CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201300969

A Novel Base-Induced Isomerization Gives Access to Unprecedented (*E*)-*exo*-Glycals

Guillaume Eppe,[a] Lidia Dumitrescu,[a] Olivier Pierrot,[a] Tianlei Li,[a, b] Weidong Pan,[b] and Stéphane P. Vincent*[a]

exo-Glycals, that is, glycosides presenting an exocyclic enol ether next to the ring oxygen, constitute a very large family of polyhydroxylated chiral synthons, exploited both as synthetic intermediates,[1] but also as final molecules for biochemical applications.[2] Interestingly, the first natural *exo*-glycal was recently identified as a precursor of the tunicamycins,[3] a family of antibiotics produced by *Streptomyces lysosuperificus* and *chartreusis* strains. *exo*-Glycals are versatile synthetic building blocks allowing for a straightforward and stereoselective access to *C*-glycosides through double bond reduction.[1,4] As enol-ethers, they are susceptible to electrophilic addition[5] and may be valuable precursors of ketosides. Interestingly, they were used in 1,3-cylcoadditions to prepare *N*-glycosides[6] as well as spiroglycosides.[7] The most popular and robust methods to construct *exo*-glycals are the Wittig-like olefinations,[8] the Ramberg–Bäcklund rearrangement,[9] and the stepwise addition-elimination on a sugar lactone.[10] Newer methods have been developed as well, including modified Julia olefination[7a,c,11] and alkynol cycloisomerization.[12] Furthermore, tetrasubstituted *exo*-glycals have been prepared through different functionalizations,[13] such as the Sonogashira,[14] the Suzuki[4i,5b,15] and the Stille cross-coupling reactions.[16]

Beyond their synthetic interest, *exo*-glycals have been exploited for the inhibition of biologically relevant enzymes, including glycosidases and glycosyltransferases.[2] In particular, phosphonylated *exo*-glycals (phosphono-*exo*-glycals), such as **1**–**11**, have been successfully designed and employed either as potent inhibitors or as biochemical probes (Figure 1). For instance, Schmidt et al. developed molecule **1** as a competitive inhibitor of UDP-GlcNAc 2-epimerase,[17] and nucleotide-sugars analogues **4**–**11** as inhibitors of α-(2-6)-sialyl-transferase, an extremely important enzyme in glycobiology. It is noteworthy that *Z* phosphonate **9** is a low

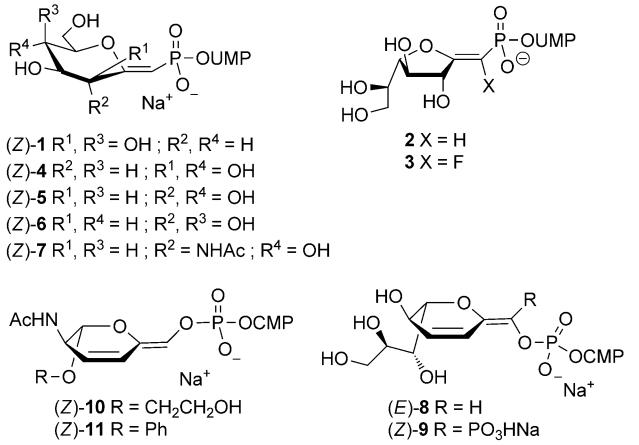


Figure 1. Examples of *exo*-glycals designed as enzyme inhibitors.

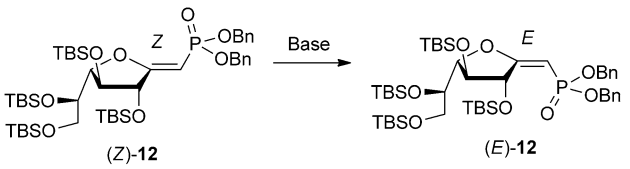
nanomolar inhibitor of the latter enzyme, and one of the very best inhibitors of glycosyltransferases in general.[18] Our group has developed synthetic pathways to prepare phosphono-*exo*-glycals **1**–**3** and discovered that they displayed strong inhibition or time-dependent inactivation of UDP-galactopyranose mutase (UGM).[4d,5a,19] Because it is essential for the growth of *Mycobacterium tuberculosis*, the causative agent of tuberculosis,[20] this enzyme is now a validated target for the development of novel antitubercular drugs.

