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The Total Synthesis of Agglomerin A and (±)-Carolinic Acid. A General Method for the Preparation of 3-Acyl Tetronic Acids Via Direct Acylation of O-Methyl 3-Stannyl Tetronates

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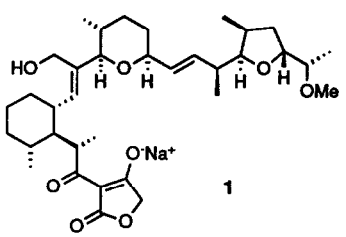
Abstract: *A variety of O-methyl-3-acyl tetronates were prepared in good yield from the corresponding acid chlorides via a palladium catalyzed acylation of O-methyl 3-(tri-n-butylstannyl) tetronate* **5**. *This new synthetic method was then exploited for the total synthesis of the novel antibiotic agglomerin A* **3a**, *as well as the fungal metabolite (±)-carolinic acid* **15**.

In recent years a number of natural products have been isolated which possess either an unsubstituted or a 5-substituted 3-acyl tetronate unit. Many of these natural products, such as tetronasin **1**[1], tetronomycin **2**[2] and the agglomerins **3a-d**[3], have been found to exhibit antibiotic activity. The 3-acyl tetronate unit of the ionophore antibiotics **1** and **2** serves as the primary metal binding site[4]. In light of the biological importance of these compounds, new impetus now exists for the development of synthetic methods which will allow for the facile construction of complex 3-acyl tetronic acids.



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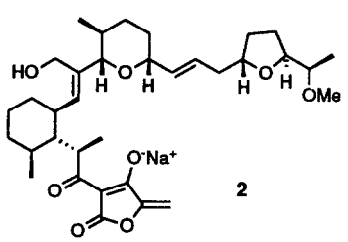

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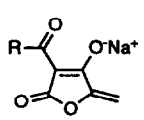


Agglomerins

A **3a**: R =

B **3b**. R =

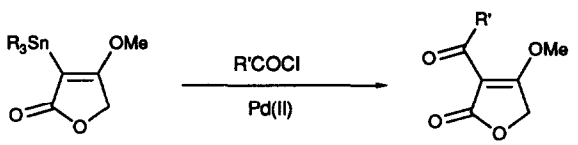
C **3c**: R =

D **3d**: R =

As part of a programme directed towards the total synthesis of **1**[5-8], we sought to develop a mild synthetic method for the preparation of complex unsubstituted 3-acyl tetronates. Currently, there are several reports in the literature which describe approaches for the preparation of 3-acyl tetronic acids.[9-20] However, many of these approaches are limited to specific and/or simple systems and are often intolerent of complex functionality. To date, the base promoted Dieckmann cyclization of glycolyl acetoacetates is one of the most synthetically useful methods for the preparation of 3-acyl tetronates.[11,16,17] It has been demonstrated that cyclization of α'-substituted glycolyl acetoacetates to the corresponding 5-substituted 3-acyl tetronic acids is a very facile process.[16] However, the cyclization of the unsubstituted analogues requires much more vigorous reaction conditions, which are often unsuitable for highly functionalized substrates.[11,17]

It was our desire to develop a direct acylation procedure for the coupling of an acid chloride to an unsubstituted C-3 metallated tetronate. Previous work directed towards the development of this approach has demonstrated that direct acylation of 5-substituted tetronic acids lithiated at C-3 is possible;[18-20] however, unsubstituted tetronates have been shown to undergo preferential deprotonation at C-5 when treated with strong base.[19,21] In addition, as we reported earlier, attempts to acylate the unsubstituted tetronate lithiated dianion resulted in an unresolvable mixture of mono- and dialkylated products.[22,23]

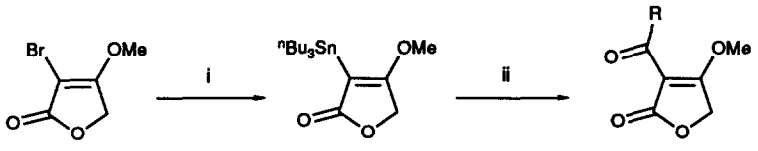
In order to avoid the problems associated with the unsubstituted lithiated tetronates we envisaged a palladium catalyzed acylation of an O-methyl 3-stannyl tetronate by an acid chloride for the preparation of



O-methyl 3-acyl tetronates. The palladium catalyzed acylation of organotin compounds has been extensivly explored in recent years.[24] These reactions are normally mild, high yielding and tolerate a wide variety of functionality. However, to explore this direct acylation approach it was necessary to develop an efficient method for the preparation of 3-stannyl tetronates.

