HETEROCYCLES, Vol. 70, 2006, pp. 223 - 233. © The Japan Institute of Heterocyclic Chemistry
Received, 23rd June, 2006, Accepted, 25th August, 2006, 2006, Published online, 29th August, 2006. COM-06-S(W)12

A DE NOVO ASYMMETRIC APPROACH TO ACHIRAL DEOXY-MELODORINOL ANALOGUES[1]

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Abstract – A short and highly efficient route to deoxy-Melodorinol analogues has been developed. The key to the overall transformation is the use of an enantioselective Sharpless asymmetric dihydroxylation of an (*Z,E*)-dienoate to control the regioselectivity of the dihydroxylation reaction and a Mitsunobu elimination reaction to control the *E*-stereochemistry of the γ,δ-double bond. The highly efficient synthesis stereoselectively prepared four analogues in 3 steps from 4-substituted crotonaldehydes.

INTRODUCTION

The butenolide natural product Protoanemonin possess broad-spectrum antimicrobial activity. Unfortunately, its therapeutic use has been prevented by its general toxicity. In an effort to modulate this toxicity various analogues have been prepared. Like the related natural products Melodorinol[2] and Pandamarilactam[3] the majority of these Protoanemonin analogues were substituted at the C-5 position (Figure 1). Most successful approaches to this structural motif have used transition metal cross coupling reactions for double bond control.[4] Unfortunately some more direct synthetic efforts have suffered in terms of yields and/or poor double bond selectivity.[5]

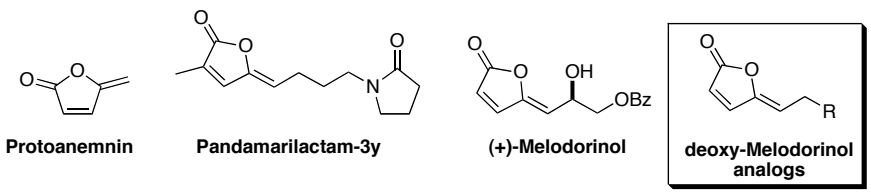
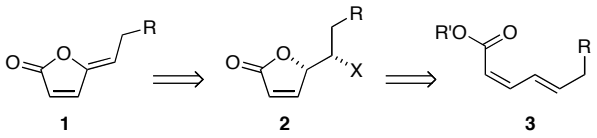


Figure 1. Protoanemonin, Pandamarilactam-3y, Melodorinol and analogs

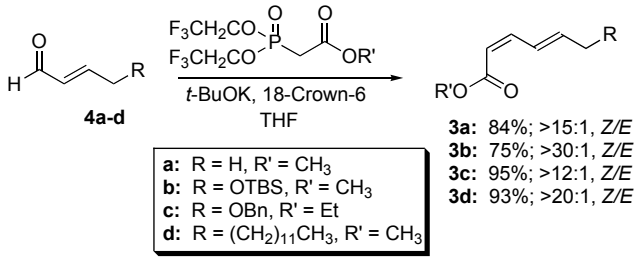
As part of a project directed toward the synthesis of biologically active chemical libraries, we were interested in developing a general approach toward the synthesis of deoxy-Melodorinol with the γ,δ-double bond in the *Z*-geometry (Scheme 1). We envisioned installing the *Z*-γ,δ-double bond of **1** *via* an *anti*-elimination reaction[6] of a butenolide with a leaving group at C-5 (**2** to **1**). In turn, we planned to prepare butenolide like **2** by means of a regioselective oxidative cyclization of the (*Z,E*)-dienoates (**3**). Reported herein is our successful development of a general synthesis of variously *C*-5 substituted deoxy-Melodorinol analogues (i.e. **1** in only 2 steps from **3**, Scheme 1). Key to the success of this strategy was the realization that the use of the Sharpless asymmetric dihydroxylation of *Z,E*-dienoates to control the regioselectivity (olefin selectivity) as well as to prevent over-oxidation.



