Tetrahedron 67 (2011) 9273–9282

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Povarov reactions of *exo*-glycals: preparation of C-linked, quinoline analogues

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ARTICLE INFO

Article history:
Received 22 August 2011
Received in revised form 16 September 2011
Accepted 19 September 2011
Available online 24 September 2011

Keywords:
exo-Glycal
Povarov reaction
p-Substituted benzanilines
Quinolines
Cytotoxicity

ABSTRACT

A one-pot approach based upon the Povarov reaction has been efficiently employed with a number of *exo*-glycals and *para*-substituted benzanilines to synthesize novel open-ring, carbohydrate-derived quinolines. The mechanism of this reaction was studied and an explanation for the observed stereoselectivity is proposed. Treatment of the compounds with the Lewis acid, boron trichloride, successfully removes the benzyl ether protecting groups in good yields. Several of the prepared compounds have been screened in the National Cancer Institute's (NCI's) 60 cell line model. Moderate activity was observed for several leukemia cell lines.

1. Introduction

Carbohydrates and glycoconjugates are crucial for the survival of living entities due to their integral involvement in numerous life sustaining processes.[1] As a result of the diversity and functional specialization of carbohydrates, stable and bioavailable sugar-based compounds present themselves as promising platforms for drug design.[2] In fact, saccharide derivatives are recognized as biologically relevant scaffolds that offer a high density of functional groups in addition to numerous chiral centers.[3] Aside from cell-surface interactions, sugars are able to pass through membranes via carbohydrate-specific transport mechanisms and function within cells.[4] Consequently, carbohydrate-derived compounds as well as glycomimetics have been utilized as therapeutics for a wide array of medical conditions.[5]

As is the case with sugars, nitrogen-containing heterocycles, including quinolines, are present in a variety of biologically active molecules and have been applied in several therapeutic areas.[6] For example, fluoroquinolones, such as ciprofloxacin[7] and levofloxacin[8] are used as antibacterial therapies while other quinoline derivatives show promise as antitumor agents.[9] Developments in the area of quinoline chemistry are therefore due, in part, to the pharmacological properties of their derivatives. Consequently, the synthesis of quinolines has been a subject of great importance in the field of organic chemistry.[10] Numerous preparative methods for the formation of substituted quinolines have been developed, and some of the most widely used name reactions include the Camps, Combes, Doebner–Miller, Friedlander, Knorr, Niementowski, Pfitzinger, Pictet–Spengler, Pomeranz–Fritsch, Riehm, and Skraup syntheses.[11]

We became interested in the preparation of sugar-based quinolines because of the biological activity associated with both classes of compounds. The unique structure and glycosidase inhibitory activity of the spironucleoside natural product (+)-hydantocidin[12] **1** and its synthetic glucose analogues[13] **2** and **3** provided additional inspiration to target sugar-based heterocycles (Fig. 1). Furthermore, a recent study focused on the synthesis and evaluation of quinoline-glucose hybrids **4** and **5** also validates the potential application of sugar-derived heterocycles as DNA intercalators.[14] We surmised that C-linked monosaccharide-derived quinolines have the potential to possess antitumor properties as intercalating agents. The incorporation of a carbohydrate group onto the molecule may facilitate delivery of the compound as well as enhance its drug-like properties. We hypothesized that the sugar component of the molecule might also help to stabilize the complex with DNA (via sugar–phosphate backbone interactions), enabling the planar quinoline to insert between the base pairs of DNA. In addition, a carbon–carbon bond linkage between the sugar and quinoline is likely to be more stable toward endogenous enzymes compared to a carbon–oxygen bond found in other reported carbohydrate–quinoline hybrids.[14,15]

Despite the large number of publications covering the synthesis of quinolines, we chose to focus our research around applications of the Povarov reaction. We theorized that a variation of the Povarov reaction would permit access to glycosylidene-linked quinolines.

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doi:10.1016/j.tet.2011.09.077

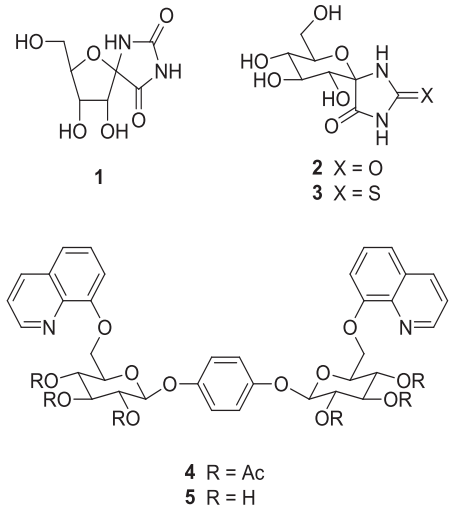
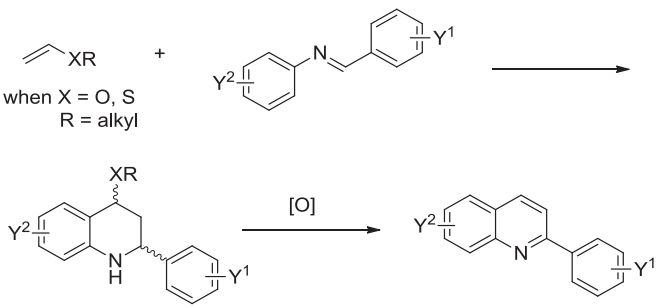


Fig. 1. Carbohydrate-based heterocycles.

Over 40 years ago, Povarov and colleagues described an addition reaction between aromatic Schiff bases (dienes) and activated alkenes (dienophiles) to give tetrahydroquinolines[16] (Scheme 1). In these manuscripts, they also reported that the tetrahydroquinoline products could subsequently be oxidized to the corresponding fully aromatized dihydroquinolines with the elimination of the alkoxy- or alkyl sulfide group. Interest in the Povarov reaction was rekindled in the 1990s, and significant improvements relating to this method's utility have been made. While the mechanism for this reaction has been the subject of debate, the Povarov reaction has now grown into a popular and useful strategy for the preparation of substituted tetrahydroquinolines.[17]



Scheme 1. Generalized Povarov reaction sequence.

Previously we have published our preliminary results surrounding the development of a facile one-pot methodology that was utilized to convert an *exo*-glycal directly into a novel C-linked, glycosylidene-based quinoline.[18] We herein report additional synthetic efforts in this area, namely the application of the reaction methodology to several *exo*-glycals[19] and *para*-substituted benzanilines.[20] These benzaniline precursors were chosen because steric effects of the substituents on reactivity would be minimal and because the product quinolines were desired for subsequent transformations. We also disclose the results of a series of deprotection screening experiments as well as the outcome of the anticancer evaluation of several glucose-derived compounds.

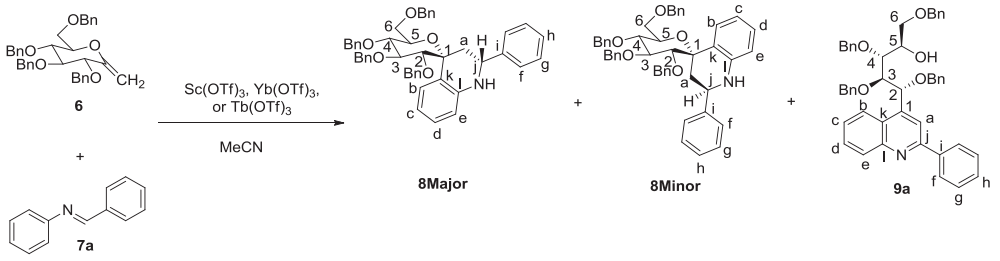
2. Results and discussion

In a previous communication, we reported screening experiments utilizing rare earth metal triflates [$Sc(OTf)_3$, $Yb(OTf)_3$, and $Tb(OTf)_3$] as catalysts for the Povarov reaction between a glucose-based *exo*-glycal and benzaniline.[18] We observed the formation of a 4:1 mixture of spiroanellated tetrahydroquinolines, as well as the oxidized, open-ring product (Scheme 2). The percentage of the open-ring compound present in the reaction mixture was catalyst dependent. For instance, when $Sc(OTf)_3$ was utilized as the catalyst, more than 70% of the reaction mixture consisted of the open-ring product. Lanthanide triflate reaction catalysis, however, produced nearly a 1:1 mixture of open-ring product and spiro tetrahydroquinolines.[21] Nuclear Overhauser effect (NOE) experiments confirmed the stereochemistry of both spiro isomers, **8Major** and **8Minor**, and extensive 1D and 2D NMR experiments were required to determine the structure of the open-ring compound **9a**. For **8Major**, NOEs were observed between the hydrogens attached to the following carbon atoms (for atom labels, see structure in Scheme 2): 2 with both j and a, b with both 3 and 5, and 4 with a. These interactions indicate that the stereochemistry is (*R*) at both carbons 1 and j. For **8Minor**, 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. The stereochemistry of this isomer is (*S*) at carbon 1 and (*R*) at carbon j. Evidence supporting the formation of open-ring compound **9a** includes the ^{13}C shift of C1 (145.9 ppm) and the coupling constant for the hydrogen attached to C2 (3.1 Hz). The broad ^{13}C resonance of C2 (78.5 ppm) sharpened upon increased temperature, indicating 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, observed between the hydrogen and hydroxyl group attached to C5, also helped to confirm the assignment of **9a**.

