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Modified Routes to the "Designer" Surfactant PQS

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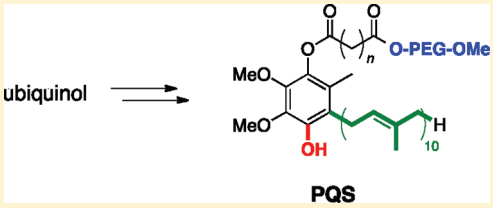
Supporting Information

ABSTRACT: Described herein are newly developed, straightforward entries to polyethyleneglycol ubiquinol succinate (PQS, n = 2), a designer surfactant that serves as precursor to micelle-forming, covalently bound catalysts for a variety of transformations in water with in-flask catalyst recycling.



INTRODUCTION

Catalysis is now considered among the major milestones of last century's developments in organic chemistry. Catalyst recycling, in particular the case of homogeneous catalysis, despite its many advantages (e.g., reduced waste and/or more efficient energy usage) still remains challenging. This is especially true when costly ligands and/or precious metals are involved. Aqueous biphasic systems have become an important industrial technique and offer one solution: the catalyst can be recovered from the aqueous phase, although the overall transformation occurs in the organic solvent.[1,2] We have previously shown that a variety of transition-metal-catalyzed transformations can be carried out within micellar media, generated by simply mixing a selected surfactant in water.[3] Organic solvents, therefore, are no longer needed, as the self-assembled micelles provide the lipophilic interior that serves, in essence, as the solvent for catalysis, i.e., as nanoreactors *in* water. Moreover, since only 1−2 wt % of surfactant in water easily exceeds the required critical micelle concentration (CMC), a catalytic amount of the amphiphile is sufficient. While other surfactants typically contain only lipophilic and hydrophilic subsections, polyethyleneglycol ubiquinol sebacate (PQS) was originally designed to accommodate a third component: an internally connected catalyst (Figure 1).[4] Hence, the three major subsections of PQS consist of the following: (1) the readily available hydroquinone, ubiquinol (i.e., the reduced form of CoQ_{10}), that supplies the lipophilicity in its 50-carbon side-chain, within which organic substrates are to be dissolved. Importantly, it also bears a second phenolic handle enabling covalent attachment of a catalyst that will reside *inside* the nanoreactor of its micellar array; (2) polyethyleneglycol monomethyl ether (MPEG-2000), which ensures water solubility; and (3) a linker unit, either sebacic acid, n = 8, or succinic acid, n = 2, that connects the lipophilic interior (i.e., ubiquinol) to the hydrophilic exterior (i.e., MPEG).

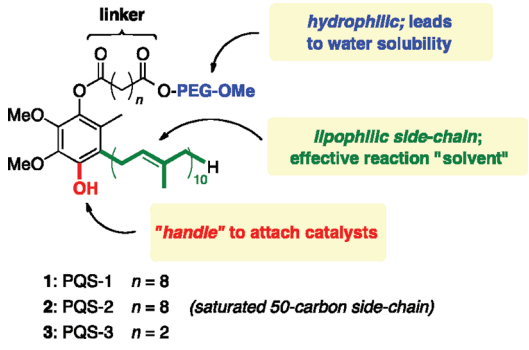


Figure 1. Designed components of PQS.

The concept of in-flask catalyst recycling was successfully demonstrated on olefin ring-closing and cross-metathesis reactions in water employing Grubbs−Hoveyda's first- and second-generation catalysts, which were independently covalently attached to PQS (**4**: PQS-GH-1 and **5**: PQS-GH-2, Figure 2).[4] A study of up to 10 recycles without significant loss of catalyst activity highlighted the potential of the PQS platform. Likewise, a related system based on PQS that does not focus on transition metal catalysts, e.g., PQS-proline (**7**) for use in organocatalysis, has recently appeared.[5]

Although a first generation synthesis (i.e., for **1**) gave satisfactory results, limited selectivity in each coupling step using sebacoyl chloride resulted in purification issues.[4] Moreover, scale-up experiments suggested that removal of impurities would be impractical through chromatographic means. Therefore, a synthetically more attractive route to the PQS platform was sought. Herein, we describe two novel and improved entries to the designer surfactant PQS-1 (**1**). We also disclose a synthesis of PQS-3 (**3**), a third generation surfactant, employing a succinic acid linker that enhances significantly the availability of the PQS platform.

