Asymmetric Synthesis of α-Methyl α-Amino Acids through Diastereoselective Alkylation under Mild Reaction Conditions of an Iminic Alanine Template with a 1,2,3,6-Tetrahydro-2-pyrazinone Structure

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Keywords: Amino acids / Asymmetric synthesis / Pyrazinones / Phase-transfer catalysis / Palladium

(6*R*)-6-Isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone, obtained from (*R*)-valine and (*S*)-alanine, is highly diastereoselectively alkylated at room temperature by: a) activated alkyl halides under solid-liquid PTC conditions, b) non-activated alkyl halides with organic bases, c) electrophilic olefins employing both solid–liquid PTC conditions and organic bases, and d) allylic carbonates by means of palladium catalysis under neutral conditions. Enantiomerically pure (*S*)-α-methyl α-amino acids **8** are obtained by hydrolysis of the alkylated pyrazinones.

Introduction

Natural and unnatural modified α-amino acids in an enantiomerically pure form and their peptides constitute some of the most important areas of research in the fields of medicinal chemistry and protein engineering. As a consequence, new and versatile synthetic methodologies have become an important goal for organic chemists.[1] When incorporated into natural or synthetic peptides, and because of the tetrasubstituted asymmetric carbon, the family of α-methyl α-amino acids (AMAAs)[1b] result in the decrease of both enzymatic and chemical hydrolysis[2] and also stabilize β-turn and α-helical conformations[3] of such peptides. Natural peptides such as peptaibols,[4] TAN-1057A,[5] MS681b,[6] etc., exhibit potent antibiotic activity and synthetic peptides such as CI-998 and PD161182 are high-affinity ligands for CCK-B and NK_3 receptors, respectively.[7] Amongst other properties, AMAAs possess antibiotic activity,[8] they can act as enzyme and protein inhibitors,[9] they have anti-hypertensive properties as (*S*)-α-methyl-DOPA (Aldomet)[9b] and are potent antagonists of mGluR[10] and EAA.[11] Furthermore, they are frequently used as chiral building blocks in organic synthesis.[7,8,12]

Chiral cyclic enolates derived from alanine, especially Schölkopf's, Seebach's and Williams' reagents, have provided the most direct and reliable synthetic routes to AMAAs through diastereoselective α-alkylation reactions.[1a] However, the reaction normally takes place under anhydrous conditions and at very low temperatures because very strong and sensitive bases (LDA, BuLi, KHMDS, LiHMDS, KO*t*Bu, etc.) are required. These reaction conditions do not allow these methodologies to be applied to economical and large-scale synthesis. Furthermore, the hydrolysis of the resulting α-alkylated heterocycles can also be problematic, since harsh reaction conditions are usually needed. Acyclic alanine aromatic aldehyde imines are very soft nucleophiles and have recently been alkylated under mild reaction conditions. These systems can also be hydrolyzed smoothly employing a combined diluted acidic−basic protocol.[13] In this field, phase-transfer catalysis (PTC) using TADDOL[14a] and NOBIN[14b] as chiral ligands have been successfully applied in the alkylation reaction of benzaldehyde alaninates with NaH, in toluene at room temperature, with activated alkyl halides up to 82 and 68% *ee*, respectively. Cinchonidinium and cinchoninium salts[15] act as phase-transfer catalysts with high enantioselectivity (up to 87% *ee*[15g] and 50%[15h] *ee*, respectively) in alkylation reactions of alanine-derived imines in the presence of activated halides. New and efficient chiral alanine iminic derivatives should be developed for optimizing a useful scalable process to synthesize AMAAs. To achieve this goal, we have already studied the reactivity of oxazinones **1a**−**b** as chiral cyclic alanine templates for alkylations under mild reaction conditions and these reactions show very high levels of diastereoselectivity.[16] However, these types of oxazinones are rather sensitive to aqueous, acidic or basic conditions and alkylated derivatives can be obtained up to 75% yield.

