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SYNTHESIS OF POLYFUNCTIONAL, LINEARLY CONDENSED SIX-MEMBERED RING SYSTEMS BY REGIOSELECTIVE TANDEM DIELS-ALDER ADDITIONS. SYNTHESIS AND REACTIVITY OF 6,7-BIS(CHLOROMETHYL)-8,9-BIS(METHYLENE)-2-OXABICYCLO[3.2.1]NONAN-3-ONE

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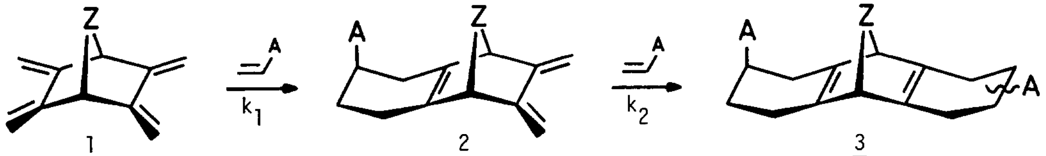
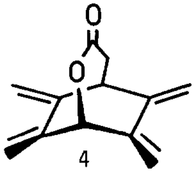
Summary. The title compound is a useful starting material for the preparation of complex linearly condensed six-membered ring sytems via tandem Diels-Alder additions.

Polyenes 1 are useful starting materials for the synthesis of polycylic, polyfunctional compounds via tandem Diels-Alder additions.[1] When Z = O, CH_2 or CH=CH, the rate constant ratio k_1/k_2 for the two successive cycloadditions can be > 100.[1,2] This allows one to isolate the corresponding monoadducts 2 in good yields and to use a second dienophile different than the first one to generate the corresponding bis-adducts. This principle has been applied in our doubly-convergent synthesis[3] of anthracyclinones.[4]



1 2 3

The Diels-Alder reactivity of 1 and 2 depends on the nature of the bridge Z.[1a,2] For instance, the tetraene 1 (Z = CH_2) reacts 170 times as fast as 1 (Z = O) towards tetracyanoethylene (toluene, 25°C).[2a] This was attributed to the inductive effect of the O(7) bridge which increases the ionization potential of the tetraene and makes 1 (Z = O) less reactive than 1 (Z = CH_2, CH_2-CH_2, etc.). This observation suggested to us that a lactone or a lactame bridge as in 4 and 5, respectively, could make the two successive cycloadditions regioselective, thus making 4 and 5 potential starting materials for the preparation of non-symmetrical, linearly-condensed six-membered ring systems.



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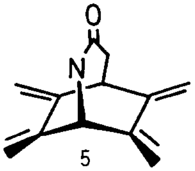

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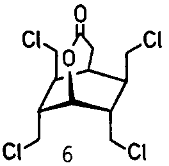

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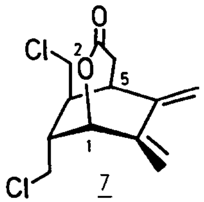

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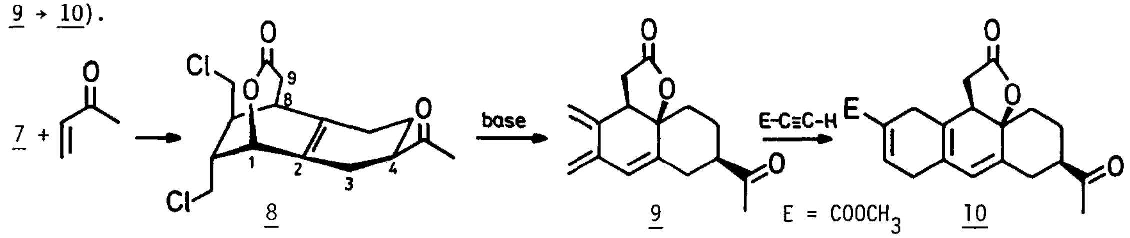
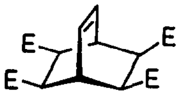
We report on the synthesis of 4 and 5. Unfortunately k_1/k_2 was found to be near unity for the two successive Diels-Alder additions of these tetraenes, thus limiting their synthetic potential. Moreover, 4 and 5 had a strong tendency to polymerize. We found, however, that the mono-diene 7 could be derived readily from the tetrachloride 6, the precursor of 4. We shall show that 7 adds to strong dienophiles with good regio- and stereoselectivity (e.g. 7 → 8). We have found also that adduct 8 can be transformed in one step to the corresponding triene 9 which adds to non-symmetrical dienophiles with good regioselectivity (see e.g.: 9 → 10).