RESULTS AND DISCUSSION

Initial attempts toward **1** focused on commercially available sebacic acid (**8**), which, after anhydride (**9**) formation,[6] was treated with MPEG-2000 to obtain PEGylated sebacic acid **10** (Scheme 1; Route **A**). Subsequent coupling with ubiquinol,

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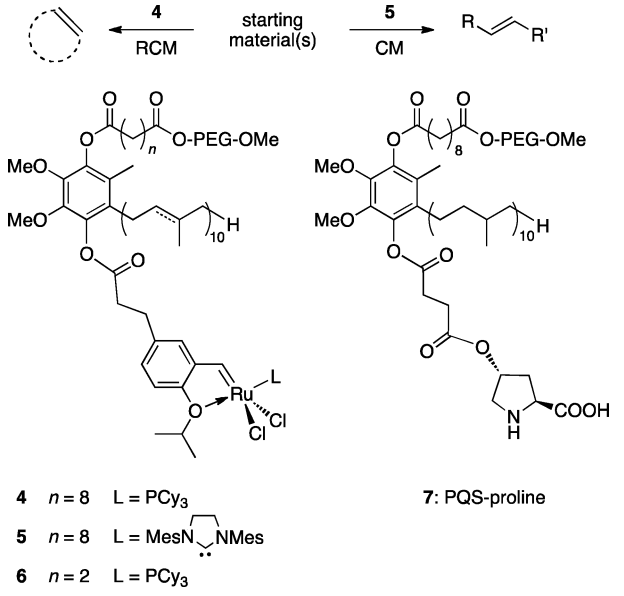
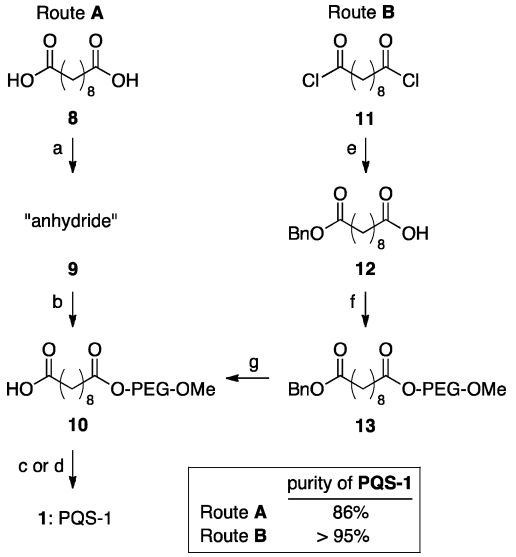


Figure 2. PQS as a platform for covalent attachment of a catalyst.

Scheme 1. [a]

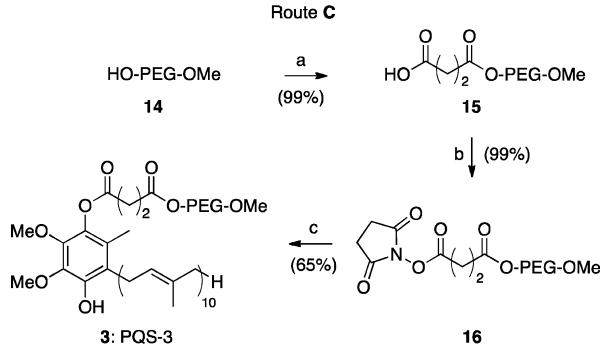


[a]Reagents and conditions: (a) Ac_2O, reflux, 76%. (b) HO-PEG-OMe, DMAP, pyridine, 100 °C, 99%. (c) $SOCl_2$, reflux, then redissolution in THF, ubiquinol, NaH, THF, rt, 80%. (d) EDCI, DMAP, ubiquinol, NEt_3, CH_2Cl_2, rt, 31%. (e) BnOH, NEt_3, Et_2O, −78 °C to rt, then 1 N HCl, 57%. (f) $SOCl_2$, reflux, then HO-PEG-OMe, NEt_3, CH_2Cl_2, rt, 92%. (g) Pd/C, H_2, MeOH, rt, 98%.

either through its acid chloride or via EDCI/DMAP, led to PQS-1 (**1**) in high isolated yield and of good purity. To obtain **1** of higher quality, a modified approach from sebacoyl chloride (**11**) was investigated (Route **B**). Formation of monobenzylated sebacic acid **12** (57% yield after chromatography) and then coupling and deprotection steps via **13** gave mono-PEGylated sebacic acid **10** in high purity following simple precipitation from Et_2O. Although the overall yield for PQS-1 (**1**) was generally lower using route **B**, the quality of the material was consistently higher than that obtained via route **A**.[7,8]

The linker unit between ubiquinol and MPEG in PQS-1 (**1**) is derived from 10-carbon sebacic acid (**8**), which underwent both mono- and (undesired) diacylation due to the open chain nature of sebacoyl chloride. Replacement of the C_{10} unit by a C_4 fragment originating from succinic anhydride would eliminate opportunities for undesired by-products due to reactions at both termini. Thus, starting with (inexpensive) MPEG-2000 (**14**) and succinic anhydride, mono-PEGylated succinic acid **15** was formed in excellent yield (Scheme 2).

