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Enantioselective Synthesis of *erythro*-β-Hydroxyglutamic Acid

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Abstract: An enantioselective synthesis of *N*-Boc-(2*S*,3*S*)−3-hydroxy glutamic acid dimethyl ester (92% ee) is described. Starting from enantiomerically enriched (93% ee) (2*S*,3*S*)-2,3-epoxy-5-hexen-1-ol, easily available by Sharpless asymmetric epoxidation, the protected amino acid was prepared in 11 steps.

Keywords: β-Hydroxyglutamic, Sharpless epoxidation, epoxide ring opening

INTRODUCTION

β-Hydroxy-α-amino acids are constituents of many biologically active natural products and medicinally important compounds.[1−9] Because both the relative and absolute stereochemistry of their chiral centers are crucial for its biological activity, many stereoselective syntheses have been reported up to now.[2−12] Although some of these synthetic approaches are highly efficient, most of them involve unfunctionalised side chains. In contrast, few syntheses of *erythro*-β-hydroxy-glutamic acid (**1**) have been developed,[13−17] despite its biological activity and its interest as a glutamic acid analogue.[18−22] For instance, some analogues of the anticancer drug methotrexate (MTX) have shown to be potent inhibitors of dihydrofolate reductase.[23]

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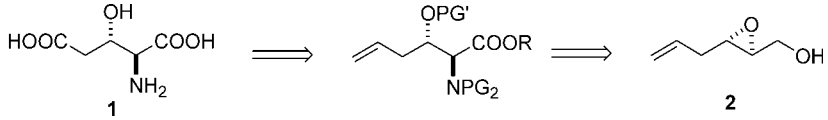
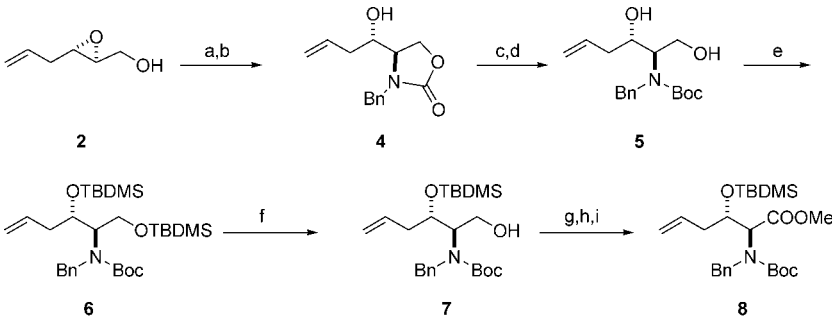
During the last several years we have been involved in a project directed to the synthesis of amino acids from epoxy alcohols [see *inter alia*:[24–30]] because these compounds are easily available in any configuration by Sharpless epoxidation.[31,32] The C-2 ring opening of an epoxy alcohol affords a 2-amino-1,3-diol with *anti* stereoselectivity, ideally suited for the preparation of *erythro*-β-hydroxy-α-amino acids. We planned the enantioselective preparation of *erythro*-β-hydroxyglutamic acid setting the stereochemistry of the diol by a regio and estereoselective ring opening of the readily available epoxy alcohol **2** and using a terminal alkene as a masked carboxylic acid function.



Up to now, the most reliable method for the regioselective C-2 ring opening of epoxy alcohols is the intramolecular cyclization of benzyl carbamate, developed by Roush and Adam.[33] However, very often it has the drawback that the reaction product is a mixture of isomeric oxazolidinones due to the easy acyl-migration in these compounds.[34,35] Some years ago, we found that the use of NaHMDS as a base in the carbamate cyclization minimize this acyl migration so we decided to explore this approach.[36] We describe here the enantioselective synthesis of a protected form of 3-hydroxy glutamic acid **1**, based on the C-2 ring opening of the easily available 2,3-epoxy-5-hexen-1-ol (**2**).

