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REGIOSELECTIVE [2,3] SIGMATROPIC REARRANGEMENT TO THE PYRROLO[3,2-e] INDOLE RING SYSTEM OF CC-1065

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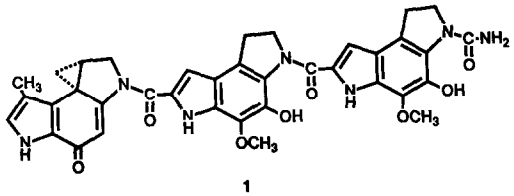
Abstract: A short and efficient synthesis of the 1,2-dihydro-3H-pyrrolo[3,2-e]indole (**2**) ring system of the antitumor antibiotic CC-1065 (**1**) from ethyl-5-aminoindole-2-carboxylate **3** was made possible by the inherent regioselectivity of the [2,3] sigmatropic rearrangement of the azasulfonium ylide **4** and a thiation-reduction sequence for oxindole to indoline conversion.

As part of our ongoing study of structure-activity relationships of analogs of the novel and highly potent antitumor antibiotic, CC-1065 (**1**)[1], we were interested in efficiently preparing the 1,2-dihydro-3H-pyrrolo[3,2-e]indole ring system (**2**) contained in the middle and right-hand segments of the natural product.[2]



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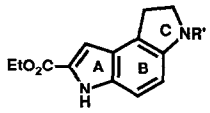


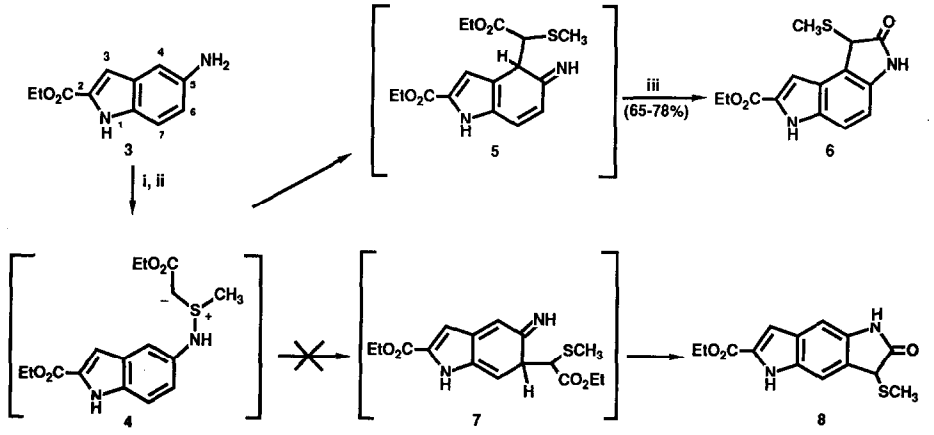
2a R'=H
2b R'=Ac

Several novel approaches to the 1,2-dihydro-3H-pyrrolo[3,2-e]indole **2** have recently appeared.[2e,f,4] These syntheses involve either the formation of ring A[2e,4] or ring B[2f] as the final key transformation in multi-step sequences. Herein we describe a short synthesis of **2** from readily available ethyl-5-aminoindole-2-carboxylate **3**, forming ring C in the final stage.

The known propensity of 5-hydroxyindoles to alkylate in the 4-position of the indole benzenoid ring either by Mannich or other electrophilic substitution reactions[5,6] or via Claisen rearrangement of the corresponding 5-allyloxy-indoles[6] led us to anticipate that a similar alkylation reaction of a suitable 5-aminoindole derivative should also afford C-4 alkylation. The observed regioselectivity of these reactions of indoles[7] as well as certain other aromatic systems[8] has been rationalized in terms of lowest energy valence-bond resonance forms, or the preservation of aromaticity in the ring distant to the substitution. Gassman has shown that the [2,3] sigmatropic rearrangement of the azasulfonium ylides derived from β-naphthylamine is subject to these same considerations.[9] As we anticipated, (Scheme 1) reaction of ethyl 5-aminoindole-2-carboxylate **3**[10]

with the chlorosulfonium salt of ethyl (methylthio) acetate, followed by base promoted ylide (**4**) formation, [2,3] sigmatropic rearrangement, and ring closure[11] afforded exclusively the oxindole **6** (65-78%), presumably *via* **5**. No evidence for the formation of the less sterically hindered regioisomer **8** *via* resonance-interrupted **7** could be found. The ^{1}H n.m.r. spectrum of **6** clearly showed the vicinal coupling (J = 8.3 Hz) of the 6H and 7H protons.

