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# THE BICYCLO [2.1.0] PENTANE WAY TO THE DIQUINANE ALCOHOL PART OF NATURAL TRIQUINANES. A HIGH YIELD ACCESS STARTING FROM TRIMETHYLSILYLOXYCYCLOPENTENE.

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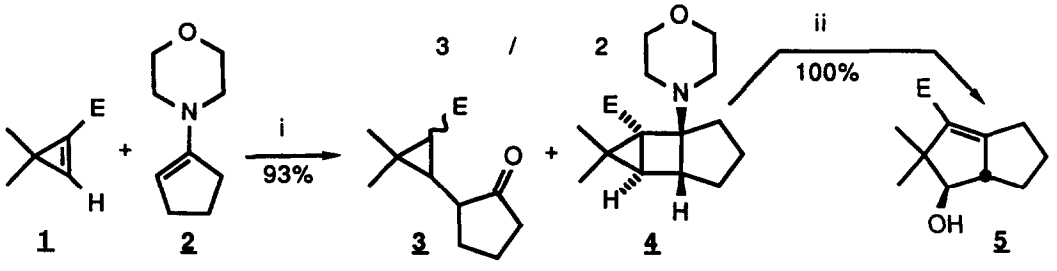
*Summary : Trimethylsilyloxycyclopentene reacts exclusively with ethyl propiolate in the presence of $ZrCl_4$ to give a [2+2] adduct (alcohol 6, 90 %). After protection, the stereoselective cyclopropanation via 1,3-dipolar addition of 2-diazopropane followed by sensitized photocleavage, leads with good yields to the bicyclo [2.1.0] pentane derivative 11. By deprotection and solvolytic cleavage with dilute mineral acid, the diquinane alcohol 5 is obtained quantitatively and stereospecifically.*

We have previously shown that the reaction of 3,3-dimethyl-1-methoxycarbonyl cyclopropene 1 with N-(cyclopenten-1-yl) morpholine 2 leads to two types of product : α-cyclopropanic ketones 3 (mixture of diastereomers), isolated with 55 % yield, and the tricyclic derivative 4, a formal [2+2] cycloaddition product isolated with 38 % yield. The acidic solvolysis of compound 4 gives quantitatively and stereospecifically the diquinane 5 (1).




E = $CO_2Et$ i : $Et_2O$ , 20°C , 24h ; $H_2O$ ii : $H_2SO_4$ 10% , $C_6H_5CH_3$ 80°C

By use of this reaction sequence, we were able to achieve the total syntheses of the natural triquinanes (±) Hirsutene and (±) Silphinene (2).

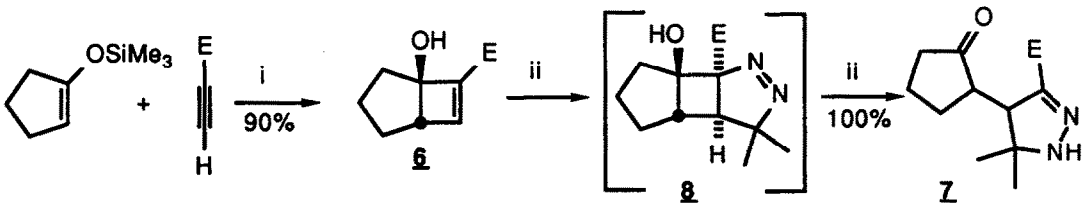
The major problem inherent to this methodology for the synthesis of polyquinanes comes from the fact that the formation of the ketones 3 is slightly easier than the formation of the cycloadduct 4.

We propose now a new synthetic method leading exclusively to the cycloadducts of type 4.

Cyclobutenes react with 2-diazopropane (DAP) by 1,3-dipolar cycloaddition to give $\Delta^{-1}$ pyrazolines. Their UV irradiation leads to bicyclo [2.1.0] pentanes (3), especially if the photolysis is sensitized (4).

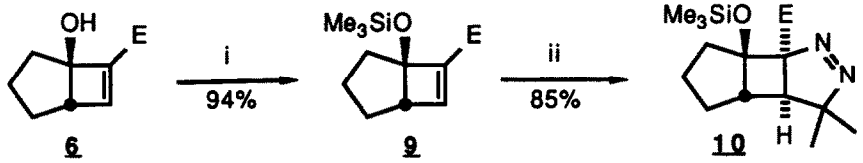
If the replacement of the nitrogen substituent of the amino-bicyclo [2.1.0] pentanes by an oxygen substituent still permits the solvolysis to cyclopentenols, then an easy access to the starting cyclobutenes is given by the reaction described by Clark and Untch (5). These authors reported that the cyclobutene **6** is obtained with 48 % yield by cycloaddition of ethyl propiolate with (trimethylsilyloxy) cyclopentene in the presence of $TiCl_4$ in $CH_2Cl_2$ at -78° C (5).

We improved this reaction by the use of 1 equivalent of $ZrCl_4$ in a mixture of $CH_2Cl_2$ and $Et_2O$ (6) at 25° C : the yield is now up to 90 %.