A unique aspect of this Povarov addition is the observed facial selectivity and stereocontrol of the reaction. Only two of the four possible glycosylidene-spiroanellated stereoisomers were formed, and the isomers with the (*S*)-configuration at the benzylic carbon j were absent. The regiochemistry of addition to *exo*-glycal **6** to produce the spiroanellated products can be explained on the basis of a non-concerted reaction pathway.[22] According to the two-step process that has been proposed,[23] attack of the imine carbon by the more nucleophilic C2 carbon of the vinyl ether occurs first. This is followed by electrophilic attack of the resulting oxonium ion by the *ortho* carbon of the aniline ring. The observed axial facial preference for addition to **6** leading to the β-substituted methylene group at the anomeric carbon is likely due to the influence of steric effects experienced by the bicyclic component in the equatorial plane.[24] The steric effects may account for the observation that only 20% of the spiro mixture consists of product (**8Minor**) in which the axial substituent from the anomeric carbon is derived from the C2 carbon of the vinyl ether. In addition, we hypothesize that kinetic and or thermodynamic factors involving the formation of a transition state also impact the stereocontrol of the reaction and hence the play a role in the observed spiro product distribution.[25]

During the course of our experiments, we made note of the instability of the spiro isomers. In addition to the presence of open-ring compound **9a** in the reaction mixtures, we also observed the slow, partial conversion of **8Major** and **8Minor** after chromatographic isolation to **9a** at room temperature. We surmise that **9a** is more favorable from the perspective of Gibb's free energy ($\Delta G = \Delta H - T\Delta S$) than its spiro precursors.

We hypothesize that the observed transformation is driven enthalpically by the aromatization of the tetrahydroquinoline to the dihydroquinoline. It is widely accepted that aromatization is an enthalpically favored process, and it confers additional stability to the resulting compound due to the delocalization of the pi electrons within the ring system. Perhaps alkoxy elimination followed by α,β-unsaturated iminium ion formation and single electron transfer leads to the formation of the fully aromatized quinoline (Fig. 2). Aside from enthalpic considerations, **9a** has five additional rotatable bonds, which make an entropic contribution to the overall favorability of the process. The capacity for bond rotation of the



Scheme 2. Preparation of sugar-based tetrahydro- and dihydroquinolines.

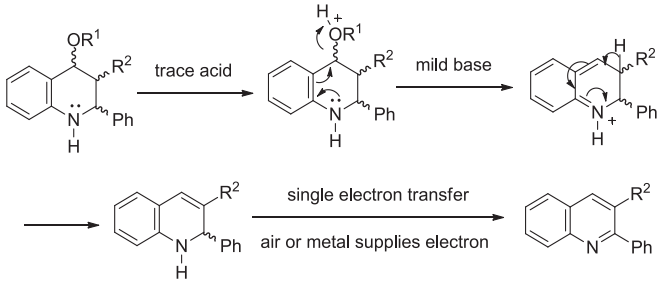
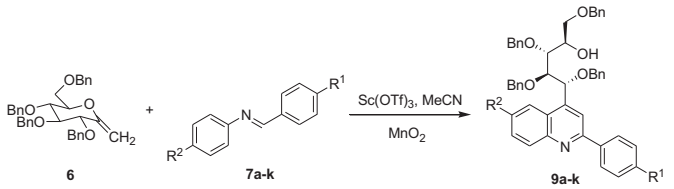


Fig. 2. Proposed mechanism for tetrahydroquinoline conversion to the aromatized dihydroquinoline.

Table 1
Synthesis of glucose-based quinolines



Entry	Benzaniline	R^1-group	R^2-group	Product	Isolated yield
1	**7a**	H	H	**9a**	65%
2	**7b**	F	H	**9b**	60%
3	**7c**	Br	H	**9c**	64%
4	**7d**	CN	H	**9d**	43%
5	**7e**	CF_3	H	**9e**	46%
6	**7f**	OCH_3	H	**9f**	45%
7	**7g**	H	F	**9g**	39%
8	**7h**	H	Br	**9h**[a]	38%
9	**7i**	H	CN	**9i**	Not isolated
10	**7j**	H	CF_3	**9j**[a]	18%
11	**7k**	H	OCH_3	**9k**	56%

[a] Reaction required 8 equiv of MnO_2 for complete conversion to open-ring product.

open-ring form contrasts with the conformationally ordered pyranose sugar and spiroanellated ring system, and the freely rotatable bonds create a more disordered compound. We theorize that the rotational capabilities of **9a** provide for an entropic enhancement to the overall favorability of the process. The observed lack of stability of the spiro conformers also correlates well with the Povarov addition/oxidation pathway in which alkoxy group elimination results in an aromatized compound.[16]

As a result of the instability of the spiro isomers, we decided to develop reaction conditions to exclusively obtain the open-ring product, preferably from a one-pot reaction. On the basis of previously reported catalyst screening results,[18] we focused exclusively on $Sc(OTf)_3$ because it gave the highest ratio of **9a** to **8Major**+**8Minor** as well as the cleanest reaction.[26] In consideration of original literature by Povarov et al.,[16] we decided to add oxidizing agents to the reaction mixture and quickly determined that 2 equiv of MnO_2 resulted in complete conversion to the open-ring compound **9a** in 65% yield.[18]

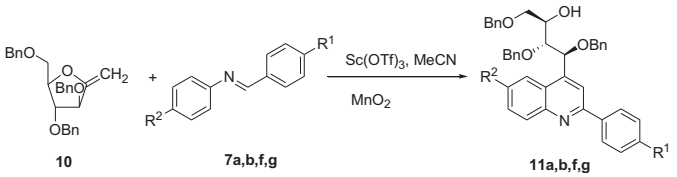
With these reaction conditions in hand, we applied this one-pot Povarov addition/oxidation procedure to a series of *para*-substituted benzanilines in order to evaluate the electronic effect of substituents on this reaction. First we chose to examine *para*-substituted benzanilines in which the R-group is derived from the benzaldehyde precursor. The halogen substituted benzanilines **7b** and **7c** (Table 1, entries 2 and 3) reacted efficiently to form the resulting open-ring, glucose-based quinolines. The yields, which exceeded 60%, were very similar when compared to benzaniline **7a** (entry 1). The electron-withdrawing inductive effect of the halogens acts in a manner opposite to the electron-donating resonance effect, resulting in no net impact on the reaction yields. Reactions of imines with an electron-withdrawing group, such as a cyano or trifluoromethyl substituent, resulted in lowered yields of product (entries 4 and 5). Product recovery was also reduced when benzaniline was substituted with an electron-donating methoxy group (entry 6).

We next employed this methodology with imines in which the aniline-derived phenyl ring is *para*-substituted. In these experiments, reactions of all substituted benzanilines resulted in diminished yields when compared to the non-substituted phenyl ring (entries 1, 7–11). Of the substituents evaluated in this series, the imine substituted with the electron-donating methoxy group gave the best reaction yield at 56% (entry 11). This compound marks the only instance in which the product yield in this series is higher than its counterpart in the series involving the benzaldehyde-derived phenyl substitutions. The halogen substituted imines **7g** and **7h** gave modest yields in the Povarov addition/oxidation sequence (entries 7 and 8). For these benzanilines, the electron-withdrawing inductive effect of the halogens appears to be more influential than the electron-releasing resonance effect. In addition, the experiment involving the benzaniline with the electron-withdrawing trifluoromethyl group gave the lowest yield at 18% (entry 10). In the case of cyano-substituted imine **7i**, the expected product was not isolated (entry 9). In general, the reaction yield in the aniline ring substituted series is negatively affected by the presence of *para*-substituents. This effect is most pronounced with imines containing an electron-withdrawing group in the *para* position. We theorize that removal of electron density from the aniline-derived phenyl group renders the pi-bond electrons of the aromatic ring less available for attack of the positively charged anomeric carbon. In contrast, release of electron density into the ring by the methoxy group more favorably impacts ring closure. Nevertheless, this procedure represents an effective way to access unique carbohydrate-based quinolines.

