New Chiral Didehydroamino Acid Derivatives from a Cyclic Glycine Template with 3,6-Dihydro-2*H*-1,4-oxazin-2-one Structure: Applications to the Asymmetric Synthesis of Nonproteinogenic α-Amino Acids

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New chiral (*Z*)-α,*β*-didehydroamino acid (DDAA) derivatives with 3,5-dihydro-2*H*-1,4-oxazin-2-one structure **11a**−**f** have been stereoselectively prepared after condensation of chiral glycine equivalent **7** with aldehydes in the presence of K_2CO_3 under mild solid−liquid phase-transfer catalysis reaction conditions. These new systems have been used in diastereoselective cyclopropanation reactions using Corey's ylide for the asymmetric synthesis of 1-aminocyclopropane-1-carboxylic acids (ACCs) such as *allo*-corononamic and *allo*-norcoronamic acids. The hydrogenation reaction of these systems at ambient pressure in the presence of formaldehyde affords saturated oxazinones and *N*-methylated oxazinones which have been transformed into the *N*-methyl-α-amino acids (*N*-MAAs) (*S*)-2-(methylamino)butanoic acid and (*S*)-*N*-methylleucine. In addition, the parent α,*β*-didehydroalanine derivative **11g** has been prepared by a direct aminomethylation−elimination sequence from **7** and Eschenmoser's salt and has been used in Diels−Alder cycloaddition with *endo* selectivity for the synthesis of the enantiomerically pure bicyclic α-amino acids (−)-2-aminobicyclo[2.2.1]heptane-2-carboxylic and (−)-2-aminobicyclo[2.2.2]octane-2-carboxylic acids.

Introduction

α,*β*-Didehydro-α-amino acids (DDAAs) constitute a family of conformationally constrained amino acids found in many biologically active natural peptides.[1] Their presence in peptide chains enhances resistance to enzymatic and chemical degradation.[2] Chiral DDAA derivatives are versatile intermediates in the synthesis of a variety of α-amino acids. For example, the asymmetric hydrogenation of chiral DDAA derivatives has been used for the synthesis of enantiomerically enriched monoalkylated α-amino acids,[3] and the diastereoselective cyclopropanation with diazoalkanes[4] and phosphonium[5] or sulfoxonium ylides[4a,6] leads to important 1-aminocyclopropane-1-carboxylic acids (ACCs).[7] The carbon−carbon double bond is active in ene reactions, hydrogenation, nucleophilic or radical additions,[3] Heck coupling with aryl halides,[8] and as a dienophile in asymmetric Diels−Alder cycloaddition reactions for the preparation of bicyclic α-amino acids with interesting biological activities.[9]

Several chiral DDAA derivatives have been previously described showing *E* (**1**,[10] **2**[4a]) and *Z* (**3**,[11] **4**,[4f] **5**,[4b,c,6]) configuration. Their preparation has been achieved (a) by direct condensation with aldehydes under strong basic conditions (*t*-BuOK) and very low reaction temperature for the pinanone derivative **5**[4b,c,6] and diketopiperazine **3**[11] giving *Z*-derivatives, respectively, with low diastereoselectivity, (b) by Horner−Wadsworth−Emmons olefination of phosphonate derivatives for imidazolidinones **1**[10b] and oxazinones **2**,[4a] and (c) by transformation of (*Z*)-alkylidenoxazolones into diketopiperazines **4**.[4f]

The cyclopropanation of some of these chiral DDAA derivatives has been carried out by (a) 1,3-dipolar cycloaddition of diazomethane with rather low diastereo-

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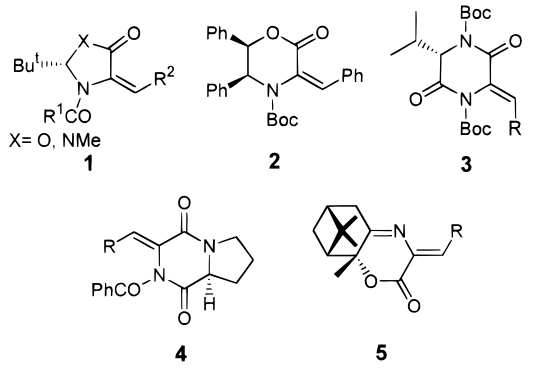
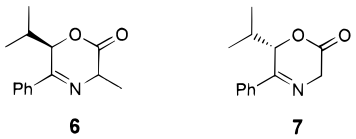
selectivity in the case of compounds **2**,[4a] **4**,[4f] and **5**,[4b,c] and (b) Michael addition of sulfoxonium[4a,6] or phosphonium[5] ylides in the case of compounds **1** (X = O) and **2**[6] or **5**,[4a]



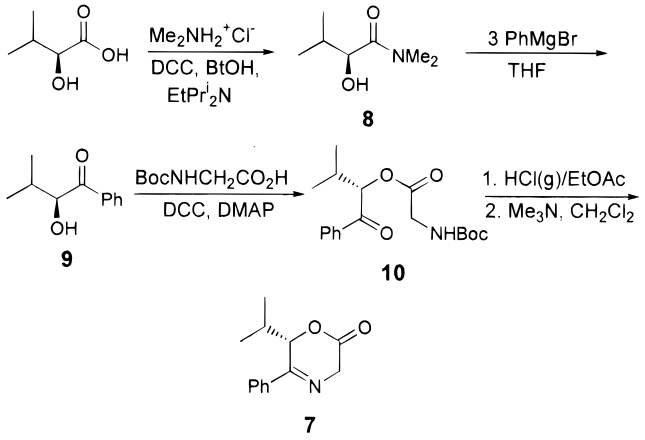
respectively. In addition, the diastereoselective hydrogenation of chiral DDAA derivatives has been studied on diketopiperazine derivatives **3**[11] and **4**[3a] and also on cyclic imino esters **5**.[4c] Diastereoselective Diels−Alder reactions have been carried out using oxazolidinones **1** (X = O, R^2 = H) or related,[12] chiral acyclic didehydroalanine derivatives[13] or even nonchiral systems employing chiral catalysts.[13]

All these antecedents suggest that the development of synthetically useful chiral DDAA derivatives by means of a simple and stereoselective direct condensation reaction between a chiral glycine equivalent and carbonyl compounds under mild reaction conditions should be desirable.

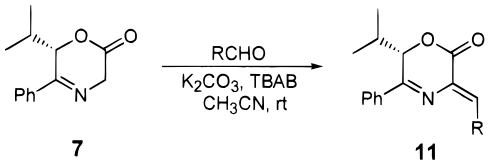
We have recently reported the synthesis of a new iminic alanine chiral template with the 3,6-dihydro-2*H*-1,4-oxazin-2-one structure **6** prepared from α-bromoisovalerophenone and (*S*)-alanine.[14] This heterocycle can be alkylated with high diastereoselectivity at room temperature under a variety of mild reaction conditions, such as phase-transfer or palladium(0) catalysis or using organic bases giving rise to an asymmetric synthesis of α-methyl-α-amino acids. In the present paper we describe the stereoselective synthesis of new chiral (*Z*)-DDAA derivatives from an enantiomerically pure glycine equivalent **7** with an analogous 1,4-oxazin-2-one structure.[15] The synthetic applications of these new chiral DDAA derivatives in diastereoselective cyclopropanation,[15] hydrogenation, and Diels−Alder[16] reactions are also studied.



Scheme 1



Scheme 2



Results and Discussion

Starting chiral (*S*)-oxazinone **7** was prepared by reaction between (*S*)-2-hydroxyisovalerophenone **9** and *N*-Boc-glycine in the presence of 1,3-dicyclohexylcarbodiimide (DCC) to give the chiral ester **10**. Further deprotection of the Boc group and subsequent treatment with a CH_2Cl_2 solution of Me_3N afforded oxazine **7** in 56% overall yield. The synthesis of the chiral auxiliary **9** was carried out from (*S*)-2-hydroxyisovaleric acid[17] by amidation with dimethylamine hydrochloride under DCC-1-hydroxy-1*H*-benzotriazole (HOBt) conditions,[18] followed by addition of 3 equiv of phenylmagnesium bromide (Scheme 1) (53% overall yield).

