19 in a ratio of 1:1.5 (^{1}H NMR analysis).

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Registry No. 8, 27491-70-9; 10, 937-31-5; 12, 28289-83-0; (*E*)-13, 80907-77-3; (*Z*)-13, 80907-78-4; 14, 55944-43-9; 16, 104-88-1; 17, 555-16-8; 18, 873-73-4; 3-phenyl-1-propyne, 10147-11-2; 2-ethynylfuran, 2-ethynylfuran; 4-methoxyphenylethyne, 123-11-5; 1,2-diphenylethyne, 501-65-5; (*E*)-4,8-dimethylnona-3,7-dien-1-yne, 71869-03-9; (*Z*)-4,8-dimethylnona-3,7-dien-1-yne, 80907-79-5; (*E*)-3-methyl-4-phenyl-3-buten-1-yne, 80907-80-8; (*E*)-2-methyl-3-phenyl-2-propenal, 15174-47-7; 1-phenyl-1-propyne, 673-32-5; acetophenone, 98-86-2; 4-nitroacetophenone, 100-19-6; 2-ethylhexanal, 123-05-7; 2-phenylethanal, 122-78-1; 2-furaldehyde, 98-01-1; 4-onethoxybenzaldehyde, 123-11-5; (*E*)-3-phenyl-2-propenal, 104-55-2; (*E*)-3,7-dimethyl-2,6-octadienal, 141-27-5; (*Z*)-3,7-dimethyl-2,6-octadienal, 106-26-3.

Total Synthesis of (±)-Modhephene and Its Epimer, (±)-Epimodhephene

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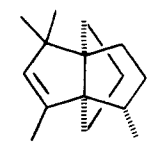
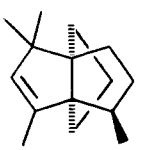
This report presents three synthetic approaches to (±)-modhephene (1α) and (±)-epimodhephene (1β) from enones **10**, **11**, and **14**, the overall yield of modhephene being 10%, 7%, and 1.7%, respectively. The approaches converge upon formation of [3.3.3]propellenone (**9**), the latter derived from acid-catalyzed rearrangement of tricyclic octenones **8** and **12**. β,γ-Unsaturated ketones **8** and **12**, in turn, were prepared from enones **10** and **11** by [2 + 2] photoaddition of 1,2-dichloroethylene and subsequent dehalogenation. Enone **14**, on the other hand, was transformed into the tricyclic octenone **12** via a similar photoaddition–dehalogenation sequence followed by conversion of the ester moiety to a methyl group. Elaboration of propellenone (**9**) to modhephene (1α) and its epimer (1β) was then accomplished via (a) an alkylative 1,3-carbonyl transposition (methyllithium, Jones oxidation), (b) conjugate addition with lithium dimethylcuprate, (c) high-temperature Wittig olefination (methyltriphenylphosphonium bromide, potassium *tert*-amylate in toluene at 92 °C), and (d) isomerization of the exocyclic olefin (*p*-TsOH in dichloromethane) to afforded (±)-modhephene (1α) and its C(6) epimer (1β). Finally, a discussion of the Wiesner model as it pertains to the stereoselectivity in the [2 + 2] photoaddition of acetylene and dichloroethylene to enones **10**, **11**, and **14** is also presented.

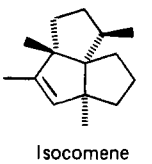
In 1978 Zalkow and colleagues[2] isolated a new cyclopentanoid sesquiterpene (1α) from hexane extracts of



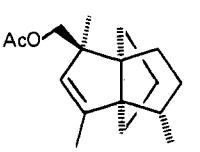
Modhephene
(1α)



Epimodhephene
(1β)



Isocomene
(2)



(3)

rayless goldenrod (*Isocoma wrightii*), a plant indigenous to the southwestern United States, known for its toxicity to cattle and sheep,[3] and from which Zalkow, a year earlier, had isolated the closely related sesquiterpene isocomene (**2**).[4] Given the trivial name modhephene, the structure including absolute configuration was established rigorously via a single-crystal X-ray analysis of a diol prepared via cis hydroxylation.[2] Central to the derived structure was a fused network of cyclopentane rings, the characteristic feature of the triquinane family of compounds, other members of which now include such natural products as pentalenolactone,[5] hirsutene,[6] hirsutic acid,[7] and coriolin.[8] Modhephene, however, was unique in that it was the first

(1) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Cancer Institute Career Development Awardee, 1980–1985.

(2) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D. *J. Chem. Soc., Chem. Commun.* **1978**, 420.

(3) Zalkow, L. H.; Burke, N.; Cabat, G.; Grula, E. A. *J. Med. Chem.* **1962**, *5*, 1342.

(4) (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 453. For recent synthesis see: (b) Chatterjee, S. *Ibid.* **1979**, 620. (c) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493. (d) Paquette, L. A.; Han, Y.-K. *J. Org. Chem.* **1979**, *44*, 4014. (e) Pirring, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. (f) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103.

(5) Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chiduster, C. G.; *Tetrahedron Lett.* **1970**, 4901. Also see: Takeuchi, S.; Ogawa, Y.; Yonehara, H. *Ibid.* **1969**, 2737. For a synthesis see: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Bergman, E.; Shuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536.

(6) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195. For synthesis see: Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1979**, *101*, 6116. Green, A. E. *Tetrahedron Lett.* **1980**, 3059. Hudlicky, T.; Kutchan, T.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351.

(7) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Scott, A. I. *Tetrahedron* **1967**, *23*, 476. Comer, F. W.; Trotter, J. *J. Chem. Soc. B* **1966**, *11*. For synthesis see: Sakan, F.; Hashimoto, H.; Ichihara, A.; Shirohama, H.; Matsumoto, T. *Tetrahedron Lett.* **1971**, 3703. Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Ibid.* **1971**, 1829; **1972**, 2053. Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Ibid.* **1974**, 3745. Hayanao, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1978**, 1991. Trost, B. M.; Shuey, C. D.; DiNinno F., Jr.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284.

(8) Takashi, S.; Naganawa, H.; Inuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. For a synthesis of coriolin see: Danishefsky, S.; Zamboni, M.; Kahn, M.; Etheredge, S. J. *J. Chem. Soc.* **1980**, *102*, 2097.

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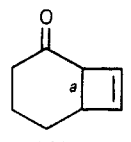
naturally occurring carbocylic compound to have the [3.3.3]propellane skeleton. In fact, until Bohlmann isolated acetoxymodhephene (3) in 1979 from *Liabum eggersii*,[9] modhephene was the only naturally occurring sesquiterpene of the propellane class.

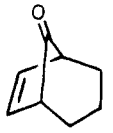
In view of the novel carbon skeleton, modhephene presented itself as a challenging synthetic target. In this, a full report, we document the details of the first[10] total synthesis of modhephene (1α) as well as its epimer, epimodhephene (1β). We note in advance that during the course of this effort *three* convergent approaches modeled after a common photochemical theme have been achieved. Two routes are short and highly efficient (i.e., proceed in 10% and 7% overall yield); however, only one demonstrated, at best, modest stereoselectivity. Finally, we present stereochemical information on several [2 + 2] photocycloaddition reactions (i.e., enones with dichloroethylene) which is in general accord with the Wiesner hypothesis.[11] The degree of stereoselectivity, however, is by no means as high as that observed with allene, thus suggesting that allene is indeed a special olefin.

Results and Discussion

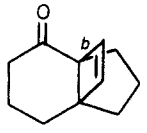
(i) A Strategy for Construction of Modhephene. From the retrosynthetic perspective, construction of the propellane nucleus of modhephene must be the central thrust to any viable synthetic strategy. Here, we found precedent in the early work of Cargill on the acid-catalyzed isomerization of β,γ-unsaturated ketones.[12] In particular, Cargill demonstrated that acid treatment of *bicyclic* ketones such as **4** afford exclusively bicyclo[3.2.1]octenones



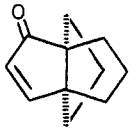
(4)



(5)



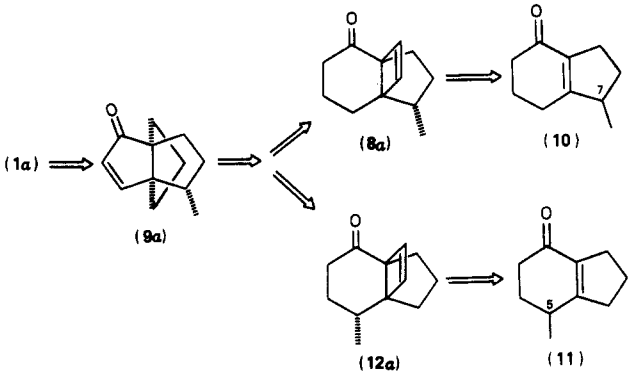
(6)



(7)

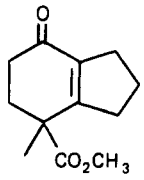
(i.e., **5**), while *tricyclic* systems **6** isomerize to [3.3.3]propellanes (**9**), the former by a process involving migration of the central bond (a), the latter via migration of a peripheral bond (b).[13] Ring contraction driven by rehybridization of the carbonyl then leads to the observed ketones.[12a-c]

Scheme I

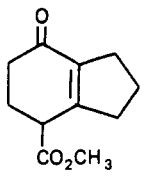


The rearrangement **6** → **7** appeared ideal for construction of the carbon framework of modhephene in that after similar isomerization of an appropriately substituted methyl derivative, the derived propellenone **9a** could easily be transformed into modhephene via a few straightforward synthetic operations (Scheme I).

Initially two tricyclic ketones (**8a** and **12**) were envisioned as potential substrates for the Cargill rearrangement. Each was expected to be readily available via [2 + 2] photoaddition of an etheno bridge to bicyclic enones **10** and **11**, respectively. It should be noted that the location of the methyl substituent [i.e., at C(5) or C(7)] on the bicyclic framework is irrelevant, except for stereochemistry, in that execution of the Cargill rearrangement would afford the same propellenone (**9a**) and thereby establish a point of convergence. Finally, tricyclic ketone **10** was envisioned to be readily available via the method of Piers,[14] while **11** could be prepared from either of two vinylogous β-keto esters (i.e., **13** and **14**).

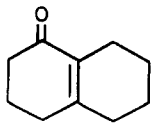


(13)

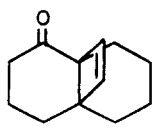


(14)

Concerning the photoaddition of the etheno bridge, two synthons were considered. Undoubtedly the most direct way would be to employ acetylene. Significantly, Dalton and Cargill effected such a transformation with a similar substrate, Δ^9-octalone (**15**), albeit in only modest yield



(15)



(16)

(34%).[15] In the event that we would also experience difficulty with acetylene, 1,2-dichloroethylene could be employed as a synthetic equivalent. Dehalogenation with sodium in liquid ammonia would then provide the requisite β,γ-unsaturated ketone.[16]

(9) Bohlmann, F.; Zdero, C.; Boldmann, R.; King, P. M.; Robinson, H. *Phytochemistry* **1980**, *19*, 579.

