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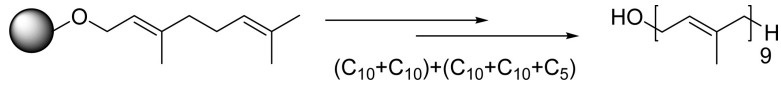

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Solid-Phase Synthesis of Solanesol

Xiongjie Yu,[†] Suxi Wang,[†] and Fener Chen*[,†]

Department of Chemistry, Fudan University, No. 220 HanDan Road, Shanghai, 200433, P. R. China

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An efficient and convergent solid-phase strategy for the total synthesis of All-*E* solanesol is described. This method features avoidance of iterative and difficult purifications comparing with solution-phase synthesis and is suitable for the preparation of other oligoprenols.

Introduction

Solanesol (all-*E* nonaprenol, **1**), widely existing in higher plant mammal and microorganisms such as tobacco leaves,[1a] mulberry leaves, and unsaponifiable matter of silkworm faeces,[1b] is an important member of All-*E* oligoprenols' family not only in its antibacterial, styptic, antiphlogistic efficacies and potential high anticancer activities but also as a main starting material for the synthesis of many high-value biochemicals bearing oligoprenyl structure as well as coenzyme Q_{10} and vitamin K_2.[2] It can be also used as a main coenzyme against cardiac insufficiency, muscular dystrophy, and anemia and a potentiating agent which can increase the effects distinctly by introducing the "solanesol" radical into the structure of some medicines.[3] Although many efforts[4] have been made on the solution-phase synthesis of **1** during the past half century, these methods require chromatographic purification at every terminal functionalization and growth stage. Conversely, the solid-phase synthetic strategy provides facile isolation of support-bound reaction products by washing away reagents with appropriate solvents, high translation on polymer supports by using excess reagents, and suppression of unwanted reactions by site isolation conditions.[5] We reported here is a novel solid-phase method for the total synthesis of **1** to demonstrate the efficiency of solid-phase synthesis.

Results and Discussion

Initially, we selected commercially available geraniol (**2**) as the starting material for the synthesis of **1** since hydrotyl group provides a convenient site for attachment onto the solid support. A tetrahydropyranyl linker is also chosen to connect the alcohol to the support since the resulting THP ether could withstand strong bases that are performed in the synthesis sequence and its cleavage can be accomplished with mild acid catalysis.

As shown in Scheme 1, 2-(hydroxymethyl)-3,4-dihydro-2*H*-pyran was converted to its sodium salt and then treated with Merrifield's resin (1.34 mequiv of Cl/g, 1% DVB cross-linking, 100−200 mesh) in DMF at room temperature to afford the dihydropyran-modified resin **3**.[6] Geraniol (**2**) was coupled to **3** using PPTS in 1,2-dichloroethane at 80 °C for 48 h to yield **4**. The loading level of **2** in **4** was determined by cleaving the alcohol from the resin employing PPTS in 1:1 *n*-butanol/1,2-dichloroethane at 80 °C.[7] Compound **4** (0.95 mequiv of **2**/g) was oxidated with *t*BuOOH in the presence of SeO_2 and 4-hydroxybenzoicacid in CH_2Cl_2[8] to produce alcohol **5** and aldehyde **6** which could be reduced into **5** with $LiAlH_4$.[9] Reaction of **5** with PBr_3 (3 equiv, CH_2Cl_2, 0 °C to room temperature, 15 h) gave bromide **7**.[10] Compound **7** was then cross-coupled with (*E*)-1-(3,7-dimethylocta-2,6-dienylsulfonyl)-4-methylbenzene (**8**) (6 equiv, DMF, 0 °C to room temperature), derived from **2** as Sato reported,[4c] by means of NaH to afford sulfone **9**. Excess **8** was easily recovered by filtration. Subsequently, palladium-catalyzed reductive desulfurization[11] of **9** gave polymer-support tetramer **10**. Repeating the three-step sequence of compounds **4** to **7**, **10** was transformed to fragment **13** successfully. With the pivotal intermediate in hand, we could focus on the construction of the framework of solanesol.

One portion of **13** was coupled with sulfone **14**[12] (6 equiv, DMF, 0 °C to room temperature) using NaH to yield sulfone **15** and then treated with $LiHBEt_3$/Pd(dppp)Cl_2 to afford polymer-support pentamer **16** (Scheme 2). Alcohol **17** was librated from polymer-support utilizing acid. Tolyl-sulfone **18**, obtained from **17** according to the procedure described by Lipshutz et al.,[13] was ready to be coupled with another portion of **13**. This coupling reaction could not go on easily under NaH/DMF system. We could not observed any Ts group in the IR spectrum of the polymer-support product. Gratifyingly, we obtained sulfone **19** successfully when we used potassium *t*butyl-hydroxide as the base instead of sodium hydride (Scheme 3). Recovery of excess **18** was achieved simply by filtration. Desulfurization of **19** via the procedure used above gave polymer-support nonamer **20**. Thus, we have realized the construction of a linear nonaprenol chain based on solid polymer. Finally, treatment of **20** with PPTS to complete the total solid-phase synthesis of solanesol (**1**).

