A Short Synthesis of a Biphenomycin B Analogue *via* a Double Heck Coupling Procedure

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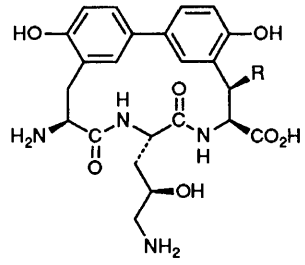
A biphenomycin B analogue has been prepared using the double Heck coupling of 3,3'-diiodo-4,4'-dimethoxybiphenyl and two orthogonally protected 2-amidoacrylates followed by two peptide bond forming steps for the incorporation of L-lysine as the middle amino acid residue.

The biphenomycins are cyclic tripeptide antibiotics particularly active against Gram-positive bacteria and are produced by *Streptomyces griseorubiginosus*.[1,2] Recent literature reports concerning the synthesis of natural biphenomycin B[3] as well as analogues of the biphenomycins[4] prompted us to communicate our results.

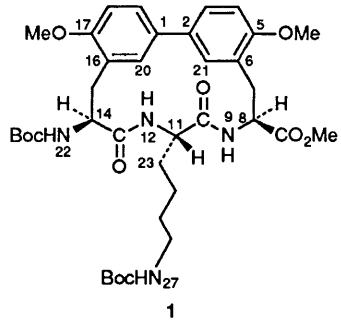
By applying our previously reported Heck coupling methodology for synthesis of aromatic amino acids[5–7] we have synthesised an analogue **1** of biphenomycin B, having L-lysine instead of γ-hydroxyornithine and carrying 4,4'-dimethoxy instead of hydroxy groups in the aromatic rings.‡

Diiodide **2** (Scheme 1) was prepared in two steps from commercially available 4,4'-dihydroxybiphenyl in 52% yield by *O*-methylation[8] followed by iodination.[7] Compound **2** was then coupled with the 2-amidoacrylates H_2C=(NHBoc)-(CO_2Bn)[5] and H_2C=(NHTEOC)(CO_2Me)[7] in sequence applying Pd^0-catalysis[7] to give compound **4**. Double asymmetric induction using [Rh(cod)(dipamp)]$^+BF_4^-$ as catalyst[9] in the hydrogenation of the double bonds of **4** gave the optically active saturated bis-amino acid derivative **5** {$[\alpha]_D^{22}$ + 6.5° (*c* 2.0 $CHCl_3$), m.p. 44–49 °C (from EtOAc–light petroleum)}. This compound was obtained in 25% yield after three steps from the easily accessible diiodide **2**. As a comparison, the corresponding compound **7** in Schmidt's biphenomycin B sequence was obtained in 25% yield and high stereochemical purity after *ca.* 15 steps.[3] Since the diastereoisomeric excess (d.e.) and enantiomeric excess (e.e.) of compound **5** could not be determined by NMR analysis or by chiral phase (Chiralcel OJ) HPLC, the product was used in the next step as a presumed mixture of stereoisomers.

Fluoride ion deprotection of the *N*-TEOC group[10] of **5** followed by active ester peptide synthesis[11] with N^{ε}-Boc-N^{α}-Z-L-lysine *p*-nitrophenyl ester gave **6** {$[\alpha]_D^{22}$ + 1.1° (*c* 1.8 $CHCl_3$)}, which by ^1H NMR analysis in $(CD_3)_2SO$ showed two methyl ester singlets in a 6:1 ratio, indicating a mixture of stereoisomers. Debenzylation of this mixture (purified by column chromatography; SiO_2; toluene–CH_2Cl_2–acetone, 4:2:1) gave a crude product that on TLC analysis (SiO_2; heptane–EtOAc–methanol, 1:1:1) showed one major, less polar spot and one minor, more polar spot. (Both spots showed signs of being composed of two compounds, in total presumably representing the four possible stereoisomers.) Cyclisation of this mixture using the diphenylphosphoryl azide method[12] gave, after chromatography (SiO_2; toluene–CH_2Cl_2–acetone, 10:5:4), 37% of **1**§ as a mixture of two isomers in a 15:1 ratio as shown by HPLC {SiO_2 (heptane–EtOAc, 5:4), C-18 (MeOH–H_2O, 2:1), and Chiralcel OJ (hexane–propan-2-ol, 95:5, containing 0.2% H_2O at 35 °C)}. The purified (HPLC; SiO_2; heptane–EtOAc, 5:4) major isomer gave one set of ^1H and ^{13}C NMR signals and a single peak on HPLC using the three phases mentioned above. Based on these analyses the isolated product was considered as diastereomerically pure {$[\alpha]_D^{22}$ + 6.9° (*c* 0.4, $CHCl_3$)}. This means, assuming negligible racemisation at the L-lysine residue, that **1** is enantiomerically pure as well. Since the [Rh(cod) (dipamp)]$^+BF_4^-$ catalyst generally produces amino acid derivatives of *S*-configuration, that of **1** should be *SSS*. Further structural proof of **1** was obtained by NMR experiments (COSY, NOESY and HECTOR). NMR data agree well with those reported for similar structures.¶[1,2]



