An Improved Convergent Strategy for the Synthesis of Oligoprenols

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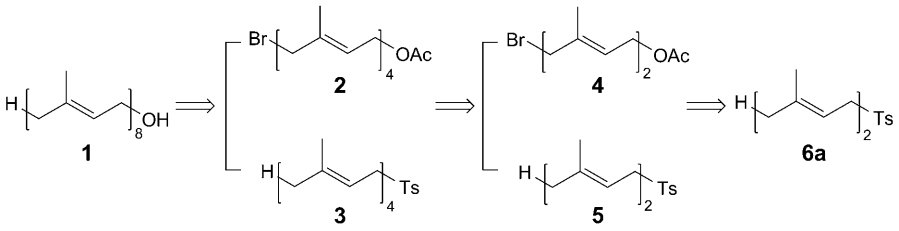
A practical and highly regio- and stereoselective synthesis of oligoprenols starting from commercially available geraniol is described. The convergent synthetic strategy features the iterative allyl-allyl coupling of monomers easily derived from geraniol that contain one reacting terminal functional 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 occurrent 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 C_{40} 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 C_{20} building blocks should be obtained from the two C_{10} 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].

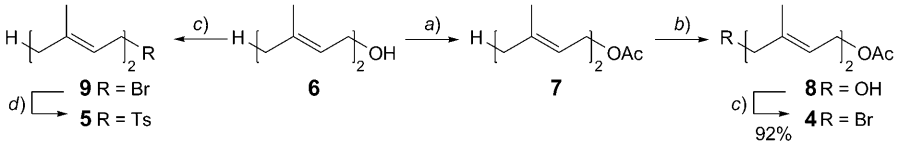
The synthesis of the two precursors for the elaboration of the polyprenyl chain is illustrated in *Scheme 2*. (all-*E*)-8-Bromogeraniol acetate (**4**) was obtained from geraniol (**6**) in 72% overall yield according to an improved literature procedure

Scheme 1



described by *Sato et al.* [2b]. The second precursor, (all-*E*)-geranyl tolyl 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 CBr_4 and polymer-supported triphenylphosphine [6] in CH_2Cl_2 at 0°.

Scheme 2

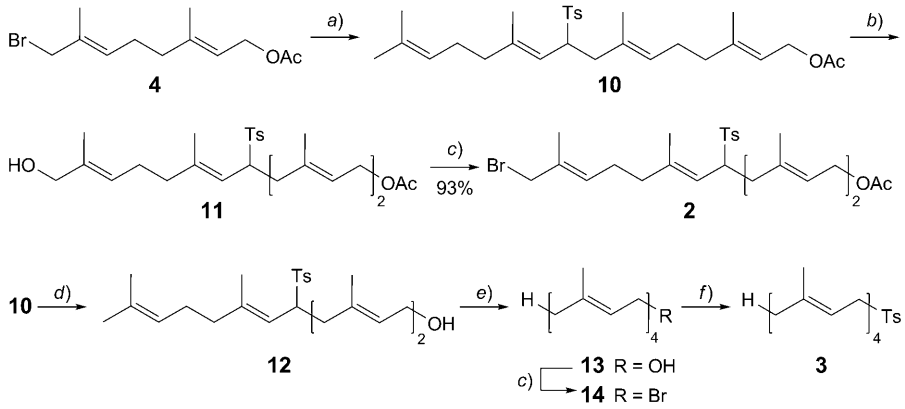


a) Ac_2O, pyridine, r.t., 6 h; 98%. *b*) SeO_2, *t*-BuOOH, salicylic acid, CH_2Cl_2, r.t., 20 h; 80%. *c*) CBr_4, •-$C_6H_4PPh_2$, CH_2Cl_2, 0°, 4 h. *d*) Sodium *p*-toluenesulfinate, DMF, r.t., 20 h; 89% over two steps.

