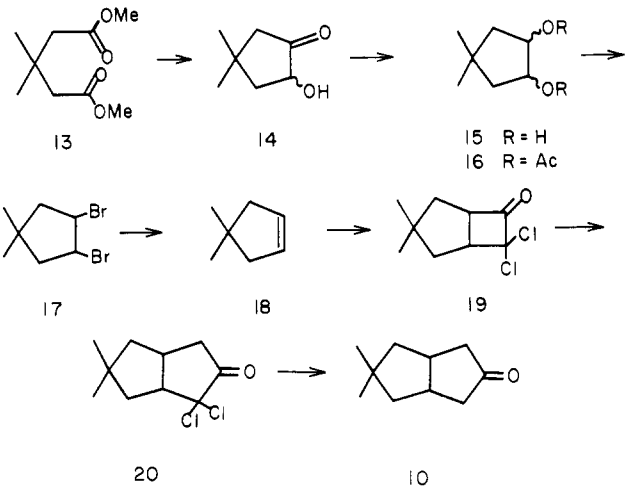
pentalenic acid[12] and pentalenolactones E and F.[13] Meanwhile, Danishefsky has reported the first total synthesis of pentalenolactone itself by an approach which exploits Diels–Alder methodology for the control of several key stereocenters and the elaboration of the δ-lactone ring system.[14] An alternative synthesis of **1** was achieved by Schlessinger who relied on selective acylation and alkylation of enolate ions to generate a bicyclo[3.3.0]octane system appropriately functionalized for introduction of the fused δ-lactone ring.[15] Yet another approach to the δ-lactone system was demonstrated by Paquette in the course of the total synthesis of pentalenolactone E by way of a suitably constructed bicyclo-[3.3.0]octan-3-one derivative.[16] We now report our own synthetic efforts in this area which have resulted in the synthesis of the methyl esters of (±)-pentalenolactones E and F, based on the use of an intramolecular carbene insertion sequence to elaborate the key δ-lactone ring with complete stereochemical and high regiochemical control.

Synthesis of Pentalenolactones E and F

In designing our approach to pentalenolactone E we set as our first target the preparation of the bicyclic ketone 7,7-dimethylbicyclo[3.3.0]octan-3-one (**10**) (Scheme I). Using this symmetric intermediate as a template we planned to append a (diazoacetoxy)methyl substituent α to the carbonyl group, taking advantage of the strong thermodynamic preference for exo substitution. Intramolecular C–H insertion by the derived acylcarbene species was expected to effect selective closure to the desired δ-lactone (**11**). While this work was in progress, the conversion of the ketoacetal **12** to pentalenolactone E was reported by Paquette.[16] We therefore chose to link up our own synthesis of **5** with the latter intermediate.

Intramolecular C–H insertions by acyl carbenes have not been extensively used in organic synthesis.[17] Nonstabilized carbenes are relatively nonselective in intermolecular reactions with unactivated C–H bonds.[18] The corresponding α-keto- or α-carboalkoxy-substituted carbenes are significantly less reactive

Scheme II



while exhibiting enhanced selectivity, showing a slight preference for tertiary over secondary over primary centers. Bis(carboethoxy)methylene, generated photochemically from the corresponding diazomalonate, has been reported to show a 12–20:8:1 preference for reaction with 3°, 2°, and 1° C–H bonds, respectively. One of the earliest applications of intramolecular C–H insertions in synthetic chemistry was Corey's preparation of a β-lactam from the corresponding α-diazo amide.[19] Wenkert has examined the reactions of α-diazo ketones in the formation of several model compounds and has studied the effects of various soluble and insoluble copper catalysts as well as the use of inert Freon solvent.[20] Several groups have exploited intramolecular acylcarbene insertions into 3° C–H bonds in the preparation of tetracyclic diterpenes.[21] Most recently, Ratcliffe has described the use of $Rh_2(OAc)_4$ as a catalyst for the intramolecular reaction of α-diazo β-keto esters with N–H bonds leading to the formation of carbapenems and carbacephems.[22] Nonetheless the relative lack of selectivity and the often modest yields of desired products have

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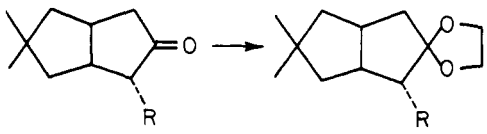
(22) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, 31.

Scheme III



10 R = H
21 R = CO_2Me
22 R = CO_2Me
23 R = CH_2OH

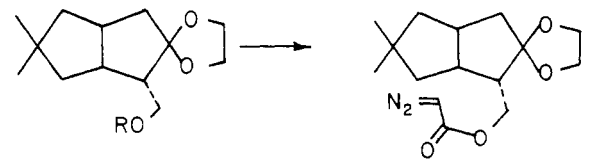
restricted the more general application of acylcarbene C–H insertion reactions. Although the intramolecular C–H insertion reaction already overcomes some of these obstacles by imposing significant geometric limitations on the choice of reactive centers open to the transiently generated acylcarbene species, we felt that even greater selectivity might be achieved by judicious design of the cyclization substrate.

The synthesis of 7,7-dimethylbicyclo[3.3.0]octan-3-one (**10**) was achieved in seven steps starting from dimethyl 3,3-dimethylglutarate (**13**) and using the cyclopentanone annulation method of Greene (Scheme II).[23] Treatment of **13** with sodium in liquid ammonia[24] gave a 76% yield of 4,4-dimethyl-2-hydroxycyclopentanone (**14**) which was reduced with lithium aluminum hydride to provide 4,4-dimethylcyclopentane-1,2-diol (**15**) in 88% yield. Initial attempts to convert this diol to the corresponding dibromide by using hydrogen bromide in glacial acetic acid in the presence of sulfuric acid[25] resulted primarily in the formation of the diacetate **16**. It was found that the formation of **16** could be avoided by the use of slightly wet hydrogen bromide–acetic acid solution. Thus heating a solution of the diol **15** in hydrogen bromide–acetic acid solution containing ca. 10% water and a catalytic amount of sulfuric acid for 8 h at 100 °C gave the desired dibromide **17** in 65% yield. Reductive elimination of bromine from **17** was effected by refluxing an ether solution in the presence of zinc–copper couple to generate 4,4-dimethylcyclopentene (**18**), which was not isolated but treated directly with dichloroketene[23] generated in situ by addition of trichloroacetyl chloride to the reaction mixture.[26] The resulting cycloadduct **19** was obtained in overall 91% yield, based on **17**. Ring expansion with diazomethane[23] afforded the α,α-dichlorobicyclo[3.3.0]octan-3-one derivative **20** in 91% yield. Reductive elimination of chlorine by zinc in acetic acid followed by chromatographic purification provided bicyclooctanone **10** in 65% yield.

Having prepared the desired bicyclooctanone, we turned our attention to the introduction of the (diazoacetoxy)methyl side chain. Treatment of bicyclic ketone **10** with 2 equiv of sodium hydride in the presence of excess dimethyl carbonate[27] gave **21** as a keto–enol mixture in 72% yield (Scheme III). Ketalization of **21** was effected by dioxolane exchange with 2-methyl-1,3-dioxolane in the presence of a catalytic amount of slightly wet BF_3–Et_2O[28] at 35 °C for 24 h. A single stereoisomer of **22** was obtained in 75% yield and assigned the more stable exo configuration on thermodynamic grounds. Lithium aluminum hydride reduction of the ester **22** then afforded a 64% yield of the hydroxymethyl derivative **23**.

In order to prepare the corresponding diazoacetate ester, the alcohol **23** was treated with glyoxalyl chloride tosylhydrazone and 2 equiv of triethylamine according to the method of House[29] and the product obtained was subjected to flash chromatographic purification (Scheme IV). Spectroscopic analysis of the isolated diazo ester indicated that it was contaminated with an unexpected

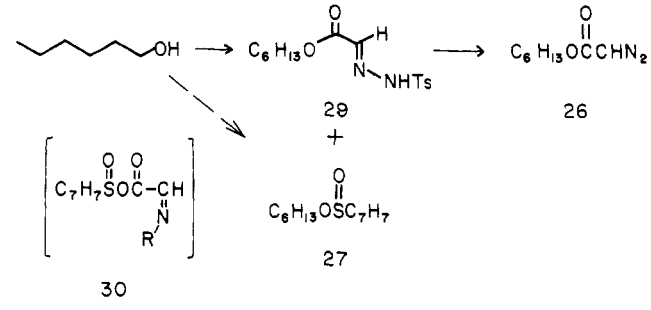
Scheme IV



23 R = H
25 R = TsNHN=CCO
28 R = $C_7H_7S(O)$

24

Scheme V



29 + 27

30

side product. Thus although the IR spectrum of **24** exhibited characteristic diazo ester absorbtions (2130 and 1700 cm^{-1} for –CH–N_2– and –CO–O–, respectively) and the mass spectrum showed a distinct peak at *m/e* 294 corresponding to the parent ion of the diazo ester **24**, the ^1H NMR spectrum contained additional resonances for aromatic protons.

In order to obtain the diazo ester **24** in pure form we explored several modifications of the acylation–elimination sequence. Use of only 1 equiv of triethylamine failed to stop the reaction at the acylation stage, yielding instead a mixture of the diazo ester and the unwanted side product. When sodium carbonate replaced triethylamine as base, acylation proceeded very slowly; the reaction was incomplete even after 2 days. On the other hand, the small amount of ester **25** obtained in this way furnished the pure diazo ester **24** upon treatment with triethylamine. At this point it became clear that the undesired side product was not formed during the decomposition of **25** to the diazo ester and that the problem might be solved if the glyoxalyl tosylhydrazone ester could be obtained in pure form. We therefore examined the acylation reaction itself, using *n*-hexyl alcohol as a model compound.