The synthesis of the required O-methyl 3-(tri-*n*-butylstannyl) tetronate **5** was achieved in a straightforward fashion from the readily available O-methyl 3-bromo tetronate **4**.[25] Preliminary attempts to prepare **5** by generation of the lithiated C-3 anion *via* metal-halogen exchange, followed by quenching of the anion with tri-*n*-butyltin chloride were unsuccessful. Presumably, **4** did not undergo metal-halogen exchange upon treatment with *t*-butyl lithium due to preferential deprotonation at C-5.[19,21] This problem was easily overcome by treatment of **4** with excess sodium naphthalenide in THF at -78°C. The C-3 anion was generated *in situ* by two one-electron transfer steps and then immediately quenched with excess tri-*n*-butyltin chloride. This afforded O-methyl 3-(tri-*n*-butylstannyl) tetronate **5** in 69% yield (Scheme 1) as a viscous oil which is stable for several weeks when stored at low temperature (-20°C).

Scheme 1

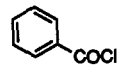
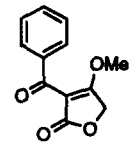
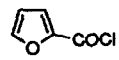
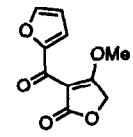
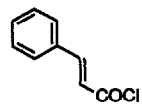
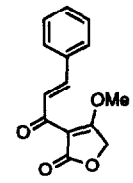
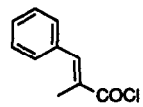
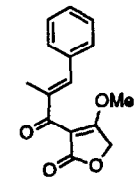
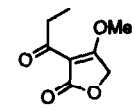
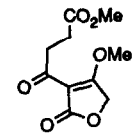
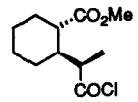
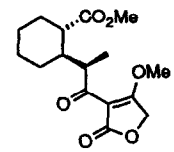


4 **5 (69%)**

(i) $Na^+[nap]^-$, n-Bu_3SnCl, THF, -78°C to r.t. (ii) RCOCl, *trans*-Bn(Cl)Pd(PPh_3)$_2$ (cat.), $ClCH_2CH_2Cl$, 60°C, 16h.

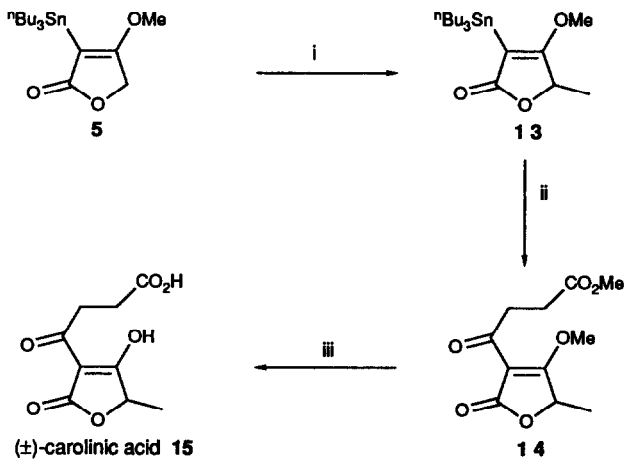
With stannyl tetronate **5** in hand, the palladium catalyzed acylation reaction was explored. Direct acylation of **5** with a variety of acid chlorides provided the desired O-methyl 3-acyl tetronates in good yields (Table 1) compared to previous procedures. In a typical acylation experiment (Scheme 1), a solution of stannyl tetronate **5** (1.1 eqiuv.), the acid chloride (1 equiv.) and *trans*-benzyl(chloro)-*bis*-triphenylphospine palladium (II) (0.4 mol%) in dichloroethane was heated to 60°C for 16 h under an argon atmosphere. Although the choice of solvent ($CHCl_3$, HMPA, $ClCH_2CH_2Cl$) did not typically effect the yield of the acylation products, reactions performed in dichloroethane were found to be much cleaner with easier work-up. In general, we found the acylation reaction to be very sensitve to moisture. Product yields were significantly improved if care was taken to remove all trace amounts of water from the reaction system.(i.e., dry atmosphere, freshly distilled solvents). In addition, the purity of the stannyl tetronates was found to be a crucial factor for obtaining consistent yields of the 3-acyl tetronates. Similar to other palladium catalyzed reactions of this nature, completion of the reaction was indicated upon precipitation of black palladium metal.[24] Significantly, the highly functionalized acid chlorides **11a** and **12a** underwent smooth conversion into the corresponding 3-acyl tetronates **11b** and **12b**, close models of carolinic acid and the CD ring system of tetronasin **1**.

