Stereoselective and Convergent Syntheses of Retinoic Acid and its Ester Derivatives by the Sulfone Olefination Reaction

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Abstract: An extensive study on the stereoselective and convergent syntheses of retinoic acid and its ester derivatives utilizing the Julia sulfone olefination reaction has been reported. Various C_5 units of the acid **4a**, the esters **4b–e** from the chemically and biologically important alcohols, and the furanone **6** have been prepared and coupled with the C_{15} allylic sulfone **3** to give the C_{20} compounds **10** and **11**, which provided all-(*E*)-retinoic acid (**1a**), its ester derivatives **1b–e**, and the furanone analogue **12b** in a highly stereoselective manner after dehydrosulfonation reaction. The Julia olefination reaction of the C_5 diester **13** and the C_{15} allylic sulfone **3** produced the known C_{20} diacid **15** which underwent stereoselective mono-decarboxylation to provide either 13-(*Z*)-retinoic acid (**2**) or all-(*E*)-retinoic acid (**1**) depending on the reagent used.

Key words: allylations, esters, alkenation, stereoselective synthesis, sulfones

Retinoic acid, a metabolite of vitamin A, mediates cellular growth and differentiation, and shows broad treatment effects on a wide spectrum of dermatological disorders including photo-damaged skin.[1] This biologically and therapeutically important compound also exhibits a prophylaxis effect on certain cancers, which spurs the structure–activity relationship studies of retinoid cancer inhibition.[2] There have been extensive synthetic efforts for retinoic acid and its analogues.[3] Traditional methods based on the Wittig reaction[4] and the Julia sulfone olefination[5] have been utilized for the commercial synthesis of retinoids. It is only recent years that the importance of the stereoselective synthesis of retinoic acid has been recognized. This recognition is a result of the discovery and characterization of the retinoid receptor proteins, where binding of the specific retinoic acid with a certain stereochemistry to the receptor proteins triggers each different biological activity.[6] Stereoselective synthetic approaches to retinoic acid using the Suzuki reaction,[7] the Stille coupling,[8] and so on[9] have appeared recently in the literature, which are, however, less attractive for a large scale synthesis. Olefination based on the Julia sulfone chemistry provides several advantages in the syntheses of retinoid and carotenoid compounds: (1) stable and solid intermediary sulfone compounds can be easily handled and purified by recrystallization; (2) base-promoted dehydrosulfonation reaction proceeds in a highly stereoselective manner to produce the *E* configuration of the double bond;[10] (3) the byproduct, metal sulfinate, is easily removable from the reaction mixture. To our surprise, there has been only a limited approach to the stereoselective synthesis of retinoic acid and its derivatives based on the Julia sulfone chemistry.[11] This sulfone olefination method seemed to be best suited for the stereoselective convergent synthesis of the ester derivatives of all-(*E*)-retinoic acid because the direct esterification required activation of retinoic acid, where the stereochemical integrity of all-(*E*)-retinoic acid might be lost. We have thus extensively studied the stereoselective syntheses of various subunits required for retinoic acids and its ester derivatives utilizing the Julia sulfone chemistry, and accomplished the stereoselective syntheses of all-(*E*)-retinoic acid and its ester derivatives, furanone analogues, and 13-(*Z*)-retinoic acid. The details of which are reported herein.

The disconnection approach to all-(*E*)-retinoic acid and its ester derivatives **1** and 13-(*Z*)-retinoic acid (**2**) is delineated in Scheme 1. The C_{15} allylic sulfone **3**, which can be prepared from β-ionone in two steps, has been efficiently utilized in the syntheses of retinoids[5a–5c] and carotenoids.[12] The key to this approach is to prepare each of the corresponding C_5 allylic halide units **4** and **5** in a highly stereoselective manner. (*Z*)-4-Halo-2-butenoic acid (**5**) does not exist under the basic condition of the Julia coupling, but forms a furanone ring. It was thus envisioned that 5-halogenated furanone **6** might be a good substitute for the compound **5** for the synthesis of 13-(*Z*)-retinoic acid.

Highly stereoselective synthesis of (*E*)-4-chloro-3-methyl-2-butenoic acid ethyl ester **4** (X = Cl, R = Et) was not feasible by the conventional Wittig reaction, where a 1.4:1 mixture of the *E* and the *Z* isomers was obtained.[13] Allylic bromination of 3-methyl-2-butenoic acid by a stoichiometric amount of NBS also produced a 1.5:1 mixture of the *E* and *Z* stereoisomers,[14] however, (*Z*)-4-bromo-3-methyl-2-butenoic acid (**5**) was easily removed from this mixture by treating with aqueous basic solution to convert **5** into the furanone derivative **7** (29%) and extracting with organic solvent (Scheme 2). Acidification of the above aqueous basic solution and extraction with organic solvent then provided stereoisomerically pure (*E*)-4-bromo-3-methyl-2-butenoic acid (**4a**) in 43% yield. The furanone compound **7**, on the other hand, can be exclusively and efficiently obtained from 3-methyl-2-butenoic acid by allylic di-bromination with 2 equiv of NBS and washing with a base solution to produce the mono-brominated furanone

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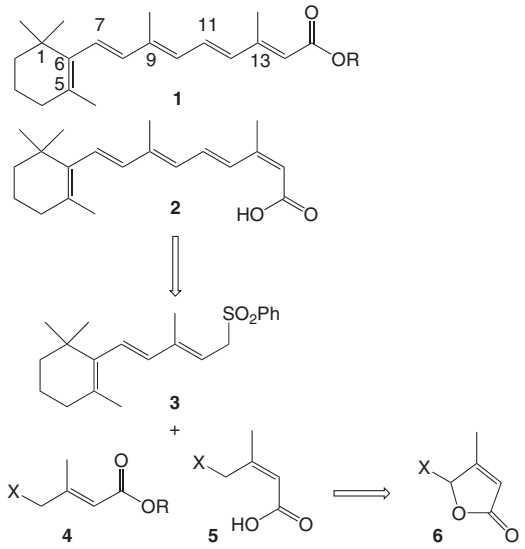
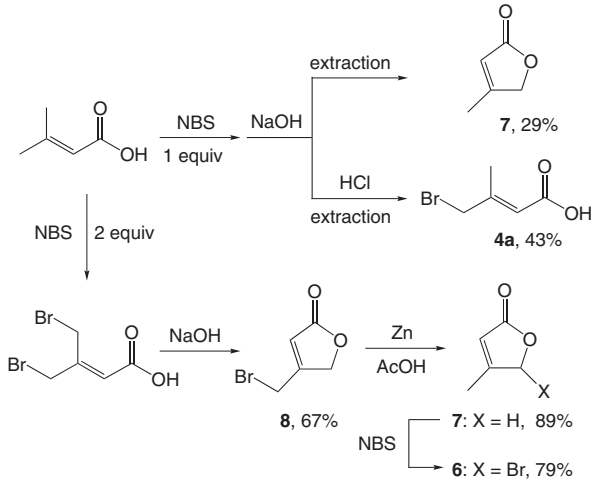
8 (67% yield) in the side chain,[11,15] followed by debromination reaction (89% yield) under a mild condition using Zn in AcOH. Allylic bromination of 4-methyl-5*H*-furan-2-one (**7**) by NBS again produced 5-brominated furanone **6** in 79% yield (Scheme 2).[16]



Scheme 1 Disconnection approach to all-(*E*)-retinoic acid and its ester derivatives **1** and 13-(*Z*)-retinoic acid (**2**) using the Julia sulfone chemistry.

