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Synthesis and Structure Revision of Calyxin Natural Products

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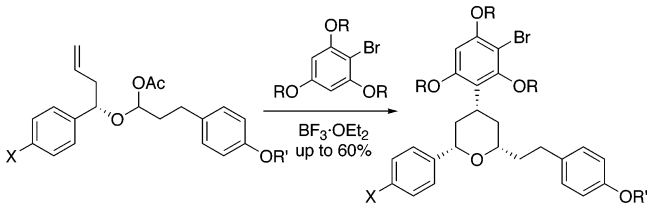

Tandem Prins cyclization and Friedel−Crafts reaction with an electron-rich aromatic ring were used to prepare the core structures of calyxin natural products. The proposed structure of epicalyxin F was prepared and shown to be incorrect. Several calyxin natural products, including calyxin F and L, were synthesized, and the structures were reassigned on the basis of NMR data and synthetic correlations.

Introduction

A new family of natural products was isolated recently from the *Alpinia blepharocalyx* seeds, which are used for the treatment of stomach disorders in Chinese medicine (Figure 1).[1] Several of these natural products show interesting antiproliferative activity against carcinoma cells. Epicalyxin F is the most potent member of the class and showed ca. 1 μM activity against human HT-1080 fibrosarcoma and murine 26-L5 carcinoma. It is accompanied by calyxin F and a host of related diarylheptanoid natural products. Described herein are a synthesis of the reported structure of epicalyxin F using a tandem Prins cyclization Friedel−Crafts arylation strategy and the synthesis and structure revision of several calyxin natural products.

Prins cyclizations normally lead to tetrahydropyran rings with a heteroatom at the C4 position. We found that under some circumstances the electrophilic C4 position reacts with an aromatic ring in a Friedel−Crafts alkylation reaction to introduce an aryl group in the equatorial position.[2] This carbon trapping of the cyclized carbenium ion rapidly builds structural complexity and could be a useful synthetic method. Very recently, Li's group reported a three-component Prins−Friedel−Crafts cyclization closely related to our work.[3,4] The isolation of epicalyxin F, whose structure is very well suited to a Prins cyclization and Friedel−Crafts trapping strategy, led us to

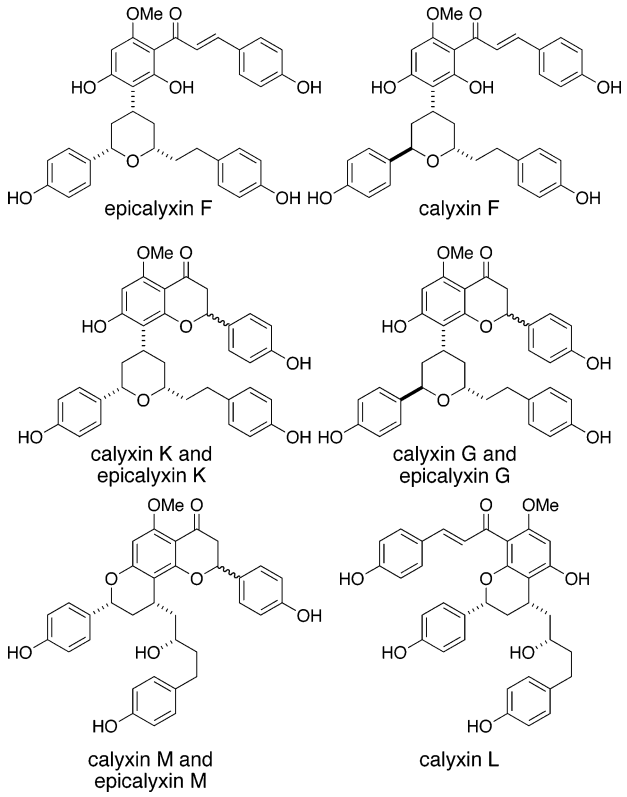

FIGURE 1. Proposed structures of epicalyxin F, calyxin F, and several related natural products isolated from *A. blepharocalyx* seeds.

(1) (a) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733−1736. (b) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208−213. (c) Kadota, S.; Tezuka, Y.; Prasain, J. K.; Ali, M. S.; Banskota, A. H. *Curr. Top. Med. Chem.* **2003**, *3*, 203−225. (d) Praisin, J. K.; Li, J. X.; Tezuka, Y.; Tanaka, K.; Basnee, P.; Dong, H.; Namba, T.; Kadota, S. *J. Chem. Res.* **1998**, 265−279.

(2) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679−8682.

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

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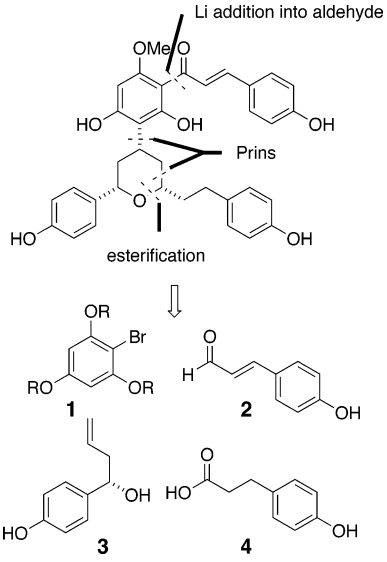


FIGURE 2. Retrosynthetic analysis of epicalyxin F.

initiate a study of this reaction directed toward the synthesis of epicalyxin F.[5]

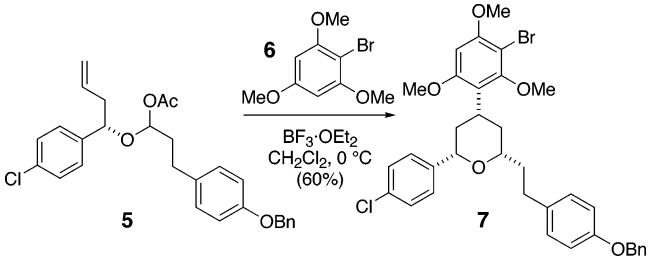
The synthetic disconnections for epicalyxin F are shown in Figure 2. The central Prins cyclization precursor, an α-acetoxy ether, would be prepared from the ester of alcohol **3** and acid **4**. Prins cyclization and in situ Friedel−Crafts arylation with brominated phloroglucinol **1** would assemble the bulk of the structure. The unsaturated ketone fragment would be added by lithiation of an aryl bromide and addition to the unsaturated aldehyde **2**. The strategy used readily available starting materials and was highly convergent. The implementation of this strategy turned out to be more challenging than anticipated.[5]

Results and Discussion

The key Prins cyclization was successful. However, the protecting group strategy was not. Initial studies ruled out the use of a benzyl protecting group in component **3** because it led to solvolysis rather than Prins cyclization, as previously observed by Willis and co-workers.[6] The use of chloride as an oxygen surrogate led to cyclization precursor **5**. Prins reaction in the presence of 2 equiv of the aryl bromide **6** gave tetrahydropyran **7** as a single diastereomer in 60% yield (Scheme 1). Trimethoxybenzene could be used in place of **6**, but it led to a reduced yield of the product (42%) and more side products.[7] The Prins cyclization and Friedel−Crafts trapping of acetoxy ether **5** assemble most of the carbon skeleton for epicalyxin F in a single step. The tetrahydropyran **7** was not a viable precursor to epicalyxin F, however, because conversion of the chloride to an alcohol using Buchwald−Hartwig[8] chemistry worked poorly with this substrate, and the three methyl ethers could not be differentiated effectively.[5]

A second synthesis was developed with sulfonate protecting groups to avoid the problematic Buchwald substitution,[6b,c,9] and

