Solid-phase organic synthesis of polyisoprenoid alcohols with traceless sulfone linker

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Solid-phase organic synthesis of polyisoprenols with a traceless sulfone linker is described. The polymer-bound benzene sulfinate is first linked with the “tail” building blocks of isoprenyl chlorides via S-alkylation. With use of dimethyl anion as an appropriate base, the polymer-bound R-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 LiEt3BH as the reducing agent, the desired polyisoprenols 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 polyisoprenols 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) nicotine and betulaprenols with ditrans-poly cis configuration, and (iv) ficaprenol with tritrans-poly cis configuration (Figure 1).3

The phosphate or pyrophosphate derivatives of polyisoprenols are intermediates in the biosynthesis of various glycoproteins, peptidoglycans, and polysaccharides. For example, undecaprenol phosphate (C55-OP) is an important substrate for biosynthesis and betulaprenols with ditrans-poly cis configuration, and (iv) ficaprenol with tritrans-poly cis configuration (Figure 1).3

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FIGURE 1. General structures of natural polyisoprenols.

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[References]

of undecaprenyl GlcNAc-MurNac(pentapeptide)-pyrophosphate (lipid II, Figure 2), which is the precursor of bacterial cell wall peptidoglycan. 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., betulahyptapotanol (C35-OH), can serve as an alternative substrate of bacterial transglycosylase. In the post-translational modification of nascent polypeptide chains, the oligosaccharide Glc3-Man9-GlcNAc2 bearing a dolichol pyrophosphate moiety renders an N-glycosylation to certain asparagines residues. Mannosyl-β-1-phosphodolichol (C35-MPD) is a synthetic polyprenol glycolipid, which is presented by CD1c for T cell recognition. 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, various solution-phase synthetic approaches have been reported. 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, SPOS has several advantages over the solution-phase organic synthesis. 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.

The previous studies by us and other groups have shown that a sulfone linker, such as that derived from the polymer-bound sultine I (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 and the availability of suitable building blocks, we proposed a strategy entailing attachment of the polymer-bound sultine I 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) were selected to show the generality of this method (Figure 4). These building blocks were easily prepared from inexpensive nerol, geraniol, farnesol, and citronellol. Note-worthily, the RO functional groups present in building blocks 12–14 can be further transformed into chromophores and photoaffinity labels for bioassay and mechanistic studies.

On the basis of the above consideration, the synthesis of a 25-carbon pentaprenol 7a29 was first conducted in the solution phase (Scheme 1). Treatment of (E,E)-farnesyl chloride 23 with sodium benzenesulfinate gave (E,E)-farnesyl phenyl sulfone 3, which underwent monolithiation with dimethyl anion (3 equiv) at room temperature and reacted subsequently with a C10 isoprenoid building block 428 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 1H NMR analysis. Compound 7b was characterized by showing the C11-methyl group as a doublet at 0.94 ppm and the C8-methylene group as a multiplet at δ 2.66 ppm. These two isomers were inseparable by silica gel column chromatography.10 Fortunately, we found that the reductive desulfonation of 6 was effectively carried out by using LiBH4 (Super-Hydride) in the presence of PdCl2(dppp) catalyst in THF solution to furnish a single product of 7a in 83% yield.

Solid-Phase Organic Synthesis of Polyisoprenoids. Using the reaction protocols developed in the above-mentioned solution-phase synthesis, we constructed a small library of polyisoprenols 7a, 11, and 17–2248-30 by SPOS in 32–59% isolated yields (Table 2 and Figure 6). These products were diverse polyisoprenoid structures including the all-trans, all-cis, bacteria, betula, and dolichol types. A typical procedure for the SPOS of polyisoprenol 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 dimethyl anion (3 equiv) at room temperature to give the corresponding α-sulfonylethylcarbanion, 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

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)\textsuperscript{b} in 37% overall yield.

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.\textsuperscript{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\textsubscript{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\textsubscript{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).

