DDQ-Induced, Anomeric Specific, and Diastereoselective Benzylic Glycosidation: A Novel Approach to Heterocyclic Anthracycline Antibiotics

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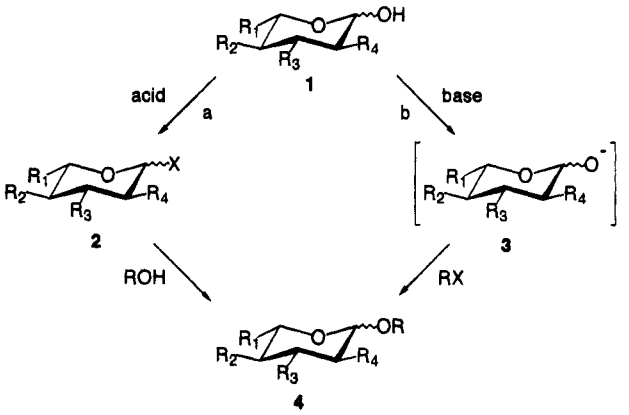
A novel and efficient method for the oxidative glycosidation at the heterosubstituted benzylic positions with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is described. The reaction is stereospecific with 3-substituted isochromans and isothiochroman, as well as diastereoselective with non-3-substituted isochromans. The glycosidation with a mixture of α- and β-anomeric free sugars gives α-glycosides with absolute stereochemical control on the anomeric center. The synthetic utility of this novel methodology is demonstrated by a short, efficient, and stereoselective total synthesis of heteroanthracycline antitumor reagents.

The efficient construction of glycosidic bonds in a stereocontrolled manner bears heavily on the successful synthesis of a number of naturally occurring glycosides such as anthracyclines,[1] erythromycin,[2] and calicheamicin,[3] which exhibit important biological activities. Consequently, an assortment of methods have been developed for achieving such glycosidic linkage.[4] As summarized by Schmidt,[4c] these chemical methods can be generally divided into two pathways (a and b) as depicted in Scheme 1. In the modified Koenigs–Knorr approach (a),[5] the glycosyl donor is activated through the formation of intermediates **2** (X = Br, Cl, etc.), and its subsequent

Scheme 1



reaction with glycosyl acceptor (ROH) in the presence of catalyst provides glycoside **4.** In approach b, glycoside **4** is formed from the alkylation reaction of anomeric alkoxide **3** with a glycosyl acceptor RX.[4c,6] Both method a and b require either strong acid or base to activate the protected sugar, which are sometimes sensitive to such conditions.

Recently, we have reported that the reaction of heteroatom-substituted benzylic substrate **5** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) can form charge transfer complex **6** (Scheme 2), a highly reactive intermediate, which could undergo coupling reactions with a variety of nucleophiles, including alcohols, silyl enol ethers, allyl tins, allylsilane, alkyl Grignard and organolithium compounds.[7] We realized that the extension of this chemistry by employing carbohydrates as nucleophiles would constitute a novel methodology to prepare benzylic glycosides. The effort to undertake such investigation was further warranted by the following interesting aspects associated with this reaction: First of all, glycosidation using a nonactivated glycosyl donor such as **1** and an activated glycosyl acceptor **6** is conceptually new. Secondly, anomeric selectivity is particularly challenging on

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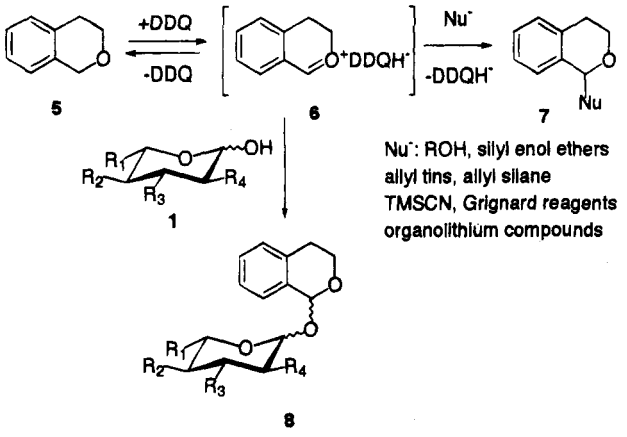
Scheme 2



the basis of the fact that most anomeric free sugars (hydroxy at anomeric center is not protected) exist in a mixture of α- and β-forms. Third, this glycosidation presents the opportunity to study the diastereoselectivity deriving from the newly generated chiral center at benzylic position by the introduction of a chiral sugar. Herein, we wish to report the results of this novel and oxidative benzylic glycosidation methodology, and also the application of this method to the synthesis of heterocyclic anthracycline antitumor reagent.

Results and Discussion

A. Glycosidation with 3-Substituted Isochromans and Isothiochroman. We began to investigate this glycosidation with 3-substituted isochromans because it has been previously demonstrated that incoming nucleophiles preferentially reside at the activated benzylic position *trans* to the 3-substituted group.[7] When the racemic isochroman **9a**[8] was treated with a 1:1 mixture of α- and β-anomers of 3,4-di-*O*-acetyl-2,6-dideoxy-L-*lyxo*-hexopyranose (**10a**)[9] (1.1 equiv) in the presence of 1.1 equiv of DDQ (Scheme 3), oxidative glycosidation took place smoothly and was completed at room temperature in 24 h to give two *trans* diastereomeric α-glycosides **11a** and **11b** (1:1), in 88% isolated yield, and two *trans* diastereomeric β-glycosides **12a** and **12b** (1:1), in 2% yield. The reaction is stereospecific at the benzylic center with the sugar bonded *trans* to the acetyl group, which is consistent with previous observation.[7] Interestingly, the α-glycosides were formed preferentially over the β (**11/12** = 44:1), even though a 1:1 mixture of α and β free sugar was employed.

In order to understand the mechanism of this observed anomeric selectivity, it was essential to determine first whether the selectivity of this reaction was kinetically or thermodynamically controlled. Therefore, the same reaction was carried out again with a longer reaction time (48 h). Surprisingly, diastereomeric α-glycosides **11a** and **11b** (1:1) were obtained exclusively in 93% yield, and no β-glycosides were detected (Table 1). The same results were obtained when the reaction was carried out at elevated temperature (40 °C) for 20 h. These observations not only extended the synthetic potential of this methodology, which allows stereoselective synthesis of α-glycosides, but also indicated that the anomeric selectivity was a thermodynamically-controlled process. Fur-

