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General Preparation and Controlled Cyclization of Acyclic Terpenoids

Jinchul Kuk,[†] Beom Soo Kim,[‡] Heejung Jung,[‡] Seyoung Choi,[‡] Jung-Youl Park,[‡,§] and Sangho Koo*[,†,‡]

Department of Nano Science and Engineering and Department of Chemistry, Myong Ji University, Yongin, Kyunggi-Do, 449-728, Korea

sangkoo@mju.ac.kr

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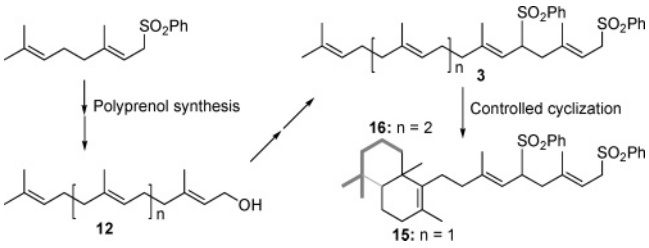
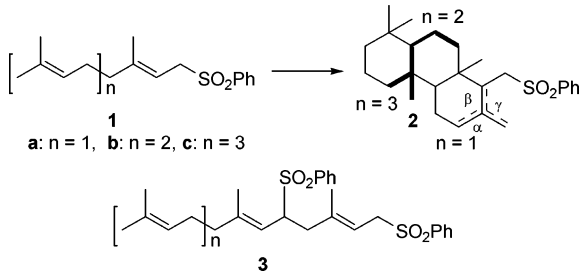


A general preparation method of the *all*-(*E*)-polyprenols **12** has been developed from readily available geranyl sulfone by the chain-extension process utilizing the C_5 unit **5** and the chain-termination process utilizing the C_5 unit **10** together with the chemoselective reductive desulfonylation. The polyprenols **12** were converted to compounds **3** containing two consecutive prenyl sulfone moieties at the tail end, which underwent the controlled electrophilic cyclization only at the carbon−carbon double bonds that were remote from the flat and rigid benzenesulfonyl groups.

It is surprising that nature produces tens of thousands of cyclic terpenoid secondary metabolites from just a few acyclic polyprenyl substrates: geranyl, farnesyl, and geranylgeranyl pyrophosphates.[1] The terpene cyclase enzymes control the mode of these diverse cyclizations to produce a plethora of cyclic terpenoids from the simplest menthol to the much more complex taxol.[2] Organic chemists have challenged the total syntheses of the biologically important cyclic terpenoids, in which each specific cyclization method was applied to different substrates

SCHEME 1. Controlling the Electrophilic Cyclization of the Polyprenyl Sulfones



to construct the diverse cyclic structures.[3] It is desirable to have a general, but still controllable, cyclization method for the acyclic polyprenyl compounds in order to synthesize the diverse cyclic terpenoids.

Terpenoid cyclization in nature is electrophilic, and various acidic conditions in vitro have been found to induce the efficient cyclization of the polyprenyl compounds as a mimic of the biological process.[4] These conditions were mostly very strong, and unstoppable cyclization cascades of the polyprenyl sulfones **1** gave rise to the polycyclic terpenoid compounds **2**, in which deprotonation of the cyclized tertiary carbocation intermediates produced the regioisomeric alkene products (α-, β-, and γ-forms in Scheme 1).[5] It was envisioned that the degree of the cyclization cascades would be controlled by inserting a benzenesulfonyl group into the polyprenyl sulfone chain such as in compound **3**.[6] The flat and rigid nature of the two consecutive benzenesulfonyl moieties in compound **3** would prevent the nearby carbon−carbon double bonds from taking the required conformations for cyclization, thereby allowing the cyclization only at the remote carbon−carbon double bonds (Scheme 1). Since sulfone chemistry has been efficiently utilized in the chain-extension process for isoprenoid synthesis,[7] the controlled cyclization, together with the chain-extension process using the sulfonyl group, would constitute a general and efficient synthetic method of the cyclized terpenoid compounds.