With the electrophilic C_{10} monomer **4** and nucleophilic monomer **5** in hands, we focused our attention on the construction of two C_{20} 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 SeO_2 and salicylic acid [7], followed by bromination with CBr_4 and polymer-supported triphenylphosphine in CH_2Cl_2. 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/$EtNH_2$ [8a], Na/EtOH [8b], Na/naphthalin [8c], and $LiHBEt_3$/Pd(dppp)Cl_2 [9]. $LiHBEt_3$ in the presence of [Pd(dppp)Cl_2] 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 C_{40} 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



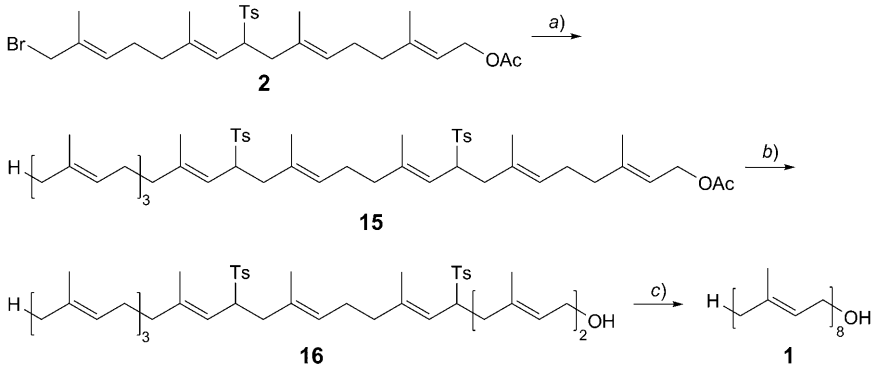
a) **5**, NaH, DMF, −5°, 16 h; 78%. *b*) SeO_2, *t*-BuOOH, salicylic acid, CH_2Cl_2, r.t., 10 h; 78%. *c*) CBr_4, •-$C_6H_4PPh_2$, CH_2Cl_2, 0°, 4 h. *d*) MeONa, MeOH, r.t., 2 h; quant. *e*) $LiHBEt_3$, 10% Pd(dppp)Cl_2, 0° – r.t., 10 h; 90%. *f*) Sodium *p*-toluenesulfinate, DMF, r.t., 20 h; 85% over two steps.

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

Entry	Base	Temperature	*t* [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.

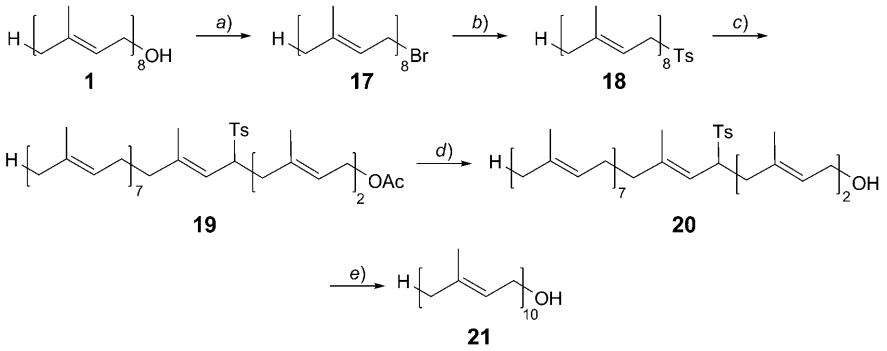
Scheme 4



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%.

Finally, (all-*E*)-decaprenol (**21**) was obtained in an overall yield of 45% from **1** (*Scheme 5*) by a sequence completely parallel to that depicted in *Scheme 3*. The structure of the synthetic decaprenol was confirmed by comparison of its spectroscopic data (IR, NMR, and MS) with those disclosed in the literature [2b].

Scheme 5



a) CBr_4, •-$C_6H_4PPh_2$, CH_2Cl_2, 0°, 4 h. *b*) Sodium *p*-toluenesulfinate, DMF, r.t., 20 h; 89% over two steps. *c*) **4**, *t*-BuOK, DMF, −10°, 5 h; 63%. *d*) NaOMe, MeOH, r.t., 10 h; quant. *e*) $LiHBEt_3$, 10% $Pd(dppp)Cl_2$, 0° – r.t., 10 h; 81%.

