Synthetic Methods

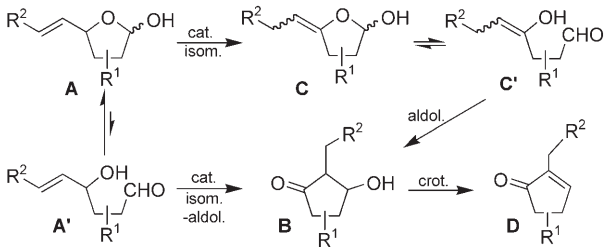
DOI: 10.1002/anie.200701663

A Catalytic Method for Converting Vinylic Furanoses into Cyclopentenones**

*Julien Petrignet, Ireddy Prathap, Srivari Chandrasekhar, Jhillu Singh Yadav, and René Grée**

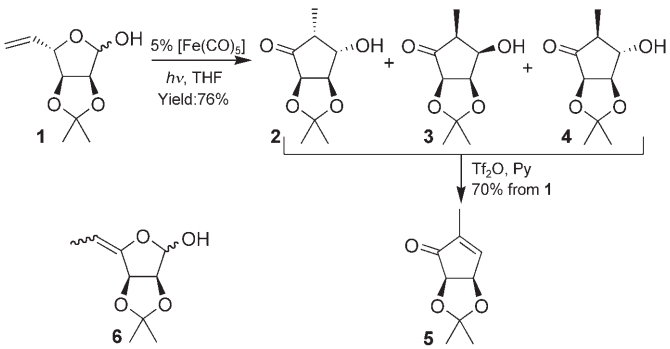
The conversion of carbohydrates into carbocycles is a very useful strategy in organic synthesis since it affords functionalized and optically active key intermediates for the total synthesis of various types of bioactive molecules.[1] Furthermore, it is also an excellent route to carbasugars, which are of pharmacological interest; noteworthy in this area are the carbocyclic nucleosides.[2] Starting from the seminal Ferrier reaction,[3] many methodologies have been developed recently in order to perform such transpositions. They involved Claisen rearrangements, either by thermal[4] or by titanium-catalyzed processes,[5] as well as 1,3 dipolar cycloadditions[6] and radical cyclizations.[7] Various metal-mediated reactions have also been employed,[8] and the samarium-promoted ring contractions have been very successful.[9] In recent years, ring-closing metathesis (RCM)[10] has also played a major role in this area.[11] Although these elegant methods have proved to be very fruitful, only a few of them are catalytic reactions, proceeding under mild and neutral reaction conditions and requiring cheap reagents. As an extension of our work on the tandem isomerization–aldolization reaction of allylic alcohols,[12] we have discovered a new conversion of five-membered vinyl sugar derivatives into cyclopentenones. Here, we describe our results in this field, leading to the preparation of key intermediates for the synthesis of several natural products, including prostaglandins (PGs).

The strategy we have designed for this conversion is indicated in Scheme 1. If our tandem reaction could be applied, in an intramolecular manner, to the open form (**A′**) of a vinyl sugar derivative **A**, it would give directly the aldol product **B** and after crotonization the target cyclopentenone **D**. An alternative possibility would be migration of the double bond in sugar **A** to give the enol ether intermediate **C**. Then ring opening to **C′**, followed by aldolization would give the same aldol **B** and the desired cyclopentenone **D**.



Scheme 1. Strategy for the transposition of vinyl sugars **A** into cyclopentenones **D**.

The known vinyl derivative **1**, easily available in three steps and 43% overall yield from D-ribose,[13] was selected as a first model to screen the different catalysts and optimize the reaction conditions. In the presence of 5 mol% $[Fe(CO)_5]$ and under irradiation for 1 h, **1** was converted (76% overall yield) into a mixture of three aldol products **2** (67%), **3** (14%), and **4** (19%) (Scheme 2). These labile compounds could be separated by chromatography, and their stereochemistry was established from their NMR data. However, the crude mixture of aldols was submitted directly to an elimination reaction via the corresponding triflates to afford the target enone **5**, whose data were in agreement with literature,[14] in 70% overall yield from **1**. It is worth noting that previous syntheses of **5** involved multistep sequences. In particular, the cyclopentenone without substituents on the double bond had to be prepared first[11,15] and then subjected to iodination and a Pd-catalyzed reaction with $SnMe_4$ to introduce the methyl group.[14] Nevertheless, both **5** and *ent*-**5** have been used already as key intermediates for the total synthesis of several natural products.[14,16,17]



Scheme 2. Synthesis of cyclopentenone **5** starting from vinyl sugar **1**.

