expected for premonensin (**1a**).

The synthesis of isotopically labeled premonensin is now under way. Incorporation experiments will be reported in due course

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Supplementary Material Available: Physical data and selected experimental procedures (14 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of (±)-Cyanocycline

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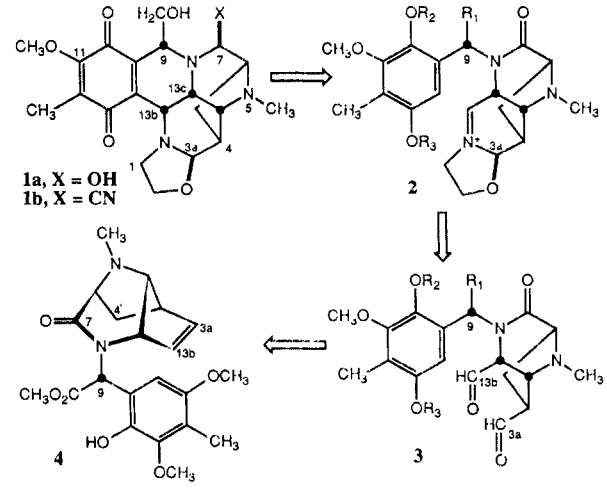
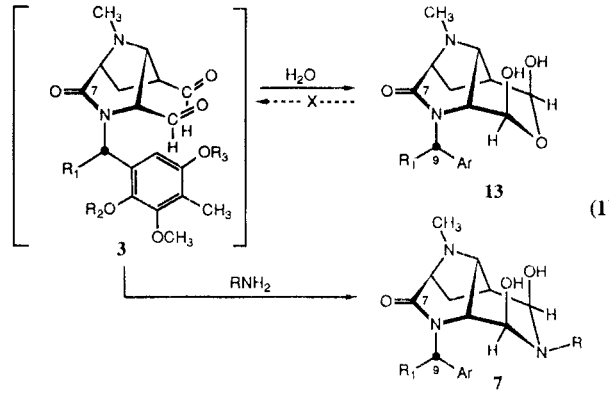
For some time we have been concerned with the development of a synthesis of the antitumor quinone antibiotic naphthridinomycin (**1a**) and its closely related congener cyanocycline (**1b**).[1,2] This latter compound, first produced from naphthyridinomycin by cyanation and subsequently isolated from *Streptomyces flavogriseus*,[3,4] was chosen as the principle targent for total synthesis as a consequence of its improved stability over **1a**.[5] The successful synthesis plan developed for cyanocycline (**1b**) is illustrated below (Scheme I). In previous papers a stereoselective synthesis of the tricyclic lactam **4** has been described.[1] The purpose of this paper is to describe the utilization of this intermediate in a successful stereoselective synthesis of cyanocycline.

Earlier studies have provided us with a number of important lessons relative to oxidation state control during the evolving synthesis. For example, in our hands the only effective precursor to the quinoid ring in this family of structures has been the derived hydroquinone. Second, the congested environment surrounding the C(9) substituent in the target structure demands that the correct oxidation state of this moiety be established prior to, rather than after, the hexacyclic ring system is established. Both of these issues were addressed in the refunctionalization of the tricyclic lactam **4**. Reduction of **4** ($LiBEt_3H$, THF, 3 h, 25 °C) followed by DDQ oxidation ($MeCN-H_2O$, 1 h, −5 °C) afforded the quinone **5** in 91% yield (Scheme II).[6] This intermediate was then successively acylated (Ac_2O, pyr, DMAP, 30 min, 0 °C, 91%), subjected to reductive silylation with activated zinc[7] and *tert*-butyldimethylsilyl (TBS) chloride (*i*-Pr_2NEt, DMAP, CH_2Cl_2, 1 h, 25 °C, 96%), and finally oxidized to the diol **6** with osmium tetroxide by using the Kelly procedure.[8] The overall yield of **6** from **4** was 65%. Preliminary studies on the oxidative cleavage of diols related to **6** with periodate revealed that the resultant dialdehyde **3** ($R_1 = CO_2Me$, R_2 = Bz, R_3 = Me) was exceptionally prone to aldehyde hydration and subsequent ring closure to the

