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Facile Syntheses of [8,9-$^2H_2$]- and [8-^2H]-Digeranyl

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SUMMARY

[8,9-$^2H_2$]- and [8-^2H]-(2*E*,6*E*,10*E*,14*E*)-2,6,11,15-tetramethyl-2,6,10,14-hexadecatetraene (digeranyl) (**1** and **2**) have been synthesized from geraniol by the condensation of geranyl *p*-tolylsulfone and reductive desulfonylation in the key steps.

Key words: digeranyl, geraniol, regioselective ^2H-label

INTRODUCTION

"Tail to tail" condensed isoprenoids, e.g. squalene (C_{30}) and phytoene (C_{40}), from corresponding isoprenyl diphosphates are biosynthesized in plants and are converted into cyclic triterpenoids and carotenoids, respectively. However, no naturally occuring C_{20}-isoprenoid, digeranyl, produced by the "tail to tail" condensation of geranyl diphosphate has been found. In the course of studies on the cyclization of "tail to tail" condensed isoprenoids by cultured plant cells, we needed to produce the regioselectively deuterium-labeled digeranyl. We have now synthesized [8,9-$^2H_2$]- and [8-^2H]-digeranyl (**1** and **2**) from geraniol (**3**) by condensation of *p*-tolylsulfonylated geraniol and reductive desulfonylation as the key steps.

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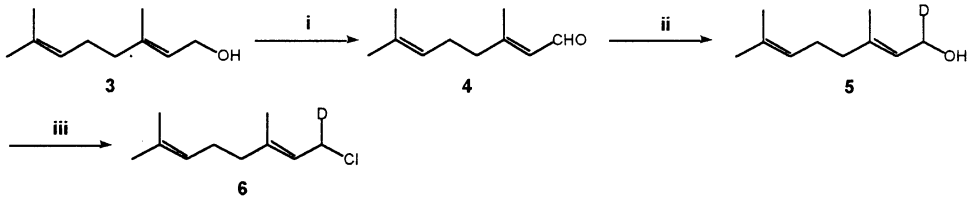
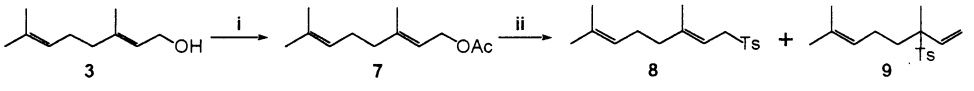
RESULTS AND DISCUSSION

[8,9-$^2H_2$]-Digeranyl (1) was synthesized by reductive desulfonylation of *p*-tolylsulfone **10** (Scheme 3), which was prepared by allylication from **6** (Scheme 1) and **8** (Scheme 2).

The synthesis of [1-^{2}H]-geranyl chloride (**6**) is summarized in Scheme 1. Oxidation of geraniol (**3**) with MnO_2 in petroleum ether gave the aldehyde **4** in 55% yield. Reduction of **4** with $NaBD_4$, $CeCl_3(H_2O)_7$ in MeOH gave [1-^{2}H]-geraniol (**5**) in 70% yield.[1] [1-^{2}H]-geraniol (**5**) was identified by ^{1}H and ^{2}H NMR spectral analyses (^{2}H-NMR δ = 4.10). **5** was treated with *N*-chlorosuccinimide and dimethyl sulfide in CH_2Cl_2 to give **6** in 97% yield.[2]



Scheme 1. Reagents and conditions: i) MnO_2, Petroleum ether, rt; ii) $NaBD_4$, $CeCl_3(H_2O)_7$, MeOH, rt; iii) *N*-Chlorosuccinimide, Dimethyl sulfide, CH_2Cl_2, 0 °C.

