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INTRAMOLECULAR DIELS-ALDER REACTION WITH FURAN-DIENE[1]. A NOVEL POTENTIAL ENTRY TO STEROIDS.

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ABSTRACT

Depending on the reaction conditions the intramolecular Diels-Alder reaction of furan-diene 14 yields predominantly either one of two adducts 16a and 16b, which possess the necessary functionality for eventual transformation into corticosteroids. The dienophile was introduced via alkylation of the enolate, formally obtained upon lithium-liq. ammonia reduction of 3-furyl-2-methyl-2-cyclopentenone (7).

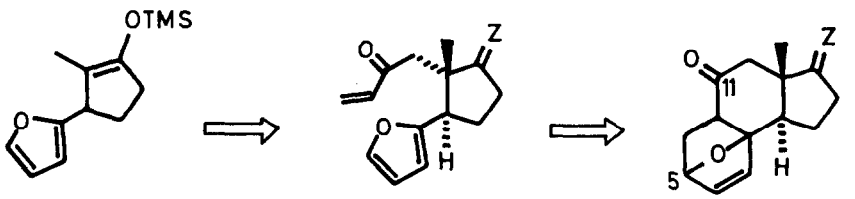
Although the intramolecular version of the Diels-Alder reaction has received considerable attention in natural product synthesis[3], little work has been devoted so far to the case where a furan functions as a diene partner[3a,4,5]. Yet this particular reaction should offer considerable synthetic potential due to the presence of an oxygenated cyclohexene system in the adduct (cf. gibberellins) and to the availability of a large number of functionalized furans. In this connection we wish to report here on the successful application of this reaction type to the construction of potential steroid precursors.

1 2

a n=2, X=O
b n=2, X=H,OH
c n=1, X=O
d n=1, X=H,OH

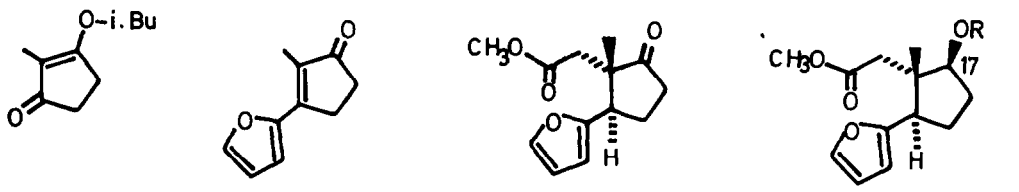
In a series of model experiments we have found that for the construction of the simple oxatricyclo|6.2.1.$0^{1,6}$|undecene (2, n = 2) system activation of the dienophile 1 (n = 2) is necessary. Indeed, whereas 1a readily led to the corresponding exo-adduct 2a (CH_2Cl_2, reflux : 82 % conversion; CH_2Cl_2, florisil, r.t. : 93 % conversion), the corresponding alcohol 1b did not yield any 2b (CH_2Cl_2 or benzene, reflux, 6 days)[1,5]. Encouraged by these preliminary results we decided to apply this methodology to steroid synthesis. The projected route rests on the simultaneous formation of the BC-rings of the steroid nucleus via Diels-Alder reaction, i.e., 4 to 5. The dienophile side chain of the precursor 4 would be introduced via alkylation of the enolate derived from 3. In the expected adduct 5 the 11-carbonyl group would then serve as a means to open the bridged ring system and the thereby released oxygen at C-5 as a handle to append the A-ring. With this strategy a novel entry to cortico-

steroids would be at hand[6].

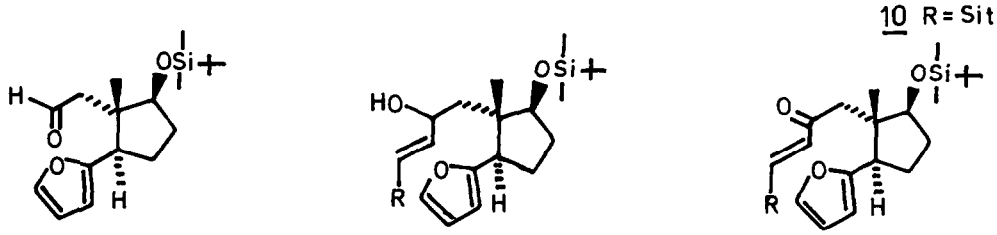


3 4 5

Reaction of the readily available enolether 6[7] with furyllithium (3 eq, THF; 1 h at 0°C, 12 h at r.t.), followed by acid hydrolysis (NH_4Cl-HCl-H_2O, 20 min at -10°C) and purification (gradient elution on silica gel with successively 8 % EtOAc-hexane and 14 % EtOAc-hexane; Kugelrohr-distillation : 110°C at 0.1 mm Hg; crystallization from 20 % EtOAc-hexane, m.p. 58°C) led to enone 7[8] in 74 % yield. Lithium-liquid ammonia reduction of this enone (3 eq Li, 0.8 eq t.BuOH, THF; isoprene after 30 min), followed by trapping of the enolate obtained after thorough removal of the ammonia (THF, successive treatment with 5 eq Et_3N and 5 eq Me_3SiCl at -15°C) gave 3 (b.p. 76-81°C at 0.04 mm Hg) in 70 % yield.



