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The synthesis of polyoxygenated, enantiomerically pure cyclopentane derivatives on route to neplanocin A stereoisomers via alkylidenecarbene species prepared from sugar templates

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ABSTRACT

Our new method for the generation of alkylidenecarbenes, based on the reaction of trimethylsilylazide/Bu_2SnO with α-cyanomesylates, has been applied to the synthesis of enantiomerically pure polyhydroxylated cyclopentane derivatives from conveniently functionalized sugar intermediates prepared from D-mannose. The stereoselectivity of the 1,5 C–H insertion reaction leading to the major *trans*-isomers (**8a**,**b**) has been assigned by ^{1}H RMN spectroscopic data, and correctly rationalized by a computational analysis at DFT level. Compounds **8a** and **8b** have been designed as suitable intermediates for the synthesis of neplanocin A enantiomer.

1. Introduction

In the last years, the synthesis and subsequent transformation of reactive species such as alkylidenecarbenes have 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]

Czernecki was the first to use α-cyanomesylates for this purpose; upon treatment with sodium azide/DMF a presumed alkylidenecarbene species were formed that after 1,2-H shift gave acetylenic derivatives.[3] 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.[4,5]

Some years ago,[6] and starting from α-cyanomesylates, we have reported that the synthesis of 5-substituted tetrazoles, according to Wittenberger's method[7] (trimethylsilyl azide, 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 (see for instance the transformation of compound **1** to **2**, via intermediate **A**, Scheme 1) via rare 1,6 C–H bond insertion reactions.[8]

As a proof of concept, and in order to extend these results to other substrates, we have now directed our attention to the synthesis and reactivity of conveniently functionalized precursors for the synthesis of polyhydroxylated cyclopentane derivatives after 1,5 C–H insertion reactions, a simple methodology that has proved its efficiency in the synthesis of several natural products including cyclopentene scaffold such as neplanocin A.[9,10] In these approaches major *trans*-isomers were isolated and characterized by ^{1}H NMR analysis, due to a presumed steric hindrance that shifts the equilibrium of the alkylidenecarbene species (**X1**/**X2**) to **X2**, and taking into account the vicinal coupling constants at the newly formed stereocenters (Scheme 2). In this communication we describe the results that we have obtained on related chemistry but using D-mannose as precursor for the synthesis of suitable intermediates leading to advanced compounds targeted for the preparation of neplanocin A stereoisomers (Fig. 1).[9,10]

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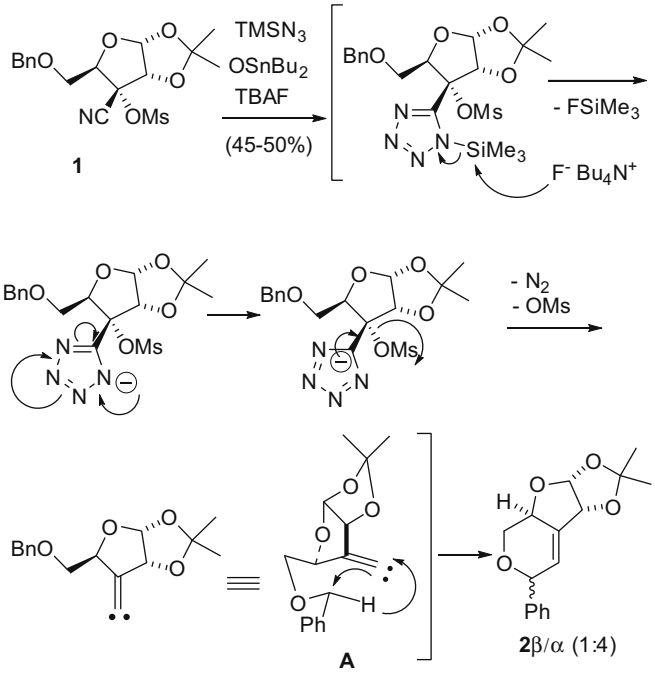


Scheme 1.

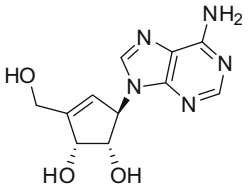
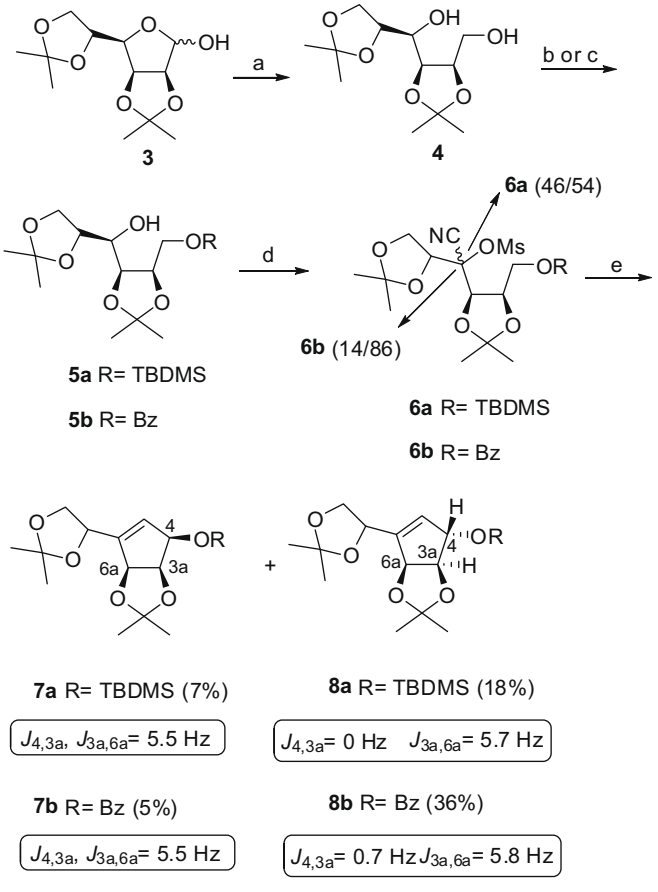