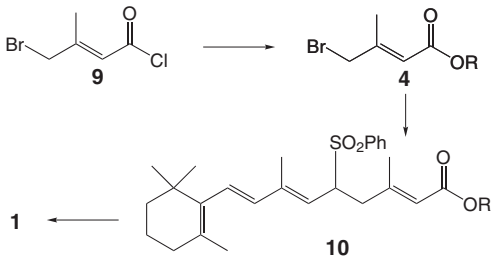


Scheme 2 Stereoselective syntheses of the C_5 units required for retinoic acids.

Novel but rather unstable (*E*)-4-bromo-3-methyl-2-butenoyl chloride (**9**), which was prepared from the corresponding acid **4a** by chlorination with oxaly chloride, was efficiently utilized without purification in the preparation of various (*E*)-C_5 units **4b**–**e** required for the synthesis of the esters **1b**–**e** of all-(*E*)-retinoic acid (Table 1). The Li or Na salts of the chemically and biologically important alcohols such as *dl*-tocopherol, butylated hydroxyanisol (BHA),[17] β-cholesterol, and β-estradiol[18] selectively replaced the acyl chloride of compound **9** to give the (*E*)-C_5 ester derivatives **4b**–**e** in good yields (65–99%).

The Julia coupling of the C_{15} allylic sulfone **3** and the (*E*)-C_5 unit **4** produced the C_{20} sulfone compound **10**, which underwent base-promoted dehydrosulfonation reaction to produce all-(*E*)-retinoic acid and its ester derivatives **1**. Contrary to the case of retinol synthesis, the dehydrosulfonation step is facile due to the acidic γ-proton of the α,β-unsaturated acid or ester functional group. This two-step olefination procedure can be undertaken in one pot using excess base such as *t*-BuOK. The reaction of the C_{15} sulfone **3** and the C_5 acid **4a** under four equivalents of *t*-BuOK in THF directly gave rise to all-(*E*)-retinoic acid (**1a**) in 65% yield via the formation of the C_{20} coupling product **10a** (R = H) and the subsequent dehydrosulfonation reaction (entry 1, Table 1). The one pot olefination reaction of the C_{15} sulfone **3** and the C_5 ester **4b** of tocopherol under three equivalents of *t*-BuOK in THF produced the desired retinoic acid ester **1b** in only 33% yield, in which an appreciable amount of tocopherol was obtained as a side product. This was presumably due to the presence of excess base, which caused hydrolysis of the ester group. It was thus beneficial to perform the olefination reaction in two separate steps of coupling and dehydrosulfonation for the synthesis of the ester derivatives of retinoic acid. Good yields (69–96%) of the Julia coupling products **10b**–**e** were obtained using a stoichiometric amount of BuLi in THF. A mild dehydrosulfonation reaction can be conducted using a non-nucleophilic base

Table 1 Yields of the Reaction for the (*E*)-C_5 Units **4** from **9**, the Coupling Reaction with **3** to give **10**, and the Dehydrosulfonation Reaction to Produce All-(*E*)-retinoic Acid and its Ester Derivatives **1**



Entry	Compound	ROH	Yield **4** (%)	Yield **10** (%)	Yield **1** (%)
1	**a**	H_2O	–	–	65[a]
2	**b**	*dl*-Tocopherol	99[b]	74[c]	85[d]
3	**c**	BHA	99[b]	96[c]	89[d]
4	**d**	β-Cholesterol	74[b]	69[c]	92[d]
5	**e**	β-Estradiol	65[e,f]	83[c,f]	72[d,f]

[a] (1) Compound **3** and *t*-BuOK (4 equiv) in THF at –20 °C; (2) **4a** in THF at –20 °C to 60 °C.
[b] (1) ROH and BuLi in THF at –78 °C; (2) **9** (2 equiv) in THF at –78 °C.
[c] (1) Compound **3** and BuLi in THF at –78 °C; (2) **4** in THF at –78 °C.
[d] Compound **10** and DBU (2 equiv) in THF.
[e] (1) β-Estradiol and NaH in THF at 0 °C; (2) **9** (2 equiv) in THF; (3) Ac_2O and pyridine in CH_2Cl_2.
[f] The ester of β-estradiol acetate was obtained.

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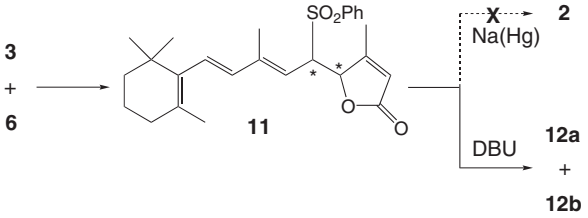
such as DBU to give the esters **1b–e** of all-(*E*)-retinoic acid in 72–92% yields.

The coupling of the C_{15} sulfone **3** and 5-bromo-4-methyl-5*H*-furan-2-one (**6**) gave the C_{20} sulfone compound **11**, in which two diastereoisomers were obtained in different yields and ratios depending on the coupling conditions used (Table 2). It was impossible to distinguish the *anti* and the *syn* diastereomers of compound **11** by comparing the vicinal coupling constants in the ^{1}H NMR spectra, where similar values of 2.9 and 1.7 Hz were observed, respectively. When THF was used as a solvent at –78 °C with BuLi as a base for the coupling (entry 1, Table 2), the more polar isomer was obtained as a major product with the ratio of 1:2. Similar selectivity of 1:3 favoring the more polar isomer was observed when *t*-BuOK was used in DMF at –20 °C (entry 2, Table 2). This ratio was reversed (2:1) when a 4:1 mixed solvent of THF and HMPA was used (entry 3, Table 2), where an equilibrium condition might be established favoring the formation of the more stable and the less polar isomer.[19]

