Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7433-7436, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01749-8

S_NAr Macrocyclisation : A New Approach Towards the Synthesis of D-O-E- Segment of Vancomycin

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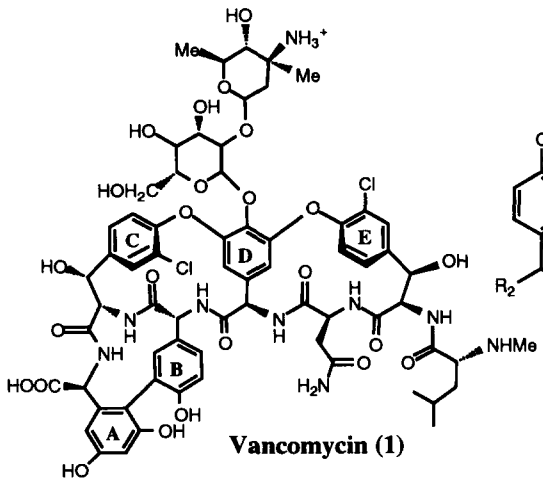
Abstract: A new approach towards the synthesis of D-O-E- segment of vancomycin by S_NAr macrocyclisation is described. © 1997 Elsevier Science Ltd.

Vancomycin (**1**) is an useful antibacterial antibiotic and currently its synthesis is the most formidable challenge in natural product synthesis. During the evolutionary process, many original strategies and tactics toward vancomycin synthesis have been developed, however, the S_NAr approach by far the most promising protocol as exemplified by the work done by Beugelman, Evans, Boger and our group.[1] One of the many



Vancomycin (1)

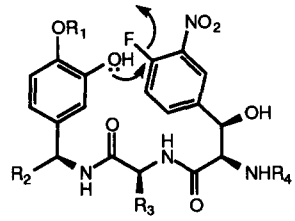


Figure 1a

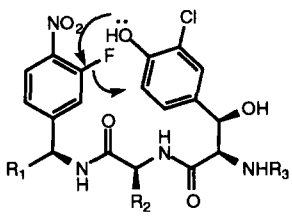


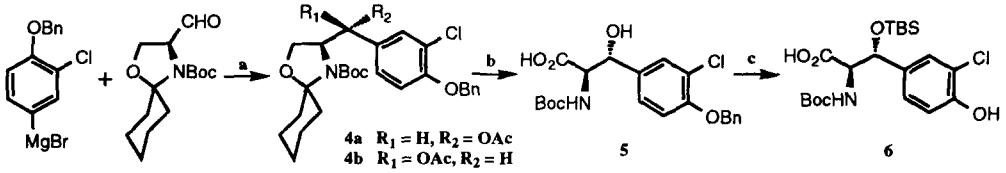
Figure 1b

goals in the synthesis of vancomycin was to understand the issues that govern the atropdiastereoselection in S_NAr macrocyclisation step.[2] Beugelmans reported in a less functionalised tetrapeptide model system, the S_NAr macrocyclisation with CsF/DMF to occur with complete atropdiastereoselection leading to the natural conformer of DOE segment.[3] Later studies on double S_NAr macrocyclisation with a model pentapeptide system at low temperature (-5°C) revealed the exclusive formation of one atropisomer, however with opposite conformation.[4] Contrary to these observations, Boger[5] and Evans[6] reported with fully functionalised system, the invariable

formation of a mixture of atropisomers during S_NAr macrocyclisation. Evans[6] concluded that the issue of atropdiastereoselection in vancomycin synthesis by S_NAr approach remains unresolved. The same group recently reported truly some outstanding efforts in dechlorovancomycin aglycone synthesis however, in this manifestation the issue of atropisomerism did not exist.[7]

In all these S_NAr studies, one common feature to highlight was the substitution pattern on C, D and E rings. The ring C or E contains the *o*-nitrofluoro substitution, whereas the centrally located ring D encompasses the nucleophilic phenolic group (Figure 1a). As a part of our continuing research,[8] we rationalised that if these substitution patterns could be reversed *i.e.* *o*-nitrofluoro groups are placed on ring D while (2R,3R)-β-hydroxy-(4-hydroxy-3-chlorophenyl)-alanine represents the ring E of vancomycin, then the outcome of atropdiastereo-selection in S_NAr macrocyclisation would be interestingly investigative (Figure 1b). In addition we believe that our strategy has distinctive operational advantages during functional group manipulation after the C-O-D-O-E synthesis by double S_NAr macrocyclisation has been effected. This contention forms the basic premise of this communication.

