Transition Metal Mediated Synthesis of (±)-Chuangxinmycin Methyl Ester

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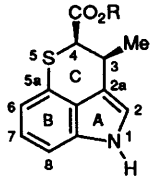
Chromium mediated synthesis of 4-iodo-1-triisopropylsilylindole followed by 4-methoxycarbonylmethylthiation by palladium catalysed cross coupling with methoxycarbonylmethylthio(trialkyl)stannane and aldol condensation gave the key α-thioacrylate intermediate **5**. The *Z*-geometry of the major isomer of **5** was determined by X-ray crystal analysis. Closure of ring C by a novel fluoride ion catalysed formation of the 2a–3 bond completed a short synthesis of (±)-chuangxinmycin methyl ester **1** (R = Me).

Chuangxinmycin **1**, (R = H) is a broad spectrum antibiotic isolated from *Actinoplanes jinanensis*, a soil microorganism first described from China in 1976.[1] It has been used in China for the treatment of *Escherischia coli* infections and appears to block or inhibit the tryptophan biosynthetic pathway in that organism.[1]



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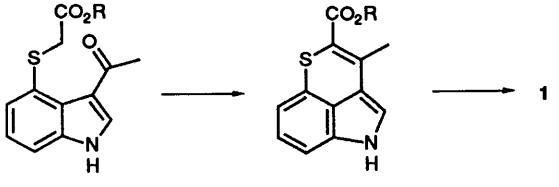
The structure **1** (R = H) was determined by spectroscopic[2] and synthetic[3] means. A number of syntheses of **1**, complete or formal, have been reported[3] all of which construct the system by the introduction, in various ways, of C_2 and C_2S units at C-3 and C-4 respectively of the indole nucleus with subsequent closure of ring C (Scheme 1).

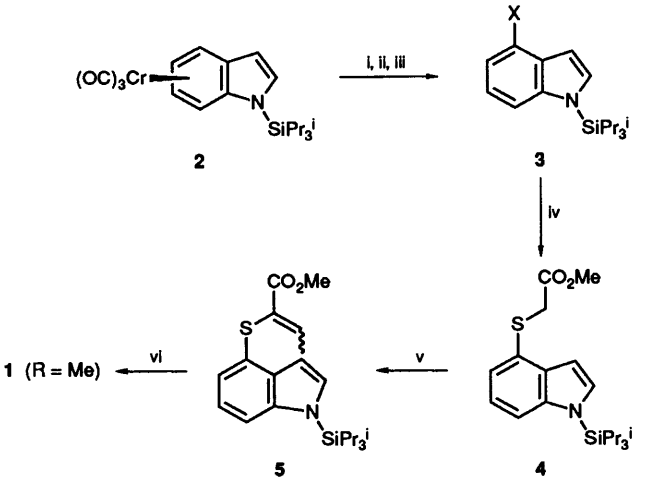


Scheme 1

As a part of our interest in the chromium mediated 4-functionalisation of indoles,[4] we were intrigued by the possibility of introducting the ring C fragment of chuangxinmycin at C-4 of the indole nucleus and completing the ring C formation by a novel C(2a)–C(3) (chuangxinmycin numbering) bond formation to give directly the target molecule (Scheme 2). We now report the realisation of that strategy.

4-Iodo-1-triisopropylsilylindole **3** (X = I) has been prepared previously[4] by lithiation/iodination of 1-triisopropylsilylindole-(tricarbonyl)chromium(0) **2** but, in practice, we found it more convenient to use the more efficient stannylation, decomplexation, iodination sequence (overall yield, 65%) given in Scheme 2.

The 4-iodoindole **3** (R = I) was coupled with methoxycarbonylmethylenethiotrimethylstannyl under palladium(0) catalysis[5] to give the 4-thiated indole[4] (98%). Deprotonation of **4** with LDA and reaction with acetaldehyde gave an 18:1 *E*/*Z* mixture of the condensation products **5**. The identity of the major isomer was determined (as *Z*) by a single crystal X-ray analysis†[6] (Fig. 1 and Table 1).