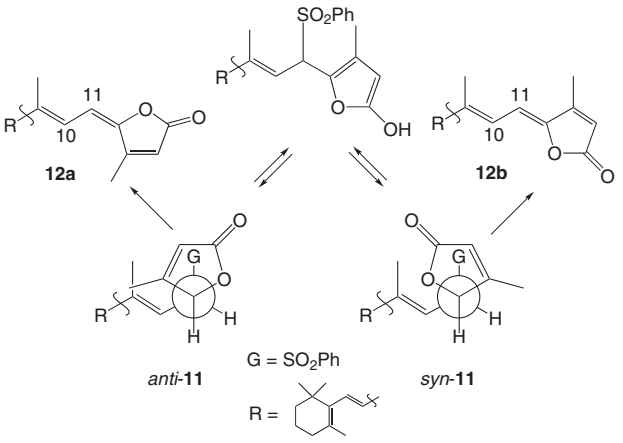
We anticipated that the desulfonation reaction of the compound **11** by a radical process would generate the carbanion that would open the furanone ring by an E1cb mechanism to give 13-(*Z*)-retinoic acid (**2**). Unfortunately, the reaction of **11** with Na(Hg) did not produce the desired 13-(*Z*)-retinoic acid (**2**), but furnished a complicated mixture of products in low yields. Efforts to open the furanone ring of compound **11** by hydrolysis were also in vain due to the easy aromatization of the furanone ring. On the other hand, DBU-promoted dehydrosulfonation of the compound **11** proceeded efficiently and highly stereoselectively to provide the furanone derivative **12b**, which is the cyclized homologue of 13-(*Z*)-retinoic acid (**2**). It is interesting to note that the same *E*–*Z* ratio of 1:10 at C(11) was obtained in the dehydrosulfonation reaction regardless of the *anti*–*syn* ratio of the starting compound **11** (Table 2). The *anti* alignment of the β-hydrogen and the benzenesulfonyl group is required for the dehydrosulfonation reaction,[10] and the structure of *anti*-**11** seems to be energetically less favorable than that of *syn*-**11** due to the steric interactions between the methyl substituents (Scheme 3). It is the easy aromatization process of the furanone ring that causes the less favorable *anti*-**11** to equilibrate to the more favorable *syn*-**11**, which gives rise to **12b** after the dehydrosulfonation reaction. This accomplished an overall improved synthesis of the furanone derivative **12b** of retinoic acid comparing to the synthesis based on the Wittig reaction.[20]

It has been recently reported that the C_{20} diacid **15** underwent stereoselective mono-decarboxylation to give all-(*E*)-retinoic acid (**1a**) or 13-(*Z*)-retinoic acid **2** depending on the regent used (Scheme 4).[21] We devised a plan for the stereoselective synthesis of 13-(*Z*)-retinoic acid (**2**) via the formation of the C_{20} diacid **15**, in which the C_5 diester **13** played a key role. Lewis acid ($FeCl_3$) mediated coupling of diethyl malonate and acetone,[22] followed by allylic bromination[23] of the resulting diethyl 2-isopropylidenemalonate provided the C_5 diester unit **13** in 57% overall

Table 2 Coupling Reaction of the C_{15} Sulfone **3** and the C_5 Furanone **6**, and the Dehydrosulfonation Reaction of **11** to give the Furanone Derivatives **12a** and **12b** of Retinoic Acid (see Scheme 3)



Entry	Coupling condition of **3** and **6**	Yield (%) **11** (isomeric ratio)	Yield (%) **12** (**a**:**b**)
1	*n*-BuLi–THF	70 (1:2)	78 (1:10)
2	*t*-BuOK–DMF	49 (1:3)	68 (1:10)
3	*n*-BuLi–THF, HMPA	66 (2:1)	73 (1:10)



Scheme 3 Equilibration of *anti*-**11** to *syn*-**11** through aromatization, and the dehydrosulfonation reaction to produce **12a**,**b**.

yield. The Julia coupling reaction of the C_{15} sulfone **3** and the C_5 diester **13** using BuLi in THF at –78 °C (75% yield) or *t*-BuOK in DMF at –20 °C (60% yield) produced the C_{20} sulfone compound **14**. Alkaline hydrolysis of the C_{20} sulfone diester **14** accompanied the dehydrosulfonation reaction to give the C_{20} diacid **15**, which was easily purified by recrystallization from $CHCl_3$. 13-(*Z*)-Retinoic acid was exclusively synthesized by mono-decarboxylation of the diacid **15** under refluxing lutidine. Upon treatment with pyridine, all-(*E*)-retinoic acid (**1a**) was obtained (Scheme 4) as reported.[23]

In conclusion, we have developed stereoselective and convergent synthetic methods of all-(*E*)-retinoic acid (**1a**), its ester derivatives **1b–e** of the chemically and biologically important alcohols, 13-(*Z*)-retinoic acid (**2**), and its furanone homologue **12b** utilizing the industrially applicable Julia sulfone olefination reaction. The success of these approaches relied on the stereoselective preparation and the efficient manipulation of the required C_5 units. Stereoselective large-scale syntheses of these biologically and therapeutically important retinoic acid esters may now be possible by the application of our synthetic methods.

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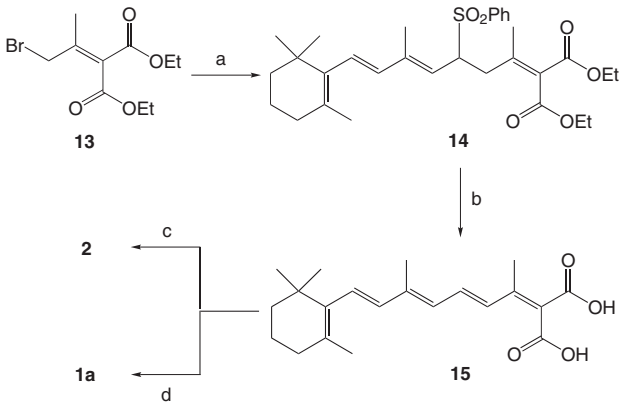

Scheme 4 Stereoselective synthesis of 13-(*Z*)-retinoic acid (**2**) and all-(*E*)-retinoic acid (**1a**) by the Julia olefination and stereoselective mono-decarboxylation reactions. *Reagents*: (a) (1) **3** and BuLi in THF at –78 °C, (2) **13** in THF at –78 °C, 75%; or (1) **3** and *t*-BuOK in DMF at –20 °C, (2) **13** in DMF at –20 °C, 60%; (b) (1) **14** and KOH (5 equiv) in *i*-PrOH, (2) aq HCl (3 M; pH 1), (3) recrystallization from $CHCl_3$, 58%; (c) **15** in refluxing lutidine, 63%; (d) **15** and pyridine in CH_2Cl_2, 67%.

The C_5 acyl chloride **9** was prepared by the reaction of the bromo acid **4a** (1 equiv) and oxalyl chloride (2 equiv) in benzene. The reaction mixture was concd under reduced pressure, and used without purification. ^{1}H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded in $CDCl_3$ unless mentioned otherwise. Solvents for extraction and chromatography were reagent grade and used as received. The column chromatography was performed by the method of Still with silica gel 60, 230–400 mesh ASTM supplied by Merck. Solvents used as reaction media were dried over pre-dried molecular sieve (4 Å) by microwave oven. All reactions were performed under a dry argon atmosphere in oven-dried glassware except for those using H_2O as a reaction medium.

