An Efficient and Flexible Route to (+)-Polyoxamic Acid using Diastereoselective Epoxidation of 1-Arylthio-1-nitroalkenes

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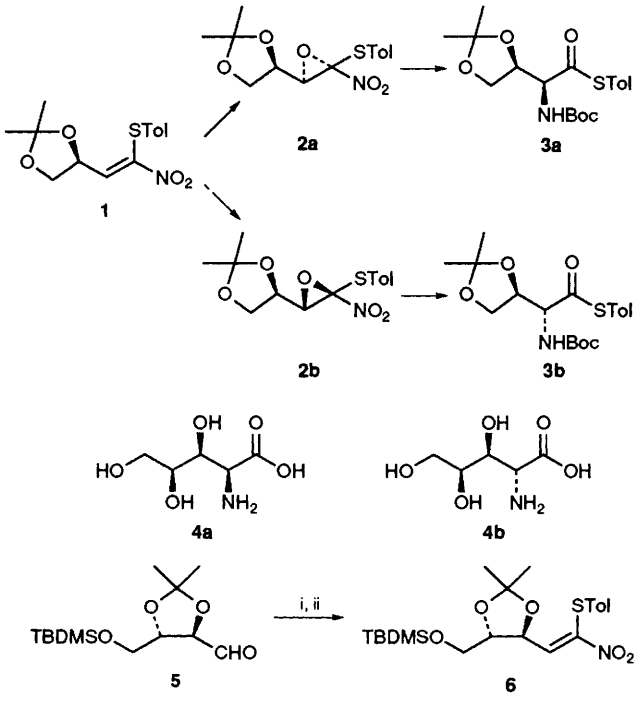
Polyoxamic acid **4a** is prepared by a short and efficient process in which the key steps are the highly diastereoselective nucleophilic epoxidation of the D-threitol-derived alkene **6** using potassium *tert*-butylperoxide, followed by reaction of the oxirane **7a** with ammonia.

We have shown recently that diastereoisomerically pure γ-hydroxy threonine derivatives **3** can be prepared by reaction of the stereoisomeric 2-nitro-2-(*p*-tolylthio)oxiranes **2** with ammonia in a stereospecific process which occurs with inversion of configuration.[1] The oxiranes were prepared by nucleophilic epoxidation of the 1-nitro-1-(*p*-tolylthio)alkene **1** derived from D-isopropylideneglyceraldehyde; use of potassium *tert*-butylperoxide gave predominantly the *anti* stereoisomer, whilst use of lithium *tert*-butylperoxide gave predominantly the *syn* stereoisomer, both with moderate selectivity. We now report an application of this method to a concise and flexible approach to polyoxamic acid **4a**,[2,3] which is also applicable in principle to the C-2 epimer **4b**.

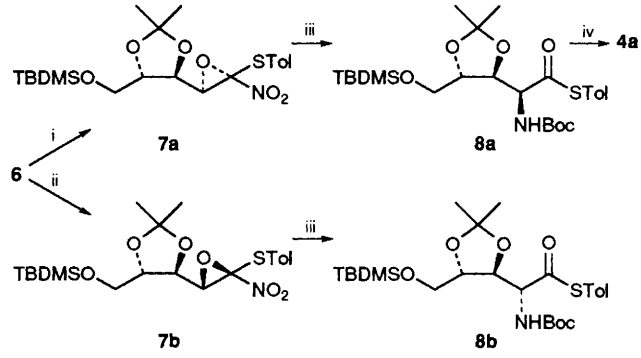
The alkene **6** was prepared by condensation of (*p*-tolylthio)nitromethane[4] with the aldehyde **5**,[5] itself prepared in two steps from commercially available 2,3-isopropylidene-L-threitol (Scheme 1). Nucleophilic epoxidation of the alkene **6** with potassium *tert*-butylperoxide gave a mixture of the two stereoisomeric oxiranes **7a** and **7b**, (87%). Analytical HPLC indicated a d.e. of 92% in favour of the major isomer, to which we have assigned *anti*-stereochemistry **7a** on the basis of our previous experience,[1] and also on the basis of subsequent transformations. Epoxidation of the alkene **6** with lithium *tert*-butylperoxide gave the oxiranes **7a** and **7b** (86%), with a d.e. of 66% in favour of **7b**. On the basis of our previous results,[1] the oxirane **7a** was an ideal precursor to (+)-polyoxamic acid.

