Tetrahedron Letters, Vol. 34, No. 26, pp. 4157-4160, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .0
Pergamon Press Ltd

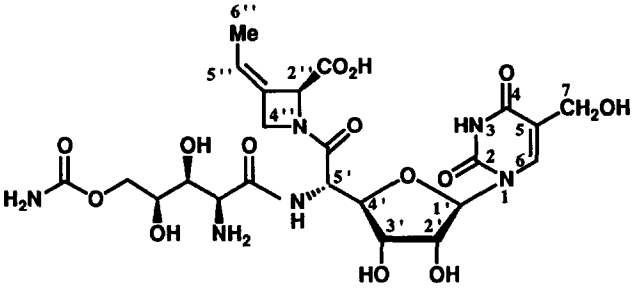
TOTAL SYNTHESIS OF (+)-POLYOXIMIC ACID – *CIS*-3-ETHYLIDENE-L-AZETIDINE-2-CARBOXYLIC ACID

Stephen Hanessian*, Jian-Min Fu, José-Luis Chiara and Romano Di Fabio
Department of Chemistry, Université de Montréal
P.O. Box 6128, Station A, Montréal, P.Q., CANADA, H3C 3J7

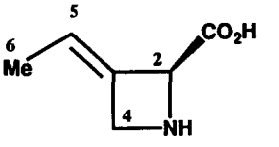
Abstract: The stereocontrolled total synthesis of (natural) *cis*- and (unnatural) *trans*-polyoximic acids is described starting with D-serine as a chiral template.

The nucleoside antifungal antibiotics of the polyoxin group have been the subject of extensive structural,[1] biosynthetic,[2] synthetic,[3] and biological studies. An unusual structural feature in polyoxins A,F,H and K (represented by A, **1**, Scheme 1) is the presence of an unsaturated amino acid component, polyoximic acid **2**,[4] which is peptidically linked to polyoxin C. Based on chemical degradative and NMR spectroscopic studies at 60 MHz, the structure of polyoximic acid was determined as being *trans*-3-ethylidene-L-azetidine 2-carboxylic acid **2**, by Isono and coworkers.[5] In spite of its diminutive size, efforts directed at the total synthesis of polyoximic acid have been complicated by the delicate balance of functionality including the presence of an exocyclic ethylidene group, the choice of protective groups, and the tendency of the molecule to racemize and/or rearrange.[4,5]

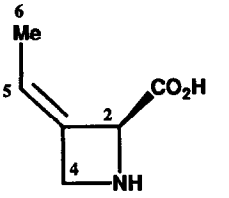
Scheme 1



1, Polyoxin A (revised structure)



2, *trans*-Polyoximic Acid



3, *cis*-Polyoximic Acid

In the preceding paper,[6] we reported a revision of the stereochemistry of the double bond in polyoximic acid. The amino acid obtained by acid hydrolysis of polyoxin A is in fact the *cis*- and not the *trans*-isomer. After completion of our work, Emmer[7] reported a total synthesis of racemic *trans*-polyoximic acid under the assumption that it was the natural amino acid. We now describe the first total syntheses of *cis*- and *trans*-polyoximic acids in enantiomerically pure form.

