Dialkylation of α-Diketone Ketals with 1,8-Bis(trimethylsilyl)octa-2,6-diene

Hélène Pellissier,* Robert Faure and Maurice Santelli*

URA au CNRS no. 1411, Faculté de St-Jérôme, 13397 Marseille Cedex 20, France

Titanium tetrachloride-mediated dialkylation of α-diketone ketals (*cis*-6-alkyl-1-methyl-2,5,7,10-tetraoxabicyclo-[4.4.0]decanes) by 1,8-bis(trimethylsilyl)octa-2,6-diene leads to a pair of isomers of 6-alkyl-7,10-divinyl-1-methyl-2,5-dioxabicyclo[4.4.0]decanes which can be stereoselectively isomerized into the corresponding 1-acyl-1-alkyl-2,5-divinylcyclopentanes.

Important progress in steroid synthesis has come from the strategy involving an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes.[1] This methodology has a remarkable advantage for the formation of the *B/C* rings starting from an *o*-quinodimethane precursor and a cyclopentane derivative bearing a vinyl group.

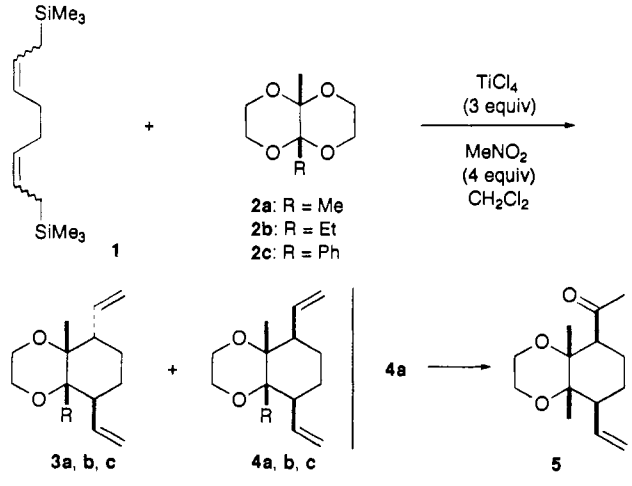
In connection with our interest in steroid synthesis,[2] we have recently reported on a new strategy for the synthesis of 1,1-disubstituted-2,5-divinylcyclopentanes. These latter arise from the addition of 1,8-bis(trimethylsilyl)octa-2,6-diene **1** (BISTRO) to different electrophilic reagents.[3] We previously reported that addition of allyltrimethylsilane to α-diketone diketals **2** (*cis*-6-alkyl-1-methyl-2,5,7,10-tetraoxabicyclo-[4.4.0]decanes) in the presence of titanium tetrachloride led to 2,3-diallyl-2,3-dialkyl-1,4-dioxanes with very high diastereoselectivity involving an invertive ('S_N2-like') substitution.[4]

We report here that titanium tetrachloride (3 equiv.)-mediated dialkylation of α-diketone diketals **2**[5] with BISTRO **1**† (2 equiv.) at −90 °C in the presence of nitromethane (4 mol equiv.)‡ affords dioxadecaline derivatives **3** and **4** in moderate yields (**3a** + **4a** = 60%, **3a**:**4a** = 1.22:1; **3b** + **4b** = 60%, **3b**:**4b** = 1:1.14; **3c** + **4c** = 48%, **3c**:**4c** = 3.0:1).

Compounds **3** and **4** could be easily separated by liquid chromatography on silica gel and their structures were established by a series of 1D, COSY and NOESY NMR experiments (400 MHz). Both isomers **3** and **4** exhibit a *cis*-ring junction. In particular, for dioxane **3b**, NOESY experiments confirmed the vicinal *cis*-relationship between the ethyl group and its adjacent vinyl group. The *trans*-disposition between the two other substituents was also demonstrated. However, in the case of dioxane **4a**, the relative stereochemistry of the substituents remained uncertain because of the symmetry of the molecule. In order to confirm the *meso*-configuration, we prepared ketone **5** by selective Wacker-type oxidation of **4a** [$Pd(OAc)_2$, benzoquinone, $HClO_4$, 30% yield].[8] Ketone **5**, which is no longer symmetric, has spectroscopic data in agreement with a *cis*-ring-junction. Particularly, in the NOESY experiment, we observed that only one methyl group (δ 1.28) gives cross peaks with one axial hydrogen of the 1,4-dioxane moiety.