Scheme 3

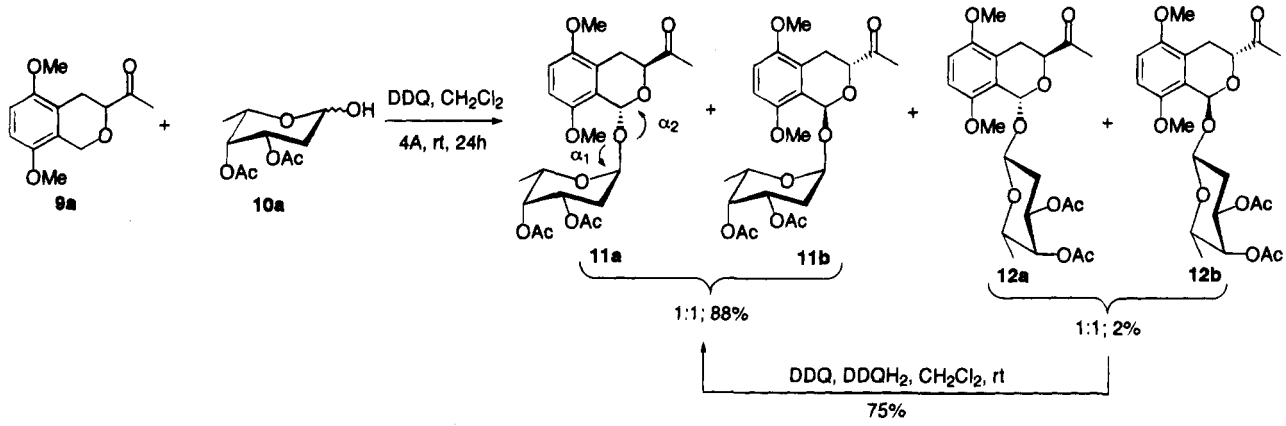
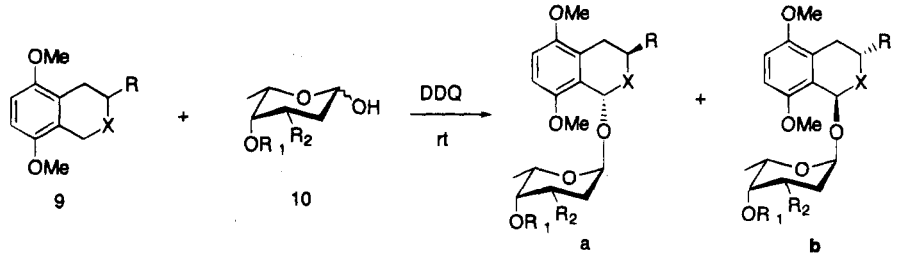


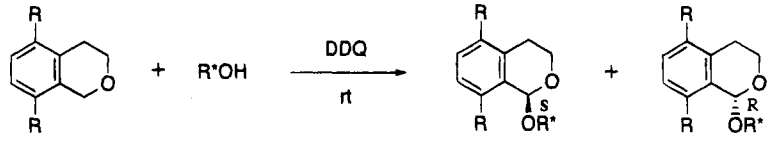
Table 1. DDQ-Induced Stereoselective Glycosidation with 3-Substituted Isochromans and Isothiochroman



entry	X	R	isochromans	R_1	R_2	sugar (α/β)	t(h)	product and ratio	yield (%)
1	O	Ac	**9a**	Ac	OAc	**10a** (1:1)	48	**11a/11b** (1:1)	93
2	S	Ac	**9b**	Ac	OAc	**10a** (1:1)	2	**13a/13b** (3:2)	79
3	S	Ac	**9b**	$-C(CH_3)_2O-$		**10b** (5:1)	2	**14a/14b** (2:1)	63
4	O	Me	**9c**[a]	PNB	$NHCOCF_3$	**10c** (1:1)	48	**15b**[b]	99

[a] Isochroman **9c** is chiral with *S* configuration at position 3. [b] Only one diastereoisomer was obtained.

Table 2. DDQ-Induced Diastereoselective Glycosidation with Non-3-Substituted Isochromans



16
a, R=H; **b**, R=OMe

a **b**

entry	isochroman	R*OH	conditions	product and ratio	yield (%)
1	**16a**	**10a**	rt, 48 h	**17a/17b** (92:8)	87
2	**16a**	**10c**	40 °C, 24 h	**18a/18b** (85:15)	86
3	**16b**	**10a**	rt, 48 h	**19a/19b** (88:12)	95
4	**16b**	**10c**	40 °C, 24 h	**20a/20b** (86:14)	99
5	**16a**	(+)-neomenthol	rt, 48 h	**21a/21b** (50:50)	76

ther support for this thermodynamic-controlled α-selectivity was evidenced by the fact that the mixture of β-glycosides **12a** and **12b** (1:1) could be converted to a mixture of α-glycosides **11a** and **11b** (1:1) exclusively in 75% yield under the conditions (DDQ, $DDQH_2$, CH_2Cl_2) that mimic the original glycosidation (Scheme 3). The thermodynamic driving force for the α-anomeric selectivity, and the *trans* specificity as well,[7] can be explained by structure **11a** as shown. The bis ketal configuration is displayed with the anomeric carbons preferring axial orientation in order to gain the stabilization energy resulting from two exo-anomeric effects (α_1 and α_2).[10] The stereochemistry of α-glycosides was confirmed by the coupling constant of the anomeric proton (1′-H, doublet, $J = 0-3.2$ Hz).[11]

Glycosidations of isochromans and isothiochroman[12] with different sugars are presented in Table 1. Taking advantage of the thermodynamic selectivity, all reactions were carried out with longer reaction time to avoid the isolation of β-glycosides. It is interesting to note that reactions with isothiochroman proceed much faster than that with its oxygen analog. This can probably be explained by the higher electrophilicity of the intermediate DDQ/isothiochroman charge transfer complex. At the same time, we observed that glycosides with isothiochroman are less stable than their oxygen analogs, which likely accounted for the lower yields associated with these reactions. Since this glycosidation employs virtually neutral conditions, both acid- and base-sensitive functional groups presented on reactants such as ketal on sugar **10b**[13] and esters on sugars **10a** and **10c**[13] were well tolerated. The glycosidation of chiral isochroman **9c**[13] with sugar **10c** gave a single compound of *trans* α-glycoside **15b** as an optically pure isomer in 99% yield.

B. Glycosidation with 3-Nonsubstituted Isochromans. Assuming the same anomeric selectivity could be retained, it was expected that glycosidation of nonsubstituted isochromans would generate a 1:1 mixture of two diastereoisomers (α-glycosides) resulting from the attack of the anomeric hydroxy functionality on both faces of isochroman. To our surprise, the glycosidation of isochroman lacking a 3-substituent such as **16a** and **16b** was rather diastereoselective. Table 2 shows examples of highly enhanced diastereoselectivity resulting from selective facial attack at the benzylic position (1−4) by sugars **10a** and **10c**. For example, the asymmetric glycosidation of 5,8-dimethoxyisochroman **16b** with sugar **10a** (entry 3) afforded two α-glycosides **19a** and **19b** in a ratio of 88:12 in 95% isolated yield. The same reaction with daunosamine sugar **10c** (entry 4) gave **20a** and **20b** in a ratio of 86:14 in 99% yield. To determine the benzylic configuration of these glycosides, we failed to obtain X-ray crystallography in several attempted experiments. It was finally determined by correlation of NMR spectroscopic data with structurally known and similar glycosides such as **15b**, **22a**, and **22b**.[14] We found the major diastereoisomers having *S* the configuration at the activated benzylic position and the minor ones with *R* configuration. In all cases, the sugar anomeric configuration was α, as observed previously.

It was further observed that the minor diastereoisomer could be converted to the major diastereoisomer. For example, the treatment of minor isomer **20b** with DDQ in CH_2Cl_2 gave a mixture of **20a** and **20b** in the same ratio (86:14) as the original reaction. Therefore, higher diastereoselectivity can be achieved by repeating this process (97.5:2.5 after one such treatment). Since both **20a** and **20b** have a proton on the activated benzylic position, they could also react with DDQ to form charge transfer complexes. The mechanism for the interconversion of **20a** and **20b** in the presence of DDQ could be explained by the reversible formation between these glycosides and their charge transfer complexes with DDQ. Introduction of two sugars at the activated benzylic position have never been observed; however, lactones sometimes could be formed if the reaction was carried out under nonanhydrous conditions.

In order to probe the origin of the diastereoselectivity, the coupling reaction of isochroman **16a** with (+)-

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(9) Kolar, C.; Dehmul, K.; Moldenhauer, H.; Gerken, M. *J. Carbohydr. Chem.* **1990**, *9* (6), 873.

