Enantioselective Synthesis of Dihydrofuranylglycine, Furanylglycine, Furanylalanine and homo-Furanylalanine Derivatives

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Abstract: Enantiomerically pure nor-furanomycin, furanylglycine, furanylalanine and homo-furanylalanine derivatives were prepared from appropriate amino acid derived dienes using ring-closing metathesis as the key step.

Key-words: α-amino acids, ring-closing metathesis, aromatization, enantioselective

There has been considerable interest in the design of new synthetic routes for the preparation of non-proteinogenic α-amino acids and their derivatives for use in biological studies or as chemical building blocks.[1] Although superb asymmetric syntheses are continuously discovered,[2] the transformation of simple coded amino acids into more complex but useful compounds is a rich source of diverse substances.[3] Several amino acid derived building blocks have thus emerged.[4] Amino acid derived aldehydes represent one of such class of valuable synthons. Herein we wish to report new synthetic routes to enantiomerically pure dihydrofuranylglycine, furanylglycine, furanylalanine and homo-furanylalanine derivatives from the appropriate amino acid derived aldehyde as chiron (Figure 1).

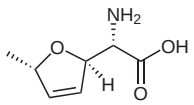
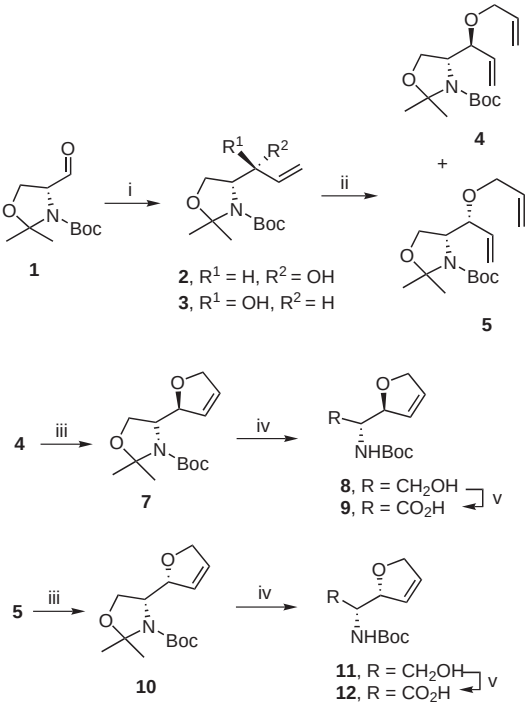


Figure 1 Furanomycin

Over the years, Garner's aldehyde[5,6] has emerged as a versatile reagent for the synthesis of amino acids and related biologically interesting substances.[7,8] We anticipated that the known D-serine derived Garner's aldehyde **1** could serve as an appropriate starting material for the synthesis of the dihydrofuranylglycine ring system present in the important antibiotic substance furanomycin.[9] Thus, addition of vinylmagnesium bromide to **1** (prepared following an improved procedure)[6] proceeded smoothly to provide a separable mixture of the known diastereomeric alcohols **2** and **3** (ca. 3:7, Scheme 1).

The stereochemical outcome of this reaction, although not in favor of the natural configuration in furanomycin, may not prove to be a serious problem since both *syn*- and *anti*-



Scheme 1 *Reagents and conditions*: (i) vinylmagnesium bromide, –78 °C to –20 °C, 1.5 h, 92%; (ii) allyl bromide, *t*-BuOK, DMF, 0 °C, 18 h, 48%; (iii) Grubbs' catalyst **6** (5 mol%), CH_2Cl_2, r.t., 4 h, 75% **7**, 71% **8**; (iv) MeOH–HCl (5%), 0 °C, 0.5 h, 82% **9**, 78% **11**; (v) H_2CrO_4, Et_2O-H_2O, r.t., 2 h, 54% **10**, 51% **12**

selective vinylation of **1** has been developed.[10,11] Accordingly, the mixture of alcohols (**2** and **3**) was treated with allyl bromide to provide the mixture of the corresponding allyl ethers **4** and **5** which could be better separated at this stage. Ring-closing metathesis of the major isomer **4** with Grubbs' catalyst benzylidene bistricyclohexylphosphinoruthenium(IV) dichloride[12] (**6**) smoothly provided the dihydrofuran derivative **7**, $[\alpha]_D$ +13.9 (*c* 1.44, $CHCl_3$), in good yield**.** Deprotection of the oxazolidine unit in the latter under conventional conditions proceeded uneventfully to provide the N-protected amino alcohol derivatives **8** in high yield. Oxidation of this alcohol under biphasic Jones' conditions[13] led to the N-protected dihydrofuranylglycine derivatives **9**. Similarly, from the minor isomer **5**, the epimeric dihydrofuranylglycine derivative **12** was prepared.

Arylglycines constitute an interesting and important class of non-proteinogenic amino acids and a number of aryl- and heteroarylglycine derivatives have been prepared[14]

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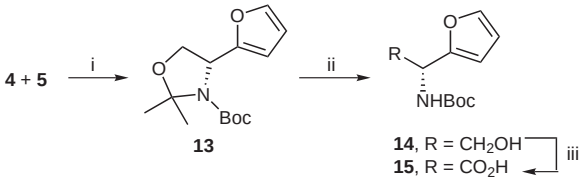
for various reasons. Furanylglycine derivatives have also been prepared[15] through a creative application of enzymatic resolution. Althouh separate aromatization of the dihydrofuran derivatives **7**–**12** at any stage would lead to the corresponding aromatic compounds, a one-pot ring-closing metathesis and aromatization protocol was developed following our related work.[16] Thus, treatment of the mixture of the epimeric ethers **4** and **5** with Grubbs' catalyst **6** and then with DDQ in a one-pot manner directly provided the furanylglycine derivative **13** in 56% yield (Scheme 2). Deprotection of the oxazolidine unit in the latter neatly provided the amino alcohol **14**, which on oxidation provided the protected furanylglycine derivative **15**.

