Tetrahedron Letters, Vol. 33, No. 28, pp. 4045-4048, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

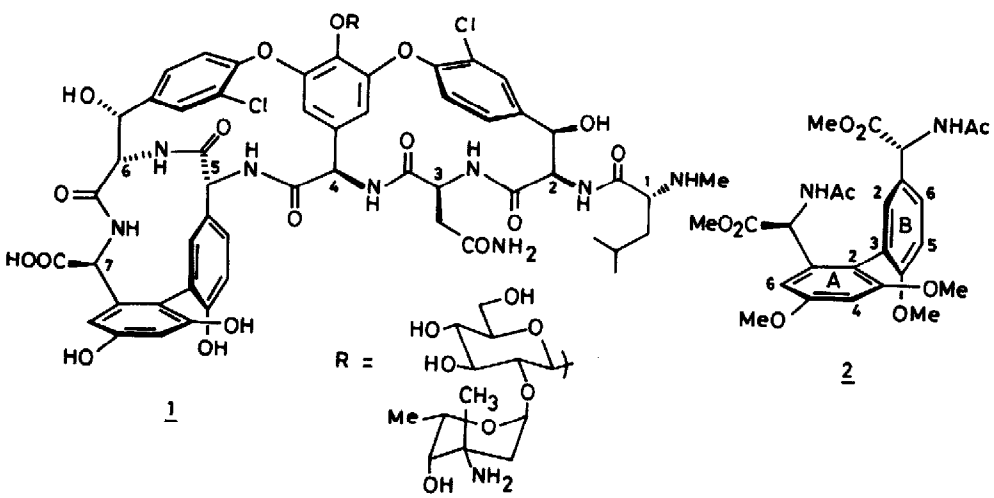
The First Synthesis of C-Terminal Biphenyl Moiety of Vancomycin

A V Rama Rao*, Tushar K Chakraborty and Subodh P Joshi
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Keywords: Vancomycin, Pd-Catalysed biaryl coupling, Asymmetric Strecker synthesis.

Summary: A successful Palladium catalysed intramolecular coupling of phenyl rings corresponding to amino acids (R)-4-hydroxyphenylglycine (5) and (S)-3,5-dihydroxyphenylglycine (7) of vancomycin is achieved.

Vancomycin[1] (1), the most well-known member of the vancomycin-ristocetin family of glycopeptide antibiotics (or dalbaheptides[2]), is a human anti-infective agent routinely used against staphylococcal infections. It expresses its antibiotic activity by inhibiting bacterial cell wall biosynthesis by selectively binding the C-terminal D-Ala-D-Ala residues of a peptidoglycan precursor, muramylpentapeptide. Though known for over thirty years no total synthesis

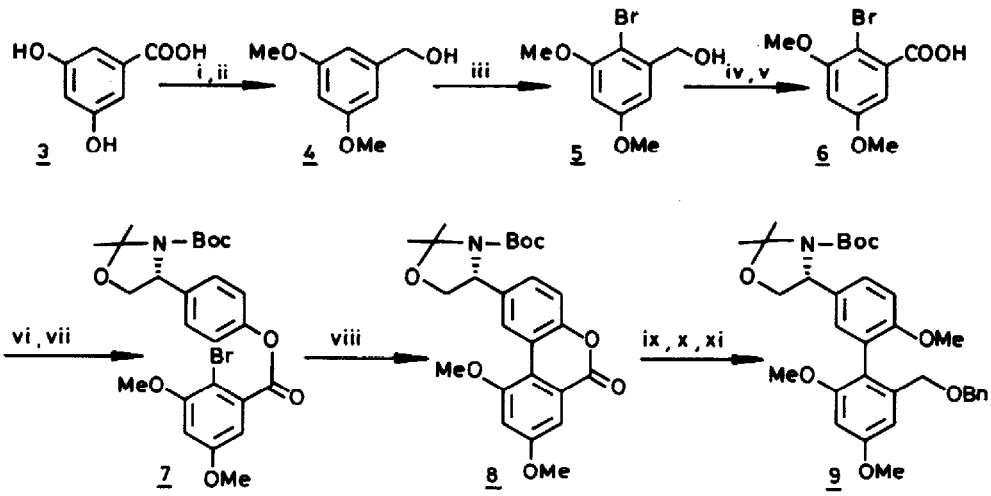


1 2

of any of these compounds has been reported so far due to their structural complexities[3]. One of the major obstacles yet to be overcome for achieving success in the total synthesis of vancomycin is the construction of its C-terminal cycle having a very characteristic biphenyl linkage between phenyl rings of amino acids 5 and 7. Unlike the N-terminus which varies in different glycopeptides the C-terminal biphenyl moiety is common to all members of this family and plays a crucial role in its binding with peptides. Herein, we report the first synthesis of this biphenyl unit **2** following an intramolecular palladium catalyzed condensation of two phenyl rings[4].