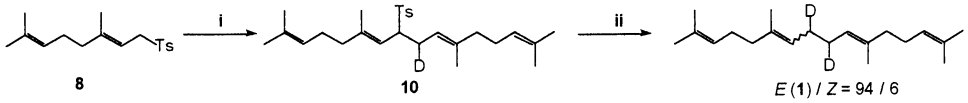


Scheme 2. Reagents and conditions: i) Ac_2O, Pyridine, DMAP, rt; ii) $TsNa \cdot 4H_2O$, $Pd(PPh_3)_4$, THF : MeOH = 2 : 1, rt.

According to a reported method,[3] geranyl *p*-tolylsulfone (**8**) was obtained by the sulfonylation of geranyl acetate (**7**) with $Pd(PPh_3)_4$, $TsNa\text{-}4H_2O$ in THF : MeOH in 85% yield. Accompanying the formation of **8**, this reaction afforded a little of linalyl *p*-tolylsulfone (**9**).

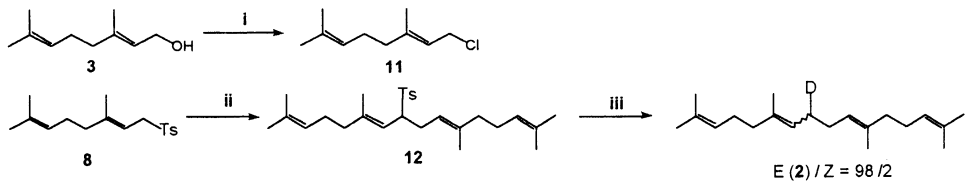
8 was selectively lithiatated with *n*-BuLi and TMEDA, followed by addition of [1-^{2}H]-geranyl chloride (**6**) to give *p*-tolylsulfone **10** in 60% yield. According to Mohri and co-workers,[4] **10** was reduced with $PdCl_2$(dppp) and $LiDBEt_3$ in THF to

give [8,9-$^2H_2$]-digeranyl (**1**) with the preservation of the original stereochemistry (*E*/*Z* = 94/6; 85% yield).



Scheme 3. Reagents and conditions: i) *n*-BuLi, TMEDA, **6**, THF, -10 °C; ii) $LiDBEt_3$, $PdCl_2$(dppp), THF, 0 °C.

[8-^2H]-Digeranyl (2) was synthesized from geraniol (**3**) in about 54% overall yield as shown in Scheme 4. Geranyl *p*-tolylsulfone (**8**) was lithiated, followed by addition of geranyl chloride (**11**) to give **12**, which was reduced with $PdCl_2$(dppp) and $LiDBEt_3$ in THF to give [8-^2H]-digeranyl **(2)** (*E* / *Z* = 98 / 2).



Scheme 4. Reagents and conditions: i) *N*-Chlorosuccinimide, Dimethyl sulfide, CH_2Cl_2, 0 °C; ii) *n*-BuLi, TMEDA, **11**, THF, -10 °C; iii) $LiDBEt_3$, $PdCl_2$(dppp), THF, 0 °C.

Thus, the syntheses of [8,9-$^2H_2$]- and [8-^2H]-digeranyl (**1** and **2**) from geraniol were achieved by the condensation of geranyl *p*-tolylsulfone and reductive desulfonylation with a deuterium-labeled reagent as the key steps.

EXPERIMENTAL

General. Analytical TLC was performed on precoated TLC plates (Merck 60 F_{254}). Column chromatography was conducted using silica-gel (Merck Silica gel 60 and Wakogel C-300). IR spectra were acquired on a JASCO FT/IR-7300

spectrometer. ^{1}H, ^{2}H and ^{13}C NMR spectra were obtained using a JEOL JNM-LA500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were produced on JEOL JMS-SX102A and HEWLETT PACKARD MSD-5971A mass spectrometers.