RESULTS

Our synthesis of the unsaturated β-hydroxy-α-amino acid is outlined in Scheme 1. Epoxy alcohol **2** was prepared in 93% ee by Sharpless epoxidation of 2,5-hexadien-1-ol.[37] The benzyl carbamate of **2** was prepared by treatment with benzylisocyanate in ether, and it was cyclized to oxazolidinone **4** using sodium bistrimethylsilylamide as a base[36] in high yield. Under these conditions, only 7% of the trans-acyl isomer was observed by ^{1}H NMR. Our initial approach was to protect the secondary alcohol as *tert*-butyldimethylsilyl ether and liberate the primary alcohol by hydrolysis of the carbamate, but, unfortunately, this protecting group was not stable to the carbamate hydrolysis. Consequently, we hydrolyzed carbamate **4** by treatment with NaOH and protected the amine as a Boc-derivative, affording diol **5** in good yield. Protection of the secondary alcohol could be conveniently performed by silylation of both alcohols followed by selective hydrolysis of the primary one. Alcohol oxidation in **7** gave the

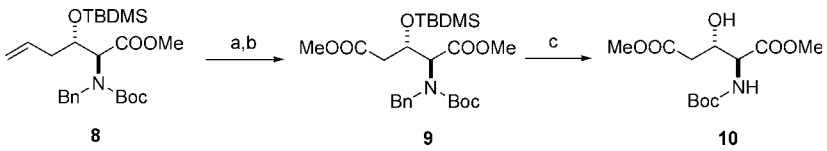


Scheme 1. (a) Bn-NCO, THF reflux (95%). (b) $NaN(TMS)_2$, THF (91%). (c) NaOH, reflux, 16 hr (78% yield). (d) Boc_2O, $NaHCO_3$, MeOH, 3.5 hr (78% yield) (e) $tBuMe_2$-SiTf, Lutidine, (86% yield), (f) PTSA cat, MeOH, 2.5 hr (70% yield). (g) TEMPO, NaClO, $NaHCO_3$, KBr. (h) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene tBuOH, 16 hr room temperature. (i) MeI, $KHCO_3$, DMF (65% three steps).

fully protected 3-hydroxy-4-amino-5-hexenoic acid, which was converted into its methyl ester **8** to facilitate isolation and characterization. It is worth noting that this synthetic scheme should allow the preparation of many other β-hydroxy-α-amino acids.

The final steps in our synthesis were performed as shown in Scheme 2. Oxidative cleavage of the terminal olefin gave the corresponding amino acid that was esterified with methyl iodide/sodium bicarbonate to afford diester **9** in good yield. Compound **9** is a fully protected form of the target *erythro*-β-hydroxyglutamic acid. If desired, the preparation and purification of **8** can be skipped. To this end, the carboxylic acid obtained in the oxidation of **7** was treated with $NaIO_4/RuCl_3$, and the diacid was esterified with MeI to give diester **9** in 28% overall yield from **7** (four steps).

The sometimes problematic deprotection of the benzyl group was achieved, after some experimentation, by hydrogenolysis catalyzed by palladium chloride. Somewhat surprisingly, this treatment also cleaved the silyl ether, yielding the known[13] *N*-Boc-β-hydroxyglutamic dimethyl ester (**10**). All compounds gave satisfactory ^1H and ^{13}C NMR spectra with no detectable impurities above 5%.



Scheme 2. (a) $RuCl_3$ cat, $NaIO_4$. (b) MeI, $KHCO_3$, DMF (50% two steps), (c) $PdCl_2$, H_2, 16 hr (73% yield).

Compound **10** was derivatized to the corresponding Mosher's esters by treatment with (*R*) and (*S*)-2-methoxy-2-trifluoromethylphenylacetic acid chlorides, NEt_3, and DMAP in CH_2Cl_2. Analysis by ^1H NMR of both reaction crudes established an enantiomeric excess of 92% ee for **10**, in complete agreement with the optical purity of the starting epoxy alcohol.

