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THE STEREOSPECIFIC SYNTHESIS OF CIS-β-BERGAMOTENE

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Recently Bhattacharyya et al. (1) isolated a new sesquiterpene hydrocarbon from Indian valerian root oil, which was named β-bergamotene, and assigned structure 1. On the basis of a comparison of the chemical shift of the quaternary methyl group in β-bergamotene with the chemical shifts of the methyl groups in β-pinene, the stereochemistry as depicted by 1 was favored over the alternative possibility 2. We wish to report an unambiguous synthesis of 1 which serves to eliminate this structure for the natural material, and which suggests that natural β-bergamotene does indeed have the trans structure 2.

Although the alcohol 3a may exist in two conformations, inspection of Dreiding models clearly suggests the conformer shown[a]. Measurement of the distance between the hydroxyl and syn-methyl groups in 3a revealed an ideal situation for effecting substitution at this methyl group by means of an intramolecular hydrogen abstraction by the alkoxy radical (3).

The alcohol 3a, synthesized from (-)-β-pinene by ozonolysis (4) followed by addition of methyl lithium (5), when treated with lead tetraacetate and iodine in cyclohexane during irradiation by a tungsten lamp (6), afforded the cyclic ether 4a as the only product in 80-92% yield. Similar results could be obtained under more convenient conditions by treatment of 3a with mercuric oxide and bromine in refluxing pentane (7). The structure of 4a was established on the basis of its physical data and chemical degradation to

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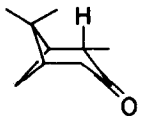
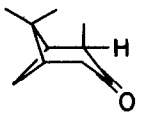
[a] Indeed, the nmr spectral properties of pinocamphone (A) and isopinocamphone (B) indicate that both isomers prefer the conformation with the keto function "down", even with the severe 1,3-diaxial interaction in B (2).



A



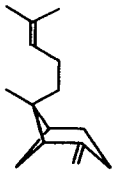
B

α-pinene (8). The cyclic ether 4a, b.p.$_{10.5}$ 64°, n_D^{26} 1.4702, and $[\alpha]_{5461}$ +51.7° (3.0, EtOH), showed λ_{max} 9.7 μ, molecular weight 152 (mass spec.) and nmr signals at τ 8.73 (6H, singlet), and an AB quartet at 6.41 (2H, J = 8.6 cps, δ/J = 5.6) (9).

Similar treatment (HgO, Br_2) of the alcohols 3b and 3c, prepared by lithium aluminum hydride reduction (10), and the Reformatsky reaction (11), respectively, of nopinone, gave the ethers 4b and 4c in nearly quantitative yields. Some nopinone was formed from 3b under these conditions, but no fragmentation products were observed in any of these reactions (12).

With the structures of the cyclic ethers firmly established, we turned our attention to the synthesis of the hydrocarbon 1. Mild hydrolysis of the ether-ester 4c gave the corresponding carboxylic acid 5, which on treatment with lead tetraacetate and sodium chloride in refluxing carbon tetrachloride (13) gave in 54% yield the β-chloroether 6 (b.p.$_{1.3}$ 65°, λ_{max} 9.7 and 13.3 μ, and nmr signals at τ 8.75 (3H, singlet), 8.55 (1H, doublet, J = 8.5 cps), 6.47 (2H, singlet), and 6.33 (AB quartet, J = 9.0 cps). The use of other modifications of the Hunsdiecker reaction was less successful, apparently because of the instability of the β-haloethers to the more strenuous conditions. The chloroether 6 could be opened cleanly to the alcohol 7a (b.p.$_{0.5}$ 55°, λ_{max} 2.95, 3.23, 6.10, 9.8, and 11.4 μ) in 48% yield on treatment with sodium in refluxing monoglyme (14). While 7a is completely stable to neutral and basic conditions, attempted chromatography or treatment with acids leads to complete conversion to the cyclic ether 4a. The crystalline tosylate 7b, m.p. 115°, could be formed under mild conditions and converted in quantitative yield to the iodide 8 [λ_{max} 3.20, 6.07, and 11.35 μ, and nmr signals at τ 8.63 (3H, singlet), 8.65 (1H, doublet, J = 9.5 cps), 7.02 (2H, AB quartet, J = 9.0), 5.23 (2H, broad)] on treatment with sodium iodide in refluxing acetone (15). Formation of the Grignard reagent of 8, followed by quenching in water, gave only the monocyclic dienes, limonene and p-mentha-1(7),8-diene, a reaction for which there is ample precedent (16), and which prevented the use of a coupling reaction for the synthesis of 1.