Scheme 1



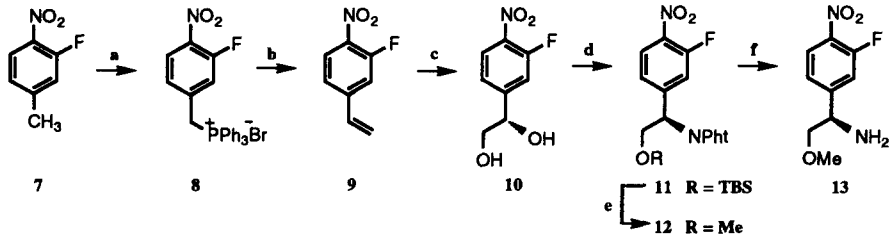
2 **3** **5** **6**

(a)(i) THF, 0°C, 1 h, 75%, (ii) Ac_2O, py., CH_2Cl_2, rt, 2 h, 98%, (b)(i) aq.TFA, CH_2Cl_2, rt, 1 h, 70%, (ii) Jones reag., Me_2CO, 0°C, 1 h, 54%, (iii) K_2CO_3, MeOH, rt, 30 min., 94%, (c)(i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, 88%, (ii) Pd/C, H_2, EtOAc, rt, 3 h, 96%.

A new and effecient synthesis of (2R,3R)-3-tert.butyldimethylsilyloxy-(4-benzyloxy-3-chloro-phenyl) N-tert.butyloxycarbonyl alanine (**6**) (ring E) has been accomplished as described below. The salient feature includes the highly stereocontrolled Grignard reaction of 4-benzyloxy-3-chlorophenyl magnesium bromide (**2**) with Garner's aldehyde (**3**)[9] at 0°C followed by acetylation to give a 8:1 mixture of *anti* (**4a**) and *syn* (**4b**) amino alcohols separated by silica gel chromatography.[10] Trifluoroacetic acid mediated hydrolysis of cyclohexylidene group of **4a** was followed by Jones oxidation (Jones reagent, acetone, 0°C) of the resulting free hydroxy methyl group and deacetylation (K_2CO_3, MeOH) to give the β-hydroxy phenylalanine derivative (**5**). Its consequent elaboration to the target molecule (**6**) was effected as delineated in scheme 1.

3-Fluoro-4-nitrotoluene (**7**) was chosen as the starting material for the synthesis of (R)-3-fluoro-4-nitrophenylglycinol (**13**) (ring D) (Scheme 2). Conversion of **7** into the corresponding Wittig salt (**8**) was accomplished in two steps. Subsequent condensation with formaldehyde afforded[11] the substituted styrene derivative (**9**) with an overall yield of 40%. The Sharpless asymmetric dihydroxylation[12] was carried out with $(DHQ)_2$ PHAL as a ligand leading to the (S)-diol (**10**) in 90% yield. The high enantiomeric excess > 98% e.e was established by ^{19}F NMR spectrum of its MTPA ester. The primary hydroxy group of **10** was selectively blocked as TBS-ether and then subjected to pthalimide induced S_N2 displacement reaction under Mitsunobu condition (Ph_3P, DEAD, THF, 0°C) to afford **11**. The derived methyl-ether derivative (**12**) was hydrolysed with HCl to give the requisite amine (**13**).

