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BISANNULATION REACTION: A SINGLE STEP SYNTHESIS OF ENDO-2-ETHOXYCARBONYL-EXO-2-CYANO-3,3-DIMETHYL-BICYCLO[2,2,2]-OCTAN-5-ONE AND ENDO-2-ETHOXYCARBONYL-EXO-2-CYANO-1,3,3-TRIMETHYL-BICYCLO[2,2,2]OCTAN-5-ONE.

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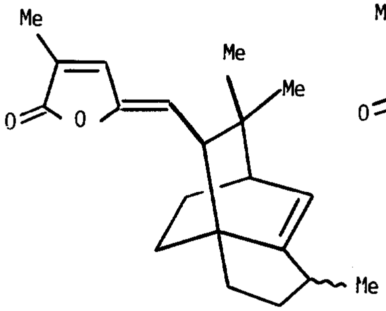
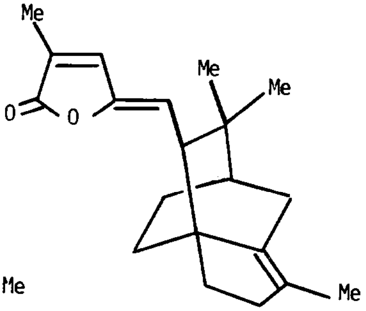
Summary: A regio- and stereo-selective bisannulation reaction is reported.

The synthesis of the biogenetically novel diterpene eremolactone (1)[1] or its acid-catalysed rearrangement product (2)[2] could in principle be carried out using Diels-Alder reactions to construct the bridged ring. This has been accomplished[3,4] but with two severe drawbacks which have prevented completion of the synthesis. No Diels-Alder addition has been found possible with addenda containing the potential gem-Me_2, and although classical approaches through 1-acetoxyacrylonitrile, basic hydrolysis and dimethylation of the resulting ketone introduce this Me_2, the resulting ketone of type (3) is so unreactive that so far no side-chain can be added at this position.[4] These results are noted in order to underline the importance of a workable procedure involving addition of a dienophile with gem-dialkyl groups at the terminus.[5]



(1)



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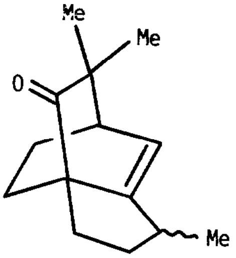
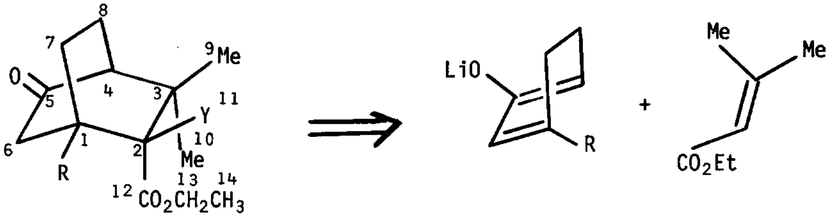


(3)

The difficulty is not unexpected, since the reactive diene cyclopentadiene gives[6] only about 5% yield of product with 3,3-dimethylacrylic acid and none with cyclohexadiene. This lack of reactivity might be due to the adverse electronic and steric effects of the two methyl groups. Also the diene required for syntheses such as that above is much more hindered, and rather unreactive even with good dienophiles.

As model studies towards our objective, we directed our initial efforts to the synthesis of relatively simple bicyclic adducts (4) and (5) by an appropriate interaction between a α'-dienolate (6, R=H or Me) and ethyl 3,3-dimethylacrylate. However, no bicyclic adduct was obtained, although use of methylacrylate has been well documented[7,8]



(4) R=H, Y=H

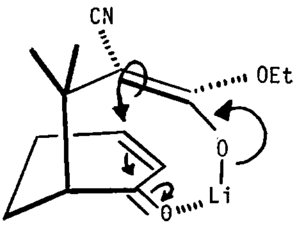
(5) R=CH_3, Y=H

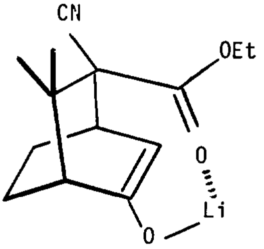
(6) R=H or Me

for a facile synthesis of bicyclo[2,2,2]-octan-2-ones, and in recent years some natural product syntheses have utilized[9-11] such bisannulation reactions as their key step.

We now report a successful bis-annulation reaction, which introduces the gem-dimethyl group, utilising alkyl S-propylidenecyanoacetate as the dienophile. The additional CN group is necessary to activate this partner, reaction then occurring with the cross-conjugated dienolate salt (6, R=H or Me). The process represents a regio- and stereo-selective synthesis of endo-2-ethoxycarbonyl-exo-2-cyano-3,3-dimethyl-bicyclo [2,2,2]-octan-5-one and endo-2-ethoxycarbonyl-exo-2-cyano-1,3,3-trimethyl-bicyclo[2,2,2]-octan-5-one in ∿55-60% isolated yields.

