characterization in the next oxidation step as follows. To a stirred solution of oxalyl chloride (0.2 mL, 2.2 mmol) in CH_2Cl_2 (5 mL) at −60 °C was added a solution of 0.34 mL of DMSO (4.4 mmol) and CH_2Cl_2 (1 mL). After the mixture was stirred for 3 min, a solution of triols **35a,b** (0.12 g, 0.32 mmol) in CH_2Cl_2 (5 mL) was added and stirring was continued for 15 min at −60 °C. The mixture was then cooled to −78 °C, and triethylamine (1.2 mL, 8.6 mmol) was added. After the mixture was stirred for 10 min, the cooling bath was removed, and after an additional 5 min, brine and $CHCl_3$ were added. Workup as shown for **34** and chromatography (pentane–ether, 1:1, and 5% CH_2Cl_2) gave 70 mg of **36** as white crystals (59%). An analytical sample had mp 164–165 °C ($CHCl_3$–hexane): IR (KBr) 1701, 1687, 1610, 1559 cm^{-1}; ^1H NMR δ 1.84–3.76 (m, 9 H), 3.84 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.61 (s, OH), 6.89 (dd, J = 2, 6.5 Hz, 1 H), 7.43–7.70 (m, 2 H); MS, m/e (relative intensity) 370 (M^+) (100), 285 (16), 271 (18), 243 (42). The diketone **36** (80 mg, 0.26 mmol) was reacted with $Ag^{II}O$ and then with ethylene glycol as described for **34** to give 49 mg of **37** (71%), which was also converted to **38**, as shown above.

2-Acetyl-2,5-dihydroxy-7-methoxy-6,11-naphthacenedione (40). To a cooled (−78 °C) solution of (trimethylsilyl)acetylene (0.47 mL, 3.4 mmol) in THF (6 mL) was added *n*-butyllithium in hexane (2 mL, 2.8 mmol) under argon. After being stirred for 30 min at −78 °C, the above solution was added by syringe via septum to a reaction flask containing a stirred suspension of anhydrous cerium(III) chloride[25] (0.740 g, 3 mmol) in THF (8 mL), which was cooled to −78 °C, after being initially stirred overnight at room temperature. After further stirring for 30 min at −78 °C, a suspension of the ketone **38** (98 mg, 0.3 mmol) in THF (8 mL) was added via syringe and the resulting brown mixture was stirred at −78 °C for a further 6 h, then quenched with aqueous HCl, and extracted with EtOAc (3×). The combined organic layers were washed several times with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. A TLC test of the residue showed the presence of two colorless components of close polarity, which turned violet on standing. This mixture was purified by chromatography (pentane–ethyl acetate, 4:1) to give 75 mg of the first component and 53 mg of the second (**39a** and **39b**, total yield 82%). Elution with pentane–ethyl acetate, 1:1, gave 8 mg of recovered **38** (8%). The mixture of the two components was used directly for the next step, and chromatographic separation was effected for spectroscopic identification. The less polar component had mp 185–186 °C dec (benzene–hexane): IR (KBr) 1660, 1592 cm^{-1}; ^1H NMR δ 0.08 (s, 9 H), 0.12 (s, 9 H), 1.57 (br s, 1 H, OH), 2.14 (t, J = 7 Hz, 2 H), 3.02 (t, J = 7 Hz, 2 H), 3.20 (br s, 2 H), 4.09 (s, 3 H), 5.95 (s, 1 H, OH), 7.30–8.01 (m, 4 H), 8.43 (s, 1 H, OH); MS, m/e (relative intensity), 518 (M^+) (3), 500 (36), 482 (11), 427 (12), 251 (15). The second component had mp 172–174 °C dec (benzene–hexane): IR (KBr) 1662, 1593 cm^{-1}; ^1H NMR δ 0.06 (s, 9 H), 0.12 (s, 9 H), 2.01 (br, 1 H, OH), 2.13 (t, J = 7 Hz, 2 H), 3.03 (t, J = 7 Hz, 2 H), 3.16–3.21 (br, 2 H), 4.09 (s, 3 H), 5.95 (s, 1 H, OH), 7.30–8.02 (m, 4 H), 8.46 (s, 1 H, OH); MS, m/e (relative intensity) 500 (M^+ − 18) (40), 427 (5), 402 (12), 367 (10). To a solution of diastereomeric **39a,b** (0.103 g, 0.2 mmol) in THF (10 mL) were added HgO (50 mg), aqueous 9 N H_2SO_4 (2 mL), and water (4 mL), and the mixture was vigorously stirred at 70 °C for 2 h. After cooling, 10% aqueous HCl was added and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by chromatography (benzene–ethyl acetate, 3:1) to give 42 mg of **40** (58%). An analytical sample had mp 208–210 °C (lit.[4f,h,p] mp 209–211 °C): IR (KBr) 3480, 1709, 1670, 1625 cm^{-1}; ^1H NMR δ 1.92–2.09 (m, 2 H), 2.37 (s, 3 H), 2.77 (d, J = 17 Hz, 1 H), 2.87–3.15 (m, 2 H), 3.30 (d, J = 17 Hz, 1 H), 3.79 (s, 1 H, OH), 4.07 (s, 3 H) 7.45 (s, 1 H), 7.73 (t, J = 8 Hz, 1 H), 7.92 (d, J = 8 Hz, 1 H), 13.37 (s, 1 H); MS, m/e (relative intensity) 366 (M^+) (12), 323 (100).

Acknowledgment. We thank Dr. Felix Frolow for the determination of the X-ray structure.

An Asymmetric Synthesis of 5-*O*-Carbamoylpolyoxamic Acid from D-Serine

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Received August 12, 1987

A stereocontrolled and asymmetric synthesis of 5-*O*-carbamoylpolyoxamic acid (**2**), the major acyclic component of the polyoxin family of antifungal antibiotics, is reported. The sequence began with an erythro-selective addition of vinylmagnesium bromide to the oxazolidine aldehyde **6** (prepared from D-serine) to give the secondary allylic alcohols **7**/**8**. The derived urethane **12** underwent clean allylic rearrangement upon exposure to $PdCl_2(MeCN)_2$, yielding the primary allylic urethane **13**. Mild acidic methanolysis then gave the homoallylic alcohol **14**, which was shown to be configurationally pure by a Mosher ester analysis. Oxidation of **14** with $KMnO_4$ under CO_2-buffered conditions gave a mixture of lactols **19**/**20**. Further oxidation of these lactols with *N*-bromourea yielded a (2.5:1) mixture of γ-lactones **21** and **22** which was purified by chromatography and crystallization. Treatment of **21** with trifluoroacetic acid resulted in quantitative formation of lactone salt **23**, whereas hydrolysis of **21** with aqueous HCl gave **25** (=**2**·HCl) directly.

