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Cyclopropanation of 5-methylene galactopyranosides by dihalo-, ethoxycarbonyl-, and unsubstituted carbenes

Antonino Corsaro, Maria Assunta Chiacchio, Venerando Pistarà *, Antonio Rescifina *, Elisa Vittorino

Università degli Studi di Catania, Dipartimento di Scienze Chimiche, Viale A. Doria 6, 95125 Catania, Italy

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ABSTRACT

Cyclopropanation reactions of 6-deoxyhex-5-enopyranosides by methylene-zinc-iodide complex, dichlorocarbene, and rhodium ethoxycarbonyl complex addition afford optimum yields of the corresponding spirocyclopropanes. Surprisingly, a stereospecific spirocyclopropane derivative with the two halogens on the upper face of the 4-hydroxy substituent is obtained. To get more insight on the dichlorocarbene cyclopropanation process a computational study, based on DFT quantomechanic calculation was conducted.

1. Introduction

C-Glycosydenes and 5-methylene pyranosides are unsaturated sugar derivatives with a *exo*-double bond near the pyranoid-ring oxygen; the first ones, called *exo*-glycals, with a double bond at the anomeric centre, have been largely studied,[1] and are very useful compounds in relation to the reduction of their double bond, since they are precursor of hydrolytically stable *C*-glycosides;[1] the second ones, frequently termed as 6-deoxyhex-5-enopyranosides, are further enol ethers with *exo*-glycal functionality and are also interesting intermediates for the formation of a carbon–carbon bond,[2] for the well known Ferrier-II carbocyclization,[3] and in other rearrangement reactions with Lewis acid.[4] Recently, the chemistry of 5,6-unsaturated pyranosides has found interesting developments in the reduction of their double bond and functionalizations such as oxidation to epoxides.[5] However, their chain extension by the cyclopropanation of the *exo*-double bond has not been thoroughly explored, though the resulting spirocyclopropyl-functionalized sugars are very important as synthetic building blocks, glycosidase inhibitors, or useful scaffolds for carbohydrates mimics.

Indeed, very few 5-spirocyclopropyl pyranosides[6] were prepared directly with the Simmons–Smith cyclopropanation reaction because their synthesis resulted arduous under the several used variations. Therefore, the addition of dichloro- or dibromocarbene to the 5-methylene pyranoside was used to obtain the corresponding 5-spirohalocyclopropyl adducts as diastereoisomeric mixtures,[7] which were then reduced with lithium aluminum hydride in order to afford the unsubstituted spirocyclopropanes.

Within our research on chemical valorisation of lactose,[8] we needed to prepare its 5′-spirocyclopropane together with the corresponding derivatives of α- and β-galactopyranoside, on the analogy of 4,5-cyclopropanated galactopyranosides,[9] with the aim to obtain 1,5-dicarbonyl intermediates. From these latter, through further reactions, interesting sugars derivatives such as cyclitols[8a–c] or aza-sugars[10] can be synthesized.

2. Results and discussion

5-Methylene galactopyranosides **1**,[11] **2**,[5,12] and **3**,[13] were prepared with good global yields starting from commercial methyl-α- and methyl-β-D-galactopyranoside, and lactose, respectively, following our previously reported method.[13]

These 5,6-unsaturated pyranosides were then subjected to the cyclopropanation reaction with the Furukawa modification[14] of the Simmons–Smith[15] reaction, addition of halocarbene,[16] already employed for L-*threo*-hex-4-enopyranosides,[8d] and furthermore to the addition of methoxycarbonyl-carbene,[17] with the aim at confirming that these methods are also applicable to methylene galactopyranose derivates and establishing the stereochemical course of the cyclopropanation reactions.

Therefore, the Furukawa cyclopropanation of 5-methylene galactopyranosides **1**–**3** with diethyl zinc and diiodomethane, performed in dry diethyl ether as a solvent and in a sealed vessel at

* Corresponding authors. Tel.: +39 095 7385017; fax: +39 095 580138.
E-mail addresses: vpistara@unict.it (V. Pistarà), arescifina@unict.it (A. Rescifina).

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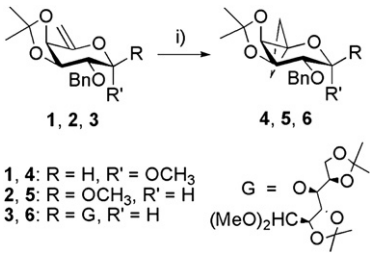
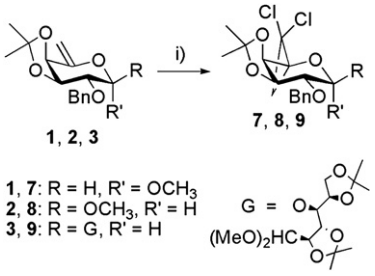
40 °C, gave after 2 h a nearly quantitative yield of cycloadducts **4**–**6** (Scheme 1).



Scheme 1. (i) CH_2I_2, Et_2Zn, dry Et_2O, 40 °C, 2 h.

The structures of spiroadducts **4**–**6** were unambiguously confirmed on the basis of their spectral data. Particularly, their ^1H and ^{13}C NMR spectra show the characteristics signals of the two methylenic protons of the spirocyclopropane moiety in the range 0.62–1.39 ppm, analogous to those reported in the literature[7c] for the 5-spiroderivative of glucopyranose.

The dichlorocyclopropanation reactions of **1**–**3** were performed in chloroform by adding 50% aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride as phase-transfer catalyst and then allowing the mixture to react at room temperature for 5 h (Scheme 2).



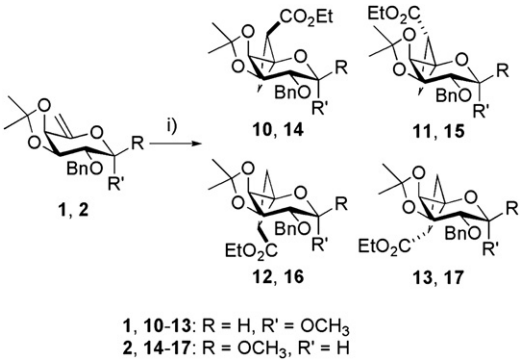
Scheme 2. (i) $CHCl_3$, 50% aq NaOH, BTEAC, rt, 5 h.

Surprisingly, in spite of previously reported dihalocyclopropanation reactions of differently protected galactose,[7a] the reactions of compounds **1**–**3** were highly stereospecific affording exclusively the corresponding spirocycloadducts **7**–**9**; only a single diastereoisomer was observed in the ^1H NMR spectra of the crude reaction mixtures.

The structures of the spirocyclopropane adducts **7**–**9** were assigned on the basis of their ^1H NMR spectra, which show one AB system for the cyclopropane methylene protons in the range between 1.91 and 1.64 ppm (J=9.0 Hz). NOE experiments easily allowed the stereochemical assignation of these adducts, since, for example, in the case of spiroderivative **8**, a positive enhancement (about 2.9%) was apparent on the H-6a proton (at 1.82 ppm) by irradiating the H-4 proton (at 4.46 ppm) and vice versa, whereas the H-6b proton, which is near the pyranoside oxygen atom, resonates at upper fields (1.64 ppm) and does not show any appreciable NOE effect.