(10) A preliminary account of this work, wherein the total synthesis of (±)-modhephene was disclosed, was presented at the 179th National Meeting of the American Chemical Society, Houston TX, Mar 1980; Abstract ORGN 63. Also see: Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194. Four alternative approaches to modhephene have been reported; see: Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1980**, 4569. Also see: Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1981**, *64*, 1123. Schostarez, H.; Paquette, L. A. *Ibid.* **1981**, *103*, 722. Oppolzer, W. Marazza, F. *Helv. Chim. Acta* **1981**, 64, 1981. Oppolzer, W.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 2489.

(11) (a) Wiesner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can J. Chem.* **1969**, *47*, 433. (b) For a review see: Wiesner, K. *Tetrahedron* **1975**, *31*, 1655.

(12) (a) Cargill, R. L.; Crawford, J. W. *Tetrahedron Lett.* **1967**, 169. (b) Cargill, R. L.; Crawford, J. W. *J. Org. Chem.* **1970**, *35*, 356. (c) Cargill, R. L.; Pond, D. M.; LeGrand, S. O. *Ibid.* **1970**, *35*, 359. (d) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106.

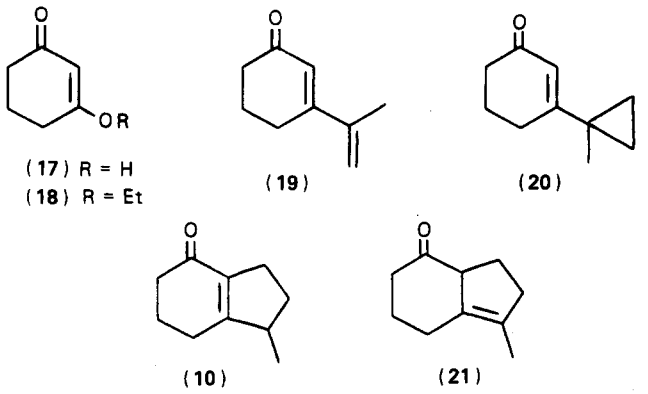
(13) For an example of migration of the central bond in a propellane system see: Eaton, P. E.; Tobe, P. G.; Hyi, K. *J. Am. Chem. Soc.* **1980**, *102*, 6638.

(14) (a) The experimental procedure for the preparation of bicyclic enone **10** was kindly provided by Professor Edward Piers of the University of British Columbia (private communication to A. B. Smith, III). (b) Piers, E.; Lau, C. K.; Nagakura, I. *Tetrahedron Lett.* **1976**, 3233.

(15) Dalton, J. W. Ph.D. Dissertation, University of South Carolina, Columbia, SC, 1978.

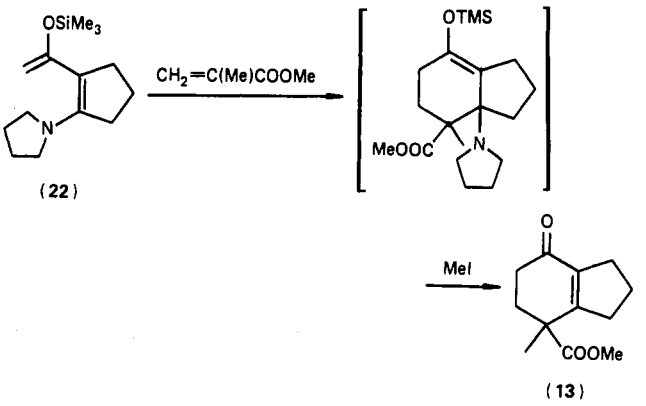
Finally, let us consider the stereochemical consequences of the [2 + 2] photocycloaddition process. Since both acetylene and dichloroethylene are symmetrical, regiochemistry is not a factor. However, it is essential that the etheno bridge and the methyl substituent bear an anti relationship in the photoadduct to assure the requisite stereochemistry of modhephene. In developing this strategy, we were not unfamilar with the elegant work of Wiesner concerning the stereochemical consequences of the photocycloaddition of allene to enone substrates.[11] Indeed, determination of the stereochemical outcome of the addition of acetylene or dichloroethylene with enones **10**, **11**, and **14** would provide an opportunity to assess further the Wiesner postulate. It should be emphasized that these rules have only been investigated *in detail* with allene as the olefinic partner.

(ii) Preparation of Enones 10, 14, and 14: Substrates for the Proposed Photoaddition. As eluded to above, enone **10** was prepared via the method of Piers.[14] Toward this end, dihydroresorcinol (**17**) was esterified with



ethanol (benzene/TsOH/H_2O) to afford 3-ethoxy-2-cyclohexenone (**18**).[17] Subsequent reaction with isopropenylmagnesium bromide followed by acidic hydrolysis yielded **19**, which in turn was converted to **20** via application of Corey's dimethyloxosulfonium methylide.[18] Finally, pyrolysis at 450 °C afforded a 7:2 mixture of β,γ- and α,β-unsaturated enones **21** and **10**, respectively. This mixture was readily isomerized in methanol containing sodium methoxide to yield *only* the desired isomer (**10**); characteristically **10** displayed a doublet (δ 1.10, J = 6 Hz) in the NMR and absorptions at 1660 and 1640 cm^{-1} in the IR.[19]

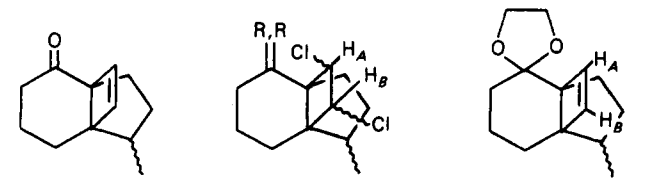
Bicyclic enone **11**, on the other hand, was derived from vinylogous β-keto ester **13**, which in turn was prepared through aegis of a Diels–Alder-"like" reaction between enamine enolsilyl ether **22** and methyl methacrylate.[20] Subsequent treatment of the initial adduct with excess methyl iodide at −78 °C unraveled the enone moiety. Presumably this transformation involves initial quaternization of the amine with subsequent iodide ion induced cleavage of the enol silyl ether and expulsion of *N*-methylpyrrolidine. Hydrolysis and decarboxylation were then achieved efficiently (85%) in one step via treatment



with barium hydroxide in water at reflux.[21] That the product mixture consisted only of the α,β-unsaturated isomer was clear from the high-field (250 MHz) NMR spectrum which displayed a doublet at δ 1.16 (J = 6.9 Hz, 3 H) for the C(5) methyl.

In a similar fashion enone **14** was prepared from **22** and methyl acrylate.[20] Significantly, only the α,β-unsaturated isomer was observed.[22] Our strategy in this case was to add the etheno bridge via a photochemical [2 + 2] cycloaddition and then to reduce the C(5) carbomethoxyl group to a methyl substituent. Not only would this approach intersect our initial strategies at tricyclic ketone **12** but it would also afford the opportunity to contrast the effect of a C(5) carbomethoxy vs. a C(5) methyl group with respect to the steric course of the [2 + 2] photochemical addition.

(iii) Synthesis of Modhephene and Its Epimer: A First Encounter. With substrates **10**, **11**, and **14** in hand, we focused initially on addition of an etheno bridge to bicyclic enone **10**. Preliminary attempts involved irradiation of **10** in the presence of acetylene. Unfortunately, the yield of the tricyclic adduct **8** was poor (ca. ~30%); furthermore, the photoaddition proved to be totally nonstereoselective as indicated by NMR. In particular, two overlapping AB quartets (δ 5.9–6.15, J_{AB} = 3 Hz) of equal intensity for the olefinic protons of the syn and anti epimers (8α and 8β) were prominent.



In view of the poor efficiency as well as lack of stereocontrol, we turned next to 1,2-dichloroethylene. It was anticipated (i.e., hoped) that the steric bulk of the chloride substituents would aid in directing the addition to the face of the enone opposite the methyl group. Toward this end, bicyclic enone **10** was irradiated through Corex in the presence of 1,2-dichloroethylene (mixture of isomers). The progress of the photolysis was unusually easy to monitor by thin-layer chromatography, since the products were no longer UV active. The reaction was complete within 5 h,

(16) (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. For pertinent reviews on Birch reductions see: (b) A. J. Birch, *Q. Rev., Chem. Soc.* **1950**, *4*, 69. (c) Kaiser, E. M. *Synthesis* **1972**, 391.

(17) Gannon, W. F; House, H. O. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 539.

(18) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(19) Dyer, J. R. "Applications of Absorption Spectroscopy of Organic Compounds"; Prentice-Hall: Englewood Cliffs, NJ, 1965; pp 33–34. R. T. Conley, "Infrared Spectroscopy", 2nd ed.; Allyn and Bacon: Boston, 1972; pp 146–160, 179.

(20) Unpublished results of B. A. Wexler of this laboratory. A detailed account of the generality of this Diels–Alder-"like" condensation will be provided in due course.

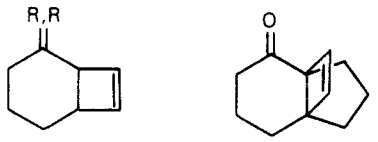
(21) A similar hydrolysis–decarboxylation sequence has been reported by Danishefsky et al. in the synthesis of (±)-pentalenolactone (see ref 5).

(22) In contrast, hydrolysis of Diels–Alder adducts derived from *trans*-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene often afford mixtures of the respective 2-cyclohexenone and β-methoxycyclohexanone; see: Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

affording a 67% yield of **23a** after distillation.

Definitive statements concerning the stereochemistry of **23a** could not be made since the ^1H NMR spectrum even at high field (360 MHz) was particularly complex. Suffice it to say here that two multiplets at δ 4.08–4.24 and 4.40–4.80 (1 H, each H_A and H_B) were assigned to the protons on the halogen-bearing carbons.

To gain insight into the stereoselectivity of the photoaddition process, as well as to prepare the initial substrate for Cargill rearrangement, we turned to the reductive removal of the halogens. Such transformations are not without precident. Indeed, House and Cargill exploited similar processes in their synthesis, respectively, of bicyclic and tricyclic ketones **25** and **26**. Interestingly, Cargill[12b]



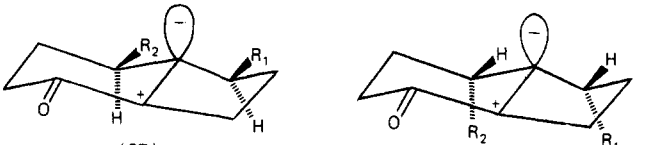
(25a) R,R = O (26)
(25b) R,R = OCH_2CH_2O

claimed that reduction of the carbonyl was not observed when precautions were taken to ensure the anhydrous nature of the ammonia; in contrast, House employed the derived ethylene ketal. In our hands dehalogenation of **23a** by employing the Birch conditions could not be achieved without simultaneous reduction of the carbonyl. Furthermore, attempts to oxidize the resulting mixture by employing Jones reagent[23] provided, at best, a 38% yield of the desired β,γ-unsaturated ketone 8, along with a number of uncharacterized products. Poor recovery of 8 came as no great surprise since similar systems are known to undergo skeletal rearrangements in the presence of mineral acid.[12c,d]

In view of these results, ketal **23b**, prepared in the usual manner, was employed in the reductive dehalogenation process, the result being that ketal **24** was obtained in 78% yield. Indicative of an epimeric mixture, the high-field ^1H NMR (250 MHz) spectrum revealed two overlapping AB quartets [δ 5.96–6.12 (each with J = 2.5 Hz)] for the olefinic protons on the etheno bridge and two doublets [δ 0.82 and 0.88 (J = 7 and 6 Hz, respectively)] for the secondary methyls. Integration indicated the isomeric ratio to be 2:1. No attempt was made at this point to separate epimers.