SCHEME 1. Arene-Terminated Prins Cyclization To Assemble a Partial Structure for Epicalyxin F



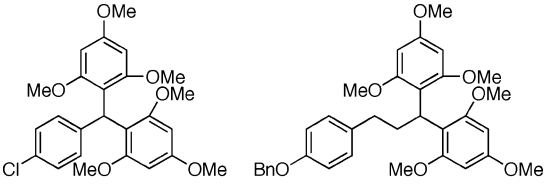
a more labile benzyl group replaced one of the methyl ethers.[5] The optically pure α-acetoxy ether **8** was prepared from the appropriately protected precursors **3** and **4** as illustrated in Scheme 2. Prins cyclization and aryl substitution worked well to produce the tetrahydropyran, but now as a mixture of two isomers, **10a** and **10b**, in a 1:2 ratio. NMR analysis demonstrated that both isomers had the expected stereochemical configuration, and initially we attributed the structural difference to slow rotation around the hindered aryl−THP bond.[10] Ultimately, we found that the major product resulted from ipso substitution and bromine migration, leading to unexpected aryl regioisomer **10b**.[11] The bromine migration may be related to the reported debromination of an electron-rich aromatic ring under acidic conditions, using a bromonium ion scavenger.[12] The isomeric mixture of **10a** and **10b** was metalated with PhLi.[13] Addition of aldehyde **11** gave the allylic alcohol, which was oxidized with DDQ to produce enones **12a** and **12b**. Deprotection of **12a**/**b** required the removal of the more hindered methyl ether. The deprotection was accomplished in very modest yield by treatment with BCl_3 to remove the benzyl ethers. Incomplete deprotection of the methyl ethers from the two different starting materials led to a mixture of monomethyl and dimethyl phenols. Selective removal of the more hindered methyl ether was expected on the basis of literature precedent and previous studies with adduct **7**, but it was not independently confirmed on the mixture of products from **12a**/**b**. Hydrolysis of the sulfonate with KOH in MeOH/H_2O resulted in less than 4% yield of a

(4) Hanessian's group reported a related Azonia−Prins/Friedel−Crafts reaction based on *N*-acyloxyiminium ion cyclizations: Hanessian, S.; Tremblay, M. *Org. Lett.* **2004**, *6*, 4683−4686.

(5) Jaber, J. J. Ph.D. Thesis, University of California, Irvine, 2002.

(6) (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407−3410. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580. (c) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727−3729.

(7) The side products in the reaction were tentatively identified (LRMS) as bis(trimethoxybenzene) adducts with the aldehyde components. These adducts presumably arise from addition to the oxocarbenium ion intermediate, followed by solvolysis and addition of a second equivalent of trimethoxybenzene. Use of the more electron-deficient bromotrimethoxybenezene **6** minimized this side reaction.



MW = 458 MW = 558

(8) (a) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498−2500. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225.

(9) Sulfonates have been used as phenol protecting groups. For example, see: (a) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 232−236. (b) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962−3964.

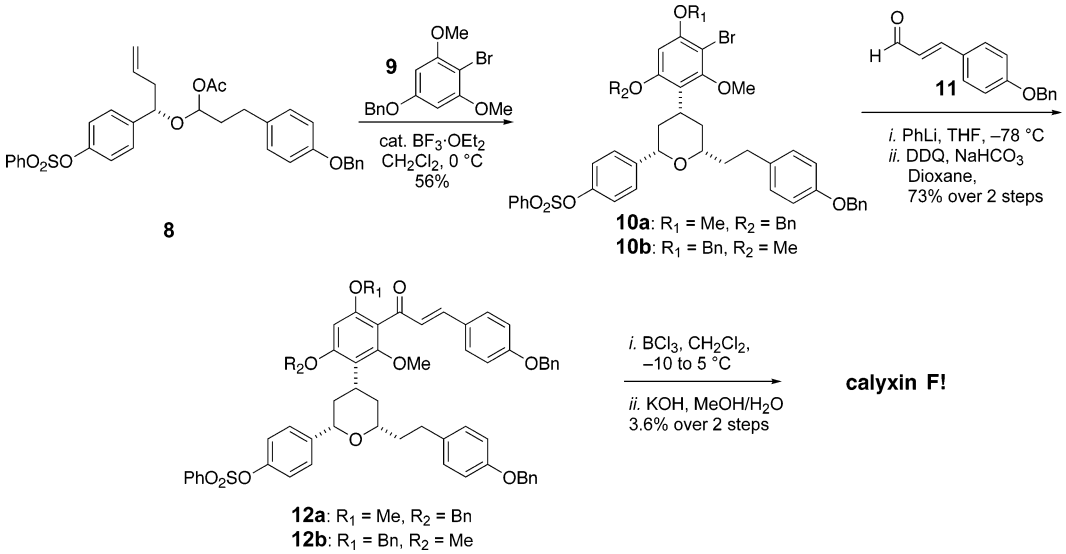
(10) Debenzylation and methylation of **10a** and **10b** led to a single compound, and therefore their structures must be closely related.

(11) Debromination of compound **10b** led to a symmetrically substituted aryl ring only consistent with the assigned structure.

(12) Choi, H. Y.; Chi, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 9202−9203.

(13) Metal−halogen exchange with *n*-BuLi, *s*-BuLi, or *t*-BuLi produced only protonated product.

SCHEME 2. Unexpected Synthesis of Calyxin F



product with the expected molecular weight. Comparison with the reported spectroscopic data demonstrated that the material was not epicalyxin F, but instead was the reported epimer, calyxin F.[5] The assembly of the carbon framework worked very well, but the final deprotection was not at all practical. Unfortunately, the isolation of calyxin F raised more questions than it answered.

The isolation of calyxin F from the deprotection sequence suggested that the structure reported for the natural product might be erroneous or that the vigorous conditions used in the deprotection might have isomerized the starting material, **12a/b**. The latter view received some support because the proton NMR spectrum of synthetic calyxin F was significantly different from that of the protected precursors **12a/b**. The structure assignments were also suspect because both calyxin F and epicalyxin F had been assigned boat conformations based on ROESY correlations, but extensive molecular modeling in our hands provided no support for these conformations.[14] Finally, entering the deprotection with a mixture of regioisomers (**12a/b**) just confused the situation.[15] We decided to develop a new synthesis with a very safe protecting group strategy that would avoid any possibility of rearrangement. Hopefully such a strategy would allow us to unambiguously determine the structure of epicalyxin F.

The new synthesis of epicalyxin F is outlined in Scheme 3. Protection and enantioselective allylation[16] of 4-hydroxybenzaldehyde generated alcohol **14** with 93% ee. Esterification and reductive acylation[17] produced the Prins cyclization precursor **16**. Prins cyclization in the presence of the tribenzyl aryl bromide **17**[18] and $BF_3{\cdot}OEt_2$ gave the expected adduct as a single diastereomer. Debromination produced the symmetric tribenzyl compound **18** in 42% yield over two steps. Selective removal of the least hindered benzyl ether, methylation, and hydrogenation delivered the diphenol **19**. The symmetry apparent in the NMR spectra of **19** unambiguously established the position of the methyl ether.

The completion of the synthesis was straightforward. Reprotection of the phenols in **19** with SEMCl,[19] bromination, and coupling with aldehyde **20** as previously described (Scheme 2) gave the complete carbon skeleton of epicalyxin F, compound **21**. Removal of the SEM groups with HF·pyridine, followed by hydrolysis of the sulfonate protecting groups with K_2CO_3 in MeOH produced the proposed structure of epicalyxin F, compound **22**. Unfortunately, the spectral data did not match that reported for the natural product. The C7 proton appeared at 4.31 ppm (dd, 12.0, 2.0 Hz) rather than at 5.05 ppm (dd, 12.0, 2.0 Hz). Thus the structure of epicalyxin F is not **22**. On inspection, we found that the NMR data for our synthetic material (**22**) did match another natural product isolated from the same plant, calyxin L.[20] The correct structure for calyxin L is shown in Scheme 3.

