Total Synthesis of (+)-Intricarene using a Biogenetically Patterned Pathway from (-)-Bipinnatin J, Involving a Novel Transannular [5+2] (1,3-dipolar) Cycloaddition

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Experimental procedures and data for compounds **15b**, **16**, **18**, **10**, **20**, **21a** and **21b**; copies of ^{1}H and ^{13}C NMR spectra for compounds **28a**, **28b**, **4a** and **1**.

Toluene-4-sulfonic acid (*Z*)-(*S*)-2-hydroxy-5-iodo-4-methyl-pent-4-enyl ester 15b

A solution of trimethylaluminium (2.0 M) in hexane (43.5 ml, 87.0 mmol) was added dropwise, over 10 mins, to a stirred solution of *bis*(cyclopentadienyl)zirconium dichloride (1.41 g, 4.83 mmol) in anhydrous $ClCH_2CH_2Cl$ (20 ml) under an argon atmosphere. The mixture was stirred at room temperature for 10 mins. A solution of (*S*)-pent-4-yne-1, 2-diol **14b**[19] (1.93 g, 19.3 mmol) in anhydrous $ClCH_2CH_2Cl$ (60 ml) was added dropwise cautiously *via* syringe over 10 mins (Careful!!). The yellow solution was stirred at room temperature for 19 hrs, and then heated under reflux for 3 days, whereupon a red solution was formed. The mixture was cooled to -30 ºC and a solution of iodine (10.1 g, 40.0 mmol) in anhydrous THF (50 ml) was then added dropwise *via* a syringe over 10 mins. The dark/red solution was stirred at -30 ºC for 10 mins and then allowed to warm to room temperature over 2 hrs. The mixture was quenched very carefully with a saturated solution of aqueous Rochelle's salt (2.5 ml) at 0 ºC, and then poured into a mixture of a saturated solution of aqueous Rochelle's salt (190 ml) and ethyl acetate (190 ml). The mixture was stirred vigorously overnight and the organic layer was then separated. The aqueous layer was extracted with ethyl acetate (3 × 150 ml), and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue (3.99 g) was used in the next step without further purification. For characterisation purposes, a sample was purified by chromatography on silica, eluting with light petroleum (bp 40-60 ºC)-ethyl acetate (3: 1), to give the vinyl iodide **15a**[20] as a colourless viscous oil. $[\alpha]_D^{25}$. 2.80 (*c* 1.15 $CHCl_3$); ν_{max} (film)/cm^{-1} 3373, 1455; δ_H (360 MHz; $CDCl_3$) 6.04 (1 H, q, *J* 1.4, =C*H*), 3.98 (1 H, dddd, *J* 3.2, 5.4, 6.9 and 8.4, C*H*OH), 3.72 (1 H, dd, *J* 3.2 and 11.2, CH*H*OH), 3.55 (1 H, dd, *J* 6.9 and 11.2, C*H*HOH), 2.51 (1 H, dd, *J* 8.4 and 13.6, =C(CH_3)CH*H*), 2.38 (1 H, dd, *J* 5.4 and 13.6, =C(CH_3)C*H*H), 2.01 (2 H, br s, O*H* and O*H*), 1.98 (3 H, d, *J* 1.4, =C(CH_3)); δ_C (90 MHz; $CDCl_3$) 144.2 (s), 77.1 (d), 70.4 (d), 66.3 (t), 42.1 (t), 24.4 (q); HRMS (EI^+) 241.9816 (M^+, $C_6H_{11}IO_2$ requires 241.9804);

