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Selective iodination of vicinal *cis*-diols on ketopyranose templates

Ana Catarina Simao [a,b], Arnaud Tatibouët [a,*], Amelia P. Rauter [b], Patrick Rollin [a]

[a] ICOA—UMR 6005, Université d'Orléans, CNRS, BP6759, F-45067 Orléans Cedex 2, France
[b] Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

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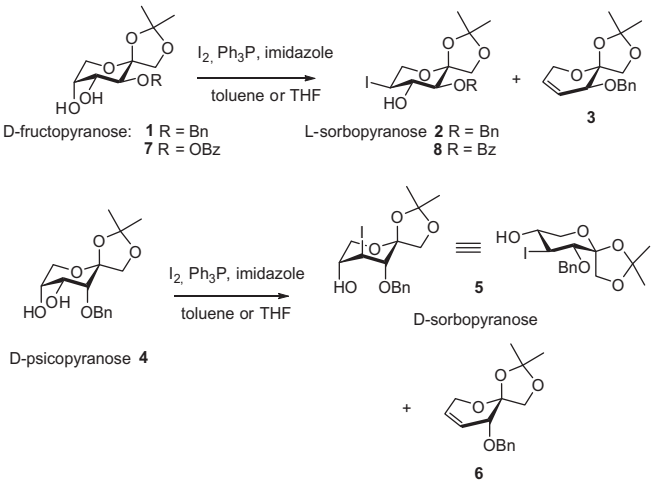
ABSTRACT

A regio- and stereoselective iodination has been performed on vicinal diols located on ketopyranose templates using the controlled- Garegg conditions. 3-*O*-Benzyl-1,2-*O*-isopropylidene-β-D-fructo- or psicopyranoses (**1** or **4**) were selectively iodinated, respectively, at C-5 or C-4 of the ketoses to afford the L-sorbo or D-sorbo iodohydrins.

Direct conversion of an alcohol function into an iodo derivative is a valuable transformation in organic chemistry: more specifically in glycochemistry, this has received considerable attention over the years.[1] A number of reagents—many of them being phosphorus-based—have been explored for the replacement of an hydroxyl by an iodine atom.[2] The most popular iodination systems are indisputably those developed by Garegg and Samuelsson.[3] However, deoxy-iodo sugars can also be obtained through standard nucleophilic displacement of sulfonates,[4] but also with more original approaches.[5] Selective substitution of primary over secondary hydroxyls can be achieved on unprotected carbohydrate but reacting a specific secondary alcohol usually requires masking of the other hydroxyls.[6] On the other hand, Garegg's reagent system has also been used for the one-step conversion of vicinal diols into olefins.[7] Herein, we report a preliminary study, of a program devoted to iminosugars[6] and thionocarbamates on carbohydrate scaffolds,[8] of the Garegg's conditions applied to the selective conversion of ketopyranose-derived *cis*-diols into iodohydrins.

When applying to 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose **1** the standard elimination procedure previously described by Lichtenthaler et al.,[7b] the olefin **3** was exclusively formed in 63% yield (3 equiv Ph_3P, 3 equiv imidazole and 2 equiv of iodine). Through By slightly changing the conditions (3 equiv Ph_3P, 3 equiv imidazole and 1.4 equiv of iodine), we observed after 1 h reaction that olefin **3** was formed in 53% yield together with a monosubstituted derivative **2** in which an iodine atom had been stereoselectively introduced at C-5, thus giving a 40% yield of a L-sorbo- configurated 5-deoxy-5-iodopyranose. This result reveals a high efficiency of the reaction with over 93% conversion yield but moreover the possibility to selectively iodinate a diol. With that in mind, we have carried out an optimization study on the D-fructo diol **1** and its D-psico epimer **4** (Scheme 1).

To selectively substitute only one hydroxyl group of the vicinal diol, we have reduced the number of equivalents for triphenylphosphine (1.5 equiv) and iodine (1.4 equiv). By limiting severely the amounts of both reagents compared to the original procedure (respectively, 4 equiv and 3 equiv),[3b] we thought to attain a better selectivity. In both D-fructo and D-psico series (Table 1, entries 1 and 2) we observed that even under such conditions after 1 h only, olefination was the predominant process over iodination. Lowering the temperature (entries 3 and 4) resulted in no reaction even after



Scheme 1. Selective iodination of ketopyrano diols.