Scheme I



derived dihydroxytetrahydropyran **13** (eq 1). This reaction proved



(1)

to be so facile that the detection of **3** was precluded during the periodate cleavage of diol **6**. Once formed, **13** ($R_1 = CO_2Me$, R_2 = Bz, R_3 = Me) proved to be completely intractable as a dialdehyde synthon due to the apparent irreversibility of this reaction. The successful interception of the elusive dialdehyde **3** ($R_1 = CH_2OAc$, R_2, R_3 = TBS) was ultimately accomplished by executing the oxidation of **6** under nonaqueous conditions with tetraethylammonium periodate (2.0 equiv, CH_2Cl_2, 24 h, 25 °C)[9] in the presence of 1.6 equiv of *O-tert*-butyldimethylsilyl-protected ethanolamine. Although the amino diol **7**, which was obtained as a mixture of C(3a) and C(13b) diastereomers, resisted all attempts at chromatographic purification, it could be effectively carried on to the next step. Treatment of **7** with trifluoroacetic acid (25 °C, 24–30 h) afforded the desired hexacyclic lactam **8**, in 74–77% yield after chromatographic purification.[6] Extensive ^1H NMR analysis confirmed that both of the new stereocenters at C(3a) and C(13b) possessed the desired configurations as illustrated.[10]

Although it might appear that the conversion of lactam **8** to cyanocycline (**1b**) might be a routine exercise, this latter series of transformations proved to be one of the most challenging aspects of the synthesis. In particular, reduction of the C(7) lactam carbonyl proved to be exceptionally difficult. A series of metal hydride reagents were examined in conjunction with the reduction of both **8** and **9**.[11] It was concluded from these studies that, under

(1) Evans, D. A.; Biller, S. A. *Tetrahedron Lett.* **1985**, *26*, 1907–1910, 1911–1914.
(2) For leading references to the isolation and structure elucidation of **1a–b**, see ref 1.
(3) Zmijewski, M. J.; Goebel, M. *J. Antibiot.* **1982**, *35*, 524–525.
(4) Hayashi, T.; Noto, T.; Nawata, Y.; Okazuki, H.; Sawada, M.; Ando, K. *J. Antibiot.* **1982**, *35*, 771–777.
(5) Authentic samples of **1a** kindly provided to us by Professor S. Hanessian had completely decomposed.
(6) Satisfactory infrared, proton and carbon NMR spectroscopic data, and combustion analysis or mass spectrometric data were obtained for each intermediate.
(7) Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1968**, 1494–1495.
(8) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.
(9) Qureshi, A. K.; Sklary, B. *J. Chem. Soc. C* **1966**, 412–415.
(10) The protons at C(3a) and C(13b) appeared only as singlets in the high-field proton NMR and, consequently, the stereochemistry at the two newly formed centers was determined by nuclear Overhauser enhancement studies. Irradiation of the proton at C(13c) resulted in an enhancement of the protons at C(13b) and C(4a) demonstrating a syn relationship between the three atoms. Similarly, irradiation of the proton at C(3a) produced an enhancement of the proton on the bridge at C(4′) projecting under the ring, thus confirming that the correct stereochemistry at both new centers had been established.
(11) Compound **9** was prepared by the reduction of **8** ($LiBEt_3H$, 2.1 equiv, 25 °C) in 73–78% yield based on 74% conversion.