Introduction

The polyoxins are a family of important agricultural antibiotics isolated from *Streptomyces cacaoi* var. asoensis that exhibit marked and selective activity against phytopathogenic fungi.[1] They function by inhibiting chitin synthase, an enzyme which catalyzes the final step in the biosynthesis of chitin, a process necessary for proper cell wall assembly. Recent studies suggest that these compounds (or analogues thereof) may also be therapeutically useful against *Candida albicans*, a fungal pathogen which commonly affects humans.[2] There remains, however, the need for a more general synthetic approach to these and related peptidyl nucleoside antibiotics.[3,4]

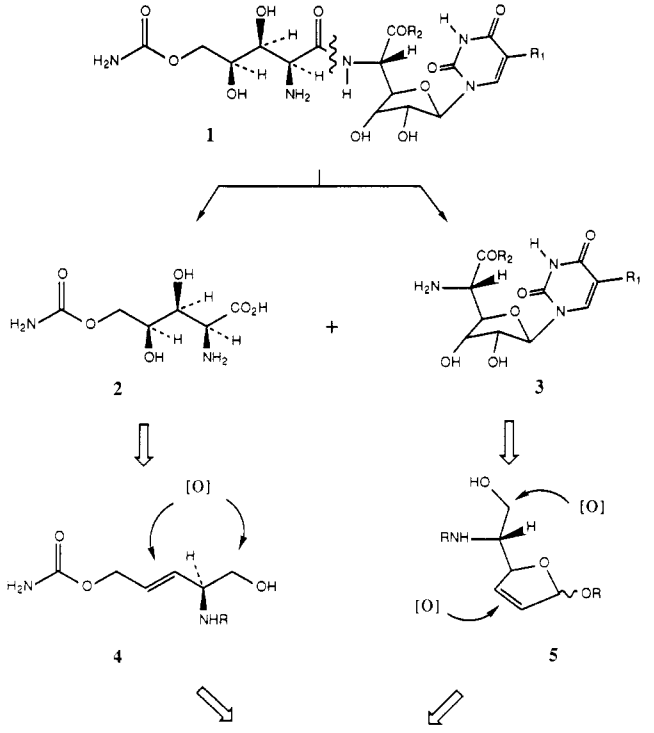
(1) For a comprehensive review of the polyoxins, see: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333 and references cited therein.

(2) Cf.: Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518.

(3) Synthetic efforts directed toward the polyoxins include: (a) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024. (b) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. (c) Kuzuhara, H.; Kimura, M.; Emoto, S. *Carbohydr. Res.* **1975**, *45*, 245. (d) Kuzuhara, H.; Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1973**, 5055. (e) Kuzuhara, H.; Emoto, S. *Ibid.* **1973**, 5051. (f) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Ibid.* **1971**, 4267. (g) Ohdan, S.; Okamota, T.; Maeda, S.; Ichikawa, T.; Araki, Y.; Ishido, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 981. (h) Damodaran, N. P.; Jones, G. H.; Moffatt, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 3812.

0022-3263/88/1953-2979$01.50/0

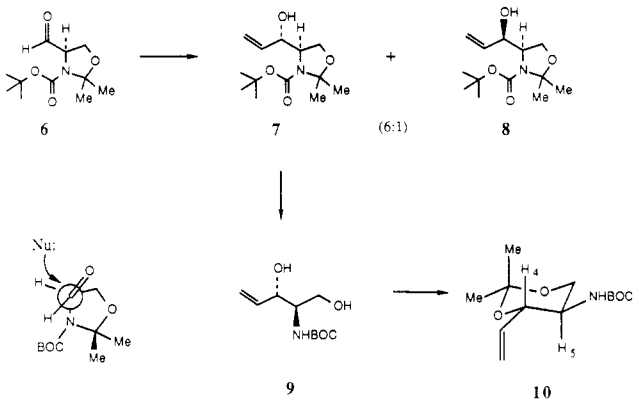
The gross structure for 8 of the 13 polyoxins is shown below and it may be seen that they all incorporate unusual α-aminoaldonic and α-aminouronic residues connected by a peptide linkage. Mild acid hydrolysis of the intact antibiotics led to the isolation of 5-*O*-carbamoylpolyoxamic acid (**2**) and nucleoside **3**. The stereochemistry of these two segments was deduced from a combination of chemical, spectral, and X-ray data and later confirmed by rational total synthesis. Thus Kuzuhara had shown that suitably protected versions of **2** and **3** could be used to synthesize polyoxin J (**1**, R_1 = Me, R_2 = OH) and in doing so established them as logical targets for us as well.



We felt that both targets **2** and **3** could arise from controlled oxidation of the N-protected allylic and homoallylic amino alcohols **4** and **5**. These intermediates are themselves both derived from D-serine, making the approach highly convergent. The use of amino acids as chiral, nonracemic starting materials for the asymmetric construction of the polyoxins contrasts with previous work in the area, which had relied primarily on carbohydrates as building blocks. Herein we wish to report on our work which has culminated in a stereocontrolled and asymmetric synthesis of 5-*O*-carbamoylpolyoxamic acid (**2**), the acyclic component of polyoxins A, B, D, F, H, J, K, and L.

Results and Discussion

The starting material for this synthesis is the oxazolidine aldehyde **6**, a compound which we readily prepared in four steps from D-serine (60% overall yield) and have shown to be 95% enantiomerically pure.[5a] We have already demonstrated the viability of **6** as a "penaldic acid equivalent" for the synthesis of other β-hydroxy-α-amino acids.[5b] Addition of vinylmagnesium bromide to **6** proceeded at −78 °C in tetrahydrofuran to give a (6:1) mixture of diastereomeric secondary allylic alcohols **7** and **8** in 80% combined yield after vacuum distillation. Though inconsequential for the synthesis of **2** (vide infra), the major product was unambiguously identified as the erythro diastereomer after conversion to its corresponding dioxolane **10** (via the intermediate diol **9**).



