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Asymmetric Synthesis of (2*S*,3*R*) β-(4-F-3-NO_2) phenyl Serine, D-(*R*)-4-methoxy-3,5-Bis^{t}Butyldimethylsiloxy Phenylglycine and Their Assemblage to C-O-D Ring of Vancomycin

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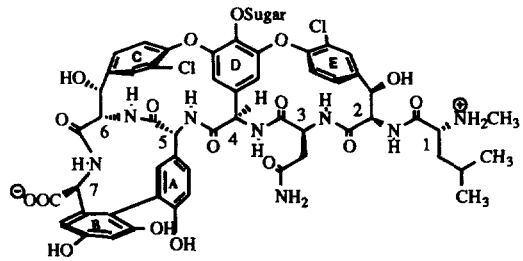
Abstract: The asymmetric synthesis of two appropriately functionalized non-proteinogenic amino acids **2** and **3** needed for the total synthesis of vancomycin was described. The assemblage of these amino acids into linear tripeptide followed by biaryl ether formation *via* intramolecular S_NAr reaction led to the fully functionalized C-O-D ring of vancomycin.

The glycopeptide antibiotic, vancomycin **1**, (figure 1) has found extensive clinical use over the last quarter of a century and is the drug of choice for the treatment of infections due to methicillin-resistant *staphylococcus aureus* and other gram-positive organisms in patients allergic to β-lactam antibiotics.[1] The unique mode of action,[1c] the complexity of the molecule and the recent emerged vancomycin-resistance phenomenon[2] have rendered it an attractive synthetic target and some new synthetic methodology has been developed resulting from the efforts of a number of research groups.[3] Our interest in this field has uncovered an efficient macrocyclisation procedure *via* biaryl ether formation based on the intramolecular aromatic nucleophilic substitution (S_NAr) reaction and have applied it to the synthesis of 14-,[4] 16-[5] and 17-membered[6] macrocycles. To achieve the total synthesis of vancomycin using this methodology, four non-proteinogenic amino acids need to be prepared. We report herein the asymmetric synthesis of two of them (**2**, **3**) and their assemblage to the C-O-D ring (**4**), fully functionalized for further elaboration towards the total synthesis of vancomycin.

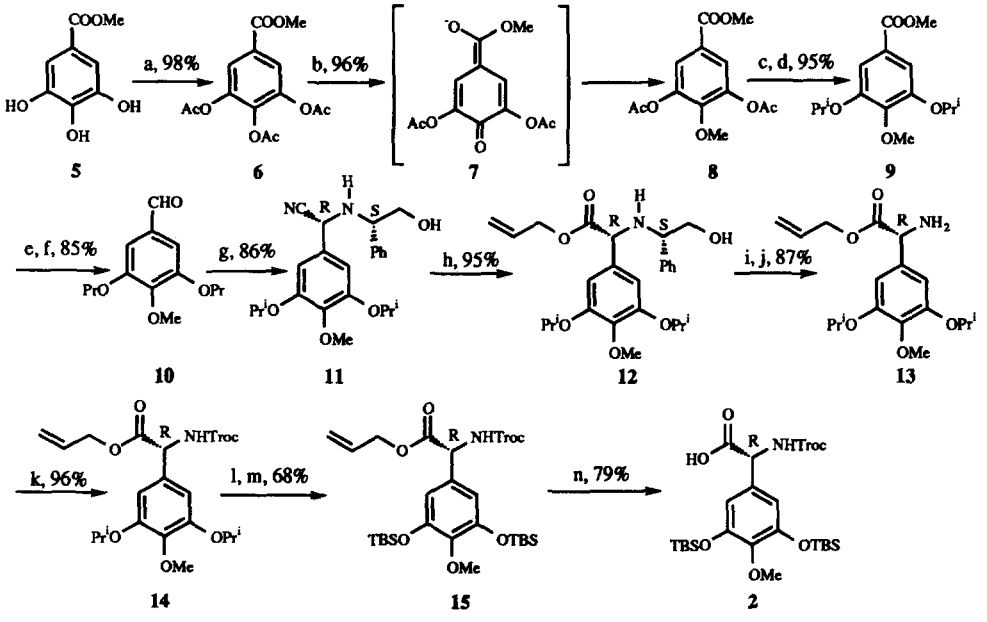


Vancomycin **1**

Figure 1

The asymmetric Strecker reaction[7] has been employed as a key step for the synthesis of the central aminoacid: D-(*R*)-4-methoxy-3,5-bis^{t}butyldimethylsiloxy phenylglycine (**2**) starting from methyl gallate (**5**). To facilitate the following synthetic steps towards the elaboration of macrocycle (**4**), the 4-hydroxy group of methyl

