Tetrahedron 65 (2009) 9378–9394

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly functionalized, enantiomerically pure furo[*x*,*y*-*c*]pyrans via alkylidenecarbenes derived from sugar templates: synthesis and mechanism study via computational chemistry

Albert Nguyen Van Nhien [a,*], Romaric Cordonnier [a], Marie-Delphine Le Bas [a], Sébastien Delacroix [a], Elena Soriano [b], José Marco-Contelles [b], Denis Postel [a,*]

[a] *Laboratoire des Glucides, Université de Picardie Jules Verne, Faculté des Sciences, 33, rue Saint Leu, 80039 Amiens, France*
[b] *Laboratorio de Radicales Libres y Química Computacional (IQOG, CSIC), C/ Juan de la Cierva, 3, 28006 Madrid, Spain*

ARTICLE INFO

Article history:
Received 24 June 2009
Received in revised form 24 August 2009
Accepted 29 August 2009
Available online 3 September 2009

ABSTRACT

The new method for the generation of alkylidenecarbenes based on the reaction of trimethylsilylazide/Bu_2SnO with α-cyanomesylates has been applied to readily available sugar derivatives for the synthesis of highly functionalized, enantiomerically pure furo[*x*,*y*-*c*]pyrans. The furo[*x*,*y*-*c*]pyran heterocyclic ring system is present in a number of natural or non-natural products of biological interest such as the mi-haramycins, and deserve particular attention. The scope and extent of the present new methodology has been investigated by systematic modification of the starting sugar precursor (D-glucose, D-galactose, etc.) in the hexo-α(β)-D-pyranoside forms, bearing also different *O*-protecting groups, the effect of the absolute configuration of the substituent at the anomeric position, the location (C-2, -3 and -4) of the alkylidenecarbene species on the pyran nucleus, as well as the substitution (H or Ph) at the 'carbon donor' in the 1,5 C–H bond insertion process. In overall, using these key 1,5 C–H bond insertion reactions a simple protocol results for the synthesis of the furo[*x*,*y*-*c*]pyrans, difficult to be prepared by other methodologies, from moderate to good yields. To examine the reactivity of the alkylidenecarbene, we have undertaken a systematic investigation of the insertion reactions of various alkylidenecarbene derivatives into C–H bonds using density functional theory.

1. Introduction

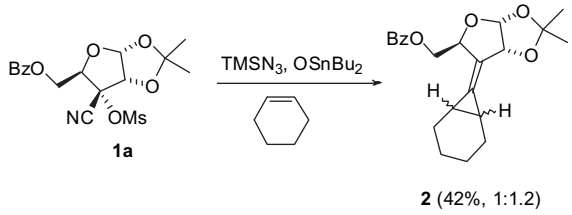
Over the last few years, the synthesis and subsequent transformation of reactive species such as alkylidenecarbenes has been the object of a continuous interest.[1] Accordingly, a number of methods have been documented for the generation of these highly reactive species, such as fluoride-induced α-elimination of α-chlorovinylsilanes or silylvinyl triflates,[2a,b] thermal decomposition of tosylazoalkenes,[2c] or diazoalkenes,[2d] weak base-induced α-elimination of alkenyliodonium salts,[2e] samarium diiodide reaction with 1,1-dihalogenoalkenes,[2f] or from α,β-epoxy-*N*-aziridinyl imines.[2g] Particularly, in carbohydrate chemistry Czernecki was the first to use α-cyanomesylates, upon treatment with sodium azide/DMF, to form a presumed alkylidenecarbene species that after 1,2-H shift gave acetylenic derivatives.[3] Some years later it was reported that the reaction of sodium azide in methylene chloride, at room temperature, in the presence of tetrabutylammonium hydrogenosulfate, with α-cyanomesylates derived from conveniently functionalized uloses, produced alkylidenecarbenes as very reactive intermediates that were trapped in situ in *intermolecular* processes with an azide anion, the solvent, or alkenes to give branched sugars and nucleosides.[4] The obvious interest of this methodology was hampered by the well known explosive combination of sodium azide and halogenated solvents[4]; in fact, and unfortunately, this protocol has been neglected and these papers scarcely cited in the current carbene chemistry. However, Czernecki's discovery[3] paved the way for further improvements on this subject.[5] In this context, in a recent communication[6] we have reported a new and more friendly protocol for the preparation of alkylidenecarbenes in sugar templates and some *intramolecular* transformations of these species, such as the rare 1,6 C–H bond insertion reactions.[7] Taking into account the presumed mechanism for the generation of alkylidenecarbenes from α-cyanomesylates,[4] based on the tetrazolyl anion formation after the reaction of the azide anion with the cyano moiety followed by α-elimination of the mesylate group, we reasoned that Wittenberger's method[8] for the synthesis of 5-substituted tetrazoles, using trimethylsilylazide,

* Corresponding authors. Tel.: +33 3 22827570; fax: +33 3 22827568.
E-mail addresses: albert.nguyen-van-nhien@u-picardie.fr (A. Nguyen Van Nhien), denis.postel@u-picardie.fr (D. Postel).

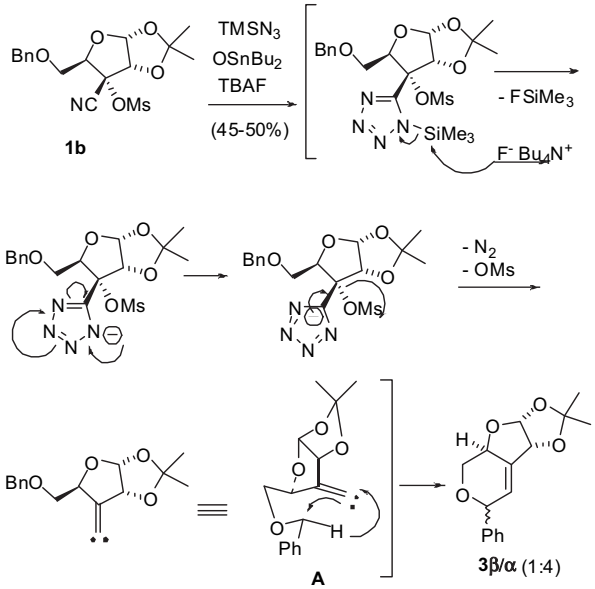
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.08.080

dibutyltin oxide, in toluene, when applied to selected precursors would presumably yield these α-mesyltetrazolyl intermediates that smoothly and in mild reaction conditions would lead to the desired alkylidenecarbenes species.

In our preliminary experiments[6] we made a comparative study with the reported[4] intermolecular reaction of the alkylidenecarbene derived from the benzoate **1a** with cyclohexene to give the *exo*-methylenecyclopropyl derivative **2**. Using our conditions, the reaction of **1a** with cyclohexene (40 equiv) in the presence of $TMSN_3$ (1.2 equiv) and Bu_2SnO (1 equiv), at 98 °C for 6 h, afforded **2** in a higher yield, 42% (vs 35%)[4] in the isomeric ratio 1/1.2 (Scheme 1). Under similar experimental conditions, precursor **1b** afforded an isomeric mixture of **3α/β** in 45% yield, in a 4/1 ratio (Scheme 2).



Scheme 1.



Scheme 2.

With this promising results in mind, next we planned a simple approach for the synthesis of chiral, advanced intermediates[9] in route to miharamycins[10] (Chart 1) starting from α-D-glucose. In the structure of these natural products, a perhydrofuro[2,3-*c*]pyran motif is present that could be possibly implemented in a synthetic sequence using intermediates **I**–**III** prepared from sugar **IV**, via a key 1,5 C–H bond insertion on the alkylidenecarbene **A** (Chart 1). The successful accomplishment of this objective (see below) led us to investigate in depth the scope and limitations of the present methodology for the synthesis of a series of differently functionalized furo[*x*,*y*-*c*]pyrans. In this work we will describe the synthesis of all these key precursors, the generation of the alkylidenecarbenes, and the 1,5 C–H insertion results, accompanied by a DFT computational analysis in order to explain the regioselectivity or regiochemistry of some of these processes.

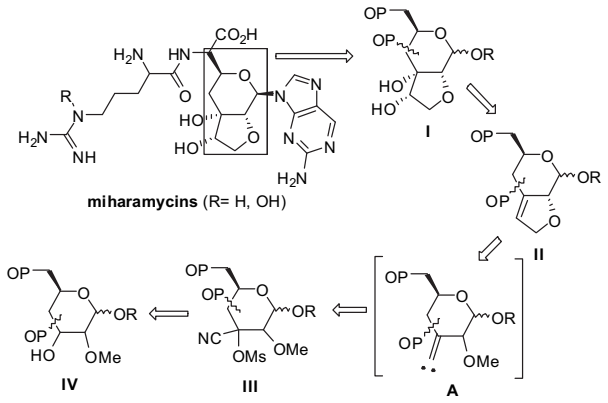
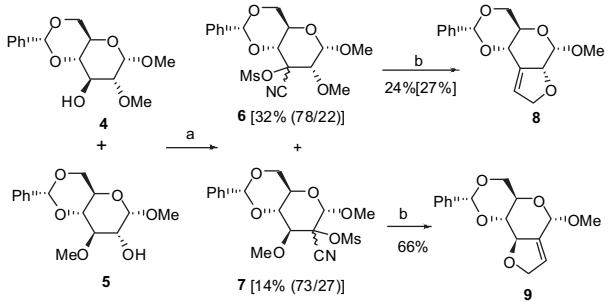


Chart 1.

2. Results and discussion

2.1. Synthesis and reactivity

2.1.1. D-Glucose derivatives. Starting with a mixture of the 2-*O*- and 3-*O*-methyl ethers **4** and **5** that we were unable to separate,[11] the one-pot-two-step oxidation plus cyanomesylate formation protocol provided pure methyl glucosides **6** and **7**, as a mixture of diastereomers at C-3 and C-2, respectively. The C2–OMe substituted derivatives (**6**) were separated from their C3–OMe isomers (**7**), and independently, submitted to further reaction (Scheme 3). Under the standard conditions (see Experimental part) diastereomers **6** gave the expected alkylidenecarbene intermediate that afforded the 1,5 C–H insertion product **8** in 24% yield (Scheme 3). The structure of this compound was unequivocally assigned by detailed spectroscopic analysis as well as by comparison with the data reported for the same compound by Amelia P. Rauter and colleagues.[12] Compound **8** has been synthesized from 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-hexopyranoside, in four steps comprising Wittig–Horner reaction, iodine-double bond isomerization, LAH-promoted reduction and heterocyclization, in 79% overall yield, as a model study for the synthesis of miharamycins.[12] A related derivative has been also recently synthesized in good yield, an intramolecular ring-closing-metathesis reaction being the key step for the installation of the fused dihydrofuran ring moiety.[10]

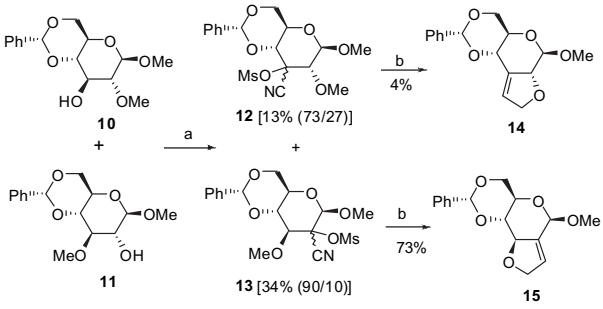


Scheme 3. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

Certainly the chemical yield of our 1,5 C–H bond insertion reaction leading to product **8** was low, but very interestingly, this result proved to be substrate-dependent, as the isomers **7**, under the same experimental conditions, gave compound **9** in higher and more synthetically useful yield (66%) (see Experimental part) (Scheme 3). These observations coupled to the obvious synthetic interest of the resultant chiral furo[2,3-*c*]pyran type of compounds prompted us to undertake an extensive study in order to understand more deeply the stereo- and regiochemical outcome of

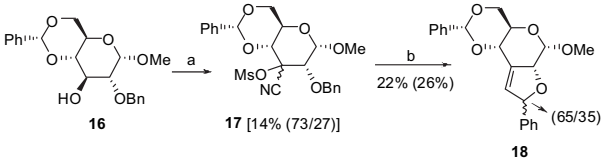
the 1,5 C–H bond insertion reaction on these alkylidenecarbene reactive intermediates. In this study, we have taken into account the different structural and functional parameters at hand for modification, such as the location of the alkylidenecarbene at C2, C3 and C4, the anomeric configuration and the substitution at the 'carbon donor' in the 1,5 C–H insertion reaction.

Thus, for the next experiment we considered the same D-glucose derivatives as intermediates, but as their β-anomers (**12** and **13**). These precursors were prepared following similar synthetic protocols from known glycosides **10** and **11** (Scheme 4).[11] As shown before (Scheme 3), now diastereomers **12**, where the alkylidenecarbene functional moiety is located at C-3 (sugar numbering) provided the expected product **14**, albeit in very poor yield. Conversely, intermediates **13** leading to an alkylidenecarbene, located at C-2, gave only one product (**15**), in good yield, as the result of a total regiochemical 1,5 C–H bond insertion reaction favouring exclusively the transfer of the proton linked to C–O–(C-3) instead of the proton linked to C–O–(C-1).

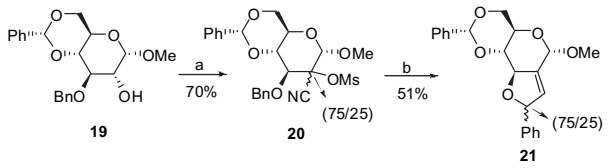


Scheme 4. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

In the examples described above we have used *O*-methyl ethers as the 'donor' partner in the insertion process. In order to investigate the effect of a substituent such a phenyl group, we considered as starting material the known D-*gluco* derivative **16**[11] bearing a *O*-benzyl group at C-2 (Scheme 5). Following the usual synthetic sequence we isolated compound **17** as a diastereomeric mixture of epimers at C-3, in a complex reaction, where we could detect also the corresponding unreacted intermediate ulose (see Experimental part). Very interestingly, under the standard reaction conditions, the diastereomeric mixture of cyamomesylates **17** provided compounds **18** in low yield, in an uncomplete reaction, and as a mixture of isomers (65/35) at the newly formed stereocenter (C-8) that we did not try to separate, and configurationally identify. Consequently, the most important fact from this reaction is that the 1,5 C–H bond insertion process is still possible, that the presence of a phenyl group linked to the carbon forming the new C–C bond do not preclude the reaction by steric hindrance, and that the partial failure of the process from the synthetic point of view must be ascribed to a general reactivity pattern for the alkylidienecarbene species when located at C-3 in these substrates [compare with the results obtained from precursors **6** (Scheme 3) and **13** (Scheme 4)]. This was nicely confirmed when we repeated the process starting from known D-*gluco* derivative **19**,[13] via intermediates **20**, leading to the furo[3,2-*c*]pyran derivatives **21** (Scheme 6), isolated in a convenient chemical yield (51%) as a mixture of diastereomers (75/25) at C-8.

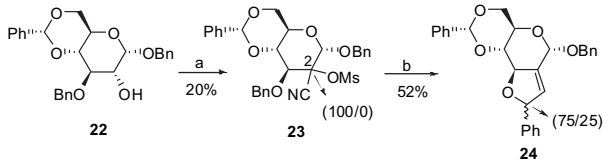


Scheme 5. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.



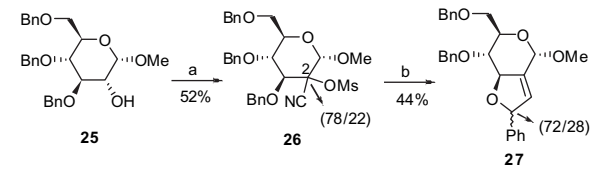
Scheme 6. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

The possible competitive 1,5 C–H bond insertion reactions between protons located in the methylene moiety of the *O*-benzyl groups, at C-3 or C-1, in the α-anomer **23**, a precursor prepared from sugar **22**,[14] has also been investigated. In the usual conditions, only one compound (**24**), as a mixture of diastereomers, was isolated in good yield, and characterized (Scheme 7). This reactivity is similar to the one observed in the di-*O*-methyl precursor **7** (Scheme 2), and strongly points out to a systematic preferred regiochemical migration of the proton located at the ether located at C-3, regardless of the spatial orientation of *O*-methyl ether at C-1, in the 1,5 C–H process with alkylidenecarbenes located at C-2.



Scheme 7. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

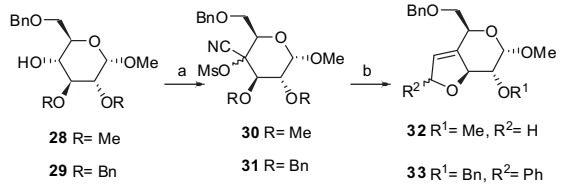
Note also that in the previous investigated precursors the hydroxyl groups at positions C-4 and C-6 were part of a benzylidene nucleus that conferred to the corresponding substrates an obvious rigidity, preventing free conformational mobility, hence possibly favouring the 1,5 C–H bond insertion reactions. This was the reason why a per-*O*-benzylated D-*gluco* derivative was of interest in order to test the influence of this structural feature. Consequently, methyl 3,4,6-tri-*O*-benzyl-α-D-glucofuranoside (**25**) was synthesized as described,[15] and submitted to oxidation and cyanomesylation reactions to afford the key intermediate **26**. The subsequent reaction with trimethylsilylazide and dibutyltin oxide provided the alkylidenecarbene species that smoothly cyclized to the mixture of diastereomers **27** (Scheme 8) in a similar yield to the one obtained for precursor **20** leading to compound **21** (Scheme 6). This result means that a restricted conformation induced by benzylidene protecting group for the hydroxyl groups at C-4 and C-6 is not a condition for the 1,5 C–H insertion takes place, and that simple *O*-benzyl protecting groups are enough to afford the same result.



