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# $Sc(OTf)_3$-catalyzed synthesis of pyrano[3,2-*b*]-1-benzopyrans from D-glycals†

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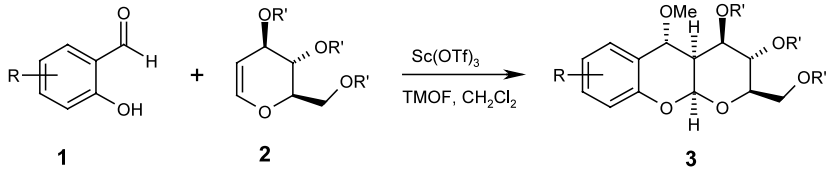
**Abstract**—Glycals react smoothly with *o*-hydroxybenzaldehydes and trimethyl orthoformate in the presence of a catalytic amount of scandium triflate under mild reaction conditions to afford the corresponding *cis*-annelated pyranobenzopyrans in good yields with high diastereoselectivity. 

The fused acetal moiety is an important structural subunit of a variety of biologically active natural products[1,2] such as aflatoxin, clerodin, asteltoxin, rhyacophiline, acmimycin and others.[3] In particular, fused tetrahydropyrano[3,2-*b*]benzopyran derivatives are frequently found in naturally occurring bioactive molecules and direct methods for their synthesis are needed.[4,5] However, there are no reports on the synthesis of *cis*-fused pyranobenzopyrans from salicylaldehydes and D-glucal. Lanthanide triflates are unique Lewis acids that are currently of great research interest. They are quite stable to water and reusable as well as being highly efficient.[6] Therefore, lanthanide triflates have significant catalytic activity compared to conventional Lewis acids in several carbon–carbon bond forming reactions and have found widespread applications in organic synthesis.[7]

In this report, we describe a new and efficient method for the synthesis of fused pyranobenzopyrans from *o*-hydroxybenzaldehydes and glycals using a catalytic amount of scandium triflate. Thus treatment of *o*-




**Scheme 1.**

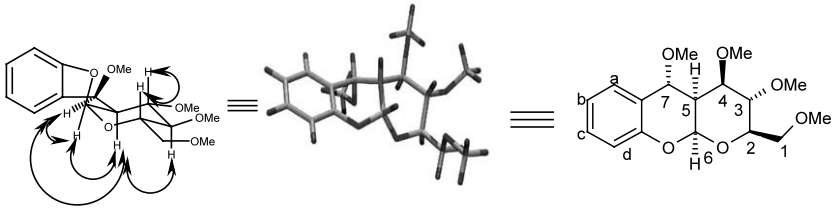



**Figure 1.** Important NOEs, energy-minimized structure[8] and chemical structure of **3a**.

*Keywords*: D-glucal; scandium triflate; *cis*-fused pyranobenzopyrans.

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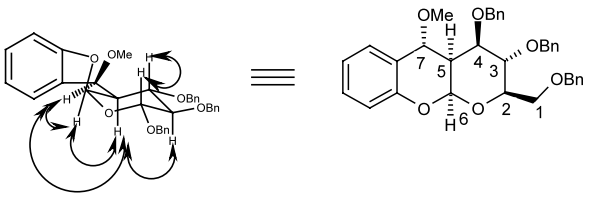
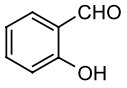
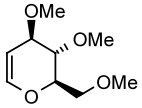
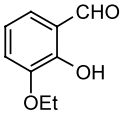
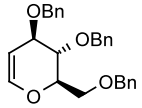
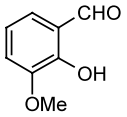
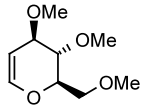
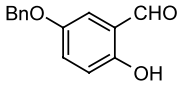
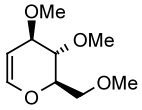
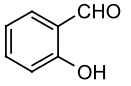
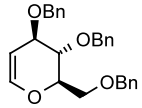
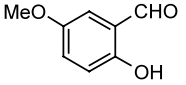
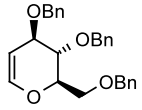
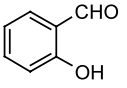
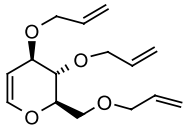
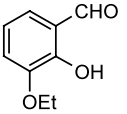
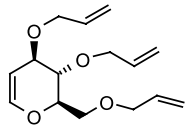
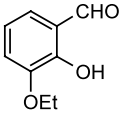
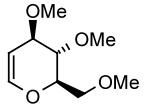


