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Note

A simple and mild synthesis of a 4,5-cyclopropanated carbohydrate

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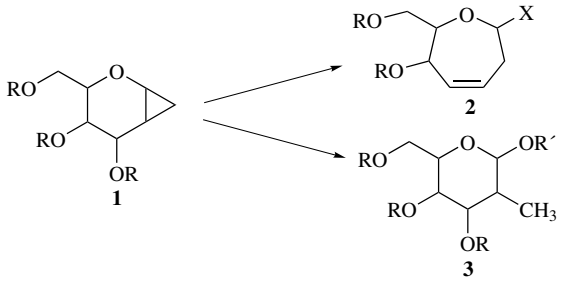
Abstract—The synthesis of a 4,5-cyclopropanated carbohydrate was achieved in five steps from methyl α-D-mannopyranoside under mild conditions that avoid the use of carbene chemistry.

Keywords: Cyclopropane; Silver fluoride

The cyclopropano moiety is a widely occurring structure in natural products and therapeutic agents and has a high degree of reactivity that can be useful for a vast array of synthetic applications. The formation of a cyclopropane ring in a sugar scaffold provides a valuable platform for the development and application of a new class of enantiopure building blocks. In recent years, these strained carbohydrate derivatives have appeared in a growing number of reports.[1] Most of the work in this field was done on cyclopropanation of 1,2-unsaturated carbohydrates (glycals) by the reaction with carbenes, which are a class of reagents with a very high reactivity and hence a poor tolerance for other functional groups in the molecule.

The three main methods used for the cyclopropanation of glycals are the following: the Simmons–Smith reaction,[2] dihalocarbene cycloaddition[3] and diazo ester cyclopropanation.[4] Cyclopropanated carbohydrates have been utilized in two main synthetic strategies, the ring opening of the cyclopropane and ring expansion of the carbohydrate (Scheme 1).[1a]

Unfortunately, the above-mentioned reactive nature of carbenes has precluded a wider use of these appealing synthetic strategies. Herein we wish to report a simple and mild procedure for the synthesis of a different type of cyclopropanated carbohydrate derivative.



Scheme 1.

We started from methyl α-D-mannopyranoside (**4**), which was benzylidenated with α,α-dimethoxytoluene following a modification of a standard procedure,[5] to give the 2,3:4,6-dibenzylidene acetal **5** in 86% yield as a crystalline mixture of diastereoisomeric products at the acetal position of the dioxolane ring. Treatment of the mixture with butyllithium allowed the conversion of **5** into **6**, isolated in 60% yield.[6] The regioselective ring opening of the 1,3-dioxane ring was achieved with *N*-bromosuccinimide in carbon tetrachloride by the general procedure described by Hanessian and Plessas,[7] and led to formation of the 4-*O*-benzoyl-6-bromo-6-deoxy analogue **7** in 65% yield (Scheme 2).

At this point we found in a serendipitous way that treatment of the bromo sugar **7** with silver fluoride in pyridine gave the cyclopropane **9** in 56% yields. The

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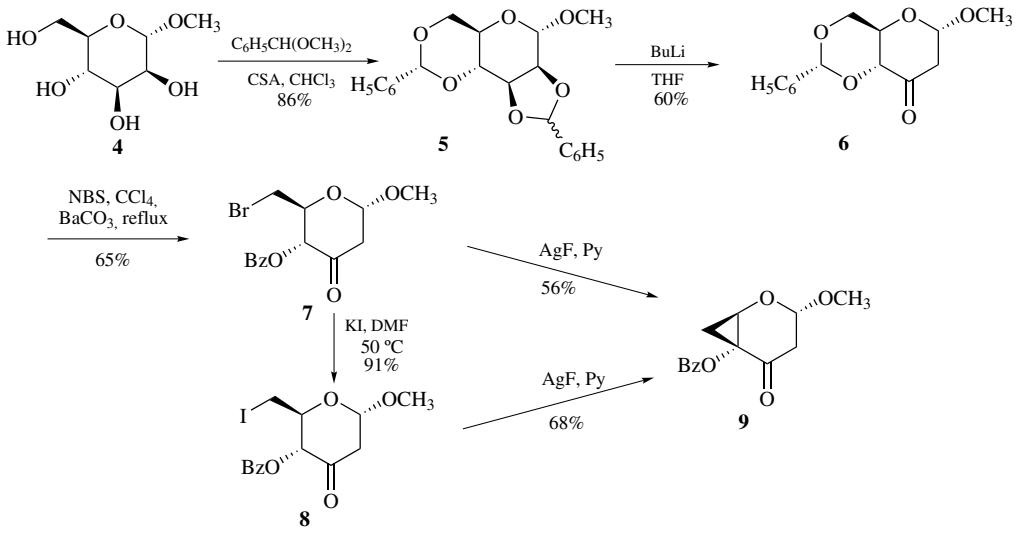

