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A Synthesis of (±)-epi-Seychellene

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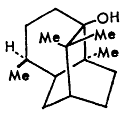
Synopsis. Starting from a mixture of two diastereomeric ketols, (±)-seychellene and (±)-epi-seychellene were synthesized in six steps.

Patchouli alcohol (**1**)[1] and seychellene (**2**),[2] constituents of patchouli oil, contain commonly the novel carbon framework, a tricyclo[5.3.1.0^{3,8}]undecane skeleton, and their synthetic studies have actively been carried out.[3]

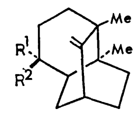
In the previous investigation[4] we reported a method of constructing a tricyclo[5.3.1.0^{3,8}]undecane skeleton in one step by intramolecular cyclization of a conjugated cyclohexenone derivative. We have recently made a total synthesis of patchouli alcohol **1** and seychellene **2** in racemic form utilizing this method of cyclization:[5] a 1:1 mixture of the diastereomeric α,β-enones (**4**) was cyclized with potassium *t*-butoxide in *t*-butyl alcohol to afford two ketols, (**5**) (23%) and (**6**) (3%), only the former being obtained in pure form.[5] These ketols, **5** and **6**, were deduced to be diastereomers regarding C-4. Stereochemical assignments of **5** and **6** were made by consideration of the steric course of cyclization[5] and confirmed by the synthesis of the sesquiterpenes of defined structures, **1** and **2**, employing the major isomer **5**.[5]

In this note a synthesis of (±)-epi-seychellene (**3**) together with a synthesis of (±)-**2** is described, starting from a mixture of two diastereomers, **5** and **6**, and this result provides an additional evidence for the validity of the assigned stereochemistry of **5** and **6**. A synthesis of (±)-epi-seychellene was previously carried out by Fráter.[3d]

The mixture of the two ketols, **5** and **6**, was converted to a mixture of two thioacetals, (**7**) and (**9**), under the standard conditions, which was desulfurized with W-2 Raney nickel in ethanol under reflux, affording a mixture of two diastereomeric alcohols, (**8**) and (**10**) in 99% overall yield. On oxidation with chromium trioxide in pyridine, a mixture of **8** and **10** gave a mixture of the corresponding ketones, (**11**) and (**13**) in 95% yield. Treatment of a mixture of the two ketones, **11** and **13** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by reaction with methyl iodide at −50 °C afforded a mixture of two ketones, (**12**) and (**14**) in 93% yield. The mixture was separated by preparative gas chromatography (GC) to give (±)-norseychellanone **12** (liquid) identified by spectral (IR and NMR) data of the authentic specimen and the crystalline ketone **14**, mp 145—146 °C. Reaction of the mixture of **12** and **14** with methyllithium in ether and subsequent dehydration with thionyl chloride in pyridine–benzene produced a mixture of two olefins in 85% yield, which was purified by preparative GC to give (±)-seychellene **2** (liquid) and (±)-epi-seychellene **3**, mp 145—147 °C. The spectral (IR and NMR) data of the latter was in agreement with those[3d] of (±)-epi-seychellene reported.

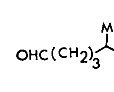


1

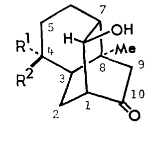


2: R^1=H, R^2=Me

3: R^1=Me, R^2=H

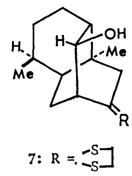


4



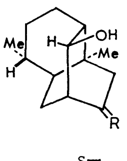
5: R^1=H, R^2=Me

6: R^1=Me, R^2=H



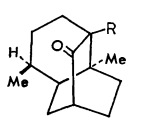
7: R = $\langle{}^{S}_{S}\rangle$

8: R = H_2



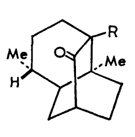
9: R = $\langle{}^{S}_{S}\rangle$

10: R = H_2



11: R = H

12: R = Me



13: R = H

14: R = Me

Experimental

Melting points were uncorrected. IR spectra ($CHCl_3$) were recorded with JASCO Model IRS and JASCO DS-402G instruments. NMR spectra ($CDCl_3$) were obtained on a Varian HA-100D spectrometer using TMS as an internal standard. Low resolution and high resolution mass spectra were determined on Hitachi RMU-6C and JEOLCO GMS-01SG mass spectrometers, respectively. A Varian 1820-4 gas chromatograph was used for GC (5 ft. ×0.25 in. column packed with 5% SE-30 on Celite 545; helium as the carrier gas). For TLC silica gel 60 F_{254} and 60 PF_{254} (E. Merck, A. G., Germany) were used. Organic solutions were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated by a vacuum rotary evaporator.