In order to probe the generality of the reaction and further expand our one-pot methodology to other sugars, we chose to utilize an *exo*-glycal that is derived from a five-membered ring sugar. This

addition/oxidation procedure was successfully applied to *exo*-glycal **10**, and a small series of compounds was prepared. Arabinose-derived quinoline **11a** was synthesized in 57% yield from benzaniline **7a** (Table 2, entry 1). We also attempted this reaction with several *para*-substituted benzanilines and isolated open-ring arabinose-derived quinolines in moderate yields (entries 2–4). With exception of the reaction with benzaniline **7a**, none of the reaction yields exceeded 50%. Interestingly, all of the oxidations with arabinose-derived *exo*-glycal **10** ultimately required 8.0 equiv of MnO_2 to help drive the reaction toward complete conversion to the open-ring form. This observation indicates that the arabinose-spiroanellated tetrahydroquinoline diastereomers are less susceptible to ring opening than the spiro products in the glucose series. Perhaps this is due to entropic factors, as only four rotatable bonds result from a ring-opening event as compared to five for the glucose series. This one-pot procedure, however, can be utilized to effectively synthesize novel carbohydrate-based quinolines from pentose-derived *exo*-glycals.

Table 2
Synthesis of arabinose-based quinolines



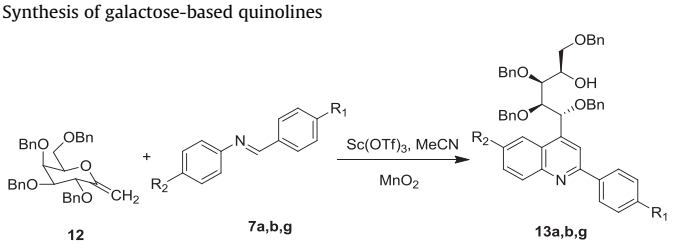
10 7a,b,f,g 11a,b,f,g

Entry	Benzaniline	R^1-group	R^2-group	Product	Isolated yield (%)
1	**7a**	H	H	**11a**[a]	57
2	**7b**	F	H	**11b**[a]	47
3	**7f**	OCH_3	H	**11f**[a]	44
4	**7g**	H	F	**11g**[a]	49

[a] Reaction required 8 equiv of MnO_2 for complete conversion to open-ring product.

We also decided to target a small series of galactose-derived quinolines in order to increase the breadth of the one-pot reaction that we developed with glucose and successfully applied to arabinose. Galactose was selected as the monosaccharide portion of the compound because this hexose is a close analogue of glucose, differing only by the configuration of the C4 chiral center. For this series of galactose-based compounds, we performed reactions with several benzanilines (**7a**, **7b**, and **7g**) utilized previously. Parent compound **13a** was synthesized in 51% yield (Table 3, entry 1). We also attempted this reaction with the *para*-fluoro-substituted benzanilines and isolated moderate yields of open-ring galactose-derived quinolines **13b** and **13g** (entries 2 and 3). As with the arabinose series, the yields for the open-ring products in the galactose series are lower than the glucose series. This series further expands the *exo*-glycal substrate scope and successfully demonstrates that the method works for hexoses other than glucose.

Table 3
Synthesis of galactose-based quinolines



12 7a,b,g 13a,b,g

Entry	Benzaniline	R^1-group	R^2-group	Product	Isolated yield (%)
1	**7a**	H	H	**13a**	51
2	**7b**	F	H	**13b**	48
3	**7g**	H	F	**13g**	45

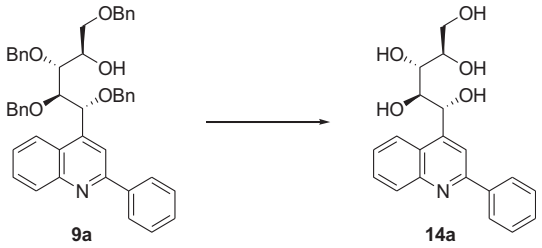
In order to validate the synthetic utility of the one-pot chemistry, we needed to determine conditions to successfully remove the benzyl protecting groups. Our first attempted debenzylation experiment with **9a** involved a room temperature hydrogenolysis reaction catalyzed by Pd/C. Unfortunately, after overnight stirring, no reaction was observed (Table 4, entry 1). We next turned our focus to Pd-based catalysts at conditions involving higher pressure and temperature. We did not observe debenzylation of **9a** with the Pd-based catalysts attempted at 40 °C and 40 psi (entries 2 and 3). Instead we noticed that two double bonds within the quinoline system were reduced. Subsequent overnight heating of these reactions at 60 °C enabled debenzylation, but the remaining three double bonds of the quinoline system were also hydrogenated (entries 4 and 5). The results of these screening experiments indicate that conditions involving high pressure and high temperature do not remove the benzyl groups while leaving the quinoline system intact.

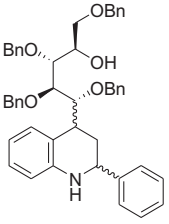
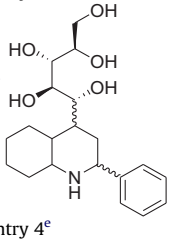
We next turned our attention to sealed-tube transfer hydrogenation conditions with Pearlman's catalyst and either cyclohexene[27] or ammonium formate[28] as the hydrogen donor. The conditions with cyclohexene resulted in debenzylation of compound **9a** (entry 6). In addition to **14a**, however, we also observed two unidentified by-products (approximately 25% of the crude reaction mixture) that were not separable from the desired product. We attempted similar transfer hydrogenation conditions with ammonium formate. However, **9a** was unreactive toward these conditions, and we detected only a trace amount of compound in which one benzyl group was removed (entry 7).

Other deprotection attempts focused on the use of Lewis acids to debenzylate **9a**. Although ferric chloride[29] successfully removed the benzyl protecting groups when stirred at room temperature overnight, the reaction afforded multiple unidentified by-products (entry 8). Given the promising results with ferric chloride, we decided to try another Lewis acid, boron trichloride.[30] To our delight, this reagent successfully and cleanly cleaved the protecting groups after 2 h of stirring at −78 °C (entry 9).[18] The boron trichloride-based deprotection of perbenzylated intermediates **9a**, **9b**, **11a**, and **13a** were carried out, giving the perhydroxylated products in good yields (Table 5).

The anticancer properties of several of the synthesized glucose-based quinolines were evaluated in the National Cancer Institute's (NCI's) 60 cell line screening model.[31] Specifically compounds **9a**, **14a**, **14a HCl Salt**[32] and **14b** were tested at a 10 μM concentration. Surprisingly, perbenzylated compound **9a** displayed the best anticancer profile of the four compounds (Table 6). This compound exhibited more than 40% growth inhibition for eight separate cell lines. In addition, leukemia cell lines were most susceptible to **9a**. Deprotected compounds **14a**, **14a HCl Salt**, and **14b**, on the other hand, displayed an overall similar profile and resulted in little to no growth inhibitory effect for a majority of the cell lines. The most favorable results were 20.5% growth inhibition (RXF 393, Renal) for **14a** and 17.8% growth inhibition (SR, Leukemia) for **14b**. Interestingly, **14a HCl Salt** was highly effective against the CCRF-CEM leukemia cell line and led to 68.7% cell growth inhibition. As a general trend, the tested glucose-based quinolines were most effective against leukemia cell lines and least effective for melanoma cell lines. Despite the modest anticancer properties of **9a**, it was not selected by NCI for dose titration experiments. We conclude that the lipophilic benzyl ether protecting groups present in **9a** are the structural features responsible for the observed growth inhibition. Based upon the data, we surmise that the lack of tumor

Table 4
Selected debenzylation screening experiments



Entry	Reagent	Conditions[a]	Result[b]
1	Pd/C (5%, wet)[c]	H_2 balloon, room temperature, ethanol	No reaction
2	Pd/C (10%, wet)[d]	40 °C, 40 psi H_2	MW=719[e] 
3	$Pd(OH)_2/C$ (20%, wet)[d]	40 °C, 40 psi H_2	Same as entry 2[e]
4	Pd/C (10%, wet)[d]	60 °C, 40 psi H_2	MW=365[e] 
5	$Pd(OH)_2/C$ (20%, wet)[d]	60 °C, 40 psi H_2	Same as entry 4[e]
6	$Pd(OH)_2/C$ (20%, wet)[d]	90 °C (sealed tube), cyclohexene, ethanol	**14a**, ~25% by-products (MW-18, MW-16)
7	$Pd(OH)_2/C$ (20%, wet)[d]	90 °C (sealed tube), ammonium formate, ethanol	Mostly **9a**, trace loss of 1 Bn group
8	$FeCl_3$ (4.0 equiv per Bn)	Dichloromethane, 0 °C to room temperature, overnight	**14a**, numerous unidentified by-products
9	BCl_3 (1.5–2.0 equiv per Bn)	Dichloromethane, 2 h	**14a**, clean

[a] Stirred overnight in methanol unless otherwise noted.
[b] Determined by HPLC/MS analysis.
[c] Substrate to catalyst ratio is (1:0.5 wt_{sub}/wt_{cat}).
[d] Substrate to catalyst ratio is (1:1 wt_{sub}/wt_{cat}).
[e] Tentative structural assignment.

cell growth suppression involving **14a**, **14a HCl Salt**, and **14b** may be attributed to insufficient DNA intercalation.

