Phosphonate Aldehyde Annulation − A One-Pot Synthesis of Hydroxycycloalkenoic Esters − Application to Analogs of Glycinoeclepin A

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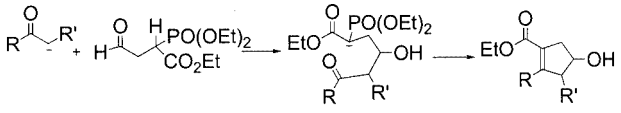
The reaction of ketone enolates with phosphonate aldehydes afforded cyclopentenols or cyclohexenols in a one-pot procedure.

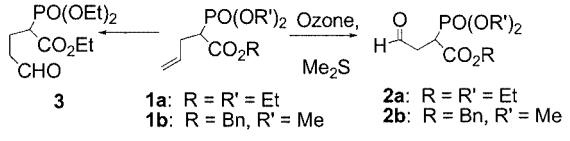
Introduction

The synthesis of functionalized bicyclic systems by carbanion-based annulation reactions is well established.[1] The formation of cyclohexenones by Michael addition/aldol/dehydration protocols[2] and the generation of cyclohexanediones by Michael addition/Claisen condensation pathway[3] are well-known examples. We recently described the one-pot carbanionic annulation reaction shown below.[4,5]



Scheme 1

Phosphonate aldehydes **2a** and **2b** were prepared from **1a** and **1b**[6] by ozonolysis at −78 °C in dichloromethane/methanol in 75% and 88% yields, respectively. Phosphonate aldehyde **3** was synthesized from **1a** using a hydroboration/oxidation protocol. On a multigram scale, this sequence was superior to alkylation of triethyl phosphonoacetate with 4-bromo-1-butene followed by ozonolysis.



Scheme 2

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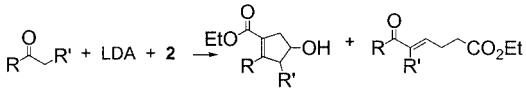
Results and Discussion

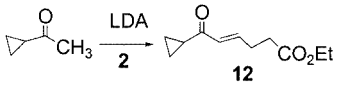
The reaction of **2a** with the enolates of both cyclic and acyclic ketones afforded hydroxy esters *directly* in good isolated yield. Aromatic ketones, such as acetophenone and several aliphatic ketones, gave good yields of cyclopentenols. The results with representative ketones are collated in Table . Interestingly, the final three Entries in Table 1 show a keto ester product rather than a cyclopentenol. These results were unexpected and illustrate a limitation of this annulation reaction. The stereochemistry of the homoallylic alcohol in product **4** was determined by ^{1}H NMR spectroscopy. Specifically, **4** was converted quantitatively into the acetate, an inseparable 10:1 mixture of diastereomers as evidenced by the absorption of the acetoxyl group in the ^{1}H NMR spectrum.[7] An NOE experiment demonstrated that the methyl group and the methine proton attached to the carbon bearing the acetoxy group are *cis*.

Table 1. Reactions of enolates with **2a**



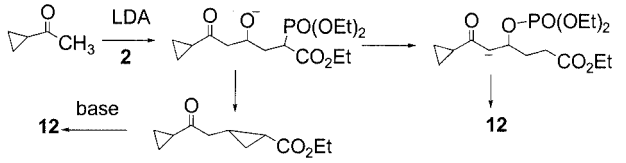
R	R′	% Yield	% Yield
C_2H_5	CH_3	53 (**4**)	0
Ph	H	40 (**5**)	0
C_5H_{11}	H	46 (**6**)	2
PhCH=CH	H	30 (**7**)	0
CH_3	$Me_2C=CHCH_2$	43 (**8**)	5
C_6H_5	CH_3	43 (**9**)	0
$CH_2CH_2CH_2$		60 (**10**)	5
$CH_2CH_2CH_2CH_2$		65 (**11**)	5
C_3H_5	H	0	48 (**12**)
$C_6H_4CH_2CH_2$		0	36 (**13**)
*i*Pr	H	0	33 (**14**)

