

An Improved Convergent Strategy for the Synthesis of Oligoprenols

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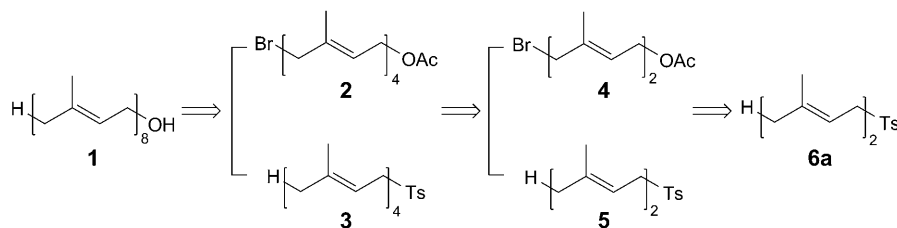
A practical and highly regio- and stereoselective synthesis of oligoprenols starting from commercially available geraniol is described. The convergent synthetic strategy features the iterative allyl-allyl coupling of monomers easily derived from geraniol that contain one reacting terminal functional group and the repetitive reductive elimination of the *p*-toluenesulfonyl (Ts) groups.

Introduction. – Every member of the (all-*E*)-oligoprenol family is an indispensable precursor for the synthesis of isoprenoids of biological importance [1]. However, most of them, especially those bearing long carbon skeletons such as (all-*E*)-nonaprenol and decaprenol, are minutely occurring in quantity in natural products [2]. Consequently, the development of efficient synthetic methods for the preparation of (all-*E*)-polyprenyl alcohols is apparently desirable. To present, several synthetic strategies have been applied in the synthesis of (all-*E*)-oligoprenols including the construction of the prenyl structure step by step at the end of alcohol [3] and elongation of the carbon chain by coupling reactions [4]. But all of them have certain disadvantages such as long routes [3a], difficulties in the synthesis of key intermediates [4b], and low yields in terminal functionalizations [4a]. Reported herein is an efficient and convergent route for the synthesis of (all-*E*)-oligoprenols that have long polyprenoid chains based on the *Biellmann–Ducep* coupling and its strategical importance is demonstrated by the syntheses of (all-*E*)-octaprenol and (all-*E*)-decaprenol starting from commercially available geraniol.

Results and Discussion. – The strategy for the total synthesis of (all-*E*)-octaprenol (**1**) involves the iterative allyl-allyl coupling of monomers and the repetitive removal of *p*-toluenesulfonyl (Ts) groups as shown in *Scheme 1*. (all-*E*)-Octaprenol (**1**) with a C₄₀ linear carbon skeleton should be available from the coupling of allylic bromide **2** and allylic sulfone **3** each of which have four prenyl units. By means of the similar coupling reaction, the C₂₀ building blocks should be obtained from the two C₁₀ units **4** and **5** derived from the geraniol derivative **6a** respectively. As described in the retrosynthetic analysis (*Scheme 1*), our proposed synthetic scheme included a convergent synthetic strategy based on geraniol (**6**), a most readily available natural building block [5].

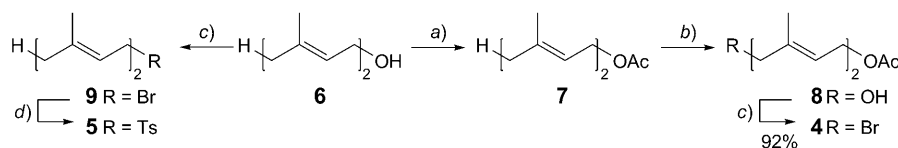
The synthesis of the two precursors for the elaboration of the polyprenyl chain is illustrated in *Scheme 2*. (all-*E*)-8-Bromogeraniol acetate (**4**) was obtained from geraniol (**6**) in 72% overall yield according to an improved literature procedure

Scheme 1



described by *Sato et al.* [2b]. The second precursor, (all-*E*)-geranyl tosyl sulfone (**5**) was easily prepared from sodium *p*-toluenesulfinate and (all-*E*)-geranyl bromide (**9**) in DMF, which was prepared from bromination of **6** with CBr₄ and polymer-supported triphenylphosphine [6] in CH₂Cl₂ at 0°.

Scheme 2

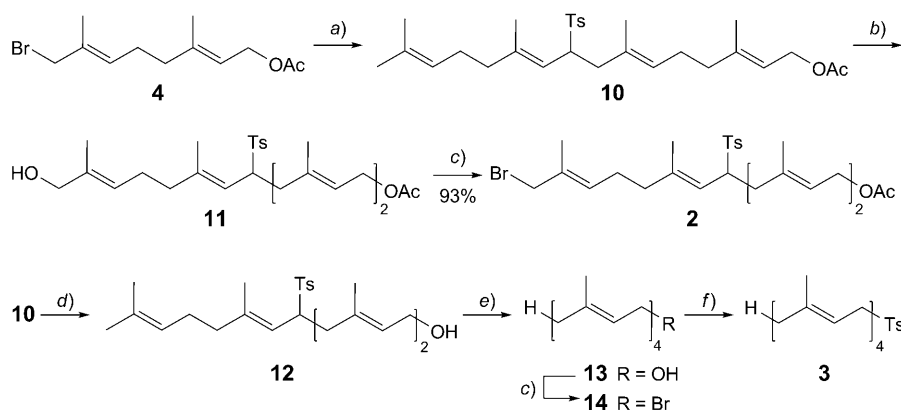


a) Ac₂O, pyridine, r.t., 6 h; 98%. b) SeO₂, *t*-BuOOH, salicylic acid, CH₂Cl₂, r.t., 20 h; 80%. c) CBr₄, •-C₆H₄PPh₂, CH₂Cl₂, 0°, 4 h. d) Sodium *p*-toluenesulfinate, DMF, r.t., 20 h; 89% over two steps.

