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# Solid-Phase Organic Synthesis of Polyisoprenoid Alcohols with Traceless Sulfone Linker

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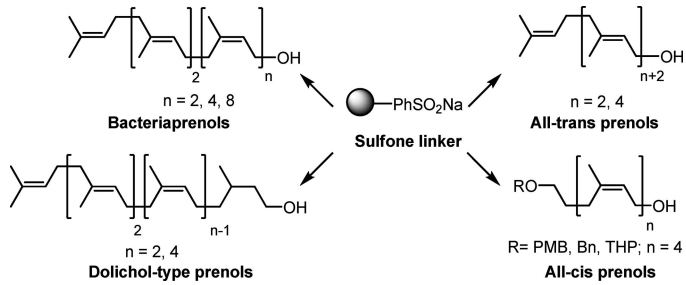


Solid-phase organic synthesis of polyprenols with a traceless sulfone linker is described. The polymer-bound benezenesulfinate is first linked with the "tail" building blocks of isoprenyl chlorides via *S*-alkylation. With use of dimsyl anion as an appropriate base, the polymer-bound α-sulfonyl carbanion is generated and coupled with other "body" building blocks in an efficient manner. After repeated processes and a global palladium-catalyzed desulfonation with $LiEt_3BH$ as the reducing agent, the desired polyprenols with various chain lengths and geometrical configurations are obtained in 32−59% overall yields. The solid-phase synthesis offers the advantage in facile isolation of polyprenols without tedious operation or time-consuming purification.

## Introduction

Many biologically important molecules contain polyisoprenoid alcohols as the essential moieties to fulfill their functions.[1,2] Naturally occurring polyisoprenoid alcohols can be classified into four categories according to their structures: (i) all-trans prenols, (ii) dolichol type prenols with ditrans-poly cis configuration and a saturated isoamyl moiety, (iii) bacteria- and betulaprenols with ditrans-poly cis configuration, and (iv) ficaprenol with tritrans-poly cis configuration (Figure 1).[3]

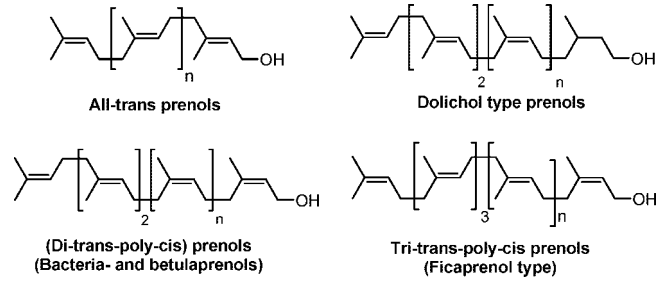


**FIGURE 1.** General structures of natural polyprenols.

The phosphate or pyrophosphate derivatives of polyprenols are intermediates in the biosynthesis of various glycoproteins, peptidoglycans, and polysaccharides. For example, undecaprenol phosphate (C55-OP) is an important substrate for biosynthesis

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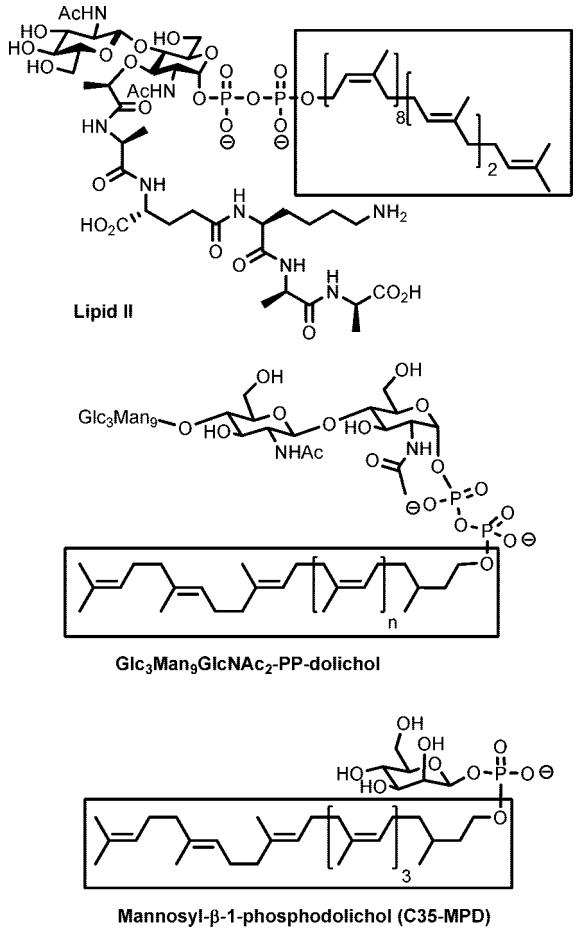


**FIGURE 2.** Examples of polyprenol-containing biologically interesting molecules.

of undecaprenyl GlcNAc-MurNAc(pentapeptide)-pyrophosphate (lipid II, Figure 2), which is the precursor of bacterial cell wall peptidoglycan.[4] The truncated lipid II without the polyprenol moiety cannot be recognized by the cell wall biosynthetic enzymes. However, the lipid II analogy bearing a shorter polyprenol chain, e.g. betulaheptaprenol (C35-OH), can serve as an alternative substrate of bacterial transglycosylase.[5] In the post-translational modification of nascent polypeptide chains, the oligosaccharide $Glc_3$-$Man_9$-$GlcNAc_2$ bearing a dolichol pyrophosphate moiety renders an *N*-glycosylation to certain asparagines residues.[6] Mannosyl-$\beta$-1-phosphodolichol (C35-MPD) is a synthetic polyprenol glycolipid, which is presented by CD1c for T cell recognition.[7] Thus, polyprenols with different chain lengths and configurations may play important roles in diverse biological applications.