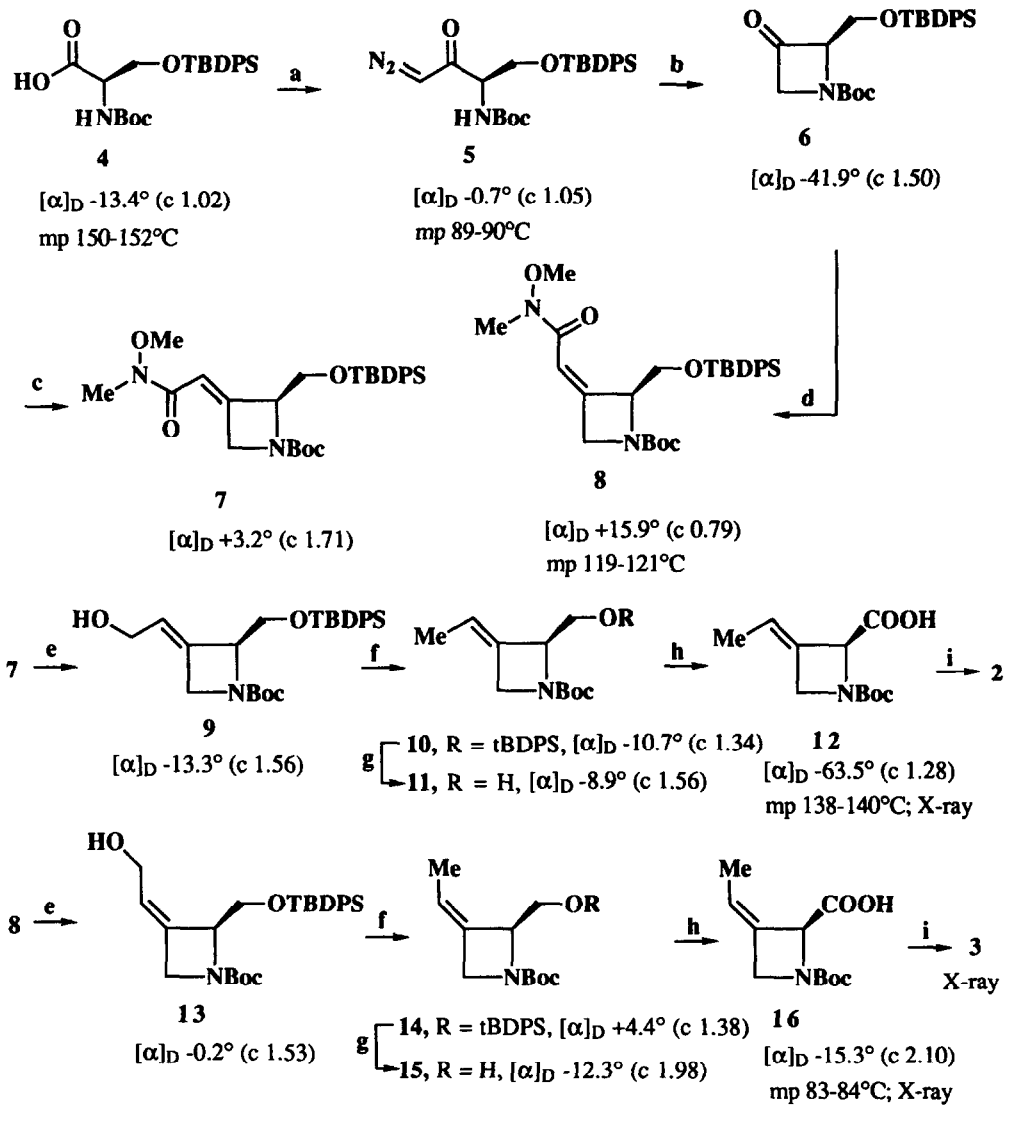
Inspection of the target structures **2** and **3** reveals a number of challenges that include *a.* a strategy for the construction of the azetidine ring with appropriate functionality, *b.* a protocol for the introduction of the exocyclic ethylidene group with *cis*- and *trans*- stereochemistry independently, *c.* functional group adjustments and protective group choices, and *d.* the prospects of obtaining enantiomerically pure products.

These challenges were met in highly stereocontrolled syntheses starting with D-serine as an obvious chiral template and proceeding through to a L-3-azetidinone-2-hydroxymethyl chiron using a rhodium-mediated diazoketone insertion reaction[8] (Scheme 2). Although such carbenoid reactions have been popularized by a number of groups,[8] few examples are known where diazoketones of amino acids were systematically used to produce 3-azetidinones.[9] After several model studies in which the suitability of N- and O-protective groups was investigated, we initiated the syntheses with the D-serine derivative **4**, readily prepared from the amino acid.[10] Treatment of the mixed anhydride with diazomethane led smoothly to the diazoketone derivative **5** which was treated with rhodium diacetate to produce the chiron **6** in 67% yield. The next challenge was to introduce the ethylidene group with stereochemical control. The most obvious approach involved direct ethylidenation by a Wittig process which led to an unseparable mixture of olefins (*cis/trans*, 3:2). A variety of modifications involving stabilized ylids, various phosphonates, and related reagents, all led to mixtures which were either difficult to separate or impractical in the context of a viable synthesis plan. We then discovered that the N-methyl-N-methoxycarbonyl variants of the Horner-Wadsworth-Emmons and Wittig reagents was admirably suited to produce the *cis*- or the *trans* isomers as major products. Moreover, the products were separable by chromatography. Thus, treatment of **6** with sodium diethyl (N-methoxy-N-methylcarbonylmethyl) phosphonate[11] in *THF* led to the preponderant formation of the *trans*-olefin **7** in 78% yield (*trans/cis* 94:6). On the other hand, using N-methoxy-N-methyl 2-(triphenylphosphoranylidene) acetamide[12] in *methanol* led to a majority of the *cis*-isomer **8** (73% yield, *cis/trans* 89:11). Since **7** and **8** could be separated by column chromatography, they were individually manipulated en route to the intended targets **2** and **3** respectively.