It is also worth mentioning the effect of the stereochemistry of the exocyclic double bond on the inhibition/inactivation processes described above has never been assessed because the (*E*)-*exo*-glycals analogues of molecules **1**, **2** and **4**–**7** have not been synthetically accessible to date. The few easily accessible (*E*)-*exo*-glycals can mainly be obtained as diastereomeric mixtures through Wittig-like olefinations, and the diastereoselectivity highly depends on the sugar lactone and the ylide.[4g,k,8a] In those methods, the (*E*)-*exo*-glycal is often the less abundant product or in some cases not even accessible. However, these methods are not applicable for the synthesis of phosphonylated *exo*-glycals. Indeed, the only synthetic methodology allowing their efficient preparation consists in the nucleophilic addition of a lithiated methyl-phosphonate to a sugar lactone followed by dehydration, a methodology developed by Lin[10a–c] and further exemplified by others.[4d,5a,19] Following this methodology, the *Z* stereoisomer is exclusively formed, thus providing no access to the corresponding *E* stereoisomer. Here, we

[a] Dr. G. Eppe, Dr. L. Dumitrescu, O. Pierrot, T. Li, Prof. S. P. Vincent
University of Namur (UNamur), Département de Chimie
Laboratoire de Chimie Bio-Organique, rue de Bruxelles 61
5000 Namur (Belgium)
E-mail: stephane.vincent@fundp.ac.be

[b] T. Li, Dr. W. Pan
The Key Laboratory of Chemistry for Natural Products of
Guizhou Province and Chinese Academy of Sciences
202, Sha-chong South Road, Guiyang, 550002 (P.R. China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300969.



Scheme 1. The base-induced *Z*-to-*E* *exo*-glycal isomerization.

report the serendipitous discovery of the *Z*-to-*E* isomerization of phosphono *exo*-glycals, the optimization of the procedure and the scope of this novel transformation with regards to the carbohydrate unit and the electron-withdrawing group (Scheme 1).

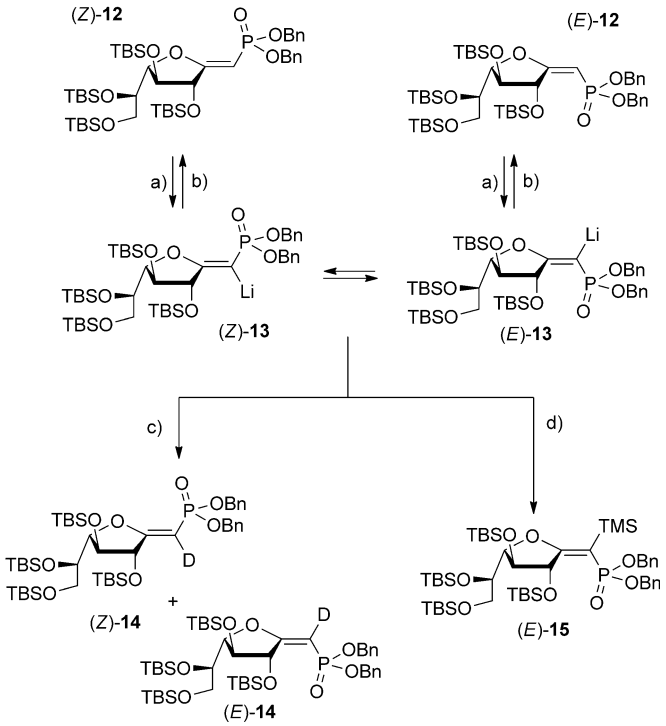
Given the importance of galactofuranose (Gal*f*) in the cell wall of major pathogens,[21] we naturally investigated the synthesis of modified phosphonylated analogues of this carbohydrate. Typically, the phosphonylated *exo*-glycal **12** was prepared as a single *Z* diastereomer.[19] In order to further functionalize **12**, we had planned to deprotonate it with a strong base and quench the vinylic carbanion by an electrophile. However, treatment of (*Z*)-**12** with *t*BuLi for 45 min at −78 °C afforded a mixture of two molecules: the starting material (66%) and a new *exo*-glycal (34%) isolated and identified as the *E*-diastereoisomer (*E*)-**12** (Scheme 2; Table 1, entry 1). The ^{31}P NMR analysis of the crude reaction mixture showed no detectable side-products at all: under these conditions, the transformation is very clean. This isomerization was not expected since vinyl anions are known to be configurationally stable.[22]