Reaction of the *anti*-oxirane **7a** with ammonia, followed by treatment with *tert*-butylpyrocarbonate, gave the *syn* Boc-protected α-amino thioester **8a** (65%), after chromatographic separation of a trace of the *anti* thioester **8b**. Analogous treatment of the *syn*-oxirane **7b** gave the *anti*-Boc-protected α-amino thioester **8b** (55%). Each of these compounds appeared to be stereoisomerically pure by ^{1}H NMR analysis. Under these reaction conditions there was no evidence of epimerisation of either α-amino thioester. Subsequent treatment of the α-amino thioester **8a** with aqueous trifluoroacetic acid gave polyoxamic acid **4a** (95%) (Scheme 2), whose spectroscopic properties were identical with those previously reported.[5]

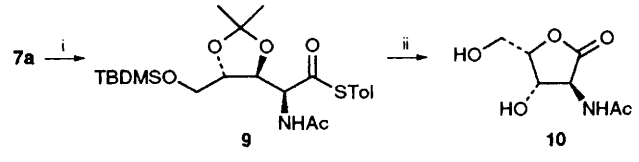
For further confirmation of the structure, the oxirane **7a** was converted to the corresponding *N*-acetyl γ-lactone **10** (Scheme 3). Lactone **10** has frequently been prepared as a stable derivative of polyoxamic acid itself.[5,6,7,8] Reaction of the oxirane with ammonia as before, followed by treatment with acetic anhydride, gave the corresponding *N*-acetyl amino thioester **9** (84%), which could not be separated from trace amounts of the corresponding *anti* isomer. However, treatment of this mixture with trifluoroacetic acid in methanol resulted in conversion to the γ-lactone **10** (64%), which was isolated by chromatography and recrystallisation and found to be identical by comparison of ^{1}H NMR and ^{13}C NMR with spectra of authentic material supplied by earlier workers.[5,6] In addition, the mp and optical rotation of our sample compared favourably with the literature values.† We have prepared a 100 mg sample of lactone **10** using this method, and the procedure is certainly amenable to the preparation of gram quantities.



Scheme 1 *Reagents and conditions*: i, $TolSCH_2NO_2$, $KOBu^t$, Bu^tOH/THF, 0 °C, then room temp. 3 h; ii, $MeSO_2Cl$ (3 equiv.), Pr^i_2NEt (3 equiv.), −78 °C, 2 h, 61% overall yield



Scheme 2 *Reagents and conditions*: i, $KOBu^t$, THF, −78 °C, 2 h; ii, $LiOOBu^t$, THF, −78 °C, 2 h; iii, NH_3 (0.880 aq., 5 equiv.), CH_2Cl_2, room temp., 2h, followed by Boc_2O (10 equiv.), room temp. 2 h; iv, CF_3CO_2H/H_2O (9 : 1), room temp. 1 h



Scheme 3 *Reagents and conditions*: i, NH_3 (0.880 aq., 5 equiv.), CH_2Cl_2, room temp., 2h, followed by Ac_2O (10 equiv.), CH_2Cl_2, room temp., 2 h; ii, CF_3CO_2H/MeOH (1 : 1), room temp., 24 h

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Footnote

† Our sample of lactone **10** had mp 141–142 °C and $[\alpha]_D^{20}$ −105.5 (*c* 3.25, MeOH); literature values are 141–142 °C and $[\alpha]_D^{20}$ −99.7 (*c* 2, MeOH).[7] Previous reports had indicated a slightly higher mp: 150–152 °C[2] and 147–150 °C.[8]

References

1 R. F. W. Jackson, J. M. Kirk, N. J. Palmer, D. Waterson and M. J. Wythes, *J. Chem. Soc., Chem. Commun.*, 1993, 889.
2 For the isolation and structure determination, see: K. Isono, K. Asahi and S. Suzuki, *J. Am. Chem. Soc.*, 1969, **91**, 7490.
3 For the most recent synthetic approach and references to previous work, see: A. Dondoni, S. Franco, F. L. Merchán, P. Merino and T. Tejero, *Tetrahedron Lett.*, 1993, **43**, 5479.
4 M. Miyashita, T. Kumazawa and A. Yoshikoshi, *J. Org. Chem.*, 1980, **45**, 2945; A. G. M. Barrett, G. G. Graboski and M. A. Russell, *J. Org. Chem.*, 1986, **51**, 1012; A. G. M. Barrett, *Chem. Soc. Rev.*, 1991, **20**, 95.
5 I. Savage and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1989, 717; E. J. Thomas, personal communication.
6 B. K. Banik, M. S. Manhas and A. K. Bose, *J. Org. Chem.*, 1993, **58**, 307; M. S. Manhas, personal communication.
7 N. Ikota, *Chem. Pharm. Bull.*, 1989, **37**, 3399.
8 A. K. Saksena, R. G. Lovey, V. M. Girijvallabhan, A. K. Ganguly and A. T. McPhail, *J. Org. Chem.*, 1986, **51**, 5024.