Reduction of **7** with LAH afforded the corresponding aldehyde which was further reduced to the primary allylic alcohol. Bromination and subsequent reduction with lithium borohydride in DMSO gave the *trans*-ethylidene derivative **10**. Desilylation and oxidation gave the acid **12**, whose structure was unambiguously determined by single crystal X-ray analysis.[10] Finally, treatment of **12** with formic acid, following by careful evaporation led to the *trans*-acid **2**, which was different than the natural product by ^{1}H NMR spectroscopy.[6,13]

In a similar sequence, compound **8** was converted into the allylic alcohol **13**. Reduction and functional group manipulation gave the *cis*-acid **16** the structure and stereochemistry of which were confirmed by single crystal X-ray analysis.[10] Treatment with formic acid, followed by evaporation and exhaustive drying at room temperature gave a crystalline residue. Trituration with cold methanol gave polyoximic acid **3**, mp 153-155°C; $[\alpha]_D$ +41.3° (c 0.55 MeOH) identical with the racemic product derived from acid hydrolysis of the polyoxin A (^{1}H, ^{13}C NMR, X-ray powder diffraction diagram). The amino acid **3** was partially racemized in methanol containing a drop of Et_3N (~50% within 20h at room temperature).

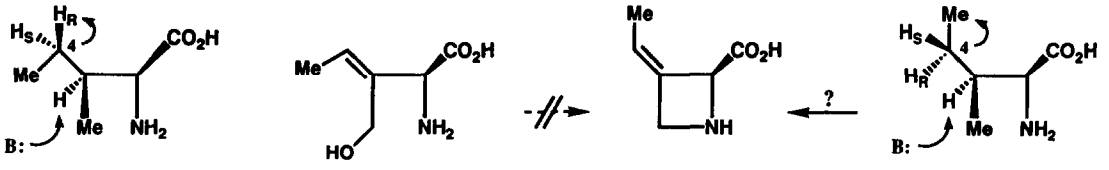
Scheme 2



(a) ^{i}BuOCOCl, N-methylmorpholine, 30 min, CH_2N_2-Et_2O, CH_2Cl_2, 0°C, 90%; (b)$Rh_2(OAc)_4$,CH_2Cl_2, -95°C to rt, 18 h, 67%; (c) NaH, THF, 0°C, Diethyl (N-methoxy-N-methylcarbonylmethyl)phosphonate, 78%, trans:cis = 94:6; (d) N-methoxy-N-methyl-2-(triphenylylphosphoranylidene)acetamide, CH_3OH, -78°C to rt, 73%, cis:trans = 89:11; (e) i, $LiAlH_4$, THF, -78°C, 3 h; ii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 30 min. trans: 72%, cis: 75%; (f) i, CBr_4, PPh_3, CH_2Cl_2, rt, 18 h; ii, $LiBH_4$, DMSO, rt, 18 h. trans: 50%, cis: 63%; (g) TBAF, THF, 0°C to rt, 3 h. trans: 94%, cis: 97%; (h) Jones reagent, acetone, 0°C to rt, 3 h. trans: 40%, cis: 40%; (i) HCOOH, rt, 4 h. quant.

With the establishment of the *cis*-stereochemistry for polyoximic acid, the proposal of an elimination of the *pro-R* hydrogen at C-4 of L-isoleucine,[14a] and the possible intermediacy of a hypothetical precursor, L-2-amino-3-hydroxymethyl-3-pentenoic acid[14b] must be reassessed (Scheme 3). If the double bond is indeed introduced by an enzymatic process, it most likely involves a synperiplanar elimination.

Scheme 3



Finally, it is of interest to point out that the structures of polyoximic acids **2** and **3** and related structures resulting from the methodology developed in this work represent constrained analogs of amino acids such as L-isoleucine, L-vinyl glycine,[15] and their congeners . As such, they are interesting structures for exploitation as β-turn mimetics[16] in a variety of peptide-like motifs.

Acknowledgments - We thank NSERCC, FCAR and Ciba Geigy (Agro) for generous financial assistance. We also thank Prof. K. Isono for samples of polyoxin A and of racemic polyoximic acid. We acknowledge the skillful assistance of Michel Simard and Francine Bélanger-Gariépy in determining the X-ray crystal structures.

