Tetrahedron Vol. 35, pp. 293–298
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TOTAL SYNTHESIS OF (±)-PATCHOULI ALCOHOL AND (±)-SEYCHELLENE VIA A COMMON HOMOISOTWISTANE INTERMEDIATE[1]

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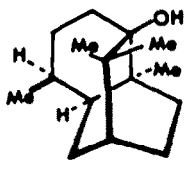
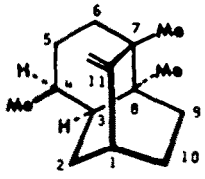
(*Received in Japan 6 May 1978*)

Abstract—Base-catalyzed cyclization of a conjugated cyclohexenone derivative 16 afforded in a single step a homoisotwistane derivative 17, which was converted to a ketone 22. Both (±)-patchouli alcohol 1 and (±)-seychellene 2 were synthesized using reactions at the bridgehead position (C-7) of a bicyclo[3.3.1]nonan-2-one system contained in 22.

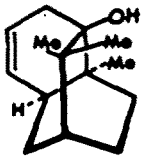
Patchouli alcohol, the major component of patchouli oil, has been known since the nineteenth century[2] and was shown to have the structure 1 in 1963.[3] From the same source seychellene was isolated as a minor constituent[4,5] and the structure determined to be 2.[5]



1 (patchouli alcohol)



2 (seychellene)

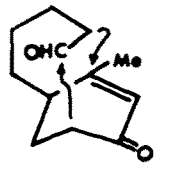


3 (norpatchoulenol)

Isolation and the structure of norpatchoulenol 3 which has the odour of patchouli oil was reported by Teisseire *et al.* in 1974.[6a,b]

These three compounds each possess the novel carbon framework, a tricyclo[5.3.1.0^{4,9}]undecane skeleton. The synthesis of 1,[7] 2,[8] and 3[6c,9] has been reported by several groups. Construction of the carbon skeleton has been achieved by various routes, which may be classified as: intramolecular cyclization of a properly functionalized bicyclic system (a derivative of a *cis*-decalin or a bicyclo[2.2.2]octane), or intramolecular Diels–Alder reaction of a conjugated cyclohexadiene derivative. Owing to the marked difference in the functionalities both at the bridgehead position (C-7) and at the adjacent position (C-11) between patchouli alcohol 1 and seychellene 2, previous work has concentrated on the construction of either 1 or 2 except for one case.[7c,8b]

We describe the synthesis of both patchouli alcohol 1 and seychellene 2 in racemic form via a common intermediate 22 using reactions at the bridgehead position in a bicyclo[3.3.1]nonan-2-one system. Previously we developed a method of forming a tricyclo[5.3.1.0^{4,9}]undecane (homoisotwistane) skeleton by base-catalyzed double cyclization of a conjugated cyclohexenone derivative in a single step as illustrated in the reaction, 4→5.[10] The ketol 5 was converted to a keto ketal 6 by ketalization and subsequent oxidation. The carbon skeleton of 6 is a bicyclo[3.3.1]nonan-2-one in which the 6-membered ring containing the keto group is held rigidly in the boat conformation,[11] and the acidity of a hydrogen at the bridgehead position (C-7) in this system was found to be significantly enhanced as compared with the acidity of the corresponding hydrogen in 3,3-dimethylbicyclo[3.3.1]nonan-2-one.[12] It was thus expected that various substituents could easily be introduced in the bridgehead position (C-7) using the enolate of 6: on treatment of 6 with lithium diisopropyl amide (LDA) in THF followed by reaction with methyl iodide, a product 7 was obtained in good yield. We have examined and executed the introduction of a variety of substituents in C-7 of 6 and the related compounds under conditions



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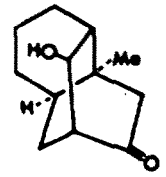

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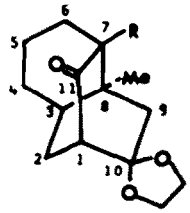
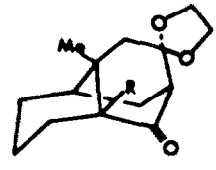
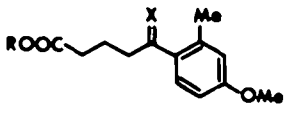




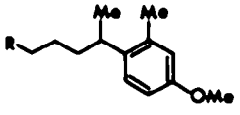
6 : R = H
7 : R = Me

similar to the reaction, 6→7, and were convinced that the reactions at the bridgehead position in this system would enable us to synthesize both patchouli alcohol 1 and seychellene 2 employing a common intermediate 22.