The product from the reaction of the enolate of methyl cyclopropyl ketone and aldehyde **2a** was unexpected and not trivial to determine. The ^{1}H NMR spectrum of **12** has two methylene groups centered at 2.49 and 2.56 and other resonances at 6.26 (J = 11.8 Hz) and 6.88 (J = 11.8, 5 Hz). The latter two resonances suggested a *trans* double bond conjugated with a carbonyl group. In support of the structure assigned to **12**, we synthesized the methyl ester corresponding to **12**. The reaction of the enolate of methyl cyclopropyl ketone with methyl 4-oxobutenoate produced an aldol. Facile dehydration of the β-hydroxy ketone with methanesulfonyl chloride and triethylamine at 0 °C afforded the methyl ester corresponding to **12**.



Scheme 3

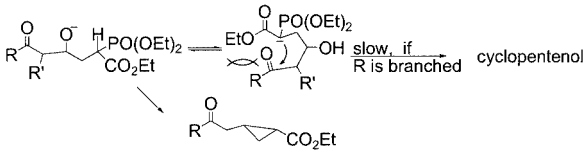
A possible mechanism for the formation of compound **12** is shown below. Although certain γ-hydroxyphosphane oxides have been reported by Warren and co-workers to produce cyclopropanes,[8] this reaction appears to be unknown for hydroxyphosphonates. The last step in the mechanism, the base-mediated ring opening of cyclopropanes, has precedent in the work of Mitra and co-workers.[9] Alternatively, the alkoxide might react with the phosphonate to generate a phosphate, which should readily eliminate.



Scheme 4

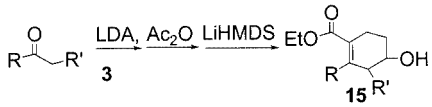
In a few cases as much as 5% of the keto ester was coproduced with the hydroxycyclopentenoic ester. Increasing the reaction temperature from −10 °C to 0 °C and extending the reaction time did not affect the product distribution. Unfortunately, the enolates of aldehydes such as cyclohexanecarboxaldehyde afforded only decomposition products.

Our rationale for the production of keto esters **12**, **13** and **14** is depicted below. If R was a branched group such as an isopropyl group or the rigid tetralone framework, it would likely present greater non-bonding interactions as the intramolecular cyclization step proceeded. Slowing the rate of cyclization might lead to an increased alkoxide concentration that would enhance the phosphonate-transfer step.



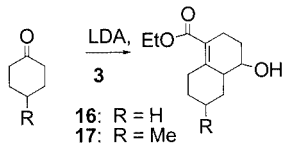
Scheme 5

Recently, we reported that ketone enolates react with the phosphonate aldehyde **3** to give β-hydroxy ketones, which were protected as the acetate and cyclized with lithium hexamethyldisilazane (LiHMDS) to produce hydroxy esters.[5] This three-step procedure is illustrated below and afforded only modest overall yields of products.



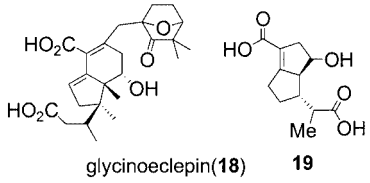
Scheme 6

There are only small differences between the experimental procedures that produced the aldol product with **3** and the cyclopentenol with **2a**. When phosphonate aldehyde **3** was subjected to the annulation conditions used with **2a**, bicyclic alcohols **16** and **17** were produced in 52% and 40% yields, respectively, in a one-pot procedure as a 4:1 mixture of diastereomers.



Scheme 7

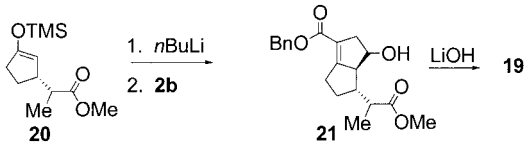
We then sought to apply the annulation reaction to glycinoeclepin A analogs. Glycinoeclepin A (**18**) is the hatching stimulus for the soybean cyst nematode. We have proposed that a hydroxy diacid is the minimal necessary functionality for hatching stimulus activity.[10] As a further test of that hypothesis, we set out to synthesize hydroxy diacid **19** using our annulation protocol.