Due to the difficulties in isolation of pure polyprenols from natural sources and the limitations of chemical transformations of natural polyprenols, the organic synthesis obviously provides an alternative approach to produce various desired polyprenols, which can be converted to their phosphate and pyrophosphate derivatives as well as the polyprenol-based chemical probes for biological studies. Indeed, several solution-phase synthetic methods have been reported.[8−10] However, all these methods have common drawbacks of tedious operation and limited diversity. We thus explore a more efficient approach using solid-phase organic synthesis (SPOS) to prepare a library of polyprenols with various lengths and geometrical configurations. As a general strategy for the preparation of peptides, nucleosides, and oligosaccharides,[11] SPOS has several advantages over the solution-phase organic synthesis.[12] In particular, isolation of the polymer-bound intermediates is typically accomplished by a simple filtration. To the best of our knowledge, however, this technology has not been applied to the synthesis of polyprenols.

In any SPOS-based strategy, selection of an appropriate linker (the moiety that covalently connects the polymeric support to the building block) is essential. The ideal linker allows easy attachment of the substrate to the solid support, is stable to the reaction conditions used to produce the desired product, and can be cleaved under specific and orthogonal conditions.[13] The previous studies by us[14] and other groups[15] have shown that a sulfone linker, such as that derived from the polymer-bound sulfinate **1** (Figure 3), fulfills these requirements.

## Results and Discussion

**Strategy and Design of Solid-Phase Organic Synthesis.** On the basis of our previous experience with sulfone linkers[14] and the availability of suitable building blocks, we proposed a strategy entailing attachment of the polymer-bound sulfinate **1** to the tail building block, followed by extension of the carbon chain toward a headgroup (Figure 3). In this study, four tail building blocks (**2**, **12**, **13**, and **14**), three body building blocks (**4**, **15**, and **26**), and four head building blocks (**4**, **15**, **16**, and **26**)[9,16,17] were selected to show the generality of this method (Figure 4). These building blocks were easily prepared from inexpensive nerol, geraniol, farnesol, and citronellol.[16,17] Noteworthily, the RO functional groups present in building blocks **12**−**14** can be further transformed into chromophores and photoaffinity labels for bioassay and mechanistic studies.

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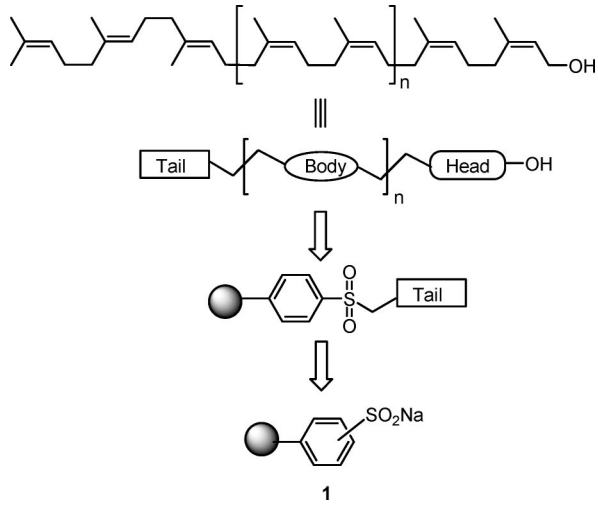


**FIGURE 3.** General synthetic route to polyprenols from the polymer-bound benzenesulfinate resin **1**.

Inspired by the stepwise principle of solid-phase peptide synthesis,[18] our synthesis of polyprenols relies on seven key steps (Figure 5): (i) *S*-alkylation of the sulfinate resin **1**, (ii) generation of α-sulfonyl carbanion followed by the coupling reaction with the respective building block, (iii) *O*-deprotection, (iv) activation of the hydroxyl group by mesylation, halogenation, and sulfonation, (v) iterative coupling reaction to link other building blocks, (vi) *O*-deprotection, and (vii) global desulfonation with concomitant release of the target molecule of polyprenols from the solid support. The repeated cycle of steps iv → vi by activation, coupling, and deprotection would allow for diversity of the desired products.

**Model Synthetic Studies in the Solution Phase.** Preliminary solution-phase experiments were undertaken to explore the feasible reaction conditions, and to establish the required modifications for a practical SPOS. For example, the choice of base and solvent is an important issue for the coupling reaction between allylic sulfones and alkyl halides. The conventional use of aqueous sodium hydroxide as a base[19] is not suitable for the solid-phase synthesis because of the low-swelling behavior of polystyrene-based resins in aqueous solution.[14,15,20] Use of *n*-butyllithium as a base may cause undesired dialkylation,[14,15,20] even the reaction is conducted at low temperature (−78 °C).[21] To circumvent these problems, we chose to perform the coupling reactions in THF solution by using dimsyl anion as the appropriate base. The dimsyl anion can be formed in situ from DMSO with *n*-BuLi, and utilized to generate the carbanion of the sulfone resin for monoalkylation.[22]

Several *O*-protecting groups, such as Bn and THP, can be used in the tail building blocks **12**−**14**, whereas the TBDPS group was the choice for incorporation into the body and head building blocks **4**, **15**, and **16** because it is stable in the basic conditions involving dimsyl anion and can be removal by TBAF selectively.

