Direct Stereocontrolled Synthesis of Isocomene†[1]

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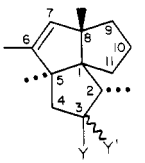
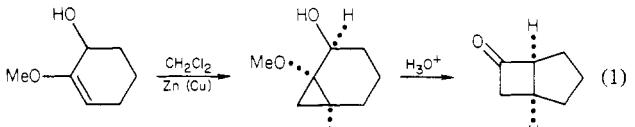
Abstract: A total synthesis of the racemic, sesquiterpenic hydrocarbon isocomene is described. The 17-step route is initiated by a Robinson annelation of 2-methylcyclopentanone with 1,4-dimethoxy-2-butanone and involves a crucial α-oxycyclopropylcarbinol-to-cyclobutanone rearrangement as the central theme of the synthesis.

During the last decade an appreciable number of natural, terpenic substances based on the hitherto unrepresented tricyclo[6.3.0.0^{1,5}]undecane skeleton have come on the scene.[3] Isocomene (berkheyaradulene) (**1a**), a sesquiterpenic hydrocarbon initially isolated from *Isocoma wrightii* (Gray) Rydb.[3b,e] and *Berkheya radula* (Harv.) de Willd.,[3c] is an early example of a compound encompassing the unusual structure pattern of three, fused, five-membered carbocycles with a common carbon center. This intriguing feature made isocomene a challenging goal of total synthesis and led to the stereorational construction of the natural hydrocarbon in racemic form (compound **1**).[4]

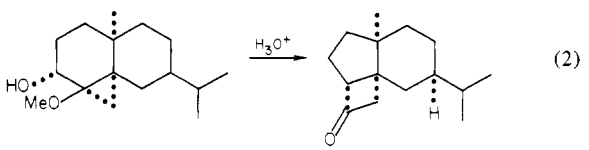


1a, Y = Y′ = H
b, Y + Y′ = O
c, Y = H; Y′ = OH
d, Y = H; Y′ = OPO(NMe$_2$)$_2$

The oxycyclopropane unit has served for some time as an excellent building block in syntheses of natural products, especially terpenes.[5] Among the various oxycyclopropane-dependent schemes of synthesis one has been concerned with the formation of α-oxycyclopropylcarbinols and their conversion into cyclobutanones,[6] a reaction sequence that in the case of substrates derived from 2-oxy-2-cyclohexenones has involved the transformation of bicyclo[4.1.0]heptanols into bicyclo[3.2.0]heptanones (cf. eq 1).[7,8] In view of the latter being lower homologues of the



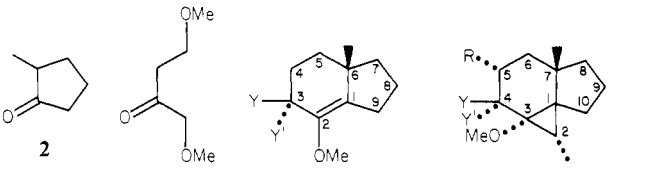
(1)



(2)

bicyclo[3.3.0]octane units present in the isocomene structure (**1a**), a ready isocomene synthesis based on the facile α-oxycyclopropylcarbinol → cyclobutanone rearrangement and subsequent ring expansion could be envisaged. This view was strengthened by the rearrangement depicted in eq 2, discovered serendipitously during a synthesis of the sesquiterpenic ketone valeranone,[9] in the light of the product containing the isocomene-like feature of three fused rings with a common carbon center.

The synthesis of isocomene (**1a**) was initiated with 2-methylcyclopentanone (**2**) as starting material, serving as the precursor of the unsubstituted ring of isocomene. In a manner similar to the first steps of the valeranone synthesis[9] the ketone was condensed with the annelating reagent 1,4-dimethoxy-2-butanone (**3**)[9,10] under the influence of potassium ethoxide and the resultant bicyclic ketone (**4a**) reduced with lithium aluminum hydride. The products, alcohols **4b** and **4c** in ca. 7:1 ratio,[11] required no sep-



2 **3** **4a**, Y + Y′ = O; b, Y = OH; Y′ = H; c, Y = H; Y′ = OH **5a**, R = Y′ = H; Y = OH; b, R = H; Y + Y′ = O; c, R = Y = H; Y′ = OH; d, R = Me; Y + Y′ = O

† Dedicated to the memory of Professor Franz Sondheimer.

(1) This work was presented at the Ernest Guenther Award Symposium, honoring Dr. Sukh Dev, 179th ACS National Meeting, Houston, TX, March 24-28, 1980 (E. Wenkert, abstract 86), and at the Eighth International Congress of Essential Oils, Cannes, France, Oct 12-17, 1980 (Wenkert, E. *Koryo* **1981**, *133*, 26).

