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Asymmetric synthesis of α-amino acids from α,β-(*Z*)-didehydroamino acid derivatives with 1,2,3,6-tetrahydropyrazin-2-one structure

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Abstract—Chiral (*Z*)-α,β-didehydroamino acid (DDAA) derivatives **14**, **15** and **16** are obtained from a new chiral iminic cyclic glycine template with 1,2,3,6-tetrahydropyrazin-2-one structure **10** by condensation with carbonyl compounds, Eschenmoser's salt and Bredereck's reagent, respectively. The didehydroalanine derivative **15** and the enaminone **16** can give DDAA derivatives **14** using Heck olefination and vinylic nucleophilic substitution. These DDAA derivatives **14** and **15** undergo diastereoselective cyclopropanation, 1,3-dipolar and Diels–Alder cycloaddition reactions giving, after hydrolysis, the corresponding cyclic and bicyclic α-amino acids.

1. Introduction

The increasing number of nonproteinogenic amino acids (Fig. 1) has prompted the development of new methodologies and strategies exclusively focussed on their asymmetric synthesis.[1] α,β-Didehydroamino acids (DDAAs) **I** are one of these conformationally constrained noncoded amino acids. They act as antimicrobial and phytotoxic agents (lantibiotics)[2] and, once incorporated in the peptidic sequence, an enhanced resistance to enzymatic and chemical degradation of the resulting proteins occurs.[2,3] On the analogy of the nature, which biosynthesises DDAAs **I** by dehydration of serine and threonine residues, organic synthesis mainly uses β-elimination reactions for obtaining DDAAs. In this way, chiral DDAA derivatives with *E* (**1**[4] and **2**[5]) and *Z* (**3**,[6] **4**,[7] **5**[8] and **6**[9]) configuration (Fig. 2) have been diastereoselectively generated using a Wittig-type olefination and Knoevenagel condensation from their corresponding chiral glycine templates. The Knoevenagel condensation reaction of chiral oxazinone **7** with aldehydes using, by first time, phase-transfer catalysis (PTC) conditions at room temperature, represented a relevant achievement in order to apply this methodology in a large-scale process. The high diastereoselectivity, together with the mild reaction conditions required, are in contrast with the reported synthesis of other DDAA derivatives **1**–**5**. Usually, strong bases (KOBu^t) and very low temperatures are needed

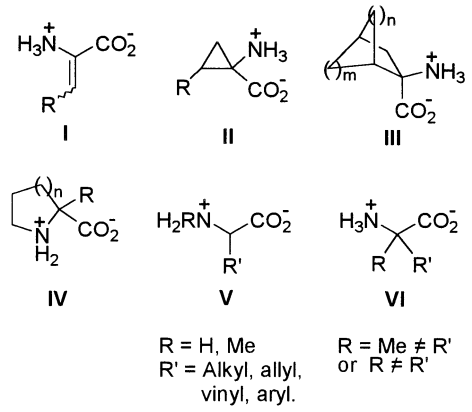

Figure 1. Nonproteinogenic α-amino acids.

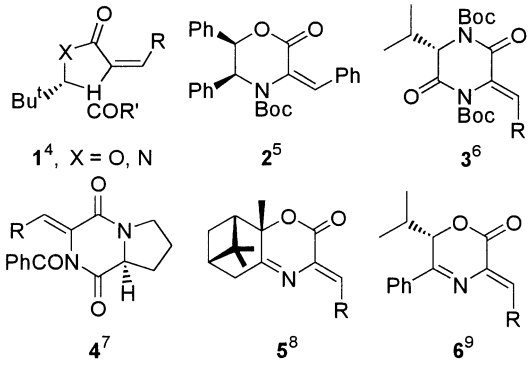

Figure 2. Chiral DDAA derivatives.

Keywords: amino acids; pyrazinones; asymmetric synthesis; phase-transfer catalysis; DDAA derivatives; Knoevenagel condensation; cyclopropanation; Heck reaction; enaminones; Diels–Alder reaction.

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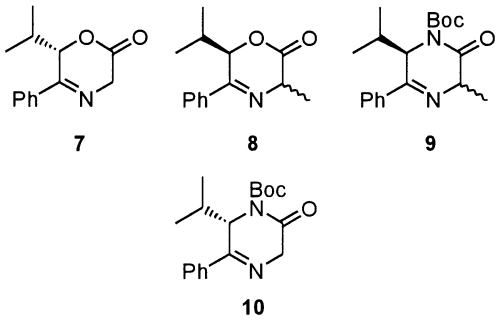


Figure 3. Chiral cyclic iminic templates with oxazinone and pyrazinone structures.

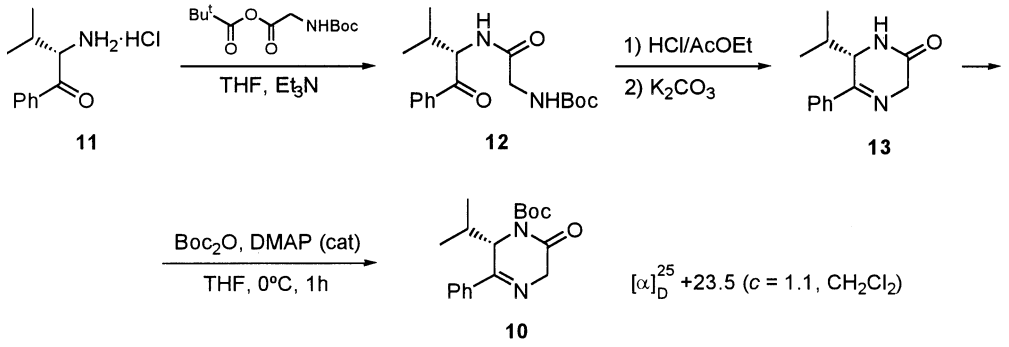
in the case of the pinanone derivative **5**[8] and diketopiperazine **3**[6] obtaining low diastereoselectivities. A Horner–Wadsworth–Emmons olefination of the corresponding phosphonate derivatives afforded heterocycles **1**[4] and oxazinones **2**,[5] while diketopiperazines (DKP) **4**[7] were prepared by chemical transformation of the (*Z*)-alkylideneoxazolones. Chiral DDAA derivatives are very versatile starting compounds for the enantiomerically pure synthesis of a wide series of α-aminoacids.[1] For example, 1-aminocyclopropanecarboxylic acids (ACCs) **II** can be obtained by diastereoselective cyclopropanation with diazoalkenes[5,7,8b,c,10] and phosphonium[11] or sulfoxonium ylides.[5,8a,9] As electrophilic olefins, DDAA derivatives **1**, **2** and **6** underwent Diels–Alder cycloaddition reactions with dienophiles[9a,b,12,13] furnishing, after hydrolysis, bicyclic α-amino acids **III**. An example of the 1,3-dipolar cycloaddition reaction has been reported in the synthesis of (−)-cucurbitine (type **IV** see Fig. 1), a naturally occurring heterocyclic α-amino acid, from DDAA derivative **2**.[14a] Hydrogenation reactions of derivatives **3**,[6] **5**[8b] and **6**[9a,c] using heterogeneous catalysis yield, after hydrolysis, α-amino acids and its *N*-methyl derivatives **V**. Michael addition reactions allow to obtain **V** and **VI** as well. Thus, the addition of L-selectride® onto **5**[8b] and lithium or magnesium cuprates to DKP **3**[15] afforded good diastereoselectivities of monoalkylated heterocycles. Analogously, radical additions to **3**[16] for obtaining monoalkylated DKP have been described.

According to these antecedents, and considering the similar chemical behaviour existing between oxazinones **8**[17] and pyrazinones **9**,[18] we will survey in this work the synthetic applications of the chiral iminic cyclic glycine derivative with pyrazinone structure **10**[19] (Fig. 3) for the synthesis of nonproteinogenic α-amino acids. The previously demonstrated higher stability of pyrazinones **9**[18] and **10**,[19] as well as their reactivity versus the parent oxazinones **7** and **8**, also justify the use of the pyrazinone **10** for this purpose.

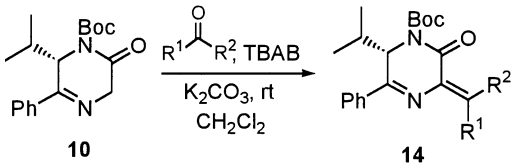
2. Results and discussion

The starting N-Boc protected pyrazine-2-one **10** was obtained, in 77% global yield, following the methodology described previously for the synthesis of pyrazinone **9**.[18a] Chiral auxiliary α-aminoketone hydrochloride **11**,[18a,19] obtained from (*S*)-valine in 70% overall yield, underwent N-acylation with the N-Boc-glycine pivalic acid mixed anhydride generating amide **12** in 97% yield. After deprotection in acidic media (HCl/AcOEt) and cyclisation using a saturated aqueous solution of potassium carbonate, pyrazinone **13** was obtained in 90% yield. Final N-Boc protection was accomplished with di-*tert*-butyl dicarbonate at 0°C in the presence of substoichiometric amounts of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) affording compound **10**[20] in 89% yield (Scheme 1).

The Knoevenagel condensation reaction of **10** with aldehydes (2.5–5.0 equiv.) and acetone (2.5 equiv.) was carried out under a solid–liquid phase transfer catalysis with potassium carbonate (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 sodium and potassium carbonate was required in order to prevent the partial isomerisation of the double bond to an all *endo* conjugated pyrazinone[9a] (Table 1, entry 5, footnote d). DDAAs derivatives **14** were obtained in more than 98% de and isolated as single (*Z*)-diastereomers in good yields after chromatographic purification without any significant decomposition. The oxazinone glycine equivalent obtained from hydroxypinanone, precursor of compounds **5**, is the unique example reported in the literature[8c] able to be condensed with acetone, in the presence of KOBu^t in THF at −78°C, affording a 10% yield of the corresponding DDAA derivative. However, pyrazinone **10** furnished **14h** in 51% yield under these PTC reaction conditions. Reactions with other ketones were attempted (acetophenone, 3-pentanone and cyclopentanone) but no reaction was observed in any case. In the condensation reaction of **10** with acetaldehyde using several reaction conditions like stronger bases (*n*-BuLi, LHMDS, LDA,



Scheme 1. Synthesis of chiral cyclic iminic template **10**.

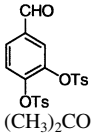
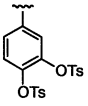


Scheme 2. Synthesis of DDAA derivatives **14** by Knoevenagel condensation.

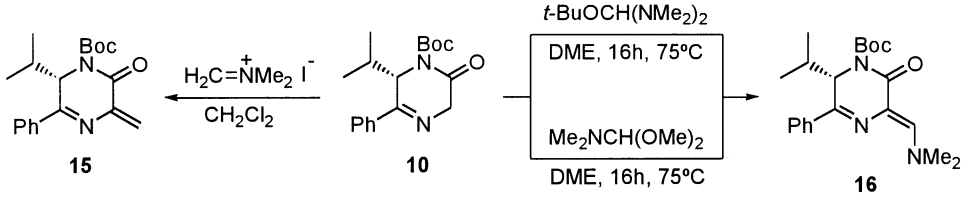
t-BuOLi and *t*-BuOK) at low temperatures (from −78 to 0°C) almost 1:1 mixtures of (*Z*)- and (*E*)-diastereomers **14a** were always detected.