para-Toluenesulfonyl chloride (1.58 g, 8.30 mmol) was added in one portion to a stirred solution of the diol vinyl iodide **15a** (2.0 g, 8.30 mmol) in pyridine (27 ml), and the resulting mixture was stirred at 4 ºC for 21 hrs. Another portion of *para*-toluenesulfonyl chloride (1.18 g, 6.23 mmol) was added and the mixture was again stirred at 4 ºC for a further 7 hrs. The mixture was partitioned between DCM (80 ml) and a saturated solution of aqueous NH_4Cl (60 ml), and the separated aqueous layer was then extracted with DCM (3 × 75 ml). The combined organic extracts were washed successively with a saturated solution of aqueous $CuSO_4$ (to remove most of pyridine), water (3 × 10 ml), and brine (10 ml), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum (bp 40–60 ºC)-diethyl ether (5 : 1), to give the *tosylate* (1.59 g, 48%) as a colourless oil. $[\alpha]_D^{25}$ -4.62 (*c* 1.17, $CHCl_3$); ν_{max} (sol $CHCl_3$)/cm^{-1} 3591, 1359, 874; δ_H (360 MHz; $CDCl_3$) 7.81 (2 H, d, *J* 8.4, Ph*H*), 7.37 (2 H, d, *J* 8.4, Ph*H*), 6.02 (1 H, q, *J* 1.4, =C*H*), 4.10-4.07 (2 H, m, CH*H*OTs and HOC*H*), 3.98-3.93 (1 H, m, C*H*HOTs), 2.46 (3 H, s, PhCH_3), 2.46-2.33 (2 H, m, =CCH_2), 2.15 (1 H, br, O*H*), 1.92 (3 H, d, *J* 1.4, =CCH_3); δ_C (90MHz; $CDCl_3$) 145.1 (s), 143.5 (s), 132.4 (s), 129.9 (2 × d), 127.9 (2 × d), 77.6 (d), 73.4 (t), 68.0 (d), 41.7 (t), 24.3 (q), 21.6 (q); HRMS (EI^+) 377.9778 (M^+-H_2O, $C_{13}H_{15}IO_3S$ requires 377.9787); A satisfactory microanalysis could not be secured for this compound.

(*S*)-2-((*Z*)-3-Iodo-2-methyl-allyl)-oxirane 16

Anhydrous potassium carbonate powder (378 mg, 2.74 mmol) was added in one portion to a stirred solution of the tosylate **15b** (724 mg, 1.83 mmol) in anhydrous MeOH (10 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 hr, then diluted with diethyl ether (30 ml) and filtered through a short plug of celite. The celite was washed with ether (3 × 20 ml), and the combined ether washings were then washed with water (3 × 5 ml) and brine (5 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on florisil, eluting with DCM to give the *epoxide* (300 mg, 73%) as a colourless liquid. $[\alpha]_D^{25}$ -3.88 (*c* 1.03, $CHCl_3$); ν_{max} (film)/cm^{-1} 1436, 1401, 848; δ_H (360 MHz; $CDCl_3$) 6.04-6.03 (1 H, m, =C*H*I), 3.03 (1 H, dddd, *J* 2.6, 3.9, 5.0 and 6.3, OC*H*CH_2), 2.79 (1 H, dd, *J* 3.9 and 4.9, C*H*HO), 2.59-2.53 (2 H, m, CH*H*O and =C(CH_3)C*H*H), 2.45 (1 H, dd, *J* 6.3 and 14.1, =C(CH_3)CH*H*), 2.00 (3 H, d, *J* 1.4, =CCH_3); δ_C (90 MHz) 143.9 (s), 76.4 (d), 50.3 (d), 46.5 (t), 41.4 (t), 24.5 (q); HRMS (EI^+) 223.9695 (M+ C_6H_9IO requires 223.9698). The compound was quite volatile, and efforts to obtain a satisfactory microanalysis were unsuccessful.

(±)-5-((*Z*)-3-Iodo-2-methyl-allyl)-dihydro-furan-2-one 18

A solution of ^{n}BuLi (2.5 M) in hexane (3.13 ml, 7.81 mmol) was added dropwise over 5 mins to a stirred solution of ethoxyacetylene (50 % solution w/w in hexane, 1.83 ml, 9.38

mmol) in THF (10.5 ml) at -78 ºC under an atmosphere of nitrogen. The mixture was stirred at -78 ºC for 20 mins, and then BF_3•OEt_2 (1.10 g, 0.96 ml, 7.81 mmol) was added *via* syringe over 1 min. The mixture was stirred at -78 ºC for 2 mins before a solution of the racemic oxirane **16** (700 mg, 3.13 mmol) in THF (5.5 ml) was added dropwise over 5 mins. The mixture was stirred at -78 ºC for 2 hrs and then warmed up to 0 ºC before it was quenched with a saturated solution of aqueous $NaHCO_3$ (70 ml). The mixture was diluted with diethyl ether (70 ml) and water (56 ml), and the separated aqueous phase was then extracted with diethyl ether (2 × 110 ml). The combined organic layers were washed successively with water (2 × 5 ml) and brine (5 ml), then dried (Na_2SO_4) and concentrated *in vacuo* to leave the crude substituted ethoxyacetylene **17** as an oil. *p*-Toluenesulfonic acid (43 mg) was added to the residue, and the mixture was then dissolved in ethanol (14 ml) and stirred at room temperature for 2 hrs. The solvent was removed *in vacuo* and the residue was dissolved in chloroform (28 ml) and heated under reflux for 16 hrs. The mixture was cooled to room temperature and then quenched with a saturated solution of aqueous $NaHCO_3$ (9 ml). The separated aqueous layer was extracted with $CHCl_3$ (3 × 42 ml) and the combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with light petroleum-ethyl acetate (10 : 1), to give the *lactone* (620 mg, 81 %) as a pale yellow liquid. ν_{max} (film)/cm^{-1} 1769; δ_H (400 MHz; $CDCl_3$) 6.09 (1 H, q, *J* 1.5, IC*H*=), 4.70 (1 H, app. ddt, *J* 7.5, 7.5, 6.6 and 5.8, OC*H*), 2.70-2.49 (4 H, m, =C(CH_3)CH_2, O=CCH_2), 2.36 (1 H, dddd, *J* 12.8, 8.9, 6.6 and 5.3, CH_2C*H*H), 2.05-1.94 (1 H, m, CH_2CH*H*), 1.99 (3 H, d, *J* 1.5, CH_3); δ_C (100 MHz; $CDCl_3$) 176.8 (s), 143.0 (s), 78.9 (d), 77.9 (d), 43.8 (t), 28.5 (t), 27.6 (t), 24.5 (q); HRMS (ES+) 266.9878 ($M+H^+$, $C_8H_{12}O_2I$ requires 266.9882).