[*] J. Petrignet, Dr. I. Prathap, Dr. R. Grée
Synthèse et Electrosynthèse Organiques
CNRS UMR 6510, Université de Rennes 1
Avenue du Général Leclerc, 35042 Rennes Cedex (France)
Fax: (+33) 2-2323-6978
E-mail: rene.gree@univ-rennes1.fr
Dr. S. Chandrasekhar, Dr. J. S. Yadav
Indian Institute of Chemical Technology
500007, Hyderabad (India)

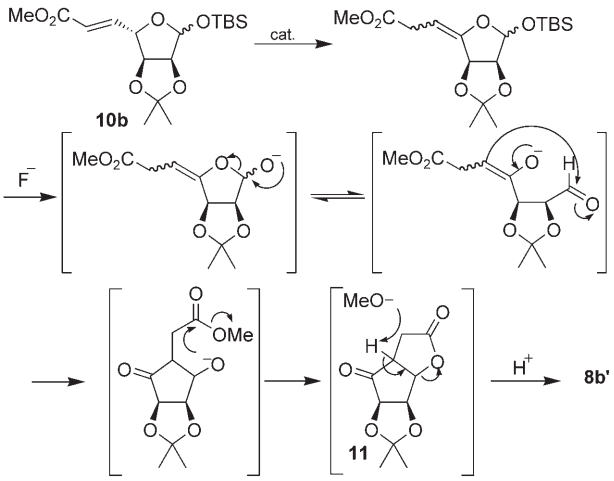
[**] We thank IFCPAR/CEFIPRA for support (Project No. 7106) and Dr. B. V. Rao for useful information on sugar **1**. We thank P. Guénot and CRMPO (Rennes) for the analysis, D. Grée for the NMR experiments, and A. Lancou for preliminary experiments in these series. Very fruitful discussions with Saibal Das are gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

From a mechanistic point of view, several aspects are noteworthy. When the reaction was stopped before complete conversion (after 30 min), it was possible to isolate by chromatography a small amount (5%) of the labile isomerized enol ether **6**, in addition to the aldol products and the starting material. This indicates that the process could occur, at least in part, through intermediates of type **C**. In this case, the transposition would have analogies with the Ferrier rearrangement.[1,3] However, it is well known that the latter process is not suitable for the transformation of furanosides into cyclopentane derivatives,[1] contrary to the results obtained with our new system. Furthermore, it has been clearly established also that the direct aldol cyclization of ketoaldehydes is difficult to perform for the preparation of cyclopentenones of this type.[1a] Finally, as far as the catalysts are concerned, the lactol **1** was found to be unreactive towards two other catalysts known to mediate the intermolecular isomerization–aldolization reaction [NiHCl(dppe)] (dppe = 1,2-bis(diphenylphosphanyl)ethane)[12d] as well as [RhH-$(PPh_3)_3$].[12b]

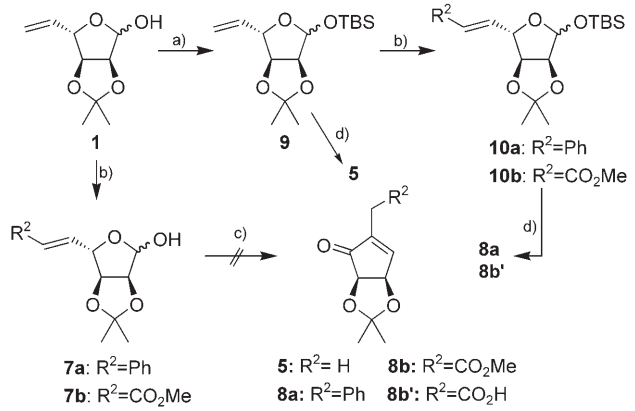
To extend the scope of this reaction, we set out to introduce R^2 substituents on the methyl group of the cyclopentenone. Towards this goal, the cross-metathesis reaction (CM)[10] of lactol **1** appeared the method of choice, and two representative substituents were selected (R^2 = Ph and R^2 = CO_2Me). Using the 2nd generation Grubbs catalyst,[10b] the CM reaction afforded the desired alkenes **7a** and **7b** in moderate yields (44% and 56% respectively, Scheme 3). However, starting from these compounds, the transposition into the target cyclopentenones afforded only low yields of the corresponding aldols in the case of **7a** and mostly degradation products starting from **7b**. Therefore a complementary strategy was considered through an isomerization–Mukaiyama aldol process.[18] To check the possible use of this tandem process, the silyl ether **9** was first prepared in 92% yield by protection of lactol **1**. The iron-carbonyl-catalyzed isomerization, followed by treatment with TBAF, afforded directly in a one-pot process the desired cyclopentenone **5** in 52% overall yield from **1**. The next intermediates, alkenes **10a** and **10b**, were prepared in 58% and 66% yields from **9** by the CM reaction. Then, starting from **10a** and following the same sequence as above, the desired cyclopentenone **8a** was obtained in 42% yield.

