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New Total Synthesis of (±)-Chuangxinmycin

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Summary: (±)-4'-Iodoindolmycenate **6** was stereoselectively converted into the (±)-(2,3)-*syn*-2-thioacetoxy ester **16** with retention of C_2-stereochemistry in (±)-**6**. Palladium-catalysed cyclisation of indolyl iodide and the internal C_2 thiol group of the substrate (±)-**17** derived from (±)-**16** gave the (±)-*cis* methyl ester **2** of natural chuangxinmycin (**1**).

Chuangxinmycin (**1**), isolated from *Actinoplanes tsinanensis* n. sp. in China, exhibits *in vitro* an antibacterial spectrum that includes a number of Gram-positive and Gram-negative bacteria. This material was reported to be active in mice against *Escherichia coli* and *Shigella dysenteria* infections *in vivo*, and effective in the treatment of septicaemia, urinary, and biliary infections caused by *E. coli* in preliminary clinical results.[1]

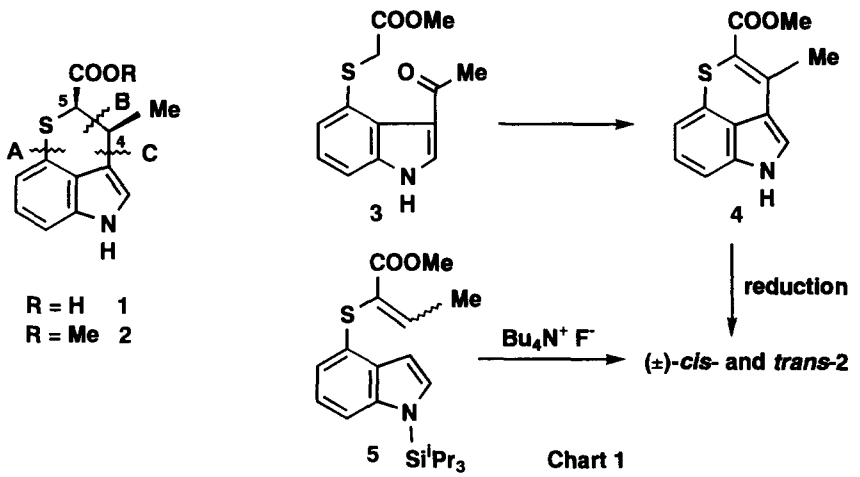


Chart 1

The relative structure of **1** was confirmed by synthesis[2,3] and the absolute configurations were determined as 4*S*, 5*R* based on the degradation study of the natural product (**1**)[4] and optical resolution of (±)-**1** with *S*-(-)-α-phenylethyl amine.[5] Synthetic attempts were made using two published routes. One is an internal Knoevenagel condensation of 4-substituted-3-acetyl indole **3** and the subsequent reduction of **4** to give a mixture of (±)-*cis*-methyl ester **2** of **1** and *trans*-**2** *via* pathway B.[2] In the other route treatment of **5** with fluoride ion liberated 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 *via* pathway C.[3] (chart 1) But these routes were found to be unacceptable for the synthesis of the desirable optically active form of **1**. We now report a highly stereoselective synthesis of (±)-**1** *via* pathway A directed toward chiral synthesis starting with the requisite **6** possessing two definite absolute configurations at the C_2- and C_3-positions. The synthesis of indolmycenate (**7**), being an important intermediate for the synthesis of indolmycin[6], was achieved by the reaction of indole and (±)-*trans*-

(2,3)-epoxy butanoate **9**[7] in the presence of $SnCl_4$ along with nucleophilic displacement with inversion at the C-3 carbon of the coordinated epoxide.[8] This strategy appeared to be the most promising from a stereochemical standpoint for the stereoselective construction of C_2- and C_3-configurations of **6** by the reaction of 4-iodoindole **8** and (±)-**9** in the presence of $SnCl_4$. (chart 2)

By applying the reported procedure,[9] 4-nitroindole **12** was synthesized from 2-amino-6-nitrotoluene **10** *via* imidate ester **11** in 69% overall yield. Conversion of **12** into the desired 4-iodoindole **8** was carried out by the