Scheme 8. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

Finally, we have synthesized additional useful intermediates in order to prepare alkylidenecarbene species located at C-4 in the sugar skeleton, and tested their reactivity. In these cases opportunities to evaluate the competition between the 1,5 versus 1,6 C–H bond insertion reactions are possible, and will be discussed.

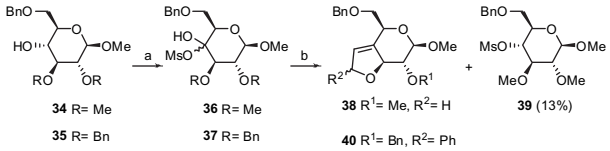
Starting from known per-*O*-alkylated D-*gluco* derivatives **28**[16] (OMe) and **29** (OBn),[17] the diastereomeric mixtures of α-cyano-mesylates **30** and **31**, were obtained, respectively. Next, the generation of the alkylidenecarbene as usual provided compound **32** and **33** (Scheme 9) in moderate yield (49%) as the only insertion products, and in the case of furopyran **33**, as a diastereomeric mixture at the newly formed stereocenter in 81/19 ratio. This result rules out the formation of 1,6 C–H bond insertion products, the 1,5 C–H mode of cyclization being the only observed.



Scheme 9. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl [**28**–**30** (56/44): 62%; **29**–**31** (70/30): 89%]; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux [**30**–**32**: 49%; **31**–**33** (81/19): 49%].

In the β-anomeric series we were very pleased to see similar and good overall results. Starting with the known methyl glycosides **34**[18] and **35**,[17] the synthesis of the corresponding precursors **36** and **37** was easily achieved as usual (see Experimental part). For the diastereomeric mixture of sugar **36** we obtained a mixture of compounds **38** and **39**, that we could separate and characterize (Scheme 10).

Major compound (**38**) is the expected and exclusive 1,5 C–H bond insertion product, and was isolated in the highest yield (81%)



Scheme 10. Reagents and conditions: (a) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl [**34**–**36** (80/20): 83%; **35**–**37** (60/40): 50%]; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux [**36**–**38**: 81%; **37**–**40** (74/26: 47%)].

until now on these studies. Product **39** was the decyano derivative of **36** with the β-D-*gluco* configuration as we could easily assign in view of the high vicinal (9.5 Hz) constant for H-4/H-5, showing that these protons are in a *trans*-arrangement, in a chair like conformation. A detailed analysis of the reaction leading to intermediate **36** clearly showed that compound **39** was also formed in traces in this step due to an incomplete oxidation reaction, followed by mesylation of unreacted alcohol **34**. On the other hand the transformation of diastereomers **37** afforded the expected compounds **40** in moderate yield.

In Charts 2 and 3 we have shown the most relevant facts associated with the observed insertion reactions on D-*gluco* derivatives for the synthesis of chiral, densely functionalized furo[2,3-*c*]([3,2-*c*])pyrans. The synthetic methodology is simple and flexible as it works on a number of different types of substrates, affording the expected molecules from moderate to good yield. Of particular interest is the high regiochemical control regarding the 'C–H donor' moiety, as well as the prevalent 1,5 versus 1,6 C–H insertion process, when competition is possible. All these experimental facts need to be evaluated and considered in a more rational basis using computational chemistry. Accordingly, in the last section we present a theoretical study aimed at explaining these results.

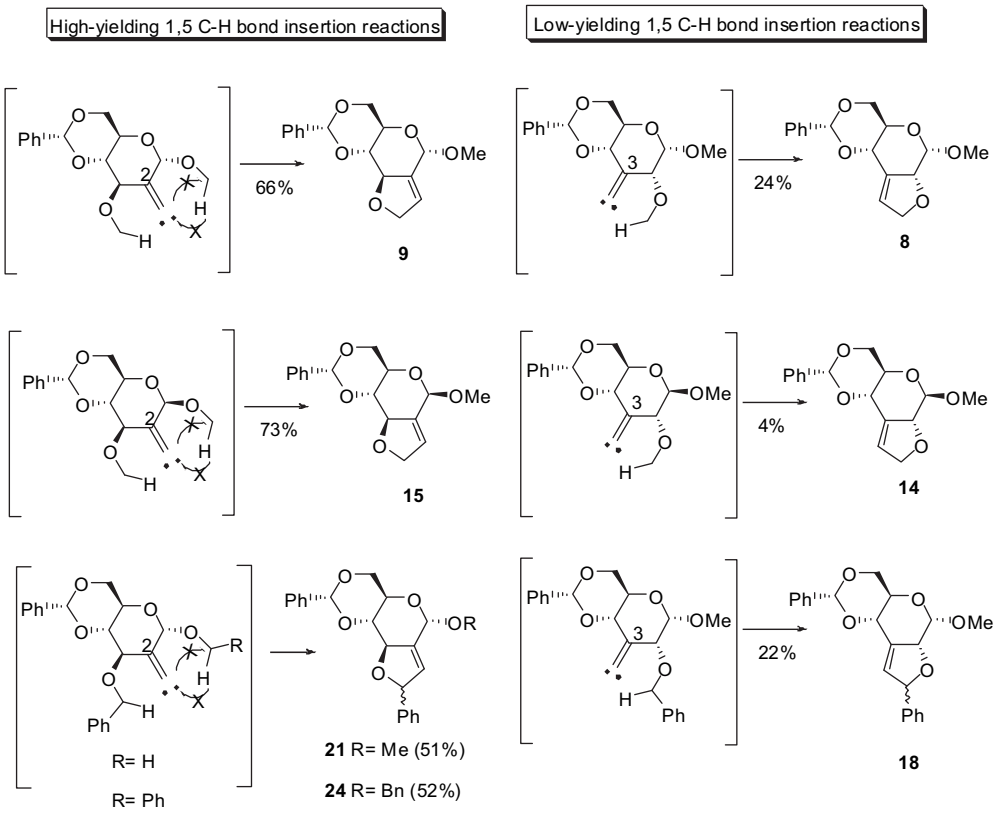


Chart 2.

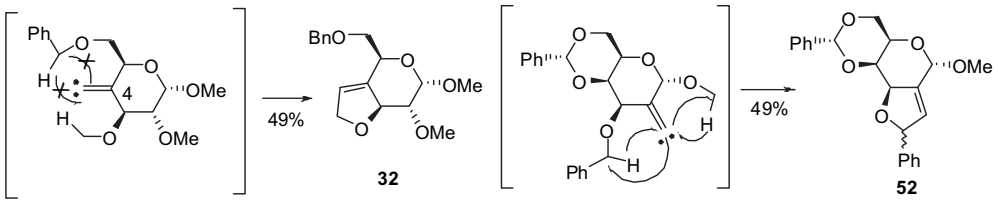
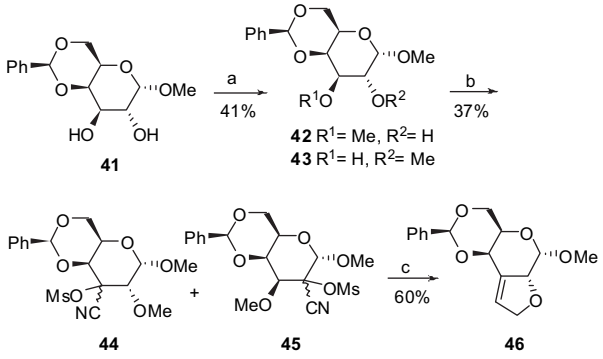


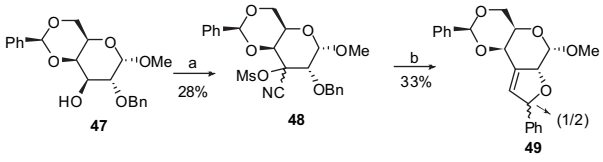
Chart 3.

2.1.2. D-Galactose derivatives. With the reactivity on the D-*gluco* derivatives in mind, next we investigated the synthesis and cyclization of series of D-*galacto* intermediates, as their epimers at C-4. In fact, to start with this analysis we used also similar precursors (**44** and **45**) (see Scheme 3). These compounds have been synthesized from commercial methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**41**), after unselective methylation to give an unseparable mixture of *O*-methyl ethers **42** and **43**, followed by standard oxidation, cyanohydrin formation and mesylation. Very interestingly, under the usual conditions, the unseparable mixture of regioisomers **44**+**45** (61/39 ratio) gave only one compound (**46**) in 60% yield (Scheme 11). The structure of this compound was clearly established by ^{1}H NMR analysis as protons H_6 and H_{6a} are vicinal showing 4.0 Hz as coupling constant. Neither the presumed derivative from precursor **45** nor the same intermediate was detected in the crude reaction; we have no explanation for this unexpected result. This result was very surprising, and in sharp contrast with the sluggish reactivity observed on the same alkylidenecarbene species at C-3 in the D-*gluco* series, as described above. In order to test the extent of this particular and different type of reactivity we have prepared precursors **48** (Scheme 12) and **51** (Scheme 13), similar to the D-*gluco* derivatives **17** (Scheme 5) and **20** (Scheme 6).

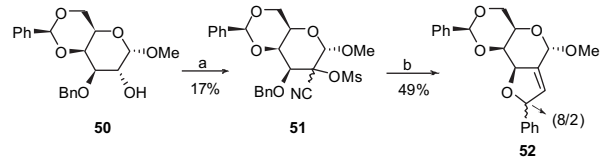
The synthesis of compounds **49** and **52** proceeded as expected starting from alcohols **47**[19] and **50**,[19] respectively, via cyanomesylates **48** and **51**. Compounds **49** and **52** were isolated as mixtures of diastereomers at the newly formed stereocenter, that we did not try to separate, and whose structures were in good agreement with their spectroscopic data. Although the yield of furopyran **52** (49%) arising from an alkylidenecarbene located at C-2 was significantly higher than the yield of compound **49** (33%), obtained from an alkylidenecarbene at C-3, the difference was not so high as we have previously found in related substrates in D-*gluco* series (see above). In addition, the cyclization leading to compound **52** from intermediate **51** is apparently contradictory with the unsuccessful cyclization on related compound **45** (Scheme 11), although the presence of a phenyl group in the carbon donor partner in intermediate **51** must have some positive influence. It is also important to highlight that in the formation of furopyran **52**, only the proton in the *O*-benzyl side is transferred to the carbene in preference to the proton in the *O*–Me vicinal group (see Chart 3).



Scheme 11. Reagents and conditions: (a) i. Bu_2SnO, MeOH, then IMe; (b) i. PCC; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

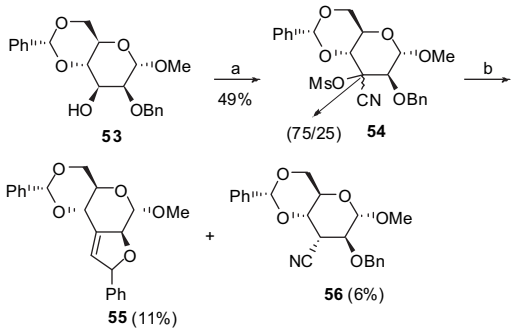


Scheme 12. Reagents and conditions: (a) i. Dess–Martin; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.



Scheme 13. Reagents and conditions: (a) i. Dess–Martin; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

2.1.3. D-Mannose derivatives. In view of the results obtained in the D-*galacto* series we decided to prepare precursors **54** (Scheme 14) and compare results with the ones obtained with the α-methyl glycosides and epimers at C-2 (compounds **17**; Scheme 5), and epimers at C-4 (compound **48**, Scheme 12). In addition, with compounds **54** we will deal with an alkylidenecarbene at C-3, the most favourable situation until now that we have observed in our studies from the synthetic point of view.



Scheme 14. Reagents and conditions: (a) i. Dess–Martin; ii. NaCN, $NaHCO_3$, then MsCl; (b) $TMSN_3$, $OSnBu_2$, toluene, reflux.

Starting from alcohol **53**[20] and following the usual steps we were able to prepare and isolate a mixture of diastereomers **54** in 75/25 ratio, that were submitted to the standard cyclization protocol, giving compound **55** as a pure diastereomer at C-8, and the deoxygenated derivatived **56**, in 11 and 6%, respectively.

3. Reactivity and mechanism based on a DFT approach

The results summarized above describe regioselective 1,5 C–H insertions of key transient intermediates alkylidenecarbenes as a means to construct functionalized furo[*x*,*y*-*c*]pyrans. The insertion

of simple carbenes (such as halogenated dimethyl carbenes) into C–H[21] bonds and alkylidenecarbenes into O–H[22] bonds has already been treated by theory. However, to our knowledge, there is still no computational report on the insertion reaction of alkylidenecarbenes into C–H bonds.

To examine the reactivity of the alkylidenecarbene, we have undertaken a systematic investigation of the insertion reactions of various alkylidenecarbenes derivatives into C–H bonds using density functional theory. The relative reactivity of various types of carbon–hydrogen bonds for the process has been assessed, and the results have been compared to those observed experimentally.

Alkylidenecarbenes can exist in singlet state (S_0) in singlet state (S_1) and the triplet state (T_1). In S_0 there is an empty p_π orbital on the carbene carbon, and the nonbonding unshared spin-paired electrons occupy an sp orbital in the plane of the molecule. Singlet state (S_1) refers to two singly occupied orbitals. In the triplet state (T_1) two nonbonding electrons have parallel spins and occupy an sp orbital as well as an orbital with substantial p character.[1a]

Singlet carbenes are expected to show electrophilic and nucleophilic behaviour because of the lone pair and the vacant orbital, whereas triplet carbenes are expected to exhibit diradical reactivity. The relative stability, reactivity, singlet–triplet gap (ΔE_{ST}), lifetime and philicity of carbenes are dependent on π-electron delocalization and the substituents bonded to the electron-deficient carbene carbon atom (spectator substituents), neighbouring substituents (by-stander substituents) and remote substituents.

Because the reactivity of a carbene is dependent on whether it is in the singlet or triplet state, the magnitude of the singlet–triplet gap is of great importance. According to Hund's rule, the triplet state of a carbene should be more stable than the singlet state. However, the singlet–triplet gap (ΔE_{ST}) is dependent on the energy separation between the two nonbonding orbitals. If that gap is small, Hund's rule is operative, and the triplet state is favoured. As the separation between the two orbitals increases, it eventually outweighs the greater Coulombic repulsion between the two electrons in the singlet state, and the singlet form becomes the ground state.

3.1. The reactivity of alkylidenecarbene at C-2/C-3

Firstly, we have focussed on an alkylidenecarbene at C-2, and accordingly, we have analyzed the alkylidenecarbene **B** as theoretical model of the carbene derived from **13** (Scheme 4). Conformers **B1**–**B3** (Fig. 1) in the single state show a suitable conformation of the methyl ether moiety in relation to the carbene to undergo the insertion process. Noteworthy, **B1** showing the lowest energy should give rise to the observed cyclopentene **C**

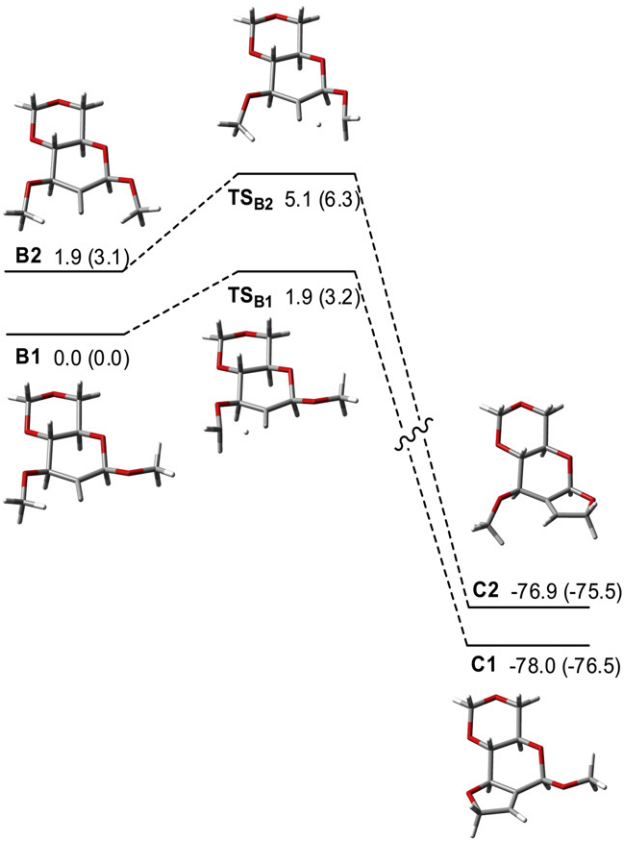


Figure 2. Enthalpy profile (in kcal mol^{-1}) for the 1,5 C–H insertion process of the alkylidenecarbene into the substituents at C-1 and C-3. (Free energy differences are shown in parenthesis.)

(Fig. 2). In this conformation, the non-reactive methoxy group forms a weak hydrogen bond with the endocyclic oxygen (C–H···O=2.608 Å),[23,24] whereas the electrostatic repulsion between both heteroatoms (endo- and exocyclic oxygens) is minimized. These effects could block, at least partially, the formation of the regioisomeric adduct. Rotamers **B2**–**B3** involve both heteroatoms partially aligned, and therefore repelling each other. Hence, these results suggest that the formation of a five-membered CH/O hydrogen bond plays an important role in making conformation **B1** as the most favourable for both the states.