Compounds 4a and 7

To a solution of 3,3-dimethylacrylic acid (3.00 g, 30.0 mmol) in CCl_4 (30 mL) were added NBS (6.40 g, 36.0 mmol) and AIBN (99mg, 0.06 mmol). The mixture was heated at reflux for 30 min, cooled to r.t., and filtered to remove succinimide. The filtrate was concd and aq NaOH (1 M; 30 mL) was added. The mixture was stirred at r.t. for 1 h and then extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **7**.

Yield: 0.77 g, 8.7 mmol (29%).

The above aq phase was acidified with aq HCl (3 M; 30 mL), extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **4a**.

Yield: 2.30 g, 12.9 mmol (43%).

Compound 4b

To a stirred solution of *dl*-tocopherol (1.30 g, 3.0 mmol) in THF (10 mL) at –78 °C was added a solution of BuLi in hexane (1.6 M; 2.0 mL, 3.3 mmol). The mixture was stirred at that temperature for 40 min, and a solution of **9** (1.08 g, 6.0 mmol) in THF (2 mL) was added. The reaction mixture was stirred at –78 °C for 30 min, and the cold bath was removed. Upon standing for 30 min, the mixture was diluted with EtOAc, washed with aq HCl (1 M), dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **4b**.

Yield: 1.75 g, 2.96 mmol (99%).

IR (KBr): 2927, 1733, 1651, 1458, 1378, 1222, 1129 cm^{-1}.

^{1}H NMR: δ = 0.84 (d, *J* = 6.4 Hz, 3 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 6 H), 1.00–1.64 (m, 21 H), 1.24 (s, 3 H), 1.68–1.87 (m, 2 H), 1.97 (s, 3 H), 2.01 (s, 3 H), 2.09 (s, 3 H), 2.34 (s, 3 H), 2.59 (t, *J* = 6.6 Hz, 2 H), 4.02 (s, 2 H), 6.27 (s, 1 H).

^{13}C NMR: δ = 11.8, 12.2, 13.1, 17.4, 19.6, 19.7, 19.8, 20.6, 21.0, 22.6, 22.7, 23.9, 24.4, 24.8, 27.9, 31.1, 32.7, 32.8, 37.3, 37.4, 37.4, 37.5, 38.0, 39.4, 75.0, 117.3, 118.5, 123.0, 124.9, 126.7, 140.2, 149.4, 154.7, 164.5.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{34}H_{56}BrO_3$: 591.3413; found: 591.3423.

Compound 4c

Following the above general procedure for **4b**, the reaction of **9** (1.08 g, 6.0 mmol) and the lithium salt of BHA which was generated by the addition of a BuLi solution in hexane (1.6 M; 2.25 mL, 3.6 mmol) to BHA (0.55 g, 3.0 mmol) in THF (15 mL) at –78 °C for 50 min produced **4c**.

Yield: 1.00 g, 2.98 mmol (99%).

IR (KBr): 2959, 1735, 1646, 1486, 1189, 1122, 913, 744 cm^{-1}.

^{1}H NMR: δ = 1.32 (s, 9 H), 2.35 (d, *J* = 1.2 Hz, 3 H), 3.79 (s, 3 H), 4.03 (s, 2 H), 6.22 (br s, 1 H), 6.71–6.77 (m, 1 H), 6.91–6.96 (m, 2 H).

^{13}C NMR: δ = 17.5, 30.1, 34.6, 37.8, 55.5, 110.5, 113.8, 118.8, 124.5, 142.3, 144.4, 155.3, 156.9, 164.7.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{16}H_{21}BrO_3$: 340.0674; found: 340.0677.

Compound 4d

Following the above general procedure for **4b**, the reaction of **9** (0.72 g, 4.0 mmol) and the lithium salt of β-cholesterol which was generated by the addition of a BuLi solution in hexane (1.6 M; 1.8 mL, 3.0 mmol) to β-cholesterol (0.81 g, 2.0 mmol) in THF (15 mL) at –78 °C for 50 min produced **4d**.

Yield: 0.80 g, 1.48 mmol (74%).

IR (KBr): 2943, 1711, 1645, 1450, 1228, 1158, 913, 744 cm^{-1}.

^{1}H NMR: δ = 0.68 (s, 3 H), 0.86 (d, *J* = 6.6 Hz, 6 H), 0.80–1.68 (m, 21 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.02 (s, 3 H), 1.76–2.06 (m, 5 H), 2.27 (s, 3 H), 2.34 (d, *J* = 7.9 Hz, 2 H), 3.94 (s, 2 H), 4.58–4.72 (m, 1 H), 5.38 (br d, *J* = 4.6 Hz, 1 H), 5.94 (s, 1 H).

^{13}C NMR: δ = 11.8, 17.2, 18.7, 19.3, 21.0, 22.5, 22.8. 23.8, 24.3, 27.8, 28.0, 28.2, 31.8, 31.9, 35.8, 36.2, 36.6, 37.0, 38.2, 38.4, 39.5, 39.7, 42.3, 50.0, 56.1, 56.7, 73.8, 119.9, 122.7, 139.6, 152.0, 165.3.

HRMS (CI$^+$): *m*/*z* calcd for $C_{32}H_{52}BrO_2$: 547.3151; found: 547.3156.

Compound 4e

Following the above general procedure for **4b**, the reaction of **9** (0.68 g, 3.8 mmol) and the sodium salt of β-estradiol which was generated by the addition of NaH (0.086 g, 2.1 mmol) to β-estradiol (0.53 g, 1.9 mmol) in THF (20 mL) at 0 °C for 30 min, followed by acetylation with acetyl chloride (0.27 mL, 3.8 mmol) and pyridine (0.31 mL, 3.8 mmol) in CH_2Cl_2 (10 mL) produced **4e**.

Yield: 0.59 g, 1.24 mmol (65%).

IR (KBr) 2929, 1734, 1491, 1247, 1124, 913, 744 cm^{-1}.

^{1}H NMR: δ = 0.83 (s, 3 H), 1.20–1.81 (m, 9 H), 1.84–1.94 (m, 2 H), 2.06 (s, 3 H), 2.15–2.29 (m, 2 H), 2.34 (br s, 3 H), 2.83–2.91 (m, 2 H), 4.01 (s, 2 H), 4.69 (dd, *J* = 8.8, 8.1 Hz, 1 H), 6.18 (br s, 1 H), 6.82 (d, *J* = 2.4 Hz, 1 H), 6.87 (dd, *J* = 8.6, 2.4 Hz, 1 H).