Reaction of *n*-hexyl alcohol with glyoxalyl chloride tosylhydrazone in the presence of triethylamine gave the diazo ester **26** accompanied by an aromatic ring-containing side product **27**, again as a mixture inseparable by chromatography (Scheme V). Unexpectedly, when the acylation was carried out in the presence of 2 equiv of 4-(dimethylamino)pyridine, only **27** was obtained. The IR spectrum of **27** indicated the absence of carbonyl and hydroxyl absorbtions. Analysis of the high-resolution mass spectrum (*m/e* 240.1206, parent) and 250-MHz ^1H NMR spectrum identified **27** as hexyl toluenesulfinate. Two doublets centered at δ 7.6 (2 H) and 7.33 (2 H) and a singlet at δ 2.43 (3 H) corresponded to a para-substituted aromatic residue with an attached methyl group and electron-withdrawing substituent. Two sets of doublets of triplets (J = 10 and 6 H) centered at δ 4.02 and 3.61 suggested the presence of two diastereotopic protons on an oxygen-bearing carbon, consistent with the presence of a chiral sulfite moiety. The analogous mixture of diastereomeric sulfinate esters **28** was obtained by treatment of the bicyclooctyl carbinol **23** with glyoxalyl chloride tosylhydrazone and 2 equiv of 4-(dimethylamino)pyridine. The ^1H NMR spectrum and thin-layer chromatographic behavior of **28** were identical with those of the previously observed aromatic side product of the preparation of the diazo ester **24**. The sulfinate esters **27** and **28** might result from reaction of hexanol or **23**, respectively, with *p*-toluenesulfinyl chloride or the mixed anhydride **30** generated under the reaction conditions. Thus toluenesulfinate released by the action of base on glyoxalyl chloride tosylhydrazone or on esters

(23) Greene, A. E.; Depres, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 4003.
(24) (a) Meinwald, J.; Lee, P. C. *J. Am. Chem. Soc.* **1960**, *82*, 699. (b) Rouse, R. S.; Tyler, W. E. *J. Org. Chem.* **1961**, 26, 3525. (c) Ryono, D. E.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, 98, 1889. (d) Schrapler, U.; Ruhlmann, K. *Chem. Ber.* **1964**, *97*, 1383.
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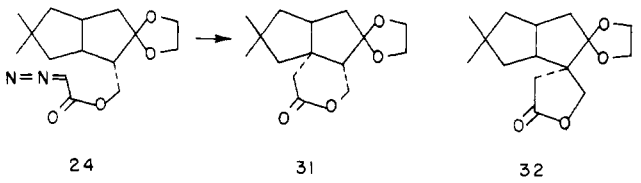
Scheme VI



25 or **29**, respectively, could react either with unreacted glyoxalyl chloride tosylhydrazone or with the derived diazoacetyl chloride to provide the mixed anhydride **30**. Reaction of **30** with chloride ion would then furnish *p*-toluenesulfinyl chloride.

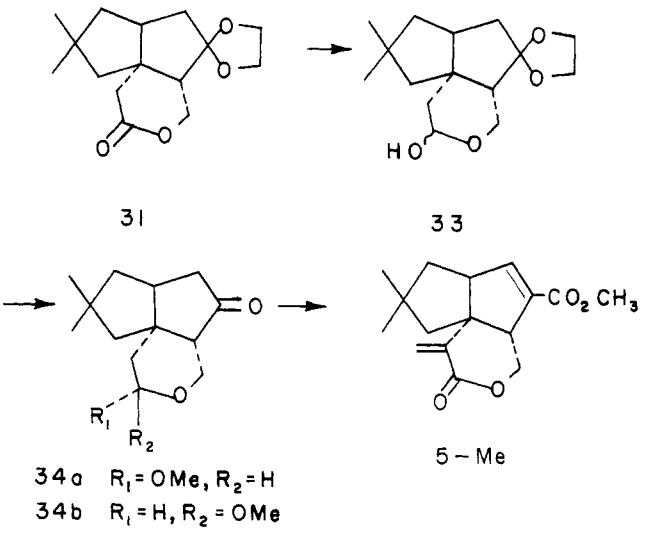
On the basis of the above results, it seemed reasonable to assume that acylation under neutral conditions might prevent the formation of the unwanted sulfinate ester. An initial attempt to effect esterification of glyoxylic acid tosylhydrazone in the presence of dicyclohexylcarbodiimide[30] failed to yield the desired ester. Takimoto[31] has recently reported that sterically hindered esters can be prepared from an alcohol and an acid chloride in the presence of silver cyanide. In fact, acylation of **23** with glyoxalyl chloride tosylhydrazone in the presence of silver cyanide proceeded smoothly to give the desired glyoxalyl ester **25**. Treatment of **25** with 1 equiv of triethylamine afforded the pure diazo ester **24** in 73% overall yield after chromatographic purification.

With the diazoacetate ester in hand, the stage was now set for the key intramolecular carbene insertion reaction at the unactivated C-1 bridgehead C–H bond to generate the δ-lactone ring. Competing carbene insertion at C-2 to generate the γ-lactone ring was expected to be disfavored due to steric hindrance by the adjacent ethylene ketal, while reaction at H-4, H-5, or the ketal carbinyl hydrogens would lead to 7- or 8-membered rings. Due to the puckering of the bicyclo[3.3.0]octane framework, all additional C–H bonds in the substrate would be geometrically inaccessible to the *exo*-acylcarbene residue. In the event, slow addition by motor-driven syringe of a solution of **24** to a refluxing suspension of $Rh_2(OAc)_4$ in Freon TF[20] (1,1,2-trichloro-1,2,2-trifluoroethane) effected the desired intramolecular carbene insertion to deliver **31** in 43–47% yield after chromatographic purification (Scheme VI). An additional 20-25% of two or three poorly resolved products was also obtained. Due to the difficulty in obtaining the individual components in pure form, the latter mixture was not further characterized, although IR analysis indicated the absence of any absorbtions corresponding to a γ-lactone.

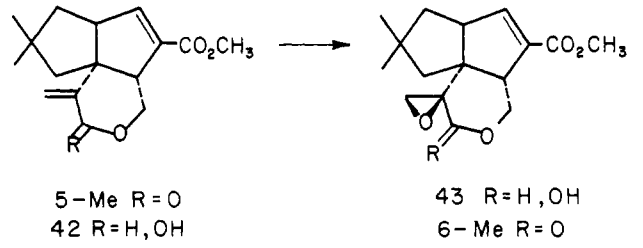
The structure of **31** was readily deduced from 250-MHz ^{1}H NMR studies with the aid of homonuclear decoupling. The carbinyl protons of the lactone ring appeared as a doublet at δ 4.21 (J = 6.8 Hz) which collapsed to a singlet upon irradiation at δ 2.15, while the triplet at δ 2.15 collapsed to a broad singlet upon irradiation at δ 4.21. These results indicated coupling between H-5 and H-11, thereby ruling out the alternative γ-lactone insertion product **32**. The IR spectrum of **31** exhibited a carbonyl absorption at 1755 cm^{-1} consistent with the presence of a δ-lactone. Structure **31** was also in full accord with the ^{13}C NMR spectrum.

Reduction of lactone **31** (Scheme VII) with diisobutylaluminum hydride gave the mixture of epimeric lactols **33** which were then deketalized by exchange with methyl ethyl ketone in the presence of BF_3–Et_2O. Treatment of the crude product thus obtained with acidic methanol gave a mixture of epimeric acetals (**34a,b**) in 72% overall yield after chromatographic purification. Examination of the 250-MHz ^{1}H NMR spectra of the individual acetals revealed that the anomeric proton resonance of the more polar isomer was shifted upfield (δ 4.22) relative to that of less polar isomer (δ 4.61). On the basis of reported upfield shift of the axial protons of analogous anomeric pairs,[32] the more polar isomer was assigned

Scheme VII



Scheme VIII



structure **34a**. These assignments were reinforced by complementary trends for the anomeric methoxyl protons. The ^{13}C NMR spectrum of **34a** was in agreement with that reported by Paquette,[16] although the configuration of the latter compound had not been assigned.

Since the conversion of one of the epimers of **34** to pentalenolactone E had already been described by Paquette, the formal synthesis of **5** was now complete. In the event, the conversion of our synthetic **34** to pentalenolactone E methyl ester was carried out both on the mixture of isomers and on the separated anomers as well, by use of the sequence developed earlier by Paquette. The IR and ^{1}H NMR spectra and the chromatographic properties of the synthetic pentalenolactone E methyl ester were identical by direct comparison with those of authentic pentalenolactone E methyl ester obtained by fermentation.[7] With dimethyl 3,3-dimethylglutarate as starting material, the synthesis of *dl*-pentalenolactone E methyl ester was thus achieved in 21 steps in an overall yield of 0.2%.

Pentalenolactone F methyl ester (**6**-Me) could be prepared from pentalenolactone E methyl ester by stereospecific epoxidation of the exocyclic double bond, using the method reported by Danishefsky for the synthesis of pentalenolactone.[14] Accordingly **5**-Me was reduced with diisobutylaluminum hydride to generate the lactol **35** (Scheme VIII). The product thus obtained was not purified but was used directly for the next step. The IR spectrum of crude **35** showed the presence of a hydroxyl group and the absence of lactone absorption. Epoxidation of **35** using the Sharpless procedure[33] gave **36** whose ^{1}H NMR spectrum indicated the absence of exocyclic methylene protons. Oxidation of **36** with Jones reagent followed by chromatographic purification afforded pure *dl*-pentalenolactone F methyl ester (**6**-Me) in 22% overall yield. The IR and ^{1}H NMR spectra of the synthetic pantalenolactone F methyl ester were identical with those of authentic material.[8] A trace amount of another product, presumably *epi*-pentalenolactone F methyl ester, was also isolated from the reaction mixture. Pentalenolactone F methyl ester could also be

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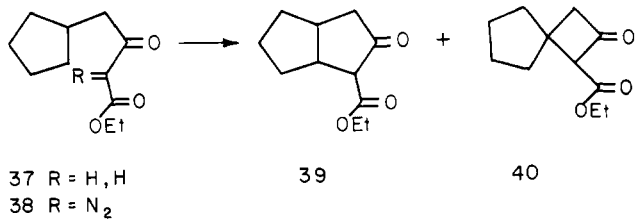
(33) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. G.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254.