Scheme 8

The starting material for our synthesis is the known enol silyl ether **20**, available as a mixture of epimers in one step from cyclopentenone according to the method of Kita.[11] When **20** was converted into the enolate with n-butyllithium and treated with benzyl ester **2b**, diester **21** was produced in 48% yield. Hydrolysis of the benzyl and methyl esters with lithium hydroxide in THF/water afforded the diacid **19** in quantitative yield. Interestingly, when the enolate derived from **20** was treated with ethyl ester **2a**, the resulting diester

could not be converted into the diacid. NMR analysis shows that diacid **19** is a 2:1.4:1:1 mixture of diastereomers. This set of compounds has been submitted for testing as a hatching stimulus.



Scheme 9

The reaction of phosphonate aldehydes **2a**, **2b** or **3** with ketone enolates provides a convenient one-pot route to hydroxycycloalkenoic esters. The reaction conditions are mild and should be compatible with complex molecule synthesis.

Experimental Section

General Procedures: Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, benzene and diisopropylamide were distilled from over calcium hydride. All experiments were performed under argon. Organic extracts were dried with anhydrous $MgSO_4$. Infrared spectra were obtained with a Perkin−Elmer model 1320 spectrophotometer. NMR experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. High resolution mass spectra were recorded with a Kratos model MS-50 spectrometer. Silica gel (60 Å) was used for flash chromatography (SiO_2).

Synthesis of 2a and 2b: Ozone was bubbled through a solution of **1a** (5.28 g, 20 mmol) or **1b** (1.04 g, 3.48 mmol) in CH_2Cl_2/MeOH (70 ml/30 mL) at −78 °C for 1 h. Argon was passed through the solution at room temp. for five minutes, then dimethyl sulfide (10 equiv.) was added to the mixture. The reaction mixture was stirred at room temp. for 12 h under argon. Solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (SiO_2) with hexane/ethyl acetate to furnish compound **2a** (75% yield, 3.99 g) or **2b** (88% yield, 0.92 g) as a colorless oil.

Compound 2a: Purified using hexane/ethyl acetate (1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10−1.20 (m, 9 H), 2.77−2.85 (m, 1 H), 3.06−3.17 (m, 1 H), 3.27−3.36 (m, 1 H), 3.96−4.07 (m, 6 H), 9.59 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 16.37 (d, *J* = 10.2 Hz), 16.38, 38.7 (d, *J* = 132.3 Hz), 40.7, 61.9, 63.1 (d, *J* = 7.2 Hz), 167.9 (d, *J* = 5.7 Hz), 198.1 (d, *J* = 15.5 Hz) ppm. HRMS calcd. for $C_{10}H_{19}O_6P$ 266.0925; found 266.0919. IR (neat): ṽ = 2984, 2339, 1734, 1233, 1161 cm^{-1}.

Compound 2b: Purified using ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79−2.90 (m, 1 H), 3.08−3.21 (m, 1 H), 3.41−3.49 (m, 1 H), 3.54−3.61 (m, 6 H), 5.00−5.13 (m, 2 H), 7.16−7.24 (m, 5 H), 9.56 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7 (d, *J* = 131.9 Hz), 40.0 (d, *J* = 2.7 Hz), 52.99, 53.0 (d, *J* = 6.1 Hz), 67.1, 127.8, 127.9, 128.1, 135.0, 167.3 (d, *J* = 5.3 Hz), 197.6 (d, *J* = 15.2 Hz) ppm. HRMS calcd. for $C_{13}H_{17}O_6P$, 300.0762; found 300.0769. IR (neat): ṽ = 2957, 2339, 1734, 1259, 1158 cm^{-1}.

Preparation of 3: Borane/dimethyl sulfide (3 mL, 30 mmol) was placed in an oven-dried, argon-flushed 100 mL round-bottomed flask. The flask was cooled in an ice/salt mixture (−14 °C) and 2-methyl-2-butene (6.6 mL, 62.1 mmol) was added dropwise with stirring. The reaction mixture was brought to 0 °C after 15 minutes and maintained at this temperature whilst stirring for 2 h. Diethyl ether (10 mL) was added to the white slurry to prepare a homogeneous solution. The homogeneous solution of disiamylborane (1.2 equiv.) in diethyl ether was added dropwise to allyl triethyl phosponoacetate (6.6 g, 25 mmol) in diethyl ether (10 mL) at 0 °C. The mixture was stirred for 5 h at 0 °C for completion of the hydroboration. Diethyl ether and dimethyl sulfide were removed in vacuo.