Scheme 1. Retrosynthesis of substituted deoxy-Melodorinol analogs (**1**)

RESULTS AND DISCUSSION

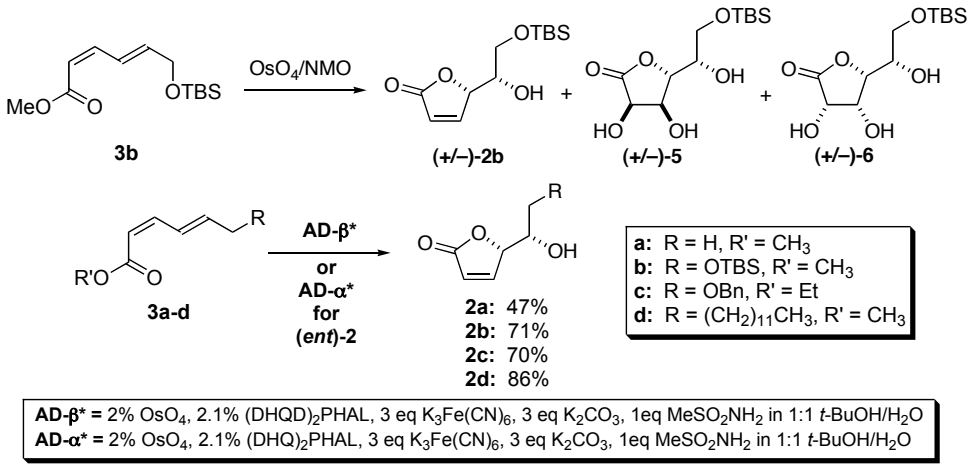
Retrosynthetically, we targeted the *Z,E*-dienoate (**3**), which we envisioned preparing by means of a Still-Gennari olefination[7] of various substituted crotonaldehydes (**4**), which are either commercially available or had previously been prepared (Scheme 2).[8] In practice enal (**4**) coupled smoothly under the typical Still-Gennari conditions to give the desired *Z,E*-dienoate (**3**) in good to excellent yields (70-95%) and stereoselectivities (dr = 12-30:1; *Z,E* to *E,E*).



Scheme 2. Synthesis of *Z,E*-dienoate **3**

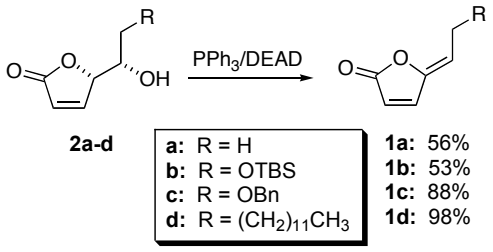
We next investigated the dihydroxylation/lactonization of the dienoates (**3a-d**). Our initial studies, with dienoate (**3b**) and the Upjohn conditions (OsO_4/NMO), were rather unsuccessful. Exposing the dienoate (**3b**) to a catalytic amount of OsO_4 and NMO in MeOH gave low yields of desired lactone (**2b**) along with significant amounts of the over oxidized products (**5** and **6**). Simply switching to the chiral AD mix reagent system prevented this over oxidation problem.[9] Thus exposing the *Z,E*-dienoates (**3a-d**) to the

Sharpless conditions (**AD-β*:** 2% OsO_4/$(DHQD)_2PHAL$, 3 equiv $K_3Fe(CN)_6/K_2CO_3$ and 1 equiv $MeSO_2NH_2$ in *t*-BuOH/H_2O)[10] afforded good yields to lactone products (**2a-d**) (47-86%). Lower yields of **2a** were presumably due to the products water solubility.



Scheme 3. Selective oxidative lactonization of dienoate (**3**)

With access to significant amounts of lactones (**2a-d**), we next examined the *anti*-elimination reaction to form butenolide (**1a-d**). In practice, we found it quite easy to effect the dehydration. For instance, our efforts to prepare the Mosher ester of **2a** using DCC lead exclusively to elimination products. We found the most reliable and stereoselective method for the formation of **1a-d** was to use the Mitsunobu conditions. Thus slowly adding a THF solution of **2a-d** and *p*-nitrobenzoic acid to a solution of PPh_3/DEAD provided good to excellent yields of butenolide (**1a-d**) (56-98%). Once again significantly lower yields of the least substituted analogue (**1a**) were recorded. The stereoselectivity of the elimination reaction was confirmed by a NOESY NMR experiment (Figure 2).



