Acknowledgment. We thank the Deutsche Forschungsgemeinschaft for generous financial support of this work. M. Dörr is grateful to the Fonds der Chemischen Industrie for a doctoral fellowship (1984-1986). Appreciation for spectral services is expressed to Dr. G. Lange (MS) and Dr. D. Scheutzow (NMR).

Total Synthesis of Zincophorin

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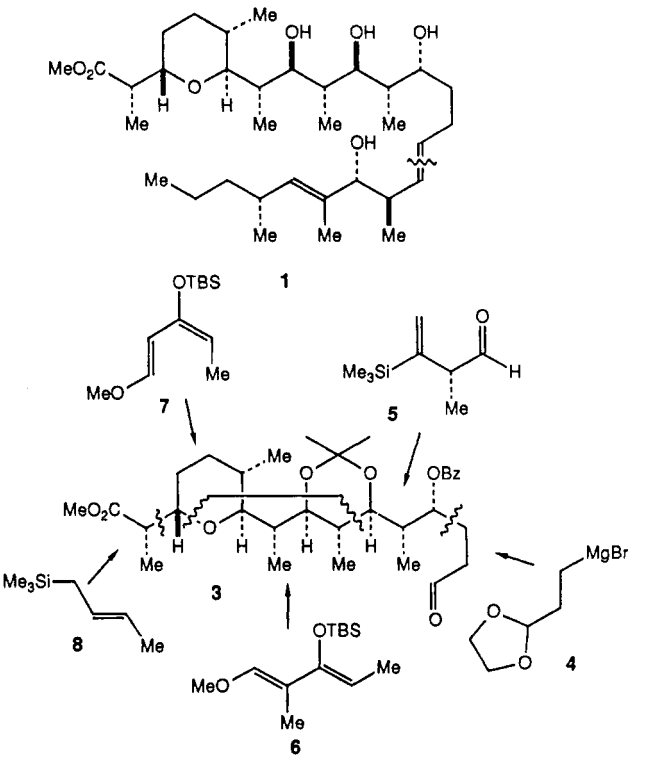
During a search for new ruminant growth-promoting factors, the ionophore zincophorin (**1**) was isolated from a strain of *Streptomyces griseus*.[1] As its name implies, zincophorin has a very high affinity for zinc(II) cations. The affinity also extends to magnesium (II) and in fact a combined zinc-magnesium salt complex has been obtained. The gross structure and stereochemistry of zincophorin are known from crystallographic measurements. Several novel structural features of zincophorin, as well as its strong antibacterial properties, render this ionophore a worthy target for synthetic exploration. Our plan called for the coupling of two enantiomerically homogeneous subunits, sulfone **2** and the aldehyde **3** (see disconnection line in structure **1**).

Elsewhere[2] we have described a degradation which starts with zincophorin and leads to differentially protected aldehyde enantiomer **3** and to sulfone enantiomer **2**. A stereoselective synthesis of enantiomerically pure **2** was also achieved. In this paper we describe the synthesis of aldehyde **3** and its coupling with sulfone **2**. The *first total synthesis of zincophorin has thus been achieved.* In so doing we were obliged to deal with several stereochemical patterns which had not previously been addressed in our program. The solutions are described in Scheme I.

Grignard reagent **4**[3a] reacts with the known *S* aldehyde **5**[3b] (THF, -78 °C) in a diastereofacially specific reaction to afford (90%) carbinol **9**.[4] Treatment with sodium hydride-HMPA occasions C → O silicon migration. Aqueous workup provides alcohol **10**. Protection of the hydroxyl group of **10** was accomplished (91%) with benzyloxymethyl chloride and Hunig's base. Compound **11**, upon ozonolysis, gave rise (80%) to aldehyde **12**, which was to serve as the heterodienophile in a cycloaddition with the known diene **6**.[5]

The reaction, mediated by anhydrous magnesium bromide (CH_2Cl_2, -50 °C), occurs with exo topography under apparent chelation control.[5] Compound **13a** was obtained in 80% yield.[6] Clean reduction ($NaBH_4$-$CeCl_3$)[7a] to **13b** set the stage for a Ferrier displacement[7b] using 3,4-dimethoxybenzyl alcohol as the nucleophile (*p*-TsOH, benzene). Compound **14**, thus available from **13a** in 78% yield, was subjected to hydroboration (BH_3-THF)-oxidation (H_2O_2-NaOH), thereby producing alcohol **15** in 68% yield. Swern oxidation followed by reduction (L-Selectride), and deprotection with DDQ,[8] led successively to compounds **16**, **17**, and hemiacetal **18** (55% overall yield) (Scheme II).