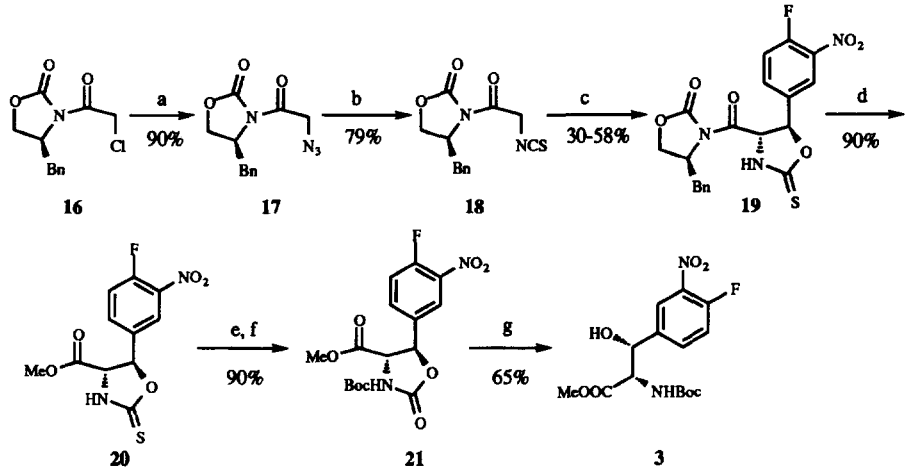
3,4,5-trihydroxy benzoate **5** needs to be chemoselectively protected. Methylation of triacetate (**6**), under normal methylation conditions (K_2CO_3, MeI, Me_2CO, reflux) provided a simple solution to this rather difficult problem.[8] We think that trace of water in the reaction medium may hydrolyse chemoselectively the 4-acetyl group leading to the intermediate **7** stabilized by conjugating effect of the ester function, whose methylation gave then the desired product **8**. As shown in Scheme 1, 4-methoxy-3,5-diisopropyloxy benzaldehyde (**10**) could be efficiently prepared in 6 steps (62% overall yield) from methyl gallate **5** without any columun chromatographic purification. Treatment of (**10**) with (*S*)-phenylglycinol in CH_2Cl_2 at rt for 1 h followed by sequential addition of MeOH and TMSCN at 0°C afforded a mixture of two readily separable diastereoisomers from which the desired stereoisomer (**11**) was isolated in 86% yield. Hydrolysis of α-aminonitrile to the corresponding amino acid under acidic conditions was found to be troublesome in our case. In view of the mild, racemization free deprotection conditions of allyl ester,[9] compound **11** was transformed into α-amino allyl ester **12** using gaseous HCl saturated allyl alcohol in 95% yield. No γ-lactone resulting from the internal attack of primary hydroxy group onto the nitrile was found. Oxidative cleavage of the chiral auxiliary with $Pb(OAc)_4$,[10] and protection of the resulting primary amine as 2,2,2-trichloroethoxycarbamate (Troc) afforded compound **14** in 84% overall yield which was converted into TBS ether **15** without event. Deprotection of allyl ester was realized employing our recently developed conditions [$Pd(PPh_3)_4$, $NaBH_4$, THF][11] to provide the desired aminoacid **2** in 79% yield whose optical purity was determined by conversion to the corresponding (*S*)-α-methyl benzylamide. ^1H and ^{13}C NMR spectra of this derivative indicated a diastereomeric ratio of 9 to 1 and compound **2** was used as such without further purification.



