$Mo_4X_{11}^{2-}$ can be obtained from $Mo_4X_{12}^{3-}$ by loss of X^- from an inner position of the cluster $(Mo_4X_8)X_4^{3-} \rightarrow (Mo_4X_7)X_4^{2-} + X^-$. Alleviation of steric congestion, caused by the large size of I atoms, presumably leads to loss of I^- and stabilization of $Mo_4I_{11}^{2-}$. Finally, the square-pyramidal cluster $Mo_5Cl_{13}^{2-}$ can be considered as a fragment of the $Mo_6Cl_{14}^{2-}$ anion[14] and formed as a result of addition of $MoCl^+$ to the $Mo_4Cl_{12}^{3-}$ cluster unit. The structural relationships noted here indicate the possibility of rational syntheses of both homonuclear and heteronuclear clusters containing four, five, or six metal atoms. Such chemistry is under active investigation in this laboratory.

Acknowledgment. This work was supported by NSF Grant CHE-8406822. We thank Professor Robert Shelton for help with magnetic susceptibility measurements.

Supplementary Material Available: Complete listings of positional parameters, anisotropic thermal parameters, and bond distances and angles for $(Ph_4As)_2(Et_4N)Mo_4Cl_{12}\cdot 2CH_2Cl_2$ and $(Et_4N)_3Mo_4Cl_{12}$ (14 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of Premonensin, a Potential Intermediate in the Biosynthesis of Monensin

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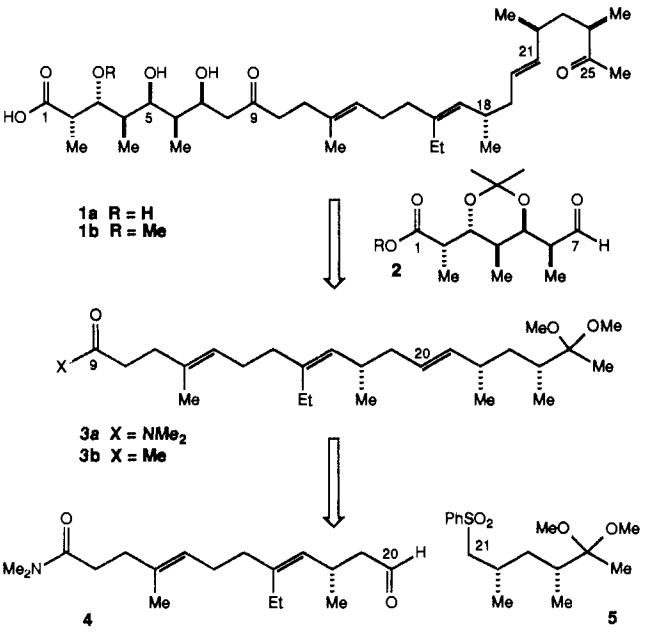
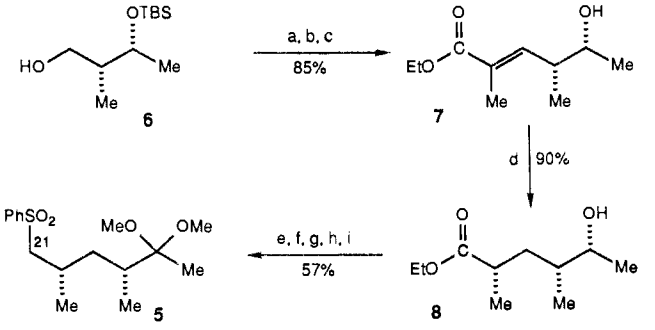
The Cane, Celmer, and Westley hypothesis on the biosynthesis of polyether antibiotics is an innovative contribution to the field of natural products chemistry.[1] Although the assemblage of the carbon skeleton of this class of compounds generally mimics fatty acid biosynthesis,[2] the construction of the polyether portion of these structures is without precedent. In 1982, Cane and co-workers proposed a mechanism for the formation of this structural element of monensin A.[3] Their isotopic labeling experiments, combined with projections provided by Westley,[4] implicated the triene **1a**, premonensin triene, as a probable intermediate in the biosynthesis of monensin. Recently, a synthesis of premonensin methyl ether (**1b**) has been reported;[5] however, indirect evidence implicates **1a** as a more likely intermediate in the biosynthesis.[6] In conjunction with projected studies which might illuminate the later events in the biosynthesis of monensin A, we have completed an asymmetric synthesis of premonensin (**1a**). The obvious disconnection strategy for the structure is illustrated in Scheme I.

