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STEREOCONTROLLED ADDITION TO A PENALDIC ACID EQUIVALENT: AN ASYMMETRIC SYNTHESIS OF THREO-β-HYDROXY-L-GLUTAMIC ACID

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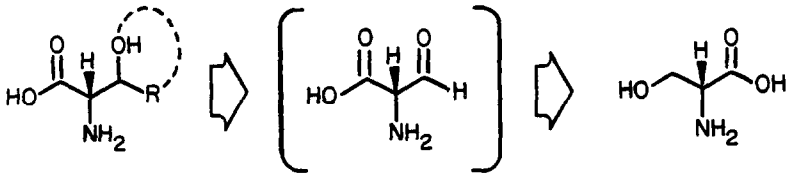
Abstract: The asymmetric synthesis of threo-β-hydroxy-L-glutamic acid (7) via a stereoselective addition to the chiral penaldic acid equivalent 3 is described.

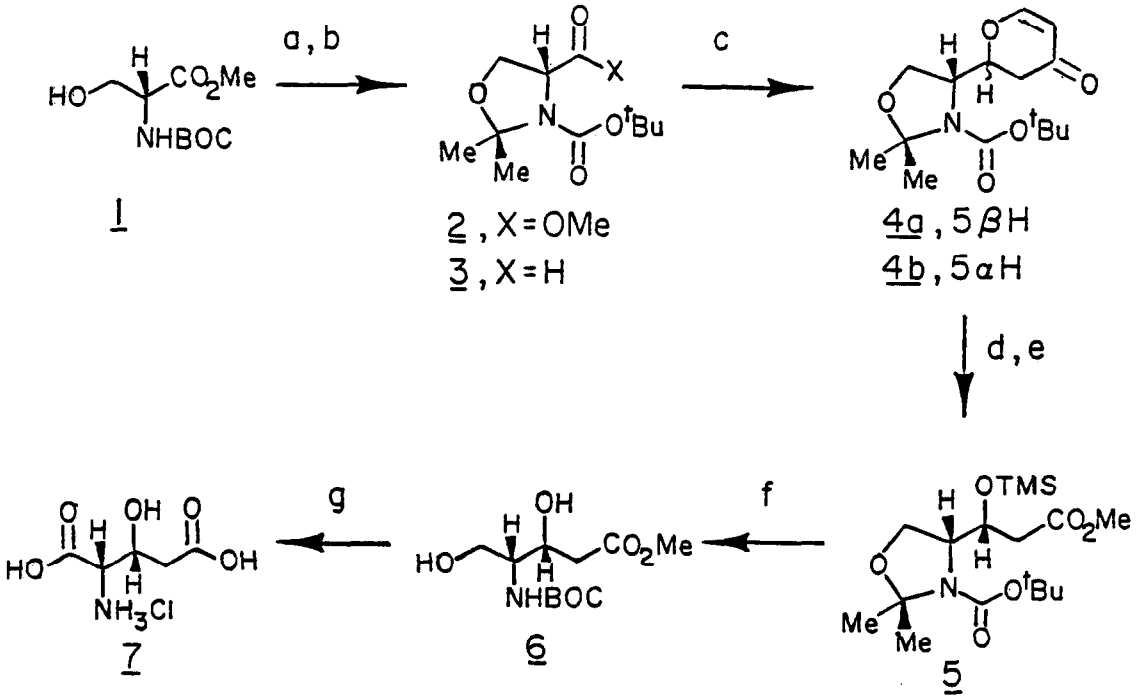
Over the past fifty years, a number of unusual amino acids have been isolated from natural sources.[1] While their biological roles (and genesis) are not always obvious, the antibiotic activity demonstrated by many of these compounds themselves or as components of larger (i.e. polypeptide) systems make them attractive synthetic targets. In particular, hydroxy amino acids of varying complexity offer considerable challenge to the synthetic chemist in terms of stereocontrol and efficiency.

As part of a program directed towards the asymmetric synthesis of polyfunctional amino acids, we have focussed on additions to a penaldic acid equivalent wherein all chirality derives from a readily available precursor as shown below:[2]



For such a strategy to be generally useful, both enantiomers of the penaldic acid equivalent should be easily prepared in good yield, participate stereoselectively in addition reactions, and allow for final unmasking of the α-amino acid moiety - all without attendant epimerization or β-elimination. Herein, we describe our initial work in this area resulting in an asymmetric synthesis of threo-β-hydroxy-L-glutamic acid (7),[3a] a unique amino acid which has found use in synthesis,[3b] and is a component of the peptide antibiotic S-520.[3c]

