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Asymmetric synthesis of substituted 1-aminocyclopropane-1-carboxylic acids from a new chiral glycine equivalent with 3,6-dihydro-2*H*-1,4-oxazin-2-one structure[†]

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Abstract

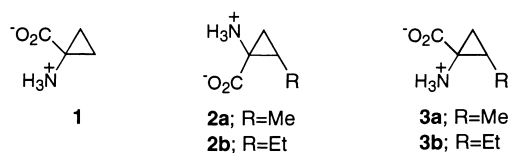
Condensation of the new chiral glycine equivalent **10** with aldehydes at room temperature in the presence of K₂CO₃ under solid–liquid phase-transfer-catalysed conditions afforded stereoselectively new chiral (*Z*)- α,β -didehydroamino acid (DDAA) derivatives with oxazinone structure **14**. These systems have been used in diastereoselective cyclopropanation reactions for the synthesis of enantiomerically pure 1-aminocyclopropanecarboxylic acids (ACCs) such as (–)-*allo*-norcoronamic and (–)-*allo*-coronamic acids. © 1998 Elsevier Science Ltd. All rights reserved.

1-Aminocyclopropane-1-carboxylic acids (ACCs), also referred to as 2,3-methanoamino acids, constitute an important family of conformationally constrained α -amino acids because of their biological activity and as components of peptides, being present in nature in the unbound form or as simple dipeptides.¹ The parent compound (ACC, **1**), a biosynthetic precursor of the plant hormone ethylene² and ammonia and 2-ketobutyrate in *Pseudomonas*,³ is a non-chiral compound but other important ACCs have two stereogenic centers with *cis* and *trans* (or *Z* and *E*) relative configuration. Some representative naturally occurring ACCs are coronamic acid **2b**, an inhibitor of certain ACC-metabolizing enzymes including ethylene forming enzyme (EFE) (isolated by hydrolysis of the vivotoxin coronatin)^{1b,2} and also *allo*-norcoronamic **3a** and *allo*-coronamic **3b** acids, which play an important role in the control of enzymatic processes for plant growth and fruit ripening.^{1b,3,4}

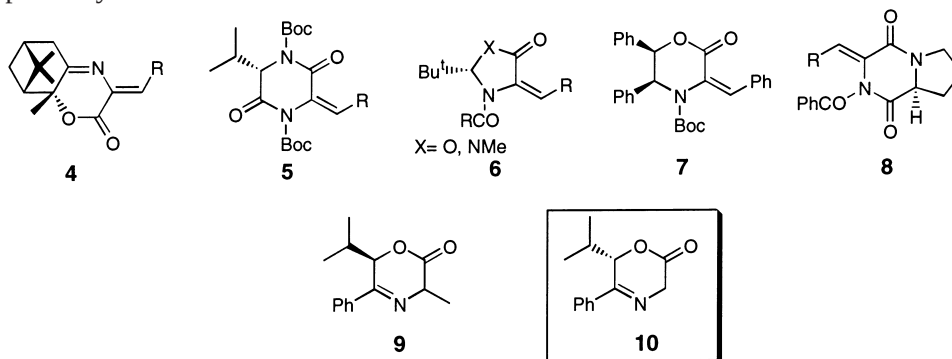
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[†] Dedicated to the memory of Professor Antonino Fava.