Finally, we investigated the cyclopropanation reactions of α- **1** and β-5-hexenopyranosides **2** with ethyl diazoacetate in dry dichloromethane in the presence of a large excess of rhodium acetate (Scheme 3).

From **1**, a mixture of the four spirocyclopropanecarboxylate stereoisomers **10**–**13**, in the 1.0:1.1:0.5:0.55 ratio,[18] respectively, was obtained with a 82% global yield; while stereoisomers **14**–**17** in the ratio 1.2:0.8:2.0:1.8,[18] respectively, were obtained with a global yield of 89% from **2**. By flash chromatography (silica gel, Cy/AcOEt



Scheme 3. (i) EDA, dry CH_2Cl_2, $Rh_2(OAc)_4$, N_2, rt, 5 h.

15%), the stereoisomers **13** (30%) and **17** (10%) were separated from the two crude reaction mixtures, while the residual stereoisomers **10**–**12** and **14**–**16** were obtained as pure samples by the HPLC purification in the sequence **12** (37%), **10** (12%), and **11** (14%) from **1**, and **16** (37%), **14** (12%), and **15** (14%) from **2**.

The formation of the spirocyclopropane ring in adducts **10**–**13** and **14**–**17** was evident from their mono- and bi-dimensional ^1H NMR spectra, which showed the δ and J reported in Table 1 easily attributable to the protons directly bonded to carbon atoms of the two rings, while NOE experiments (Table 2) have allowed us to assign their stereochemistry. ^{13}C NMR confirmed structural assignments.

3. Computational studies

To get more insight on the dichlorocarbene cyclopropanation process in which an unexpected stereospecificity was observed, we conduct an in silico study, employing density functional theory (DFT) quantomechanic calculations. It is well known that intermolecular cyclopropanations of alkenes by carbenoid species, such as those derived from diazoacetates, are not particularly diastereoselective,[19] because can be regarded as triplet species.[20] Then, we have focused our attention on the process concerning the addition of dichlorocarbene to β-5-hexenopyranosides **2** upon the considerations that the dichlorocarbene exists undoubtedly as a singlet[21] and its reactivity is independent of the method used to generate it.[22]

After a conformational Monte Carlo analysis[23] at the molecular mechanics level and successive refinement of lower energy conformers, such as located, at semiempirical PM3 level of calculation,[24] the two lowest energy conformers **A** and **B** of **2** were used for high level computational studies (Fig. 1). The lower conformer **A** adopts a twist conformation with the benzyl substituent in axial position and conformer **B** has a boat-like conformation with the benzyl group in an equatorial position.

Geometry optimizations of the critical points (reactants, transition structures, and products) were studied at the DFT level,

Table 1
Selected ^1H NMR chemical shifts (ppm) and coupling constants (Hz) of spirocyclopropanecarboxylates **10**–**17** ($CDCl_3$, 500 MHz)

	H-6a	H-6b	H-7	J_{cis}	J_{trans}	J_{gem}
10	1.12	1.66	2.03	7.0	9.0	6.0
11	1.24	1.51	2.07	7.0	9.0	5.5
12	1.31	1.60	1.86	7.0	9.0	6.0
13	1.40	1.46	1.97	7.5	9.5	6.5
14	1.08	1.66	2.21	7.0	9.0	6.0
15	1.66		1.88	8.0	9.0	6.5
16	1.39	1.89	1.84	6.5	8.5	6.0
17	1.67		1.88	8.0	9.2	6.5

Table 2
NOE experiments: positive enhancements on irradiation of H-4, H-6a, H-6b, and/or H-7 protons of spirocyclopropanecarboxylates **10**–**17**

	Irradiated H (δ)	NOE with (%)
10	H-6a (1.12)	H-7 (6.1), H-4 (7.0)
	H-6b (1.66)	OCH_3 (4.4)
11	H-4 (3.92)	H-6b (4.25)
	H-7 (2.07)	H-1 (4.1), H-6a (3.4)
12	H-4 (3.91)	H-7 (8.8)
	H-7 (1.86)	H-4 (8.2), H-6a (3.5)
13	H-4 (4.20)	H-6b (3.1)
	H-7 (1.97)	OCH_3 (5.8), H-6a (3.3)
14	H-6b (1.66)	H-1 (4.5)
	H-6a (1.08)	H-4 (4.9), H-7 (3.1)
15	H-6b (1.66)	H-4 (2.8)
	H-7 (1.88)	OCH_3 (4.6)
16	H-6a (1.39)	H-6b (27.1), H-7 (4.1), H-4 (3.0)
	H-4 (3.84)	H-7 (6.7), H-6a (2.6)
17	H-6a,b (1.67)	H-7 (1.9), H-4 (3.5)
	H-7 (1.88)	H-1 (5.2)

employing the B3LYP exchange correlation functional and 6-311+G(d) basis set.[25] Frequency calculation was used to confirm the nature of the stationary points. Transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all B3LYP/6-311+G(d) optimized structures and used, unscaled, to compute both ZPVE and activation energies. The electronic structures of critical points were studied by the natural bond orbital (NBO) method.[26] The enthalpy and entropy changes were calculated from standard statistical thermodynamic formulas.[27] The intrinsic reaction coordinates[28] (IRC analysis) were also calculated to analyze in detail the mechanism for all the obtained transition structures. DFT calculations were carried out with the G03 system of programs.[29] In all the cases, full geometry optimization was carried out without any symmetry constraints.

From inspection of the two conformers, it was apparent that the dichlorocarbene moiety can approach conformer **A** only from the upper side of alkene moiety (*Re*-face), because the lower one is very crowded; on the contrary, for the same reason, conformer **B** can be approached only from the lower side of double bond (*Si*-face). So, the two possible products of the cyclopropanation reaction, **8-(*Re*)** and **8-(*Si*)** can be originated through the two transition states **TSA** and **TSB** as shown in Figure 2.

The energetic of the whole process, reported in Table 3, shows that the reaction is very exothermic with an activation free energy of 11.1 kcal/mol for both the transition state pathways, which is almost exclusively imputable to entropic contributions rather than enthalpic ones. All these parameters are in good agreement with those reported in the literature for similar reactions.[30]

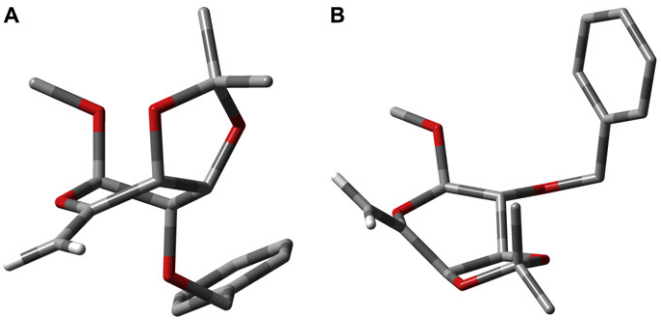


Figure 1. Conformers **A** and **B** of compound **2** with only olefinic hydrogens shown for clarity.