A close look at these glycopeptide antibiotics reveals that the biphenyl linkage is always formed between the 3-position of (R)-4-hydroxyphenylglycine (amino acid 5) and 2-position of (S)-3,5-dihydroxyphenylglycine (amino acid 7). The former, available commercially, was chosen as the most suitable starting material for our synthesis (Scheme I). For the other α-arylglycine segment the choice fell on 3,5-dihydroxybenzoic acid **3** which had to be converted to the reduced form **4** in order to achieve selective bromination at 2-position[5]. Primary hy-

Scheme - I



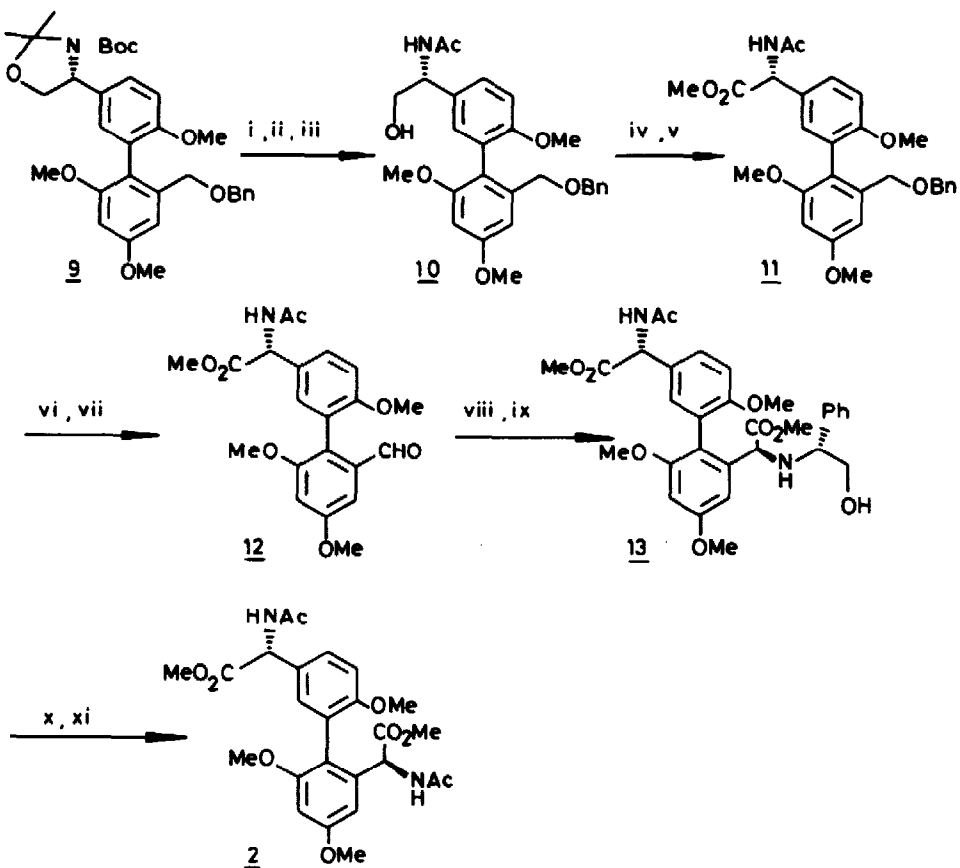
i) Me_2SO_4 (3.1 equiv.), K_2CO_3 (3.1 equiv.) acetone, reflux 4 h, 90%; ii) $LiAlH_4$ (2.5 equiv.), THF, rt, 10 h, 92%; iii) NBS (1.0 equiv.), $CHCl_3$, 45°C, 96%; iv) PDC (3.0 equiv.), $CHCl_3$, 90%; v) $NaClO_2$ (14 equiv.), DMSO, rt, 12 h, 85%; vi) $SOCl_2$, reflux; vii) A/Et_3N (4.0 equiv.), DMAP (0.1 equiv.), $CHCl_3$, 0°C, 76%; viii) $Pd(PPh_3)_2Cl_2$ (0.2 equiv.), NaOAc (2.5 equiv., DMA, 130°C, 25% [32% starting material recovered. Also, debrominated product was formed.]; ix) $LiAlH_4$ (2.0 equiv.), THF, rt, 68%; x) Me_2SO_4 (1.0 equiv.), K_2CO_3 (2.0 equiv.), acetone, rt, 3 h, 90%; xi) $PhCH_2Br$ (1.1 equiv.), NaH (1.1 equiv.), THF, 20 h, rt, 80%.