Scheme 2 *Reagents and conditions:* i, BuLi, Me_3SnCl, −78 °C, THF; ii, py/heat; iii, I_2, CCl_4, 0 °C; iv, $Me_3SnSCH_2CO_2Me$, $Pd(PPh_3)_4$, reflux 8h; v, LDA, MeCHO, −78 °C; vi, TBAF, THF, heat

Of note for the proposed cyclisation step is that, in the solid state, the butenoate unit conformation is *anti*- to the pyrrolic ring and perpendicular to the heteroaromatic system. Nevertheless, we considered that treatment of **5** with fluoride ion would liberate the indol-1-yl anion by desilylation and Michael addition of the ambident C-3 anion to the powerful α-thioacrylate acceptor could bring about the required cyclisation. The presence of the sulfur atom should obviate any stereoelectronic problems involved with the cyclisation.[6] After much experimentation, cyclisation of **5** was brought about by refluxing the *Z*/*E*-isomeric mixture with 1 mol dm^{-3} TBAF in 5% aqueous THF for 140 min. This gave a 2:1 mixture of *anti*- to *syn*- isomers of the racemic target molecule (28%). These were separated by HPLC to give the pure (±)-chuangxinmycin methyl ester **1** (R = Me), spectroscopically identical[2] with the reported material.

Under the reaction conditions used for ring closure, the *syn*-/*anti*-ratio may be expected to represent the thermodynamic equilibrium proportions of the two isomers of **1**. Methods to shift the equilibrium in favour of the *syn*-isomer are under investigation.

† Bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, See Instructions for Authors (1992), *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1.

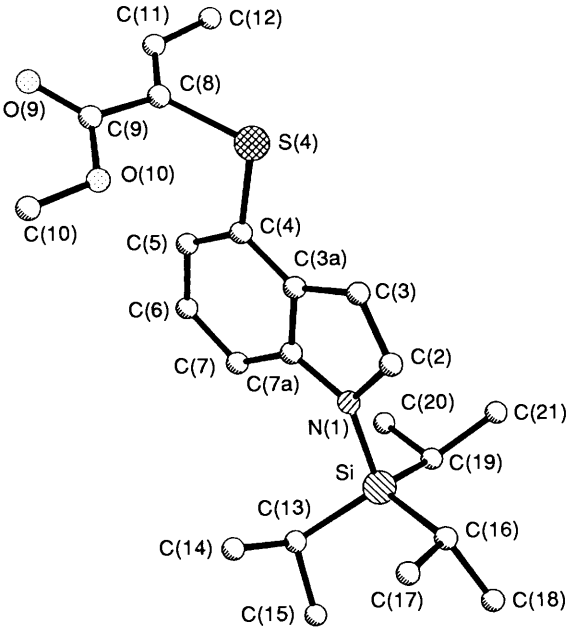


Fig. 1

Table 1 Atom coordinates (× 104) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	2 811(8)	3 844(4)	2 231(3)
C(2)	2 932(11)	2 884(6)	2 369(4)
C(3)	4 356(10)	2 702(5)	2 857(4)
C(3a)	5 166(10)	3 550(5)	3 041(4)
C(4)	6 642(10)	3 807(6)	3 499(4)
S(4)	7 901(4)	2 896(2)	3 922(1)
C(5)	7 136(11)	4 725(6)	3 579(4)
C(6)	6 136(11)	5 395(6)	3 192(4)
C(7)	4 670(10)	5 177(6)	2 720(4)
C(7a)	4 213(9)	4 249(5)	2 647(3)
C(8)	9 279(15)	3 472(7)	4 609(5)
C(9)	8 497(16)	3 702(7)	5 188(6)
O(9)	9 332(12)	3 960(7)	5 702(4)
O(10)	6 845(11)	3 645(5)	5 098(4)
C(10)	6 006(17)	3 894(9)	5 630(6)
C(11)	10 882(14)	3 612(8)	4 616(6)
C(12)	11 976(18)	3 464(8)	4 096(6)
Si	1 278(3)	4 322(2)	1 567(1)
C(13)	609(10	5 485(6)	1 841(4)
C(14)	235(13)	5 509(7)	2 542(6)
C(15)	−871(12)	5 890(6)	1 350(6)
C(16)	−509(10)	3 459(7)	1 387(4)
C(17)	−1 568(12)	3 334(7)	1 936(5)
C(18)	−1 715(12)	3 642(7)	713(5)
C(19)	2 378(10)	4 435(7)	819(4)
C(20)	3 822(12)	5 142(7)	927(4)
C(21)	3 002(13)	3 530(8)	617(5)

Experimental

General materials and techniques were as previously described.[4] Compounds or methods not previously described in full are given below. *J* Values are recorded in Hz.

