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Chiral 2-*C*-methylene glycosides and carbohydrate-derived pyrano[2,3-*b*][1]benzopyrans: synthesis via $InCl_3$ catalyzed stereoselective Ferrier rearrangement of 2-*C*-acetoxymethyl glycal derivatives

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Abstract—2-*C*-Acetoxymethyl glycal derivatives react with aliphatic alcohols in the presence of $InCl_3$ (30 mol %) to furnish the corresponding 2-*C*-methylene glycosides in excellent yields and with exclusive α-selectivity except for the methyl 2-*C*-methylene glycosides, which are formed in ~2:1 anomeric ratio in favour of the α-anomer. The reaction of 2-*C*-acetoxyglycals with phenols, however, produces the corresponding chiral carbohydrate-derived pyranobenzopyran derivatives via initial Ferrier rearrangement followed by tandem cyclization in excellent yields and moderate to high stereoselectivities in favour of the corresponding 10a-*R*-pyrano[2,3-*b*][1]benzopyran derivatives.

Due to the presence of branched chain sugars as structural units in Nature and also because of the importance of 2-*C*-branched chain sugars,[1] their synthesis has drawn much attention.[2] Moreover, the 2-*C*-methylene group is a key structural feature of molecules involved in the inactivation of the enzyme ribonucleotide diphosphate reductase,[3] and 2-*C*-methylene glycosides are precursors for the synthesis of *C*-disaccharides.[4] The fused acetal moiety is an important subunit of a number of biologically active natural products[5] such as aflatoxin, clerodane, asteltoxin, etc. Fused tetrahydropyrano[2,3-*b*]benzopyrans, which are annulated pyranosides are formed in naturally occurring bioactive molecules.[6] Only a few reports towards the synthesis of pyrano[2,3-*b*]benzopyrans have been given.[7] The syntheses of chiral 2-*C*-methylene-*O*-glycosides[8] and chiral pyrano[2,3-*b*][1]benzopyrans[9,10] were first published by Balasubramanian et al. based on $BF_3{\cdot}OEt_2$ mediated Ferrier rearrangement of 2-*C*-acetoxymethyl glycals[8] with alcohols and phenols, respectively, with the subsequent report on the synthesis of the first group of compounds by Vankar et al.[11] being based on the use of montmorillonite K-10, Nafion-H or $LiClO_4$. The reactions with phenols and β-naphthol under Vankar's conditions, however, followed a different course from those of Balasubramanian, generating the corresponding aryl 2-*C*-methylene *O*-/*C*-glycosides. In continuation of our interest in In(III)-based organic reactions,[12] particularly on glycals,[12a,d,h] we have examined $InCl_3$ catalyzed reactions[13] of different glycal systems viz., 2-*C*-acetoxymethyl glycals with different nucleophiles such as aliphatic alcohols and phenols and the results are summarized in Scheme 1 and Table 2.

2-*C*-Acetoxymethylglycals **2a**–**d** were prepared following the reported procedure.[8,11] At the outset, the catalytic efficacies of $InCl_3$, $In(OTf)_3$ and $Yb(OTf)_3$ were examined for the Ferrier rearrangement of 2-*C*-acetoxymethyl-3,4,6-tri-*O*-benzyl-D-glucal **2a** with methanol in dichloromethane (Table 1) and the best result was obtained using 30 mol % $InCl_3$ (entry 2, Table 1 and entry 1, Table 2). The same Ferrier substrate **2a** on treatment with benzyl alcohol furnished the corresponding 2-*C*-methylene glycoside in 77% yield with exclusive α-selectivity (entry 2, Table 2). The similar Ferrier system, 2-*C*-acetoxymethyl-3,4,6-tri-*O*-methyl-D-glucal **2b** reacted with benzyl alcohol to afford exclusively the

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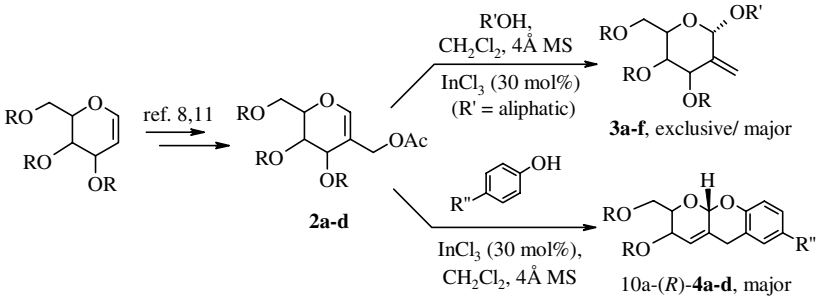


Scheme 1.