This research commenced with the preparation of compound **3** containing two consecutive prenyl sulfone moieties at the tail end, which can be synthesized from the polyprenyl sulfones **1** utilizing our chain-extension strategy (Scheme 2).[7] The polyprenyl sulfones **1** can be obtained from the corresponding polyprenols by a straightforward sequence of reactions: bromination and sulfonylation. It is not practical, however, to purchase long-chain polyprenols such as geranylgeraniol and geranylfarnesol. Thus, a direct chain-extension method from readily available geranyl sulfone **1a** ($n = 1$) to the higher homologous sulfones **1** ($n = 2$ or higher) was investigated by modifying the chain-extension procedure. Each iteration sequence in Scheme 2 produces a C_5-extended polyallylic sulfone

* To whom correspondence should be addressed. Phone: (+82)-31-330-6185. Fax: (+82)-31-335-7248.
[†] Department of Nano Science and Engineering.
[‡] Department of Chemistry.
[§] Current address: C&C Research Lab. ChoongWae Pharma Corporation, 148-141, Annyeong-Dong, Hwaseong-Shi, Kyunggi-Do, 445-380, Korea.

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SCHEME 2. General Chain-Extension Method and Possibility for the Chemoselective Reductive Elimination of Sulfone

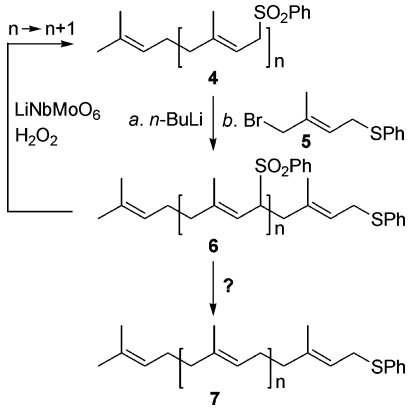
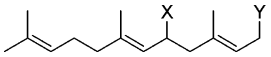
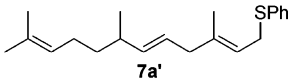


TABLE 1. Tests for the Chemoselective Reductive Elimination of the Sulfonyl Group in 6a



6a: X = SO_2Ph, Y = SPh
7a: X = H, Y = SPh
8 : X = H, Y = H
9 : X = SO_2Ph, Y = H



7a'

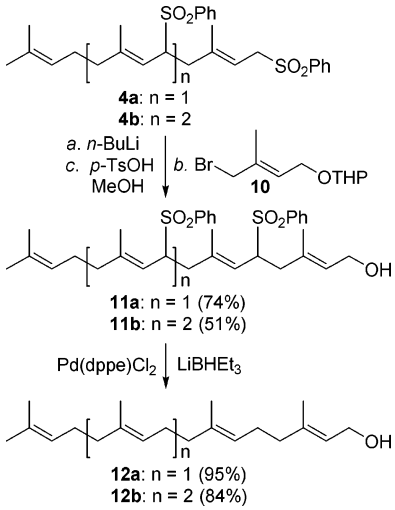
entry	reagent	**7a** (%)	**7a′** (%)	**8** (%)	**9** (%)
1	Na(Hg), MeOH	34	33	0	0
2	$Pd(dppe)Cl_2$, $LiBHEt_3$	17	0	30	23
3	Li, $EtNH_2$	0	0	76	0

4, which may react with the C_5 unit **5** again to give rise to the allylic sulfide **6** containing the internal allylic sulfone moieties.[7] The chemoselective reductive elimination of all the benzenesulfonyl groups in **6** would produce the polyprenyl sulfide **7**, which would lead to the C_5-extended polyprenyl sulfone **1** upon oxidation of the sulfide group. The success of this approach depends on the feasibility of the chemoselective reductive elimination of a sulfonyl group in the presence of a sulfide group.