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

General. THF was distilled from Na/benzophenone under N_2. DMF and CH_2Cl_2 was freshly distilled from CaH_2. Petroleum ether (PE) for column chromatography (CC) had a boiling point of 60–90°. All other reagents and chemicals were obtained from commercial suppliers and used without further purification. TLC: silica gel GF_{254} plates. HPLC analyses were performed on *Shimadzu-LC-10AT* liquid chromatograph with *Spd-10A-UV-VIS* detector. M.p.: *WRB-1B* digital melting-point apparatus. IR Spectra: *Jasco/IR-4200*. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AV II 400*; at 400 MHz, referenced to internal Me_4Si (^{1}H); at 125 MHz, referenced to the ^{13}C signals of the solvent (^{13}C); chemical shifts (δ) are reported in parts per million [ppm] and coupling constants (J) in Hertz [Hz]. MS Spectra: *Waters 2695* with *Waters 2487 Dual λ Absorbance* spectrometer. GC/MS Spectra: *Agilent Technologies 6890N GC* system with *5975* inter MS spectrometer.

*(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl Acetate* (**8**). Salicylic acid (1.38 g, 0.01 mol), SeO_2 (333 mg, 3 mmol) and 65% *t*-BuOOH (34.6 g, 0.25 mol) were stirred in CH_2Cl_2 (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°. Et_2O (30 ml) was added, and the org. layer was washed with 10% KOH (3 × 15 ml), H_2O (3 × 20 ml), and brine (20 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 6:1) to afford **8** (16.9 g, 80%). Colorless oil. IR (film): 3427 (OH). ^{1}H-NMR ($CDCl_3$): 5.34–5.37 (*m*, 2 C=CH); 4.58 (*d*, ^3J = 7.3, CH_2OAc); 3.99

(*s*, CH_2O); 2.17 (*m*, CH_2); 2.09 (*m*, CH_2, COMe); 1.71 (*s*, Me); 1.67 (*s*, Me). EI-MS: 152 (2, $[M-HOAc]^+$), 84 (49), 58 (51), 43 (100).

*(2*E*,6*E*)-8-Bromo-3,7-dimethylocta-2,6-dien-1-yl Acetate* (**4**). To a stirred soln. of **8** (2.97 g, 14 mmol) in CH_2Cl_2 (30 ml), successively CBr_4 (6.05 g, 18.2 mmol) and polymer-supported Ph_3P (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 CBr_4 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. ^{1}H-NMR ($CDCl_3$): 5.57 (*t*, $^3J = 7.3$, C=CH); 5.34 (*t*, $^3J = 7.1$, C=CH); 4.58 (*d*, $^3J = 7.3$, CH_2OAc); 3.96 (*s*, CH_2); 2.06–2.18 (*m*, 2 CH_2, COMe); 1.71 (*s*, Me); 1.75 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 170.95 (CO); 141.19 (=C); 132.42 (=C); 130.39 (=CH); 118.91 (=CH); 61.21 (CH_2O); 41.49 ($BrCH_2$); 38.53 (=C(Me)CH_2); 26.37 (=CHCH_2); 21.00 (CO*Me*); 16.40 (Me); 14.65 (Me). EI-MS: 216, 214 (1, $[M-HOAc]^+$), 195 (1), 135 (83), 43 (100).

*(2*E*)-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 CH_2Cl_2 (200 ml), successively CBr_4 (43.2 g, 0.13 mol) and polymer-supported Ph_3P (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 CBr_4 was removed under reduce pressure. Without further purification, the product **9** was added into the soln. of sodium *p*-toluenesulfinate (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 (SO_2). ^{1}H-NMR ($CDCl_3$): 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*, $^3J = 6.3$, TsCH_2); 2.45 (*s*, *Me*–Ar); 2.02 (*m*, 2 CH_2); 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).