1-*Triisopropylsilyl*-4-*trimethylstannylindole* **3** (X = $SnMe_3$).—Tricarbonyl, η^6-(1-triisopropylsilyl-4-trimethylstannylindole)chromium(0) (2.92 g, 5 mmol)[4] was dissolved in dry pyridine (10 ml) and the solution degassed and set to reflux under nitrogen for 2 h. The resulting liquid was allowed to cool to room temperature before ether (10 ml) was added and the red precipitate which formed was filtered off. The solvents were then removed by azeotropic distillation with toluene under reduced pressure and the yellow residual oil was purified by flash column chromatography (FCC) [adsorbent: alumina; eluent: light petroleum (b.p. 40–60 °C)] to give the *stannylindole* **3** (X = $SnMe_3$) as a white, waxy solid (2.11 g, 4.8 mmol, 95%), m.p. 51–54 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 2948, 2869 and 1466; $\delta_H(CDCl_3)$ 0.40 (9 H, s + dd, $J^{119}Sn-H$ 55, $J^{117}Sn-H$ 53), 1.17 (18 H, d, *J* 7.6), 1.73 (3 H, sept, *J* 7.6), 6.62 (1 H, dd, *J* 3.2, 0.7), 7.15 (1 H, dd, *J* 15.2, 8.3), 7.26 (1 H, dd, *J* 7.8, 1.2), 7.30 (1 H, d, *J* 3.4), 7.52 (1 H, dt, *J* 8.3, 1.0); $\delta_C(CDCl_3)$ −8.9 (d. $J^{119}Sn-C$ 346, d, $J^{117}Sn-C$ 330), 13.0 (d, $J^{29}Si-C$ 59), 18.3, 106,6, 114.2 (d, J_{Sn-C} 10), 121.0 (d, J_{Sn-C} 51), 127.6 (d. J_{Sn-C} 53), 131.2, 133.5, 137.9 and 139.4; *m/z* 437 (M^+ [^{120}Sn], 26%) 422 (84), 420 (63), 273 (40), 230 (79), 71 (56) and 57 (100) (Found: C, 55.01; H, 8.10; N, 2.96. $C_{20}H_{35}NSiSn$ requires C, 55.06; H, 8.09; N 3.21%).

4-*Iodo*-1-*triisopropylsilylindole* **3** (X = I).—1-Triisopropylsilyl-4-trimethylstannylindole (2.11 g, 4.8 mmol) in stirred carbon tetrachloride (30 ml) at 0 °C was treated, *via* a syringe, with a solution of iodine in carbon tetrachloride until a pink colouration persisted in the reaction mixture. This was then washed with 1 mol dm^{-3} aqueous sodium thiosulfate (25 ml) and water (25 ml). The aqueous layers were extracted with ether (2 × 15 ml) and the combined organic layers were dried before removal of the solvents to give the 4-*iodoindole* **3** (X = 1) (1.91 g, 4.8 mmol, 99%) as a white solid, m.p. 50–53 °C; $\nu_{max}(CCl_4)/cm^{-1}$ 2951, 2871, 1466 and 1417; $\delta_H(CDCl_3)$ 1.15 (18 H, d, *J* 9.6), 1.69 (3 H, sept, *J* 9.6), 6.57 (1 H, dd, *J* 3.2, 0.8), 6,87 (1 H, dd, *J* 8.2, 77), 7.30 (1 H, d, *J* 3.2), 7.47 (1 H, d, *J* 8.3), 7.51 (1 H, dd, *J* 7.7, 0.5); $\delta_C(CDCl_3)$ 12.8 (d, $J^{29}Si-C$ 59), 18.1, 87.3, 108.5, 113.9, 122.7, 129.4, 131.5, 135.9 and 139.7; *m/z* 399 (M^+, 100%), 400 (42), 356 (44), 230 (12), 229 (42), 150 (16) and 149 (14) (Found: C, 51.4; H, 6.65; N, 3.6. $C_{17}H_{26}INSi$ requires C, 51.12; H, 6.56; N, 3.51%).

