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Synthesis of the Angular Triquinane (±)-Pentalenene via Small Ring Intermediates.

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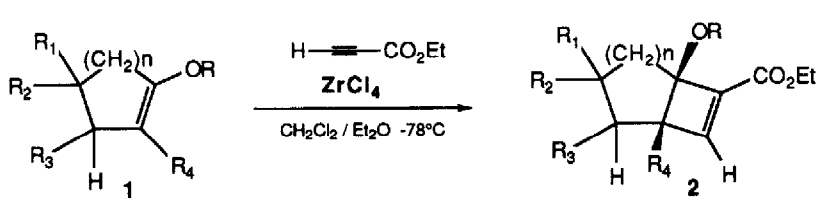
Key Words : Cyclobutene hydroxy esters, bicyclo [2.1.0] pentan-2-ols, diquinanes, [2+2] cycloaddition, diazoalkanes, 1,3-dipolar addition, silyl enol ethers, silyl-assisted Nazarov reaction, pentalenene.

Abstract : Dimethyl t-butylsilyl enol ethers of cycloalkanones react with ethyl propynoate in the presence of $ZrCl_4$ to give protected cyclobutenic hydroxy esters. Cyclopropanation by cycloaddition of diazoalkanes followed by sensitized photocleavage, leads to bicyclo [2.1.0] pentan-2-ol derivatives which are then cleaved with acids to 3-cyclopenten-1-ols. This reaction sequence was used for the synthesis of the angular triquinane (±)-pentalenene, starting from 3,3-dimethylcyclopentanone and diazoethane (→ ring A and B), the ring C being obtained by a silyl-assisted Nazarov type cyclization.

By [2+2] cycloaddition at room temperature in the presence of $ZrCl_4$, ethyl propynoate reacts with the trimethylsilyl enol ether of cyclopentanone **1a** to give the cyclobutene adduct **2a** in high yield[1]. This electrophilic cyclobutene hydroxy-ester could be cyclopropanated to a bicyclo [2.1.0] pentan-2-ol by 1,3-dipolar cycloaddition with 2-diazopropane, followed by sensitized photochemical nitrogen cleavage. The solvolysis in aqueous sulfuric acid of this compound yielded finally a 3-cyclopenten-1-ol[1]. This reaction sequence has previously been used for a total synthesis of the gem-dimethylated natural angular triquinane silphinene[2].

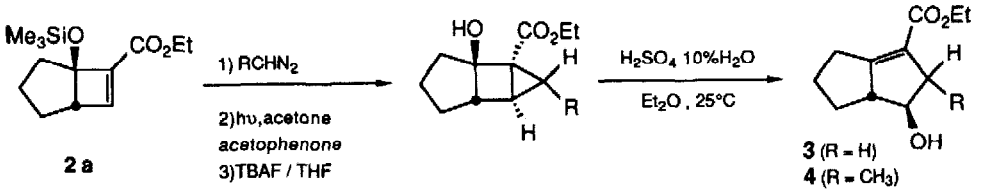
We have now extended the [2+2] cycloaddition reaction to other silyl enol ethers of substituted cyclopentanones or other cycloalkanones. The use of tert.butyldimethylsilyl (TBDMS) enol ethers proved to be necessary, the reaction being performed at -78° C. In general trimethylsilyl enol ethers led mainly to the starting cycloalkanones and not to cycloaddition products.



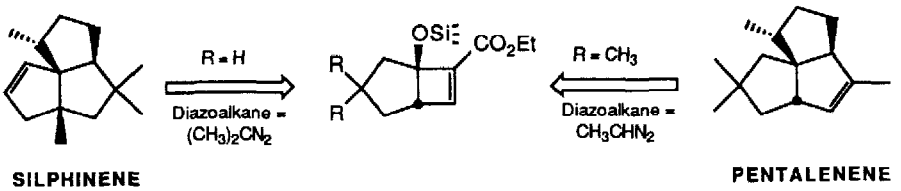
Enol ether	R	n	R_1	R_2	R_3	R_4	Yield	Product	
1a	$SiMe_3$	1	H	H	H	H	90 %	**2a** *	(R = H)
1b	$SiMe_2tBu$	1	H	H	H	CH_3	74 %	**2b**	(R = $SiMe_2tBu$)
1c	$SiMe_2tBu$	1	H	H	CH_3	H	60 %	**2c**	(R = $SiMe_2tBu$)
1d	$SiMe_2tBu$	1	CH_3	CH_3	H	H	32 %[3]	**2d**	(R = $SiMe_2tBu$)
1e	$SiMe_2tBu$	4	H	H	H	H	77 %	**2e**	(R = $SiMe_2tBu$)

* Reaction performed at room temperature.

