Synthesis of Aphidicolin: Preliminary Studies[1a]

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A scheme for the synthesis of aphidicolin (1) is presented. Attempted photoisomerization via a 1,3-acyl shift was unsuccessful in a series of β,γ-unsaturated ketones **10**. Dienone **12**, on the other hand, did undergo 1,3-acyl shift to produce **20**, a tricyclic ketone that embodies the BCD ring system of **1**. The mechanism of the **12** $\rightleftarrows$ **20** change is discussed. The known tricyclic enone **7** was converted into the cyclobutane **26**, the stereochemistry of which was established by X-ray analysis of diketone **27**. An alternative scheme starting with cyclohexane-1,3-dione produced the AB-cis-fused keto alcohol **34**.

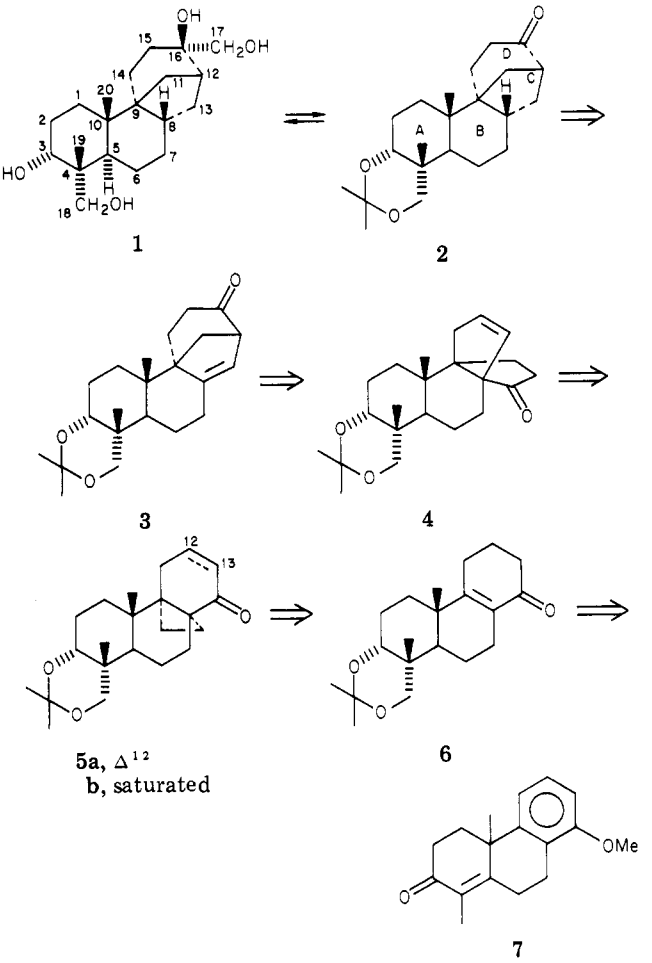
The structure of a new tetracyclic diterpene, aphidicolin (**1**), produced by *Cephalosporum aphidicola* Petch, was reported in 1972 by Hesp et al.,[2,3] and shortly thereafter, a group of related diterpenes isolated from *Stemodia maritima* was described.[4,5] The two families of diterpenes possess the same carbon framework but are epimeric at C-9 and C-12. Since that time, reports of the biological activities,[6] a proposed biosynthesis,[7] and five synthetic routes to **1**[8-12] have been described. The construction of the BCD ring system is the major synthetic challenge presented by aphidicolin. Here the bicyclo[3.2.1]octane is attached to the *trans*-decalin AB system in a previously unknown manner. In this paper we describe an approach to the synthesis of aphidicolin via norketone **2**, a degradation product of aphidicolin that has been converted back into **1**,[3,11] based on the propellane chemistry developed in our laboratory.[13]

The construction of ring A is conceptually straightforward. Both Trost[8] and McMurry[9] report the reductive hydroxymethylation of a 3-oxo-4-methyl 4-ene precursor, followed by reduction of the 3-ketone with a hindered hydride donor, to produce the desired array of functionality in ring A.

Our analysis of structure **2** suggests that in the catalytic hydrogenation of **3**, hydrogen will be delivered to the convex β face of the bicyclooctene moiety to produce **2** and establish the proper stereochemistry at C-8 (see Scheme I). Since **3** is a β,γ-unsaturated ketone, it is related to its isomer **4** by a photochemical 1,3-acyl shift, and **4** is the expected product of an acid-catalyzed isomerization of the cyclobutane **5**. The latter may be seen as the cycloadduct of ethylene and enone **6** (after introduction of a double bond), and the relationship of **6** to the known **7**[14] is obvious.

Propellanone **8** embodies the essential structural features of **5** and is readily available;[13b] therefore, in a model study with cheap tricyclic material, we could ascertain the validity of our planned synthesis. Conversion of **8** into **9** via

Scheme I



1 2 3 4 5a, Δ^{12} b, saturated 6 7

(1) (a) Grateful acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, the National Institutes of Health, and the University of South Carolina for financial support of this research. A portion of this work was presented at the ACS–JCS Chemical Congress, Honolulu, HI, Apr 1979, Abstract No. ORGN 381. (b) Address correspondence to this author at Post Office Box 992, Longview, TX 75606.

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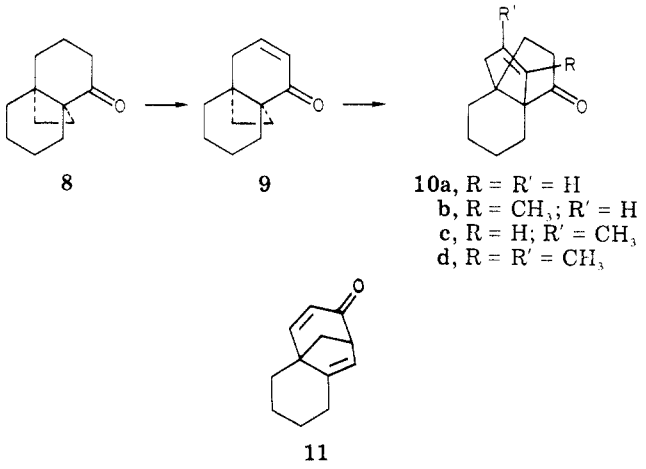
(13) (a) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106. (b) Peet, N. P., Cargill, R. L. *J. Org. Chem.* **1973**, *38*, 4281. (c) Peet, N. P.; Cargill, R. L.; Bushey, D. F. *Ibid.* **1973**, *38*, 1218.

(14) Shiozaki, M.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1972**, *36*, 2539.

0022-3263/81/1946-3389$01.25/0

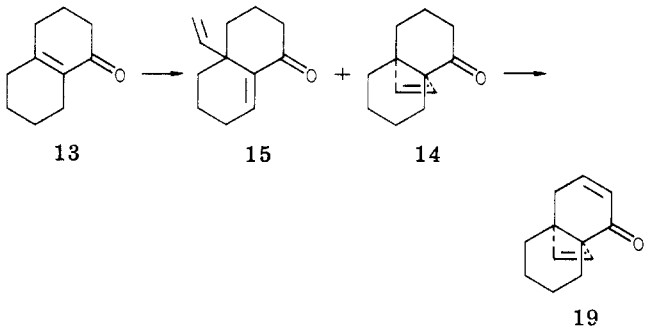
Scheme II



8 9 10a, R = R' = H; b, R = CH_3; R' = H; c, R = H; R' = CH_3; d, R = R' = CH_3

11

Scheme III

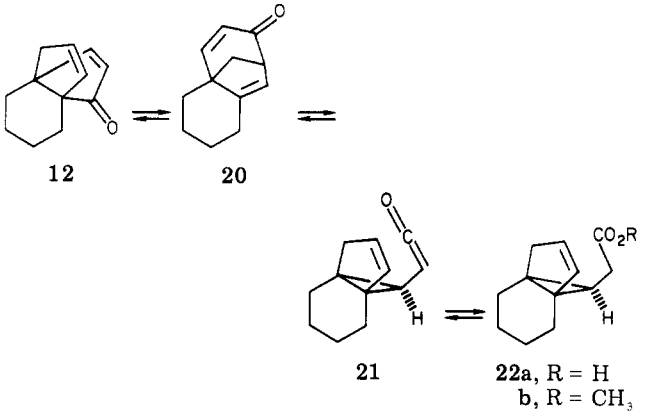


13 15 14 19

the α-phenylselenenyl derivative (75%)[15] was preferable to dehydrogenation of the trimethylsilyl enol ether with trityl fluoroborate (25%).[16] Isomerization of **9** (Scheme II) was best accomplished with boron trifluoride in acetonitrile (42%); thus equilibration of **10a** with the γ,δ-unsaturated isomer is avoided. Irradiation of **10a** under a variety of conditions led to disappearance of **10a**, but no volatile product could be detected by gas chromatographic analysis. Whether **11** was formed and subsequently decomposed could not be ascertained. One possible solution to the dilemma presented by the failure of **10a** to undergo a photochemical 1,3-acyl shift was to increase the interaction of olefinic and carbonyl groups by the introduction of alkyl groups on the former.[17,18] However, irradiations of **10b–d** (see Experimental Section for syntheses) failed to produce any volatile products. Then, the fact that some α,β,β',γ'-unsaturated ketones undergo the 1,3-acyl shift[19] encouraged our exploration of the chemistry of dienone **12**.

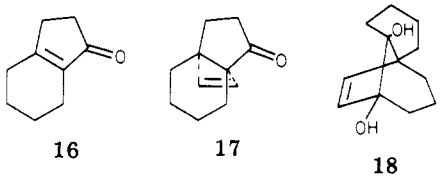
Conversion of **10a** into **12** (63%) via the α-phenylselenenyl derivative was unexceptional; but a potentially more efficient route was also explored. Irradiation of octalone **13** in methylene chloride saturated with acetylene gave the desired cycloadduct **14** along with the isomeric

Scheme IV



12 20 21 22a, R = H; b, R = CH_3

vinyloctalone **15** (35% and 20%, respectively, Scheme III). The formation of **15** is of potential synthetic interest because of the obvious structural similarity of it and the sesquiterpene vernolepin.[20] One is tempted to suggest that both **14** and **15** are formed from a common biradical intermediate in which hydrogen abstraction and ring closure are competitive. The hydrogen abstraction reaction is not observed in the additions of ethylene or 1,2-dichloroethylene to **13** or in the addition of acetylene too hydrindanone **16**. In these cases cycloaddition occurs to the exclusion of all other processes.[21] Vinyloctalone **15** is not a photoproduct of **14** since irradiation of the latter produced only **8**.[17a]



16 17 18

When the synthesis of **14** was attempted in the standard manner (photoaddition of **13** and dichloroethylene, ketalization, dechlorination, and hydrolysis),[13] the only product of the overall sequence was the rearranged glycol **18** (86%, overall).[24] The rearrangement occurs during the hydrolytic step with all acids tested including Dowex 50 or 3% H_2SO_4. On the other hand, the mixture of cycloadducts could be reduced with sodium borohydride, the resulting alcohols dechlorinated, and the resulting cyclobutene alcohol oxidized with pyridinium chlorochromate to give the desired ketone **14** in 37% yield from **13**.

Irradiation of **12** in hexane (Pyrex, −78 °C) gave a photostationary mixture of **12** (45%) and **20** (55%) (Scheme IV). A pure sample of the new isomer, which embodies the carbon skeleton of rings BCD of aphidicolin, was obtained by preparative gas chromatography. Irradiation of **20** gave the same mixture. Thus, although the originally planned 1,3-acyl shift was unsuccessful, the introduction of a second double bond seems to provide a path by which this overall change may occur and thereby provides a possible solution of the aphidicolin problem.