Scheme 4. Synthesis of Protoanemonin analogues (**1**)

In conclusion, a highly diastereoselective route to four deoxy-Melodorinol analogues has been developed. Interestingly, the route used a chiral reagent system to control the double bond stereochemistry in an achiral compound. That is to say an asymmetric dihydroxylation is used to install the desired *C*-4/*C*-5

stereochemistry need for the *anti*-elimination, as well as to prevent over oxidation. Further work toward the evaluation of these products for biological activity is ongoing.

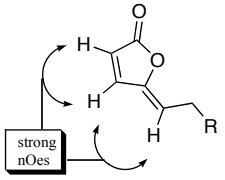


Figure 2. NOESY analysis of **1**

EXPERIMENTAL[11]

General Methods and Materials. ^{1}H and ^{13}C NMR spectra were recorded on 270 MHz and 600 MHz spectrometers. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR. Infrared (IR) spectra were obtained on FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Flash column chromatography was performed on 60-200 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (60Å, F_{254}) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values are obtained by elution in the stated solvent ratios (v/v). Ether, THF, methylene chloride and triethylamine were dried by passing through activated alumina columns with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Melting points are uncorrected. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven-dried glassware and standard syringe/septa techniques.

(2*Z*,4*E*)-Methyl hexa-2,4-dienoate (3a).[12] A solution of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$ (5.5 g, 17 mmol) and 18-crown-6 (15.9 g, 60 mmol) in THF (150 mL) was cooled to –78 °C and treated with *t*-BuOK (1.9 g, 17 mmol). After the mixture was stirred for 15 min, a solution of the crotonaldehyde (**4a**) (1.0 g, 14.3 mmol) in THF (10 mL, plus 5 mL of rinse) was added by cannula. The resulting mixture was stirred at –78 °C for 2.5 h and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the bulk of THF was removed under reduced pressure. The residue was extracted with ether (3 x 40 mL) and the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (20:1 (v/v) hexane/EtOAc) to yield (2*Z*,4*E*)-methyl hexa-2,4-dienoate (**3a**) (1.51 g, >15:1 *Z*/*E* ratio, 84% yield) as a viscous oil. Major isomer (**3a**): R_f (10% EtOAc/ hexane) = 0.7; IR (thin film, cm^{-1}) 3642, 2952, 2917, 1717, 1641, 1603, 1435, 1410, 1230, 1194, 1175, 999, 962, 836; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.35 (m,

1H), 6.50 (dd, *J* = 11.4, 11.4 Hz, 1H), 6.05(dtd, *J* = 15, 7.2, 1.2 Hz, 1H), 5.54 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.70 (s, 3H), 1.85 (dd, *J* = 7.2, 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.8, 145.2, 140.2, 128.2, 114.8, 50.9, 18.5.

(*R*)-5-((*R*)-1'-Hydroxyethyl)furan-2(5*H*)-one (2a).[13] Into a 100 mL round bottom flask was added 20 mL of *t*-BuOH, 20 mL of water, $K_3Fe(CN)_6$ (11.8 g, 36 mmol), K_2CO_3 (5.0 g, 36 mmol), $MeSO_2NH_2$ (1.2 g, 12 mmol), $(DHQD)_2PHAL$ (194 mg, 0.25 mmol, 2.1 mol%), and OsO_4 (30 mg, 0.12 mmol, 1 mol%). The mixture was stirred at rt for about 15 min and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-methyl hexa-2,4-dienoate (**3a**) (1.4 g, 11 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (150 mg) at rt. Stirred for 10 min and the solution was filtrated with a column filled with celite and washed with EtOAc (200 mL). The organic fraction was dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, flash chromatography on silica gel (4:1 (v/v) Et_2O/EtOAc) afforded 720 mg (47% yield) of (*R*)-5-((*R*)-1**'**-hydroxyethyl)furan-2(5*H*)-one (**2a**) as a low melting solid: R_f (50% EtOAc/ether) = 0.5; $[\alpha]^{25}_D$ +46 ° (*c* 1.18, MeCN); IR (thin film, cm^{-1}) 3260, 3113, 1739, 1564, 1416, 1311, 1143, 1099, 985, 899, 873, 851, 820, 766, 707 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz): δ 7.65 (dd, *J* = 6, 1.2 Hz, 1H), 6.19(dd, *J* = 6, 1.8 Hz, 1 H), 5.02 (ddd, *J* = 4.2, 1.8, 1.8 Hz, 1H), 3.96 (dq, *J* = 6, 5.4, 4.8, 4.2 Hz, 1H), 1.25 (d, *J* = 6 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz): δ 156.9, 123.0, 89.0, 68.2, 43.4, 19.2.

