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Synthesis of 3,5-Dihydroxyphenylglycine Derivatives and the C-Terminal Dipeptide of Vancomycin

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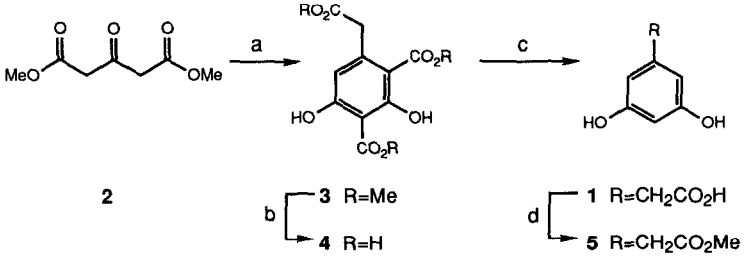
Abstract: Syntheses of optically active 3,5-DMPG and racemic 3,5-DHPG, the latter suitably protected for incorporation into linear peptides modelled on vancomycin, are described and a synthesis of the optically pure protected C-terminal dipeptide of vancomycin is presented.

(S)-3,5-Dihydroxyphenylglycine (3,5-DHPG) is a naturally occurring amino acid found in vancomycin and related glycopeptide antibiotics.[1] No previous synthesis of this amino acid has been reported, although Phadtare *et al* [2] have prepared 3,5-dimethoxyphenylglycine (3,5-DMPG) of undetermined optical purity. In this communication we describe syntheses of optically active 3,5-DMPG and racemic 3,5-DHPG, the latter suitably protected for incorporation into the peptide backbone of linear analogues of vancomycin. In addition, we present an efficient route to the optically pure protected C-terminal dipeptide of vancomycin.

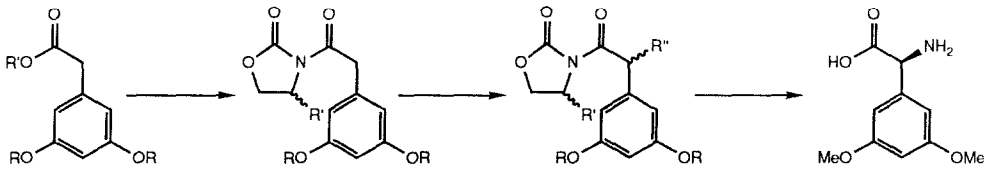
All routes described here to 3,5-DHPG analogues required as starting materials the commercially unavailable 3,5-dihydroxyphenylacetic acid (3,5-DHPA) **1** skeleton . The most direct approach to this precursor involved self-condensation of commercially available dimethyl 1,3-acetonedicarboxylate **2**, hydrolysis of the esters groups of **3**, and decarboxylation of **4**.[3] Subsequent methylation gave 3,5-DHPA methyl ester **5** in 56% overall yield.



Scheme 1: (a) Na, Δ; (b) NaOH, Δ; (c) c.H_2SO_4, Δ; (d) $SOCl_2$, MeOH.

The asymmetric synthesis of (S)-3,5-DMPG **23** (**Scheme 2**) was achieved using the methodology of Evans.[4,5] Sidechain methylation of **5** with dimethyl sulphate and base hydrolysis of the ester **6** occurred in 88% yield. Subsequent attachment of the chiral auxiliary (S)-4-benzyl-2-oxazolidinone to give **12** in 77% yield, proceeded *via* the mixed anhydride **8**, which was generated *in situ*.[4] α-Deprotonation of **12** with

potassium hexamethyldisilazide followed by stereoselective azide transfer from the hindered electrophile 2,4,6-triisopropylbenzenesulphonyl azide [trisyl azide; prepared in quantitative yield from trisyl chloride[6,7]] afforded the chiral azide **15**;[5] hydrogenation of the azide and acid hydrolysis of the oxazolidinone yielded (S)-3,5-DMPG **23,** in >80% optical purity, as determined by chiral GC analysis. Cleavage of the sidechain methyl ethers in either **15** or its precursors was unsuccessful with a variety of reagents (TMSI, (trimethylsilyl iodide), BBr_3, $AlBr_3$/EtSH, NaCN, NaSEt, PhP_2Li, HBr/HOAc), but **23** proved useful as a reference derivative of (S)-3,5-dihydroxyphenylglycine (see below).



5 R=H, R'=Me
6 R=Me, R'=Me
7 R=Me, R'=H
8 R=Me, R'=CO^{t}Bu
9 R=Bn, R'=Me
10 R=Bn, R'=H
11 R=Bn, R'=CO^{t}Bu

12 R=Me, R'=(S)-Bn
13 R=Bn, R'=(S)-Bn
14 R=Bn, R'=(R)-Bn

15 R=Me, R'=(S)-Bn, R''=(S)-N_3
16 R=Bn, R'=(S)-Bn, R''=(S)-NHN_2SO_2Ar
17 R=Bn, R'=(S)-Bn, R''=(S)-N_3
18 R=Bn, R'=(R)-Bn, R''=(R)-Br
19 R=Bn, R'=(R)-Bn, R''=(S)-Br
20 R=Bn, R'=(R)-Bn, R''=(S)-N_3
21 R=Bn, R'=(R)-Bn, R''=(R)-N_3
22 R=H, R'=(R)-Bn, R''=(S)-NH_2

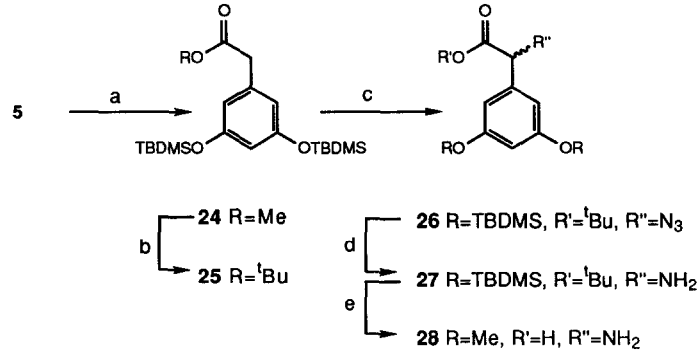
2 3

Scheme 2.

