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ARTICLE

An alternative total synthesis of Patulolide A

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A new total synthesis of [*R*]-Patulolide A from readily available (*R*)-propylene epoxide obtained using the asymmetric synthetic approach is reported. The key reactions involved are **ozonolysis** and Yamaguchi macrolactonization, resulting in the ring system.

KEYWORDS

(*R*)-Patulolide A, 2c Ylide, ozonolysis, Yamaguchi macrolactonization

1 | INTRODUCTION

The interesting biological properties of medium-sized ring lactone systems tend to attract the scientists across the world because many of the molecules[1] belonging to this group have revealed diverse and significant biological activities. Most of the physiologically active macrolactones often have a double bond at the α,β-position and a keto or hydroxy functional group at the γ-position.

Patulolide A (Figure 1) is a 12-member macrolide, and it was isolated from Penicillium urticae S11R59 by Yamada and his coworkers.[2] Patulolide A showed antifungal, antibacterial, and anti-inflammatory activities.[2,3] Moreover, Patulolide A inhibits the IgE-induced release of histamine for human leucocytes better than the degeneration inhibitor, theophylin.[4]

To date, several approaches[5–9] for the synthesis of Patulolide A have been reported due to its interesting biological activities. Here, we report a concise and facile synthesis of Patulolide A from chiral epoxide.

The reported synthetic routes to Patulolide A mainly associated with some of the disadvantages such as long reaction sequences and lower yields. To overcome the problems associated with the earlier approaches, herein, we report an alternative, concise and efficient route for the synthesis of Patulolide A.

2 | RESULTS AND DISCUSSION

Our retrosynthetic analysis of **1** is outlined in Scheme 1. The macrolide **1** could be obtained by Yamaguchi macrolactonization followed by the elimination of the 1,3 **thioacetal** group of hydroxy acid **2**, which in turn could be synthesized from olefin **3**. Olefin **3** could be obtained from (*R*)-propylene epoxide **4**.

The total synthesis of **1** was initiated with (*R*)-propylene epoxide **4**, which was obtained from (±)-propylene oxide.[10–12] Accordingly, the reaction of the known PMB ether **3**[13] (prepared from **4**) on ozonolysis, followed by the Wittig olefination, afforded the ester **5** in 76% yield. Reduction of ester **5** on the reaction with LAH[14] yielded alcohol **6**, which was converted into bromide **7** using CBr_4 in the presence of Ph_3P in CH_2Cl_2 in 76% yield. Bromo compound **7** on alkylation with 2-vinyl-1,3-dithiane in dry THF gave compound **8** in 73% yield. Next, the double bond in **8** was subjected to ozonolysis followed by the Wittig olefination of the resulting aldehyde, which afforded **9** in 76% yield. Ester **9,** on subsequent hydrolysis (LiOH in THF:MeOH:H_2O-3:1:1), afforded acid **10**, which—on selective cleavage of PMB ether in the presence of DDQ in aq. CH_2Cl_2—gave the hydroxy-acid **2** in 86% yield (Scheme 2).

After the successive synthesis of hydroxy-acid **2**, we aimed for the synthesis of the final molecule by using macrolactonization. Accordingly, hydroxy-acid **2** was subjected to macrolactonization under Yamaguchi high-dilution

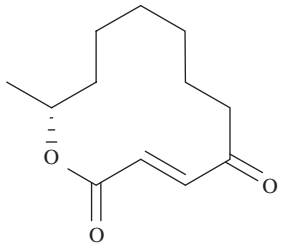


FIGURE 1 Patulolide A

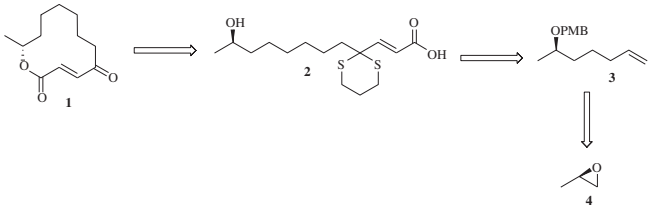
conditions[15] using 2,4,6-trichlorobenzoyl chloride and Et_3N in dry THF to afford the lactone **11** in 64% yield. Finally, deprotection of the 1,3 **thioacetal** group[16] in compound **11** with $CaCO_3$ and I_2, in THF:H_2O for 5 hr, afforded Patulolide A **1** in 66% yield. The analytical data of our synthetic compound are in agreement with the reported data.[4] Thus, we accomplished the total synthesis of Patulolide A in an enantioselective way.