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(3) (a) Kaneda, M.; Takahashi, R.; Iitaka, Y. *Tetrahedron Lett.* **1972**, 4609. (b) Zalkow, L. H.; Harris, R. N.; Van Derver, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. (c) Bohlmann, F.; Le Van, N.; Pickardt, J. *Chem. Ber.* **1977**, *110*, 3777. (d) Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411. (e) Zalkow, L. H.; Harris, R. N.; Burke, N. I. *J. Nat. Prod.* **1979**, *42*, 96. (f) Corbett, R. E.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans.* **1979**, 1774. (g) Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *Ibid*, **1979**, 1791. (h) Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 1747. (i) Bohlmann, F.; Le Van, N.; Van Cuong Pham, T.; Jacupovic, J.; Schuster, A.; Zabel, V.; Watson, W. H. *Ibid.* **1979**, *18*, 1831. (j) Bohlmann, F.; Jacupovic, J. *Ibid*, **1980**, *19*, 259. (k) Bohlmann, F.; Zdero, C.; Bohlmann, R.; King, R. M.; Robinson, H. *Ibid.* **1980**, *19*, 579. (l) de Pascual Teresa, J.; San Feliciano, A.; Barrero, A. F.; Medare, M.; Tomé, F. *Ibid*, **1981**, *20*, 166. (m) Bohlmann, F.; Ziesche, J.; Robinson, H.; King, R. M. *Ibid.* **1981**, *20*, 1146. (n) Bohlmann, F.; Gupta, R. K.; Jacupovic, J.; King, R. M.; Robinson, H. *Ibid.* **1981**, *20*, 1155.

(4) For other syntheses see: (a) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493; *Tetrahedron* **1981**, *37*, 4359. (b) Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835. (c) Pirrung, M. C. *Ibid.* **1979**, *101*, 7130; **1981**, *103*, 82. (d) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. (e) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445.

(5) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.

(6) The earliest clues for the possible utility of this rearrangement in natural products synthesis came from observations and mechanistic interpretations of acid-catalyzed cyclobutanone isomerizations (Wenkert, E.; Bakuzis, P.; Baumgarten, R. J.; Doddrell, D.; Jeffs, P. W.; Leicht, C. L.; Mueller, R. A.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1970**, *92*, 1617. Erman, W. F.; Treptow, R. S.; Bakuzis, P.; Wenkert, E. *Ibid.* **1971**, *93*, 657) and the *homo*-Favorskii rearrangement (Wenkert E.; Bakuzis, P.; Baumgarten, R. J.; Leicht, C. L.; Schenk, H. P. *Ibid.* **1971**, *93*, 3208).

(7) Wenkert, E.; Golob, N. F.; Hatch, R. P.; Wenkert, D.; Pellicciari, R. *Helv. Chim. Acta* **1977**, *60*, 1.

(8) A synthesis of the monoterpenic alcohol grandisol was based on this rearrangement.[9]

(9) Wenkert, E.; Berges, D. A.; Golob, N. F. *J. Am. Chem. Soc.* **1978**, *100*, 1263.

(10) Wenkert, E.; Golob, N. F.; Sathe, S. S.; Smith, R. A. J. *Synth. Commun.* **1973**, *3*, 205.

(11) Whereas the stereochemistry of the alcohols was not determined, its assignment was based on the precedent of hydride reductions of ketones of type **4a**, yielding preponderantly alcohols with a cis relationship of their hydroxy and angular methyl groups[9,12] (Henbest, H. B.; McEntee, J. *J. Chem. Soc.* **1961**, 4478).

(12) Dauben, W. G.; Ashcraft, A. C. *J. Am. Chem. Soc.* **1963**, *85*, 3673.

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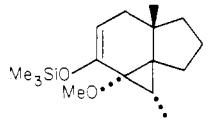
aration, since the next reaction, a cyclopropanation of the enol ether mixture with ethylidene diiodide and diethylzinc,[13] converted alcohol **4b** into tricycle **5a** while leaving the minor compound unchanged.[14,15] Oxidation of carbinol **5a** with chromic acid in pyridine–acetic acid[16] yielded tricyclic ketone **5b**.[17] Thus in four reactions the construction of a three-ring system with a common carbon center and incorporating three of isocomene's four chiral centers in proper relative configuration, the three contiguous carbons of ketone **5b** between its methyl groups, had been achieved.

The next task involved the functionalization of the central ring of tricycle **5b**. Since direct methylation α to its keto group by any means capable of leaving the sensitive cyclopropyl ether unit unaltered proved not easily controllable, the oxycyclopropane route for α-methylation of aldehydes and ketones[9,18] was adopted. Exposure of ketone **5b** to lithium diisopropylamide and trimethylsilyl iodide[19] led to the enol ether **6**, whose interaction with



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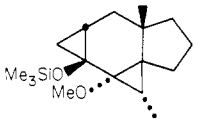

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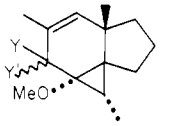
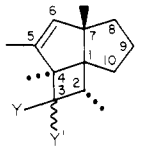


8a, Y + Y′ = O
b, Y = Me; Y′ =



9a, Y + Y′ = O
b, Y = CH_2SMe; Y′ = OH
c, Y = $CH_2S^+Me_2$; I^-, Y′ = OH
d, Y + Y′ = CH_2O

methylene iodide and diethylzinc[20] produced the double cyclopropyl ether **7**.[21] Treatment of the latter with methanolic sodium hydroxide[22] transformed it into ketone **5d**. Base-induced condensation of this substance with methyl benzenesulfinate[23] yielded ketone **8a**.[24] The stage now was set for the crucial α-oxycyclopropylcarbinol–cyclobutanone rearrangement. Treatment of ketone **8a** with methyllithium afforded a stereoisomer mixture of α-oxycyclopropylcarbinols (**8b**), whose exposure to acid led to ketone **9a**. Thus the vital rearrangement had succeeded and in its wake had introduced the fourth of the four chiral centers of isocomene (**1a**) in proper orientation. The six-step reaction sequence **5b** → **9a** had yielded a tricycle, which required merely cyclobutanone ring enlargement and deoxygenation for completion of the isocomene synthesis.