How was calyxin F produced in Scheme 2? Presumably, the harsh deprotection conditions led to an isomerization of **12a** or **12b**, perhaps through solvolysis to a stabilized C7 cation. With an eye toward reproducing the earlier structural rearrangement, calyxin L was exposed to acidic conditions. Synthetic calyxin L produced a mixture of products when heated in neat acetic acid at 90 °C (Scheme 4). Calyxin F[21] and L were isolated as

(14) Conformational searches with the proposed structures for calyxin F and epicalyxin F did not identify any low energy twist boat conformations and only led to low energy chair conformations. The searches were carried out using Macromodel with the Monte Carlo algorithm.

(15) One possible explanation was that calyxin F arose from deprotection of **12b**, and that the actual structure of calyxin F was that reported for epicalyxin F except with the methyl ether para to the ketone. More recently, we have synthesized this compound and shown that it does not match the data for any of the calyxin natural products. Spectroscopic data for this compound is reported in the Supporting Information.

(16) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (b) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001−7002.

(17) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.

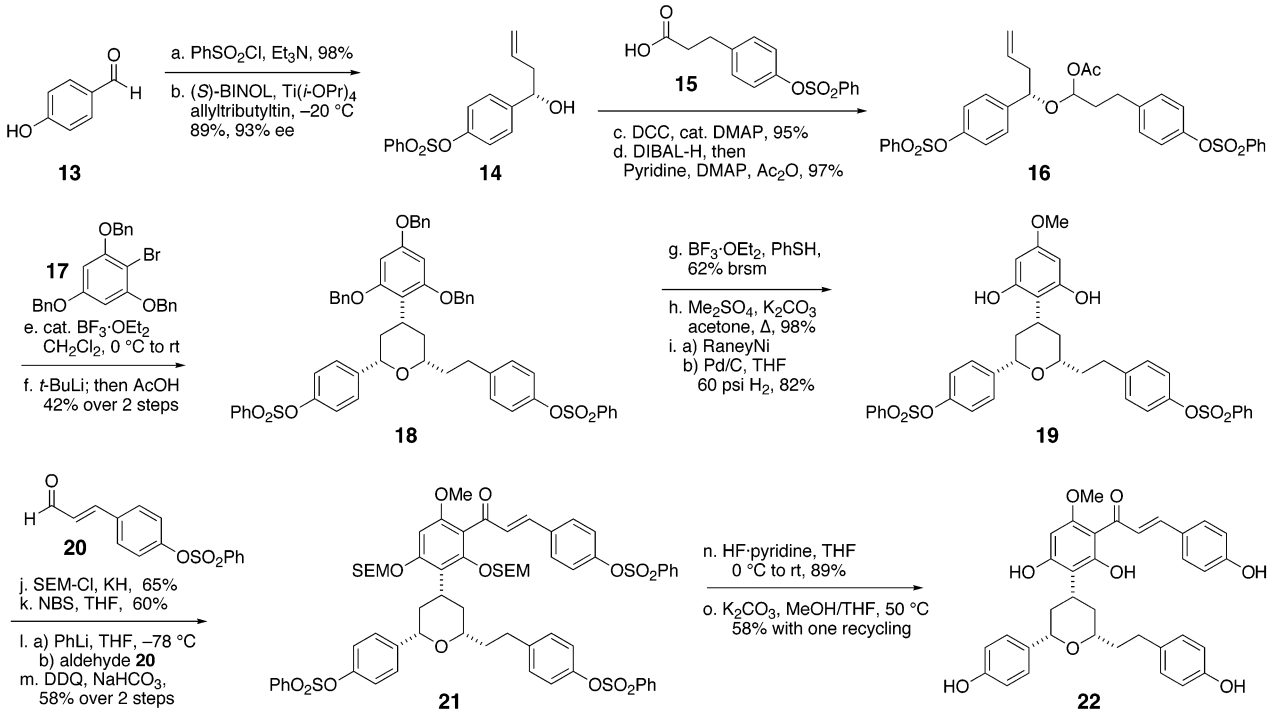
(18) Kawamoto, H.; Nakatsubo, F.; Murakami, K. *Synth. Commun.* **1996**, *26*, 531−534.

(19) For an example of the SEM ether used as a phenol protecting group, see: Fürstner, A.; Gastner, T. *Org. Lett.* **2000**, *2*, 2467−2470.

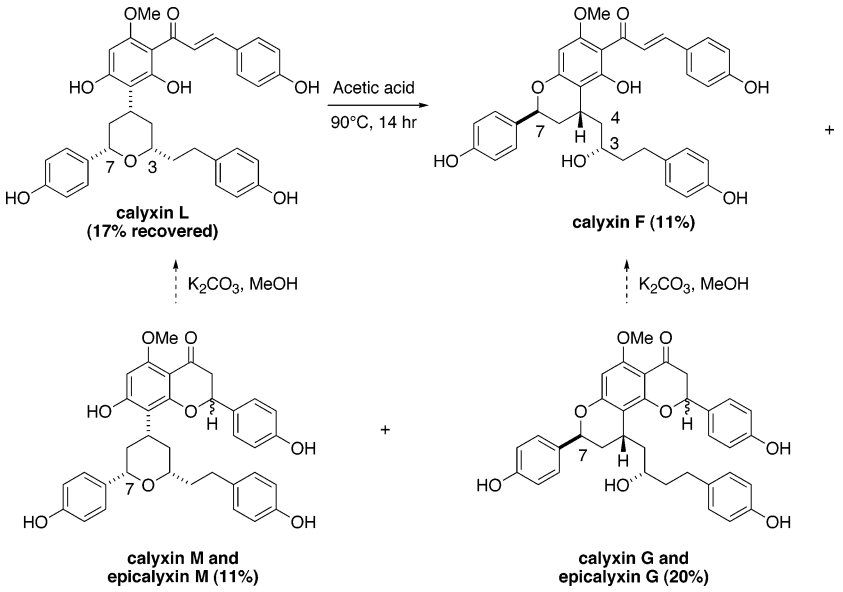
(20) Natural calyxin L: $[\alpha]^{24}_D$ +77.1 (*c* 0.05, MeOH); synthetic calyxin L: $[\alpha]^{25}_D$ −6 (*c* 0.08, MeOH). Measurements of the optical rotation of calyxin L were completely unreliable, and we do not draw any conclusion about the absolute configuration or optical purity of the samples based on these data. We observed both positive and negative rotations of differing magnitudes from the same sample. A systematic investigation of concentration versus rotation is presented in the Supporting Information.

(21) Natural calyxin F: $[\alpha]^{25}_D$ +5.7 (*c* 0.26, MeOH). Synthetic calyxin F: $[\alpha]^{25}_D$ +16.3 (*c* 0.175, MeOH).

