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Experimental and computational investigation of the unexpected formation of β-substituted polyoxygenated furans from conveniently functionalized carbohydrates

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ABSTRACT

In the course of our current studies on the reactivity of alkylidenecarbenes, prepared with the trimethylsilylazide/Bu_2SnO method, on conveniently functionalized α-cyanomesylates derived from D-allose, D-arabinose, and D-threose, we have observed the unexpected, but mechanistically interesting formation of enantiomerically β-substituted polyhydroxylated furans. These compounds are the result of a series of cascade fragmentation reactions on unstable intermediates obtained during 1,5C–H insertion reactions from alkylidenecarbenes. The mechanism of the reaction has been investigated by computational methods using DFT analysis.

1. Introduction

The insertion reaction of alkylidenecarbenes is demonstrated to be an effective method for the synthesis of various cyclic systems through 1,5-, 1,6- or heteroinsertions.[1] Most of the classical route to generate these highly reactive species involved an unsaturated *C,C*-bond with leaving groups. [2a–f] Several authors exploited the low stability of the unsaturated *N,N*-bond to generate a (alkylidene)carbene functionality. In this context, Vasella reported a sizable work on the reactivity of glycosylidene carbenes derived from diaziridines.[3a] Czernecki was the first to use α-cyanomesylates as precursor for alkylidenecarbenes: upon treatment with sodium azide/DMF a presumed alkylidenecarbene species was formed, that after 1,2-H shift gave acetylenic derivatives.[3b] Subsequent studies have shown that the reaction of sodium azide in methylene chloride, at room temperature, in the presence of tetrabutylammonium hydrogenosulfate, with α-cyanomesylates derived from uloses, produced alkylidenecarbenes that were trapped in situ in *intermolecular* reactions 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.[4,5] Some years ago, and also starting from α-cyanomesylates, we have reported[6] that the synthesis of 5-substituted tetrazoles, according to Wittenberger's method[7] (trimethylsilylazide, dibutyltin oxide, toluene), provided α-mesyltetrazolyl intermediates that smoothly and in mild reaction conditions led to the desired alkylidenecarbenes species, giving some useful *intramolecular* transformations via rare 1,6C–H bond insertion reactions.[8] Very recently, we have described[9a] the synthesis of chiral cyclopentane intermediates for the synthesis of neplanocin A[10] and trehazolin,[11] via 1,5C–H insertion processes on suitable substituted alkylidencarbene species.

Continuing with our studies on this area, we report here the unexpected, but mechanistically interesting formation of enantiomerically pure β-substituted polyhydroxylated furans,[12] that we have isolated in the course of the generation of alkylidenecarbenes on conveniently functionalized α-cyanomesylates derived from D-allose, D-arabinose, and D-threose.

2. Results and discussion

2.1. Synthesis and reactivity of the precursors

Starting with commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allopyranose (**1**), after standard *O*-methylation, acid

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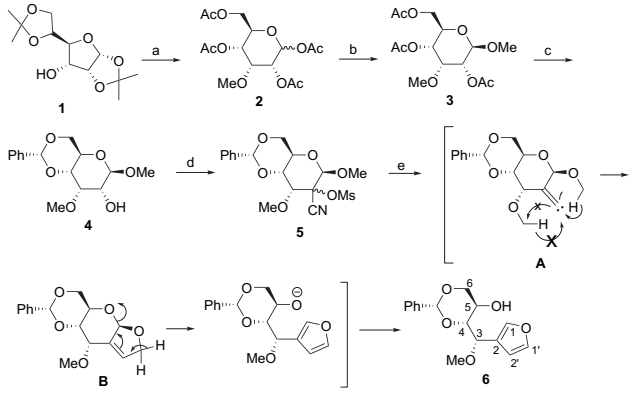
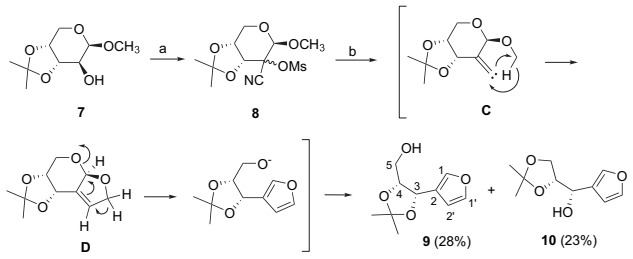
hydrolysis and peracetylation, acetyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α(β)-D-allopyranoside (**2**) was isolated as a mixture of anomers, that without separation were submitted to glycosylation with methanol to give stereospecifically methyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-β-D-allopyranoside (**3**)[13] in good overall yield (Scheme 1). Basic hydrolysis of peracetate **3** followed by reaction with benzaldehyde dimethyl acetal provided compound **4**, that was submitted to the 'OCS' (=Oxidation to give the known, not isolated, methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*ribo*-hexopyranosid-2-ulose[14]+Cyanhydrin formation+Sulfonation) three-step protocol to provide intermediate **5** as a mixture of isomers at C2 (see Experimental section), ready to react under our standard methodology ($TMSN_3$, Bu_2SnO, toluene)[6,9] for the preparation of the alkylidenecarbene species. Unfortunately, under these conditions, the reaction was very complex, and only compound **6** could be isolated and characterized, albeit in low yield (10%) (Scheme 1). The full analysis of this molecule clearly showed that this compound did not correspond with the expected dihydrofuran-type of compound obtained previously by us under similar conditions, in related substrates.[9b] Conversely, the electron impact spectrum mass showed a molecular mass in agreement with a $C_{16}H_{18}O_5$ molecular formula. In the IR spectrum, a wide band at 2919 cm^{-1} indicated the presence of at least one free hydroxyl group. The ^1H NMR analysis revealed that the phenyl, the methoxy, and five protons (H–C–O: 4.46–3.66 ppm) possibly bonded to oxygen atoms still remained in the molecule; these signals showed their corresponding data in the ^{13}C NMR spectrum. In addition, we observed three signals for three protons [δ (sugar numbering)] at 7.51 (H-1), 7.49 (H-1′), and 6.50 (H-2′), and four carbons [δ (sugar numbering)] at 143.5 (C-1), 141.3 (C-1′), 118.9 (C-2), 108.9 (C-2′), that perfectly fit with a β-susbtituted furan. Accordingly, the structure of (2*R*,4*R*,5*R*)-4-((*S*)-furan-3-yl(methoxy)methyl)-2-phenyl-1,3-dioxan-5-ol was assigned to compound **6**. The formation of this compound was unexpected, and reveals that the 1,5C–H insertion on the alkylidenecarbene **A** (Scheme 1) was very regioselective implicating exclusively the protons in the methyl group at the oxygen in the anomeric center, to give the presumed intermediate **B** (Scheme 1), essentially unstable, that in a fragmentation process, possibly promoted by the excess of the $TMSN_3$ used, would yield the final observed molecule.



