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FORMAL SYNTHESIS OF TELEOCIDIN A VIA INDOLE-$Cr(CO)_3$ COMPLEXES

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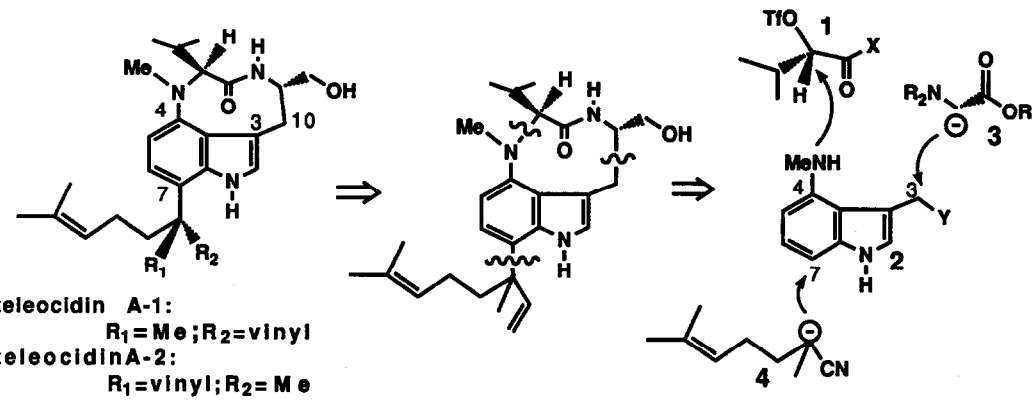
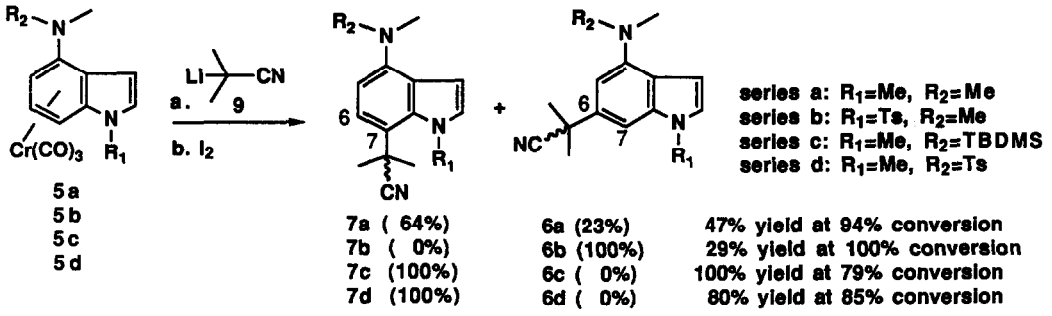
Summary: The addition of a cyano-stabilized anion to a 4-aminoindole-$Cr(CO)_3$ complex can be directed to selective C-7 substitution, and the resulting intermediate is part of a formal total synthesis of teleocidin A1/A2.

Teleocidin A-1 and A-2 have significant biological activity[1] including an interesting dependence on conformation.[2] One synthesis has been recorded, leading to a mixture of stereoisomers at the side chain at C-7 (mixture of A-1 and A-2).[3] We were attracted to a synthesis plan which would take advantage of nucleophilic addition to the arene ring activated by $Cr(CO)_3$[4] as a means of attachment of the side chain at C-7. The peptide linkage spanning C-3 and C-4 would be constructed as for indolactam V, using stereospecific displacement of a homochiral triflate (**1**) by a C-4 methylamino substituent (in **2**)[5,6] and of a leaving group at C-10 by a homochiral equivalent of and α-aminoenolate anion (**3**), such as the Schöllkopf version from a bislactim ether of a diketopiperizide.[6,7] The critical new question is the selectivity for carbanion addition at C-7. It is known that C-7 can be favored (after C-4) in addition of anions of the type **4** with unsubstituted indole-$Cr(CO)_3$ complexes.[8] Nothing is reported regarding the effect of substituents such as the C-4 amino group in **2** on regioselectivity of anion addition to the corresponding chromium complexes.



