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A TRANSANNULAR REACTION DURING THE BASE CATALYSED REARRANGEMENT OF BICYCLO(4.3.0)-2β-HYDROXY-2α-VINYL-1β-METHYL-8-OXO-$\Delta^{6,7}$-NONENE[6]

K. Y. Geetha, K. Rajagopalan and S. Swaminathan*
Department of Organic Chemistry, University of Madras, A.C. College Campus, Madras-600 025, India

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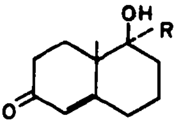
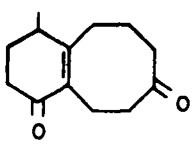
Abstract—Synthesis and rearrangement of bicyclo(4.3.0) - 2β - hydroxy - 2α - vinyl - 1β - methyl - 8 - oxo - Δ^6 - nonene was observed to yield a transannular reaction product tricyclo - (6.3.0.$0^{1,6}$) - 2 - methyl - 8α - hydroxy - 4 - oxo - Δ^2 - undecene **16**. Spectral evidence supports the assigned structure.

Bicyclic δ - hydroxy - α,β - enones have been found to undergo facile base catalysed rearrangement—the product of the rearrangement of **1**, being the ring enlarged dione **5**.[1]





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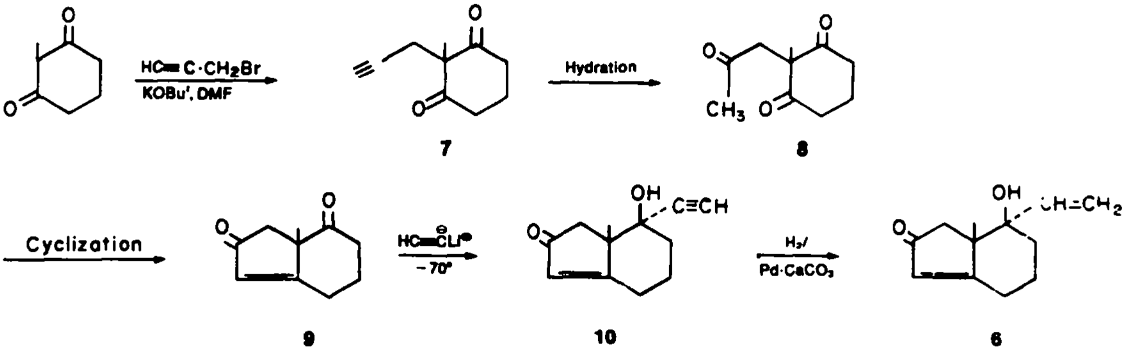
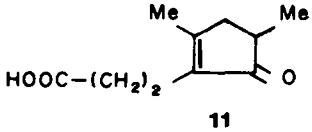
1: R = —CH=CH$_2$
2: R = —C≡CH
3: R = Me
4: R = H

Wirh a view to extend the generality of this rearrangement, the vinyl alcohol **6** was chosen and was sought to be prepared as detailed in Scheme 1.



Scheme 1.

The trione **8** was obtainable in good yields, but cyclization to the dione **9** failed under a variety of conditions. Base treatment of **8** under fairly vigorous conditions furnished an acidic product **11**.[2]