In order to improve the overall yields, we have designed a further template with a 1,2,3,6-tetrahydro-2-pyrazinone structure **2**[17] that has features similar to the oxazinones **1**. These features include: a) a highly acidic C_α hydrogen atom, presumably as acidic as the oxazinone one because of the presence of an electron-withdrawing group at N-1, and b) a bulky group at C-6 able to block one of the two diastereotopic faces of the enolate and allow for a 1,4-transannular asymmetric induction. The only significant difference between the two molecules is the substitution of the lactone moiety by an imido group, which presumably would convert 2-pyrazinone **2** into a more stable compound.

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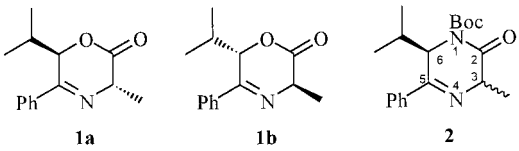
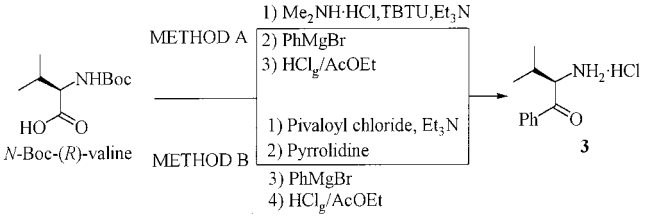


Results and Discussion

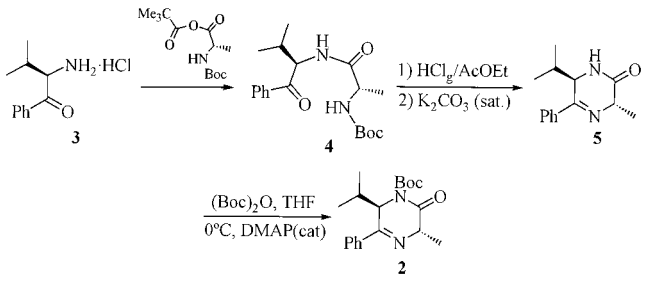
Only one example of a 1,2,3,6-tetrahydro-2-pyrazinone has been previously described, furnishing the 2-pyrazinone with two methyl groups at the 6-position, by reaction of 2,2-dimethyl-3-phenyl-2*H*-azirine with glycine ethyl ester.[18] In this work, we report the synthesis of the chiral pyrazinone **2** based on the coupling of the chiral amino ketone **3**, obtained in an optically pure form, and alanine. Chiral α-aminoisovalerophenone hydrochloride **3**[19,20] was initially prepared (Method A),[17] from D-valine *N*,*N*-dimethylamide, obtained by the reaction with dimethylamine hydrochloride in the presence of triethylamine and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) in acetonitrile at room temperature. The crude amide was allowed to react with phenylmagnesium bromide (3 equiv.) in THF at room temperature giving, after hydrolysis with a saturated solution of hydrogen chloride in ethyl acetate, the α-amino ketone hydrochloride **3** in 78% overall yield [from (*R*)-valine] (Scheme 1).[17] Alternatively, the chiral auxiliary **3** could be prepared (Method B) by modifying the amidation step. *N*-Boc-(*R*)-valine−pivalic acid mixed anhydride was generated in situ and treated with excess pyrrolidine (3 equiv.) for 6 h, affording the corresponding amide. This pyrrolidine amide was treated as described in the case of the dimethylamide analogue to afford **3** in 69% overall yield [from (*R*)-valine] (Scheme 1). In spite of the slightly lower yield achieved, the latter method is more suitable for a multigram-scale preparation, since cheaper reagents are employed.

The amidation reaction of compound **3** with the *N*-Boc-(*S*)-alanine-pivalic acid mixed anhydride gave compound **4** in 95% yield. The 2-pyrazinone **5** was prepared in 86% yield after deprotection of **4** with HCl in EtOAc, followed by an extractive workup with a saturated aqueous solution of potassium carbonate. Under these reaction conditions, some epimerization took place at C-3 and pyrazinone **5** was isolated as a 22:1 mixture of *trans*/*cis* diastereomers. Final *N*-Boc protection was achieved with di-*tert*-butyl dicarbonate [$(Boc)_2O$] at 0 °C in THF affording, in 84% yield, a 20:1 mixture of *trans*/*cis* diastereomers determined by ^1H NMR spectroscopy and HPLC (Scheme 2). This epimerization,