The asymmetric synthesis of the C_{21}–C_{26} synthon **5** (Scheme II) evolved from the monoprotected diol **6** which was efficiently constructed via the asymmetric aldol reactions reported earlier.[7]

Scheme I

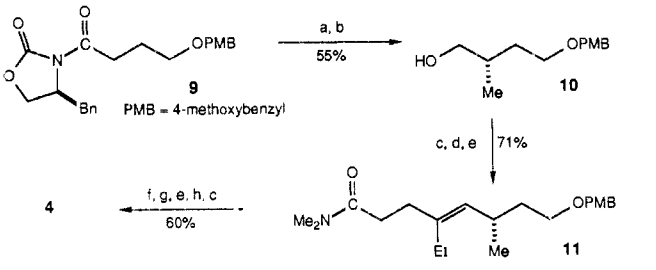


Scheme II[a]



[a] (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N; (b) (carboethoxyethylidene)triphenylphosphorane, toluene, 50 °C; (c) HF, CH_3CN; (d) [Rh(NBD)(+)-BINAP]BF_4, H_2, 1000 psi, CH_2Cl_2; (e) TBSCl, imidazole, DMF; (f) DIBAL, CH_2Cl_2, −78 °C; (g) $(PhS)_2$, *n*-Bu_3P, CH_2Cl_2; Oxone, MeOH, H_2O; (h) pyr-SO_3, Me_2SO, Et_3N; (i) $HC(OMe)_3$, PPTS, MeOH.

Scheme III[a]



[a] (a) $NaN(TMS)_2$, THF, −78 °C; MeI; (b) LAH, Et_2O, −30 °C; (c) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C; Et_3N; (d) 2-lithiobutene, THF, −78 °C; (e) $Me_2NC(OMe)_2Me$, cyclohexane, 80 °C; (f) $Li(EtO)_3AlH$, Et_2O, −30 °C; (g) 2-lithiopropene, THF, −78 °C; (h) DDQ, CH_2Cl_2, H_2O.

Successive oxidation[8] of **6** and subsequent Wittig reaction of the resultant aldehyde with the illustrated phosphorane (toluene, 70 °C, 12 h) afforded exclusively the derived *E*-α,β-unsaturated ester which was disilylated (HF, MeCN, 25 °C, 1 h)[9] to hydroxy ester **7** (85% overall). Recent results from this laboratory have doc-

(1) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.
(2) Hutchinson, C. R. *Acc. Chem. Res.* **1983**, *16*, 7.
(3) (a) Cane, D. E.; Liang, T. C.; Hasler, H. *J. Am. Chem. Soc.* **1981**, *103*, 5962. (b) Cane, D. E.; Liang, T. C.; Hasler, H. *J. Am. Chem. Soc.* **1982**, *104*, 7274. (c) Ajaz, A. A.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1983**, 679.
(4) Westley, J. W.; Blount, J. F.; Evans, R. H., Jr.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 597.
(5) VanMiddlesworth, F.; Patel, D. V.; Donaubauer, J.; Gannett, D.; Sih. C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2996.
(6) Cane and co-workers have isolated 3-demethyl 26-dehydroxy monensin A from *Streptomyces cinnamonensis* broths, implying methylation occurs after the furan-forming sequence, private communication.
(7) **6** was prepared as follows: (1) (*S*)-3-(1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone, *n*-Bu_2BOTf, Et_3N, 0 °C; −78 °C, CH_3CHO; 0 °C, H_2O_2, MeOH, pH 7 buffer; (2) TBS-Cl, imidazole, DMF (85% overall); (3) $C_6H_5CH_2OLi$, THF, 0 °C (75%); (4) DIBAL, CH_2Cl_2, −78 °C (75%). 61% overall yield. For chiral aldol methodology, see: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. Full details are included in the supplementary material.
(8) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(9) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