The starting material for the synthesis of 1 and 2 was γ-(4-methoxy-2-methylbenzoyl)butyric acid 8,[13] which was subjected to the Wittig reaction using methylenetriphenylphosphorane–DMSO and subsequent esterification gave an olefinic ester 9 (67%). Catalytic hydrogenation of 9 afforded an ester 10 (97%), which was reduced to the alcohol 11 (98%). On oxidation with pyridinium chlorochromate[14], 11 was converted to an aldehyde 12, which, after chromatographic purification, was transformed to the corresponding acetal 13 (70% from 11). Birch reduction of 13 followed by hydrolysis of

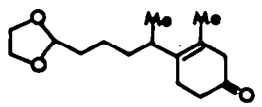


8: R = H, X = O
9: R = Me, X = CH_2



10: R = COOMe
11: R = CH_2OH
12: R = CHO
13: R = 

the resulting enol ether afforded a β,γ-unsaturated ketone 14 (85%), which was isomerized (NaOMe–MeOH) to a 1:1 diastereomeric mixture of the conjugated ketone 15 (77%). Deacetalization of 15 gave a mixture of two diastereomers 16 (98%), whose structural assignment was fully substantiated by spectral (IR, NMR and mass) means. Intramolecular cyclization of a diastereomeric mixture of 16, afforded three products, two tricyclic ketols, 17 (23%) and 18 (3%), and a conjugated ketone 19 (6%). Both 17 (m.p. 165–167°) and 19 were obtained in the pure state by chromatographic separation and recrystallization. The spectral data made it possible to assign the spiro structure 19 to the conjugated ketone. In the NMR spectrum of the major product 17, a signal due to H-11 appeared at δ 3.94 as a doublet of doublets with coupling constants of 4.0 and 2.0 Hz, establishing the stereochemistry of the OH group as depicted in 17. The configuration of the OH group in the minor product 18 was shown to be identical with the one in 17 based on the NMR spectral evidence (H-11 of 18: δ 4.12, dd, J = 4.0, 2.0 Hz). Therefore the two tricyclic compounds, 17 and 18 must be epimers regarding the secondary Me group at C-4. Further, the major product 17 was deduced to be the one with the desired, natural configuration at C-4, if one considers the steric course of the cyclization reaction of two diastereomers 16. Intramolecular Michael addition of two diastereomers 16 would give two *cis*-decalones, A and B, respectively. In the second stage of cyclization, A and B which necessarily assume the conformations as shown for intramolecular aldol condensation would yield the tricyclic ketols, 17 and 18, respectively. There must be a 1,3-diaxial Me–Me interaction in the transition state from B to 18, which inhibits the formation of 18. In contrast, no such unfavorable steric factor is present in going from A to 17. A similar explanation was presented for the preferential formation of a tricyclic compound having the secondary Me group with the desired stereochemistry at C-4 in the synthesis of patchouli alcohol[7b,d] and seychellene.[8c] The validity of the stereostructure 17



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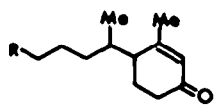
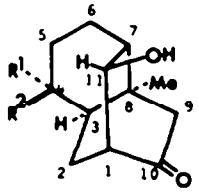
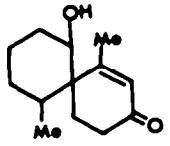


15: R = 
16: R = CHO



17: R^1 = H, R^2 = Me
18: R^1 = Me, R^2 = H



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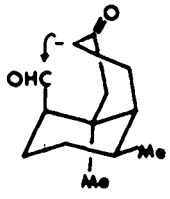
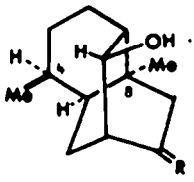


A

B

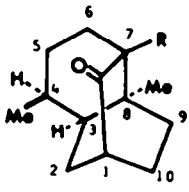
assigned to the major product of cyclization was substantiated by conversion of 17 to (±)-seychellene 2, which was conducted as follows. Reduction of 17 with zinc in ether saturated with HCl[15] afforded an alcohol 21 (76%) (reduction of 17 to 21 was also effected by conversion to a thioketal 20 followed by desulfurization with Raney nickel in 98% overall yield). On oxidation (CrO_3–pyridine) the alcohol 21 gave a ketone 22 (95%), which was used as a common intermediate for the synthesis of patchouli alcohol and seychellene. Methylation at the bridgehead position (C-7) of 22 was achieved by treatment of 22 with LDA in THF and subsequent reaction with methyl iodide, affording a ketone 23 (79%), being identified as (±)-norseychellanone by spectral comparison. Conversion of 23 to (±)-seychellene 2 was performed quantitatively under conditions similar to those reported.[8a] The IR and NMR spectra of (±)-2 purified by preparative GLC were in complete agreement with those of natural 2.[5]

For the synthesis of patchouli alcohol 1, an OH group was introduced in C-7 of 22: the enolate generated from 22 and LDA was reacted with the molybdenum peroxide reagent,[16] affording an α-ketol 24 (74%). Reaction of 24 with MeLi gave a 1,2-diol as expected, which on dehydration yielded a complex mixture. This result must be due to the presence of the OH group at the bridgehead position in 24, considering the success of a similar dehydration in the final stage (23→2) of the synthesis of (±)-seychellene. In order to circumvent this difficulty, the OH group in 24 was protected as a methyl ether. The α-ketol 24 was methylated to a keto ether 25 (83%). On



20: R = [S,S]

21: R = H_2

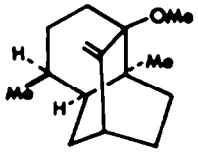


22: R = H

23: R = Me

24: R = OH

25: R = OMe



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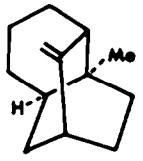