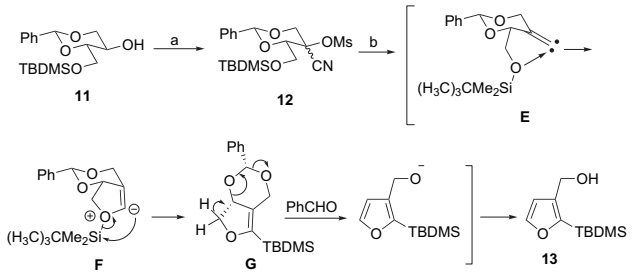
Scheme 1. Reagents and conditions. (a) (i). NaOH, CH_3I, acetone, rt, (ii). Dowex resin 50 W-X8, H_2O, 80 °C, (iii). Ac_2O, pyridine, DMAP (89%); (b) (i). HBr, CH_2Cl_2, 0 °C, ii. $CaSO_4$, CH_2Cl_2–MeOH, HgO, HgO (52%); (c) (i). MeONa, MeOH, ii. $C_6H_5C(OMe)_2$, camphorsulfonic acid (49%); (d) (i). Dess–Martin (71%), (ii). Ti(*i*-PrO)$_4$, TMSCN, MeOH (14%) (iii). ClMs, Py (80%); (e) $TMSN_3$, Bu_2SnO (10%).

In view of this results, and in order to check the generality and scope of this reactivity, next we prepared precursor **8** from known methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside (**7**),[15] following the standard synthetic sequence (Scheme 2) (see Experimental Part). Under the same experimental conditions, compound **8** afforded a mixture of two β-susbtituted furans **9** and **10**, in 28% and 23% chemical yields, respectively (Scheme 2). The structure of compound **10** was assigned based on its analytical and spectroscopic data, and unambiguously established by comparison of these values with those described in the literature for identical compounds prepared by a different and inequivocal route.[12] In the case of compound **9**, the analysis showed that it was an isomer of compound **10**, differing only in the location of the isopropylidene moiety (see Experimental section). From a mechanistic point of view, it is also evident that again the key alkylidenecarbene **C** leads to intermediate **D**, that spontaneously fragments to provide a mixture of compound **9** and **10** in moderate overall yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) (i). PDC, Ac_2O, molecular sieves, CH_2Cl_2, reflux, (ii) Ti(OiPr)$_4$, TMSCN, MeOH, (iii) MsCl, Et_3N, CH_2Cl_2, rt (57%); (b) $TMSN_3$, Bu_2SnO, toluene, 100 °C.

Based on the previous results, next we selected the known protected threitol **11**[16] to prepare a suitable precursor **12** in order to test if in this substrate a similar series of events leading to furan derivatives could be possible. To our delight, under the standard conditions (see Experimental Part) compound **12** gave the known furan **13**[17] in 20% yield (Scheme 3). In this case, the initial formation of alkylidenecarbene **E** is followed by 1,5 O–Si insertion to give dihydrofuran **F**, that is, followed by *t*-butyldimetylsilyl migration[18] to provide intermediate **G**, ready for the fragmentation cascade process that ends with the formation of compound **13** (Scheme 3).

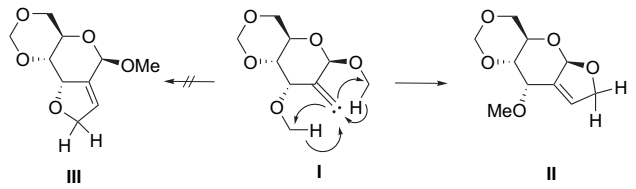


Scheme 3. Reagents and conditions: (a) (i). Swern oxidation, (ii) KCN, $NaHCO_3$, CH_2Cl_2, H_2O, rt, (iii) MsCl, Et_3N, CH_2Cl_2, rt (32%); (b) $TMSN_3$, Bu_2SnO, toluene, 100 °C (20%).

2.2. Reactivity and mechanisms based on a DFT study

The results described above leading to the β-substituted furans **6**, **9**, **10**, and **13** (Schemes 1–3) have not been optimized, but although limited from the synthetic point of view, deserve further investigation and interest regarding the mechanism of the diverse reactions implicated. In order to investigate these aspects and explain the reactivity of the key intermediates and regiochemistry of these processes, we decided to carry out a DFT-based computational study.

