

TOTAL SYNTHESIS OF (±)-CYCLOSEYCHELLENE, A NOVEL TETRACYCLIC SESQUITERPENE

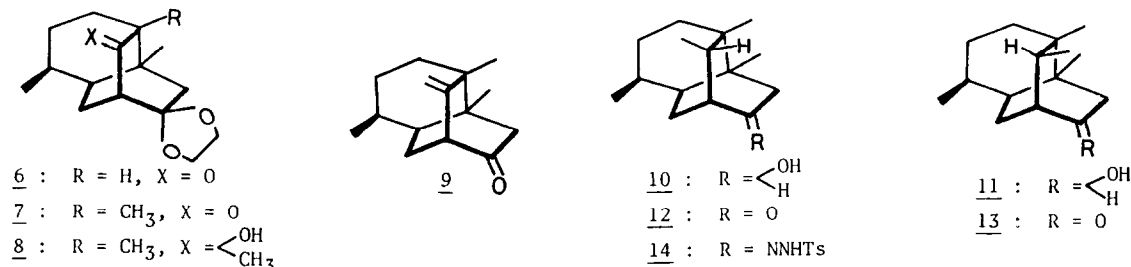
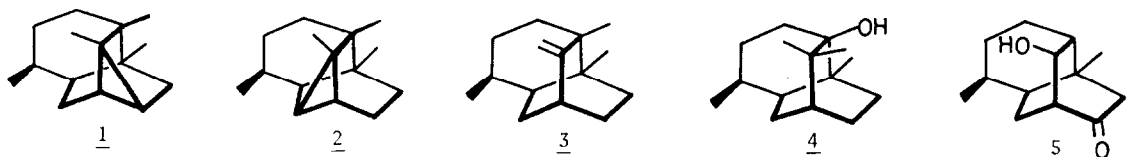
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Abstract. The first total synthesis of (±)-cycloseychellene (1), a novel tetracyclic sesquiterpene with a cyclopropane ring isolated from *Pogostemon cablin* Benth. is described.

Cycloseychellene, a novel tetracyclic sesquiterpene with a cyclopropane ring was isolated from the essential oil of *Pogostemon cablin* Benth. (Patchouli oil) as a minor component.¹ The structure of cycloseychellene was originally assigned as the formula 2 on the basis of ¹H-NMR spectral data, co-occurrence with seychellene (3), and equilibration with 3.¹ Recently Welch and coworkers have synthesized the hydrocarbon possessing the structure 2 reported for cycloseychellene.² However, the spectral and chromatographic properties of the synthetic hydrocarbon 2 were significantly different from those of natural cycloseychellene.^{2,3} Based on reinvestigation of the 400 MHz ¹H-NMR spectrum of natural cycloseychellene Welch and coworkers revised the structure of cycloseychellene to be the formula 1.³ Herein we wish to describe the first, unambiguous synthesis of (±)-cycloseychellene having the structure 1, which has confirmed the correctness of the revised structure 1 for cycloseychellene presented by Welch.

We have chosen the known tricyclic ketone 5 as starting material, which was previously employed in our synthesis of (±)-seychellene (3) and (±)-patchouli alcohol (4).⁴ Acetalization of the ketone 5 (ethylene glycol-p-TsOH, benzene, reflux, 2.5 h) and subsequent oxidation (PCC, CH₂Cl₂-Py, room temp., 3.5 h) afforded the keto acetal 6^{5a} (colorless oil, 89% overall yield after purification⁶). Introduction of the methyl group into the bridgehead position⁴ of 6 was achieved by generating the corresponding enolate with LDA (THF, -78 °C, 1 h)



followed by quenching with CH_3I (-78°C , 2 h) to give the ketone 7^{5b} (colorless oil, 93%). Treatment of 7 with excess CH_3Li (ether, room temp., 3.5 h) afforded the alcohol 8^{5a,7} [mp $89.5\text{--}91^\circ$ (pentane), 94%] as a single product. Deacetalization of 8 [$\text{AcOH-H}_2\text{O-THF}$ (1:1:2), 50°C , 3 h] and subsequent dehydration ($\text{SOCl}_2\text{-Py}$, -78°C , 45 min.) gave the enone 9^{5b,8} (colorless oil, 83% overall yield). Reduction of 9 with NaBH_4 (MeOH, room temp., 40 min.) followed by catalytic hydrogenation (PtO_2 , EtOAc, room temp., 2 h) gave a 3:1 mixture of the alcohols, 10^{5a,9} (colorless oil, 60% after purification⁶) and 11^{5a,9} (colorless oil, 20% after purification⁶), which was readily separated by preparative TLC. Individual oxidation of 10 and 11 (PCC, CH_2Cl_2 , room temp., 40 min.) afforded the ketones, 12^{5b,10} (colorless oil, ~100%) and 13^{5b} (colorless oil, ~100%), respectively. The stereochemistry of the newly formed secondary methyl group in 12 was established by $^1\text{H-NMR}$ spectral analysis of both isomers, 12 and 13 in the presence of the shift reagent $\text{Eu}(\text{fod})_3$, and successive conversion of 12 to cycloseychellene (1). Final transformation of the desired ketone 12 to (\pm)-cycloseychellene (1) was effected as follows: the ketone 12 was quantitatively converted (TsNHNH_2 , benzene, reflux, 2.5 h) to the corresponding tosylhydrazone 14^{5a} (amorphous powder), treatment of which with NaH^{11} (DMF, 150°C , 1 h) afforded (\pm)-cycloseychellene (1)^{5a} (colorless liquid) in 34% yield after purification by preparative GLC.¹² The 400 MHz $^1\text{H-NMR}$, IR, and mass spectra of synthetic 1 was identical with those of natural cycloseychellene. Thus the structure of cycloseychellene has been confirmed as the formula 1 by the synthesis described above.

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5. a) Satisfactory IR, $^1\text{H-NMR}$, mass, and exact mass spectral data were obtained for purified, chromatographically homogeneous sample.
b) Satisfactory IR, $^1\text{H-NMR}$, and mass spectral data were obtained for this compound, which was homogeneous on TLC and used for next reaction without further purification.
6. By preparative TLC on silica gel with *n*-hexane-ether (1:1).
7. Stereochemistry of the hydroxyl group was not determined.
8. This compound could also be prepared from 8 by changing the reaction sequence (i. dehydration; ii. deacetalization) in lower yield.
9. Each of the alcohols, 10 and 11 was proved to be an inseparable mixture of two diastereomers as to the hydroxyl group.
10. Although direct conversion of the enone 9 to the ketone 12 was desirable, catalytic hydrogenation of 9 under various conditions gave exclusively the undesired ketone 11. These results led us to choose the reaction sequence described in the text (9 \rightarrow 10 \rightarrow 12).
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12. Column conditions: a column of 6 mm x 1.5 m, packed with 5% SE-30, 115°C , flow rate (He gas) 136 ml/min. Retention time was 10.2 min. under these conditions.

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