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Evidence for π-Stacking as a Source of Stereocontrol in the Synthesis of the Core Pyranochromene Ring System common to Calyxin I, Calyxin J, and Epicalyxin J

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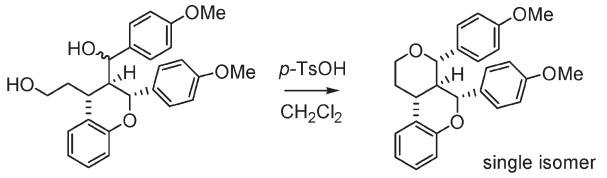
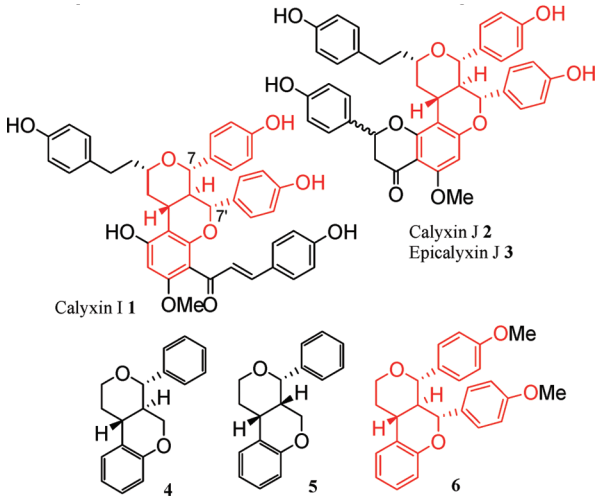


A diastereoselective synthesis of the tetrahydropyranochromene ring system common to several natural product isolates of *Alpinia blepharocalyx* is reported. We have shown that a stereochemical preference exists for a *syn* configuration between the anomeric aryl substituents, representative of the *C*-7 and *C*-7′ substituents in the natural products. Further, our results show that stereocontrol is under kinetic control, and calculations suggest that a favorable π-stacking interaction may be the source of this stereocontrol.

More than 50 polyphenolic constituents of the seeds of *Alpinia blepharocalyx* have been isolated by Kadota and coworkers,[1] and several of them have been shown to possess significant antiproliferative activity against colon 26-L5 carcinoma and HT-1080 fibrosarcoma cells. Not surprisingly, these compounds have attracted the attention of several groups, resulting in both partial[2] and total[3] syntheses of a number of analogues. Calyxin I (**1**) along with the epimeric analogues calyxin J (**2**) and epicalyxin J (**3**) comprise a subset of isolates that are characterized by the presence of a novel bis-*C*-arylpyranoside moiety embedded in a tetrahydropyranochromene framework. To date, synthetic work in this area has been sparse. Li and coworkers have reported stereoselective syntheses of compounds **4** and **5** using the Prins cyclization,[4] but they did not report the formation of bis-aryl derivatives by their route. We therefore chose compound **6** as a model synthetic target to see if a stereochemical preference exists for the aryl substituents to be *syn* to each other as indicated, analogous to the *C*-7 and *C*-7′ positions in the natural products. The nature of the interaction between the two aromatic rings at these positions would be important, and the possibility of a favorable π-stacking effect was not ruled out as a controlling factor.[5]



Our route began with the racemic lactone **8**, which was prepared in 56% yield by a palladium-catalyzed addition of 2-benzyloxyiodobenzene **7**[6] to 5,6-dihydro-2*H*-pyran-2-one (Scheme 1). A directed aldol reaction of lactone **8** with *p*-methoxybenzaldehyde, via its boron enolate, then gave alcohol **9** in a 91% yield as a single isomer,[7] which was cleanly converted to the diol **10** in 94% yield under standard hydrogenation conditions. Exposure of diol **10** to Lewis acid then provided compound **11** diastereomerically pure (79% from compound **9**). The stereochemistry of compound **11** was easily assignable based on proton NMR coupling constants. A doublet at δ 5.22 ($J = 10$ Hz) established the *trans*-diaxial relationship between H_a and H_b, while a doublet of doublets at δ 3.08 ($J = 10$, 13 Hz) confirmed the same relationship between H_a and H_c. Although the formation of **11** from diol **10** proceeded with complete inversion of configuration, establishment of the newly formed ring stereocenter in this reaction, with a pseudoequatorial aryl substituent, is most likely the result of an S_N1 mechanism involving

(1) (a) Ali, M. S.; Bankskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2001**, *24*, 525–528. (b) Gewali, M. B.; Tezuka, Y.; Banskota, A. H; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733–1736. (c) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208–213.