4-*Methoxycarbonylmethylthio*-1-*triisopropylsilylindole* **4**.—Methoxycarbonylmethylthiotrimethylstannane[5] (0.37 ml, 0.538 g, 2 mmol), 4-iodo-1-triisopropylsilylindole **3** (X = 1) (0.701 g, 1.76 mmol) and tetrakistriphenylphosphinepalladium(0) (0.197 g, 0.017 mmol, 9.7 mol%) in toluene (40 ml) were heated to reflux under a nitrogen atmosphere until reaction was complete (tlc assay, 8 h). 10% Aqueous potassium fluoride and ether were added, the layers separated and the aqueous phase was washed with ether (3 × 20 ml). The combined organic phases were washed with 10% aqueous potassium fluoride (2 × 20 ml) and water (20 ml), dried ($MgSO_4$) and evaporated. The residue was purified by FCC over silica gel (eluent: light petroleum–ether, 95 : 5) to give the *indole* **4** as a colourless oil (0.652 g, 1.73 mmol, 98%) which turned yellow on exposure to air; ν_{max}(film)/cm^{-1} 2948, 2868, 1741, 1467 and 1417; $\delta_H(CDCl_3)$ 1.14 (18 H, d, *J* 7.6), 1.70 (3 H, sept, *J* 7.6), 3,67 (3 H, s), 3.73 (2 H, s), 6.80 (1 H, dd, *J* 3.2, 0.7), 7.10 (1 H, dd, *J* 8.3, 7.6), 7.21 (1 H, dd, *J* 7.3, 0.8), 7.30 (1 H, d, *J* 3.2) and 7.44 (1 H, d, *J* 8.3); $\delta_C(CDCl_3)$ 12.8, 18.1, 36.4, 42.4, 103.8, 113.5, 121.8, 122.4, 125.4, 131.7, 132.5, 140.6 and 170.6; *m/z* 377 (M^+, 100%), 378 (28), 59 (24), 145 (23), 292 (20), 123 (16), 379 (12) and 73 (10) (Found: C, 63.75; H, 8.3; N, 3.55; S, 8.35. $C_{20}H_{31}NO_2SSi$ requires C, 63.61; H, 8.27; N, 3.71; S, 8.49%).

4-[1-*Methoxycarbonyl*(Z)-*propenylthio*]-1-*triisopropylsilylindole* **5**.—LDA (0.5 mol dm^{-3}; 10.4 ml, 5.15 mmol) was added, *via* a syringe, to a cooled (solid CO_2–acetone) THF solution (20 ml) of 4-methoxycarbonylmethylthio-1-triisopropylsilylindole (0.97 g, 2.58 mmol) under nitrogen. The solution was stirred for 4 h before it was added dropwise, over a period of 5 min., and cooled *via* a syringe, to a stirred (solid CO_2–acetone) THF solution (5 ml) of acetaldehyde (0.73 ml, 0.58 g, 13.06 mmol). This solution was then stirred for 6 h before it was allowed to warm to room

temperature overnight. The reaction mixture was treated with 15% aqueous NH_4Cl (25 ml) and ether (20 ml) and the aqueous washings were extracted with ether (2 × 10 ml). The combined organic phases were dried and absorbed onto silica before separation of the components by FCC [silica; light petroleum (b.p. 40–60 °C) ether] to give the (*Z*)-*butenoate ester* **5** as white needles (0.53 g, 1.31 mmol, 51%), m.p. 98–99.5 °C (from MeOH); $\nu_{max}(CCl_4)/cm^{-1}$ 2950, 2870, 1717, 1468 and 1417; $\delta_H(CDCl_3)$ 1.19 (18 H, d, *J* 7.6), 1.38 (3 H, sept, *J* 7.6, 2.15, (3 H, d, *J* 7.0), 3.65 (3 H, s), 6.80 (1 H, dd, *J* 3.4, 0.9), 6.95 (1 H, dd, *J* 7.3, 0.6), 7.08 (1 H, t, *J* 7.8, 7.32 (1 H, d, *J* 3.4), 7.40 (1 H, d, *J* 8.2) and 7.52 (1 H, q, *J* 7.0); $\delta_C(CDCl_3)$ 12.8 (d, J^{29}Si–C 61), 16.7, 18.1, 52.3, 103.6, 112.3, 119.7, 121.6, 126.1, 127.7, 130.9, 131.2, 140.7, 147.6 and 166.3; *m/z* 403 (M^+, 100%), 405 (14), 404 (30), 391 (17), 388 (18), 145 (12), 73 (13) and 59 (35) (Found: C, 65.65; H, 8.4; N, 3.45; S, 7.9. $C_{22}H_{33}NO_2SSi$ requires C, 65.46; H, 8.24; N, 3.47; S, 7.94%).