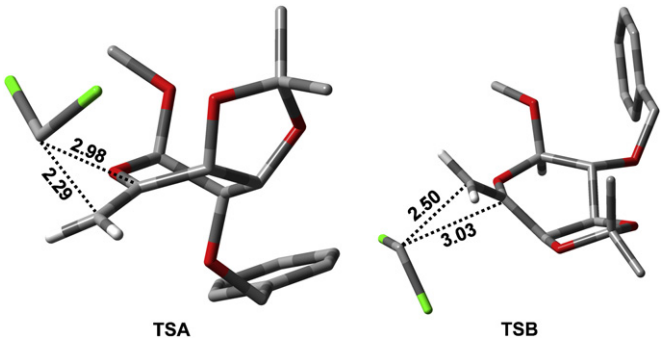


Figure 2. Transition state structures for dichlorocarbene approach to *Re*-face of conformer **A** and *Si*-face of conformer **B**. Only olefinic hydrogens are shown for clarity. Distances are in Å.

Finally, the reaction shows an inverse ΔG energetic barrier of 45–51 kcal/mol and thus it can be considered irreversible. Then, based on the predicted low and realistically identical activation ΔG values and knowledge of the rate constant in the order of 6.00×10^{-4} s^{-1} for this type of reaction,[31] we can expect that the ratio between the two diastereomeric products coincides with that one of **A** and **B** conformers at equilibrium. Introducing the $\Delta\Delta G$ value of 1.11 kcal/mol, relative to the energy difference between the two conformers **A** and **B**, in the Boltzman's distribution equation, we get 95.77% of conformer **A** at the equilibrium (**A**/**B** ratio of 22.64:1). Moreover, observing that the dipole moment of the two conformers is considerably different (ΔD=1.17 D), it is plausible to presume that the solvent polarity affects the conformer ratio. So, in order to obtain more insight on the solvent influence, we minimized the two conformers in the presence of a continuum model of chloroform solvation (PCM model)[32] at the same level of calculation (Table 3).

The obtained results confirm that in the most polar environment (chloroform vs gas phase) the amount of conformer **A** increases with respect to conformer **B** (**A**=98.13%; **A**/**B** ratio of 52.47:1), and on this basis, we must expect to practically observe only one product, namely that one derived from the attack of dichlorocarbene to the *Re*-face of conformer **A**, in agreement to the experimental results.

Insofar as concerns the reaction mechanism, transition structures and IRC analysis showed that the formation of the two new σ-bonds proceeds via a concerted pathway in which the carbene approaches to the olefin in an asymmetric fashion. The results provide unambiguous evidence for a nonlinear attack in which bond formation is more advanced at the terminal alkene unsubstituted carbon in accord with the non-least-motion approach[34] of

Table 3
B3LYP/6-311+G(d,p) relative electronic (ΔE), enthalpic (ΔH), and free (ΔG) energies (kcal/mol), and molecular dipole moments (D) (Debye)

	Direct ΔE[a]	Direct ΔH[a]	Direct ΔG[a]	Inverse ΔG[b]	D
A	0.00	0.00	0.00		1.74
	0.00[c]	0.00[c]	0.00[c]		2.19[c]
B	0.85	0.85	1.11		0.57
	1.86[c]	1.86[c]	2.36[c]		0.78[c]
TSA	−0.05	−0.64	11.10	45.77	5.07
TSB	1.10	0.51	11.13	51.04	3.13
P1	−48.53	−49.12	−34.67		4.48
P2	−53.42	−54.01	−39.91		2.50

[a] Since **2** exists in equilibrium between **A** and **B** conformers, the Curtin–Hammett principle[33] was applied and their relative energies were calculated with reference to **A**+dichlorocarbene.
[b] Referred to the corresponding products.
[c] Values calculated in chloroform as solvent.

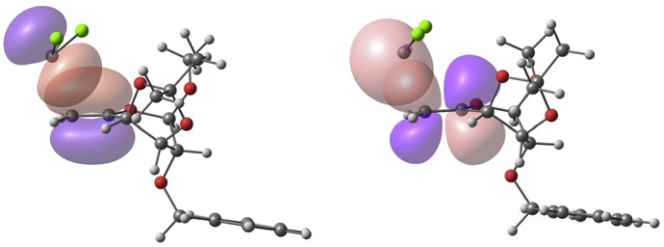


Figure 3. TSA displayed the π→p (left) and σ→π* (right) interactions between exocyclic double bond and dichloromethane moieties depicted by PNBO framework.

a carbene to a double bond, first proposed by Skell[35] and successively experimentally demonstrated by Houk.[36]

The Second Order Perturbation Theory Analysis (SOPT) of Fock Matrix in NBO Basis evidenced that, at the transition state, two pairs of orbital interactions exist between :CCl_2 carbene and C=C double bond (Fig. 3). For **TSA**, the primary one, which is the most important, involves the π→p stabilizing delocalization of the olefinic double bond with the empty p-like orbital of dichlorocarbene moiety (41.95 kcal/mol), whereas the secondary one, of type σ→π* (11.41 kcal/mol), is established between the carbon lone pair of :CCl_2 carbene and the antibonding orbital of the olefinic double bond; this last orbital interaction explains why the carbene approach is asymmetric, exhibiting concerted, but asynchronous, formation of the new two σ bonds. So, the addition trajectory begins as an electrophilic attack, but it involves a subsequent rotation of the carbene to achieve a final nucleophilic stage, which completes product formation as previously evidenced in similar reactions.[30b,c,37]

Moreover, the charge transfer between the two reactant at the TS geometry, evaluated by natural population analysis,[38] in terms of the residual charge on dichlorocarbene is of −0.188 electrons (a.u.) for **TSA** and it is indicative of an electron flow from the pyranose HOMO to the dichlorocarbene LUMO, in agreement with the primary dichloromethane electrophilic attack. The same considerations can be applied to **TSB**.

Further, the charge transfer analysis along the IRC pathway provide an additional and clear evidence for the two-phase (electrophilic/nucleophilic) mechanism, in that, for both **TSA** and **TSB** pathways, there is a distinct turning point (charge minimum) in the charge/IRC curves, which occurs just before the TS. In other words, the TS is reached near the starting point of the nucleophilic phase (Fig. 4).

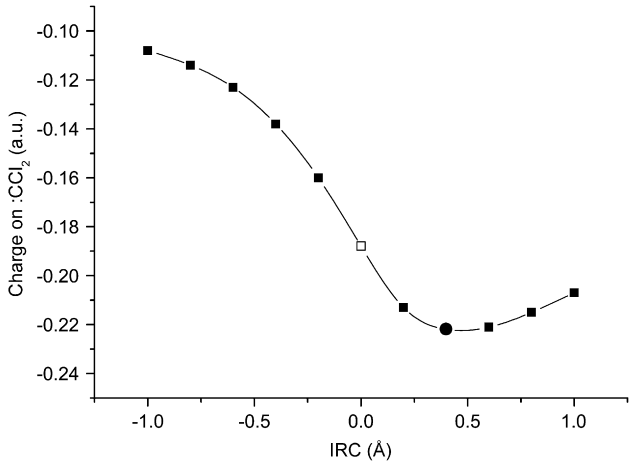


Figure 4. Charge analysis along the IRC for :CCl_2 cycloaddition to **2**; (□) and (●) correspond to the transition state and turning point, respectively; electrophilic phase-region right to the turning point and nucleophilic ones left.