Scheme 2. [a]



[a]Reagents and conditions: (a) succinic anhydride, NEt_3, toluene, 60 °C, 99%. (b) *N*-hydroxysuccinimide, EDCI, CH_2Cl_2, rt, 99%. (c) ubiquinol, NaH, THF, 0 °C to rt, 65%.

EDCI-mediated coupling of acid **15** and *N*-hydroxysuccinimide led to activated ester **16**. Neither of these two steps required product purification. Lastly, ester **16** was coupled with ubiquinol[9] in THF to provide PQS-3 (**3**) after straightforward purification on silica gel.[8] This streamlined, cleaner procedure could be successfully repeated on various scales[10] in up to 64% overall yield.

After lyophilization, PQS-3 (**3**) appears as a white, fluffy solid, which readily dissolves in water to provide micelles having an average diameter size of 21 nm, as determined by DLS measurements (Figure 3; r = radius). By contrast, PQS-1

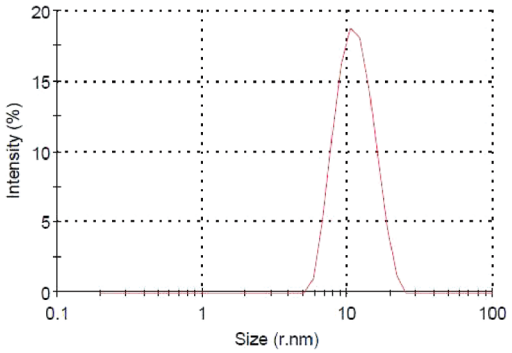


Figure 3. Particle size of PQS-3 (**3**) measured by DLS (r = radius).

(**1**) in water consists of particles of ca. 9 nm. The spherical nature of these self-aggregated nanoparticles, which can appear, in part, to be agglomerated and therefore oblong in shape, was confirmed by cryo-TEM measurements (Figure 4).

To ensure that the minor difference between PQS-1 and PQS-3 (i.e., the 10- vs 4-carbon linker) does not translate into differences in the observed catalysis, **3** was attached to acid **17**[11] to yield carbene precursor **18** (Scheme 3). Subsequent insertion of Ru yielded **6** in good overall yield. PQS-3-GH1 (**6**) appears as a brown solid that is freely soluble in water and

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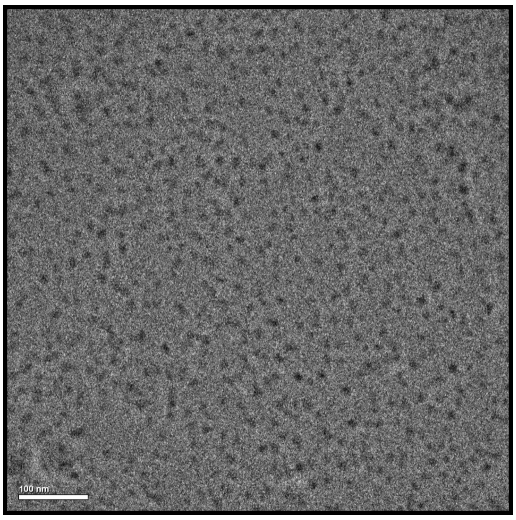
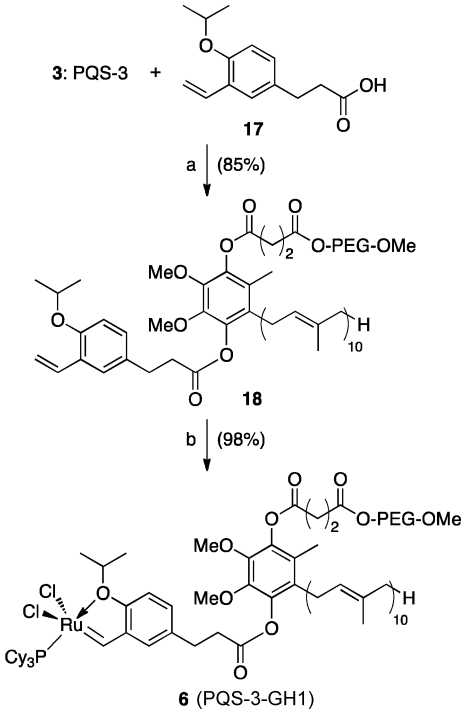


Figure 4. Cryo-TEM measurements of PQS-3 (**3**).

Scheme 3. [a]



[a]Reagents and conditions: (a) EDCI, DMAP, NEt_3, CH_2Cl_2, rt, 85%. (b) Grubbs first generation, CuCl, CH_2Cl_2, rt, 98%.

forms nanoreactors with an average diameter of 30 nm by DLS (Figure 5; r = radius).

Cryo-TEM measurements of PQS-3-GH1 (**6**) confirmed the size of these particles and showed their spherical appearance (Figure 6).

