

TosMIC-free synthesis of bempedoic acid, a hypercholesterolemia drug

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Dedication to Dr Srivari Chandrasekhar on the occasion of his 60th Birthday

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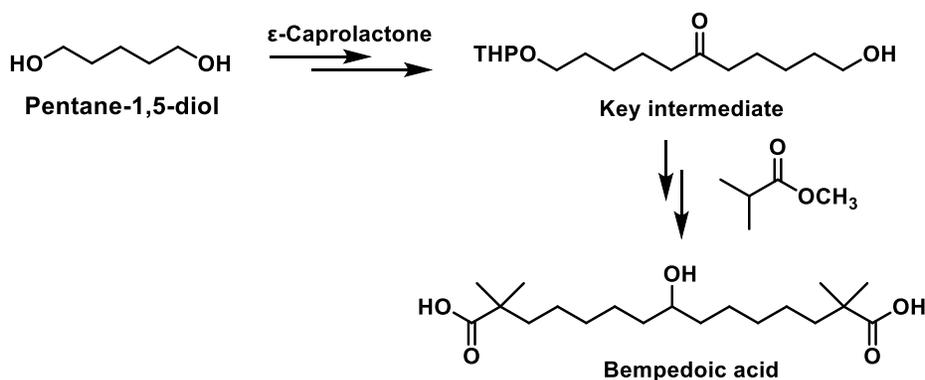
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Abstract

A novel concise and convergent approach for the preparation of bempedoic acid, a new group of non-statin LDL-lowering drug has been developed starting from pentane-1,5-diol in 8 steps with an overall yield of 20%. Result: The synthesis of a key precursor i.e. 1,11-dihydroxyundecan-6-one, has been accomplished through the ring opening of ϵ -caprolactone with alkyl Grignard reagent. This method doesn't require the use of *p*-toluenesulfonylmethylisocyanide (TosMIC) for the construction of dihydroxyketone, a key intermediate of bempedoic acid. The key steps involved in this approach are the bromination of dihydroxyketone and base-catalyzed alkylation of methyl isobutyrate with 1,11-dibromoundecan-6-ol followed by the hydrolysis of dimethyl ester into bempedoic acid.



Keywords: ϵ -Caprolactone; 1,5-pentanediol; methyl isobutyrate; Grignard reaction; bempedoic acid

Introduction

The cardiovascular disease is one of the leading causes of death worldwide due to high cholesterol levels.¹⁻⁴ Among various medications, statins are known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors because they catalyse the conversion of HMG-CoA into mevalonate that regulates the synthesis of cholesterol.⁵⁻⁷ In particular, ATP-citrate lyase (ACL) is a central metabolic enzyme and catalyses the ATP-dependent conversion of citrate and coenzyme A (CoA) into oxaloacetate and acetyl-CoA in the metabolic pathway. The acetyl-CoA is crucial for the metabolism of fatty acids and the biosynthesis of cholesterol and also the acetylation and prenylation of proteins (Figure 1).^{8,9}

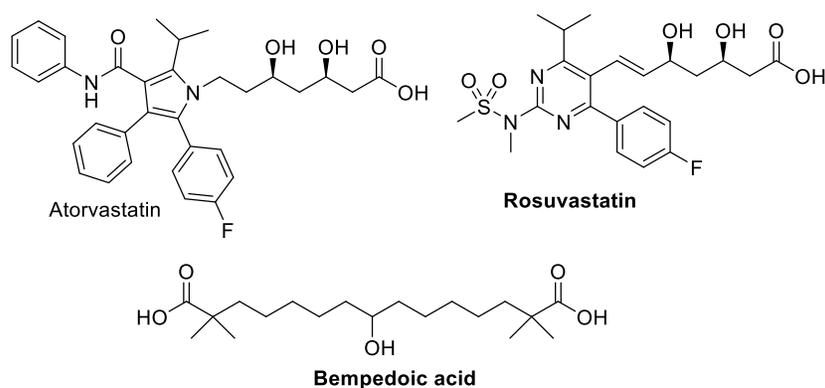


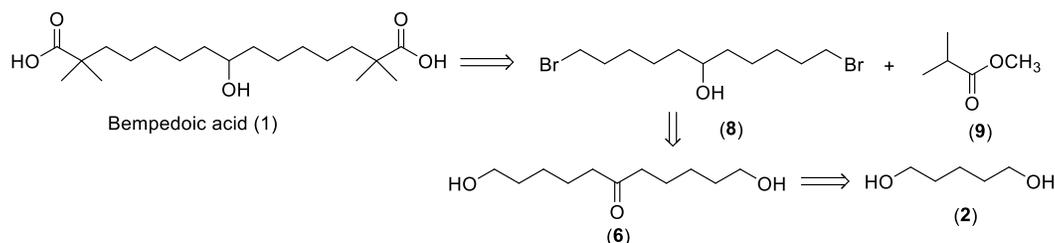
Figure 1. Examples of LDL cholesterol lowering drugs