Firstly, we have focussed on an alkylidenecarbene at C-2 derived from **5** (**A**, Scheme 1), and accordingly, we have analyzed carbene **I** (Scheme 4) as theoretical model. As described above, the 1,5C–H insertion on the alkylidenecarbene **A** (Scheme 1) was very regioselective since the process involved exclusively the methoxy group at the anomeric position.



Scheme 4.

Previous observations[9] on related alkylidenecarbenes have shown us that they exist in singlet state, S_0, as ground state. According to the traditional assumption, in S_0 there is an empty p_π orbital on the carbene carbon, and the non-bonding unshared spin-paired electrons electrons occupy a sp.-like orbital in the plane of the molecule.

Two regioisomers can be formed by 1,5C–H insertion of the alkylidencarbene, **II** and **III** (Scheme 4). The reactive carbene intermediate **I** shows short H···C_{CARB} (1.943 Å) distance and long C–H bond (1.117 Å) with the methoxy moiety at C-2 (Fig. 1), so it can be view as a precursor complexes[19] or even ylide-like complexes, since it possess a similar ylide structure. The formation of **II** takes place through the half chair-like transition structures $\mathbf{TS_{II}}$ showing the moving hydrogen atom 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 11.1°). In this arrangement (Fig. 1), the alkane C–H bond molecular orbital is periplanar with and therefore can overlap with the empty orbital of the alkylidenecarbene.[20] Analogously to our previous results,[9] the key geometric parameters of the transition state structure [long C–H (1.551 Å) and $C_{CARBENE}$–C (2.224 Å) distances and a nearly formed C–H bond (1.144 Å)] reveal that the new carbon–hydrogen bond forms much faster than does the new carbon–carbon bond. Therefore, the cyclization is a concerted process, although strongly asynchronous.[9]

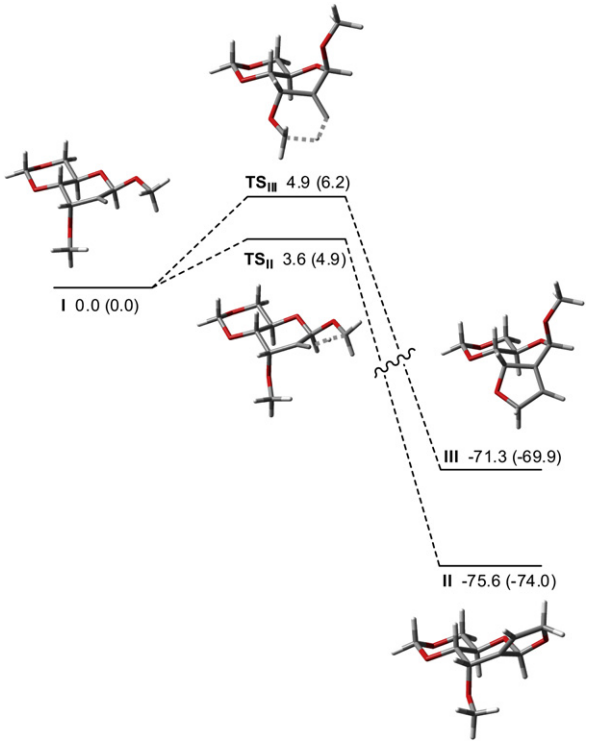
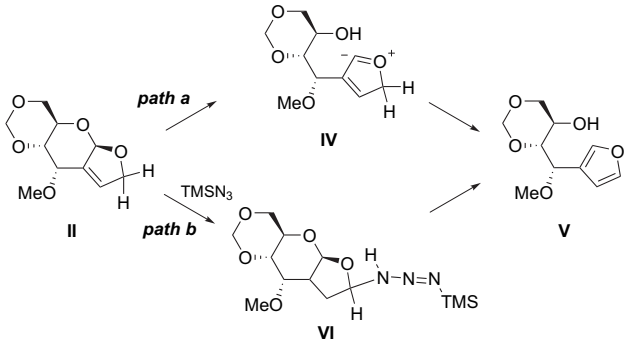


Figure 1. Enthalpy profile (in kcal mol^{-1}) for the 1,5C–H insertion processes of the alkylidencarbene **I** into the substituents at C-2 and C-4. (Free energy differences are shown in parenthesis).

A different picture is found in the formation of **III**. In order to achieve the required orbital interaction of the σ_{C-H} electrons with the empty p orbital of the carbene carbon, the transition structure $\mathbf{TS_{III}}$ adopts a less stable conformation: the forming heterocycle adopts an envelope conformation, which forces the pyranose ring to a skew-boat type conformation. The moving H atom shows a larger deviation from the plane defined by the carbon atom and the doubly bound carbon atoms of the carbene (deviation of 14.7°, Fig. 1).

From an energetic point of view, our results clearly reveal a kinetic preference for the formation of the regioisomer **II** over **III** (3.6 vs 4.9 kcal mol^{-1}, Fig. 1), due to the structural distortion needed to get an efficient orbital overlap and achieve the transition state. The 1,5-insertion reaction with C–H is strongly exothermic (≈ -70 kcal mol^{-1}, Fig. 1), and hence irreversible, although the formation of **II** is thermodynamically favored (by 4 kcal mol^{-1}) over **III**. These results are supported by the experimental results, which describe the formation of the furan **6** from **5** (Scheme 1).

The close proximity of the endocyclic oxygen atoms in the presumed fused furopyran intermediate **B** (Scheme 1) likely promotes the fragmentation process to yield the final furan product. Two plausible routes can be envisaged to account for this transformation. First, a spontaneous opening to relieve the annular tension could take place where the breaking alkoxy group would take the H atom away from the five-membered ring **II** to afford the furan scaffold **V** (path ***a***). However, we have found that this process implies a very high activation barrier and leads to high-energy intermediate **IV**, which suggests that it is most likely promoted by the excess of the $TMSN_3$ used. Accordingly, we have conducted the analysis of the reaction pathway ***b*** depicted in Scheme 5.



