Formal Total Synthesis of (±)-Isocomene[1]

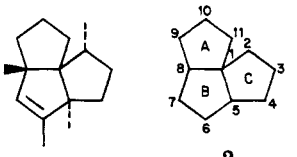
William G. Dauben* and Daniel M. Walker

Department of Chemistry, University of California, Berkeley, California 94720

Received October 16, 1980

A new synthesis of tricyclic ketone **21**, which has been carried on to (±)-isocomene (**1**), is described. The key intermediate, tricyclic dione **3**, was formed by the acid-catalyzed cyclization of diketo acid **11**. Several methods of differentiating the carbonyls of diketone **12** were studied. The monoprotected diketone **18** led in three steps to **21**.

The sesquiterpene isocomene (**1**) is a representative member of a growing class of compounds isolated from natural sources which possess the tricyclo[6.3.0.0^{1,5}]undecane skeleton **2**. In 1972, the first molecule containing

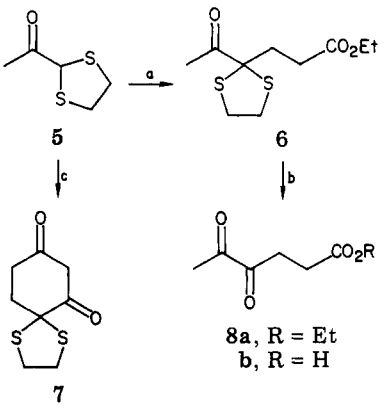


1 **2**

this unique triquinane ring system, retigeranic acid, a pentacyclic sesterterpene, was isolated by Shibata and co-workers.[2] An X-ray-determined structure of isocomene, isolated from the rayless goldenrod (*Isocoma wrightii*), was published by Zalkow in 1977.[3] Bohlmann independently isolated isocomene from the roots of *Berkheya radula* that same year and proved its structure via an X-ray determination of a rearrangement product.[4] Other compounds recently characterized which contain this interesting skeleton are β-isocomene,[5] senoxyden,[6] silphenen, three isomeric silphiperfolenes,[7] an oxosilphiperfolene,[8] pentalenic acid,[9] laurenene,[10] and tricyclodehydroisohumulone.[11] As a result of our previous work with this ring system[12] and our general interest in constructing quaternary centers at ring junctures, isocomene was an appealing target. Herein we detail the formal total synthesis of isocomene **1** and discuss results found in the course of this work which may be of value in future work with the tricyclo[6.3.0.0^{1,5}]undecane skeleton.

Prior to the recent flurry of synthetic activity directed toward isocomene,[13] only three synthetically useful approaches to the tricyclo[6.3.0.0^{1,5}]undecane system had been reported.[12,14] Of these three, the method of Weiss and Cook appeared best suited to the synthesis of isocomene. This method involves the condensation of 2 equiv of dimethyl 1,3-acetonedicarboxylate with an α-dicarbonyl compound and decarboxylation of the product to form a *cis*-bicyclo[3.3.0]octa-3,7-dione. By use of an appropriately substituted α-diketone, the third five-membered ring can be formed by cyclization. A retrosynthetic analysis of isocomene leads one to the key intermediate 1,3-diketone **3**, which could in turn be derived from diketo acid **4a**.

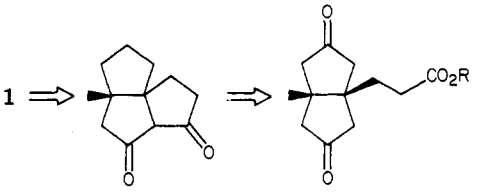
Scheme I[a]



5 **6** **7**

8a, R = Et
b, R = H

[a] (a) LDA, THF, $BrCH_2CH_2CO_2Et$, −78 °C to room temperature; (b) NBS, 80% aqueous CH_3CN, 5 min; (c) LDA, THF, $CH_2{=}CHCO_2Et$, −78 °C to room temperature.



3

4a, R = H
b, R = Me

Diketo acid **4a** would be readily available by the condensation of the appropriate α-diketone with dimethyl 1,3-acetonedicarboxylate. The main problems to be solved in this approach are the differentiation of the carbonyls in diketones **3** and **4a**.

The requisite starting material, the α-diketo acid **8b**, had been previously synthesized by the nitrosation of the Michael adduct of ethyl acetoacetate and ethyl acrylate, followed by hydrolysis of the resultant α-oximino ketone.[15] However, the oxime hydrolysis gave erratic results in our

(1) This research was supported by the National Science Foundation, Grant No. 78-04811.

(2) Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1972**, 4609.

(3) Zalkow, L. H.; Harris, R. N.; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456.

(4) Bohlmann, F.; Le Van, N.; Pickardt, J. *Chem. Ber.* **1977**, *110*, 3777.

(5) Bohlmann, F.; Le Van, N.; Pham, T. V. C.; Jakupovic, J.; Schuster, A.; Zabel, V.; Watson, W. H. *Phytochemistry* **1979** *18*, 1831.

(6) Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 1747.

(7) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.

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

(9) Seto, H.; Saski, T.; Uzawa, J.; Setsuo, T.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411.

(10) Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1774, 1791.

(11) Elvidge, J. A.; Laws, D. R. J.; McGuinness, J. D.; Davis, A.-M.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1250.

(12) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 3787.

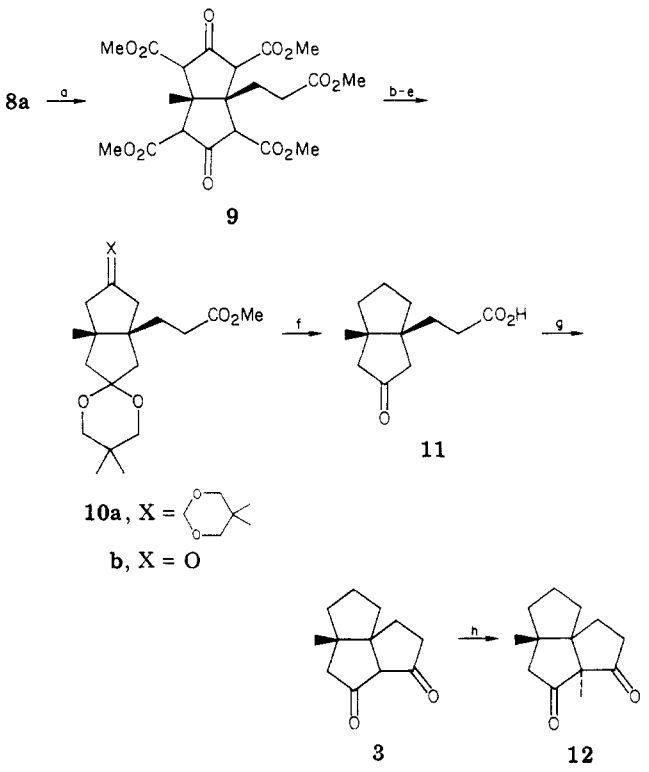
(13) (a) Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979**, 620. (b) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493. (c) Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014. (d) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130.