4. Conclusions

Besides the reactions of **1**–**3** under Furukawa conditions, which afford optimum yields of expected spirocyclopropanes **4**–**6**, the synthetic strategy of the dihalocarbene addition to the 5,6-double bond of the pyranose ring provides a stereospecific method for obtaining spirocyclopropanated galactopyranosides with the two halogens on the upper face containing the 4-hydroxy substituent, which were never reported for the differently protected galactopyranosides. On the contrary, the reaction of **1** and **2** with the rhodium ethoxycarbonyl complex does not present any significant *endo*/*exo*, nor facial stereoselectivity.

Moreover this is, at our best knowledge, the first in silico study of a dichlorocyclopropanation reaction upon a 5-methylene pyranoside at this level of theory.

These synthetic reactions assume a considerable importance since the cyclopropane ring can be open to various manipulations, which can lead to natural and unnatural ketoses, higher sugars, 3-deoxy-2-glyculosonates, and 2-amino sugars. Furthermore, the application of these cyclopropanation reactions to unsaturated lactose allows a further chemical valorisation of this natural disaccharide, obtainable in great amounts from whey (a by-product of cheese industry), opening new prospects for its utilization.

5. Experimental

5.1. 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 25±2 °C. ^{1}H NMR spectra were recorded with a Varian Unity INOVA instrument at 200 and 500 MHz in the stated solvent (Me_4Si was used as the internal standard). ^{13}C NMR spectra were recorded at 50 MHz. Assignments were made, when possible, with the aid of DEPT experiments, for comparison with values for known compounds. High-resolution mass spectra were recorded on a VG ZAB-2SE double focusing magnetic sector mass spectrometer operating at 70 eV. All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulfuric acid, and heating. Kieselgel 60 (E. Merck, 70–230 and 230–400 mesh, respectively) was used for column and flash chromatography. HPLC purifications were made with a Microsorb silica Dinamax-100 Å preparative column (250×21 mm) at a flow rate of 21 mL/min with a Varian Pro Star instrument. Solvents were dried by distillation according to standard procedure,[39] and stored over 4 Å molecular sieves activated for at least 24 h at 400 °C. $MgSO_4$ was used as the drying agent for solutions.

5-Methylene galactopyranosides **1**,[11] **2**,[5,12] and **3**[13] were prepared from commercially available methyl-α- and methyl-β-D-galactopyranoside and lactose, respectively, following our previously reported method.[13]

5.2. General procedures for the cyclopropanation of 6-deoxyhex-5-enopyranosides 1–3

5.2.1. Procedure using the Simmons–Smith modified method

To a suspension of 6-deoxyhex-5-enopyranosides **1**–**3** (0.78 mmol) in Et_2O (3 mL), diethyl zinc (520 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 (5%, 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 pyranosides **4**–**6**.

*5.2.1.1. (3a′R,6′S,7′R,7a′S)-7′-(Benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran] **4***. Yield 90%; amorphous solid; $[\alpha]_D^{25}$ +22.38 (*c* 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35–7.26 (m, 5H, aromatic H), 4.83 and 4.69 (AB system, 2H, *J*=12.5 Hz, CH_2Ph), 4.60 (d, 1H, *J*=3.5 Hz, H-1), 4.43–4.39 (m, 1H, H-3), 3.71–3.69 (m, 1H, H-4), 3.64–3.61 (m, 1H, H-2), 3.44 (s, 3H, OCH_3), 1.24–1.21, 0.93–0.88, 0.79–0.75, and 0.71–0.67 (4m, each 1H, 2×CH_2); ^{13}C NMR (CD_3CN, 50 MHz): δ 138.5 (aromatic C), 128.4, 128.3, and 127.2 (aromatic CH), 109.4 ($C(CH_3)_2$), 98.4 (C-1), 83.6, 75.3, and 74.8 (C-2, C-3, and C-4), 73.1 (CH_2Ph), 56.6 (OCH_3), 54.8 (C-5), 27.5 (CH_3), 26.3 (CH_3), 11.7 (CH_2), 9.5 (CH_2). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.44; H, 7.52.

*5.2.1.2. (3a′R,6′R,7′R,7a′S)-7′-(Benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran] **5***. Yield 98%; colourless solid: mp 39–41 °C (from hexane); $[\alpha]_D^{25}$ −9.26 (*c* 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41–7.25 (m, 5H, aromatic H), 4.82 (s, 2H, CH_2Ph), 4.31 (d, 1H, *J*=7.8 Hz, H-1), 4.23 (dd, 1H, *J*=5.8, 7.1 Hz, H-3), 3.72 (d, 1H, *J*=5.8 Hz, H-4), 3.53 (dd, 1H, *J*=7.1, 7.8 Hz, H-2), 3.42 (s, 3H, OCH_3), 1.16–1.11, 0.93–0.88, 0.78–0.73, and 0.66–0.61 (4m, each 1H, 2×CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.4 (aromatic C), 128.2, 128.1, and 127.5 (aromatic CH), 109.8 ($C(CH_3)_2$), 103.2 (C-1), 88.2, 78.7, and 78.5 (C-2, C-3, and C-4), 73.5 (CH_2Ph), 56.2 (OCH_3), 55.1 (C-5), 27.7 (CH_3), 26.1 (CH_3), 11.3 (CH_2), 9.6 (CH_2). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.52; H, 7.57; HRMS (EI) *m*/*z*: calcd for $C_{18}H_{24}O_5$, 320.3801; found, 320.3803.

*5.2.1.3. (1S,3a′R,6′R,7′R,7a′S)-7′-(Benzyloxy)-2,2-dichloro-6′-{(R)[(4S,5R)-5-(dimethoxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl][(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran] **6***. Yield 96%; amorphous solid; $[\alpha]_D^{25}$ −17.04 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.25 (m, 5H, aromatic H), 4.84 and 4.76 (AB system, 2H, *J*=12.0 Hz, CH_2Ph), 4.64 (d, 1H, *J*=8.0 Hz, H-1′), 4.45 (dd, 1H, *J*=6.2, 7.8 Hz, H-2), 4.33 (d, 1H, *J*=6.2 Hz, H-1), 4.26 (dd, 1H, *J*=6.0, 8.8 Hz, H-5), 4.20 (dd, 1H, *J*=5.8, 7.2 Hz, H-3′), 4.17 (dd, 1H, *J*=6.0, 8.8 Hz, H-6b), 4.02 (dd, 1H, *J*=1.4, 7.8 Hz, H-3), 3.94 (dd, 1H, *J*=6.0, 7.0 Hz, H-6a), 3.73 (dd, 1H, *J*=1.4, 5.5 Hz, H-4), 3.61 (d, 1H, *J*=5.8 Hz, H-4′), 3.47 (dd, 1H, *J*=8.0, 7.2 Hz, H-2′), 3.30 (s, 6H, 2×OCH_3), 1.41 (s, 3H, CH_3), 1.40 (s, 6H, 2×CH_3), 1.35, 1.32, and 1.30 (3s, each 3H, CH_3), 1.15–1.12, 0.89–0.85, 0.78–0.73, and 0.74–0.69 (4m, each 1H, CH_2); ^{13}C NMR (CD_3CN, 50 MHz): δ 138.4 (C aromatic), 128.8, 128.0, and 127.4 (aromatic CH), 110.9, 110.7, and 109.2 (3×$C(CH_3)_2$), 106.9 (C-1), 104.2 (C-1′), 88.1 (C-3′), 80.2, 78.5, 77.9, 77.8, and 76.9 (C-2, C-3, C-4, C-2′, C-4′), 76.3 (C-2), 73.2 (CH_2Ph), 72.6 (C-6), 55.0 and 54.1 (2×OCH_3), 54.5 (C-5′), 27.9, 27.5, 26.1, 26.2, 27.4, and 26.1 (6×CH_3), 11.1 and 9.5 (2×CH_2). Anal. Calcd for $C_{31}H_{46}O_{11}$: C, 63.05; H, 8.04. Found: C, 63.28; H, 8.07; HRMS (EI) *m*/*z*: calcd for $C_{31}H_{46}O_{11}$, 594.6903; found, 594.6905.

