Regio- and Stereospecific Synthesis of Mono-β-D-Glucuronic Acid Derivatives of Combretastatin A-1

Rajendra P. Tanpure,[†] Tracy E. Strecker,[†] David J. Chaplin,[‡] Bronwyn G. Siim,[‡] Mary Lynn Trawick,[†] and Kevin G. Pinney*[,†]

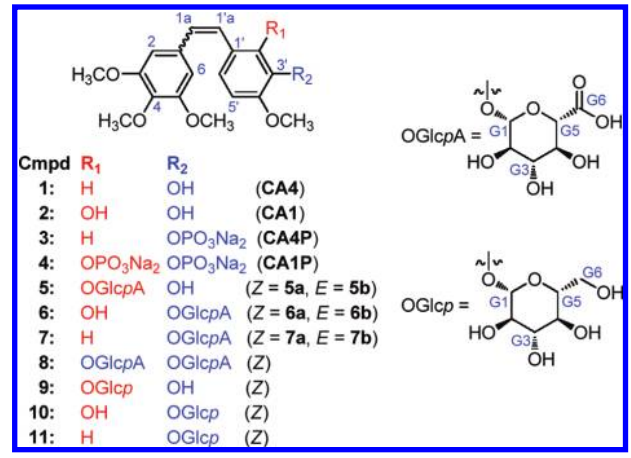
Department of Chemistry and Biochemistry, Baylor University, One Bear Place #97348, Waco, Texas 76798-7348, and OXiGENE Inc., Magdalen Centre, Robert Robinson Avenue, The Oxford Science Park, Oxford, OX4 4GA, U.K.

Received February 16, 2010

Synthetic routes have been established for the preparation of regio- and stereoisomerically pure samples of the mono-β-D-glucuronic acid derivatives of combretastatin A-1, referred to as CA1G1 (**5a**) and CA1G2 (**6a**). Judicious choice of protecting groups for the catechol ring was required for the regiospecific introduction of the glucuronic acid moiety. The tosyl group proved advantageous in this regard. The two monoglucuronic acid analogues demonstrate low cytotoxicity (compared to CA1, **2**) against selected human cancer cell lines, with CA1G1 being slightly more potent than CA1G2.

The members of the combretastatin family of natural products,[1] isolated from the African bush willow tree, *Combretum caffrum* Kuntze (Combretaceae), are exemplary in terms of both their relative simplicity in chemical structure and their pronounced biochemical and biological activity. Two *Z*-(*cis*)-stilbenoid compounds from this family (Figure 1), combretastatin A-4 (CA4, **1**)[2,3] and combretastatin A-1 (CA1, **2**),[4] are potent inhibitors of tubulin assembly (IC_{50} = 1.0 and 1.1 μM, respectively)[5] and are highly cytotoxic toward selected human cancer cell lines (for example, CA4, GI_{50} = 0.001 μM, and CA1, GI_{50} = 0.013 μM against DU-145 prostate cancer cells).[6] The corresponding phosphate prodrugs (Figure 1), combretastatin A-4 phosphate (**3**; CA4P, Zybrestat, fosbretabulin)[7−10] and combretastatin A-1 phosphate (**4**; CA1P, Oxi4503),[11−13] are both in human clinical trials as vascular disrupting agents (VDAs). VDAs represent a relatively new and rapidly emerging field of anticancer therapy.[14,15] These compounds are characterized by their ability to interfere with the dynamics of the tubulin−microtubule protein system in the endothelial cells lining the microvessels that feed tumors. This results in a cascade of cell signaling events involving activation of RhoA and subsequently RhoA kinase, leading to morphological changes in the endothelial cells and eventual microvessel occlusion, thus starving the tumor of necessary nutrients and oxygen.[16−18] In addition, disruption of vascular endothelial (VE) cadherins leads to further microvessel permeability and damage.[19]

CA4 (**1**) and CA1 (**2**) are almost identical structurally, with the only difference being an additional hydroxy substituent at the C-2′ position of CA1. The enhanced effectiveness of CA1P (**4**) in delaying growth of tumor xenografts in mice is thought to be related to a combination of the vascular disrupting effect along with a distinct secondary mechanism of biological activity involving formation of the highly reactive *ortho* quinone analogue, obtainable through biological oxidation of the 1,2-diol functionality present in CA1.[20,21] Owing to the additional hydroxy group, the oxidation/reduction properties of CA1 are different from those of CA4, rendering it susceptible to oxidative metabolism in the liver by hepatic enzymes and to formation of free radical species, hence implicating it in the formation of at least 13 additional metabolites, in comparison to those formed from CA4.[20] Some of these CA1P metabolites have been identified as monophosphates, monoglucuronides, and bisglucuronides (**8**).[22] Pharmacokinetic data have indicated that CA4P (**3**) once converted to CA4 (**1**), most likely by nonspecific phosphatase enzymes, is further metabolized to its corresponding glucuronide derivative (CA4G), **7a** (Figure 1), which is rapidly cleared from the human body.[23] Enzymatic conjugation resulting in glucuronidation is a major mechanism to convert exogenous compounds to less active and more water-soluble metabolites for excretion. Each of the CA1 monoglucuronides (CA1G1, **5a**,**b**; CA1G2, **6a**,**b**) (Figure 1) has distinct chemical and biological properties. Initial clinical data from an ongoing phase I study indicates that CA1G1(**5a**) is structurally stable and has a long half-life in human plasma, while CA1G2 (**6a**) has a much shorter plasma half-life and appears less stable owing to *ortho*-phenolic-mediated isomerization from the *Z*- to the corresponding *E*-isomer.[24] Accordingly, it became necessary to develop robust, regio- and stereospecific synthetic routes for both of the CA1 monoglucuronides (CA1G1, **5a**; CA1G2, **6a**) in order to have sufficient quantities of these compounds available for further biological evaluation in support of the ongoing human clinical development of CA1P.



Cmpd	R_1	R_2	
1:	H	OH	(**CA4**)
2:	OH	OH	(**CA1**)
3:	H	OPO_3Na_2	(**CA4P**)
4:	OPO_3Na_2	OPO_3Na_2	(**CA1P**)
5:	OGlcpA	OH	(*Z* = **5a**, *E* = **5b**)
6:	OH	OGlcpA	(*Z* = **6a**, *E* = **6b**)
7:	H	OGlcpA	(*Z* = **7a**, *E* = **7b**)
8:	OGlcpA	OGlcpA	(*Z*)
9:	OGlcp	OH	(*Z*)
10:	OH	OGlcp	(*Z*)
11:	H	OGlcp	(*Z*)

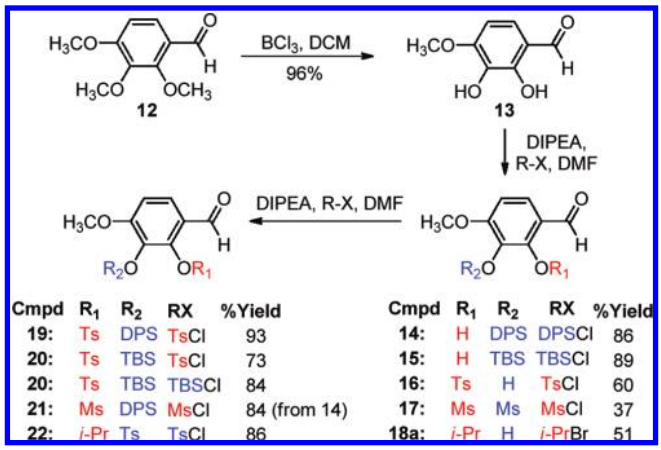
Figure 1. Combretastatin A-1 (CA1) and combretastatin A-4 (CA4) derivatives.

The monoglucuronides of CA1 have been previously prepared, in an unpublished study, through an enzymatic route.[24] While this enzymatic route yielded relatively pure samples of CA1G1 (**5a**) and CA1G2 (**6a**), it did not allow unequivocal regioisomeric assignment. In addition, the enzymatic route is cost prohibitive for use as a scale-up procedure. To the best of our knowledge, the regio- and stereospecific chemical synthesis of the monoglucuronic acid derivatives of CA1 reported herein represents the first available synthetic route to these important glucuronide analogues. This work was based, in part, on the previous synthesis of CA4G (**7a**) by Pettit and co-workers.[25]

* To whom correspondence should be addressed. Tel: (254) 710-4117. Fax: (254) 710-4272. E-mail: Kevin_Pinney@baylor.edu.
[†] Baylor University.
[‡] OXiGENE Inc.

10.1021/np100108e
Published on Web 05/24/2010

Scheme 1. Selective Protection of OH-2′ and OH-3′ of Combretastatin A-1 (CA1)



Cmpd	R_1	R_2	RX	%Yield	Cmpd	R_1	R_2	RX	%Yield
19:	Ts	DPS	TsCl	93	**14:**	H	DPS	DPSCl	86
20:	Ts	TBS	TsCl	73	**15:**	H	TBS	TBSCl	89
20:	Ts	TBS	TBSCl	84	**16:**	Ts	H	TsCl	60
21:	Ms	DPS	MsCl	84 (from 14)	**17:**	Ms	Ms	MsCl	37
22:	*i*-Pr	Ts	TsCl	86	**18a:**	*i*-Pr	H	*i*-PrBr	51

It is instructive to note that glucoside derivatives of CA1 are also known. Isolation of combretastatin A-1 2′-*O*-*β*-D-glucoside (**9**) from *Combretum krausii*[26] as well as from *Combretum erythrophyllum*[27] and its synthesis have been reported.[28] The glucoside analogue combretastatin A-1 3′-*O*-*β*-D-glucoside (**10**) has not been reported as an isolated natural product; however, its synthesis has been achieved.[28] Both **9** and **10** have been described to possess cytotoxicity against B16F10 cancer cell lines, and analogue **10** is reportedly 5 times more active compared to **9**.[28] In addition, glucoside analogues **9** and **10** demonstrate antimitotic activity by microtubule disassembly.[28] The synthesis of combretastatin A-4 3′-*O*-*β*-D-glucoside (**11**) has also been reported.[25]

Results and Discussion

The Koenigs−Knorr methodology[29] was adopted to synthesize the mono-*β*-D-glucuronic acid derivatives of combretastatin A-1 (CA1) using methyl α-D-(1-deoxy-1-bromo,2,3,4-triacetyl)glucuronate (**31**) as the glucuronide donor and CA1 as the glucuronide acceptor. Substitution of the bromide at the anomeric center of the glucuronide donor, by a phenolate of an appropriately protected CA1 analogue (**28**−**30**), achieved the required stereochemistry.[30,31] While yields for the glucuronidation step were only modest, attempts to increase yield were not successful, presumably due to the sterically crowded phenolic moiety and instability of **31** at room temperature. Syntheses of CA1 and its various derivatives have been efficiently achieved using the Wittig approach.[4,32,33] In order to achieve the required regiospecificity in the synthesis of the CA1 monoglucuronides, it was important to distinguish between the two vicinal phenolic functional groups at C-2 and C-3 of the corresponding pre-Wittig aldehyde **13** with a strategically chosen selective protecting group. This selectivity was achieved by treating aldehyde **13** with Hunig's base (DIPEA) followed by a stoichiometric amount of DPSCl or TBSCl. In each case, silylation occurred exclusively at the C-3 position, leaving the C-2 phenol intact, to provide **14** or **15**, respectively (Scheme 1). Selective protection of the C-2 phenol of aldehyde **13** was achieved upon treatment with a stoichiometric amount of *p*-TsCl to form sulfonyl ester **16** (Scheme 1). Interestingly, the reaction of a stoichiometric amount of 2-bromopropane with aldehyde **13** in the presence of K_2CO_3 provided the C-2 monoisopropyl ether **18** as the major product in a mixture of mono- and di-isopropyl ethers (Scheme 1), which were readily separated by column chromatography. The yield of this reaction was improved by utilizing a sealed vessel in a microwave oven (Scheme 1).