Conclusions

In summary, we have reported a novel solid-phase synthesis of solanesol (**1**) in 50% overall yield starting from

* Corresponding author. Current address: Institution of Biomedical Science, Fudan University, Shanghai, 200031, P. R. China. E-mail: rfchen@fudan.edu.cn. Tel.: 86-21-65643811. Fax: 86-21-65643811.

[†] Department of Chemistry.

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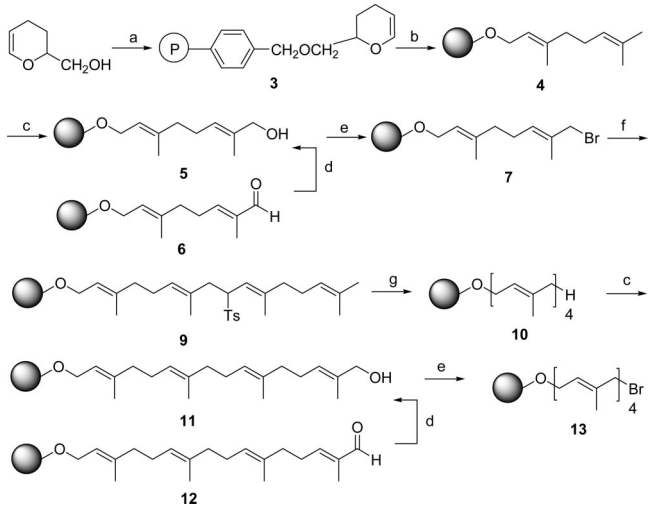
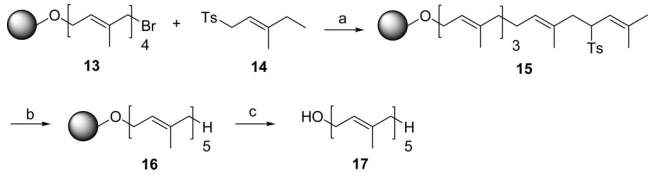
Scheme 1. Synthesis of Polymer-Supported Bromide **13**[a]



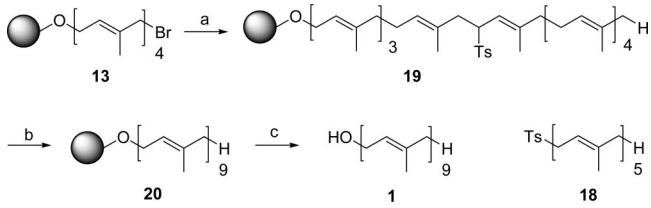
[a] Conditions: (a) 1. NaH, THF, rt, 2 h; 2. Merrifield's resin, rt, 16 h; (b) **2**, PPTS, 1,2-dichloroethane, 80 °C, 2 d; (c) SeO_2, *t*BuOOH, salicylic acid, CH_2Cl_2, rt, 2 d; (d) $LiAlH_4$, THF, 0 °C−rt, 4 h; (e) PBr_3, CH_2Cl_2, 0 °C−rt, 15 h; (f) **8**, NaH, DMF, 0 °C-rt, 2 d; (g) $LiHBEt_3$, $Pd(dppp)Cl_2$, THF, 0 °C−rt, 15 h.

Scheme 2. Synthesis of Pentaprenol **17**[a]



[a] Conditions: (a) NaH, DMF, 0 °C, 2 d; (b) $LiHBEt_3$, $Pd(dppp)Cl_2$, THF, 0 °C−rt, 15 h; (c) PPTS, 1:1 *n*-butanol/1,2-dichloroethane, 80 °C, 16 h.

Scheme 3. Synthesis of Solanesol (**1**)[a]



[a] Conditions: (a) **18**, potassium *t*-butyl-hydroxide, DMF, 0 °C, 10 h; (b) $LiHBEt_3$, $Pd(dppp)Cl_2$, THF, 0 °C−rt, 20 h; (c) PPTS, 1:1 *n*-butanol/1,2-dichloroethane, 80 °C, 16 h.

commercially available geraniol which is coupled to DHP resin via its alcohol. Using the solid-phase methodology, the yield of solanesol is increased notably compared with the solution-phase synthesis by using excess of reagents. Additionally, this method is suitable for the synthesis of other all-*E* oligoprenols.

Experimental Section

General Remarks. THF was distilled from Na/benzophenone under N_2. DMF and CH_2Cl_2 was freshly distilled from CaH_2. Petroleum ether for column chromatography (CC) has a boiling point of 60−90 °C. All other reagents and chemicals were obtained from commerial suppliers and used without further purification. Melting points (mp) were determined on WRB-1B digital melting-point apparatus. MS spectra were recorded on Waters 2695 with Waters 2487

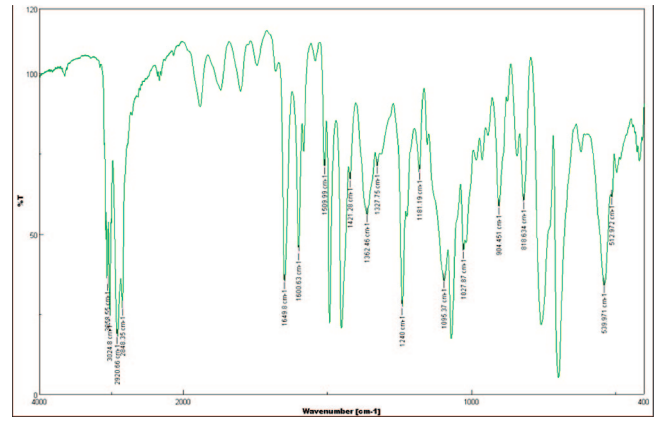


Figure 1. IR spectrum of **3**.

