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Steric course of some cyclopropanation reactions of L-*threo*-hex-4-enopyranosides☆

Antonino Corsaro,[a,*] Ugo Chiacchio,[a] Roberto Adamo,[a] Venerando Pistarà,[a] Antonio Rescifina,[a] Roberto Romeo,[b] Giorgio Catelani,[c] Felicia D'Andrea,[c] Manuela Mariani[c] and Emanuele Attolino[c]

[a]*Dipartimento di Scienze Chimiche, Università di Catania, viale A. Doria 6, 95125 Catania, Italy*
[b]*Dipartimento Farmaco Chimico, Università di Messina, viale Annunziata, 98100 Messina, Italy*
[c]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, via Bonanno 33, 56126 Pisa, Italy*

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Abstract—Completely protected 4-deoxy-α-L-*threo*-hex-4-enopyranosides **1c**,**d** undergo the dichlorocarbene addition affording exclusively diastereomeric adducts **5c**,**d** with the cyclopropane ring *anti* to the C-3 alkyloxy substituent, while the reaction with 3-unprotected derivatives **1a**,**b** affords a mixture of *syn* and *anti* derivatives. Under the Simmons–Smith cyclopropanation adducts **2a**-**d** with a *syn* stereochemistry are obtained. Starting from **5b**, the cyclopropanated sugar **3b** is obtained by reduction with $LiAlH_4$, thus the two diastereomers **2b** and **3b** can be stereoselectively obtained through the two different pathways. For a useful comparison, 4-deoxy-β-L-*threo*-hex-4-enopyranoside **1e** was also subjected to the above two cyclopropanation methods affording the expected cycloadduct **2e** and a diastereomeric mixture of dichlorocycloadducts **4e** and **5e** (**4e**/**5e**=2.8:1).

1. Introduction

Among several methods for the synthesis of cyclopropanes starting from unsaturated carbohydrates,[2] the most commonly used are the additions of the methylene–zinc–iodide complex, generated from diethyl zinc and diiodomethane (the Furukawa modification[3] of the Simmons–Smith reaction[4,5]), and additions of carbenes generated by the formal elimination of hydrogen halide from haloform with a strong base[6] or by transition metal-catalyzed decomposition of diazo compounds.[7] Other routes such as the additions of sulfur ylides[8] are used rather sparingly.

While cyclopropanation reactions of 1,2-glycals have been extensively studied because of their easy accessibility,[2,9] on the contrary, those of the other unsaturated sugars have attracted very little attention. The cyclopropanation of 2,3-unsaturated sugars was accomplished by using the classic Simmons–Smith reaction with diiodomethane and the Zn/Cu couple,[10] and by addition of the dichlorocarbene with chloroform and 50% aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride (TEBAC)[11] and by the addition of sulfur ylides.[12,13] 2,3-Cyclopropanated carbohydrates were also obtained by benzophenone sensitized addition of methanol and subsequent treatment with toluene-*p*-sulfonyl chloride in the presence of pyridine.[14,15]

To our best knowledge, there are no reports in literature on the cyclopropanation of 3,4-unsatutared sugars and only a single example is reported on the cyclopropanation of a 4,5-unsaturated α-D-pyranoside with a modified Simmons–Smith reaction.[16]

As a part of a research project on the exploitation in sugar chemistry of hex-4-enopyranosides derived from lactose,[17] we here report the results of our investigations on cyclopropanation reactions of α-L-*threo*-hex-4-enopyranosides **1a**-**d** and, for a useful comparison, on those of protected methyl anomer **1e** by means of the two classical methods, which uses the methylene–zinc–iodide complex and dichlorocarbene.

2. Results and discussion

The Simmons–Smith cyclopropanation with diethyl zinc reagent and diiodomethane in dry diethyl ether of hex-4-enopyranosides **1a**,[17c] **1b**[18] gave a nearly quantitative yield of diastereomerically pure cycloadducts **2a**,**b**, as judged by

☆ See Ref. 1.

Keywords: Cyclopropanations; Dichlorocarbene; Simmons–Smith; Hex-4-enopyranosides; Lactose; Dehalogenations.
* Corresponding author. Tel.: +39-095-7385017; fax: +39-095-580138; e-mail address: acorsaro@unict.it

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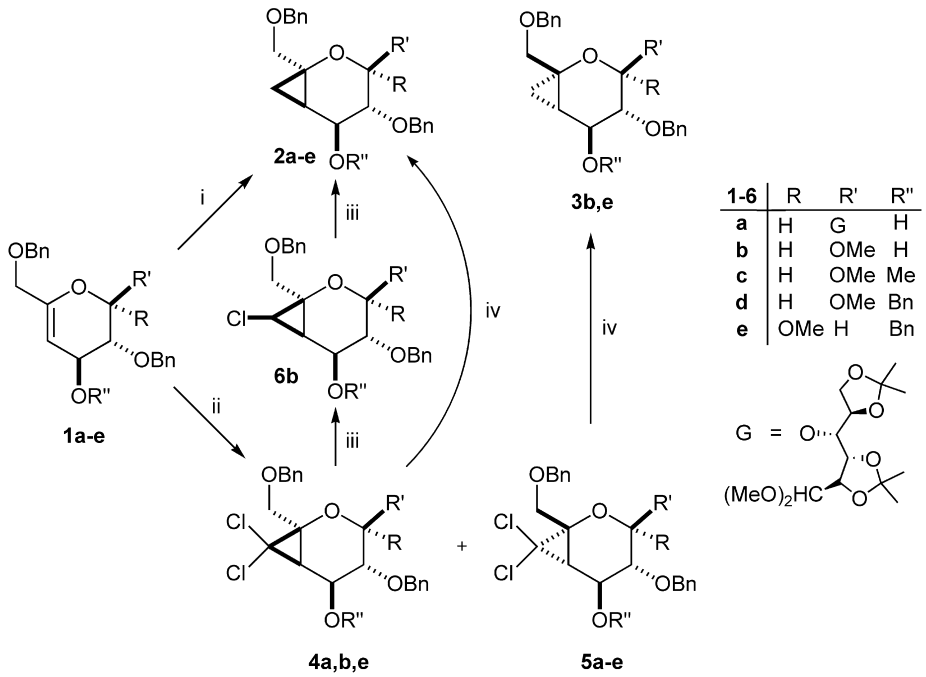


Scheme 1. i) CH_2I_2, Et_2Zn, Et_2O; ii) $CHCl_3$, NaOH 50%, $Et_3N^+PhCl^-$; iii) $LiAlH_4$ 6 eq., dry THF; iv) $LiAlH_4$ 12 eq., dry THF.

TLC and inspection of the ^1H NMR spectra[19] of the crude reaction mixtures (Scheme 1).

The structures of **2a**,**b** deriving from the formation of the cyclopropane ring on the upper face of the double bond bearing the C-3 hydroxyl group, was assigned on the basis of the values of coupling constants between H-3 and H-4 protons and the NOE enhancements upon their irradiation.

The high value of $J_{3,4}$ (7.5 Hz) is consistent with a *cis*-relationship between the two H-3 and H-4 protons[20] and with the hydroxyl directed cyclopropanation of the allylic C-3 oxygen by coordination with zinc under Simmons–Smith conditions.[21] Moreover, diagnostic enhancements were the positive ones of H-7a [3.7% (glucosyl, **2a**) and 4.0% (methyl, **2b**)] and H-7b [3.9% (glucosyl, **2a**) and 3.4% (methyl, **2b**)] protons upon irradiation of H-2 and H-4 protons, respectively (Fig. 1). Besides the signals of the pyranoside ring, the ^{13}C NMR spectra of **2a** and **2b** show diagnostic cyclopropane carbons patterns at 14.51 (C-7′), 22.10 (C-4′) and 65.43 (C-5′), and 14.63 (C-7), 22.25 (C-4) and 59.63 (C-5) ppm, respectively.