The reaction of (*S*)-oxazinone **7**[19] with aldehydes was carried out under solid−liquid-phase transfer catalysis (PTC) conditions using K_2CO_3 (3 equiv) as base and tetrabutylammonium bromide (TBAB, 0.1 equiv) as phase transfer reagent in CH_3CN as solvent at room temperature, yielding stereoselectively the (*Z*)-DDAA derivatives **11** in 96% diastereomeric excess independently of the substitution on the aldehyde, the pure *Z*-isomers being isolated after flash chromatography (see Scheme 2 and Table 1). In the case of the condensation of **7** with benzaldehyde (see Table 1, entry 5), the reaction was carried out at 0 °C for ca. 8 h in order to avoid partial isomerization of the double bonds to an all-*endo* conjugated position. When the condensation reaction was carried out using ketones such as acetone or benzophenone, the reaction failed and only partial decomposition of the starting oxazinone was observed.

Configurational assignments were made from ^{1}H NMR spectra (300 MHz, $CDCl_3$) of crude *Z*/*E* diastereomeric

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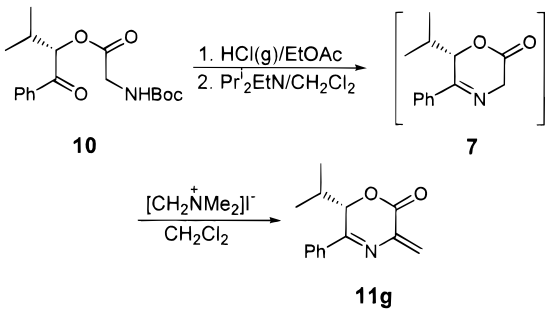
(19) The *S*-configuration of compound **7** is the appropriate for the preparation of *S*-amino acids.

Table 1. Synthesis of Chiral α,β-Didehydroamino Acid Derivatives 11

entry	R	no.	reaction time (h)	yield[a] (%)
1	Me	**11a**	12	50
2	Et	**11b**	12	55
3	i-Pr	**11c**	12	63
4	*t*-Bu[b]	**11d**	40	62
5	Ph	**11e**	8[c]	64
6	*N*-Boc-2-indolyl	**11f**	24	60

[a] Isolated yield after flash chromatography (silica gel) based on **7**; partial decomposition was observed. [b] 2 equiv of pivalaldehyde were used. [c] The reaction was carried out at 0 °C.

Scheme 3



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 is typical of a *Z*-configuration.[4c] The assignment of the *Z* stereochemistry was unequivocally stablished for **11a** by X-ray crystallographic analysis.[15]

Attempted preparation of the methylenic DDAA derivative **11g** (**11**, R = H) by condensation of oxazinone **7** with aqueous or organic solutions of formaldehyde under different basic reaction conditions proved sluggish, and very low yields of **11g** were detected. However, an in situ procedure was developed consisting of treatment of the hydrochoride obtained from deprotection of **10** with diisopropylethylamine, followed by addition of *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) (Scheme 3). Thus, the chiral α,β-didehydroalanine derivative **11g** was obtained in 50% isolated yield after this one-pot cyclization−aminomethylation−elimination process, crude purity being high enough for synthetic purposes (>90% by GLC and 300 MHz ^{1}H NMR).[16]

Corey's dimethylsulfoxonium methylide,[20] prepared with NaH in DMF, was the less toxic and safest reagent to carry out the stereoselective cyclopropanation[21] of DDAA derivatives **11**. Upon treatment of **11a** and **11b** with this ylide during 1 h at room temperature, a ca. 9:1 mixture of diastereomers (determined by GC and ^{1}H NMR) was obtained, the major diastereomers **12a** and **12b** being isolated after flash chromatography in 52 and 63% yield, respectively (Scheme 4). When the cyclopropanation reaction was carried out at −55 °C in DMF, similar diastereoselectivities were observed. The configuration of compounds **12** was unequivocally stablished by X-ray diffraction analysis of **12b**[22] (Figure 1). The

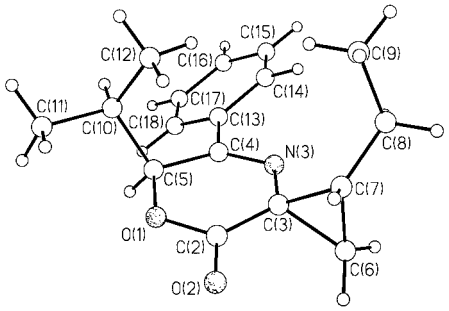
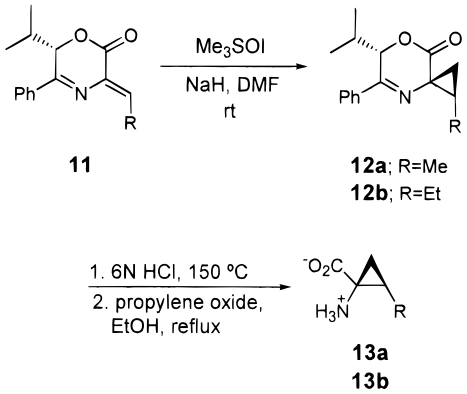


Figure 1. X-ray structure of compound **12b**.

Scheme 4



facial diastereoselectivity of this reaction is in agreement with expectations that attack of the cyclopropanating reagent should occur anti to the isopropyl group from the less-hindered face of the oxazinone. The minor diastereoisomers result presumably from attack to the opposite side, instead from a β,γ-rotation of the enolate adduct prior to the intramolecular displacement of DMSO.[23]

This methodology was applied to the synthesis of (−)-*allo*-norcoronamic (**13a**) and (−)-*allo*-coronamic (**13b**) acids, which play an important role in the control of enzymatic processes for plant growth and fruit ripening. For example, *allo*-norcoronamic acid is the strongest known competitive inhibitor of the ethylene-forming enzyme (EFE) in mung bean hypocotyls.[24] Thus, spirocyclic compounds **12a** and **12b** were hydrolyzed with 6 N HCl at 150 °C (pressure tube) for 1 d and, after treatment of the corresponding hydrochlorides with propylene oxide, the free amino acids **13a** and **13b** were obtained in 60 and 67% yield, respectively (Scheme 4).

The diastereoselective hydrogenation of derivatives **11** took place under heterogeneous catalysis with PtO_2[25] in MeOH at room temperature and normal pressure in 30 min to give the all-*cis* saturated oxazinones **14** (see Table 2). When the same reaction was carried out in the presence of aqueous formaldehyde, the corresponding all-*cis* saturated *N*-methyloxazinones **15** were stereoselectively obtained (see Scheme 5 and Table 2).

The hydrogenation of the carbon−nitrogen double bond of **11** showed highly stereoselective, and only on the

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(21) For a recent review on asymmetric ylide reactions see: Li, A.-H.; Dai, L.-X.; Aggarzwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372.

(22) For the structural details, see the Supporting Information.

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(25) The hydrogenation reaction using Pd/C as catalyst gave lower ds (ca. 75% de).

Scheme 5

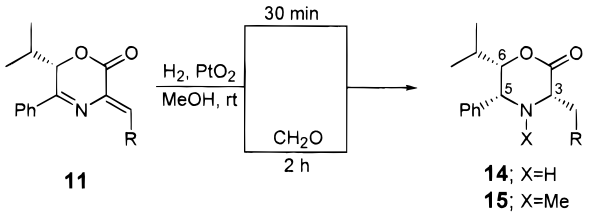


Table 2. Hydrogenation of Chiral DDAA Derivatives 11

entry	R	no.	dr[a]	yield[b] (%)
1	i-Pr	**14c**	97:3	95
2	*t*-Bu	**14d**	97:3	62[c]
3	Ph	**14e**	96:4	83
4	Me	**15a**	98:2	72
5	i-Pr	**15c**	97:3	70
6	*t*-Bu	**15d**	95:5	63[c]
7	Ph	**15e**	91:9	75

[a] Determined by GC for (3*S*,5*R*,6*S*) and (3*R*,5*R*,6*S*) diastereomers. [b] Isolated yield of the major isomer after flash chromatography based on compound **11**. [c] After crystallization.

