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SYNTHESES OF NEW HUMULENE DERIVATIVES; (2E,6E,9E)- AND (2Z,6E,9E)-CYCLOUNDECATRIENONES, BY INTRAMOLECULAR ALKYLATION OF PROTECTED CYANOHYDRIN. A ROUTE TO HUMULENE

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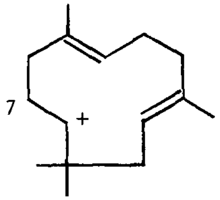
Summary: Syntheses of (2*E*,6*E*,9*E*)-2,5,5,9-tetramethyl-2,6,9-cycloundecatrienone (4) and (2*Z*,6*E*,9*E*)-2,5,5,9-tetramethyl-2,6,9-cycloundecatrienone (16) based on the intramolecular alkylation of protected cyanohydrin and conversion of the (*E*,*E*,*E*)-trienone 4 to humulene (3) are presented.

Hendrickson1) reported a biogenetic hypothesis for bi- and tricyclic sesquiterpenes and suggested that cation 1 and cation 2, derived from *trans*- and *cis*-farnesyl pyrophosphate respectively, were the most important key intermediates in the biosynthesis of sesquiterpenes. On the other hand, Parker2) suggested that one could obtain the C(7)-cation from humulene by the selective protonation of E-$^{6}\Delta$-olefin. So far many chemists have studied conversions of humulene and its derivatives, promoted by various acids, into bi- and tricyclic sesquiterpenes. However, most of these conversions were non-selective and gave many products. Recently Matsumoto3) succeeded in the chemical conversions of humulene into naturally occurring tricyclic terpenes such as sterpurene, hirstene, and capnellene. These results suggest that the use of transannular cyclization of medium-ring compounds would be an interesting synthetic method for syntheses of the above mentioned tricyclic terpenes, if one could prepare the humulene derivatives, in which the selective activation of functional groups is possible, starting from easily available compounds. In this paper we wish to report syntheses of new humulene derivatives, (2*E*,6*E*,9*E*)-2,5,5,9-tetramethyl-2,6,9-cycloundecatrienone (4) and (2*Z*,6*E*,9*E*)-2,5,5,9-tetramethyl-2,6,9-cycloundecatrienone (16) based on the intramolecular alkylation4) of the protected cyanohydrin and the conversion of 4 to humulene (3).



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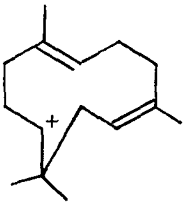

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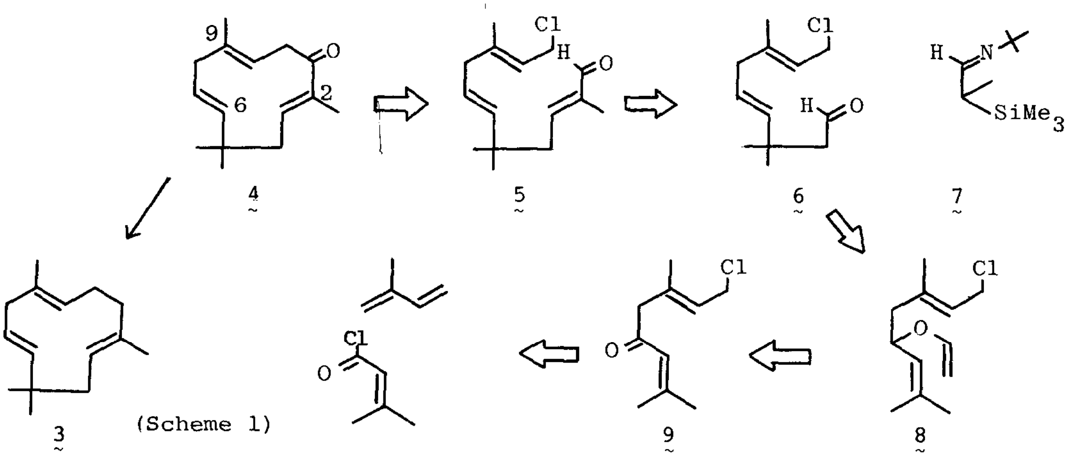
In our synthetic plan (Scheme 1) for the preparation of (2*E*,6*E*,9*E*)-trienone 4, the construction of the 11-membered ring5) is carried out by the intramolecular alkylation of protected cyanohydrin 10, derived from (2*E*,6*E*,9*E*)-trienal 5. Yield of this cyclization is high but neither the intermolecular reaction nor the isomerization of double bond takes place. The three double bonds in 4 are introduced by the following reactions. The *E*-$^{9}\Delta$-olefin is generated in the preparation of 9 by Friedel-Crafts reaction, reported by Cookson,6) with isoprene and senecioyl chloride. The *E*-$^{6}\Delta$-olefin, gem-dimethyl group at C(5) and the aldehyde group at C(3) in 6 are sumultaneously introduced by the stereoselective Claisen rearrangement of vinyl ether 8. The *E*-enal moiety in 5 is constructed by applying Corey's method7) using α-trimethylsilylpropionaldehyde *N-tert*-butylimine (7) and aldehyde 6. The conversion of 4 to humulene (3) is carried out by reductive removal cf oxygen in three steps.