The didehydroalanine derivative **15**[9a] and the enaminone **16** were also prepared by condensation reaction. Thus, *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt)[9,19] (2 equiv.) reacted with **10** in dichloromethane for

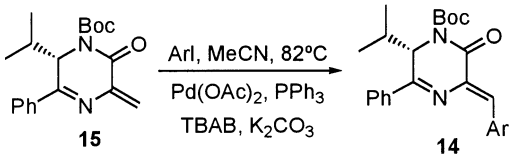
Table 1. Synthesis of chiral (*Z*)-α,β-didehydroamino acid derivatives **14**

Entry	Carbonyl compound	Product					
		No.	R^1	R^2	Yield (%)[a]	R_f[b]	$[\alpha]_D^{25}$[c]
1	CH_3CHO (5.0)	**14a**	CH_3	H	88	0.70	−101.3
2	CH_3CH_2CHO (2.5)	**14b**	CH_3CH_2	H	86	0.83	−179.0
3	$(CH_3)_2CHCHO$ (2.5)	**14c**	$(CH_3)_2CH$	H	83	0.75	−129.3
4	$(CH_3)_3CCHO$ (3.0)	**14d**	$(CH_3)_3C$	H	47	0.77	−90.8
5	PhCHO[d] (2.5)	**14e**	Ph	H	85	0.67	−156.8
6	 (2.2)	**14f**		H	58	0.61	−34.7
7	 (2.2)	**14g**		H	53	0.47	−93.4
8	$(CH_3)_2CO$ (2.5)	**14h**	Me	Me	51	0.75	+59.5

[a] Based on pyrazinone **10** after purification by flash chromatography (silica gel).
[b] Hexane/ethyl acetate 3/2.
[c] In dichloromethane.
[d] A 1:1 mixture of Na_2CO_3 and K_2CO_3 was employed.



Scheme 3. Synthesis of the didehydroalanine derivative **15** and the enaminone **16**.



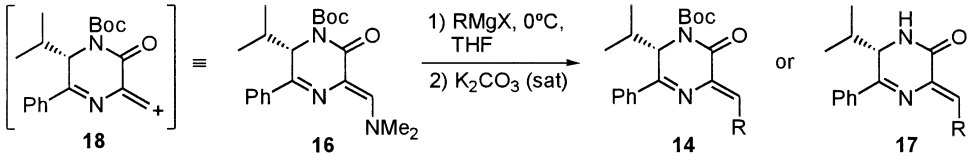
Scheme 4. Synthesis of DDAA derivatives **14** using Heck reaction.

4h (Scheme 3) giving derivative **15** in 88% yield through one pot aminomethylation–elimination process. In addition, *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent) or the cheaper *N*,*N*-dimethylformamide dimethylacetal,[21] in 1,2-dimethoxyethane (DME), afforded (*Z*)-**16** in 96 and 95% yield, respectively (Scheme 3).

Table 2. Synthesis of chiral (*Z*)-α,β-didehydroamino acid derivatives **14** using Heck arylation reaction

Entry	Ar–I	Reaction time (h)	Product			
			No.	Yield (%)[a]	R_f[b]	$[\alpha]_D^{25}$[c]
1	PhI	20	**14e**	54[d]	0.67	−156.8
2	1-Naphthyl–I	20	**14i**	40	0.65	−489.0
3	4-$MeOC_6H_4I$	10	**14j**	70	0.60	−215.0
4	2-MeC_6H_4I	20	**14k**	56	0.80	−128.3

[a] Based on 2-pyrazinone **15** after chromatography (silica gel).
[b] *n*-Hexane/ethyl acetate:3/2.
[c] In dichloromethane.
[d] A 11% of the N-deprotected compound **17e** was also isolated.



Scheme 5. Synthesis of DDAA derivatives **14** and **17** by vinylic nucleophilic substitution of **16**.

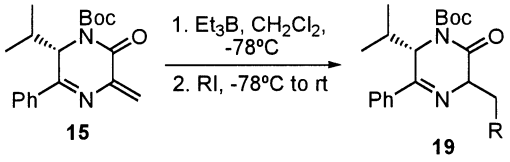
Table 3. Synthesis of chiral (*Z*)-α,β-didehydroamino acid derivatives **14** from enaminone **16**

Entry	RMgX	Reaction time (h)	Product			
			No.	Yield[a]	$[\alpha]_D^{25b}$	R_f[c]
1	$Me_2CHMgCl$	24	**14c**	50	−129.3	0.75
2	Me_3CMgBr	24	**14d**	44	−90.8	0.77
3	PhMgBr	19	**14e**[d]	60	−156.8	0.67
4	1-NaphthylMgI	24	**17i**[e]	54	−189.0	0.50
5	CH_2=CHMgBr	24	**14l**[f]	31	−32.9	0.70

[a] Based on 2-pyrazinone **4** after chromatography (silica gel).
[b] In dichloromethane.
[c] *n*-Hexane/ethyl acetate:3/2.
[d] 2 equiv. of organomagnesium reagent were required.
[e] Under typical Barbier conditions.
[f] Some decomposition took place during purification.

Configurational assignments of DDAA derivatives **14** and **16** were made from ^{1}H NMR data (300 and 500 MHz) obtained from the crude reaction product. For series of compounds **14**, the 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, for compounds **14** and **16**, C–H coupling constants between the olefinic protons and the carbonylic carbon (close to 5 Hz) in proton coupled ^{13}C NMR are consistent with the (*Z*)-configuration.[8b,9a,c]

DDAA derivatives **14** can also be prepared from DDAA derivatives **15** and **16** through two alternative and complementary routes to the Knoevenagel condensation. Both processes, which control the configuration of the C–C double bond, are based on the alkylation of the dehydroalanine **15** by Heck arylation reaction[22,23] and on the vinylic



Scheme 6. Synthesis of pyrazinones **19** by radical Michael-type addition.

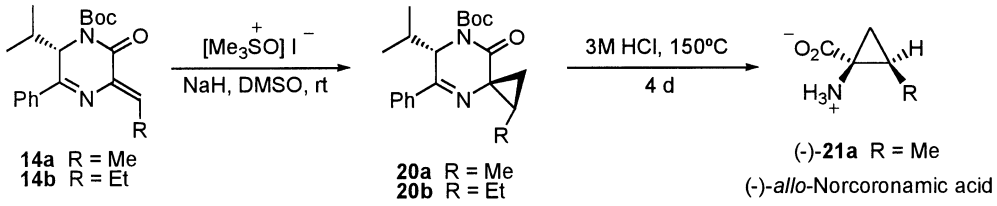
Table 4. Synthesis of monoalkylated derivatives **19** by radical Michael addition

Entry	RI	Reaction time (h)	Product		
			19	Yield[a] (%)	dr
1	Bu^t	23	**19a**	23	1:1
2	Bu	21	**19b**	31	3:2
3	Pr^i	20	**19c**	32	1:1
4	Bu^i	20	**19d**	30	1:1

[a] Determined after column chromatography (silica gel).

nucleophilic substitution onto enaminone **16**.[24] First, pyrazinone **15** reacted with aryl iodides under Jeffery's conditions[22,23,25] using $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) as catalyst in the presence of TBAB (10 mol%) and potassium carbonate (3 equiv.) in refluxing acetonitrile. DDAA derivatives **14** were diastereoselectively obtained in moderate to good yields (Scheme 4 and Table 2). Electron-deficient aryl iodides such as *p*-nitroiodobenzene and aryl bromides did not react under this reaction conditions, however, electron-rich aryl iodides react faster than iodobenzene affording good yields in spite of the steric hindrance showed by *o*-iodotoluene (Table 2, entries 3 and 4). This result is contrary with the normal tendency observed in the Heck arylations with electrophilic olefins.[26] Although the oxidative addition is the determining step in the catalytic cycle, the coordination step between the very low LUMO[27] of the alkene **15** and the higher HOMO of the palladium complex is essential in this coupling reaction. Using iodobenzene as organic electrophile, a little amount of the N-deprotected compound **17e** was also isolated (Table 2, entry 1, footnote d).

Enaminone **16** underwent vinylic nucleophilic substitution, acting as a β-acylvinyl cation **18**,[28] at 0°C by organomagnesium compounds (4 equiv.) affording diastereoselectively (*Z*)-DDAA derivatives **14** in moderate yields (Scheme 5 and Table 3). When phenylmagnesium bromide was employed, the corresponding (*Z*)-DDAA **14e** was obtained in good yield (Table 3, entry 3, footnote d), nevertheless isopropyl and *tert*-butylmagnesium chlorides (Table 3, entries 1 and 2) gave lower yields of products **14**. This result could be justified because both reagents acted as hydride source, which reacted with enaminone **16** furnishing also the didehydroalanine derivative **15**. Conjugated diene **14l** (Table 3, entry 5, footnote f), isolated in 31% yield, was a very sensitive compound, which could not be accessed by the Knoevenagel condensation of acrolein with the corresponding enolate of pyrazinone **10**. The possibility to run



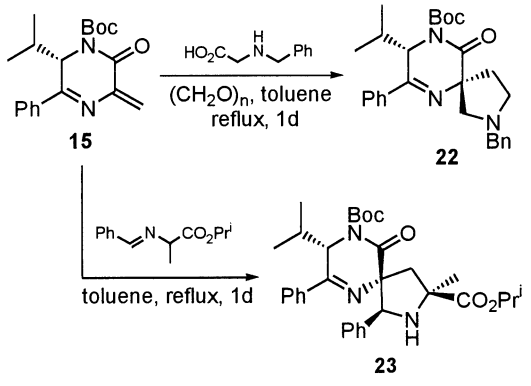
Scheme 7. Synthesis of ACC (−)-*allo*-norcoronamic acid **21**.

the reaction under Barbier conditions[29] at room temperature was also tested by using 1-iodonaphthalene (5 equiv.) and magnesium powder (10 equiv.) affording deprotected compound **17i** in good yield after purification (Table 3, entry 4, footnote e). When the same strategy was applied to isopropylmagnesium chloride, a very low yield (less than 20%) of the deprotected product **17c** and high amounts of decomposition products were detected. In general, yields depicted in Table 3 could not be improved neither using catalytic amounts nor stoichiometric quantities of copper(I) iodide at −78°C raising the temperature to 0°C. More nucleophilic organomagnesium compounds such as benzyl, methyl or butylmagnesium bromides caused N-Boc deprotection and subsequent decomposition. Again, the (*Z*)-configuration of the new DDAA derivatives was confirmed as described before.

Monoalkylated α-amino acids derivatives could not be generated from the chiral glycine template **10** due to the easy second deprotonation after the first alkylation reaction affording 3,3-dialkylated 1,2,3,6-tetrahydropyrazin-2-ones. Other useful strategies for obtaining monoalkylated heterocycles such as hydrogenation of the corresponding DDAA derivatives **14** [Pd/C, PtO_2, $Pd(OH)_2$] and ionic Michael-type addition reactions onto **14** or **15** gave very disappointing results due to the lability of the *tert*-butoxycarbonyl protecting group. However, **15** suffered radical Michael addition reaction of alkyl iodides (6 equiv.) using triethylborane (3 equiv.) in anhydrous dichloromethane from −78°C to room temperature [16,30] (Scheme 6 and Table 4). Monoalkylated products **19** were obtained in moderate yields with very low diastereoselectivity, the best result being the reaction with *n*-butyl iodide whose diastereomer ratio was 3:2 (Table 4, entry 2). These dr were determined by ^{1}H NMR experiments of the crude reaction products.