Treatment of aldehydes **14**−**18** with Hunig's base followed by the appropriate silyl halide or sulfonyl halide formed aldehydes **19**−**22**, respectively (Scheme 1). A Wittig reaction between salt **23** and the accompanying aldehyde (**19**−**22**) provided a mixture of *E* and *Z* stilbenes **24**−**27**, which were readily separated by column chromatography (Scheme 2). Subsequent sonication of stilbenes **24**−**26** in the presence of KF and catalytic HBr successfully displaced the DPS or TBS group, while leaving intact the sulfonate ester at the C-2′ position, producing phenols **28** and **29** (Scheme 2). Single-crystal X-ray diffraction provided structural confirmation for compounds **22**, **25a**, and **27a**.[34] Treatment of bromotriacetylglucuronate **31** with phenol **28** or **29** in the presence of Cs_2CO_3 successfully displaced bromide at the anomeric carbon, providing stilbene-triacetylglucuronates **32a** and **33a** (Scheme 2). The coupling constant (**32a** $J = 7.6$ Hz, **33a** $J = 7.7$ Hz) in the ^{1}H NMR spectrum for the hydrogen [**32a** (δ_H 4.86), **33a** (δ_H 5.13)] on the anomeric carbon confirmed that the bromide displacement proceeded in the anticipated fashion to afford the requisite *β*-linkage.[35,36] Hydrolysis of acetyl and sulfonyl esters of stilbene-glucuronates **32a** (R_1 = tosyl) and **33a** (R_1 = mesyl) in the presence of NaOH in a microwave oven (sealed vessel) readily provided monoglucuronide CA1G2 **6a** (Scheme 2).

The successful synthesis of CA1G1 relied on the protecting group differentiation present in stilbene **27a**. Selective cleavage of the isopropyl group upon treatment with a variety of Lewis acids ($AlCl_3$, BCl_3, and $TiCl_4$) was accompanied by undesired *Z* to *E* partial isomerization. The binary salt [TMAH][Al_2Cl_7], which is described as an acidic ionic liquid, has been utilized for the selective deprotection of alkyl-aryl ethers.[37] Treatment of **27a** with ionic liquid [TMAH][Al_2Cl_7] resulted in selective cleavage of the isopropyl group to generate stilbene phenol **30a**. Reaction of phenol **30a** with bromotriacetylglucuronate **31** in the presence of Cs_2CO_3 provided stilbene-glucuronate **34a**. The coupling constant ($J = 7.8$ Hz) in the ^{1}H NMR spectrum for the hydrogen (δ_H 5.17) on the anomeric carbon confirmed that the bromide displacement proceeded in the anticipated fashion to afford the requisite *β*-linkage. Treatment of **34a** with NaOH in a microwave oven (sealed vessel) readily hydrolyzed acetyl, methyl, and *p*-tosyl ester functionalities to provide CA1G1 (**5a**).

Characterization of Compounds 5a and 5b Using ^{1}H NMR, ^{13}C NMR, NOE, and HMBC Data. For CA1G1 (**5a**), the doublet in the ^{1}H NMR spectrum at δ_H 4.85 with a coupling constant of $J_{G1,G2} = 7.8$ Hz confirmed the stereochemistry of the glucuronic acid moiety with a *β*-acetal linkage at its anomeric carbon (δ_C 105.8). The regioselective incorporation of the glucuronide at the C-2′ phenol was determined with the long-range HMBC correlation between the proton H-G1 (δ_H 4.85) on the anomeric carbon and C-2′ (δ_C 143.7) of CA1G1 (**5a**). In addition, observation of an NOE between H-G1 (δ_H 4.85) and H-1′a (δ_H 6.89) in the 1D NOESY spectrum confirmed the regioselectivity of the acetal linkage between C-2′ and C-G1 of the glucuronic acid CA1G1. The presence of the carboxylic acid functionality was substantiated by a long-range correlation between H-G5 (δ_H 3.96) and C-G6 (δ_C 169.1). The $J_{1a,1'a}$ value of 12.0 Hz for **5a** confirmed the *Z* stereochemistry of the stilbene bridge, while the $J_{1a,1'a}$ value of 17.0 Hz attested to the *E* stereochemistry for **5b**. In a similar manner, CA1G2 (**6a** and **6b**) were characterized using ^{1}H NMR, ^{13}C NMR, NOE, and HMBC data (see Supporting Information).

Characterization of Compounds 6a and 6b Using ^{1}H NMR, ^{13}C NMR, NOE, and HMBC Data. For CA1G2 (**6a**), the doublet in the ^{1}H NMR spectrum at δ_H 4.56 with a coupling constant of $J_{G1,G2} = 7.5$ Hz confirmed the stereochemistry of the glucuronic acid moiety with a *β*-ether linkage at its anomeric carbon (δ_C 106.1). The regioselective incorporation of the glucuronide at the C-3′ phenol was determined with the long-range HMBC correlation between the proton H-G1 (δ_H 4.56) on the anomeric carbon and C-3′ (δ_C 135.2) of CA1G2. In addition, observation of an NOE between H-G1 (δ_H 4.56) and H-4′OCH$_3$ (δ_H 3.73) in the 1D NOESY spectrum confirmed the regioselectivity of the ether linkage between C-3′ and C-G1 of glucuronic acid CA1G2. The presence of the carboxylic acid functionality was confirmed by a long-range correlation between H-G5 (δ_H 4.56) and C-G6 (δ_C

Scheme 2. Synthesis of Combretastatin A-1-*O*-β-D-Glucuronic Acids (CA1G1 and CA1G2)

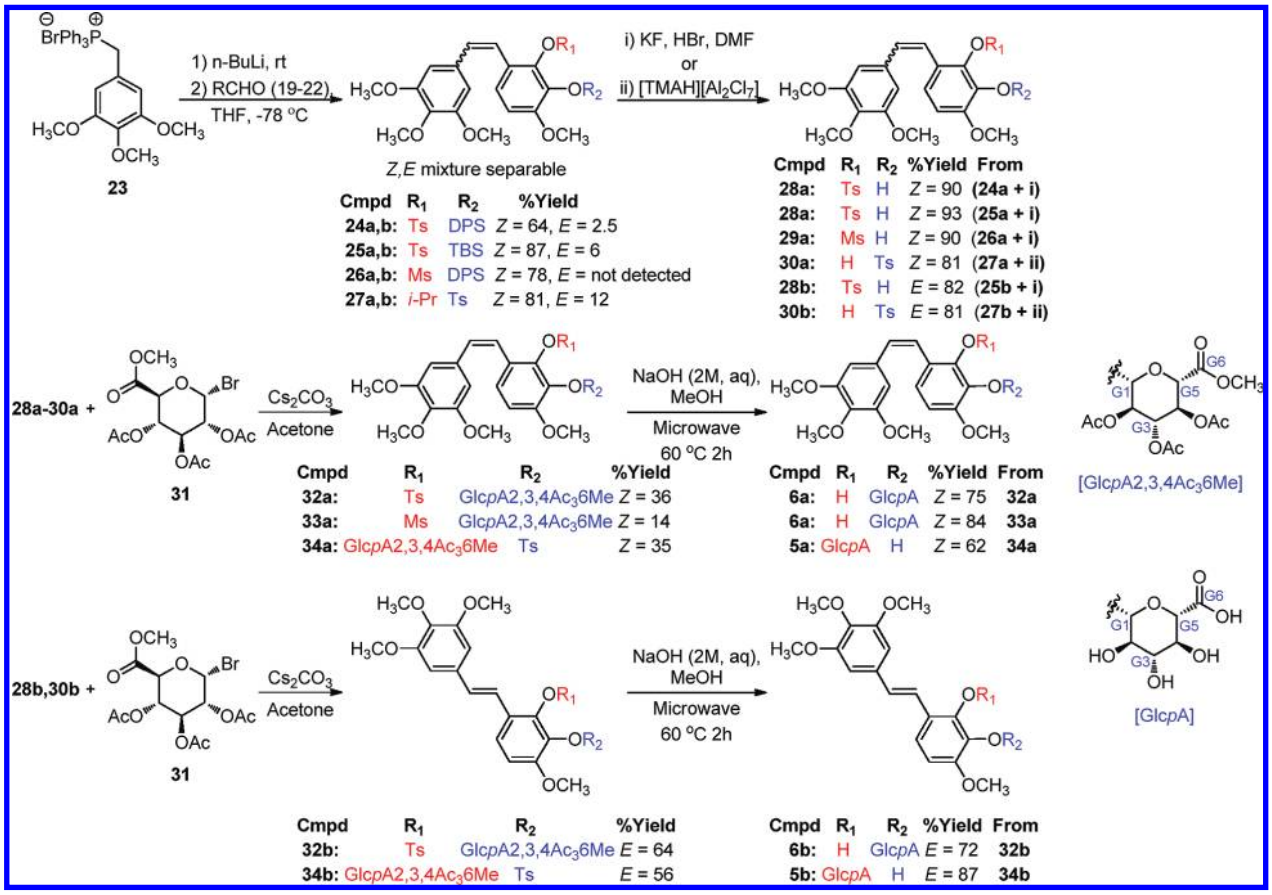


Table 1. Cytotoxicity against Human Cancer Cell Lines DU-145, SK-OV-3, and NCI-H460

	GI_{50} (μM) SRB assay[a]		
compound	DU-145	SK-OV-3	NCI-H460
CA1 (*Z*)	0.013[b]	na[c]	0.046[b]
5a (*Z*)	4.4	2.3	3.0
5b (*E*)	>88	30	26
6a (*Z*)	3.3	2.1	1.8
6b (*E*)	>98	>85	26

[a] Average of $n \geq 3$ independent determinations. [b] Ref 6. [c] Not available.

172.8). The $J_{1a,1'a}$ value of 12.0 Hz for **6a** substantiated the *Z* stereochemistry of the stilbene bridge, while the $J_{1a,1'a}$ value of 17.0 Hz confirmed the *E* stereochemistry for **6b**.

Biological Evaluation. The cytotoxicity of the glucuronides CA1G1 (**5a**,**b**) and CA1G2 (**6a**,**b**) was evaluated using a panel of three human cancer cell lines, prostate (DU-145), ovarian (SK-OV-3), and lung (NCI-H460), with doxorubicin as a reference compound. This procedure was based on the standard sulforhodamine B (SRB) assay.[33,38,39] The GI_{50} values are shown in Table 1. A comparison of the CA1 glucuronide analogues (**5a**,**b** and **6a**,**b**) showed that the *Z*-isomers (**5a** and **6a**) were more potent against all three cancer cell lines; however, all of the glucuronide analogues were found to be substantially less active than CA1.

