

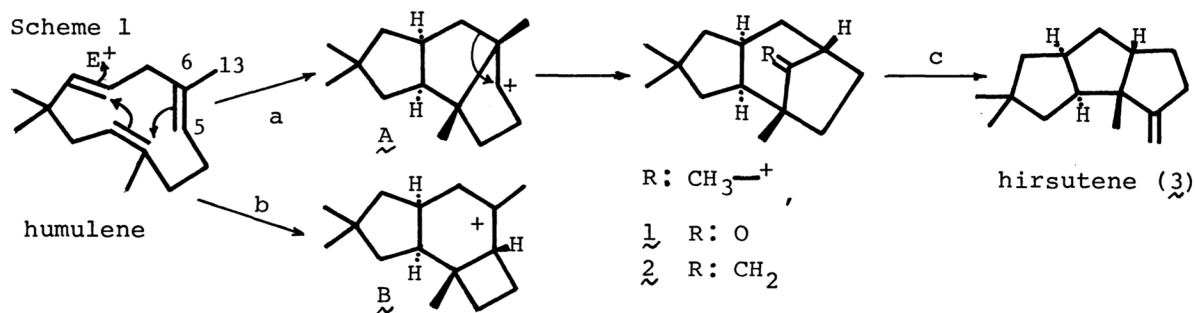
A CONVERSION OF HUMULENE TO HIRSUTENE

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Humulene has been transformed into 1,4,4-trimethyltricyclo-[6.2.1.0^{2,6}]undecan-11-one, a key intermediate for the synthesis of hirsutene, through a process which simulates the biosynthetic pathway assumed for the latter sesquiterpene.

In the previous paper¹⁾ we reported chemical synthesis of tricyclic compound 2 and its rearrangement to hirsutene 3 through a biogenetic-like path (Scheme 1, c)²⁾. Compound 2 in turn was prepared from its norketone 1. In another paper we showed³⁾ that humulene can be converted to protoilludyl cation B under suitable conditions, but not to secondary cation A, presumably because of the presence of the 13-methyl group. It was therefore anticipated that a properly substituted 13-norhumulene would give an A type cation rather than a B type cation. We should like to describe herein transformation of humulene into the norketone 1 through 13-nor-cation of A. The transformation means the success of the first, even if not direct, synthesis of tricyclic hirsutene from its monocyclic biogenetic precursor.



A 3,6-secoprotilludene derivative 4, which was previously derived from humulene by us,³⁾ was first converted to 5⁴⁾ (OsO₄-NaIO₄/^tBuOH-H₂O/rt/2 hr, 95%). The ketone was then reduced to a 1:1 mixture of epimeric alcohols, 6 and 7 (DIBAH/THF/-78°/10 min, almost quantitative) which was separated by passing through a silica gel column [6⁴⁾: mp 108-110 °C⁵⁾; ir(CCl₄, 10⁻³ mol) 3610 cm⁻¹, 7⁴⁾: oil; ir(CCl₄, 10⁻³ mol) 3515 cm⁻¹]. Configuration of the hydroxyl group of each

isomer was determined by the presence of an intramolecular H-bond in the ir spectrum of 7. Treatment of 6 with $\text{CBr}_4/\phi_3\text{P}$ gave β -bromide 8⁴⁾ ($\phi\text{H}/\text{reflux}/5\text{ min}$, 95%) (mp 91-2°). The β -configuration of the bromine atom was deduced from resemblance of the nmr coupling constants of the proton at C-6 (dt, 11, 4 Hz) to those of the C-6 proton of 6 (dt 10, 5 Hz). On the other hand, α -ol 7 gave exclusively olefin 9⁴⁾ on the similar treatment (95%). Cleavage of the ether linkage of 8 ($\text{Zn-EtOH}/\text{reflux}/12\text{ hr}$) afforded 10⁴⁾ (90%). The nmr spectrum of 10 in the presence of Eu^{3+} [$\text{Eu}(\text{fod})_3/\text{10}=0.51$, CCl_4] showed two double triplets at δ 7.75 ($J=6, 10\text{ Hz}$, 6-H) and at 7.25 ($J=7, 10\text{ Hz}$, 7-H). Therefore the configuration of the double bond was assigned to be cis on the basis of the coupling constant 10 Hz. The cyclooctenol 10 was heated to reflux in $\text{HCO}_2\text{H-Ac}_2\text{O}$ for 30 min under argon to give rise to a mixture of formates, 11 and 12 (80%, 3:1(glc)). The formates were treated as such with LiAlH_4 (THF/reflux/10 min, nearly quantitative) and the product was next oxidized with Jones reagent (0°/15 min, 95%) to yield a mixture of ketones (13⁴⁾ and 14⁴⁾, 3:1(glc)), which was separated into two isomers by silica gel chromatography (13: ir 1745 cm^{-1} ; nmr δ 0.92(3H, s), 1.06(6H, s), 14: ir 1740 cm^{-1} , nmr δ 0.99(3H, d, 7 Hz), 1.02, 1.10(each 3H, s)].

