

Tetrahedron Letters 40 (1999) 1389-1392

TETRAHEDRON LETTERS

Enantioselective Synthesis Of Dityrosine And Isodityrosine Via Asymmetric Phase-Transfer Catalysis.

Barry Lygo

Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT, UK.

Received 2 November 1998; accepted 8 December 1998

Abstract: Application of N-anthracenylmethyl cinchonidinium chloride quaternary ammonium phase-transfer catalysts to the enantio- and diastereoselective synthesis of dityrosine and isodityrosine is reported. Under liquid-liquid phase-transfer conditions the key α -amino acid substituents are introduced with high enantioselectivity (\geq 95%e.e.). © 1999 Elsevier Science Ltd. All rights reserved.

The dityrosine 1^1 and isodityrosine 2^2 represent the simplest members of a group of naturally-occurring tyrosine-derived α -amino acids and peptides that contain oxidatively coupled aromatic nuclei. This family of compounds also includes the higher homologues, trityrosine,³ isotrityrosine⁴ and diisodityrosine,⁵ as well as a number of isodityrosine-containing peptides of which the ACE inhibitor K-13 3,⁶ the aminopeptidase inhibitor OF4949-III 4⁷ and the anti-tumour antibiotic deoxybouvardin 5⁸ are prominent examples. In recent years this group of molecules have attracted considerable interest as synthetic targets and a wide variety of synthetic approaches have been developed.^{9,10}



As part of our continuing study into the use of *Cinchona* alkaloid derived asymmetric phase-transfer catalysts in synthesis¹¹ we have recently developed an efficient enantioselective approach to simple bis- α -amino acids,¹² and here we report extension of this study to the synthesis of the more complex bis- α -amino acids dityrosine 1 and isodityrosine 2.

For the synthesis of dityrosine 1, we envisaged that access to a dibromide of the type 8 should allow the introduction of the two amino acid functions in a single step *via* asymmetric phase-transfer catalysed alkylation (scheme 1). It was found that the dibromide 8 could be easily prepared from the readily-available biphenyl derivative 6^{13} via a two-step sequence involving *O*-methylation, followed by radical bromination. In the latter of these two transformations it was found that in order to minimise competing electrophilic bromination of the electron rich aryl groups it was necessary to use both a radical initiator (AIBN) and irradiation (100W sunlight lamp).¹⁴ Under these conditions the desired dibromide 8 was formed in good yield.



Scheme 1

Reagents: (i) K₂CO₃, MeI, DMF, RT, 18h (78%); (ii) NBS, AIBN, hv, reflux, CCl₄, 30min. (93%).

We then investigated the coupling of dibromide 8 with imine 10 using the cinchonidine-derived catalyst 9.11



It was found that reaction of the dibromide 8 with imine 10 gave, after hydrolysis of the imine functions, the required bis- α -amino acid ester 11 in good overall yield. Conversion of 11 into the corresponding di-*N*-benzoyl derivative followed by HPLC analysis (Chiralcel OD-H column, 13%dioxane-87%hexane, 232nm) indicated that the desired (S), (S)-isomer 11 had been formed with high enantioselectivity (\geq 95% e.e.) and good diastereoselectivity (80% d.e.). This level of selectivity is consistent with that observed for other alkylations of imine 10 under these reaction conditions^{11, 12} and further emphasises the generality of this reaction process.



Scheme 2

Reagents: (i) 8 (0.5mol. eq.), cat 9 (0.1mol. eq.), 50% aq. KOH, PhMe, RT, 18h; (ii) 15% Aq. citric acid, THF, RT, 3h (63% from 10); (iii) TfOH, TFA, PhSMe, -5°C, 30min.; aq. HCl (89%).

In order to complete the synthesis of dityrosine we required to remove the carboxyl and phenol protecting groups. After investigation of a range of methods it was found that this was best achieved using triflic acid and thioanisole in trifluoroacetic acid at -5° C.¹⁵ Under these conditions all four protecting groups were removed to give, after purification by ion exchange chromatography and recrystallisation, dityrosine 1 as a white solid. For characterisation purposes we prepared the corresponding bis-hydrochloride salt 12¹⁶ which gave ¹³C nmr

and optical rotation measurements in agreement with those previously reported^{9h} suggesting that stereochemical integrety is preserved during the deprotection step.