Pyridinium chlorochromate (43 g, 200 mmol) and dry dichloromethane (150 mL) were placed in a 500 mL, two-necked, round-bottomed flask equipped with a reflux condenser. With vigorous stirring, the solution prepared above in dry dichloromethane (25 mL) was added slowly dropwise (exothermic reaction). The mixture was heated under reflux for 3 h, cooled to room temp., and diluted with diethyl ether (200 mL). The solution was filtered through Celite. The residue in the flask was washed with ethyl acetate (3 × 100 mL) and filtered through the same Celite. The filtrates were concentrated in vacuo and purified by SiO_2 chromatography with hexane/ethyl acetate (1:4) as eluent to yield aldehyde **3** as a colorless liquid in 55% yield (3.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13−1.21 (m, 9 H), 2.03−2.10 (m, 2 H), 2.38−2.54 (m, 2 H), 2.83−2.92 (m, 1 H), 3.99−4.08 (m, 6 H), 9.61 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 16.2 (d, *J* = 5.4 Hz), 19.4 (d, *J* = 4.5 Hz), 41.7 (d, *J* = 12.8 Hz), 44.2 (d, *J* = 130.9 Hz), 61.4, 62.8 (t, *J* = 6.4 Hz), 168.5 (d, *J* = 5.3 Hz), 200.5 ppm. IR (neat): ṽ = 2985, 2360, 1733, 1235 cm^{-1}. HRMS calcd. for $C_{11}H_{21}O_6P$ 280.1076; found 280.1083.

General Procedure for the Annulation: A solution of the ketone (1 mmol) in THF (1 mL) was added dropwise at −78 °C to a freshly prepared lithium diisopropylamide (LDA) solution (1 mmol, 2 mL) and the reaction was stirred at −78 °C for 1 h. A solution of the aldehyde (1 mmol) in THF (1 mL) was then added and the mixture was stirred at −78 °C for 1 h. Stirring was continued until the temperature reached between −15° and −10 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried with Na_2SO_4 and concentrated and purified by SiO_2 chromatography.

Spectrum for the Main Diastereomer of 4: ^{1}H 300 MHz NMR ($CDCl_3$): δ = 1.06 (t, *J* = 7.7 Hz, 3 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.67−1.83 (m, 1 H), 2.16−2.25 (m, 1 H), 2.49 (d, *J* = 16.7 Hz, 1 H), 2.67−2.69 (m, 1 H), 2.90−2.98 (m, 2 H), 3.92−3.99 (m, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6, 14.5, 15.9, 21.3, 41.4, 52.8, 60.0, 77.1, 123.4, 162.7, 166.1 ppm. HRMS calcd. for $C_{11}H_{18}O_3$ 198.1255; found 198.1259.

Compound 4: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.7 Hz, 6 H), 1.27 and 1.29 (t, *J* = 7.1 Hz, 3 H), 1.78 (br. d, *J* = 6.2 Hz, 1 H), 2.20 (m, 1 H), 2.49 (d, *J* = 16.7 Hz, 1 H), 2.68 (m, 1 H), 2.94 (m, 2 H), 3.96 (br. s, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6, 14.5, 15.9, 21.3, 41.4, 52.8, 60.0, 77.1, 123.4, 162.7, 166.1 ppm. HRMS calcd. for $C_{11}H_{18}O_3$ 198.1255; found 198.1259. IR (neat): ṽ = 3447, 2985, 2966, 1700, 1635, 1222 cm^{-1}.

Compound 5: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.1 Hz, 3 H), 1.77 (br. s, 1 H), 2.83 (dt, *J* = 17.5, 1.3 Hz, 2 H), 3.12−3.24 (m, 2 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 4.55−4.59 (m, 1 H), 7.30−7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 45.2, 49.8,

60.4, 69.7, 126.6, 127.9, 128.0, 128.3, 136.5, 150.6, 165.8 ppm. HRMS calcd. for 232.1099; found 232.1101.

