Pergamon

Bioorganic & Medicinal Chemistry, Vol. 4, No. 10, pp 1755–1769, 1996

PII: S0968-0896(96)00192-7
0968-0896/96 $15.00 + 0.00

Stereoselective Syntheses of Substituted Pterocarpans with Anti-HIV Activity, and 5-Aza-/5-Thia-pterocarpan and 2-Aryl-2,3-dihydrobenzofuran Analogues

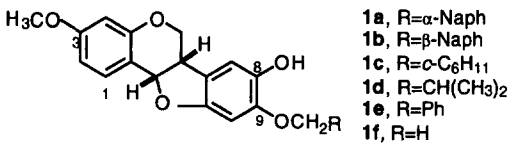
Thomas A. Engler,* Kenneth O. LaTessa,† Rajesh Iyengar, Wenying Chai and Konstantinos Agrios

Department of Chemistry, University of Kansas, Lawrence, KS 66045, U.S.A.

Abstract—Oxygenated pterocarpans and 5-azapterocarpans are prepared utilizing Lewis acid-promoted reactions of 2-alkoxy-1,4-benzoquinones with 2*H*-chromenes and *N*-tosyl-1,2-dihydroquinolines, respectively. Similarly, benzannulated analogues are prepared via reactions of 5-alkoxy-1,4-naphthoquinones with chromenes, and related 2-aryl-2,3-dihydrobenzofurans result from reactions of styrenes with the quinones. Syntheses of 5-thiapterocarpans are also described utilizing Pd(0)-coupling of *o*-chloromercuriophenols with 2*H*-chromenes. Copyright © 1996 Elsevier Science Ltd

Introduction

Substituted pterocarpan natural products display a variety of interesting biological activities; for example, as antimicrobial, antitumor, antiulcer, and antitubercular agents, and as venom antidotes.[1] In addition, several synthetic pterocarpans **1a–e** were shown recently to protect cells at μM levels from the cytotoxic effects of HIV-1.[2] Such activity was unprecedented for the pterocarpans, although there have been reports of antiviral activity in related isoflavonoids.[3] There has also been interest in synthesis of heteroatom isosteres of the naturally occurring pterocarpans.[4] Because of the significant anti-HIV activity found in **1**, we embarked on a study to further explore the generality and potential limitations of a new pterocarpan synthesis[5] in order to prepare molecules for a preliminary structure–activity relationship study. Herein, we report the full details of the synthesis of the initial lead compounds **1** as well as the results of studies designed to extend the synthetic method to include heteroatom substituted pterocarpans including 5-aza/thia analogues. The results demonstrate that in addition to unsubstituted 2*H*-chromenes and simple styrenes, methyl-substituted chromenes, 1,2-dihydroquinolines, and cinnamyl ethers can be employed in Lewis acid-promoted reactions with quinones[5,7a,b] to afford a number of new pterocarpans, azapterocarpans, and related 2-aryl-2,3-dihydrobenzofurans.

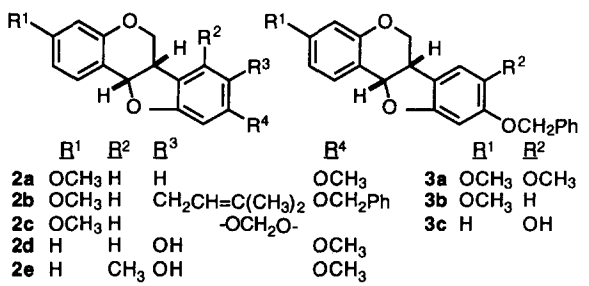


1a, R=α-Naph
1b, R=β-Naph
1c, R=*c*-C_6H_{11}
1d, R=$CH(CH_3)_2$
1e, R=Ph
1f, R=H

Results and Discussion

In routine screening carried out by the National Cancer Institute on compounds provided by us, pterocarpan **1e**, prepared as a general synthetic intermediate to pterocarpans bearing oxygen substituents at C-3, C-8, and C-9,[5] was found to display significant anti-HIV activity; compounds **1f** and **2a–e** were far less active. These preliminary data indicated that the structural features required for anti-HIV activity were a methoxy group at C-3, a hydroxy group at C-8, and an alkoxy group at C-9—though not a methoxy or methylenedioxy group. Compounds lacking any one of these groups were considerably less active or inactive. We felt the somewhat unusual nature of the C-9 benzyloxy substituent demanded further scrutiny, as did the specific nature of the C-3 and C-8 substituents. Thus, compounds **1a–d** and **3a–c** were targeted for synthesis and evaluation.

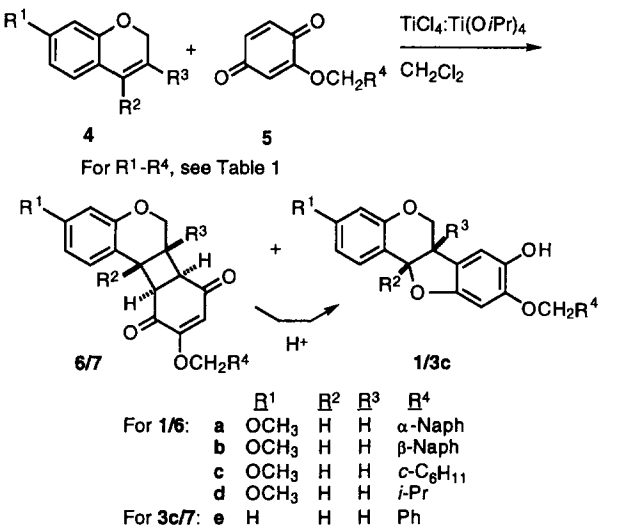
Key Words: pterocarpans, azapterocarpans, thiapterocarpans, HIV, 2-aryl-2,3-dihydrobenzofurans.
†Formerly Kenneth O. Lynch, Jr. Current address: Stephens College, Columbia, MO 65215, U.S.A.



Following our general method,[5] Ti(IV)-promoted reactions of chromenes **4** with 2-alkoxy-1,4-benzoquinones **5**[6] produced cyclobutanes **6/7** and/or pterocarpans **1/3c** depending on the makeup and number of equivalents of the Lewis acid and the reaction temperature (Scheme 1 and Table 1). The relative proportions of the two types of product were consistent with previous experiments probing the effects of temperature and the nature and quantity of Lewis acid used.[5,7] Treatment of the cyclobutanes with protic acids effected their rearrangement to the pterocarpans. The structures and stereochemistry of all products were assigned by spectral comparison to molecules previously reported.[5] Dimethoxypterocarpan **3a** was prepared by methylation of **1e**,[5] and conversion of the phenol in the latter to its corresponding triflate[5] followed by Pd(0)-catalyzed triethylammonium formate reduction[8] provided **3b**. Pterocarpan **3c** was obtained by protic acid-catalyzed rearrangement of cyclobutane **7**.

In studies conducted in collaboration with Burroughs Wellcome Co., pterocarpan **1e** was found to be an inhibitor of HIV-1 reverse transcriptase (RT).[9] Another part of our strategic approach was to synthesize molecules that may fit a proposed model for the design of inhibitors of HIV-1 RT (Fig. 1).[10] We postulated that the aryl groups in pterocarpans **1** were spacially situated close to what the model suggested for binding to the 'benzene ring' and 'extended π-binding' regions. As perhaps a better fit, molecules **8** and **9** were considered for synthesis; the methyl groups in the former were designed to fit into the lipophilic site and the naphthalene ring of the latter into the 'extended π-binding' region.

For synthesis of **8a–c**, methylated 2*H*-chromenes **4c–e** were prepared from 7-methoxychroman-4-one by the following three sequences: (1) (a) LDA/MeI (90%), (b) LAH (85%), (c) [pTsOH]/PhH (60%); (2) (a) MeMgI (88%), (b) [pTsOH]/PhH (42%); and (3) (a) LDA/MeI (90%), (b) MeMgI/3N HCl/THF (72% for two steps), respectively. Cycloadditions of **4c** and **d** with 2-benzyloxy-1,4-benzoquinone (**5e**) in the presence of Ti(IV) proceeded without incident and gave pterocarpans **8a/b**, respectively (Table 1); no cyclobutane products were found, or expected, under the conditions used.[5,7] The *cis* ring fusion in **8a/b** was determined by ^1H–^1H NOE experiments (Fig. 2). Reactions of dimethyl-2*H*-chromene **4e** failed under a variety of conditions examined. Presumably, steric hindrance provided by the two methyl groups prevents the cycloaddition (or

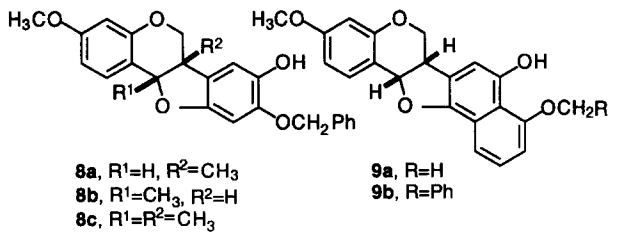


Scheme 1.

Table 1. Lewis acid-promoted reactions of 2*H*-chromenes **4** with 2-alkoxy-1,4-benzoquinones **5**

	Chromene			Quinone (R^4)	Lewis Acid[a] (equiv)[c]	Temp (°C)	% Yield(s)[b]	
	R^1	R^2	R^3				**6**	**1**
4a	OCH_3	H	H	**5a** (α-naph)	2:1 (1)	−78	51	26
4a	OCH_3	H	H	**5a** (α-naph)	1:1 (3)	−78→−40	—	54
4a	OCH_3	H	H	**5b** (β-naph)	1.1:1 (2)	−78	—	79
4a	OCH_3	H	H	**5c** (c-C_6H_{11})	1:1 (1.1)	−78	65	—
4a	OCH_3	H	H	**5c** (c-C_6H_{11})	2:1 (1)	−78	—	53
4a	OCH_3	H	H	**5d** (*i*-Pr)	1.4:1 (1.1)	−78	—	80
							7	**3c**
4b	H	H	H	**5e** (Ph)	1.9:1 (1)	−78→−40	61	11
								8
4c	OCH_3	H	CH_3	**5e** (Ph)	1:1 (1)	−78→−30	—	61
4d	OCH_3	CH_3	H	**5e** (Ph)	1:1 (1)	−78→−25	—	64
4e	OCH_3	CH_3	CH_3	**5e** (Ph)	see text		0	0

[a]Ratio of $TiCl_4$:$Ti(OiPr)_4$. All reactions were carried out in CH_2Cl_2 under N_2 or Ar.
[b]Isolated yields.
[c]Total equiv of Ti(IV) with respect to the quinone.



alkylation) mechanism.[7] Ti(IV)- and $SnCl_4$-promoted reactions of chromene **4a** with alkoxynaphthoquinones **10a/b**[6] also gave benzannulated-pterocarpan analogues **9a/b**, respectively (eq 1). The appearance of the phenolic hydrogen at ~9 ppm in the ^{1}H NMR spectra of **9a/b** and IR absorbances at ~3420 cm^{-1} support the structure assignment.

2-Aryl-2,3-dihydrobenzofurans **11/13** and -benzofurans **12/14** were of interest as analogues of **1** in which the B-ring of the pterocarpan core was disconnected and the relative stereochemistry at C-6a and C-11a inverted or eliminated (Fig. 3). These compounds were prepared by Ti(IV)-promoted cycloaddition of styrenes **15/16** with quinones **5c/e** (Scheme 2); again, no cyclobutane products were found (or expected under the conditions employed).[5,7] The *trans* stereochemistry in **11/13** was established by ^{1}H–^{1}H NOE experiments (Fig. 4). DDQ oxidation of the dihydrobenzofurans afforded benzofurans **12/14**.

Methods for preparation of heteroatom substituted pterocarpans were also of interest to access analogues with different physical/chemical properties (solubility, polarity, etc.). Initial focus was on nitrogen substituted pterocarpans **17** and **18**[11] and sulfur analogue **19**. Treatment of triflate **20**[5] with $LiNEt_2$ gave amino-pterocarpan **17** via benzyne **21** (Scheme 3). Amine **17** colorizes in air and is best handled as its hydrochloride salt. The position of the diethylamino group in **17** was assigned from a $J_{H\text{-}8/H\text{-}10}$ of 2 Hz and was further supported by a small coupling between H-8 and H-10 observed in the COSY spectrum of the hydrochloride salt. In addition, NOE enhancement of the NCH_2 multiplet was observed on irradiation of H-6α/H-6a, which appear as an overlapping multiplet at 3.52 ppm. The regioselectivity of the addition of Et_2N- to the benzyne is apparently controlled by the greater stability of the aryllithium product **22**, with an *o*-alkoxy group, as compared to the alternative aryllithium **23**.

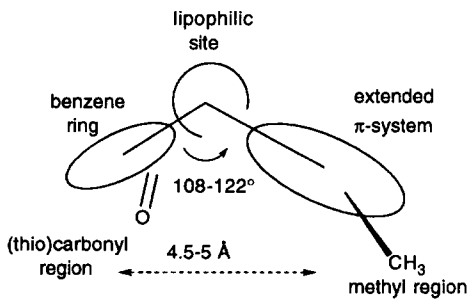
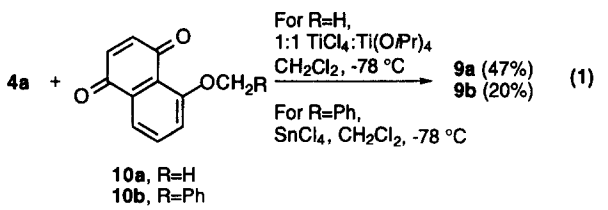


Figure 1. Proposed model for the design of inhibitors of HIV-1 RT.[10]



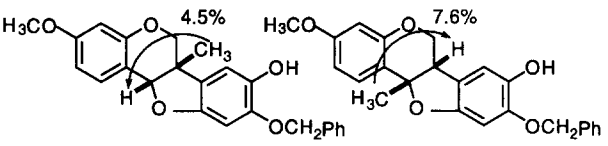


Figure 2. Results on ^{1}H–^{1}H NOE experiments on **8a** and **b**.