3. Conclusion

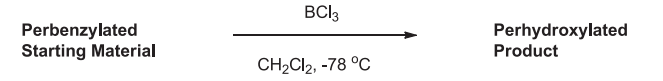
We have developed and expanded the scope of a facile, one-pot method based upon the Povarov reaction to prepare novel *C*-glycosylated quinolines. The reaction proceeds through the stereoselective formation of sugar-spiroanellated tetrahydroquinoline intermediates. These compounds are subsequently oxidized and undergo sugar ring opening to form the fully aromatized quinolines. This one-pot methodology has been efficiently employed with several sugar *exo*-glycals and a series of *para*-substituted benzanilines to prepare novel open-ring, glycosylidene-derived quinolines. Extensive deprotection experiments were carried out, and facile debenzylation occurs with the use of boron trichloride. The successful debenzylation chemistry demonstrates that this one-pot, scandium triflate-catalyzed Povarov reaction followed by manganese dioxide oxidation is an expeditious way to obtain novel *C*-glycosylated quinolines. Some of the glucose analogues have been tested in the NCI60 human tumor cell line anticancer screen. Although several leukemia cell lines experienced modest growth inhibition when treated with **9a**, the glucose-linked quinolines do not possess sufficient broad-based anticancer activity to warrant further dose titration studies.

4. Experimental section

4.1. General remarks

All reactions were performed under a nitrogen atmosphere unless otherwise noted. Anhydrous solvents were purchased commercially and were used as received. Unless otherwise specified, commercially available reagents were used without further purification. Nuclear magnetic resonance spectra were taken on a 500 or 600 MHz spectrometer in $CDCl_3$, CD_3CN, or CD_3OD as solvent using tetramethylsilane as an internal standard. High resolving power accurate mass measurement electrospray (ESI^+) mass spectral data were acquired by use of a Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR MS). External calibration was accomplished with oligomers of polypropylene glycol. IR spectra were obtained as thin films on NaCl plates. Melting points values are uncorrected unless otherwise noted. Rotation values were obtained through use of a polarimeter at room temperature. Silica gel column chromatography was conducted with an automated chromatography system and Teledyne Isco columns. Thin layer chromatography

Table 5
Boron trichloride-based debenzylation



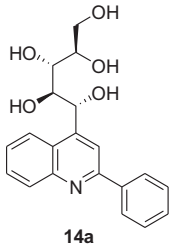
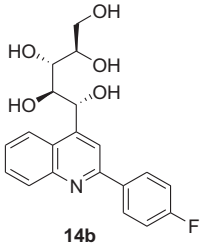
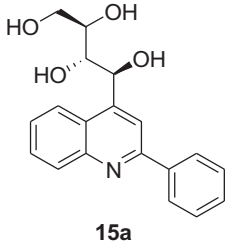
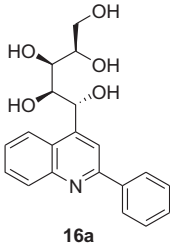
Entry	Perbenzylated starting material	Perhydroxylated product	Isolated yield (%)
1	**9a**	 **14a**	69
2	**9b**	 **14b**	63
3	**11a**	 **15a**	63
4	**13a**	 **16a**	60

Table 6
Selected results from the NCI60 human tumor cell line anticancer drug screen assay

Compound	Cell line	Growth percent at 10 μM
9a	MOLT-4 (Leukemia)	40.0
9a	HL-60(TB) (Leukemia)	45.8
9a	HOP-92 (Non-Small Cell Lung)	54.3
9a	T-47D (Breast)	56.6
9a	PC-3 (Prostate)	57.1
9a	MDA-MB-468 (Breast)	58.1
9a	HCT-116 (Colon)	58.4
9a	NCI-H23 (Non-Small Cell Lung)	59.9
14a	RXF 393 (Renal)[a]	79.5
14a HCl Salt	CCRF-CEM (Leukemia)	31.3
14b	(SR, Leukemia)[a]	82.2

[a] Denotes compound's best result; no cell line tested for the compound had a growth percent under 60.

was carried out with Whatman MK6F silica gel TLC plates. Preparative scale HPLC was conducted with a mass directed reverse phase HPLC system. Analytical HPLC/MS was conducted on an HPLC system equipped with a 3.0×50 mm XTerra C-18 column utilizing solvents buffered with 0.05% TFA. The following method was used: a gradient of 10–98% MeCN in H_2O for 3.75 min, then 98% MeCN in H_2O for 1.0 min. Low resolution mass spectrometry electrospray (ES) analysis was performed on the analyte. Preparative scale HPLC of chiral samples was carried out with a semi-preparative HPLC equipped with a 20×250 mm ChiralPak IB column, 5 μm, 9 mL/min flow rate. Screening conditions of chiral samples were performed with an analytical HPLC equipped with chiral columns.

4.2. Procedure for the preparation and separation of 8Major+8Minor

To a solution of *exo*-glycal **6** (100 mg; 0.186 mmol) in acetonitrile (1 mL, unopened Sure/Seal™ bottle) was added benzaniline **7a** (33.7 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 for 1 h. The reaction was concentrated in vacuo, and the crude material was purified over silica gel, eluting with a gradient of 0–40% ethyl acetate in hexane to give **8Major**+**8Minor** as a colorless oil (4:1 mixture of diastereomers) in 65% yield. The isomers were separated by applying the preparative scale version (20×250 mm ChiralPak IB column, 5 μm, 9 mL/min flow rate) of the following analytical chromatography conditions: ChiralPak IB 4.6×250 mm column, 5 μm particle size, 10% ethanol in heptane (isocratic), 0.5 mL/min flow rate, 254 nm wavelength, retention time: **8Minor** (8.48 min), **8Major** (13.89 min).

*4.2.1. (2R,2′R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy) methyl]-2′-phenyl-2′,3,3′,4,5,6-hexahydro-1H′-spiro[pyran-2,4′-quinoline] (**8Major**).* Isolated as a colorless oil; $[\alpha]_D^{22}$ −13.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J*=7.5 Hz, 1H), 7.42–7.37 (m, 2H), 7.36–7.25 (m, 19H), 7.20–7.11 (m, 5H), 6.78 (t, *J*=7.25 Hz, 1H), 6.58 (d, *J*=6.5 Hz, 1H), 4.73 (d, *J*=11.0 Hz, 1H), 4.67–4.54 (m, 4H), 4.54–4.43 (m, 2H), 4.41–4.31 (m, 2H), 4.31–4.24 (m, 1H), 4.15–4.12 (m, 1H), 4.06–4.03 (m, 1H), 4.02–3.97 (m, 1H), 3.84–3.75 (m, 2H), 2.64 (dd, *J*=13.25, 4.75 Hz, 1H), 2.22–2.16 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.1, 144.4, 139.0, 138.8, 138.4, 138.2, 129.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.95, 127.91, 127.87, 127.5, 126.9, 123.2, 116.9, 113.7, 84.9, 79.9, 78.9, 76.3, 73.8, 73.6, 73.3, 72.4, 70.2, 55.2, 42.8; IR (NaCl): 3405, 3038, 2911, 2795, 1778, 1607, 1491, 1362, 1094, 698 cm^{-1}; HRMS calcd for $C_{48}H_{48}NO_5^+$ [M+H$^+$]: 718.3527, found 718.3529.

*4.2.2. (2S,2′R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy) methyl]-2′-phenyl-2′,3,3′,4,5,6-hexahydro-1H′-spiro[pyran-2,4′-quinoline] (**8Minor**).* Isolated as a colorless oil; $[\alpha]_D^{22}$ +40.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J*=7.5 Hz, 1H), 7.46–7.12 (m, 26H), 6.68 (t, *J*=7.25 Hz, 1H), 6.60 (d, *J*=8.0 Hz, 1H), 5.07–5.00 (m, 2H), 4.98–4.88 (m, 3H), 4.80–4.67 (m, 2H), 4.68–4.56 (m, 3H), 3.89–3.85 (m, 1H), 3.83–3.75 (m, 2H), 3.68–3.62 (m, 2H), 2.22 (t, *J*=12.75 Hz, 1H), 1.91 (dd, *J*=12.75, 3.75 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.9, 144.4, 138.9, 138.8, 138.6, 130.8, 129.3, 128.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.5, 127.4, 127.2, 117.7, 115.4, 114.9, 87.1, 86.6, 79.9, 76.3, 76.1, 75.8, 75.2, 73.4, 71.3, 69.3, 52.5, 44.4; IR (NaCl): 3405, 3038, 2911, 2795, 1778, 1607, 1491, 1362, 1094, 698 cm^{-1}; HRMS calcd for $C_{48}H_{48}NO_5^+$ [M+H$^+$]: 718.3527, found 718.3529.

4.3. Representative example of the general procedure for the preparation of open-ring glycosylidene-derived quinolines

To a solution of *exo*-glycal **6** (100 mg; 0.186 mmol) in acetonitrile (1 mL, unopened Sure/Seal™ bottle) was added substituted

benzaniline derivative **7a** (33.7 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. The crude material was purified over silica gel, eluting with a gradient of 0–40% ethyl acetate in hexane, to give **9a**.