(2*E*,6*E*)-3,7-Dimethyl-octa-2,6-dienal (4). Geraniol (**3**) (5.0 g, 32.4 mmol) was suspended in 230 ml of petroleum ether, and MnO_2 (22.5 g, 0.26 mol) was added under N_2. After stirring at room temperature for 4 h, the precipitate was filtered through celite and the solvent was evaporated to give **4** (2.7 g, 55% yield). The crude product was used in the next step without purification. A sample for analysis was purified by preparative TLC (hexane : EtOAc = 3 : 1): EI-MS *m/z* 152 (M^+), 137, 123, 109, 95, 84, 69; IR (neat) 2970, 2930, 2858, 1675, 1633, 1445, 1378, 1195, 1123, 915 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 9.94 (d, 1H, J = 8.1 Hz), 5.82 (d, 1H, J = 8.1 Hz), 5.02 (t, 1H, J = 6.7 Hz), 2.16 (m, 4H), 2.12 (s, 3H), 1.63 (s, 3H) and 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 191.1, 163.7, 132.8, 127.3, 122.5, 40.5, 25.6, 25.5, 17.6 and 17.5.

[1-^{2}H]-(2*E*,6*E*)-3,7-Dimethyl-octa-2,6-dienol (5). To a solution of aldehyde **4** (2.8 g, 18.4 mmol) in dry MeOH (120 ml) was added $CeCl_3(H_2O)_7$ (7.8 g, 22.1 mmol) and $NaBD_4$ (924 mg, 22.1 mmol) under a N_2 atmosphere. After stirring at room temperature for 1 h, 1 M HCl was added dropwise to the reaction mixture until the pH was adjusted to 1.0, so as to destroy the excess $NaBD_4$. After evaporation of MeOH, the reaction mixture was extracted with ether to afford **5** (2.0 g, 70%). The crude product was used in the next step without purification. A sample for analysis was purified by preparative TLC (hexane : EtOAc = 3 : 1): EI-MS *m/z* 155 (M^+), 137, 123, 112, 108, 94, 81, 69; IR (neat) 3344, 2969, 2919, 2858, 1668, 1447, 1377, 1108 and 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 5.37 (d, 1H, J = 6.7 Hz), 5.06 (t, 1H, J = 6.5 Hz), 4.07 (d, 1H, J = 6.7 Hz), 2.02 (m, 4H), 1.64 (s, 3H), 1.63 (s, 3H) and 1.56 (s, 3H); ^{2}H NMR ($CDCl_3$) δ = 4.10; ^{13}C NMR ($CDCl_3$) δ = 139.1, 131.5, 123.8, 123.3, 58.8, 39.4, 26.3, 25.5, 17.5 and 16.1.

[1-^{2}H]-(2*E*,6*E*)-1-Chloro-3,7-dimethyl-2,6-octadiene (6). The reaction was run under a blanket of N_2. *N*-Chlorosuccinimide (1.7 g, 13.1 mmol) was dissolved in 45 ml of dry CH_2Cl_2. Dimethyl sulfide (1.0 ml, 14.2 mmol) was added dropwise to the stirred reaction mixture at –30 °C. To the mixture, [1-^{2}H]-geraniol (**5**) in 10 ml of dry CH_2Cl_2 was added at –40 °C. After stirring at 0 °C for 1 h, the reaction mixture was extracted with ether to give **6** (1.84 g, 97%). The crude product was used in the next step without purification. A sample for analysis was prepared by purification with preparative TLC (hexane : EtOAc = 3 : 1): IR (neat) 2970, 2924, 2814, 1647, 1449, 1377 and 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 5.34 (d, 1H, J = 6.7 Hz), 5.10 (t, 1H, J = 6.9 Hz), 3.91 (d, 1H, J = 6.7 Hz), 2.08 (m, 4H), 1.68 (s, 3H), 1.68 (s, 3H) and 1.60 (s, 3H); ^{2}H NMR ($CDCl_3$) δ = 3.94; ^{13}C NMR ($CDCl_3$) δ = 142.3, 131.5, 123.4, 120.1, 40.5, 39.2, 26.0, 25.4, 17.4 and 15.8.