Three representative conditions for the reductive desulfonylation have been evaluated for **6a** (Table 1). Contrary to the base-promoted elimination of the benzenesulfonyl group in **6a,** which proceeded chemoselectively to produce the allylic sulfide containing the conjugated triene moiety,[8] none of the above conditions provided a satisfactory result. The relatively mild condition of using Na(Hg) with $NaHPO_4$ buffer in MeOH at 0 °C produced the required polyprenyl sulfide **7a** chemoselectively, which was, however, contaminated by the same amount of inseparable regioisomeric allylic sulfide **7a′** (entry 1). The formation of **7a′** under the condition using Na(Hg) was considered to be inevitable considering the resonance forms of the intermediate allylic radical species.[9]

Palladium(II)-catalyzed, hydride-promoted reductive desulfonylation has been devised to overcome the above regioisomeric problem in allylic sulfone compounds.[10] The combination of $Pd(dppe)Cl_2$ and $LiBHEt_3$ consistently worked best for the reductive desulfonylation without migration of the carbon−carbon double bond.[11] However, Pd(II) activated not only the benzenesulfonyl group, but also the thiophenyl group in **6a**, and thus hydride eliminated either group indiscriminately to produce the mixtures of **7a**, **8**,[12] and **9** (entry 2). The dissolving metal reduction condition utilizing Li in $EtNH_2$ at −78 °C[13] was so strong that both functional groups were eliminated to give rise to compound **8** exclusively (entry 3). The chemoselective reductive elimination of the sulfonyl group over the sulfide group in **6** was not feasible, so the synthetic plan had to be modified.

SCHEME 3. General Preparation of Polyprenols: Geranylgeraniol (12a) and Geranylfarnesol (12b)



It was envisioned that the chemoselective reductive elimination of the sulfonyl group would be possible under the condition using $Pd(dppe)Cl_2/LiBHEt_3$ if a terminal hydroxyl group was utilized in place of the sulfide group. A hydroxyl is converted into an alkoxide, a poor leaving group, under the basic condition using $LiBHEt_3$, and may survive the reaction condition. A new scheme has been devised to apply the chemoselective reductive elimination of sulfonyl groups in the presence of a terminal hydroxyl group, which would lead to the polyprenol **12** instead of the polyprenyl sulfone **1** (Scheme 3). The iteration strategy for the chain-extension of isoprenoids was used again. The chain-extended, polyprenyl sulfones **4** finally reacted with the chain-terminating C_5 unit **10**, tetrahydropyranyl (THP) ether of (*E*)-4-bromo-3-methyl-2-buten-1-ol,[14] to produce the allylic alcohols **11** after deprotection of the THP group. The chemoselective reductive elimination of the sulfonyl groups using the above condition worked very well for **11** to give rise to the *all*-(*E*)-polyprenols **12**. Neither migration nor *E*/*Z* isomerization of the carbon−carbon double bond was observed during the

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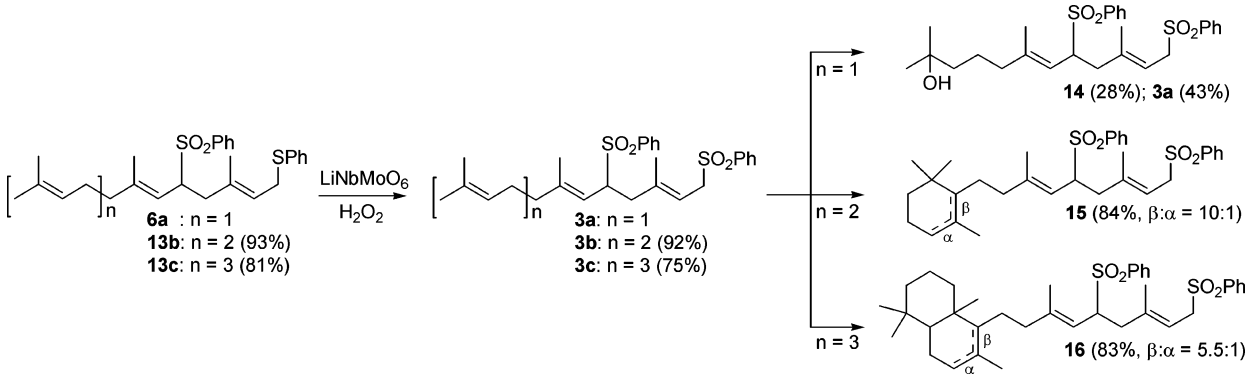
SCHEME 4. Controlled Electrophilic Cyclization of Acyclic Terpenoids Containing the Structurally Rigid Sulfone Moieties



hydrodesulfonylation. Thus, a general synthetic method for the *all*-(*E*)-polyprenols **12** from readily available geranyl sulfone **1a** was established. The efficiency of this process has been demonstrated for the syntheses of *all*-(*E*)-geranylgeraniol (**12a**)[15] and *all*-(*E*)-geranylfarnesol (**12b**) in Scheme 3.

