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Stereoselective total synthesis of simplactone A

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ABSTRACT

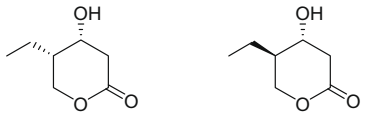
The efficient and simple stereoselective approach toward the total synthesis of simplactone A is described. The key features of this synthetic strategy include stereoselective C-ethylation, selective triol protection, and Wittig olefination for the formation of the six-membered ring.

1. Introduction

The δ lactone ring system is found in many natural products and is also featured in many intermediates used for the synthesis of biologically active important compounds. The δ lactones have been shown to exhibit a wide range of biological activities such as antibiotic, anticancer, anti-inflammatory, and bactericidal activities. In view of their interesting structural features and biological activities, different synthetic routes have been developed for these compounds.

The δ lactones, simplactones A **1** and B **2** have been isolated from the Caribbean sponge,[1] *plakortis simplex* (as shown in Fig. 1). Their structures have been proposed on the basis of their spectroscopic data, and they are known to possess in vitro cytotoxic activity against WEHI 164. Some approaches have been developed in the literature[2a–d] for the synthesis of these δ lactones by employing different procedures. Ogasawara synthesized simplactones A and B from enantiopure 4-cumyloxy-2-cyclopentene-1-one.[2a] Ogasawara also proposed that their spectroscopic values are identical with those of the proposed (isolated) simplactones B and A, respectively. Recently, Olivo and coworkers synthesized the simplactones A and B utilizing a doubly diastereoselective acetate aldol reaction in five steps from *N*-acyl thiazolidinethione chiral auxiliaries[2d] and in order to avoid confusion, the reference has been made to these lactones based on their absolute configuration. As part of our studies directed toward the synthesis of lactones and other biologically active molecules,[3] we herein report a new synthetic route to simplactone A utilizing a stereoselective ethylation and selective protection of the triol from commercially available (*S*)-malic acid.

The present approach for the synthesis of simplactone A is depicted in Scheme 1. The key for this approach is the synthesis of **4** and **6a** starting from the commercially available (*S*)-malic acid.



simplactone A **1** simplactone B **2**

Figure 1.

2. Results and discussion

(*S*)-Malic acid **2** was subjected to esterification using $BF_3{\cdot}OEt_2$ in methanol to give dimethyl malate **3** in 98% yield. The dianion of **3**, formed on treatment with LHMDS in THF, was alkylated with ethyl iodide according to Seebach's procedure to provide **4** as the predominant diastereomer (*anti*/*syn* 9:1) in 76% yield after flash column chromatography.[4] Treatment of the anti-diastereomer **4** with lithium aluminum hydride in THF afforded the desired triol **5** in 82% yield. Selective 1,3-protection of triol **5** afforded a six-membered acetal,[5] as *p*-methoxybenzylidene acetal **6a** (*p*-methoxybenzaldehyde dimethylacetal, CSA, CH_2Cl_2) in 85% yield, and 1,2-protection afforded a five-membered acetal as *p*-methoxybenzylidene acetal **6b** in 12% yield. These two acetals **6a** and **6b** were separated by column chromatography (Scheme 2).

Alcohol **6a** was oxidized under Swern's oxidative conditions to give the corresponding aldehyde, which without purification (as a crude) on Wittig olefination with MeTPPI and *n*-BuLi in THF gave the olefin **7** in 72% yield. Selective hydroboration of the terminal olefin **7** was achieved with dicyclohexylborane [$(Cy)_2BH$] followed by oxidative workup to provide the homologated primary alcohol **8** (88% yield) as the exclusive product.[6] Primary alcohol in **8** was oxidized under Swern's oxidative conditions to provide the aldehyde, which without further purification underwent further oxidation with $NaClO_2$, NaH_2PO_4, and DMSO to give the acid in 77% yield, which was treated with diazomethane to afford the ester in 87% yield. This compound **10** was treated with $AcOH/H_2O$ (4:1) which resulted in *p*-methoxybenzylidene deprotection and subsequent