*4.3.1. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-(2-phenylquinolin-4-yl)-D-arabinitol (**9a**).* Isolated in 65% yield as a colorless oil; $[\alpha]_D^{22}$ +67.3 (*c* 1.0, $CHCl_3$); ^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 (m, 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, 128.86, 128.77, 128.72, 128.70, 128.66, 128.3, 128.25, 128.18, 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; IR (NaCl): 3676, 2836, 2364, 2016, 1724, 1598, 1075, 697 cm^{-1}; HRMS calcd for $C_{48}H_{46}NO_5^+$ [M+H$^+$]: 716.3371, found 716.3377.

Compounds **9b**, **9c**, **9d**, **9e**, **9f**, **9g**, **9h**, **9j**, **9k**, **11a**, **11b**, **11f**, **11g**, **13a**, **13b**, and **13g** were prepared in a manner analogous to **9a** utilizing the appropriate *exo*-glycal and benzaniline starting materials.

*4.3.2. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-[2-(4-fluorophenyl)quinolin-4-yl]-D-arabinitol (**9b**).* Isolated in 60% yield as a colorless oil; $[\alpha]_D^{22}$ +74.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J*=8.0 Hz, 1H), 8.12 (t, *J*=6.7 Hz, 3H), 8.03 (d, *J*=7.5 Hz, 1H), 7.74 (t, *J*=7.75 Hz, 1H), 7.42–7.31 (m, 14H), 7.30–7.26 (m, 2H), 7.20 (t, *J*=8.75 Hz, 2H), 7.09 (t, *J*=7.5 Hz, 1H), 7.00 (t, *J*=7.5 Hz, 2H), 6.88 (d, *J*=7.0 Hz, 2H), 5.64 (d, *J*=2.0 Hz, 1H), 4.68–4.55 (m, 6H), 4.44 (d, *J*=11.5 Hz, 1H), 4.14–4.10 (m, 1H), 4.10–4.03 (m, 1H), 4.04 (br s, 1H), 3.92 (m, 1H), 3.76 (dd, *J*=9.75, 3.75 Hz, 1H), 3.68 (dd, *J*=9.75, 4.75 Hz, 1H), 3.05 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.1, 163.2, 155.9, 148.6, 145.9, 138.4, 138.3, 137.5, 137.3, 130.6, 129.9, 129.8, 129.7, 128.85, 128.79, 128.7, 128.6, 128.4, 128.3, 128.2, 128.18, 128.15, 128.0, 127.9, 126.7, 125.5, 123.1, 118.3, 116.1, 115.9, 81.9, 78.0, 77.0, 75.1, 74.0, 73.8, 72.1, 71.9, 71.3; IR (NaCl): 3649, 2911, 2537, 2356, 2051, 1502, 1090, 697 cm^{-1}; HRMS calcd for $C_{48}H_{45}FNO_5^+$ [M+H$^+$]: 734.3276, found 734.3276.

*4.3.3. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-[2-(4-bromophenyl)quinolin-4-yl]-D-arabinitol (**9c**).* Isolated in 64% yield as a colorless oil; $[\alpha]_D^{22}$ +39.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (br s, 1H), 8.11 (s, 1H), 8.05–7.97 (m, 3H), 7.74 (t, *J*=7.3 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 2H), 7.44–7.32 (m, 14H), 7.29–7.26 (m, 2H), 7.09 (t, *J*=7.5 Hz, 1H), 7.01–6.96 (m, 2H), 6.86 (d, *J*=7.0 Hz, 2H), 5.64 (d, *J*=2.0 Hz, 1H), 4.67–4.56 (m, 6H), 4.43 (d, *J*=11.5 Hz, 1H), 4.14–4.04 (m, 2H), 4.03 (s, 1H), 3.93 (m, 1H), 3.76 (dd, *J*=9.75, 3.75 Hz, 1H), 3.67 (dd, *J*=9.75, 5.0 Hz, 1H), 3.03 (br s,1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7, 138.4, 138.3, 137.4, 137.3, 132.2, 130.8, 129.8, 129.5, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.17, 128.09, 128.03, 127.95, 127.9, 126.8, 125.6, 123.1, 118.2, 81.8, 78.0, 77.5, 75.1, 74.0, 73.8, 72.1, 71.9, 71.3; IR (NaCl): 3567, 3030, 2868, 1958, 1596, 1073, 698 cm^{-1}; HRMS calcd for $C_{48}H_{45}BrNO_5^+$ [M+H$^+$]: 794.2476, found 794.2504.

*4.3.4. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-[2-(4-cyanophenyl)quinolin-4-yl]-D-arabinitol (**9d**).* Isolated in 43% yield as a colorless oil; $[\alpha]_D^{22}$ +56.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J*=8.5 Hz, 1H), 8.20 (d, *J*=8.0 Hz, 2H), 8.14 (s, 1H), 8.05 (d, *J*=8.0 Hz, 1H), 7.82–7.74 (m, 3H), 7.44 (t, *J*=7.5 Hz, 1H), 7.40–7.32 (m, 13H), 7.28 (m, 2H), 7.07 (t, *J*=7.25 Hz, 1H), 6.97 (t, *J*=7.5 Hz, 2H), 6.84 (d, *J*=7.5 Hz, 2H), 5.66 (d, *J*=1.5 Hz, 1H), 4.70–4.54 (m, 6H), 4.44 (d, *J*=11.50 Hz, 1H), 4.10–4.05 (m, 2H), 4.02 (br s, 1H), 3.94 (m, 1H), 3.77 (dd, *J*=10.0, 3.5 Hz, 1H), 3.67 (dd, *J*=10.0, 5.0 Hz, 1H), 3.01 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.6, 148.7, 146.4, 143.7, 138.4, 138.3, 137.4, 137.3, 132.8, 131.0, 130.0, 129.0, 128.8, 128.7, 128.5, 128.4, 128.24, 128.19, 128.1, 127.9, 127.4, 125.9, 123.2, 119.2, 118.4, 113.0, 82.0, 77.9, 76.9, 75.1, 74.1, 73.8, 72.2, 72.0, 71.3; IR (NaCl): 3556, 3030, 2829, 2227, 1779, 1597, 1073, 699 cm^{-1}; HRMS calcd for $C_{49}H_{45}N_2O_5^+$ [M+H$^+$]: 741.3323, found 741.3322.

*4.3.5. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-{2-[4-(trifluoromethyl)phenyl]quinolin-4-yl}-D-arabinitol (**9e**).* Isolated in 46% yield as a colorless oil; $[\alpha]_D^{22}$ +53.7 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J*=8.5 Hz, 1H), 8.21 (d, *J*=8.0 Hz, 2H), 8.15 (s, 1H), 8.04 (d, *J*=8.0 Hz, 1H), 7.79–7.73 (m, 3H), 7.45–7.31 (m, 14H), 7.29–7.26 (m, 2H), 7.07 (t, *J*=7.5 Hz, 1H), 6.97 (t, *J*=7.5 Hz, 2H), 6.84 (d, *J*=7.5 Hz, 2H), 5.65 (d, *J*=2.0 Hz, 1H), 4.68–4.55 (m, 6H), 4.44 (d, *J*=11.5 Hz, 1H), 4.14–4.05 (m, 2H), 4.03 (s, 1H), 3.93 (m, 1H), 3.76 (dd, *J*=9.75, 3.75 Hz, 1H), 3.67 (dd, *J*=10.0, 5.0 Hz, 1H), 3.01 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.3, 148.5, 146.4, 142.8, 138.4, 138.3, 137.4, 137.2, 130.8, 129.9, 128.83, 128.8, 128.7, 128.5, 128.4, 128.22, 128.18, 128.1, 128.0, 127.9, 127.2, 125.95, 125.92, 125.8, 123.2, 118.5, 81.8, 77.9, 77.3, 75.1, 74.1, 73.8, 72.2, 72.0, 71.3; IR (NaCl): 3549, 3030, 2865, 1598, 1324, 1107, 698 cm^{-1}; HRMS calcd for $C_{49}H_{45}F_3NO_5^+$ [M+H$^+$]: 784.3244, found 784.3242.