(10) Anomeric effect can take place only when the electron lone pair of the oxygen is antiperiplanar to an alkoxy group; see: (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag Press: New York, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983.

(11) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2249.

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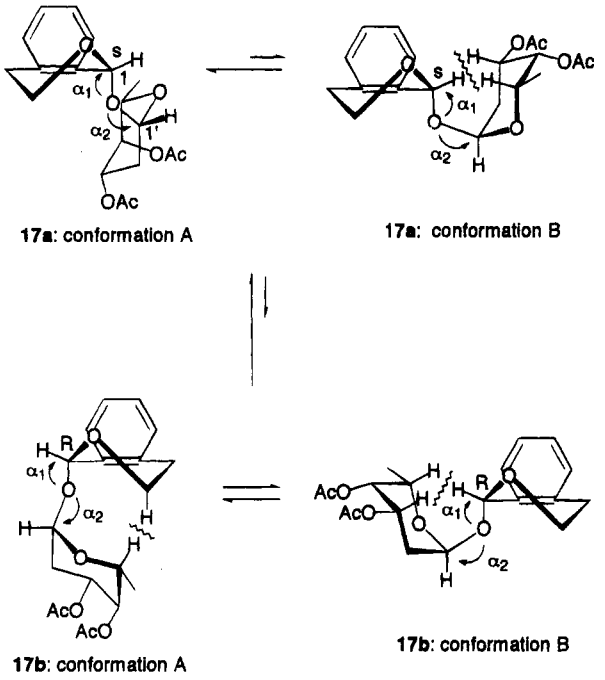
(13) Xu, Y. C.; Lebeau, E. Unpublished results.

(14) The configurations of these two diastereoisomers were determined by comparing their spectroscopic data with structurally known compounds such as **15b**, **22a**, and **22b**, which have a similar glycoside structure. It was observed from ^1H NMR in $CDCl_3$ or benzene-d_6 that the benzylic proton (singlet) of the major isomer (**17a-21a**) is about 0.18 ppm downfield of that of the minor isomer (**17b-21b**), and the 5′-H (quartet) of the major isomer is about 0.30 ppm downfield of that of the minor isomer.

Scheme 4

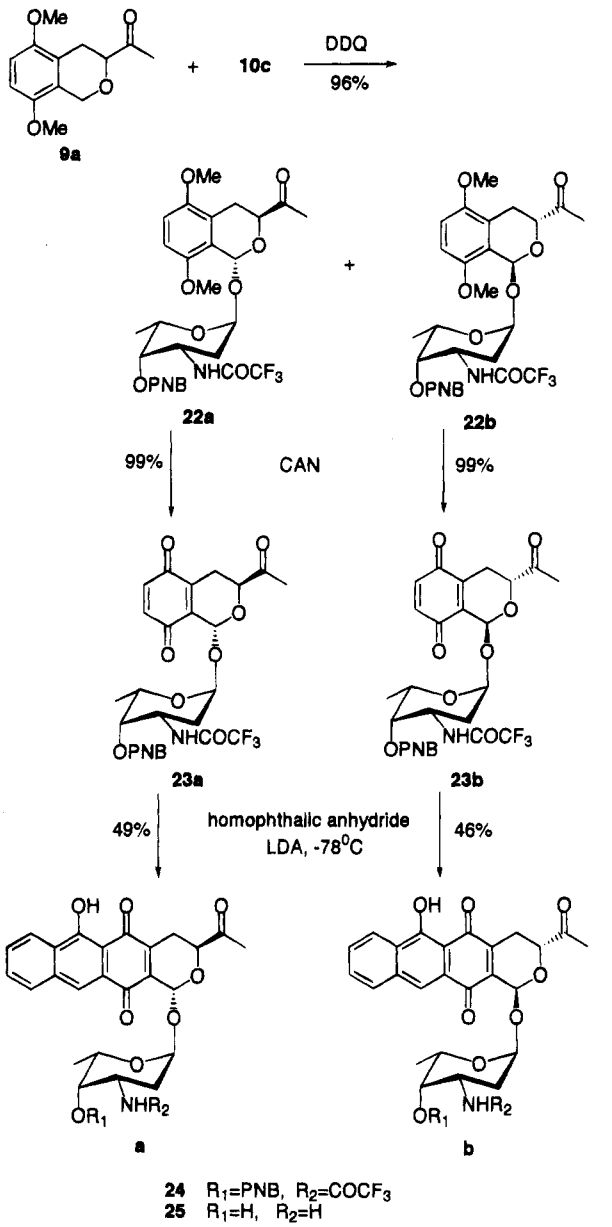


(1*S*,2*S*,5*R*)-neomenthol (entry 5) was investigated. No diastereoselectivity was observed at all (50:50), indicating the ring oxygen is essential to the observed diastereoselectivity.

A possible explanation for the thermodynamically-controlled facial selectivity is proposed by the reversible reactions shown in Scheme 4. First, the sugar can rotate along the C_1—O axial. Only two out of three possible staggered conformations can provide the α_1-anomeric stabilization effect[10] (α_1 is the exo-anomeric effect derived from the interaction of the electron lone pair of the anomeric oxygen and the alkoxy group of isochroman). The staggered conformation with sugar lying under the isochroman ring (not shown) is eliminated because of the highly steric interactions. The structures shown in Scheme 4 are the other staggered conformation with α_1 effect. Secondly, the sugar can rotate along the $C_{1'}$—O axial. Similarly, in order to have the α_2-anomeric stabilization effect[10] (α_2 is the exo-anomeric effect derived from the interaction of the electron lone pair of the anomeric oxygen and the alkoxy group of pyranose), only two staggered conformations (A and B) are possible. As indicated in Scheme 4, conformation A for **17a** does not experience major steric restriction, however, conformation B for **17a** as well as conformation A and B for **17b** have severe steric interactions as shown in the structures. Therefore, the equilibrium lies far toward the conformation A of the major product **17a**, which has *S* configuration at the benzylic center as observed. The loss of the stereoselectivity for neomenthol (entry 5) is consistent with this argument because this chiral cyclohexanol does not have the ring oxygen, which can no longer provide the α_2-anomeric effect.

C. Synthesis of Heterocyclic Anthracycline Antitumor Reagent. The synthetic utility of the DDQ-induced oxidative glycosidation is illustrated by the synthesis of 5-deoxypyranoanthracycline **24a** and **24b**, novel analogs of the anticancer drug idarubicin (Scheme 5). Heterocyclic anthracyclines **25a** and **25b** have recently been reported to possess a potent and broad

Scheme 5



spectrum of antitumor activity.[8,16] The synthetic approach to this type of molecule has recently appeared in the literature.[15] Glycosidation of isochroman **9a** with daunosamine **10c** proceeded smoothly in refluxing dichloromethane to afford two 1,3-*trans* α-glycosides **22a** and **22b** in 96% isolated yield in 1:1 ratio. These two glycosides could be separated by two successive conventional flash chromatography purifications. Oxidative demethylation of **22a** with ceric ammonium nitrate in the presence of $NaHCO_3$ gave rise to pyranoquinones **23a** in almost quantitative yield. Treatment of **23a** with the lithium enolate of homophthalic anhydride[17] gave a 49%

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(16) (a) Attardo, G.; Courchesne, M.; Xu, Y. C.; Rej, R.; Lavallee, J.-F; Lebeau, E.; Kraus, K.; Lamothe, S.; Nguyen, D.; Wang, W.; St-Denis, Y.; Belleau, B. Carbohydrate Chemistry #12; presented at the 205th National Meeting of the American Chemical Society, Denver, CO, 1993. (b) Lavallee, J.-F; Rej, R.; Courchesne, M.; Nguyen, D.; Attardo, G. Carbohydrate Chemistry #34; presented at the 205th National Meeting of the American Chemical Society, Denver, CO, 1993. (c) Lebeau, E.; Attardo, G.; Xu, Y. C. Carbohydrate Chemistry #35; presented at the 205th National Meeting of the American Chemical Society, Denver, CO, 1993.