(2) (a) Polat Cakir, S.; Mead, K. T. *Tetrahedron Lett.* **2006**, *47*, 2451–2454. (b) Washio, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2007**, 2606–2612.

(3) (a) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176–3183. (b) Tian, X.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4955–4958.

(4) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, 1912–1916.

(5) For a recent example, see: Fustero, S.; Navarro, A.; Pina, B.; Soler, J. G.; Bartolome, A.; Asensio, A.; Simon, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621–2624.

(6) Portscheller, J. L.; Malinakova, H. C. *Org. Lett.* **2002**, *4* (21), 3679–3681.

(7) The stereochemistry assigned to compound **9** was based on literature precedent. See: Ito, H.; Momose, T.; Konishi, M.; Yamada, E.; Watanabe, K.; Iguchi, K. *Tetrahedron* **2006**, *62*, 10425–10433.

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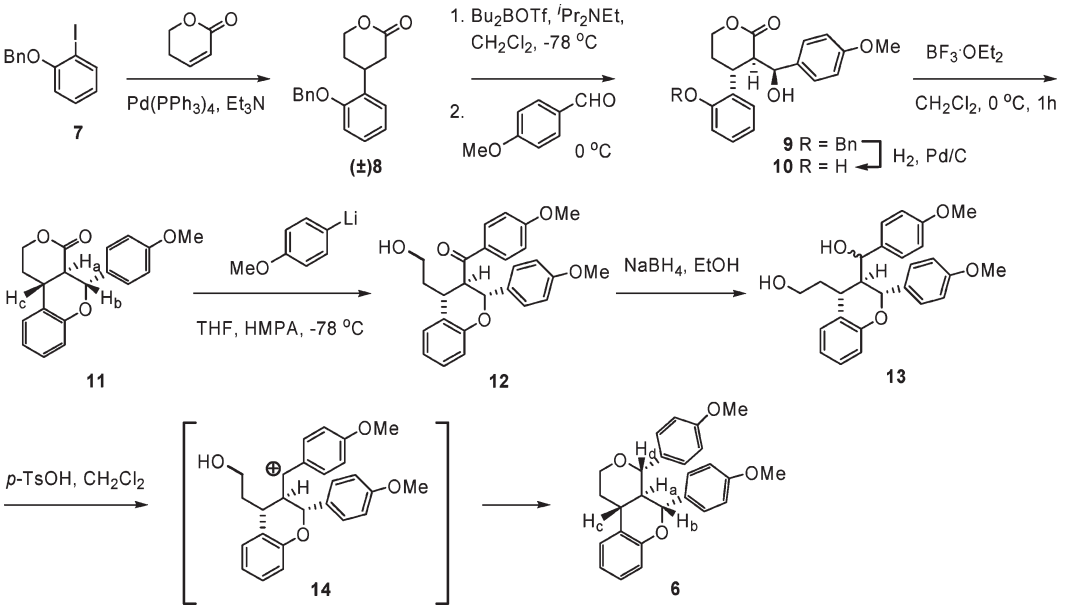
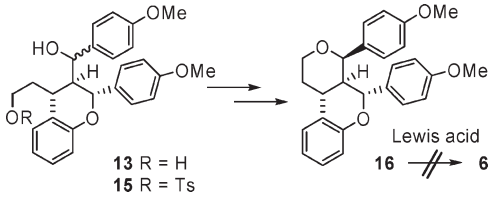
SCHEME 1