Diene **19** was subjected to RCM to yield the cyclized product **20** using **6** as the micelle forming catalyst (Scheme 4.). Compared to results obtained previously with **4**,[4a] the newly developed third generation platform (i.e., **6**) functions virtually identically.

New systems, such as PQS-(*R*)-BINAP (**21**) are currently under investigatation for applications to asymmetric Rh- and

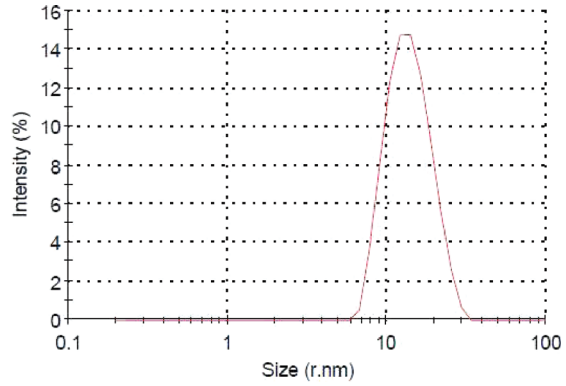


Figure 5. Particle size of PQS-3-GH1 (**6**) measured by DLS (r = radius).

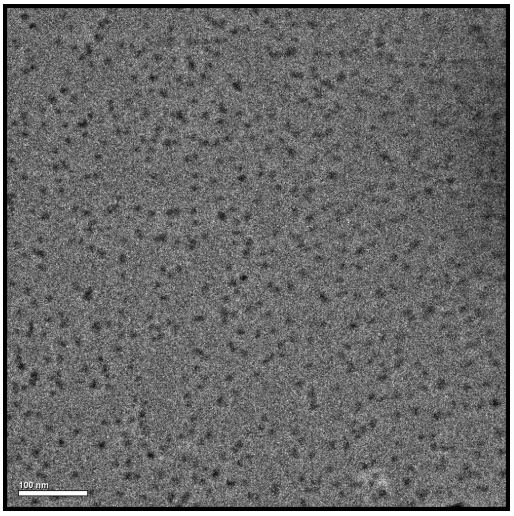
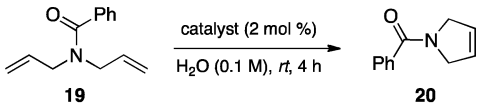


Figure 6. Cryo-TEM measurements of PQS-3-GH1 (**6**).

Scheme 4.



catalyst	yield [%]
4[4a]	94
6	96

Pd-catalyzed transformations in water, providing similar options for straightforward catalyst recycling (Figure 7).

CONCLUSIONS

Two alternative synthetic entries to PQS-1 (**1**) are presented. A further improved, third-generation designer surfactant in the PQS series, PQS-3 (**3**), has been developed, the synthesis of which is straightforward, higher yielding than existing routes, and potentially scalable. Both surfactants function equally well, as manifested by the representative case of a covalently derivatized ruthenium catalyst, which enables olefin metathesis reactions to be carried out under homogeneous conditions in water at room temperature with in-flask catalyst recycling.

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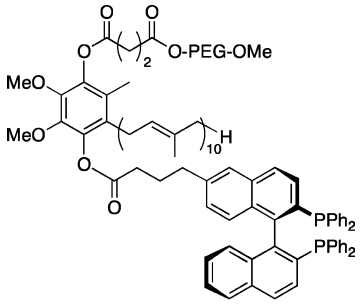

21: PQS-(*R*)-BINAP

Figure 7. PQS-(*R*)-BINAP (**21**) for Rh and/or Pd catalysis.

EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise noted, all reactions were performed in oven-dried glassware under an atmosphere of argon. Poly(ethylene glycol) methyl ether (**14**, MPEG-2000) was obtained from Aldrich (catalog # 202509). ^{1}H and ^{13}C spectra were recorded at 22 °C on a 400 or 500 MHz NMR spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale.