Cautioned by the fact that Cargill had observed skeletal rearrangement upon attempting to hydrolize ketal **25b** in aqueous HCl,[12c,d] we exposed **24** initially to aqueous oxalic acid. However, only starting ketal was recovered. Increasing the acidity of the media to 2% aqueous H_2SO_4 in acetone[24] effected complete hydrolysis in 14 h to afford a 91% yield of 8 as a 2:1 mixture of epimers which in this case were cleanly separated by preparative vapor-phase chromatography (VPC). Although each isomer was fully characterized (i.e., IR, 250-MHz NMR, and high-resolution mass spectroscopy and C and H analysis), it was not possible to assign individual stereochemistries at this time.

Employing the Wiesner's hypothesis developed for allene,[11] one could anticipate predominate syn addition of dichloroethylene to bicyclic enone **10**. That is, molecular model studies indicate that conformer **27** in which the methyl group resides in the pseudoequatorial vs. the pseudoaxial position (i.e., **28**) is the more stable form. Our



(27) (28)

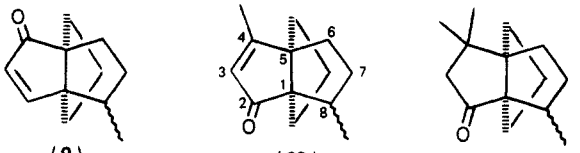
(a) $R_1 = CH_3$; $R_2 = H$
(b) $R_1 = H$; $R_2 = CH_3$

observation, however, was that the photocycloaddition was not highly stereoselective (i.e., epimeric ratio = 2:1). Furthermore, there were no assurances of the validity of the Wiesner postulate with dichloroethylene. Indeed, a number of inconsistencies with olefins rather than allene have been noted. For example, Cargill observed that ethylene adds predominantly anti to the alkyl substituent in 4-*tert*-butyl-2-cyclohexenone.[25] Well aware that the relative configurations of **8a** and **8b** could not be established with certainty until spectral comparisons were made between synthetic and natural modhephene, we had little choice but to carry the epimeric mixture through the remainder of the synthesis.

With access to tricyclic ketone 8 secure, we focused next on the pivitol acid-catalyzed isomerization, which was to establish the propellane skeleton. To our delight, treatment of 8 with 0.6 equiv of *p*-TsOH in benzene at reflux for 4 h afforded an excellent yield (93%) of the desired propellenones **9a** and **9b** which for characterizational purposes could be efficiently separated by preparative VPC. Again no definitive information regarding the stereochemistry of **9a** and **9b** could be gleaned from the high-field NMR, although differences were clearly evident.

The yield of the Cargill rearrangement was found to be an extremely sensitive function of the reaction conditions. For example, it was imperative to add the *p*-TsOH in two equal portions, with the second addition being midway in the total reaction time. When the catalyst was added in one portion, complete conversion of **9** could not be achieved even upon prolonged heating. Alternatively, rearrangements attempted with $BF_3{\cdot}Et_2O$ as catalyst in acetonitrile at reflux[12] led to considerable decomposition of the desired product.

With the propellane skeleton constructed, all that remained to complete the synthesis was to append three methyl substituents to the propellane framework by employing the functionality of the enone. Here we envisioned treatment of **9** with a series of nucleophilic methyl reag-



(9) (29) (30)

ents. Toward this end, addition of methyllithium followed by Jones oxidation[23] effected an alkylative 1,3-carbonyl transposition,[26] providing rearranged enone **29** in 88% yield as a mixture of syn and anti epimers. Addition of the second methyl group was anticipated to be achieved via conjugate addition of lithium dimethylcuprate.[27] Due,

(23) (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc. 1946*, 39. (b) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; pp 142–144.

(24) Similar conditions were used Tasura et al. in a synthesis of (±)-hirsutene (see ref 6).

(25) Cargill, R. L., Jr.; Morton, G. A.; Bordner, J. *J. Org. Chem.* **1980**, *45*, 3929.

(26) For example see: (a) Buchi, G.; Egger, D. *J. Org. Chem.* **1971**, *36*, 2021. (b) Grieco, P. *Ibid.* **1972**, *37*, 2363. (c) Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 4446. (d) McCurry, P. M., Jr.; Singh, R. K. *J. Org. Chem.* **1974**, *39*, 2316. (e) Dutcher, J. S.; MacMillan, J. G.; Heathcock, C. H. *Ibid.* **1976**, *41*, 2663. (f) Dauben, W. G.; Michno, D. M. *Ibid.* **1977**, *42*, 682.

(27) Posner, G. H. *Org. React.* **1972**, *19*, 1.

however, to the neopentyl environment proximate to C(4), enone **29** was totally unreactive toward the standard cuprate reagent even when forcing conditions were employed. Fortunately, this problem could be overcome by adding 1.8 equiv of BF_3·Et_2O to an ethereal solution of the cuprate cooled to −78 °C. Although 1,4-addition could be realized in this manner, the addition failed to go to completion. Composition of the product mixture was easily determined by IR; **29** possessed carbonyl absorption at 1710 cm^{-1}, while in the saturated system (**30**) the absorption was shifted to 1730 cm^{-1}. Although complete conversion required recycling, in the end the epimeric propellanones **30** were obtained in 70% yield.

Precedent for modifying the cuprate protocol in this manner can be found in the recent work of Yamamoto,[28] who reported the successful conjugate addition of alkyl groups to normally unreactive α,β- and β,β-disubstituted enolate esters by employing an alkyl copper–boron trifluoride reagent. Interestingly, in our hands[29] **29** was unreactive toward Yamamoto's reagent, but reacted readily with $LiMe_2Cu$ in the presence of BF_3·Et_2O. Although purely speculative, we believe that the observed enhancement of reactivity derives from boron coordination with the carbonyl, thereby increasing the electrophilicity of the β-carbon.

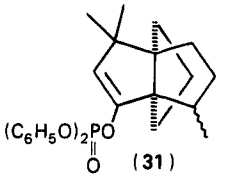
With saturated ketone **30** in hand, no further complications en route to modhephene were anticipated. Such was not to be the case! In principle, at least, addition of the final methyl group could be effected by any one of the following methods: (a) 1,2-addition with a methyl nucleophile followed by dehydration; (b) Wittig olefination[30] with methylenetriphenylphosphorane and subsequent isomerization; (c) generation of the C(2) vinyl anion and then in situ trapping with methyl iodide.

Initial attention was directed toward addition of methyl nucleophiles to the carbonyl group. Common methyl nucleophiles such as methylmagnesium bromide, methyllithium, and a lithium dimethylcuprate–methyllithium complex,[31] each reacted in a variety of solvents and for a range of times and temperatures, could not be induced to undergo 1,2-addition to **30**. Ketone **30** was even unreactive toward methylmagnesium bromide in toluene, conditions known to enhance 1,2-addition to easily enolizable substrates.[32] Furthermore, both [(phenylthio)methyl]lithium[33] and diethylaluminum cyanide[34] failed to add to **30**.

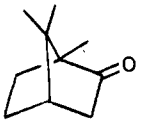
Undaunted by lack of initial success, we focused upon the second alternative, Wittig olefination. Initial efforts in this regard were likewise unsuccessful. Ketone **30** even resisted the addition of methylenetriphenylphosphorane generated from dimsyl sodium in dimethyl sulfoxide (70 °C for 3 days).[35] This result was particularly disappointing in that similar conditions were used by Pirrung in his isocomene synthesis for the olefination of a sterically hindered tricyclic ketone.[4d,e]

Finally, we attempted to prepare the 2,4,6-triisopropylbenzenesulfonylhydrazone derivative[36] of **30** in the hope of effecting a Shapiro reaction[37] in the presence of methyl iodide. At this point, however, we were not surprised to discover that we could not form the hydrazone of **30**.

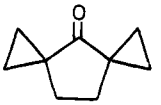
Without a doubt the severe steric hindrance in the region of the carbonyl, in conjunction with the facile enolization of the cyclopentanone system, prevented the desired addition process. Support for the latter derived from the facility with which the enol diphenyl phosphate ester **31** was prepared.[38] With access to **31** available we attempted to effect coupling with lithium dimethylcuprate. In this regard, Blaszczak[38] reported the preparation of a variety of alkyl-substituted olefins from the respective ketones by reducing the derived enol diphenyl phosphate esters with lithium di-*n*-alkyl- and diarylcuprates. Unfortunately, lithium dimethylcuprate was reported to proceed only in poor yield (ca. 12%). Indeed, in our case, no hydrocarbons could be detected even under forcing conditions (3 equiv of $LiMe_2Cu$, −50 °C, 14 h).[39]



(31)



(32)



(33)

Two recent examples in which 1,2-additions have been effected in sterically encumbered ketones are particularly noteworthy. One is found in Paquette's isocomene synthesis wherein successful addition was finally accomplished by repeated exposure to methyllithium.[4d] The second is found in Boeckman's synthesis of β-gorgonene.[40] Here, reaction of a hindered carbonyl with [(trimethylsilyl)methyl]magnesium chloride[41] was found to be superior to treatment with the phosphorane Wittig. To our dismay, propellanone **30** proved to be inert when subjected to both protocols. At this point we were delighted to learn that methylenetriphenylphosphorane generated with sodium *tert*-amylate and reacted at *high temperature* according to the method of Conia[42] and McMorris and Schow[43] was particularly successful in effecting olefination of hindered ketones such as camphor (**32**) and dispiro[2.1.2.2]nonan-4-one (**33**), the yields being 72% and 90%, respectively.[42] The camphor result appeared particularly promising, in that camphor is not only hindered but also undergoes facile enolization.

Consequently, we attempted again the Wittig olefination

(28) (a) Maruyama, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8068. (b) Yamamto, Y.; Maruyama, K. *Ibid.* **1978**, *100*, 3240.

(29) This result must be contrasted to that of Drieding, who reports that $CuCH_3$·BF_3 is in fact effective in the conjugate addition process (i.e., **29** → **30**; see ref 10).

(30) For a review of the Wittig reagent, see: Johnson, A. W. "Ylid Chemistry"; Academic Press: New York, 1966.

(31) (a) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Tetrahedron Lett.* **1977**, 1709.

(32) (a) Ashby, E. C.; Reed, R. *J. Org. Chem.* **1966**, *31*, 971. (b) Canonne, P.; Foscolos, G. B.; Lemay, G. *Tetrahedron Lett.* **1979**, 4383.

(33) (a) Kuwajima, I.; Sato, S.; Kurata, Y. *Tetrahedron Lett.* **1972**, 737. (b) Sowerby R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758. (c) McMurry, J. E.; von Beroldingen, L. A. *Tetrahedron* **1974**, *30*, 2027.