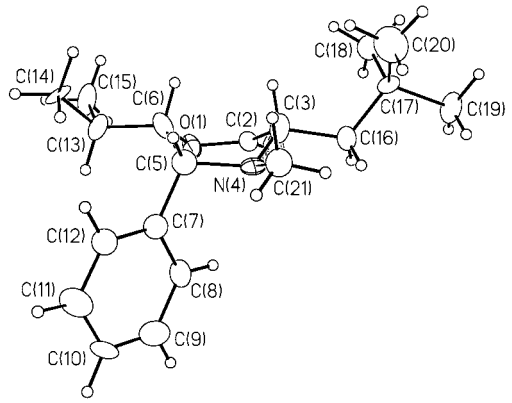
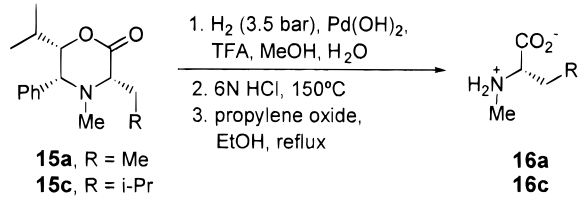


Figure 2. X-ray structure of compound **15d**.

olefinic system was detected the formation of diastereomers. The phenyl group seems to be the cause of the easy hydrogenation of the imine group,[26] because oxazinones **5** do not react under similar reaction conditions.[4c] The all-*cis* configuration for compounds **14** and **15** were stablished on the basis of the coupling constant values between H_5 and H_6 (ca. 4 Hz) which are consistent with a *cis* configuration, as shown by the most stable conformation of **14c** determined using molecular mechanics calculations.[27] This assignation was also supported by NOESY experiments which showed correlations between H_6, H_5, and H_3. The configuration was fully confirmed by X-ray diffraction analysis in the case of oxazinone **15d** (Figure 2).[22]

Saturated oxazinones with similar structural features than **14** have been used as a source of chiral azomethine ylids in asymmetric 1,3-dipolar cycloaddition reactions for the synthesis of different enantiomerically enriched amino acids.[28] In addition, *N*-methylated oxazinones **15** result particularly attractive, as they are potential precursors of enantiomerically enriched *N*-methyl-α-amino acids (*N*-MAAs). This family of α-amino acids are constituents of various peptides and depsipeptides isolated from plant strains, microorganisms, and marine species. They can also be incorporated into strategic positions of peptides, leading to enhanced proteolytic stability, to an increase in lipophilicity, and to profound conformational changes, their synthesis being therefore of high interest.[29]

Scheme 6



The liberation of the free amino acids from heterocycles **14** proved troublesome. All attempted hydrogenolytic procedures using ambient or high hydrogen pressure, or transfer hydrogenation or other conditions used with similar oxazinones,[30] failed or afforded the final amino acids contaminated with mixtures of peptides of different length. However, it was possible to obtain the corresponding enantiomerically enriched *N*-MAAs from the *N*-methylated oxazinones **15**. Thus, hydrogenolysis of oxazinones **15a** and **15c** at 3.5 bar with Pearlman's catalyst[28b] in the presence of trifluoroacetic acid (TFA), followed by hydrolysis with 6 N HCl and final treatment with propylene oxide, afforded (*S*)-2-(methylamino)-butanoic acid (**16a**) and (*S*)-*N*-methylleucine (**16c**) in 66 and 83% overall yields, respectively (Scheme 6).

When use of DDAA derivatives **11a** and **11b** as dienophiles was attempted for Diels−Alder cycloaddition reactions with cyclopentadiene under thermal conditions, only recovery of the starting material was observed. However, the methylenic DDAA derivative **11g** reacted readily with cyclopentadiene, and total consumption of the starting material was observed in 3 h at room temperature (Scheme 7). Analysis of the reaction crude (^{1}H NMR, 300 MHz) showed the presence of a major diastereomer **17a** (85% **17a** + 15% other diastereomers) which was isolated in 55% yield after flash chromatography (Scheme 7), its *endo* stereochemistry being unequivocally determined by X-ray diffraction analysis.[16,22] The high reactivity of **11g** toward cyclopentadiene compared with other DDAA derivatives[12a,b] could be justified by its rather low energy of its LUMO.[31]

Similarly, this cycloaddition reaction was carried out using 1-methoxy-1,3-cyclohexadiene as diene at room tempererature, affording again a major diastereomer **17b** (94% **17b** + 6% other diastereomers, ^{1}H NMR, 300 MHz) (Scheme 7). This isomer was isolated in 66% after flash chromatography, and its absolute stereochemistry was assigned by X-ray diffraction analysis[22] (Figure 3) show-

(26) It has been shown that substituted 3,6-dihydro-2*H*-1,4-oxazin-2-ones suffer hydrogenation at atmospheric pressure: (a) Caplar, V.; Kajfez, F.; Kolbah, D.; Sunjic, V. *J. Org. Chem.* **1978**, *43*, 1355−1360. (b) Lingibé, O.; Graffe, B.; Sacquet, M.-C.; Lhommet, G. *Heterocycles* **1994**, *37*, 1469−1472.

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(29) Spengler, J.; Burger, K. *Synthesis* **1998**, 67, and references cited therein.

(30) (a) Dellaria, J. F., Jr.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079−6082. (b) Dellaria, J. F., Jr.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916−3926. (c) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276−9286.

(31) AM1 calculated frontier orbital energies of compound **7**: $E_{HOMO} = -9.46$ eV, $E_{LUMO} = -0.94$ eV. For example, for compound **1** (X = O, R^1 = Ph, R^2 = H): $E_{HOMO} = -9.60$ eV, $E_{LUMO} = -0.33$ eV (Hyperchem 5.0 from Hypercube, Inc.).

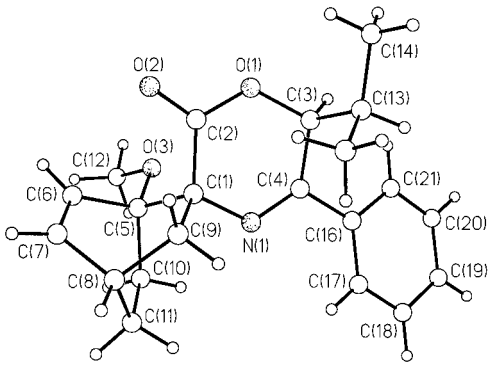
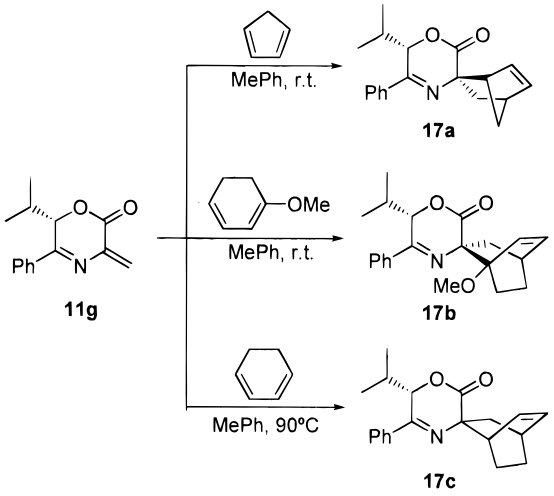


Figure 3. X-ray structure of compound **17b**.

Scheme 7

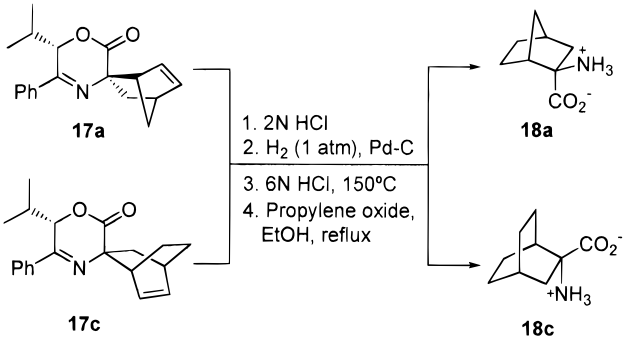


ing the expected regiochemistry in the Diels−Alder reaction between an electron-deficient dienophile and an electron-rich diene. As previously, an *endo*-carbonyl selectivity with approximation of the diene by the less-hindered face of the dienophile was observed.