(2*E*,6*E*)-1-Acetoxy-3,7-dimethyl-2,6-octadiene (7). To the mixture of geraniol (**3**) (5.0 g, 32.4 mmol) and DMAP (396 mg, 3.24 mmol), acetic anhydride (6.1 ml, 64.8 mmol) and pyridine (5.2 ml, 64.8 mmol) were added dropwise at 0 °C under a N_2 atmosphere. The mixture was stirred at room temperature for 1 h, and then 6 M HCl was added dropwise at 0 °C. The reaction mixture was extracted with ether to give **7** (6.3 g, 99%). The crude product was used in the next step without purification. A sample for analysis was obtained after purification by preparative TLC (hexane : EtOAc = 3:1): EI-MS *m/z* 196 (M^+), 154, 137, 136, 121, 107, 93, 80, 69; IR (neat) 2969, 2925, 2858, 1741, 1445, 1378, 1367, 1233, 1023 and 955 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 5.35 (bt, 1H), 5.10 (bt, 1H), 4.59 (d, 2H, J = 6.7 Hz), 2.08 (m, 7H), 1.71 (s, 3H), 1.69 (s, 3H) and 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 170.9, 142.0, 131.7, 123.7, 118.3, 61.3, 39.5, 26.2, 25.6, 20.9, 17.6 and 16.4.

(2*E*,6*E*)-3,7-Dimethyl-1-*p*-tolylsulfonyl-2,6-octadiene (8). Following the method described in reference 3, to the solution of sodium *p*-tolylsulfonate tetrahydrate (5.6 g, 22.4 mmol) in THF (28 ml) and MeOH (14 ml) was added acetate **7** (4.0 g, 20.4 mmol) and $Pd(PPh_3)_4$ in THF (24 ml) under a N_2 atmosphere. After stirring at room temperature overnight, aqueous KCN was added dropwise at 0 °C to

deactivate the palladium catalyst. The reaction mixture was extracted with ether to give a crude product, which was purified by column chromatography on silica gel using hexane–ethyl acetate (7 : 1) as eluent to give a product **8** (5.1 g, 85%): FAB-MS *m/z* 293 (MH^+); IR (neat) 2969, 2923, 2857, 1598, 1449, 1316, 1303, 1290, 1150, 1130, 1087, 817 and 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.73 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 5.17 (t, 1H, J = 7.9 Hz), 5.03 (m, 1H), 3.78 (d, 2H, J = 7.9 Hz), 2.42 (s, 3H), 2.00 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H) and 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 145.5, 144.0, 135.6, 131.3, 129.1, 128.1, 123.2, 110.2, 55.7, 39.2, 25.8, 25.3, 21.2, 17.2 and 15.8 and linalyl *p*-tolylsulfone (**9**): FAB-MS *m/z* 293 (MH^+); IR ($CHCl_3$) 2973, 2930, 2878, 1598, 1495, 1452, 1413, 1375, 1286, 1145, 1070, 1020, 1001, 816, 795, 609, 567 and 531 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.67 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 5.91 (dd, 1H, J = 17.5, 10.9 Hz), 5.35 (d, 1H, J = 10.9 Hz), 5.06 (d, 1H, J = 17.5 Hz), 5.06 (bt, 1H), 2.42 (s, 3H), 1.90 (m, 4H), 1.66 (s, 3H), 1.56 (s, 3H) and 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 144.2, 135.1, 132.3, 132.2, 130.5, 128.8, 123.0, 120.1, 68.0, 32.7, 25.4, 22.3, 21.3, 17.4 and 16.1.