To understand this unexpected transformation, we first used NMR spectroscopy techniques to demonstrate the structure of the newly formed molecule. It is well established in the literature that the stereochemistry of a vinyl-phosphonate can be determined by $^{3}J_{C-P}$ carbon–phosphorus coupling.[23] In the ^{13}C NMR spectra, the carbon atoms being *cis* to a phosphorus have a smaller coupling constant than their *trans* counterparts. The difference is clear in this case since C-2 is a singlet for (*E*)-**12** and a doublet ($^{3}J_{C-P}$ = 12.0 Hz) for (*Z*)-**12**. The next evidence for the determination of the stereochemistry of *exo*-glycals is the relative chemical shift of the allylic H-2.[4g,k,8a] Indeed, in (*E*)-*exo*-glycals, H-2 are deshielded by a value of, typically, 0.5 ppm. In this case, the allylic H-2 is indeed strongly deshielded: $\delta = 5.2$ ppm for (*E*)-**12** and $\delta = 4.5$ ppm for (*Z*)-**12**. In the case of (*Z*)-**12**, a nOe correlation of the protons H-1′ and H-2 is also observed. On the contrary, the absence of nOe correlation for the vinylic proton in (*E*)-**12** confirmed the *E* stereochemistry for the new compound. Complete NMR analysis of (*E*)-**12** ruled out other possible isomeric structures, such as a C-2 epimer or a double-bond migration to the C-1:C-2 position. Indeed, the chemical shift of the phosphonate in ^{31}P as well as the chemical shift of C-1′ in the ^{13}C NMR spectra demonstrate that the double bond is exocyclic. Moreover, ^{1}H–^{1}H coupling constants and nOe analysis proved that an epimerization at C-2 did not occur.

Table 1. Scope and optimization of the isomerization of *exo*-glycal (*Z*)-**12**.

	Base	Base [equiv]	*t* [h]	*T* [°C]	*Z* [%][a]	*E* [%][a]	Byproducts [%][a]
1	*t*BuLi	1.05	2	−78	88	12	0
2	*t*BuLi	2.1	2	−78	38	46	16
3	*s*BuLi	1.1	2	−78	40	52	8
4	*n*BuLi	1.0	2	−78	40	52	8
5	*n*BuLi	2.2	2	−78	25	47	28
6	*n*BuLi	3.0	2	−100	39	61	0
7	LDA	3.2	0.5	−78	48	33	19
8	KHMDS	1.1	1	0	65	0	35
9	NaHMDS	1.1	2	0	30	30	40
10	LiHMDS	1.1	2	0	70	30	0
11	LiHMDS	2.2	5 min	RT	56	44	0
12	LiHMDS	2.2	14	RT	88	12	0
13	LiHMDS	3.0	10 min then 2 h	RT then −10	39	61	0

[a] Determined by ^{31}P NMR spectroscopy.



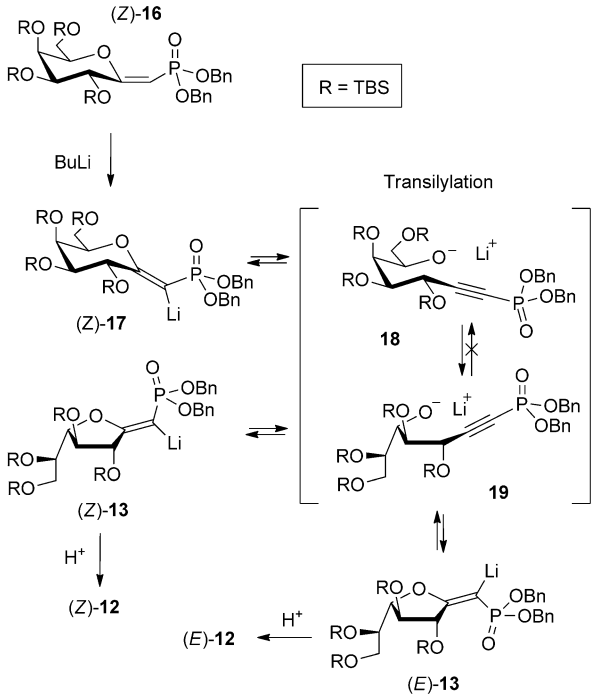
Scheme 2. a) *n*BuLi (3.0 equiv), THF, −100 °C, 2 h, (*Z*)-**12** 66%, (*E*)-**12** 34%; b) phosphate buffer aqueous, pH 7; c) CD_3COOD/CD_3OD (6:1), −78 °C to RT; d) TMSCl, −78 °C to RT.