Compound 6: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.27−1.31 (m, 7 H), 1.45 (quintet, *J* = 5.9 Hz, 2 H), 2.48 (d, *J* = 18.3 Hz, 1 H), 2.59−2.64 (m, 3 H), 2.81 (dd, *J* = 18.2, 5.9 Hz, 1 H), 2.91−2.96 (m, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 4.42−4.44 (br. m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 14.5, 22.7, 27.8, 30.1, 32.0, 44.0, 47.9, 60.0, 69.7, 124.7, 157.3, 166.00 ppm. HRMS calcd. for $C_{13}H_{22}O_3$ 226.1569; found 226.1572.

Compound 7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H), 1.7 (br. s, 1 H), 2.76−2.87 (m, 2 H), 3.07 (dt, *J* = 18.1, 3.9 Hz, 2 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 4.52−4.58 (br. m, 1 H), 6.76 (d, *J* = 16.3 Hz, 1 H), 7.29 (d, *J* = 7.3 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.51 (d, *J* = 7.4 Hz, 2 H), 8.08 (d, *J* = 16.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 44.0, 44.6, 60.4, 69.6, 123.8, 126.9, 127.4, 128.7, 128.9, 136.0, 137.0, 149.5, 165.7. HRMS calcd. for $C_{16}H_{18}O_3$, 258.1256; found 258.1260.

Compound 8: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27−1.31 (m, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 2.12−2.16 (m, 2 H), 2.47−2.64 (m, 4 H), 2.79−2.96 (m, 2 H), 4.16−4.21 (m, 2 H), 4.39−4.47 (br. m, 1 H), 5.1−5.12 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 17.9, 25.9, 26.7, 30.2, 44.0, 48.1, 60.0, 69.7, 123.83, 123.84, 125.0, 132.4, 156.6, 165.9 ppm. HRMS calcd. for $C_{14}H_{22}O_3$ 238.1569; found 238.1572.

Compound 9: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.2 Hz, 3 H), 0.96 and 0.97 (t, *J* = 7.1 Hz, 3 H), 2.23 (br. s, 1 H), 2.61 (dd, *J* = 17.0, 2.0 Hz, 1 H), 2.67−2.72 (m, 1 H), 2.90−2.97 (m, 1 H), 3.08 (dd, *J* = 17.0, 6.2 Hz, 1 H), 3.90−3.99 (m, 2 H), 4.00−4.04 (m, 1 H), 7.10−7.27 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 14.0, 16.2, 42.0, 42.3, 50.0, 55.2, 60.2, 72.3, 76.9, 125.8, 127.87, 127.89, 128.0, 136.2, 156.5, 165.9 ppm. HRMS calcd. for $C_{15}H_{18}O_3$ 246.1256; found 246.1259.

Compound 10: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 1.55−1.72 (m, 2 H), 1.91−2.14 (m, 3 H), 2.41−2.61 (m, 2 H), 2.80 (d, *J* = 16.5 Hz, 1 H), 3.02−3.14 (m, 2 H), 4.11−4.17 (m, 2 H), 4.32 (t, *J* = 4.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 22.7, 26.7, 26.9, 28.9, 29.3, 29.6, 45.0, 47.2, 60.0, 61.1, 71.4, 79.2, 119.8, 120.4, 165.8, 168.5 ppm. HRMS calcd. for $C_{11}H_{16}O_3$ 196.1099; found 196.1100.

Compound 11: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H), 1.32−1.55 (m, 2 H), 1.80−1.95 (m, 5 H), 2.51−2.58 (m, 2 H), 2.82 (dt, *J* = 16.7, 4.9 Hz, 1 H), 2.93 (dd, *J* = 16.2, 7.6 Hz, 1 H), 3.52 (d, *J* = 14.6 Hz, 1 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 4.30 (t, *J* = 5.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 24.9, 25.3, 25.4, 25.7, 26.6, 28.0, 32.6, 41.7, 42.6, 52.7, 56.9, 59.9, 70.8, 76.6, 121.7, 122.3, 157.7, 158.4, 166.3 ppm. HRMS calcd. for $C_{12}H_{18}O_3$ 210.1256; found 210.1259. IR (neat): $\tilde{\nu}$ = 3446, 2955, 2360, 1700, 1652, 1228 cm^{-1}.

