consistent with the native state: (1) it binds δ-anilino-1-naphthalenesulfonate with a dissociation constant of approximately 50 μM; (2) the resonances in the proton NMR spectrum are somewhat broader than expected for a protein of this molecular weight, suggesting some mobility or aggregation. These results are not surprising, since only one of the helix/helix interfaces has been optimized. We are therefore working on further optimizing the packing of α_2C.

Acknowledgment. We thank Sharon Jackson and Arlene Rockwell for assistance in peptide synthesis and Tracy Handel for helpful discussions.

Supplementary Material Available: Fast atom bombardment mass spectrum of α_2C and plots of the intensity of the resolved methyl resonances in the NMR spectrum of α_2C as a function of temperature and of the intensity of the far-UV CD signal at 222 nm as a function of temperature (3 pages). Ordering information is given on any current masthead page.

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Total Synthesis of Kuanoniamines and Dercitins

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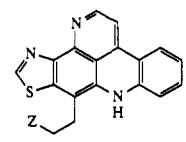
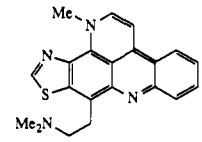
Received September 3, 1992

Kuanoniamines B–D (**1–3**)[2] and dercitins (**4, 5**)[3] are structurally unique, highly cytotoxic thiazolopyridoacridine alkaloids obtained from marine sources (Scheme I).[4] Interestingly, the moderate potency observed for kuanoniamines is greatly enhanced in **5**, which exhibits not only strong antitumor activity in vitro and in vivo but also immunosuppressive and antiviral properties.[5] It should be noted that materials structurally related to **1–5** are known to be inhibitors of reverse transcriptase,[6] raising the possibility that kuanoniamines and dercitins may be active against HIV. Indeed, a recent report provides some support for this hypothesis.[7]

Scheme I



1 Z = *i*-BuCONH
2 Z = EtCONH
3 Z = MeCONH
4 Z = NMe_2



5

The new alkaloids are very rare substances, and in any event their compact aromatic framework does not lend itself to modification for the purpose of SAR studies. No synthetic approaches to this class of alkaloids are known.[8] Furthermore, the structure of **5** was originally misassigned and later corrected.[3] These problems conspire to seriously complicate any further investigation of the potentially important biological properties of **1–5**. In light of these facts, we launched a synthetic program with the intent of solving such problems. This effort has now culminated with the first total synthesis of **3–5**, as described below.

Construction of the ring system of **1–5** relied on the application of our pyridine-forming reaction as a key step.[9] Thus, ytterbium(III)-mediated cycloaddition of ethyl vinyl ether to enone **6** and treatment of the intermediate adduct with $HONH_2$·HCl in MeCN at reflux furnished the pyridine **7**, which was converted to ketone **8** (Scheme II).[10] It was anticipated that the thiazole unit would be most readily installed at the stage of **8**. Indeed, bromination of the α-position of the carbonyl group (pyridinium tribromide)[11] and Traumann reaction[13] of crude **9**[12] furnished the expected aminothiazole **10**, which was efficiently deaminated[14] to the desired **11**.[15] Cleavage of the acetate gave alcohol **12**, from which mesylate **13** was obtained quantitatively. The routes to dercitins and kuanoniamines diverged at this point.

Kuanoniamine D (**3**), an especially active member of the omonimous family, was selected as our primary target. Thus, the mesylate **13** was advanced to amide **16** (Scheme III), from which totally synthetic **3**[15] was secured in a single step and in 62% chromatographed yield by triplet-sensitized photolysis (acetophenone, 150-W Sylvania sunlamp, Pyrex)[16] of the aromatic azide. This reaction proceeded with in situ oxidation of the primary photoproduct **17**, presumably through H-atom transfer to photoexcited acetophenone. The overall yield of **3**[17] from **6** was 10.0% over 12 steps.