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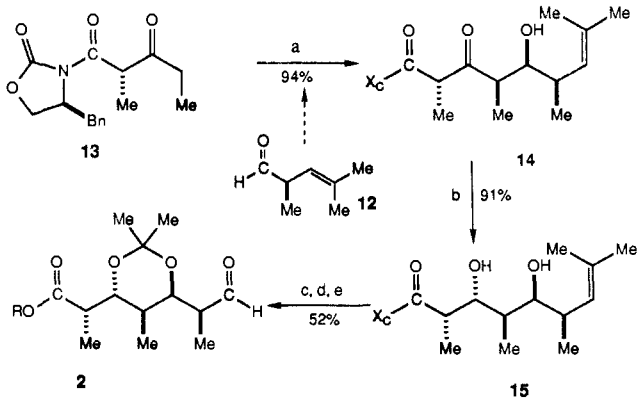
Scheme IV[a]



[a] (a) $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, −78 °C; **12**, (b) $Na(AcO)_3BH$, AcOH; (c) 2-methoxypropene, PPTS; (d) $2\text{-}NO_2C_6H_4CH_2OLi$, THF; (e) O_3, CH_2Cl_2, −78 °C; $(CH_3)_2S$.

umented the effective use of $[Rh(NBD)(DIPHOS\text{-}4]BF_4$ in the hydroxyl-directed reductions of hydroxy olefins.[10] When this catalyst was employed to hydrogenate **7** (CH_2Cl_2, 1000 psi of H_2, 3 h), subsequent analysis revealed an 85:15 mixture of methyl diastereomers. The diastereoselection in this reduction was improved when the chiral catalyst $[Rh(NBD)(+)\text{-}BINAP]BF_4$[11] was employed. In this double diastereodifferentiating reduction, the diastereoselection was improved to 98:2 after which the desired major diastereomer **8** was isolated by flash chromatography (90% yield).[12] The following series of functional group manipulations resulted in the conversion of **8** to the C_{21}–C_{26} synthon **5**. Reprotection of the hydroxyl function in **8** (*t*-$BuMe_2SiCl$, imidazole, DMF)[13] and subsequent reduction of the ester function (DIBAL, CH_2Cl_2, −78 °C) afforded the primary alcohol, which was transformed to the derived phenyl sulfide (*n*-Bu_3P, $(PhS)_2$, CH_2Cl_2).[14] Subsequent treatment of this sulfide with oxone[15] effected both the desired oxidation to the sulfone and concomitant desilylation. The liberated secondary alcohol was oxidized to the methyl ketone (Me_2SO, pyr·SO_3) and protected as the dimethyl ketal (PPTS, MeOH, $(MeO)_3CH$, 25 °C, 16 h) in 57% overall yield from **8**. Under these conditions no epimerization of the methyl-bearing stereocenter adjacent to the ketal function was detected in synthon **5**.