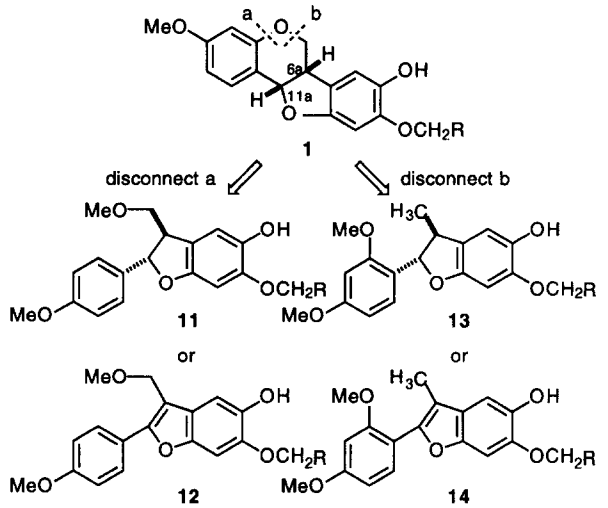


Figure 3. Disconnection of the pterocarpan core structure into 2-aryl-2,3-dihydrobenzofuran and -benzofuran analogues.

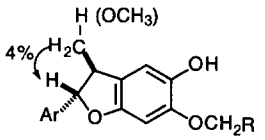
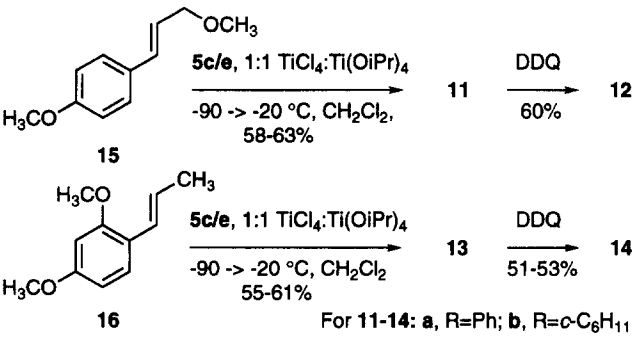
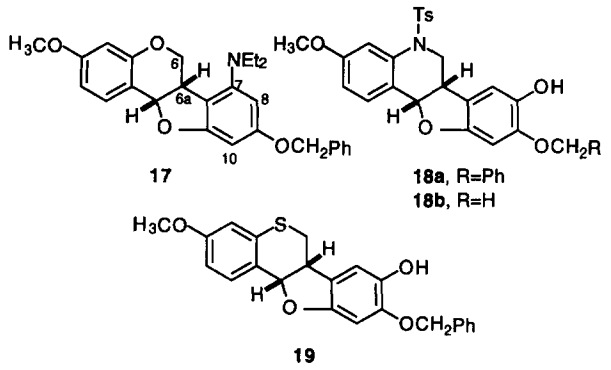


Figure 4. Results of ^{1}H–^{1}H NOE experiments on **11/13**.

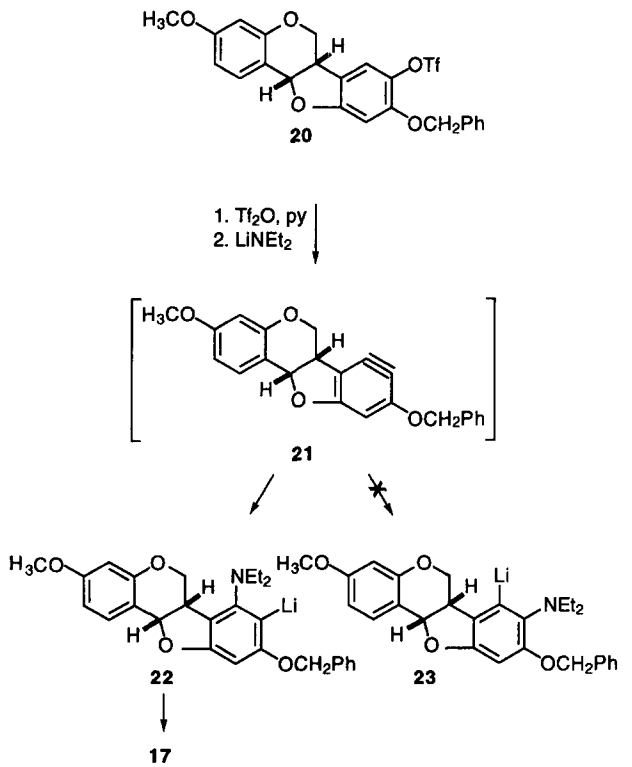


Scheme 2.

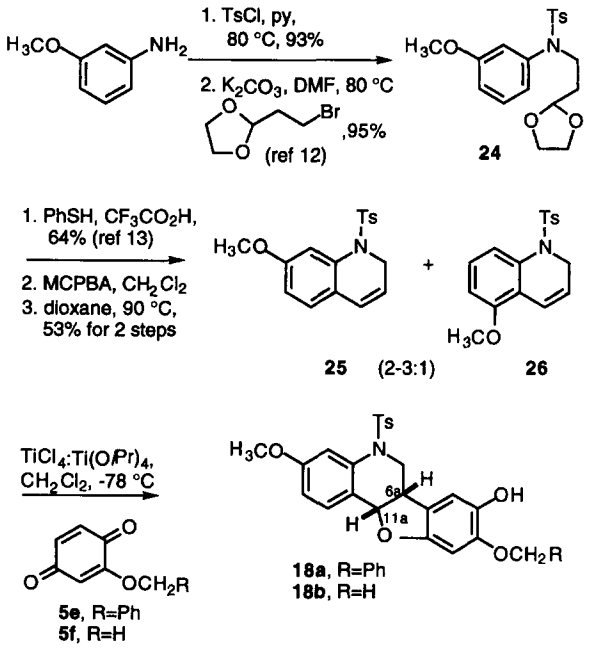


Reactions of *N*-tosyl-7-methoxy-1,2-dihydroquinoline (**25**) provided access to azapterocarpans **18**. The dihydroquinoline was actually prepared and used as 2–3:1 mixtures with its C-5 methoxy isomer **26** (Scheme 4). Ti(IV)-promoted reactions of this mixture with quinones **5e** and **5f** gave **18a** (83%) and **18b** (100%), respectively.[11] Dihydroquinoline **26** was recovered cleanly along with the desired 5-azapterocarpan products. The *cis* ring juncture in **18a/b** was again based upon results of ^1H–^1H NOE experiments; enhancement of the H-11a signal was observed on irradiation of H-6a (8.2%) and vice versa (3.1%).

Utilizing a strategy similar to the reactions outlined above, we initially approached the synthesis of 5-thiapterocarpan **19** utilizing Lewis acid-promoted reactions of 7-methoxy-2*H*-thiachromene (**28**) with 1,4-benzoquinones. The thiachromene[14c] was prepared by reduction and dehydration of thiachromanone **27** (Scheme 5).[14a,b]



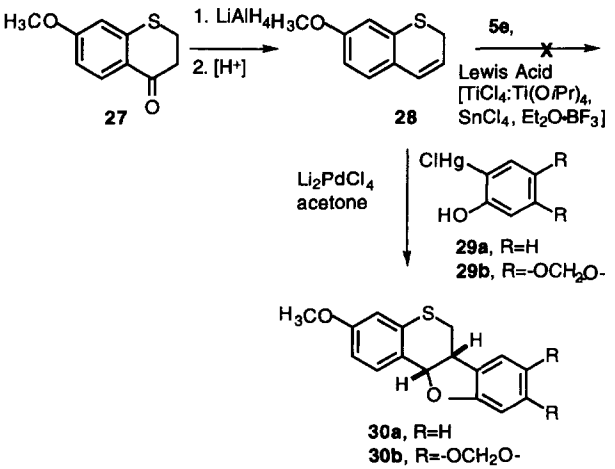
Scheme 3.



Scheme 4.

However, attempted Lewis acid-promoted reactions of **28** with quinones **5e/f**, under a variety of conditions [$TiCl_4$, $TiCl_4$:$Ti(OiPr)_4$, $SnCl_4$, $Et_2O \cdot BF_3$, etc.] failed to provide isolable products. One possible explanation is that the Lewis acid–quinone complexes were acting as hydride abstracting agents[14c] to give thiachromylium ions.[14c,d] Attempts to effect Ti(IV)-promoted reactions of quinone **5e** with sulfoxide or sulfone derivatives of **28** were also unsuccessful.

Changing strategic approach, we examined Horino–Inoue coupling[15] of thiachromene **28** with chloromercuriophenols **29** with moderate success. Thus, Li_2PdCl_4-promoted reactions of **29a/b** with 7-methoxy-2*H*-thiachromene gave **30a/b** in 26% and 17% yields, respectively. As before, results of ^1H–^1H NOE experiments confirmed the stereochemistry of the ring juncture. Because of the stoichiometric amounts of



Scheme 5.

palladium required in these reactions and the low yields of **30** obtained, the synthesis of originally desired thiapterocarpan **19** was not pursued further via this method.

In addition to the compounds reported previously,[2] compounds **8a/b**, **9a/b**, **11a**, **13a**, **17**·HCl and **18a** were submitted to the National Cancer Institute for evaluation of their in vitro anti-HIV activity. Unfortunately, although the initial leads **1a–e** demonstrated activity in the μM range,[2] analogues **1f**, **2a–e**, **3a–c**, **8a/b**, **9a/b**, **11a**, **13a**, **17**·HCl and **18a** were inactive (Table 2). Thus, the structural requirements for anti-HIV activity in the pterocarpans appear to be quite specific including an intact pterocarpan core and C-8 hydroxy, C-3 methoxy, and substituted C-9 methoxy substituents.

Experimental

General[16]

Quinones **5** were prepared by Fremy's salt oxidation of the corresponding 2-alkoxyphenols. 5-Methoxy-1,4-naphthoquinone (**10a**) was prepared by methylation of juglone,[17] and 5-benzyloxy-1,4-naphthoquinone (**10b**) was prepared by $Tl(NO_3)_3$ oxidation of 5-benzyloxynaphthol.[18] Thiachromanone **27**,[14a,b] thiachromene **28**[14c] and chloromercurials **29a/b**[15] were prepared by literature procedures. NMR spectra were recorded on samples dissolved in deuteriochloroform ($CDCl_3$) and chemical shifts are reported in parts-per-million (δ) relative to tetramethylsilane or residual chloroform unless otherwise noted. Abbreviations for NMR multiplicities are as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet-of-doublets; ddd, doublet-of-doublet-of-doublets; dt, doublet-of-triplets; dq, doublet-of-quartets; bs, broad singlet; bd, broad doublet; bt, broad triplet. Coupling constants (*J*) are reported in Hertz (Hz). Melting points are uncorrected and were obtained on a Thomas–Hoover capillary melting point apparatus. Thin-layer chromatography (TLC) was done on precoated silica-gel plates (Merck) containing a fluorescent indicator and developed in the indicated solvent; visualization was effected by staining with *p*-anisaldehyde/H_2SO_4 or under a UV lamp. Chromatographic separations were done by flash chromatography with MN-Keiselgel 60 silica gel (0.04–0.063 mm mesh). Infrared data are reported in cm^{-1}. All reactions were done in oven/flame dried glassware under an atmosphere of argon or nitrogen with magnetic stirring unless otherwise stated.

Table 2. In vitro anti-HIV activity of selected pterocarpans and analogues[a]

Compd	IC_{50} (μM)[b]	EC_{50} (μM)[c]	# of experiments
1a	38.5	0.43	4
1b	28.4	>3.35	8
1c	22.2	1.46	4
1d	24.5	2.28	4
1e	40.5	1.21	8
1f	1.75	—[d]	4
2a	>25	—	1
2b	35.8	—	4
3a	>82.2	5.97	6
3b	>200	31.2	4
3c	2.48	—	4
8a	10.1	—	2
8b	18.2	—	2
9a	>15	—	4
9b	>51	—	4
11a	18.7	—	2
13a	51.4	—	3
17·HCl	>200	—	1
18a	80	—	2

[a]Data provided by the NCI (for a description of the experimental procedure, see Weislow, O. W.; Kiser, R.; Fine, D.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989** *81*, 577).
[b]Growth inhibitory properties of the compound on cells free of HIV-infection.
[c]Anti-HIV activity; concentration at which 50% of HIV-infected cells treated with the compound survive.
[d]No protection observed relative to controls.

9-Benzyloxy-3,8-dimethoxypterocarpan (3a). Sodium hydride (60% dispersion in mineral oil, 0.049 g, 1.2 mmol) was washed with hexanes (2 × 5 mL), THF (5 mL) added, and the slurry warmed to 40 °C (oil bath temperature). A solution of pterocarpan **1e**[5] (0.201 g, 0.534 mmol) in THF (3 mL) was added dropwise, the mixture stirred until the evolution of H_2 ceased (about 10 min), and then treated with iodomethane (350 μL, 5.6 mmol). After 3 h, the reaction mixture was cooled to room temperature and the excess sodium hydride was quenched by careful addition of satd aq NH_4Cl. The mixture was filtered and the solid was washed with ether. The filtrate was extracted with ether (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), decanted and concd to a pale tan solid. Recrystallization from EtOAc/hexanes afforded **3a** (0.142 g, 68%) as a white solid, mp 141–142 °C: TLC R_f 0.27 (20% EtOAc/hexanes); ^1H NMR (500 MHz): δ 7.41 (d, *J* = 7.4, 2H), 7.36–7.27 (m, 3H), 7.38 (d, *J* = 8.5, 1H), 6.85 (s, 1H), 6.63 (dd, *J* = 2.5, 8.5, 1H), 6.50 (s, 1H), 6.46 (d, *J* = 2.5, 1H), 5.46 (d, *J* = 6.9, 1H), 5.11 (s, 2H), 4.26 (dd, *J* = 5.0, 11, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.65 (t, *J* = 11, 1H), 3.55–3.49 (m, 1H); ^{13}C NMR (125 MHz): δ 161.0, 156.5, 153.6, 149.3, 144.2, 136.9, 131.7, 128.6, 127.8, 127.1, 117.6, 112.4, 109.6, 109.1, 101.6, 98.0, 78.2, 71.1, 66.5, 57.3, 55.4, 40.4; IR (CCl_4) 2978, 2865, 1621, 1492, 1381, 1345, 1158, 1119, 1036; EIMS *m/z* (rel. int.) 390 (M^+, 56), 300 (28), 299 (100), 91 (99), 84 (29), 65 (33), 51 (30), 49 (75); HRMS *m/z* 390.1469 (calcd for $C_{24}H_{22}O_5$, 390.1467).