(14) (a) Cargill, R. L.; Foster, A. M. *J. Org. Chem.* **1970**, *35*, 1971. (b) Oehldrich, J.; Cook, J. M.; Weiss, U. *Tetrahedron Lett.* **1976**, 4549.

(15) (a) Baldracco, G. *J. Prakt. Chem.* **1894**, *49*, 197. (b) Wieland, T.; Stark, J. *Chem. Ber.* **1963**, *96*, 2410.

0022-3263/81/1946-1103$01.25/0

Scheme II[a]



[a] (a) 2 equiv of $MeO_2CCH_2C(O)CH_2CO_2Me$, pH 6.8, aqueous MeOH, 3 days; (b) 6 N HCl, HOAc, reflux; (c) $KF \cdot 2H_2O$, MeI, DMF; (d) $HOCH_2C(Me)_2CH_2OH$, TsOH, PhH, reflux, $-H_2O$; (e) 0.3 equiv of TsOH, 5% aqueous acetone; (f) NH_2NH_2, KOH, $(HOCH_2CH_2)_3N$, 205 °C, H_3O^+; (g) TsOH, PhH, reflux, $-H_2O$; (h) LDA, THF, MeI or sodium *tert*-amylate, DME, MeI.

hands,[16] and an alternative synthesis of **8b** was developed.

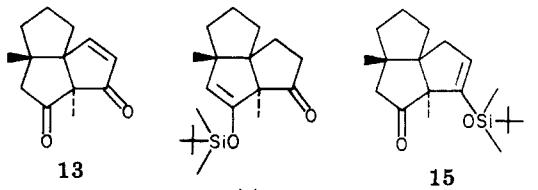
The keto thioacetal **5**[17] was synthesized in 89% yield by the reaction of ethylene dithiotosylate[18] with 2,4-pentanedione.[19] The anion of **5** was alkylated with ethyl 3-bromopropionate to afford **6** in 74% yield (Scheme I). Hydrolysis of the α-oxodithiolane **6** was best accomplished by Corey's method of NBS in aqueous acetonitrile[20] to afford **8a** in a reproducible 49% yield. Attempts to improve this yield by a number of hydrolytic methods[21] were unsuccessful. Interestingly, when the anion of **5** was added to ethyl acrylate, the only product that was isolated was 1,3-cyclohexanedione **7**. This undesired product is the result of the expected Michael addition,[22] followed by anion equilibration to the methyl ketone and subsequent ring closure. Attempts at preventing this cyclization by using *tert*-butyl acrylate as the Michael acceptor or by utilizing careful temperature control were unsuccessful.

The purified α-diketone **8a** was condensed with 2 equiv of dimethyl 1,3-acetonedicarboxylate in aqueous methanol to afford the crystalline pentaester **9**, in 80% yield (Scheme II). The condensation product was hydrolyzed and decarboxylated in refluxing aqueous acid, and the resultant diketo acid **4a** was esterified[23] to give **4b** in a 76% overall yield.

At this point in the planned synthetic sequence, the two carbonyls of the diketo ester **4b** must be differentiated. Various attempts at monoreduction with L-Selectride or sodium borohydride were unfruitful. Also unsuccessful were experiments aimed at forming a monotosylhydrazone, which could be reduced with sodium cyanoborohydride to the hydrocarbon.[24] The problem was solved by forming the diketal **10a** with 3,3-dimethylpropane-1,3-diol (96%) followed by partial hydrolysis to the monoketal **10b**. The hydrolysis product was easily separated by medium-pressure liquid chromatography to afford a 63% yield of pure monoketal **10b**, 14% of diketal **10a**, and an ester mixture which could be saponified to the diketo acid **4a** (11%). This method of ketone differentiation[25] leaves open the possibility of maintaining a functionality in ring A and could be useful in the synthesis of differently substituted systems. Keto acid **11** was obtained in 69% yield by Wolff–Kishner reduction of the monoketal **10b** and subsequent acidic hydrolysis of the protecting group.

The acid- and base-sensitive tricyclic diketone **3** was obtained by *p*-toluenesulfonic acid catalyzed cyclization of **11** in refluxing benzene. A yield of 88% was achieved with a single recycle of unreacted keto acid. The β-diketone **3** is completely nonenolized, which is consistent with data on other 2,6-diones in bicyclo[3.3.0]octane systems.[26] Due to the nonenolizable nature of the β-dicarbonyl system, the common problem of O- vs. C-alkylation was expected to be minimal.[27] The anion of **3** was generated with LDA in THF at −78 °C and was allowed to react with methyl iodide to give a 64% yield of **12**, along with 12% of starting diketone. When the base was changed to sodium *tert*-amylate in DME, an 84% yield of alkylated product was obtained.

The synthetic plan at this point called for generation of the kinetic enolate of the diketone **12**,[28] which was predicted to be that derived from abstraction of the apparently least hindered acidic hydrogens on C-3. This enolate could be trapped with either trimethylsilyl chloride or phenylselenenyl chloride to ultimately afford enone **13**.[29]



(16) A number of methods were tried to hydrolyze the oxime, including the following: (a) $NaNO_2$/HCl (see ref 15b); (b) $NaHSO_3$ (Pines, S. H.; Chemerda, J. M.; Kozlowski, M. A. *J. Org. Chem.* **1966**, *31*, 3446); (c) $TiCl_3$ (Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 195); (d) CH_2O/HCl (Cava, M. P.; Little, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257); (e) Raney nickel (Staskun, B.; van Es, T. *J. Chem. Soc. C* **1966**, 531).

