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SYNTHESIS OF POLYQUINANES I: INTRAMOLECULAR DIELS-ALDER REACTION[1]

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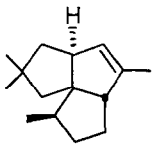
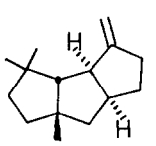
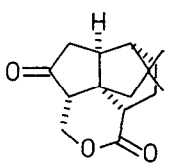
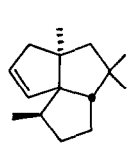
Abstract: The intramolecular Diels-Alder reaction of several substituted cyclopentadienes to functionalized tricyclic products, suitable for transformation to polyquinane natural products, is described.

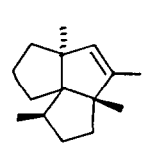
We have embarked on what promises to be an extremely versatile strategy for the synthesis of natural products containing more than one 5-membered carbocyclic ring (a sampling of which are depicted below). The basic strategy involves an intramolecular Diels-Alder[4] reaction with cyclopentadiene (to 2) followed by cleavage of the double bond to form a [3.3.0]-bicyclooctane


PENTALENENE

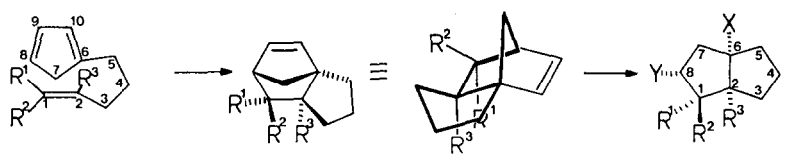

$\Delta^{9(12)}$ CAPNELLENE


QUADRONE


SILPHINENE


ISOCOMENE

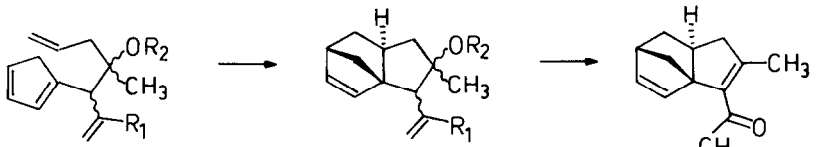
ring system (eq. 1). Three points about this strategy are noteworthy. First, up to three quaternary centers could be formed in the cyclization, depending on the substitution at the dienophile. Second, the stereochemistry of the four chiral centers shown in 3 is well defined because of the exo nature of the intramolecular Diels-Alder reaction (vide infra). Third, all of the ring carbons in 3 except for C-7 may bear substituents depending on the choice of the bridging chain.


1 2 3 eq. 1

In this intramolecular Diels-Alder Reaction the diene and the dienophile are tethered by a three carbon chain. In similar ring systems it has been determined that the bridging chain of this length always occupies the exo position.[5] This has been interpreted as a consequence of the cis[3.3.0]bicyclooctane ring system that is formed in the exo approach (outlined in boldface

in 2) as opposed to the much less stable trans[3.3.0] skeleton that would result from an endo approach. Thus, cleavage of the double bond in 2 leads to a diquinane with up to 5 substituents positioned stereospecifically as shown in 3. We would like to report some of our preliminary results aimed at the synthesis of intermediates suitable for transformation to pentalenene, capnellene, quadrone, silphinene and isocomene. In the course of this investigation we have shed some light on substituent effects (both on the dienophile and on the bridging chain) and stereochemical consequences of substituents on the bridging chain.

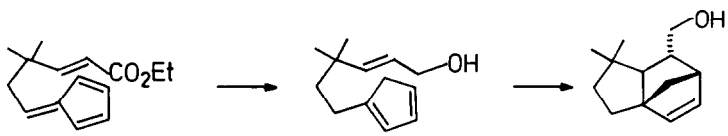
Reaction of the unactivated monosubstituted dienophile in 4(R_1=OEt, R_2=Bn) is complete after heating at 110° for 4 hrs. The mixture of isomeric products is best analyzed after hydrolysis of the enol ether which is accompanied by elimination of the benzyloxy group to yield isomerically pure 6[7] in 26% overall yield. When 4 (R_1=CH_3 R_2=Bn) was used instead a