*(2*E*,6*E*,10*E*)-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 N_2, and the mixture was stirred for 16 h, then poured into brine (50 ml) and extracted with Et_2O (3 × 10 ml). The org. layer was washed with H_2O (3 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by CC (SiO_2; PE/EA 10:1) to give **10** (1.29 g, 78%). Colorless oil. IR (film): 1738 (CO), 1312, 1232 (MeCOOR), 1144 (SO_2). ^{1}H-NMR ($CDCl_3$): 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*, $^3J = 7.1$, CH_2OAc); 3.87 (*m*, $CHSO_2$); 2.85 (*dd*, $^3J = 2.4$, $^2J = -12.8$, 1 H of CH_2); 2.43 (*s*, *Me*–Ar); 2.25 (*dd*, $^3J = 3.2$, $^2J = -12.8$, 1 H of CH_2); 1.93–2.06 (*m*, 4 CH_2, COMe); 1.19, 1.52, 1.59, 1.66 (4*s*, 5 Me). ^{13}C-NMR ($CDCl_3$): 171.02 (CO); 144.81 (arom. C); 144.23 (=C); 141.78 (2 =C); 135.04 (SO_2Ar); 131.82 (Me_2C=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 (CH_2O); 61.28 (SO_2CH); 39.67 (=C(Me)CH_2CH); 39.18 (=C(Me)CH_2); 37.54 (ArCHCH_2); 26.32 (=CHCH_2); 26.23 (=CHCH_2); 25.67 (Me); 21.62 (*Me*–Ar); 21.02 (CO*Me*); 17.64 (Me); 16.40 (Me); 16.39 (Me); 15.93 (Me). ESI-MS: 486.3 (20, M^+), 426.4 (39), 224.4 (100).

*(2*E*,6*E*,10*E*,14*E*)-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 CH_2Cl_2 (30 ml), salicylic acid (44 mg, 0.32 mmol) and SeO_2 (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 Et_2O (80 ml) was added. The org. layer was washed with 10% KOH (4 × 20 ml), H_2O (3 × 20 ml), and brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; 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 CH_2Cl_2 (10 ml), CBr_4 (0.8 g, 2.41 mmol) and polymer-supported Ph_3P (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 CBr_4 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 (SO_2), 665 (Br). ^{1}H-NMR ($CDCl_3$): 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*, $^3J = 7.1$, CH_2O); 3.95 (*s*, CH_2Br); 3.87 (*m*, $CHSO_2$); 2.84 (*dd*, $^3J = 2.4$, $^2J = -12.8$, 1 H of CH_2); 2.45 (*s*, *Me*–Ar); 2.25 (*dd*, $^3J = 3.2$, $^2J = -12.8$, 1 H of CH_2); 1.99–2.07 (*m*, 4

CH_2, COMe); 1.24, 1.52, 1.67, 1.74 (4*s*, 4 Me). ^{13}C-NMR ($CDCl_3$): 171.08 (CO); 144.16 (arom. C); 141.77 (=C); 135.05 (SO_2Ar); 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 (CH_2O); 61.03 (SO_2CH); 41.38 ($BrCH_2$); 39.22 (=C(Me)*C*H_2); 38.77 (=C(Me)*C*H_2); 37.66 (=C(Me)*C*H_2); 26.59 (=CH*C*H_2); 26.07 (=CH*C*H_2); 21.66 (*Me*–Ar); 21.07 (CO*Me*); 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 $C_{29}H_{41}BrO_4S$ (565.60): C 61.58, H 7.31, Br 14.13; found: C 61.45, H 7.43, Br 14.33.

*(2*E*,6*E*,10*E*)-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)Cl_2] (120 mg, 0.2 mmol) at 0° under N_2. $LiHBEt_3$ (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 Et_2O (3 × 20 ml). The combined org. phase was washed with H_2O (3 × 15 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 7:1) to give **13** (0.54 g, 90%). Colorless oil. IR (film): 3331 (OH). ^{1}H-NMR ($CDCl_3$): 5.42 (*t*, ^3J = 6.6, C=CH); 5.11–5.09 (*m*, 3 C=CH); 4.15 (*d*, ^3J = 6.6, CH_2O); 2.13–1.96 (*m*, 6 CH_2); 1.68–1.58 (*m*, 5 Me); 1.33 (br., OH). ^{13}C-NMR ($CDCl_3$): 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 (CH_2O); 39.76 (=C(Me)*C*H_2); 39.74 (=C(Me)*C*H_2); 39.58 (=C(Me)*C*H_2); 26.78 (=CH*C*H_2); 26.72 (=CH*C*H_2); 26.35 (=CH*C*H_2); 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-{[(2*E*,6*E*,10*E*)-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 CH_2Cl_2 (40 ml), CBr_4 (6.48 g, 19.5 mmol) and polymer-supported Ph_3P (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 CBr_4 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 Et_2O (3 × 50 ml). The combined org. phase was washed sequentially with H_2O (3 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated to give **3** (5.46 g, 85%, purity 94% by HPLC). Colorless oil. IR (film): 1317, 1149. ^{1}H-NMR ($CDCl_3$): 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, CH_2SO_2); 2.37 (*s*, *Me*–Ar); 1.88–2.01 (*m*, 6 CH_2); 1.60 (*s*, Me); 1.49–1.52 (*m*, 3 Me); 1.26 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 146.22 (arom. C); 144.42 (=C); 135.85 (=C); 135.69 (=C); 135.02 (SO_2Ar); 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 (Ts*C*H_2); 39.73 (3 =C(Me)*C*H_2); 26.77 (=CH*C*H_2); 26.61 (=CH*C*H_2); 26.23 (=CH*C*H_2); 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).

