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SYNTHESIS OF ISOCLOVENE

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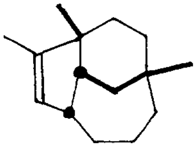
Summary: Isoclovene 1, a prominent transformation-rearrangement product of caryophyllene, has been synthesised as its racemate in 15 steps from the unsaturated nitrile 3.

The title compound is a member[1,2,3] of the still largely unexplored family of rearrangement and transformation products based on caryophyllene whose rich variety of molecular structure as so far revealed has in the past prompted much interest as regards structure elucidation, mechanism of formation and synthesis[4]. The suggested structure of 1, a main product (among at least twenty-five others[5]) of dehydration of 1-caryolanol 2 with phosphorus pentaoxide[1] or with polyphosphoric acid[6], has so far rested almost entirely on an X-ray analysis of a crystalline compound obtained from reaction with hydrogen chloride[7], and has given rise to speculation on its possible mode of formation[3,6]. Work on the actual chemistry of 1 has been limited[1,8]; and it has probably never been isolated in a pure state.

It seemed appropriate in this context to devise an unambiguous synthesis of 1. The following sequence does not itself include a carbocation rearrangement step; and incidentally does without protective groups *per se*.



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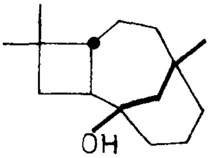

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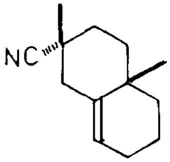

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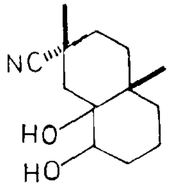
Hydroxylation (OsO_4 catal., N-methylmorpholine oxide, dioxan-tert. butanol-water, 20-40°, 2 d.[9]) of the unsaturated nitrile 3[10] gave in 85% yield the *cis*-glycol 4, m.p. 116-116.5°[11]. This was cleaved with lead tetraacetate in methanol - trichloroacetic acid[12] to give a keto-acetal which was converted (Li diisopropylamide, THF, -50°; Me_3SiCl) into the corresponding enol silyl ether 5. Internal cyclisation of this with $TiCl_4$[13] (CH_2Cl_2, -50 to -30°, 2 hr.) led to the formation of a single crystalline (m.p. 75-76°) bicyclo[4,3,1]decane derivative 6[11,14] in 74.5% overall yield from 4. Direct removal of the keto group in this proved impossible. Hydride reduction under forcing conditions ($NaBH_4$, tert. butanol-water, 60-65°, 5 hr.) gave a single alcohol epimer 7[11,14] in 92% yield. This was converted (NaH, CS_2, MeI, THF) into its S-methyl thioncarbonate whose hydrogenolysis[15] (Bu_3SnH, toluene, 110°) followed by oxidation of the total product (CrO_3-acetone[16]) led to the methoxy-nitrile 8[11]. Here the methyl ether was cleaved using propane-2-thiol[17] - $AlCl_3$[18], and to the resulting hydroxy-nitrile an excess of methyl-lithium was added. The resulting ketimine 9 was stable in pH 1 solution at room temperature, enabling removal of all byproducts at this stage. Hydrolysis at pH 2.5/85°, followed by oxidation of the hydroxyl group (CrO_3-acetone) gave the crystalline (m.p. 73.5-74°) diketone 10[11] (43% overall yield in six steps). Cyclisation to the unsaturated ketone 11[11] (KOH-MeOH) and subsequent catalytic hydrogenation (Pd/C) to give ketone 12[11] both proceeded in almost quantitative yield. Reaction of the latter with a large excess of methyl-lithium, followed by dehydration (DMSO, 155°, 24 hr.[19]) gave (±)-1 (more than 98% pure[5]).



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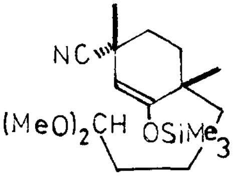

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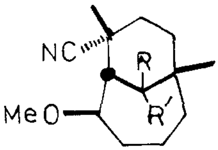
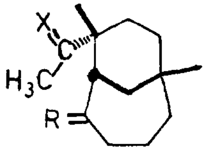
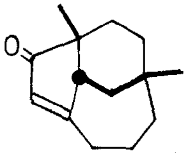


6: R, R': =O
7: R=OH, R'=H
8: R=R'=H



9: X=NH, R=OH, H
10: X=R=O



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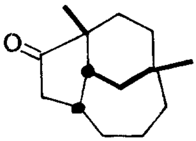
Alcohol 2 (from natural caryophyllene) was converted into a mixture of dehydration-rearrangement products (P_2O_5-H_3PO_4 1:1 w/w, 95-100°, 45 min.); this was fractionated (spinning-band column) and the fraction of b.p. 68-70°/0.5 mm subjected to preparative G.C. (SE-30 on Celite, 9.5 mm by 2 m, center cut only). The resulting naturally derived 1, though found gas-chromatographically identical[5] on co-injection with the above (±)-1, still contained impurities[5] which caused slight spectral (i.r., ^{1}H n.m.r.) differences between the two. Each was therefore subjected to hydroboration ($NaBH_4$, Me_2SO_4, THF, 0-20°, NaOH-H_2O_2), and the resulting alcohols purified by crystallisation and fractional sublimation, giving naturally derived 13, m.p. 131.5° (reported[8]: 131-132°) and (±)-13, m.p. 122-124°. The i.r. and ^{1}H n.m.r. spectra of these were completely identical.



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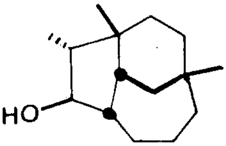

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References and Footnotes.

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5. Determined by capillary G.C. (Packard 427 instrument, 25 m column with Superox 0.1, column temp. 90°, gas speed 1 ml/min. We are grateful to Mr. Y. Klopstock for these measurements.
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11. All these intermediates gave satisfactory analytical (high resolution m.s.) and spectral (i.r., ^{1}H-n.m.r.) data.
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16. This served to convert the tin-sulphur byproducts into non-volatile sulphones and polymers, from which the desired product could be separated by simple distillation.
17. This gave better results than the corresponding primary thiol, presumably because of greater tendency on the part of a more hindered sulphur nucleophile to attack the less hindered carbon atom in the intermediate ether - $AlCl_3$ complex.
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