Screening other lithiated strong bases showed that besides *t*BuLi, LDA, *s*BuLi and *n*BuLi can also be used (Table 1). Moreover, by increasing the amount of base the proportion of the desired *E* isomer can be drastically improved, however, with an increased amount of side products (entries 1, 2, 4, 6). Eventually, we found that 3 equivalents of *n*BuLi at −100 °C (entry 6) gave a very reproducible 61% yield in (*E*)-**12** without any detectable side products. Overall, a lower temperature seems to result in a larger amount of

E isomer. The same yield could be obtained from the dimethylphosphonate corresponding to **12** (data not shown), thus showing that the reaction is not limited to dibenzylphosphonate and that the change of protective group on the phosphonate does not affect the yield in *E* isomer. Although *t*BuOK, DBU or KHMDS did not produce any *E* isomer in our hands, we could show that bases such as LiHMDS and NaHMDS can also be used (Table 1, entries 8–10). Although lithiated bases seem to give far better results in general, all attempts to use lithium chloride and crown-ethers as adjuvants did not change the course of the reaction (data not shown). In the case of LiHMDS, the larger range of possible reaction temperature allowed a better understanding of the process. At room temperature, the (*E*)-*exo*-glycal is formed very quickly but isomerizes back to the *Z* isomer over time (entries 11 and 12). We could also observe that the reaction is much slower if the temperature of the deprotonation step is lowered to −10 or −40 °C. These results clearly show that a sufficiently high temperature is necessary to allow the deprotonation of the vinylphosphonate by LiHMDS whereas a subsequent lower temperature is necessary to enhance the ratio in the desired *E* isomer. We could thus optimize a novel procedure taking advantage of LiHMDS which is easy to handle: 1) addition of three equivalents of LiHMDS at room temperature, 2) stirring at the same temperature for ten minutes to ensure the deprotonation of the substrate, 3) cooling at −100 °C for two hours to favor the *E* isomer (entry 13). This simple procedure gives very reproducible yields and, interestingly, the *E*/*Z* diastereomeric ratio is the same as that with *n*BuLi at −100 °C (entry 6).

To the best of our knowledge, there is, currently, no known reaction describing a base catalyzed isomerization of an *exo*-glycal, or a cyclic enol ether to its diastereoisomer. The mechanism was thus investigated by different means. When the isolated (*E*)-**12** was put into reaction under the same isomerization conditions, it gave the same mixture of (*E*)-**12** and (*Z*)-**12** (Scheme 2), thus evidencing that this *Z*-to-*E* transformation is in fact an equilibrium between the two stereoisomers. Thus, if a deprotonation occurs at the vinylic position, the two carbanions (*E*)-**13** and (*Z*)-**13** must be able to transform into one another (Scheme 2). The hypothesis of a vinylic deprotonation driven by the adjacent electron-withdrawing phosphonate and thus the existence of (*E*)-**13** and (*Z*)-**13**, was demonstrated by the quantitative deuteration of the two *exo*-glycals **12** (Scheme 2). Deprotonation by *n*BuLi followed by an addition of a mixture of CD_3OD/CD_3CO_2D afforded the two deuterated *exo*-glycals (*E*)-**14** and (*Z*)-**14**. Mass spectrometry confirmed the monodeuteration whereas only the C-1′ and H-1′ signals disappeared from the NMR spectra.[24] It must be noted that this deuteration was surprisingly difficult. Attempts to quench the anions (*E*)-**13** and (*Z*)-**13** with D_2O or CD_3OD failed. As a control experiment, we could show that when (*Z*)-**12** was treated with CD_3OD/CD_3CO_2D, no deuteration occurred. To further confirm the formation of carbanionic species, we performed this trapping experiment by using trimethylsilyl chloride (TMSCl, Scheme 2). In that case *exo*-glycal (*E*)-**15** was obtained as sole product, thus demonstrating the formation of a vinylic anion.

To investigate the scope of this reaction, we turned our attention to *exo*-glycal **16**, the pyranosidic isomer of **12**. When we applied the conditions optimized for the furanoside **12** (Table 1, entry 6) to pyranoside (*Z*)-**16**, we surprisingly observed the formation of furanosides (*Z*)-**12** and (*E*)-**12** in 10 and 8%, respectively (Scheme 3). This result suggested a



Scheme 3. Proposed equilibrium between vinylic carbanions **13**.