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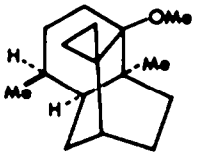

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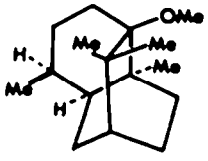

29

reaction with MeLi and subsequent dehydration 25 was converted to an allyl ether 26 (67%). Cyclopropanation of the double bond in 26 was examined using 27 as a model compound, which was prepared from 5 by five steps.[12] The olefin 27 was converted to a cyclopropane derivative (55%) by the Simmons–Smith reaction,[17,18] whereas under similar conditions 26 was recovered unchanged or gave a complex mixture at elevated temperatures (e.g. 50°). These results suggest that neutral or basic conditions are necessary for cyclopropanation of 26. When the allyl ether 26 was treated with methylene,[19] no reaction occurred. Cyclopropanation of the double bond in 26 could be achieved by treatment with diazomethane in the presence of a copper chelate,[20] affording a cyclopropane compound 28 (47% based on reacted 26) together with the starting 26 (40% recovery). The cyclopropane ring in 28 was catalytically hydrogenated to give (±)-patchouli alcohol methyl ether 29, m.p. 62–64° (83%), spectral properties of which were identical with those of an authentic specimen prepared by methylation of natural patchouli alcohol. Oxidation under mild conditions[21] was a method of choice for removal of the ethereal protecting group in 29: thus, 29 was converted to (±)-patchouli alcohol 1, m.p. 37–38° (57), identification of which with natural 1 was made by spectral and tlc comparison.

EXPERIMENTAL

M.ps were uncorrected. IR spectra were taken in $CHCl_3$ and recorded with JASCO Model IRS and JASCO DS-402G instruments. NMR spectra were obtained in $CDCl_3$ using a Varian HA-100D (100 MHz) spectrometer: chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants in Hz. Low resolution mass spectra were determined on a Hitachi RMU-6C mass spectrometer. High resolution mass spectra were recorded on a JEOLCO GMS-01SG mass spectrometer. A Varian 1828-4 gas chromatograph was used for analytical and preparative GLC (5 ft. × 0.25 in. column packed with 5% SE-30 on Celite 545). For TLC silica gel 60 F_{254} (No. 5715) and 60 PF_{254} (No. 7747) (E. Merck, A. G., Germany) were used: thickness employed was 1.50 mm for preparative layer chromatography (plc). For column chromatography silicic acid (Silica Gel 60, No. 7734, E. Merck, A. G., Germany) was used. Ion exchange resin used for neutralization was Amberlite CG-50 (Type I). Reagents and solvents used for reactions under anhydrous conditions were purified and dried as follows. i-Pr_2NH: distilled from NaH under N_2; $SOCl_2$: distilled in the presence of quinoline; MeI and CH_2Cl_2: distilled from $CaCl_2$; THF and DME: dried over Na and distilled from K-benzophenone ketyl under N_2; ether: dried over Na and distilled; pyridine: distilled from BaO; benzene and toluene: distilled from Na; MeOH: distilled from $Mg(OMe)_2$ under N_2; BF_3-OEt_2, t-BuOH, and DMSO: distilled from CaH_2 under N_2. A dry ice-acetone bath was used for conducting all the reactions below 0°. Organic solns were washed with saturated NaCl soln, dried over Na_2SO_4, evaporated by vacuum rotary evaporator.

Keto ketal 6. A stirred mixture of 5[10] (10 mg), p-TsOH·H_2O (4 mg), and ethylene glycol (4 ml) in toluene (25 ml) was refluxed with azeotropic removal of H_2O using a Dean-Stark apparatus for 4 hr. The mixture was cooled, washed with sat. $NaHCO_3$ aq (2 ml) and subsequently with H_2O (2 ml), dried, and concentrated to give an oily hydroxy ketal (13 mg), which was used directly for the next step. To a stirred soln of the hydroxy ketal (13 mg) in pyridine (0.5 ml) was added a mixture of CrO_3 (28 mg)-pyridine (0.5 ml) at 0°. The mixture was stirred at room temp for 2.5 hr, diluted with ice-water (4 ml), and extracted with benzene (4 × 10 ml). The benzene extracts were dried and concentrated to afford an oily residue, which was purified by plc [benzene–ether (1:1)], yielding 6 (8.5 mg, 70% from 5) as a colorless liquid; IR 1715 cm^{-1}; NMR 1.05 (3H, s), 3.8–4.0 (4H, m, A_2B_2 type); Mass 236 (M^+). [High resolution mass spectrum. Found: 236.1396 (M^+). $C_{14}H_{20}O_3$ requires: 236.1412].