Analysis of the ^{1}H NMR spectrum of **10** showed $^3J_{4,5}$ = 10 Hz which is consistent with a trans-diaxial arrangement of these protons and the erythro stereochemistry. Conversely, related dioxolanes which possess the threo stereochemistry tend to exhibit $^3J_{4,5}$ on the order of 1–2 Hz as expected for gauche coupling.[5b] The erythro selectivity associated with this Grignard reaction may be ascribed to a Felkin–Anh transition state model[6] and is consistent with a series of observations which we have made regarding the stereoselectivity of nucleophilic additions to the oxazolidine aldehyde **6** in the absence of chelation control.[7]

The mixture of secondary allylic alcohols **7** and **8** obtained above was converted to the secondary allylic urethane(s) **12** by using a standard two-step sequence.[8] This involved treatment of **7**/**8** with *p*-nitrophenyl chloroformate to form the activated carbonate **11** followed by ammonolysis to give **12** in 68% overall yield after chromatography. Following Overman's lead with related *N*,*N*-dimethyl allylic urethanes,[9] we found that exposure of **12** to $PdCl_2(MeCN)_2$ resulted in clean allylic rearrangement to the primary allylic urethane **13** in 86% chromatographed yield. This result was most pleasing since the possibility of nitrogen migration to give a primary allylic amine (after decarboxylation) had been of some concern to us. Confirmation that the primary urethane was still intact came primarily from the IR spectrum of **13**, which showed the characteristic NH_2 bend at 1600 cm^{-1}. The need for this rather indirect route to **13** (as opposed to say a Wittig-based sequence) was due in part to a surprising instability associated with the primary allylic alcohol corresponding to decarbamoylated **13**.

The oxazolidine moiety of **13** was selectively removed in the presence of the acid sensitive *N*-*tert*-butoxycarbonyl (NBOC) group by treatment of this compound with methanolic *p*-toluenesulfonic acid. Competitive removal of the BOC group was observed when the reaction was allowed to proceed to completion but the optimal conditions (see Experimental Section) afforded a crystalline

(4) Nikkomycins: (a) Zimmermann, G.; Hass, W.; Faasch, H.; Schmalle, H.; König, W. A. *Liebigs Ann. Chem.* **1985**, 2165. (b) Banks, B. J.; Barrett, A. G. M.; Russell, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1983**, 873. (c) Jäger, V.; Grund, H.; Buss, V.; Schwab, W.; Mueller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039. (d) Neopolyoxins: Uramoto, M.; Kobinata, K.; Isono, K.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron Lett.* **1980**, 3395.

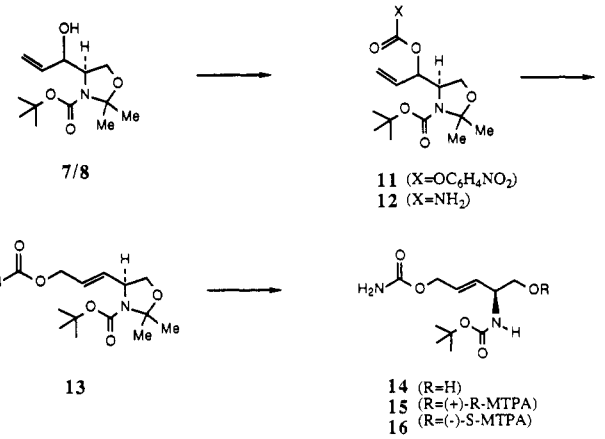
(5) (a) Garner, P.; Park, J. M. *J. Org. Chem* **1987**, *52*, 2361. (b) Garner, P. *Tetrahedron Lett.* **1984**, 5855.

(6) Anh, N. T. *Top. Curr. Chem* **1980**, *88*, 145 and references cited therein.

(7) Cf.: Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.

(8) Millar, A.; Kim, K. H.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1986**, *51*, 189.

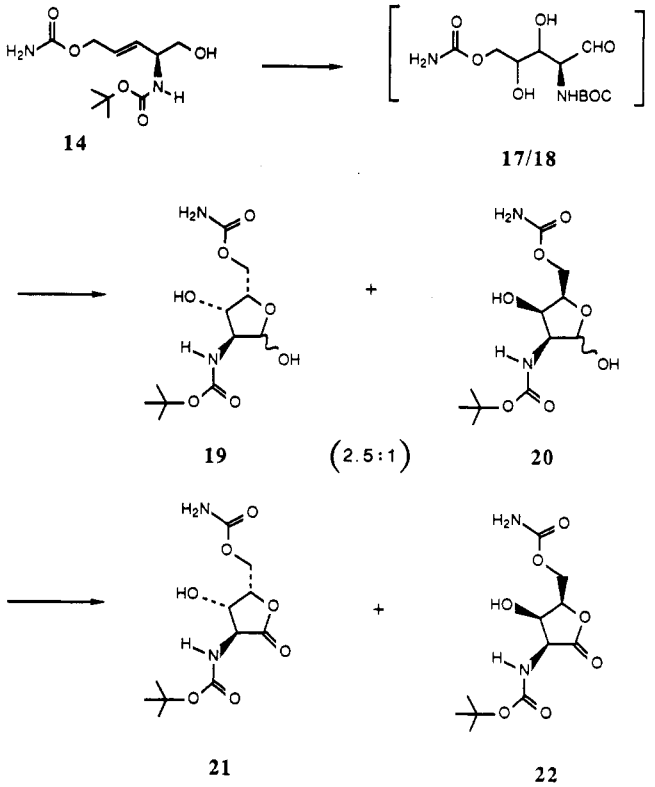
(9) Overmann, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.



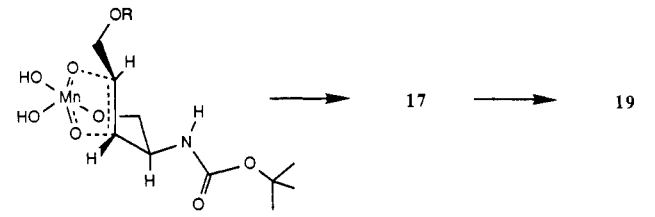
homoallylic alcohol **14** (=**4**) in 80% yield after one recycle of unreacted **18**. This (recrystallized) compound was shown to be configurationally pure via ^{19}F NMR analysis of the diastereomeric Mosher esters derived from (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[10] We now were ready for the key oxidation sequence which would involve both a cis hydroxylation of the double bond and oxidation of the primary alcohol to a carboxylic acid.

In considering various oxidants for this transformation, we settled on a one-step procedure using potassium permanganate since this reagent is capable of both cis hydroxylation and selective oxidation of primary alcohols in the presence of secondary alcohols. In the event, homoallylic alcohol **14** reacted with $KMnO_4$ under carefully defined, CO_2-buffered conditions to give an inseparable mixture of (SiO_2 sensitive) lactols **19** and **20** in 97% crude yield.[11] Apparently, the first formed hydroxy aldehydes **17**/**18** undergo spontaneous hemiacetal formation, and further oxidation is precluded under these reaction conditions. If the reaction mixture was allowed to become more basic (a condition necessary for further oxidation to the lactone), the urethane group was lost, and the resulting primary alcohol underwent oxidation as well. In spite of this we still felt that the lactol to lactone oxidation should be possible since a very facile dehydrogenation had been observed in the electron impact mass spectrum of **19**/**20**.