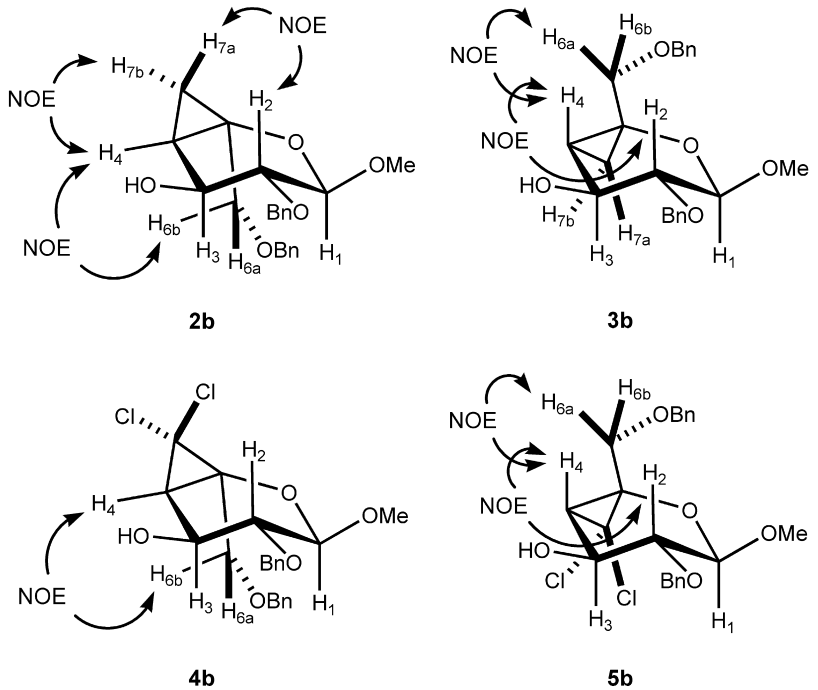


Figure 1. NOE effect in cyclopropanated sugars **2b**-**5b**.

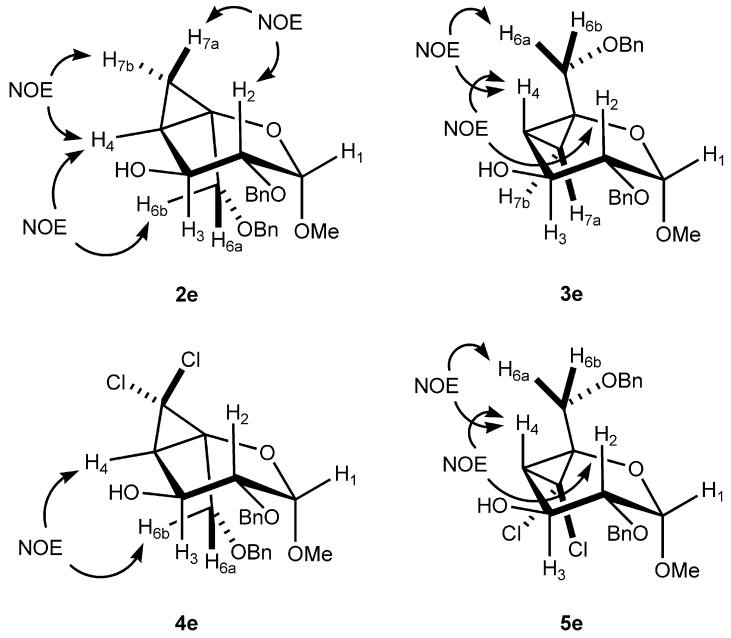


Figure 2. NOE effect in cyclopropanated sugars **2e**-**5e**.

The treatment of **1a**,**b** with chloroform and 50% aqueous sodium hydroxide in the presence of catalytic amount of triethylbenzyl ammonium chloride afforded mixtures of two dichloromethylene adducts **4a**,**b** and **5a**,**b**, which were separated by flash chromatography and then stereochemically defined on the basis of their ^{1}H NMR spectra. Global yields of 64% (diastereomeric ratio **4a/5a**=60:40)[22] and 65% (diastereomeric ratio **4b/5b**=90:10)[22] were obtained starting from **1a** and **1b**, respectively. Stereoisomers **4a**,**b** were characterized by a high value of $J_{3,4}$ (8.0 and 8.3 Hz, respectively) and NOE enhancements of vicinal protons almost the same of those observed for **2a**,**b**, and then to these a stereochemistry with the cyclopropane ring in *cis* to the coordinating C-3 oxygenated substituent was assigned and it was confirmed[23] by the conversion of **4a**,**b** into **2a**,**b** by treatment with a large excess (12 equiv.) of lithium aluminium hydride ($LiAlH_4$).

Stereoisomers **5a**,**b**, in which the cyclopropane ring was on the opposite side to that of C-3 oxygenated group, instead, showed a $J_{3,4}$ of 4.5 and 5.0 Hz, respectively, and characteristic NOE enhancements (3.8 and 3.0%, respectively) of H-2 proton upon irradiation of H-4 proton, confirmed by the corresponding enhancement of H-4 proton (4.0 and 3.4%, respectively) upon irradiation of H-2 proton.

As expected, the dechlorination of **5b** by reduction with an excess of $LiAlH_4$, as above described, to give **3b** with the stereochemistry opposite to that one of **2b**, was apparent from the value of $J_{3,4}$ of 5.5 Hz and NOE enhancement of their H-2 proton (5.7%) upon irradiation of H-4 proton, respectively.

In order to improve the face-selectivity of the cyclopropanation, the pyranoside **1b** was converted into the sterically more demanding 3-*O*-methyl (**1c**) and 3-*O*-benzyl (**1d**)[24] derivatives. These compounds, subjected to the Simmons–Smith cyclopropanation gave exclusively **2c**,**d** confirming the involvement of the zinc coordination, while by means of the dichlorocyclopropanation reaction these afforded exclusively adducts **5c**,**d** indicating the influence of an effect of steric hindrance exerted by C-3 and C-1 substituents, both shielding the upper face.

Finally, with the aim of determining the role of the orientation of the anomeric substituent on the stereochemical course of the cyclopropanations, the reactions of the fully protected 4-deoxy-β-L-*threo*-hex-4-enopyranoside **1e**[25] were studied. Owing to previous observations[26] on the regioselective formation of **1e** as a by-product during the preparation of methyl 2,3,6-tri-*O*-benzyl-4-imidazylsulfonyl-α-D-galactopyranoside (**7**), we studied some base-promoted elimination reactions of **7**, in order to improve the somewhat unsatisfactory yield reported[25] for the preparation of **1e** by treatment of the triflate analogous of **7** with methyl lithium. We found, however, a series of unexpected results giving a complex picture of the leaving group properties of this type of sulfonate, that we will be present in a forthcoming paper.[27] A low yield (24%) preparation of **1e** was, however, achieved by treatment of **7** with potassium *t*-butoxide (*t*-BuOK) in DMF, giving also the hex-3-enopyranoside **8** (20%), previously reported only as 4-deuterated derivative.[28]

The addition reaction of **1e** with methylene–zinc–iodide complex gave nearly quantitative yield of the expected adduct **2e**, while the dichlorocarbene addition afforded a diastereomeric mixture of both adducts **4e** and **5e** in the 2.8:1 ratio indicating a balance between the steric effects of the C-1 and C-3 substituents. The structures of **2e**, **4e** and **5e** were assigned on the basis of their spectroscopic analyses (Fig. 2), as well as the structure of **3e** obtained by reduction of **5e** with $LiAlH_4$.

