CHEMISTRY LETTERS, pp. 855-858, 1982.

A CONVERSION OF HUMULENE TO HIRSUTENE

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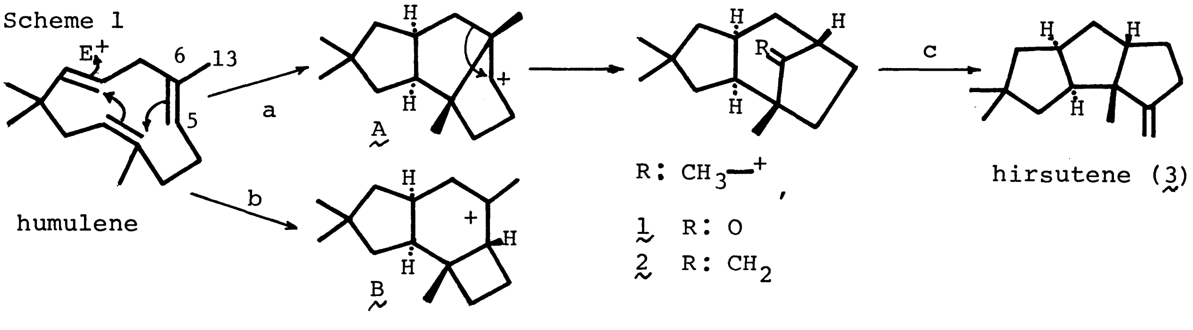
Humulene has been transformed into 1,4,4-trimethyltricyclo-[6.2.1.0^{2,6}]undecan-11-one, a key intermediate for the synthesis of hirsutene, through a process which simulates the biosynthetic pathway assumed for the latter sesquiterpene.

In the previous paper[1)] 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 showed[3)] 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.


Scheme 1

A 3,6-secoprotoilludene derivative 4, which was previously derived from humulene by us,[3)] was first converted to 5[4)] (OsO_4-$NaIO_4$/$^{t}BuOH$-H_2O/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 [6[4)]: mp 108-110 °C[5)]; ir(CCl_4, 10^{-3} mol) 3610 cm^{-1}, 7[4)]: oil; ir(CCl_4, 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 CBr_4/ϕ_3P gave β-bromide **8**4) (ϕH/reflux/5 min, 95%)(mp 91-2°). The β-configuration of the bromine atom was deduced from resembrance 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 **9**4) on the similar treatment (95%). Cleavage of the ether linkage of **8** (Zn-EtOH/reflux/12 hr) afforded **10**4) (90%). The nmr spectrum of **10** in the presence of Eu^{3+} [$Eu(fod)_3$/**10**=0.51, CCl_4] showed two double triplets at δ 7.75(J=6, 10 Hz, 6-H) and at 7.25(J=7, 10 Hz, 7-H). Therefore the configuration of the double bond was assigned to be <u>cis</u> on the basis of the coupling constant 10 Hz. The cyclooctenol **10** was heated to reflux in HCO_2H-Ac_2O 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 (**13**4) and **14**4), 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 [$Eu(fod)_3$/**13**=0.3, CCl_4, δ 7.01(S=11.87, 1H, d, $J_{4\alpha-5\alpha}$=8 Hz, 5αH), 6.97(S=11.17, 1H, dd, $J_{4\beta-5\beta}$=8 Hz, $J_{4\alpha-5\beta}$=4 Hz, 5βH), 6.55(S=11.17, 1H, t, $J_{7\beta-8\alpha}=J_{7\beta-8\beta}$=9 Hz, 7βH), 4.85(S=7.85, 1H, dt, $J_{7\beta-8\alpha}=J_{8\alpha-9\alpha}$=9 Hz, $J_{8\beta-8\alpha}$=13 Hz, 8αH), 3.95(S=2.61, 1H, m, 9αH), 3.64(S=5.48, 1H, dd, $J_{8\alpha-8\beta}$=13 Hz, $J_{7\beta-8\beta}$=9 Hz, 8βH), 3.20(S=3.91, 1H, ddd, $J_{4\alpha-4\beta}$=12 Hz, $J_{4\beta-5\alpha}$=5 Hz, $J_{4\beta-5\beta}$=8 Hz, 4βH), 2.28(S=3.22, 3H, s, 12Me), 2.25(S=1.00, 1H, dd, $J_{9\alpha-10\alpha}$=7 Hz, $J_{10\alpha-10\beta}$=13 Hz, 10αH), 2.05 (S=1.20, 2H, d, $J_{1\alpha,\beta-2\alpha}$=9 Hz, 1α,βH), 1.82(S=1.83, 1H, dd, $J_{9\alpha-10\beta}$=8 Hz, $J_{10\alpha-10\beta}$=13 Hz, 10βH). Moreover, the large S value of 9αH in camparison with that of 8βH and the observed J values($J_{7\beta-8\alpha}=J_{7\beta-8\beta}=J_{8\alpha-9\alpha}$=9 Hz, $J_{8\beta-9\alpha}$=0 Hz) indicated a <u>cis</u>-<u>anti</u>-<u>cis</u> 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, **15** 7) [(1) MeMgI/ether/reflux/2 hr, 90%, (2) MsCl/py/rt/12 hr, 90%]. Reduction of **13** ($NaBH_4$/ether/0°/10 min) furnished a pair of epimeric alcohols **16**4) (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