[9-^{2}H]-(2*E*,6*E*,10*E*,14*E*)-2,6,11,15-Tetramethyl-8-*p*-tolyl sulfonyl-2,6,11,15-tetramethyl-2,6,10,14-hexadecatetraene (10). To the suspension of **8** (1.8 g, 6.16 mmol) and TMEDA (1.1 ml, 7.39 mmol) in 10 ml of THF, 1.5 M *n*-BuLi (4.9 ml, 7.39 mmol) in THF and **6** (1.3 g, 7.39 mmol) in THF (3 ml) were added dropwise at –15 °C under a N_2 atmosphere. After stirring at –10 °C for 30 min, the reaction mixture was treated with aqueous NH_4Cl and extracted with ether to give a crude product, which was purified by column chromatography on silica-gel with hexane–ethyl acetate (15 : 1) to give product **10** (1.6 g, 60%): FAB-MS *m/z* 430 (MH^+); IR (neat) 2968, 2923, 2857, 1597, 1449, 1378, 1314, 1301, 1289, 1146, 1087, 816, 664 and 581 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.66 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 4.94 (m, 4H), 3.66 (m, 1H), 2.79 (m, 0.5H), 2.36 (s, 3H), 2.27 (m, 0.5H), 1.91 (m, 8H), 1.62 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H),1.53 (s, 3H), 1.50 (s, 3H) and 1.18 (s, 3H); ^2H NMR ($CDCl_3$) δ = 2.84 and 2.30; ^{13}C NMR ($CDCl_3$) δ = 144.6,

144.0, 138.1, 135.1, 131.5, 131.1, 129.1, 128.9, 123.8, 123.5, 118.6, 117.0, 64.6, 39.5, 26.3, 26.0, 25.4, 21.3, 17.4, 16.3 and 16.1.

[8,9-$^2H_2$]-(2*E*,6*E*,10*E*,14*E*)-2,6,11,15-Tetramethyl-2,6,10,14-hexadecatetraene (1). Following the method described in reference 4, to the solution of **10** (83 mg, 193 μmol) and $PdCl_2$(dppp) (5.7 mg, 9.7 μmol) in THF (6.3 ml), $LiDBEt_3$ (46 μl, 386 μmol) was added at 0 °C under a N_2 atmosphere. After stirring at 0 °C for 1 h, 3 M NaOH and a small amount of aqueous KCN was added to the reaction mixture, and then the mixture was extracted with hexane to give the crude product. GLC analysis showed that the product was composed of 94% of (2*E*,6*E*,10*E*,14*E*)-isomer and 6% of the (2*E*,6*Z*,10*E*,14*E*)-isomer. It was subjected to column chromatography on silica-gel and eluted with hexane to give [8,9-$^2H_2$]-2,6,11,15-tetramethyl-2,6,10,14-hexadecatetraene (**1**) (45 mg, 85%): HRMS (EI) *m/z* calculated for $C_{20}H_{32}D_2$ 276.2786, observed 276.2780; EI-MS *m/z* 276 (M^+), 261, 233, 207, 190, 179, 150, 123,109, 95, 69; IR (neat) 2968, 2925, 2857, 1448, 1377, 1107 and 984 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.11 (m, 4H), 2.03 (m, 10H), 1.68 (s, 6H) and 1.60 (s, 12H); ^2H NMR ($CDCl_3$) δ = 2.01; ^{13}C NMR ($CDCl_3$) δ = 135.1, 131.2, 124.4, 124.2, 39.8, 27.8, 26.8, 25.7, 17.7 and 16.0. The deuterium enrichment of **1** was found to be 99% by mass spectral analysis.

(2*E*,6*E*)-1-Chloro-3, 7-dimethyl-2,6-octadiene (11). The reaction was carried out under a blanket of N_2. *N*-Chlorosuccinimide (10.4 g, 77.8 mmol) was dissolved in 210 ml of dry CH_2Cl_2. To the solution, dimethyl sulfide (6.2 ml, 84.2 mmol) was added dropwise at –30 °C and then geraniol (**3**) (10.0 g, 64.8 mmol) in 110 ml of dry CH_2Cl_2 was added at –40 °C. After stirring at 0 °C for 1 h, the reaction mixture was extracted with ether to give (2*E*, 6*E*)-1-chloro-3, 7-dimethyl-2,6-octadiene **(11)** (14.1 g, quant.): IR (neat) 2970, 2927, 2857, 1663, 1450, 1378, 1254, 839 and 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.43 (t, 1H, *J* = 7.9 Hz), 5.07 (t, 1H, *J* = 6.7 Hz), 4.06 (d, 2H, *J* = 7.9 Hz), 2.07 (m, 4H), 1.71 (s, 3H), 1.67 (s, 3H) and 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 142.5, 131.8, 123.5, 120.3, 41.0, 39.4, 26.2, 25.6, 17.6 and 16.0.