Bempedoic acid is a first-in-class medication to inhibit the ATP-citrate lyase enzyme that lowers LDL cholesterol levels in patients who are resistant to statins.^{10,11} Indeed, it lowers LDL cholesterol levels by preventing the synthesis of cholesterol in the liver.¹²

Bempedoic acid does not cause myositis, a side effect that is typically observed with statin therapy due to its distinct mode of action.¹³ It was developed by M/s Esperion Therapeutics Inc and was approved by FDA in 2020. The combination of bempedoic acid and ezetimibe has been approved for lowering the LDL cholesterol levels. Recently, bempedoic acid has been also identified as a histone deacetylase-6 inhibitor.¹⁴ Therefore, the development of novel approaches is of prime importance. Consequently, there are some reports on the synthesis of bempedoic acid.¹⁵⁻¹⁹ Dasseux *et al.* reported the synthesis of bempedoic acid by employing TosMIC to the formation of keto-diacid. Wang *et al.*, reported the synthesis of bempedoic acid by electrochemical decarboxylation of dialkylated malonic acid for ketone formation.^{15,16} D.C.Oniciu *et al.*, reported in their review, how the bempedoic acid molecule was discovered and discusses the synthetic pathways to make it in comparison with its close relative gemcabene calcium.²⁰ Because of its high efficiency and significant market potential, we were interested in developing a simple, cost-effective, and highly convergent synthesis technique for bempedoic acid.

