Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6713–6715

TETRAHEDRON LETTERS

The sulfinyl moiety as an internal nucleophile. Part 8: Efficient, stereospecific synthesis of (+)-polyoxamic acid☆

Sadagopan Raghavan* and Suju C. Joseph

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 30 May 2003; revised 23 June 2003; accepted 27 June 2003

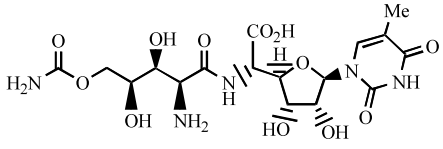
Abstract—A straightforward and stereospecific synthesis of (+)-polyoxamic acid is disclosed. The key step of the synthesis involves the regio- and stereospecific bromohydration of an olefin via intramolecular participation by the sulfinyl group.

Polyoxins,[1] isolated from *Streptomyces cacoi* var. asoensis, are peptidonucleosides comprising a nucleosidic amino acid and a hydroxylated amino acid, 5-*O*-carbamoyl polyoxamic acid, linked by an amide bond. The polyoxins are important agricultural antibiotics that exhibit marked and selective activity against phytopathogenic fungi by inhibiting chitin synthase.[2] They are also therapeutically useful against *Candida albicans*, a fungal pathogen that affects humans.[3] Polyoxamic acid has been the subject of many synthetic studies[4] which have employed carbohydrates or amino acids as building blocks except for that reported by Kim et al.,[4b] Baltas et al.,[4c] and Trost et al.[4i] There however remains the need for a more general, efficient and a stereoselective approach to polyoxamic acid. By way of demonstrating the potential of our methodology, of taking advantage of the sulfinyl moiety as an intramolecular nucleophile to functionalize olefins complexed to electrophiles,[5] we report herein a novel, concise and a highly stereoselective synthesis of polyoxamic acid (**1**).

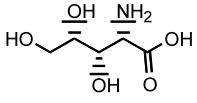
The synthesis commenced from the β-hydroxy sulfoxide (**3**) obtained by diastereoselective reduction (>95% d.e.) of β-keto sulfoxide (**2**)[6] with DIBAL/$ZnCl_2$.[7] Treatment of **3** with NBS in toluene in the presence of water afforded the bromohydrin (**4**) regio- and stereospecifically. The orientation as indicated for the hydroxy group and bromine at C_3 and C_4 respectively is expected from an overall *anti* addition across the double bond. The bromodiol (**4**) was transformed into acetonide (**5**) by reaction with 2,2-dimethoxypropane catalyzed by CSA. The ^{13}C spectrum of **5** revealed signals for the methyl groups of the acetonide at δ 27.0, 27.4 and for the quaternary carbon at δ 110.5 proving beyond doubt the *syn* disposition[8] of the hydroxy groups in bromodiol (**4**). The observed stereo- and regioselectivity can be rationalized through the intermediacy of a sulfoxonium salt (**I**) (Scheme 1). The 5-*exo* nucleophilic attack by the sulfinyl group onto the olefin π-complexed[9] to the bromonium ion would result in the formation of the sulfoxonium salt (**I**), which upon hydrolysis by attack of water on sulfur in a S_N2 fashion,[10] would yield the bromohydrin (**4**), with inversion of sulfur configuration.

Subjecting acetonide (**5**) to treatment with excess sodium azide in DMF afforded cleanly the azido acetonide (**6**), which has all the three stereogenic centers disposed as in (+)-polyoxamic acid, both in a relative and absolute sense.

The acetonide (**6**) was transformed to the alcohol (**8**) in a one pot operation by subjecting it to Pummerer rearrangement[11] to yield the intermediate (**7**) which was



