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Diels-Alder Reactions of Protoanemonin with Heterosubstituted Dienes. Synthesis of Polyfunctional Oxaspiro[4.5]decanes.

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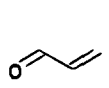
Abstract: Cycloadditions of protoanemonin (**1**) with different kinds of heterosubstituted dienes have been tried under several reaction conditions; **1** has revealed to be a good dienophile towards electron-rich dienes giving adducts that can be easily transformed into useful synthetic building blocks.

The spirolactone and spiroketal moiety is present in the structure of several interesting molecules. Among them, the macrolide antibiotics chlorothricin,[1] and tetrocarcin A,[2] and some insect pheromones (e.g. chalcograne,[3] and Paravespula vulgaris pheromones[4]) are examples of naturally occurring products. Moreover, many unnatural spirolactones are also very appreciated in the industry of flavours and perfumes.[5,6] Different methods are reported in the literature for the preparation of such a kind of compounds,[5,7] but they often involve long synthetic routes, and/or the use of elaborate starting materials.

In this paper we describe the efficient synthesis of several spirolactones through the Diels-Alder reaction of electron-rich dienes and protoanemonin (**1**).[8] We had previously studied the dienophilicity of **1** towards C-substituted dienes, and we found that **1** reacts exclusively at the exocyclic double bond giving spiro adducts in good yields.[9,10] With this knowledge in hand we decided to exploit this behaviour of protoanemonin (**1**) as dienophile, combined with the synthetic potential of the heterosubstituted dienes to give polyfunctionalized cyclohexenes, in order to prepare versatile spiro compounds in a high regio and stereocontrolled manner.

The Diels-Alder cycloadditions targeted include the use of the

electron-deficient dienes **2-4**, the donor-acceptor diene **5**,[11] and the electron-rich dienes **6** and **7**. Thermal (uncatalyzed and catalyzed) and high pressure activation conditions have been tried.



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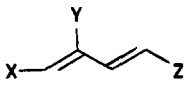


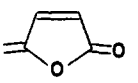
X = Y = H, Z = OAc **3**

X = Me, Y = H, Z = CO_2Me **4**

X = OMe, Y = Et, Z = CO_2Me **5**

X = Y = H, Z = OTMS **6**

X = H, Y = OTMS, Z = OMe **7**



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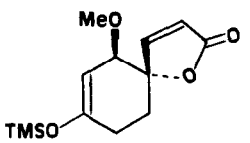

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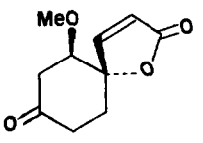

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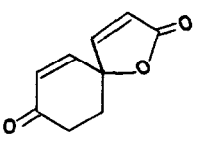

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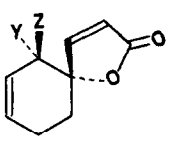
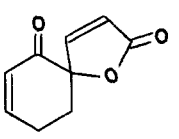


Z = OTMS, Y = H **11a**

Z = H, Y = OTMS **11b**

Z = OH, Y = H **12**



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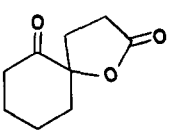

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No reaction was observed when protoanemonin (**1**) and excess acrolein (**2**) considered as heterodiene were heated in dichloromethane at 145 °C for 17 h, the starting materials being partially recovered along with much polymer. Attempts to react **1** with 1-acetoxy-1,3-butadiene (**3**),ethyl sorbate (**4**), and methyl 4-ethyl-5-methoxy-2,4-pentadienoate (**5**), were also unsuccessful.