Methylation of keto ketal 6. To a cooled (−78°) soln of i-Pr_2NH (0.075 ml) in THF (1 ml) under N_2, a soln (0.3 ml) of 1.6 M n-BuLi in n-hexane was added slowly with stirring. After 10 min, a soln of 6 (2.5 mg) in THF (0.2 ml) was added to the LDA soln slowly. The temp. of the cooling bath was raised (−50°) and the stirring continued for 20 min. MeI (0.1 ml) was added and the mixture stirred at −50° for 30 min. Excess NH_4Cl was added to the mixture and after 5 min H_2O (0.5 ml) was added. The mixture was concentrated, diluted with H_2O (1 ml), and extracted with benzene twice. The benzene extracts were dried and concentrated. The oily residue was purified by plc [benzene–Et_2O (1:1)] to give 7 (2.6 mg, 98%) as a colorless liquid; IR 1715 cm^{-1}; NMR 0.98 (3H, s), 1.00 (3H, s), 3.8–4.0 (4H, m, A_2B_2 type); Mass 250 (M^+). [High resolution mass spectrum. Found: 250.1582 (M^+). $C_{15}H_{22}O_3$ requires: 250.1569].

Olefinic ester 9. To a stirred mixture of methyltriphenylphosphonium bromide (19.0 g, 0.053 mol) in DME (140 ml) at −30° under N_2 was added a soln (26.3 ml, 0.067 mol) of methylsulfinyl carbanion (2.55 M: prepared from 1.93 g of NaH and 31.5 ml of DMSO). The mixture was kept at room temp. for 20 min, again cooled (−30°), and DME (175 ml) added. A soln of 8 (5 g, 0.021 mol) in DMSO (27.5 ml) was added dropwise to the red suspension at −30°. The mixture was stirred for 3 hr, while the temp. of the cooling bath was raised gradually to room temp. The mixture was diluted with H_2O (30 ml) and concentrated. The aqueous mixture was washed with benzene (4 × 30 ml), acidified (pH 2) with oxalic acid, and extracted with benzene (4 × 40 ml). The benzene extracts were dried and concentrated to give an oil, which was methylated with ethereal CH_2N_2. The residue obtained on evaporation of solvent was chromatographed with $CHCl_3$ giving a liquid, distillation of which afforded pure 9 (4.2 g, 67%), b.p. 151–152° (2 mmHg); IR 1735, 1605, 1500, 900 cm^{-1}; NMR 1.5–1.8 (2H, m), 2.2–2.5 (4H, m), 2.27 (3H, s), 3.66 (3H, s), 3.79 (3H, s), 4.88 (1H, d, J = 2.0), 5.18 (1H, d, J = 2.0), 6.67 (1H, dd, J = 8.0, 2.0), 6.72 (1H, br.s), 6.99 (1H, br.d, J = 8.0); Mass 248 (M^+). (Found: C, 72.78; H, 8.12. $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%).

Ester 10. A mixture of 9 (15.1 g, 0.061 mol) and 10% Pd–C (1.65 g) in EtOH (200 ml) was stirred at room temp. for 18 hr under the atmosphere of H_2. The catalyst was removed by filtration and the filtrate was concentrated, giving a colorless liquid, distillation of which yielded 10 (14.8 g, 97%), b.p. 146–147° (2 mmHg); IR 1735, 1667, 1500 cm^{-1}; NMR 1.19 (3H, d, J = 7.0), 1.5–1.7 (4H, complex m), 2.2–2.4 (2H, m), 2.30 (3H, s), 2.91 (1H, m), 3.65 (3H, s), 3.78 (3H, s), 6.69 (1H, br.s), 6.73 (1H, dd, J = 8.0, 2.0), 7.09 (1H, br.d, J = 8.0); Mass 250 (M^+). (Found: C, 72.21; H, 8.80. $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86%).

Alcohol 11. A soln of 10 (4.77 g, 19.1 mmol) in ether (65 ml) was added dropwise to a stirred soln of LAH (726 mg, 19.1 mmol) in ether (15 ml) at −20°. Then the mixture was stirred at 0° for 50 min, diluted with 10% MeOH–ether, and added with a saturated aqueous soln of potassium sodium tartrate. The ppts were filtered off with the aid of Super Cel and washed thoroughly with ether. The combined filtrates were dried and concentrated to give a colorless liquid, distillation of which afforded 11 (4.2 g, 98%), b.p. 149–150° (2 mmHg); IR 3680, 1607, 1508, 1045 cm^{-1}; NMR 1.17 (3H, d, J = 7.0), 1.3–1.8 (6H, complex m), 2.30 (3H, s), 2.90 (1H, m), 3.50 (2H, t, J = 6.0), 3.78 (3H, s), 6.68 (1H, br.s), 6.72 (1H, dd, J = 8.0, 2.0), 7.09 (1H, br.d, J = 8.0); Mass 222 (M^+). (Found: C, 75.55; H, 9.81. $C_{14}H_{22}O_2$ requires: C, 75.63; H, 9.97%).

