Total Syntheses of (±)-Seychellene, (±)-Isocycloseychellene, and (±)-Isoseychellene

Steven C. Welch,* Chih-Yueh Chou, John M. Gruber, and Jean-Marie Assercq

Department of Chemistry, University of Houston, Houston, Texas 77004

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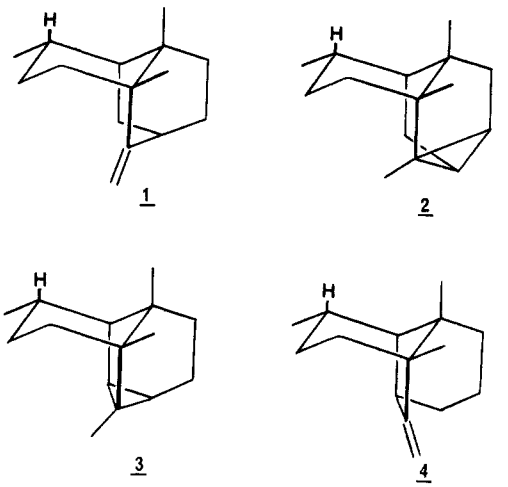
Stereoselective total syntheses of (±)-seychellene (1), (±)-isocycloseychellene (3), and (±)-isoseychellene (4) from 2,5-dimethylcyclohexanone are described. Reisolation and structural elucidation of natural cycloseychellene (2) are presented.

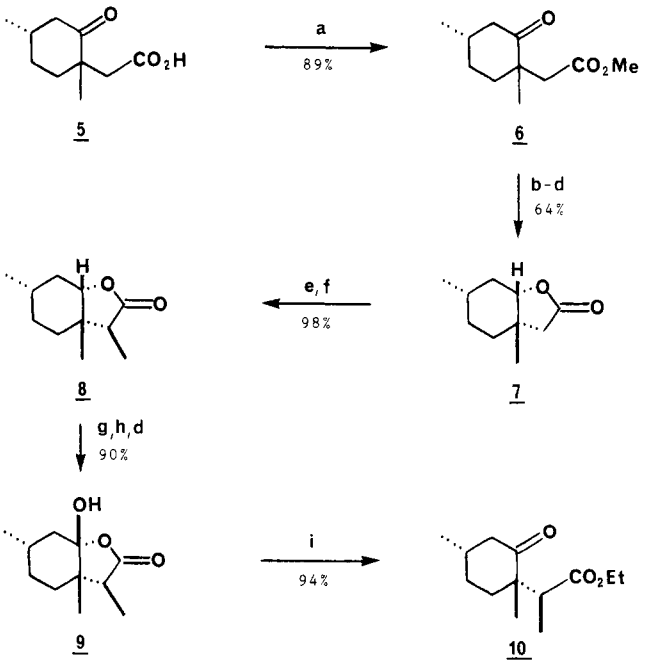
The sesquiterpene (−)-seychellene (1) was first isolated from patchouli oil (*Pogostemon cablin.* Benth.) in 1967.[1] The structure and absolute stereochemistry of tricyclic hydrocarbon 1 were elegantly established by Wolff and Ourisson in 1969.[2] Since the isolation and structural elucidation of seychellene (1) (Scheme I), a number of total syntheses of this unique natural product have been published.[3] In 1974 Lawrence and co-workers isolated the tetracyclic sesquiterpene cycloseychellene from the same essential oil.[4] On the basis of 220-MHz NMR data as well as co-occurrence and equilibration studies [$Cu(OAc)_2$, HOAc, 90 °C] with seychellene (1), these authors proposed structure 3 for natural cycloseychellene. In 1981 we reported stereoselective total syntheses of (±)-seychellene (1) and (±)-tetracyclic hydrocarbon 3 via a common intermediate.[3i] The NMR data for synthetic compound 3 were completely different than those data reported for natural cycloseychellene. So we then reisolated this sesquiterpene and unequivocally established tetracyclic structure 2 for natural cycloseychellene by 400-MHz NMR analysis.[5] Recently, Yamada and co-workers have confirmed our structural assignment by a total synthesis of (±)-cycloseychellene (2).[6] We now report, herein, the full details of our total synthesis of (±)-seychellene (1), (±)-isocycloseychellene (3), and (±)-isoseychellene (4), as well as the reisolation and structural elucidation of natural cycloseychellene (2).

Our syntheses commence with keto acids 5 (Scheme II) which we used in our successful syntheses of (±)-trichodiene.[7] Keto acids 5 were prepared in 75–88% overall yield by regioselective alkylation of 2,5-dimethylcyclohexanone [(a) NaH, DME; (b) $BrCH_2CH{=}CH_2$] followed by oxidative cleavage [$RuCl_3$ (catalytic amount), $NaIO_4$, H_2O, *t*-BuOH). The stereoselectivity of the alkylation reaction of 2,5-dimethylcyclohexanone with allyl bromide was observed to be 70:30 with the major isomer having the

Scheme I



Scheme II. Synthesis of Keto Ester 10[a]



[a] (a) CH_3I, K_2CO_3, acetone; (b) KBH_4, MeOH, −15 °C to 23 °C; (c) NaOH, H_2O, EtOH; (d) 10% HCl; (e) LDA, THF, −70 °C; (f) CH_3I; (g) 2.4 equiv of NaOH, H_2O, *t*-BuOH; (h) 3.3 equiv of $NaIO_4$, $RuCl_3 \cdot xH_2O$ (cat.); (i) EtI, K_2CO_3, acetone.

2- and 5-methyl substituents trans. There is adequate precedent for this structural assignment of the major isomer. Alkylation of the thermodynamic enolate anions derived from 2,5-dialkylcyclohexanones[8] occurs by axial

(1) Tsubaki, N.; Nishimura, K.; Hirose, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 597.
(2) Wolff, G.; Ourisson, G. *Tetrahedron* **1969**, *25*, 4903.
(3) (a) Piers, E.; De Waal, W.; Britton, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5113. (b) Mirrington, R. N.; Schmalzl, K. J. *J. Org. Chem.* **1972**, *37*, 2877. (c) Fukamiya, N.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1843. (d) Frâter, G. *Helv. Chim. Acta* **1974**, *57*, 172. (e) Spitzner, D. *Tetrahedron Lett.* **1978**, 3349. (f) Jung, M. E.; McCombs, C. A. *J. Am. Chem. Soc.* **1978**, *100*, 5207. (g) Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. *Tetrahedron* **1979**, *35*, 293. (h) Jung, M. E.; Pan, Y.-G. *Tetrahedron Lett.* **1980**, 3127. (i) Welch, S. C.; Gruber, J. M.; Chou, C.-Y.; Willcott, M. R.; Inners, R. *J. Org. Chem.* **1981**, *46*, 4816. (j) Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677. (k) Welch, S. C.; Gruber, J. M.; Morrison, P. A. *Tetrahedron Lett.* **1984**, *25*, 5497.
(4) (a) Terhune, S. J.; Hogg, J. W.; Lawrence, B. M. *Tetrahedron Lett.* **1973**, 4705. (b) Paknikar, S. K. *Indian J. Chem.* **1974**, *12*, 1016.
(5) Willcott, M. R.; Morrison, P. A.; Assercq, J.-M.; Welch, S. C.; Inners, R. *J. Org. Chem.* **1981**, *46*, 4819.
(6) Niwa, H.; Ban, N.; Yamada, K. *Tetrahedron Lett.* **1983**, *24*, 937.
(7) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077.

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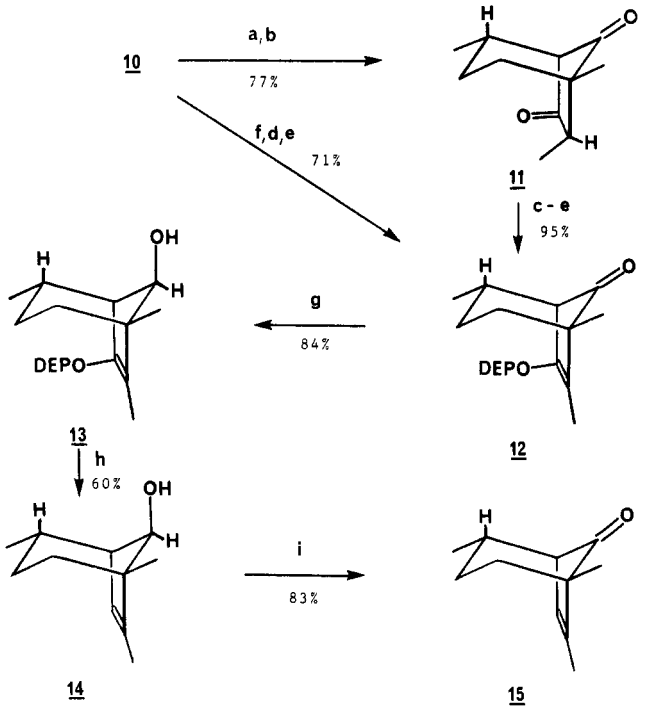
Scheme III. Synthesis of Bicyclic Ketone 15[a]

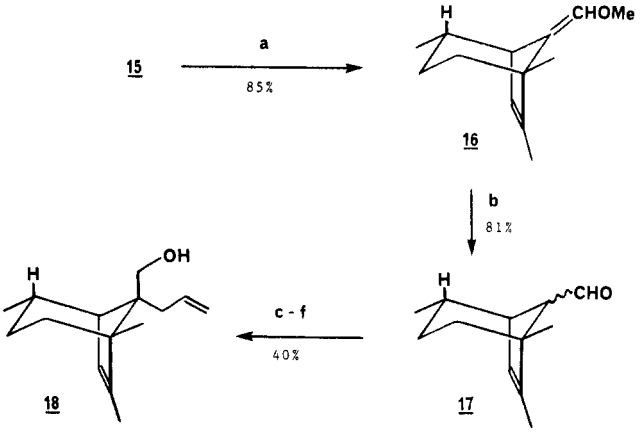


[a] (a) 3.2 equiv of $NaN(SiMe_3)_2$, C_6H_6, Δ; (b) HOAc, H_2O, 0 °C; (c) 1.2 equiv of $NaN(SiMe_3)_2$, THF, 23 °C; (d) TMEDA; (e) $ClPO(OEt)_2$; (f) 2.5 equiv of $NaN(SiMe_3)_2$, THF, Δ; (g) $NaBH_4$, EtOH, 0 °C; (h) 10 equiv of Li, $EtNH_2$, Et_2O, *t*-BuOH, 0 °C; (i) H_2CrO_4, acetone.

attack upon the more stable chair-like conformations for the enolate anions via prechair transition states.[9]

Esterification of keto acids **5** with methyl iodide in the presence of anhydrous potassium carbonate/acetone produces keto esters **6** in 89% yield as a 70:30 mixture of diastereomers. Examination of Dreiding molecular models for each diastereomer of keto esters **6** in conjunction with an analysis of steric approach controlled nucleophilic attack on each of the ketone functional groups suggests that a chemoselective separation might be feasible.[10] To test this hypothesis, keto esters **6** were reduced with potassium borohydride in methanol at −15 °C to 23 °C followed by saponification (NaOH, H_2O, EtOH), acidification, and careful separation (cold 5% NaOH, H_2O) to afford lactone **7** in 64% overall yield as a single diastereomer. Hydroxy acid **7a** was also isolated in 25% yield.[10] Alkylation of lactone **7** with lithium diisopropylamide in tetrahydrofuran at −70 °C and quenching with methyl iodide gives lactones **8** in 98% yield as a 86:14 ratio of isomers.[11] Saponification of lactones **8** with 2.4 equiv of sodium hydroxide in aqueous/*tert*-butyl alcohol followed by the addition of 3.3 equiv of sodium metaperiodate together with a catalytic amount of ruthenium trichloride produces after acidification lactol **9** in 90% overall yield.[12] Esterification of lactol **9** with ethyl iodide in the presence of anhydrous potassium carbonate/acetone gives keto ester **10** in 94% yield.