droxyl of the bromo compound **5** was oxidized back to the acid **6** in two steps[6]. Esterification of **6** with N-BOC-O,N-isopropylidene-4-hydroxy-(R)-phenylglycinol[7] (**A**), obtained from (R)-N-BOC-4-hydroxy-phenylglycine methyl ester in two steps[8], gave the very important intermediate **7**.

The much desired intramolecular coupling of two phenyl rings was achieved smoothly using $Pd(PPh_3)_2Cl_2$ in dimethylacetamide at 130°C with sodium acetate as buffer[9]. The formation of the coupled product **8** was easily confirmed by its ^1H n.m.r. spectrum which shows a characteristic B-2H signal at δ 8.9[10]. Reduction of the lactone, methylation of the phenolic hydroxyl, and finally, protection of primary hydroxyl as benzyl ether gave the compound **9**. Once the biphenyl unit was constructed, the amino acid centres were developed (Scheme II). Accordingly, the amino acid function on ring B was regenerated following standard methods[11]. Debenzylation of **11** followed by oxidation provided the aldehyde function of ring A (**12**), necessary to build up the second amino acid. A simple method, recently developed in our laboratory,

which uses phenylglycinol as chiral auxiliary for diastereoselective Strecker synthesis[12], was successfully employed to achieve this goal. Available in both enantiomeric forms, this excellent chiral auxiliary is suitable for the synthesis of both (R)- as well as (S)-amino acids; the (R)-phenylglycinol being used as the auxiliary for (S)-product and vice versa. Thus, reaction of our aldehyde **12** with (R)- phenylglycinol gave the E-imine which on treatment with trimethylsilyl cyanide gave the desired (S)-aminonitrile. This, on treatment with dry methanolic HCl gave the corresponding methyl ester **13**[13]. The chiral auxiliary was removed from **13** by oxidative cleavage with lead tetraacetate followed by acid hydrolysis of the intermediate aldimine[13]. The resulting amino group on acylation gave di-N-acetyldiester **2**, the same as obtained by degradation[14].

Scheme - II



i) p-TsOH (1.2 equiv.), MeOH, 60°C, 6 h; ii) Ac_2O (2.0 equiv.), Et_3N (3.0 equiv.), DMAP (0.1 equiv.), $CHCl_3$, rt; iii) K_2CO_3 (1.0 equiv.), dry MeOH, 10 min, 70% (from **9**); iv) PDC (8.0 equiv.), DMF, 10 h, rt; v) CH_2N_2, ether/MeOH, 42% (from **10**); vi) Pd/C (10%), H_2, 80%; vii) PDC (2.0 equiv.), $CHCl_3$, 86%; viii) (R)-phenylglycinol (1.1 equiv.) followed by Me_3SiCN (2.0 equiv.) in MeOH/$CHCl_3$ (1:3), 80%; ix) MeOH/dry HCl, 65%; x) $Pb(OAc)_4$ (1.2 equiv.), $CHCl_3$/-MeOH, aqs. HCl (3N), 60%; xi) Ac_2O (1.0 equiv.), Et_3N (1.1 equiv.), $CHCl_3$, 60%.

The success achieved in this first synthesis of biphenyl moiety of vancomycin will ultimately help accomplish its long awaited total synthesis[15].

References :

