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Facile one-pot method for the synthesis of novel glycosylidene-based quinolines

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ABSTRACT

A one-pot approach to the synthesis of novel glycosylidene-based quinolines is described. The reaction involves a Lewis acid catalyzed Povarov addition followed by oxidation of the resulting spiroanellated tetrahydroquinoline intermediates to yield the open-ring glycosylidene-derived quinoline.

The importance of cell-surface carbohydrates in biological processes such as recognition, fertilization, and signal transduction cannot be overstated.[1] In addition to these surface interactions, hexoses such as glucose are readily transported across a range of cellular membranes via glucose transporter proteins and are thus also able to act within the cell.[2] The biological prevalence and bioavailability of carbohydrates make stable sugar derivatives attractive scaffolds for drug design.[3]

Quinolines are another group of compounds that are of interest from a therapeutic point of view.[4] This structural class includes fluoroquinolone antibiotics such as ciprofloxacin[5] **1** and antitumor alkaloids related to streptonigrin[6] **2** (Fig. 1). Other therapeutic areas in which quinoline derivatives have shown promising activity include asthma,[7] Alzheimers' disease,[8] and AIDS.[9]

Due to the medicinal importance of quinolines, we became interested in the synthesis of molecules that contained carbohydrates conjugated to these heterocycles. We hypothesized that incorporation of a sugar would not only facilitate drug delivery, but may also aid in the DNA intercalation of the quinoline ring. The sugar moiety could help to stabilize DNA binding by interacting with the sugar–phosphate backbone once the quinoline is in contact with the DNA.[10] Furthermore, if the quinoline and sugar were appended via carbon–carbon bonds, (rather than carbon–oxygen bonds) this would impart an additional measure of stability to the molecule from endogenous glycosidases in the body.

In order to synthesize these interesting target molecules, we surmised that a variation of the Povarov reaction could allow us access to glycosylidene-spiroanellated quinolines. In the 1960s, Povarov et al. described a [4+2] cycloaddition reaction between an aromatic Schiff base and activated alkene to give tetrahydroquinolines.[11] They also reported that these products could be readily oxidized to the corresponding dihydroquinolines. Subsequent studies by other researchers showed that this reaction actually involved a polar addition to a vinyl ether, and intermediates from this process were trapped and characterized.[12] Recent publications have documented the utility of the Povarov reaction,[13] and new catalysts, including lanthanide triflates, have led to improved reaction conditions.[14]

Povarov additions have recently been described in which Lewis acid catalyzed multicomponent reactions were carried out with protected glycals.[15] However, to the best of our knowledge, an application with *exo*-glycals has not yet been reported. We have developed a one-pot methodology utilizing a substituted benzaniline, scandium triflate, and manganese dioxide to convert an *exo*-glycal directly into a novel C-linked, glycosylidene-based quinoline. In this Letter, we herein demonstrate the utility of this one-pot reaction.

In order to investigate Povarov reaction conditions, we screened several rare earth metal triflates as Lewis acid catalysts for the reaction between *exo*-glycal[16] **3** and benzaniline **4a** (Table 1). With all three catalysts (entries 1–3), we observed the complete conversion of **3** to a mixture of products. Isolation and structural characterization of the resulting compounds indicated the formation of spiroanellated tetrahydroquinoline[17] **5** as a 4:1 mixture of diastereomers in addition to the open-ring glycosylidene-based quinoline[18] **6a**. The spiro-compounds **5** are also interesting due to their structural resemblance to (+)-hydantocidin[19] and its glucose-based analogues,[20] all of which are potent glycosidase inhibitors.

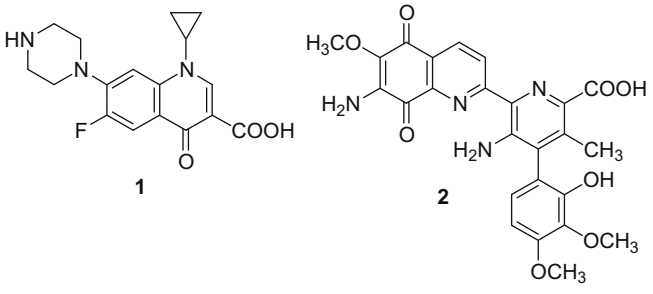

Figure 1. Biologically active quinoline derivatives.

