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Stereoselective synthesis of 2-*epi*-jaspine B via base-catalyzed intramolecular oxy-Michael conjugate addition approach

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A B S T R A C T

2-*epi*-Jaspine B has been synthesized starting from (−)-diethyl tartrate in 12 simple steps and 26.6% overall yield. The key intermediate was obtained via stereoselective base-catalyzed intramolecular oxy-Michael conjugate addition followed by tandem hydrogenation/hydrogenolysis.

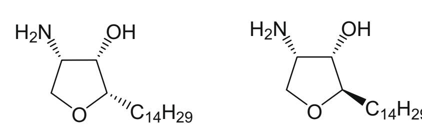
1. Introduction

Phytosphingosine is present in large quantities in yeast and plants, as both the free sphingoid base and an integral component of (glyco)phytosphingolipids.[1] Several biological processes, including heat–stress response and endocytic events involve phytosphingosine.[2] Sphingosine-1-phosphate has been found to induce a rapid and relevant release of arachidonic acid, and increase phospholipase D activity in A549 cells.[3] Phytosphingosine has also been found to be a key intermediate from which more complex metabolites are derived.[4] Apart from the linear structures, phytosphingosine derivatives also exist as anhydro forms that were shown to be potent inhibitors of a variety of glycosidase activities.[5] One of the naturally occurring anhydrophytosphingosine derivatives isolated from marine sponges, *Pachastrissa* sp. and *Jaspis* sp.,[6] exhibited a significant cytotoxicity against P388, A549, HT29, and MEL28 carcinoma cell lines in vitro.[7] The impressive biological activity and novel structural features have prompted several research groups to explore the preparation of this compound.[6,8,9] As part of our research program in the synthesis and evaluation of enzyme inhibitors we have carried out the stereoselective total synthesis of 2-*epi*-jaspine B **12**, a diastereomer of jaspine B **11** (Fig. 1).

Our approach to 2-*epi* jaspine B **12** is depicted retrosynthetically in Scheme 1. The *syn*-(*S*,*S*)-stereochemical center in commercially available (−)-diethyl tartrate can be utilized in the preparation of protected *anti*-aminoalcohols,[10] which can be subjected to a base-catalyzed intramolecular oxy-Michael conjugate addition.[11]

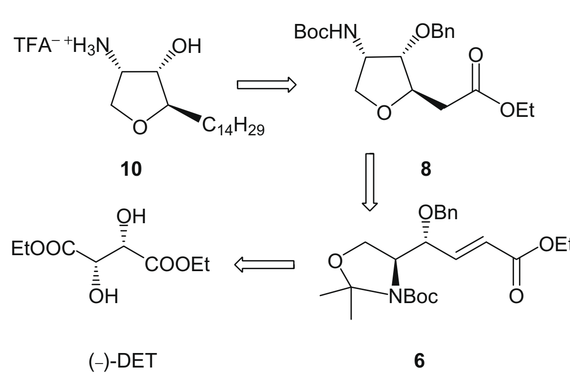
2. Results and discussion

Commercially available (−)-diethyl tartrate was treated with thionyl chloride to form cyclic sulfite **1**, which was treated with sodium azide in DMF[10] at room temperature to yield azide **2** in 68% yield. Treatment of **2** with benzyl bromide in Ag_2O/DCM gave **3** in 95% yield. Reduction of **3** with lithium aluminum hydride in THF, followed by *N*-Boc protection in a single-pot reaction gave diol **4** in 90% overall yield. Acetonide protection by treatment with 2,2-dimethoxy propane gave regioselective product **5** in 85% yield.[11] Oxidation of **5** with Dess–Martin periodinane followed by Wittig olefination with ethoxycarbonyl methylene triphenylphosphorane gave **6** in 92% yield. Deprotection of the acetonide with PTSA in MeOH gave N-protected amino alcohol **7** (97%) which was treated with 0.1 equiv of sodium hydride in THF at 0 °C for 1 h to obtain the diastereoselective intramolecular oxy-Michael



jaspine B **11**   2-*epi*-jaspine B **12**

Figure 1.



Scheme 1.

