With ample quantities of **13** assured, we turned to the final task, introduction of the requisite C(6,7) unsaturation. Thwarted initially by the inability of LDA/THF to effect deprotonation at a temperature commenserate with survival of the derived enolate, we examined a number of related amide bases. To our delight treatment of **13** with 1.2 equiv of lithium tetramethylpiperidine (LiTMP) first at −10 °C for 1.5 h, then at 0 °C for 0.5 h with addition of 3 equiv of HMPA, and then at −20 °C with addition of 2.0 equiv of phenylselenyl chloride in THF (2 h), afforded the desired exo selenide (**6**)[12] in 49% yield after flash chromatography [silica gel/hexane–ether (3:1)]. Subsequent oxidative-elimination [$NaIO_4$ (excess)/$H_2O$/MeOH] with concomitant removal of the TES protecting group afforded (±)-paniculide A (**1**) in 72% yield after thin-layer chromatography [silica gel/ether]. That indeed (±)-paniculide A was in hand was confirmed by careful comparison of the IR, high-field NMR (250 MHz), and TLC retention characteristics (three solvent systems) to those of an authentic sample of paniculide A kindly provided by Professor Overton.[20]

In summation, the first total synthesis of (±)-paniculide A (**1**) has been achieved in stereocontrolled fashion. The approach proved to be both economical, proceeding in ten steps, and efficient, 4.2% overall yield from enone **8** (average yield/step, 73%). Studies to improve this sequence as well as to effect the total synthesis of paniculides B and C paralleling the above strategy will be reported in due course.

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(20) We thank Professor Karl H. Overton of the University of Glasgow for providing us with generous samples of paniculides A as well as copies of the spectral data (i.e., $^1H$ and $^{13}C$ NMR).

(21) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; Recipient of a National Institutes of Health (National Center Institute) Career Development Award, 1980–1985.

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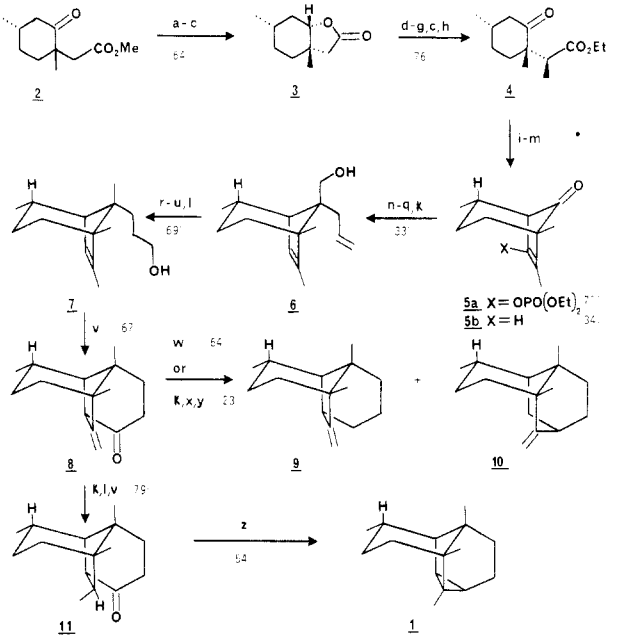
## Synthesis of Seychellene and the Original Structure Reported for Cycloseychellene

*Summary:* A stereoselective total synthesis of the original structure **1** reported for cycloseychellene from 2,5-dimethylcyclohexanone is described. A synthesis of (±)-seychellene (**10**) is also presented.

*Sir:* Cycloseychellene, a tetracyclic sesquiterpene biogenetically related to seychellene (**10**), was isolated from *Pogostemon cablin* Benth. (Patchouli oil).[1,2] The structure of cycloseychellene was assigned as **1** on the basis of 220-MHz NMR data, as well as co-occurrence and equilibration [$Cu(OAc)_2$, HOAc, 90 °C] with seychellene (**10**).[2] A number of successful syntheses of seychellene (**10**) have been published;[3] however, no report on a synthesis of structure **1** has appeared in the chemical literature. The purpose of this communication is to present successful stereoselective syntheses of structure **1** and (±)-seychellene (**10**).