Compound 12: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89−0.93 (m, 2 H), 1.06−1.10 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 2.08−2.14 (m, 1 H), 2.47−2.51 (m, 2 H), 2.54−2.60 (m, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 6.26 (dt, *J* = 11.8, 1.0 Hz, 1 H), 6.88 (dt, *J* = 11.8, 4.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 14.4, 19.1, 27.7, 32.8, 60.9, 131.2, 144.3, 172.5, 200.2 ppm. HRMS calcd. for $C_{11}H_{16}O_3$ 196.1099; found 196.1103. IR (neat): $\tilde{\nu}$ = 2937, 2360, 1733, 1684, 1180 cm^{-1}.

Compound 13: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (t, *J* = 7.1 Hz, 3 H), 2.40−2.55 (m, 4 H), 2.75 (t, *J* = 5.9 Hz, 2 H), 2.89 (t, *J* = 6.6 Hz, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 6.77 (t, *J* = 7.3 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 7.39 (td, *J* = 7.4 1.3 Hz), 8.01 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 23.8, 25.9, 29.2, 33.4, 60.8, 127.0, 128.3, 128.4, 133.3, 133.6, 136.3, 137.3, 143.9, 172.7, 187.5 ppm. HRMS calcd. for $C_{16}H_{18}O_3$ 258.1256; found 258.1259. IR (neat): $\tilde{\nu}$ = 2980, 2361, 1733, 1675, 1178 cm^{-1}.

Compound 14: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 3 H), 1.11 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 2.46−2.50 (m, 2 H), 2.52−2.55 (m, 2 H), 2.80 (sept, *J* = 6.8 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 6.20 (dt, *J* = 15.6, 1.5 Hz), 6.82−6.89 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 18.6, 27.7, 32.8, 38.9, 60.8, 129.1, 144.6, 172.5, 203.8 ppm. HRMS calcd. for $C_{11}H_{18}O_3$ 198.1256; found 198.1259.

Compound 16: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 1.32−1.48 (m, 3 H), 1.58−1.70 (m, 2 H), 1.73−1.89 (m, 4 H), 1.93−1.97 (m, 1 H), 3.20−3.26 (m, 1 H), 3.52 (sept, *J* = 3.2 Hz, 1 H), 3.92 (sept, *J* = 2.9 Hz, 1 H), 4.17 (q, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 24.5, 24.7, 26.1, 26.2, 27.7, 28.0, 28.3, 28.4, 29.5, 31.7, 32.2, 33.09, 44.7, 47.9, 60.4, 68.7, 72.8, 122.39, 148.0, 169.6 ppm. HRMS calcd. for $C_{13}H_{20}O_3$ 224.1412; found 224.1415.

Compound 17: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.3 Hz, 3 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 1.50−2.00 (m, 12 H), 2.17−2.25 (m, 3 H), 2.39−2.44 (m, 4 H), 2.90−2.99 (m, 1 H), 3.14−3.19 (m, 1 H), 3.36−3.45 (m, 1 H), 3.82−3.88 (m, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 18.1, 18.4, 22.0, 22.2, 24.0, 24.4, 24.6, 24.8, 26.0, 26.7, 27.04, 27.06, 27.9, 29.4, 29.5, 31.1, 31.6, 32.2, 32.7, 33.4, 35.7, 36.4, 36.6, 38.0, 38.3, 41.2, 41.9, 44.0, 47.2, 60.1, 60.2, 68.3, 68.36, 72.4, 72.5, 122.2, 122.3, 122.4, 122.7, 147.1, 147.7, 148.6, 149.0, 169.4, 169.5 ppm. HRMS calcd. for $C_{14}H_{22}O_3$ 238.1568; found 238.1574. IR (neat): $\tilde{\nu}$ = 3295, 2978, 2360, 1692, 1635, 1249 cm^{-1}.