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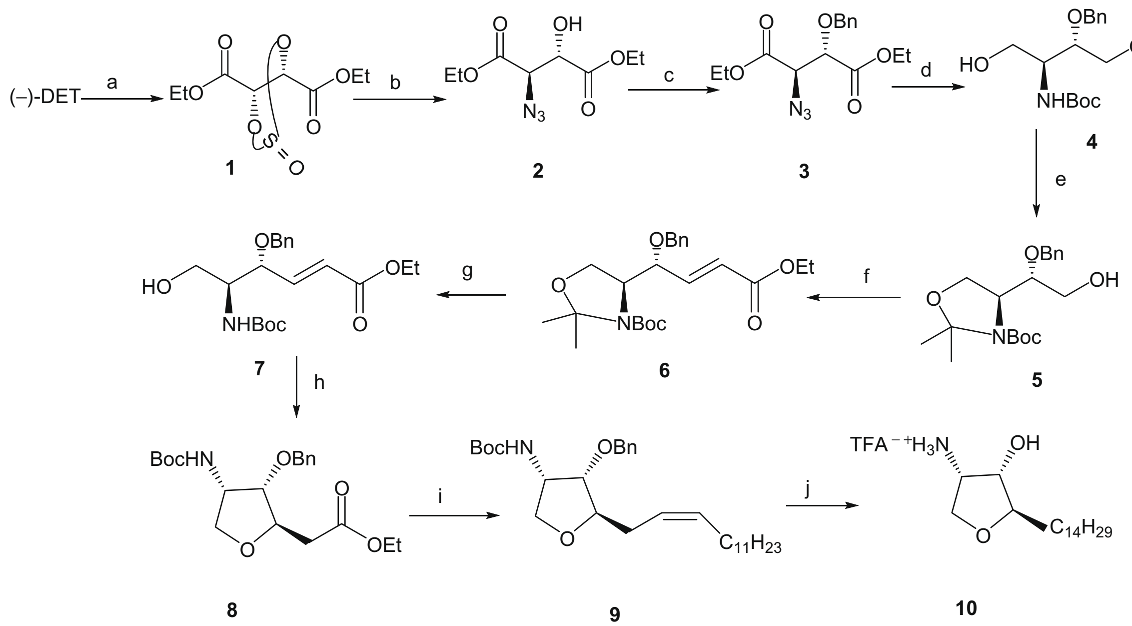

Scheme 2. (a) $SOCl_2$, TEA, DCM, 0 °C, 3 h; (b) NaN_3, DMF, rt, 5 h (68%); (c) BnBr, Ag_2O, DCM, rt, 10 h, 95%; (d) LAH/THF, 4 h reflux, 2 m NaOH, $(Boc)_2O$, rt, 30 min, 90%; (e) 2,2-DMP, DCM, rt, 3 h, 85%; (f) (i) Dess–Martin periodinane, DCM, rt, 1 h; (ii) $Ph_3P{=}CH{-}COOEt$, DCM, rt, 30 min, 92%; (g) PTSA/MeOH, rt, 2 h, 97%; (h) NaH/THF, 0 °C to rt 1 h, 90%; (i) i) DIBAL-H/THF, −78 °C, 1.5 h; (ii) $Br^{-+}PPh_3C_{12}H_{25}$, *n*-BuLi, −78 °C to rt, 3 h (73%); (j) $Pd(OH)_2/C$, H_2, MeOH, TFA, rt 5 h, 92%.

product[12] **8** in 90% yield. The formation of *anti* product **8** was deduced from the ^{13}C NMR spectra in which the *anti*-C2 resonates at 78.5 ppm. In the case of a *syn*-product, the C2 is expected to resonate at 70 ppm (Scheme 2).

Having attained the required stereochemistry in the terahydrofuranyl ring, the attachment of the alkyl side chain was achieved by reduction of the ester group with DIBAL-H to the aldehyde, followed by a Wittig olefination with dodecanylidene triphenyl phosphorane. Thus, **8** was successfully transformed into **9** in 73% yield. Tandem hydrogenation/hydrogenolysis of **9** over palladium hydroxide on carbon in MeOH/TFA gave the corresponding TFA salt of 2-*epi*-jaspine B **10** in 92% yield. The formation of *anti*-product **10** was confirmed from the ^{13}C NMR spectra in which the *anti*-C3 resonates at 74.3 ppm. In the case of the *syn*-product, C3 is expected to resonate at 71 ppm as reported in the literature.[6,8a] Datta et al. have previously reported the preparation of 2,3-*syn*-**11** by an oxy-Michael approach,[8d] but critical analysis of their spectroscopic data by Davies et al. has shown that the product is an *anti*-product formed via retro-Michael/Michael epimerization pathway. Our results are in full agreement with the proposed mechanism of Davies,[8a] which predicts a thermodynamically favorable 2,3-*anti* product after the attack of the oxy-anion during the Michael addition.

