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The Cyclobutenic Way to Triquinanes. Synthesis of (±) Silphinene

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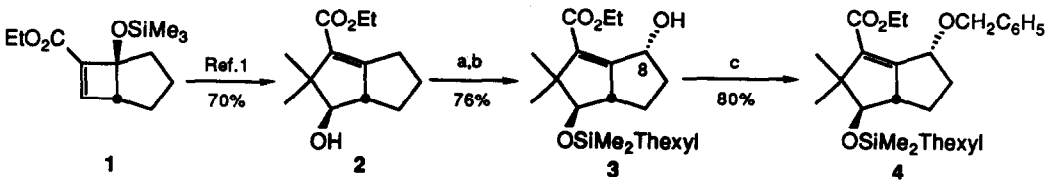
Key Words : cyclobutene ester, diquinane alcohol, benzylation, sila-Nazarov reaction, Silphinene.

Abstract : The easily accessible alcohol 2 is oxidized, after protection, to the allylic alcohol 3. The benzyl ether of this diquinanic alcohol is transformed into the triquinanic precursor 9 of (±) Silphinene, using a similar reaction sequence as described previously, but using the opposite epimer.

We have recently shown that functionalized diquinanes, which represent important substructures of the natural triquinanes, are easily obtained from the cyclobutenic adducts of silyl enol ethers with acetylenic esters, after cyclopropanation with diazoalkanes and solvolysis[1].

We have now succeeded in using the diquinane alcohol **2**, accessible in 70 % yield from the cyclobutene ester **1**, as the starting material for the total synthesis of the angular natural triquinane Silphinene[2]. The final steps of this synthesis were already developed during our previous work on the "cyclopropenic" synthesis of (±) Silphinene[3]. To obtain a suitable product to exploit our previous work, it was necessary to functionalize the diquinane alcohol **2** in position 8 and to make use of a number of selective protection reactions.

The starting alcohol **2** was first protected as a silyl ether and subjected to allylic oxidation[4] which introduced stereospecifically an hydroxyl group in the required position. It was then necessary to protect the alcohol **3**, preferably as a benzyl ether[5]. However, classical methods (NaH or KH/$PhCH_2Br$; NaH, $nBu_4NI/PhCH_2Br$; $Ag_2O/PhCH_2Br$...) gave only poor yields (< 20 %) or complete decomposition of the starting material. The introduction of the benzyl group was finally achieved, as indicated[6] to give the benzyl ether **4**[7] which is the epimer at position 8 of the compound used in our previous synthesis of Silphinene[8]. It was therefore necessary to demonstrate that **4** could undergo the same transformations to give a common intermediate[9].

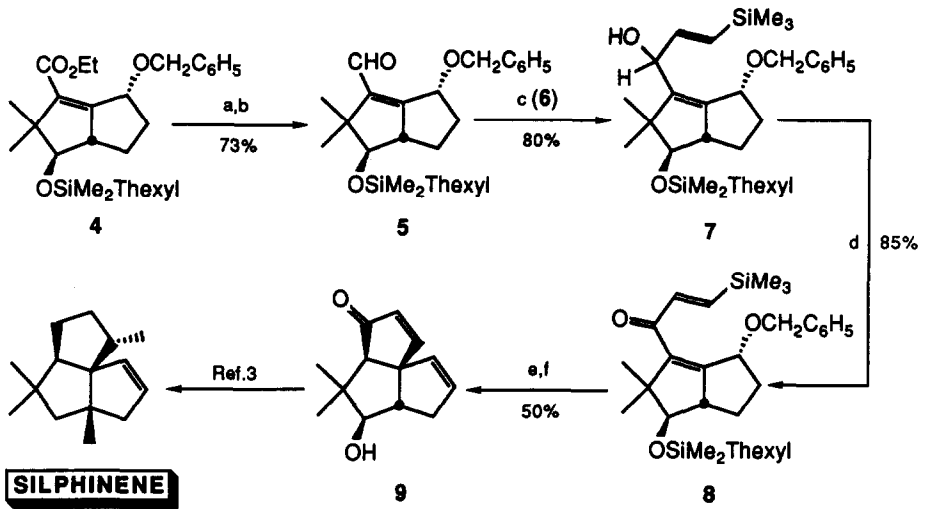


1 2 3 4

a : $CF_3SO_3SiMe_2Thexyl$, NEt_3 , CH_2Cl_2 , 40°C ; b : SeO_2 , dioxane , 101°C[4]
c : $C_6H_5CH_2OCNHCCl_3$, CF_3SO_3H cat. , CH_2Cl_2 , C_6H_{12} , 40°C[6] .