Compound 19: Lithium hydroxide (0.06 g, 1.45 mmol) was added to a solution of compound **21** (0.05 g, 0.145 mmol) in THF/H_2O (3 mL/1 mL). The reaction was stirred at room temp. under argon for 12 h. The reaction mixture was quenched with five drops of concentrated HCl at 0 °C and extracted with ethyl acetate (50 mL), dried, and concentrated in vacuo to yield a white solid which was precipitated from diethyl ether to obtain pure diacid **19** in quantitative yield. White solid, m.p. 212−218 °C (dec.). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.22 and 1.25 (d, *J* = 7.0 Hz, 3 H, 1.4:1), 1.75−1.91 (m, 2 H), 2.20−2.33 (m, 3 H), 2.38−2.45 (m, 2 H), 2.53−2.55 (br. m, 3 H), 2.69−2.76 (m, 2 H), 2.88−2.90 (br. m, 2 H), 2.99−3.08 (m, 2 H), 4.20 and 4.29 (t, *J* = 4.5 Hz, 1 H, 1.8:1) ppm. ^{13}C NMR (100 MHz, CD_3 OD): δ = 16.6, 16.7, 16.8, 26.9, 27.1, 34.7, 34.9, 35.4, 40.10, 40.14, 45.3, 45.5, 45.6, 46.0, 46.6, 47.8, 54.9, 64.6, 65.3, 65.34, 71.9, 72.7, 121.4, 121.6, 122.2, 169.3, 169.7, 169.9, 180.4 ppm. HRMS calcd. for $C_{12}H_{16}O_5$ [M^+ − H_2O] 222.0898; found 222.0892. IR (neat): $\tilde{\nu}$ = 3419, 2948, 2360, 1684, 1652, 1207 cm^{-1}.

Compound 21: *n*BuLi (1.24 mL, 3.1 mmol) was added dropwise at −40 °C to a solution of compound **20** (0.75 g, 3.1 mmol) in anhydrous THF (8 mL). After one hour, aldehyde **2b** (0.93 g, 3.1 mmol) in anhydrous THF (5 mL) was added to the reaction and stirring was continued whilst the mixture warmed from −40 °C to 0 °C (1.5 h to 2.0 h). The reaction mixture was quenched with 10% HCl and extracted with EtOAc (3 × 50 mL), dried and the organic portion was concentrated in vacuo to furnish colorless liquid which was purified by SiO_2 chromatography (hexane/ ethyl acetate, 4:1) to obtain compound **21** as a colorless liquid in 48% yield (0.511 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 and 1.15 ppm(d, *J* = 7.1 Hz, 3 H, 1.25:1), 1.57−1.87 (m, 4 H), 1.91−1.97 (m, 1 H), 2.02−2.16 (m, 2 H), 2.23−2.33 (m, 8 H), 2.61−2.63 (m, 1 H), 2.74−2.81 (m, 5 H), 2.93−3.08 (m, 3 H), 3.60, 3.61 and 3.63 (s, 3 H, 1.35:1.10:1.0), 4.02 (t, *J* = 4.48 Hz, 1 H), 4.22 (t, *J* = 4.5 Hz, 1 H) (1.25:1), 4.08 (q, *J* = 7.9 Hz, 1 H), 5.07 (s, 5 H), 7.21−7.27 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 14.0, 14.3, 17.4, 25.9, 26.03, 26.09, 33.4, 34.1, 34.7, 37.9, 38.7, 41.4, 41.9, 44.1, 45.1, 45.2, 45.9, 46.2, 52.04, 52.09, 52.3, 61.8, 62.2, 65.0, 65.8, 70.3, 71.1, 77.9, 120.2, 120.6, 120.9, 128.04, 128.08, 128.5, 136.5, 164.8, 165.3, 167.0, 167.4, 167.9, 177.5, 178.3, 178.8 ppm. HRMS calcd. for $C_{20}H_{24}O_5$ [$M^+ - H_2O$] 326.1522; found 326.1518. IR (neat): $\tilde{\nu}$ = 3450, 2950, 2338, 1733, 1701 cm^{-1}.

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