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TETRAHEDRON: *ASYMMETRY*

# Chiral (*Z*)-α,β-didehydroamino acid derivatives from a new chiral glycine equivalent with a 1,2,3,6-tetrahydropyrazin-2-one structure: applications to the synthesis of 1-amino-cyclopropanecarboxylic acids and bicyclic α-amino acids

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**Abstract**

The new chiral glycine equivalent **9**, easily obtained from (+)-α-aminoisovalerophenone and glycine, afforded chiral (*Z*)-α,β-didehydroamino acid (DDAA) derivatives **13** and **14** with a 1,2,3,6-tetrahydropyrazin-2-one structure. Compounds **13** and **14** were synthesised by reaction of **9** with Eschenmoser's salt and by condensation reactions with aldehydes or acetone under PTC conditions, respectively. The diastereoselective cyclopropanation of **14**, followed by hydrolysis, furnished (−)-*allo*-norcoronamic acid with high ee, whilst diastereoselective Diels–Alder reaction of dienophile **13** and cyclopentadiene afforded, after double bond hydrogenation and hydrolysis, (−)-2-aminonorbornane-2-carboxylic acid. 

α,β-Didehydroamino acids (DDAAs) are conformationally constrained non-proteinogenic amino acids. As components of biologically natural peptides with potent antimicrobial and phytotoxic activities, they also restrict the conformation and enhance the resistance to enzymatic and chemical degradation.[1] DDAAs are also important building blocks for the synthesis of biologically active cyclic amino acids such as 1-aminocyclopropanecarboxylic acids (ACCs) and bicyclic α-amino acids. ACCs are biosynthetic precursors of plant hormones, act as enzyme inhibitors and play an important role in the regulation of enzymatic processes in plants.[2] These cyclic amino acids, also called 2,3-methanoamino acids, are mainly obtained from chiral DDAA derivatives such as **1**–**6** by cyclopropanation reactions, through a 1,3-dipolar cycloaddition reaction with diazomethane[3a,4,5] and by Michael addition of sulfoxonium[4,6a,b,7] or phosphonium ylides.[8] The best diastereoselectivities were achieved when sulfoxonium ylides reacted with enantiomerically pure (*E*)-**2**,[4] (*Z*)-**5**[7] or (*Z*)-**6**[6a,b] DDAA oxazinone derivatives. On the other hand, bicyclic α-amino acids are interesting molecules from the pharmaceutical and biological point of view. For instance, 2-aminonorbornane-2-carboxylic

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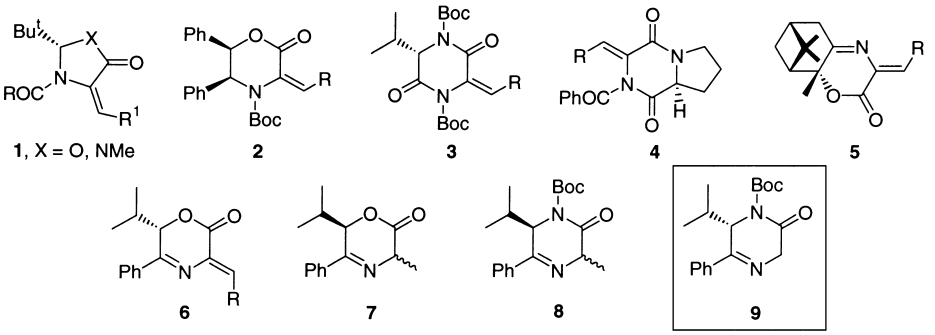
acids inhibit the transport of non-polar amino acids across cell membranes, act as an insulin-releasing factor and inhibit the flavoprotein amino acid oxidases.[9] For their diastereoselective preparation chiral α-alkylideneoxazolidinones **1**[10] (and related structures) and chiral α-alkylideneoxazinone **6**[6b,c] have been used as dienophiles in a non-catalysed process, while acyclic didehydroalanine derivatives,[11] as well as chiral and non-chiral oxazolones,[12] have been tested under a catalysed cycloaddition reaction.