5.2.2. Cyclopropanation by dichlorocarbene addition

To a suspension of **1**–**3** (0.98 mmol) in $CHCl_3$ (5 mL) containing benzyltriethylammonium chloride (BTEAC) (0.007 g, 0.037 mmol) as phase-transfer catalyst, a 50% aqueous NaOH (4 mL) was added under agitation. The suspension was stirred for 5 h and the reaction course was monitored by TLC (cyclohexane/AcOEt 70:30). Water (10 mL) and $CHCl_3$ (10 mL) were added and the layers separated. The aqueous layer was further extracted with $CHCl_3$. The combined organic extracts were washed with water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Flash chromatography (cyclohexane/AcOEt 90:10) of the residual syrup gave **7**–**9** as pure samples together with a little amount of starting unreacted 5-methylene galactopyranosides.

*5.2.2.1. (1S,3a′R,6′S,7′R,7a′S)-7′-(Benzyloxy)-2,2-dichloro-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran] **7***. Yield 80%; colourless solid: mp 52–54 °C (from hexane); $[\alpha]_D^{25}$ +25.89 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40–7.28 (m, 5H, aromatic H), 4.87 (d, 1H, *J*=3.0 Hz, H-1), 4.76 and 4.69 (AB, 2H, *J*=12.0 Hz, CH_2Ph), 4.46 (t, 1H, *J*=6.5 Hz, H-4), 4.44 (1H, dd, *J*=6.0, 6.5 Hz, H-3), 3.70 (dd, 1H, *J*=3.0, 6.5 Hz, H-2), 3.49 (s, 3H, OCH_3), 1.82 (1/2 AB system, 1H, *J*=9.0 Hz, H-6b), 1.64 (1/2 AB system, 1H, *J*=9.0 Hz, H-6a), 1.40 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.1 (aromatic C), 128.9, 127.9, and 127.7 (aromatic CH), 109.1 ($C(CH_3)_2$), 100.0 (C-1), 75.5, 74.5, and 73.4 (C-2, C-3, C-4), 73.1 (CH_2Ph), 63.5 (CCl_2), 63.2 (C-5), 58.4 (OCH_3), 29.6 (C-6), 27.3 (CH_3), 25.5 (CH_3). Anal. Calcd for $C_{18}H_{22}Cl_2O_5$: C, 55.54; H, 5.70. Found: C, 55.62; H, 5.71; HRMS (EI) *m*/*z*: calcd for $C_{18}H_{22}Cl_2O_5$, 389.2703; found, 389.2706.

*5.2.2.2. (1S,3a′R,6′R,7′R,7a′S)-7′-(Benzyloxy)-2,2-dichloro-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran] **8***. Yield 65%; amorphous solid; $[\alpha]_D^{25}$ −16.24 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41–7.25 (m, 5H, aromatic H), 4.79 and 4.84 (AB system, *J*=11.8 Hz, CH_2Ph), 4.58 (d, 1H, *J*=7.5 Hz, H-1), 4.36 (d, *J*=6.0 Hz, H-4), 4.32 (dd, 1H, *J*=6.0, 7.5 Hz, H-3), 3.54 (s, 3H, OCH_3), 3.51 (d, 1H, *J*=7.5 Hz, H-2), 1.91 and 1.87 (AB system, 1H, *J*=9.1 Hz, CH_2), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.0 (aromatic C), 128.2, 128.0, and 127.6 (aromatic CH), 110.1 ($C(CH_3)_2$), 104.0 (C-1), 78.8, 77.8, and 73.8 (C-2, C-3, C-4), 73.6 (CH_2Ph), 61.6 (C-5), 61.5 (CCl_2), 57.0 (OCH_3), 30.1 (CH_2), 27.6 (CH_3), 26.2 (CH_3). Anal. Calcd for $C_{18}H_{22}Cl_2O_5$: C, 55.54; H, 5.70. Found: C, 55.69; H, 5.68.

*5.2.2.3. (1S,3a′R,6′R,7′R,7a′S)-7′-(Benzyloxy)-2,2-dichloro-6′-{(R)[(4S,5R)-5-(dimethoxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl][(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran] **9***. Yield 70%; syrup; $[\alpha]_D^{25}$ −2.95 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDC1_3$, 500 MHz): δ 7.40–7.26 (m, 5H, aromatic H), 4.93 (d, 1H, *J*=7.9 Hz, H-l′), 4.86 and 4.75 (AB system, 2H, *J*=11.8 Hz, CH_2Ph), 4.44 (dd, 1H, *J*=6.2, 7.5 Hz, H-2), 4.33 (d, 1H, *J*=6.2 Hz, H-l), 4.29–4.21 (m, 3H, H-3′, H-4′, H-5), 4.20 (dd, 1H, *J*=1.2, 5.2 Hz, H-4), 4.14 (dd, *J*=6.2, 7.0 Hz, H-6b), 4.05 (d, 1H, *J*=1.2 Hz, H-3), 3.99 (dd, 1H, *J*=7.0, 8.7 Hz, H-6a), 3.47 (dd, 1H, *J*=6.0, 7.9 Hz, H-2′), 3.38 (2s, each 6H, 2×OCH_3), 1.86 and 1.82 (AB system, 2H, *J*=8.9 Hz, CH_2), 1.41 (s, 6H, 2×CH_3), 1.39 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.33 (2s, each 6H, 2×CH_3); ^{13}C NMR (CD_3CN, 50 MHz): δ 138.6 (aromatic C), 128.2, 128.1, and 127.6 (aromatic CH), 110.8, 110.4, and 108.9 (3×$C(CH_3)_2$), 105.9 (C-1), 103.7 (C-1′), 89.0 (C-3′), 81.7, 77.8, 76.9, and 75.5 (C-2, C-3, C-4, C-2′, C-4′), 75.8 (C-2), 73.2 (CH_2Ph), 71.5 (C-6), 61.6 (C-5′), 61.5 (CCl_2), 57.0 and 56.1 (2×OCH_3), 32.5 (CH_2), 27.9, 27.2, 26.8, 26.3, 26.0, and 25.9 (6×Me). Anal. Calcd for $C_{31}H_{44}Cl_2O_{11}$: C, 56.11; H, 6.68. Found: C, 55.99; H, 6.70; HRMS (EI) *m*/*z*: calcd for $C_{31}H_{44}Cl_2O_{11}$, 663.5804; found, 663.5802.

