Communications to the Editor

Coupling of Cyclopropapyrroloindole (CPI) Derivatives. The Preparation of CC-1065, ent-CC-1065, and Analogues

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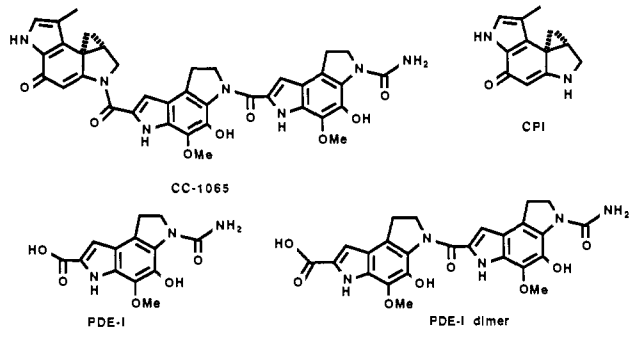
CC-1065, a novel antitumor antibiotic,[1] has drawn significant synthetic attention[2] due to its unusual structure and potent biological properties. Interest in this area waned to some extent with the discovery of dealyed deaths[3] caused by CC-1065 but has been reignited by the recent disclosure of highly potent and active analogues which do not produce this unusual toxicity.[4]

Most of the synthetic efforts have been directed at the synthesis of either the left hand segment (i.e., CPI) or at PDE-I and its dimer. Warpehoski[4a] describes a method for the coupling of the

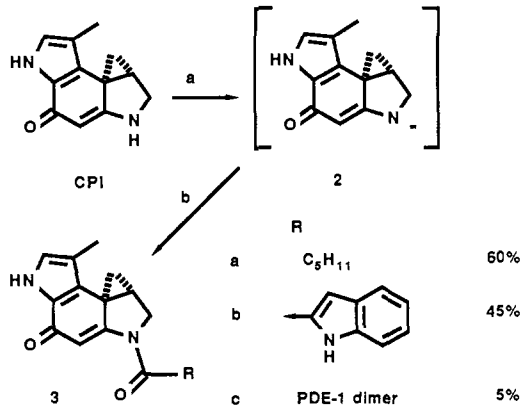


two portions, suitable for analogues but not for the preparation of CC-1065 itself.[5] We report here coupling of CPI and its derivatives with a variety of acids including PDE-I dimer.[6] This provides the first synthesis of CC-1065 as well as its enantiomer[7] and allows rapid and efficient preparation of a wide range of CC-1065 analogues.

Conceptually, the ideal approach to CC-1065 and its analogues is the direct coupling of CPI to PDE-I dimer or other acids. We felt that it might be possible to prepare specifically the anion of the vinylogous amide of CPI without deprotonating the pyrrole nitrogen (Scheme I).

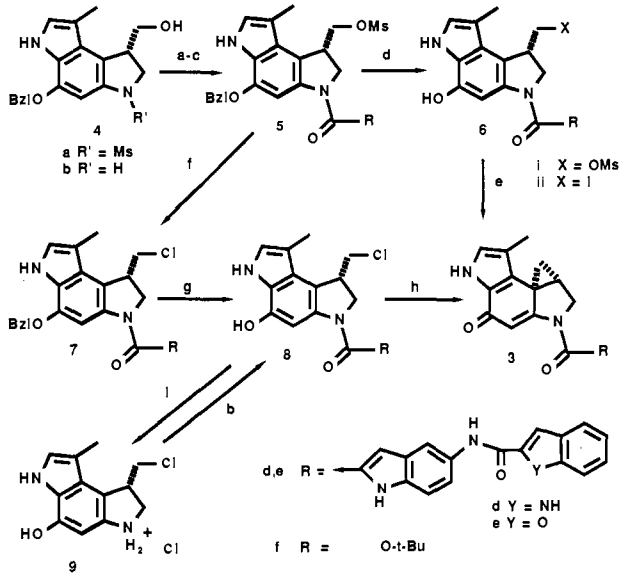
In the event, treatment of CPI with LDA in THF containing HMPA at −78 °C followed by the addition of an acid chloride such as hexanoyl chloride or indole-2-carboxylic acid chloride resulted in the direct formation of **3a** and **3b**, respectively, in 40–60% yields.[8,9]

Scheme I[a]



[a] (a) LDA, THF–HMPA, −78 °C; (b) RCOCl (from RCOOH and $(COCl_2)$ or RCOOH, EDC, and hydroxybenzotriazol.