(17) Previously synthesized by the reaction of ethyl acetoacetate with 1,2-ethylenedisulfenyl chloride followed by decarboxylation (Leir, C. M. *J. Org. Chem.* **1972**, *37*, 887).

(18) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *Org. Synth.* **1974**, *54*, 33.

(19) Prepared analogously to 2-acetyl-1,3-dithiane (Bryant, R. J.; McDonald, E. *Tetrahedron Lett.* **1975**, 3841).

(20) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(21) Methods tried included the following: (a) $NCS/AgNO_3$ (see ref 20); (b) isoamyl nitrite (Fuji, K.; Ichikawa, K.; Fujita, E. *Tetrahedron Lett.* **1978**, 3561); (c) $NaNO_2/CF_3CO_2H$ (Olah, G. A.; Narang, S. C.; Salem, F. G.; Gupta, B. G. B. *Synthesis* **1979**, 273); (d) $Ce(NH_4)_2(NO_2)_6$ (Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791); (e) SO_2Cl_2/wet SiO_2 (Hojo, M.; Masada, R. *Synthesis* **1976**, 678).

(22) Hermann, J. L.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2599.

(23) Clark, J. H.; Miller, J. M. *Tetrahedron Lett.* **1977**, 599.

(24) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.

(25) For another method of removing one carbonyl from a bicyclo[3.3.0]octa-3,7-dione, see: Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765.

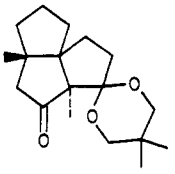
(26) (a) Stetter, H.; Hansen, I. K.; Rizk, M. *Chem. Ber.* **1961**, *94*, 2702. (b) Eaton, P. E.; Giordano, G.; Schloemer, G.; Vogel, U. *J. Org. Chem.* **1976**, *41*, 2238.

(27) House, H. O, "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: New York, 1972; p 520.

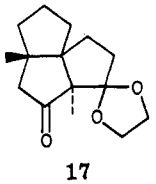
(28) We are aware of only three other reports in the literature concerning monoenolate formation in diketone systems (see: Grieco, P. A.; Ferriño, S.; Oguri, T. *J. Org. Chem.* **1979**, *44*, 2593.

Reaction of 13 with lithium dimethylcuprate would introduce the C-2 methyl stereospecifically from the α face. The diketone 12 was treated with 1 equiv of LDA in THF at −78 °C, followed by trapping with *tert*-butyldimethylsilyl chloride to give, surprisingly, a 78:22 mixture of silyl enol ethers 14 and 15, respectively. This ratio was determined by GC and NMR of the mixture, which showed a singlet at δ 4.23 and a multiplet at δ 4.45 for the respective vinyl proton resonances. When the bulk of the base was increased by using lithium 2,2,6,6-tetramethylpiperidide, the ratio of 14 to 15 changed only slightly to 65:35. Interestingly, a 95:5 ratio of 14/15 was obtained when less than 1 equiv of LDA was used, and the resultant enolate mixture was allowed to equilibrate at room temperature for 1 h. The monoprotected diketone 14 could be useful in the elaboration of ring C, but due to the sensitivity of a silyl enol ether, a different approach was investigated.

The β-diketone 12 was allowed to react with 2,2-dimethyl-1,3-propanediol, *p*-toluenesulfonic acid, and trimethyl orthoformate at room temperature to give a 46% yield of monoketal 16 plus ring-opened products. The



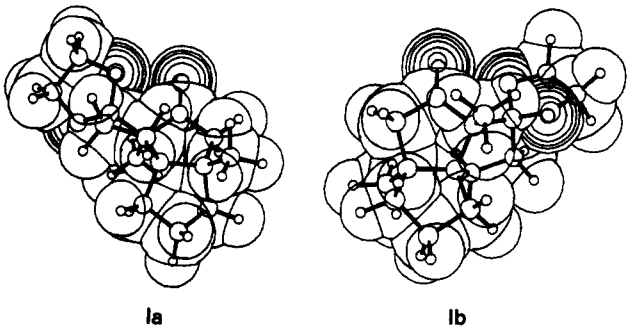
16



17

structure of 16 was confirmed by the conversion of 16 to a single trimethylsilyl enol ether which showed a singlet vinyl absorption in the NMR at δ 4.18. The regiospecific formation of 16 was anticipated due to the large difference in the steric hindrance of the two ketones at C-4 and C-6. With monoketal 16 in hand, attempts were made to introduce a methyl group at C-6. Treatment of 16 with triphenylphosphonium methylide in Me_2SO at 60 °C for 2 days or with excess methyllithium in THF at temperatures ranging from −78 °C to reflux afforded no adduct. The ethylene ketal protected diketone 17 was synthesized in 60% yield from 12. The hope was that the ethylene ketal would provide less steric hindrance to nucleophilic addition to the C-6 carbonyl than the 2,2-dimethyltrimethylene ketal of 16. However, when 17 was treated with [*N*-(methylphenyl)sulfonimidoyl]methyllithium,[30] or excess methyllithium in THF or DME at temperatures ranging from −78 °C to reflux, no adduct was obtained. Similarly, treatment with methylmagnesium chloride in refluxing ether or DME gave no desired product. The problem in these cases is presumably enolization of the sterically hindered ketone.

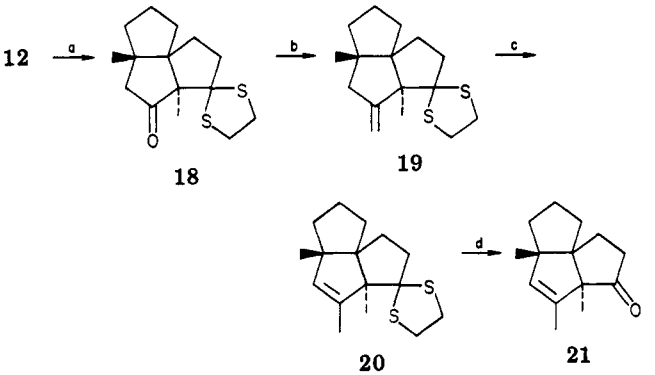
Space-filling projections[31] of the conformation of 17 calculated by Allinger's MM2 force field program[32] show the hindered nature of the C-6 carbonyl carbon. Figure 1a is the view sighting toward C-6 of 17 from the β face at an approach vector of 109.5°.[33] The path of the incoming nucleophile would be severely hindered by the C-2 β-hydrogen and the C-8 methyl. The view from the α face,



Ia Ib

Figure 1. SPACFIL projections of 17 overlaid on ORTEP structures. Views are sighting toward the C-6 carbonyl carbon from the β face in 1a and from the α face in 1b. Oxygen atoms are marked with concentric circles.