* Corresponding author. Tel.: +33 238 49 48 54; fax: +33 238 41 72 81.
E-mail address: arnaud.tatibouet@univ-orleans.fr (A. Tatibouët).

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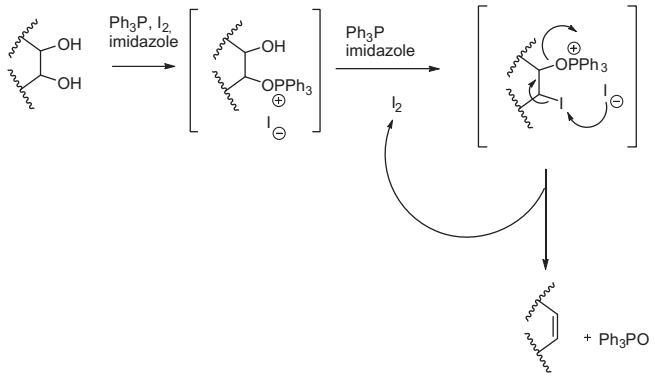
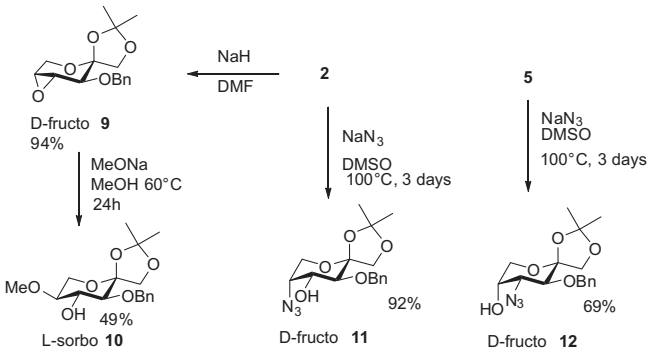
Table 1
Conditions applied to promote selective iodination, **1/7**, in D-fructo series

Entry	Starting ketose	Solvent	I_2 (equiv)	Temperature (C°)	Time (h)	**Iodo** (%)	**Olefin** (%)
1	**1**	Toluene	1.4	110	1	**2** (40)	**3** (54)
2	**4**	Toluene	1.4	110	1	**5** (8)	**6** (67)
3	**1**	Toluene	1.4	rt	24	—[a]	—
4	**4**	Toluene	1.4	rt	24	—[a]	—
5	**1**	THF	1.4	rt	15	**2** (7)	—
6	**4**	THF	1.4	rt	15	—[a]	—
7	**1**	THF	1.0	Reflux	4	**2** (94)	—
8	**4**	THF	1.0	Reflux	4	**5** (56)	—
9	**1**	1,4-Dioxane	1.0	65	72	**2** (67)	—
10	**4**	1,4-Dioxane	1.0	65	72	**5** (43)	—
11	**7**	THF	1.0	Reflux	4	**8** (70)	

[a] The starting material was not isolated but observed by TLC.



Scheme 2. The elimination mechanism using Garegg's conditions.[3a]



Scheme 3.

24 h. However, replacing toluene by THF (entries 5–8) enhanced both solubility and reactivity. Substitutive iodination was optimized in D-fructo and D-psico series, no reactivity was observed at room temperature (entries 5 and 6) while in refluxing THF during 4 h, good to excellent yields were obtained (entries 7 and 8).

The above- established protocol using an excess of iodine (1.4 equiv) led us to reconsider the mechanism postulated by Garegg (Scheme 2).[3a] The elimination process takes place during the terminal phase together with the regeneration of iodine. In this last step, we postulated that iodine could be seen acting as a catalyst. Thus by lowering the amount of I_2 to strictly 1 equiv, a selective mono-substitution should occur avoiding the elimination process.