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^{13}C NMR: δ = 12.0, 17.5, 21.2, 23.2, 26.0, 27.0, 27.5, 29.5, 36.8, 37.9, 38.2, 42.8, 43.9, 49.8, 82.6, 118.6, 118.6, 121.5, 126.4, 137.9, 138.1, 148.1, 155.0, 164.5, 171.2.

HRMS (EI$^+$): *m*/*z* calcd for $C_{25}H_{31}BrO_4$: 474.1406; found: 474.1393.

Compound 10b

To a stirred solution of C_{15}, sulfone **3** (0.90 g, 2.60 mmol) in THF (20 mL) at –78 °C was added a solution of BuLi in hexane (1.6 M; 2.1 mL, 3.4 mmol). The mixture was stirred at that temperature for 30 min, and a solution of **4b** (1.85 g, 3.10 mmol) in THF (10 mL) was added. The reaction mixture was stirred at –78 °C for 1 h, quenched with aq HCl (1 M; 20 mL), extracted with Et_2O, dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **10b**.

Yield: 1.65 g, 1.93 mmol (74%).

IR (KBr): 2927, 1731, 1647, 1377, 1307, 1224, 1149, 1130 cm^{-1}.

^{1}H NMR: δ = 0.84 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.4 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 6 H), 0.95 (s, 3 H), 0.98 (s, 3 H), 1.00–1.67 (m, 25 H), 1.22 (s, 3 H), 1.26 (s, 3 H), 1.65 (s, 3 H), 1.68–1.85 (m, 2 H), 1.90 (br s, 3 H), 1.94 (br s, 3 H), 1.99 (t, *J* = 6.0 Hz, 2 H), 2.06 (s, 3 H), 2.17 (s, 3 H), 2.56 (t, *J* = 6.6 Hz, 2 H), 2.62 (dd, *J* = 13.0, 12.8 Hz, 1 H), 3.21 (dd, *J* = 13.0, 3.0 Hz, 1 H), 4.15 (ddd, *J* = 12.8, 10.6, 3.0 Hz, 1 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 5.97 (s, 3 H), 7.46–7.56 (m, 2 H), 7.59–7.68 (m, 1 H), 7.81–7.89 (m, 2 H).

^{13}C NMR: δ = 11.7, 12.0, 12.3, 12.9, 18.8, 19.1, 19.6, 19.7, 20.5, 21.0, 21.5, 22.6, 22.7, 23.9, 24.4, 24.7, 27.9, 28.7, 28.8, 31.0, 32.6, 32.7, 32.8, 34.0, 37.2, 37.3, 37.4, 37.5, 38.5, 39.3, 63.4, 74.9, 117.2, 117.7, 120.4, 122.9, 124.9, 126.7, 128.8, 129.4, 129.6, 133.7, 135.7, 137.2, 140.2, 142.8, 149.2, 156.3, 164.6.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{49}H_{77}O_3$ ($C_{55}H_{83}O_5S$ – $C_6H_6O_2S$): 713.5873; found: 713.5881.

Compound 10c

Following the general procedure for **10b**, the reaction of **4c** (1.43 g, 4.2 mmol) and the lithium salt of **3** that was generated by the addition of a solution of BuLi in hexane (1.6 M; 2.3 mL, 3.67 mmol) to **3** (1.20 g, 3.5 mmol) in THF (15 mL) at –78 °C for 1 h produced **10c**.

Yield: 2.02 g, 3.34 mmol (96%).

IR (KBr): 2958, 1736, 1649, 1485, 1447, 1306, 1191, 1123 cm^{-1}.

^{1}H NMR: δ = 0.96 (s, 3 H), 0.99 (s, 3 H), 1.24 (s, 3 H), 1.26 (s, 9 H), 1.42–1.48 (m, 2 H), 1.56–1.65 (m, 2 H), 1.66 (s, 3 H), 2.00 (t, *J* = 6.0 Hz, 2 H), 2.20 (s, 3 H), 2.65 (dd, *J* = 13.8, 11.6 Hz, 1 H), 3.23 (d, *J* = 13.8 Hz, 1 H), 3.77 (s, 3 H), 4.16 (ddd, *J* = 11.6, 10.6, 2.8 Hz, 1 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 5.91 (s, 1 H), 5.97 (s, 2 H), 6.68–6.74 (m, 1 H), 6.86–6.94 (m, 2 H), 7.44–7.55 (m, 2 H), 7.60–7.68 (m, 1 H), 7.80–7.88 (m, 2 H).

^{13}C NMR: δ = 12.3, 19.0, 19.1, 21.6, 28.8, 29.9, 32.8, 34.1, 34.4, 38.3, 39.3, 55.4, 63.4, 110.4, 113.7, 117.9, 120.3, 124.5, 128.8, 128.8, 129.4, 129.7, 133.7, 135.6, 137.1, 142.3, 142.4, 142.9, 156.7, 157.0, 164.8.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{31}H_{43}O_3$ ($C_{37}H_{49}O_5S$ – $C_6H_6O_2S$): 463.3212; found: 463.3224.

Compound 10d

Following the general procedure for **10b**, the reaction of **4d** (0.65 g, 1.18 mmol) and the lithium salt of **3** that was generated by the addition of a solution of BuLi in hexane (1.6 M; 0.81 mL, 1.29 mmol) to **3** (0.37 g, 1.07 mmol) in THF (15 mL) at –78 °C for 1 h produced **10d**.

Yield: 0.60 g, 0.74 mmol (69%).

IR (KBr): 2936, 1715, 1648, 1447, 1307, 1222, 1148 cm^{-1}.

^{1}H NMR: δ = 0.67 (s, 3 H), 0.81–1.61 (m, 26 H), 0.86 (d, *J* = 6.6 Hz, 6 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.95 (s, 3 H), 0.98 (s, 3 H), 1.01 (s, 3 H), 1.23 (s, 3 H), 1.65 (s, 3 H), 1.70–2.05 (m, 6 H), 2.10 (s, 3 H), 2.24–2.36 (m, 2 H), 2.51 (dd, *J* = 13.0, 11.4 Hz, 1 H), 3.11 (d, *J* = 13.0 Hz, 1 H), 4.07 (ddd, *J* = 11.4, 10.6, 3.8 Hz, 1 H), 4.56–4.65 (m, 1 H), 5.07 (d, *J* = 10.6 Hz, 1 H), 5.35 (br s, 1 H), 5.64 (s, 1 H), 5.95 (s, 2 H), 7.44–7.55 (m, 3 H), 7.58–7.66 (m, 1 H), 7.78–7.86 (m, 2 H).