5-((*Z*)-3-Iodo-2-methyl-allyl)-3-phenylselanyl-dihydro-furan-2-one 10

A solution of the lactone **18** (434 mg, 1.63 mmol) in THF (3.5 ml) was added dropwise over 10 mins *via* syringe to a stirred solution of LiHMDS (1.0 M in THF, 1.79 mmol) in THF (1.79 ml) at -78 ºC under a nitrogen atmosphere. The mixture was stirred at -78 ºC for 15 mins, and then TMSCl (194 mg, 226 µl, 1.79 mmol) was added dropwise over 1 min. The mixture was stirred at -78 ºC for 0.5 hr and then a solution of PhSeBr (422 mg, 1.79 mmol) in THF (3 ml) was added *via* syringe over 1 min. The mixture was stirred at -78 ºC for 0.5 hr, then allowed to warm to room temperature over 0.5 hr and quenched by the addition of a saturated solution of aqueous NH_4Cl (20 ml). The solution was diluted with water (45 ml) and Et_2O (100 ml), and the separated aqueous layer was then extracted with Et_2O (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to leave a residue which was purified by chromatography on silica, eluting with light petroleum-diethyl ether (5 : 1), to give a mixture of diastereoisomers of the *phenylselenyl lactone* (575 mg, 83 %) as a yellow oil. Diastereoisomer-1: δ_H (360 MHz; $CDCl_3$) 7.70-7.67 (2 H, m, PhH), 7.42-7.32 (3 H, m, PhH), 6.06 (1 H, q, *J* 1.5, IC*H*=), 4.44 (1 H, tdd, *J* 8.6, 7.4, 6.0 and 6.0, OC*H*), 3.98 (1 H, dd, J 8.2 and 3.1, PhSeC*H*), 2.62-2.33 (4 H, m, =C(CH_3)CH_2, PhSeCHCH_2), 1.90 (3 H, d, *J* 1.5, CH_3); δ_C (90 MHZ; $CDCl_3$) 175.4 (s), 142.7 (s), 135.9 (2 × d), 129.5 (2 × d), 129.3 (d), 126.5 (s), 78.1 (d), 77.5 (d), 43.4 (t), 36.7 (d), 36.2 (t), 24.5 (q); Diastereoisomer-2: δ_H (360 MHz; $CDCl_3$) 7.70-7.66 (2 H, m, PhH), 7.41-7.31 (3 H, m, PhH), 6.02 (1 H, q, *J* 1.5, IC*H*=), 4.63-4.55 (1 H, m, OC*H*), 4.02 (1 H, dd, *J* 9.9 and 9.3, PhSeC*H*), 2.76 (1 H, ddd, *J* 13.5, 9.3 and 6.4, PhSeCHC*H*H), 2.54 (1 H, dd, *J* 14.0 and 5.0, =C(CH_3)C*H*H), 2.43 (1 H, dd, *J* 14.0 and 7.7, =C(CH_3)CH*H*), 2.10-2.01 (1 H, m, PhSeCHCH*H*), 1.88 (3 H, d, *J* 1.5, CH_3); δ_C (100 MHZ; $CDCl_3$) 175.3 (s), 142.8 (s), 135.9 (2 × d), 129.4 (2 × d), 129.0 (d), 126.8 (s), 78.0 (d), 77.5 (d), 43.7 (t), 37.2 (d), 35.5 (t), 24.8 (q).

