Pergamon

Tetrahedron Letters 39 (1998) 6457–6460

TETRAHEDRON LETTERS

Wittig Olefination of Partially Protected Sugar Lactones: A Direct Entry to Dioxabicyclic and Trioxatricyclic Systems

M. Lakhrissi,[a, b] C. Taillefumier,[a] A. Chaouch,[b] C. Didierjean,[c] A. Aubry,[c] and Y. Chapleur[a]*

a) Groupe SUCRES, Unité Mixte CNRS-Université H. Poincaré-Nancy I, BP 239, F-54506 Vandoeuvre (France)

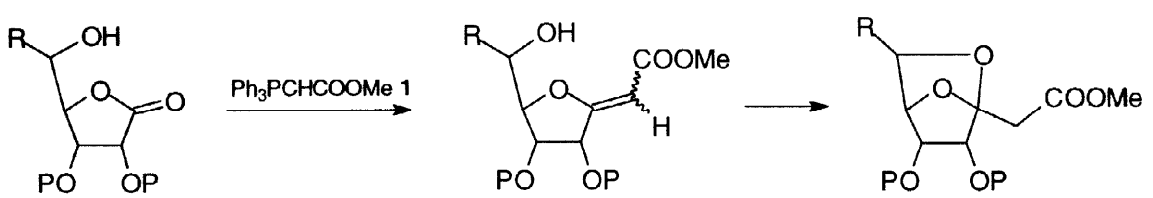
b) Laboratoire de Chimie Organique Appliquée, Université Ibn Tofail, Faculté des Sciences, Kenitra, (Morroco)

c) Groupe Biocristallographie associé au CNRS,Université H. Poincaré-Nancy I, BP 239, F-54506 Vandoeuvre (France)

Received 6 March 1998; accepted 24 March 1998

Abstract : Partially protected sugar lactones reacts with stabilized phosphoranes at high temperature yielding activated olefins which undergo subsequent 1,4-addition to give bicyclic adducts, simultaneous furan formation being also observed.

We are interested for some years now in the olefination of sugar lactones as a mean to synthesise C-glycosidenes compounds,[1] key intermediates in the stereocontrolled preparation of C-glycosides by subsequent manipulation of the double bond.[2] Direct olefination of ester carbonyls is seldom exploited.[3] Some years ago we have introduced the dichloroolefination of lactones using carbon tetrachloride and tris(dimethylamino)-phosphine,[4] which can be efficiently replaced with triphenylphosphine under suitable conditions.[5] More recently, we studied the reaction of stabilized phosphoranes which reacted at high temperature with lactones, allowing the introduction of a carbomethoxymethylene chain at the anomeric centre.[6] Given that the Wittig reaction with stabilized phosphoranes might be *a priori* performed in the presence of hydroxyl groups, we have investigated the reaction of partially protected lactones having one, two or three hydroxyl groups with carbomethoxymethylene triphenylphosphorane. We have found that one or two of the free hydroxyl groups can add efficiently to the activated double bond to form dioxabicyclic systems. We report in this letter our preliminary results which additionally provide further evidence that carbomethoxy triphenylphosphorane **1** can act as an acylating and activating agent of alcohols.



Scheme 1

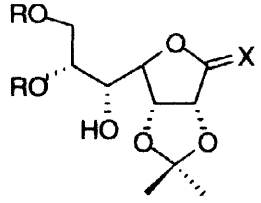
Readily available D-*gluco*-heptonolactone derivative **2** was reacted under our standard conditions (toluene, 140°C, sealed vessel).[6] The expected olefins **3** were formed as a *E* and *Z* mixture in an approximately 1:1 ratio (25% and 18%). A third product **5** (30% yield) was formed whose structure was established on the basis of spectral data. The presence of a pendant carbomethoxy methylene function was revealed by the presence of the two singlets corresponding to the CH_2 (δ = 2.9), and OMe (δ = 3.75) group, indicating the presence of a quaternary carbon at the anomeric centre. The absence of hydroxyl group suggested that the 7-OH group (see

* Email: yves.chapleur@meseb.u-nancy.fr

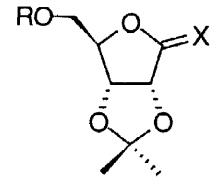
0040-4039/98/$ - see front matter
PII: S0040-4039(98)00676-5

numbering in structures) was involved in a reaction with the activated double bond. The coupling constants of the other protons of the sugar ring were in favour of the proposed strained tricyclic arrangement. The structure was confirmed by single crystal X-ray analysis.[7] Formation of compound **5** was believed to proceed first via olefin formation and subsequent 1,4-addition of the alcohol at C-5 on the activated olefin. This was confirmed by separate treatment of olefins **3** (*E* and *Z* isomers) with DBU in refluxing THF to give compound **5** in 73 and 68% yield respectively.[8] According to this procedure, it is thus possible to prepare compound **5** in a 60% combined yield.