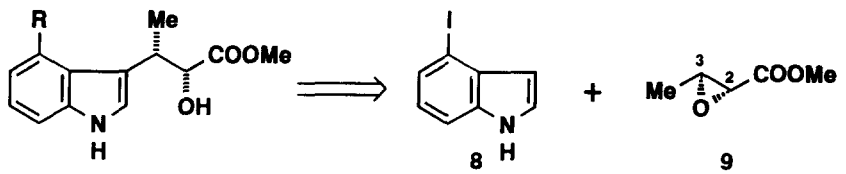
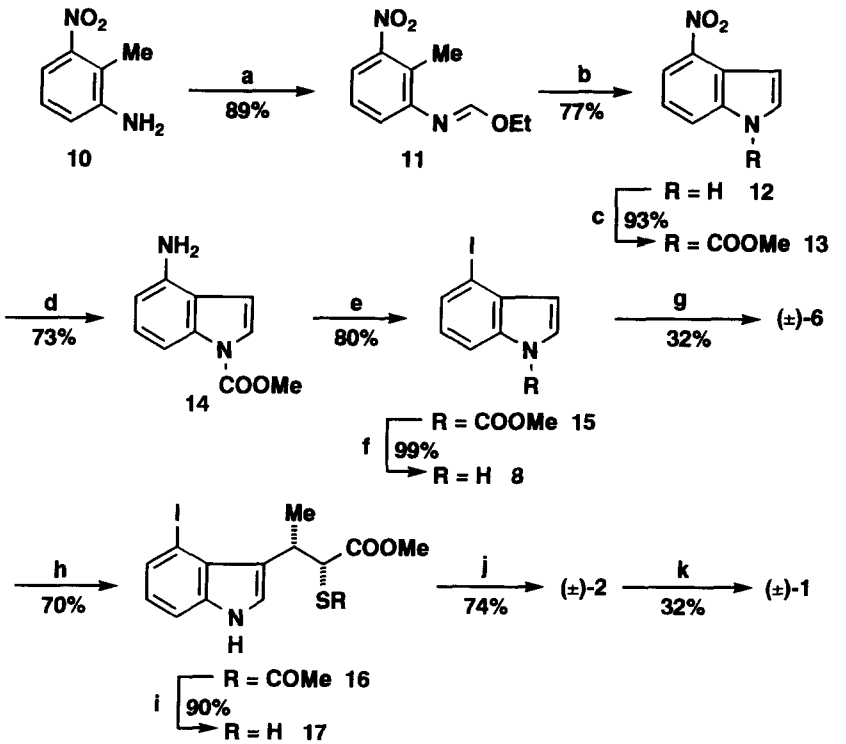


Chart 2



a; $CH(OEt)_3$/p-TsOH b; $(COOEt)_2$/KOEt c; NaH/ClCOOMe
d; H_2/20% $Pd(OH)_2$-C e; $NaNO_2$-H^+/KI f; NaOMe/MeOH
g; 8/$SnCl_4$ h; 1) MsCl/pyridine 2) CsSAc i; K_2CO_3/MeOH
j; $Pd(PPh_3)_4/Et_3N$ k; NaOH/EtOH-H_2O

Chart 3

reported procedure[10] as shown in chart 3. Protection (**13**; 93% yield) of the nitrogen group of **12** as a methoxy carbonyl group followed by catalytic hydrogenation gave 4-amino indole derivative **14** (73% yield). Diazotization of **14** with sodium nitrite and hydrogen chloride and subsequent treatment of KI afforded 4-iodoindole derivative **15** (80% yield), which was converted into the desired 4-iodoindole **8** (99% yield) by hydrolysis. The reaction of **8** and (±)-**9** in the presence of $SnCl_4$ afforded (±)-4'-iodoindolmycenate **6** (32% yield)[11] along with 4-iodoindole dimer (11% yield) and (±)-(2,3)-*anti*-3-chloro-2-hydroxy butanoate (52% yield). Treatment of (±)-**6** with MsCl in pyridine followed by treatment with CsSAc[12] gave the desired (±)-(2,3)-*syn*-2-thioacetoxy ester **16** in 70% overall yield with complete retention of C_2-stereochemistry. Deacetylation of (±)-**16** with K_2CO_3 in MeOH followed by treatment with $Pd(PPh_3)_4$[13] in the presence of Et_3N afforded the (±)-*cis* methyl ester **2** in 67% overall yield, whose spectral data (mp 147-148 °C, IR, NMR) were identical with those (mp 145-146 °C[2c]) of the reported (±)-**2**. An alkaline hydrolysis of (±)-**2** was carried out by the reported procedure[2c] to provide the racemic form of **1** (mp 189-190 °C), which is consistent with the reported (±)-**1** (mp 190-191 °C,[2d] 186-187 °C[2f]).

As shown in chart 4, it is proposed that neighbouring-group participation involving the electron-rich C-3 of the indole ring accounts for the stereoselective conversion of (±)-**6** to (±)-**16**. The preferred conformation of the mesylate **18**[14] derived from (±)-**6**, in which steric interactions are minimized, is shown in **18**. In this rotamer, the mesyloxy group is *trans* to the indol C-3, so that ready displacement can occur. Nucleophilic attack by the thioacetoxy ion takes place at the C_2-position because the charge in the cyclopropylium ion intermediate is still predominantly centered on the C-2 carbon atom.[15] Since this is essentially a double S_N2 mechanism, the *syn*-stereochemistry of the (±)-*syn*-2-hydroxy ester **6** is retained in the (±)-*syn*-2-thioacetoxy ester **16**.