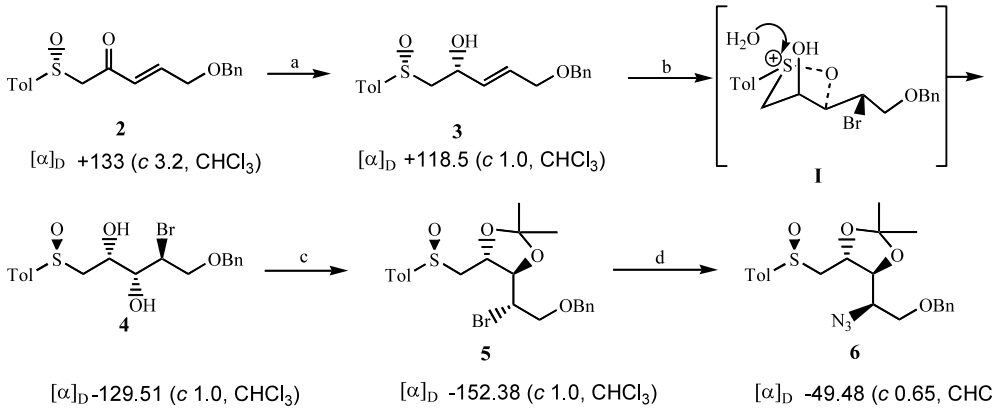
Polyoxin J



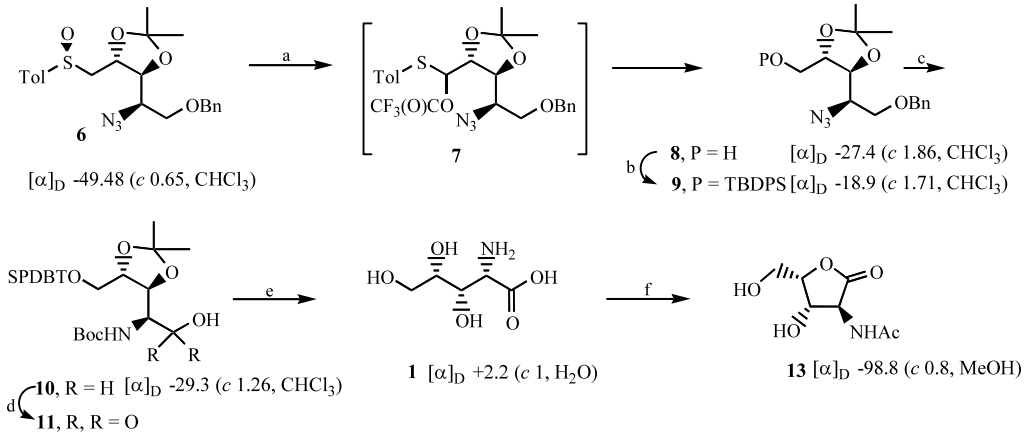
(+)-Polyoxamic acid **1**

Keywords: (+)-polyoxamic acid; sulfinyl group; bromohydrin; stereospecific.
☆ IICT Communication No. 030303.
* Corresponding author. E-mail: purush101@yahoo.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01650-2



Scheme 1. *Reaction conditions*: (a) DIBAH, $ZnCl_2$, THF, −78°C, 30 min, 91%; (b) NBS, H_2O, toluene, rt, 15 min, 88%; (c) 2,2-DMP, cat. CSA, acetone, rt, 2 h, 86%; (d) NaN_3, DMF, 85°C, 5 h, 75%.



Scheme 2. *Reaction conditions*: (a) TFAA, Et_3N, CH_2Cl_2, 0°C, 15 min then aq. $NaHCO_3$, $NaBH_4$, 0°C, 20 min, 73%; (b) TBDPS-Cl, imidazole, DCM, rt, 2 h, 94%; (c) 10% $Pd(OH)_2/C$, H_2, $(Boc)_2O$, EtOAc, rt, 8 h, 76%; (d) TEMPO, $PhI(OAc)_2$, H_2O/CH_3CN (1:1), 6 h, rt, 82%; (e) TFA, H_2O (9:1), rt, 16 h, 93%; (f) Ac_2O, MeOH, rt, 16 h, 60%.