(15) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
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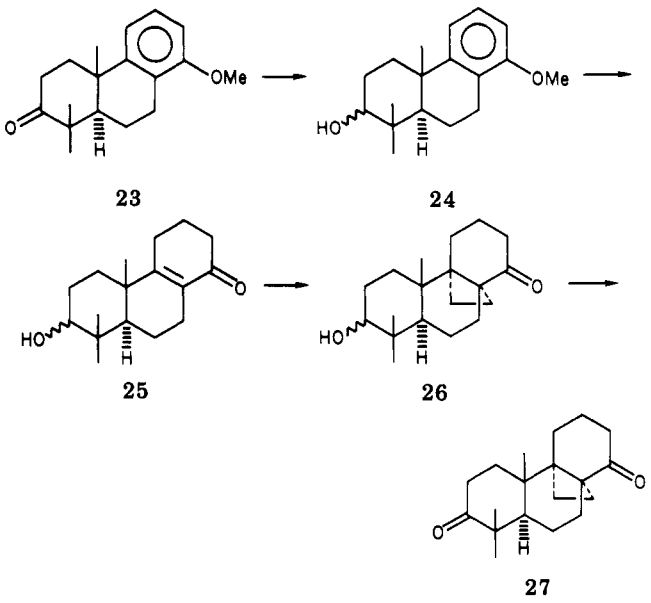
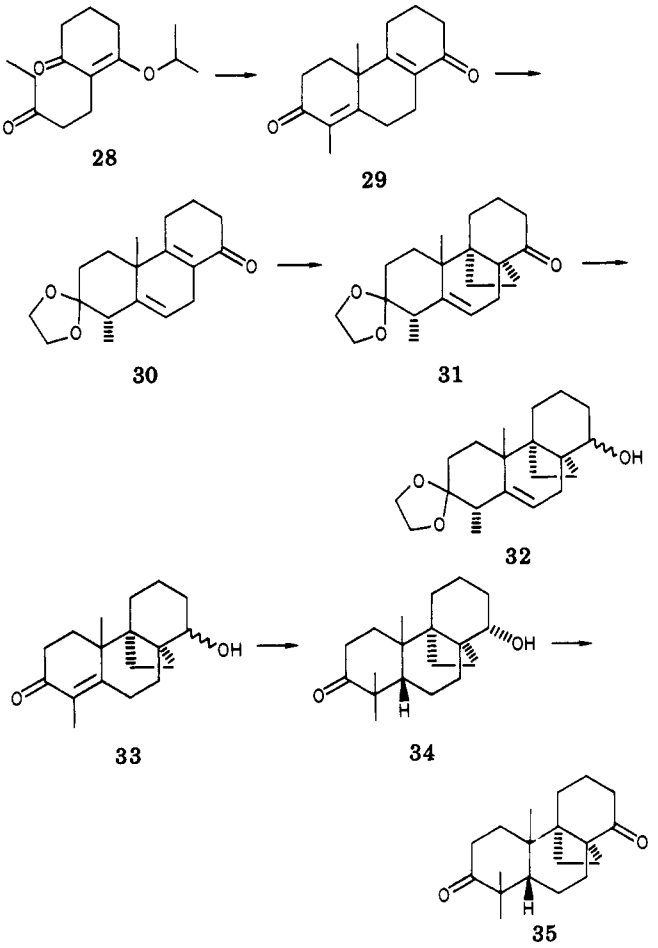
(18) For reviews of the photochemistry of β,γ-unsaturated ketones, see: (a) Dauben, W. G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* **1975**, *54*, 73. (b) Houk, K. *Chem. Rev.* **1976**, *76*, 1.
(19) (a) Hart, H.; Love, G. M. *Tetrahedron Lett.* **1971**, 3563. (b) Murata, I., Sugihara, Y. *Chem. Lett.* **1972**, 625.
(20) See: Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1979**, *101*, 6076 and references cited therein.
(21) We reported earlier[13c] that cycloadditions with **13** are sluggish at best; however, when these irradiations are carried out at ca. −70 °C with a 1000-W lamp, these cycloadditions are preparatively useful. See also ref 39.
(22) The use of a triplet sensitizer is not helpful, as can be seen by comparison of our addition with 1,2-dichloroethylene and that of Rae and Umbrasas.[23]
(23) Rae, I. D.; Umbrasas, B. N. *Aust. J. Chem.* **1975**, *28*, 2669.
(24) Cargill, R. L.; Pond, D. M.; LeGrand, S. O. *J. Org. Chem.* **1970**, *35*, 359.

Scheme V



Scheme VI



The interconversion of **12** and **20** may occur by an ordinary photochemical 1,3-acyl shift made possible by a reordering of triplet energy levels in the dienones.[25] Thus, the n,π^* singlet obtained upon excitation of **10** may undergo α-cleavage (and ultimate degradation) more rapidly than intersystem crossing to the presumably lower lying π,π^* triplet. The latter species usually undergoes the oxa-di-π-methane rearrangement or other nonproductive (in the present context) process. On the other hand, the lower lying triplet of the conjugated ketone **12** is probably mostly n,π^* in character. Either the S^1 or T^1 state of **12**, both being n,π^* states, could undergo the 1,3-acyl shift to give **20**. A similar argument can be made for the reconversion of **20** into **12**. An alternative path is the isomerization of **12** to the syn cyclopropylketene **21**[26] followed by thermal isomerization of the latter to **20**.[27] Irradiation of **12** in wet ether gave a single acid, **22a**, which was converted into ester **22b** with diazomethane. The same ester was the sole product of irradiation of either **12** or **20** in hexane containing methanol. The syn stereochemistry of **22** was demonstrated by its conversion into dienone **20** via ketene **21**. Since there is no reason to believe that the photochemical conversion of **12** into a cyclopropyl ketene should be stereospecific, nor do *trans*-divinylcyclopropanes undergo thermal isomerization at temperatures below ca. 190 °C, we conclude that **12** and **20** are interconverted via a real 1,3-acyl shift. Isomerization of **20** to **21**[29] and thermal reversion of **21** to **20** are competitive with the 1,3-acyl shift. The latter processes go unobserved in the absence of nucleophiles, but in their presence, all of **12** or **20** may be trapped as a derivative of acid **22**. Isolation of **22**, coupled with its nonphotochemical transformation into dienone **20**, provides a method for the conversion of all of **12** into the latter. This discovery suggests the best method for the final stages of our projected synthesis of aphidicolin.

We turn now to discussion of the construction of aphidicolin. We have explored two routes to the required tetracyclic precursors of 18-deoxyaphidicolin in order to ascertain as rapidly as possible whether the proposed set of rearrangements (described above) could be applied in the tetracyclic series. The first to be discussed is similar to that outlined in Scheme I.

Reductive methylation of **7** gave **23**,[30] which could be reduced with lithium aluminum hydride to give the equatorial alcohol **24e** or with L-Selectride to yield a mixture of axial (**24a**) and equatorial (**24e**) alcohols in which the former predominated by 4:1 (Scheme V). The axial alcohol was separated by fractional crystallization. Reduction of **24a** with excess lithium in a mixture of ammonia, ethanol, and THF[31] gave, after hydrolysis with aqueous oxalic acid and heating with rhodium trichloride trihydrate,[32] a mixture from which the desired enone **25a** could be isolated in 35% yield (on the best run). The other components of the reduction mixture are described in the Experimental Section. Similar reduction of **24e** gave **25e**, but a detailed examination of the byproducts was not carried out.

(25) Some 1,3 acyl shifts are reported to occur in the n,π^* triplet state when that state is the upper triplet (T_2). This arrangement is more likely in the dienones **12** and **20** than in **10**. See: (a) Dalton, J. C.; Shen, M.; Snyder, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 5023; (b) Mirbach, M., Henne, A.; Schaffner, K. *Ibid.* **1978**, *100*, 7127.

(26) (a) Agosta, W. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **1971**, *93*, 5513. (b) Agosta, W. C.; Wolff, S. *Ibid.* **1975**, *97*, 456. (c) Agosta, W. C.; Wolff, S. *Ibid.* **1976**, *98*, 4182. Agosta, W. C.; Wolff, S. *Ibid.* **1977**, *99*, 3355.

(27) (a) Freeman, P. K.; Kuper, D. J. *Chem. Ind. (London)* **1965**, 425. (b) Uyehara, T.; Kitahara, Y. *Synth. Commun.* **1972**, *2*, 405. (c) Saski, T.; Kanamatsu, K.; Okamura, N. *Chem Lett.* **1976**, 743. The thermal isomerization of *cis*-divinylcyclopropanes such as **21** occur at temperatures well below 25 °C.[28]

(28) Baldwin, J. E.; Gilbert, K. E. *J. Am. Chem. Soc.* **1976**, *98*, 8283.

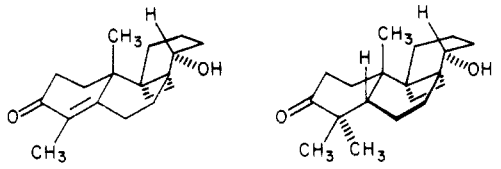
(29) (a) Chapman, O. L.; Kane, M.; Lassila, J. D.; Loeschem, R. L.; Wright, H. E. *J. Am. Chem. Soc.* **1969**, *91*, 6856. (b) Kende, A. S.; Goldschmidt, Z.; Izzo, P. T. *Ibid.* **1969**, *91*, 6858.

(30) ApSimon, J. W.; Baker, P.; Bucini, J.; Hooper, J. W.; Macaully, S. *Can. J. Chem.* **1972**, *50*, 1944.

(31) The ratios of each component are critical. See the Experimental Section. See also: Johnson, W. S.; Bannister, B.; Pappo, R. *J. Am. Chem. Soc.* **1956**, *78*, 6331.

(32) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehman, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

Chart I



33 34

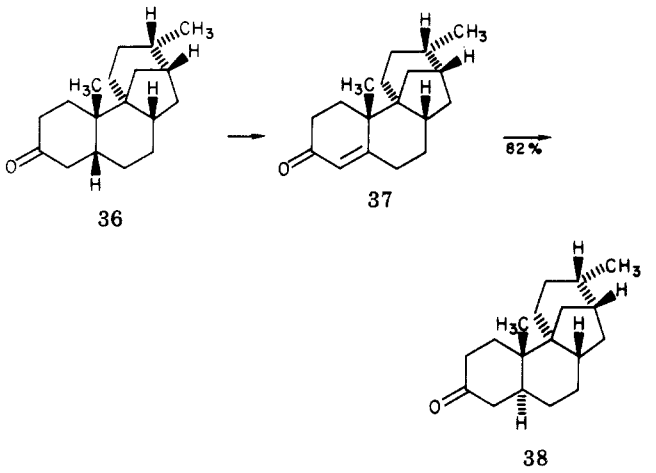
Photochemical cycloaddition of the epimers **25** with ethylene gave in each case a single adduct **26**. Since this reaction establishes the stereochemistry at C-9, it is critical that the stereochemistry of the cycloaddition be established. Each epimer of **26** was oxidized to give the same dione **27**, and single-crystal X-ray analysis of **27** showed that cycloaddition had occurred from the α face of **25**. This mode of addition is consistent wiith all models for photochemical cycloadditions[33] and is unexceptional.