Scheme II[a]



[a] (a) REDAL, THF–toluene or glyme 85 °C; (b) EDC, RCOOH; (c) MsCl, pyridine; (d) H_2, Pd/C or TMSCl, NaI, CH_3CN; (e) Et_3N–THF or EtOAc; (f) LiCl, DMF, 80–100 °C; (g) NH_4OHCO, Pd/C, MeOH; (h) Et_3N, H_2O, CH_3CN–1:1:1; (i) HCl, EtOAc.

(1) (a) Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629. (b) Martin, D. G.; Biles, C.; Gerpheide, S. A.; Hanka, L. J.; Krueger, W. C.; McGovren, J. P.; Mizsak, S. A.; Neil, G. L.; Stewart, J. C.; Visser, J. *J. Antibiot.* **1981**, *34*, 1119. (c) Reynolds, V. L.; McGovren, J. P.; Hurley, L. H. *J. Antibiot.* **1986**, *39*, 319.

(2) Where more than one paper has been published by a group only the most recent paper is listed. (a) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (b) Bryson, T. A.; Roth, G. A. *Tetrahedron Lett.* **1986**, *27*, 3689. (c) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19. (d) Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 283. (e) Carter, P.; Fitzjohn, S. H.; Magnus, P. *J. Am. Chem. Soc.* **1987**, *109*, 2711. (f) Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *Tetrahedron Lett.* **1987**, *28*, 3163. (g) Sundberg, R. J.; Baxter, E. W. *Tetrahedron Lett.* **1986**, *27*, 2687. (h) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621.

(3) McGovren, J. P.; Clarke, G. L.; Pratt, E. A.; DeKoning, T. F. *J. Antibiot.* **1984**, *37*, 63.

(4) (a) Warpehoski, M. A. *Tetrahedron Lett.* **1986**, *27*, 4103. (b) Warpehoski, M. A.; Kelly, R. C.; McGovren, J. P.; Wierenga, W. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 870.

(5) Warpehoski, M. A., private communication.

(6) Martin, D. G.; Mizsak, S. A.; Krueger, W. C. *J. Antibiot.* **1985**, *38*, 746.

(7) Natural CC-1065 and its congeners all possess the spirocyclopropyl ring down as shown in this paper. The enantiomeric (= ent) series (not shown) differs only in that the spirocyclopropyl ring of the CPI moiety protrudes above the plane. Both enantiomers of CPI derivative **4** are available (ref 4a).

(8) The conditions of this reaction are quite critical. Using different bases such as NaH or KH or conducting the reaction in THF in the absence of HMPA resulted in much lower yields.

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No product of the acylation of the pyrrole nitrogen could be found.[10] However, the yield of CC-1065 by this route was only 5%.[11]

We then reexamined the earlier route, which had carried out the coupling on the amine **4b** (Scheme II), but had encountered difficulties in removing the benzyl protecting group.[4]

Condensation of **4b** with a carboxylic acid gives the amides in 70–80% yield. Reaction with mesyl chloride quantitatively yields the mesylates **5**. These compounds, however, are unstable and cannot be chromatographed without decomposition. Further, they often cyclize during attempted hydrogenolysis of the benzyl ether, leading to products of hydrogenolysis of the spirocyclopropyl ring system. In situ generated TMSI[4a] is highly unpredictable and often gives very poor yields of the desired product **6** or **3** (as is the case of CC-1065). Extensive efforts to find suitable substitute protecting groups for the benzyl moiety failed. We then tried changing the leaving group. Reaction of **5** with LiCl in DMF gives excellent yields of the chlorides **7** (70–90%). These compounds are significantly more stable and soluble than the mesylates and can readily be chromatographed. Phase transfer catalytic hydrogenolysis of **7** produces **8** in essentially quantitative yield. Interestingly, unlike **6**, the phenol chloride **8** does not close to **3** simply by treatment with 1–2 equiv of triethylamine in anhydrous solvents. In fact treatment of **8** with strong bases (LDA, NaH, KH, or KO-*t*-Bu) in a variety of solvents leads to **3** in only poor yield. The spirocyclopropyl derivative **3** can be produced, however, in essentially quantitative yield by reacting **8** (10 mg/mL) with a 1:1:1 mixture of triethylamine/acetonitrile/water at 25 °C. Thus, the closure appears to require, in addition to the push of the anion, also the pull of the hydration of the chloride by water in order to proceed. In this manner the CC-1065 analogues **3d** and **3e** were prepared from **4a** in an overall yield of 46% each.[4a,9]

While this multistep sequence has been greatly improved, it is still not a feasible route to CC-1065 or other complex analogues. It is, however, an efficient route to the Boc derivative **8f** (54% from **4a**), which is stable, highly soluble, and readily purified.

