39. Synthesis and *Diels-Alder* Reactivity of 1-(Dimethoxy)methyl-2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane[1])

Preliminary Communication

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A short synthesis of the title compound **13** is reported. The acetal group in **13** enables one to control the regio- and stereoselectivity of the two successive *Diels-Alder* additions of the tetraene. The first addition is significantly faster than the second one, thus making **13** a versatile reagent for regio- and stereoselective 'tandem' cycloadditions.

The 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane (**1**), readily obtained from furan and maleic anhydride [3], can be used to prepare various anthracycline precursors [4] [5]. The principle of our strategy rests upon the fact that the rate constant for the *Diels-Alder* addition of **1** is much larger than that for the reaction of the corresponding monoadduct with the same dienophile [6] [7]. The utility of this principle[3]) would be highly enhanced if the regio and the stereoselectivity of the two successive or 'tandem'[4]) cycloadditions could be controlled. This has been realized recently through stereoselective substitution of the two diene moieties in **1** by arenesulfenyl groups (*e.g.* **2**) [11]. Another possibility would be to use a 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]-heptane (**3**) substituted at one of the bridgehead atom with a group Z capable of directing the regio- (*e.g.* **4**, **5** *vs.* **6**, **7**) and the stereoselectivity (*e.g.* **4**, **6** *vs.* **5**, **7**) of the two successive *Diels-Alder* additions. We report results that manifest this new principle and which demonstrate that the simple technique developed for the preparation of tetraene **1** can also be applied to the synthesis of more complex derivatives, starting from an abundant starting material, furfural.

The addition of maleic anhydride to the dimethylacetal of furfural **8** (prepared according to [12]) (20°C, Et_2O, 7 days) gave the adduct **9** in 70% yield [13] *(Scheme)*. When treated in a Parr apparatus with CO (3.5–4 atm.), abs. MeOH, 12 mol-equiv. of $CuCl_2$ and a small amount of 10% Pd/C (0.008 equiv. of Pd), **9** was transformed (20°C), 5–7 days to the tetraester **10** (70% isolated, m.p. 165–6°C). The all-*exo*-configuration of

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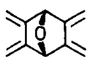
[1]) Interaction between non-conjugated chromophores, Part 22; Part 21: [1]; Part 20: [2].

[2]) Part of the Ph. D. thesis of *J.-L. Métral*, Ecole polytechnique fédérale de Lausanne, Dec., 1984.

[3]) It has been called a 'doubly, doubly convergent' synthesis, see [8].

[4]) This term has been used recently by *Trost* and *Shimizu* [9] for classifying the 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene which allows the generation to two rings in two successive cycloadditions. One should notice that the two diene moieties in **1**, **2** and **13** are generated in the same synthetic step whereas for *Trost*'s reagent, two different series of synthetic steps are required to generate the two diene moieties. See also the 'timed *Diels-Alder* reactions' [10].



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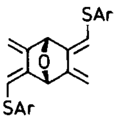

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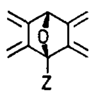

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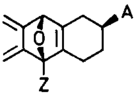
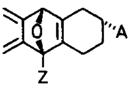
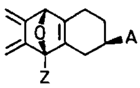


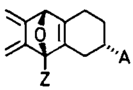
4 *para-β*



5 *para-α*



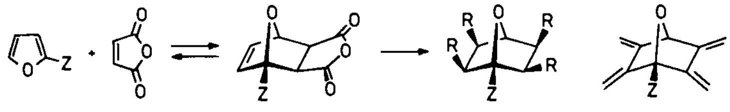
6 *meta-β*



7 *meta-α*

the four ester groups was indicated by the ^{1}H-NMR spectrum which showed the following vicinal coupling constants: ^3J(H–C(4),H–C(3)) = ^3J(H–C(4),H–C(5)) ≃ 0 Hz and ^3J(H–C(2),H–C(3)) = ^3J(H–C(5),H–C(6)) = 10 Hz [3] [14]. The reduction of **10** with $LiAlH_4$ (THF, 0 °C to 65 °C, 4 h) led to the tetrol **11** (72%, isolated, m.p. 144–145 °C). The reaction of **11** with an excess of MsCl in pyridin (0 °C, 20 min) afforded the tetramesylate **12** (75%, m.p. 104–105 °C). On treatment with an excess of *t*-BuOK (0 °C, DMF/HMPT 6:1, 2 h) **12** yielded the tetraene **13** in 60% yield, as a white crystalline product (m.p. 66–68 °C).