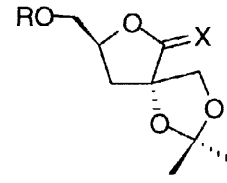
The D-ribono-1,4-lactone derivative **6** was treated with phosphorane **1** in toluene at 140°C in a sealed stainless steel vessel to yield a 1:1 mixture of the bicyclic compound **8** together with acetate **7** in 45% overall yield. This unexpected acylation of the starting material was also observed as the only reaction on the sterically congested isosaccharinolactone derivative **9**[9] to produce acetate **10.** In this case the Wittig olefination is very difficult due to the steric congestion of the lactone carbonyl, thus the phosphorane acts as an acylating reagent. Such acylating properties have been reported for amine, alcohol and carboxylic acids by Desmaële.[10] Decomposition of the phosphorane reagent occurs at room temperature in methanol and is catalysed by methoxide ion itself (see Scheme 2). In our case, an alcohol group of the substrate may be deprotonated by the phosphorane and then react with the phosphonium salt with formation of ketene responsible for the acylation of the free hydroxyl group. Thus with sterically congested lactones, the Wittig olefination is slower than the decomposition of the phosphorane which acts as an acylating agent.



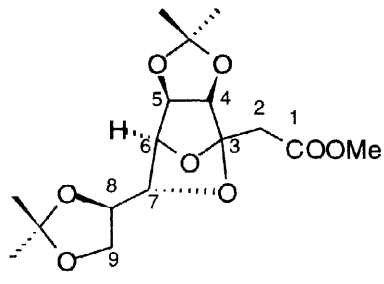
2 R = $CHMe_2$, X = O
3 R = $CHMe_2$, X = CHCOOMe
4 R = H, X = O