Scheme III[a]



[a] (a) $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, HOAc; (b) sodium *tert*-amylate, Ph_3PCH_3Br, toluene, reflux; (c) TsOH, CH_2Cl_2, reflux; (d) MeI, 80% aqueous CH_3CN, $CaCO_3$, reflux, 3 days.

depicted in Figure 1b, also shows considerable hindrance, predominantly by the C-5 methyl.[34] In addition, a nucleophile approaching from this face would encounter the unhindered, pseudoaxial, C-7 α-hydrogen which could readily be abstracted. The problem of enolate formation in preference to carbonyl addition is greater for cyclopentanones than for the more often studied cyclohexanones. The combined effect of lower carbonyl reactivity, due to I strain,[35] in conjunction with the greater rate of base-catalyzed enolization[36] often leads to low yields of nucleophilic addition products for cyclopentanones.[37]

Further attempts to add a methyl group to the C-6 carbonyl were carried out with the thioketal monoprotected diketone 18 which could be regiospecifically formed in better yield (74%) than the oxygen ketals 16 and 17. The reaction of 18 with trimethylsilyl cyanide[38] was very sluggish, even under forcing conditions. However, the Wittig reaction, when run with sodium *tert*-amylate as the base[39] in refluxing toluene, gave an 81% yield of exocyclic methylene compound 19 (Scheme III). Presumably an equilibrium is established between the cyclopentanone

(29) Dehydrogenation of the trimethylsilyl enol ether with palladium acetate (Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011) or oxidation of the α-phenylseleno ketone and elimination (Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434) would afford enone 13.

(30) Johnson, C. R.; Kirchoff, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 3602.

(31) Smith, G. M.; Gund, P. *J. Chem. Inf. Comput. Sci.* **1978**, *18*, 207.

(32) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(33) Burgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563. See also: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(34) Figure 1b is drawn with the freely rotating C-5 methyl shown in a position to demonstrate the greatest steric hindrance to the carbonyl carbon and not in its lowest energy rotamer.

(35) (a) Brown, H. C.; Brewster, J. H.; Schechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467. (b) Brown, H. C.; Ishikawa, K. *Tetrahedron* **1957**, *1*, 221.

(36) Schechter, H.; Collis, M. J.; Dessy, R.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2905.

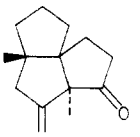
(37) For example see: Martin, J. L.; Tou, J. S.; Reusch, W. *J. Org. Chem.* **1979**, *44*, 3666; Buhler, J. D. *Ibid.* **1973**, *38*, 904.

(38) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914. Also note: Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.

(39) Conia, J.-M.; Limasset, J.-C. *Bull. Soc. Chim. Fr.* **1967**, *6*, 1936.

enolate and *tert*-amyl alcohol, so that there is always free ketone present to react with the ylide. These conditions appear to be a general solution to the problem of adding a carbon nucleophile to a readily enolizable but sterically hindered carbonyl compound.[40]

The exocyclic double bond in **19** was isomerized with anhydrous *p*-toluenesulfonic acid in refluxing dichloromethane to give a quantitative crude yield of the thermodynamic mixture of endo/exo isomers, determined by GC and NMR spectroscopy to be 92:8. The thioketal of **20** was hydrolyzed by being refluxed with excess methyl iodide in 80% aqueous acetonitrile buffered with calcium carbonate[41] for 3 days. The product was separated by chromatography to give a 69% yield of the desired endocyclic enone **21** along with 6% of the exocyclic enone **22**.



22

During the course of this work, Paquette published a synthesis of ketone **21**, which was efficiently carried on to isocomene in three steps.[13c] The IR, NMR, and ^{13}C NMR spectral data of **21** prepared in the present studies were identical with those reported by Paquette.[42] Therefore, this work constitutes a formal total synthesis of isocomene **1** and may be of general interest in the synthesis of tricyclo[6.3.0.0^{1,5}]undecane ring systems.

Experimental Section

All melting points were determined on a Büchi melting point apparatus and are uncorrected, as are boiling points. Proton NMR spectra were recorded on a Varian T-60, a Varian EM-390, or a UCB-250 spectrometer. The UCB-250 uses a Nicolet 1180 data system and has a Cryo Magnet Systems 5.7-T magnet. Carbon-13 NMR were recorded on a Nicolet Systems NTC-TT-23 spectrometer equipped with a Varian 2.3-T magnet. Chemical shifts are reported in units of δ from internal tetramethylsilane. IR spectra were recorded on a Perkin-Elmer Model 281 or Model 710A spectrometer. Mass spectral data were collected on an AEI-MS-12 (low resolution) or Du Pont CEC 21-110B (high resolution) instrument. Combustion analyses were carried out by the University of California Microanalytical Laboratory.

Solvents were dried and distilled prior to use when deemed necessary: THF, ether, DME (from sodium–benzophenone ketyl), dichloromethane (P_2O_5), toluene (Na metal), and hexane (CaH_2). Analytical and preparative gas chromatographs were carried out on Hewlett-Packard 402 and Varian Aerograph A-90-P instruments, respectively. Dry nitrogen was used in reactions requiring an inert atmosphere. Preparative thin-layer chromatography was performed on 1- or 2-mm thick, 12-cm (diameter) circular plates which were rotated by using a Model 7824 Chromatatron.

2-Acetyl-1,3-dithiolane (5).[17] A solution of ethylene dithiotosylate (75.0 g, 0.187 mol),[18] 2,4-pentanedione (22.4 g, 0.224 mol), and potassium acetate (73.7 g, 0.752 mol) in methanol (1.25 L) was refluxed under nitrogen for 4 h. The solution was concentrated, and the residue was thoroughly extracted with dichloromethane–hexane (1:1). The extract was filtered through a short silica gel column, and the solvent was evaporated to yield an orange oil (30.17 g, 109%). The residual liquid was distilled to afford 24.67 g (89%) of dithiolane **5**: bp 73–83 °C (0.15 mm) [lit.[17] bp 70–73 °C (0.05 mm)]; IR (CCl_4) 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (s, 3), 3.32 (s, 4), 4.72 (s, 1).