Scheme I[a]




[a] (a) $KBH_4$, MeOH, 0 °C; (b) NaOH, EtOH, $H_2O$; (c) $H_3O^+$; (d) LDA, THF; (e) $CH_3I$, (f) NaOH, *t*-BuOH, $H_2O$; (g) $RuCl_3$ 5 mol % and $NaIO_4$ added to f; (h) $K_2CO_3$, EtI, acetone; (i) 2.5 equiv of $NaN(SiMe_3)_2$, THF; (j) $ClPO(OEt)_2$, TMEDA; (k) $NaBH_4$, EtOH; (l) Li, $EtNH_2$, $Et_2O$, *t*-BuOH; (m) $H_2CrO_4$, acetone; (n) $Ph_3P{=}CHOMe$, $Me_2SO$; (o) $HClO_4$, $H_2O$, $Et_2O$; (p) $Ph_3CK$, DME; (q) $BrCH_2CH{=}CH_2$; (r) *n*-BuLi, THF, TMEDA; (s) $ClPO(NMe_2)_2$; (t) $Sia_2BH$, THF; (u) $H_2O_2$, $OH^-$; (v) $pyrH^+ClCrO_3^-$, $CH_2Cl_2$; (w) $N_2H_4$, KOH, DEG; (x) $Ph_3P$, NCS, THF; (y) $LiAlH_4$, THF; (z) *p*-TsNHNH$_2$, $C_6H_6$; NaH, DMF.

These syntheses begin with keto ester **2** which exists as a 70:30 mixture of *trans*-/*cis*-dimethyl diastereomers, respectively. Keto ester **2** is prepared from 2,5-dimethylcyclohexanone in 57% overall yield.[4] Reduction of keto ester **2** with $KBH_4/CH_3OH$ at −15 °C followed by sequential treatment with NaOH/$H_2O$/EtOH and then 10% HCl for 20 h affords lactone **3** in 64% overall yield as a single diastereomer.[5] Alkylation of lactone **3**[6] by generating the enolate anion with LDA/THF and quenching with $CH_3I$ affords the monomethylated lactone in 95%

(1) Wolff, G.; Ourisson, G., *Tetrahedron* **1969**, *25*, 4903.

(2) Terhune, S. J.; Hogg, J. W.; Lawrence, B. M., *Tetrahedron Lett.* **1973**, 4705.

(3) (a) Piers, E.; Britton, R. W.; de Waal, W. *J. Am. Chem. Soc.* **1971**, *93*, 5113. (b) Schmalzl, K. J.; Mirrington, R. N. *J. Org. Chem.* **1972**, *37*, 2877. (c) Fukamiya, N.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1843. (d) Frater, 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.

(4) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077.

(5) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408. Diastereomeric *cis*-dimethyl-*trans*-hydroxy acid was isolated in 25% yield.

(6) Posner, G. H.; Loomis, G. L. *J. Chem. Soc., Chem. Commun.* **1972**, 892.

0022-3263/81/1946-4816$01.25/0 

yield. This latter lactone was then saponified with 2.4 equiv of $NaOH/H_2O/t$-BuOH followed by the addition of a catalytic amount of $RuCl_3$ and 3.3 equiv of $NaIO_4/H_2O$ for 24 h.[7] Acidification of this reaction mixture followed by extraction and esterification produces keto ester **4** in 76% overall yield from lactone **3**. Intramolecular Claisen condensation of keto ester **4** with 2.5 equiv of $NaN(SiMe_3)_2$ in refluxing THF (1h for addition, 1h reflux) followed by quenching with $ClPO(OEt)_2$/TMEDA gives bicyclic keto enol phosphate **5a** in 71% yield.[8] Selective reduction of the ketone group of intermediate **5a** with $NaBH_4$/EtOH followed by reductive deoxygenation of the diethyl phosphate moiety with $Li/EtNH_2/Et_2O$ in the presence of $t$-BuOH[9] affords bicyclic ketone **5b** in 34% yield after oxidation with $H_2CrO_4$ in acetone.[10,11]

A Wittig reaction on ketone **5b** with $Ph_3P{=}CHOCH_3$ in $Me_2SO$[12] followed by hydrolysis produces an epimeric mixture of aldehydes. Stereoselective alkylation of this epimeric mixture of aldehydes with allyl bromide using $Ph_3CK$ in DME[13] to generate the respective enolate anion followed by reduction of the resulting product with $NaBH_4$/EtOH at −10 °C produces alcohol **6** in 33% overall yield from ketone **5b**. Esterification of alcohol **6** with $n$-BuLi in THF/TMEDA (4:1, respectively) followed by addition of $ClPO(NMe_2)_2$ gives the corresponding phosphate ester. Selective hydroboration of the monosubstituted alkene with disiamylborane/THF followed by oxidation with $H_2O_2/NaOH$ produces a primary alcohol–phosphate ester.[14] Reduction of the latter with $Li/EtNH_2/Et_2O$ in the presence of $t$-BuOH[9] affords alcohol **7** in 69% overall yield from alcohol **6**. Intramolecular Prins reaction was effected by oxidation of alcohol **7** with $PCC/CH_2Cl_2$[15] to give tricyclic enone **8** in 67% yield. Wolff–Kishner reduction[16] of enone **8** produces crystalline hydrocarbon **9** in 64% yield. Reduction of enone **8** with $NaBH_4$/EtOH gives a single isomeric alcohol. Sequential treatment of this alcohol with $NCS/Ph_3P/THF$[17] followed by reduction of the intermediate chlorides with $LiAlH_4$ in refluxing THF affords a mixture of hydrocarbon **9** and (±)-seychellene (**10**) (6:94 ratio, respectively) in 23% overall yield from enone **8**. The spectral data of **10** (IR, NMR) were identical with those reported for the natural product.[1,3]