SCHEME 2



formation of a stabilized benzyl carbocation. Unfortunately, attempts to open the lactone ring of **11** by reaction with commercially available *p*-methoxyphenylmagnesium bromide gave only starting material. However, use of the corresponding aryllithium reagent provided **12** in 72% yield. The final ring closure was accomplished in two steps (81%) by treatment of **12** with $NaBH_4$ followed by exposure of the crude mixture of diols **13** to *p*-TsOH. To our surprise, compound **6** was formed diastereomerically pure by NMR analysis. The stereochemistry was confirmed by assignments of the alicyclic ring protons, which were supported by GIAO calculations of the chemical shifts. Both anomeric protons H_b and H_d appeared as doublets with coupling constants of 9.7 Hz, thereby confirming the *trans*-diaxial relationship between H_a and H_d. A final verification of the stereochemistry was provided by the NOESY spectrum, which showed the expected cross peaks for H_b-H_c, H_b-H_d, and H_c-H_d, but not for H_a (see the Supporting Information).

We considered the possibility that both anomeric stereocenters in **6** were formed under equilibrating conditions, given their potential acid lability.[8] Formation of benzyl carbocation **14** from the diol mixture **13** would be expected to be facile by virtue of the stabilizing effect of the *p*-methoxy group. However, the question of whether this effect was sufficient to allow its formation reversibly from the pyranochromene product remained to be addressed. To test for thermodynamic control in the formation of compound **6**, the mixture of diols **13** was converted to an equal mixture of **6** and its anomer **16** via the primary tosylate **15** (Scheme 2), and the two diastereomers were separated by column chromatography. However, treatment of compound **16** with *p*-TsOH, $TiCl_4$, or $BF_3\cdot OEt_2$ failed to yield any of the *syn* isomer **6**, suggesting that its formation from intermediate **14** is most likely under kinetic control.

In an attempt to determine the origin of the stereocontrol in the formation of **6** from **14**, we decided to calculate the relative energies of the *syn* and *anti* conformers of carbocation **14**, leading to the formation of **6a** and **16a**, respectively (see Figure 1). These two conformations have been labeled **14-*syn*** and **14-*anti*** to designate the *syn* and *anti* relationship, respectively, between the two 4-methoxyphenyl groups. Calculations were carried out using the MP2/cc-pVDZ approach, as this method takes into account the possibility of weak interactions such as π-stacking effects.[9] We felt that this could be a significant factor in carbocation **14**, as there is the potential for a donor−acceptor interaction, given that one aromatic ring is electron deficient by virtue of the benzylic cationic center. Indeed, our calculations show that conformer **14-*syn*** is 5.7 kcal/mol lower in energy than conformer **14-*anti*** and that the corresponding ring-closed product, **6a**, is 5.0 kcal/mol more stable than **16a**. Interestingly, the smaller distances separating the two *4*-methoxyphenyl rings in **14-*syn*** indicate that attractive forces are involved. The interatomic separation between carbon atoms 1 and 1′, for example, is 3.07 Å, while carbon atoms 4 and 4′ are separated by a distance of 3.30 Å. This suggests that the stabilization calculated for this conformer might be due to a favorable π-stacking interaction that is obviously absent in **14-*anti***. On the basis of these calculations, stereocontrol in the formation of compound **6** (see Scheme 1) can be explained by making the reasonable assumptions that carbocation conformer **14-*syn*** is formed from both diastereomers of

(8) For evidence of this, see: Polat Cakir, S.; Mead, K. T. *J. Org. Chem.* **2004**, *69*, 2203–2205.

(9) (a) Hobza, P.; Sezle, H. L.; Schlag, E. W. *J. Phys. Chem.* **1996**, *100*, 18790–18794. (b) Špirko, V.; Enqvist, O.; Soldăn, P.; Sezle, H. L.; Schlag, E. W; Hobza, P. *J. Chem. Phys.* **1999**, *111*, 572–582.