Dual λ Absorbance spectrometer. IR spectra were recorded on Jasco/IR-4200. ^1H NMR spectra were recorded on Bruker AV II 400 (400 MHz) and were referenced to internal Me_4Si. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are in hertz (Hz).

Dihydropyran-Modified Resin 3. To a nitrogen-purged flask with 60% NaH (5.29 g, 132.20 mmol) were added THF (200 mL) and 2-(hydroxymethyl)-3,4-dihydro-2*H*-pyran (13.68 g, 120.00 mmol). The mixture was stirred at room temperature for 2 h and then concentrated. To the residue were added DMF (500 mL) and Merrifield's resin (40 g). The mixture was stirred at room temperature for 16 h and then poured onto a preweighed fritted funnel. The beads were washed sequentially with 1:1 DMF/H_2O (4×), DMF (3×), and DCM (3×) and dried in a vacuum oven at 60 °C for 12 h to afford 44.1 g of the dihydropyran functionalized resin. FTIR (KBr) 3025, 2920, 1650, 1601, 1493, 1451, 1240, 1069, 1027, 904, 758, 697, 540 cm^{-1} (see Figure 1).

Polymer-Supported Geraniol 4. Resin **3** (37.50 g, 45 mmol of the DHP moiety) was suspended in 1,2-dichloroethane (800 mL). Geraniol (**2**) (20.79 g, 135 mmol) and PPTS (22.59 g, 90 mmol) were added. The mixture was stirred at 80 °C for 2 d. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 44.36 g of the desired product. The loading level was 1.0 mequiv of **2** per gram of polymer as determined by PPTS-induced cleavage (vide infra) and recovery of **2**. FTIR (KBr) 3025, 2922, 1601, 1493, 1452, 1374, 1110, 1069, 1028, 758, 699, 539 cm^{-1} (see Figure 2).

Polymer-Supported Alcohol 5 and Aldehyde 6. SeO_2 (2.88 g, 26.0 mmol) and salicylic acid (3.60 g, 26.0 mmol) were suspended in DCM (450 mL) at 0 °C. 65% *t*BuOOH (70 g, 0.50 mol) was added dropwise. The result mixture was stirred for 30 min, and then, **4** (40.00 g) was added. The mixture was stirred for 2 d at room temperature. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 40.51 g desired product. FTIR (KBr) 3433, 3025, 2922, 1685, 1600, 1493, 1452, 1362, 1106, 1028, 758, 698, 539 cm^{-1} (see Figure 3).

Polymer-Supported Alcohol 5. 5 and **6** (40.30 g) were suspended in THF (400 mL) under nitrogen, and $LiAlH_4$

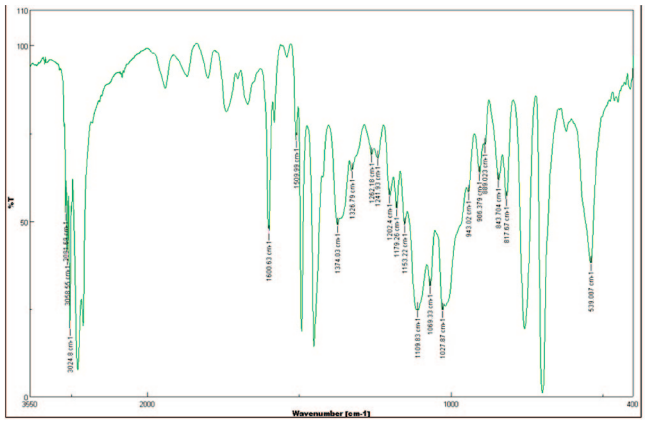


Figure 2. IR spectrum of **4**.

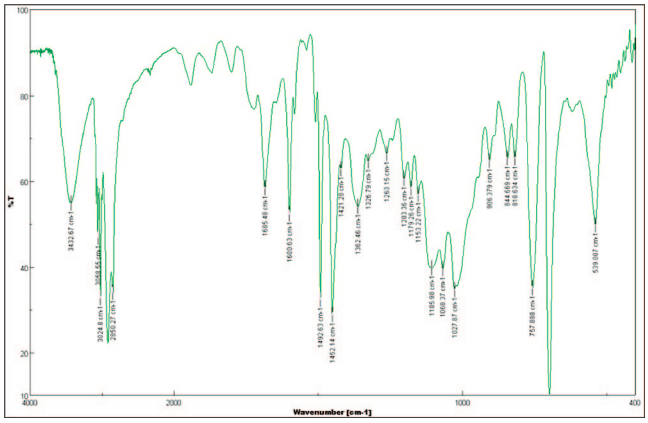


Figure 3. IR spectrum of **5** and **6**.