9-Benzyloxy-3-methoxypterocarpan (3b). Palladium(II) acetate trimer (0.065 g, 0.096 mmol), 1,1′-bis(diphenylphosphino)ferrocene (0.109 g, 0.198 mmol), triethylamine (1.02 mL, 7.32 mmol), and 98–100% formic acid (280 μL, 7.32 mmol) were added to a soln of triflate **20**[5] (0.186 g, 0.366 mmol) in DMF (3.5 mL). The mixture was stirred at 75 °C (oil bath temperature) for 12 h, cooled to room temperature and dild with EtOAc (30 mL) and water (40 mL). The aq layer was separated and extracted with EtOAc (3 × 20 mL). The extracts were combined, filtered, washed with satd aq

NH_4Cl (50 mL) and brine (50 mL), dried (Na_2SO_4), decanted and concd to a black residue. Chromatography (20% EtOAc:hexanes) afforded **3b** (0.099 g, 75%) as shiny, colorless plates, mp 122–123 °C (EtOAc:hexanes): TLC R_f 0.49 (30% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 7.45–7.29 (m, 6H), 7.13 [H-7 (d, J=8.8)], 6.65 (dd, J=2.3, 8.5, 1H), 6.55–6.51 (m, 2H), 6.48 (d, J=2.3, 1H), 5.51 (d, J=6.4, 1H), 5.02 (s, 2H), 4.25 (dd, J=4.7, 11, 1H), 3.79 (s, 3H), 3.64 (t, J=11, 1H), 3.57–3.47 (m, 1H); ^{13}C NMR (75 MHz): δ 161.0, 160.6, 160.2, 156.6, 136.8, 131.8, 128.6, 127.9, 127.4, 124.7, 119.4, 112.3, 109.1, 107.3, 101.6, 97.8, 78.5, 70.2, 66.5, 55.3, 39.5; IR (CCl_4) 2919, 1621, 1494, 1461, 1442, 1380, 1344, 1274, 1200, 1156, 1130, 1111, 1083, 1035, 953, 845; EIMS *m/z* (relative intensity) 360 (M^+, 40), 269 (90), 92 (26), 91 (100), 65 (60); HRMS *m/z* 360.1354 (calcd for $C_{23}H_{20}O_4$, 360.1362). Anal. calcd for $C_{23}H_{20}O_4$: C, 76.64; H, 5.60. Found: C, 76.70; H, 5.48.

Preparation of methylated 7-methoxy-2*H*-chromenes (4c–e)

A. 7-Methoxy-3-methylchroman-4-one. A 2.5 M soln of *n*-BuLi (0.206 mL, 0.519 mmol) in hexanes was added to diisopropylamine (0.081 mL, 0.574 mmol) in THF (3 mL) at −78 °C followed by a soln of 7-methoxychroman-4-one (0.089 g, 0.504 mmol) in THF (3 mL). The mixture was stirred for 15 min, CH_3I (0.094 mL, 4.512 mmol) was added and the mixture was allowed to warm to room temperature over 10 h. The reaction was quenched with brine (5 mL) and the mixture extracted with CH_2Cl_2 (3×20 mL). The extracts were dried ($MgSO_4$) and concd to give a colorless oil (0.087 g, 90%) which was used in the next step without purification: TLC R_f 0.20 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.18 (d, J=7.2 , 3H), 2.71–2.84 (m, 1H), 3.81 (s, 3H), 4.11 (t, J=11, 1H), 4.46 (dd, J=5.1, 11, 1H), 6.37 (d, J=2.4, 1H), 6.55 (dd, J=2.4, 9, 1H), 7.81 (d, J=9, 1H); ^{13}C NMR (75 MHz): δ 10.9, 40.3, 55.6, 72.6, 100.6, 109.9, 114.4, 129.0, 163.6, 165.8, 193.6; IR ($CHCl_3$) 2937, 2876, 2843, 1677, 1608, 1576, 1496, 1463, 1442, 1388, 1342, 1279, 1161, 1129, 1111, 1092, 1030, 997, 970, 943, 918, 857, 839.

B. 7-Methoxy-3-methylchroman-4-ol. A soln of 7-methoxy-3-methylchroman-4-one (0.087 g, 0.453 mmol) in Et_2O (3 mL) was added dropwise to a suspension of LAH (0.020 g, 0.544 mmol) in Et_2O (5 mL) at 0 °C. The reaction mixture was stirred for 1 h at this temperature, after which time the reaction was quenched by addition of satd aq NH_4Cl (5 mL). The mixture was extracted with Et_2O (3×20 mL) and the combined extracts dried ($MgSO_4$) and concd to give a diastereomeric mixture (2:1) of the title compound as a colorless oil (0.074 g, 85%), which was used in the next step without purification: TLC R_f 0.17/0.24 (25% EtOAc:hexanes); Major: ^{1}H NMR (300 MHz): δ 0.98 (d, J=7.2, 3H), 1.75 (d, J=4.5, 1H), 1.96–2.06 (m, 1H), 3.75 (s, 3H), 3.88–4.02 (m, 1H), 4.21 (d, J=2.7, 1H), 4.31 (br t, J=3.9, 1H), 6.35 (t, J=2.4, 1H), 6.46–6.52 (m, 1H), 7.21 (d, J=8.4, 1H); ^{13}C NMR (75 MHz): δ 13.8, 34.8, 55.3, 67.5, 69.4, 101.1, 107.9, 116.2, 130.4, 130.9, 160.7; Minor: ^{1}H NMR (300 MHz): δ 1.06 (d, J=7.2, 3H), 1.55 (d, J=3.9, 1H), 2.06–2.18 (m, 1H), 3.75 (s, 3H), 3.71–3.83 (m, 1H), 4.25 (d, J=3, 1H), 4.5 (bt, J=1.2, 1H), 6.35 (t, J=2.4, 1H), 6.46–6.52 (m, 1H), 7.15 (d, J=8.4, 1H); ^{13}C NMR (75 MHz): δ 11.8, 32.9, 55.3, 66.5, 66.6, 101.2, 107.7, 116.2, 130.4, 130.9, 160.7; IR ($CHCl_3$) 3596, 3378, 2926, 1619, 1585, 1503, 1463, 1442, 1286, 1160, 1118, 1035, 997, 963, 904, 837.

C. 7-Methoxy-3-methyl-2*H*-chromene (4c). A soln of 7-methoxy-3-methylchroman-4-ol (0.074 g, 0.385 mmol), prepared as described above, in benzene (5 mL) was added to *p*-TsOH (3 mg, 0.008 mmol) in benzene (3 mL) at room temperature. The reaction mixture was stirred for 3 h, and then quenched with satd aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×30 mL). The extracts were dried ($MgSO_4$) and concd to a colorless oil. Chromatography (10% EtOAc:hexanes) afforded **4c** as a clear oil (0.040 g, 60%): TLC R_f 0.47 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.77 (d, J=1.2, 3H), 3.76 (s, 3H), 4.65 (t, J=1.3, 2H), 6.10 (d, J=1.4, 1H), 6.38 (m, 1H), 6.42 (d, J=2.5, 1H), 6.82 (d, J=8.0, 1H); ^{13}C NMR (75 MHz): δ 18.9, 55.3, 69.3, 101.4, 106.6, 116.1, 118.9, 126.2, 128.0, 153.7, 159.8; IR ($CHCl_3$) 2930, 2837, 1722, 1616, 1582, 1500, 1457, 1291, 1155, 1114, 985; 911, 841; EIMS *m/z* (relative intensity) 176 (M^+, 62), 161 (100), 132 (10), 77 (20), 51 (15); HRMS *m/z* 176.0828 (calcd for $C_{11}H_{12}O_2$: 176.0837).

D. 7-Methoxy-4-methyl-2*H*-chromene (4d). A soln of 7-methoxychroman-4-one (0.250 g, 1.4 mmol) in THF (5 mL) was added dropwise to a 3 M Et_2O soln of MeMgI (0.513 mL, 1.54 mmol) in THF (3 mL) at 0 °C. The mixture was stirred 4 h, quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 (4×20 mL). The extracts were dried ($MgSO_4$), filtered, and concd to give 7-methoxy-4-methylchroman-4-ol as a colorless oil (0.240 g, 88%), which was used in the next step without purification: TLC R_f 0.44 (35% EtOAc:hexanes).

A soln of 7-methoxy-4-methylchroman-4-ol (0.240 g, 1.23 mmol) in benzene (5 mL) was added to *p*-TsOH (2 mg, 0.0127 mmol) in benzene (5 mL) at room temperature. The reaction mixture was stirred 4 h, quenched with satd aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (4×15 mL). The extracts were dried ($MgSO_4$), filtered, and concd to a colorless oil. Chromatography (10% EtOAc:hexanes) afforded **4d** as a clear oil (0.090 g, 42%): TLC R_f 0.56 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.97 (apparent q, J=1.8, 3H), 3.75 (s, 3H), 4.7 (apparent sextet, J=1.8, 2H), 5.41 (apparent octet, J=1.8, 1H), 6.38 (d, J=2.4, 1H), 6.44 (dd, J=2.4, 8.4, 1H), 7.03 (d, J=8.4, 1H); ^{13}C NMR (75 MHz): δ 17.9, 55.2, 65.6, 101.5, 106.6, 115.4, 117.5, 124.2, 130.0, 155.4, 160.4; IR ($CHCl_3$) 2935, 2839, 1655, 1613, 1571, 1499, 1458, 1381, 1352, 1310, 1279, 1147, 1133, 1073, 1015, 895, 856, 839, 837; EIMS *m/z* (relative intensity) 190 (M^+, 2.6), 176 (100), 161 (44); HRMS *m/z* 176.0828 (calcd for $C_{11}H_{12}O_2$: 176.0837).

E. 7-Methoxy-3,4-dimethyl-2*H*-chromene (4e). A soln of 7-methoxy-3-methylchroman-4-one (0.100 g, 0.520 mmol) in Et_2O (5 mL) was added to a 3 M Et_2O solution of MeMgBr (0.174 mL, 0.520 mmol) (5 mL) at room temperature. The reaction mixture was stirred 5 h, after which time it was quenched by the addition of 3 N HCl (pH ~2.0) and stirred for an additional 30 min. Satd aq $NaHCO_3$ (10 mL) was added and the aq soln was extracted with CH_2Cl_2 (3 × 20 mL). The extracts were dried ($MgSO_4$) and concd to a colorless oil. Chromatography (5% EtOAc:hexanes) afforded **4e** as a clear oil (0.071g, 72%): TLC R_f 0.56 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.76 (m, 3H), 1.95 (m, 3H), 3.77 (s, 3H), 4.58 (apparent dd, J = 1.7, 2H), 6.39 (d, J = 2.5, 1H), 6.46 (dd, J = 2.5, 8.5, 1H), 7.05 (d, J = 8.5, 1H); ^{13}C NMR (75 MHz): δ 12.6, 15.5, 55.2, 69.8, 101.4, 106.5, 118.3, 122.3, 122.5, 123.6, 154.4, 159.4; IR ($CHCl_3$) 2927, 2842, 1614, 1575, 1502, 1461, 1313, 1279, 1161, 1144, 1093, 1031, 839; EIMS *m/z* (relative intensity) 206 (M^+, 2.5), 190 (60), 175 (100), 161 (14), 91 (11), 77 (14), 65 (9), 51 (13), 43 (14); HRMS *m/z* 190.0988 (calcd for $C_{12}H_{14}O_2$: 190.0994).

Synthesis of Styrenes 15 and 16

A. Ethyl (*E*)-4-methoxycinnamate. (*E*)-4-Methoxycinnamic acid (5.00 g, 28.1 mmol) was dissolved in a mixture of EtOH (50 mL) and conc H_2SO_4 (5 mL) and heated at reflux for 16 h. The reaction mixture was cooled to room temperature and quenched by addition of satd aq $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (5 × 30 mL) and the extracts dried ($MgSO_4$) and concd to a colorless oil (5.75 g, 99%) which was used without purification: TLC R_f 0.91 (35% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.31 (t, J = 7.1, 3H), 3.81 (s, 3H), 4.23 (q, J = 7.1, 2H), 6.29 (d, J = 16, 1H), 6.80–6.95 (m, 2H), 7.40–7.50 (m, 2H), 7.62 (d, J = 16, 1H); ^{13}C NMR (75 MHz): δ 14.3, 15.3, 60.3, 114.3, 115.8, 127.2, 129.7, 144.2, 161.3, 167.3; IR ($CHCl_3$) 2945, 2839, 1704, 1633, 1605, 1575, 1509, 1462, 1422, 1368, 1306, 1159, 1108, 1029, 982, 884, 832. Anal. calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.52; H, 7.00.

B. (*E*)-4-Methoxycinnamyl alcohol. A soln of ethyl (*E*)-4-methoxycinnamate (5.75 g, 28 mmol) in THF (50 mL) was added dropwise over a period of 20 min to a suspension of LAH (1.21 g, 32.0 mmol) in THF (30 mL) at −10 °C. The reaction mixture was allowed to warm to room temperature over 1 h, after which time it was quenched by the addition of brine (5 mL) and filtered through a Celite pad. The Celite was washed thoroughly with Et_2O (5 × 30 mL). The combined filtrate and ether washings were dried ($MgSO_4$) and concd to afford a pale-yellow solid (4.50 g, 98%), mp 72–74 °C (ether:hexanes), which was used without purification: TLC R_f 0.53 (35% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.79 (bs, 1H), 3.78 (s, 3H), 4.26 (dd, J = 1.2, 6.0, 2H), 6.20 (dt, J = 6.0, 16, 1H), 6.53 (d, J = 16, 1H), 6.84 (d, 2H), 7.30 (d, 2H); ^{13}C NMR (7.5 MHz): δ 55.3, 63.8, 114.0, 126.3, 127.7, 129.3, 130.8, 159.3; IR ($CHCl_3$) 3603, 3446, 2998, 2936, 2838, 1653, 1607, 1576, 1509, 1463, 1442, 1379, 1294, 1174, 1085, 1034, 997, 968, 840. Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.36. Found: C, 72.80; H, 7.43.