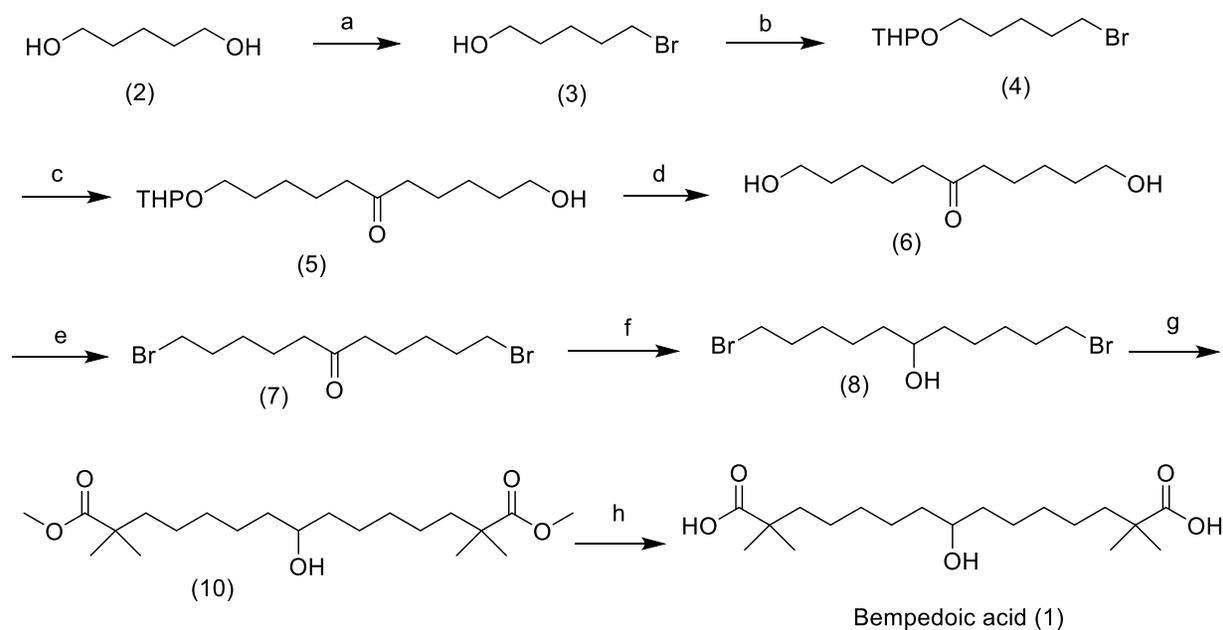
Results and Discussion

Following our interest on the total synthesis of biologically active molecules,²¹⁻²³ we herein report a novel strategy for the synthesis of bempedoic acid, which is used for the treatment of hypercholesterolemia approved by FDA in 2020. In this report, we propose the synthesis of bempedoic acid started from 1,5-pentandiol. As per our retrosynthetic analysis, bempedoic acid (**1**) can be synthesized from dibromo alcohol **8** and methyl isobutyrate (**9**). Indeed, the compound **8** could be prepared from dihydroxy ketone **6**, which in turn derived from pentane-1,5-diol (**2**) (Scheme 1).



Scheme 1. Retrosynthesis of bempedoic acid¹¹

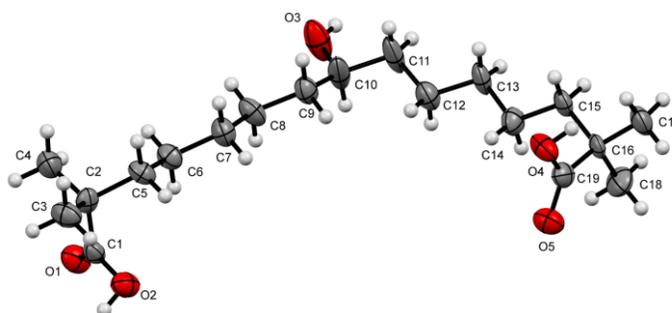
Accordingly, the pentane-1,5-diol (**2**) was converted into a mono-bromo derivative **3** in 81% yield using 48% aqueous HBr in toluene under reflux conditions. Then the hydroxyl group of **3** was protected as its THP ether **4** in 93% yield using DHP and a catalytic quantity of *p*-TSA in DCM at 25 °C. Further, the bromo compound **4** was treated with Mg metal in THF at 25 °C to generate the alkyl Grignard reagent, which was then reacted with ϵ -caprolactone to afford the keto derivative **5** in 52% yield. The formation of key intermediate **5** was characterized by the appearance of a strong absorption at 1720 cm⁻¹ (C=O) in IR spectrum and also confirmed by NMR and HRMS.



Reaction conditions: (a) 48% aqueous HBr, toluene, reflux, 81%; (b) DHP, *p*-TsOH, DCM, 93%; (c) ϵ -caprolactone, THF, Mg, 0°C-rt, 52%; (d) *p*-TsOH, MeOH, 0°C-rt, 90%; (e) CBr₄, PPh₃, DCM, 0°C-rt, 94%; (f) NaBH₄, MeOH, 0°C-rt, 93%; (g) methyl isobutyrate (**9**), LDA, dry THF, 70%; (h) KOH, EtOH: H₂O (4:1), reflux, 84%.

Scheme 2. Synthetic route of bempedoic acid

Subsequently, the deprotection of THP ether using *p*-TsOH in methanol gave the dihydroxyketone (**6**) in 90% yield, which was then converted into dibromoketone **7** in 94% yield using CBr₄ and PPh₃ in DCM at 0 to 25 °C. Subsequently, the ketone was reduced to the corresponding dibromo alcohol **8** in 93% yield using NaBH₄ in methanol. Further, the coupling of dibromoalcohol **8** with methyl isobutyrate (**9**) using LDA in dry THF afforded the hydroxy diester **10** in 70% yield. Finally, the hydrolysis of diester **10** using KOH in ethanol:water (4:1) afforded the target molecule, bempedoic acid (**1**) in 84% yield, (Scheme 2) which was thoroughly characterized by IR, ¹H NMR, ¹³C NMR and HRMS and also compared with the data reported in the literature.¹⁶ The structure of bempedoic acid (**1**) was confirmed by single crystal X-ray crystallography (Fig 2).²⁴

**Figure 2.** ORTEP diagram of bempedoic acid (**1**)**Conclusions**

In summary, we have developed a novel and efficient approach to the total synthesis of bempedoic acid through the ring opening of ϵ -caprolactone by alkyl Grignard reaction. The use of readily available key starting materials like 1,5-pentanediol, ϵ -caprolactone, methyl isobutyrate makes this approach simple, convenient and scalable.