Biphenomycin A R = OH
Biphenomycin B R = H



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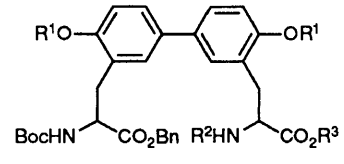

5 R^1 = Me, R^2 = TEOC, R^3 = Me
7 R^1 = Bn, R^2 = Z, R^3 = TMSE

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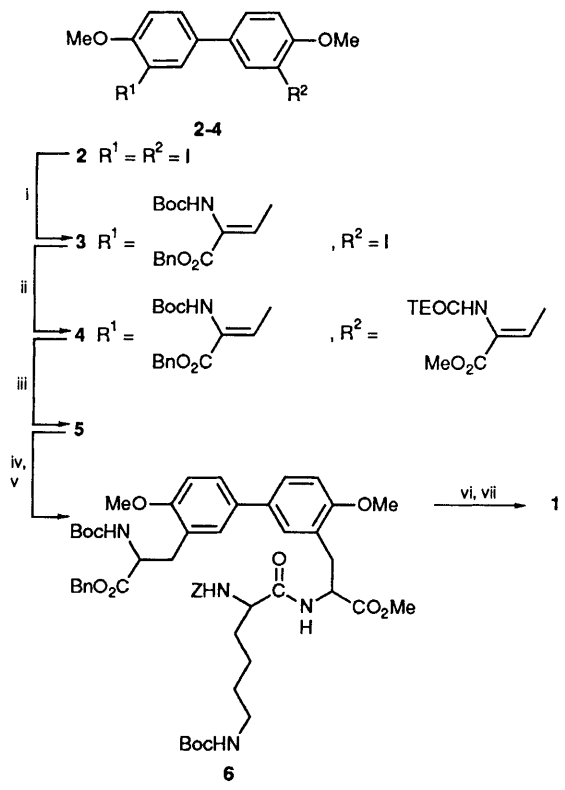
‡ New compounds had satisfactory elemental analyses and exhibited spectroscopic (IR, ^1H NMR and ^{13}C NMR) data in agreement with their structures. Abbreviations: Boc = *tert*-butoxycarbonyl; TEOC = trimethylsilylethoxycarbonyl; Z = benzyloxycarbonyl; Bn = benzyl; TMSE = trimethylsilylethyl; cod = cycloocta-1,5-diene; dipamp = (*R*,*R*)-1,2-bis-[(2-methoxyphenyl)phenylphosphino] ethane; DMF = dimethylformamide.

§ MS(EI, 30 eV) *m/z* (rel. intensity) 712 (M^+, 30).

¶ NMR data for compound **1**: ^1H NMR (300 MHz; CD_3SOCD_3; 50 °C): δ 1.30 (H-24), 1.38, 1.41 (CMe_3), 1.45 (H-25), 1.60 (H-23), 2.78 (H-15), 2.83 (H-7), 2.90 (H-26), 3.33 (H-7'), 3.41 (H-15'), 3.72 (CO_2Me), 3.78, 3.83 (OMe), 4.42 (H-14), 4.60 (H-11), 4.81 (H-8), 5.63 (H-22), 6.56 (H-27), 6.98 (H-4, H-18), 7.06 (H-20), 7.34 (H-21), 7.45 (H-3, H-19), 8.40 (H-12), 8.86 (H-9); ^{13}C NMR (CD_3SOCD_3): δ 22.5 (C-24), 27.7 (C-7), 28.1, 28.2 (CMe_3), 29.1 (C-25), 30.2 (C-15), 32.6 (C-23), 39.7 (C-26), 50.4 (C-8), 51.5 (C-11), 52.2 (CO_2Me), 53.2 (C-14), 55.4, 55.5 (OMe), 77.2, 78.0 (CMe_3), 110.5, 110.8 (C-4, C-18), 124.0, 124.2 (C-3, C-19), 124.7, 125.9 (C-6, C-16), 125.3 (C-21), 128.7 (C-20), 131.0, 131.3 (C-1, C-2), 154.0, 155.5, 155.6, 156.6 (C-5, C-17, two C=O in carbamates), 169.6, 171.9, 172.0 (CO_2Me, C-10, C-13).