With the electrophilic C₁₀ monomer **4** and nucleophilic monomer **5** in hands, we focused our attention on the construction of two C₂₀ units **2** and **3** via the allyl-allyl coupling reaction as shown in Scheme 3. The carbanion of the readily available geranyl sulfone **5** was coupled with allylic bromide **4** in anhydrous DMF in the presence of NaH at –5° to produce the chain-extended sulfonyl acetate **10** in 78% yield. Also other bases, including BuLi, LDA, and KHMDS gave good yields at different temperatures (Table). Allylic bromide **2** was prepared from **10** via oxidation with *t*-BuOOH in the presence of SeO₂ and salicylic acid [7], followed by bromination with CBr₄ and polymer-supported triphenylphosphine in CH₂Cl₂. Alcohol **12** was obtained quantitatively by the hydrolysis of **10** with MeONa. Different conditions were explored to perform the desulfonylation reaction of **12** into (all-*E*)-geranylgeraniol (**13**) with use of various reductive reagents such as Li/EtNH₂ [8a], Na/EtOH [8b], Na/naphthalin [8c], and LiHBET₃/Pd(dppp)Cl₂ [9]. LiHBET₃ in the presence of [Pd(dppp)Cl₂] in THF at 0° afforded the best results (90% yield). The resulting alcohol **13** was converted to sulfone **3** in 85% yield via a similar procedure to the preparation of **5**.

The required C₄₀ skeleton **15** for the synthesis of (all-*E*)-octaprenol (**1**) was built up by a second allyl-allyl coupling of the carbanion of allyl sulfone **3** with the allyl bromide **2** under the same conditions used for the synthesis of **10**, in 70% yield, as outlined in Scheme 4. The two arylsulfonyl groups were simultaneously removed by an analogous process as used for the preparation of **13**, after base-hydrolysis of the ester group in the chain-elongated bisulfonyl acetate **15**, to produce pure alcohol **1** in 84% yield over two steps.

Scheme 3



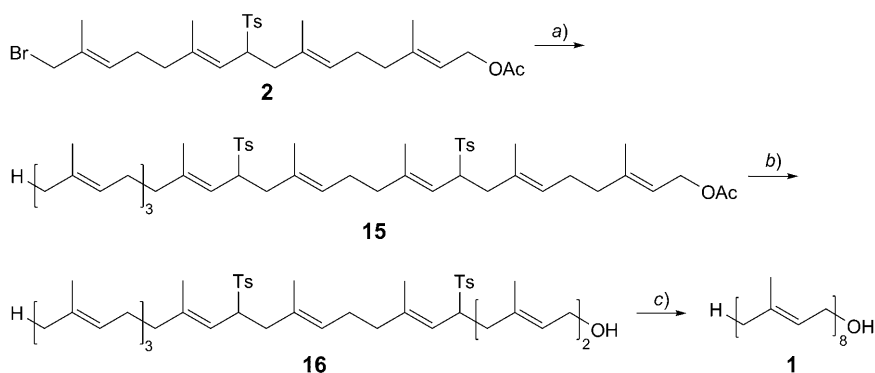
a) **5**, NaH, DMF, -5° , 16 h; 78%. b) SeO_2 , *t*-BuOOH, salicylic acid, CH_2Cl_2 , r.t., 10 h; 78%. c) CBr_4 , $\bullet\text{-C}_6\text{H}_4\text{PPh}_2$, CH_2Cl_2 , 0° , 4 h. d) MeONa, MeOH, r.t., 2 h; quant. e) LiHBEt_3 , 10% Pd(dppp)Cl_2 , 0° – r.t., 10 h; 90%. f) Sodium *p*-toluenesulfonate, DMF, r.t., 20 h; 85% over two steps.