Extension of this approach to the synthesis of isodityrosine 2 required access to the dibromide 16. This was achieved via a three step sequence starting with commercially-available 2-bromo-4-methylphenol 13 (scheme 3). Thus O-methylation, followed by Ullmann coupling with p-cresol, and radical bromination as before gave the target dibromide 16 in good overall yield. Asymmetric phase-transfer alkylation with glycine imine 10, followed by hydrolysis of the imine functions then gave the isodityrosine derivative 17. As with the other bis- α -amino acid derivatives we were able to assess the stereochemical purity of 17 via conversion to the corresponding di-N-benzoyl derivative followed by HPLC analysis. This indicated that the desired (S), (S)-isomer 17 had been generated with similar stereoselectivity ($\geq 95\%$ e.e., 80% d.e.)¹⁷ to that observed for the corresponding dityrosine derivative.



Scheme 3

Reagents: (i) K₂CO₃, MeI, DMF, RT, 18h (94%); (ii) *p*-Cresol, pyridine, CuO, K₂CO₃, reflux, 6d (86%); (iii) NBS, AIBN, hv, reflux, CCl₄, 20min. (79%); (iv) 10 (1.8eq.), cat 9 (0.2eq.), 50%aq. KOH, PhMe, RT, 18h; (v) 15% Aq. citric acid, THF, RT, 3h (65% from 16); (vi) TfOH, TFA, PhSMe, -5°C, 30min.; aq. HCl (87%)

The synthesis of isodityrosine 2 was then completed by global deprotection as before, then purification *via* ion exchange chromatography followed by recrystallisation. Again for characterisation purposes the bishydrochloride salt 18¹⁸ was prepared and gave ¹³C nmr and optical rotation measurements in agreement with those previously reported.^{9h,9k}

In conclusion, we have successfully applied the asymmetric phase-transfer mediated alkylation of glycine imines to the enantioselective synthesis of dityrosine and isodityrosine. We are now seeking to extend this methodology to more complex synthetic targets.

Acknowledgements: We would like to thank the Salford University Science Research Institute for research funding, Dr. J. Crosby (Zeneca Pharmaceuticals) for helpful discussions and Mrs. R. Howard for mass spectra.

References and Notes

- 1. Andersen, S.O; Biochim. Biophys. Acta, 1964, 93, 213.
- 2. Fry, S.C. Biochem. J., 1982, 204, 449.
- 3. Fujimoto, D. Comp. Biochem. Physiol., 1975, 51B, 205.
- 4. Fujimoto, D; Horiuchi, K; Hirama, M; Biochem. Biophys. Res. Commun., 1981, 99, 637
- 5. Brady, J.D; Sadler, I.H; Fry, S.C. Biochem. J., 1996, 315, 323.