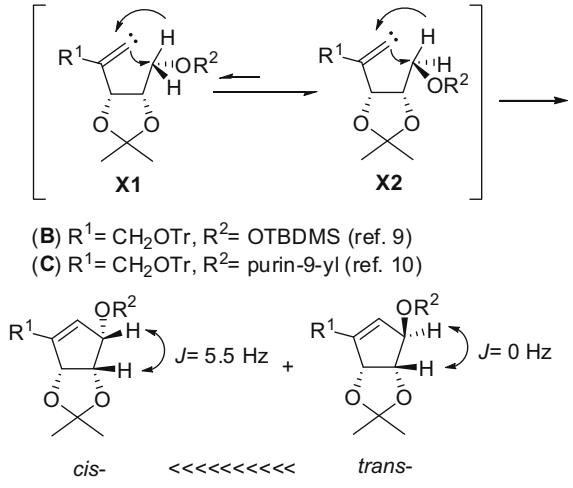
Figure 1. Neplanocin A.



Scheme 3. Reagents and conditions: (a) $AlLiH_4$, THF, 0 °C to rt (96%); (b) TBDMSCl, imidazole, DMF (87%); (c) BzCl, pyridine, CH_2Cl_2 (70%); (d) (i) PDC, Ac_2O, molecular sieves, CH_2Cl_2, reflux; (ii) KCN, $NaHCO_2$, CH_2Cl_2, H_2O, rt; (iii) MsCl, Et_2N, CH_2Cl_2, rt (**5a** to **6a** (75%), **5b** to **6b** (72%); (e) $TMSN_3$, Bu_2SnO, toluene, 100 °C.

2. Results and discussion

Starting from commercial 2,3:5,6-di-*O*-isopropylidene-D-mannose (**3**), reduction with LAH as described,[11] provided diol **4** (Scheme 3) that after routine transformations involving selective O-protection as the monosilyl (**5a**)[12] and monobenzoate (**5b**)[13] derivatives, followed by oxidation of the remaining secondary alcohol, addition of cyanide, and subsequent mesylation gave compounds **6a** and **6b**, respectively, as a mixture of diastereoisomers at C4, which we did not try to separate, but were submitted together to further reaction. Formation of the alkylidenecarbene species as usual[6] gave the cyclopentane derivatives **7a** (7%) and **8a** (18%), isolated in a 25% total yield (Scheme 3). Similarly, but using benzoate **5b**, the 1,5 C–H insertion reaction gave the expected carbocyclic derivatives **7b** and **8b** in 5% and 36% chemical yield, respectively (Scheme 3). The assignment of the absolute configuration at the newly formed stereocenter (C4) in compounds **7** and **8** as shown has been established by comparison of the observed vicinal couplings constant for H3a, with the values reported for similar compounds described in the literature.[9] Consequently, and as expected,[9] the formation of major isomers **8a**,**b** takes place from the opposite face where the bulky *O*-isopropylidene group is located (see Scheme 2), leading to major *trans*-isomers.



Scheme 2. 1,5 C–H insertion reactions leading to cyclopentane derivatives.

These results compared favorably with those reported in the literature for the synthesis of related cyclopentane intermediates, using lithiotrimethylsilyldiazomethane in THF at 0 °C,[14] as in the case of compound of type **B** (Scheme 2), bearing a *O*-trityl substituent at C-5 and a *O*-*tert*-butyldimethylsilyl group at C-1, the global yield for the cyclization reaction was 55–65%, and the ratio of isomer was 2:7,[9] while for compounds of type **C** (Scheme 2), bearing

an *O*-trityl substituent at C-5 and a purin-9-yl group at C-1, the global yield for the cyclization reaction was 30%, and the ratio of isomer was 1:2.[10] However, and in spite of these clear evidences, we decided to undertake a computational analysis in order to clearly evaluate the preferred way for the formation of the major isomers observed in these cyclizations.

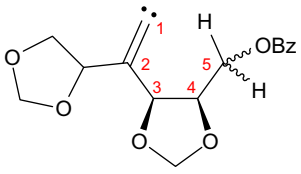
3. Computational study

We have also carried out a DFT computational analysis to explain the stereoselectivity observed for the 1,5-C–H insertion. This transformation takes place through the key transient intermediates alkylidenecarbenes. Accordingly, in the present study, carbene **9** has been selected as theoretical model **9** (Chart 1, see labeling).

Previous observations[6b] 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 nonbonding unshared spin-paired electrons occupy an sp-like orbital in the plane of the molecule. The computed HOMO of the alkylidencarbene **9** is delocalized over several atoms, but a great contribution to the HOMO comes from C1 (Fig. 2; for numbering, see Chart 1). On the other hand, the LUMO orbital is a p_π orbital mainly located at the carbene carbon C1.

In addition, the NBO analysis on **9** shows that the carbene carbon is approximately $sp^{1.5}$ hybridized ($sp^{1.46}$) and contains a lone pair in the NBO of predominant s character with 36.5% p mixing. These facts indicate the reactive site in **9**.[15]

Two stereoisomers can be formed by 1,5 C–H insertion of the alkylidencarbenes, **10** and **11**. The half chair-like transition structures **TS_{10}** and **TS_{11}** found (Fig. 3), respectively, show the hydrogen atom of interest in a plane defined by the carbon atom to which it is originally attached and the doubly bound carbon atoms of the carbene (deviation of 0.7° and 10.3°, respectively, Table 1).