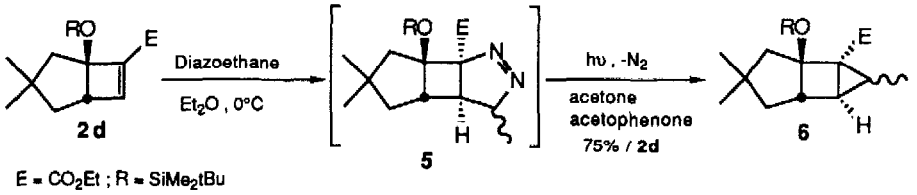
Other diazoalkanes were also used for the cyclopropanation, giving access to various bicyclo [2.1.0] pentan-2-ols, and from there, by solvolytic cleavage, to the corresponding functionnalized diquinanes. With diazomethane and diazoethane, **2a** led to the diquinanes **3** and **4** bearing no or only one methyl substituent (60 % overall yield) :



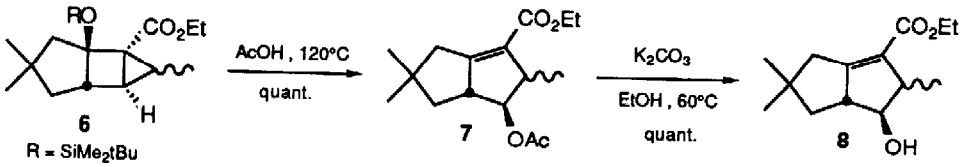
This opened up the possibility to apply our reaction sequence to the synthesis of a differently substituted angular triquinane, pentalenene. This triquinane, isolated from *Streptomyces griseochromogenes*[4], represents the parent hydrocarbon of the pentalenolactone sesquiterpene antibiotics. Its angular triquinane structure is indeed very different from that of silphinene in view of the methyl substitution pattern. This difficulty should be circumvented by introducing the gem-dimethyl group from the beginning (cyclopentacyclobutene **2d**), the 1,3-dipolar addition with diazoethane permitting then the introduction of a potential vinylic methyl substituent :



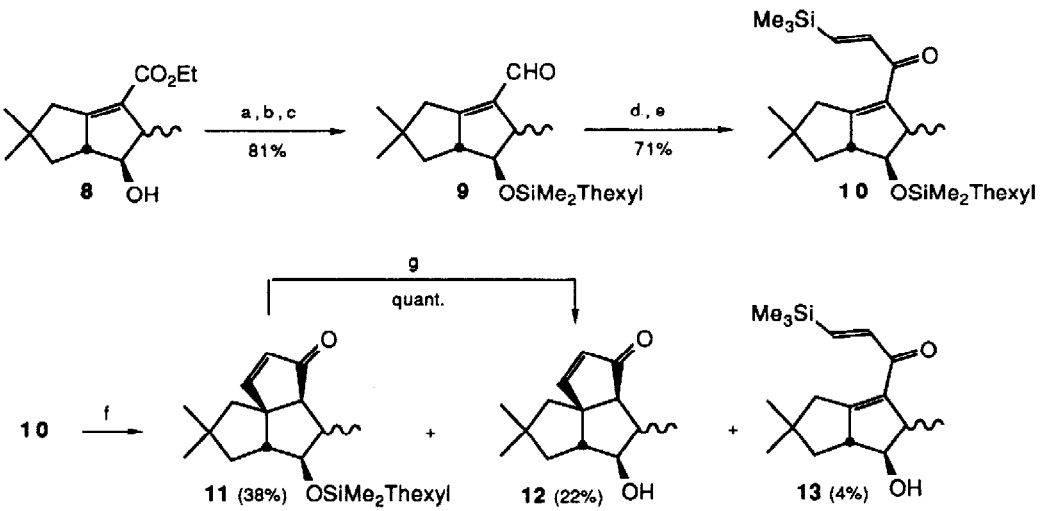
The 1,3-dipolar cycloaddition of diazoethane with the crowded cyclobutene ester **2d** led to two epimeric poorly stable Δ^{-1} pyrazolines, **5**. These were however not isolated, but directly photolysed in acetone in the presence of acetophenone as a triplet sensitizer[5]. The epimeric tricyclic adducts **6** (1:1.3) were thus obtained in 75 % overall yield[6].