Scheme 5.

The intermolecular azide-assisted proton abstraction seems more likely since it requires a softer steric distortion than the unassisted intramolecular mechanism. The two-step pathway proceeds first through the late transition structure $\mathbf{TS_{VI}}$, which shows the nearly full C–H bond cleavage (1.954 Å, Fig. 2). This transition structure drives to the formation of the unstable triazene **VI** by development of the C–N (1.448 Å) and N–H (1.013 Å) bonds, as IRC calculations confirm. Although the preparation of triazene structures is usually fruitless because of the high unstability, silylated triazenes have been successfully isolated under certain conditions.[21] The transient triazene then fragments via the transition structure $\mathbf{TS_V}$ by formation of the O–H (1.474 Å) bond and cleavage

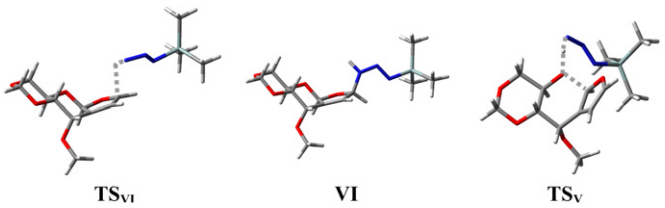


Figure 2. Computed structures for the azide-assisted fragmentation.

of the C–N bond (1.985 Å). At this point, the opening of the dihydropyrane by breaking of the O–C bond seems evident (1.675 Å) as a result of the incipient formation of the alcohol moiety. There is a nearly linear arrangement N/H/O in the transition state (160.7°), with the hydrogen atom being clearly transferred from nitrogen to oxygen. Finally, $\mathbf{TS_V}$ leads to the furan derivative **V**. The formation of the triazene **VI** from **II** proceeds with a barrier of 32.8 kcal/mol (−42.8 kcal/mol from **I**) and is thermoneutral in terms of enthalpy (0.1 kcal/mol), although it is endothermic if entropy effects are taken into account (9.8 kcal/mol). The last step takes place with a similar barrier 30.1 kcal/mol (−45.4 kcal/mol from **I**) but is clearly exothermic thus ensuring the formation of the product. The overall transformation of **I** into **V** is very exothermic (ΔG=−82.8 kcal/mol). The drawings of the computed structures are presented in Figure 2.

The formation of **13** is also interesting since, besides the ring fragmentation, points to a 1,5 Si–O insertion on the alkylidenecarbene. For this simulation, the TBDM moiety has been replaced for the computationally less expensive TMS group.

Alkylidenecarbenes are known to undergo intramolecular 1,5 O–Si insertion reactions to yield 2,3-dihydrofuran derivatives, and this pathway has been shown to proceed more rapidly than 1,5C–H insertion.[6,18,22] Two possible pathways have been postulated to account for this process: a concerted route and through the formation of an ylide intermediate followed by the 1,2-alkylsilyl shift.[18b] To note that, as we described previously for related systems, the reactive alkylidenecarbene **VII** resembles a oxonium ylide structure,[23] as it shows a strong interaction of the vacant orbital on the carbene with an oxygen lone pair of the *O*-TMS oxygen (C–O=1.739, Fig. 3). In fact, it has been reported that the absence of expected 1,5 O–Si insertion products can be ascribed to the need to adopt a conformation that allows this required orbital overlap.[24] In this case, the lone pairs on oxygen is periplanar to the p orbital on the carbene in the lowest energy conformation,[25] so the alkylidenecarbene can indeed be viewed as the initial ylide-like complex.

At the transition state $\mathbf{TS_{VIII}}$ (Fig. 3), the attacked O–Si bond is slightly enlarged (1.840 Å), whereas the forming C–O distance (1.526 Å) suggests an advanced bond formation. The Si–$C_{CARBENE}$ distance (2.264 Å) is still rather large, suggesting a remarkable asynchronicity in the insertion. However, IRC calculations have ruled out additional steps and $\mathbf{TS_{VIII}}$ evolves to the expected dihydrofuran **VIII**, able to provide the furan derivative through the assisted fragmentation mechanism described above.

In summary, as was found for the 1,5C–H insertion, the process is concerted as the insertion is concomitant with the 1,2-silyl shift.

3. Conclusions

In our current studies on the reactivity of alkylidenecarbenes, prepared with the trimethylsilylazide/Bu_2SnO method, on conveniently functionalized α-cyanomesylates derived from D-allose, D-arabinose, and D-threose, we have observed the unexpected, certainly low-yielding, but mechanistically interesting formation of enantiomerically β-substituted polyhydroxylated furans. These compounds are the result of a series of cascade fragmentation reactions on unstable intermediates obtained during 1,5C–H insertion reactions from alkylidenecarbenes. As the computational chemistry on the reactivity of carbine species, and in particular in alkylidenecarbenes, has been scarcely investigated, the mechanism of the 1,5C–H and Si–O insertion reactions from alkylidenecarbenes has been studied by DFT-based computational methods. The results account for the regiochemical bond insertion and show an analogous concerted path for the insertion/1,2-shift events. The following fragmentation cascade to the β-substituted polyhydroxylated furan most probably proceeds by an azide-assisted intermolecular proton abstraction mechanism, which is supported by the calculations.