9

Chart 1.

In this arrangement, the alkane C–H bond molecular orbital is periplanar with and therefore can overlap with the empty orbital of the alkylidenecarbene.[16] It could be thought that steric interactions between the H and the carbons would be reduced if the breaking C–H bond were out of the plane defined by C1–C2–C5.[17] However, the geometric parameters of the structures in the transition state (long C5–H and C1–C5 distances and a nearly formed C1–H bond, Table 1) ensure minor van der Waals repulsions. Furthermore, these distances reveal that the new carbon–hydrogen bond forms much faster than does the new carbon–carbon bond. To note that it is due to an acute asynchronicity in the formation of the C–C and C–H bonds in a single step, as IRC calculations have confirmed. H lies between C1 and C5 in the molecular plane. As the C5–H distance increases, C1 approaches C5. In the further course of the reaction the C1–C5 and C1–H bonds are built, and cyclopentenes **10** and **11** are obtained. Therefore, the cyclization is a concerted process, although strongly asynchronous.

As we have observed previously in related calculations,[6b] the C–H insertion can be viewed as having an electrophilic phase (involving the empty p empty orbital) followed by a nucleophilic phase (involving the nonbonding orbital). The initial electrophilic stage consists of the formation of a complex by interaction of the σ electrons of the C–H bond with the empty p orbital of the carbene carbon (NPA charge of 0.155 for C1 in **9**, Table 2). This flow of charge is maximum at the transition state and is followed by a nucleophilic phase where the nonbonding electrons of the carbene interact with the hydrogen atom. This interaction is favored by the C–H elongation promoted in the first phase of the C–H insertion step. Namely, the insertion 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 (Table 2).

The transition structures **TS_{10}** and **TS_{11}** show similar key distances between the involved atoms, although they suggest a slightly earlier transition state for **TS_{11}**. Selected structural parameters of transition states and intermediates are given in Table 1.

From an energetic point of view, our results clearly reveal a kinetic preference for the formation of **11** (2.9 vs 5.4 kcal mol^{-1}, Fig. 2), where the bulky protecting group is located in the opposite face of the *O*-benzoylic moiety at the new stereocenter. This result is supported by the experimental results which describe the formation of major *trans*-isomers **8a**,**b**.

The kinetic preference is due to an electrostatic repulsion between the oxygen atoms of the dioxolane and benzoate moieties. Thus, while in **TS_{11}** we have not observed critical destabilizing

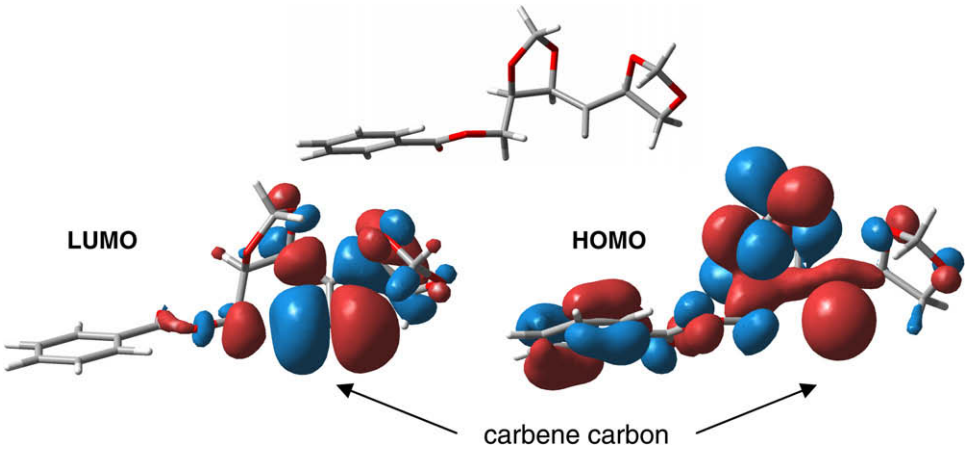


Figure 2. LUMO and HOMO of **9**.