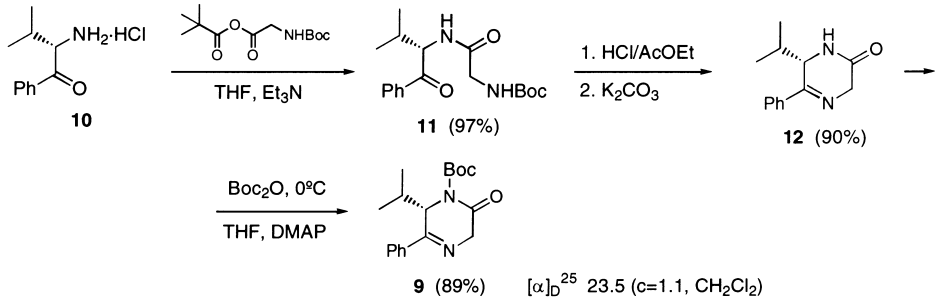
Direct syntheses of cyclic chiral (*E*)- or (*Z*)-DDAA derivatives **1**–**5** have been achieved by condensation of their corresponding glycine enolates with aldehydes under strong basic conditions and very low temperatures (for compounds **3**[13] and **5**[3,7]), by Horner–Wadsworth–Emmons olefination (for products **1**[14] and **2**[4]) or by chemical transformations of (*Z*)-alkylideneoxazolones (for compound **4**[5]). Milder reaction conditions (PTC, $K_2CO_3$ and acetonitrile at room temperature) have recently been used by our group for the synthesis of oxazinone derivatives **6**.[6a,b] However, moderate yields have been obtained due to the sensitivity shown by these DDAA derivatives to acidic or basic aqueous media and silica gel chromatography.




According to this experimental fact, and considering the similar chemical behaviour reported between oxazinone **7**[15] and tetrahydropyrazin-2-one **8**,[16] we have prepared a new chiral glycine template *N*-Boc-(*S*)-6-isopropyl-5-phenyl-1,2,3,6-terahydropyrazin-2-one **9** for the asymmetric synthesis of novel chiral (*Z*)-DDAA derivatives by a Knoevenagel-type condensation under mild reaction conditions. In addition, the diastereoselectivity of cyclopropanation and Diels–Alder reaction with sulfoxonium ylides and cyclopentadiene, respectively, was also studied.

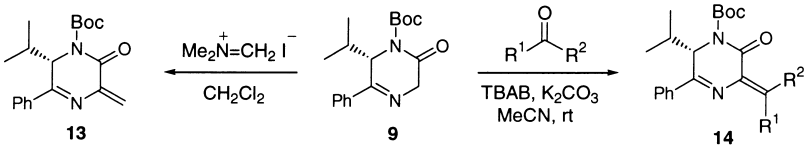
The starting *N*-Boc protected pyrazin-2-one **9** was prepared following the same methodology previously described for the synthesis of compound **8**.[16] Chiral auxiliary α-aminoketone hydrochloride **10**,[17,18] obtained in 70% overall yield from (*S*)-valine, underwent *N*-acylation with the *N*-Boc-glycine pivalic acid mixed anhydride obtaining amide **11** in 97% yield. After deprotection in acidic media and cyclisation using a saturated aqueous solution of potassium carbonate, pyrazinone **12** was obtained in 90% yield. Final *N*-Boc protection of heterocycle **12** was carried out with di-*tert*-butyl dicarbonate at 0°C in the presence of catalytic amounts of 4-*N,N*-dimethylaminopyridine (DMAP) furnishing pyrazin-2-one **9** in 89% yield (Scheme 1).

The condensation reaction of **9** with aldehydes (2.5 equiv.) and acetone (2.5 equiv.) took place under solid–liquid phase transfer catalysis with $K_2CO_3$ (3 equiv.) and tetra-*n*-butylammonium bromide (TBAB, 0.1 equiv.) in dichloromethane at room temperature (Scheme 2 and Table 1). All tested aldehydes reacted with potassium carbonate except benzaldehyde, where a 1:1 mixture of $Na_2CO_3$ and $K_2CO_3$ was required in order to avoid partial isomerisation of double bonds to all *endo* conjugated position (Table 1, entry 5). DDAA derivatives **14** were obtained in >98% de and as single (*Z*)-diastereoisomers in good yields after chromatographic purification without any




Scheme 1.

significant decomposition. It is noticeable that the condensation reaction of **9** with acetone took place in 51% yield (Table 1, entry 6). To date, the condensation reaction of the precursor of **5** with acetone in 10% yield is the only example of condensation reaction with ketones reported in the literature.[3a] For the preparation of the corresponding didehydroalanine derivative, Eschenmoser's salt (2 equiv.) reacted with **9** in dichloromethane at room temperature for 4 h (Scheme 2 and Table 1, entry 1) affording directly dehydroalanine derivative **13**.




Scheme 2.