(*S*)-3-{(*S*)-2-[(*S*)-Hydroxy-(3-methyl-furan-2-yl)-methyl)-3-methyl-but-3-enoyl}-4-isopropyl-oxazolidin-2-one 20

A solution of dibutylboryl triflate (6.0 ml, 6.0 mmol, 1.0 M) in DCM was added dropwise, *via* a syringe, over 5 mins, to a stirred solution of (*S*)-4-isopropyl-3-(3-methylbut-2-enoyl)oxazolidin-2-one **19**[21] (1.06 g, 5.0 mmol) in anhydrous DCM (20 ml) at -78 ºC under an atmosphere of argon. The mixture was stirred at -78 ºC for 5 mins, and then Et_3N (0.97 ml, 7.0 mmol) was added dropwise over 3 mins. The mixture was stirred at -78 ºC for 1 hr and then at 0 ºC for 15 mins. The solution was recooled to -78 ºC and then a solution of 3-methylfurfural[22] (550 mg, 5.0 mmol) in anhydrous DCM (3 ml) was added dropwise over 5 mins. The mixture was stirred at -78 ºC for 1 hr, then at 0 ºC for 1 hr, and diluted with aqueous sodium bisulfate (150 ml, 1.0 M), ethyl acetate (75 ml) and hexane (75 ml). The separated organic layer was washed with brine (2 × 5 ml) and concentrated *in vacuo* to leave a residue which was dissolved in ether (25 ml). The ether solution was cooled to 0 ºC and treated with 5 ml phosphate buffer (pH 7, 5 ml) and 30 % hydrogen peroxide (5 ml). The mixture was stirred at 0 ºC for 1 hr then poured into a mixture of water (125 ml), ethyl acetate (62 ml) and hexane (62 ml). The separated aqueous layer was extracted with ether (125 ml), and the combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography on silica, neutralised with 3 % Et_3N in light petroleum (bp 40-60 ºC) (100 ml), eluting with light petroleum (bp 40-60 ºC)-ethyl acetate (5 : 1), to give the *furanmethanol* as a colourless solid (639 mg, 61 %). δ_H (400 MHz; $CDCl_3$) 7.28 (1 H, d, *J* 1.8, OC*H*=CH), 6.17 (1 H, d, *J* 1.8, OCH=C*H*), 5.27 (1 H, br s, CH_3CC=*H*H), 5.21-5.18 (3 H, m, CH_3CC=H*H*, C*H*OH and CH(OH)C*H*), 4.28 (1 H, ddd, *J* 7.0, 4.7 and 3.9, NC*H*), 4.15-4.11 (2 H, m, OCH_2), 2.30-2.22 (1 H, m, C*H*(CH_3)$_2$), 2.19 (1 H, br s, O*H*), 2.08 (3 H, s, CCH_3), 1.93 (3 H, dd, *J* 1.3 and 0.8, CH_2=CCH_3), 0.87 (3 H, d, *J* 7.0, CHCH_3), 0.81 (3 H, d, *J* 7.0, CHCH_3); δ_C (100 MHz; $CDCl_3$) 170.8 (s), 153.2 (s), 148.5 (s), 141.4 (d), 140.2 (s), 117.7 (s), 117.6 (t), 113.1 (d), 65.2 (d), 62.9 (t), 58.1 (d), 54.6 (d), 28.3 (d), 20.9 (q), 17.9 (q), 14.5 (q), 9.7 (q); HRMS (ES+) 344.1497 ($M + Na^+$, $C_{17}H_{23}NO_5Na$ requires 344.1474);