The results of our investigations on the dichlorocyclopropanation of sugars **1a**-**e** were not completely in line with those of 1,2-glycals, which are known to undergo the

carbene addition to the opposite side to that of 3-alkyloxy substituent because of steric effects.[2,20] While sterically demanding derivatives **1c**,**d** react with dichlorocarbene giving **5c**,**d** like 1,2-glycals, hexenopyranosides **1a**,**b** gave exclusively or predominantly the cyclopropanated sugars **4a**,**b** arising from the *syn* addition to the C-3 substituent and furthermore **1e** afforded a mixture of 2.8:1 adducts **4e** and **5e**.

For this reason, the steric course of dichlorocyclopropanation reactions of the two fully benzylated α- and β-hexenopyranosides **1d** and **1e** was rationalized on the basis of molecular mechanics and semiempirical calculations. (The ab initio methods are to be discarded because of the complexity of substrates.)

At first, a conformational analysis at the molecular mechanics level was performed and thereafter the lower energy conformers, located within 2.0 kcal/mol from the lowest one, were subjected to full minimization at semiempirical PM3 level[29] of calculation. The lowest energy conformer of **1e** and **1d** with the anomeric substituent in both equatorial (*E*) and axial (*A*) conformations (Fig. 3) was then selected for the optimization at PM3 level of their transition states (TS). For each case the attachment of dichlorocarbene was considered on both faces of C-4–C-5 double bond: the up one (U) and the down one (D) referred to the sugar moiety in the Haworth projection, respectively. The obtained results are reported in Table 1.

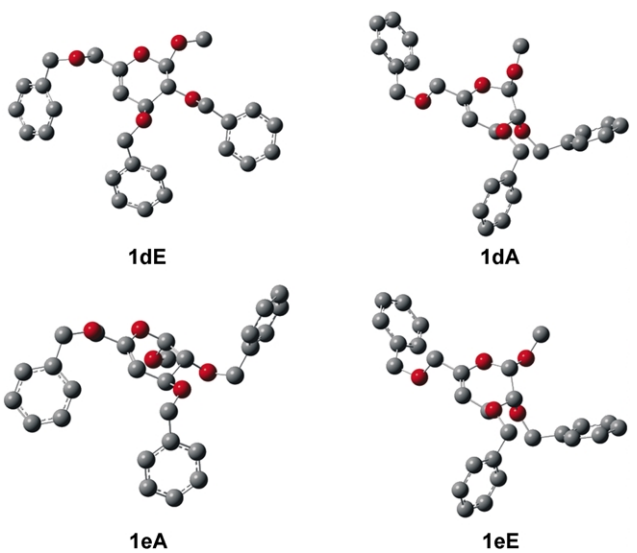


Figure 3. Preferred conformations of compounds **1d** and **1e**.

Table 1. PM3 values for dichlorocyclopropanation reaction of compounds **1d**,**e**

	ΔH_f (kcal/mol)	$\Delta\Delta H_f$ (kcal/mol)[a]	Calculated ratio (%)[b]
1dE	−100.29	0.00	63.9
1dA	−99.95	0.34	36.1
1eA	−99.58	0.00	94.7
1eE	−97.86	1.72	5.3
1dEU-TS	−25.57	8.66	0.0
1dED-TS	−33.74	0.49	30.5
1dAU-TS	−30.76	3.47	0.2
1dAD-TS	−34.23	0.00	69.3
1eAU-TS	−31.32	0.00	49.8
1eAD-TS	−30.65	0.67	16.2
1eEU-TS	−30.94	0.38	26.3
1eED-TS	−30.21	1.11	7.7

[a] Since **1d**,**e** exists in equilibrium between E and A conformers, the Curtin–Hammett principle[30] was applied and their relative energies were calculated assuming the energy of the most stable TS as point zero.
[b] On the basis of the Boltzmann distribution.

From these data it is evident that the *E* conformation is the preferred one for **1d**, which exists in a *E*/*A* ratio of 1.8:1, whereas there is an inversion for compound **1e** (*E*/*A* ratio=1:17.8). For the cyclopropanation of **1d**, the most favored approaches take place clearly at the down face of the double bond in both *E* and *A* conformations, even if the lowest energy value corresponds to **1dAD-TS**. Therefore, the less stable conformer **1dA** reacts more quickly than the most stable **1dE**, in completely accord with the Curtin–Hammett principle.[30] These results are in very good agreement with the exclusive formation of **5d**, as experimentally observed. Furthermore, the geometries **1dED-TS** and **1dAD-TS**, which lead to compound **5d**, are the only ones in which both benzyl groups at C-3 and C-5 positions lie in the upper rim of the pyranoside moiety, so facilitating the attack of dichlorocarbene at the pyranoside bottom (Fig. 4).

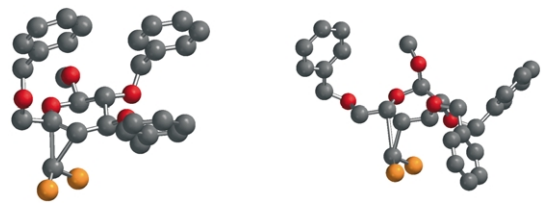
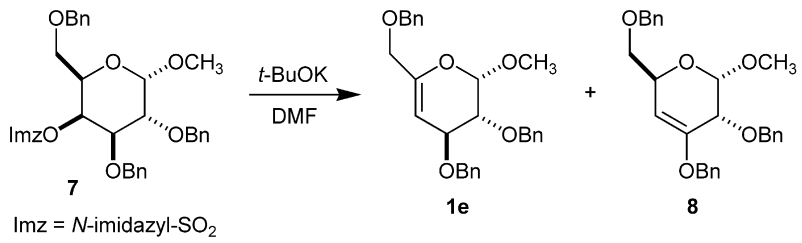


Figure 4. 1dED-TS and **1dAD-TS**, where hydrogen atoms have been omitted for better clarity.

For the cyclopropanation of β-hex-4-enopyranoside **1e**, the calculated TS energies predict the formation of both products **4e** and **5e** in a 3.2:1 ratio, which is not far from the experimentally observed 2.8:1 ratio.

Interestingly, by using a ratio of 6 equiv. of lithium aluminium hydride with respect to **4b**, the reduction was partially realized and a single monochlorocyclopropane derivative **6b** was obtained with a 90% yield. Its stereochemistry, characterized by the replacement of chlorine atom in *cis*-position with respect to H-4 proton, was deduced from NOE experiments which show a positive enhancement (4.3%) of the signal of the unique H-7b proton on irradiation of H-4 proton, confirmed by the enhancement (7.8%) of H-4 proton on irradiation of H-7b proton. The interest in this reaction derives just from its stereochemistry due to the attack of the hydride to the *exo*-halogen atom, which is the most reactive because of the reduced steric hindrance in line with the literature report.[31]

The incorporation of a cyclopropane ring into a carbohydrate provides an interesting method for obtaining strained and reactive three-membered systems combined with the carbohydrate stereochemistry. Now we are investigating the cyclopropanation of α- and β-hex-4-enopyranosides with ethyl diazoacetate in the presence of rhodium acetate as catalyst and the electrophilic



Scheme 2.

cyclopropane ring opening into a branched sugar or expansion of carbohydrate moiety to seven-membered oxacycles.

3. Experimental

3.1. General methods

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20±2 °C. ^{1}H NMR spectra were recorded in the stated solvent with a Varian Unity Inova (500 MHz for the proton and 125 MHz for the carbon spectra) and with a Brucker 200 AC instruments (200 MHz for the proton and 50 MHz for the carbon spectra). In all cases Me_4Si was used as the internal standard. All reactions were followed by TLC on Kieselgel 60 F254 with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulphuric acid, and heating. Kieselgel 60 (E. Merck, 70–230 and 230–400 mesh, respectively) was used for the column and flash chromatography. Solvents were dried by distillation according to standard procedure,[32] and storage over 4 Å molecular sieves activated at least 24 h at 400 °C. $MgSO_4$ was used as the drying agent for solutions. New starting compounds were prepared as follows.