Scheme 2.

structure of compound **9** was unambiguously proven by IR, NMR and mass spectroscopy. The IR spectrum confirmed the presence of two carbonyl groups at 1740 and 1717 cm^{-1}. The ^1H NMR spectrum showed the disappearance of the signal corresponding to H-4 and a shifting to higher fields of the protons H-6a,b (δ 2.01 and 1.81 ppm). Besides, the ^{13}C NMR revealed the disappearance of a methine signal and the appearance of a quaternary carbon at 62.1 ppm that was assigned to C-4. The HRMS showed a peak for the $[M+H]^+$ 263.0922 that is in agreement with a calculated molecular formula of $C_{14}H_{14}O_5$. All these data are consistent with the structure of the cyclopropane ketone **9**.

To the best of our knowledge, there is only one precedent reported in the literature[2e] of a carbohydrate with a cyclopropane ring between C-4 and C-5, and its synthesis was achieved by a carbene addition. In our case, the reaction presumably involved the intramolecular nucleophilic attack of the carbanion formed at C-4 on C-6. This strategy avoids the formation of diastereoisomers by taking advantage of the C-5 configuration for controlling the facial selectivity of ring closure.

After recognizing the potential utility of this discovery, we reasoned that the deoxyiodo derivative could provide the cyclopropyl ketone **9** with better yields. To optimize the procedure, an efficient interchange of halogen was carried out to furnish the 6-deoxy-6-iodo derivative **8** in 91% yield, which was subsequently treated with pyridine and silver fluoride to obtain **9** in higher yields (68%).

In order to confirm the role of silver fluoride in this reaction, the deoxyiodo derivative **8** was dissolved in pyridine and stirred for 24 h at room temperature. After a standard workup, the starting material was completely recovered. A precedent for the peculiar chemical behaviour of bromo ketone **7** has recently been reported by Wiedemeyer and Wünsch.[8]

In conclusion, we have achieved the synthesis of the 4,5-cyclopropano sugar derivative by an unconventional cyclopropanation reaction. The procedure does not require the use of carbenes, and the reaction conditions are simple and mild. The studies on the potential applications of this new chiral building block are underway and will be reported in due course.

1. Experimental

1.1. General

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage, Model 350 apparatus, and are uncorrected. Optical rotations were recorded with a Jasco DIP 1000 polarimeter. IR spectra were recorded on a Nicolet Impact Model 410 instrument. Nuclear magnetic resonance spectra were recorded on a Bruker AC-200 spectrometer with Me_4Si as internal standard and chloroform-*d* as solvent. Reactions were monitored by TLC on 0.25 mm E. Merck Silica Gel 60 plates (F_{254}), using UV light and anisaldehyde–H_2SO_4–AcOH as detecting agents. Flash column chromatography using E. Merck Silica Gel 60H was performed by gradient elution created by mixtures of hexanes and increasing amounts of EtOAc. Reactions were performed under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated.

1.2. Preparation of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (5)

Methyl-α-D-mannopyranoside (**4**) (0.4 g, 2.06 mmol) was dissolved in $CHCl_3$ (20 mL), and camphorsulfonic acid (18 mg, 0.072 mmol) and α,α-dimethoxytoluene (0.71 mL, 4.74 mmol) were added successively. The resulting mixture was stirred and refluxed in a flask fitted with a Dean–Stark trap for solvents heavier than water and loaded with 4 Å molecular sieves (1.5 g, activated at 350 °C for 3 h) for 3 h. K_2CO_3 (85 mg, 0.6 mmol) was then added, and the reaction mixture was refluxed for an additional 30 min. The hot reaction mixture was filtered through a filter funnel with a porosity E sintered glass fritted disc with suction, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by flash chromatography to furnish a mixture of isomers **5** (655 mg, 1.77 mmol, 86%) and used without further purification in the next synthetic transformation. Spectroscopic data were in complete agreement with those previously reported.[6,8]