In summary, starting from 2,3-epoxy-5-pentenol, we have described an enantioselective synthesis of (2*S*, 3*S*)-2-*tert*-butoxycarbonyl-3-hydroxy glutamic acid dimethyl ester (92% ee), a protected derivative of the biologically important *erythro*-β-hydroxyglutamic acid. The key steps in our approach are asymmetric Sharpless epoxidation, regioselective C-2 ring opening of an epoxy carbamate and use of a terminal double bond as a masked carboxylic acid group.

EXPERIMENTAL

General

Optical rotations were measured at room temperature on a Perkin–Elmer 241MC automatic polarimeter (concentration in g/100 mL). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Nicolet 510FT-IR instrument using NaCl film or KBr pellet techniques. NMR spectra were acquired on a Varian XL-200 or Varian Mercury 400 instruments. ^1H-NMR were obtained at 200 or 400 MHz (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet, and b = broad). ^{13}C-NMR were obtained at 50.3 MHz or 100.6 MHz. ^1H chemical shifts are quoted relative to TMS and ^{13}C shifts relative to solvent signals. High-resolution mass spectra (CI) were measured by the Servicio de Espectrometría de Masas de la Universidad de Santiago de Compostela. Chromatographic separations were carried out by using NEt_3-pretreated (2.5% v/v) SiO_2 (70–230 mesh) and eluting with hexane/ethyl acetate mixtures of increasing polarity. (2*S*,3*S*)-2,3-Epoxy-5-hexen-1-ol (**2**) was prepared according to the procedure described by Ref. [37].

(2*S*, 3*S*)-*N*-Benzyl-carbamic Acid 3-allyl-oxiranylmethyl Ester (**3**)

To a solution of epoxide **2** (263 mg, 2.30 mmol) in ether (20 mL), NEt_3 (698 μL, 4.95 mmol, 2.15 eq.) was slowly added, and the mixture was stirred 15 min under nitrogen. Benzyl isocyanate (428 μL 3.45 mmol) was added, and the resulting mixture was stirred at reflux during 16 hr. It was allowed to cool at room temperature, and NH_4Cl (20 mL) was added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography to afford 539 mg (2.18 mmol, 95%) of **3** as a white solid. M.p. 43–46°C $[\alpha]_D = -23.4$

(c = 1.1 in $CHCl_3$) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.33–2.38 (m, 2H), 2.94–3.05 (m, 2H), 3.94 (dd, $J_1 = 5.8$ Hz, $J_2 = 12$ Hz, 1H), 4.30–4.50 (m, 3H), 5.00–5.20 (m, 2H). 5.70–5.90 (m, 1H), 7.20–7.40 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) 29.7 35.5, 45.1, 55.2, 64.1, 117.8, 127.4, 127.5, 128.6, 132.4 ppm. IR (NaCl): $\nu = 3322$, 2927, 1692 cm^{-1}. HRMS (CI, CH_4) Calc. for $C_{14}H_{18}NO_3$ ($M + H^+$) 248.1287, found 248.1275.

(4*R*, 1′*S*)-*N*-Benzyl-4(1-hydroxy-3-butenyl)-oxazolidin-2-one (**4**)

To a solution of epoxycarbamate **3** (2.64 g, 10.69 mmol) in anhydrous THF (250 mL) at room temperature, a solution of sodium bistrimethylsilylamide (11.76 mmol) in THF (50 mL) was added dropwise under nitrogen. The reaction mixture was stirred for 30 min, being monitored by TLC. When the reaction was complete, the mixture was quenched with 120 mL of ammonium chloride-saturated solution. The stirring was maintained 10 min, the mixture was extracted with dichloromethane, and the combined organic phases were washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford 2.40 g (9.71 mmol, 91%) of **4** (as a 13 : 1 mixture of **4** and its trans-acyl isomer). $[\alpha]_D = -5.14$ (c = 0.56 in $CHCl_3$). ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.60 (bs, 1H), 2.00–2.20 (m, 2H), 3.66 (ddd, $J_1 = 2$ Hz, $J_2 = 6.8$ Hz, $J_3 = 9.2$ Hz, 1H), 3.87 (t, J = 6 Hz, 1H), 4.21 (t, J = 8.8 Hz, 1H), 4.28–4.36 (m, 2H), 4.70 (d, J = 15.2 Hz, 1H), 5.07–5.13 (m, 2H) 5.60–5.80 (m, 1H) 7.20–7.40 (m, 5H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 36.7, 46.1, 58.0, 62.0, 66.7, 118.3, 128.0, 128.8, 128.9, 133.3, 135.8, 159.1 ppm. IR (NaCl): v = 3413, 2925, 1728 cm^{-1}. HRMS (CI, CH_4) Calc. for $C_{14}H_{18}NO_3$ ($M + H^+$) 248.1287, found 248.1282.