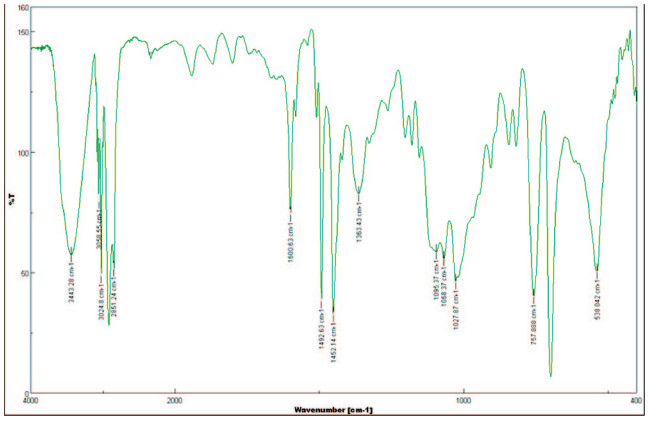


Figure 4. IR spectrum of **5**.

(4.56 g, 120.0 mmol) was added in small portions. The result mixture was stirred for 4 h at room temperture. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 40.33 g of the desired product. FTIR (KBr) 3443, 3025, 2922, 1600, 1493, 1452, 1363, 1095, 1028, 758, 698, 538 cm^{-1} (see Figure 4).

Polymer-Supported Bromide 7. The alcohol **5** (40.00 g) was suspended in DCM (300 mL) at 0 °C, and PBr_3 (10 mL, 99.6 mmol) was added. The mixture was stirred for 5 h at 0 °C and then slowly allowed to warm to room temperature over the following 10 h. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×),

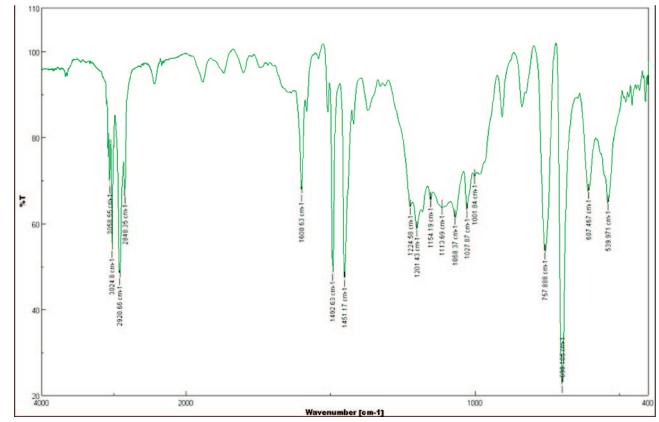


Figure 5. IR spectrum of **7**.

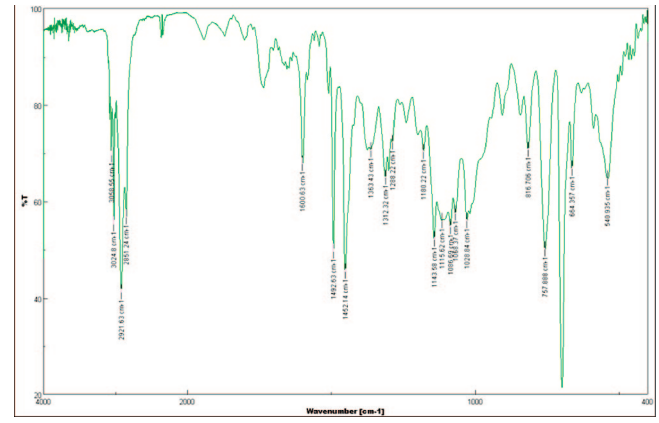


Figure 6. IR spectrum of **9**.

and dried in a vacuum oven at 40 °C for 12 h to afford 41.98 g of the desired product. FTIR (KBr) 3025, 2921, 1601, 1493, 1451, 1201, 1028, 758, 698, 607, 540 cm^{-1} (see Figure 5).

Polymer-Supported Sulphone 9. Bromide **7** (40.00 g) and sulfone **8** (52.6 g, 0.18 mol) were suspended in DMF (400 mL) at 0 °C under nitrogen, and 60% NaH (7.86 g, 0.20 mol) was added in portions. The mixtrure was stirred for 10 h at 0 °C and 2 d at room temperature. The result ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 DMF/H_2O (4×), DMF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 45.9 g the desired product. FTIR (KBr) 3025, 2922, 1601, 1493, 1452, 1363, 1312, 1144, 1029, 758, 699, 664, 541 cm^{-1} (see Figure 6).

