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STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-HYDROXY PATCHOULI ALCOHOL AND THE CORRESPONDING (±)-CARBOXYLIC ACID, METABOLITES OF PATCHOULI ALCOHOL, AND (±)-NORPATCHOULENOL

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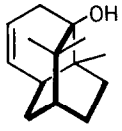
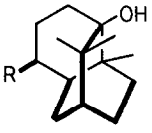
Abstract. The first total synthesis of (±)-hydroxy patchouli alcohol (3) and the corresponding (±)-carboxylic acid 4, the biooxidation products of patchouli alcohol (2) has been achieved. (±)-Norpatchoulenol (1) has also been synthesized by the biogenetic route via 3 and 4.

Norpatchoulenol (1), a minor component isolated from patchouli oil, has been known as the real odoriferous substance of this essential oil and belongs to a novel tricyclic norsesquiterpene alcohol of patchoulane type.[1]

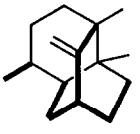
The biogenesis of norpatchoulenol (1) from patchouli alcohol (2), a major component of patchouli oil, as shown in Scheme I has been proposed by Ourisson based on the administration experiments of patchouli alcohol (2) to rabbits: in the experiments two biooxidation products were isolated, the structures of which were determined to be hydroxy patchouli alcohol (3) and the corresponding carboxylic acid 4, respectively.[2] Recently microbial conversion of patchouli alcohol (2) into hydroxy patchouli alcohol (3) has been reported.[3]



1
(norpatchoulenol)



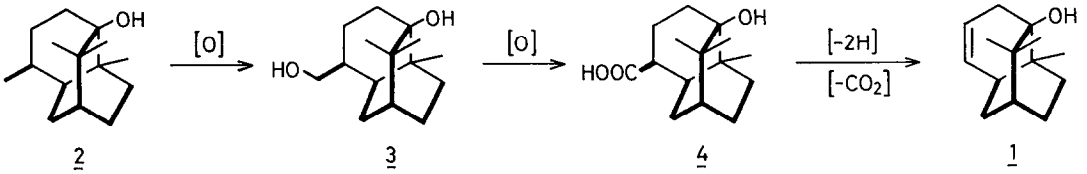
2 R = CH_3
(patchouli alcohol)
3 R = CH_2OH
4 R = COOH



5
(seychellene)

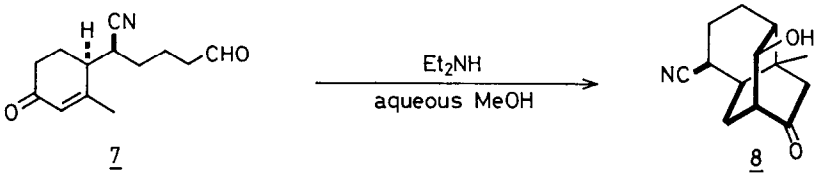
6
(cycloseychellene)

Scheme I



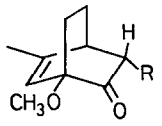
2 3 4 1

While several groups reported total[4] and partial[2] synthesis of norpatchoulenol (1), there seems to be no reports of the synthetic studies on the metabolites of patchouli alcohol (2), 3 and 4. During the past several years, we have been engaged in synthetic studies on the sesquiterpenoids of patchoulane type, culminating in the synthesis of patchouli alcohol (2),[5a] seychellene (5),[5a] and cycloseychellene (6).[5b] As part of our continuing studies in this field, we describe herein the first total synthesis of hydroxy patchouli alcohol (3) and the carboxylic acid 4 in racemic forms. Synthesis of racemic norpatchoulenol (1) from 3 in biogenetic manner is also described.