4 5 6 eq. 2

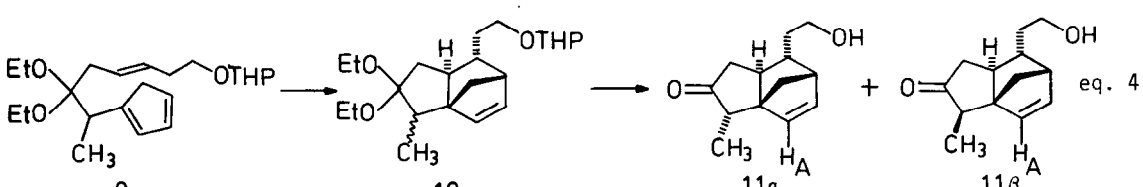
60% yield of 5(R_1=CH_3,R_2=Bn) could be isolated after heating at 160°C for 5 hrs, as a mixture of epimers after chromatography. The yield of 5 improved to >95% if R_2=CH_3.

A high yield of the Diels-Alder product is obtained from the trans disubstituted olefin 7. In this case 88 hrs at 160°C were required for production of 8[7] in essentially quantitative yield (NMR).



7 8 eq. 3

A much faster reaction occurs when the quaternary carbon on the bridging chain is positioned as in 9. Although the double bond is still trans and disubstituted the cyclization is over in 4 hrs. This rate enhancement is reminiscent of the similar substituents effects that we have observed in furan Diels-Alder reactions[8] and those observed by Boeckman.[9]

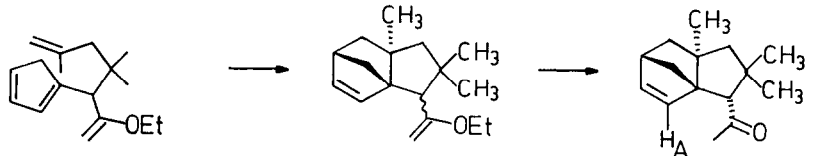


9 10 11α 11β eq. 4

It is interesting to observe the reaction progress of 9 by NMR. Initially (at 100°C) the complex olefin region becomes even more complex presumably due to dimer formation. On heating longer at 160° this region dramatically simplifies, finally showing only the two olefin protons found in the product. In this case two isomers are present in about a 1:1 mixture.

Hydrolysis of the ketal and simultaneous cleavage of the THP ether yields 11[7] (as a 1:1 mixture of epimers) in 87% overall yield from the substituted cyclopentadiene. Base catalyzed epimerization of the methyl group may be carried out enriching the mixture in the β isomer (8:2). The assignment of the stereochemistry was based on an NOE experiment. Observing H_A and irradiating the methyl group in both the major and minor isomers showed a 13% NOE enhancement for the minor isomer only. Molecular models indicate that in the α isomer the irradiated methyl group is quite close to H_A.

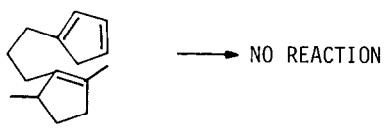
Interestingly when an α,α-disubstituted dienophile is used (eq. 5) the reaction is over in two hrs at 160°C. Compound 13 is formed as a mixture of epimers with one greatly predominating



12 13 14 eq. 5

After hydroylsis one ketone (14[7]) is present in 74% overall yield. The stereochemistry of the methyl ketone has been tentatively assigned the α configuration because of an anomolous shielding of H_A (5.96) which presumably spends some time in the shielding cone of the carbonyl.

In an attempt to find the limitations of this intramolecular Diels-Alder reaction a tetrasubstituted unactivated dienophile was used. Three contiguous quaternary centers would be formed in this reaction. Compound 15 was found to be unreactive at temperatures up to 250° in solution and 500°C in the gas phase. Attempts to electronically activate the dienophile for



15 eq. 6

this particular reaction are under way. Conversion of some of these products to naturally occurring polyquinanes will be the subject of future reports.

Acknowledgement

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REFERENCES

1. Preparation of the starting materials used in this paper will be described elsewhere.

2. Undergraduate research participant.

3. Conoco Chemicals Company Summer Undergraduate Research Fellow (1982)

4. For some recent reviews see: G. Brieger and J. N. Bennett, Chem. Rev. **80** 63 (1980); W. Oppolzer, Angew Chem. Int. Ed. Engl. **16** 10 (1977).

5. E. J. Corey and R. S. Glass, J. Amer. Chem. Soc. **89** 2600 (1967). For some other examples see: E. G. Breitholle and A. G. Fallis. J. Org. Chem. 43, 1964 (1978), G. Brieger J. Amer. Chem. Soc. 85 3783 (1963).