Table 1. Unsubstituted O-methyl 3-acyl tetronates

entry	acid chloride (a)	3-acyl tetronate (b)	% yield
6			47
7			48
8			59
9			44
10	CH_3CH_2COCl		49
11	$CH_3O_2CCH_2CH_2COCl$		47
12			40

In our preliminary report, we demonstrated that the palladium catalyzed acylation of 3-stannyl tetronates could also be applied to the synthesis of 5-substituted 3-acyl tetronates.[22] The stability of the carbon-tin bond of **5** permitted functionalization of the tetronate ring system to allow for the preparation of the desired 5-substituted 3-stannyl tetronates. As shown in Scheme 2, deprotonation at C-5 was achieved with LDA in THF at -78°C. The lithiated C-5 anion was quenched with methyl iodide to afford O-methyl 5-methyl 3-(tri-*n*-butylstannyl) tetronate **13** in 78% yield. The palladium catalyzed acylation of **13** with 3-carbomethoxypropionyl chloride afforded (±)-dimethyl carolinic acid **14** in 62% yield. Lastly, hydrolysis of the diester **14** was accomplished with aqueous HCl (3 M)[16] to afford the fungal metabolite (±)-carolinic acid **15**[26,27] in 51% yield.

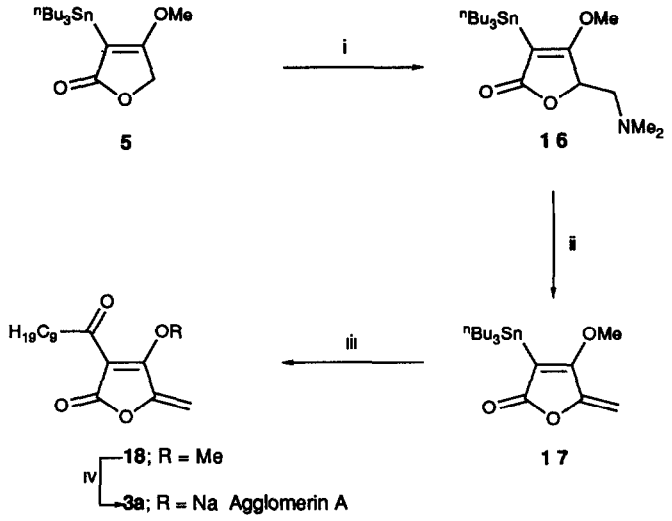
Scheme 2



(i) LDA, THF, -78°C, MeI, 78%. (ii) $MeO_2CCH_2CH_2COCl$, *trans*-Bn(Cl)Pd(PPh_3)$_2$ (cat.), $ClCH_2CH_2Cl$, 60°C, 16 h, 62%. (iii) HCl (3M), 3 days, 51%.

Recently, further development of this acylation methodolgy has led to an efficient four-step total synthesis of the antibiotic agglomerin A **3a.** As illustrated in Scheme 3, the required 5-methylene 3-(tri-*n*-butylstannyl) tetronate **17** was prepared from **5** by treatment with LDA in THF at -78°C, followed by the addition of Eschenmoser's salt.[28] This afforded the 5-methyldimethylamino derivative **16**. Quaternization of **16** with methyl iodide followed by subsequent base promoted elimination gave the 5-methylene 3-(tri-*n*-butylstannyl) tetronate **17** in 68% overall yield. Palladium catalyzed acylation of **16** with decoyl chloride furnished O-methyl agglomerin A **18** in 49% yield. Demethylation with aqueous NaOH (1 M) in a solution of methanol provided the natural product, agglomerin A **3a,** in 58% yield.