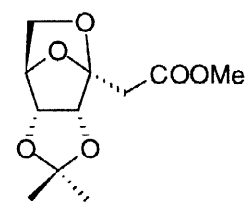
6 R = H, X = O
7 R = Ac, X = O



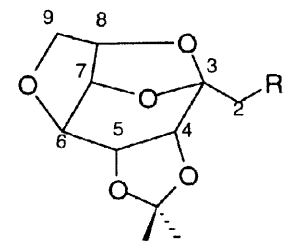
9 R = H, X = O
10 R = Ac, X = O



5



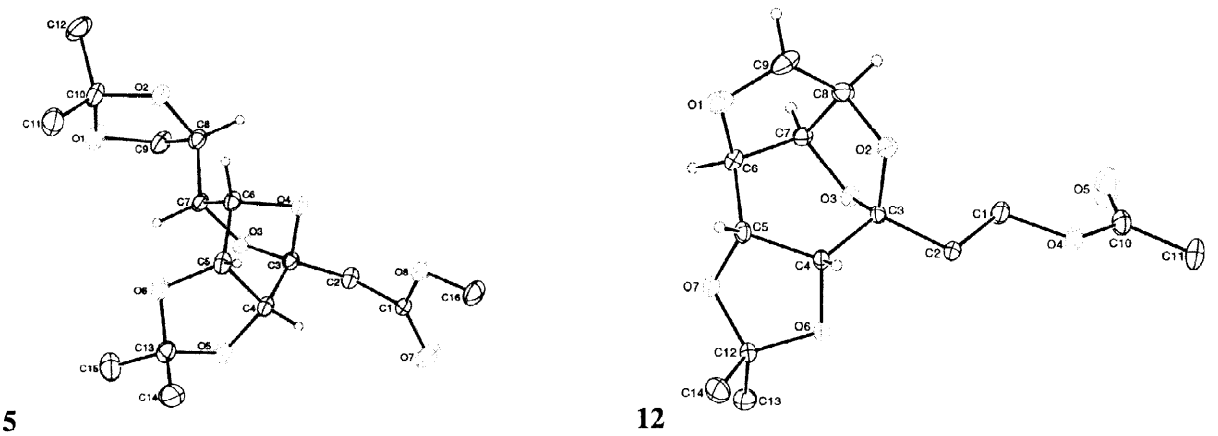
8



11 R = COOMe
12 R = CH_2OAc

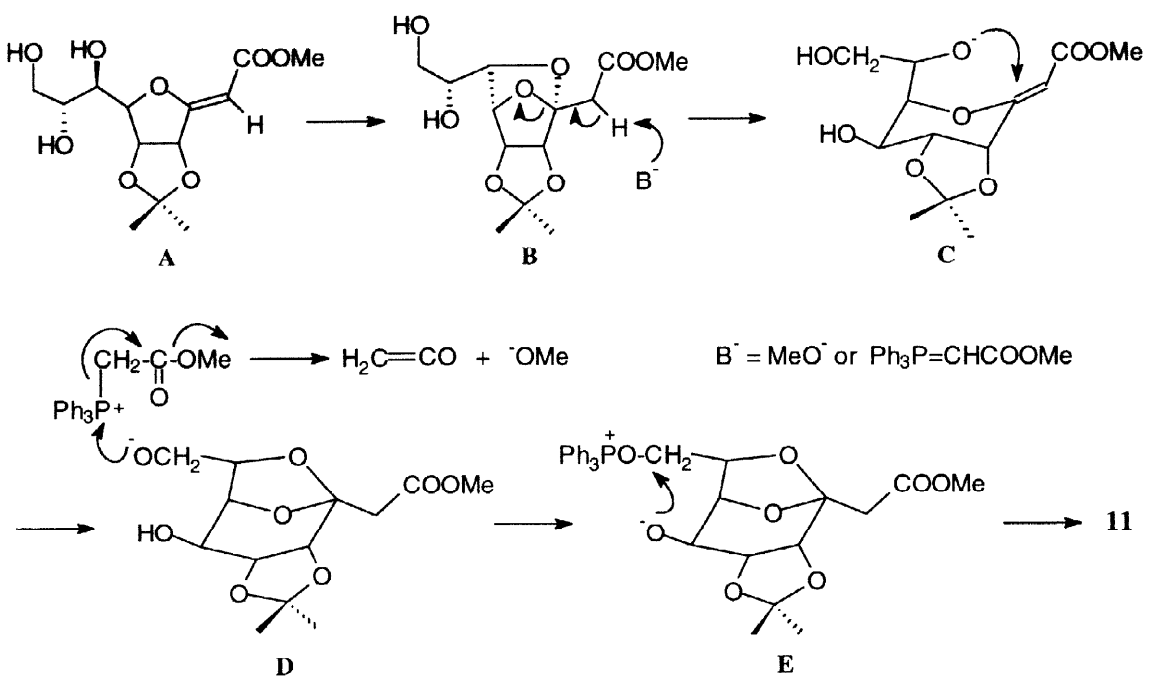
Finally we attempted to treat lactone **4** with **1**. After a few hours at 140°C in a mixture of toluene and dimethylformamide, a non-polar product **11** was formed (60%) together with very polar, yet unidentified, products.[8] According to i.r spectroscopy no hydroxyl group was present in compound **11** as shown by the absence of reaction upon conventional acetylation (Ac_2O, pyridine). Mass spectrum showed a molecular ion at m/z 286 indicating that in addition to the expected 1,4-addition, a dehydration reaction had occured. ^1H nmr spectroscopy showed a set of two doublets at δ = 2.8 and 3.0, J = 16 Hz, in agreement with the presence of a

CH_2 group supporting the 1,4-addition reaction on the activated double bond. Other signals were attributed on the basis of COSY and showed that H-7 was the more shifted proton at δ = 5.17 suggesting that the environment around this proton had been modified. Furthermore the coupling constant of $J_{4,5}$ = 11 Hz shows that these protons are located on a six membered ring. Finally we transformed compound **11** into acetate **12** by reduction with lithium aluminium hydride followed by conventional acetylation using acetic anhydride in pyridine. This compound promptly yielded crystals suitable for X-ray diffraction studies.[7]



5 12

Figure 1 : X-Ray crystal structures of compounds 5 and 12



Scheme 2: Possible mechanism of formation of **11**.

We have not yet established the exact mechanism accounting for the formation of this unusual tricyclic structure, depicted on Figure 1, however a tentative explanation is given on Scheme 2. The first step of the reaction could be the expected Wittig reaction which form the corresponding olefin **A**. In a second step 1,4-addition of the free hydroxyl group at C-7 (see structures) occurs to form **B** but base-induced β-elimination should open the bicyclic adduct forming **C**. 1,4-addition of the alcoholate at C-8 then gives the less congested

structure **D** in which the primary alcohol reacts with phosphorane **1** in excess to form the alkoxytriphenylphosphonium salt **E**. [11] Tetrahydrofuran ring formation occurs by nucleophilic displacement of the phosphonium salt gives **11**.[12] A definitive proof could be obtained using partially protected derivatives of lactone **4**.

