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Diastereoselective tandem reactions of substituted 3-sulfolenes with bis-vinyl ketones leading to highly functionalized bicyclic and tricyclic frameworks†

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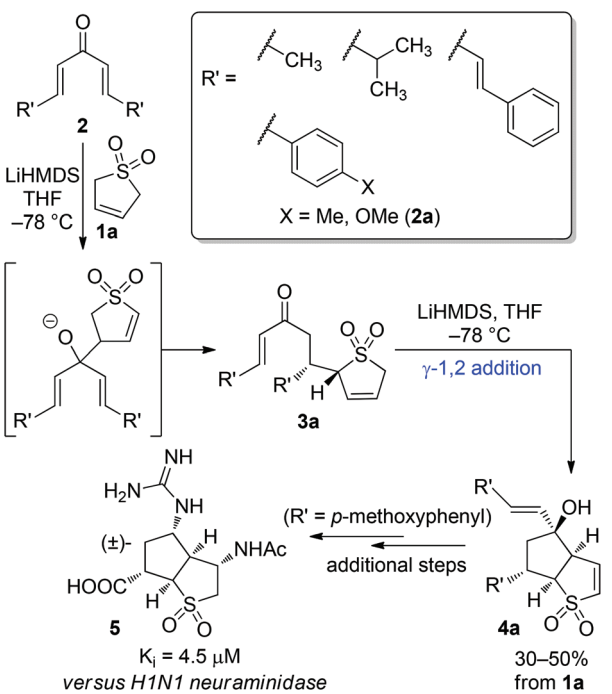
The base-promoted reaction of 3-sulfolene with bis-vinyl ketones was shown in earlier work to proceed through a γ-1,2 addition/anionic oxy-Cope cascade; a subsequent treatment with base induced a second γ-1,2 addition to provide a [3.3.0] bicyclic framework that our group then exploited in the design of rigidified enzyme inhibitors for influenza neuraminidase. Out of a desire to expand the range of structural archetypes accessible through these couplings (and hopefully access additional conformationally-constrained inhibitor platforms) we have revisited this methodology, this time using substituted starting reagents. We show that judicious choice of the newly added substituent can control the exclusive formation of one of four new structural types, each formed as a single diastereomer. These include bicyclo[3.2.1] sulfones and spiro[5.4] sulfones, as well as an expanded collection of our original bicyclo[3.3.0] sulfone scaffolds, this time incorporating adjacent quaternary centres or additional rings.

Introduction

The use of functionalized cyclic sulfones for enzyme inhibitor design, and the development of synthetic methodology for the generation of sulfone-containing cyclic scaffolds have received considerable attention.[1–7] For example, a previous report from our laboratory demonstrated that reactions of bis-vinyl ketones (**2**) with the unsubstituted 3-sulfolene **1a** in the presence of LiHMDS afforded exclusive formation of a [3.3.0]bicyclooctane framework (Scheme 1).[8] The reaction was shown to occur by a tandem γ-1,2 addition of the 3-sulfolene anion to the ketone function of **2**, followed by a diastereoselective anionic oxy-Cope. Treatment with a second equivalent of LiHMDS resulted in a second γ-1,2 addition providing the fused [3.3.0]bicycles as single diastereomers (Scheme 1).[8] In a separate communication, we reported the preparation, on decagram scale, of **4a**



Scheme 1 Rapid access to an orthogonally functionalized [3.3.0]bicyclic scaffold.

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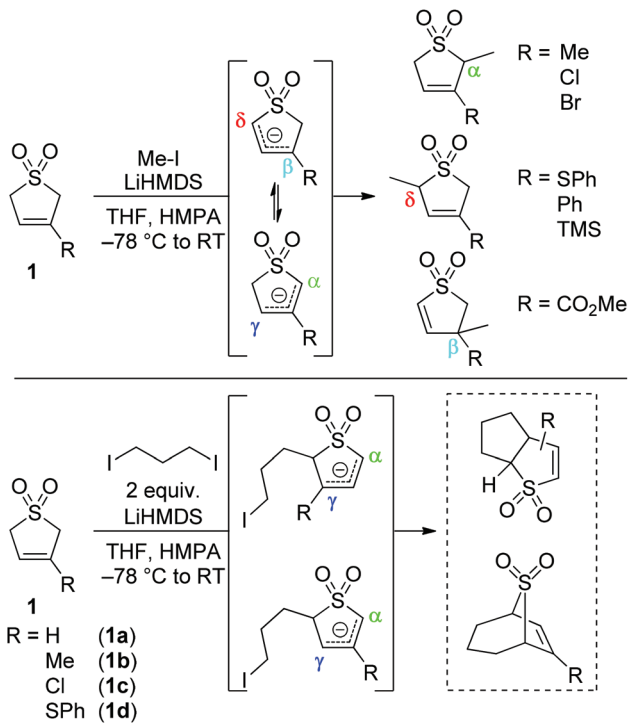
†Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds, as well as expanded X-ray data for crystal structures. CCDC 1025137, 1025139, 1025138, 1025140 and 1025141. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00387c

(R′ = *p*-methoxyphenyl) and its elaboration to a small family of conformationally-restricted inhibitors of viral neuraminidase (Scheme 1).[9] Herein we report an expansion of our methodology, making use of 3-substituted 3-sulfolenes and bis-vinyl ketones, facilitating the diastereoselective construction of additional highly functionalized rigid bicyclic sulfone systems.

The reactivity profile of various 3-substituted-3-sulfolene anions with the electrophile methyl iodide has been shown to be dependent on the nature of the substituent (Scheme 2).[10] Anion destabilizing substituents (*e.g.* alkyl and halogens) cause formation of the α-substituted products while electron withdrawing substituents (**1f**) promote alkylation at the β-position.[10] 3-Substituted-3-sulfolenes possessing functionality that imposes a significant steric barrier in the α-position or that can stabilize an anion through resonance delocalization (*e.g.* trimethylsilyl, thiophenyl and phenyl) react to form δ-alkylated products.[10] The reaction of 3-sulfolenes (**1a–d**) with disubstituted alkyl halides has also been reported. 1,3-Diiodopropane, 1,2-bis(bromomethyl)benzene and 1,2-bis(iodomethyl)ethene have been reported to react with **1a–d** to afford fused [3.3.0]-bicycles and/or bridged [3.2.1]bicycles (Scheme 2).[11,12] [5.4]-spirocycles were obtained from the reaction of **1d** and 1,4-diiodobutane or 1,5-diiodopentane.[13]

We speculated that the reaction between 3-substituted 3-sulfolenes (**1b–g**) with bis-vinyl ketones could produce analogous reactivity to that seen for the dialkylative couplings using disubstituted alkyl halides (Scheme 2) to afford additional highly functionalized archetypes in a diastereoselective fashion.