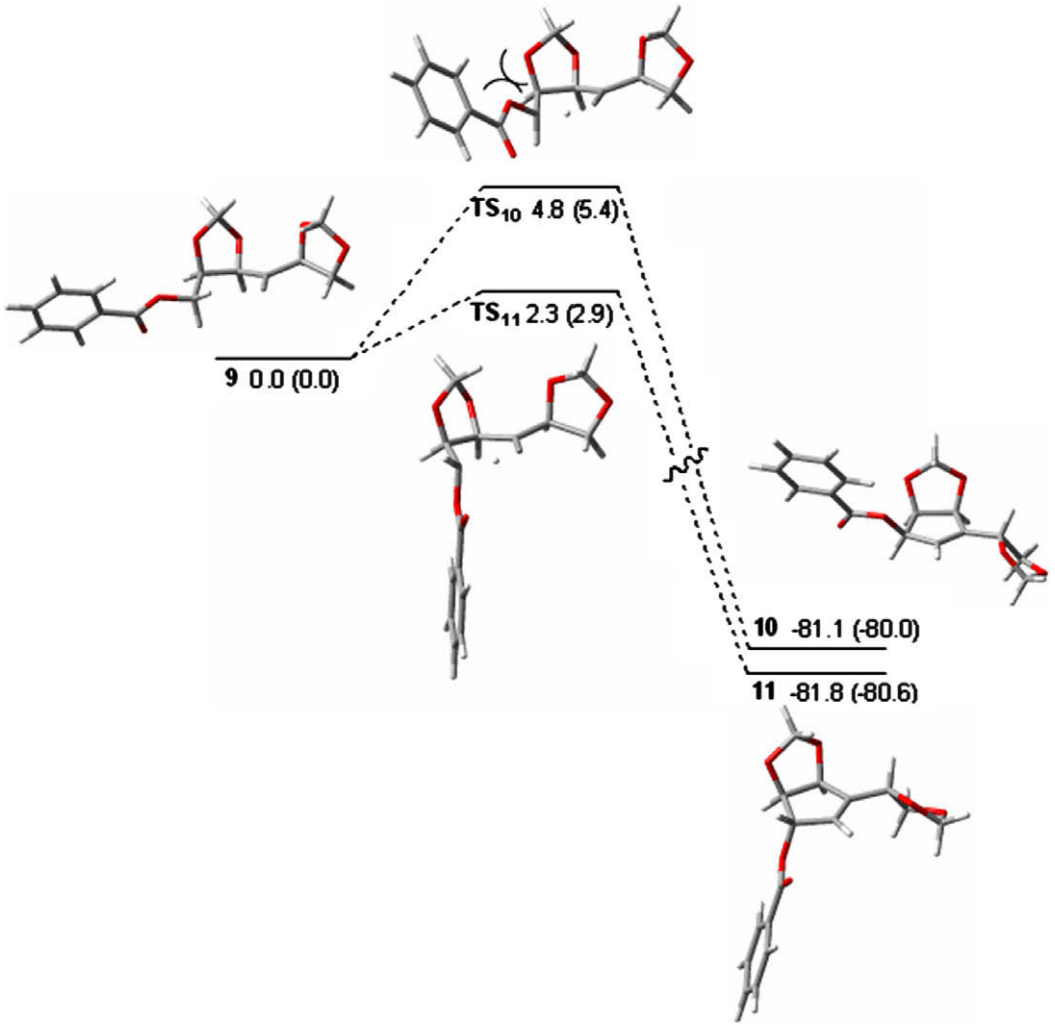


Figure 3. Enthalpy profile (in kcal mol^{-1}) for the 1,5 C–H insertion process of the alkylidenecarbene into the alkane carbon C5, to yield two possible stereoisomers, **10** and **11** (free energy differences are shown in parentheses).

Table 1
Structural key parameters (distances in Å, bond angles and dihedral angles in °) during the 1,5 C–H insertion process

	9	**TS_{10}**	**10**	**TS_{11}**	**11**
C1–C2	1.305	1.324	1.337	1.324	1.337
C2–C3	1.541	1.530	1.515	1.530	1.517
C3–C4	1.537	1.539	1.561	1.540	1.557
C4–C5	1.517	1.508	1.566	1.503	1.543
C5–H	1.096	1.461		1.440	
H–C1	**2.180**	**1.159**	**1.084**	**1.168**	**1.083**
C1–C5	**2.857**	**2.271**	**1.500**	**2.245**	**1.505**
C1–C2–C3	127.8	124.1	112.0	124.1	112.0
C2–C3–C4	116.7	109.1	104.8	108.4	104.0
C3–C4–C5	116.8	112.1	105.5	112.8	106.1
C4–C5–H	110.4	119.5		118.9	
C5–H–C1	117.5	119.7		118.5	
C5–C1–C2	85.5	93.6	112.9	94.0	112.3
C2–C1–H–C5	33.8	−0.7	0.5	10.3	0.5

interactions, in **TS_{10}** a short O···O distance can be detected (2.666 Å), shorter than the sum of the van der Waals radii. This repulsive interaction destabilizes the transition structure **TS_{10}** that leads to the *S*-isomer. From a thermodynamic perspective, the 1,5-insertion reaction with C–H by the carbene is strongly exothermic (∼−80 kcal mol^{-1}, Fig. 2), whatever the configuration at the new stereocenter, and hence irreversible.

Table 2
NPA charges in the 1,5 C–H insertion process

	9	**TS_{10}**	**10**	**TS_{11}**	**11**
C1	0.155	−0.172	−0.215	−0.167	−0.219
C2	−0.392	−0.229	−0.072	−0.227	−0.071
C3	0.070	0.0553	0.038	0.056	0.039
C4	0.041	0.029	0.050	0.027	0.057
C5	−0.143	0.049	0.027	0.039	0.027
H	0.252	0.258	0.259	0.267	0.267

4. Conclusions

The generation of alkylidenecarbene species, based on the reaction of trimethylsilylazide/Bu_2SnO with α-cyanomesylates, has been applied to the synthesis of enantiomerically pure polyhydroxylated cyclopentane derivatives from conveniently functionalized sugar intermediates prepared from D-mannose. The stereoselectivity of the 1,5 C–H insertion reaction leading to the major *trans*-isomers (**8a**,**b**) has been assigned by ^{1}H RMN spectroscopic data, and correctly rationalized by a computational analysis at DFT level. Compounds **8** have been designed as suitable intermediates for the synthesis of neplanocin A stereoisomers.

5. Experimental

5.1. 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, $CHCl_3$, and MeOH, with a digital polarimeter using a 1 dm cell. ^1H 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 oxidation with PDC (A)

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 portion wise 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.

5.3. 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). 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.

5.4. 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).