Happily, treatment of **8f** (8 mg/mL) with HCl gas in ethyl acetate (half to fully saturated at 25 °C) readily gives **9** (Scheme II). The free amine corresponding to **9** and the hydrochloride itself are extremely unstable, and short exposure to air turns them black. However, under an inert atmosphere it is possible to convert **9** to **8** by coupling with a carboxylic acid and EDC in overall yields of 70–90%. Cyclization in aqueous triethylamine affords **3**. With use of this chemistry the analogues **3a**,**b**,**d**,**e** were prepared.[9] Similarly natural CC-1065 and its enantiomer[12] were made on a 10–20-mg scale. The yields in this case are only 40–50% due to the greater complexity and insolubility in comparison with simpler analogues. The natural CC-1065 produced by this route is identical in all respects with CC-1065 isolated from natural sources.[1a,b,13] When taken with the total synthesis of PDE-1 dimer[2a,f,14] this constitutes a total synthesis of this important natural product. The ent-CC-1065 is also an extremely interesting material. Earlier reports[4a] of compounds in the ent series have disclosed them to be essentially inactive in the biological systems. Ent-CC-1065 on the other hand possesses both cytotoxicity[13] and biological effectiveness in its own right at similar concentrations to CC-1065 itself in the treatment of P388 leukemia in mice.[15] Further discussion in this area will be the subject to a separate communication.

Registry No. 3a, 110314-40-4; **3b**, 110352-06-2; **3d**, 101222-80-4; **3e**, 110314-48-2; (*S*)-**4a**, 101222-79-1; (*R*)-**4a**, 108867-95-4; **5d**, 108833-15-4; **5e**, 110314-43-7; **5f**, 110314-49-3; **7d**, 110314-44-8; **7e**, 110314-45-9; **7f**, 110314-50-6; **8a** (R = C_5H_{11}), 110314-52-8; **8b** (R = 1*H*-indol-2-yl), 110314-53-9; **8d**, 110314-46-0; **8e**, 110314-47-1; **8f**, 110314-51-7; **9**, 110314-54-0; CC-1065, 69866-21-3; ent-CC-1065, 110352-07-3; CPI, 110352-05-1; PE-I dimer, 98296-23-2; PDE-I dimer acid chloride, 110314-41-5; $CH_3(CH_2)_4CO_2H$, 142-62-1; *t*-$BuOCO_2H$, 51300-90-4; hexanoyl chloride, 142-61-0; 1*H*-indole-2-carbonyl chloride, 58881-45-1; 5-[[(1*H*-indol-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylic acid, 101134-91-2; 5-[[(benzofuran-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylic acid, 110314-42-6; 1*H*-indole-2-carboxylic acid, 1477-50-5.