We have also explored an alternative approach to enone **25** based on methods reported by Wilds.[34] Condensation of 1,3-cyclohexanedione with ethyl vinyl ketone, followed by alkylation of the product with isopropyl iodide, gave the ether **28**. Conversion of **28** into tricyclic diketone **29** (Scheme VI) was accomplished by ring closure in base, acid-catalyzed hydrolysis of the ether function, and a second annulation with ethyl vinyl ketone.[34d] This route leads to the ring-C enone quickly and avoids the difficult Birch reduction of the previous route; however, we now faced the difficulty of distinguishing two ketones.

Treatment of **29** with ethylene glycol and *p*-toluenesulfonic acid followed by chromatography over silica gel gave the desired monoketal **30** (44%), along with diketal (20%) and recovered **29** (33%). The last probably arises from hydrolysis of **30** during chromatography. Although the stereochemistry at C-4 of the monoketal is destroyed later, the isolated material is stereochemically homogeneous, with the methyl group occupying the equatorial position (See Experimental Section for spectral data). Photochemical cycloaddition of **30** with ethylene as above gave a single crystalline product **31** in 81% yield. Now the stereochemistry at C-9 is established, but that at C-5 remains to be set.

Reduction of **31** gave an epimeric mixture of alcohols **32** (88%) which was hydrolyzed to yield keto alcohols **33** (70%). Analysis of **33** by ^{1}H NMR spectroscopy indicated 68% of equatorial alcohol **33e** and 32% of axial alcohol **33a**. Reductive methylation of **33e** gave, after chromatography, keto alcohol **34** (46%), which was oxidized to yield diketone **35**. When it became obvious that diketones **35** and **27** were different (melting point, mixture melting point, spectra), we submitted both for crystallographic analysis. Dione **27** has the structure already described, and **35** is the C-5 epimer (AB cis). The formation of the AB-cis product in the reductive alkylation was not completely unexpected. When ring B of related enones is in the boat (or boatlike) conformation, the more stable cis-fused isomer is usually the major product[35] (see Chart I). This result may be contrasted with Ireland's reduction of **37** to yield the trans-fused **38**[10] (Scheme VII). Thus, we could

Scheme VII



36 37 38

Table I. Crystal and Refinement Parameters

compd formulas	$C_{19}H_{26}O_2$ (35)	$C_{19}H_{26}O_2$ (27)
cell dimensions		
a, Å	18.029 (2)	14.565 (2)
b, Å	7.433 (1)	11.103 (1)
c, Å	11.891 (1)	11.045 (2)
β, deg	103.20 (1)	120.24 (1)
V, Å^3	1551.3 (3)	1543.1 (4)
space group	$P2_1/c$	$P2_1/c$
density obsd, g/cm^3	1.21	1.22
density calcd, g/cm^3	1.226	1.233
final R index ($R = \Sigma \|\|F_o\| - \|F_c\|\|/\Sigma \|F_o\|$)	0.066	0.064
final shifts	0.1σ	0.1σ

delay reductive alkylation until after the propellane rearrangements have given the bicyclo[3.2.1]octane moiety of aphidicolin and have reasonable assurance of success.

X-ray Analyses. The stereochemistry of compounds **35** and **27** was unambiguously established by routine, single-crystal, X-ray analyses. Crystal and refinement parameters of both compounds are given in Table I. One-angstrom data sets (maximum $(\sin\theta)/\lambda = 0.5$) were collected on a Syntex P$\bar{1}$ diffractometer using copper radiation ($\lambda = 1.5418$ Å). The diffractometer was equipped with an incident-beam graphite monochromator. All diffraction data were collected at room temperature.

Crystallographic calculations were facilitated by the CRYM crystallographic computer system.[36] Trial structures were obtained by using the MULTAN direct methods package.[37] These trial structures refine to acceptable R indices (see Table I). The final cycles of full-matrix least-squares refinement contained the scale factor, secondary extinction coefficient, nonhydrogen coordinates, and anisotropic temperature factors in a single matrix. Hydrogen positions were calculated wherever possible. Methyl hydrogens were located by using difference Fourier techniques. While the hydrogen parameters were added to the structure factor calculations during the later stages of refinement, they were not refined. Final difference Fourier maps revealed no missing or misplaced electron density. Stereoviews of the molecules are given in Figure 1. Other pertinent crystallographic data are given as supplementary material.

In this paper we have presented the basic strategy for a total synthesis of aphidicolin. The validity of this ap-

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(34) (a) Wilds, A. L.; Ralls, J. W.; Wildman, W. C.; McCaleb, K. E. *J. Am. Chem. Soc.* **1950**, *72*, 5794. (b) Wilds, A. L.; Ralls, J. W.; Tyner, D. A.; Daniels, R.; Kraychy, S.; Harnik, M. *Ibid.* **1953**, *75*, 4878. (c) Ralls, J. W.; Wildman, W. C.; McCaleb, K. E.; Wilds, A. L. U.S. Patent 2674627, 1954; *Chem. Abstr.* **1955**, *49*, 1813e. (d) This preparation of **29** from **28** is based on revised procedures using methyl vinyl ketone: Heather, J. B. Ph.D. Thesis, University of Wisconsin, 1972.

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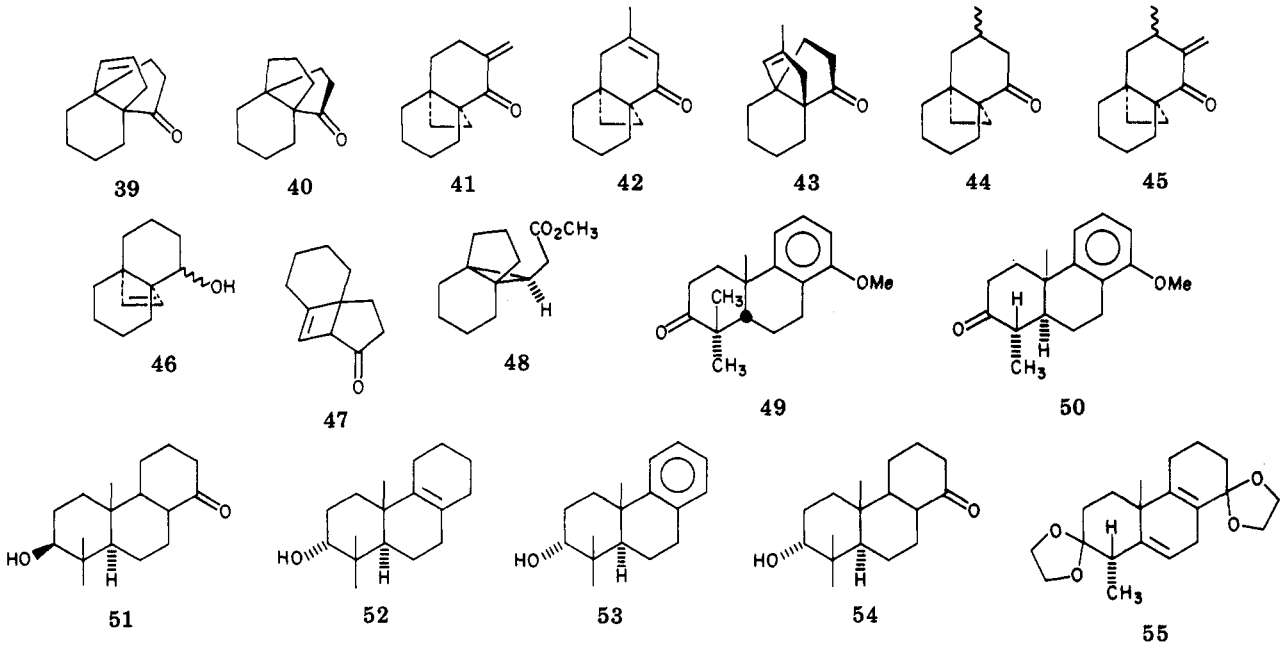
(36) Duchamp, D. J. American Crystallographic Association Meeting, Bozeman, MT, 1964, Paper B-14, p 29.

(37) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.* A27, 368 (1971).

Chart II. Structures for Experimental Section



proach has been demonstrated by the model studies leading to the conversion of dienone **12** into **20** via ketene **21**. Two routes to tetracyclic material, each of which has its own set of problems, have been outlined. We shall report shortly on the conversion of tetracycle **26** into 18-deoxy-17-noraphidicolin-16-one.

Experimental Section[38]

Tricyclo[4.4.2.0]dodecan-2-one (8)[13c] was prepared by the photoaddition of ethylene and **13** (71% on a 10-g scale) as described.[39]

Tricyclo[4.4.2.0]dodec-3-en-2-one (9). (A). From α-Phenylselenenyl Ketone. To a solution of 3.41 g (4.7 mL, 34 mmol) of diisopropylamine in 200 mL of THF at −78 °C was added 14.6 mL (33 mmol) of 2.3 M *n*-butyllithium in hexane. The resulting pale yellow solution was stirred for 15 min, 5.00 g (22.8 mmol) of **8** in 20 mL of THF was added, and the mixture was stirred at −78 °C for 15 min. To this solution was added 6.45 g (34 mmol) of phenylselenenyl chloride in 60 mL of THF. The resulting solution was immediately poured into cold saturated aqueous $NaHCO_3$ and extracted with ether. The ether layer was washed with saturated $NaHCO_3$, 10% HCl, and brine, dried ($MgSO_4$), and concentrated to yield 10.0 g of crude phenylselenenyl ketone. This crude product was dissolved in 100 mL of THF and cooled to −20 °C, and then 14.5 mL (145 mmol) of 30% H_2O_2 was added such that the temperature of the reaction mixture remained below −10 °C. The cold solution was stirred for 15 min and then added slowly to a refluxing solution of diisopropylamine (20 mL) in 100 mL of methylene chloride. After a reflux period of 5 min, the reaction mixture was poured into cold saturated $NaHCO_3$ and extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$), and concentrated to yield an oil which was chromatographed on silica gel (1:9 ether–hexane) to yield 0.95 g of **8** and 2.93 g (73%) of **9** as a clear oil: bp 100–105 °C (0.6 torr); IR (CCl_4) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.5 (m, 14), 6.09 (dt, 1, $J_{\alpha,\beta}$ = 11 Hz, $J_{\alpha,\gamma}$ = 2 Hz), 6.85 (ddd, 1, $J_{\alpha,\beta}$ = 11 Hz, $J_{\beta,\gamma}$ = 5 Hz, $J_{\beta,\gamma'}$ = 4 Hz).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.61; H, 8.98.

(B) From Trimethylsilyl Enol Ether. A solution of the enolate prepared as described above (LDA) from 1.78 g (10.0 mmol) of **8** in 15 mL of DME was allowed to warm to 0 °C for 15 min and then quenched with a solution of 1.85 g (17 mmol) of chlorotrimethylsilane and 0.45 g (4.5 mmol) of triethylamine in 6 mL of DME. The resulting mixture was brought to 25 °C, stirred for 30 min, and partitioned between aqueous $NaHCO_3$ and hexane. The hexane layer was dried ($MgSO_4$) and concentrated to yield 2.5 g of crude trimethylsilyl enol ether of **8** as an oil: ^1H NMR (CCl_4) δ 0.18 (s, 9), 1.2–2.2 (m, 16), 4.6 (t, 1, J = 4 Hz); IR ($CHCl_3$) 1665 cm^{-1}. The crude product was utilized directly in the next step.

