Pergamon

Tetrahedron Letters, Vol. 35, No. 28, pp. 5043-5046, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00932-5

An Expeditious Approach for the Synthesis of β-Hydroxy Aryl α-Amino Acids present in Vancomycin

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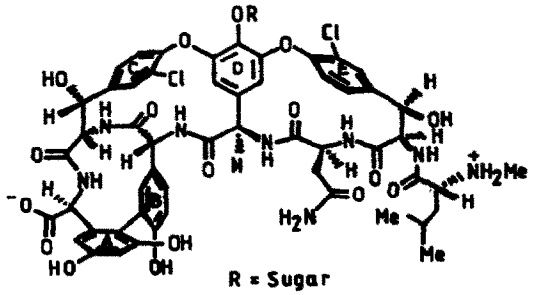
Keywords: Vancomycin, β-hydroxy aryl amino acids, Diastereoselective synthesis, Asymmetric dihydroxylation.

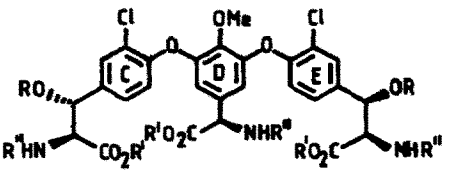
Abstract : Stereoselective synthesis of the β-hydroxyaryl amino acids which constitute C and E rings of vancomycin is described making use of benzylic oxidation and asymmetric dihydroxylation as the key steps.

Vancomycin (**1**)[1], the widely used antibiotic in the treatment of methicillin-resistant staphylococcus aureus is an attractive target molecule for total synthesis. Although, known for more than thirty years, only recently some trend for viable synthetic approaches has set in. Evans and his colleagues[2] have reported the biaryl diamino diacid (ABC segment) containing tripeptide of vancomycin. In addition several groups[3] have achieved the simplified segments of vancomycin. Having achieved the synthesis of biaryl diamino diacid[4] (AB segment) our efforts were directed towards the synthesis of CDE diaryl ether cross linked amino acid segment (**2**)[5]. To achieve this, our first target was to synthesize the two aryl amino acids **3** and **4** (C and E segments) and then to complete the synthesis of **2** by a methodology recently developed by us[6].



R = Sugar

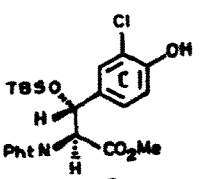
Vancomycin 1



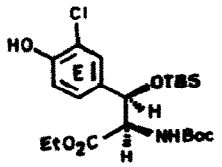
2

The desired two β-hydroxyaryl-α-amino acids (**3** and **4**) are diastereomeric differing only in the configurations at the α-carbons. While amino acid **3** has 2S,3R absolute configuration, that of **4** is 2R and 3R. Herein, we report the synthesis of these two arylamino acids by a simple sequence of reactions.

In our approach for the synthesis of **3** and **4**, we preferred to have different protecting groups on the amino functions so that selectively deprotection is possible for subsequent manipulation of the right and left segments of vancomycin molecule.