(34) For the synthesis of α-cyanohydrins, see: (a) Nagata, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4654. (b) Nagata, W.; Yoshioka M.; Murakami, M. *Org. Synth.* **1972**, *52*, 96.

(35) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. (b) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(36) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(37) For a review of the Shapiro reaction, see: Shapiro, R. H. *Org. React.* **1975**, *23*, 405.

(38) Blaszczak, L.; Winkler, J.; O'Kuhn, S. *Tetrahedron Lett.* **1976**, 4405.

(39) After completion of this project, improvements in the conversion of enol derivatives (i.e., enol triflate) to methyl ketone appeared; see: McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, 4313. Also see: Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2247.

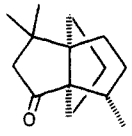
(40) Boeckman R. K.; Jr.; Silver, S. M. *Tetrahedron Lett.* **1973**, 3497.

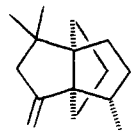
(41) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Chan, T. H.; Chang, E.; Vinokur, E. *Tetrahedron Lett.* **1970**, *1137*. (c) Chan, T. H.; Chang, E. *J. Org. Chem.* **1974**, *39*, 3264. (d) Chan, T.-H. *Acc. Chem. Res.* **1977**, *10*, 442.

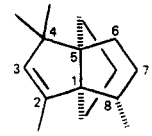
(42) Conia, J.-M.; Limasset, J.-C. *Bull. Soc. Chim.* **1967**, 1936.

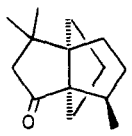
(43) (a) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760. (b) Schow, S. R., of our laboratory, private communication.

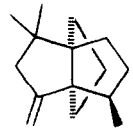
sequence, this time employing *tert*-amyl oxide as the base. Following a suggestion of Schow,[43b] we modified the Conia procedure slightly in that the ketone was added to a *preheated* solution of the Wittig reagent.[44b] More specifically, the isomeric mixture of ketones **30** was treated with a sevenfold excess of methylenephosphorane generated from an equimolar amount of potassium *tert*-amylate (1.77 M in benzene) in toluene at 92 °C. The reaction was complete within 2 h. After an aqueous workup and elution through silica to remove triphenylphosphine oxide, olefins **34α,β** were purified by preparative thin-layer chromatography. To our delight, only carbon–hydrogen absorptions were observed in the IR spectrum of each isomer. Particularly characteristic was the absorption at 885 cm^{-1} for the C–H out-of-plane bending deformation of the exomethylene group.[19]

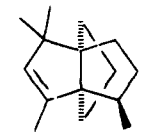

(30α)


(34α)


Modhephene (1α)


(30β)


(34β)


Epimodhephene (1β)

The success of the high-temperature Wittig reaction was dependent upon three critical factors. First, it was essential to use a substantial excess of Wittig reagent. Second, the reagent had to be generated in a minimum amount of solvent. For example, a solution of the Wittig reagent typically consisted of a seven-fold excess of methyltriphenylphosphonium bromide and an equimolar amount of potassium *tert*-amylate with only enough toluene to bring the mixture to homogeneity. Finally, it was imperative that the ketone was added to a preheated (92 °C) solution of the reagent.

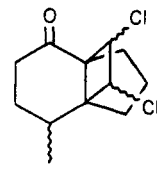
After the achievement of olefination, all that remained was isomerization of the exocyclic double bond. To this end, isomodhephenes **34α,β** (2:1 epimeric mixture) were treated with 0.4 equiv of *p*-TsOH in methylene chloride at ambient temperature for 3 h.[4d] The ^1H NMR (250 MHz) spectrum revealed that isomerization was complete by the presence of two olefinic absorptions at δ 4.84 and 4.94, which integrated as a 1:2 epimeric mixture, respectively.

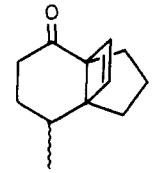
Neither preparative thin-layer chromatography nor vapor-phase chromatography proved effective in separating modhephene from its C(8) epimer. We therefore elected to separate the isomeric ketones **30** by preparative VPC and then to subject each individually to the olefinic reaction sequence. In the event modhephene and epimodhephene were isolated in 43% and 46% overall yields, respectively, from their corresponding ketones. Synthetic modhephene was identical in all respects with a sample of the natural product generously provided by Professor Zalkow.

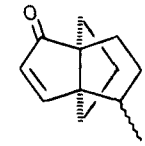
(44) This value is from Eliel, E. L. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 764. See also tables in: Eliel, E. L., Allinger, N. L., Augyal, S. J., and Morrison, G. A. "Conformational Analysis"; Interscience: New York, 1965; pp 44, 436–442.

At this point we were able to demonstrate conclusively that modhephene was in fact the minor epimer; that is, epimodhephene predominated by 2:1. Hence the photoaddition of dichloroethylene to enone **10** had proceeded to add the etheno bridge predominantly syn to the methyl group in accord with the Wiesner theory.[11]

(iv) Return to the Photocycloaddition of the Etheno Bridge: Two Alternate Approaches to Modhephene and Its Epimer. The lack of significant selectivity with enone **10** and dichloroethylene led us to examine next the steric course of the photoaddition process with closely related enones **11** and **14** in the hope of achieving a stereoselective modhephene synthesis. Toward this end, **11** was irradiated in the presence of 1,2-dichloroethylene for 12.5 h. A mixture of chloroketones **35** resulted; the yield


(35)

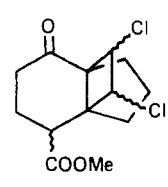

(12)

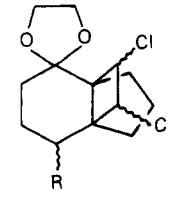

(9)

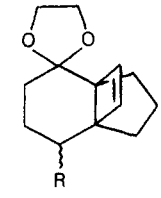
was 68%. This mixture of ketones was subsequently ketalized, dehalogenated, and hydrolyzed by employing protocols identical with those previously developed. The result was an epimeric mixture of tricyclic β,γ-unsaturated ketones **12**. Acid-catalyzed isomerization then led to the previously characterized propellenone **9**. In this case a syn to anti ratio of 43:57 was obtained, *the major product having the necessary stereochemistry for elaboration to modhephene*. These epimers were separated by preparative VPC and shown to be identical in all respects (250-MHz NMR, IR, and GC retention time data), with those isolated from the original synthetic route (i.e., **8** → **9**).

In this case the ratio of photoproducts was opposite to that predicted by the Wiesner model.[11] Indeed, according to Wiesner, the most stable conformer for the excited state of enone **1** would be anticipated to have the C(5) methyl in the equatorial position, as opposed to the conformer **27b** having the methyl group axial. As a result dichloroethylene would be predicted to add syn to the methyl substituent. The alternative conformer **28b** would be the less stable by approximately 1.7 kcal/mol, the difference in energy between an axial and equatorial methyl substituent on a cyclohexenone ring.[44] It is conceivable, however, that the ring in **28b** would assume a boatlike conformation which would place the C(5) methyl group in a pseudoequatorial position, and thereby diminish the nonbonded interactions. If such were the case, addition would not be favored significantly from either face of the enone.

Attention next was focused on the photoaddition of **14** which bears a carboxylate group at C(5). When subjected to similar photolysis, adducts **36** were obtained in 73% yield. That the photocycloaddition was not stereoselective


(36)


(37a) R = COOMe
(37b) R = CH_2OH


(38a) R = CH_2OH
(38b) R = CH_2OMs
(38c) R = CH_3

was clear from the high-field ^1H NMR (250 MHz) spectrum which possessed two methoxy singlets at δ 3.71 and 3.74, respectively, the latter signal predominanting by 2:1.

To define the stereochemical outcome in this case, we carried out a chemical correlation between **36** and **12**. Significant in this regard, keto ester **36** differs from the previous two systems (**23** and **35**) in that the C(5) center is epimerizable. Ketalization, therefore, could not be attempted via the standard conditions (i.e., *p*-TsOH/benzene). This problem was easily overcome by employing the nonequilibrating ketalization conditions recently introduced by Noyori.[45] To this end, treatment of **37** at ambient temperature with the bis(trimethylsilyl) ether of ethylene glycol[46] in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst afforded ketal ester **37a** in 68% yield. Reduction with diisobutylaluminum hydride[47] in toluene at −78 °C for 3 h afforded a mixture of chloro alcohols **37b**; this mixture was easily dehalogenated to **38a** by treatment with sodium in liquid ammonia. The hydroxy methyl group was then converted to a methyl substituent by reduction of the corresponding mesylate **38b** with lithium triethylborohydride.[48] Finally, hydrolysis under the usual conditions provided β,γ-unsaturated ketone **12** as a 2:1 mixture of syn and anti isomers, respectively. Each epimer was isolated by preparative VPC and found to correspond in all respects (250-MHz NMR, IR, GC retention time) to those prepared from bicyclic enone **11**. Thus, in this case, the addition of dichloroethylene proceeds with the selectivity predicted by the Wiesner hypothesis.[11,49]

(v) Temperature Dependence of the [2 + 2] Cycloaddition. To explore further the stereochemical consequences of the photocycloaddition process, we examined briefly the effect of low-temperature irradiation. It is noteworthy that Wiesner has observed an increase in stereoselectivity, in accord with his rule, when irradiations were carried out at low temperature.[50] In our case, photolysis of **11** in hexane at −78 °C (Pyrex filter, 1.5 h) followed by ketalization, dehalogenation, and hydrolysis yielded tricyclic ketone **12** as a 55:45 mixture of syn and anti isomers, respectively. Although the low-temperature photoaddition was by no means highly stereoselective, it is significant that the 12% reversal in the epimeric ratio was in the direction of the Wiesner postulate.

Summary

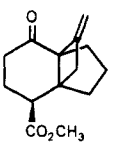
(±)-Modhephene and (±)-epimodhephene have been synthesized from enones **10**, **11**, and **14**. From bicyclic enone **11** the epimeric ratio, at room temperature, was 57:43 in favor of modhephene. Although somehwat disappointing, the lack of high stereocontrol detracts little from the efficiency of our synthesis in that all reactions proceed in good to excellent yields. Furthermore, no chromatographic separations are required until the final olefination step. Finally, although by no means highly stereoselective, the stereochemical consequences of the photocycloaddition of dichloroethylene to enones **10**, **11**, and **14** are in accord with the Wiesner hypothesis.

Experimental Section[51]

3-Isopropenyl-2-cyclohexen-1-one (19).[14a] To a slurry containing 2.5 g (0.1 mol) of magnesium and a trace of mercuric chloride in 40 mL of THF was added dropwise, under nitrogen, 12 g (0.1 mol) of isopropenyl bromide in 20 mL of THF. The temperature was maintained below 50 °C by using an ice–water bath. After the addition was complete, the resulting black solution of isopropenylmagnesium bromide was stirred 1 h at ambient temperature, cooled to 0 °C, and diluted with 60 mL of ether. A solution of 7 g (0.05 mol) of 3-ethoxy-2-cyclohexen-1-one (**18**)[17] in 10 mL of ether was added dropwise and stirred for 4 h. After the mixture was cooled to 0 °C, 100 mL of 10% aqueous sulfuric acid was added very slowly, and the mixture was stirred 10 min. The mixture was finally poured into ether, and the organic layer was washed with 10% sodium carbonate and water and dried. Concentration in vacuo and distillation (0.6 mmHg, 69–78 °C) yielded **19**: 5.1 g (76%); IR (CCl_4) 3100 (w), 2875–3000 (s), 1670 (s), 1590 (m), 1460 (m), 1440 (m), 1375 (m), 1360 (m), 1330 (m), 1270 (s), 1250 (s), 1200 (s), 1145 (m), 970 (m), 910 (s), 890 (s) cm^{-1}; NMR (60 MHz, CCl_4) δ 2.2–2.7 (m, br s, 9 H), 5.3 (br s, 1 H), 5.5 (br, s, 1 H), 6.0 (br s, 1 H).