Scheme 2 Regiochemical outcome of monoalkylation and dialkylative cyclization of 3-substituted-3-sulfolenes.

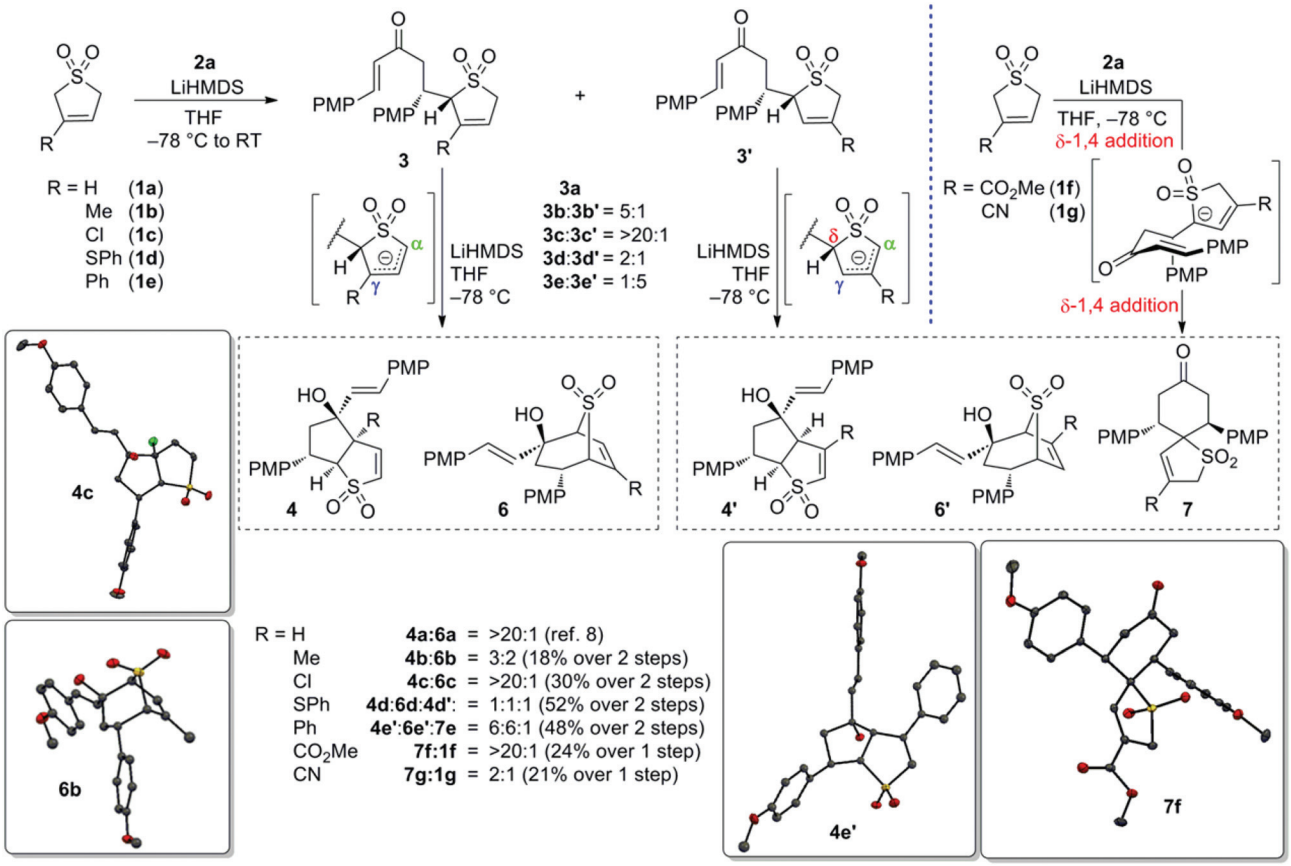
Results and discussion

We began our study by exploring the reactivity of 3-substituted 3-sulfolenes **1b–e** with model ketone **2a** (where R′ = *p*-methoxyphenyl, PMP) using the previously optimized conditions used for the synthesis of **4a** (Scheme 3). We first attempted the tandem-1,2 addition/anionic oxy-Cope reaction using the commercially available 3-methyl-3-sulfolene (**1b**) and the simple 3-chloro-3-sulfolene (**1c**). Sulfone **1b** provided a 5 : 1 mixture of regioisomers **3b** and **3b′**. Cyclization of the crude mixture of **3b** and **3b′** provided two identifiable products in a 3 : 2 ratio: γ-1,2 addition product **4b**, as well as the direct α-1,2 addition product **6b** possessing a [3.2.1]bicyclic framework. The relative stereochemistry of the latter product was confirmed through single crystal X-ray diffraction (Scheme 3).[14] In comparison, 3-chloro-3-sulfolene (**1c**) reacted smoothly with ketone **2a** to provide a single regioisomer of **3c** (by ^{1}H NMR). Cyclization with LiHMDS produced the γ-1,2 addition product **4c** with a chlorine atom at the quaternary bridgehead carbon. Single crystal X-ray diffraction studies were used to confirm the relative stereochemistry of **4c**.[14,15]

