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 C3 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 C15 allylic sulfone 3 to give the C20 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 dehydrodrosulfonation reaction. The Julia olefination re-action of the C3 diester 13 and the C15 allylic sulfone 3 produced the known C20 diacid 15 which underwent stereoselective mono-decarboxylation to provide either 13-(Z)-retinoic acid (2) or all-(E)-retinoic acid (I) 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 prophylactic 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. 5 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 dehydrodrosulfonation 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 C15 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 C3 allylic halide units 4 and 5 in a highly stereoselective manner. (Z)-4-Halo-2-butenolic 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-butenolic 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-butenolic 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-butenolic 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-butenolic acid (4a) in 43% yield. The furanone compound 7, on the other hand, can be exclusively and efficiently obtained from 3-methyl-2-butenolic acid by allylic di-bromination with 2 equiv of NBS and washing with a base solution to produce the mono-brominated furanone.
The Julia coupling of the C₁₅ allylic sulfone 3 and the (E)-C₅ unit 4 produced the C₂₀ 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 C₁₅ sulfone 3 and the C₅ 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 C₂₀ coupling product 10a (R = H) and the subsequent dehydrosulfonation reaction (entry 1, Table 1). The one pot olefination reaction of the C₁₅ sulfone 3 and the C₅ 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)-C₅ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound ROH</th>
<th>Yield 4 (%)</th>
<th>Yield 10 (%)</th>
<th>Yield 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a H₂O</td>
<td>–</td>
<td>–</td>
<td>65&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>b dl-Tocopherol</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
<td>74&lt;sup&gt;c&lt;/sup&gt;</td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>c BHA</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>d β-Cholesterol</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>92&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>e β-Estradiol</td>
<td>65&lt;sup&gt;e&lt;/sup&gt;</td>
<td>83&lt;sup&gt;f&lt;/sup&gt;</td>
<td>72&lt;sup&gt;f&lt;/sup&gt;</td>
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<sup>a</sup> (1) Compound 3 and t-BuOK (4 equiv) in THF at −20 °C; (2) 4a in THF at −20 °C to 60 °C.
<sup>b</sup> (1) ROH and BuLi in THF at −78 °C; (2) 9 (2 equiv) in THF at −78 °C.
<sup>c</sup> (1) Compound 3 and BuLi in THF at −78 °C; (2) 4b in THF at −78 °C.
<sup>d</sup> The ester of β-estradiol acetate was obtained.
<sup>e</sup> (1) Compound 3 and BuLi in THF at −78 °C; (2) 4 in THF at −78 °C.
<sup>f</sup> (1) Compound 10 and DBU (2 equiv) in THF.

Novel but rather unstable (E)-4-bromo-3-methyl-2-butenoic chloride (9), which was prepared from the corresponding acid 4a by chlorination with oxalyl chloride, was efficiently utilized without purification in the preparation of various (E)-C₅ 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),<sup>17</sup> β-cholesterol, and β-estradiol<sup>18</sup> selectively replaced the acyl chloride of compound 9 to give the (E)-C₅ ester derivatives 4b–e in good yields (65–99%).

The one-pot olefination procedure can be undertaken in one pot using excess base such as t-BuOK. The reaction of the C₁₅ sulfone 3 and the C₅ acid 4 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 C₂₀ coupling product 10a (R = H) and the subsequent dehydrosulfonation reaction (entry 1, Table 1). The one pot olefination reaction of the C₁₅ sulfone 3 and the C₅ 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.

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<td>e β-Estradiol</td>
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<sup>c</sup> (1) Compound 3 and BuLi in THF at −78 °C; (2) 4b in THF at −78 °C.
<sup>d</sup> The ester of β-estradiol acetate was obtained.
<sup>e</sup> (1) Compound 3 and BuLi in THF at −78 °C; (2) 4 in THF at −78 °C.
<sup>f</sup> (1) Compound 10 and DBU (2 equiv) in THF.

(1) β-Estradiol and NaH in THF at 0 °C; (2) 9 (2 equiv) in THF; (3) Ac₂O and pyridine in CH₂Cl₂.
such as DBU to give the esters 1b–e of all-(E)-retinoic acid in 72–92% yields.