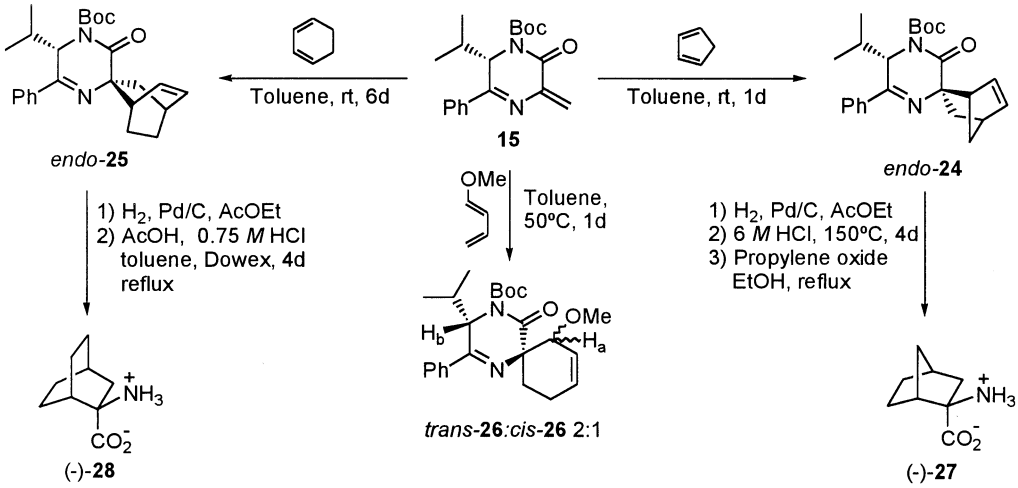
The diastereoselective cyclopropanation of DDAA derivatives **14** was also studied.[31] The reaction of **14a** (R=Me) and **14b** (R=Et) with the less toxic and safest Corey's dimethylsulfoxonium methylide,[32] prepared with NaH in DMSO, furnished spiro-compounds **20** as 11:1 (R=Me) and 23:1 (R=Et) mixtures of diastereoisomers (Scheme 7). These ratios were determined by GC, HPLC, ^{1}H- and ^{13}C NMR. When using DMF instead of DMSO as solvent at −20°C any improvement of the diastereoselectivity was observed. Pure major stereoisomers **20a** (R=Me) and **20b** (R=Et) were isolated after flash chromatography in 70 and 79% yield, respectively. The supposed stereochemistry of **20a** and **20b** was confirmed by the optical rotation of the ACC **21a**, obtained from **20a** after acidic hydrolysis (Scheme 7). Many efforts to hydrolyse **20a** afforded decomposed products, only a 24% yield of *allo*-norcoronamic acid **21a**, in high enantiomerically pure form (>98% ee), was obtained after treatment with 3 M hydrochloric acid, at 100°C during four days (Scheme 7). This ACC is a biosynthetic precursor of plants hormones, acts as enzyme inhibitor and plays an important role in the regulation of enzymatic processes in plants.[33] Similarly, **21a** is the strongest known competitive inhibitor of the ethylene-forming enzyme (EFE) in mung bean hypocotyls.[34]

1,3-Dipolar cycloaddition reactions using **15** as dipolarophile and in situ generated azomethine ylides derived from *N*-benzylglycine and formaldehyde, was performed in refluxing toluene for 1d. Cycloadduct **22** (precursor of natural product (−)-cucurbitine)[14] was detected in the reaction mixture but it could not be purified (Scheme 8). Alternatively, the direct hydrolysis of this reaction crude was attempted, followed by Dowex 50X-100 chromatography, but no traces of the heterocyclic α-amino acid could be obtained. The same behaviour was observed with the cycloadduct **23**, generated from the thermal 1,3-dipolar cycloaddition reaction between **15** and isopropyl *N*-benzylidene alaninate[35] (Scheme 8).



Scheme 8. Pyrazinone **15** acting as 1,3-dipole.

Didehydroalanine derivative **15** was further tested as dienophile in Diels–Alder cycloaddition reactions (Scheme 9). The reaction with cyclopentadiene took place diastereoselectively at room temperature, in toluene for 3 h affording, after chromatographic purification, cycloadduct **24** in 42% yield. By other side, cyclohexadiene needed longer reaction time (6 days) for achieving high reaction conversions at room temperature. Again, only one stereoisomer was detected from the reaction mixture and spiro-compound **25** was finally isolated in 95% yield. 1-Methoxybutadiene reacted with **15** at 50°C for 1 day achieving a 2:1 mixture of diastereomers *trans*-**26** and *cis*-**26** in 66% isolated yield. The presumed absolute configuration of the *endo*-adduct **24** was confirmed later by the optical rotation of the bicyclic α-amino acid **27**,[9a] which was isolated in 61% yield by

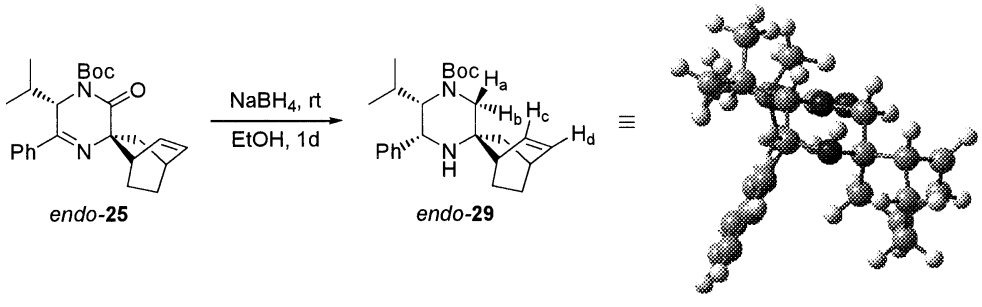


Scheme 9. Synthesis of the bicyclic α-amino acids.

hydrogenation, followed by acidic hydrolysis of the amide and imino groups at 150°C for 4 days (Scheme 9). Nevertheless, the same information could not be extracted from the bicyclic α-amino acid **28** because the hydrogenation of the carbon–carbon double bond removed the structural key clue. X-Ray diffraction experiments could not be done due to the oily nature of adduct **25**, so we thought that the reduction of the imino group and subsequent generation of the corresponding salt with a chiral carboxylic acid would be a possible solution for elucidating its stereochemistry. Surprisingly, amide carbonyl group was completely reduced with an excess of sodium borohydride in EtOH at room temperature for 1 day (Scheme 10). The structure and the more stable conformation of the resulting perhydropyrazine **29** was totally assigned combining ^{1}H NMR experiments (COSY, HETCOR, HMQC, HMBC, NOESY and GOESY) together with molecular mechanics calculations (Scheme 10).[36] The stereochemistry of the *endo*-**29** adduct was supported by the observed NOE effects of H_c with both H_a and H_b, and H_d with H_b, and they are not represented in Scheme 9 for simplicity. According to these data, the resulting structure of **25** was the *endo*-adduct shown in Scheme 9.

A similar study was done when 1-methoxy-1,3-butadiene was allowed to react with **15**. The structure of the cycloadducts *trans*-**26** and *cis*-**26** (2:1) was assigned by NMR experiments and they are in agreement with the predominant HOMO(diene)-LUMO (**15**) interaction,[27,37] which could be justified by two facts: first, the H_a protons in both stereoisomers appears as a singlet shifted downfield due to the geminal methoxy group, and second, no coupling with the vicinal olefinic proton was observed because the value of its dihedral angle with the double bond was close to 90°. The more stable conformation of the two diastereomers was obtained from molecular mechanics calculations[36] being each one in total concordance with NMR data. The major stereoisomer *trans*-**26** showed a relative *trans* configuration as a result of the *endo* approach. These assumptions were supported by comparing the large ^{3}J H–C coupling constant between H_a and the carbonyl group (dihedral angle near to 180°) exhibited by *trans*-**26** with the analogous one of the *cis*-**26** (dihedral angle close to 60°). Small NOE effects between H_a and H_b, and H_a with the aromatic protons were only observed in the *trans* isomer *trans*-**26**, as it was expected from their corresponding conformations.

Enantiomerically pure (>98% ee) bicyclic α-amino acids (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid **27** and (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.2]octane-2-carboxylic acid **28** were obtained in 61 and 38% overall yield (based on pyrazinone **15** and avoiding the intermediate purification). The general features of these amino acids such as bulkiness and apolarity of the bicyclic moiety confer a maximal resistance to metabolic attack. Furthermore, the conformational rigidity and the presence of a substituent on the ring is a very useful tool in order to clarify the conformational role of substituents in bioreceptorial interactions.[38] Particularly, **27** inhibits the transport of nonpolar amino acids across cell membranes, acts as an insulin releasing factor and inhibits the flavoprotein amino acid



Scheme 10. Synthesis and more stable conformation of **29**.

oxidases, whereas **28** perturb selectively the levels of neutral amino acids in the cerebral cortex.[39]

3. Conclusion

We conclude that 1,2,3,6-tetrahydropyrazin-2-one **10** is a versatile glycine template for preparing diastereoselectively (*Z*)-α,β-didehydroamino acid (DDAA) derivatives using, as occurred in the case of oxazinone **7**, the condensation reaction with aldehydes under mild reaction conditions (PTC, inorganic bases and room temperature). Yields obtained starting from pyrazinone **10** are higher than the reported for the analogous oxazinone **7**. Also slightly higher diastereoselectivities were observed with this new glycine template. Synthesis of the enaminone **17** in high yields and its reactivity as a β-acylvinyl cation, the Heck olefination using DDAA derivatives **15** as well as the radical Michael-type addition, have not been reported in the case of the oxazinone **7**. The diastereoselectivity was very high in these reactions except for the 1,4 radical addition. Cyclopropanation reaction of the DDAA derivatives **14** was more stereoselective and efficient than the corresponding reaction carried out with oxazinone derivatives, unfortunately, the resulting spiro-compounds proved to be very unstable giving ACCs in poor yields. Finally, cycloaddition reactions with dehydroalanine derivative **15** demonstrated than spiro-compounds, obtained through 1,3-dipolar reaction, are also very sensitive products. However, Diels–Alder reaction took place smoothly with very high *endo*-selectivity affording, after hydrolysis, bicyclic α-amino acids improving the results previously obtained with the chiral oxazinone template. The LUMO of the pyrazinone **15** is lower than the oxazinone **7**,[27] which allowed run the reactions at lower temperatures arising higher selectivity. All these results confirm once more that pyrazinones are more reactive and more stable compounds than the oxazinones being a versatile precursor for obtaining a wide series of non-proteinogenic α-amino acids.

4. Experimental

4.1. General

Melting points were determined with a Reichert Thermovar hot plate apparatus are uncorrected. IR were recorded on a Nicolet 510 P-FT and only the structurally most important peaks are listed. NMR spectra were performed by the NMR Service of the University of Alicante on a Bruker AC-300 and DRX-500 using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. Optical rotations were measured on a Jasco DIP-1000 polarimeter. HPLC analyses were performed on a Shimadzu LC-10AD equipped with an APEX-silica 5 μm and DAICEL OD-H columns, eluting with mixtures of acetonitrile/water and *n*-hexane/isopropyl alcohol, respectively. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000 and low-resolution electrospray ionisation (ESI) mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed by the Microanalyses Service of the University of Alicante. Analytical TLC was performed on Schleicher and Schuell F1400/LS silica gel plates and the spots visualised with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040–0.063 mm).

4.1.1. Synthesis of (2*S*)-2-*tert*-butoxycarbonylamino-3-methyl-1-phenyl-1-butanone hydrochloride 11. The synthesis of hydrochloride **11** was performed as indicated in the literature[18a] using (*S*)-valine. $[\alpha]_D^{25}=+61.4$ (c=0.65, H_2O).