Scheme 1

which takes place under basic cyclization conditions owing to the high acidity of the C-3 hydrogen, is not a serious drawback for the diastereoselective alkylation of **2**. It is worth noting that no epimerization took place at C-6 during the cyclization and *N*-protection steps. The use of (*S*)-alanine, instead of the racemic mixture, in the synthesis of that pyrazinone is justified because of the instability of the *cis*-diastereomer during the final *N*-Boc protection. Similar behaviour was observed in the case of the oxazinones, showing that both reagents have a similar acidity.[16]



Scheme 2

The relative configuration of the *trans*-2-pyrazinone **2** was determined by NOE experiments and by comparison of the chemical shifts of the C-3 methyl groups of *trans* and *cis* diastereomers (δ = 1.72 and 1.65, respectively) with the analogous oxazinone **1** groups[16] (δ = 1.74 and 1.70, respectively). X-ray diffraction analyses could not be performed, but molecular mechanics calculations[21] predict a *quasi*-boat conformation where the isopropyl group adopts an axial "flagpole" position (Figure 1) such as that found in the case of oxazinone **1**.[16]

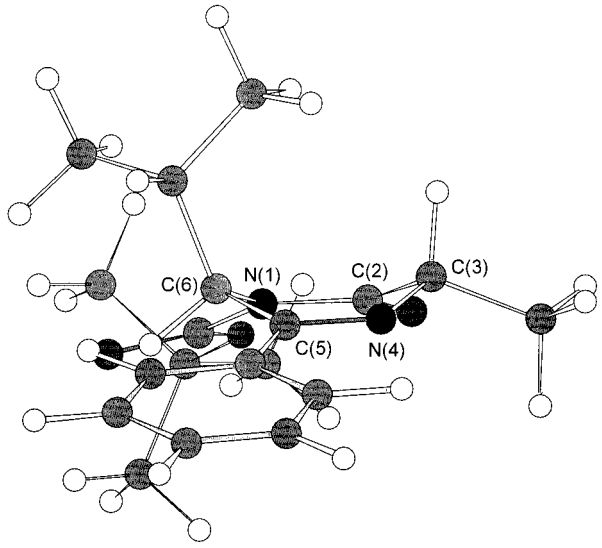
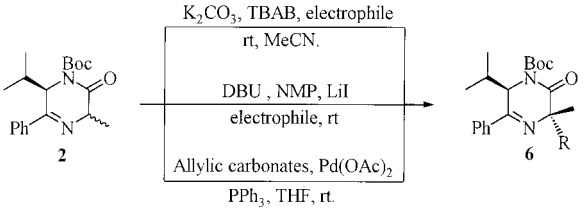


Figure 1. Molecular mechanics calculations of 2-pyrazinone **2**

The alkylation of compound **2** was performed under very mild PTC reaction conditions employing potassium carbonate in acetonitrile and tetra-*n*-butylammonium bromide (TBAB, 10 mol-%) as catalyst (Scheme 3).[16] The alkylated product **6**, whose stereochemistry was determined by NOE experiments, was obtained in good yields (60−86%) and

high diastereomeric excesses (96−98%) when very reactive alkyl halides such as allylic bromides and iodides, propargyl bromide, benzyl bromide, ethyl haloacetates and *N*-Boc-3-bromomethylindole (entries 2−9 of Table 1) were employed. An aldol reaction was performed with paraformaldehyde in 71% yield and 81% *de* (entry 10 of Table 1). Michael additions were studied using ethyl crotonate and acrylic acid derivatives. However, the reaction only took place in good yields (44−82%) and high *de* (95−96%) with monosubstituted olefins (entries 11−14 of Table 1). The observed high diastereoselectivity could be justified by molecular mechanics calculations[21] of the enolate depicted in Figure 2. The conformation of the cyclic enolate is almost planar and its isopropyl group is orthogonally orientated, blocking the top face of this alanine iminic derivative. Although X-ray diffraction analyses could not be obtained, molecular mechanics calculations were performed for the 3-propargylic derivative (6*R*)-**6c** (Figure 3).These calculations show that the pyrazinone heterocycle has a planar structure. The structure indicated in Figure 3 shows striking similarities to the X-ray structure determined for the analogous 3-propargyloxazinone.[16b]