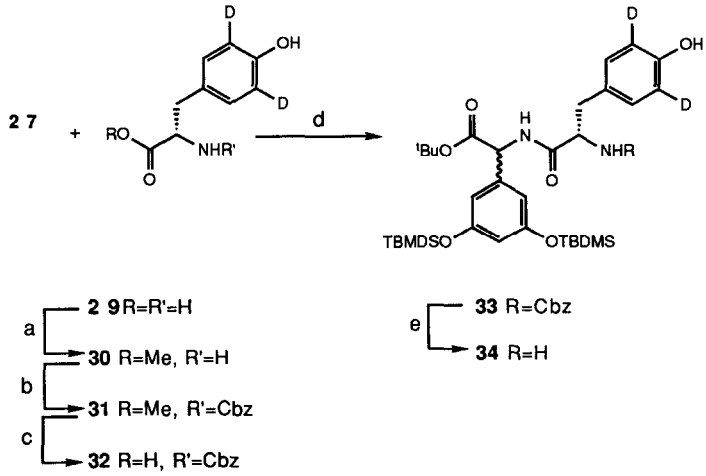
Analogous methodology was followed with the series of compounds bearing benzyl rather than methyl groups on the sidechain phenols (**Scheme 2**). However, treatment of the α-deprotonated (S)-N-acyloxazolidinone **13** with trisyl azide afforded only the triazine **16** which could not be broken down to the desired azide **17**.[7] In an alternative approach, the (R)-N-acyloxazolidinone **14** was treated with di-n-butyl boron triflate in Hünig's base followed by N-bromosuccinimide to give a mixture of the diastereomeric bromides **18** and **19**, which was reacted with tetramethylguanidinium azide to give the chromatographically separable diastereomeric azides **20** and **21**, in 40% and 14% yields respectively.[8] Hydrogenation of the azide **20** gave **22**, (S)-3,5-DHPG bearing a C-terminal oxazolidinone, but coupling of **22** to N-protected tyrosine was unsuccessful, presumably due to interference from the unprotected sidechain phenols.

The synthesis of racemic 3,5-DHPG bearing *tert*-butyldimethylsilyl (TBDMS) phenolic protecting groups and a C-terminal *tert*-butyl ester was accomplished by the sequence presented in **Scheme 3**. TBDMS protection[9] of the phenols, in near quantitative yield, was followed by conversion of the methyl ester **24** to the *tert*-butyl ester **25**, using lithium *tert*-butoxide as a nucleophile. α-Deprotonation of **25** with lithium diisopropylamide and electrophilic azide transfer from trisyl azide was followed by catalytic hydrogenation to give **27**, that is, 3,5-DHPG suitably protected for synthesis of vancomycin peptide analogues, in 57% overall yield from **5** (32% from commercially available starting materials). We note that synthesis of vancomycin analogues requires the use of protecting groups that are labile to either acid, hydrogenation or alternative mild conditions, rather than to base, treatment with which could result in epimerisation of the

hydroxyphenylglycine residues.[10] Sequential treatment of **27** with pyridine:acetic anhydride (1:1), tetra-n-butylammonium fluoride (TBAF), diazomethane and 6M hydrochloric acid at 105°C afforded racemic 3,5-DMPG **28**, which was compared by chiral GC with the product of the asymmetric synthesis of **23**, allowing confirmation of both structure and stereochemistry.



Scheme 3: (a) TBDMSCl, imidazole,DMF; (b) ^{t}BuOLi, toluene, 80°C; (c) LDA, trisyl azide, AcOH, AcOK; (d) H_2/Pd-C; (e) (i) pyridine:acetic anhydride (1:1), (ii) TBAF, (iii) diazomethane, (iv) 6M HCl, 105°C.



Scheme 4: (a) $SOCl_2$, MeOH; (b) $C_6H_5CH_2OCOCl$, $NaHCO_3$; (c) 1M LiOH, THF; (d) EDC, (1-(3 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), HOBt, (1-hydroxybenzotriazole), NMM, (N-methylmorpholine); (e) H_2/Pd-C.

Resolution of the protected 3,5-DHPG racemate **28** by cocrystallisation with chiral acids[11,12] proved

unsuccessful. However, coupling the amine (**27**) to N-protected 3,5-d_2-tyrosine using EDC/HOBt/NMM[13,14] gave the dipeptide **33**, in 89% yield. 3,5-d_2-N-Benzyloxycarbonyltyrosine **32** was prepared from 3,5-d_2-tyrosine **29** in 3 steps *via* the methyl ester **30**. The incorporation on the tyrosine ring of deuterium labels, necessary for intended biosynthetic studies, was achieved according to the method of Matthews *et al.*[15] Catalytic hydrogenation of **33** proceeded in near quantitative yield to give a mixture of diastereomers **34** separable by flash chromotography,[16] using a 0.1-0.5% methanol in chloroform gradient. The absolute configuration of the separated diastereomers was determined by sequential treatment with pyridine:acetic anhydride (1:1), TBAF, diazomethane, and 6M hydrochloric acid at 105°C, followed by chiral GC comparison with the product of the asymmetric synthesis of **23.** By this route, the isolated diastereoisomers of **34** are each available in *ca.* 20% yield from **5**, and hence in *ca.* 11% yield from commercially available starting materials.

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