Treatment of the lactol mixture with *N*-bromourea (prepared in situ) did result in the desired oxidation under very mild conditions,[12] producing a (2.5:1) mixture of γ-lactones **21** and **22** in ca. 40% combined yield (based on recovered starting material). In spite of the modest yield, this procedure was found to be superior to other known methods for the chemical oxidation of lactols to lactones (i.e., Br_2/aqueous buffer or $BaCO_3$; NBS/CH_2Cl_2; DMSO–Ac_2O; Ag_2CO_3/Celite, Δ; CrO_3–pyridine). Purification of **21** and **22** was achieved through a combination of flash chromatography and crystallization. That the observed ratio was, in fact, due to diastereofacial preference during the cis hydroxylation step and not an artifact of epimerization of the γ-lactones at C-2 was shown by converting the lactol mixture to a (2.5:1) mixture of diastereomeric triacetates via a reduction/acetylation sequence. Furthermore, separate control experiments with purified **21** and **22** confirmed that the lactones were indeed stable to the conditions of their formation. At this point we felt



that the major product **21** should have the required 2*S*,3*S*,4*R* configuration based on a (presumed) bicyclic transition state which places the NHBOC substituent at C-2 in a less demanding equatorial position. It should be noted that cis hydroxylation of **14** and related compounds using OsO_4 was uniformly nonselective as expected for N-protected allylic amines.[13] Surprisingly, attempted cis hydroxylation of **13** with $KMnO_4$ under the buffered conditions described above led to formation of compounds tentatively identified as α-hydroxy ketones instead of the expected diols.



Exposure of either **21** or **22** to trifluoroacetic acid resulted in N-deprotection and afforded the corresponding γ-lactone salts **23** and **26**, each in quantitative yield. An NOE difference experiment was performed on the salt derived from the minor lactone and showed a 12–25% enhancement of H-4 when H-2 was irradiated, thereby supporting our initial stereochemical assignments. Hydrolysis of **21** with 1 N HCl at 95 °C gave the amino acid hydrochloride **25** (=**2**·HCl) in quantitative yield, though it was contaminated with a small amount of its respective γ-lactone salt **24** as judged by NMR, IR, and TLC. Prolonged reaction times at this temperature did not drive the reaction to completion, suggesting the existence of an

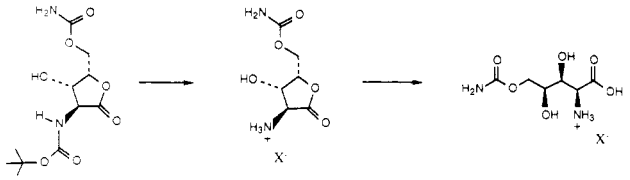
(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353. An in depth review of oxidations with permanganate has just recently been published: Fatiadi, A. J. *Synthesis* **1987**, 85.

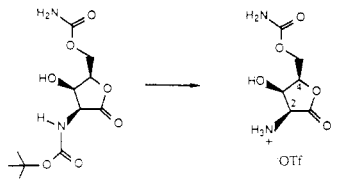
(12) Kiss, J. v.; Spiegelberg, H. *Helv. Chim. Acta* **1964**, *47*, 398.

(13) The α-chiral center of N-protected allylic amines apparently exerts little if any effect on the diastereoselectivity of osmylation: Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236. Dyong, I.; Friege, H.; Luftmann, H.; Merten, H. *Chem. Ber*, **1981**, *114*, 2669. However, incorporation of an additional chiral auxillary capable of chelation can be beneficial—even though it might be further removed from the prochiral π-system: Dyong, I.; Wiemann, R. *Ibid.* **1980**, *113*, 1592.

equilibrium between **24** and **25**. Similar behavior had been reported for the analogous acyclic γ-hydroxy-α-amino acid component of the nikkomycins as well.[4] In any event, the 400-MHz ^{1}H NMR spectrum of **25** was superimposible with one obtained for an authentic specimen of 5-*O*-carbamoylpolyoxamic acid (**2**·DCl). Thus we had succeeded in completing an efficient (seven steps from **6**), asymmetric synthesis of the acyclic target **2**, using a strategy wherein all chirality was derived from D-serine.[14] Further work dealing with construction of the remaining nucleoside segment **3** starting from the oxazolidine aldehyde **6** and application of these results to the total synthesis of polyoxin J is currently under way.



21 **23** (X=OTf) **24** (X=Cl) **25** (=2·HCl)



22 **26**

Experimental Section

TLC analysis was performed on Merck silica gel 60 F-254 plates and visualized with UV illumination and/or charring with 0.3% ninhydrin in (97:3) *n*-BuOH–AcOH. Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter and are average of at least four measurements. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz, ^{13}C NMR at 50.4 MHz, and ^{19}F NMR at 188 MHz with a Varian XL-200 spectrometer; 400-MHz ^{1}H NMR spectra and NOE difference data were obtained with a Bruker MSL 400 NMR spectrometer. Residual $CHCl_3$ (δ 7.24), C_6H_6 (δ 7.16), DMSO (δ 2.49), and HDO (δ 4.67) were used as internal standards for the ^{1}H NMR spectra, whereas $CDCl_3$ (δ 77.0), C_6D_6 (δ 128.0), and TMS (δ 0.00) were used as standards for ^{13}C NMR spectra. TFA (δ 0.00) was used as an external standard for the ^{19}F NMR spectra. Mass spectral data was obtained with a Kratos MS30 mass spectrometer. Combustion analyses were performed on TLC homogeneous and in some case recrystallized samples by Galbraith Labs, Inc.