However, under the same conditions, the alkene **10b** did not afford the expected cyclopentenone **8b** but instead the corresponding carboxylic acid **8b′** in 52% overall yield. A mechanistic proposal to explain the formation of this derivative is given in Scheme 4. After migration of the double bond, the silyl ether is deprotected to give an alcoholate in equilibrium with the corresponding enolate, which is suitable for an intramolecular aldol reaction. The intermediate aldolate can react with the ester function to form the lactone **11**. Then, abstraction of the acidic proton with concomitant ring opening of the lactone and acidification gives carboxylic acid **8b′**.[19]

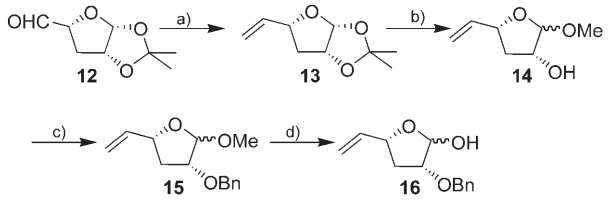


Scheme 4. Mechanistic proposal for the formation of **8b′**.

A second series of cyclopentenones was of interest to us, the 4-alkoxy-substituted derivatives, since they are extremely useful precursors of PGs. The vinyl sugar **16** was selected as the starting material for studying the transposition. This lactol was prepared in four steps and 58% overall yield from the known aldehyde **12**,[20] as indicated in Scheme 5.[21]

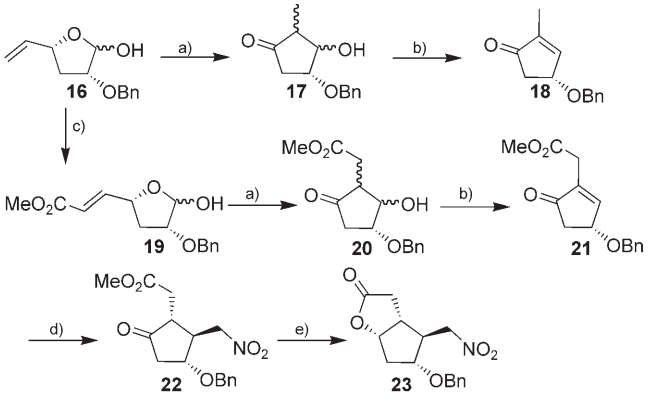


Scheme 3. Synthesis of cyclopentenones **5** and **8** starting from vinyl sugar **1**. Conditions: a) TBSCl, imidazole, CH_2Cl_2, RT, 16 h, 93%; b) Styrene or methyl acrylate, 2nd generation Grubbs catalyst (5%), CH_2Cl_2, 40°C, 6 h, **7a** (44%), **7b** (56%), **10a** (58%), **10b** (66%, as a 86:14 *E*/*Z* mixture); c) [$Fe(CO)_5$] (5 mol%), *hν*, THF; d) [$Fe(CO)_5$] (5 mol%), *hν*, THF then TBAF (1 equiv) −78°C to RT, 1 h, overall yield **8a** (42%), **8b′** (52%). TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride.



Scheme 5. Synthesis of vinyl sugar **16**. Conditions: a) $Ph_3P^+CH_3,Br^-$, *t*BuOK, THF, 0°C, 2 h, 94%; b) H_2SO_4, MeOH, 60°C, 12 h, 85%; c) NaH, BnBr, THF, 40°C, 6 h, 90%; d) H_2O, AcOH, 70°C, 12 h, 80%. Bn = benzyl.

Under the same conditions as described for **1**, vinyl sugar **16** gave a complex mixture of aldols **17**, which were submitted directly to the elimination conditions to afford the desired cyclopentenone **18** in 88% overall yield (Scheme 6). Starting from vinyl sugar **16**, the CM reaction afforded the alkene **19** in excellent yield, and the same two-step process was conducted to give the desired functionalized cyclopentenone **21** in 55% overall yield from **16**. Although **21** itself is a new compound, the corresponding 4-OH cyclopentenone, several esters, and the tetrahydropyranyl ether derivative have been prepared previously by multistep sequences.[22,23] Furthermore, in these series the corresponding optically active derivatives have been obtained in relatively low yields by tedious chemical or enzymatic resolution methods.[22]



Scheme 6. Synthesis of cyclopentenones **18** and **21** and PGs precursors **22** and **23**. Conditions: a) $[Fe(CO)_5]$ (5 mol%), *hν*, THF, 1 h; b) Tf_2O, pyridine, CH_2Cl_2, 0°C to 25°C, 2 h, 87% from **16**; c) methyl acrylate, 2nd generation Grubbs catalyst (5%), CH_2Cl_2, 40°C, 6 h, 85%; d) tetramethylguanidine, CH_3NO_2, 0°C, 2 h, 72%; e) LiAlH-$(OtBu)_3$, THF, 50°C, 2 h, 55%.