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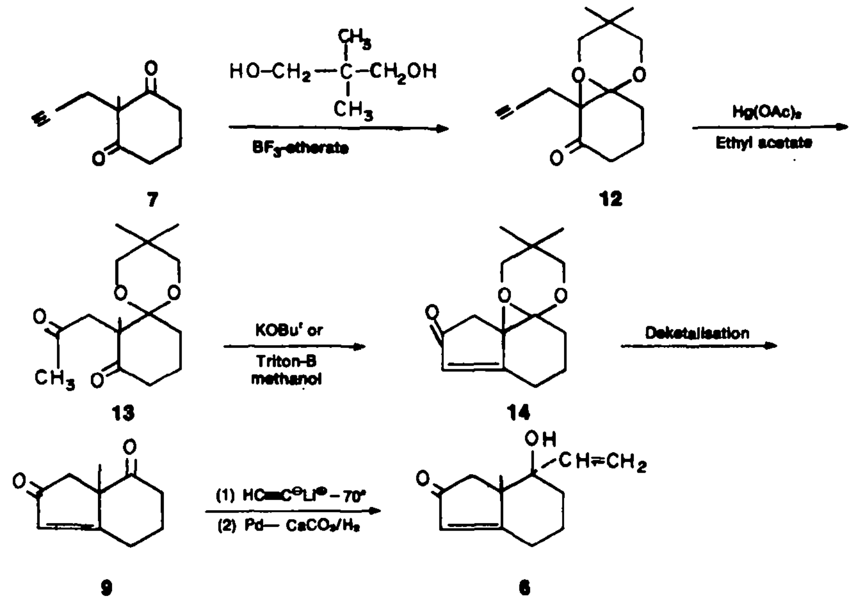
It was felt that masking of one of the carbonyl functions in **7** as a ketal would reduce the base sensitivity so that strong bases could be used for cyclization of the hydration product. The vinyl alcohol **6** was synthesized by this modified approach as depicted in Scheme 2.

Reaction of propargyl dione **7** with neopentyl glycol under mild conditions—BF$_3$ etherate at 0°C—overnight furnished the mono ketal **12** in 58% yield as white crystalline solid, m.p. 150–152°C. Spectral data and elemental analysis lend strong support to the structure **12**.

Hydration of **12** with mercuric acetate in ethyl acetate afforded the trione mono ketal **13** in 60% yield—m.p. 80–82°C. IR (KBr) showed, significantly, the absence of the acetylenic -CH. NMR and MS data also support the assigned structure.

Cyclization of **13** to **14** in 75% yield was realized by the agency of KOBu^t or Triton-B in refluxing methanol. IR (KBr) of **14** showed a doublet at 1690 and 1670 cm^{-1} besides an olefinic absorption at 1615 cm^{-1}. Cyclopentenones possessing an olefinic hydrogen have been reported to exhibit a doublet in the carbonyl region.[3]

Conventional methods of deketalization failed to remove the ketal function in compound **14**. However, brief treatment with conc. H$_2$SO$_4$ (till the dissolution of the material is complete) and work up furnished a compound melting at 63–65°C in 84% yield. Based on spectral evidence and elemental analysis this compound was assigned the structure **9**.