To evade this problem, the side-chain was constructed in a stepwise fashion as follows. Displacement of the iodide 8 by the ethylenediamine complex of lithium acetylide in DMSO afforded a 71% yield of the acetylenic olefin 9 [λ_{max} 3.00, 3.22, 4.71, 6.08, and 11.4 μ $[\alpha]_{5461}$ +41° (1.95, EtOH)], contaminated with small amounts of the isomer with the internal triple bond. Hydroboration (17) of 9 with disiamylborane, followed by oxidation,



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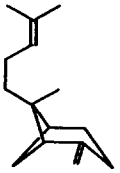

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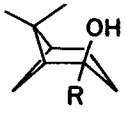
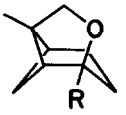


3a,R=Me
b,R=H
c,R=CH_2CO_2Et



4a,R=Me
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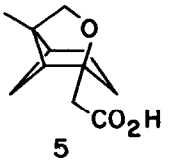

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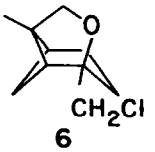

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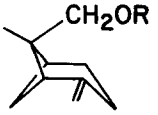
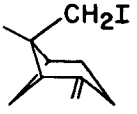


7a,R=H
b,R=Ts



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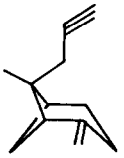

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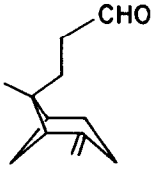

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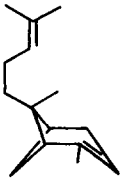

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afforded the unstable aldehyde 10 (b.p.$_{0.6}$ 95°, λ_{max} 3.25, 3.70, 5.80, 6.08, and 11.4 μ). Treatment of this aldehyde with triphenylisopropylidenephosphorane in tetrahydrofuran (18) gave the desired hydrocarbon 1 in 32% yield from the acetylene.

The hydrocarbon showed physical properties in excellent accord with the structure 1, but differed in many respects from the data reported for the natural isomer. Thus, synthetic 1 showed b.p.$_{0.5}$ 105-125° (bath), $[\alpha]_D^{25}$ +40.2° (1.74, $CHCl_3$), λ_{max} 3.22, 6.06, 7.25, 11.42, and 11.95 μ and nmr signals at τ 8.78 (3H, singlet, C_8), 8.60 (1H, doublet, J = 9.4 cps, endo-C_7H), 8.43 and 8.35 (both 3H, broad singlets, C_{14} and C_{15}), 5.36 and 5.43 (2H, exocyclic double bond), and 4.94 (1H, broad triplet, proton on trisubstituted double bond). The mass spectrum revealed a molecular weight of 204, as expected for a hydrocarbon with molecular formula $C_{15}H_{24}$.

The major difference between 1 and the natural isomer was observed in their nmr spectra. In the nmr spectrum published for β-bergamotene (1), the signal for the methyl group on the quaternary carbon appears at τ 9.05, while the corresponding signal in the synthetic material appears at τ 8.78. Since it is known that in both α- and β-pinene that methyl group which lies over the double bond is shifted to higher field relative to the other methyl group (19), these data suggest that the natural isomer of β-bergamotene has the configuration shown by structure 2. This would be consistent with the stereochemistry of α-bergamotene, which has been shown on the basis of similar nmr reasoning to possess structure 14 (20), and with copaene (21) and mustakone (22). We are now in the process of synthesizing the remaining isomers of these compounds in order to verify these structural assignments.

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