3 | CONCLUSIONS

Thus, in conclusion through a combination of the chiron approach and asymmetric synthesis, the synthesis of Patulolide A (**1**) was achieved from (*R*)-propylene epoxide using regioselective ring opening, Wittig olefination, and Yamaguchi macrolactonization as key steps.

4 | GENERAL PROCEDURES

Solvents were dried over standard drying agents and freshly distilled prior to use. All commercially available chemicals were used without further purification. All reactions were performed under nitrogen. ^{1}H NMR and ^{13}C NMR spectra were measured using a Varian Gemini FT 200 MHz spectrometer, Bruker Avance 300 MHz, Unity 400 MHz, and Inova 500 MHz, with tetramethylsilane as the internal standard for solutions in $CDCl_3$ and $CDCl_3$ + DMSO. *J* values are given in Hz. Chemical shifts were reported in ppm relative to solvent signal. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. IR spectra were recorded on an FT IR (Perkin-Elmer IR-683) spectrophotometer with NaCl optics. The JASCO DIP 300 digital polarimeter was used for the measurement of optical rotations at 25 °C. Mass spectra were recorded on a direct inlet system or LC by MSD trap SL (Agilent Technologies), and the HRMS data were obtained using Q-TOF mass spectrometry.



SCHEME 1 Retro-analysis of Patulolide A (**1**)

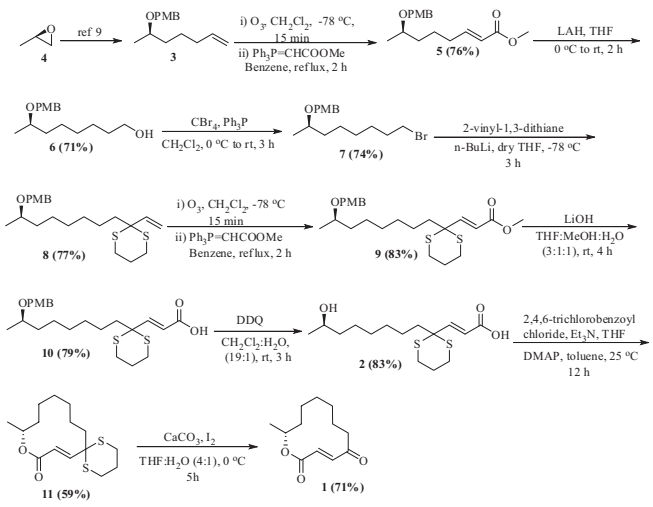
5 | EXPERIMENTAL SECTION

5.1 | (*R*,*E*)-methyl 7-(4-methoxybenzyloxy)oct-2-enoate (5)

Ozone was bubbled through a cooled (−78 °C) solution of **3** (7.4 g, 31.62 mmol) in CH_2Cl_2 (70 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (2 mL) and stirred for 15 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde, which was used for further reaction. A solution of the above aldehyde in benzene (50 mL) was treated with (methoxy- carbonylmethylene)triphenyl phosphorane (12.6 g, 37.94 mmol) at reflux temperature. After 2 hr, the solvent was evaporated, and the residue was purified by column chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to furnish **5** 7.17 g (78%) as a yellow liquid; $[\alpha]^{25}_D$ = +34.8 (*c* 0.74, $CHCl_3$); IR (neat): 3085, 3,050 2,955, 2,840, 1,705, 1,610, 1,440, 1,370, 1,260, 910, 730, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, 2H, *J* = 8.8 Hz), 6.97–6.85 (m, 1H), 6.81 (d, 2H, *J* = 8.8 Hz), 5.86 (d, 1H, *J* = 15.8 Hz), 4.59 (d, 1H, *J* = 11.3 Hz), 4.39 (d, 1H, *J* = 11.3 Hz,), 3.79 (s, 3H), 3.74 (s, 3H), 3.40 (m, 1H), 2.31–2.24 (m, 2H), 1.57–1.32 (m 4H), 1.16 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 160.1, 148.3, 129.6, 128.1, 121.2, 114.3, 74.6, 72.3, 56.3, 53.1, 35.3, 32.3, 24.6, 22.3; HRMS (ESI): *m/z* calculated for $C_{17}H_{24}O_4Na$ $[M + Na]^+$ 315.1675 found 315.1680.