(1*S*, 2*R*)-2-Isopropenyl-1-(3-methyl-furan-2-yl)-propane-1,

3-diol 21a

Anhydrous MeOH (42 µl) was added to a stirred solution of the amide **20** (100 mg, 0.31 mmol) in anhydrous THF (3.5 ml) at 0 ºC under an atmosphere of nitrogen, followed by a solution of lithium borohydride (1.56 mmol, 2.0 M) in THF (0.78 ml). The mixture was stirred at 0 ºC overnight while it was allowed to warm to room temperature. The reaction was diluted with saturated potassium sodium tartrate solution (40 ml) and ethyl acetate (100 ml) and then stirred vigorously for 1 hr. The separated aqueous layer was extracted with ethyl acetate (2 x 50 ml), and the combined organic extracts were dried (Na_2SO_4), and then concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum (bp 40-60 ºC)-ethyl acetate (5 : 1), to give the *1, 3-diol* (22 mg, 42 % over 2 steps) as an oil. δ_H (360 MHz; $CDCl_3$) 7.33 (1 H, d, *J* 1.8, OC*H*=CH), 6.21 (1 H, d, *J* 1.8, OCH=C*H*), 5.16-5.15 (1 H, m, CH_3C=C*H*H), 5.03 (1 H, br s, CH_3C=CH*H*), 4.75 (1 H, d, *J* 9.3, C*H*OH), 3.46-3.38 (2 H, m, OHCH_2), 2.97-2.90 (1 H, m, CH(OH)C*H*), 2.05 (3 H, s, CCH_3), 1.84 (3 H, app. dd, *J* 1.4 and 0.8, CH_2=CCCH_3); δ_C (100 MHz; $CDCl_3$) 148.5 (s), 143.0 (s), 141.5 (d), 117.8 (s), 115.9 (t), 113.0 (d), 64.6 (t), 61.3 (d), 54.9 (d), 20.0 (q), 9.7 (q); HRMS (ES+) 219.0982 (M + Na^+, $C_{11}H_{16}O_3Na$ requires 219.0997).

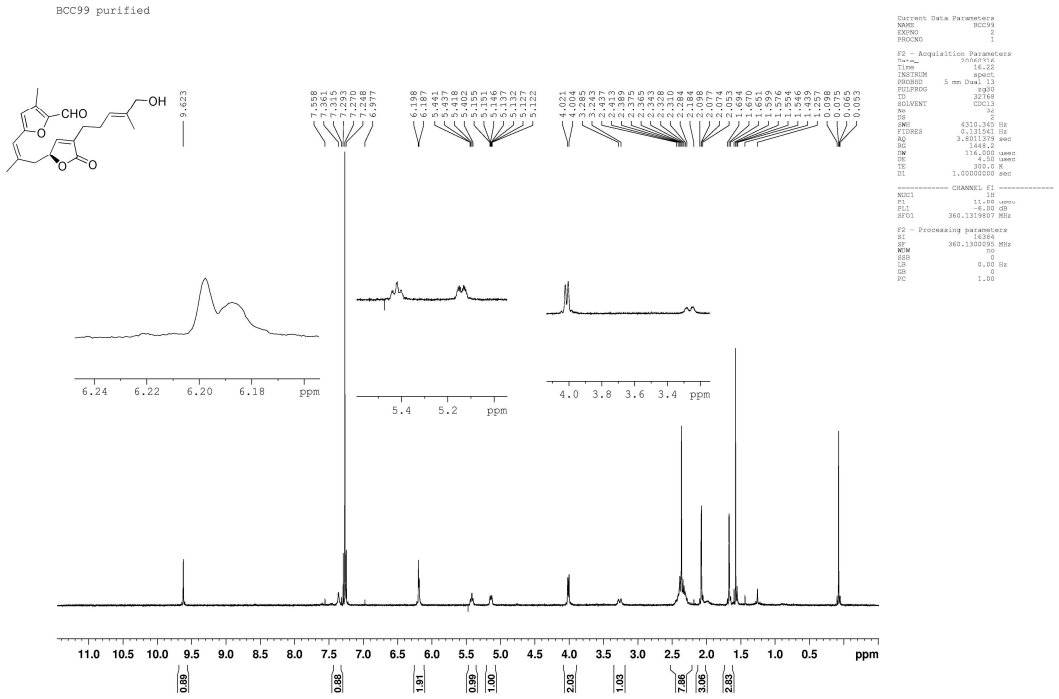
Toluene-4-sulfonic acid (*R*)-2-[(*S*)-hydroxy-(3-methyl-furan-2-yl)-methyl]-3-methyl-but-3-enyl ester 21b