The stereochemistry of the addition of diallysilane **1** to **2b** is particularly informative with respect to the mechanistic pathway since only the two *cis*-fused diastereoisomers are obtained. The stereochemical features can be rationalized in terms of a synchronous (S_N2-like) substitution process.§ Fig. 1 shows the two possible S_N2-like routes, **B′** or **B″**, which afford the final products. We assume that the first allylation of the ketal–Lewis acid complex occurs with a synchronous mechanism **A** leading to an intermediate monocyclic derivative. The latter is then coordinated with titanium tetrachloride to give transition states **B′** or **B″** from which the second invertive allylation occurs affording **3a, b** or **4a, b**, respectively. Both transition states **A** and **B** are assisted and stabilized through the anomeric effect.[10]

Each isolated dioxane derivative **3** or **4** respectively was stereospecifically transformed into its corresponding acyldivinylcyclopentane **6** or **7** by treatment with 2 equiv. of titanium tetrachloride at −50 °C. In this way, (±)-1-acetyl-1-alkyl-2,5-divinylcyclopentane **6a, b** arises from **3a, b**, while *meso*-1-acyl-1-methyl-2,5-divinylcyclopentane **7a, b** comes from **4a, b**. Compounds **6c** and **7c** [(±)- and *meso*-1-acetyl-1-phenyl-2,5-divinylcyclopentanes] were obtained by treatment of **3c** and



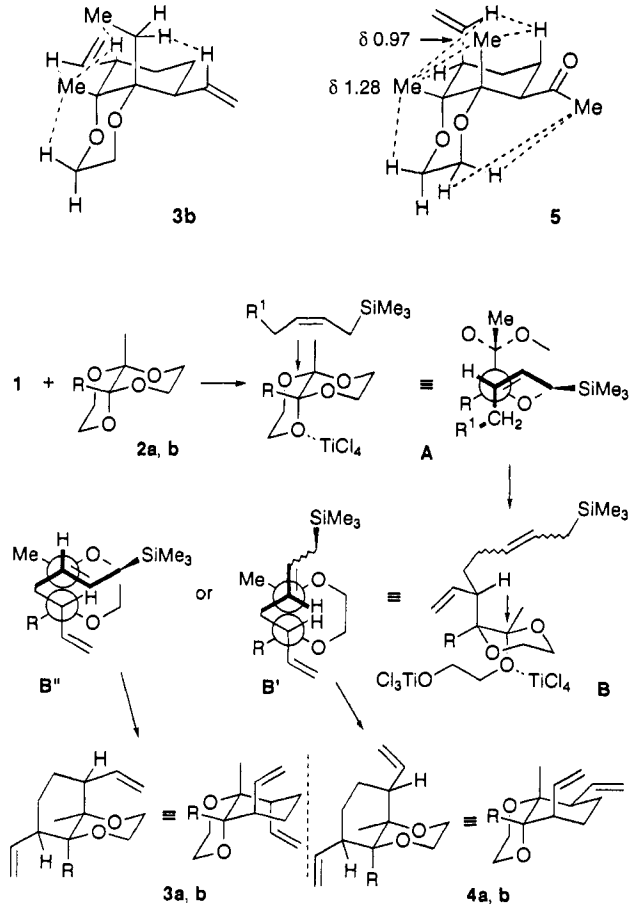


Fig. 1 The two possible S_N2 routes

4c (**6a** from **3a**, 95%; **7a** from **4a**, 100%; **6b** from **3b**, 57%; **7b** from **4b**, 83%; **6c** from **3c**, 40%; **7c** from **4c**, 48%).