Scheme IV. Synthesis of Diene-Alcohol 18[a]

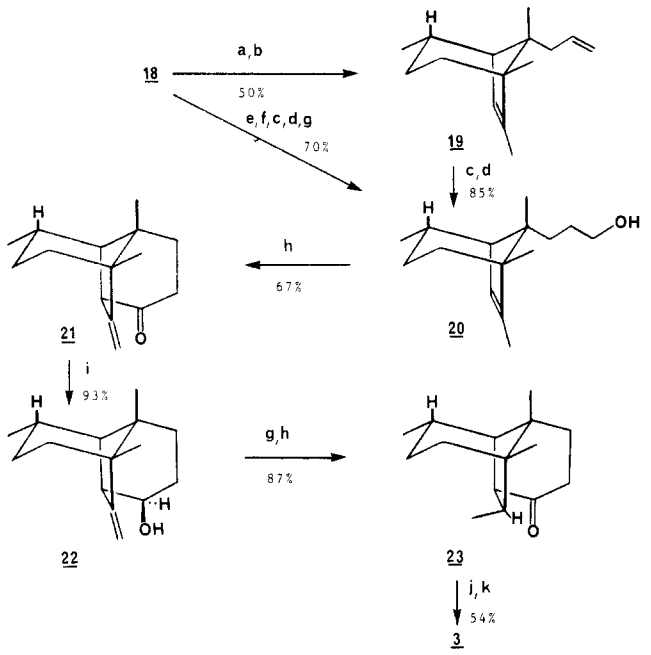


[a] (a) Ph_3P=CHOMe, Me_2SO; (b) 31% $HClO_4$, Et_2O, 1 h, 23 °C; (c) Ph_3CK, DME, Me_2SO (cat.); (d) $BrCH_2CH$=CH_2; (e) $NaBH_4$, EtOH; (f) chromatography on silica gel 60 using 30% Et_2O/petroleum ether as an eluant.

Scheme III depicts the synthesis of bicyclic ketone **15**. Two approaches were explored initially. The first involved a two-stage construction of bicyclic keto enol phosphate ester **12**. An intramolecular Claisen condensation of keto ester **10** with 3.2 equiv of sodium bis(trimethylsilyl)amide in refluxing benzene followed by quenching with aqueous/acetic acid at 0 °C produces diketone **11** in 77% yield. Treatment of diketone **11** with 1.2 equiv of sodium bis(trimethylsilyl)amide in tetrahydrofuran at 23 °C followed by the sequential addition of tetramethylethylenediamine and diethyl chlorophosphate affords enol phosphate ester **12** in 95% yield. The second approach involved an intramolecular Claisen condensation of keto ester **10** using 2.5 equiv of sodium bis(trimethylsilyl)amide in refluxing tetrahydrofuran followed by the sequential addition of tetramethylethylenediamine and diethyl chlorophosphate to give enol phosphate ester **12** directly in 71% overall yield from keto ester **10**.[13] Reduction of bicyclic keto enol phosphate ester **12** with sodium borohydride in 100% ethanol at 0 °C stereoselectively produces alcohol **13** in 84% yield as a single isomer. This stereochemical assignment is supported by the concept of steric approach control as well as an NMR coupling constant J = 5 Hz for the CHO/bridgehead-H protons which is consistent with a dihedral angle of 40 °C. Treatment of enol phosphate ester **13** with 10 equiv of lithium metal in ethylamine/ether/*tert*-butyl alcohol at 0 °C affords alcohol **14** in 60% yield.[14] The stereochemistry of the secondary methyl group in alcohol **14** was established by a europium NMR shift analysis [$Eu(DPM)_2$].[15] The equatorial-methyl isomer **14** (4.4 Å, 2°-CH_3/OH distance, Dreiding model) shows a slope in the europium NMR shift experiment[15] which was 0.25 times that of the corresponding axial-

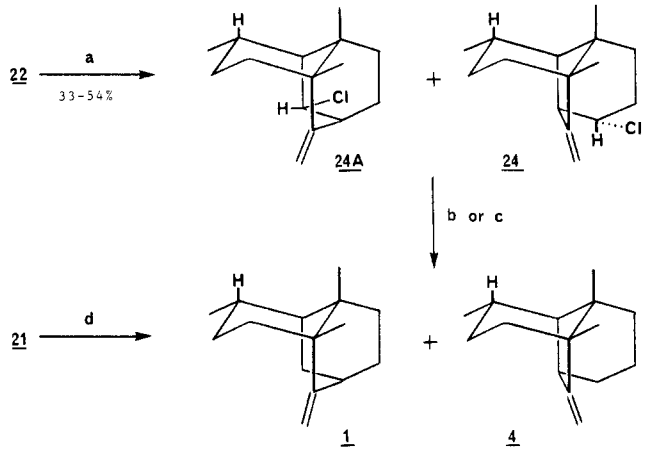
(8) Conia, J.-M. *Rec. Chem. Prog.* **1963**, *24*, 42.
(9) For selected examples of this type of stereoselective alkylation, see: (a) Howe, R.; McQuillin, F. J. *J. Chem. Soc.* **1958**, 1194. (b) Hikino, H.; Kohama, T.; Takemoto, T. *Tetrahedron* **1969**, *25*, 1037. (c) Hortmann, A. G.; Martinelli, J. E.; Wang, Y. *J. Org. Chem.* **1969**, *34*, 732. (d) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000. (e) Büchi, G.; Wüest, A. *J. Org. Chem.* **1979**, *44*, 543. (f) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548 and 3554.
(10) (a) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107. (b) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.
(11) Posner, G. H.; Loomis, G. L. *J. Chem. Soc., Chem. Commun.* **1972**, 892.
(12) (a) Sakan, T.; Abe, K. *Tetrahedron Lett.* **1968**, 2471. (b) Moriarty, R. M.; Chien, C. C.; Adams, T. B. *J. Org. Chem.* **1979**, *44*, 2210.
(13) Piers, E.; Isenring, H. P. *Can. J. Chem.* **1977**, *55*, 1039.
(14) (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Ireland, R. E.; Pfister, G. *Tetrahdedron Lett.* **1969**, 2145.
(15) (a) Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160. (b) Demarco, P. V.; Elzey, J. K.; Lewis, R. B.; Wenkert, E. *J. Am. Chem. Soc.* **1970**, *92*, 5734. The slopes for the eq-2°-CH_3 vs the ax-2°-CH_3 were calculated from a plot of $\Delta\delta_{Me}$ vs. Δ[$Eu(DPM)_2$]/[ROH].

Scheme V. Synthesis of Isocycloseychellene (3)[a]



[a] (a) *p*-TsCl, py; (b) $LiEt_3BH$, THF; (c) 1.9–2.2 equiv of $(Sia)_2BH$, THF; (d) H_2O_2, OH^-, 0°C; (e) *n*-BuLi, THF, TMEDA; (f) $ClOP(NMe_2)_2$; (g) Li, $EtNH_2$, Et_2O, *t*-BuOH; (h) PCC, CH_2Cl_2; (i) $NaBH_4$, EtOH, 0 °C; (j) *p*-$TsNHNH_2$, C_6H_6, Δ; (k) NaH, DMF, 140 °C, 1 h.

Scheme VI. Synthesis of Seychellene (1) and Isoseychellene (4)[a]



Method	yield	ratio
b	80%	76 : 24
c	62%	94 : 6
d	64%	0 : 100

[a] (a) Ph_3P, NCS, THF; (b) Li, NH_3, *t*-BuOH; (c) $LiAlH_4$, THF, Δ, 48 h; (d) $N_2H_4 \cdot H_2SO_4$, KOH, DEG, Δ.

methyl isomer (2.6 Å, 2°-CH_3/OH distance, Dreiding model).[16] Chromic acid oxidation of alcohol **14** in acetone gives bicyclic ketone **15** in 83% yield.[17]

A Wittig reaction on bicyclic ketone **15** (Scheme IV) with (methoxymethylene)triphenylphosphorane in dimethyl sulfoxide produces vinyl ethers **16** in 81% yield as a 60:40 ratio of isomers by NMR.[18] Hydrolysis of vinyl ethers **16** with 31% aqueous perchloric acid in ether for 1 h at 23 °C gives aldehydes **17** in 81% yield as a 60:40 ratio of equatorial-to-axial-aldehyde isomers by NMR. Alkylation of aldehydes **17** by generating the enolate anion with potassium triphenylmethanide in 1,2-dimethoxyethane containing a catalytic amount of dimethyl sulfoxide and quenching with allyl bromide produces a 27:73 ratio of O-:C-alkylated products in 87% combined yield.[19] Attempted Claisen rearrangement of this mixture in refluxing toluene causes the trisubstituted alkene to isomerize to the exocyclic position. However, immediate reduction of the mixture of O-:C-alkylated products with sodium borohydride in 100% ethanol followed by chromatography on silica gel (30% ether/petroleum ether eluant) affords alcohol **18** in 46% yield. This represents a 40% overall yield for alcohol **18** from aldehydes **17**.

