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First example of carbohydrate-based Prins cyclization: a novel class of sugar-annulated tetrahydropyrans

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ABSTRACT

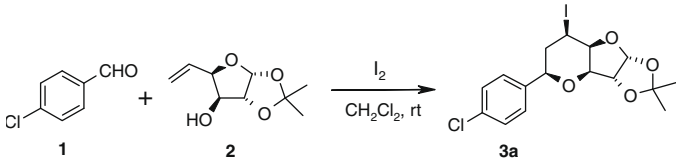
The secondary homoallylic alcohol derived from D-glucose undergoes smooth coupling with aldehydes in the presence of molecular iodine under mild reaction conditions to produce 7-iodofurano[3,2-*b*]pyrans in good yields. This method is highly stereoselective, affording *cis*-tetrahydropyrans exclusively.

The Prins cyclization is very useful method for the synthesis of six-membered tetrahydropyran derivatives.[1] The tetrahydropyran ring is frequently found in various natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins, and acutiphycins.[2] Tetrahydropyran derivatives are usually prepared via Prins cyclization using acid catalysis.[3] The Prins cyclization between homoallylic alcohols and aldehydes has been reported using a variety of catalysts and nucleophiles to produce a large number of tetrahydropyrans.[4] Besides homoallylic alcohols, homopropargylic alcohols are also known to undergo the Prins-type cyclization to furnish dihydropyrans.[5] In addition, silyl-modified Prins cyclization has also been reported to furnish tri-, tetra-, and penta-substituted dihydropyrans.[6] However, to the best of our knowledge, there have been no reports on the Prins cyclization of sugar-based homoallyl alcohols.

In continuation of our interest on the application of Prins cyclization for new chemical entities,[7] we herein report a simple and metal catalyst-free Prins cyclization for the synthesis of highly substituted tetrahydropyrans from sugar-based homoallylic alcohols and aldehydes using molecular iodine under neutral conditions. Initially, we have attempted the coupling of *p*-chlorobenzaldehyde (**1**) with chiral secondary homoallylic alcohol (**2**), derived from D-glucose in the presence of molecular iodine at room temperature. The reaction was complete in 7 h and the corresponding product **3a** was obtained in 76% yield with all *cis*-selectivity (Scheme 1).

The product **3a** was characterized thoroughly with the help of various NMR experiments including 2-D nuclear Overhauser effect spectroscopy (NOESY, Fig. 1) and double quantum filter correlation spectroscopy (DQFCOSY). The coupling constants: $^3J_{H3-H4}$ = 1.7, $^3J_{H4-H5}$ = 3.4, $^3J_{H5-H6}$ = 12.3, $^3J_{H5-H6'}$ = 4.5, $^3J_{H6-H7}$ = 11.7, and $^3J_{H6-H7}$ = 1.7 Hz are consistent with $^3C_6$ chair form of the six-membered ring. Further, nOe cross peaks between H3/H5, H3/H7, and H5/H7 support their 1–3 axial disposition and are consistent with the equatorial position of the iodo and phenyl moieties. NOe cross peaks between CH_3(*pro-s*) and H1 and H2 also support enveloped conformation for the isopropylidene ring. Further support for the assigned conformation comes from energy-minimized structure (Fig. 2).

This result provided the incentive for further study of reactions with other aldehydes. Interestingly, various aryl aldehydes such as benzaldehyde, *m*-chlorobenzaldehyde, *o*-hydroxybenzaldehyde,



Scheme 1. Prins cyclization of *p*-chlorobenzaldehyde with chiral homoallyl alcohol.

