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CYCLOPROPANE CHEMISTRY RELATED TO THE ALKALOID CC-1065

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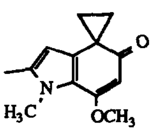
Abstract: Aspects of cylcopropane chemistry relative to the subunits of CC-1065 are discussed.

The synthesis of 1,2-dihydropyrrolo[3,2-e]indoles and related ring systems[1] has attracted considerable attention since the isolation of the antitumor agent CC-1065, 1.[2] Previously we described initial efforts in the construction of similar ring systems[3] *via* suitably substituted pyrroles and subsequent intramolecular cyclization providing cyclopropylenones such as 2-4. We now wish to report our findings concerning the chemistry of such systems and conversion into compounds similar to the A, B and C subunits of CC-1065.



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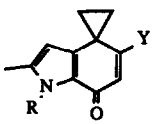
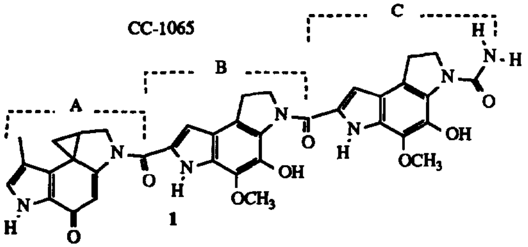


3 R=Me, Y=OCH$_3$
4 R=BOM, Y=NH$_2$

CC-1065



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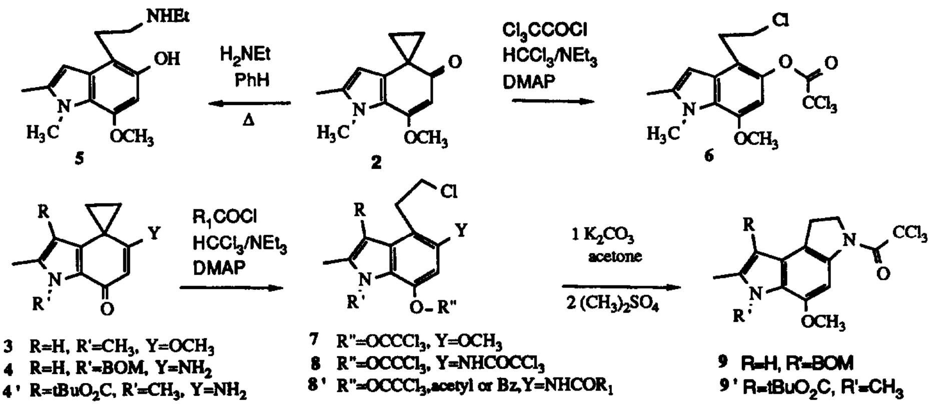
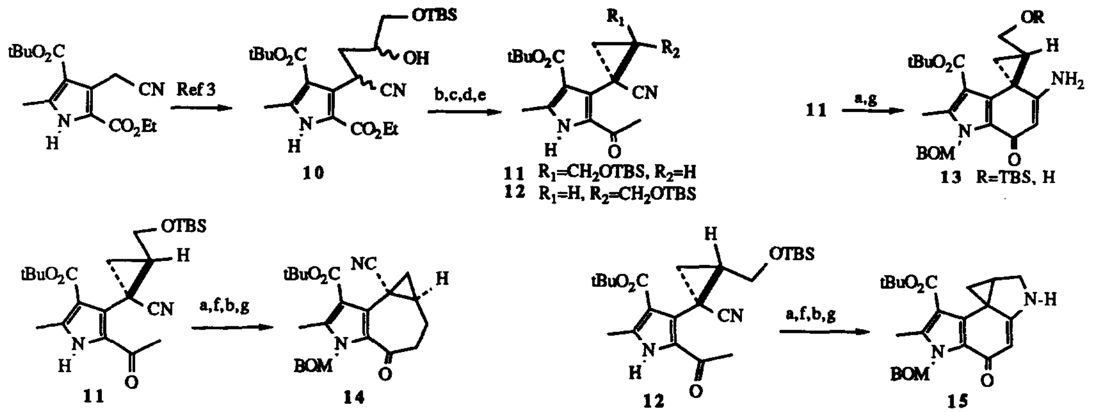
In light of the reaction of the A subunit in 1 with an adenine of DNA[4], we anticipated that nucleophiles would open the cyclopropane ring of indolenones such as 2-4 forming aromatic systems. The initial attempts at opening the cyclopropyl-4-spiroindol-7-one group of 3 under nucleophilic conditions in all cases either led to recovery of starting material or complex mixtures[5]. More forcing conditions (sealed tube, ethylamine in benzene, 110°C for 7 days) with isomer 2 provided the indolphenol 5[6] (60%).