1,1-Dimethylethyl [*S*-(*R,*S**)]-4-(1-hydroxy-2-propenyl)-2,2-dimethyl-3-oxazolidinecarboxylate (7) and 1,1-Dimethylethyl [*S*-(*R**,*R**)]-4-(1-hydroxy-2-propenyl)-2,2-dimethyl-3-oxazolidinecarboxylate (8).** To a −78 °C solution of oxazolidine aldehyde **6** (12.02 g, 0.05242 mol) in dry THF (350 mL, distilled from sodium–benzophenone ketyl) under N_2 was added 175 mL of 1 M vinylmagnesium bromide (Aldrich Chem. Co.) in THF over a 30-min period. The yellow solution was stirred for 2 h at −78 °C when the TLC in (2:1) hexane–EtOAc showed the clean formation of product, R_f 0.33, at the expense of starting aldehyde, R_f 0.43. The solution was warmed to 0 °C and partitioned between 120 mL of saturated NH_4Cl solution and 2 X 1000 mL of Et_2O. The combined organic layers were washed with 300 mL of brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give 14.48 g of crude product. The ^{1}H NMR spectrum (vide infra) of this material indicated a (6:1) mixture of diastereomers **7** and **8**. Fractional vacuum distillation using a 10-cm Vigreux column yielded 10.80 g (80% yield) of a (4:1) mixture of **7** and **8** as a colorless oil, bp 102 °C (0.6–0.7 mm), $[\alpha]_D$ +26.6° (*c* 1.03 $CHCl_3$), which was used directly for the next transformation. For characterization purposes, pure samples of **7** and **8** were obtained by careful flash chromatography using (5:1) hexanes–EtOAc. Compound **7**: $[\alpha]_D$ +55.0° (*c* 1.47 $CHCl_3$); IR (neat): 3450, 3080, 1700 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 1.36 (s, 9 H), 1.42 (s, 3 H), 1.60 (s, 3 H), 3.54–3.76 (br dd, *J* = 7.7 and 4.3 Hz, 2 H), 3.82 (br s, H exchanged with D_2O), 3.92 (br s, H), 4.30 (br s, H), 5.08 (dd, *J* = 10.5 and 1.4 Hz, H), 5.36 (dd, *J* = 17.5 and 1.2 Hz, H), 5.84 (ddd, *J* = 17.5, 10.7, and 6.4 Hz, H); ^{13}C NMR (C_6D_6, 60 °C) δ 23.9, 26.4, 28.0, 61.9, 64.3, 73.5, 79.9, 94.2, 115, 138.1, 153.2. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.11; H, 9.19; N, 5.75. Compound **8**: ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 1.38 (s, 9 H), 1.42 (s, 3 H), 1.62 (s, 3 H), 3.63 (dd, *J* = 9.4 and 6.3 Hz, H), 3.70 (br s, H exchanged with D_2O), 3.82 (dd, *J* = 9.4 and 2.0 Hz, H), 3.91 (dd, *J* = 6.7 and 6.3 Hz, H), 4.40 (pseudo-t, *J* = 6.7 Hz, H), 5.04 (dd, *J* = 10.3 and 1.5 Hz, H), 5.26 (dd, *J* = 17.2 and 1.5 Hz, H), 5.83 (ddd, *J* = 17.0, 10, and 6.7 Hz, H).

1,1-Dimethylethyl (4*S*-*trans*)-(4-Ethenyl-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (10). The major secondary allylic alcohol **7** (56 mg, 0.22 mmol) was dissolved in MeOH (3.0 mL) containing $TsOH·H_2O$ (6 mg, 0.03 mmol). After 3 h at ambient temperature the TLC in (2:1) hexanes-EtOAc showed the clean formation of product, R_f 0.12, at the expense of starting material, R_f 0.67. The reaction mixture was partitioned between 10 mL of saturated $NaHCO_3$ solution and 3 × 30 mL of EtOAc. The combined organic extracts were washed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to give 51 mg of crude product. Flash chromatography on silica gel eluting with (3:2) hexanes–EtOAc afforded 41 mg (85% yield) of pure diol **9** as an oil: IR ($CHCl_3$) 3500, 3440, 3000, 1700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, room temperature) δ 1.44 (s, 9 H), 2.80 (br s, 2 H, exchanged with D_2O), 3.65 (m, H), 3.77 (dd, *J* = 17.0 and 4.1 Hz, H), 3.93 (dd, *J* = 11.1 and 3.5 Hz, H), 4.39 (m, H), 5.26 (dd, *J* = 10.4 and 1.5 Hz, H), 5.37 (br s, H, exchanged with D_2O), 5.38 (dd, *J* = 17.3 and 1.5 Hz, H), 5.93 (ddd, *J* = 17.3, 10.4, and 5.7 Hz, H). A sample of **9** (19 mg, 0.086 mmol) was dissolved in 2,2-dimethoxypropane (1.0 mL) containing $TsOH·H_2O$ (1 mg, 0.005 mmol). The reaction mixture was stirred for 3–4 h at ambient temperature when the TLC in (1:1) EtOAc–hexanes showed the clean formation of product, R_f 0.76, at the expense of starting material, R_f 0.17. After extractive workup as described above, the crude product (23 mg) was flash chromatographed on silica gel by eluting with (3:1) hexanes–EtOAc, giving 16 mg (71% yield) of dioxolane **10** as a low-melting solid, mp 60–65 °C: IR ($CHCl_3$) 3440, 3000, 1700 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6 + D_2O, 60 °C) δ 1.28 (s, 3 H), 1.40 (br s, 9 H), 1.41 (s, 3 H), 3.39 (pseudo-t, *J* = 10.5 Hz, H), 3.55 (ddd, *J* = 10.5, 10.0, and 5.3 Hz,[15] H-5), 3.82 (dd, *J* = 11.2 and 5.3 Hz, H), 3.87 (br s, H), 5.04 (dd, *J* = 10.6 and 1.8 Hz, H), 5.24 (dd, *J* = 17.1 and 1.8 Hz, H), 5.86 (ddd, *J* = 17.1, 10.6, and 6.1 Hz, H).

1,1-Dimethylethyl [*S*-(*R,*S**)]-4-[1-[(Aminocarbonyl)oxy]-2-propenyl]-2,2-dimethyl-3-oxazolidinecarboxylate (12).** To a solution of secondary allylic alcohols **7**/**8** (5.80 g, 0.0225 mol) in dry pyridine (550 mL, distilled from CaH_2) was added *p*-nitrophenyl chloroformate (11.46 g, 0.02253 mol). The resulting emulsion was stirred at ambient temperature for 24 h under N_2, during which time it was replaced by a clear yellow solution. TLC in (2:1) hexanes–EtOAc showed the clean formation of product, R_f 0.65, at the expense of the starting material at R_f 0.35. The reaction mixture was diluted with 1 L of benzene and extracted with 5 × 1 L of 0.5 M H_2SO_4, 5 × 1 L of saturated $NaHCO_3$ solution, and 2 × 1 L of water. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to give 18.07 g of crude

(14) For a recent example of asymmetric aminosugar synthesis via β-hydroxy-α-amino acid precursors, see: Mauer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325. A treatise on the use of amino acids in synthesis has recently been published: Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

(15) Complete analysis of this four-spin system was accomplished by computer simulation using LAOCOON5 (least-squares adjustment of calculated on observed NMR). This program is part of the LAB ONE NMR1 Spectroscopic Data Analysis Software System, New Methods Research, Inc., Syracuse University.