5.4.1. 2,3:5,6-Di-*O*-isopropylidene-D-mannitol (4)

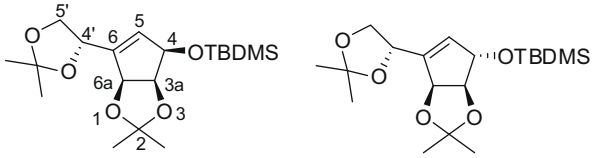
A solution of commercial 2,3:5,6-di-*O*-isopropylidene-D-mannose (**3**) (6.0 g, 23.07 mmol) in dry THF (50 mL), cooled at 0 °C, was treated with $AlLiH_4$ (3.07 g, 80.76 mmol). After stirring for 4 h at room temperature, EtOAc and HCl 2 M were carefully added. The aqueous layer was extracted with EtOAc (×3). The organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness to give alditol **4** (5.83 g, 96%) as a white solid [mp 156–157 °C; $[\alpha]_{20}^{D}$ +15.0 (*c* 0.08, H_2O)], showing spectroscopic data {IR (ATR) *ν* 3190, 2931, 1450, 1325, 1261, 1078, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 75 MHz) *δ* 4.92 (t, $J_{1a,OH} = J_{1B,OH} = 5.3$ Hz, 1H, OH), 4.67 (d, $J_{4,OH} = 6.8$ Hz, 1H, OH), 4.16 (m, 2H, H-2, H-3), 3.95 (m, 2H, H-5, H-6A), 3.82 (dd, $J_{5,6A} = 8.1$ Hz, $J_{6A,6B} = 11.1$ Hz, 1H, H-6B), 3.66 (m, 2H, H-1), 3.38 (m, 1H, H-4), 1.38, 1.30, 1.26, 1.25 (s, 12H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) *δ* 109.1, 108.1 (2 × [$OC(CH_3)_2$]), 78.2, 76.6, 76.5 (C-2, C-3, C-4), 70.2 (C-5), 67.3 (C-6), 60.5 (C-1), 27.5, 27.4, 26.2, 26.0 (4 × CH_3)} in good agreement with those reported in the literature.[11]

5.4.2. 1-*O*-*tert*-Butyldimethylsilyl-2,3:5,6-di-*O*-isopropylidene-D-mannitol (5a)

To a solution of compound **4** (2.0 g, 7.63 mmol) in DMF (10 mL) were added imidazole (1.04 g, 15.26 mmol) and TBDMSCl (1.26 g, 8.39 mmol). After stirring overnight at room temperature, DMF was eliminated under reduced pressure. The residue was extracted with diethyl ether and a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuo. The residue was purified by flash chromatography (EtOAc/cyclohexane, 20/80) to give product **5a** (2.50 g, 87%) as a colorless syrup {$[\alpha]_{20}^{D}$ −16.0 (*c* 0.59, $CHCl_3$); IR (ATR): *ν* 2985, 2931, 2858, 1724, 1462, 1371, 1251, 1213, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 4.39 (d, $J_{2,3} = 7.0$ Hz, 1H, H-3), 4.24 (dt, $J_{2,3} = J_{1a,2} = 7.0$ Hz, $J_{1,2} = 3.8$ Hz, 1H, H-2), 4.11 (m, 2H, H-5, H-6A), 4.02 (m, 2H, H-1A, H-6B), 3.83 (dd, $J_{1a,1b} = 10.9$ Hz, 1H, H-1B), 3.67 (m, 1H, H-4), 3.17 (m, 1H, OH), 1.50, 1.41, 1.39, 1.36 (s, 12H, 4 × CH_3), 0.91 [s, 9H, $SiC(CH_3)$], 0.11 (s, 6H, 2 × $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 109.6 [$OC(CH_3)_2$], 108.6 [$OC(CH_3)_2$], 76.9, 76.2, 76.1 (C-2, C-3, C-5), 70.7 (C-4), 67.9 (C-6), 61.9 (C-1), 27.2, 27.0, 25.7, 25.2 (4 × CH_3), 26.2 [$C(CH_3)$], 18.6 [$C(CH_3)$], −5.0, −5.1 (2 × $SiCH_3$). HRMS: $C_{18}H_{36}O_6NaSi$ calcd 399.2203, found 399.2191}, in good agreement with those reported in the literature.[12]

5.4.3. 1-*O*-*tert*-Butyldimethylsilyl-4-*C*-cyano-4-*O*-mesyl-2,3:5,6-di-*O*-isopropylidene-D-mann(tall)itol (6a)

Following the general method **A**, compound **5a** (1.0 g, 2.66 mmol), Ac_2O (0.87 mL, 9.30 mmol), and PDC (0.70 g, 1.86 mmol) for 4 h gave a crude ulose, which following the general method **B**, was dissolved in CH_2Cl_2 (20 mL), and treated with added $NaHCO_3$ (446 mg, 5.32 mmol), in water (6.18 mL) and with KCN (370 mg, 5.69 mmol). After stirring for 17 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (20 mL) followed by addition of Et_3N (2.99 mL, 21.28 mmol) and MsCl (1.13 mL, 14.63 mmol). After 2 h and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 15/85) to give compound **6a** (960 mg, 75%) as an inseparable mixture of diastereoisomers in a 46/54 ratio: IR (ATR): *ν* 2949, 2932, 2857, 1472, 1464, 1373, 1361, 1253, 1220, 1183, 1068, 957 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 4.77–4.09 (m, 7H, 2H-1, H-2, H-3, H-5, 2H-6), 3.27 (s, 3H, OSO_2CH_3), 1.56, 1.51, 1.40, 1.34 (s, 12H, 4 × CH_3), 0.90 [s, 9H, $SiC(CH_3)_3$], 0.10, 0.08 (s, 6H, 2 × $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 114.2 (CN), 110.8, 110.7 {2 × [$OC(CH_3)_2$]}, 83.5 (C-4), 79.7 (C-5), 77.6 (C-3), 77.0, (C-2), 67.5 (C-6), 61.3 (C-1), 41.0 (OSO_2CH_3), 27.1–25.1 (4 × CH_3, *t*Bu), 18.8 [$Si(CH_3)_3$], −4.7, −4.8 ($SiCH_3$). HRMS: $C_{20}H_{37}NO_8SSi$ calcd 502.1907, found 502.1902.