3. Conclusion

In conclusion, we have synthesized the epimer of jaspine B in 26.6% overall yield in 12 simple steps. The strategy of the stereoselective intramolecular oxy-Michael conjugate addition reaction can be applied to synthesis of a variety of products.

4. Experimental

4.1. General

All reagents were purchased from Aldrich. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance-300 MHz spectrometer. Optical rotations were measured with a Horiba-SEPA-300 digital polarimeter. Mass spectra were recorded on a Q STAR mass spectrometer (Applied Biosystems, USA).

4.1.1. 1-[(1*R*,2*S*)-3-Ethoxy-1-(ethoxycarbonyl)-2-hydroxy-3-oxopropyl]-1,2-triazadien-2-ium 2

Thionyl chloride (2.2 mL, 30.1 mmol) was added drop wise to a stirred solution of diethyl (*S*,*S*)-tartrate (3.1 g, 15.0 mmol) and anhydrous triethylamine (4.9 mL, 31.1 mmol) in 30 mL of dry CH_2Cl_2 at 0 °C. The temperature was allowed to reach room temperature in 2 h. Next, CH_2Cl_2 (20 mL) and saturated NaCl (40 mL) were added to the reaction mixture, after which the layers were separated, and the aqueous phase was extracted thoroughly with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield **1** quantitatively as brown oil which was used without further purification.

To a solution of **1** in 30 mL of DMF at room temperature, sodium azide (1.35 g, 20.74 mmol) was added and the mixture was stirred at rt for 5 h. The solvent was then evaporated under reduced pressure, the residue was dissolved in 50 mL of EtOAc, washed with saturated NaCl (3 × 30 mL), and dried with anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 1:3) yielding **2** (2.36 g, 68%) as a viscous oil. $[\alpha]_D^{25} = -30.5$ (*c* 1, EtOH). IR(neat) ν_{max} = 1211, 1744, 2119, 2931, 2986, 3485 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.39 (m, 6H), 3.21–3.25 (d, *J* = 6.0 Hz, 1H), 4.21–4.37 (m, 4H), 4.59 (qt, *J* = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0, 62.3, 62.6, 64.3, 72.0, 166.9, 170.7. ESI-MS: *m/z* = 254 (M+Na).

4.1.2. 1-[(1*R*,2*S*)-2-(Benzyloxy)-3-ethoxy-1-(ethoxycarbonyl)-3-oxopropyl]-1,2-triazadien-2-ium 3

To a solution of **2** (2 g, 8.7 mmol) in 20 mL of dry CH_2Cl_2 was added silver oxide (3.05 g, 13.0 mmol) followed by benzyl bromide (1.23 mL, 10.4 mmol). The reaction mixture was stirred for 10 h at room temperature and then filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by column chromatography on silica gel (60–120 mesh, EtOAc/hexane, 4:96). Compound **3** was obtained as a colorless oil (2.64 g, 95%). $[\alpha]_D^{25} = +5.5$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 1202, 1753, 2113, 2906, 2939, 2983 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (m, 6H), 4.08–4.20 (m, 1H), 4.21–4.33 (m, 4H), 4.36–4.62 (m, 2H), 4.85–4.92 (m, 1H), 7.28–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1, 61.6, 61.8, 62.3, 63.1, 73.3, 78.3, 127.9, 128.2, 128.4, 136.4, 167.0. ESI-MS: *m/z* = 344 (M+Na).

4.1.3. *tert*-Butyl *N*-[(1*S*,2*S*)-2-(benzyloxy)-3-hydroxy-1-(hydroxymethyl)propyl] carbamate 4

To a solution of lithium aluminum hydride (0.54 g, 14.6 mmol) in 50 mL of dry THF was added azide **3** (1.55 g, 4.8 mmol) in dry THF drop wise at 0 °C for 20 min, after which the reaction mixture was refluxed for 4 h. The reaction was quenched with 10 mL of cold saturated NH_4Cl solution, after which a 1 M NaOH solution and Boc-anhydride (1.58 mL, 7.2 mmol) were added to the reaction mixture and stirred for 30 min. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (2 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 2:3) yielding **4** (1.35 g, 90%) as a white solid. $[\alpha]_D^{25} = -45.45$ (*c* 1, $CHCl_3$). IR (KBr) ν_{max} = 1674, 2884, 2944, 3251, 3475 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.40–3.46 (m, 1H), 3.57–3.66 (m, 2H), 3.70–3.86 (m, 2H), 3.88–3.97 (m, 1H), 4.53–4.64 (m, 2H), 7.26–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 51.5, 60.1, 61.7, 71.6, 78.2, 80.1, 128.0, 128.1,128.5, 137.8, 156.6. ESI-MS: *m/z* = 334 (M+Na).