3

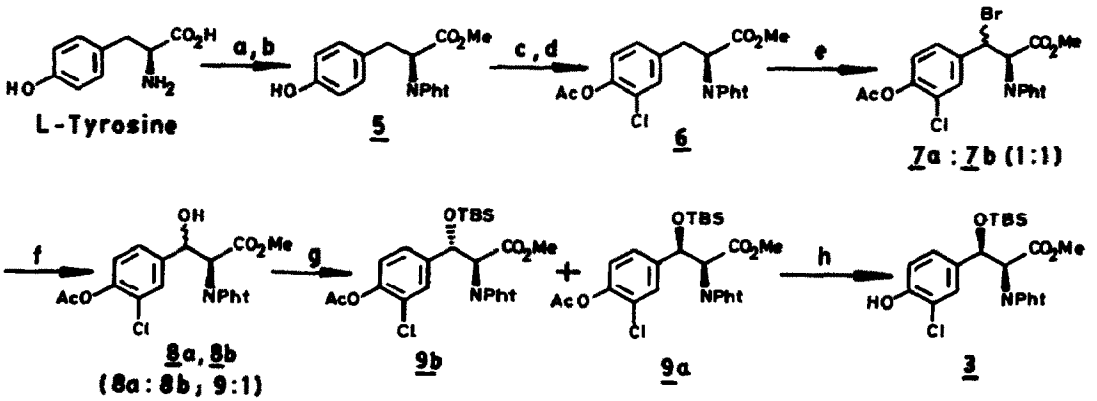


4

Diastereoselective synthesis of (2S,3R)-methyl 2-phthalimido-3-(^{t}butyldimethylsilyloxy)-3-(3'-chloro-4'-hydroxy phenyl)propionate (3):

β-Hydroxyarylamino acid 3 was made by simple approach involving the oxidation of the benzylic position taking advantage of the adjacent chiral center to induce diastereoselectivity. Thus treatment of N-phthaloyl methyl ester 5 with SO_2Cl_2 in ether afforded the ortho-mono chlorinated tyrosine derivative which after acetylation with Ac_2O/Py was subjected to benzylic photobromination with NBS in CCl_4 to afford a 1:1 mixture of the diastereomeric bromides (7a, 7b) (Scheme 1). The phthalimido group is essential for benzylic bromination.

SCHEME - I



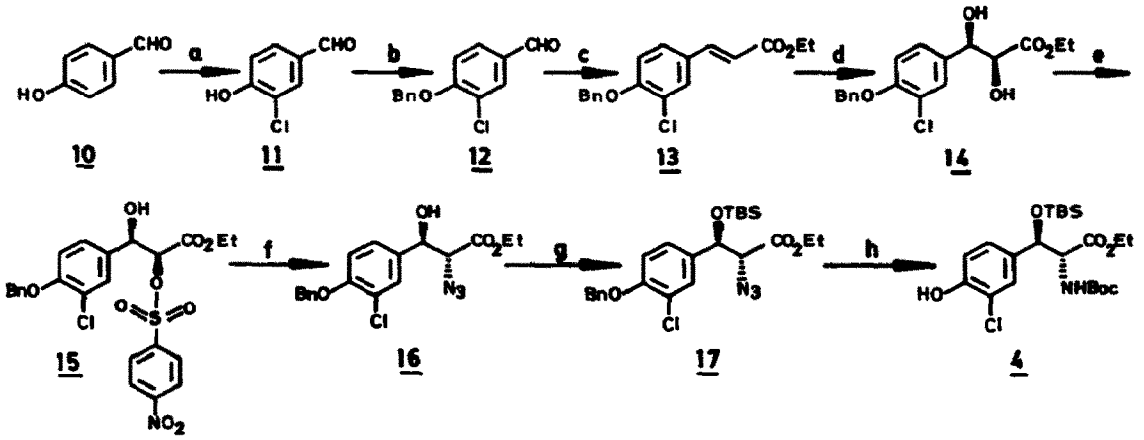
a) N-Ethoxycarbonylphthalimide (1.1 eq); NaOH (2.0 eq), 0°C, 0.5 h, 72%; b) MeOH, H_2SO_4, reflux, 6 hr, 83%; c) SO_2Cl_2 (1.05 eq), ether, RT, 15 min, 94%; d) Ac_2O (1.1 eq), Py (1.5 eq), CH_2Cl_2, RT, 3 h, 96%; e) NBS (1.05 eq), AIBN, CCl_4, reflux, 6 h, 98%; f) $AgNO_3$ (1.5 eq), CH_3COCH_3-H_2O, RT, 3 h, 76%; g) TBDMS-OTf (1.0 eq), 2,4,6-collidine (1.1 eq), CH_2Cl_2, 0°C, 10 min, 91%; h) NaOMe (1.0 eq), MeOH, RT, 5 min. 71%.