As depicted in Figure 1, our calculations indicate that carbene **B** should have a singlet ground state. Experimental evidence for

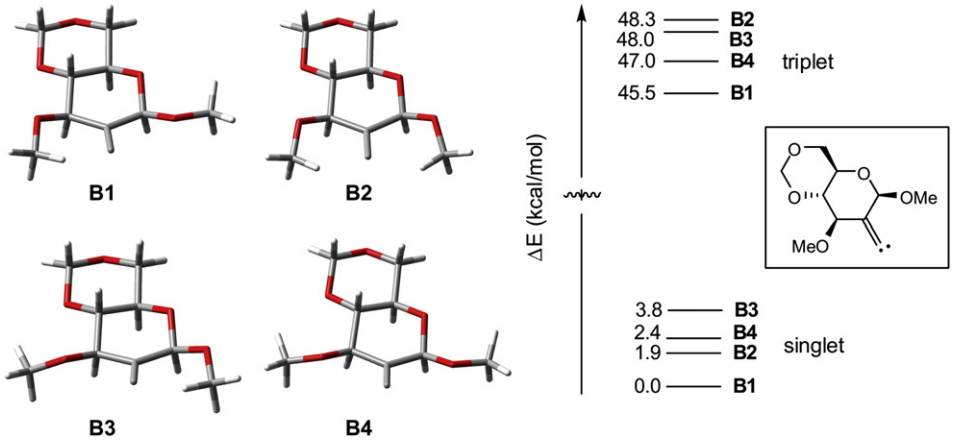


Figure 1. Relative energy (in kcal mol^{-1}) of the singlet and triplet state for conformers **B1**–**B4**.

a singlet state may be found in earlier work by Gilbert and Ohira who have confirmed that C–H insertion into a stereochemically defined methine proceeded with retention of absolute configuration.[5c,25] Moreover, it should be noted that the excitation energies from the singlet ground state to the first triplet excited state are quite large (45.5–48.3 kcal mol^{-1}). This means that production of the first excited triplet state under experimental conditions is practically impossible. Thus, only the singlet potential surface was considered throughout this work.[26]

The conformers **B1**–**B3** show short H···C_{CARB} distance and long C–H bond so they can be viewed as precursor complexes[25] or even ylide-like complexes, since they all possess a similar ylide structure. They are true minima on the potential energy surface, with energy values in the range −2.4–(+1.4) kcal mol^{-1} in relation to the corresponding uncoordinated carbene structure **B4**.

The optimized six-membered transition structure to form $\mathbf{TS_{B1}}$ resembles a half chair, showing the hydrogen atom of interest in a plane defined by the carbon atom to which it originally is attached and the doubly bound carbon atoms of the carbene (deviation of 10.4°). In this arrangement, methyl C–H bond molecular orbital is periplanar with and therefore can overlap with the empty orbital of the alkylidenecarbene.[27] This is a late transition structure, since the C–H length is long (1.517 Å) and the C_{CARB}–H bond is nearly formed (1.156 Å).

However, the C–C_{CARB} distance is still rather large, suggesting a strong asynchronicity in the formation of both the C–C and C–H bonds. These results might put forward a stepwise insertion mechanism, a reaction path that indeed we have found for the triplet state (see Supplementary data). However, IRC calculations have verified that this transition structure connects precursor complex **B1** to the insertion product **C1**. The 1,5-insertion reaction with C–H by alkylidenecarbenes is strongly exothermic (−78.0 kcal mol^{-1}, Fig. 2), and hence irreversible.

Alkylidenecarbenes are expected to be electrophilic because of their electron deficiency. This is confirmed by the computed NPA atomic charge on the carbene carbon on **B1** (+0.148). The NPA computation also reveals a charge of −0.295 for the alkane carbon (+0.151 for the CH_2 fragment). These results contrast with those of the cyclized product, that shows values of −0.217 and −0.123 (+0.319), respectively. The charge for the moving hydrogen varies from +0.242 in **B1** to +0.256 in **C1**.

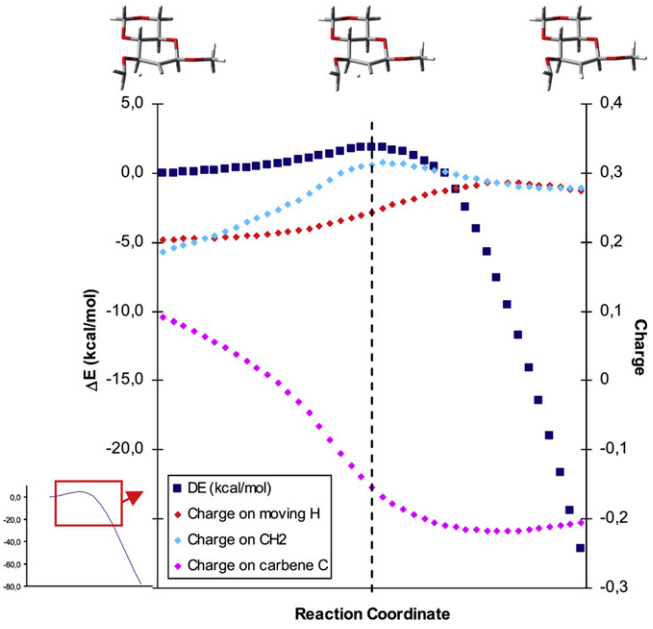


Figure 3. Evolution of the charge on the reactive moieties around the transition state.

A close inspection by IRC calculations of the electronic nature of the involved moieties around the transition state (Fig. 3) indicates a notable development of negative charge at the carbene atom, on going from the open to the cyclized form. As can be seen in Figure 3, the insertion of the alkylidenecarbene into the C–H bond occurs initially through an electrophilic phase followed by a nucleophilic phase resulting in a net charge flow from the alkane to the inserting carbene during the first part of the reaction.

The experimental observations indicated that glycoside **13** (and its α-anomer **7**) gives rise to **15** (and **9**), suggesting a total regiochemical 1,5 C–H bond insertion of the alkylidenecarbene intermediate into the methyl ether at C-3. The calculations on the alternative path (i.e., insertion into the substituent at C-1) for the theoretical model reveal that the likely carbene intermediate **B2** is isoenergetic with the transition structure $\mathbf{TS_{B1}}$ in the reaction path driving to **C1**. Going from **B2** to $\mathbf{TS_{B2}}$ the C–H bond is lengthened from 1.109 to 1.515 Å, whereas the distance from the carbene carbon to the alkene carbon and moving hydrogen decrease dramatically from 2.235 and 1.154 Å. The alkene insertion leads to the formation of **C2**, which lies 78.8 kcal/mol below carbene **B2** (Fig. 2). The free energy required to reach $\mathbf{TS_{B2}}$ from **B2** is 3.2 kcal/mol, being 3.1 kcal mol^{-1} less stable than the regioisomeric transition structure $\mathbf{TS_{B1}}$.

These results account for the experimental evidences (regioselective formation of cyclopentenes **9** and **15**), which indicated a selective 1,5 C–H bond insertion reaction favouring exclusively the transfer of the proton linked to the substituent at C-3 instead of the proton linked to that at C-1, and suggest that the regioselectivity may be related to the anomeric effect. Thus, the conformation of the anomeric methoxy moiety in **B1** and the ensuing $\mathbf{TS_{B1}}$ and product **C1**, involving a weak hydrogen bond with the endocyclic oxygen and minimization of electrostatic repulsion between heteroatoms, would promote the regioselective C–H insertion of the carbene into the substituent at C-3. To verify this hypothesis, we have estimated the activation barrier for this step from conformer **B2** devoid of these stabilizing interactions. As expected, the transition structure $\mathbf{TS'_{B1}}$ is 2.4 kcal mol^{-1} higher than $\mathbf{TS_{B1}}$ so the conformation of the substituent at the anomeric position has a critical effect in the reactivity and regioselectivity in the insertion step in an apolar medium.

While **13** bearing the 'donor carbon' at C-3 afforded regioselectively **15** in high yield, its isomer **12** bearing the 'donor carbon' at C-2 provided the cyclized product **14** in very poor yield. Furthermore, this outcome appears independent of the anomeric configuration, since the alkylidenecarbene epimers from **6** and **7** provided the cyclized adduct in low and high yield, respectively (Scheme 3). These striking results were also analyzed by DFT methodology. The

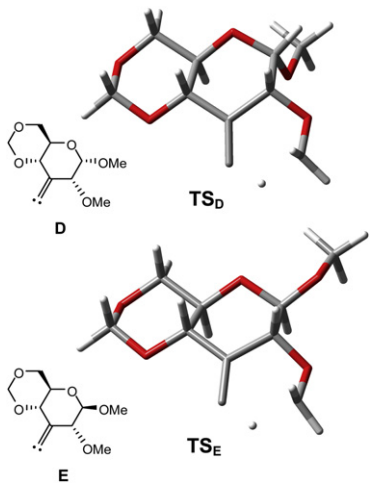
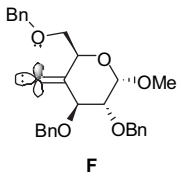


Figure 4. Transition structure for alkylidenecarbene intermediates **D** and **E**.



F

Figure 5.

computed data reveal that the insertion of the alkylidenecarbene models **D** (α-anomer) and **E** (β-anomer) (Fig. 4) proceeds by overcoming an enthalpy barrier of 4.0 and 3.3 kcal/mol, respectively (free energy barriers of 5.1 and 4.6 kcal mol^{-1}, respectively). In every case, the interatomic distances of the endocyclic and methoxy oxygen in the transition state (2.671 and 2.814, respectively; see Fig. 4) are shorter than the sum of the van der Waals radii of the oxygen atoms. This effect could account for the destabilization of the transition structure, even if the substituent at the anomeric site adopts the most favourable conformation.

On other hand, the electronic properties indicate that the effect of two ether groups at the anomeric carbon C-1, enhances the charge separation in the alkylidenecarbene group C-2–C_{CARB}, making a more electrophilic C_{CARB}, whereas this effect is negligible and the charge separation lower when carbene is located at C-3 (−0.393 and +0.148 in **B1**, −0.371 and +0.134 in **D**). However, the computed barriers seem low and cannot wholly justify the low yield for this process, so likely other factors must come into play.

The results summarized above rationalize some of the experimental evidences regarding the position of the alkylidenecarbene on the pyran and anomeric configuration.

Our next target was the analysis of the substitution (H or Ph) at the 'carbon donor' in the 1,5 C–H bond insertion process and the competition with a 1,6 C–H bond insertion (Scheme 9).

3.2. The analysis of the substitution (H or Ph) at the 'carbon donor' in the 1,5 C–H bond insertion process

We have selected structure **F** as theoretical model. In this case, it is remarkable that the structure of the alkylidenecarbene, which shows a strong interaction of the vacant orbital on the carbene with an oxygen lone pair of the *O*-benzyl oxygen (Fig. 5). This interaction produces the transient oxonium ylide, which would block the insertion with that branch, hence driving the insertion with the substituent at C-3.

The 1,5 C–H insertion is initiated by interaction of the LUMO of the carbene with the alkane, i.e., the hydrogen moves towards the carbenic carbon by following a trajectory in the plane of C4–C_{CARB}–C plane. At the transition state $\mathbf{TS_{F5}}$ (Fig. 5), the attacked C–H bond is almost broken (1.513 Å), whereas with 1.159 Å the distance between the carbene carbon and the hydrogen corresponds almost to a C–H bond. The forming C–C bond presents a large value (2.317 Å). The insertion proceeds with an enthalpy barrier of 1.1 kcal mol^{-1} ($\Delta G^{\#}$=2.5 kcal mol^{-1}).

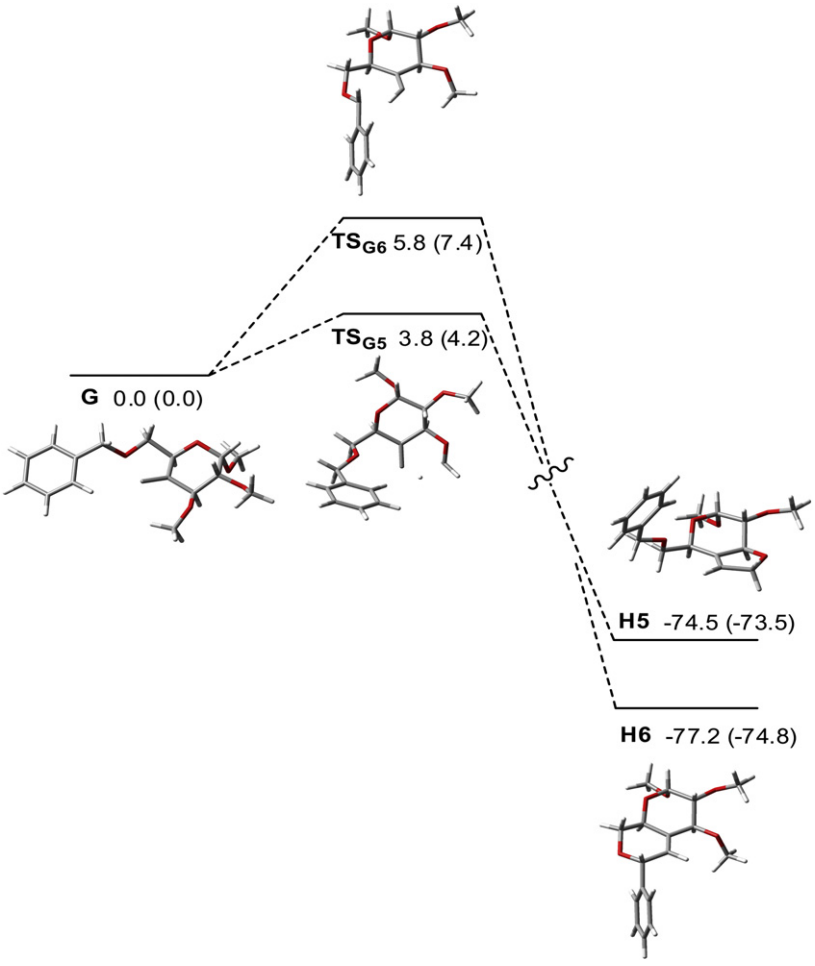


Figure 6. Enthalpy profile (in kcal mol^{-1}) for the 1,5 and 1,6 C–H insertion processes of the alkylidenecarbene **G** into the substituents at C-3 and C-5. (Free energy differences are shown in parenthesis.)

On the other hand, the transition structure for the 1,5 C–H insertion of the methyl ether analogue, **G**, shows similar lengths for the forming (1.151 Å) and breaking (1.526 Å) C–H bonds. In contrast, it displays a shorter distance for the forming C–C bond than the *O*-benzyl analogue, which suggests a later transition state with larger synchronicity. The enthalpy barrier to achieve the transition state is 3.8 kcal mol^{-1} ($\Delta G^{\#}$=4.2 kcal mol^{-1}), and expectedly the reaction is strongly exothermic (ΔH=−74.5, ΔG=−73.5 kcal mol^{-1}).

The computed results for **F** and **G** agree with previous findings, which suggest that the intramolecular 1,5 C–H bond insertion reaction of alkylidenecarbenes is dependent on, among other things, the dissociation energy of the C–H bond undergoing insertion. That is to say, the efficiency of the 1,5 mode in aliphatic systems is inversely related to the dissociation energy of the C–H bond undergoing insertion[2d,28] (i.e., primary>benzylic).

3.3. The site selectivity with regard to insertion at C-5 versus C-6

The site selectivity with regard to insertion at C-5 versus C-6 of the alkylidenecarbene was qualitatively assessed by examination of the cyclation for both alkylidenecarbenes **F** and **G**. Gilbert et. al have suggested a stepwise pathway for this less frequent insertion process where a intermolecular H exchange takes place with the medium.[7b] In contrast, Feldman et al. have found evidences that rule out any mechanism that requires H exchange.[7a]

The 1,6 C–H insertion takes place through a seven-membered transition structure, that is very similar for both alkylidenecarbenes from structural and energetic standpoints. As example, we describe here the results for **G**, whose transition structure **TS$_{G6}$** shows the moving H bonded to the carbene carbon (1.122 Å) at a distance of 1.601 Å of the donor carbon. The distance C–C is large at this stage (2.443 Å) pointing to a highly asynchronic transition structure. The enthalpy barrier for this step is higher than that for the 1,5 C–H insertion process, 5.8 kcal mol^{-1} ($\Delta G^{\#}$=7.4 kcal mol^{-1}, Fig. 6).

These results are in agreement with experimental findings and justify the total regioselectivity. This preference has its origin in the enthalpic and additionally entropic factors that favour six- versus seven-membered cyclic transition states. Thus, the 1,5 C–H insertion step is accompanied by an entropic change, $\Delta S^{\#}$, of −1.7 cal mol^{-1} K^{-1}, whereas for the 1,6 process it increases to −5.2 cal mol^{-1} K^{-1}.

These data also help to understand the present and precedent results[6,7] showing that only when the 1,5 C–H insertion is blocked, the reaction pathway redirects the carbene to a less common, kinetically less favoured, 1,6-C–H insertion.

4. Conclusion

To sum up, our new method for the generation of alkylidenecarbenes based on the reaction of trimethylsilylazide/Bu_2SnO with α-cyanomesylates has been applied to readily available sugar derivatives for the synthesis of highly functionalized, enantiomerically pure furo[*x*,*y*-*c*]pyrans. The furo[*x*,*y*-*c*]pyran heterocyclic ring system is present in a number of natural or non-natural products of biological interest such as the miharamycins, and deserve particular attention. The scope and extent of the present new methodology has been investigated by systematic modification of the starting sugar precursor (D-glucose, D-galactose, D-mannose) in the hexo-α(β)-D-pyranoside forms, bearing also different *O*-protecting groups, the effect of the absolute configuration of the substituent at the anomeric position, the location (C-2, -3 and -4) of the alkylidenecarbene species on the pyran nucleus, as well as the substitution (H or Ph) at the 'carbon donor' in the 1,5 C–H bond insertion process. In overall, using these key 1,5 C–H bond insertion reactions a simple protocol results for the synthesis of the furo [*x*,*y*-*c*]pyrans, difficult to be prepared by other methodologies, from moderate to good yields. Finally, the DFT study of different structural parameters such as the location of the alkylidenecarbene (C2, C3 and C4), the anomeric configuration and the substitution at the 'carbon donor' in the 1,5 C–H insertion reaction has allowed us to rationalize the experimental findings and get insights into the acute regioselectivity observed when a 1,6 C–H insertion is also possible.