4.1.4. *tert*-Butyl (4*S*)-4-[(1*S*)-1-benzyloxyethyl]-2,2 dimethyl-1,3-oxazolane-3-carbamate 5

To a solution of the amino-protected diol **4** (1.08 g, 3.5 mmol) in 20 mL of dry CH_2Cl_2, were added 2,2-dimethoxypropane (1.35 mL, 10.4 mmol) and PTSA (32 mg, 0.14 mmol) and the reaction mixture was stirred at ambient temperature for 3 h. The organic layer was evaporated under reduced pressure to afford the crude acetonide which was purified by column chromatography on silica gel (60–120 mesh, EtOAc/hexane, 2:8) to yield **5** (0.96 g, 85%) as a colorless oil. $[\alpha]_D^{25} = -50.05$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 1370, 1395, 1456, 1693, 2926, 2975, 3448 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.47–1.53 (m, 15H), 3.32 (dd, *J* = 10, 16 Hz, 2H), 3.72–3.96 (m, 3H), 4.0–4.13 (m, 2H), 4.4–4.8 (m, 2H), 7.27–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 27.4, 28.1, 56.6, 58.2, 65.2, 71.2, 78.9, 81.2, 93.7, 127.5, 127.7, 128.2, 137.8, 153.9. ESI-MS: *m/z* = 374 (M+Na).

4.1.5. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*)-1-(benzyloxy)-4-ethoxy-4-oxo-2-butenyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate (6)

To a stirred solution of compound **5** (0.756 g, 2.2 mmol) in 15 mL of dry CH_2Cl_2, Dess–Martin periodinane (1.20 g, 2.9 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was then quenched with 5 mL of saturated $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude aldehyde. The crude aldehyde was dissolved in dichloromethane (15 mL) and treated with ethoxycarbonyl methylene triphenylphosphorane (1.29 g, 3.0 mmol) for 30 min. The organic layer was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (60–120 mesh, EtOAc/hexane, 4:96) to yield compound **6** (0.81 g, 92%) as a colorless oil. $[\alpha]_D^{25} = -22.2$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 1375, 1699, 2929, 2977, 3449 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.57 (m, 18H), 3.80–4.06 (m, 4H), 4.13–4.28 (qt, *J* = 7.35 Hz, 2H), 4.30–4.43 (m, 1H), 4.54–4.64 (m, 2H), 5.94 (d, *J* = 15.43, 1H), 6.83 (dd, *J* = 5.9, 9.55 Hz, 1H), 7.26–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 23.0, 24.7, 27.0, 28.2, 28.3, 29.7, 59.8, 60.5, 60.6, 64.2, 65.3, 71.8, 78.4, 79.31, 80.4, 123.5, 124.1, 127.7, 127.9, 128.0, 128.4, 128.5, 137.33, 145.7, 165.8. ESI-MS: *m/z* = 442 (M+Na).

4.1.6. Ethyl 2-((2*R*,3*S*,4*S*)-3-(benzyloxy)-4-[(*tert*-pentyloxy)carbonyl] aminotetrahydro-2-furanyl) acetate 8

Compound **6** (0.49 g, 1.16 mmol) was stirred with a solution of PTSA (13 mg, 0.05 mmol) in methanol (15 mL) for 2 h at room temperature. Methanol was removed by evaporation under reduced pressure, after which sodium carbonate solution (1 mL, 10%) was added and the product was extracted with ethyl acetate (3 × 15 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate and evaporated. The deprotected product **7** obtained as an oil (0.43 g, 1.14 mmol, 97%) was dissolved in 15 mL of dry THF. Sodium hydride (catalytic amount, 60% dispersion in mineral oil, 7 mg) was added at 0 °C, after which the reaction mixture was allowed to return to room temperature and stirred for 1 h. The reaction mixture was then cooled in ice and quenched with 2 mL of saturated NH_4Cl solution. The solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (2 × 15 mL) and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate, the residue was chromatographed over silica gel (60–120 mesh, EtOAc/hexane, 1:9) yielding **8** (0.375 g, 90%) as a colorless oil. $[\alpha]_D^{25} = +11.5$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 1500, 1713, 2857, 2925, 2974, 3442 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 2.51(dd, *J* = 1.9, 6.8 Hz, 2H), 3.63 (t, *J* = 8.35 Hz, 1H), 3.80–3.85 (m, 1H), 4.04–4.19 (m, 3H), 4.21–4.32 (m, 2H), 4.53–4.64 (m, 2H), 5.12 (d, *J* = 7.7 Hz, NH), 7.28–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 28.3, 29.6, 38.5, 51.1, 60.7, 71.2, 72.0, 78.5, 79.7, 80.7, 127.9, 128.0, 128.5, 137.3, 155.5, 170.5. ESI-MS: *m/z* = 380 (M+1), 402 (M+Na).