(5*Z*)-5-Ethylidienfuran-2(5*H*)-one (1a). [14] Into a 25 mL round bottom flask was added triphenylphosphine (553 mg, 2.1 mmol) and 5 mL of THF and then cooled to 0 °C. To this solution diethyl azodicarboxylate (367 mg, 2.1 mmol) was added dropwise and stirred for 5 min. Then (*R*)-5-((*R*)-1**'**-hydroxyethyl)furan-2(5*H*)-one (**2a**) (135 mg, 1.05 mmol) in 1 mL THF and *p*-nitrobenzoic acid (175 mg, 2.1 mmol) was added to the solution. The reaction mixture was allowed to stirred for 2 h, quenched with saturated aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo* and flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) afforded (5*Z*)-5-ethylidienfuran-2(5*H*)-one (**1a**) (65 mg, 56% yield) as a viscous oil. R_f (20% EtOAc/ hexane) = 0.6; IR (thin film, cm^{-1}) 1752, 1765, 1736, 1677, 1556, 1446, 1325, 1225, 1122, 1086, 1065, 993, 906, 872, 825, 735, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.32 (d, *J* = 5.4 Hz, 1H), 6.1 (dd, *J* = 5.4, 0.6 Hz, 1H), 5.35 (q, *J* = 7.2 Hz, 1H), 1.96 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 170.0, 150.4, 143.4, 118.9, 112.2, 11.9.

(2*Z*,4*E*)-Methyl 6-(*tert*-butyldimethylsilanyloxy)hexa-2,4-dienoate (3b). A solution of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$ (763 mg, 2.4 mmol) and 18-crown-6 (2.2 g, 8.4 mmol) in THF (50 mL)

was cooled to –78 °C and treated with *t*-BuOK (270 mg, 2.4 mmol). After the mixture was stirred for 15 min, a solution of the (*E*)-4-(*tert*-butyldimethylsilanyloxy)but-2-enal (**4b**) (400 mg, 2 mmol) in THF (3 mL, plus 1.5 mL of rinse) was added by cannula. The resulting mixture was stirred at –78 °C for 2.5 h and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the bulk of THF was removed under reduced pressure. The residue was extracted with Et_2O (3 x 20 mL) and the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane) to yield (2*Z*,4*E*)-methyl 6-(*tert*-butyldimethylsilanyloxy)hexa-2,4-dienoate (**3b**) (387 mg, 1.5 mmol, >30:1 *Z,E*/*E,E* ratio, 75% yield) as a viscous oil. Major isomer (**3b**): R_f (10% EtOAc/ hexane) = 0.75; IR (thin film, cm^{-1}) 3449, 2953, 2929, 2857, 1763, 1463, 1362, 1253, 1188, 1117, 1082, 1006, 977, 836, 777, 677; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49 (m, 1H), 6.57 (dd, *J* = 11.4, 11.4 Hz, 1H), 6.07 (dt, *J* = 15.0, 4.8 Hz, 1H), 5.56 (d, *J* = 11.4, 1H), 4.31(d, *J* = 4.8, 1H), 3.72 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.6, 144.0, 142.7, 125.6, 116.9, 63.2, 51.1, 25.8 (3C), 18.3, –5.2 (2C); HRMS(ESI): Calculated for $[C_{18}H_{32}O_2Na]^+$: 281.1185, Found: 281.1179.