5. Experimental

5.1. General

Materials and methods. Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. Optical rotations were recorded in CH_2Cl_2, $CHCl_3$, MeOH, with a digital polarimeter using a 1 dm cell. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, Me_2SO-d_6, or MeOD-d_3 (internal $SiMe_4$), respectively, at 300.13 MHz and at 75.47 MHz. TLC was performed on Silica F254 and detection by UV light at 254 nm or by charring with phosphomolybdic acid–H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (230 mesh). Acetone, hexane, cyclohexane, ethyl acetate and diethyl ether were distilled before use. Bases and solvents were used as supplied. ^{13}C NMR resonances have been assigned by using standard NMR (DEPT, COSY, HSQC) experiments. FTIR spectra were obtained neat using ATR and are reported in cm^{-1}.

5.2. General method for Swern oxidation (A)

DMSO (3.0 equiv) was added dropwise to oxalyl chloride (2.0 equiv) in CH_2Cl_2 at −55 °C and the solution stirred (0.5 h). The alcohol (1.0 equiv) in CH_2Cl_2 was then added dropwise to the solution and the resulting solution stirred at −55 °C (1.5 h). The solution was then warmed to −30 °C followed by dropwise addition of Et_3N (3.0 equiv). The solution was then warmed to rt and standard workup (CH_2Cl_2) yielded the ketone that was used in the next step without any further purification.

5.3. General method for oxidation with PCC (B)

To a solution of PCC (2.5 equiv) and powder molecular sieves 3 Å (2.5 equiv w/w) in CH_2Cl_2 was slowly added a solution of starting material in CH_2Cl_2. The mixture was stirred at rt under argon. After evaporation of the solvent, the reaction mixture was dissolved with EtOAc, and filtered through a silica pad. The filtrate was concentrated under vacuum and the crude ulose was used in the next step without further purification.

5.4. General method for Dess–Martin periodinane oxidation (C)

To a solution of Dess–Martin reagent (3 or 4 equiv) in anhydrous CH_2Cl_2 was slowly added a solution of starting material in anhydrous CH_2Cl_2. The mixture was stirred at rt under argon overnight. Diethyl ether (100 mL), a saturated solution of $NaHCO_3$ (100 mL) and $Na_2S_2O_3$ (10 g) were added and stirred for 5 min. After extraction, the organic layer was successively washed with a saturated solution of $NaHCO_3$ (100 mL) and water (100 mL). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to dryness. The crude ulose was used in the next step without further purification.

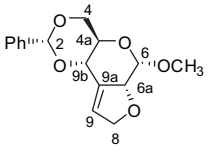
5.5. General method for cyanomesylation (D)

To a solution of crude ulose in CH_2Cl_2 was added a solution of $NaHCO_3$ (2 equiv) in water and KCN (2.1 equiv). The resulting mixture was stirred vigorously at rt then extracted with CH_2Cl_2 (×2) or the crude ulose was added to a solution of diethyl ether/H_2O (2/1), NaCN (1 equiv) and $NaHCO_3$ (2 equiv) and vigorously stirred at rt. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to dryness. The crude cyanohydrins were dissolved in CH_2Cl_2 followed by addition of Et_3N (8 equiv) and MsCl (5.5 equiv) at 0 °C. After stirring at rt, the mixture was extracted by slow addition of water and CH_2Cl_2. The residue was purified by flash chromatography. Alternatively, to a solution of crude ulose in MeOH was added $Ti(O^iPr)_4$ (2 equiv) and the solution was stirred at rt for 5 h or overnight; then, TMSCN (2 equiv) was added. After 24 h, a few drops of water were added, and EtOAc to dilute the solution. After evaporation of the solvent, the reaction mixture was dissolved in EtOAc and filtered through a silica pad. The filtrate was concentrated under vacuum and the crude cyanohydrins were used in the next step without further purification.

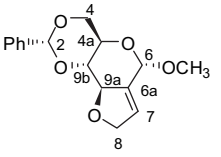
5.6. General method for alkylidenecarbene generation (E)

To a solution of cyanomesylate in dry toluene under argon, dibutyltin oxide (1 equiv) and $TMSN_3$ (2 equiv) were added. The reaction was heated to 100–108 °C and stirred for 1 h 30 min to 19 h and then the solvent was removed under vacuum. The crude product was submitted to flash chromatography (EtOAc/cyclohexane).

*5.6.1. Methyl 4,6-O-benzylidene-3-C-cyano-3-O-mesyl-2-O-methyl-α-D-gluco(allo)pyranoside (**6**) and methyl 4,6-O-benzylidene-2-C-cyano-2-O-mesyl-3-O-methyl-α-D-gluco(manno)pyranoside (**7**).* Following the general method **B**, a mixture of **4** and **5**[11] (5.0 g, 16.9 mmol), PCC (8.3 g, 38.7 mmol), powdered molecular sieves 3 Å (15 g) and CH_2Cl_2 (2×50 mL), reacted for 18 h 30 min to give the corresponding crude ulose (2.8 g) that was used in the next step without further purification. Following the general method **D**, to a solution of this crude ulose in ethyl ether (195 mL) and water (95 mL) was added $NaHCO_3$ (1.6 g, 19.04 mmol) and NaCN (466 mg, 9.52 mmol). After stirring for 22 h 30 min, the crude cyanohydrins were dissolved in pyridine (38 mL) followed by slow addition of MsCl (2.2 mL, 28.56 mmol). After 19 h and extraction ($CHCl_3/H_2O$), the residue was purified by flash chromatography (EtOAc/cyclohexane, 5/5–7/3) to give successively mixtures of diastereoisomers **6** [2.15 g (32%), 78/22 ratio], and **7** [949 mg, (14%), 73/27 ratio]. Compound **6**: solid; IR (ATR) ν 1368, 1184, 1091, 1047, 959 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.36 (m, 5H, 2×C_6H_5), 5.61 (m, 1H, 2×H-7), 5.00 (m, 1H, 2×H-1), 4.41–4.37 (m, 1H, 2×H-6A), 4.19–4.09 (m, 2H, 2×H-4, 2×H-5), 3.84 (m, 1H, 2×H-2), 3.81–3.77 (m, 1H, 2×H-6B), 3.67 (s, 3H, 2×OMe), 3.52 (s, 3H, 2×OMe), 3.19 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 129.9–126.7 (2×C_6H_5), 112.4 (2×CN), 102.7/102.3 (C-7), 97.9 (2×C-1), 82.5 (2×C-3), 81.8/81.3 (C-2), 79.1 (2×C-4), 69.0/68.8 (C-6), 61.4 (2×C-5), 61.0/60.7 (OMe), 56.5 (2×OMe), 40.4 (2×OSO_2CH_3); HRMS $C_{17}H_{21}NO_8NaS$: calcd 422.0886, found 422.0873. Compound **7**: solid; IR (ATR) ν 1374, 1184, 1091, 1002, 964 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.38 (m, 5H, 2×C_6H_5), 5.61 (m, 1H, 2×H-7), 5.41/5.27 (s, 1H, 2×H-1), 4.33–4.30 (m, 1H, 2×H-6A), 4.01–3.88 (m, 4H, 2×H-3, 2×H-4, 2×H5, 2×H-6B), 3.76 (s, 3H, 2×OMe), 3.56 (s, 3H, 2×OMe), 3.32 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.5–126.3 (2×C_6H_5), 114.3 (2×CN), 102.2 (2×C-7), 99.5 (2×C-1), 80.6 (2×C-2), 79.3/79.1 (C-3), 78.4 (2×C-4), 68.8/68.7 (C-6), 63.9 (2×C-5), 62.9/62.8 (OMe), 57.0/56.9 (OMe), 40.4/40.3 (OSO_2CH_3); HRMS $C_{17}H_{21}NO_8NaS$: calcd 422.0886, found 422.0893.



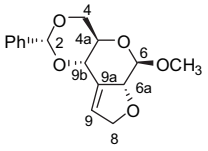
*5.6.2. (2R,4aR,6S,6aR,9bS)-4,4a,6,6a,8,9b-Hexahydro-6-methoxy-2-phenyl-furo[3′,2′:4,5]pyrano[3,2-d]1,3-dioxin (**8**).* Following the general method **E**, compound **6** (165 mg, 0.41 mmol), Bu_2SnO (102 mg, 0.41 mmol) and $TMSN_3$ (0.09 mL, 0.68 mmol) in toluene (6.5 mL) reacted for 18 h 30 min, at 100 °C, to give after flash chromatography (EtOAc/cyclohexane, 1/1), compound **8** (28 mg, 24%) and unreacted starting material (**6**) (24 mg (14%)). Compound **8**: white solid; mp 171–173 °C; $[\alpha]_D^{20}$ +148 (*c* 0.22, MeOH); IR (ATR) ν 1382, 1147, 1094, 1042, 962 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56–7.40 (m, 5H, C_6H_5), 5.79 (br s, 1H, H-9), 5.67 (s, 1H, H-2), 4.90 (d, $J_{6,6a}$=3.5 Hz, 1H, H-6), 4.86 (br s, 1H, H-6a), 4.84–4.81 (m, 2H, H-8), 4.31 (dd, $J_{4a,4A}$=4.2 Hz, $J_{4A,4B}$=9.9 Hz, 1H, H-4A), 4.28–4.24 (m, 1H, H-9b), 3.87 (t, $J_{4a,4B}$=9.9 Hz, 1H, H-4B), 3.79 (dt, $J_{4a,9b}$=9.9 Hz, 1H, H-4a), 3.47 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.6–126.7 (C_6H_5), 133.4 (C-9a), 117.0 (C-9), 102.3 (C-2), 100.7 (C-6), 84.4 (C-6a), 78.4 (C-8), 78.2 (C-9b), 69.9 (C-4), 65.1 (C-4a), 55.7 (OMe). HRMS $C_{16}H_{18}O_5Na$: calcd 313.1052, found 313.1066.



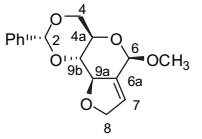
*5.6.3. (2R,4aR,6S,9aR,9bS)-4,4a,6,8,9a,9b-Hexahydro-6-methoxy-2-phenyl-furo[2′,3′:4,5]pyrano[3,2-d]1,3-dioxin (**9**).* Following the general method **E**, compound **7** (100 mg, 0.25 mmol), Bu_2SnO (62.5 mg, 0.25 mmol) and $TMSN_3$ (0.05 mL, 0.37 mmol), in toluene (4 mL) reacted for 17 h at 100–103 °C, to give after flash chromatography (EtOAc/cyclohexane, 3/7), compound **9** (48 mg, 66%), as a white solid: mp 146–148 °C; $[\alpha]_D^{20}$ +75 (*c* 0.14, MeOH); IR (ATR) ν 2107, 1453, 1378, 1180, 1084, 1053, 1058, 961 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.35 (m, 5H, C_6H_5), 5.92 (br s, 1H, H-7), 5.60 (s, 1H, H-2), 5.33 (s, 1H, H-6), 5.08–5.10 (m, 1H, H-9a), 4.76–4.78 (m, 2H, H-8), 4.34 (dd, $J_{4a,4A}$=4.9 Hz, $J_{4A,4B}$=10.0 Hz, 1H, H-4A), 3.93 (dt, $J_{4a,4B}$=$J_{4a,9b}$=9.5 Hz, 1H, H-4a), 3.79 (t, $J_{4a,4B}$=10.0 Hz, 1H, H-4B), 3.66 (t, $J_{9a,9b}$=9.5 Hz, 1H, H-9b), 3.45 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5–126.7 (C_6H_5), 135.2 (C-6a), 123.8 (C-7), 101.8 (C-2), 97.7 (C-6), 84.4 (C-9b), 83.5 (C-9a), 76.0 (C-8), 69.3 (C-4), 62.2 (C-4a), 55.3 (OMe); HRMS $C_{16}H_{18}NO_5Na$: calcd 313.1052, found 313.1053.

*5.6.4. Methyl 4,6-O-benzylidene-3-C-cyano-3-O-mesyl-2-O-methyl-β-D-gluco(allo)pyranoside (**12**) and methyl 4,6-O-benzylidene-2-C-cyano-2-O-mesyl-3-O-methyl-β-D-gluco(manno)pyranoside (**13**).* Following the general method **B**, a mixture of **10** and **11**[11] (3.27 g (10.92 mmol)), PCC (5.4 g, 25.11 mmol), molecular sieves 3 Å (5.4 g) and CH_2Cl_2 (2×50 mL) reacted for 18 h to give a crude ulose (2.35 g), which was used in the next step without further purification. Following the general method **D**, to a solution of this crude ulose in ethyl ether (160 mL) and water (80 mL) were added $NaHCO_3$ (1.34 g, 15.98 mmol) and NaCN (392 mg, 15.98 mmol). After stirring for 23 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (40 mL) followed by addition of Et_3N (2.0 mL, 14.35 mmol) and MsCl (3.4 mL, 43.94 mmol). After 4 h 45 min and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 5/5) to give a mixture of diastereoisomers **12** [584 mg (13%), 73/27] and a mixture of diastereoisomers **13** [1.52 g (34%), 90/10]. Compound **12**: colourless oil; IR (ATR) ν 2358, 1451, 1363,

1183, 1083, 1012, 961, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.28 (m, 5H, 2×C_6H_5), 5.64, 5.60 (s, 1H, 2×H-7), 4.58, 4.57 (d, $J_{1,2}$=7.6 Hz, 1H, 2×H-1), 4.46 (m, 1H, 2×H-6A), 4.13 (m, 1H, 2×H-4), 3.87–3.78 (m, 2H, 2×H-6B, 2×H-5), 3.76, 3.72 (s, 3H, 2×OMe), 3.62, 3.58 (s, 3H, 2×OMe), 3.56 (m, 1H, 2×H-2), 3.18 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.7–126.6 (2×C_6H_5), 112.3 (2×CN), 104.0 (2×C-1), 102.3 (2×C-7), 82.2/83.3 (C-2), 83.2 (2×C-3), 80.0/79.0 (C-4), 69.0/68.7 (C-6), 65.4/63.3 (C-5), 62.5/62.2 (OMe), 58.3/58.0 (OMe), 40.5 (2×OSO_2CH_3). HRMS $C_{17}H_{21}NO_8NaS$: calcd 422.0886, found 422.0886. Compound **13** (major isomer): white solid; mp 151–153 °C; IR (ATR) ν 2249, 1456, 1372, 1186, 1097, 965, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.38 (m, 5H, C_6H_5), 5.61 (s, 1H, H-7), 4.79 (s, 1H, H-1), 4.41 (dd, $J_{5,6A}$=4.9 Hz, $J_{6A,6B}$=10.5 Hz, 1H, H-6A), 3.98–3.85 (m, 3H, H-3, H-4, H-6B), 3.74 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.55 (m, 1H, H-5), 3.27 (s, 3H, OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.0–126.3 (C_6H_5), 112.4 (CN), 101.0, 101.8 (C-7, C-1), 83.4 (C-2), 81.9, 80.8 (C-3, C-4), 68.4 (C-6), 67.2 (C-5), 62.3 (OMe), 58.5 (OMe), 40.7 (OSO_2CH_3). HRMS $C_{17}H_{21}NO_8NaS$: calcd 422.0886, found 422.0886.

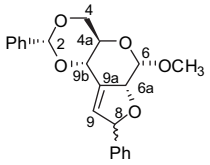


*5.6.5. (2R,4aR,6R,6aR,9bS)-4,4a,6,6a,8,9b-Hexahydro-6-methoxy-2-phenyl-furo[3′,2′:4,5]pyrano[3,2-d]1,3-dioxin (**14**).* Following the general method **E**, compound **12** (169 mg, 0.42 mmol), Bu_2SnO (105 mg, 0.42 mmol) and $TMSN_3$ (0.10 mL, 0.75 mmol) in toluene (6.7 mL) reacted for 17 h at 103 °C to give after flash chromatography (EtOAc/cyclohexane, 2/8), compound **14** (5 mg, 4%) as a white solid: mp 177–179 °C; $[\alpha]_D^{20}$ −28 (*c* 0.06, $CHCl_3$); IR (ATR) ν 2109, 1452, 1369, 1210, 1092, 1022, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.35 (m, 5H, C_6H_5), 5.81–5.80 (m, 1H, H-9), 5.67 (s, 1H, H-2), 4.82–4.79 (m, 2H, H-8), 4.60–4.55 (m, 1H, H-6a), 4.39 (dd, $J_{4a,4A}$=4.7 Hz, $J_{4A,4B}$=10.5 Hz, 1H, H-4A), 4.32 (d, $J_{6,6a}$=7.1 Hz, 1H, H-6), 4.27–4.23 (m, 1H, H-9b), 3.90 (t, $J_{4a,4B}$=10.5 Hz, 1H, H-4B), 3.60 (s, 3H, OMe), 3.37 (dt, $J_{9b,4a}$=9.3 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5 (C-9a), 136.2–126.6 (C_6H_5), 117.8 (C-9), 107.4 (C-6), 102.2 (C-2), 86.3 (C-6a), 78.1 (C-9b), 77.7 (C-8), 71.3 (C-4a), 69.6 (C-4), 57.6 (OMe) HRMS $C_{16}H_{18}O_5Na$: calcd 313.1052, found 313.1059.