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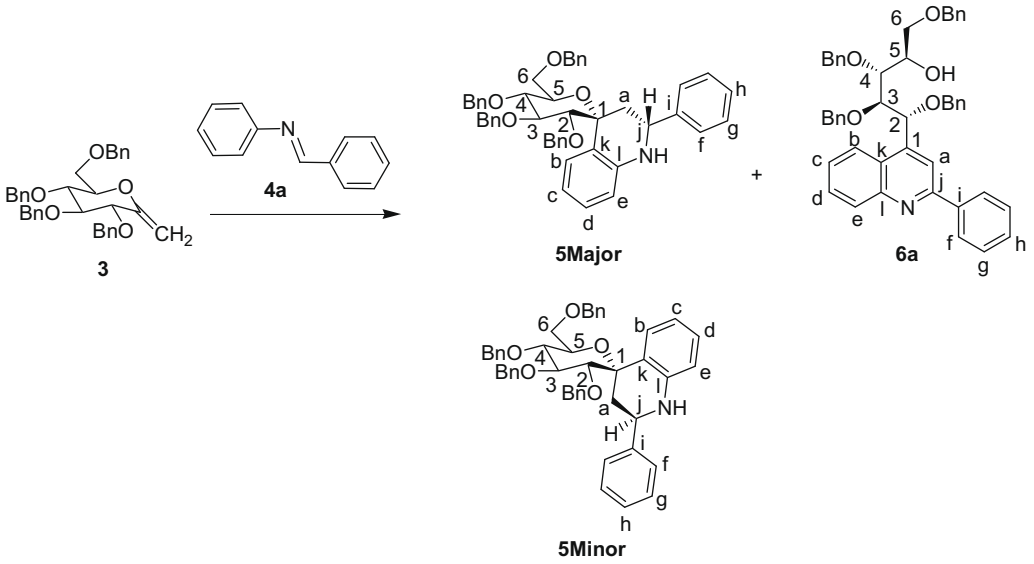
Table 1
Catalyst and reaction conditions screening[a]



Entry	Catalyst	Reaction conditions	Ratio of **6a**:[b] (**5Major** + **5Minor**)
1	$Sc(OTf)_3$	Room temperature, overnight	2.67:1
2	$Yb(OTf)_3$	Room temperature, overnight	0.92:1
3	$Tb(OTf)_3$	Room temperature, overnight	0.96:1
4	$Sc(OTf)_3$	Reflux, overnight	2.51:1
5	$Sc(OTf)_3$	Room temperature, MnO_2,[c] overnight	1:0

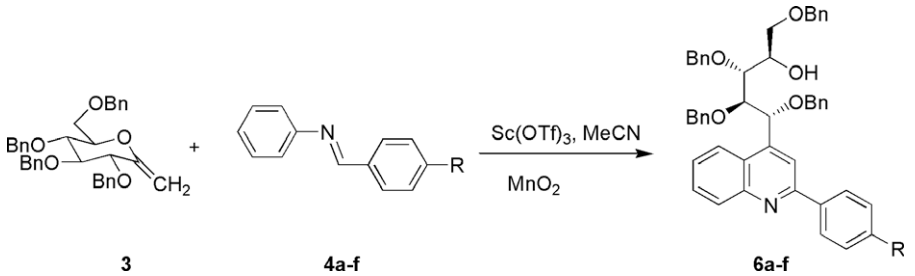
[a] Compounds **3** (1.0 equiv), **4a** (1.0 equiv), and catalyst (0.2 equiv) were dissolved in MeCN and allowed to react under the specified conditions.
[b] Determined by HPLC/MS analysis.
[c] Two equivalents added after 2 h.