**Figure 2.** Important NOEs, and chemical structure of **3e**.

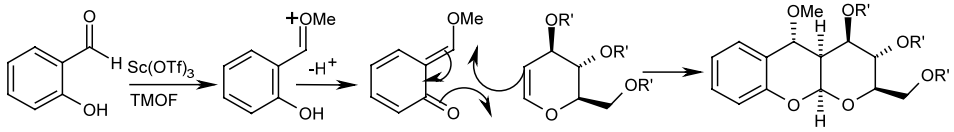
hydroxybenzaldehyde with 3,4,6-tri-*O*-methyl-D-glucal and trimethyl orthoformate (TMOF) in the presence of 3 mol% of $Sc(OTf)_3$ in dichloromethane at ambient temperature resulted in the formation of *cis*-fused pyrano[3,2-*b*]benzopyran in 80% yield (Scheme 1).

Similarly, several salicylaldehydes reacted well to give the corresponding *cis*-annelated acetals in excellent yields. In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. Only one diastereomer was obtained in each reaction, the structure of which was established with the help of various NMR experiments like double quantum filtered correlation spectroscopy, nuclear Overhauser effect spectroscopy and selective homonuclear decoupling studies.

**Table 1.** $Sc(OTf)_3$-catalyzed synthesis of *cis*-fused pyranobenzopyrans[a]

| Entry | *o*-Hydroxyaldehyde | D-Glycal | Time (h) | Yield(%)[b] |
|---|---|---|---|---|
| a |  |  | 0.5 | 80 |
| b |  |  | 1.5 | 75 |
| c |  |  | 1.0 | 78 |
| d |  |  | 1.5 | 75 |
| e |  |  | 1.0 | 77 |
| f |  |  | 1.5 | 74 |
| g |  |  | 0.5 | 83 |
| h |  |  | 1.0 | 78 |
| i |  |  | 1.5 | 80 |

[a] All products were characterised by $^1H$, $^{13}C$ NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.




**Scheme 2.**

In product **3a**, the two six-membered rings are *cis*-fused consistent with the small coupling constant value $J_{H5-H6}=3.0$ Hz, as well as the observation of a strong NOE cross peak between H5 and H6 in the NOESY spectrum. The coupling constant $J_{H5-H7}=4.7$ Hz and H6–H7 cross peaks in the NOESY spectrum shows that H5, H6 and H7 are on the same side of the six-membered ring which adopts a twist conformation ($^5T_6$, here 5 and 6 refer to the 5th and 6th carbons in the rings, respectively). The other six-membered sugar ring adopts a ($^1C_4$) chair conformation, which is supported by NOE cross peaks between $H_{2ax}$–$H_{4ax}$, $H_{3ax}$–$H_5$ and large coupling constants $J_{H2ax-H3ax}=10.2$ Hz, $J_{H3ax-H4ax}=10.5$ Hz and $J_{H4ax-H5}=8.5$ Hz. In this conformation most of the substituents are equatorially disposed resulting in an energetically favored structure, which is further supported by energy-minimized structure (Fig. 1).[8]

For product **3e**, the observed conformation is similar to that of **3a**. The two six-membered rings are *cis* fused as shown by the small coupling constant $J_{H5-H6}=3.0$ Hz and the presence of strong cross peaks between H5 and H6 in the NOESY spectrum. The small value of $J_{5-7}=$ 4.5 Hz as well as the NOE cross peak between H6 and H7 imply that the H5, H6 and H7 protons are on the same side of the ring, while the central six-membered ring adopts a twist conformation, the six-membered sugar ring has a chair conformation similar to that of **3a** (Fig. 2).

The reaction is highly selective, which affords exclusively *cis*-fused acetals under the present reaction conditions. The reaction was successful only with *o*-hydroxybenzaldehydes and glycals. Simple aryl and aliphatic aldehydes failed to react with glycals under similar reaction conditions. Several examples illustrating this novel method, for the synthesis of fused pyranobenzopyrans, are listed in Table 1.[9] This synthetic protocol utilizes readily available starting materials and a reusable catalyst, i.e. scandium triflate. The reaction may proceed through the formation of *o*-quinonemethides generated in situ from salicylaldehydes and trimethyl orthoformate as shown in Scheme 2.