Table 1. Lewis acid catalyzed Ferrier rearrangement of **2a** with MeOH

Entry	Catalyst	Mol % of catalyst	Time (h)	% Yield[a] of **3a**
1	$InCl_3$	20	24	37
2	$InCl_3$	30	1	72
3	$In(OTf)_3$	30	24	Incomplete
4	$Yb(OTf)_3$	30	24	Incomplete

[a] Isolated chromatographed yield.

corresponding 2-*C*-methylene-α-D-glucoside in 83% yield (entry 3, Table 2). Excellent yields and exclusive α-selectivities were also obtained in the reaction of the galactal-based Ferrier system, 2-*C*-acetoxymethyl-3,4,6-tri-*O*-methyl-D-galactal **2d** with benzyl, allyl and *tert*-butyl alcohols (entries 4–6, Table 2). It is noteworthy that even with *tert*-butanol no β-product could be identified from the corresponding NMR spectrum and the yield of the chiral *tert*-butyl 2-*C*-methylene α-D-galactoside **3f** was also quite high (76%, entry 6, Table 2).

When phenols were used as nucleophiles, a different class of products viz., aromatic pyranopyrans **4a–d** resulted via initial exocyclic Ferrier rearrangement

Table 2. $InCl_3$ catalyzed synthesis of 2-*C*-methylene-*O*-glycosides and pyranobenzopyran derivatives

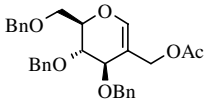
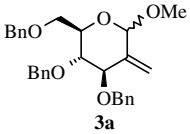
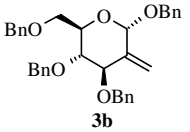
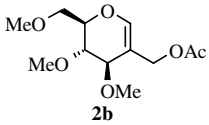
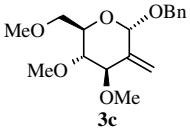
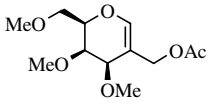
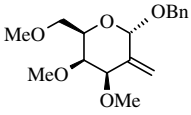
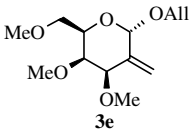
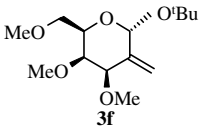
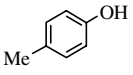
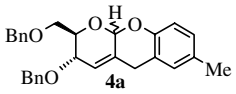
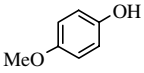
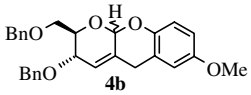
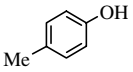
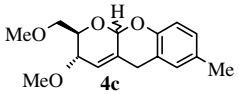
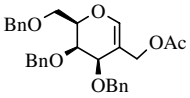
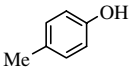
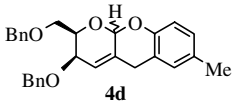
Entry	Substrate	Nucleophile	Time (h)	Product	%Yield[a]	α/β[b]	$[\alpha]_D$/mp of major isomer (lit. values)
1	 **2a**	MeOH	1	 **3a**	72	2:1	Not isolated
2	**2a**	BnOH	1	 **3b**	77	α-only	+43.25/— (+44.2 /—)[c,d]
3	 **2b**	BnOH	1	 **3c**	83	α-only	+118.2/— (+166.4/—)[e]
4	 **2d**	BnOH	3	 **3d**	87	α-only	+123.4/— (+122.6/—)[c,e]
5	**2d**		7	 **3e**	88	α-only	+76.3/— (+78.0/—)[c,e]
6	**2d**	*t*-BuOH	2.5	 **3f**	76	α-only	+66.01/— (+64/—)[c,e]