This *pinacol-like* rearrangement with ring contraction involves the equatorial substituent of the cyclohexane moiety. Effectively, the O–C and C–C bonds must have the antiperiplanar relationship appropriate for 1,2-migration.[11] Cleavage of dioxanes **3a**, **b**, **c** into the corresponding ketones **6a**, **b**, **c** involves transition state **C** [activation of O(2)] rather than **C'** [activation of O(5)]. A lanthanide NMR shift experiment involving **3b** and tris(dipivaloylmethanato)europium was carried out. It indicates that 'Euro-shift' preferentially interacts with O(2) (the induced shift is the largest for the 3-methylene group) (Fig. 2).

On the other hand, formation of **7a,b** involves the activation of O(5) leading to transition state **D** (Fig. 3). A similar NMR shift reagent experiment with **4b** shows that the induced shift is the largest for the 4-methylene group indicating a coordination of O(5). In the case of **4c**, the regioselectivity was reversed suggesting a dissociative pathway with formation of ion pairs prior to the carbon bond migration.[12]

It is worth noting that during the addition of **1** to **2**, the use of 4 equiv. of $TiCl_4$ combined with a higher temperature (up to −50 °C) results in the direct formation of **6** and **7** in similar yields and ratio as for the dioxane synthesis (56% for **6a** + **7a**; 60% for **6b** + **7b**; 48% for **6c** + **7c**). However, ketones **6** and **7** are generally more difficult to separate by chromatography on silica gel than the corresponding dioxanes **3** and **4**.

The authors thank Dr I. D. R. Stevens (The University of Southampton) for reading the manuscript and for valuable comments.

Received, 12th June 1995; Com. 5/03781F

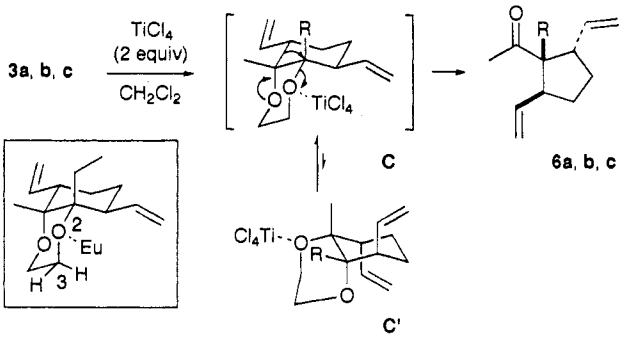


Fig. 2 Formation of **6a–c**

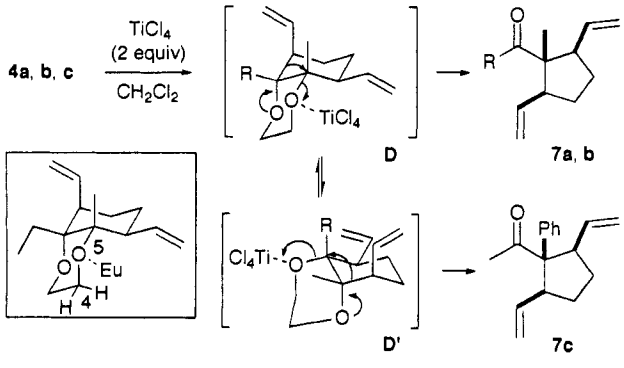


Fig. 3 Formation of **7a, b**

Footnotes

† The reductive dimerisation of buta-1,3-diene (Li, $ClSiMe_3$, THF) leads to bis(trimethylsilyl)octa-2,6-diene as a mixture of (*Z,Z*) (*ca.* 50%), (*Z,E*) (*ca.* 40%) and (*E,E*) (4%) isomers contaminated with *ca.* 4% of (*Z*)-1,6-bis(trimethylsilyl)octa-2,7-diene and *ca.* 2% of (*E*)-1,6-bis(trimethylsilyl)octa-2,7-diene (this mixture is difficult to separate even by preparative gas chromatography.[6]

‡ The influence of the nitro group during the reaction of allylsilanes with various electrophilic compounds has been discussed previously (*cf.* ref. 7).

§ The complete retention of *cis*-ring fusion requires either two successive retentions (S_Ni) or two successive inversions (S_N2). Evidence from the replacement of α-oriented leaving groups in sugar chemistry shows that the S_Ni process is not totally stereospecific and hence one is forced to the S_N2-like mechanism (*cf.* ref. 9).

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