carbonate **11** as a pale yellow solid, which was dissolved in CH_2Cl_2 (150 mL) and treated with 300 mL of saturated NH_3/MeOH at ambient temperature for 1 h when the TLC showed clean formation of product **14**, R_f 0.22, at the expense of carbonate **11**, R_f 0.62. After concentration of this mixture in vacuo, the resulting yellow solid was dissolved in 1 L of CH_2Cl_2 and washed with 3 × 1 L of 0.5 M $NaHCO_3$ solution followed by 2 × 1 L of water. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to give 6.86 g of crude **12** as a yellow oil. Flash chromatography on silica gel eluting with (1:1) hexane–EtOAc gave 4.61 g of secondary urethane **12** (68% yield overall) as a (4:1) mixture of erythro/threo diastereomers: $[\alpha]_D$ +38.4° (*c* 4.06, $CHCl_3$); IR (neat) 3350, 3100, 1730, 1700, 1600 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C, major isomer) δ 1.46 (s, 9 H), 1.51 (s, 3 H), 1.70 (s, 3 H), 3.72 (dd, *J* = 6.7 and 1.8 Hz, H), 3.85 (dd, *J* = 8.8 and 1.8 Hz, H), 4.17 (br s, 3 H), 5.02 (dd, *J* = 10.5 and 1.3 Hz, H), 5.25 (dd, *J* = 17.2 and 1.4 Hz, H), 5.60–5.71 (br s, H), 5.89 (br s, H); ^{13}C NMR (C_6D_6, 60 °C) δ 26.8, 29.2, 62.8, 63.7, 74.9, 79.5, 94.2, 119.1, 136.0, 155.8, 156.1. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.97; H, 8.07; Found, C, 56.04; H, 8.17.

1,1-Dimethylethyl [*S*-(*E*)]-4-[3-[(Aminocarbonyl)oxy]-1-propenyl]-2,2-dimethyl-3-oxazolidinecarboxylate (13). To a solution of the secondary urethanes **12** (4.50 g, 0.0149 mol) in dry THF (150 mL) was added $PdCl_2(MeCN)_2$ (77.2 mg, 0.257 mmol). The resulting yellow solution was stirred at ambient temperature under N_2 for 8 h when the TLC in (1:1) hexanes–EtOAc (three developments) was constant and showed the formation of a new product at R_f 0.23 as well as some remaining starting material at R_f 0.31. The reaction mixture was partitioned between 500 mL of water and 3 × 500 mL of EtOAc. The combined organic layers were washed with 500 mL of brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give 4.27 g crude product as a yellow oil. Flash chromatography on silica gel eluting with (6:1) hexanes–EtOAc gave 3.01 g of pure primary urethane **13** (86% yield based on recovered **12**): $[\alpha]_D$ +10.0° (*c* 1.06, $CHCl_3$); IR (neat) 3350, 1730, 1700, 1600 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.43 (s, 9 H), 1.53 (s, 3 H), 1.69 (s, 3 H), 3.50 (dd, *J* = 9.3 and 6.2 Hz, H), 3.60 (dd, *J* = 9.3 and 2.5 Hz, H), 4.10 (m, 3 H), 4.46 (d, *J* = 4.2 Hz, H), 5.64 (br s, 2 H); ^{13}C NMR (C_6D_6, 60 °C) δ 26.85, 27.06, 28.42, 60.02, 64.52, 68.04, 79.52, 94.05, 126.98, 133.34, 154.96, 157.12. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.97; H, 8.07. Found: C, 56.00; H, 8.20.

1,1-Dimethylethyl [*S*-(*E*)]-[4-[(Aminocarbonyl)oxy]-1-(hydroxymethyl)-2-butenyl]carbamate (14). A solution of **13** (2.86 g, 0.009 51 mol) and $TsOH \cdot H_2O$ (144 mg, 0.760 mmol) in methanol (170 mL) was stirred at ambient temperature for 14 h when the TLC in EtOAc showed the partial formation of a product at R_f 0.46 along with starting material at R_f 0.77. Prolonged reaction times resulted in cleavage of the BOC moiety as evidenced by increasing amounts of intensely ninhydrin active material near the origin so the reaction was worked up at this point. The mixture was partitioned between 450 mL of saturated $NaHCO_3$ solution and 3 × 500 mL of EtOAc, and the combined organic layers were washed with 450 mL of brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give 2.7 g of an oil. Flash chromatography on silica gel eluting with (1:1) hexanes–EtOAc afforded alcohol **14** as a white solid, which recrystallized from hot EtOAc as needles, mp 107–108 °C: $[\alpha]_D$ +11.4° (*c* 0.94, MeOH); IR (KBr) 3350, 1690, 1605 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6 room temperature) δ 1.39 (s, 9 H), 2.7 (br s, H, disappears with D_2O exchange), 3.59 (pseudo-t, *J* = 5.8 Hz, 2 H), 4.07 (br s, H), 4.47 (d, *J* = 3.5, H), 5.67 (br s, 2 H), 5.73–5.90 (br s, 3 H); ^{13}C NMR (acetone-d_6, room temperature) δ 28.6, 54.8, 64.8, 65.1, 78.0, 127.0, 133.0, 156.23, 157.47. Anal. Calcd for $C_{11}H_{20}NO_5$: C, 50.75; H, 7.76. Found: C, 50.92; H, 7.79.

[*R*-[*R,*S**-(*E*)]]-5-[(Aminocarbonyl)oxy]-2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pentenyl α-Methoxy-α-(trifluoromethyl)benzeneacetate (15) and [*S*-[*R**,*R**-(*E*)]]-5-[(Aminocarbonyl)oxy]-2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pentenyl α-Methoxy-α-(trifluoromethyl)benzeneacetate (16).** To a solution of **14** (3.8 mg, 0.015 mmol), 1,3-dicyclohexylcarbodiimide (3.6 mg, 0.017 mmol), and 4-(dimethylamino)pyridine (0.5 mg, 0.004 mmol) in dry CH_2Cl_2 (1.0 mL, distilled from P_2O_5) was added 0.17 mL of 0.09 M (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) in CH_2Cl_2. This solution was stirred at room temperature overnight when the TLC in EtOAc showed the formation of product, R_f 0.77, at the expense of starting material, R_f 0.43. The reaction mixture was filtered through cotton and concentrated in vacuo to give 16.1 mg of an oily residue. Preparative TLC on a 0.5 mm thick plate eluting with ethyl acetate gave 5.2 mg (75%) of pure **15** as a colorless oil: ^1H NMR (200 MHz, C_6D_6, room temperature) δ 1.38 (s, 9 H), 3.39 (s, 3 H), 3.68–3.79 (br s, 2 H, exchanged with D_2O), 3.87 (dd, *J* = 11.0 and 6.1 Hz, H), 3.98 (dd, *J* = 13.0 and 4.7 Hz, H), 4.25 (br s, H), 4.28 (d, *J* = 5.6 Hz, 2 H), 4.32–4.42 (br s, H), 5.16 (dd, *J* = 15.7 and 5.44 Hz, H), 5.40 (dt, *J* = 16 and 5.6 Hz, H), 7.12 (m, 3 H), 7.67 (d, *J* = 7.5 Hz, 2 H); ^{19}F NMR (C_6D_6, room temperature) δ 5.26. The diastereomeric product **16** was prepared from **14** in 78% yield as described above but by using (*S*)-(−)-MTPA: ^1H NMR (200 MHz, C_6D_6, room temperature) δ 1.38 (s, 9 H), 3.42 (s, 3 H), 3.77–3.84 (br s, 2 H, exchanged with D_2O), 3.91 (m, 2 H), 4.27 (br s, H), 4.28 (d, *J* = 5.34 Hz, 2 H), 4.34–4.39 (m, H), 5.16 (dd, *J* = 15.6 and 5.2 Hz, H), 5.38 (dt, *J* = 15.8 and 5.4 Hz, H), 7.12 (m, 3 H), 7.70 (d, *J* = 7.6 Hz, 2 H); ^{19}F NMR (C_6D_6, room temperature) δ 5.44.