4. Experimental section

4.1. 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

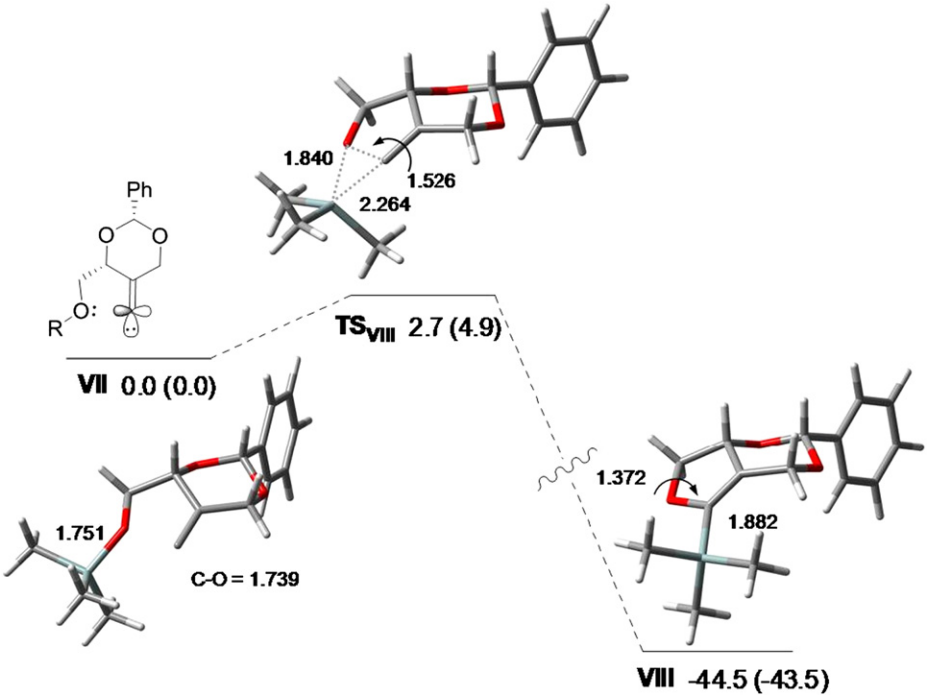


Figure 3. Enthalpy profile (in kcal mol^{-1}) for the 1,5 O–Si insertion processes of the alkylidenecarbene **VII**. (Free energy differences are shown in parenthesis).

$CDCl_3$, 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 F_{254} 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}.

4.2. General method for Dess–Martin periodinane oxidation (A1)

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.

4.3. General method for oxidation with PDC (A2)

To a solution of starting material in CH_2Cl_2 and powder molecular sieves 3 Å (2.5 equiv w/w), Ac_2O (3.5 equiv) was added and the mixture was refluxed. PDC (0.7 equiv) was added portionwise and the reaction mixture was stirred for 4–22 h. 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.

4.4. General method for oxidation (Swern) (A3)

DMSO (3.0 equiv) in CH_2Cl_2 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 the dropwise addition of Et_3N (3.0 equiv). The solution was then warmed to room temperature and a standard workup (CH_2Cl_2) yielded the ketone that was used in the next step without any further purification.

4.5. General method for cyanomesylation (B)

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 $Ti(OiPr)_4$ (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 was 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.

4.6. General method for alkylidenecarbene generation (C)

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 °C and stirred for 22–23 h and then the solvent was removed under vacuo. The crude product was submitted to flash chromatography (EtOAc/cyclohexane).

4.7. Acetyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α(β)-D-allopyranoside (2)

To a solution of commercial 'diacetone-D-allose' (**1**) (18 g, 0.07 mol) in acetone (250 mL) was added NaOH (2.8 g, 0.084 mol) and iodomethane (4.35 mL, 0.077 mol). After stirring at rt for 4 h, the reaction mixture was filtered and the filtrate evaporated to dryness to afford crude 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-α-D-allopyranose in a quantitative yield, which was used in the next step without further purification. Then, the diacetonide was treated with resin Dowex 50 W-X8-100(H^+), and stirred in distilled water (250 mL) for 10 h at 80 °C. After cooling at rt, the resin was removed by filtration and the solvent eliminated under reduced pressure. Pyridine (113 mL) was added to the reaction mixture at 0 °C followed by addition of DMAP (catalytic) and Ac_2O (97 mL). After stirring for 13 h at rt, the solvent was eliminated and the residue extracted with ethyl acetate (3×100 mL). The organic layers were gathered, dried (Na_2SO_4) and filtered. After flash chromatography (EtOAc/cyclohexane, 4/6), compound **2** (22.4 g, 89%) was obtained as a slight yellow syrup; IR(ATR) ν 1733, 1366, 1242, 1118, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.94/5.91 (m, 2H, H-1), 4.76 (m, 4H, H-2, H-5), 4.11 (m, 2H, H-6a), 4.03 (m, 2H, H-4, H-3), 4.00 (m, 2H, H-6b), 3.95 (dd, $J_{3,4}$=9.5 Hz, $J_{4,5}$=6.8 Hz, 2H, H-4), 3.42/3.28 (s, 6H, OCH_3), 2.01 (m, 24H, 6×$COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 170.9, 170.3, 169.9, 169.8, 169.4, 169.0 (8×*C*OCH_3), 98.6/90.5 (C-1), 80.4/7.2 (C-4), 79.9/1.2 (C-3), 73.4/1.0 (C-2), 71.7/8.5 (C-5), 62.8/2.4 (C-6), 61.8/9.3 (OCH_3), 20.9 (8×*C*OCH_3). HRMS $C_{15}H_{22}O_{10}Na$: calcd 385.1111, found 385.1114.