3.2. Synthesis of methyl 2,6-di-*O*-benzyl-3-*O*-methyl-4-deoxy-(α-L-*threo*-hex-4-enopyranoside, 1c

To a stirred solution of **1b** (290 mg, 0.81 mmol) in dry acetone (5 mL), potassium hydroxide powder (45 mg, 0.81 mmol) and methyl iodide (0.1 mL, 1.62 mmol) were added and the solution was then refluxed. After 5 h, the reaction mixture was evaporated at reduced pressure and then extracted twice with dichloromethane (10 mL); the combined organic layers were washed with brine (20 mL), water (20 mL), and dried (Na_2SO_4). Flash chromatography of the crude gave derivative **1c** with nearly quantitative yield.

3.2.1. Methyl 2,6-di-*O*-benzyl-3-*O*-methyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside, 1c. Clear syrup, 98% yield, $[\alpha]_D^{25}$=+101.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.34 (s, 3H, C1–OCH_3), 3.50 (s, 3H, C3–OCH_3), 3.66 (dd, 1H, *J*=4.2, 5.0 Hz, H-2), 3.82 (dd, 1H, *J*=3.6, 4.2 Hz, H-3), 3.98 (s, 2H, H-6a, H-6b), 4.54 (s, 2H, CH_2), 4.65–4.81 (AB system, 2H, J_{AB}=12 Hz, CH_2), 4.88 (d, 1H, *J*=5.0 Hz, H-1), 5.10 (d, 1H, *J*=3.6 Hz, H-4) 7.22–7.28 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.35 (C1–OCH_3), 56.67 (C3–OCH_3), 68.77 (C-6), 71.94 and 72.73 (CH_2), 74.82 (C-3), 75.99 (C-2), 98.45 (C-1), 100.79 (C-5), 127.38, 127.43, 127.52, 127.64, 128.12, 128.14 (aromatic CH), 137.75, 137.81 (aromatic C), 148.99 (C_4). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07%. Found: C, 71.41; H, 7.11.

3.3. Synthesis of methyl-2,3,6-tri-*O*-benzyl-4-deoxy-β-L-*threo*-hex-4-enopyranoside, 1e

A solution of **7**[26] (1.50, 2.52 mmol) in dry DMF (25 mL) was treated with solid *t*-BuOK (850 mg, 7.50 mmol) at 0 °C under vigorous stirring. The reaction mixture was left to reach room temperature and further stirred until TLC analysis (1:1, hexane/AcOEt) showed the complete disappearance of the starting material. Excess *t*-BuOK was destroyed by adding solid Et_3N·HCl followed by 10 min stirring. The dark mixture was diluted with water (25 mL), extracted with Et_2O (3×50 mL). Organic phases were collected, dried (Na_2SO_4), filtered, concentrated at reduced pressure to give a crude residue that was directly subjected to a chromatography over silica gel (7:3, hexane /AcOEt) to give pure samples of **1e** (304 mg, 27% yield) and **8** (225 mg, 20% yield) (Scheme 2).

3.3.1. Methyl 2,3,6-tri-*O*-benzyl-4-deoxy-β-L-*threo*-hex-4-enopyranoside, 1e. Syrup, 27% yield, $[\alpha]_D^{25}$=+76 (*c* 1.2, $CHCl_3$); lit:[25] $[\alpha]_D^{25}$=+78 (*c* 1.0, $CHCl_3$); ^{1}H NMR in complete accordance with reported data;[25] ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.6 (OCH_3), 69.0 (C-6), 71.3, 72.1 and 73.0 (CH_2), 73.2 and 76.1 (C-2, C-3), 99.4 and 99.7 (C-1, C-4), 127.6–128.3 (aromatic CH), 137.9, 138.1 and 138.4 (aromatic C), 148.6 (C-5).

3.3.2. Methyl-2,3,6-tri-*O*-benzyl-4-deoxy-β-L-*threo*-hex-3-enopyranoside, 8. Syrup, 20% yield, $[\alpha]_D^{25}$=−35 (*c* 1.0, $CHCl_3$); lit:[28] $[\alpha]_D^{25}$=−40 for the 4-deuterated analogous; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.45 (dd, 1H, *J*=5.1, 10.0 Hz, H-6a), 3.52 (s, 3H, OCH_3), 3.53 (dd, 1H, $J_{5,6b}$= 6.0 Hz, H-6b), 4.17 (ddd, 1H, *J*=0.9, 2.8, 3.7 Hz, H-2), 4.53–4.61 (AB system, 2H, $J_{A,B}$=12.1 Hz, CH_2Ph), 4.54 (m, 1H, *J*=1.8, 2.8 Hz, H-5), 4.63–4.81 (AB system, 2H, $J_{A,B}$=11.5 Hz, CH_2Ph), 4.76 (dd, 1H, *J*=0.9, 1.8 Hz, H-4), 4.81–4.89 (AB system, 2H, $J_{A,B}$=11.3 Hz, CH_2Ph), 4.86 (d, 1H, *J*=3.7 Hz, H-1), 7.25–7.39 (m, 15H, aromatic H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.2 (OCH_3), 68.2 and 71.4 (C-2, C-5), 69.1 (C-6), 72.9, 73.3 and 73.4 (CH_2), 95.9 (C-4), 98.3 (C-1), 127.4–128.3 (aromatic CH), 136.7, 138.1 and 138.5 (aromatic C), 151.4 (C-3). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77%. Found C, 75.29; H, 6.78.

3.4. Cyclopropanation under Simmons–Smith conditions of 1a-e

To a stirred solution of 4,5-unsatured carbohydrate

(0.84 mmol) in dry diethyl ether (3 mL), diethyl zinc (420 μL of a 1 M solution in hexane, 4.2 mmol) and diiodomethane (340 μL, 4.2 mmol) were added at room temperature. The solution was then heated at 40 °C in a sealed vessel. After 2 h, a saturated solution of $NaHCO_3$ (2 mL) was added to the reaction mixture which was then neutralized with diluted HCl (2 mL) and extracted twice with diethyl ether (10 mL); the combined organic layers were washed with brine (20 mL), water (20 mL), and dried (Na_2SO_4). Flash chromatography of the crude gave the cyclopropanated sugars.

3.4.1. 4-*O*-[(1*R*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-2-oxabicyclo[4.1.0]heptan-3-yl]-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal, 2a. Syrup, 96% yield, $[\alpha]_D^{25}=-48.1$ (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (dd, 1H, *J*=6.0, 10.0 Hz, H-7′a), 0.86 (dd, 1H, *J*=6.0, 6.5 Hz, H-7′b) 1.35, 1.41, 1.42 and 1.43 (s×4, each 3H, CH_3), 1.49 (ddd, 1H, *J*=6.5, 8.5, 10.0 Hz, H-4′), 3.21–3.86 (AB system, 2H, J_{AB}=10.0 Hz, H-6′a, H-6′b), 3.41 and 3.42 (s×2, each 3H, OCH_3), 3.62 (dd, 1H, *J*=1.0, 6.5 Hz, H-2′), 3.99 (dd, 1H, *J*=6.0, 6.5 Hz, H-4), 4.02 (dd, 1H, *J*=6.0, 7.5 Hz, H-3), 4.13–4.19 (AB system, 2H, J_{AB}=8.0 Hz, H-6a, H-6b), 4.27 (t, 1H, *J*=8.5 Hz, H-3′), 4.29 (dd, 1H, *J*=6.5, 8.0 Hz, H-5), 4.39 (t, 1H, *J*=6.5 Hz, H-1), 4.49–4.61 (AB system, 2H, J_{AB}=12.0 Hz, CH_2Ph), 4.54–4.97 (AB system, 2H, J_{AB}=12.0 Hz, CH_2Ph), 4.63 (dd, 1H, *J*=6.5, 7.5 Hz, H-2), 4.84 (d, 1H, *J*=8.0 Hz, H-1′), 7.27–7.35 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.51 (C-7′), 22.10 (C-4′), 25.24, 26.71, 26.90 and 27.21 (CH_3), 55.46 and 55.52 (OCH_3), 65.43 (C-5′), 66.65 (C-6), 70.62 (C-3′), 73.13 (C-6′), 74.15 and 74.16 (CH_2Ph), 74.57 (C-2), 75.11 (C-4), 77.55 (C-5), 77.57 (C-3), 81.98 (C-2′), 102.35 (C-1′), 105.00 (C-1), 108.36 and 109.94 (CMe_2), 127.26, 127.41, 127.56, 127.76, 127.88, 128.03, 128.21 and 128.29 (aromatic CH), 138.13 and 138.44 (aromatic C). Anal. Calcd for $C_{35}H_{48}O_{11}$: C, 65.20; H, 7.50%. Found: C, 65.31; H, 7.59.