On the basis of the above consideration, the synthesis of a 25-carbon pentaprenol **7a**[16] was first conducted in the solution phase (Scheme 1). Treatment of (*E*,*E*)-farnesyl chloride **2**[23] with sodium benzenesulfinate gave (*E*,*E*)-farnesyl phenyl sulfone **3**, which underwent monolithiation with dimsyl anion (3 equiv) at room temperature and reacted subsequently with a $C_{10}$ isoprenoid building block **4**[16] to afford the coupling product **5** in 78% yield over two steps. After removal of the TBDPS group in **5**, the alcohol **6** was subject to reductive desulfonation in varied conditions (Table 1).[16,24−27] Compound **6** was rather inert to magnesium, whereas the reaction with lithium was complicated to give a low yield (10%) of the desulfonation product **7a**. Treatment of **6** with sodium in ethanol gave a mixture of **7a** and its isomer **7b** in a ratio of 7:3 as shown by $^1$H NMR analysis. Compound **7b** was characterized by showing the $C_{11}$-methyl group as a doublet at $\delta$ 0.94 ppm and the $C_8$-methylene group as a multiplet at $\delta$ 2.66 ppm. These two isomers were inseparable by silica gel column chromatography.[16] Fortunately, we found that the reductive desulfonation of **6** was effectively carried out by using $LiBHEt_3$ (Super-Hydride) in the presence of $PdCl_2$(dppp) catalyst in THF solution to furnish a single product of **7a** in 83% yield.

**Solid-Phase Organic Synthesis of Polyprenols.** Using the reaction protocols developed in the above-mentioned solution-phase synthesis, we constructed a small library of polyprenols **7a**, **11**, and**17**−**24**[28−30] by SPOS in 32−59% isolated yields (Table 2 and Figure 6). These products were diverse polyprenol structures including the all-trans, all-cis, bacteria, betula, and dolichol types. A typical procedure for the SPOS of polyprenol **11** was delineated in Scheme 2.

The synthetic work began with the *S*-alkylation of the sulfinate resin **1** (sulfinate loading = 0.8 mmol/g) with the tail building block **2**. The reaction was easily monitored by FTIR spectra, which showed disappearance of sulfinate absorption at 1028 $cm^{-1}$ along with occurrence of the sulfone absorptions at ∼1300 and ∼1140 $cm^{-1}$. Resin **8** was treated with dimsyl anion (3 equiv) at room temperature to give the corresponding α-sulfonyl carbanion, which reacted with the building block **4** to furnish a chain elongation product, resin **9a**. This transformation was confirmed by a diagnostic absorption of the Si−O bond at ∼1110 $cm^{-1}$ in the single-bead FTIR spectrum of **9a**.

The TBAF-mediated *O*-deprotection of **9a**, followed by mesylation, chlorination, and sulfonation, afforded resin **9d**. The process of carbanion generation and coupling reaction with building block **4** was repeated to give resin **10**, which contained one sulfone moiety on the resin linker and the other sulfone

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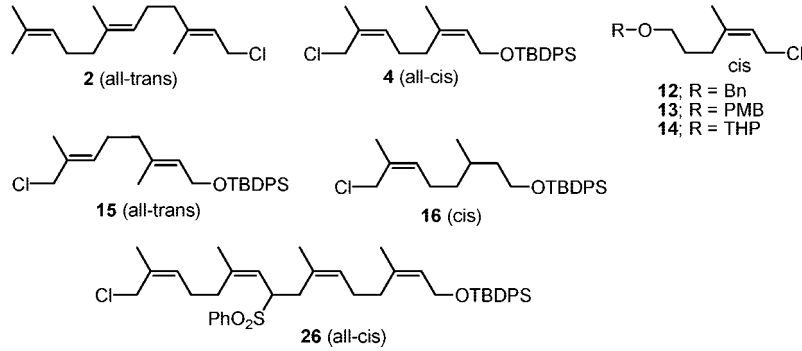



**FIGURE 4.** Chemical structures of building blocks for tail, body, and head groups.

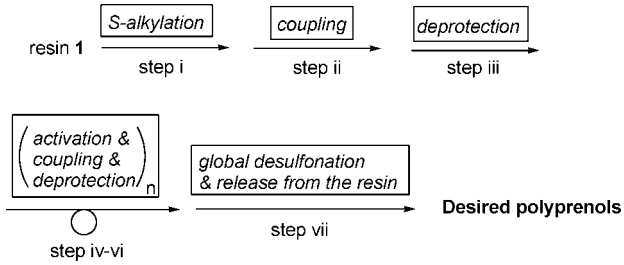
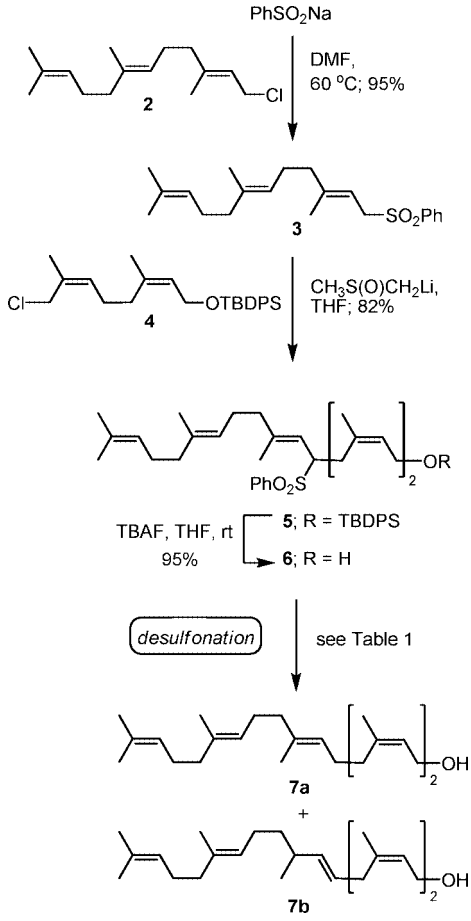