Reacting 1.0 equiv I_2 duringfor 4 h in refluxing THF resulted in selective iodination at C-5 with an excellent 94% yield (**2**, entry 7).[9] The same conditions were applied to the D-psico derivative **4** (entry 8), effecting selective iodination with a moderate 54% yield of D-sorbo derivative **5**.[10] Trying to improve the conversion yields by replacing THF by 1,4-dioxane at the same temperature afforded iodo compounds **2** and **5**, albeit with inferior yields (entries 9 and 10). In D-fructo series, iodination of **1** took place regio- and stereoselectively at position 5. In contrast in D-psico series, iodination of **4** regio- and stereoselectively occurred at position 4. In both cases the iodine atom was introduced with inversion of configuration, according to NMR spectrometric assignments.[9,10]

A postulated explanation for the selectivities observed could be the driving force of the most thermodynamically stable isomer to be formed. On the D-fructopyrano frame, iodo-inversion at C-5 results in a L-sorbopyrano frame, for which the $^2C_5$ conformer exhibits all the substituents in equatorial position. On the D-psicopyrano frame, inversion at C-4 results in a D-sorbopyrano frame, for which the $^5C_2$ conformer also points all the substituents in equatorial position.

A comparative experiment was performed on substrate **7**, a 3-*O*-benzoyl analogue of **1**: a regio- and stereoselective iodo-inversion at C-5 was also observed, affording the L-sorbo derivative **8** in 70% yields.

Such efficient functionalizations of ketopyranose templates paved the way to preliminary reactivity testing of ketose-derived iodohydrins confronted with nucleophiles (Scheme 3). Under basic conditions, the L-sorbo iodohydrin **2** readily underwent intramolecular cyclization to deliver the D-fructo 4,5-epoxide **9** in 94% yield. This epoxide could in turn be opened with sodium methoxide to give selectively the L-sorbo derivative **10** in 49% yield. A comparable efficiency was observed through converting **2** by nucleophilic substitution into the 5-azido-D-fructo derivative **11** in 92% yield.[11] The same experiment applied to the D-sorbo iodohydrin **5** effected azido-inversion to produce the 4-azido-D-fructo derivative **12** in 69% yield.

In short, we have disclosed a regio- and stereoselective conversion of fructo- and psicopyrano-based vicinal diols into iodohydrins, using modified Garegg conditions. This reaction has proven useful for introducing through the nucleophilic displacement of new functionalities onto ketopyranose templates. Despite its selectivity, this selective iodination approach greatly depends on the carbohydrate series; further explorations are ongoing to decipher the general rules and mechanism underlying the reaction.