The cycloaddition reaction was also performed using cyclohexa-1,3-diene, but now heating at 90 °C during 6 h was necessary to get full completion. Analysis of the crude (^{1}H NMR, 300 MHz) showed a major diastereomer **17c** (88% **17c** + 12% other diastereomers) which was isolated by flash chromatography as an oil in 49% yield (Scheme 2). The absolute stereochemistry of this major compound **17c** could not be determined, although it can be tentatively assigned as an *endo*-adduct.

Acid hydrolysis of the imine moiety of cycloadduct **17a** with 2 N HCl in THF, followed by catalytic hydrogenation at normal pressure of the double bond and subsequent hydrolysis of the ester function with 6 N HCl at 150 °C (pressure tube), yielded the corresponding amino acid hydrochloride (Scheme 8). Final treatment with propylene oxide in refluxing ethanol allowed the isolation of the free enantiomerically pure (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (**18a**) in 85% overall yield. An identical hydrolytic procedure from cycloadduct **17c** afforded (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.2]-octane-2-carboxylic acid (**18c**) in 75% overall yield, its absolute stereochemistry confirmed by ^{1}H NMR data and optical rotation values (see Experimental Section). These bicyclic amino acids have shown interesting biological properties; thus, **18a** inhibits the transport of nonpolar amino acids across cell membranes, acts as an insulin-releasing factor, and also inhibits the flavoprotein amino acid oxidases,[9a] whereas **18c** and its homologues 2-aminobicyclo[2.2.2]octane-2-carboxylic acids perturb selectively the levels of neutral amino acids in the cerebral cortex.[9b]

Scheme 8



Conclusions

We conclude that oxazinone **7** is an appropriate glycine template for the stereoselective synthesis of new enantiomerically pure (*Z*)-α,*β*-didehydroamino acid (DDAA) derivatives. The preparation of these derivatives takes place in an easier and milder way than when using other previously described systems, just by simple condensation with aldehydes under easily scalable PTC conditions at room temperature and, in the case of the methylenic derivative, by a direct aminomethylation−elimination sequence. These new chiral DDAA derivatives can be easily and diastereoselectively cyclopropanated or hydrogenated to the immediate precursors of interesting enantiomerically pure 1-aminocyclopropane carboxylic acids (ACCs) or *N*-methyl-α-amino acids (*N*-MAAs). The corresponding α,*β*-didehydroalanine derivative can be employed as a very reactive dienophile for the asymmetric synthesis of bicyclic α-amino acids.

Experimental Section

General. Melting points are uncorrected. NMR spectra were determined at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. Mass spectra (EI) were obtained at 70 eV. Elemental analyses were performed by the Microanalyses Service of the University of Alicante. High-resolution mass spectra (EI) were determined by the corresponding services at the University of Zaragoza or Alicante. X-ray data were collected using Mo Kα radiation (graphite crystal monochromator, $\lambda = 0.71073$ Å).

(*S*)-2-Hydroxy-3,*N*,*N*-trimethylbutanamide (8).[32] To a magnetically stirred mixture of (*S*)-hydroxyisovaleric acid (2.36 g, 20 mmol), dimethylamine hydrochloride (1.63 g, 20 mmol), and 1-hydroxy-1*H*-benzotriazole (2.70 g, 20 mmol) in THF (10 mL) was added diisopropylethylamine (3.49 mL, 20 mmol) dropwise at −20 °C under argon. After 2 min, dicyclohexylcarbodiimide (DCC, 4.34 g, 21 mmol) was added at once, and the mixture was stirred overnight, allowing the temperature to rise to room temperature. The formed precipitate was filtered off and washed with EtOAc. The combined filtrates were concentrated in vacuo and filtered through a plug of silica gel (hexane/EtOAc = 7/3). The solvent was evaporated in vacuo and the residue distilled (kügelrohr, 150 °C, 0.01 Torr) to afford **8** (2.18 g, 75%): $[\alpha]^{25}_D$ +54.0 ($c = 1$; $CHCl_3$); IR (thin film) ν 3423, 1640 cm^{-1}; ^{1}H NMR δ 4.26 (d, 1 H, $J = 3.0$ Hz), 3.66 (br

(32) Ohta, H.; Ikemoto, M.; Ti, H.; Okamoto, Y.; Tsuchihashi, G. *Chem. Lett.* **1986**, 1169−1172.

s, 1 H), 3.01 (s, 3 H), 3.00 (s, 3 H), 1.90 (dsept, 1 H, J = 6.9, 3.0 Hz), 1.07 (d, 3 H, J = 6.9 Hz), 0.80 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 173.9, 72.1, 36.5, 35.8, 31.1, 19.7, 15.0; MS *m/e* (relative intensity) 145 (M^+, 1), 73 (100).

(*S*)-α-Hydroxyisovalerophenone (9). To a solution of **8** (2.18 g, 15 mmol) in THF (60 mL) was added dropwise phenylmagnesium bromide (3 M solution in ether, 15 mL, 45 mmol) at 0 °C under argon, and the mixture was stirred overnight, allowing the temperature to rise to room temperature. The reaction was quenched at 0 °C with saturated NH_4Cl and water and extracted with EtOAc. The organics were dried (Na_2SO_4), filtered, and evaporated in vacuo, and the residue was purified by column chromatography (silica gel) to afford **9** (1.87 g, 70%): R_f 0.59 (hexane/EtOAc = 7/3); $[\alpha]_{546}$ +25.4 (c = 2.2; EtOH) (lit.[33] $[\alpha]_{546}$ +20 (c = 2.2; EtOH)); IR (thin film) ν 3474, 1678 cm^{-1}; ^{1}H NMR δ 7.90 (m, 2 H), 7.62 (m, 1 H), 7.50 (m, 2 H), 4.98 (dd, 1 H, J = 6.4, 2.4 Hz), 3.61 (d, 1 H, J = 6.4 Hz), 2.14 (dsept, 1 H, J = 6.7, 2.4 Hz), 1.17 (d, 3 H, J = 6.7 Hz), 0.66 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 202.2, 134.1, 133.8, 128.8, 128.4, 77.3, 32.6, 20.1, 14.3; MS *m/e* (relative intensity) 178 (M^+, 1), 105 (100).

(1*S*)-1-Benzoyl-2-(*tert*-butoxycarbonylamino)-2-methylpropyl Ethanoate (10). To a solution of DCC (2.27 g, 11 mmol), *N*-Boc-glycine (1.89 g, 10 mmol), and a catalytic amount of *N*,*N*-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 (25 mL) was added a solution of hydroxy ketone **9** (1.78 g, 10 mmol) in CH_2Cl_2 (25 mL), and the mixture was stirred overnight at room temperature. The formed precipitate was filtered off, the filtrate concentrated in vacuo, and the residue purified by column chromatography to afford compound **10** (2.68 g, 80%): R_f 0.43 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ +17.5 (c = 1.5; $CHCl_3$); IR (thin film) ν 3390, 1754, 1698 cm^{-1}; ^{1}H NMR δ 7.93 (m, 2 H), 7.59 (m, 1 H), 7.48 (m, 2 H), 5.80 (d, 1 H, J = 4.6 Hz), 5.1 (br s, 1 H), 4.13 (dd, 1 H, J = 18.3, 6.4 Hz), 4.00 (dd, 1 H, J = 18.3, 5.2 Hz), 2.31 (dsept, 1 H, J = 6.7, 4.6 Hz), 1.44 (s, 9 H) 1.05 (d, 3 H, J = 6.7 Hz), 0.92 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 196.1, 170.2, 155.6, 135.2, 133.5, 128.7, 128.3, 80.0, 79.8, 42.2, 30.1, 28.2, 19.4, 16.7.