Scheme I



The scheme now called for disconnection of the properly configured pyran ring followed by elaboration of a new aldehyde from the anomeric carbon. Compound **19**, obtained via the reduction ($LiBH_4$) of **18**, was protected at its primary alcohol as a mono-*tert*-butyldiphenylsilyl ether.[9] The two secondary alcohols were engaged as a cyclic acetonide (dimethoxypropane, PPTS). After deprotection (*n*-Bu_4NF) followed by Swern oxidation, aldehyde **20** was in hand (70% from **19**), setting the stage for the all crucial second cyclocondensation reaction.

To reach the required **21**, a trans topography and a Cram-Felkin diastereofacial sense has to be attained.[5] It will be recalled[10] that the 4*Z* version of diene **7**, upon cyclocondensation (mediated by BF_3·Et_2O) with simple aldehydes, leads to cis pyrones. *However, reaction of the 4E diene 7 with aldehyde 20 leads selectively to the required trans pyrone 21.*[11] After reduction of the ketone, and acetylation, the acetate **22** was in hand. Upon treatment with (*E*)-crotylsilane **8**, in an extension of our recently developed carbon Ferrier displacement methodology,[12] compound **22** gave **23** as the major product.[12b]

The side chain was adjusted (i, OsO_4-$NaIO_4$; ii, Jones oxidation; iii, CH_2N_2) to produce **24** (45% overall). Finally, a three-step sequence (i, H_2-Pd/C; ii, BzCl, Py; iii, *p*-TsOH, acetone) led to the isolation (43%) of fully synthetic **3**. The infrared and NMR spectra of the material thus obtained, as well as its chromatographic mobility and optical rotation,[13] were identical with those

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(4) All new compounds reported herein exhibited satisfactory ^1H NMR, IR, optical rotation, and MS or combustion analytical data.
(5) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.
(6) Compound **13** was obtained as the major product of a 7:1 trans/cis mixture.
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(8) Cf.: Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(9) Hanessian, S.; Lavelle, P. *Can. J. Chem.* **1977**, *55*, 562.
(10) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.
(11) (a) The initial products of the reaction were identified as threo and erythro aldol products (cf. ref 10), as well as the *trans*-pyrone **21** in a ratio of 4:1:0.5 after chromatographic separation (68% combined yield). The threo isomer was then cyclized (PPTS, benzene) to the *trans*-pyrone **21** in 75% yield. The total combined yield of **21** was 46% overall from **20**. (b) See ref 10 for a discusion of the reactivity differences between (4*E*)-**7** and (4*Z*)-**7**.
(12) (a) Danishefsky, S. J.; Lartey, P.; DeNinno, S. *J. Am. Chem. Soc.*, in press. (b) With BF_3·Et_2O as the catalyst (propionitrile, -78 °C), compound **23** is obtained as the major product (3.5:1) relative to its C-2 (zincophorin numbering) epimer in 60%. With $ZnBr_2$ in nitromethane, yields up to 77% have been realized, but the epimer ratio is less favorable (2.8:1).