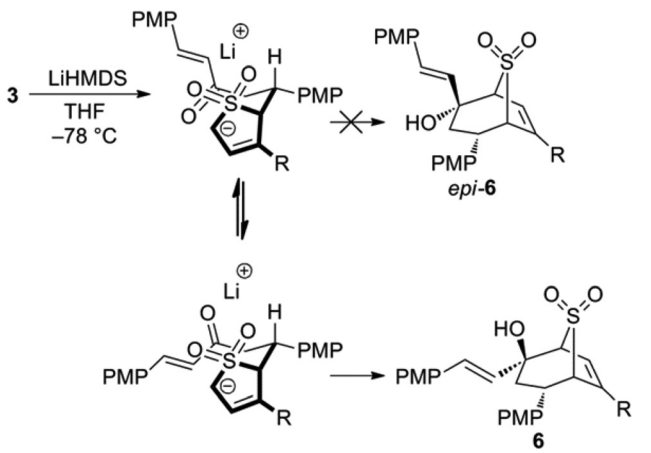
Upon reaction of 3-thiophenyl-3-sulfolene (**1d**)[16] with bis-vinyl ketone **2a**, both regioisomers **3d** (formed through a γ-1,2 addition followed by an anionic oxy-Cope) and **3d′** (formed from a β-1,2 addition followed by an anionic oxy-Cope) were formed in a 2 : 1 ratio. The formation of **3d′** can be rationalized on the basis of the sterically large, anion-stabilizing thiophenyl group of **1d** directing deprotonation at the δ-position, facilitating the nucleophilic 1,2-addition from the hindered β-position. Upon subjection of the crude mixture to LiHMDS, the major regioisomer **3d** cyclized to produce a 1 : 1 mixture of γ-1,2 addition product **4d** and α-1,2 addition product **6d**. The increase in the ratio of α-1,2 addition to γ-1,2 addition products (when compared with **3b**) was expected, due to the larger steric size of the γ-thiophenyl in **3d** *versus* γ-methyl substituent in **3b**. Regioisomer **3d′** cyclized to form **4d′**, with no α-1,2 addition product **6d′** observed. This suggests that γ-1,2 addition is the preferred reaction trajectory for **3a–d** and **3d′**, and that α-1,2 addition is only observed for these substrates because of a significant steric barrier which disfavours attack from the γ-position.

To rationalize the high level of diastereoselectivity in the formation of bridged [3.2.1]bicycle **6** (and **6′**), we propose that the reaction trajectory of the α-1,2 addition may involve a six-membered, chair-shaped transition state (Scheme 4). In the likely chair conformation leading to **6**, the α-anion approaches the 1,2 carbonyl function from the axial position, with the much larger vinyl-PMP group in the equatorial position. The transition state leading to **6** (and **6′**) may also be favoured due to chelation of the lithium counter-ion by both the carbonyl and sulfone functions. In the proposed pathway leading to *epi*-**6** the vinyl-PMP group would experience significant 1,3-diaxial repulsion.

Reaction of 3-phenyl-3-sulfolene (**1e**)[17] with **2a** resulted in a 1 : 5 mixture of **3e** and **3e′** regioisomers. The formation of the **3e′** isomer is now preferred since the 3-phenyl group is able to



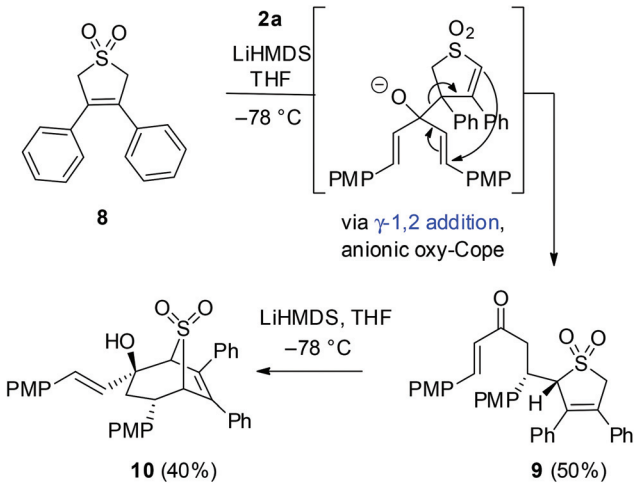
Scheme 3 Dialkylative coupling of 3-substituted-3-sulfolenes **1b–g** (and **1a**) with bis-vinyl ketone **2a**.



Scheme 4 Proposed origin of diastereoselectivity in the conversion of **3** to **6**.

directly stabilize the anion at the δ-position of **1e** through resonance. Upon cyclization, an equimolar mixture of **4e′** and **6e′** was isolated, along with a relatively minor third product determined to be [5.4]spirocycle **7e**. The formation of **4e′** is consistent with the cyclization of **3d′** to produce **4d′**, however the formation of **6e′** may be the result of the 3-phenyl group imposing a significant steric effect on the γ-position. The 3-phenyl group also facilitated the formation of **7e** *via* stabilization of the δ-anion of **3e′** by resonance. The product distribution varied slightly upon additional replicates, giving between a 6 : 6 : 1 and 6 : 9 : 2 distribution of **4e′** : **6e′** : **7e**, upon slow or fast addition of the base respectively. Attempts to improve the product ratios by using different bases (*n*-BuLi, LDA, NaHMDS), or by varying the temperature or stirring time were unsuccessful.

Substituted 3-sulfolenes with electron withdrawing substituents in the 3-position (**1f** and **1g**)[18] were found to react smoothly with **2a** to produce exclusively the [5.4]spirocycles **7f** and **7g** upon a single treatment with one equivalent of LiHMDS (Scheme 3). The high level of selectivity for the [5.4]-spirocycle **7** can be attributed to the fact that the anion of **3f′–g′** is highly stabilized in the δ-position by resonance with the electron-withdrawing ester or nitrile functions. This leads to a softening of the anion, and selective attack onto the 4-position of the vinyl carbonyl function. When the reaction mixtures were quenched at −78 °C or −41 °C, no β-1,2 addition product, anionic oxy-Cope product **3f′–g′** or **7f–g** was isolated. The formation of **7f** and **7g** likely occurs through two consecutive δ-1,4 additions upon warming the reaction mixtures to room temperature (Scheme 3). The relative stereochemistry of the spirocycles was determined using ^{1}H and NOESY NMR



Scheme 5 Exclusive access to the [3.2.1] structural archetype.

experiments (indicating that the two PMP groups are *trans* with respect to one another) and later confirmed using single crystal X-ray diffraction.[14]