To a solution of 2.45 g (7.5 mmol) of triphenylcarbonium tetrafluoroborate and 0.74 g (6.0 mmol) of collidine in 50 mL of methylene chloride was added a solution of 1.25 g (5.0 mmol) of crude trimethylsilyl enol ether in 10 mL of methylene chloride, and the resulting solution was stirred for 2 h at 25 °C and then quenched with aqueous $NaHCO_3$. The organic phase was washed with saturated $CuSO_4$ and H_2O, dried ($MgSO_4$), and concentrated. The crude material was applied to 100 g of alumina, the triphenylmethane removed with 250 mL of hexane, and the product eluted with 300 mL of ether. The ether was removed and the residue distilled [Kugelrohr, <90 °C (0.25 torr)] to give 450 mg (25%) of enone **9**.

Tricyclo[4.3.3.0]dodec-11-en-7-one (10a). A solution of 2.70 g (15.0 mmol) of **9** and 10.1 g (77 mmol) of boron trifluoride etherate in 400 mL of dry acetonitrile was heated at reflux for 3 h. The resulting solution was allowed to cool for 10 min, poured into cold saturated $NaHCO_3$, and extracted with ether. The organic phase was washed with $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to yield 2.4 g of crude product which was eluted through 200 g of silica gel with 1:9 ether–hexane. The yield

(38) All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Beckman IR 4210 instrument, and nuclear magnetic resonance (NMR) spectra were recorded with a Varian EM 360 spectrometer for proton NMR and with a Varian CFT-20 spectrometer operating in the Fourier transform mode for ^{13}C NMR. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane [δ(Me_4Si) 0 for ^1H NMR] and deuterated chloroform [δ-($CDCl_3$) 77.0 for ^{13}C NMR] as internal standards. Gas–liquid chromatographic (VPC) analyses were determined on a Varian Aerograph Model 1200 Hi-Fi or Series 1400 FID chromatograph using nitrogen as the carrier gas at a flow rate of 60 mL/min. All analytical VPC was conducted on 8 ft × $^1/_8$ in. columns packed with the indicated stationary phase on 90–100 mesh Anachrom support. Silica gel columns used the 0.063–0.200-mm silica gel manufactured for column chromatography by E. Merck. "Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran were distilled from Na–benzophenone ketyl. Triethylamine and diisopropylamine were distilled from phosphorus pentoxide. All water used in the reactions and workups was distilled water. Brine refers to a saturated aqueous solution of sodium chloride. All reaction flasks and syringes were dried for at least 12 h in an oven (at 120 °C) and cooled under a N_2 atmosphere by using serum caps and syringe needles. All reactions (except the photoaddition) were run under an atmosphere of nitrogen. Microanalyses were performed by Robertson Laboratory.

(39) Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E., submitted for publication in *Org. Synth.*

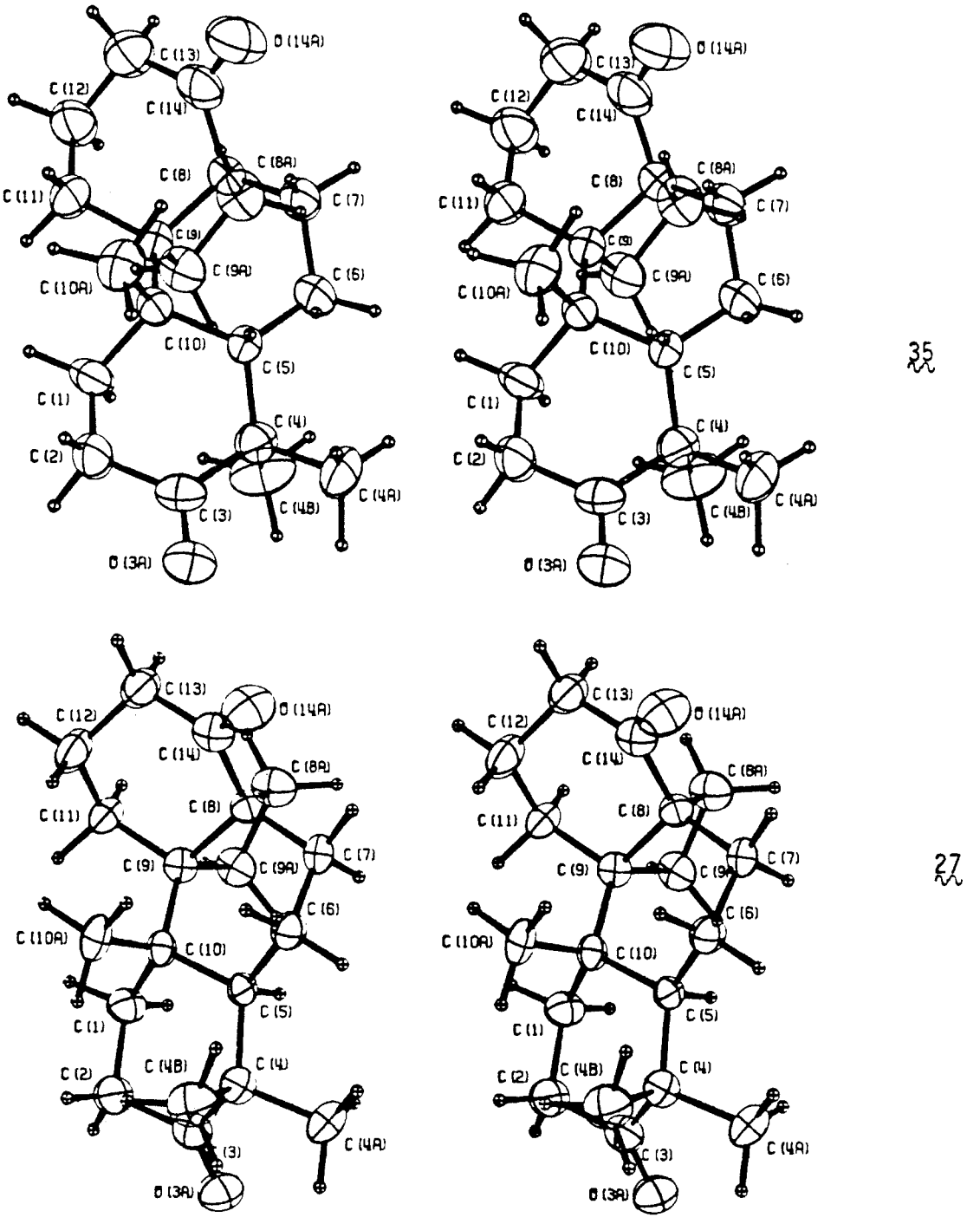


Figure 1. Stereoviews of **35** and **27** and their numbering system.

of **10a**, a clear oil, was 1.12 g (42%): IR (CCl_4) 1722, 1660 cm^{-1}; UV (95% EtOH) 297 nm (ϵ 86); ^1H NMR (CCl_4) δ 0.8–2.0 (m, 10), 2.0–2.65 (m, 4), 5.43 (dt, 1, J = 6 Hz, J' = 3 Hz), 5.75 (dt, 1, J = 6 Hz, J' = 2 Hz).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.68; H, 9.19.

When the isomerization was catalyzed with *p*-toluenesulfonic acid (1.9 g, 10 mmol), 1.7 g (10 mmol) of **9** in 75 mL of refluxing benzene for 5 h gave the crude product (1.7 g) which contained 77% of **10a** and 23% of the isomeric γ,δ-unsaturated ketone **tricyclo[4.3.3.0]dodec-10-en-7-one (39)** (VPC, 10% Carbowax 1000; see Chart II).

Tricyclo[4.3.3.0]dodecan-7-one (40). Catalytic hydrogenation of 262 mg (1.49 mmol) of the 77:23 mixture (above) in 25 mL of ethyl acetate over 150 mg of 5% palladium on charcoal at atmospheric pressure for 3 h gave 222 mg (84%) of **tricyclo-[4.3.3.0]dodecan-7-one (40)** which was identical with an authentic sample.[13c]

12-Methyltricyclo[4.3.3.0]dodec-11-en-7-one (10b). Treatment of **8** with ethyl formate (NaOMe) and then formaldehyde (K_2CO_3) according to the method of Manson and Wood[40,41] gave **3-methylenetricyclo[4.4.2.0]dodecan-2-one (41)**: 64% yield; IR ($CHCl_3$) 1680, 1620 cm^{-1}; UV (95% EtOH) 233 nm (ϵ 3095) 273 (1000); ^1H NMR ($CDCl_3$) δ 6.00–5.90 (m, 1), 5.25–5.17 (m, 1), 2.80–2.55 (m, 2), 2.30–1.30 (m, 14). A mixture containing 6.0 g of *p*-toluenesulfonic acid monohydrate and 122 mg (0.64 mmol) of crude **41** in 150 mL of benzene was heated at reflux under argon and with water separation for 15 h, allowed to cool to 25 °C, diluted with ether, washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 125 mg of dark oil. Preparative layer chromatography on silica gel (1:4 ether–hexane) and distillation [Kugelrohr, 90–100 °C (1 torr)] gave 22 mg (19%) of **10b**: IR

(40) Manson, A. J.; Wood, R. *J. Org. Chem.* **1967**, *32*, 3434.
(41) Cargill, R. L.; Bundy, W. A.; Pond, D. M.; Sears, A. B.; Saltiel, J.; Winterle *Mol. Photochem.* **1971**, *3*, 123.

($CHCl_3$) 1725 cm^{-1}; UV (95% EtOH) 302 nm (ϵ 144); ^1H NMR ($CDCl_3$) δ 5.43–5.32 (m, 1), 2.40–2.15 (m, 4), 1.90–1.10 (m, 13, with d, J = 2 Hz, at 1.61).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.77; H, 9.27.

11-Methyltricyclo[4.3.3.0]dodec-11-en-7-one (10c). A solution of 1.25 g (23.2 mmol) of sodium methoxide and 1.04 g (5.84 mmol) of **8** in 10 mL of ether was stirred for 10 min at 25 °C and cooled to 0 °C before a solution of 4.0 g (25 mmol) of bromine in 5 mL of methylene chloride was added dropwise. The reaction mixture was stirred at 25 °C for 12 h, quenched with water, and extracted with ether. The organic phase was washed successively with $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated to give 1.62 g (83%) of crude **3,3-dibromotricyclo[4.4.2.0]dodecan-2-one**: IR ($CHCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10–2.87 (m, 2), 2.30–1.30 (m, 14); mass spectrum (70 eV), m/e (relative intensity) 310 (2), 308 (4), 306 (2). A mixture of 4.21 g (12.5 mmol) of crude dibromo ketone and 0.5 g (12 mmol) of lithium chloride in 45 mL of DMF was heated at 100 °C for 1 h, cooled, and partitioned betwen hexane and water. The hexane layer was washed with water, dried ($MgSO_4$), and concentrated to give 2.98 g of an oil which was filtered through alumina with ether and distilled [Kugelrohr, 140–150 °C (0.5 torr)] to give 1.85 g (58%) of **3-bromotricyclo[4.4.2.0]dodec-3-en-2-one** as a clear oil: IR ($CHCl_3$) 1675 cm^{-1}; NMR ($CDCl_3$) δ 7.38–7.25 (dd, 1, J = 4 Hz, J' = 5 Hz), 2.40–1.40 (m, 14); mass spectrum (70 eV), m/e (relative intensity) 256 (9), 254 (9). To a solution of lithium dimethylcuprate [from 494 mg (2.60 mmol) of cuprous iodide, 8 mL of ether, and 2.63 mL (5.0 mmol) of 1.9 M ethereal methyllithium] was added dropwise at 0 °C a solution of 622 mg (2.44 mmol) of the bromo enone above in 12 mL of ether. The resulting mixture was stirred for 2 h at 0 °C, poured into 100 mL of 1 M HCl, and filtered through Celite. The aqueous phase was extracted with ether, and the combined ethereal solution was washed with brine, dried ($MgSO_4$), and concentrated to give 547 mg of **4-methyl-3-bromotricyclo[4.4.2.0]dodecan-2-one**: mp 88–92 °C; IR ($CHCl_3$) 1715, 1700 (sh) cm^{-1}; NMR ($CDCl_3$) δ 4.53 (d, 1, J = 12 Hz), 2.35–1.20 (m, 18, with d, J = 7 Hz, at 1.23); mass spectrum (70 eV), m/e (relative intensity) 272 (1), 270 (1). Dehydrobromination of the bromo ketone as described above gave **4-methyltricyclo[4.4.2.0]dodec-3-en-2-one (42)** as a clear oil in 71% yield: IR ($CHCl_3$) 1650 cm^{-1}; NMR ($CDCl_3$) δ 5.95 (m, 1), 2.45–1.20 (m, 17, with br s at 1.95). Rearrangement of **42** as described for formation of **10b** gave **10c** and **43** as an inseparable mixture (ratio 1:2, respectively, by NMR) in 41% yield. When boron trifluoride etherate was used as the catalyst (in 10-fold excess, 82-h reflux) the ratio of products was 4:6. The mixture was distilled [Kugelrohr, 100–120 °C (0.5 torr)]: IR ($CHCl_3$) 1730 cm^{-1}; UV (95% EtOH) 299 nm (ϵ 258); ^1H NMR ($CDCl_3$) δ 5.18 (s), 5.03 (s), 2.50–1.00 (m with singlets at 1.72 and 1.65).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.73; H, 9.31.