Polymer-Supported Alcohol 10. Sulfone **9** (40.00 g) and $PdCl_2$(dppp) (1.44 g, 2.44 mmol) were suspended in THF (300 mL) at 0 °C under nitrogen and $LiHBEt_3$ (244 mL, 1.0 mol/L in THF) was added dropwise. The result mixture was stirred 5 h at 0 °C and additional 10 h at room temperature. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 36.24 g of the desired product. FTIR (KBr) 3025, 2922, 1601, 1493, 1452, 1376, 1108, 1028, 757, 698, 539 cm^{-1} (see Figure 7).

Polymer-Supported Alcohol 11 and Aldehyde 12. SeO_2 (1.74 g, 15.68 mmol) and salicylic acid (2.16 g, 15.68 mmol) were suspended in DCM (400 mL) at 0 °C. 65% *t*BuOOH (70 g, 0.15 mol) was added dropwise. The result mixture

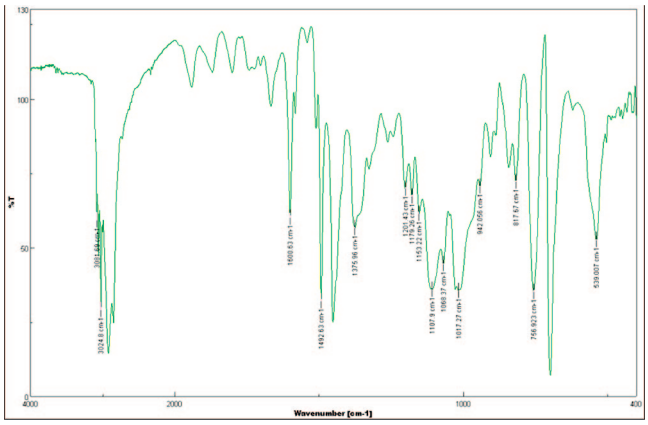


Figure 7. IR spectrum of **10**.

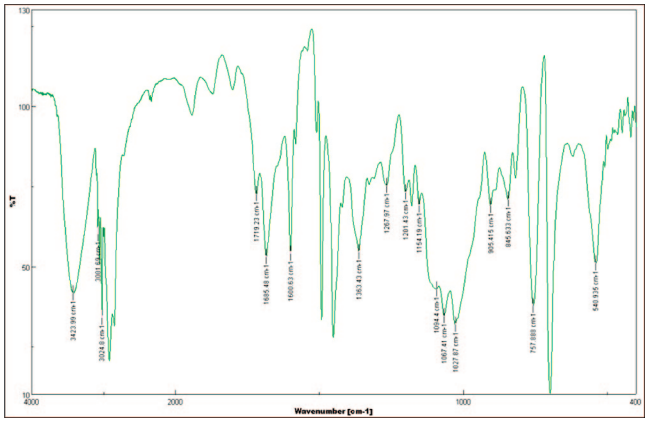


Figure 8. IR spectrum of **11** and **12**.

was stirred for 30 min, and then, **10** (36.00 g) was added. The mixture was stirred for 2 d at room temperature. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 36.32 g of the desired product. FTIR (KBr) 3424, 3025, 2923, 1685, 1601, 1493, 1452, 1362, 1067, 1028, 758, 698, 541 cm^{-1} (see Figure 8).

Polymer-Supported Alcohol 11. 11 and **12** (36.00 g) were suspended in THF (400 mL) under nitrogen, and $LiAlH_4$ (2.74 g, 72.1 mmol) was added in small portions. The resulting mixture was stirred for 4 h at room temperture. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 36.34 g desired product. FTIR (KBr) 3422, 3025, 2922, 1601, 1493, 1452, 1364, 1067, 1028, 758, 698, 538 cm^{-1} (see Figure 9).

Polymer-Supported Bromide 13. The alcohol **11** (36.00 g) was suspended in DCM (300 mL) at 0 °C, and PBr_3 (6.2 mL, 62.6 mmol) was added. The mixture was stirred for 5 h at 0 °C and then slowly allowed to warm to room temperature over the following 10 h. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C for 12 h to afford 37.26 g of the desired product. FTIR (KBr) 3025, 2921, 1601, 1493, 1451, 1364, 1201, 1067, 1028, 757, 698, 607, 539 cm^{-1} (see Figure 10).

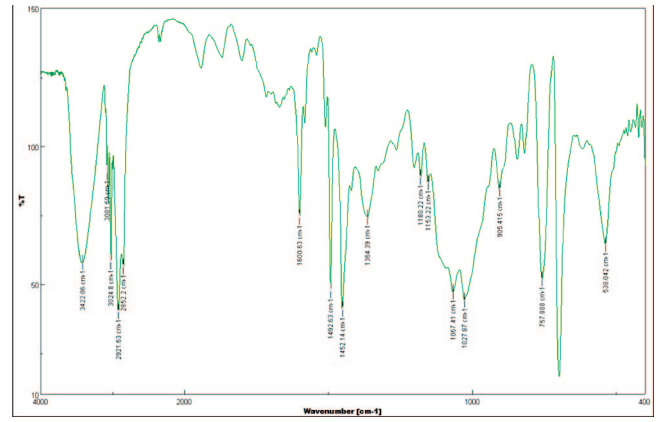


Figure 9. IR spectrum of **11**.