(2*E*,6*E*,10*E*,14*E*)-2,6,11,15-tetramethyl-8-*p*-tolylsulfonyl-2,6,11,15-tetramethyl-2,6,10,14-hexadecatetraene (12). To the mixture of (2*E*,6*E*)-3,7-7.39 mmol) in 8.0 ml of THF, 1.5 M *n*-B dimethyl-1-*p*-tolylsulfonyl-2,6-octadiene **(8)** (1.8 g, 6.16 mmol) and TMEDA (1.1 ml, uLi (2.1 ml, 7.39 mmol) and **11** (1.3 g, 7.39 mmol) in THF (4.0 ml) were added dropwise at –15 °C under a N_2 atmosphere. After stirring at –10 °C for 30 min, the reaction mixture was treated with aqueous NH_4Cl and extracted with ether to yield a crude product. The latter was purified by column chromatography on silica-gel eluting with hexane–ethyl acetate (15 : 1) to give (2*E*,6*E*,10*E*,14*E*)-2, 6, 11, 15-tetramethyl-8-*p*-tolyl sulfonyl-2, 6, 11, 15-tetramethyl-2,6,10,14-hexadecatetraene **(12)** (1.6 g, 61%); FAB-MS *m/z* 429 (MH^+); IR (neat) 2968, 2923, 2857, 1597, 1448, 1377, 1315, 1301, 1289, 1145, 1087, 816, 666 and 581 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.71 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 5.00 (m, 4H), 3.73 (m, 1H), 2.84 (m, 1H), 2.42 (s, 3H), 2.32 (m, 1H), 1.96 (m, 8H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H) and 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 144.6, 143,9, 138.1, 135.1, 131.5, 131.1, 129.1, 129.0, 123.8, 123.5, 118.7, 117.1, 64.6, 39.5, 26.4, 26.1, 25.5, 21.4, 17.4, 16.4 and 16.1.

[8-^{2}H]-(2*E*,6*E*,10*E*,14*E*)-2,6,11,15-tetramethyl-2,6,10,14-hexadecatetraene (2). Following the method described in reference 4, to the solution of **12** (200 mg, 467 μ mol) and $PdCl_2$(dppp) (13.9 mg, 23.4 μmol) in THF (16 ml), $LiDBEt_3$ (111 ml, 934 mmol) was added dropwise at 0 °C under a N_2 atmosphere. After stirring at 0 °C for 1 h, 3 M NaOH was added and a small amount of aqueous KCN for 30 min whilst continuing the stirring. The reaction mixture was extracted with hexane to give the crude product, which was purified by column chromatography on silica-gel eluting with hexane to give [8-^{2}H]-(2*E*,6*E*,10*E*,14*E*)-2,6,11,15-tetramethyl-2,6,10,14-hexadecatetraene **(2)** (115 g, 89%). GLC analysis indicated that the purified product composed of 98% of **2** and 2% of its (2*E*,6*Z*,10*E*,14*E*)-isomer. HRMS (EI) *m/z* calculated for $C_{20}H_{33}D$ 275.2723, observed 275.2720; EI-MS *m/z* 275 (M^+), 260, 247, 232, 206, 193, 176, 151, 137, 123, 108, 95, 69; IR (neat) 2968, 2924, 2857, 1448, 1376, 1108, 985 and 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.11 (m, 4H), 2.02 (m,

11H), 1.68 (s, 6H) and 1.60 (s, 12H); ^2H NMR ($CDCl_3$) δ = 2.04; ^{13}C NMR ($CDCl_3$) δ = 135.1, 131.2, 124.4, 124.2, 39.8, 27.8, 26.8, 25.7, 17.7 and 16.0. The deuterium enrichment of **2** was found to be 99% by mass spectral analysis.

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