Route A:[7] Synthesis of Mono-PEGylated Sebacic Acid 10. A 250 mL round-bottom flask containing a strong magnetic stir bar was charged with poly(ethylene glycol) methyl ether (**14**, 10.00 g, 5.00 mmol, typical M_n 2000), sebacic acid derivative[6] (1.38 g, 7.50 mmol), 4-dimethylaminopyridine (90 mg, 0.75 mmol), and pyridine (25 mL). After a reflux condenser was attached, the system was purged with argon and heated to 100 °C in an oil bath for 4 h, whereby all solids dissolved. After the clear solution was cooled to room temperature, the reaction mixture was acidified with 1.5 N aq HCl until pH < 7 and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated, and placed overnight under a high vacuum to give **10** as a white waxy solid (10.84 g, 4.96 mmol, 99% isolated yield). Alternatively, the product can be purified by the following procedure: after concentration and high vacuum (∼1 h), the crude product mixture was dissolved in a minimal amount of CH_2Cl_2, a strong stir bar was added, and under continuous stirring, an excess of Et_2O (∼1 L) was added to precipitate out the product (if necessary, cooling to −20 °C using an NaCl/ice bath helps the precipitation process). Stirring was continued for 1 h at −20 °C, and the formed white precipitate was filtered to yield **10** as a white crystalline solid. Special care needs to be taken during the filtration step: water has to be excluded, and a glass frit should be used. A regular empty glass column (4.5 × 30 cm) with frit was used for this purpose. The cooled suspension was poured into the column, and a positive pressure of dried argon was applied immediately. The residue was washed twice with cold Et_2O and dried under a stream of argon. To finally dry the product, the stopcock of the column was closed and a high vacuum was applied. The product **10** was isolated as a white crystalline solid.

Synthesis of PQS-1 (1). An oven-dried 50 mL round-bottom flask (A) containing a magnetic stir bar was charged with MeOPEG sebacic acid **10** (3.08 g, 1.41 mmol), a reflux condenser was attached, and the system was purged with argon. Thionyl chloride (5 mL) was added through the reflux condenser and heated to reflux for 2 h while the evolving gas was bubbled through water and aq NaOH. The reaction mixture was cooled to room temperature under argon, and excess thionyl chloride was taken off using an aspirator. Further drying on a high vacuum overnight gave a pale orange solid that was dissolved in dry THF (10 mL, distilled from Na/benzophenone) and used in the next step without further purification. In a glovebox, an oven-dried 250 mL round-bottom flask (B) was loaded with a strong magnetic stir bar, ubiquinol (4.89 g, 5.65 mmol), and sodium hydride (170 mg, 4.24 mmol, 60% w/w in mineral oil). Outside the glovebox, under an atmosphere of argon, dry THF (10 mL, distilled from Na/benzophenone) was added, and the suspension was stirred at room temperature for 1 h and cooled to 0 °C. The solution of MeOPEG sebacic chloride in THF (flask A) was added via canulla dropwise to flask B at 0 °C. Flask A was rinsed with additional dry THF (5−10 mL) and transferred to flask B. Under continuous stirring, the orange suspension was slowly warmed to room temperature overnight. The reaction was quenched by the dropwise addition of water and subsequent addition of 1 N aq HCl until pH < 7. The mixture was extracted using CH_2Cl_2 (1 × 100 mL, 2 × 50 mL); the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield a pale orange oil that can be purified by two different procedures.

Purification A, Short Path Column. An empty 240 g single step column (Thomson Instrument Company) was slurry packed with ∼240 g of silica gel in Et_2O. The pale orange oil was evenly loaded onto the column using a minimal amount of CH_2Cl_2, and the column was carefully closed using a head space frit. Using a Biotage SP4 system, the column was flashed with Et_2O (500 mL, flow rate 45 mL/min) and CH_2Cl_2 (500 mL, flow rate 40 mL/min) and eluted with 10−15% MeOH/CH_2Cl_2 over 2 L (flow rate 30 mL/min). Fractions containing PEG-ylated material were combined, evaporated, and dried on a high vacuum overnight to yield PQS-1 (**1**) as an amber solid (3.45 g, 1.12 mmol, 86% pure by NMR). Obtained spectral data matched the previously reported compound.[4a]

Purification B, Precipitation in Ether. The pale orange oil was dissolved in a minimal amount of CH_2Cl_2, a strong stir bar was added, and under continuous stirring, an excess of Et_2O (∼1 L) was added and if necessary cooled to −20 °C using an NaCl/ice bath. Stirring was continued for 1 h to yield a white suspension of PEG-ylated material in Et_2O. Because of the fine particle size, all attempts for filtration failed, and centrifugation was used instead. Unfortunately, the centrifuge used for this purpose could not be cooled during the centrifugation process, which led to a significant loss of material. Furthermore, the centrifuge could only be operated with 6 × 10 mL and was therefore not suited for scale-up purposes. An analytical sample (∼50 mg) confirmed the purity of PQS.