1. (a) M.H. McCormic, W.M. Stark, G.E. Pittenger, R.C. Pittenger and J.M. McGuire, Antibiot. Annual, 1955-56, H. Welch and F. Marti-Ibanez (Eds.), Medical Encyclopedia Inc. 1956, 606; (b) C.M. Harris, H. Kopecka and T.M. Harris, J. Am. Chem. Soc., 1983, **105**, 6915.
2. F. Parenti and B. Cavalleri, Drugs Future, 1990, **15**, 57.
3. (a) For oxidative macrocyclization of phenolic peptides to construct diaryl ether linkages of Vancomycin see : D.A. Evans, J.A. Ellman, K.M. DeVris, J. Am. Chem. Soc., 1989, **111**, 8912; (b) For the synthesis of some simple analogues see : i) M.J. Mann, N. Pant and A.D. Hamilton, J. Chem. Soc. Chem. Comm., 1986, 158; ii) N. Pant and A.D. Hamilton, J. Am. Chem. Soc., 1988, **110**, 2002; iii) D.W. Hobbs and W.C. Still, Tetrahedron Lett., 1987, **28**, 2805.
4. For related work see: D.A. Evans, D.A. Evrard, S.D. Rychnovsky, T. Fruh, W.G. Whittingham and K.M. DeVries, Tetrahedron Lett., 1992, **33**, 1189. P.D. Edwards, A.G. Brown, M.J. Crimmin, J. Chem. Soc. Perk. Trans. I, 1992, **1**, 123. D.H. Williams, M.J. Stone, R.A. Maplestone and S.K. Rahaman, Tetrahedron Lett., 1991, **32**, 2663.
5. C.A. Townsend, S.G. Davis, S.B. Christensen, J.C. Link and C.P. Lewis, J. Am. Chem. Soc., 1981, **103**, 6885.
6. E. Dalcanale and F. Montanari, J. Org. Chem., 1986, **51**, 567.
7. It was necessary to start with the reduced form in order to carry out selective manipulation of the ester function on ring A.
8. (R)-N-BOC-4-hydroxyphenylglycine methyl ester on reduction with $LiAlH_4$ followed by heating in 2,2-dimethoxypropane with catalytic amounts of p-TsOH yielded **A**.
9. (a) G. Bringmann, R. Walter and R. Weirich, Angew. Chem., Int. Ed. Eng., 1990, **29**, 977; (b) G. Bringmann, J.R. Jansen and H.P. Rink, Angew. Chem., Int. Ed. Eng., 1986, **25**, 913; (c) D.E. Ames and A. Opalko, Tetrahedron, 1984, **40**, 1919.
10. The 1,3-oxazolidine ring in all compounds exists as two distinct conformers as observed in their ^1H NMR spectra. ^1H NMR of **8** (mixture of conformers, $CDCl_3$, 200 MHz): δ 8.90 (s, 1H, B-2H), 7.50 (d, 1H, J=2.4 Hz, A-4H), 7.20-7.35 (m, 2H, B-5H and B-6H), 6.90 (d, 1H, J=2.4 Hz, A-6H), 4.90 and 4.95 (broad singlets, 1H, -NCH(Ar)CH_2-), 4.30 (dd, 1H, J=8.9 and 6.7 Hz, -OCH_2-), 3.90 and 4.05 (two s, total 6H, OCH_3), 3.85-3.95 (m, 1H, -OCH_2-), 1.60 and 1.80 (two s, total 6H, $C(CH_3)_2$), 1.20 and 1.45 (singlets, total 9H, ^{t}Bu).
11. (a) From O,N-diacetate stage the ^1H NMR spectrum started showing the presence of ca. 1:1 mixture of atropdiastereoisomers which did not separate on T.L.C.; (b) In the PDC oxidation step α-keto acid, formed by deamination followed by methylene oxidation was the major side product.
12. T.K. Chakraborty, G.V. Reddy and K.A. Hussain, Tetrahedron Lett., 1991, **52**, 7597.
13. After evaporation of the solvent and excess acid, neutralization was carried out using phosphate buffer of pH 7 or sodium acetate in order to prevent any possible epimerization of the highly base sensitive chiral centres.
14. ^1H NMR of **2** (DMSO-d_6, 200 MHz): δ 8.70 (d, 1H, J=7.0 Hz, -NH-), 8.40 (d, 1H, J=7.1 Hz, -NH-), 7.35 (dd, 1H, J=8.4 and 2.3 Hz, B-6H), 7.08 (d, 1H, J=2.3 Hz, B-2H), 7.03 (d, 1H, J=8.4 Hz, B-5H), 6.66 and 6.57 (d, 2H, J=2.2 Hz, A-4H, -6H), 5.35 (d, 1H, J=7.0 Hz, -CH-NH), 4.96 (d, 1H, J=7.1 Hz, -CH-NH), 3.50-3.82 (5s, 15H, OCH_3), 1.82 and 1.90 (2s, 6H, $NCOCH_3$).
15. To shorten the synthesis, a biaryl ester corresponding to **7** was made from (R)-N-BOC-4-hydroxyphenylglycine methyl ester and (S)-6-bromo-3,5-dihydroxy-N-BOC-phenylglycine. However, intramolecular coupling of this ester, involving 7-membered ring formation, did not proceed with $Pd(TPP)_4$. Efforts are on to achieve this coupling using other palladium catalysts.

IICT Communication No. 2982

(Received in UK 22 April 1992)