(*R*)-5-((*R*)-2'-(*tert*-Butyldimethylsilanyloxy)-1-hydroxyethyl)furan-2(5*H*)-one (2b). Into a 50 mL round bottom flask was added 8 mL of *t*-BuOH, 8 mL of water, $K_3Fe(CN)_6$ (3.85 g, 11.7 mmol), K_2CO_3 (1.6 g, 11.7 mmol), $MeSO_2NH_2$ (370 mg, 3.9 mmol), $(DHQD)_2PHAL$ (63 mg, 82 μmol, 2.1 mol%), and OsO_4 (10 mg, 39 μmol, 1 mol%). The mixture was stirred at rt for about 15 min and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-methyl 6-(*tert*-butyldimethylsilanyloxy)hexa-2,4-dienoate (**2b**) (1.0 g, 3.9 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (50 mg) at rt. EtOAc (20 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the EtOAc (2 x 40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo*, flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) afforded (*R*)-5-((*R*)-2'-(*tert*-butyldimethylsilanyloxy)-1-hydroxyethyl)furan-2(5*H*)-one (**2b**) (710 mg, 2.75 mmol, 71% yield) as a clear oil: R_f (50% EtOAc/hexane) = 0.55; $[\alpha]^{25}_D$ +49 ° (*c* 1.5, CH_2Cl_2); IR (thin film, cm^{-1}) 3438, 2954, 2929, 2884, 2857, 1789, 1744, 1472, 1463, 1253, 1160, 1112, 1076, 1006, 977, 907, 834, 776, 721, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.53 (dd, *J* = 5.4, 1.8 Hz, 1H), 6.14 (dd, *J* = 5.4, 1.8 Hz, 1H), 5.15 (ddd, *J* = 5.4, 1.8, 1.8 Hz, 1H), 3.88 (dddd, *J* = 10.2, 7.2, 5.4, 5.4 Hz, 1H), 3.72 (dd, *J* = 10.2, 6 Hz, 1H), 3.69 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.48 (d, *J* = 6 Hz, 1H), 2.1 (m, 1H), 1.59 (m, 2H), 1.52 (m, 2H), 1.32-1.25 (m, 20H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.8, 154.0, 121.9, 83.4, 71.4, 62.9, 25.8, 25.7 (2C), 18.1, –5.49, –5.51; HRMS(ESI): Calculated for $[C_{17}H_{30}O_3Na]^+$: 279.1392, Found: 229.1386.

(5*Z*)-5-(2'-(*tert*-Butyldimethylsilanyloxy)ethylidene)furan-2(5*H*)-one (1b). Into a 25 mL round bottom flask was added triphenylphosphine (262 mg, 1 mmol) and 5 mL of THF and then cooled to 0 °C. To this solution diethyl azodicarboxylate (174 mg, 1 mmol) was added dropwise and stirred for 5 min. Then (*R*)-5-((*R*)-2'-(*tert*-butyldimethylsilanyloxy)-1-hydroxyethyl)furan-2(5*H*)-one (**2b**) (129 mg, 0.5 mmol) in 1 mL THF and *p*-nitrobenzoic acid (167 mg, 1 mmol) was added to the solution. The reaction mixture was allowed to stirred for 2 h, quenched with saturated aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo* and flash chromatography on silica gel (20:1 (v/v) hexane/EtOAc), (5*Z*)-5-(2'-(*tert*-butyldimethylsilanyloxy)ethylidene)furan-2(5*H*)-one (**1b**) (85 mg, 71%) was afforded as a viscous oil: R_f (10% EtOAc/ hexane) = 0.65; IR (thin film, cm^{-1}) 2953, 2915, 2848, 1763, 1735, 1679, 1557, 1469, 1363, 1142, 1074, 1074, 927, 812, 718, 659 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.35 (d, J = 5.4 Hz, 1H), 6.20 (d, J = 5.4 Hz, 1H), 5.39 (t, J = 6 Hz, 1H), 4.53 (d, J = 6 Hz, 2H), 0.89(s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.3, 148.2, 143.6, 120.2, 115.7, 57.9, 25.8 (3C), 18.2, –5.3.