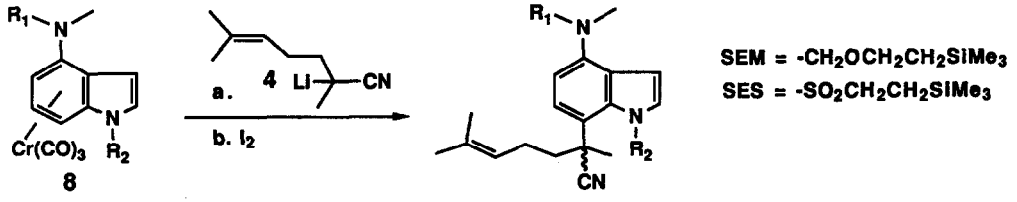
In order to probe regioselectivity, 4-aminoindole[9] was converted to the four derivatives **5a-d**[10] and the addition/oxidation procedure[4,11] with anion **9** was tested. When the amino group is N,N-dimethylamino (**5a**), substitution at C-7 (**7a**) and C-6 (**6a**) is observed in the ratio of 3:1.[12] With **5b**, the only product is **6b**, although in low yield. The tert-butyldimethylsilyl group on the C-4 amino substituent in **5c** enhances the selectivity for C-7, as does the more strongly electron withdrawing group, p-toluenesulfonate, in **5d**.[13] It was not always possible to achieve complete conversion

even at extended reaction time and with excess anion **9**, possibly due to reversal of anion addition during the oxidative quenching[14] or direct arene ligand displacement.



5a	**7a (64%)**	**6a (23%)**	**47% yield at 94% conversion**
5b	**7b (0%)**	**6b (100%)**	**29% yield at 100% conversion**
5c	**7c (100%)**	**6c (0%)**	**100% yield at 79% conversion**
5d	**7d (100%)**	**6d (0%)**	**80% yield at 85% conversion**

A series of protected derivatives **8a-c** showed selective addition at C-7 with anion **4.** The more useful derivatives are **8a** and **8c** leading to **10a** (spontaneous deprotection at the 4-amino group)[15] and to **10c,** with the easily removable SES group[16] at the C-4 amino group.



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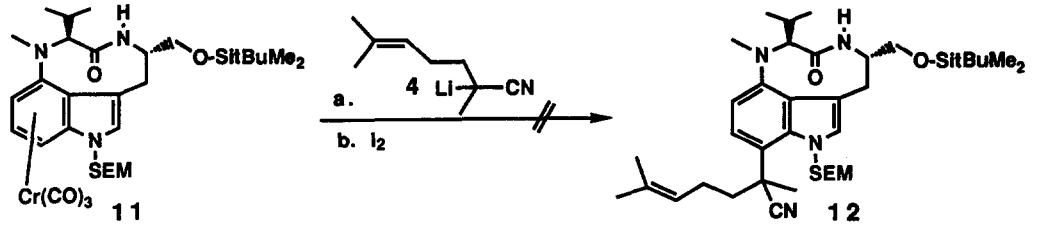
8a: R_1=tBuMe$_2$Si-, R_2=SEM
8b: R_1=Ts, R_2=Bn
8c: R_1=SES, R_2=SEM

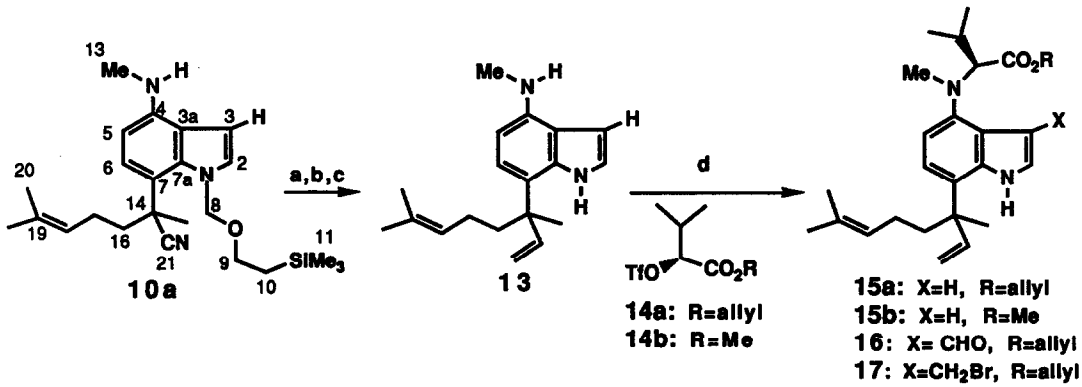
10a: R_1=H, R_2=SEM	**75% yield at 79% conversion**
10b: R_1=Ts, R_2=Bn	**100% yield at 85% conversion**
10c: R_1=SES, R_2=SEM	**71% yield at 100% conversion**