*4.3.6. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-[2-(4-methoxyphenyl)quinolin-4-yl]-D-arabinitol (**9f**).* Isolated in 45% yield as a colorless oil; $[\alpha]_D^{22}$ +40.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J*=8.5 Hz, 1H), 8.13 (d, *J*=9.0 Hz, 3H), 8.02 (br s, 1H), 7.72 (t, *J*=8.5 Hz, 2H), 7.58 (m, 1H), 7.52–7.47 (t, *J*=8.5 Hz, 1H), 7.40–7.31 (m, 12H), 7.30–7.26 (m, 2H), 7.12–6.97 (m, 4H), 6.91 (d, *J*=7.0 Hz, 2H), 5.63 (br s, 1H), 4.68–4.53 (m, 6H), 4.44 (d, *J*=11.5 Hz, 1H), 4.20–4.12 (m, 1H), 4.07 (m, 3H), 3.94 (s, 3H), 3.76 (dd, *J*=10.0, 3.75 Hz, 1H), 3.68 (dd, *J*=9.85, 5.0 Hz, 1H), 3.09 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.4, 138.3, 137.4, 137.1, 133.2, 132.4, 132.3, 132.2, 128.9, 128.8, 128.72, 128.67, 128.4, 128.18, 128.14, 128.1, 128.1, 128.0, 125.2, 123.1, 118.5, 114.6, 81.6, 77.9, 77.0, 75.0, 74.1, 73.8, 72.2, 72.0, 71.3, 55.7; IR (NaCl): 3555, 2912, 2008, 1601, 1503, 1118, 697 cm^{-1}; HRMS calcd for $C_{49}H_{48}NO_6^+$ [M+H$^+$]: 746.3476, found 746.3478.

*4.3.7. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-(6-fluoro-2-phenyl quinolin-4-yl)-D-arabinitol (**9g**).* Isolated in 39% yield as a colorless oil; $[\alpha]_D^{22}$ +48.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.26–8.20 (m, 1H), 8.18–8.09 (m, 3H), 7.77 (d, *J*=9.25 Hz, 1H), 7.56–7.48 (m, 4H), 7.41–7.28 (m, 15H), 7.06 (t, *J*=7.25 Hz, 1H), 6.97 (t, *J*=7.5 Hz, 2H), 6.84 (d, *J*=7.5 Hz, 2H), 5.48 (d, *J*=2.5 Hz, 1H), 4.69–4.56 (m, 6H), 4.42 (d, *J*=11.5 Hz, 1H), 4.20–4.11 (m, 1H), 4.09–4.04 (m, 1H), 4.02–3.97 (m, 1H), 3.95–3.90 (m, 1H), 3.75 (dd, *J*=9.75, 3.75 Hz, 1H), 3.63 (dd, *J*=9.75, 5.25 Hz, 1H), 3.00 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5, 159.6, 156.4, 146.1, 145.0, 144.9, 139.5, 138.3, 138.2, 137.4, 137.1, 133.34, 133.27, 129.7, 129.1, 128.82, 128.79, 128.7, 128.4, 128.36, 128.32, 128.2, 128.1, 127.9, 127.8, 126.2, 126.1, 119.7, 119.5, 119.3, 107.2, 107.0, 81.3, 77.8, 77.6, 75.0, 74.1, 73.7, 72.1, 71.9, 71.2; IR (NaCl): 3419, 2927, 2360, 1724, 1625, 1073, 697 cm^{-1}; HRMS calcd for $C_{48}H_{45}FNO_5^+$ [M+H$^+$]: 734.3276, found 734.3300.

*4.3.8. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-(6-bromo-2-phenyl quinolin-4-yl)-D-arabinitol (**9h**).* Isolated in 38% yield as a colorless oil; $[\alpha]_D^{22}$ +59.8 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.17–8.06 (m, 4H), 7.80 (dd, *J*=9.0, 2.0 Hz, 1H), 7.57–7.49 (m, 3H), 7.40–7.28 (m, 15H), 7.06 (t, *J*=7.25 Hz, 1H), 6.98 (t, *J*=7.25 Hz, 2H), 6.85 (d, *J*=7.5 Hz, 2H), 5.53 (d, *J*=2.5 Hz, 1H), 4.70–4.62 (m, 3H), 4.61–4.55 (m, 3H), 4.43 (d, *J*=11.5 Hz, 1H), 4.16–4.08 (m, 2H), 3.99–3.96 (m, 1H), 3.93–3.89 (m, 1H), 3.74 (dd, *J*=9.75, 3.75 Hz, 1H), 3.63 (dd, *J*=9.75, 5.25 Hz, 1H), 3.04 (s, 1H); ^{13}C NMR (126 MHz,

$CDCl_3$): δ 157.3, 147.6, 144.7, 139.3, 138.3, 137.4, 137.1, 132.9, 132.6, 129.9, 129.1, 128.79, 128.75, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 126.8, 125.7, 120.6, 119.5, 81.4, 77.5, 77.3, 74.9, 73.9, 73.8, 72.2, 71.9, 71.3; IR (NaCl): 3442, 2927, 2091, 1643, 1072, 697 cm^{-1}; HRMS calcd for $C_{48}H_{45}BrNO_5^+$ [M+H^+]: 794.2476, found 794.2513.

*4.3.9. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-[2-phenyl-6-(trifluoromethyl) quinolin-4-yl]-D-arabinitol (**9j**).* Isolated in 18% yield as a colorless oil; $[\alpha]_D^{22}$ +47.0 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.31 (d, *J*=8.5 Hz, 1H), 8.20 (s, 1H), 8.17–8.14 (m, 2H), 7.91–7.87 (m, 1H), 7.57–7.52 (m, 3H), 7.40–7.29 (m, 13H), 7.27–7.24 (m, 2H), 7.02 (t, *J*=7.25 Hz, 1H), 6.93 (t, *J*=7.5 Hz, 2H), 6.81 (d, *J*=7.5 Hz, 2H), 5.58 (d, *J*=2.5 Hz, 1H), 4.73–4.49 (m, 6H), 4.43 (d, *J*=11.5 Hz, 1H), 4.20–4.14 (m, 1H), 4.10–4.05 (m, 1H), 4.01–3.97 (m, 1H), 3.89–3.84 (m, 1H), 3.70 (dd, *J*=9.75, 3.5 Hz, 1H), 3.58 (dd, *J*=9.75, 5.5 Hz, 1H), 2.99 (d, *J*=4.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0, 150.0, 146.6, 139.1, 138.3, 138.2, 137.3, 137.0, 132.0, 130.2, 129.2, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 128.04, 127.98, 127.9, 125.1, 124.7, 121.6, 119.8, 81.2, 77.5, 77.3, 77.0, 74.9, 73.9, 73.7, 72.3, 71.5; IR (NaCl): 3555, 2927, 1727, 1274, 1073, 698 cm^{-1}; HRMS calcd for $C_{49}H_{45}F_3NO_5^+$ [M+H^+]: 784.3244, found 784.3267.

*4.3.10. (1R)-1,2,3,5-Tetra-O-benzyl-1-C-(6-methoxy-2-phenyl)quinolin-4-yl]-D-arabinitol (**9k**).* Isolated in 56% yield as a colorless oil; $[\alpha]_D^{22}$ +56.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.21–8.13 (m, 4H), 7.54 (t, *J*=7.5 Hz, 2H), 7.53–7.47 (m, 1H), 7.45–7.33 (m, 15H), 7.28–7.24 (m, 2H), 7.14 (t, *J*=7.25 Hz, 1H), 7.07 (t, *J*=7.25 Hz, 2H), 6.99 (d, *J*=7.0 Hz, 2H), 5.58 (d, *J*=3.0 Hz, 1H), 4.70–4.54 (m, 6H), 4.43 (d, *J*=11.5 Hz, 1H), 4.31–4.23 (m, 1H), 4.14–4.07 (m, 2H), 3.90–3.84 (m, 1H), 3.74 (dd, *J*=9.5, 3.5 Hz, 1H), 3.69–3.64 (m, 4H), 3.00 (d, *J*=4.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 154.8, 145.1, 143.8, 139.9, 138.6, 138.3, 137.7, 137.6, 132.3, 129.2, 129.04, 128.96, 128.8, 128.7, 128.6, 128.32, 128.29, 128.2, 128.1, 128.0, 127.9, 127.7, 126.7, 122.0, 119.0, 101.9, 81.9, 77.7, 77.6, 77.1, 75.4, 73.7, 72.2, 71.7, 71.5, 55.6; IR (NaCl): 3418, 2930, 2015, 1622, 1497, 1073, 697 cm^{-1}; HRMS calcd for $C_{49}H_{48}NO_6^+$ [M+H^+]: 746.3476, found 746.3508.

*4.3.11. (2R,3R,4S)-1,3,4-Tris(benzyloxy)-4-(2-phenylquinolin-4-yl) butan-2-ol (**11a**).* Isolated in 57% yield as a colorless oil; $[\alpha]_D^{22}$ −44.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.31–8.27 (m, 2H), 8.21 (d, *J*=7.5 Hz, 2H), 7.98 (d, *J*=8.0 Hz, 2H), 7.78 (t, *J*=7 Hz, 1H), 7.59–7.47 (m, 4H), 7.61–7.14 (m, 10H), 7.07 (t, *J*=7.5 Hz, 1H), 6.98 (t, *J*=7.5 Hz, 2H), 6.76 (d, *J*=7.0 Hz, 2H), 5.69 (s, 1H), 4.75 (d, *J*=12.0 Hz, 1H), 4.56 (s, 2H), 4.41 (d, *J*=12.0 Hz, 1H), 4.31–4.27 (m, 1H), 4.11 (d, *J*=11.0 Hz, 1H), 3.86 (d, *J*=7.5 Hz, 1H,), 3.77–3.65 (m, 3H), 2.70 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.2, 148.8, 145.3, 139.8, 138.0, 137.6, 137.0, 131.0, 129.7, 129.5, 129.3, 129.1, 129.08, 129.02, 128.84, 128.81, 128.79, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 126.7, 125.6, 122.8, 118.5, 80.7, 75.5, 74.8, 73.8, 72.2, 71.3, 70.2; IR (NaCl): 3449, 3027, 2983, 1723, 1597, 1484, 1075, 745, 696 cm^{-1}; HRMS calcd for $C_{40}H_{38}NO_4^+$ [M+H^+]: 596.2801, found 596.2812.