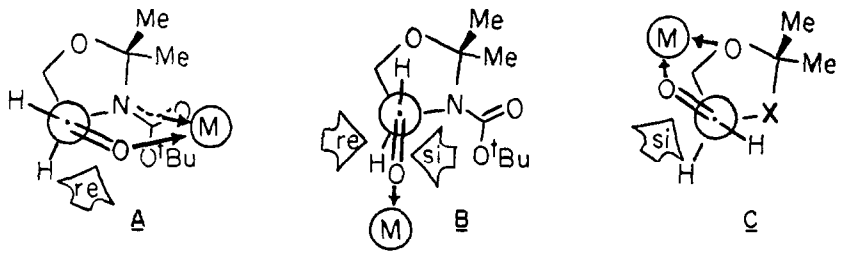
Condensation of N-BOC-D-serine methyl ester (1)[4] with 2,2-dimethoxypropane (DMP) in the presence of TsOH resulted in a 60% yield of oxazolidine ester 2,[5] bp 99-103°C/0.75mm, $[\alpha]_D^{29}$ +54°(c 1.0, $CHCl_3$).[6] Controlled reduction of 2 with DIBAH at -78°C gave the aldehyde 3, $[\alpha]_D^{27}$ +103°(c 1.0, $CHCl_3$),[6] in 80% yield. Though N-protected-α-amino aldehydes are often prone to racemize during chromatography, compound 3 was shown to be configurationally stable, even after prolonged exposure to silica gel.[7] Lewis acid-mediated cyclocondensation of Danishefsky's



(a) DMP; cat. TsOH; (b) DIBAH, -78°C; (c) 1-methoxy-3-(trimethysiloxy)-1,3-butadiene, cat. (see text); HCl; (d) $NaIO_4$, cat. $RuO_2 \cdot H_2O$; NaOH then HCl; CH_2N_2; (e) Et_2NTMS; flash chromatography; (f) MeOH, cat. TsOH; (g) $KMnO_4$, aq, NaOH; HCl.

dieme to our penaldic acid equivalent 3 proceeded with modest to good threo-selectivity, depending on the strength (and steric bulk?) of the catalyst employed (2 mol% EUFOD/CH_2Cl_2,[8a] 4a:4b = 3, 81% yield; 5 mol% $ZnCl_2/CH_2Cl_2$,[8b] 4a:4b > 9, 70% yield). Pure threo-pyranone 4a, mp 75-76°C, $[\alpha]_D^{27}$ +3.08° (c 1.56, $CHCl_3$),[6] could be obtained from the $ZnCl_2$ catalyzed reaction by crystallization, though it was more efficient to process the mixture as follows: Oxidative degradation of 4a/4b with $NaIO_4$ + cat. RuO_4, followed by formate saponification, esterification with CH_2N_2, and TMS-ether formation resulted in a 76% yield of diastereomers which were easily separated using flash chromatography. Deprotection of the major isomer 5, $[\alpha]_D^{30}$ +46.0° (c 1.13, $CHCl_3$),[6] by the action of methanolic TsOH at 60-65°C gave a 69% yield of the diol 6, mp 63-64°C, $[\alpha]_D^{29}$ +49.5° (c 1.09, $CHCl_3$).[6a,b] Surprisingly, the N-BOC group proved stable to the acidic reaction conditions. At this point, the threo stereochemistry was confirmed via the acetonide derivative of 6.[6,9] Selective oxidation of 6 with basic $KMnO_4$ followed by treatment with aqueous HCl resulted in a 61% yield of threo-β-hydroxy-L-glutamic acid (7),[10] mp 180°C, (dec), $[\alpha]_D^{28}$ +21° (c 1.4, 20% HCl)[6a,b] [lit. $[\alpha]_D^{3}$ +18.9° (c 1.6, 20% HCl)].[3a]

We tentatively ascribe the threo-selectivity of the Zn(II)-mediated reaction to some sort of chelation control wherein an interaction between the N-BOC group and the coordinated aldehyde favors addition from the re-face as shown for intermediate A.



This result stands in sharp contrast to the reported Zn(II)-catalyzed cyclocondensation to the analogous glyceraldehyde acetonide which shows complete erythro-selectivity,[8b] presumably via a chelate with the β-oxygen as in C (X=O). The moderate threo-selectivity observed with the EuFOD catalyst may reflect an increased propensity for β-chelation as in C (X=NBOC) and/or a nonchelated intermediate B with re-attack being slightly favored by an anti-periplanar effect.[11,12]

Further investigation into the scope of these processes and their application to a variety of synthetic problems are currently underway.

ACKNOWLEDGEMENT: We wish to thank the Research Corporation for financial support.