isolated yield of a yellow crystalline product that was found to be identical to the heterocyclic anthracycline analog **24a** reported recently.[15] Similarly, oxidative demethylation of **22b** followed by treatment with homophthalic anhydride in the presence of LDA afforded another tetracyclic analog, **24b**, which has spectral data identical as reported.[15]

In conclusion, we have reported a novel and efficient method to prepare heterosubstituted benzylic glycosides. The advantages of this DDQ-mediated glycosidation are high yields, high diastereoselectivity, and anomeric selectivity, as well as the neutral conditions employed, which can accommodate a variety of functional groups. The direct oxidative introduction of the sugars is another interesting feature of this glycosidation because it does not require the glycosyl acceptor in its higher oxidation stage. The synthetic utility of this novel reaction has been demonstrated by the efficient synthesis of heterocyclic anthracycline antibiotics.

Experimental Section

General. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined in open capillary tubes using a IA9000 Digital Melting Point Apparatus and are uncorrected. Routine ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AM 250 and Varian Gemini 300 spectrometers. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer. High-resolution mass spectra (HRMS) were run by Centre Regional de Spectrometrie de Masse at Universite de Montreal, Quebec, Canada. Elemental analysis were carried out by Galbraith Labs, Inc., Knoxville, TN. All reactions requiring anhydrous conditions were performed under a positive pressure of argon.

Representative Procedure for DDQ-Induced Glycosidation: Glycosidation of Isochroman 9a with Sugar 10a. To a stirred solution of isochroman **9a** (253.0 mg, 1.07 mmol) in 10 mL of anhydrous CH_2Cl_2 were added **10a** (α/β = 1:1; 273.6 mg, 1.18 mmol), DDQ (267.3 mg, 1.18 mmol), and molecular sieves (200 mg). After the mixture was stirred at room temperature under argon for 24 h, 20 mL of aqueous $NaHCO_3$ solution (5%) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried and evaporated. The residue was purified by flash chromatography with hexanes and ethyl acetate (1:1, v/v) to give two *trans* diastereomeric α-glycosides **11a** and **11b** (1:1; 440.1 mg, 88%) and two *trans* diastereomeric β-glycosides **12a** and **12b** (1:1; 10.1 mg, 2%). When the same reaction was repeated at room temperature with a longer reaction time (48 h) or at 40 °C for 20 h, respectively, the two *trans* diastereomeric α-glycosides **11a** and **11b** were obtained in 93% yield, and no β-glycosides **12a** and **12b** were detected by ^1H NMR in both cases.

11a and **11b.** The two *trans* diastereoisomers were separated by HPLC using hexanes and ethyl acetate (7:3, v/v) as eluent. Fast-running isomer: mp 168.5–169.5 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (d, 3H, J = 6.6 Hz), 1.70–2.20 (m, 2H), 1.95 (s, 3H), 2.17 (s, 3H), 2.30 (s, 3H), 2.54 (dd, 1H, J = 17.6, 12.2 Hz), 3.05 (dd, 1H, J = 17.7, 4.3 Hz), 3.78 (s, 6H), 4.50–4.62 (m, 2H), 5.16–5.28 (m, 2H), 5.55 (d, 1H, $-OC_1HO-$, J = 3.0 Hz), 6.19 (s, 1H, $-OC_1HO-$), 6.70 (d, 1H, J = 9.0 Hz), 6.78 (d, 1H, J = 9.0 Hz); IR (neat) 2998m, 2947m, 2839m, 1745s, 1720s, 1486s, 1368m, 1260s, 1094s, 976m cm^{-1}; HRMS for $C_{23}H_{30}O_{10}$ calcd 466.1839, found 466.1825. Slow-running isomer: mp 61.5–62.5 °C; ^1H NMR ($CDCl_3$, 250 M Hz) δ 1.14 (d, 3H, J = 6.4 Hz), 1.90–2.20 (m, 2H), 1.96 (s, 3H), 2.16 (s, 3H), 2.32 (s, 3H), 2.50 (dd, 1H, J = 17.5, 12.3 Hz), 3.08 (dd, 1H, J = 17.5, 3.9 Hz), 3.78 (s, 6H), 4.19 (q, 1H, J = 6.5 Hz), 4.57 (dd, 1H, J = 12.3, 4.0 Hz), 5.17–5.29 (m, 2H), 5.54 (d, 1H, $-OC_1HO-$, J = 2.7 Hz), 5.98 (s, $-OC_1HO-$, 1H), 6.70 (d, 1H, J = 8.9 Hz), 6.77 (d, 1H, J = 8.8 Hz); IR (neat) 2992m, 2948s, 1748s, 1718s, 1487s, 1367m, 1269s, 1198m, 980m cm^{-1}; HRMS for $C_{23}H_{30}O_{10}$ calcd 466.1839, found 466.1837. Elemental analysis was carried out on 1:1 mixture of the two diastereomeric isomers. Anal. Calcd for $C_{23}H_{30}O_{10}$: C, 59.22; H, 6.48. Found: C, 58.97; H, 6.70.

12a and **12b.** Due to a small quantity of the two β-diastereoisomers isolated from the reaction, the separation of this mixture was found to be difficult by conventional flash chromatography; however, enriching one of the two isomers (about 80:20) could be achieved after two successive flash chromatography purifications using hexanes and ethyl acetate (7:3, v/v). The following proton NMR spectral data were deduced from the enriched mixture. Fast-running isomer: ^1H NMR ($CDCl_3$, 250 Hz) δ 1.23 (d, 3H, J = 6.1 Hz), 1.85–2.16 (m, 2H), 1.99 (s, 3H), 2.12 (s, 3H), 2.31 (s, 3 H), 2.55 (dd, 1H, J = 17.7, 12.1 Hz), 3.08 (dd, 1H, J = 17.6, 4.5 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 4.64 (dd, 1H, J = 12.4, 4.7 Hz), 4.95–5.45 (m, 4H), 6.25 (s, 1H), 6.71 (d, 1H, J = 8.8 Hz), 6.75 (d, 1H, J = 8.8 Hz). Slow-running isomer: ^1H NMR ($CDCl_3$, 250 Hz) δ 1.15 (d, 3H, J = 6.2 Hz), 1.85–2.16 (m, 2H), 2.00 (s, 3H), 2.12 (s, 3H), 2.32 (s, 3 H), 2.54 (dd, 1H, J = 17.7, 12.1 Hz), 3.08 (dd, 1H, J = 17.6, 4.5 Hz), 3.78 (s, 3H), 3.80 (s, 3H), 4.79 (dd, 1H, J = 12.6, 4.8 Hz), 4.95–5.45 (m, 4H), 6.02 (s, 1H), 6.69 (d, 1H, J = 8.9 Hz), 6.74 (d, 1H, J = 8.8 Hz). The following spectral data were collected on the 1:1 mixture of **12a** and **12b**: IR (neat) 2940m, 1746s, 1710s, 1607m, 1487s, 1367m, 1264m, 1222m, 1095s, 1071m, 1041m, 974m cm^{-1}; mass spectrum m/e (% rel intensity) 466 M^+ (6), 252 (5), 235 (30), 209 (15), 191 (15), 155 (30), 95 (100); HRMS for $C_{23}H_{30}O_{10}$ calcd 466.1839, found 466.1827.