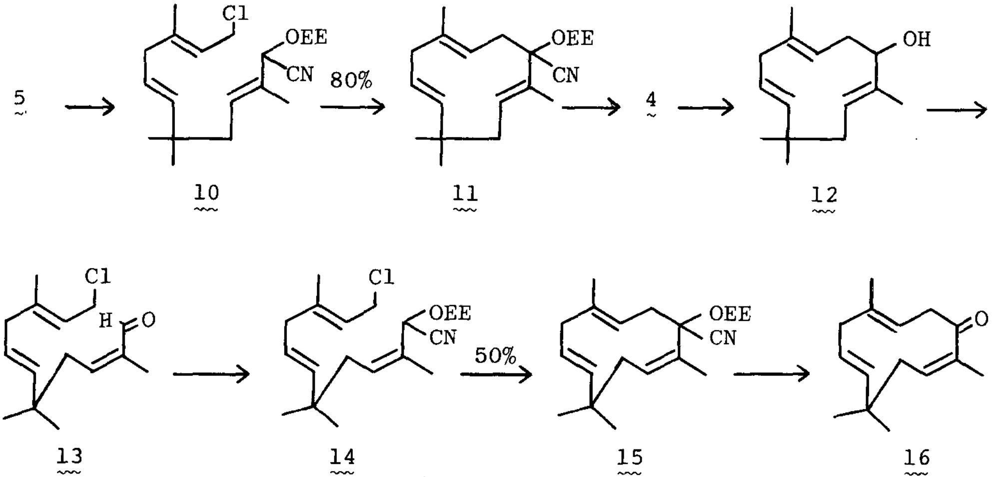


(Scheme 1)

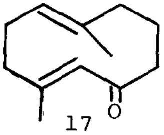
Thus the (2*E*,6*E*,9*E*)-trienal 5 is our initial synthetic target and is easily prepared in the following way. Addition of isoprene to a solution of senecioyl chloride and stannic chloride in CH_2Cl_2 at -78°C gave the enone 9 in 93% yield [NMR (CCl_4) : δ 1.68, 1.81, 2.06 (s, methyls), 5.48 (t, *J* = 7.6, 1H), 6.02 (bs, 1H); IR (neat) 1620 cm^{-1}]. Not a trace (-5%) of the olefinic isomer could be detected in the crude product 9 on the basis of an examination of NMR spectrum. The carbonyl group in 9 was reduced with $NaBH_4$ in EtOH at -10°C (80% yield). The resultant allyl alcohol was converted [$Hg(OAc)_2/CH_2$=CHOEt, two days] to the vinyl ether 8 in 54% yield with recovery of the allyl alcohol (41% yield). The Claisen rearrangement of 8 was carried out at 140°C for 30 min in collidine under nitrogen to give the aldehyde 6 in 75% yield [NMR (CCl_4): δ 1.14 (s, 6H, gem-methyls), 1.68 (bs, 3H, methyl), 4.73-5.63 (m, 3H, olefinic), 9.61 (t, *J* = 3.0, 1H); IR (neat) 1720 cm^{-1}; Mass m/e 214(M^+)]. Metalation of the imine 7 (*tert*-BuLi in THF at -20°C for 5 min then at 0°C for 30 min), followed by addition of the aldehyde 6 at -100°C in THF then at -78°C for two hours, and hydrolysis of the resultant unsaturated imine with acid (oxalic acid/THF/H_2O, at 5°C, 30 min) gave a mixture of the enals 58) and 138) in 79% yield. NMR spectra of the crude mixture 5 and 13 showed at least a 3 : 1 ratio in favor of the *E*-enal 5.