4.1.2. Synthesis of *N*-1-[(1*S*)-1-benzoyl-2-methylpropyl]-2-[(*tert*-butoxycarbonyl)amino]acetamide 12. To a suspension of freshly prepared N-Boc-glycine-pivalic acid mixed anhydride[40] (10 mmol) containing triethylamine (4.17 mL, 30 mmol) at 0°C was added hydrochloride **11** (2.13 g, 10 mmol) and the reaction stirred at room temperature for 3 h. Water (40 mL) and ethyl acetate (30 mL) were added, the organic phase separated, dried (Na_2SO_4) and evaporated in vacuo. The residue was washed with hot *n*-hexane yielding ketone **12** (3.18 mg, 97%) as viscous colourless oil. $[\alpha]_D^{25}=-20{,}6$ (c=0.80, CH_2Cl_2); R_f 0.35 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3500–3100 and 1715–1650 cm^{-1}; δ_H 0.77, 1.01 (2d, J=6.7 Hz, 6H, $(CH_3)_2CH$), 1.46 (s, 9H, $(CH_3)_3C$), 2.22 (m, 1H, $CH(CH_3)_2$), 3.82 (dd, J=9.5, 5.8 Hz, 2H, CH_2), 4.97 (d, J=10.0, 1H, NHBoc), 5.57 (dd, J=8.4, 3.5 Hz, 1H, CHN) and 7.08–8.00 (m, 6H, ArH and $NHCOCH_2$); δ_C 16.46, 19.85 ($(CH_3)_2CH$), 28.14 ($(CH_3)_3C$), 31.59 ($CH(CH_3)_2$), 44.25 (CH_2), 57.85 (CHN), 81.66 ($(CH_3)_3C$), 125.52, 128.51, 133.67, 135.06 (ArC), 155.97, 169.64 (2×NCO) and 198.84 (ArCO); m/z(ESI) 335 (M^++1, 34%). HRMS calcd for $C_{18}H_{26}N_2O_4$: 334.1893. Found: 334.1894.

4.1.3. Synthesis of (6*S*)-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 13. A solution of ketone **12** (3.70 g, 10 mmol) in a 3 M solution of hydrogen chloride in ethyl acetate (50 mL) was stirred for 1 h. The solvent was evaporated, dissolved in 0.1 M hydrochloric acid (10 mL) and washed with ether (10 mL). The organic phase was discarded and the aqueous phase was treated with a saturated solution of K_2CO_3 (50 mL) and extracted with ethyl acetate (3×15 mL). The organic phase was separated, dried (Na_2SO_4) and evaporated affording pure pyrazinone **13**. When cyclisation was not complete in this step (^1H NMR monitoring) the pure mixture was dissolved in dichloromethane (10 mL) and triethylamine (1.5 mL, 10 mmol) and the resulting solution was stirred overnight at room temperature. Solvents were evaporated and compound **13** was obtained (1.80 g, 90%) as a pale yellow oil. $[\alpha]_D^{25}=16.6$ (c=1.63, CH_2Cl_2); R_f 0.35 (ethyl acetate); ν_{max} (film) 3500–3200 and 1740–1680 cm^{-1}; δ_H 0.78, 0.92 (2d, J=7.0 Hz, 6H, $(CH_3)_2CH$)), 2.16 (m, 1H, $CHCH_3$), 4.30 (dd, J=22.0, 3.1 Hz, 1H, CH_2), 4.58 (dd, J=22.0, 2.4 Hz, 1H, CH_2), 4.70 (m, 1H, CHN), 7.20–7.71 (m, 5H, ArH) and 7.81 (br. s, 1H, NH); δ_C 14.09, 19.13 ($(CH_3)_2CH$)), 32.70 ($CHCH_3$), 52.93 (CHN), 60.11 (CH_2), 126.68, 128.63, 130.43, 136.49 (ArC), 164.98 (C=N) and 169.54 (CO); m/z(ESI) 217 (M^++1, 93%). HRMS calcd for $C_{13}H_{16}N_2O$: 216.1263. Found: 216.1262.

4.1.4. Synthesis of (6*S*)-*N*-1-(*tert*-butoxycarbonyl)-5-phenyl-6-isopropyl-1,2,3,6-tetrahydro-2-pyrazinone 10. Di-*tert*-butyl-dicarbonate (2.64 g, 11 mmol) dissolved in THF (6 mL) was added to a stirred solution of **13** (2.16 g,

10 mmol) and 4-dimethylaminopyridine (70 mg, 0.1 mmol) in THF (30 mL) at 0°C and stirring continued for 90 min at the same temperature. THF was evaporated under vacuo and the residue chromatographed (SiO_2) eluting with *n*-hexane yielding **10** (2.8 g, 89%) as a red oil. $[\alpha]_D^{25}$=23.5 (*c*=1.10, CH_2Cl_2); R_f 0.43 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 1780–1700 cm^{-1}; δ_H 0.87, 0.92 ((2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CH)), 1.59 (s, 9H, (CH_3)$_3$C), 2.13 (m, 1H, C*H*CH_3), 4.36, 4.76 (2d, *J*=21.7 Hz, 2H, CH_2), 5.60 (d, *J*=7.3 Hz, 1H, CHN) and 7.26–7.82 (m, 5H, ArH); δ_C 19.21, 19.99 ((CH_3)$_2$CH)), 27.96 ((CH_3)$_3$C), 33.07 (*C*HCH_3), 56.26 (CH_2), 59.88 (CHN), 84.16 ((CH_3)$_3$*C*), 126.87, 128.76, 130.86, 137.17 (ArC), 151.90 (C=N), 167.97 and 171.00 (2×CO); *m*/*z*(ESI) 316 (M^+, 50%). HRMS calcd for $C_{18}H_{24}N_2O_3$: 316.1787. Found: 316.1785.

4.2. Synthesis of (*Z*)-α,β-didehydroamino acids 14 by condensation reaction with aldehydes. General procedure

To a solution of pyrazinone **10** (316 mg, 1 mmol) in anhydrous dichloromethane (5 mL) under an argon atmosphere, K_2CO_3 (407 mg, 3 mmol) (using benzaldehyde a 1:1 mixture of K_2CO_3/Na_2CO_3 was required, see text and Table 1) and Bu_4NBr (46 mg, 0.1 mmol) were added. The aldehyde or acetone was then added to the resulting suspension (see Table 1) and stirring continued for 20 h (compound **14d** required 48 h for completion at room temperature). Solvent was evaporated under vacuo and the residue purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate: 90/10), affording DDAA derivatives **14**. Physical and analytical data follow:

4.2.1. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-3-[(*Z*)-ethylidene]-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14a. Pale yellow oil (88%). $[\alpha]_D^{25}$=−101.3 (*c*=1.90, CH_2Cl_2); R_f 0.70 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3061, 1771, 1720, 1629 and 852, cm^{-1}; δ_H 0.85 [(2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CH)], 1.58 (s, 9H, (CH_3)$_3$C), 2.06 (m, 1H, C*H*(CH_3)$_2$), 2.16 (d, *J*=7.3 Hz, 3H, CH_3CH=C), 5.59 (d, *J*=6.5 Hz, 1H, CHN), 6.93 (*c*, *J*=7.3 Hz, 1H, CH_3CH=C) and 7.27–8.00 (m, 5H, ArH); δ_C 13.32 (*C*H_3CH=C), 18.83, 19.73 ((CH_3)$_2$CH)), 28.03 ((CH_3)$_3$C), 34.66 (*C*H(CH_3)$_2$), 58.88 (CHN), 83.65 ((CH_3)$_3$*C*), 127.24, 128.72, 131.03, 134.91, 136.82, 137.92 (ArC and CH=C), 152.36, 161.67 and 162.84 (2×CO and C=N); *m*/*z*(ESI) 343 (M^++1, 4%). HRMS calcd for $C_{20}H_{26}N_2O_3$: 342.1943. Found: 342.1942.

4.2.2. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-5-phenyl-3-[(*Z*)-propylidene]-1,2,3,6-tetrahydro-2-pyrazinone 14b. Sticky pale yellow oil (86%). $[\alpha]_D^{25}$=−179.0 (*c*=0.90, CH_2Cl_2); R_f 0.83 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3061, 1772–1716, 1625 and 823 cm^{-1}; δ_H 0.83, 0.87 (2d, *J*=7.3 Hz, 6H, (CH_3)$_2$CH), 1.11 (t, *J*=7.9 Hz, 3H, CH_3CH_2), 1.54 (s, 9H, (CH_3)$_3$C), 2.13 (m, 1H, C*H*CH_3), 2.60, 2.73 (2m, 2H, CH_2), 5.61 (d, *J*=6.1 Hz, 1H, CHN), 6.73 (t, *J*=7.9 Hz, 1H, CH=C) and 7.51–8.08 (m, 5H, ArH); δ_C 13.35 (*C*H_3CH_2), 19.08, 19.87 ((CH_3)$_2$CH)), 21.03 (CH_2), 27.96 ((CH_3)$_3$C), 35.43 (*C*H(CH_3)$_2$), 59.65 (CHN), 83.38 ((CH_3)$_3$*C*), 128.12, 129.53, 131.87, 137.82, 137.84, 140.20 (ArC and CH=C), 153.01 (C=N), 161.55 (CONBoc) and 163.92 (COO); *m*/*z* (ESI) 357 (M^++1, 17%). HRMS calcd for $C_{21}H_{28}N_2O_3$: 356.2100. Found: 356.2099.

4.2.3. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-[(*Z*)-2-methylpropylidene]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14c. Pale yellow oil (83%). $[\alpha]_D^{25}$=−129.3 (*c*=0.90, CH_2Cl_2); R_f 0.75 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3064, 1770–1716, 1623 and 857 cm^{-1}; δ_H 0.82, 0.88 (2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CHCN), 1.07, 1.15 (2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CHC=C), 1.57 (s, 9H, (CH_3)$_3$C), 2.10 (m, 1H, (CH_3)$_2$C*H*CN), 3.48 (m, 1H, (CH_3)$_2$C*H*C=C), 5.58 (d, *J*=6.7 Hz, 1H, CHN), 6.65 (d, *J*=9.8 Hz, 1H, C*H*=C) and 7.42–7.98 (m, 5H, ArH); δ_C 19.11, 19.82 ((CH_3)$_2$CHCN), 22.03, 22.36 ((CH_3)$_2$-CHC=C), 27.04 ((CH_3)$_2$*C*HC=C), 28.09 ((CH_3)$_3$C), 35.44 ((CH_3)$_2$*C*HCN), 59.68 (*C*HCH(CH_3)$_2$), 83.40 ((CH_3)$_3$*C*), 128.13, 129.56, 131.89, 136.65, 137.66, 144.80 (ArC and C=CH), 153.01 (C=N), 161.65 and 163.97 (2×CO); *m*/*z* (ESI) 371 (M^++1, 2%). HRMS calcd for $C_{22}H_{30}N_2O_3$: 370.2256. Found: 370.2257.

4.2.4. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl-6-isopropyl-3-[(*Z*)-2,2-dimethylpropylidene)]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14d. Pale yellow oil (47%). $[\alpha]_D^{25}$=−90.8 (*c*=1.00, CH_2Cl_2); R_f 0.77 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3062, 1770–1726, 1630 and 815 cm^{-1}; δ_H 0.83, 0.87 (2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CH), 1.35 (s, 9H, (CH_3)$_3$CC=C), 1.57 (s, 9H, (CH_3)$_3$CO), 2.11 (m, 1H, (CH_3)$_2$C*H*), 5.57 (d, *J*=6.7 Hz, 1H, CHN), 6.80 (s, 1H, C=CH) and 7.26–7.97 (m, 5H, ArH); δ_C 18.98, 19.74 ((CH_3)$_2$CH), 28.03 ((CH_3)$_3$CO), 30.27 ((CH_3)$_3$CC=C), 33.65 ((CH_3)$_2$*C*H), 58.33 (CHN), 68.50 ((CH_3)$_3$*C*C=C), 83.63 ((CH_3)$_3$*C*O), 127.21, 128.77, 130.85 136.18, 136.74, 146.60 (ArC and *C*=CH), 152.48 (C=N), 161.99 and 162.45 (2×CO); *m*/*z* (ESI) 385 (M^++1, 5%). HRMS calcd for $C_{23}H_{32}N_2O_3$: 384.2413. Found: 384.2414.

