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SYNTHETIC STUDIES DIRECTED AT THE B/C RING SYSTEMS OF CC-1065; PREPARATION OF SUBSTITUTED CYCLOPROPYL INDOLENONES

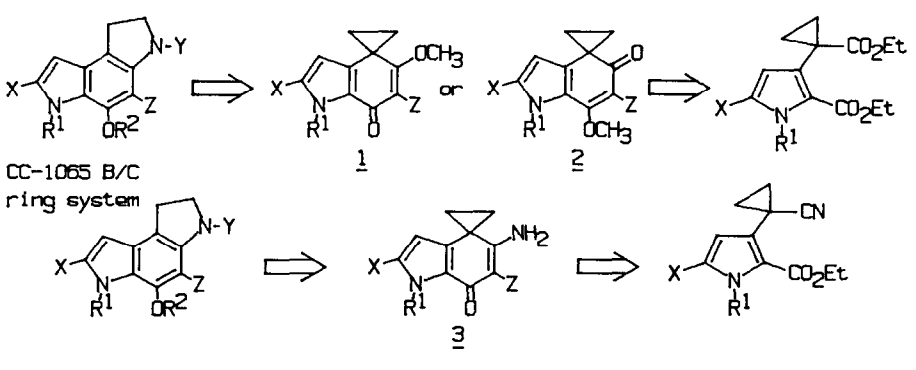
Thomas A. Bryson* and Gary A. Roth

Department of Chemistry
University of South Carolina, Columbia, South Carolina 29201

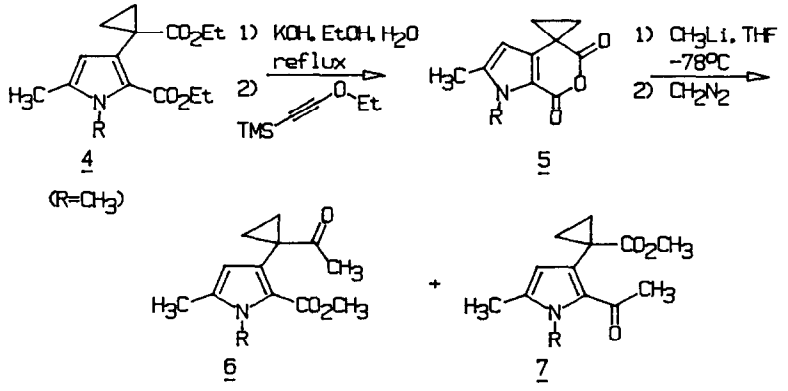
Abstract: Cyclopropyl indolenones are synthesized in good overall yields. The key reaction is an intramolecular enolate ring closure giving rise to the six membered carbocyclic ring.

In a previous communication we described the base induced cyclopropanation of 2,5-disubstituted-3-pyrrole acetic acid esters and acetonitriles [1] Herein we report the conversion of these pyrroles to cyclopropyl indolenones **1** - **3**. Compounds **1** - **3** each contain a cyclopropane conjugated-dienone system similar to the DNA alkylating A ring of the antitumor antibiotic CC-1065. Our strategy for the synthesis of the B/C ring systems of CC-1065 (Scheme I) also incorporates **1** - **3** as important intermediates. For example, opening of the cyclopropane ring of **1** and **2** by a nitrogen nucleophile would provide access to the pyrroline portion of the B/C ring system. Alternatively, ketimine formation at the carbonyl of **2** followed by acid catalyzed cyclopropyl imine rearrangement[2] would give the desired pyrroline. The indolenone **3** already possesses a nitrogen atom in the correct position, treatment with acid and heat should afford the desired ring.

