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Double diastereocontrol in the synthesis of enantiomerically pure polyoxamic acid

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Polyoxamic acid 4 is prepared by a short and efficient process involving diastereochemically matched cycloaddition of 5-(*S*)-phenylmorpholin-2-one 1 with (*S*)-glyceraldehyde acetonide 2, followed by sequential hydrolysis and hydrogenolysis of the adduct.

We have demonstrated the use of 5-(*S*)-phenylmorpholin-2-one **1**† as a chiral template in the rapid, diastereo- and enantiocontrolled synthesis of β-hydroxy-α-amino acids.[1] In this process, the chiral azomethine ylide intermediate generated by condensation with an aldehyde is trapped by excess of the aldehyde to furnish a cycloadduct which can be subsequently dismantled to lead to *threo*-(2*S*, 3*R*)-configured products of high stereochemical integrity (Scheme 1).

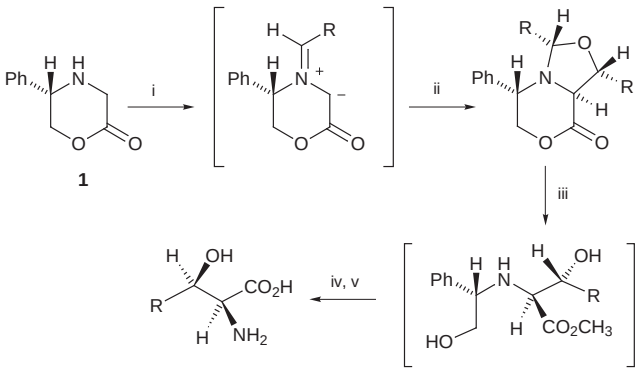
In the cycloaddition step, stereochemical discrimination arises from the chiral azomethine ylide reacting with an achiral aldehyde dipolarophile. Utilizing a chiral aldehyde in such a reaction therefore poses the question as to whether there might be diastereochemical 'match' or 'mismatch' in either the ylide generation step or the cycloaddition step between the chiral reacting partners.

We now report an efficient synthesis of polyoxamic acid **4**,[2] the unique polyhydroxyamino acid constituting the side chain moiety of the antifungal polyoxin antibiotics.[3] The key conversion in our synthesis involves reaction of 5-(*S*)-phenylmorpholin-2-one **1** with excess (*S*)-glyceraldehyde acetonide **2** (obtained from commercially available 5,6-*O*-isopropylidene-L-gulono-1,4-lactone.[4]) in refluxing toluene with removal of water.‡ It would appear that this combination of starting materials leads to matched diastereocontrol as close examination of the crude product mixture isolated from reaction between (*S*)-**2** with 5-(*S*)-phenylmorpholin-2-one **1** indicated the presence of only a single product. This could be isolated in 53% yield and showed spectroscopic features consistent with those expected of a cycloadduct resulting from highly diastereoselective reaction of two equivalents of (*S*)-**2** with (*S*)-**1**.

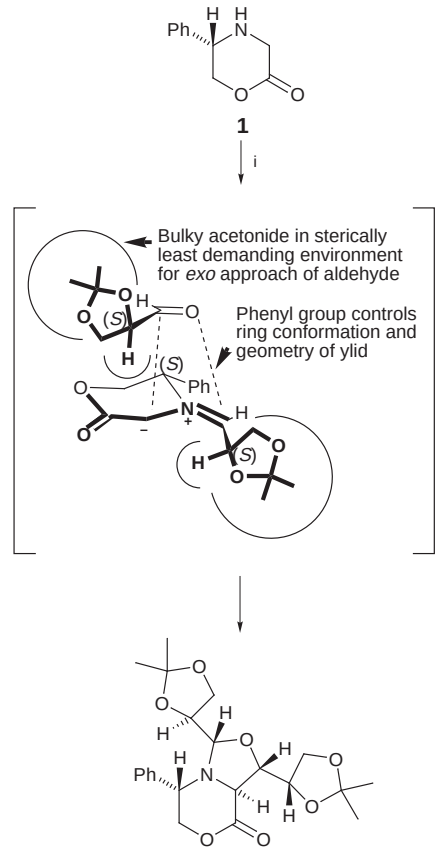
By analogy with our earlier rationale for stereocontrol in both ylide generation and trapping steps, cycloaddition of the aldehyde dipolarophile to the *E*-isomer of the azomethine ylide from the face opposite the 5-phenyl substituent would be predicted to furnish cycloadduct **3** (Scheme 2).[1]

Although a solid, crystals of sufficient quality for X-ray structural analysis could not be obtained. A combination of 2-dimensional ^{1}H NMR and NOE difference studies supported the predicted stereochemical outcome of the cycloaddition step, enhancements of signals corresponding to H_2 and $H_{3\beta}$ on irradiating H_7 proving diagnostic of their mutual *syn*-relationship, but the stereochemistry at C-9 remained unresolved.‡