C. (*E*)-4-Methoxy-1-(3-methoxy-1-propenyl)benzene (15). A 60% wt/wt suspension of NaH in mineral oil (0.80 g, 33.5 mmol) was washed with THF (2 × 5 mL) and suspended in THF (10 mL). A soln of 4-methoxycinnamyl alcohol (4.50 g, 27.4 mmol) in THF (20 mL) was added at room temperature, the reaction mixture was stirred for 30 min and then cooled to −10 °C. MeI (9.70 mL, 140 mmol) was added and stirring was continued for an additional 6 h. Brine (5 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 40 mL). The extracts were dried ($MgSO_4$) and concd to a colorless oil. Chromatography (10% EtOAc:hexanes) afforded **15** as a clear oil (4.40 g, 90%): TLC R_f 0.95 (35% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 3.37 (s, 3H), 3.77 (s, 3H), 4.06 (dd, J = 0.9, 6.2, 2H), 6.16 (dt, J = 6.2, 16, 1H), 6.55 (d, J = 16, 1H), 6.85 (d, 2H), 7.33 (d, 2H); ^{13}C NMR (75 MHz): δ 54.9, 57.6, 73.0, 113.7, 123.4, 127.4, 129.2, 131.9, 159.1; IR ($CHCl_3$) 2995, 2932, 2834, 1655, 1607, 1577, 1510, 1481, 1373, 1298, 1174, 1111, 1034, 968, 908, 841. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.94; H, 7.92.

D. (*E*)-2,4-Dimethoxy-1-(1-propenyl)benzene (16). A soln of ethylmagnesium bromide, prepared in situ by mixing EtBr (2.24 mL, 30 mmol) and magnesium turnings (0.729 g, 30.0 mmol) in Et_2O (15 mL), was added dropwise over 20 min to a soln of 2,4-dimethoxybenzaldehyde (3.32 g, 20.0 mmol) in Et_2O (15 mL) at room temperature. The reaction mixture was stirred 3 h, after which time it was quenched by addition of satd aq NH_4Cl (5 mL). The mixture was extracted with Et_2O (4 × 30 mL), and the extracts were dried ($MgSO_4$) and concd to a pale-yellow oil (3.38 g, 97.4%) which was used without purification. The oil was added dropwise under vacuum (20 mm Hg) to a mixture of fused potassium hydrogen sulfate (0.275 g, 2.00 mmol) and 4-*t*-butylcatechol (5 mg) maintained at a temperature of 220 °C in a salt bath. The distillate was collected, extracted with Et_2O (3 × 30 mL) and the extracts were dried ($MgSO_4$), and concd to a colorless oil. Chromatography (10% EtOAc:hexanes) afforded **16** as a clear oil (2.04 g, 59%): TLC R_f 0.52 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.90 (dd, J = 1.7, 6.5, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 6.13 (dq, J = 6.5, 16, 1H), 6.44–6.50 (m, 2H), 6.65 (dd, J = 1.7, 16, 1H), 7.32 (d, J = 8.1, 1H); ^{13}C NMR (75 MHz): δ 18.9, 55.3, 55.4, 98.4, 104.7, 120.2, 124.4, 125.3, 127.1, 157.2, 159.8; IR ($CHCl_3$) 2939, 2838, 1606, 1501, 1461, 1287, 1158, 1122, 1037, 970, 836. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.77; H, 8.16.

General procedure for Ti(IV)-promoted reactions of chromenes 4 and styrenes 15/16 with quinones 5 and 10

$TiCl_4$ was added to a soln of $Ti(OiPr)_4$ in CH_2Cl_2 at 0 °C to room temperature. After stirring for 5–15 min,

the mixture was added to a soln of the quinone in CH_2Cl_2 maintained at −78 °C, unless indicated otherwise, followed after 5–15 min by the chromene, either neat or as a soln in CH_2Cl_2. The reaction mixture was stirred for the time indicated and then quenched by the sequential addition of solid sodium bicarbonate (~1 g), *i*-PrOH (~3 mL) and water (30–40 mL). The resulting mixture was filtered through Celite, the Celite rinsed with CH_2Cl_2, and the combined filtrate and rinse extracted with CH_2Cl_2. The extracts were washed with water and brine, dried (Na_2SO_4) and concd to afford yellow–brown oils.

***i*. Reaction of 4a with 5a: formation of 1a.** According to the general procedure, a mixture of $TiCl_4$ (160 μL, 1.5 mmol), and $Ti(OiPr)_4$ (450 μL, 1.5 mmol) in CH_2Cl_2 (2 mL) was added to quinone **5a** (0.266 g, 1.01 mmol) in CH_2Cl_2 (5 mL) followed by chromene **4a** (0.188 g, 1.16 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was allowed to warm to −40 °C over 4 h and quenched. Work up and chromatography (20% EtOAc:hexanes) furnished **1a** (0.233 g, 54%) as a white solid, mp 90–91 °C (EtOAc:hexanes): TLC R_f 0.41 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 8.02–7.98 (m, 1H), 7.91–7.89 (m, 1H), 7.88 (d, J=8.2, 1H), 7.54–7.51 (m, 3H), 7.47 (t, J=7.7, 1H), 7.40 (d, J=8.4, 1H), 6.85 (s, 1H), 6.68 (s, 1H), 6.63 (dd, J=2.5, 8.5, 1H), 6.47 (d, J=2.5, 1H), 5.47 (d, J=6.8, 1H), 5.76 (s, 2H), 5.24 (s, 1H), 4.25 (dd, J=5.0, 11, 1H), 3.78 (s, 3H), 3.66 (t, J=11, 1H), 3.56–3.49 (m, 1H); ^{13}C NMR (125 MHz): δ 161.0, 156.6, 152.8, 146.0, 140.3, 133.8, 131.8, 131.6, 131.5, 129.6, 128.8, 127.3, 126.8, 126.1, 125.3, 123.4, 118.7, 112.5, 110.6, 109.2, 101.6, 96.2, 78.1, 70.1, 66.5, 55.4, 40.3; IR (CCl_4) 3557, 2965, 2870, 1622, 1154; EIMS *m/z* (relative intensity) 426 (M^+, 2), 285 (27), 149 (41), 142 (40), 141 (100), 115 (40), 71 (23), 69 (21), 57 (33), 55 (23), 43 (37); HRMS *m/z* 426.1474 (calcd for $C_{27}H_{22}O_5$, 426.1467).

***ii*. Reaction of 4a with 5a: formation of 6a and 1a.** According to the general procedure, a mixture of $TiCl_4$ (80 μL, 0.73 mmol) and $Ti(OiPr)_4$ (110 μL, 0.37 mmol) in CH_2Cl_2 (1 mL) was added to quinone **5a** (0.292 g, 1.10 mmol) in CH_2Cl_2 (4 mL) followed by chromene **4a** (0.161 g, 0.99 mmol) in CH_2Cl_2 (0.5 mL). After 7.5 h, work up and chromatography (20, 30, and then 50% EtOAc:hexanes) afforded **1a** (0.112 g, 26%) as white needles and **6a** (0.216 g, 51%) as a white solid, mp 181–183 °C (EtOAc:hexanes). Data for **6a**: TLC R_f 0.14 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.97 (d, J=8.3, 1H), 7.89 (apparent t, J=7.7, 8.4, 2H), 7.60–7.51 (m, 3H), 7.47 (apparent t, J=8.1, 7.2, 1H), 7.07 (d, J=8.5, 1H), 6.57 (dd, J=2.5, 8.5, 1H), 6.51 (d, J=2.5, 1H), 6.35 (s, 1H), 5.49 (s, 2H), 4.22 (dd, J=2.9, 12, 1H), 3.88 (dd, J=3.5, 12, 1H), 3.77 (s, 3H), 3.64 (dd, J=4.1, 9.4, 1H), 3.51 (apparent t, J=7.5, 1H), 3.09 (dd, J=4.1, 9.4, 1H), 3.09–3.02 (m, 1H); ^{13}C NMR (125 MHz): δ 197.6, 192.2, 161.7, 159.6, 156.2, 133.8, 131.2, 130.0, 129.9, 129.3, 128.9, 127.0, 126.9, 126.2, 125.2, 123.1, 117.2, 115.3, 109.4, 102.9, 69.8, 66.9, 55.4, 50.1, 42.8, 39.9, 36.7; IR (CCl_4) 1697, 1656, 1593, 1504, 1317, 1154; EIMS *m/z* (relative intensity) 426 (M^+, 0.51), 162 (100), 161 (97), 141 (83), 115 (36); HRMS *m/z* 426.1466 (calcd for $C_{27}H_{22}O_5$, 426.1467).

***iii*. Reaction of 4a with 5b: formation of 1b.** According to the general procedure, a mixture of $TiCl_4$ (60 μL, 0.55 mmol) and $Ti(OiPr)_4$ (150 μL, 0.50 mmol) in CH_2Cl_2 (2 mL) was added to quinone **5b** (0.133 g, 0.503 mmol) in CH_2Cl_2 (4 mL) followed by chromene **4a** (0.121 g, 0.74 mmol). After 2 h, work up and chromatography (20% EtOAc:hexanes) afforded **1b** (0.169 g, 79%) as a white solid, mp 157–158 °C (EtOAc:hexanes): TLC R_f 0.37 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.88–7.83 (m, 4H), 7.51–7.49 (m, 3H), 7.38 (d, J=8.5, 1H), 6.87 (s, 1H), 6.62 (dd, J=2.5, 8.6, 1H), 6.58 (s, 1H), 6.46 (d, J=2.4, 1H), 5.45 (d, J=6.8, 1H), 5.34 (s, 1H), 5.22 (s, 2H), 4.25 (dd, J=5.0, 11, 1H), 3.78 (s, 3H), 3.64 (t, J=11, 1H), 3.53–3.47 (m, 1H); ^{13}C NMR (125 MHz): δ 161.0, 156.6, 152.7, 146.0, 140.2, 133.5, 133.2, 131.7, 128.7, 128.0, 127.8, 126.9, 126.5, 126.4, 125.3, 118.6, 112.4, 110.6, 109.2, 106.1, 101.6, 96.2, 78.1, 71.6, 66.5, 55.4, 40.3; IR (CCl_4) 3547, 2939, 1621, 1586, 1488, 1466, 1342, 1154, 1139, 1079, 905, 859; EIMS *m/z* (relative intensity) 426 (M^+, 3), 285 (40), 142 (25), 141 (100), 115 (31); HRMS *m/z* 426.1470 (calcd for $C_{27}H_{22}O_5$, 426.1467).

***iv*. Reaction of 4a with 5c: formation of 1c.** According to the general procedure, a soln of $Ti(OiPr)_4$ (100 μL, 0.34 mmol) and $TiCl_4$ (80 μL, 0.73 mmol) in CH_2Cl_2 (1 mL) was added to quinone **5c** (0.220 g, 1.00 mmol) in CH_2Cl_2 (2 mL) followed by chromene **4a** (0.179 g, 1.10 mmol) in CH_2Cl_2 (0.5 mL). After 1 h, work up and chromatography (15% EtOAc:hexanes) furnished **1c** (0.204 g, 53%) as a pale-pink solid. Recrystallization from EtOAc:hexanes resulted in a fluffy-white solid, mp 132–133 °C: TLC R_f 0.48 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.40 (d, J=8.5, 1H), 6.83 (s, 1H), 6.63 (dd, J=2.5, 8.5, 1H), 6.47 (d, J=2.5, 1H), 6.45 (s, 1H), 5.45 (d, J=6.9, 1H), 5.29 (s, 1H), 4.24 (dd, J=5.0, 11, 1H), 3.79 (s, 3H), 3.78 (apparent t, J=6.0, 2H), 3.63 (t, J=11, 1H), 3.54–3.48 (m, 1H), 1.86–1.69 (m, 6H), 1.34–1.15 (m, 3H), 1.09–1.00 (m, 2H); ^{13}C NMR (125 MHz): δ 161.0, 156.6, 152.7, 146.3, 140.0, 131.7, 117.7, 112.5, 110.1, 109.1, 101.6, 95.6, 78.0, 74.5, 66.5, 55.3, 40.2, 37.4, 29.8, 26.4, 25.7; IR (CCl_4) 3560, 2930, 2855, 1622, 1489, 1467, 1378, 1342, 1270, 1219, 1202, 1156, 1130, 1080, 1036, 936; EIMS *m/z* (relative intensity) 382 (M^+, 6), 286 (37), 86 (24), 84 (38), 55 (100), 51 (33), 49 (97); HRMS *m/z* 382.1777 (calcd for $C_{23}H_{26}O_5$, 382.1780).

***v*. Reaction of 4a with 5c: formation of 6c.** According to the general procedure, a mixture of $TiCl_4$ (30 μL, 0.27 mmol) and $Ti(OiPr)_4$ (80 μL, 0.27 mmol) in CH_2Cl_2 (1 mL) was added to quinone **5c** (0.112 g, 0.508 mmol) in CH_2Cl_2 (2 mL) followed by chromene **4a** (0.087 g, 0.54 mmol). After 20 min, work up and chromatography (20% EtOAc:hexanes) afforded **6c** (0.126 g, 65%) as a white solid, mp 114–115 °C (EtOAc:hexanes): TLC R_f 0.43 (50% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.09 (d, J=8.5, 1H), 6.59 (dd,

J=2.5, 8.5, 1H), 6.52 (d, J=2.5, 1H), 6.10 (s, 1H), 4.23 (dd, J=3.0, 12, 1H), 3.90 (dd, J=3.5, 12, 1H), 3.78 (s, 3H), 3.76–3.68 (m, 3H), 3.64 (dd, J=4.1, 9.3, 1H), 3.49 (apparent t, J=7.5, 1H), 3.08 (dd, J=4.1, 9.3, 1H), 3.08–3.01 (m, 1H), 1.95–1.81 (m, 3H), 1.80–1.69 (m, 2H), 1.36–1.15 (m, 3H), 1.10–1.01 (m, 2H); ^{13}C NMR (125 MHz): δ 197.8, 192.4, 162.3, 159.6, 156.2, 130.0, 117.3, 114.3, 109.4, 102.9, 74.7, 67.0, 55.4, 50.1, 42.7, 39.8, 36.8, 36.7, 29.6, 26.2, 25.5; IR (CCl_4) 2931, 2855, 1698, 1653, 1618, 1593, 1503, 1353, 1154, 990; EIMS *m/z* (relative intensity) 382 (M^+, 1), 162 (100), 161 (79), 97 (22), 55 (84); HRMS *m/z* 382.1792 (calcd for $C_{23}H_{26}O_5$, 382.1780).