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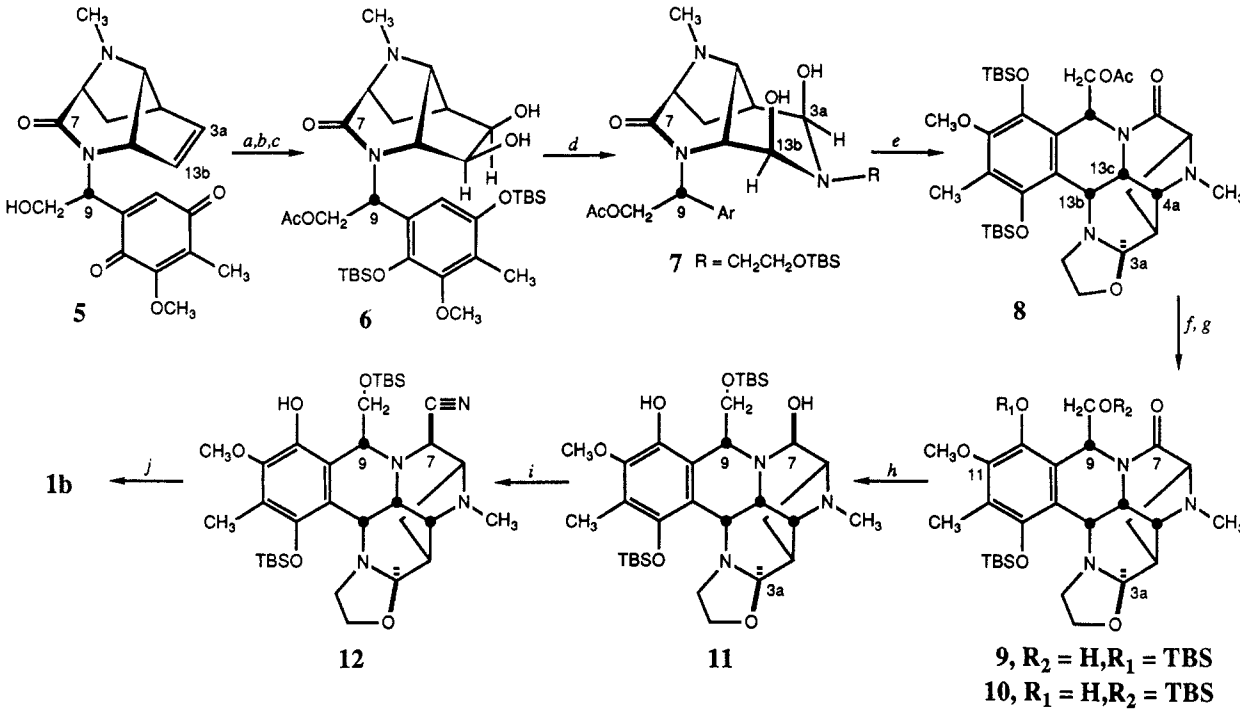
Scheme II



[a] Ac_2O, pyr, DMAP, CH_2Cl_2, 0 °C, 30 min. [b] Zn dust, TBSCl, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 0.13 M concentration, 0–25 °C, 1 h. [c] OsO_4, *N*-methylmorpholine *N*-oxide, acetone, 25 °C, 30 min. [d] Et_4NIO_4, $TBSOCH_2CH_2NH_2$, CH_2Cl_2, 25 °C, 16–24 h. [e] Neat TFA, 25 °C, 24–30 h. [f] $LiBEt_3H$, THF, 25 °C, 3 h. [g] $KN(Me_3Si)_2$, THF, 0 °C, 45 min. [h] Li, NH_3-THF, −33 °C, 10 min, then EtOH over 45 min; NH_4Cl; aqueous $NaHCO_3$ wash. [i] NaCN, 0.2 M pH 8.0 Tris buffer, CH_3CN, 25 °C, 2 h. [j] $(HF)_x$·pyr(xs), CH_3CN, 50 °C, 3.0 h; then aqueous Na_2CO_3 to pH 10, O_2, 25 °C.