However, reaction of **1** with the Danishefsky's diene (**7**) at 140 °C

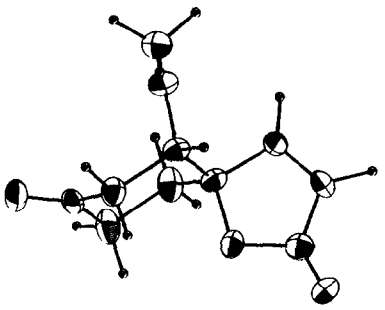

Fig. 1 ORTEP view of the X-ray structure of compound **9**

for 15 h gave the adduct **8**, that upon acid hydrolysis (0.1 N HCl, THF, r.t. 20 min) afforded compound **9** as a single regio and diastereoisomer, in 35%. overall yield from **1**. The structure of **9** was unambigously determined by means of X-ray diffraction (Fig. 1), that proved the trans-relationship between the methoxy group and the lactone ring oxygen. Furthermore, adduct **8** was obtained in better yield (ca. 55%) when the cycloaddition was performed under 10 kbar pressure at r.t. for 16 h, showing that this technique is a very suitable method when sensitive dienes and dienophiles are used. In certain instances the hydrolysis of **8** led to the formation of enone **10**.[12]

Reaction of **1** with 1-trimethylsilyloxy-1,3-butadiene (**6**) at 145 °C for 17 h afforded regioselectively a 86:14 mixture of the diastereoisomeric adducts **11a/11b** in 84% yield. Experiments carried out at lower temperature or shorter reaction time resulted in a partial recovering of the starting materials. The major isomer **11a** could be isolated by flash column chromatography (SiO_2, hexane-ethyl acetate), and characterized by its spectroscopic data; the relative stereochemistry was mainly assigned by NMR spectral correlation with other similar adducts,[9] and by comparison with the stereochemical outcome found in the formation of **9**.

Mild acid hydrolysis (e.g. diluted HCl) gave quantitatively the allylic alcohol **12**. Alternatively, treatment of the mixture **11a/11b** with Jones reagent afforded the enone **13**, in 60% yield, which was quantitatively hydrogenated to give the saturated ketone **14**, m.p. 48-49 °C (Lit.[13] m.p. 49-50 °C). This product has been used as a key intermediate in the synthesis of pheromones containing an oxa-spiro moiety.[14]

From the studies presented herein we can conclude that protoanemonin (**1**) behaves as a good dienophile in the cycloadditions to electron-rich heterosubstituted dienes, under thermal and high pressure conditions. Excellent regiospecificity is found in all cases and good stereospecificity is also observed. Simple chemical transformations performed on these adducts lead to polyfunctional oxaspiro[4.5]decanes, which are precursors of more complicated structures, proving the usefulness of our method.

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EXPERIMENTAL SECTION

Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts was effected in a bulb-to-bulb distillation apparatus; only the bath temperatures are given.

General procedures for high pressure-induced cycloadditions.
The particular conditions for each reaction are given below. The dienophile and the diene in dichloromethane or THF were introduced, by means of a syringe, into a 1 or 3 mL pyrex glass cells (1.5 mm wall-thickness) fitted with a 1 mm inner diameter capillary orifice. All reactions were performed in a piston-cylinder high pressure apparatus for pressures up to 20 kbar. Cells were immersed into hexane, used as piezotransmitter liquid which was contained in the high pressure apparatus, closed on the bottom side with a steel stopper. Then the mobile piston was inserted and the whole assembly was placed between the pistons of a hydraulic press. The pressure was raised depending on the reaction conditions used in each case, and the reaction mixture was kept under these conditions for the convenient time. After decompression the solvent was removed and the residue analyzed using spectroscopic technics.

Reactions of 1 with the electron-poor dienes 2, 3, 4 and 5.
Conditions were chosen regarding the stability of the particular diene used in each case (molar ratio diene-dienophile given): Diene **2** (2:3): 145 ^{o}C, 17 h, dichloromethane. Diene **3** (5:1): (a) 120 ^{o}C, 19 h, toluene; (b) Et_2O-BF_3, r.t., 19 h, dichloromethane. Diene **4** (1:1): 12 kbar, r.t., 42 h, THF. Diene **5** (0.9:1): (a) 140 ^{o}C, 22 h, chlorobenzene; (b) 12 kbar, r.t., 42 h, THF.

(5R*,6S*)-6-Methoxy-1-oxaspiro(4.5)dec-3-en-2,8-dione (9).