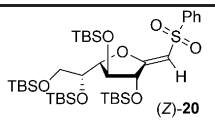
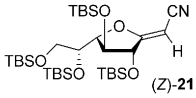
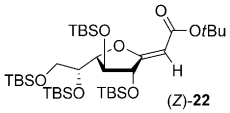
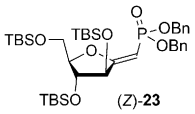
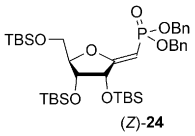
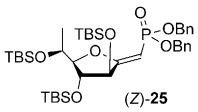
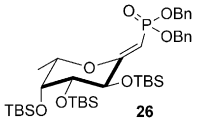
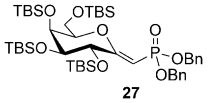
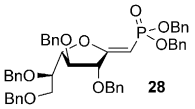
mechanism involving a *trans*-silylation and retro-Michael addition (Scheme 3). The *trans*-silylation from position O-4 to O-5 under basic conditions has already been observed by our group for TBS protected galactosides.[4d] This rearrangement results in a pyranose to furanose ring contraction. It is thus reasonable to postulate that the intermediates that allow the formation of the furanosides **12** from pyranosides **17** are the two acyclic alkynyl phosphonate **18** and **19**, products of a reversible retro-Michael reaction (Scheme 3). A subsequent 5-*exo*-dig intramolecular Michael addition explains the interconversion of (*Z*)-**13** and (*E*)-**13**, the direct precursors of (*Z*)-**12** and (*E*)-**12**. Such a mechanism is supported by precedents on standard organic molecules, such as the alkynol cyclization under basic conditions[25] and the hydroalkoxylation of conjugated 7-hydroxyheptynoates.[26] However, the trapping experiments described in Scheme 2 (deuteration and TMSCl quenches) did not allow the isolation of acyclic species showing that the hypothetical intermediates **18** and **19** would be transient species rather than highly concentrated intermediates.

To assess the scope of this novel reaction, we varied both the carbohydrate unit and the substituent on the *exo*-glycal

structure. Due to the vinylic deprotonation and the required Michael acceptor intermediate, we hypothesized that the prerequisite for the isomerization was the presence of an electron-withdrawing substituent on the double bond. *exo*-Glycals **20**–**22** were thus prepared from the same γ-galactonolactone[19] with different electron-withdrawing substituents (Table 2; see the Supporting Information for the procedures).

The phosphonylated *exo*-glycals **23**–**28** were also prepared as single *Z* stereoisomers using Lin's procedure.[10c] The optimized procedures employing *n*BuLi or LiHMDS were first applied to *exo*-glycals **20**–**22**. Pleasingly, the *E* configured sulfonyl and cyano derivatives could be generated in 37 and 68% yield, respectively (Table 2, entries 1–3). However, the isomerization of ester **22** never generated the expected isomerization product, whatever the nature of the base (entries 4–7). Surprisingly, deuteration of the putative carbanionic intermediate did not provide any deuterated species but only the starting material (*Z*)-**22** (entries 4 and 5). We hypothesized that the steric hindrance might prevent the deprotonation by the base, thus explaining the lack of isomerization. Forcing the conditions (entries 6 and 7) resulted in the decomposition of the starting material. Gratifyingly, arabinofuranosyl **23**, ribofuranosyl **24**, fucofuranosyl **25**, fucopyranosyl **26** and galactopyranosyl **27** *exo*-glycals could also be isomerized in the presence *n*BuLi (Table 1). These novel *exo*-glycals displayed the characteristic coupling constants and chemical shifts of *E* isomers (see discussion above). Moreover, for the fuco-, arabino-, and ribofuranosyl derivatives, higher amounts of (*E*)-*exo*-glycals could be reached with a lower excess of base compared to the galactofuranosyl-*exo*-glycal **12**. In a general manner, similarly to **12**, an increase in the amount of base and/or in reaction time results in a larger amount of *E* isomer. The results depicted in Table 2 show that the final *E*/*Z* diastereomeric ratio was highly dependent on the structures of both carbohydrate

Table 2. Scope of the base promoted *exo*-glycal isomerization.