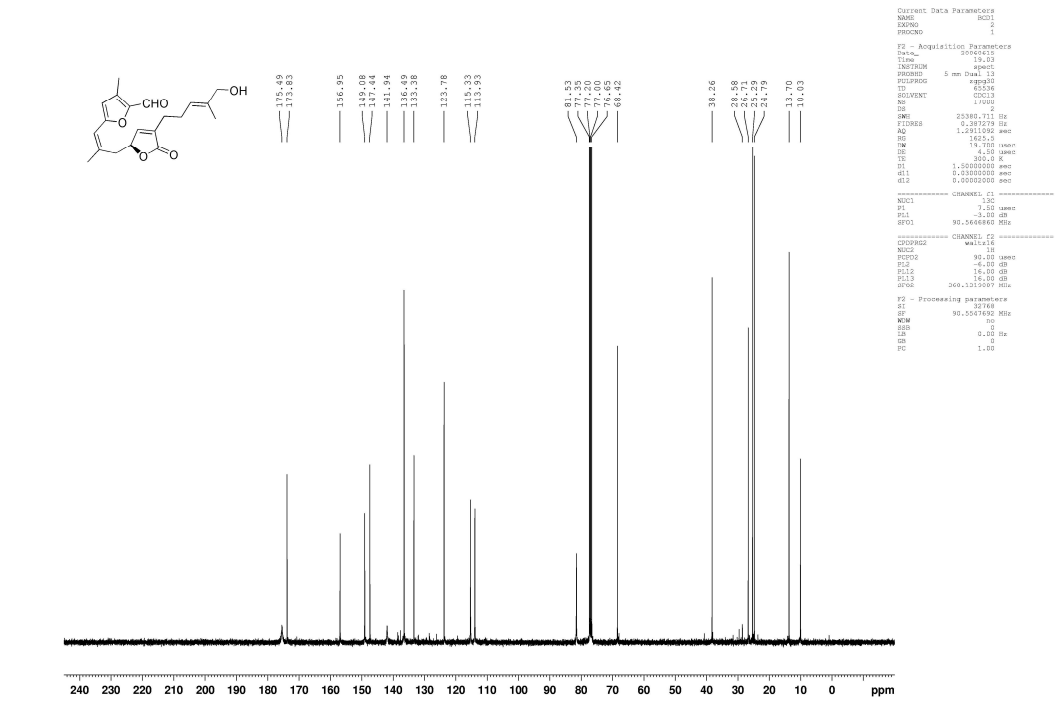
Triethylamine (11.3 mg, 16 µl, 0.11 mmol), 4-(dimethylamino)pyridine (1.3 mg, 0.01 mmol) and tosyl chloride (12.3 mg, 0.06 mmol) were added to a stirred solution of the 1, 3-diol **21a** (11 mg, 0.06 mmol) in anhydrous DCM (0.5 ml) at room temperature under an atmosphere of nitrogen. The mixture was stirred at room temperature for 27 hrs then diluted with DCM (15 ml) and washed successively with aqueous citric acid (10 % w/w, 2 ml) and a saturated solution of aqueous $NaHCO_3$ (2 ml). The separated organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with light petroleum-ethyl acetate (6 : 1), to give to the *mono-tosylate* (6 mg, 49 % based on the recovery of the starting material) as an oil. δ_H (400 MHz; $CDCl_3$) 7.73-7.71 (2 H, m, PhH), 7.34-7.32 (2 H, m, PhH), 7.26 (1 H, br s, OC*H*=CH), 6.18 (1 H, br s, OCH=C*H*), 5.05-5.04 (1 H, br s, CH_3C=C*H*H), 4.92-4.91 (1 H, m, CH_3C=CH*H*), 4.77-4.67 (1 H, m, C*H*OH), 3.94-3.85 (2 H, m, TsOCH_2), 2.99-2.94 (1 H, m, CH(OH)C*H*), 2.46 (3 H, s, Ph-CH_3), 2.06 (1 H, br s, OH), 2.01 (3 H, s, CCH_3), 1.69-1.68 (3 H, br s, CH_2=CCCH_3); δ_C (100 MHz; $CDCl_3$) 147.5 (s), 144.7 (s), 141.6 (d), 141.3 (s), 132.8 (s), 129.8 (2 × d), 127.9 (2 × d), 118.2 (s), 116.4 (t), 113.1 (d), 68.9 (t), 63.8 (d), 51.3 (d), 21.6 (q), 20.3 (q), 9.7 (q).