7a **8a**

5.4.4. *tert*-Butyl {(3a*S*,4*R*,6a*S*)-6-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-yloxy}dimethylsilane (7a), and *tert*-butyl {(3a*S*,4*S*,6a*S*)-6-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-yloxy}dimethylsilane (8a)

Following the general method **C**, compound **6a** (456 mg, 0.95 mmol), Bu_2SnO (237 mg, 0.95 mmol) and $TMSN_3$ (0.25 mL, 1.9 mmol) in toluene (9.5 mL) for 23 h at 100 °C gave after flash chromatography (EtOAc/cyclohexane, 10/90), compounds **7a** (25 mg, 7%) and **8a** (63 mg, 18%) as slight yellow solids. Compound **7a**: $[\alpha]_{20}^{D}$ +47.0 (*c* 0.10, $CHCl_3$); IR (ATR): *ν* 2985, 2929, 2856, 1471,

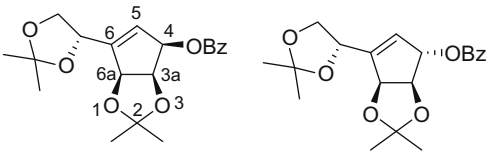
1369, 1244, 1209, 1157, 1107, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.77 (s, 1H, H-5), 4.85 (t, $J_{3a,4}$ = 5.5 Hz, $J_{3a,6a}$ = 5.5 Hz, 1H, H-3a), 4.66 (m, 3H, H-4, H-6a, H-4′), 4.22 (dd, $J_{4',5'A}$ = 6.1 Hz, $J_{5'A,5'B}$ = 8.1 Hz, 1H, H-5′A), 3.81 (t, $J_{4',5'B}$ = 8.1 Hz, 1H, H-5′B), 1.45, 1.42, 1.40, 1.37 (s, 12H, 4 × CH_3), 0.93 [SiC(CH_3)], 0.14 ($SiCH_3$), 0.13 ($SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.9 (C-6), 130.4 (C-5), 112.6 [O*C*(CH_3)$_2$], 109.3 [O*C*(CH_3)$_2$], 83.5 (C-3a), 79.0, 74.8, 73.8 (C-4, C-6a, C-4′), 69.6 (C-5′), 27.8, 27.0, 26.8, 26.3 (4 × CH_3), 26.3 [SiC(*C*H_3)$_3$], 18.9 [SiC(*C*H_3)$_3$], −3.9 ($SiCH_3$), −4.3 ($SiCH_3$). HRMS: $C_{19}H_{34}O_5Si$ calcd 393.2073, found 393.2089. Compound **8a**: $[\alpha]_{20}^{D}$ +73.0 (*c* 0.32, $CHCl_3$); IR (ATR) *ν* 2985, 2929, 2856, 1471, 1464, 1369, 1249, 1209, 1155, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75 (s, 1H, H-5), 5.16 (d, $J_{3a,6a}$ = 5.7 Hz, 1H, H-3a), 4.72 (s, 1H, H-4), 4.63 (m, 1H, H-4′), 4.50 (d, 1H, H-6a), 4.21 (dd, $J_{4',5'A}$ = 6.3 Hz, $J_{5'A,5'B}$ = 8.3 Hz, 1H, H-5′A), 3.74 (t, $J_{4',5'B}$ = 8.3 Hz, 1H, H-5′B), 1.44, 1.42, 1.38, 1.33 (s, 12H, 4 × CH_3), 0.91 [SiC(CH_3)], 0.13 ($SiCH_3$), 0.11 ($SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9 (C-6), 128.8 (C-5), 112.2 [O*C*(CH_3)$_2$], 109.3 [O*C*(CH_3)$_2$], 87.5 (C-6a), 84.2 (C-3a), 81.2 (C-4), 74.2 (C-4′), 69.5 (C-5′), 27.3, 26.7, 26.3, 26.2 (4 × CH_3), 26.1 [SiC(*C*H_3)$_3$], 18.5 [SiC(*C*H_3)$_3$], −4.2 ($SiCH_3$), −4.3 ($SiCH_3$). HRMS: $C_{19}H_{34}O_5Si$ calcd 393.2073, found 393.2075.

5.4.5. 1-*O*-Benzoyl-2,3:5,6-di-*O*-isopropylidene-D-mannitol (5b)