Starting from **21**, the addition of the anion of nitromethane afforded the nitro derivative **22** in good yield and in high stereoselectivity. A final selective reduction of the ketone function yielded the target lactone **23**.

Derivatives of type **21**–**23** are already known as versatile intermediates in the total synthesis of prostanoids. For instance, the tetrahydropyranyl ether analogue of **22** was used previously in the preparation of $PGF_{2\alpha}$ through the 1,3 dipolar cycloaddition reactions of the corresponding nitrile oxide.[23] Alternatively this tetrahydropyranyl ether analogue was transformed, by the Nef reaction, into the corresponding Corey lactone aldehyde,[23] another very useful intermediate for the synthesis of PGs.[24]

In conclusion, we have developed a new strategy for the conversion of vinyl-substituted furanose derivatives into the corresponding cyclopentenones. This method appears complementary to the synthesis developed recently using the RCM reaction as the key step, which affords essentially cyclopentenones with an hydrogen on position 2.[11] In our approach the CH_2R^2 substituent is already introduced, deliberately and at an early stage of the synthesis. This very simple process appears to be versatile and suitable for the asymmetric synthesis of various types of natural products and analogues, as already demonstrated by the preparation of **5**, **8**, **18**, and **21**. The development of new catalysts[25] and the extension of this reaction to other sugar derivatives are currently under investigation in our groups.

Received: April 16, 2007
Published online: July 2, 2007

Keywords: aldol reaction · carbocycles · carbohydrates · iron · prostaglandins

[1] a) R. J. Ferrier, S. Middleton, *Chem. Rev.* **1993**, *93*, 2779; b) P. I. Dalko, P. Sinaÿ, *Angew. Chem.* **1999**, *111*, 819; *Angew. Chem. Int. Ed.* **1999**, *38*, 773, and references therein.
[2] a) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229; b) M. Ferrero, V. Gotor, *Chem. Rev.* **2000**, *100*, 4319; c) S. Ghosh, T. Bhaumik, N. Sarkar, A. Nayek, *J. Org. Chem.* **2006**, *71*, 9687, and references therein.
[3] R. J. Ferrier, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1455.
[4] a) B. Weschkun, J. Thiem, *Angew. Chem.* **1997**, *109*, 2905; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2793; b) A. V. R. L. Sudha, M. Nagarajan, *Chem. Commun.* **1998**, 925.
[5] a) M. Sollogoub, J.-M. Mallet, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 370; *Angew. Chem. Int. Ed.* **2000**, *39*, 362; b) W. Wang, Y. Zhang, M. Sollogoub, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 2588; *Angew. Chem. Int. Ed.* **2000**, *39*, 2466; c) W. Wang, Y. Zhang, H. Zhou, Y. Blériot, P. Sinaÿ, *Eur. J. Org. Chem.* **2001**, 1053.
[6] T. K. M. Shing, D. A. Elsley, J. G. Gillhouley, *J. Chem. Soc. Chem. Commun.* **1989**, 1280.
[7] a) T. V. RajanBabu, *Acc. Chem. Res.* **1991**, *24*, 139; b) A. Martínez-Grau, J. Marco-Contelles, *Chem. Soc. Rev.* **1998**, *27*, 155, and references therein.
[8] a) H. Ito, Y. Motoki, T. Taguchi, Y. Hanzawa, *J. Am. Chem. Soc.* **1993**, *115*, 8853; b) A. Lubineau, I. Billaut, *J. Org. Chem.* **1998**, *63*, 5668; c) J. M. Aurrecoechea, M. Arrate, J. H. Gil, B. Lopez, *Tetrahedron* **2003**, *59*, 5515.
[9] a) A. Chénedé, P. Pothier, M. Sollogoub, A. J. Fairbanks, P. Sinaÿ, *J. Chem. Soc. Chem. Commun.* **1995**, 1373; b) J. J. C. Grové, C. W. Holzapfel, D. B. G. Williams, *Tetrahedron Lett.* **1996**, *37*, 1305; c) J. L. Chiara, S. Martinez, M. Bernabé, *J. Org. Chem.* **1996**, *61*, 6488; d) J. M. Aurrecoechea, B. Lopez, *Tetrahedron Lett.* **1998**, *39*, 2857; e) T. Kan, S. Nara, T. Ozawa, H. Shirahama, F. Matsuda, *Angew. Chem.* **2000**, *112*, 363; *Angew. Chem. Int. Ed.* **2000**, *39*, 355; f) J. M. Aurrecoechea, B. Lopez, M. Arrate, *J. Org. Chem.* **2000**, *65*, 6493.
[10] a) R. H. Grubbs, *Adv. Synth. Catal.* **2007**, *349*, 34; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360.
[11] R. Masden, *Eur. J. Org. Chem.* **2007**, 399, and references therein.
[12] a) C. Crévisy, M. Wietrich, V. Le Boulaire, R. Uma, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 395; b) R. Uma, M. Davies, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 3069; c) V. Branchadell, C. Crevisy, R. Grée, *Chem. Eur. J.* **2004**, *10*, 5795; d) D. Cuperly, J. Petrignet, C. Crévisy, R. Grée, *Chem. Eur. J.* **2006**, *12*, 3261; e) J. Petrignet, T. Roisnel, R. Grée, *Tetrahedron Lett.* **2006**, *47*, 7745, and references therein.
[13] a) T. K. M. Singh, D. A. Elsley, J. G. Gillhouley, *J. Chem. Soc. Chem. Commun.* **1989**, 1280; b) J. A. Lee, H. R. Moon, H. O. Kim, K. R. Kim, K. M. Lee, B. T. Kim, K. J. Hwang, M. W. Chun, K. A. Jacobson, L. S. Jeong, *J. Org. Chem.* **2005**, *70*, 5006.
[14] K. Tanaka, H. Nakashima, T. Taniguchi, K. Ogasawara, *Org. Lett.* **2000**, *2*, 1915.
[15] H. Nakashima, M. Sato, T. Taniguchi, K. Ogasawara, *Synthesis* **2000**, *817*.