(6*S*)-6-Isopropyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (7). A saturated solution of HCl in EtOAc (25 mL) was added to compound **10** (2.68 g, 8 mmol), and the mixture was stirred 1 h. The solvent was evaporated in vacuo, and the solid was washed with ether and filtered. The solid was dissolved in CH_2Cl_2 (3 mL) and a solution of Me_3N in CH_2Cl_2 (5 mL), obtained by extracting a NaCl saturated 45% solution of Me_3N in water (3 mL) with CH_2Cl_2 (6 mL), was added. The resulting mixture was stirred 1 h and cooled to 0 °C, hexane (8 mL) was added, and the formed precipitate was filtered off and washed with a 1/1 hexane/CH_2Cl_2 mixture (2 × 5 mL). The combined filtrates were evaporated in vacuo, affording crude oxazinone **7** (1.73 g, 85% pure by GC). A sample was purified by flash chromatography (neutral silica gel) for analytical purposes: R_f 0.34 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ +102.6 (c = 1.13; CH_2Cl_2), IR (thin film) ν 1746, 1693 cm^{-1}; ^{1}H NMR δ 7.70 (m, 2 H), 7.48 (m, 3 H), 5.52 (m, 1 H), 4.75 (dd, 1 H, J = 22.3, 2.1 Hz), 4.36 (dd, 1 H, J = 22.3, 2.1 Hz), 2.20 (d sept, 1 H, J = 6.9, 2.9 Hz), 1.09 (d, 3 H, J = 6.9 Hz), 0.90 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 167.0, 165.3, 135.5, 131.1, 128.9, 126.6, 83.9, 50.3, 32.9, 19.1, 16.1; MS *m/e* (relative intensity) 217 (M^+, 11), 117 (100).

Synthesis of Didehydroamino Acid Derivatives 11a−f. General Procedure. A heterogeneous mixture of crude **7** (255 mg, equiv to 1 mmol), tetrabutylammonium bromide (33 mg, 0.1 mmol), finely ground, technical-grade K_2CO_3 (414 mg, 3 mmol), and the corresponding aldehyde (1.2 mmol) in CH_3CN (3 mL) was stirred at room temperature until total consumption of the starting material (GC, see Table 1). The mixture was filtered through a pad of silica gel, the solvent removed in vacuo, and the residue purified by flash chromatography on silica gel to afford derivatives **11a−f**.

(6*S*)-3-[(*Z*)-Ethylidene]-6-isopropyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (11a). R_f 0.60 (hexane /EtOAc = 7/3); mp 111−112 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −477.2 (c = 1; CH_2Cl_2); IR (KBr) ν 1715, 1632 cm^{-1}; ^{1}H NMR δ 7.87 (m, 2 H), 7.47 (m, 3 H), 7.00 (q, 1 H, J = 7.2 Hz), 5.56 (d, 1 H, J = 3.4 Hz), 2.18 (d, 3 H, J = 7.2 Hz), 2.18 (m, 1 H), 1.12 (d, 3 H, J = 6.7 Hz), 0.80 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 161.3, 160.4, 137.2, 135.1, 131.5, 131.2, 128.7, 126.9, 84.6, 33.7, 19.1, 15.6, 12.9; MS *m/e* (relative intensity) 243 (M^+, 29), 143 (100). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.05; N, 5.76. Found: C, 74.32; H, 7.09; N, 5.42.

(6*S*)-6-Isopropyl-5-phenyl-3-[(*Z*)-propylidene]-3,6-dihydro-2*H*-1,4-oxazin-2-one (11b). R_f 0.55 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −417.4 (c = 2; CH_2Cl_2); IR (thin film) ν 1727, 1631 cm^{-1}; ^{1}H NMR δ 7.86 (m, 2 H), 7.48 (m, 3 H), 6.92 (t, 1 H, J = 7.8 Hz), 5.56 (d, 1 H, J = 3.3 Hz), 2.82−2.57 (m, 2 H), 2.19 (dsept, 1 H, J = 6.9, 3.3 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 1.13 (d, 3 H, J = 6.9 Hz), 0.80 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 161.6, 160.5, 143.4, 135.2, 131.2, 130.3, 128.8, 126.9, 82.7, 33.8, 20.3, 19.1, 15.7, 13.0; MS *m/e* (relative intensity) 257 (M^+, 25), 54 (100); HRMS *m/e* Calcd for $C_{16}H_{19}NO_2$: 257.1416. Found: 257.1416.

(6*S*)-6-Isopropyl-3-[(*Z*)-2-methylpropylidene]-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (11c). R_f 0.65 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −381.8 (c = 1; CH_2Cl_2); IR (thin film) ν 1727, 1631 cm^{-1}; ^{1}H NMR δ 7.86 (m, 2 H), 7.48 (m, 3 H), 6.74 (d, 1 H, J = 9.8 Hz), 5.56 (d, 1 H, J = 3.4 Hz), 3.51 (m, 1 H), 2.20 (dsept, 1 H, J = 6.9, 3.4 Hz), 1.15 (d, 6 H, J = 7.0 Hz), 1.11 (d, 3 H, J = 6.9 Hz), 0.80 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 161.9, 160.5, 148.0, 135.1, 131.2, 129.1, 128.8, 126.9, 82.7, 33.8, 26.2, 22.1, 21.7, 19.1, 15.6; MS *m/e* (relative intensity) 271 (M^+, 17), 228 (100); HRMS *m/e* Calcd for $C_{17}H_{21}NO_2$: 271.1572. Found: 271.1577.

(6*S*)-3-[(*Z*)-2,2-Dimethylpropylidene]-6-isopropyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (11d). R_f 0.66 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −277.6 (c = 0.7; CH_2Cl_2); IR (thin film) ν 1728, 1622 cm^{-1}; ^{1}H NMR δ 7.85 (m, 2 H), 7.50 (m, 3 H), 6.90 (s, 1 H), 5.54 (d, 1 H, J = 3.2 Hz), 2.23 (dsept, 1 H, J = 6.9, 3.2 Hz), 1.37 (s, 9 H), 1.12 (d, 3 H, J = 6.9 Hz), 0.83 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 162.4, 159.7, 149.1, 135.2, 131.3, 130.0, 128.9, 126.9, 82.4, 34.0, 33.9, 30.3, 19.1, 15.9; MS *m/e* (relative intensity) 285 (M^+, 28); HRMS *m/e* Calcd for $C_{18}H_{23}NO_2$: 285.1729. Found: 285.1732.

(6*S*)-6-Isopropyl-5-phenyl-3-[(*Z*)-1-phenylmethylidene]-3,6-dihydro-2*H*-1,4-oxazin-2-one (11e). R_f 0.54 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −800.0 (c = 0.94; CH_2Cl_2); IR (thin film) ν 1726, 1614 cm^{-1}; ^{1}H NMR δ 8.09 (m, 2 H), 7.92 (m, 2 H), 7.55−7.36 (m, 7 H), 5.61 (d, 1 H, J = 3.5 Hz), 2.25 (dsept, 1 H, J = 6.6, 3.5 Hz), 1.14 (d, 3 H, J = 6.6 Hz), 0.88 (d, 3 H, J = 6.6 Hz); ^{13}C NMR δ 162.3, 162.1, 135.0, 134.3, 133.3, 132.5, 131.5, 129.8, 129.1, 128.9, 128.4, 127.1, 82.5, 34.0, 19.1, 15.9; MS *m/e* (relative intesity) 305 (M^+, 40), 262 (100); HRMS *m/e* Calcd for $C_{20}H_{19}NO_2$: 305.1416. Found: 305.1427.

(*S*)-*tert*-Butyl 3-[(6*S*)-6-Isopropyl-2-oxo-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-3-ylidenmethyl]-1*H*-1-indolecarboxylate (11f). R_f 0.47 (hexane/EtOAc = 7/3); mp 145−146 °C (EtOAc); $[\alpha]^{25}_D$ −17.2 (c = 1; CH_2Cl_2); IR (KBr) ν 1731, 1615 cm^{-1}; ^{1}H NMR δ 8.76 (s, 1 H), 8.25 (m, 1 H), 7.95 (m, 2 H), 7.84 (m, 2 H), 7.50 (m, 3 H), 7.37 (m, 2 H), 5.65 (d, 1 H, J = 3.4 Hz), 2.26 (dsept, 1 H, J = 6.9, 3.4 Hz), 1.73 (s, 9 H), 1.16 (d, 3 H, J = 6.9 Hz), 0.89 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 161.7, 161.5, 149.2, 135.4, 135.1, 131.4, 130.9, 129.8, 130.0, 128.2, 127.2, 125.1, 124.6, 123.5, 118.7, 115.3, 114.9, 84.3, 82.8, 34.1, 28.2, 15.9, 14.1; MS *m/e* (relative intensity) 444 (M^+, 8), 273 (100). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 71.17; H, 6.65; N, 5.66.