Ethyl 4,4-(Ethylenedithio)-5-oxo-hexanoate (6). Acetyl dithiolane **5** (12.55 g, 84.8 mmol) was slowly added to a stirred solution of LDA [84.8 mmol; prepared from diisopropylamine (12.0 mL, 84.8 mmol) and *n*-butyllithium (84.8 mmol, 55.1 mL, 1.54 M in hexane)] in dry THF (150 mL) at −78 °C under nitrogen. The deep red reaction solution was stirred for 45 min, and ethyl 3-bromopropionate (11.5 mL, 89.7 mmol) was added. The reaction was slowly allowed to warm to room temperature and was stirred for 10 h. The reddish orange mixture was poured into a stirred solution of saturated aqueous ammonium chloride (150 mL), and most of the THF was evaporated on a rotary evaporator. The aqueous solution was extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride (40 mL). The extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield an orange oil (18.93 g, 90%). This product was filtered through 220 g of silica gel by using 20% ethyl acetate–hexane as eluent. The solvent was evaporated to give 15.45 g (74%) of ester **6** which was 91% pure by GC analysis. An analytical sample was isolated by preparative GC on a 5% SE-30 column at 180 °C: IR (CCl_4) 1738, 1710 cm^{-1}; NMR (CCl_4) δ 1.27 (t, 3), 2.38 (s, 7), 3.40 (s, 4), 4.08 (q, 2); ^{13}C NMR δ 14.2, 25.2, 31.8, 34.0, 41.0, 60.5, 74.5, 172.8, 202.8.

Anal. Calcd for $C_{10}H_{16}O_3S_2$: C, 48.36; H, 6.49; S, 25.82. Found: C, 48.39; H, 6.35; S, 25.66.

Ethyl 4,5-Dioxohexanoate (8a). A solution of 15.45 g (62.3 mmol) of ester **6** (91% pure by GC) in acetonitrile (60 mL) was rapidly (1 min) added to a stirred solution of *N*-bromosuccinimide (70.05 g, 0.394 mol) in 80% aqueous acetonitrile (500 mL). The reaction temperature was maintained at 20–25 °C by using an ice bath. The red solution was stirred for 5 min, and the reaction was then quenched by the addition of 65 mL of saturated aqueous sodium sulfite. Dichloromethane–hexane (1:1, 600 mL) was added, and the aqueous layer was separated. The organic layer was washed with saturated aqueous sodium bicarbonate (100 mL) and saturated aqueous sodium chloride (100 mL), dried ($MgSO_4$), and concentrated. The resultant yellow oil and precipitate were extracted with carbon tetrachloride (250 mL), and the solvent was evaporated to yield 10.09 g (94%) of a yellow oil. The product was filtered through 150 g of silica gel by using 20% ethyl acetate-hexane as eluent to give 5.23 g (49%) of a yellow oil (pure by GC). An analytical sample was obtained by preparative GC on a 5% SE-30 column at 130 °C: IR (CCl_4) 1737, 1720 cm^{-1}; NMR (CCl_4) δ 1.27 (t, 3), 2.32 (s, 3), 2.55 (m, 2), 2.90 (m, 2), 4.09 (q, 2).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.57; H, 6.97.

***cis*-1-[2-(Carboethoxy)ethyl]-5-methyl-2,4,6,8-tetrakis(carbomethoxy)bicyclo[3.3.0]octa-3,7-dione (9).** The α-diketone **8a** (14.95 g, 86.9 mmol), dimethyl 1,3-acetonedicarboxylate (31.25 g, 174 mmol), methanol (200 mL), and pH 6.8 citrate–phosphate buffer (400 mL) were mixed with a Vibromixer for 1 day and stirred for an additional 2 days. The resultant precipitate was filtered, washed with water, and dried to yield 33.66 g (80%) of material with a melting point of 108–111 °C. The product was recrystallized from chloroform–hexane to give an analytical sample: mp 112.5–115 °C; IR ($CHCl_3$) 3200–2800, 1730, 1665 (sh, 1655), 1445, 1325, 1265, 1190 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3), 1.37 (s, 3), 1.83–2.60 (m, 4), 3.75 (s, 6), 3.87 (s, 6), 3.93 (s, 1), 4.10 (q, 2), 4.12 (s, 1), 10.77 (br s, 1), 11.15 (br s, 1).

Anal. Calcd for $C_{22}H_{28}O_{12}$: C, 54.54; H, 5.83. Found: C, 54.30; H, 5.82.

***cis*-1-(2-Carboxyethyl)-5-methylbicyclo[3.3.0]octa-3,7-dione (4a).** A suspension of crude pentaester **9** (48.91 g, 0.101 mol) in 8 N aqueous HCl (300 mL) and acetic acid (300 mL) was refluxed under nitrogen with mechanical stirring for 1 h. Most of the acetic acid was removed under reduced pressure, and the aqueous solution was exhaustively extracted with ethyl acetate (1.8 L). The organic layers were washed with saturated aqueous sodium chloride (2 × 200 mL), dried ($MgSO_4$), and concentrated to give 22.36 g (99%) of a light brown solid which was recrystallized from

(40) See also: Smith, A. B., III; Jerris, P. J., "Abstracts of Papers" 179th National Meeting of the American Chemical Society, Houston, TX, Mar. 1980; American Chemical Society: Washington, DC; ORGN 63.

(41) Chang, H.-L. W. *Tetrahedron Lett.* **1972**, 1989. Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382. Other reagents tried were the following: (a) $Tl(NO_3)_3$ (Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1976**, *24* 1115; Smith, R. A. J.; Hannah, D. J. *Synth. Commun.* **1979**, *9*, 301); (b) I_2/Me_2SO (Chattopadhyaya, J. B.; Rao, A. V. *Tetrahedron Lett.* **1973**, 3735); (c) $HgCl_2$ (see ref 20).

(42) The δ 1.27 reported for one of the methyls in the NMR of ketone **21** in ref 13c was a typographical error and should have read δ 1.17 (personal communication from L. A. Paquette).

ethyl acetate–hexane to yield 17.21 g of **4a**. The mother liquors were chromatographed on Florex XXS to give an additional 1.25 g of product for a total yield of 19.46 g (86%) of **4a**. A second recrystallization from acetone–hexane gave analytically pure prisms: mp 174.5–176.5 °C; IR ($CHCl_3$) 3600–2400, 1740 (sh, 1720), 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 3), 1.53–2.50 (m, 4), 2.35 (m, 11), 6.00 (br s, 1).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.16.