^{13}C NMR: δ = 11.8, 12.4, 18.5, 18.7, 19.2, 19.3, 21.0, 21.5, 22.5, 22.8, 23.8, 24.3, 27.8, 28.0, 28.2, 28.8, 31.8, 31.9, 32.8, 34.1, 35.8, 36.2, 36.6, 37.0, 38.2, 38.5, 39.4, 39.5, 39.7, 42.3, 50.0, 56.1, 56.7, 63.5, 73.3, 119.3, 120.5, 122.5, 128.7, 128.8, 129.4, 129.6, 133.6, 135.7, 137.2, 137.3, 139.7, 142.7, 153.4, 165.5.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{47}H_{73}O_2$ ($C_{53}H_{79}O_4S$ – $C_6H_6O_2S$): 669.5611; found: 669.5610.

Compound 10e

Following the general procedure for **10b**, the reaction of **4e** (0.37 g, 0.79 mmol) and the lithium salt of **3** that was generated by the addition of a solution of BuLi in hexane (1.6 M; 0.37 mL, 0.60 mmol) to **3** (0.17 g, 0.50 mmol) in THF (15 mL) at –78 °C for 40 min produced **10e**.

Yield: 0.32 g, 0.40 mmol (83%).

IR (KBr): 2928, 1734, 1559, 1360, 1210, 1148, 913, 745 cm^{-1}.

^{1}H NMR: δ = 0.82 (s, 3 H), 0.97 (s, 3 H), 0.99 (s, 3 H), 1.20–1.80 (m, 12 H), 1.23 (s, 3 H), 1.67 (s, 3 H), 1.83–1.92 (m, 2 H), 2.00 (t, *J* = 6.2 Hz, 2 H), 2.06 (s, 3 H), 2.15–2.34 (m, 3 H), 2.16 (s, 3 H), 2.62 (dd, *J* = 13.8, 11.4 Hz, 1 H), 2.78–2.88 (m, 2 H), 3.20 (br d, *J* = 13.8 Hz, 1 H), 4.13 (ddd, *J* = 11.4, 10.5, 2.9 Hz, 1 H), 4.68 (dd, *J* = 9.0, 7.9 Hz, 1 H), 5.12 (d, *J* = 10.5 Hz, 1 H), 5.89 (s, 1 H), 5.97 (s, 2 H), 6.75 (d, *J* = 2.6 Hz, 1 H), 6.80 (dd, *J* = 8.4, 2.6 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.47–7.55 (m, 2 H), 7.61–7.68 (m, 1 H), 7.80–7.87 (m, 2 H).

^{13}C NMR: δ = 12.0, 12.4, 18.7, 19.1, 21.2, 21.6, 23.2, 26.0, 27.0, 27.5, 28.8, 28.9, 29.5, 32.8, 34.1, 36.8, 38.1, 38.6, 39.3, 42.8, 43.9, 49.7, 63.3, 82.7, 117.9, 118.7, 120.3, 121.6, 126.4, 128.8, 129.4, 129.8, 133.8, 135.7, 137.0, 137.2, 137.7, 138.1, 143.0, 148.1, 156.9, 164.7, 171.3.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{40}H_{53}O_4$ ($C_{46}H_{59}O_6S$ – $C_6H_6O_2S$): 596.3944; found: 596.3951.

Compound 1a

To a stirred solution of C_{15} sulfone **3** (0.96 g, 2.79 mmol) in THF (50 mL) at –20 °C was added *t*-BuOK (1.25 g, 11.16 mmol). The mixture was stirred at that temperature for 30 min, and a solution of **4a** (0.50 g, 2.79 mmol) in THF (10 mL) was added. The reaction mixture was stirred at –20 °C for 2 h, heated at 60 °C for 2 h, and cooled to r.t. The mixture was diluted with Et_2O, washed with aq HCl (1 M; 20 mL), dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **1a**.

Yield: 0.54 g, 1.81 mmol (65%).

Compound 1b

To a stirred solution of **10b** (1.42 g, 1.66 mmol) in THF (20 mL) was added DBU (0.50 mL, 3.31 mmol). The reaction mixture was stirred at r.t. for 3 h. The mixture was diluted with Et_2O, washed with aq HCl (1 M) and H_2O, dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **1b**.

Yield: 1.01 g, 1.41 mmol (85%).

IR (KBr): 2927, 1726, 1559, 1457, 1231, 1126 cm^{-1}.

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^{1}H NMR: δ = 0.85 (d, *J* = 6.0 Hz, 3 H), 0.86 (d, *J* = 6.0 Hz, 3 H), 0.87 (d, *J* = 6.4 Hz, 6 H), 0.98–1.87 (m, 27 H), 1.04 (s, 3 H), 1.24 (s, 3 H), 1.73 (s, 3 H), 1.97–2.06 (m, 2 H), 1.99 (s, 3 H), 2.02 (s, 3 H), 2.03 (s, 3 H), 2.10 (s, 3 H), 2.41 (s, 3 H), 2.59 (t, *J* = 6.6 Hz, 2 H), 6.09 (s, 1 H), 6.17 (A of ABq, J_{AB} = 15.9 Hz, 1 H), 6.19 (d, *J* = 11.2 Hz, 1 H), 6.30 (B of ABq, J_{AB} = 15.9 Hz, 1 H), 6.39 (d, *J* = 15.0 Hz, 1 H), 7.07 (dd, *J* = 15.0, 11.2 Hz, 1 H).

^{13}C NMR: δ = 11.8, 12.2, 12.9, 13.1, 14.0, 19.2, 19.6, 19.7, 19.7, 20.6, 21.0, 21.7, 22.6, 22.7, 23.9, 24.4, 24.8, 28.0, 29.0, 31.1, 32.7, 32.8, 33.1, 34.2, 37.3, 37.4, 37.4, 39.3, 39.6, 40.0, 74.9, 117.2, 117.4, 122.9, 125.1, 126.9, 128.9, 129.5, 130.1, 131.6, 135.0, 137.2, 137.6, 140.0, 140.4, 149.2, 154.8, 165.8.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{49}H_{77}O_3$: 713.5873; found: 713.5865.

Compound 1c

Following the general procedure for **1b**, the reaction of **10c** (1.52 g, 2.56 mmol) and DBU (0.78 g, 5.12 mmol) in THF (20 mL) at r.t. for 1 h produced **1c**.

Yield: 1.05 g, 2.28 mmol (89%).

IR (KBr): 2957, 1726, 1607, 1580, 1485, 1360, 1220, 1119, 965, 772 cm^{-1}.

^{1}H NMR: δ = 1.04 (s, 6 H), 1.33 (s, 9 H), 1.43–1.50 (m, 2 H), 1.57–1.68 (m, 2 H), 1.81 (s, 3 H), 1.97–2.06 (m, 2 H), 2.02 (s, 3 H), 2.42 (s, 3 H), 3.78 (s, 3 H), 6.02 (br s, 1 H), 6.16 (A of ABq, J_{AB} = 16.0 Hz, 1 H), 6.17 (d, *J* = 11.3 Hz, 1 H), 6.30 (B of ABq, J_{AB} = 16.0 Hz, 1 H), 6.39 (d, *J* = 15.0 Hz, 1 H), 6.70–6.77 (m, 1 H), 6.90–6.97 (m, 2 H), 7.08 (dd, *J* = 15.0, 11.3 Hz, 1 H).