1.3. Preparation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (6)

A solution of the diastereoisomeric mixture of acetals **5** (819 mg, 2.2 mmol) in THF (16 mL) under nitrogen was cooled to −40 °C. Butyllithium in hexane (1.36 M, 3.5 mL, 4.8 mmol) was added, and the temperature was kept for 30 min below −30 °C. When all the starting material disappeared, the solution, still at −30 °C was poured into ice water containing NH_4Cl (2.2 g). Without separation of the layer, the THF was removed on a rotatory evaporator. The aqueous slurry remaining was cooled to 0 °C, and the crystalline deoxy ketone **6** was filtered and dried. The resulting crude product was purified by flash chromatography to furnish the ketone **6** (352 mg, 1.33 mmol, 60%). Spectroscopic data were in complete agreement with those previously reported.[6,8]

1.4. Preparation of methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*erythro*-hexopyranosid-3-ulose (7)[8]

Ba_2CO_3 (1.6 g) and *N*-bromosuccinimide (216 mg, 1.2 mmol) were added to a solution of compound **6** (267 mg, 1.01 mmol) in dry CCl_4 (30 mL). The mixture was boiled under reflux for 1 h under normal room illumination. The mixture, originally colourless, became orange and finally yellow. The suspension was filtered, and the filtrate was evaporated. The residue was extracted with EtOAc, washed with water, dried with Na_2SO_4 and evaporated. The resulting residue was purified by flash chromatography, followed by crystallization from $CHCl_3$–hexanes to give the bromodeoxy derivative **7** (225 mg, 0.65 mmol, 65%) as long white needles: $[\alpha]_D$ 123.07 (*c* 1.51, $CHCl_3$); mp 100–101 °C [lit.[8] mp 92 °C]; IR (NaCl) ν_{max} 2943, 1747, 1727, 1273, 1130, 1111, 1044, 931, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10–8.05 (m, 2H, aromatics); 7.65–7.57 (m, 1H, aromatics); 7.50–7.42 (m, 2H, aromatics); 5.44 (d, 1H, *J* 10.1 Hz, H-4); 5.22 (d, 1H, *J* 3.97 Hz, H-1); 4.42–4.34 (m, 1H, H-5); 3.75–3.58 (m, 2H, H-6); 3.45 (s, 3H, C–OC*H*$_3$); 2.92 (ddd, 1H, *J* 14.2 Hz, *J* 4.0 Hz, *J* 0.84 Hz, H-2a); 2.72 (dd, 1H, *J* 14.3 Hz, *J* 1.09 Hz, H-2b); ^{13}C NMR ($CDCl_3$): δ 32.5 (C-6); 46.0 (C-2); 55.3 (C-14); 70.4 (C-5); 75.7 (C-4); 99.5 (C-1); 128.4 (2C, C-*meta*); 128.7 (C-*ipso*); 129.9 (2C, C-*ortho*); 133.5 (C-*para*); 164.7 (C-7); 196.8 (C-3). Anal. Calcd for $C_{14}H_{15}BrO_5$: C, 49.00; H, 4.41; Br, 23.28. Found: C, 49.09; H, 4.46; Br, 23.28.

