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A NEW APPROACH TO INDOLE ALKALOIDS VIA INDOLE CHROMIUM COMPLEXES

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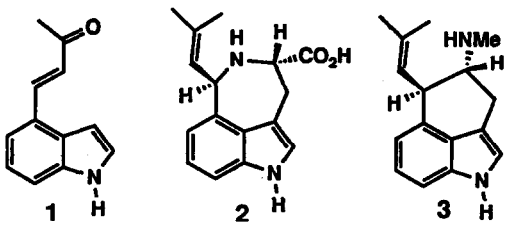
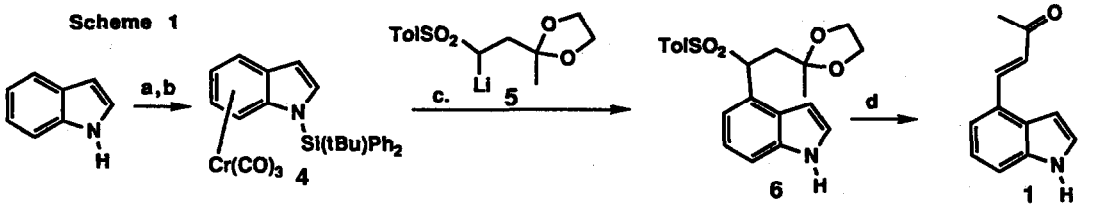
Summary: The activating effect of pi complexation of a $Cr(CO)_3$ unit allows selective nucleophilic substitution in indoles such as tryptophan derivatives and provides intermediates for the synthesis of clavicipitic acid and related indole natural products.

The addition of a nucleophile to an N-protected indole-$Cr(CO)_3$ complex allows regioselective introduction of a substituent at C-4 or C-7 on the indole ring, depending on the substituents at C-3 and N-1, as well as the nature of the nucleophile.[1] We report application of this methodology in efficient procedures relating to the C-4 substituted indole alkaloids such as clavicipitic acid (**2**).



The enone **1**, which is a key intermediate in syntheses of clavicipitic acid (**2**)[2a] and 6,7-seco-agroclavine (**3**)[2b] was prepared in four operations directly from indole with an overall yield of 44-50% (Scheme 1). Indole is readily transformed into the corresponding tricarbonylchromium complex[3] and silylated with t-butylchlorodiphenylsilane to produce the orange, crystalline complex **4**.[4] The addition of **4** to a solution of the lithiated sulfone **5**[5] followed by oxidative quenching with iodine and desilylation furnished the C-4 substituted indole **6** in 90% yield.[6] Indole **6** was converted into the enone **1** in 78% yield by sequential acid and base treatment.