Table. Base-Catalyzed Coupling of **4** and **5**

Entry	Base	Temperature	<i>t</i> [h]	Yield [%] ^a
1	BuLi ^b	-78°	4.5	77
2	LDA ^b	-78°	3.5	79
3	KHMDS ^b	-78°	3	72
4	60% NaH ^c	-5°	16	78

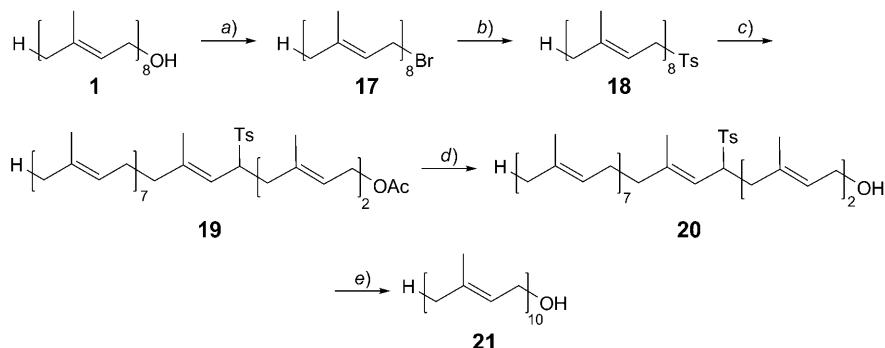
^a) Yields of isolated **10**. ^b) All reactions were conducted with base (1.05 equiv.), **5** (1 equiv.), **4** (1.1 equiv.) in anh. THF. ^c) Reaction was carried out with base (1 equiv.), **4** (1.05 equiv.), **5** (1.0 equiv.) in anh. DMF.

Scheme 4



a) **3**, NaH, DMF, -5° , 20 h; 70%. b) NaOMe, MeOH, r.t., 2 h; quant. c) LiHBEt_3 , 10% Pd(dppp)Cl_2 , 0° – r.t., 12 h; 84%.

Scheme 5



Conclusions. – In conclusion, for the synthesis of (all-*E*)-oligoprenols with long linear polyprenoid frameworks, we have developed a convergent strategy, which was exemplified by the total syntheses of (all-*E*)-octaprenol and (all-*E*)-decaprenol *via* selectively coupling of monomers, easily derived from geraniol. Compared with the method where the prenyl units are introduced step by step, our present method is more efficient and practical.

Experimental Part

(2E,6E)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl Acetate (**8**). Salicylic acid (1.38 g, 0.01 mol), SeO₂ (333 mg, 3 mmol) and 65% *t*-BuOOH (34.6 g, 0.25 mol) were stirred in CH₂Cl₂ (150 ml) for 15 min at r.t., then **7** (19.6 g, 0.1 mol) was added. After being stirred for another 20 h at r.t., the mixture was concentrated under reduce pressure below 30°. Et₂O (30 ml) was added, and the org. layer was washed with 10% KOH (3 × 15 ml), H₂O (3 × 20 ml), and brine (20 ml), dried (MgSO₄), and concentrated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 6:1) to afford **8** (16.9 g, 80%). Colorless oil. IR (film): 3427 (OH). ¹H-NMR (CDCl₃): 5.34–5.37 (*m*, 2 C=CH); 4.58 (*d*, ³*J* = 7.3, CH₂OAc); 3.99

(s, CH₂O); 2.17 (m, CH₂); 2.09 (m, CH₂, COMe); 1.71 (s, Me); 1.67 (s, Me). EI-MS: 152 (2, [M – HOAc]⁺), 84 (49), 58 (51), 43 (100).

(2E,6E)-8-Bromo-3,7-dimethylocta-2,6-dien-1-yl Acetate (**4**). To a stirred soln. of **8** (2.97 g, 14 mmol) in CH₂Cl₂ (30 ml), successively CBr₄ (6.05 g, 18.2 mmol) and polymer-supported Ph₃P (7.0 g, 21 mmol) were added at 0°. The suspension was stirred at 0° for 4 h and then filtered. The solvent was evaporated and the excess of CBr₄ was removed under reduce pressure to afford **4** (3.6 g, 92%, purity 98% by HPLC). Colorless oil. The product was used without further purification. IR (film): 1739 (CO), 1233 (MeCOOR), 666, 607. ¹H-NMR (CDCl₃): 5.57 (t, ³J = 7.3, C=CH); 5.34 (t, ³J = 7.1, C=CH); 4.58 (d, ³J = 7.3, CH₂OAc); 3.96 (s, CH₂); 2.06–2.18 (m, 2 CH₂, COMe); 1.71 (s, Me); 1.75 (s, Me). ¹³C-NMR (CDCl₃): 170.95 (CO); 141.19 (=C); 132.42 (=C); 130.39 (=CH); 118.91 (=CH); 61.21 (CH₂O); 41.49 (BrCH₂); 38.53 (=C(Me)CH₂); 26.37 (=CHCH₂); 21.00 (COMe); 16.40 (Me); 14.65 (Me). EI-MS: 216, 214 (1, [M – HOAc]⁺), 195 (1), 135 (83), 43 (100).