3.4.2. (1*R*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 2b. Syrup, 97% yield, $[\alpha]_D^{25}=+21.3$ (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.79 (dd, 1H, *J*=6.0, 10.0 Hz, H-7a), 0.91 (dd, 1H, *J*=6.0, 6.5 Hz, H-7b), 1.50 (ddd, 1H, *J*=6.0, 7.5, 10.0 Hz, H-4), 2.31 (bs, 1H, OH), 3.01 (dd, 1H, *J*=7.5, 8.0 Hz, H-2), 3.24–3.87 (AB system, 2H, J_{AB}=10.5 Hz, H-6a, H-6b), 3.54 (s, 3H, OCH_3), 4.29 (bt, 1H, *J*=7.5 Hz, H-3), 4.42 (d, 1H, *J*=8.0 Hz, H-1), 4.56–4.61 (AB system, 2H, J_{AB}=12.0 Hz, C6–OCH_2–Ph), 4.57–4.92 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2–Ph), 7.26–7.35 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.63 (C-7), 22.25 (C-4), 56.83 (C-5), 59.63 (OCH_3), 70.41 (C-3), 73.03 (C-6), 74.13 (CH_2), 74.34 (CH_2), 81.50 (C-2), 103.40 (C-1), 127.33, 127.54, 127.69, 127.88, 128.31 and 128.40 (aromatic CH), 138.21 and 138.51 (aromatic C). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07%. Found: C, 71.39; H, 7.12.

3.4.3. (1*R*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-3,5-dimethoxy-2-oxabicyclo[4.1.0]heptane, 2c. Syrup, 96% yield, $[\alpha]_D^{25}=+58.1$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80 (dd, 1H, *J*=10.0, 6.0 Hz, H-7a), 0.89 (dd, 1H, *J*=6.0, 7.0 Hz, H-7b), 1.50 (ddd, 1H, *J*=7.0, 7.5, 10.0 Hz, H-4), 3.09 (dd, 1H, *J*=7.0, 8.0 Hz, H-2), 3.25–3.91 (AB system, 2H, J_{AB}=10.5 Hz, H-6a, H-6b), 3.45 (s, 3H, C1–OCH_3), 3.54 (s, 3H, C3–OCH_3), 3.97 (dd, 1H, *J*=7.0, 7.5 Hz, H-3), 4.45 (d, 1H, *J*=8.0 Hz, H-1), 4.55–4.61 (AB system, 2H, J_{AB}=12.0 Hz, C6–OCH_2Ph), 4.64–4.85 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 7.24–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.52 (C-7), 19.87 (C-4), 56.51 (C1–OCH_3), 56.68 (C3–OCH_3), 60.28 (C-5), 73.05, 74.04 and 74.63 (CH_2), 79.80 (C-3), 81.90 (C-2), 103.28 (C-1), 127.28, 127.31, 127.50, 127.60, 128.10 and 128.28 (aromatic CH), 138.20 and 139.02 (aromatic C). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34%. Found: C, 71.92; H, 7.29.

3.4.4. (1*R*,3*R*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptane, 2d. Syrup, 97% yield, $[\alpha]_D^{25}=-3.6$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (dd, 1H, *J*=6.0, 10.5 Hz, H-7a), 0.97 (dd, 1H, *J*=6.0, 7.0 Hz, H-7b), 1.48 (ddd, 1H, *J*=6.0, 7.0, 10.5 Hz, H-4), 3.19 (dd, 1H, *J*=7.5, 8.0 Hz, H-2), 3.24–3.90 (AB system, 2H, J_{AB}=11.0 Hz, H-6a, H-6b), 3.54 (s, 3H, OCH_3), 4.18 (dd, 1H, *J*=7.0, 7.5 Hz, H-3), 4.44 (d, 1H, *J*=8.0 Hz, H-1), 4.54–4.60 (AB system, 2H, J_{AB}=12.0 Hz, C6–OCH_2Ph), 4.59–4.77 (AB system, 2H, J_{AB}=12.0 Hz, C2–OCH_2Ph), 4.66–4.86 (AB system, 2H, J_{AB}=11.0 Hz, C3–OCH_2Ph), 7.24–7.36 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.85 (C-7), 20.45 (C-4), 56.77 (OCH_3), 60.56 (C-5), 70.68, 74.33 and 74.42 (CH_2), 77.87 (C-3), 81.32 (C-2), 103.51 (C-1), 127.43, 127.60, 127.50, 127.72, 127.81, 128.18 and 128.36 (aromatic CH), 138.25, 138.54 and 138.90 (aromatic C). Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00%. Found: C, 75.71; H, 7.09.

3.4.5. (1*R*,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptane, 2e. Clear syrup, 98% yield, $[\alpha]_D^{25}=+101,9$ (*c* 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (ddd, 2H, *J*=6.0, 7.5, 9.5 Hz, H-7a, H-7b), 1.58 (ddd, 1H, *J*=6.0, 7.5, 9.5 Hz, H-4), 3.28 (dd, 1H, *J*=2.7, 8.5 Hz, H-2), 3.44–3.62 (AB system, 2H, J_{AB}=10.5 Hz, J_{6a-7b}=0.75 Hz, H-6a, H-6b), 3.36 (s, 3H, OCH_3), 4.24 (dd, 1H, *J*=6.5, 8.5 Hz, H-3), 4.44 (d, 1H, *J*=2.7 Hz, H-1), 4.55–4.61 (AB system, 2H, J_{AB}=12.1 Hz, C6–OCH_2Ph), 4.64–4.81 (AB system, 2H, J_{AB}=12.2 Hz, C3–OCH_2Ph), 4.65–4.79 (AB system, 2H, J_{AB}=11.8 Hz, C2–OCH_2Ph), 7.25–7.39 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.90 (C-7), 20.40 (C-4), 56,37 (OCH_3), 59.36 (C-5), 70.97 and 72.84 (CH_2), 73.19 (C-2), 73.30 (C-6), 78.34 (C-3), 99.69 (C-1), 127.48, 127.66, 127.89 and 128.33, (aromatic CH), 138.15, 138.44 and 138.77 (aromatic C). Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00%. Found: C, 75.71; H, 7.11.

3.5. Cyclopropanation under the dichlorocarbene conditions of 1a-e

To a vigorously stirred solution of 4,5-unsaturared carbohydrate **1a-e** (1.92 mmol) in chloroform (6 mL), containing benzyltriethylamonium chloride (10 mg), aqueous sodium hydroxide (2.5 g in 5 mL) was added. The reaction mixture was stirred for 2 h at room temperature, diluted with water (12 mL) and then extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), concentrated and the residue was purified by flash

chromatography to give the dichlorocyclopropanated sugars **4a**,**b**,**e** and **5a**-**e**.