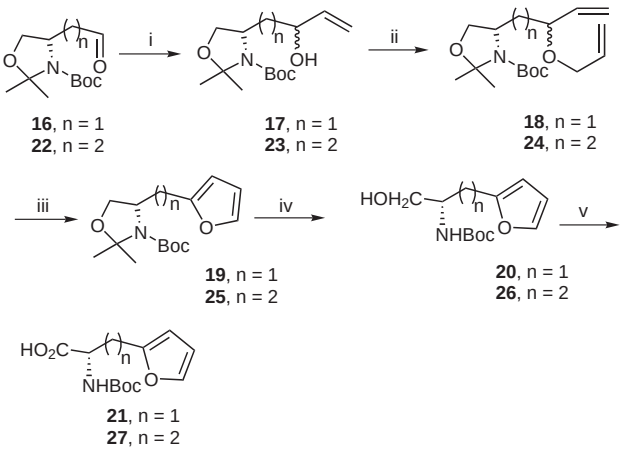


Scheme 2 *Reagents and conditions*: (i) Grubbs' catalyst **6** (5 mol%), CH_2Cl_2, r.t., 4 h, then DDQ, benzene, reflux, 16 h, 56% over two steps (ii) MeOH–HCl (5%), 0 °C, 0.5 h, 82%; (iii) H_2CrO_4, Et_2O–H_2O, r.t., 2 h, 49%

The aspartic acid derived chiral aldehyde **16** (Scheme 3), prepared following the established methodology,[17] on treatment with vinylmagnesium bromide furnished a mixture (ca. 1:1) of the epimeric allylic alcohols **17** which were not separated. The lack of stereocontrol in the vinylation is not important as subsequent aromatization removes the stereocenter. This mixture was then alkylated with allyl bromide to provide the corresponding ethers **18** which when subjected to the developed one-pot RCM–aromatization sequence provided the protected furanylalanine derivative **19**, $[\alpha]_D$ +6.5 (*c* 0.75, CH_2Cl_2). Deprotection of the latter to the aminoalcohol **20** followed by its oxidation led to the *N*-Boc-furanylalanine **21**.

Similarly, the glutamic acid derived aldehyde **22**, prepared analogously, when subjected to the same sequence of reactions viz. vinylation to the epimeric allyl alcohols **23**, etherification of the latter to the mixture of the epimeric allyl ethers **24**, one-pot ring-closing metathesis–aromatization to the furan derivative **25** followed by its sequential deprotection (leading to **26**) and oxidation led to the N-protected homo-furanylalanine **27** in an overall yield of 10.7% over five steps.[18]

In short, we have demonstrated that optically pure dihydrofuranylglycine, furanylglycine, furanylalanine and homo-furanylalanine derivatives could be conveniently prepared from enantiomerically pure aldehydes derived from serine, aspartic acid and glutamic acid using a novel one-pot RCM–aromatization reaction as the key step. The prepared compounds may find application in chemistry and biology.



Scheme 3 *Reagents and conditions*: (i) vinylmagnesium bromide, –78 °C to –20 °C, 1.5 h, **17**, 78%; **23**, 92%; (ii) allyl bromide, *t*-BuOK, DMF, 0 °C to r.t., 18 h, **18**, 52%; **24**, 57%; (iii) Grubbs' catalyst **6** (5 mol%), CH_2Cl_2, r.t., 4 h, then DDQ, benzene, reflux, 16 h, **19**, 54%; **25**, 57%; (iv) MeOH–HCl (5%), 0 °C, 0.5 h, **20**, 82%; **26**, 78%; (v) H_2CrO_4, Et_2O–H_2O, r.t., 2 h, **21**, 46%; **27**, 49%

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Experimental Procedure for the One-Pot RCM and DDQ Oxidation.

Grubbs' catalyst **6** (5 mol%) was added under argon atmosphere to a solution of **18** (62 mg, 0.2 mmol) in dry degassed CH_2Cl_2 (10 mL) and the resulting mixture was stirred at r.t. for 4 h. A solution of DDQ (91 mg, 0.4 mmol) in benzene (16 mL) was then added and the resulting mixture was heated to reflux for 16 h. Evaporation of the solvent in vacuo followed by chromatography of the residual mass on silica gel using 5% EtOAc–petroleum ether afforded **19** as a viscous liquid (30 mg, 54%). $[\alpha]_D$ +6.5 (*c* 0.75, CH_2Cl_2). IR (neat): 2979, 1699, 1390, 1366 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.31 (1 H, s), 6.27 (1 H, s), 6.04 (1 H, d, *J* = 4.1 Hz), 4.14 (1 H, d, *J* = 5.8 Hz), 4.03 (1 H, d, *J* = 4.2 Hz), 3.88–3.86 (2 H, m), 3.12 (1 H, d, *J* = 14.3 Hz), 3.01 (1 H, d, *J* = 14.3 Hz), 2.85–2.77 (2 H, m), 1.48 (s, 9 H), 1.24 (6 H, merged s). MS (TOF MS ES+): *m/z* = 304 $[M^+ + Na]$. Anal. Calcd for $C_{15}H_{23}NO_4$ (%): C, 64.0; H, 8.2; N, 5.0. Found: C, 64.3; H, 8.4; N, 4.8.