*5.6.6. (2R,4aR,6R,9aR,9bS)-4,4a,6,8,9a,9b-Hexahydro-6-methoxy-2-phenyl-furo[2′,3′:4,5]pyrano[3,2-d]1,3-dioxin (**15**).* Following the general method **E**, compound **13** (400 mg, 1.0 mmol), Bu_2SnO (249 mg, 1.0 mmol) and $TMSN_3$ (0.23 mL, 1.73 mmol) in toluene (16 mL) reacted for 16 h 30 min at 98–103 °C to give after flash chromatography (EtOAc/cyclohexane, 3/7), compound **15** (214 mg, 73%) as a white solid: mp 176–8 °C; $[\alpha]_D^{20}$ −75 (*c* 0.22, $CHCl_3$); IR (ATR) ν 1454, 1382, 1207, 1076, 1049, 1010, 946 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.35 (m, 5H, C_6H_5), 6.00 (br s, 1H, H-7), 5.59 (s, 1H, H-2), 5.06 (s, 1H, H-6), 4.92–4.90 (m, 1H, H-9a), 4.79–4.77 (m, 2H, H-8), 4.39 (dd, $J_{4a,4A}$=5.0 Hz, $J_{4A,4B}$=10.5 Hz, 1H, H-4A), 3.85 (t, $J_{4a,4B}$=10.2 Hz, 1H, H-4B), 3.64 (t, $J_{9a,9b}$=$J_{9b,4a}$=9.5 Hz, 1H, H-9b), 3.64 (s, 3H, OMe), 3.52 (dt, 1H, H-4a); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5–126.6 (C_6H_5), 135.7 (C-6a), 122.8 (C-7), 101.7 (C-2), 99.7 (C-6), 85.0 (C-9a), 83.8 (C-9b), 76.5 (C-8), 69.2 (C-4), 66.2 (C-4a), 57.6 (OMe). HRMS $C_{16}H_{18}O_5Na$: calcd 313.1052, found 313.1057.

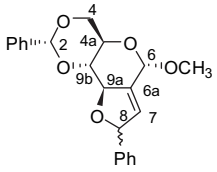
*5.6.7. Methyl 4,6-O-benzylidene-3-C-cyano-3-O-mesyl-2-O-benzyl-α-D-gluco(allo)pyranoside (**17**).* Following the general method **B**, **16**[11] (4.35 g, 11.69 mmol), PCC (5.56 g, 26.81 mmol), molecular sieves 3 Å (10 g) and CH_2Cl_2 (2×50 mL) reacted for 18 h to give crude ulose (3.73 g), which was used in the next step without further purification. Following the general method **D**, to a solution of this crude ulose in CH_2Cl_2 (190 mL) were added $NaHCO_3$ (1.69 g, 20.07 mmol) in water (95 mL) and KCN (654 mg, 10.03 mmol). After stirring for 2 days and 12 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (190 mL) followed by addition of Et_3N (14.3 mL, 102.6 mmol) and MsCl (4.3 mL, 55.20 mmol). After 2 days and 4 h and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 1/1) to give a mixture of the two diastereoisomers **17** [693 mg (14%) 73/27 ratio], and a mixture of unreacted ulose, cyanohydrins and cyanomesylate (1.65 g). Compound **17**: solid; IR (ATR) ν 2253, 1962, 1360, 1184, 1078, 970, 947 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.37 (m, 10H, 2×C_6H_5), 5.62, 5.60 (s, 1H, 2×H-7), 5.03/4.88 (d, $J_{A,B}$=11.9 Hz, 1H, O$CH_2C_6H_5$), 4.94/4.75 (d, 1H, OCH_2Ph), 4.65/4.59 (d, $J_{1,2}$=3.6 Hz, 1H, H-1), 4.34 (m, 1H, 2×H-6A), 4.19–4.11 (m, 1H, 2×H-5), 3.95/3.89 (d, 1H, H-2), 3.83 (d, $J_{4,5}$=9.5 Hz, 1H, 2×H-4), 3.71 (t, $J_{6A,6B}$=$J_{5,6B}$=10.4 Hz, 1H, 2×H-6B), 3.43/3.41 (s, 3H, 2×OMe), 3.23/3.14 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.0–126.7 (2×C_6H_5), 115.5/112.6 (CN), 102.4/102.3 (C-7), 98.8/98.5 (2×C-1), 79.7/79.2 (C-4), 78.8/77.1 (C-2), 76.5 (2×C-3), 74.8/74.2 (O$CH_2C_6H_5$), 68.9 (2×C-6), 61.4/58.4 (C-5), 56.8/56.5 (OMe), 40.7, 40.5 (OSO_2CH_3). HRMS $C_{23}H_{25}NO_8NaS$: calcd 498.1199, found 498.1195.



*5.6.8. (2R,4aR,6S,6aR,8R,9bS)- and (2R,4aR,6S,6aR,8S,9bS)-6-Methoxy-4,4a,6,6a,9b-pentahydro-2,8-di-phenyl-furo[3′,2′:4,5]pyrano[3,2-d]1,3-dioxin (**18**).* Following the general method **E**, products **17** (200 mg, 0.42 mmol), Bu_2SnO (105 mg, 0.42 mmol) and $TMSN_3$ (0.09 mL, 0.68 mmol), in toluene (8.5 mL) reacted for 18 h at 108 °C to give after flash chromatography (EtOAc/cyclohexane, 2/8), compounds **18** [34 mg (22%), 65/35 ratio], and unreacted starting material (**17**) (35 mg, 17%). Compound **18**: solid; IR (ATR) ν 1647, 1454, 1370, 1091, 1043, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57–7.30 (m, 10H, 4×C_6H_5), 6.01, 5.94 (m, 1H, 2×H-8), 5.88, 5.74 (m, 1H, 2×H-9), 5.69 (s, 1H, 2×H-2), 5.06–4.98 (m, 2H, 2×H-6, 2×H-6a), 4.39–4.31 (m, 2H, 2×H-9b, 2×H-4A), 3.98–3.82 (m, 2H, 2×H-4a, 2×H-4B), 3.53/3.50 (s, 3H, 2×OMe); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.6/141.2 (C-9a), 137.6–126.7 (4×C_6H_5), 120.8/120.6 (C-9), 102.3 (2×C-2), 100.1 (2×C-6), 90.9/90.6 (2×C-8), 84.2 (2×C-6a), 78.0/77.9 (C-9b), 66.9 (2×C-4) 65.4/64.6 (2×C-4a), 55.8/55.6 (OMe). HRMS $C_{22}H_{22}O_5Na$: calcd 389.1365, found 389.1362.

*5.6.9. Methyl 4,6-O-benzylidene-2-C-cyano-2-O-mesyl-3-O-benzyl-α-D-manno(gluco)pyranoside (**20**).* Following the general method **C**, product **19**[13] (1.0 g, 2.68 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with Dess–Martin reagent (3.42 g, 8.06 mmol, 3 equiv) in anhydrous CH_2Cl_2 (20 mL) for 24 h to give the crude ulose (430 mg). Following the general method **D**, to a solution of the crude ulose (300 mg, 0.81 mmol) in MeOH (20 mL), reacted with $Ti(O^iPr)_4$ (0.48 mL, 1.62 mmol) and TMSCN (0.22 mL, 1.62 mmol) to provide the

crude cyanohydrins, which were dissolved in CH_2Cl_2 (20 mL). After addition of Et_3N (0.91 mL, 6.48 mmol) and CH_3SO_2Cl (0.34 mL, 4.46 mmol), the reaction mixture was stirred overnight; then, extracted and the residue purified by flash chromatography (EtOAc/cyclohexane, 25/75) to give a mixture of diastereoisomers **20** [270 mg (70%), (75/25 ratio)] as a slight yellow syrup; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.36 (m, 5H, 2×C_6H_5), 5.64/5.63 (s, 2H, H-7), 5.44/5.28 (s, 2H, H-1), 4.97–4.81 (m, 3H, OC*H*$_2C_6H_5$), 4.78 (d, J=11.8 Hz, 1H, OC*H*$_2C_6H_5$), 4.37–4.29 (m, 3H, 2×H-6A, H-4), 4.20 (d, $J_{3,4}$=9.6 Hz, 1H, H-4), 4.05 (d, 1H, H-3), 4.01–3.97 (m, 2H, 2×H-3, H-5), 3.93–3.89 (m, 3H, H-5, 2×H-6B), 3.55 (s, 3H, 2×OCH_3), 3.25/3.12 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9–137.2, 129.6–126.4 (2×C_6H_5), 114.6/114.5 (CN), 102.2/102.1 (C-7), 99.6/99.5 (C-1), 80.9/79.5 (C-2), 80.4/78.4, 78.0/77.2 (2×C-3, 2×C-4), 76.5/76.4 ($OCH_2C_6H_5$), 68.8/68.7 (C-6), 63.9/63.1 (C-5), 57.0/56.9 (OCH_3), 40.2 (2×OSO_2CH_3). HRMS $C_{23}H_{25}NO_8NaS$: calcd 498.1199, found 498.1187.

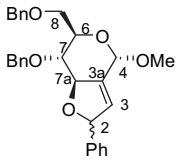


*5.6.10. (2R,4aR,6S,8R,9aR,9bS)- and (2R,4aR,6S,8S,9aR,9bS)-6-Methoxy-4,4a,6,9a,9b-pentahydro-2,8-di-phenyl-furo[2′,3′:4,5]pyrano[3,2-d]1,3-dioxin (**21**).* Following the general method **E**, compound **20** (500 mg, 1.05 mmol), Bu_2SnO (260 mg, 1.05 mmol) and $TMSN_3$ (0.28 mL, 2.10 mmol) in toluene (10.5 mL) reacted for 18 h at 100 °C to give after flash chromatography (EtOAc/cyclohexane, 1/9), products **21** (196 mg, 51%, 25/75 ratio) as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57–7.42 (m, 10H, 4×C_6H_5), 5.96–5.89 (m, 2H, 2×H-7, 2×H-8), 5.66 (s, 1H, 2×H-2), 5.40/5.38 (s, 1H, 2×H-6), 5.28–5.23 (m, 1H, 2×H-9b), 4.40 (dd, $J_{4a,4A}$=4.8 Hz, $J_{4A,4B}$=10.5 Hz, 1H, 2×H-4A), 4.09, 3.98 (m, 1H, 2×H-4a), 3.91–3.79 (m, 2H, 2×H-4B, 2×H-9a), 3.49 (s, 3H, 2×OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9 (2×C-6a), 137.6–135.6, 129.4–126.8 (4×C_6H_5, 2×C-7), 101.8 (2×C-2), 97.8/97.6 (C-6), 88.8/88.4 (C-8), 85.3/85.0 (C-9a), 83.7/83.6 (C-9b), 69.3 (C-4), 62.3/62.2 (C-4a), 55.3 (2×OCH_3). HRMS $C_{22}H_{22}O_5Na$: calcd 389.1365, found 389.1356.

*5.6.11. Benzyl 4,6-O-benzylidene-2-C-cyano-2-O-mesyl-3-O-benzyl-α-D-gluco(manno)pyranoside (**23**).* Following the general method **B**, product **22**[14] (1.4 g, 3.12 mmol), PCC (1.5 g, 7.19 mmol), molecular sieves 3 Å (2.8 g) and CH_2Cl_2 (2×14 mL) reacted for 17 h to give a crude ulose (937 mg), which was used in the next step without further purification. Following the general method **D**, to a solution of this crude ulose in ethyl ether (40 mL) and water (15 mL) were added $NaHCO_3$ (353 g, 4.2 mmol) and NaCN (103 mg, 2.1 mmol). After stirring for 2 days and 12 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (14 mL) followed by addition of Et_3N (2.9 mL, 20.80 mmol) and MsCl (0.89 mL, 11.5 mmol). After 19 h 30 min and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 3/7) to give compound diastereomerically pure **23** (230 mg, 20%) and a complex mixture of cyanomesylate and unreacted alcohol (632 mg). Compound **23**: oil; IR (ATR) ν 2351, 1455, 1374, 1185, 1076, 1017, 962 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.33 (m, 15H, 3×C_6H_5), 5.66 (s, 1H, H-7), 5.64 (s, 1H, H-1), 4.98, 4.88 (d, J=11.6 Hz, 2H, OC*H*$_2C_6H_5$), 4.78, 4.74 (d, 2H, OC*H*$_2C_6H_5$), 4.27–4.22 (m, 2H, H-6A, H-3), 4.04–3.95 (m, 2H, H-5, H-4), 3.85 (t, $J_{6A,6B}$=$J_{5,6B}$=9.9 Hz, 1H, H-6B), 3.09 (s, 3H, OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.1–126.4 (3×C_6H_5), 114.4 (CN), 102.4 (C-7), 98.4 (C-1), 80.9 (C-2), 80.5, 78.2 (C-3, C-4), 76.5 (OC*H*$_2C_6H_5$), 72.4 (OC*H*$_2C_6H_5$), 68.7 (C-6), 63.4 (C-5), 40.2 (OSO_2CH_3). HRMS $C_{29}H_{29}NO_8NaS$: calcd 574.1512, found 574.1500.

*5.6.12. (2R,4aR,6S,8R,9aR,9bS)- and (2R,4aR,6S,8S,9aR,9bS)-6-Benzyloxy-4,4a,6,9a,9b-pentahydro-2,8-di-phenyl-furo[2′,3′:4,5]pyrano[3,2-d]1,3-dioxin (**24**).* Following the general method **E**, compound **23** (100 mg, 0.18 mmol), Bu_2SnO (45 mg, 0.18 mmol) and $TMSN_3$ (0.04 mL, 0.31 mmol) in toluene (3 mL) reacted for 18 h at 93–96 °C to give after flash chromatography (EtOAc/cyclohexane, 2/8), compound **24** [41 mg (52%), 25/75 ratio] as a white solid; IR (ATR) ν 2922, 2108, 1454, 1373, 1093, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58–7.36 (m, 15H, 6×C_6H_5), 5.95–5.91 (m, 1H, 2×H-7), 5.88–5.87 (m, 1H, 2×H-8), 5.68/5.65 (s, 1H, 2×H-2), 5.60/5.57 (s, 1H, 2×H-6), 5.38–5.28 (m, 1H, 2×H-9a), 4.84–4.80 (m, 1H, 2×OC*H*$_2C_6H_5$), 4.68–4.64 (m, 1H, 2×OC*H*$_2C_6H_5$), 4.35–4.30 (m, 1H, 2×H-4A), 4.14–4.10 (m, 1H, 2×H-4a), 3.89–3.78 (m, 2H, 2×H-9b, 2×H-4B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9 (2×C-6a), 137.5–127.4 (6×C_6H_5), 126.8/126.5 (2×C-7), 101.8 (2×C-2), 96.0 (2×C-6), 88.8/88.4 (C-8), 85.3/85.0 (C-9b), 83.7 (2×C-9a), 69.9/69.6 ($OCH_2C_6H_5$), 69.3 (2×C-4), 62.5 (2×C-4a). HRMS $C_{28}H_{26}O_5Na$: calcd 465.1678, found 465.1688.

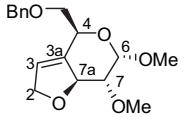
*5.6.13. Methyl 3,4,6-tri-O-benzyl-2-C-cyano-3-O-mesyl-α-D-gluco(manno)pyranoside (**26**).* Following the general method **B**, compound **25**[15] (1.0 g, 2.15 mmol), PCC (1.16 g, 5.38 mmol), molecular sieves 3 Å (2.5 g) and CH_2Cl_2 (2×30 mL) reacted for 24 h to give the crude ulose (950 mg), which was used in the next step without further purification. Following the general method **D**, to a solution of this crude ulose in CH_2Cl_2 (30 mL) were added $NaHCO_3$ (361 mg, 4.3 mmol) in water (4.98 mL) and KCN (299 mg, 4.60 mmol). After stirring for 27 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (30 mL) followed by addition of Et_3N (2.41 mL, 17.2 mmol) and MsCl (0.91 mL, 11.82 mmol). After 5 h and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 20/80) to give an unseparable mixture of diastereoisomers **26** [637 mg (52%), 78/22 ratio] as a slight yellow syrup; IR (ATR) ν 2929–2864, 1454, 1372, 1185, 1061, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.21 (m, 15H, 6×C_6H_5), 5.49/5.40 (s, 1H, 2×H-1), 5.09–4.54 (m, 6H, 6×OC*H*$_2C_6H_5$), 4.32/4.23 (d, $J_{3,4}$=8.8 Hz, 1H, 2×H-3), 4.02–3.93 (m, 2H, 2×H-4, 2×H-5), 3.83 (dd, $J_{5,6A}$=4.0 Hz, $J_{6A,6B}$=11.0 Hz, 1H, 2×H-6A), 3.75 (dd, $J_{5,6B}$=1.5 Hz, 1H, 2×H-6B), 3.57/3.55 (s, 3H, 2×OCH_3), 3.21/3.06 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4–137.4 (6×C*q* C_6H_5), 129.0–128.0 (C_6H_5), 115.2/114.5 (CN), 98.3 (2×C-1), 81.5/78.8 (C-2), 77.0/74.7 (C-4), 77.0/76.9/76.0/75.9/74.0/73.9 ($OCH_2C_6H_5$), 72.2/71.3 (C-5), 68.5/68.4 (C-6), 56.8/56.7 (OCH_3), 40.5/40.1 (OSO_2CH_3). HRMS $C_{27}H_{32}N_3O_{10}S$: calcd 590.1808, found 590.1812.