5.2 | (*R*)-7-(4-Methoxybenzyloxy)octan-1-ol (6)

To a stirred suspension of $LiAlH_4$ (1.03 g, 27.12 mmol) in THF (50 mL), ester **6** (6.06 g, 22.6 mmol) in THF (25 mL)



SCHEME 2 Synthesis of Patulolide A (**1**)

was added at 0 °C and stirred for 5 hr. The reaction mixture was quenched with aq. Na_2SO_4 (20 mL) at 0 °C dropwise and stirred for an additional 2 hr. It was filtered through celite and extracted with EtOAc (4 × 20 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by column chromatography (Silica gel, 60–120 mesh, 25% EtOAc in pet. ether) to give an inseparable mixture of alcohols as colorless oil. The mixture of alcohols in EtOAc (5 mL) was treated with solid $NaHCO_3$ (0.5 g) and a catalytic amount of PtO_2 under H_2 gas pressure. After 2 hr, the reaction mixture was diluted with EtOAc (50 mL), filtered through celite, dried (Na_2SO_4), and concentrated, and the residue was purified by column chromatography (Silica gel, 60–120 mesh, 25% EtOAc in pet. ether) to afford alcohol **6** (4.2 g, 71%) as a yellow liquid; $[\alpha]^{25}_D = +8.7$ (*c* 0.74, $CHCl_3$); IR (neat): 3540, 3,070, 3,025 2,958, 2,836, 1,470, 1,310, 1,280, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, 2H, *J* = 8.6 Hz), 6.79 (d, 2H, *J* = 8.6 Hz), 4.51 (d, 1H, *J* = 11.0 Hz), 4.41 (d, 1H, *J* = 11.0 Hz), 3.77 (s, 3H), 3.71 (t, 2H, *J* = 6.3 Hz), 3.43 (m, 1H), 2.06 (brs, 1H), 1.51–1.44 (m, 3H), 1.40–1.27 (m, 7H), 1.14 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 130.1, 128.3, 114.3, 75.4, 72.3, 62.4, 56.7, 36.3, 32.8, 31.3, 28.2, 26.3, 22.3; HRMS (ESI): *m/z* calculated for $C_{16}H_{26}O_3Na$ $[M + Na]^+$ 289.1883 found 289.1888.

5.3 | 2-((*R*)-7-(4-Methoxybenzyloxy)octyl)-2-vinyl-1,3-dithiane (8)

To a stirred solution of **6** (4.0 g, 15.03 mmol) in CH_2Cl_2 (50 mL), CBr_4 (5.97 g, 18.04 mmol) and Ph_3P (5.9 g, 22.54 mmol) were added at 0 °C and stirred at room temperature for 3 hr. The reaction mixture was evaporated, and the residue was purified by column chromatography (60–120 Silica gel, 5% EtOAc in pet. ether) to afford **7** (3.6 g, 74%) as a colorless syrup.

To a stirred solution of 2-vinyldithiane (1.76 g, 12.07 mmol) in dry THF (30 mL) cooled at −78 °C was added a 1.6M solution of n-BuLi in hexane (9.0 mL, 13.16 mmol) dropwise. The reaction mixture was stirred at −20 °C for 1.5 hr. After cooling to −78 °C, a solution of bromide **7** (3.6 g, 10.97 mmol) in THF (5 mL) was added dropwise, and the mixture was maintained at −30 °C for 2 hr. The reaction was quenched with water (100 mL), and the mixture was extracted with Et_2O (2 × 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to give **8** (3.3 g, 77%) as a colorless oil; $[\alpha]^{25}_D = -78.2$ (*c* 0.74, $CHCl_3$); IR (neat): 3090, 3,065 2,925, 2,840, 2,460, 1,610, 1,440, 1,370, 1,240, 950, 740, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, *J* = 8.0 Hz), 6.79 (d, 2H, *J* = 8.60 Hz), 5.83 (m, 1H), 5.03–4.91(m, 2H), 4.47 (s, 2H), 3.73 (s, 3H), 3.41 (m, 1H), 2.82–2.66 (m, 4H), 2.05–1.96 (m, 2H), 1.83–1.63 (m, 4H), 1.47–1.21 (m, 7H), 1.17 (d, 3H), 1.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ160.3, 135.6, 130.3, 128.9, 120.1, 114.3, 75.6, 72.3, 56.7, 54.3, 40.1, 36.6, 31.3, 29.1, 28.2, 27.4, 25.6, 24.3, 24.0, 22.3; HRMS (ESI): *m/z* calculated for $C_{22}H_{34}O_2S_2Na$ $[M + Na]^+$ 417.2001 found 417.2008.

5.4 | (*E*)-methyl 3-(2-((*R*)-7-(4-methoxybenzyloxy) octyl)-1,3-dithian-2-yl)acrylate (9)

Ozone was bubbled through a cooled (−78 °C) solution of **8** (3.1 g, 7.86 mmol) in CH_2Cl_2 (30 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (2 mL) and stirred for 15 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde, which was used for further reaction.