SCHEME 3. New Protecting Group Strategy for the Synthesis of Epicalyxin F



SCHEME 4. Acid-Catalyzed Isomerization of Calyxin L Produces Calyxin F and Related Natural Products



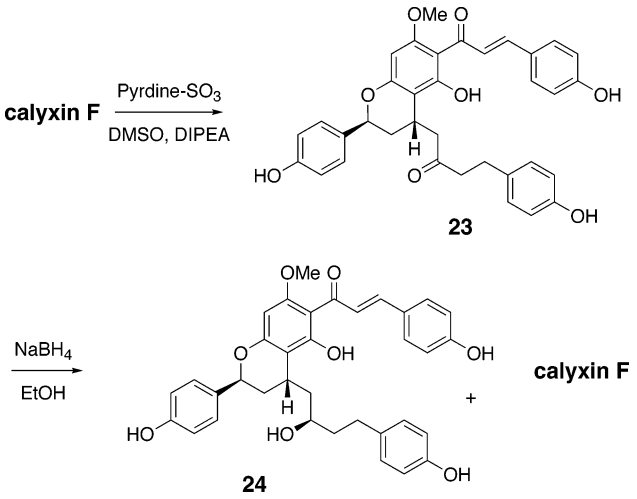
well as mixtures of compounds tentatively assigned as calyxin G & epicalyxin G and calyxin M & epicalyxin M.[22] Unfortunately, the structures proposed in the literature (Figure 1) did not appear to be consistent with the NMR data for these products.

The calyxins F, G, and epi-G all showed a C7 proton above 5.0 ppm, whereas calyxins L, M, and epi-M all had a C7 proton below 4.5 ppm. The C7 proton shift for calyxins F, G, and epi-G suggested an aryl ether rather than an aliphatic ether in the THP ring. Solvolysis of the labile C7 oxygen and reclosure on one of the adjacent phenols could account for the C7 proton shifts above 5.0 ppm. Such a rearrangement would expose a C3 alcohol. Acetylation of calyxin F formed a tetraacetate (not shown) that shifted the C3 proton from 3.79 to 5.06 ppm, suggesting a free alcohol at that position. Calyxin F was oxidized to the corresponding C3 ketone (Scheme 5).[23] Ketone **23** showed the expected spectral characteristics. Subsequent reduction with $NaBH_4$ returned calyxin F and 3-epicalyxin F (**24**). The spectral

(22) The NMR data for synthetic calyxin F and calyxin L match the reported data very well. However, there are small deviations in the proton and ^{13}C data for calyxin G and epicalyxin G and calyxin M and epicalyxin M. Most of the NMR data matches perfectly. The NMR data for these compounds were collected on mixtures, and some of the discrepancies may be due to the complexity of the mixtures or to concentration dependence of the chemical shifts. Without the original compounds or original spectra, we cannot resolve these discrepancies.

(23) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

SCHEME 5. Oxidation and Reduction of Calyxin F



data for alcohol **24** did not match that reported for the natural product epicalyxin F.

The configuration of calyxin F is apparent on inspection of the spectral data. All of the C7 protons for the calyxin natural products in Scheme 4 showed a large coupling constant consistent with a diaxial arrangement of vicinal protons in a chair conformation. Calyxin F showed an NOE correlation between the C7 proton and a C4 proton, indicating a trans relationship between the C7 aryl substituent and the C4 carbon chain. Treatment of the calyxin G and epicalyxin G mixture with K_2CO_3 in MeOH produced calyxin F, which rules out the regioisomeric aryl THP ring structure. Similarly, treatment of calyxin M and epicalyxin M gave calyxin L. These data led to the reassignment of these calyxins to the structures shown in Scheme 4.

The Friedel−Crafts arylation of Prins intermediates is a viable approach to highly substituted tetrahydropyran rings. We have discovered a facile acid-catalyzed rearrangement of several different calyxin natural products. This project has led to syntheses and structural reassignments for calyxins F, G, L, and M and epicalyxins G and M. The structure of the most active member of the family, epicalyxin F, has yet to be determined.

Experimental Section

Benzenesulfonic Acid 4-Formylphenyl Ester. To a 0 °C solution of 4-hydroxybenzaldehyde (8.0 g, 65 mmol) in methylene chloride (120 mL) was added benzenesulfonyl chloride (8.4 mL, 65 mmol) followed by dropwise addition of triethylamine (9.2 mL, 65 mmol). At the end of the addition, the homogeneous solution was removed from the ice bath and stirred at room temperature for 2 h. The reaction was diluted with 1 M HCl (30 mL) and shaken in a separatory funnel. The organic layer was further washed with 2 × 30 mL 1 M HCl followed by 2 × 30 mL saturated aqueous $NaHCO_3$ and finally with 40 mL of brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue in 20% EtOAc/hexanes yielded the product (17 g, 98%) as a white solid: IR (neat/NaCl) 3070, 2360, 1704, 1377, 1201 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 9.98 (s, 1H), 7.87−7.83 (m, 4H), 7.71 (tt, J = 7.5, 1.2 Hz, 1H), 7.56 (dt, J = 7.6, 1.7, 2H), 7.18 (dd, J = 6.8, 1.9, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 153.8, 135.1, 134.9, 134.6, 131.3, 129.4, 128.4, 123.0; mp 82−84 °C, lit. 81−82 °C.[24]

Alcohol 14. A 250-mL round-bottom flask was charged with (*S*)-BINOL (1.78 g, 6.21 mmol, 0.1 equiv) and 62 mL of methylene chloride. To this solution was added powdered four molecular sieves (18.5 g, kept in 120 °C oven for 2 days) followed by Ti(O-*i*Pr)4 (1.86 mL, 6.21 mmol, 0.1 equiv), and the resultant dark red mixture was refluxed for 1 h and then allowed to cool to room temperature. A solution of benzenesulfonic acid 4-formylphenyl ester (16.3 g, 62.1 mmol, 1 equiv) in 12.3 mL of methylene chloride was added to the mixture and stirred for 10 min. The solution was cooled to −78 °C, and allyltributyltin (23.3 mL, 74.5 mmol, 1.2 equiv) was added as a steady stream over 5 min. The flask was sealed with an unpunctured septa and placed in a −20 °C freezer without stirring for 108 h. The reaction was quenched with 50 mL of saturated aqueous $NaHCO_3$. The mixture was diluted with 50 mL of methylene chloride, allowed to warm to room temperature, and stirred for 2 h. Following filtration through Celite, the filter cake was washed thoroughly with 3 × 30 mL methylene chloride, and the combined filtrate was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (10 to 25% EtOAc/hexanes) to yield **14** as a yellow oil (16.8 g, 89%): $[\alpha]^{24}_D$ −31.4 (*c* 1.42, $CHCl_3$); IR (neat/NaCl) 3350, 3412, 3073, 1504, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.4, 1.2, 2H), 7.71 (tt, J = 7.5, 1.2, 1H), 7.59−7.54 (m, 2H), 7.35−7.30 (m, 2H), 7.02−6.97 (m, 2H), 5.85−5.75 (m, 1H), 5.20−5.15 (m, 2H), 4.74 (dt, J = 7.9, 3.4, 1H), 2.55−2.43 (m, 2H), 2.20 (d, J = 3.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 142.9, 135.3, 134.2, 133.9, 129.1, 128.4, 127.0, 122.2, 118.9, 72.4, 43.9; HRMS (CI/NH_3) *m/z* calcd for $C_{16}H_{16}O_3S$ $[M - OH]^+$ 287.0742, found 287.0750. Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 63.17; H, 5.49; the enantiomeric excess was determined by chiral HPLC on a Chiracel OJ column with 82:18 hexanes/IPA as eluant. Retention time of the major *S*-isomer was 22.27 min, and the minor *R*-isomer had a retention time of 25.28 min.