Scheme IX



37 R = H,H
38 R = N_2

39 40

obtained directly from **5**-Me by treatment with basic hydrogen peroxide.[14] The latter reaction proceeded very slowly with predominant recovery of starting material even after 36 h. Small quantities of a 1:1 mixture of pentalenolactone F and *epi*-pentalenolactone F methyl esters were isolated and separated by preparative thin-layer chromatography.

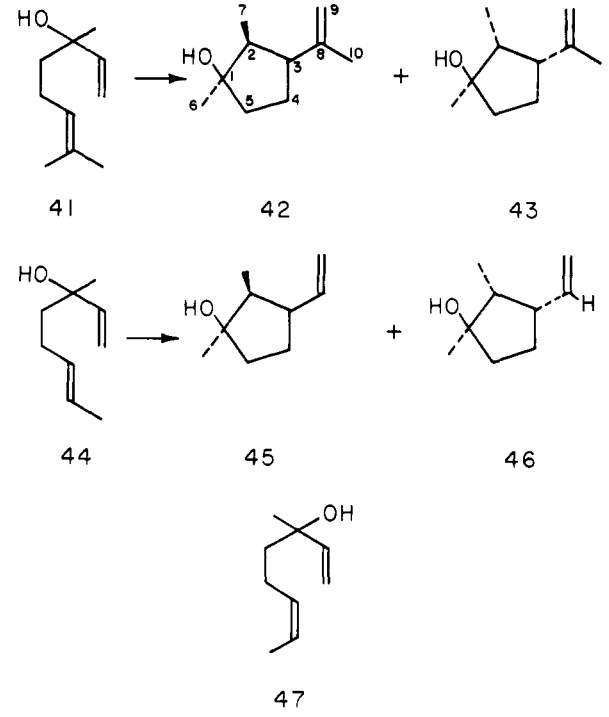
Approach to Pentalenolactone

In an effort to explore the generality of the acylcarbene insertion reaction as a useful tool for the construction of functionalized polyquinane systems, we have also attempted to use this tactic for the preparation pentalenolactone **1** itself. Our intention was to start with a suitably functionalized cyclopentane precursor and to append both the second cyclopentane ring and the δ-lactone by variations of the basic carbene insertion sequence. Although in the event this approach has failed, our results do provide some insight into the subtle interplay of substrate structure, product ring size, and competition between 2° and 3° sites in the determination of the outcome of the carbene insertion reaction.

We initially chose as our model system ethyl 4-cyclopentylacetoacetate (**37**), which was conveniently prepared in four steps from cyclopentylacetic acid. Exposure of **37** to tosyl azide and triethylamine in benzene effected diazo transfer[34] to generate the corresponding β-keto α-diazo ester **38** (78% yield) which served as the acylcarbene precursor (Scheme IX). Attempted thermal decomposition of **38** in Freon TF in the presence of a variety of copper catalysts, including copper sulfate, copper powder, and bis(hexafluoroacetylacetonato)diaquocopper(II), was uniformly disappointing, only starting material being recovered. On the other hand, although copper powder in boiling chlorobenzene catalyzed carbene formation, a complex mixture of only partially characterized products was formed. After evaluation of a number of catalysts, rhodium(II) acetate in refluxing Freon proved to be the catalyst of choice. Decomposition of diazo ester **38** at 50–55 °C in the presence of 0.25 mol % of rhodium(II) acetate afforded the desired bicyclo[3.3.0]octane derivative **39** along with the spirocyclobutanone **40** in a ratio of 1.5:1 and 83% combined yield. The keto ester **39** existed mainly in the enol form, as evidenced by ^{1}H NMR. Since the formation of **39** is favored on purely statistical grounds by 2:1, generation of the cyclobutane product by insertion into a 3° C–H bond is therefore seen to be favored kinetically over reaction at the 2° centers to give the cyclopentane derivative by a factor of 4:3. Nonetheless we were encouraged by the reasonable outcome of the model studies and turned our attention to the reactions of the more complex substrates.

Pentalenolactone differs from its cometabolites by the presence of a secondary methyl group and an allylic methyl in place of the more commonly encountered geminal methyl pair. The synthesis of the A ring of pentalenolactone is therefore considerably more challenging. The stereochemical problem presented by the secondary methyl group of **1** was solved by Danishefsky by a stereospecific reduction of an exo methylene double bond.[14] It appeared to us that an alternative solution to this problem might be based on the long-known intramolecular thermal ene reaction of linalool (**41**) (Scheme X).[35,36] In fact, in preliminary experiments we discovered that the stereospecificity of the latter reaction might be considerably improved by carrying out the required thermolysis in toluene at 290 °C, leading to a 10:1 mixture of plinols C (**42**) and D (**43**) uncontaminated by either of the trans isomers, plinols A and B.[37] Although pyrolysis of *trans*-norlinalool (**44**) under similar conditions resulted largely in dehydration and polymerization, pyrolysis of a dilute solution of **44** in toluene containing 10% diisopropylethylamine for 12 h at 290 °C led to the formation of *cis,cis*-1,2-dimethyl-3-vinylcyclopentanol (**45**) and *trans,cis*-1,2-dimethyl-3-vinylcyclopentanol (**46**) in a ratio of 4:1 in 50% combined yield after purification by chromatography.[38]

Scheme X



41 42 43

44 45 46

47

Table I. ^{13}C NMR Spectra of Linalool and Norlinalool Cyclization Products

C	49	52	50	53
1	80.2 (s)	80.3 (s)	82.6 (s)	82.4 (s)
2	45.7 (d)	46.9 (d)	47.4 (d)	49.5 (d)
3	48.9 (d)	46.9 (d)	48.3 (d)	45.5 (d)
4	25.4 (t)	28.3 (t)	24.3 (t)	27.2 (t)
5	39.4 (t)	40.5 (t)	37.8 (t)	38.5 (t)
6	29.5 (q)	27.2 (q)	25.4 (q)	24.7 (q)
7	9.4 (q)	9.5 (q)	11.0 (q)	11.4 (q)
8	146.8 (s)	142.4 (d)	146.3 (s)	140.6 (d)
9	110.6 (t)	113.5 (t)	109.9 (t)	114.3 (t)
10	23.3 (q)		23.5 (q)	

The gross structures of the ene reaction products were deduced from ^{1}H NMR and IR spectroscopic data. In order to assign the stereochemistry of these products, it was decided to compare their ^{13}C NMR spectral data with that of plinols C (**42**) and D (**43**). As summarized in Table I, the chemical shift for C-6 of plinol D is shifted upfield by about 4 ppm relative to the corresponding C-6 resonance in plinol C, due to the γ-effect of the adjacent C-7 methyl group in **43**. A similar upfield shift is also observed for C-6 of **46** compared to C-6 in **45**, indicating the structural sim-

(34) (a) Peace, B. W.; Carman, F.; Wulfman, D. S. *Synthesis* **1971**, 658. (b) Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. V, p 179.

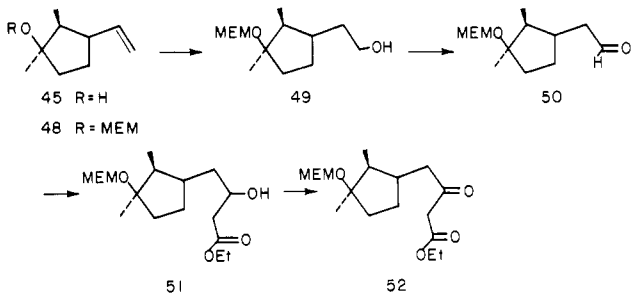
(35) (a) Ikeda, T.; Wataksuki, K. *J. Chem. Soc. Jpn.* **1936**, *57*, 425; *Chem. Abstr.* **1936**, *30*, 5937. (b) Strickler, H.; Ohloff, G.; Kovats, E. sz. *Helv. Chim. Acta* **1967**, *50*, 759. (c) Prickenhagen, W.; Ohloff, G.; Russel, R. K.; Roth, W. D. *Helv. Chim. Acta* **1978**, *61*, 2249.

(36) For a review of intramolecular ene reactions, see Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, 17, 476.

(37) Cane, D. E.; Sinsheimer, J., unpublished results.

(38) Pyrolysis of *cis*-norlinalool (**47**) gave rise to the same product mixture, **45** and **46**, but required higher temperature (325 °C) and longer reaction time (24 h). ^{13}C NMR studies of the reaction mixture obtained after heating **47** to 290 °C for 12 h suggested that isomerization to *trans*-norlinalool took place prior to cyclization. (Cane, D. E.; Burns, S., unpublished observations.)

Scheme XI



ilarity between plinol D and **46**. Furthermore the upfield chemical shifts (2 ppm) observed for C-1, C-2, and C-7 of plinol C and of **45** indicate the configurational similarity between the latter two substances. The major norlinalool pyrolysis product was therefore assigned as *cis,cis*-1,2-dimethyl-3-vinylcyclopentanol (**45**) and the minor isomer as *trans,cis*-1,2-dimethyl-3-vinylcyclopentanol (**46**).

The ene reaction products **45** and **46** differ only in the configuration of the tertiary hydroxyl group. Since this tertiary alcohol would eventually be converted to the required double bond of pentalenolactone, in principle, therefore, both isomers could be used for the eventual synthesis. Only **45**, however, was employed for the subsequent studies.

Having obtained the desired *cis,cis*-dimethylvinylcyclopentanol, the sequence of reactions shown in Scheme XI was employed for the conversion of **45** to β-keto ester **52**. Olefin **45** was protected as the MEM ether and subjected to hydroboration–oxidation to give the primary alcohol derivative **49** in 40% yield after chromatography. **49** was converted in turn to the corresponding aldehyde **50** in 76% yield by pyridinium chlorochromate oxidation.[39] Reaction of **50** with 2-lithioethyl acetate gave the diastereomeric alcohols **51** (72% yield) which were further oxidized with pyridinium chlorochromate to give the desired β-keto ester **52** in 57% yield after chromatographic purification.

