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Diels-Alder Reactivity of 1-alkoxyphenyl-3-trialkylsiloxy-1,3-dienes

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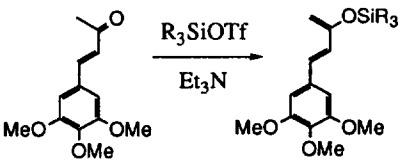
Abstract.- The synthesis of 1-(3,4,5-trimethoxyphenyl)-3-trialkylsiloxy-1,3-butadienes and their Diels-Alder reaction with selected dienophiles at room temperature is described. These aryldienes are useful building blocks for the synthesis of natural and pharmacological active products, as has been shown by the preparation of a tetracyclic ketone needed for the synthesis of new anthracycline analogues.

Polyalkoxy and polyhydroxyphenyl residues are interesting structural moieties, because they can be found in many natural and synthetic compounds of pharmacological relevance. Among the natural products: lignans,[1] alkaloids,[2] flavones,[3] duocarmycines,[4] lamelarins[5] etc... are representatives of such class of compounds. Antifolates such as the antitumoral trimetrexate[6] and the antibacterial agent trimethoprim[7], are examples of synthetic pharmaceuticals in the market carrying this type of substructures. There are a lot of strategies for the preparation of compounds with polyoxygenated phenyl moieties and many others can be adapted for this purpose, but none of them is based on the Diels-Alder reaction of phenyldienes.

In a recent paper[8] we described the synthesis of new hexahydropyrrolo[3,4-*c*]carbazole derivatives, as open analogues of the PKC inhibitors staurosporine and rebeccamycin, carried out by the use of a trimethoxyphenyldiene as starting material. There are several examples in the literature describing the synthesis and use in the Diels-Alder reaction of phenyldienes[9] but none on 1-(substituted)phenyl-3-trialkylsiloxy butadienes. Only recent papers presented the nucleophilic reactions[10] of this class of compounds with different electrophilic species.

In order to extend the application of these dienes in the synthesis of polyalkoxyphenyl substituted cyclic compounds, we decided to study their Diels-Alder reactions with other dienophiles and to use this methodology for the preparation of a new class of cytotoxic agents.

Dienes **1a**, **1b** and **1c** were synthesized by trimethyl, *tert*-butyldimethyl and triisopropyl silylation of the corresponding enone, prepared by condensation of the aromatic aldehyde with acetone[8].



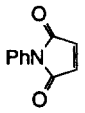
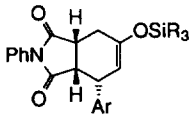
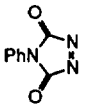
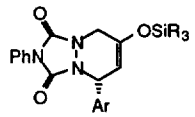
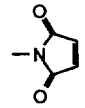
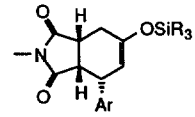
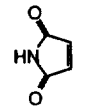
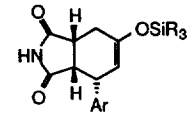
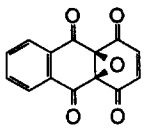
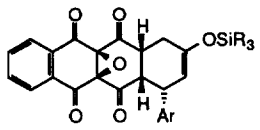
1a R=Me
1b R_3=^{t}BuMe$_2$
1c R=^{i}Pr

For the study of the Diels-Alder reaction of these dienes we selected as dienophiles: *N*-phenylmaleimide, 4-phenyl-1,2,4-triazoline-3,5-dione, methylmaleimide, maleimide and 4*a*,9*a*-epoxy-4*a*,9*a*-dihydroanthracene-1,4,9,10-tetraone (**2**).[11] Other dienophiles such as: 1,4-naphtoquinone, 2,3-chloro-1,4-naphtoquinone,

dimethylfumarate, dimethyl acetylenedicarboxylate and maleic anhydride, did not give any reaction product with these dienes under the same conditions. This reactivity is summarized in table I. The products of the reaction were isolated as silylenol ethers or directly hydrolyzed to the parent ketone by reaction with HOAc / H_2O / THF or HCl 2N.