Scheme 3



(i) LDA, THF, -78°C, $Me_2NCH_2^+I^-$. (ii) MeI, MeOH, r.t., 24 h, then NaOH (1M), 68% (overall).
(iii) $H_{19}C_9COCl$, *trans*-Bn(Cl)Pd(PPh_3)$_2$ (cat.), $ClCH_2CH_2Cl$, 60°C, 16 h, 49% (iv) NaOH (1M)/MeOH, 58%

In summary, the palladium catalyzed acylation of O-methyl 3-stannyl tetronates is a facile and efficient method for the preparation O-methyl 3-acyl tetronates. This is a general methodology, useful for the preparation of unsubstituted and 5-substituted 3-acyl tetronate derivatives with potential application for the synthesis of pharmacologically active compounds. In addition, the acylation reaction takes place under relatively mild conditions and is tolerant of a wide variety of functionality. Application of this methodology to the synthesis of more complex 3-acyl tetronate systems is currently under investigation.

Acknowledgements: We thank the SERC, ICI Strategic Research Grant and The Polehampton Charities for their generous financial support.

Experimental

Infrared spectra were recorded on a Perkin Elmer 983G Infrared Spectrophotometer. ^{1}H NMR were recorded with either a 270 MHz JEOL FX 90Q or a 500 MHz Bruker AM 500 spectrometer. Mass spectra were recorded on a VG Micromass 7070 B spectrometer. Melting points were measured on a Reichert melting point apparatus and are uncorrected. Elemental mircoanalyses were performed in the Imperial College Microanalytical Laboratory. Diethyl ether and THF were distilled from sodium-benzophenone ketyl. Dichloromethane and dichloroethane were distilled over phosphorous pentoxide. Chloroform was passed through a long column of activated alumina immediately prior to use. Petrol refers to light petroleum ether (b.p. 40-60°C) and was distilled prior to use. Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60, F254) and visualized under U.V. Preparative chromatography was performed under pressure on Merck Kieselgel 60 (230 - 400 mesh). All chemicals were purchased from Aldrich Chemical Company unless otherwise noted.

4-Methoxy-3-bromo-furan-2(5H)-one **4.**

3-Bromo-tetronic acid[25] (10.0 g, 0.055 mol) was dissolved in dry acetone (100 mL over $MgSO_4$) and potassium carbonate (15.4 g, 0.11 mol) was added in one portion. The reaction mixture was stirred for ten minutes at room temperature followed by addition of dimethyl sulfate (7.89 mL, 0.083 mol). The reaction mixture was then heated to reflux for two hours. The reaction mixture was allowed to cool to room temperature and the inorganic salts were filtered and washed with chloroform. The filtrate was concentrated under reduced pressure and the residue was dissolved in chloroform (150 mL). The organic solution was washed with sodium bicarbonate solution (100 mL), water (100 mL) and brine (100 mL). The organic solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The solid residue was then recrystallized from EtOAc to afford the *furan-2(5H)-one* **4** (5.27g, 49%). m.p. 118-120°C. IR (nujol mull) 1745, 1636, 1451, 1368, 1314, 1048, 1038, 990 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.15 (3H, s, OMe), 4.70 (2H, s, 5-H_2). MS (70 ev) *m/z* 194 (M^+), 165 (M^+-CHO), 149 (M^+-C_2H_5O). Found: C, 31.50; H, 2.45. $C_5H_5BrO_3$ requires: C, 31.12; H, 2.61%.

4-Methoxy-3-(tri-n-butylstannyl)-furan-2(5H)-one **5.**

A solution of sodium naphthalenide [5.00 mL of a 1.0 M solution in THF, 5 mmol, prepared from naphthalene (6.41 g, 0.05 mol), and sodium metal (1.15g, 0.05 mol) in THF (50 mL) with ultrasonication for two hours] was added to a solution of bromide **4** (194 mg, 1.0 mmol) in THF (5 mL) at -78°C. The reaction mixture was then allowed to warm to -50°C. After five minutes, the brown slurry was cooled to -78°C followed by the addition of tri-*n*-butyltin chloride (1.36 mL, 5.0 mmol). The mixture was then allowed to warm to room temperature. After 16 hours the reaction was poured into a saturated ammonium chloride solution (10 mL) and ether (50 mL). The organic layer was separated, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resultant oil was chromatographed (SiO_2, 20 - 50% ether/petrol, gradient elution) to afford the *3-stannyl tetronate* **5** (278 mg, 69%) as a pale-yellow oil. IR (film) 2956, 2924, 2854, 1733, 1603, 1461, 1366, 1296 1085 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (9H, t, J = 6.9 Hz, 4'-Me), 1.05 - 1.50 (18H, m, 1'-H_2, 2'-H_2, 3'-H_2), 3.80 (3H, s, OMe) and 4.72 (2H, s, 5-H_2). MS (70 ev) *m/z* 402 (M^+) and 343 (M^+-^{n}Bu). Found: C, 50.77; H, 8.03. $C_{17}H_{32}O_3Sn$ requires: C, 50.66; H, 8.00%.