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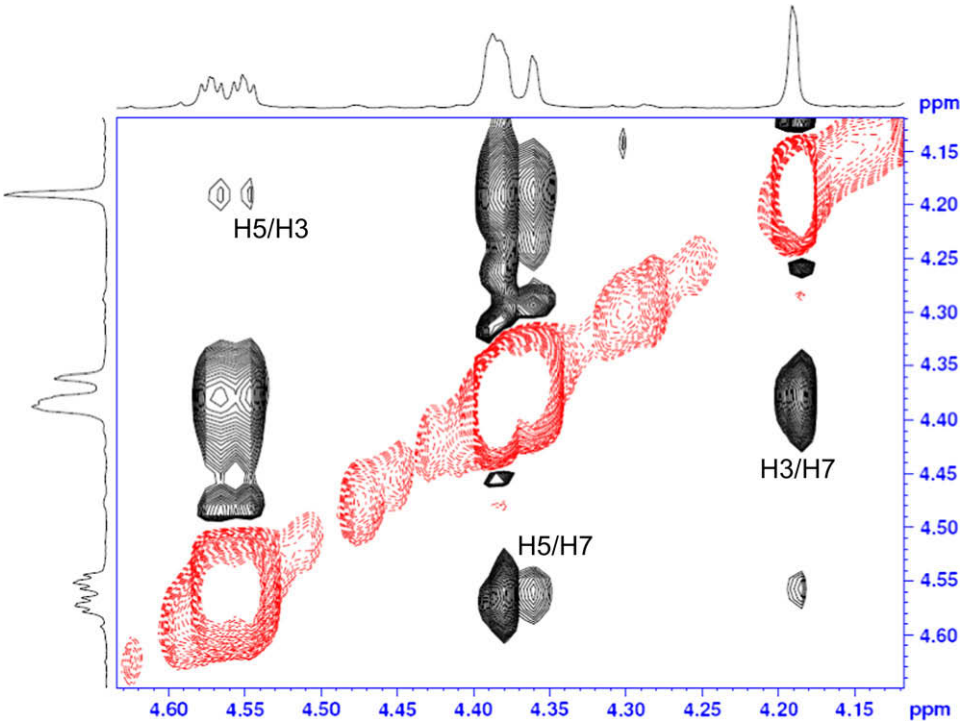


Figure 1. Expansion of the NOESY spectrum showing the characteristic nOe correlations.

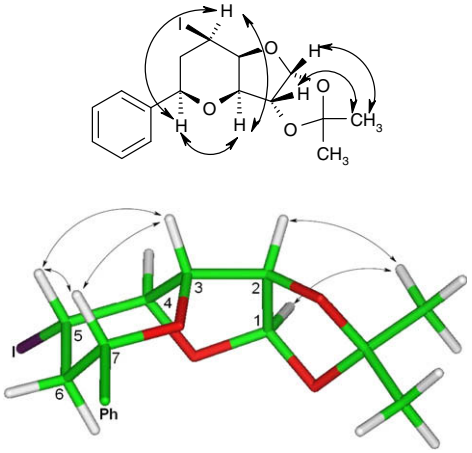


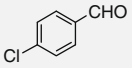
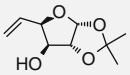
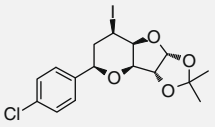
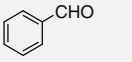
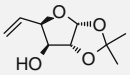
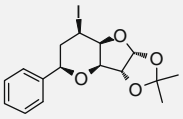
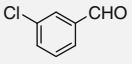
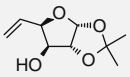
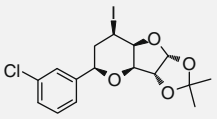
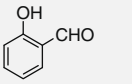
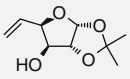
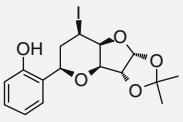
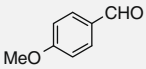
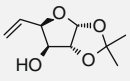
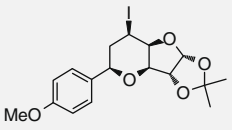
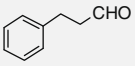
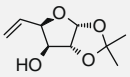
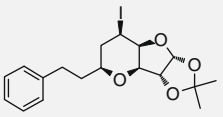
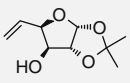
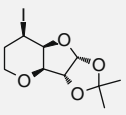
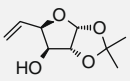
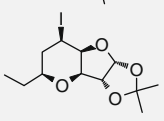
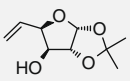
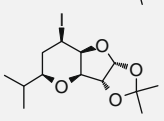
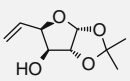
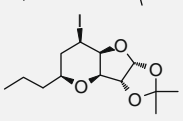
Figure 2. Energy-minimized structure of **3a**.

