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A SYNTHESIS OF (-)-INDOLACTAM V

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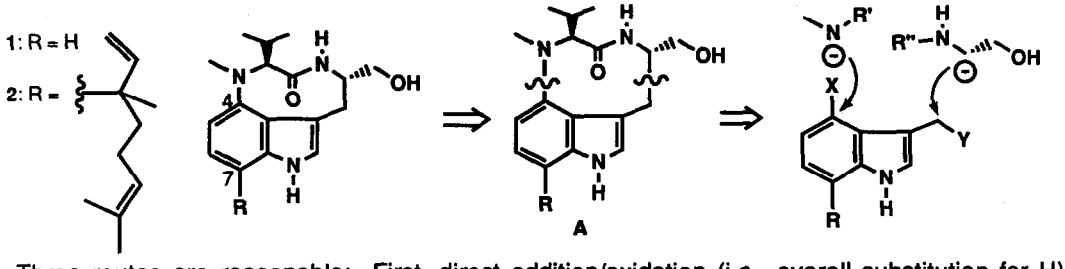
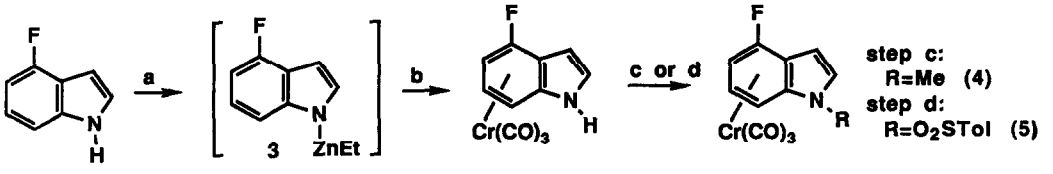
Summary: (-)-Indolactam V (**1**) was synthesized in 14 steps from 2,6-dinitrotoluene in 15% overall yield via enantiospecific S_N2 displacement of a chiral triflate with the 4-amino group of a 4-aminoindole and coupling of 3-bromomethyl indole with Schöllkopf's asymmetric bislactim ether.

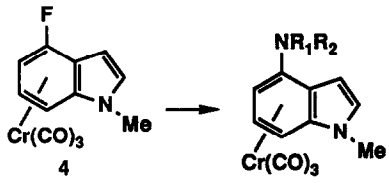
As a prelude to the synthesis of teleocidin A (**2**) via arene-$Cr(CO)_3$ complexes, we focused on (-)- indolactam V (**1**)[1,2] in order to test new protocols for the preparation of 4-amino substituted indoles and the introduction of the two stereogenic centers in the nine-membered lactam ring. Since coordination of a $Cr(CO)_3$ unit to indole activates the six-membered ring towards nucleophilic addition at C-4 (most common) and at C-7 (special cases),[3] we evaluated substitution at C-4 with amine nucleophiles using transition metal π–coordination.



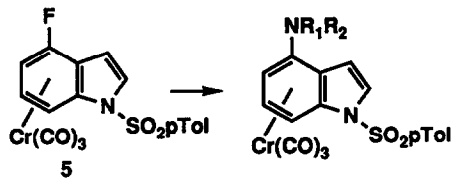
Three routes are reasonable: First, direct addition/oxidation (i.e., overall substitution for H), requires coupling of a highly reactive amine nucleophile with the arene ligand to give an anionic intermediate which is then trapped with an oxidizing agent.[4] This approach would make use of the natural selectivity for C-4. The addition/oxidation process is successful only with a limited number of nitrogen nucleophiles[5] and was not attempted here. Second, metallation of the C-4 position by selective proton abstraction from specific indole-$Cr(CO)_3$ complexes and trapping with electrophiles is known,[6] but we were unsuccessful in using nitrogen or halide electrophiles in this process. Third, a 4-halo indole ligand could undergo metal activated addition/elimination, overall substitution for halide.[4] The regioselectivity is then dictated by the position of the halide. In a preliminary investigation, 4-fluoroindole was prepared from 2-fluoro-6-nitrotoluene in 74% yield via the Leimgruber-Batcho procedure.[7] Complexation of indole derivatives with a $Cr(CO)_3$ unit can be inefficient, and the fluoro substituent leads to particularly poor results with standard methods of complexation. Adding electron density to the indole system gives improved results, most effective in practical terms by transient generation of the EtZn derivative (**3**).[8]



From a substantial list of amine nucleophiles, only three (ammonia, benzyl amine, and pyrrolidine) led to significant substitution for F in complex **4**. With complex **5**, substitution was observed using 2-aminoethanol but both glycine methyl ester and L-valine ethyl ester failed. In all cases, failure was due to competitive, often exclusive, decomplexation of the indole ligand induced by the amine nucleophile.