Following several unsuccessful attempts at opening of the cyclopropane ring of 4 under standard nucleophilic conditions, cleavage was effected with trichloroacetyl chloride. Facile cyclopropane cleavage occured with concomitant O- and N-acylation giving rise to indole 8 (excess trichloroacetyl chloride, 0°C). Further investigations showed that both alkoxyenones 2 and 3 and amine 4' undergo facile cyclopropane opening and O/N-acylation under the acid chloride reaction conditions (*i.e* 2→6, 3→7 and 4'→8'). These ring opening-aromatization reactions are assumed to involve initial acyloxonium ion formation, and nucleophilic opening of the cylcopropane ring by chloride ion, providing the desired ring system. Conversion of indole 8 to the dihydropyrrolo[3,2-e]indole 9 was conveniently achieved by treatment with potassium carbonate in wet acetone causing intramolecular N-alkylation and trichloroacetate hydrolysis. O-Alkylation with dimethylsulfate gave pyrroloindole 9[6] (68% from 4).



Having shown that opening of the cyclopropane spiroindole is a viable route to the dihydropyrrolo-[3,2-e]indole ring system, attention was directed toward the A subunit. Pyrrolo acetonitrile dianion alkylation[3] with the iodide derived from the acetonide of glycerine, ketal cleavage and protection of the primary hydroxyl provided 10 as a mixture (1/1) of diastereomers. *A priori*, it was anticipated that cyclopropane formation by intramolecular alkylation would give 11 and 12 in a 1/1 ratio. However, conversion of alcohols 10 to the mesylates, *in situ* iodide formation and intramolecular alkylation provided a 5/1 mixture of preparatively inseparable cyclopropane isomers. The mixture of ethyl esters were converted[7] to methyl ketones (11 and 12) and separated by careful chromatography. Assignment of the isomers (E/Z) based on subsequent ring formation appeared easier than *via* spectroscopic techniques. N-Protection of the major methyl ketone isomer (*i.e.* 11) as its benzyloxymethyl (BOM) ether, followed by removal of the silicon protecting group, mesylation of the resulting alcohol and intramolecular cyclization provided a less polar material (78%, 11→14) to which we have assigned the structure 14[6]. The stereochemistry of 11 was thus interpreted to be as shown. Only the isomer in which the hydroxymethyl substituent and the pyrrole unit are cis on the cyclopropane ring could have undergone this cyclization. Similarly, protection of the pyrrole nitrogen of the minor methyl ketone isomer (*i.e.* 12), silicon protecting group removal, mesylation and treatment with KOtBu/THF resulted in facile cyclization providing a more polar material, 15 (71%, 12→15), a cyclopropylpyrroloindole similar in structure to the CC-1065 A subunit. The probable reaction pathway leading to this product involves intramolecular attack of the methyl ketone enolate on the nitrile followed by intramolecular

N-alkylation of the resulting imine anion and subsequent tautomerization to **15**. Initial attempts at converting the major methyl ketone



a) NaH, THF, BOMCl b) MsCl, NEt_3, CH_2Cl_2 c) NaI, THF, KOtBu
d) $LiCH_2SOCH_3$, THF, DMSO e) Al[Hg], THF, H_2O f) Bu_4NF, THF g) KOtBu, THF

isomer **11** to cyclopropylpyrroloindole **15** were unsuccessful due to our inability to regioselectively open the cyclopropanes of **13** using the trichloroacetyl chloride reaction conditions.

In conclusion, it has been shown that opening of cyclopropane spiro indoles is a viable route to functionalized dihydropyrrolo[3,2-e]indoles. The stereochemical outcome of the conversion of **10** to **11** and **12** presents a result that warrants further studies to give an understanding of this intramolecular alkylation and to increase the efficiency of cyclopropylpyrroloindole synthesis.

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References and Notes

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M. Warpehoski and V. Bradford, *Tetrahedron Lett.*, **1986**, *27*, 2735. For a general review of A, B and C ring synthesis see V. Reynolds, J. McGovren, L. Hurley, *J. Antibiot.* **1986**, *39*, 319.