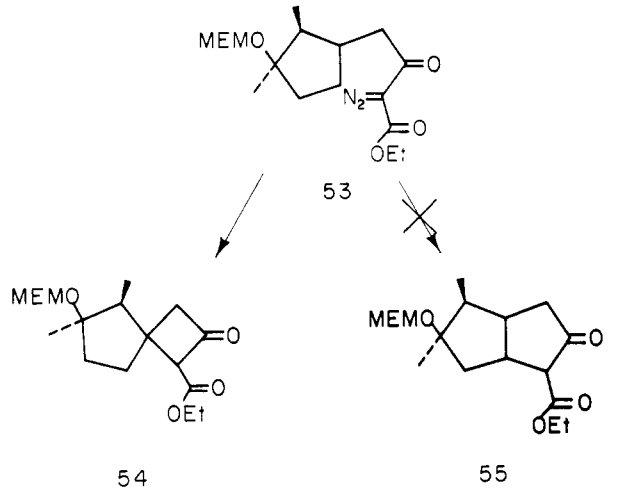
Treatment of β-keto ester **52** with tosyl azide and triethylamine gave the corresponding diazo ester **53** (52% yield). When **53** was heated in refluxing Freon TF in the presence of 0.25 mol % rhodium(II) acetate, conditions which had been found to favor formation of the bicyclo[3.3.0]octanone derivative in the model series, the undesired spirocyclobutanone **54** was unexpectedly obtained in 55% yield (Scheme XII). In fact, the desired bicyclo[3.3.0]octanone derivative **55** was not detected at all. Only minor amounts (10%) of an as yet unidentified side product were also isolated. The ^{1}H NMR spectrum of this latter compound showed the presence of an intact MEM group, as well as the tertiary and secondary methyl groups. On the other hand the characteristic signals of the ethyl group of the ester functionality were now absent. The corresponding IR spectrum exhibited absorptions in the carbonyl region (1760, 1740, 1660 cm^{-1}). The molecular ion peak was not observed in either the EI or CI mass spectrum. The structure of this minor product has not been assigned.

The reasons for the striking differences between the favorable outcome of the carbene insertion sequence in the model substrate and the complete absence of desired bicyclo[3.3.0]octanone derivative in the actual synthetic series is not at all apparent. It is possible that the combined 1,3-interactions of the MEM ether and the secondary methyl group hinder approach of the acylcarbene to the 2° C–H bond, thereby directing attack to the opposite face of the cyclopentane ring, on which only the 3° C-3 hydrogen is accessible, thus leading to the observed spirocyclobutanone.

In summary, we have explored the use of intramolecular carbene insertions of α-diazocarbonyl substrates as a strategy for the construction of polycyclic ring systems. Although the method proved to be of limited utility for the elaboration of functionalized

(39) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

Scheme XII



bicyclo[3.3.0]octanones, we have successfully applied this approach to the total synthesis of two sesquiterpene metabolites, pentalenolactones E and F.

Experimental Section

1,2-Dibromo-4,4-dimethylcyclopentane (17). A solution of 1 g (7.6 mmol) of diol **15**, 0.05 mL of concentrated H_2SO_4, 5 mL of glacial acetic acid, 30 mL of HBr–acetic acid (Eastman Kodak), and 3 mL of water was allowed to stir at room temperature for 8 h and then heated 4 h at 100 °C. An additional 10 mL of HBr–acetic acid was added and heating was continued for 4 h at 100 °C. The solution was cooled, poured into ice water and extracted with petroleum ether (bp 30–60 °C). The organic layer was washed successively with water and brine and dried over anhydrous sodium sulfate. Removal of the solvent followed by purification by flash chromatography (column diameter 30 mm, 5% ethyl acetate in hexanes) gave 1.3 g (65%) of **17**: bp 45–48 °C (0.35 mm) [lit.[24b] bp 65–67 °C (1 mm)]; ^{1}H NMR ($CDCl_3$) δ 4.60–4.28 (m, 2 H, BrCHCHBr), 2.65–1.55 (m, 4 H, methylene protons), and 1.21 (s, 6 H, 2-CH_3).

7,7-Dichloro-3,3-dimethylbicyclo[3.2.0]heptan-6-one (19). To a solution of 1 g (3.9 mmol) of dibromide **17** in 25 mL of ether was added 1 g of activated zinc. The mixture was refluxed for 12 h (bath temperature 50 °C), then cooled, and an additional 350 mg of activated zinc was added. To this mixture, under nitrogen, a solution of trichloroacetyl chloride (0.9 g, 4.9 mmol) and $POCl_3$ (0.75 g, 4.9 mmol) in 20 mL of ether was introduced during a period of 1 h. The mixture was refluxed for 5–6 h and stirred at room temperature for an additional 5–6 h, then filtered through a pad of Celite, the unreacted zinc being washed with ether. The filtrate was concentrated in vacuo to roughly 25% of its original volume and an equal volume of pentane was added. The solution was then stirred for a few minutes to precipitate the zinc salts, decanted from the residue, and washed successively with water, saturated sodium bicarbonate solution, and brine, before drying over anhydrous sodium sulfate. Removal of the solvent followed by distillation at reduced pressure afforded 0.75 g (90%) of **19**; bp (Kugelrohr) 90–95 °C (0.5 mm); IR (neat) 1805 cm^{-1} (ketone); ^{1}H NMR (250 MHz) ($CDCl_3$) δ 4.13 (m, 1 H, $CHCCl_2$), 3.47 (m, 1 H, CHCO), 2.03–1.68 (m, 4 H, methylene protons), 1.10 (s, 3 H, CH_3), and 0.98 (s, 3 H, CH_3); mass spectrum, *m/e* 206.0218 (calcd for $C_9H_{12}OCl_2$, 206.0265).

2,2-Dichloro-7,7-dimethylbicyclo[3.3.0]octan-3-one (20). To a flask containing 40 mL of 40% aqueous KOH and 40 mL of ether at 0 °C was slowly added 1.75 g (16.9 mmol) of nitrosomethylurea with swirling of the flask. After completion of the reaction the mixture was transferred to a separatory funnel. The separated ether layer containing diazomethane was dried over potassium hydroxide pellets for 10 min. The dry diazomethane solution was slowly added to a solution of **19** (0.75 g, 3.6 mmol) in ether, followed by 2 mL of methanol. After 20 min remaining diazomethane was destroyed with a few drops of acetic acid. Removal of the solvent followed by distillation at reduced pressure gave 0.7 g (91%) of **20**: bp (Kugelrohr) 100–105 °C (0.3 mm); IR (CCl_4) 1765 and 1780 cm^{-1} (ketone); ^{1}H NMR (250 MHz) ($CDCl_3$) δ 3.40–3.30 (m, 1 H, $CHCCl_2$), 3.11–2.86 (m, 2 H, bridgehead H and 1 H of $-CH_2CO$), 2.13–1.95 (m, 2 H), 1.83–1.75 (m, 1 H), 1.39–1.24 (m, 2 H), 1.09 (s, 3 H, CH_3), and 1.02 (s, 3 H, CH_3); mass spectrum, *m/e* 220.0417 (calcd for $C_{10}H_{14}OCl_2$, 220.0422).

7,7-Dimethylbicyclo[3.3.0]octan-3-one (10). To a solution of **20** (1.44 g, 6.5 mmol) in 14 mL of glacial acetic acid was added 4 g of zinc dust.

After the initial exothermic reaction the mixture was heated to 70 °C for 2 h. The reaction mixture was cooled and passed through a column of silica gel and eluted thoroughly with pentane. The clear solution thus obtained was washed with water, sodium bicarbonate solution, and brine and dried over anhydrous sodium sulfate. Removal of the solvent followed by purification by flash chromatography (column diameter 30 mm, 10% ethyl acetate in hexanes) afforded 0.64 g (64.5%) of **10** as an oil: IR (neat) 1740 cm^{-1} (ketone); ^1H NMR (250 MHz) ($CDCl_3$) δ 2.86 (m, 2 H, bridgehead hydrogens), 2.52 (dd, J = 18.5 and 9 Hz, 2 H, $-CHCOCH$), 2.06 (dd, J = 18.5 and 5 Hz, 2 H, $CHCOCH$), 1.85 (dd, J = 13.5 and 6.7 Hz, 2 H, $CHCCH$), 1.24 (dd, J = 13.5 and 8.4 Hz, 2 H, $-CHCCH-$), 1.09 (s, 3 H, CH_3), and 1.01 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 220.66 (s, CO), 48.93 (t, 2 C, CCOC), 44.94 (t, 2 C, CH_2CCH_2), 40.77 (s, quaternary carbon), 38.75 (d, 2 C, bridgehead carbons), 29.77 (q, CH_3), and 28.38 (q, CH_3); mass spectrum, m/e 152.1200 (calcd for $C_{10}H_{16}O$, 152.1201).

2-Carbomethoxy-7,7-dimethylbicyclo[3.3.0]octan-3-one (21). To a stirred suspension of sodium hydride (150 mg of 50% dispersion in mineral oil, 3 mmol, washed with pentane to remove oil) in 2 mL of anhydrous dimethyl carbonate was added a solution of 200 mg (1.3 mmol) of **10** in 0.5 mL of dimethyl carbonate containing one drop of absolute ethanol. The mixture was stirred for 15 min at 25 °C and then heated at 70 °C for 1 h. After cooling to room temperature, the mixture was poured into a saturated solution of ammonium chloride (20 mL) and extracted with ether. The ether layer was washed with cold water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash chromatography (column diameter 20 mm, 10% ethyl acetate in hexanes) afforded 0.20 g (72%) of the keto ester **21** as oil: IR (CCl_4) 1755 (ketone), 1730 (ester), 1660 (congugated ester), 1620 cm^{-1} (conjugated double bond); ^1H NMR (250 MHz) ($CDCl_3$) δ 10.33 (s, enol, OH), 3.75 and 3.73 (two singlets for $COOCH_3$ due to keto–enol mixture), 3.52–2.62, 2.28–2.13, 1.97–1.72, and 1.42–1.10 (series of multiplets, 9 H including enol OH), and 1.09, 1.02, 1.00, and 0.93 (4 singlets for geminal methyl groups due to keto–enol mixture); mass spectrum, m/e 210.1255 (calcd for $C_{12}H_{18}O_3$, 210.1256).