Conversion of 12 to 11. To a stirred solution of two *trans* β-glycosides **12a** and **12b** (1:1; 32.3 mg, 0.069 mmol) in 3 mL of dry CH_2Cl_2 were added DDQ (16.0 mg, 0.070 mmol) and $DDQH_2$ (16.4 mg, 0.071 mmol). After the mixture was stirred at room temperature for 14 h, an aqueous solution of $NaHCO_3$ (5%) was added. The reaction was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic solvents were dried and evaporated to a residue that was purified by flash chromatography using hexanes and ethyl acetate (1:1 v/v) to give two *trans* α-glycosides, **11a** and **11b** (1:1, 24.3 mg, 75%).

Glycosidation of Isothiochroman 9b with Sugar 10a. Following the previously described general procedure, the DDQ-assisted glycosidation of isothiochroman **9b** (258.0 mg, 1.02 mmol) with anomeric free sugar **10a** (272.4 mg, 1.17 mmol) was completed at room temperature in 2 h, yielding two *trans* diastereomeric α-glycosides, **13a** and **13b** (389.1 mg, 0.81 mmol), in 79% yield after purification by flash chromatography (hexanes and ethyl acetate, 7:3, v/v). The two *trans* diastereoisomers could not be separated by conventional flash chromatography. The ratio of these two isomers was found to be 3:2 by proton NMR. The following spectral data were recorded on the mixture. Major isomer: ^1H NMR ($CDCl_3$, 250 Hz) δ 1.20 (d, 3H, J = 6.2 Hz), 1.70–2.30 (m, 2H), 1.94 (s, 3H), 2.20 (s, 3H), 2.29 (s, 3 H), 2.98 (dd, 1H, J = 16.5, 10.5 Hz), 3.28 (dd, 1H, J = 16.5, 5.1 Hz), 3.80 (s, 6H), 4.14 (dd, 1H, J = 10.5, 5.1 Hz), 4.42 (q, 1H, J = 6.3 Hz), 5.10–5.25 (m, 2H), 5.65 (d, 1H, J = 3.2 Hz), 6.27 (s, 1H), 6.72 (d, 1H, J = 9.8 Hz), 6.81 (d, 1H, J = 9.8 Hz). Minor isomer: ^1H NMR ($CDCl_3$, 250 Hz) δ 1.19 (d, 3H, J = 6.2 Hz), 1.70–2.30 (m, 2H), 1.95 (s, 3H), 2.19 (s, 3H), 2.34 (s, 3 H), 2.96 (dd, 1H, J = 16.5, 10.5 Hz), 3.30 (dd, 1H, J = 16.5, 5.1 Hz), 3.81 (s, 6H), 4.22 (dd, 1H, J = 10.5, 5.1 Hz), 4.42 (q, 1H, J = 6.3 Hz), 5.10–5.25 (m, 2H), 5.50 (d, 1H, J = 3.2 Hz), 6.03 (s, 1H), 6.70 (d, 1H, J = 9.8 Hz), 6.79 (d, 1H, J = 9.8 Hz); IR (neat) 2949s, 1748s, 1709s, 1602m, 1476s, 1368m, 1255s, 1084s, 1021m, 975m, 941m, 799m, 731m cm^{-1}; HRMS for $C_{23}H_{30}O_9S$ calcd 482.1611, found 482.1616.

Glycosidation of Isothiochroman 9b with Sugar 10b. Following the previously described general procedure, the DDQ-assisted glycosidation of isothiochroman **9b**[12] (84.2 mg, 0.33 mmol) with anomeric unprotected sugar **10b**[13] (74.7 mg, 0.40 mmol) was completed at room temperature in 2 h, yielding two *trans* diastereomeric α-glycosides, **14a** and **14b** (91.1 mg, 0.208 mmol), in 63% yield after purification by flash chromatography (hexanes and ethyl acetate, 7:3, v/v). The two

(17) Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, *49*, 473.

diastereoisomers (2:1) were difficult to separate by conventional flash chromatography and gradually decomposed at room temperature. The following spectral data were collected on the mixture of two diastereoisomers. Major isomer: ^{1}H NMR ($CDCl_3$, 250 Hz) δ 1.30 (d, 3H, J = 6.5 Hz), 1.32 (s, 3H), 1.50 (s, 3H), 1.72 (m, 1H), 2.19 (m, 1H), 2.29 (s, 3H), 2.98 (dd, 1H, J = 16.4, 10.3 Hz), 3.24 (dd, 1H, J = 16.4, 5.0 Hz), 3.78 (s, 6H), 4.02 (m, 3H), 4.46 (m, 1H), 5.60 (t, 1H, J = 5.8 Hz), 6.40 (s, 1H), 6.77 (m, 2H). Minor isomer: ^{1}H NMR ($CDCl_3$, 250 Hz) δ 1.24 (d, 3H, J = 6.5 Hz), 1.31 (s, 3H), 1.49 (s, 3H), 1.73 (m, 1H), 2.20 (m, 1H), 2.30 (s, 3H), 2.98 (dd, 1H, J = 16.4, 10.3 Hz), 3.26 (dd, 1H, J = 16.4, 5.1 Hz), 3.80 (s, 6H), 4.04 (m, 3H), 4.45 (m, 1H), 5.46 (m, 1H), 6.49 (s, 1H), 6.77 (m, 2H); IR (neat) 2985m, 2935m, 1714s, 1475s, 1369s, 1257s, 1084s, 1000s cm^{-1}.

Glycosidation of Chiral Isochroman 9c with Sugar 10c. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **9c** (182.1 mg, 0.87 mmol) with anomeric unprotected sugar **10c** (411.8 mg, 1.05 mmol) was completed at room temperature in 48 h, yielding a single *trans* α-glycoside, **15b** (515.0 mg, 0.86 mmol), in 99% yield after purification by flash chromatography (hexanes and ethyl acetate, 1:1, v/v): mp 122–124 °C; ^{1}H NMR ($CDCl_3$, 250 Hz) δ 1.24 (d, 3H, J = 6.4 Hz), 1.36 (d, 3H, J = 6.2 Hz), 1.92 (m, 1H), 2.10 (m, 1H), 2.34 (dd, 1H, J = 17.4, 11.5 Hz), 2.82 (dd, 1H, J = 17.4, 3.4 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 4.24 (m, 1H), 4.66 (m, 1H), 4.74 (q, 1H, $CH_3C_{5'}HO$—, J = 6.6 Hz), 5.46 (br s, 1H), 5.62 (br s, 1H), 6.07 (s, —OC_1HO—, 1H), 6.27 (d, 1H, —N*H*—, J = 7.5 Hz), 6.70 (d, 1H, J = 8.9 Hz), 6.78 (d, 1H, J = 8.9 Hz), 8.26 (d, 2H, J = 9.3 Hz), 8.30 (d, 2H, J = 9.1 Hz); ^{13}H NMR ($CDCl_3$, 60 Hz) δ 16.92, 21.36, 29.77, 29.84, 45.71, 55.45, 55.66, 62.42, 65.34, 72.01, 89.19, 91.02, 107.83, 109.91, 113.16, 117.74, 122.54, 123.68, 124.93, 130.87, 134.66, 150.48, 150.54, 156.77 (q, $J_{C\text{-}F}$ = 37.5 Hz), 164.49; IR (neat) 3342brm, 2946m, 1740s, 1704s, 1527m, 1485s, 1267s, 1166s, 1119s, 976s, 947m, 722m cm^{-1}; HRMS for $C_{27}H_{29}N_2F_3O_{10}$ calcd 598.1775, found 598.1749. Anal. Calcd for $C_{27}H_{29}N_2F_3O_{10}$: C, 54.18; H, 4.88; N, 4.68. Found: C, 54.55; H, 5.26; N, 4.29.