Scheme V depicts the syntheses of (±)-isocycloseychellene (**3**). Esterification of alcohol **18** with *p*-toluenesulfonyl chloride in pyridine followed by reduction of the intermediate ester with Super-Hydride ($LiEt_3BH$) in tetrahydrofuran gives diene **19** in 50% overall yield.[20] Regioselective hydroboration of diene **19** with 2.2 equiv of disiamylborane in tetrahydrofuran followed by oxidation with basic hydrogen peroxide produces alcohol **20** in 85% yield.[21] Alternatively, esterification of alcohol **20** by sequential treatment with *n*-butyllithium in tetrahydrofuran–tetramethylethylenediamine, followed by the addition of bis(dimethylamino)phosphorochloridate gives an intermediate phosphoramidate ester. Regioselective hydroboration of the latter with 1.9 equiv of disiamylborane in tetrahydrofuran, followed by oxidation with basic hydrogen peroxide, affords a primary alcohol.[21] Finally reduction of this phosphoramidate alcohol with lithium metal in ethylamine/ether/*tert*-butyl alcohol produces alcohol **20** in 70% overall yield from alcohol **18**.[14] An intramolecular oxidative Prins (ene) reaction was performed on alcohol **20** with pyridinium chlorochromate in dichloromethane to produce tricyclic ketone **21** in 67% yield.[13,22] Reduction of ketone **21** with sodium borohydride in 100% ethanol gives alcohol **22** in 93% yield as a single isomer by steric approach control.[10] A europium-induced NMR shift analysis [$Eu(DPM)_2$] is consistent with the stereochemistry represented in structure **22**.[15] Stereoselective reduction of the exocyclic alkene of alcohol **22** with lithium metal in ethylamine/ether/*tert*-butyl alcohol produces a single saturated tricyclic alcohol. Oxidation of the latter with pyridinium chlorochromate in dichloromethane affords ketone **23** as a single stereoisomer in 87% overall yield from alcohol **22**.[23] Ficini and Touzin have observed stereoselective reductions of exocyclic alkenes when a hydroxyl group is in close proximity.[24] Apparently this hydroxyl group of **23** can intramolecularly protonate the intermediate radical-anion or carbanion to control the stereochemistry of the secondary methyl group generated by reduction of the exocyclic alkene. The synthesis of structure **3** was completed by a Shapiro carbene insertion reaction into the 3°-carbon/H bond in close proximity.[25] Treatment of ketone **23** with (*p*-tolyl-

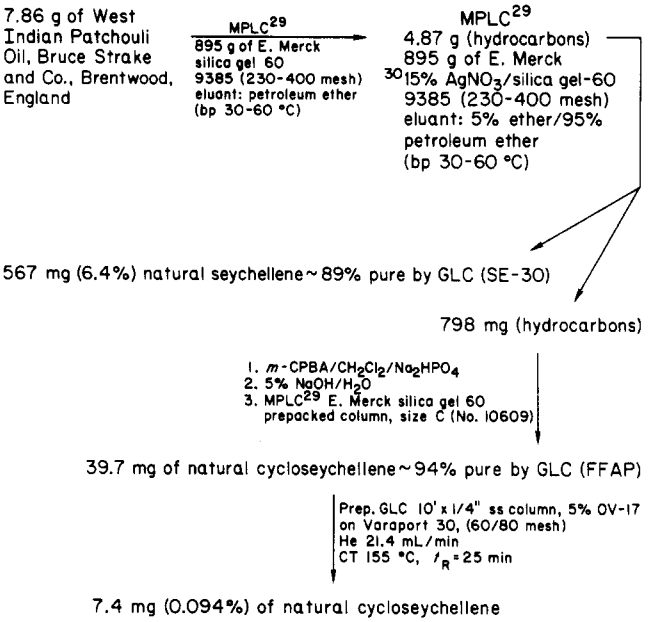
(16) The corresponding axial isomer was prepared by a synthetic scheme analogous to that of Scheme III by C.-Y. Chou (Ph.D. Dissertation, 1980).
(17) Eisenbraun, E. J. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 310.
(18) (a) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. (b) Wittig, G.; Krauss, E. *Angew. Chem.* **1959**, *71*, 127. (c) Maercker, A. *Org. React. (N.Y.)* **1965**, *14*, 270.
(19) Huffman, J. W.; Harris, P. G. *J. Org. Chem.* **1977**, *42*, 2357.
(20) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064; **1983**, *48*, 3085.
(21) Zweifel, G.; Brown, H. C. *Org. React. (N.Y.)* **1963**, *13*, 1.
(22) (a) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (c) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639.
(23) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(24) Ficini, J.; Touzin, A. M. *Tetrahedron Lett.* **1977**, 1081.
(25) Shapiro, R. H.; Duncan, J. H.; Clopton, J. C. *J. Am. Chem. Soc.* **1967**, *89*, 1442.

sulfonyl)hydrazide in benzene gives an intermediate (*p*-tolylsulfonyl)hydrazone. Decomposition of this tosyllhydrazone with sodium hydride in *N,N*-dimethylformamide at 140 °C for 1 h affords (±)-isocycloseychellene (**3**) in 54% overall yield as a crystalline substance. The NMR data for tetracyclic **3** were found to be completely different than those data reported for natural cycloseychellene.

Scheme VI shows the syntheses of (±)-seychellene (**1**) and (±)-isoseychellene (**4**) from tricyclic alcohol **22**. One of the initial approaches explored for the construction of tetracyclic hydrocarbon **3** involved the hydride reduction of homoallylic chloride **24B**.[26] Treatment of alcohol **22** with *N*-chlorosuccinimide (NCS) and triphenylphosphine in tetrahydrofuran at 23 °C unexpectedly produces a mixture of chlorides **24AB** in 33–54% yield.[27] The ratio of **24A**:**24B** is reaction time dependent and it ranges from 76–0:24–100, respectively, with longer reaction times (24 h) favoring chloride **24A**. These results were quite surprising since these mild reaction conditions are known to afford inversion of stereochemistry in the production of homoallylic chlorides without concomitant rearrangement.[27] Reduction of a sample of chlorides **24AB** (75:25, respectively) with lithium metal in liquid ammonia/*tert*-butyl alcohol at −78 °C gives (±)-seychellene (**1**) and (±)-isoseychellene (**4**) in 80% yield as 76:24 ratio of products. However, reduction of another sample of chlorides **24AB** (62:38, respectively) with lithium aluminum hydride in refluxing tetrahydrofuran for 48 h serendipitously affords (±)-seychellene (**1**) and (±)-isoseychellene (**4**) in 62% yield as a 96:4 ratio of products, respectively. No tetracyclic structure **3** was observed or isolated. Synthetic seychellene (**1**) was identical with a sample of the natural product by GLC, NMR, IR, and mass spectra. Wolff–Kishner reduction of ketone **21** with hydrazine sulfate and potassium hydroxide in diethylene glycol at 200 °C produces (±)-isoseychellene (**4**) in 64% yield as a crystalline hydrocarbon.[28]

Because synthetic tetracyclic hydrocarbons **3** (isocycloseychellene) exhibited different NMR spectral data than those reported for natural cycloseychellene, we decided to verify the structure of synthetic compound **3** and to reinvestigate the structure of the natural product by high-field NMR. Scheme VII concisely outlines the methods used to reisolate both natural seychellene (**1**) and cycloseychellene (**2**).[29-31] Our previous paper on the structural revision of natural cycloseychellene clearly outlines the 400-MHz NMR decoupling experiments which were used to establish the structures of both natural cycloseychellene (**2**) and synthetic isocycloseychellene (**3**).[5,31]

Scheme VII. Isolation of Natural Seychellene and Cycloseychellene



Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting point apparatus and are uncorrected. All boiling points were measured external to the bulb-to-bulb distillation pot in a Büchi GKR-50 Kugelrohr apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 237B spectrometer using 0.10-mm NaCl solution cells in spectroquality solvent or as thin films between NaCl plates. NMR spectra were recorded on Bruker W.H. 400 (MHz) [NSF-NMR Laboratory at the University of S. Carolina 29208], Nicolet NT-300 (300 MHz), Varian XL-100 (100 MHz and 25.2 MHz), Varian FT-80A (80 MHz, 20.2 MHz), or Varian T-60 (60 MHz) spectrometers in the solvents indicated. High-resolution mass spectra were obtained on a DuPont Flash CEC 21-110B spectrometer at 70 eV. Low-resolution mass spectra were recorded on a Finnigan 3300 spectrometer at 70 eV by Dr. T. Merriott at the Rice University Mass Spectroscopy Laboratory. Microanalyses were performed by Spang Microanalytical Laboratory. Analytical gas-phase chromatography (GLC) was performed on a Varian Aerograph Model 1400 equipped with a flame-ionization detector with He as the carrier gas (15 mL/min flow rate at ambient temperature) using $^1/_8$ in. × 6 ft stainless steel columns packed with (a) 3% SE-30 on Varaport-30 (100–120 mesh, Varian); (b) 5% OV-17 on Varaport 30 (80/100 mesh, Varian); (c) 5% FFAP on Varaport 30 (100/120 mesh, Varian). Silica gel 60 and (E. Merck No. 7734, 70–230 mesh) PF 254+366 (E. Merck No. 7748) were used for thin-layer and column chromatography, respectively. Medium-pressure liquid chromatography (MPLC) was performed by using a Fluid Metering Pump, Model RRPSY-SS, and columns packed with silica gel 60 (E. Merck No. 9385, 230–400 mesh).[29] Silica gel 60 (E. Merck No. 9385, 230–400 mesh) inpregnated with 15% $AgNO_3$ (w/w)[30] packed in a 2 in. × 35 in. stainless-steel column with a $^1/_2$ in. × 15 in. precolumn (1685-mL total column volume) was used to separate naturally occurring hydrocarbons.

Ethereal solvents (Et_2O, THF, DME) were purified by fresh distillation of anhydrous commercial solvents from $LiAlH_4$ under N_2 immediately before use in all reactions. Amine solvents and reagents [*i*-Pr_2NH, $HN(SiMe_2)_2$, TMEDA, Py] as well as C_6H_6, $PhCH_3$, and *t*-BuOH were distilled from CaH_2 (40 mesh) under N_2. Hexane, EtOAc, and CH_2Cl_2 were distilled from P_2O_5 under N_2. Hexamethylphosphoric triamide (HMPA) and DMF were vacuum distilled from CaH_2 (40 mesh) onto freshly activated molecular sieves of types 13X and 4A, respectively. Dimethyl sulfoxide was vacuum distilled (3×) from 95% CaH_2 (40 mesh)–5% $NaNH_2$ with the last distillation onto freshly activated molecular sieves of type 4A. Reagent-grade acetone was dried over anhydrous $CaSO_4/MgSO_4$. Ethylamine ($EtNH_2$) and NH_3 were distilled through KOH towers and dried over Li/Na metal and then distilled just prior to use. For all anhydrous reactions performed under an atmosphere of dry N_2 or Ar the equipment was dried in an oven at 120 °C for several hours and then allowed

(26) For some successful examples of this type of cyclopropane synthesis, see: (a) Chen, S.-C. *Synthesis* **1974**, 691. (b) Kelly, R. B.; Alward, S. J. *Can. J. Chem.* **1977**, *55*, 1786. (c) Kelly, R. B.; Beckett, B. A.; Eber, J.; Hung, H.-K.; Zamecnik, J. *Can. J. Chem.* **1975**, *53*, 143. (d) Marshall, J. A.; Faubl, H.; Warne, T. M. *Chem. Commun.* **1967**, 753.

(27) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937.

(28) Todd, D. *Org. React. (N.Y.)* **1948**, *4*, 378.

(29) MPLC refers to a medium pressure liquid chromatography apparatus. See: Meyers, A. L.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

(30) Gupta, A. S.; Dev, S. *J. Chromatogr.* **1963**, *12*, 189.