**FIGURE 5.** Key steps of solid-phase polyprenol synthesis.

**SCHEME 1. Solution-Phase Synthesis of Polyprenol 7a (Model Study)**




group attached to the polyprenol backbone. After deprotection of the TBDPS group from resin **10**, a global desulfonation afforded the desired product **11** (C35-OH)[8] in 37% overall yield from the starting resin **1**, i.e., an average yield of 88% for each of the eight solid-phase reactions.

**TABLE 1. Reductive Desulfonation of Compound 6**

| entry | reagents | solvent/ temp/ time | isolated yield (%)[a] of **7a** |
|---|---|---|---|
| 1 | Mg/ethanol | EtOH/rt/48 h | 0[b] |
| 2 | Mg/methanol | MeOH/rt/48 h | 23[c] |
| 3 | Li/naphthalene | THF/0 °C/1 h | 10[d] |
| 4 | Na/ethanol | EtOH/rt/2 h | 45[e] |
| 5 | $LiBHEt_3/PdCl_2$(dppp) | THF/0 °C/2 h | 83 |

[a] Isolated by silica-gel column chromatography. [b] Only the starting material of **6** was recovered. [c] The starting material was recovered in 77% yield. [d] The reaction was complicated by other intractable products. [e] The crude product mixture consisted of **7a** and its isomer **7b** in a ratio of 7:3 as shown by the $^1$H NMR analysis.

**TABLE 2. Solid-Phase Synthesis of Polyprenols**

| product[a] | building blocks | total steps | overall yields (%) based on resin **1**[b] |
|---|---|---|---|
| **7a** | **2** + **4** | 4 | 56 |
| **11** | **2** + **4** + **4** | 8 | 37 |
| **17** | **2** + **15** | 4 | 57 |
| **18** | **2** + **15** + **15** | 8 | 38 |
| **19** | **12** + **4** + **4** | 8 | 36 |
| **20** | **13** + **4** + **4** | 8 | 39 |
| **21** | **14** + **4** + **4** | 8 | 32 |
| **22** | **2** + **16** | 4 | 59 |
| **23** | **2** + **4** + **16** | 8 | 40 |
| **24** | 2 + 4 + 4 + 4 + 4 | 16 | 11 |
| **24** | 2 + 26 + 26 | 8 | 34 |

[a] Purification by silica-gel column chromatography. [b] The sulfinate loading on resin **1** is 0.8 mmol/g.

In connection with our research on the transglycosylation of bacterial cell wall, the undecaprenol **24** is needed for the synthesis of lipid II (see in Figure 2) as the substrate of transglycosylase.[30] Because isolation of the undecaprenol **24** from bacteria is difficult, a practical synthesis of **24** is desirable (Figure 7). In our original approach, resin **8** was subject to four cycles of reaction sequence with the $C_{10}$ building block **4** to generate the corresponding resin **25** possessing 11 isoprene units. All the sulfonyl groups on resin **25** were then removed by a Pd-catalyzed reduction to afford the target molecule **24** in 11% overall yield, from the starting resin **1**, after purification by silica-gel column chromatography. Alternatively, the $C_{20}$ building block **26** was used in two elongation cycles on resin **8** to afford **25**, and ended up with formation of undecaprenol **24** in 34% overall yield. The dramatic improved yield was attributable to the fewer reaction steps in the latter approach. This is the first report on the efficient solid-phase synthesis of undecaprenol **24** (C55-OH).