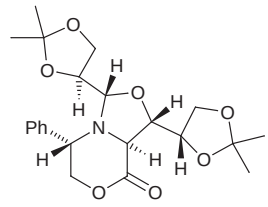
Final confirmation of the stereochemical outcome of the ylide generation and trapping sequence came by conversion of **3** to polyoxamic acid as its natural (2*S*,3*S*,4*S*) enantiomer. Treatment of the cycloadduct with aqueous methanolic HCl gave the deketalized methyl ester which was not isolated but subjected immediately to hydrogenolysis (H_2, Pearlman's catalyst, aq. MeOH, TFA) leading to the isolation of a homogeneous material in 95% overall yield with a specific rotation $[\alpha]_D^{24}$ +2.4 (*c* 1.0, H_2O), [lit.,[2d] +2.2 (*c* 1.0, H_2O)] and spectroscopic data identical with those of authentic polyoxamic acid **4** (Scheme 3).§ In the same manner, the non-natural enantiomer



Scheme 1 *Reagents and conditions*: i, RCHO, solvent, reflux; ii, RCHO (excess); iii, 1 M HCl, MeOH, reflux; iv, H_2 (5 atm), $Pd(OH)_2$/C, TFA (1 equiv.), aq. MeOH; v, basic ion-exchange resin.



Scheme 2 *Reagents and conditions*: i, (*S*)-glyceraldehyde acetonide **2** (3 equiv.), toluene, reflux.



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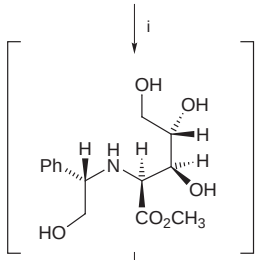

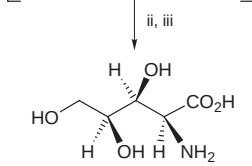

(+)–polyoxamic acid

4

Scheme 3 *Reagents and conditions*: i, 1 M HCl, MeOH, reflux; ii, H_2 (5 atm), $Pd(OH)_2/C$, TFA (1 equiv.), aq. MeOH; iii, basic ion-exchange resin.

of polyoxamic acid was obtained by reacting (*R*)-glyceraldehyde acetonide (prepared by oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol[5]) with (*R*)-**1**, followed by sequential degradation of the cycloadduct. Pure *ent*-polyoxamic acid was isolated in excess of 50% yield over the whole sequence, with a specific rotation, $[\alpha]_D^{24}$ −2.5 (*c* 1.0, H_2O).

Having successfully prepared polyoxamic acid and its enantiomer it was decided to investigate the synthesis of diastereoisomers by employing the alternative combination of reactant enantiomers. However, under the same conditions as before, reaction of 5-(*S*)-phenylmorpholin-2-one **1** with (*R*)-**2** resulted in a product mixture consisting of roughly equal quantities of three products which were found to be diastereoisomers of **3** by spectroscopic analysis. Unfortunately none could be isolated with sufficient purity to permit definitive structural assignment, nor was it possible to separate the deprotected acids at the ultimate stage of the synthetic route. However, the observation of three cycloadducts indicates diastereochemical mismatch in more than one element of the ylide generation and trapping sequence, be it reactant ylide geometry, diastereofacial control or *exo*/*endo* approach of the dipolarophile.

In conclusion, we have demonstrated that diastereochemically matched and mismatched reactions can occur in the generation and trapping of azomethine ylides in which both starting materials are chiral and have established a rapid diastereocontrolled synthesis of polyoxamic acid *via* a diastereochemically matched reaction of 5-(*S*)-phenylmorpholin-2-one with (*S*)-glyceraldehyde acetonide. We are currently investigating the scope of this process and applying it to the synthesis of other enantiomerically pure β-hydroxy-α-amino acids with additional stereogenic centres.

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Notes and references

† We use the trivial morpholin-2-one nomenclature to describe the 2,3,5,6-tetrahydro-*4H*-oxazin-2-one ring system.