Experimental Section

General Experimental Procedures. Methylene chloride (CH_2Cl_2), acetone, and tetrahydrofuran (THF) were used in their anhydrous form as obtained from the chemical suppliers. Reactions were performed under an inert atmosphere using nitrogen gas unless specified. Thin-layer chromatography (TLC) plates (precoated glass plates with silica gel 60 F_{254}, 0.25 mm thickness) were used to monitor reactions. Purification of intermediates and products was carried out with a flash purification system using silica gel (200−400 mesh, 60 Å) or RP-18 prepacked columns. Intermediates and products synthesized were characterized on the basis of their ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), gDQCOSY, NOESY1d, gHSQC, and gHMBC spectroscopic data. All the chemical shifts are expressed in ppm (δ), coupling constants (*J*) are presented in Hz, and peak patterns are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). HRMS were obtained using electron impact (EI) ionization or electrospray ionization (ESI) or (+ve or −ve) atmospheric pressure chemical ionization (APCI)/atmospheric pressure photoionization (APPI) techniques. Purity of the final compounds was further analyzed at 25 °C using a HPLC system with a diode-array detector (λ = 190−400 nm), a Zorbax XDB-C18 HPLC column (4.6 mm ×150 mm, 5 μm), and a Zorbax reliance cartridge guard-column (eluents, solvent A, 0.025% ammonium trifluoroacetate in water; solvent B, acetonitrile; gradient, 90% A/10% B → 40% A/60% B over 0 to 18 min; flow rate 1.0 mL/min; injection volume 20 μL; monitored at wavelengths λ 254, 280, and 300 nm).

(*Z*)/(*E*)-(3,4,5-Trimethoxy)-{2′-(*p*-toluenesulfonyloxy)-3′-[(*tert*-butyldiphenylsilyl)oxy]}stilbene (24a/24b). *n*-BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) was added dropwise to a well-stirred solution of Wittig salt **23** (1.6 g, 3.0 mmol) in THF (60 mL, anhydrous) at 0 °C. The reaction mixture was then warmed to rt, stirred for 15 min, and then cooled to −78 °C. A solution of aldehyde **19** (1.4 g, 2.5 mmol) in THF (5 mL, anhydrous) was added dropwise to the reaction mixture, and the reaction was stirred until the temperature gradually warmed to room temperature. The reaction was quenched by careful addition of H_2O (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 10% A/90% B over 3.18 min (1 CV), 10% A/90% B → 50% A/50% B over 33.0 min (10 CV), 50% A/50% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded the *Z*-isomer **24a** (1.17 g, 1.6 mmol, 64% yield) as an off-white solid and the *E*-isomer **24b** (0.0460 g, 0.0063 mmol, 2.5% yield) as an off-white solid.

***Z*-Isomer 24a:** mp 92−94 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.68 [4H, d, J = 8.0 Hz, Ph(H-2, H-6)], 7.36 [2H, m, Ph(H-4)], 7.31 [4H, m, Ph(H-3, H-5)], 7.21 (2H, d, J = 8.5 Hz, H-3″, H-5″), 6.66 (1H, d, J = 8.6 Hz, H-6′), 6.44 (2H, s, H-2, H-6), 6.25 (1H, d, J = 8.6 Hz, H-5′), 6.10 (1H, d, J = 12.0 Hz, H-1′a), 6.04 (1H, d, J = 12.0 Hz, H-1a), 3.83 (3H, s, OCH_3-4), 3.68 (6H, s, OCH_3-3, -5), 2.77 (3H, s, OCH_3-4′), 2.37 (3H, s, CH_3-4″), 1.06 [9H, s, −C(CH_3)$_3$]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7 (C, C-3, C-5), 149.9 (C, C-4′), 144.8 (C, C-4″), 139.34 (C, C-3′), 139.28 (C, C-2′), 137.1 (C, C-4), 134.6 [C, Ph(C-1)], 134.5 (C, C-1″), 134.4 [CH, Ph(C-2, C-6)], 132.2 (C, C-1), 129.9 (CH, C-1a), 129.6 (CH, C-3″, C-5″), 129.0 [CH, Ph(C-4)], 128.5 (CH, C-2″, C-6″), 127.1 [CH, Ph(C-3, C-5)], 124.9 (C, C-1′), 124.6 (CH, C-1′a), 121.8 (CH, C-6′), 109.5 (CH, C-5′), 106.2 (CH, C-2, C-6), 60.9 (CH$_3$, OCH_3-4), 56.0 (CH$_3$, OCH_3-3, -5), 54.0 (CH$_3$, OCH_3-4′), 26.4 [CH$_3$, −C(CH_3)$_3$], 21.6 (CH$_3$, CH_3-4″), 20.0 [C, −C(CH$_3$)$_3$]; HRMS m/z 725.2596 [M + 1]$^+$ (calcd for $C_{41}H_{45}O_8SSi^+$, 725.2599); *anal*. C 67.78, H 6.05%, calcd for $C_{41}H_{44}O_8SSi$, C 67.93, H 6.12%.

***E*-Isomer 24b:** mp 179−181 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.70 [4H, dd, J = 8.0 Hz, 1.5 Hz, Ph(H-2, H-6)], 7.35 [2H, m, Ph(H-4)], 7.32 [4H, m, Ph(H-3, H-5)], 7.06 (2H, d, J = 8.0 Hz, H-3″, H-5″), 7.02 (1H, d, J = 8.7 Hz, H-6′), 6.64 (1H, d, J = 16.2 Hz, H-1′a), 6.58 (1H, d, J = 16.2 Hz, H-1a), 6.44 (1H, d, J = 8.5 Hz, H-5′), 6.43 (2H, s, H-2, H-6), 3.88 (6H, s, OCH_3-3, -5), 3.87 (3H, s, OCH_3-4), 2.82 (3H, s, OCH_3-4′), 2.12 (3H, s, CH_3-4″), 1.11 [9H, s, −C(CH_3)$_3$]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.1 (C, C-3, C-5), 150.1 (C, C-4′), 145.2 (C, C-4″), 139.5 (C, C-3′), 139.0 (C, C-2′), 137.7 (C, C-4), 134.5 [CH, Ph(C-2, C-6)], 134.3 [C, Ph(C-1)], 133.8 (C, C-1″), 133.1 (C, C-1), 129.5 (CH, C-3″, C-5″), 129.0 [CH, Ph(C-4)], 128.5 (CH, C-2″, C-6″), 127.8 (CH, C-1a), 127.1 [CH, Ph(C-3, C-5)], 124.7 (C, C-1′), 122.2 (CH, C-1′a), 117.1 (CH, C-6′), 110.1 (CH, C-5′), 103.5 (CH, C-2, C-6), 60.9 (CH$_3$, OCH_3-4), 56.1 (CH$_3$, OCH_3-3, -5), 54.0 (CH$_3$, OCH_3-4′), 26.4 [CH$_3$, −C(CH_3)$_3$], 21.4 (CH$_3$, CH_3-4″), 20.0 [C, −C(CH$_3$)$_3$]; HRMS m/z 725.2596 [M + 1]$^+$ (calcd for $C_{41}H_{45}O_8SSi^+$, 725.2599).

(*Z*)/(*E*)-(3,4,5-Trimethoxy)-(2′-(*p*-toluenesulfonyloxy)-3′-[(*tert*-butyldimethylsilyl)oxy])stilbene (25a/25b). *n*-BuLi (2.5 M in hexanes, 6.0 mL, 15.0 mmol) was added dropwise to a well-stirred solution of Wittig salt **23** (7.85 g, 15.0 mmol) in THF (250 mL, anhydrous) at 0 °C. The reaction mixture was then warmed to rt, stirred for 15 min, and cooled to −78 °C. Aldehyde **20** (3.70 g, 8.47 mmol) in THF (30 mL, anhydrous) was added dropwise to the reaction mixture and stirred until the temperature gradually warmed to rt. The reaction was quenched by careful addition of H_2O (100 mL) and extracted with Et_2O (3 × 200 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 10% A/90% B over 3.18 min (1 CV), 10% A/90% B → 50% A/50% B over 33.0 min (10 CV), 50% A/50% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded the *Z*-isomer **25a** (4.44 g, 7.39 mmol, 87% yield) as an off-white solid and the *E*-isomer **25b** (0.293 g, 0.487 mmol, 6% yield) as an off-white solid.

***Z*-Isomer 25a:** mp 139−141 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.24 (2H, d, J = 8.4 Hz, H-3″, H-5″), 6.76 (1H, d, J = 8.6 Hz, H-6′), 6.60 (1H, d, J = 8.6 Hz, H-5′), 6.44 (2H, s, H-2, H-6), 6.16 (2H, s, H-1a, H-1′a), 3.82 (3H, s, OCH_3-4), 3.75 (3H, s, OCH_3-4′), 3.66 (6H, s, OCH_3-3, -5), 2.38 (3H, s, CH_3-4″), 0.95 [9H, s, −C(CH_3)$_3$], 0.04 [6H, s, −Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.6 (C, C-3, C-5), 151.3 (C, C-4′), 144.7 (C, C-4″), 140.2 (C, C-2′), 139.1 (C, C-3′), 137.0 (C, C-4), 134.6 (C, C-1″), 132.2 (C, C-1), 130.4 (CH, C-1a), 129.5 (CH, C-3″, C-5″), 128.4 (CH, C-2″, C-6″), 125.3 (C, C-1′), 124.7 (CH, C-1′a), 122.1 (CH, C-6′), 109.5 (CH, C-5′), 106.1 (CH, C-2, C-6), 60.8 (CH$_3$, OCH_3-4), 55.9 (CH$_3$, OCH_3-3, -5), 55.4 (CH$_3$, OCH_3-4′), 25.7 [CH$_3$, −C(CH_3)$_3$], 21.6 (CH$_3$, CH_3-4″), 18.6 [C, −C(CH$_3$)$_3$], −4.5 [CH$_3$, −Si(CH_3)$_2$]; HRMS m/z 600.2223 [M]$^+$ (calcd for $C_{31}H_{40}O_8SSi^+$, 600.2208); *anal*. C 61.77, H 6.74%, calcd for $C_{31}H_{40}O_8SSi$, C 61.97, H 6.71%. Single-crystal X-ray diffraction further confirmed the *Z*-configuration of **25a**.[34] X-ray CCDC #736463.

***E*-Isomer 25b:** mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.13 (1H, d, J = 8.8 Hz, H-6′), 7.08 (2H, d, J = 8.0 Hz, H-3″, H-5″), 6.78 (1H, d, J = 8.8 Hz, H-5′), 6.67 (1H, d, J = 16.2 Hz, H-1′a), 6.62 (1H, d, J = 16.1 Hz, H-1a), 6.46 (2H, s, H-2, H-6), 3.88 (6H, s, OCH_3-3, -5), 3.87 (3H, s, OCH_3-4), 3.82 (3H, s, OCH_3-4′), 2.16 (3H, s, CH_3-4″), 1.01 [9H, s, −C(CH_3)$_3$], 0.13 [6H, s, −Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.1 (C, C-3, C-5), 151.6 (C, C-4′), 145.1 (C, C-4″), 140.1 (C, C-2′), 139.4 (C, C-3′), 137.7 (C, C-4), 133.9 (C, C-1″), 133.1 (C, C-1), 129.5 (CH, C-3″, C-5″), 128.4 (CH, C-2″, C-6″), 128.0 (CH, C-1′a), 125.0 (C, C-1′), 122.1 (CH, C-1a), 117.3 (CH, C-6′), 110.2 (CH, C-5′), 103.5 (CH, C-2, C-6), 60.9 (CH$_3$, OCH_3-4), 56.1 (CH$_3$, OCH_3-3, -5), 55.4 (CH$_3$, OCH_3-4′), 25.8 [CH$_3$, C(CH_3)$_3$-3′], 21.4 (CH$_3$, CH_3-4″), 18.7 [C, −C(CH$_3$)$_3$], −4.4 [CH$_3$, −Si(CH_3)$_2$]; HRMS m/z 601.2286 [M + 1]$^+$ (calcd for $C_{31}H_{41}O_8SSi^+$, 601.2286); *anal*. C 62.05, H 6.76%, calcd for $C_{31}H_{40}O_8SSi$, C 61.97, H 6.71%.