Ketone **9** was prepared through hydrolysis of **(5R*,6S*)-6-methoxy-8-trimethylsilyloxy-1-oxaspiro(4.5)deca-3,7-dien-2-one (8).** This compound was an unstable oil which was used in the next step without further purification. Its expected structure was verified by ^{1}H NMR.

(i) Cycloaddition between **1** and the Danishefsky's diene (**7**).

(a) **Thermal cycloaddition.** A solution of freshly distilled **1** (65 mg, 0.68 mmol) and diene **7** (0.35 mL, 1.62 mmol) in 10 mL of dichloromethane was heated in a reactor closed with a teflon stopper, at 140 ^{o}C (bath) for 15 h. Then the reaction mixture was cooled and the solvent and excess diene were removed at reduced pressure to give a residue (275 mg) containing adduct **8**.

(b) **High pressure-induced cycloaddition.** The reaction was performed at 10 kbar for 16 h, using 109 mg of **1** (1.14 mmol) and 0.74 mL of diene **7** (3.41 mmol) in THF (2 mL) as a solvent, to afford crude adduct **8** (390 mg); 90 MHz ^{1}H NMR ($CDCl_3$): 1.50-2.40 (4 H, complex abs.), 3.27 (3 H, s), 3.69 (1 H, d, J = 4.7 Hz), 4.98 (1 H, d, J = 4.7), 6.07 (1 H, d, J = 6.0), 7.60 (1 H, d, J = 6.0).

(ii) Hydrolysis of adduct **8**.

A solution of the crude adduct **8** (390 mg) and 0,1 N HCl (0.5 mL) in THF (10 mL) was stirred at room temperature overnight. The mixture was poured into 35 mL saturated aqueous $NaHCO_3$ and the aqueous solution was extracted with dichloromethane(2x35 mL). The combined extracts were dried

and the solvents were removed at reduced pressure. The residue (212 mg) was submitted to column chromatography on silica gel (mixtures of hexane-ethyl acetate as eluents), affording ketone **9** (120 mg, 55% overall yield from **1**, obtained following method (b)); m.p. 44-46 °C; IR ($CHCl_3$): 1768, 1721, 1602 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$): 1.80 (1H, m), 2.37 (1H, m), 2,48 (1H, m), 2.64-2.74 (2H, complex absorption), 2.83 (1H, dd, J = 15.14 Hz, J' = 3.13 Hz), 3.31 (3 H, s), 3.48 (1 H, m), 6.11 (1 H, d, J = 5.86), 7.61 (1 H, d, J = 5.86); 100 MHz ^{13}C NMR ($CDCl_3$): 30.1, 37.1, 41.6, 57.0, 82.8, 86.7, 121.5, 158.7, 171.3, 206.6. Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22: H, 6.16. Found: C, 60.89; H, 6.12.

In some instances ketone **9** was obtained contaminated with **1-oxaspiro(4.5)deca-3,6-dien-2,8-dione (10)** which was isolated by column chromatography as an oil and characterized by its spectroscopic data; IR ($CHCl_3$): 1771, 1688, 1603 cm^{-1}; 400 MHz ^1H NMR (CDL_3), 2.20 (1H, m), 2.39-2.55 (2H, complex absorption), 2.70 (1H, m), 6.08 (1 H, d, J = 10.16 Hz), 6.16 (1 H, d, J = 5.53 Hz), 6.41 (1 H, d, J = 10.16 Hz), 7.48 (1 H, d, J = 5.53 Hz).

(5R*,6S*)-6-Trimethylsilyloxy-1-oxaspiro(4.5)deca-3,7-dien-2-one (11a).