Glycosidation of Isochroman 16a with Sugar 10a. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **16a** (150.6 mg, 1.12 mmol) with sugar **10a** (287.5 mg, 1.24 mmol) was completed at room temperature in 48 h, giving a mixture of two diastereomeric α-glycosides, **17a** and **17b** (353.8 mg, 0.97 mmol), in 87% yield after purification by flash chromatography (hexanes and ethyl acetate, 7:3, v/v). The two diastereoisomers (92:8) were difficult to separate by conventional flash chromatography and gradually decomposed at room temperature. The absolute configurations were assigned by correlating the chemical shifts of the characteristic anomeric protons with those of known structures **15b, 22a**, and **22b**.[14] **17a:** ^{1}H NMR (acetone-d_6, 250 MHz) δ 1.20 (d, 3H, J = 6.4 Hz), 1.80 (m, 1H), 1.90 (s, 3H), 2.13 (s, 3H), 2.18 (m, 1H), 2.67 (m, 1H), 2.99 (m, 1H), 3.88 (m, 1H), 4.09 (m, 1H), 4.41 (q, 1H, J = 6.5 Hz), 5.18 (m, 2H), 5.49 (d, 1H, J = 3.1 Hz), 5.83 (s, 1H), 7.25 (m, 4H); ^{1}H NMR ($CDCl_3$, 250 Hz) δ 6.10 (s, 1H, —OC_1HO—). **17b**: ^{1}H NMR (acetone-d_6, 250 MHz) δ 1.18 (d, 3H, J = 6.4 Hz), 1.79 (m, 1H), 1.90 (s, 3H), 1.98 (s, 3H), 2.15 (m, 1H), 2.67 (m, 1H), 3.00 (m, 1H), 3.88 (m, 1H), 4.10 (m, 1H), 4.41 (q, 1H, J = 6.5 Hz), 5.17 (m, 2H), 5.49 (d, 1H, J = 3.1 Hz), 5.83 (s, 1H), 7.24 (m, 4H); ^{1}H NMR ($CDCl_3$, 250 Hz) δ 5.94 (s, 1H, —OC_1HO—). The following spectral data were collected on the mixture: IR (neat): 2944m, 1744s, 1461m, 1365m, 1247s, 1169m, 1091m, 1018m, 977m cm^{-1}; HRMS for $C_{19}H_{24}O_7$ calcd 364.1522, found 364.1541. Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.80; H, 7.01.

Glycosidation of Isochroman 16a with Sugar 10c. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **16a** (145.2 mg, 1.08 mmol) with sugar **10c** (510.0 mg, 1.30 mmol) was completed at 40 °C in 24 h, affording a mixture of two diastereomeric α-glycosides, **18a** and **18b** (487.0 mg, 0.93 mmol), in 86% yield after purification by flash chromatography (hexanes and ethyl acetate, 1:1, v/v). The two diastereoisomers (85:15) were difficult to separate by conventional flash chromatography. The absolute configurations were assigned by correlating the chemical shifts of the characteristic anomeric protons with those of known structures **15b, 22a**, and **22b**.[14] **18a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.30 (d, 3H, J = 6.5 Hz), 1.93 (m, 1H), 2.12 (m, 1H), 2.67 (m, 1H), 3.10 (m, 1H), 3.97 (m, 1H), 4.13 (m, 1H), 4.76 (q, 1H, $CH_3C_{5'}HO$, J = 6.5 Hz), 4.65 (m, 1H), 5.18 (m, 1H), 5.39 (br s, 1H), 6.04 (s, 1H, —OC_1HO—), 6.44 (d, 1H, —N*H*—, J = 7.5 Hz), 7.24 (m, 4H), 8.24 (d, 2H, J = 9.0 Hz), 8.30 (d, 2H, J = 9.0 Hz). **18b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, 3H, J = 6.4 Hz), 2.00 (m, 1H), 2.15 (m, 1H), 2.68 (m, 1H), 3.09 (m, 1H), 3.98 (m, 1H), 4.17 (m, 1H), 4.47 (q, 1H, $CH_3C_{5'}HO$, J = 6.6 Hz), 4.65 (m, 1H), 5.49 (br s, 1H), 5.63 (br s, 1H), 5.88 (s, 1H, —OC_1HO—), 6.33 (d, 1H, —N*H*—, J = 7.6 Hz), 7.25 (m, 4H), 8.24 (d, 2H, J = 9.1 Hz), 8.30 (d, 2H, J = 9.0 Hz). The following spectral data were collected on the mixture: IR (neat) 3330brm, 3082m, 2945m, 1730s, 1715s, 1527s, 1350m, 1269s, 1213s, 1162s, 1117s, 1107m, 955s cm^{-1}; HRMS for $C_{24}H_{22}N_2F_3O_8$ calcd 523.1329, found 523.1320. Anal. Calcd for $C_{24}H_{23}N_2F_3O_8$: C, 54.96; H, 4.42; N, 5.34. Found: C, 54.85; H, 4.69; N, 5.00.

Glycosidation of Isochroman 16b with Sugar 10a. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **16b** (95.2 mg, 0.49 mmol) with sugar **10a** (130.8 mg, 0.56 mmol) was completed at room temperature in 48 h, affording a mixture of two diastereomeric α-glycosides, **19a** and **19b** (197.4 mg, 0.465 mmol), in 95% yield after purification by flash chromatography (hexanes and ethyl acetate, 7:3, v/v). The two diastereoisomers (88:12) were difficult to separate by conventional flash chromatography. The absolute configurations were assigned by correlating the chemical shifts of the characteristic anomeric protons with those of known structures **15b, 22a**, and **22b**.[14] **19a:** ^{1}H NMR (C_6D_6, 250 MHz) δ 1.24 (d, 3H, J = 6.5 Hz), 1.71 (s, 3H), 1.80 (s, 3H), 1.86 (m, 1H), 2.30 (m, 1H), 2.70 (m, 2H), 3.30 (s, 3H), 3.36 (s, 3H), 3.71 (m, 1H), 4.07 (m, 1H), 4.76 (q, 1H, $CH_3C_{5'}HO$, J = 6.6 Hz), 5.61 (m, 2H), 5.77 (d, 1H, —$OC_{1'}$-HO—, J = 3.1 Hz), 6.38 (d, 1H, J = 8.9 Hz), 6.42 (s, 1H, -OC_1-HO-), 6.46 (d, 1H, J = 9.0 Hz). **19b**: ^{1}H NMR (C_6D_6, 250 MHz) δ: 1.18 (d, 3H, J = 6.5 Hz), 1.74 (s, 3H), 1.78 (s, 3H), 1.82 (m, 1H), 2.10 (m, 1H), 2.81 (m, 2H), 3.33 (s, 3H), 3.36 (s, 3H), 3.78 (m, 1H), 4.15 (m, 1H), 4.30 (q, 1H, $CH_3C_{5'}HO$, J = 6.5 Hz), 5.59 (m, 2H), 5.77 (d, 1H, —$OC_{1'}$HO—, J = 3.1 Hz), 6.14 (s, 1H, —OC_1HO—), 6.38 (d, 1H, J = 8.9 Hz), 6.46 (d, 1H, J = 9.0 Hz). The following spectral data were collected on the mixture: IR (neat) 2938m, 1745s, 1489s, 1370m, 1257s, 1107s, 973s cm^{-1}; HRMS for $C_{21}H_{28}O_9$ calcd 424.1733, found 424.1733. Anal. Calcd for $C_{21}H_{28}O_9$: C, 59.43; H, 6.65. Found: C, 59.78; H, 7.07.