11,12-Dimethyltricyclo[4.3.3.0]dodec-11-en-7-one (10d). Ketone **9** was converted into **4-methyltricyclo[4.4.2.0]dodecan-2-one (44)** by treatment with lithium dimethylcuprate as described above in 94% yield. The oil **44** has the following: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40–1.90 (m with d, J = 6 Hz, at 1.02). **4-Methyl-3-methylenetricyclo[4.4.2.0]dodecan-2-one (45)** was prepared as a mixture of epimers from **44** as described for **41** in 65% yield and has the following: IR ($CHCl_3$) 1685, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.08–5.83 (2 m centered at 6.03 and 5.98, total area equivalent to 1 H), 5.32–5.20 (m, 1), 3.00–1.00 (m, 18). A solution of 411 mg (2.01 mmol) of **45** and 3.0 g of *p*-toluenesulfonic acid monohydrate in 150 mL of benzene was heated at reflux for 2 h with separation of water. The reaction mixture was worked up as described above, and the crude product was filtered through alumina and distilled [Kugelrohr, 100–120 °C (0.25 torr)] to give 175 mg (43%) of **10d**: IR ($CHCl_3$) 1720 cm^{-1}; UV (95% EtOH) 303 nm (ϵ 264); ^1H NMR ($CDCl_3$) δ 2.50–0.90 (m, with broadened singlets at 1.61 and 1.48); mass spectrum (70 eV), m/e (relative intensity) 205 (4), 204 (30), 148 (100), 105 (26), 91 (20), 79 (11). Satisfactory combustion analysis was not obtained for this substance.

Irradiations of 10a–d were carried out with the usual Hanovia 450-W, medium-pressure mercury arc, with ten 15-W "black lights" (360 nm), and with ten 15-W "germicidal" lamps (254 nm) in hexane, methylene chloride, cyclohexane, acetone, or methanol at temperatures from −78 to +25 °C. In every case VPC analysis of the reaction progress showed the disappearance of starting material, but no similarly volatile product could be detected. Removal of solvent left only polymeric material.

Tricyclo[4.4.2.0]dodec-11-en-2-one (14). (A) From 13 and Acetylene. A solution of 8.0 g (53 mmol) of **13** in 1.1 L of methylene chloride in the preparative irradiation apparatus[39] was cooled to −70 °C and saturated with acetylene [which was purified by being passed successively through H_2SO_4, solid $CaSO_4$ (8 mesh), KOH (pellet), alumina (Alcoa F-20), and a cold (−78 °C) trap]. After saturation (ca. 3 h, flow rate ca. 100 mL/min) irradiation was commenced (1000-W street lamp[39]) while acetylene was bubbled though the solution. After 13 h all the **13** had reacted (VPC, 10% Carbowax 1000, 160 °C), and two new products had been formed. The irradiation was stopped, and the solution was warmed to 25 °C while being degassed (N_2), dried ($MgSO_4$), and concentrated to yield 8.24 g of crude product. Chromatography of the crude product on 800 g of silica gel (1:9 ether–hexane) gave 3.21 g (34%) of **14** as a clear oil: IR (CCl_4) 1690 cm^{-1}; ^1H NMR (CCl_4) (90 MHz) δ 6.15 (AB q, 2, Δ_{AB} = 13 Hz, J = 3 Hz), 1.2–2.6 (m, 14).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.82; H, 9.07.

Further elution with 1:9 ether–hexane gave 1.88 g (20%) of **6-vinylbicyclo[4.4.0]dec-1(10)-en-2-one (15)** as a clear oil: IR (CCl_4) 1685, 1620, 1005, 935 cm^{-1}; ^1H NMR (CCl_4) δ 1.20–2.02 (m, 8), 2.02–2.60 (m, 4), 4.71 (dd, J = 2 Hz, J' = 18 Hz, 1), 5.20 (dd, J = 2 Hz, J'' = 11 Hz, 1), 5.57 (dd, J' = 18 Hz, J'' = 11 Hz, 1), 6.63 (t, J = 4 Hz, 1).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.06; H, 9.20.

(B) From 11,12-Dichlorotricyclo[4.4.2.0]dodecan-2-one. Photoaddition of 1,2-dichloroethylene and **13** as described in ref 39 gave a diastereomeric mixture in which one adduct (unspecified) clearly predominated (^1H NMR), as a brown semisolid.[23]

Reduction of the crude cycloadduct (9.18 g, 37.2 mmol) in 150 mL of methanol with 2.0 g (53 mmol) of sodium borohydride gave, after the usual workup, 8.99 g (98%) of a brown oil, **11,12-dichlorotricyclo[4.4.2.0]dodecan-2-ol**: IR (CCl_4) 3400 cm^{-1}; ^1H NMR (CCl_4) δ 0.9–2.6 (m, 15), 3.2–3.6 (m, 1), 4.21 (unresolved AB q, J_{AB} = 9 Hz, 2).

Dechlorination of this alcohol according to ref 41 gave, after filtration through 200 g of Florisil, 5.64 g of tricyclo[4.4.2.0]dodec-11-en-2-ol (**46**) as a pale yellow oil: IR (CCl_4) 3620, 3480 cm^{-1}; ^1H NMR (CCl_4) δ 1.2–1.7 (m, 14), 2.0 (m, 1), 3.3–3.8 (m, 1), 6.12 (s, 2).

Oxidation of 4.00 g of **46** as described below (**26** → **27**) gave, after filtration through Florisil and distillation, 2.28 g (37% from **13**) of ketone **14**, bp 94–100 °C (4 torr).

Tricyclo[5.3.2.$0^{1,6}$]dodec-11-ene-6,7-diol (18). The crude cycloadduct from **13** and 1,2-dichloroethylene (above) was converted into the ethylene ketal, dechlorinated, and hydrolyzed according to ref 41. When the hydrolysis was conducted with 3% H_2SO_4 or stronger acids, the sole product isolated was diol **18**: mp 117–118 °C; IR ($CHCl_3$) 3600, 3430, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.46 (s, 2), 2.65 (s, 2), 1.15–2.5 (m, 14 with br s at 1.65). Satisfactory elemental analysis was not obtained.

Tricyclo[4.4.2.0]dodeca-3,11-dien-2-one (19). (A). α-Phenylselenenyl Ketone Route. To a solution of LDA from 0.67 g (6.6 mmol) of diisopropylamine and 2.9 mL of 2.3 M *n*-butyllithium in 30 mL of THF at −78 °C was added 0.97 g (5.5 mmol) of **14** in 5 mL of THF. The mixture was stirred at −78 °C for 15 min and then quenched with phenylselenenyl bromide [from 1.03 g (3.3 mmol) of diphenyl diselenide and 527 mg (3.3 mmol) of bromine] in 10 mL of THF. The resulting mixture was poured into cold saturated $NaHCO_3$ and extracted with ether. The organic phase was washed with $NaHCO_3$, 10% HCl, and brine, dried ($MgSO_4$), and concentrated to yield 1.78 g of crude α-phenylselenenyl ketone. Oxidation and workup as described previously gave 650 mg (68%) of dienone **19**: [Kuegelrohr, 100 °C (1 torr)]; IR (CCl_4) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.18 (apparent s, 2), 6.75–6.5 (m, 1), 5.98 (dt, 1, J = 10 Hz, J' = 2 Hz), 2.1–1.3 (m, 10).

(B) Trimethylsilyl Enol Ether Route. Formation of the trimethylsilyl enol ether from 528 mg (3.0 mmol) of ketone **14**

as described above gave 843 mg of crude enol ether: IR (CCl_4) 1640, 1250 cm^{-1}; ^1H NMR (CCl_4) δ 6.04 (AB q, 2, Δ_{AB} = 16 Hz, J = 3 Hz), 4.80 (dd, 1, J = 7 Hz, J' = 4 Hz), 0.8–2.4 (m, 10), 0.15 (s, 9). Reaction of 496 mg (2.0 mmol) of crude trimethylsilyl enol ether with 994 mg (3.0 mmol) of triphenylcarbonium tetrafluoroborate as described above gave 110 mg (21%) of dienone **19**.

Tricyclo[4.3.2.0]undec-10-en-7-one (17). Irradiation of 1.0 g (7.3 mmol) of bicyclo[4.3.0]non-1(6)-en-7-one (**16**) in 1.1 L of methylene chloride saturated with acetylene as described above for 165 min gave 1.1 g of crude photoadduct, which, after chromatography on silica gel (1:9 ether–hexane), afforded 120 mg of **17**[24] and 100 mg of **tricyclo[5.4.0.0^{1,5}]undec-6-en-4-one (47)**.[24]

Tricyclo[4.3.3.0]dodeca-8,11-dien-7-one (12). (A) From 10a. Ketone **10a** was converted into the α-phenylselenenyl derivative with phenylselenenyl chloride as described above. The crude product was oxidatively eliminated as described above to yield 1.1 g of crude dienone. Chromatography on silica gel (1:9 ether–hexane) gave 465 mg (62%) of **12** as a clear oil: IR (CCl_4) 1700 cm^{-1}; UV (95% EtOH) 225 nm (ϵ 6800) 326 (126); ^1H NMR (CCl_4) δ 7.22 (d, 1, J = 7 Hz), 5.69 (d, 1, J = 7 Hz), 5.63–5.34 (m, 2), 2.42 (br s, 2), 2.15–1.0 (m, 8).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.54; H, 8.27.

(B) From 19. A solution containing 450 mg (2.6 mmol) of **19** and 1.6 mL (13 mmol) of boron trifluoride etherate in 200 mL of benzene was heated at reflux for 20 min, cooled for 15 min, and partitioned between cold $NaHCO_3$ and ether. The organic phase was washed with $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to yield 230 mg (51%) of **12** [Kugelrohr, 100 °C (1 torr)].