(2*R*, 3*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-2-amino-5-hexen-1,3-diol (**5**)

To a solution of carbamate **4** (300 mg, 1.21 mmol) in MeOH/H_2O 9 : 1 (25 mL) was added 6N NaOH (6 mL), and the mixture was heated under reflux 16 hr. Then it was allowed to reach the room temperature and the mixture was extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure affording 209 mg of an oil that was dissolved in MeOH (4 mL). To this solution, $NaHCO_3$ (239 mg, 2.85 mmol) and Boc_2O (227 mg, 1.04 mmol) in MeOH (6 mL) were added and the mixture stirred 2.5 hr at room temperature. Then inorganic salts were filtered and solvent was removed under reduced pressure. The residue was taken with ether (30 mL) and filtered again. The ethereal solution was concentrated and purified by chromatography to afford 235 mg (0.73 mmol, 60%) of **5** as an oil. $[\alpha]_D = -12.4$ (0.65, $CHCl_3$) ^{1}HNMR (400 MHz, $CDCl_3$) $\hat{\delta}$ 1.47 (s, 9H), 1.65 (bs, 1H), 2.15–2.33 (m, 2H), 3.25 (bs, 1H), 3.75–4.15 (m, 3H), 4.34–4.58 (m, 2H), 5.00–5.10 (m, 2H), 5.62–5.74

(m, 1H), 7.20–7.36 (m, 5H) ppm.^{13}CNMR (100.6 MHz, $CDCl_3$) $\dot{\delta}$ 28.4, 39.3, 53.4*, 53.7, 62.1, 64.2, 71.4, 81.1, 117.8, 127.5, 127.6, 128.6, 134.6 ppm (signals marked with an asterisk correspond to a rotamer). IR (film) v = 3412, 2976, 2931, 1666 cm^{-1}. HRMS (CI, CH_4) for $C_{18}H_{28}NO_4$ ($M + H^+$) 322.2018, found 322.2017.

(1*R*, 2*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-2-*tert*-butyldimethylsilanyloxy-1-*tert*-butydimethylsilanyloxymethyl-4-pentenylamine (**6**)

To a solution **5** (465 mg, 1.44 mmol) in CH_2Cl_2 (10 mL) at 0°C, 2,6-lutidine (504 mL, 4.36 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (826 mL, 3.59 mmol) were added. After 2 hr stirring, H_2O (10 mL) was added, the organic layer was washed with sat $NaHCO_3$, dried, and concentrated in vacuo to give an oil that was purified by chromatography affording 680 mg (1.24 mmol, 86%) of **6** as an oil. $[\alpha]_D = +15.1$ (0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.0 (s, 12H), 0.85 (s, 18H) 1.28 (s, 5H) 1.47 (s, 4H), 1.94–2.30 (m, 2H), 3.65–4.00 (m, 4H), 4.36 (s, 1H), 4.45 (s, 1H) 4.86–5.00 (m, 2H), 5.60–5.78 (m, 1H), 7.14–7.34 (m, 5H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) $\dot{\delta}$ −5.5, −5.4, −4.6, −3.8, 18.0, 18.2, 25.9, 28.2, 28.5, 38.5*, 38.9, 51.0 (b), 61.3, 63.2 (b), 71.2, 71.6*, 79.4, 79.9*, 117.2, 126.5, 126.7*, 127.3, 128.0, 128.2*, 134.4, 140.2 (b), 155.7 (b) ppm (signals marked with an asterisk correspond to a rotamer). IR (film): v = 2929, 2857, 1696 cm^{-1}. HRMS (CI, CH_4) for $C_{30}H_{56}NO_4Si_2$ ($M + H^+$) 550.3748, found 550.3738.