1.5. Methyl 4-*O*-benzoyl-2,6-dideoxy-6-iodo-α-D-*erythro*-hexopyranosid-3-ulose (8)

A mixture of the bromodeoxy derivative **7** (97 mg, 0.283 mmol) and KI (280 mg) in *N*,*N*-dimethylformamide (1 mL) was stirred for 15 h at 50 °C. The mixture was poured onto ice and then dissolved in EtOAc. The solution was washed successively with 5% aq $NaHSO_3$ and water, and the dried (Na_2SO_4) organic layer was evaporated. The resulting crude product was purified by flash chromatography to furnish the deoxyiodo derivative **8** (100 mg, 0.257 mmol, 91%); mp 127–128 °C; $[\alpha]_D$ 99.70 (*c* 0.515, $CHCl_3$); IR (NaCl) ν_{max} 2940, 1751, 1727, 1272, 1234, 1126, 1109, 1045, 921, 703 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10–8.05 (m, 2H, aromatics); 7.65–7.57 (m, 1H, aromatics); 7.50–7.42 (m, 2H, aromatics); 5.30 (d, 1H, *J* 9.92 Hz, H-4); 5.21 (d, 1H, *J* 3.93 Hz, H-1); 4.13–4.03 (m, 1H, H-5); 3.57(dd, 1H, *J* 11.0 Hz, *J* 2.43 Hz, H-6a); 3.47 (s, 3H, C–OC*H*$_3$); 3.40 (dd, 1H, *J* 11.0 Hz, *J* 7.11 Hz, H-6b); 2.93 (ddd, 1H, *J* 14.2 Hz, *J* 4.1 Hz, *J* 0.75 Hz, H-2a); 2.71 (dd, 1H, *J* 14.2 Hz, *J* 1.12 Hz, H-2b); ^{13}C NMR ($CDCl_3$): δ 5.7 (C-6); 45.8 (C-2); 55.4 (C-14); 70.3 (C-5); 77.6 (C-4); 99.4 (C-1); 128.4 (2C, C-*meta*); 128.6 (C-*ipso*); 129.9 (2C, C-*ortho*); 133.5 (C-*para*); 164.7 (C-7); 196.9 (C-3); HRCIMS: Calcd for $C_{14}H_{15}IO_5$: ($M+H^+$) 391.0042. Found: ($M+H^+$) 391.0052.

1.6. Preparation of methyl 4-*O*-benzoyl-2,6-dideoxy-4,5-*C*-methylene-α-D-*erythro*-hexopyranosid-3-ulose (9)

1.6.1. From methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*erythro*-hexopyranosid-3-ulose (7). The bromodeoxy derivative **7** (55 mg, 0.16 mmol) was dissolved in dry pyridine (2 mL), and AgF (63 mg, 0.49 mmol) was added. The mixture was stirred for 1 h at room temperature, protected from light. After complete reaction, the mixture was filtered through a filter funnel with a porosity E sintered glass fritted disc with Celite and suction.

Toluene was added to the filtrate, and the mixture was concentrated under reduced pressure (to remove all of the pyridine). The resulting syrup was purified by flash chromatography to furnish the cyclopropano derivative **9** (24 mg, 0,0915 mmol, 56%).

1.6.2. From methyl 4-*O*-benzoyl-2,6-dideoxy-6-iodo-α-D-*erythro*-hexopyranosid-3-ulose (8). The deoxyiodo derivative **8** (19 mg, 0.05 mmol) was dissolved in dry pyridine (0.66 mL), and AgF (19 mg, 0.15 mmol) was added. The mixture was stirred for 1 h at room temperature, protected from light. After complete reaction, the mixture was filtered through a filter funnel with a porosity E sintered glass fritted disc with Celite and suction. Toluene was added to the filtrate, and the mixture was concentrated under reduced pressure (to remove all of the pyridine). The resulting syrup was purified by flash chromatography to furnish the cyclopropano derivative **9** (8.8 mg, 0,0335 mmol, 68%); $[\alpha]_D$ 194.46 (*c* 1.2, $CHCl_3$); IR (NaCl) ν_{max} 2932, 1740, 1717, 1272, 1245, 1151, 1110, 1068, 711 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.07–8.03 (m, 2H, aromatics); 7.61–7.39 (m, 3H, aromatics); 5.03 (t, 1H, *J* 2.43 Hz, H-1); 4.16–4.11 (m, 1H, H-5); 3.50 (s, 3H, C–OCH_3); 2.67–2.63 (m, 2H, H-2); 2.01 (dd, 1H, *J* 8.43 Hz, *J* 4.68 Hz, H-6a); 1.81 (t, 1H, *J* 8.43 Hz, H-6b); ^{13}C NMR ($CDCl_3$): δ 27.0 (C-6); 43.4 (C-2); 55.2 (OCH_3); 59.3 (C-5); 62.1 (C-4); 102.4 (C-1); 128.2 (2C, C-*meta*); 129.0 (C-*ipso*); 129.9 (2C, C-*ortho*); 133.3 (C-*para*); 164.7 (C-7); 195.3 (C-3); HRCIMS: Calcd for $C_{14}H_{14}O_5$: ($M+H^+$) 263.0919. Found: ($M+H^+$) 263.0922.

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