and *p*-methoxybenzaldehyde participated well in this reaction (Table 1, entries b–e). Acid-sensitive hydrocinnamaldehyde is also effective for the Prins cyclization (Table 1, entry f). 1,3,5-trioxane also underwent smooth coupling with homoallyl alcohol to give the corresponding product (Table 1, entry g). The Prins cyclization also proceeded smoothly with aliphatic aldehydes such as propanaldehyde, isobutaraldehyde, and butaraldehyde (Table 1, entries h–j). The scope and generality of this reaction are illustrated with respect to various aldehydes, and the results are summarized in Table 1.[7] In all the cases, the desired six-membered tetrahydropyrans were exclusively formed in good yields. The reaction works well with a wide range of aldehydes. In the absence of iodine, the reaction failed to give the desired products even after long reaction time (12 h) under reflux conditions. No reaction was observed when metal salts such as LiI, NaI, and KI were used as promoters. The reactions proceeded only with iodine at room temperature with complete diastereocontrol, affording the *cis*-tetrahydropyrans exclusively. As a solvent, dichloromethane appeared to give the best results. The reactions were clean and the products were obtained in good yields and with high diastereoselectivity as determined from the NMR spectrum of the crude product. Only a single diastereoisomer was obtained from each reaction, the structure of which was confirmed by NMR studies. Mechanistically, the reaction may proceed via an acetal formation by in situ generated HI from iodine and alcohol as described in our earlier Letter.[4b] Thus initially formed acetal may undergo dehydration to generate the oxocarbenium ion. This highly reactive intermediate may undergo Prins cyclization to give β-carbocation which may subsequently be trapped by iodide ion to give the desired product (Scheme 2).

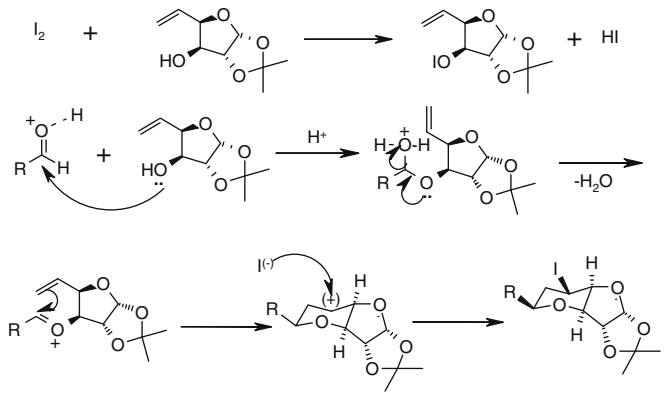
A rationale for the all *cis*-selectivity involves the formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased the stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favors equatorial attack of the activated π-bond nucleophiles.[8]

In summary, we have demonstrated an efficient approach for the synthesis of sugar-based furano[3,2-*b*]pyrans under mild and neutral conditions. The use of iodine makes this method simple, convenient, and practical. This method provides an easy access for a novel class of sugar-annulated pyrans in a single-step operation which may find application in drug discovery and also in natural products synthesis.

Table 1
Synthesis of polyhydroxylated tetrahydropyrans from sugar-based homoallyl alcohol

Entry	Aldehyde	Alcohol	Product[a]	Reaction time (h)	Yield[b] (%)
a				7.0	76
b				8.0	74
c				6.0	72
d				7.0	76
e				8.0	74
f				6.0	76
g				8.0	68
h				8.0	72
i				7.0	75
j				6.0	76

[a] All products were characterized by ^{1}H,^{13}C NMR, IR, and mass spectroscopy.
[b] Yield calculated after column chromatography.



Scheme 2. A plausible reaction mechanism.