(2*Z*,4*E*)-Ethyl 6-(benzyloxy)hexa-2,4-dienoate (3c). A solution of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_2CH_3$ (3 g, 9.0 mmol) and 18-crown-6 (7.1 g, 27.0 mmol) in THF (60 mL) was cooled to –78 °C and treated with *t*-BuOK (1.2 g, 10.8 mmol). After the mixture was stirred for 15 min, a solution of the aldehyde (**4c**) (1.6 g, 9.1 mmol) in THF (10 mL, plus 5 mL of rinse) was added by cannula. The resulting mixture was stirred at –78 °C for 2.5 h and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the bulk of THF was removed under reduced pressure. The residue was extracted with Et_2O (3 x 30 mL) and the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (25:1 (v/v) hexane/EtOAc) to yield (2*Z*,4*E*)-ethyl 6-(benzyloxy)hexa-2,4-dienoate (**3c**) (2.1 g, 12:1 *Z*/*E* ratio, 95% yield) as a viscous oil. Major isomer (**3c**): R_f (30% EtOAc/ hexane) = 0.6; IR (thin film, cm^{-1}) 2983, 2928, 2872, 1766, 1650, 1620, 1496, 1454, 1436, 1362, 1268, 1141, 1073, 1029, 953; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.58 (dddd, J = 15.6, 11.4, 1.2, 1.2 Hz, 1H), 7.33 (m, 5H), 6.59 (dd, J = 11.4, 11.4 Hz, 1H), 6.12 (ddd, J = 15.6, 6, 6 Hz, 1H), 5.68 (d, J = 11.4 Hz, 1H), 4.54 (brs, 2H), 4.20 (q, J = 7.2 Hz, 2H), 4.17 (d, J = 6 Hz, 1H), 4.16 (d, J = 6 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.2, 143.6, 139.3, 137.9, 128.4 (2C), 128.1, 127.7 (2C), 127.6, 118.1, 72.5, 70.0, 60.0, 14.2; CIHRMS: Calculated for $[C_{15}H_{18}O_3+Na]^+$: 269.2914, Found: 269.2917.

(*S*)-5-((*S*)-2'-(Benzyloxy)-1-hydroxyethyl)furan-2(5*H*)-one (*ent*-2c). Into a 100 mL round bottom flask was added 20 mL of *t*-BuOH, 20 mL of water, $K_3Fe(CN)_6$ (9.6 g, 29 mmol), K_2CO_3 (4.03 g, 29 mmol), $MeSO_2NH_2$ (0.93 g, 9.7 mmol), $(DHQ)_2PHAL$ (158 mg, 0.2 mmol, 2.1 mol%), and OsO_4 (49 mg,

0.19 mmol, 2 mol%). The mixture was stirred at rt for about 15 min and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-ethyl 6-(benzyloxy)hexa-2,4-dienoate (**3c**) (2.4 g, 9.7 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (100 mg) at rt. EtOAc (30 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2 x 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo*, flash chromatography on silica gel (7:3 (v/v) hexane/EtOAc) afforded 1.6 g (70% yield) of (*S*)-5-((*S*)-2'-(benzyloxy)-1-hydroxyethyl)furan-2(5*H*)-one ((***ent*)-2c**) as a white solid: mp 74-75 °C; R_f (50% EtOAc/hexane) = 0.16; $[\alpha]^{25}_D$ –52 ° (*c* 1.2, CH_2Cl_2); IR (thin film, cm^{-1}) 3424, 2927, 2899, 1745, 1602, 1500, 1475, 1454, 1399, 1365, 1340, 1266, 1217, 1167, 1096, 1072, 993, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.47 (dd, *J* = 6, 1.2 Hz, 1 H), 7.33 (m, 5H), 6.14 (dd, *J* = 6, 1.8 Hz, 1 H), 5.16 (ddd, *J* = 4.2, 1.8, 1.8 Hz, 1 H), 4.58 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* =12 Hz, 1H), 4.01 (dddd, *J* = 6, 5.4, 4.8, 4.2 Hz, 1H), 3.64 (dd, *J* = 9.6, 5.4 Hz, 1 H), 3.58 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.42 (d, *J* = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.9, 153.8, 137.2, 128.5 (2C), 128.0, 127.8 (2C), 122.2, 83.7, 73.6, 70.2, 70.0; CIHRMS: Calculated for $[C_{13}H_{14}O_4+Na]^+$: 257.0784, Found: 257.0782; The COSY spectral analysis confirmed the γ-lactone.