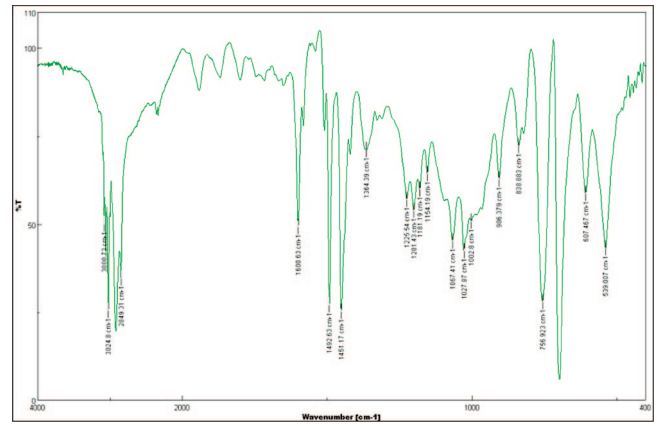


Figure 10. IR spectrum of **13**.

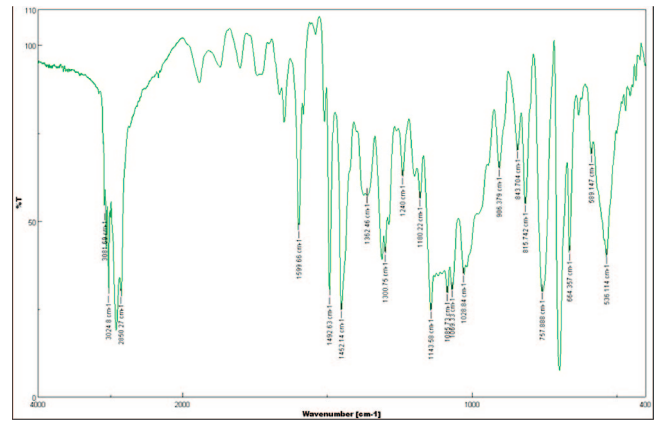


Figure 11. IR spectrum of **15**.

Polymer-Supported Sulphone 15. Bromide **13** (26.00 g) and sulfone **14** (18.93 g, 84.5 mmol) were suspended in DMF (300 mL) at 0 °C under nitrogen, and 60% NaH (11.56 g, 0.29 mol) was added in portions. The mixtrure was stirred for 10 h at 0 °C and 2 d at room temperature. The result ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 DMF/H_2O (4×), DMF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 27.89 g of the desired product. FTIR (KBr) 3025, 2922, 1600, 1493, 1452, 1375, 1362, 1312, 1301, 1144, 1069, 758, 698, 664, 536 cm^{-1} (see Figure 11).

Polymer-Supported Alcohol 16. Sulfone **15** (27.50 g) and $PdCl_2$(dppp) (0.77 g, 1.30 mmol) were suspended in THF (250 mL) at 0 °C under nitrogen and $LiHBEt_3$ (130 mL, 1.0 mol/L in THF) was added dropwise. The resulting mixture

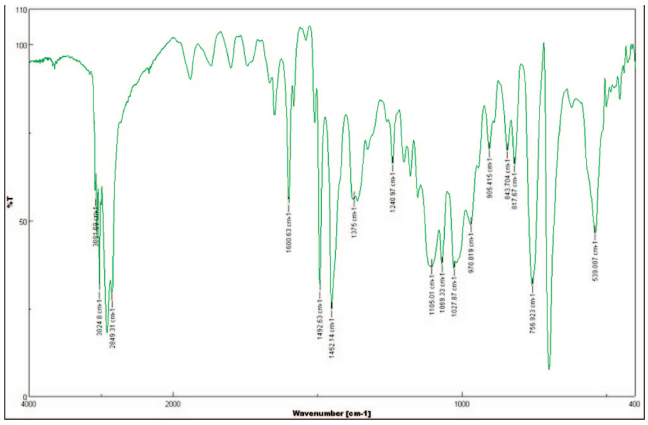


Figure 12. IR spectrum of **16**.

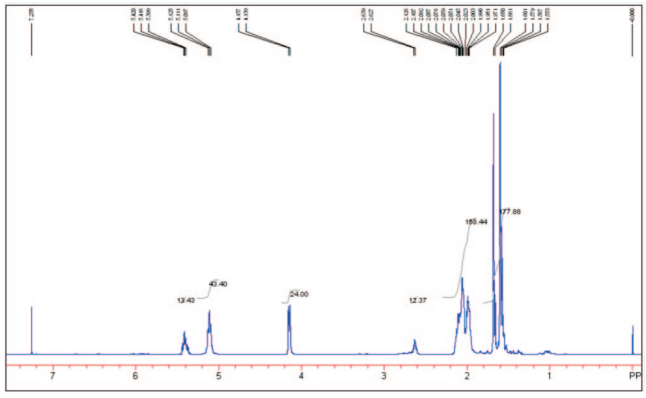


Figure 13. ^{1}H NMR spectrum of **17**.

was stirred for 5 h at 0 °C and additional 10 h at room temperature. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 25.50 g of the desired product. FTIR (KBr) 3025, 2921, 1601, 1493, 1452, 1375, 1362, 1105, 1028, 757, 698, 539 cm^{-1} (see Figure 12).