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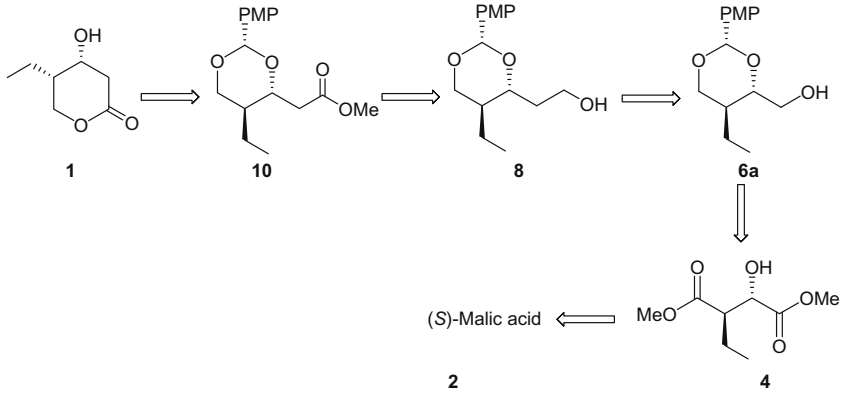
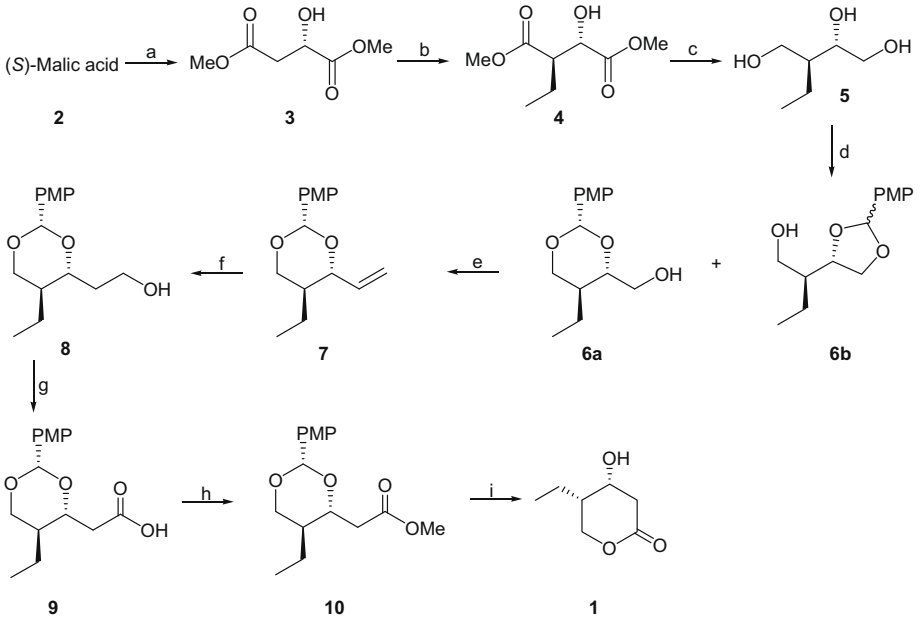


Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, MeOH, 0 °C to rt, 6 h, 98%; (b) LHMDS, EtI, THF, −78 °C to 0 °C, 24 h, 76%; (c) LAH, THF, 55 °C, 12 h, 82%; (d) $PMB(OMe)_2$, CSA, CH_2Cl_2, 0 °C, 2 h, 85%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (ii) MeTPPBr, *n*-BuLi, THF, −78 °C, 1 h, 72% over two steps; (f) Cy_2BH, THF, 0 °C to rt, 6 h, then H_2O_2, NaOH, 0 °C to rt, 2 h, 88%; (g) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (ii) $NaClO_2$, NaH_2PO_4, DMSO, 0 °C to rt, 10 h, 77% over two steps; (h) CH_2N_2, ether, 0 °C, 1 h, 87%; (i) 4:1 AcOH/H_2O, 0 °C to rt, 6 h, 85%.

lactonization afforded the target molecule. The spectroscopic and analytical data were comparable to the previously reported data in the literature.[2a,d]

3. Conclusion

In conclusion, we have developed a simple, convenient, and efficient approach for the synthesis of naturally occurring simplactone A utilizing stereoselective ethylation and selective protection of a triol from commercially available (*S*)-malic acid. The synthesis of related compounds of this family is underway in our laboratory.