2-Carbomethoxy-3-(ethylenedioxy)-7,7-dimethylbicyclo[3.3.0]octane (22). A solution of **31** (0.2 g, 0.95 mmol) in 4 mL of 2-ethyl-2-methyl-1,3-dioxolane[40] containing 0.04 mL of slightly wet BF_3–Et_2O[28] (20:1 BF_3–Et_2O/water, v/v) was stirred at 35 °C for 24 h. The solution was diluted with ether (20 mL) and washed successively with water, sodium bicarbonate solution, and brine. Drying over anhydrous sodium sulfate, removal of the solvent, and flash chromatography (column diameter 20 mm, 10% ethyl acetate in hexanes) afforded 180 mg (75%) of **22**: IR (neat) 1745 cm^{-1} (ester); ^1H NMR (250 MHz) ($CDCl_3$) δ 4.03–3.81 (m, 4 H, OCH_2CH_2O), 3.69 (s, 3 H, $COOCH_3$), 3.81–2.66 (m, 3 H, bridgehead hydrogens and $HCCOOCH_3$), 2.24 (dd, J = 13.35 and 9 Hz, 1 H), 1.93–1.21 (m, 5 H), 1.05 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3); mass spectrum, m/e 254.1530 (calcd for $C_{14}H_{22}O_4$, 254.1518).

3-(Ethylenedioxy)-2-(hydroxymethyl)-7,7-dimethylbicyclo[3.3.0]octane (23). Reduction of ester **22** (180 mg, 0.7 mmol) with lithium aluminum hydride (36 mg, 0.94 mmol) as described for **14**, followed by flash chromatography (column diameter 20 mm, 30% ethyl acetate in hexanes) gave the alcohol **23** (102 mg, 64%): IR (neat) 3450 cm^{-1} (OH); ^1H NMR (250 MHz) ($CDCl_3$) δ 3.98–3.88 (m, 4 H, OCH_2CH_2O), 3.68 (m, 2 H, CH_2OH), 2.65–2.48 (m, 3 H), 2.08 (dd, J = 13.5 and 8.5 Hz, 1 H), 1.94 (m, 1 H), 1.79–1.64 (m, 2 H), 1.47 (dd, J = 13.2 and 6 Hz, 1 H), 1.23 (m, 2 H), 1.06 (s, 3 H, CH_3), and 0.90 (s, 3 H, CH_3); ^{13}C NMR δ 120.90 (s), 64.62 (t), 64.14 (t), 61.90 (t), 53.69 (d), 48.85 (t), 47.88 (t), 42.75 (s), 42.17 (d), 41.57 (t), 38.42 (d), 28.96 (q), and 27.22 (q); mass spectrum, m/e 226.1581 (calcd for $C_{13}H_{22}O_3$, 226.1569).

Hexyl *p*-Toluenesulfinate (27). To a stirred solution of hexyl alcohol (50 mg, 0.49 mmol) and glyoxalyl chloride tosylhydrazone (264 mg, 1 mmol) in 2 mL of methylene chloride at 0 °C was added slowly a solution of 4-(dimethylamino)pyridine (120 mg, 1 mmol) in methylene chloride (1 mL). The mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature. The solvent was removed and the residual liquid was treated with 2 mL of benzene and thoroughly mixed with 0.5 g of Florisil and filtered. Evaporation of the solvent followed by flash chromatography (column diameter 10 mm, 10% ethyl acetate in hexanes) gave 92 mg (79%) of sulfinic ester **27**: ^1H NMR (250 MHz) ($CDCl_3$) δ 7.6 (d, J = 6.5, 2 H, aromatic CH), 7.33 (d, J = 6.5 Hz, 2 H, aromatic CH), 4.02 (dt, J = 10 and 6 Hz, 1 H, $-CHHO-$), 3.61 (dt, J = 10 and 6 Hz, $-CHHO-$), 2.43 (s, 3 H, CH_3), 1.72–1.15 (m, 8 H, methylene protons), and 0.87 (t, J = 6.5 Hz, CH_3); mass spectrum m/e 240.1206 (calcd for $C_{13}H_{20}O_2S$, 240.1184.)

3-(Ethylenedioxy)-2-((*p*-tolylsulfinyl)methyl)-7,7-dimethylbicyclo-[3.3.0]octane (28). By following the procedure described for **27**, the mixture of sulfinic esters **28** was prepared. Thus reaction of 25 mg (0.11 mmol) of **23** with 57.5 mg (0.22 mmol) of acid chloride and 27 mg (0.22 mmol) of 4-(dimethylamino)pyridine followed by flash chromatography (column diameter 10 mm, 10% ethyl acetate in hexanes) gave **28** (30.19 mg, 75%): ^1H NMR (250 MHz)($CDCl_3$) δ 7.6 (d, J = 6.5 Hz, 2 H, aromatic CH), 7.31 (d, J = 6.5 Hz, 2 H, aromatic CH), 4.2–3.45 (m, 6 H, OCH_2CH_2O- and $-CH_2OSO-$), 2.43 (s, 3 H, CH_3), 2.7–1.09 (m, 9 H), and 1.04 (s), 1.03 (s), 0.87 (s), and 0.85 (s) (four singlets integrating for six protons, 2 CH_3); mass spectrum, m/e 364.1707 (calcd for $C_{20}H_{28}O_4S$, 364.1708).

2-((Diazoacetoxy)methyl)-3-(ethylenedioxy)-7,7-dimethylbicyclo-[3.3.0]octane (24). A magnetically stirred mixture of **23** (200 mg, 0.88 mmol), glyoxalyl chloride tosylhydrazone (230 mg, 0.88 mmol), and silver cyanide (235 mg, 1.8 mmol) was heated at 80 °C for 1.5–2 h. The mixture was cooled, filtered, and evaporated. The residual oil was dissolved in 10 mL of methylene chloride and to this stirred mixture at 0 °C was added 120 mg (1.18 mmol) of triethylamine. After this mixture was stirred at 0 °C for 2 h, the solvent was evaporated. The residue was treated with 20 mL of hexanes–ethyl acetate (9:1) and stirred for 10 min, and the solution was decanted from the residue. The residue was again treated with hexane–ethyl acetate (10 mL) and stirred, and the supernatant was decanted as above. The combined solution was evaporated, and the residue on purification by flash chromatography (column diameter 20 mm, 10% ethyl acetate in hexanes) gave 193 mg of the diazo ester **24** (73%): IR (neat) 2130 ($=N_2$) and 1700 cm^{-1} (OCO—); ^1H NMR ($CDCl_3$) δ 4.73 (s, 1 H, $—OCOCH=N_2$), 4.43–4.08 (m, 2 H, $—OCH_2$), 3.9 (s, 4 H, $—OCH_2CH_2O—$), 2.96–1.26 (m, 9 H), 1.06 (s, 3 H, CH_3), and 0.91 (s, 3 H, $—CH_3$); mass spectrum, m/e 294.1602 (calcd for $C_{15}H_{22}O_4N_2$, 294.1579).

Octahydro-5-(ethylenedioxy)-8,8-dimethyl-2-oxopentaleno[1,6*a*-*c*]-pyran (31). A solution of 193 mg (0.65 mmol) of the diazo ester **24** in 200 mL of Freon TF was added slowly over a 3 h period by means of a mechanical syringe to a refluxing suspension of rhodium(II) acetate (100 mg, 0.22 mmol) in 200 mL of Freon. After 15 min the reaction mixture was cooled and filtered through a fritted-glass funnel packed with Celite (to remove rhodium(II) acetate). Removal of the solvent followed by flash chromatography (column diameter 20 mm, 20% ethyl acetate in hexanes) afforded 78 mg (43%) of **31**: IR (CCl_4) 1755 cm^{-1} (lactone); ^1H NMR (250 MHz) ($CDCl_3$) δ 4.21 (d, J = 6.8 Hz, 2 H, $-OCH_2$, collapsed to a singlet on irradiation of δ 2.15), 3.97–3.79 (m, 4 H, $-OCH_2CH_2O-$), 2.59 (s, 2 H, $-COCH_2-$), 2.38 (m, 1 H, bridgehead hydrogen), 2.15 (t, J = 6.8 Hz, 1 H, tertiary hydrogen, collapsed to a broad singlet on irradiation at δ 4.21), 2.04 (dd, J = 13.7 and 8.7 Hz, 1 H), 1.82–1.58 (m, 5 H), 1.05 (s, 3 H, $-CH_3$), and 1.01 (s, 3 H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 172.7 (s), 117.96 (s), 66.58 (t), 64.42 (t), 64.19 (t), 56.32 (t), 54.23 (d), 51.00 (s),48.09 (d), 47.30 (t), 42.62 (t), 40.72 (s), 39.60 (t), 29.85 (q), and 28.10 (q); mass spectrum, m/e 266.1516 (calcd for $C_{15}H_{22}O_4$, 266.1518).