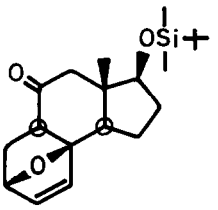
6 7 8 9 R=H 10 R=Sit.BuMe2



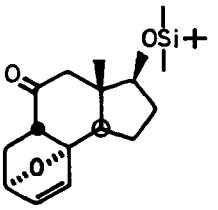
11 12 R=H 13 R=Me 14 R=H 15 R=Me

The introduction of the dienophile first involved the alkylation of the preformed enolate of 3 (1 eq MeLi, THF, 0°C) with methyl bromoacetate in HMPA (7 eq; 4.5 h at r.t.) which led after purification on silica gel (10 % EtOAc-isooctane; removal of ca 7 % cis-isomer) to pure ketone 8[8] in 67 % yield. Subsequent reduction with lithium tri-t-butoxyaluminumhydride (2 eq, THF) to alcohol 9[8] (81 % yield) and protection (2.2 eq t-$BuMe_2SiCl$, 1.1 eq imidazole in DMF, 6 h at r.t.; purification on silica gel with 5 % EtOAc-isooctane) afforded 10 in 79 % yield. Only a single diastereoisomer is formed upon reduction; the shown configuration is

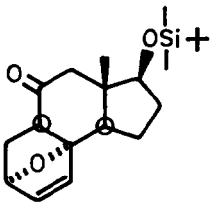
substantiated by the large sum of vicinal J-values (ca 17 Hz) for H-17. After reduction of the ester group with diisobutylaluminum hydride (toluene, 75 min at -70°C; MeOH work-up at -70°C and further 16 h at r.t.) a 74 % yield of aldehyde 11[8] was obtained (next to 24 % over-reduced diol; 2 % EtOAc-isooctane). Originally, the present route was chosen since aldehyde 11 allows for the synthesis of a variety of dienophiles. Reaction with vinyl- and propenyl-magnesium bromide gave 12 (as a 7:3 mixture at C-11; 88 % yield) and 13 (91 % yield), respectively. Allylic oxidation (12 with MnO_2 in benzene, 20 h at r.t. and 13 with $BaMnO_4$ in CH_2Cl_2, 36 h at r.t.) led to the corresponding enones 14[8] and 15[8] in 88 % and 63 % yields, respectively.



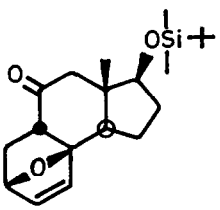
16a



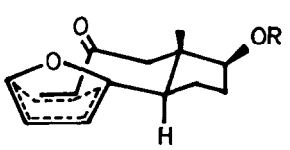
16b



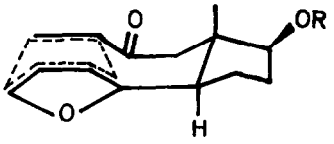
16c



16d



16a - TTS



16b -TTS

Much to our surprise we discovered that enone 14 gave rise predominantly to either one of two adducts, depending on the reaction conditions : in CH_2Cl_2 at r.t. (6 days) a 1:8 ratio 16a and 16b (61 % conversion) was observed, while in benzene (6 days) at 80°C 16a and 16b were formed in a ratio of 9:1 (50 % conversion), respectively[9]. Using the same reaction conditions, no adduct could be detected in the case of the methyl-substituted enone 15. Distinction between the four possible adducts 16a-d is readily made by ^{1}H-NMR. Both 16a[8] and 16b[8] are identified as exo-adducts in view of their H(endo)-10/H-9 J values (8.5 Hz)[1c]. Furthermore, the torsion constraints in the adducts impose a chair-conformation for the C-ring of 16a (m.p. 90.5°C) and a boat-like form in 16b (m.p. 60°C); these can be inferred from the $|^2J|$-value at C-12 (12.5 and 18.5 Hz for 16a and 16b, respectively)[11].