*5.6.14. (2R,4S,6R,7S,7aR)- and (2S,4S,6R,7S,7aR)-7-(Benzyloxy)-6-(benzyloxymethyl)-4-methoxy-2-phenyl-4,6,7,7a-tetrahydro-2H-furo[3,2-c]pyran (**27**).* Following the general method **E**, compounds **26** (325 mg, 0.57 mmol), Bu_2SnO (142 mg, 0.57 mmol) and $TMSN_3$ (0.15 mL, 1.14 mmol) in toluene (5.7 mL) reacted for 19 h at 100 °C to give after flash chromatography (EtOAc/cyclohexane, 15/85), compound **27** [117 mg (44%), 72/28 ratio] and unreacted starting material (**26**) (48 mg (6.7%)). Compound **27**: yellow syrup; IR (ATR) ν 2917–2856, 1495, 1454, 1357, 1099, 1064, 1026, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.25 (m, 15H, 6×C_6H_5), 5.94/5.91 (d, $J_{7,7a}$=4.4 Hz, 1H, 2×H-7), 5.87/5.80 (m, 1H, 2×H-3), 5.41/5.38 (s, 1H, 2×H-4), 5.31/5.23 (m, 1H, 2×H-2), 5.07–4.96/4.72–4.58 (m, 4H, 4×OC*H*$_2C_6H_5$), 4.02–

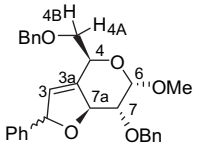
3.90 (m, 1H, 2×H-6), 3.85–3.81 (m, 2H, 2×H-8a, 2×H-8b), 3.79–3.72 (m, 1H, 2×H-7a), 3.49–3.48 (s, 3H, 2×OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4 (2×C-3a), 138.6–135.8 (6×C*q* C_6H_5), 129.0–126.9 (6×C_6H_5), 125.8/125.3 (C-3), 97.0/96.7 (C-4), 88.6/88.5 (C-7), 88.3 (2×C-2), 80.5/80.4 (C-7a), 73.9 (2×O*C*$H_2C_6H_5$), 73.3/73.1 (2×O*C*$H_2C_6H_5$), 69.8 (2×C-6), 69.3/69.1 (2×C-8), 55.1 (2×OCH_3). HRMS $C_{29}H_{30}O_5Na$: calcd 481.2000, found 481.1991.

*5.6.15. Methyl 2,3-di-O-methyl-6-O-benzyl-4-C-cyano-4-O-mesyl-α-D-gluco(galacto)pyranoside (**30**).* Following the general method **C**, product **28**[16] (1.88 g, 6.02 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with Dess–Martin reagent (7.67 g, 18.1 mmol, 3 equiv) in anhydrous CH_2Cl_2 (20 mL) for 24 h to give the crude ulose (1.87 g, 6.02 mmol). Following the general method **D**, this ulose reacted with $Ti(O^iPr)_4$ (3.61 mL, 12.05 mmol) and TMSCN (1.61 mL, 12.05 mmol) in MeOH (20 mL) to give the crude cyanohydrins, which were dissolved in CH_2Cl_2 (20 mL). After addition of Et_3N (6.78 mL, 48.2 mmol) and CH_3SO_2Cl (2.57 mL, 33.1 mmol), the reaction mixture was stirred overnight then, extracted and the residue purified by flash chromatography (EtOAc/cyclohexane, 35/65) to provide a mixture of diastereomers **30** [1.56 g (62%), 56/44 ratio] as a slight yellow syrup. A fraction of pure isomer has been isolated for analysis: oil; $[\alpha]^{20}_D$ +91 (*c* 0.26, CH_2Cl_2); IR (ATR) ν 2970–2849, 1456, 1364, 1187, 1155, 1108, 1057, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.26 (m, 5H, C_6H_5), 4.91 (d, $J_{1,2}$=3.5 Hz, 1H, H-1), 4.61 (d, *J*=11.9 Hz, 1H, O*CH*$_2C_6H_5$), 4.55 (d, 1H, O*CH*$_2C_6H_5$), 4.12 (dd, 1H, H-5), 3.98 (dd, $J_{5,6A}$=2.5 Hz, $J_{6A,6B}$=10.9 Hz, 1H, H-6A), 3.85 (d, $J_{2,3}$=9.6 Hz, 1H, H-3), 3.78 (dd, $J_{5,6B}$=6.8 Hz, 1H, H-6B), 3.66 (s, 3H, OCH_3), 3.52 (m, 4H, H-2, OCH_3), 3.45 (s, 3H, OCH_3), 3.14 (s, 3H, OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.0–128.1 (C_6H_5), 112.9 (CN), 97.2 (C-1), 81.6, 81.4 (C-2, C-3), 80.5 (C-4), 74.0 (O*CH*$_2C_6H_5$), 70.2 (C-5), 68.3 (C-6), 62.3, 59.6, 56.1 (3×OCH_3), 40.2 (OSO_2CH_3). HRMS $C_{18}H_{25}O_8NSNa$: calcd 438.1196, found 438.1199.



*5.6.16. (4S,6S,7R,7aS)-4-(Benzyloxymethyl)-6,7-dimethoxy-4,6,7,7a-tetrahydro-2H-furo[3,2-c]pyran (**32**).* Following the general method **E**, compound **30** (583 mg, 1.40 mmol), Bu_2SnO (350 mg, 1.40 mmol) and $TMSN_3$ (0.37 mL, 2.80 mmol), in toluene (14 mL) reacted for 19 h at 100 °C to give after flash chromatography (EtOAc/cyclohexane, 30/70), compound **32** (188 mg, 49%): syrup; $[\alpha]^{20}_D$ +85.6 (*c* 0.32, CH_2Cl_2); IR (ATR) ν 2932–2822, 1454, 1201, 1127, 1094, 1045, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.28 (m, 5H, C_6H_5), 5.60 (m, 1H, H-3), 4.94–4.88 (m, 2H, H-6, H-7a), 4.70–4.56 (m, 4H, 2×H-2, O*CH*$_2C_6H_5$), 4.43 (m, 1H, H-4), 3.80 [dd, *J*=4.7 Hz, *J*=10.1 Hz, 1H, $C_6H_5CH_2OCH(A)_2$], 3.74 [dd, *J*=5.9 Hz, 1H, $C_6H_5CH_2OCH(B)_2$], 3.54 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.24 (dd, $J_{6,7}$=3.3 Hz, $J_{7,7a}$=8.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2–128.1 (C_6H_5), 135.8 (C-3a), 119.6 (C-3), 98.9 (C-6), 85.1 (C-7a), 83.9 (C-7), 75.6/73.9 (C-2, O*CH*$_2C_6H_5$), 70.4 ($C_6H_5CH_2OCH_2$), 65.7 (C-4), 58.8/56.0 (2×OCH_3). HRMS $C_{17}H_{22}O_5Na$: calcd 329.1373, found 329.1365.

*5.6.17. Methyl 2,3,6-tri-O-benzyl-4-C-cyano-4-O-mesyl-α-D-gluco(galacto)pyranoside (**31**).* Following the general method **C**, compound **29**[17] (941 mg, 2.02 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with Dess–Martin reagent (2.58 g, 6.06 mmol, 3 equiv) in anhydrous CH_2Cl_2 (20 mL) for 24 h to give the corresponding ulose (974 mg, 93%). Following the general method **D**, this crude ulose was reacted with $Ti(O^iPr)_4$ (3.78 mL, 3.78 mmol) and TMSCN (0.50 mL, 3.78 mmol) in MeOH (20 mL) to give the crude cyanohydrins, which were dissolved in CH_2Cl_2 (20 mL). After addition of Et_3N (2.16 mL, 15.37 mmol) and CH_3SO_2Cl (0.81 mL, 10.57 mmol), the reaction mixture was stirred overnight; then, extracted and the residue purified by flash chromatography (EtOAc/cyclohexane, 20/80) to give a mixture of diastereoisomers **31** [960 mg (89%), 70/30 ratio] as slight yellow syrup; IR (ATR): ν 1454, 1371, 1186, 1112, 1028, 961 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.36 (m, 15H, 6×C_6H_5), 5.04 (m, 1H, O*CH*$_2C_6H_5$), 4.89–4.57 (m, 6H, 2×H-1, 5×O*CH*$_2C_6H_5$), 4.33–4.23 (m, 2H, 2×H-3, 2×H-5), 4.08–4.01 (m, 1H, 2×H-6A), 3.92–3.75 (m, 2H, 2×H-2, 2×H-6B), 3.47/3.45 (s, 3H, 2×OSO_2CH_3), 3.03/2.92 (s, 3H, 2×OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.1–137.2, 129.2–128.0 (6×C_6H_5), 114.4/113.0 (CN), 98.2/97.8 (C-1), 80.5/79.1 (C-4), 80.1/79.8/76.0 (2×C-2, 2×C-3), 77.6/76.6/74.3/74.2/74.1 (6×O*CH*$_2C_6H_5$), 71.4/70.3 (C-5), 68.8/68.4 (C-6), 56.3/56.2 (OCH_3), 40.4/40.1 (OSO_2CH_3). HRMS $C_{30}H_{33}O_8NSNa$: calcd 590.1848, found 590.1825.



*5.6.18. (2S,4S,6S,7R,7aS)- and (2R,4S,6S,7R,7aS)-7-Benzyloxy-4-(benzyloxymethyl)-6,7-dimethoxy-2-phenyl-4,6,7,7a-tetrahydro-2H-furo[3,2-c]pyran (**33**).* Following the general method **E**, product **31** (984 mg, 1.73 mmol), Bu_2SnO (431 mg, 1.73 mmol) and $TMSN_3$ (0.46 mL, 3.46 mmol) in toluene (17.3 mL), in 17 h at 100 °C, gave after flash chromatography (EtOAc/cyclohexane, 30/70), compound **33** [393 mg (49%) 19/81 ratio] as a slight yellow syrup; IR (ATR) ν 2929–2835, 1454, 1089, 1044, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 15H, 3×C_6H_5), 5.88 (m, 1H, H-2), 5.58 (m, 1H, H-3), 5.22 (m, 1H, H-7a), 4.93 (d, *J*=12.5 Hz, 1H, O*CH*$_2C_6H_5$), 4.87 (d, $J_{6,7}$=3.4 Hz, 1H, H-6), 4.81 (d, 1H, O*CH*$_2C_6H_5$), 4.62 (m, 2H, O*CH*$_2C_6H_5$), 4.55 (m, 1H, H-4), 3.83 [dd, $J_{4,4A}$=4.7 Hz, $J_{4A,4B}$=10.2 Hz, 1H, $C_6H_5CH_2O$-*CH*$(A)_2$], 3.75 [dd, $J_{4,4B}$=5.9 Hz, 1H, $C_6H_5CH_2OCH(B)_2$], 3.60 (dd, $J_{7,7a}$=8.7 Hz, 1H, H-7), 3.52 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.6 (C-3a), 138.6–127.3 (2×C_6H_5), 123.6 (C-3), 99.7 (C-6), 88.3 (C-2), 85.8 (C-7a), 81.3 (C-7), 73.9/72.4 (O*CH*$_2C_6H_5$), 70.5 [$C_6H_5CH_2OCH_2$], 65.8 (C-4), 56.1 (OCH_3). HRMS $C_{29}H_{30}O_5Na$: calcd 481.2000, found 481.1991.

*5.6.19. Methyl 2,3-di-O-methyl-6-O-benzyl-4-C-cyano-4-O-mesyl-β-D-gluco(galacto)pyranoside (**36**).* Following the general method **A**, product **34**[18] (850 mg, 2.72 mmol), DMSO (0.58 mL, 8.17 mmol), oxalyl chloride (0.46 mL, 5.44 mmol) and Et_3N (1.14 mL, 8.17 mmol) in CH_2Cl_2 (20 mL) gave the crude ulose (840 mg), which was used in the next step without further purification. Following the general method **D**, to a solution of the crude ulose in CH_2Cl_2 (20 mL) were added $NaHCO_3$ (457 mg, 5.44 mmol) in water (6.3 mL) and KCN (378 mg, 5.82 mmol). After stirring for 20 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (20 mL) followed by addition of Et_3N (3.06 mL, 21.76 mmol) and MsCl (1.15 mL, 14.96 mmol). After 4 h 30 min and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 25/75) to give an unseparable mixture of the two diastereomers **36** [943 mg (83%), 80/20 ratio]. Compound **36**: slight yellow syrup; $[\alpha]^{20}_D$ −21.0 (*c* 0.23, CH_2Cl_2); IR (ATR) ν 2966–2853, 1453, 1353, 1174, 1080, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.28 (m, C_6H_5), 5.29 (s, 1H, 2×H-1), 4.61 (m, 2H, 2×O*CH*$_2C_6H_5$), 4.27 (m, 1H, 2×H-5), 4.05 (m, 1H, 2×H-6A), 3.86–3.79 (m, 2H, 2×H-3, 2×H-6B), 3.70 (s, 3H, 2×OCH_3), 3.64–3.54 (m, 7H, 4×OCH_3, 1×H-2), 3.25/3.17 (s, 3H, OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.0–128.0 (2×C_6H_5), 114.4/112.9 (CN), 104.7/104.6 (C-1), 85.3/84.2/83.7/80.6 (C-2, C-3), 83.6/80.7 (C-4), 76.0/74.9 (C-5), 74.2/74.0 (O*CH*$_2C_6H_5$), 68.8/68.7 (C-6), 62.8/62.3/61.4/

61.0/57.7/57.6 (OCH_3), 40.4/40.3 (OSO_2CH_3). HRMS $C_{18}H_{25}O_8NSNa$: calcd 438.1183, found 438.1199.

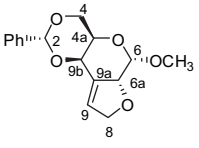
*5.6.20. (4S,6R,7R,7aS)-4-(Benzyloxymethyl)-6,7-dimethoxy-4,6,7,7a-tetrahydro-2H-furo[3,2-c]pyran (**38**) and methyl 6-O-benzyl-4-O-methanosulfonyl-2,3-di-O-methyl-β-D-glucopyranoside (**39**).* Following the general method **E**, compound **36** (720 mg, 1.73 mmol), Bu_2SnO (431 mg, 1.73 mmol) and $TMSN_3$ (0.46 mL, 3.46 mmol) in toluene (17.3 mL), in 16 h at 100 °C, gave after flash chromatography (EtOAc/cyclohexane, 25/75) products **38** (368 mg, 81%) and **39** (106 mg, 13%). Compound **38**: yellow syrup; $[\alpha]_D^{20}$ +71 (*c* 0.05, MeOH); IR (ATR): *ν* 2966–2837, 1755, 1453, 1103, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 7.36–7.28 (m, 5H, C_6H_5), 5.66 (m, 1H, H-3), 4.69–4.57 (m, 5H, H-7a, 2×H-2, $OCH_2C_6H_5$), 4.31 (d, $J_{6,7}$=7.6 Hz, 1H, H-6), 4.22 (m, 1H, H-4), 3.83 [dd, $J_{4,4A}$=5.1 Hz, $J_{4A,4B}$=10.0 Hz, 1H, $C_6H_5CH_2OCH(A)_2$], 3.79 [dd, $J_{4,4B}$=6.1 Hz, 1H, $C_6H_5CH_2OCH(B)_2$], 3.59 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.06 (dd, $J_{7,7a}$=7.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 138.2, 128.8–128.1 (C_6H_5), 136.0 (C-3a), 119.8 (C-3), 103.8 (C-6), 88.3 (C-7a), 85.4 (C-7), 76.4/74.0 (C-2, $OCH_2C_6H_5$), 70.6 ($C_6H_5CH_2OCH_2$), 69.7 (C-4), 59.957.4 (2×OCH_3). HRMS $C_{17}H_{22}O_5Na$: calcd 329.1373, found 329.1365. Compound **39**: yellow syrup; $[\alpha]_D^{20}$ +49 (*c* 0.22, MeOH); IR (ATR) *ν* 2966–2853, 1453, 1353, 1174, 1080, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 7.35–7.26 (5H, m, C_6H_5), 4.59 (m, 2H, $OCH_2C_6H_5$), 4.46 (t, $J_{3,4}$=$J_{4,5}$=9.5 Hz, 1H, H-4), 4.21 (d, $J_{1,2}$=7.7 Hz, 1H, H-1), 3.84 (dd, $J_{4,4A}$=2.2 Hz, $J_{4A,4B}$=10.9 Hz, 1H, H-4A), 3.65 (m, 1H, H-4B), 3.60 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.51 (m, 1H, H-5), 3.32 (t, 1H, H-3) 3.13 (dd, 1H, H-2), 3.07 (s, 3H, OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 138.4–128.0 (C_6H_5), 104.5 (C-1), 84.2 (C-2), 83.6 (C-3), 78.5 (C-4), 74.0 ($OCH_2C_6H_5$), 73.5 (C-5), 69.1 (C-6), 60.9 (OCH_3), 57.5 (OCH_3), 57.5 (OCH_3), 39.0 (OSO_2CH_3). HRMS $C_{17}H_{26}O_8NaS$: calcd 413.1246, found 413.1245.

*5.6.21. Methyl 2,3,6-tri-O-benzyl-4-C-cyano-4-O-mesyl-β-D-gluco (galacto)pyranoside (**37**).* Following the general method **A**, product **35**[17] (411 mg, 0.88 mmol), DMSO (0.19 mL, 2.65 mmol), oxalyl chloride (0.15 mL, 1.77 mmol) and Et_3N (0.37 mL, 2.65 mmol) in CH_2Cl_2 (20 mL) gave the crude ulose (400 mg), which was used in the next step without further purification. Following the general method **D**, to a solution of this crude ulose in CH_2Cl_2 (20 mL) were added $NaHCO_3$ (148 mg, 1.77 mmol) in water (2.1 mL) and KCN (123 mg, 1.89 mmol). After stirring for 20 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (20 mL) followed by addition of Et_3N (0.99 mL, 7.08 mmol) and MsCl (0.37 mL, 4.86 mmol). After 4 h 30 min, and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 60/40) to give an unseparable mixture of the two diastereoisomers **37** [251 mg (50%) 80/20 ratio] as a syrup; IR (ATR) *ν* 2936–2837, 1454, 1371, 1185, 1100, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 7.42–7.35 (m, 15H, 6×C_6H_5), 5.12–4.94 (m, 2H, 2×$OCH_2C_6H_5$), 4.85–4.65 (m, 4H, 4×$OCH_2C_6H_5$), 4.47–4.41 (m, 1H, 2×H-1), 4.17–4.05 (m, 1H, 2×H-6A), 3.97–3.76 (m, 3H, 2×H-6B, 2×H-5, 2×H-3), 3.66–3.59 (m, 4H, 2×H-2, 2×OCH_3), 3.01/2.92 (s, 3H, 2×OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 135.0–127.9 (6×C_6H_5), 114.6/112.9 (CN), 105.0 (2×C-1), 83.1/82.6/82.0/78.5 (C-2, C-3), 80.8/77.9 (C-4), 76.5/75.1 (C-5), 77.5/76.5/75.6/74.3 (6×$OCH_2C_6H_5$), 68.9/68.8 (C-6), 57.9/57.8 (OCH_3), 40.3/40.2 (OSO_2CH_3). HRMS $C_{30}H_{33}NO_8NaS$: calcd 590.1825, found 590.1830.