Experimental Section

General. All solvents were dried by a standard literature procedure. Crude products were purified by column chromatography on silica gel of 60–120 or 100–200 mesh. Thin layer chromatography (TLC) plates were visualized by exposure to ultraviolet light at 254 nm, and by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250°C). Organic solvents were concentrated on rotary evaporator at 35–40 °C. Melting points (m.p) were measured on Buchi B-540. ¹H and ¹³C NMR (proton-decoupled) spectra were recorded in CDCl₃ solvent on 300, 400 or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in hertz (Hz). IR spectra were recorded on a Bruker Alpha II-ATR-FTIR (Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy). Mass spectra and HRMS were recorded on mass spectrometer by Electrospray ionization (ESI).

5-Bromopentan-1-ol (3): To a stirred mixture of 1,5-pentanediol (**2**) (20 g, 192.3 mmol) dissolved in toluene (200 mL) was added aq.48% HBr (35.65 mL) at room temperature and the reaction mixture was heated under reflux using Dean-Stark apparatus for 4-5 h. The progress of the reaction was monitored by TLC as completion was shown by the TLC and then extracted with ethyl acetate (EtOAc) (2 x 150 mL). The combined organic layers were washed with brine solution (100 mL) dried over Na₂SO₄ then evaporated under reduced pressure to give the crude product, which was purified by column chromatography with 20-25% EtOAc/hexane to give the desired product, 5-bromopentan-1-ol (**3**) yellow oil, (26.21 g, 81%);

IR(ATR) ν (cm⁻¹): 3311(O-H), 2936(C-H), 2862, 1724, 1443, 1237, 1045, 865, 733, 641. ¹H NMR (400 MHz, CDCl₃) δ 3.60 (t, *J* = 6.3 Hz, 2H), 3.36 (t, *J* = 6.8 Hz, 2H), 1.87-1.82 (m, 2H), 1.58 – 1.52 (m, 2H), 1.51 – 1.43 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 62.6, 3.74, 32.5, 31.8, 24.4; HRMS (ESI) *m/z* calcd for C₅H₁₀Br [M-OH]⁺ 148.99604; found 148.99539.

2-((5-Bromopentyl)oxy)tetrahydro-2H-pyran (4): To a stirred solution of 5-bromopentan-1-ol (**3**) (25g, 149.7 mmol) was dissolved in dichloromethane and chilled to 0°C, followed by 3,4-dihydropyran (DHP) (18.8g, 224.55 mmol), *p*-toluenesulfonic acid (*p*-TsOH) (2.57g, 14.97mmol) were added and then allowed the mixture to stir at room temperature overnight. After completion of the reaction, the mixture was diluted with water and then extracted with dichloromethane (DCM). The organic layer was washed with brine solution and dried over anhydrous sodium sulphate (Na₂SO₄) and then concentrated under reduced pressure. The crude product was purified by column chromatography with 5-10% EtOAc/hexane to afford the product 4 as light yellow oil, (35.1 g, 93%); IR(ATR) ν (cm⁻¹): 2937(C-H), 2864, 1446, 1354, 1263, 1194, 1126, 1071, 1027, 981, 904, 871, 812. ¹H NMR (400 MHz, CDCl₃) δ 4.57 (t, *J* = 3.6 Hz, 1H), 3.89-3.83 (m, 1H), 3.73-3.76 (m, 1H), 3.54-3.46 (m, 1H), 3.45-3.36 (m, 3H), 1.95 – 1.86 (m, 2H), 1.85 – 1.78 (m, 1H), 1.76 – 1.66 (m, 2H), 1.66 – 1.58 (m, 3H), 1.56-1.49(m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 98.9, 67.2, 62.4, 33.7, 32.6, 30.7, 28.9, 25.5, 25.0, 19.70. HRMS (ESI) *m/z* calcd for C₁₀H₁₉O₂BrNa [M+Na]⁺ 273.04606; found 273.04578.