4.2.5. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-5-phenyl-3-[(*Z*)-1-phenylmethylidene]-1,2,3,6-tetrahydro-2-pyrazinone 14e. Pale yellow oil (85%). $[\alpha]_D^{25}$=−156.8 (*c*=1.20, CH_2Cl_2); R_f 0.67 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3081, 1770–1714, 1608 and 817 cm^{-1}; δ_H 0.92 (2d, 6H, (CH_3)$_2$CH), 1.60 (s, 9H, (CH_3)$_3$C), 2.15 (m, 1H, (CH_3)$_2$C*H*), 5.66 (d, *J*=7.0 Hz, 1H, CHN), 7.23–8.08 (m, 11H, ArH and CH=C); δ_C 18.89, 19.86 ((CH_3)$_2$CH), 27.95 ((CH_3)$_3$C), 34.66 ((CH_3)$_2$*C*H), 58.61 (CHN), 83.76 ((CH_3)$_3$*C*), 127.49, 128.38, 128.88, 129.36, 131.27, 132.43, 134.81, 135.48, 128.83, 136.47 (ArC and C=CH), 152.21 (C=N), 162.16 and 164.49 (2×CO); *m*/*z*(ESI) 405 (M^++1, 5%) and *m*/*z* (EI) 304 (M^+−100, 23%). HRMS calcd for $C_{25}H_{28}N_2O_3$: 404.2100. Found: 404.2099.

4.2.6. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-3-[(*Z*)-*N*-1-(*tert*-butoxycarbonyl)-1H-indolylmethylidene]-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14f. Pale yellow oil (58%). $[\alpha]_D^{25}$=−34.7 (*c*=0.40, CH_2Cl_2); R_f 0.61 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3063, 1741, 1679 and 845 cm^{-1}; δ_H 0.90 (2d, *J*=7.0 Hz, 6H, (CH_3)$_2$CH), 1.60 (s, 9H, NCO_2Bu^t), 1.70 (s, 9H, $CONCO_2Bu^t$), 2.15 (m, 1H, (CH_3)$_2$C*H*)), 5.70 (d, *J*=6.6 Hz, 1H, CHN) and 7.20–8.30 (m, 11H, In-H, C=CH and ArH); δ_C 18.83, 19.73 ((CH_3)$_2$CH), 28.03 (2×(CH_3)$_3$C), 34.70 ((CH_3)$_2$*C*H), 58.90 (CHN), 85.65 (2×(CH_3)$_3$*C*), 114.56, 115.00, 115.54, 119.00,

120.83, 122.06, 123.76, 125.00, 127.04, 128.40, 130.10, 138.25 (ArC and CH=C), 151.34 (C=N), 163.39 (2×CO_2Bu^t) and 173.87 ($CONCO_2Bu^t$); *m/z*(EI) 343 (M^+-200, 1%), 186 (1), 145 (80), 144 (100), 116 (33), 90 (8), 89 (34), 77 (2), 44 (22) and 41 (20). HRMS calcd for $C_{32}H_{37}N_3O_5$: 543.2733. Found: 543.2730.

4.2.7. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-5-phenyl-3-{(*Z*)-1-[3,4-bis(4-methylphenylsulfonyloxy)-phenyl]methylidene}-1,2,3,6-tetrahydro-2-pyrazinone 14g. Sticky pale yellow oil (53%). $[\alpha]_D^{25}=-93.4$ (*c*=1.60, CH_2Cl_2); R_f 0.47 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3097, 1700, 1731, 1400 and 863 cm^{-1}; δ_H 0.90 (2d, *J*=6.6 Hz, 6H, (CH_3)$_2$CH), 1.60 (s, 9H, (CH_3)$_3$C), 2.06 (m, 1H, (CH_3)$_2$C*H*)), 2.46 (s, 6H, 2×CH_3Ph), 5.68 (d, *J*=6.4 Hz, 1H, CHN) and 7.28–8.29 (m, 17H, ArH and C=CH); δ_C 18.92, 19.88 ((CH_3)$_2$CH), 21.80 (2×CH_3Ph), 28.04 ((CH_3)$_3$C), 35.14 ((CH_3)$_2$*C*H), 58.96 (CHN), 84.14 ((CH_3)$_3$*C*), 124.94, 125.24, 128.52, 128.82, 129.91, 131.86, 131.89, 131.92, 132.31, 134.94, 135.41, 136.14, 136.75, 141.56, 141.96, 145.66, 145.80, 145.86, 146.11, 146.20 (ArC and C=C), 152.07 (C=N), 161.75 (*C*O_2Bu^t) and (*C*ONBoc). *m/z*(ESI) 746 (M^++2, 4%). HRMS calcd for $C_{39}H_{40}N_2O_9S_2$: 744.2082. Found: 744.2090.

4.2.8. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-3-(methylethylidene)-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14h. Pale yellow oil (51%). $[\alpha]_D^{25}=+59.5$ (*c*=1.60, CH_2Cl_2); R_f 0.77 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3062, 1803, 1720, 1651 and 847 cm^{-1}; δ_H 0.79, 0.88 (2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CH)), 1.48 (s, 6H, (CH_3)$_2$C=C), 1.54 (s, 9H, (CH_3)$_3$C), 1.93 (m, 1H, C*H*(CH_3)$_2$), 5.41 (d, *J*=7.3 Hz, 1H, CHN) and 7.26–7.98 (m, 5H, ArH); δ_C 19.15, 20.44 ((CH_3)$_2$CH)), 26.79 ((CH_3)$_2$C=C), 28.02 ((CH_3)$_3$C), 34.43 (*C*H(CH_3)$_2$), 60.99 (CHN), 83.17 ((CH_3)$_3$*C*), 127.26, 127.41, 128.47, 128.79, 130.47, 137.99 (ArC and (CH_3)$_2$*C*=*C*), 152.17, 166.39 and 168.82 (2×CO, C=N); *m/z*(ESI) 357 (M^++1, 5%). HRMS calcd for $C_{21}H_{28}N_2O_3$: 356.2100. Found: 356.2102.

4.2.9. Synthesis of (6*S*)-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methylidene-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 15. To a stirred solution of dimethylmethyleneammonium iodide (371 mg, 2 mmol) in anhydrous dichloromethane (3 mL) was added a solution of **10** (316 mg, 1 mmol) in dry dichloromethane (2 mL). The mixture was stirred at room temperature for 20 h and an aqueous saturated solution of sodium bicarbonate (10 mL) was added at 0°C. The organic phase was washed with water (2×15 mL) and the organic layer was dried (Na_2SO_4) and evaporated under vacuo obtaining **15** (289 mg, 88%) as a pale yellow oil. $[\alpha]_D^{25}=-118.9$ (*c*=1.00, CH_2Cl_2); R_f 0.74 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3061, 1774–1723, 1642 and 882 cm^{-1}; δ_H 0.85, 0.88 (2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CH), 1.59 (s, 9H, (CH_3)$_3$C), 2.11 (m, 1H, (CH_3)$_2$C*H*), 5.63 (d, *J*=6.0 Hz, 1H, CHN), 5.81, 6.33 (2s, 2H, C=CH_2) and 7.27–7.97 (m, 5H, ArH); δ_C 18.80, 19.64 ((CH_3)$_2$CH), 27.97 ((CH_3)$_3$C), 35.08 ((CH_3)$_2$CH), 59.70 (CHN), 84.02 ((CH_3)$_3$*C*), 121.76 (C=*C*H_2), 127.34, 128.78, 131.40, 136.28, 143.85 (ArC and *C*=CH_2), 152.06 (C=N), 161.17 and 165.58 (2×CO); *m/z* (ESI) 329 (M^++1, 10%). HRMS calcd for $C_{19}H_{24}N_2O_3$: 328.1787. Found: 328.1789.

4.2.10. Synthesis of (6*S*)-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-[(*Z*)-1-dimethylaminomethyliden]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 16. To a stirred solution of pyrazinone **10** (316 mg, 1 mmol) in 1,2-dimetoxyethane (4 mL), was added dimethylformamide dimethylacetal (200 μl, 1.5 mmol) or *tert*-butoxy-bis(dimethylamino)-methane (Bredereck′s reagent) (310 μl, 1.5 mmol) and the mixture was stirred at 75°C for 16 h. Solvent was evaporated obtaining pure compound **16** (353 mg and 358 mg, 95 and 96%, respectively). $[\alpha]_D^{25}=-739.6$ (*c*=0.65, CH_2Cl_2); R_f 0.21 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3064, 1770–1716, 1623 and 857 cm^{-1}; δ_H 0.84, 0.91 ((2d, *J*=7.0 Hz, 6H, (CH_3)$_2$CH)), 1.52 (s, 9H, (CH_3)$_3$C), 2.11 (m, 1H, (CH_3)$_2$C*H*)), 3.14, 3.54 (2s, 6H, (CH_3)$_2$N), 5.41 (d, *J*=7.3 Hz, 1H, CHN), 7.31–7.99 (m, 5H, ArH) and 7.46 (s, 1H, C=CH); δ_C 18.78, 20.01 ((CH_3)$_2$CH), 28.05 ((CH_3)$_3$C), 32.26 ((CH_3)$_2$*C*H), 39.90, 47.39 ((CH_3)$_2$N), 57.23 (CHN), 82.07 ((CH_3)$_3$*C*), 112.45 (*C*=CH), 125.96, 127.96, 128.39, 137.78 (ArC), 144.38 (C=*C*H), 150.45, 152.95 and 163.34 (2×C=O and C=N); *m/z*(EI) 271 (M^+-100, 11%), 228 (100), 187 (36), 185 (20), 91 (10), 77 (8) and 44(69). HRMS calcd for $C_{21}H_{29}N_3O_3$: 371.2209. Found: 371.2204.

4.3. Synthesis of (*Z*)-DDAA derivatives 14 by Heck reaction of 15 with aryl iodides. General procedure

$Pd(OAc)_2$ (11 mg, 0,05 mmol), PPh_3 (26 mg, 0.1 mmol), Bu_4NBr (32 mg, 0.1 mmol), K_2CO_3 (414 mg, 3 mmol), methylenic derivative **15** (328 mg, 1 mmol) and the corresponding iodoarene (1.2 mmol), were suspended in acetonitrile (5 mL). The resulting mixture was refluxed for times depicted in Table 2. Acetonitrile was evaporated under vacuo and water was added (10 mL). The aqueous phase was extracted with ethyl acetate (3×15 mL), and the resulting organic layer was dried (Na_2SO_4) and evaporated under vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate), obtaining DDAA derivatives **14**. Physical and analytical data follow:

4.3.1. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-[(*Z*)-1-(1-naphthyl)methylidene]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14i. Pale yellow oil (40%). $[\alpha]_D^{25}=-489.0$ (*c*=0.70, CH_2Cl_2); R_f 0.60 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3067, 1716, 1604 and 840 cm^{-1}; δ_H 0.96, 0.98 (2d, *J*=6.9 Hz, 6H, (CH_3)$_2$CH), 1.63 (s, 9H, (CH_3)$_3$C), 2.21 (m, 1H, (CH_3)$_2$C*H*), 5.71 (d, *J*=6.9 Hz, 1H, CHN) and 7.26–8.36 (m, 13H, ArH, CH=C); δ_C 19.04, 19.94 ((CH_3)$_2$CH), 28.07 ((CH_3)$_3$C), 34.81 ((CH_3)$_2$CH), 58.75 (CHN), 83.97 ((CH_3)$_3$*C*), 124.08, 125.21, 125.92, 126.68, 127.57, 127.94, 128.85, 129.89, 130.85, 131.24, 131.31, 132.62, 133.52, 136.42, 136.49 (ArC and C=CH), 152.40 (C=N), 162.24 and 164.94 (2×CO); *m/z* (EI) 355 (M^+-100, 3%), 183 (100), 105 (40), 91 (13), 77 (28) and 44 (59). HRMS calcd for $C_{29}H_{30}N_2O_3$: 454.2256. Found: 434.2249.