Alcohols, 8 and 10. A solution of the 1 : 1 mixture of **5** and **6**[5] (200 mg) and $BF_3\cdot OEt_2$ (0.24 ml, distilled from CaH_2) in 1,2-ethanedithiol (10 ml) was stirred at room temperature for 20 min and diluted with a saturated $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$ (4×20 ml). The residue obtained on evaporation of the $CHCl_3$ extracts was dissolved in toluene and the solution was concentrated for complete removal of 1,2-ethanedithiol. Purification of the residue by preparative TLC ($CHCl_3$–EtOAc, 10:1) gave a mixture of thioacetals, **7** and **9** (273 mg) as a colorless liquid: IR 3520, 3360 cm^{-1}; NMR (δ) 0.77 and 1.10 (total 3H, d each, *J*=7.0 Hz), 0.88 and 0.96 (total 3H, s each), 2.9—3.6 (4H, complex m), 3.78 and 3.98 (total 1H, m each). To a solution of the mixture of **7** and **9** (273 mg) in EtOH (32 ml) was added W-2 Raney nickel (*ca.* 5.2 g). The suspension was refluxed for 30 min and filtered. The filtrate was evaporated, giving a mixture of alcohols, **9** and **10** (185 mg, 99% from the ketols, **5** and **6**) as a colorless liquid: IR 3550, 3400 cm^{-1}; NMR (δ) 0.76 and 1.10 (total 3H, d each, *J*=6.0 Hz), 0.86 and 0.95 (total 3H, s each), 3.65 and 3.73 (total 1H, dd each, *J*=2.0, 4.0 Hz); MS 194(M^+). Found: *m/e* 194.1666. Calcd for $C_{13}H_{22}O$:

194.1671.

*Ketones, **11** and **13**.* A suspension of CrO_3 (230 mg) in dry pyridine (5.6 ml, distilled from BaO) was added to a solution of the mixture of **8** and **10** (190 mg) in dry pyridine (2.5 ml). The mixture was stirred at room temperature for 6 h and diluted with ether (50 ml). The precipitates were filtered and washed with ether (40 ml). The combined filtrates were washed with 1M HCl (5×10 ml) and H_2O (3×10 ml), dried, and concentrated. The residue was purified by preparative TLC ($CHCl_3$), affording a mixture of **11** and **13** (181 mg, 95%) as a colorless liquid: IR 1715 cm^{-1}; NMR (δ) 0.80 and 1.17 (total 3H, d each, $J=7.0$ Hz), 1.10 and 1.11 (total 3H, s each); MS 192 (M^+). Found: *m/e* 192.1522. Calcd for $C_{13}H_{20}O$: 192.1514.

*(±)-Norseychellanone **12** and Ketone **14**.* To a stirred solution of *i*-Pr_2NH (0.66 ml, distilled from NaH) in dry THF (8.7 ml, distilled from potassium–benzophenone ketyl under nitrogen) at −78 °C was added under nitrogen a solution (2.6 ml) of 1.6M BuLi in hexane. A solution of the mixture of **11** and **13** (53 mg) in dry THF (2.6 ml) was added dropwise over a period of 20 min to the above LDA solution at −78 °C. The mixture was stirred at −50 °C for 20 min. Then MeI (0.87 ml, distilled from $CaCl_2$) was added at −50 °C. After 30 min NH_4Cl was added. The mixture was diluted with H_2O (1 ml). The cooling bath was removed. After 5 min the mixture was concentrated, diluted with H_2O (2 ml), and extracted with benzene (3×10 ml). The benzene extracts were dried and concentrated. The residue was purified by preparative TLC ($CHCl_3$–EtOAc, 200:1), giving a mixture of **12** and **14** (53 mg, 93%) as a colorless liquid. The mixture was separated by preparative GC (120 °C, 160 ml/min) to give (±)-**12** (retention time 14 min) and **14** (retention time 16 min). **14**: mp 145—146 °C (sealed tube); IR 1710 cm^{-1}; NMR (δ) 0.98 (3H, s), 1.04 (3H, s), 1.15 (3H, d, $J=7.5$ Hz), 2.31 (1H, m); MS 206 (M^+). Found: *m/e* 206.1690. Calcd for $C_{14}H_{22}O$: 206.1671.

*(±)-Seychellene **2** and (±)-epi-Seychellene **3**.* To a stirred solution of the mixture of **12** and **14** (10 mg) in dry ether (0.07 ml, distilled from Na) was added a solution (0.40 ml) of 1.15 M MeLi in ether under nitrogen. The mixture was stirred at room temperature for 4 h. Water (1 ml) was added and the mixture extracted with ether (4×10 ml). The ethereal extracts were dried and concentrated. The residue (10.8 mg) was dissolved in dry benzene (0.23 ml, distilled from Na)–dry pyridine (0.15 ml). To the cooled (0 °C) solution was added $SOCl_2$ (4.7 μl, freshly distilled) in dry benzene (0.14 ml). The mixture was stirred for 35 min at 0 °C, poured into ice–water (2 ml), and extracted with benzene (4×10 ml). The benzene extracts were dried and concentrated. The residue was purified by preparative TLC (pentane), affording a mixture of **2** and **3** as a colorless oil (8.5 mg, 85%). Separation of the mixture was made by preparative GC (110 °C, 150 ml/min) to give (±)-**2** (retention time 15 min) and (±)-**3** (retention time 17 min). (±)-**3**: mp 145—147 °C (sealed tube); IR (neat) 3060, 3000(sh), 2920, 2860, 1640, 1460, 1380, 1370, 1110, 1102, 1060, 1020, 980, 970 945, 888(strong) cm^{-1}; NMR (δ) 0.93 (3H, s), 0.96 (3H, s), 1.08 (3H, d, $J=7.5$ Hz), 4.61 (1H, d, $J=1.5$ Hz), 4.81 (1H, d, $J=1.5$ Hz); MS 204 (M^+). Found: *m/e* 204.1883. Calcd for $C_{15}H_{24}$: 204.1878.

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