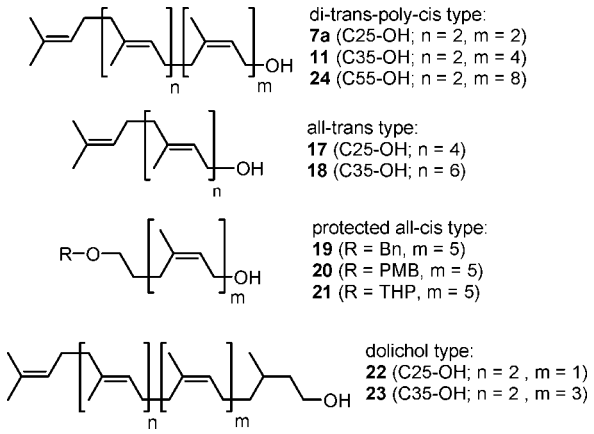
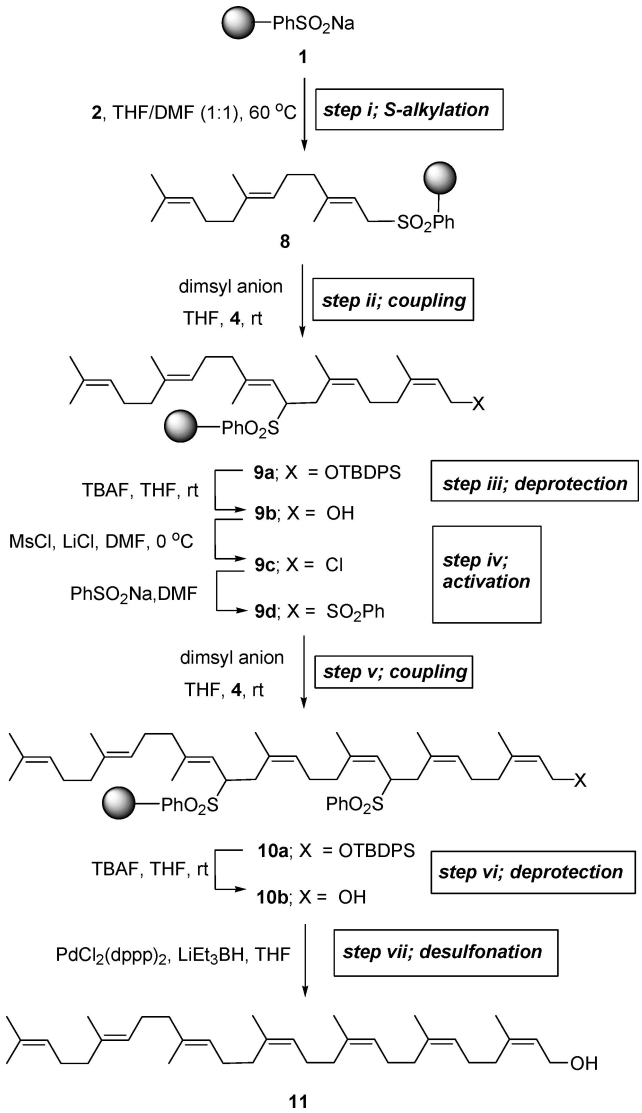



**FIGURE 6.** Chemical structures of the polyprenols prepared in this study.

**SCHEME 2. Solid-Phase Synthesis of Polyprenol 11 (Representative Example)**




## Conclusion

In this study, we have devised a practical solid-phase synthetic route to varied polyprenols by using sulfone resin as a traceless and robust linker. A library of polyprenols, including undecaprenol **24** of lipid II component, is thus successfully constructed in reasonable yields. Our approach has several merits: (i) iterative elongation cycle (a sequence of coupling, deprotection, and activation) on solid support is remarkably efficient; (ii) no tedious operation or time-consuming purification are required; (iii) the *S*-alkylation, deprotection, and activation (steps i, iii, iv, and vi) are easily monitored by FTIR analysis; and (iv) all sulfonyl groups on the resin and the molecular backbone are simultaneously removed by a Pd-catalyzed reduction. Transformation of polyprenols **7a** and **11** to their corresponding phosphate derivatives has been performed in our laboratory. Modification of the polyprenols by incorporation of chromophores and photoaffinity labels will be conducted in due course for further biological studies.