Treatment of ketone **9a** with ((methylthio)methyl)lithium and alkylation of the resultant thioether **9b** with methyl iodide in nitromethane solution yielded a salt (**9c**), whose exposure to sodium hydride led to spiro epoxide **9d**.[26] The latter underwent rearrangement on interaction with anhydrous lithium iodide in tetrahydrofuran, producing an isocomene-like ketone (**1b**).[27] Lithium aluminum hydride reduction of the latter was followed by conversion of the resultant alcohol (**1c**) into a phosphoramidate (**1d**) with *n*-butyllithium, (dimethylamino)phosphoryl dichloride, and subsequently dimethylamine.[28] Reduction of the ester (**1d**) with lithium in ethylamine[29] afforded (±)-isocomene (**1a**).[4,30] The third phase of the natural product synthesis, the seven-step, **9a** → **1a** sequence, thus completed the third ring of the desired substance and concluded a 17-step synthesis of the terpenic hydrocarbon.

Experimental Section

Melting points were observed on a Reichert micro hotstage and are uncorrected. Infrared spectra were taken on Beckman IR 4230 and Acculab 8 as well as Pye Unicam 3-200 spectrophotometers. ^{1}H NMR spectra of carbon tetrachloride solutions (unless noted otherwise) with Me_4Si as internal standard (δ = 0) were recorded on a Varian EM-390 spectrometer and a 360-MHz instrument with a highly modified Varian HR-220 console, an Oxford magnet, and a Nicolet 1180-E computer system, while ^{13}C NMR spectra of deuteriochloroform solutions were obtained on Varian XL-100-15, JEOL JNM-PS-100, and Nicolet NT-200 (wide-bore, broad-band, with Oxford magnet) spectrometers operating in the Fourier transform mode at 25.02, 25.03, and 50.31 MHz, respectively. The carbon shifts are downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. All reactions were run under argon and on workup all extracts dried over anhydrous magnesium sulfate. Column chromatography was carried out with Merck silica gel (70–230 mesh), TLC with 0.25-mm precoated Merck silica gel 60 F-254 plates, and medium-pressure chromatography with Merck Lobar (A, B, or C) silica gel columns, equipped with a Fluid Metering, Inc., pump. Analytical GC was performed on a Varian 1420 gas chromatograph, outfitted with a 3 ft × $^1/_8$ in. stainless-steel column containing 1.5% OV-101 on 100/120 Chromasorb W, and preparative GC on a Hewlet-Packard 5700 gas chromatograph with TC detector, outfitted with a 6 ft × $^1/_4$ in. glass column containing 3% OV-1 on 100/120 Supelcoport.

2-Methoxy-6-methyl-3,4,5,6-tetrahydroindan-3-one (4a). A solution of 21.3 g (162 mmol) of 1,4-dimethoxy-2-butanone (**3**) in 200 mL of dry ether was added dropwise over a 5-h period to a stirring, ice-cold solution of 16.6 g (170 mmol) of 2-methylcyclopentanone (**2**) and ethanolic po-

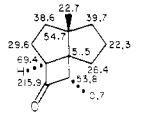
(13) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647.

(14) Whereas the relative configuration of the cyclopropylmethyl group was not determined directly, it was surmised to be as depicted in formula **5a** on the assumption of the cyclopropanation proceeding in a manner in which the incipient secondary methyl group is as far removed from the angular methyl function as possible. The first clue confirming this view emanated from a comparison of the ^{1}H NMR spectrum of alcohol **5a** with that of **5c**, one of the products of reduction of ketone **5b** with lithium aluminum hydride. Due to the deshielding influence of the proximate hydroxy group on the cyclopropyl hydrogen of alcohol **5a** the cyclopropyl hydrogen quartet of the latter resided ca. 0.5 ppm downfield of that of **5c**.

(15) The higher rate of cyclopropanation of allyl alcohols of configuration type **4b**, compared with that of type **4c**, is precedented.[9,12]

(16) Stensiö, K. E.; Wachtmeister, C. A. *Acta Chem. Scand.* **1964**, *18*, 1013. Stensiö, K. E. *Ibid.* **1971**, *25*, 1125.

(17) Attempted Jones oxidation of alcohol **5a** caused its rearrangement into cyclobutanone i [IR (neat) C=O 1770 (s) cm^{-1}; ^{1}H NMR δ 1.01 (s, 3, angular



i

Me), 1.01 (d, 3, J = 6 Hz, Me), 1.4–1.9 (m, 10, methylenes), 2.7–3.0 (m, 2, methines); ^{13}C NMR on formula i]. This observation constituted the first omen for the likelihood of success in the later crucial α-oxycyclopropylcarbinol–cyclobutanone rearrangement (vide infra).

(18) Wenkert, E.; Mueller, R. A.; Reardon, E. J., Jr.; Sathe, S. S.; Scharf, D. J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, *92*, 7428.

(19) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(20) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353; *Tetrahedron* **1968**, *24*, 53.

(21) The stereochemistry of the new cyclopropane remains undetermined. Its tentative assignment as depicted in formula **7** is based on the assumption of the α face of precursor **6** being less hindered than its β face and of the allylic methoxy possibly participating in the cyclopropanation process (Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468).