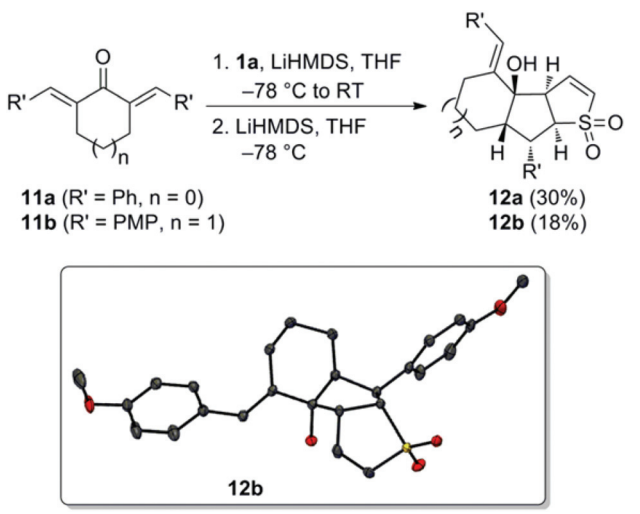
In order to obtain the [3.2.1]bicyclic ring system exclusively we turned our attention to the 3,4-disubstituted-3-sulfolene **8** (Scheme 5). In the case of the anion of 3,4-diphenyl-3-sulfolene (**8**)[19] negative charge density at the γ-positions should be reduced due to the electron donating phenyl groups: thereby disfavouring γ-1,2-addition. In the event, reaction of **8** with **2a** led to the formation of 3-sulfolene **9**. The purified 3-sulfolene **9** was cyclized with LiHMDS to provide exclusively the desired [3.2.1]bicycle **10**.

To further expand the structural diversity available through this methodology, we wondered whether cyclic bis-vinyl ketones **11a** and **11b** would be competent electrophilic partners (Scheme 6). Gratifyingly, when we reacted these compounds with **1a** under our usual conditions, the tricyclic products **12a** and **12b** were obtained in 30% and 18% yield respectively over two steps. Each product, containing five contiguous stereocenters, was obtained as a single diastereomer (Scheme 6). The low yield of **12b** can be partially attributed to the lack of solubility of **11b** in THF at −78 °C. The additional fused ring of **12a** and **12b** was determined to possess a *cis* geometry about the bicyclic core by ^{1}H NMR and single crystal X-ray diffraction experiments (for **12b**).[14]

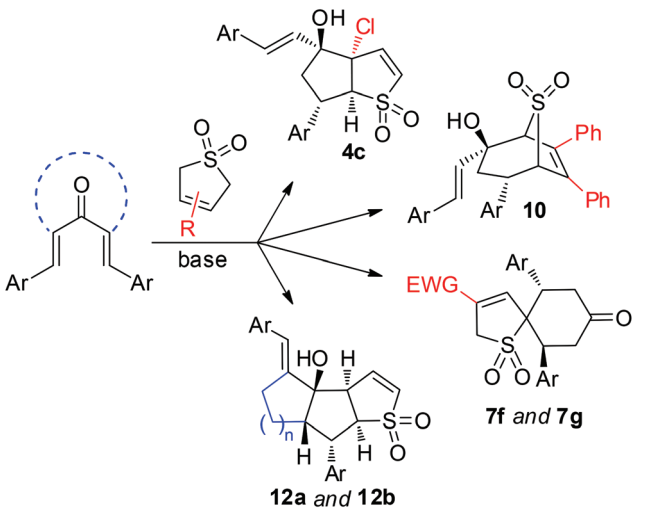
Conclusion

We have shown that by varying the sterics and electronics of the starting 3-sulfolene, three unique ring systems are easily accessible upon reaction with bis-vinyl ketones in a diastereoselective fashion. Despite the modest yields over one or two steps, the final bicyclic and tricyclic structures are formed as single diastereomers, from simple, inexpensive and easily accessible achiral starting materials with each archetype possessing up to five contiguous stereocenters. While in a few cases mixtures are obtained, as illustrated in Scheme 7 we are also able to tune the substrates to afford single isomers of each archetypal ring system (*i.e.* [3.3.0]bicycle **4c**, [3.2.1]bicycle **10** and [5.4]spirocycles **7f** and **7g**).

We have previously shown the elaboration of our simplest fused bicycle, **4a**, into a viable scaffold for the generation of conformationally rigidified inhibitors of important enzyme targets. We anticipate that some of the highly functionalized, rigid systems presented in this report may also have useful structural characteristics for employment as scaffolds in medicinal chemistry or other applications.



Scheme 6 Reaction of cyclic bis-vinyl ketones with **1a** (yield over two steps).



Scheme 7 Summary of selective transformations available by modification of the two coupling partners. In each illustrated example, only a single product is formed, as a single regio- and diastereomer.

Experimental

General experimental procedures

All reactions were performed in single-neck, flame-dried, round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Liquid reagents were transferred *via* glass syringe. Solvents were transferred *via* syringe with a stainless steel needle. Organic solutions were concentrated at 35 °C by rotary evaporation under vacuum. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with silica gel (0.20 mm, 60 Å pore-size, 230–400 mesh, Macherey-Nagel) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Flash-column chromatography was carried out over silica gel (60 Å, 63–200 μM, Caledon).

Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran was dried by distillation over sodium and benzophenone. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane, and are referenced to residual protium in the NMR solvent $CDCl_3$, δ 7.26; Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 75 MHz at 23 °C. Carbon chemical shifts are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent $CDCl_3$, δ 77.16. Infrared (IR) spectra were obtained using a Perkin Elmer 1000 FT-IR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}). Mass spectra were obtained at the University of Victoria Mass Spectrometry Facility and UVic Genome BC Proteomics Centre.

General procedure for γ/β-1,2 addition/anionic oxy-Cope and subsequent γ- and/or α-1,2 addition. The 3-sulfolene (**1a–e** or **8**) (1 eq.) and ketone **2a** (or **11a–b**) (1 eq.) were dissolved in tetrahydrofuran (10 mL per 1 mmol), and the solution was cooled to −78 °C. LiHMDS (1 M in THF, 1.1 eq.) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C, then removed from the cooling bath and stirred 1 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), and the resulting solution was extracted twice with ethyl acetate. The organic fraction was dried with Na_2SO_4 then concentrated *in vacuo* at 30 °C to provide the anionic oxy-Cope sulfone product as a light orange foam. The crude product was typically carried to the next step with no further purification. 3-Sulfolenes **3c** and **9** were obtained by purification by flash column chromatography using 100 : 0–25 : 1 dichloromethane–ethyl acetate gradient. The crude 3-sulfolene (or purified **9**) (1 eq.) was dissolved in tetrahydrofuran (20 mL per 1 mmol), and the solution was cooled to −78 °C. LiHMDS (1 M in THF, 1.1 eq.) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), and the resulting solution was warmed to room temperature then extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, concentrated *in vacuo*, and purified by flash column chromatography using 100 : 0–25 : 1 dichloromethane–ethyl acetate gradient. (Note: on scales larger than 500 mg the THF was removed prior to liquid–liquid extraction).