Aldehyde 12 *and acetal* 13. To a stirred suspension of $C_5H_5NHCrO_3Cl$ (9.50 g, 44.1 mmol) in CH_2Cl_2 (58 ml) was added rapidly a soln of 11 (6.45 g, 29.3 mmol) in CH_2Cl_2 (14 ml) at room temp. The stirring was continued for 1.5 hr, and the black mixture was diluted with ether (100 ml). The ppts were filtered off and washed with ether repeatedly. The combined filtrates were concentrated and the residual liquid was chromatographed with $CHCl_3$, giving 12 (6.39 g) as a colorless liquid; IR 2730, 1725, 1607, 1500 cm^{-1}; NMR 1.18 (3H, d, J = 7.0), 1.4–1.9 (4H, complex m), 2.30 (3H, s), 2.2–2.6 (2H, m), 2.90 (1H, m), 3.77 (3H, s), 6.69 (1H, br.s), 6.73 (1H, dd, J = 8.0, 2.0), 7.09 (1H, br.d, J = 8.0); Mass 220 (M^+). A stirred mixture of 12 (5 g, 22.7 mmol), *p*-TsOH·H_2O (20 mg), and ethylene glycol (20 ml) in toluene (90 ml) was refluxed with azeotropic removal of H_2O using a Dean-Stark apparatus for 8 hr. After cooling, the mixture was added with K_2CO_3, washed with H_2O (4 × 20 ml), dried, and concentrated to give a pale yellow liquid, distillation of which afforded 13 (4.19 g, 70% from 11) as a colorless liquid, b.p. 176–178° (4 mmHg); IR 1606, 1500 cm^{-1}; NMR 1.17 (3H, d, J = 7.0), 1.2–1.8 (6H, complex m), 2.28 (3H, s), 2.90 (1H, m), 3.78 (3H, s), 3.7–4.0 (4H, m, A_2B_2 type), 4.71 (1H, t, J = 5.0), 6.68 (1H, br.s), 6.72 (1H, dd, J = 8.0, 3.0), 7.09 (1H, br.d, J = 8.0); Mass 264 (M^+). (Found: C, 72.92; H, 9.16. $C_{16}H_{24}O_3$ requires: C, 72.69; H, 9.15%).

β,γ-Unsaturated ketone 14 *and conjugated ketone* 15. To a stirred soln of 13 (2.81 g, 11.2 mmol) in THF (112 ml), t-BuOH (112 ml), and liquid NH_3 (280 ml) under N_2 was added Li wire (1.0 g) cut into small pieces in portions. After stirring at −33° for 40 min, NH_3 was allowed to evaporate at room temp. To the mixture EtOH was added dropwise, concentrated, H_2O (70 ml)–benzene (50 ml) added and again concentrated. Water (20 ml) was added to the residue and the mixture extracted with benzene (4 × 70 ml). The benzene extracts were dried and concentrated to give an oil (3.1 g). A mixture of the oil in MeOH (85 ml) and a saturated oxalic acid soln (17 ml) was stirred at room temp. for 30 min, sat. $NaHCO_3$aq added (pH 8), and concentrated. The residual aqueous mixture was extracted with benzene (4 × 70 ml). The benzene extracts were dried and concentrated. The residue was chromatographed with $CHCl_3$ to give 14 (2.40 g, 85%) as a colorless liquid; IR 1712 cm^{-1}; NMR 0.97 (3H, d, J = 7.0), 1.1–1.5 (6H, complex m), 1.5–1.8 (2H, m), 1.68 (3H, s), 2.2–2.6 (3H, complex m), 2.82 (2H, br.s), 3.8–4.0 (4H, m, A_2B_2 type), 4.83 (1H, t, J = 5.0); Mass 252 (M^+). To a soln of 14 (1.27 g, 5.0 mmol) in MeOH (48 ml) was added a soln (6.7 ml, 2.9 mmol) of 0.44 M NaOMe in MeOH under N_2.The soln was stirred at room temp. for 2 hr, ion-exchange resin (6.5 g) added, and stirred for 10 min. The mixture was passed through a column of ion-exchange resin (3 g) with MeOH (60 ml). The combined MeOH soln was concentrated to give a brown liquid. Purification by column chromatography with $CHCl_3$ and subsequent distillation afforded 15 (0.98 g, 77%), b.p. 181–182° (4 mmHg); IR 1660, 1618 cm^{-1}; NMR 0.80 (d, J = 7.0) and 1.04 (d, J = 7.0) (total 3H), 1.95 (3H, br.s), 3.8–4.1 (4H, complex m), 4.84 (t, J = 4.5) and 4.88 (t, J = 4.5) (total 1H), 5.94 (br.s) and 5.96 (br.s) (total 1H); Mass 252 (M^+). [Found: C, 70.98; H, 9.48. $C_{15}H_{24}O_3$ requires: C, 71.39; H, 9.59%. High resolution mass spectrum. Found: 252.1716 (M^+). $C_{15}H_{24}O_3$ requires 252.1725].

Keto aldehyde 16. A soln of 15 (2.3 g, 9.1 mmol) in AcOH (34 ml)–H_2O (17 ml) was stirred at 90° for 4 hr, concentrated and H_2O (70 ml)–benzene (20 ml) added. The aqueous phase of the mixture was made basic (pH 8) by adding $NaHCO_3$. The benzene layer was separated and the aqueous phase further extracted with benzene (4 × 20 ml). The combined benzene extracts were dried and concentrated to give 16 (1.86 g, 98%), which was directly used for the next step without further purification; IR 2740, 1730, 1661, 1618 cm^{-1}; NMR 0.80 (d, J = 7.0) and 1.05 (d, J = 7.0) (total 3H), 1.98 (3H, br.s), 5.94 (1H, br.s), 9.74 (t, J = 2.0) and 9.77 (t, J = 2.0) (total 1H); Mass 208 (M^+). [High resolution mass spectrum. Found: 208.1484 (M^+). $C_{13}H_{20}O_2$ requires: 208.1463].