(22) Conia, J. M.; Girard, C. *Tetrahedron Lett.* **1973**, 2767. Girard, C.; Conia, J. M. *Ibid.* **1974**, 3327.

(23) Monteiro, H. J.; de Souza, J. P. *Tetrahedron Lett.* **1975**, 921. Coates, R. M.; Pigott, H. D. *Synthesis* **1975**, 319

(24) Whereas the products were expected to be stereoisomeric α-keto sulfoxides, they had undergone an unusually facile elimination. The ease of this olefin formation became manifest more directly, when enone **8a** could be shown to be the product of oxidation of α-keto sulfides, prepared by the interaction of ketone **5d** with lithium diisopropylamide and diphenyl disulfide,[25] with sodium metaperiodate[25] at room temperature.

(25) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(26) Shanklin, J. R.; Johnson, C. R.; Ollinger, J.; Coates, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3429.

(27) Leriverend, M. L.; Leriverend, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 791; *Chem. Ber.* **1976**, *109*, 3492. Trost, B. M.; Latimer, L .H. *J. Org. Chem.* **1978**, *43*, 1031. Morton, D. R.; Brokaw, F. C. *Ibid.* **1979**, *44*, 2880.

(28) Liu, H. J.; Lee, S. P.; Chan, W. H. *Can. J. Chem.* **1977**, *55*, 3797.

(29) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(30) Whereas the hydrocarbon was also the product of reduction of ketone **1b** by direct means, either the Wolff–Kishner method or sequential thioketal formation and desulfurization, it always was accompanied by an uncharacterized minor hydrocarbon, thus necessitating the development of the described, longer route of deoxygenation.

tassium ethoxide, from 1.50 g of potassium in 15 mL of dry ethanol, in 250 mL of dry ether at 0 °C and the mixture then left at room temperature for 16 h.[31] It was neutralized with glacial acetic acid, washed with saturated sodium bicarbonate solution and with saturated brine solution, dried, and evaporated. Distillation of the residue yielded 16.8 g (57%) of liquid ketone **4a**: bp 103–105 °C (2.3 torr); IR (neat) C=O 1670 (s), C=C 1645 (m) cm^{-1}; ^1H NMR δ 1.19 (s, 3, Me), 1.3–2.1 (m, 6, methylenes), 2.2–2.8 (m, 4, $COCH_2$, allyl CH_2); ^{13}C NMR δ C(8) 21.2, Me 21.8, C(9) 24.6, C(4) 34.5, C(5) 35.1, C(7) 41.0, C(6) 43.1, OMe 58.7, C(1) 144.7, C(2) 159.6, C=O 193.6. Exact mass: *m/e* 180.1144 (calcd for $C_{11}H_{16}O_2$, *m/e* 180.1150).

2-Methoxy-6β-methyl-3,4,5,6-tetrahydroindan-3β-ol (4b) and Its Isomer 4c. A solution of 5.00 g (28 mmol) of ketone **4a** in 15 mL of dry ether was added dropwise to an ice-cold, stirring suspension of 570 mg (15 mmol) of lithium aluminum hydride in 40 mL of dry ether and the mixture then stirred for 30 min. Saturated ammonium chloride solution was added to the stirring mixture for neutralization and hydrolysis and the organic solution dried and evaporated. Distillation of the residue gave a 7:1 liquid mixture (by ^1H NMR spectroscopy) of alcohols **4b** and **4c**: bp 88–90 °C (0.1 torr); IR (neat) OH 3400 (br, m), C=C 1685 (m) cm^{-1}; ^1H NMR δ (**4b**) 1.04 (s, 3, Me), 1.1–2.6 (m, 10, methylenes), 3.59 (s, 3, OMe), 4.0–4.3 (m, 1, OCH); δ (**4c**) 0.90 (s, 3, Me), 1.1–2.6 (m, 10, methylenes), 3.55 (s, 3, OMe), 4.0–4.3 (m, 1, OCH); ^{13}C NMR δ (**4b**) C(8) 21.2, Me 24.0, C(9) 24.6, C(4) 29.3, C(5) 35.1, C(7) 41.5, C(6) 42.3, OMe 58.1, C(3) 66.7, C(1) 130.1, C(2) 147.3. Exact mass: *m/e* 182.1307 (calcd for $C_{11}H_{18}O_2$, *m/e* 182.1307).

3α-Methoxy-2α,7β-dimethyltricyclo[5.3.0.0^{1,3}]decan-4β-ol (5a). A solution of 10.81 g (59 mmol) of the above mixture of alcohols **4b** and **4c** in 30 mL of dry ether was added dropwise over a 30-min period to an ice-cold, stirring solution of 9.25 mL (90 mmol) of diethylzinc in 90 mL of dry ether. Thereafter, 11.9 mL (120 mmol) of ethylidene diiodide[32] was added dropwise over a 30-min period at room temperature. In order to permit access to oxygen,[33] the argon inlet tube was replaced by a calcium chloride tube and the mixture stirred at room temperature for 12 h. It then was poured into 200 mL of saturated ammonium chloride solution and extracted with ether. The extract was washed with saturated sodium bicarbonate and sodium thiosulfate and brine solutions, dried, and evaporated. Distillation of the residue gave a forerun, containing **4c** and 10.14 g (93%, based on the conversion of **4b**) of solid alcohol, bp 105–107 °C (2 torr), whose crystallization from hexane afforded colorless, crystalline **5a**: mp 60–61 °C; IR (neat) OH 3360 (m), 3260 (m) cm^{-1}; ^1H NMR δ 0.80 (s, 3, angular Me), 0.7–1.3 (m, 4, Me, CH), 1.3–2.3 (m, 10, methylenes), 3.23 (s, 3, OMe), 4.08 (t, 1, J = 7 Hz, OCH); ^{13}C NMR δ Me 8.4, C(2) 18.0, C(9) 24.5, angular Me 24.5, C(5) 26.1, C(10) 26.9, C(6) 35.0, C(1) 38.7, C(7) 38.7, C(8) 43.3, OMe 54.8, C(4) 68.4, C(3) 68.9. Exact mass: *m/e* 210.1619 (calcd for $C_{13}H_{22}O_2$, *m/e* 210.1620). Anal. ($C_{13}H_{22}O_2$) C, H.