4. Experimental

4.1. General

Reagents and chemicals were purchased from Aldrich. All solvents and reagents were purified by standard techniques. THF was freshly distilled from $LiAlH_4$. Crude products were purified by column chromatography on 60–120 silica gel. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Horiba 360 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Brucker Avance 300. Chemical shifts are reported in parts per million with respect to the internal TMS. Mass spectra were recorded on VG micromass-7070H (70 Ev).

4.2. Dimethyl (2*R*,3*S*)-2-ethyl-3-hydroxybutanedioate 4

To a stirred solution of dimethyl malate **3** (4 g, 24.69 mmol) in dry THF (40 mL) at −78 °C LHMDS (54.3 mL, 54.32 mmol, 1 M in THF) was added slowly and stirred for 1 h at the same temperature. Ethyl iodide (2.96 mL, 37.03 mmol) in THF (7 mL) was added slowly and stirred at −78 °C for 3 h. Then the temperature was gradually increased to 0 °C for 20 h. After completion of the reaction, the reaction mixture was quenched with aqueous NH_4Cl at −78 °C. Later the reaction mixture was acidified with dil HCl, THF was evaporated and extracted with EtOAc (2 × 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column

chromatography (silica gel, 60–120 mesh, EtOAc/hexane 10:90) to afford the compound **4** (3.56 g, 76%) as a yellow oil. $[\alpha]_D^{20} = +9.3$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max}: 3490, 2959, 1741, 1440, 1205, 1135 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.5 Hz, 3H), 1.71 (m, 1H), 1.86 (m, 1H), 2.72 (td, *J* = 7.5 Hz, 1H), 3.07 (d, *J* = 7.5 Hz, 1H), 3.68 (s, 3H), 3.8 (s, 3H), 4.24 (dd, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 21.2, 50.1, 51.7, 52.5, 70.6, 173.2, 173.8; MS-EIMS: *m/z* 213 $(M+Na)^+$.

4.3. (2*S*,3*S*)-3-Ethylbutane-1,2,4-triol 5

To a stirred suspension of $LiAlH_4$ (1.97 g, 52.10 mmol) in dry THF (40 mL) at 0 °C compound **4** (3.3 g, 17.36 mmol) in THF (10 mL) was added slowly and allowed to stir at 55 °C for 12 h. After completion of the reaction, it was quenched with aqueous NH_4Cl and filtered. THF and water were evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 80:20) to afford compound **5** (1.90 g, 82%) as a colorless liquid. $[\alpha]_D^{25} = +19.5$ (c 1.1, $CHCl_3$); IR (neat): ν_{max}: 3356, 2932, 1461, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.946 (t, *J* = 7.54 Hz, 3H), 1.23–1.46 (m, 2H), 1.52 (m, 1H), 2.33 (br s, 1H), 3.62 (m, 2H), 3.68–3.86 (m, 3H), 3.95 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 21.1, 43.9, 62.6, 65.1, 74.5; MS-EIMS: *m/z* 167 $(M+Na)^+$.

4.4. [(2*S*,4*S*,5*S*)-5-Ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-methanol 6a

To a stirred solution of compound **5** (1.7 g, 12.68 mmol) in dry dichloromethane (30 mL) at 0 °C, *p*-methoxybenzylidene dimethylacetal (2.58 mL, 15.22 mmol) and a catalytic amount of CSA were added. The mixture was stirred at 0 °C for 2 h. After completion of the reaction, it was quenched with Et_3N and extracted with dichloromethane (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 20:80) to afford the compound **6a** (2.71 g, 85%) as a colorless liquid. $[\alpha]_D^{25} = +31.5$ (c 1.1, $CHCl_3$); IR (neat): ν_{max}: 3457, 2964, 1615, 1517, 1248, 1081, 985, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.948 (t, *J* = 7.4 Hz, 3H), 1.08 (m, 1H), 1.43 (m, 1H), 1.91 (m, 1H), 3.5 (t, *J* = 11.3 Hz, 1H), 3.61 (m, 2H), 3.74–3.85 (m, 4H), 4.27 (dd, *J* = 4.9, 11.3 Hz, 1H), 5.4 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 20.4, 36.1, 55.2, 63.1, 70.8, 81.9, 100.9, 113.5, 127.4, 130.8, 159.9; MS-EIMS: *m/z* 275 $(M+Na)^+$.