3-(1-Methylcyclopropyl)-2-cyclohexen-1-one (20).[14a] Sodium hydride (4.1 g of a 50% mineral oil dispersion, 85 mmol) was added to a 250-mL three-necked flask and washed twice with pentane. The flask was then equipped with a nitrogen inlet, additional funnel, and ground-glass stopper. A three-way stopcock was then connected to the nitrogen inlet and water aspirator, and the system was evacuated to remove the last trace of pentane. After the vacuum was broken, 18 g (82 mmol) of trimethyloxosulfonium iodide[18] was added. The system was then flushed with nitrogen and evacuated three consecutive times and then finally filled with nitrogen. Dimethyl sulfoxide (90 mL) was added slowly,

(45) Tsunada, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 1357.
(46) Fuchs, B.; Auerbach, Y.; Sprecher, M. *Tetrahedron* **1974**, *30*, 437. For preparation, see: Pasto, D.; Johnson, C. "Organic Structure Determination"; Prentice-Hall: Englewood Cliffs, NJ, 1969; p 368.
(47) Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627.
(48) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166.
(49) We have also examined the addition of allene to enone **12**. As predicted by the Wiesner hypothesis, the syn addition product (i) predominated 14:1: unpublished results of B. A. Wexler of our laboratory. Additional examples concerning the stereoselectivity of the [2 + 2] photocycloaddition of olefins to bicyclic enones will be reported in due course.



(*i*)

(50) Wiesner, K., personal communication to A. B. S., III.

(51) **Materials and Equipment.** All solvents used were reagent grade and were distilled prior to use: ether and tetrahydrofuran from sodium benzophenone, methylene chloride from phosphorus pentoxide, hexane and dimethyl sulfoxide from calcium hydride, benzene and toluene from sodium ribbon, and boron trifluoride etherate from calcium hydride. Cuprous iodide (Fisher Scientific Co.) employed for the preparation of lithium dimethylcuprate was purified according to the procedure of House (House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893). A Hanovia Model L mercury lamp (No. 679A-36) in a quartz immersion well was employed for all room-temperature photochemical reactions. Low-temperature (−78 °C) photolyses were carried out by using a 1000-W mercury lamp (with the outer globe removed) equipped with a G. E. ballast No. 35-9627-6009 power source. A Lindberg hot tube apparatus (Type 59344, No. 787160) operated at 450 °C was used for pyrolyses. All VPC separations were achieved by using a Varian Aerograph Model 920 gas chromatograph fitted with a 25% Carbowax 20M column (20 ft × 0.25 in.). The helium carrier gas flow rate ranged from 60 to 100 mL/min, and the oven was operated at 180–200 °C. Precoated silica gel plates (250 μm) with a fluorescent indicator (E. M. Merck) were used for analytical thin-layer chromatography (TLC). For preparative separations precoated silica gel GF (Analtech) plates (500 or 1000 μm) were used. Silica gel 60 (particle size 0.040–0.063 mm) supplied by E. M. Merck was used for flash column chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923). Melting points, obtained on a Thomas-Hoover instrument, are corrected; boiling points are uncorrected. Unless otherwise stated ether extracts were washed with water and brine and dried for several hours over magnesium sulfate. Proton NMR spectra were obtained for carbon tetrachloride and deuteriochloroform solutions on either a Varian Model A-60 (60 MHz), a Varian T-60 A (60 MHz), a Bruker WP-250 FT (250 MHz), or a Bruker WH-360 (360 MHz) spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00). All infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer for carbon tetrachloride solutions. High-resolution mass spectra were obtained from the University of Pennsylvania Mass Spectrometry Service on a Hitachi Perkin-Elmer RMH-2 high-resolution double-focusing electron-impact spectrometer connected to a Kratos DS-50-S data system.

and the resulting milky solution containing dimethyloxosulfonium methylide was stirred at ambient temperature for 30 min. After being cooled to 0 °C, the mixture was diluted with 40 mL of THF, and 11 g (79 mmol) of **19** in 10 mL of THF was added dropwise with stirring. The resulting orange mixture was stirred overnight at room temperature. The solution was then poured into cold water, extracted with ether, washed, and dried. After concentration in vacuo distillation (3 mmHg, bp 89–100 °C) gave **20**: 6 g (50%); isolated as a colorless oil; IR (CCl_4) 3100 (w), 2875–3000 (s, br), 1600 (s), 1590 (m), 1440 (m), 1420 (m), 1370 (m), 1340 (m), 1330 (m), 1270 (s), 1200 (s), 1145 (m), 1030 (m), 890 (m) cm^{-1}; NMR (60 MHz, CCl_4) δ 0.65–1.00 (m, 4 H), 1.3 (s, 3 H), 1.9–2.4 (m, 6 H), 5.9 (br s, 1 H).

7-Methylbicyclo[4.3.0]non-1(6)-en-2-one (10).[14a] Ketone (**20**; 2.3 g, 15.3 mmol) was dissolved in 10 mL of hexane and added dropwise to a vertically held glass tube heated to 450 °C under an argon atmosphere. The thermosylate was concentrated in vacuo, yielding 2 g of crude product, which was shown by spectroscopic analysis to consist of a 7:2 mixture of β,γ- and α,β-unsaturated ketones, respectively. Isomerization was readily achieved by dissolving the mixture in 20 mL of methanol containing a small amount of sodium methoxide and stirring at 0 °C for 1 h. After concentration in vacuo, the residue was taken up in ether, washed, and dried. Kugelrohr distillation [bp 70–80 °C (0.3 mmHg)] yielded **10**: 1.9 g (86%); IR (CCl_4) 2850–2950 (s), 1660 (s), 1630 (m), 1430 (m), 1390 (m), 1210 (m), 1140 (w) cm^{-1}; NMR (60 MHz, CCl_4) δ 1.1 (d, J = 6 Hz, 3 H), 2.0–2.5 (m, 11 H).

7-Methyl-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one (23a). A degassed solution containing 10 g (0.07 mol) of **10** and 15.4 mL (0.2 mol) of a mixture of *cis*- and *trans*-1,2-dichloroethylene in 220 mL of distilled (CaH_2) hexane was irradiated through a Corex filter for 5.5 h. The reaction was monitored by thin-layer chromatography [5% ether–methylene chloride (v/v)]. Removal of the solvent in vacuo and distillation [bp 102–132 °C (0.4 mmHg)] yielded 11 g (67%) of **23a** as a viscous yellow oil which, after chromatography (silica gel, eluting with methylene chloride), was isolated as white flakes: mp 50–52 °C (mixture of isomers); IR (CCl_4) 2950 (s), 2880 (s), 1710 (s), 1495 (m), 1150 (m), 940 (s), 865 (m), 720 (m), cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 0.84–1.00 (m, 3 H), 1.40–2.60 (m, 11 H), 4.08–4.24 (m, 1 H, H_A), 4.40–4.48 (m, 1 H, H_B); mass spectrum, m/e 246.0572 (M^+; calcd for $C_{12}H_{16}OCl_2$ 246.0580).

7-Methyl-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one Ethylene Ketal (23b). A solution of 742 mg (3 mmol) of **23a**, 0.3 mL (5.3 mmol) of ethylene glycol, and 41 mg (0.2 mmol) of *p*-toluenesulfonic acid monohydrate in 30 mL of benzene was heated to reflux overnight with azeotropic removal of water. After cooling, the mixture was poured into sodium bicarbonate–ether, washed with sodium bicarbonate and water, and dried. Filtration through magnesium sulfate–silica, removal of the solvent in vacuo, and distillation [bp 120 °C (0.1 mmHg)] yielded 735 mg (86%) of (**23b**) as a viscous yellow oil (isomeric mixture) which, after chromatography (silica gel, eluting with methylene chloride), was isolated as a white crystalline solid: mp 38–39.5 °C; IR (CCl_4) 2860–2940 (s), 1440 (m), 1120–1160 (s), 680 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.82–1.00 (m, 3 H), 1.36–2.26 (m 11 H), 3.82–4.00 (m, 4 H), 4.06, 4.07, 4.23, 4.44, 4.62 (five sets of doublets, each with J = 7.5 Hz, 2 H, H_A and H_B); mass spectrum, m/e 290.0829 (M^+; calcd for $C_{14}H_{20}O_2Cl_2$ 290.0842).

Anal. Calcd for $C_{14}H_{20}O_2Cl_2$: C, 57.74; H, 6.92; Cl, 24.25. Found: C, 57.99; H, 6.99; Cl, 24.10.

7-Methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one Ethylene Ketal (24). To a flask containing 1 L of freshly distilled anhydrous ammonium was added under an argon atmosphere 1.15 g (3.7 mmol) of **23b** dissolved in 100 mL of dry ether. Small pieces of sodium metal were added until the solution remained dark blue for 15 min. Ammonium chloride was then added to quench excess sodium, and the ammonia was evaporated overnight under a stream of argon. The solid residue was taken up in water and the organic material extracted into ether. Removal of the solvent in vacuo followed by distillation [bp 65 °C (1 mmHg)] afforded **24**: 684 mg (78%); colorless oil (isomeric mixture); IR (CCl_4) 3050 (w), 2950 (s, br), 2900 (s), 1450 (w), 1150 (m), 945 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.82, 0.88 (2 d, J = 7.1 Hz J = 6 Hz, respectively, 3 H), 1.22–2.04 (m, 11 H), 3.82–4.04 (m, 4 H), 5.96–6.12 (four overlapping doublets each with J = 2.5 Hz, 2 H, H_B); mass spectrum, m/e 220.1470 (M^+; calcd for $C_{14}H_{20}O_2$ 220.1464).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.13; H, 9.28.

7-Methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one (8α,β). A solution containing 575 mg (2.4 mmol) of **29** (mixture of isomers), 0.2 mL of concentrated sulfuric acid in 10 mL of water (2% aqueous sulfuric acid), and 30 mL of acetone was stirred overnight at room temperature. The reaction mixture was then poured into saturated sodium bicarbonate–ether, washed, and dried. After filtration through magnesium sulfate–silica, evaporation of the solvent in vacuo, and Kugelrohr distillation [bp 40 °C (0.25 mmHg)], 384 mg (91%) of **8** was isolated as a 2:1 mixture of syn (8β) and anti (8α) isomers, respectively, which were separated by vapor-phase chromatography (VPC) at 200 °C.