Route B: Synthesis of Monobenzylated Sebacic Acid 12. A 100 mL round-bottom flask was charged with sebacoyl chloride (**10**, 8.42 g, 35.2 mmol) and closed with a rubber septum. Et_2O (25 mL) was added, and the solution was cooled to −78 °C. Benzyl alcohol (2.51 g, 23.2 mmol) and NEt_3 (4.9 mL, 35.2 mmol) were added slowly, the cooling bath was removed, and the reaction was warmed to rt. After addition of 1 N HCl, the aqueous phase was extracted with Et_2O (3 × 25 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with hexanes to 1:1 EtOAc/hexanes gradient to afford monobenzylated sebacic acid **12** (3.90 g, 57%) as a white solid: mp 52−53 °C (recrystallized from hexanes); IR (thin-film) 2934, 2914, 2849, 1737, 1699, 1463, 1412, 1299, 1225, 1194, 1172, 940, 906, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, 5H), 5.12 (s, 2H), 2.36 (t, J = 7.0 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 1.67−1.60 (m, 4H), 1.34−1.27 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 173.9, 136.3, 128.7, 128.39, 128.38, 66.3, 34.5, 34.2, 29.22, 29.21, 29.15, 25.1, 24.8; MS (EI) m/z (%) 292 (M, 1), 274 (6), 264 (13), 185 (19), 107 (41), 98 (29), 91 (100); HRMS (EI) calcd for $C_{17}H_{24}O_4$ $[M]^+$ = 292.1675, found 292.1671.

Synthesis of Benzyl-Protected PEG Sebacic Acid 13. Monobenzylated sebacic acid **12** (2.00 g, 6.85 mmol) was dissolved and refluxed in $SOCl_2$ (4 mL). After 3 h, excess $SOCl_2$ was removed through distillation under reduced pressure. The residue was taken up in dry CH_2Cl_2 (6 mL). A solution of poly(ethylene glycol) methyl ether (**14**, 6.17 g, 3.08 mmol) and NEt_3 (1.0 mL, 6.85 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise and stirred overnight at rt. After addition of 1 N HCl, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried and concentrated in vacuo. The residue was taken up in a minimal amount of CH_2Cl_2, and an excess of ice cold Et_2O was added to form a

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white precipitate. After further cooling for 1 h, the precipitate was filtered to yield **13** (6.45 g, 92%) as a white solid: IR (thin-film) 3484, 2885, 2740, 2695, 1734, 1469, 1414, 1360, 1344, 1280, 1235, 1147, 1118, 1062, 947, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.09 (s, 2H), 4.21−4.19 (m, 2H), 3.77−3.46 (m, PEG), 3.36 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.64−1.56 (m, 4H), 1.27 (br s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 173.7, 136.3, 128.7, 128.3, 72.1, 70.75, 70.70, 70.65, 69.3, 66.2, 63.5, 59.2, 34.4, 34.3, 29.2, 25.03, 24.97; MS (ESI) $m/2z \sim 1167$ $(M + 2Na)^{+2}$.

Synthesis of Mono-PEGylated Sebacic Acid 10. A round-bottom flask was charged with **13** (6.41 g, 2.82 mmol) and Pd/C (0.60 g, 0.28 mmol, 5% Pd/C, Fluka) and closed with a rubber septum. MeOH (30 mL) was added, and an atmosphere of H_2 was provided (balloon). After stirring overnight, the reaction was filtered through Celite, washed with MeOH, and concentrated in vacuo. The residue was taken up in a minimal amount of CH_2Cl_2, and an excess of ice cold Et_2O was added to form a white precipitate. After further cooling for 1 h, the precipitate was filtered to afford **10** (6.05 g, 98%) as a white solid: IR (thin-film) 3527, 2887, 1735, 1639, 1467, 1346, 1281, 1243, 1148, 948, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.24−4.21 (m, 2H), 3.79−3.48 (m, PEG), 3.38 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.64−1.58 (m, 4H), 1.31 (br s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 173.5, 71.7−69.0 (m, PEG), 63.1, 58.8, 33.9, 33.7, 28.87, 28.84, 28.79, 24.6; MS (ESI) $m/2z \sim 1122$ $(M + 2Na)^{+2}$.

Route C: Synthesis of Mono-PEGylated Succinic Acid 15. To a solution of poly(ethylene glycol) monomethyl ether-2000 (**14**, 15.00 g, 7.50 mmol) and succinic anhydride (1.50 g, 15.00 mmol) in toluene (7.5 mL), Et_3N (0.53 mL, 3.75 mmol) was added at rt with stirring, and the stirring was continued at 60 °C for 8 h. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl (3 × 50 mL) and brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the poly(ethylene glycol) monomethyl ether-2000 succinate **15** (15.6 g, 99%) as a white solid: IR (thin-film) 3512, 2874, 1734, 1647, 1468, 1349, 1284, 1250, 1109, 949, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28−4.25 (m, 2H), 3.83−3.46 (m, PEG), 3.38 (s, 3H), 2.69−2.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 171.7, 71.4−68.5 (m, PEG), 63.2, 58.5, 28.6, 28.2; MS (ESI) $m/4z \sim 551$ $(M + 4Na)^{+4}$.