(2*E*,6*E*,10*E*,14*E*)-3,7,11,15,19-Pentamethylicosa-2,6,10,14,18-pentaen-1-ol (17). 16 (25.00 g) was suspended in 1:1 *n*-butanol/1,2-dichloroethane (150 mL) under nitrogen. PPTS (11.2 g, 44.62 mmol) was added. The mixture was heated to 80 °C for 16 h. The reaction mixture was cooled and passed through a fritted funnel. The resin was washed with DCM. The combined filtrate was washed with water (50 mL × 3) and brine (50 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purification by flash chromatography on silica gel (15:1 petroleum ether/AcOEt) to afford 4.39 g of **17** as a colorless oil. ^{1}H NMR (400 MHz) δ 5.42 (t, $^3J_{H-H}$ = 4.2 Hz, 1H, C=CH), 5.11 (t, $^3J_{H-H}$ = 6.2 Hz, 4H, C=CH), 4.148 (d, $^3J_{H-H}$ = 7.2 Hz, 2H, C=CH), 2.63 (d, $^3J_{H-H}$ = 4.8 Hz, 1H, C=CH), 1.97−2.13 (m, 16 H, CH_2), 1.55−1.68 (m, 18 H, CH_3) (see Figure 13); ESIMS *m*/*z* 381.4 [$(M+Na)^+$, 68], 329.1 (100), 301.2 (37), 179.0 (37) (see Figure 14).

Polymer-Supported Sulphone 19. Bromide **13** (5.00 g) and sulfone **18** (8.05 g, 16.2 mmol) prepared from **17** (6.83 g, 19.1 mmol) according to the procedure described by Lipshutz et al.,[13] were suspended in DMF (150 mL) at 0 °C under nitrogen and *t*BuOK (1.98 g, 17.7 mmol) was added.

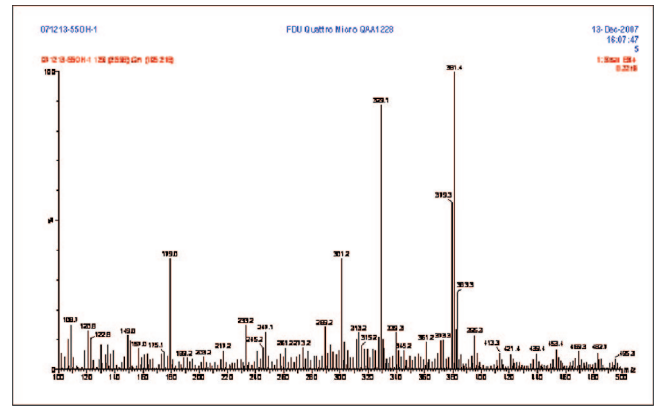


Figure 14. Mass spectrum of **17**.

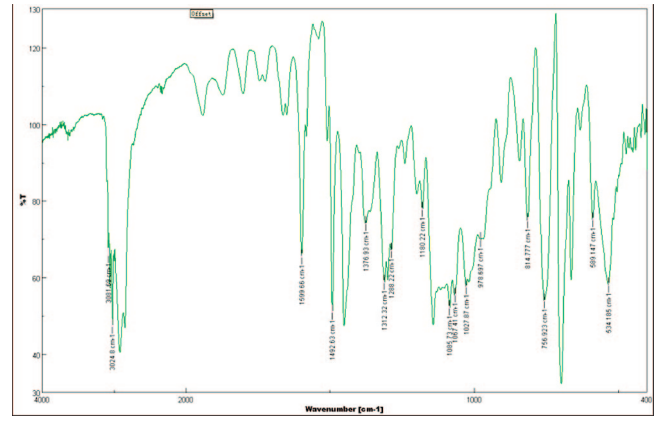


Figure 15. IR spectrum of **19**.

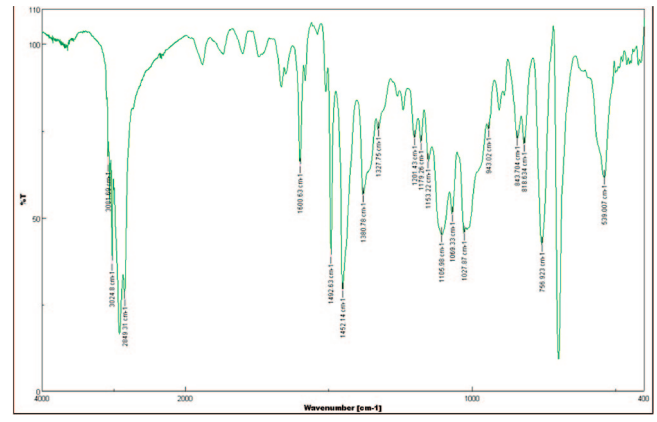


Figure 16. IR spectrum of **20**.

