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THE TOTAL SYNTHESIS OF (±)-SEYCHELLENE

K.J. Schmalzl and R.N. Mirrington

Department of Organic Chemistry, University of W. Australia, Nedlands, W.A.

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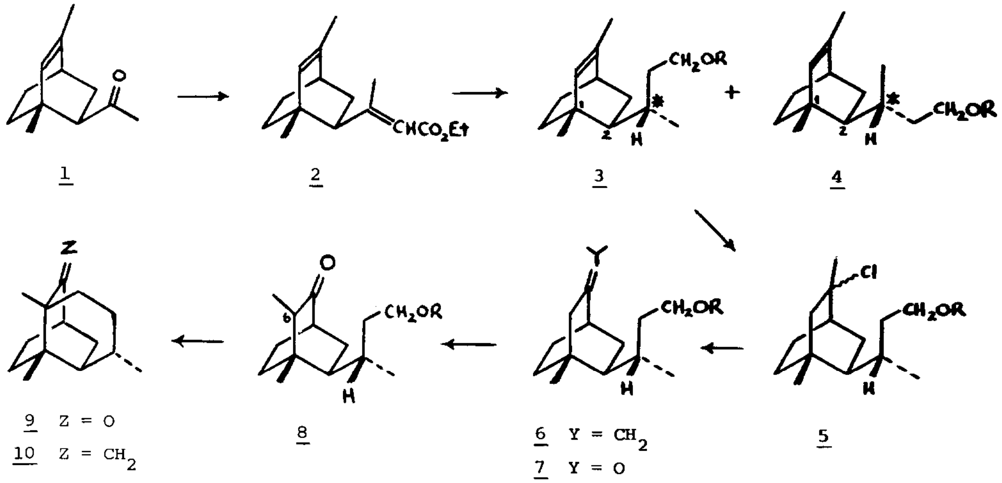
The sesquiterpene hydrocarbon (-)-seychellene, isolated[1,2] from the leaves of *Pogostemon patchouli*, has been assigned[2] the structure and absolute stereochemistry depicted in 10. We now report a total synthesis of (±)-seychellene via bicyclo[2.2.2]octene intermediates as shown diagrammatically below. Our synthetic plan essentially involved the modification of the olefinic bridge in 3 to a compound of type 8 which, it was anticipated, would undergo intramolecular alkylation to norseychellanone 9.

The mixture of esters 2 (trans:cis = 3:1), obtained by the modified[3] Reformatsky reaction on the known ketone 1[4], was reduced with lithium/ammonia/ethanol/ether[5] in 94% crude yield to a mixture (4:1) of isomeric alcohols 3a and 4a which could be separated by column chromatography on alumina. The oily 3a, thus isolated in 60% overall yield from 2, was characterised as the trityl ether 3c[6], m.p. 105-106° (EtOH); pmr:broad s at 5.47δ (olefinic). The configurations of 3a and 4a were assigned from their pmr spectra which showed distinctly different chemical shifts for the C* methyl doublet but were very similar in other respects. The



1 2 3 4

9 Z = O
10 Z = CH$_2$

8

6 Y = CH$_2$
7 Y = O

5

a R = H b R = Ac c R = C(Ph)$_3$ d R = Ts reasonable assumption that the side chain at C_2 will adopt a preferred conformation in which the 1,3-interactions with the C_1-methyl group are minimised (see diagrams), leads to the prediction[7] that the C*-methyl group in 4a will be more shielded by the olefinic bridge than the C*-methyl group in 3a. Since the minor isomer showed a doublet at 0.55δ, compared with a doublet at 0.78δ for the major isomer, the latter is consequently assigned structure 3a[8].

Acetylation of 3a (acetic anhydride/pyridine) gave 3b which was hydrochlorinated[9] to 5b. Treatment of this with ethanolic sodium ethoxide[10] (reflux, 0.5 hr.) afforded a mixture (3:2) of 6a and 3a, which were cleanly separated by chromatography on 10% silver nitrate/alumina to give 6a in 38% overall yield from 3a [50% based on unrecovered 3a]. The oily alcohol 6a was characterised as the trityl ether 6c, m.p. 104-105° (EtOH) [pmr:one proton multiplets at 4.49 and 4.66δ (exocyclic methylene)] which also served to protect the alcohol function in the next two steps of the sequence.

Oxidative cleavage of the exocyclic methylene group in 6c was achieved smoothly with an aqueous dioxane solution of sodium metaperiodate containing a catalytic amount of osmium tetroxide[11] to give 7c, m.p. 176° (EtOAc), ir (CCl_4)1720 cm^{-1}, in 75% yield from 6c. Ketone 7c was monomethylated[12] to 8c (configuration at C_6 not determined) using potassium triphenylmethide and methyl iodide, and the trityl ether removed by hydrogenolysis (3 atmospheres) with 5% Pd/C in ethanol to give alcohol 8a, which was isolated by chromatography on alumina in 80% yield from 7c.

The alcohol 8a afforded a tosylate 8d which cyclized immediately when treated with potassium triphenylmethide in dimethoxyethane at room temperature to give the tricyclic ketone 9, isolated in 70% overall yield from 8a by chromatography on alumina. This oily ketone, homogeneous by vpc (5% Ucon on Chromosorb W), showed spectroscopic properties (pmr, ir, ms) identical with those of authentic (-)-norseychellanone.

The above sequence constitutes a total synthesis of (±)-seychellene 10, because the preparation of this racemic hydrocarbon from (±)-9 (synthesised by quite a different route) has been recently described[13].

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References and Footnotes

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6. All new compounds showed spectral properties in complete agreement with structures proposed. Satisfactory analytical data were obtained for compounds whose melting points are recorded.
7. For a recent review on shielding by carbon-carbon double bonds see L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 2nd Edition, 1969, pp.83-88.
8. The very remote possibility of the group at C_2 being *exo* - instead of *endo-* in the major isomer can be discounted, because of the subsequent reactions of this isomer leading to the successful cyclization **8d** → **9**.
9. S.P. Acharya and H.C. Brown, *Chem. Commun.*, 305 (1968).
10. Ethoxide was chosen because model experiments using triethylmethoxide[9] on the hydrochloride of **1** gave low proportions of the corresponding exocyclic olefin, whereas sodium ethoxide gave much more favourable results. Two further advantages of ethoxide in the present case with **5b** were its easy removal from the product and the concomitant transesterification of the protecting acetate function.
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