*4.3.12. (2R,3R,4S)-1,3,4-Tris(benzyloxy)-4-[2-(4-fluorophenyl)quinolin-4-yl]butan-2-ol (**11b**).* Isolated in 47% yield as a colorless oil; $[\alpha]_D^{22}$ −43.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J*=8.5 Hz, 1H), 8.21 (s, 1H), 8.19–8.16 (m, 2H), 7.97 (d, *J*=8.5 Hz, 1H), 7.80 (t, *J*=7.5 Hz, 1H), 7.50 (t, *J*=7.5 Hz, 1H), 7.40–7.33 (m, 9H), 7.21 (t, *J*=8.5 Hz, 2H), 7.08 (t, *J*=7.5 Hz, 2H), 6.98 (t, *J*=7.5 Hz, 2H), 6.74 (d, *J*=7.5 Hz, 2H), 5.69 (s, 1H), 4.74 (d, *J*=11.5 Hz, 1H), 4.56 (s, 2H), 4.41 (d, *J*=12.0 Hz, 1H), 4.31–4.27 (m, 1H), 4.12 (d, *J*=11.0 Hz, 1H), 3.84 (dd, *J*=7.75, 1.75 Hz, 1H), 3.7–3.68 (m, 3H), 2.68 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.1, 163.1, 156.1, 148.7, 145.5, 137.9, 137.6, 137.0, 136.0, 130.9, 129.85, 129.78, 129.7, 129.0, 128.83, 127.9, 128.6, 128.5, 128.3, 128.2, 128.0, 126.8, 125.4, 122.7, 118.1, 116.1, 115.9, 80.7, 75.4, 74.8, 73.8, 72.2, 71.3, 70.1; IR (NaCl): 3448, 3030, 2962, 2360, 1724, 1598, 1450, 1073, 737, 698 cm^{-1}; HRMS calcd for $C_{40}H_{37}FNO_4^+$ [M+H^+]: 614.2706, found 614.2707.

*4.3.13. (2R,3R,4S)-1,3,4-Tris(benzyloxy)-4-[2-(4-methoxyphenyl)quinolin-4-yl]butan-2-ol (**11f**).* Isolated in 44% yield as a colorless oil; $[\alpha]_D^{22}$ −31.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.25–8.23 (m, 2H), 8.18 (d, *J*=9.0 Hz, 2H), 7.95 (d, *J*=8.5 Hz, 1H), 7.75 (t, *J*=7.5 Hz, 1H), 7.46 (t, *J*=7.25 Hz, 1H), 7.39–7.33 (m, 10H), 7.08–7.06 (m, 3H), 6.98 (t, *J*=7.5 Hz, 2H), 6.76 (d, *J*=7.5 Hz, 2H), 5.67 (s, 1H), 4.74 (d, *J*=12.0 Hz, 1H), 4.55 (s, 2H), 4.40 (d, *J*=12.0 Hz, 1H), 4.16 (s, 1H), 4.08 (d, *J*=10.5 Hz, 1H), 3.94 (s, 3H), 3.85 (m, 1H), 3.74–3.68 (m, 3H), 2.68 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.1, 156.7, 148.8, 145.0, 138.0, 137.6, 137.0, 132.4, 130.8, 129.4, 129.3, 129.0, 128.82, 128.78, 128.7, 128.4, 128.3, 128.27, 128.24, 127.9, 126.3, 125.3, 122.7, 118.0, 114.4, 80.7, 75.4, 74.8, 73.8, 72.1, 71.3, 70.2, 55.7; IR (NaCl): 3450, 3033, 2927, 1723, 1599, 1453, 1072, 737, 698 cm^{-1}; HRMS calcd for $C_{41}H_{40}NO_5^+$ [M+H^+]: 626.2906, found 626.2918.

*4.3.14. (2R,3R,4S)-1,3,4-Tris(benzyloxy)-4-[6-fluoro-2-phenylquinolin-4-yl]butan-2-ol (**11g**).* Isolated in 49% yield as a colorless oil; $[\alpha]_D^{22}$ −21.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.28–8.21 (m, 2H), 8.16 (d, *J*=7.0 Hz, 2H), 7.63 (d, *J*=9.0 Hz, 1H), 7.58–7.48 (m, 5H), 7.40–7.31 (m, 9H), 7.05 (t, *J*=7.5 Hz, 1H), 6.96 (t, *J*=7.5 Hz, 2H), 6.74 (d, *J*=7.5 Hz, 2H), 5.51 (s, 1H), 4.70 (d, *J*=12.0 Hz, 1H), 4.62–4.51 (m, 2H), 4.39 (d, *J*=12.0 Hz, 1H), 4.28–4.23 (m, 1H), 4.18–4.12 (m, 1H), 3.82–3.65 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6, 159.6, 156.5, 145.9, 145.1, 145.0, 139.4, 137.8, 137.4, 136.8, 133.3, 133.2, 129.7, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 128.25, 128.21, 127.9, 127.8, 126.2, 126.1, 119.8, 119.6, 119.2, 106.9, 106.7, 80.5, 76.0, 74.7, 73.9, 72.3, 71.1, 70.1; IR (NaCl): 3461, 3031, 2925, 2363, 1723, 1623, 1496, 1072, 738, 697 cm^{-1}; HRMS calcd for $C_{40}H_{37}FNO_4^+$ [M+H^+]: 614.2706, found 614.2731.

*4.3.15. (5R)-1,2,3,5-Tetra-O-benzyl-5-C-(2-phenylquinolin-4-yl)-D-arabinitol (**13a**).* Isolated in 51% yield as a colorless oil; $[\alpha]_D^{22}$ −6.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.22 (s, 1H), 8.16 (d, *J*=6.5 Hz, 2H), 8.03 (s, 1H), 7.79 (t, *J*=7.5 Hz, 1H), 7.58–7.48 (m, 4H), 7.40–7.27 (m, 13H), 7.20 (d, *J*=6.5 Hz, 2H), 7.08 (t, *J*=7.5 Hz, 1H), 6.99 (t, *J*=7.5 Hz, 2H), 6.90 (d, *J*=7.0 Hz, 2H), 5.56 (s, 1H), 4.70 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 4.46–4.42 (m, 2H), 4.34–4.22 (m, 3H), 4.09–4.07 (m, 2H), 3.83–3.76 (m, 1H), 3.68–3.63 (m, 1H), 3.58–3.53 (m, 1H), 2.56 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9, 138.2, 138.1, 137.6, 137.0, 130.6, 129.9, 129.1, 128.80, 128.77, 128.74, 128.7, 128.3, 128.25, 128.19, 128.1, 128.0, 127.9, 127.0, 125.6, 122.9, 118.6, 80.4, 78.0, 77.3, 75.4, 74.3, 73.5, 71.7, 71.6, 69.5; IR (NaCl): 3674, 2835, 2364, 2015, 1724, 1598, 1073, 697 cm^{-1}; HRMS calcd for $C_{48}H_{46}NO_5^+$ [M+H^+]: 716.3371, found 716.3405.

*4.3.16. (5R)-1,3,4,5-Tetra-O-benzyl-5-C-[2-(4-fluorophenyl)quinolin-4-yl]-D-arabinitol (**13b**).* Isolated in 48% yield as a colorless oil; $[\alpha]_D^{22}$ −6.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, *J*=8.5 Hz, 1H), 8.15–8.06 (m, 3H), 8.02 (s, 1H), 7.78 (t, *J*=7.75 Hz, 1H), 7.53 (t, *J*=7.75 Hz, 1H), 7.40–7.27 (m, 13H), 7.23–7.16 (m, 4H), 7.08 (t, *J*=7.0 Hz, 1H), 7.00 (t, *J*=7.5 Hz, 2H), 6.89 (d, *J*=7.5 Hz, 2H), 5.56 (s, 1H), 4.67 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=12.0 Hz, 1H), 4.55–4.39 (m, 3H), 4.33–4.27 (m, 2H), 4.27–4.21 (m, 1H), 4.13–4.03 (m, 2H), 3.75–3.71 (m, 1H), 3.67–3.64 (m, 1H), 3.58–3.55 (m, 1H), 2.55 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.2, 163.2, 155.8, 138.2, 137.6, 137.1, 130.7, 129.9, 128.8, 128.74, 128.69, 128.6, 128.3, 128.25, 128.19, 128.1, 128.0, 127.9, 127.0, 125.5, 123.6, 118.2, 116.1, 115.9, 80.5, 78.0, 77.3, 75.4, 74.4, 73.6, 71.8, 71.6, 69.5; IR (NaCl): 3549, 2915, 2360, 1725, 1503, 1080, 697 cm^{-1}; HRMS calcd for $C_{48}H_{45}FNO_5^+$ [M+H^+]: 734.3276, found 734.3306.