***cis*-1-[2-(Carbomethoxy)ethyl]-5-methylbicyclo[3.3.0]-octa-3,7-dione (4b).** To a stirred mixture of potassium fluoride dihydrate (25.6 g, 0.272 mol) and methyl iodide (10.8 mL, 0.173 mol) in DMF (250 mL) was added the diketo acid **4a** (19.01 g, 84.9 mmol). The reaction was stirred overnight at room temperature and was poured into water (1 L), and the aqueous solution was extracted with ethyl acetate (5 × 200 mL). The organic layers were washed with saturated aqueous sodium sulfite (2 × 50 mL) and saturated aqueous sodium chloride (100 mL), dried ($MgSO_4$), and concentrated to give 17.74 g (88%) of light tan crystals. The product was recrystallized from carbon tetrachloride–hexane to give an analytical sample: mp 84.5–85.0 °C; IR ($CHCl_3$) 1735, 1190, 1170, 1105 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (s, 3), 1.67–2.50 (m, 12), 3.70 (s, 3); ^{13}C NMR δ 21.6, 29.5, 30.6, 46.2, 47.6, 48.5, 51.1, 51.9, 173.3, 215.2.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.32; H, 7.62.

***cis*-1-[2-(Carbomethoxy)ethyl]-5-methylbicyclo[3.3.0]-octa-3,7-dione Bis(2,2-Dimethyltrimethylene) Acetal (10a).** Diketo ester **4b** (6.16 g, 25.9 mmol), 2.2-dimethylpropane-1,3-diol (10.82 g, 104 mmol), and *p*-toluenesulfonic acid monohydrate (170 mg) were dissolved in 250 mL of benzene and the mixture refluxed under nitrogen for 2 h with the use of a Dean–Stark trap. The cool reaction mixture was washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL), and saturated aqueous sodium chloride (50 mL), dried ($MgSO_4$), and concentrated to yield 10.18 g (96%) of product. The product was recrystallized from hexane to give analytically pure chunky crystals: mp 154.5–155.5 °C; IR ($CHCl_3$) 1735 (br), 1095, 1005 cm^{-1}; NMR (CCl_4) δ 0.88 (s, 6), 0.92 (s, 6), 0.98 (s, 3), 1.30–2.42 (m, 12), 3.35 (s, 8), 3.58 (s, 3).

Anal. Calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.48; H, 9.13.

***cis*-1-[2-(Carbomethoxy)ethyl]-5-methylbicyclo[3.3.0]-octa-3,7-dione 2,2-Dimethyltrimethylene Acetal (10b).** Diketal ester **10a** (23.95 g, 58.4 mmol) and *p*-toluenesulfonic acid monohydrate (3.30 g, 17.3 mmol) were dissolved in 600 mL of 5% aqueous acetone. The light yellow solution was stirred at room temperature for 1 h, and the reaction was quenched by the addition of 150 mL of saturated aqueous sodium bicarbonate. The acetone was evaporated under reduced pressure, and the aqueous solution was extracted with ether (5 × 60 mL). The ether layers were washed with saturated aqueous sodium chloride (55 mL), dried ($MgSO_4$), and concentrated to give 20.49 g of semicrystalline product. This product was combined with 6.53 g of product from another run under identical conditions and derived from 7.63 g (18.6 mmol) of the diketal ester. The mixture was separated by medium-pressure LC using 50% ether–hexane as eluent to give, despite some mechanical losses, 15.74 g (63%) of pure monoketal and 4.44 g (14%) of diketal. The ether washes of the LC column were concentrated and saponified with KOH in aqueous methanol to give 1.97 g (11%) of diketo acid **4a**. The monoketal **10b** was recrystallized from chloroform–hexane to give fine needles: mp 87–88 °C; IR ($CHCl_3$) 1738 (br), 1110, 1092, 1010 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 3), 1.00 (s, 3), 1.17 (s, 3), 1.47–2.50 (m, 12), 3.45 (s, 4), 3.68 (s, 3).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.67; H, 8.63.

***cis*-1-(2-Carboxyethyl)-5-methylbicyclo[3.3.0]octan-3-one (11).** Keto ketal ester **10b** (15.74 g, 48.6 mmol), 85% hydrazine hydrate (30 mL, 0.51 mol), and triethanolamine (80 mL) were heated at 130 °C for 3 h. Potassium hydroxide (32.9 g, 0.50 mol) dissolved in hot triethanolamine (80 mL) was added to the reaction, and the reaction temperature was rapidly raised to 205 °C and maintained there for 6 h as water and hydrazine distilled. The cool reaction was diluted with water (400 mL) and acidified with concentrated HCl (160 mL). The reaction was allowed to stand overnight and was extracted with dichloromethane (5 × 150 mL). The organic layers were washed with saturated aqueous sodium bicarbonate (2 × 200 mL) and saturated aqueous sodium chloride (150 mL), dried ($MgSO_4$), and concentrated to give 8.14 g (80%) of a yellow solid. The product was chromatographed on 250 g of silica gel with ethyl acetate–hexane–formic acid (50:50:1) as eluent to give 7.04 g (69%) of pure **11** which was recrystallized from chloroform–hexane to afford an analytical sample: mp 86.0–86.5 °C; IR ($CHCl_3$) 3600–2400, 1735, 1712, 1215 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (s, 3), 1.77 (m, 8), 2.23 (m, 6), 9.67 (s, 1).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.49; H, 8.52.

8β-Methyl-5α-tricyclo[6.3.0.0^{1,5}]undeca-4,6-dione (3). A solution of keto acid **11** (7.94 g, 37.8 mmol) and *p*-toluenesulfonic acid monohydrate (5.02 g, 26.4 mmol) in 250 mL of benzene was refluxed under nitrogen for 18 h with the use of a Dean–Stark trap filled with 3A molecular sieves. The benzene solution was concentrated, and the residue was flash chromatographed[43] by using 40% ethyl acetate–hexane as eluent to give 4.91 g of pure **3**. Recovered keto acid **11** was resubmitted to the reaction conditions and subsequent flash chromatography gave an additional 1.44 g for a total yield of 6.35 g (88%). The product was recrystallized from carbon tetrachloride–hexane to give an analytical sample: mp 80–81 °C; IR ($CHCl_3$) 1765 (s), 1720 (w) cm^{-1}; NMR ($CDCl_3$) δ 1.17 (s, 3), 1.43–2.57 (m, 12), 2.83 (s, 1); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.8, 29.1, 36.4, 39.5, 40.4, 46.8, 51.4, 59.0, 70.2, 207.3, 208.1.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.17; H, 8.48.