The solvolytic cleavage of the tricyclic TBDMS-ethers **6** was performed in refluxing concentrated acetic acid, to give quantitatively and sterospecifically the acetates **7**. The diquinane hydroxy-esters **8** were then obtained quantitatively by saponification of the acetates under mild conditions :

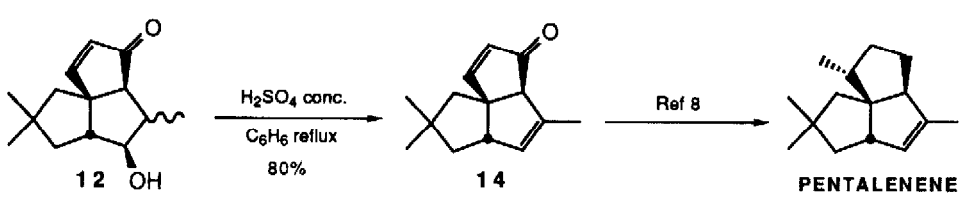


The third five membered ring of pentalenene was constructed using the same strategy as previously for the synthesis of silphinene[2]. The α,β-unsaturated esters **8** were transformed, after protection of the alcohol as the dimethylthexylsilyl ether (90 %), via the α,β-unsaturated aldehydes **9** (reduction followed by reoxidation, 90 %) into the cross-conjugated ketones **10** (Grignard reaction, 79 %, followed by oxidation, 90 %). The cyclization was then obtained by a silyl-assisted Nazarov-type reaction[7]. With 2.8 equivalents of $BF_3.Et_2O$, in refluxing ethylbenzene, the triquinanes **11** and **12** were respectively obtained with 38 % and 22 % yield in addition to 4 % of the deprotected starting hydroxy dienone **13**. Since the silyl ether **11** could be quantitatively deprotected to the triquinane alcohol **12** by tetrabutylammonium fluoride (TBAF), the total yield for **12** could exceed 60 %.



a : $CH_3SO_3SiMe_2Thexyl$, NEt_3, CH_2Cl_2, 40° C; b : DIBAH , Toluene, 25° C; c : MnO_2, CH_2Cl_2, 25° C;
d : BrMg (CH=CH) $SiMe_3$, THF, -30° C; e : MnO_2, CH_2Cl_2, 40° C; f : $BF_3.Et_2O$ (2.8 eq.), Ethylbenzene, reflux;
g : TBAF,THF, 25° C.

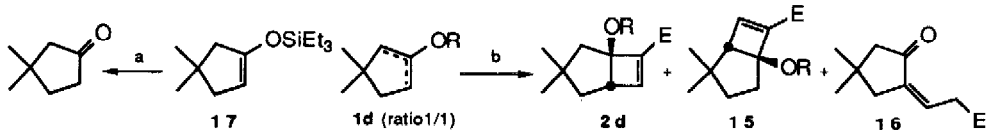
The synthesis was brought to an end by dehydrating the alcohols **12** into the sole triquinane **14** (80 %), which has already been transformed into pentalenene by Paquette et coll.[8].



Acknowledgments : *we are grateful to Rhône-Poulenc for financial support and to the BASF for repeated gifts of ethyl propynoate.*

References and Notes :

1. Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.*, **31**, 5027 (1990).
2. Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.*, **32**, 2135 (1991).
3. This cycloaddition was in fact performed starting from a 1/1 mixture of the TBDMS enol ethers of 3,3-dimethylcyclopentanone. The sole other product formed and recovered with 41 % yield was the starting ketone. The same reaction, performed in the presence of $TiCl_4$ as Lewis acid gave the cycloadducts **2d** and **15** (1/1, unseparable mixture, 47 %) beside the enone **16**. If this reaction is done with the sole triethylsilyl enol ether **17** [cf. : Exon, C.; Nobbs, M.; Magnus, P. *Tetrahedron Lett.*, **37**, 4515 (1981)] 3,3-dimethylcyclopentanone is recovered quantitatively.