A direct approach to teleocidin A might involve addition of a nitrile-stabilized anion (**4**) to the $Cr(CO)_3$ complex of indolactam V. For this purpose indolactam V was protected as shown in complex **11.**[17] Complex **11** is highly air sensitive and resistant to efficient purification. The crude complex after removal of solvent and trituration to remove Cr residues was allowed to react with anion **4.** After a series of trials, no substitution product (e.g., **12**) was obtained, and the primary product was the arene ligand from **11.**



As a less direct alternative, intermediate **10a** was carried through the conventional sequence of reduction with diisobutylaluminum hydride followed by hydrolysis (89% yield overall to an

aldehyde), Wittig reaction with methylenetriphenylphosphorane (97%), and cleavage of the SEM group (88%) to produce the proper 10-carbon unit at C-7 (**13**). Introduction of the L-valine unit was carried out with homochiral triflate **14a** as for indolactam V,[5,6] to give **15a**. Unfortunately, after formylation to give **16**, all efforts failed to introduce a bromomethyl group (**17**) or equivalent at C-3, preparatory to the addition of the homochiral Schöllkopf anion.[7] Similar difficulty was observed when the SEM group was maintained on the indole nitrogen. Apparently, an electron donor group (or H) at the indole nitrogen contributes so strongly to the reactivity of CH_2X at C-3 that the key intermediate (e.g., **17**) could not be isolated nor usefully applied in the next stage. In other examples of the Schöllkopf strategy for introducing the tryptophane side chain, an electron withdrawing group is present (e.g., tBOC) at the indole nitrogen.[6,7a] Unfortunately, efforts to introduce an acyl or sulfonyl unit at the indole nitrogen of **15a** and **16** failed, apparently due to severe steric hindrance.



a. DIBAL, toluene, -78°→25 °C, 2.5 h, 89%. b. $Ph_3P{=}CH_2$ (methyltriphenylphosphonium iodide, *n*-BuLi, THF, -78°→25 °C, 30 min), THF, 0°→25 °C, 4 h, 97%. c. *n*-Bu_4NFxH_2O, ethylenediamine, DMF, 50 °C, 4 d, 88%. d. 2,6-lutidine, $ClCH_2CH_2Cl$, 70°C, 24 h, 92% yield of **15a**.

Compound **13** was also coupled with the **14b** to give the methyl ester analog, **15b**. Since **15b**, obtained by a different route,[3] has been converted to teleocidin A, a formal synthesis of teleocidin A is complete, based on the indole-$Cr(CO)_3$ intermediates.[18]

References

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10. Complexes **5a** (83%), **5b** (52%) and **5d** (23%) were prepared by direct complexation of the corresponding indole derivative with $(CH_3CN)Cr(CO)_3$ in dioxane at 60 °C for 0.8-1.5 h. Complex **5c** was prepared in 63% overall yield from 4-N-(t-butyldimethylsilyl)aminoindole following the sequence: (a) $(CH_3CN)_3Cr(CO)_3$, dioxane, 60 °C, 1.5 h, 96% (b). NaH, THF, 0°→25 °C, 10 min; (c) CH_3I, 0°→25 °C, 30 min, 81% (d) *n*-BuLi, THF, -78 °C, 30 min; (e) CH_3I, -78→25 °C, 2 h, 81%

11. General procedure for addition/oxidation: To a solution of lithium diisopropylamide (1.2-5.0 mol-eq.) in THF (0.05-0.07 *M*) at -78 °C under argon was added isobutyronitrile (1.2-2.0 mol-eq.) *via* syringe all at once. The reaction mixture was stirred at -42 °C for 30 min. To the reaction mixture at -78 °C was added *via* cannula dropwise over 5-10 min a solution of indole complex (1.0 mol-eq.) in THF (0.05-0.07 *M*). After being stirred at -78 °C for 1 h, the mixture was allowed to warm to -42 °C. After 0.5-1.0 h, a solution of iodine (4.0-5.0 mol-eq.) in THF (0.6-0.7 *M*) was added *via* cannula all at once to the reaction mixture at -78 °C. The dark purple solution was stirred for 1 h at -78 °C and then allowed to warm to 25 °C and stirred for an additional 1 h. The solvent was removed by rotary-evaporation, and the residue dissolved in ethyl acetate was washed first with excess saturated sodium bisulfite ($NaHSO_3$) solution and then with saturated brine solution (2X). The solution was dried over anhydrous $MgSO_4$, filtered, concentrated, and the residue was purified by flash column chromatography.