(2E)-3,7-Dimethylocta-2,6-dien-1-yl 4-Methylphenyl Sulfone (**5**). To a stirred soln. of geraniol (15.4 g, 0.1 mol) in CH₂Cl₂ (200 ml), successively CBr₄ (43.2 g, 0.13 mol) and polymer-supported Ph₃P (50 g, 0.15 mol) were added at 0°. The suspension was stirred at 0° for 4 h and then filtered. The solvent was evaporated and the excess of CBr₄ was removed under reduce pressure. Without further purification, the product **9** was added into the soln. of sodium *p*-toluenesulfonate (28 g, 0.16 mol) in DMF (200 ml) at 0°. The resulting mixture was stirred for 20 h at r.t., then poured into brine (200 ml), and filtered to give **5** (26 g, 89%, purity 93% by HPLC). White solid. M.p. 44.0–44.5° from hexane ([10]: 44–45°). IR (KBr): 1315, 1149 (SO₂). ¹H-NMR (CDCl₃): 7.74 (d, ³J = 6.4, 2 arom. H); 7.32 (d, ³J = 6.4, 2 arom. H); 5.18 (t, ³J = 6.3, C=CH); 5.04 (m, C=CH); 3.79 (t, ³J = 6.3, TsCH₂); 2.45 (s, Me–Ar); 2.02 (m, 2 CH₂); 1.69 (s, Me); 1.59 (s, Me); 1.34 (s, Me). EI-MS: 292 (3, M⁺), 224 (16), 137 (19), 81 (28), 69 (100).

(2E,6E,10E)-3,7,11,15-Tetramethyl-9-[(4-methylphenyl)sulfonyl]hexadeca-2,6,10,14-tetraen-1-yl Acetate (**10**). To a stirred soln. of **4** (0.99 g, 3.6 mmol) and **5** (0.99 g, 3.4 mmol) in anh. DMF (10 ml) was added 60% NaH (0.136 g, 3.4 mmol) at –5° under N₂, and the mixture was stirred for 16 h, then poured into brine (50 ml) and extracted with Et₂O (3 × 10 ml). The org. layer was washed with H₂O (3 × 20 ml) and brine (20 ml), dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by CC (SiO₂; PE/EA 10:1) to give **10** (1.29 g, 78%). Colorless oil. IR (film): 1738 (CO), 1312, 1232 (MeCOOR), 1144 (SO₂). ¹H-NMR (CDCl₃): 7.70 (d, ³J = 8.2, 2 arom. H); 7.29 (d, ³J = 8.2, 2 arom. H); 5.29 (t, ³J = 7.1, C=CH); 5.11 (t, ³J = 6.6, C=CH); 5.01 (m, C=CH); 4.87 (d, ³J = 10.4, C=CH); 4.55 (d, ³J = 7.1, CH₂OAc); 3.87 (m, CHSO₂); 2.85 (dd, ³J = 2.4, ²J = –12.8, 1 H of CH₂); 2.43 (s, Me–Ar); 2.25 (dd, ³J = 3.2, ²J = –12.8, 1 H of CH₂); 1.93–2.06 (m, 4 CH₂, COMe); 1.19, 1.52, 1.59, 1.66 (4s, 5 Me). ¹³C-NMR (CDCl₃): 171.02 (CO); 144.81 (arom. C); 144.23 (=C); 141.78 (2 =C); 135.04 (SO₂Ar); 131.82 (Me₂C=CH); 130.43 (2 arom. CH); 129.30 (arom. CH); 129.25 (arom. CH); 127.50 (=CH); 123.64 (=CH); 118.43 (=CH); 117.39 (=CH); 63.46 (CH₂O); 61.28 (SO₂CH); 39.67 (=C(Me)CH₂CH); 39.18 (=C(Me)CH₂); 37.54 (ArCHCH₂); 26.32 (=CHCH₂); 26.23 (=CHCH₂); 25.67 (Me); 21.62 (Me–Ar); 21.02 (COMe); 17.64 (Me); 16.40 (Me); 16.39 (Me); 15.93 (Me). ESI-MS: 486.3 (20, M⁺), 426.4 (39), 224.4 (100).

(2E,6E,10E,14E)-16-Bromo-3,7,11,15-tetramethyl-9-[(4-methylphenyl)sulfonyl]hexadeca-2,6,10,14-tetraen-1-yl Acetate (**2**). To a stirred soln. of 65% *t*-BuOOH (1.66 g, 12 mmol) in CH₂Cl₂ (30 ml), salicylic acid (44 mg, 0.32 mmol) and SeO₂ (14 mg, 0.13 mmol) were added successively. The mixture was stirred for 15 min at r.t., and then **10** (1.56 g, 3.2 mmol) was added. The resulting mixture was stirred for another 10 h. The solvent was evaporated *in vacuo* below 30°, then Et₂O (80 ml) was added. The org. layer was washed with 10% KOH (4 × 20 ml), H₂O (3 × 20 ml), and brine (10 ml), dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 7:1) to give **11** (1.25 g, 78%). Then, to a stirred soln. of **11** (0.93 g, 1.85 mmol) in CH₂Cl₂ (10 ml), CBr₄ (0.8 g, 2.41 mmol) and polymer-supported Ph₃P (0.93 g, 2.78 mmol) were added successively at 0°. The suspension was stirred at 0° for 4 h and then filtered. The solvent was evaporated, and the excess of CBr₄ was removed under reduce pressure to give **2** (0.97 g, 93%, purity 97% by HPLC). Colorless oil. IR (film): 1736 (CO), 1312, 1233 (MeCOOR), 1144 (SO₂), 665 (Br). ¹H-NMR (CDCl₃): 7.70 (d, ³J = 8.0, 2 arom. H); 7.31 (d, ³J = 8.0, 2 arom. H); 5.51 (t, ³J = 7.1, C=CH); 5.30 (t, ³J = 6.9, C=CH); 5.12 (t, ³J = 6.8, C=CH); 4.89 (d, ³J = 10.4, C=CH); 4.56 (d, ³J = 7.1, CH₂O); 3.95 (s, CH₂Br); 3.87 (m, CHSO₂); 2.84 (dd, ³J = 2.4, ²J = –12.8, 1 H of CH₂); 2.45 (s, Me–Ar); 2.25 (dd, ³J = 3.2, ²J = –12.8, 1 H of CH₂); 1.99–2.07 (m, 4