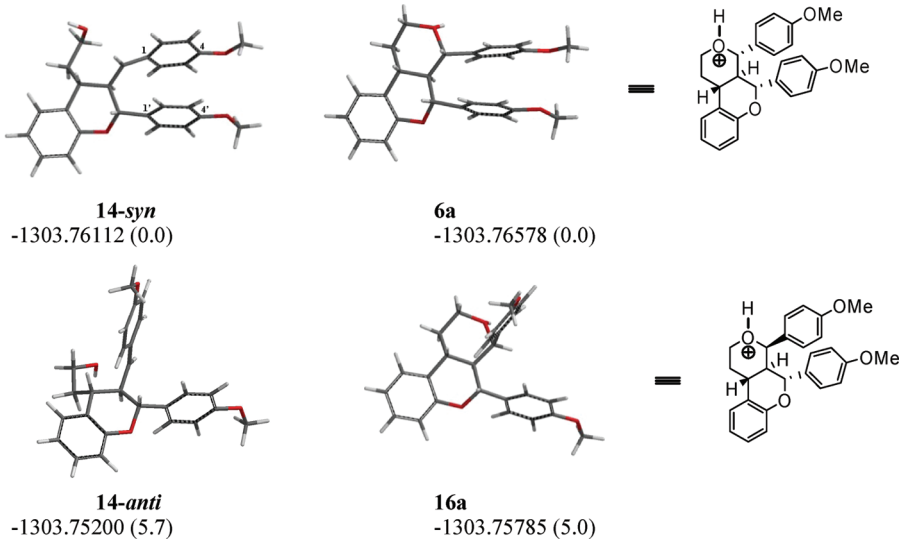


FIGURE 1. MP2/cc-pVDZ-optimized structures and energies (in Hartrees) of *syn* (top) and *anti* (bottom) conformers of carbocation **14** (left), as well as initial ring-closed products **6a** and **16a** (right). Relative energies (kcal/mol) of the *syn*−*anti* pairs are given in parentheses.

diol **13** at a faster rate than **14-*anti*** and that ring closure from **14-*syn*** is fast relative to conformational interchange. Efforts are currently underway to apply these results to the enantioselective syntheses of both calyxin J and epicaylyxin J.

Experimental Section

4-(2-Benzyloxyphenyl)tetrahydropyran-2-one ((±)-8). A mixture of 1-benzyloxy-2-iodobenzene **7**[6] (174 mg, 0.56 mmol), 5,6-dihydro-2*H*-pyran-2-one (50 mg, 0.51 mmol), tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.02 mmol), and triethylamine (57 mg, 0.56 mmol) was purged with N_2 gas and heated to 80 °C for 10 h. The solution was quenched with 10% HCl and extracted with EtOAc. The organic layer was washed with water and then dried over anhydrous $MgSO_4$. The crude oil was subjected to column chromatography using an ethyl acetate/hexane mixture as the eluting solvent to afford the product (81 mg, 56%) as a crystalline white solid (mp 82−84 °C): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.36 (m, 5H), 7.24 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.00−6.96 (m, 2H), 5.09 (s, 2H), 4.43−4.25 (m, 2H), 3.65−3.55 (m, 1H), 2.90 (dd, J = 5.9 and 17.3 Hz, 1H), 2.67 (dd, J = 10.2, 17.3 Hz, 1H), 2.10−2.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 155.9, 136.7, 131.1, 128.6, 128.0, 127.2, 126.8, 121.1, 112.0, 70.1, 68.4, 35.8, 31.8, 28.5; FT-IR ($CHCl_3$) 3033, 2904, 1736, 1234, 752 cm^{-1}; HRMS calcd for $C_{18}H_{18}O_3$ 282.1255, found 282.1256.