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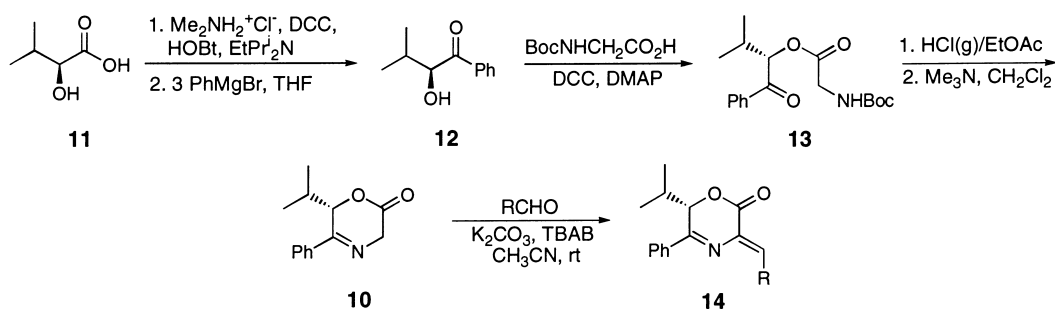
The synthetic challenge in the preparation of ACCs lies in controlling the relative and absolute stereochemistry in the cyclopropane ring. Some developed syntheses are based on naturally occurring chirons by several step procedures.^{1b,5} However, the most direct synthetic strategy for creating the two required stereogenic centers involves the transformation of a chiral glycine equivalent into chiral α,β -didehydroamino acid (DDAA) derivatives,⁶ followed by a diastereoselective cyclopropanation reaction. The preparation of chiral DDAA derivatives also requires the control of the stereochemistry of the carbon–carbon double bond, which has been achieved: (a) by direct condensation with aldehydes under strong basic conditions (Bu^tOK) and a very low reaction temperature for the pinanone derivative **4**^{7a–c} and diketopiperazine **5**^{7d} giving *Z*- and *E*-derivatives respectively with low diastereoselectivity; (b) by Horner–Wadsworth–Emmons olefination of phosphonate derivatives for imidazolidinones **6**^{7e,f} and oxazinones **7**;^{7g} and (c) by transformation of (*Z*)-alkyldienoxazolones into chiral diketopiperazines **8**.^{7h} The cyclopropanation of some of these DDAA derivatives has been carried out by: (a) 1,3-dipolar addition of diazomethane with low diastereoselectivity in the case of compounds **4**,^{7a,b} **7**,^{7g} and **8**;^{7h} and (b) Michael addition of sulfoxonium^{7c,g} or phosphonium ylides⁸ in the case of **4**^{7c} and **7**,^{7g} or **6**⁸ ($\text{X}=\text{O}$), respectively.



We have previously reported the synthesis of a new iminic alanine chiral template with 3,6-dihydro-2*H*-1,4-oxazin-2-one structure **9**.⁹ This heterocycle can be alkylated with high diastereoselectivity at room temperature either under solid–liquid phase-transfer catalysis using K_2CO_3 as base, or by palladium-catalysis under neutral conditions allowing after hydrolysis the asymmetric synthesis of (*S*)- α -methyl- α -amino acids. In this communication we describe the preparation of enantiomerically pure 1,4-oxazin-2-one **10**, a new glycine equivalent for the asymmetric synthesis of ACCs after diastereoselective cyclopropanation of new chiral (*Z*)-DDAA derivatives prepared by a Knoevenagel-type condensation under very mild reaction conditions.

Starting oxazinone **10** was prepared in 56% overall yield by 1,3-dicyclohexylcarbodiimide (DCC)-mediated reaction of (*S*)-2-hydroxyisovalerophenone **12**¹⁰ with *N*-Boc-glycine to give ester **13**, followed by deprotection of the Boc group and subsequent treatment with a CH_2Cl_2 solution of Me_3N . The synthesis of the chiral auxiliary **12** was carried out in 53% overall yield from (*S*)-2-hydroxyisovaleric acid¹¹ **11** by amidation with dimethylamine hydrochloride under DCC-1-hydroxy-1*H*-benzotriazole (HOBt) conditions,¹² followed by addition of 3 equiv. of phenylmagnesium bromide (Scheme 1).

The reaction of oxazinone **10** with aldehydes was carried out under solid–liquid phase transfer catalysis



Scheme 1.

Table 1

Synthesis of chiral α,β -didehydroamino acid derivatives **14**

entry	R	no. ^a	reaction time (h)	yield ^b (%)	$[\alpha]_D^{25,c}$	mp ^d (°C) or R_f^e
1	Me	14a	12	50	-477.2 (c, 1)	111–112
2	Et	14b	12	55	-417.4 (c, 2)	0.55
3	Pr ⁱ	14c	12	63	-381.8 (c, 1)	0.65
4	Bu ^t ^f	14d	40	62	-277.6 (c, 0.7)	0.66
5	Ph	14e	8 ^g	64	-800.0 (c, 0.95)	0.54

^a All products were pure (300 MHz ^1H NMR, GC) and gave satisfactory spectral data (IR, ^1H and ^{13}C NMR and MS). ^b Isolated yield after flash chromatography (silica gel) based on compound **10**; partial decomposition was observed. ^c Measured in CH_2Cl_2 . ^d From hexane/EtOAc. ^e Hexane/EtOAc: 7/3. ^f 2 Equiv of pivalaldehyde were used. ^g The reaction was carried out at 0°C.

