An Anomalous Outcome in the Wittig Olefination of an Aldose

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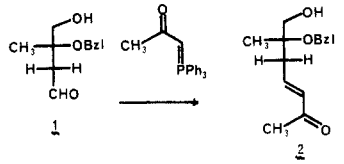
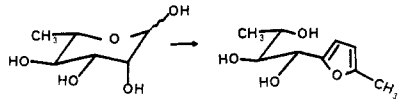
The use of acetonyltriphenylphosphorane as a chain extender in carbohydrate chemistry is common.[1-3] The typical product of the Wittig reaction is the trans unsaturated ketone, as exemplified by the conversion of **1** to **2**

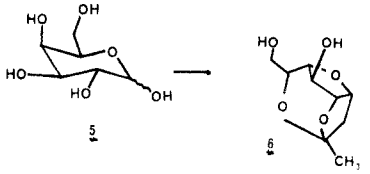


1 **2**

in a frontalin synthesis.[3b] There is only one report of nonketonic products resulting from the reaction of acetonyltriphenylphosphorane with carbohydrates. L-Rhamnal **3** forms furan **4** in 5% yield and D-galactose **5** forms internal ketal **6**, also in low yield.[4] We have been interested in unsaturated sugars as dienophiles in Diels–Alder reactions[5,6] and have therefore examined the reaction of acetonyltriphenylphosphorane with several carbohydrate derivatives.



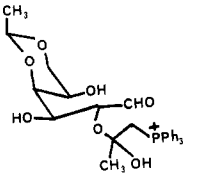
3 **4**



5 **6**

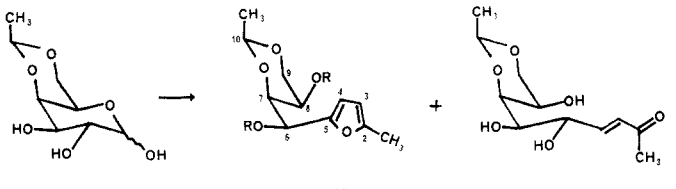
We now report that in the reaction of galactose derivative **7** with essentially 1 equiv of acetonyltriphenylphosphorane there is produced furan **8a** in 50% yield and ketone **9** in 15% yield.

The structure of **8a** was determined by examination of its ^{1}H NMR spectrum, which inter alia revealed two furan protons at δ 5.85 and 6.14. The ^{13}C NMR spectrum of the diacetate **8b** revealed all 15 carbons (Table I). The furan is not the result of cyclodehydration of the desired product, ketone **9**. A control experiment, in which **9** was submitted to the conditions of the Wittig reaction, did not produce furan **8**. Increasing the ratio of Wittig reagent to carbohydrate from 1.4:1 to 4:1 had a beneficial effect on the production of **9**. We speculate that the furan is formed via an intramolecular Wittig reaction.[7] Thus, there is probably a significant concentration of the conjugate acid of the acetonyl Wittig reagent because of its protonation by the OH groups of the sugar. The conjugate acid should be a reactive ketone toward hemiketalization by alcohol groups of the sugar. When such a hemiketal A is formed



A

with the 2-OH, then the Wittig salt, upon deprotonation, is in perfect location to react with sugar aldehyde to form a dihydrofuran which upon elimination of H_2O forms **8**. That dihydrofurans can be formed in this manner was shown by Schweizer in his pioneering work with vinyltriphenylphosphonium bromide.[8] Of course, Wittig reagent formation from A will be slow because the phosphorane would no longer be subject to carbonyl stabilization. Hence, the presence of excess stabilized Wittig reagent would compete successfully in an intermolecular reaction with the sugar aldehyde to produce ketone **9**.



7 **8** a R=H, b R=Ac **9**

Table I

C no.	ppm	m	C no.	ppm	m
2	147.9	s	7	65.2	d
2a	13.5	q	8	63.8	d
3	106.4	d	8a	169.0	s
4	111.9	d	8b	20.7	q
5	152.5	s	9	68.9	t
6	99.2	d	10	75.8	d
6a	170.7	s	10a	20.9	q
6b	20.7	q			

Experimental Section[9]

Preparation of 2,5-Disubstituted Furan 8a. 4,6-*O*-Ethylidene-D-galactose (**7**) (1.03 g, 5 mmol), Wittig reagent (2.31 g, 7 mmol), and acetonitrile (30 mL) were refluxed with stirring for 60 h. The reaction mixture was cooled to room temperature and poured into ice-cold water, and excess Wittig reagent and triphenylphosphine oxide were filtered off. The aqueous portion was saturated with sodium chloride and thoroughly extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered to remove the dessicant, and concentrated in vacuo to afford a pale-yellow oil. The mixture was purified by preparative thin-layer chromatography, using ethyl acetate as the eluent to give the 2,5-disubstituted furan derivative **8a** (0.50 g) in 50%

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(7) Becker, K. B. *Tetrahedron* **1980**, *36*, 1717–1745.
(8) Schweizer, E. E., Liehr, J. G. *J. Org. Chem.* **1968**, *33*, 583–584.
(9) Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 710B instrument. NMR spectra were obtained on a Varian XL-100 machine. TLC was done on glass plates coated with Merck silica gel PF-254. Reverse-phase column chromatography was done with EM Reagents silanized silica gel.
(10) Ball, D. H.; Jones, J. K. N. *J. Chem. Soc.* **1958**, 905–907.

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yield: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6 Hz, CH_3CH), 2.23 (s, 3 H, $O(CH_3)C{=}C$), 4.74 (q, 1 H, H10), 5.85 (d, J = 3 Hz, H3, 6.14 (d, J = 3 Hz, H4); $[\alpha]^{25}_D$ -4.90° ($CHCl_3$).