*5.6.22. (2S,4S,6R,7R,7aS)- and (2R,4S,6R,7R,7aS)-7-(Benzyloxy)-4-(benzyloxymethyl)-6-methoxy-2-phenyl-4,6,7,7a-tetrahydro-2H-furo[3,2-c]pyran (**40**).* Following the general method **E**, product **37** (163 mg, 0.287 mmol), Bu_2SnO (71 mg, 0.287 mmol) and $TMSN_3$ (77 μL, 0.574 mmol) in toluene (2.87 mL), in 15 h at 100 °C, gave after flash chromatography (EtOAc/cyclohexane, 17/83), compound **40** [63 mg (47%) 74/26 ratio] as a slight yellow syrup; IR (ATR) *ν* 3087–3007, 2936–2834, 1453, 1098, 1071, 1043, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 7.37–7.21 (m, 15H, 6×C_6H_5), 5.89 (s, 1H, 2×H-2), 5.73, 5.64 (m, 1H, 2×H-3), 4.97–4.84 (m, 3H, 2×H-7a, 2×$OCH_2C_6H_5$), 4.70–4.57/4.52–4.47 (m, 1H, 2×H-6), 4.35 (m, 1H, 2×H-4), 3.89–3.77 (m, 2H, 4×$BnOCH_2$), 3.63 (m, 3H, 2×OCH_3), 3.57–3.50 (m, 1H, 2×H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 141.8/141.3 (C-3a), 138.7–126.6 (6×C_6H_5), 123.9/123.3 (C-3a), 104.2/104.1 (C-6), 89.1/89.0 (C-2), 88.7/88.4 (C-7a), 84.1/83.7 (C-7), 74.1/74.0/73.7/73.5 ($OCH_2C_6H_5$), 70.7/70.6 ($BnOCH_2$), 69.9/69.8 (C-4), 57.6 (2×OCH_3). HRMS $C_{29}H_{30}O_5Na$: calcd 481.1991, found 481.1999.

*5.6.23. Methyl 4,6-O-benzylidene-2-O-methyl-α-D-galactopyranose (**42**) and methyl 4,6-O-benzylidene-3-O-methyl-α-D-galactopyranose (**43**).* To a solution of commercial methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**41**) (4 g, 14.2 mmol) in toluene (100 mL) and MeOH (10 mL) was added Bu_2SnO (3.53 g, 14.2 mmol). The reaction mixture was stirred at reflux for 25 min until the solution became clear. After stirring overnight at 50 °C, the solvent was removed under vacuum. The residue was dissolved in dry toluene (150 mL) and tetrabutylammonium iodide (5.24 g, 14.2 mmol), iodomethane (3.89 mL, 62.5 mmol) and molecular sieves 4 Å (12.15 g) were added. After stirring overnight at 100 °C and removal of the solvent under vacuum, EtOAc was added to the mixture, which was filtered through a gel silica pad. The filtrate was concentrated and the crude purified by flash chromatography (EtOAc/cyclohexane, 2/8) to afford compounds **42**+**43** (1.72 g, 41%) as a mixture of diastereoisomers in a 55/45 ratio. HRMS $C_{15}H_{20}O_6Na$: calcd 319.1158, found 319.1163.

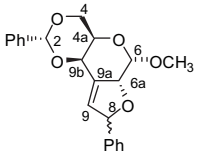
*5.6.24. Methyl 4,6-O-benzylidene-2-C-cyano-2-O-mesyl-3-O-methyl-α-D-galacto(talo)pyranoside (**44**) and methyl 4,6-O-benzylidene-3-C-cyano-3-O-mesyl-2-O-methyl-α-D-galacto(ido)pyranoside (**45**).* Following the general method **A**, compounds **42**+**43** (1.06 g, 3.58 mmol), Dess–Martin periodinane (6.08 g, 14.3 mmol) in CH_2Cl_2 (30 mL) in 12 h led to the corresponding mixture of crude uloses (0.76 g, 72%). HRMS $C_{15}H_{18}O_6Na$: calcd 317.1001, found 317.0988. Following the general method **B**, these uloses (0.76 g, 2.59 mmol), $Ti(O^iPr)_4$ (0.93 mL, 3.11 mmol), TMSCN (0.69 mL, 5.17 mmol) in MeOH (5 mL) led after flash chromatography (EtOAc/cyclohexane, 2/8) to a mixture of cyanohydrins (0.64 g, 76%) in a 49/51 ratio. HRMS $C_{16}H_{19}NO_6Na$: calcd 344.1110, found 344.1108. Following the general method **C**, these cyanohydrins (0.64 g, 1.98 mmol), MsCl (0.84 mL, 11 mmol), Et_3N (0.97 mL, 6.93 mmol) in CH_2Cl_2 (10 mL) in 12 h led after flash chromatography (EtOAc/cyclohexane, 4/6) to compounds **44**+**45** (0.47 g, 59%) as a mixture of diastereoisomers in a 61/39 ratio: syrup; IR (ATR): *ν* 1361, 1192, 1155, 1086, 1055, 1014 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.55–7.34 (m, 15H, 2×C_6H_5), 5.75 (s, 1H, 2×CHC_6H_5), 5.01 (d, $J_{1,2}$=3.9 Hz) and 4.69 (s) (1H, H-1), 4.93 (d, $J_{3,4}$=3.9 Hz, 1H, H-3), 4.31 (dd, $J_{6A,6B}$=12.7 Hz, 2H, H-6A), 4.13 (m, 1H, H-4), 3.98 (m, 1H, H-6B), 3.96 (d, 1H, H-2), 3.70 (m, 1H, H-5), 3.63/3.45 (s, 6H, 4×OCH_3), 3.08 (s, 3H, 2×O_2SCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 137.0–126.4 (2×C_6H_5), 115.0/114.2 (CN), 101.3/101.8 (2×CHC_6H_5), 98.9/96.6 (C-1), 77.6/75.9 (C-2), 76.7/75.2 (C-3), 77.0 (2×C-4), 70.0/68.8 (C-6), 62.4/58.4 (C-5), 60.0/58.7/56.6/56.4 (OCH_3), 40.2/40.0 (O_2SCH_3). HRMS $C_{17}H_{21}NO_8NaS$: calcd 422.0886, found 422.0892.



*5.6.25. (2R,4aR,6S,6aR,9bR)-4,4a,6,6a,8,9b-Hexahydro-6-methoxy-2-phenyl-furo[3′,2′:4,5]pyrano[3,2-d]1,3-dioxin (**46**).* Following the general method **D**, a mixture of compounds **44**+**45** (0.38 g, 0.96 mmol), $TMSN_3$ (0.26 mL, 1.92 mmol) and Bu_2SnO (0.24 g, 9.59 mmol) reacted for 12 h to give after flash chromatography

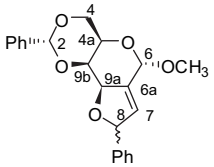
(EtOAc/cyclohexane, 28/72) compound **46** (86 mg, 60%) as a yellow syrup: $[\alpha]_D^{20}$ +85 (*c* 0.1; MeOH); IR (ATR): *ν* 2924, 1454, 1338, 1145, 1051 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.54–7.28 (m, 5H, C_6H_5), 6.01 (d, 1H, H-9), 5.62 (s, 1H, H-2), 5.12 (m, 1H, H-6a), 5.01 (d, $J_{6,6a}$=4.0 Hz, 1H, H-6), 4.81 (s, 1H, H-9b), 4.74 (m, 2H, H-8), 4.36 (dd, $J_{4A,4a}$=1.3 Hz, $J_{4A,4B}$=12.7 Hz, 1H, H-4A), 4.17 (dd, $J_{4A,4a}$=2.0 Hz, 1H, H-4B), 3.59 (m, 1H, H-4a), 3.47 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 138.1 (C-9a), 133.0–126.7 (C_6H_5), 124.3 (C-9), 101.2 (C2), 100.9 (C-6), 81.0 (C-6a), 76.6 (C-8), 73.4 (C-9b), 69.9 (C-4), 63.0 (C-4a), 56.0 (OCH_3) HRMS $C_{16}H_{18}NO_5Na$: calcd 313.1052, found 313.1063.

*5.6.26. Methyl 4,6-O-benzylidene-2-O-benzyl-3-C-cyano-3-O-mesyl-α-D-galacto(ido)pyranoside (**48**).* Following the general method **A**, compound **47**[19] (900 mg, 2.43 mmol), Dess–Martin periodinane (4.11 g, 9.68 mmol) in CH_2Cl_2 (50 mL) for 14 h led to a crude ulose (750 mg, 84%): syrup, $[\alpha]_D^{20}$ +49 (*c* 0.22, $CHCl_3$); IR (ATR) *ν* 1750, 1453, 1372, 1163, 1090, 1050, 1034 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.51–7.35 (m, 10H, 2×C_6H_5), 5.56 (s, 1H, CHC_6H_5), 4.97 (d, *J*=12.6 Hz, 1H, $CH_2C_6H_5$), 4.84 (s, 1H, H-1), 4.63 (m, 2H, $CH_2C_6H_5$, H-4), 4.58 (d, $J_{1,2}$=4.0 Hz, 1H, H-2), 4.29 (d, $J_{6A,6B}$=12.4 Hz, 1H, H-6A), 4.09 (d, 1H, H-6B), 4.02 (s, 1H, H-5), 3.48 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 199.1 (C-3), 137.5–126.6 (C_6H_5), 102.6 (CHC_6H_5), 100.9 (C-1), 82.1 (C-4), 79.6 (C-3), 73.1 ($CH_2C_6H_5$), 69.1 (C-6), 64.7 (C-5), 56.2 (OCH_3); HRMS $C_{21}H_{22}O_6Na$: calcd 393.1314, found 393.1305. Following the general method **B**, the crude ulose (0.11 g, 0.29 mmol), Ti(O^{i}Pr)$_4$ (0.11 mL, 0.35 mmol), TMSCN (0.08 mL, 0.59 mmol) in MeOH (5 mL) led after flash chromatography (EtOAc/cyclohexane, 3/7) to an intermediate cyanohydrin (one diastereomer) (0.10 g, 85%) as a yellow syrup {$[\alpha]_D^{20}$ +90 (*c* 0.28, $CHCl_3$)}; IR (ATR) *ν* 2914, 1450, 1371, 1250, 1147, 1109, 1082, 1064 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.50–7.28 (m, 10H, 2×C_6H_5), 5.40 (s, 1H, CHC_6H_5), 5.00 (m, 1H, H-1), 4.86 (m, 2H, $CH_2C_6H_5$), 4.24 (m, 3H, $CH_2C_6H_5$, H-4), 4.12 (d, $J_{6A,6B}$=12.7 Hz, 1H, H-6A), 4.11 (d, 1H, H-6B), 4.01 (m, 1H, H-2), 3.64 (s, 1H, H-5), 3.48 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 137.4–126.1 (C_6H_5), 118.5 (CN), 102.2 (CHC_6H_5), 101.8 (C-1), 73.8 (C-2), 73.4 (C-4), 72.4 ($CH_2C_6H_5$), 71.6 (C-3), 69.4 (C-6), 62.9 (C-3), 56.8 (OCH_3) HRMS $C_{22}H_{23}NO_6Na$: calcd 420.1423, found 420.1426. Following the general method **C**, this cyanohydrin (0.65 g, 1.64 mmol), MsCl (0.70 mL, 9.01 mmol), Et_3N (0.81 mL, 5.74 mmol) in CH_2Cl_2 (7 mL) for 8 h led after flash chromatography (EtOAc/cyclohexane, 3/7) to compound **48** (0.31 g, 40%) (one diastereoisomer): mp 106–108 °C; $[\alpha]_D^{20}$ +52 (*c* 0.19, $CHCl_3$); IR (ATR) *ν* 2937, 1454, 1367, 1172, 1109, 1078 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.58–7.36 (m, 10H, 2×C_6H_5), 5.45 (m, 2H, CHC_6H_5, H-1), 4.90 (m, 2H, $CH_2C_6H_5$), 4.30 (d, $J_{6A,6B}$=12.8 Hz, 1H, H-6A), 4.21 (d, $J_{1,2}$=2.5 Hz, 1H, H-2), 4.10 (m, 2H, H-4, H-6B), 3.06 (m, 1H, H-5), 3.51 (s, 3H, OCH_3), 3.05 (s, 3H, O_2SCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 136.1–126.9 (2×C_6H_5), 115.6 (CN), 101.5 (CHC_6H_5), 99.4 (C-1), 76.3 (C-2), 75.0 (C-3), 72.9 ($CH_2C_6H_5$), 71.2 (C-4), 69.2 (C-6), 62.7 (C-5), 57.2 (OCH_3), 40.7 (O_2SCH_3); HRMS $C_{23}H_{25}NO_8NaS$: calcd 498.1199, found 498.1188.



*5.6.27. (2R,4aR,6S,6aR,8R,9bR)- and (2R,4aR,6S,6aR,8S,9bR)-6-Methoxy-4,4a,6,6a,9b-pentahydro-2,8-di-phenyl-furo[3′,2′:4,5]pyrano[3,2-d]1,3-dioxin (**49**).* Following the general method **D**, compound **48** (0.30 g, 0.63 mmol), $TMSN_3$ (0.17 mL, 1.26 mmol) and Bu_2SnO (0.16 g, 0.63 mmol) for 12 h led after flash chromatography (EtOAc/cyclohexane, 3/7) to product **49** (8 mg, 33%) as a mixture of diastereomers (1/2): syrup; IR (ATR) *ν* 2961, 1356, 1260, 1084, 1049, 1023, 797 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.56–7.35 (m, 10H, 2×C_6H_5), 7.09 (d, $J_{8,9}$=6.0 Hz, 1H, H-8), 6.19 (s, 1H, H-2), 5.96 (d, 2H, H-9), 5.85 (m, 1H, H-6a), 5.68 (s, 1H, H-6), 5.24/5.12 (d, $J_{9b,4a}$=3.2 Hz; d, $J_{9b,4a}$=3.8 Hz, 1H, H-9b), 4.34 (s, 3H, OCH_3), 4.13 (d, $J_{4A,4B}$=12.4 Hz, 1H, H-4A), 4.11 (d, 1H, H-4B), 3.93(m, 2H, H-4a); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 140.8/140.3 (C-9a), 138.4–137.5, 131.2–128.3 (2×C_6H_5), 127.0, 126.6 (C-9), 101.6/100.9 (C-2 and C-6), 89.8/88.8 (C-6a), 86.4/86.2 (C-9b), 81.3/81.2 (C-8), 76.5/75.2 (C-4a), 70.0/69.9 (C-4), 64.6/64.5 (OCH_3); HRMS $C_{22}H_{22}O_5Na$: calcd 389.1365, found 389.1373.

*5.6.28. Methyl 3-O-benzyl-4,6-O-benzylidene-2-C-cyano-2-O-mesyl-α-D-galacto(talo)pyranoside (**51**).* Following the general method **A**, compound 50[19] (710 mg, 1.91 mmol), Dess–Martin periodinane (3.24 g, 7.63 mmol) in CH_2Cl_2 (20 mL) for 15 h led to the corresponding crude ulose (650 mg, 92%) {syrup, $[\alpha]_D^{20}$ +49 (*c* 0.22, $CHCl_3$)}; IR (ATR): *ν* 2928, 1716, 1267, 1049, 1016 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.51–7.35 (m, 10H, 2×C_6H_5), 5.58 (s, 1H, CHC_6H_5), 5.11 (d, $J_{1,2}$=3.9 Hz, 1H, H-1), 4.90 (d, *J*=11.6 Hz, 1H, $CH_2C_6H_5$), 4.80 (d, 1H, H-4), 4.52 (d, 1H, $CH_2C_6H_5$), 4.47 (d, $J_{4,3}$=1.4 Hz, 1H, H-3), 4.34 (dd, $J_{6A,5}$=1.4 Hz, $J_{6A,6B}$=12.8 Hz, 1H, H-6A), 4.13 (d, $J_{6B,5}$=1.6 Hz, 1H, H-6B), 3.85 (m, 1H, H-5); ^{13}C ($CDCl_3$ 75 MHz) *δ* 199.1 (C-3), 137.5–126.6 (C_6H_5), 102.6 (CHC_6H_5), 100.9 (C-1), 82.1 (C-4), 79.6 (C-2), 73.1 ($CH_2C_6H_5$), 69.1 (C-6), 64.7 (C-5), 56.2 (OCH_3). HRMS $C_{21}H_{22}O_6Na$: calcd 393.1314, found 393.1306. Following the general method **B**, the crude ulose (0.64 g, 1.73 mmol), Ti(O^{i}Pr)$_4$ (0.40 mL, 2.08 mmol), TMSCN (0.48 mL, 3.46 mmol) in MeOH (6 mL) led after flash chromatography (EtOAc/cyclohexane, 3/7) to the expected cyanohydrin (0.32 g, 47%) (one diastereoisomer) {syrup; $[\alpha]_D^{20}$ +60 (*c* 0.23, MeOH)}; IR (ATR): *ν* 3373, 1450, 1147, 1134, 1082, 1064, 1041 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.50–7.28 (m, 10H, C_6H_5), 5.65 (s, 1H, CHC_6H_5), 4.91(d, *J*=11.8 Hz, 1H, $CH_2C_6H_5$), 4.78 (d, $J_{3,4}$=3.6 Hz, 1H, H-4), 4.73 (d, 1H, $CH_2C_6H_5$), 4.54 (s, 1H, H-1), 4.32 (dd, $J_{6A,5}$=1.5 Hz, $J_{6A,6B}$=12.6 Hz, 1H, H-6A), 4.23 (s, 1H, OH), 4.08 (dd, $J_{6B,5}$=1.4 Hz, 1H, H-6B), 4.07 (d, $J_{3,4}$=3.6 Hz, 1H, H-3), 3.91(m, 1H, H-5), 3.41 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 137.3–126.4 (C_6H_5), 118.7 (CN), 101.2 (CHC_6H_5), 99.0 (C-1), 78.0 (C-3), 73.8 ($CH_2C_6H_5$), 73.4 (C-4), 72.0 (C-2), 69.5 (C-6), 59.0 (C-5), 56.8 (OCH_3). HRMS $C_{23}H_{25}NO_8SNa$: calcd 498.1199, found 498.1194. Following the general method **C**, the cyanohydrin (0.32 g, 0.80 mmol), MsCl (0.34 mL, 4.43 mmol), Et_3N (0.40 mL, 2.82 mmol) in CH_2Cl_2 (5 mL) for 18 h led after flash chromatography (EtOAc/cyclohexane, 3/7) to compound **51** (0.15 g, 39%) (one diastereoisomer): syrup, $[\alpha]_D^{20}$ +18 (*c* 0.17, MeOH); IR (ATR): *ν* 1367, 1172, 1109, 1076, 1045 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) *δ* 7.58–7.36 (m, 10H, 2×C_6H_5), 5.69 (s, 1H, CHPh), 4.94 (d, *J*=11.68 Hz, 1H, CH_2Pha), 4.77 (d, 1H, CH_2Phb), 4.73 (d, $J_{4,3}$=3.94 Hz, 1H, H-4), 4.69 (s, 1H, H-1), 4.30 (dd, $J_{6a,6b}$=12.75 Hz, 1H, H-6a), 4.14 (m, 2H, H-3, H-5), 4.01 (m, 1H, H-6b), 3.40 (s, 3H, OCH_3), 3.33 (s, 3H, O_2SCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) *δ* 137.0–126.4 (2×C_6H_5), 114.7 (CN), 101.5 (CHPh), 98.0 (C-1), 77.7 (C-2), 75.8 (C-4), 74.9 (CH_2Ph), 74.2 (C-3), 69.2 (C-6), 58.7 (C-5), 56.8 (OCH_3), 40.4 (O_2SCH_3); HRMS $C_{23}H_{25}NO_8SNa$: calcd 498.1199, found 498.1212.