A solution of the above aldehyde in benzene (50 mL) was treated with (methoxy- carbonylmethylene)triphenyl phosphorane (3.14 g, 9.44 mmol) at reflux temperature. After 2 hr, the solvent was evaporated, and the residue was purified by column chromatography (60–120 Silica gel, 8% EtOAc in pet. ether) to furnish **9** (2.95 g, 83%) as a yellow liquid; $[\alpha]^{25}_D = -56.1$ (*c* 0.74, $CHCl_3$); IR (neat): 3067, 3,082, 2,955, 2,870, 2,840, 1,695, 1,602, 1,440, 1,350, 1,220, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, 2H, *J* = 8.2 Hz), 6.87 (d, 1H, *J* = 15.6 Hz), 6.77 (d, 2H, *J* = 8.2 Hz), 5.81 (d, 1H, *J* = 15.6 Hz), 4.51 (d, 1H, *J* = 10.9 Hz), 4.42 (d, 1H, *J* = 10.9 Hz), 3.73 (s, 3H), 3.69 (s, 3H), 3.39 (m, 1H), 2.87–2.71 (m, 4H), 1.97–1.86 (m, 2H), 1.77–1.64 (m, 3H), 1.54–1.43 (m, 2H), 1.41–1.20 (m, 7H), 1.17 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 160.3, 145.3, 130.1, 129.6, 128.7, 125.3, 114.3, 75.7, 72.3, 68.3, 56.3, 52.3, 49.3, 36.1, 31.2, 29.4, 29.0, 26.2, 25.8, 24.2, 21.2; HRMS (ESI): *m/z* calculated for $C_{24}H_{36}O_4S_2Na$ $[M + Na]^+$ 475.2055 found 475.2061.

5.5 | (*E*)-3-(2-((*R*)-7-(4-Methoxybenzyloxy)octyl)-1,3-dithian-2-yl)acrylic acid (10)

To a solution of **9** (2.7 g, 5.97 mmol) in THF: MeOH: water (3:1:1, 20 mL), LiOH (0.21 g, 8.96 mmol) was added and stirred at room temperature for 4 hr. The pH of the reaction mixture was adjusted to acidic with 1N HCl solution and extracted with ethyl acetate (30 mL). Organic layers were washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), evaporated under reduced pressure, and purified the residue through column chromatography (60–120 Silica gel, 30% EtOAc in pet. ether) to give **10** (2.0 g, 79%) as a colorless oil; $[\alpha]^{25}_D = -48.4$ (*c* 0.74, $CHCl_3$); IR (neat): 3570, 3,060, 3,032 2,965, 2,880, 2,840, 1,690, 1,605, 1,420, 1,350, 1,270, 940, 730, 678 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 1H, *J* = 15.6 Hz,), 6.81 (d, 2H, *J* = 8.5 Hz), 5.79 (d, 1H, *J* = 15.5 Hz), 4.48 (s, 2H), 3.73 (s, 3H), 3.51 (m, 1H), 2.91–2.77 (m, 4H), 1.93–1.81 (m, 2H), 1.77–1.51 (m, 5H), 1.44–1.21 (m, 7H), 1.19 (d,

3H, $J = 6.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 160.1, 143.3, 130.1, 129.3, 125.2, 114.1, 74.7, 72.3, 69.3, 56.3, 48.2, 36.2, 31.3, 29.4, 28.3, 26.2, 25.8, 24.3, 21.0; HRMS (ESI): *m/z* calculated for $C_{23}H_{35}O_4S_2$ $[M + H]^+$ 439.1899 found 439.1902.

5.6 | (*E*)-3-(2-((*R*)-7-Hydroxyoctyl)-1,3-dithian-2-yl) acrylic acid (2)

To a solution of **10** (1.19 g, 4.33 mmol) in aq. CH_2Cl_2 (10 mL, 19:1), DDQ (1.18 g, 5.20 mmol) was added and stirred at room temperature for 3 hr. The reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL), filtered, and washed with CH_2Cl_2 (50 mL). The filtrate was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (60–120 Silica gel, 40% EtOAc in pet. ether) to furnish **2** (0.6 g, 83%) as a white solid; $[\alpha]^{25}_D = -23.4$ (*c* 0.9, $CHCl_3$); IR (neat): 3540, 3,500, 2,945, 2,930, 2,825, 1,690, 1,610, 1,414, 1,312, 1,240, 1,190, 980, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, 1H, $J = 15.4$), 5.83 (d, 1H, $J = 15.4$), 3.67 (m, 1H), 2.87–2.73 (m, 4H), 2.46 (brs, 1H), 1.97–1.84 (m, 3H), 1.64–1.47 (m, 3H), 1.44–1.27 (m, 8H), 1.16 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 142.9, 125.7, 69.3, 68.1, 49.0, 40.1, 29.3, 28.7, 28.0, 25.8, 25.0, 24.3, 23.1; HRMS (ESI): *m/z* calculated for $C_{15}H_{27}O_3S_2$ $[M + H]^+$ 319.1323 found 319.1326.