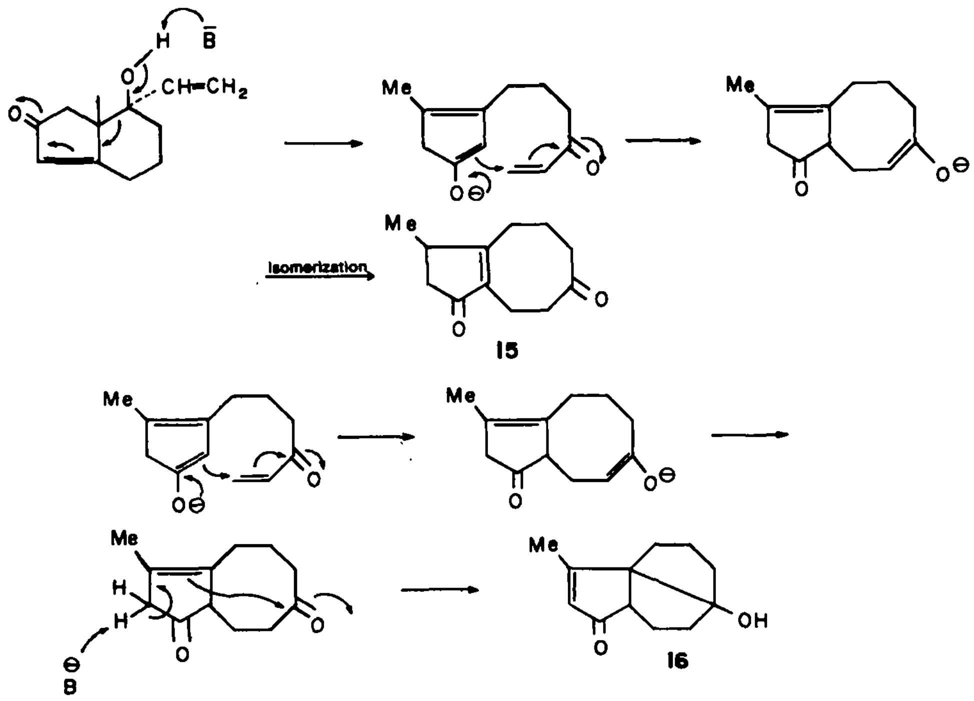


Scheme 2.

The ethynyl alcohol **10** (m.p. 150–152°C) was obtained in 65% yield by treating the dione **9** with lithium acetylide at −70°C. Partial hydrogenation of **10** over Pd–$CaCO_3$ at 40 psi afforded the desired vinyl alcohol **6** (m.p. 86–88°C) in 69% yield. Once again spectral data and elemental analysis firmly established the structure.

Refluxing the vinyl alcohol **6** with 5% methanolic KOH for 2 hr followed by work up gave a 40% yield of a liquid product which proved to be a mixture of two products. Chromatography over silica gel and elution with 10% ethyl acetate–petroleum ether furnished the major product—a liquid found to be homogeneous on TLC. IR ($CHCl_3$) showed the presence of an OH at 3460 cm^{-1} and a CO at 1700 cm^{-1}. NMR ($CDCl_3$) clearly indicated the absence of the complex pattern due to the vinyl protons present in the starting vinyl alcohol but showed a weakly coupled vinyl proton at δ 5.8. Besides this a weakly coupled vinyl methyl at δ 1.78 was also observed. The failure to observe significant deuterium exchange coupled with the difficulty experienced in derivatising the hydroxyl function indicated its tertiary nature. Mass spectrum indicated the compound to be isomeric with the starting material. Two possible products **15** and **16** can be envisaged to be formed from this reaction as indicated in Scheme 3.

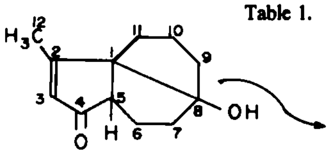
The spectral data could be interpreted in terms of



Scheme 3.

structure **16** which could conceivably arise by an initial base-catalyzed ring enlargement of the vinyl alcohol **6** followed by a transannular reaction. This was confirmed by hydrogenating the compound **16** with Pd–C to yield a liquid product which showed the absence of vinyl proton and the appearance of a methyl doublet at δ 1.2 (7 Hz). IR showed a CO absorption at 1735 cm^{-1}. Confirmatory proof for the structure **16** was provided by the ^{13}C NMR spectrum of the compound. The chemical shifts for the various carbons are given in Table 1.

Table 1.

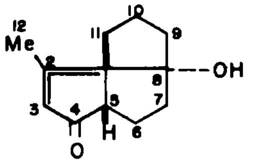


Carbon position	C_1	C_2	C_3	C_4	C_5	C_8	C_{12}
Chemical shifts in ppm	66.0 (s)	181.6 (s)	131.7 (d)	210.5 (s)	59.5 (d)	91.4 (s)	17.3 (q)

δ $CHCl_3$/TMS: s—singlet; d—doublet; q—quartet.

The resonance for other carbons were found to occur as triplets at 41.4, 39.4, 35.5, 25.4 and 24.5 ppm.

Models show that compound **16** most probably exists with the stereochemistry indicated, in view of the extreme stability of *cis* fused 5-membered ring systems.



Our studies[4,5] seem to indicate that such trans-annular reactions are a common feature of these bicyclic ring systems which rearrange to intermediates containing an 8-membered ring.