General procedure for intermolecular δ-1,4-addition followed by intramolecular δ-1,4-addition. 3-Sulfolene (**1f–g**) (1 eq.) and ketone **2a** (1 eq.) were dissolved in tetrahydrofuran (10 mL per 1 mmol), and the solution was cooled to −78 °C. LiHMDS (1 M in THF, 1.1 eq.) was added dropwise. The reaction mixture was stirred for 0.5 h at −78 °C, then removed from the cooling bath and stirred 0.5 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), then extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, concentrated *in vacuo*, and purified by flash column chromatography using 100 : 0–10 : 1 dichloromethane–ethyl acetate gradient to provide **7f** and **7g**.

Compound **3c**: white solid (251 mg, 44% yield); R_f = 0.5 (dichloromethane–ethyl acetate, 50 : 1); IR (film) 1683, 1319, 1131, 835 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.60 (d, J = 16.2 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 6.81 (d, J = 8.8 Hz, 2 H), 6.66 (d, J = 16.1 Hz, 1 H), 5.88 (ddd, 4.4, 2.0, 0.8 Hz, 1 H), 4.15–4.06 (m, 1 H), 4.04–4.00 (m, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.69 (dd, J = 17.7, 8.0 Hz, 1 H), 3.48 (dd, J = 17.6, 6.6 Hz, 1 H), 3.45 (dd, J = 16.0, 4.4 Hz, 1 H), 2.85 (dt, J = 16.0, 1.8 Hz, 1 H); ^{13}C NMR (75 MHz) δ 197.3 (C), 162.0 (C), 159.2 (C), 143.4 (CH), 131.5 (C), 130.9 (CH), 130.4 (CH), 128.6 (C), 127.1 (C), 124.0 (CH), 121.7 (CH), 114.6 (CH), 113.5 (CH), 71.9 (CH), 56.4 (CH_2), 55.5 (CH_3), 55.3 (CH_3), 40.9 (CH_2), 39.1 (CH); HRMS (ESI) calcd for $C_{23}H_{23}{}^{35}ClO_5S$ (M + Na): 469.0847. Found: 469.0846.

Compound **4b**: white solid (160 mg, 13% yield); R_f = 0.1 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 3479, 1283, 1122, 830 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.36 (d, J = 8.8 Hz, 2 H), 7.28 (d, J = 8.8 Hz, 2 H), 6.98–6.87 (m, 4 H), 6.71 (d, J = 16.0 Hz, 1 H), 6.53 (d, J = 6.7 Hz, 1 H), 6.49 (d, J = 6.6 Hz, 1 H), 6.22 (d, J = 16.0 Hz, 1 H), 4.20 (ddd, J = 12.8, 8.2, 6.7 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.34 (d, J = 8.2 Hz, 1 H), 2.61 (t, J = 12.8 Hz, 1 H), 2.39 (dd, J = 12.9, 6.7 Hz, 1 H); ^{13}C NMR (75 MHz) δ 159.8 (C), 158.7 (C), 142.3 (CH), 133.2 (C), 130.8 (CH), 130.5 (CH), 128.8 (C), 128.4 (CH), 128.0 (CH), 126.9 (CH), 114.4 (CH), 114.3 (CH), 82.5 (C), 75.8 (CH), 62.6 (C), 55.4 (CH_3), 55.4 (CH_3), 47.8 (CH_2), 41.7 (CH), 25.7 (CH_3); HRMS (ESI) calcd for $C_{24}H_{26}O_5S$ (M + Na): 449.1393. Found: 449.1390.

Compound **4c**: light yellow solid (95 mg, 30% yield); R_f = 0.2 (dichloromethane–ethyl acetate, 50 : 1); IR (film) 3465, 1290, 1135, 831, 733 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.37 (d, J = 8.7 Hz, 2 H), 7.30 (d, J = 8.7 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 6.72 (d, J = 15.2 Hz, 1 H), 6.69 (d, J = 6.6 Hz, 1 H), 6.58 (d, J = 6.7 Hz, 1 H), 6.44 (d, J = 15.9 Hz, 1 H), 4.18 (dt, J = 12.4, 6.7 Hz, 1 H), 4.02 (d, J = 7.4 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.89 (dd, J = 13.1, 12.6 Hz, 1 H), 2.47 (dd, J = 13.2, 6.7 Hz, 1 H); ^{13}C NMR (75 MHz) δ 160.0 (C), 159.1 (C), 137.0 (CH), 133.7 (CH), 132.3 (C), 132.3 (C), 131.5 (CH), 128.6

(CH), 128.2 (CH), 125.5 (CH), 114.7 (CH), 114.4 (CH), 84.1 (C), 82.1 (C), 78.2 (CH), 55.5 (CH_3), 55.5 (CH_3), 48.4 (CH_2), 41.7 (CH); HRMS (ESI) calcd for $C_{23}H_{23}{}^{35}ClO_5S$ (M + Na): 469.0847. Found: 469.0849.

Compound **4d**: light yellow solid (66 mg, 16% yield); R_f = 0.1 (dichloromethane–ethyl acetate, 25 : 1); IR (film) 3468, 1305, 1128, 831, 732, 693 cm^{-1}; ^1H NMR (300 MHz) δ 7.51–7.23 (m, 9 H), 6.95–6.82 (m, 4 H), 6.77 (d, J = 16.1 Hz, 1 H), 6.69 (d, J = 6.7 Hz, 1 H), 6.43 (d, J = 6.6 Hz, 1 H), 6.40 (d, J = 15.8 Hz, 1 H), 4.22 (dt, J = 12.9, 6.7 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.56 (d, J = 7.5 Hz, 1 H), 3.10 (t, J = 13.0 Hz, 1 H), 2.49 (dd, J = 13.1, 6.7 Hz, 1 H); ^{13}C NMR (75 MHz) δ 160.0 (C), 158.9 (C), 139.9 (CH), 137.2 (CH), 133.0 (C), 133.0 (C), 132.2 (CH), 131.8 (CH), 130.5 (C), 129.7 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 125.3 (CH), 114.6 (CH), 114.3 (CH), 83.8 (C), 72.8 (C), 72.8 (CH), 55.5 (CH_3), 55.5 (CH_3), 48.3 (CH_2), 42.2 (CH); HRMS (ESI) calcd for $C_{29}H_{28}O_5S_2$ (M + Na): 543.1270. Found: 543.1276.