The sole formation of exo-adducts upon Diels-Alder reaction of 14 is not surprising in view of the high strain that one would expect in 16c and 16d[12]. More surprising was the finding that 16b was the preferred adduct at lower temperature. Examination of the transition states reveals however a BCC-like conformation for the pseudo-tenmembered ring in 16a and a BCB-like form in 16b. Force field calculations have shown the BCB-conformation to be the preferred form in cyclodecane[13], thus suggesting 16b-TTS as the preferred transition state for Diels-Alder reaction.

The present synthesis demonstrates the viability of the intramolecular Diels-Alder reaction with furan-diene for the construction of elaborate polycyclic systems provided that the proper dienophile is used. Eventual application of this route to the synthesis of corticosteroids will be reported in due course.

References and Notes

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2. Research Associate of the National Fund for Scientific Research (N.F.W.O.).
3. For recent reviews, see : (a) G. Brieger and J.N. Bennett, Chem. Rev., 80, 63 (1980); (b) W. Oppolzer, Angew. Chem., 89, 10 (1977).
4. For examples where the furan-diene and the dienophile are connected by a 4-carbon chain, see ref. 1. By a 3-carbon chain, see : K.A. Parker and M.R. Adamchuck, Tetrahedron Lett., 1689 (1978); D.D. Sternbach and D.M. Rossana, Ibid., 303 (1982).
5. In contrast we could not isolate any 2c or 2d from 1c and 1d (ØH, ΔT, 6d), respectively.
6. For the application of intramolecular Diels-Alder reactions in steroid synthesis, see : T. Kametani and H. Nemoto, Tetrahedron, 37, 3 (1981). Whereas BC-ring formations via 9-8/6-7 and 9-8/11-12 D-A closures have been reported, to the best of our knowledge the present route is the first one aiming at a 9-8/5-10 closure.
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8. Satisfactory spectral data were obtained for all compounds. Relevant NMR data (360 MHz, $CDCl_3$, δ ppm); 3 (90 MHz,CCl_4) : 7.16 (1H,d; 3.0 Hz), 6.1 (1H,m), 5.8 (1H,d; 1.8 Hz), 1.3 (3H,s). 7 (90 MHz,CCl_4) : 7.6 (1H,bs), 6.75 (1H,m), 6.53 (1H,m), 2.0 (3H,bs). 8 (90 MHz) : 7.35 (1H,m), 6.31 (1H,m), 6.10 (1H,m), 3.67 (1H,m), 3.65 (3H,s), 0.68 (3H,s). 9 (90 MHz) : 7.32 (1H,m), 6.29 (1H,m), 6.06 (1H,m), 4.14 (1H,t; 8.4 Hz), 3.81 (1H,s), 3.65 (3H,s), 2.88 (1H,t; 9.0 Hz), 0.74 (3H,s). 10 (90 MHz) : 3.75 (3H,s), 0.86 (9H,s), 0.60 (3H, s). 11 : 9.73 (1H,t; 3.0 Hz), 2.38 and 2.48 (2H,ABd; 15.0, 3.0 Hz). 12 (7:3 mxt) : 5.86/5.90 (1H,m), 5.24/5.21 (1H,dt; 17.5, 1.5 Hz), 5.04 (1H,dt; 10.5, 1.5 Hz), 0.93/0.91 (9H,s), 0.76/0.75 (3H,s). 14 : 6.41 (1H,ABX; 17.5, 10.0 Hz), 6.20 (1H,ABX; 17.5, 1.5 Hz), 5.72 (1H, dd; 10.0, 1.5 Hz). 16a : 6.39 (1H,dd; 5.5, 1.5 Hz), 6.16 (1H,d; 5.5 Hz), 4.98 (1H,dd; 4.5, 1.5 Hz), 3.88 (1H,t; 8.5 Hz), 2.57 and 2.24 (2H,AB; 12.5 Hz), 2.45 (1H,dd; 8.5, 11.5 Hz), 2.37 (1H,dt; 12.0, 4.5 Hz), 2.13 (1H,dd; 8.0, 4.0 Hz), 1.52 (1H, dd; 12.0, 8.5 Hz); 16b : 6.46, 6.40 (2H,m), 4.91 (1H,dd; 4.5, 1.5 Hz), 3.79 (1H,t; 8.5 Hz), 2.56 (1H,dd; 8.0, 4.5 Hz), 2.51 and 2.21 (2H,AB; 18.5 Hz), 2.32 (1H,dt; 12.0, 4.5 Hz), 1.96 (1H,~t; 10 Hz), 1.42 (1H,dd; 8.5, 12.0 Hz).
9. In the benzene case a true equilibrium is involved since the same ratios were obtained when either pure 16a or 16b were subjected to the same conditions.
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