The regiochemistry of addition to the glycal to produce the spiro products is as what would be anticipated; attack of the imine carbon by the more nucleophilic C2 carbon of the vinyl ether followed by electrophilic attack of the resulting oxonium ion by the *ortho* carbon of the aniline ring. This two-step process, as has been described by others,[12] was further supported by our isolation of an intermediate addition product in which the imine carbon of the benzaniline was added to C2, and water was added to the C1 carbon of the vinyl ether. The observed axial facial preference for addition to the *exo*-glycal leading to the β-substituted methylene group at the anomeric carbon most likely arises because of steric effects experienced by the bicyclic component in the equatorial plane.[21]

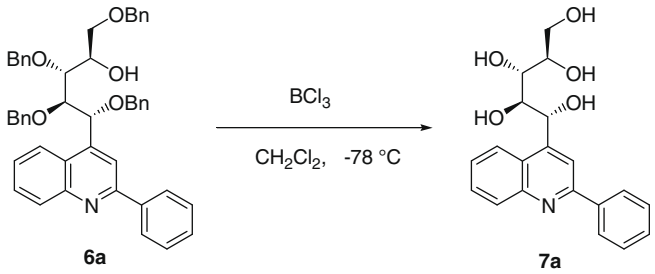
The aromatization of the tetrahydroquinoline portion of **5** likely drives the opening of the glucopyranose ring. Although the spiro-compound mixture **5** is stable while refrigerated, we observed the slow, partial oxidation to **6a** at room temperature.

In consideration of these initial results, it was therefore our desire to exclusively obtain the oxidized product **6a**, preferably from a one-pot reaction. Of the screened catalysts, $Sc(OTf)_3$ gave the highest ratio of **6a** to **5Major** + **5Minor** as well as the cleanest reaction. Heating the $Sc(OTf)_3$ mixture to reflux overnight did not have an effect on the ratio of products compared to the reaction maintained at room temperature (entries 1 and 4). We then turned our attention to the addition of oxidizing agents, and quickly

Table 2
One-pot synthesis of glycosylidene-based quinolines[22]



Entry	Benzaniline R-group[23]	Product	Isolated yield (%)
1	H	**6a**	65
2	F	**6b**	60
3	Br	**6c**	64
4	CN	**6d**	43
5	CF_3	**6e**	46
6	OCH_3	**6f**	45



Scheme 1. Deprotection of perbenzylated quinolone **6a**.

discovered that complete conversion to **6a** could be obtained with 2 equiv of MnO_2 (entry 5).

We next applied this one-pot reaction to a series of *para*-substituted benzanilines in order to evaluate the electronic effect of substituents on this reaction (Table 2). In general, the halogen substituted benzanilines (entries 2 and 3) reacted efficiently to produce the corresponding open-ring glycosylidene-based quinolines. The yields, which exceeded 60%, were very similar when compared to the non-substituted phenyl ring (entry 1). However, reactions that involved a benzaniline with an electron-withdrawing group, such as a cyano- or trifluoromethyl-substituent, resulted in lower yields of the desired product (entries 4 and 5). The reaction yields also suffered when benzaniline was substituted with an electron-donating methoxy group (entry 6). These observations suggest that benzanilines containing strongly electron-donating or withdrawing moieties in the *para* position resulted in diminished reaction yields in comparison to halogen substituents. Nonetheless, this procedure represents an effective way to access unique carbohydrate-based quinolines.

Deprotection of perbenzylated intermediate **6a** was carried out utilizing BCl_3 (Scheme 1).[24] Successful removal of the protective groups validates this sequence as an expeditious approach toward sugar-derived quinolines. Biological evaluation of these novel compounds is underway and will be reported in due course.

In conclusion, we have demonstrated that carbon-linked glucose-derived quinolines can be obtained from a one-pot, scandium triflate-catalyzed Povarov reaction followed by oxidation with manganese dioxide. We have also shown that the reaction proceeds through the glucose–spiroanellated tetrahydroquinoline intermediates. The utility of this procedure has been effectively employed with different *para*-substituted benzanilines to access several novel open-ring glycosylidene quinolines. Facile deprotection of the sugar benzyl ether groups is realized by using boron trichloride. Novel C-glycosylated quinolines have been obtained that are currently being evaluated in cancer cell line screenings.