Photoisomerization of 12. A solution of 336 mg (1.9 mmol) of **12** in 240 mL of hexane was cooled to −78 °C and irradiated with a Hanovia 450-W, medium-pressure mercury arc. After ca. 1 h the composition of the reaction mixture ceased to change (VPC, 10%; HiEff 1-BP, 165 °C, 45% of **12** and 55% of **20**). The irradiation was stopped, and the mixture was warmed to 25 °C and concentrated to yield 313 mg of product mixture. The products were isolated by preparative VPC (10% HiEff 1-BP, 160 °C).[42] Recovered **12** was identified by appropriate comparisons. The new ketone **20**, a clear oil, had the following: IR (CCl_4) 1690, 1680 cm^{-1}; UV (95% EtOH) 238 nm (ϵ 5300) 353 (145); ^1H NMR (CCl_4) δ 7.17 (dd, 1, J = 10.5 Hz, J' = 1.5 Hz), 5.52 (br s, 1), 5.33 (dd, 1, J = 10.5 Hz, J' = 2 Hz), 3.10 (br s, 1), 2.70–2.35 (m, 2), 2.35–1.1 (m, 8).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.36; H, 8.10.

***syn*-Tricyclo[4.3.1.0]dec-7-en-10-ethanoic Acid (22a).** A solution of 480 mg (2.76 mmol) of **12** in 600 mL of ether containing 60 mL of water was maintained at 5–10 °C while being irradiated with a Hanovia 450-W mercury arc (Pyrex) until the absorption at 320 nm disappeared (7.5 h). Water was removed, and the ethereal layer was dried ($MgSO_4$) and concentrated to yield a brown oil. The latter was dissolved in ether and extracted with 5% NaOH, the aqueous extract was acidified with H_2SO_4, and the product was extracted into chloroform. The combined organic extract was dried ($MgSO_4$) and concentrated to yield 280 mg of **22a** as an oil: IR (CCl_4) 1710 cm^{-1}; ^1H NMR (CCl_4) δ 0.85–2.4 (m, 13), 5.45 (s, 2), 11.5 (s, 1).

The methyl ester **22b** was obtained from **22a** by the action of ethereal diazomethane and was identical with the ester obtained from irradiation of **12** described below.

Irradiation of 12 in Hexane Containing Methanol. A solution of 250 mg (1.4 mmol) of dienone **12** in 200 mL of hexane containing 5 mL of methanol was irradiated (Pyrex) as described above (at −78 °C) for 3.5 h (VPC, 10% Carbowax 1000 M, 175 °C). The resulting solution was warmed to ambient temperature and concentrated to yield 330 mg of yellow oil. The single volatile component, ester **22b**, was isolated by preparative VPC (10% HiEff 1-BP, 160 °C): IR (CCl_4) 1739 cm^{-1}; ^1H NMR (CCl_4) δ 1.08 (t, 1, J = 7 Hz), 0.95–1.50 (m, 6), 1.50–1.75 (m, 1), 1.75–2.10 (m, 6, with sharp signals at 2.03, 2.01, 1.94), 2.22 (br s, 2), 3.58 (s, 3), 5.51 (s, 2).

(42) The injector temp. was held at 170 °C and the detector at 180 °C.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.00; H, 8.75.

Irradiation of 20 in Hexane Containing Methanol. A solution of 20 mg (0.11 mmol) of dienone **20** in 15 mL of hexane containing 3% of methanol was irradiated as above at 0 °C for 3 h. The sole product was isolated and found to be identical (VPC and ^1H NMR) with ester **22b** obtained above.

Hydrogenation of 22b. A solution of 20 mg (0.11 mmol) of ester **22b** was hydrogenated over 5 mg of platinum oxide in 5 mL of methanol at 1 atm (20 h at 25 °C). Normal isolation gave 18 mg (90%) of ester **48**: ^1H NMR (CCl_4) δ 0.91 (t, 1, J = 7 Hz), 1.0–2.0 (m, 14), 2.19 (d, 2, J = 7 Hz), 3.62 (s, 3). The ^{13}C NMR spectrum (see Table II) showed the symmetry of **48**. No combustion analysis was obtained.

Dienone 20 from 22a. To a solution of 56 mg (0.29 mmol) of **22a** in 15 mL of benzene was added 46 mg (0.36 mmol) of oxalyl chloride. The resulting solution was stirred at 25 °C for 1 h. The solvent was removed [25 °C (1 torr)], and the remaining oil was dissolved in fresh benzene. To this solution was added 50 mg (0.50 mmol) of triethylamine, and the resulting mixture was heated at reflux for 14 h. The nonionic product was extracted into ether and filtered through a short plug of basic alumina. Removal of solvent gave 45 mg (90%) of pure dienone **20**.

Reductive Methylation of Ketone 7.[30] A solution of 15.0 g (58.6 mmol) of enone **7**[14] in 750 mL of THF containing 0.95 g (53 mmol) of water was added at a moderate rate to a solution of 2.31 g (0.35 mol) of lithium in 750 mL of dry ammonia. The resulting blue solution was stirred for 10 min and then quenched with 55 mL (125 g, 0.87 mol) of dry methyl iodide. At first, the methyl iodide was added slowly in order to avoid a violent reaction. After the reaction mixture lost its blue color, the addition was rapid. The resulting cloudy mixture was opened to the atmosphere and stirred for 15 h at 25 °C so that ammonia could escape. The cloudy mixture was diluted with 800 mL of ether and 1 L of ice. The aqueous layer was removed, and the ethereal solution was washed with one L of 10% HCl (which was set aside) and saturated $NaHSO_3$, dried ($MgSO_4$), and concentrated to yield 9.2 g of a mixture of ketones. Chromatography of this residue on 700 g of silica gel (1:12 ethyl acetate–hexane) gave, after a 1-L forerun, from 20-mL fractions 20–100, 2.1 g of ketone **49**: IR (CCl_4) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 6), 1.45 (s, 3), 1.5–3.5 (m, 9), 3.8 (s, 3), 6.5–7.3 (m, 3). Fractions 125–160 gave 4.75 g of ketone **23**: mp 92–95 °C (lit.[43] mp 90–93 °C, lit.[44] 95.5–96.5 °C); IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3), 1.17 (s, 3), 1.31 (s, 3), 1.50–3.00 (m, 9), 3.80 (s, 3), 6.50–7.25 (m, 3). Fractions 160–300 yielded 2.2 g of a mixture of **23** and **50**; later fractions gave pure **50**: mp 134–137 °C; IR (CCl_4) 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 3), 1.33 (s, 3), 1.35–3.0 (m, 10), 3.78 (s, 3), 6.5–7.3 (m, 3). No analytical sample was obtained.

Nitrogen was bubbled through the acid wash (above) for 48 h to produce a precipitate which was isolated by filtration and dried [25 °C (1 torr)] to yield 6.33 g of **23**. The total yield of ketone **23** was 11.08 g (70%). Evidently the imine of ketone **23** is formed by reaction with the ammonia solvent. The imine is stable in cold 10% HCl. Overlooking this possibility can result in the loss of a large portion of product.

Tricyclic Alcohol 24e. To a solution of 4.75 g (17.5 mmol) of ketone **23** in 200 mL of anhydrous ether (cooled to 0 °C) was added 0.7 g (100 mmol) of lithium aluminum hydride. The resulting solution was stirred at 25 °C for 16 h. Excess LAH was destroyed by the successive addition of 0.7 mL of water, 0.7 mL of 15% NaOH, and 2.1 mL of water and stirring of the resulting mixture at 25 °C for 2 h. The slurry was filtered through Na_2SO_4, and the solvent was removed to yield 4.75 g of alcohol **24e**. Recrystallization from ether–hexane gave **24e** as colorless needles: mp 131–133 °C (lit.[43] 133.5–134 °C); IR ($CHCl_3$) 3610, 3470, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3), 1.05 (s, 3), 1.18 (s, 3), 1.30–3.10 (m, 9), 3.17–3.37 (m, 1), 3.77 (s, 3), 6.50–7.20 (m, 3).

Tricyclic Alcohol 24a. A 3.68-mL (3.68 mmol, 1 M in THF) quantity of lithium tri-*sec*-butyl borohydride (L-Selectride, Aldrich Chemical Co.) was placed in a dry flask under a nitrogen atmo-

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Table II. ^{13}C NMR Chemical Shifts

entry	compd	chemical shifts, ppm
1	**8**	216.13, 52.63, 43.71, 38.14, 35.95, 32.74, 28.87, 27.78, 24.78, 22.83, 22.50, 21.81
2	**9**	204.79, 148.01, 128.25, 49.38, 39.43, 35.77, 33.02, 29.53, 26.36, 22.14, 21.99
3	**10a**	220.37, 134.88, 131.38, 64.86, 48.45, 43.99, 36.66, 32.70, 32.19, 30.71, 21.89
4	**12**	212.00, 169.58, 134.67, 130.19, 129.35, 63.99, 53.25, 41.97, 30.72, 26.62, 18.10, 18.00
5	**13**	198.12, 156.44, 132.14, 37.91, 31.60, 31.44, 22.58, 22.27, 22.19
6	**14**	213.84, 143.32, 137.64, 60.11, 51.50, 40.33, 32.30, 25.63, 18.19, 17.40, 17.39
7	**15**	201.75, 144.94, 140.04, 136.50, 118.51, 43.99, 40.18, 37.13, 35.54, 26.14, 19.32, 17.31
8	**18**	139.26, 135.93, 93.90, 87.02, 59.55, 39.29, 38.06, 36.62, 32.82, 24.05, 23.52
9	**19**	202.62, 144.34, 141.98, 127.09, 58.35, 47.11, 33.50, 33.14, 24.41, 17.81, 17.39
10	**20**	198.47, 158.07, 157.81, 123.95, 120.60, 56.99, 55.55, 49.67, 34.10, 28.00, 25.03, 22.75
11	**48**	51.47, 33.96, 31.21, 29.98, 29.38, 26.50, 25.16, 21.41, carbonyl too weak to observe
12	**22a**	179.91, 133.03, 128.15, 39.54, 35.81, 29.60, 27.33, 26.78, 25.82, 25.61, 20.44, 20.25
13	**22b**	174.28, 134.09, 129.10, 51.31, 40.64, 36.91, 30.81, 28.43, 27.60, 27.03, 21.59, 21.42
14	**46**	144.12, 138.87, 74.05, 52.45, 49.64, 31.24, 30.25, 27.38, 17.68, 17.35
15	**47**	217.89, 158.65, 58.58, 36.68, 35.78, 35.40, 26.96, 25.58, 25.39, 21.96
16	**7**	197.92, 162.09, 156.48, 146.34, 128.28, 127.19, 124.55, 117.85, 107.19, 55.34, 39.84, 36.47, 34.28, 26.96, 26.42, 23.61, 10.80
17	**23**	156.96, 148.73, 126.38, 124.02, 117.26, 106.70, 55.15, 50.12, 47.26, 37.65, 37.28, 34.60, 26.64, 22.31, 21.09, 18.48
18	**49**	216.71, 157.09, 149.04, 126.23, 123.70, 116.14, 106.73, 54.99, 51.32, 47.72, 47.11, 37.59, 37.04, 25.26, 24.47, 21.86, 19.16, 15.65
19	**50**	212.28, 156.85, 146.91, 125.98, 123.82, 116.81, 106.69, 54.92, 48.52, 44.79, 38.00, 37.78, 36.74, 23.49, 21.97, 21.60, 11.41
20	**24a**	157.09, 151.16, 126.06, 124.14, 116.50, 106.44, 75.64, 55.16, 43.14, 37.70, 37.47, 34.36, 34.22, 31.64, 28.10, 25.93, 24.58, 24.33, 22.08, 18.00
21	**24e**	156.88, 150.60, 125.97, 123.92, 116.41, 106.30, 78.46, 54.98, 49.14, 38.73, 37.38, 36.96, 27.84, 24.61, 18.01, 15.20
22	**25a**	200.31, 165.57, 130.25, 75.18, 43.38, 39.04, 37.71, 33.99, 28.54, 25.38, 25.13, 24.10, 23.20, 22.14, 19.06, 17.49
23	**25e**	199.17, 164.26, 129.16, 76.89, 48.54, 37.98, 37.73, 36.52, 32.68, 26.86, 26.08, 24.02, 23.39, 21.99, 18.03, 16.50, 14.54
24	**26a**	215.44, 75.26, 53.03, 48.85, 39.49, 38.57, 38.33, 37.48, 30.02, 28.77, 28.44, 25.69, 25.35, 24.88, 23.10, 22.32, 18.04, 17.90
25	**26e**	214.53, 78.79, 53.38, 49.58, 46.63, 38.88, 38.78, 38.20, 30.82, 30.32, 29.37, 28.84, 26.37, 26.09, 23.72, 18.33, 17.89, 15.81
26	**52**	137.80, 124.92, 75.95, 44.85, 37.53, 37.35, 32.23, 30.62, 29.15, 28.06, 25.62, 23.74, 23.44, 22.89, 22.15, 19.04, 18.49
27	**54**	213.67, 75.76, 56.75, 49.47, 47.49, 41.74, 37.46, 37.23, 31.85, 28.39, 26.34, 26.15, 25.50, 24.22, 22.38, 20.14, 13.73
28	**27**	217.12, 212.92, 53.25, 49.83, 48.60, 47.02, 38.22, 37.83, 33.87, 30.83, 30.73, 29.51, 29.27, 27.51, 27.00, 24.69, 21.44, 19.83, 17.55
29	**35**	216.42, 214.32, 51.10, 49.31, 46.94, 46.75, 38.69, 37.72, 33.63, 30.55, 30.09, 28.36, 27.45, 27.08, 24.81, 24.41, 20.87, 18.68, 18.25
30	**49**	216.94, 149.07, 126.22, 123.74, 116.16, 106.76, 55.02, 51.31, 47.76, 47.10, 37.57, 27.08, 25.24, 24.46, 21.89, 19.15, 15.65, 13.99
31	**51**	213.62, 75.53, 56.93, 53.64, 49.31, 41.71, 38.85, 37.43, 37.37, 28.19, 27.45, 26.41, 26.11, 24.34, 20.20, 15.62, 13.84