(5*Z*)-5-(2'-(Benzyloxy)ethylidene)furan-2(5*H*)-one (1c). Into a 100 mL round bottom flask was added triphenylphosphine (223 mg, 0.8 mmol) and 1 mL of THF and then cooled to 0 °C. To this solution 0.15 mL diethyl azodicarboxylate (0.8 mmol) was added dropwise and stirred for 5 min. Then (*S*)-5-((*S*)-2-(benzyloxy)-1-hydroxyethyl)furan-2(5*H*)-one (**(*ent*)-2c**) (100 mg, 0.4 mmol) in 1 mL THF and *p*-nitrobenzoic acid (143 mg, 0.8 mmol) was added to the solution. The reaction mixture was allowed to stirred for 2 h, quenched with saturated aq $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo* and flash chromatography on silica gel (9:1 (v/v) hexane/EtOAc) afforded (5*Z*)-5-(2'-(benzyloxy)ethylidene)furan-2(5*H*)-one (**1c**) (74 mg, 80% yield) as a viscous oil. R_f (30% EtOAc/ hexane) = 0.3; IR (thin film, cm^{-1}) 2857, 1773, 1749, 1677, 1558, 1454, 1363, 1309, 1201, 1102, 1068, 920, 877 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.37 (dd, *J* = 6 Hz, 1H), 7.34 (m, 5H), 6.23 (d, *J* = 6 Hz, 1H), 5.45 (dd, *J* = 7.2, 6.6 Hz, 1H), 4.55 (s, 2H), 4.40 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.1, 149.9, 143.4, 137.6, 128.4 (3C), 127.8 (2C), 120.7, 112.2, 73.0, 64.2; CIHRMS: Calculated for $[C_{13}H_{12}O_3]^+$: 216.0786, Found: 216.0798.

(2*Z*,4*E*)-Methyl heptadeca-2,4-dienoate (3d). A solution of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$ (1.03 g, 4.58 mmol) and 18-crown-6 (5.13 g, 19.4 mmol) in THF (100 mL) was cooled to –78 °C and treated with

t-BuOK (0.62 g, 5.5 mmol). After the mixture was stirred for 15 min, a solution of the (*E*)-pentadecthyl-2-enal (**4d**) (1.03 g, 4.58 mmol) in THF (10 mL, plus 5 mL of rinse) was added by cannula. The resulting mixture was stirred at –78 °C for 2.5 h and the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the bulk of THF was removed under reduced pressure. The residue was extracted with Et_2O (3 x 30 mL) and the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane) to yield (2*Z*, 4*E*)-methyl heptadeca-2,4-dienoate (**3d**) (1.2 g, 4.26 mmol, >20:1 *Z,E*/*E,E* ratio, 93% yield) as a viscous oil. Major isomer (**3d**): R_f (10% EtOAc/ hexane) = 0.85; IR (thin film, cm^{-1}) 2922, 2853, 1719, 1639, 1437, 1192, 1074, 999, 962, 895, 816, 721; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.34 (ddt, *J* = 15.0, 11.4, 1.2 Hz, 1H), 6.54 (dd, *J* = 11.4, 11.4 Hz, 1H), 6.07 (dt, *J* = 15.0, 7.2 Hz, 1H), 5.56 (d, *J* = 11.4, 1H), 3.71 (s, 3H), 2.2 (m, 2H), 1.25 (m, 20H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.9, 146.0, 145.6, 126.8, 114.9, 51.0, 33.0, 31.9, 29.65, 29.62 (2C), 29.55, 29.44, 29.3, 29.2, 28.8, 22.6, 14.0; MS(EI): Calculated for $[C_{18}H_{32}O_2]^+$: 280, Found: 280.