Scheme 3

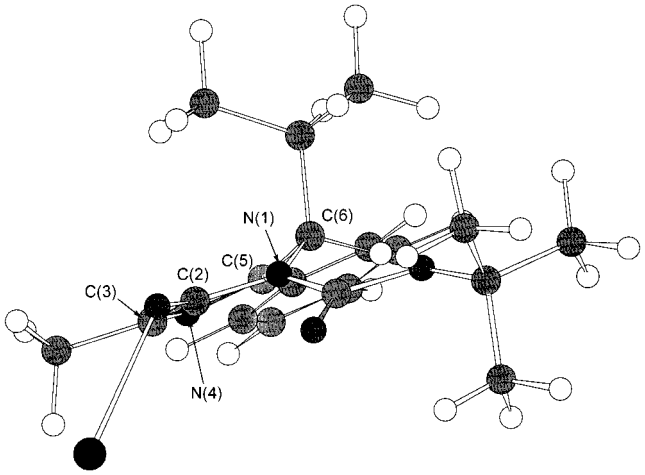
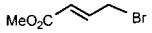
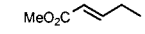
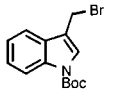


Figure 2. Molecular mechanics calculations of potassium enolate of **2**

The pyrazinone **2** permitted dialkylated products to be obtained with slightly better *de* and higher chemical yields than those obtained with oxazinones **1a**.[16] Heterocycles **6** are more stable under both neutral and basic aqueous conditions and they could be purified by column chromatography on silica gel without any significant loss of yield. Another significant difference was found when less reactive ethyl iodide was allowed to react with **2**. In this case, **6a** was obtained in a moderate yield (entry 1 of Table 1) whilst oxazinones **1** did not react with this electrophile under the

Table 1. Diastereoselective alkylation of 2-pyrazinone **2** under solid−liquid PTC conditions

Entry	Electrophile	R	t(h)[a]	Product Ratio **6**:**7**[b]	**6** (%)[c]	% de[b]
1	EtI	Et	24	3:5	(6*R*)-**6a** (35)	97
2	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	15	20:1	(6*R*)-**6b** (74)	97
3	CH_2=$CHCH_2I$	CH_2=$CHCH_2$	5	44:1	(6*R*)-**6b** (81)	97
4	HC≡CCH_2Br	HC≡$CHCH_2$	5	>100:1	(6*R*)-**6c** (86)	98
5	BnBr	Bn	5	100:3	(6*R*)-**6d** (81)	98
6	EtO_2CCH_2Br	EtO_2CCH_2	12	20:1	(6*R*)-**6e** (68)	98
7	EtO_2CCH_2I	EtO_2CCH_2	5	10:1	(6*R*)-**6e** (81)	96
8			5	>100:1	(6*R*)-**6f** (75)	98
9			6	30:1	(6*R*)-**6g** (60)	98
10	$(CH_2O)_n$	$HOCH_2$	16	>100:1	(6*R*)-**6h** (71)	81
11	CH_2=CHCN	CH_2CH_2CN	19	24:1	(6*R*)-**6i** (47)	96
12	CH_2=CHCOMe	CH_2CH_2COMe	19	60:1	(6*R*)-**6j** (82)	96
13	CH_2=$CHCO_2Me$	$CH_2CH_2CO_2Me$	19	24:1[d]	(6*R*)-**6k** (62)	95
14	CH_2=$CHCO_2Me$	$CH_2CH_2CO_2Me$	19	3:1	(6*R*)-**6k** (44)	95

[a] Acetonitrile was used as solvent and monitored by TLC. − [b] Determined by ^{1}H NMR (300 and 500 MHz) and HPLC analysis of the reaction crude. − [c] Isolated yield of the major diastereomer observed after flash chromatography. − [d] The reaction was carried out in dichloromethane.