4.8. Methyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-β-D-allopyranoside (3)[13]

To a solution of compound **2** (10 g, 0.03 mol) in CH_2Cl_2 cooled at 0 °C was slowly added bromhydric acid (250 mL). After stirring for 1 h at rt, the reaction was quenched with cold water (500 mL) and extracted. The organic phase was washed with a saturated solution of $NaHCO_3$ (×2) and water (500 mL). The organic layers were gathered, dried (Na_2SO_4) and filtered. The crude (10.7 g, 0.03 mol) was dissolved in CH_2Cl_2 (85 mL) and MeOH (30 mL) and then $CaSO_4$ (10.4 g, 0.06 mol) was added. After stirring for 15 min, HgO (5.2 g, 0.024 mol) and Hg_2O (0.26 g, 0.72 mmol) were added and the reaction mixture was stirred for 13 h. After filtration through a silica pad, the filtrate was concentrated under reduced pressure and purified by flash chromatography (EtOAc/cyclohexane, 25/75) to give compound **3**[13] (4.84 g, 52%) as a yellow syrup; IR(ATR) ν 1739, 1372, 1221, 1112, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.82 (dd, $J_{4,3}$=2.7 Hz, $J_{4,5}$=10.0 Hz 1H, H-4), 4.69 (m, 2H, H-1, H-2), 4.24 (dd, $J_{6a,5}$=4.6 Hz, $J_{6a,6b}$=12.2 Hz, 1H, H-6a), 4.13 (dd, $J_{6b,5}$=2.4 Hz, 1H, H-6b), 4.06 (ddd, 1H, H-5), 3.94 (t, 1H, H-3), 3.47 (s, 6H, OCH_3), 2.10, 2.06, 2.03 (s, 9H, $COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 169.6, 169.5 (*C*OCH_3), 99.5 (C-1), 77.1 (C-2), 71.6 (C-4), 69.8 (C-3), 68.7 (C-5), 62.5 (C-6), 61.5, 56.9 (2×OCH_3), 20.9, 20.8 (*C*OCH_3). HRMS $C_{14}H_{22}O_9Na$: calcd 357.1162, found 357.1154.

4.9. Methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-allopyranoside (4)

Compound **3** (1.22 g, 3.65 mmol) and MeONa (0.59 g, 0.01 mol) were dissolved in MeOH (10 mL), and stirred for 2 h at rt. The reaction mixture was filtered through a silica pad and the filtrate was concentrated to afford crude deacetylated (0.75 g, 3.61 mmol), which was dissolved in CH_3CN (20 mL). After addition of benzaldehyde dimethyl acetal (0.65 mL, 4.33 mmol) and camphorsulfonic acid (3.0 g), the reaction mixture was stirred at rt for two days. Neutralization with Et_3N (pH=7) followed by filtration and usual work-up afforded after flash chromatography (EtOAc/cyclohexane, 10/90) the desired compound **4** (0.53 g, 49%) as a yellow syrup; $[\alpha]_D^{20}$ +76 (*c* 0.09, MeOH); IR (ATR) ν 2932, 1253, 1164, 1093, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.28 (m, 5H, C_6H_5), 5.84 (s, 1H, C*H*C_6H_5), 4.52 (d, $J_{1,2}$=7.9 Hz, 1H, H-1), 4.40 (q, $J_{3,2}$=5.2 Hz, $J_{4,3}$=10.3 Hz, 1H, H-3), 3.96 (m, 2H, H-6), 3.76 (s, 1H, H-2), 3.61 (m, 2H, H-4, H-5), 3.67, 3.58 (s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8–126.5 (C_6H_5), 103.2 (*C*HC_6H_5), 102.4 (C-1), 80.7 (C-2), 78.9 (C-4), 71.6 (C-3), 69.6 (C-6), 63.8 (C-5), 61.6, 57.8 (2×OCH_3). HRMS $C_{15}H_{20}O_6Na$: calcd 319.1158, found 319.1169.

4.10. Methyl 4,6-*O*-benzylidene-2-*C*-cyano-2-*O*-mesyl-3-*O*-methyl-α-D-allo(*altro*)pyranoside (5)

Following the general method **A1**, compound **4** (0.63 g, 2.13 mmol) in dry CH_2Cl_2 (20 mL) was treated with Dess–Martin reagent (3.61 g, 2.13 mmol) in dry CH_2Cl_2 (20 mL) for 11 h to give the crude ulose (0.44 g, 71%). Following the general method **B**, to a solution of the crude ulose[14] in MeOH (5 mL), reacted with $Ti(OiPr)_4$ (0.45 mL, 1.51 mmol) and TMSCN (0.41 mL, 3.02 mmol) to provide the crude cyanohydrins (67 mg, 14%), which were dissolved in pyridine (5 mL). After addition of CH_3SO_2Cl (0.05 mL, 0.62 mmol) at 0 °C, the reaction mixture was stirred for 16 h at rt; then, extracted and the residue purified by flash chromatography (EtOAc/cyclohexane, 30/70) to give a mixture (9/1 ratio) of diastereoisomers **5** (67 mg, 80%) as a slight yellow syrup: IR (ATR): ν 2942, 1353, 1316, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.30 (m, 5H, 2×C_6H_5), 5.59 (s, 1H, C*H*C_6H_5), 4.84 (s, 1H, H-1), 4.63 (d, $J_{3,4}$=2.1 Hz, 1H, H-3), 4.44 (dd, $J_{6a,6b}$=10.5 Hz, 1H, H-6a), 4.12 (m, $J_{6,5}$=4.9 Hz, 1H, H-5), 4.04 (dd, $J_{4,5}$=3.8 Hz, 1H, H-4), 3.86 (d, 1H, H-6b), 3.73, 3.64 (s, 6H, 2×OCH_3), 3.31 (s, 3H, SO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.8–126.1 (2×C_6H_5), 113.6 (2×CN), 102.3, 102.1(2×*C*HC_6H_5), 99.5/99.3(C-1), 79.4/78.8(C-3), 78.1/76.7(C-4), 75.4 (2×C-2), 68.5/65.3(C-6), 64.3/64.1(C-5), 62.1, 61.8, 58.6, 58.0 (4×OCH_3), 40.1/39.9 (O_2SCH_3). HRMS $C_{17}H_{21}O_8SNa$: calcd 422.0886, found 422.0875.