CH₂, COMe); 1.24, 1.52, 1.67, 1.74 (4s, 4 Me). ¹³C-NMR (CDCl₃): 171.08 (CO); 144.16 (arom. C); 141.77 (=C); 135.05 (SO₂Ar); 132.52 (=C); 130.41 (=C); 130.17 (=C); 129.66 (2 arom. CH); 129.39 (arom. CH); 129.20 (arom. CH); 128.47 (=CH); 127.56 (=CH); 118.48 (=CH); 117.87 (=CH); 63.38 (CH₂O); 61.03 (SO₂CH); 41.38 (BrCH₂); 39.22 (=C(Me)CH₂); 38.77 (=C(Me)CH₂); 37.66 (=C(Me)CH₂); 26.59 (=CHCH₂); 26.07 (=CHCH₂); 21.66 (Me–Ar); 21.07 (COMe); 16.44 (Me); 16.26 (Me); 15.98 (Me); 14.68 (Me). EI-MS: 486 (1, [M–Br+1]⁺), 351, 349 (29), 283, 281 (32), 95, 93 (100). Anal. calc. for C₂₉H₄₁BrO₄S (565.60): C 61.58, H 7.31, Br 14.13; found: C 61.45, H 7.43, Br 14.33.

(2E,6E,10E)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraen-1-ol (**13**). To a stirred soln. of **10** (1 g, 2.06 mmol) in MeOH (10 ml) was added MeONa (6 mg, 0.2 mmol), and the mixture was stirred for 2 h to give deprotected product **12** in quant. yield. Without further purification, the residue was dissolved in dry THF (60 ml) in the presence of [Pd(dppp)Cl₂] (120 mg, 0.2 mmol) at 0° under N₂. LiHBEt₃ (1.0M in THF, 4.1 ml, 4.1 mmol) was added dropwise over 10 min. The resulting mixture was allowed to warm to r.t. over 3 h and then stirred for another 7 h. The reaction was quenched with 3M NaOH (20 ml) and small amount of KCN, and extracted with Et₂O (3 × 20 ml). The combined org. phase was washed with H₂O (3 × 15 ml) and brine (10 ml), dried (MgSO₄), and evaporated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 7:1) to give **13** (0.54 g, 90%). Colorless oil. IR (film): 3331 (OH). ¹H-NMR (CDCl₃): 5.42 (t, ³J = 6.6, C=CH); 5.11–5.09 (m, 3 C=CH); 4.15 (d, ³J = 6.6, CH₂O); 2.13–1.96 (m, 6 CH₂); 1.68–1.58 (m, 5 Me); 1.33 (br., OH). ¹³C-NMR (CDCl₃): 139.84 (=C); 135.42 (=C); 134.94 (=C); 131.27 (=C); 124.43 (=CH); 124.27 (=CH); 123.77 (=CH); 123.34 (=CH); 59.42 (CH₂O); 39.76 (=C(Me)CH₂); 39.74 (=C(Me)CH₂); 39.58 (=C(Me)CH₂); 26.78 (=CHCH₂); 26.72 (=CHCH₂); 26.35 (=CHCH₂); 25.72 (Me); 17.70 (Me); 16.31 (2 Me); 16.04 (Me). EI-MS: 290 (1, M⁺), 272 (2), 81 (43), 69 (100).