[16] K. Tanaka, T. Taniguchi, K. Ogasawara, *Tetrahedron Lett.* **2001**, *42*, 1049.
[17] J. F. Bickley, S. M. Roberts, M. G. Santoro, T. J. Snape, *Tetrahedron* **2004**, *60*, 2569.
[18] For a recent review on the Mukaiyama aldol reaction, see: R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095, and references therein.
[19] In these series of Mukaiyama-type reactions, the isomerized enol ether intermediates could be characterized by NMR spectroscopy. However a one-pot process was found to be more convenient and more efficient.
[20] J. S. Yadav, I. Prathap, B. P. Tadi, *Tetrahedron Lett.* **2006**, *47*, 3773.
[21] A similar series of reactions has been reported for the preparation of a diastereoisomer of **16** see: G. V. M. Sharma, K. R. Kumar, *Tetrahedron: Asymmetry* **2004**, *15*, 2323.
[22] a) I. Veinberga, J. Freimanis, *Lat. Kim. Z.* **1992**, 103; b) I. Veinberga, J. Freimanis, *Lat. Kim. Z.* **1995**, 116; c) I. Veinberga, J. Freimanis, *Lat. Kim. Z.* **1995**, 122, and references therein.
[23] P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, D. Simoni, V. Zanirato, *Tetrahedron* **1987**, *43*, 4669.
[24] The benzyl-ether-protected Corey lactone has been reported already as a key intermediate for the synthesis of various prostanoids: a) difluoro-PGs for glaucoma and ocular hypertension, see P. G. Klimko, J. Bishop, L. Desantis, Jr., V. L. Sallee (Alcon Laboratories Inc), EP 639563, **1995** [*Chem. Abstr.* **1995**, *122*, 290579]; b) difluoro-PGs for treatment of eye diseases, see T. Tanaka, Y. Matsumura, N. Mori, T. Nakano, N. Miyawaki, T. Matsugi, A. Shimazaki (Asahi Glass Company Ltd), WO2001055102, **2001** [*Chem. Abstr.* **2001**, *135*, 137338]; c) Latanoprost, see K. E. Henagar (Pharmacia and Upjohn Company), WO 2003008368, **2003** [*Chem. Abstr.* **2003**, *138*, 137085].
[25] For recent reviews on the transition-metal-mediated isomerization of allylic alcohols see: a) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem.* **2002**, *650*, 1; b) R. Uma, C. Crevisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27, and references therein.