Crystal Data.—$C_{22}H_{33}NO_2SSi$, *M* = 403.7, monoclinic, *a* = 7.882(2), *b* = 14.536(4), *c* = 20.337(5) Å, β = 100.64(2)°, *V* = 1328 Å^3, space group $P2_1/c$, *Z* = 4, D_c = 1.17 g cm^{-3}, Cu radiation, λ = 1.54178 Å, μ(Cu-Kα) = 19 cm^{-1}, *F*(000) = 872. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromater) using ω-scans. 2880 Independent reflections were measured (20 ≤ 110 °), of which 2279 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The non-hydrogen atoms were refined anisotropically. The leading protons on the methyl groups on the sp^2 centres were located from a Δ*F* map. The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, assigned isotropic thermal parameters, *U*(H) = $1.2U_{eq}$(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to *R* = 0.104, R_w = 0.109 [$w^{-1} = \sigma^2(F) + 0.00050F^2$]. The maximum and minimum residual electron densities in the final Δ*F* map were 1.17 and −0.52 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.001 and 0.008 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

Also formed was the (*E*)-butenoate ester (0.03 g, 0.07 mmol, 3%); $\delta_H(CDCl_3)$ 1.14 (18 H, d, *J* 7.4), 1.69 (3 H, sept, *J* 7.4), 2.03 (3 H, d, *J* 7.0), 3.68 (3 H, s), 6.28 (1 H, q, *J* 7.4), 6.74 (1 H, dd, *J* 3.0, 0.9), 7.08 (1 H, t, *J* 7.4), 7.12 (1 H, dd, *J* 7.4, 1.7), 7.27 (1 H, d, *J* 3.0) and 7.43 (1 H , ddd, *J* 7.4, 1.7, 0.9); $\delta_C(CDCl_3)$ 12.9, 16.8, 18.2, 52.1, 104.1, 113.7, 121.7, 121.8, 123.4, 124.4, 127.2, 131.8, 141.2 and 147.6.

(±)-*Chuangxinmycin Methyl Ester* **1** (R = Me) *and its* trans-*Isomer.*—Tetrabutylammonium fluoride (1.0 mol dm^{-3} in THF, ≈ 5 wt% H_2O; 0.10 ml, 0.1 mmol) was added at room temperature to a stirred THF (2 cm^3) solution of 4-[1-methoxycarbonyl-(*Z*)-propenylthio]-1-triisopropylsilylindole (0.039 g, 0.01 mmol) under nitrogen. The solution turned yellow. Upon heating it darkened to orange and then, just before reflux, a red colour formed. After 140 min at reflux a faint black precipitate had formed and the solution was allowed to cool before it was washed with a 1:2 mixture of 15% aqueous NH_4Cl and ether (8 ml). The aqueous layer was washed with ether (2 × 5 ml) and the combined organic layers were dried before the solvents were removed to give a brown oil. FCC (silica, 1:1 ether–petroleum) gave a 1:2 mixture of chuangxinmycin and its *trans*-isomer respectively (7 mg, 28%). The components were separated by HPLC (Dynamax macro-HPLC, SiO_2, 8 μm, 250 × 22 mm; 1:1 hexane–dichloromethane); first eluted was (±)-chuangxinmycin methyl ester **1** (R = Me), m.p. 146–147 °C (CH_2Cl_2–hexane) (lit.,[1,3] 145–146 °C); $\nu_{max}(CCl_4)/cm^{-1}$ 3488, 2955, 2928, 1745, 1584 and 1435; $\delta_H(CDCl_3)$ 1.37 (3 H, d, *J* 6.8), 3.75 (4 H, s + m), 4.20 (1 H, d, *J* 3.7), 6.95 (1 H, dd, *J* 5.3, 2.8), 6.99 (1 H, dd, *J* 2.3, 0.9), 7.13 (1 H, d, *J* 5.4), 7.13 (1 H, d, *J* 2.9), 8.00 (1 H, br s); *m/z* 247 (M^+, 100%), 248 (16), 188 (47), 187 (53), 174 (36), 173 (63) and 87 (13) (Found: 247.0667. Calc. for $C_{13}H_{13}NO_2S$; M^+, 247.0667).

The second eluate gave the *trans* isomer; $\nu_{max}(CCl_4)/cm^{-1}$ 3487, 2953, 1744, 1585 and 1434; $\delta_H(CDCl_3)$ 1.42 (3 H, d, *J* 6.8), 3.61 (1 H, d quintet, *J* 6.8, 1.0), 3.74 (3 H, s), 3.75 (1 H, d, *J* 7.5), 6.94 (1 H, dd, *J* 5.9, 2.0), 7.01 (1 H, dd, *J* 2.0, 1.0 H), 7.12 (1 H, d, *J* 5.9), 7.13 (1 H, d, *J* 2.0) and 8.02 (1 H, br s); *m/z* 247 (M^+, 100%), 248 (16), 188 (48), 187 (67), 186 (17), 174 (39), 173 (55) and 87 (13) (Found: M^+, 247.0667. Calc. for $C_{13}H_{13}NO_2S$; M^+, 247.0667).

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