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A NEW ROUTE TO SELECTIVELY PROTECTED *CIS* 4A-METHYL-HEXAHYDRONAPHTHALENE-1(2*H*),7(8*H*)-DIONES

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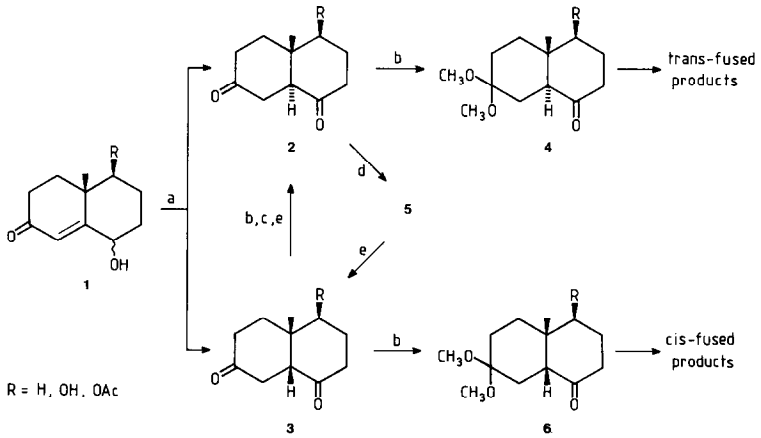
Summary: A two steps transformation of *trans*-fused bicyclic 1,7-diones into their *cis* isomers is described.

Recently we reported the acid-catalyzed isomerization of bicyclic 8-hydroxy enones (**1**) into 1,7-diones as mixtures of *trans*- and *cis*-fused isomers (**2** & **3**) in high yield by using hydrogen bromide in ether.[1] Selective acetalization followed by epimerization with base afforded exclusively C-7 monoacetalized *trans*-fused 1,7-diones (**4**) in good yield[2], which are valuable intermediates in the synthesis of a great number of *trans*-fused natural products.[3]

We now report on a procedure for the synthesis of the corresponding selectively protected *cis*-fused 1,7-diones, which enlarges the synthetic utility of this approach. Treatment of a 2:1 mixture of *trans*- and *cis*-fused diones (**2** & **3**) with trimethyl orthoformate and 0.5-1.0 equiv of acid (*p*-toluenesulfonic acid or sulfuric acid) in methanol as solvent at room temperature for 3-5 days gave exclusively the *cis*-fused diacetals (**5**) in 70-80% yield. Mild hydrolysis with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone for 1 h gave in nearly pure form the *cis*-fused 1,7-diones (**3**) in almost quantitative yield. Treatment of **3** with trimethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate in dichloromethane as solvent afforded the selectively protected *cis*-fused products (**6**)[4] (Scheme I).

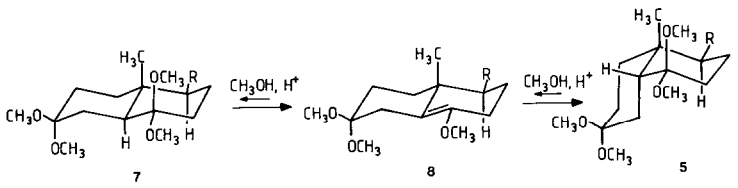
Scheme I[a]



[a] (a) HBr, ether ; (b) $(CH_3O)_3CH$, H^+, CH_2Cl_2 ; (c) $NaOCH_3$, CH_3OH ; (d) $(CH_3O)_3CH$, H^+, CH_3OH ; (e) PPTS, H_2O, acetone.

The *cis* steroid conformation was assigned to 5(R=OAc) based upon the magnitude of the J values for the C-4 proton: ^{1}H NMR (C_6D_6, 300 MHz) δ 5.50 (dd, J = 4.3, 11.9 Hz, C_4-H_{ax}). The formation of *cis*-fused diacetal (5) can be explained in terms of an elimination-addition mechanism[5] (Scheme II).

Scheme II



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The *trans*-fused diacetal (7) is equilibrated to its *cis* isomer (5) via acid-catalyzed anti elimination (7→8) and renewed addition of methanol (8→5). In the latter compound (5) the reverse reaction e.g. elimination of methanol is much slower because the β-hydrogen on C-8a and the α-methoxy group of the C-1 acetal lack an anti-periplanar orientation.

The different reaction outcome of the acetal formation in dichloromethane versus methanol is obvious. The less hindered carbonyl group at C-7 is converted selectively[6] when dichloromethane is used as solvent. In methanol the acetalization is accelerated dramatically and the more hindered C-1 carbonyl function reacts as well. Although some examples of acid-catalyzed enolization of cyclic acetals have been published[7] its application to the 1-decalone chemistry represents the first example in which a more stable *trans*-fused 1-decalone system is converted to its less stable *cis* isomer.

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