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

Bencan Tang, Christopher D. Bray and Gerald Pattenden*

Experimental procedures and data for compounds 15b, 16, 18, 10, 20, 21a and 21b; copies of 1H and 13C 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 CHCl₃CH₂Cl (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 14b¹⁰ (1.93 g, 19.3 mmol) in anhydrous CHCl₃CH₂Cl (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 °C 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 °C 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 °C, 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 (Na₂SO₄) and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with light petroleum (bp 40-60 °C)-ethyl acetate (3:1), to give the vinyl iodide 15a²⁰ as a colourless viscous oil. [α]D²⁵ 2.80 (ε 1.15 CHCl₃); νmax (film)/cm⁻¹ 3373, 1455; δH (360 MHz; CDCl₃) 6.04 (1 H, q, J 1.4, =CH), 3.98 (1 H, dddd, J 1.4, =CC(CH₃)CH₂), 2.38 (1 H, dd, J 5.4 and 13.6, =C(CH₃)CH₂H), 2.01 (2 H, br s, OH and OH), 1.98 (3 H, d, J 1.4, =C(CH₃)H); δC (90 MHz; CDCl₃) 144.2 (s), 77.1 (d), 70.4 (d), 66.5 (t), 42.1 (t), 24.4 (q); HRMS (EI⁺) 241.9816 (M⁺, C₆H₁₁IO₂ 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 °C 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 °C for a further 7 hrs. The mixture was partitioned between DCM (80 ml) and a saturated solution of aqueous NH₄Cl (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 CuSO₄ (to remove most of pyridine), water (3 × 10 ml), and brine (10 ml), then dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with light petroleum (bp 40–60 °C)-diethyl ether (5 : 1), to give the tosylate (1.59 g, 48%), as a colourless oil. [α]D²⁵ -4.62 (ε 1.17, CHCl₃); νmax (sol CHCl₃)/cm⁻¹ 3591, 1359, 874; δH (360 MHz; CDCl₃) 7.81 (2 H, d, J 8.4, PhH), 7.37 (2 H, d, J 8.4, PhH), 6.02 (1 H, q, J 1.4, =CH), 4.10-4.07 (2 H, m, CHHO Ts), 2.46 (3 H, s, PhCCH₃), 2.46-2.33 (2 H, m, =CCH₂), 2.15 (1 H, br, OH), 1.92 (3 H, d, J 1.4, =CCH₂); δC (90 MHz; CDCl₃) 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⁺-H₂O, C₁₇H₁₅IO₃S requires 377.9778); A satisfactory microanalysis could not be secured for this compound.

**((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 × 5 ml) and brine (5 ml), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on florisor, eluting with DCM to give the epoxide (300 mg, 73%) as a colourless liquid. [α]D²⁵ -3.88 (ε 1.03, CHCl₃); νmax (film)/cm⁻¹ 1436, 1401, 848; δH (360 MHz; CDCl₃) 6.04-6.03 (1 H, m, =CHH), 3.03 (1 H, dddd, J 2.6, 3.9, 5.0 and 6.3, OCH₂CH₂), 2.79 (1 H, dd, J 3.9 and 4.9, CHHO), 2.59-2.53 (2 H, m, CHHO and =C(CH₃)CH₂H), 2.45 (1 H, dd, J 6.3 and 14.1, =C(CH₃)CH₂), 2.00 (3 H, d, J 1.4, =CCH₂); δC (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⁺+ C₆H₄IO 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 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 °C under an atmosphere of nitrogen. The mixture was stirred at -78 °C for 20 mins, and then BF₄⁻OEt₂ (1.10 g, 0.96 ml, 7.81 mmol) was added via syringe over 1 min. The mixture was stirred at -78 °C 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 °C for 2 hrs and then warmed up to 0 °C before it was quenched with a saturated solution of aqueous NaHCO₃ (9 ml). The mixture was stirred at -78 °C for 0.5 hr, then 5-(Z)-CH₂C₃H₇ (700 mg, 8.1 %) as a pale yellow liquid.

5-(Z)-3-Iodo-2-methyl-allyl)-3-phenylselenyl-dihydrofuran-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 °C under a nitrogen atmosphere. The mixture was stirred at -78 °C 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 °C 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 °C 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 NH₄Cl (20 ml). The solution was diluted with water (45 ml) and Et₂O (100 ml), and the separated aqueous layer was then extracted with Et₂O (3 × 30 ml). The combined organic layers were then dried (MgSO₄) 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. νmax (film)/cm⁻¹ 1769; δₗH (400 MHz; CDCl₃) 6.99 (1 H, q, J 1.5, ICH=), 4.70 (1 H, app. ddt, J 7.5, 7.5, 6.6 and 5.8, OCH), 2.70-2.49 (4 H, m, =C(CH₃)CH₂), 2.36 (1 H, dddd, J 12.8, 8.9, 6.6 and 5.3, CH₂=CHH), 2.05-1.94 (1 H, m, CH₂=CHH), 1.99 (3 H, d, J 1.5, CH₃); δc (100 MHz; CDCl₃) 175.4 (s), 142.7 (s), 135.9 (2 × d), 129.4 (2 × d), 129.0 (d), 126.8 (s), 78.0 (d), 77.5 (d), 43.8 (t), 28.5 (t), 27.6 (t), 24.8 (q); HRMS (ES⁺) 344.1497 (M + Na⁺, C₁₇H₂₃NO₅Na requires 344.1474).