### TABLE 1. Reductive Desulfonation of Compound 6

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents</th>
<th>solvent/ temp/ time</th>
<th>isolated yield (%) of 7a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg/ethanol</td>
<td>EtOH/rt/48 h</td>
<td>0\textsuperscript{b}</td>
</tr>
<tr>
<td>2</td>
<td>Mg/methanol</td>
<td>MeOH/rt/48 h</td>
<td>23\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>Li/naphthalene</td>
<td>THF/0 °C/1 h</td>
<td>10\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>Na/ethanol</td>
<td>EtOH/rt/2 h</td>
<td>45\textsuperscript{d}</td>
</tr>
<tr>
<td>5</td>
<td>LiBHEt\textsubscript{3}/PdCl\textsubscript{2}(dppp)</td>
<td>THF/0 °C/2 h</td>
<td>83\textsuperscript{e}</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>product\textsuperscript{a}</th>
<th>building blocks</th>
<th>total steps</th>
<th>overall yields (%) based on resin 1\textsuperscript{f}</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>2 + 4</td>
<td>4</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>2 + 4 + 4</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td>17</td>
<td>2 + 15</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>18</td>
<td>2 + 15 + 15</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>19</td>
<td>12 + 4 + 4</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>20</td>
<td>13 + 4 + 4</td>
<td>8</td>
<td>39</td>
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<td>21</td>
<td>14 + 4 + 4</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>22</td>
<td>2 + 16</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>23</td>
<td>2 + 4 + 16</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>24</td>
<td>2 + 4 + 4 + 4</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>25</td>
<td>2 + 26 + 26</td>
<td>8</td>
<td>34</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Purification by silica-gel column chromatography. \textsuperscript{f} The sulfinate loading on resin 1 is 0.8 mmol/g.

from the starting resin 1, i.e., an average yield of 88% for each of the eight solid-phase reactions.

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.\textsuperscript{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\textsubscript{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\textsubscript{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).
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 undeca-prenol, 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 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.

Experimental Section

(2Z,6Z,10E,14E)-3,7,11,15,19-Pentamethylicosa-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) was added to this mixture. The mixture was stirred at ambient temperature for 4 h, and the reaction was quenched with satd. NH4Cl solution (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), washed with satd. NaCl (3 × 20 mL), dried (MgSO4), 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: 1H NMR (600 MHz, CDCl3) δ 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); 13C NMR (150 MHz, CDCl3) δ 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 [C31H46O3S]+ 516.3506, found 516.3505.

(2Z,6Z,10E,14E)-3,7,11,15,19-Pentamethyl-2,6,10,14,18-pentaen-1-ol (7a). 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)propane palladium(II) dichloride ([dppp]PdCl2) (3 mg,
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.

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: 1H NMR (600 MHz, CDCl₃) δ 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); 13C NMR (150 MHz, CDCl₃) δ 139.9, 136.3, 135.4, 135.1, 131.4, 124.7, 124.6, 124.5, 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 [C₁₉H₂₆O⁺ Na⁺]⁺ 381.3128, found 381.3126.

(2F,6E)-1-(PS/DVB-sulfonyle)-3,7,11-trimethylodeca-2,6,10-triene (8). The polymer-bound benzenesulfinate (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, 40 mmol) was added. The mixture was gently stirred for 2 h at 60 °C for 48 h. The resin was collected by filtration, then washed with MeOH/H₂O (2×20 mL). The combined organic extracts were extracted with ether (3×10 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.

(2F,6E)-1-(tert-Butyldiphenyl)siloxy-3,7,11,15,19-pentamethyl-9-(PS/DVB-sulfonyle)icoso-2,6,10,14,18-pentaene (9a). Polymer 8 (500 mg) was swollen in THF (3 mL) for 15 min, and the freshly prepared dimethyl anion THF solution (equiv, 2 mmol, 2 mL) was added dropwise. The mixture was gently stirred for 2 h, the excess dimethyl 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/H₂O (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.

(2F,6E)-1-(tert-Butyldiphenyl)siloxy-3,7,11,15,19-pentamethyl-9-(PS/DVB-sulfonyle)icoso-2,6,10,14,18-pentaene-1-ol (9b). Polymer 9a (500 mg) was swollen in THF (3 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/H₂O (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) 1596.4, 1491.5, 1451.7, 1300.6, 1143.3 cm⁻¹.

(2F,6Z,10E,14E)-1-(tert-Butyldiphenyl)siloxyltriaconta-2,6,10,14,18,22,26-hepta-3,6,10,14,18,22-trien-1-ol (10a). Polymer 10a (100 mg) was swollen in THF (0.5 mL) for 15 min, and bis(diphenylphosphino)propane palladium(II) dichloride [dpppPdCl₂] (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 sat NH₄Cl (1×20 mL), MeOH (2×10 mL), and ether (10 mL). The resin was then collected by filtration, washed with MeOH/H₂O (2×10 mL), DCM (2×10 mL), MeOH (2×10 mL), and ether (10 mL). The resin was 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.
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 [C35H54O3 + Na]+ 545.3965, found 545.3961.

(2Z,6Z,10Z,14Z,18Z)-3,7,11,15,19-Pentamethyl-22-(tetrahydro-2H-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) tR = 5.5 min; 1H NMR (600 MHz, CDCl3) δ 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 [C35H54O3 + Na]+ 545.3965, found 545.3961.

Acknowledgment. This work was supported by the National Science Council and Academic Sinica.

Supporting Information Available: General procedures and preparation procedures for compounds 3, 17, 18, 22, and 23 and copies of 1H and 13C 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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