References

See reference list main article

^{1}H-NMR and ^{13}C-NMR Spectra for Furan butenolide 28a





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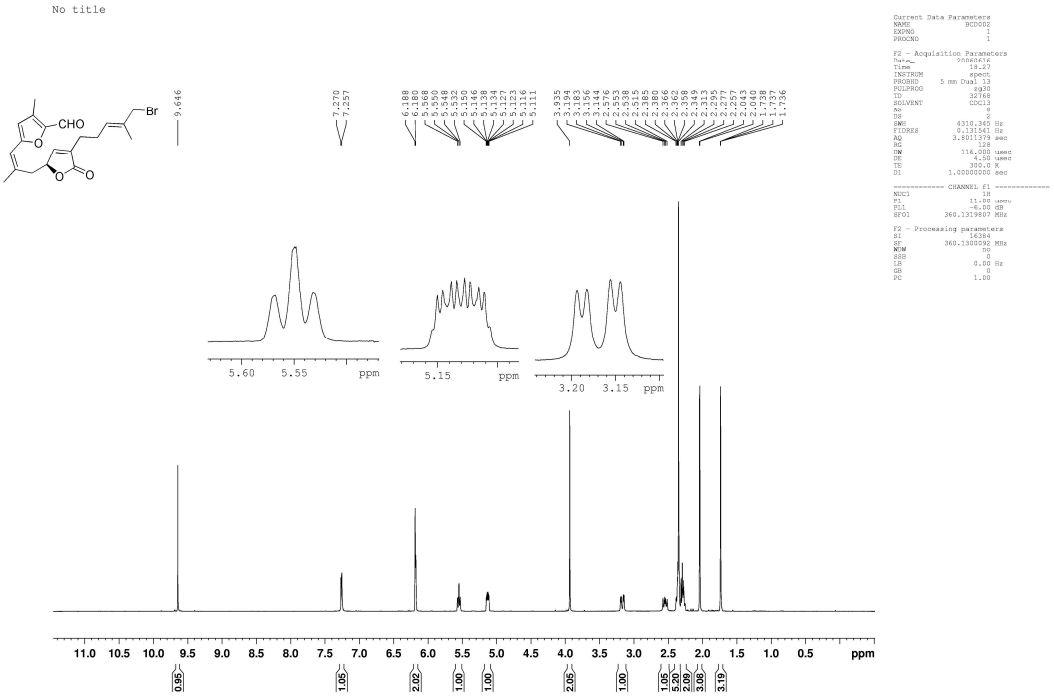
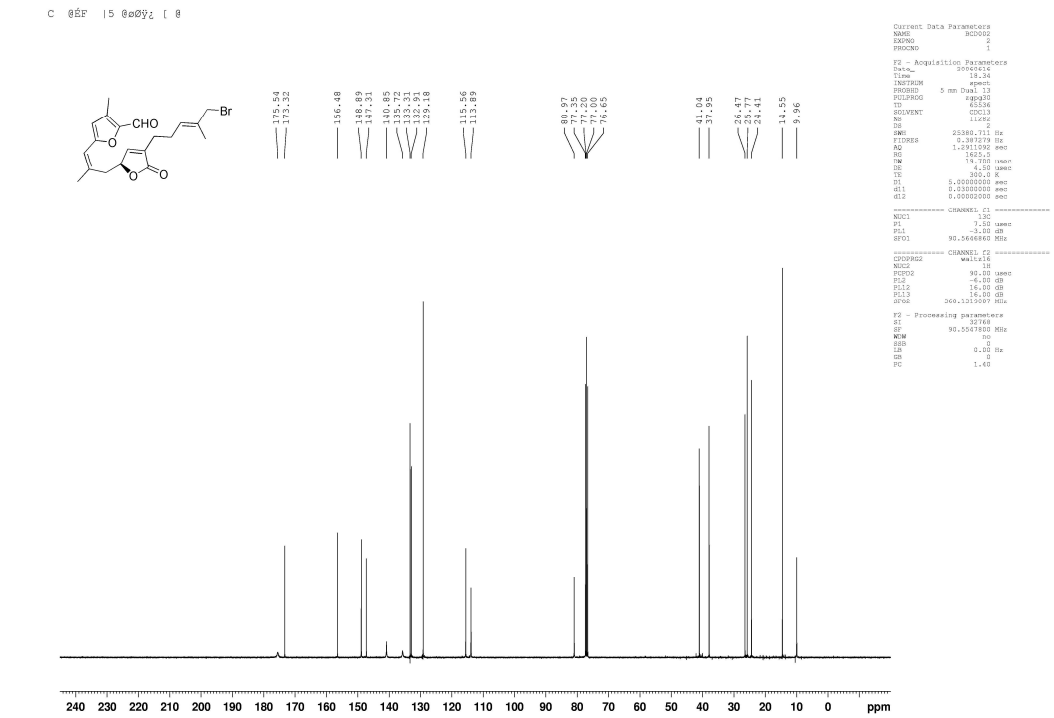