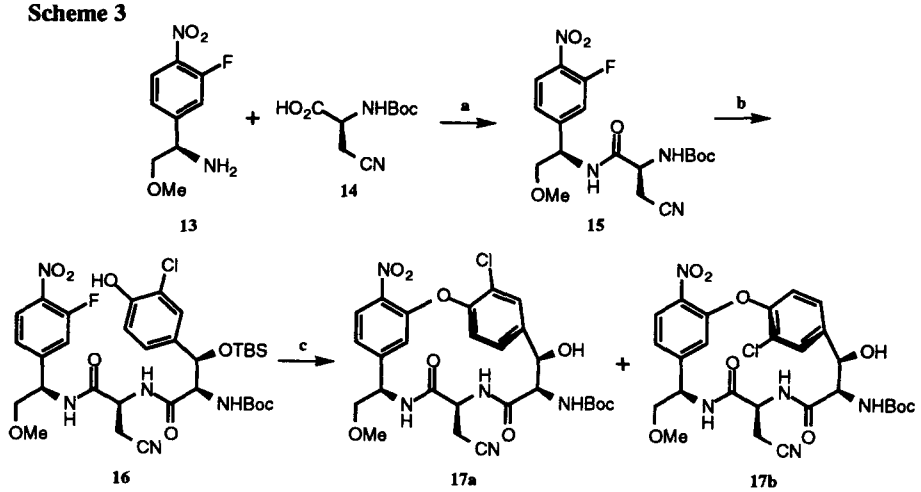
Scheme 2



(a)(i) NBS, AIBN, CCl_4, hυ (250W), 8 h, 65%, (ii) PPh_3, C_6H_6, rt, 26 h, 100%, (b) aq. Na_2CO_3, aq.CH_2O (40%), $CHCl_3$, rt, 1 h, 60%, (c) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, OsO_4, $^tBuOH:H_2O$ (1:1), 0°C, 8 h, 90%, (d)(i) TBSCl, Imid, CH_2Cl_2, 0°C, 1 h, 95%, (ii) PPh_3, DEAD, phthalimide, THF, 0°C, 6 h, 90%, (e)(i) 1N HCl, MeOH, rt, 1 h, 93%, (ii) MeOTf, 2,6-lutidine, CH_2Cl_2, 80°C, 2 h, 85%, (f) Conc.HCl, 100°C, 12 h: aq.$NaHCO_3$, 90%.

The coupling reaction between **13** and cyanoalanine derivative (**14**) was promoted in the presence of EDC and HOBT as coupling reagent to give the dipeptide (**15**) (Scheme 3). The possibility of racemisation during the amide bond formation was minimal (<5%) as supported by ^1H NMR spectral analysis. The structure of **15** was further supported by HRMS. The removal (CF_3COOH, CH_2Cl_2, 0°C) of N-Boc followed by second coupling reaction with the hydroxy tyrosine derivative (**6**) gave the tripeptide (**16**) whose ^1H NMR and MS studies were concurrent with the assigned structure.

Scheme 3



(a) EDC, HOBT, DMF, rt, 8 h, 60%, (b)(i) TFA, CH_2Cl_2, rt, 30 min., 85%, (ii) EDC, HOBT, 6, DMF, rt, 8 h, 65%, (c) CsF, DMF, rt, 1 h, 45%.

The critical S_NAr macrocyclisation of **16** was undertaken in the presence of 3 eq. of CsF in DMF (0.008 M) at room temperature. The reaction was completed in 1 h giving rise to a mixture of two atropisomers (**17a**) and (**17b**) which were conveniently separated by silica gel chromatography in 1:1 ratio (45% yield). Their structures were suggested by ^1H NMR and mass spectral studies.[13]

It is important to notice from the above results that when the substituent pattern in S_NAr cyclisation as described above are reversed, the effect on atropdiastereoselectivity was not significant. Boger and Evans also observed low atropdiastereoselection during S_NAr macrocylisation of fully functionalised polypeptide substrates.

By carefully analysing the molecular structures of polypeptides employed by us as well as by Boger[4] and Evans[5] with the polypeptides used by Beugelmans[2], the distinctive differences were visible in the structure of tyrosine residue (C and E rings). Beugelmans' polypeptide lack the hydroxyl substituent present on tyrosine residue of vancomycin. This could be the major issue in dictating the stereochemical course of S_NAr cyclisation, an interpretation that has to be further investigated in greater details.