4.11. (2*R*,4*R*,5*R*)-4-((*S*)-Furan-3-yl(methoxy)methyl)-2-phenyl-1,3-dioxan-5-ol (6)

Following the general method **C**, compound **5** (66.8 mg, 0.17 mmol), $TMSN_3$ (45 μL, 0.34 mmol), and Bu_2SnO (41.6 mg, 0.17 mmol) after 15 h led after flash chromatography (EtOAc/cyclohexane, 2/8) to compound **6** (5 mg, 10%) as a yellow syrup; $[\alpha]_D^{20}$ +42 (*c* 0.6, MeOH); IR(ATR) ν 2919, 1369, 1259, 1058, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (sugar numbering) 7.51 (m, 1H, H-1), 7.49 (m, 1H, H-1′), 7.44–7.30 (m, 5H, C_6H_5), 6.50 (d, $J_{1',2'}$=1.1 Hz, 1H, H-2′), 5.45 [s, 1H, C*H*(C_6H_5)], 4.46 (d, $J_{3,4}$=8.2 Hz, 1H, H-3), 4.38 (dd, $J_{5,6a}$=5.3 Hz, 1H, H-6a), 3.96 (m, 1H, H-5), 3.74 (t, $J_{4,5}$=8.2 Hz, 1H, H-4), 3.66 (dd, $J_{6a,6b}$=11.8, $J_{5,6b}$=7.8 Hz, 1H, H-6b), 3.38 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (sugar numbering) 143.5 (C-1), 141.3 (C-1′), 136.1, 128.4–125.9 (C_6H_5), 118.9 (C-2), 108.9 (C-2′), 100.5 [*C*H(C_6H_5)], 81.5 (C-4), 79.7 (C-3), 70.3 (C-6), 66.0 (C-5), 56.7 (OCH_3). HRMS $C_{16}H_{18}O_5Na$: calcd 313.1052, found 313.1059.

4.12. Methyl 2-*C*-cyano-3,4-*O*-isopropylidene-2-*O*-mesyl-β-D-*ribo*(*arabino*)pyranoside (8)

Following general method **A2**, compound **7**[15] (1.8 g, 8.82 mmol), Ac_2O (2.90 mL, 30.88 mmol), and PDC (2.32 g, 6.17 mmol) reacted for 20 h to give the corresponding crude ulose. This ulose, following the general method **B** [$Ti(OiPr)_4$ (3.16 mL, 10.58 mmol) and TMSCN (2.36 mL, 17.64 mmol) in MeOH (20 mL)] gave the crude cyanohydrins, which were dissolved in CH_2Cl_2 (50 mL), and treated with Et_3N (9.91 mL, 70.56 mmol) and CH_3SO_2Cl (3.75 mL, 48.51 mmol). The reaction mixture was stirred overnight then extracted and the residue purified by flash chromatography (EtOAc/cyclohexane, 50/50) to give compound **8** (1.54 g, 56%) as a mixture (56/44) of diastereoisomers: yellow syrup; IR (ATR) ν 2943, 1365, 1253, 1217, 1182, 1145, 1082, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.32, 5.17 (s, 2H, H-1), 4.57 (d, $J_{3,4}$=5.7 Hz, 1H, H-3), 4.25 (m, 1H, H-4), 3.99 (m, 4H, 4×H-5), 3.45, 3.43 (s, 6H, 2×OCH_3), 3.20, 3.19 (s, 6H, 2×OSO_2CH_3), 1.50, 1.32 (s, 12H, 4×CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.5 (CN), 111.1 [O*C*(CH_3)$_2$], 97.9/97.8 (C-1), 74.0 (2×C-2), 75.3/73.7 (C-4), 72.8/70.5 (C-3), 59.4/58.6 (C-5), 57.2/57.1 (OCH_3), 40.7/40.4 (OSO_2CH_3), 26.1, 25.9, 25.8, 25.3 (4×CH_3); HMRS $C_{11}H_{17}NO_7NaS$: calcd 330.0623, found 330.0635.

4.13. ((4*R*,5*S*)-5-(Furan-3-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (9)/(*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(furan-3-yl)methanol (10)[12]