*(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-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 N_2, and the mixture was stirred for 20 h at −5°, then poured into brine (15 ml), and extracted with Et_2O (3 × 10 ml). The combined org. phase was washed with H_2O (3 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 10:1) to give **15** (1.00 g, 70%). Colorless oil. IR (film): 1737 (CO), 1321, 1300, 1232 (MeCOOR), 1144 (SO_2). ^{1}H-NMR ($CDCl_3$): 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, CH_2O); 3.84–3.86 (*m*, 2 H of Ts*CH*); 2.79–2.94 (*m*, 2 H of TsCH*C*H_2); 2.43, 2.44 (2*s*, 2 *Me*–Ar); 2.19–2.31 (*m*, 2 H of TsCH*C*H_2); 1.92–2.07 (*m*, 10 CH_2, COMe); 1.60–1.68 (*m*, 6 Me); 1.59 (2*s*, 2 Me); 1.22 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 171.15 (CO); 146.12 (arom. C); 145.14 (arom. C); 144.64 (=C); 144.59 (=C); 144.33 (=C); 135.85 (SO_2Ar); 135.70 (SO_2Ar); 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

(CH_2O); 61.31 (Ts*C*H); 61.30 (Ts*C*H); 39.79 (=C(Me)*C*H_2); 39.71 (=C(Me)*C*H_2); 39.41 (=C(Me)*C*H_2); 39.19 (=C(Me)*C*H_2); 37.27 (=C(Me)*C*H_2); 37.54 (=C(Me)*C*H_2); 37.65 (=C(Me)*C*H_2); 26.73 (=CH*C*H_2); 26.61 (=CH*C*H_2); 26.56 (=CH*C*H_2); 26.45 (=CH*C*H_2); 26.23 (=CH*C*H_2); 25.73 (Me); 21.66 (*Me*–Ar); 21.65 (*Me*–Ar); 21.07 (CO*Me*); 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 ($[M+Na]^+$, $C_{56}H_{80}NaO_6S_2^+$). Anal. calc. for $C_{56}H_{80}O_6S_2$ (913.36): C 73.64, H 8.83; found: C 73.48, H 8.97.