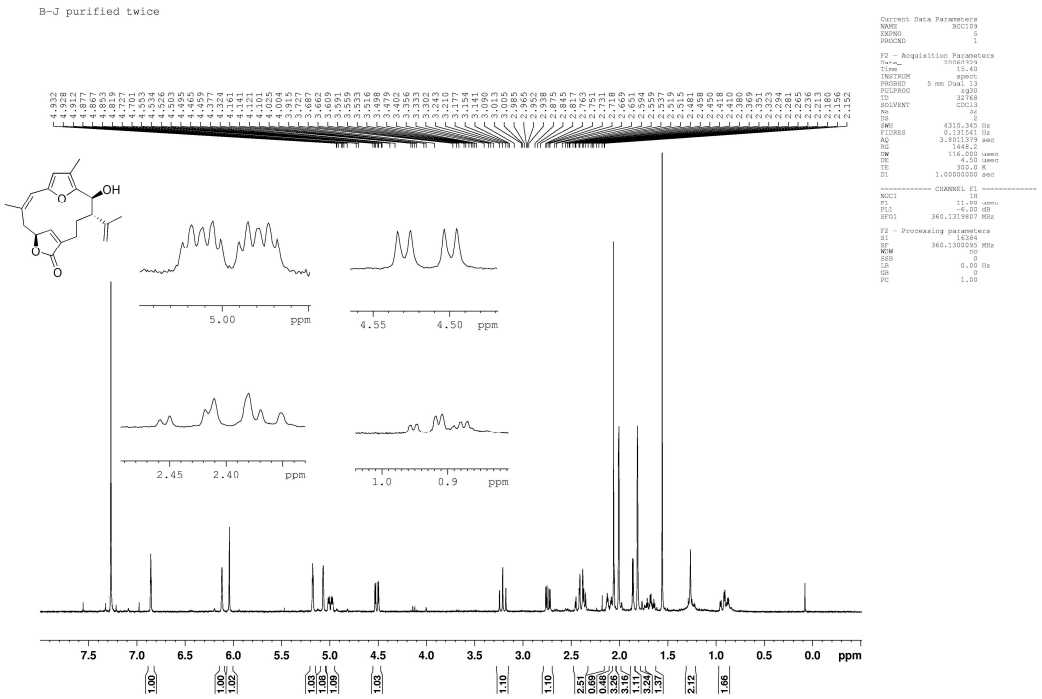
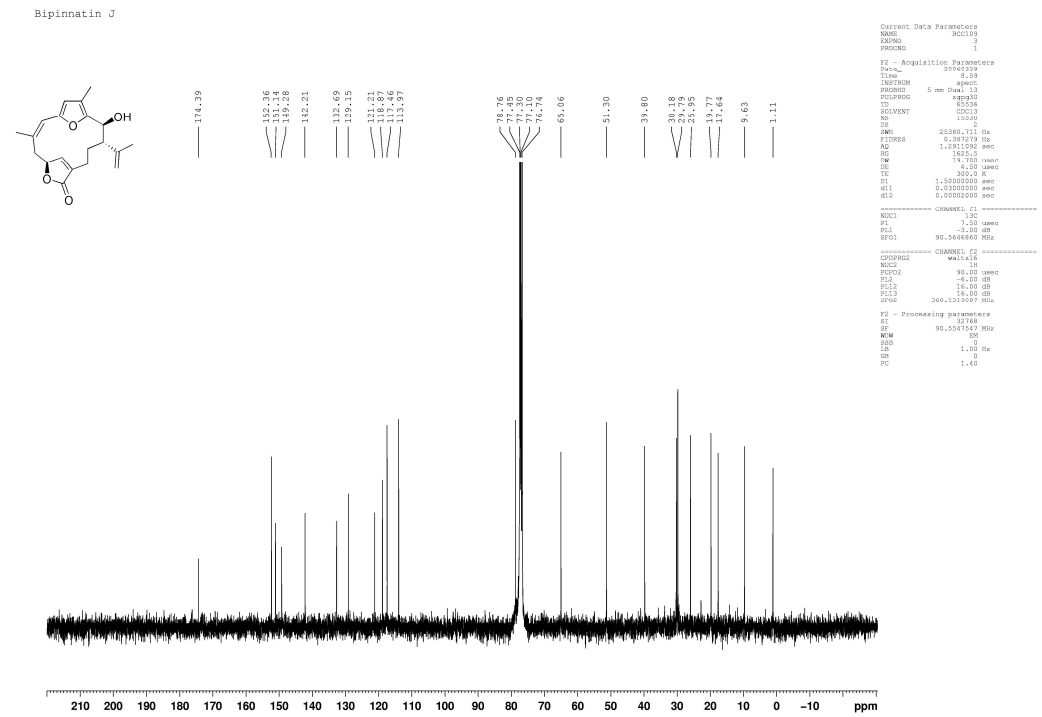




^{1}H-NMR and ^{13}C-NMR Spectra for (-)-Bipinnatin J (4a)





^{1}H-NMR and ^{13}C-NMR Spectra for (+)-Intricarene (1)