(*Z*)-(3,4,5-Trimethoxy)-(2′-(methylsulfonyloxy)-3′-[(*tert*-butyldiphenylsilyl)oxy])stilbene (26a). *n*-BuLi (2.5 M in hexanes, 3.10 mL, 7.75 mmol) was added dropwise to a solution of Wittig salt **23** (2.10 g, 4.01 mmol) in THF (50 mL, anhydrous) at 0 °C. The reaction mixture was then warmed to rt, stirred for 15 min, and then cooled to −78 °C. A solution of aldehyde **21** (1.23 g, 2.54 mmol) in THF (15 mL, anhydrous) was added dropwise to the reaction mixture, and the reaction was stirred until the temperature gradually warmed to rt. The reaction was quenched by careful addition of H_2O (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 50 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 10% A/90% B over 1.39 min (1 CV), 10% A/90% B → 50% A/50% B over 16.3 min (10 CV), 50% A/50% B over 3.18 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded the *Z*-isomer **26a** (1.28 g, 1.97 mmol, 78% yield) as an off-white solid: mp 70−72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 [4H, m, Ph(H-2, H-6)], 7.35 [2H, m, Ph(H-4)], 7.33 [4H, m, Ph(H-3, H-5)], 6.73 (1H, d, J = 8.6 Hz, H-6′), 6.69 (1H, d, J = 12.0 Hz, H-1′a), 6.61 (1H, d, J = 12.0 Hz, H-1a), 6.52 (2H, s, H-2, H-6), 6.33 (1H, d, J = 8.6 Hz, H-5′), 3.82 (3H, s, OCH$_3$-4), 3.67 (6H, s, OCH$_3$-3, -5), 3.25 (3H, s, −OSO$_2$CH$_3$), 2.85 (3H, s, OCH$_3$-4′), 1.07 [9H, s, −C(CH$_3$)$_3$]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.8 (C, C-3, C-5), 149.9 (C, C-4′), 139.0 (C, C-2′), 138.7 (C, C-3′), 137.3 (C, C-4), 134.4 [CH, Ph(C-2, C-6)], 134.2 [C, Ph(C-1)], 132.0 (C, C-1), 131.5 (CH, C-1a), 129.2 [CH, Ph(C-4)], 127.3 [CH, Ph(C-3, C-5)], 125.4 (C, C-1′), 125.1 (CH, C-1′a), 122.4 (CH, C-6′), 109.7 (CH, C-5′), 106.3 (CH, C-2, C-6), 60.9 (CH$_3$, OCH$_3$-4), 55.9 (CH$_3$, OCH$_3$-3, -5), 54.1 (CH$_3$, OCH$_3$-4′), 40.1 (CH$_3$, −OSO$_2$CH$_3$), 26.6 [CH$_3$, −C(CH$_3$)$_3$], 20.0 [C, −C(CH$_3$)$_3$]; HRMS m/z 649.2285 [M + 1]$^+$ (calcd for $C_{35}H_{41}O_8SSi^+$, 649.2286); *anal*. C 64.61, H 6.28%, calcd for $C_{35}H_{40}O_8SSi$, C 64.79, H 6.21%.

(*Z*)/(*E*)-(3,4,5-Trimethoxy)-(2′-isopropyloxy-3′-[*p*-toluenesulfonyloxy])stilbene (27a/27b). *n*-BuLi (2.5 M in hexanes, 22.0 mL, 55.0 mmol) was added dropwise to a well-stirred solution of Wittig salt **4** (25.85 g, 49.39 mmol) in THF (250 mL, anhydrous) at 0 °C. The reaction mixture was then warmed to rt, stirred for 30 min, and then cooled to −78 °C. A solution of aldehyde **21** (15.00 g, 41.16 mmol) in THF (30 mL, anhydrous) was added dropwise to the reaction mixture, and the reaction was stirred until the temperature gradually warmed to rt. The reaction was quenched by careful addition of H_2O (100 mL) and extracted with Et_2O (3 × 200 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 20% A/80% B over 3.18 min (1 CV), 20% A/80% B → 70% A/30% B over 33.0 min (10 CV), 70% A/30% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded the *Z*-isomer **27a** (17.68 g, 33.44 mmol, 81% yield) as a white solid and the *E*-isomer **27b** (2.620 g, 4.956 mmol, 12% yield) as an off-white solid.

***Z*-Isomer 27a:** mp 153−155 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (2H, d, J = 8.5 Hz, H-2″, H-6″), 7.32 (2H, d, J = 8.5 Hz, H-3″, H-5″), 7.08 (1H, d, J = 8.5 Hz, H-6′), 6.55 (1H, d, J = 12.5 Hz, H-1′a), 6.53 (1H, d, J = 8.5 Hz, H-5′), 6.47 (1H, d, J = 12.0 Hz, H-1a), 6.44 (2H, s, H-2, H-6), 4.37 [1H, sept, J = 6.5 Hz, −CH(CH$_3$)$_2$], 3.83 (3H, s, OCH_3-4), 3.69 (3H, s, OCH_3-4′), 3.67 (6H, s, OCH_3-3, -5), 2.46 (3H, s, CH_3-4″), 1.06 [6H, d, J = 6.5 Hz, −CH(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.9 (C, C-4′), 152.8 (C, C-3, C-5), 150.0 (C, C-2′), 144.6 (C, C-4″), 137.1 (C, C-4), 135.1 (C, C-1″), 133.3 (C, C-3′), 132.5 (C, C-1), 129.9 (CH, C-1a), 129.2 (CH, C-3″, C-5″), 128.6 (CH, C-6′), 128.5 (CH, C-2″, C-6″), 125.4 (CH, C-1′a), 125.3 (C, C-1′), 106.8

(CH, C-5′), 106.0 (CH, C-2, C-6), 76.0 [CH, −*C*H(CH$_3$)$_2$], 60.9 (CH$_3$, O*C*H$_3$-4), 56.0 (CH$_3$, O*C*H$_3$-4′), 55.8 (CH$_3$, O*C*H$_3$-3, -5), 22.1 [CH$_3$, −CH(*C*H$_3$)$_2$], 21.6 (CH$_3$, *C*H$_3$-4″); HRMS *m*/*z* 528.1817 [M]$^+$ (calcd for $C_{28}H_{32}O_8S^+$, 528.1812); *anal*. C 63.63, H 6.16%, calcd for $C_{28}H_{32}O_8S$, C 63.62, H 6.10%. Single-crystal X-ray diffraction further confirmed the *Z*-configuration of **27a**.[34] X-ray CCDC #736601.

***E*-Isomer 27b:** mp 161−163 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.89 (2H, d, J = 8.4 Hz, H-2″, H-6″), 7.45 (2H, d, J = 8.8 Hz, H-6′), 7.35 (1H, d, J = 8.0 Hz, H-3″, H-5″), 7.23 (1H, d, J = 16.5 Hz, H-1′a), 6.89 (1H, d, J = 16.4 Hz, H-1a), 6.72 (2H, s, H-2, H-6), 6.68 (1H, d, J = 8.8 Hz, H-5′), 4.31 [1H, sept, J = 6.2 Hz, −C*H*(CH$_3$)$_2$], 3.90 (6H, s, OC*H*$_3$-3, -5), 3.87 (3H, s, OC*H*$_3$-4), 3.67 (3H, s, OC*H*$_3$-4′), 2.47 (3H, s, C*H*$_3$-4″), 1.14 [6H, d, J = 6.2 Hz, −CH(C*H*$_3$)$_2$]; ^{13}C NMR (CDCl$_3$, 125 MHz) δ 153.4 (C, C-3, C-5), 152.7 (C, C-4′), 149.7 (C, C-2′), 144.6 (C, C-4″), 137.8 (C, C-4), 134.9 (C, C-1″), 133.5 (C, C-1), 133.3 (C, C-3′), 129.2 (CH, C-3″, C-5″), 128.6 (CH, C-2″, C-6″), 127.8 (CH, C-1a), 125.8 (C, C-1′), 124.0 (CH, C-6′), 122.8 (CH, C-1′a), 107.6 (CH, C-5′), 103.4 (CH, C-2, C-6), 76.9 [CH, −*C*H(CH$_3$)$_2$], 61.0 (CH$_3$, O*C*H$_3$-4), 56.1 (CH$_3$, O*C*H$_3$-3, -5), 55.9 (CH$_3$, O*C*H$_3$-4′), 22.2 [CH$_3$, −CH(*C*H$_3$)$_2$], 21.7 (CH$_3$, *C*H$_3$-4″); HRMS *m*/*z* 529.1891 [M + 1]$^+$ (calcd for $C_{28}H_{33}O_8S^+$, 529.1891); *anal*. C 63.68, H 6.29%, calcd for $C_{28}H_{32}O_8S$, C 63.62, H 6.10%.

[TMAH][Al$_2$Cl$_7$].[37] To a suspension of AlCl$_3$ (13.52 g, 101.4 mmol) in 100 mL of CH$_2$Cl$_2$ cooled to 0 °C was added with stirring trimethylammonium chloride [TMAH] (4.85 g, 50.67 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for 2 h. This clear yellow solution of the ionic liquid was used as such for the deprotection of isopropyl ether of CA-1.

(*Z*)- (3,4,5-Trimethoxy)-(2′-[*p*-toluenesulfonyloxy]-3′-hydroxy)stilbene (28a). A mixture of stilbene **24a** (1.26 g, 1.74 mmol) and KF (0.151 g, 2.60 mmol) in DMF (20 mL, anhydrous) was stirred for a few minutes. HBr (0.100 mL, 48% solution in water) was added to the reaction mixture, and the reaction mixture was sonicated in a water bath at rt and monitored by TLC to completion. After 60 min, water was added to the reaction mixture followed by extraction with Et$_2$O (2 × 100 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 20% A/80% B over 3.18 min (1 CV), 20% A/80% B → 75% A/25% B over 33.0 min (10 CV), 75% A/25% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded phenol **28a** (0.760 g, 1.56 mmol, 90% yield) as a white solid.

(*Z*)-(3,4,5-Trimethoxy)-(2′-[*p*-toluenesulfonyloxy]-3′-hydroxy)stilbene (28a). A mixture of stilbene **25a** (1.22 g, 2.03 mmol) and KF (0.420 g, 7.23 mmol) in DMF (20 mL, anhydrous) was stirred for a few minutes. HBr (0.3 mL, 48% solution in water) was added to the reaction mixture, sonicated in a water bath at rt, and monitored by TLC to completion. After 60 min, water was added to the reaction mixture followed by extraction with Et$_2$O (2 × 100 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 20% A/80% B over 3.18 min (1 CV), 20% A/80% B → 75% A/25% B over 33.0 min (10 CV), 75% A/25% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded phenol **28a** (0.921 g, 1.89 mmol, 93% yield) as a white solid: mp 137−138 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.91 (2H, d, J = 8.4 Hz, H-2″, H-6″), 7.29 (2H, d, J = 8.0 Hz, H-3″, H-5″), 6.71 (1H, d, J = 8.6 Hz, H-6′), 6.62 (1H, d, J = 8.6 Hz, H-5′), 6.43 (2H, s, H-2, H-6), 6.36 (1H, d, J = 12.0 Hz, H-1a), 6.32 (1H, d, J = 12.0 Hz, H-1′a), 5.89 (1H, b, O*H*-3′), 3.86 (3H, s, OC*H*$_3$-4′), 3.82 (3H, s, OC*H*$_3$-4), 3.67 (6H, s, OC*H*$_3$-3, -5), 2.42 (3H, s, C*H*$_3$-4″); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 152.7 (C, C-3, C-5), 147.4 (C, C-4′), 145.3 (C, C-4″), 139.4 (C, C-3′), 137.2 (C, C-4), 135.4 (C, C-2′), 133.5 (C, C-1″), 132.1 (C, C-1), 131.3 (CH, C-1a), 129.5 (CH, C-3″, C-5″), 128.5 (CH, C-2″, C-6″), 125.7 (C, C-1′), 124.2 (CH, C-1′a), 120.8 (CH, C-6′), 109.2 (CH, C-5′), 106.2 (CH, C-2, C-6), 60.9 (CH$_3$, O*C*H$_3$-4), 56.4 (CH$_3$, O*C*H$_3$-4′), 55.9 (CH$_3$, O*C*H$_3$-3, -5), 21.7 (CH$_3$, *C*H$_3$-4″); HRMS *m*/*z* 487.1421 [M + 1]$^+$ (calcd for $C_{25}H_{27}O_8S^+$, 487.1421); *anal*. C 61.75, H 5.57%, calcd for $C_{25}H_{26}O_8S$, C 61.72, H 5.39%.