A solution of freshly distilled **1** (312 mg, 3.25 mmol) and diene **6** (2.91 mL, 1.95 mmol) in methylene chloride (9mL) was heated in a reactor at 145 °C (bath) for 17 h. Then the solvent and excess diene were removed at reduced pressure. The residue (920 mg) was chromatographed on silica gel (mixtures of hexane-ethyl acetate as eluents) to afford 649 mg (84% yield) of a 86:14 mixture of adducts **11a/11b.** Further chromatography allowed the isolation of the major diastereoisomer **11a** as a liquid, oven temperature 100 °C (0.08 Torr); IR (film) 1764, 1605 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$): 0.11 (9 H, br s), 1.96 (2 H, m), 2.55 (2 H, m), 4.31 (1 H, br s), 5.73 (2 H, m), 6.10 (1 H, d, J = 5.79 Hz), 7.52 (1 H, d, J = 5.79 Hz); 20 MHz ^{13}C NMR ($CDCl_3$): -0.24, 23.8, 28.9, 70.2, 89.3, 121.7, 128.0, 128.7, 157.3, 171.9. Anal. Calcd. for $C_{12}H_{18}O_3Si$: C, 60.47; H, 7.61. Found: C, 60.28; H, 7.45.

1-Oxaspiro(4.5)deca-3,7-dien-2,6-dione (13) .

A solution of compound **11a** (370 mg, 1.56 mmol) and 0.1 N HCl (0.5 mL) in THF (10 mL) was stirred at room temperature overnight. The mixture was poured into saturated aqueous $NaHCO_3$ (35 mL) and the resulting solution was extracted with dichloromethane (2x35 mL). The combined extracts were dried and the solvents were removed under reduced pressure. The residue was distilled at oven temperature 180 °C (0.08 Torr) to give **6-hydroxy-1-oxaspiro(4.5)deca-3,7-dien-2-one (12)**, (240 mg, 92% yield) which was characterized by its spectroscopic data; IR (film): 3714-3436 (br), 1745, 1603 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$): 1.85-2.61 (5 H, complex abs.), 4.31 (1 H, br s), 5.68-6.04 (2 H, complex abs.), 6.16 (1 H, d, J = 5.5 Hz), 7.62 (1 H, d, J = 5.5 Hz).

Jones reagent was added dropwise to an ice-cooled solution of alcohol **12** (240 mg, 1.5 mmol) in acetone (15 mL) until persistent orange colour was observed and thin layer chromatography showed the total consumption of the starting material. Then, excess of isopropanol and hexane were added. Salts were filtered out over celite and the filtrate was concentrated. The residue was taken in ethyl acetate (30 mL) and washed successively with water (20 mL), 5% aqueous sodium bicarbonate (25 mL), water (20 mL), and saturated aqueous ammonium chloride (20 mL). The organic layer was dried and the solvent was removed at reduced pressure. Column chromatography on silica gel of the residue (mixtures of hexane-ethyl acetate as eluent), afforded 134 mg (78% yield) of enone **13** as a solid that was crystallized from pentane-ether; m.p. 122-123 °C; IR (film) 1755, 1690, 1603 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$): 2.36 (2 H, m), 2.66 (2 H, m), 6.15 (1 H, m), 6.20 (1 H, d, J = 7.09 Hz), 7.21 (1 H, m), 7.53 (1 H, d, J = 7.09 Hz); 20 MHz ^{13}C NMR ($CDCl_3$): 24.2, 32.2, 88.9, 122.6, 128.5, 151.2, 153.4, 171.4, 189.7. Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.90; H, 4.90.

Enone **13** was alternatively prepared through direct oxidation of the

isomeric adducts **11a/11b** following the method described above for the oxidation of alcohol **12a**.

1-Oxaspiro(4.5)deca-2,6-dione (14)

Compound **13** (100 mg, 0.61 mmol) in ethyl acetate (20 mL) was hydrogenated overnight in the presence of 10% Pd/C, at 2 atmospheres pressure. The catalyst was removed by filtration over celite and the solvent was evaporated to give **14** (83 mg, 81% yield) as a solid that was crystallized from pentane-ether; m.p. 48-49 °C (Lit[13] m.p. 49-50 °C); IR ($CHCl_3$): 1781, 1729 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) : 1.5-2.4 (8H, m), 2.4-2.9 (4H, m).

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