(S)-3-[(S)-3-Methylene-(2-methyl-furan-2-yl)-methyl]-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 (1.06 g, 5.0 mmol) in anhydrous DCM (20 ml) at -78 °C under an atmosphere of argon. The mixture was stirred at -78 °C for 5 mins, and then Et₃N (0.97 ml, 7.0 mmol) was added dropwise over 3 mins. The mixture was stirred at -78 °C for 1 hr and then at 0 °C for 15 mins. The solution was recooled to -78 °C and then a solution of 3-methylisofurfural (550 mg, 5.0 mmol) in anhydrous DCM (3 ml) was added dropwise over 5 mins. The mixture was stirred at -78 °C for 1 hr, then at 0 °C for 1 hr, and then 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 °C and treated with 5 ml phosphate buffer (pH 7, 5 ml) and 30 % hydrogen peroxide (5 ml). The mixture was stirred at 0 °C 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 NaHCO₃ (10 ml), dried (Na₂SO₄) and evaporated in vacuo.

The residue was purified by chromatography on silica, neutralised with 3 % Et₃N in light petroleum (bp 40-60 °C) (100 ml), eluting with light petroleum (bp 40-60 °C)-ethyl acetate (5 : 1), to give the furanmethanol as a colourless solid (639 mg, 61 %). δₗH (400 MHz; CDCl₃) 7.28 (1 H, d, J 1.8, OCH=CH), 5.27 (1 H, br s, CH₃CC=HH), 5.21-5.18 (3 H, m, CH₃CC=HH), 4.28 (1 H, ddd, J 7.0, 4.7 and 3.9, NCH), 4.15-4.11 (2 H, m, OCH₂), 2.30-2.22 (1 H, m, CH₂(CH₃)₂), 2.19 (1 H, br s, OH), 2.08 (3 H, s, CH₃(CH₃)₂), 1.93 (3 H, dd, J 1.3 and 0.8, CH₂=CHH), 0.87 (3 H, d, J 7.0, CHCH₃), 0.81 (3 H, d, J 7.0, CHCH₃); δc (100 MHz; CDCl₃) 170.8 (s), 153.2 (s), 148.5 (s), 141.4 (d), 140.2 (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).
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 (Na2SO4), and then concentrated in vacuo. The residue was purified by chromatography on silica, eluting with light petroleum (bp 40-60 °C)-ethyl acetate (5 : 1), to give the 1, 3-diol (22 mg, 42 % over 2 steps) as an oil. δH (360 MHz; CDCl3) 7.33 (1 H, d, J 1.8, OC=CH), 6.21 (1 H, d, J 1.8, OCH=CH), 5.16-5.15 (1 H, m, CH 3C=CH), 4.75 (1 H, d, J 9.3, CHOH), 3.46-3.38 (2 H, m, OHCH₂), 2.97-2.90 (1 H, m, CH(OH)CH), 2.05 (3 H, s, CH₃), 1.84 (3 H, app. dd, J 1.4 and 0.8, CH₂=CCCH₃); δC (100 MHz; CDCl₃) 148.5 (s), 143.0 (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+, C11H16O3Na 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 NaHCO₃ (2 ml). The separated organic layer was dried (Na2SO4) 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 the mono-tosylate (6 mg, 49 % based on the recovery of the starting material) as an oil. δH (400 MHz; CDCl₃) 7.73-7.71 (2 H, m, PhH), 7.34-7.32 (2 H, m, PhH), 7.26 (1 H, br s, OCH=CH), 6.18 (1 H, br s, OCH=CH), 5.05-5.04 (1 H, br s, CH₂=C=CHH), 4.92-4.91 (1 H, m, CH₂=C=CH₂), 4.77-4.67 (1 H, m, CHOH), 3.94-3.85 (2 H, m, TsOCH₂), 2.99-2.94 (1 H, m, CH(OH)CH), 2.46 (3 H, s, Ph-CH₃), 2.06 (1 H, br s, OH), 2.01 (3 H, s, CCH₃), 1.69-1.68 (3 H, br s, CH₂=CCCH₃); δC (100 MHz; CDCl₃) 147.5 (s), 144.7 (s), 141.6 (d), 141.3 (s), 132.8 (s), 129.8 (2 x d), 127.9 (2 x 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
$^1$H-NMR and $^{13}$C-NMR Spectra for Furan butenolide 28b
$^1$H-NMR and $^{13}$C-NMR Spectra for (-)-Bipinnatin J (4a)
\(^1\)H-NMR and \(^{13}\)C-NMR Spectra for (+)-Intricarene (1)