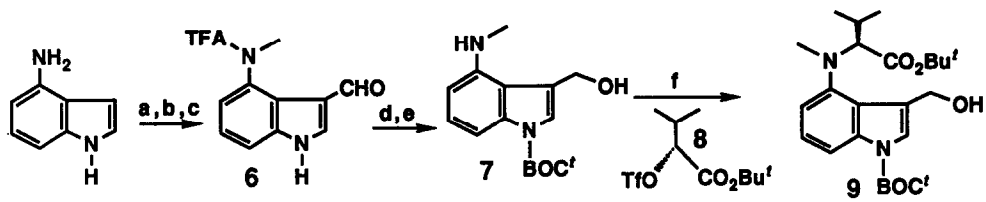


a. NH_3, neat, 25°C, 1.2 h, R_1,R_2 = H, 11%
b. $BnNH_2$, neat, 25°C, 2 h, R_1= Bn,R_2 = H, 49%
c. pyrrolidine, neat, 25°C, 0.5 h, R_1-R_2 = $(CH_2)_4$, 87%



a. $H_2N(CH_2)_2OH$, 3 mol-eq, DMF, 25°C, 0.5 h, R_1=H, R_2=$(CH_2)_2OH$, 79%
(all yields based on isolation of the free ligand after oxidative decomplexation)

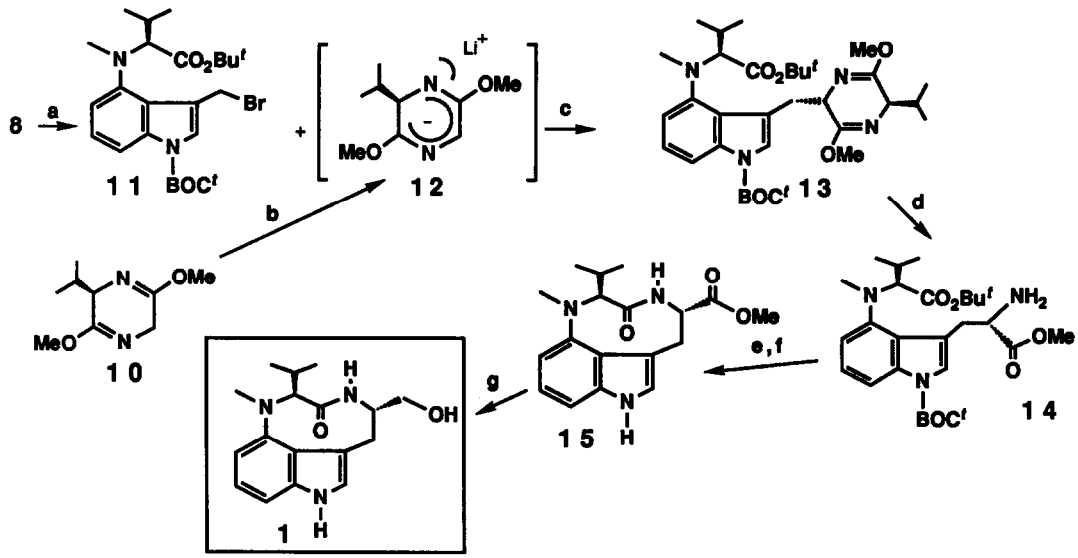
Due to the limited success of the amine substitution pathway, a more traditional approach was followed. Protection of 4-aminoindole[9] as its trifluoroacetyl derivative allowed selective methylation of the 4-amino substituent (91% yield). Subsequent reaction with $POCl_3$ followed by base treatment introduced a C-3 formyl group (**6**, 76% yield). The presence of the TFA group is necessary to minimize formylation at C-5.[10] Protection of the indole nitrogen as its tert-butoxycarbonyl (tBoc) derivative followed by sodium borohydride reduction gave 1-(t-butoxycarbonyl)-3-hydroxymethyl-4-(N-methylamino)indole (**7**, 98% yield). Alkylation of **7** with the homochiral triflate **8** (prepared from D-valine[11]) according to the method of Kogan[2b] gave **9** in 86% yield (based on 17% recovered starting material).