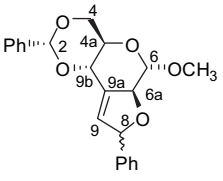


*5.6.29. (2R,4aR,6S,8R,9aR,9bR)- and (2R,4aR,6S,8S,9aR,9bR)-6-Methoxy-4,4a,6,9a,9b-pentahydro-2,8-di-phenyl-furo[2′,3′:4,5]pyrano[3,2-d]1,3-dioxin (**52**).* Following the general method **D**, compound **51** (0.10 g, 0.21 mmol), $TMSN_3$ (0.06 mL, 0.42 mmol) and Bu_2SnO (0.05 g, 0.21 mmol) for 12 h led after flash chromatography

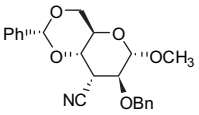
(EtOAc/cyclohexane, 3/7) to product **52** (15 mg, 49%) as a mixture of diastereomer (8/2): isolated diastereomer: syrup; $[\alpha]_D^{20}$ +22 (*c* 0.1, MeOH); IR (ATR): ν 2849, 1454, 1362, 1100, 1052, 1006 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.46–7.22 (m, 10H, 2×C_6H_5), 6.01 (d, $J_{7,8}$=1.8 Hz, 1H, H-7), 5.92 (m, 1H, H-8), 5.65 (s, 1H, H-2), 5.32 (m, 1H, H-9a), 5.24 (m, $J_{6,6a}$=3.9 Hz, 1H, H-6), 4.94 (m, 1H, H-9b), 4.41 (dd, $J_{4A,4a}$=1.1 Hz, $J_{4A,4B}$=12.65 Hz, 1H, H-4A), 4.20 (dd, $J_{4B,4a}$=1.9 Hz, 1H, H-4B), 3.63 (m, 1H, H-4a), 3.52 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 141.1 (C-6a), 138.1–126.7 (C_6H_5), 126.5 (C-7), 101.3 (2C, C-2, C-6), 89.3 (C-8), 81.0 (C-9a), 73.7 (C-9b), 69.9 (C-4), 63.3 (C-4a), 56.1 (OCH_3) HRMS $C_{22}H_{22}O_5Na$: calcd 389.1365, found 389.1358.

*5.6.30. Methyl 4,6-O-benzylidene-3-C-cyano-3-O-mesyl-2-O-benzyl-α-D-altro(manno)pyranoside (**54**).* Following the general method **C**, alcohol **53**[20] (1.07 g, 2.87 mmol) dissolved in anhydrous CH_2Cl_2 (30 mL) was treated with Dess–Martin reagent (4.88 g, 11.5 mmol, 4 equiv) in anhydrous CH_2Cl_2 (20 mL) for 24 h to give the crude ulose (0.96 g, 91%). Following the general method **D**, $Ti(O^iPr)_4$ (1.72 mL, 5.75 mmol) and TMSCN (0.77 mL, 5.75 mmol) in MeOH (20 mL) gave crude cyanohydrins (0.91 g), which were dissolved in CH_2Cl_2 (20 mL). After addition of Et_3N (2.58 mL, 18.3 mmol) and CH_3SO_2Cl (0.97 mL, 12.6 mmol), the reaction mixture was stirred overnight then, extracted and the residue purified by flash chromatography (EtOAc/cyclohexane, 25/75) to give a mixture of diastereoisomers **54** [667 mg (49%) 75/25 ratio] as a slight yellow syrup; IR (ATR): ν 2938, 1372, 1184, 1105, 1075, 1001, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.41 (m, 10H, 2×C_6H_5), 5.64 (s, 1H, C*H*C_6H_5), 4.96 (d, *J*=11.0 Hz, 1H, OC*H*$_2C_6H_5$), 4.76 (d, 1H, OC*H*$_2C_6H_5$), 4.70 (s, 1H, H-1), 4.58 (s, 1H, H-2), 4.35 (dd, $J_{5,6A}$=5.3 Hz, $J_{6A,6B}$=10.1 Hz, 1H, H-6A), 4.31 (d, $J_{4,5}$=9.5 Hz, 1H, H-4), 4.22 (dt, $J_{5,6B}$=$J_{4,5}$=9.5 Hz, 1H, H-5), 3.79 (dd, 1H, H-6B), 3.39 (s, 3H, OCH_3), 3.22 (s, 3H, OSO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.0, 136.4, 129.7–126.6 (2×C_6H_5), 114.8 (CN), 102.6 (C-7), 99.2 (C-1), 76.8 (C-4), 76.2 (C-3), 76.1 (C-2), 75.7 (OC*H*$_2C_6H_5$), 58.9 (C-5), 56.1 (OCH_3), 40.3 (OSO_2CH_3). HRMS $C_{23}H_{25}NO_8NaS$: calcd 498.1199, found 498.1178.

*5.6.31. Cyclization of methyl 4,6-O-benzylidene-3-C-cyano-3-O-mesyl-2-O-benzyl-α-D-altro(manno)pyranoside (**54**).* Following the general method **E**, 350 mg (0.73 mmol) of **10a**,**a**′, 183 mg (0.73 mmol) of Bu_2SnO and 0.19 mL (1.47 mmol) of $TMSN_3$ in toluene (7.3 mL) for 20 h at 100 °C gave successively after flash chromatography (EtOAc/cyclohexane, 15/85), (2*R*,4a*R*,6*R*,6a*R*,8*R*,9b*S*)- and (2*R*,4a*R*,6*R*,6a*R*,8*S*,9b*S*)-6-methoxy-4,4a,6,6a,9b-pentahydro-2,8-di-phenyl-furo[3′,2′:4,5]pyrano[3,2-*d*]1,3-dioxin (**55**) (30 mg, 11%) (one diastereomer) and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-deoxy-3-*C*-cyano-α-D-tallopyranoside (**56**) (18 mg, 6%).



Compound **55**: $[\alpha]_D^{20}$ +73 (*c* 0.06, MeOH); IR (ATR): ν 2919, 1451, 1383, 1322, 1194, 1128, 1084, 1044, 1002, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.34 (m, 10H, 2×C_6H_5), 6.19 (m, 1H, H-9), 5.85 (m, 1H, H-8), 5.67 (s, 1H, H-2), 5.14 (m, 1H, H-6a), 4.80 (d, $J_{6,6a}$=5.6 Hz, 1H, H-6), 4.45 (m, 2H, H-9b, H-4A), 4.02 (ddd, $J_{4A,4a}$=4.5 Hz, $J_{9b,4a}$=9.8 Hz, 1H, H-4a), 3.82 (t, $J_{4a,4B}$=$J_{4A,4B}$=10.0 Hz, 1H, H-4B), 3.52 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.6 (C-9a), 137.4, 134.8, 129.6–126.7 (2×C_6H_5), 132.0 (C-9), 105.6 (C-6), 102.6 (C-2), 89.5 (C-8), 86.0 (C-6a), 75.3 (C-9b), 70.5 (C-4), 65.4 (C-4a), 55.9 (OCH_3). HRMS $C_{22}H_{22}O_5Na$: calcd 389.1365, found 389.1361.



Compound **56**: $[\alpha]_D^{20}$ +61 (*c* 0.1, MeOH); IR (ATR): ν 2914, 1455, 1378, 1133, 1102, 1093, 1046, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.33 (m, 10H, 2×C_6H_5), 5.61 (s, 1H, C*H*C_6H_5), 4.74 (d, $J_{1,2}$=1.1 Hz, 1H, H-1), 4.64 (m, 2H, OC*H*$_2C_6H_5$), 4.34 (dd, $J_{5,6A}$=4.9 Hz, $J_{6A,6B}$=10.3 Hz, 1H, H-6A), 4.22 (ddd, $J_{4,5}$=9.7 Hz, 1H, H-5), 4.11 (d, $J_{3,4}$=5.0 Hz, 1H, H-4), 3.84 (t, $J_{5,6B}$=10.3 Hz, 1H, H-6B), 3.95 (dd, $J_{2,3}$=2.2 Hz, 1H, H-2), 3.46 (s, 3H, OCH_3), 3.39 (dd, 1H, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2, 136.8, 129.8–126.8 (2×C_6H_5), 116.3 (CN), 102.7 (C-7), 98.8 (C-1), 75.6 (C-2), 73.1 (OC*H*$_2$Ph), 72.5 (C-4), 69.2 (C-6), 61.4 (C-5), 55.5 (OCH_3), 32.8 (C-3). HRMS $C_{22}H_{23}NO_5Na$: calcd 404.1474, found 404.1463.

5.7. Theoretical methods

All calculations were carried out with the Gaussian 03 program.[29] No constraints were imposed on the structures in the equilibrium-geometry calculations or in the transition-state optimizations. Molecular geometries were optimized at the restricted level (closed-shell) for singlets and the unrestricted level (open-shell) for triplets. The optimizations were carried out using hybrid density functional B3LYP[30] with the 6-31G(d,p) basis set. Single-point energy calculations with 6-311+G(d,p) were later performed on the optimized geometries. Basis sets with diffuse functions are recommended for molecules with lone pairs, for anions, and for systems with significant negative charge. Vibrational frequency analyses were carried out in order to assess the nature of the stationary points and obtain the zeropoint vibrational energies (ZPVEs) and thermodynamic parameters. IRC calculations were used to connect the transition state to its respective precedent and ensuing minima. Natural bond orbital (NBO) analyses[31] have been performed by the module NBO v.3.1 implemented in Gaussian 03 to evaluate the NPA charges at the optimization level.

Acknowledgements

R.C. thanks the Ministère Français de la Recherche for a fellowship. D.P. and A.N.V.N. thank the Conseil Régional de Picardie and the Ministère Français de la Recherche for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.08.080.

References and notes

1. For reviews: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383; (b) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274; (c) Kirmse, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 1164; (d) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795.
2. (a) Cunico, R. F. *J. Organomet. Chem.* **1976**, *105*, C29–C31; (b) Stang, P. J.; Christensen, S. B. *J. Org. Chem.* **1981**, *46*, 823; (c) Stang, P. J.; Fox, D. P. *J. Org. Chem.* **1977**, *42*, 1667; (d) Gilbert, J. C.; Giamalva, D. H. *J. Org. Chem.* **1983**, *48*, 5251; (e) Ochiai, M.; Takaoka, Y.; Nagao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 6565; (f) Kunishima, M.; Hioki, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, *35*, 7253; (g) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1995**, *36*, 4845.
3. Czernecki, S.; Valéry, J.-M. *J. Carbohydr. Chem.* **1986**, *5*, 235.
4. (a) Pérez-Pérez, M. J.; Camarasa, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1403; (b) Pérez-Pérez, M. J.; Camarasa, M. J. *Tetrahedron* **1994**, *50*, 7269.
5. For some useful transformations of alkylidenecarbenes in sugar templates, see: (a) Tronchet, J.; González, A.; Zumwald, J. B.; Perret, F. *Helv. Chim. Acta* **1974**, *57*, 1505; (b) Hauske, J. R.; Guadliana, M.; Desai, K. *J. Org. Chem.* **1982**, *47*, 5019; (c) Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537; (d)

Niizuma, S.; Shuto, S.; Matsuda, A. *Tetrahedron* **1997**, *53*, 13621; (e) Wardrop, D. J.; Zhang, W.; Frtz, J. *Org. Lett.* **2002**, *4*, 489.
6. Nguyen Van Nhien, A.; León, R.; Postel, D.; Carreiras, M. C.; García, A. G.; Marco-Contelles, J. *J. Carbohydr. Chem.* **2005**, *24*, 369.
7. Examples of 1,6-C–H insertions on alkylidenecarbenes are rare: (a) Feldman, K. S.; Perkins, A. L. *Tetrahedron Lett.* **2001**, *42*, 6031; (b) Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1990**, *31*, 4727; (c) Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J.; McMullen, G. L. *Aust. J. Chem.* **1974**, *27*, 2393.
8. (a) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139; (b) For a review on the synthesis of 5-substituted 1*H*-tetrazoles, see: Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
9. For the synthesis of related pyrano-anellated pyranosides, see: Thiele, G.; Feist, H.; Peseke, K. *J. Carbohydr. Chem.* **2005**, *24*, 209.
10. (a) Marcelo, F.; Jiménez-Barbero, J.; Marrot, J.; Rauter, A. P.; Sinaÿ, P.; Blériot, Y. *Chem.—Eur. J.* **2008**, *14*, 10066; (b) Ethève-Quelquejeu, M.; Xie, J.; Valéry, J.-M. *Synlett* **2004**, 1089 and references cited therein.
11. Qin, H.; Grindley, T. B. *J. Carbohydr. Res.* **1996**, *15*, 95.
12. Rauter, A. P.; Oiliveira, O.; Canda, T.; Leroi, E.; Ferreira, H.; Ferreira, M. J.; Ascenso, J. A. *J. Carbohydr. Chem.* **2002**, *21*, 257.
13. Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662.
14. Dong, L.; Roosenberg, J. M., II; Miller, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15001.
15. Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Sïnaÿ, P. *Chem.—Eur. J.* **2004**, *10*, 2960.
16. Fürstner, A.; Weidmann, H. *J. Org. Chem.* **1989**, *54*, 2307.
17. Deninno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669.
18. Kenichi, S.; Tetsutaro, I.; Yukio, Y.; Nobuya, K.; Hironobu, H.; Juji, Y. *Chem. Lett.* **1988**, *10*, 1699.
19. Attolino, E.; Cumpstey, I.; Fairbanks, A. J. *Carbohydr. Res.* **2006**, *341*, 1609.
20. Tanaka, N.; Ogawa, I.; Yoshigase, S.; Nokami, J. *Carbohydr. Res.* **2008**, *343*, 2675.
21. For some examples, see: (a) Jeziorek, D.; Zurawski, B. *Int. J. Quantum Chem.* **1979**, *16*, 277; (b) Krishnan, R.; Pople, J. A. *Int. J. Quantum Chem. Symp.* **1980**, *14*, 91; (c) Gordon, M. S.; Gano, D. R. *J. Am. Chem. Soc.* **1984**, *106*, 5421; (d) Ramalingam, M.; Ramasami, K.; Venuvanalingam, P.; Sethuraman, V. *THEOCHEM* **2005**, *755*, 169; (e) Ramalingam, M.; Ramasami, K.; Venuvanalingam, P. *Chem. Phys. Lett.* **2006**, *430*, 414.
22. (a) Fang, R.; Geng, Z. Y.; Wang, Y. C.; Zhao, C. Y.; Yang, L. Z.; Zhang, X. H. *Chem. Phys. Lett.* **2005**, *414*, 174; (b) Yao, K.; Geng, Z.-Y.; Wang, Y.-C.; Jia, B.-L. *THEOCHEM* **2007**, *821*, 106.
23. Takahashi, O.; Yamasaki, K.; Kohno, Y.; Ohtaki, R.; Ueda, K.; Suezawa, H.; Umezawad, Y.; Nishio, M. *Carbohydr. Res.* **2007**, *342*, 1202.
24. For the importance of the CH/O hydrogen bond in chemistry and biochemistry, see Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999.
25. Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557.
26. A question of mechanistic relevance is the ground state multiplicity of these species. The computed mechanism for the insertion process in the triplet state (stepwise) diverges from that in the singlet state (concerted pathway). See Supplementary data for details.
27. Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.
28. (a) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 13; (b) Koller, M.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2760.
29. *Gaussian 03*; Gaussian: Wallingford, CT, 2004; (see Supplementary data).
30. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Lee, W.; Yang, R. G.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
31. Glendening E. D.; Reed A. E.; Carpenter J. E.; Weinhold F., *NBO Version 3.1*. For original literature, see: (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066; (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.