Structure of 13 was revealed by nmr decoupling experiments in the presence of a shift reagent [$\text{Eu}(\text{fod})_3/\text{13}=0.3$, CCl_4 , δ 7.01(S=11.87, 1H, d, $J_{4\alpha-5\alpha}=8\text{ Hz}$, 5 α H), 6.97(S=11.17, 1H, dd, $J_{4\beta-5\beta}=8\text{ Hz}$, $J_{4\alpha-5\beta}=4\text{ Hz}$, 5 β H), 6.55(S=11.17, 1H, t, $J_{7\beta-8\alpha}=J_{7\beta-8\beta}=9\text{ Hz}$, 7 β H), 4.85(S=7.85, 1H, dt, $J_{7\beta-8\alpha}=J_{8\alpha-9\alpha}=9\text{ Hz}$, $J_{8\beta-8\alpha}=13\text{ Hz}$, 8 α H), 3.95(S=2.61, 1H, m, 9 α H), 3.64(S=5.48, 1H, dd, $J_{8\alpha-8\beta}=13\text{ Hz}$, $J_{7\beta-8\beta}=9\text{ Hz}$, 8 β H), 3.20(S=3.91, 1H, ddd, $J_{4\alpha-4\beta}=12\text{ Hz}$, $J_{4\beta-5\alpha}=5\text{ Hz}$, $J_{4\beta-5\beta}=8\text{ Hz}$, 4 β H), 2.28(S=3.22, 3H, s, 12Me), 2.25(S=1.00, 1H, dd, $J_{9\alpha-10\alpha}=7\text{ Hz}$, $J_{10\alpha-10\beta}=13\text{ Hz}$, 10 α H), 2.05(S=1.20, 2H, d, $J_{1\alpha,\beta-2\alpha}=9\text{ Hz}$, 1 α,β H), 1.82(S=1.83, 1H, dd, $J_{9\alpha-10\beta}=8\text{ Hz}$, $J_{10\alpha-10\beta}=13\text{ Hz}$, 10 β H). Moreover, the large S value of 9 α H in comparison with that of 8 β H and the observed J values($J_{7\beta-8\alpha}=J_{7\beta-8\beta}=J_{8\alpha-9\alpha}=9\text{ Hz}$, $J_{8\beta-9\alpha}=0\text{ Hz}$) indicated a cis-anti-cis stereochemistry as depicted in Fig. 1 for this ketone. On the other hand, structure of 14 was determined by leading it to the known compound, pentalenene, 15⁷⁾ [(1) $\text{MeMgI}/\text{ether}/\text{reflux}/2\text{ hr}$, 90%, (2) $\text{MsCl}/\text{py}/\text{rt}/12\text{ hr}$, 90%]. Reduction of 13 ($\text{NaBH}_4/\text{ether}/0^\circ/10\text{ min}$) furnished a pair of epimeric alcohols 16⁴⁾ (quantitative) which in turn was treated with MsCl-py (100°/30 min) to give epimeric chlorides (34%) and two olefins 17 and 18 (42%, 9:1, glc). The chlorides were separated from the olefins by column chromatography(SiO_2) (19: nmr