a. TFAA, NEt_3, CH_2Cl_2, 0 °C, 1.5 h, 93%. b. (i) NaH, THF/10% DMPU, 0 °→25 °C, 10 min; (ii) MeI, 0 →25 °C, 2.5 h, 98%. c (i) $POCl_3$, DMF, 0 °→85 °C, 2 h; (ii) NaOH, H_2O, reflux, 1 min, 76% d. $(tBOC)_2O$, NEt_3, 10 mol-% DMAP, CH_2Cl_2, 25 °C, 20 min, 98%. e. $NaBH_4$, abs. EtOH, 0 °C→25 °C, 16 h, 98 %. f. proton sponge, $ClCH_2CH_2Cl$, 70 °C, 70 h, 86% (83% conversion).

Introduction of the remaining chiral center (an L-tryptophan unit) was achieved stereoselectively using the chiral bislactim ether **10** according to a related procedure.[12] Conversion of alcohol **9** to bromide **11** was achieved with dibromotriphenylphosphorane [prepared by premixing bromine (1 mol-eq) and triphenylphosphine (1 mol-eq) in dry carbon tetrachloride] in 95% yield. Compound **11** decomposed to alcohol **9** on attempted silica gel chromatography and was used for the next reaction after the following sequence: The precipitated triphenylphosphine oxide (a byproduct of

the reaction) was removed by suction filtration and the filtrate was concentrated *in vacuo*. The solid residue was triturated with copious amounts of hexane and, upon concentration of the hexane solution, the bromide **11** was isolated. This procedure was repeated until a negligible amount of triphenylphosphine oxide was detected by ^{1}H NMR analysis. The lithiated bislactim ether **12** was successfully alkylated with the bromide **11** to give **13** (86%) as a single diastereomer.[13] Hydrolysis (0.1 *N* HCl, THF, 25 °C, 5 d, 85%) of the bislactim ether unit of **13** liberated the methyl ester **14**. Cleavage of the t-BOC and t-butyl ester groups of **14** was accomplished at 25 °C in a solution of nitromethane saturated with anhydrous HCl gas.



a. Ph_3PBr_2 (Br_2, PPh_3, CCl_4, 25 °C), NEt_3, CCl_4, 25 °C, 3 d, 95% (crude yield). b. *n*-BuLi, THF, 70 °C, 20 min. c. THF, -70°→-50 °C, 22 h, 86%. d. 0.1 N HCl, THF, 25 °C, 5 d, 85%. e. HCl(g), CH_3NO_2, 0 °C, 20 min→25 °C, 19 h. f. BOP, HOBT, N-methylmorpholine, DMA, 25 °C, 67 h, 78%. g. $LiBH_4$, MeOH, Et_2O, reflux, 15 min, 72%.

The very polar and air-sensitive intermediate free carboxylic acid was not characterized but was immediately treated with benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluoro phosphate (BOP), 1-hydroxybenzotriazole hydrate (HOBT), and N-methylmorpholine in dimethylacetamide[2b,14] to give the nine-membered lactam **15** (78%). Epimerization of **15** during ring closure was not observed, consistent with the recent observation of Webb et al.[15] Compound **15** exists in two conformations in the ratio 1.4:1 [based upon integration of the methyl peak of the isopropyl unit (L-valine) in the ^{1}H NMR]. The conformational relation is referred to as *sofa/twist* and has previously been observed in the teleocidin-olivoretin systems.[16] The last step in the synthesis of (-)-indolactam V (**1**) was reduction of **15** with lithium borohydride,[15,17] which proceeded in 72% yield. Spectral data for **1** also demonstrated the presence of two conformers in a ratio of 4.4:1 (based on integration of the peak due to the proton on the indolic nitrogen in the ^{1}H NMR) The spectral data of **1** were consistent with the published spectral data of a sample isolated from *Sterptoverticillium blastmyceticum* NA34-17[16b] and in comparison with data of a sample obtained by synthesis.[18]

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8. Complexation was attempted with a various groups attached to the indole nitrogen, including H, Me, SiR_3, MgMe, Na, Cu, and ZnBr. Only in the case of Zn reagents was a yield in excess of 15% obtained.