3α-Methoxy-2α,7β-dimethyltricyclo[5.3.0.0^{1,3}]decan-4-one (5b). A solution of 10.82 g (52 mmol) of alcohol **5a** in 15 mL of pyridine was added to a solution of 17.00 g (170 mmol) of chromic trioxide in 100 mL of pyridine and 100 mL of glacial acetic acid at 5 °C and the mixture maintained at 16 °C for 25 min. It was diluted with 800 mL of water and extracted with ether. The extract was washed with 3 N hydrochloric acid, saturated sodium bicarbonate, and brine solutions, dried, and evaporated. Distillation of the residue gave 9.59 g (89%) of liquid ketone **5b**: bp 113–115 °C (2.2 torr); IR (neat) C=O 1690 (s) cm^{-1}; ^1H NMR δ 0.98 (s, 3, angular Me), 1.02 (d, 3, J = 6 Hz, Me), 1.1–2.2 (m, 11, methylenes, CH), 3.28 (s, 3, OMe); ^{13}C NMR δ Me 8.8, angular Me 23.7, C(9) 24.4, C(10) 26.1, C(2) 28.7, C(5) 34.0, C(6) 38.7, C(1) 39.5, C(8) 42.4, C(7) 51.6, OMe 56.6, C(3) 71.0, C=O 207.8. Anal. ($C_{13}H_{20}O_2$) C, H.

3α-Methoxy-2α,7β-dimethyl-4-((trimethylsilyl)oxy)tricyclo[5.3.0.0^{1,3}]dec-4-ene (6). A solution of 5.28 g (25 mmol) of ketone **5b** in 10 mL of dry tetrahydrofuran was added dropwise to a solution of lithium diisopropylamide (28 mmol) in 15 mL of dry tetrahydrofuran at −78 °C and the mixture permitted to warm to −10 °C. It then was recooled to −78 °C, treated with 3.58 mL (28 mmol) of trimethylsilyl chloride, and permitted to warm to room temperature. After the addition of 4.18 mL (30 mmol) of triethylamine the mixture was poured into water and extracted with ether. The extract was washed with water, dried, and evaporated. Kugelrohr distillation (110 °C (1.5 torr)) of the residue yielded 6.75 g (95%) of liquid, whose medium-pressure chromatography and elution with 10:1 hexane–ethyl acetate gave liquid ether **6**: IR (neat) C=C 1657 (m) cm^{-1}; ^1H NMR δ 0.15 (s, 9, Me_3Si), 0.82 (s, 3, angular Me), 0.8–1.1 (m, 4, Me, CH), 1.46 (dd, 1, J = 16, 5 Hz, allyl H), 1.5–1.8 (m, 6, methylenes), 2.09 (dd, 1, J = 16, 4 Hz, allyl H), 3.18 (s, 3, OMe), 4.61 (dd, 1, J = 5, 4 Hz, olefinic H). Anal. ($C_{16}H_{28}O_2Si$) C, H.

3α-Methoxy-2α,8β-dimethyl-4β-((trimethylsilyl)oxy)tetracyclo[6.3.0.0^{1,3}0^{4,6}]undecane (7). A solution of 6.65 g (24 mmol) of ether **6**, 4.12 mL (40 mmol) of diethylzinc, and 3.87 mL (48 mmol) of methylene iodide in 60 mL of dry ether was refluxed under dry air[33] for 36 h. It then was poured into 60 mL of saturated ammonium chloride solution and extracted with ether. The extract was washed with saturated sodium thiosulfate and brine solutions, dried, and evaporated. Kugelrohr distillation (130 °C (0.1 torr)) of the residue yielded 7.00 g (99%) of liquid, whose medium-pressure chromatography and elution with 25:1 hexane–ethyl acetate gave liquid diether **7**: ^1H NMR δ (internal benzene standard) 0.10 (s, 9, Me_3Si), 0.69 (dd, 1, J = 4, 2 Hz, H of cyclopropyl CH_2), 0.78 (s, 3, angular Me), 0.8–1.0 (m, 4, Me, H-2), 1.14 (br d, 1, J = 4 Hz, H of cyclopropyl CH_2), 1.2–1.7 (m, 9, methylenes, CH), 3.38 (s, 3, OMe). Anal. ($C_{17}H_{30}O_2Si$) C, H.