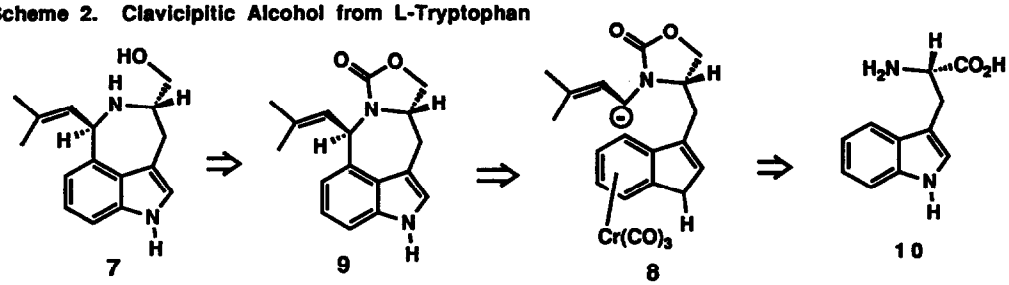
Scheme 1



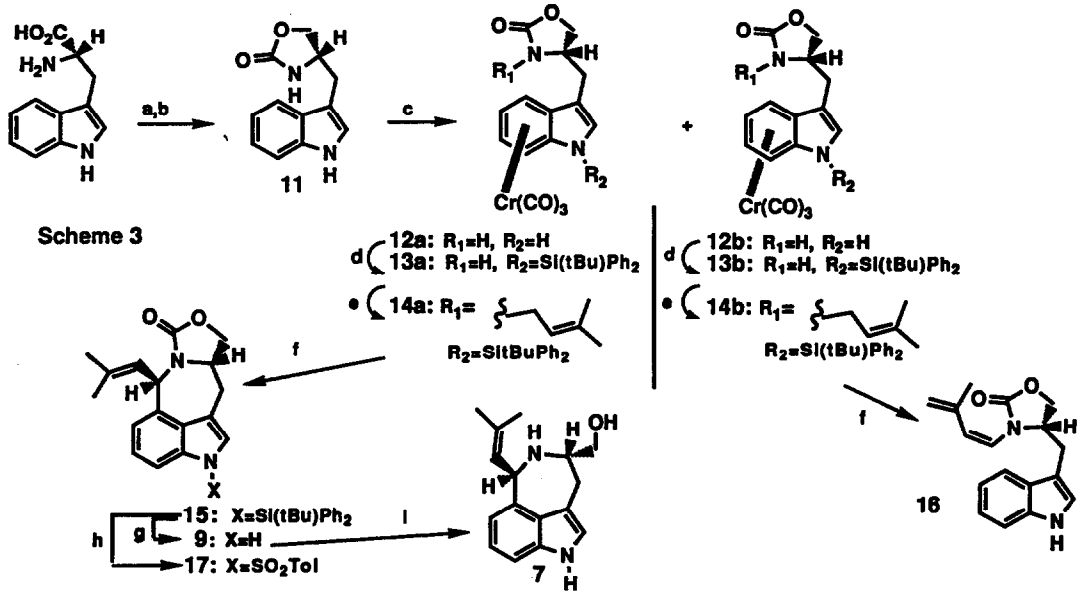
(a) ($Cr(CO)_6$, 1.4 mol-eq, 72 h reflux, Bu_2O with 5% THF; 75-80%). (b) (i) NaH, 1.15 mol-eq, THF, 0°C 10 min; (ii) t-butylchlorodiphenylsilane, 1.1 mol-eq, 0°C 10 min, 89%. (c) (Bu_4NF, 2 mol-eq, THF, 5 min, 93-100%). (d) (i) catalytic TsOH in acetone, 25 °C, 50 h, (ii) excess Et_3N in CH_2Cl_2, 0.5 h, 24 °C, 78%

An intramolecular approach to the homochiral clavicipitic acid skeleton started from natural L-tryptophan (**10**) with clavicipitic alcohol (**7**) as the target. The key step in the retrosynthetic analysis is the 7-membered ring closure from **8** to **9** (Scheme 2).

Scheme 2. Clavicipitic Alcohol from L-Tryptophan



Reduction of L-tryptophan (**10**) and conversion of the resulting amino alcohol into an oxazolidinone (**11**) proceeded in 82% yield. Formation of the corresponding $Cr(CO)_3$ complex gave a diastereomeric mixture (ratios ranging from 1:1 to 45:55) of the complexes **12a** and **12b** (arbitrary structure assignment at this stage).



Scheme 3

a. LAH, THF, 14 h, 65°C; **b**. (i) 7 mol-eq 15% aqueous NaOH, THF, (ii) 3.5 mol-eq $COCl_2$, THF, 0.5 h, 0°C, 82% for a+b; **c**. 1.5 mol-eq $Cr(CO)_3(MeCN)_3$, dioxane, 10 min, 100°C, 85%; **d**. (i) 1.0 mol-eq NaH, THF, 20 min, 0°C; (ii) 1.0 mol-eq $tBuPh_2SiCl$, THF, 20 min, 20°C, 84%; **e**. (i) 1.0 mol-eq MeLi, ether, -78°C; 5 min, (ii) add 10% by vol of DMPU[8], (iii) excess 1-bromo-3-methyl-2-butene, 25°C, 0.5 h, 66%; **f**. (i) 1.25 mol-eq LDA, THF, 2 h at -78°C, then 2 h at -60°C, (ii) 3.4 mol-eq I_2, -78°C for 1 h, then 3 h at 25°C, 77% from **14a** and 70% from **14b**; **g**. nBu_4NF, THF, 10 min, 25°C, 94%; **h**. excess NaH, THF, pTsCl, 3 h, 25°C, 30% yield after several crystallizations **I**. 3N KOH, dioxane, $HOCH_2CH_2NH_2$ 12 h, 105°C, 76-82%.