***vi*. Reaction of 4a with 5d: formation of 1d.** According to the general procedure, a mixture of Ti(O*i*Pr)$_4$ (60 μL, 0.20 mmol) and $TiCl_4$ (30 μL, 0.27 mmol) in CH_2Cl_2 (2 mL) was added to quinone **5d** (0.074 g, 0.41 mmol) in CH_2Cl_2 (2 mL) followed by chromene **4a** (0.100 g, 0.616 mmol). After 2 h, work up and chromatography (15% EtOAc:hexanes) gave **1d** (0.113 g, 80%) as a pale-pink oil. Crystallization from EtOAc:hexanes afforded a white solid, mp 134–135 °C: TLC R_f 0.37 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.40 (d, J=8.5, 1H), 6.84 (s, 1H), 6.63 (dd, J=2.2, 8.5, 1H), 6.47 (d, J=2.2, 1H), 6.45 (s, 1H), 5.44 (d, J=6.9, 1H), 5.31 (s, 1H), 4.23 (dd, J=5.0, 11, 1H), 3.78 (s, 3H), 3.74 (apparent t, J=6.9, 2H), 3.63 (t, J=11, 1H), 3.52–3.48 (m, 1H), 2.16–2.05 (m, 1H), 1.00 (d, J=6.7, 6H); ^{13}C NMR (125 MHz): δ 160.9, 156.6, 152.7, 146.2, 140.0, 131.7, 117.8, 112.5, 110.2, 109.1, 101.5, 95.5, 78.0, 75.4, 66.4, 55.3, 40.2, 28.1, 19.2; IR (CCl_4) 3559, 2932, 2855, 1622, 1489, 1467, 1342, 1274, 1201, 1156, 1130, 1077, 1041; EIMS *m/z* (relative intensity) 342 (M^+, 20), 286 (66), 285 (41), 148 (26), 86 (31), 84 (52), 69 (33), 57 (29), 51 (37), 49 (100), 47 (26); HRMS *m/z* 342.1458 (calcd for $C_{20}H_{22}O_5$, 342.1467).

***vii*. Reaction of 4b with 5e: formation of 3c and 7.** According to the general procedure, a soln of Ti(O*i*Pr)$_4$ (100 μL, 0.34 mmol) and $TiCl_4$ (70 μL, 0.64 mmol) in CH_2Cl_2 (1 mL) was added dropwise to quinone **5e** (0.215 g, 1.00 mmol) in CH_2Cl_2 (4 mL) followed by 2*H*-chromene **4b** (0.151 g, 1.14 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was allowed to warm to −40 °C over 7 h. Work up and chromatography (15 and then 30% EtOAc:hexanes) gave **3c** (0.038 g, 11%) as a colorless oil and **7** (0.211 g, 61%) as a white crystalline solid.

Data for **3c**; mp 59–60 °C (EtOAc:hexanes): TLC R_f 0.42 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.50 (dd, J=1.5, 7.6, 1H), 7.40–7.34 (m, 5H), 7.28–7.25 (m, 1H), 7.04 (dt, J=1.0, 7.4, 1H), 6.95 (d, J=8.0, 1H), 6.87 (s, 1H), 6.54 (s, 1H), 5.49 (d, J=6.8, 1H), 5.31 (bs, 1H), 5.06 (ABq, J=12, Δν=15 Hz, 2H), 4.27 (dd, J=4.7, 11, 1H), 3.63 (t, J=11, 1H), 3.59–3.53 (m, 1H); ^{13}C NMR (125 MHz): δ 152.6, 146.0, 140.2, 136.0, 130.9, 130.0, 128.7, 128.4, 127.8, 121.6, 120.2, 118.4, 117.4, 110.5, 109.7, 96.1, 78.0, 71.4, 66.5, 40.4; IR (CCl_4) 3559, 2981, 1620, 1490, 1466, 1346, 1226, 1152, 1102, 1080, 1038, 937, 867; EIMS *m/z* (relative intensity) 346 (M^+, 4), 255 (100), 91 (85), 69 (40), 65 (29); HRMS *m/z* 346.1199 (calcd for $C_{22}H_{18}O_4$, 346.1205).

Data for **7**; mp 164–165 °C (EtOAc:hexanes): TLC R_f 0.19 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.41–7.37 (m, 5H), 7.21–7.16 (m, 2H), 7.01–6.94 (m, 2H), 6.20 (s, 1H), 5.07 (ABq, J=12, Δν=17 Hz, 2H), 4.24 (dd, J=2.8, 12, 1H), 3.89 (dd, J=3.4, 12, 1H), 3.70 (dd, J=4.1, 9.3, 1H), 3.53 (apparent t, J=7.5, 1H), 3.13 (dd, J=4.1, 9.3, 1H), 3.10–3.05 (m, 1H); ^{13}C NMR (125 MHz): δ 197.5, 192.2, 161.6, 156.1, 133.9, 129.4, 128.9, 128.9, 128.2, 127.6, 125.2, 122.6, 118.0, 115.4, 71.2, 66.9, 49.7, 42.8, 40.0, 37.2; IR (CCl_4) 1698, 1657, 1594, 1488, 1458, 1351, 1153, 1082, 982; EIMS *m/z* (relative intensity) 346 (M^+, 100); HRMS *m/z* 346.1189 (calcd for $C_{22}H_{18}O_4$, 346.1205).

***viii*. Reaction of 4c with 5e: formation of 8a.** According to the general procedure, a mixture of $TiCl_4$ (22 μL, 0.20 mmol) and Ti(O*i*Pr)$_4$ (50 μL, 0.17 mmol) in CH_2Cl_2 (2 mL) was added to quinone **5e** (0.086 g, 0.4 mmol) in CH_2Cl_2 (2 mL) followed by the addition of chromene **4c** (0.072 g, 0.41 mmol). The reaction mixture was allowed to warm to −30 °C over 8 h. Work up and chromatography (10% EtOAc:hexanes) furnished **8a** (0.095 g, 61%) as a white solid, mp 137–138 °C (EtOAc:hexanes): TLC R_f 0.14 (10% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 1.37 (s, 3H), 3.65 (d, J=11, 1H), 3.79 (s, 3H), 3.89 (d, J=11, 1H), 4.96 (s, 1H), 5.05 (s, 2H), 5.32 (s, 1H), 6.47 (d, J=2.4, 1H), 6.54 (s, 1H), 6.63 (dd, J=2.5, 8.5, 1H), 6.77 (s, 1H), 7.35–7.40 (m, 6H); ^{13}C NMR (125 MHz): δ 18.3, 42.7, 55.3, 70.7, 71.4, 84.3, 96.3, 101.4, 109.0, 109.2, 111.3, 123.7, 127.8, 128.4, 128.7, 132.3, 136.1, 140.2, 145.8, 152.2, 155.8, 161.2; IR ($CHCl_3$) 3438, 2918, 1620, 1585, 1490, 1336, 1270, 1196, 1136, 1102, 1031, 911, 837, 728; EIMS *m/z* (relative intensity) 390 (M^+, 10), 299 (55), 175 (10), 151 (26), 91 (100), 65 (35), 51 (13); HRMS *m/z* 391.1548 (calcd for $m^+ + 1$ $C_{24}H_{23}O_5$, 391.1545).

***ix*. Reaction of 4d with 5e: formation of 8b.** According to the general procedure, a mixture of $TiCl_4$ (26 μL, 0.24 mmol) and Ti(O*i*Pr)$_4$ (72 μL, 0.24 mmol) in CH_2Cl_2 (3 mL) was added to quinone **5e** (0.103 g, 0.48 mmol) in CH_2Cl_2 (2 mL) followed by addition of chromene **4d** (0.085 g, 0.48 mmol). The reaction mixture was allowed to warm to −25 °C over 9 h. Work up and chromatography (10% EtOAc:hexanes) furnished **8b** (0.119 g, 64%) as a foamy white solid, mp 53–55 °C (dec) (EtOAc:hexanes): TLC R_f 0.10 (10% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 1.68 (s, 3H), 3.37 (dd, J=4.8, 9, 1H), 3.75 (s, 3H), 3.82 (dd, J=9, 11, 1H), 4.24 (dd, J=4.8, 11, 1H), 5.00 (d, J=1.8, 2H), 5.32 (br s, 1H), 6.39 (d, J=2.4, 1H), 6.47 (s, 1H), 6.62 (dd, J=2.4, 8.7, 1H), 6.84 (s, 1H), 7.36 (m, 5H), 7.46 (d, J=8.7, 1H); ^{13}C NMR (125 MHz): δ 27.3, 47.6, 55.3, 66.8, 71.3, 83.7, 96.2, 101.4, 109.3, 110.5, 117.9, 127.7, 128.4, 128.7, 129.0, 136.1, 139.9, 146.0, 151.8, 155.6, 160.3, 169.7; IR ($CHCl_3$) 3449, 2929, 1620, 1582, 1488, 1378, 1328, 1223, 1156, 1067, 1029, 874, 794, 738, 698. EIMS *m/z* (relative intensity) 390 (M^+, 5), 299

(55), 91 (100), 65 (30), 49 (89); HRMS *m/z* 390.1463 (calcd for $C_{24}H_{22}O_5$, 390.1467).

***x*. Reaction of 4a with 10a: formation of 9a.** According to the general procedure, a mixture of $TiCl_4$ (20 μL, 0.18 mmol) and $Ti(OiPr)_4$ (120 μL, 0.40 mmol) in CH_2Cl_2 (2 mL) was added to a soln of 5-methoxy-1,4-naphthoquinone (0.094 g, 0.50 mmol) in CH_2Cl_2 (1 mL) followed by chromene **4a** (0.096 g, 0.59 mmol). After 20 min, the mixture was treated with additional $TiCl_4$ (20 μL, 0.18 mmol) and then stirred for 17 h, during which time it warmed to room temperature. Work up and chromatography (20% EtOAc:hexanes) furnished **9a** as a white fluffy solid (0.082 g, 47%), mp 182–184 °C (EtOAc:hexanes): TLC R_f 0.36 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 9.03 (s, 1H), 7.55 (d, J=8.5, 1H), 7.52 (d, J=8.5, 1H), 7.28 (apparent t, J=7.9, 8.5, 1H), 6.81 (s, 1H), 6.75 (d, J=7.9, 1H), 6.67 (dd, J=2.5, 8.5, 1H), 6.48 (d, J=2.5, 1H), 5.62 (d, J=6.5, 1H), 4.35 (dd, J=4.0, 10, 1H), 4.04 (s, 3H), 3.79 (s, 3H), 3.74 (t, J=10, 1H), 3.72–3.66 (m, 1H); ^{13}C NMR (125 MHz): δ 161.0, 156.7, 156.2, 148.9, 147.9, 132.0, 125.5, 122.3, 121.9, 115.7, 114.7, 112.7, 109.2, 106.2, 104.3, 101.6, 77.9, 66.5, 56.1, 55.4, 41.4; IR ($CHCl_3$) 3417, 2940, 1616, 1506, 1462, 1408, 1373, 1270, 1159, 1115, 1064, 900; EIMS *m/z* (relative intensity) 350 (M^+, 100), 333 (23), 175 (25). Anal. calcd for $C_{21}H_{18}O_5$: C, 71.98; H, 5.19. Found: C, 71.60; H, 4.80.

***xi*. Reaction of 4a with 10b: formation of 9b.** $SnCl_4$ (70 μL, 0.599 mmol) was added to a soln of 5-benzyloxy-1,4-naphthoquinone (0.134 g, 0.507 mmol) and chromene **4a** (0.120 g, 0.740 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was stirred for 2 h and then quenched and worked up as described for reactions of **4** with **5**. Chromatography of the resultant yellow oil (15% and then 20% EtOAc:hexanes) afforded **9b** (0.043 g, 20%) as a white solid, mp 181–183 °C (dec) (EtOAc:hexanes): TLC R_f 0.44 (30% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 9.02 (s, 1H), 7.57 (d, J=8.4, 1H), 7.53 (d, J=8.5, 1H), 7.49–7.38 (m, 5H), 7.28 (apparent t, J=7.9, 8.4, 1H), 6.84 (d, J=7.6, 1H), 6.79 (s, 1H), 6.67 (dd, J=2.5, 8.5, 1H), 6.48 (d, J=2.5, 1H), 5.62 (d, J=6.6, 1H), 5.25 (ABq, J=11, Δν=13 Hz, 2H), 4.34 (dd, J=4.0, 11, 1H), 3.79 (s, 3H), 3.73 (t, J=11, 1H), 3.71–3.65 (m, 1H); ^{13}C NMR (125 MHz): δ 161.0, 156.7, 155.4, 148.9, 147.9, 135.2, 132.0, 129.0, 128.8, 128.0, 125.5, 122.4, 122.0, 116.0, 114.8, 112.7, 109.2, 106.3, 105.6, 101.6, 77.9, 71.6, 66.5, 55.4, 41.4; IR ($CHCl_3$) 3422, 2929, 1616, 1506, 1461, 1408, 1375, 1269, 1161, 1115, 1036; EIMS *m/z* (relative intensity) 426 (M^+, 11), 335 (100), 91 (53); HRMS *m/z* 426.1458 (calcd for $C_{27}H_{22}O_5$, 426.1467).