5α,8β-Dimethyltricyclo[6.3.0.0^{1,5}]undeca-4,6-dione (12). Method A. To a solution of LDA [3.88 mmol; prepared from diisopropylamine (0.54 mL, 3.88 mmol) and *n*-butyllithium (3.88 mmol, 2.5 mL, 1.55 M in hexane)] in THF (4 mL) at −78 °C under nitrogen was added a solution of diketone **3** (0.727 g, 3.79 mmol) in 5 mL of THF. The reaction was stirred for 20 min at −78 °C, and methyl iodide (1.20 mL, 17.9 mmol) was added. The reaction was allowed to slowly warm to room temperature and was stirred there for 20 h. Saturated aqueous ammonium chloride (5 mL) was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL), dried ($MgSO_4$), and concentrated to give 0.749 g (96%) of product. The product was chromatographed with 20% ethyl acetate–hexane as eluent to give 0.501 g (64%) of **12** and 86.5 mg (12%) of starting material **3**.

Method B. To a solution of diketone **3** (0.260 g, 1.35 mmol) in DME (10 mL) at 0 °C was added 0.65 mL (1.42 mmol) of a 2.19 M solution of sodium *tert*-amylate in toluene. The cream-colored sodium enolate precipitated from the solution. The reaction was stirred 15 min, and methyl iodide (0.42 mL, 6.74 mmol) was added. The reaction was allowed to warm to room temperature, was stirred for 1 h, and was poured into 30 mL of saturated aqueous ammonium chloride solution. The aqueous solution was extracted with ether (3 × 20 mL), and the ether layers were washed with saturated aqueous sodium chloride (15 mL), dried ($MgSO_4$), and concentrated to give 0.273 g (98%) of a white crystalline solid. The product was filtered through a short column of neutral alumina with 40% ethyl acetate–hexane to yield 0.234 g (84%) of **12** with a melting point of 185–190 °C, which was recrystallized from hexane at 0 °C: mp 194–197 °C; IR (CCl_4) 1763 (s), 1725 (m) cm^{-1}; NMR (CCl_4) δ 1.07 (s, 3), 1.27 (s, 3), 1.40–2.50 (m, 12).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.45; H, 8.67.

5α,8β-Dimethyl-4,4-(ethylenedithio)tricyclo[6.3.0.0^{1,5}]undecan-6-one (18). To the diketone **12** (1.618 g, 7.85 mmol) dissolved in acetic acid (15 mL) were added boron trifluoride etherate (2.15 mL, 17.5 mmol) and 1,2-ethanedithiol (0.72 mL, 8.60 mmol) with cooling in an ice bath. The reaction was stirred at room temperature for 1.5 h and was then poured into water (150 mL). The aqueous solution was extracted with ether (4 × 40 mL), and the ether extracts were washed with saturated aqueous sodium carbonate (2 × 25 mL), water (25 mL), and saturated aqueous sodium chloride (30 mL), dried ($MgSO_4$), and

(43) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

concentrated to give 2.132 g (96%) of white crystals. The product was recrystallized from dichloromethane–pentane at −78 °C to give 1.269 g of pure **18**. The mother liquors were separated by medium-pressure LC to give an additional 0.383 g of product for a total yield of 1.652 g (75%) of **18**. A portion of the product was recrystallized from methanol to give an analytical sample: mp 93.5–94.5 °C; IR (CCl_4) 1735 cm^{-1}; NMR (CCl_4) δ 1.12 (s, 6), 1.37–2.15 (m, 10), 2.22 (s, 2), 3.05 (s, 4).

Anal. Calcd for $C_{15}H_{22}OS_2$: C, 63.78; H, 7.85; S, 22.70. Found: C, 63.59; H, 7.79; S, 22.80.

5α,8β-Dimethyl-6-methylene-4,4-(ethylenedithio)tricyclo[6.3.0.0^{1,5}]undecane (19). To a stirred suspension of methyl triphenylphosphonium bromide (0.724 g, 2.03 mmol) in dry toluene (2 mL) was added 0.92 mL (2.01 mmol) of a 2.19 M solution of sodium *tert*-amylate in toluene. To the resultant yellow suspension was added a solution of ketone **18** (0.285 g, 1.01 mmol) in 1.5 mL of toluene, and the reaction was refluxed under nitrogen for 3 h. The cool reaction mixture was poured into water (30 mL) and was extracted with pentane (3 × 20 mL). The pentane layers were washed with saturated aqueous sodium chloride (30 mL), dried ($MgSO_4$), and concentrated. The crude product was taken up in THF (5 mL), 1 mL of methyl iodide was added, and the solution was stirred at room temperature for 2 h. The precipitated methyltriphenylphosphonium iodide was filtered, and the pentane was evaporated under reduced pressure to give 0.232 g (82%) of white crystals, mp 76.5–79.5 °C. The product was recrystallized from pentane at −78 °C to give an analytical sample: mp 81.5–82.0 °C; IR (CCl_4) 3080, 1642, 895 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (s, 3), 1.30 (s, 3), 1.33–2.10 (m, 10), 2.20 (m, 2), 3.10 (m, 4), 4.92 (m, 1), 5.08 (m, 1).

Anal. Calcd for $C_{16}H_{24}S_2$: C, 68.51; H, 8.62; S, 22.86. Found: C, 68.74; H, 8.77; S, 22.82.