References and Notes

1. Suzuki, S.; Isono, K.; Nagatsu, J.; Mizutani, T.; Kawashina, K., Mizuno, T. *J. Antibiotics*, **1965**, *A18*, 131; Isono, K.; Nagatsu, J.; Kawashima, Y.; Suzuki, S. *Agr. Biol. Chem., (Tokyo)*, **1965**, *29*, 848; Suzuki, S.; Isono, K.; Nagatsu, Kawashima, Y.; Yamagata, K.; Sasaki, K.; Hashimoto, *Agr. Biol. Chem. (Tokyo)*, **1966**, *30*, 817; Isono, K.; Kobinata, K.; Suzuki, S. *Agr. Biol. Chem. (Tokyo)*, **1968**, *32*, 792.
2. Isono, K.; Funayama, K.; Suhadolnik, R.J. *Biochemistry*, **1975**, *14*, 2992.
3. For recent examples, see Banik, K.B.; Manhas, M.S.; Bose, A.J. *J. Org. Chem.*, **1993**, *58*, 307; Garner, P.; Park, J.M. *J. Org. Chem.*, **1990**, *55*, 3772, and references cited therein.
4. For previous approaches to synthesis, see Baumann, H.; Duthaler, R.O., *Helv. Chim. Acta*, **1988**, *71*, 1025, 1035.
5. Isono, K., Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.*, **1969**, *91*, 7490 and references cited therein.
6. Hanessian, S.; Fu, J.-M., Tu, Y.; Isono, K. preceding paper.
7. For a recent total synthesis of rac. *trans*-polyoximic acid, see Emmer, G. *Tetrahedron*, **1992**, *48*, 7165.
8. For recent reviews, see Padwa, A.; Krumpe, K.E. *Tetrahedron*, **1992**, *48*, 5385.
9. Brunner, H. *Angew Chem. Int. Ed. Engl.*, **1992**, *31*, 1183; Taber, D.F. in *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I.; Pattenden, G., Eds, Pergamon Press, N.Y., **1991**, vol. 3, p. 1045; Adams, J.; Spero, D.M. *Tetrahedron*, **1991**, *47*, 1765; Padwa, A.; Hornbuckle, S.F. *Chem. Rev.*, **1991**, *91*, 263 and references cited therein.
10. All new compounds gave satisfactory spectroscopic and analytical data. X-ray crystal structures and data for compounds **12, 16** and **3** are available. Optical rotations were recorded at 25°C in $CHCl_3$.
11. Nuzilliard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.*, **1989**, *30*, 3779; Netz, D.F.; Seidel, J.L. *Tetrahedron Lett.*, **1992**, *33*, 1957.
12. Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.*, **1990**, *112*, 700.
13. For the *trans*-acid **2**, mp 149-151°C, dec.; $[\alpha]_D$ -2.0° (c 1.0, MeOH); see also ref. 7.
14. a. Hill, R.K.; Rhee, S.W.; Isono, K.; Crout, D.H.G.; Suhadolnik, R.J. *Biochemistry*, **1981**, *20*, 7040; b. Doyle, R.; Levenberg, B. *Biochemistry*, **1968**, *7*, 2457.
15. Hanessian, S.; Sahoo, S.P. *Tetrahedron Lett.*, **1984**, *25*, 1425; Afzali-Ardakin, A.; Rapoport, H. *J. Org. Chem.*, **1980**, *45*, 4817; Mzengeza, S.; Whitney, R.A. *J. Org. Chem.*, **1989**, *53*, 4024; Barton, D.H.R.; Crich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron*, **1985**, *41*, 4347. Krol, W.J.; Mao, S.; Steele, D.L.; Townsend, C.A. *J. Org. Chem.*, **1991**, *56*, 728.
16. For some reviews, see Rizo, J.; Giersach, L.M. *Ann. Rev. Biochem.*, **1992**, *61*, 387; Hölzmann, G. *Kontakte*, **1991**, 3; Ball, J.B.; Alewood, P.F. *J. Mol. Recogn.*, **1990**, *3*, 55; Kahn, M.; Wilke, S.; Chen, B.; Fujita, K., Lee, Y.-H.; Johnson, M.E. *J. Mol. Recogn.*, **1988**, *1*, 75.

(Received in USA 18 February 1993; accepted 29 April 1993)