The syn isomer (8β, VPC I) had the following spectral data: IR (CCl_4) 3050 (w), 2950 (s, br), 2870 (m), 1690 (s), 1450 (w), 1270 (w), 890 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 3 H), 1.22–2.62 (m, 11 H), AB pattern centered at δ 6.04 (J_{AB} = 2.6 Hz, $\Delta\nu_{AB}$ = 52.6 Hz, δ_A 5.94, δ_B 6.15, 2 H, H_A and H_B); mass spectrum m/e 176.1200 (M^+; calcd for $C_{12}H_{16}O$ 176.1202).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.98; H, 9.18.

VPC II, the anti isomer **8a**, was characterized as follows: IR (CCl_4) 3050 (w), 2850–2950 (s, br), 1690 (s), 1450 (w), 1270 (w), 890 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.81 (d, J = 7.8 Hz, 3 H), 1.22–2.64 (m, 11 H), AB pattern centered at δ 6.01 (J_{AB} = 2.7 Hz, $\Delta\nu_{AB}$ = 67.5 Hz, δ_A 5.88, δ_B 6.15, 2 H, H_A and H_B); mass spectrum, m/e 176.1199 (M^+; calcd for $C_{12}H_{16}O$ 176.1202).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.93; H, 9.21.

6-Methyltricyclo[3.3.3.0^{1,5}]undec-3-en-2-one (9α,β). To a solutioin of 1.6 g (9.2 mmol) of the epimeric ketones **8** in 30 mL of benzene was added 560 mg of *p*-toluenesulfonic acid monohydrate, and the resulting solution was heated at reflux under an argon atmosphere for 2 h. A second portion of *p*-toluenesulfonic acid monohydrate (520 mg; total 5.76 mmol, 0.6 equiv) was added, and the solution was refluxed for an additional 2 h. Progress of the reaction was monitored by TLC [5% ether–methylene chloride (v/v)]. After cooling, the solution was poured into 10% aqueous sodium bicarbonate–ether, washed with 10% sodium bicarbonate and brine, and dried. Removal of the solvent in vacuo and Kugelrohr distillation [bp 55–60 °C (0.3 mmHg)] afforded 1.5 g (93%) of **9** as a 2:1 mixture of anti (9α) and syn (9β) isomers, respectively, which were separated by VPC (180 °C).

The first component (9α, anti isomer), a colorless oil, displayed the following spectral data: IR (CCl_4) 3100 (w), 2900 (s), 2870 (s), 1710 (s), 1590 (m), 1495 (m), 1145 (m), 835 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.02 (d, J = 6.7 Hz, 3 H), 1.06–2.06 (m, 11 H), 6.08 (d, J = 5.3 Hz, 1 H, H_A), 7.47 (d, J = 5.3 Hz, 1 H, H_B); mass spectrum, m/e 176.1204 (M^+; calcd for $C_{12}H_{16}O$ 176.1202).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.54; H, 9.09.

The second component (9β, syn isomer) was isolated as white needles (mp 52–53 °C) with the following spectral data: IR (CCl_4) 2950 (s), 2880 (m), 1710 (s), 1610 (m), 1475 (m), 1095 (w), 840 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.02 (d, J = 6.6 Hz, 3 H), 1.13–1.93 (m, 10 H), 2.09 (dd, J = 12.6, 4.8 Hz, 1 H), 5.94 (d, J = 5.6 Hz, 1 H, H_A), 7.45 (d, J = 5.6 Hz, 1 H, H_B); mass spectrum, m/e 176.1199 (M^+; calcd for $C_{12}H_{16}O$ 176.1202).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.93; H, 9.16.

4,8-Dimethyltricyclo[3.3.3.0^{1,5}]undec-3-en-2-one (29α,β). To an ethereal solution of 1.27 g (7.3 mmol) of the isomeric ketones **9** cooled to −78 °C under argon was added 9.0 mL (14.4 mmol) of methyllithium (1.6 M). The mixture was stirred for 45 min at −78 °C, slowly warmed to room temperature, and stirred for 2 h. After the mixture was cooled to 0 °C, 0.5 mL of water was added followed by 10 mL (14 mmol) of Jones reagent (1.4 M).[41] The resulting mixture was stirred 2 h at ambient temperature, poured into saturated sodium bicarbonate–ether, washed, and dried. Evaporation of the solvent in vacuo followed by distillation [bp 90–100 °C (0.5 mmHg)] afforded 1.2 g (88%) of **29** as a 2:1 mixture of anti (29α) and syn (29β) isomers, respectively, which were separated by VPC (190 °C).

The first component (29α, anti isomer) was isolated as a colorless oil: IR (CCl_4) 2960 (s), 2880 (m), 1710 (s), 1630 (m), 1460

(m), 875 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.00 (d, J = 6.7 Hz, 3 H), 1.20–1.94 (m, 11 H), 2.05 (d, J = 1 Hz, 3 H), 5.75 (m, 1 H); mass spectrum, m/e 190.1360 (M^+; calcd for $C_{13}H_{18}O$ 190.1358).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.95; H, 9.56.

The second component (**29**α, syn isomer) was isolated as white flakes: mp 35–37 °C; IR (CCl_4) 2970 (s), 2880 (m), 1710 (s), 1685 (m), 1450 (m), 1140 (m), 880 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.06 (d, J = 6.7 Hz, 3 H), 1.19–2.00 (m, 11 H), 2.04 (d, J = 1.1 Hz, 3 H), 5.66 (m, 1 H); mass spectrum, m/e 190.1356 (M^+; calcd for $C_{13}H_{18}O$ 190.1358).

4,4,8-Trimethyltricyclo[3.3.3.0^{1,5}]undecan-2-one (30α,β). To a cold slurry (−30 °C) of 870 mg (4.6 mmol) of purified cuprous iodide and 8.0 mL of ether was added under argon 6.0 mL (9.6 mmol) of methyllithium (1.2 M). The clear solution of lithium dimethylcuprate was stirred for 5 min and cooled to −78 °C, and 0.19 mL (1.54 mmol) of freshly distilled boron trifluoride etherate was added. After the mixture was stirred 5 min, a solution of 310 mg (1.6 mmol) of isomeric enones **35** in 2 mL of ether was added dropwise; an immediate precipitation of methylcopper was observed. The mixture was stirred at −78 °C for 15 min, an additional 0.08 mL (0.75 mmol) of boron trifluoride etherate was added, and the mixture was stirred at −78 °C for 1 h. After the mixture slowly warmed to room temperature, the organic material was extracted into ether and washed with saturated ammonium chloride, water, and brine and dried. Evaporation of the solvent in vacuo afforded 277 mg of crude product which was shown by IR to consist of approximately at 60:40 mixture of saturated ketone and enone, respectively. Without prior isolation of the ketone **30**, the crude product mixture was recycled in the same manner as described above. Kugelrohr distillation [bp 90–100 °C) (0.4 mm Hg)], afforded 233 mg (71%) of **30** as a 2:1 mixture of anti (**30**α) and syn (**30**β) isomers, respectively; VPC (195 °C) cleanly separated the mixture.

The first component (30α, anti isomer) had the following spectral data: IR (CCl_4) 2880–3000 (s, br) 1730 (s), 1460 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.01, 1.05, 1.08 (d, J = 6.5 Hz, and 2 s, 9 H), 1.24–2.16 (m, 11 H), AB q centered at 2.25 (J_{AB} = 15.7 Hz, $\Delta\nu_{AB}$ = 40 Hz, δ_A 2.16, δ_B 2.33, 2 H, H_A and H_B); mass spectrum, m/e 206.1679 (M^+; calcd for $C_{14}H_{22}O$ 206.1675).

The second component (30β, syn isomer) displayed the following data: IR (CCl_4) 2870–3000 (s, br), 1730 (s), 1450 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.95, 0.99, 1.08 (s, d, J = 6.5 Hz, and s, 9 H), 1.16–2.12 (complex m, 12 H, containing H_A of an AB pattern at 1.97, J_{AB} = 15 Hz), 2.67 (d, 1 H, H_B of an AB pattern centered at 2.32, $\Delta\nu_{AB}$ = 175 Hz, J_{AB} = 15 Hz); mass spectrum, m/e 206.1673 (M^+; calcd for $C_{14}H_{22}O$ 206.1675).

Isomodhephene (34α). To a flask containing 334 mg (0.93 mmol) of methyltriphenylphosphonium bromide and heated to 80 °C under argon were added 0.47 mL of potassium *tert*-amylate (1.765 M in benzene)[52] and 0.1 mL of toluene. The resulting bright yellow solution of the methylidenephosphorane was stirred for 30 min, maintaining the temperature between 85–92 °C. At 92 °C, 24.7 mg (0.12 mmol) of **30**α was added in 0.1 mL of toluene. After being stirred at 90–92 °C for 2 h, the mixture was cooled, extracted into ether, washed, and dried. The solvent was removed in vacuo, and the residue was dissolved in pentane, passed through a short silica column to remove the triphenylphosphine oxide, and finally purified by preparative thin-layer chromatography (PLC; 500-μm silica plate, eluting with pentane) to afforded 12 mg (49%) of isomodhephene (**30**α): colorless oil; IR (CCl_4) 3050 (w), 2850–3000 (s, br), 1630 (m), 1450 (m), 1350 (m), 885 (s) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.87, 0.90, 0.92 (s, s, and d, J = 6.7 Hz, 9 H), 1.02–1.99 (complex m, 12 H), 2.47 (d, J = 14 Hz, 1 H), 4.64–4.66 (m, 1 H, H_A), 4.70–4.72 (m, 1 H, H_B); mass spectrum, m/e 204.1868 (M^+; calcd for $C_{15}H_{24}$ 204.1879).

Isoepimodhephene (34β). To a flask containing 391 mg (1.09 mmol) of methyltriphenylphosphonium bromide heated to 80 °C under argon was added 0.6 mL potassium *tert*-amylate (1.765 M in benzene) and 0.2 mL toluene. The mixture was then stirred for 30 min with the temperature being maintained between 85 and 92 °C. To the resulting bright yellow solution of Wittig reagent was added at 92 °C 31 mg (0.15 mmol) of **30**β in 0.1 mL of toluene. After being stirred at 90–92 °C for 2 h, the mixture was cooled, extracted into ether, washed, and dried. The solvent was removed in vacuo, and the residue was dissolved in pentane, eluted through a short silica column, and finally purified by PLC (500-μm silica gel plate, eluting with pentane) to afford 17 mg (56%) of isoepimodhephene (**31**β): colorless oil; IR (CCl_4) 2850–3000 (s, br), 1450 (m), 885 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.72–1.00 (s, s, and overlapping d, 9 H), 1.00–2.12 (complex m, 12 H), 2.22–2.34 (m, 1 H), 4.58–4.62 (m, 1 H, H_A), 4.82–4.86 (m, 1 H, H_B); mass spectrum, m/e 204.1870 (M^+; calcd for $C_{15}H_{24}$ 204.1879).