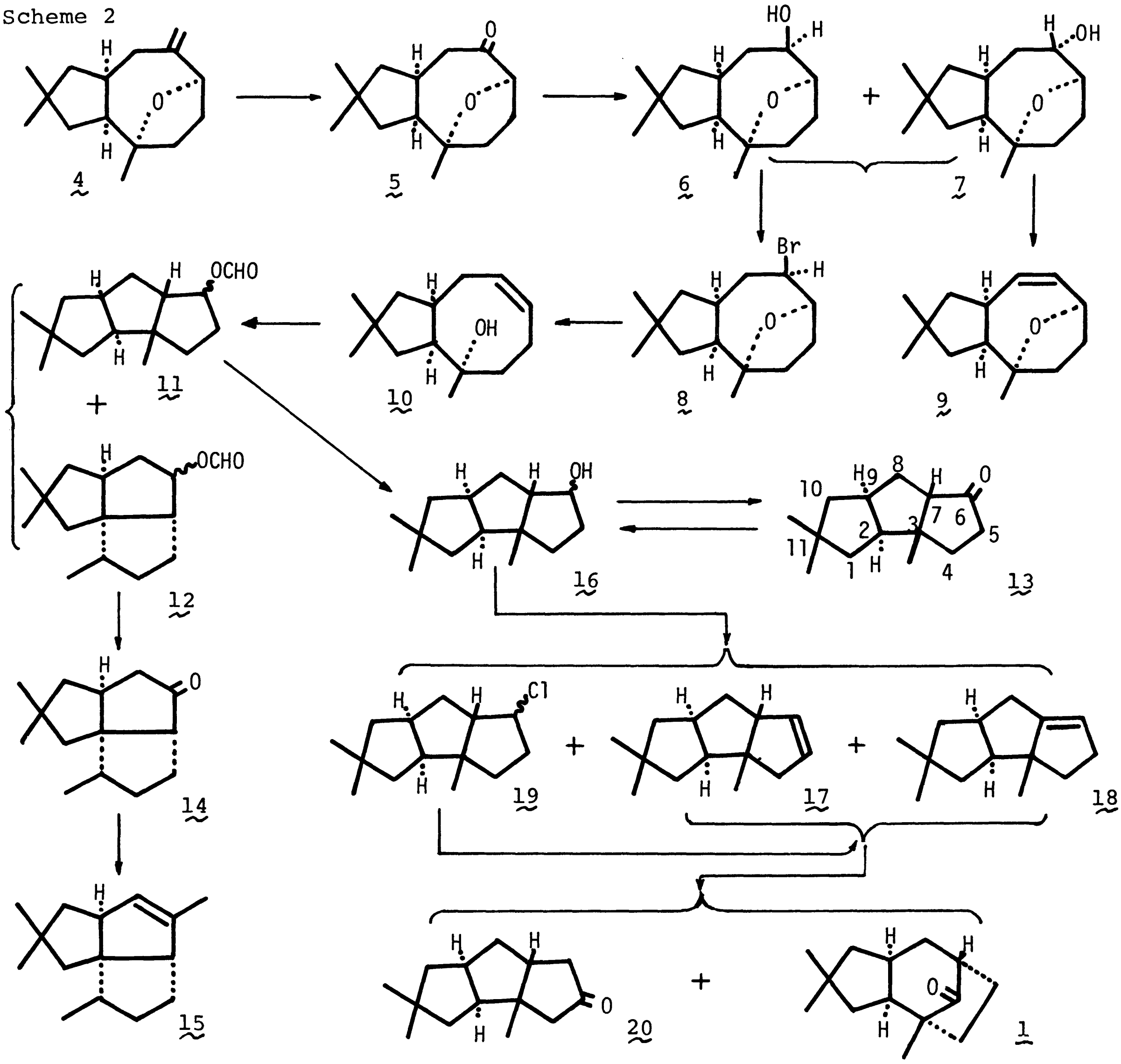
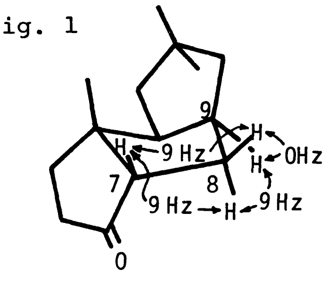


Fig. 1



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$6) (^{t}BuOH-H_2O(1:1)/rt/3 hr) to give two ketones (53%, 20/1 =5/1, silica gel column, 20: ir 1745 cm^{-1}, nmr δ 0.91, 1.02, 1.07(each 3H, s), 1: ir 1750 cm^{-1}; nmr δ 0.90, 0.98, 1.10(each 3H, s)). Stereostructure of 20 was deduced from the decoupling experiments of the nmr spectrum in the presence of Eu^{3+}: ($Eu(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), 6βH), 7.82(S=15.00, 1H, dd, $J_{6\alpha-6\beta}$=19 Hz, $J_{6\alpha-7\beta}$=2.5 Hz, 6αH), 7.80 and 7.68 (S=15.20 and 14.60, 2H, ABq, $J_{4\alpha-4\beta}$=19 Hz, 4α and 4βH), 4.40(S=4.52, 1H, m, 7βH), 4.10(S=3.12, 2H, m, 9α, 8αH), 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, 2αH), 3.20(S=2.40, 1H, dd, $J_{8\alpha-8\beta}$=12 Hz, $J_{7\beta-8\beta}$=8 Hz, 8βH), 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-norprotohirsutan-7-one, which had already been transformed to hirsutene[1].

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 (IH, m). 16a/16b=5/4.
5. Mps were noted for all crystalline compounds.
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(Received March 25, 1982)