8 9 E = COOCH$_3$ 10

The tetraenes 1 (Z = CH$_2$-CH$_2$, CH$_2$CH(OH)) and pentaene 1 (Z = CH=CH) were derived from the tetraester 11.[5] Base-induced isomerization of 11 in MeOH gave the all-trans derivative 12 as major product.[6] It was transformed to 13.[5b] Treatment with O-mesitylenesulfonylhydroxylamine (CH$_2$Cl$_2$, 20°C, 3 h)[7] afforded 14 (85%, one unique isomer). Heating in EtOH (75°C, 4 h) gave the lactam 15 (73%) which furnished tetraene 5 (73%) on treatment with tBuOK in THF (60°C, 8 h). The structure of 5 was given by its spectral data;[8] it confirmed that the Beckmann rearrangement of 14 implies the migration of the secondary alkyl group, rather than that of the primary alkyl group. In contrast, all our attempts to generate the corresponding lactone 17 by Baeyer-Villiger oxidation of 13 gave only the unexpected isomer 16.



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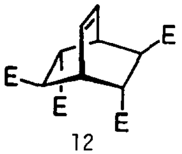

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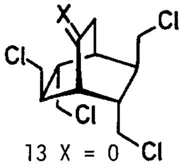
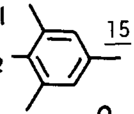
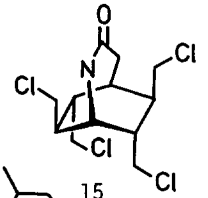


13 X = O

14 X = NOSO$_2$–





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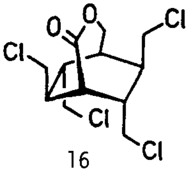

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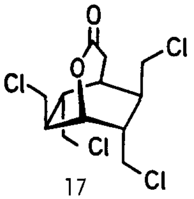

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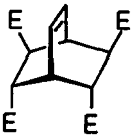

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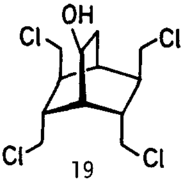

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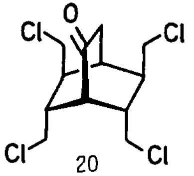

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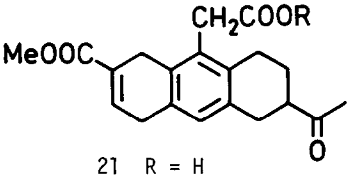
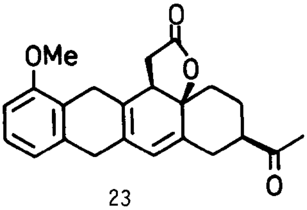
Since the conformation of the intermediates in the Baeyer-Villiger rearrangement can influence the stereoselectivity of the reaction,[9] we looked for an isomer of 13 in which the ClCH$_2$ substituents would not perturb the neighbourhood of the carbonyl group as much as in 13. We found that an equilibrated mixture of the tetraesters obtained by treatment of 11 with MeONa in MeOH at 65°C yielded a precipitate of 18 (20%) on addition to ice. The other isomers (composed mostly of 12) were reequilibated with MeONa/MeOH. Reduction of 18 (LiAlH$_4$, THF, 65°C, 3d), followed by treatment with SOCl$_2$/pyridine (80°C, 2 h) gave the corresponding tetrachloride (57%) which was then transformed into alcohol 19 (97%) by oxidative hydroboration. Oxidation with CrO$_3$/pyridine in CH$_2$Cl$_2$ (0°C-20°C, 1 h), followed by treatment with silica gel (CH$_2$Cl$_2$), gave ketone 20 (66%) whose structure was established by its spectral data,[10] and more specifically by 360 MHz ^{1}H-NMR with the help of NOE and LIS(Eu(thd)$_3$)