Synthesis of Activated PEGylated Succinic Acid 16. Poly(ethylene glycol) monomethyl ether-2000 succinate **15** (2.10 g, 1.00 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. *N*-Hydroxysuccinimide (0.14 g, 1.20 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDCI, 0.25 g, 1.30 mmol) were then directly added in succession to the mixture as solids. The resulting mixture was stirred at rt for 12 h. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo to afford **16** (2.17 g, 99%) as a white waxy solid: IR (thin-film) 2883, 1814, 1784, 1739, 1645, 1468, 1360, 1280, 1234, 1205, 1147, 1116, 1062, 947, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29−4.27 (m, 2H), 3.83−3.46 (m, PEG), 3.38 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 2.84 (br s, 4H), 2.79 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.9, 167.6, 71.8−68.8 (m, PEG), 64.1, 59.0, 28.6, 26.2, 25.5; MS (ESI) $m/4z \sim 576$ $(M + 4Na)^{+4}$.

Synthesis of PQS-3 (3). NaH (0.026 g, 0.65 mmol, 60% suspension in mineral oil) was added to a stirred solution of ubiquinol (0.52 g, 0.60 mmol) in THF (5.0 mL) at 0 °C. After addition, the reaction mixture was stirred at 22 °C for 1 h. A solution of **16** (1.10 g, 0.50 mmol) in THF (5.0 mL) was added to the mixture at 0 °C, and the stirring was continued for 30 min. The mixture was then stirred for another 8 h at rt. It was then cooled to 0 °C, and saturated aqueous NH_4Cl was added and then extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo, affording a yellowish liquid, which was purified by flash column chromatography on silica gel eluting with a CH_2Cl_2 to 1:19 MeOH/CH_2Cl_2 gradient to afford **3** (0.95 g, 65%, mixture of two regioisomers) as a white waxy solid: IR (thin-film) 3518, 2885, 2740, 1761, 1738, 1663, 1467, 1360, 1343, 1280, 1242, 1147, 1114, 1062, 964, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 0.3H), 5.74 (s, 0.7H), 5.12−5.06 (m, 9H), 4.98−4.93 (m, 1H), 4.27−4.24 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.70−3.44 (m, PEG), 3.37 (s, 3H), 3.31 (d, J = 6.4 Hz, 1.4H), 3.16 (d, J = 6.4 Hz, 0.6H), 2.94−2.89 (m, 2H), 2.80−2.75 (m, 2H), 2.11−1.96 (m, 39H), 1.74 (s, 2.1H), 1.72 (s, 0.9H), 1.66 (s, 3H), 1.58−1.56 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.04, 171.96, 170.9, 170.7, 145.4, 145.0, 142.1, 141.9, 137.8, 137.6, 135.3, 135.1, 135.0, 134.9, 134.8, 131.1, 128.4, 124.9, 124.4, 124.2, 124.1, 124.0, 121.9, 121.6, 117.9, 71.9−69.0 (m, PEG), 63.9, 60.9, 60.8, 60.6, 60.5, 59.0, 39.7, 29.0, 28.8, 28.7, 26.7, 26.6, 26.0, 25.7, 25.3, 17.7, 16.3, 16.2, 16.0, 12.0, 11.3; MS (ESI) $m/4z \sim 763$ $(M + 4Na)^{+4}$.

Synthesis of Carbene Precursor 18. **3** (0.50 g, 0.17 mmol) was dissolved in CH_2Cl_2 (2.2 mL) and cooled to 0 °C. 1-(*p*-Isopropoxy-*m*-vinylphenyl)propionic acid (**17**)[11] (0.05 g, 0.22 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDCI) (0.04 g, 0.26 mmol), and DMAP (0.008 g, 0.07 mmol) were then directly added in succession to the mixture as solids. Et_3N (0.04 mL, 0.30 mmol) was added through a syringe. The resulting mixture was stirred at 22 °C for 20 h. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine, dried, and concentrated in vacuo, affording a colorless liquid, which was purified by flash column chromatography on silica gel, eluting with Et_2O, followed by CH_2Cl_2 to 1:12 MeOH/CH_2Cl_2 gradient, affording the compound **18** (0.45 g, 85%, mixture of two regioisomers) as a white foam: IR (thin-film) 2885, 1765, 1737, 1467, 1360, 1344, 1280, 1242, 1147, 1113, 1061, 963, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.37 (m, 1H), 7.12−7.08 (m, 1H), 7.03 (dd, J = 18.0, 11.2 Hz, 1H), 6.84−6.81 (m, 1H), 5.74 (dt, J = 18.0, 1.6 Hz, 1H), 5.23 (d, J = 11.2 Hz, 1H), 5.13−5.06 (m, 9H), 4.97−4.94 (m, 1H), 4.50 (sep, J = 6.4 Hz, 1H), 4.28−4.25 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.72−3.45 (m, PEG), 3.38 (s, 3H), 3.19−3.14 (m, 2H), 3.06−3.00 (m, 2H), 2.97−2.87 (m, 4H), 2.82−2.76 (m, 2H), 2.10−1.94 (m, 39H), 1.72−1.58 (m, 33H), 1.34 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.9, 169.9, 169.7, 169.4, 169.3, 152.9, 142.7, 142.5, 139.9, 139.8, 139.6, 139.5, 134.6, 134.0, 133.8, 131.4, 131.1, 130.1, 127.8, 127.4, 127.0, 125.6, 125.57, 124.0, 123.9, 123.6, 123.5, 123.2, 120.7, 113.8, 113.7, 113.1, 71.2, 70.9−69.3 (m, PEG), 68.2, 63.1, 59.8, 59.6, 58.1, 39.0, 38.9, 34.9, 29.4, 28.2, 28.1, 26.1, 25.9, 25.5, 25.0, 21.5, 17.0, 15.6, 15.4, 11.4, 11.3; MS (ESI) $m/4z \sim 839$ $(M + 4Na)^{+4}$.