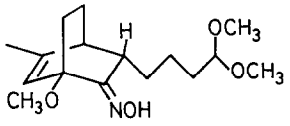
7 8

One of the key steps in the present synthesis is a double cyclization reaction of a conjugated cyclohexenone aldehyde 7 having desired stereochemistry at two asymmetric centers to give a tricyclic keto nitrile 8. The preparation of the compound 7 started from readily available 1-methoxy-5-methylbicyclo[2.2.1]oct-5-en-2-one (9).[6] Stereoselective alkylation of the lithium enolate derived from the ketone 9 (LDA, THF, -78 °C, 1 h) with 4-iodobutanal dimethyl acetal[7,12a] (THF-HMPA, -20 °C, 1 h) afforded the alkylated ketone 10[8] (colorless oil, 78%[9a]) as a single isomer. This high stereoselectivity in the alkylation may be due to kinetic preference for approach of alkylating reagent from less hindered face of the bicyclic enone 9 (i.e., syn to the double bond in 9).[10] The alkylated ketone 10 was converted ($NH_2OH \cdot HCl$-AcONa, aqueous MeOH, reflux, 9 h) into the oxime 11[8] (colorless oil, 99%[9b]). Beckmann fragmentation reaction of the oxime 11 under the controlled conditions (TsCl-LiCl, Py, room temp., 7 h) yielded the conjugated enone 12[8] [mp 55-56 °C (cyclohexane), 54%[9b]],[11] which was deacetalized ($AcOH-H_2O$, 60 °C, 2.5 h) to provide the desired conjugated cyclohexenone aldehyde 7[12] (colorless oil).

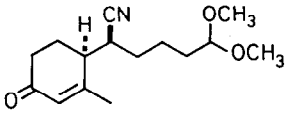


9 R = H

10 R = $(CH_2)_3CH(OCH_3)_2$

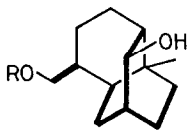


11



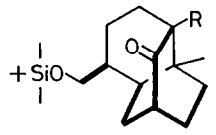
12

Double cyclization of the enone aldehyde 7 proceeded smoothly on treatment with Et_2NH (aqueous MeOH, 70 °C, 2 h) to give the tricyclic keto nitrile 8[8,13] [mp 205-206 °C ($CHCl_3$), 40% overall yield[9c] from 12]. Conversion of the keto nitrile 8 into the diol 13,[8] mp 128-130 °C (hexane-ether), was executed in 75% overall yield[14a] by four steps: (1) thioacetalization ($HSCH_2CH_2SH$, $BF_3 \cdot OEt_2$, room temp., 1.5 h); (2) reduction (DIBAL, toluene-CH_2Cl_2, -78 °C, 1.5 h); (3) reduction ($NaBH_4$, MeOH, room temp., 30 min); (4) desulfurization (Raney Ni, EtOH, reflux, 1 h). The primary hydroxyl group of the diol 13 was selectively protected (t-$BuMe_2Si$-



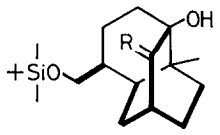
13 R = H

14 R = $SiMe_2{}^tBu$



15 R = H

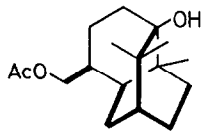
16 R = OH



17 R = $=CH_2$

18 R = 

19 R = 



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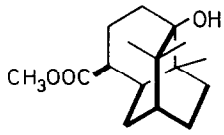