*4.3.17. (5R)-1,3,4,5-Tetra-O-benzyl-5-C-(6-fluoro-2-phenylquinolin-4-yl)-D-arabinitol (**13g**).* Isolated in 45% yield as a colorless oil; $[\alpha]_D^{22}$

−5.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.25–8.21 (m, 1H), 8.18 (s, 1H), 8.14–8.10 (m, 2H), 7.67 (br s, 1H), 7.55–7.49 (m, 4H), 7.40–7.27 (m, 13H), 7.19 (d, *J*=7.0 Hz, 2H), 7.07 (t, *J*=6.75 Hz, 1H), 7.00 (t, *J*=7.5 Hz, 2H), 6.91 (d, *J*=7.0 Hz, 2H), 5.36 (s, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.56 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 4.47–4.42 (m, 2H), 4.28–4.21 (m, 3H), 4.07 (d, *J*=7.5 Hz, 1H), 4.00 (d, *J*=9.0 Hz, 1H), 3.81 (d, *J*=10.5 Hz, 1H), 3.66–3.62 (m, 1H), 3.57–3.53 (m, 1H), 2.58–2.54 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.4, 146.1, 144.7, 139.4, 138.2, 138.1, 137.5, 137.0, 133.42, 133.38, 129.7, 129.1, 128.81, 128.76, 128.7, 128.4, 128.2, 128.1, 128.08, 128.02, 127.7, 119.9, 119.6, 119.1, 82.2, 80.3, 77.9, 75.4, 74.3, 73.5, 71.7, 71.6, 69.4; IR (NaCl): 3543, 2913, 2360, 1724, 1524, 1073, 697 cm^{-1}; HRMS calcd for $C_{48}H_{45}FNO_5^+$ [M+H^+]: 734.3276, found 734.3307.

4.4. Representative example of the general procedure for the preparation of perhydroxylated open-ring glycosylidene-derived quinolines

To a solution of perbenzylated intermediate **9a** (70 mg; 0.098 mmol) in dichloromethane (2.0 mL) 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 1 h, additional BCl_3 (1 M in hexane; 0.195 mL; 0.195 mmol) was introduced, and the reaction was maintained at −78 °C for 1 h. The reaction was quenched with the addition of methanol (2.0 mL). The crude material was concentrated in vacuo. The residue was coevaporated twice with methanol, and then purified with a mass directed reverse phase preparative HPLC system. The following chromatographic conditions were used: (a) column: Waters XbridgeC-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 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. The resulting fractions that contained the desired compound **14a** were lyophilized.

*4.4.1. (1R)-1C-(2-Phenylquinolin-4-yl)-D-arabinitol (**14a**).* Isolated in 69% yield as a white solid; mp 178–180 °C; $[\alpha]_D^{22}$ +22.3 (*c* 1.0, CH_3OH); ^1H 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; IR (NaCl): 3631, 2822, 1794, 1599, 1554, 1415, 1027, 697 cm^{-1}; HRMS calcd for $C_{20}H_{22}NO_5^+$ [M+H^+]: 356.1492, found 356.1496.

Compounds **14b**, **15a**, and **16a** were prepared in a manner analogous to **14a.**

*4.4.2. (1R)-1C-[2-(4-Fluorophenyl)quinolin-4-yl]-D-arabinitol (**14b**).* Isolated in 63% yield as a white solid; mp 188–189 °C; $[\alpha]_D^{22}$ +22.0 (*c* 0.5, CH_3OH); ^1H NMR (CD_3OD): δ 8.32 (d, *J*=8.5 Hz, 1H), 8.23–8.17 (m, 3H), 8.13 (d, *J*=8.5 Hz, 1H), 7.76 (t, *J*=7.25 Hz, 1H), 7.60 (t, *J*=7.5 Hz, 1H), 7.29 (t, *J*=8.75 Hz, 2H), 5.72 (d, *J*=5.0 Hz, 1H), 4.24 (dd, *J*=5.0, 2.0 Hz, 1H), 3.78–3.72 (m, 2H), 3.58 (dd, *J*=8.0, 2.0 Hz, 1H), 3.53–3.50 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD): δ 156.4, 149.7, 148.3, 129.8, 129.7, 129.6, 129.3, 126.4, 125.2, 123.8, 117.8, 115.5, 115.3, 72.9, 72.4, 71.9, 71.6, 63.6; IR (NaCl): 3630, 2820, 1793, 1598, 1554, 1503, 1412, 1027, 697 cm^{-1}; HRMS calcd for $C_{20}H_{21}FNO_5^+$ [M+H^+]: 374.1404, found 374.1417.

*4.4.3. (1S,2S,3R)-1-(2-Phenylquinolin-4-yl)-butane-1,2,3,4-tetrol (**15a**).* Isolated in 64% yield as a white solid; mp 175–176 °C; $[\alpha]_D^{22}$ −16.6 (*c* 0.5, CH_3OH); ^1H NMR (500 MHz, CD_3OD): δ 8.28 (s, 1H), 8.18 (d, *J*=8.50 Hz, 1H), 8.15 (d, *J*=8.5 Hz, 3H), 7.76 (t, *J*=7.25 Hz, 1H), 7.60 (t, *J*=7.25 Hz, 1H), 7.56 (t, *J*=7.5 Hz, 2H), 7.50 (t, *J*=7.25 Hz, 1H), 5.99 (s, 1H), 4.00–3.95 (m, 1H), 3.88 (dd, *J*=11.5, 3.5 Hz, 1H), 3.78 (d, *J*=9.0 Hz, 1H), 3.70 (dd, *J*=11.5, 5.5 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD): δ 157.6, 150.8, 148.0, 140.0, 129.3, 129.3, 128.7, 127.7, 126.3, 124.8, 123.1, 117.7, 73.8, 72.0, 67.6, 64.0; IR (NaCl): 3632, 2821, 1794, 1599, 1553, 1505, 1415, 1027, 697 cm^{-1}; HRMS calcd for $C_{19}H_{20}NO_4^+$ [M+H^+]: 326.1392, found 326.1402.

*4.4.4. (5R)-5-C-(2-Phenylquinolin-4-yl)-D-arabinitol (**16a**).* Isolated in 60% yield as a white solid; mp 158–162 °C; $[\alpha]_D^{22}$ −4.8 (*c* 0.5, CH_3OH); ^1H NMR (500 MHz, CD_3OD): δ 8.29 (s, 1H), 8.20 (d, *J*=8.0 Hz, 1H), 8.17–8.14 (m, 3H), 7.76 (t, *J*=8.25 Hz, 1H), 7.62–7.54 (m, 3H), 7.52–7.48 (m, 1H), 6.01 (s, 1H), 4.01–3.92 (m, 3H), 3.74–3.70 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD): δ 157.6, 151.2, 148.0, 140.0, 129.3, 129.2, 128.7, 127.8, 126.3, 124.8, 123.2, 117.7, 115.3, 72.9, 70.7, 70.6, 67.5, 64.0; IR (NaCl): 3630, 2823, 1795, 1599, 1555, 1415, 1027, 697 cm^{-1}; HRMS calcd for $C_{20}H_{22}NO_5^+$ [M+H^+]: 356.1492, found 356.1506.

Acknowledgements

P.H.D. gratefully acknowledges Merck Research Laboratories, Rahway, NJ for financial support. P.H.D. also thanks the following scientists from Merck Research Laboratories: Dr. George A. Doss and Dr. Mikhail Reibarkh for their assistance with NMR experiments, Dr. R. Scott Hoerrner for assistance with high pressure hydrogenolysis experiments, Dr. Charles W. Ross III and Kithsiri B. Herath for HRMS analysis, Eric C. Streckfuss for chromatography suggestions, Dorothy A. Levorse for salt stoichiometry analysis, and Dr. Vincent J. Colandrea for useful conversations. P.H.D. expresses gratitude to Prof. David W. C. MacMillan of Princeton University for insightful discussions of mechanistic principles. The authors recognize the National Cancer Institute for testing compounds in the 60 human tumor cell line screen.

Supplementary data

Characterization data and ^1H and ^{13}C NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.077.

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32. The monohydrochloride **14a HCl Salt** was easily formed in quantitative yield by treatment of **14a** with excess hydrogen chloride in diethyl ether (1 M solution). The salt stoichiometry was determined by potentiometric titration to be 1:1.