Cyclization of keto aldehyde 16. To a soln of 16 (274 mg, 1.32 mmol) in t-BuOH (9.8 ml) was added a soln (7.30 ml, 1.88 mmol) of 0.26 M t-BuOK in t-BuOH under N_2. The soln was stirred at room temp. for 30 min, ion-exchange resin (3.5 g) added, and diluted with MeOH (4 ml). After 10 min, the mixture was passed through a column of ion-exchange resin (2 g) with MeOH (30 ml). Concentration of the soln gave a brown oil, which was separated by plc [$CHCl_3$–EtOAc (1:1)] affording a crystalline mixture of 17 and 18, and a colorless oil 19. Recrystallization of a mixture of 17 and 18 from n-hexane–benzene afforded pure 17 (55 mg, 20%). From the mother liquor crystals of 17 and 18 (*ca.* 1:1) were obtained (9.5 mg, 6%), the ratio being determined by NMR. Purification of 19 was repeated by plc to give pure 19 (16 mg, 6%). 17, m.p. 165–167° (sealed tube); IR 3630, 3400, 1720 cm^{-1}; NMR 0.81 (3H, d, J = 7.0), 1.04 (3H, s), 3.94 (1H, dd, J = 4.0, 2.0); Mass 208 (M^+). (Found: C, 74.77; H, 9.56. $C_{13}H_{20}O_2$ requires: C, 74.96; H, 9.68%). Mixture (1:1) of 17 and 18; NMR 0.81 (d, J = 7.0) and 1.14 (d, J = 7.0) (total 3H), 1.04(s) and 1.13(s) (total 3H), 3.94 (dd, J = 4.0, 2.0) and 4.12 (dd, J = 4.0, 2.0) (total 1H). 19; IR 3640, 3460, 1660, 1616 cm^{-1}; NMR 0.85 (3H, d, J = 7.0), 1.97 (3H, d, J = 1.0), 3.80 (1H, dd, J = 10.0, 4.0), 6.13 (1H, q, J = 1.0); Mass 208 (M^+).

Thioacetal 20. A soln of 17 (100 mg, 0.48 mmol) and BF_3·OEt_2 (0.12 ml) in ethanedithiol (5 ml) was stirred at room temp. for 20 min and diluted with a sat. $NaHCO_3$aq. The mixture was extracted with $CHCl_3$ (4 × 10 ml). The $CHCl_3$ extracts were dried and concentrated. The residue dissolved in toluene was concentrated for removal of ethanedithiol to give an oil. Purification by plc [$CHCl_3$–EtOAc (10:1)] afforded 20 (137 mg, *ca.* 100%) as a colorless oil; IR 3560, 3400 cm^{-1}; NMR 0.77 (3H, d, J = 7.0), 0.88 (3H, s), 3.2–3.5 (4H, m, A_2B_2 type), 3.80 (1H, dd, J = 4.0, 2.0); Mass 284 (M^+). [High resolution mass spectrum. Found: 284.1246 (M^+). $C_{15}H_{24}OS_2$ requires: 284.1268].

Alcohol 21. (a) To a soln of 20 (137 mg, 0.48 mmol) in EtOH (16 ml) was added W-2 Raney nickel (*ca.* 2.6 g). The suspension was refluxed for 30 min, cooled, and filtered. Evaporation of the filtrate gave 21 (92 mg, 98%) as a colorless oil which was homogeneous on tlc analysis; IR 3660, 3450 cm^{-1}; NMR 0.76 (3H, d, J = 6.0), 0.86 (3H, s), 3.65 (1H, br.s); Mass 194 (M^+). [High resolution mass spectrum. Found: 194.1675 (M^+). $C_{13}H_{22}O$ requires: 194.1671]. (b) To a stirred soln of 17 (7 mg) in ether saturated with HCl gas was added at −20° activated Zn powder (150 mg) in portions. The mixture was stirred at 0° for 2 hr and during this period additional Zn (200 mg) was added in portions. The mixture was poured into ice-water (20 ml) and extracted with ether (4 × 30 ml). The ethereal extracts were dried and concentrated to give an oil, purification by plc [$CHCl_3$–EtOAc (7:1)] afforded 21 (5 mg, 76%).

Ketone 22. To a stirred soln of 21 (130 mg, 0.67 mmol) in pyridine (1.7 ml) was added a suspension of CrO_3 (153 mg, 1.53 mmol) in pyridine (3.8 ml). The mixture was stirred at room temp. for 12 hr and diluted with ether (60 ml). The ppts were filtered off and washed with 1N HCl (5 × 10 ml) and H_2O (3 × 10 ml), dried, and concentrated to give an oil. Purification by plc ($CHCl_3$) afforded 22 (124 mg, 95%) as a colorless oil, which was

homogeneous on tlc analysis; IR 1712 cm^{-1}; NMR 0.80 (3H, d, J = 7.0), 1.60 (3H, s), 2.2–2.4 (2H, m); Mass 192 (M^+). [High resolution mass spectrum. Found: 192.1498 (M^+). $C_{13}H_{20}O$ requires: 192.1514].