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(5) Kuanoniamine D, a particularly active member of the family, shows an IC_{50} value against KB cells equal to 1.0 μg/mL (ref 2). Reported data against P388 leukemia for dercitin are as follows: IC_{50} = 50 ng/mL; T/C = 170% at 5 mg/kg. Immunosuppressant activity: 0% murine MLR at 10 ng/mL. Antiviral activity: strong inhibition of Herpes simplex I at 5 μg/well with moderate cytotoxicity; complete inhibition of murine A59 coronavirus at 1 μg/well with no cytotoxicity (ref 3).
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(10) Ciufolini, M. A.; Byrne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016. Compounds **8–16** and **18–19** emerged as 1:1 mixtures of diastereomeric rotamers as a result of axial dissymetry caused by restricted rotation of the azidophenyl group.
(11) Cf. Kornfeld, E. C.; Fornefeld, E. J.; Kline, B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.
(12) This material is difficult to purify because of its propensity to undergo aromatization (-HBr).
(13) Traumann, V. *Liebigs Ann. Chem.* **1888**, *249*, 31.
(14) Cf. Doyle, M. P.; Dellaria, J. F., Jr.; Siegfrid, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494.
(15) Melting points of selected compounds (uncorrected): **11**, mp 163–164 °C; synthetic **3**, yellow microcrystals changing to red-violet in acidic medium, decomposed at 260 °C without melting, lit.[2] mp >300 °C; synthetic **4**, yellow microcrystals changing to red-violet in acidic medium, mp 177–179 °C, lit.[3] mp 176 °C; **19**, 167–168 °C; **20**, 171–172 °C; **21**, 170–171 °C; synthetic **5**, purple microcrystals changing to red in acidic medium, mp 165–167 °C, lit.[3] mp 168 °C.
(16) (a) Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzsky, H. *Tetrahedron Lett.* **1976**, *17*, 4513. (b) Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzsky, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2194. See also ref 10.
(17) The spectral data for this synthetic material, including HRMS measurements, were in complete agreement with the literature. Unfortunately, we were unable to obtain an authentic sample of the natural product for the purpose of direct comparison.

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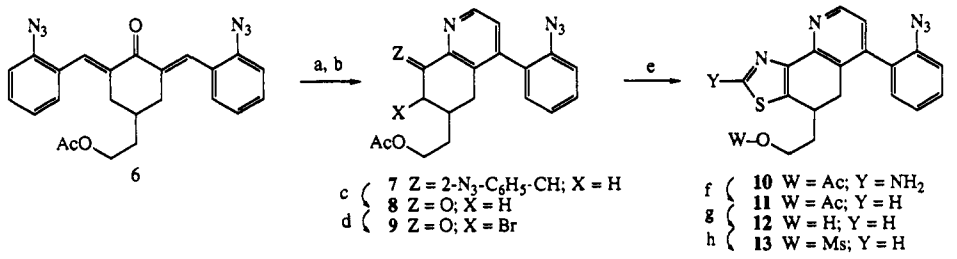
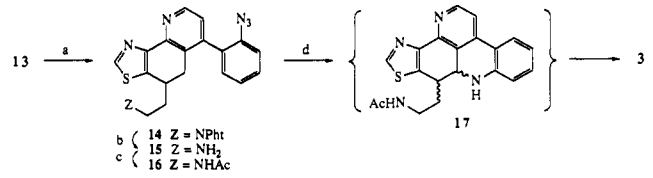
Scheme II[a]