Table 2 (*continued*)

Entry	Substrate	Nucleophile	Time (h)	Product	%Yield[a]	α/β[b]	$[\alpha]_D$/mp of major isomer (lit. values)
7	**2a**		3.5	 **4a**	96	5:2	−79.8/85 °C (−81/85 °C)[f]
8	**2a**		4	 **4b**	89	5:1	−79.19/104 °C (−83/103 °C)[f]
9	**2b**		Overnight	 **4c**	84	5:2	−113.9/107 °C
10	 **2c**		3.5	 **4d**	83	>96% α	−258.9/98–99 °C (−268/99 °C)[f]

[a] Isolated chromatographed yield.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Optical rotation was measured using a Hg vapour lamp (578 nm).
[d] Ref. 8.
[e] Ref. 11.
[f] Ref. 9.

followed by a tandem $InCl_3$ catalyzed intramolecular cyclization. Thus, when 2-*C*-acetoxy-3,4,6-tri-*O*-benzyl-D-glucal **2a** was reacted under our standard reaction conditions with *p*-cresol in the presence of 30 mol % $InCl_3$, the corresponding pyrano[2,3-*b*][1]benzopyran **4a** was formed in almost quantitative yield although with moderate stereoselectivity (10a*R*:10a*S* = 5:2, entry 7, Table 2). Compounds **2a** and **2b** also reacted with *p*-methoxyphenol and *p*-cresol affording the respective benzopyranopyrans **4b** and **4c** in excellent yields with moderate to good stereoselectivities (entries 8 and 9, Table 2). The structure and stereochemistry of 10a-(*R*)-**4c** was established by ^{1}H, ^{13}C NMR and mass spectroscopy, CH-analysis and further by X-ray crystallographic analysis[14] (Figs. 1 and 2). Compounds 10a-(*R*)-**4c** and 10a-(*S*)-**4c** have negative and positive specific rotations, respectively, and these show opposite 'bisignate' CD-curves (Fig. 3). The yield and anomeric selectivity of the pyranobenzopyran from the reaction of 2-*C*-acetoxy-3,4,6-tri-*O*-benzyl-D-galactal **2c** with *p*-cresol were also excellent (entry 10, Table 2). The stereoselectivities of the pyranobenzopyrans were in general in favour of the corresponding 10a-(*R*)-compounds. No 2-*C*-methylene *O*-/*C*-arylglycosides could be isolated from any of these reaction mixtures. Our results of such reactions based on aromatic hydroxy compounds were similar to those of Balasubramanian et al.[9] and differed from those of Vankar et al.[11] who obtained the corresponding 2-*C*-methylene *C*-/*O*-arylglycosides from similar reactions of Ferrier systems based on montmorillonite K-10, Nafion-H or $LiClO_4$.

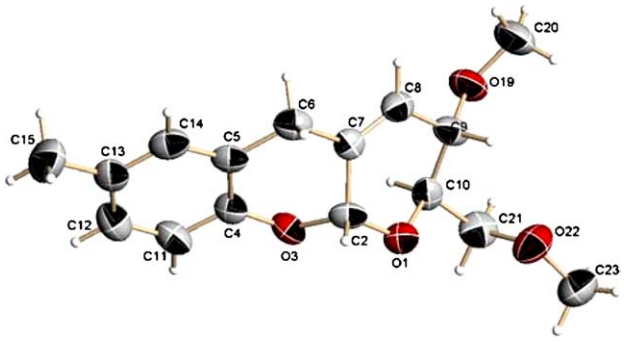


Figure 1. Crystal structure of compound 10a-(*R*)-**4c** (numberings are arbitrary, ellipsoids are drawn at 50% probability).