3-Acyl-4-methoxy-furan-2(5H)-ones. ***General Procedure.***

A mixture of the acid chloride (1.0 equiv., prepared from the acid by treatment with oxalyl chloride in dichloromethane at room temperature or as purchased), 3-stannyl tetronate **5** (1.1 equiv.) and *trans*-benzyl(chloro)-*bis*-triphenylphosphine palladium (II) (0.4 mol%) in anhydrous dichloroethane (2 mL) was heated to 60°C for 16 hours. After cooling, the solution was poured into ether (50 mL) and washed with saturated potassium fluoride solution, water, and brine and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resultant oil was then purified by column chromatography or crystallized from an appropriate solvent system.

3-Benzoyl-4-methoxy-furan-2(5H)-one **6b.**

General procedure; (10.3 mg, 47% yield). m.p. (ether:petrol, 1:1) 118-120°C. IR (nujol mull) 2954, 2953, 2853, 1764, 1746, 1638, 1617, 1465, 1404, 1376, 1337, 1277, 1215, 1090, 1043, 943, 881, 804, 770, 694, 664 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 3.96 (3H, s, OMe), 4.78 (2H, s, 5-H_2), 7.46 - 7.51 (2H, m, *o*-PhH), 7.58 - 7.64 (1H, m, *p*-PhH), 7.89 - 7.92 (2H, m, *m*-PhH). MS (70 ev) *m/z* 218 (M^+), 201 (M^+-OH), 187 (M^+-OMe), 176 (M^+-C_2H_2O) and 105 ($C_7H_5O^+$). Found: C, 66.05; H, 4.62. $C_{12}H_{10}O_4$ requres: C, 65.73; H, 4.47%.

3-Furanoyl-4-methoxy-furan-2(5H)-one **7b.**

General procedure; chromatography: SiO_2, EtOAc; (12 mg, 48%). m.p. (ether) 151-153°C (dec). IR (nujol mull) 2953, 2923, 2853, 1746, 1639, 1617, 1559, 1458, 1405, 1378, 1293, 1235, 1163, 1054, 934, 883, 845, 790, 780, 748, 722, 663 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 4.02 (3H, s, OMe), 4.76 (2H, s, 5-H_2), 6.60 (1H, dd, J = 3.7 Hz, J = 1.7 Hz, 9-H), 7.33 (1H, dd, J = 3.7 Hz, J = 0.7Hz, 8-H), 7.67 (1H, dd, J = 1.7 Hz, J = 0.7 Hz, 10-H). MS (70 ev) *m/z* 208 (M^+), 190 (M^+-H_2O), 179 (M^+-CHO), 161 (M^+-C_4H_3O), 95 ($C_5H_3O_2^+$). Found: C, 57.91; H, 3.93. $C_{10}H_8O_5$ requires: C, 57.70; H, 3.87%. Structure confirmed by X-ray crystallographic analysis.[22,23]

3-[(1-Oxo-3-phenyl)-2-propenyl]-4-methoxy-furan-2(5H)-one **8b.**

General procedure; (14.4 mg, 59%). m.p. (ether) 169-172°C (dec). IR (nujol mull) 2922, 2853, 1743, 1663, 1902, 1576, 1463, 1402, 1376, 1340, 1327, 1311, 1285, 1241, 1204, 1164, 1059, 1052, 997, 926, 878, 779, 711, 662 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$), δ 4.14 (3H, s, OMe), 4.81 (2H, s, 5-CH_2), 7.38 - 7.65 (5H, m, PhH), 7.67 (1H, d, J = 15.9 Hz, 3'-H), 7.72 (1H, d, J = 15.9 Hz, 2'-H). MS (70 ev) m/z 244 (M^+), 229 (M^+-Me), 216 (M^+-MeOH). Observed: M^+, 244.0730. $C_{14}H_{12}O_4$ requires M, 244.0736.