5.7 | (*R,E*)-11-Methyl-10-oxa-1,5-dithiaspiro[5.11] heptadec-7-en-9-one (11)

To a stirred solution of **2** (0.26 g, 0.81 mmol) and Et_3N (0.34 mL, 2.43 mmol) in dry THF (3 mL), a solution of 2, 4, 6-trichlorobenzoyl chloride (0.2 mL, 1.21 mmol) in dry THF (1 mL) was added. The resulting mixture was stirred for 2 hr at room temperature under nitrogen atmosphere and evaporated to afford the mixed anhydride. It was diluted with toluene (10 mL) and filtered quickly through celite. The filtrate was added dropwise to a stirred solution of DMAP (0.1 g, 0.89 mmol) in toluene (250 mL) at 90 °C over a period of 8 hr. After the complete addition, the reaction mixture was stirred at 100 °C for 2 hr. It was cooled; washed with 7% aq $NaHCO_3$ (20 mL), 2 M aqueous HCl (20 mL), and brine (20 mL); and dried (Na_2SO_4). The organic layer was evaporated, and the obtained residue was purified by column chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to give **11** (0.14 g, 59%) as a syrup. $[\alpha]^{25}_D = +6.4$ (*c* 0.74, EtOH); IR (neat): 3080, 3,052 2,955, 2,880, 1,705, 1,470, 1,370, 1,260, 910, 730, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.98 (d, 1H, $J = 16.1$ Hz, olefinic), 6.26 (d, 1H, $J = 16.1$ Hz, olefinic), 5.09–5.09 (m, 1H, -OCH), 2.94–2.62 (m, 4H, 2× $-SCH_2$), 2.07–1.99 (m, 2H, $-CH_2$), 1.93–1.61 (m, 5H, 5× –CH), 1.62–1.37 (m, 7H, 7× –CH), 1.31 (d, 3H, $J = 6.2$ Hz, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 152.1, 125.1, 99.0, 73.2, 54.3, 42.4, 33.3, 28.2, 27.6, 27.3, 25.4, 22.4, 21.6, 19.7; HRMS (ESI): *m/z* calculated for $C_{15}H_{24}O_2S_2Na$ $[M + Na]^+$ 323.1218 found 323.1222.

5.8 | (*R,E*)-12-Methyloxacyclododec-3-ene-2,5-dione (1)

To a solution of compound **11** (110 mg, 0.36 mmol) and $CaCO_3$ (360 mg, 3.66 mmol) in THF/H_2O (v/v, 4:1, 10 mL) was added I_2 (270 mg, 1.02 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 5 hr. The reaction was quenched by adding saturated aqueous $Na_2S_2O_3$; filtered through a pad of Celite; and then extracted with EtOAc (3 × 20 mL), water, and brine; dried over Na_2SO_4; and concentrated in vacuo. Purification by flash chromatography on silica gel (60–120 Silica gel, 15% EtOAc in pet. ether) gave Patulolide A **1** (54 mg, 71% yield) as a colorless oil: M.P. 82–84 °C; (lit.:[1] 83–85 °C); $[\alpha]^{25}_D = +33.4$ (*c* 0.39, EtOH); (lit.:[1] + 30.1 (c 0.95, EtOH); IR (neat): 3400, 3,325, 3,070, 3,025, 2,935, 2,855, 1,700, 1,680, 1,620, 1,460, 1,340, 1,260, 1,200, 980, 776, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, 1H, $J = 15.9$ Hz, olefinic), 6.82 (d, 1H, 15.9 Hz, olefinic), 4.91–4.86 (m, 1H, –OCH), 2.81–2.72 (m, 1H, –CH), 2.50–2.42 (m, 1H, –CH), 1.91–1.83 (m, 2H, $-CH_2$), 1.69–1.61 (m, 4H, 2× $-CH_2$), 1.57–1.44 (m, 4H, 2× $-CH_2$), 1.37 (d, 3H, $J = 7.1$ Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 166.5, 141.3, 130.1, 74.7, 38.6, 34.9, 25.6, 25.3, 24.5, 22.3, 20.3; HRMS (ESI): *m/z* calculated for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1251 found 233.1257.

Full experimental details, spectral data of the products, and ^1H NMR and ^{13}C NMR of all the new compounds can be found in Appendix S1 (Supporting Information).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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