6. Selected spectral data:

   6 ^{1}H NMR (δ, $CDCl_3$, 80 Mhz) - 6.30 (d, J = 6.4 Hz, 1H); 6.00 (dd, J = 6.4 Hz, 3.2 Hz); 3.07 (br.s, 1H); 2.25 (s, 3H); 2.08 (s, 3H); 1.90-2.70 (mults., 2H); 1.25-1.75 (mults., 5H).

   8 ^{1}H NMR (δ, $CDCl_3$, 250 Mhz) - 6.23 (d, J = 5.7 Hz, 1H); 5.93 (dd, J = 5.7 Hz, 2.8 Hz, 1H); 3.34 (dd, J = 10.4 Hz, 6.6 Hz, 1H); 3.25 (dd, J = 10.4 Hz, 8.5 Hz); 2.93 (br.s., 1H); 2.24 (ddd, J = 8.5 Hz, 6.6 Hz, 5.3 Hz, 1H); 1.1-1.86 (mults., 7H); 1.04 (s, 3H); 1.01 (s, 3H); 0.80 (dd, J = 5.3 Hz, 1.9 Hz, 1H).

   ^{13}C NMR (δ, $CDCl_3$, 22.5 Mhz) - 143.0, 132.0, 67.4, 64.9, 60.5, 51.4, 45.9, 45.1, 44.6, 36.8, 33.0, 27.6, 26.7.

   I.R. ($CDCl_3$, cm^{-1}) - 3625(m), 3450(br., w), 3050(w), 2960(s), 2875(s), 1465(m), 1365(m), 1015(m).

   11α ^{1}H NMR (δ, $CDCl_3$, 250 Mhz) - 6.26 (d, J = 5.9 Hz, 1H); 5.09 (dd, J = 5.9 Hz, 2.9 Hz, 1H); 3.65 (t, J = 6.6 Hz, 2H); 2.89 (br.s., 1H); 2.68 (dd, J = 18.9 Hz, 9.0 Hz, 1H); 2.32 (q, J = 7.7 Hz, 1H); 2.07 (dd, J = 18.6 Hz, 8.6 Hz, 1H); 2.00-2.10 (mult., 1H); 1.69 (br.s., 1H); 1.35-1.60 (mult., 5H); 1.19 (d, J = 7.7 Hz, 3H).

   11β ^{1}H NMR (δ, $CDCl_3$, 250 Mhz) - 6.18 (d, J = 5.5 Hz, 1H); 6.09 (dd, J = 5.5 Hz, 2.9 Hz, 1H); 3.65 (t, J = 6.8 Hz, 2H); 2.91 (br.s., 1H); 2.72 (dd, J = 19.3 Hz, 10.5 Hz, 1H); 2.50 (q, J = 7.0 Hz, 1H); 1.98 (dd, J = 19.1 Hz, 9.9 Hz, 1H); 1.92-2.04 (mult., 2H); 1.39-1.59 (mult., 5H); 1.05 (d, J = 7.0 Hz, 3H).
   ^{13}NMR (δ, $CDCl_3$, 22.5 Mhz) - 220.7(s), 139.0(d), 1342.(d), 63.5(s), 61.4(t), 47.5(t), 46.7(d), 46.3(d), 45.2(d), 44.9(d), 44.1(t), 37.3(t), 10.7(q).

   14 ^{1}H NMR (δ, $CDCl_3$, 250 Mhz) - 6.05 (dd, J = 5.7 Hz, 3.0 Hz, 1H); 5.96 (d, J = 5.6 Hz, 1H); 3.16 (s, 1H); 2.88 (br.s., 1H); 2.21 (s, 3H); 1.94-1.63 (mult., 5H); 1.38 (s, 3H); 1.01 (s, 3H); 0.87 (s, 3H); 0.87 (mult., 1H).

   ^{13}C NMR (δ, $CDCl_3$, 22.5 Mhz)- 209.6(s), 137.5(d), 135.3(d), 67.5(s), 60.2(d), 56.6(t), 50.8(t), 48.4(s), 44.8(d), 42.6(t), 42.0(s), 34.1(q), 33.2(q), 29.4(q), 25.9(q).

8. D. D. Sternbach and D. R. Rossana, Tetrahedron Lett., **23**, 303 (1982); D. D. Sternbach and D. R. Rossana, J. Amer. Chem. Soc., **104** 5853 (1982).

9. R. K. Boeckman and S. S. Ko, J. Amer. Chem. Soc., **104** 1033 (1982).

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