Scheme 2

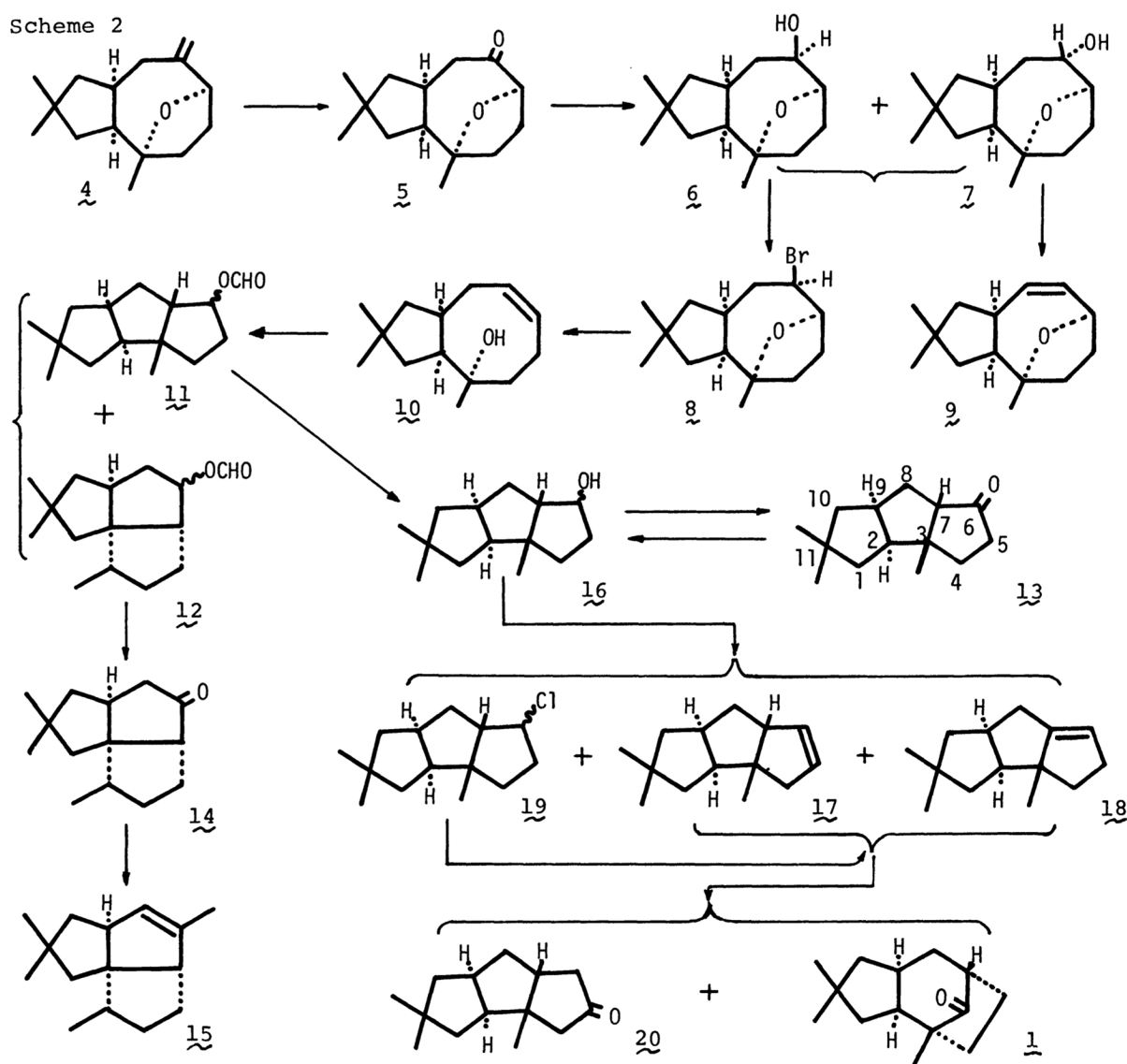
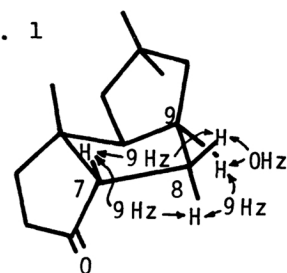