(±)-Modhephene (1α). A solution of 8.9 mg (0.04 mmol) of isomodhephene (**34**α) and 3.6 mg (0.019 mmol) of *p*-toluenesulfonic acid monohydrate in 0.3 mL of methylene chloride was stirred for 3 h at room temperature. Purification on a short silica column (eluting with methylene chloride) afforded 7.7 mg (87%) (±)-modhephene (1α): clear liquid; IR (CCl_4) 2850–3000 (s, br), 1430 (m), 1360 (m), 838 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.74–2.14 (complex m, 23 H, containing two overlapping s and a d centered at 0.96 and a doublet at 1.62, J = 1.5 Hz), 4.85 (m, 1 H); mass spectrum, m/e 204.1882 (M^+; calcd for $C_{15}H_{24}$ 204.1879). Synthetic modhephene was identical in all respects (IR, 250-MHz NMR, and mass spectra) with a sample of the natural product generously supplied by Professor Zalkow of the Georgia Institute of Technology.

(±)-Epimodhephene (1β). A solution of 17 mg (0.08 mmol) of (±)-isoepimodhephene (**34**β) and 7.5 mg (.04 mmol) of *p*-toluenesulfonic acid monohydrate in 0.6 mL of methylene chloride was stirred at room temperature for 3 h. Purification was effected on a short silica column (eluting with methylene chloride), affording 17 mg (100%) of (±)-epimodhephene (1β): clear liquid; IR (CCl_4) 2850–3000 (s, br), 1430 (m), 1360 (m), 845 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.33 (d, J = 7.2 Hz, 3 H), 0.98, 1.01 (s, s, 9 H), 1.04–2.00 (complex m, 14 H, containing a d at 1.61, J = 1.6 Hz), 4.95 (m, 1 H); mass spectrum, m/e 204.1895 (M^+; calcd for $C_{15}H_{24}$ 204.1879).

5-Methylbicyclo[4.3.0]non-1(6)-en-2-one (11). A solution of 1.39 g (6.68 mmol) of **13** and 2.56 g (8.1 mmol) of barium hydroxide octahydrate in 200 mL of water was heated at reflux for 4 h. After the mixture was cooled to room temperature, concentrated hydrochloric acid was added until the pH of the solution was 1.00. The mixture was then stirred at room temperature for 1.5 h, extracted into ether, washed, and dried. Removal of the solvent in vacuo and Kugelrohr distillation [bp 70–80 °C (0.3 mmHg)] afforded **11**: 0.85 g (85%); colorless oil; IR (CCl_4) 2850–3000 (s, br), 1660 (s), 1630 (sh), 1440 (m), 1380 (s), 1210 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.16 (d, J = 6.9 Hz, 3 H), 0.40–2.81 (complex m, 11 H); mass spectrum, m/e 150.1037 (M^+; calcd for $C_{10}H_{14}O$ 150.1045).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.89; H, 9.34.

5-Methyl-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one (35). A degassed solution containing 477 mg (3.18 mmol) of **11** and 0.8 mL (10.4 mmol) of a mixture of *cis*- and *trans*-1,2-dichloroethylenes in 70 mL of hexane was irradiated through Pyrex for 1.25 h. Removal of the solvent in vacuo and Kugelrhohr distillation [bp 100 °C (0.1 mmHg)] yielded 535 mg (68%) of the isomeric chloro ketones **35**: viscous yellow oil; IR (CCl_4) 2900–3000 (s, br), 2860 (m), 1700 (s), 1450 (m), 1285 (m), 1155 (w), 915 (m), 810 (m), 720 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.89–1.03 (overlapping d, J = 7.5 Hz, 3 H), 1.17 –2.63 (m, 11 H), 3.97, 4.05 (2 d J = 5 Hz, 1 H, H_A), 4.40, 4.50 (2 d, J = 5 Hz, 1 H, H_B); mass spectrum, m/e 246.0590 (M^+; calcd for $C_{12}H_{16}OCl_2$ 246.0580).

5-Methyl-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one Ethylene Ketal. A solution of 516 mg (2.10 mmol) of **35**, 0.25 mL (4.4 mmol) of ethylene glycol, and 40 mg (0.2 mmol) of *p*-toluenesulfonic acid monohydrate in 60 mL of benzene was heated to reflux overnight with azeotropic removal of water. The reaction mixture was worked up by being poured into sodium bicarbonate–ether, washed, and dried. After filtration through a magnesium sulfate silica pad and removal of the solvent in vacuo, the product was purified by flash column chromatography[50] (1:1 hexane–methylene chloride) to afford 454 mg of 5-methyl-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undec-2-one ethylene ketal; the yield was 94% based on recovered ketone. This ketal displayed the following spectral properties: IR (CCl_4) 2900–3000 (s, br),

(52) Potassium *tert*-amylate was prepared according to the procedure of Schow and McMorris.[43a]

2870 (s), 1450 (m), 1295 (m, br) 1100–1175 (s, br), 1045 (s, br), 945 (m), 850 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.75–0.97 (overlapping doublets, J = 7.5 Hz, 3 H), 1.23–2.43 (complex m, 11 H), 3.83–4.13 (complex m, 5 H, containing H_A), 4.42, 4.71 (2 d, J = 6.0 Hz, 1 H, H_B); mass spectrum, m/e 290.0885 (M^+; calcd for $C_{14}H_{20}O_2Cl_2$ 290.0842).

5-Methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one Ethylene Ketal. To a flask containing 250 mL of freshly distilled anhydrous ammonia was added under argon 454 mg (1.56 mmol) of the above isomeric chloro ketals (dissolved in 40 mL of ether). Small pieces of sodium metal were added until the solution remained dark blue for 15 min. Excess sodium was then quenched by the addition of ammonium chloride, and the ammonia was allowed to evaporate overnight. The solid residue was dissolved in water and extracted several times into ether. Evaporation of the solvent in vacuo and Kugelrohr distillation [bp 80–100 °C (0.5 mmHg)] yielded 253 mg (74%) of 5-methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one ethylene ketal: IR (CCl_4) 3030 (w), 2900–2950 (s, br), 2810 (s), 1110–1170 (s, br), 1055 (s), 995 (m), 950 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.84, 0.86 (2 d, J = 7.5 Hz, 3 H), 0.900–2.44 (complex m, 11 H), 3.80–4.06 (m, 4 H), 5.92, 6.03, 6.10, 6.13 (4 d, J = 2.5 Hz, 2 H, H_A and H_B); mass spectrum, m/e 220.1458 (M^+; calcd for $C_{14}H_{20}O_2$ 220.1464).

5-Methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one (12α,β). A solution containing 250 mg (1.14 mmol) of the above isomeric ketals, 0.2 mL of concentrated sulfuric acid in 10 mL water (2% aqueous sulfuric acid), and 15 mL of acetone was stirred overnight at room temperature. The reaction mixture was then poured into saturated sodium bicarbonate–ether, washed, and dried. After filtration through a magnesium sulfate–silica pad, concentration in vacuo and Kugelrohr distillation [bp 50–70 °C (0.2 mmHg)], 175 mg (88%) of **12** was isolated as a 57:43 mixture of anti (12α) and syn (12β) isomers, respectively. Separation was effected by VPC (185 °C).

The first component (12β, syn isomer) had the following spectral data: IR (CCl_4) 3040 (w), 2900–3000 (s, br), 2860 (m), 1680 (s), 1270 (m), 880 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.00 (d, J = 7.5 Hz, 3 H), 1.06–2.64 (m, 11 H), AB q centered at 6.07 (J_{AB} = 2.5 Hz, $\Delta\nu_{AB}$ = 70 Hz, δ_A 5.93 δ_B 6.21, 2 H, H_A and H_B); mass spectrum, m/e 176.1204 (M^+; calcd for $C_{12}H_{16}O$ 176.1202).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.83; H, 9.21.

The second component (12α, anti isomer) had the following spectral data: IR (CCl_4) 3040 (w), 2930–3000 (s, br), 2880 (m), 1690 (s), 1270 (m), 880 (m), cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.91 (d, J = 7.5 Hz, 3 H), 1.20–2.52 (m, 11 H), AB q centered at 6.06 (J_{AB} = 2.5 Hz, $\Delta\nu_{AB}$ = 72.5 Hz, δ_A 5.91, δ_B 6.20, 2 H, H_A and H_B); mass spectrum, m/e 176.1204 (M^+; calcd for $C_{12}H_{16}O$ 176.1202).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.46; H, 9.25.

6-Methyltricyclo[3.3.3.0^{1,5}]undec-3-en-2-one (9α,β). To a solution of 52 mg (0.3 mmol) of the epimeric ketones **12** in 6.0 mL of benzene was added 16 mg (0.08 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was heated to reflux under an inert atmosphere for 2 h. A second portion of *p*-toluenesulfonic acid was added (16 mg, total 0.16 mmol), and the mixture was refluxed for an additional 2 h. The reaction was followed by TLC [5% ether–methylene chloride (v/v)]. After cooling, the solution was poured into 10% aqueous sodium bicarbonate–ether, washed with 10% sodium bicarbonate, and dried. Evaporation of the solvent in vacuo followed by PLC [1000-μm silica plate, 20% ether–methylene chloride (v/v)] afforded 33.4 mg (64%) of a 57:43 mixture of syn (9α) and anti (9β) isomers, respectively. The isomers were separated by VPC (185 °C); each was identical with respect to IR, 250-MHz NMR, and VPC retention time with the isomer isolated from the acid-catalyzed rearrangement of 8.

5-(Carbomethoxy)-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one (36). A degassed solution containing 1.1 g (6.17 mmol) of 14 and 1.4 mL (18 mmol) of 1,2-dichloroethylene (cis and trans) in 60 mL of benzene was irradiated through Pyrex for 1.5 h. Evaporation of the solvent in vacuo followed by flash column chromatography [7% ether–methylene chloride (v/v)] yielded 1.1 g (73% based on recovered starting material) of **36** as a sticky yellow solid with the following spectral properties: IR (CCl_4) 2850–3000 (m, br), 1730 (s), 1710 (s), 1170 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.48–3.30 (complex m, 11 H), 3.71, 3.74 (s, s, 3 H), 4.00, 4.17, 4.46, 4.59, 4.77 (5 d, $J \simeq$ 6 Hz, 2 H, H_A and H_B); mass spectrum, m/e 290.0491 (M^+; calcd for $C_{13}H_{16}O_3Cl_2$ 290.0478).

5-(Carbomethoxy)-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one Ethylene Ketal (37a). To a solution containing 8 mg (0.36 mmol) of trimethylsilyl trifluoromethanesulfonate in 0.5 mL of methylene chloride under argon were added 354 mg (1.7 mmol) of the bis(trimethylsilyl) ether of ethylene glycol[46] and 369 mg (1.27 mmol) of **36** in 0.5 mL of methylene chloride. After the mixture was stirred 3 h at room temperature, the reaction was quenched with 26 μL (0.32 mmol) of pyridine. The organic material was then extracted into ether, washed with saturated sodium bicarbonate, and dried. Removal of the solvent in vacuo followed by flash column chromatography[50] (eluting with methylene chloride) afforded 290 mg (68%) of **37a**: viscous yellow oil; IR (CCl_4) 2900–3000 (s, br), 2800 (s), 1730 (s), 1150–1200 (s, br), 910 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.60–2.67 (complex m, 11 H), 3.68, 3.69 (s, s, 3 H), 3.81–4.17 (complex m, 5 H, contains H_A), 4.67, 4.75 (2 d, J = 7.5 Hz, 1 H, H_B); mass spectrum, m/e 334.0772 (M^+· calcd for $C_{15}H_{20}O_4Cl_2$ 334.0740).