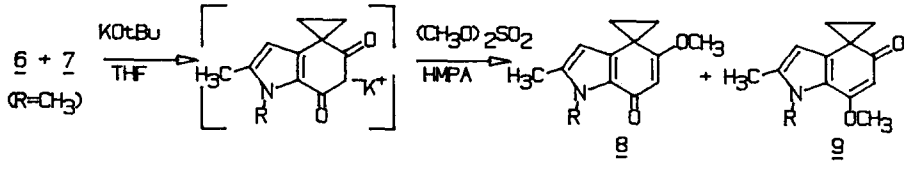
SCHEME I



The key intermediates in our synthesis of compounds such as **1** and **2** were the anhydrides **5**. Basic hydrolysis of diesters **4** provided the corresponding diacids in greater than 90% yield. Dehydration was accomplished with trimethylsilyl ethoxy acetylene[3] in refluxing THF to afford cyclic anhydrides **5** (72-82% yield). Treatment of these anhydrides with methyllithium[4] (1.1eq. for R = CH_3 and 2.1eq. for R = H) followed by diazomethane esterification resulted in a mixture of the methyl ketones **6** and **7** (for R = H, 73%, > 8/1; for R = CH_3, 65%, 4/1). The selectivity of the addition may be attributed to steric and/or electronic factors[5].



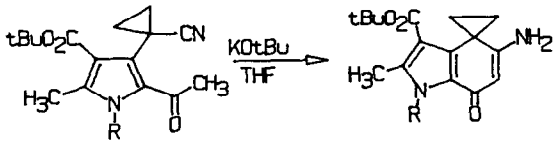
Attempted enolate ring closure of **6** (R = H) lead only to slow dealkylation of the methyl ester giving the pyrrole-2-carboxylate. Similarly, **7** (R = H) failed to give any indole products. However, upon exposure of the N-alkylated methyl ketones **6** and **7** (R = CH_3) to potassium t-butoxide in THF, cyclization of both isomers[6] occurred to give the dione enolate. O-alkylation with dimethylsulfate provided a mixture of the isomers **8** and **9**[7] (3/1 respectively), which could be separated by column chromatography.



Only slight chemical shift differences in the 90-MHz proton NMR of **8** and **9** made structural assignment, on this basis, difficult. Although on comparison of the carbon-13 spectra of each isomer with the carbon-13 spectra of the natural product, CC-1065, the structures of **8** and **9** became

evident. The carbonyl carbon resonance of **8** was 178.2ppm, while the carbonyl carbon resonance of **9** was found at 197.9 ppm. The A ring system carbonyl carbon of CC-1065 is reported to be 176.4 ppm.[8] Therefore, isomer **8** is assumed to have a conjugated-dienone system very similar to that found in CC-1065.

Similarly, exposure of the keto-nitrile **10**[9] (R = H) to a variety of bases lead only to recovery of starting material. N-alkylation (R = CH_3) followed by treatment with potassium t-butoxide in THF resulted in facile cyclization to produce the enamino-ketone **11** in good yield. It is interesting to note that the enone carbonyl carbon resonance of **11** is found at 178.0 ppm.[7]



10 (R=CH_3) **11**

In conclusion, the present communication describes the synthesis of indoleneones **8, 9** and **11**, each of which contain cyclopropane conjugated-dienone systems similar to that found in CC-1065. Studies on the conversion of these indolenones to the B/C ring systems of CC-1065 are currently underway.

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REFERENCES AND NOTES

1. T. Bryson, Kiu, Jing-hau and G. Roth, *Tetrahedron Lett.*, **1986**, *27*, submitted.
2. See R.V. Stevens, in "The Total Synthesis of Natural Products", Vol. 3, pp. 439-543, John Wiley & Sons, Inc., New York, 1977.
3. Y. Kita, S. Akai, M. Yoshigi, Y. Nakajima, H. Yasuda, and Y. Tamura, *Tetrahedron Lett.*, 6027 (1984).
4. Other nucliophiles were found to open anhydrides **5** equally as well. We have added sodium methoxide, lithium trimethyl silyl acetylide and α-lithio ethyl acetate.