Fig. 1



δ 0.92(3H, s), 1.08(6H, s), 3.86 and 4.28(1H, each m), 40%) and were further dehalogenated (t AmONa/DMSO/80°/8 hr) to afford a similar mixture of the olefins, 17 and 18 (9:1(glc)). Since the olefins could not be separated by the usual methods, they were treated as such with $Tl(ClO_4)_3$ (t BuOH-H₂O(1:1)/rt/3 hr) to give two ketones (53%, 20/1=5/1, silica gel column, 20: ir 1745 cm⁻¹, nmr δ 0.91, 1.02, 1.07(each 3H, s), 1: ir 1750 cm⁻¹; nmr δ 0.90, 0.98, 1.10(each 3H, s)). Stereostructure of 20 was deduced from the decoupling experiments of the nmr spectrum in the presence

of Eu^{3+} : ($\text{Eu}(\text{fod})_3/20=0.35$, (CCl_4) δ 8.22(S=15.40, 1H, dd, $J_{6\alpha-6\beta}=19$ Hz, $J_{6\beta-7\beta}=6$ Hz), 6 β H), 7.82(S=15.00, 1H, dd, $J_{6\alpha-6\beta}=19$ Hz, $J_{6\alpha-7\beta}=2.5$ Hz, 6 α H), 7.80 and 7.68 (S=15.20 and 14.60, 2H, ABq, $J_{4\alpha-4\beta}=19$ Hz, 4 α and 4 β H), 4.40(S=4.52, 1H, m, 7 β H), 4.10(S=3.12, 2H, m, 9 α , 8 α H), 4.00(S=5.04, 1H, dt, $J_{1\alpha-2\alpha}=14$ Hz, $J_{1\beta-2\alpha}=J_{2\alpha-9\alpha}=9$ Hz, 2 α H), 3.20(S=2.40, 1H, dd, $J_{8\alpha-8\beta}=12$ Hz, $J_{7\beta-8\beta}=8$ Hz, 8 β H), 2.92(S=4.20, 3H, s, 12Me), 1.72(S=0.92, 3H, s, 14Me), 1.60(S=1.08, 3H, s, 14Me). Ketone 1 was identified with an authentic sample of 13-norprotophirsutan-7-one, which had already been transformed to hirsutene¹⁾.

References

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4. Satisfactory spectral data were obtained for this compound.
 5: ir 1710 cm^{-1} ; nmr δ 1.01, 1.08, 1.20 (each 3H, s), 4.15 (1H, d, 8 Hz).
 6: nmr δ 0.97, 1.04, 1.16 (each 3H, s), 3.62 (1H, dt, 10, 5 Hz), 4.08 (1H, m).
 7: nmr δ 0.99, 1.04, 1.19 (each 3H, s), 3.40 (1H, dt, 5, 2.5 Hz), 4.20 (1H, m).
 8: ir 1070, 1055 cm^{-1} ; nmr δ 0.95, 1.02, 1.13 (each 3H, s), 4.00 (1H, dt, 11, 4 Hz), 4.35 (1H, m).
 9: ir 1650, 1090, 1065 cm^{-1} ; nmr δ 0.99, 1.05, 1.11 (each 3H, s), 4.50 (1H, m), 5.25 (1H, dd, 2, 12 Hz), 5.35 (1H, d, 12 Hz).
 10: ir 3400, 1100 cm^{-1} ; nmr δ 1.01, 1.11, 1.13 (each 3H, s), 5.80 (2H, m).
 13: ir 1743 cm^{-1} ; nmr δ 0.90 (3H, s), 1.04 (6H, s).
 14: ir 1740 cm^{-1} ; nmr δ 0.97 (3H, d, $J=6.5$ Hz), 1.02, 1.10 (each 3H, s).
 16:(a) ir 3100, 1070 cm^{-1} ; nmr δ 0.92, 0.97, 1.01 (each 3H, s), 4.24 (1H, m).
 (b) nmr δ 0.92, 1.07, 1.12 (each 3H, s), 3.83 (1H, m). 16a/16b=5/4.
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