sphere. The flask was cooled to −78 °C before 500 mg (1.84 mmol) of ketone **23**, dissolved in 10 mL of dry THF, was added dropwise. The reaction mixture was stirred at −78 °C for 3 h and then warmed to 25 °C. This solution was then quenched with 3 mL of 4 M NaOH followed by 5 mL of 30% H_2O_2 and stirred for 0.5 h (exothermic reaction). The aqueous layer was saturated with K_2CO_3, and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 478 mg (95%) of white solid. Analysis by NMR (Varian XL-100) using the integration of methyl peaks showed the product to be a 4:1 mixture of compounds **24a** and **24e**, respectively. The mixture was recrystallized from ether–hexane to give 402 mg (78%) of pure alcohol **24a**: mp 196–198 °C; IR ($CHCl_3$) 3400 (br), 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3), 1.02 (s, 3), 1.20 (s, 3), 1.50–2.15 (m, 7), 2.40–3.05 (m, 2), 3.43–3.51 (m, 1), 3.78 (s, 3), 6.50–7.15 (m, 3).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.61; H, 9.26.

Reduction of Alcohol 24e with Lithium in Ammonia.[30,31] To a solution of 4.0 g (14.6 mmol) of **24e** in 300 mL of THF, 300 mL of ethanol, and 300 mL of dry ammonia (cooled to −30 °C in a dry ice–CCl_4 bath) was added 32 g (4.6 mol) of lithium wire over a period of 2.2 h. An initial 6-g portion of lithium wire was added, followed by 2-g portions at 10-min intervals. The resulting blue mixture, which had an upper bronze phase, was stirred at −30 °C until the bule color disappeared, and the ammonia was allowed to evaporate overnight at ambient temperature. The remaining cloudy solution was diluted with 1 L of ice and 2 L of water and extracted with three 1-L portions of ether. The combined ethereal extracts were washed with brine until the wash was neutral and dried ($MgSO_4$), and the solvent removed was to yield 5.2 g of residue (no starting material remained in the enol

ether mixture, ^1H NMR). To a solution of the residue in 300 mL of methanol was added a solution of 5 g of oxalic acid in 25 mL of water. The resulting solution was stirred for 3 h at 25 °C before the methanol was removed in vacuo. The crude product was dissolved in ethyl acetate, washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to yield 4.9 g of a mixture of ketones (no methyl ether, ^1H NMR). A solution of 9.8 g of crude ketone mixture (from two runs as above) and 500 mg of rhodium trichloride trihydrate in 50 mL of 95% ethanol was degassed with argon, sealed in a heavy-walled glass bottle, and heated at 110 °C for 14 h.[32] The mixture was cooled and filtered, and the residue was rinsed with ethyl acetate. The filtrate and washings were concentrated to give 9.8 g of crude enone (no olefinic proton, ^1H NMR). Chromatography of 19.8 g of crude product (two runs) on 1.5 kg of silica gel (3:1 ether–hexane, 1.6 L of forerun, 25-mL fractions) gave in fractions 150–235 2.0 g of saturated keto alcohol **51**: mp 142–146 °C; IR (CCl_4) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3), 0.97 (s, 3), 1.00 (s, 3), 1.05–2.50 (m, 18), 3.05–3.38 (m, 1).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.29; H, 10.82.

After 275 fractions had been collected, the column was washed with 5 L of ether to give, after evaporation of solvent, 5.87 g (29%) of **25e**. Recrystallization from ether gave an analytical sample: mp 159–160 °C; IR (CCl_4) 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3), 1.02 (s, 3), 1.08 (s, 3), 1.20–2.55 (m, 16), 3.05–3.45 (m, 1).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.61; H, 10.17.

Reduction of alcohol 24a (5.00 g) as above gave 4.87 g of crude product. Chromatography as above (800 g of silica gel, 3:1 ether–hexane, 20-mL fractions, analysis by VPC on 3% SE-52, 220 °C) gave the following results. Fractions 38–48 gave 1.1 g of olefinic alcohol **52**: ^1H NMR ($CDCl_3$) δ 0.87 (s, 3), 0.95 (s, 6), 1.1–2.1 (m, 18), 3.42 (br s, 1). Fractions 49–53 gave 310 mg of **52** and **53** (below). Fractions 54–56 gave 160 mg of aromatic alcohol **53**: IR ($CHCl_3$) 3475, 3550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3), 1.05 (s, 3), 1.20 (s, 3), 1.30–2.20 (m, 8), 2.80–3.05 (m, 2), 3.50 (br s, 1), 7.00–7.40 (m, 4). Fractions 64–80 gave 180 mg of recovered **24a**. Fractions 152–200 gave 500 mg of saturated ketone **54**. Recrystallization from ethyl acetate gave an analytical sample: mp 177–178 °C; IR ($CHCl_3$) 3560, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3), 0.95 (s, 6), 1.15–2.45 (m, 18), 3.40 (t, J = 3 Hz, 1). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.19; H, 10.80. Fractions 300–350 and two 500-mL washings gave 1.4 g of solid. Recrystallization from ethyl acetate gave 1.1 g of enone **25a**, mp 162–163 °C. One further recrystallization gave an analytical sample: mp 165–166 °C; IR ($CDCl_3$) 3580, 3450, 1670, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3), 1.00 (s, 3), 1.10 (s, 3), 1.45–2.15 (m, 9), 2.15–2.45 (m, 5), 3.45 (br s, 1).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.58; H, 9.99.

Photoaddition of ethylene and 25e was carried out as described in ref 39. A solution of 5.80 g (22 mmol) of enone **25e** in 1.2 L of methylene chloride was cooled to −78 °C, saturated with ethylene, and irradiated with a 1000-W mercury lamp for 7.5 h (VPC OV-101, 250 °C). The solution was warmed to 25 °C over a 16-h period and dried ($MgSO_4$), and the solvent was removed to yield 5.85 g (91%) of tetracycle **26e**. Recrystallization from ether gave and analytical sample: mp 151–152 °C, IR (CCl_4) 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 6), 1.07 (s, 3), 1.15–2.78 (m, 20), 3.05–3.50 (m, 1). Satisfactory analysis was not obtained.

Photoaddition of ethylene and 25a as described above gave **26a**: 67% yield; mp 167–168 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3), 0.93 (s, 3), 1.01 (s, 3), 1.20–2.75 (m, 20), 3.45 (br s, 1). Satisfactory analysis was not obtained.

Tetracyclic Dione 27. A solution of 100 mg (0.35 mmol) of keto alcohol **26a** and 110 mg (0.52 mmol) of pyridinium chlorochromate in 15 mL of methylene chloride was stirred at 25 °C for 3 h. The mixture was diluted with ether and filtered through a plug of Florisil. Removal of solvent gave 88 mg (87%) of dione **27**. Recrystallization from ether gave a sample suitable for X-ray analysis: mp 117–118 °C; IR (CCl_4) 1695, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3) 1.07 (s, 3), 1.13 (s, 3), 1.15–3.10 (m, 19).

Oxidation of keto alcohol 26e as above gave dione **27** (93%) identified by melting point and mixture melting point (117–118 °C) and by IR and ^1H NMR spectra which are identical with those of the previous sample.

2-(3-Oxopentyl)cyclohexane-1,3-dione. To a gently refluxing solution of 8.65 g (77 mmol) of commercial cyclohexane-1,3-dione in 60 mL of dry benzene and 5 mL (36 mmol) of triethylamine was added 10 mL (100 mmol) of commercial ethyl vinyl ketone (Aldrich Chemical Co.) dropwise over a period of 35 min. The resulting dark red solution was stirred at reflux for 6 h. At the end of this period the mixture was cooled and acidified by the slow addition of 45 mL of cold 1 N HCl. The organic layer was separated, and the aqueous layer was extracted three times with 50-mL portions of chloroform. The combined organic layer was washed with 50 mL of brine and dried over anhydrous Na_2SO_4. Removal of the solvent afforded a dark residue (17.05 g) which was distilled under vacuum to yield 7.13 g (51%) of 2-(3-oxopentyl)cyclohexane-1,3-dione: bp 135–145 °C (0.1 torr) [lit.[34c] bp 125–131 °C (0.08 torr)]; IR (CCl_4) 3200 (br), 1720 (sh), 1710 (sh), 1695 cm^{-1}; ^1H NMR (CCl_4) δ 4.32 (m, 0.37), 3.58 (t, J = 6 Hz, 0.63), 3.0–1.3 (m, 12), 1.0–0.9 (2 t, J = 8, 6 Hz, 3). These spectroscopic data show that keto and enol forms are present in a ratio of 2:1, respectively.