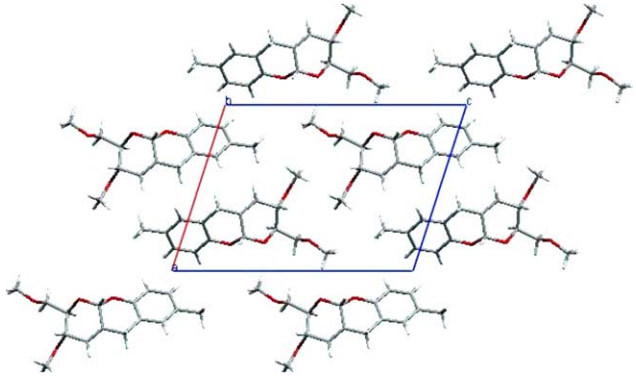


Figure 2. Crystal structure showing packing down the '*b*' axis for compound 10a-(*R*)-**4c**.

In conclusion, we have demonstrated that $InCl_3$ efficiently catalyzes the formation of 2-*C*-methylene glycosides and chiral carbohydrate-derived pyranobenzopyrans from the reactions of 2-*C*-acetoxymethyl glycal derivatives with aliphatic and aromatic hydroxy

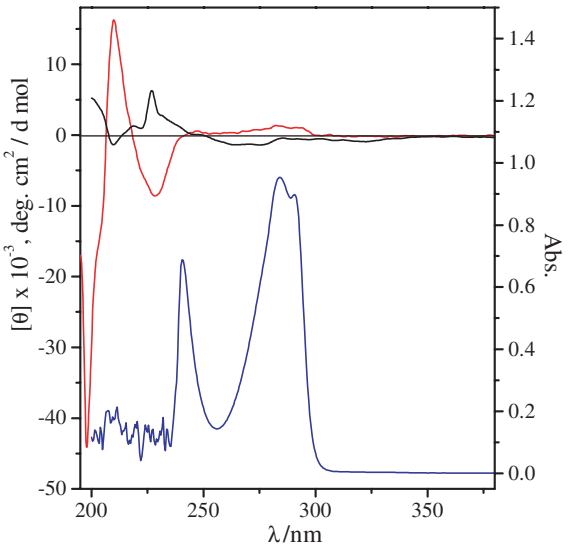


Figure 3. UV and CD spectra of compound **4c** [—— CD spectrum of 10a-(*S*)-**4c** (4.4×10^{-4} M in $CHCl_3$); —— CD spectrum of 10a-(*R*)-**4c** (4.0×10^{-4} M in MeOH); —— UV spectrum of 10a-(*R*)-**4c** (3.8×10^{-4} M in $CHCl_3$)].

compounds, respectively. $InCl_3$ has advantages of low toxicity, moisture compatibility, is easy to handle and has useful catalytic activity under simple reaction conditions giving excellent stereoselectivity particularly with the 2-*C*-methylene glycosides. This represents another example of an efficient route promoted by $InCl_3$ especially towards the synthesis of chiral pyrano[2,3-*b*]-[1]benzopyrans.

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13. General experimental procedure: To a solution of the Ferrier substrate (1 equiv) in dry dichloromethane containing molecular sieves 4 Å, dry alcohol, or substituted phenol (1.5 equiv) was added. Finally, anhydrous $InCl_3$ (30 mol %) was added to the reaction at 0 °C and the mixture was stirred at ambient temperature. After completion of the reaction (TLC, pet. ether–ethyl acetate 3:1), the mixture was filtered through a Celite bed and extracted with dichloromethane (3×10 ml). The combined filtrate and extracts were washed (for **4a**–**d**, with cold 2% NaOH solution to remove excess substituted phenol and then with water) with water (2×20 ml). The pooled organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel and eluted with ethyl acetate–pet. ether to afford the pure 2-*C*-methylene α-glycoside or the pyranobenzopyran as an epimeric mixture. Compound **4c**: The epimers were separated on silica gel using 2–3% diethyl ether–benzene.
(2*R*,3*S*,10a*R*)-2,3,5,10a-Tetrahydro-2-methoxymethyl-3-methoxy-7-methylpyrano[2,3-*b*][1]benzopyran: White needle shaped crystals; mp 107 °C (pet. ether 60–80 °C). $[\alpha]_D^{25}$ −113.9 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.24 (s, 3H), 3.33–3.39 (d, $J = 17.6$ Hz, 1H), 3.42 (s, 3H), 3.46 (s, 3H), 3.66–3.75 (m, 3H), 3.82–3.86 (m, 1H), 3.99–4.04 (dd, $J = 9.1$ and 3.3 Hz, 1H), 5.50 (s, 1H), 6.00 (s, 1H), 6.78–