The polyprenols **12** were converted to the polyprenyl sulfones **1** by bromination (PBr_3) and sulfonylation ($PhSO_2Na$), which were then applied to the chain-extension process to produce the substrates **3** for the controlled cyclization reaction (Scheme 4). Farnesyl sulfone **1b** ($n = 2$) and geranylgeranyl sulfone **1c** ($n = 3$) reacted with the C_5 unit **5** to generate **13b** (93%) and **13c** (81%), respectively. The mild oxidation reaction of the allylic sulfides **13b** and **13c** utilizing H_2O_2 and the $LiNbMoO_6$ catalyst provided the corresponding allylic disulfones **3b** (92%) and **3c** (75%), respectively.[16]

In vitro electrophilic cyclizations of acyclic terpenoids require strongly acidic conditions. Several sulfonic acids including superacids have been utilized for initiation of the cyclization.[17] We decided to use the relatively mild condition of methanesulfonic acid ($MeSO_3H$) in *i*-$PrNO_2$ at room temperature for the controlled electrophilic cyclization of the polyprenyl compounds **3**. The sesquiterpene **3a** did not undergo the cyclization reaction because it contained only one carbon−carbon double bond far away from the disulfonyl moieties. Instead, the hydration product **14** (28%) was obtained together with the recovered starting material (43%). The diterpene **3b** and the higher homologue **3c** underwent the electrophilic cyclization only at the remote carbon−carbon double bonds away from the disulfone moieties to produce the monocyclic compound **15** (84%, β:α = 10:1) and the bicyclic compound **16** (83%, β:α = 5.5:1), respectively.[18] It is noteworthy that the β-isomers were obtained as the major products in the controlled cyclization, while the α-isomers were reported to be the major products for the cyclization cascades of the polyprenyl sulfones **1**,[5] which manifested the thermodynamic stability of each product.

In conclusion, a general and efficient preparation method of *all*-(*E*)-polyprenols **12** starting from readily available geranyl sulfone was developed. The synthesis in this study highlights the chain-extension process utilizing the C_5 unit **5** and the chain-termination process that makes use of the C_5 unit **10** and the chemoselective reductive elimination of the sulfonyl groups. Also demonstrated was the possibility of controlling the cyclization cascades of acyclic terpenoids under an acidic condition by inserting the flat and rigid benzenesulfonyl group into the polyprenyl chains. The sulfone-mediated chain-extension and controlled cyclization strategy can be usefully applied to the syntheses of diverse cyclic terpenoid natural products.

Experimental Section

(2*E*,6*E*,10*E*)-5,9-Bis(benzenesulfonyl)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-ol (11a). To a stirred solution of **4a** (1.88 g, 3.87 mmol) in THF (10 mL) was added a 1.6 M solution of *n*-BuLi in hexane (3.14 mL, 5.03 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min, and a solution of **10** (1.25 g, 5.03 mmol) in THF (4 mL) was added. The reaction mixture was stirred at −78 °C for 1 h, quenched with 1 M HCl, and extracted with EtOAc. The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then dissolved in MeOH (20 mL), and *p*-TsOH (1.27 g, 6.7 mmol) was added. The mixture was stirred for 20 min in a cold water bath, and then most of the solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **11a** (1.63 g, 2.86 mmol) in 74% yield. Data for **11a** (the major stereoisomer from 2:1 mixture): ^{1}H NMR δ 1.13 (d, J = 1.3 Hz, 3H), 1.39 (d, J = 1.1 Hz, 3H), 1.55 (s, 3H), 1.57 (s, 3H), 1.67 (s, 3H), 1.82−2.00 (m, 4H), 2.17−2.35 (m, 2H), 2.72−2.95 (m, 2H), 3.77−3.99 (m, 2H), 4.03 (d, J = 6.6 Hz, 2H), 4.92 (d, J = 13.2 Hz, 1H), 4.96 (d, J = 11.3 Hz, 1H), 4.98 (br s, 1H), 5.36 (t, J = 6.9 Hz, 1H), 7.46−7.57 (m, 4H), 7.58−7.68 (m, 2H), 7.76−7.84 (m, 4H) ppm; ^{13}C NMR δ 16.0, 16.3, 16.5, 17.6, 25.6, 26.0, 37.2, 37.9, 39.6, 58.9, 62.8, 62.9, 117.1, 119.9, 123.3, 127.6, 128.7, 128.8, 129.0, 129.1, 131.9, 133.2, 133.6, 133.6, 137.2, 137.4, 141.1, 145.4 ppm; IR (KBr) 3522, 2918, 1447, 1304, 1145, 1084 cm^{-1}; HRMS (CI^+) calcd for $C_{26}H_{35}O_2S$ [$C_{32}H_{43}O_5S_2$ − ($C_6H_6SO_2$) − (H_2O)] 411.2352, found 411.2358.