measurements. On treatment with citraconic anhydride, H_2O_2 90% and a trace of tosylic acid (CH_2Cl_2, 20°C, 8 d) the lactone 6 was obtained in 38% yield (m.p. 138-139°C; IR(KBr): 1710 cm^{-1}). Heating of 6 with 5 mol equiv of CsF, 1 mol equiv of Cs_2CO_3 in anh DMF/HMPT 15:2 (80°C, 75 min) gave an oily mixture containing the diene 7[11] and a small amounts of 6 and 4.[12,13] Prolonged heating (80°C, 12 h) under the same conditions afforded tetraene 4 in 62% yield.

The thermal Diels-Alder additions of methyl propynoate, butynone and methyl vinyl ketone (MVK) to 7 were not regioselective. However, in the presence of 5 mol equiv of MVK pre-complexed with $BF_3 \cdot Et_2O$ or $EtAlCl_2$, 7 reacted at -78°C (CH_2Cl_2, 3h, quenching with Et_3N at -78°C) to give one unique adduct 8[14] (69%) whose structure was determined by LIS, NOE measurements in the ^1H-NMR spectra and by 2D-NMR (H-H and H-^{13}C correlations).[15] Treatment of 8 with 4 mol equiv of CsF and 1 mol equiv of Cs_2CO_3 in anh DMF/HMPT 15:2 (80°C, 7h) gave triene 9 (48%, isolated). The double elimination of HCl was accompanied by an anionotropic rearrangement. The electron-donating ability of the endocyclic double bond in 9 renders its exocyclic butadiene moiety highly "para" regioselective[16] (95% by ^1H-NMR of the crude reaction mixture) in its cycloaddition to methyl propynoate (C_6H_6, 50°C, 10 h) to give adduct 10. Purification on silica gel led to the formation of acid 21, whose methyl ester 22 was isolated (76%) after treatment with CH_2N_2/Et_2O.[17]



21 R = H
22 R = CH_3



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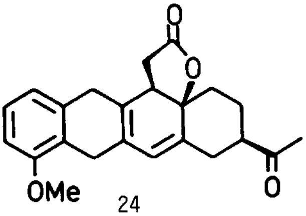

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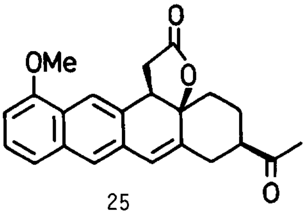

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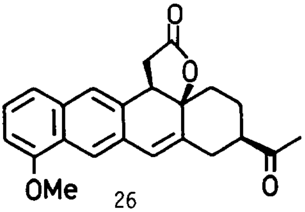

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The Diels-Alder addition of 2,3-didehydroanisole, generated by deamination of 2-amino-6-methoxybenzoic acid[18] (pentyl nitrile, dioxane, 70°C), to 9 afforded a 4:1 mixture of 23/24 which were oxidized under our reaction conditions to give a 4:1 mixture of 25/26 (35%, isolated). The structure of 22[17] and 25[19] were given by their spectral data and with the help of NOE measurements in their ^1H-NMR spectra.[15] The relatively good regioselectivity of the cycloadditions of 2,3-didehydroanisole to 9 is noteworthy.

Our preliminary results demonstrate a new principle for the synthesis of linearly condensed six-membered ring sytems by regioselective tandem Diels-Alder additions. This technology might be useful for the preparation of anthracyclinone analogs.

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References and Notes.