(±)-Norcycloheliannone 23. To a stirred soln of i-Pr_2NH (0.18 ml, 1.27 mmol) in THF (2.1 ml) at −78° under N_2 was added slowly a soln (0.71 ml, 1.14 mmol) of 1.6 M n-BuLi in n-hexane. After 10 min, a soln of 22 (4.5 mg, 0.023 mmol) in THF (0.48 ml) was added dropwise to the LDA soln slowly. Then the temp. of the cooling bath was raised to −50° and the stirring was continued for 20 min. MeI (0.24 ml, 3.8 mmol) was added to the stirred soln, kept at −50° for 30 min, then NH_4Cl was added, and after 10 min H_2O (0.5 ml) was added. After the mixture reached to room temp. by removal of the cooling bath, the mixture was concentrated, H_2O (1 ml) added and extracted with benzene (3 × 5 ml). The benzene extracts were dried and concentrated giving an oil, purification by plc [$CHCl_3$–EtOAc (200:1)] afforded 23 (3.8 mg, 79%) as a colorless liquid; IR 1710 cm^{-1}; NMR 0.81 (3H, d, J = 7.0), 0.96 (3H, s), 0.98 (3H, s), 2.26 (1H, br.s); Mass 206 (M^+). [High resolution mass spectrum. Found: 206.1647 (M^+). $C_{14}H_{22}O$ requires: 206.1671]. A pure sample of 23 was secured by preparative GLC (120°).

(±)-Seychellene 2. To a stirred soln of 23 (15 mg, 0.073 mmol) in ether (0.42 ml) was added a soln (0.59 ml, 0.67 mmol) of 1.15 M MeLi in ether under N_2. The mixture was stirred at room temp. for 40 min, cooled (0°), H_2O (1 ml) added, and extracted with ether (4 × 10 ml). The ethereal extracts were washed with H_2O (3 ml), dried, and concentrated to give an alcohol (16 mg) as an oil; IR 3550, 3400 cm^{-1}; NMR 0.78 (3H, s), 0.82 (3H, s), 0.81 (3H, d, J = 6.0), 1.24 (3H, s); Mass 222 (M^+). To a stirred soln of the alcohol (16 mg, 0.073 mmol) in benzene (0.35 ml), pyridine (0.22 ml) was added under N_2 and a soln of $SOCl_2$ (7.1 μl, 0.10 mmol) in benzene (0.20 ml) at 0°. The soln was stirred at 0° for 30 min, and poured into ice-water (2 ml). The mixture was extracted with benzene (4 × 5 ml). The benzene extracts were washed with H_2O (2 × 3 ml), dried, and concentrated, giving an oil, purification by plc (n-hexane) afforded (±)-2 (15 mg, 99% from 23) as a colorless oil; IR 3060, 1637, 881 cm^{-1}; NMR 0.74 (3H, d, J = 7.0), 0.81 (3H, s), 0.95 (3H, s), 4.58 (1H, d, J = 2.0), 4.78 (1H, d, J = 2.0); Mass 204 (M^+). [High resolution mass spectrum. Found: 204.1863 (M^+). $C_{15}H_{24}$ requires: 204.1877]. A pure sample of (±)-2 was obtained by preparative GLC (110°).

α-Ketol 24. A soln of 23 (35 mg, 0.18 mmol) in THF (1.8 ml) was generated by the procedure described in the preparation of 23 using the following reagents; i-Pr_2NH (0.46 ml, 3.3 mmol) in THF (6.1 ml), 1.6 M n-BuLi (1.8 ml, 2.9 mmol) in n-hexane. To the cooled (−78°) soln of the enolate, MoO_5·Py·HMPA (350 mg, 0.81 mmol) was added at once under N_2. The mixture was stirred at −78° for 1 hr and H_2O (2 ml) added. The cooling bath was removed and the mixture allowed to reach room temp. The mixture was evaporated, H_2O (1 ml) added, and extracted with $CHCl_3$ (4 × 10 ml). The $CHCl_3$ extracts were dried and concentrated. Purification of the residue by plc [$CHCl_3$–EtOAc (100:1)] gave 24 (28 mg, 74%) as a colorless liquid; IR 3530, 3400, 1718, 1701 cm^{-1}; NMR 0.84 (3H, d, J = 7.0), 1.04 (3H, s); Mass 208 (M^+). [High resolution mass spectrum. Found: 208.1482 (M^+). $C_{13}H_{20}O_2$ requires: 208.1463].

Keto ether 25. To a stirred suspension of 24 (16 mg, 0.076 mmol) and NaH (*ca.* 50 mg, *ca.* 2 mmol) in DME (3.7 ml) MeI (0.30 ml, 4.70 mmol) was added under N_2. The mixture was stirred at room temp. for 1 hr, NH_4Cl added, and after 10 min concentrated. Water (2 ml) was added to the residue, and the mixture was extracted with $CHCl_3$ (4 × 7 ml). The $CHCl_3$ extracts were dried and concentrated giving an oil. Purification by plc ($CHCl_3$) gave 25 (14 mg, 83%) as a colorless liquid; IR 1707, 1104 cm^{-1}; NMR 0.80 (3H, d, J = 7.0), 0.88 (3H, s), 3.40 (3H, s); Mass 222 (M^+). [High resolution mass spectrum. Found: 222.1617 (M^+). $C_{14}H_{22}O_2$ requires: 222.1620].