the forcing conditions required for reduction, the oxazolidine ring was unexpectedly labile toward reduction at C(3a).[12] Efforts to obtain a selective reduction of **8** via the derived thioamide were also unsuccessful. The use of dissolving metal reduction conditions provided the eventual solution to this problem. Although amide reduction under these conditions is precedented,[13] competitive reduction of the aromatic remains as a potential complication. Preliminary dissolving metal reduction studies carried out with lactam **9** indicated that aromatic ring reduction preempted C(7) carbonyl reduction, the principal product being that derived from loss of the C(11) methoxyl group. To suppress this process, silyl transfer from the C(10) oxygen moiety was effected. Treatment of **9** with potassium hexamethyldisilylamide (1.1 equiv, 45 min, 0 °C, 90%) resulted in the efficient silylatropic isomerization to phenol **10** which was anticipated to be more resistant to aromatic ring reduction. The successful reduction of **10** was achieved by treatment with excess lithium (100 equiv) in NH_3–THF at reflux followed by the slow addition of ethanol (120 equiv, 45–50 min). The unstable carbinolamine **11**, which could be isolated in 67% yield, was best directly transformed to the derived α-amino nitrile **12** under conditions similar to those employed in the conversion of **1a** to **1b** (1.2 equiv, NaCN, MeCN–H_2O, pH 8.0 Tris buffer, 30 min, 25 °C, 41% from **10**).[3] The final steps of the cyanocycline synthesis were accomplished by treatment of **12** with pyridine hydrofluoride (excess, 3 h, 50 °C) followed by careful adjustment of the reaction to pH 10 with aqueous sodium carbonate in the presence of molecular oxygen. These conditions afforded synthetic cyanocycline (**1b**) in 84% yield. The material thus obtained proved to be identical with a sample of (+)-cyanocycline (**1b**) via all spectroscopic and chromatographic comparisons.[14]

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Supplementary Material Available: Physical data and selected experimental procedures for **1b**, **5**, **6**, **8–12**, and **14–16** (16 pages). Ordering information is given on any current masthead page.

(12) Danishefsky has fully reduced a similar lactam in the synthesis of quinocarcinol methyl ester but has failed to achieve partial reduction in attempts with either DIBAL or diborane. Danishefsky, S.; Harrison, P. J.; Webb, R. R., II; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421–1423 and private communication.

(13) Dissolving metal reduction of amides is precedented; however, yields are generally very poor except in the cases of aromatic and *N*-aryl amides. (a) Birch, A. J.; Cymerman-Craig, J.; Slaytor, M. *Aust. J. Chem.* **1955**, *8*, 512–518. (b) Clemo, G. R.; King, T. J. *J. Chem. Soc.* **1948**, 1661–1666. (c) Benkeser, R. A.; Watanabe, H.; Mels, S. J.; Sabol, M. A. *J. Org. Chem.* **1970**, *35*, 1210–1211. (d) Kaiser, E. M. *Synthesis* **1972**, 391–415.

(14) The authors thank Professor S. Gould, Department of Chemistry, Oregon State University, for providing us with an authentic sample of (+)-**1b**.

Luminescence Behavior of Copper(I)–Imidazole Complexes. A Spectroscopic Model for the Carbonyl Derivative of Hemocyanin

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Many derivatives of hemocyanin have been investigated in the attempt to define the molecular structure of its binuclear-copper active site.[2] These include the deoxy, carbonyl, oxy, half-met (mixed valence), and met (oxidized) forms of the protein. Until

(1) Fellow of the Alfred P. Sloan Foundation, 1985–1987.

(2) (a) Solomon, E. I. In *Copper Proteins*; Spiro, T. G., Ed.; Wiley: New York, 1981; Chapter 2. (b) Solomon, E. I.; Penfield, K. W.; Wilcox, D. E. *Struct. Bonding (Berlin)* **1983**, *53*, 1–57.

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