4-Phenylsulfonylphenylpropionic Acid 15. 4-Hydroxyphenylpropionic acid (13.2 g, 79.2 mmol, 1 equiv) was dissolved in a 4:1 mixture of water and dioxane and cooled to 0 °C. KOH (8.87 g, 158 mmol, 2 equiv) was added slowly, and the homogeneous solution was stirred at 0 °C for 1 h. Benzensulfonyl chloride (10.1 mL, 79.2 mmol, 1 equiv) was then added as a steady stream, and the reaction was stirred overnight, allowing the bath to warm to room temperature. The solution was acidified to pH 1 with 1 M $NaHSO_4$, at which point the product precipitated as a white solid. The solid was collected by filtration and then dissolved in 150 mL of ether and washed with 50 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure to give **15** as a white powder (15.5 g, 64%): mp 118−119 °C; IR (neat/NaCl) 3046, 1709, 1507, 1448, 1442, 1369 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.3, 2H), 7.66 (t, J = 7.5, 1H), 7.52 (t, J = 7.9, 2H), 7.11 (d, J = 8.5, 2H), 6.90 (d, J = 8.5, 2H), 2.93 (t, J = 7.7, 2H), 2.65 (t, J = 7.7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 148.0, 139.2, 135.4, 134.2, 129.5, 129.1, 128.5, 122.4, 35.1, 29.8. Found: C, 63.07; H, 4.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}O_5S$ $[M + Na]^+$ 329.0460, found 329.0458.

Sulfonate Ester from 14 and 15. To a 0 °C solution of homoallylic alcohol **14** (18.0 g, 59.0 mmol, 1 equiv), 4-phenylsulfonylphenylpropionic acid (20.8 g, 67.8 mmol, 1.15 equiv), and DMAP (1.40 g, 11.8 mmol, 0.2 equiv) in 200 mL of methylene chloride was added DCC (14.6 g, 70.8 mmol, 1.2 equiv) in one portion, and the reaction was stirred overnight, allowing the ice bath to warm to room temperature. After 20 h, the DCU precipitate was filtered, and the filter cake was washed with methylene chloride (2 × 20 mL). The combined filtrate was concentrated and purified by flash chromatography (60% hexanes/35% dichloromethane/5% ether) to give the product as a yellow oil (33 g, 95%): $[\alpha]^{24}_D$ −11.0 (*c* 0.95, $CHCl_3$); IR (neat/NaCl) 3078, 2938, 1737, 1504, 1374, 1200, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85−7.83 (m, 4H), 7.69−7.66 (m, 2H), 7.55−7.51 (m, 4H), 7.18 (d, J = 8.6,

(24) (a) Palmieri, G.; Natile, G.; Gasparrini, F.; Giovannoli, M.; Misiti, D. *Synth. Commun.* **1988**, *18*, 69−76. For ^1H and ^{13}C data, see: (b) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224−226.

2H), 7.07 (d, $J = 8.4$, 2H), 6.95 (d, $J = 8.5$, 2H), 6.87 (d, $J = 8.4$, 2H), 5.74 (t, $J = 6.1$, 1H), 5.57 (dddd, $J = 17.3$, 14.1, 10.5, 6.9, 1H), 5.02−4.98 (m, 2H), 2.89 (t, $J = 7.6$, 2H), 2.66−2.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 149.0, 147.9, 139.4, 138.9, 135.5, 135.4, 134.3, 134.2, 132.6, 129.4, 129.2, 129.1, 128.5, 128.4, 127.8 (2), 122.3, 118.5, 74.4, 40.6, 35.6, 30.1; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{28}O_8S_2$ $[M + Na]^+$ 615.1123, found 615.1127. Anal. Calcd for $C_{31}H_{28}O_8S_2$: C, 62.82; H, 4.76.

α-Acetoxy Ether 16. A two-necked 1000-mL round-bottom flask was charged with sulfonate ester (above) (31.4 g, 53 mmol, 1 equiv), diluted with 250 mL of methylene chloride, and cooled to −78 °C. The internal temperature was monitored with a low temperature thermometer on one of the two necks. In a separate flask, DIBAL-H (1 M solution in toluene, 74.3 mL, 74.3 mmol, 1.4 equiv) was cooled to −78 °C and then cannulated into the 1 L flask slowly, keeping the internal temperature less than −72 °C. After 30 min, another 0.15 equiv of DIBAL-H was added in the same way, and the mixture was stirred for an additional 45 min at which point no more starting ester was observed by TLC. Pyridine (12.8 mL, 159 mmol, 3 equiv) was cooled to −78 °C and added via cannula. A solution of DMAP (12.9 g, 106 mmol, 2 equiv) in 100 mL of methylene chloride was then added down the side of the flask by syringe, followed by addition of acetic anhydride (15 mL, 159 mmol, 3 equiv). Throughout the additions, the internal temperature never rose above −72 °C. The solution was stirred at −78 °C for 3 h, and then the bath was removed. The solution was allowed to warm in air to −10 °C over 30 min, then placed in an ice bath for 30 min. The reaction was quenched with addition of 150 mL saturated aqueous ammonium chloride and 150 mL of saturated aqueous sodium potassium tartrate. The resultant biphasic suspension was stirred vigorously at 0 °C for 2 h until phase separation occurred. The milky white aqueous layer was extracted with 3 × 75 mL of methylene chloride, and the combined organic layers were washed with 3 × 100 mL of 1 M $NaHSO_4$, followed by 3 × 100 mL of saturated aqueous $NaHCO_3$, then 2 × 100 mL of brine. The brine and $NaHCO_3$ layers were back-extracted with 2 × 50 mL of methylene chloride. The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude α-acetoxy ether **16** (32.8 g, 97%), which was used without purification: IR (neat/NaCl) 3072, 2935, 1734, 1729, 1502, 1374 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.81 (m, 6H), 7.69−7.65 (m, 3H), 7.54−7.49 (m, 6H), 7.20−7.17 (m, 3H), 7.08 (d, $J = 8.5$, 2H), 6.97−6.94 (m, 4H), 6.89 (d, $J = 8.5$, 2H), 6.84 (d, $J = 8.1$, 1H), 5.97 (t, $J = 5.1$, 1H), 5.69−5.58 (m, 2H), 5.04−4.98 (m, 3H), 4.53−4.48 (m, 1.5H), 2.69−2.31 (m, 6.3H), 2.03−1.85 (m, 3H), 2.04 (s, 1.8H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 149.2, 148.6, 147.8, 147.7, 141.4, 140.2, 140.1, 140.0, 135.6, 135.5, 135.4, 135.4, 134.2, 134.2, 134.1, 133.7, 133.5, 129.4, 129.3, 129.13, 129.11, 129.08, 128.5, 128.43, 128.41, 128.4, 128.3, 127.6, 122.4, 122.24, 122.19, 121.9, 118.0, 117.5, 97.4, 95.5, 81.6, 79.1, 42.6, 41.9, 35.9, 35.7, 29.6, 29.3, 21.1, 20.5; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{32}O_9S_2$ $[M + Na]^+$ 659.1385, found 659.1380. Anal. Calcd for $C_{33}H_{32}O_9S_2$: C, 62.25; H, 5.07. Found: C, 62.16; H, 4.96.

Tetrahydropyran 18. To a solution of α-acetoxy ether **16** (5 g, 7.86 mmol, 1 equiv) and arene **17** (7.45 g, 15.7 mmol, 2 equiv) in 13 mL of methylene chloride was added 5 g of 3 D sieves (pellets, activated in furnace at 270 °C overnight), and the mixture was stirred for 1 h at room temperature. The solution was cannulated into a fresh flask, and the sieves were rinsed with 3 × 2 mL of methylene chloride, which was also transferred via cannula. The solution was cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (99.6 μL, 0.786 mmol, 0.1 equiv) was added dropwise. After 5 min, the bath was removed. The reaction was stirred at room temperature for 5 h and then quenched at 0 °C with 10 drops of triethylamine. Addition of 10 mL of saturated aqueous bicarbonate was followed by dilution with 20 mL of methylene chloride. The aqueous layer was extracted with 2 × 20 mL of methylene chloride, and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (55% hexanes/45% dichloromethane/5% diethyl ether) yielded the product as a white foam (4.48 g, as a 2:1 inseparable mixture of brominated and protonated compounds).