Synthesis of PQS-3-GH1 Catalyst (6). **18** (0.44 g, 0.137 mmol) was weighed into a 25 mL round-bottom flask and dissolved in 6.5 mL of CH_2Cl_2. $(PCy_3)_2Cl_2Ru{=}CHPh$ (0.14 g, 0.17 mmol) and CuCl (0.018 g, 0.18 mmol) were added directly to this solution as solids. The mixture was stirred for a period of 4 h at 22 °C, during which time the original purple solution turned dark brown. The following workup procedures were conducted in air with reagent-grade solvents. The mixture was concentrated at reduced pressure and passed through a short column of silica gel eluting with CH_2Cl_2 followed by Et_2O. Finally, the column was flushed with 8% MeOH/CH_2Cl_2, at which point the product eluted (brown band). Solvent removal afforded the catalyst **6** (0.49 g, 98%, mixture of two regioisomers) as dark brown foam: IR (thin-film) 2883, 1764, 1737, 1644, 1468, 1449, 1359, 1344, 1280, 1234, 1146, 1113, 1061, 946, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 17.40 (d, J_{PH} = 4.4 Hz, 1H), 7.60−7.58 (m, 1H), 7.56−7.52 (m, 1H), 7.02−7.00 (m, 1H), 5.25 (sep, J = 6.4 Hz, 1H), 5.13−5.10 (m, 9H), 5.00−4.95 (m, 1H), 4.29−4.25 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.70−3.47 (m, PEG), 3.38 (s, 3H), 3.22−3.16 (m, 2H), 2.97−2.87 (m, 4H), 2.82−2.76 (m, 2H), 2.36−2.28 (m, 2H), 2.10−1.98 (m, 39H), 1.81−1.58 (m, 66H), 1.42−1.24 (m, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 279.1, 171.95, 171.86, 170.8, 170.7, 170.3, 170.2, 151.5, 144.0, 143.4, 143.3, 143.2, 140.6, 140.4, 140.3, 135.8, 135.1, 134.8, 134.43, 134.39, 131.1, 129.45, 129.37, 128.4, 128.3, 125.0, 124.9, 124.4, 124.2, 124.0, 123.9, 122.5, 121.1, 116.0, 113.3, 75.5, 71.9, 70.5−69.0 (m, PEG), 63.90, 63.87, 60.6, 59.0, 39.7, 39.6, 35.9, 35.8, 35.7, 35.6, 31.7, 30.1, 29.7, 29.0, 28.8, 28.7, 27.74, 27.7, 26.9, 26.7, 26.67, 26.64, 26.3, 26.24, 26.16, 26.1, 25.7, 22.1, 22.0, 17.7, 16.34, 16.3, 16.0, 12.1; MS (ESI) $m/4z \sim 927$ $(M + 4Na)^{+4}$.

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***N*-Benzoyl-3-pyrroline (20).** Diene **19** (20 mg, 0.10 mmol) and catalyst **6** (7.5 mg, 0.002 mmol) were both added into a Teflon-coated stir-bar-containing Biotage 2−5 mL microwave reactor vial at room temperature and sealed with a septum. H_2O (1.0 mL) was added via syringe, and the resulting solution was allowed to stir at rt for 4 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL) and filtered through a bed of silica gel layered over Celite, and the bed was further washed (2 × 4 mL) with EtOAc to collect all of the cyclized material. The volatiles were removed in vacuo to afford the crude product, which was subsequently purified by flash chromatography using silica gel (40% EtOAc/hexanes) to afford the title compound **20** as a colorless liquid (17 mg, 96%). The ^{1}H NMR spectral data obtained was in accord with data previously reported for this compound.[4a]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

A detailed comparison of route **A** vs **B** and spectral data, including copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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