2-Deoxy-2-[[(1,1-dimethylethoxy)carbonyl]amino]-L-xylofuranose 5-Carbamate (19) and 2-Deoxy-2-[[(1,1-dimethylethoxy)carbonyl]amino]-L-lyxofuranose 5-Carbamate (20). A solution of $KMnO_4$ (1.0667 g, 0.006 751 3 mol) in 10% aqueous acetone (48 mL) was added dropwise over 30 min to an ice-cold solution of homoallylic alcohol **14** (1.1991 g, 0.004 606 0 mol) in 10% aqueous acetone (14 mL). During this reaction, CO_2 was continuously bubbled through the reaction mixture. The TLC in EtOAc indicated the clean formation of product(s), R_f 0.32, at the expense of starting material, R_f 0.42. Water (20 mL) was added, and SO_2 gas was passed through the cooled reaction mixture for 5–10 s, during which time the pH changed from 6–7 to 1–2 and the dark brown suspension was replaced by a clear solution.[16] This solution was extracted with 3 × 200 mL of EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 1.301 g (96% yield) of lactols **19/20** as a white foam, mp 42–44 °C: IR (neat) 3500, 1700, 1600 cm^{-1}; ^{13}C NMR (DMSO-d_6, room temperature, mixture of isomers) δ 14.04, 20.69, 28.16, 55.41, 58.97, 59.34, 59.69, 60.43, 60.72, 60.88, 61.20, 63.45, 63.97, 64.42, 64.69, 64.98, 68.99, 70.11, 73.04, 73.28, 74.13, 74.32, 75.28, 77.91, 78.32, 93.96, 94.88, 99.82, 100.76, 155.07, 155.29, 156.53, 156.70, 208.19 (aldehyde); HRMS (20 eV), calcd for $C_{11}H_{18}N_2O_7$ (M^+ − 2H) 290.1114, found 290.1159.

2-Deoxy-2-[[(1,1-dimethylethoxy)carbonyl]amino]-L-xylonic Acid, γ-Lactone, 5-Carbamate (21) and 2-Deoxy-2-[[(1,1-dimethylethoxy)carbonyl]amino]-L-lyxonic Acid, γ-Lactone, 5-Carbamate (22). A mixture of urea (15.0 g, 0.250 mol) and $CaCO_3$ (14.3 g, 0.143 mol) in H_2O (45 mL) was stirred at room temperature for 2 h, whereupon molecular bromine (10.0 mL, 31.0 g, 0.194 mol) was added over a period of 1 h, and the mixture was stirred at room temperature for an additional hour. A solution of lactols **19/20** (1.7056 g, 0.005 844 1 mol) in EtOAc (20 mL) was added to the resultant brown-yellow suspension over a 15-min period. The brown suspension was stirred at room temperature for 8 h when the TLC in EtOAc showed the formation of the desired lactone products, R_f (major) 0.51 and R_f (minor) 0.57, at the expense of starting material at R_f 0.34. Two other minor products could be detected as broad overlapping spots centered at R_f 0.12. The reaction mixture was partitioned between EtOAc (50 mL) and water (20 mL). The aqueous phase was extracted further with 3 × 30 mL of EtOAc, and the combined organic layers were washed with 40 mL of 20% $NaHSO_3$ solution, 40 mL of $NaHCO_3$ solution, and 20 mL of H_2O. The organic phase was then dried with $MgSO_4$, filtered, and concentrated to give 1.2328 g of a white solid. An NMR analysis (vide infra) at this point revealed a (2.5:1) mixture of lactones **21** and **22** in the crude mixture. Trituration of this material with 2 × 10 mL of EtOAc left 342 mg (20% yield) of the major lactone **21** as a white solid, mp 204–206 °C. Recrystallization from hot MeOH gave 289 mg of analytically pure **21** as rhomboids, mp 215–216 °C. Flash chromatography of the EtOAc soluble material (604 mg) eluting with (2:1) EtOAc–hexanes afforded 190 mg (11% yield) of the

(16) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 943. This commendable procedure converts the generally intractable MnO_2 byproduct to water soluble $MnSO_4$ and thus facilitates the subsequent extractive workup.

minor lactone **22** as a white solid, mp 122–124 °C, 60 mg (4% yield) of more of **21**, and 50 mg of recovered starting material. Spectral data for the major lactone **21**: $[\alpha]_D$ −78° (*c* 0.35, DMF); IR (KBr) 3500, 3300, 1770, 1720, 1680, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, room temperature) δ 1.39 (br s, 9 H), 4.05 (t, *J* = 8.0 Hz, H), 4.13 (dd, *J* = 7.0 and 6.1 Hz, H), 4.24 (dd, *J* = 12.5 and 1.9 Hz, H), 4.48 (dd, *J* = 7.0 and 6.1 Hz, H), 4.66 (ddd, *J* = 7.0, 6.3, and 1.9 Hz, H), 5.91 (d, *J* = 5.2 Hz, H, exchanged with D_2O), 6.59 (br s, 2 H, exchanged slowly with D_2O), 7.52 (d, *J* = 8.1 Hz, H, exchanged slowly with D_2O); ^{13}C NMR (pyridine-d_5, room temperature) δ 28.38, 58.61, 63.12, 71.95, 79.10, 79.34, 156.90, 157.74, 174.04. Anal. Calcd for $C_{11}H_{18}N_2O_7$: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.54; H, 6.10; N, 9.64. Spectral data for the minor lactone **22**: $[\alpha]_D$ +48° (*c* 0.77, DMF); IR (KBr) 3500, 3300, 1700, 1720, 1680, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, room temperature) δ 1.40 (s, 9 H), 4.03 (dd, *J* = 12.3 and 8.8 Hz, H), 4.20 (dd, *J* = 12.3 and 4.2 Hz, H), 4.26 (dd, *J* = 4.5 and 3.2 Hz, H), 4.64 (dt, *J* = 8.8 and 2.8 Hz, H), 4.72 (dd, *J* = 9.2 and 4.8 Hz, H), 5.72 (d, *J* = 5.7 Hz, H, exchanged with D_2O), 6.54–6.71 (br s, 2 H, exchanged slowly with D_2O), 6.66 (d, *J* = 9.2 Hz, H, exchanged slowly with D_2O); ^{13}C NMR (pyridine-d_5, room temperature) δ 28.40, 56.88, 63.74, 69.61, 79.18, 80.36, 156.93, 157.99, 175.20. Anal. Calcd for $C_{11}H_{18}N_2O_7$: C, 45.51; H, 6.25; N, 9.65. Found: C, 45.41; H, 6.09; N, 9.61.