The diquinane ester **4** was transformed into the aldehyde **5** which was then treated with the Grignard reagent **6** giving the alcohol **7**. The ketone **8**, obtained by oxidation of the bis-allylic alcohol **7**, undergoes a silyl-assisted Nazarov type cyclisation. The elimination of the O-benzyl group followed by formation of a double

bond occurs during the reaction, giving directly the triquinane **9**. After deprotection, the angular triquinane 9[10] is obtained in a overall yield of 50 % from **8**.



a : DIBAH , C_6H_6 , 20°C ; b : MnO_2 , CH_2Cl_2 , 20°C ; c : **6**: BrMg(CH=CH)$SiMe_3$, THF , -30°C ;
d : MnO_2 , CH_2Cl_2 , 40°C ; e : BF_3Et_2O , C_6H_5Et , 125°C ; f : TBAF ,THF , 20°C .

As we have already transformed the triquinane **9** into (±) Silphinene, the present reaction sequence completes the total synthesis of this product.

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References and Notes

1. Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.*, **31**, 5027 (1990).
2. Bohlmann, F.; Jakupovic, J. *Phytochemistry*, **19**, 259 (1980).
3. Franck-Neumann, M.; Miesch, M.; Lacroix, E. *Tetrahedron Lett.*, **30**, 3533 (1989).
4. Furlenmeier, A.; Fürst, A.; Langemann, A.; Waldvogel, G.; Kerb, U.; Hocks, P.; Wiechert, R. *Helv. Chim. Acta*, **49**, 1591 (1966).
5. Although other protective groups, mainly silylated, were easier to introduce, such products led to very poor yields or even complete failure for the subsequent steps.
6. Widmer, U. *Synthesis*, 568 (1987).
7. **4** : $C_{28}H_{44}O_4Si$; IR (CCl_4) : 1709 (C=O) and 1655 (C=C) cm^{-1} ; NMR (400 MHz, C_6D_6) : d = 0.05 (s, 6H), 0.91 (s, 3H), 0.93 (s, 3H), 0.97 (d, 3H, J = 7 Hz), 0.98 (d, 3H, J = 7 Hz), 0.99 (t, 3H, J = 7 Hz), 1.36 (s, 3H), 1.44-1.56 (m, 2H), 1.49 (s, 3H), 1.69 (h, 1H, J = 7 Hz), 1.73-1.79 (m, 1H), 1.98-2.03 (m, 1H), 2.74-2.82 (m, 1H), 3.68 (d, 1H, J = 8 Hz), 4.02 (dq, 1H, J = 32 Hz, J = 7 Hz), 4.10 (dq, 1H, J = 32 Hz, J = 7 Hz), 4.37 (d, 1H, J = 5 Hz), 4.44 (d, 1H, J = 11.5 Hz), 4.52 (d, 1H, J = 11.5 Hz), 7.04-7.09 (m, 1H), 7.13-7.19 (m, 2H), 7.36-7.40 (m, 2H).
8. NOE-experiments confirm the relative configuration indicated for the alcohol **3**.
9. This question was justified *a priori*, as we had encountered so many difficulties during the benzylation of the alcohol **3**. We expected, therefore, unusual reactivities in the epimeric series, which, fortunately, was found not to be the case.
10. **9** : $C_{13}H_{16}O_2$; IR (CCl_4) : 3620 , 3200-3580 (OH), 1700 (C=O) and 1575 (C=C) cm^{-1} ; NMR (200 MHz, $CDCl_3$) : d = 0.79 (s, 3H), 1.21 (s, 3H), 2.25 (s, 1H), 2.35-2.55 (m, 2H), 1.80-2.15 (s, 1H), 2.72 (qt, 1H, J = 2.2 Hz, J = 8 Hz, J = 17.2 Hz), 3,45 (d, 1H, J = 9.5 Hz), 5.39 (dt, 1H, J = 2.2 Hz, J = 4.5 Hz), 5.77 (dt, 1H, J = 2.2 Hz, J = 4.5 Hz), 5.99 (d, 1H, J = 5.5 Hz), 7.36 (d, 1H, J = 5.5 Hz).

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