The coupling of the C₁₅ sulfone 3 and 5-bromo-4-methyl-5H-furan-2-one (6) gave the C₂₀ 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 ¹H 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 carbocation 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 compared to the synthesis based on the Wittig reaction.²⁰

It has been recently reported that the C₅ₐ 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 C₂₀ diacid 15, in which the C₅ diester 13 played a key role. Lewis acid (FeCl₃) mediated coupling of diethyl malonate and acetone,²² followed by allylic bromination²³ of the resulting diethyl 2-isopropylidene-malonate provided the C₅ diester unit 13 in 57% overall yield. The Julia coupling reaction of the C₁₅ sulfone 3 and the C₃ diester 13 using BuLi in THF at −78 °C (75% yield) or t-BuOK in DMF at −20 °C (60% yield) produced the C₂₀ sulfone compound 14. Alkaline hydrolysis of the C₂₀ sulfone diester 14 accompanied the dehydrosulfonation reaction to give the C₂₀ diacid 15, which was easily purified by recrystallization from CHCl₃. 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 C₅ 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.

### Table 2 Coupling Reaction of the C₁₅ Sulfone 3 and the C₅ Furanone 6, and the Dehydrosulfonation Reaction of 11 to give the Furanone Derivatives 12a and 12b of Retinoic Acid (see Scheme 3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Coupling condition of 3 and 6</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi–THF</td>
<td>70 (1:2)</td>
<td>78 (1:10)</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOK–DMF</td>
<td>49 (1:3)</td>
<td>68 (1:10)</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi–THF, HMPA</td>
<td>66 (2:1)</td>
<td>73 (1:10)</td>
</tr>
</tbody>
</table>

### Scheme 3 Equilibration of anti-11 to syn-11 through aromatization, and the dehydrosulfonation reaction to produce 12a,b.
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) 14 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 CHCl3, 58%; (c) 15 in refluxing lutidine, 63%; (d) 15 and pyridine in CH2Cl2, 67%.

The C5 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 cooled under reduced pressure, and used without purification. 1H (300 MHz) and 13C NMR (75.5 MHz) spectra were recorded in CDCl3, 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 vents used as reaction media were dried over pre-dried molecular

Compounds 4a and 7
To a solution of 3,3-dimethylacrylic acid (3.00 g, 30.0 mmol) in CCl4 (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 reduced pressure. The crude product was purified by SiO2 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 CH2Cl2, dried (Na2SO4), filtered, and concd under reduced pressure. The crude product was purified by SiO2 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 (Na2SO4), filtered, and concd under reduced pressure. The crude product was purified by SiO2 column chromatography to give 4b.

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

IR (KBr): 2927, 1733, 1651, 1458, 1378, 1222, 1129 cm–1.

1H 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).

13C 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, 37.5, 38.0, 39.4, 75.0, 117.3, 118.5, 123.0, 124.9, 140.2, 149.4, 154.7, 164.5.

HRMS (FAB+): m/z calc for C23H35BrO2: 591.3413; found: 591.3423.

Compounds 4d
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 cm–1.

1H 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).

13C 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.


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-cholestereol which was generated by the addition of a BuLi solution in hexane (1.6 M; 1.8 mL, 3.0 mmol) to β-cholestereol (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.

1H 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).

13C 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 (Cl–): m/z calc for C34H56BrO3: 547.3151; found: 547.3156.

Compounds 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 CH2Cl2 (10 mL) produced 4e.

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

IR (KBr): 2929, 1734, 1491, 1247, 1124, 913, 744 cm–1.

1H 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).
**Compound 10b**

To a stirred solution of C$_{15}$ sulfoxide 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$_2$O, dried (Na$_2$SO$_4$), filtered, and concd under reduced pressure. The crude product was purified by SiO$_2$ column chromatography to give 10b.

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

IR (KBr): 2927, 1731, 1647, 1377, 1302, 1249, 1149, 1130 cm$^{-1}$.

1H NMR: $\delta$ = 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), 0.98–1.01 (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).