Octahydro-2-methoxy-8,8-dimethylpentaleno[1,6*a*-*c*]pyran-5(6*H*)-one (34a,b). To a stirred solution of **31** (50 mg, 0.18 mmol) in 1 mL of dry ether at 0 °C was added 0.2 mL of diisobutylaluminum hydride (1 M solution in hexane, 0.2 mmol) over a period of 15 min. After 1 h, 2 mL of saturated sodium chloride solution was added and stirring was continued for another 20 min. The mixture was then poured into 5 mL of water, extracted with ether, and dried over anhydrous magnesium sulfate. The crude product obtained after evaporation of the solvent was reacted with ethyl methyl ketone (10 mL) and 0.1 mL of BF_3–Et_2O–H_2O (BF_3–Et_2O:H_2O, 20:1) at room temperature for 24 h. The mixture was then taken up in ether, washed with water, sodium bicarbonate, and brine, and dried over anhydrous magnesium sulfate. The crude product obtained after removal of the solvent was treated with 5 mL of methanolic hydrochloric acid (methanol:HCl, 30 mL:1 drop) for 12 h at room temperature and then concentrated, poured into 5 mL of water, and extracted with ether. The ether solution was washed with water, sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent followed by flash chromatography (column diameter 10 mm, 10% ethyl acetate in hexanes) afforded in the order of elution the acetals **34b** and **34a** (combined yield 32 mg, 72%). Although a complete separation of the acetals was not achieved by flash chromatography, a few fractions of pure **34a** and pure **34b** were obtained. **34a**: IR (CCl_4) 1745 cm^{-1} (ketone); ^1H NMR (250 MHz) ($CDCl_3$) δ 4.38 (dd, J = 12.3 and 1.9 Hz, $-OCHH-$), 4.22 (dd, J = 9 and 2 Hz, 1 H, CH_3OCHCH_2), 3.61 (dd, J = 12.3 and 4.5 Hz, 1 H, $-OCHH-$), 3.41 (s, 3 H, $-OCH_3$), 2.5–1.25 (series of m, 10 H), 1.11 (s, 3 H, $-CH_3$), and 1.08 (s, 3 H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 216.60, 100.45, 59.71, 55.66, 54.12, 53.57, 49.23, 47.75, 44.41, 41.28, 40.62 (2 C), 31.16 and 30.49. **34b**: IR (CCl_4) 1745 cm^{-1} (ketone); ^1H NMR (250 MHz) ($CDCl_3$) δ 4.61 (br s, 1 H, CH_3OCHO), 4.01 (d, J = 12.5 Hz, 1 H, $-OCHH-$), 3.77 (dd, J = 12.5 and 5 Hz, 1 H $-OCHH-$), 3.33 (s, 3 H, $-OCH_3$), 2.49–1.24 (m, 10 H), 1.10 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3);

(40) Dauben, H. J., Jr.; Loken, B.; Ringold, H. J. *J. Am. Chem. Soc.* **1954**, *76*, 1359.

^{13}C NMR ($CDCl_3$) δ 217.50, 97.60, 54.90, 54.41, 53.29, 53.20, 47.06, 46.13, 44.62, 40.38, 40.29, 38.70, 31.40, and 30.86; mass spectrum, *m/e* 238.1549 (calcd for $C_{14}H_{22}O_3$, 238.1569).

Pentalenolactone F Methyl Ester (6-Me). To a solution of pentalenolactone E methyl ester (**5**-Me) (6.5 mg, 0.023 mmol) in 0.5 mL dry ether under nitrogen at −78 °C was added diisobutylaluminum hydride (0.04 mL of 1 M solution, 0.04 mmol) over a period of 5 min. The solution was stirred for 25 min and 0.2 mL of a saturated aqueous sodium bicarbonate solution was added. The resulting solution was stirred at −78 °C for 10 min and allowed to warm to room temperature. Then 0.5 mL of water was added to this mixture which was extracted with ether and dried over anhydrous sodium sulfate. Removal of the solvent gave 6 mg of the lactol **35** which was used directly for the next step.

A solution of the lactol **35**, vanadyl acetylacetonate (0.5 mg), and *tert*-butyl hydroperoxide (6 μL, 0.05 mmol) in 0.5 mL of dry benzene was heated under reflux for 35 min. Saturated aqueous sodium bisulfite (0.5 mL) was added, and the mixture was extracted with ether and dried over anhydrous sodium sulfate. Removal of the solvent gave the epoxylactol **36** which was used directly for the next step.

36 was dissolved in 1 mL of acetone and cooled to 0 °C, and the solution was treated with Jones reagent (0.7 M solution) until a reddish color persisted (ca. 50 μL). After 20 min at 0 °C, the mixture was then extracted with ether, washed successively with water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent followed by purification by preparative thin-layer chromatography (silica gel, 30% ethyl acetate in hexanes, R_f 0.2) afforded 1.5 mg (overall 21% yield) of pentalenolactone F methyl ester, whose spectroscopic properties and chromatographic behavior were identical by direct comparison with an authentic sample of **6**-Me: IR (CCl_4); 1765 (lactone), 1715 (ester), and 1630 cm^{-1} (double bond); ^1H NMR (250 MHz) ($CDCl_3$ δ 6.85 (br s, 1 H, CH=CCOOCH$_3$), 4.76 (dd, J = 11.8 and 2.2 Hz, 1 H, –CHHO–), 4.43 (dd, J = 11.8 and 2.8 Hz, 1 H, –CHHO–), 3.77 (s, 3 H, –COOCH$_3$), 3.44 (m, 2 H, allylic hydrogens), 3.03 (d, J = 5.2 Hz, ^1H of epoxide methylene), 2.99 (d, J = 5.2 Hz, 1 H, 1 H of epoxide methylene), 1.76–1.43 (m, 4 H, methylene protons), 1.03 (s, 3 H, –CH$_3$), and 1.01 (s, 3 H, –CH$_3$).

(Methylvinyl)carbinyl 3-Oxobutyrate. To a well-stirred solution of 3-buten-2-ol (18 g, 0.25 mol) and sodium methoxide (0.25 g, 4.6 mmol) in 20 mL of toluene under nitrogen at 20 °C was added dropwise 23.1 g (0.275 mol) of freshly distilled diketene over a period of 2 h. The reaction temperature was maintained at 25–30 °C by external cooling. The mixture was further stirred for 5 h and then taken up in ether and washed successively with dilute sulfuric acid, saturated sodium bicarbonate solution, water, and brine. After the mixture was dried over anhydrous sodium sulfate and the solvent was evaporated, distillation at reduced pressure afforded 31.8 g (81%) of (methylvinyl)carbinyl 3-oxobutyrate: bp 107–108 °C (35 mm) [lit.[41] bp 92–93 °C (18 mm)]; IR ($CHCl_3$) 1720 (br, ketone and ester) and 1630 cm^{-1} (double bond); ^1H NMR ($CDCl_3$) δ 6.16–4.95 (m, 4 H), olefinic protons and –OCH–), 3.4 (s, 2 H, –COCH$_2$CO–), 2.21 (s, 3 H, CH$_3$CO–), 1.33 (d, J = 6 Hz, 3 H, –CH$_3$).

***trans*-5-Hepten-2-one.** A solution of 20 g of the above-prepared acetoacetate ester in 500 mL of hexane was added to the glass-lined reaction chamber of a Parr pressure reactor (Model 4522, capacity 2 L). The system was evacuated and flushed with nitrogen. The temperature of the reactor was maintained at 200 °C for 12 h with stirring. Removal of the solvent followed by distillation yielded 9.3 g (65%) of *trans*-5-hepten-2-one: bp 152–155 °C [lit[41] bp 152–155 °C]; IR (neat) 1720 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 5.50–5.30 (m, 2 H, olefinic protons), 2.60–2.18 (m, 4 H, —CH$_2$CH$_2$—), 2.01 (s, 3 H, CH$_3$CO), 1.57 (m, 3 H, H, =CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ 207.48 (s), 129.15 (d), 125.23 (d), 42.92 (t), 29.20 (q), 26.29 (t), 17.25 (q).

3-Methyl-1,6-heptadien-3-ol (44). To a solution of *trans*-5-hepten-2-one (6 g, 0.054 mol) in 200 mL of methylene chloride under nitrogen at 0 °C was added 195 mL (0.214 mol) of 1.1 M vinylmagnesium bromide in tetrahydrofuran. The mixture was stirred at room temperature for 2–3 h. The Grignard complex was then decomposed by careful addition of a saturated solution of ammonium chloride and filtered. The filtrate was extracted with ether, washed successively with saturated ammonium chloride solution, EDTA (sodium salt) solution (3 times), water, and brine. Drying over anhydrous sodium sulfate followed by removal of the solvent and distillation gave 5.82 g (77%) of **44**: bp 82–85 °C (35–38 mm); IR (CCl_4) 3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 6.17–4.92 (m, 5 H, olefinic protons), 2.47–1.39 (m, 8 H, —CH$_2$CH$_2$—, =CCH$_3$, and OH), 1.24 (s, 3 H, —CH$_3$); ^{13}C NMR ($CDCl_3$) δ 145.27 (d), 131.49 (d), 124.90 (d), 111.70 (t), 73.27 (s), 42.10 (t), 27.80 (q), 27.30 (t), 17.9 (q).

(1*R,2*S**,3*R**)-1,2-Dimethyl-3-vinylcyclopentanol (45) and (1*R**,2*R**,3*S**)-1,2-Dimethyl-3-vinylcyclopentanol (46).** A solution of **44** (0.5 g) in 5 mL of toluene containing 10% diisopropylethylamine was placed in a glass tube which had been preconditioned with ammonium hydroxide to remove traces of acid from the glass. After being sealed under a vacuum, the tube was heated in a pyrolysis oven at 290 °C for 12 h. The solvent was removed by rotary evaporation, and the combined residues derived from 1 g of **44** were subjected to medium-pressure LC (E. Merck prepacked column, size "C" 440-37, 10% ethyl acetate in hexanes) to afford, in order of elution, 0.42 g of **45** and 0.102 g of **46** as oils (combined yield 50%).

45: IR (neat) 3400 (br, OH), 1635 cm^{-1} (double bond); ^1H NMR ($CDCl_3$) δ 6.28–5.68 (m, 1 H, olefinic proton), 5.15–4.76 (m, 2 H, olefinic protons), 2.86–2.53 (m, 1 H, allylic proton), 2.08–1.58 (m, 6 H, –CH$_2$CH$_2$–, –CHCH$_3$, and OH), 1.28 (s, 3 H, –CH$_3$), 0.88 (d, J = 7 Hz, 3 H, –CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ 142.4 (d), 113.5 (t), 80.2 (s), 46.9 (d, 2 C), 40.52 (t), 28.3 (t), 27.18 (q), 9.54 (q); mass spectrum, *m/e* 140.1202 (calcd for $C_9H_{16}O$, 140.1201).