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7. *Typical procedure*: A mixture of homoallylic alcohol (0.312 g, 2 mmol), aldehyde (0.2 g, 1.2 mmol), and iodine (0.127 g, 1 mmol) in dichloromethane (5 mL) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction was quenched with water and extracted with ether (2 × 10 mL). The combined organic layers were washed with aq sodium thiosulfate and brine, and dried over anhyd Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5–9.5) gave the pure tetrahydropyran. The products thus obtained were characterized by IR, NMR, and mass spectroscopy. (**3b**) IR (neat): ν 3449, 3033, 2959, 2925, 2855, 1732, 1603, 1495, 1455, 1377, 1262, 1216, 1142, 1090, 1019, 860, 798, 699 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H, Ph), 6.08 (d, 1H, J = 3.7 Hz, C_1H), 4.72 (d, 1H, J = 3.7 Hz, C_2H), 4.56 (ddd, 1H, J = 3.4, 4.5, 12.3, C_5H), 4.38 (dd, 1H, J = 1.7, 11.7 Hz, C_4H), 4.37 (dd, 1H, J = 1.7, 11.7 Hz, C_7H), 4.19 (d, 1H, J = 1.7 Hz, C_3H), 2.56 (q, 1H, J = 12.4 Hz, C_6H), 2.29 (ddd, 1H, J = 1.7, 4.3, 12.2, C'_6H), 1.54 (s, 3H, CH_3), 1.33 (s, 3H, CH'_3). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.1, 26.1, 26.6, 40.5, 79.3, 79.7, 84.8, 100.0, 104.7, 125.8, 128.4, 128.5, 128.5, 130.1, 133.7, 172.0. ESI-MS: *m/z*: 402 (M+H). (**3c**): White solid, IR (neat): ν 3499, 2923, 2853, 1730, 1673, 1601, 1431, 1379, 1266, 1215, 1094, 1020, 966, 871, 791, 725 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32–7.24 (m, 4H Ph), 6.20 (d, 1H, J = 3.9 Hz), 4.77 (d, 1H, J = 2.9 Hz), 4.50 (ddd, 1H, J = 3.9, 7.8, 12.6 Hz), 4.30–4.38(q, 2H, J = 13.6, Hz), 4.11 (s, 1H), 2.41–2.48 (q, 1H, J = 12.6 Hz), 2.29 (dd, 1H, J = 3.9, 8.7 Hz), 1.54 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.3, 29.6, 40.1, 79.2, 78.7, 85.5, 105.0, 105.1, 114.2, 123.7, 124.4, 125.8, 126.3, 128.2, 129.7, 129.6. ESI-MS: *m/z*: 475 (M+K). (**3d**): White solid, IR (neat): ν 3437, 2922, 2853, 1600, 1503, 1457, 1376, 1245, 1161, 1085, 1016, 859 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 6H), 2.31 (ddd, 1H, J = 5.0, 6.9, 2.2 Hz), 2.71 (q, 1H, J = 12.8 Hz), 4.16 (s, 1H), 4.32, (s, 1H), 4.44–4.57 (m, 2H), 4.67 (d, 1H, J = 3.5 Hz), 6.01 (d, 1H, J = 3.5 Hz), 6.58 (s, 1H, Ph), 6.80 (t, 1H, J = 5.6 Hz), 6.94 (d, 1H, J = 6.2 Hz), 7.11–7.17 (m, 1H), 9.80 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.1, 17.3, 26.1, 26.5, 29.7, 38.4, 53.4, 79.5, 79.8, 84.6, 96.1, 104.5, 112.2, 117.0, 120.3, 126.7, 129.6. ESI-MS: *m/z*: 441 (M+ Na). (**3i**): White solid, IR (neat): ν 2964, 2926, 1734, 1468, 1367, 1274, 1099, 1022, 870, 797, 682 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.82–0.92 (m, 12H methyl), 2.02 (q, 1H, J = 4.9, 6.2 Hz), 2.16 (dd, 1H, J = 3.9,5.2 Hz), 2.96 (q, 1H, J = 4.9, 5.8 Hz), 3.38 (q, 1H, J = 4.9 Hz), 3.95 (d, 1H, J = 16.2 Hz), 4.28 (m, 1H), 4.42 (d, 1H, J = 3.7 Hz), 4.62 (d, 1H, J = 4.9 Hz), 5.85 (d, 1H, J = 3.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.0, 20.4, 22.6, 29.6, 31.8, 32.4, 35.6, 79.2, 79.4, 82.8, 85.3, 104.2, 108.7. ESI-MS: *m/z*: 407 (M+K).
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