	exo-Glycal	Base (equiv)	Time (*T* [°C])	*Z* [%][a]	*E* [%][a]	Byproducts [%][a]
1	 (*Z*)-**20**	LiHMDS (3.0)	10 min (RT) then 2 h (−100 °C)	53	47	0
2	 (*Z*)-**21**	LiHMDS (3.0)	10 min (RT) then 2 h (−100 °C)	42	49	8
3		*n*BuLi (1.5)	1 h (−100 °C)	32	68	0
4	 (*Z*)-**22**	LiHMDS (3.0)	10 min (RT) then 2 h (−100 °C)	100	0	0
5		LDA (2.0)	1 h (−78 °C)	100	0	0
6		*n*BuLi (3.0)	45 min (−100 °C)	0	0	100
7		*t*BuLi (1.2)	2 h (−78 °C)	0	0	100
8	 (*Z*)-**23**	*n*BuLi (1.2)	1 h (−100 °C)	30	70	0
9	 (*Z*)-**24**	*n*BuLi (2.0)	1 h (−100 °C)	29	71	0
10	 (*Z*)-**25**	*n*BuLi (3.0)	1.5 h (−100 °C to RT)	21	79	0
11	 **26**	*n*BuLi (1.5)	2 h (−100 °C)	35	31	34
12	 **27**	*n*BuLi (2.0)	2 h (−100 °C)	31	44	25
13	 **28**	*n*BuLi (1.5)	2 h (−100 °C)	0	0	100

[a] Determined by ^{31}P NMR spectroscopy.

and electron-withdrawing groups. In general, the reactions performed with all the furanosides were very clean, but we could observe the formation of side-products, under the same conditions, when pyranosides were used (entries 11 and 12). Interestingly, (*E*)-*exo*-glycals were very easy to separate from their *Z* diastereomers, since they displayed very different R_f values on silica-gel chromatography. As observed for the fluoro-*exo*-glycals,[5a] the (*Z*)-*exo*-glycals were always more polar than their *E* isomers. As illustrated in Scheme 3, some of the side-reactions were due to *trans*-silylations giving the corresponding furanosides. Then, we explored the effect of protective groups on the isomerization process. Changing the dibenzyl phosphonate into a dimethylphosphonyl group (for instance in the galactofuranose series, see the Supporting Information, and entry 12 of Table 1 for the corresponding galactopyranose) did not change the course of the reaction. On the other hand, the standard isomerization protocols (using BuLi or LiHMDS) applied to perbenzylated *exo*-glycal **28** only led to the decomposition of the starting material, even at −100 °C. Moreover, with perbenzylated molecule **28**, a decrease of the number of equivalent of base, to prevent side-reactions, did not allow us to generate the corresponding *E* isomer. The latter results evidence that silylated protective groups are mandatory to cleanly generate (*E*)-*exo*-glycals by this isomerization protocol.

In conclusion, this study reports the serendipitous discovery of the base-induced *Z*-to-*E* isomerization of *exo*-glycals bearing an electron-withdrawing group, the improvement in the isomerization process and the role of the carbohydrate unit in the products obtained. Moreover, the mechanism was investigated and elucidated. Importantly, this method allowed the preparation of (*E*)-*exo*-glycals that have been out of reach following all the methods available to date. Given the importance of these species as intermediates for more complex structures and/or as biochemically relevant molecular probes, one can anticipate that this novel transformation will find many useful applications. Work is in progress in our laboratories to further functionalize these species and evaluate them as inhibitor or inactivator of carbohydrate processing enzymes.

Experimental Section

The detailed synthetic procedures are gathered in the Supporting Information along with their analytical data.

Acknowledgements

This work was funded by an ARC grant from the Académie Louvain (A.R.C. 08/13-012), by FNRS (FRFC grant 2.4.625.08.F, and F.R.I.A. fellowship to G.E.). PhD thesis fellowship for T.L. was funded by China Scholarship Council.

Keywords: carbohydrates · enol ethers · isomerization · phosphonates · stereochemistry