Scheme 1 *Reagents and conditions*: i, $H_2C{=}C(NHBoc)(CO_2Bn)$, $Pd(OAc)_2$ (3 mol %), Bu_4NCl, $NaHCO_3$, DMF, 85 °C, 16 h, 42%; i, $H_2C{=}(NHTEOC)(CO_2Me)$, $Pd(OAc)_2$ (3 mol %), Bu_4NCl, $NaHCO_3$, DMF, 85 °C, 16 h, 77%; iii, H_2, $[Rh(cod)(dipamp)]^+BF_4^-$, EtOH, 40 °C, 3.5 atm, 3 days, 78%; iv, Et_4NF, MeCN, 55 °C, 4 h; v, N^{ε}-Boc-*N*-α-Z-L-lysine *p*-nitrophenyl ester, imidazole, EtOAc, 20 °C, 15 h, 65% from **5**; vi, H_2, Pd/C, EtOH, 20 °C, 1 atm, 2 h; vii, diphenylphosphoryl azide, 8 mmol dm^{-3}, DMF, 0 °C, 72 h, 37% from **6**

Notably, the NOESY experiment clearly showed the following correlations: NH-12 ⟷ H-14, NH-9 ⟷ H-11, NH-9 ⟷ H-21, H-8 ⟷ H-21, H-14 ⟷ H-20. Similar correlations were previously found for biphenomycin A.[2,13]

Interestingly, when the compounds giving the TLC spots after hydrogenolysis of **6** were separated by column chromatography and then, individually, exposed to the conditions for peptide synthesis, only the less polar pair of compounds gave compound **1**. The more polar pair gave oligomers or polymers as judged by their complex NMR spectrum. Further experiments are necessary to clarify this point, but the results could be taken as a preliminary indication that there is some stereoselection in the peptide-forming step, *i.e.* that only the stereoisomers with suitable configuration at the C-8 and C-14 centres give peptide bond formation with cyclisation, while the other ones give rise to intermolecular peptide bond formation.

In the present reaction sequence we utilised the fact that two of the termini of the bis-amino acid **5** have different protecting groups, but we point out that it is possible to attach four different peptide or other chains to structures such as **5**, since it has four orthogonal protecting groups. These aspects as well as the obvious improvement to replace the phenolic methyl groups with more suitable protecting groups, will be utilized in further work.

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References

1 I. Uchida, M. Ezaki, N. Shigematsu and M. Hashimoto, *J. Org. Chem.*, 1985, **50**, 1341; M. Ezaki, M. Iwami, M. Yamashita, S. Hashimoto, T. Komori, K. Umehara, Y. Mine, M. Kohsaka, H. Aoki and H. Imanaka, *J. Antibiot.*, 1985, **38**, 1453; I. Uchida, N. Shigematsu, M. Ezaki, M. Hashimoto, H. Aoki and H. Imanaka, *J. Antibiot.*, 1985, **38**, 1462.
2 R. Kannan and D. H. Williams, *J. Org. Chem.*, 1987, **52**, 5435.
3 U. Schmidt, R. Meyer, V. Leitenberger, A. Lieberknecht and H. Griesser, *J. Chem. Soc., Chem. Commun.*, 1991, 275.
4 U. Schmidt, R. Meyer, V. Leitenberger and A. Lieberknecht, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 929; A. G. Brown and P. D. Edwards, *Tetrahedron Lett.*, 1990, **31**, 6581.
5 A.-S. Carlström and T. Frejd, *Synthesis*, 1989, 414.
6 A.-S. Carlström and T. Frejd, *J. Org. Chem.*, 1990, **55**, 4175.
7 A.-S. Carlström and T. Frejd, *J. Org. Chem.*, 1991, **56**, 1289.
8 C. Finkentey, E. Langhals and H. Langhals, *Chem. Ber.*, 1983, **116**, 2394.
9 B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946.
10 L. A. Carpino, J.-H. Tsao, H. Ringsdorf, E. Fell and G. Hettrich, *J. Chem. Soc., Chem. Commun.*, 1978, 358.
11 R. H. Mazur, *J. Org. Chem.*, 1963, **28**, 2498.
12 S. F. Brady, R. M. Freidinger, W. J. Paleveda, C. D. Colton, C. F. Homnick, W. L. Whitter, P. Curley, R. F. Nutt and D. F. Veber, *J. Org. Chem.*, 1987, **52**, 764; S. F. Brady, S. L. Varga, R. M. Freidinger, D. A. Schwenk, M. Mendlowski, F. W. Holly and D. F. Veber, *J. Org. Chem.*, 1979, **44**, 3101. For a recent example of a cyclisation using DPPA, see: D. L. Boger and D. Yohannes, *J. Org. Chem.*, 1988, **53**, 487.
13 J. C. Hempel and F. K. Brown, *J. Am. Chem. Soc.*, 1989, **111**, 7323; F. K. Brown, J. C. Hempel, J. S. Dixon, S. Amato, L. Mueller and P. W. Jeffs, *J. Am. Chem. Soc.*, 1989, **111**, 7328.