3-[(1-Oxo-2-methyl-3-phenyl)-2-propenyl]-4-methoxy-furan-2(5H)-one **9b.**

General procedure; (17 mg, 44%). m.p.(ether) 110-112°C. IR ($CHCl_3$) 2955, 1755, 1653, 1559, 1451, 1404, 1331, 1257, 1061, 991, 903, 694 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$), δ 2.18 (3H, d, J = 1.3 Hz, Me), 3.97 (3H, s,OMe), 4.74 (2H, s, 5-H_2), 7.49 - 7.63 (6H, m, 3'-H, PhH). MS (70 ev) 258 (M^+), 243 (M^+-Me), 226 (M^+-MeOH). Observed: M^+, 258.0890. $C_{15}H_{14}O_4$ requires M, 258.0892.

3-Propionyl-4-methoxy-furan-2(5H)-one **10b.**

General Procedure; chromatography: SiO_2, EtOAc; (50 mg, 49%). IR (film) 2922, 1757, 1676, 1611, 1474, 1405, 1329, 1246, 1064, 965, 903 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.3 Hz, 3'-Me), 2.91 (2H, q, J = 7.3 Hz, 2'-H_2), 4.09 (3H, s, OMe), 4.77 (2H, s, 5-H_2). MS (70 ev) *m/z* 170 (M^+), 155 (M^+-Me). Product was pure by NMR but decomposed upon storage at -10°C after one month.

3-(3-Methoxycarbonyl)-propionyl-4-methoxy-furan-2(5H)-one **11b.**

General procedure; chromatography: SiO_2, EtOAc; (30 mg, 47%). IR (film) 2954, 1734, 1677, 1609, 1405, 1332, 1249, 1065, 801 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$), δ 2.66 (2H, t, J = 6.9 Hz, 3'-H_2), 3.21 (2H, t, J = 6.8 Hz, 2'-H_2), 3.67 (3H, s, OMe), 4.11 (3H, s, OMe), 4.78 (2H, s, 5-H_2). MS (70 ev) *m/z* 228 (M^+), 213 (M^+-Me), 196 (M^+-MeOH). Observed: M^+, 228.0639. $C_{10}H_{12}O_6$ requires M, 228.0634.

[3-(2R-(1R*,2S*))]-4-Methoxy-3-[2-[2-(methoxycarbonyl)-cyclohexyl]-1-oxopropyl]-furan-2(5H)-one* **12b.**

General procedure; acid chloride **12a** was prepared from the corresponding acid[29]; chromatography: SiO_2, EtOAc; (12 mg, 40%). IR (film) 2988, 2855, 1758, 1731, 1676, 1611, 1592, 1465, 1436, 1400, 1367, 1328, 1241, 1191, 1168, 1064, 1024, 975, 959, 902, 860, 828, 780, 750, 727, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.78 -1.92 (8H, m, 3"-H_2, 4"-H_2, 5"-H_2, 6"-H_2), 1.04 (3H, d, J = 7.0 Hz, 2'-Me), 2.02 (1H, m, 1"-H), 2.32 (1H, dd, J = 11.1Hz, J = 3.1 Hz, 2"-H), 3.49 (1H, dq, J = 7.0 Hz, J = 3.2 Hz, 2'-H), 3.71 (3H, s, OMe), 4.06 (3H, s, OMe), 4.76 (2H, s, 5-H_2). MS (70 ev) *m/z* 310 (M^+), 292 (M^+-H_2O), 278 (M^+-MeOH), 260 (M^+-H_2O-MeOH), 250 (M^+-CO-MeOH). Observed: M^+, 310.1414. $C_{16}H_{22}O_6$ requires M, 310.1416