2-Amino-2-deoxy-L-xylonic Acid, γ-Lactone, 5-Carbamate, Mono(trifluoroacetate) (Salt) (23) and 2-Amino-2-deoxy-L-lyxonic Acid, γ-Lactone, 5-Carbamate, Mono(trifluoroacetate) (Salt) (26). A mixture of lactone **21** (6.0 mg, 0.021 mmol) in 4% trifluoroacetic acid/CH_2Cl_2 was stirred at room temperature for 3–4 h at which time the TLC in EtOAc showed the clean formation of product, R_f 0.06, at the expense of starting material, R_f 0.42. The solvent was evaporated to leave 6.9 mg of **23** as a white solid, mp 138–140 °C: IR (KBr) 3440, 3300, 1790, 1700, 1650, 1580 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.35 (dd, *J* = 12.7 and 2.6 Hz, H-5), 4.38 (dd, *J* = 12.7 and 2.8 Hz, H-5′), 4.42 (d, *J* = 9.5 Hz, H-2), 4.86 (dd, *J* = 9.5 and 8.1 Hz, H-3), 4.94 (ddd, *J* = 8.1, 2.8, and 2.6 Hz, H-4). Anal. Calcd for $C_8H_{11}N_2O_7F_3$: C, 31.59; H, 3.65; N, 9.21. Found: C, 31.55; H, 3.51; N, 8.86. In a similar manner, treatment of **22** with TFA afforded 6.9 mg of the diastereomeric triflate salt **26** as a white solid, mp 140–141 °C: IR (KBr) 3430, 3300, 1800, 1660, 1600 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 4.32 (dd, *J* = 12.3 and 7.7 Hz, H-5), 4.33 (dd, *J* = 12.3 and 3.9 Hz, H-5′), 4.54 (d, *J* = 5.0 Hz, H-2), 4.78 (dd, *J* = 5.0 and 2.8 Hz, H-3), 4.83 (ddd, *J* = 7.7, 3.9, and 2.8 Hz, H-4).

2-Amino-2-deoxy-L-xylonic Acid, 5-Carbamate (5-*O*-Carbamoylpolyoxamic Acid), Hydrochloride (25). A stirred mixture of lactone **21** (49.7 mg, 0.170 mmol) in 1 N HCl (5.0 mL) was heated at 95 °C for 1 h when the TLC in (3.6:3.6:2.1:0.7) pyridine–EtOAc–H_2O–HOAc showed clean formation of a product that corresponded to 5-*O*-carbamoylpolyoxamic acid (**2**), R_f 0.30. A small amount of an intermediate lactone corresponding to **24**, R_f 0.76, was also detected. The reaction mixture was cooled, and the solvent was removed in vacuo to afford 45.3 mg of product as a crystalline foam, which decomposed at 150 °C, $[\alpha]_D$ −6.2°, $[\alpha]_{365}$ −23° (*c* 0.76, H_2O). IR (KBr) 3700–2300 br, 1780 (lactone salt), 1720, 1590 cm^{-1}; ^1H NMR of **25** (400 MHz, D_2O + DCl, pD = 2.0, room temperature) δ 4.06 (br s, 3 H), 4.08 (d, *J* = 3.4 Hz, H), 4.24 (ddd, *J* = 3.4, 1.5, and 0.6 Hz, H-4). This spectrum also showed the presence of a small amount of lactone salt **24** whose signals matched those reported for **23** (vide supra). The overall ratio of **25** to **24** was determined to be (4:1) by integration. The NMR spectrum of synthetic **25** was identical with one obtained with an authentic sample of 5-*O*-carbamoylpolyoxamic acid (**2**) in D_2O + DCl.

Acknowledgment. This work was supported by Public Health Service Grant GM 35557 administered by the National Institute of General Medical Sciences. We thank Dr. Kiyoshi Isono for providing us with an authentic sample of **2** for comparison and Dr. Kurt Loening for assistance with the nomenclature.

Registry No. **6**, 95715-87-0; **7**, 114301-34-7; **8**, 114301-35-8; **9**, 114301-36-9; **10**, 114376-27-1; **11** (isomer 1), 114301-37-0; **11** (isomer 2), 114301-51-8; **12** (isomer 1), 114301-38-1; **12** (isomer 2), 114301-39-2; **13**, 114324-28-6; **14**, 114301-40-5; **15**, 114301-41-6; **16**, 114301-42-7; **19**, 114301-43-8; **20**, 114301-52-9; **21**, 114301-44-9; **22**, 114301-45-0; **23**, 114301-47-2; **24**, 114301-50-7; **25**, 114324-36-6; **26**, 114301-49-4; (*R*)-(+)-MTPA, 20445-31-2; (*S*)-(−)-MTPA, 17257-71-5; polyoxin, 11113-80-7.

Enantioselective Ring Construction with Control of Side-Chain Stereochemistry: Synthesis of (+)-Isoneonepetalactone

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Received June 17, 1987

Intramolecular cyclopropanation of **13**, directed by R*OH **1**, proceeds with significant face selectivity, to give **14** as the major product. The influence of both transition metal catalyst and olefin substitution and geometry on the diastereomeric excess and chemical yield of this reaction has been explored. Opening of enantiomerically pure cyclopropane **8** with lithium divinylcuprate, followed by further synthetic modification, leads to (+)-isoneonepetalactone (**26**).

The development of new methods for ring construction is fundamental to the development of synthetic organic chemistry. In particular, as striking differences in the physiological activity of enantiomers have appeared, and as convergent design has come to dominate synthetic planning, there has been a need for the development of methods for ring construction with the control of absolute stereochemistry. While several elegant methods have appeared in recent years,[2] little work has been directed toward the development of methods for ring construction with control of side-chain stereochemistry.[3] We report

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(2) Several strategies for the enantioselective preparation of carbocycles have been reported. For leading references, see: Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.

0022-3263/88/1953-2984$01.50/0