The mixture from the previous reaction was dissolved in 20 mL of THF and cooled to −94 °C. *t*-BuLi (3 mL, 5.1 mmol, 1.2 equiv) was added dropwise over 5 min, and the mixture was stirred for an additional 5 min, at which point acetic acid (0.5 mL, 8.5 mmol, 2 equiv) was added slowly and the bath was removed. After the mixture had warmed to 0 °C, it was diluted with EtOAc and washed with saturated aqueous bicarbonate and brine. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (60% hexanes/35% dichloromethane/5% ether) to give **18** (3.2 g, 42% over 2 steps) as a white foam: $[\alpha]^{24}_D$ −6.57 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 3064, 3033, 2921, 2858, 2361, 1603, 1586, 1501, 1373 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.81 (m, 4H), 7.69−7.63 (m, 2H), 7.57−7.49 (m, 4H), 7.40−7.30 (m, 15H), 7.17 (d, $J = 8.6$, 2H), 7.05 (d, $J = 8.6$, 2H), 6.88 (d, $J = 8.5$, 2H), 6.84 (d, $J = 8.5$, 2H), 6.29 (s, 2H), 5.03 (s, 4H), 4.99 (s, 2H), 4.33 (dd, $J = 11.7$, 1.2, 1H), 3.65 (dddd, $J = 13$, 13, 4, 4, 1H), 3.49−3.47 (m, 1H), 2.69−2.62 (m, 2H), 2.28 (q, $J = 11.9$, 1H), 2.19 (q, $J = 13$, 1H), 1.80−1.70 (m, 2H), 1.61−1.58 (m, 1H), 1.46−1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 158.2, 148.4, 147.5, 142.9, 141.7, 137.0, 136.8, 135.6, 135.5, 134.09, 134.07, 129.5, 129.1, 129.0, 128.63, 128.55, 128.50, 128.50, 128.1, 127.9, 127.5, 127.3, 127.1, 114.6, 94.1, 79.1, 77.3, 77.0, 76.8, 70.8, 70.2, 37.6, 37.2, 34.4, 32.1, 30.9; HRMS (ESI) *m*/*z* calcd for $C_{58}H_{52}O_{10}S_2$ $[M + Na]^+$ 995.2900, found 995.2855.

Phenol from 18. To a 0 °C solution of **18** (7.8 g, 7.4 mmol, 1 equiv) in 20 mL of dichloromethane was added 12 mL of PhSH followed by dropwise addition of $BF_3{\cdot}OEt_2$ (5.6 mL, 44.5 mmol, 6 equiv). The mixture was stirred for 45 min, and then the bath was removed. Stirring was continued for an additional 5 h. The reaction was quenched at 0 °C with the addition of 6 mL of a 1:1 mixture of methanol/triethylamine. The solution was poured into a separatory funnel and washed with 2 × 10 mL of 1 M $NaHSO_4$ and dried over sodium sulfate. Concentration followed by flash chromatography (80−70−60−50% hexanes/15−25−35−45% dichloromethane/5% ether) yielded the monophenol (3 g, 46%, plus 1.6 g of recovered starting material): $[\alpha]^{24}_D$ −7.50 (*c* 0.4, $CHCl_3$); IR (neat/NaCl) 3484, 2921, 2360, 2342, 1598, 1501, 1449, 1372 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.80 (m, 4H), 7.66−7.62 (m, 2H), 7.52−7.48 (m, 4H), 7.40−7.26 (m, 10H), 7.14 (d, $J = 8.5$, 2H), 7.03 (d, $J = 8.5$, 2H), 6.87 (d, $J = 8.7$, 2H), 6.83 (d, $J = 8.5$, 2H), 6.14 (s, 2H), 5.02 (s, 4H), 4.76 (s, 1H), 4.31 (dd, $J = 11.5$, 2.0, 1H), 3.62 (dddd, $J = 13$, 13, 3.5, 3.5, 1H), 3.48−3.44 (m, 1H), 2.70−2.59 (m, 2H), 2.27 (q, $J = 12.5$, 1H), 2.15 (q, $J = 12.5$, 1H), 1.82−1.68 (m, 2H), 1.61−1.57 (m, 1H), 1.44 (d, $J = 13$, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 155.1, 148.3, 147.5, 142.9, 141.7, 136.9, 135.5, 135.4, 134.11, 134.10, 129.5, 129.09, 129.06, 128.6, 128.50, 128.49, 127.9, 127.2, 127.1, 122.1, 122.0, 121.9, 114.0, 94.2, 79.1, 70.7, 37.6, 37.2, 34.4, 32.0, 30.9; HRMS (ESI) *m*/*z* calcd for $C_{51}H_{46}O_{10}S_2$ $[M + Na]^+$ 905.2430, found 905.2442. Anal. Calcd for $C_{51}H_{46}O_{10}S_2$: C, 69.37; H, 5.25. Found: C, 69.59; H, 5.37.

Methyl Ether from Phenol. The phenol derived from **18** (200 mg, 0.22 mmol, 1 equiv) was dissolved in 2 mL of distilled acetone, and dimethyl sulfate (44 μL, 0.44 mmol, 2 equiv) was added followed by K_2CO_3 (60 mg, 0.44 mmol, 2 equiv). The mixture was heated at reflux for 2 h. After the flask cooled to room temperature, triethylamine (100 μL) was added, and the mixture was stirred for 1 h at room temperature. The solids were removed by filtration, and the filtrate was concentrated. The residue was purified by flash chromatography (60% hexanes/35% dichloromethane/5% ether) to give the product (200 mg, 98%): $[\alpha]^{24}_D$ −7.80 (*c* 0.85, $CHCl_3$); IR (neat/NaCl) 3064, 3033, 2919, 2845, 1605, 1587, 1501, 1449, 1373 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.81 (m, 4H), 7.66−7.62 (m, 2H), 7.52−7.48 (m, 4H), 7.41−7.30 (m, 10H), 7.15

(d, J = 8.6, 2H), 7.03 (d, J = 8.5, 2H), 6.87 (d, J = 8.6, 2H), 6.83 (d, J = 8.5, 2H), 6.21 (s, 2H), 5.05 (s, 4H), 4.31 (dd, J = 11.2, 1.8, 1H), 3.73 (s, 3H), 3.63 (dddd, J = 12, 13, 4, 4, 1H), 3.48−3.42 (m, 1H), 2.70−2.58 (m, 2H), 2.28 (q, J = 12.4, 1H), 2.16 (q, J = 12.4, 1H), 1.84−1.69 (m, 2H), 1.60−1.57 (m, 1H), 1.44 (d, J = 13, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 158.3, 148.4, 147.6, 142.9, 141.7, 137.1, 135.60, 135.56, 134.08, 134.07, 129.5, 129.08, 129.06, 128.6, 128.51, 128.50, 127.91, 127.90, 127.3, 127.1, 122.0, 121.9, 114.3, 93.1, 79.2, 70.8, 55.3, 37.6, 37.2, 34.4, 32.2, 30.9; HRMS (ESI) m/z calcd for $C_{52}H_{48}O_{10}S_2$ $[M + Na]^+$ 919.2587, found 919.2559; Anal. Calcd for $C_{52}H_{48}O_{10}S_2$: C, 69.62; H, 5.39. Found: C, 69.64; H, 5.20.