(*R*)-5-((*R*)-1'-Hydroxytridecyl)furan-2(5*H*)-one (2d). Into a 10 mL round bottom flask was added 1 mL of *t*-BuOH, 1 mL of water, $K_3Fe(CN)_6$ (1.6 g, 4.7 mmol), K_2CO_3 (0.6 g, 4.7 mmol), $MeSO_2NH_2$ (0.2 g, 1.57 mmol), $(DHQD)_2PHAL$ (26 mg, 34 μmol, 2.1 mol%), and OsO_4 (4 mg, 16 μmol, 1 mol%). The mixture was stirred at rt for about 15 min and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-methyl heptadeca-2,4-dienoate (**3d**) (0.4 g, 1.57 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (10 mg) at rt. EtOAc (5 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the EtOAc (2 x 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo*, flash chromatography on silica gel (4:1 (v/v) hexane/EtOAc) afforded (*R*)-5-((*R*)-1'-hydroxytridecyl)furan-2(5*H*)-one (**2d**) (379 mg, 1.35 mmol, 86% yield) as a white solid: mp 89-91 °C; R_f (50% EtOAc/hexane) = 0.55; $[\alpha]^{25}_D$ +69 ° (*c* 1.8, CH_2Cl_2); IR (thin film, cm^{-1}) 3370, 2952, 2913, 2849, 1715, 1603, 1471, 1179, 1108, 1020, 919, 866, 836, 827, 801, 718, 658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.45 (dd, *J* = 6, 1.8 Hz, 1H), 6.18 (dd, *J* = 6, 1.8 Hz, 1H), 4.98 (ddd, *J* = 5.6, 1.8, 1.8 Hz, 1H), 3.75 (ddd, *J* = 12, 6, 6 Hz, 1H), 2.1 (m, 1H), 1.59 (m, 2H), 1.52 (m, 2H), 1.32-1.25 (m, 20H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.7, 153.5, 122.7, 86.0, 71.9, 33.2, 31.9, 29.63, 29.60 (2C), 29.52, 29.46, 29.40, 29.3, 25.4, 22.6, 14.0; HRMS(ESI): Calculated for $[C_{17}H_{30}O_3Na]^+$: 305.2093, Found: 305.2086.

(5*Z*)-5-Tridecylidenefuran-2(5*H*)-one (1d). Into a 25 mL round bottom flask was added triphenylphosphine (262 mg, 1 mmol) and 5 mL of THF and then cooled to 0 °C. To this solution

diethyl azodicarboxylate (174 mg, 1 mmol) was added dropwise and stirred for 5 min. Then (*R*)-5-((*R*)-1'-hydroxytridecyl)furan-2(5*H*)-one (**2d**) (141 mg, 0.5 mmol) in 1 mL THF and *p*-nitrobenzoic acid (167 mg, 1 mmol) was added to the solution. The reaction mixture was allowed to stirred for 2 h, quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvents *in vacuo* and flash chromatography on silica gel (20:1 (v/v) hexane/EtOAc), (5*Z*)-5-tridecylidenefuran-2(5*H*)-one (**1d**) (129 mg, 98%) was afforded as a pink solid: mp 36-37 °C; R_f (10% EtOAc/ hexane) = 0.8; IR (thin film, cm^{-1}) 2953, 2915, 2848, 1763, 1735, 1679, 1557, 1469, 1363, 1142, 1074, 1074, 927, 812, 718, 659 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.31 (d, J = 5.4 Hz, 1H), 6.13 (t, J = 5.4 Hz, 1H), 5.29 (t, J = 7.8 Hz, 1H), 2.40 (dt, J = 7.8, 7.2 Hz, 2H), 1.47(tt, J =7.2, 7.2 Hz, 2H), 1.26 (m, 16H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 170.1, 149.6, 143.5, 118.9, 117.8, 31.8, 29.63, 29.60, 29.58, 29.51, 29.33, 29.32, 29.26, 28.93, 26.46, 22.66, 14.0; HRMS(ESI): Calculated for $[C_{17}H_{28}O_2Na]^+$: 287.1987, Found: 287.1980.

ACKNOWLEDGEMENTS

We thank the National Institute of General Medical Sciences (GM63150) for their generous support of our program. Funding by the National Science Foundation (NSF-EPSCoR award #0314742) for a 600 MHz spectrometer and NMR facility is gratefully acknowledged.

REFERENCES AND NOTES

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