^{13}C NMR: δ = 12.9, 14.0, 19.2, 21.7, 28.9, 30.0, 33.1, 34.2, 34.6, 39.6, 55.4, 110.4, 113.7, 117.7, 124.7, 129.0, 129.4, 130.1, 131.8, 134.8, 137.2, 137.6, 140.2, 142.5, 142.6, 155.3, 156.6, 165.9.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{31}H_{43}O_3$: 463.3212; found: 463.3216.

Compound 1d

Following the general procedure for **1b**, the reaction of **10d** (0.53 g, 0.65 mmol) and DBU (0.22 g, 1.43 mmol) in THF (20 mL) at 50 °C for 4 h produced **1d**.

Yield: 0.40 g, 0.60 mmol (92%).

IR (KBr): 2935, 1707, 1608, 1583, 1358, 1238, 1153, 966, 759 cm^{-1}.

^{1}H NMR: δ = 0.68 (s, 3 H), 0.80–2.08 (m, 32 H), 0.87 (d, *J* = 6.4 Hz, 6 H), 0.92 (d, *J* = 6.1 Hz, 3 H), 1.03 (s, 6 H), 1.56 (s, 3 H), 1.71 (s, 3 H), 2.00 (s, 3 H), 2.31–2.39 (m, 2 H), 2.35 (s, 3 H), 4.56–4.72 (m, 1 H), 5.38 (br s, 1 H), 5.75 (s, 1 H), 6.13 (d, *J* = 11.9 Hz, 1 H), 6.14 (A of ABq, J_{AB} = 15.7 Hz, 1 H), 6.27 (B of ABq, J_{AB} = 15.7 Hz, 1 H), 6.28 (d, *J* = 15.2 Hz, 1 H), 6.99 (dd, *J* = 15.2, 11.9 Hz, 1 H).

^{13}C NMR: δ = 11.9, 12.9, 13.8, 18.7, 19.2, 19.3, 21.0, 21.7, 22.5, 22.8, 23.8, 24.3, 28.0, 28.2, 28.9, 31.9, 31.9, 33.1, 34.2, 35.8, 36.2, 36.6, 37.1, 38.3, 39.5, 39.6, 39.8, 42.3, 50.1, 56.2, 56.7, 73.2, 119.0, 122.5, 128.6, 129.5, 129.9, 130.8, 135.3, 137.3, 137.7, 139.4, 139.9, 152.5, 166.5.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{47}H_{72}O_2$: 668.5532; found: 668.5527.

Compound 1e

Following the general procedure for **1b**, the reaction of **10e** (0.28 g, 0.40 mmol) and DBU (0.12 g, 0.80 mmol) in THF (10 mL) at r.t. for 3 h produced **1e**.

Yield: 0.18 g, 0.29 mmol (72%).

IR (KBr): 2928, 1728, 1578, 1491, 1355, 1240, 1124, 913, 743 cm^{-1}.

^{1}H NMR: δ = 0.83 (s, 3 H), 1.04 (br s, 6 H), 1.22–1.81 (m, 12 H), 1.73 (s, 3 H), 1.84–1.95 (m, 2 H), 1.98–2.11 (m, 2 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.13–2.36 (m, 3 H), 2.40 (s, 3 H), 2.82–2.94 (m, 2 H), 4.69 (dd, *J* = 9.0, 7.7 Hz, 1 H), 5.98 (s, 1 H), 6.17 (A of ABq, J_{AB} = 16.1 Hz, 1 H), 6.18 (d, *J* = 11.3 Hz, 1 H), 6.31 (B of ABq, J_{AB} = 16.1 Hz, 1 H), 6.36 (d, *J* = 15.0 Hz, 1 H), 6.83 (d, *J* = 2.6 Hz, 1 H), 6.86 (dd, *J* = 8.4, 2.6 Hz, 1 H), 7.07 (dd, *J* = 15.0, 11.3 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR: δ = 12.0, 12.9, 14.0, 19.2, 21.2, 21.7, 23.2, 26.0, 27.0, 27.5, 28.9, 29.5, 33.1, 34.2, 36.8, 38.2, 39.5, 42.8, 43.9, 49.7, 82.7, 117.3, 118.8, 121.7, 126.3, 129.0, 129.4, 130.1, 131.8, 134.8, 137.2, 137.5, 137.6, 138.0, 140.2, 148.4, 155.2, 165.8, 171.2.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{40}H_{52}O_4$: 596.3866; found: 596.3852.

Compound 11 (Entry 1, Table 2)

To a stirred solution of C_{15} sulfone **3** (3.19 g, 9.3 mmol) in THF (30 mL) at –78 °C was added a solution of BuLi in hexane (1.6 M; 6.4 mL, 10.2 mmol). The mixture was stirred at that temperature for 30 min and a solution of **6** (1.97 g, 11.1 mmol) in THF was added. The reaction mixture was stirred at –78 °C for 1 h, quenched with aq HCl (1 M; 50 mL), extracted with Et_2O, dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give the less polar diastereomer **11** (0.95 g, 2.16 mmol) and the more polar diastereomer **11** (1.91g, 4.33 mmol) in total 70% yield.

Data for the Less Polar Diastereomer 11

R_f 0.43 (3:2, EtOAc–hexanes).

^{1}H NMR: δ = 0.96 (s, 3 H), 0.98 (s, 3 H), 1.32 (s, 3 H), 1.42–1.48 (m, 2 H), 1.55–1.65 (m, 2 H), 1.66 (s, 3 H), 2.00 (t, *J* = 6.2 Hz, 2 H), 2.37 (s, 3 H), 4.50 (dd, *J* = 11.2, 2.9 Hz, 1 H), 5.18 (d, *J* = 11.2 Hz, 1 H), 5.58 (s, 1 H), 5.94 (br s, 1 H), 5.96 (A of ABq, J_{AB} = 16.3 Hz, 1 H), 6.07 (B of ABq, J_{AB} = 16.3 Hz, 1 H), 7.50–7.68 (m, 3 H), 7.80–7.83 (m, 2 H).

^{13}C NMR: δ = 12.3, 15.3, 19.1, 21.6, 28.8, 28.8, 32.9, 34.1, 39.4, 66.5, 81.6, 114.3, 119.5, 129.0, 129.1, 130.0, 130.1, 134.1, 135.3, 137.1, 138.0, 145.2, 166.0, 171.6.

Data for the More Polar Diastereomer 11

R_f 0.30 (3:2, EtOAc–hexanes).