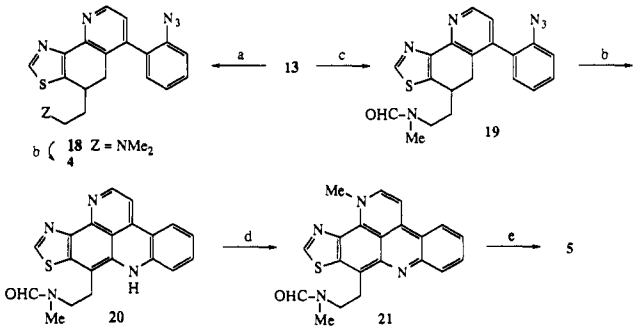
[a] (a) Ethyl vinyl ether, $Yb(fod)_3$, $(CH_2Cl)_2$, reflux, 99%; (b) $HONH_3^+Cl^-$, MeCN, reflux, 61%; (c) O_3, CH_2Cl_2/MeOH, -78 °C, then Me_2S, -78 °C to room temperature, 78%; (d) pyridinium tribromide, AcOH, 50 °C, 70%; (e) thiourea, EtOH, 35 °C, 15 min, 95%; (f) *i*-AmONO, DMF, 80 °C, 82%; (g) K_2CO_3, MeOH, 94%; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%.

Scheme III[a]



[a] (a) K-phthalimide, DMF, 50 °C, 84%; (b) $N_2H_4 \cdot H_2O$, MeOH, room temperature, 30 min, 94%; (c) Ac_2O, pyridine, room temperature, 86%; (d) *hν*, 9:1 chlorobenzene/acetophenone, 110 °C, 62% chromatographed.

Scheme IV[a]



[a] (a) 40% aqueous Me_2NH, DMF, 86%; (b) *hν*, 9:1 chlorobenzene/acetophenone, 110 °C, 61% (chromatographed) for **4**, 63% (chromatographed) for **20**; (c) MeNHCHO, NaH, 0 °C, 77%; (d) MeI, K_2CO_3, PhH, 70 °C, 99%; (e) $POCl_3$, then $NaBH_4$, DME, 87%.

Fully synthetic nordercitin[15] was obtained from **13** by mesylate displacement with dimethylamine and photolysis (61% chromatographed yield) of the intermediate **18**.[17] The synthesis of dercitin itself required selective N-methylation of the pyridine ring. It was surmised that such selectivity might be achieved within the domain of compound **19**, where the highly nucleophilic side chain dimethylamino group, which would interfere with the methylation step, is present in latent form. It was further assumed that the feeble nucleophilicity of the dihydroacridine segment of the molecule should permit full expression of the well-established 20-fold greater reactivity of the pyridine nitrogen vs its thiazole counterpart toward methyl iodide.[18] These expectations were realized. Thus, reaction of **13** with *N*-sodio-*N*-methylformamide[19] generated amide **19**,[15] which was converted into the aromatized pentacyclic compound **20**[15] in 63% chromatographed yield by the now familiar photolytic step. Treatment of **20** with MeI provided derivative **21**[15] in quantitative yield. The formamide was best reduced to a dimethylamine by the method of Kuehne,[20] a transformation that secured fully synthetic dercitin[15] in 87% yield.[17] The overall yields of **4** and **5** from **6** were 12.5% and 10.0% over 10 steps and over 12 steps, respectively.

These practical syntheses dramatically increase the availability of the new natural products. In addition, they confirm the structure of **5** and define a general entry to the thiazolopyridoacridine alkaloids. The synthetic plan should permit introduction of diverse structural variations into side chain and ring system analogues of **1–5**, facilitating eventual medicinal chemistry work. From a chemical standpoint, this work reaffirms the value of our pyridine-forming reaction and of photochemical transformations of azides in the construction of complex polycyclic heteroaromatic molecules. Further ramifications of these principles will be described in due course.

Acknowledgment. We thank the National Institutes of Health (CA-55268), the National Science Foundation (CHE 91-16820), the Robert A. Welch Foundation (C-1007), and the donors of the Petroleum Research Fund, administered by the American Chemical Society (AC-20399), for support of our research.

Supplementary Material Available: Listings of spectral data for selected compounds (4 pages). Ordering information is given on any current masthead page.

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Total Synthesis of Calicheamicin γ_1^I

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Received September 30, 1992

As one of Nature's most extraordinary molecular constructions, with phenomenal biological activity and a fascinating mode of action, calicheamicin γ_1^I (**1**, Figure 1)[1,2] has captured the imagination of synthetic organic chemists around the world.[3-6]

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