Geranylgeraniol (12a). To a stirred solution of **11a** (420 mg, 0.73 mmol) in THF (2 mL) was added a 1 M solution of $LiBHEt_3$ in THF (7.34 mL, 7.34 mmol). The mixture was stirred at room temperature for 40 min, and $Pd(dppe)Cl_2$ (130 mg, 0.22 mmol) was added. The resulting mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2, washed with 1 M NaOH, dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **12a** (200 mg, 0.69 mmol) in 95% yield.

(2*E*,6*E*,10*E*,14*E*)-5-(Benzenesulfonyl)-3,7,11,15,19-pentamethylicosa-2,6,10,14,18-pentaenyl Phenyl Sulfide (13c). To a stirred

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(18) The controlled cyclization of compound **13b** also worked to give the corresponding monocyclization product in 63% yield, which was 21% lower than that of the cyclization of disulfone **3b**, presumably due to instability of the C−S bond under an acidic condition.

solution of geranylgeranyl sulfone **1c** (2.23 g, 5.37 mmol) in THF (10 mL) was added a 1.6 M solution of *n*-BuLi in hexane (4.7 mL, 7.52 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h, and a solution of **5** (2.76 g, 10.74 mmol) in THF (5 mL) was added. The reaction mixture was stirred at −78 °C for 1.5 h, quenched with 1 M HCl, extracted with EtOAc, dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **13c** (2.71 g, 4.58 mmol) in 85% yield. Data for **13c**: ^{1}H NMR δ 1.13 (d, J = 1.3 Hz, 3H), 1.53 (s, 3H), 1.59 (s, 9H), 1.67 (s, 3H), 1.86−2.13 (m, 12H), 2.31 (dd, J = 13.4, 11.3 Hz, 1H), 2.90 (br d, J = 13.4 Hz, 1H), 3.47 (d, J = 7.7 Hz, 2H), 3.87 (ddd, J = 11.3, 10.5, 3.1 Hz, 1H), 4.88 (d, J = 10.5 Hz, 1H), 4.99−5.17 (m, 3H), 5.32 (t, J = 7.7 Hz, 1H), 7.11−7.31 (m, 5H), 7.45−7.55 (m, 2H), 7.56−7.65 (m, 1H), 7.79−7.88 (m, 2H) ppm; ^{13}C NMR δ 15.9, 15.9, 16.0, 16.3, 17.6, 25.6, 26.2, 26.5, 26.6, 31.8, 37.0, 39.6, 39.6, 39.6, 63.1, 116.7, 123.0, 123.4, 124.0, 124.3, 125.9, 128.6, 128.6, 129.1, 129.4, 131.1, 133.3, 134.5, 134.9, 135.5, 136.4, 137.7, 145.5 ppm; IR (KBr) 2919, 1447, 1305, 1147, 1086 cm^{-1}; HRMS (CI$^+$) calcd for $C_{37}H_{51}O_2S_2$ 591.3330, found 591.3327.