E = $CO_2Et$ i : $ZrCl_4$ , 25°C , $Et_2O/CH_2Cl_2$ ii : DAP , -55°C to 25°C

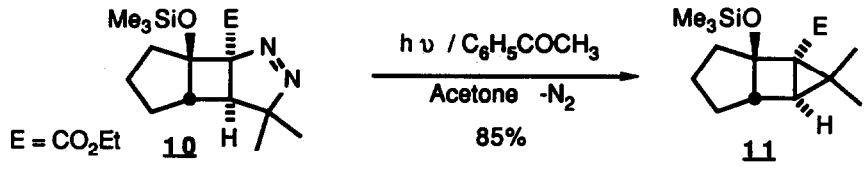
However 2-diazopropane reacts with the cyclobutene **6** to give directly the $\Delta^{-2}$ pyrazoline **7**. We were unable to detect the presence of the $\Delta^{-1}$ pyrazoline **8** which probably rearranges spontaneously to the $\Delta^{-2}$ pyrazoline **7** (7). This problem was circumvented by protecting the hydroxyl group as a trimethylsilyl ether ($\Delta^{-1}$ pyrazoline **10** 85 %).



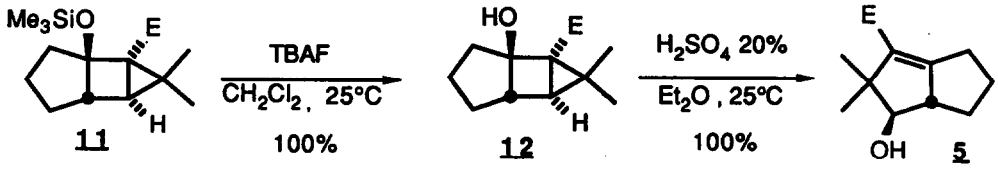

E = $CO_2Et$ i : $CF_3SO_3SiMe_3$ ,$NEt_3$ , $CH_2Cl_2$ reflux ii : DAP , -55°C to 25°C

The necessity of protecting the alcohol **6** for the 1,3-dipolar addition led us also to use 1-(t-butyldimethylsilyloxy)-cyclopentene as starting material. The TBDMS protected alcohol **6** is then obtained with 57 % yield by reaction with ethyl propiolate in the presence of $ZrCl_4$ (no yield improvement as compared to $TiCl_4$ (5) in this case). However the reaction sequence described below is handicapped in the case of the TBDMS-ether by a very sluggish deprotection step to the alcohol **12**.

The photolytic cleavage of the $\Delta^{-1}$ pyrazoline **10**, used without purification (8) was best achieved in acetone in the presence of acetophenone as sensitizer (3), giving the tricyclic adduct **11** with 85 % yield.




The diquinane **5** (1 diastereomer of the indicated configuration) is then obtained by successive treatment of the tricyclic adduct with $nBu_4NF$ (TBAF), leading to the alcohol **12** (9), followed by treatment with dilute sulfuric acid (10).




The overall yield of this 6-step synthesis, starting from (trimethylsilyloxy) cyclopentene, reaches 61 %. Other diazoalkanes such as diazomethane or diazoethane can be used instead of 2-diazopropane for the same reaction sequence. Diquinane alcohols bearing no methyl substituent or only one are then obtained. This is another advantage of the bicyclo [2.1.0] pentane synthesis via electrophilic cyclobutenes, as compared with the former way which made necessarily use of gem-*dimethyl* substituted cyclopropenes. We are now using this new methodology for the total synthesis of bioactive compounds such as pentalenic acid and coriolin.

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6) This Lewis acid gave particularly good results for the cycloaddition reaction of ethyl propiolate with ketenealkylsilylacetals,
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7) Cyclobutenes of type **6**, bearing an amino group instead of an hydroxyl group are also known [cf. : C.F. HUEBNER, L. DORFMAN, M.M. ROBISON, E. DONOGHUE, W.G. PIERSON, P. STRACHAN, *J. Org. Chem.*, **28**, 3134 (1964) ;
K.C. BRANNOCK, R.D. BURPITT, V.W. GOODLETT, J.G. THWEATT,
*J. Org. Chem.*, **29**, 818 (1968)]. The cycloaddition of DAP with these cyclobutenes leads however exlusively to $\Delta^{-2}$ pyrazolines of type **7** after hydrolysis.
8) If the $\Delta^{-1}$ pyrazoline **10** is submitted to a chromatography over silicagel, an important loss of material is observed : probably a deprotection reaction occurs giving the $\Delta^{-1}$ pyrazoline **8**, which rearranges to the $\Delta^{-2}$ pyrazoline **7**. Indeed the TBDMS protected $\Delta^{-1}$ pyrazoline **8** is stable under the same chromatographic conditions.
9) Alcohol **12** : $C_{13}H_{20}O_3$ ; colorless liquid ; calc. % C : 69.61, % H : 8,98 ; found % C : 69.8, % H : 9.1 ; IR ($cm^{-1}$) : $\upsilon$ (C=O) : 1717, $\upsilon$ (OH) : 3434, 3608 ; NMR ($CDCl_3$, $\delta$ ppm) : 1.14 (3H, s), 1.27 (1H, t, $J$ = 7 Hz), 1.50 (3H, s), 1.50-1.95 (5H, m), 2.00-2.10 (2H, m), 2.17 (2H, d, $J$ = 6 Hz) ; $CO_2CH_AH_BCH_3$ : $ABX_3$ $\delta_A$ : 4,14, $\delta_B$ : 4.22 ($J_{AX}$ = 7 Hz, $J_{BX}$ = 7 Hz, $J_{AB}$ = 16 Hz).
10) The use of other protecting groups like THP and analogous ethers was also investigated giving however no distinct advantage as compared to the TMS ethers :
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