5-Methyl-4-methoxy-3-(tri-n-butylstannyl)-furan-2(5H)-one **13.**

LDA (600 μL of 1.0 M solution in THF, 0.6 mmol) was added to a solution of 3-stannyl tetronate **5** (200 mg, 0.5 mmol) in THF (5 mL) at -78°C. After 15 minutes, MeI (70 μL, 1.1 mmol) was added and the reaction mixture was allowed to warm to 0°C. The reaction mixture was quenched by addition of a saturated solution of ammonium chloride (5 mL) and poured into ether (50 mL). The organic solution was removed and washed with water and brine and dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resultant oil was purified by column chromatography (SiO_2, 50% ether/petrol) to furnish the *furan-2(5H)-one* **13** (220 mg, 78%) as a pale-yellow oil. IR(film) 2956, 2853, 1730, 1597, 1456, 1337, 1276, 1154, 961 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.80 (3H, t, J = 7.0 Hz, 4'-Me), 1.05 -1.50 (18H, m, 1'-H_2, 2'-H_2, 3'-H_2), 1.43 (3H, d, J = 6.6 Hz, 5-Me), 3.85 (3H, s, OMe), 4.80 (1H, q, J = 6.6 Hz, 5-H). MS (70 ev) *m/z* 417 (M^+-H), 361 (M^+-^{n}Bu). Found: C, 51.95; H, 8.25. $C_{18}H_{34}O_3Sn$ requires C, 51.83; H, 8.22%.

(±)-Dimethyl carolinic acid **14.**

A mixture of 3-carbomethoxypropionyl chloride (27 μL, 0.22 mmol), 5-methyl stannyl tetronate **13** (80 mg, 0.20 mmol) and *trans*-benzyl(chloro)-*bis*-triphenylphosphine palladium (II) (5 mg) in anhydrous dichloroethane (2 mL) was heated to 60°C for 16 hours. After cooling, the solution was poured into ether (20 mL) and washed with saturated potassium fluoride solution, water, and brine and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resultant oil was then purified by column chromatography (SiO_2, 80% ether/petrol) to furnish **14** as an oil (30 mg, 62%). IR (film) 2947, 1745, 1682, 1628, 1451, 1363, 1296, 1244, 1160, 1086, 1057, 1016, 982, 944, 805, 702, 663 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.49 (3H, d, J = 6.8 Hz, 5-Me), 2.65 -2.69 (2H, m, 2'-H_2), 3.23 - 3.26 (2H, m, 3'-H_2), 3.66 (3H, s, OMe), 4.11 (3H, s, OMe), 4.83 (1H, q, J = 6.8 Hz, 5-H). MS (70ev) *m/z* 242 (M^+), 224 (M^+-H_2O), 210 (M^+-MeOH), 183 (M^+-C_2H_3O). Observed: M^+, 242.0791. $C_{11}H_{14}O_6$ requires M, 242.0791.

(±)-Carolinic acid **15.**

The diester **14** (20 mg, 0.083 mmol) was stirred in aqueous HCl (3 M, 0.5 mL) under ambient conditions for three days. The aqueous solution was extracted with chloroform (5 x 5 mL) and the combined extracts were dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure to afford (±)-carolinic acid **15** as a white solid (9 mg, 51%). m.p. 137-139°C (Lit.[26] 141-142°C). ^1H NMR (270 MHz, DMSO-d_6) δ 1.43 (3H, d, J = 6.9 Hz, 5-Me), 2.20-3.24 (4H, m, 2'-H_2, 3'-H_2), 4.90 (1H, q, J =7.0 Hz, 5-H).

5-N,N-(Dimethylaminomethyl)-4-methoxy-3-(tri-n-butylstannyl)-furan-2(5H)-one **16.**

A solution of LDA (750 μL of a 1.5 M solution in cyclohexane, 1.12 mmol) was addded to a solution of 3-stannyl tetronate **5** (400 mg, 1.0 mmol) in THF (20 mL) at -78°C. Stirring was continued for one hour followed by addition of Eshenmoser's salt (555 mg, 3.0 mmol). The reaction mixture was stirred for one hour then allowed to warm to room temperture. The reaction mixture was poured into saturated sodium bicarbonate solution (30 mL) and extracted with ether (100 mL). The etheral extacts were washed with water and brine and dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resultant oil was purified by column chromatography (SiO_2, EtOAc) to furnish the *furan-2(5H)-one* **16** as a colorless oil (195 mg, 93% conversion based on recovered starting material). IR (film) 2954, 2922, 2851, 2771, 1733, 1597, 1453, 1375, 1339, 1318, 1291, 1200, 1146, 1100, 1069, 1037, 952, 858, 766, 663 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (9H, t, J = 7.4 Hz, 4'-Me), 1.07 - 1.51 (18H, m, 1'-H_2, 2'-H_2, 3'-H_2), 2.33 (6H, s, NMe_2), 2.41 (1H, dd, J = 13.8 Hz, J = 7.7 Hz, 6-H_b), 2.88 (1H, dd, J = 13.8 Hz, J = 2.1 Hz, 6-H_a), 3.85 (3H, s, OMe), 4.86 (1H, dd, J = 7.7 Hz, J = 2.1 Hz, 5-H). MS (70ev) *m/z* 415 (M^+-C_2H_7N). Found: C, 51.99; H, 8.37. $C_{20}H_{39}NO_3Sn$ requires C, 52.19; H,

