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Total Synthesis of U-71,184, A Potent New Antitumor Agent Modeled on CC-1065

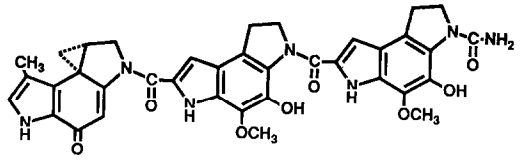
by: M.A. Warpehoski*, Cancer and Viral Diseases Research,
The Upjohn Company, Kalamazoo, MI 49001

Abstract: The synthesis of U-71,184 (**2**), a highly potent analog of the novel antitumor antibiotic CC-1065, is described, the penultimate step of which involves the unmasking of a *p*-hydroxy phenethyl mesylate, which undergoes facile intramolecular elimination to afford the reactive cyclopropylspirocyclohexadienone. Its enantiomer, U-71,185, was also prepared and shown to be biologically inactive.

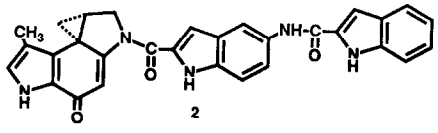
CC-1065 (**1**) is one of the most potent antitumor antibiotics known.[1] It possess a unique DNA alkylating capability in its cyclopropylpyrroloindole "left-hand segment,"[2] and an extraordinary affinity and specificity for binding to the minor groove of B-DNA, apparently attributable in large measure to its DNA groove-complementary shape.[1,2] The novel structural features of its component pyrroloindole segments has stimulated a great deal of recent synthetic interest in CC-1065.[3] Since the publication of the first synthesis of the biologically active but much less potent left-hand segment,[3a] **3**, our own efforts have been motivated by the search for potent and active analogs of CC-1065, which might be devoid of the delayed toxicity that precludes the clinical development of the natural product.[4]

We wish to report here the synthesis of U-71,184 (**2**) a new antitumor agent modeled on CC-1065 with greatly superior activity against a variety of murine tumors and human tumor xenografts.[5] Like CC-1065, U-71,184 binds to double stranded B-DNA, and is equipotent with the natural product both in vitro and in vivo, but unlike CC-1065, it does not cause delayed death in mice.[5]

U-71,184 may be viewed as a simplified model of CC-1065, possessing its essential electronic features and general shape and dimensions, but synthetically much more accessible, given an adaptable left-hand segment synthesis and a viable strategy for convergence with a right-hand appendage.



1



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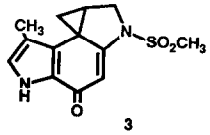
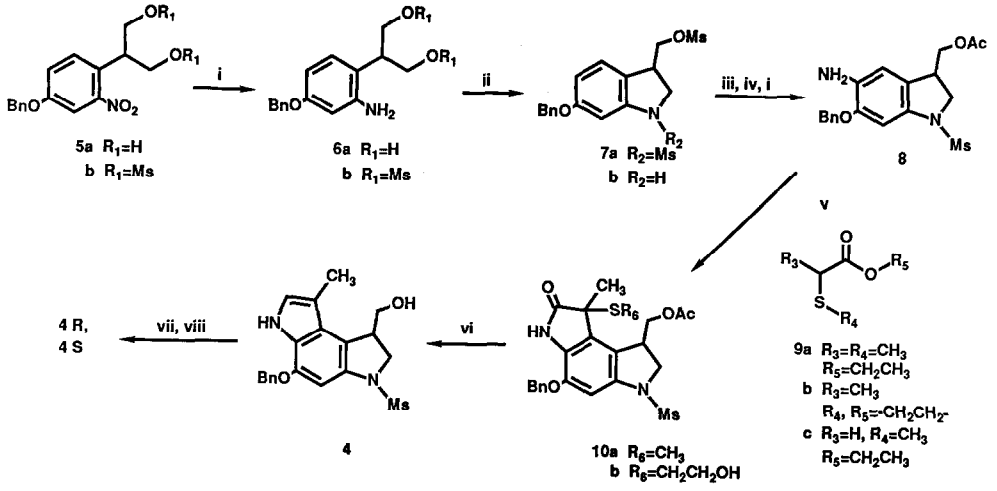


3

We employed the Wierenga strategy,[3a] with the modifications discussed below, for the construction of the key dihydropyrrolo[3,2-e]indole intermediate **4**, which was then resolved through its diasteriomeric esters with N-BOC-L-tryptophan, to afford **4R** and **4S** (Scheme 1).