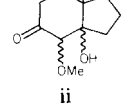
3α-Methoxy-2α,5α,7β-trimethyltricyclo[5.3.0.0^{1,3}]decan-4-one (5d). A solution of 6.86 g (23 mmol) of diether **7** in 50 mL of 0.1 methanolic sodium hydroxide was refluxed for 24 h, then neutralized with glacial acetic acid, and concentrated to low volume. Water was added and the mixture extracted with ether. The extract was dried and evaporated. Kugelrohr distillation (120 °C (0.1 torr)) of the residue led to 4.47 g (91%) of liquid ketone **5d**: IR (neat) C=O 1690 (s) cm^{-1}; ^1H NMR δ 0.89 (d, 3, J = 6 Hz, 5-Me), 1.01 (s, 3, angular Me), 0.9–1.9 (m, 12, Me, CH, methylenes), 2.10 (m, 1, α-keto H), 3.40 (s, 3, OMe); ^{13}C NMR δ 2-Me 9.0, 5-Me 14.3, 7-Me 24.1, C(9) 24.7, C(10) 26.7, C(2) 29.7, C(5) 35.1, C(1) 39.1, C(8) 43.3, C(6) 49.2, C(7) 52.4, OMe 56.8, C(3) 71.6, C=O 209.7. Anal. ($C_{14}H_{22}O_2$) C, H.

3α-Methoxy-2α,5,7β-trimethyltricyclo[5.3.0.0^{1,3}]dec-5-en-4-one (8a). A solution of 5.55 g (25 mmol) of ketone **5d** in 15 mL of 1,2-dimethoxyethane was added dropwise over a 20-min period to a stirring, refluxing suspension of 1.27 g (53 mmol) of sodium hydride and 6.24 g (40 mmol) of methyl benzenesulfinate in 60 mL of 1,2-dimethoxyethane. After the cessation of hydrogen evolution 2.25 g (14 mmol) of methyl benzenesulfinate was added and refluxing continued for 15 min. The mixture was poured into 100 mL of saturated ammonium chloride solution and extracted with ether. The extract was washed with brine solution, dried, and evaporated. Distillation of the residue yielded liquid ketone **8a**: bp 88–90 °C (0.1 torr); IR (neat) C=O 1660 (s) cm^{-1}; ^1H NMR δ 0.98 (s, 3, angular Me), 1.0–1.2 (m, 4, Me, CH), 1.67 (d, 3, J = 2 Hz, 5-Me), 1.6–1.9 (m, 6, methylenes), 3.37 (s, 3, OMe), 6.01 (q, 1, J = 2 Hz, olefinic H). Anal. ($C_{14}H_{20}O_2$) C, H.

2α,4α,5,7β-Tetramethyltricyclo[5.3.0.0^{1,4}]dec-5-en-3-one (9a). A solution of 1.63 g (7 mmol) of ketone **8a** in 10 mL of dry tetrahydrofuran was added dropwise to a solution of methylithium (10 mmol in 5 mL of hexane) in 15 mL of dry tetrahydrofuran at −78 °C. The mixture was allowed to warm to room temperature, poured into 50 mL of water, and extracted with 40 mL of 1:1 hexane–ethyl acetate. The extract was dried and evaporated. Flash chromatography[34] of the residue and elution with 7:1 hexane–ethyl acetate gave 1.57 g (90%) of a liquid mixture of alcohols **8b**: IR (neat) OH 3480 (m) cm^{-1}; ^1H NMR δ (isomer a) 0.40 (q, 1, J = 6 Hz, cyclopropyl H), 0.78 (s, 3, angular Me), 0.97 (d, 3, J = 6 Hz, cyclopropyl Me), 1.28 (s, 3, Me), 1.60 (d, 3, J = 1 Hz, olefinic Me), 1.5–2.0 (m, 6, methylenes), 3.42 (s, 3, OMe), 5.02 (q, 1, J = 1 Hz, olefinic H); δ (isomer b) 0.68 (q, 1, J = 6 Hz, cyclopropyl H), 0.78 (s, 3, angular Me), 1.02 (d, 3, J = 6 Hz, cyclopropyl Me), 1.23 (s, 3, Me), 1.60 (d, 3, J = 1 Hz, olefinic Me), 1.5–2.0 (m, 6, methylenes), 3.39 (s, 3, OMe), 4.98 (q, 1, J 1 Hz, olefinic H).

A mixture of 3.95 g (18 mmol) of alcohols **8b** in 30 mL of hexane and 12 mL of 30% sulfuric acid was stirred rapidly for 20 min and extracted exhaustively with ether. The extract was washed with water and saturated sodium bicarbonate and brine solutions, dried, and evaporated. Kugelrohr distillation (100 °C (0.2 torr)) of the residue yielded 3.20 g (89%) of liquid ketone **9a**: IR (neat) C=O 1770 (s) cm^{-1}; ^1H NMR δ 1.02 (d, 3, J = 8 Hz, Me), 1.08, 1.11 (s, 3 each, angular methyls), 1.2–1.9 (m, 6, methylenes), 1.57 (d, 3, J = 2 Hz, olefinic Me), 3.18 (q, 1, J = 8 Hz, α-keto H), 5.17 (q, 1, J = 2 Hz, olefinic H); ^{13}C NMR δ 2-Me

(31) Earlier workup of the reaction led to a mixture of enone **4a** and the aldol precursor ii [IR (neat) OH 3500 (br, m), C=O 1720 (s) cm^{-1}; ^1H NMR



ii

δ 1.07 (s, 3, Me), 1.4–3.2 (m, 10, methylenes), 3.22 (s, 1, OCH), 3.24 (s, 3, OMe)].