8.54%.

5-Methylene-4-methoxy-3-(tri-n-butylstannyl)-furan-2(5H)-one **17**.

A solution of **16** (285 mg, 0.62 mmol) and MeI (6.0 mL, excess) in methanol (6 mL) was stored in the dark overnight. The reaction mixture was concentrated under reduced pressure and the residue dissolved in dichloromethane (50 mL). The solution was then treated with aqueous sodium hydroxide (1M, 25 mL). The organic solution was removed and washed with water and brine, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resultant oil was then purified by column chromatography (SiO_2, 3% ether/petrol) to afford the *furan-2(5H)-one* **17** (211 mg, 82%) as a colorless oil. IR (film) 2955, 2922, 1770, 1743, 1660, 1569, 1485, 1456, 1437, 1378, 1343, 1253, 1154, 1116, 1075, 992, 974, 918, 860, 663 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (9H, t, J = 7.3 Hz, 4'-Me), 1.11 -1.55 (18H, 1'-H_2, 2'-H_2, 3'-H_2), 3.91 (3H, s, OMe), 4.88 (1H, d, J = 2.4 Hz, 6-H_b), 4.91 (1H, d, J = 2.4 Hz, 6-H_a). MS (70ev) 416 (M^+), 382 (M^+-Me-H_2O), 359 (M^+-^{n}Bu). Found: C, 52.22; H, 7.80. $C_{18}H_{32}O_3Sn$ requires C, 52.07; H, 7.77%.

Methyl agglomerin A **18**.

A mixture of decoyl chloride (8.5 mg, 0.5 mmol), 5-methylene 3-stannyl tetronate **17** (20 mg, 0.50 mmol) and *trans*-benzyl(chloro)-*bis*-triphenylphosphine palladium (II) (2 mg) in anhydrous dichloroethane (1 mL) was heated to 60°C for 16 hours. After cooling, the solution was poured into ether (20 mL) and washed with saturated potassium fluoride solution, water, and brine and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resultant oil was then purified by column chromatography (SiO_2, 30% ether/petrol) to furnish **18** as an oil (6.8 mg, 49%). IR (film) 2932, 2855, 1755, 1683, 1609, 1451, 1358, 1305, 1104, 986 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.1 Hz, 9'-Me), 1.30 - 1.25 (12H, m, 3'-8'-H_2), 1.57 (2H, m, 2'-H_2), 2.95 (2H, t, J = 7.3 Hz, 1'-H_2), 4.09 (3H, s, OMe), 5.03 (1H, d, J = 2.6 Hz, 6-H_b), 5.07 (1H, d, J = 2.6 Hz, 6-H_a). MS(70 ev) *m/z* 280 (M^+), 249 (M^+-Me). Observed: M^+, 280.1678. $C_{16}H_{24}O_4$ requires M, 280.1674.

Agglomerin A **3a**.

The O-methyl tetronate **18** (5 mg, 0.017 mmol) was dissolved in methanol (0.5 mL). A solution of NaOH (3 M, 250 μL) added and the mixture stirred for 16 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and the inorganic salts were removed by filtration. The solvent was removed under reduced pressure to afford agglomerin A **3a** as a white solid (2.3 mg, 58%): m.p. 112-113°C (Lit.[3] 113-115°C). ^1H NMR (500 MHz, $CDCl_3/CD_3OD$, 15:1) δ 0.87 (3H, t, J = 7.1 Hz, 9'-Me), 1.25 - 1.31 (12H, m) 1.54 (2H, m, 2'-H_2), 2.73 (2H, m, 1'-H_2), 4.83 (1H, br s, 6-H_b), 5.11 (1H, br s, 6-H_a).

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