13C NMR: $\delta$ = 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, 71.7, 117.2, 117.7, 120.4, 122.9, 124.9, 126.7, 128.8, 129.4, 126.9, 153.7, 153.7, 157.2, 142.0, 142.8, 149.2, 156.3, 164.6.

HRMS (FAB$^+$): $m/z$ calcd for C$_{49}$H$_{77}$O$_3$: 699.5818; found: 699.5816.

**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$^{-1}$.

1H NMR: $\delta$ = 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), 1.66–1.78 (m, 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).

13C NMR: $\delta$ = 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, 128.9, 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$_{40}$H$_{53}$O$_4$: 596.3944; found: 596.3945.

**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 (0.357 g, 1.07 mmol) in THF (15 mL) at –78 °C for 1 h produced 10d.

Yield: 0.60 g, 0.74 mmol (69%).
1H 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, JAB = 15.9 Hz, 1 H), 6.19 (d, J = 11.2 Hz, 1 H), 6.30 (B of ABq, JAB = 15.9 Hz, 1 H), 6.39 (d, J = 15.0 Hz, 1 H), 7.07 (dd, J = 11.2, 15.0 Hz, 1 H).

IR (KBr): 2957, 1726, 1607, 1580, 1485, 1360, 1220, 1119, 965, 743 cm⁻¹.

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

To a stirred solution of C15 sulfone (0.95 g, 2.16 mmol) and DBU (1.7 mL, 11.5 mmol). The reaction mixture was stirred at r.t. for 5 h, diluted with Et2O, washed with aq HCl (1 M; 50 mL), extracted with Et2O, dried (Na2SO4), filtered, and concd under reduced pressure. The crude product was purified by SiO2 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.

IR (KBr): 2935, 1707, 1608, 1533, 1288, 1193, 966, 759 cm⁻¹.

1H 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 (s, 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, JAB = 16.3 Hz, 1 H), 6.07 (B of ABq, JAB = 16.3 Hz, 1 H), 7.50–7.68 (m, 3 H), 7.80–7.83 (m, 2 H).

13C NMR: δ = 12.3, 15.3, 19.1, 21.6, 28.8, 28.8, 32.9, 34.1, 39.4, 66.5, 81.1, 114.3, 119.5, 129.0, 130.1, 130.0, 134.1, 135.3, 137.1, 138.0, 145.2, 166.0, 171.6.


Compound 1c
Following the general procedure for 1b, the reaction of 10c (1.52 g, 2.26 mmol) and DBU (0.78 g, 5.12 mmol) in THF (20 mL) at r.t. for 3 h produced 1c.


IR (KBr): 2928, 1728, 1578, 1491, 1355, 1240, 1124, 913, 743 cm⁻¹.

1H 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, JAB = 16.1 Hz, 1 H), 6.18 (d, J = 11.3 Hz, 1 H), 6.31 (B of ABq, JAB = 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).

IR (KBr): 2957, 1726, 1607, 1533, 1288, 1193, 966, 743 cm⁻¹.

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

To a solution of C15 sulfone (0.81 g, 2.7 mmol, 7%) and DBU (0.27 g, 0.82 mmol) in THF was added. The reaction 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 EtO2, dried (Na2SO4), filtered, and concd under reduced pressure. The crude product was purified by SiO2 column chromatography to give the less polar diastereomer 11 (0.83 g, 2.28 mmol) and the more polar diastereomer 11 (1.73 g, 4.55 mmol).

IR (KBr): 2957, 1726, 1607, 1533, 1288, 1193, 966, 743 cm⁻¹.
Data for 12a

$^1$H NMR: $\delta = 1.05$ (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: $\delta = 11.7$, 19.1, 21.1, 21.9, 29.0, 33.1, 34.2, 39.4, 106.3, 115.4, 120.9, 129.8, 130.6, 132.0, 138.0, 141.1, 148.9, 154.1, 169.2.

Data for 12b

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

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

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References


(18) The phenolic OH of β-estradiol reacted with the compound 9 to give the (E)-C₅ ester derivative 4e.