4.5. (2*S*,4*R*,5*S*)-5-Ethyl-2-(4-methoxyphenyl)-4-vinyl-1,3-dioxane 7

To a stirred solution of oxalyl chloride (1.69 mL, 19.04 mmol), in dry CH_2Cl_2 (30 mL), DMSO (2.7 mL, 38.09 mmol) was added at −78 °C and stirred at the same temperature for 30 min. Compound **6** (2.4 g, 9.52 mmol) in dry CH_2Cl_2 (10 mL) was added at −78 °C to the reaction mixture and stirred for 1 h at the same temperature. Then Et_3N (5.29 mL, 38.09 mmol) was added at −78 °C, and the reaction mixture was allowed to warm to room temperature for 30 min. The reaction mixture was diluted with water (15 mL) and extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude aldehyde as a yellow syrup. To methyltriphenylphosphonium bromide (10.1 g, 28.56 mmol) in dry THF (50 mL) at −78 °C n-BuLi (14.87 mL, 23.8 mmol, 1.6 M in hexane) was added and stirred for 45 min at −78 °C. Then to the orange yellow ylide, the above crude aldehyde (3.96 g, 15.84 mmol) in dry THF (10 mL) was added slowly, and stirring was continued for 1 h at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with ether (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 5:95) to afford the compound **7** (1.69 g, 72%) as a colorless liquid. $[\alpha]_D^{25} = +15.5$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max}: 2962, 2925, 1615, 1516, 1248, 1032, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.901 (t, *J* = 7.3 Hz, 3H), 1.01 (m, 1H), 1.46 (m, 1H), 1.72 (m, 1H), 3.56 (t, 1H), 3.78 (s, 3H), 3.92 (dd, *J* = 7.3 Hz, 1H), 4.29 (dd, *J* = 10.9 Hz, 1H), 5.26 (m, 2H), 5.47 (s, 1H), 5.88 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9, 20.5, 40.0, 55.2, 71.2, 83.5, 100.8, 113.5, 118.2, 127.4, 131.1, 136.3, 159.9; MS-EIMS: *m/z* 271 $(M+Na)^+$.

4.6. 2-[(2*S*,4*R*,5*S*)-5-Ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-1-ethanol 8

To a stirred solution of alkene **7** (1.4 g, 5.64 mmol) in dry THF (15 mL) at 0 °C dicyclohexylborane (13.54 mL, 6.77 mmol, 0.5 M in THF) was added slowly. The mixture was stirred at room temperature for 12 h. Then it was cooled to 0 °C and treated with aqueous NaOH (28.22 mL, 28.22 mmol, 1.0 M aqueous solution) followed by H_2O_2 (1.91 mL, 28.22 mmol, 50% aqueous solution). The reaction mixture was stirred for 2 h at room temperature. Aqueous NH_4Cl was added and the reaction mixture was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 30:70) to afford the compound **8** (1.32 g, 88%) as a colorless liquid. $[\alpha]_D^{25} = +81.5$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max}: 3419, 2924, 1361, 1176, 977, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.921 (t, *J* = 7.5 Hz, 3H), 1.06 (m, 1H), 1.45 (m, 1H), 1.8 (m, 2H), 2.02 (m, 1H), 2.38 (br s, 1H), 3.55 (t, *J* = 11.3 Hz, 1H), 3.73–3.85 (m, 6H), 4.28 (dd, *J* = 4.5, 11.3 Hz, 1H), 5.4 (s, 1H), 6.89 (d, *J* = 7.0 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7, 20.6, 34.6, 39.9, 55.3, 60.6, 71.2, 81.3, 100.8, 113.7, 127.1, 130.8, 160.0; MS-EIMS: *m/z* 289 $(M+Na)^+$.