*5.2.3. Cyclopropanation by addition of ethoxycarbonyl-carbene to **1** and **2***

To a suspension of **1** or **2** (0.456 g, 1.47 mmol) in anhydrous CH_2Cl_2 (3 mL), containing $Rh_2(OAc)_4$ (0.013 g, 0.027 mmol) as catalyst, a solution of ethyl diazoacetate (0.47 mL, 1.5 mmol) in anhydrous CH_2Cl_2 (15 mL) was slowly added under constant agitation and under a nitrogen atmosphere. The reaction was monitored by TLC (cyclohexane/AcOEt 70:30) until starting **1**, **2** disappeared (about 5 h). A mixture of four products **10**, **11**, **12**, and **13** was formed in the ratio 1.2:0.8:2.0:1.8, respectively, as it appeared from the ^{1}H NMR spectra of the crude. After filtration of catalyst, the solvent

was removed under reduced pressure. The flash chromatography (cyclohexane/AcOEt 85:15) of the residue gave **13** and a mixture of the other diastereoisomers **10**, **11**, and **12**; preparative HPLC (hexane/isopropanol 10%) of this latter mixture yielded isomerically pure samples of **12** (t_R 15 min), **10** (t_R 18 min) and **11** (t_R 19 min).

An analogous procedure was followed for the cyclopropanation of **2**, which yielded **14**, **15**, **16**, and **17** in the ratio 0.5:0.5:1.1:1.0 after the flash chromatography, which gave only **17** and preparative HPLC, which afforded in the sequence **16** (t_R 13 min), **14** (t_R 16 min), and **15** (t_R 17 min) as pure samples.

5.2.3.1. Ethyl (1R,2R,3a′R,6′S,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]-pyran]-2-carboxylate ***10***. Yield 10%; amorphous solid; $[\alpha]_D^{25}$ +17.2 (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.27 (m, 5H, aromatic H), 4.84 and 4.68 (AB, 2H, *J*=12.5 Hz, *CH*$_2$Ph), 4.67 (d, 1H, *J*=3.0 Hz, H-1), 4.49 (dd, 1H, *J*=6.5, 7.5 Hz, H-3), 4.15 and 4.08 (2dq, 2H, *J*=6.5, 7.5 Hz, CH_3CH_2O), 4.07 (d, 1H, *J*=6.5 Hz, H-4), 3.77 (dd, 1H, *J*=3.0, 7.5 Hz, H-2), 3.41 (s, 3H, OCH_3), 2.03 (dd, 1H, *J*=7.0, 9.0 Hz, H-7), 1.66 (dd, 1H *J*=6.0, 9.0 Hz, H-6b), 1.48 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.20 (t, 3H, *J*=7.5 Hz, CH_3CH_2O), 1.12 (dd, 1H, *J*=6.0, 7.0 Hz, H-6a); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.7 (C=O), 138.1 (aromatic C), 128.3, 127.9, and 127.7 (CH aromatic), 109.6 (*C*-(CH_3)$_2$), 99.5 (C-1), 76.3, 75.9, and 75.3 (C-2, C-3, C-4), 72.5 (*CH*$_2$Ph), 61.0 (C-5), 60.7 (CH_3CH_2O), 56.3 (OCH_3), 27.1 (C-7), 25.5 (CH_3), 22.5 (CH_3), 16.2 (C-6), 14.2 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.39; H, 7.22.

5.2.3.2. Ethyl (1R,2S,3a′R,6′S,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]-pyran]-2-carboxylate ***11***. Yield 13%; amorphous solid; $[\alpha]_D^{25}$ −18.1 (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.28 (m, 5H, aromatic H), 4.82 and 4.72 (AB system, 2H, *J*=11.5 Hz, *CH*$_2$Ph), 4.29 (d, 1H, *J*=3.5 Hz, H-1), 4.03 (dd, 1H, *J*=5.5, 8.0 Hz, H-3), 3.98 (2dq, 2H, *J*=6.0, 7.5 Hz, CH_3CH_2O), 3.92 (d, 1H, *J*=5.5 Hz, H-4), 3.63 (dd, 1H, *J*=3.5, 8.0 Hz, H-2), 3.37 (s, 3H, OCH_3), 2.07 (dd, 1H, *J*=7.0, 9.0 Hz, H-7), 1.51 (dd, 1H, *J*=5.5, 9.0 Hz, H-6b), 1.39 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.26 (t, 3H, *J*=7.5 Hz, CH_3CH_2O), 1.24 (dd, 1H, *J*=5.5, 7.0 Hz, H-6a); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.8 (C=O), 139.0 (aromatic C), 129.1, 129.0, and 128.1 (aromatic CH), 110.1 (*C*(CH_3)$_2$), 101.0 (C-1), 78.8, 77.1, and 76.1 (C-2, C-3, C-4), 73.4 (*CH*$_2$Ph), 62.0 (C-5), 60.5 (CH_3CH_2O), 57.1 (OCH_3), 27.9 (CH_3), 27.2 (CH_3), 27.0 (C-7), 18.2 (C-6), 14.2 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.23.

5.2.3.3. Ethyl (1S,2S,3a′R,6′S,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran]-2-carboxylate ***12***. Yield 22%; amorphous solid; $[\alpha]_D^{25}$ −16.1 (*c* 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.27 (m, 5H, aromatic H), 4.82 and 4.70 (AB system, 2H, *J*=12.5 Hz, *CH*$_2$Ph), 4.77 (dd, 1H, *J*=6.5, 7.5 Hz, H-3), 4.68 (d, 1H, *J*=3.5 Hz, H-1), 4.20 and 4.08 (2dq, 2H, *J*=11.0, 7.5 Hz, CH_3CH_2O), 3.91 (d, 1H, *J*=6.5 Hz, H-4), 3.71 (dd, 1H, *J*=3.5, 7.5 Hz, H-2), 3.31 (s, 3H, OCH_3), 1.86 (dd, 1H, *J*=7.0, 9.0 Hz, H-7), 1.60 (dd, 1H, *J*=6.0, 7.0 Hz, H-6b), 1.44 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.31 (dd, 1H, *J*=6.0, 9.0 Hz, H-6a), 1.26 (t, 3H, *J*=7.5 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.9 (C=O), 138.1 (aromatic C), 128.4, 127.8, and 127.7 (aromatic CH), 109.2 (*C*(CH_3)$_2$), 100.1 (C-1), 77.4, 76.0, and 75.1 (C-2, C-3, C-4), 72.8 (*CH*$_2$Ph), 61.1 (C-5), 60.6 (CH_3CH_2O), 57.4 (OCH_3), 27.41 (CH_3), 25.5 (CH_3), 25.7 (C-7), 14.9 (C-6), 14.2 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.13; H, 7.22.