(31) During these investigations no significant quantity of isoseychellene (**4**) could be detected in natural seychellene (Scheme VII) by either analytical GLC (FFAP), preparative GLC (SE-30), or GC–MS (SE-30). No significant quantity of isocycloseychellene (**3**) could be detected in the sample of 94% pure cycloseychellene (Scheme VII) by GC–MS (SE-30) or 400-MHz NMR at δ 0.70.

to cool in an atmosphere of dry N_2 or Ar. All liquid transfers were made with N_2 or Ar filled syringes. The nomenclature utilized is that preferred by Chemical Abstracts.[32]

Methyl 1,4-Dimethyl-2-oxocyclohexaneacetate (6). To a solution of keto acid **5** (256 mg, 1.39 mmol) and anhydrous K_2CO_3 (4.36 mg, 2.09 mmol) in reagent acetone (15 mL) was added methyl iodide (6.14 g, 43.3 mmol). After being stirred overnight at 23 °C, the resultant mixture was then quenched with 10% K_2CO_3 solution (10 mL) and extracted with Et_2O (10 × 10 mL). The combined ethereal solutions were concentrated in vacuo, and the residue was partitioned in 10% K_2CO_3–ether (15 mL–30 mL). The ethereal layer was separated and washed with H_2O (5 × 10 mL) until neutral and saturated NaCl solution (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Distillation (bulb-to-bulb) gave 244 mg (88.5%) of keto ester **6**: bp 60–65 °C (0.8 mmHg); IR (CCl_4) 1725 (CO_2Me), 1700 (C=O, ketone) cm^{-1}; NMR (CCl_4) δ 1.04 (s, CH_3), 1.17 (s, CH_3 overlapping secondary CH_3 pattern) 3.58 (s, 3, CO_2CH_3). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.45; H, 9.11.

(3aα,6β,7aα)-Hexahydro-3a,6-dimethyl-2(3*H*)-benzofuranone (7). To a solution of keto ester **6** (99 g, 500 mmol) in MeOH (1.0 L) at −15 °C (ice–methanol bath) was added KBH_4 (21.2 g, 400 mmol) in small portions over 2 h. After stirring overnight at 23 °C most of the MeOH was removed in vacuo. The residue was taken up in Et_2O (400 mL), washed with saturated NaCl solution (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting liquid was dissolved in 95% EtOH (750 mL) and treated with NaOH (70 g). After being stirred overnight this solution was acidified to pH 2 with 10% HCl. After 20 h, 5% HCl (1.0 L) was added followed by saturation with NaCl and extraction with 50% ether/petroleum ether (4 × 400 mL). The organic extracts were combined, washed twice with cold 5% NaOH (500 mL, 200 mL), dried ($MgSO_4$), and concentrated in vacuo. Bulb-to-bulb distillation (95 °C, 1.5 mmHg) affords 53.6 g (64%) of lactone **7**: IR (CCl_4) 2950, 2920 (C—H), 1785 (C=O), 1160, 990 (C—O) cm^{-1}; NMR (CCl_4, 100 MHz) δ 0.98 (d, 3, J = 6 Hz, $CHCH_3$), 1.16 (s, 3, CH_3), 2.12 (AB, 2, J = 17 Hz, CH_2C=O), 4.12 (d of d, 1, J = 10, 6 Hz, CHO). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.60.

Hexahydro-3,3a,6-trimethyl-2(3*H*)-benzofuranone (8). To a solution of a small amount of bipyridine in dry THF (500 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 45 mL, 72 mmol) at −50 to −70 °C, followed by addition of freshly distilled diisopropylamine (15 mL, 106 mmol) in 15 min. This solution was allowed to stir for another 45 min at this temperature. To this deep red solution was added lactone **7** (10.4 g, 62.1 mmol) dissolved in dry THF (100 mL) over a period of 20 min. The reaction mixture was stirred for 1 h at the same temperature and then allowed to warm to 23 °C. Methyl iodide (7.74 mL, 124 mmol) was added to this enolate anion solution in one portion. After being stirred overnight, the cloudy yellow reaction mixture was diluted with H_2O at 0 °C, poured into an ice–water mixture, extracted with Et_2O (5 × 100 mL), washed with H_2O (3 × 100 mL) and saturated NaCl solution (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. After distillation (bulb-to-bulb), 11.1 g (98%) of methyl lactone **8** was obtained: bp 70–75 °C (0.7 mmHg); IR (CCl_4) 1765 (C=O) cm^{-1}; NMR (CCl_4) δ 0.92 (d, 3 H, J = 6 Hz, C-6 CH_3), 0.94 (s, 3, CH_3), 1.02 (d, 3, J = 7 Hz, CH_3CHCO), 2.62 (q, 1, J = 7 Hz, CH_3CHCO), 4.05 (d of d, 1, J = 6 Hz, 10 Hz, CHOCO). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.30; H, 9.86.

Hexahydro-7a-hydroxy-3,3a,6-trimethyl-2(3*H*)-benzofuranone (9). To a solution of lactone **8** (5.78 g, 31.7 mmol) in *t*-BuOH (120 mL) was added NaOH solution (1.92 M, 40 mL), followed by addition of enough H_2O to make a homogeneous solution. This solution was then stirred overnight. To this alkaline solution was added an $NaIO_4$ solution (22.5 g, 105 mmol) in H_2O (250 mL), followed by the addition of $RuCl_3 \cdot xH_2O$ (38.5 mg/mL, 10 mL). After being stirred at 23 °C for 24 h, the resultant mixture was acidified with concentrated HCl and then extracted with Et_2O (10 × 50 mL). The combined ethereal solutions were washed with water (3 × 50 mL) and saturated NaCl solution (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 6.36 g (90%) of white solid hydroxy lactone **9**. An analytically pure sample was obtained by recrystallization from petroleum ether: mp 117–117.5 °C; IR (CCl_4) 3585, 3350 (OH), 1760 (C=O), 935, 925 cm^{-1} (C—O): NMR ($CDCl_3$) δ 0.97 (s, 3, CH_3), 1.12 (d, 3, J = 7 Hz, CH_3CHCO), 2.90 (q, 1, J = 7 Hz, CH_3CHCO), 3.57 (br s, 1, OH). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.69; H, 9.06.

Ethyl α,1,4-Trimethyl-2-oxocyclohexaneacetate (10). Hydroxy lactone **9** (0.92 g, 4.65 mmol), anhydrous K_2CO_3 (0.96 g, 6.97 mmol), ethyl iodide (11.2 mL, 139 mmol) and reagent acetone (50 mL) were placed in a reaction flask under an N_2 atmosphere. After 2 h of reflux, the reaction mixture was cooled to 23 °C and quenched with 10% K_2CO_3 solution (50 mL) and extracted with Et_2O (8 × 20 mL), and the combined ethereal extracts were concentrated in vacuo. The residue was then partitioned in 10% K_2CO_3 solution (150 mL) and Et_2O (300 mL). The ethereal solution was then washed with H_2O (8 × 20 mL) until neutral and saturated NaCl solution (3 × 25 mL), dried (Na_2SO_4), and concentrated in vacuo to afford 988 mg (94%) of keto ester **10**: bp 50–55 °C (0.7 mmHg); IR (CCl_4) 1745 (CO_2Et), 1715 (C=O, ketone), 1190 cm^{-1} (OC—O); NMR (CCl_4) δ 0.88 (s, 3, CH_3), 1.15 (t, 3, J = 7 Hz, OCH_2CH_3), 2.99 (q, 1, J = 7 Hz, CH_3CHCO), 3.93 (q, 2, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.95; H, 9.74.

***endo*,*endo*-1,4,7-Trimethylbicyclo[3.2.1]octane-6,8-dione (11).** To a solution of sodium bis(trimethylsilyl)amide (3.93 g, 21.4 mmol) in dry C_6H_6 (300 mL) was added a solution of keto ester **10** (1.52 g, 6.69 mmol) in dry C_6H_6 (100 mL) dropwise over a period of 100 min at 79–80 °C (internal temperature). The reaction mixture was maintained at this temperature for another 60 min. The reaction mixture was cooled to 0 °C and then poured to an ice-cold acetic acid–H_2O (40 mL–400 mL) solution at 0 °C. The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined organic solutions were washed with saturated $NaHCO_3$ solution (2 × 100 mL), H_2O (3 × 100 mL), and saturated NaCl solution (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. After bulb-to-bulb distillation gave 933 mg (77.4%) of white solid diketone **11**, analytically pure sample was obtained by recrystallization from petroleum ether: mp 69.6–70.4 °C; IR (CCl_4) 1767 (C=O, C-8), 1730 cm^{-1} (C=O, C-6); NMR (CCl_4) δ 1.10 (s, 3, CH_3), 1.23 (d, 3, J = 5 Hz, $COCHCH_3$), 2.27 (q, 1, J = 7 Hz, $COCHCH_3$), 2.45 (br s, 1, bridgehead H). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 9.04.

Diethyl *endo*-1,4,7-Trimethyl-8-oxobicyclo[3.2.1]oct-6-en-6-yl Phosphate (12). Method A. Diketone **11** (2.38 g, 13.2 mmol) dissolved in dry THF (60 mL) was added to a solution of sodium bis(trimethylsilyl)amide (2.90 g, 15.8 mmol) in dry THF (100 mL) dropwise. After stirring at 23 °C for 1.5 h, TMEDA (40 mL) was added to this reaction mixture, followed by the addition of $(EtO)_2POCl$ (3.41 g, 19.8 mmol). After being stirred overnight at 23 °C, the resultant mixture was then diluted with H_2O at 0 °C and extracted with Et_2O (5 × 100 mL), and the combined ethereal solutions were washed with H_2O (5 × 100 mL) and saturated NaCl solution (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to obtain 3.89 g (95%), after bulb-to-bulb distillation, of a colorless liquid of keto enol phosphate **12**: bp 110–115 °C (0.7 mmHg); IR (film) 2860 (C—H), 1765 (C=O), 1675 (C=C), 1035 (P—OC), 1250–1295 cm^{-1} (P=O); NMR (CCl_4) δ 1.00 (s, 3, CH_3), 1.03 (d, 3, J = 6 Hz, CH_3CH), 1.33 (t, 6, J = 7 Hz, $PO(OCH_2CH_3)_2$), 1.69 (m, 3, C=CCH_3), 2.82 (br s, 1, bridgehead H), 3.87–4.42 (quintet, 4, $PO(OCH_2CH_3)_2$).