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10.8, 4-Me 13.0, 5-Me 13.3, 7-Me 22.3, C(9) 24.3, C(10) 27.0, C(8) 40.7, C(2) 53.1, C(1) or C(7) 56.2 or 56.4, C(4) 79.3, C(6) 136.0, C(5) 136.9, C=O 214.5. Exact mass: *m/e* 204.1512 (calcd for $C_{14}H_{20}O$, *m/e* 204.1514). Anal. ($C_{14}H_{20}O$) C, H.

2α,4α,5,7β-Tetramethyl-3ξ-((methylthio)methyl)tricyclo[5.3.0.0^{1,4}]-dec-5-en-3ξ-ol (9b). A mixture of 220 μL (3 mmol) of dimethyl sulfide, 455 μL (3 mmol) of tetramethylethylenediamine, and *n*-butyllithium (3 mmol) in 4 mL of hexane was stirred at room temperature for 24 h[35] and then cooled to −78 °C. Dry tetrahydrofuran (3 mL) and subsequently a solution of 295 mg (1.4 mmol) of ketone **9a** in 5 mL of dry tetrahydrofuran were added, and the solution was permitted to warm slowly to room temperature. Saturated ammonium chloride solution was added and the mixture extracted with ether. The extract was washed with water and brine, dried, and evaporated. Chromatography and elution with 20:1 hexane–ethyl acetate yielded 350 mg (93%) of liquid alcohol **9b**: IR (neat) OH 3500 (m), C=C 1640 (w) cm^{-1}; ^{1}H NMR δ 0.87 (d, 3, *J* = 7 Hz, 2-Me), 0.95 (s, 6, angular methyls), 1.1–1.9 (m, 6, methylenes), 1.58 (d, 3, *J* = 1 Hz, 5-Me), 2.10 (s, 3, SMe), 2.15 (q, 1, *J* = 7 Hz, H-2), 2.60 (s, 2, SCH_2), 5.10 (q, 1, *J* = 1 Hz, olefinic H). Anal. ($C_{16}H_{26}OS$) C, H.

2α,4α,5,7β-Tetramethyl-3-spiroepoxymethanotricyclo[5.3.0.0^{1,4}]dec-5-ene (9d). A solution of 1.75 g (7 mmol) of sulfide **9b** and 1.5 mL (24 mmol) of methyl iodide in 10 mL of nitromethane was stirred at room temperature for 12 h and then evaporated. Trituration of the residue with hexane afforded 2.72 g (99%) of pale yellow solid salt **9c**: mp 121–125 °C; IR (KBr) OH 3390 (m), C=C 1635 (w) cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.98 (d, 3, *J* = 7 Hz, 2-Me), 1.00, 1.12 (s, 3 each, angular methyls), 1.0–1.9 (m, 6, methylenes), 1.65 (d, 3, *J* = 1 Hz, 5-Me), 2.35 (q, 1, *J* = 7 Hz, H-2), 3.21, 3.40 (s, 3 each, S-methyls), 3.51 (d, 1, *J* = 14 Hz, H of SCH_2), 4.48 (d, 1, *J* = 14 Hz, H of SCH_2), 5.29 (q, 1, *J* = 1 Hz, olefinic H).

A suspension of 450 mg (1 mmol) of salt **9c** and 100 mg (4 mmol) of sodium hydride in 20 mL of dry tetrahydrofuran was stirred at room temperature for 2 h and then poured into water and extracted with ether. The extract was dried and evaporated. Medium-pressure chromatography of the residue and elution with 25:1 hexane–ethyl acetate yielded 149 mg (62%) of liquid epoxide **9d**: IR (neat) C=C 1650 (w) cm^{-1}; ^{1}H NMR δ 0.71 (d, 3, *J* = 7 Hz, 2-Me), 0.91, 1.06 (s, 3 each, angular methyls), 1.1–1.9 (m, 6, methylenes), 1.47 (d, 3, *J* = 2 Hz, 5-Me), 2.34 (d, 1, *J* = 5 Hz, H of OCH_2), 2.60 (d, 1, *J* = 5 Hz, H of OCH_2), 2.60 (q, 1, *J* = 7 Hz, H-2), 5.07 (q, 1, *J* = 2 Hz, olefinic H); ^{13}C NMR δ 2-Me 11.3, 5-Me 13.2, 4-Me 13.4, C(9) 23.8, 7-Me 23.8, C(10) 28.8, C(2) 35.8, C(8) 40.9, OCH_2 48.5, C(7) 55.2, C(1) 57.8, C(3) 60.2, C(4) 66.9, C(6) 135.5, C(5) 140.0. Anal. ($C_{15}H_{22}O$) C, H.