The experimental procedure is very simple and the products were obtained in good yields with high diastereoselectivity. The reactions were clean and complete in very short periods. The catalyst was recovered from the aqueous layer during work-up and recycled in subsequent reactions with gradual decrease in activity. For example, *o*-hydroxybenzaldehyde with 3,4,6-tri-*O*-methyl-D-glucal and trimethyl orthoformate in the presence of 3 mol% of $Sc(OTf)_3$ afforded 80, 75 and 71% yields over three cycles. Among the various metal triflates such as $In(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$ and $Ce(OTf)_3$ used for this reaction, scandium triflate was found to be most effective in terms of conversion and reaction time. In contrast, protic acids such as PTSA and camphorsulfonic acid (CSA) were found to be ineffective for this transformation.

In summary, we have demonstrated a new method for the synthesis of *cis*-annelated pyranobenzopyrans from *o*-hydroxybenzaldehydes, trimethyl orthoformate and D-glycal using a catalytic amount of scandium triflate. In addition to its simplicity and mild reaction conditions, this method provides good yields of products with high diastereoselectivity, which makes it a useful process for the synthesis of *cis*-fused pyranobenzopyrans.

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9. *General procedure*: A mixture of *o*-hydroxybenzaldehyde (5 mmol), trimethyl orthoformate (5 mmol) and scandium triflate 3 mol% in dichloromethane (10 mL) was stirred at ambient temperature for 10–15 min. Then D-glycal (12.5 mmol) was added slowly at 0°C to the above reaction mixture. The resulting reaction mixture was stirred at ambient temperature for an appropriate time (see Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2×15 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate/hexane, 1:9) to afford pure *cis*-fused acetal.

**3e**: $^1$H NMR (500 MHz, $CDCl_3$): $[\alpha]_D^{25}$ 6.6 (*c* 1.0, $CHCl_3$); $\delta$ 7.53 (d, $J=7.7$, 1H, Ha), 7.38–7.08 (m, 15H, aromatic), 7.19 (t, $J=7.7$, 1H, Hc), 6.97 (t, $J=7.8$, 1H, Hb), 6.82 (d, $J=8.1$, 1H, Hd), 5.63 (d, $J=3.0$, 1H, H6), 4.81–4.45 (m, 6H, $OCH_2$), 4.76 (d, $J=4.5$, 1H, H7), 4.06 (dt, $J=3.5$, 10.2, 1H, H2), 3.82 (dd, $J=3.5$, 10.7, 1H, H1a), 3.81 (t, $J=10.2$, 1H, H3), 3.74 (dd, $J=10.2$, 10.7, 1H, H1b), 3.66 (dd, $J=9.0$, 10.2, 1H, H4), 3.54 (s, 3H, OMe), 2.83 (ddd, $J=3.0$, 4.5, 10.5, 1H, H5).

**3i**: $^1$H NMR (500 MHz, $CDCl_3$): $[\alpha]_D^{25}$ 8.9 (*c* 1.0, $CHCl_3$); $\delta$ 7.06 (d, $J=7.9$, 1H, Ha), 6.83 (t, $J=7.9$, 1H, Hb), 6.76 (d, $J=7.9$, 1H, Hc), 5.54 (d, $J=3.0$, 1H, H6), 4.68 (d, $J=4.7$, 1H, H7), 4.04 (m, 2H, $OCH_2$), 3.85 (qd, $J=2.6$, 10.2, 1H, H2), 3.66 (dd, $J=3.2$, 10.5, 1H, H1a), 3.63 (dt, $J=2.6$, 10.5, 1H, H1b), 3.57 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.35 (dd, $J=10.2$, 10.5, 1H, H3), 3.21 (ddd, $J=1.8$, 8.5, 10.5, 1H, H4), 2.63 (ddd, $J=3.0$, 4.7, 8.5, 1H, H5), 1.41 (t, $J=7.0$, 3H, $CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$, proton decoupled): $\delta$ 146.6, 141.5, 123.1, 121.6, 120.7, 119.3, 118.3, 117.7, 113.0, 98.7, 97.2, 80.1, 79.9, 78.5, 75.9, 73.9, 71.7, 70.8, 70.6.