Method B. To a heated solution (oil bath; 80 °C) of sodium bis(trimethylsilyl)amide (9.16 g, 50 mmol) in dry THF (200 mL) was added keto ester **10** (4.52 g, 20 mmol) in THF (200 mL, addition time approximately 1 h). After an additional 1 h at reflux the solution was cooled to −20 °C and treated with dry TMEDA (15 mL) and freshly distilled $(EtO)_2POCl$ (10.0 mL, 60 mmol). The cooling bath was removed and the mixture was stirred overnight at 23 °C. After the addition of saturated $NaHCO_3$ (15 mL), the resulting mixture was transferred to a 1-L round-bottomed flask and concentrated in vacuo to approximately 100 mL. This residue was partitioned between Et_2O (300 mL) and H_2O (200 mL). The organic phase was washed with saturated $NaHCO_3$ solution (2×, 150 mL) and the aqueous extracts were reextracted, in turn, with additional Et_2O (100 mL). The ethereal extracts

(32) Loenig, K. L., Nomenclature Director, Chemical Abstracts Service, Columbus, OH 43210.

were combined, dried ($MgSO_4$), and concentrated in vacuo. MPLC using silica gel (230–400 mesh) and 70% Et_2O/petroleum ether as eluent afforded 4.50 g (71%) of keto enol phosphate **12**: bp 110–115 °C (0.7 mmHg); IR (film) 2860 (C—H), 1765 (C=O), 1675 (C=C), 1035 (P—OR), 1250–1295 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 1.03 (s, 3, CH_3), 1.05 (s, 3, J = 6 Hz, $CHCH_3$), 1.35 (t, 6, J = 8 Hz, OCH_2CH_3), 1.73 (m, 3, C=CCH_3), 2.93 (br s, 1, C=CCH), 4.17 (quintet, 4, OCH_2CH_3); mass spectrum, m/z (relative intensity) 316 (M^+, 3), 81 (35), 41 (53), 29 (100), 26 (53); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{25}O_5P$ 316.1439, found 316.1442; 0.9 ppm error.

Diethyl *endo,syn*-8-Hydroxy-1,4,7-trimethylbicyclo[3.2.1]oct-6-en-6-yl Phosphate (13). To a solution of keto enol phosphate **12** (2.52 g, 7.97 mmol) in 100% EtOH (90 mL) was added a solution of $NaBH_4$ (0.50 g, 13.3 mmol) dissolved in 100% EtOH (25 mL) over a period of 10 min at 0 °C. The mixture was then allowed to stir for another 10 min at 0 °C and then quenched with glacial HOAc at 0 °C. The acidic mixture was diluted with H_2O and extracted with Et_2O (8 × 60 mL). The combined ethereal solutions were washed with saturated $NaHCO_3$ solution (3 × 50 mL) until neutral, H_2O (3 × 60 mL), and saturated NaCl solution (3 × 60 mL), dried ($MgSO_4$), and concentrated in vacuo to afford after bulb-to-bulb distillation 2.12 g (84%) of solid hydroxy enol phosphate **13**. An analytically pure sample was obtained by recrystallization from petroleum ether: mp 67.5–68 °C; IR (CCl_4) 3425 (O—H), 1678 (C=C), 1260 (P=O), 1040 cm^{-1} (P—OC); NMR (CCl_4) δ 0.88 (d, 3, J = 7 Hz, CH_3CH), 0.93 (s, 3, C-1 CH_3), 1.35 (t, 6, J = 7 Hz, $PO(OCH_2CH_3)_2$), 1.55 (d, 3, J = 3 Hz, C=CCH_3), 2.36 (br d, 1, J = 5 Hz, bridgehead H), 3.53 (d, 1, J = 5 Hz, CHOH), 4.17 (quintet, 4, J = 8 Hz, 1 Hz, $PO(OCH_2CH_3)_2$); mass spectrum, m/z (relative intensity) 318 (M^+, 6), 164 (31), 99 (44), 43 (45), 41 (42), 29 (100), 26 (38); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{27}O_5P$ 318.1596, found 318.1600; 1.2 ppm error.

***endo,syn*-1,4,7-Trimethylbicyclo[3.2.1]oct-6-en-8-ol (14).** In a 100-mL round-bottomed flask, equipped with gas inlet, cold finger condenser, and stopper, was introduced monoethylamine (freshly distilled through an NaOH drying tower, 40 mL). Lithium metal (245 mg, 35 mmol) in small pieces was added to this rapidly stirring solution, and then the flask was sealed under Ar and cooled to 0 °C. A blue solution appeared in 10 min and was allowed to stir for 35 min. A solution of hydroxy enol phosphate **12** (1.11 g, 3.48 mmol) in dry Et_2O (10 mL) and dry *t*-BuOH (1.28 mL) was then added to this blue solution in 7 min. The resulting mixture was allowed to stir for another 15 min. The reaction mixture was quenched with saturated NH_4Cl solution slowly, diluted with H_2O, and extracted with Et_2O (6 × 50 mL). The combined ethereal solutions were washed with H_2O (3 × 50 mL) and saturated NaCl solution (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography on silica gel using 10% ether–90% petroleum ether as an eluant gave 346 mg (60%) of alkene alcohol **14**: bp 50–55 °C (0.7 mmHg); IR (CCl_4) 3615, 3400 (O—H), 3030, 2850 (C—H), 1628 (C=C), 1070, 1060 cm^{-1} (C—O); NMR (CCl_4) δ 0.73 (d, 3, J = 6 Hz, CH_3CH), 0.88 (s, 3, CH_3), 1.61 (d, 3, J = 1 Hz, C=CCH_3), 2.22 (br s, 1, bridgehead H), 3.40 (s, 1 H, OH), 3.60 (d, 1, J = 5 Hz, CHOH), 5.45 (m, 1, C=CH); NMR ($CDCl_3$, 100 MHz) δ 0.78 (d, 3, J = 6.7 Hz), 0.92 (s, 3, CH_3), 1.625 (d of d, 3, J = 0.6 Hz, J = 1.6 Hz, C=CCH_3), 2.21 (m, 1, bridgehead H), 3.63 (d, 1, J = 5.1 Hz, CH—O), 5.45 (m, 1, C=CH). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.48; H, 10.97.

***endo*-1,4,7-Trimethylbicyclo[3.2.1]oct-6-en-8-one (15).** To a solution of alkene alcohol **14** (793 mg, 4.77 mmol) in reagent acetone (60 mL) was added chromic acid reagent[17] (2.67 M, 5 mL) dropwise over a period of 10 min at −5 °C. The mixture was akllowed to stir at 23 °C for 15 min. The orange-brown solution was then cooled to −5 °C and quenched with reagent *i*-PrOH until the solution turned green. The mixture was diluted with H_2O and thoroughly extracted with Et_2O (15 × 10 mL), and the combined ethereal solutions were washed with H_2O (5× 20 mL) until neutral and saturated NaCl solution (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was bulb-to-bulb distilled to afford 647 mg (83%) of alkene ketone **15**: bp 30–35 °C (0.7 mmHg); IR (CCl_4) 1760 (C=O), 3035, 1630 (C=C); NMR (CCl_4) δ 0.89 (d, 3, J = 6 Hz, CH_3CH), 0.97 (s, 3, CH_3), 1.72 (d, 3, J = 1 Hz, C=CCH_3), 2.50 (br s, 1, bridgehead H), 5.75 (m, 1, C=CH). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.30; H, 9.75.

***endo*-8-(Methoxymethylene)-1,4,7-trimethylbicyclo[3.2.1]oct-6-ene (16).** Sodium hydride (61.1% dispersion, 614 mg, 15.7 mmol) was washed with dry Et_2O (3 × 30 mL), and the last trace of Et_2O was removed in vacuo. Dry Me_2SO (30 mL) was added. The mixture was heated at 60–62 °C for 45 min and then cooled to 23 °C. The Wittig salt ($Ph_3PCH_2OCH_3Cl$, 8.19 g, 23.9 mmol) was then added to this clear solution, and the resulting deep red solution was stirred at 23 °C for an additional 15 min. Alkene ketone **15** (425 mg, 2.61 mmol) dissolved in dry Me_2SO (10 mL) was added to this solution dropwise. This mixture was then allowed to stir at 40–45 °C overnight. The resultant mixture was cooled to 23 °C and then poured into an ice–H_2O solution and extracted with petroleum ether thoroughly, and the combined organic solutions were washed with H_2O (3 × 50 mL) and saturated NaCl solution (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a colorless liquid (428 mg, 85%), after bulb-to-bulb distillation, alkene enol ether **16**: bp 50–55 °C (0.7 mmHg); IR (CCl_4) 3040 (C—H), 1705 (C=CHOMe) 1635 (C=C), 1240, 1210, 1115 cm^{-1} (C—O); NMR (CCl_4) δ 0.75 (d, 1.8, J = 8 Hz, CH_3CH), 0.86 (d, 1.2, J = 10 Hz, CH_3CH), 0.97 (s, 1.2, C-1 CH_3), 1.20 (s, 3, C-1 CH_3), 1.60 (m, 3, J = 1 Hz, C—CCH_3), 3.38 (s, 1.8, OCH_3), 3.43 (s, 1.2, OCH_3), 5.33 (s, 0.4, C=$CHOCH_3$), 5.40–5.48 (m, 1, C=CH), 5.50 (s, 0.6, C=$CHOCH_3$). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.19; H, 10.59.

1,4,7-Trimethylbicyclo[3.2.1]oct-6-ene-8-carboxaldehyde (17). To a solution of Et_2O (90 mL) and 31% $HClO_4$ (21 mL) was added a solution of enol ether **16** (448 mg, 2.33 mmol) in Et_2O (15 mL). After stirring 1 h at 23 °C, solid $NaHCO_3$ was slowly added to neutralize this acidic solution. The resultant basic solution was diluted with H_2O and thoroughly extracted with Et_2O (10 × 20 mL), and the combined ethereal solutions were then washed with H_2O (3 × 30 mL) and saturated NaCl solution (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product thus obtained was dissolved in MeOH (10 mL) and added to a solution of K_2CO_3 (1 g) in H_2O (5.2 mL) and MeOH (50 mL). After being stirred at 23 °C for 2 h, the mixture was concentrated in vacuo, then diluted with H_2O and extracted with Et_2O (10 × 20 mL). The combined ethereal solutions were washed with saturated NaCl solution (3 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo to afford, after bulb-to-bulb distillation, 337 mg (81%) of colorless liquid alkene aldehyde (**17**, as a 40:60 ratio of axial and equatorial isomers, respectively): bp 45–50 °C (0.7 mmHg); IR (CCl_4) 2820, 2720 (CHO), 1720 (C=O), 3040, 1640 cm^{-1} (C=C); NMR (CCl_4) δ 0.77 (d, 1.2, J = 6 Hz, CH_3CH), 0.83 (d, 1.8, J = 6 Hz, CH_3CH), 1.05 (s, 1.8, CH_3), 1.14 (s, 1.2 H, CH_3), 1.63 (d, 1.2, J = 1 Hz, C=CCH_3), 1.66 (d, 1.8, J = 1 Hz, C=CCH_3), 1.88 (d, 1, J = 4 Hz, CHCHO), 2.42 (br s, 1, bridgehead H), 5.43 (br s, 1, C=CH), 9.56 (d, 0.6, J = 4 Hz, equat CHO), 9.87 (br s, 0.4, axial CHO). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.50; H, 10.25.