Silylation of complexes **12ab** afforded complexes **13ab** (diastereomers) which were allylated with an excess of 1-bromo-3-methyl-2-butene in a THF/DMPU mixture. The diastereoisomers (**14a** and **14b**) were separated by careful flash chromatography.[7]

The two diastereoisomers show contrasting behavior when treated with LDA. Whereas the complex **14a** rapidly cyclizes to the pure trans tetracyclic compound **15** (77% yield), the second diastereomer **14b** gives under the same reaction conditions only the diene **16** (70% yield). Longer reaction time at higher temperatures (5 h at -15 °C) leads to the same result. The relative configuration of **15** was determined by an X-ray analysis of the sulfonamide, **17**.[9] The reactivity difference between **14a** and **14b** as well as the observed stereospecificity are not easily rationalized by inspection of models. We assume that the vinyl group in the transition state is always directed away from the aromatic ring (fig 1, as opposed to that shown in fig. 2) With this assumption, the formation of the trans product from **14a** is reasonable, and **14b** would lead to a cis cyclic product. Force field calculations[10] on the trans 1,4-cyclohexadiene **18a** and the analogous cis cyclohexadiene **18a** (as models for the anionic chromium intermediate **19**) suggest that the cis isomer is 5.3 Kcal/mol less stable than the trans isomer. Product formation may well be determined by equilibrium generation of the cyclohexadienyl anions (i.e., **19** in fig 1);[11] the fast oxidative quenching can convert the cyclized intermediate **19** into the tetracyclic product, while the starting allyl anion (e.g., **20**) would be converted to the diene **16** upon treatment with iodine.

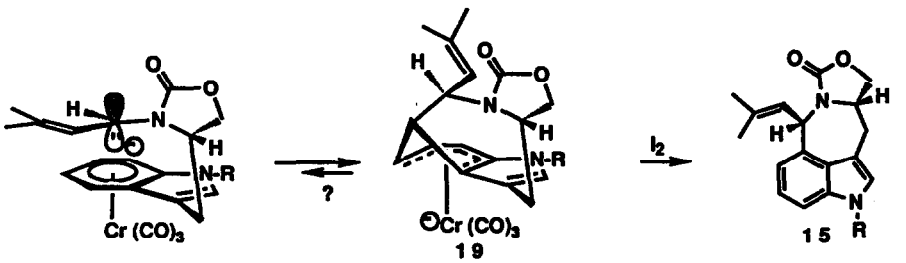


Fig. 1. Favored conformer from **14a** leads to **15** R = $tBuPh_2Si$-

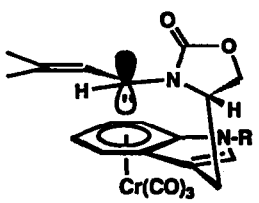


Fig. 2. Less favored conformer from **14b**

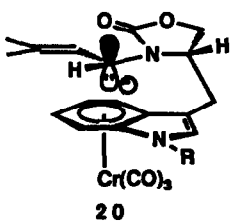
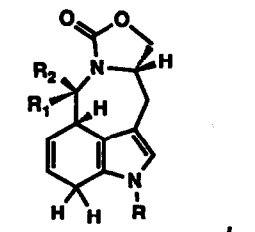


Fig. 3. Favored conformer from **14b**



18a: R_1=H, R_2= 

18a: R_1=  , R_2=H

Compound **11** was desilylated to give **9** and the oxazolidinone was disassembled using particularly mild conditions (KOH in dioxane with ethanolamine as cosolvent) to give clavicipitic alcohol (**7**) in 76-82% yield.[12,13]

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3. E. O. Fischer, H. A. Goodwin, C. G. Kreiter, H. D. Simmons, K. Sonogashira, and S. B. Wild, *J. Organomet. Chem.*, **1968**, *14*, 359; see also C. A. L. Mahaffy and P. L. Pauson, *Inorganic Syntheses*, **1979**, *19*, 154. Following strictly the conditions described by E. O. Fischer leads to **4** in 29% yield.

4. Complex **4** was obtained from ether/hexane as yellow crystals, mp 123-129^{0}C. ^{1}HNMR($CDCl_3$): δ 7.40(m,11H), 6.03-6.46(m,2H), 4.91(m,3H, arene coordinated to Cr), 1.23(s,9H,tBu). IR($CHCl_3$): 1948(s), 1860(s), 1422(m), 1260(w), 1030(m) cm^{-1}. Mass spectrum (70eV, EI): 491(7%), 408(51), 407(100), 355(35), 294(38). MS mole wt: calc. for $C_{27}H_{25}NO_3SiCr$: 491.1009. Found: 491.0984.