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References and notes

1. Varki, A. *Glycobiology* **1993**, *3*, 97.
2. Pessin, J. E.; Bell, G. I. *Annu. Rev. Physiol.* **1992**, *54*, 911.
3. Witczak, Z. J. *Curr. Med. Chem.* **1995**, *1*, 392.
4. For a review, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.
5. For a review, see: Campoli-Richards, D. M.; Monk, J. P.; Price, A.; Benfield, P.; Todd, P. A.; Ward, A. *Drug* **1988**, *35*, 373.
6. Shaikh, I. A.; Johnson, F.; Grollman, A. P. *J. Med. Chem.* **1986**, *29*, 1329.
7. Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669.
8. Normand-Bayle, M.; Benard, C.; Zouhiri, F.; Mouscadet, J.-F.; Leh, H.; Thomas, C.-M.; Mbemba, G.; Desmaele, D.; d'Angelo, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4019.
9. Polanski, J.; Zouhiri, F.; Jeanson, L.; Desmaele, D.; d'Angelo, J.; Mouscadet, J.-F.; Gieleciak, R.; Gasteiger, J.; Le Bret, M. *J. Med. Chem.* **2002**, *45*, 4647.
10. Li, W.; Zhang, Z.-W.; Wang, S.-X.; Ren, S.-M.; Jiang, T. *Chem. Biol. Drug Des.* **2009**, *74*, 80.
11. (a) Povarov, L. S.; Grigos, V. I.; Karakhanov, R. A.; Mikhailov, B. M. *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)* **1965**, 344; (b) Povarov, L. S.; Grigos, V. I.; Mikhailov, B. M. *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)* **1966**, 120.
12. (a) Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633; (b) Hermitage, S.; Howard, J. A. K.; Jay, D. A.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451; (c) Beifuss, U.; Ledderhose, S.; Ondrus, V. *Arkivoc* **2005**, *v*, 147; (d) Alves, M. J.; Azoia, N. G.; Fortes, A. G. *Tetrahedron* **2007**, *63*, 727; (e) Mayr, H.; Ofial, A. R.; Sauer, J.; Schmied, B. *Eur. J. Org. Chem.* **2000**, 2013.
13. For reviews, see: (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656; (b) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137; (c) Koutznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.
14. (a) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801; (b) Cheng, D.; Zhou, J.; Saiah, E.; Beaton, G. *Org. Lett.* **2002**, *4*, 4411.
15. Jimenez, O.; de la Rosa, G.; Lavilla, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6521.
16. Tetra-*O*-benzyl-D-glucopyranose oxidation with Dess–Martin periodinane followed by lactone olefination with Tebbe reagent gave *exo*-glycal **3** in two steps. For the lactone synthesis experimental procedure, see: Csuk, R.; Dorr, P. *J. Carbohydr. Chem.* **1995**, *14*, 35; for the olefin synthesis experimental procedure, see: RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458.
17. **5Major** and **5Minor** were isolated in 65% yield as a ~4:1 mixture of diastereomers by stopping the room temperature reactions after 3 h. NOE experiments have confirmed the stereochemistry of both isomers of **5**. For **5Major**, NOEs were observed between the hydrogens attached to the following carbon atoms (for atom labels, see structure in Table 1): 2 with both j and a, b with both 3 and 5, and 4 with a. For **5Minor**, NOEs were observed between the hydrogens attached to the following carbon atoms: b with both 2 and 4, 3 with a, and 5 with j.
18. Both 1D and 2D NMR experiments, conducted in CD_3CN, were required to confirm the open-ring structure of **6a** (for atom labels, see structure in Table 1). Evidence includes the ^{13}C shift of C-1 (146 ppm) and the coupling constant for the hydrogen attached to C-2 (3.1 Hz). The broad ^{13}C resonance of 2 sharpens upon increased temperature and indicates restricted rotation about the C1–C2 bond. NOEs were observed between the hydrogens attached to the following carbon atoms: 2 with both a and b. COSY and NOESY signals were also observed between the hydrogen and hydroxyl group attached to 5.
19. (a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Honma, T.; Tohjigamori, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 293; (b) Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1637.
20. (a) Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.; Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. K.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2145; (b) Osz, E.; Szilagyi, L.; Somsak, L.; Benyei, A. *Tetrahedron* **1999**, *55*, 2419.
21. Similar α-facial selectivity has been reported for other addition reactions for *exo*-glycals. See for example: (a) Colinas, P.; Jager, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071; (b) Enderlin, G.; Taillefumier, C.; Didierjean, C.; Chapleur, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2459; (c) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263.
22. *Representative procedure*: To a solution of *exo*-glycal **3** (100 mg; 0.186 mmol) in acetonitrile (1 mL) was added benzaniline **4a** (33.8 mg; 0.186 mmol) followed by $Sc(OTf)_3$ (18.3 mg; 0.0372 mmol). The reaction was stirred at room temperature under an atmosphere of nitrogen. After 2 h, MnO_2 (32.4 mg; 0.372 mmol) was added and the mixture was stirred overnight. The reaction was diluted with ethyl acetate (15 mL), filtered through Celite, and concentrated in vacuo. The crude material was purified over silica gel, eluting with a gradient of 0–40% ethyl acetate in hexanes, to obtain the product **6a** as a colorless oil (87 mg, 65% yield). ^1H–NMR (500 MHz, $CDCl_3$): δ 8.27 (d, J = 8.5 Hz, 1H), 8.19 (s, 1H), 8.16 (d, J = 7.0 Hz, 2H), 8.03 (d, J = 6.5 Hz, 1H), 7.74 (t, J = 7.75 Hz, 1H), 7.56–7.49 (m, 3H), 7.42–7.31 (m, 14H), 7.30–7.25 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 2H), 6.89 (d, J = 7.5 Hz, 2H), 5.65 (d, J = 1.5 Hz, 1H), 4.67–4.56 (m, 6H), 4.39 (d, J = 11.5 Hz, 1H), 4.16 (d, J = 8.5 Hz, 1H), 4.11–4.03 (m, 2H), 3.92 (m, 1H), 3.76 (dd, J = 10.0, 3.75 Hz, 1H), 3.68 (dd, J = 10.0, 5.0 Hz, 1H), 3.05 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.0, 148.7, 145.7, 139.5, 138.4, 138.3, 137.5, 137.3, 130.8, 129.7, 129.6, 129.1, 128.8, 128.8, 128.7, 128.7, 128.7, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 126.6, 125.6, 123.1, 118.7, 81.7, 78.0, 77.0, 75.1, 74.0, 73.8, 72.1, 71.9, 71.4. HRMS calcd for $C_{48}H_{46}NO_5^+$ [M+H$^+$]: 716.3371, found 716.3377.
23. Benzanilines were purchased commercially or synthesized according to published literature. For a representative experimental procedure, see: Bigelow, L. A.; Eatough, H. *Org. Synth.* **1928**, *8*, 22.
24. To a solution of perbenzylated intermediate **6a** (70 mg; 0.098 mmol) in dichloromethane at −78 °C was added BCl_3 (1 M in hexane; 0.39 mL; 0.39 mmol). The reaction was stirred at −78 °C under an atmosphere of nitrogen. After one hour, additional BCl_3 (1 M in hexanes; 0.195 mL; 0.195 mmol) was introduced, and the reaction was maintained at −78 °C for