‡ *Cycloaddition procedure*: Freshly prepared aldehyde **2** (780 mg, 6 mmol, 3 equiv.) was added to a solution of the morpholin-2-one **1** (177 mg, 1 mmol, 1 equiv.) in dry toluene (60 ml) and the reaction mixture heated to reflux for 48 h under nitrogen with a Soxhlet extractor containing activated 3Å sieves. Solvent was removed *in vacuo* to yield a pale yellow oil which solidified on cooling. Column chromatography, eluting with Et_2O–light petroleum (1:4) and recrystallisation from Et_2O furnished **3** as colourless fine needles (220 mg, 53%), mp 199–202 °C ($C_{22}H_{29}NO_7$ requires C, 63.0; H, 7.00; N, 3.3. Found C, 62.8; H, 6.85; N, 3.2%); ν_{max}(KBr)/cm^{-1} 1737; δ_H(250 MHz, $CDCl_3$) 7.47–7.33 (m, 5H), 4.47 (t, *J* 11.3, 1H), 4.44 (d, *J* 9.0, 1H), 4.42 (ddd, *J* 8.9, 6.4, 2.3, 1H), 4.32 (d, *J* 8.0, 1H), 4.27 (dd, *J* 11.3, 3.1, 1H), 4.18 (dd, *J* 9.0, 2.3, 1H), 4.10–4.02 (m, 3H), 3.99 (dd, *J* 11.3, 3.1, 1H), (3.91 (t, *J* 8.9, 1H), 3.84 (dd, *J* 8.7, 4.2, 1H), 1.40 (s, 6H), 1.26 (s, 3H) and 1.07 (s, 3H); NOE H7→H2 (4.0%)→H3β (3.8%)→H10 (1.2%); δ_C(100 MHz, $CDCl_3$) 167.4, 135.3, 129.2, 128.9, 128.6, 109.9, 109.3, 96.6, 74.3, 74.1, 73.3, 66.2, 66.0, 60.1, 59.3, 26.3, 26.2, 25.4 and 24.8; *m*/*z* (CI) 420 (MH^+); $[\alpha]_D^{25}$ +23.2 (*c* 1.0, $CHCl_3$).

§ *Preparation of polyoxamic acid*: To a solution of cycloadduct **3** (0.2 mmol) in MeOH (4 ml) was added 1 M HCl (1 ml) and the reaction mixture heated to reflux under nitrogen for 1 h. The solvent was removed *in vacuo* and the residue transferred to a Fischer–Porter bottle. TFA (15 μl), Pearlman's catalyst (70 mg), MeOH (3 ml) and water (0.3 ml) were added, the solution degassed and subjected to hydrogen at 5 atm. for 48 h. Catalyst was removed by centrifugation, the solvent removed *in vacuo* and the crude mixture purified on a Dowex® basic ion-exchange column to yield **4** as a colourless powder (31 mg, 95%), mp 152–154 °C (decomp.) (lit., 165–170 °C,[2d] 162–168 °C[2g]). Spectroscopic data as in ref. 2(*c*); $[\alpha]_D^{24}$ +2.4 (*c* 1.0, H_2O), [lit.,[2d] +2.2 (*c* 1.0, H_2O)]; *ent*-**4** $[\alpha]_D^{24}$ −2.5 (*c* 1.0, H_2O). We thank Professor R. F. W. Jackson for providing copies of ^1H and ^{13}C NMR spectra of polyoxamic acid.

1 L. M. Harwood, J. Macro, D. J. Watkin, C. E. Williams and L. F. Wong, *Tetrahedron*: *Asymmetry*, 1992, **3**, 1127; D. A. Alker, G. Hamblett, L. M. Harwood, S. M. Robertson and C. E. Williams, *Tetrahedron*, 1998, **54**, 6089.

2 For recent synthetic approaches to polyoxamic acid and derivatives, see: (*a*) A. Dondoni, S. Franco, F. L. Merchàn, P. Merino and T. Tejero, *Tetrahedron Lett*., 1993, **34**, 5479; (*b*) R. F. W. Jackson , N. J. Palmer and M. J. Wythes, *J. Chem. Soc*., *Chem. Commun*., 1994, 95; (*c*) R. F. W. Jackson, N. J. Palmer, M. J. Wythes, W. Clegg and M. R. J. Elsegood, *J. Org*. *Chem*., 1995, **60**, 6431; (*d*) B. M. Trost, A. C. Krueger, R. C. Bunt and J. Zambrano, *J. Am*. *Chem*. *Soc*., 1996, **118**, 6520; (*e*) S. H. Kang and H-W. Choi, *Chem*. *Commun*., 1996, 1521; (*f*) G. Casiraghi, G. Rassu, P. Spanu and L. Pinna, *Tetrahedron Lett*., 1994, **35**, 2423; (*g*) A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan, A. K. Ganguly and A. T. McPhail, *J. Org*. *Chem*., 1986, **51**, 5024.

3 K. Isono, K. Asahi and S. Suzuki, *J. Am*. *Chem*. *Soc*., 1969, **91**, 7490.

4 C. Hubschwerlen, *Synthesis*, 1986, 962; C. Hubschwerlen, J-L. Speclin and J. Higelin, *Org*. *Synth*., 1995, **72**, 1.

5 J. Mann, N. K. Partlett and A. Thomas, *J. Chem*. *Res*. (*S*), 1987, 369.

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