5-(Hydroxymethyl)-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one Ethylene Ketal (37b). To a solution of 290 mg (0.8 mmol) of **37a** in 3.0 mL of toluene cooled to −78 °C under argon was added 2.2 mL (2.2 mmol) of diisobutylaluminum hydride (1.0 M in toluene). After being stirred 3.5 h at −78 °C, the mixture was warmed to room temperature, and excess hydride was quenched by adding in succession 2.2 mL of water, 2.2 mL of 15% sodium hydroxide, and 6.6 mL of water. After the mixture was stirred 1 h, 2.2 mL of methanol was added. The resulting mixture was then stirred 30 min longer, and the organic material was extracted into ether–ethyl acetate, washed, and dried. Removal of the solvent in vacuo followed by flash column chromatography [15% ether–methylene chloride (v/v)] afforded 155 mg (63%) hydroxy ketal **37b**. Further purification by PLC [10% ether–methylene chloride (v/v)] effected separation of two compounds (2:1), which were isomeric about the hydroxymethyl substituent.

The major component (syn isomer) had the following spectral data: IR (CCl_4) 3650–3300 (br), 2850–3000 (s, br), 1150 (m, br), 1000–1060 (s, br), 950 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.78–2.40 (complex m, 12 H), 3.37 (dd, J = 10, 7 Hz, 1 H, H_1) 3.74 (dd, J = 10, 5 Hz, 1 H, H_2), 3.84–4.00 (m, 4 H), 4.05 (d, J = 7.5 Hz, 1 H, H_A), 4.66 (d, J = 7.5 Hz, 1 H, H_B); mass spectrum, m/e 306.0820 (M^+; calcd for $C_{14}H_{20}O_3Cl_2$ 306.0791).

The minor component (anti isomer) was characterized as follows: IR (CCl_4) 3300–3650 (br), 2870–3000 (s, br), 1150 (s, br), 1030–1070 (s, br), 970 (m), 920 (m) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.800–2.40 (complex m, 12 H), 3.48–3.80 (m, 2 H, H_1 and H_2), 3.86–4.16 (m, 5 H, containing a d at 4.06, J = 7.5 Hz, H_A), 4.56 (d, J = 7.5 Hz, 1 H, H_B); mass spectrum, m/e 306.0820 (M^+; calcd for $C_{14}H_{20}O_3Cl_2$ 306.0791).

5-(Hydroxymethyl)tricyclo[4.3.2.0^{1,6}]undec-10-en-2-one Ethylene Ketal (38a). To a flask containing 50 mL of freshly distilled anhydrous ammonia was added under argon 146 mg (0.476 mmol) of ketal (**37b**). Small pieces of sodium metal were added until the solution remained dark blue for 20 min. Ammonium chloride was then added to quench excess sodium, and the ammonia was evaporated. The residue which remained was dissolved in water and the organic material extracted into ether. Evaporation of the solvent in vacuo yielded 107 mg (96%) of **38a** as a 2:1 mixture of syn and anti isomers, respectively. Spectral data of the epimeric mixture were obtained on a sample purified by PLC [500-μm silica gel plate, 15% ether–methylene chloride (v/v)]: IR (CCl_4) 3300–3650 (br), 3030 (w), 3850–3000 (s, br), 1120–1170 (s, br), 1020–1080 (s, br), 955 (w) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.00–2.69 (complex m, 12 H), 3.40–3.72 (m, 2 H, hydroxymethyl H's), 3.76–3.86 (m, 4 H), 2 AB q with one centered at 5.97 (J_{AB} = 2.6 Hz, $\Delta\nu_{AB}$ = 55 Hz, δ_A 5.86, δ_B 6.08) and the other centered at 5.99 (J_{AB} = 2.8 Hz, $\Delta\nu_{AB}$ = 10 Hz, δ_A 5.97, δ_B 6.01, 2 H, H_A and H_B); mass spectrum, m/e 236.1421 (M^+; calcd for $C_{14}H_{20}O_3$ 236.1413).

Reduction to 5-Methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one Ethylene Ketal (38c). To a solution consisting of 52 mg (0.22 mmol) of **38a**, 1.0 mL of tetrahydrofuran, and 0.22 mL (1.58 mmol) of triethylamine cooled to 0 °C under argon was added 0.03 mL (0.388 mmol) of methanesulfonyl chloride in 1.0 mL of tetra-

hydrofuran. After the mixture was stirred 1 h at 0 °C, the material was taken up in ether and eluted through a silica gel column, yielding 65 mg (94%) of crude mesylate **38b**: IR (CCl_4) 3030 (w), 2850–3000 (s, br), 1380 (s), 1360 (s), 1190 (s) cm^{-1}; NMR (60 MHz, CCl_4) δ 0.80–2.00 (complex m, 11 H), 2.90, 3.12 (s, s, 3 H), 3.80–4.20 (m, 6 H), 5.80–6.20 (m, 2 H). Mesylate **38b** was reduced immediately without further purification.

Toward this end, to a solution of 65 mg (0.21 mmol) of the isomeric methanesulfonate esters **38b** in 0.8 mL of tetrahydrofuran was added 0.43 mL (0.43 mmol) of lithium triethylborohydride (1 M in tetrahydrofuran). The resulting solution was stirred under argon for 20 min at room temperature and then heated to reflux for 1.5 h. After the mixture was cooled to 0 °C, excess hydride was quenched by the slow addition of 1.4 mL of water, 1.4 mL of 3 N sodium hydroxide, and 1.4 mL of 30% hydrogen peroxide. The mixture was heated at reflux for 1 h, cooled, poured into 2 mL of water, and extracted into pentane. After the mixture was dried, removal of the solvent in vacuo and purification by PLC (500-μm silica gel plate, eluting with methylene chloride) yielded 17.3 mg (38%) of ene ketals **38c**, which were identical in all respects with those prepared from **11**.

5-Methyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one (12α,β). A solution containing 15 mg (0.068 mmol) of ene ketal **38c**, 13 μL of concentrated sulfuric acid in 0.7 mL of water (2% aqueous sulfuric acid), and 1 mL of acetone was stirred overnight at room temperature. The mixture was then poured into saturated sodium bicarbonate–ether, washed, and dried. After filtration through magnesium sulfate–silica and evaporation of the solvent in vacuo, **12** was isolated quantitatively as a 2:1 mixture of syn (**12β**) and anti (**12α**) isomers, respectively. Separation was effected by VPC (185 °C). Each isomer was identical with respect to IR, 250-MHz NMR, and VPC retention time with the same isomer prepared from **11**.

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Registry No. (±)-**1α**, 76739-64-5; (±)-**1β**, 76739-65-6; (±)-**8α**, 76685-65-9; (±)-**8β**, 76739-60-1; (±)-**9α**, 76740-73-3; (±)-**9β**, 76685-66-0; (±)-**10**, 73537-33-4; (±)-**11**, 78676-01-4; (±)-**12α**, 80953-79-3; (±)-**12β**, 80996-28-7; (±)-**13**, 78676-00-3; (±)-**14**, 80953-80-6; **18**, 5323-87-5; **19**, 61765-62-6; **20**, 61765-54-6; (±)-**21**, 80953-81-7; **23a**, 80953-82-8; **23b**, 80953-83-9; (±)-**24** (isomer I), 80953-84-0; (±)-**24** (isomer II), 80996-29-8; (±)-**29α**, 76685-67-1; (±)-**29β**, 76739-61-2; (±)-**30α**, 76685-68-2; (±)-**30β**, 76739-62-3; (±)-**34α**, 76685-69-3; (±)-**34β**, 76739-63-4; **35**, 80953-85-1; **36**, 80953-86-2; **37a**, 80953-87-3; **37b**, 80953-88-4; (±)-**38a** (isomer I), 80953-89-5; (±)-**38a** (isomer II), 80996-30-1; (±)-**38b** (isomer I), 80953-90-8; (±)-**38b** (isomer II), 80996-31-2; (±)-**38c** (isomer I), 80953-91-9; (±)-**38c** (isomer II), 80996-32-3; (±)-**i**, 80953-93-1; isopropenyl bromide, 557-93-7; 5-methyl-10,11-dichlorotricyclo[4.3.2.0^{1,6}]undecan-2-one ethylene ketal, 80953-92-0; 1,2-dichloroethylene, 540-59-0.

Stereocontrolled Total Synthesis of (±)-Pentenomycins I–III, Their Epimers, and Dehydropentenomycin I

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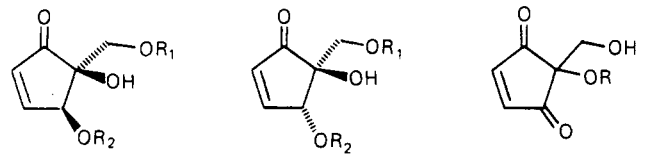
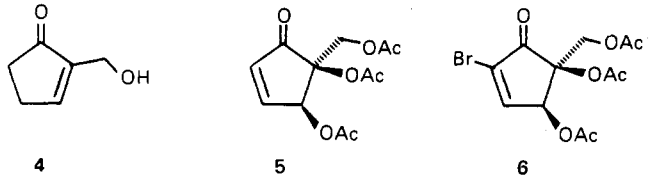
The total synthesis of (±)-pentenomycins I–III (**1a–c**), their epimers (**2a–c**) termed by us epipentenomycins (I–III), and dehydropentenomycin I (**3**), seven members of the novel cyclopentanoid class of antibiotics, has been achieved. The synthetic routes are short (ca. five to seven steps), stereocontrolled, and for the most part highly efficient. Key elements of the strategies were (i) the development of a versatile α-ketovinyl anion equivalent which permitted large-scale preparation of 2-(hydroxymethyl)-2-cyclopentenone (**4**), the common starting material for each antibiotic, (ii) the stereocontrolled cis hydroxylation of derivatives of either **4** or protected allylic alcohols derived from **4** [i.e., selective 1,2-reduction employing the method of Luche (i.e., $NaBH_4/CeCl_3{\cdot}H_2O$)], and (iii) introduction of the requisite α,β-unsaturation via SeO_2 oxidation.

Recently, we successfully completed the stereocontrolled total synthesis of (±)-pentenomycins I–III (**1a–c**),[2] their epimers (**2a–c**),[3] and the closely related dehydropentenomycin I (**3**),[2] seven members of the novel cyclopentanoid class of antibiotics.[4] We record here a full account of that effort. We note in advance that the synthetic stragegies are short, ranging from five to seven steps from 2-(hydroxymethyl)-2-cyclopentenone (**4**), stereocontrolled, and for the most part highly efficient. Furthermore, 2-(hydroxymethyl)-2-cyclopentenone serves as the *common synthetic precursor* for each of the pentenomycins, the latter readily available through application of a versatile latent α-ketovinyl anion equivalent recently developed in our laboratory.[5]



1 **2** **3**

(a) $R_1 = R_2 = H$
(b) $R_1 = H$; $R_2 = Me$
(c) $R_1 = Ac$; $R_2 = H$



4 **5** **6**

Pentenomycin I (**1a**), an amorphous powder, and pen-

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