- Kase, H; Kaneko, M; Yamada, K. J. Antibiot., 1987, 40, 450; Yasuzawa, T, Shirahata, K; Sano, H. J. Antibiot., 1987, 40, 455.
- Sano, S; Ikai, K; Kuroda, H; Nakamura, T; Obayashi, A; Ezure, Y; Enomoto, H. J. Antibiot., 1986, 39, 1674; Sano, S; Ikai, K; Katayama, K; Takesako, K, Nakamura, T; Obayashi, A; Ezure, Y; Enomoto, H. J. Antibiot., 1986, 39, 1685.
- 8. Jolad, S.D; Hoffmann, J.J; Torrance, S.J; Wiedhopf, R.M; Cole, J.R; Arora, S.K; Bates, R.B; Gargiulo, R.L; Kriek, G.R. J. Am. Chem. Soc., 1977, 99, 8040.
- For leading references on synthetic approaches to the dityrosines and related peptides see: (a) Guo, Z.W; Salamonczyk, G.M; Han, K; Machiya, K; Sih, C.J. J. Org. Chem., 1997, 62, 6700; (b) Malencik, D.A; Sprouse, J.F; Swanson, C.A; Anderson, S.R. Anal. Biochem., 1996, 242, 202; (c) Yamamura, S; Nishiyama, S. J. Synth. Org. Chem. Jpn., 1997, 55, 1029; (d) Bigot, A; Zhu, J. Tetrahedron Lett., 1998, 39, 551; (e) Jung, M.E; Starkey, L.S. Tetrahedron, 1997, 53, 8815; (f) Janetka, J.W; Rich, D.H. J. Am. Chem. Soc., 1997, 119, 6488; (g) Pearson, A.J; Bignan, G; Zhang, P; Chelliah, M. J. Org. Chem., 1996, 61, 3940; (h) Nishiyama, S; Kim, M.H; Yamamura, S. Tetrahedron Lett., 1994, 35, 8397; (i) Boger, D.L; Zhou, J. J. Am. Chem. Soc., 1994, 116, 1601; (j) Casella, L; Gullotti, M; De Gioia, L; Monzani, E; Chillemi, F. J. Chem. Soc., Dalton Trans., 1991, 2945; (k) Jung, M.E; Jachiet, D; Rohloff, J.C. Tetrahedron Lett., 1989, 30, 4211; (l) Gross, A.J; Sizer, I.W; J. Biol. Chem., 1959, 234, 1611; (m) Reetz, M.T; Merk, C; Mehler, G. Chem. Commun., 1998, 2075.
- For leading references on synthetic apporaches to the more complex, but structurally related vancomycin glycopeptides see: Pearson, A.J; Chelliah, M.V. J. Org. Chem., 1998, 63, 3087; Evans, D.A; Dinsmore, C.J; Ratz, A.M; Evard, D.A; Barrow, J.C. J. Am. Chem. Soc., 1997, 119, 3417; Evans, D.A; Barrow, J.C; Watson, P.S; Ratz, A.M; Dinsmore, C.J; Evard, D.A; DeVries, K.M; Ellman, J.A; Rychnovsky, S.D; Lacour, J. J. Am. Chem. Soc., 1997, 119, 3419; Nicolaou, K.C; Boddy, C.N.C, Natarajan, S; Yue, T-Y; Li, H; Bräse, S; Ramanjulu, J.M. J. Am. Chem. Soc., 1997, 119, 3421.
- 11. Lygo, B; Wainwright, P.G. Tetrahedron Lett., 1997, 38, 8595; Lygo, B; Wainwright, P.G. Tetrahedron Lett., 1998, 39, 1599.
- 12. See preceding paper.
- For preparation of compound (7) in one step from p-cresol see: Barrett, A.G.M; Itoh, T; Wallace, E.M. Tetrahedron Lett., 1993, 34, 2233; Sartori, G; Maggi, R; Bigi, F; Arienti, A; Casnati, G; Bocelli, G; Mori, G. Tetrahedron, 1992, 48, 9483.
- 14. Carter, S.D; Wallace, T.W. Synthesis, 1983, 1000.
- Kiso, Y; Nakamura, S; Ito, K; Ukawa, K; Kitagawa, K. J. Chem. Soc., Chem. Commun., 1979, 971; Qian, X; Russell, K.C; Boteju, L.W; Hruby, V.J. Tetrahedron, 1995, 51, 1033.
- Dityrosine dihydrochloride 12 data: [α]_D -7 (c=1, 1M HCl);^{9h} ¹H nmr (300MHz, D₂O) δ 6.96(2H, br.d, J=8.0Hz), 6.82(2H, br. s), 6.73(2H, br. d, J=8.0Hz), 4.03-4.07(2H, m), 3.04(2H, dd, J=5.0, 14.5Hz), 2.90(2H, dd, J=7.5, 14.5Hz); ¹³Cnmr (75MHz, D₂O) δ 172.5, 153.7, 133.2, 131.5, 127.0, 126.5, 117.4, 55.2, 35.7.
- 17. We were unable to resolve the (S), (R)- and (R), (S)-isomers by HPLC.
- 18. Isodityrosine dihydrochloride **18** data: $[\alpha]_D$ -5 (c=1, 1M HCl);^{9k} ¹H nmr (300MHz, D₂O) δ 7.05(2H, d, J=8.5Hz), 6.82(2H, app.s), 6.73(2H, d, J=8.5Hz), 6.70(1H, s), 4.13-4.02(2H, m), 3.10(1H, dd, J=5.5, 14.5Hz), 3.10-2.93(2H, m), 2.88(1H, dd, J=7.5, 14.5Hz); ¹³Cnmr (75MHz, D₂O) δ 172.4, 172.3, 157.9, 148.1, 144.2, 131.9, 129.5, 127.8, 127.7, 123.3, 118.7, 118.3, 55.2, 55.1, 35.5(2C).