Reagents and Conditions: a) Ac_2O, Et_3N; b) K_2CO_3, MeI, acetone; c) K_2CO_3, MeOH-H_2O; d) K_2CO_3, ^{i}PrBr, DMF; e) LAH, THF; f) PCC, CH_2Cl_2; g) (*S*)-phenylglycinol, CH_2Cl_2-MeOH, TMSCN; h) CH_2CHCH_2OH HCl; i) $Pb(OAc)_4$, CH_2Cl_2 MeOH; j) aq. HCl; k) TrocCl, $NaHCO_3$, H_2O-CH_2Cl_2; l) BCl_3; m) TBSOTf, 2,6-lutidine; n) $Pd(PPh_3)_4$, $NaBH_4$, THF.

Scheme 1

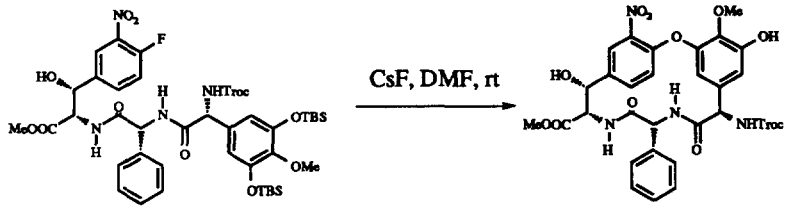
The β-hydroxyl α-amino acid: (2*S*,3*R*)-β-(4-fuoro-3-nitro) phenyl serine (**3**) was synthesized as shown in scheme 2. Aldol condensation between isothiocyanate **18**, prepared in two steps from the chloroacetate precursor **16** and 4-fluoro-3-nitrobenzaldehyde under Evans conditions[12] [Sn $(OTf)_2$[13], N-ethyl piperidine] afforded *syn* aldol, isolated as the internally derivatized heterocycle **19** in moderate chemical yield and *syn/anti* selectivity. Other metal enolates such as Li, B, and Ti have also been attempted for the key aldol process, however, none of them gave satisfactory yield. We think that the presence of fluoro and nitro functions in the aromatic ring may have some deleterious effect, at least on the facial selectivity.[14] Treatment of **19** with magnesium methoxide in methanol gave the corresponding methyl ester which was transformed into oxazolidinone **21** in a two step sequence. Hydrolysis of **21** was carried out under different conditions and was found to be problematic due to the competitive attack of nucleophile onto the *endo* imide carbonyl and *exo* carbamate function. The best result was obtained when $CsCO_3$ in MeOH [15] was employed. Under these conditions, the desired compound **3** was isolated in 65% yield. The corresponding didehydroamino ester was inevitablely produced in 10 to 20% yield.



Reagents and Conditions: a) NaN_3, $^nBu_4NHSO_4$, CH_2Cl_2-H_2O; b) CS_2, PPh_3; c) $Sn(OTf)_2$, N-Et-piperidine, THF, 4-fluoro-3-nitrobenzaldyde; d) MeMgBr, MeOH; e) Boc_2O, DMAP, CH_2Cl_2; f) H_2O_2; g) $CsCO_3$, MeOH.

Scheme 2

With compounds **2** and **3** in hands, the linear tripeptide **22** resulting from the coupling of amino acids **2**, **3** and D-(*R*)-phenylglycine was efficiently prepared under standard conditions employing EDC as coupling reagent in the presence of HOBt as additive. Less than 5% racemization occured under these conditions and diastereomeric pure compound **22**[16] was obtained by flash chromatography. Treatment of **22** with anhydrous CsF in DMF (0.01 M) allowed for the deprotection of silyl ether and intramolecular S_NAr reaction in one single step and the macrocyle **4** (Scheme 3) was isolated in 42% non optimized yield as a mixture of two atropisomers.[5b] This result further demonstrates the efficiency of intramolecular S_NAr reactions[4-6].



22 4

Scheme 3

In conclusion, we have reported the asymmetric synthesis of two non-proteinogenic amino acids **2** and **3** and cyclisation of the linear tripeptide **22** into the corresponding macrocycle **4** of vancomycin which possesses all the functionality required for the further elaboration towards the total synthesis of this antibiotic.

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