REFERENCES AND NOTES

1. Cf. V. I. Wagner and H. Musso, Angewandte Chem., 95, 827 (1983), and references therein.

2. An analogous methionine-derived serine equivalent has been reported: Y. Ohfune and N. Kurokawa, Tetrahedron Lett., 1071 (1984). See also: Y. Ohfune and H. Nishio, ibid., 4133 (1984).

3.(a) T. Kaneko, R. Yoshida, and H. Katura, Nippon Kagaku Zasshi, 80, 316 (1959). (b) T. Kamiya, Chem. Pharm. Bull., 14, 1307 (1966). (c) J. Shoji and R. Sakazaki, J. Antibiotics, 23, 418 (1970).

4. Prepared from D-serine in high yield via a two step sequence: (a) di-t-butyl dicarbonate $(BOC)_2O$/NaOH according to L. Moroder, A. Hallett, E. Wunch, O. Keller, and G. Wersin, Hoppe-Seylers Z. Physiol. Chem., 357, 1651 (1976). (b) CH_2N_2.

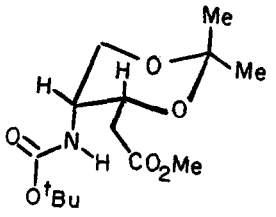
5. A similar procedure was successful with certain acetamido sugars: A. Hasegawa and H. G. Fletcher, Jr., Carbohyd. Res., 29, 223 (1973).

6. Satisfactory (a) (IR, (b) ^{1}H NMR, and (c) MS data have been obtained for this compound. It should be noted that the oxazolidine derivatives exist as slowly interconverting rotomers on the NMR time scale and samples require heating to obtain averaged spectra.

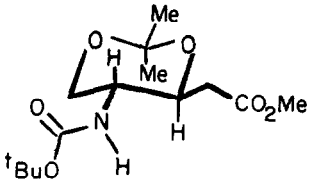
7. Cf. A. Ito, R. Takahashi, and Y. Baba Chem Pharm. Bull., 23, 3081 (1975). In our case, enolization would create an unfavorable interaction with the rigid N-BOC moiety.

8.(a) M. Bednarski and S. Danishefsky, J. Amer. Chem. Soc., 105, 3716 (1983). (b) S. Danishefsky, S. Koboyashi, and J. F. Kerwin, Jr., J. Org. Chem., 47, 1981 (1982); S. Danishefsky, E. R. Larson, and D. Askin, J. Am. Chem. Soc., 104, 6457 (1982).

9. Acetonides i and ii were prepared individually from diol 6 and its C(3)-epimer with DMP + cat. TsOH. Stereochemical assignments arise from their respective 300MHz ^1H NMR spectra in $CDCl_3$ relative to TMS(0.00ppm).



i



ii

Compound i: δ1.39(s,3H), δ1.45(s,9H), δ1.49(s,3H), δ2.49(d,J=6.1Hz,2H), δ3.59(br d, J=10.4Hz,1H), δ3.69(s,3H), δ3.74(dd,J=12.1,1.4Hz,1H), δ4.13(dd,J=12.1,1.5Hz,1H), δ4.48 (dt,J=1.1,6.3Hz,C(4)H), δ5.32(br d,J=9.9Hz,1H). Compound ii: δ1.37(s,3H), δ1.43(s.9H) δ1.45(s,3H), δ2.53(dd,J=16.1,8.3Hz,1H), δ2.68(dd,J=16.1,3.8Hz,1H), δ3.5-3.6(m, 2 overlapping H), δ3.69(S,3H), δ3.92(br d,J=6.0Hz,1H), δ4.07(ddd,J=9.6,8.3,3.8Hz,C(4)H), δ4.7(br s,1H).

10. (a) 300MHz ^1H NMR data for 7/D_2O (0.12M) relative to DSP(0.00ppm): δ2.76(dd,J=16.5, 8.5Hz,1H), δ2.84(dd,J=16.5,4.5Hz,1H), δ4.11(d,J=4.5Hz,1H), δ4.63(dt,J=8.5,4.5Hz,1H).
(b) The possibility of β-elimination/addition was excluded by the observation that when a mixture of 6 and its C(3)-epimer was used, a mixture of 7 and its C(3)-epimer resulted (Partial 300MHz ^1H NMR: δ4.22(d,J=3.0Hz,1H). On the other hand, pure 6 led to product 7 uncontaminated with epimeric material.

11. Compare (a) M. M. Midland and R. S. Graham, J. Am. Chem. Soc., 106, 4294 (1984), and (b) S. J. Danishefsky, W. H. Pearson, and D. F. Harvey, ibid., 106, 2456 (1984).
12. P. Carmella, N. G. Rondon, M. N. Paddon-Row, and K. N. Houk, ibid., 103, 2437 (1981).

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