3-Oxoisocomene (1b). A solution of 684 mg (3 mmol) of epoxide **9d** and 535 mg (4 mmol) of anhydrous lithium iodide[36] in 30 mL of dry tetrahydrofuran was stirred at room temperature for 24 h and then evaporated. A hexane solution of the residue was washed with sodium thiosulfate, dried, and evaporated. Medium-pressure chromatography and elution with 15:1 hexane–ethyl acetate gave 622 mg (91%) of crystalline ketone **1b**: mp 64–65 °C; IR (evaporated CH_2Cl_2 solution) C=O 1740 (s) cm^{-1}; ^{1}H NMR δ 0.92, 1.14 (s, 3 each, angular methyls), 1.02 (d, 3, *J* = 8 Hz, 2-Me), 1.2–1.9 (m, 6, methylenes), 1.58 (d, 3, *J* = 2 Hz, 6-Me), 2.11 (br s, 2, $COCH_2$), 2.30 (q, 1, *J* = 8 Hz, COCH), 4.89 (q, 1, *J* = 2 Hz, olefinic H); ^{13}C NMR δ 6-Me 13.4, 2-Me 15.1, 5-Me 23.7, C(10) 24.9, 8-Me 25.1, C(11) 32.5, C(9) 41.4, C(2) 50.1, C(4) 50.4, C(8) 55.4, C(5) 57.9, C(1) 61.5, C(7) 133.1, C(6) 143.6, C=O 217.9. Anal. ($C_{15}H_{22}O$) C, H.

3ξ-Hydroxyisocomene (1c). A solution of 47 mg (0.2 mmol) of ketone **1b** in 1 mL of dry ether was added dropwise to a stirring suspension of 19 mg (0.5 mmol) of lithium aluminum hydride in 6 mL of dry ether at 0 °C and the mixture then warmed to room temperature. Saturated ammonium chloride solution was added dropwise and the mixture filtered. The organic solution was dried and evaporated. Kugelrohr distillation (120 °C (0.3 torr)) of the residue led to 40 mg (84%) of crystalline alcohol **1c**: mp 90–91 °C; IR (KBr) OH 3235 (m) cm^{-1}; ^{1}H NMR δ 0.88 (d, 3, *J* = 6 Hz, 2-Me), 0.94, 1.01 (s, 3 each, angular methyls), 1.1–2.0 (m, 9, methylenes, CH), 1.53 (d, 3, *J* = 1 Hz, 6-Me), 3.48 (ddd, 1, *J* = 3, 3, 2 Hz, OCH), 4.75 (q, 1, *J* = 1 Hz, olefinic H); ^{13}C NMR δ 6-Me 13.0, 2-Me 14.7, 5-Me or 8-Me 22.4 or 24.6, C(10) 24.6, C(11) 31.3, C(9) 41.7, C(2) 46.8, C(4) 48.3, C(8) 56.9, C(5) 57.4, C(1) 61.7, C(3) 78.9, C(7) 131.2, C(6) 144.1. Anal. ($C_{15}H_{24}O$) C, H.

(±)-Isocomene (1a). A solution of *n*-butyllithium (2 mmol) in 1 mL of hexane was added to a solution of 245 mg (1 mmol) of alcohol **1c** and 1.2 mL of tetramethylethylenediamine in 15 mL of dry tetrahydrofuran at room temperature, followed after 15 min by the addition of 828 μL (7 mmol) of (dimethylamino)phosphoryl dichloride.[37] After 24 h the mixture was cooled to 0 °C, 5 mL of dimethylamine added, and the mixture poured into water and extracted with ether. The extract was dried and evaporated. Medium-pressure chromatography of the residue and elution with ethyl acetate yielded 327 mg (84%) of liquid phosphoramidate **1d**: IR (neat) P=O 1210 (m) cm^{-1}; ^{1}H NMR δ 0.93 (d, 3, *J* = 7 Hz, 2-Me), 1.02, 1.06 (s, 3 each, angular methyls), 1.0–2.1 (m, 9, methylenes, CH), 1.56 (d, 3, *J* = 1 Hz, 6-Me), 2.51, 2.62 (d, 6 each, *J* = 3 Hz, *N*-methyls), 4.03 (m, 1, OCH), 4.76 (q, 1, *J* = 1 Hz, olefinic H).

A solution of 327 mg (1 mmol) of phosphoramidate **1d** in 5 mL of dry tetrahydrofuran was poured into a refluxing suspension of 64 mg (9 mmol) of lithium wire in 15 mL of dry ethylamine and the refluxing continued for 10 min. The mixture was poured into water and extracted with ether. The extract was dried and evaporated. Kugelrohr distillation yielded 143 mg (76%) of colorless solid, whose GC purification gave (±)-isocomene (**1a**): mp 60–63 °C (lit.[4b,c,e] mp 59–62, 60–62, 61–63 °C, respectively); infrared and ^{1}H NMR spectra identical with those recorded previously;[3c,4] ^{13}C NMR δ 6-Me 13.0, 2-Me 17.2, 5-Me 23.0, C(10) 23.6, 8-Me 24.0, C(11) 31.9, C(3) 33.5, C(4) 37.2, C(2) 39.8, C(9) 42.6, C(8) 56.5, C(5) 59.8, C(1) 63.7, C(7) 132.6, C(6) 142.7.

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Registry No. (±)-**1a**, 71629-00-0; (±)-**1b**, 84559-09-1; **1c**, 84559-10-4; **1d**, 84559-11-5; (±)-**2**, 32854-37-8; **3**, 25680-86-8; (±)-**4a**, 84559-12-6; (±)-**4b**, 84559-13-7; (±)-**4c**, 84559-14-8; (±)-**5a**, 84559-15-9; (±)-**5b**, 84559-16-0; (±)-**5d**, 84559-17-1; (±)-**6**, 84559-18-2; (±)-**7**, 84559-19-3; (±)-**8a**, 84559-20-6; **8b**, 84559-21-7; (±)-**9a**, 84559-22-8; **9b**, 84559-23-9; **9c**, 84559-24-0; **9d**, 84559-25-1.

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