4-(2-Benzyloxyphenyl)-3-[hydroxy(4-methoxyphenyl)methyl]-tetrahydropyran-2-one (9). Dibutylboron trifluoromethanesulfonate (1 M solution in dichloromethane, 6.6 mL, 6.6 mmol) and *N*,*N*-diisopropylethylamine (1.4 mL, 8.25 mmol) were added to a solution of lactone **8** (930 mg, 3.3 mmol) in dichloromethane (20 mL) at −78 °C. The resultant mixture was stirred at the same temperature for 2 h, and then *p*-methoxy benzaldehyde (0.8 mL, 6.6 mmol) was added to the mixture and stirred for another 2 h. After the mixture was stirred for an additional 2 h at 0 °C, phosphate buffer solution (pH = 7.0, 8 mL), methanol (15 mL), and H_2O_2 (30 wt. % solution in water, 8 mL) were added and the mixture stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate/hexane mixture as eluting solvent to give the product (1.25 g, 91%) as a crystalline white solid: mp 122−124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.36 (m, 5H), 7.33 (dt, J = 1.6 and 8.3 Hz, 1H), 7.11 (d, J = 8.5 Hz, 3H), 6.95 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 8.7 Hz, 2H), 5.07 (d, J = 11.2 Hz, 1H), 5.04 (d, J = 11.2 Hz, 1H), 4.72 (s (broad), 1H), 4.24−4.19 (m, 1H), 4.08−4.04 (m, 1H), 3.81−3.80 (m, 1H), 3.76 (s, 3H), 3.56−3.49 (m, 2H), 2.18−2.11 (m, 1H), 2.05−1.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 158.7, 155.8, 136.3, 133.8, 130.7, 129.7, 128.7, 128.3, 128.2, 127.7, 127.3, 121.1, 113.4, 112.0, 72.6, 70.2, 67.0, 55.1, 50.3, 36.0, 29.1; FT-IR ($CHCl_3$) 3445 (broad), 2935, 1716, 1512, 1248, 752 cm^{-1}

3-[Hydroxy(4-methoxyphenyl)methyl]-4-(2-hydroxyphenyl)tetrahydropyran-2-one (10). Lactone **9** (700 mg, 1.7 mmol) was dissolved in 15 mL of EtOAc/EtOH (2:1), and 10 mol % of Pd/C was added to the solution. The resultant mixture was stirred overnight at room temperature under H_2 gas atmosphere. The reaction mixture was filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography using ethyl acetate/hexane mixture as eluting solvent to provide the product (515 mg, 94%) as a crystalline white solid: mp 48−50 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2H), 7.08−7.02 (m, 2H), 7.00−6.97 (m, 1H), 6.79 (t, J = 7.0 Hz, 1H), 6.76 (d, J = 8.7 Hz, 2H), 4.80 (s (broad), 1H), 4.41 (ddd, J = 4.2, 7.2, and 11.3 Hz, 1H), 4.07−4.02 (m, 1H), 3.73 (s, 3H), 3.53 (dd, J = 4.2 and 9.1 Hz, 1H), 3.47−3.40 (m, 1H), 2.11−2.05 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 158.8, 153.7, 133.4, 129.3, 128.2, 127.2, 120.7, 116.4, 114.2, 113.5, 72.9, 67.6, 55.2, 51.4, 35.6, 29.1; FT-IR ($CHCl_3$) 3362 (broad), 2933, 1705, 1513, 1249, 755 cm^{-1}; HRMS: calcd for $C_{19}H_{20}O_5$ 328.1305, found 328.1311.

5-(4-Methoxyphenyl)-1,4a,5,10b-tetrahydro-2*H*-pyrano[3,4-*c*]-chromen-4-one (11). To a solution of diol **10** (130 mg, 0.39 mmol) in dichloromethane (10 mL) were added crushed 4 Å molecular sieves and $BF_3 \cdot OEt_2$ (24 μL, 0.2 mmol, 0.5 equiv) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h and then quenched with water and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate/hexane mixtures as eluting solvent to give the product (102 mg, 84%) as a crystalline white solid: mp 218−220 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 8.6 Hz, 2H), 7.20−7.14 (m, 2H), 6.98 (t, J = 7.1 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.1 Hz, 1H), 5.22 (d, J = 10.0 Hz, 1H), 4.50 (ddd, J = 3.6, 7.5, and 11.4 Hz, 1H), 4.40 (ddd, J = 6.3, 9.5, and 11.9 Hz), 3.82 (s, 3H), 3.37 (td, J = 8.9

and 13.0 Hz, 1H), 3.08 (dd, J = 10.0 and 13.0 Hz, 1H), 2.82−2.74 (m, 1H), 2.14−2.08 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 159.7, 153.9, 132.0, 129.0, 128.3, 126.1, 123.9, 121.1, 117.1, 113.7, 77.3, 65.4, 55.2, 44.4, 33.2, 27.0; FT-IR ($CHCl_3$) 2910, 1737, 1230, 754 cm^{-1}; HRMS calcd for $C_{19}H_{18}O_4$ 310.1199, found 310.1196.