(2*R*, 3*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-2-amino-3-*tert*-butydimethylsilyloxy-5-hexen-1-ol (**7**)

A solution of **6** (620 mg, 1.13 mmol) and *p*-toluenesulfonic acid (21 mg, 0.11 mmol) in MeOH (30 mL) was stirred 2.5 hr at room temperature. The reaction was monitored by TLC. When complete, sat $NaHCO_3$ (20 mL) was added, and extracted with CH_2Cl_2 (2 × 60 mL). The combined organic phases were dried, concentrated, and purified by chromatography to afford 345 mg (0.85 mmol, 70%) of **7** as an oil. $[\alpha]_D = +19.8$ (0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\dot{\delta}$ 0.0 (s, 6H), 0.80 (s, 9H) 1.33 (s, 9H) 2.15–2.25 (m, 2H), 3.11 (sa, 1H) 3.40–3.75 (m, 3H), 4.00–4.38 (m, 2H), 4.61 (d, J = 15.6 Hz, 1H) 4.98–5.05 (m, 2H), 5.70–5.85 (m, 1H), 7.14–7.26 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.2, 18.0, 25.9, 28.4, 39.1, 52.4 (b), 62.7, 63.6 (b), 70.6 (b), 80.6, 117.6 (b), 127.3, 128.6, 134.2 (b), 139.2, 156.6 ppm. IR (film): v = 3446, 2929, 2857, 1694 cm^{-1}. HRMS (CI, CH_4) for $C_{24}H_{42}NO_4Si$ ($M + H^+$) 436.2883, found 436.2884.

(2*S*, 3*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-2-amino-3-*tert*-butydimethylsilyloxy-5-hexenoic Acid Methyl Ester (**8**)

To a solution of **7** (65 mg, 0.149 mmol) in sat. $NaHCO_3$ (1 mL) and acetone (2 mL) at 0°C, TEMPO (26 mg, 0.164 mmol), KBr (2 mg, 0.015 mmol) and NaClO (353 μL, 0.55M, 0.194 mmol) were added. The mixture was stirred 1 hr, NaClO (180 μL, 0.55M, 0.1 mmol) was added, and it was stirred for an additional 1 hr. It was concentrated in vacuo and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give an oil (80 mg) that was dissolved in ^{t}BuOH (2 mL). To this solution, 2-methyl-2-butene (57 μL, 0.51 mmol) in THF (1 mL), a solution of $NaClO_2$ (20 mg, 0.23mmol) and NaH_2PO_4 (28 mg, 0.20 mmol) in H_2O (1 mL) were sequentially added and the mixture stirred 25°C for 15 hr. Then, it was extracted with CH_2Cl_2 dried with $MgSO_4$ and evaporated affording an oil (60 mg) that was dissolved in DMF (3 mL). To this solution, $KHCO_3$(45 mg, 0.45 mmol) and MeI (55 μL, 0.89 mmol) were added, and the mixture stirred 16 hr under nitrogen. H_2O (20 mL) was added, and it was extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The crude was chromatographed to afford 45 mg (0.097 mmol, 65%) of **8** as an oil. $[\alpha]_D = +17.5$ (0.5, $CHCl_3$) ^{1}H NMR (400 MHz, CDCl3) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.83 (s, 9H) 1.33, 1.47 (m, 9H) 2.00–2.45 (m, 2H), 3.52 (s, 3H), 4.26–4.36 (m, 2H), 4.45–4.48 (m, 1H) 4.52–4.76 (m, 1H) 5.00–5.10 (m, 2H), 5.74–5.86 (m, 1H), 7.14–7.32 (m, 5H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) −5.0, −4.1, 18.0, 25.8, 28.2, 38.4 (b), 49.5, 51.5, 61.9 (b), 63.0* (b), 71.2 (b), 80.7 (b), 117.8, 126.7 (b), 128.1, 134.0, 139.0, 155.5, 170.7 ppm. (Signals marked with an asterisk correspond to a rotamer.) IR (film): $\nu = 2929$, 1744, 1703 cm^{-1}. HRMS (CI, CH_4) for $C_{25}H_{42}NO_5Si$ ($M + H^+$) 464.2832, found 464.2835.