***xii*. Reaction of 15 with 5e: formation of 11a.** According to the general procedure, a mixture of $TiCl_4$ (55 μL, 0.5 mmol) and $Ti(OiPr)_4$ (148 μL, 0.5 mmol) in CH_2Cl_2 (3 mL) was added to quinone **5e** (0.214 g, 1.0 mmol) in CH_2Cl_2 (2 mL) at −90 °C, followed by addition of styrene **15** (0.178 g, 1.0 mmol). The reaction mixture was allowed to warm to −20 °C over 3 h. Work up and chromatography (20% EtOAc:hexanes) furnished **11a** (0.227 g, 58%) as a white solid, mp 121–122 °C (EtOAc:hexanes): TLC R_f 0.10 (10% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 3.38 (s, 3H), 3.56–3.62 (m, 3H), 3.80 (s, 3H), 5.07 (ABq, J=12, Δν small, 2H), 5.31 (bs, 1H), 5.44 (d, J=4.9, 1H), 6.56 (s, 1H), 6.82 (s, 1H), 6.88 (d, J=8.6, 2H), 7.30 (d, J=8.6, 2H), 7.37–7.42 (m, 5H); ^{13}C NMR (125 MHz): δ 51.1, 55.3, 59.0, 71.4, 74.9, 87.4, 95.6, 110.5, 113.9, 118.6, 127.1, 127.8, 128.4, 128.7, 133.8, 136.2, 139.9, 145.8, 152.8, 159.3; IR ($CHCl_3$) 3353, 2987, 2923, 2831, 1615, 1493, 1389, 1317, 1250, 1178, 1151, 1095, 1030, 1000, 969, 867, 826, 769, 720. EIMS *m/z* (relative intensity) 392 (M^+, 4), 269 (21), 91 (34), 51 (24), 45 (100); HRMS *m/z* 392.1619 (calcd for $C_{24}H_{24}O_5$: 392.1624). Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.26; H, 6.41.

***xiii*. Reaction of 15 with 5c: formation of 11b.** According to the general procedure, a mixture of $TiCl_4$ (34 μL, 0.309 mmol) and $Ti(OiPr)_4$ (91 μL, 0.309 mmol) in CH_2Cl_2 (2 mL) was added to quinone **5c** (0.136 g, 0.618 mmol) in CH_2Cl_2 (2 mL) at −90 °C, followed by addition of styrene **15** (0.110 g, 0.618 mmol). The reaction mixture was allowed to warm to −20 °C over 4 h. Work up and chromatography (20% EtOAc:hexanes) furnished **11b** (0.238 g, 60%) as a clear oil: TLC R_f 0.15 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.05–1.35 (m, 5H), 1.70–1.87 (m, 6H), 3.39 (s, 3H), 3.54–3.62 (m, 3H), 3.79 (s, 3H), 3.805 (d, J=6, 2H), 5.31 (s, 1H), 5.45 (d, J=4.9, 1H), 6.47 (s, 1H), 6.79 (s, 1H), 6.87 (d, J=8.8, 2H), 7.30 (d, J=8.8, 2H); ^{13}C NMR (75 MHz): δ 25.7, 26.4, 29.9, 37.5, 51.2, 55.3, 59.1, 74.5, 75.1, 87.4, 94.9, 110.2, 113.9, 117.8, 127.1, 134.1, 139.9, 146.2, 153.0, 159.3; IR ($CHCl_3$) 3539, 2928, 2852, 1608, 1490, 1464, 1264, 1158, 1108, 984, 908. EIMS *m/z* (relative intensity) 398 (M^+, 30), 270 (25), 257 (34), 229 (30), 121 (15), 84 (26), 69 (10), 55 (100); HRMS *m/z* 398.2076 (calcd for $C_{24}H_{30}O_5$: 398.2093). Anal. calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.00; H, 7.60.

***xiv*. Reaction of 16 with 5e: formation of 13a.** According to the general procedure, a mixture of $TiCl_4$ (55 μL, 0.5 mmol) and $Ti(OiPr)_4$ (148 μL, 0.5 mmol) in CH_2Cl_2 (3 mL) was added to quinone **5e** (0.214 g, 1.0 mmol) in CH_2Cl_2 (2 mL) at −90 °C, followed by addition of styrene **16** (0.178 g, 1.0 mmol). The reaction mixture was allowed to warm to −20 °C over 3 h. Work up and chromatography (20% EtOAc:hexanes) furnished **13a** (0.215 g, 55%) as a white solid, mp 132–133 °C (EtOAc:hexanes): TLC R_f 0.11 (10% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 1.37 (d, J=6.8, 3H), 3.37 (m, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 5.08 (m, 2H), 5.32 (bs, 1H), 5.50 (d, J=6.9, 1H), 6.45–6.49 (m, 2H), 6.57 (s, 1H), 6.74 (s, 1H), 7.29 (d, J=8.4, 1H), 7.37–7.44 (m, 5H); ^{13}C NMR (125 MHz): δ 19.5, 44.6, 55.3, 55.4, 71.4, 87.2, 95.4, 98.5, 104.1, 109.8, 121.9, 123.9, 127.3, 127.8, 128.3, 128.6, 136.4, 139.8, 145.1, 152.3, 157.8, 160.4; IR ($CHCl_3$) 3466,

2942, 1616, 1590, 1492, 1469, 1385, 1324, 1258, 1214, 1157, 1124, 1094, 1045, 1005, 957, 860, 793, 758, 701; EIMS *m/z* (relative intensity) 392 (M^+, 31), 301 (41), 255 (16), 91 (100); HRMS *m/z* 392.1625 (calcd for $C_{24}H_{24}O_5$: 392.1624). Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.37; H, 6.08.

xv. **Reaction of 16 with 5c: formation of 13b.** According to the general procedure, a mixture of $TiCl_4$ (123 μL, 1.13 mmol) and $Ti(OiPr)_4$ (335 μL, 1.13 mmol) in CH_2Cl_2 (5 mL) was added to quinone **5c** (0.494 g, 2.25 mmol) in CH_2Cl_2 (3 mL) at −90 °C, followed by addition of styrene **16** (0.400 g, 2.25 mmol). The reaction mixture was allowed to warm to −20 °C over 4 h. Work up and chromatography (20% EtOAc:hexanes) furnished **13b** (0.210 g, 53%) as a white solid, mp 101–102 °C (EtOAc:hexanes): TLC R_f 0.20 (10% EtOAc); ^{1}H NMR (300 MHz): δ 1.00–1.30 (m, 5H), 1.36 (d, J=6.9, 3H), 1.70–1.87 (m, 6H), 3.34 (apparent quintet, J=6.9, 1H), 3.80 (s, 3H), 3.81 (partially hidden d, 2H), 3.82 (s, 3H), 5.26 (s, 1H), 5.48 (d, J=6.9, 1H), 6.43 (d, J=2.4, 1H), 6.46–6.48 (dd, J=9, 2.4, 1H), 6.47 (s imposed on dd, 1H), 6.70 (s, 1H), 7.29 (d, J=9, 1H); ^{13}C NMR (75 MHz): δ 19.7, 25.7, 26.5, 29.9, 37.6, 44.7, 55.4 (2 c), 74.6, 87.2, 94.9, 98.5, 104.1, 109.5, 122.2, 123.2, 127.3, 139.8, 145.5, 152.4, 157.9, 160.5; IR ($CHCl_3$) 3542, 2928, 2852, 1607, 1492, 1404, 1265, 1158, 954, 907; EIMS *m/z* (relative intensity) 398 (M^+, 100), 302 (18), 163 (14), 151 (30), 137 (10), 84 (21), 69 (12), 55 (61), 43 (20); HRMS *m/z* 399.2162 (calcd for $m^+ + 1$ $C_{24}H_{31}O_5$: 399.2171). Anal. calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.61; H, 7.88.

Rearrangement of 6a to 1a. Cyclobutane **6a** (0.059 g, 0.14 mmol) was dissolved in CH_2Cl_2 (2 mL) and *p*-toluenesulfonic acid (3 mg, 0.015 mmol) added. The reaction mixture was stirred for 1 h and then poured into satd aq $NaHCO_3$ (20 mL). The aq layer was separated and extracted with CH_2Cl_2 (2 × 20 mL), and the combined extracts washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), decanted and concd. Chromatography of the resultant tan oil (30% EtOAc:hexanes) furnished **1a** (0.059 g, 100%) as a white solid.

Rearrangement of 6c to 1c. Concd H_2SO_4 (2 drops) was added to a soln of **6c** (0.100 g, 0.261 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 5 min and then poured into satd aq $NaHCO_3$ (15 mL). The aq layer was separated and extracted with CH_2Cl_2 (2 × 15 mL), and the combined extracts were washed with brine (30 mL), dried (Na_2SO_4) and concd to a tan oil. Chromatography (15% EtOAc:hexanes) afforded **1c** (0.040 g, 40%) as a white solid.

Rearrangement of 7 to 3c. The same procedure used for the rearrangement of **6c** was used to afford **3c** as a white solid (0.079 g, 79%).

General procedure for DDQ oxidation of dihydrobenzofurans 11/13 to benzofurans 12/14

A soln of the dihydrobenzofuran in benzene (5 mL) was added dropwise over 10 min to a soln of DDQ in benzene (5 mL). The reaction mixture was stirred at room temperature for 45–60 min, after which time it was filtered, and the filtrate diluted with Et_2O. The ether soln was washed with satd aq $NaHCO_3$ (15 mL), dried ($MgSO_4$) and concd to a yellow–tan oil.

6-Benzyloxy-3-methoxymethyl-2-(4-methoxyphenyl)benzofuran-5-ol (12a). According to the general procedure, dihydrobenzofuran **11a** (0.075 g, 0.19 mmol) was oxidized with DDQ (0.057 g, 0.25 mmol). Work up and chromatography (10% EtOAc:hexanes) afforded **12a** as a white solid (0.044 g, 60%), mp 107–108 °C (EtOAc:hexanes): TLC R_f 0.10 (10% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 3.45 (s, 3H), 3.86 (s, 3H), 4.64 (s, 2H), 5.30 (s, 2H), 5.63 (bs, 1H), 6.90 (d, J=8.7, 2H), 7.10 (s, 1H), 7.18 (s, 1H), 7.36–7.46 (m, 5H), 7.72 (d, J=8.7, 2H); ^{13}C NMR (125 MHz): δ 55.3, 57.9, 64.8, 71.6, 95.9, 103.5, 111.2, 113.9, 114.1, 123.3, 127.8, 128.4, 128.5, 128.7, 136.1, 142.9, 144.2, 147.7, 153.8, 159.8; IR ($CHCl_3$) 3541, 2930, 2837, 2358, 1604, 1508, 1464, 1372, 1323, 1293, 1258, 1177, 1143, 1081, 1028, 884, 836, 601; EIMS *m/z* (rel. int.) 390 (M^+, 2.5), 299 (52), 91 (38), 65 (11), 45 (100); HRMS *m/z* 390.1487 (calcd for $C_{24}H_{22}O_5$: 390.1467). Anal. calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68. Found: C, 73.87; H, 6.00.

6-(Cyclohexylmethyl)oxy-3-methoxymethyl-2-(4-methoxyphenyl)benzofuran-5-ol (12b). According to the general procedure, dihydrobenzofuran **11b** (0.055 g, 0.138 mmol) was oxidized with DDQ (0.040 g, 0.179 mmol). Work up and chromatography (10% EtOAc:hexanes) afforded **12b** (0.033 g, 60%) as a white solid, mp 92–94 °C (EtOAc:hexanes): TLC R_f 0.15 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.06–1.35 (m, 5H), 1.76–1.91 (m, 6H), 3.45 (s, 3H), 3.86 (s, 3H), 3.89 (d, J=6.1, 2H), 4.63 (s, 2H), 5.60 (s, 1H), 7.02 (s, 1H), 7.01 (d, J=9, 2H), 7.15 (s, 1H), 7.72 (d, J=9, 2H); ^{13}C NMR (75 MHz): δ 25.7, 26.4, 29.7, 29.9, 37.5, 55.3, 57.9, 64.8, 74.8, 95.3, 103.2, 111.2, 114.2, 122.8, 123.5, 128.4, 142.9, 144.5, 147.9, 159.7; IR ($CHCl_3$) 3539, 2928, 2851, 2348, 1602, 1508, 1480, 1462, 1373, 1323, 1255, 1143, 1081, 840; EIMS *m/z* (rel. int.) 396 (M^+, 31), 300 (44), 269 (44), 69 (10), 55 (100), 45 (96); HRMS *m/z* 396.1937 (calcd for $C_{24}H_{28}O_5$: 396.1937). Anal. calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.43; H, 7.15.

6-Benzyloxy-2-(2,4-dimethoxyphenyl)-3-methylbenzofuran-5-ol (14a). According to the general procedure, dihydrobenzofuran **13a** (0.075 g, 0.19 mmol) was oxidized with DDQ (0.057 g, 0.25 mmol). Work up and chromatography (10% EtOAc:hexanes) afforded **14a** (0.039 g, 53%) as a clear oil: TLC R_f 0.10 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 2.16 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 5.15 (s, 2H), 5.61 (s, 1H),

6.57 (t, $J=2.5$, 2H), 6.60 (d, $J=2.5$, 1H), 7.04 (s, 1H), 7.09 (s, 1H), 7.36–7.47 (m, 5H); ^{13}C NMR (75 MHz): δ 9.3, 55.5, 55.6, 71.7, 96.1, 98.9, 103.3, 104.6, 112.4, 113.2, 124.0, 127.8, 128.4, 128.8, 131.9, 136.3, 142.5, 143.8, 148.2, 148.7, 158.4, 161.4; IR ($CHCl_3$) 3542, 2934, 2839, 2351, 1597, 1464, 1368, 1318, 1298, 1160, 1141, 1057, 1001, 866; EIMS *m/z* (relative intensity) 390 (M^+, 21), 299 (100), 91 (38), 65 (13), 49 (17), 43 (14); HRMS *m/z* 390.1490 (calcd for $C_{24}H_{22}O_5$: 390.1467).