(*E*)-(3,4,5-Trimethoxy)-(2′-[*p*-toluenesulfonyloxy]-3′-hydroxy)stilbene (28b). A mixture of **25b** (0.21 g, 0.35 mmol) and KF (0.26 g, 4.5 mmol) in DMF (25 mL, anhydrous) was stirred for a few minutes. HBr (0.30 mL, 48% solution in water) was added to the reaction mixture, which was subjected to sonication in a water bath at rt. The reaction mixture was monitored by TLC to completion. After 60 min, water was added to the reaction mixture followed by extraction with Et$_2$O (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 25 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 20% A/80% B over 1.19 min (1 CV), 20% A/80% B → 75% A/25% B over 13.12 min (10 CV), 75% A/25% B over 2.38 min (2 CV); flow rate 25.0 mL/min; monitored at λ 254 and 280 nm] afforded phenol **28b** (0.14 g, 0.29 mmol, 82% yield) as a pink solid: mp 175−177 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.84 (2H, d, J = 8.4 Hz, H-2″, H-6″), 7.18 (2H, d, J = 9.1 Hz, H-3″, H-5″), 7.11 (1H, d, J = 8.6 Hz, H-6′), 6.85 (1H, d, J = 16.2 Hz, H-1′a), 6.81 (1H, d, J = 8.6 Hz, H-5′), 6.72 (1H, d, J = 16.2 Hz, H-1a), 6.55 (2H, s, H-2, H-6), 5.83 (1H, b, O*H*-3′), 3.93 (3H, s, OC*H*$_3$-4′), 3.89 (6H, s, OC*H*$_3$-3, -5), 3.88 (3H, s, OC*H*$_3$-4), 2.29 (3H, s, C*H*$_3$-4″); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 153.2 (C, C-3, C-5), 147.6 (C, C-4′), 145.4 (C, C-4″), 139.5 (C, C-3′), 137.9 (C, C-4), 135.2 (C, C-2′), 133.3 (C, C-1″), 133.0 (C, C-1), 129.6 (CH, C-3″, C-5″), 129.0 (CH, C-1a), 128.5 (CH, C-2″, C-6″), 125.5 (C, C-1′), 121.7 (CH, C-1′a), 116.2 (CH, C-6′), 109.7 (CH, C-5′), 103.7 (CH, C-2, C-6), 60.9 (CH$_3$, O*C*H$_3$-4), 56.4 (CH$_3$, O*C*H$_3$-4′), 56.1 (CH$_3$, O*C*H$_3$-3, -5), 21.6 (CH$_3$, *C*H$_3$-4″); HRMS *m*/*z* 486.1346 [M]$^+$ (calcd for $C_{25}H_{26}O_8S^+$, 486.1343); *anal*. C 61.69, H 5.39%, calcd for $C_{25}H_{26}O_8S$, C 61.72, H 5.39%.

(*Z*)-(3,4,5-Trimethoxy)-(2′-[methanesulfonyloxy]-3′-hydroxy)stilbene (29a). To a solution of **26a** (1.05 g, 1.62 mmol) in THF (25 mL, anhydrous) was added TBAF (1.70 mL, 1.0 M solution in THF), and the solution was stirred for a few minutes. The reaction mixture was monitored by TLC to completion. After 60 min, water (10 mL) was added to the reaction mixture followed by extraction with Et$_2$O (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 25 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 20% A/80% B over 3.18 min (1 CV), 20% A/80% B → 70% A/30% B over 33.0 min (10 CV), 70% A/30% B over 6.36 min (2 CV); flow rate 25.0 mL/min; monitored at λ 254 and 280 nm] afforded phenol **29a** (0.599 g, 1.46 mmol, 90% yield) as a white solid: mp 55−58 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 6.73 (1H, d, J = 8.6 Hz, H-6′), 6.64 (1H, d, J = 8.6 Hz, H-5′), 6.63 (1H, d, J = 12.1 Hz, H-1a), 6.60 (1H, d, J = 12.0 Hz, H-1′a), 6.48 (2H, s, H-2, H-6), 3.88 (3H, s, OC*H*$_3$-4′), 3.81 (3H, s, OC*H*$_3$-4), 3.65 (6H, s, OC*H*$_3$-3, -5), 3.37 (3H, s, −OSO$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 152.8 (C, C-3, C-5), 146.8 (C, C-4′), 138.7 (C, C-3′), 137.2 (C, C-4), 135.3 (C, C-2′), 132.05 (C, C-1), 132.12 (CH, C-1a), 126.2 (C, C-1′), 124.1 (CH, C-1′a), 120.9 (CH, C-6′), 108.9 (CH, C-5′), 106.2 (CH, C-2, C-6), 60.8 (CH$_3$, O*C*H$_3$-4), 56.5 (CH$_3$, O*C*H$_3$-4′), 55.9 (CH$_3$, O*C*H$_3$-3, -5), 40.0 (CH$_3$, −OSO$_2$*C*H$_3$); HRMS *m*/*z* 411.1108 [M + 1]$^+$ (calcd for $C_{19}H_{23}O_8S^+$, 411.1108); *anal*. C 55.37, H 5.67%, calcd for $C_{19}H_{22}O_8S$, C 55.60, H 5.40%.

(*Z*)-(3,4,5-Trimethoxy)-(2′-hydroxy-3′-[*p*-toluenesulfonyloxy])stilbene (30a). To a solution of **27a** (3.990 g, 7.546 mmol) in CH$_2$Cl$_2$ (100 mL) cooled to 0 °C was added dropwise ionic liquid (46.00 mL, 23.32 mmol, 0.507 M [TMAH][Al$_2$Cl$_7$] solution in CH$_2$Cl$_2$) while stirring the solution. The reaction was monitored by TLC. After the reaction was complete (typically 5−10 min), ice cold water was added to quench the reaction. The mixture was stirred vigorously for 2 min and the organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 100 mL), and the combined organic phase was washed with brine, dried over MgSO$_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 40% A/60% B over 3.18 min (1 CV), 40% A/60% B → 80% A/20% B over 33.0 min (10 CV), 80% A/20% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded phenol **30a** (2.99 g, 6.145 mmol, 81%) as an off-white solid: mp 137−138 °C; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.85 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.34 (2H, d, J = 8.4 Hz, H-3″, H-5″), 7.03 (1H, d, J = 8.8 Hz, H-6′), 6.67 (1H, d, J = 8.8 Hz, H-5′), 6.56 (1H, d, J = 11.8 Hz, H-1a), 6.43 (2H, s, H-2, H-6), 6.35 (1H, d, J = 11.8 Hz, H-1′a), 3.81 (3H, s, OC*H*$_3$-4), 3.66 (6H, s, OC*H*$_3$-3, -5), 3.66 (3H, s, OC*H*$_3$-4′), 2.46 (3H, s, C*H*$_3$-4″); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 152.8

(C, C-3, C-5), 152.3 (C, C-4′), 144.9 (C, C-4″), 143.0 (C, C-2′), 137.2 (C, C-4), 134.5 (C, C-1″), 132.4 (CH, C-1a), 131.9 (C, C-1), 131.8 (C, C-3′), 129.4 (CH, C-3″, C-5″), 128.6 (CH, C-6′), 128.4 (CH, C-2″, C-6″), 125.1 (C, C-1′), 123.5 (CH, C-1′a), 109.8 (CH, C-5′), 106.2 (CH, C-2, C-6), 60.8 (CH_3, OCH_3-4), 56.1 (CH_3, OCH_3-4′), 55.9 (CH_3, OCH_3-3, -5), 21.7 (CH_3, CH_3-4″); HRMS *m*/*z* 486.1349 $[M]^+$ (calcd for $C_{25}H_{26}O_8S^+$, 486.1343); *anal*. C 61.46, H 5.35%, calcd for $C_{25}H_{26}O_8S$, C 61.72, H 5.39%.

(*E*)-(3,4,5-Trimethoxy)-(2′-hydroxy-3′-[*p*-toluenesulfonyloxy])stilbene (30b). To a solution of **27b** (0.53 g, 1.0 mmol) in CH_2Cl_2 (25 mL) cooled to 0 °C was added dropwise ionic liquid (6.00 mL, 3.04 mmol, 0.517 M $[TMAH][Al_2Cl_7]$ solution in CH_2Cl_2) while stirring the solution. The reaction was monitored by TLC. After the reaction was complete (typically 5−10 min), ice cold water was added to quench the reaction. The mixture was stirred vigorously for 2 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography of the crude product using a prepacked 25 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 40% A/60% B over 1.19 min (1 CV), 40% A/60% B → 80% A/20% B over 13.12 min (10 CV), 80% A/20% B over 2.38 min (2 CV); flow rate 25.0 mL/min; monitored at λ 254 and 280 nm] afforded phenol **30b** (0.392 g, 0.80 mmol, 81%) as an off-white solid: mp 137−138 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (2H, d, *J* = 8.2 Hz, H-2″, H-6″), 7.36 (1H, d, *J* = 8.8 Hz, H-6′), 7.33 (2H, d, *J* = 8.0 Hz, H-3″, H-5″), 7.26 (1H, d, *J* = 16.4 Hz, H-1′a), 6.99 (1H, d, *J* = 16.4 Hz, H-1a), 6.74 (2H, s, H-2, H-6), 6.37 (1H, d, *J* = 8.8 Hz, H-5′), 3.91 (6H, s, OCH_3-3, -5), 3.87 (3H, s, OCH_3-4), 3.48 (3H, s, OCH_3-4′), 2.46 (3H, s, CH_3-4″); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.3 (C, C-3, C-5), 151.8 (C, C-4′), 147.7 (C, C-2′), 145.9 (C, C-4″), 137.7 (C, C-4), 133.6 (C, C-1), 131.5 (C, C-1″), 129.4 (CH, C-3″, C-5″), 129.0 (CH, C-2″, C-6″), 128.3 (CH, C-1a), 126.9 (C, C-3′), 125.0 (CH, C-6′), 122.0 (CH, C-1′a), 120.0 (C, C-1′), 103.9 (CH, C-5′), 103.5 (CH, C-2, C-6), 60.9 (CH_3, OCH_3-4), 56.1 (CH_3, OCH_3-3, -5), 55.5 (CH_3, OCH_3-4′), 21.7 (CH_3, CH_3-4″); HRMS *m*/*z* 487.1418 $[M + 1]^+$ (calcd for $C_{25}H_{27}O_8S^+$, 487.1421).