1-Methyl-4-[[[(2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl]sulfonyl]benzene (**3**). To a stirred soln. of **13** (4.35 g, 15 mmol) in CH₂Cl₂ (40 ml), CBr₄ (6.48 g, 19.5 mmol) and polymer-supported Ph₃P (7.5 g, 22.5 mmol) were added successively at 0°. The suspension was stirred at 0° for 4 h and then filtered. The solvent was evaporated, and the excess of CBr₄ was removed under reduce pressure. Without further purification, the product **14** was added into a soln. of sodium *p*-toluenesulfinate (4.0 g, 22.5 mmol) in DMF (30 ml) at 0°. The resulting mixture was stirred for 20 h at r.t., then poured into brine (30 ml), and extracted with Et₂O (3 × 50 ml). The combined org. phase was washed sequentially with H₂O (3 × 20 ml) and brine (20 ml), dried (MgSO₄), and evaporated to give **3** (5.46 g, 85%, purity 94% by HPLC). Colorless oil. IR (film): 1317, 1149. ¹H-NMR (CDCl₃): 7.66 (d, ³J = 7.2, 2 arom. H); 7.24 (d, ³J = 7.2, 2 arom. H); 5.11 (t, ³J = 7.2, C=CH); 4.98–5.04 (m, C=CH); 3.71 (d, ³J = 7.2, CH₂SO₂); 2.37 (s, Me–Ar); 1.88–2.01 (m, 6 CH₂); 1.60 (s, Me); 1.49–1.52 (m, 3 Me); 1.26 (s, Me). ¹³C-NMR (CDCl₃): 146.22 (arom. C); 144.42 (=C); 135.85 (=C); 135.69 (=C); 135.02 (SO₂Ar); 131.23 (=C); 129.55 (2 arom. CH); 128.57 (2 arom. CH); 124.37 (=CH); 124.11 (=CH); 123.39 (=CH); 110.47 (=CH); 56.15 (TsCH₂); 39.73 (3 =C(Me)CH₂); 26.77 (=CHCH₂); 26.61 (=CHCH₂); 26.23 (=CHCH₂); 25.72 (Me); 21.64 (Me–Ar); 17.70 (Me); 16.26 (Me); 16.03 (Me); 16.01 (Me). EI-MS: 428 (7, M⁺), 273 (7), 137 (31), 91 (30), 69 (100).

(2E,6E,10E,14E,18E,22E,26E)-3,7,11,15,19,23,27,31-Octamethyl-9,17-bis[(4-methylphenyl)sulfonyl]dotriaconta-2,6,10,14,18,22,26,30-octaen-1-yl Acetate (**15**). To a stirred soln. of **2** (1.15 g, 2.03 mmol) and **3** (0.67 g, 1.56 mmol) in anh. DMF (10 ml) was added 60% NaH (68 mg, 1.7 mmol) at –5° under N₂, and the mixture was stirred for 20 h at –5°, then poured into brine (15 ml), and extracted with Et₂O (3 × 10 ml). The combined org. phase was washed with H₂O (3 × 10 ml) and brine (10 ml), dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 10:1) to give **15** (1.00 g, 70%). Colorless oil. IR (film): 1737 (CO), 1321, 1300, 1232 (MeCOOR), 1144 (SO₂). ¹H-NMR (CDCl₃): 7.72 (d, ³J = 7.8, 4 arom. H); 7.36 (d, ³J = 7.8, 4 arom. H); 5.32 (t, ³J = 7.2, C=CH); 5.09–5.11 (m, 4 C=CH); 4.83–4.91 (m, 2 C=CH); 4.56 (d, ³J = 7.2, CH₂O); 3.84–3.86 (m, 2 H of TsCH); 2.79–2.94 (m, 2 H of TsCHCH₂); 2.43, 2.44 (2s, 2 Me–Ar); 2.19–2.31 (m, 2 H of TsCHCH₂); 1.92–2.07 (m, 10 CH₂, COMe); 1.60–1.68 (m, 6 Me); 1.59 (2s, 2 Me); 1.22 (s, Me). ¹³C-NMR (CDCl₃): 171.15 (CO); 146.12 (arom. C); 145.14 (arom. C); 144.64 (=C); 144.59 (=C); 144.33 (=C); 135.85 (SO₂Ar); 135.70 (SO₂Ar); 135.10 (=C); 134.95 (=C); 131.32 (=C); 131.25 (=C); 131.23 (=C); 130.55 (arom. CH); 130.52 (arom. CH); 129.25 (arom. CH); 129.20 (arom. CH); 128.71 (=CH); 127.56 (=CH); 124.32 (=CH); 124.01 (=CH); 118.37 (=CH); 117.41 (=CH); 117.37 (=CH); 117.21 (=CH); 63.38

(CH₂O); 61.31 (TsCH); 61.30 (TsCH); 39.79 (=C(Me)CH₂); 39.71 (=C(Me)CH₂); 39.41 (=C(Me)CH₂); 39.19 (=C(Me)CH₂); 37.27 (=C(Me)CH₂); 37.54 (=C(Me)CH₂); 37.65 (=C(Me)CH₂); 26.73 (=CHCH₂); 26.61 (=CHCH₂); 26.56 (=CHCH₂); 26.45 (=CHCH₂); 26.23 (=CHCH₂); 25.73 (Me); 21.66 (Me–Ar); 21.65 (Me–Ar); 21.07 (COMe); 17.71 (Me); 16.52 (Me); 16.47 (Me); 16.44 (Me); 16.36 (2 Me); 15.96 (Me); 15.88 (Me). MALDI-MS: 935.9 ([M + Na]⁺, C₅₆H₈₀NaO₆S₂⁺). Anal. calc. for C₅₆H₈₀O₆S₂ (913.36): C 73.64, H 8.83; found: C 73.48, H 8.97.