To a solution of compound **4** (1.96 g, 7.48 mmol) in pyridine (10 mL) and CH_2Cl_2 (50 mL) was added benzoyl chloride (0.95 mL, 8.23 mmol) at 0 °C. After stirring for 19 h at room temperature, water and diethyl ether were added. The organic layer was washed with HCl 1 M, dried over Na_2SO_4, filtered, and evaporated under vacuo. The residue was purified by flash chromatography (EtOAc/cyclohexane, 25/75) to give product **5b** (1.94 g, 70%) as a white solid [mp 98–99 °C; $[\alpha]_{20}^{D}$ +19.0 (*c* 0.3, H_2O)], showing spectroscopic data {IR (ATR) *ν* 3466, 2989, 2939, 2885, 1691, 1456, 1365, 1286, 1215, 1128, 1068, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07, 7.56–7.28 (m, 5H, C_6H_5), 4.68–4.48 (m, 5H, OH, 2H-1, H-2, H-3), 4.13–4.02 (m, 3H, H-5, H-6A, H-6B), 3.67 (dd, $J_{4,OH}$ = 7.5 Hz, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 1.54 (s, 3H, CH_3), 1.42 (s, 6H, 2 × CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6 (CO), 133.5–128.7 (C_6H_5), 109.9, 109.2 [2 × O*C*(CH_3)$_2$], 76.6, 75.8, 75.4 (C-2, C-3, C-4), 70.6 (C-5), 67.6 (C-6), 64.6 (C-1), 27.2 (CH_3), 27.1 (CH_3), 25.6 (CH_3), 25.0 (CH_3). HRMS: $C_{19}H_{26}O_7Na$ calcd 389.1576, found 389.1578}, in good agreement with those reported in the literature.[13]

5.4.6. 1-*O*-Benzoyl-4-*C*-cyano-4-*O*-mesyl-2,3:5,6-di-*O*-isopropylidene-D-mann(tall)itol (6b)

Following general method **A**, compound **5b** (1.94 g, 5.30 mmol), Ac_2O (1.74 mL, 18.55 mmol), and PDC (1.39 g, 3.71 mmol) for 22 h gave crude ulose. Following the general method **B**, to a solution of this crude ulose in CH_2Cl_2 (50 mL) were added $NaHCO_3$ (890 mg, 10.6 mmol) in water (12.33 mL) and KCN (737 mg, 11.34 mmol). After stirring for 19 h, the crude cyanohydrins were dissolved in CH_2Cl_2 (50 mL) followed by addition of Et_3N (5.95 mL, 42.4 mmol) and MsCl (2.25 mL, 29.15 mmol). After 22 h and extraction, the residue was purified by flash chromatography (EtOAc/cyclohexane, 30/70) to give product **6b** (1.8 g, 72%) as an inseparable mixture of diastereoisomers in 86/14 ratio, as a slight yellow syrup: IR (ATR) *ν* 2993, 2983, 1724, 1454, 1384, 1363, 1271, 1249, 1215, 1182, 1118, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07, 7.55–7.40 (m, 5H, C_6H_5), 5.09 (m, 1H, H-1A), 4.83–4.75 (m, 3H, H-1B, H-2, H-5), 4.63 (d, $J_{2,3}$ = 4.8 Hz, 1H, H-3), 4.26 (dd, $J_{5,6A}$ = 6.9 Hz, $J_{6A,6B}$ = 10.1 Hz, 1H, H-6A), 4.20 (dd, $J_{5,6B}$ = 7.4 Hz, 1H, H-6B), 3.32 (s, 3H, OSO_2CH_3), 1.62, 1.54, 1.42, 1.38 (s, 12H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5 (CO), 133.5–128.7 (C_6H_5), 114.1 (CN), 111.5, 111.1 (2 × [O*C*(CH_3)$_2$]), 82.8 (C-4), 77.7 (C-5), 77.0 (C-3), 76.4, (C-2), 67.3 (C-6), 62.6 (C-1), 41.0 (OSO_2CH_3), 27.0, 26.4, 26.1, 25.4 (4 × CH_3). HRMS: $C_{21}H_{27}O_9NSNa$ calcd 492.1304, found 492.1296.



7b **8b**

5.4.7. (3a*R*,4*R*,6a*S*)-6-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-yl benzoate (7b), and (3a*R*,4*S*,6a*S*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[*d*][1,3]dioxol-4-yl benzoate (8b)

Following the general method **C**, compound **6b** (924 mg, 1.97 mmol), Bu_2SnO (490 mg, 1.97 mmol), and $TMSN_3$ (0.52 mL, 3.94 mmol) in toluene (19.7 mL) for 22 h at 100 °C gave after flash chromatography (EtOAc/cyclohexane, 15/85), compounds **7b** (39 mg, 5%) and **8b** (258 mg, 36%). Compound **7b**: $[\alpha]_{20}^{D}$ +28.0 (*c* 0.29, $CHCl_3$); IR (ATR): *ν* 2985, 2935, 1718, 1452, 1371, 1269, 1209, 1155, 1109, 1062, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11–7.42 (m, 5H, C_6H_5), 5.97 (t, $J_{4,5}$ = $J_{5,6a}$ = 1.7 Hz, 1H, H-5), 5.61 (ddd, $J_{4,6a}$ = 1.7 Hz, $J_{4,3a}$ = 5.5 Hz, 1H, H-4), 5.09 (t, $J_{6a,3a}$ = 5.5 Hz, 1H, H-3a), 5.00 (d, 1H, H-6a), 4.71 (m, 1H, H-4′), 4.28 (dd, $J_{4',5'A}$ = 6.3 Hz, $J_{5'A,5'B}$ = 8.3 Hz, 1H, H-5′A), 3.88 (t, $J_{4',5'B}$ = 8.3 Hz, 1H, H-5′B), 1.49, 1.43, 1.38, 1.35 (s, 12H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3 (CO), 147.2 (C-6), 133.4-128.7 (C_6H_5), 126.0 (C-5), 113.5 [O*C*(CH_3)$_2$], 109.6 [O*C*(CH_3)$_2$], 83.7 (C-6a), 77.6 (C-3a), 75.8 (C-4), 73.9 (C-4′), 69.5 (C-5′), 27.8, 27.1, 26.8, 26.2 (4 × CH_3). HRMS: $C_{20}H_{24}O_6Na$ calcd 383.1471, found 383.1483. Compound **8b**: $[\alpha]_{20}^{D}$ +133.0 (*c* 0.63, $CHCl_3$); IR (ATR): *ν* 2985, 2935, 1716, 1452, 1371, 1247, 1207, 1153, 1109, 1062, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.46 (m, 5H, C_6H_5), 5.98 (s, 1H, H-5), 5.79 (d, $J_{4,3a}$ = 0.7 Hz, 1H, H-4), 5.21 (dd, $J_{6a,3a}$ = 5.8 Hz, 1H, H-3a), 4.80 (d, 1H, H-6a), 4.67 (m, 1H, H-4′), 4.25 (dd, $J_{4',5'A}$ = 6.3 Hz, $J_{5'A,5'B}$ = 8.3 Hz, 1H, H-5′A), 3.78 (dd, $J_{4',5'B}$ = 8.3 Hz, 1H, H-5′B), 1.45, 1.43, 1.42, 1.31 (s, 12H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3 (CO), 149.8 (C-6), 133.5–128.7 (C_6H_5), 124.9 (C-5), 113.0 [O*C*(CH_3)$_2$], 109.5 [O*C*(CH_3)$_2$], 84.3 (C-6a), 84.0 (C-3a), 83.1 (C-4), 74.1 (C-4′), 69.5 (C-5′), 27.6, 26.7, 26.2, 26.1 (4 × CH_3). HRMS: $C_{20}H_{24}O_6Na$ calcd 383.1471, found 383.1483.