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3. T. Bryson, G. Roth and Liu Jing-hau, *Tetrahedron Lett.*, **1986**, *27*, 3685. T. Bryson and G. Roth, *Tetrahedron Lett.*, **1986**, *27*, 3689.
4. L. Hurley, V. Reynolds, D. Swenson, G. Petzold and T. Scahill, *Science*, **1984**, *226*, 843.
5. Examples of the reaction conditions tried: TMSI, MeCN; Et_2AlCl, $CHCl_3$, pyrrolidine; $Me_2AlNHBn$, toluene; 48% HBr, THF; H_2NEt, benzene, 110°, sealed tube.
6. All spectral data are in accord with the assigned structure and all compounds have provided satisfactory mass spectra and carbon, hydrogen and nitrogen combustion analysis. Data for **9**: mp 165-167°C; ^{1}HNMR ($CDCl_3$, 300 MHz, ppm) 2.46 (s, 3 H, pyrrole C$\underline{H}_3$), 3.25 (t, 2 H, J = 7.8 Hz, C$\underline{H}_2$CH$_2$N), 3.88 (s, 3H, OC$\underline{H}_3$), 4.43 (s, 2 H, OC$\underline{H}_2$Ph), 4.64 (t, 2 H, J = 7.8 Hz, CH$_2$C$\underline{H}_2$N), 5.91 (s, 2 H, NC$\underline{H}_2$OBn), 6.18 (s, 1 H, pyrrole $\underline{H}$), 7.24 (m, 5 H, Ar $\underline{H}$'s), 7.78 (s, 1 H, Ar $\underline{H}$); IR ($CHCl_3$, cm^{-1}) 3000, 2940, 2850, 1665. Data for **13**: mp 155-159°C; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) -0.21 (s, 3 H, SiC$\underline{H}_3$), -0.16 (s, 3 H, SiC$\underline{H}_3$), 0.70 (s, 9 H, SiC(C$\underline{H}_3$)$_3$), 1.56 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.67 (m, 1 H), 1.90 (m, 1 H), 2.48 (s, 3 H, pyrrole C$\underline{H}_3$), 3.19 (t, J = 8.3 Hz, 1 H), 3.55 (dd, J = 11 Hz and 9 Hz, 1 H), 3.85(dd, J = 12 Hz and 5 Hz, 1 H), 3.99 (bs, 2 H, N$\underline{H}_2$), 4.59, 4.62 (AB quartet, J = 11.7 Hz, C$\underline{H}_2$Ph), 5.61 (s, 1 H, vinyl $\underline{H}$), 6.09, 6.37 (AB quartet, J = 10.5 Hz, 2 H, NC$\underline{H}_2$O), 7.26 (m, 5 H, Ar$\underline{H}$); IR ($CHCl_3$, cm^{-1}) 3500, 3420, 3240, 2980, 2880, 1690, 1600. Data for **14**: mp 95-96°C; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.14-1.32 (m, 2 H), 1.90 (m, 1 H), 2.39 (m, 1 H), 2.60 (s, 3 H, pyrrole C$\underline{H}_3$), 2.61-2.88 (m, 2 H), 4.47, 4.51 (AB quartet, J = 11.9 Hz, 2 H, C$\underline{H}_2$Ph), 5.53, 5.87 (AB quartet, J = 10.4 Hz, 2 H, NC$\underline{H}_2$O), 7.28 (m, 5 H, Ar$\underline{H}$). IR ($CHCl_3$, cm^{-1}) 3000-2830, 2220, 1690, 1640. Data for **15**: mp 205-225°C decomposition; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.18 (m, 1 H), 1.54 (s, 9 H, C(C$\underline{H}_3$)$_3$), 2.11 (m, 1 H), 2.54 (s, 3 H, pyrrole C$\underline{H}_3$), 3.55 (m, 2 H), 3.70 (m, 1 H), 4.60 (s, 2 H, C$\underline{H}_2$Ph), 4.80 (bs, 1 H, N$\underline{H}$), 5.47 (s, 1 H, vinyl $\underline{H}$), 6.22, 6.27 (AB quartet, J = 10.5 Hz, 2 H, NC$\underline{H}_2$O), 7.26 (m, 5 H, Ar$\underline{H}$). IR $CHCl_3$, cm^{-1}) 3450, 3240 (b), 2990, 2880, 1690, 1615, 1570. The ^{13}C NMR spectrum of **15**: (20 MHz, $CDCl_3$, ppm) 178.3, 170.4, 164.1, 141.3, 138.1, 130.1, 128.1, 127.8, 127.7, 127.5, 127.4, 110.4, 96.5, 80.5, 73.0, 70.1, 68.1, 50.4, 31.6, 28.4, 27.7, 26.0, 12.0. CC-1065 has a carbonyl resonances at 176.4 ppm.
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