Diphenol 19. A solution of methyl ether (490 mg, 0.55 mmol, 1 equiv) in THF was added to a slurry of Raney nickel (washed with water, then ethanol, then THF) in THF. The mixture was sonicated for 1 h and then filtered through Celite. The filtrate was concentrated, then dissolved in 3 mL of THF, 10% Pd/C (40 mg) was added, and the flask was placed in a Parr apparatus and filled to 60 psi with hydrogen. After being stirred for 12 h at room temperature, the solution was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (40% hexanes/55% dichloromethane/5% ether) to give **19** (320 mg, 82%): $[\alpha]^{24}_D$ −5.36 (c 1.1, $CHCl_3$); IR (neat/NaCl) 3479, 2922, 2845, 1622, 1602, 1527, 1467, 1449; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83−7.80 (m, 4H), 7.66−7.62 (m, 2H), 7.52−7.48 (m, 4H), 7.30 (d, J = 8.6, 2H), 7.06 (d, J = 8.5, 2H), 6.91 (d, J = 8.7, 2H), 6.84 (d, J = 8.6, 2H), 5.90 (s, 2H), 5.05 (s, 2H), 4.41 (dd, J = 11.2, 1.2, 1H), 3.66 (s, 3H), 3.55−3.50 (m, 1H), 3.42 (dddd, J = 12, 12, 4, 4, 1H), 2.80−2.64 (m, 2H), 2.27 (q, J = 12.3, 1H), 2.17 (q, J = 12.4, 1H), 1.92−1.89 (m, 1H), 1.78−1.76 (m, 2H), 1.55−1.52 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 155.6, 148.4, 147.5, 142.3, 141.6, 135.4, 134.2, 129.6, 129.5, 129.13, 129.11, 128.5, 127.2, 127.1, 122.1, 122.0, 121.99, 110.1, 94.9, 79.0, 77.6, 55.2, 37.5, 36.6, 34.6, 32.2, 31.1; HRMS (ESI) m/z calcd for $C_{38}H_{36}O_{10}S_2$ $[M + Na]^+$ 739.1647, found 739.1647.

Bis SEM Ether from 19. To a solution of KH (washed with hexanes, 12 mg, 0.28 mmol, 2 equiv) in 1 mL of THF was added catalytic 18-crown-6 (spatula tip) then cooled to 0 °C. Diphenol **19** (100 mg, 0.14 mmol, 1 equiv) dissolved in 1.2 mL of THF was added dropwise to the KH solution. The purplish mixture was stirred for 5 min, then SEM-Cl (48 μL, 0.28 mmol, 2 equiv) was added dropwise, and the bath was removed. After 2 h, the reaction was cooled in an ice bath, and saturated aqueous ammonium chloride (2 mL) was added slowly followed by brine (2 mL). The aqueous layer was extracted with 5 × 5 mL of EtOAc, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography (15−25% EtOAc/hexanes) to give the bis SEM ether (88 mg, 65%): $[\alpha]^{24}_D$ −4.89 (c 0.45, $CHCl_3$); IR (neat/NaCl) 2953, 2921, 1608, 1590, 1376, 1200, 1152; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.84 (m, 4H), 7.69−7.66 (m, 2H), 7.55−7.52 (m, 4H), 7.32 (d, J = 8.6, 2H), 7.09 (d, J = 8.4, 2H), 6.94 (d, J = 8.5, 2H), 6.88 (d, J = 8.3, 2H), 6.41 (s, 2H), 5.19 (s, 4H), 4.42 (dd, J = 11, 1.2, 1H), 3.80 (s, 3H), 3.73 (t, J = 8.1, 4H), 3.61−3.50 (m, 2H), 2.80−2.70 (m, 2H), 2.22 (q, J = 12.3, 1H), 2.11 (q, J = 10, 1H), 1.95−1.88 (m, 1H), 1.79−1.72 (m, 2H), 1.52 (d, J = 13, 1H), 0.95 (t, J = 8.3, 4H), −0.02 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 156.9, 148.4, 147.6, 142.4, 141.5, 135.6, 135.5, 134.1, 131.5, 129.6, 129.11, 129.08, 128.5, 127.0, 122.1, 122.0, 118.2, 114.3, 94.9, 93.0, 78.8, 77.5, 66.3, 55.3, 37.8, 36.7, 35.1, 32.4, 31.2, 18.0, −1.41; HRMS (ESI) m/z calcd for $C_{50}H_{64}O_{12}S_2Si_2$ $[M + Na]^+$ 999.3276, found 999.3289; Anal. Calcd for $C_{50}H_{64}O_{12}S_2Si_2$: C, 61.45; H, 6.60. Found: C, 61.61; H, 6.48.

Bromination of SEM Protected 19. The bis SEM ether (95 mg, 0.097 mmol, 1 equiv) was dissolved in 2 mL of THF and cooled to 0 °C. NBS (17 mg, 0.097 mmol, 1 equiv) dissolved in 1 mL of THF was added dropwise. The reaction was stirred for 30 min at 0 °C and then quenched with addition of 100 mg of $NaHCO_3$. Stirring was continued for 30 min more at room temperature. The solution was filtered, and the solids were washed with ether. The mother liquor was concentrated and loaded directly onto a silica column and chromatographed in 15−25% EtOAc/hexanes to give the product (62 mg, 60%): $[\alpha]^{24}_D$ +0.46 (c 1.4, $CHCl_3$); IR (neat/NaCl) 3066, 2952, 2360, 1591, 1502, 1449, 1376, 1249, 1200, 1152; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.82 (m, 4H), 7.68−7.65 (m, 2H), 7.54−7.51 (m, 4H), 7.30 (d, J = 8.7, 2H), 7.07 (d, J = 8.5, 2H), 6.94 (d, J = 8.6, 2H), 6.87 (d, J = 8.5, 2H), 6.65 (s, 1H), 5.22 (s, 2H), 5.09 (s, 2H), 4.40 (dd, J = 10, 1.2, 1H), 3.95−3.90 (m, 2H), 3.85 (s, 3H), 3.72−3.68 (m, 2H), 3.60−3.55 (m, 2H), 2.81−2.67 (m, 2H), 2.22 (q, J = 12, 3, 1H), 2.12 (q, J = 11.6, 1H), 1.96−1.88 (m, 1H), 1.82−1.72 (m, 2H), 1.58−1.56 (m, 1H), 1.01−0.91 (m, 4H), 0.026 (s, 9H), −0.049 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 155.5, 153.8, 148.5, 147.6, 142.1, 141.4, 135.53, 135.49, 134.15, 134.12, 129.5, 129.13, 129.08, 128.5 (2), 126.9, 122.1, 122.0, 120.6, 99.5, 98.7, 96.3, 92.7, 78.8, 77.8, 68.0, 66.5, 56.4, 37.9, 36.7, 35.0, 34.3, 31.3, 18.3, 18.0, −1.36, −1.43; LRMS (ESI) m/z calcd for $C_{50}H_{63}BrO_{12}S_2Si_2$ $[M + Na]^+$ 1079.24, found 1079.19; Anal. Calcd for $C_{50}H_{63}BrO_{12}S_2Si_2$: C, 56.86; H, 6.01. Found: C, 56.66; H, 5.98.

Enone 21. To a solution of bromide (200 mg, 0.19 mmol, 1 equiv) in 3 mL of THF at −78 °C was added PhLi (0.86 M, 664 μL, 0.57 mmol, 3 equiv) quickly, and the mixture was stirred for 5 min. Aldehyde **20** (156 mg, 0.57 mmol, 3 equiv) in 669 μL of THF was then added quickly, and the mixture was stirred for 2 h at −78 °C. The reaction was quenched with 5 mL of pH 7 buffer, and the bath was removed. Once the mixture warmed to room temperature, the aqueous layer was extracted with ethyl acetate (5 × 5 mL), and the combined organic layers were dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated in vacuo to give the crude diastereomeric alcohols.