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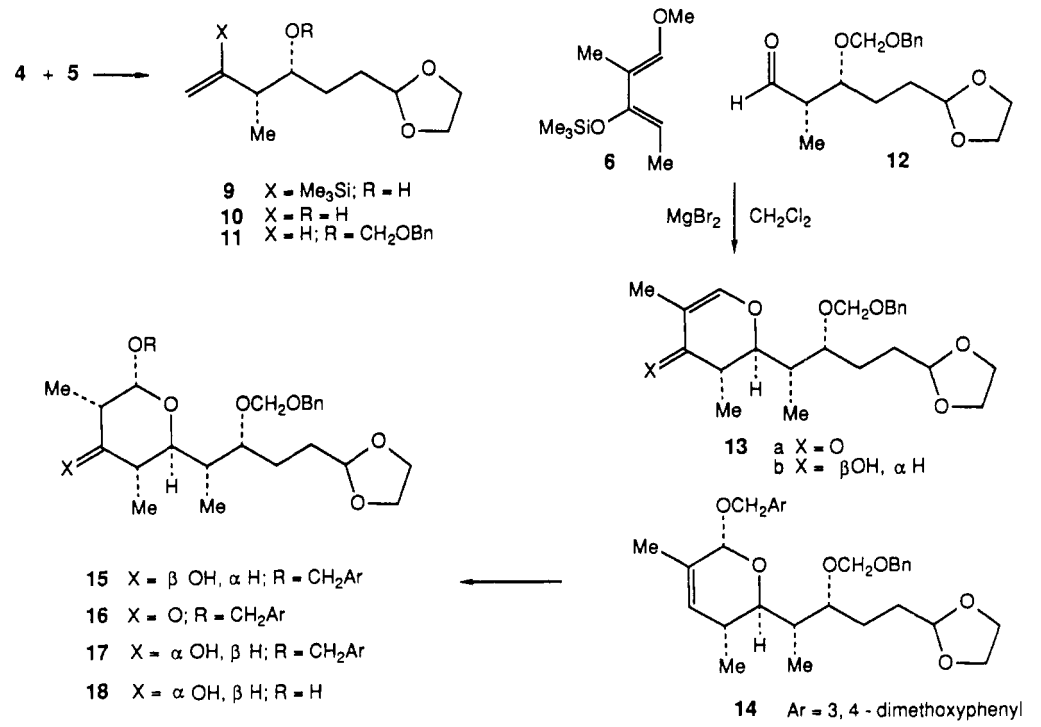
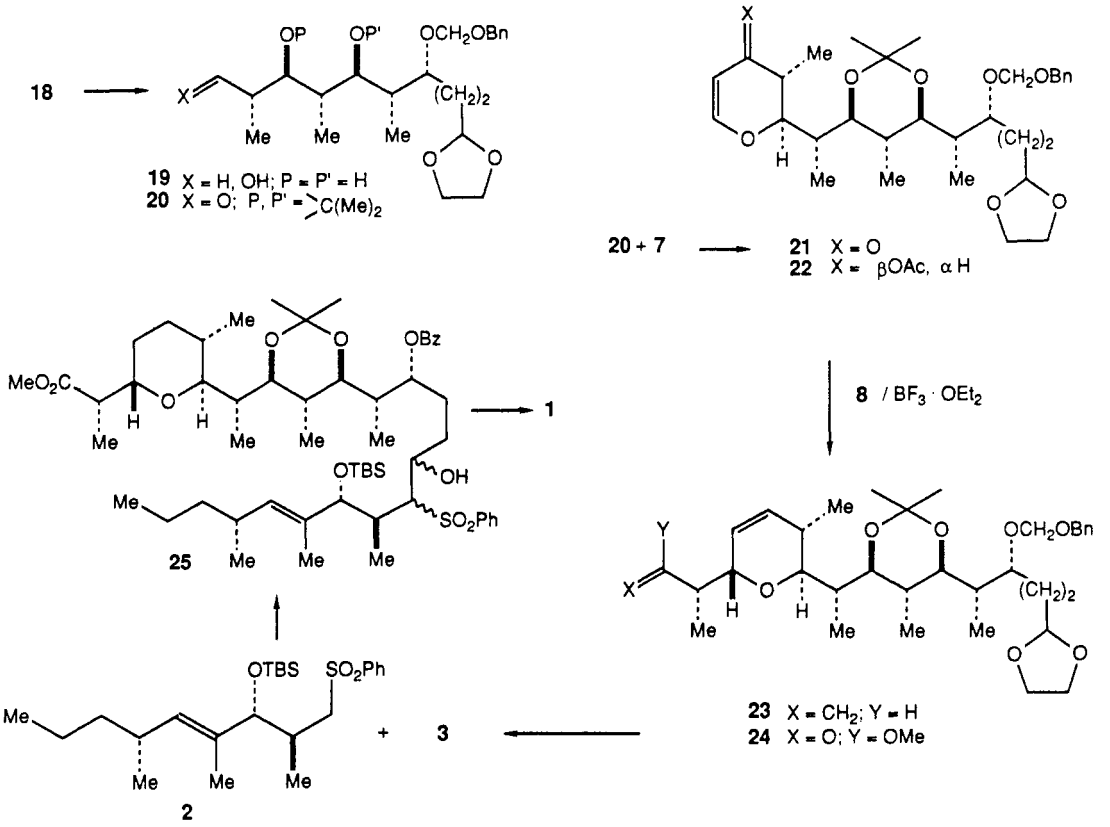
Scheme II