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10. In our hands, using a 4-(N,N-dialkylamino)indole substrate, formylation leads to reaction at C-3 and C-5 in a ratio of 2:3. For related earlier results see: (a) Clementi, S.; Linda, P.; Marino, G. *J. Chem. Soc., Chem. Commun.* **1972**, 427. (b) Anthony, W. C. *J. Org. Chem.* **1960**, *25*, 2049. (c) Nogrady, T.; Morris, L. *Can. J. Chem.* **1969**, *47*, 1999. (d) Smith, G. F. *J. Chem. Soc.* **1954**, 3842. (e) Tyson, F. T.; Shaw, J. T. *J. Am. Chem. Soc.* **1952**, *74*, 2273.

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13. An analytical sample was obtained by recrystallization from dichloromethane and hexane: mp 43-45 °C; $[\alpha]_D$ = -35.5 (c = 0.08, CH_2Cl_2, 20 °C); IR (Thin film) 2973, 2943, 1732, 1694, 1460, 1426, 1369, 1288, 1236, 1159, 1118, 1013, 735 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, at 53 °C) δ 7.95 (dd, 1H, *J* = 7.4, 1.5 Hz, H at C-7), 7.68 (s, 1H, H at C-2), 7.15 (t, 1H, *J* = 7.8 Hz, H at C-6), 7.11 (dd, 1H, *J* = 7.8, 1.7 Hz, H at C-5), 4.32 (m, 1H, H at C-9), 4.01 (dd, 1H, *J* = 15.3, 3.6 Hz, H at C-8 H_a/H_b), 3.98 (d, 1H, *J* = 6.9 Hz, H at C-12), 3.69 (s, 6H, H's at C-11 and C-16), 3.53 (d, 1H, *J* = 7.3 Hz, H at C-18), 3.07 (dd, 1H, *J* = 15.8, 8.9 Hz, H at C-8 H_a/H_b), 2.81 (s, 3H, H at C-17), 2.26 (m, 2H, H's at C-13 and C-19), 1.64 (s, 9H, H at C-26), 1.28 (s, 9H, H at C-23), 1.09 (d, 3H, *J* = 6.9 Hz, H at C-20/20'), 1.07 (d, 3H, *J* = 6.9 Hz, H at C-14/14'), 1.00 (d, 3H, *J* = 6.6 Hz, H at C-20/20'), 0.75 (d, 3H, *J* = 6.6 Hz, H at C-14/14'); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 171.57 (s, C-21), 163.90 (s, C-10/15), 163.29 (s, C-10/15), 149.71 (s, C-24), 147.37 (s, C-7a), 136.63 (s, C-4), 126.55 (d, C-2), 124.06 (d, C-7), 123.47 (s, C-3), 118.22 (s, C-3a), 116.74 (d, C-6), 111.62 (d, C-5), 82.85 (s, C-25), 80.48 (s, C-22), 73.24 (d, C-18), 60.80 (q, C-11/16), 55.94 (d, C-9), 52.37 (d, C-12), 52.21 (q, C-11/16), 31.81 (q, C-17), 30.88 (t, C-8), 28.55 (d, C-19/13), 28.19 (q, C-26), 27.89 (q, C-23), 20.14 (d, C-13/19), 19.08 (q, C-20 and C-20'), 16.77 (q, C-14 and C-14'); MS (EI) *m/e* (rel intensity) 598 (M^+, 8.3), 555 (20.4), 497 (38.4), 441 (26.5), 397 (60.2), 259 (15.0), 213 (96.5), 184 (22.1), 171 (19.0), 141 (31.4), 78 (100.0).

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