3-Isopropoxy-2-(3-oxopentyl)-2-cyclohexenone (28). The triketone from the previous preparation (22 g, 0.11 mol), isopropyl iodide (33 mL, 0.33 mol), and anhydrous K_2CO_3 (63 g, 46 mol) in 200 mL of acetone were heated at reflux (N_2) for 48 h. The mixture was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with cold 5% KOH, water, and brine, dried (Na_2SO_4), and concentrated at 25 °C to give 23 g of crude **28**:[34b] IR (neat) 1710, 1645 cm^{-1}; ^1H NMR (CCl_4) δ 4.58 (septet, J = 6 Hz, 1), 2.75–1.75 (m, 12), 1.33 (d, J = 6 Hz, 6), 1.03 (t, J = 7 Hz, 3). This sample of **28** was used immediately in the following experiment.

4b,8-Dimethyl-1,7-dioxo-1,2,3,4,4b,5,5b,7,9,10-decahydrophenanthrone (29).[34d] To a solution of sodium methoxide (from 9.4 g, 0.41 mol, of sodium) in 100 mL of methanol, maintained at 5–10 °C, was added 23 g (0.10 mol) of **28** in 45 mL of methanol. The resulting solution was stirred (N_2) at 30–33 °C for 3.5 h. The mixture was again cooled to 5–10 °C, and 145 mL of cold 3.75 N HCl was added (N_2) slowly such that the temperature of the mixture remained below 10 °C. The resulting solution was stirred att 0–10 °C for 3 h. The pH of this mixture was then adjusted to 7.0 by the addition of a solution of 17 g of NaOH in 30 mL of water and then 6 g of $NaHCO_3$. Further addition of 3 g of Na_2CO_3 in 16 mL of water brought the pH to 8.5. To this basic solution, maintained at 0–5 °C, was added 5 mL of ethyl vinyl ketone in one portion. A second 5-mL portion of ethyl vinyl ketone (EVK) was added over a period of 15 min, and the mixture was stirred at 0–5 °C for 2 hr and then left in a refrigerator overnight. The cold reaction mixture was acidified (0–5 °C) with 80 mL of 10 N HCl, stirred for 2 h, and then made basic again by the addition of 16.75 g of NaOH in 30 mL of water, 8.05 g of $NaHCO_3$ (solid), and 3.0 g of Na_2CO_3 in 16 mL of water. To the resulting solution which had a pH of 8.5 was added 5 mL of EVK, and the resulting mixture was stirred for 3 h at 0–5 °C. The reaction mixture was acidified with 200 mL of 6 N HCl and extracted with chloroform. The organic extract was washed with cold 5% NaOH and brine, dried (Na_2SO_4), and concentrated. The residue was taken up in methanol and reconcentrated to give a brown oil.

To a solution of sodium methoxide (from 28.5 g of sodium) in 250 mL of methanol cooled to 0 °C was added 78 mL of diethyl malonate. The cold mixture (a slurry too thick for magnetic stirring) was shaken manually, the brown oil (above) was added, and the resulting mixture was stirred at 40 °C for 7 h. The reaction mixture was then cooled to 0 °C, acidified with 195 mL of 6 N HCl, and extracted with chloroform. The chloroform extract was washed as before, dried (Na_2SO_4), and concentrated to give 15 g of a red oily residue. Chromatography of this oil over silica gel (1:1 hexane–ethyl acetate) gave 11.5 g (49%) of **29**: mp 97–98.5 °C; IR ($CHCl_3$) 1660, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3), 1.70 (s, 3), 1.9–3.1 (m, 14).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.52; H, 8.08.

4b,8-Dimethyl-1,2,3,4,4b,5,6,7,8,10-decahydrophenanthrene-1,7-dione 7-Ethylene Ketal (30). A solution of 2.36 g (9.65 mmol) of **29**, 180 mg (0.95 mmol) of *p*-toluenesulfonic acid monohydrate, 15 mL of dioxane, 12 mL of ethylene glycol, and 330 mL of benzene was heated at reflux by using a Dean–Stark apparatus for 48 h. At the end of this period the reaction

mixture was cooled and poured into 150 mL of saturated $NaHCO_3$. The organic layer was separated, washed twice with 100-mL portions of saturated $NaHCO_3$ and once with brine, and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 3.03 g of crude product. Chromatography on silica gel (1:1 ether–hexane) afforded 644 mg (20%) of diketal **55**, 1.23 g (44%) of **30**, and 791 mg (33%) of recovered **29**. The required monoketal was crystallized from ether: mp 139–141 °C; IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 6 Hz, 3), 1.23 (s, 3), 1.3–2.9 (m, 13), 3.77 (s, 4), 5.37 (t, 1).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.72; H, 8.27.

Diketal **55**, a clear oil, has no carbonyl absorption (IR) and has the following: ^1H NMR (CCl_4) δ 0.95 (d, J = 6 Hz, 3), 1.22 (br s, 3), 1.0–3.0 (m, 13), 3.82 (br s, 8), 5.8 (br s, 1). No elemental analysis was obtained.

Photoaddition of Ethylene and 30. The cycloaddition was conducted as previously described (**25** → **26**) by using 1.39 g (4.83 mmol) of **30** in 1.1 L of methylene chloride. Reaction was complete after 1 h of irradiation. Chromatography of the crude product (1.54 g) on Florisil with 1:1 ether–hexane gave 1.26 g (81%) of cycloadduct **31**: mp 93–93.5 °C; IR (CCl_4) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3), 0.93 (d, J = 6 Hz, 3), 1.1–2.8 (m, 17), 3.73 (s, 4), 5.55 (m 1).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.02; H, 8.88.

Tetracyclic Hydroxy Enone 33. To a slurry of 2.47 g (65 mmol) of lithium aluminum hydride in 100 mL of THF was added 2.94 g (77 mmol) of **31** in 50 mL of THF over a period of 30 min. The resulting mixture was heated at reflux for 8 h and cooled to 10 °C, and the excess LAH was decomposed by the successive addition of 2.5 mL of water, 2.5 mL of 15% NaOH, and 7.5 mL of water. The resulting mixture was filtered and washed with ether, and the organic filtrate was dried (Na_2SO_4). Removal of solvent gave 2.62 g (88%) of crude alcohols **32**: IR (neat) 3440 cm^{-1}, no carbonyl absorption.

A solution of crude **32** in 150 mL of THF was combined with 25 mL of 2 N HCl and stirred at 25 °C for 5 h, washed with brine, saturated $NaHCO_3$, and brine, and dried (Na_2SO_4). Removal of solvent gave 2.26 g of a mixture of axial and equatorial alcohols **33a** and **33e** (1:2, respectively). Chromatography on silica gel (1:4 ethyl acetate–hexane) gave 958 mg (42%) of **33e** and 459 mg (20%) of **33a**. Recrystallization of **33e** from ether gave an analytical sample: mp 123–124 °C; IR ($CHCl_3$) 3440, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3), 1.25–2.80 (m with s at 1.75, 22), 3.58 (unresolved t, 1).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.93; H, 9.72.

Keto alcohol 33a, an oil, had the following: IR (neat) 3450, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3), 1.40–2.90 (m with s at 1.75, 22), 3.57 (unresolved d, 1).

Reductive methylation of 33e as described above (**7** → **23**) gave 312 mg of keto alcohol **34** (from 360 mg of **33e**). Chromatography on silica gel (1:4 ethyl acetate–hexane) gave 174 mg of pure **34e** as an oil: IR (neat) 3450, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3), 1.10 (s, 3), 1.17 (s, 3), 1.20–2.65 (m, 20), 3.20–3.70 (m, 1). No elemental analysis was obtained.

Oxidation of 34e (150 mg, 0.52 mmol) as described above (**26** → **27**) gave 131 mg of solid [90% **35** and 10% **27** (?) by ^1H and ^{13}C NMR] which was recrystallized from ether to give pure dione **35**: mp 149–150 °C; IR ($CHCl_3$) 1695 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3), 1.08 (s, 3), 1.18 (s, 3), 1.20–2.70 (m, 19).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.16; H, 9.53.

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Registry No. 1, 38966-21-1; 7, 40266-30-6; 8, 38312-61-7; 8 α-phenylselenenyl derivative, 77827-76-0; 8 trimethylsilyl enol ether, 77827-77-1; 9, 77827-78-2; 10a, 77827-79-3; 10a α-phenylselenenyl derivative, 77827-80-6; 10b, 77827-81-7; 10c, 77827-82-8; 10d, 77827-83-9; 12, 77827-84-0; 13, 18631-96-4; 14, 77827-85-1; 14 α-phenylselenenyl derivative, 77827-86-2; 14 trimethylsilyl enol ether, 77827-87-3; 15, 77827-88-4; 16, 22118-00-9; 17, 77827-89-5; 18, 77827-90-8; 19, 77827-91-9; 20, 77827-92-0; 22a, 77827-93-1; 22b, 77846-76-5; 23, 77827-94-2; 24a, 77827-95-3; 24e, 77827-96-4; 25a, 77827-97-5; 25e, 77827-98-6; 26a, 77827-99-7; 26e, 77880-87-6; 27, 77828-00-3; 28, 77828-01-4; 29, 77828-02-5; 30, 77828-03-6; 31, 77828-04-7; 32a, 77828-05-8; 32e, 77880-88-7; 33a, 77846-77-6; 33e, 77881-62-0; 34e, 77846-78-7; 35, 77881-63-1; 39, 77828-06-9; 40, 38312-62-8; 41, 77828-07-0; 42, 77828-08-1; 43, 77828-09-2; 44 (epimer 1), 77828-10-5; 44 (epimer 2), 77880-89-8; 45 (epimer 1), 77828-11-6; 45 (epimer 2), 77880-90-1; 46, 77828-12-7; 47, 77828-13-8; 48, 77828-14-9; 49, 77828-15-0; 50, 59633-34-0; 51, 77828-16-1; 52, 77828-17-2; 53, 38301-79-0; 55, 77828-18-3; 3,3-dibromotricyclo[4.4.2.0]dodecan-2-one, 77828-19-4; 3-bromotricyclo[4.4.2.0]dodec-3-en-2-one, 77828-20-7; 4-methyl-3-bromotricyclo[4.4.2.0]dodecan-2-one, 77828-21-8; 11,12-dichlorotricyclo[4.4.2.0]dodecan-2-one, 77880-91-2; 11,12-dichlorotricyclo[4.4.2.0]dodecan-2-ol, 77880-92-3; cyclohexane-1,3-dione, 504-02-9; ethyl vinyl ketone, 1629-58-9; 2-(3-oxopentyl)cyclohexane-1,3-dione, 77828-22-9.

Supplementary Material Available: Tables of coordinates and anisotropic temperature factors for nonhydrogen atoms, hydrogen coordinates, distances, and angles (4 pages). Ordering information is given on any current masthead page.

Computer-Assisted Carbon-13 Nuclear Magnetic Resonance Spectrum Analysis and Structure Prediction for the C_{19}-Diterpenoid Alkaloids

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Computer programs for the analysis of ^{13}C NMR spectra and for structure prediction from the structural information thus inferred have been used successfully for structure elucidation of C_{19}-diterpenoid alkaloids. A data base created from the structures and the ^{13}C NMR spectra of 93 alkaloids and their derivatives was used by the programs to interpret the spectra of several unknown structures. Three examples are described in detail. The examples demonstrate that the programs can quickly limit possible structures for even complicated C_{19}-diterpenoid alkaloids to two or three when an aconitine-type skeleton is assumed for the unknown. The efficiency of the programs is based in part on their ability to utilize structural constraints during both spectrum analysis and structure generation.

The C_{19}-diterpenoid alkaloids have been known for their extreme toxicity for hundreds of years and studied by chemists for over a century. Elucidating the structures of these compounds was a formidable challenge until the

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