*(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-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)Cl_2 (394 mg, 0.67 mmol) at 0° under N_2. LiHBEt$_3$ (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 Et_2O (3×50 ml). The combined org. phase was washed with H_2O (2×45 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 7:1) to give **1** (3.15 g, 84%). Colorless oil. IR (film): 3343 (OH). ^{1}H-NMR ($CDCl_3$): 5.42 (*t*, ^3J = 6.8, C=CH); 5.12–5.10 (*m*, 7 C=CH); 4.15 (*d*, ^3J = 6.8, CH_2O); 1.97–2.09 (*m*, 14 CH_2); 1.68 (*s*, 2 Me); 1.60 (*s*, 7 Me). ^{13}C-NMR ($CDCl_3$): 139.83 (=C); 135.42 (=C); 135.02 (2 =C); 134.94 (2 =C); 134.89 (=C); 131.25 (Me_2C=*C*H); 124.43 (=CH); 124.27 (2 =CH); 124.18 (2 =CH); 123.79 (2 =CH); 123.34 (=CH); 59.44 (CH_2O); 39.76 (3 =C(Me)*C*H_2); 39.74 (3 =C(Me)*C*H_2); 39.58 (=C(Me)*C*H_2); 26.78 (2 =CH*C*H_2); 26.72 (3 =CH*C*H_2); 26.69 (=CH*C*H_2); 26.35 (=CH*C*H_2); 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-{[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-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 CH_2Cl_2 (15 ml), CBr_4 (1.29 g, 3.9 mmol) and polymer-supported Ph_3P (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 CBr_4 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 Et_2O (3×50 ml). The combined org. phase was washed sequentially with H_2O (3×20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated to give **18** (1.87 g, 89%, purity 93% by HPLC). Colorless oil. IR (film): 1318, 1150 (SO_2). ^{1}H-NMR ($CDCl_3$): 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, SO_2CH_2); 2.37 (*s*, *Me*–Ar); 1.89–2.08 (*m*, 14 CH_2): 1.26, 1.50, 1.60 (3*s*, 9 Me). ^{13}C-NMR ($CDCl_3$): 146.21 (arom. C); 144.40 (=C); 135.89 (=C); 135.72 (=C); 135.07 (SO_2Ar); 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 (SO_2CH_2); 39.76 (6 =C(Me)*C*H_2); 39.74 (=C(Me)*C*H_2); 26.79 (2 =CH*C*H_2); 26.73 (2 =CH*C*H_2); 26.68 (2 =CH*C*H_2); 26.24 (=CH*C*H_2); 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).

*(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-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 anh. DMF (5 ml) was added *t*-BuOK (40 mg, 0.35 mmol) at −20° under N_2. 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 Et_2O (3×5 ml). The combined org. phase was washed with H_2O (3×10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 7:1) to give **19** (164 mg, 63%). Colorless oil. IR (film): 1740 (CO), 1318, 1301, 1231 (MeCOOR), 1144 (SO_2). ^{1}H-NMR ($CDCl_3$): 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, CH_2O); 3.89–3.84 (*m*, SO_2CH); 2.88 (*dd*, ^3J = 2.4, ^2J = −12.4, 1 H of CH_2); 2.45 (*s*, *Me*–Ar); 2.27 (*dd*, ^3J = 2.4, ^2J = −12.4, 1 H of CH_2); 1.93–2.07 (*m*, 16 CH_2, COMe); 1.22, 1.54, 1.60, 1.62, 1.68, 1.70 (6*s*, 11 Me). ^{13}C-NMR ($CDCl_3$): 171.04 (CO); 144.90 (arom. C); 144.21 (=C); 141.80 (=C); 135.64 (2 =C); 135.11 (SO_2Ar); 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 (CH_2O); 61.30 (SO_2CH); 39.75 (6 =C(Me)*C*H_2); 39.20 (=C(Me)*C*H_2); 37.54 (=C(Me)*C*H_2); 26.77 (3 =CH*C*H_2); 26.70 (3 =CH*C*H_2); 26.45 (=CH*C*H_2); 26.26 (=CH*C*H_2); 25.70 (Me); 21.62 (*Me*–Ar); 21.02 (CO*Me*); 17.68 (Me); 16.47 (7 Me); 16.42 (Me); 16.03 (Me). MALDI-MS: 917.7 ($[M+Na]^+$, $C_{59}H_{90}NaO_4S^+$).

*(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-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 Me_2CO (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 $[Pd(dppp)Cl_2]$ (7.38 mg, 0.0125 mmol) at 0° under N_2. $LiHBEt_3$ (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 Et_2O (3 × 10 ml).The combined org. phase was washed with H_2O (3 × 15 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; 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). ^{1}H-NMR ($CDCl_3$): 5.43 (*t*, ^3J = 7.2, C=CH); 5.11–5.14 (*m*, 9 C=CH); 4.16 (*d*, ^3J = 6.8, CH_2O); 2.14–1.99 (*m*, 18 CH_2); 1.69 (*s*, 2 Me); 1.61 (*s*, 9 Me). ^{13}C-NMR ($CDCl_3$): 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 (CH_2O); 39.76 (=C(Me)*C*H_2); 39.58 (8 =C(Me)*C*H_2); 26.78 (3 =CH*C*H_2); 26.72 (3 =CH*C*H_2); 26.68 (2 =CH*C*H_2); 26.34 (=CH*C*H_2); 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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