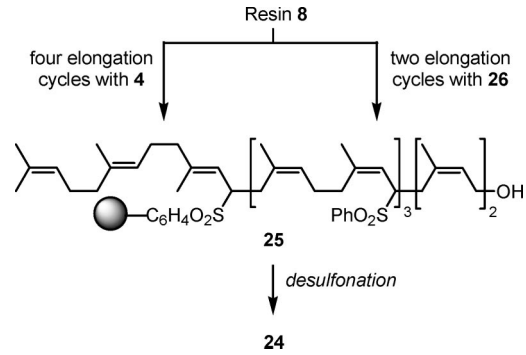



**FIGURE 7.** Solid-phase synthesis of polyprenol **24** (a component of lipid II).

## Experimental Section

**(2*Z*,6*Z*,10*E*,14*E*)-3,7,11,15,19-Pentamethyl-9-(phenylsulfonyl)icosa-2,6,10,14,18-pentaen-1-ol (6).** Dimsyl anion was prepared by the dropwise addition of *n*-BuLi (0.18 mL, 0.44 mmol) to a solution of DMSO (0.04 g, 0.03 mL, 0.44 mmol) in THF (0.5 mL) at ambient temperature, followed by stirring for 20 min. The freshly prepared dimsyl anion was added dropwise to a solution of **3** (0.10 g, 0.29 mmol) in THF (0.5 mL), and the color of the reaction mixture changed from white to orange. After 2 h, the building block **4** (0.12 g, 0.27 mmol) in THF (0.7 mL) was added to this mixture. The mixture was stirred at ambient temperature for 4 h, and the reaction was quenched with satd. $NH_4Cl$ solution (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), washed with satd. NaCl (3 × 20 mL), dried ($MgSO_4$), and concentrated to give **5** (0.16 g, 0.22 mmol). The solution of compound **5** in THF (2 mL) was stirred with TBAF (1.0 M in THF, 0.87 mL, 0.87 mmol) at ambient temperature for 4 h. The mixture was concentrated and purified by CC (33% EtOAc in hexanes) to give **6** (0.11 g, 0.22 mmol, 76% for two steps from **3**) as a colorless oil: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.11 (s, 3H), 1.55 (s, 3H), 1.57 (s, 3H), 1.58 (s, 3H), 1.65 (s, 3H), 1.71 (s, 3H), 1.90−2.01 (m, 12H), 2.47 (dd, 1H, $J$ = 13.3, 11.0 Hz), 2.80 (dd, 1H, $J$ = 13.3, 3.0 Hz), 2.84 (td, 1H, $J$ = 11.0, 3.0 Hz), 4.06 (d, 2H, $J$ = 7.1 Hz), 4.93 (d, 1H, $J$ = 10.3 Hz), 4.99 (t, 1H, $J$ = 4.4 Hz), 5.05 (t, 1H, $J$ = 6.8 Hz), 5.17 (t, 1H, $J$ = 6.8 Hz), 5.41 (t, 1H, $J$ = 7.1 Hz), 7.47−7.60 (m, 3H), 7.82 (m, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 145.6, 139.6, 138.0, 136.0, 133.6, 131.6, 131.2, 129.4, 129.4, 128.9, 128.8, 128.2, 124.9, 124.4, 123.5, 117.2, 63.8, 59.1, 39.9, 39.8, 32.1, 29.6, 26.9, 26.8, 26.3, 25.9, 23.8, 23.7, 17.9, 16.4, 16.1; HRMS calcd for $[C_{31}H_{46}O_3S + NH_4]^+$ 516.3506, found 516.3505.

**(2*Z*,6*Z*,10*E*,14*E*)-3,7,11,15,19-Pentamethylicosa-2,6,10,14,18-pentaen-1-ol (7a).**[16] **a. Solution-Phase Synthesis.** Lithium triethylborohydride (Super-Hydride) (0.5 mL, 0.5 mmol) was added dropwise over 2 h to a solution of **6** (50 mg, 0.1 mmol) and bis(diphenylphosphino)propanepalladium(II) dichloride [(dppp)$PdCl_2$] (3 mg,

0.005 mmol) in THF (1 mL) at 0 °C. After the mixture was stirred for 12 h, satd. $NH_4Cl$ solution (10 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with satd. NaCl solution (3 × 20 mL), dried ($MgSO_4$), concentrated, and purified by CC (17% EtOAc in hexanes) to give **7a** (31 mg, 0.087 mmol, 87%) as a colorless oil.

**b. Solid-Phase Synthesis.** Starting from resin **1** with building blocks **2** and **4**, the reaction sequence (**1** → **8** → **9a** → **9b** → **7a**) was carried out, as that described for **11**, to give **7a** (16 mg, 0.045 mmol, 56% overall yield from **1**) as a colorless oil.

**7a**: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.58 (s, 9H), 1.66 (s, 6H), 1.72 (s, 3H), 1.93−2.07 (m, 16H), 4.05 (d, 2H, $J$ = 7.0 Hz), 5.06−5.10 (m, 4H), 5.41 (t, 1H, $J$ = 7.0 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 139.9, 136.3, 135.4, 135.1, 131.4, 124.7, 124.6, 124.5, 124.4, 124.2, 59.1, 39.9, 39.8, 32.4, 32.1, 27.0−26.5 (several, m), 25.8, 23.6, 23.5, 17.8, 16.1; HRMS calcd for $[C_{25}H_{42}O + Na]^+$ 381.3128, found 381.3126.

**(2*E*,6*E*)-1-(PS/DVB-sulfonyl)-3,7,11-trimethyldodeca-2,6,10-triene (8).** The polymer-bound benzenesulfinate **1** (1 g, 0.8 mmol; sulfinate loading = 0.8 mmol/g) was swollen in DMF/THF (1:1, 5 mL) at room temperature for 15 min, and the building block **2** (5 equiv., 0.96 g, 4.0 mmol) was added. The mixture was gently stirred at 60 °C for 48 h. The resin was collected by filtration, then washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL). The resin was then dried overnight in a vacuum oven (40 °C, 5 mmHg) to afford resin **8** as yellow beads: IR (single bead reflectance) 1596.6, 1492.9, 1450.4, 1303.2, 1146.0 cm$^{-1}$.

**(2*Z*,6*Z*,10*E*,14*E*)-1-(*tert*-Butyldiphenyl)silyloxy-3,7,11,15,19-pentamethyl-9-(PS/DVB-sulfonyl)icosa-2,6,10,14,18-pentaene (9a).** Polymer **8** (500 mg) was swollen in THF (3 mL) for 15 min, and the freshly prepared dimsyl anion THF solution (3 equiv, 1.2 mmol) was added dropwise. The mixture was gently stirred for 2 h, the excess dimsyl anion was removed, and the resin was washed with dry THF (2 × 1 mL). The building block **4** (340 mg, 0.8 mmol) in THF (5 mL) was added, and the mixture was gently stirred at ambient temperature for 12 h. The resin was collected by filtration, then washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL). The resin was then dried overnight in a vacuum oven (40 °C, 5 mmHg) to afford **9a** as yellow beads: IR (single bead reflectance) 1596.6, 1492.9, 1451.0, 1301.9, 1142.8, 1110.4 cm$^{-1}$.