21

Cl, DMAP-Et_3N, CH_2Cl_2, room temp., 6 h)[15] to afford the silyl ether 14[8] (colorless oil, 99%[14b]), which upon PCC oxidation[16] (CH_2Cl_2, room temp., 45 min) provided the ketone 15[8] (amorphous solid, 87%[14c]). Bridgehead hydroxylation[5a] of the lithium enolate generated from the ketone 15 (LDA, THF, -78 °C, 1 h) with MoO_5·Py·HMPA[17] (THF, -50 °C, 1 h) yielded the α-hydroxy ketone 16[8] [mp 76-79 °C (pentane), 73%[9d]], conversion of which into the olefin 17[8] [mp 65-66 °C (without recrystallization)] was effected in 77% overall yield[9d] by the Johnson's procedure[18]: (1) PhSO(=NMe)CH_2Li (THF, 0 °C, 1 h); (2) Al-Hg [THF-AcOH-H_2O (100:100:1),[19] room temp., 30 min]. Cyclopropanation[20] of the olefin 17 (CH_2N_2-CuOTf, benzene, room temp., 15 min) proceeded smoothly to give the cyclopropane derivative 18[8] (colorless oil, 79%[9d]), which was catalytically hydrogenated (PtO_2, AcONa-AcOH, room temp., 1.5 h) to furnish the gem-dimethyl alcohol 19[8] (colorless oil, 83%[9d]). Desilylation of the alcohol 19 (Bu_4NF, THF, room temp., 3 h) gave (±)-hydroxy patchouli alcohol (3)[8] [mp 132.5-133 °C (hexane-benzene), 97%[9e]], the ^1H NMR spectrum of which was identical to that of natural 3. In order to confirm the structure of synthetic 3, acetylation of 3 (Ac_2O-Py, room temp., 2.5 h) was made to give the corresponding acetate 20[8] (amorphous solid, 85%[14d]), the spectral (IR, ^1H NMR, and mass) properties of which were identical in all respects to those of the authentic sample derived from natural 3. PDC oxidation[21] of (±)-3 (DMF, room temp., 13 h) afforded the (±)-carboxylic acid 4[8] (colorless oil, 97%[9a]), another biooxidation product of patchouli alcohol (2). The ^1H NMR spectrum of the methyl ester 21[8] (colorless oil, 47%[14e]) derived from the (±)-carboxylic acid 4 (CH_2N_2) was identical to that of the authentic sample obtained from natural 4.

Finally, decarboxylative oxidation of (±)-4 under the Kochi's conditions[2,22] gave (±)-norpatchoulenol (1)[8] (amorphous solid, 33%[14f]). Sublimation (35 °C, 1 mmHg) afforded pure (±)-1, mp 155-160 °C (sealed tube).[23] The ^1H NMR, IR, and mass spectral properties of synthetic 1 were completely identical in all respects to those of natural 1.

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References and Notes

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7. Prepared conveniently from ethyl γ-bromobutyrate by the sequential reactions in 65% overall yield: (1) reduction (DIBAL, hexane-toluene, -100 °C, 1 h); (2) acetalization (MeOH, NH_4Cl, reflux, 10 min); (3) substitution reaction (NaI-$CaCO_3$, acetone, 25 °C, 1.5 h).

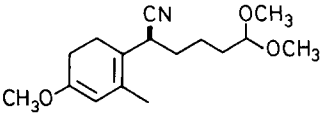
8. Satisfactory spectral (IR, ^1H NMR, and mass) and analytical (microanalyses or high resolution mass spectra) data were obtained for this compound.

9. Yield after purification by column chromatography on silica gel with: (a) 2:1 hexane-ether; (b) 1:1 hexane-EtOAc; (c) 6:1 benzene-acetone; (d) 10:1 hexane-ether; (e) 1:1 hexane-ether.

10. During our investigations the similar stereoselective alkylation of 9 was reported: Monti, S. A.; Dean, T. R. J. Org. Chem. 1982, 47, 2679.

11. The reaction under the same conditions in the absence of LiCl provided a considerable amount of an undesired product i[12a] (ca. 30%).

12. (a) IR, ^1H NMR, and mass spectral data of this compound were in accord with the structure assigned.
(b) This compound was used for the next reaction without further purification.



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13. Stereochemistry of the hydroxyl group was not determined.

14. Yield after purification by preparative TLC on silica gel with: (a) 2:1 benzene-acetone; (b) 3:1 benzene-acetone; (c) 1:1 hexane-ether; (d) 1:2 hexane-ether; (e) 2:1 hexane-ether; (f) 3:1 hexane-ether.

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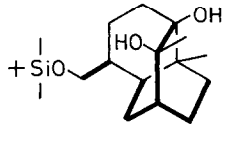
19. This reductive elimination reaction with Al-Hg depends heavily on the content of H_2O in the solvent system: e.g., the reaction in 15:5:1 THF-AcOH-H_2O gave an undesired product ii[12a] (stereochemistry of the newly formed tert-methyl group was not elucidated) in 34% yield together with 17 (31%).



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23. Lit.[4b] mp 135-141 °C (Conditions for measurement of mp were not described in ref. 4b).

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