All these products were obtained as single diastereoisomers and their stereochemistry was assigned by comparison with different products obtained in the Diels-Alder reaction between other dienes and similar dienophiles[11,12], which also produce single diastereoisomers. The *cis* relationship between the substituents in the cyclohexene ring is the result of the expected *endo* reaction. Furthermore, molecular modelling of the Diels-Alder transition state to compound **7** shows a preferred *endo* disposition close to that described in reference 12. The unusual shielding of 4'-OMe (2.95 ppm), due to the anisotropic effect of the benzene D ring, confirms the α disposition of the aryl moiety opposite to the oxirane bridge, similar to that depicted in figure 1 for ketone **12**.

Table 1. Cycloaddition reactions of 1-(3,4,5-trimethoxyphenyl)-3-trialkylsiloxy-1,3-butadienes **1a**, **1b** and **1c** with selected dienophiles

Entry	Diene	Dienophile	Product	Yield(%)
1[a]	**1a**		 **3** (R=Me)[c]	55
2[a]	**1a**		 **4** (R=Me)[c]	70
3[a]	**1b**		 **5** (R_3=^{t}BuMe$_2$)[c]	87
4[a]	**1b**		 **6** (R_3=^{t}BuMe$_2$)[c]	100
5[b]	**1b**	 **2**	 **7** (R_3=^{t}BuMe$_2$)	48
6[a]	**1c**		**8** (R=^{i}Pr)	33

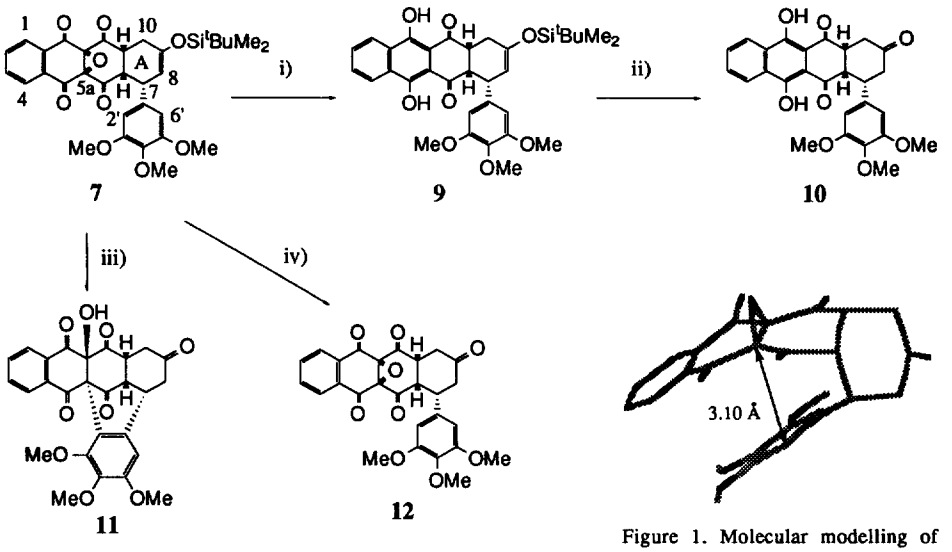
Ar= 3,4,5-trimethoxyphenyl

a) All these reactions were carried out in benzene under Argon, at r. t. for 18-40 h, except b) that was carried out in acetone.
c) Isolated as the ketone by hydrolysis of the trialkylsiloxy product

Once proved the utility of dienes **1a**, **1b** and **1c** in the stereospecific synthesis of cyclohexene and cyclohexanone derivatives carrying a trimethoxyphenyl moiety, we decided to complete the transformation of compound **7**, into a new type of 7-deoxy-7-phenyl anthracycline analogue. With this purpose, the Diels-Alder reaction between anthracenetetraone **2** and the diene **1b** was followed by the hydrolysis of the trialkylsilylether **7**. Treatment with HCl in CH_2Cl_2, gave only the polycyclic complex molecule **11**[13] after column

chromatography, instead of the expected ketone **12**. The formation of this product can be explained through the intramolecular nucleophilic attack by the activated aromatic ring, to the highly electro-deficient carbon of the protonated oxirane in intermediate **12**. A close proximity between both groups is required for this reaction, as it was shown by molecular modelling[14] of compound **12** (figure 1), which produced a preferred conformation with the phenyl moiety placed under the tetracyclic system in a planar disposition, with C-2' (or C-6') close to C-5a (3.10 Å). Rotational restrictions in ring A and π-stacking stabilization account for this preferred conformation, which explains the observed cyclization.