3.5.1. 4-*O*-[(1*S*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-2-oxabicyclo-[4.1.0]heptan-3-yl]-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal, 4a. Syrup, 38% yield, $[\alpha]_D^{25}=-9.3$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34, 1.39, 1.42 and 1.44 (s×4, each 3H, CH_3), 1.60 (bs, 1H, OH), 2.19 (d, 1H, *J*=8.0 Hz, H-4′), 3.36 and 3.42 (s×2, each 3H, OCH_3), 3.55 (t, 1H, *J*=8.5 Hz, H-2′), 3.71–4.05 (AB system, 2H, J_{AB}=10.5 Hz, H-6′a, H-6′b), 4.00 (dd, 1H, *J*=6.5, 9.0 Hz, H-6a), 4.04 (dd, 1H, *J*=1.0, 7.0 Hz, H-4), 4.10 (dd, 1H, *J*=6.5, 8.5 Hz, H-6b), 4.17 (dd, 1H, *J*=1.0, 7.5 Hz, H-3), 4.27 (dd, 1H, *J*=8.0, 8.5 Hz, H-3′), 4.30 (dd, 1H, *J*=6.5, 7.0 Hz, H-5), 4.41 (d, 1H, *J*=6.5 Hz, H-1), 4.52–4.64 (AB system, 2H, J_{AB}=12.0 Hz, CH_2), 4.56–4.94 (AB system, 2H, J_{AB}=11.5 Hz, CH_2), 4.68 (dd, 1H, *J*=6.5, 7.5 Hz, H-2) 4.97 (d, 1H, *J*=8.5 Hz, H-1′), 7.28–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.34, 26.44, 26.55 and 27.33 (CH_3), 37.34 (C-4′), 55.78 (2×OCH_3), 63.97 (C-5′), 64.40 (C-7′), 65.43 (C-6), 70.93 (C-3′), 71.71 (C-6′), 73.74, (CH_2), 73.96 (C-2), 74.48 (CH_2), 74.99 (C-4), 77.51 and 77.53 (C-3, C-5), 80.70 (C-2′), 103.27 (C-1′), 105.13 (C-1), 108.48 and 110.05 (*C*Me_2), 127.58, 127.86, 127.92, 128.16, 128.50 and 128.46 (aromatic CH), 137.70 and 138.26 (aromatic C). Anal. Calcd for $C_{36}H_{46}Cl_2O_{11}$: C, 58.91; H, 6.50%. Found: C, 58.99; H, 6.53.

3.5.2. (1*S*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 4b. Syrup, 26% yield, $[\alpha]_D^{25}=+37.6$ (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19 (d, 1H, *J*=8.5 Hz, H-4), 2.28 (d, 1H, *J*=6 Hz, OH), 3.54 (t, 1H, *J*=8.5 Hz, H-2), 3.58 (s, 3H, OCH_3), 3.69–4.09 (AB system, 2H, J_{AB}=10.5 Hz, H-6a, H-6b), 4.31 (bq, 1H, spl. ≅ 8 Hz, H-3), 4.50 (d, 1H, *J*=8.5 Hz, H-1), 4.57–4.62 (AB system, 2H, J_{AB}=12.5 Hz, C6–OCH_2Ph), 4.65–4.89 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 7.27–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.44 (C-4), 57.41 (OCH_3), 64.01 (C-5), 64.40 (C-7), 71.10 (C-3), 71.59 (C-6), 73.59 and 74.49 (CH_2), 80.41 (C-2), 104.62 (C-1), 127.60, 127.82, l27.89, 127.94, 128.21 and 128.46 (aromatic CH), 137.64 and 138.22 (aromatic C). Anal. Calcd for $C_{22}H_{24}Cl_2O_5$: C, 60.15; H, 5.51%. Found: C, 60.21; H, 5.58.

3.5.3. (1*S*,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptane 4e. Yellow oil, 48% yield, $[\alpha]_D^{25}=+11.9$ (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.01 (d, 1H, *J*=8.0 Hz, H-4), 3.33 (s, 3H, OCH_3), 3.58–3.86 (AB system, 2H, J_{AB}=11.4 Hz, H-6a, H-6b), 3.85 (dd, 1H, *J*=3.3, 8.0 Hz, H-2), 4.19 (t, 1H, *J*=8.0 Hz, H-3), 4.57–4.81 (AB system, 2H, J_{AB}=11.9 Hz, CH_2Ph), 4.59–4.64 (AB system, 2H, J_{AB}=12.1 Hz, CH_2Ph), 4.61 (d, 1H, *J*=3.3 Hz, H-1), 4.73–4.81 (AB system, 2H, J_{AB}=12.0 Hz, C2–OCH_2Ph), 7.26–7.43 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.10 (C-4), 56,90 (OCH_3), 63.34 (C-5), 65.13 (C-7), 71.33 (C-6), 71.90 (CH_2), 72.37 (C-3), 72.95 (CH_2), 73.59 (CH_2) 76.70 (C-2), 100.64 (C-1), 127.76, 127.84, 127.94, 128.22, 128.33, 128.40 and 128.51 (aromatic CH), 137.77, 138.16 and 138.24 (aromatic C). Anal. Calcd for $C_{29}H_{30}Cl_2O_5$: C, 65.79; H, 5.71%. Found: C, 65.71; H, 5.68.

3.5.4. 4-*O*-[(1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-2-oxabicyclo-[4.1.0]heptan-3-yl]-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal, 5a. Syrup, 7% yield, $[\alpha]_D^{25}=+7.1$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32, 1.39, 1.40 and 1.42 (s×4, each 3H, CH_3), 1.44 (bs, 1H, OH), 1.86 (d, 1H, *J*=4.5 Hz, H-4′), 3.38 (t, 1H, *J*=7.5 Hz, H-2′), 3.46 and 3.47 (s×2, each 3H, OCH_3), 3.75–3.99 (AB system, 2H, J_{AB}=11.0 Hz, H-6′a, H-6′b), 4.00 (dd, 1H, *J*=6.5, 8.5 Hz, H-6a), 4.11 (dd, 1H, *J*=1.5, 7.0 Hz, H-4), 4.13 (dd, 1H, *J*=6.5, 8.5 Hz, H-6b), 4.22 (dd, 1H, *J*=1.5, 4.5 Hz, H-3), 4.32 (dd, 1H, *J*=6.5, 8.5 Hz, H-5), 4.35 (dd, 1H, *J*=4.5, 7.5 Hz, H-3′), 4.47 (d, 1H, *J*=7.5 Hz, H-1), 4.52–4.73 (AB system, 2H, J_{AB}=12.0 Hz, CH_2), 4.53 (dd, 1H, *J*=4.5, 7.5 Hz, H-2), 4.54–4.98 (AB system, 2H, J_{AB}=11.0 Hz, CH_2), 5.14 (d, 1H, *J*=7.5 Hz, H-1′), 7.28–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.37, 26.44, 26.84 and 27.32 (CH_3), 29.68 (C-7), 32.35 (C-4′), 53.08 and 55.81 (OCH_3), 62.69 (C-5′), 65.40 (C-6), 65.50 (C-7′) 69.49 (C-3′), 72.01 (C-6′), 73.55 and 74.30 (CH_2Ph), 74.96 (C-2), 75.38 (C-4), 77.53 and 77.54 (C-3, C-5), 81.47 (C-2′), 102.13 (C-1′), 105.40 (C-1), 108.47 and 110.17 (*C*Me_2), 127.47, 127.64, 128.00, 128.15, 128.39 and 128.61 (aromatic CH), 138.12 and 138.26 (aromatic C). Anal. Calcd for $C_{36}H_{48}Cl_2O_{11}$: C, 58.91; H, 6.50%. Found: C, 59.02; H, 6.59.