Following the general method **C**, compound **8** (983 mg, 3.20 mmol), Bu_2SnO (797 mg, 3.20 mmol), and $TMSN_3$ (0.86 mL, 6.40 mmol) in toluene (32 mL) for 18 h at 100 °C gave after flash chromatography (EtOAc/cyclohexane, 35/65) compounds **9** (171 mg, 28%) and **10** (144 mg, 22.7%) as pure diastereoisomers. Compound **9**: yellow syrup; $[\alpha]^{20}_D$ +28 (*c* 0.51, $CHCl_3$); IR (ATR) ν 3421, 3342, 1985, 2887, 1506, 1373, 1246, 1217, 1153, 1066, 1039, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (sugar numbering) 7.41, 7.36 (m, 2H, H-1, H-1′), 6.37 (m, 1H, H-2′), 4.77 (d, $J_{3,4}$=4.6 Hz, 1H, H-3), 4.23 (dt, $J_{5a,4}$=$J_{5b,4}$=6.5 Hz, 1H, H-4), 3.95 (dd, $J_{5a,5b}$=8.1 Hz, 1H, H-5a), 3.90 (dd, 1H, H-5b), 1.43, 1.35 (s, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (sugar numbering) 143.7, 140.0 (C-1, C-1′), 125.1 (C-2), 110.0 [O*C*(OCH_3)], 108.9 (C-2′), 79.0 (C-4), 67.0 (C-3), 65.3 (C-5), 26.8, 25.5 (CH_3). HRMS. $C_{10}H_{14}O_4Na$: calcd 221.0790, found 221.0800. Compound **10**[12]: yellow syrup; $[\alpha]^{20}_D$ +130 (*c* 0.02, $CHCl_3$); IR (ATR) ν 3423, 2987, 2935, 1504, 1371, 1211, 1157, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (sugar numbering) 7.40 (m, 2H, H-1, H-1′), 6.35 (m, 1H, H-2′), 5.21 (d, $J_{3,4}$=6.7 Hz, 1H, H-3), 4.35 (m, 1H, H-4), 3.43 (dd, $J_{5a,4}$=7.7 Hz, $J_{5a,5b}$=11.6 Hz, 1H, H-5a), 3.33 (dd, $J_{5b,4}$=4.4 Hz, 1H, H-5b), 2.12 (br s, 1H, OH), 1.55, 1.42 (s, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (sugar numbering) 143.9, 140.7 (C-1, C-1′), 121.8 (C-2), 109.5 (C-2′), 109.1 [O*C*(OCH_3)], 78.7 (C-4), 72.3 (C-3), 63.0 (C-5), 27.9, 25.4 (2×CH_3). HRMS $C_{10}H_{14}O_4Na$: calcd 221.0790, found 221.0792.

4.14. 1,3-*O*-(Phenylmethylene-4-*O*-*tert*-butyldimethylsilyl-3-*C*-cyano-3-*O*-mesyl-thre(erythr)itol) (12)

Following the general method **A3**, compound **11**[16] (4.0 g, 12.34 mmol), DMSO (2.63 mL, 37.03 mmol), oxalyl chloride (2.12 mL, 24.68 mmol), and Et_3N (5.2 mL, 37.03 mmol) in CH_2Cl_2 (50 mL) gave the intermediate crude ulose (3.69 g), that was used in the next step without further purification; following the general method **B**. To a solution of crude ulose in CH_2Cl_2 (143 mL) was added $NaHCO_3$ (2.07 g, 24.68 mmol) in water (28.6 mL) and KCN (1.71 g, 26.4 mmol). After stirring for 19 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (143 mL) followed by addition of Et_3N (13.8 mL, 98.72 mmol) and MsCl (5.25 mL, 67.87 mmol). After 3 h and work-up, the residue was purified by flash chromatography (EtOAc/cyclohexane, 15/85) to give an unseparable mixture (3/97)

of diastereoisomers **12** (1.58 g, 32%) as an orange syrup: IR (ATR) ν 2962–2856, 1462, 1360, 1259, 1185, 1118, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.41 (m, 5H, C_6H_5), 5.59 (s, 1H, H-5), 5.02 (d, $J_{4A,4B}$=11.1 Hz, 1H, H-4A), 4.15–4.04 (m, 4H, H-2, 2×H-1, H-4B), 3.19 (s, 3H, OSO_2CH_3), 0.94 [s, 9H, $SiC(CH_3)_3$], 0.13, 0.10 [s, 6H, 2×$SiCH_3$]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1–126.8 (C_6H_5), 115.0 (CN), 102.8 (C-5), 81.4 (C-2), 72.1 (C-4), 71.6 (C-3), 62.7 (C-1), 40.4 (OSO_2CH_3), 26.2 [$SiC(CH_3)_3$], 18.8 [$SiC(CH_3)_3$], −4.8, −4.9 [2×$SiCH_3$]. HRMS $C_{19}H_{29}NO_6SSiNa$: calcd 450.1374, found 450.1383.

4.15. 2-*tert*-Butyldimethylsilyl-3-hydroxymethylfuran (13)

Following the general method **C**, compound **12** (590 mg, 1.49 mmol), Bu_2SnO (372 mg, 1.49 mmol), and $TMSN_3$ (0.40 mL, 2.98 mmol) in toluene (14.9 mL) for 19 h at 100 °C gave after flash chromatography (EtOAc/cyclohexane, 1/9), compound **13** (63 mg, 20%), which showed spectroscopic data [^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, $J_{4,5}$=1.6 Hz, 1H, H-5), 6.49 (d, 1H, H-4), 4.59 (s, 2H, CH_2OH), 1.69 (s, 1H, OH), 0.92 (s, 9H, ^{t}Bu), 0.31 (s, 6H, 2×$SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.2 (C-3), 147.1 (C-5), 136.2 (C-2), 110.9 (C-1), 57.5 (CH_2OH), 26.7 (^{t}Bu), 17.7 (Cq ^{t}Bu), −5.3 (2×CH_3Si)] in accordance with the literature.[17]

4.16. Computational methods

All calculations were performed with Gaussian 03.[26] The method applied for optimizing structures was B3LYP.[27] The basis set was 6−31+G(d,p) including polarization and diffuse functions. Basis sets with diffuse functions are recommended for molecules with lone pairs, for anions, and for systems with significant negative charge. All geometry optimizations were complete, and the stationary points were identified as local minima or transition states through the number of negative eigenvalues in their hessian matrices. IRC calculations[28] were used to connect the transition state to its respective precedent and ensuing minima. Vibrational frequency analyses were carried out also to obtain the zero-point vibrational energies (ZPVEs) and thermodynamic parameters.

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