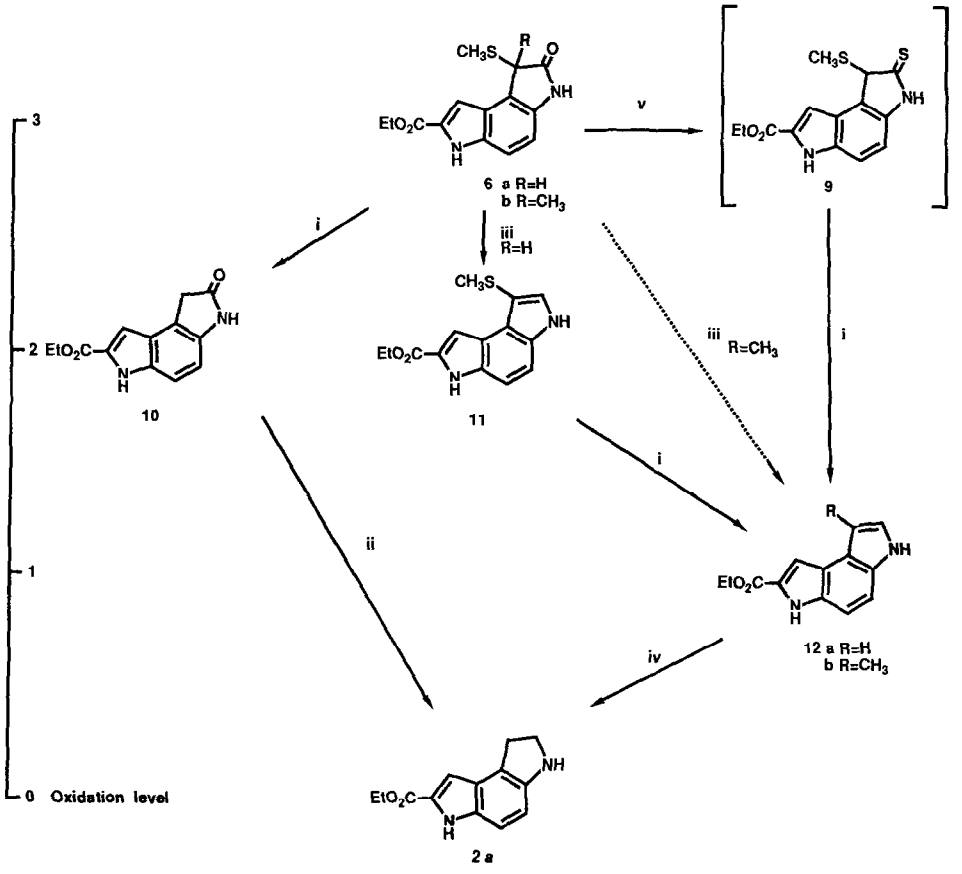
Scheme 1



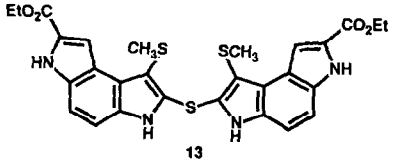
i. $CH_3SCH_2CO_2Et$, SO_2Cl_2, Proton Sponge, CH_2Cl_2, -78°; *ii* Et_3N, -79° → 20°; *iii* HOAc

The success of this approach also depended upon selective reduction across three levels of oxidation separating **6a** from **2** (Scheme 2).[12] The conceptually simple desulfurization-reduction path was unsuccessful. In contrast to oxindole itself, which was reduced to indoline in 70% yield with "internally generated diborane"[13a], oxindole **10** failed to give any identifiable product when treated with this reagent.[13b] Borane-dimethylsulfide, has been shown to reduce 3-substituted, 3-thiomethyl oxindoles to 3-substituted indoles (e.g. the hypothetical compounds **6b** to **12b**) in high yields,[14a] effecting a change in formal oxidation state of two. However, this reaction afforded a 2:1 mixture of the single reduction step product **11** and **12a** (35-54%) from **6a**[14b], still requiring two more steps to produce **2a**. A more reliable route to **2a** involved thiation of **6a** with Lawesson's reagent,[16] followed by Raney nickel desulfurization of the crude product mixture,[17] which afforded **12a** in 55-67% yield from **6a**. The apparent simplicity of this route is belied by our isolation, in a separate run, not of the expected 2-indolinethione **9**, but of the indole **11**[18] and an equimolar amount of a dimer tentatively identified as **13**[19] from the Lawesson reaction.

Scheme 2



i Raney nickel; *ii* $LiBH_4$, THF BF_3OET_2; EtOH; *iii* BH_3SMe_2, THF;
iv BH_3SMe_2, TFA, THF, 0°; *v* 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide,toluene, 85°



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Both **11** and **13** were cleanly desulfurized to **12a**. Borane-trifluoroacetic acid reduction[15] of **12a** produced the desired indoline **2a** (~90%), which was converted to its acetyl derivative **2b** for further characterization.[20]

Exploitation of the regiochemical control inherent in the mild and versatile ortho alkylation chemistry developed by Gassman, coupled with an efficient oxindole reduction procedure, has provided us a short, high yield route (four steps, ~40%) to **2** from **3**.

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20. All new compounds reported were homogeneous by TLC and gave satisfactory ir, NMR, m.s. and exact mass and/or combustion analysis.^{1}H NMR:2a ($CDCl_3$) δ 1.43 (t, 3H), 3.03-3.80 (dt, 4H), 4.43 (q, 2H), 6.88 (d, J = 9 Hz, 1H), 7.09 (s, 1H), 7.14 (d, J = 9 Hz, 1H), 9.49 (br s, 1H); **2b** (DMSO-d_6) δ 1.33 (t, 3H), 2.17 (s, 3H), 3.30 (m, 2H), 4.17 (m, 2H), 4.36 (q, 2H), 7.11 (s, 1H), 7.31 (d, J = 9 Hz, 1H), 8.25 (d, J = 9 Hz, 1H), 11.93 (br s, 1H).

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