Acknowledgements: Authors (PLP, MN, SP, B V N B S S and NKT) thank CSIR for financial support.

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10. Ravi Kumar J.S.; Datta, A. *Tetrahedron Lett.*, **1997**, 38, 473-476. The unwanted *syn* isomer **4b** was transformed into anti isomer **4a** by oxidation (IBX-DMSO) and reduction ($ZnBH_4$, Et_2O) sequence.
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13. All the new compounds were characterised by ^1H NMR, MS and HRMS analysis. The ^1H NMR (200 MHz, $CDCl_3$) spectral data of some selected compounds are described:
Compound **15** : δ 8.04 (dd, 1 H, J = 7.2,8.5 Hz), 7.3 (m, 2H), 5.35 (d, 1H, J = 7.9 Hz), 5.11 (m, 2 H), 4.47 (m, 1 H), 3.67 (m, 2 H), 3.36 (s, 3 H), 2.98 (dd, 2 H, J = 6.2, 13.2 Hz), 2.82 (dd, 2 H, J = 4.4, 13.2 Hz), 1.49 (s, 9 H). FABMS : m/z 411 (M^++1). Compound **16** : δ 8.04 (dd, 1 H, J = 7.2,8.5 Hz), 7.58 (bs, 1H), 7.2 - 7.4 (m, 4 H), 7.06 (d, 1 H, J = 8.5 Hz), 6.61 (bd, 1 H, J = 8.5 Hz), 5.87 (bs, 1 H), 5.18 (m, 1 H), 5.03 (d, 2 H, J = 5.3 Hz), 4.72 (m, 1 H), 4.18 (t, 1 H, J = 4.9 Hz), 3.75 (m, 2 H), 3.48 (s, 3 H), 3.06 (dd, 1 H, J = 4.9, 16.5 Hz), 2.66 (dd, 1 H, J = 6.6, 16.5 Hz), 1.38 (s, 9 H), 0.91 (s, 9 H), 0.1 (s, 3 H), -0.1 (s, 3 H). FABMS : m/z 737 (M^+). Compound **17** : more polar isomer : δ 8.01 (d, 1 H, J = 8.4 Hz), 7.5 (dd, 1H, J = 2.0, 8.4 Hz), 7.41 (d, 1 H, J = 8.4 Hz), 7.35 (d, 1 H, J = 2.0 Hz), 7.01 (d, 1 H, J = 8.4 Hz), 6.87 (d, 1 H, J = 7.1 Hz), 6.72 (bs, 1 H), 6.12 (s, 1 H), 5.35-5.5 (m, 2 H), 4.9 (m, 1 H), 4.57-4.72 (m, 2 H), 3.77 (m, 2 H), 3.32 (s, 3 H), 3.05 (dd, 1 H, J = 4.2, 16.4 Hz), 2.87 (bs, 1 H), 2.67 (dd, 1 H, J = 6.9, 16.4 Hz), 1.49 (s, 9 H). FABMS : m/z 603 (M^+) : less polar isomer : δ 8.04 (d, 1 H, J = 8.4 Hz), 7.75 (d, 1H, J = 2.0 Hz), 7.12-7.3 (m, 2 H), 7.02 (dd, 1 H, J = 2.0, 8.4 Hz), 6.75 (m, 1 H), 6.01 (d, 1 H, J = 2.0 Hz), 5.62 (d, 1 H, J = 7.1 Hz), 5.5 (m, 1 H), 5.08 (m, 1 H), 4.72 (m, 1 H), 4.62 (m, 1 H), 3.72 (d, 2 H, J = 4.2 Hz), 3.32 (s, 3 H), 3.20 (dd, 1 H, J = 4.5, 16.4 Hz), 2.79 (m, 1 H), 2.59 (dd, 1 H, J = 6.4, 16.4 Hz), 1.50 (s, 9 H). FABMS : m/z 603 (M^+).

IICT Communication No. 3851

(*Received in UK* 11 *July* 1997; *accepted* 22 *August* 1997)