(2E,6E,10E,14E,18E,22E,26E)-3,7,11,15,19,23,27,31-Octamethyldotriaconta-2,6,10,14,18,22,26,30-octaen-1-ol (**1**). To a stirred soln. of **15** (6.1 g, 6.68 mmol) in MeOH (50 ml), MeONa (80 mg, 1.3 mmol) was added, and the mixture was stirred for 4 h at r.t. to give deprotected product **16** in quant. yield. Without further purification, the residue was dissolved in dry THF (150 ml) in the presence of Pd(dppp)Cl₂ (394 mg, 0.67 mmol) at 0° under N₂. LiHBEt₃ (1.0M in THF, 22.0 ml, 22.0 mmol) was added dropwise over 15 min. The resulting mixture was allowed to warm to r.t. over 3 h and then stirred for a further 9 h. The reaction was quenched with 3M NaOH (60 ml) and a small amount of KCN, and extracted with Et₂O (3 × 50 ml). The combined org. phase was washed with H₂O (2 × 45 ml) and brine (30 ml), dried (MgSO₄), and evaporated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 7:1) to give **1** (3.15 g, 84%). Colorless oil. IR (film): 3343 (OH). ¹H-NMR (CDCl₃): 5.42 (t, ³J = 6.8, C=CH); 5.12–5.10 (m, 7 C=CH); 4.15 (d, ³J = 6.8, CH₂O); 1.97–2.09 (m, 14 CH₂); 1.68 (s, 2 Me); 1.60 (s, 7 Me). ¹³C-NMR (CDCl₃): 139.83 (=C); 135.42 (=C); 135.02 (2 =C); 134.94 (2 =C); 134.89 (=C); 131.25 (Me₂C=CH); 124.43 (=CH); 124.27 (2 =CH); 124.18 (2 =CH); 123.79 (2 =CH); 123.34 (=CH); 59.44 (CH₂O); 39.76 (3 =C(Me)CH₂); 39.74 (3 =C(Me)CH₂); 39.58 (=C(Me)CH₂); 26.78 (2 =CHCH₂); 26.72 (3 =CHCH₂); 26.69 (=CHCH₂); 26.35 (=CHCH₂); 25.72 (Me); 17.70 (Me); 16.31 (6 Me); 16.04 (Me). MS (ESI): 585.9 (59, [M + Na]⁺), 473.4 (100), 399.4 (85).

1-Methyl-4-[[[(2E,6E,10E,14E,18E,22E,26E)-3,7,11,15,19,23,27,31-Octamethyldotriaconta-2,6,10,14,18,22,26,30-octaen-1-yl]sulfonyl]benzene (**18**). To a stirred soln. of **1** (1.7 g, 3.0 mmol) in CH₂Cl₂ (15 ml), CBr₄ (1.29 g, 3.9 mmol) and polymer-supported Ph₃P (1.5 g, 4.5 mmol) were added successively at 0°. The suspension was stirred at 0° for 4 h and then filtered. The solvent was evaporated, and the excess of CBr₄ was removed under reduced pressure. Without further purification, **17** was added into the soln. of sodium *p*-toluenesulfinate (0.80 g, 4.5 mmol) in DMF (30 ml) at 0°. The resulting mixture was stirred for 20 h at r.t., then poured into brine (30 ml), and extracted with Et₂O (3 × 50 ml). The combined org. phase was washed sequentially with H₂O (3 × 20 ml) and brine (20 ml), dried (MgSO₄), and evaporated to give **18** (1.87 g, 89%, purity 93% by HPLC). Colorless oil. IR (film): 1318, 1150 (SO₂). ¹H-NMR (CDCl₃): 7.66 (d, ³J = 8.0, 2 arom. H); 7.24 (d, ³J = 8.0, 2 arom. H); 5.11 (t, ³J = 7.8, C=CH); 4.99–5.05 (m, 7 C=CH); 3.71 (d, ³J = 7.8, SO₂CH₂); 2.37 (s, Me–Ar); 1.89–2.08 (m, 14 CH₂); 1.26, 1.50, 1.60 (3s, 9 Me). ¹³C-NMR (CDCl₃): 146.21 (arom. C); 144.40 (=C); 135.89 (=C); 135.72 (=C); 135.07 (SO₂Ar); 134.95 (=C); 134.92 (=C); 134.89 (=C); 134.86 (=C); 131.20 (=C); 129.55 (2 arom. CH); 128.57 (2 arom. CH); 124.42 (=CH); 124.28 (2 =CH); 124.24 (2 =CH); 124.10 (=CH); 123.36 (=CH); 110.48 (=CH); 56.16 (SO₂CH₂); 39.76 (6 =C(Me)CH₂); 39.74 (=C(Me)CH₂); 26.79 (2 =CHCH₂); 26.73 (2 =CHCH₂); 26.68 (2 =CHCH₂); 26.24 (=CHCH₂); 25.71 (Me); 21.64 (Me–Ar); 17.70 (Me); 16.27 (6 Me); 16.04 (Me). ESI-MS: 723.9 (3, [M + Na]⁺), 672.9 (5), 448.9 (9), 135 (49), 69 (100).