(2*E*,6*E*,10*E*,14*E*)-1,5-Bis(benzenesulfonyl)-3,7,11,15,19-pentamethylicosa-2,6,10,14,18-pentaene (3c). To a stirred solution of **13c** (1.12 g, 1.9 mmol) in MeOH (20 mL) and benzene (2 mL) were added $LiNbMoO_6$ (10 mg, 0.04 mmol) and 28% aqueous H_2O_2 solution (1.2 mL, 11.4 mmol) in a cold water bath. The reaction mixture was stirred for 11 h, and most of the solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2, washed with H_2O and 1 M HCl, dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **3c** (880 mg, 1.42 mmol) in 75% yield. Data for **3c**: ^{1}H NMR δ 1.14 (d, J = 1.3 Hz, 3H), 1.35 (s, 3H), 1.58 (d, J = 1.1 Hz, 3H), 1.60 (s, 6H), 1.68 (s, 3H), 1.91−2.01 (m, 8H), 2.01−2.12 (m, 4H), 2.34 (dd, J = 13.6, 11.2 Hz, 1H), 2.93 (br d, J = 13.6 Hz, 1H), 3.75 (d, J = 8.0 Hz, 2H), 3.86 (ddd, J = 11.2, 10.5, 3.1 Hz, 1H), 4.88 (d, J = 10.4 Hz, 1H), 5.03 (br s, 1H), 5.09 (t, J = 6.8 Hz, 2H), 5.18 (t, J = 8.0 Hz, 1H), 7.49−7.58 (m, 4H), 7.60−7.68 (m, 2H), 7.80−7.86 (m, 4H) ppm; ^{13}C NMR δ 16.0, 16.0, 16.3, 16.4, 18.9, 25.6, 26.2, 26.5, 26.7, 37.1, 39.8, 39.9, 40.2, 55.8, 62.9, 113.5, 116.5, 123.3, 124.0, 124.3, 128.3, 128.7, 129.0, 129.2, 131.2, 133.6, 133.7, 135.0, 135.7, 137.4, 138.7, 141.4, 146.2 ppm; IR (KBr) 2918, 1447, 1306, 1147, 1085 cm^{-1}; HRMS (EI$^+$) calcd for $C_{37}H_{50}O_4S_2$ 622.3150, found 622.3150.

(2*E*,6*E*)-1,5-Bis(benzenesulfonyl)-3,7-dimethyl-9-(2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalenyl)nona-2,6-diene (16). To a stirred solution of **3c** (290 mg, 0.47 mmol) in *i*-$PrNO_2$ (15 mL) was added $MeSO_3H$ (0.15 mL, 2.33 mmol). The mixture was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$ solution, extracted with ether, dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **16** (240 mg, 0.39 mmol) in 83% yield. Data for **16** (β:α = 5.5:1): ^{1}H NMR δ 0.78 (s, 3H), 0.97 (s, 3H), 0.98 (s, 3H), 1.10 (s, 3H), 1.36 (s, 6H), 1.01−2.05 (m, 15H), 2.33 (dd, J = 13.6, 10.4 Hz, 1H), 2.93 (br d, J = 13.6 Hz, 1H), 3.75 (d, J = 7.7 Hz, 2H), 3.77−3.93 (m, 1H), 4.84 (br s, 1H), 5.18 (br s, 1H), 5.31 (br s, 1H; from α-isomer), 7.47−7.58 (m, 4H), 7.59−7.68 (m, 2H), 7.77−7.87 (m, 4H) ppm; ^{13}C NMR δ 16.1, 16.3, 16.3, 16.4, 19.9, 21.1, 25.1, 27.0, 27.6, 29.2, 33.4, 33.4, 34.3, 34.4, 37.1, 39.8, 40.4, 55.8, 62.9, 113.6, 113.7, 116.1, 116.2, 128.2, 128.7, 129.0, 129.2, 133.6, 137.3, 137.6, 138.8, 141.3, 147.1 ppm; IR (KBr) 2927, 1447, 1306, 1147, 1085 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{37}H_{51}O_4S_2$ 623.3229, found 623.3222.

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Supporting Information Available: General experimental, experimental procedures, and data for **7a**, **8**, **9**, **10**, **11b**, **12b**, **13b**, **3b**, **14**, and **15** and ^{1}H/^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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