12. Two regioisomers were obtained in a 3:1 ratio and could not be separated by silica-gel column chromatography. The regioisomers were identified by an NOE difference experiment. Irradiation at δ 1.92 (the methyl group of the 1-methyl-1-cyanoethyl substituent in the major isomer) caused an enhancement of the two peaks at δ 4.25 (s, 3H) and 7.07 (d, *J*= 8.3 Hz, 1H). Irradiation at δ 1.80 (the methyl group of the 1-methyl-1-cyanoethyl substituent in the minor isomer) caused an enhancement of the two peaks at δ 6.52 (s, 1H) and 7.00 (s, 1H). Therefore, the major product was identified as a C-7 addition product (**7a**) and the minor product was identified as a C-6 addition product (**6a**).

13. The factors which influence regioselectivity are insufficiently understood to allow confident prediction in multisubstituted cases. Analysis of conformational effects and charge vs orbital control is useful in simple systems,[4] and a full analysis of the 4-aminoindole system will be presented in a subsequent report.

14. Reversible addition typically is significant during trapping with electrophiles but not with the usual oxidation conditions. See ref 4 and Kundig, E. P. *Pure Appl. Chem.*, **1985**, *57*, 1855.

15. Characterization of **10a**: (R_f: 0.30, SiO_2, hexane/diethyl ether 4/1) 1.019 g, 59%, as a pale yellow oil. IR (thin film) 3421, 2952, 2893, 2226, 1604, 1585, 1516, 1363, 1248, 1070, 859, 836, 712 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.15 (d, 1H, *J* = 3.6 Hz, H at C-2), 7.10 (d, 1H, *J* = 8.3 Hz, H at C-6), 6.49 (d, 1H, *J* = 3.6 Hz, H at C-3), 6.28 (d, 1H, *J* = 8.3 Hz, H at C-5), 5.90 (d, 1H, *J* = 10.9 Hz, H at C-8 H_a/H_b), 5.75 (d, 1H, *J* = 10.9 Hz, H at C-8 H_a/H_b), 5.11 (m, 1H, H at C-18), 4.05 (br s, 1H, H at N-12), 3.48 (AA'XX' system, 2H, H at C-9), 2.98 (s, 3H, H at C-13), 2.42 (m, 1H, H at C-16 H_a/H_b), 2.24 (m, 2H, H at C-17), 1.94 (s, 3H, H at C-15), 1.93 (m, 1H, H at C-16 H_a/H_b), 1.68 (d, 3H, *J* = 1.0 Hz, H at C-20/20'), 1.61 (d, 3H, *J* = 0.7 Hz, H at C-20/20'), 0.88 (AA'XX' system, 2H, H at C-10), -0.03 (s, 9H, H at C-11); NOE experiment: irradiation of H at C-15 (d 1.94) enhances H at C-8 H_a/H_b (δ 5.75 and 5.90) and H at C-6 (δ 7.10); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 142.50 (s, C-7a/4), 133.50 (s, C-4/7a), 132.69 (s, C-19), 129.56 (d, C-2), 124.86 (s, C-7), 122.68 (d, C-18/6), 122.16 (d, C-6/18), 120.77 (s, C-3a), 114.33 (s, C-21), 99.51 (d, C-5), 99.08 (d, C-3), 79.46 (t, C-8), 65.56 (t, C-9), 39.63 (s, C-14), 38.47 (t, C-17), 30.60 (q, C-13), 26.55 (q, C-20/20'), 25.65 (q, C-15), 24.22 (t, C-16), 17.83 (t, C-10), 17.75 (q, C-20/20'), -1.48 (q, C-11); MS (EI) *m/e* (relative intensity) 412 (M^++1, 38.5), 411 (M^+, 85.2), 294 (50.6), 271 (48.8), 255 (44.1), 254 (100.0), 239 (43.7), 211 (37.1), 186 (31.8), 73 (86.6).

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17. The preparation of complex **11** was attempted under various conditions. Most effective appeared to be the use of 2.0 mol-equiv of $(CH_3CN)_3(CO)_3Cr$ in dioxane at 60 °C.

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