46: IR (neat) 3360 (br, OH), 1635 cm^{-1} (double bond); ^1H NMR ($CDCl_3$) δ 6.21–4.83 (m, 3 H, olefinic protons), 3.26–2.91 (m, 1 H, allylic proton), 2.16–1.53 (m, 6 H, –CH$_2$CH$_2$–, –CHCH$_3$, and OH), 1.25 (s, 3 H, –CH$_3$), 0.77 (d, J = 7 Hz, 3 H, –CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ 140.6 (d), 114.3 (t), 82.4 (s), 49.5 (d), 45.5 (d), 38.5 (t), 27.2 (t), 24.7 (q), 11.4 (q); mass spectrum, *m/e* 140.1191 (calcd for $C_9H_{16}O$, 140.1201).

(1*R,2*S**,3*R**)-1,2-Dimethyl-3-vinylcyclopentyl (Methoxyethoxy)methyl Ether (48).** To a stirred solution of **45** (200 mg, 1.42 mmol) and diisopropylethylamine (1.85 g, 14.3 mmol) in methylene chloride (5 mL) at 60–65 °C under nitrogen was added (methoxyethoxy)methyl (MEM) chloride (0.53 g, 4.2 mmol) in three equal portions at 1-h intervals. The mixture was allowed to stir for an additional 2 h, cooled, poured into water (10 mL), and extracted with ether. The ether solution was washed successively with cold water, 0.1 N HCl, and brine. Drying over anhydrous sodium sulfate and evaporation of the solvent gave 0.323 g of MEM ether **48**: IR (CCl_4) 1635 (weak) cm^{-1} (double bond); ^1H NMR ($CDCl_3$) δ 6.23–5.53 (m, 1 H, olefinic proton), 5.03–4.65 (m, 4 H, –OCH$_2$O and olefinic protons), 3.86–3.45 (m, 4 H, –OCH$_2$CH$_2$O–), 3.40 (s, 3 H, –OCH$_3$), 2.90–2.36 (m, 1 H, allylic H), 2.2–1.40 (m, 5 H, –CH$_2$CH$_2$– and –CHCH$_3$), 1.30 (s, 3 H, CH$_3$), 0.85 (d, J = 7 Hz, 3 H, –CHCH$_3$). The parent ion was not observed in the high-resolution mass spectrum; *m/e* of the fragment [M − $C_4H_9O_3$(O-MEM)]$^+$, 123.1178 (calcd for C_9H_{15}, 123.1173).

2-[(1′*R,2′*S**,3′*R**)-2′,3′-Dimethyl-3′-((methoxyethoxy)methoxy)cyclopentyl]ethanol (49).** To a stirred solution of **48** (320 mg, 1.4 mmol) in 1 mL of dry tetrahydrofuran at 0 °C under nitrogen was added 3 mL of BH_3–THF solution (2.0 M, 6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h, and 1 mL of water was added slowly. After the reaction mixture was cooled to 0 °C, 1.5 mL of 3 N sodium hydroxide solution and 1.5 mL of hydrogen peroxide solution (30% H_2O_2 solution, 13.2 mmol) were added and the mixture was stirred for 1 h at 50 °C. The reaction mixture was cooled, poured into water, and extracted with ether, and the ether layer was washed with water and brine. Drying over anhydrous sodium sulfate, evaporation of the solvent, and chromatography of the residue using medium-pressure LC (E. Merck prepacked column, size "B" 310-25, 50% ethyl acetate in hexanes) afforded 0.14 g (40%) of **49**: IR (CCl_4) 3600, 3440 cm^{-1} (–OH); ^1H NMR ($CDCl_3$) δ 4.77 (s, 2 H, –OCH$_2$O–), 3.82–3.50 (m, 6 H, OCH$_2$CH$_2$O– and CH$_2$OH), 3.38 (s, 3 H, –OCH$_3$), 2.35–1.40 (m, 9 H, methylene and methine protons and –OH), 1.29 (s, 3 H, –CH$_3$), 0.88 (d, J = 7 Hz, 3 H, CHCH$_3$). The parent ion was not observed in the high-resolution mass spectrum; *m/e* of the fragment [M − $C_4H_{10}O_3$(MEMOH)]$^+$, 140.1191 (calcd for $C_9H_{16}O$, 140.1201).

2-[(1′*R,2′*S**,3′*R**)-2′,3′-Dimethyl-3′-((methoxyethoxy)methoxy)cyclopentyl]acetaldehyde (50).** To a stirred mixture of dry pyridinium chlorochromate (420 mg, 1.95 mmol) in dry methylene chloride (5 mL), **49** (300 mg, 1.2 mmol) was added in one lot. Stirring was continued for 3 h at room temperature. To this mixture, ether (25 mL) was added and the supernatant solution was decanted from the black gum which was thoroughly washed with ether. The combined extracts were passed through a bed of Florisil (10 g). Removal of the solvent gave 228 mg of the aldehyde **50** which was used immediately for the subsequent reaction: IR (CCl_4) 2710, 1720 cm^{-1} (aldehyde); ^1H NMR ($CDCl_3$) δ 9.83 (m, 1 H, CHO), 4.75 (s, 2 H, OCH$_2$O), 3.77–3.47 (m, 4 H, OCH$_2$CH$_2$O–), 3.39 (s, 3 H, –OCH$_3$), 2.54 (br s, 2 H, CH$_2$CHO), 2.16–1.13 (m, 6 H, methylene and methine protons), 1.28 (s, 3 H, –CH$_3$), 0.88 (d, J = 7 Hz, 3 H, –CHCH$_3$).

Ethyl 4-[(1′*R,2′*S**,3′*R**)-2′,3′-Dimethyl-3′-((methoxyethoxy)methoxy)cyclopentyl]-3-hydroxybutyrate (51).** A 25-mL flask was charged with 8 mL of dry tetrahydrofuran containing 0.3 g (2.9 mmol) of diisopropylamine and the solution was cooled to −78 °C before addition of 0.88 mL (2.2 mmol) of 2.5 M *n*-butyllithium under nitrogen. After 10

(41) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.

min at −78 °C, the solution was cooled to −90 °C and ethyl acetate (0.21 g, 2.3 mmol) in 1 mL of tetrahydrofuran was added dropwise over a period of 15 min. The reaction mixture was stirred for an additional 15 min at −90 °C and warmed to −78 °C, and 0.54 g (2.2 mmol) of the aldehyde **50** in 2 mL of tetrahydrofuran was added. After 30 min, 5 mL of saturated ammonium chloride solution was added and the mixture was allowed to warm to room temperature. The tetrahydrofuran was evaporated and the residual mixture was extracted with ether. The ether extracts were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.53 g of the diastereomeric alcohols **51**: IR (neat) 3500 (OH), 1730 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 4.76 (s, 2 H, OCH_2O–, 4.25 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 3.66–3.60 (m, 5 H, $-OCH_2CH_2O$, –CHOH), 3.4 (s, 3 H, $-OCH_3$), 2.4 (m, 2 H, $-CH_2COO$), 2.26–1.5 (m, 9 H, methylene, methine and –OH protons), 1.3 (t, J = 7 Hz, 3 H, $-OCH_2CH_3$, 1.3 (s, 3 H, $-CH_3$), 0.86 (d, J = 7 Hz, 3 H, $-CHCH_3$).

Ethyl 4-[(1′*R,2′*S**,3′*R**)-2′,3′-Dimethyl-3′-((methoxyethoxy)methoxy)cyclopentyl]-3-oxobutyrate (52).** Oxidation of **51** (0.53 g, 1.6 mmol) with pyridinium chlorochromate (1.1 g, 5.1 mmol) in the manner described for the preparation of **50**, followed by purification by flash chromatography (column diameter 20 mm, 40% ethyl acetate in hexanes) gave 0.32 g (57%) of the β-keto ester **52**: IR (neat) 1730 (ester), 1720 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 4.73 (s, 2 H, OCH_2O), 4.20 (q, J = 6.5 Hz, OCH_2CH_3), 3.8–3.53 (m, 4 H, $-OCH_2CH_2O$–), 3.44 (s, 2 H, $-COCH_2CO$–), 3.40 (s, 3 H, $-OCH_3$), 2.63 (d, J = 2 Hz, 2 H, $-OCH_2CH$), 2.30–1.13 (m, 6 H, methylene and methine protons), 1.28 (t, J = 6.5 Hz, 3 H, OCH_2CH_3), 1.28 (s, 3 H, $-CH_3$), 0.85 (d, J = 7 Hz, 3 H, $-CHCH_3$). The parent ion was not observed in the high-resolution mass spectrum; m/e of the fragment [M − $C_4H_9O_3$(OMEM group)]$^+$, 225.1504 (calcd for $C_{13}H_{21}O_3$, 225.1490).

2-Cyclopentylethanol. To a stirred suspension of lithium aluminum hydride (9.58 g, 0.25 mol) in dry tetrahydrofuran (50 mL), cyclopentylacetic acid (6.48 g, 0.05 mol) in dry tetrahydrofuran (20 mL) was added dropwise. The reaction mixture was refluxed for 2 h and stirred at room temperature for 12 h. The mixture was then diluted with 100 mL of ether and a saturated solution of sodium sulfate was added dropwise until the formation of a white granular precipitate. The organic layer was decanted and the residue was thoroughly washed with ether. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent gave 5.5 g of 2-cyclopentylethanol: IR (neat) 3610, 3315 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 3.66 (t, J = 6 Hz, 3 H, $-CH_2OH$), 2.2 (br s, OH), 2.15–1.40 (m, 11 H, methylene and methine protons).