The crude alcohol was dissolved in 4 mL of dioxane and added to a stirred suspension of $NaHCO_3$ (200 mg) and DDQ (129 mg, 0.57 mmol, 3 equiv) in 1 mL of dioxane. The yellow suspension immediately turned dark green upon addition of the alcohol. The mixture was stirred at room temperature for 30 min. The mixture was filtered and concentrated, and the residue was filtered through a plug of neutral alumina eluting with dichloromethane. The filtrate was concentrated and chromatographed in 20−50% EtOAc/hexanes over silica to give 140 mg of enone **21** (58% from bromide): $[\alpha]^{24}_D$ +650.6 (c 0.8, $CHCl_3$); IR (neat/NaCl) 2952, 2927, 1597, 1502, 1449, 1376, 1199; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−7.83 (m, 6H), 7.70−7.65 (m, 3H), 7.55−7.51 (m, 6H), 7.44 (d, J = 8.5, 2H), 7.34 (d, J = 16, 1H), 7.31 (d, J = 8.5, 2H), 7.08 (d, J = 8.5, 2H), 7.00 (d, J = 8.5, 2H), 6.95−6.93 (m, 2.5 H), 6.89−6.86 (m, 2.5H), 6.62 (s, 1H), 5.26 (s, 2H), 4.91 (s, 2H), 4.40 (dd, J = 12.2, 2.1, 1H), 3.75 (s, 3H), 3.72−3.68 (m, 4H), 3.54−3.52 (m, 2H), 2.83−2.65 (m, 2H), 2.22 (q, J = 12, 1H), 2.14 (q, J = 12, 1H), 1.94−1.92 (m, 1H), 1.82−1.76 (m, 2H), 1.58−1.56 (m, 1H), 0.94 (t, J = 8.5, 2H), 0.88 (t, J = 8.5, 2H), −0.04 (s, 9H), −0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 159.0, 156.6, 154.1, 150.7, 148.5, 147.6, 142.1, 142.0, 141.4, 135.6, 135.5, 135.2, 134.4, 134.2, 134.1, 133.8, 129.6, 129.5, 129.4, 129.2, 129.1, 129.09, 128.48 (2), 128.47 (2), 122.9, 122.1, 122.06, 119.1, 117.8, 99.9, 95.3, 92.5, 78.8, 77.7, 67.8, 66.7, 55.9, 37.9, 36.8, 35.0, 33.5, 31.3, 18.2, 18.0, −1.41, −1.43; LRMS (ESI) calcd for $C_{65}H_{74}O_{16}S_3Si_2$ $[M + Na]^+$ 1285.36, found 1285.31.

Bisphenol from 21. Enone **21** (245 mg, 0.194 mmol) was dissolved in 6 mL of THF and cooled to 0 °C. HF·pyridine (6 mL) was added dropwise, and the bath was removed. The reaction was stirred at room temperature for 4 h. The reaction was cooled with an ice bath and diluted with 10 mL of ether and washed with 1 M $NaHSO_4$ (3 × 3 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-TLC to give 174 mg of bisphenol (89%): $[\alpha]^{24}_D$ +18.0 (c 0.25, $CHCl_3$); IR (neat/NaCl) 3436, 2923, 1613, 1502, 1373, 1199, 1150; ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.57 (s, 1H), 7.86−7.82 (m, 6H),

7.76 (d, $J = 16$, 1H); 7.70−7.63 (m, 4H), 7.55−7.48 (m, 8H), 7.33 (d, $J = 8.5$, 2H), 7.08 (d, $J = 8.5$, 2H), 7.01 (d, $J = 8.5$, 2H), 6.92 (d, $J = 8.5$, 2H), 6.86 (d, $J = 8.5$, 2H), 6.38 (s, 1H), 5.79 (s, 1H), 4.45 (dd, $J = 11.2$, 1.1, 1H), 3.82 (s, 3H), 3.60−3.52 (m, 2H), 2.83−2.66 (m, 2H), 2.30 (q, $J = 12.4$, 1H), 2.18 (q, $J = 12.3$, 1H), 1.96−1.88 (m, 1H), 1.82−1.74 (m, 2H), 1.56−1.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 165.9, 161.4, 161.0, 155.2, 150.4, 148.5, 147.5, 142.2, 141.5, 140.2, 135.3, 135.2, 134.6, 134.5, 134.2, 130.4, 129.6, 129.5, 129.3, 129.2, 129.1, 128.7, 128.5 (2), 127.2 (2), 122.8, 122.1, 122.0, 110.5, 106.1, 91.3, 78.9, 77.6, 55.8, 37.5, 35.9, 34.0, 31.6, 31.1; LRMS (ESI) *m*/*z* calcd for $C_{53}H_{46}O_{14}S_3$ $[M + H]^+$ 1003.21, found 1003.18.

Calyxin L. The bisphenol derived from **21** (59 mg, 0.059 mmol, 1 equiv) was dissolved in 2.4 mL of a 1:1 mixture of methanol and THF (degassed by sparging with Ar for 30 min) and ignited K_2CO_3 (81 mg, 0.59 mmol, 10 equiv) was added. The mixture was heated at 50 °C for 15 h, then another 5 equiv of K_2CO_3 was added, and heating continued for 2 h. The orange-colored solution was then cooled to room temperature and diluted with 10 mL of ether and washed with 5 mL of saturated aqueous ammonium chloride. Mixing was continued until the color of the solution changed from orange to yellow. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by prep-TLC (10% 9:1 MeOH/AcOH, 90% dichloromethane) yielded the title compound as a yellow film (12 mg, 35%) plus a mixture of mono- and bis-sulfonates (8 mg). Total combined yield after one recycling was 58%: $[\alpha]^{24}_D$ −6 (*c* 0.08, MeOH); IR (neat/NaCl) 3436, 2920, 1603, 1508, 1399, 1227; ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 (d, $J = 15.5$, 1H), 7.67 (d, $J = 15.5$, 1H), 7.49 (d, $J = 8.6$, 2H), 7.24 (d, $J = 8.6$, 2H), 7.01 (d, $J = 8.4$, 2H), 6.82 (d, $J = 8.6$, 2H), 6.76 (d, $J = 8.6$, 2H), 6.68 (d, $J = 8.4$, 2H), 6.02 (s, 1H), 4.35 (dd, $J = 11.1$, 1.2, 1H), 3.89 (s, 3H), 3.60−3.55 (m, 2H), 2.71−2.58 (m, 2H), 2.46 (q, $J = 12.3$, 1H), 2.23 (q, $J = 12.3$, 1H), 1.90−1.83 (m, 1H), 1.76−1.72 (m, 1H), 1.62 (d, $J = 13$, 1H), 1.50 (d, $J = 13$, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 194.2, 166.8, 164.4, 162.5, 161.1, 157.7, 156.2, 143.4, 135.6, 134.6, 131.3, 130.4, 128.7, 128.4, 125.9, 116.9, 116.1, 115.9, 111.9, 106.6, 92.1, 81.7, 79.5, 56.2, 39.7, 37.3, 35.6, 33.3, 32.0; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{34}O_8$ $[M + Na]^+$ 605.2151, found 605.2137.

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Supporting Information Available: Experimental procedures and NMR spectra of the new compounds, including detailed comparisons between the synthetic and isolated natural products described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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