EXPERIMENTAL

2 - *Methyl - 2 - propargyl - 3,3 - (2,2 - dimethyl trimethylene dioxy) - cyclohexanone* **12**

A mixture of 2 - methyl - 2 - propargyl - cyclohexane - 1,3 - dione[2] (16.4 g, 0.1 mole) and 2,2-dimethyl propane 1,3-diol (11.2 g, 0.11 mole) in dry ether was cooled to 0°C and a drop of BF_3-etherate was added and the reaction mixture was stirred overnight. The crystalline solid that had separated was filtered, washed with water and dried to furnish 14 g (58%) of the mono ketal **12**; m.p. 150–152°C. IR (KBr): 3200 cm^{-1} (–C≡CH) and 1690 cm^{-1} ($>$C=O). NMR ($CDCl_3$/TMS) δ values: 1.2 (singlet, CH_3, 3H); 1.4 (doublet, gem dimethyl, 6H); 3.6 (quartet, O–CH_2, 4H); and 2.0–3.0 (multiplet, 9H). (Calcd for $C_{15}H_{22}O_3$: C, 72.7; H, 8.81. Found: C, 71.69; H, 9.2%).

2 - *Acetonyl - 2 - methyl - 3,3 - (2,2 - dimethyl trimethylene dioxy) cyclohexanone* **13**

To a soln of compound **12** (2.5 g, 0.01 mole) in moist ethyl acetate (125 ml), mercuric acetate (6.16 g, 0.02 mole) was added with stirring and the mixture was stirred at room temp overnight. Hydrogen sulfide was passed through the soln and the precipitated mercuric sulfide was filtered off. The organic layer from the filtrate was washed sequentially with sodium bicarbonate soln, water and dried ($MgSO_4$). Solvent was distilled off under reduced pressure and the residue cooled to afford a solid—1.75 g (60%); m.p. 80–82°C (ethyl acetate–petroleum ether). IR (KBr): 1700 cm^{-1} ($>$C=O). NMR ($CDCl_3$/TMS) δ values: 1.2 (singlet, CH_3, 3H); 1.5 (doublet, gem dimethyl, 6H); 1.7–2.2 (multiplet, 11H) and 3.6 (quartet, O–CH_2, 4H); *m/e* – 268. (Calcd for $C_{15}H_{24}O_4$: C, 67.17; H, 8.95. Found: C, 67.2; H, 9.17%).

Cyclodehydration of compound **13**

To a soln of compound **13** (8 g, 0.032 mole) in methanol (30 ml) Triton-B (5 ml) was added and the soln refluxed for 15 hr. Solvent was distilled off under reduced pressure and the residue poured into ice water and the resulting solid was filtered, washed with water and dried to afford 6 g (75%) of the cyclized product **14**; m.p. 130–132°C (ethyl acetate–petroleum ether); λ^{max}_{EtOH} 235 nm (ε = 26,060): IR (KBr) 1690, 1670 and 1615 cm^{-1}; NMR ($CDCl_3$/TMS) δ values: 1.28 (singlet, CH_3, 3H); 1.4 (doublet, gem dimethyl, 6H); 1.7–3.0 (multiplet, methylene protons, 8H); 3.6 (quartet, O–CH_2, 4H) and 5.8 (broad singlet, vinyl proton, 1H): *m/e* – 250. (Calcd for $C_{15}H_{22}O_3$: C, 72.0; H, 8.8. Found: C, 71.62; H, 8.84%).