Scheme



8 **9** **10** R = $COOCH_3$ **13**
11 R = CH_2OH
Z = $CH(OCH_3)_2$ **12** R = $CH_2OSO_2CH_3$

The ^{1}H-NMR spectrum of **13** displayed typical singulets at δ_H = 5.40, 5.35, 5.30 and 5.10 ppm for the olefinic protons, at δ_H = 5.0 ppm for the bridgehead proton H–C(4), at δ_H = 4.85 ppm for the acetal group and at δ_H = 3.6 ppm for the two CH_3O groups. The UV absorption spectrum of **13** was similar to that of **1** and showed typical absorptions witnessing transannular interactions between the two homoconjugated s-*cis*-butadiene moieties [15]: λ_{max} = 265 nm (ε = 2600, sh), 250 (7600, sh), 240 (9400, sh), 229 (18100), 222 (17800), 216 (14000, sh) in isooctane[5]).

On treatment with 1 equiv. of ethylenetetracarbonitrile at 20 °C the tetraene **13** afforded the monoadduct **14** (m.p. 151–152 °C, λ_{max} = 246 nm (ε, 7700, CH_3CN)). In the presence of an excess of the same dienophile and under more severe conditions (toluene, 110 °C) the corresponding bis-adduct **15** was formed slowly, concomitantly with the decomposition of **14**.

The reaction of methyl vinyl ketone complexed to $EtAlCl_2$ (3 mol-equiv.) with tetraene **13** in CH_2Cl_2/hexane 11.5:1 (−85 °C, 1 h) gave a mixture of monoadducts whose major component (> 80%) had the structure **16**. The ^{1}H-NMR (360 MHz) spectrum of **16** showed a typical long-range, homoallylic coupling constant of 1.2 Hz between the

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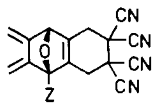
[5]) All the new compounds reported here were fully characterized by their spectral data, their elemental analysis, their mode of formation and their mode of reactions. Details will be presented later.



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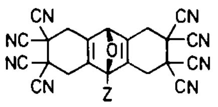

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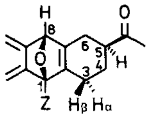
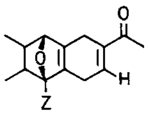


16



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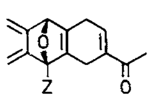

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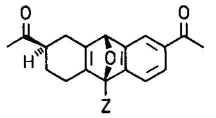

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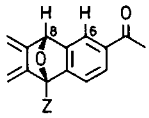

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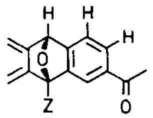

20

Z = $CH(OCH_3)_2$

bridgehead proton H–C(8) and the methylene proton H_β–C(3) *syn* with respect to the oxa bridge [16]. Double irradiation experiments in the ^{1}H-NMR spectrum confirmed the structure **16**[6][7].

The reaction of the tetraeneacetal **13** with an excess of butynone complexed with $BF_3 \cdot Et_2O$ in CH_2Cl_2 (–75 °C, 3 days) gave a 7:3 mixture of the monoadducts **17** and **18**. As for the *Diels-Alder* addition of methyl vinyl ketone, the reaction was *'para'*-regioselective (see **4**). The two adducts **17** and **18** (90%, isolated) were readily separated by column chromatography on silica gel. Treatment of **17** and **18** with 1.1 mol-equiv. of dichlorodicyanobenzoquinone afforded the aromatic ketones **19** (90%) and **20** (85%), respectively. Their structure was given by their ^{1}H-NMR (360 MHz) spectra and by observing nuclear *Overhauser* effects on the aromatic protons H–C(6) while irradiating the bridgehead protons H–C(8) of **19** and **20**. The diene moiety in **19** is more reactive than that in **17** toward strong dienophiles. On treating **19** with an excess of methyl vinyl ketone complexed with $BF_3 \cdot Et_2O$ in CH_2Cl_2 (–75 °C, 80 h) a 1:1.2:5.2:17.2 mixture of the corresponding bis-adducts was obtained (75%, isolated). The major component **21** could be isolated and purified by two or three recrystallizations from acetone (60%, m.p. 130–132 °C). Its structure was derived from its ^{1}H-NMR (360 MHz) spectrum[6].

The preliminary results reported here demonstrate the general character of our technique developed for the synthesis of 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptanes **3**. We have established a new synthetic principle, *i.e.*, the substituent, Z at one of the bridgehead centre of the bicyclic system can be used to control the regio- and stereoselectivity of the two successive *Diels-Alder* additions of the exocyclic tetraene **3**. The first addition is significantly faster than the reaction of the second equivalent of dienophile, thus making the tetraene **13**, and possibly other derivatives **3**, a versatile reagent for the tandem regio- and stereoselective cycloadditions.

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[6] The complete ^{1}H-NMR analyses have been carried out by Prof. *J. Lauterwein*, University of Lausanne. They will be reported later.

[7] The atom numbering given with formulae **16** and **17** does not corresponds to that of the IUPAC rules.

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