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6. Cpn **6** was isolated by flash chromatography (3% ether in dichloromethane). ^{1}HNMR($CDCl_3$, 300 MHz): δ 8.6 (br s,1H,NH), 7.4 (d,J=10Hz,2H), 7.3-6.95 (m,4H), 7.01 (d,J=10Hz,2H), 6.22 (br s,1H), 4.82 (m,1H), 3.90-3.70 (m, 3H), 3.58 (m,1H), 2.95 (br d,J=15Hz,1H), 2.72 (br s at 300 MHz, m at 90MHz,1H), 2.30 (s,3H), 1.06 (s,3H). Some signals of this spectrum were broad due to the hindered rotation at C-4. ^{13}CNMR($CDCl_3$, 75.5MHz): 144.2, 134.5, 131.9, 129.6, 129.3, 129.1, 125.0, 121.6, 119.7(br), 111.6, 109.0, 99.7(br), 64.7, 64.5, 58.7, 36.7(br), 24.7, 21.6. Mass spectral mole wt(EI): 385.

7. Separation and characterization of **14a** and **14b**. The yellow oil from allylation of **13a/13b** was chromatographed (flash) on silica gel (hexane/ethyl acetate; 2/1) to give pure samples of **14a** and **14b** as yellow oils. Before separation, the mixtures of **14a/14b** showed: IR(CH_2Cl_2): 3060(m), 2995(m), 1950(s), 1870(s), 1750(s), 1420(m), 1260(s), 890(m) cm^{-1}. Mass spectral mole wt (EI): 506. Characterization of **14a**. ^{1}HNMR(acetone-d_6, 300MHz): δ 7.8(m,2H), 7.6-7.4(m,9H), 6.44(dd,J=4 and 8Hz,1H), 5.35-5.05(m,4H), 4.4-3.8(m,5H), 3.28(dd,J=4 and 12 Hz,1H), 2.92(dd,J=10 and 12Hz, 1H), 1.82(s,3H), 1.76(s,3H), 1.26(s,9H). *Anal.* calc for $C_{36}H_{38}CrN_2O_5Si$: C,65.63; H,5.81; N,4.25. Found: C,65.40; H,5.98; N,4.33. Characterization of **14b**. ^{1}HNMR(acetone-d_6, 300MHz): δ 7.8 (m,2H), 7.6-7.4 (m,9H), 6.41 (d,J=8Hz,1H), 5.4-5.2 (m,4H), 4.15 (m,2H), 4.15-4.00 (m,2H), 3.90 (m,1H), 3.2(m,1H), 2.95 (dd,J=10Hz,12Hz,1H), 1.82 (s,3H), 1.76 (s,3H), 1.23 (s,9H). *Anal.* calc for $C_{36}H_{38}CrN_2O_5Si$: C,65.63; H,5.81. Found: C,65.37; H,5.91.

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9. An X-ray diffraction study on sulfonamide **17**, mp 121-122^{0}C, by Dr. Donna van Engen at the Princeton X-ray Facility confirmed the details of the structure including the trans ring fusion of the new ring.

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11. For examples of reversible addition of carbanions, see: (a) E. P. Kundig, V. Desobry, D. P. Simmons, and E. Wenger, *J. Am. Chem. Soc.*, **1989**, *111*, 1804; (b) B. Ohlsson and C. Ullenius, *J. Organomet. Chem.*, **1984**, *267*, C34; (c) B. Ohlsson and C. Ulennius, *J. Organomet. Chem.*, **1988**, *350*, 35; (d) M. F. Semmelhack, in "Comprehensive Organic Synthesis," Vol 4, Pergamon Press, Oxford, 1992, p 534-535.

12. For **7**: mp 145-146^{0}C. ^{1}HNMR($CDCl_3$,300 MHz): δ 8.1(br s, 1H), 7.22 (d,J=8Hz,1H), 7.12 (t,J=8Hz,1H), 7.0(s,1H), 6.80 (d,J=8,1H), 5.38 (ABq becomes dd in benzene d_6, at 5.22 and 5.08, 2H), 3.68 (dd,J=3,15Hz,1H), 2.79 (dd,J=15,10Hz,1H), 2.45 (br s, 2H), 1.90 (s,3H), 1.80 (s,3H). ^{13}CNMR ($CDCl_3$,75.5MHz): δ 140.7,137.2,133.6,126.9,125.3,122.1,121.1,117.3,113.7,109.4,65.3,56.3,55.2, 32.2,25.9,18.4. IR($CDCl_3$): 3485(s),3970(m),3938(m),3860(m),1610(w),1430(m),1420(m),1050 (m), 1020(m), 850(m), 780(m) cm^{-1}. HMS: calcd for $C_{16}H_{20}N_2O$: 256.1576; found: 256.1585.

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