Synthesis of Didehydroamino Acid Derivative 11g. A saturated solution of HCl in EtOAc (5 mL) was added to compound **10** (335 mg, 1 mmol), and the mixture was stirred 1 h. The solvent was evaporated in vacuo, and the solid was washed with ether and filtered. The solid was dissolved in dry CH_2Cl_2 (1 mL), *N*,*N*-diisopropylethylamine (174 μL, 1 mmol) was added, and the mixture was stirred for 1 h at room temperature. The mixture was diluted with dry CH_2Cl_2 (7 mL), *N*,*N*-dimethylmethyleneammonium iodide was added (371 mg, 2 mmol), and the suspension was stirred overnight at room temperature. The slurry was filtered through a plug of silica

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gel (hexane/EtOAc = 8/2), and the solvent was evaporated in vacuo yielding 128 mg of crude **11g** (90% pure, GLC). An analytical sample was obtained after flash chromatography using neutral silica gel: R_f 0.63 (hexane/EtOAc) = 7/3); $[\alpha]^{25}_D$ −360 (c = 2.0; CH_2Cl_2); IR (thin film) ν 1739, 1615 cm^{-1}; ^1H NMR δ 7.84 (m, 2H), 7.49 (m, 3H), 6.38 (s, 1H), 5.94 (s, 1H), 5.60 (d, 1H, J = 3.4 Hz), 2.20 (dsept, 1H, J = 6.9, 3.4 Hz), 1.14 (d, 3H, J = 6.9 Hz), 0.81 (d, 3H, J = 6.9 Hz); ^{13}C NMR δ 163.6, 160.8, 137.4, 134.7, 131.6, 128.9, 127.0, 124.0, 83.7, 33.9, 19.1, 15.6; MS *m/e* (relative intensity) 229 (M^+, 39), 129 (100); HRMS *m/e* Calcd for $C_{14}H_{15}NO_2$: 229.1103. Found: 229.1098.

Cyclopropanation of 11. General Procedure. Trimethylsulfoxonium iodide (440 mg, 2 mmol) was added to a suspension of NaH (60% in mineral oil, 80 mg, 2 mmol) in dry DMF (1.5 mL), and the mixture was stirred under argon at room temperature for 30 min. A solution of **11** (1 mmol) in DMF (1.5 mL) was then added, and the resulting mixture was stirred under argon at room temperature for 1 h. The suspension was diluted with EtOAc (15 mL) and filtered through a pad of silica gel, the eluted solution washed with water, the solvent dried (Na_2SO_4), removed in vacuo, and the residue purified by flash chromatography on silica gel to afford compounds **12**.

(1*R*,3*S*,6*S*)-6-Isopropyl-1-methyl-7-phenyl-5-oxa-8-azaspiro[2.5]oct-7-en-4-one (12a). R_f 0.64 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −131.4 (c =1.63; CH_2Cl_2); IR (thin film) ν 1735, 1644; ^1H NMR δ 7.68 (m, 2 H), 7.44 (m, 3 H), 5.62 (d, 1 H, J = 2.8 Hz), 2.22−2.04 (m, 3 H), 1.45 (dd, 1 H, J = 7.6, 3.7 Hz), 1.37 (d, 3 H, J = 6.1 Hz), 1.13 (d, 3 H, J = 7.0 Hz), 0.86 (d, 3 H, J = 7.0 Hz); ^{13}C NMR δ 170.5, 163.0, 135.6, 130.5, 128.7, 126.2, 83.3, 44.6, 32.5, 30.4, 30.1, 19.0, 15.6, 13.0; MS *m/e* (relative intensity) 257 (M^+, 20), 54 (100); HRMS *m/e* Calcd for $C_{16}H_{19}NO_2$: 257.1416. Found: 257.1427.

(1*R*,3*S*,6*S*)-1-Ethyl-6-isopropyl-7-phenyl-5-oxa-8-azaspiro[2.5]oct-7-en-4-one (12b). R_f 0.57 (hexane/EtOAc = 7/3); mp 94−95 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −91.4 (c = 2.1; CH_2Cl_2); IR (thin film) ν 1735, 1646 cm^{-1}; ^1H NMR δ 7.65 (m, 2 H), 7.43 (m, 3 H), 5.61 (d, 1 H, J = 3.1 Hz), 2.21−2.02 (m, 3 H), 1.75 (m, 2 H), 1.45 (dd, 1H, J = 6.9, 2.9 Hz), 1.11 (d, 3 H, J = 7.3 Hz), 1.07 (t, 3 H, J = 7.3 Hz), 0.87 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 170.4, 162.7, 135.9, 130.5, 128.7, 126.2, 83.4, 44.8, 37.1, 32.7, 29.5, 21.5, 19.0, 15.4, 13.3; MS *m/e* (relative intensity) 271 (M^+, 16), 228 (100). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.23; H, 7.81; N, 5.16. Found: C, 75.59; H, 7.86; N, 4.99.

Hydrolysis of 12. General Procedure. Compounds **12** (110 mg, 0.4 mmol) were dissolved in 6 N HCl (1.5 mL) and heated at 150 °C in a pressure tube for 1 d. Water (5 mL) was added, and the mixture was extracted with EtOAc (2 × 5 mL). The aqueous layer was evaporated in vacuo and the solid residue dissolved in ethanol (2 mL). Propylene oxide was added (1 mL) and the mixture refluxed for 30 min. The solid was filtered, washed with ethanol, and dried, affording amino acids **13a** (28 mg, 60%) and **13b** (35 mg, 67%).

(−)-*allo*-Norcoronamic acid (13a). $[\alpha]^{25}_D$ −72 (c = 0.3; H_2O) (lit.[34] $[\alpha]_D$ −69 (c = 0.3; H_2O)); ^1H NMR (D_2O) δ 1.45 (m, 1 H), 1.24 (dd, 1 H, J = 9.8, 6.1 Hz), 0.99 (d, 3 H, J = 6.7 Hz), 0.68 (t, 1 H, J = 6.7 Hz); ^{13}C NMR (D_2O, acetone) δ 176.2, 40.0, 19.2, 18.5, 11.8.

(−)-*allo*-Coronamic acid (13b). $[\alpha]^{25}_D$ −51 (c =1.83; H_2O) (lit.[4b] $[\alpha]_D$ −52 (c = 1.83; H_2O)); ^1H NMR (D_2O) δ 1.38−1.11 (m, 4 H), 0.85 (t, 3 H, J = 7.0 Hz), 0.70 (m, 1 H); ^{13}C NMR (D_2O, acetone) δ 176.3, 40.1, 26.0, 20.9, 18.1, 13.1.

Hydrogenation of 11. General Procedure. A mixture of **11** (1 mmol) and PtO_2 (40 mg) in MeOH (3 mL) was stirred under a hydrogen atmosphere (1 atm) for 30 min. The suspension was filtered through Celite, the solvent removed in vacuo, and the residue purified by flash chromatography or crystallization to afford **14**. The preparation and isolation of **15** was similar: a solution of CH_2O (33% in water, 0.9 mL) was added to a mixture of **11** and PtO_2 in MeOH (12 mL) and stirred under hydrogen (1 atm) for 2 h.

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(3*S*,5*R*,6*S*)-3-Isobutyl-6-isopropyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (14c). R_f 0.57 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −120.5 (c = 1.8; CH_2Cl_2); IR (thin film) ν 3359, 3321, 1741 cm^{-1}; ^1H NMR δ 7.33 (m, 5 H), 4.43 (d, 1 H, J = 4.3 Hz), 4.24 (dd, 1 H, J = 8.2, 4.3 Hz), 3.73 (m, 1 H), 1.89 (m, 2 H), 1.65−1.42 (m, 3 H), 1.03 (d, 3 H, J = 6.7 Hz), 0.96 (m, 6 H), 0.83 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 173.6, 139.8, 128.8, 127.9, 84.2, 59.0, 53.0, 40.1, 28.9, 24.4, 23.3, 21.5, 19.1, 19.1; MS *m/e* (relative intensity) 275 (M^+, 2), 132 (100).