(*Z*)-3(*S*),4(*S*),5(*R*)-Triacetoxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-2′-[*p*-toluenesulfonyloxy]-3′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid Methyl Ester (32a). A mixture of phenol **28a** (0.762 g, 1.57 mmol) and Cs_2CO_3 (2.15 g, 6.60 mmol) in acetone (20 mL, anhydrous) was stirred for 10 min under N_2. Bromide **31** (1.21 g, 3.05 mmol) was added to this reaction mixture, which was subsequently stirred for 24 h. The suspension formed was filtered through a Buchner funnel, and the solid was washed with acetone and ether. The organic solvents were evaporated under reduced pressure to afford a viscous dark liquid. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 40% A/60% B over 3.18 min (1 CV), 40% A/60% B → 70% A/30% B over 33.0 min (10 CV), 70% A/30% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded glucuronate **32a** (0.450 g, 0.562 mmol, 36% yield) as an off-white solid: mp 95−97 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (2H, d, *J* = 8.3 Hz, H-2″, H-6″), 7.45 (2H, d, *J* = 8.0 Hz, H-3″, H-5″), 6.97 (1H, d, *J* = 8.8 Hz, H-6′), 6.63 (1H, d, *J* = 8.8 Hz, H-5′), 6.61 (1H, d, *J* = 12.1 Hz, H-1a), 6.58 (1H, d, *J* = 12.1 Hz, H-1′a), 6.52 (2H, s, H-2, H-6), 5.09 (1H, t, *J* = 9.4 Hz, H-G3), 4.98 (1H, t, *J* = 9.8 Hz, H-G4), 4.86 (1H, d, *J* = 7.6 Hz, H-G1), 4.28 (1H, dd, *J* = 7.6, 9.1 Hz, H-G2), 3.83 (3H, s, OCH_3-4), 3.78 (1H, d, *J* = 9.8 Hz, H-G5), 3.77 (3H, s, OCH_3-4′), 3.75 (3H, s, COOCH_3-G6), 3.68 (6H, s, OCH_3-3, -5), 2.54 (3H, s, CH_3-4″), 2.03 (3H, s, OCOCH_3-G3), 2.02 (3H, s, OCOCH_3-G2), 2.00 (3H, s, OCOCH_3-G4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0 (C, O*C*OCH$_3$-G3), 169.4 (C, O*C*OCH$_3$-G4), 169.1 (C, O*C*OCH$_3$-G2), 166.6 (C, *C*OOCH$_3$-G6), 152.8 (C, C-3, C-5), 151.7 (C, C-4′), 144.8 (C, C-4″), 142.6 (C, C-2′), 137.5 (C, C-3′), 137.1 (C, C-4), 135.0 (C, C-1″), 132.3 (C, C-1), 131.9 (CH, C-1a), 129.6 (CH, C-3″, C-5″), 128.7 (CH, C-2″, C-6″), 126.7 (CH, C-6′), 126.5 (C, C-1′), 124.1 (CH, C-1′a), 110.2 (CH, C-5′), 106.3 (CH, C-2, C-6), 100.4 (CH, C-G1), 72.3 (CH, C-G5), 72.1 (CH, C-G3), 71.4 (CH, C-G2), 68.8 (CH, C-G4), 60.9 (CH_3, OCH_3-4), 56.2 (CH_3, OCH_3-4′), 56.0 (CH_3, OCH_3-3, -5), 52.8 (CH_3, COOCH_3-G6), 21.6 (CH_3, CH_3-4″), 20.7 (CH_3, OCOCH_3-G2/-G3), 20.6 (CH_3, OCOCH_3-G2/-G3), 20.5 (CH_3, OCOCH_3-G4); HRMS *m*/*z* 825.2030 $[M + Na]^+$ (calcd for $C_{38}H_{42}O_{17}SNa^+$, 825.2035); *anal*. C 56.74, H 5.41, S 3.82%, calcd for $C_{38}H_{42}O_{17}S$, C 56.85, H 5.27, S 3.99%.

(*E*)-3(*S*),4(*S*),5(*R*)-Triacetoxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-2′-[*p*-toluenesulfonyloxy]-3′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid Methyl Ester (32b). A mixture of phenol **28b** (0.114 g, 0.234 mmol) and Cs_2CO_3 (0.450 g, 1.38 mmol) in acetone (10 mL, anhydrous) was stirred for 10 min under N_2. Bromide **31** (0.301 g, 0.758 mmol) was added to this reaction mixture, which was subsequently stirred for 24 h. The suspension formed was filtered through a Buchner funnel, and the solid was washed with acetone and ether. The organic solvents were evaporated under reduced pressure to afford a viscous dark liquid. Flash chromatography of the crude product using a prepacked 25 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 40% A/60% B over 1.19 min (1 CV), 40% A/60% B → 70% A/30% B over 13.12 min (10 CV), 70% A/30% B over 2.38 min (2 CV); flow rate 25.0 mL/min; monitored at λ 254 and 280 nm] afforded the glucuronate **32b** (0.120 g, 0.150 mmol, 64% yield) as a pink-white solid: mp 118−121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (2H, d, *J* = 8.2 Hz, H-2″, H-6″), 7.45 (1H, d, *J* = 8.9 Hz, H-6′), 7.42 (2H, d, *J* = 8.4 Hz, H-3″, H-5″), 7.31 (1H, d, *J* = 16.2 Hz, H-1′a), 6.90 (1H, d, *J* = 16.2 Hz, H-1a), 6.84 (1H, d, *J* = 8.9 Hz, H-5′), 6.75 (2H, s, H-2, H-6), 5.11 (1H, t, *J* = 9.4 Hz, H-G3), 4.93 (1H, t, *J* = 9.8 Hz, H-G4), 4.92 (1H, d, *J* = 7.7 Hz, H-G1), 4.34 (1H, dd, *J* = 7.7, 9.2 Hz, H-G2), 3.91 (6H, s, OCH_3-3, -5), 3.86 (3H, s, OCH_3-4), 3.84 (3H, s, OCH_3-4′), 3.78 (1H, d, *J* = 10.0 Hz, H-G5), 3.73 (3H, s, COOCH_3-G6), 2.49 (3H, s, CH_3-4″), 2.03 (6H, s, OCOCH_3-G2, -G3), 2.00 (3H, s, OCOCH_3-G4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0 (C, O*C*OCH$_3$-G3), 169.4 (C, O*C*OCH$_3$-G4), 169.1 (C, O*C*OCH$_3$-G2), 166.6 (C, *C*OOCH$_3$-G6), 153.3 (C, C-3, C-5), 151.9 (C, C-4′), 144.9 (C, C-4″), 142.1 (C, C-2′), 138.0 (C, C-4), 137.6 (C, C-3′), 134.7 (C, C-1″), 133.1 (C, C-1), 129.6 (CH, C-3″, C-5″), 129.3 (CH, C-1a), 128.7 (CH, C-2″, C-6″), 126.1 (C, C-1′), 121.5 (CH, C-1′a), 121.4 (CH, C-6′), 110.9 (CH, C-5′), 103.7 (CH, C-2, C-6), 100.3 (CH, C-G1), 72.2 (CH, C-G5), 72.0 (CH, C-G3), 71.3 (CH, C-G2), 68.8 (CH, C-G4), 60.9 (CH_3, OCH_3-4), 56.2 (CH_3, OCH_3-4′), 56.1 (CH_3, OCH_3-3, -5), 52.7 (CH_3, COOCH_3-G6), 21.5 (CH_3, CH_3-4″), 20.6 (CH_3, OCOCH_3-G2, -G3), 20.5 (CH_3, OCOCH_3-G4); HRMS *m*/*z* 803.2212 $[M + 1]^+$ (calcd for $C_{38}H_{43}O_{17}S^+$, 803.2216); *anal*. C 57.04, H 5.32%, calcd for $C_{38}H_{42}O_{17}S$, C 56.85, H 5.27%.

(*Z*)-3(*S*),4(*S*),5(*R*)-Triacetoxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-2′-(methanesulfonyloxy)-3′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid Methyl Ester (33a). A mixture of phenol **29a** (0.722 g, 1.76 mmol) and Cs_2CO_3 (1.55 g, 4.76 mmol) in acetone (20 mL, anhydrous) was stirred for 10 min under N_2. Bromide **31** (0.886 g, 2.23 mmol) was added to this reaction mixture, which was subsequently stirred for 24 h. The suspension formed was filtered through a Buchner funnel, and the solid was washed with acetone and ether. The organic solvents were evaporated under reduced pressure to afford a viscous dark liquid. Flash chromatography of the crude product using a prepacked 50 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 40% A/60% B over 1.39 min (1 CV), 40% A/60% B → 70% A/30% B over 16.3 min (10 CV), 70% A/30% B over 3.18 min (2 CV); flow rate 40.00 mL/min; monitored at λ 254 and 280 nm] afforded glucuronate **33a** (0.177 g, 0.244 mmol, 14% yield) as an off-white solid: mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (1H, d, *J* = 8.8 Hz, H-6′), 6.66 (1H, d, *J* = 8.8 Hz, H-5′), 6.63 (1H, d, *J* = 11.9 Hz, H-1a), 6.57 (1H, d, *J* = 11.9 Hz, H-1′a), 6.47 (2H, s, H-2, H-6), 5.31 (2H, m, H-G3, H-G4), 5.22 (1H, m, H-G2), 5.13 (1H, d, *J* = 7.7 Hz, H-G1), 4.01 (1H, m, H-G5), 3.82 (3H, s, OCH_3-4′), 3.80 (3H, s, OCH_3-4), 3.74 (3H, s, COOCH_3-G6), 3.63 (6H, s, OCH_3-3, -5), 3.40 (3H, s, −OSO$_2$CH_3), 2.07 (3H, s, OCOCH_3-G2), 2.03 (3H, s, OCOCH_3-G3), 2.02 (3H, s, OCOCH_3-G4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0 (C, O*C*OCH$_3$-G3), 169.5 (C, O*C*OCH$_3$-G2), 169.4 (C, O*C*OCH$_3$-G4), 166.7 (C, *C*OOCH$_3$-G6), 152.8 (C, C-3, C-5), 151.2 (C, C-4′), 141.7 (C, C-2′), 137.6 (C, C-3′), 137.1 (C, C-4), 132.1 (C, C-1), 126.85 (CH, C-6′), 126.82 (C, C-1′), 123.9 (CH, C-1a, C-1′a), 110.4 (CH, C-5′), 106.2 (CH, C-2, C-6), 101.3 (CH, C-G1), 72.9 (CH, C-G5), 71.9 (CH, C-G3), 71.3 (CH, C-G2), 69.3 (CH, C-G4), 60.9 (CH_3, OCH_3-4), 56.4 (CH_3, OCH_3-4′), 55.9 (CH_3, OCH_3-3, -5), 53.0 (CH_3, COOCH_3-G6), 40.2 (CH_3, −OSO$_2$CH_3), 20.7 (CH_3, OCOCH_3-G2), 20.6 (CH_3, OCOCH_3-G3), 20.5 (CH_3, OCOCH_3-G4); HRMS *m*/*z* 727.1897 $[M + 1]^+$ (calcd for $C_{32}H_{39}O_{17}S^+$, 727.1902).