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8. Data of 5 : white crystals, polymerise quickly. UV(EtOH 95%): λmax 247 (8930), 237 (9995), 231 (10 100). IR(KBr): 3600-3000, 3230, 3100, 2940, 2910, 1645, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.1 (br.d, 7 Hz, NH); 5.43 (s, 4H); 5.03 (br.s, 4 H); 4.15 (d, 7, H-C(1)); 3.33 (t, 4, H-C(5)); 2.73 (d, 4, $H_2C(4)$).
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10. Data of 20: m.p. 109-110°C. IR(KBr): 2980, 2955, 2900, 1740, 1455 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 3.80 (dd, 7, 11 Hz, 2H); 3.76 (dd, 5, 11, 2H); 3.57 (dd, 7.5, 11, 2H); 3.44 (dd, 9.5, 11, 2H); 2.87 (br.t, 1.5, H-C(1)); 2.75 (br.tt, 2, 3, H-C(4)); 2.33 (d, 3, $H_2C(3)$); 1.93 & 1.89 (2 m, 4H).
11. Data of 7: unstable oil. ^{1}H-NMR($CDCl_3$): δ 5.76, 5.50, 5.32 & 5.08 (4s, 4H); 4.84 (d, 1.5, H-C(1)); 3.71 (dd, 12, 6, 2H); 3.49 (m, 2H); 3.20 (dd, 10, 12, 1H); 3.02 (dd, 4, 19, H-C(4)); 2.91 (m, H-C(5)); 2.80 (ddd, 19, 4, 1, H-C(4)); 2.34 & 1.88 (2m, 2H).
12. Data of 4: unstable oil. ^{1}H-NMR($CDCl_3$): δ 5.68, 5.43, 5.32 & 5.05 (4s, 8H); 5.07 (s, H-C(1)); 3.28 (t, 4, H-C(5)); 2.92 (d, 4, $H_2C(4)$).
13. Selective double elimination of HCl from 2,3,5,6-tetrakis(chloromethyl)-7-oxanorbornane to give a conjugated mono-diene has already been noted: C. Mahaim, P. Vogel, Helv. Chim. Acta 65 (1982) 866.
14. Data of 8: oil; ^{1}H-NMR(CD_2Cl_2): δ 4.58 (d, 1.6, H-C(1)); 3.79, 3.58, 3.55 & 3.34 (4dd, 2 CH_2Cl); 2.84 (dd, 19.5, 3) & 2.63 (ddd, 19.3, 4, 1.3, $H_2C(9)$); 2.6 & 2.51 (2m, 2H); 2.44 & 1.91 (2m, 2H); 2.24 (m, 3H); 2.16 (s, CH_3CO); 2.04 & 1.58 (2m, 2H).
15. Details will be given in a full paper.
16. K.N. Houk, J. Am. Chem. Soc. 95 (1973) 4092; K. Fukui, Acc. Chem. Res. 4 (1971) 57.
17. Data of 22: m.p. 107.5-108°C. IR(KBr): 1710, 1700, 1685 cm^{-1}; UV(EtOH 95%): λmax 247 (12 700), 285 (2000), 296 (1880); ^{1}H-NMR(CD_2Cl_2): δ 7.12 (m, 1H); 6.89 (br.s, 1H); 3.76 & 3.67 (2s, 2 COOMe); 3.71 (s, 2H); 3.58 & 3.50 (2m, 4H); 2.87 (d, 8, 2H), 2.87-2.59 (m, 3H); 2.2 (s, CH_3CO); 2.18 & 1.71 (2m, 2H).
18. R.N. Warrener, R.A. Russell, S.M. Marcuccio, Aust. J. Chem. 33 (1980) 2777.
19. Data of 25: IR(CH_2Cl_2): 1770, 1715, 1600 cm^{-1}; ^{1}H-NMR(CD_2Cl_2): δ 7.96 & 7.5 (2s, 2H); 7.35 (d, 4, 1H); 7.35 (d, 5, 1H); 6.82 (dd, 4,5, 1H); 6.47 (d, 2, 1H); 3.98 (s, 3H); 3.68 (dd, 11, 9, 1H); 2.92 & 2.68 (2dd, H_2C); 2.71 (m, 1H); 2.54 (m, 2H); 2.16 (s, Me); 2.15-1.83 (m, 4H).

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