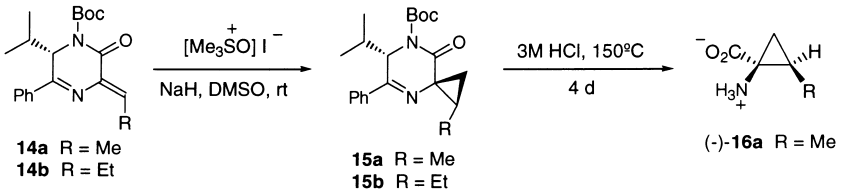
Table 1
Synthesis of chiral (*Z*)-α,β-didehydroamino acid derivatives **13** and **14**

| Entry | $R^1$ | $R^2$ | Reaction time (h) | no. | Yield[a] | $[\alpha]_D^{25}$ [b] | $R_f$ [c] |
|---|---|---|---|---|---|---|---|
| 1 | H | H | 4 | **13** | 88 | -119.0 | 0.74 |
| 2 | Me | H | 20 | **14a** | 88 | -101.3 | 0.70 |
| 3 | Et | H | 20 | **14b** | 86 | -179.0 | 0.83 |
| 4 | Bu$^t$ | H | 48 | **14c** | 47 | -90.8 | 0.77 |
| 5 | Ph | H | 20 | **14d**[d] | 87 | -156.8 | 0.67 |
| 6 | Me | Me | 20 | **14e** | 51[e] | 59.5 | 0.75 |

[a] Based on 2-pyrazinone **9** after flash silica gel chromatography. All products showed satisfactory spectroscopic data (IR, $^1$H and $^{13}$C NMR, and MS). [b] In dichloromethane. [c] *n*-Hexane/ethyl acetate:3/2. [d] A 1:1 mixture of $Na_2CO_3$ and $K_2CO_3$ was used. [e] Based on 2-pyrazinone **12** after flash chromatography.

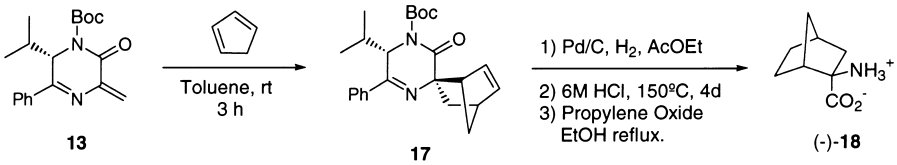
Configurational assignments were made from $^1$H NMR data (300 MHz, $CDCl_3$) obtained from crude reaction product. Olefinic protons ranging between 6.74 and 7.00 ppm belong to (*Z*)-isomers whilst (*E*)-isomer protons are shifted upfield (6.48–6.73 ppm). Moreover, C–H coupling constants between olefinic protons and carbonylic carbon (close to 5 Hz) in proton-coupled $^{13}$C NMR are consistent with the (*Z*)-configuration.[3b,6] Several attempts were made using stronger bases (Bu$^n$Li, LHMDS, LDA, Bu$^t$OLi, Bu$^t$OK) at lower temperatures in order to invert the stereochemistry of alkene **14**, but almost 1:1 mixtures of diastereoisomers were achieved in all cases.

The reaction of **14a** and **14b** with Corey's dimethylsulfoxonium methylide,[19,20] which was generated in situ from trimethylsulfoxonium iodide and sodium hydride in DMSO, took place in 1 h at room temperature affording spiro-compounds as 11:1 and 23:1 mixtures of diastereoisomers, respectively, determined by GC, $^{1}H$ and $^{13}C$ NMR spectroscopy (Scheme 3). Pure major isomers **15a** and **15b** were isolated after flash chromatography in 70% and 79% yields, respectively. When using DMF instead of DMSO as solvent at −20°C an improvement of the diastereoselectivity was observed. Product **15a** was submitted to acidic hydrolysis (3 M hydrochloric acid, 150°C for 4 d) to provide (−)-*allo*-norcoronamic acid (−)-**16a**[6a,b] in enantiomerically pure form (>98% ee) in 24% yield (Scheme 3).




Scheme 3.

When DDAA derivative **13** was tested as dienophile in Diels–Alder cycloaddition reaction with cyclopentadiene at room temperature for 3 h, the adduct **17** was isolated in 42% yield after flash chromatography as a single diastereoisomer. The probable structure of *endo*-adduct **17**[21] could not be determined by X-ray diffraction analysis. Its stereochemistry was confirmed after generation of bicyclic α-amino acid (−)-**18**,[6b,c] which was isolated, after hydrogenation (Pd/C in EtOAc at rt) followed by acidic hydrolysis, in 84% overall yields and >98% ee (Scheme 4).




Scheme 4.

In conclusion, the synthesis of a new chiral glycine template **9** and its DDAA derivatives with pyrazinone structure have been prepared in better yields than related oxazinones **6**. The obtained enantiomerically pure (*Z*)-DDAA derivatives from aldehydes were diastereoselectively cyclopropanated with Corey's ylide with better de and higher yields than the oxazinones **6**. Hydrolysis of spiro-compound **15a** afforded (−)-*allo*-norcoronamic acid. Diels–Alder reaction with cyclopentadiene took place with *endo*-selectivity under similar conditions as oxazinones to give (−)-2-aminonorbornane-2-carboxylic acid. Further work to exploit the synthetic uses of these heterocycles is underway.

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21. Cyclic dehydroalaninates with oxazolidinone structure **1** (X = O) reacted with cyclopentadiene with *exo*-selectivity.[10]