5α,6,8β-Trimethyl-4,4-(ethylenedithio)tricyclo[6.3.0.0^{1,5}]undec-6-ene (20). To a solution of exocyclic olefin **19** (0.627 g, 2.24 mmol) in dry dichloromethane (40 mL) was added anhydrous *p*-toluenesulfonic acid (0.39 g, 2.3 mmol). The reaction mixture was refluxed under nitrogen for 2 h. GC analysis of a worked up aliquot on a 3% OV-225 column at 210 °C after 1 h and again after 2 h showed a constant isomer ratio of 92:8. The reaction was washed with saturated aqueous sodium bicarbonate (30 mL), and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride (20 mL), dried ($MgSO_4$), and evaporated to give 0.63 g (101%) of a yellow oil, which slowly crystallized on standing. The semicrystalline product was recrystallized from pentane at −78 °C: mp 54–56 °C; IR (CCl_4) 850 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (s, 3), 1.30 (s, 3), 1.68 (d, J = 1.5 Hz, 3), 1.17–2.37 (m, 10), 3.17 (s, 4), 4.87 (br s, 1).

Anal. Calcd for $C_{16}H_{24}S_2$: C, 68.51; H, 8.62; S, 22.86. Found: C, 68.77; H, 8.52; S, 22.88.

5α,6,8β-Trimethyltricyclo[6.3.0.0^{1,5}]undec-6-en-4-one (21). A stirred mixture of crude olefinic thioacetal **20** (102.6 mg, 0.366 mmol), methyl iodide (2.3 mL, 36.6 mmol), and powdered calcium carbonate (0.110 g, 0.80 mmol) in 80% aqueous acetonitrile (10 mL) was refluxed under nitrogen for 3 days in the dark. The cool reaction was poured into water (20 mL) and was extracted with ether (4 × 20 mL). The ether layers were washed with 2 N aqueous sodium hydroxide (25 mL), water (to neutrality), and saturated aqueous sodium chloride (20 mL), dried ($MgSO_4$), and evaporated to give 85.2 mg (114%) of crude product. The product was chromatographed on a 1-mm Chromatatron plate with 5% ether–hexane as the eluent to give 51.7 mg (69%) of endocyclic olefin **21** and 4.6 mg (6%) of exocyclic olefin **22**. Preparative GC of **21** (5% SE-30 at 150 °C) gave a white waxy solid: mp 84.5–85.0 °C (sealed capillary); IR (CCl_4) 3020, 1735, 847, 832 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 1.06 (s, 3), 1.17 (s, 3), 1.21–1.66 (m, 6), 1.61 (d, J = 1.34 Hz, 3), 1.85–1.91 (m, 1), 2.03–2.17 (m, 2), 2.37–2.54 (m, 1), 5.09 (br s, 1); ^{13}C NMR ($CDCl_3$) δ 12.3, 15.5, 22.4, 24.0, 28.7, 37.0, 38.6, 42.2, 56.6, 60.0, 65.4, 136.2, 138.7, 220.0; mass spectrum (70 eV), m/e (relative intensity) 204 (M^+, 39), 176 (17), 161 (14), 149 (37), 148 (100), 133 (25), 120 (60), 105 (34), 91 (27); exact mass calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1509.

For exocyclic olefin **22**: IR (CCl_4) 1720, 1655, 908, 892 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (s, 3), 1.17 (s, 3), 1.43–2.73 (series of m, 12), 4.78 (s, 1), 4.89 (s, 1); mass spectrum (70 eV), m/e (relative intensity) 204 (M^+, 100), 175 (62), 162 (67), 148 (57), 147 (50), 133 (52), 120 (43), 119 (91), 105 (54), 91 (45); exact mass calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1513.

Acknowledgment. We thank David Moreland and Molecular Design Limited for their assistance with the MM2 calculations and the SPACFIL and ORTEP drawings.

Registry No. (±)-**1**, 71629-00-0; **4a**, 76251-18-8; **4b**, 76251-19-9; **5**, 33406-25-6; **6**, 76251-20-2; **8a**, 76251-21-3; **9**, 76251-22-4; **10a**, 76251-23-5; (±)-**10b**, 76251-24-6; (±)-**11**, 76251-25-7; (±)-**12**, 76251-26-8; (±)-**18**, 76251-27-9; (±)-**19**, 76251-28-0; (±)-**20**, 76251-29-1; (±)-**21**, 71718-85-9; (±)-**22**, 76251-30-4; ethylene dithiotosylate, 2225-23-2; 2,4-pentanedione, 123-54-6; ethyl 3-bromopropionate, 539-74-2; dimethyl 1,3-acetonedicarboxylate, 1830-54-2; 2,2-dimethylpropane-1,3-diol, 126-30-7; (±)-**3**, 76251-31-5.

Isolation and Structure Determination of Piptocarphins A–F, Cytotoxic Germacranolide Lactones from *Piptocarpha chontalensis*[1]

Patricia L. Cowall, John M. Cassady,* Ching-jer Chang, and John F. Kozlowski

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received August 25, 1980

Six novel sesquiterpenes, piptocarphins A–F, were isolated from *Piptocarpha chontalensis* Pall. Their structures were elucidated as a series of closely related germacranolide sesquiterpene lactones possessing an unusual conjugated enol lactone and an intramolecular hemiketal functionality on the basis of an extensive spectral analysis. All compounds exhibited cytotoxic activity against the 9KB human nasopharynx carcinoma cells. Piptocarphins A and C also showed borderline activity in the P-388 lymphoid leukemia system.

Piptocarpha chontalensis Pall. (family, Asteraceae; tribe, Vernonieae) is a small, flowering, leafy plant native to tropical America[2] which has not received phytochemical investigation. Our investigation of *P. chontalensis* was prompted by reproducible cytotoxic activity shown by ethanolic extracts in the KB in vitro cell system (human carcinoma of the nasopharanx).[3,4] Six, novel, cytotoxic,

(1) Paper 14 in the series "Potential Antitumor Agents". For paper 13 see: Cassady, J. M.; Abramson, D.; Cowall, P.; Chang, C.-j.; McLaughlin, J. L. *J. Nat. Prod.* **1979**, *42*, 427.

(2) Hoffman, O. In "Die Naturlichen Pflanzenfamilien"; Engler, A., Prantl, K., Eds.; W. Engelman: Leipzig, 1897; Vol. 4, Bands 4–5, pp 118–131.

(3) Significant in vitro activity is shown for crude extracts by an ED_{50} < 20 μg/mL and for pure compounds by ED_{50} < 4 μg/mL. Significant in vivo activity is indicated by a therapeutic index (T/C) ≥130. The protocols followed are detailed in ref 4.

0022-3263/81/1946-1108$01.25/0