Scheme 1

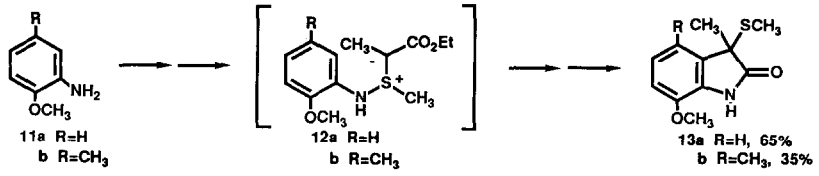


i. H_2, PtO_2; *ii.* MsCl, pyr., 0°; *iii.* NaOAc, DMF, EtOH, Δ; *iv.* HNO_3, CH_2NO_2, 0°; *v.* 1) SO_2Cl_2, **9**, Proton Sponge, CH_2Cl_2, -78°; *2)* Et_3N; *3)* HOAc (for **9c**); *vi.* BH_3SMe_2, THF, mol-sieves; *vii.* N-BOC-L-tryptophan, EDC, CH_2Cl_2; separation *viii.* NaOH

In the original synthesis[3a] **5a** was converted to **5b**, before reduction to, presumably, **6b**, and spontaneous cyclization to the indoline **7b**, which was quickly mesylated. This route often gave poor yields on scale-up, presumably because of intermolecular reactions of **6b** and **7b** in concentrated solutions. To circumvent this problem diol **5a** was directly hydrogenated to the anilino diol **6a** (75%), which was mesylated and cyclized in situ to **7a** (90%). Acetyl exchange, nitration, and reduction[3a] afforded **8** (40% from **7a**).

The most problematic step in the Wierenga synthesis was the elaboration of the 8-methylindole ring of **4**, which was carried out elegantly, but in a disappointingly low 20% yield, via Gassman's oxindole synthesis[6] from aniline **8** and sulfide **9a**, followed by efficient reduction of the resulting **10a** to **4** with borane-dimethylsulfide.[7] Model studies (Scheme 2) on *o*-anisidine (**11a**) and 5-methyl-*o*-anisidine (**11b**) indicated that a substituent adjacent to the ring position attacked by the

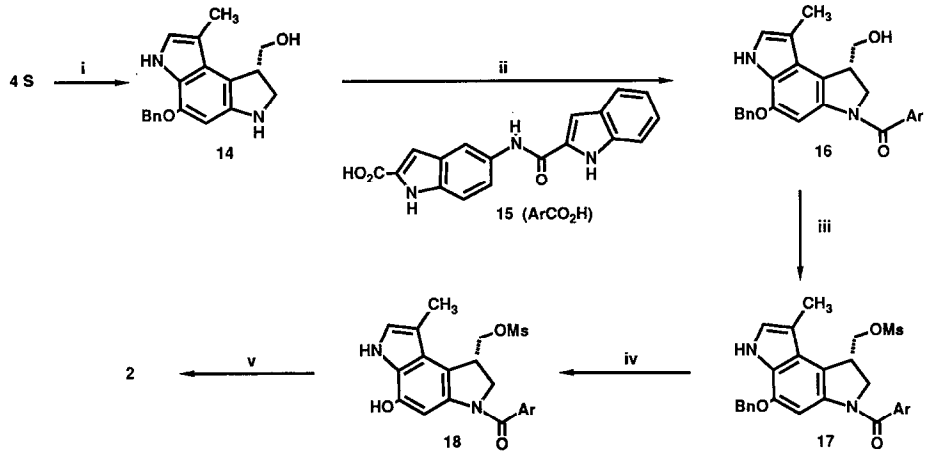
Scheme 2



intermediate azasulfonium ylide (**12**) presented a steric impediment that significantly reduced the yields in this reaction.[8] Consistent with this argument was our observation that the less sterically demanding sulfide **9c** (Scheme 1) afforded the corresponding oxindole upon reaction with **8** in 85-90% yield. While this oxindole could be α-methylated with Na_2CO_3/CH_3I to afford, after careful purification from N-methylated side products, **10a** (60%), a shorter and cleaner alternative was the use of the cyclic sulfide **9b**[9] in the Gassman reaction with **8**. The relief of steric crowding occasioned by tying back the substituents on the sulfide into a ring system was reflected in the 58% yield of **10b**, directly from **8**. Borane-dimethyl-sulfide smoothly reduced **10b** to racemic **4** (81%).[7]