Glycosidation of Isochroman 16b with Sugar 10c. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **16b** (199.0 mg, 1.02 mmol) with sugar **10c** (481.7 mg, 1.23 mmol) was completed at 40 °C in 24 h, affording a mixture of two separable diastereomeric α-glycosides, **20a** (507.4 mg, 0.87 mmol, 85%) and **20b** (82.6 mg, 0.14 mmol, 14%), after purification by flash chromatography (hexanes and ethyl acetate, 1:1, v/v). The absolute configurations were assigned by correlating the chemical shifts of the characteristic anomeric protons with those of known structures **15b, 22a**, and **22b**.[14] **20a:** ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, 3H, J = 6.5 Hz), 1.95 (m, 1H), 2.10 (m, 1H), 2.72 (m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 3.94 (m, 1H), 4.12 (m, 1H), 4.69 (m, 1H), 4.77 (q, 1H, $CH_3C_{5'}HO$, J = 6.5 Hz), 5.48 (br s, 1H), 5.60 (d, 1H, —$OC_{1'}$HO—, J = 3.0 Hz), 6.06 (s, 1H, —OC_1HO—), 6.19 (d, 1H, —N*H*—, J = 7.5 Hz), 6.70 (d, 1H, J = 8.9 Hz), 6.78 (d, 1H, J = 8.9 Hz), 8.28 (d, 2H, J = 9.1 Hz), 8.34 (d, 2H, J = 9.1 Hz); IR (neat) 3316s, 2946s, 1738s, 1704s, 1533s, 1487s, 1348s, 1269s, 1170s, 965s, 720s cm^{-1}; HRMS for $C_{26}H_{27}N_2F_3O_{10}$ calcd 584.1618, found 584.1628. **20b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.20 (d, 3H, J = 6.5 Hz), 1.94 (m, 1H), 2.08 (m, 1H), 2.71 (m, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 3.94 (m, 1H), 4.15 (m, 1H), 4.45 (q, 1H, $CH_3C_{5'}HO$, J = 6.5 Hz), 4.66 (m, 1H), 5.48 (br s, 1H), 5.60 (d, 1H, —$OC_{1'}$HO—, J = 3.0 Hz), 5.89 (s, 1H, —OC_1HO—), 6.19 (d, 1H, —N*H*—, J = 7.5 Hz), 6.68 (d, 1H, J = 8.9 Hz), 6.75 (d, 1H, J = 9.0 Hz), 8.27 (d, 2H, J = 9.1 Hz), 8.33 (d, 2H, J = 9.1 Hz); IR (neat) 3309m, 2945s, 1740s, 1710s 1533s, 1488s, 1350s, 1270s, 1170s,

1115s, 966s, 720s cm^{-1}; HRMS for $C_{26}H_{27}N_2F_3O_{10}$ calcd 584.1618, found 584.1635.

Glycosidation of Isochroman 16a with (+)-(1S,2S,5R)-Neomenthol. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **16a** (189.6 mg, 1.41 mmol) with (+)-(1S,2S,5R)-neomenthol (265.0 mg, 1.70 mmol) was completed at room temperature in 48 h, yielding a mixture of two diastereomeric α-glycosides, **21a** and **21b** (308.8 mg, 1.07 mmol), in 76% yield. The two diastereoisomers (1:1) could not be separated by conventional flash chromatography. The following spectral data were collected on the mixture: ^1H NMR ($CDCl_3$, 250 MHz) δ 0.82–1.00 (m, 2H), 0.84–1.07 (6d, 9H, J = 6.7 Hz), 1.32 (m, 2H), 1.52–1.95 (m, 4H), 2.22 (m, 1H), 2.60 (m, 1H), 3.02 (m, 1H), 3.88 (m, 1H), 4.05–4.30 (m, 2H), 5.64 (s, 1H), 7.07–7.30 (m, 4H); ^1H NMR (C_6D_6, 250 MHz) the anomeric protons for the two diastereoisomers appear at different chemical shifts; δ 5.74 (s, 1H), 5.76 (s, 1H); IR (neat) 2968s, 2845s, 1452s, 1381s, 1325s, 1273m, 1207m, 1089s, 1074s, 1022s cm^{-1}, HRMS for $C_{19}H_{29}O_2$ calcd 289.2169, found 289.2175. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.89; H, 9.94.

Conversion of **20b** to **20a**. To a stirred solution of **20b** (46.6 mg, 0.08 mmol) in 3 mL of anhydrous CH_2Cl_2 was added DDQ (20.0 mg, 0.09 mmol). The resulting mixture was stirred at room temperature under argon for 24 h. Usual workup followed by flash chromatography (hexanes and ethyl acetate, 1:1, v/v) afforded a mixture of **20a** and **20b** (86:14; 38.2 mg, 0.065 mmol) in 82% yield.

Glycosidation of Isochroman 9a with Sugar 10c. Following the previously described general procedure, the DDQ-assisted glycosidation of isochroman **9a** (251.1 mg, 1.06 mmol) with sugar **10c** (501.0 mg, 1.28 mmol) was completed at 45 °C in 36 h, affording two separable diastereomeric α-glycosides, **22a** (329.3 mg, 0.526 mmol, 50%) and **22b** (308.1 mg, 0.492 mmol, 46%), after purification by flash chromatography (hexanes and ethyl acetate, 1:1, v/v). This reaction has been repeated several times in 1–3-mmol scales under same conditions, giving α-glycosides **22a** and **22b** in consistent yield.

22a: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.18 (d, 3H, J = 6.5 Hz), 1.92 (m, 1H), 2.11 (m, 1H), 2.34 (s, 3H), 2.52 (dd, 1H, J = 14.8, 9.8 Hz), 3.08 (dd, 1H, J = 14.7, 5.0 Hz), 3.79 (s, 6H), 4.34 (q, 1H, CH_3C_5HO, J = 6.5 Hz), 4.61 (dd, 1H, J = 9.8, 5.0 Hz), 4.64 (m, 1H), 5.42 (br s, 1H), 5.63 (br s, 1H, $-OC_1HO-$), 6.03 (s, 1H, $-OC_1HO-$), 6.31 (d, 1H, $-NH-$, J = 7.5 Hz), 6.72 (d, 1H, J = 9.0 Hz), 6.80 (d, 1H, J = 9.0 Hz), 8.29 (d, 2H, J = 9.1 Hz), 8.34 (d, 2H, J = 9.1 Hz); IR (neat) 3319s, 2949m, 1738s, 1715s, 1531s, 1487s, 1349m, 1268s, 1170s, 1108s, 1069m, 970s, 730s cm^{-1}; HRMS for $C_{28}H_{29}N_2O_{11}F_3$ calcd 626.1724; found 626.1741. Elemental analysis was carried out on the 1:1 mixture of **22a** and **22b**. Anal. Calcd for $C_{28}H_{29}N_2O_{11}F_3$: C, 53.68; H, 4.67; N, 4.47. Found: C, 54.02; H, 4.98; N, 4.18.