IR (KBr): 2928, 1770, 1646, 1308, 1149 cm^{-1}.

^{1}H NMR: δ = 0.96 (s, 3 H), 1.00 (s, 3 H), 1.42–1.48 (m, 2 H), 1.55–1.63 (m, 2 H), 1.64 (s, 3 H), 1.71 (s, 3 H), 1.99 (t, *J* = 6.2 Hz, 2 H), 2.02 (s, 3 H), 4.35 (dd, *J* = 10.5, 1.7 Hz, 1 H), 4.74 (d, *J* = 10.5 Hz, 1 H), 5.79 (s, 1 H), 5.83 (d, *J* = 1.7 Hz, 1 H), 5.87 (A of ABq, J_{AB} = 16.1 Hz, 1 H), 6.16 (B of ABq, J_{AB} = 16.1 Hz, 1 H), 7.28–7.67 (m, 3 H), 7.83–7.86 (m, 2H).

^{13}C NMR: δ = 13.1, 13.7, 19.0, 21.5, 28.7, 28.8, 32.8, 34.0, 39.3, 65.5, 80.9, 112.1, 118.6, 127.6, 128.6, 129.8, 130.0, 130.2, 134.1, 135.4, 136.9, 144.9, 165.3, 171.9.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{27}O_2$ ($C_{26}H_{33}SO_4$ – $C_6H_6SO_2$): 299.2011; found: 299.2009.

Compounds 12a and 12b (Entry 1, Table 2)

To a solution of **11** (a 1:2 stereoisomeric mixture, 1.69 g, 3.8 mmol) in THF (20 mL) was added DBU (1.7 mL, 11.5 mmol). The reaction mixture was stirred at r.t. for 5 h, diluted with Et_2O, washed with aq HCl (1 M), dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **12a** (0.08 g, 0.27 mmol, 7%) and **12b** (0.81 g, 2.7 mmol, 71%).

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Data for 12a

^{1}H NMR: δ = 1.05 (s, 6 H), 1.47–1.51 (m, 2 H), 1.62–1.67 (m, 2 H), 1.76 (s, 3 H), 2.04–2.09 (m, 2 H), 2.07 (s, 3 H), 2.20 (s, 3 H), 5.91 (s, 1 H), 6.27 (A of ABq, J_{AB} = 12.2 Hz, 1 H), 6.40 (A of ABq, J_{AB} = 15.9 Hz, 1 H), 6.49 (B of ABq, J_{AB} = 12.2 Hz, 1 H), 6.62 (B of ABq, J_{AB} = 15.9 Hz, 1 H).

^{13}C NMR: δ = 11.7, 19.1, 21.1, 21.9, 29.0, 33.1, 34.2, 39.4, 106.3, 115.4, 120.9, 128.9, 130.6, 132.0, 138.0, 141.1, 148.9, 154.1, 169.2.

Data for 12b

IR (KBr): 2933, 1776, 1749, 1542 cm^{-1}.

^{1}H NMR: δ = 1.04 (s, 6 H), 1.46–1.50 (m, 2 H), 1.59–1.67 (m, 2 H), 1.73 (s, 3 H), 2.03 (s, 3 H), 2.00–2.07 (m, 2 H), 2.20 (s, 3 H), 5.91 (s, 1 H), 6.20 (A of ABq, J_{AB} = 12.0 Hz, 1 H), 6.25 (A of ABq, J_{AB} = 15.9 Hz, 1 H), 6.38 (B of ABq, J_{AB} = 15.9 Hz, 1 H), 6.58 (B of ABq, J_{AB} = 12.0 Hz, 1 H).

^{13}C NMR: δ = 11.6, 12.8, 19.1, 21.8, 29.0, 33.2, 34.2, 39.6, 107.7, 115.3, 122.5, 130.3, 131.1, 137.0, 137.4, 142.1, 149.5, 153.8, 169.2.

HRMS (CI$^+$): *m*/*z* calcd for $C_{20}H_{27}O_2$: 299.2011; found: 299.2009.

Compound 14

To a stirred solution of C_{15} sulfone **3** (1.00 g, 2.9 mmol) in THF (30 mL) at –78 °C was added a solution of BuLi in hexane (1.6 M; 2 mL, 3.19 mmol). The mixture was stirred at that temperature for 30 min and a solution of **13** (1.10 g, 3.8 mmol) in THF was added. The reaction mixture was stirred at –78 °C for 0.5 h and at r.t. for 1 h, quenched with aq HCl (1 M; 50 mL), extracted with Et_2O, dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by SiO_2 column chromatography to give **14**.

Yield: 1.16 g, 2.1 mmol (74%).

IR (KBr): 2934, 1722, 1636, 1447, 1306, 1244 cm^{-1}.

^{1}H NMR: δ = 0.96 (s, 3 H), 0.97 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.29 (d, *J* = 1.3 Hz, 3 H), 1.43–1.47 (m, 2 H), 1.56–1.62 (m, 2 H), 1.65 (s, 3 H), 1.97–2.03 (m, 2 H), 2.01 (s, 3 H), 2.87 (dd, *J* = 12.7, 11.0 Hz, 1 H), 3.23 (dd, *J* = 12.7, 3.9 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.23 (dq, J_d = 2.4, J_q = 7.1 Hz, 2 H), 4.32 (ddd, *J* = 11.0, 10.8, 3.9 Hz, 1 H), 5.21 (d, *J* = 10.8, 1 H), 5.95 (A of ABq, J_{AB} = 16.2 Hz, 1 H), 5.99 (B of ABq, J_{AB} = 16.2 Hz, 1 H), 7.46–7.53 (m, 2 H), 7.58–7.65 (m, 1 H), 7.80–7.86 (m, 2 H).

^{13}C NMR: δ = 12.3, 13.9, 14.0, 19.2, 21.5, 21.8, 28.8, 32.8, 34.1, 34.2, 39.4, 61.0, 61.2, 63.7, 120.1, 127.4, 128.6, 128.7, 129.3, 129.6, 133.6, 135.8, 137.2, 137.4, 142.6, 152.4, 164.9, 165.0.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{25}H_{37}O_4$ ($C_{31}H_{43}SO_6$ – $C_6H_6SO_2$): 401.2692; found: 401.2700.

Compound 15

To a solution of diester **14** (1.70 g, 3.13 mmol) in *i*-PrOH (20 mL) was added pulverized KOH (0.88 g, 15.7 mmol). The reaction mixture was stirred at r.t. for 27 h, and treated with aq HCl (3 M; 50 mL) to adjust the pH to ca. 1. The mixture was extracted with EtOAc, dried (Na_2SO_4), filtered, and concd under reduced pressure. The crude product was purified by recrystallization from $CHCl_3$ to give diacid **15**.

Yield: 0.99 g, 1.82 mmol (58%).

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