**(2*Z*,6*Z*,10*E*,14*E*)-3,7,11,15,19-pentamethyl-9-(PS/DVB-sulfonyl)icosa-2,6,10,14,18-pentaen-1-ol (9b).** Polymer **9a** (500 mg) was swollen in THF (3 mL) for 15 min, and TBAF (1.0 M in THF, 5 equiv, 2 mmol, 2 mL) was added. The reaction was stirred at ambient temperature for 8 h, and the resin was collected by filtration, then washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL). The resin was then dried overnight in a vacuum oven (40 °C, 5 mmHg) to afford **9b** as yellow beads: IR (single bead reflectance) 1596.6, 1492.9, 1451.0, 1301.9, 1142.8 cm$^{-1}$.

**(2*Z*,6*Z*,10*E*,14*E*)-1-Chloro-3,7,11,15,19-pentamethyl-9-(PS/DVB-sulfonyl)icosa-2,6,10,14,18-pentaene (9c).** Polymer **9b** (500 mg) was swollen in DMF (5 mL) for 15 min. After addition of LiCl (0.17 g, 4.0 mmol) and collidine (0.78 g, 6.4 mmol), MsCl (0.28 g, 2.4 mmol) was added dropwise into the mixture at 0 °C. The mixture was gently stirred for 2 h and quenched with $H_2O$, then the resin was collected by filtration, washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL), and allowed to dry in air at ambient temperature for 2 h to afford **9c** as yellow beads: IR (single bead reflectance) 1596.5, 1492.6, 1451.4, 1301.8, 1141.5 cm$^{-1}$.

**(2*Z*,6*Z*,10*E*,14*E*)-3,7,11,15,19-Pentamethyl-1-phenylsulfonyl-9-(PS/DVB-sulfonyl)icosa-2,6,10,14,18-pentaene (9d).** Polymer **9c** (500 mg) was swollen in DMF/THF (1:1, 3 mL) at room temperature for 15 min, and benzenesulfinic acid sodium salt (3.3 g, 2 mol) was added. The mixture was gently stirred at 60 °C for 48 h. The resin was collected by filtration, then washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL). The resin was then dried overnight in a vacuum oven (40 °C, 5 mmHg) to afford resin **9d** as yellow beads: IR (single bead reflectance) 1596.4, 1493.1, 1446.3, 1304.8, 1143.2 cm$^{-1}$.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*E*,22*E*)-1-(*tert*-Butyldiphenyl)siloxy-3,7,11,15,19,23,27-heptamethyl-9-phenylsulfonyl-17-(PS/DVB-sulfonyl)triaconta-2,6,10,14,18,22,26-heptaene (10a).** Polymer **9d** (100 mg) was swollen in THF (0.5 mL) for 15 min, and the freshly prepared dimsyl anion (5 equiv., 0.4 mmol) in THF (0.5 mL) was added dropwise. The mixture was gently stirred for 2 h, the excess dimsyl anion was removed, and the resin was washed with dry THF (2 × 0.5 mL). The building block **4** (68 mg, 0.16 mmol) in THF (1 mL) was added to the reaction and the mixture was gently stirred at ambient temperature for 12 h. The resin was collected by filtration, then washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL). The resin was then dried overnight in a vacuum oven (40 °C, 5 mmHg) to afford **10a** as yellow beads: IR (single bead reflectance) 1595.9, 1492.5, 1449.3, 1302.5, 1143.9, 1111.2 cm$^{-1}$.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*E*,22*E*)-3,7,11,15,19,23,27-Heptamethyl-9-phenylsulfonyl-17-(PS/DVB-sulfonyl)triaconta-2,6,10,14,18,22,26-heptaen-1-ol (10b).** Polymer **10a** (100 mg) was swollen in THF (0.5 mL) for 15 min, and TBAF (1.0 M in THF, 0.4 mmol, 0.4 mL) was added. The reaction was stirred at ambient temperature for 8 h, and the resin was collected by filtration, then washed with MeOH/$H_2O$ (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), and ether (10 mL). The resin was then dried overnight in a vacuum oven (40 °C, 5 mmHg) to afford **10b** as yellow beads: IR (single bead reflectance) 1596.4, 1491.5, 1451.7, 1300.6, 1143.3 cm$^{-1}$.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*E*,22*E*)-3,7,11,15,19,23,27-Heptamethyltriaconta-2,6,10,14,18,22,26-heptaen-1-ol (11).**[8] Lithium triethylborohydride (Super Hydride) (1.0 M in THF, 0.4 mmol, 0.4 mL) was added dropwise over 2 h to a solution of **10b** (100 mg) and bis(diphenylphosphino)propanepalladium(II) dichloride [(dppp)$PdCl_2$] (2.3 mg, 0.004 mmol) in THF (1.0 mL) at 0 °C. After the mixture was stirred for 12 h, the reaction was quenched with satd. $NH_4Cl$ (1 mL) and the resin was removed by filtration. The filtrate was extracted with ether (3 × 2 mL). The combined organic extracts were washed with satd. $NH_4Cl$ (1 × 2 mL) and brine (2 × 2 mL), concentrated, and then purified by CC (17% EtOAc in hexanes) to give **11** (14.6 mg, 0.029 mmol, 37% for 8 steps from **1**) as a colorless oil: Analytical RP-HPLC (Method A) $t_R$ = 12.5 min; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.58 (s, 9H), 1.66 (s, 12H), 1.72 (s, 3H), 1.94−2.07 (m, 24H), 4.07 (d, 2H, $J$ = 7.0 Hz), 5.07−5.11 (m, 6H), 5.41 (t, 1H, $J$ = 7.0 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 139.8, 136.0, 135.4, 135.3, 135.2, 134.9, 131.2, 125.0, 124.9, 124.6, 124.5, 124.4, 124.2, 124.1, 59.0, 39.8, 39.7, 32.3, 32.2, 32.0, 31.9, 26.8−26.3 (several, m), 25.6, 23.4, 23.3, 17.6, 16.0; HRMS calcd for $[C_{35}H_{58}O + Na]^+$ 517.4380, found 517.4379.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*Z*)-22-Benzyloxy-3,7,11,15,19-pentamethyldocosa-2,6,10,14,18-pentaen-1-ol (19).** Starting from resin **1** with building blocks **12** and **4** (two cycles), the reaction was carried out, as that described for **11**, to give **19** (14.2 mg, 0.029 mmol, 36% overall yield from **1**) as a colorless oil after purification with CC (17% EtOAc in hexanes): Analytical RP-HPLC (Method A) $t_R$ = 5.1 min; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.58−1.69 (m, 14H), 1.72 (s, 3H), 1.91−2.07 (m, 18H), 3.43 (t, 2H, $J$ = 6.6 Hz), 4.07 (t, 2H, $J$ = 5.0 Hz), 4.48 (s, 2H), 5.09−5.13 (m, 4H), 5.42 (d, 1H, $J$ = 6.8 Hz), 7.25−7.32 (m, 5H); HRMS calcd for $[C_{34}H_{52}O_2 + Na]^+$ 515.3860, found 515.3864.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*Z*)-22-(4-Methoxybenzyloxy)-3,7,11,15,19-pentamethyldocosa-2,6,10,14,18-pentaen-1-ol (20).** Starting from resin **1** with building blocks **13** and **4** (two cycles), the reaction was carried out, as that described for **11**, to give **20** (16.3 mg, 0.031 mmol, 39% overall yield from **1**) as a colorless oil after purification with CC (17% EtOAc in hexanes): Analytical RP-HPLC (Method A) $t_R$ = 5.3 min; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.58−1.67 (m, 14H), 1.72 (S, 3H), 1.95−2.07 (m, 18H), 3.40 (t, 2H, $J$ = 6.6 Hz),

