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Total Synthesis of (±) Indolmycin

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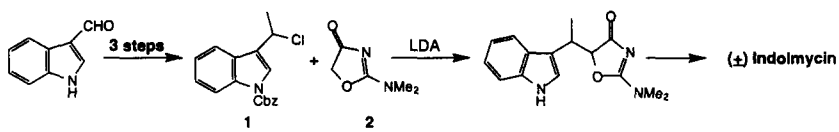
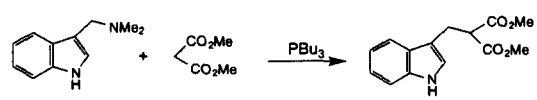
Abstract: A practical and short synthesis of a novel antibiotic, (±) indolmycin, has been accomplished. The overall process requires only 4 chemical steps by starting from gramine derivative **3** and oxazolinone **2**. Copyright © 1996 Elsevier Science Ltd

Indolmycin, an antibiotic produced by *Streptomyces griseus*,[2] inhibits prokaryotic tryptophanyl tRNA synthetase (TrpRS) with relatively weak inhibition of the corresponding eukaryotic enzyme.[3] This antibiotic is active against drug resistant *Staphylococci*.[4] Competition experiments in *Staphylococcus aureus* and *Bacillus subtilis* suggest that indolmycin is transported into bacterial cells by the tryptophan uptake system.[5] It is interesting to note that indolmycin is also active against *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* with MICs ranging from 31 to 250 μg/ml for the former and from 6 to 16 μg/ml for the latter.[6]

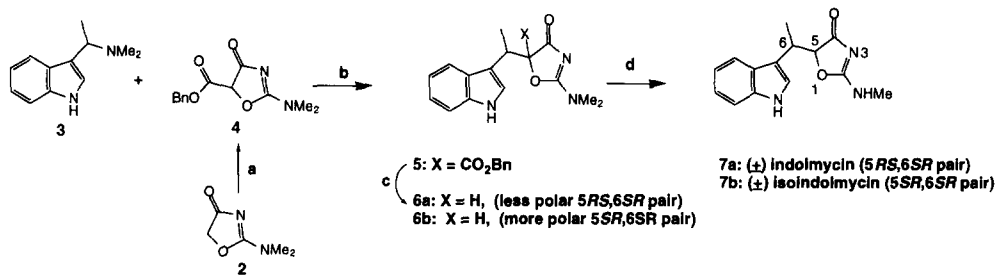
The reported synthesis of (±) indolmycin[6] gave low yield of the oxazolinone ring at the final step of synthesis. A convergent synthesis of (±) indolmycin[7] that circumvented the low yield step of the previous synthesis proceeded through alkylation of N-protected 3-(1-chloroethyl) indole **1** with the anion of oxazolinone **2**.[7] An asymmetric synthesis of indolmycin was reported by Takeda and Mukaiyama but required 14 chemical steps.[8]



A strategy analogous to that of Dirlam's synthesis, ultilizing the gramine alkylation protocol developed by Somei[9] can yield a more efficient route by allowing the construction of the indolmycin skeleton without the need for indole ring protection. This turned out to be the case and here is the account of our results.



The gramine derivative, 3-(1-*N,N*-dimethylethyl) indole **3** was prepared according to the literature procedure.[10] The prerequisite α-carbobenzyloxy oxazolinone **4** was prepared from 2-(dimethylamino)-4-(5*H*)-oxazolinone **2**[7] and benzyl cyanoformate. As expected, alkylation of 3-(1-*N,N*-dimethylethyl) indole **3** with α-carbobenzyloxy oxazolinone **4** proceeded smoothly (acetonitrile/reflux/4 h) to give **5** in quantitative yield. Hydrogenation (H_2 baloon/10% Pd/C/EtOH) and decarboxylation (EtOH/reflux/30 min.) gave **6**, a precursor to Dirlam's synthesis of (±) indolmycin, in 83% yield. The diasteromeric ratio in compound **6** is 1.5 to 1 in favor of the isoindolmycin racemic pair. Compound **6** can be separated by flash column chromatography (2% $MeOH/CH_2Cl_2$ as eluent) to give diasteromeric pairs **6a** (less polar, indolmycin pair) and **6b** (more polar, isoindolmycin pair). By following a literature procedure,[11] **6a** and **6b** were converted separately into (±) indolmycin **7a** and (±) isoindolmycin **7b** without racemization at the C5 position of the oxazolinone. The spectral data of **6a** ,**6b**, **7a** and **7b** were identical with the reported values.[7]



Reagents and conditions: a. LDA (2 eq.)/NC-CO_2Bn (66%), b. PBu_3/CH_3CN/reflux /4hr (95%), c. H_2/10% Pd/C/EtOH (83%) then separation, d. H_2NMe/reflux 1hr (90%)

In conclusion, we have developed an efficient route to (±) indolmycin requiring only 4 chemical steps from readily available building blocks with 47% overall yield. This process will be used to develop indolmycin analogs with improved biological profiles.

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