5.2.3.4. Ethyl (1S,2R,3a′R,6′S,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran]-2-carboxylate ***13***. Yield 20%; amorphous solid; $[\alpha]_D^{25}$ +4.8 (*c* 0.17, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.24 (m, 5H, aromatic H), 4.80 and 4.68 (AB system, 2H, *J*=12.5 Hz, *CH*$_2$Ph), 4.60 (d, 1H, *J*=3.5 Hz, H-1), 4.35 (d, 1H, *J*=6.0 Hz, H-4), 4.26 (dd, 1H, *J*=6.0, 7.5 Hz, H-3), 4.08 and 4.03 (2dq, *J*=11.0, 7.0 Hz, CH_3CH_2O), 3.61 (dd, 1H, *J*=3.5, 7.5 Hz, H-2), 3.41 (s, 3H, OCH_3), 1.97 (dd, 1H, *J*=7.5, 9.5 Hz, H-7), 1.46 (dd, 1H, *J*=6.5, 9.5 Hz, H-6b), 1.42 (s, 3H, CH_3), 1.40 (dd, 1H, *J*=6.5, 7.5 Hz, H-6a), 1.32 (s, 3H, CH_3), 1.20 (t, 3H, *J*=7.0 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.0 (C=O), 139.0 (aromatic C), 128.3, 127.8, and 127.7 (aromatic CH), 108.6 (*C*(CH_3)$_2$), 99.9 (C-1), 75.8, 74.3, and 72.8 (C-2, C-3, C-4), 72.7 (*CH*$_2$Ph), 60.7 (CH_3CH_2O), 58.9 (C-5), 56.9 (OCH_3), 27.9 (CH_3×2), 26.1 (C-7), 15.3 (C-6), 14.1 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.44; H, 7.21.

5.2.3.5. Ethyl (1R,2R,3a′R,6′R,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran]-2-carboxylate ***14***. Yield 12%; amorphous solid; $[\alpha]_D^{25}$ −64.5 (*c* 1.21, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.25 (m, 5H, aromatic H), 4.83 and 4.78 (AB system, 2H, *J*=12.0 Hz, CH_2Ph), 4.52 (d, 1H, *J*=7.5 Hz, H-1), 4.25 (t, 1H, *J*=7.5 Hz, H-3), 4.20 (d, 1H, *J*=6.0 Hz, H-4), 4.17 and 4.08 (2dq, 2H, *J*=6.5, 7.0 Hz, CH_3CH_2O), 3.69 (t, 1H, *J*=7.5 Hz, H-2), 3.35 (s, 3H, OCH_3), 2.21 (dd, 1H, *J*=7.0, 9.0 Hz, H-7), 1.66 (dd, 1H, *J*=6.0, 7.0 Hz, H-6b), 1.44 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.27 (t, 3H, *J*=7.5 Hz, CH_3CH_2O), 1.08 (dd, 1H, *J*=6.0, 9.0 Hz, H-6a); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.6 (C=O), 138.5 (aromatic C), 128.2, 127.9, and 127.8 (CH aromatic), 110.5 (*C*(CH_3)$_2$), 103.2 (C-1), 79.4, 78.2 (C-2 and C-3), 73.5 (CH_2Ph), 73.1 (C-4), 61.2 (CH_3CH_2O), 60.8 (C-5), 56.6 (OCH_3), 27.3 (CH_3), 27.0 (CH_3), 23.6 (C-7), 18.1 (C-6), 14.2 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.35; H, 7.17.

5.2.3.6. Ethyl (1R,2S,3a′R,6′R,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran]-2-carboxylate ***15***. Yield 14%; amorphous solid; $[\alpha]_D^{25}$ +41.2 (*c* 0.98, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.28 (m, 5H, aromatic H), 4.79 (s, 2H, CH_2Ph), 4.29 (d, 1H, *J*=8.5 Hz, H-1), 4.26 (dd, 1H, *J*=6.5, 7.5 Hz, H-3), 4.16 (d, 1H, *J*=6.5 Hz, H-4), 4.08 and 4.15 (2dq, 2H, *J*=6.0, 7.0 Hz, CH_3CH_2O), 3.51 (dd, 1H, *J*=7.5, 8.5 Hz, H-2), 3.46 (s, 3H, OCH_3), 1.88 (dd, 1H, *J*=8.0, 9.0 Hz, H-7), 1.66 (2dd, 1H×2, *J*=6.5, 8.0, 9.0 Hz, H-6a, H-6b), 1.42 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.27 (t, 3H, *J*=7.0 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.9 (C=O), 138.1 (aromatic C), 128.0, 127.6, and 127.5 (aromatic CH), 110.7 (*C*(CH_3)$_2$), 103.6 (C-1), 80.2, 77.7, and 75.2 (C-2, C-3, and C-4), 73.5 (CH_2Ph), 61.2 (CH_3CH_2O), 60.8 (C-5), 56.0 (OCH_3), 27.8 (CH_3), 27.2 (CH_3), 26.3 (C-7), 15.1 (C-6), 14.2 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.36; H, 7.16.

5.2.3.7. Ethyl (1S,2S,3a′R,6′R,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran]-2-carboxylate ***16***. Yield 37%; amorphous solid; $[\alpha]_D^{25}$ −4.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.25 (m, 5H, aromatic H), 4.80 (s, 2H, *CH*$_2$Ph), 4.29 (dd, *J*=6.5, 8.0 Hz, H-3), 4.20 (d, 1H, *J*=7.5 Hz, H-1), 4.12 and 4.18 (2dq, 2H, *J*=7.0, 7.5 Hz, CH_3CH_2O), 3.84 (d, 1H, *J*=6.5 Hz, H-4), 3.55 (dd, 1H, *J*=7.5, 8.0 Hz, H-2), 3.42 (s, 3H, OCH_3), 1.89 (dd, 1H, *J*=6.0, 8.5 Hz, H-6b), 1.84 (dd, 1H, *J*=6.5, 8.5 Hz, H-7), 1.40 (s, 3H, CH_3), 1.39 (dd, 1H, *J*=6.0, 8.5 Hz, H-6a), 1.32 (s, 3H, CH_3), 1.29 (t, 3H, *J*=7.5 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.6 (C=O), 138.4 (aromatic C), 128.2, 128.1, and 127.6 (aromatic CH), 110.2 (*C*(CH_3)$_2$), 103.2 (C-1), 79.9, 78.1, and 77.5 (C-2, C-3, and C-4), 73.6 (*CH*$_2$Ph), 60.9 (CH_3CH_2O), 60.7 (C-5), 56.4 (OCH_3), 27.4 (CH_3), 25.9 (CH_3), 24.9 (C-7), 15.7 (C-6), 14.2 (OCH_2CH_3). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.22; HRMS (EI) *m*/*z*: calcd for $C_{21}H_{28}O_7$, 392.44282; found, 392.44291.