further hydrolyzed and reduced by treatment with aq. saturated $NaHCO_3$ and $NaBH_4$. Treatment of alcohol (**8**) with *t*-butyldiphenylsilyl chloride and imidazole afforded the silyl ether (**9**), which upon treatment with $Pd(OH)_2$ under an atmosphere of hydrogen in the presence of $(Boc)_2O$ afforded the aminoalcohol derivative (**10**). Oxidation of the primary hydroxy group in **10** by treatment with $PhI(OAc)_2$ and Tempo[12] afforded the acid (**11**) which was characterized as its methyl ester (**12**) by treatment of a small portion with excess ethereal diazomethane. Removal of the protecting groups in **11** by treatment with aq. TFA yielded polyoxamic acid (**1**) after purification by passing through Dowex ion exchange resin (Scheme 2). The physical characteristics of **1** were in full agreement with the reported values in the literature.[4s] (+)-Polyoxamic acid (**1**) was further transformed by treatment with Ac_2O to afford the known lactone **13**.[4s]

In summary, we have disclosed a concise and a highly stereospecific synthesis of (+)-polyoxamic acid. The key step of the route include efficient transfer of chirality from sulfur to carbon in the transformation of β-keto-sulfoxide (**2**) to the β-hydroxy sulfoxide (**3**), stereo- and regiospecific synthesis of the bromodiol (**4**) by sulfinyl group participation and one-pot multistep transformation of **9** to **10**. The route disclosed herein is to be contrasted with other approaches based on dihydroxylation of unsaturated substrates possessing the requisite carbon skeleton that afford products with poor stereocontrol.[4i,4t] Finally, it is worthwhile to note that starting from the diastereomer of hydroxy sulfoxide (**3**) that differs at the hydroxy center and following the same sequence of reactions, (−)-polyoxamic acid can be elaborated.

Acknowledgements

S.R. is thankful to Dr. J. S. Yadav, Head, Org. Div. I and Dr. K. V. Raghavan, Director, IICT for constant support and encouragement. S.C.J. is thankful to CSIR, New Delhi for a fellowship. Financial assistance from DST (New Delhi) is gratefully acknowledged. We thank Dr. A. C. Kunwar for the NMR spectra.

References

1. (a) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333; (b) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490.
2. Mori, M.; Kakiki, K.; Misato, T. *Agric. Biol. Chem.* **1974**, *38*, 699.
3. Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518.
4. (a) Davis, F. A.; Prasad, K. R.; Carrol, P. J. *J. Org. Chem.* **2002**, *67*, 7802; (b) Kim, K. S.; Lee, Y. J.; Kim, J. H.; Sung, D. K. *J. Chem. Soc., Chem. Commun.* **2002**, 1116; (c) Dehoux, C.; Monthieu, C.; Baltas, M.; Gorrichon, L. *Synthesis* **2000**, 1409; (d) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291; (e) Ghosh, A. K.; Wang, Y. *Tetrahedron* **1999**, *55*, 13369; (f) Uchida, K.; Kato, K.; Akita, H. *Synthesis* **1999**, 1541; (g) Harwood, L. M.; Robertson, S. M. *J. Chem. Soc., Chem. Commun.* **1998**, 2641; (h) Kang, S. H.; Choi, H.-W. *J. Chem. Soc., Chem. Commun.* **1996**, 1521; (i) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520; (j) Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431; (k) Matsuura, F.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* **1994**, *35*, 733; (l) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139; (m) Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 111; (n) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990; (o) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307; (p) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479; (q) Dureault, A.; Carreaux, F.; Depezay, J. C. *Synthesis* **1991**, 150; (r) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265; (s) Ikota, N. *Chem. Pharm. Bull. Jpn.* **1989**, *37*, 3399; (t) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979; (u) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024; (v) Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1973**, 5051.
5. (a) Raghavan, S.; Ramakrishna Reddy, S.; Tony, K. A.; Naveen Kumar, Ch.; Varma, A. K.; Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838; (b) Raghavan, S.; Rasheed, M. A.; Joseph, S. C.; Rajender, A. *J. Chem. Soc., Chem. Commun.* **1999**, 1845.
6. Solladie, G.; Frechou, C.; Hutt, G.; Demailly, G. *Bull. Soc. Chim. Fr.* **1987**, 827.
7. (a) Solladie, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435; (b) Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912; (c) Carreno, M. C.; Garcia Ruano, J. L.; Martin, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120.
8. Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, 395.
9. Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.
10. Khuddus, M. A.; Swern, D. *J. Am. Chem. Soc.* **1973**, *95*, 8393.
11. (a) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282; (b) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, 881; (c) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.
12. De Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.