(9) NMR and mass spectral data are presented. Compound **3a**: NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 7 Hz), 1.15–1.45 (6 H, m), 1.6–1.8 (1 H, m), 2.0 (4 H, s + m), 2.5 (2 H, t, J = 7 Hz), 2.75–3.0 (1 H, m), 3.9–4.25 (2 H, m), 6.7 (1 H, m), 6.9 (1 H, m), 10.35 (1 H, brs); MS (FAB), calcd for $C_{18}H_{23}N_2O_2$ 299.1759, found 299.1745. Compound **3b**: NMR (DMSO-d_6) δ 1.38 (1 H, t, J = 4 Hz), 2.0 (4 H, brs), 3.2 (1 H, m), 4.45 (2 H, m), 6.72 (1 H, s), 6.95 (1 H, m), 7.15–7.8 (5 H, m), 11.55 (1 H, brs); MS, m/e 343 (M^+), 326, 200, 199, 144. Compound **3d**: see ref 4a. Compound **3e**: NMR (DMF-d_7) δ 1.51 (1 H, t, J = 5 Hz, 2.04–210 (1 H, m), 2.102 (3 H, s), 3.24–3.31 (1 H, m), 4.60 (1 H, d, J = 10 Hz), 4.69 (1 H, dd, J = 4, 10 Hz), 6.84 (1 H, s), 7.03 (1 H, s), 7.32 (1 H, s), 7.39–7.92 (7 H, m), 8.46 (1 H, d, J = 2 Hz), 10.6 (1 H, s), 11.83 (1 H, s); MS (FAB), calcd for $C_{30}H_{23}N_4O_4$ 503.1719, found 503.1742. Compound **5f**: NMR ($CDCl_3$) δ 1.6 (9 H, s), 2.3 (3 H, s), 3.4–4.4 (6 H, m), 5.15 (2 H, s), 6.9 (1 H, s), 7.2–7.8 (6 H, m), 8.5 (1 H, s); MS (FAB), calcd for $C_{24}H_{28}N_2O_4$ 408.2049, found 408.2051. Compound **7f**: NMR ($CDCl_3$) δ 1.6 (9 H, s), 2.4 (3 H, s), 3.2–4.5 (5 H, m), 5.2 (2 H, s), 7.0 (1 H, s), 7.3–7.7 (6 H, m), 8.3 (1 H, m); MS (FAB), calcd for $C_{24}H_{27}ClN_2O_3$ 426.1710, found 426.1721. Compound **8f**: NMR ($CDCl_3$, acetone-d_6) δ 1.6 (9 H, s), 2.4 (3 H, s), 3.3–4.4 (5 H, m), 7.1 (1 H, s), 7.4 (1 H, s), 8.9 (1 H, s), 9.7 (1 H, s); MS (FAB), calcd for $C_{17}H_{21}ClN_2O_3$ 336.1241, found 336.1230.

(10) The structure of the desired product could easily be shown by comparison with authentic material prepared by the Warpehoski chemistry[4] and by 500 MHz COSY experiments which showed the pyrrole N–H coupled to the 2-pyrrole hydrogen and that to the pyrrole methyl group. We thank T. A. Scahill and R. M. Jensen of the Physical and Analytical Chemistry Unit of the Upjohn Company for running these NMR spectra.

(11) The reaction was run on a 1–2-mg scale. The material was shown to be identical with CC-1065 by TLC and bioassay.

(12) Prepared from the enantiomer of compound **4**.[4a]

(13) The NMR and UV of natural, synthetic, and ent-CC-1065 are identical within experimental error (see ref 1b). The $[\alpha]_D^{25}$ for natural CC-1065, synthetic CC-1065, and ent-CC-1065 are, respectively, +97°, +98°, and −96° (c 0.2, DMF). The in vitro L 1210 is given as the concentration which inhibits the growth of logarithmically growing murine leukemia L 1210 cells by 50% [ID_{50}]: natural CC-1065, $ID_{50} = 1.9 \times 10^{-12}$ g/mL; synthetic $ID_{50} = 2.5 \times 10^{-12}$ g/mL; ent, $ID_{50} = 4.5 \times 10^{-12}$ g/mL. We thank the Upjohn scientists L. H. Li and J. W. Culp for the in vitro L 1210 data.

(14) (a) Cava, M. P.; et al., private communication. (b) Magnus, P.; et al., private communication. We thank these authors for disclosing their syntheses to us prior to publication.

(15) Private communication from L. H. Li and T. F. DeKoning of the Upjohn Cancer and Viral Diseases Unit. We thank these authors for release of this information prior to publication.

1,3-Hydrogen Shifts in Olefin Radical Cations: An ab Initio Study

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Recent work on cycloadditions[1] involving radical cations has demonstrated that molecular ions can undergo extremely facile reactions that would be Woodward–Hoffmann forbidden for the neutral molecule. Another class of reactions treated by Woodward and Hoffmann,[2] sigmatropic rearrangements, also behave differently in radical cations and neutral radicals than in closed shell molecules[3] but have not been investigated in detail, especially in the case of hydrogen shifts. Recently, however, Fujisawa et al.[4] reported that the reaction of the ethylene radical cation with ethylene in a Freon matrix leads to a radical cation that has

(1) See: Lorenz, K. T.; Bauld, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 1157 and references therein.

(2) See: Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.

(3) Hopilliard, Y.; Bouchoux, G. *Org. Mass Spectrom.* **1982**, *17*, 537. See also: Dormans et al. (Dormans, G. J. M.; fransen, H. R.; Buck, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 1213) for an analogous photochemical reaction.

(4) Fujisawa, J.; Sato, S.; Shimokoshi, K. *Chem. Phys. Lett.* **1986**, *124*, 391.

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