The C_9–C_{20} synthon **4** was constructed via the sequence of reactions illustrated in Scheme III. Alkylation of the sodium enolate of the butyric acid derivative **9**[16] with methyl iodide (4 equiv, THF, −78 °C, 6 h) afforded a 96:4 mixture of diastereomers which were separated by medium-pressure chromatography. Reduction ($LiAlH_4$, Et_2O, −30 °C) of the major diastereomer afforded the alcohol **10** in an overall yield of 55%. Swern oxidation[8] of **10** followed by treatment of the resultant aldehyde with 2-lithiobutene provided a 1:1 mixture of allylic alcohols which, upon treatment with *N,N*-dimethylacetamide dimethyl acetal in refluxing cyclohexane,[17] afforded the rearrangement product **11** contaminated with less than 2.5% of the *Z* olefin isomer.[18] After reduction ($LiAl(OEt)_3H$, Et_2O, −30 °C, 3 h)[19] of amide **11** to its corresponding aldehyde, the illustrated sequence of events was repeated to give the C_{20} *p*-methoxybenzyl ether as the immediate precursor to synthon **4** (isomeric purity >98% by capillary GLC). Successive debenzylation (DDQ, CH_2Cl_2–H_2O)[20] and Swern oxidation provided the C_9–C_{20} synthon **4**. The completion of the synthesis of the C_9–C_{20} synthon relied upon the application of the Lythgoe trans olefin synthesis which afforded a 4:1 mixture of olefins (68%) with the *E* isomer **3a** as the major constituent.[21] Treatment of this olefin mixture with methyllithium (THF, −45 °C, 0.5 h) provided the derived methyl ketone **3b** which was freed of all isomeric contaminants by chromatography on 5% silver nitrate impregnated silica gel (42% from **4** and **5**).[22]

The synthesis of the C_1–C_7 synthon **2** (Scheme IV) has provided us with the opportunity to exploit some of the unique capabilities of β-keto imides such as **13**[23] in a previously undocumented aldol bond construction.[24] The developement of the successful reaction illustrated below (**13** + **12** → **14**) was predicated on the nonconventional enolization of **13** at the less substituted methylene position followed by a stereoselective aldol addition of the derived enolate with the *R* aldehyde **12**.[25] The conditions developed to effect this transformation follow: To a cooled (−78 °C) suspension of $Sn(OTf)_2$[26] (2 equiv) and *N*-ethylpiperidine (2.2 equiv) in dichloromethane was added 1.0 equiv of **13**. After 1 h, the aldehyde **12** was added and stirring was maintained for 40 min. The reaction was then quenched with 10% aqueous $NaHSO_4$, and the desired adduct **14** was isolated by a conventional extraction. HPLC analysis of the unpurified reaction revealed a 37:1 ratio of presumed diastereomers from which the diastereomerically pure aldol adduct **14** was obtained after flash chromatography in 94% yield. The establishment of the 3(*R*)-hydroxyl-bearing stereocenter was next achieved in the highly diastereoselective reduction of **14** with sodium triscetoxyborohydride (HOAc, 25 °C, 30 min, 3*R*:3*S* > 30)[27] affording **15** in 91% yield.[24] Further elaboration of **15** to the C_1–C_7 synthon **2** was achieved by acetonide formation, transesterification with 2-nitrobenzyl alcohol, and ozonolysis.

The final bond construction joining aldehyde **2** and methyl ketone **3b** was effected via aldol addition. Enolization of **3b** (LDA, THF, −78 °C) and subsequent addition of aldehyde **2** afforded a 3:1 mixture of aldol adducts which were shown to be diastereomeric at C_7. The predominate 7*S* diastereomer was readily isolated in 57% yield by flash chromatography. Final deprotection of this acetonide ester to premonensin (**1a**) was accomplished in two steps. Photodeprotection of the carboxyl group was accomplished by irradiation with Pyrex-filtered UV light in wet THF (0 °C, 20 min).[29] This solution was then diluted with an equal portion of 0.5 N aqueous HCl (25 °C, 2 h) to remove both the acetonide and C_{25} dimethyl ketal protecting groups. Chromatographic purification afforded a 58% yield of a homogeneous material whose spectral properties matched in every way those

(10) (a) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (b) for other examples using this catalyst, see: Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.*, in press.

(11) Miyashita, A.; Yasuda, A.; Takaya, H. Toriumi, K. Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(12) The analogous reduction carried out with the enantiomeric catalyst afforded a 65:35 ratio of **8** and its methyl epimer.