5.5. Computational methods

All calculations were carried out with the GAUSSIAN 03 program.[18] The optimizations were carried out using hybrid density functional B3LYP[19] with the 6-31G(d,p) basis set. This polarized basis set adds p functions to hydrogen atoms in addition to the d functions on heavy atoms. Single-point energy calculations with the triple split valence basis set 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 to obtain the zeropoint vibrational energies (ZPVEs) and thermodynamic parameters. From the transition structures, the intrinsic reaction coordinate (IRC) was obtained using the IRC routine in Gaussian. Natural bond orbital (NBO) analyses[20] have been performed by the module NBO v.3.1 implemented in GAUSSIAN 03 at the optimization level.

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References

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. Engl.* **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, M. J.; Camarasa, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1403; (b) Pérez, M. J.; Camarasa, M. J. *Tetrahedron* **1994**, *50*, 7269.
5. For some useful transformations of alkylidenecarbenes in sugar templates, see: (a) Tronchet, J. M. 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) Wardrop, D. J.; Zhang, W.; Frtz, J. *Org. Lett.* **2002**, *4*, 489.
6. (a) Nguyen Van Nhien, A.; León, R.; Postel, D.; Carreiras, M. C.; García, A. G.; Marco-Contelles, J. *J. Carbohydr. Chem.* **2005**, *24*, 369; (b) Nguyen Van Nhien, A. et al., unpublished results.
7. (a) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139; For a review on the synthesis of 5-substituted 1*H*-tetrazoles, see: (b) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
8. 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.
9. Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537.
10. Niizuma, S.; Shuto, S.; Matsuda, A. *Tetrahedron* **1997**, *53*, 13621.
11. Fick, W.; Kuelle, T.; Schmidt, R. R. *Helv. Chim. Acta* **1991**, 435.
12. Li, L.-S.; Wu, Y.-L. *Tetrahedron* **2002**, *58*, 9049.
13. Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617.
14. Ohira, S.; Okai, K.; Moritanui, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.
15. Similar results have been reported for a related alkylidencarbene: Markovic, S.; Stankovic, S.; Radenkovic, S.; Gutman, I. *J. Chem. Inf. Model.* **2008**, *48*, 1984.
16. Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.
17. Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557.
18. Frisch, M. J.; Trucks G. W.; Schlegel H. B.; Scuseria G. E.; Robb M. A.; Cheeseman J. R.; Montgomery, Jr. J. A.; Vreven T.; Kudin K. N.; Burant J. C.; Millam J. M.; Iyengar S. S.; Tomasi J.; Barone V.; Mennucci B.; Cossi M.; Scalmani G.; Rega N.; Petersson G. A.; Nakatsuji H.; Hada M.; Ehara M.; Toyota K.; Fukuda R.; Hasegawa J.; Ishida M.; Nakajima T.; Honda Y.; Kitao O.; Nakai H.; Klene M.; Li X.; Knox J. E.; Hratchian H. P.; Cross J. B.; Bakken V.; Adamo C.; Jaramillo J.; Gomperts R.; Stratmann R. E.; Yazyev O.; Austin A. J.; Cammi R.; Pomelli C.; Ochterski J. W.; Ayala P. Y.; Morokuma K.; Voth G. A.; Salvador P.; Dannenberg J. J.; Zakrzewski V. G.; Dapprich S.; Daniels A. D.; Strain M. C.; Farkas O.; Malick D. K.; Rabuck A. D.; Raghavachari K.; Foresman J. B.; Ortiz J. V.; Cui Q.; Baboul A. G.; Clifford S.; Cioslowski J.; Stefanov B. B.; Liu G. Liashenko A.; Piskorz P.; Komaromi I.; Martin R. L.; Fox D. J.; Keith T.; Al-Laham M. A.; Peng C. Y.; Nanayakkara A.; Challacombe M.; Gill P. M. W.; Johnson B.; Chen W.; Wong M. W.; Gonzalez C.; Pople J. A. GAUSSIAN 03, Revision B.03, Gaussian, Wallingford CT, 2003.
19. (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.
20. NBO Version 3.1; Glendening E. D.; Reed A. E.; Carpenter J. E.; Weinhold F. 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.