5.2.3.8. Ethyl (1S,2R,3a′R,6′R,7′R,7a′S)-7′-(benzyloxy)-6′-methoxy-2′,2′-dimethyltetrahydrospiro[cyclopropane-1,4′-[1,3]dioxolo[4,5-c]pyran]-2-carboxylate ***17***. Yield 30%; amorphous solid; $[\alpha]_D^{25}$ +6.9 (*c* 0.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40–7.26 (m, 5H, aromatic H),

4.83–4.78 (AB system, 2H, J=11.5 Hz, CH_2Ph), 4.29 (d, 1H, J=8.0 Hz, H-1), 4.25 (d, 1H, J=6.0 Hz, H-4), 4.20 and 4.11 (2dq, 2H, J=7.0, 7.5 Hz, CH_3CH_2O), 4.10 (dd, 1H, J=6.0, 7.5 Hz, H-3), 3.51 (dd, 1H, J=7.5, 8.0 Hz, H-2), 3.46 (s, 3H, OCH_3), 1.88 (dd, 1H, J=8.0, 9.2 Hz, H-7), 1.67 (2dd, 2H, J=6.5, 8.0, 9.2 Hz, H-6a, H-6b), 1.42 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.27 (t, 1H, J=7.5 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.9 (C=O), 138.0 (aromatic C), 128.2 and 127.6 (aromatic CH), 109.8 ($C(CH_3)_2$), 103.6 (C-1), 79.4 and 78.2 (C-2, C-4), 73.7 (CH_2Ph), 73.1 (C-3), 61.1 (CH_3CH_2O), 61.0 (C-5), 56.6 (OCH_3), 27.8 (CH_3), 27.2 (CH_3), 26.3 (C-7), 18.1 (C-6), 14.2 (CH_3CH_2O). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.21.

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References and notes

1. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
2. Chapleur, Y.; Grapsas, Y. *Carbohydr. Res.* **1985**, *141*, 153–158.
3. Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831.
4. Dalko, P. I.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 773–777.
5. Enright, P. M.; Tosin, M.; Nieuwenhuyzen, M.; Cronin, L.; Murphy, P. V. *J. Org. Chem.* **2002**, *67*, 3733–3741.
6. Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099–1132.
7. (a) Duchaussoy, P.; Di Cesare, P.; Gross, B. *Synthesis* **1979**, 198–200; (b) Aubry, P. A.; Protas, J.; Duchaussoy, P.; Di Cesare, P.; Gross, B. *Acta Crystallogr., Sect. B* **1981**, *37*, 1473–1480; (c) Huber, R.; Molleyres, L. P.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 1329–1337.
8. (a) Corsaro, A.; Catelani, G.; D'Andrea, F.; Fisichella, S.; Mariani, M.; Pistarà, V. *Environ. Sci. Pollut. Res.* **2003**, *10*, 325–328; (b) Pistarà, V.; Barili, P. L.; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *41*, 3253–3256; (c) Catelani, G.; Corsaro, A.; D'Andrea, F.; Mariani, M.; Pistarà, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3313–3315; (d) Corsaro, A.; Chiacchio, U.; Adamo, R.; Pistarà, V.; Rescifina, A.; Romeo, R.; Catelani, G.; D'Andrea, F.; Mariani, M.; Attolino, E. *Tetrahedron* **2004**, *60*, 3787–3795.
9. Corsaro, A.; Pistarà, V.; Catelani, G.; D'Andrea, F.; Adamo, R.; Chiacchio, M. A. *Tetrahedron Lett.* **2006**, *47*, 6591–6594.
10. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; de Rensis, F.; Puccioni, L. *Tetrahedron* **1997**, *57*, 3407–3416.
11. Mulard, L. A.; Kováč, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1994**, *259*, 117–129.
12. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2411–2431.
13. Catelani, G.; D'Andrea, F.; Corsaro, A.; Pistarà, V.; Vittorino, E. *Carbohydr. Res.* **2003**, *338*, 2349–2358.
14. For selected examples, see: (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353–3354; (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *38*, 6885–6888.
15. For reviews, see: (a) Hovyeda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370; (b) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, NY, 1992.
16. (a) Brimacombe, J. S.; Evans, M. E.; Forbes, E. J.; Foster, A. B.; Webber, J. M. *Carbohydr. Res.* **1967**, *4*, 239–243; (b) Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1995**, 217–218; (c) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694–7703.
17. (a) Baidzhigitova, E. A.; Afanas'ev, V. A.; Dolgii, I. E. *Izv. Akad. Nauk Kirg. SSR* **1981**, 50–56; (b) Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901–8904; (c) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533–2536.
18. Determined by ^{1}H NMR integration of the signals of OCH_3 protons in the crude reaction mixture.
19. Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44–52; Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 1906–1912.
20. Chen, C.-H.; Tsai, M.-L.; Su, M.-D. *Organometallics* **2006**, *25*, 2766–2773; (b) Gaspar, P. P.; Lin, C. T.; Dunbar, B. L. W.; Mack, D. P.; Balasubramanian, P. *J. Am. Chem. Soc.* **1984**, *106*, 2128–2139; (c) Aydogan, C.; Anac, O. *Chim. Acta Turc.* **1982**, *10*, 113–120; (d) Creary, X. *J. Org. Chem.* **1978**, *43*, 1777–1783.
21. Barden, C. J.; Schaefer, H. F., III. *J. Chem. Phys.* **2000**, *112*, 6515–6516.
22. Nefedov, O. M.; Shafran, R. N. *Russ. Chem. Bull.* **1965**, *14*, 515–518.
23. Metropolis, N.; Rosenbluth, A. W.; Rosenbluth, M. N.; Teller, A. N.; Teller, E. *J. Chem. Phys.* **1953**, *21*, 1087–1092.
24. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220 and 221–264.
25. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100; (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
26. Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746.
27. Hehre, W. J.; Radom, L.; Schleyer, P. V.; Pople, J. *Ab Initio Molecular Orbital Theory*; Wiley: New York, NY, 1986.
28. (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368; (b) Head-Gordon, M.; Pople, J. A. *J. Chem. Phys.* **1988**, *89*, 5777–5786.
29. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 03 Revision D.02*; Gaussian: Wallingford, CT, 2004.
30. (a) Turro, H. J.; Lehr, G. F.; Butcher, J. A.; Moss, R. A.; Guo, W. *J. Am. Chem. Soc.* **1982**, *104*, 1754–1756; (b) Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 1919–1920; (c) Keating, A. E.; Garcia-Garibay, M. A.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 10805–10809.
31. Jayachandran, J. P.; Wang, M.-L. *J. Chin. Inst. Eng.* **2000**, *23*, 557–565.
32. Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111–128.
33. Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335.
34. Rice, F. O.; Teller, E. *J. Chem. Phys.* **1938**, *6*, 489–496 and **1939**, *7*, 199–200.
35. Skell, P. S.; Garner, A. Y. *J. Am. Chem. Soc.* **1956**, *78*, 5430–5433.
36. Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933–3938.
37. Houk, K. N.; Rondan, N. G.; Mareda, J. *J. Am. Chem. Soc.* **1984**, *106*, 4291–4293.
38. Carpenter, J. E.; Weinhold, F. *J. Mol. Struct. (Theochem)* **1988**, *169*, 41–62.
39. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980.