The mixture was treated with $AgNO_3$ in aqueous acetone[7] to obtain predominantly the syn-β-hydroxy-α-amino acid 8a and a small amount of the antidiastereomer 8b in the ratio 9:1. Diastereoselectivity in the formation of 8a was due to the nucleophilic attack from the less hindered face of the carbocation intermediate[7]. The role, if any, played by the phthalimido protecting group or the ester in inducing diastereoselectivity is not clearly understood. The mixture was O-silylated with TBDMS-OTf/collidine[8]. The benzylic silyl ethers were neatly separated by column chromatography and individually characterised. O-deacetylation with sodium methoxide in methanol afforded 3.

Enantioselective synthesis of (2R,3R)-ethyl 2-(^{t}butoxycarbonyl)amino-3-(^{t}butyldimethylsilyloxy)-3-(3'-chloro-4'-hydroxy phenyl)propionate (4).

The β-hydroxy arylamino acid **4** was made by asymmetric dihydroxylation (AD) of appropriately substituted cinnamic ester followed by regioselective manipulation of the α-hydroxy function. Para-hydroxybenzaldehyde (**10**) was chlorinated with NCS (Scheme II) to obtain the meta-monochlorinated aldehyde **11** as the sole product in 94% yield. The phenolic hydroxyl in **11** was protected as benzyl ether and the wittig reaction on **12** with ethoxycarbonylmethylenetriphenylphosphorane in benzene afforded the trans-olefin **13** in 89% yield. AD[9] of this olefin **13** (OsO_4, K_2CO_3, $K_3Fe(CN)_6$, DHQD-pCBz) resulted in the syn dihydroxy ester **14** in 91% chemical yield with 96% enantiomeric excess[10] after one recrystallisation from CH_2Cl_2-pet. ether. Regioselective-α-nosylation of this diol **14** with 4-nitrobenzenesulfonyl chloride resulted in the α-nosylate **15** exclusively, which was used as the electrophile for the azide. Treatment of the nosylate **15** with NaN_3 in DMF at 50°C for 18 hrs cleanly afforded the anti-α-azido ester **16** with 4% epimerisation of the α-center. The benzylic hydroxyl in **16** was converted into silyl ether **17** with TBDMS-OTf and 2,4,6-collidine[8]. O-Debenzylation, reduction of

SCHEME - II



a) NCS, $CHCl_3$, 50°C, 94%; b) BnBr, K_2CO_3, Acetone, reflux, 2h, 92%; c) Ph_3PCHCO_2Et, Benzene, RT, 1h, 89%; d) OsO_4, DHQDpClBz, $K_3Fe(CN)_6$, K_2CO_3, ^{t}BuOH:H_2O (1:1), 24h, 91%; e) 4-Nitrobenzenesulfonylchloride, Et_3N, CH_2Cl_2, 0°C, 14h, 87%; f) NaN_3, DMF, 50°C, 12h, 81%; g) TBDMS-OTf, 2,4,6-collidine, CH_2Cl_2, 0°C, 15 min, 94%; h) PtO_2-H_2, $(Boc)_2O$, EtOAc, RT, 24h, 85%.

the azide to the amine and further conversion to N-Boc derivative were carried out in one-pot hydrogenolysis with PtO_2 in EtOAc in presence of $(Boc)_2O$[11].

Use of these two β-hydroxy-α-amino acids **3** and **4** in the synthesis of bis-diaryl fragment (CDE) of vancomycin is described in the succeeding communication.

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8. The problem of elimination resulting in the formation of ene ester was not encountered.
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10. Enantiomeric excess was determined by chiral cell-OD column.
11. All new compounds gave satisfactory IR, NMR and Mass spectra.

IICT Communication No. 3378

(*Received in UK* 21 *March* 1994; *revised* 29 *April* 1994; *accepted* 12 *May* 1994)