***endo,syn*-1,4,7-Trimethyl-8-(2-propenyl)bicyclo[3.2.1]oct-6-ene-8-methanol (18).** To a mixture of KH (24% oil dispersion, 3 g, 18 mmol), which was washed with dry Et_2O (5 × 10 mL), and 2 drops of Me_2SO (after the hydrogen evolution has ceased) was added a solution of Ph_3CH (4.50 g, 18.4 mmol) dissolved in dry DME (17 mL). The mixture was then heated to 40 °C for 15 min until a very deep red color appeared. The red solution was then cooled to 23 °C and slowly added to a solution of alkene aldehyde **17** (547 mg, 3.07 mmol) in dry DME (4 mL) until a red color persisted. After stirring at 23 °C for 10 min, allyl bromide (freshly distilled from CaH_2, 5 mL) was added all in one portion. The color discharged instantly and a precipitate formed. After being stirred at 23 °C overnight, the reaction mixture was then poured into an ice–H_2O slurry, acidified with concentrated HCl, and extracted with Et_2O (5 × 30 mL). The combined ethereal solutions were washed with H_2O (3 × 40 mL) and saturated NaCl solution (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to obtain, after bulb-to-bulb distillation, a mixture of allyl ether (27%) and alkylated aldehyde (73%) (ratio by NMR), 580 g (86.5%): bp 70–80 °C (0.7 mmHg); IR (CCl_4) 2820, 2710, (CHO), 1720 (C=O), 3080, 3040, 1640, 1600 (C=C) 995, 920 cm^{-1} (C-H=CH_2); NMR (CCl_4) δ 0.73 (d, 3, J = 6 Hz, CH_3CH), 1.04 (s, 3, CH_3), 1.56 (d, 3, J = 1 Hz, C=CCH_3), 2.20 (d, 1, J = 7 Hz, CH_2C=CH_2), 2.38 (br s, 1, bridgehead H), 4.66–5.13 (m, 2, C=

CH_2), 5.40 (m, 1, C=CH), 5.48 (m, 1, HC=CH_2), 9.78 (s, 1, CHO). To a solution of this aldehyde and allyl ether mixture (580 mg, 2.63 mmol) in 100% EtOH (20 mL) was added a solution of $NaBH_4$ (150 mg, 3.95 mmol) in 100% EtOH (15 mL) at 5–10 °C. After being stirred for 10 min at this temperature, the reaction mixture was then diluted with saturated NaCl solution (35 mL) and extracted with Et_2O (10 × 30 mL). The combined ethereal solutions were then washed with saturated NaCl solution (3 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo to afford, after column chromatography over silica gel using a solution of 30% ether and 70% petroleum ether as an eluant, 189 mg (46%) of alcohol **18**: bp 85–90 °C (0.7 mmHg); IR (CCl_4) 3640, 3465 (OH), 3070, 3040, 1630, 995, 915 cm^{-1} (C=C); NMR (CCl_4) δ 0.70 (d, 3, J = 6 Hz, CH_3CH), 0.93 (s, 3, CH_3), 1.62 (s, 3, C=CCH_3), 1.66 (s, 1, OH), 2.15 (br d, 2 H, J = 7 Hz, CH_2CH=CH_2), 2.33 (br s, 1, bridgehead H), 3.77 (AB, J = 12 Hz, CH_2OH), 4.93 (m, 2, C=CH_2), 5.38 (br s, 1, C=CH), 5.55–6.22 (m, 1, CH=CH_2); mass spectrum, m/z (relative intensity) 200 (M^+, 13), 189 (39), 105 (33), 95 (40), 91 (42), 55 (56), 41 (100), 39 (4), 31 (24), 29 (45), 27 (35); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{24}O$ 220.1827, found 220.1836; 4.0 ppm error.

***endo,anti*-1,4,7,8-Tetramethyl-8-(2-propenyl)bicyclo-[3.2.1]oct-6-ene (19).** A solution of alkene alcohol **18** (189 mg, 0.85 mmol) in dry pyridine (2 mL) was added to a solution of *p*-TsCl (freshly recrystallized from $CHCl_3$/petroleum ether, 180 mg) in dry pyridine (3 mL) at 0 °C. The reaction mixture was stored in the freezer at −10 °C for 72 h. The resultant clear solution was then concentrated in vacuo, and residue was suspended in CCl_4 and filtered. The CCl_4 solution was then removed in vacuo for 24 h. The crude tosylated ester thus formed was dissolved in dry THF (1 mL), and a solution of Superhydride (Aldrich, 1 M in THF, 10 mL) was added at 0 °C. After being stirred at 23 °C for 40 h, the reaction mixture was the quenched with 10% cold NaOH solution (40.5 mL) at −5 °C and extracted with pentane (10 × 20 mL). The combined organic solutions were washed with saturated NaCl solution (4 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo to afford, after column chromatography (silica gel 60, 20 g, using 100% petroleum ether as an eluant), 101 mg (50%) of diene **19**: bp 30–35 °C (0.7 mmHg); NMR (CCl_4) δ 0.67 (d, 3, J = 6 Hz, CH_3CH), 0.76 (s, 3, CH_3), 0.87 (s, 3, CH_3), 1.62 (d, 3, J = 1 Hz, C=CCH_3), 4.72 (d of d, 1, J = 8 Hz, 3 Hz, CH=CH_2), 5.00 (br s, 1, CH=CH_2), 5.40 (m, 1, C=CH), 5.55–6.10 (m, 1, CH=CH_2). Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.25; H, 12.00.

***endo,anti*-1,4,7,8-Tetramethylbicyclo[3.2.1]oct-6-ene-8-propanol (20). Method A.** To a borane–THF solution (1 M, 5 mL) was added a solution of 2-methyl-2-butene in THF (1 M, 5 mL) dropwise. The resulting solution was allowed to stir for 3 h at −5 to 0 °C. To this disiamylborane reagent thus prepared was added a solution of diene **19** (458 mg, 2.25 mmol) in dry THF (2 mL) at 0 °C. The mixture was then warmed up to 23 °C and allowed to stir for 2 h. The resulting reaction mixture was then quenched with 10% NaOH solution (5 mL), followed by 30% H_2O_2 solution (5 mL) at 0 °C, and allowed to stir for 2 h at 23 °C. The resultant mixture was diluted with saturated NaCl solution (10 mL) and extracted with petroleum ether–ether solution (2:1 ratio, respectively). The combined ethereal solutions were washed with saturated NaCl solution (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography on silica gel using 40% ether–60% petroleum ether as an eluant gave 418 mg (84.5%) of alkene alcohol **20**: NMR (CCl_4, 60 MHz) δ 0.67 (d, 3, J = 6 Hz, CH_3CH), 0.74 (s, 3, C-8 CH_3), 0.87 (s, 3, CH_3), 1.60 (d, 3, J = 1 Hz, C=CCH_3), 1.83 (s, 1, OH), 1.87 (br s, 1, bridgehead H), 3.41 (m, 2, CH_2OH), 5.37 (m, 1, C=CH); mass spectrum, m/z (relative intensity) 222 (M^+, 10), 163 (44), 107 (40), 91 (41), 69 (38), 54 (55), 41 (82), 31 (100), 29 (59).

Method B. To a solution of alcohol **18** (343 mg, 1.56 mmol), dry THF, dry TMEDA (2.5 mL), and a trace of bipyridine at −15 °C (ice–MeOH bath) (10 mL) was added *n*-BuLi (1.17 ml, 1.6 M in hexane, 1.87 mmol). After stirring for 15 min, freshly distilled bis(dimethylamino)phosphorochloridate (1.15 mL, 7.8 mmol) was added. After stirring overnight at 23 °C, saturated $NaHCO_3$ (10 mL) was added, and the resulting two-phase system was stirred for 2 h. Et_2O (150 mL) was added and the organic solution was washed with saturated $NaHCO_3$ solution (20 mL), 5% HCl (25 mL), and saturated $NaHCO_3$ solution (15 mL). The aqueous extracts were reextracted, in turn, with additional Et_2O (50 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give 545 mg (99%) of crude phosphoroamide. To this material dissolved in dry THF (6 mL) at 0 °C (ice bath) was added disiamylborane (6.0 mL, 0.5 M in THF, 3.0 mmol). After 1.5 h at 0 °C, the reaction mixture was quenched with 10% NaOH (5 mL) followed by 30% H_2O_2 (5 mL), and the resulting two-phase system was stirred for 2 h at 23 °C. The reaction mixture was then poured into Et_2O (150 mL) and washed with H_2O (25 mL) and saturated NaCl solution (2×, 25 mL). The aqueous layers were reextracted, in turn, with additional Et_2O (50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give 672 mg (115%) of crude hydroxyphosphoroamide. To a solution of lithium (250 mg, 36 mmol) in ethylamine (25 mL) at 0 °C was added the 672 mg of hydroxyphosphoroamide (obtained above) dissolved in dry Et_2O (5 mL) containing *t*-BuOH (3 drops). More lithium (50 mg) was added to maintain the blue color. After 1 h at 0 °C, the excess lithium was quenched with NH_4Cl, the ethylamine was evaporated, and the residue was taken up in Et_2O (150 mL) and H_2O (50 mL). The ethereal solution was washed with saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give 323 mg of crude alcohol **20**. Column chromatography on silica gel (50 g) using 30% Et_2O/petroleum ether as eluant afforded 240 mg (69.5%) of pure **20**: bp 70–75 °C (0.7 mmHg); IR (CCl_4) 3625 (OH), 3030 (C=C), 3310 (OH), 1060 (C—O) cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 0.67 (d, 3, J = 6 Hz, CH_3CH), 0.73 (s, 3, CH_3), 0.87 (s, 3, CH_3), 1.56 (br s, 3, C=CCH_3), 3.48 (t, 2, CH_2OH), 5.32 (br s, 1, C=CH); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{26}O$ 222.1984, found 222.1996; 5.4 ppm error.

(1α,4aβ,5α,8α,8aβ)-Octahydro-4a,5,8-trimethyl-9-methylene-1,5-methanonaphthalen-2(1*H*)-one (21). To a solution of pyridinium chlorochromate (216 mg, 1.0 mmol) in dry CH_2Cl_2 (3 mL) was added a solution of alkene alcohol **20** (50.0 mg, 0.23 mmol) in dry CH_2Cl_2 (2 mL) at 23 °C. After 4.5 h at 23 °C, the solution was diluted with dry Et_2O and the supernatant liquid was passed through a short column of Florisil (20 g), and more dry Et_2O was used to elute the Florisil column. The solvent was removed in vacuo, and after bulb-to-bulb distillation followed by sublimation (85 °C, 1.5 mmHg) 33.5 mg (67%) of tricyclic ketone **21** was obtained: mp 100–101 °C; IR (CCl_4) 1m20 (C=O), 1640, 3060, 885, 860 cm^{-1} (C=C); NMR (CCl_4) δ 0.83 (d, 3, J = 6 Hz, CH_3CH), 1.02 (s, 3, CH_3), 1.05 (s, 3, CH_3), 3.08 (br s, 1, CHCO), 4.76 (br s, 1, C—CH_2), 4.91 (br s, 1, C=CH_2); NMR ($CDCl_3$) δ 0.80 (d, 1, J = 6 Hz, CH_3CH), 1.02 (s, 3, CH_3), 1.07 (s, 3, CH_3), 3.17 (br s, 1, bridgehead H), 4.78 (m, 1, C=CH_2), 4.90 (m, 1, C=CH_2); mass spectrum, m/z (relative intensity) 218 (M^+, 8), 91 (55), 41 (100), 39 (66), 29 (47), 27 (74); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{20}$ 281.1671, found 218.1675; 1.9 ppm error.