4.3.2. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-[(*Z*)-1-(4-methoxyphenyl)methylidene]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14j. Pale yellow oil (70%). $[\alpha]_D^{25}=-215.0$ (*c*=0.20, CH_2Cl_2); R_f 0.60 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3059, 1766, 1678, 1600 and 808 cm^{-1}; δ_H 0.92 (2d, *J*=6.7 Hz, 6H, (CH_3)$_2$CH)), 1.60 (s,

9H, $(CH_3)_3C$), 2.15 (m, 1H, $(CH_3)_2CH$)), 3.90 (s, 3H, OCH_3), 5.66 (d, J=7.0 Hz, 1H, CHN), and 7.00–8.08 (m, 10H, ArH and C=CH); δ_C 18.98, 19.98 (($CH_3)_2CH$), 28.07 (($CH_3)_3C$), 34.57 (($CH_3)_2CH$), 55.37 (OCH_3), 58.59 (CHN), 83.68 (($CH_3)_3C$), 114.09, 116.34, 127.47, 128.88, 128.91, 131.11, 131.50, 133.86, 134.41, 136.77 (ArC and C=CH), 152.45 (C=N), 162.46 (CO_2Bu^t) and 163.46 (CON); *m/z* (EI) 334 (M^+-100, 100%), 320 (15), 291 (13), 183 (18), 143 (14), 121 (39), 115 (17), 91 (16), 77 (27), 65 (10), 44 (16) and 41 (18). HRMS calcd for $C_{26}H_{30}N_2O_4$: 434.2206. Found: 434.2208.

4.3.3. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-[(*Z*)-1-(1-methylphenyl)methylidene]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 14k. Pale yellow oil (56%). $[\alpha]_D^{25}=-128.3$ (c=0.20, CH_2Cl_2); R_f 0.77 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3058, 1768, 1718, 1606 and 851 cm^{-1}; δ_H 0.93 (2d, J=6.5 Hz, 6H, ($CH_3)_2CH$)), 1.61 (s, 9H, $(CH_3)_3C$), 2.17 (m, 1H, $(CH_3)_2CH$)), 2.50 (s, 3H, CH_3Ph), 5.67 (d, J=7.0 Hz, 1H, CHN) and 7.27–8.14 (m, 10H, ArH and C=CH); δ_C 19.05, 19.96 (($CH_3)_2CH$), 20.38 (CH_3Ph), 28.10 (($CH_3)_3C$), 34.75 (($CH_3)_2CH$), 58.69 (CHN), 83.94 (($CH_3)_3C$), 125.69, 127.60, 128.88, 128.91, 129.29, 130.30, 131.30, 132.45, 133.42, 135.63, 136.59, 139.19 (ArC and C=CH), 152.48 (C=N), 162.29 (CO_2Bu^t) and 166.55 (CON); *m/z*(EI) 318 (M^+-100, 74%), 303 (100), 144 (14), 143 (20), 115 (28), 91 (14), 77 (18), 65 (7), 43 (14) and 41 (14). HRMS calcd for $C_{26}H_{30}N_2O_3$: 418.2256. Found: 418.2253.

4.4. Synthesis of (*Z*)-DDAA derivatives 14 by vinylic nucleophilic substitution from enaminone 16. General procedure

To a solution of enaminone **16** (371 mg, 1 mmol) in anhydrous THF (3 mL) under an argon atmosphere was added dropwise, at 0°C, the Grignard reagent and the resulting mixture was stirred for times depicted in Table 3. A saturated aqueous solution of ammonium chloride was added (10 mL) and washed with ethyl acetate (3×15 mL). The organic phase was dried (Na_2SO_4) and evaporated under vacuo and the residue was purified by column chromatography obtaining **14** or **17**. For reactions run under typical Barbier conditions magnesium powder (10 equiv.) and the corresponding aryl iodide (5 equiv.) were introduced together in the reaction mixture instead of the Grignard reagent. Physical and analytical data follow:

4.4.1. (6*S*)-6-Isopropyl-3-[(*Z*)-1-(1-naphthyl)methylidene]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 17i. Pale yellow oil (54%). $[\alpha]_D^{25}=-189.0$ (c=0.30, CH_2Cl_2); R_f 0.50 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3067, 1716, 1604 and 840 cm^{-1}; δ_H 0.89, 1.05 ((2d, J=6.9 Hz, 6H, ($CH_3)_2CH$)), 2.19 (m, 1H, $(CH_3)_2CH$)), 5.25 (dd, J=9.0, 3.5 Hz, 1H, CHN), 5.45 (br. s, 1H, NH) and 7.26–8.36 (m, 13H, ArH, C=CH); δ_C 19.04, 19.94 (($CH_3)_2CH$), 34.81 (($CH_3)_2CH$), 58.75 (CHN), 124.08, 125.21, 125.92, 126.68, 127.57, 127.94, 128.85, 129.89, 130.85, 131.24, 131.31, 132.62, 133.52, 136.42, 136.49 (ArC and C=CH), 152.40 (C=N), 162.24 (C=O); *m/z*(EI) 355 (M^++1, 3%), 183 (100), 105 (40), 91 (13), 77 (28) and 44(59). HRMS calcd for $C_{24}H_{22}N_2O$: 354.4580. Found: 354.4576.

4.4.2. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-5-phenyl-3-[(*Z*)-2-propenylidene]-1,2,3,6-tetrahydro-2-pyrazinone 14l. Pale yellow oil (31%). $[\alpha]_D^{25}=-32.9$ (c=0.80, CH_2Cl_2); R_f 0.70 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3057, 1717, 1600 and 800 cm^{-1}; δ_H 0.78, 0.81 ((2d, J=6.9 Hz, 6H, ($CH_3)_2CH$)), 1.51 (s, 9H, $(CH_3)_3C$), 2.05 (m, 1H, $(CH_3)_2CH$)), 5.51 (d, J=10.1 Hz, 1H, CH=CH_2), 5.56 (d, J=6.1 Hz, 1H, CHN), 5.65 (d, J=16.5 Hz, 1H, CH=CH_2), 7.10 (d, J=11.6 Hz, 1H, C=CHCH=CH_2) and 7.38–7.94 (m, 6H, ArH and C=CHCH=CH_2); δ_C 19.50, 20.03 (($CH_3)_2CH$), 28.04 (($CH_3)_3C$), 34.99 (($CH_3)_2CH$), 58.14 (CHN), 83.81 (($CH_3)_3C$), 125.40 (C=CHCH=CH_2), 127.34, 128.76 (C=CHCH=CH_2), 131.28, 131.94, 133.75, 135.63, 136.58 (ArC and C=CHCH=CH_2), 152.23 (C=N), 161.83 (CO_2Bu^t) and 163.35 (CON); *m/z*(EI) 354 (M^+, 4%), 105 (14), 77 (8), 65 (2), 44 (100) and 40 (66). HRMS calcd for $C_{21}H_{26}N_2O_3$: 354.1943. Found: 354.1940.

4.5. Radical Michael addition onto 15 using Et_3B and alkyl iodides. General procedure

To a solution of **15** (328 mg, 1 mmol) and the alkyl iodide (6 mmol) in anhydrous dichloromethane (3 mL) at −78°C, was added dropwise Et_3B (3 equiv., 1 M in THF). The resulting mixture was stirred for times indicated in Table 4. Solvent was evaporated and the residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate), obtaining compounds **19** as mixture of diastereoisomers. Physical and analytical data follow:

4.5.1. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-neopentyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 19a. Colourless oil (23%). $[\alpha]_D^{25}=+36.8$ (c=2.50, CH_2Cl_2); R_f 0.74 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3056, 1718, 1397 and 1375 cm^{-1}; δ_H (mixed isomers) 0.60, 0.70 (2d, J=6.0 Hz, 6H, ($CH_3)_2CH$), 1.10, 1.25 (2d, J=7.0 Hz, 6H, ($CH_3)_2CH$), 1.20 (m, 2H, CH_2), 1.35 (s, 9H, $CH_2(CH_3)_3C$), 1.55 (s, 9H, $(CH_3)_3C$), 1.90 (m, 1H, $(CH_3)_2CH$), 1.95, 2.45 (m, 1H, $CHCH_2Bu^t$), 4.70 (d, J=1.2 Hz, 1H, CHN), 5.60 (t, J=3.0 Hz, 1H, CHN) and 7.20–8.00 (m, 5H, ArH); δ_C (mixed isomers) 18.36, 19.79 ($CH_3)_2CH$), 18.88, 19.72 (($CH_3)_2CH$), 28.05 ($CH_2(CH_3)_3C$), 28.15 (($CH_3)_3C$), 34.34 (($CH_3)_2CH$), 34.71 (($CH_3)_2CH$), 36.11 (CH_2), 58.36 and 58.91 ($CHCH_2$), 62.84 and 75.21 (CHN), 82.09 and 83.65 ($CH_2(CH_3)_3C$ and $(CH_3)_3C$), 125.98, 127.24, 127.48, 127.93, 128.73, 130.59, 131.04, 137.48 (ArC), 151.87 (C=N), 165.67 (CO_2Bu^t) and 171.27 (CHCON); *m/z*(EI) 286 (M^+-100, 8%), 229 (27), 215 (100), 187 (35), 131 (25), 91 (25), 77 (19), 44 (17) and 41 (36). HRMS calcd for $C_{23}H_{34}N_2O_3$: 386.2570. Found: 386.2574.

4.5.2. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-pentyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 19b. Colourless sticky oil (31%). R_f 0.74 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 1790–1700 cm^{-1}; δ_H (mixed isomers) 0.60, 0.70 ((2d, J=6.7 Hz, 6H, ($CH_3)_2CH$)), 1.05, 1.25 ((2d, J=6.7 Hz, 6H, ($CH_3)_2CH$)), 0.90, 1.19 (2t, J=6.7 Hz, 3H, CH_3CH_2), 1.50–1.90 (m, 9H, $(CH_2)_4$ and $(CH_3)_2CH$)), 1.55 (s, 9H, $(CH_3)_3C$), 1.95, 2.50 (2m, 1H, CHPn), 4.73 (d, J=1.2 Hz, 1H, CHN), 5.60 (d, J=3.0 Hz, 1H, CHN) and 7.30–8.00 (m, 5H, ArH); δ_C (*trans* isomer) 14.82 (CH_3CH_2), 18.36, 19.42 (($CH_3)_2CH$), 19.71, 20.75, 34.33

($CH_3(CH_2)_3$), 28.15 (($CH_3)_3C$), 34.10 (($CH_3)_2CH$), 36.11 (CH_2CH), 58.91 ($CHCH_2$), 62.84 (CHN), 82.09 (($CH_3)_3C$), 127.92, 128.37, 129.03, 137.46 (ArC), 151.01 (C=N), 165.67 (CO_2Bu^t) and 171.27 (CHCON); δ_C (*cis* isomer) 14.04 (CH_3CH_2), 18.87, 19.78 (($CH_3)_2CH$), 19.71, 20.75, 34.33 ($CH_3(CH_2)_3$), 28.15 (($CH_3)_3C$), 34.10 (($CH_3)_2CH$), 36.11 (CH_2CH), 60.66 ($CHCH_2$), 75.21 (CHN), 83.68 (($CH_3)_3C$), 127.27, 128.33, 130.58, 136.85 (ArC), 151.01 (C=N), 165.67 (CO_2Bu^t) and 171.27 (CHCON); *m/z*(EI) 286 (M^+-100, 2%), 228 (97), 213 (79), 187 (14), 143 (9), 91 (10), 77 (21), 44 (72) and 41 (100). HRMS calcd for $C_{23}H_{34}N_2O_3$: 386.2570. Found: 386.2574.