6-(Cyclohexylmethyl)oxy-2-(2,4-dimethoxyphenyl)-3-methylbenzofuran-5-ol (14b). According to the general procedure, dihydrobenzofuran **13b** (0.055 g, 0.138 mmol) was oxidized with DDQ (0.040 g, 0.179 mmol). Work up and chromatography (10% EtOAc:hexanes) afforded **14b** (0.028 g, 51%) as a clear oil: TLC R_f 0.25 (10% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 1.00–1.90 (m, 11H), 2.15 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.87 (partially hidden d, $J=6$, 2H), 5.56 (bs, 1H), 6.56–6.61 (m, 2H), 7.00 (s, 1H), 7.01 (s, 1H), 7.37 (d, $J=8.3$, 1H); ^{13}C NMR (75 MHz): δ 9.2, 25.7, 26.5, 29.9, 37.5, 55.5, 55.6, 74.7, 95.4, 98.9, 102.9, 104.6, 112.4, 113.3, 123.4, 131.8, 142.4, 144.2, 148.3, 148.4, 158.4, 161.3; IR ($CHCl_3$) 3542, 2928, 2853, 2350, 1607, 1494, 1464, 1323, 1265, 1158, 954, 849; EIMS *m/z* (relative intensity) 396 (M^+, 77), 300 (76), 285 (15), 84 (28), 69 (23), 55 (100), 43 (35); HRMS *m/z* 396.1952 (calcd for $C_{24}H_{28}O_5$: 396.1937).

9-Benzyloxy-7-diethylamino-3-methoxypterocarpan (17). *n*-BuLi (2.5 M in hexane, 0.09 mL, 0.23 mmol) was added to a solution of diethylamine (0.022 mL, 0.213 mmol) in THF (2 mL) at −78 °C. After 1 h, a solution of triflate **20**[5] (45 mg, 0.089 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred for 2 h and the temperature was raised to −30 °C. The reaction was quenched with satd aq NH_4Cl solution (5 mL), the aq layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined extracts were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), and concd. Chromatography of the residue (10% EtOAc:hexanes) afforded pterocarpan **17** (20 mg, 52%) as an oil: TLC R_f 0.70 (50% EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.20 (m, 6H), 6.63 (dd, $J=2.5$, 8.5, 1H), 6.45 (d, $J=2.5$, 1H), 6.15 (s, 2H), 5.40 (d, $J=6.0$, 1H), 5.01 (s, 2H), 4.38 (dd, $J=3.5$, 10, 1H), 3.80 (s, 3H), 3.52 (m, 2H), 3.30–3.23 (m, 2H), 3.16–3.09 (m, 2H); 1.10 (t, $J=7.1$, 6H); ^{1}H NMR (300 MHz, C_6D_6): δ 7.41 (d, $J=8.0$, 1H), 7.17–6.95 (m, 5H), 6.59 (m, 2H), 6.32 (d, $J=2.1$, 1H), 6.24 (d, $J=2.1$, 1H), 5.20 (d, $J=6.6$, 1H), 4.65 (s, 2H), 4.39 (dd, $J=5.1$, 11, 1H), 3.59 (t, $J=11$, 1H), 3.31 (m, 1H), 3.18 (s, 3H), 2.92 (m, 2H), 2.72 (m, 2H), 0.81 (t, $J=7.2$, 6H); ^{13}C NMR (125 MHz): δ 161.5, 161.0, 160.7, 156.7, 148.8, 137.0, 131.8, 128.5, 127.9, 127.6, 112.4, 110.4, 108.9, 101.6, 99.3, 90.0, 77.4, 70.1, 65.5, 55.3, 46.3, 40.1, 12.8; IR (CCl_4) 2929, 1616, 1550, 1376, 1229, 1160, 1113, 1005; EIMS *m/z* (relative intensity) 431 (M^+, 52), 416 (20), 402 (100), 340 (8), 311 (18), 280 (21), 269 (17), 161 (14), 149 (29); HRMS *m/z* 431.2079 (calcd for $C_{27}H_{29}NO_4$: 431.2097).

9-Benzyloxy-7-diethylamino-3-methoxypterocarpan·HCl (17·HCl). A small test tube containing an Et_2O solution (2 mL) of amine **17** (10 mg, 0.023 mmol) was placed in a beaker containing concd HCl and the beaker was covered by a watchglass. Within several minutes, a white precipitate formed in the test tube. The test tube was removed and the precipitate was washed with Et_2O affording **17**·HCl (10 mg, 93%) as a white solid, mp 95–110 °C (dec): ^{1}H NMR (500 MHz): δ 7.41–7.32 (m, 6H), 6.62–6.60 (dd and bs overlap, $J=2.5$, 2H), 6.48 (d, $J=2.5$, 1H), 6.40 (bs, 1H), 5.48 (d, $J=5.8$, 1H), 5.06 (s, 2H), 4.37 (dd, $J=5.4$, 9.0, 1H), 4.29 (m, 1H), 3.78 (s, 3H), 3.85–3.60 (bs, 2H), 3.51 (t, $J=11$, 1H), 3.28 (bs, 1H), 3.15 (bs, 1H), 1.25 (bs, 6H); ^{13}C NMR (125 MHz): δ 162.6, 161.5, 161.4, 156.7, 135.5, 133.7, 131.5, 128.8, 128.5, 127.7, 117.4, 110.1, 109.2, 101.7, 100.1, 98.6, 80.3, 70.9, 65.4, 55.9, 55.4, 53.7, 38.4, 10.6, 10.2; IR ($CHCl_3$) 2965, 2366, 1620, 1595, 1497, 1383, 1343, 1280, 1161, 1115, 1084, 1032, 846. Anal. calcd for $C_{27}H_{32}O_5NCl$ (**17**·HCl·H_2O): C, 66.72; H, 6.64; N, 2.88. Found: C, 66.83; H, 6.50; N, 2.78.

Synthesis of Dihydroquinolines 25 and 26

A. *N*-Tosyl *m*-Anisidine. *m*-Anisidine (5 g, 0.041 mol) was mixed with *p*-toluenesulfonyl chloride (10 g, 0.052 mol) and stirred 10 min. Pyridine (30 mL) was added and the mixture was heated to 80 °C for 30 min. The mixture was then poured into H_2O (50 mL), extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were dried (Na_2SO_4) and concd to a yellow-brown oil. The crude material was purified by column chromatography (50% EtOAc:hexanes) to yield the title compound (10.5 g, 93%) as a white solid, mp 63–64 °C (EtOAc:hexanes): TLC R_f 0.50 (50% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 7.71 (d, $J=8.1$, 2H), 7.58 (s, NH, 1H), 7.17 (d, $J=8.1$, 2H), 7.08 (t, $J=8.1$, 1H), 6.72 (t, $J=2$, 1H), 6.66 (dd, $J=2.0$, 8.1, 1H), 6.58 (dd, $J=2.0$, 8.1, 1H), 3.68 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz): δ 160.0, 143.7, 137.7, 135.7, 129.7, 129.4, 127.1, 112.9, 110.5, 106.4, 55.0, 21.3; IR (CCl_4) 3254, 3002, 2944, 2835, 1603, 1495, 1461, 1441, 1397, 1332, 1284, 1197, 1160, 1093, 1047, 964, 876, 699, 664; EIMS *m/z* (relative intensity) 277 (M^+, 28), 213 (35), 212 (26), 198 (24), 155 (13), 122 (48), 107 (31), 95 (74), 91 (100), 89 (11), 79 (20), 65 (52), 52 (32); HRMS *m/z* 278.0849 ($M^+ + 1$) (calcd for $C_{14}H_{16}NO_3S$, 278.0851).

B. Acetal 24. *N*-Tosyl *m*-anisidine (2.7 g, 0.010 mol) was mixed with 3-bromopropionaldehyde ethylene acetal (2.6 g, 0.014 mol) and K_2CO_3 (0.98 g, 0.007 mol) in DMF (10 mL) and the mixture heated to 80 °C. After 15 h, the mixture was cooled to room temperature and poured into H_2O (60 mL). The aq layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and concd to yield **24** (3.7 g, 100%) as a colorless oil: TLC R_f 0.40 (50% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 7.48 (d, $J=8.1$, 2H), 7.22 (d, $J=8.1$, 2H), 7.16 (t, $J=8.1$, 1H),

6.81 (dd, $J=2.4$, 8.4, 1H), 6.61 (t, $J=2.4$, 1H), 6.55 (dd, $J=2.4$, 8.4, 1H), 4.87 (t, $J=4.8$, 1H), 3.91–3.76 (m, 4H), 3.72 (s, 3H), 3.63 (t, $J=7.5$, 2H), 2.39 (s, 3H), 1.80 (m, 2H); ^{13}C NMR (75 MHz): δ 159.8, 143.2, 140.1, 135.0, 129.4, 129.2, 127.7, 120.4, 114.6, 113.7, 102.0, 64.8, 55.2, 45.9, 32.7, 21.4; IR ($CDCl_3$) 2941, 2878, 1597, 1341, 1287, 1232, 1196, 1158, 1046; EIMS *m/z* (relative intensity) 377 (M^+, 1), 315 (1), 290 (5), 222 (12), 213 (3), 198 (2), 186 (2), 172 (3), 155 (20), 136 (88), 134 (14), 107 (17), 91 (71), 87 (100), 73 (92), 45 (64); HRMS *m/z* 378.1363 ($M^+ + 1$), (calcd for $C_{19}H_{24}NO_5S$, 378.1375).

C. *N*-Tosyl-7-methoxy-4-(thiophenyl)-1,2,3,4-tetrahydroquinoline and *N*-Tosyl-5-methoxy-4-(thiophenyl)-1,2,3,4-tetrahydroquinoline. A soln of thiophenol (110 mg, 1 mmol) in CF_3CO_2H (0.7 mL) was stirred 15 min at room temperature, cooled in an ice bath and a solution of acetal **24** (377 mg, 1 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise. The ice bath was removed and stirring was continued for 0.5 h. After dilution with CH_2Cl_2 (20 mL), the mixture was washed with H_2O (20 mL), satd aq $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4) and concd to yield a yellow oil. Chromatography (5% and then 10% EtOAc:hexanes) afforded a 2–3:1 mixture of the title compounds (273 mg, 64.2%) as a colorless oil. Data for the mixture: TLC R_f 0.65 (50% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 7.59–7.14 (m, 11H), 6.67–6.60 (m, 1H), 4.30–3.83 (m, 3H), 3.79 (s, 3H), 2.34 (s, 2/3H), 2.32 (s, 1/3H), 1.95–1.60 (m, 2H); ^{13}C NMR (125 MHz): δ 158.9, 156.9, 143.7, 143.6, 137.6, 137.3, 136.3, 135.9, 135.3, 134.4, 132.2, 132.1, 131.5, 129.6, 129.4, 129.0, 128.8, 128.2, 127.4, 127.2, 127.0, 119.1, 116.1, 115.0, 111.3, 107.9, 106.2, 55.7, 55.2, 44.6, 42.3, 42.2, 40.4, 26.1, 25.9, 21.4. This mixture was used directly in the next step.

D. Dihydroquinolines 25 and 26. The mixture of sulfides prepared as described above (273 mg, 0.642 mmol) was mixed with MCPBA (0.120 g, 0.695 mmol) in CH_2Cl_2 (5 mL). The soln was stirred for 2 h at room temperature, and then washed with H_2O (5 mL) and satd aq $NaHCO_3$ (5 mL). The soln was dried (Na_2SO_4) and concd to give a yellow oil that was dissolved in dioxane (10 mL) and heated to 90 °C for 1.5 h. Evaporation of the solvent afforded a yellow oil that was purified by chromatography (5% EtOAc:hexanes) to yield a 2–3:1 mixture of **25** and **26** (150 mg, 52.9%) as an oil, which rapidly colorizes in air. The mixture was generated and used immediately. Data for the mixture **25** and **26**: TLC R_f 0.30 (20% EtOAc:hexanes); ^{1}H NMR (300 MHz): δ 7.34–7.23 (m, 3H), 7.12 (t, 1/3H), 7.00 (d, $J=8.0$, 2H), 6.75 (d, $J=8.4$, 2/3H), 6.66–6.62 (m, 1H), 6.34 (d, $J=9.7$, 1/3H), 5.90 (d, $J=9.5$, 2H), 5.50–5.42 (m, 1/3H), 5.39–5.33 (m, 2/3H), 4.33–4.30 (m, 2H), 3.73 (s, 2/3H), 3.65 (s, 1/3H), 2.22 (s, 2/3H), 2.21 (s, 1/3H); ^{13}C NMR (75 MHz): δ 159.5, 155.1, 143.9, 143.8, 136.9, 136.9, 136.7, 136.5, 136.3, 129.5, 129.3, 128.4, 127.8, 127.64, 127.58, 125.8, 123.1, 122.5, 121.3, 120.9, 119.2, 113.0, 112.4, 108.9, 56.0, 55.8, 45.7, 45.4, 21.9; EIMS *m/z* (relative intensity) 315 (M^+, 36), 160 (100), 145 (39), 117 (69), 91 (33); 91 (91).

***N*-Tosyl-9-benzyloxy-8-hydroxy-3-methoxy-5-azapterocarpan (18a).** A 2:1 mixture of dihydroquinolines **25** and **26** (100 mg, 0.326 mmol) was mixed with quinone **5e** (73 mg, 0.343 mmol) in CH_2Cl_2 (2 mL) and the soln cooled to −78 °C. After 15 min, a soln of $TiCl_4$ (41 μL, 0.37 mmol) and $Ti(OiPr)_4$ (113 μL, 0.38 mmol) in CH_2Cl_2 (2 mL) was added. The dark-black mixture was stirred at −78 °C for 2 h and then quenched and worked up as described above for the reactions of **4** with **5**. Chromatography of the crude product (5% EtOAc:hexanes) gave starting **26** and azapterocarpan **18a** (95 mg, 83%) as a white solid, mp 76–78 °C (EtOAc:hexanes): TLC R_f 0.16 (20% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.52 (d, $J=8.0$, 2H), 7.40–7.36 (m, 6H), 7.28 (d, $J=2.4$, 1H), 7.21 (d, $J=8.0$, 2H), 6.84 (dd, $J=2.4$, 8.0, 1H), 6.77 (s, 1H), 6.42 (s, 1H), 5.27 (s, 1H, OH), 5.06 (d, $J=7.6$, 1H), 5.00 (s, 2H), 4.32 (dd, $J=4.9$, 14, 1H), 3.84 (s, 3H), 3.12 (m, 1H), 3.03 (dd, $J=12$, 14, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz): δ 159.7, 152.2, 145.9, 144.0, 140.2, 137.6, 136.9, 136.0, 130.9, 129.8, 128.7, 128.4, 127.7, 127.0, 120.0, 119.0, 113.3, 110.4, 109.2, 95.7, 78.6, 71.3, 55.5, 48.0, 39.9, 21.6; IR (CCl_4) 3558, 1613, 1490, 1466, 1350, 1296, 1232, 1205, 1163, 1121, 1091, 1041, 959, 916, 866, 694, 660; EIMS *m/z* (relative intensity) 529 (M^+, 2), 374 (10), 283 (57), 254 (13), 91 (100). Anal. calcd for $C_{30}H_{27}NO_6S$: C, 68.04; H, 5.14; N, 2.64. Found: C, 67.83; H, 5.22; N, 2.84.