Scheme III



of the material derived from degradation.[2] *The 10 stereogenic centers of aldehyde 3 had been properly arranged by stereochemical communication starting with the single center of aldehyde 5*.[3b]

The final stage of the total synthesis of zincophorin involved a modified Julia[14] coupling of the anion of sulfone **2** (*n*-BuLi, $MgBr_2$,[15] THF, −78 °C) with aldehyde **3**. There was thus obtained the ill-characterized mixture of adducts shown as **25** in 88% combined yield. The total mixture was converted to zincophorin methyl ester through the following sequence: (i) Na/Hg reduction of the hydroxy sulfone (50%), (ii) hydrolysis of the protecting groups, and (iii) reesterification with CH_2N_2 (60%) (Scheme

(13) Fully synthetic **3**: $[\alpha]_D$ +18.9° (*c* 0.29, $CHCl_3$) **3** derived from degradation: $[\alpha]_D$ +20.3° (*c* 2.23, $CHCl_3$). Zincophorin methyl ester: $[\alpha]_D$ +22.4° (*c* 0.89, $CHCl_3$); lit.[1] $[\alpha]_D$ +20.9° (*c* 2, $CHCl_3$).

(14) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans.* **1980**, 1400.

(15) The use of $MgBr_2$ had a favorable effect in preventing enolization of **3**.

III).[16] The synthetic zincophorin methyl ester was identical with a sample prepared by esterification of natural zincophorin by spectroscopic (490-MHz ^{1}H NMR, IR), optical rotation,[13] and chromatographic criteria.

Acknowledgment. This work was supported by PHS Grant HL-28548. PHS Fellowships (Grant 5 F32 GM 10369) to R.E.Z. and (Grant 3 F32 GM 10576) to H.G.S. are gratefully acknowledged. We thank Dr. J. P. Poyser of ICI Pharmaceuticals Division for a generous gift of natural zincophorin zinc salt. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916214.

(16) While we cannot rule out the presence of trace quantities of *Z* olefin, the *E* isomer was the only one isolated.

Alteration of the Sequence Specificity of Distamycin on DNA by Replacement of an *N*-Methylpyrrolecarboxamide with Pyridine-2-carboxamide

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Although there has been some encouraging success with regard to building synthetic molecules that bind large sequences of pure A,T-rich double-helical DNA, there has not been corresponding success in the development of well-understood G,C recognition.[1,2] Progress in this area is an important component in an overall strategy of coupling G,C words and A,T words into sentences that uniquely recognize long sequences of right-handed DNA.[1-3]

The natural products netropsin and distamycin are DNA groove-binding molecules that bind sites of four or five successive A,T base pairs and in general avoid regions with G,C pairs[1,3,4] (Figure 1). The recent x-ray structure of a netropsin–DNA cocrystal suggests how base sequence information retrieval is accomplished.[5] The crescent-shaped netropsin sits in the middle of the minor groove of a pure A,T sequence with the aromatic hydrogens of the *N*-methylpyrrole rings set too deep in the groove to allow room for the guanine NH_2 of a G,C pair.[5] We have been making systematic substitutions on the tris(*N*-methylpyrrolecarboxamide) framework (D) of distamycin to search for altered base pair specificity.