(2*S*, 3*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-3-*tert*-butyldimethylsilanyloxy Glutamic Acid Dimethyl Ester (**9**)

A suspension of **8** (45 mg, 0.097 mmol), $NaIO_4$ (144 mg, 0.68 mmol) and $RuCl_3 \cdot H_2O$ (3 mg, 0.014 mmol, 0.14) in CCl_4 (1 mL), CH_3CN (1 mL), and H_2O (1.5 mL) was stirred 3 hr at room temperature. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was solved in DMF (3 mL) and, to this solution, $KHCO_3$ (28 mg, 0.28 mmol, 3 eq.) and MeI (36 μL, 0.56 mmol, 6 eq) were added. The mixture was stirred 16 hr under nitrogen. After workup with H_2O (20 mL) and CH_2Cl_2 (20 mL), the combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (SiO_2/NEt_3) to afford 25 mg (0.050 mmol, 52%) of **9** as an oil. $[\alpha]_D = -35.4$ (0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\dot{\delta}$ 0.02 (s, 3H), 0.05 (s, 3H), 0.80 (s, 9H) 1.37–1.48

(m, 9H) 2.16–2.80 (m, 2H), 3.45 (s, 3H), 3.66 (s, 3H), 4.45–4.70 (m, 3H), 4.76–4.85 (m, 1H) 7.17–7.32 (m, 5H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) −5.1, −4.8, 17.9, 25.7, 28.2, 38.3, 49.8 (b), 50.7* (b), 51.6, 62.9 (b), 64.0* (b), 68.8, 80.7 (b), 127.0 (b), 128.4, 138.5 (b), 155.6, 170.0, 171.8 ppm. (Signals marked with an asterisk correspond to a rotamer.) IR (film): $\nu = 2953, 1744, 1703\,cm^{-1}$. HRMS (CI, CH_4) for $C_{25}H_{42}NO_7Si$ $(M + H^+)$ 496.2731, found 496.2743.

N-Boc-(2*S*, 3*S*)-3-hydroxy Glutamic Acid Dimethyl Ester (**10**)

A suspension of **9** (14 mg, 0.028 mmol), and $PdCl_2$ (5 mg) in MeOH (2 mL) was stirred 20 hr under hydrogen atmosphere (balloon). When the reaction was complete by TLC, it was filtered through a celite pad, and the solvent was removed under reduced pressure. The crude was purified by column chromatography affording **10** (6 mg, 73%) as an oil. $[\alpha]_D = +19.0$ (0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (ds, 9H), 1.60 (bs, 1H), 2.60 (dd, $J_1 = 16.8$ Hz, $J_2 = 3.6$ Hz, 1H), 2.68 (dd, $J_1 = 16.8$ Hz, $J_2 = 8.8$ Hz, 1H) 3.71 (s, 3H), 3.78 (s, 3H), 4.31–4.40 (m, 2H), 5.48 (bs, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$), 28.2, 37.7, 51.9, 52.6, 57.7, 69.6, 80.6, 155.7, 172.4, 173.4 ppm. IR (film): $\nu = 3380, 2956, 1739, 1716\,cm^{-1}$. HRMS (CI, CH_4) for $C_{12}H_{22}NO_7$ $(M + H^+)$ 292.1396, found 292.1390.

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