4.7. 2-[(2*S*,4*R*,5*S*)-5-Ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-acetic acid 9

To a stirred solution of oxalyl chloride (0.7 mL, 8.27 mmol), in dry CH_2Cl_2 (20 mL), DMSO (1.17 mL, 16.54 mmol) was added at −78 °C and stirred at the same temperature for 30 min. Compound **8** (1.1 g, 4.13 mmol) in dry CH_2Cl_2 (4 mL) was added at −78 °C to the reaction mixture and stirred for 1 h at the same temperature. Next, Et_3N (2.30 mL, 16.54 mmol) was added at −78 °C and the reaction mixture was allowed to warm to room temperature for 30 min. The reaction mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (2 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude aldehyde as a yellow syrup. To the above crude aldehyde in DMSO (1.0 mL) at 0 °C $NaClO_2$ (0.55 g, 6.19 mmol, dissolved in 2 mL water) was added slowly followed by NaH_2PO_4 (0.736 g, 6.19 mmol, dissolved in 2 mL water) and allowed to stir at room temperature for 10 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 40:60) to afford the compound **9** (0.89 g, 77%) as a colorless liquid. $[\alpha]_D^{25} = +55.5$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.931 (t, *J* = 7.5 Hz, 3H), 1.11 (m, 1H), 1.44 (m, 1H), 1.77 (m, 1H), 2.61 (dd, *J* = 15.9 Hz, 1H), 2.78 (dd, *J* = 15.9 Hz, 1H), 3.57 (t, *J* = 11.3 Hz, 1H), 3.79 (s, 3H), 4.02 (td, *J* = 3.8 Hz, 1H), 4.27 (dd, *J* = 4.6, 11.3 Hz,

1H), 5.47 (s, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7, 20.7, 38.4, 39.8, 55.3, 70.9, 78.0, 101.0, 113.5, 127.3, 130.6, 159.9, 176.1; MS-EIMS: m/z 303 $(M+Na)^+$.

4.8. Methyl 2-[(2*S*,4*R*,5*S*)-5-ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]acetate 10

To a stirred solution of acid **9** (0.6 g, 2.14 mmol) in dry ether (10 mL) at 0 °C freshly generated ethereal solution of diazomethane was added slowly and stirred for 10 min. After completion of the reaction, the ether was evaporated carefully. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 5:95) to afford the compound **10** (0.55 g, 87%) as a colorless liquid. $[\alpha]_D^{25} = +82.0$ (c 1.1, $CHCl_3$); IR (neat): ν_{max}: 2964, 2840, 1741, 1615, 1248, 1031, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.923 (t, J = 7.5 Hz, 3H), 1.1 (m, 1H), 1.42 (m, 1H), 1.74 (m, 1H), 2.57 (dd, J = 15.8 Hz, 1H), 2.70 (dd, J = 15.8 Hz, 1H), 3.57 (t, J = 11.3 Hz, 1H), 3.69 (s, 3H), 3.79 (s, 3H), 4.04 (td, J = 3.0, 9.0 Hz, 1H), 4.28 (dd, J = 4.6, 11.3 Hz, 1H), 5.46 (s, 1H), 6.85 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 20.5, 38.6, 39.9, 51.7, 55.2, 70.9, 78.3, 100.6, 113.4, 127.2, 130.8, 159.8, 171.6; MS-EIMS: m/z 295 $(M+H)^+$.

4.8.1. (4*R*,5*S*)-5-Ethyl-4-hydroxytetrahydro-2*H*-2-pyranone 1

To the ester **10** (0.4 g, 1.36 mmol) at 0 °C, AcOH/H_2O (4:1, 10 mL) was added and then stirred at room temperature for 6 h. After completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane 30:70) to afford the compound (0.16 g, 85%) as a colorless liquid. $[\alpha]_D^{22} = +22.9$ (c 1.1, $CHCl_3$); {lit.[2d] $[\alpha]_D^{22} = +23.3$ (c 1.0, $CHCl_3$)}; IR (neat): ν_{max}: 3424, 2966, 1718, 1400, 1195, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.32 Hz, 3H), 1.34 (m, 1H), 1.47 (m, 1H), 1.83 (m, 1H), 2.63 (dd, J = 3.1 Hz, 18.3, 1H), 2.71 (dd, J = 3.1 Hz, 18.3, 1H), 2.85 (br s, 1H), 4.17 (br s, 1H), 4.22 (dd, J = 5.2, 11.1 Hz, 1H), 4.36 (dd, J = 10.8, 11.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 19.5, 39.2, 39.3, 64.14, 69.1, 170.9; MS-EIMS: m/z 145 $(M+H)^+$.

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