(3*S*,5*R*,6*S*)-6-Isopropyl-3-neopentyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (14d). R_f 0.67 (hexane/EtOAc = 7/3); mp 132−134 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −150.8 (c = 1; CH_2Cl_2); IR (KBr) ν 3357, 1751 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H), 4.44 (d, 1 H, J = 4.3 Hz), 4.25 (dd, 1 H, J = 8.2, 4.3 Hz), 3.72 (dd, 1 H, J = 7.3, 3.1 Hz), 2.31 (dd, 1 H, J = 14.7, 3.1 Hz), 1.58 (m, 1 H), 1.30 (dd, 1 H, J = 14.7, 7.3 Hz), 1.03 (d, 3 H, J = 6.7 Hz), 1.00 (s, 9 H), 0.83 (d, 3 H, J = 6.7); ^{13}C NMR δ 173.9, 140.0, 128.7, 128.0, 128.0, 84.0, 59.1, 52.5, 44.3, 30.1, 29.8, 28.9, 19.1, 19.0; MS *m/e* (relative intensity) 289 (M^+, 1), 132 (100). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.30; H, 9.47; N, 4.73.

(3*S*,5*R*,6*S*)-3-Benzyl-6-isopropyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (14e). R_f 0.55 (hexane/EtOAc = 7/3); mp 111−112 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −178.2 (c = 1; CH_2Cl_2); IR (thin film) ν 3345, 3315, 1740 cm^{-1}; ^1H NMR δ 7.33−7.25 (m, 10 H), 4.39 (d, 1 H, J = 4.3 Hz), 4.24 (dd, 1 H, J = 6.7, 4.3 Hz), 3.97 (dd, 1 H, J = 9.2, 3.7 Hz), 3.49 (dd, 1 H, J = 14.0, 3.7 Hz), 2.89 (dd, 1 H, J = 14.0, 9.2 Hz), 1.63 (br s, 1 H), 1.56 (m, 1 H), 0.98 (d, 3 H, J = 6.7 Hz), 0.77 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 172.0, 139.4, 137.5, 129.4, 128.7, 128.0, 127.6, 126.9, 85.3, 59.0, 57.5, 37.7, 28.7, 20.0, 18.6; MS *m/e* (relative intensity) 309 (M^+, 5), 91 (100). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 78.06; H, 7.61; N, 4.43.

(3*S*,5*R*,6*S*)-3-Ethyl-6-isopropyl-4-methyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (15a). R_f 0.65 (hexane/EtOAc = 7/3); mp 76−77 °C (hexane/Et_2O); $[\alpha]^{25}_D$ −62.5 (c = 1.0; CH_2Cl_2); IR (thin film) ν 1754 cm^{-1}; ^1H NMR δ 7.30 (m, 5 H), 4.13 (dd, 1 H, J = 8.6, 4.0), 3.69 (d, 1 H, J = 4.0), 3.40 (dd, 1 H, J = 6.1, 2.4), 2.37 (s, 3 H), 2.02 (dsept, 1 H, J = 7.3, 2.4), 1.88, 1.53 (2 m, 2 H), 1.02 (t, 3 H, J = 7.3), 0.97, 0.85 (2 d, 6 H, J = 6.4); ^{13}C NMR δ 172.0, 139.1, 129.0, 128.1, 127.6, 82.4, 70.0, 61.7, 41.1, 28.6, 22.0, 19.1, 18.9, 9.0; MS *m/e* (relative intensity) 261 (M^+, 3), 42 (100).

(3*S*,5*R*,6*S*)-3-Isobutyl-6-isopropyl-4-methyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (15c). R_f 0.69 (hexane/EtOAc = 7/3); mp 75−76 °C (hexane/Et_2O); $[\alpha]^{25}_D$ −54.1 (c = 1; CH_2Cl_2); IR (thin film) ν 1749 cm^{-1}; ^1H NMR δ 7.29 (m, 5 H), 4.16 (dd, 1 H, J = 8.7, 4.1 Hz), 3.73 (d, 1 H, J = 3.7 Hz), 3.29 (dd, 1 H, J = 7.6, 3.1 Hz), 1.98 (m, 2 H), 1.62 (m, 1 H), 1.45 (m, 1 H), 1.01 (d, 3 H, J = 6.7 Hz), 0.99 (d, 3 H, J = 6.4 Hz), 0.94 (d, 3 H, J = 6.1 Hz), 0.86 (d, 3 H, J = 6.4 Hz); ^{13}C NMR δ 172.8, 138.6, 128.8, 128.3, 127.7, 82.6, 67.0, 60.3, 42.0, 39.7, 28.5, 26.0, 23.5, 22.2, 19.3, 18.9; MS *m/e* (relative intensity) 289 (M^+, 2), 100 (39). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.7; H, 9.40; N, 4.84. Found: C, 73.27; H, 9.22; N, 4.70.

(3*S*,5*R*,6*S*)-6-Isopropyl-4-methyl-3-neopentyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (15d). R_f 0.71 (hexane/EtOAc = 7/3); mp 100−101 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −39.0 (c = 1; CH_2Cl_2); IR (KBr) ν 1749 cm^{-1}; ^1H NMR δ 7.33−7.20 (m, 5 H), 4.18 (dd, 1 H, J = 9.3, 3.5 Hz), 3.80 (d, 1 H, J = 3.4 Hz), 3.24 (d, 1 H, J = 6.9 Hz), 2.51 (s, 1 H), 2.42 (dd, 1 H, J = 15.0, 6.9 Hz), 1.63 (m, 1 H), 1.42 (d, 1 H, J = 15.0 Hz), 1.02 (d, 3 H, J = 6.7 Hz), 0.98 (s, 9 H), 0.94 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 173.5, 138.8, 128.7, 128.2, 127.6, 81.7, 66.6, 58.6, 42.9, 42.7, 30.3, 29.7, 28.6, 19.1, 19.0; MS *m/e* (relative intensity) 303 (M^+, 0.3), 42 (100). Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.59. Found: C, 74.69; H, 9.59; N, 4.59.

(3*S*,5*R*,6*S*)-3-Benzyl-6-isopropyl-4-methyl-5-phenyltetrahydro-2*H*-1,4-oxazin-2-one (15e). R_f 0.60 (hexane/EtOAc = 7/3); mp 73−74 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −88.1 (c = 1; CH_2Cl_2); IR (thin film) ν 1749 cm^{-1}; ^1H NMR δ 7.36−7.17 (m, 10 H), 4.13 (dd, 1H, J = 8.2, 3.7 Hz), 3.61 (m, 1 H), 3.41 (dd, 1 H, J = 14.3, 5.8 Hz), 3.06 (dd, 1 H, J = 14.3, 4.6 Hz), 2.40 (s, 3H), 1.60 (m, 1 H), 0.86 (d, 3 H, J = 6.7 Hz), 0.77 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 171.6, 138.7, 138.2, 129.8, 128.7, 128.2,

128.1, 127.6, 126.2, 82.9, 66.7, 64.3, 42.6, 36.4, 28.4, 19.4, 18.6; MS *m/e* (relative intensity) 321 ($M^+ - H_2$, 2), 232 (100). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.30; H, 7.74; N, 4.33.

Synthesis of *N*-Methyl-α-amino Acids 16. General Procedure. To a solution of **15a** or **15c** (1 mmol) in MeOH (13 mL), H_2O (1.5 mL), and TFA (270 μL) was added $Pd(OH)_2$ on carbon (270 mg). The reaction vessel was charged with H_2, and the mixture was hydrogenated at 3.5 bar for 36 h. The mixture was then purged with nitrogen and filtered (Celite) to remove the catalyst. The filtrate was evaporated (15 Torr), and the resulting residue was dissolved in 6 N HCl (3 mL) and heated at 150 °C (pressure tube) for 24 h. Water was added, and the mixture was extracted with AcOEt. The aqueous layer was evaporated (15 Torr), and the solid residue was dissolved in EtOH (3 mL). Propylene oxide (2 mL) was added, and the mixture was refluxed for 30 min. The formed precipitate was filtered and washed with EtOH affording *N*-MAAs **16a** (77 mg, 66%) or **16c** (120 mg, 83%).