(2E,6E,10E,14E,18E,22E,26E,30E,34E)-3,7,11,15,19,23,27,31,35,39-Decamethyl-9-[(4-methylphenyl)sulfonyl]tetraconta-2,6,10,14,18,22,26,30,34,38-decaen-1-yl Acetate (**19**). To a stirred soln. of **18** (0.2 g, 0.29 mmol) and **4** (80 mg, 0.29 mmol) in anhyd. DMF (5 ml) was added *t*-BuOK (40 mg, 0.35 mmol) at –20° under N₂. The resulting soln. was stirred for 2 h at –10°, and then additional **4** (40 mg, 0.15 mmol) was added. After being stirred for another 3 h, the mixture was poured into brine (10 ml), and extracted with Et₂O (3 × 5 ml). The combined org. phase was washed with H₂O (3 × 10 ml) and brine (10 ml), dried (MgSO₄) and evaporated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 7:1) to give **19** (164 mg, 63%). Colorless oil. IR (film): 1740 (CO), 1318, 1301, 1231 (MeCOOR), 1144 (SO₂). ¹H-NMR (CDCl₃): 7.72 (d, ³J = 8.0, 2 arom. H); 7.31 (d, ³J = 8.0, 2 arom. H); 5.32 (t, ³J = 7.6, C=CH); 5.13–5.10 (m, 8 C=CH); 4.91 (d, ³J = 10.4, C=CH); 4.58 (d, ³J = 7.6, CH₂O); 3.89–3.84 (m, SO₂CH); 2.88 (dd, ³J = 2.4, ²J = –12.4, 1 H of CH₂); 2.45 (s, Me–Ar); 2.27 (dd, ³J = 2.4, ²J = –12.4, 1 H of CH₂); 1.93–2.07 (m, 16 CH₂, COMe); 1.22, 1.54, 1.60, 1.62, 1.68, 1.70 (6s, 11 Me). ¹³C-NMR (CDCl₃): 171.04 (CO); 144.90 (arom. C); 144.21 (=C); 141.80 (=C); 135.64 (2 =C); 135.11 (SO₂Ar); 134.97 (2 =C); 134.93 (2 =C); 134.90 (=C); 131.21 (=C); 130.48 (=C); 129.29 (2 arom. CH); 127.51 (2 arom. CH);

124.42 (=CH); 124.28 (3 =CH); 124.06 (2 =CH); 123.48 (2 =CH); 118.50 (=CH); 117.39 (=CH); 63.50 (CH₂O); 61.30 (SO₂CH); 39.75 (6 =C(Me)CH₂); 39.20 (=C(Me)CH₂); 37.54 (=C(Me)CH₂); 26.77 (3 =CHCH₂); 26.70 (3 =CHCH₂); 26.45 (=CHCH₂); 26.26 (=CHCH₂); 25.70 (Me); 21.62 (Me–Ar); 21.02 (COMe); 17.68 (Me); 16.47 (7 Me); 16.42 (Me); 16.03 (Me). MALDI-MS: 917.7 ([M + Na]⁺, C₅₉H₉₀NaO₄S⁺).

(2E,6E,10E,14E,18E,22E,26E,30E,34E)-3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaen-1-ol (**21**). To a stirred soln. of **19** (112 mg, 0.125 mmol) in MeOH (2 ml) and Me₂CO (3 ml), MeONa (2 mg, 0.034 mmol) was added, and the resulting mixture was stirred for 10 h at r.t. to give deprotected product **20** in quant. yield. Without further purification, the residue was dissolved in dry THF (10 ml) in the presence of [Pd(dppp)Cl₂] (738 mg, 0.0125 mmol) at 0° under N₂. LiHBEt₃ (1.0M in THF, 0.25 ml, 0.25 mmol) was added dropwise over 10 min. The resulting mixture was allowed to warm to r.t. over 3 h and then stirred for another 7 h. The reaction was quenched with 3M NaOH (1.5 ml) and small amount of KCN and extracted with Et₂O (3 × 10 ml). The combined org. phase was washed with H₂O (3 × 15 ml) and brine (10 ml), dried (MgSO₄), and evaporated *in vacuo*. The crude product was purified by CC (SiO₂; PE/AcOEt 10:1) to give **21** (71 mg, 81%). White solid. M.p. 41.9–42.7° from MeOH (lit.: 42.5–43.5° [2b]). IR (film): 3330 (OH). ¹H-NMR (CDCl₃): 5.43 (t, ³J = 7.2, C=CH); 5.11–5.14 (m, 9 C=CH); 4.16 (d, ³J = 6.8, CH₂O); 2.14–1.99 (m, 18 CH₂); 1.69 (s, 2 Me); 1.61 (s, 9 Me). ¹³C-NMR (CDCl₃): 139.85 (=C); 135.42 (=C); 135.03 (6 =C); 134.95 (=C); 131.26 (=C); 124.42 (2 =CH); 124.27 (4 =CH); 124.17 (2 =CH); 123.77 (=CH); 123.32 (=CH); 59.42 (CH₂O); 39.76 (=C(Me)CH₂); 39.58 (8 =C(Me)CH₂); 26.78 (3 =CHCH₂); 26.72 (3 =CHCH₂); 26.68 (2 =CHCH₂); 26.34 (=CHCH₂); 25.72 (Me); 17.70 (Me); 16.31 (Me); 16.04 (8 Me). ESI-MS: 722.0 (62, [M + Na]⁺), 609.6 (100), 535.6 (81).

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