A small amount of the unsaturated ketone **9** was also isolated in about 15% yield: mp 110-112 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J = 6 Hz, 3 H, CH_3CH), 2.23 (s, 3 H, $CH_3C{=}O$), 4.70 (q, 1 H, H10), 5.04 (dd, J = 2, 16 Hz, H3), 6.60 (dd, J = 4.5, 6 Hz, H4); $[\alpha]^{25}_D$ +2.99° ($CHCl_3$); mass spectrum, m/e (CI isobutane) 229 (loss of H_2O). Both **8** and **9** could be isolated by chromatography on reverse-phase silica by elution with 10% acetonitrile-water.

Acetylation of 2,5-Disubstituted Furan. The hydroxy 2,5-disubstituted furan **8a** (0.310 g, 1.36 mmol) was acetylated with a mixture of acetic anhydride (0.60 mL) and pyridine (0.72 mL). The resulting acetate was purified by preparative thin-layer chromatography, using EtOAc/PE (20:80) to give the acetoxy 2,5-disubstituted furan **8b**: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6 Hz, 3 H, CH_3CH) 2.00 (s), 2.14 (s, CH_3CO), 2.29 (s, 3 H, $O(CH_3)C{-}C$), 4.04 (dd, J = 2, 10 Hz, H9), 4.39 (dd, J = 2, 5 Hz, H7, 4.77 (q, H10), 4.90 (m, H8), 5.91 (d, J = 10 Hz, H6), 5.91 (d, J = 3 Hz, H3), 6.32 (d, J = 3 Hz, H4); mass spectrum, m/e (CI, methane) 312, 253, 209, 149.

Preparation of Ketone 9 4,6-*O*-Ethylidene-D-galactose (7) (1.03 g, 5 mmol), Wittig reagent (6.93 g, 21 mmol), and acetonitrile (50 mL) were refluxed with stirring for 60 h. The reaction mixture was cooled to room temperature and poured into ice-cold water, and excess Wittig reagent and triphenylphosphine oxide were filtered off. The aqueous portion was saturated with sodium chloride and thoroughly extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, and the solvent filtered off the sodium sulfate and concentrated in vacuo to a pale-yellow oil. The mixture was purified by preparative thin-layer chromatography, using ethyl acetate as the eluent to give the ketone **9** (0.566 g) in 55% yield.

A small amount of the 2,5-disubstituted furan **8a** derivative was also isolated in about 10% yield.

Acknowledgment. We thank Professor W. Bailey of the University of Connecticut for obtaining the ^{13}C NMR. We are grateful for financial support of the research by Grants CA 27115 and AM 21888 from the National Institutes of Health.

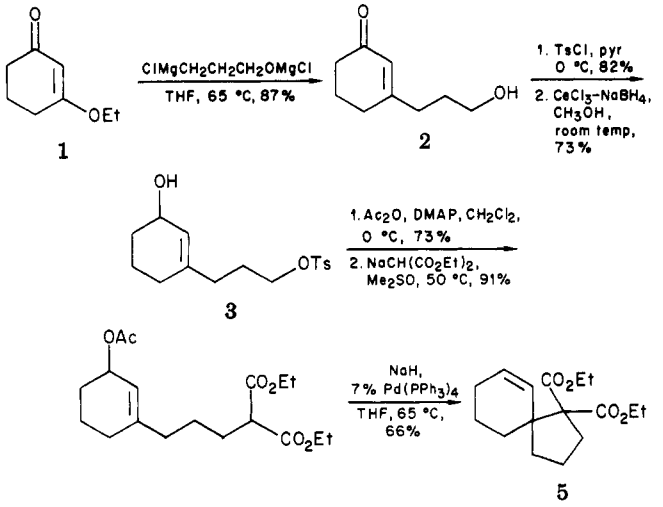
Communications

Palladium-Catalyzed Preparation of Carbon and Oxygen Spirocycles

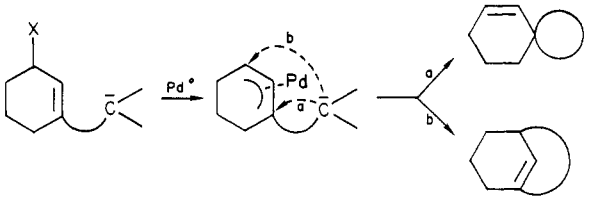
Summary: A variety of substituted spiro[5.5]undecene and spiro[5.4]decene systems have been prepared by utilizing π-allylpalladium chemistry in the key ring-forming step.

Sir: Numerous carbon-carbon bond-forming reactions[1,2] have been applied to the often considerable challenge of the preparation of spirocycles. In order to possess optimal utility, any general methodology dedicated to this purpose should provide the following features in the crucial formation of the quaternary center: (1) complete stereospecificity; (2) ease of preparation of the required precursors; (3) considerable tolerance of additional functionality; (4) potential asymmetric induction. π-Allylpalladium chemistry can fully meet all the stated criteria,[3-5] as well as allow relatively mild reaction conditions for spirocyclization and catalytic use of the metal. Its application to the preparation of spirocycles is detailed in this paper.

Scheme I



The key intermediate required for the palladium-catalyzed spirocyclization is shown below. Reaction of an



allylic ester (e.g., X = OAc) with tetrakis(triphenylphosphine)palladium(0) yields the bisphosphine allyl cation. Cyclization of this compound could, in principle, take place on either terminus of the allyl unit. Cyclization path a leads to the desired spirocycle, while b yields a *trans*-cycloalkenyl system, which for the ring sizes of most interest for spirocyclic natural products ([5.5], [5.4], [4.4]) would be an anti-Bredt olefin. Although there is the intriguing possibility of stabilization of such species[6,7] by the

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