3.78 (S, 3H), 4.07 (d, 2H, $J$ = 6.8 Hz), 4.40 (s, 2H), 5.08−5.12 (m, 4H), 5.42 (t, 1H, $J$ = 7.1 Hz), 6.85 (d, 2H, $J$ = 8.6 Hz), 7.24 (d, 2H $J$ = 8.4 Hz); HRMS calcd for $[C_{35}H_{54}O_3 + Na]^+$ 545.3965, found 545.3961.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*Z*)-3,7,11,15,19-Pentamethyl-22-(tetrahydro-2*H*-pyran-2-yloxy)docosa-2,6,10,14,18-pentaen-1-ol (21).** Starting from resin **1** with building blocks **14** and **4** (two cycles), the reaction was carried out, as that described for **11**, to give **21** (12.4 mg, 0.026 mmol, 32% overall yield from **1**) as a colorless oil after purification with CC (17% EtOAc in hexanes): Analytical RP-HPLC (Method A) $t_R$ = 5.5 min; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.47−1.70 (m, 20H), 1.72 (s, 3H), 1.98−2.07 (m, 18H), 3.35 (m, 1H), 3.47 (m, 1H), 3.69 (m, 1H), 3.84 (m, 1H), 4.06 (d, 2H, $J$ = 6.0 Hz), 4.55 (t, 1H, $J$ = 3.9 Hz), 5.08−5.11 (m, 4H), 5.41 (t, 1H, $J$ = 7.1 Hz); HRMS calcd for $[C_{32}H_{53}O_3 + Na]^+$ 508.3892, found 508.3892.

**(2*Z*,6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*Z*,34*E*,38*E*)-3,7,11,15,19,23,27,31,35,39,43-Undecamethylpentaconta-2,6,10,14,18,22,26,30,34,38,42-undecaen-1-ol (24).**[8] Starting from resin **1** with building blocks **2** and **4**, four cycles of reaction sequence were carried out, as that described for **11**, to give **24** (6.7 mg, 0.0088 mmol, 11% overall yield from starting resin **1**) as a colorless oil after purification with CC (17% EtOAc in hexanes). Alternatively, undecaprenol **24** was prepared from resin **1** with building blocks **2** and **26** (two cycles via **25**) in 34% yield after purification with CC (17% EtOAc in hexanes): Analytical RP-HPLC (Method C) $t_R$ = 6.0 min; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.62 (s, 9H), 1.70 (s, 24H), 1.77 (s, 3H), 1.98−2.12 (m, 40H), 4.11 (d, 2H, $J$ = 5.0 Hz), 5.11−5.16 (m, 10H), 5.47 (t, 1H, $J$ = 7.0 Hz); HRMS calcd for $[C_{55}H_{90}O + NH_4]^+$ 784.7330, found 784.7338.

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**Supporting Information Available:** General procedures and preparation procedures for compounds **3**, **17**, **18**, **22**, and **23** and copies of $^1$H and $^{13}$C NMR spectra for the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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