one hour. The reaction was quenched with the addition of methanol (2.0 mL). The crude material was concentrated in vacuo. The residue was co-evaporated twice with methanol, and then purified with a Waters mass directed reverse phase prep HPLC system. The following chromatographic conditions were used: (a) column: Waters Xbridge C-18, 30 × 75 mm, 5 μm; (b) flow rate: 50 mL/min; (c) mobile phase: A = water + ammonium hydroxide (pH 10), B = acetonitrile; (d) mobile phase gradient method: time = 0 min, A = 98, B = 2; time = 11 min, A = 65, B = 35; time = 11.2 min, A = 0, B = 100; time = 14.2 min, A = 98, B = 2; time = 15 min, A = 98, B = 2. Lyophilization of the resulting fractions yielded the product **7a** as a white solid (24 mg, 69% yield): ^{1}H NMR (500 MHz, CD_3OD): δ 8.34 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H), 8.17–8.13 (m, 3H), 7.77 (t, J = 7.75 Hz, 1H), 7.61 (t, J = 7.75 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.53–7.48 (m, 1H), 5.73 (d, J = 5.0 Hz, 1H), 4.24 (dd, J = 5.0, 2.0 Hz, 1H), 3.78–3.72 (m, 2H), 3.60–3.55 (m, 1H), 3.52 (dd, J = 8.0, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 157.6, 150.0, 148.1, 139.7, 129.6, 129.5, 129.1, 128.7, 127.7, 126.4, 125.3, 123.8, 118.2, 72.9, 72.5, 71.9, 71.7, 63.6; HRMS calcd for $C_{20}H_{22}NO_5^+$ [M+H$^+$]: 356.1492, found 356.1496.