(1α,2α,4aβ,5α,8α,8aβ)-Decahydro-4a,5,8-trimethyl-9-methylene-1,5-methanonaphthalen-2-ol (22). To ketone **21** (139 mg, 0.638 mmol) in 100% EtOH (5 mL) at 0 °C (ice bath) was added $NaBH_4$ (100 mg, 2.63 mmol) in one portion. After 1 h the cooling bath was removed and the reaction mixture was stirred at 23 °C for 1 h. Methanol (4 mL) was added and stirring continued for 1 h. After concentration in vacuo the residue was dissolved in Et_2O (150 mL) and washed with H_2O (2×, 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using 40% Et_2O/petroleum ether as eluant afforded 131 mg (93%) of alcohol **22**: mp 123.5–124.5 °C; IR (CCl_4) 3570, 3450 (OH), 1647, 890, 865 (C=C) cm^{-1}; NMR (CCl_4) δ 0.83 (d, 3, J = 6 Hz, $CHCH_3$), 0.87 (s, 6, 2 × CH_3), 2.49 (br s, 1, H_2C=$CCHCHOH$), 3.2–3.8 (m, 1, $CHOH$), 4.59 (br s, 1, C=CH), 4.76 (br s, 1, C=CH); mass spectrum, m/z (relative intensity) 240 (M^+, 9), 163 (19), 91 (48), 55 (57), 41 (100), 29 (76); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{24}O$ 220.1827, found 220.1826; 0.5 ppm error.

(1α,4aβ,5α,8α,8aβ,9*R)-Octahydro-4a,5,8,9-tetramethyl-1,5-methanonaphthalen-2(1*H*)-one (23).** To $EtNH_2$ (25 mL) at 0 °C (ice bath) was added lithium metal (35 mg, 5.1 mmol). After the lithium dissolved, a solution of alcohol **22** (30 mg, 0.136 mmol) and *t*-BuOH (3 drops) in Et_2O (5 mL) was added. After 1 h at 0 °C, the excess lithium was quenched with solid NH_4Cl. The residue after solvent evaporation (N_2, warm water bath, hood) was partitioned between Et_2O (100 mL) and H_2O (25 mL). The

ethereal solution was washed with H_2O (2×, 25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 29.6 mg (98%) of crude alcohol: NMR ($CDCl_3$) δ 0.73 (s, 3, CH_3), 0.82 (:, 3, J = 6 Hz, $CHCH_3$), 0.82 (s, 3, CH_3), 1.02 (d, 3, J = 6 Hz, $CHCH_3$), 3.7–4.1 (m, 1, CHOH). Without further purification this material was dissolved in CH_2Cl_2 (1.5 mL) and added to a slurry of PCC (150 mg, 0.70 mmol) in CH_2Cl_2 (1.5 mL). After 1.5 h at 23 °C, the reaction mixture was filtered through a short column of Florisil. The residue and column were thoroughly washed with Et_2O. Concentration of the eluant in vacuo afforded 27.7 mg of crude ketone **23**. Column chromatography on silica gel gave 26.2 mg (87%) of pure ketone **23**: mp 141–143 °C; IR ($CHCl_3$) 2950, 2860 (C—H), 1705 (C=O) cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.80 (s, 3, CH_3), 0.82 (d, 3, J = 6.6 Hz, $CHCH_3$), 1.02 (s, 3, CH_3), 1.05 (d, 3, J = 5.9 Hz, $CHCH_3$), 1.0–2.5 (m, 12, CH); mass spectrum, m/z (relative intensity) 220 (M^+, 17), 163 (53), 135 (37), 121 (43), 107 (44), 97 (50), 67 (42), 55 (48), 41 (100); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{24}O$ 220.1827, found 220.1824; 1.4 ppm error.

Isocycloseychellene (3). A mixture of *p*-toluenesulfonohydrazide (74.5 mg, 0.40 mmol) and ketone **23** (22.0 mg, 0.10 mmol) in C_6H_6 (1.5 mL) was refluxed with removal of H_2O for 12 h and then cooled to 23 °C and diluted with CH_2Cl_2 (2 mL) and then Et_2O (150 mL). The organic solution was washed with H_2O (2 × 15 mL) and saturated NaCl solution (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using 40% Et_2O/petroleum ether as eluant afforded 36.7 mg (90%) of tosylhydrazone: NMR ($CDCl_3$) δ 0.68 (s, 3, CH_3), 0.71 (d, 3, J = 6.5 Hz, $CHCH_3$), 0.78 (d, 3, J = 6 Hz, $CHCH_3$), 0.93 (s, 3, CH_3), 1.0–2.3 (m, 12, CH), 2.43 (s, 3, Ar CH_3), 7.30 (d, 2, J = 8 Hz, Ar H), 7.87 (d, 2, J = 8 Hz, Ar H). To NaH (7.9 mg, 0.20 mmol; 61.4% oil dispersion; washed with petroleum ether; 3×, 1.0 mL) was added tosylhydrazone (36.7 mg, 0.090 mmol) in dry DMF (1.5 mL). After 15 min at 23 °C (H_2 evolution ended) the reaction mixture was heated at 140 °C (preheated oil bath) for 1 h and then cooled, quenched with H_2O, and partitioned between H_2O (20 mL) and pentane (100 mL). The organic extract was washed with H_2O (3 × 20 mL), dried ($MgSO_4$), and concentrated to a small volume in vacuo. The resulting solution was passed a short column of silica gel using petroleum ether as eluant. Concentration of the eluant in vacuo gave 11.0 mg (54% overall yield) of cyrstalline hydrocarbon **3**: mp 61–62 °C; IR (FT, CCl_4) 3020 (cyclopropyl, C–H), 2995, 2950, 2930, 2900, 2865, 1460, 1445, 1380, 1110, 1095, 880, 842, (cyclopropyl) cm^{-1}; NMR (400 MHz, C_6D_6) δ 1.94–1.74 (m, 4, cyclopropyl-CH_2, cyclopropyl-CH, CH_3CH), 0.998 (s, 3, cyclopropyl-CH_3), 0.885 (d, 3, J = 6.8 Hz, CH_3CH), 0.851 ($^1/_2$ of d, 0.5, $J \sim 7$ Hz, cyclopropyl-H), 0.841 (s, 3.5, CH_3), 0.704 (s, 3, CH_3), 0.554 (d of t, 1, J = 2.7 Hz, J = 7.7 Hz; NMR (FT-80A, ^{13}C, C_6D_6) δ 49.11, 41.32, 40.92, 32.11, 31.26, 29.37, 28.37, 25.00, 22.10, 21.64, 19.95, 18.87, 17.37, 16.62, 15.86; mass spectrum, m/z (relative intensity) 204 (M^+, 23), 135 (27), 133 (31), 121 (60), 120 (39), 119 (43), 108 (48), 107 (56), 105 (56), 93 (56), 91 (48), 79 (43), 77 (36), 55 (43), 41 (100); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{24}$ 204.1878, found 204.1879; 0.5 ppm error.

(1α,4α,4aβ,5β,6α,8aβ)-5-Chlorodecahydro-1,4,8a-trimethyl-9-methylene-1,6-methanonophthalene (24A) and (1α,4α,4aβ,5α,6β,8aβ)-6-Chlorodecahydro-1,4a,8-trimethyl-9-methylene-1,5-methanonaphthalene (24B). A solution of Ph_3P (393 mg, 1.5 mmol) in THF (1.5 mL, degassed to remove O_2) was added to a solution of NCS (200 mg, 1.5 mmol) in THF (1 mL). After 10 min, alcohol **22** (92 mg, 0.414 mmol) dissolved in THF (1.5 mL) was added, and the resulting mixture was stirred for 18 h at 23 °C. The reaction mixture was then diluted with Et_2O (150 mL) and the ethereal solution was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using petroleum ether as eluent afforded 33 mg (33%) of a mixture of chlorides **24A** and **24B** in a ratio of 62:38 (NMR analysis): IR (CCl_4) 3060 (C=CH_2), 1639, 890 (C=CH_2) cm^{-1}; NMR (CCl_4) downfield region δ 3.77–3.97 (m, 0.62, CHCl in **18**), 4.17 (t, 0.38, CHCl in **24B**), 4.70 (br s, 1, C=CH in **24A** and **24B**), 4.83 (br s, 0.38, C=CH in **24B**), 4.90 (br s, 0.62, C=CH in **24A**); mass spectrum, m/z (relative intensity) 238 (M^+, 22), 203 (22), 122 (77), 41 (100); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{23}Cl$ 238.148825, found 238.1485; 1.4 ppm error.

In a similar experiment for 8 h pure **24A** was obtained (54%): IR (CCl_4) 3050 (C=CH), 1644 (C=C) cm^{-1}; NMR (CCl_4) δ 0.83 (d, 3, J = 6 Hz, $CHCH_3$), 0.93 (s, 6, 2 × CH_3), 1.1–2.4 (m, 10, CH), 2.78 (br d, 1, J = 6 Hz, H_2C=CCH), 4.17 (t, 1, J = 6 Hz, CHCl), 4.72 (br s, 1, C=CH), 4.83 (br s, 1, C=CH).

(±)-Seychellene (1). Method A. To a solution of lithium (50 mg, 7.2 mmol) in NH_3 (20 mL) at −78 °C (dry ice/acetone bath) was added an ethereal solution (5 mL) of the above chloride mixture (21.8 mg, 0.0915 mmol; approximately 75:25 mixture of **24A**:**24B** by NMR analysis) and *t*-BuOH (3 drops). After 10 min the excess lithium was quenched with solid NH_4Cl. The NH_3 was evaporated (N_2, water bath, hood) and the residue was partitioned between Et_2O (100 mL) and H_2O (30 mL). The ethereal solution was washed with H_2O (25 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using petroleum ether as eluent afforded 15 mg (80%) of mixture of alkenes **1** and **4**. NMR and GLC analysis (column c, 160 °C; retention times, 4.3 and 3.4 min, respectively; separate and coinjected samples) indicated a 76:24 ratio of **1**:**4**, respectively.

Method B. To a THF solution (5 mL) of a mixture of chlorides **24A** and **24B** (15 mg, 0.063 mmol 62:38 mixture **24A**:**24B** by NMR analysis) was added $LiAlH_4$ (100 mg, 2.63 mmol). This mixture was refluxed for 48 h and then cooled, quenched with saturated Na_2SO_4 solution, diluted with pentane, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in a small amount of pentane and passed through a short column of silica gel. Concentration of the eluant (20 mL) gave 8.0 mg (62%) of (±)-seychellene (**1**) (containing <6% of **4** by GLC analysis; column c, 140 °C, retention time, 6.4 min): IR (CCl_4) 3060, 1644, 800 (C=CH_2) cm^{-1}; NMR ($CDCl_3$, 80 MHz) δ 0.75 (d, 3, J = 6.7 Hz, $CHCH_3$), 0.83 (s, 3, CH_3), 0.96 (s, 3 CH_3), 2.1–2.3 (m, 1, C=CCH), 4.58 (d, 1, J = 1.4 Hz, C=CH), 4.78 (d, 1, J = 1.4 Hz, C=CH).