Compound **4d′**: light yellow solid (98 mg, 24% yield); mp = 128–131 °C (by decomposition); R_f = 0.2 (dichloromethane–ethyl acetate, 50 : 1); IR (film) 3448, 1604, 1513, 1250, 1120, 1106, 1032 cm^{-1}; ^1H NMR (300 MHz) δ 7.55–7.34 (m, 7 H), 7.27 (d, J = 8.6 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 15.9 Hz, 1 H), 6.28 (d, J = 15.7 Hz, 1 H) 5.75 (d, J = 1.0 Hz, 1 H), 4.31 (dt, J = 12.8, 7.2 Hz, 1 H), 3.98 (dd, J = 9.9, 8.0 Hz, 1 H), 3.87–3.81 (m, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 2.50 (dd, J = 12.6, 6.7 Hz, 1 H) 2.39 (t, J = 12.7 Hz, 1 H); ^{13}C NMR (75 MHz) δ 159.8 (C), 158.8 (C), 153.2 (C), 135.1 (CH), 132.8 (C), 130.7 (CH), 130.3 (CH), 130.3 (C), 130.2 (C), 129.4 (CH), 129.0 (CH), 128.4 (CH), 128.0 (CH), 122.7 (CH), 114.5 (CH), 114.3 (CH), 81.0 (C), 71.5 (CH), 59.9 (CH), 55.5 (CH_3), 55.5 (CH_3), 50.1 (CH_2), 42.6 (CH); HRMS (ESI) calcd for $C_{29}H_{28}O_5S_2$ (M + Na): 543.1270. Found: 543.1269.

Compound **4e′**: white solid (243 mg, 19% yield); R_f = 0.1 (dichloromethane–ethyl acetate, 100 : 1); IR (film); 3438, 1277, 1116 cm^{-1}; ^1H NMR (300 MHz) δ 7.44–7.39 (m, 2 H), 7.36–7.29 (m, 5 H), 7.02 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 9.0 Hz, 2 H), 6.73 (d, J = 1.1 Hz, 1 H), 6.18 (d, J = 16.1 Hz, 1 H), 5.88 (d, = 16.1 Hz, 1 H), 4.38–4.28 (m, 2 H), 4.04 (dd, J = 9.6, 7.9 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 2.50 (t, J = 12.7 Hz, 1 H) 2.42 (dd, J = 13.2, 7 Hz, 1 H); ^{13}C NMR (75 MHz) δ 159.5 (C), 158.9 (C), 149.6 (C), 133.1 (CH), 132.6 (C), 130.7 (CH), 129.9 (CH), 129.0 (C), 128.9 (C), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 114.5 (CH), 114.1 (CH), 81.2 (C), 70.7 (CH), 58.6 (CH), 55.5 (CH_3), 55.4 (CH_3), 50.4 (CH_2), 42.0 (CH); HRMS (ESI) calcd for $C_{29}H_{28}O_5S$ (M + Na): 511.1549. Found: 511.1549.

Compound **6b**: white solid (60 mg, 5% yield); R_f = 0.5 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 3476, 1292, 1106 cm^{-1}; ^1H NMR (300 MHz) δ 7.35 (d, J = 8.7 Hz, 2 H), 7.15 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.81 (d, J = 15.8 Hz, 1 H), 6.29–6.24 (m, 1 H), 5.99 (dd, J = 15.8, 1.4 Hz, 1 H), 5.37 (d, J = 1.4 Hz, 1 H), 3.94 (dd, J = 14.9, 4.7 Hz, 1 H), 3.81 (s, 3 H), 3.81 (s, 3 H), 3.59 (d, J = 4.8 Hz, 1 H), 3.53 (s, 1 H) 2.26 (dd, J = 14.8, 12.6 Hz, 1 H), 1.89 (dd, J = 15.0, 4.8 Hz, 1 H), 1.88 (d, J = 1.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 159.7 (C), 159.2 (C), 140.4 (C), 132.3 (C), 130.7 (CH), 129.4 (CH), 129.1 (C), 128.6 (CH), 128.1 (CH), 124.6 (CH), 114.5 (CH), 114.2 (CH), 73.1 (C), 68.7 (CH), 68.2 (CH), 55.5 (CH_3), 55.5 (CH_3), 38.4 (CH), 37.8 (CH_2), 20.8 (CH_3); HRMS (ESI) calcd for $C_{24}H_{26}O_5S$ (M + Na): 449.1393. Found: 449.1390.

Compound **6d**: light yellow solid (44 mg, 12% yield); R_f = 0.5 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 3468, 1293 1110 cm^{-1}; ^1H NMR (300 MHz) δ 7.53–7.47 (m, 2 H), 7.42–7.35 (m, 5 H), 7.04 (d, J = 8.7 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.79 (d, J = 15.7 Hz, 1 H), 6.30 (dd, = 15.6, 1.5 Hz, 1 H), 6.00 (d, J = 5 Hz, 1 H), 5.35 (d, J = 1.5 Hz, 1 H), 3.89–3.78 (m, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.47 (s, 1 H) 2.14 (dd, J = 15.1, 12.5 Hz, 1 H), 1.89 (dd, J = 15.1, 5.0 Hz, 1 H); ^{13}C NMR (75 MHz) δ 159.7 (C), 159.2 (C), 141.2 (C), 134.3 (CH), 133.1 (C), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.6 (CH), 129.4 (C), 129.3 (C), 128.3 (CH), 128.1 (CH), 121.0 (CH), 114.6 (CH), 114.1 (CH), 72.4 (C), 69.0 (CH), 67.0 (CH), 55.5 (CH_3), 55.5 (CH_3), 40.4 (CH_2), 39.5 (CH); HRMS (ESI) calcd for $C_{29}H_{28}O_5S_2$ (M + H): 521.1450. Found: 521.1453.