The mixtrure was stirred for 10 h at 0 °C and an additional 10 h at room temperature. The resulting ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 DMF/H_2O (4×), DMF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 6.05 g of the desired product. FTIR (KBr) 3025, 2922, 1600, 1493, 1452, 1377, 1312, 1301, 1144, 1067, 757, 697, 663, 589, 534 cm^{-1} (see Figure 15).

Polymer-Supported Solanesol 20. Sulfone **19** (6.00 g) and $PdCl_2$(dppp) (0.16 g, 0.26 mmol) were suspended in THF (100 mL) at 0 °C under nitrogen, and $LiHBEt_3$ (26 mL, 1.0 mol/L in THF) was added dropwise. The resulting mixture was stirred for 5 h at 0 °C and an additional 15 h at room temperature. The ploymer was then poured onto a preweighed fritted funnel, washed sequentially with 1:1 THF/

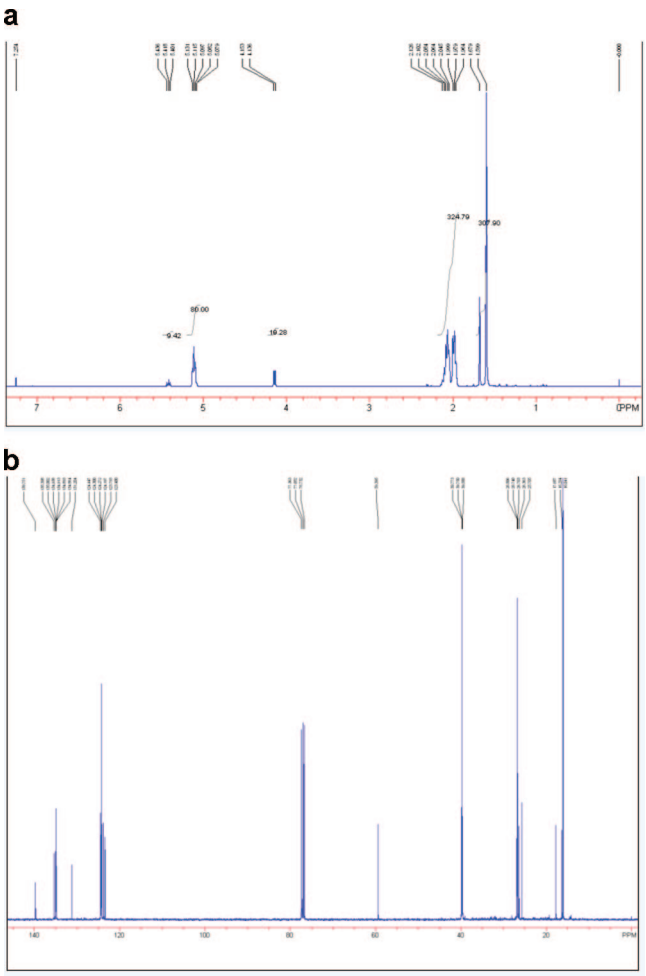


Figure 17. (a) ^{1}H NMR spectrum of **1**. (b) ^{13}C NMR spectrum of **1**.

H_2O (2×), 2:1 THF/H_2O (2×), THF (3×), and DCM (3×), and dried in a vacuum oven at 40 °C overnight to afford 5.61 g of the desired product. FTIR (KBr) 3025, 2922, 1601, 1493, 1452, 1380, 1106, 1028, 757, 699, 539 cm^{-1} (see Figure 16).

Solanesol (1). 20 (5.00 g) was suspended in 1:1 *n*-butanol/1,2-dichloroethane (100 mL) under nitrogen. PPTS (1.96 g, 7.82 mmol) was added. The mixture was heated to 80 °C for 16 h. The reaction mixture was cooled and passed through a fritted funnel. The resin was washed with DCM. The combined filtrate was washed with water (50 mL × 3) and brine (50 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The residue was purification by flash chromatography on silica gel (20:1 petroleum ether/AcOEt) to afford 1.33 g of **1** as a white solid. Mp: 41.6−42.3 °C, (literature[4c] 41.5−42.5 °C); ^{1}H NMR (400 MHz) δ 5.42 (t, $^{3}J_{H-H} = 7.0$ Hz, 1 H, C═CH), 5.08−5.13 (m, 8 H, C═CH), 4.14 (d, $^{3}J_{H-H} = 6.8$ Hz, 2H, C═CH), 1.96−2.13 (m, 32 H, CH_2), 1.60, 1.68 (2 s, 30 H, CH_3) (see Figure 17a); ^{13}C NMR (100 MHz) δ 139.8, 135.4, 135.0, 134.9, 131.2 (═*C*CH_3), 124.4, 124.3, 124.2, 123.8, 123.4 (═CH), 59.4 (CH_2OH), 39.8, 39.6 [*C*H_2C(CH_3)═], 26.8, 26.7, 26.4, 25.7 (*C*H_2CH═), 17.7, 16.3, 16.0 (CH_3) (see Figure 17b); ESIMS *m*/*z* 653.9 [$(M + Na)^+$, 62], 541.4 (100), 467.4 (80), 413.5 (30).

References and Notes

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