(1α,4α,4aβ,5α,8aβ)-Decahydro-1,4,8a-trimethyl-9-methylene-1,5-methanonaphthalene [(±)-Isoseychellene (4)]. To ketone **21** (50 mg, 0.227 mmol) was added DEG (4.0 mL), hydrazine sulfate (260 mg, 2.0 mmol), and KOH (405 mg, 8.0 mmol). This mixture was slowly heated to 200 °C over 2 h and held at that temperature for an additional 2 h. After being cooled to 23 °C, this mixture was partitioned between H_2O (100 mL) and Et_2O/petroleum ether (1:1, 200 mL). The organic phase was washed with H_2O (25 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using petroleum ether as eluant afforded 30 mg (64%) of crystalline hydrocarbon **4**: mp 94–96 °C; IR (CCl_4) 3060, 1653, 880, 875 (C=C) cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 4.74 (s, 1, C=CH_2), 4.65 (br s, 1, C=CH_2), 2.61 (br s, 1, CHC=CH_1), 0.91 (s, 3, CH_3), 0.86 (s, 3, CH_3), 0.81 (d, 3, J = 6.7 Hz); NMR (FT-80A, ^{13}C, $CDCl_3$) δ 164.13 (C=CH_2), 99.59 (C=CH_2), 55.84, 46.68, 44.64, 40.84, 38.14, 37.69, 34.18, 28.38, 28.12, 20.10, 19.51, 18.63, 16.54; mass spectrum, m/z (relative intensity) 204 (M^+, 25), 161 (31), 147 (28), 133 (27), 119 (42), 107 (40), 105 (45), 93 (54), 79 (41), 77 (33), 67 (30), 55 (48), 41 (100); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{24}$ 204.1878, found 204.1879; 0.5 ppm error.

Natural cycloseychellene (2): IR (film) 3020 (cyclopropyl C–H), 1450, 1380, 1365 (CH_3), 1030, 840 (cyclopropyl), 800 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.656 ($^1/_2$ coupled AB, 1, J_{AB} = 11.7 Hz, J = 3.5 Hz), 1.442 ($^1/_2$ AB, 1, J_{AB} = 11.7 Hz), 0.970 (s, 3, CH_3), 0.881 (d of d, 1, J = 7.7 Hz, J = 4.3 Hz, J = 3.4 Hz, cyclopropyl-H), 0.832 (s, 3, CH_3), 0.799 (s, 3, CH_3 overlaps methyl doublet), 0.791 (d, 3, CH_3CH overlaps methyl singlet), 0.590 (d of d, 1, J = 7.9 Hz, J = 4.5 Hz, cyclopropyl-H); ^{13}C NMR (20.2 MHz, C_6D_6) δ 16.48, 19.30, 19.88, 20.26, 21.04, 22.05, 23.82, 26.39, 30.18 (4°), 30.47, 31.81, 37.26, 41.30 (4°), 4.175 (4°), 44.90; mass spectrum, m/z (relative intensity) 204 (M^+, 9), 189 (9), 147 (12), 135 (17), 123 (100), 105 (48), 91 (50), 55 (54), 41 (86), 29 (78); high-resolution mass spectroscopy (m/z) calcd for $C_{15}H_{24}$ 204.1878, found 204.1881; 1.5 ppm error.

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Total Syntheses of (±)-Seychellene and (±)-Cycloseychellene

Steven C. Welch,* John M. Gruber, and Paul A. Morrison

Department of Chemistry, University of Houston—University Park, Houston, Texas 77004

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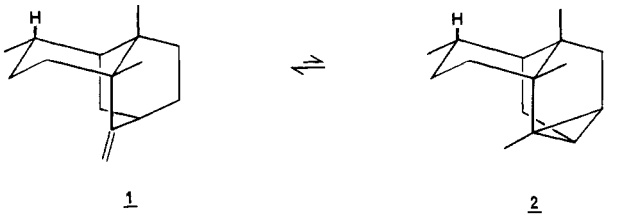
Total syntheses of (±)-seychellene (1) and (±)-cycloseychellene (2) are presented. The key step in these syntheses is the construction of tricyclic alcohols **13** by concomitant oxidative cyclization of diol **12**.

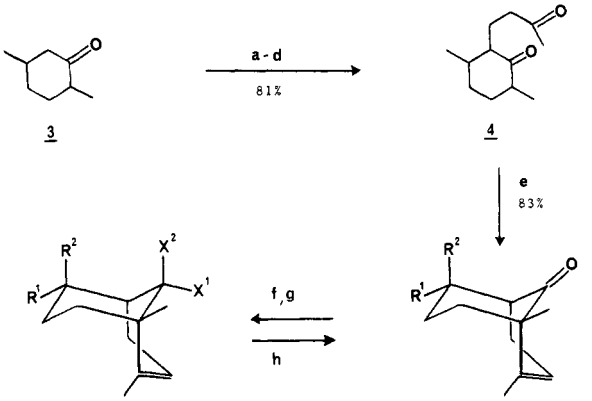
Both the tricyclic sesquiterpene seychellene (1) (Scheme I) and the tetracyclic hydrocarbon cycloseychellene (2) were isolated from Patchouli oil (*Pogostemon cablin* Benth.)[1,2] In the previous papers in this series we reported a structural revision for natural product **2**.[3] This structural assignment has been confirmed by Yamada and coworker's recent total synthesis of (±)-cycloseychellene (2).[4] Several successful total syntheses of seychellene (1) have been reported.[5] We now present, herein, the full details of our total syntheses of (±)-seychellene (1) and (±)-cycloseychellene (2) via a common tricyclic intermediate.[5]

The syntheses of sesquiterpenes **1** and **2** begin with 2,5-dimethylcyclohexanone (**3**, Scheme II). Treatment of ketone **3** with sodium hydride and ethyl formate in tetrahydrofuran followed by acidification gives a hydroxymethylene ketone. A Michael reaction of the latter substance with methyl vinyl ketone (MVK) in the presence of triethylamine followed by decarbonylation with 7.2 equiv of potassium carbonate in dilute aqueous ethanol affords diketones **4** in 81% overall yield from ketone **3**. Cyclization of diketone **4** to bicyclic ketones **5A** (R^1 = H, R^2 = CH_3) and **5E** (R^1 = CH_3, R^2 = H) was accomplished with 5.5 equiv of boron trifluoride in dichloromethane under conditions of high dilution (1.0 g of **4**/1.5 L of CH_2Cl_2, 3.4×10^{-3} M) at 0 °C for 2 h followed by 23 °C for 26 h. Under these conditions ketones **5A** and **5E** are produced in 83% yield as a 36:64 ratio of axial-CH_3 (R^1 = H, R^2 = CH_3): equatorial-CH_3 (R^1 = CH_3, R^2 = H) isomers, respectively.

Scheme I



Scheme II. Synthesis of Bicyclic Ketone 5E[a]



[a] (a) NaH, HCO_2Et, THF; (b) H_3O^+; (c) MVK, Et_3N; (d) 7.2 equiv of K_2CO_3, EtOH, H_2O, Δ, concentration 0.14 M; (e) 5.5 equiv of BF_3, CH_2Cl_2, concentration 3.4×10^{-3} M, 76 h; (f) L-Selectride, THF; −78 °C to 0 °C; (g) H_2O_2, OH^-; (h) H_2CrO_4, acetone.

These conditions represent a dramatic improvement over those used by Corey and Nozoe in the initial stages of their classic and elegant synthesis of (±)-helminthosporal.[6] Reduction of ketones **5AE** with L-Selectride (Aldrich) [Li(*sec*-Bu)$_3$H] in tetrahydrofuran from −78 °C to 0 °C and followed by a basic hydrogen peroxide workup affords three easily separable isomeric alcohols **6AA** [R^1 = H, R^2 = CH_3, X^1 = H, X^2 = OH; 31.4% yield], **6EA** [R^1 = CH_3, R^2 = H, X^1 = H, X^2 = OH; 34.9% yield], and **6EE** [R^1 = CH_3, R^2 = H, X^1 = OH, X^2 = H; 21.6% yield].[7] The stereochemistry of each isomer was established by analysis

(1) (a) Tsubaki, N.; Nishimura, K.; Hirose, Y. *Bull. Soc. Chem. Jpn.* **1967**, *40*, 597. (b) Wolff, G.; Ourisson, G. *Tetrahedron* **1969**, *25*, 4903.
(2) (a) Terhune, S. J.; Hogg, J. W.; Lawrence, B. M. *Tetrahedron Lett.* **1973**, 4705. (b) Paknikar, S. K. *Indian J. Chem.* **1974** *12*, 1016.
(3) (a) Welch, S. C.; Chou, C.-Y.; Gruber, J. M.; Assercq, J.-M. *J. Org. Chem.*, preceding paper in this issue. (b) Willcott, M. R.; Morrison, P. A.; Assercq, J.-M.; Welch, S. C.; Inners, R. *J. Org. Chem.* **1981**, *46*, 4819. (c) Welch, S. C.; Gruber, J. M.; Chou, C.-Y.; Willcott, M. R.; Inners, R. *J. Org. Chem.* **1981**, *46*, 4816.
(4) Niwa, H.; Ban, N.; Yamada, K. *Tetrahedron Lett.* **1983**, *24*, 937.
(5) (a) Piers, E.; De Waal, W.; Britton, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5113. (b) Mirrington, R. N.; Schmalzl, K. J. *J. Org. Chem.* **1972**, *37*, 2877. (c) Fukamiya, N.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans.* **1973**, 1843. (d) Fráter, G. *Helv. Chim. Acta* **1974**, *57*, 172. (e) Spitzner, D. *Tetrahedron Lett.* **1978**, 3349. (f) Jung, M. E.; McCombs, C. A. *J. Am. Chem. Soc.* **1978**, *100*, 5207, (g) Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. *Tetrahedron* **1979**, *35*, 293. (h) Jung, M. E.; Pan, Y.-G. *Tetrahedron Lett.* **1980**, 3127. (i) Welch, S. C.; Gruber, J. M.; Chou, C.-Y.; Willcott, M. R.; Inners, R. *J. Org. Chem.* **1981**, *46*, 4816. (j) Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677. (k) Welch, S. C.; Gruber, J. M.; Morrison, P. A. *Tetrahedron Lett.* **1984**, *25*, 5497.
(6) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5728.
(7) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. Krishnamurthy, S.; Brown, H. C. *Ibid.* **1976**, *98*, 3383.

0022-3263/85/1950-2676$01.50/0