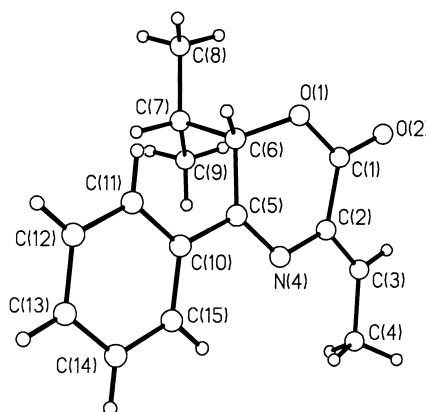
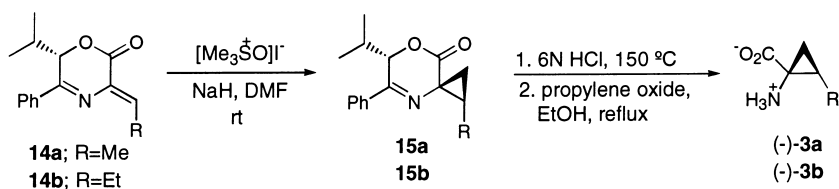
in the presence of K_2CO_3 (3 equiv.) and tetrabutylammonium bromide (TBAB, 0.1 equiv.) in CH_3CN at room temperature. The (*Z*)-DDAA derivatives **14** were thus stereoselectively obtained in >96% diastereomeric excess (^1H NMR, 300 MHz) independently of the substitution on the aldehyde, the pure *Z*-isomers being isolated after flash chromatography (see Scheme 1 and Table 1).

Configurational assignments were made from ^1H NMR spectra (300 MHz, CDCl_3) of crude *Z/E* diastereomeric mixtures, with chemical shifts for the olefinic protons ranging between 6.74 and 7.00 ppm for *Z*-isomers and lower values of 6.48–6.73 ppm for *E*-isomers, and also from the vicinal CH coupling constants close to 5 Hz in proton-coupled ^{13}C NMR which are typical of a *Z*-configuration.^{7b} The stereochemical assignment was unequivocally established for **14a** by X-ray crystallographic analysis¹³ (Fig. 1).

Treatment of **14a** and **14b** with Corey's dimethylsulfoxonium methylide,¹⁴ prepared with NaH in DMF, over 1 h at room temperature afforded *ca.* 9:1 mixture of diastereomers (determined by GC and ^1H NMR) the major ones **15a** and **15b** being isolated after flash chromatography (silica gel) in 52 and 63% yield, respectively (Scheme 2). When the cyclopropanation reaction was carried out at -55°C in DMF similar diastereoselectivities were observed.

This methodology was applied to the synthesis of (–)-*allo*-norcoronamic (–)-**3a** and (–)-*allo*-coronamic (–)-**3b** acids. Thus, spirocyclic compounds **15** were hydrolysed with 6 N HCl at 150°C (pressure tube) for 1 day and, after treatment of the corresponding hydrochlorides with propylene oxide, the free amino acids (–)-**3a**¹⁵ and (–)-**3b**¹⁶ were obtained in 60 and 67% yield, respectively (Scheme 2).

In conclusion, we have found that glycine-derived oxazinone **10** is a good precursor for the stereoselective synthesis of new enantiomerically pure (*Z*)-DDAA derivatives by simple condensation with aldehydes under solid–liquid phase-transfer catalysis at room temperature. These DDAA derivatives can

Fig. 1. X-Ray crystal structure of **14a**

Scheme 2.

be easily cyclopropanated affording, after hydrolysis, enantiomerically pure ACCs. Studies about further synthetic uses of these new chiral DDAA derivatives are underway.

Acknowledgements

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