1-Hydroxy-11-((tetrahydro-2H-pyran-2-yl)oxy) undecan-6-one (5): To a stirred suspension of magnesium (Mg) (3.19 g, 131.41 mmol) in dry tetrahydrofuran (THF) (20 mL) under nitrogen atmosphere was added a solution of 2-((5-bromopentyl)oxy)tetrahydro-2H-pyran (**4**) (26.38 g, 105.13 mmol), which was diluted in dry THF(150 mL) and heated to generate the Grignard reagent (5-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)magnesium bromide) (28.9 g, 105.09 mmol), which was then added to ϵ -caprolactone (10g, 87.61 mmol) in dry THF (100 mL). After complete addition, the reaction mixture was stirred at room temperature for overnight and then quenched with sat. ammonium chloride (NH₄Cl) solution (200 mL) and extracted with EtOAc. The combined organic layers were washed with brine solution and dried over Na₂SO₄ and evaporated under reduced pressure. The crude compound was purified by column chromatography using 20-30% EtOAc/hexane to afford compound **5** as a clear liquid, (13.21 g, 52%);

IR(ATR) ν (cm⁻¹): 3460(O-H), 2933(C-H), 2863, 1720(C=O), 1453, 1361, 1127, 1068, 1027. ¹H NMR (500 MHz, CDCl₃) δ 4.49 (t, *J* = 4.5, 2.8 Hz, 1H), 3.81-3.76 (m, 1H), 3.68-3.63 (m, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.44 – 3.40 (m, 1H), 3.33-3.28 (m, 1H), 2.36-2.32 (m, 4H), 1.77-1.71 (m, 1H), 1.65-1.61 (m, 1H), 1.57 – 1.47 (m, 12H), 1.32 – 1.26 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 211.3, 98.9, 67.4, 62.6, 62.4, 42.7, 32.4, 30.7, 29.5, 25.9, 25.0, 25.3, 23.6, 23.4, 19.7. HRMS (ESI) *m/z* calcd for C₁₆H₃₀O₄Na [M+Na]⁺ 309.20363 ; found 309.20480.

1,11-Dihydroxyundecane-6-one (6): To a stirred solution of 1-hydroxy-11-((tetrahydro-2H-pyran-2-yl)oxy)undecan-6-one (**5**) (10 g, 34.96 mmol) in methanol (MeOH) (100 mL) and was added *p*-TsOH (6.0 g, 34.96 mmol) and the resulting mixture was stirred for 30 min at room temperature. Then the solvent was evaporated and diluted with DCM. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated

under reduced pressure. The crude product was purified by column chromatography using 40-50% EtOAc/hexane to afford the desired product **6** as a white solid, (6.31 g, 90%), mp 50-52 °C; IR(ATR) ν (cm^{-1}): 3222(O-H), 2926(C-H), 2866, 1698(C=O), 1460, 1367, 1316, 1214, 1107, 1055, 1007, 964, 728, 685. ^1H NMR (400 MHz, CDCl_3) δ 3.64 (t, J = 6.5 Hz, 4H), 2.42 (t, J = 7.3 Hz, 4H), 1.63 – 1.55 (m, 8H), 1.40 – 1.32 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 211.4, 62.6, 42.7, 32.4, 25.3, 23.4; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{22}\text{O}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 225.14612; found 225.14669.

1,11-Dibromoundecane-6-one (7): To a stirred solution of 1,11-dihydroxyundecane-6-one (**6**) (5.0 g, 24.75 mmol) in DCM (50 mL) and was added PPh_3 (19.47 g, 74.2 mmol) and stirred for 5 min at ambient temperature and then carbon tetrabromide (CBr_4) (24.62g, 74.2 mmol) was added in portions at 0 °C. After complete addition, the mixture was stirred at room temperature for 5-6 h, and then quenched with water and extracted with DCM (50 mL). The combined organic layers were dried over Na_2SO_4 , evaporated under reduced pressure and the crude product was purified by column chromatography using 5-10% EtOAc/hexane to give the pure compound **7** as a colourless oil (7.56 g, 94 %); IR(ATR) ν (cm^{-1}): 2943(C-H), 1717(C=O), 1459, 1264, 1093, 759, 657(C-Br). ^1H NMR (400 MHz, CDCl_3) δ 3.34 (t, J = 6.7 Hz, 4H), 2.35 (t, J = 7.3 Hz, 4H), 1.87 – 1.75 (m, 4H), 1.59 – 1.48 (m, 4H), 1.42 – 1.30 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ 210.5, 42.5, 33.6, 32.5, 27.7, 22.8.; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{21}\text{Br}_2\text{O}$ [$\text{M}+\text{H}$] $^+$ 326.99537; found 326.99534.