2-Cyclopentylacetaldehyde. Oxidation of 2-cyclopentylethanol (5.4 g, 0.047 mol) with pyridinium chlorochromate (16.2 g, 0.075 mol) in the manner described above afforded 3.3 g of the aldehyde: IR (neat) 2715, 1725 cm^{-1} (aldehyde); ^1H NMR ($CDCl_3$) δ 9.7 (m, 1 H, CHO), 2.60–2.20 (m, 2 H, $-CH_2CHO$), 2.0–1.40 (m, 9 H, methylene and methine protons).

Ethyl 4-Cyclopentyl-3-hydroxybutyrate. The reaction of the 2-cyclopentylacetaldehyde (1.63 g, 14.5 mmol) with 2-lithioethyl acetate, prepared from ethyl acetate (1.4 g, 16 mmol), diisopropylamine (2 g, 19.8 mmol), and n-butyllithium (5.81 mL of 2.5 M solution, 14.5 mmol) as described above, gave 2.2 g of ethyl 4-cyclopentyl-3-hydroxybutyrate: IR (neat) 3480 (br, OH), 1730 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 4.11 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.90 (m, 1 H, –OCHCOO–), 3.46 (br s, 1 H, –OH), 2.42 (m, 2 H, $-OCOCH_2$), 2.26–1.4 (m, 11 H, methylene and methine protons), 1.26 (t, J = 7 Hz, 3 H, CH_3CH_2O).

Ethyl 4-Cyclopentyl-3-oxobutyrate (37). Oxidation of ethyl 4-cyclopentyl-3-hydroxybutyrate (2.2 g, 11 mmol) with pyridinium chlorochromate (7.1 g, 33 mmol) as described above followed by distillation at reduced pressure afforded 1.73 g (79%) of the β-keto ester **37**: bp 68–72 °C (0.5 mm); IR (neat) 1720 (br) cm^{-1} (ketone and ester); ^1H NMR ($CDCl_3$) δ 4.21 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.43 (s, 2 H, $COCH_2CO$), 2.66–2.5 (m, 2 H, $-CH_2CO$), 2.2–1.5 (m, 9 H, methylene and methine protons), 1.28 (t, J = 7 Hz, 3 H, $-CH_3$).

Ethyl 4-Cyclopentyl-2-diazo-3-oxobutyrate (38). A solution of tosyl azide (2.02 g, 10.2 mmol), triethylamine (1.3 g, 12.8 mmol), and the β-keto ester **37** (1.7 g, 8.58 mmol) in 10 mL of dry benzene was allowed to stir at room temperature for 3 h at which time a solid precipitated. After stirring 15 h at room temperature, the mixture was filtered and the solid on the filter washed with cold benzene. The combined solutions were concentrated by rotary evaporation, diluted with hexane (100 mL), and filtered. Removal of the solvent followed by flash chromatography (column diameter 40 mm, benzene) afforded diazo ester **38** (1.5 g, 78%): IR (neat) 2140 (=N_2), 1715 (ester), 1650 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 4.3 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 2.91 (d, J = 7 Hz, 2 H, CH_2CO–), 2.4–1.5 (m, 9 H, methylene and methine protons), 1.33 (t, J = 7 Hz, 3 H, $-CH_2CH_3$).

Optimized Conditions for the Carbene Insertion Reaction. A solution of 100 mg (0.44 mmol) of diazo ester **38** in 100 mL of Freon TF (1,1,2-trichloro-1,2,2-trifluoroethane) was added slowly over a 3-h period by means of a mechanical syringe to a refluxing suspension of rhodium(II) acetate (50 mg, 0.11 mmol) in 100 mL of Freon TF. After 15 min the reaction mixture was cooled and filtered through a fritted-glass funnel packed with Celite (to remove rhodium(II) acetate). Removal of the solvent followed by flash chromatography (column diameter 10 mm, 5% ethyl acetate in hexanes) afforded, in order of elution, 43 mg (49%) of cyclopentanone derivative **39** and 30 mg (34.3%) of spirocyclobutanone **40**. **3-Carbethoxybicyclo[3.3.0]octan-2-one (39)**: IR (neat) 1750 (ketone), 1720 (ester), 1655 (conjugated ester), 1620 cm^{-1} (double bond); ^1H NMR ($CDCl_3$) δ 10.44 (br s, enol OH), 4.21, 4.18 (two quartets due to keto–enol mixture, 2 H, OCH_2CH_3), 3.66–1.46 (m, 11 H including enol OH, methylene and methine protons), 1.3, 1.27 (two triplets due to keto–enol mixture, 3 H, $-OCH_2CH_3$); mass spectrum, m/e 196.1101 (calcd for $C_{11}H_{16}O_3$, 196.1099). **3-Carbethoxyspiro[3.4]octan-2-one (40)**: IR (neat) 1790 (ketone), 1725 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 4.18 (q, J = 6.5 Hz, 2 H, OCH_2CH_3), 3.86 (d, ^4J = 1.9 Hz, 1 H, –OOCCHCOCH–), 2.97 (m, 2 H, CH_2CO), 1.98–1.48 (m, 8 H, methylene protons), 1.30 (t, J = 6.5 Hz, 3 H, CH_3CH_2O); mass spectrum, m/e 196.1109 (calcd for $C_{11}H_{16}O_3$, 196.1099).

Ethyl 4-[(1′*R,2′*S**,3′*R**)-2′,3′-Dimethyl-3′-((methoxyethoxy)methoxy)cyclopentyl]-2-diazo-3-oxobutyrate (53).** The reaction of the β-keto ester **52** (0.25 g, 0.75 mmol) with tosyl azide (109 mg, 1 mmol) as described for the preparation of **38**, followed by flash chromatography (column diameter 20 mm, 10% ethyl acetate in hexane), afforded 140 mg (52%) of the diazo ester **53**: IR (neat) 2130 (=N_2), 1725 (ester), 1660 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ 4.8 (s, 2 H, $-OCH_2O$–), 4.3 (q, J = 6 Hz, 2 H, $-OCH_2CH_3$), 3.8–3.5 (m, 4 H, $-OCH_2CH_2O$–), 3.4 (s, 3 H, $-OCH_3$), 3.01 (m, 2 H, –CO–, CH_2–), 2.76–1.56 (m, 6 H, methylene and methine protons), 1.35 (t, J = 6 Hz, 3 H, OCH_2CH_3), 1.30 (s, 3 H, $-CH_3$), 0.91 (d, J = 6 Hz, 3 H, $-CHCH_3$).

(4*R,7*R**,8*S**)-3-Carbethoxy-7,8-dimethyl-7-((methoxyethoxy)methoxy)spiro[3.4]octan-2-one (54).** A solution of 110 mg (0.43 mmol) of the diazo ester **53** in 100 mL of Freon TF was added slowly over a 3-h period by means of a mechanical syringe to a refluxing suspension of rhodium(II) acetate (50 mg, 0.11 mmol) in 100 mL of Freon TF. After 15 min the reaction mixture was cooled and filtered through a fritted-glass funnel packed with Celite. Removal of the solvent followed by flash chromatography (column diameter 10 mm, 20% ethyl acetate in hexanes) afforded, in order of elution, 10 mg (10%) of an unidentified side product and 55 mg (55%) of spirocyclobutanone **54**: IR (CCl_4) 1790 (ketone), 1730 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 4.73 (s, 2 H, $-OCH_2O$–), 4.2 (q, J = 6 Hz, 2 H, $-OCH_2CH_3$), 3.73–3.6 (m, 5 H, $-OCH_2CH_2O$ and –COCHCOO), 3.37 (s, 3 H, $-OCH_3$), 3.00–1.50 (m, 7 H, methylene and methine protons), 1.32 (s, 3 H, $-CH_3$), 1.32 (t, J = 6 Hz, 3 H, $-OCH_2CH_3$), 1.01 (d, J = 7 Hz, 3 H, $-CHCH_3$). The parent ion was not observed in the high-resolution mass spectrum; m/e of the fragment [M − $C_4H_9O_3$(OMEM group)]$^+$, 223.1343 (calcd for $C_{13}H_{19}O_3$, 223.1334).

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Registry No. (±)-**5**-Me, 79732-66-4; (±)-**6**-Me, 89163-62-2; **10**, 91084-91-2; **13**, 19184-67-9; **14**, 54639-78-0; **15**, 66606-40-4; **17**, 91084-92-3; (±)-**19**, 91084-93-4; (±)-**20**, 91084-94-5; (±)-**21**, 91084-95-6; (±)-**22**, 91084-96-7; (±)-**23**, 91084-97-8; (±)-**24**, 91084-98-9; **27**, 74698-01-4; (±)-**28**, 91084-99-0; (±)-**31**, 91110-53-1; (±)-**34a**, 79732-65-3; (±)-**34b**, 91176-81-7; **35**, 91085-00-6; **36**, 91085-01-7; **37**, 68104-99-4; **38**, 91085-02-8; **39**, 91085-03-9; **40**, 91085-04-0; (±)-**44**, 67151-93-3; (±)-**45**, 91085-05-1; (±)-**46**, 91176-82-8; (±)-**48**, 91085-06-2; (±)-**49**, 91085-07-3; (±)-**50**, 91085-08-4; **51**, 91085-09-5; (±)-**52**, 91085-10-8; (±)-**53**, 91085-11-9; (±)-**54**, 91085-12-0; glyoxalyl chloride tosylhydrazone, 14661-69-9; (methylvinyl)carbinyl 3-oxobutyrate, 91085-13-1; 2-cyclopentylethanol, 766-00-7; 2-cyclopentylacetaldehyde, 5623-81-4; ethyl 4-cyclopentyl-3-hydroxybutyrate, 91085-14-2; trichloroacetyl chloride, 76-02-8; hexyl alcohol, 111-27-3; 3-buten-2-ol, 598-32-3; diketene, 674-82-8; *trans*-5-hepten-2-one, 1071-94-9; cyclopentaneacetic acid, 1123-00-8.