4.1.7. *tert*-Pentyl *N*-(3*S*,4*S*,5*R*)-4-(benzyloxy)-5-[(*Z*)-2-tetradecenyl] tetrahydro-3-furanylcarbamate 9

To a stirred solution of compound **8** (0.210 g, 0.55 mmol) in 20 mL of dry THF, DIBAL-H (0.094 g, 0.66 mmol) was added at −78 °C and the solution was stirred for 1.5 h. After the completion of the reaction, a saturated solution of sodium potassium tartrate in water (2 mL) was added to quench the reaction. The solvent was then evaporated under reduced pressure, the reaction mixture was extracted with EtOAc (2 × 15 mL), dried with anhydrous Na_2SO_4, and concentrated. The aldehyde product was used as such without further purification due to its instability on silica gel column.

To a stirred solution of dodecyl triphenylphosphonium bromide (1.13 g, 2.2 mmol) in 20 mL of dry THF at −78 °C was added *n*-butyllithium (1.6 M solution in hexane 1.25 mL,1.87 mmol) dropwise and the resulting solution was stirred for 45 min. The crude aldehyde obtained above was dissolved in dry THF (5 mL) and added dropwise with stirring to the ylide solution at −78 °C. The reaction mixture was then allowed to return to room temperature and stirred for 3 h. The reaction was quenched with 6 mL of saturated NH_4Cl solution at 0 °C, the solvent was evaporated under reduced pressure, the residue was extracted with EtOAc (2 × 15 mL), and dried with anhydrous Na_2SO_4. After evaporation of ethyl acetate the residue was chromatographed (silica gel, 60–120 mesh, EtOAc/hexane, 2:98) to obtain **9** (0.191 g, 73%) as a colorless oil. $[\alpha]_D^{25} = +6.8$ (*c* 1, $CHCl_3$). IR(neat) ν_{max} = 1497, 1714, 2854, 2924, 3444 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.21–1.37 (m, 8H), 1.45 (s, 9H), 2.00 (q, *J* = 6.6,13.0 Hz, 2H), 2.28 (q, *J* = 6.8,14.2 Hz, 2H), 3.57 (t, *J* = 7.55 Hz, 1H), 3.65–3.74 (m, 1H), 3.91 (q, *J* = 3.6, 9.1 Hz, 1H), 4.07–4.16 (m, 1H), 4.17–4.30 (m, 1H), 4.45–4.58 (m, 2H), 5.13 (d, *J* = 5.84 Hz, NH), 5.30–5.42 (m,1H), 5.45–5.58 (m, 1H), 7.26–7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 27.4, 28.3, 29.3, 29.5, 29.6, 31.4, 31.8, 51.4, 71.1, 72.0, 79.6, 80.7, 82.4, 123.8, 127.8, 128.0, 128.5, 133.1, 137.4, 155.6. ESI-MS: m/z = 488 (M+1), 510 (M+Na).

4.1.8. TFA salt of 2-*epi*-jaspine B 10

To a stirred solution of compound **9** (0.106 g, 0.2 mmol) in 20 mL of methanol, trifluoroacetic acid (0.2 mL, 2.6 mmol) and palladium hydroxide/C (10 mg, catalytic amount) were added. The reaction mixture was stirred under hydrogen atmosphere at rt for 5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. The residue was chromatographed (silica gel, 60–120 mesh, EtOAc/methanol, 9:1) to obtain **10** (0.080 g, 92%) as a white solid. $[\alpha]_D^{25} = +13.6$ (c 1, EtOH) {lit.[6] +14.5 (c 1.5, EtOH)}. IR(KBr) ν_{max} = 1713, 2925, 2974, 3442 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 0.89 (t, J = 7.3 Hz, 3H), 1.22–1.39 (m, 22H), 1.41–1.68 (m, 4H), 3.63–3.76 (m, 3H), 3.98–4.05 (m, 1H), 4.09–4.17 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 14.3, 23.6, 26.8, 30.3, 30.6, 30.7, 33.0, 34.0, 53.7, 69.3, 74.3, 85.2. ESI-MS: m/z = 300 (M+1_CF_3COOH).

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