Acknowledgments

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9. *Procedure for the synthesis of iodohydrin* **2**: A solution of diol **1** (1 g, 3.22 mmol) in THF (8 mL) containing imidazole (0.657 g, 9.65 mmol) and triphenylphosphine (1.18 g, 4.5 mmol) was cooled to 0 °C and then iodine (0.82 g, 3.22 mmol) was added. The mixture was stirred under reflux for 4 h, then evaporated and co-evaporated with toluene. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 19/1 then 9/1) to afford the L-sorbo iodohydrin **2** (1.27 g, 94% yield) as a white solid; R_f = 0.26 PE/EA (9:1); mp = 123–125 °C; $[\alpha]_D^{20}$ + 51 (*c* 0.14, $CHCl_3$); IR (neat): ν (cm^{-1}): 3429 (OH); 2921, 2851 (CH); 1455, 1373 (Ph). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.42 and 1.49 (2s, 6H, CH_3), 2.60 (br s, 1H, OH), 3.44 (d, 1H, $J_{3\text{-}4}$ = 8.8 Hz, H-3), 3.84 (dd, 1H, $J_{6b\text{-}6a}$ = 14.7 Hz, $J_{6b\text{-}5}$ = 4.4 Hz, H-6b), 3.85 (d, 1H, $J_{1b\text{-}1a}$ = 8.5 Hz, H-1b), 3.96 (dd, 1H, $J_{6a\text{-}5}$ = 4.4 Hz, H-6a), 3.98 (d, 1H, H-1a), 4.03 (t, 1H, H-4), 4.07 (s, 1H, H-5), 4.72 and 4.91 (2d, AB system, 2H, J_{gem} = 11.6 Hz, PhCH_2O), 7.28–7.37 (m, 5H, Ph). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 26.2, 27.2 (Me_2C), 30.5 (C-5), 65.5 (C-6), 71.9 (C-1), 75.6 (PhCH_2O), 79.6 (C-3), 105.8 (C-2), 112.6 (Me_2C), 128.1, 128.2, 128.7 (CH-Ar), 137.8 (C_{IV}-Ar). HRMS: $C_{16}H_{21}IO_5$ calcd for $[M+Na]^+$ 443.0331; found: 443.0332.
10. *Procedure for the synthesis of iodohydrin* **5**: Applying to diol **4** (1 g, 3.22 mmol) the protocol described in Ref. 8 led to the D-sorbo iodohydrin **5** (0.76 g, 56% yield) as a beige solid; R_f = 0.22 PE/EA (4:1); mp = 98–101 °C; $[\alpha]_D^{20}$ + 21 (*c* 0.54, $CHCl_3$); IR (neat): ν (cm^{-1}): 3449 (OH); 2987, 2921 (CH); 1497, 1453, 1407 (Ph). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.42 and 1.53 (2s, 6H, CH_3), 2.86 (d, 1H, $J_{5\text{-}OH}$ = 7.0 Hz, OH); 3.45 (dd, 1H, $J_{6b\text{-}6a}$ = 12.3 Hz, $J_{6b\text{-}5}$ = 7.0 Hz, H-6b), 3.76 (d, 1H, $J_{3\text{-}4}$ = 7.8 Hz, H-3), 3.91–4.00 (m, 1H, H-5), 4.04 (d, 1H, $J_{1b\text{-}1a}$ = 9.1 Hz, H-1b), 4.09–4.13 (m, 1H, H-4), 4.14 (d, 1H, H-1a), 4.24 (dd, 1H, $J_{6a\text{-}5}$ = 3.8 Hz, H-6a), 4.77 and 4.82 (2d, AB system, 2H, J_{gem} = 10.8 Hz, PhCH_2O), 7.28–7.37 (m, 5H, Ph). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 26.2, 27.1 (Me_2C), 36.7 (C-4), 64.6 (C-6), 69.2 (C-1), 74.7 (PhCH_2O), 79.7 (C-3), 105.6 (C-2), 112.4 (Me_2C), 128.3, 128.4, 128.5 (CH-Ar), 137.0 (C_{IV}-Ar). HRMS: $C_{16}H_{21}IO_5$ calcd for $[M+Na]^+$ 443.0331; found: 443.0334.
11. *Representative azido formation:* To a solution of the L-sorbo iodohydrin **2** (1 g, 2.38 mmol) in DMSO (8 mL) sodium azide (0.46 g, 3 equiv) was added and the reaction mixture was heated at 100 °C for 3 days. After cooling, the mixture was treated with water and then extracted with EtOAc (3×). The combined organic phase was washed with water (4×), then brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified on a silica gel column (petroleum ether/ethyl acetate 9/1) to afford azide **11** as colorless solid (0.73 g, 91% yield); R_f = 0.24 PE/EA (9:1); mp = 107–109 °C; $[\alpha]_D^{20}$ − 117 (*c* 0.25, $CHCl_3$); IR (neat): ν (cm^{-1}): 3541 (OH); 2993, 2909 (CH); 2119 (N_3); 1457, 1371 (Ph). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 and 1.48 (2s, 6H, CH_3), 2.31 (d, 1H, $J_{OH\text{-}4}$ = 5.2 Hz, OH), 3.67 (d, 1H, $J_{3\text{-}4}$ = 9.6 Hz, H-3), 3.74 (dd, 1H $J_{6b\text{-}6a}$ = 12.4 Hz, $J_{6b\text{-}5}$ = 1.6 Hz, H-6b), 3.93–3.95 (m, 1H, H-5), 3.96 (d, 1H, $J_{1b\text{-}1a}$ = 8.6 Hz, H-1b), 3.99 (dd, 1H, $J_{6a\text{-}5}$ = 1.6 Hz, H-6a), 4.03 (d, 1H, H-1a), 4.19 (ddd, 1H, $J_{4\text{-}3}$ = 4.4 Hz, $J_{4\text{-}OH}$ = 5.2 Hz, $J_{4\text{-}5}$ = 9.6 Hz, H-4),4.75 and 4.84 (2d, AB system, 2H, J_{gem} = 11.6 Hz, PhCH_2O), 7.32–7.38 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 27.0 (Me_2C), 61.9 (C-6), 62.4 (C-5), 71.7 (C-4), 72.0 (C-1), 73.0 (C-3), 75.8 (PhCH_2O), 105.7 (C-2), 112.3 (Me_2C), 128.1, 128.3, 128.8 (CH-Ar), 137.8 (C_{IV}-Ar). HRMS: $C_{16}H_{21}N_3O_5$ calcd for $[M+Na]^+$ 358.1379; found: 358.1377.