E = CO_2Et ; R = $SiMe_2tBu$; a : $HC{\equiv}CCO_2Et$, $ZrCl_4$, -78°C ; b : $HC{\equiv}CCO_2Et$, $TiCl_4$, -78°C

4. Seto, H.; Yonehara, H. *J. Antibiot.*, **33**, 92 (1980).
5. Franck-Neumann, M. *Tetrahedron Lett.*, 2979 (1968).
6. The ratio of diastereomers is conserved during the following steps and there was no need to separate them, a double bond being introduced at the epimeric position at the end of the synthesis.
7. Denmark, S.E.; Jones, T.K. *J. Am. Chem. Soc.*, **104**, 2642 (1982);
   Crisp, G.T.; Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.*, **106**, 7500 (1984).
8. Paquette, L.A.; Annis, G.D. *J. Am. Chem. Soc.*, **105**, 7350 (1983).
9. Selected spectroscopic data :
   2d : $C_{18}H_{32}O_2Si$, colorless oil; IR (CCl_4) : 1718 (C=O) and 1603 (C=C) cm^{-1}; NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 6H), 0.87 (s, 9H), 0.97 (s, 3H), 1.08 (s, 3H), 1.31 (t, 3H, J = 7.0 Hz), 1.66 and 1.35 (2H, ABX, J = 13.5 Hz, 8.5 Hz, 2.5 Hz, Δυ = 134.3), 2.06 and 1.62 (2H, AB, J = 13.0 Hz, Δυ = 89.5), 3.03 (ddd, 1H, J = 8.5 Hz, 2.5 Hz, 1.0 Hz), 4.22 (dq, 2H, J = 7.0 Hz, 2.0 Hz), 6.88 (d, 1H, J = 1.0 Hz).
   6 : $C_{20}H_{36}O_3Si$, colorless oil; IR (CCl_4) : 1711 (C=O) cm^{-1}; NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 3H, dia 1), 0.10 (s, 3H, dia 2), 0.15 (s, 3H, dia 2), 0.19 (s, 3H, dia 1), 0.84 (s, 9H, dia 1), 0.86 (s, 9H, dia 2), 1.02 (s, 3H, dia 2), 1.04 (s, 3H, dia 1), 1.06 (s, 3H, dia 2), 1.07 (s, 3H, dia 1), 1.20 (d, 3H, J = 6.4 Hz, dia 2), 1.27 (t, 3H, J = 7.0 Hz, dia 1), 1.30 (t, 3H, J = 7.0 Hz, dia 2), 1.39 (d, 3H, J = 6.5 Hz), 1.65-2.55 (m, 7H), 4.10-4.30 (m, 2H).
   8 : $C_{14}H_{22}O_3$, colorless oil; IR (CCl_4) : 3632, 3390 (OH), 1707 (C=O), 1660 (C=C) cm^{-1}; NMR (200 MHz, C_6D_6): δ = 0.85 (s, 3H, dia 1), 0.86 (s, 3H, dia 2), 0.93 (s, 3H, dia 1), 0.95 (s, 3H, dia 2), 1.00 (t, 3H, J = 7.0 Hz, dia 2), 1.02 (t, 3H, J = 7.0 Hz, dia 1), 1.27 (d, 3H, J = 1.0 Hz), 1.50 (d, 3H, J = 6.7 Hz), 1.15-1.80 (m, 2H), 2.10-2.30 (m, 1H), 2.40-2.60 (m, 1H), 2.85-3.30 (m, 2H), 3.40 (t, 1H, J = 8.0 Hz, dia 2), 3.86 (t, 1H, J = 8.0 Hz, dia 1), 3.95-4.15 (m, 2H).
   12 : $C_{14}H_{20}O_2Si$, yellow oil; IR (CCl_4) : 3620, 3478 (OH), 1702 (C=O) cm^{-1}; NMR (200 MHz, $CDCl_3$): δ = 1.09 (s, 3H, dia 1), 1.11 (s, 3H, dia 1), 1.13 (s, 6H, dia 2), 1.25 (d, 3H, J = 6.9 Hz, dia 1), 1.29 (d, 3H, J = 7.2 Hz, dia 2), 1.50-1.70 (m, 2H), 1.75-2.05 (m, 2H), 2.15-2.30 (m, 1H), 2.35-2.50 (m, 1H, dia 1), 2.55-2.75 (m, 1H, dia 2), 3.80-3.90 (m, 1H), 5.86 (d, 1H, J = 5.5 Hz, dia 1), 5.88 (d, 1H, J = 5.5 Hz, dia 2), 7.57 (d, 1H, J = 5.5 Hz, dia 1), 7.58 (d, 1H, J = 5.5 Hz, dia 2).

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