(*Z*)-3(*S*),4(*S*),5(*R*)-Triacetoxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-3′-(*p*-toluenesulfonyloxy)-2′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid Methyl Ester (34a). A mixture of phenol **30a** (3.500 g, 7.194 mmol), and Cs_2CO_3 (4.680 g, 14.36 mmol) in acetone (200 mL, anhydrous) was stirred for 10 min under N_2. Bromoglucuronate **31** (5.710 g, 14.38 mmol) was added to this reaction mixture, which was subsequently stirred for 24 h. The suspension was filtered through a Buchner funnel, and the solid was washed with acetone (50 mL) and ether (50 mL). The organic solvents were evaporated under reduced pressure to afford a dark viscous liquid. Flash chromatography of the crude product using a prepacked 100 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 80% A/20% B → 30% A/70% B over 0 to 66 min (20 CV), 30% A/70% B over 9.54 min (2 CV); flow rate 40.00 mL/min; monitored at λ 254 and 280 nm] afforded CA1-glucuronate **34a** (2.010 g, 2.510 mmol, 35% yield) as an off-white solid: mp 87−89 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.39 (2H, d, J = 8.2 Hz, H-3″, H-5″), 7.03 (1H, d, J = 8.8 Hz, H-6′), 6.60 (1H, d, J = 12.0 Hz, H-1′a), 6.53 (1H, d, J = 8.8 Hz, H-5′), 6.52 (1H, d, J = 12.1 Hz, H-1a), 6.39 (2H, s, H-2, H-6), 5.20 (1H, t, J = 9.4 Hz, H-G3), 5.17 (1H, d, J = 7.8 Hz, H-G1), 5.12 (1H, t, J = 9.8 Hz, H-G4), 4.85 (1H, dd, J = 7.8, 9.3 Hz, H-G2), 3.82 (3H, s, OCH_3-4), 3.80 (1H, d, J = 9.9 Hz, H-G5), 3.66 (6H, s, OCH_3-3, -5), 3.60 (3H, s, COOCH_3-G6), 3.52 (3H, s, OCH_3-4′), 2.50 (3H, s, CH_3-4″), 2.12 (3H, s, OCOCH_3-G2), 2.02 (3H, s, OCOCH_3-G3), 1.98 (3H, s, OCOCH_3-G4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0 (C, O*C*OCH$_3$-G3), 169.5 (C, O*C*OCH$_3$-G2), 169.3 (C, O*C*OCH$_3$-G4), 166.5 (CH$_3$, *C*OOCH$_3$-G6), 152.8 (C, C-3, C-5), 152.6 (C, C-4′), 147.1 (C, C-2′), 144.8 (C, C-4″), 137.2 (C, C-4), 134.7 (C, C-1″), 132.3 (C, C-3′), 132.0 (C, C-1), 130.8 (CH, C-1a), 129.4 (CH, C-3″, C-5″), 128.9 (CH, C-6′), 128.6 (CH, C-2″, C-6″), 125.1 (C, C-1′), 124.7 (CH, C-1′a), 108.4 (CH, C-5′), 106.1 (CH, C-2, C-6), 100.4 (CH, C-G1), 72.6 (CH, C-G5), 72.2 (CH, C-G3), 71.2 (CH, C-G2), 69.2 (CH, C-G4), 60.9 (CH$_3$, O*C*H$_3$-4), 55.9 (CH$_3$, O*C*H$_3$-3, -5), 55.8 (CH$_3$, O*C*H$_3$-4′), 52.7 (CH$_3$, COO*C*H$_3$-G6), 21.6 (CH$_3$, *C*H$_3$-4″), 20.8 (CH$_3$, OCO*C*H$_3$-G2), 20.6 (CH$_3$, OCO*C*H$_3$-G3), 20.5 (CH$_3$, OCO*C*H$_3$-G4); HRMS (ESI$^+$) *m*/*z* 825.2033 [M + Na]$^+$ (calcd for $C_{38}H_{42}O_{17}SNa^+$, 825.2035); *anal*. C 57.10, H 5.39, S 4.12%, calcd for $C_{38}H_{42}O_{17}S$, C 56.85, H 5.27, S 3.99%.

(*E*)-3(*S*),4(*S*),5(*R*)-Triacetoxy-6(*S*)-[(3,4,5-Trimethoxy)-(4′-methoxy-3′-(*p*-toluenesulfonyloxy)-2′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid Methyl Ester (34b). A mixture of phenol **30b** (0.650 g, 1.34 mmol) and Cs_2CO_3 (1.35 g, 4.14 mmol) in acetone (50 mL, anhydrous) was stirred for 10 min under N_2. Bromide **31** was added to this reaction mixture, which was subsequently stirred for 24 h. The suspension formed was filtered through a Buchner funnel, and the solid was washed with acetone and ether. The organic solvents were evaporated under reduced pressure to afford a viscous dark liquid. Flash chromatography of the crude product using a prepacked 25 g silica column [eluents: solvent A, EtOAc; solvent B, hexanes; gradient, 20% A/80% B over 1.19 min (1 CV), 20% A/80% B → 70% A/30% B over 13.12 min (10 CV), 70% A/30% B over 2.38 min (2 CV); flow rate 25.0 mL/min; monitored at λ 254 and 280 nm] afforded the glucuronate **34b** (0.604 g, 0.754 mmol, 56% yield) as an off-white solid: mp 108−110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (2H, d, J = 8.3 Hz, H-2″, H-6″), 7.46 (1H, d, J = 8.8 Hz, H-6′), 7.36 (2H, d, J = 8.0 Hz, H-3″, H-5″), 7.32 (1H, d, J = 16.4 Hz, H-1′a), 6.85 (1H, d, J = 16.3 Hz, H-1a), 6.78 (2H, s, H-2, H-6), 6.66 (1H, d, J = 8.9 Hz, H-5′), 5.27 (1H, sept, J = 5.0 Hz, H-G3), 5.17 (1H, m, H-G1), 5.16 (1H, m, H-G2), 5.15 (1H, m, H-G4), 3.94 (6H, s, OCH_3-3, -5), 3.92 (1H, d, J = 10.0 Hz, H-G5), 3.88 (3H, s, OCH_3-4), 3.57 (3H, s, COOCH_3-G6), 3.43 (3H, s, OCH_3-4′), 2.49 (3H, s, CH_3-4″), 2.08 (3H, s, OCOCH_3-G2), 2.03 (3H, s, OCOCH_3-G3), 2.00 (3H, s, OCOCH_3-G4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9 (C, O*C*OCH$_3$-G3), 169.7 (C, O*C*OCH$_3$-G2), 169.4 (C, O*C*OCH$_3$-G4), 166.7 (C, O*C*OCH$_3$-G5), 153.4 (C, C-3, C-5), 152.3 (C, C-4′), 147.1 (C, C-2′), 144.9 (C, C-4″), 137.9 (C, C-4), 134.3 (C, C-1″), 133.4 (C, C-1), 131.8 (C, C-3′), 129.3 (CH, C-3″, C-5″), 128.8 (CH, C-1a), 128.7 (CH, C-2″, C-6″), 125.8 (C, C-1′), 124.0 (CH, C-6′), 122.3 (CH, C-1′a), 108.8 (CH, C-5′), 103.8 (CH, C-2, C-6), 100.9 (CH, C-G1), 72.6 (CH, C-G5), 72.0 (CH, C-G3), 71.3 (CH, C-G2), 69.4 (CH, C-G4), 61.0 (CH$_3$, O*C*H$_3$-4), 56.2 (CH$_3$, O*C*H$_3$-3, -5), 55.6 (CH$_3$, O*C*H$_3$-4′), 52.7 (CH$_3$, COO*C*H$_3$-G6), 21.6 (CH$_3$, *C*H$_3$-4″), 20.8 (CH$_3$, OCO*C*H$_3$-G2), 20.6 (CH$_3$, OCO*C*H$_3$-G3), 20.4 (CH$_3$, OCO*C*H$_3$-G4); HRMS *m*/*z* 825.2031 [M + Na]$^+$ (calcd for $C_{38}H_{42}O_{17}SNa^+$, 825.2035); *anal*. C 56.81, H 5.28, S 3.85%, calcd for $C_{38}H_{42}O_{17}S$, C 56.85, H 5.27, S 3.99%.

(*Z*)-3(*S*),4(S),5(*R*)-Trihydroxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-3′-hydroxy-2′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid (5a). A solution of CA1-glucuronate **34a** (1.240 g, 1.584 mmol) and NaOH (6 mL, 2 M solution) in methanol (15 mL) in a sealed vessel was heated to 50 °C in a Biotage Initiator microwave for 30 min. The reaction was monitored by TLC, and after completion the mixture was transferred to a pear-shaped 200 mL flask, which was then cooled to −20 °C. The reaction mixture was then neutralized with HCl (6 mL, 2 M solution) in MeOH (10 mL) and cooled to −20 °C while stirring for 2 min. The aqueous solvents were evaporated under reduced pressure at 40 °C, leaving behind *Z*-CA1G1 (**5a**). Flash chromatography of the crude product using a prepacked 120 g RP-18 silica column [eluents: solvent A, water; solvent B, acetonitrile; gradient, 90% A/10% B → 60% A/40% B over 0 to 31.80 min (10 CV), 40% A/60% B over 31.80 to 38.16 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded glucuronic acid (**5a**; 0.490 g, 9.637 mmol, 62%) as an off-white solid: mp 65−67 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.15 (1H, b, O*H*-2′), 6.89 (1H, d, J = 12.2 Hz, H-1′a), 6.71 (1H, d, J = 8.6 Hz, H-6′), 6.69 (1H, d, J = 8.6 Hz, H-5′), 6.55 (2H, s, H-2, H-6), 6.44 (1H, d, J = 12.2 Hz, H-1a), 4.85 (1H, d, J = 7.8 Hz, H-G1), 3.96 (1H, d, J = 9.8 Hz, H-G5), 3.80 (3H, s, OCH_3-4′), 3.72 (1H, dd, J = 8.8, 9.6 Hz, H-G4), 3.70 (3H, s, OCH_3-4), 3.66 (1H, dd, J = 7.8, 9.1 Hz, H-G2), 3.64 (6H, s, OCH_3-3, -5), 3.60 (1H, dd, J = 8.8, 9.1 Hz, H-G3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.1 (C, *C*OOH-G6), 153.0 (C, C-3, C-5), 148.4 (C, C-4′), 143.7 (C, C-2′), 139.9 (C, C-3′), 137.5 (C, C-4), 132.7 (C, C-1), 129.3 (CH, C-1a), 126.0 (CH, C-1′a), 124.4 (C, C-1′), 119.4 (CH, C-6′), 108.8 (CH, C-5′), 106.4 (CH, C-2, C-6), 105.8 (CH, C-G1), 76.2 (CH, C-G3), 75.3 (CH, C-G5), 74.0 (CH, C-G2), 71.7 (CH, C-G4), 59.6 (CH$_3$, O*C*H$_3$-4), 55.6 (CH$_3$, O*C*H$_3$-4′), 55.2 (CH$_3$, O*C*H$_3$-3, -5); HRMS (EI$^+$) *m*/*z* 508.1580 [M]$^+$ (calcd for $C_{24}H_{28}O_{12}^+$, 508.1575); HRMS (ESI$^-$) *m*/*z* 507.1525 [M − 1]$^-$ (calcd for $C_{24}H_{27}O_{12}^-$, 507.1508).