3.5.5. (1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 5b. Syrup, 61% yield, $[\alpha]_D^{25}=-15.0$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.75, (d, 1H, *J*=5.0 Hz, H-4), 2.54 (bd, 1H, *J*=2.0 Hz, OH), 3.42 (dd, 1H, *J*=5.0, 10.0 Hz, H-2), 3.46 (s, 3H, OCH_3), 3.67–4.01 (AB system, 2H, J_{AB}=11.5 Hz, H-6a, H-6b), 3.77 (ddd, 1H, *J*=2.5, 5.0, 10.0 Hz, H-3), 4.56–4.75 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 4.59–4.65 (AB system, 2H, J_{AB}=12 Hz, C6–OCH_2Ph), 4.70 (d, 1H, *J*=5.0 Hz, H-1), 7.29–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.60 (C-4), 55.51 (OCH_3), 62.93 (C-5), 65.80 (C-7), 67.09 (C-3), 70.67 (C-6), 73.02 and 73.30 (CH_2), 82.16 (C-2), 107.11 (C-1), 127.71, 127.84, 127.95, 128.06, 128.33 and 128.55 (aromatic CH), 137.55 and 137.86 (aromatic C). Anal. Calcd for $C_{22}H_{24}Cl_2O_5$: C, 60.15; H, 5.51%. Found: C, 60.24; H, 5.57.

3.5.6. (1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-3,5-dimethoxy-2-oxabicyclo[4.1.0]heptane, 5c. Syrup, 68% yield, $[\delta]_D^{25}=-7.3$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.65, (d, 1H, *J*=4.5 Hz, H-4), 3.47 (s, 3H, C1–OCH_3), 3.53 (dd, 1H, *J*=3.5, 4.0 Hz, H-2), 3.54 (s, 3H, C3–OCH_3), 3.55 (dd, 1H, *J*=3.5, 4.5 Hz, H-3), 3.66–4.14 (AB system, 2H, J_{AB}=11.5 Hz, H-6a, H-6b), 4.63–4.68 (AB system, 2H, J_{AB}=11.0 Hz, C6–OCH_2Ph), 4.75 (d, 1H, *J*=4.0 Hz, H-1),4.69–4.82 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 7.32–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.86 (C-4), 55.68 (C1–OCH_3), 57.43 (C3–OCH_3), 63.08 (C-5), 65.46 (C-7), 70.63 (C-6), 72.98 and 73.81 (CH_2), 77.11 (C-3), 81.09 (C-2), 107.93 (C-1), 127.51, 127.61, 127.66, 127.69, 127.84, 128.27, 128.30 and 128.45 (aromatic CH), 137.80 and 138.16 (aromatic C). Anal. Calcd for $C_{23}H_{26}Cl_2O_5$: C, 60.93; H, 5.78%. Found: C, 61.02; H, 5.85.

3.5.7. (1*R*,3*R*,4*R*,5*S*,6*S*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptane, 5d. Syrup, 65%, yield, $[\alpha]_D^{25}=-11.8$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.68, (d, 1H, *J*=5.0 Hz, H-4), 3.44 (s, 3H, OCH_3), 3.57 (dd, 1H, *J*=4.5, 10.0 Hz, H-2), 3.63–4.10 (AB system, 2H, J_{AB}=11.5 Hz, H-6a, H-6b), 3.67 (dd, 1H, *J*=5.0, 10.0 Hz, H-3), 4.61 (s, 2H, C6–O*CH*$_2$Ph), 4.67–4.81 (AB system, 2H, J_{AB}=11.5 Hz, C2–O*CH*$_2$Ph), 4.68–4.75 (AB system, 2H, J_{AB}=12.0 Hz, C3–O*CH*$_2$Ph), 4.71 (d, 1H, *J*=4.5 Hz, H-1), 7.27–7.39 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.31 (C-4), 55.72 (O*CH*$_3$), 63.15 (C-5), 65.50 (C-7), 70.66 (C-6), 72.20, 73.01 and 74.98 (CH_2), 75.36 (C-3), 81.18 (C-2), 108.01 (C-1), 127.61, 127.67, 127.83, 128.27, 128.29, 128.31, 128.43 and 128.45 (aromatic CH), 137.64, 137.82 and 138.20 (aromatic C). Anal. Calcd for $C_{29}H_{30}Cl_2O_5$: C, 65.79; H, 5.71%. Found: C, 65.72; H, 5.78.

3.5.8. (1*R*,3*S*,4*R*,5*S*,6*S*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptane, 5e. Yellow oil, 47% yield, $[\alpha]_D^{25}=+36.7$ (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (d, 1H, *J*=3.3 Hz, H-4), 3.42 (s, 3H, OCH_3), 3.66–3.90 (AB system, 2H, J_{AB}=11.0 Hz, H-6a, H-6b), 3.67 (1H, dd, *J*=3.3, 8.4 Hz, H-2), 3.99 (dd, 1H, *J*=3.3, 8.4 Hz, H-3), 4.56 (s, 2H, C6–O*CH*$_2$Ph), 4.65–4.71 (AB system, 2H, J_{AB}=11.6 Hz, C3–O*CH*$_2$Ph), 4.67–4.81 (AB system, 2H, J_{AB}=12.0 Hz, C2–O*CH*$_2$Ph), 4.88 (d, 1H, *J*=3.3 Hz, H-1), 7.26–7.37 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.39 (C-4), 56,18 (OCH_3), 63.42 (C-5), 64.02 (C-7), 71.93 (C-6), 72.12 (C-3), 72.62, 73,38 and 73.68 (CH_2), 76.12 (C-2), 100.87 (C-1), 127.59, 127.73, 127.88, 127.90, 128.33, 128.40 and 128,49 (aromatic CH), 137.71, 137.86 and 138,22 (aromatic C). Anal. Calcd for $C_{29}H_{30}Cl_2O_5$: C, 65.79; H, 5.71%. Found: C, 65.84; H, 5.67.

3.6. Conversion of 4a,b into 2a,b and 5b,e into 3b,e by reduction with 12 equiv. excess lithium aluminium hydride

To a stirred solution of **4a**,**b** or **5b**,**e** (0.80 mmol) in tetrahydrofuran (10 mL) a solution containing an excess of lithium aluminium hydride (316 mg, 9.6 mmol) in dry tetrahydrofuran (4 mL) was added. After being stirred for 4 h at room temperature, the reaction mixture was cooled in ice and quenched by careful addition of saturated aqueous sodium sulphate. The salts were filtered and washed several times with hot ethyl acetate. The filtrate was dried (Na_2SO_4) and concentrated. The residue of chromatographic purification furnished cyclopropanated sugars in pure form. Cyclopropanated sugars **2a** and **2b** were separated in 23 and 75% yield, respectively, and their structures were confirmed by superimposable ^1H and ^{13}C NMR spectra.

3.6.1. (1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol 3b. Syrup, 76% yield, $[\alpha]_D^{25}=-13.5$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, 1H, *J*=7.5 Hz, H-7a), 0.96 (dd, 1H, *J*=7.5, 8.0 Hz, H-7b), 1.46 (dd, 1H, *J*=5.5, 8.0 Hz, H-4), 2.30 (bs, 1H, OH), 3.42 (s, 3H, OCH_3), 3.47–3.94 (AB system, 2H, J_{AB}=10.3 Hz, H-6a, H-6b), 3.49 (1H, d, *J*=4.5, 10.0 Hz, H-2), 3.84 (dd, 1H, *J*=5.5, 10.0 Hz, H-3), 4.50–4.56 (AB system, 2H, J_{AB}=12.1 Hz, C6–O*CH*$_2$Ph), 4.59–4.75 (AB system, 2H, J_{AB}=11.8 Hz, C2–O*CH*$_2$Ph), 4.71 (d, 1H, *J*=4.5 Hz, H-1), 7.29–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.18 (C-7), 24.98 (C-4), 55.25 (OCH_3), 60.37 (C-3), 65.32 (C-3), 71.18 (C-6), 72.99 and 73.05 (CH_2), 83.54 (C-2), 107.66 (C-1), 127.59, 127.88, 128.31, 128.39, 128.49 and 128.66 (aromatic CH), 137.80 and 138.01 (aromatic C). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07%. Found: C, 71.42; H, 7.14.