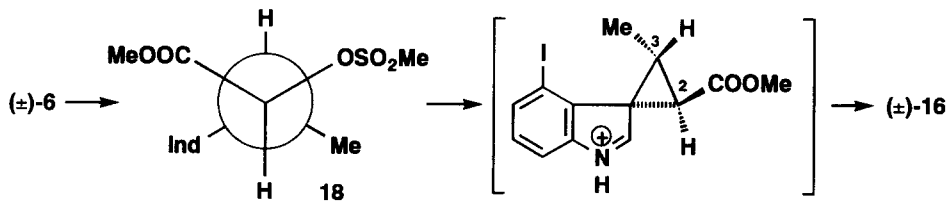


Chart 4

According to the reported synthesis of (±)-**2** *via* pathway B, catalytic hydrogenation of (±)-**4** gave the 40% yield of (±)-**2**[2c], while chemical reduction of (±)-**4** afforded a mixture of (±)-*cis*- and -*trans*-**2**.[2d,2f] It is of important significance in the present synthesis *via* pathway A that palladium-catalysed coupling of the thiolate ion itself without derivation into thiostannanes can proceed to the cyclization without isomerization at the C_5-position in high yield.

In conclusion, (±)-4-iodoindolmycenate **6** obtained by the reaction of 4-iodoindole **8** and (±)-*trans*-(2,3)-epoxy butanoate **9** in the presence of $SnCl_4$, was stereoselectively converted into the (±)-(2,3)-*syn*-4'-iodo-2-thioindolmycenate **16**, which is treated with $Pd(PPh_3)_4$ in the presence of Et_3N to afford the (±)-methyl ester **2** of natural chuangxinmycin (**1**).

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11. Satisfactory analytical data were obtained for all new compounds.
    6: mp 121-122°C (benzene); IR (KBr) 3330, 1729, 1290cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (1H, br s, NH), 7.60 (1H, d, *J*= 7.8 Hz, 5'-H), 7.31 (1H, d, *J*= 7.8 Hz, 7'-H), 7.26 (1H, d, *J*= 4.0 Hz, 2'-H), 6.83 (1H, t, *J*= 7.8, 6'-H), 4.68 (1H, dd, *J*= 4.9, 2.7 Hz, 2-H), 4.61 (1H, dq, *J*= 6.8, 2.7 Hz, 3-H), 3.87 (3H, s, OMe), 2.81 (1H, d, *J*= 4.9 Hz, OH), 1.26 (3H, d, *J*= 6.8 Hz, Me). **16**: Ms *m/z* (FAB) 418 (M^++1); IR (KBr) 3358, 1728, 1660cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (1H, br s, NH), 7.61 (1H, d, *J*= 7.8 Hz, 5'-H), 7.31(1H, d, *J*= 7.8 Hz, 7'-H), 7.21 (1H, s, 2'-H), 6.84 (1H, t, *J*= 7.8, 6'-H), 4.78 (1H, d, *J*= 7.0 Hz, 2-H), 4.73 (1H, dq, *J*= 7.0, 6.8 Hz, 3-H), 3.64 (3H, s, OMe), 2.29 (3H, s, COMe), 1.38 (3H, d, *J*= 6.8 Hz, Me). **17**: Ms *m/z* (FAB) 376 (M^++1); IR (KBr) 3382, 2561, 1723cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, br s, NH), 7.61 (1H, d, *J*= 7.3 Hz, 5'-H), 7.34 (1H, d, *J*= 7.3 Hz, 7'-H), 7.20 (1H, d, *J*= 2.4 Hz, 2'-H), 6.86 (1H, t, *J*= 7.3, 6'-H), 4.65 (1H, dq, *J*= 6.8, 6.3 Hz, 3-H), 4.05 (1H, dd, *J*= 8.3, 6.3 Hz, 2-H), 3.69 (3H, s, OMe), 1.83 (1H, d, *J*= 8.3 Hz, SH), 1.45 (3H, d, *J*= 6.8 Hz, Me).
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14. An intermedinary mesylate **18** was obtained as crystals. **18**: mp 118-119°C (decomp.) (benzene); IR (KBr) 3397, 1751, 1357, 1178cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, br s, NH), 7.62 (1H, d, *J*= 7.8 Hz, 5'-H), 7.34 (1H, d, *J*= 7.8 Hz, 7'-H), 7.30 (1H, s, 2'-H), 6.86 (1H, t, *J*= 7.8, 6'-H), 5.43 (1H, d, *J*= 2.9 Hz, 2-H), 4.90 (1H, dq, *J*= 6.8, 2.9 Hz, 3-H), 3.87 (3H, s, OMe), 2.75 (3H, s, SO_2Me), 1.39 (3H, d, *J*= 6.8 Hz, Me).
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