Despite the origin of the process, it is not certain that the mechanism is that of the Diels-Alder reaction,[12] since a possible alternative involves a double Michael addition as shown, the regio- and stereospecificity being directed by reactivity consideration and by chelation. The Diels-Alder process is also often very structure-specific in its products. Whatever the mechanism, this type of reaction clearly has considerable synthetic potential.





Reaction of α'-dienolate (6, R=H and Me) with ethyl S-propylidenecyanoacetate: The desired α'-enolate (6, R=H) of α,β-cyclohexenone was generated by the action of MeLi (5% in ether, 10 mmole) on 2-trimethylsiloxy-cyclohexa-1,3-diene (10 mmole) in dry THF (15 ml) under N_2 at -40°C. After 15 min, 10 mmole of ethyl-S-propylidenecyanoacetate in 10 ml of THF was introduced dropwise. Reaction mixture immediately acquired a yellow colour.

After stirring for 2 h at -20°C, the reaction mixture was allowed to come to ambient temperature. After usual work-up and chromatography over silica gel, it gave (yield ∿60%) a crystalline material, m.p. 107-109°C (2,4-DNP, m.p. 209-211°C, decomposition) to which structure 4 (R=H, Y=CN) was initially tentatively assigned based on the following spectral data: IR ($CDCl_3$): C=O 1710-1740 cm^{-1}, C≡N 2240 cm^{-1}; Mass: m/e 249 $C_{14}H_{19}O_3N$ (M^+, 55%), 96 ($M^+ - C_8H_{11}O_2N$, 100%). ^1H-NMR (100 MHz, $CDCl_3$, δ): 1.00 (s, C-3 $C\underline{H}_3$), 1.35 (t, J=7 Hz, $-CO_2CH_2C\underline{H}_3$), 1.48 (s, C-3 $C\underline{H}_3$), 1.49-2.50 (m, 6H, C-4 H, C-6 H endo, C-7,8 2 $C\underline{H}_2$), 2.68 (bs, C-1 H), 3.11 (ddd, J=20, 3, 2 Hz, C-6 H exo), 4.30 (q, J=7 Hz, $-CO_2C\underline{H}_2CH_3$). In the presence of shift reagent $Eu(fod)_3$[13], the ^1H-NMR spectrum was reduced to a nearly first order type, and with the help of extensive decoupling experiments following assignments were unambiguously made (δ): 1.72 (t, J=7 Hz, $-CO_2CH_2C\underline{H}_3$), 2.66 (s, C-3 $C\underline{H}_3$), 2.88 (s, C-3 $C\underline{H}_3$), 2.96-3.90 (m, $C_{7,8}$ 2 $C\underline{H}_2$), 4.12 (bs, C-1 H), 4.96 (q, J=7 Hz, $-CO_2C\underline{H}_2CH_3$), 5.64 (m, C-4 H), 5.96 (dd, J=20 Hz, 3 Hz, C-6 H endo), 6.15 (overlapping ddd C-6 H exo). Furthermore, ^{13}C-NMR (15.03 MHz, $CDCl_3$, ppm) spectrum displayed only 14 peaks: 14.033 (C-14), 18.067 (C-7), 23.390 (C-8), 26.119 (C-9), 26.508 (C-10), 35.475 (C-1), 37.165 (C-3), 40.543 (C-6), 52.109 (C-2), 55.227 (C-4), 62.634 (C-13), 118.772 (-CN, C-11), 167.243 (C-12) and 212.335 (C-5). With the help of off-resonance ^1H-decoupled spectrum the non-protonated carbons (C-2,3), CH (C-1,4), CH_2(C-6,7,8 and 13), CH_3 carbons (C-9,10 and 14) were observed as singlets, doublets, triplets and quartets, respectively, providing further support to the assigned structure.

Likewise the α'-dienolate (6, R=CH_3) reacted smoothly with ethyl S-propylidenecyanoacetate to afford a crystalline bicyclic adduct 5 (R=CH_3, Y=CN) in ∿55% yield. The absence of a broad signal (no C-1 H) in its ^1H-NMR spectrum between δ 2.5-3.0 and appearance of a dd at δ 3.36 with J=20 Hz and 2 Hz is particularly noteworthy and provides additional support to the structural assignments made earlier.

It is clear from the foregoing that a single isomer was produced in this reaction, although orientation of the -CN and $-CO_2Et$ group still remained to be defined.

Configuration of bicyclic adducts 4 (R=H, Y=CN) and 5 (R=CH_3, Y=CN): The stereo-structure of a 2,4-dinitrophenylhydrazone of the bicyclic adduct 4 (R=H, Y=CN) has been established in a single crystal X-ray diffraction experiment[14] (shown in Figure 1).

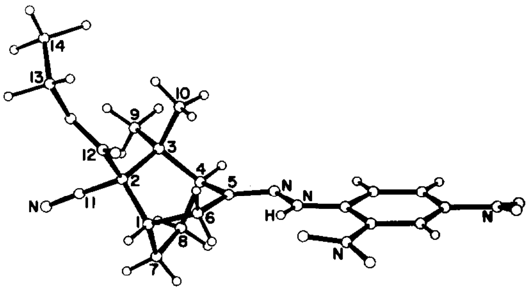


FIGURE 1

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