Allyl ether 26. A soln (0.53 ml, 0.61 mmol) of 1.15 M MeLi in ether was added to a stirred soln of 25 (13.6 mg, 0.061 mmol) in ether (0.4 ml) under N_2 at room temp. The mixture was stirred for 20 min at room temp., diluted with H_2O (1 ml) under cooling, and extracted with ether (4 × 7 ml). The ethereal extracts were dried and concentrated to give an alcohol (15 mg). To a stirred soln of the alcohol (15 mg, 0.06 mmol) in benzene (0.6 ml) and pyridine (0.4 ml), a soln of $SOCl_2$ (11.6 μl, 0.16 mmol) in benzene (0.3 ml) was added under N_2 at −5°. The mixture was stirred at −5° for 30 min, poured into ice-water (2 ml), and extracted with benzene (4 × 7 ml). The benzene extracts were washed with H_2O (2 × 3 ml), dried, and concentrated, giving an oil. Purification by plc ($CHCl_3$) afforded 26 (9.3 mg, 67%) as a colorless oil; IR 3030, 1637, 1084, 905 cm^{-1}; NMR 0.76 (3H, d, J = 7.0), 0.96 (3H, s), 3.31 (3H, s), 4.88 (1H, d, J = 1.5), 5.07 (1H, d, J = 1.5); Mass 220 (M^+). [High resolution mass spectrum. Found: 220.1835 (M^+). $C_{15}H_{24}O$ requires: 220.1827].

Cyclopropane derivative 28. Into a mixture of 26 (8 mg, 0.036 mmol) and bis(N-α-phenethylsalicylaldiminato)copper(II) (10 mg) in n-hexane (0.25 ml)–benzene (0.25 ml), CH_2N_2 using N_2 as a carrier gas was passed at 16° for 1.5 hr. During the reaction an additional amount (10 mg) of the copper chelate reagent was added. The mixture was diluted with n-hexane and filtered. An oil obtained on evaporation of the filtrate was separated by plc ($CHCl_3$) and subsequently by preparative glc (160°), affording 28 (2.4 mg, 47% based on reacted 26) as a colorless liquid and 26 (3.2 mg, 40% recovery). 28; IR 3055 (cyclopropane CH_2), 1090, 1080, 1018 cm^{-1}; NMR 0.3–0.9 (4H, complex m), 0.82 (3H, d, J = 6.0), 0.98 (3H, s), 3.26 (3H, s); Mass 234 (M^+). [High resolution mass spectrum. Found: 234.1960 (M^+). $C_{16}H_{26}O$ requires: 234.1984].

(±)-Patchouli alcohol methyl ether 29. A mixture of 28 (3 mg, 0.013 mmol), NaOAc (15 mg, 0.18 mmol), and PtO_2 (15 mg) in AcOH (0.3 ml) was stirred at room temp. for 40 min under H_2, diluted with EtOAc (2 ml), and filtered. The residue obtained on evaporation of the filtrate was treated with ethereal CH_2N_2. The soln was concentrated to give an oil, purification by plc ($CHCl_3$) afforded 29 (2.5 mg, 83%), m.p. 62–64°; IR 1111, 1070 cm^{-1}; NMR 0.79 (3H, d, J = 6.0), 0.82 (3H, s), 1.15 (2 × 3H, s), 3.21 (3H, s); Mass 236 (M^+). [High resolution mass spectrum. Found: 236.2150 (M^+). $C_{16}H_{28}O$ requires: 236.2140].

(±)-Patchouli alcohol 1. To a stirred mixture of CrO_3 (10 mg, 0.10 mmol) in AcOH (0.07 ml) was added a soln of 29 (2.5 mg, 0.01 mmol) in CH_2Cl_2 (0.1 ml). The mixture was stirred at room temp. for 40 min, diluted with ether (1 ml), and filtered. The filtrate was poured into a cooled (0°) soln (0.3 ml) of 3N KOH. The mixture was separated and the aqueous phase was extracted with ether (3 × 10 ml). The organic extracts were washed with sat NaCl$_{aq}$ in the presence of a small amount of solid $NaHSO_3$, dried, and concentrated. The residue was treated with ethereal CH_2N_2. The soln was concentrated to give an oil, purification by plc (benzene) afforded (±)-1 (*ca.* 1.3 mg, *ca.* 55%). Further purification by GLC (180°) gave crystalline (±)-1, m.p. 37–38°. [High resolution mass spectrum. Found: 222.1992 (M^+). $C_{15}H_{26}O$ requires: 222.1983].

Acknowledgements—We are grateful to Prof. Y. Hirata for his encouragement, Prof. A. Yoshikoshi for providing us with the IR and NMR spectral data of 23, and to Profs. R. Noyori and H. Takaya for generous supply of the copper chelate reagent. We wish to thank Dr. I. Sakai and his associates (Toray Industries, Inc., Analysis Center) for obtaining high resolution mass spectra.

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