(*E*)-3(*S*),4(*S*),5(*R*)-Trihydroxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-3′-hydroxy-2′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid (5b). A solution of glucuronate **34b** (0.810 g, 1.01 mmol) and NaOH (4 mL, 2 M solution) in methanol (16 mL) in a sealed vessel was heated to 60 °C in a Biotage Initiator microwave for 30 min. The reaction was monitored by TLC, and after completion, the reaction mixture was cooled to −20 °C and treated with dropwise addition of HCl (4 mL, 2 M solution) in MeOH (20 mL) while stirring for 5 min. The neutralized reaction mixture was then evaporated under reduced pressure to dryness at 40 °C, leaving behind *E*-CA1G1 (**5b**). Flash chromatography of the crude product using a prepacked 120 g RP-18 silica column [eluents: solvent A, acetonitrile; solvent B, water; gradient, 10% A/90% B → 40% A/60% B over 33.0 min (10 CV), 40% A/60% B over 6.36 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded *E*-CA1G1 (**5b**; 0.448 g, 0.881 mmol, 87%) as an off-white solid: mp 106−108 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.08 (1H, b, O*H*-2′), 7.76 (1H, d, J = 16.6 Hz, H-1′a), 7.23 (1H, d, J = 8.7 Hz, H-6′), 6.99 (1H, d, J = 16.5 Hz, H-1a), 6.91 (2H, s, H-2, H-6), 6.85 (1H, d, J = 8.8 Hz, H-5′), 4.84 (1H, d, J = 7.9 Hz, H-G1), 4.04 (1H, d, J = 9.7 Hz, H-G5), 3.88 (6H, s, OCH_3-3, -5), 3.84 (3H, s, OCH_3-4′), 3.76 (1H, m, H-G2), 3.75 (1H, m, H-G4), 3.74 (3H, s, OCH_3-4), 3.66 (1H, m, H-G3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.2 (C, *C*OOH-G6), 153.6 (C, C-3, C-5), 148.6 (C, C-4′), 143.4 (C, C-2′), 140.2 (C, C-3′), 137.9 (C, C-4), 133.8 (C, C-1), 127.6 (CH, C-1a), 124.6 (C, C-1′), 122.4 (CH, C-1′a), 114.7 (CH, C-6′), 109.9 (CH, C-5′), 106.1 (CH, C-G1), 103.8 (CH, C-2, C-6), 76.2 (CH, C-G3), 75.2 (CH, C-G5), 74.2 (CH, C-G2), 71.8 (CH, C-G4), 59.7 (CH$_3$, O*C*H$_3$-4), 55.64 (CH$_3$, O*C*H$_3$-4′), 55.61 (CH$_3$, O*C*H$_3$-3, -5); HRMS (ESI$^-$) *m*/*z* 507.1497 [M − 1]$^-$ (calcd for $C_{24}H_{27}O_{16}$, 507.1508).

(*Z*)-3(*S*),4(S),5(*R*)-Trihydroxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-2′-hydroxy-3′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid (6a). A solution of glucuronate **32a** (0.20 g, 0.25 mmol) and NaOH (1 mL, 2 M solution) in MeOH (4 mL) in a sealed vessel was heated to 60 °C in a microwave for 15 min. The reaction was monitored by TLC, and after completion, the reaction mixture was cooled to −20 °C and treated with dropwise addition of HCl (1 mL, 2 M solution) in MeOH (5 mL), while stirring for 5 min. The neutralized reaction mixture was then evaporated under reduced pressure to dryness at 40 °C, leaving behind *Z*-CA1G2 (**6a**). Flash chromatography of the crude product using a prepacked 12 g RP-18 silica column [eluents: solvent A, acetonitrile;

solvent B, water; gradient, 10% A/90% B over 1.15 min (1 CV), 10% A/90% B → 40% A/60% B over 12.3 min (10 CV), 40% A/60% B over 2.30 min (2 CV); flow rate 12.0 mL/min; monitored at λ 254 and 280 nm] afforded glucuronide **6a** (0.095 g, 0.19 mmol, 75%) as an off-white solid. Characterization of compound **6a** is detailed following an additional experimental procedure below.

(*Z*)-3(*S*),4(*S*),5(*R*)-Trihydroxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-2′-hydroxy-3′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid (6a). A solution of glucuronate **33a** (0.116 g, 0.160 mmol) and NaOH (0.250 mL, 2 M solution) in MeOH (4 mL) in a sealed vessel was heated to 50 °C in a microwave for 15 min. The reaction was monitored by TLC, and after completion, the reaction mixture was cooled to −20 °C and treated with dropwise addition of HCl (0.250 mL, 2 M solution) in MeOH (5 mL) while stirring for 5 min. The neutralized reaction mixture was then evaporated under reduced pressure to dryness at 40 °C, leaving behind *Z*-CA1G2 (**6a**). Flash chromatography of the crude product using a prepacked 12 g RP-18 silica column [eluents: solvent A, acetonitrile; solvent B, water; gradient, 10% A/90% B over 1.15 min (1 CV), 10% A/90% B → 40% A/60% B over 12.3 min (10 CV), 40% A/60% B over 2.30 min (2 CV); flow rate 12.0 mL/min; monitored at λ 254 and 280 nm] afforded glucuronide **6a** (0.068 g, 0.134 mmol, 84%) as an off-white solid: mp 65−67 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.90 (1H, d, J = 8.7 Hz, H-6′), 6.58 (2H, s, H-2, H-6), 6.54 (1H, d, J = 12.2 Hz, H-1′a), 6.40 (1H, d, J = 8.6 Hz, H-5′), 6.39 (1H, d, J = 12.3 Hz, H-1a), 4.56 (1H, d, J = 7.4 Hz, H-G1), 3.73 (3H, s, OCH_3-4′), 3.63 (3H, s, OCH_3-4), 3.59 (6H, s, OCH_3-3, -5), 3.43 (1H, d, J = 8.9 Hz, H-G5), 3.37 (1H, t, J = 7.5 Hz, H-G2), 3.26 (1H, t, J = 7.5 Hz, H-G4), 3.26 (1H, t, J = 8.6 Hz, H-G3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.6 (C, s, *C*OOH-G6), 152.4 (C, C-3, C-5), 152.2 (C, C-4′), 149.2 (C, C-2′), 136.5 (C, C-4), 134.3 (C, C-3′), 132.4 (C, C-1), 128.2 (CH, C-1a), 125.2 (CH, C-1′a), 124.9 (CH, C-6′), 118.0 (C, C-1′), 105.9 (CH, C-2, C-6), 105.5 (CH, C-G1), 103.4 (CH, C-5′), 75.7 (CH, C-G3), 75.5 (CH, C-G5), 73.4 (CH, C-G2), 71.9 (CH, C-G4), 60.0 (CH$_3$, O*C*H$_3$-4), 56.2 (CH$_3$, O*C*H$_3$-4′), 55.5 (CH$_3$, O*C*H$_3$-3, -5); HRMS (ESI$^-$) m/z 507.1524 [M − 1]$^-$ (calcd for $C_{24}H_{27}O_{12}^-$, 507.1508).

(*E*)-3(*S*),4(*S*),5(*R*)-Trihydroxy-6(*S*)-[(3,4,5-trimethoxy)-(4′-methoxy-2′-hydroxy-3′-stilbenyloxy)]tetrahydropyran-2(*S*)-carboxylic Acid (6b). A solution of glucuronate **32b** (0.105 g, 0.131 mmol) and NaOH (1 mL, 2 M solution) in MeOH (4 mL) in a sealed vessel was heated to 60 °C in a microwave for 15 min. The reaction was monitored by TLC, and after completion, the reaction mixture was cooled to −20 °C and treated with dropwise addition of HCl (1 mL, 2 M solution) in MeOH (5 mL) while stirring for 5 min. The neutralized reaction mixture was then evaporated under reduced pressure to dryness at 40 °C, leaving behind *E*-CA1G2 (**6b**). Flash chromatography of the crude product using a prepacked 60 g RP-18 silica column [eluents: solvent A, acetonitrile; solvent B, water; gradient, 10% A/90% B → 40% A/60% B over 16.3 min (10 CV), 40% A/60% B over 3.18 min (2 CV); flow rate 40.0 mL/min; monitored at λ 254 and 280 nm] afforded glucuronide **6b** (0.048 g, 0.094 mmol, 72%) as an off-white solid: mp 70−72 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.28 (1H, s, −O*H*-3′), 7.35 (1H, d, J = 8.8 Hz, H-6′), 7.29 (1H, d, J = 16.5 Hz, H-1′a), 7.09 (1H, d, J = 16.5 Hz, H-1a), 6.85 (2H, s, H-2, H-6), 6.61 (1H, d, J = 8.8 Hz, H-5′), 4.81 (1H, d, J = 7.4 Hz, H-G1), 4.01 (1H, d, J = 9.6 Hz, H-G5), 3.87 (6H, s, OCH$_3$-3, -5), 3.84 (3H, s, OCH$_3$-4), 3.73 (3H, s, OCH$_3$-4′), 3.73 (1H, t, J = 8.4 Hz, H-G4), 3.64 (2H, t, J = 8.5 Hz, H-G2), 3.62 (2H, m, J = 8.5 Hz, H-G3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 170.2 (C, s, *C*OOH-G6), 154.6 (C, C-3, C-5), 153.3 (C, C-4′), 149.7 (C, C-2′), 138.9 (C, C-4), 135.3 (C, C-1), 135.0 (C, C-3′), 128.3 (CH, C-1a), 123.8 (CH, C-6′), 123.6 (CH, C-1′a), 119.8 (C, C-1′), 107.0 (CH, C-G1), 105.1 (CH, C-5′), 104.6 (CH, C-2, C-6), 76.8 (CH, C-G3), 76.4 (CH, C-G5), 74.8 (CH, C-G2), 72.6 (CH, C-G4), 60.7 (CH$_3$, O*C*H$_3$-4), 56.8 (CH$_3$, O*C*H$_3$-4′), 56.5 (CH$_3$, O*C*H$_3$-3, -5); HRMS (ESI$^-$) m/z 507.1508 [M − 1]$^-$ (calcd for $C_{24}H_{27}O_{12}^-$, 507.1508).

X-ray Crystallographic Analysis of Compounds 22, 25a, and 27a. [34] Crystallographic data were collected on crystals with dimensions 0.28 × 0.27 × 0.17 mm^3 for **22**, 0.21 × 0.19 × 0.14 mm^3 for **25a**, and 0.32 × 0.23 × 0.22 mm^3 for **27a**. Data were collected at 110 K on a Bruker X8 Apex using Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods after correction of the data using SADABS.[40] Crystallographic data and refinement details for the complexes mentioned herein are found in the Supporting Information (Tables S1, S2, and S3). The thermal ellipsoid plots at 50% probability for compounds **22**, **25a**, and **27a** are displayed in the Supporting Information. All data were processed using Bruker AXS SHELXTL software, version 6.10.[41] All hydrogen atoms were placed in idealized positions, and all non-hydrogen atoms were refined anisotropically for **22**, **25a**, and **27a**.

Biology. Effects on Tubulin Polymerization. Bovine brain tubulin was purified as described previously.[42] To evaluate the effect of the compounds on tubulin assembly in vitro, varying concentrations were preincubated with 10 μM tubulin (1.0 μg/mL) in glutamate buffer at 30 °C and then cooled to 0 °C. After the addition of GTP, the mixtures were transferred to 0 °C cuvettes in a recording spectrophotometer and warmed to 30 °C, and the assembly of tubulin was observed turbidimetrically.[43] The IC_{50} was defined as the compound concentration that inhibited the extent of assembly by 50% after a 20 min incubation.

Cell Lines and Sulforhodamine B Assay. For details regarding the cell lines and assay conditions see the Supporting Information.

Acknowledgment. The authors are grateful to OXiGENE, Inc., and the Welch Foundation (grant no. AA-1278 to K.G.P.) for their generous financial support of this project, and to the NSF for instrumentation awards (CHE-0420802 and CHE-0321214). The authors also thank Mr. C. Carson for assisting with structural analysis of selected compounds, Dr. A. Ramirez for mass spectral analysis, and Dr. J. Karban and Dr. M. Nemec for use of the shared Molecular Biosciences Center.

Supporting Information Available: Experimental details regarding selected syntheses and the SRB assay, ^{1}H NMR, ^{13}C NMR, NOESY-1D, gHSQC, gHMBC, HRMS, HPLC, and single-crystal X-ray diffraction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP100108E