5. The electrophillic character of the conjugated anhydride carbonyl is expected to be less than that of the α-cyclopropyl anhydride carbonyl since it is in conjugation with the pyrrole nitrogen atom. Steric considerations also favor nucleophillic attack at the α-cyclopropyl carbonyl. Kayser and Morand used vector approach analysis to explain nucleophillic attack at the seemingly more hindered carbonyl of unsymmetrical cyclic anhydrides. M. Kayser and P. Morand, *Tetrahedron Lett.*, 695 (**1979**).

6. Isomers **6** and **7** could be separated by careful column chromatography (230-400mesh silica gel). It was then shown that both isomers gave the cyclic β-diketone upon treatment with potassium tert-butoxide in THF.

7. The spectral data for all new compounds are in accord with the structures assigned. Only data for **8**, **9** and **11** are reported. Spectral data for **8**: ^{13}C NMR ($CDCl_3$, 20MHz ppm): 178.2, 172.5, 137.2, 136.2, 126.0 103.3, 99.6, 55.5, 31.7, 22.3, 22.1 (two cyclopropyl carbons), 11.9. ^1H NMR ($CDCl_3$, 90MHz, ppm): 1.4 (m, 2H, 2 cyclopropane C<u>H</u>'s), 1.85 (m, 2H, 2 cyclopropane C<u>H</u>'s), 2.2 (s, 3H, ring C<u>H</u>$_3$), 3.75 (s, 3H, OC<u>H</u>$_3$), 3.97 (s, 3H, NC<u>H</u>$_3$), 5.5 (s, 1H, pyrrole ring <u>H</u>), 5.65 (s, 1H, vinyl <u>H</u>). mass spectrum (70 eV, *m/e*): 217 (M+, 100%). Spectral data for **9**; ^{13}C NMR ($CDCl_3$, 20 MHz, ppm): 197.9, 165.2, 136.2, 134.7, 120.4, 101.4, 95.5, 55.5, 32.8, 29.1, 27.8 (two cyclopropane carbons), 12.4. ^1H NMR ($CDCl_3$, 90 MHz, ppm): 1.45 (m, 2H, 2 cyclopropane C<u>H</u>'s), 1.9 (m, 2H, 2 cyclopropane C<u>H</u>'s), 2.25 (s, 3H, ring C<u>H</u>$_3$), 3.75 (s, 3H, OC<u>H</u>$_3$), 3.9 (s, 3H, NC<u>H</u>$_3$), 5.5 (s, 1H, vinyl <u>H</u>), 5.55 (s, 1H, pyrrole ring <u>H</u>). mass spectrum (70 eV, *m/e*): 217 (M+, 100%). Spectral data for **11**; ^{13}C NMR ($CDCl_3$, 20 MHz, ppm): 178.0, 165.1, 163.9, 139.4, 132.0, 127.5, 110.3, 103.8, 80.8, 32.4, 28.3, 22.7 (two cyclopropane carbons), 22.3, 11.8 ^1H NMR ($CDCl_3$, 300 MHz, ppm): 1.50 (m, 2H, 2 cyclopropane C<u>H</u>'s), 1.54 (s, 9H, C(C<u>H</u>$_3$)$_3$), 2.37 (s, 3H, ring C<u>H</u>$_3$), 2.45 (m, 2H, 2 cyclopropane C<u>H</u>'s), 3.91 (bs, 2H, N<u>H</u>$_2$), 4.02 (s, 3H, NC<u>H</u>$_3$), 5.58 (s, 1H, vinyl <u>H</u>). mass spectrum (72 eV, *m/e*): 302 (M+, 38%), 246 (100%).

8. D. Martin, C. Bites, S. Gerpheide, L. Hanka, W. Krueger, J. McGovern, S. Mizsak, G. Neil, J. Steward, and J. Visser, *J. Antibiot.*, *34*, 1119 (**1981**).

9. Compound **10** was prepared in several steps from the cyclopropyl nitrile reported in reference **1**.

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