Deketalization of compound **14**

To conc. H_2SO_4 (75 ml), compound **14** (16.4 g) was added all at once till dissolution occurred and poured onto crushed ice. The aqueous layer was extracted with methylene chloride (3 × 50 ml). The combined extracts were dried ($MgSO_4$) and solvent removed to afford an oil which solidified on cooling to yield 8 g (84%) of compound **9** m.p. 63–65°C (ethyl acetate–petroleum ether). IR (KBr): 1700, 1680 and 1615 cm^{-1}; λ^{max}_{EtOH} 239 nm (ε = 25,130); NMR ($CDCl_3$/TMS) δ values: 1.6 (singlet, CH_3, 3H); 2.0–3.4 (multiplet, methylene protons, 8H) and 5.8 (broad singlet, vinyl proton, 1H): *m/e* – 164. (Calcd for $C_{10}H_{12}O_2$: C, 73.2; H, 7.3. Found: C, 73.6; H, 7.6%).

Ethynylation of compound **9**

Lithium metal (1.4 g, 0.2 g atom) was added to liquid ammonia (200 ml) and acetylene gas was passed through the soln. After the dissolution of lithium, the mixture was cooled to −70°C (acetone–dry ice bath) and compound **9** (16.4 g, 0.1 mole) in dry ether (100 ml) was added during 10 min with vigorous stirring. After the addition the mixture was stirred for 30 min more and quenched with solid ammonium chloride (8 g). The ammonia soln was evaporated and water (100 ml) was added to the residue to furnish 12.35 g (65%) of the ethynyl alcohol **10** m.p. 150–152°C (ethyl acetate). IR ($CHCl_3$): 3300 (OH), 3200 (–C≡CH), 1670 ($>$C=O) and 1610 cm^{-1}. λ^{max}_{EtOH} 232 nm (ε = 25,940). NMR ($CDCl_3$/TMS) δ values: 1.3 (singlet, CH_3, 3H); 2.0–3.3 (multiplet, 10H) and 5.95 (broad singlet, vinyl proton, 1H). (Calcd for $C_{12}H_{14}O_2$: C, 75.7; H, 7.37. Found: C, 75.6; H, 7.6%).

Hydrogenation of ethynyl alcohol **10**

A soln of the ethynyl alcohol **10** (5 g, 0.026 mole) in dry pyridine (20 ml) was hydrogenated over Pd–$CaCO_3$ (0.5 g) at 45 psi for 25 min. The catalyst was filtered off and the solvent removed under reduced pressure. The residue was extracted with chloroform (2 × 50 ml), the combined extracts washed with water and dried ($MgSO_4$). Removal of solvent by distillation and cooling the reisdue in ice gave 3.4 g (69%) of the vinyl alcohol **6** m.p. 84–86°C (ether–petrol). IR (KBr): 3360 (–OH); 1690 ($>$C=O) and 1615 cm^{-1}. λ^{max}_{EtOH} 234 nm (ε = 25,370). NMR ($CDCl_3$/TMS) δ values: 1.25 (singlet, CH_3, 3H); 1.3–2.0 (multiplet, 9H) and 5.0–6.2 (multiplet, vinyl protons, 3H); *m/e* – 192. (Calcd for $C_{12}H_{16}O_2$: C, 75.0; H, 8.25. Found: C, 75.0; H, 8.63%).

Rearrangement of vinyl alcohol **6**

2 g of the vinyl alcohol **6** was refluxed with 5% (25 ml) methanolic KOH for 2 hr. The mixture was poured into water (75 ml) and the aqueous soln extracted with ether (3 × 50 ml). The combined ether extract was washed with water and dried ($MgSO_4$). Solvent was removed by distillation and the residual liquid chromatographed over silica gel. Elution with 10% ethyl acetate–petroleum ether afforded 0.8 g (40%) of compound **6** as a

homogeneous liquid. IR ($CHCl_3$): 3460 (–OH); 1700 ($>C=O$) and 1610 ($>C=C<$). λ_{EtOH}^{max} 244 nm ($\epsilon = 8710$). NMR ($CDCl_3$/TMS) δ values: 1.7 (weakly coupled doublet, vinyl methyl, 3H); 1.0–3.0 (multiplet, 11H) and 5.8 (weakly coupled doublet, vinyl proton, 1H). *m/e* – 192.

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