We report that replacement of a terminal *N*-methylpyrrolecarboxamide unit of distamycin with pyridine-2-carboxamide affords a new DNA groove-binding molecule, pyridine-2-carboxamide-netropsin (2-PyN), that now accepts mixed (G,C)-(A,T) base pairs *in preference* to pure A,T stretches of DNA. The design is based on placement of the lone pair of electrons of the pyridine nitrogen proximal to the NH_2 of guanine to afford a hydrogen bond for G,C base pair recognition. Based on this model, our expectations were that 2-PyN should bind the mixed four base pair sequence 5′-(G,C)(A,T)$_3$-3′ with an orientation of the pyridinecarboxamide to the G,C side.

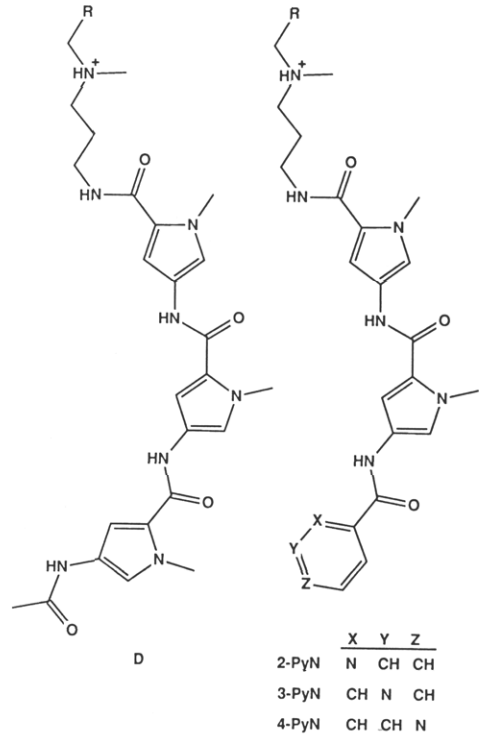

Figure 1. R = H for D and 2-, 3-, and 4-PyN. R = $(CH_2)_2NHCOC$-$H_2N(CH_2CO_2H)CH_2CH_2N(CH_2CO_2H)_2$ for ED and 2-, 3-, and 4-PyNE.

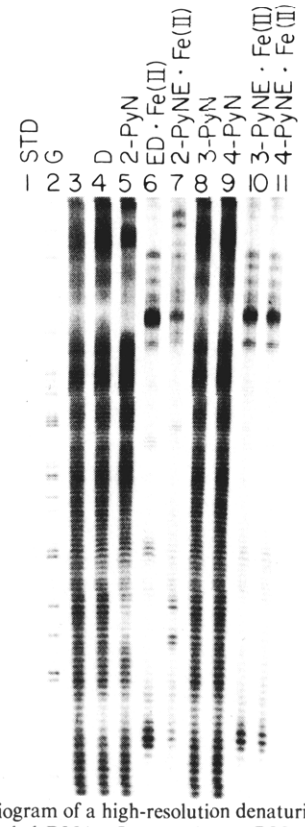

Figure 2. Autoradiogram of a high-resolution denaturing polyacrylamide gel, ^{32}P 5′ end-labeled DNA. Lane 1, intact DNA; lane 2, Maxam–Gilbert chemical sequencing G reactions; lanes 3–5, 8, and 9, footprinting lanes with MPE·Fe(II) at 5 μM; lane 3, MPE·Fe(II) control; lane 4, D at 1 μM concentration; lane 5, 2-PyN at 10 μM; lane 6, ED·Fe(II) at 2.5 μM; lane 7, 2-PyNE·Fe(II) at 50 μM; lane 8, 3-PyN at 4 μM; lane 9, 4-PyN at 4 μM; lane 10, 3-PyNE-Fe(II) at 10 μM; lane 11, 4-PyNE·Fe(II) at 7 μM.

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