4.5.3. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-3-isobutyl-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 19c. Colourless oil (32%). R_f 0.72 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 1766–1700 cm^{-1}; δ_H (mixed isomers) 0.75, 1.03, 1.24 (3d, *J*=6.8 Hz, 12H, $(CH_3)_2CH$) and $(CH_3)_2CHCH_2$), 1.45 (s, 9H, $(CH_3)_3C$), 1.50–2.15 (m, 4H, 2×$(CH_3)_2CH$ and CH_2), 3.30 (t, *J*=6.7 Hz, 1H, $CHCH_2$), 5.22 (dd, *J*=9.1, 3.6 Hz, 1H, CHN) and 7.31–7.98 (m, 5H, ArH); δ_C (mixed isomers) 16.43, 20.02, 20.27 (($CH_3)_2CH$) and $(CH_3)_2CHCH_2$), 28.04 (CH_2), 28.34 (($CH_3)_3C$), 31.62 (($CH_3)_2CH$) and $(CH_3)_2CHCH_2$), 59.59 ($CHCH_2$), 79.62 (CHN), 81.43 (($CH_3)_3C$), 128.58, 129.04, 133.57, 135.44 (ArC), 153.10 (C=N), 166.70 (CO_2Bu^t) and 173.02 (CHCON); *m/z*(EI) 272 (M^+-100, 4%), 229 (7), 203 (13), 143 (9), 91 (7), 77 (23), 57 (72), 44 (91) and 41 (100). HRMS calcd for $C_{22}H_{32}N_2O_3$: 372.2413. Found: 372.2410.

4.5.4. (6*S*)-*N*-1-(*tert*-Butoxycarbonyl)-3-isopentyl-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone 19d. Colourless oil (30%). R_f 0.76 (*n*-hexane/ethyl acetate:3/2); ν_{max} (film) 1766–1650 cm^{-1}; δ_H (mixed isomers) 0.75, 1.03, 1.24 (3d, *J*=6.8 Hz, 12H, $(CH_3)_2CH$) and $(CH_3)_2CHCH_2$), 1.45 (s, 9H, $(CH_3)_3C$), 1.65–2.20 (m, 6H, 2×$(CH_3)_2CH$ and $(CH_3)_2CHCH_2CH_2$), 1.95, 2.50 (2m, 1H, CHCO), 4.81 (d, *J*=3.5 Hz, 1H, CHN), 5.23 (dd, *J*=9.1 and 3.6 Hz, 1H, CHN) and 7.31–8.00 (m, 5H, ArH); δ_C (mixed isomers)16.43, 20.02, 20.26 (($CH_3)_2CH$) and $(CH_3)_2CHCH_2$), 22.33 (($CH_3)_2CHCH_2$), 28.34 (($CH_3)_3C$), 31.62 (($CH_3)_2CH$) and $(CH_3)_2CHCH_2$), 34.33 (CH_2CHCO), 59.59 ($CHCH_2$), 79.63 (CHN), 82.10 (($CH_3)_3C$), 128.57, 129.03, 131.03, 133.57 (ArC), 153.10 (C=N), 165.67 (CO_2Bu^t) and 171.28 (CHCON); *m/z*(EI) 386 (M^+, 1%), 214 (5), 105 (21), 91 (2), 77 (19), 72 (49), 44 (86) and 41 (100). HRMS calcd for $C_{23}H_{34}N_2O_3$: 386.2569. Found: 386.2565.

4.6. Synthesis of cyclopropane derivatives 20. General procedure

To a solution of trimethylsulfoxonium iodide (222 mg, 1 mmol) in dry DMSO (0.5 mL) sodium hydride was (24 mg, 1 mmol) was carefully added stirring the resulting suspension for 0.5 h. DDAA derivative **14a** or **14b** (1 mmol) dissolved in DMSO (0.5 mL) was added at 5°C and the mixture was stirred 0.5 h at room temperature. The product was immediately purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate), affording spiranic **20a** or **20b** as 11:1 and 23:1 mixtures of diastereoisomers, respectively. Physical and analytical data of the major diastereoisomers follow:

4.6.1. (1*R*,3*S*,6*S*)-*N*-(*tert*-Butoxycarbonyl)-6-isopropyl-1-methyl-8-oxo-5-phenyl-4,7-diazaspiro[2.5]-4-octene 20a. Pale yellow oil (70%). $[\alpha]_D^{25}=-11.5$ (*c*=3.50, CH_2Cl_2); R_f 0.69 and R_f 0.76 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3090, 1770, 1716 and 1640 cm^{-1}; δ_H 0.87, 0.89 (2d, *J*=6.7 Hz, 6H, $(CH_3)_2CH$), 1.33 (d, *J*=6.1 Hz, 3H, CH_3CHCH_2), 1.49 (dd, *J*=9.2, 3.7 Hz, 1H, CH_2), 1.57 (s, 9H, $(CH_3)_3C$), 2.08 (m, 2H, $CHCH_2$ and $(CH_3)_2CH$), 2.30 (dd, *J*=9.2, 3.7 Hz, 1H, CH_2), 5.63 (d, *J*=6.1 Hz, 1H, CHN) and 7.27–7.80 (m, 5H, ArH); δ_C 13.48 (CH_3CHCH_2), 18.77, 19.39 (($CH_3)_2CH$), 28.04 (($CH_3)_3C$), 30.44 (CH_2), 31.32 ($CHCH_2$), 33.71 (($CH_3)_2CH$), 50.22 (CH_2CCO), 59.58 (CHN), 83.42 (($CH_3)_3C$), 126.58, 128.65, 130.35, 137.54 (ArC), 151.75, 165.88 and 171.36 (2×C=O and C=N); *m/z* (EI) 356 (M^+, 7%), 256 (1), 213 (100), 91 (8), 77 (4), 44 (3). HRMS calcd for $C_{21}H_{28}N_2O_3$: 356.2100. Found: 356.2101.

4.6.2. (1*R*,3*S*,6*S*)-*N*-(*tert*-Butoxycarbonyl)-1-ethyl-6-isopropyl-8-oxo-5-phenyl-4,7-diazaspiro[2.5]-4-octene 20b. Pale yellow oil (79%). $[\alpha]_D^{25}=-14.5$ (*c*=1.25, CH_2Cl_2); R_f 0.75 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 1800 and 1710 cm^{-1}; δ_H 0.86, 0.88 (2d, *J*=7.0 Hz, 6H, $(CH_3)_2CH$), 1.06 (t, *J*=7.3 Hz, 3H, CH_3CH_2), 1.49 (dd, *J*=9.5, 3.7 Hz, 1H, $CH_2CHCH_2CH_3$), 1.56 (s, 9H, $(CH_3)_3C$), 1.62–2.16 (m, 4H, $CH_2CHCH_2CH_3$ and $(CH_3)_2CH$), 2.23 (dd, *J*=9.5, 3.7 Hz, 1H, $CH_2CHCH_2CH_3$), 5.61 (d, *J*=6.1 Hz, 1H, CHN) and 7.26–7.78 (m, 5H, ArH); δ_C 13.43 ($CH_3CH_2CHCH_2$), 18.96, 19.67 (($CH_3)_2CH$), 21.89 ($CH_3CH_2CHCH_2$), 28.07 (($CH_3)_3C$), 29.69 ($CH_3CH_2CHCH_2$), 33.70 (($CH_3)_2CH$), 38.08 ($CHCH_2$), 50.68 (CH_2CCO), 59.51 (CHN), 83.42 (($CH_3)_3C$), 126.61, 128.69, 130.34, 137.67 (ArC), 151.73, 165.69 and 171.44 (2×C=O and C=N); *m/z* (EI) 270 (M^+-100, 2%), 241 (1), 228 (18), 227 (100), 185 (21), 157 (25), 91 (15), 77 (13), 43 (18), 41 (33). HRMS calcd for $C_{22}H_{30}N_2O_3$: 370.2256. Found: 320.2253.

4.6.3. Synthesis of (−)-*allo*-norcoronamic acid (−)-21. Hydrolysis of **20a** (1 mmol) was performed using 3 M HCl (3 mL) and 150°C for 4 days. Water was evaporated under vacuo and excess of propylene oxide (0.7 mL, 10 mmol) and EtOH were added refluxing the resulting solution for 0.5 h. (−)-*allo*-Norcoronamic acid (−)-**21** was obtained as a colourless solid (ee>98%, 28 mg, 24%). $[\alpha]_D^{25}=-70,0$ (*c*=1, H_2O), lit.[9a] $[\alpha]_D^{20}=-69,0$ (*c*=1, H_2O). δ_H (D_2O)[9a] 0.68 (t, *J*=6.7 Hz, 1H, CH_2), 0.99 (d, *J*=6.7 Hz, 3H, CH_3), 1.24 (dd, *J*=9.8, 6.1 Hz, 1H, CH_2), 1.45 (m, 1H, $CHCH_3$).

4.6.4. Synthesis of cycloadduct 23. A solution of methylenic derivative **15** (328 mg, 1 mmol) in the presence of isopropyl *N*-benzylidene alaninate (219 mg, 1 mmol) in toluene (3 mL) was refluxed during 1 day. Solvent was evaporated under vacuo obtaining **23** as pure compound (433 mg, 79%). $[\alpha]_D^{25}=+21.3$ (*c*=0.60, CH_2Cl_2); R_f 0.61 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 1731 and 1100 cm^{-1}; δ_H 0.78, 0.81 (2d, *J*=7.4 Hz, 6H, $(CH_3)_2CHCH$), 1.30 (d, *J*=4.0 Hz, 6H, $CO_2CH(CH_3)_2$), 1.58 (s, 9H, $(CH_3)_3C$), 1.64 (s, 3H, CH_3), 2.05 (m, 1H,

($(CH_3)_2CH$), 2.60, 2.86 (2d, J=13.2 Hz, 2H, CH_2), 4.91 (s, 1H, CHPh), 5.17 (d, J=5.7 Hz, 1H, CHN), 5.20 (m, 1H, $CO_2CH(CH_3)_2$) and 7.06–7.67 (m, 11H, ArH and NH); δ_C 18.81, 19.63 ($(CH_3)_2CHCH$), 21.72, 21.73 ($CO_2CH(CH_3)_2$), 21.78 (CH_3), 28.00 ($(CH_3)_3C$), 34.68 ($(CH_3)_2CHCH$), 51.92 (CH_2), 59.51 (CHN), 65.20 (CCONBoc), 68.75 ($CO_2CH(CH_3)_2$), 75.46 (CHPh), 76.42 (CCO_2Pr^i), 83.30 ($(CH_3)_3C$), 126.91, 127.60, 127.64, 127.85, 128.37, 129.00, 130.49, 135.68 (ArC), 151.40 (C=N), 162.60 (CO_2Bu^t), 172.69 (CONBoc) and 176.18 (CO_2Pr^i); m/z(EI) 548 (M^++1, 7%), 229 (7), 228 (7), 105 (17), 91 (7), 77 (19), 44 (100) and 40 (97). HRMS calcd for $C_{32}H_{41}N_3O_5$: 547.3046. Found: 547.3042.