3.6.2. (1*R*,3*S*,4*R*,5*S*,6*S*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptane, 3e. Yellow oil, 68% yield, $[\alpha]_D^{25}=-56.7$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.72 (t, 1H, *J*=7.0 Hz, H-7a), 0.86 (dd, 1H, *J*=7.0, 7.5 Hz, H-7b), 1.52 (dd, 1H, *J*=1.0, 7.5 Hz, H-4), 3.35–3.70 (AB system, 2H, J_{AB}=11.0 Hz, H-6a, H-6b), 3.46 (s, 3H, OCH_3), 3.54 (1H, dd, *J*=2.0, 7.0, Hz, H-2), 4.00 (dd, 1H, *J*=1.0, 7.0 Hz, H-3), 4.57–4.65 (AB system, 2H, J_{AB}=11.0 Hz, *CH*$_2$Ph), 4.58–4.64 (AB system, 2H, J_{AB}=11.5 Hz, *CH*$_2$Ph), 4.68–4.76 (AB system, 2H, J_{AB}=12.0 Hz, *CH*$_2$Ph), 4.72 (d, 1H, *J*=2.0 Hz, H-1), 7.28–7.35 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.69 (C-7), 30.93 (C-4), 56.55 (OCH_3), 59.37 (C-5), 71.60 (C-6), 72.76, 73.00 and 73.32 (CH_2), 75.25 (C-3), 76.74 (C-2), 99.53 (C-1), 127.59, 127.89, 128.03, 128.29, 128.35, 128.49, 128.57 and 128.66 (aromatic CH), 137.87, 138.26 and 138.57 (aromatic C). Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00%. Found: C, 75.69; H, 7.07.

3.7. Conversion of 4b into 6b by reduction with 6 equiv. excess of lithium aluminum hydride

Initially, in the case of **4b** (350 mg, 0.80 mmol), when an excess of 4.80 mmol (182 mg) of lithium aluminium hydride was used, the corresponding monohalogenated cyclopropane sugar **6b** after flash chromatography was obtained with a 90% yield.

3.7.1. (1*S*,3*S*,4*R*,5*S*,6*R*,7*S*)-4-Benzyloxy-1-benzyloxymethyl]-7-chloro-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 6b. Syrup, 90% yield, $[\alpha]_D^{25}=-4.2$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.89 (dd, 1H, *J*=8.0, 8.5 Hz, H-4), 2.19 (bs, 1H, OH), 3.24 (d, 1H, *J*=8.5 Hz, H-7), 3.33–3.90 (AB system, 2H, J_{AB}=10.0 Hz, H-6a, H-6b), 3.57 (t, 1H, *J*=8.5 Hz, H-2), 3.61 (s, 3H, OCH_3), 4.40 (dd, 1H, *J*=8.0, 8.5 Hz, H-3), 4.49 (d, 1 h, *J*=8.5 Hz, H-1), 4.54–4.60 (AB system, 2H, J_{AB}=12.0 Hz, *CH*$_2$Ph), 4.72–4.95 (AB system, 2H, J_{AB}=11.5 Hz, *CH*$_2$Ph), 7.29–7.40 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.47 (C-4), 38.51 (C-7), 57.21 (OCH_3), 59.39 (C-5), 71.75 (C-3), 72.06 (C-6), 73.32 and 74.40 (*CH*$_2$Ph), 82.06 (C-2), 104.63 (C-1), 127.48, 127.63, 127.88, 128.35 and 128.45 (aromatic CH), 137.67 and 139.41 (aromatic C). Anal. Calcd for $C_{22}H_{25}ClO_5$: C, 65.26; H, 6.22%. Found: C, 65.34; H, 6.29. *m*/*z*: FAB 404 (M−1), 368 (M−35).

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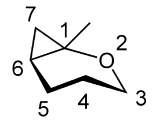
References and notes

1. Part 20 of the series: 'Chemical valorization of milk-derived sugars'. For part 19 see Ref. 33.
2. Cousins, G. C.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165.
3. Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831.
4. Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323.
5. Simmons, H. E.; Cairns, T. L.; Vladuchik, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1.
6. Makosza, M. *Pure Appl. Chem.* **1975**, *43*, 429, and references cited therein.
7. Sauers, R. R.; Schlosberg, S. B.; Pfeffer, P. E. *J. Org. Chem.* **1968**, *33*, 2175.
8. (a) Sakakibara, T.; Takamoto, T.; Sudoh, R.; Nakagawa, T. *Chem. Lett.* **1972**, 1219. (b) Sakakibara, T.; Sudoh, R.; Nakagawa, T. *Bull. Chem. Soc. Jpn* **1978**, *51*, 1189.
9. Yu, M.; Lynch, V.; Pagenkopf, L. B. *Org. Lett.* **2001**, *16*, 2563.
10. Fraser-Reid, B.; Carthy, B. J. *Can. J. Chem.* **1972**, *50*, 2928.
11. Duchaussoy, P.; Di Cesare, P.; Gross, B. *Synthesis* **1979**, 198.
12. (a) Sakakibara, T.; Sudoh, R. *Bull. Chem. Soc. Jpn* **1978**, *51*, 1279. (b) Sakakibara, T.; Sudoh, R. *J. Chem. Soc., Chem. Commun.* **1977**, 7.
13. Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984**, *40*, 1279.
14. Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3978.
15. Kawana, M.; Kuzuhara, H. *Synthesis* **1995**, 544.
16. Guriar, M. K.; Chakrabarti, A.; Rao, B. V.; Kumar, P. *Tetrahedron Lett.* **1997**, *38*, 6885.
17. (a) Pistarà, V.; Barili, P. L.; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *41*, 3253. (b) Catelani, G.; Corsaro, A.; D'Andrea, F.; Mariani, M.; Pistarà, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3313. (c) Corsaro, A.; Catelani, G.; D'Andrea, F.; Fisichella, S.; Mariani, M.; Pistarà, V. *Environ. Sci.* **2003**, *10*(5), 325. (d) Catelani, G.; Corsaro, A.; D'Andrea, F.; Mariani, M.; Pistarà, V.; Vittorino, E. *Carbohydr. Res.* **2003**, *338*, 2349.
18. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F. *Gazz. Chim. Ital.* **1992**, *122*, 135.
19. Although for the correct naming of the cyclopropanated compounds (see Section 3) the two fused systems were numbered as in formula **A**, the classical carbohydrate numbering, as in Figures 1 and 2, was used for the assignment of NMR parameters.



A

20. Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694.
21. (a) Chan, J. H.; Rickborn, B. *J. Am. Chem. Soc.* **1968**, *90*, 6406. (b) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892.
22. Ratios determined by ^{1}H NMR on the crude reaction mixtures.
23. Ascertained by superimposable ^{1}H and ^{13}C NMR spectra.
24. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F. *Tetrahedron* **1997**, *53*, 8665.
25. El Nemr, A.; Tsuchiya, T.; Kobayashi, Y. *Carbohydr. Res.* **1996**, *293*, 31.
26. Attolino, E.; Catelani, G.; D'Andrea, F. *Tetrahedron Lett.* **2002**, *43*, 1685.
27. Attolino, E.; Catelani, G.; D'Andrea, F.; Pistarà, V. Manuscript in preparation.
28. El Nemr, A.; Tsuchiya, T. *Carbohydr. Res.* **2001**, *330*, 205.
29. Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209, see also p 221.
30. (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
31. Monti, H.; Bertrand, M. *Tetrahedron* **1973**, *29*, 2821.
32. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of laboratory chemicals*; 2nd ed. Pergamon: Oxford, 1980.
33. Attolino, E.; Catelani, G.; D'Andrea, F.; Nicolardi, M. *J. Carbohydr. Chem.* **2004**, in press.