1,11-Dibromoundecan-6-ol (8): To a stirred mixture of 1,11-dibromoundecane-6-one (**7**) (6.0 g, 18.4 mmol) in methanol (60 mL), sodium borohydride (NaBH_4) (0.69 g, 18.4 mmol) was added at 0°C and then stirred it at room temperature for 1-2 h. After completion, the solvent was evaporated and then quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude, which was then purified by column chromatography using 13-15% EtOAc/hexane to get pure compound **8** as a clear liquid (5.63 g, 93%); IR (ATR) ν (cm^{-1}): 3365(O-H), 2929(C-H), 2858, 1658, 1450, 1253, 1086, 1002, 762, 734, 645. ^1H NMR (400 MHz, CDCl_3) δ 3.60 (s, 1H), 3.42 (t, J = 6.8 Hz, 4H), 1.91-1.84 (m, 4H), 1.50 – 1.33 (m, 12H). ^{13}C NMR (101 MHz, CDCl_3) δ 71.6, 37.3, 33.8, 32.7, 28.2, 24.8; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{22}\text{OBr}$ [$\text{M}-\text{HBr}+\text{H}$] $^+$ 249.08485; found 249.08390.

Dimethyl 8-hydroxy-2,2,14,14-tetramethylpentadecanedioate (10): In a clean and dry round-bottom flask, a solution of methyl isobutyrate (**9**) (3.89g, 38.1 mmol) in dry THF (40 mL) was taken under nitrogen conditions and the solution was cooled to -40 °C and then lithium diisopropyl amide (LDA) (2.5M, 15 mL, 37.3 mmol) was added dropwise. After complete addition, the stirring was continued at the same temperature for 1h and then a solution of 1,11-dibromoundecan-6-ol (**8**) (5g, 15.24mmol) in dry THF (50 mL) was added slowly. The resulting mixture was allowed to stir at 20°C for 4-6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched with water and then the pH of the mixture was adjusted to 5-6 by dil HCl. The resulting solution was stirred for another 1h. The mixture was then extracted with EtOAc (2 x 50mL). The combined organic layers were washed with brine solution followed by water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude compound, which was further purified by column chromatography using 10-15% EtOAc/*n*-hexane to afford the pure compound **10** as clear oil, (3.97g, and 70%); IR (ATR) ν (cm^{-1}): 3453(O-H), 2933(C-H), 2859, 1727(C=O), 1464, 1259, 1196, 1149, 764. ^1H NMR (500 MHz, CDCl_3) δ 3.59 (s, 6H), 3.52 – 3.46 (m, 1H), 1.46 – 1.41 (m, 5H), 1.37 – 1.31 (m, 5H), 1.29-1.21 (m, 5H), 1.17 – 1.12 (m, 5H), 1.09 (s, 12H). ^{13}C NMR (75 MHz, CDCl_3) δ 178.6, 71.9, 51.6, 42.2, 40.7, 37.4, 30.1, 25.5, 25.1, 24.9. HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{39}\text{O}_5$ [$\text{M}-\text{H}$] 371.27920; found 371.28035.

8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid (1): In a clean round-bottom flask, dimethyl 8-hydroxy-2,2,14,14-tetramethylpentadecanedioate (**10**) (3.0 g, 8.06 mmol) was dissolved in a mixture of ethanol: water (4:1,30 mL) at 0°C. To this solution, potassium hydroxide (KOH) (1.35 g, 24.19 mmol) was added and then heated under reflux for 5 h. The solvents were removed under vacuum and the residue was acidified with 2N HCl up to pH 1. After saturation with brine solution, the product was extracted with DCM (3 x 50 mL) and then concentrated under reduced pressure. The resulting crude product was purified by column chromatography using EtOAc to give the bempedoic acid (**1**) as a white solid (2.2g, 84%) m.p. 83-85°C; IR (ATR) ν (cm⁻¹): 3430(O-H), 2925, 2857, 1706(C=O), 1669, 1463, 1394, 1226, 1172, 1010, 841, 756. ¹H NMR (400 MHz, CDCl₃) δ 3.54 – 3.45 (m, 1H), 1.56-1.51 (m, 4H), 1.45 – 1.36 (m, 6H), 1.25 – 1.16 (m, 10H), 1.18 (d, *J* = 4.4 Hz, 12H). ¹³C NMR (101 MHz, CDCl₃) δ 184.7, 71.3, 42.3, 40.6, 36.7, 29.19, 25.2, 24.9, 24.7. HRMS (ESI) *m/z* calcd for C₁₉H₃₆O₅ [M-H] 343.24790; found 343.24874.

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Supplementary Material

Copies of NMR spectra are provided in supplementary information

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