In conclusion this work shows that complex dioxabicyclic and trioxatricyclic structures can be obtained in moderate yields from suitably substituted lactones on treatment with carbomethoxy triphenylphosphorane. Evidence for the decomposition of this reagent into ketene are provided by the observed acylation of hydroxyl groups. Another interesting feature is the possible formation of an alkoxyphosphonium salt from **1** and a primary alcohol, which undergoes intramolecular substitution to form furan. Our method could be a good alternative to the formation of the ketal group by acidic treatment of a keto diol. Studies are in progress to obtain synthetically significant dioxabicyclic systems like those found in natural products such as zaragozic acids (squalestatins)

Acknowledgments: We thank a referee for helpful suggestions regarding the mechanism of furan formation

References and Notes

1. For the synthesis of glycosylidene compounds see: Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559-7572; Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395-398; Lancelin, J. -M.; Pougny, J. -R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369-374; RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458-5461; Csuk, R.; Glanzer, B. I. *Tetrahedron* **1991**, *47*, 1655-1664 and references cited therein.
2. For different uses of C-glycosylidene compounds see: Noort, D.; Veeneman, G. H.; Boons, G. J. P. H.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H. *Synlett* **1990**, 205-206; Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron Lett.* **1991**, *32*, 4035-4038 and references cited therein.
3. For a review on the Wittig reaction of carbonyl compounds other than aldehydes and ketones see: Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1-30.
4. Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 449-450; Bandzouzi, A.; Chapleur, Y. *Carbohydr. Res.* **1987**, *171*, 13-24.
5. Lakhrissi, M.; Chapleur, Y. *Synlett* **1991**, 583-587; Lakhrissi, M.; Chapleur, Y. *J. Org. Chem.* **1994**, *59*, 5752-5757.
6. Lakhrissi, M.; Chapleur, Y. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 750-752.
7. Full details of the X-ray analysis are available from the authors on request.
8. Analytical data: compound **5** $[\alpha]_D$ = +34 (c 0.2, $CHCl_3$); ^1H nmr: δ :1.30, s, 3 H, CH_3, 1.36 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 2.90 (s, 2H, H-2, H-2'), 3.70 (s, 3 H, OCH_3), 3.96 (m, 3 H, H-8, H-9, H-9'), 4.28 (d, 1 H, H-7, $J_{7,8}$ = 8 Hz), 4.44 (dd, 1 H, H-4, $J_{2,4}$ = 1,5, $J_{4,5}$ = 7,5 Hz), 4.71 (m, 2 H, H-5, H-6); ^{13}C nmr : δ :25.2, CH_3; 25.6, CH_3; 26.1, CH_3; 26.8, CH_3; 36.4, C-2; 51.9, OCH_3; 66.3, C-9; 74.1, 75.5, 77.0, 80.2, 82.4, (C-4, C-5, C-6, C-7, C-8); 106.5, 109.5, 2 $C(CH_3)_2$; 119.7, C-3; 168.2, C-1. MS EI :*m/z* = 344 (M^+), 329, 313, 286, 256,271, 255, 229, 211, 111, 101. Compound **11** $[\alpha]_D$ = -33 (c 0.4, $CHCl_3$); ^1H nmr δ: 1.32, s, 3 H, CH_3, 1.45, s, 3 H, CH_3, 2.81, d, 1 H, H-2', $J_{2,2'}$ = 16 Hz, 3.06, d, 1 H, H-2, 3.70, s, 3 H, OCH_3, 3.84, dd, 1 H, H-5, $J_{4,5}$ = 11, $J_{5,6}$ = 3 Hz, 4.28, m, 3 H, H-8, H-9 et H-9', 4.48, dd, 1 H, H-6, $J_{6,7}$ = 4,5 Hz, 5,17, dd, H-7, $J_{7,8}$ = 7,5 Hz. ^{13}C nmr δ :25.3, CH_3; 26.8, CH_3; 38.7, C-2; 52.2, OCH_3 ; 70.6, C-9; 71.6, 75.4, 75.9, 80.0, C-4, C-5, C-6, C-7, C-8; 107.1, C-3; 109.90, C-acetal; 169.6, C=O. MS EI: *m/z* = 286 (M^+), 271, 255, 228, 196, 110.
9. Monneret, C.; Florent, J. C. *Synlett* **1994**, 305-318.
10. Desmaële, D. *Tetrahedron Lett.* **1996**, *37*, 1233-1236.
11. For the formation of phosphonium salts from stabilized phosphoranes and use in Mitsunobu reactions see: Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2463-2466 and references cited therein.
12. For furane formation using phosphonium salts see: Chapleur, Y.; Castro, B.; Gross, B. *Synthesis* **1983**, 447-449.