Data for **26**: ^{1}H NMR (300 MHz): δ 7.45–7.30 (apparent d, 3H), 7.19 (t, $J=8.2$, 1H), 7.06 (d, $J=8.1$, 2H), 6.70 (d, $J=8.2$, 1H), 6.37 (d, $J=9.6$, 1H), 5.60–5.47 (m, 1H), 4.37 (dd, $J=1.5$, 4.2, 2H), 3.76 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz): δ 155.1, 143.8, 143.7, 137.0, 136.4, 129.5, 128.4, 127.6, 122.6, 120.9, 119.4, 108.9, 56.1, 45.4, 21.9; IR ($CHCl_3$) 3019, 1588, 1470, 1347, 1261, 1215, 1164, 1118, 1089, 1060, 760, 670; EIMS *m/z* (relative intensity) 315 (M^+, 12), 264 (4), 250 (7), 160 (100), 145 (76), 117 (45), 91 (91); HRMS *m/z* 316.1002 ($M^+ + 1$), (calcd for $C_{17}H_{17}NO_5$, 316.1007).

***N*-Tosyl-3,9-dimethoxy-8-hydroxy-5-azapterocarpan (18b).** In a manner similar to that described for the preparation of **18a**, a soln of a 2:1 mixture of dihydroquinolines **25** and **26** (90 mg, 0.28 mmol) and quinone **5f** (26 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) at −78 °C was treated with a solution of $TiCl_4$ (27 μL, 0.25 mmol) and $Ti(OiPr)_4$ (77 μL, 0.26 mmol) in CH_2Cl_2 (2 mL). After 2 h, the reaction was quenched and the mixture worked up as described above for the reactions of **4** with **5**. Chromatography (5% EtOAc:hexanes) gave starting **26** and azapterocarpan **18b** (86 mg, 100%) as a white solid, mp 84–86 °C (EtOAc:hexanes): TLC R_f 0.14 (20% EtOAc:hexanes); ^{1}H NMR (500 MHz): δ 7.52 (d, $J=8.4$, 2H), 7.40 (d, $J=8.5$, 1H), 7.30 (d, $J=3.0$, 1H), 7.20 (d, $J=8.4$, 2H), 6.85 (dd, $J=3.0$, 8.5, 1H), 6.75 (s, 1H), 6.36 (s, 1H), 5.22 (s, 1H), 5.06 (d, $J=7.8$, 1H), 4.32 (dd, $J=5.2$, 14, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.06 (m, 1H), 3.03 (dd, $J=12$, 14, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz): δ 159.7, 159.4, 146.8, 144.0, 139.9, 137.6, 137.0, 130.9, 129.8, 127.0, 120.0, 118.5, 113.3, 110.2, 109.2, 94.3, 78.6, 56.1, 55.5, 48.0, 39.9, 21.5; IR

($CHCl_3$) 3550, 2940, 1610, 1503, 1445, 1343, 1207, 1160, 1122, 1084, 1039, 826; EIMS *m/z* (relative intensity) 453 (M^+, 5), 298 (100), 283 (45), 266 (21), 160 (15), 91 (36). Anal. calcd for $C_{24}H_{23}NO_6S$: C, 63.56; H, 5.11; N, 3.09. Found: C, 63.28; H, 5.50; N, 2.98.

3-Methoxy-5-thiapterocarpan (30a). $PdCl_2$ (365 mg, 2.06 mmol) and LiCl (175 mg, 4.12 mmol) were suspended in acetone (22 mL) and stirred 12 h at 25 °C. To the resultant dark red homogeneous solution (Li_2PdCl_4) was added a soln of 7-methoxy-2*H*-thiachromene[14c] (**28**, 228 mg, 1.28 mmol) in acetone (12 mL) followed, after 15 min, by a solution of 2-chloromercuriophenol[15a,f] (623 mg, 1.89 mmol) in acetone (19 mL). The mixture was stirred at 25 °C for 2 days, filtered to remove the black fine solid that had formed and the filtrate was concentrated. The gummy residue obtained was filtered through silica gel using 10 and 20% acetone:hexanes, successively, as eluent. Concn of the eluent followed by chromatography (10:90, acetone:hexanes) provided thiapterocarpan **30a** (90 mg, 26%) as a colorless oil (the sample turns into a white powder upon storage in the freezer): TLC R_f (20% acetone:hexanes) 0.44; ^1H NMR (300 MHz): δ 7.55 (d, $J=8.4$, 1H), 7.30 (d, $J=7.3$, 1H), 7.21 (t, $J=7.7$, 1H), 6.94 (t, $J=7.1$, 1H), 6.88–6.80 (m, 3H), 5.55 (d, $J=7.7$, 1H), 3.82 (s, 3H), 3.76 (m, 1H), 2.96 (dd, $J=13$, 4.7, 1H), 2.76 (dd, $J=13$, 10, 1H); ^{13}C NMR (75 MHz): δ 159.3, 158.8, 135.9, 132.7, 130.0, 129.1, 124.6, 124.0, 121.0, 112.8, 112.5, 109.9, 80.7, 55.4, 43.4, 30.8; IR (CH_2Cl_2) 2928, 2839, 1602, 1567, 1486, 1315, 1220, 1181, 1063, 1035, 927, 877, 846; CIMS (NH_3) *m/z* 271 ($M^+ + 1$, 100%); HRMS *m/z* 271.0786 ($M^+ + 1$) (calcd. for $M^+ + 1$ $C_{16}H_{15}O_2S$, 271.0793).

Starting 7-methoxy-2*H*-thiachromene (9 mg, 4%) was also recovered.

8,9-(Methylenedioxy)-3-methoxy-5-thiapterocarpan (30b). In a procedure analogous to that described for **30a**, a mixture of $PdCl_2$ (403 mg, 2.27 mmol) and LiCl (193 mg, 4.55 mmol) in acetone (23 mL) was stirred 12 h at 25 °C and then added via canula to a suspension of 2-chloromercurio-4,5-methylenedioxyphenol[15c] (848 mg, 2.27 mmol) in acetone (30 mL) followed by a soln of 7-methoxy-2*H*-thiachromene (**28**, 359 mg, 2.02 mmol) in acetone (10 mL). The mixture was stirred 3 days at 25 °C, filtered, and the filtrate concd. The gummy residue obtained was filtered through silica gel using 10% and 20% acetone:hexanes, successively, as eluent. Concentration of the eluent followed by chromatography (acetone:hexanes, 10:90) provided thiapterocarpan **30b** (107 mg, 17%) as a light-pink solid, mp 151 °C: TLC R_f (30% acetone:hexanes) 0.41; ^1H NMR (300 MHz): δ 7.49 (d, $J=8.6$, 1H), 6.84–6.77 (m, 2H), 6.74 (s, 1H), 6.43 (s, 1H), 5.92 (ABq, $J=2.2$, $\Delta\nu=11$ Hz, 2H), 5.52 (d, $J=7.8$, 1H), 3.80 (s, 3 H), 3.65–3.57 (m, 1H), 2.88 (dd, $J=13$, 4.5, 1H), 2.71 (dd, $J=13$, 10, 1H); ^{13}C NMR (75 MHz): δ 159.3, 153.6, 148.0, 141.8, 135.8, 132.6, 123.9, 120.9, 112.7, 112.4, 104.5, 101.3, 93.4, 81.5, 55.4, 43.5, 30.7; IR (CH_2Cl_2) 2906, 1602, 1498, 1473, 1324, 1179, 1144, 1064, 1040, 936, 862, 838; CIMS (NH_3) *m/e* 315 ($M^+ + 1$, 100%), 164 (20). Anal. calcd. for $C_{17}H_{14}O_4S$: C, 64.95; H, 4.49. Found: C, 64.67; H, 4.80.

Starting 7-methoxy-2*H*-thiachromene (44 mg, 12%) was also recovered.

Acknowledgments

Financial support for this research was provided by the National Science Foundation (CHE-9116576), the National Science Foundation-EPSCoR Program (OSR-9255223), the University of Kansas J. R. and Inez Jay and General Research Funds, the Alfred P. Sloan Foundation (as a Fellowship to TAE), and Eli Lilly and Company. We thank Mr G. Stuart Gregory for help in the preparation of quinones **5a–d**. We also acknowledge with thanks the help of the Drug Synthesis and Chemistry and Antiviral Evaluation Branches of the National Cancer Institute for performing the in vitro anti-HIV evaluations and Dr Robert J. Schultz for helpful discussions.

References and Notes

1. For reviews, see (a) Ingham, J.L. In *Progress in the Chemistry of Organic Natural Products*, Vol. 43; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer: Wien; 1983; pp 1–266. (b) Dewick, P. M. In *The Flavonoids*; Harborne, J. B., Ed.; Chapman & Hall: London; 1994; Chapter 5, and previous reviews in this series. See also references cited in refs 2, 4, and 5.

2. Engler, T. A.; Lynch, Jr K. O.; Reddy, J. P.; Gregory, G. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1229.

3. (a) Desideri, N.; Conti, C.; Sestili, I.; Tomao, P.; Stein, M. L.; Orsi, N. *Antiviral Chem. Chemother.* **1992**, *3*, 195. (b) Hatano, T.; Yasuhara, T.; Miyamoto, K.; Okuda, T. *Chem. Pharm. Bull.* **1988**, *36*, 2286. (c) Hatano, T.; Yasuhara, T.; Fukuda, T.; Noro, T.; Okuda, T. *Chem. Pharm. Bull.* **1989**, *37*, 3005. (d) For references to reports of antiviral activity of related flavonoids, see ref 1b.

4. Tökés, A. L.; Antus, S. *Liebigs Ann. Chem.* **1994**, 911.

5. Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D. *J. Org. Chem.* **1990**, *55*, 1248.

6. The quinones were prepared by Fremy's salt oxidation of the corresponding 2-alkoxyphenols. Representative experimental details for the preparation of **5e** can be found in the Supplementary Material to ref 7a.

7. (a) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, Jr K. O.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567. (b) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588. (c) Engler, T. A.; Combrink, K. D.; Takusagawa, F. *J. Org. Chem.* **1990**, *55*, 5810. (d) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135.

8. (a) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541. (b) For other examples of deoxygenations of pterocarpans via this method, see ref 5.

9. Engler, T. A.; Lynch, Jr K. O.; Reddy, J. P.; Gregory, G. S.; Chu, F.; Schloss, J. V.; Wilson, J. *Abstracts of Papers*, 207th National Meeting of the American Chemical Society,

San Diego, CA; American Chemical Society: Washington, DC, 1994; ORGN 144.

10. Schäfer, W.; Friebe, W. G.; Leinert, H.; Mertens, A.; Poll, T.; Vondersaal, W.; Zilch, H.; Nuber, B.; Ziegler, M. L. *J. Med. Chem.* **1993**, *36*, 726.

11. For a preliminary report, (a) Engler, T. A.; Lynch, Jr K. O.; Chai, W.; Meduna, S. P. *Tetrahedron Lett.* **1995**, *36*, 2713. See also (b) Engler, T. A.; Chai, W.; Lynch, Jr K. O. *Tetrahedron Lett.* **1995**, *36*, 7003. For another approach to 5-azapterocarpans, see ref 4.

12. (a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122. (b) Das, T. K.; Gupta, A. D.; Ghosal P. K.; Dutta, P. C. *Indian J. Chem., Sect. B* **1976**, *14B*, 238.

13. McCombie, S. W.; Oritz, C.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 8033.

14. (a) Speckamp, W. N.; Westra, J. G.; Huisman, H. O. *Tetrahedron* **1970**, *26*, 2353. (b) Luttringhaus, A.; Engelhard, M. *Chem. Ber.* **1960**, *93*, 1525. (c) Degani, R.; Fochi, R.; Spunta, G. *Boll. Sci. Fac. Chem. Ind. Bologna* **1966**, *24*, 75 [*Chem. Abs.* **63** 13198*c* (1967)]. (d) For a review of methods to prepare thiapyrylium ions, see Doddi, G.; Ercolani, G. *Adv. Heterocyclic Chem.* **1994**, *60*, 65. (e) For an example of a Ti(IV)-quinone complex acting as a dehydrogenating agent, see ref 7a.

15. (a) Horino, H.; Inoue, N. *J. Chem. Soc., Chem. Commun.* **1976**, 500. (b) Breytenbach, J. C.; Rall, G. J. H.; Roux, D. G. *J. Chem. Soc., Perkin Trans 1* **1981**, 2604. (c) Coelho, A. L.; Vasconcellos, M. L. A. A.; Simas, B. C.; Rabi, J. A.; Costa, P. R. R. *Synthesis* **1992**, 914. (d) Narkhede, D. D.; Iyer, P. R.; Iyer, C. S. R. *Tetrahedron* **1990**, *46*, 2031. (e) Narkhede, D. D.; Iyer, P. R.; Iyer, C. S. R. *J. Nat. Prod.* **1989**, *52*, 502. (f) For preparation of **29a**, see also Whitmore, F. C.; Hanson, E. R. In *Org. Synth., Coll. Vol. I*; John Wiley: New York, 1941; p 161. (g) Ishiguro, M.; Tatsuoka, T.; Nakatsuka, N. *Tetrahedron Lett.* **1982**, *23*, 3859. See also ref 4.

16. For descriptions of instrumentation and purifications of solvents/reagents, see refs 5, 7a.

17. Laatsch, H. *Liebigs Ann. Chem.* **1980**, 1321.

18. Crouse, D. J.; Wheeler, M. M.; Goemann, M.; Tobin, P. S.; Basu, S. K.; Wheeler, D. S. M. *J. Org. Chem.* **1981**, *46*, 1814.

(*Received in U.S.A.* 20 *May* 1996; *accepted* 11 *July* 1996)