[1] C. Taillefumier, Y. Chapleur, *Chem. Rev.* **2004**, *104*, 263–292.
[2] C. H. Lin, H. C. Lin, W. B. Yang, *Curr. Top. Med. Chem.* **2005**, *5*, 1431–1457.
[3] F. J. Wyszynski, S. S. Lee, T. Yabe, H. Wang, J. P. Gomez-Escribano, M. J. Bibb, S. J. Lee, G. J. Davies, B. G. Davis, *Nat. Chem.* **2012**, *4*, 539–546.
[4] a) A. Dondoni, A. Marra, C. Pasti, *Tetrahedron: Asymmetry* **2000**, *11*, 305–317; b) A. Caravano, W. Pan, S. P. Vincent, *ARKIVOC* **2007**, 348–364; c) A. Caravano, D. Mengin-Lecreulx, J.-M. Brondello, S. P. Vincent, P. Sinaÿ, *Chem. Eur. J.* **2003**, *9*, 5888–5898; d) A. Caravano, S. P. Vincent, *Eur. J. Org. Chem.* **2009**, 1771–1780; e) A. M. Gómez, A. Pedregosa, C. Uriel, S. Valverde, J. C. López, *Eur. J. Org. Chem.* **2010**, 5619–5632; f) A. Burton, P. Wyatt, G.-J. Boons, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2375–2383; g) G. S. Coumbarides, M. Motevalli, W. A. Muse, P. B. Wyatt, *J. Org. Chem.* **2006**, *71*, 7888–7891; h) A. Novoa, N. Pellegrini-Moïse, D. Bechet, M. Barberi-Heyob, Y. Chapleur, *Bioorg. Med. Chem.* **2010**, *18*, 3285–3298; i) A. Novoa, N. Pellegrini-Moïse, S. Lamandé-Langle, Y. Chapleur, *Tetrahedron Lett.* **2009**, *50*, 6484–6487; j) A. Bandzouzi, Y. Chapleur, *Carbohydr. Res.* **1987**, *171*, 13–24; k) M. Gascón-López, M. Motevalli, G. Paloumbis, P. Bladon, P. B. Wyatt, *Tetrahedron* **2003**, *59*, 9349–9360.
[5] a) A. Caravano, H. Dohi, P. Sinaÿ, S. P. Vincent, *Chem. Eur. J.* **2006**, *12*, 3114–3123; b) A. M. Gómez, G. O. Danelón, A. Pedregosa, S. Valverde, J. C. López, *Chem. Commun.* **2002**, 2024–2025; c) A. M. Gómez, A. Pedregosa, S. Valverde, J. C. López, *Chem. Commun.* **2002**, 2022–2023.
[6] a) G. Enderlin, C. Taillefumier, C. Didierjean, Y. Chapleur, *Tetrahedron: Asymmetry* **2005**, *16*, 2459–2474; b) C. Taillefumier, G. Enderlin, Y. Chapleur, *Lett. Org. Chem.* **2005**, *2*, 226–230.
[7] a) M. Benltifa, S. Vidal, D. Gueyrard, P. G. Goekjian, M. Msaddek, J. P. Praly, *Tetrahedron Lett.* **2006**, *47*, 6143–6147; b) M. Benltifa, J. M. Hayes, S. Vidal, D. Gueyrard, P. G. Goekjian, J. P. Praly, G. Kizilis, C. Tiraidis, K. M. Alexacou, E. D. Chrysina, S. E. Zographos, D. D. Leonidas, G. Archontis, N. G. Oikonomakos, *Bioorg. Med. Chem.* **2009**, *17*, 7368–7380; c) M. Corbet, B. Bourdon, D. Gueyrard, P. G. Goekjian, *Tetrahedron Lett.* **2008**, *49*, 750–754; d) P. H. Dobbelaar, C. H. Marzabadi, *Tetrahedron Lett.* **2010**, *51*, 201–204; e) C. Taillefumier, S. Thielges, Y. Chapleur, *Tetrahedron* **2004**, *60*, 2213–2224.
[8] a) M. Lakhrissi, Y. Chapleur, *Angew. Chem.* **1996**, *108*, 833–834; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 750–752; b) Y. Lakhrissi, C. Taillefumier, M. Lakhrissi, Y. Chapleur, *Tetrahedron: Asymmetry* **2000**, *11*, 417–421; c) Y. Lakhrissi, C. Taillefumier, F. Chrétien, Y. Chapleur, *Tetrahedron Lett.* **2001**, *42*, 7265–7268.
[9] a) F. K. Griffin, D. E. Paterson, P. V. Murphy, R. J. K. Taylor, *Eur. J. Org. Chem.* **2002**, 1305–1322; b) Y. Ohnishi, Y. Ichikawa, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 997–999; c) G. D. McAllister, D. E. Paterson, R. J. K. Taylor, *Angew. Chem.* **2003**, *115*, 1425–1429; *Angew. Chem. Int. Ed.* **2003**, *42*, 1387–1391; d) R. J. K. Taylor, G. D. McAllister, R. W. Franck, *Carbohydr. Res.* **2006**, *341*, 1298–1311; e) P. Pasetto, R. W. Franck, *J. Org. Chem.* **2003**, *68*, 8042–8060.
[10] a) W. B. Yang, C. F. Chang, S. H. Wang, C. F. Teo, C. H. Lin, *Tetrahedron Lett.* **2001**, *42*, 4657–4660; b) W. B. Yang, C. Y. Wu, C. C. Chang, S. H. Wang, C. F. Teo, C. H. Lin, *Tetrahedron Lett.* **2001**, *42*, 6907–6910; c) W. B. Yang, Y. Y. Yang, Y. F. Gu, S. H. Wang, C. C. Chang, C. H. Lin, *J. Org. Chem.* **2002**, *67*, 3773–3782.
[11] a) D. Gueyrard, R. Haddoub, A. Salem, N. S. Bacar, P. G. Goekjian, *Synlett* **2005**, 520–522; b) D. Gueyrard, P. Fontaine, P. G. Goekjian, *Synthesis* **2006**, 1499–1503; c) B. Bourdon, M. Corbet, P. Fontaine, P. G. Goekjian, D. Gueyrard, *Tetrahedron Lett.* **2008**, *49*, 747–749.
[12] Z. Miao, M. Xu, B. Hoffmann, B. Bernet, A. Vasella, *Helv. Chim. Acta* **2005**, *88*, 1885–1912.
[13] R. N. Monrad, R. Madsen, *Tetrahedron* **2011**, *67*, 8825–8850.