(13) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(14) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.

(15) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 1287.

(16) **9** was prepared as follows: (1) $HO(CH_2)_4OH$, cyclohexane, 80 °C, NaH, *p*-$MeOC_6H_4CH_2Cl$; (2) Jones reagent, acetone, 0 °C (60% overall); (3) pivaloyl chloride, Et_3N, Et_2O, THF, −78 °C; 3-lithio-4-(phenylmethyl)-2-oxazolidinone (93%). For asymmetric alkylation methodology, see: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(17) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.

(18) Ortho ester and ester enolate Claisen variants afforded 6% and 3% of the *Z* olefin isomer, respectively.

(19) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(20) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 885.

(21) (a) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (b) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

(22) Popov, S.; Carlson, R. M. K.; Wegmann, A.; Djerassi, C. *Steroids* **1976**, *28*, 699.

(23) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

(24) Unpublished results of Dr. V. Novack of these laboratories.

(25) Aldehyde **12** was prepared as follows: (1) $NaN(TMS)_2$, THF, −78 °C; (*R*)-3-(4-methyl-1-oxo-3-pentenyl)-4-(phenylmethyl)-2-oxazolidinone; MeI (72%); (2) LAH, Et_2O, 0 °C (85%); (3) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 °C (94%).

(26) For previous work on stannous triflate mediated aldol condensations, see: Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. Full details provided in the supplementary material.

(27) For the use of sodium trisacetoxyborohydride in ketone reductions, see: Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.

(28) A reliable method for the unequivocal determination of the C_7 hydroxyl stereochemistry is described in the supplementary material.

(29) (a) Barltrop, J. A.; Plant, P. J.; Schofield, P. *J. Chem. Soc., Chem. Commun.* **1966**, 822. (b) Patchornik, A.; Amit, B.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 6333.

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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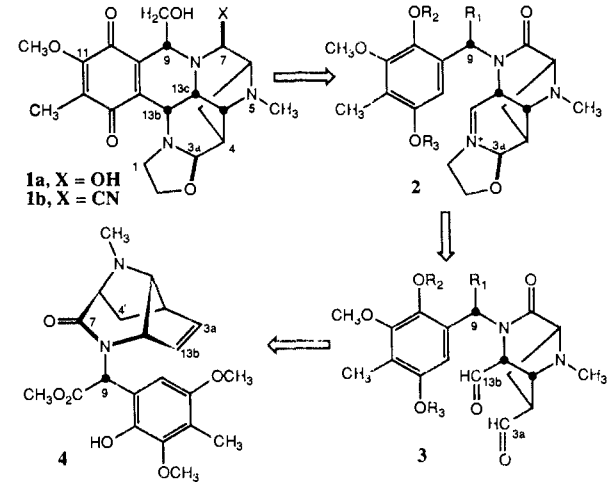
Received December 31, 1985

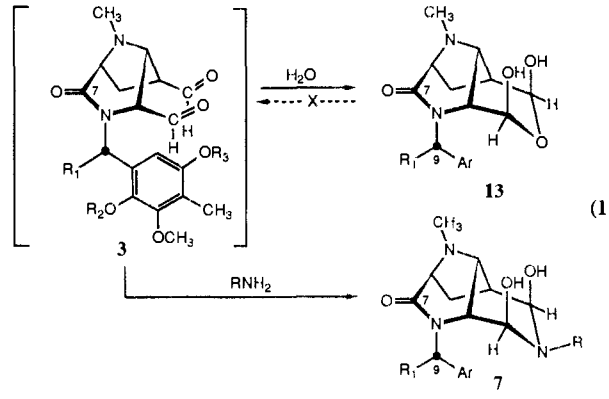
For some time we have been concerned with the development of a synthesis of the antitumor quinone antibiotic naphthridinomycin (**1a**) and its closely related congener cyanocycline (**1b**).[1,2] This latter compound, first produced from naphthyridinomycin by cyanation and subsequently isolated from *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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