[4-(2-Hydroxyethyl)-2-(4-methoxyphenyl)chroman-3-yl](4-methoxyphenyl)methanone (12). To a solution of lactone **11** (32 mg, 0.10 mmol) in anhydrous THF (2 mL) and HMPA (0.1 mL) was added freshly prepared *p*-MeOPhLi in a dropwise manner at −78 °C until the disappearance of the lactone was indicated by TLC, and the resulting solution was stirred at the same temperature for 6 h. The reaction was quenched by the addition of water and warmed to room temperature. The mixture was extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the product as an oil (31 mg, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J = 8.7 Hz, 2H), 7.33 (d, J=7.6 Hz, 1H), 7.23 (d, J= 8.4 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 6.99−6.94 (m, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 4.95 ((d, J = 9.6 Hz, 1H), 4.09 (t, J = 10.1 Hz, 1H), 3.85−3.78 (m, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.58−3.50 (m, 2H), 2.03−2.00 (m, 1H), 1.98−1.92 (m,1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 163.5, 159.4, 155.0, 130.7, 128.2, 127.5, 127.3, 125.0, 121.2, 117.2, 113.7, 113.5, 80.5, 60.0, 55.4, 55.2, 52.0, 36.6, 35.5; FT-IR ($CHCl_3$) 3471, 2935, 1660, 1598, 1514, 1251, 1174 cm^{-1}. HRMS calcd for $C_{26}H_{26}O_5$ 418.1774, found 418.1782.

4,5-Bis(4-methoxyphenyl)-1,4a,5,10b-tetrahydro-2*H*,4*H*-pyrano[3,4-*c*]chromene (6). To a solution of compound **12** (18.2 mg, 0.04 mmol) in EtOH (2 mL) was added $NaBH_4$ (1.7 mg, 0.044 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with water, and the ethanol was evaporated under reduced pressure. The residue was extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), and a catalytic amount of *p*-TsOH was added at room temperature. The reaction mixture was stirred until the disappearance of the diol was indicated by TLC. The mixture was filtered and concentrated under reduced pressure, and the crude product was purified by flash column chromatography using ethyl acetate/hexane mixtures as eluting solvent to give the product as an oil (13 mg, 81%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (d, J=7.6 Hz, 1H), 7.16 (t, J=7.5 Hz, 1H), 6.98 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.76 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.5 Hz, 2H), 6.45 (d, J = 8.5 Hz, 2H), 6.42 (d, J = 8.5 Hz, 2H), 4.83 (d, J = 9.7 Hz, 1H), 4.29 (dd, J = 3.5 and 11.4 Hz, 1H), 4.18 (d, J = 9.6 Hz, 1H), 3.82 (dt, J = 1.9 and 11.9 Hz, 1H), 3.67 (s, 6H), 3.06 (dt, J = 2.8 and 11.3 Hz, 1H), 2.39 (d (broad), J=12.9 Hz, 1H), 2.34 (q, J = 9.9 Hz, 1H), 1.91 (dq, J= 4.5 and 12.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.7, 154.4, 132.6, 132.1129.0, 128.9, 127.7, 126.7, 124.4, 120.6, 116.7, 113.3, 113.2, 83.0, 81.6, 68.1, 55.1, 47.9, 38.1, 28.9; FT-IR ($CHCl_3$) 2952, 2835, 1515, 1246 cm^{-1}; HRMS calcd for $C_{26}H_{26}O_4$ 402.1825, found 402.1822.

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Supporting Information Available: ^{1}H and ^{13}C spectra for new compounds and details of the computational studies. This material is available free of charge via the Internet at http://pubs.acs.org