[14] a) A. Gómez, A. Pedregosa, A. Barrio, S. Valverde, C. López, *Tetrahedron Lett.* **2004**, *45*, 6307–6310; b) A. M. Gómez, A. Barrio, A. Pedregosa, C. Uriel, S. Valverde, J. Cristóbal López, *Eur. J. Org. Chem.* **2010**, 2910–2920.
[15] A. Novoa, N. Pellegrini-Moïse, S. Bourg, S. Thoret, J. Dubois, G. Aubert, T. Cresteil, Y. Chapleur, *Eur. J. Med. Chem.* **2011**, *46*, 3570–3580.
[16] A. M. Gómez, A. Barrio, I. Amurrio, S. Valverde, S. Jarosz, J. C. López, *Tetrahedron Lett.* **2006**, *47*, 6243–6246.
[17] F. Stolz, M. Reiner, A. Blume, W. Reutter, R. R. Schmidt, *J. Org. Chem.* **2004**, *69*, 665–679.
[18] a) B. Müller, C. Schaub, R. R. Schmidt, *Angew. Chem.* **1998**, *110*, 3021–3024; *Angew. Chem. Int. Ed.* **1998**, *37*, 2893–2896; b) R. Schwörer, R. R. Schmidt, *J. Am. Chem. Soc.* **2002**, *124*, 1632–1637.
[19] A. Caravano, S. P. Vincent, P. Sinaÿ, *Chem. Commun.* **2004**, 1216–1217.
[20] a) F. Pan, M. Jackson, Y. Ma, M. McNeil, *J. Bacteriol.* **2001**, *183*, 3991–3998; b) M. R. Richards, T. L. Lowary, *ChemBioChem* **2009**, *10*, 1920–1938.
[21] a) P.-H. Tam, T. L. Lowary, *Curr. Opin. Chem. Biol.* **2009**, *13*, 618–625; b) I. Chlubnova, L. Legentil, R. Dureau, A. Pennec, M. Almendros, R. Daniellou, C. Nugier-Chauvin, V. Ferrières, *Carbohydr. Res.* **2012**, *356*, 44–61.
[22] a) L. A. Paquette, J. E. Hofferberth, *J. Org. Chem.* **2003**, *68*, 2266–2275; b) W. R. Roush, M. A. Adam, A. E. Walts, D. J. Harris, *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434; c) Q. Han, D. F. Wiemer, *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697; d) T. Wong, M. A. Romero, A. G. Fallis, *J. Org. Chem.* **1994**, *59*, 5527–5529.
[23] a) L. D. Quin, J. G. Verkade, *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*, VCH, Weinheim, **1994**, p. 472; b) D. G. Gorenstein, *Prog. Nucl. Magn. Reson. Spectrosc.* **1984**, *16*, 1–98.
[24] Upon deuteration, the ^{13}C peaks became multiplets because they couple with both the deuterium and the vicinal ^{31}P atoms. Moreover, deuteration is often accompanied by a dramatic, broadening of the ^{13}C peaks. See for instance: S. P. Vincent, P. Sinaÿ, M. Rohmer, *Chem. Commun.* **2003**, 782–783; W. Pan, S. P. Vincent, *Org. Biomol. Chem.* **2008**, *6*, 2394–2399.
[25] M. Xu, Z. Miao, B. Bernet, A. Vasella, B. Hoffmann, *Helv. Chim. Acta* **2005**, *88*, 1885–1912.
[26] A. Diéguez-Vázquez, C. C. Tzschucke, J. Crecente-Campo, S. McGrath, S. V. Ley, *Eur. J. Org. Chem.* **2009**, 1698–1706.

Received: March 13, 2013
Published online: July 25, 2013