22b: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.17 (d, 3H, J = 6.5 Hz), 1.91 (m, 1H), 2.12 (m, 1H), 2.32 (s, 3H), 2.58 (dd, 1H, J = 14.7, 9.7 Hz), 3.11 (dd, 1H, J = 14.7, 5.1 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 4.57 (dd, 1H, J = 9.8, 5.1 Hz), 4.65 (m, 1H), 4.76 (q, 1H, CH_3C_5HO, J = 6.5 Hz), 5.48 (br s, 1H), 5.62 (br s, 1H, $-OC_1HO-$), 6.24 (s, 1H, $-OC_1HO-$), 6.28 (d, 1H, $-NH-$, J = 7.5 Hz), 6.74 (d, 1H, J = 8.9 Hz), 6.81 (d, 1H, J = 9.0 Hz), 8.28 (d, 2H, J = 9.1 Hz), 8.33 (d, 2H, J = 9.1 Hz); IR (neat) 3319s, 2950m, 1738s, 1718s, 1531s, 1485s, 1349m, 1278s, 1170s, 1108s, 1070m, 970s, 730s cm^{-1}; HRMS for $C_{28}H_{29}N_2O_{11}F_3$ calcd 626.1724, found 626.1735. Elemental analysis was carried out on the mixture of **22a** and **22b**. Anal. Calcd for $C_{28}H_{29}N_2O_{11}F_3$: C, 53.68; H, 4.67; N, 4.47. Found: C, 54.02; H, 4.98; N, 4.18.

Preparation of Pyranoquinone Glycosides 23a and 23b. To a stirred solution of compound **22a** (374.6 mg, 0.60 mmol) in 25 mL of CH_3CN was first added a solution of $NaHCO_3$ (98.5 mg) in 3 mL of H_2O at room temperature, followed by addition of ammonium cerium(IV) nitrate (985.0 mg, 1.80 mmol) in 15 mL of H_2O. After the resulting mixture was stirred at room temperature for 20 min, the reaction was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and then concentrated. The residue thus obtained was found to be pure **23a** (355.0 mg, 0.595 mmol, 99%) without further purification. The unstable pyranoquinone glycoside was used immediately for next reaction after workup. Only ^1H NMR spectra were recorded.

23a: ^1H NMR for the other isomer ($CDCl_3$, 250 MHz) δ 1.21 (d, 3H, J = 6.8 Hz), 1.96–2.14 (m, 2H), 2.34 (s, 3H), 2.44 (dd, 1H, J = 21.5, 11.5 Hz), 2.95 (dd, 1H, J = 20.0, 5.5 Hz), 4.30 (q, 1H, CH_3C_5HO, J = 6.7 Hz), 4.42–4.65 (m, 2H), 5.43 (br s, 1H), 5.67 (br s, 1H, $-OC_1HO-$), 5.88 (s, 1H, $-OC_1HO-$), 6.32 (d, 1H, $-NH-$, J = 7.8 Hz), 6.78 (d, 1H, J = 11.0 Hz), 6.85 (d, 1H, J = 11.0 Hz), 8.28 (d, 2H, J = 11.0 Hz), 8.32 (d, 2H, J = 11.0 Hz).

Following similar procedures as described above, compound **22b** (259.8 mg, 0.41 mmol) was converted to pyranoquinone glycoside **23b** (245.0 mg, 0.411 mmol) in 99% yield. Only ^1H NMR spectra were recorded.

23b: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.34 (d, 3H, J = 6.7 Hz), 1.96–2.14 (m, 2H), 2.32 (s, 3H), 2.44 (dd, 1H, J = 21.5, 11.5 Hz), 2.92 (dd, 1H, J = 19.9, 5.5 Hz), 4.42–4.65 (m, 2H), 4.68 (q, 1H, CH_3C_5HO, J = 6.5 Hz), 5.42 (br s, 1H), 5.59 (br s, 1H, $-OC_1HO-$), 6.05 (s, 1H, $-OC_1HO-$), 6.46 (d, 1H, $-NH-$, J = 7.8 Hz), 6.80 (d, 1H, J = 11.0 Hz), 6.87 (d, 1H, J = 11.0 Hz), 8.28 (d, 2H, J = 11.0 Hz), 8.32 (d, 2H, J = 11.1 Hz).

Preparation of Heterocyclic Anthracyclines 24a and 24b. To a stirred solution of homophthalic anhydride (106.1 mg, 0.65 mmol) in 8 mL of anhydrous THF was added a solution of freshly prepared LDA (0.66 mmol) in 8 mL of anhydrous THF at −78 °C under argon. After stirring at −78 °C for 15 min, a solution of compound **23a** (obtained form previous reaction; 355.0 mg, 0.595 mmol) in 8 mL of THF was introduced dropwise over a period of 10 min. The resulting mixture was stirred at −78 °C for 30 min and then slowly warmed up to room temperature in 1 h. The reaction was quenched with HCl (0.05 N, 20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by flash chromatography using toluene and ethyl acetate (9:1 v/v) as eluent to afford **24a** (209.0 mg, 0.29 mmol) in 49% yield as a red solid. Compound **24a** was found to be spectroscopically identical with that of authentic sample provided by Lavallee et al.[15]

24a: mp 183–185 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23 (d, 3H, J = 6.6 Hz), 2.12 (m, 2H), 2.37 (s, 3H), 2.57 (dd, 1H, J = 19.7, 11.3 Hz), 3.18 (dd, 1H, J = 19.6, 4.2 Hz), 4.35 (q, 1H, CH_3C_5HO, J = 6.5 Hz), 4.54–4.70 (m, 2H), 5.46 (br s, 1H), 5.78 (br s, 1H, $-OC_1HO-$), 6.06 (s, 1H, $-OC_1HO-$), 6.31 (d, 1H, $-NH-$, J = 7.7 Hz), 7.73 (m, 2H), 7.95 (d, 1H, J = 6.9 Hz), 8.10 (s, 1H), 8.28 (d, 2H, J = 8.9 Hz), 8.34 (d, 2H, J = 8.7 Hz), 8.50 (d, 1H, J = 6.8 Hz), 13.81 (s, 1H); IR (neat) 3330m, 2924m, 1730s, 1707s, 1663m, 1609m, 1534m, 1457m, 1351m, 1270s, 1212m, 1163s, 1105m, 998m, 949m, 757m, 717m cm^{-1}.

Following similar procedures as described above, treatment of compound **23b** (245.0 mg, 0.411 mmol) with homophthalic anhydride (73.7 mg, 0.45 mmol) in the presence of LDA (0.46 mmol) afforded heterocyclic anthracycline analog **24b** (137.8 mg, 0.19 mmol) in 46% yield. Compound **24b** was also found to be spectroscopically identical with that of authentic sample provided by Lavallee et al.[15]

24b: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.40 (d, 3H, J = 6.7 Hz), 2.00–2.21 (m, 2H), 2.38 (s, 3H), 2.62 (dd, 1H, J = 18.9, 11.0 Hz), 3.15 (dd, 1H, J = 19.0, 3.6 Hz), 4.55 (dd, 1H, J = 11.0, 3.8 Hz), 4.61 (m, 1H), 4.89 (q, 1H, CH_3C_5HO, J = 6.6 Hz), 5.48 (br s, 1H), 5.64 (br s, 1H, $-OC_1HO-$), 6.24 (s, 1H, $-OC_1HO-$), 6.40 (d, 1H, $-NH-$, J = 7.5 Hz), 7.75 (m, 2H), 7.98 (d, 1H, J = 7.1 Hz), 8.15 (s, 1H), 8.30 (d, 2H, J = 8.9 Hz), 8.36 (d, 2H, J = 8.8 Hz), 8.51 (d, 1H, J = 8.9 Hz), 13.82 (s, 1H); IR (neat) 3328s, 2923m, 1732s, 1710s, 1660m, 1609s, 1533s, 1354m, 1273s, 1212m, 1165s, 1105s, 999s cm^{-1}.

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