6.92 (m, 3H). ^{13}C NMR (proton decoupled, $CDCl_3$, 75 MHz): δ 20.43, 32.91, 56.65, 59.43, 71.04, 71.50, 72.04, 93.55, 116.96, 120.55, 123.03, 128.17, 128.87, 130.34, 130.58, 151.32. IR (KBr): cm^{-1} 2980, 2920, 2810, 1590, 1495, 1425, 1390, 1220, 1195, 1180, 1145, 1110, 1050, 980, 950, 920, 820, 810, 760. UV/vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) 240.56 nm (3.25), 284.58 nm (3.39). Mass (m/z): 276 (M^+), 231, 199, 174 (base peak), 145, 101, 85, 71, 57. Anal. Calcd for $C_{16}H_{20}O_4$ (276.33): C, 69.55; H, 7.29. Found: C, 69.50; H, 7.44.

(2*R*,3*S*,10a*S*)-2,3,5,10a-Tetrahydro-2-methoxymethyl-3-methoxy-7-methylpyrano[2,3-*b*][1]benzopyran. Oil; $[\alpha]_D^{25}$ +130.6 (*c* 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.25, (s, 3H), 3.39 (s, 3H), 3.44 (s, 3H), 3.32–3.78 (m, 5H), 4.05–4.10 (dd, $J = 10.5$ and 5.3 Hz, 1H), 5.62 (s, 1H), 6.02 (s, 1H), 6.78–6.94 (m, 3H). IR (neat): cm^{-1} 2920, 2820, 1585, 1500, 1375, 1300, 1215, 1175, 1090, 945, 810. UV/vis ($CHCl_3$): λ_{max} ($\log\varepsilon$) 242.13 nm (3.49), 277.35 nm (3.52). HRMS(Qtof): calcd for $C_{16}H_{20}O_4$ [$(M+Na)^+$] 299.1261, found 299.1259.

14. Sheldrick, G. M. SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997. Crystal data for compound 10a-(*R*)-**4c** (CCDC 275626) can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK. Single crystals (colourless needles) were grown by slow evaporation from aqueous methanol. X-ray crystallography was performed on Bruker SMART APEX CCD diffractometer using MoK_α radiation with a fine focus tube at 50 kV and 30 mA. Empirical formula: $C_{16}H_{20}O_4$; formula weight: 276.32; temperature: 293(2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: *P*21; unit cell dimensions: $a = 11.0589(18)$ Å, $\alpha = 90°$, $b = 4.4835(8)$ Å, $\beta = 107.941(4)°$, $c = 15.342(3)$ Å, $\gamma = 90°$; volume: 723.7(2) $Å^3$; *Z*: 2; density (calculated): 1.268 mg/m^3; absorption coefficient: 0.090 mm^{-1}; *F*(000): 296; crystal size: $0.62 \times 0.06 \times 0.02$ mm^3; theta range for data collection: 1.4–22.49°; index ranges: $-11 \leqslant h \leqslant 11$, $-4 \leqslant k \leqslant 4$, $-16 \leqslant l \leqslant 12$; reflections collected: 2953; independent reflections: 1814 [R(int) = 0.0362]; completeness to theta = 22.49°, 99.9%; max and min transmission: 0.9983 and 0.9464; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 1814/1/184; goodness-of-fit on F^2: 1.157; final R indices [$I > 2\sigma(I)$]: $R1 = 0.0741$, $wR2 = 0.1115$: R indices (all data): $R1 = 0.0960$, $wR2 = 0.1190$; absolute structure parameter 1(3); largest diff. peak and hole: 0.161 and −0.162 e $Å^{-3}$.