Compound **6e′**: white solid (310 mg, 24% yield); R_f = 0.7 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 3479, 1284, 1119 cm^{-1}; ^1H NMR (300 MHz) δ 7.61–7.57 (m, 2 H), 7.43–7.40 (m, 3 H), 7.18 (d, J = 8.7 Hz, 2 H), 7.00 (d, J = 8.7 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 0.87 Hz, 1 H), 6.82 (d = 16.0 Hz, 1 H), 6.74 (d, J = 8.8 Hz, 2 H), 5.67 (dd, J = 16.1, 1.6 Hz, 1 H), 5.57 (d, 1.7 Hz, 1 H), 4.10 (s, 1 H), 4.02–3.93 (m, 2 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 2.16 (dd, J = 15.2, 12.0 Hz, 1 H), 1.94 (dd, J = 15.1, 5.0 Hz, 1 H); ^{13}C NMR (75 MHz) δ 159.6 (C), 159.2 (C), 143.9 (C), 133.6 (C), 133.3 (C), 130.7 (CH), 129.7 (CH), 129.7 (C), 129.3 (CH), 129.1 (CH), 128.4 (CH), 127.9 (CH), 126.1 (CH), 120.7 (CH), 114.7 (CH), 114.1 (CH), 72.9 (C), 68.0 (CH), 66.6 (CH), 55.5 (CH_3), 55.4 (CH_3), 40.5 (CH_2), 40.1 (CH); HRMS (ESI) calcd for $C_{29}H_{28}O_5S$ (M + Na): 511.1549. Found: 511.1548.

Compound **7e**: white solid (56 mg, 5% yield); R_f = 0.6 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 1715, 1302, 1128 cm^{-1}; ^1H NMR (300 MHz) δ 7.32–7.27 (m, 3 H), 7.17 (d, J = 8.9 Hz, 2 H), 7.17 (d, J = 8.8 Hz, 2 H), 7.03–7.00 (m, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 6.67 (d, J = 8.9 Hz, 2 H), 5.78 (d, J = 2.4 Hz, 1 H), 4.32 (dd, J = 7.0, 2.1 Hz, 1 H), 4.12 (dd, J = 16.1, 15.2 Hz, 1 H), 3.85 (s, 3 H), 3.77 (s, 1 H), 3.71 (m, 3 H) 3.67 (s, 1 H), 3.19 (dd, J = 16.2, 7.1 Hz, 1 H), 2.92 (dd, J = 15.4, 2.7 Hz, 1 H), 2.86–2.76 (m, 2 H); ^{13}C NMR (75 MHz) δ 209.7 (C), 159.4 (C), 159.1 (C), 136.4 (C), 134.2 (C), 131.9 (CH), 131.8 (C), 131.0 (C), 129.3 (C), 129.0 (C), 128.2 (C), 127.3 (CH), 125.5 (CH), 114.4 (CH), 113.0 (CH), 74.4 (C), 57.1 (CH_2), 55.5 (CH_3), 55.4 (CH_3), 44.3 (CH_2), 44.0 (CH), 42.9 (CH), 42.2 (CH_2); HRMS (ESI) calcd for $C_{29}H_{28}O_5S$ (M + Na): 511.1549. Found: 511.1546.

Compound **7f**: white solid (160 mg, 24% yield); R_f = 0.2 (dichloromethane–ethyl acetate, 50 : 1); IR (film) 1720, 1314, 1136 cm^{-1}; ^1H NMR (300 MHz) δ 7.12 (d, J = 8.8 Hz, 2 H), 7.08 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 6.72 (d, J = 8.8 Hz, 2 H), 6.53 (dd, J = 2.3 Hz, 1 H), 4.24 (dd, J = 6.9, 2.0 Hz, 1 H), 4.03 (dd, J = 16.4, 14.3 Hz, 1 H), 3.82 (s, 3 H), 3.74 (s, 3 H), 3.76–3.63 (m, 2 H) 3.66 (s, 3 H), 3.11 (dd, J = 16.3, 7.2 Hz, 1 H), 2.83–2.69 (m, 3 H); ^{13}C NMR (75 MHz) δ 208.8 (C), 162.2 (C), 159.5 (C), 159.3 (C), 142.6 (CH), 131.7 (CH), 130.8 (CH), 129.9 (C),

129.2 (C), 127.3 (C), 114.5 (CH), 113.1 (CH), 75.2 (C), 55.9 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 52.6 (CH_3), 43.7 (CH_2), 43.3 (CH), 42.2 (CH), 41.8 (CH_2); HRMS (ESI) calcd for $C_{25}H_{26}O_7S$ (M + Na): 493.1291. Found: 493.1291.

Compound **7g**: pale yellow solid (45 mg, 21% yield, contaminated with SM, 2 : 1 **7g** : **1g**); R_f = 0.3 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 2229, 1713, 1323, 1130 cm^{-1}; ^1H NMR (300 MHz) δ; 7.14 (d, J = 8.8 Hz, 2 H), 7.09 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 6.81 (d, J = 8.9 Hz, 2 H), 6.37 (dd, J = 2.5 Hz, 1 H), 4.24 (dd, J = 6.9, 1.9 Hz, 1 H), 4.04 (dd, J = 16.2, 14.2 Hz, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.69 (dd, J = 14, 4.6 Hz, 1 H) 3.52 (d, J = 15.8 Hz, 1 H), 3.09 (dd, J = 16.3, 7.2 Hz, 1 H), 2.87–2.71 (m, 3 H); ^{13}C NMR (75 MHz) δ 208.0 (C), 159.8 (C), 159.7 (C), 149.0 (C), 131.7 (CH), 130.8 (CH), 130.2 (C), 126.5 (C), 114.8 (CH), 113.2 (CH), 113.2 (CH), 110.1 (C), 74.2 (C), 55.5 (CH_3), 55.4 (CH_3), 55.2 (CH_2), 43.7 (CH_2), 43.6 (CH), 42.0 (CH), 41.7 (CH_2); HRMS (ESI) calcd for $C_{24}H_{23}NO_5S$ (M − H): 436.1224. Found: 436.1213.