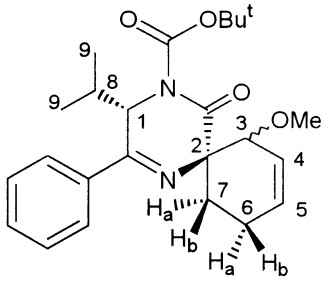
4.7. Synthesis of *endo*-adducts 24, 25 and 26. General procedure

A solution of didehydroalanine **15** (328 mg, 1 mmol) and the corresponding diene (10–20 mmol) in toluene (3 mL) was stirred at the temperatures and during reaction times described previously (see text, Section 2). The solvent was evaporated and the resulting residue was chromatographed (SiO_2, *n*-hexane/ethyl acetate) affording *endo*-cycloadducts **24**, **25** and **26**. Physical and analytical data follow:

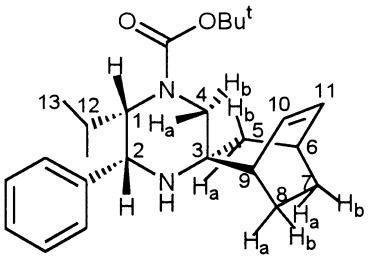
4.7.1. *endo*-Adduct 24. Colourless oil (42%); $[\alpha]_D^{25}$= +11.0 (c=1.90, CH_2Cl_2); R_f 0.80 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3031, 1770, 1650, 693 cm^{-1}; δ_H 0.76, 0.85 (2×d, J=6.7 Hz, 6H, $(CH_3)_2CH$), 1.58 (s, 9H, $(CH_3)_3C$), 1.59–2.74 (m, 9H, 3×CH_2, 2×CHC=C, $(CH_3)_2CH$), 5.53 (d, J=5.5 Hz, 1H, CHN), 5.97, 6.36 (2×m, 2H, CH=CH) and 7.37–7.84 (m, 5H, ArH); δ_C 18.64, 19.88 ($(CH_3)_2CH$), 22.89, 43.31 (CH_2CH_2), 28.02 ($(CH_3)_3C$), 30.40 (CHC=C), 34.09 ($(CH_3)_2CH$), 41.23 (CHCCO), 61.63 (CHN), 65.85 (CCO), 67.02 (CH_2CCO), 82.85 ($(CH_3)_3C$), 125.30, 127.03 (CH=CH), 128.51, 130.28, 134.31, 137.56 (ArC), 152.71 (C=N), 162.06 (CO_2Bu^t) and 175.89 (CCON); m/z (EI) 308 (M^+−100, 8%), 228 (55), 213 (65), 91 (14), 77 (42), 40 (100). HRMS calcd for $C_{25}H_{32}N_2O_3$: 408.2413. Found: 408.2415.

4.7.2. *endo*-Adduct 25. Colourless oil (95%). $[\alpha]_D^{25}$= +78.1 (c=1.15, CH_2Cl_2); R_f 0.80 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3083, 1750, 1642 and 690 cm^{-1}; δ_H 0.81, 0.83 (2×d, J=7.3 Hz, 6H, $(CH_3)_2CH$), 1.54 (s, 9H, $(CH_3)_3C$), 1.81 (dd, J=11.0, 3.4 Hz, 1H, CH_2CCO), 1.89 (dd, J=11.0, 2.5 Hz, 1H, CH_2CCO), 2.03 (m, 1H, $(CH_3)_2CH$), 2.38–3.25 (m, 4H, $CHCH_2CH$), 5.53 (d, J=6.1 Hz, 1H, CHN), 6.21 (dd, J=5.5, 3.1 Hz, 1H, CH=CH), 6,33 (dd, J=5.5, 3.1 Hz, 1H, CH=CH) and 7.78–7.82 (m, 5H, ArH); δ_C 19.04, 19.93 ($(CH_3)_2CH$), 28.05 ($(CH_3)_3C$), 34.09 ($(CH_3)_2CH$), 43.55 (CH_2CHC=C), 45.07, 49.13 (2×CH_2), 56.76 (CHCCO), 61.55 (CHN), 71.66 (CCO), 82.98 ($(CH_3)_3C$), 127.08, 128.60, 130.34, 134.97, 137.78, 138.27 (ArC and C=C), 152.47 (C=N), 163.37 (CO_2Bu^t) and 174.61 (CCON); m/z (EI) 294 (M^+−100, 0.3%), 228 (100), 227 (68), 213 (31), 185 (66), 91 (9), 77 (20), 41 (79). HRMS calcd for $C_{24}H_{30}N_2O_3$: 394.2256. Found: 394.2255.

4.7.3. Adducts *trans*-26 and *cis*-26. Pale yellow oil (66%). Required for $C_{24}H_{32}N_2O_4$: C, 69.95; H, 7.75; N, 6.80. Found: C, 70.4; H,7.85; N, 6.65%. R_f 0.75 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3040, 1717, 1654, 763 cm^{-1}; δ_H (*trans*-**26**) 0.69, 0.81 (2d, J=7.2 Hz, 6H, $(CH_3)_2CH$), 1.46 (s, 9H, $(CH_3)_3C$), 1.86–1.94 (m, 2H, H_{7b} and H_8), 2.01 (dt, J=13.7, 5.5 Hz, 1H, H_{7a}), 2.20 (m, 1H, H_{6b}), 2.41 (m, 1H, H_{6a}), 3.24 (s, 3H, CH_3O), 3.87 (br. s, 1H, H_3), 5.58 (d, J=4.6 Hz, 1H, H_1), 5.70 (m, 1H, H_4), 5.87–5.90 (m, 1H, H_5), 7.31 (m, 1H, ArH_{para}), 7.35 (m, 2H, ArH_{meta}) and 7.67 (m, 2H, ArH_{ortho}); δ_H (*cis*-**26**) 0.77, 0.78 (2d, J=6.7 Hz, 6H, $(CH_3)_2CH$), 1.50 (s, 9H, $(CH_3)_3C$), 1.76 (m, 1H, H_{7a}) 1.91 (m, 1H, H_8), 2.16 (m, 1H, H_{6b}), 2.35 (m, 1H, H_{7b}), 2.44 (m, 1H, H_{6a}), 3.27 (s, 3H, CH_3O), 4.45 (br. s, 1H, H_3), 5.51 (d, J=6.0 Hz, 1H, H_1), 5.70 (m, 1H, H_4), 5.87–5.91 (m, 1H, H_5), 7.31 (m, 1H, ArH_{para}), 7.35 (m, 2H, ArH_{meta}) and 7.67 (m, 2H, ArH_{ortho}); δ_C (*trans*-26) 18.50, 19.53 (2C_9), 23.03 (C_6), 28.04 ($(CH_3)_3C$), 30.32 (C_7), 34.33 (C_8), 58.15 (CH_3O), 62.07 (C_1), 66.32 (C_2), 83.00 ($C(CH_3)_3$), 124.47 (C_4), 127.14 (ArC_{ortho}), 128.54 (ArC_{meta}), 129.46 (C_5), 130.27 (ArC_{para}), 137.94 (ArC_{ipso}), 152.04 (OCON), 164.19 (C=N) and 172.26 (CC=O). δ_C (*cis*-**26**) 18.99, 20.22 (2C_9), 22.48 (C_6), 28.01 ($(CH_3)_3C$), 33.00 (C_7), 34.86 (C_8), 58.07 (CH_3O), 60.65 (C_1), 66.60 (C_2), 83.14 ($C(CH_3)_3$), 125.80 (C_4), 127.55 (ArC_{ortho}), 127.62 (C_5), 128.41 (ArC_{meta}), 130.23 (ArC_{para}), 138.15 (ArC_{ipso}), 151.79 (OCON), 165.50 (C=N) and 175.14 (CC=O); m/z (EI) 312 (M^+−100, 0.1%), 231 (18), 119 (16), 105 (15), 77 (19), 57 (100), 51 (10), 42 (25), 41 (50).



4.7.4. Synthesis of perhydropyrazine 29. To a solution of *endo*-adduct **25** (408 mg, 1 mmol) in ethanol (15 mL) was slowly added sodium borohydride (114 mg, 3 mmol) and stirring continued for 2 days. Solvent was evaporated under vacuo and water (10 mL) was added. Aqueous phase was extracted with ethyl acetate (2×15 mL) and the organic layer was dried (Na_2SO_4) filtered and evaporated under vacuo affording pure *endo*-adduct **29** (358 mg, 87%) as colourless oil. $[\alpha]_D^{25}$=−27.0 (c=1.00, CH_2Cl_2); R_f 0.80 (*n*-hexane/ethyl acetate: 3/2); ν_{max} (film) 3300, 3030, 1770, 1640, 700 cm^{-1}; δ_H 0.82, 1.18 (2×d, J=7.0 Hz, 6H, $(CH_3)_2CH$), 1.22 (m, 1H, H_{5b}), 1.49 (s, 9H, $(CH_3)_3C$), 1.50 (m, 1H, H_{5a})), 1.51 (m, 1H, H_{7b}), 1.70 (m, 1H, H_{7a}), 1.79, 1.84 (2m, 2H, H_{8a} and H_{8b}), 2.10 (m, 1H, H_{12}), 2.47 (m, 1H, H_9), 2.52 (m, 1H, H_6), 2.83 (d, J=11.3 Hz, 1H, H_{4b}), 3.02 (d, J=11.3 Hz, 1H, H_{4a}), 3.54 (m, 1H, H_2), 3.84 (m, 1H, NH), 4.05 (d, J=7.2 Hz, 1H, H_1), 6.06, 6.12 (2m, 2H, H_{10} and H_{11}) and 7.17–7.27 (m, 5H, ArH); δ_C 18.59, 20.92 ($(CH_3)_2CH$), 19.71 (C_8), 24.65 (C_7), 28.35 ($(CH_3)_3C$), 29.68 (C_{12}), 30.32 (C_6), 36.21 (C_9), 36.43 (C_5), 57.25 (C_2), 61.81 (C_3), 62.13 (C_1), 66.31 (C_4), 80.11 ($(CH_3)_3C$), 125.70, 126.71, 127.51, 142.00 (ArC), 133.39, 133.89 (C_{10} and C_{11}) and 156.82 (CO_2Bu^t); m/z (EI) 397 (M^++1, 8%), 105 (18), 77 (17), 43 (100) and 40 (90). HRMS calcd for $C_{25}H_{36}N_2O_2$: 396.2777. Found: 396.2774.



4.8. Synthesis of the bicyclic α-amino acids 27 and 28. General procedure

Method A. Bicycle **24** (394 mg, 1 mmol) was hydrogenated as described in method A and the resulting residue was treated with 6 M HCl (6 mL) at 150°C for 4 days. Water was evaporated under vacuo and excess of propylene oxide (0.7 mL, 10 mmol) and EtOH were added refluxing the resulting solution for 0.5 h. The colourless precipitate was filtered obtaining (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.1]-heptane-2-carboxylic acid **27** (86 mg, 61%): **27**·HCl $[\alpha]_D^{25}=-12.7$ (c=0.5, H_2O), [lit.[9a] (2*S*-enantiomer) $[\alpha]_D^{25}=+12.4$ (c=0.5, H_2O)].

Method B. A suspension of the bicyclic pyrazinone **25** (408 mg, 1 mmol) and Pd/C 10% (60 mg) in methanol (6 mL) was stirred under a hydrogen atmosphere (1 atm) at room temperature for 9 h. The resulting suspension was filtered through a Celite path and the solvent evaporated. The residue was treated with a cation-exchange resin Dowex 50X-100 (5 mg) and 0.75 M HCl (6 mL, prepared in deionised water) in acetic acid (1.6 mL) and toluene (2.4 mL). The resulting mixture was boiled for 24 h and then cooled at room temperature and transferred to a column. The resin was washed with water till neutral pH, ethanol and finally with 10% aqueous ammonia affording a suspension of the corresponding amino acid. The solid was filtered and washed with ethyl acetate and acetone affording pure amino acid (−)-(1*R*,2*R*,4*S*)-2-aminobicyclo[2.2.2]octane-2-carboxylic acid **28** (63 mg, 40%), $[\alpha]_D^{25}=-61.3$ (c=1.00, H_2O), (lit.[9a] $[\alpha]_D^{25}=-61.4$ (c=1.00, H_2O)).

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