Reduction of enone **8** with $NaBH_4$/EtOH followed by reduction of the exocyclic alkene with $Li/EtNH_2/Et_2O$ in the presence of $t$-BuOH gives a single isomeric alcohol. Oxidation of this alcohol with $PCC/CH_2Cl_2$[15] produces ketone **11** in 79% overall yield from enone **8**. Conversion of ketone **11** to a $p$-toluenesulfonylhydrazone and treatment of this derivative with NaH/DMF[18] at 140 °C for 1h affords hydrocarbon **1** in 54% overall yield from ketone **11**. The NMR spectral data of hydrocarbon **1** [80 MHz NMR ($C_6D_6$) $\delta$ 0.70 (s, 3, $CH_3$), 0.83 (s, 3, $CH_3$), 0.88 (d, 3, $J$ = 6.7 Hz, $CH_3CH$), 0.99 (s, 3, $CH_3$), 0.55 (dt, cyclopropyl H)] are significantly different than those reported for natural cycloseychellene.[2,19] We conclude that the NMR spectrum and the structure of natural cycloseychellene should be reinvestigated and revised. We report the NMR characterization of synthetic **1** and natural cycloseychellene in the accompanying paper.

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**Registry No.** (±)-**1**, 79083-63-9; (±)-*cis*-**2**, 79201-57-3; (±)-*trans*-**2**, 79201-58-4; (±)-**3**, 79201-59-5; (±)-**4**, 79201-60-8; (±)-**5a**, 79201-61-9; (±)-**5b**, 79201-62-0; (±)-**6**, 79201-63-1; (±)-**7**, 79201-64-2; (±)-**8**, 79201-65-3; (±)-**9**, 79201-66-4; (±)-**10**, 24568-69-2; (±)-**11**, 79201-67-5; 2,5-dimethylcyclohexanone, 932-51-4.

(7) Sakan, T.; Abe, K. *Tetrahedron Lett.* **1968**, 2471.
(8) Piers, E.; Isenring, H. P. *Can. J. Chem.* **1977**, *55*, 1039.
(9) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.
(10) Eisenbraun, E. J., "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. V, p 310.
(11) The stereochemistry of the secondary methyl group in **5b** was established by an europium NMR shift analysis of both the axial and equatorial methyl isomers which were prepared by an alternative synthetic scheme which will be reported at a later date.
(12) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. Wittig, G.; Krauss, E., *Angew. Chem.* **1959**, *71*, 127.
(13) Huffman, J. W.; Harris, P. G. *J. Org. Chem.* **1977**, *42*, 2357.
(14) Zweifel, G.; Brown, H. C., *Org. React.* **1963**, *13*, 1.
(15) (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.
(16) Todd, D. *Org. React.* **1948**, *4*, 378.
(17) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937.
(18) Shapiro, R. H.; Duncan, J. H.; Clopton, J. C. *J. Am. Chem. Soc.* **1967**, *89*, 1442.
(19) Copies of the IR, 220-MHz NMR ($C_6D_6$), and mass spectra were obtained from Dr. B. M. Lawrence, Director of Research and Development, R. J. Reynolds Tobacco Co. We thank Dr. Lawrence for providing these spectra.

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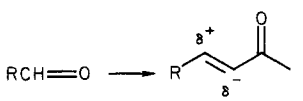
## Branching Strategy in Organic Synthesis. 2. Reversal of Olefin Polarization with Concomitant Carbon–Carbon Bond Formation[1]

*Summary:* Vinyl sulfones are smoothly converted to $\alpha,\beta$-unsaturated nitriles on exposure to KCN/dicyclohexyl-18-crown-6 in refluxing *tert*-butyl alcohol.

*Sir:* The delineation of new strategies for the construction of carbon skeleton branch points is fundamental to the development of synthetic organic chemistry. One approach to the construction of such branch points is to elaborate a specificially functionalized olefin.[2] This approach is limited, however, by the general observation that the olefin so prepared is negatively polarized in the direction of chain growth. This polarization is illustrated by the classical aldol condensation.




It is on occasion desirable in developing the branching of an olefin-containing carbon skeleton to switch chain growth to the opposite end of the olefin. This usually necessitates reversal of olefin polarization. While methods to temporarily effect such reversal (umpolung[3]) have been

(1) For part 1 in this series, see: Taber, D. F.; Gunn, B. P. *J. Org. Chem.* **1979**, *44*, 450.
(2) Faulkner, D. J. *Synthesis* **1971**, 175.

0022-3263/81/1946-4817$01.25/0 