(*S*)-2-Methylaminobutanoic acid (16a). $[\alpha]^{25}_D$ +23.1 (*c* = 0.85; 6 N HCl) (lit.[35] $[\alpha]^{25}_D$ +24.8 (*c* = 0.85; 6 N HCl)); ^{1}H NMR δ 3.53 (t, 1 H, *J* = 5.5), 2.68 (s, 3H), 1.88 (m, 2 H), 0.92 (t, 3 H, *J* = 7.6).

(*S*)-*N*-Methylleucine (16c). $[\alpha]^{25}_D$ +22.7 (*c* = 1.0; H_2O) (lit.[36] $[\alpha]_D$ +21.4); ^{1}H NMR δ 3.55 (m, 1 H), 2.68 (s, 3 H), 1.69 (m, 3 H), 0.93 (m, 6 H).

Diels−Alder reaction of 11g. General Procedure. To a solution of the oxazinone **11g** (254 mg of crude of 90% purity, equivalent to 229 mg of pure compound, 1 mmol) in toluene (2 mL) was added the corresponding diene (20 mmol for cyclopentadiene or 1,3-cyclohexadiene, 10 mmol for 1-methoxy-1,3-cyclohexadiene), and the mixture was stirred at room temperature (3 h for cyclopentadiene, 4 h for 1-methoxy-1,3-cyclohexadiene) or 90 °C (6 h for 1,3-cyclohexadiene). The solvent was evaporated (15 Torr), and the residue was purified by flash chromatography (silica gel, hexane/EtOAc gradients), affording pure major diastereomers.

(1*S*,2*R*,4*S*,6′*S*)-Bicyclo[2.2.1]hept-5-en-2-spiro{3′[6′-isopropyl-5′phenyl-3′,6′-dihydro-2′*H*-1′,4′-oxazin-2′-one]} (17a). 55%. R_f 0.63 (hexane/EtOAc = 7/3); mp 86−87 °C (hexane/Et_2O); $[\alpha]^{25}_D$ −60.0 (*c* = 1.4; CH_2Cl_2); IR (KBr) ν 1738, 1657 cm^{-1}; ^{1}H NMR δ 7.66 (m, 2 H), 7.42 (m, 3 H), 6.38 (m, 1 H), 6.25 (m, 1 H), 5.48 (d, 1 H, *J* = 4.3 Hz), 3.08 (s, 1 H), 2.97 (s, 1 H), 2.41 (d, 1 H, *J* = 8.2 Hz), 2.13 (m, 1 H), 1.95 (br s, 2 H), 1.55 (d, 1 H, *J* = 8.2 Hz), 1.02 (d, 3 H, *J* = 6.7 Hz), 0.83 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 171.6, 162.6, 138.5, 136.7, 134.6, 130.4, 128.6, 126.7, 83.9, 66.1, 56.3, 48.5, 45.7, 43.5, 32.5, 19.4, 16.4.

(1*R*,2*R*,4*R*,6′*S*)-1-Methoxybicyclo[2.2.2]oct-5-en-2-spiro-{3′[6′-isopropyl-5′phenyl-3′,6′-dihydro-2′*H*-1′,4′-oxazin-2′-one]} (17b). 66% R_f 0.54 (hexane/EtOAc = 7/3), mp 138−139 °C (hexane/EtOAc); IR (KBr) ν 1737, 1664 cm^{-1}; ^{1}H NMR δ 7.67 (m, 2 H), 7.43 (m, 3 H), 6.51 (d, 1 H, *J* = 8.6 Hz), 6.37 (m, 1 H), 5.52 (d, 1 H, *J* = 2.4 Hz), 3.27 (s, 3 H), 2.71 (bs, 1 H), 2.22−2.07 (m, 3 H), 1.95 (m, 1 H), 1.79 (dd, 1 H, *J* = 12.2, 3.1 Hz), 1.48 (m, 1 H), 1.36 (m, 1 H), 1.11 (d, 3 H, *J* = 6.7 Hz), 0.67 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 170.9, 162.0, 136.8, 133.8, 132.2, 130.1, 128.4, 126.7, 84.9, 83.6, 65.4, 51.7, 45.6, 31.9, 30.3, 24.0, 23.4, 19.1, 15.0. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 73.94; H, 7.32; N, 4.20.

(6′*S*)-Bicyclo[2.2.2]oct-5-en-2-spiro{3′[6′-isopropyl-5′-phenyl-3′,6′-dihydro-2′*H*-1′,4′-oxazin-2′-one]} (17c): 49%. R_f 0.61 (hexane/EtOAc = 7/3); $[\alpha]^{25}_D$ −45.1 (*c* = 1.3; CH_2Cl_2); IR (thin film) ν 1742, 1657 cm^{-1}; ^{1}H NMR δ 7.69 (m, 2 H), 7.43 (m, 3 H), 6.45 (t, 1 H, *J* = 7.3 Hz), 6.37 (t, 1 H, *J* = 7.3 Hz), 5.47 (d, 1 H, *J* = 4.3 Hz), 2.74 (s, 1 H), 2.66 (m, 1 H), 2.42 (m, 1 H,), 2.10 (m, 2 H), 1.77 (m, 1 H), 1.64 (dd, 1 H, *J* = 12.2, 2.4 Hz), 1.35 (dt, 1 H, *J* = 6.7, 3.7 Hz), 1.04 (d, 3 H, *J* = 6.7 Hz), 0.86 (m, 1 H), 0.78 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 172.1, 161.4, 136.5, 134.0, 132.4, 130.3, 128.5, 126.7, 84.0, 61.7, 44.2, 40.7, 32.5, 30.2, 22.8, 21.1, 19.3, 16.1; MS *m/e* (relative intensity) 309 (M^+, 13), 229 (100); HRMS *m/e* Calcd for $C_{20}H_{23}NO_2$: M^+ 309.1729. Found: M^+ 309.1721.

Synthesis of the Bicyclic α-Amino Acids 18a and 18c. General Procedure. A mixture of the corresponding bicyclic oxazinone **17a** or **17c** (0.5 mmol) in 2 N HCl (2 mL) and THF (1.5 mL) was stirred at room temperature for 3 h. The solvent was evaporated (15 Torr) and the residue disolved in MeOH (3 mL). To this solution was added Pd/C 10% (40 mg), and the mixture was stirred under an hydrogen atmosphere (1 atm) for 3 h. The resulting suspension was filtered through Celite and the solvent evaporated (15 Torr). The residue was heated in 6 N HCl at 150 °C (bath temperature) in a pressure tube for 24 h. The mixture was diluted with water (15 mL) and washed with EtOAc (10 mL) and the aqueous layer evaporated (15 Torr). The resulting solid hydrochloride was disolved in ethanol (3 mL) and refluxed with propylene oxide (2 mL) for 30 min. The formed precipitate was filtered off, yielding the corresponding free amino acids **18a** or **18c** in 85 and 75% yields, respectively.

(−)-(1*R*,2*R*,4*S*)-2-Aminobicyclo[2.2.1]heptane-2-carboxylic Acid (18a). $[\alpha]^{25}_D$ −61.0 (*c* = 1.0; H_2O) (lit.[9a] $[\alpha]_D^{25}$ −61.4 (*c*, 1; H_2O)); ^{1}H NMR δ (D_2O) 2.33 (s, 2 H), 2.06 (dd, 1 H, *J* = 13.5, 2.5 Hz), 1.59 (d, 1 H, *J* = 10.8 Hz), 1.49−1.36 (m, 4 H), 1.28 (m, 1 H), 1.19 (m, 1 H).

(−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.2]octane-2-carboxylic Acid (18c). 18c·HCl $[\alpha]^{25}_D$ −12.8 (*c* = 0.5; H_2O) (lit.[12c] (2*S*-enantiomer) $[\alpha]_D^{25}$ +12.4 (*c*, 0.5; H_2O)); ^{1}H NMR δ (D_2O) 2.49 (dt, 1 H, *J* = 14.6, 2.7 Hz), 1.81 (m, 1 H), 1.75 (m, 1 H), 1.73−1.42 (m, 9 H).

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Supporting Information Available: X-ray crystallographic data for compounds **12b**, **15d**, and **17b** including atomic position and atomic displacement parameters as well as a complete list of bond lengths and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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