To overcome this problem, the hydrolysis of **7** was performed with a lower concentration of HCl in CH_2Cl_2 for a longer period of time. Thus, ketone **12** was obtained in 50% yield after crystallization. The reduction of the oxirane in **12** with Zn/HOAc only produced complex mixtures, from which it was not possible to isolate **10**. However, by reduction of the oxirane **7** to **9** with H_2/Pd-C, prior to the hydrolysis step, ketone **10**[15] was obtained in 43% overall yield from starting diene **1b**.



Scheme I. Reaction conditions: i) H_2/Pd-C, EtOAc, 94%, ii) HCl, CH_2Cl_2, 95%, iii) HCl cc., CH_2Cl_2, 17%, iv) HCl 2N, CH_2Cl_2, 50%.

Figure 1. Molecular modelling of ketone **12**, showing distance C_{5a}-$C_{2'}$.

In conclusion, the readily available dienes type **1** are very interesting building blocks that can be used in the Diels-Alder reaction for the synthesis of compounds of pharmacological interest. Accordingly, once established the synthesis of the target intermediate **10**, 7-deoxy-7-(3,4,5-trimethoxyphenyl)anthracyclinones can be obtained by a known reaction sequence.[16] A more detailed study with several of these dienes under different conditions in the Diels-Alder reaction and the synthesis and activity of several derivatives in this series, are under way and will be published in due course.

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13. Analytical data of compound **11**: IR (NaCl): 3340-3600, 1725, 1600, 1515 and 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.39 (1H, dd, 15.0, 3.8), 2.40 (1H, dd, 18.0, 6.7), 2.80 (1H, dd, 15.0, 3.9), 3.20 (1H, dd, 18.0, 1.0), 3.26-3.35 (2H, m), 3.53 (1H, br t, 1.8), 3.75 (3H, s), 3.77 (3H, s), 3.97 (3H, s), 6.28 (1H, s), 6.94 (1H, s), 7.68-7.75 (2H, m), 7.87-7.92 (1H, m) and 7.96-8.03 (1H, m). Addition of D_2O causes the signal at 6.94 to disappear. ^{13}C-NMR ($CDCl_3$): 35.2 (d), 38.6 (t), 41.9 (d), 50.3 (d), 51.7 (t), 55.9 (q), 60.8 (q), 62.1 (q), 75.0 (s), 105.3 (s), 106.5 (d), 107.9 (s), 127.0 (d), 127.4 (d), 132.0 (s), 132.2 (s), 134.6 (d), 134.9 (d), 135.5 (s), 137.5 (s), 154.0 (s), 155.0 (s), 185.8 (s), 187.7 (s), 197.1 (s), 206.6 (s) and 206.6 (s).
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15. Analytical data of compound **10**: EA: calc: C (68,05), H (5,08). Found: C (67,82), H (4,85). ^{1}H-NMR ($CDCl_3$): 2.59 (1H, dd, 17.0, 8.5), 2.94 (1H, d, 6.0), 3.13 (1H, d, 17.0), 3.18 (3H, s), 3.65-3.97 (3H, m), 3.60 (6H, s), 3.92 (1H, dd, 8.5 y 4.5), 6.01 (2H, s), 8.25-8.30 (2H, m), 8.40-8.47 (2H, m), 13.10 (1H, s) and 13.76 (1H, s). ^{13}C-NMR ($CDCl_3$): 37.1 (t), 44.5 (d), 45.2 (d), 45.2 (t), 51.7 (d), 2x55.7 (q), 59.9 (q), 2x105.3 (d), 2x109.2 (s), 2x124.4 (d), 128.6 (s), 129.2 (s), 130.5 (d), 130.8 (d), 133.4 (s), 136.9 (s), 2x152.2 (s), 154.2 (s), 155.2 (s), 199.5 (s), 202.3 (s) and 207.5 (s).
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