Numerous attempts to resolve **4** by its esterification with chiral acids, including (+) MTPA, were unsuccessful. Finally (Scheme 1) derivatization of **4** with N-BOC-L-tryptophan resulted in an extraordinarily selective crystallization of the **S,S** diasteriomer. A single additional recrystallization (THF, hexane) afforded material of >99% diasteriomeric purity, judged by analytical HPLC, in 58% of the theoretical yield. Saponification gave **4S** (m.p. 165-166°C $[\alpha]_D^{25}$ -30, c = 0.58, EtOH). The mother liquors were carefully chromatographed (silica gel, THF/hexane) to provide a sample, after saponification, of **4R** in comparable optical purity (m.p. 163-165°C $[\alpha]_D^{25}$ +29, c = .82, EtOH).[10]

Scheme 3



i. Red-Al (6 eq.), THF, toluene, 85°, 0.5 hr; *ii.* EDC (1 eq.), DMF, 25°, 48 hr; *iii.* MsCl (4 eq.), pyridine, DMAP, 25°, 0.5 hr; *iv.* NaI (7 eq.), TMS-Cl (7 eq.), CH_3CN, PhCN, 80°, 0.5 hr; *v.* Et_3N (excess), THF, EtOAc, 25°, 0.5 hr

The convergence of the left and right-hand segment precursors and their elaboration into U-71,184 is shown in Scheme 3. As anticipated by Wierenga,[3a] Red-Al removal of the sulfonamide protecting group readily afforded the air sensitive indoline **14**, which, was condensed with **15**[11] to give the poorly soluble adduct **16** as a crude solid (70% from **4**). Activation of the homobenzylic alcohol was effected with MsCl to give **17** nearly quantitatively. Initial efforts to remove the benzyl protecting group from **17** by catalytic hydrogenation yielded only 5% (from **16**) of **2**. In situ generated TMS-I (6-8 eq) in refluxing CH_3CN was more successful. The crude product mixture, containing both **18** and **2**, was reacted with triethylamine to effect complete ring closure. The

chromatographed product (**2**, U-71,184) precipitated from a small volume of acetone containing 1% triethylamine as a light yellow powdery solid (20-30% from **16**).[12]

In like manner **4R** was converted to U-71,185, the enantiomer of U-71,184. U-71,185 was two orders of magnitude less cytotoxic to L1210 cells in vitro than was U-71,184, and was inactive in vivo in systems and at doses for which U-71,184 was highly curative.[13]

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9. Sulfide **9b** was prepared in 60% overall yield from ethyl-2-bromopropionate and mercaptoethanol by halide displacement, (K_2CO_3, acetone), saponification, acidification, and dehydration (toluene, reflux).
10. Alternatively, the mother liquors could be saponified and condensed with N-BOC-D-tryptophan. From this mixture the R:R diasteriomer could be fractionally recrystallized to >99% diasteriomeric purity.
11. **15** was prepared by condensation of indole-2-carboxylic acid and ethyl 5-amino-indole-2-carboxylate in DMF with ethyl dimethylaminopropylcarbodiimide (EDC), and saponification of the ester (50%). Ethyl 5-aminoindole-2-carboxylate was obtained nearly quantitatively by catalytic hydrogenation of ethyl 5-nitroindole-2-carboxylate [S.M. Parmerter, A.G. Cook, and W.B. Dixon, J. Amer. Chem. Soc. 80, 4621 (1958)].
12. ^{1}H-NMR (DMSO-d_6) δ: 1.4 (m, 1H), 2.0 (s + m, 3H + 1H), 3.2 (m, 1H) 4.5 (m, 2H), 6.7 (s, 1H), 6.9 (s, 1H), 7.1-7.7 (m, 9H) 8.2 (brs, 1H), 10.3 (brs, 1H), 11.8 (brs, 1H), 11.9 (brs, 1H). $[\alpha]_D^{25}$ + 155 (c = 0.278, DMF). The CD curve of U-71,184 patterned that of CC-1065, supporting its absolute stereochemistry as shown. ^{1}H-NMR for **16** (pyridine -d_5) δ: 13.2 (brs, 1H); 12.84 (brs, 1H); 12.07 (brs, 1H); 11.06 (brs, 1H); 8.93-8.64 (m, 2H + pyr.); 8.13 - 7.25 (m, 14 H + pyr); 5.3 (brs + m, 3H); 4.73 (m, 1H); 4.4-3.75 (m, 3H); 2.52 (brs, 3H). All new compounds were homogeneous by TLC and gave satisfactory ir, NMR, m.s., and exact mass and/or combustion analysis.

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