Compound **9**: white solid (560 mg, 50% yield); R_f = 0.5 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 1653, 1309, 1172 cm^{-1}; ^1H NMR (300 MHz) δ 7.51 (d, J = 16.1 Hz, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.23 (d, J = 8.9 Hz, 2 H), 7.21–7.18 (m, 5 H), 7.11–7.03 (m, 3 H), 6.81 (d, J = 8.8 Hz, 2 H), 6.75 (d, J = 8.7 Hz, 2 H), 6.73–6.70 (m, 2 H), 6.56 (d, J = 16.1 Hz, 1 H), 4.66 (d, J = 3.2 Hz, 1 H), 3.82 (dd, J = 15.9, 8.9 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.39 (d, J = 15.8 Hz, 1 H), 3.25 (dd, J = 15.8, 5.0 Hz, 1 H), 3.22 (d, J = 16 Hz, 1 H); ^{13}C NMR (75 MHz) δ 197.9 (C), 161.8 (C), 159.0 (C), 143.1 (CH), 136.1 (C), 135.7 (C), 134.8 (C), 134.0 (C), 132.3 (C), 131.2 (CH), 130.2 (CH), 129.5 (CH), 129.3 (C), 128.7 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.1 (CH), 124.0 (CH), 114.5 (CH), 113.1 (CH), 72.6 (CH), 59.5 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 41.4 (CH_2), 39.6 (CH); HRMS (ESI) calcd for $C_{35}H_{32}O_5S$ (M + Na): 587.1862. Found: 587.1861.

Compound **10**: white solid (459 mg, 40% yield) R_f = 0.5 (dichloromethane–ethyl acetate, 100 : 1); IR (film) 3481, 1293, 1175 cm^{-1}; ^1H NMR (300 MHz) δ 7.31–7.24 (m, 5 H), 7.19 (d, J = 8.7 Hz, 2 H), 7.08–7.02 (m, 1 H), 6.95 (t, J = 7.5 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 6.82 (d, = 9.5 Hz, 2 H), 6.73 (d, J = 15.6 Hz, 1 H), 6.66 (d, J = 8.7 Hz, 2 H), 5.70 (dd, J = 15.7, 1.6 Hz, 1 H), 5.47 (d, J = 1.5 Hz, 1 H), 4.20 (dd, J = 12.9, 4.1 Hz, 1 H), 4.13–4.12 (m, 1 H), 4.02 (d, J = 2.1 Hz, 1 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 2.54 (dd, J = 15.1, 13.0 Hz, 1 H), 2.03 (dd, J = 15, 4.4 Hz, 1 H); ^{13}C NMR (75 MHz) δ 159.5 (C), 159.3 (C), 138.3 (C), 136.3 (C), 135.5 (C), 135.4 (C), 132.1 (C), 130.8 (CH), 129.4 (CH), 129.2 (CH), 129.2 (C), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH) 127.9 (CH), 114.6 (CH), 114.0 (CH), 73.9 (CH), 73.2 (C), 72.3 (CH), 55.6 (CH_3), 55.4 (CH_3), 39.2 (CH), 37.8 (CH_2); HRMS (ESI) calcd for $C_{35}H_{32}O_5S$ (M + Na): 587.1862. Found: 587.1864.

Compound **12a**: white solid (103 mg, 30% yield); R_f = 0.3 (dichloromethane–ethyl acetate, 50 : 1); IR (film) 3470, 1603, 1285, 1131 cm^{-1}; ^1H NMR (300 MHz) δ 7.41–7.21 (m, 10 H), 6.78 (dd, J = 6.7, 3.4 Hz, 1 H) 6.63–6.59 (m, 2 H), 4.30 (dd, J = 9.1, 6.2 Hz, 1 H), 4.08 (t, J = 9.3 Hz, 1 H), 3.84 (dd, J = 9.5, 2.7 Hz, 1 H), 2.94–2.70 (m, 3 H), 1.94–1.80 (m, 1 H), 1.50–1.32 (m, 1 H); ^{13}C NMR (75 MHz) δ 147.0 (C), 138.7 (C), 137.2 (CH), 136.9 (C), 132.0 (CH), 130.6 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 89.7 (C), 64.5 (CH), 62.0 (CH), 60.1 (CH), 56.4 (CH), 46.2 (CH), 28.8 (CH_2), 24.8 (CH_2); HRMS (ESI) calcd for $C_{23}H_{22}O_3S$ (M + Na): 401.1182. Found: 401.1180.

Compound **12b**: white solid (701 mg, 18% yield); mp = 186–188 °C (by decomposition); R_f = 0.5 (dichloromethane–ethyl acetate, 25 : 1); IR (film) 3480, 1278, 1129 cm^{-1}; ^1H NMR (300 MHz) δ 7.21 (d, J = 8.7 Hz, 2 H), 7.16 (d, J = 8.7 Hz, 2 H), 6.92–6.86 (m, 4 H), 6.84–6.79 (m, 1 H), 6.62 (dd, J = 6.9, 1.2 Hz, 1 H), 6.58 (dd, J = 6.8, 2.6 Hz, 1 H), 4.45 (dd, J = 9.4, 6.1 Hz, 1 H), 4.10 (t, J = 9.6 Hz, 1 H), 4.02–3.96 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.08 (d, 16.1 Hz, 1 H), 2.39 (td, J = 12.3, 5.9 Hz, 1 H), 2.08–1.92 (m, 1 H), 1.83–1.45 (m, 2 H), 1.28–0.97 (m, 2 H); ^{13}C NMR (75 MHz) δ 158.7 (C), 158.7 (C), 139.8 (C), 136.8 (CH), 133.0 (CH), 130.5 (CH), 129.6 (C), 129.5 (C), 129.0 (CH), 123.9 (CH), 114.3 (CH), 113.9 (CH), 82.5 (C), 62.7 (CH), 59.3 (CH), 55.4 (CH_3), 55.4 (CH_3), 54.3 (CH), 47.2 (CH), 27.3 (CH_2), 26.5 (CH_2), 25.4 (CH_2); HRMS (ESI) calcd for $C_{26}H_{28}O_5S$ (M + Na): 475.1549. Found: 475.1550.

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