After separation of *E*- and *Z*-enals, the pure enal 5 was converted to the protected cyanohydrin 10 in three steps (Me_3SiCN/18-crown-6, $PhCH_2N^+Me_3F^-$, ethyl vinyl ether/H^+; 90% yield). The cyclization of 10 was carried out in the following way (Scheme 2). The protected cyanohydrin 10 (2.37 mmol) in THF (15 mL) was added over 15 min at 55°C under nitrogen atmosphere to $NaN(SiMe_3)_2$ (11.8 mmol) in THF (10 mL). The cyclized product 11 was isolated in 80% yield after chromatographic purification. Examination of a crude product 11 by TLC indicated only the presence of the cyclized product. Acid treatment (*p*-TsOH/MeOH at 0°C, 30 min) of the crude product 11 followed by aqueous base treatment (2%-aq. NaOH/Et_2O at room temp, 30 min) of the resultant cyanohydrin gave (*E*,*E*,*E*)-trienone 4[9] in 91% overall yield. At this stage we carefully examined whether the isomerization of olefin during the conversion of 10 to 4 took place. Not a trace (-5%) of the isomer 16 could be detected in the crude product 4 by NMR spectra and HPLC. The (*E*,*E*,*E*)-trienone 4 was converted to humulene in the following way. Reduction of 4 (*i*-Bu_2AlH in THF at -40°C; 90% yield) and acetylation of the resultant allyl alcohol 12 (Ac_2O in Py.; 80% yield) and removal of the allyl acetate (Li/$EtNH_2$ at -78°C) gave humulene (3) in 35% yield, which was identical in all respects (NMR, HPLC) with naturally occurring humulene.

Conversion of the separated *Z*-enal 13 to the protected cyanohydrin 14, its cyclization to 15 and the transformation of 15 to (*Z*,*E*,*E*)-trienone 16 were carried out in the same manner as above (Scheme 2). The cyclized product 15 was obtained in 50% yield after chromatographic purification. Again no product of the intermolecular reaction was detected in the crude product 15. However the base treatment of the cyanohydrin corresponding to 15 caused isomerization of olefin to give a mixture of (*Z*,*E*,*E*)-trienone 16[9] and (*E*,*E*,*E*)-trienone 4 in ratio of 1 : 1. It is noteworthy that (*Z*,*E*,*E*)-trienone 16 is less stable under basic condition than (*E*,*E*,*E*)-trienone 4, while (2*E*,6*E*)-cyclodecadienone 17 is less stable than (2*Z*,6*E*)-cyclodecadienone 18.[10] It is also worth emphasizing that the yields of (*E*,*E*,*E*)-trienone 4 and (*Z*,*E*,*E*)-trienone 16 are quite different, while the yields of (*E*,*E*)-dienone 17 and (*Z*,*E*)-dienone 18 are almost the same.[4e]



(Scheme 2)



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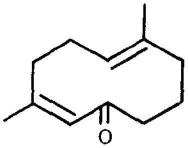

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8) Enal 5: NMR (CCl_4) δ 1.12 (s, 6H), 1.71 (bs, 6H), 2.30 (d, *J*=7.6, 2H), 2.71 (d, *J*=5.6, 2H), 4.00 (d, *J*=8.0, 2H), 5.15-5.60 (m, 3H), 6.38 (bt, *J*=7.6, 1H), 9.37 (s, 1H); IR (neat) 1685 cm^{-1}; HPLC (Si-60-5 μm, 4.0 o.d. 250 mm, flow rate 2.3 mL/min, 1%-EtOAc/*n*-hexane) Rt=15.6 min.
   Enal 13: NMR (CCl_4) δ 1.11 (s, 6H), 1.70 (bs, 3H), 1.76 (bs, 3H), 2.55 (d, *J*=8.4, 2H), 2.73 (d, *J*=5.4, 2H), 4.00 (d, *J*=8.0, 2H), 5.20-5.60 (m, 3H), 6.42 (bt, *J*=8.4, 1H), 10.1 (s, 1H); IR (neat) 1675 cm^{-1}; HPLC Rt=12.5 min; Mass m/e 219 (M^+-Cl).

9) (*E*,*E*,*E*)-Trienone 4: NMR ($CDCl_3$) δ 1.10 (s, 6H), 1.55 (bs, 3H), 1.78 (bs, 3H), 2.19 (d, *J*=7.6, 2H), 2.59 (d, *J*=7.1, 2H), 3.09 (d, *J*=8.3, 2H), 5.24-5.62 (m, 4H); IR (neat) 1685 cm^{-1}; HPLC (flow rate 2.7 mL/min, 1%-EtOAc/*n*-hexane) Rt=19.3 min; High resolution mass spectrum, calcd. for $C_{15}H_{22}O$ m/e 218.3420; found m/e 218.1688.
   (*Z*,*E*,*E*)-Trienone 16: NMR ($CDCl_3$) δ 0.96 (s, 6H), 1.83 (bs, 3H), 1.89 (bs, 3H), 2.06 (d, *J*=9.0, 2H), 2.67 (d, *J*=4.5, 2H), 3.04 (d, *J*=8.9, 2H), 5.08-5.70 (m, 4H); IR (neat) 1690 cm^{-1}; HPLC Rt=7.8 min; High resolution mass spectrum, found m/e 218.1682.

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