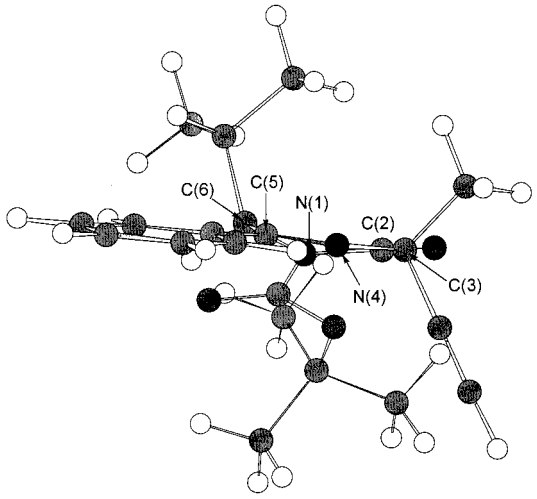
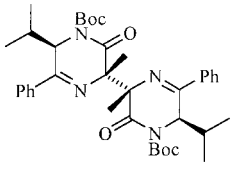


Figure 3. Molecular mechanics calculations of compound (6*R*)-**6c**

same reaction conditions. In this reaction a by-product **7** was also detected and isolated in 52% yield. In accordance with spectroscopic and analytical data, this compound seems to be the dimer of precursor **2**. The stereochemistry (see below) could not be confirmed by X-ray analysis. Although iodinated electrophiles are prone to generate this dimer **7**, very reactive brominated electrophiles did not give significant amounts, except, as shown in entries 2 and 6, where the bromides required longer reaction times to react than the analogous iodides, and in entry 9 where small amounts of bromine were present owing to the low stability of 3-bromomethylindole.[22] The same reaction has been reported by Belokon' et al. for Schiff bases of alanine with (*S*)-2-[(*N*-benzylpropyl)amino]benzaldehyde when alkyl iodides were used as electrophiles.[23]

Under PTC conditions, Michael addition reactions in the presence of electrophilic olefins also produced dimer **7**. In the case of methyl acrylate, attempts to overcome the formation of **7** were made by changing acetonitrile with THF, dichloromethane or dioxane, but no improvement was achieved. Acetonitrile and dichloromethane gave similar results in the diastereoselective alkylation, but crude product **6**/**7** ratios were 3:1 and 24:1, respectively (see entries 13 and 14 of Table 1). According to the results depicted in Table 1, nucleophilic substitution of pyrazinone **2** enolate by activated organic halides was much faster than the Michael addition with electrophilic olefins. This fact was demonstrated by the bias towards alkylation shown by the enolate when methyl 4-bromocrotonate was allowed to react as an electrophile (entry 8 of Table 1). In this reaction, the presence of the Michael adduct was not detected by ^{1}H NMR of the crude reaction mixture.



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The use of strong bases (LDA, BuLi, KO*t*Bu), even in the presence of co-solvents (HMPA, DMPU), failed when less reactive electrophiles were tested. In these reactions, complex mixtures of decomposed products were obtained. When an organic base such as Schwesinger's base[24] [2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)] was used, the reaction did not give the expected results (as in the case of oxazinones **1**).[16a,16c] However, the diastereoselective alkylation of **2** with unactivated alkyl halides and electrophilic olefins was successful when employing the cheaper 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature, in *N*-methyl-2-pyrrolidone (NMP) as solvent and using LiI as additive (Scheme 3 and Table 2). The amount of DBU required was 2 equiv. for alkyl halides and a catalytic amount for electrophilic olefins (10 mol-%), instead of 5 equiv. used for the alkylation of oxazinones **1**.[16a,16c] In general, alkylated pyrazinones **6** were obtained from alkyl halides, in better yields (64−84%, entries 1−6 of Table 2) than the analogous oxazinones[16a] (28−65%) with identical diastereomeric ratios in both cases (> 98:2). Thus, 2-pyrazinone **2** afforded **6** in moderate yields and good *de* (entries 7−11 of Table 2) when treated with electrophilic olefins under these reaction conditions. Acrylonitrile did not react when using DBU as base, but nevertheless a 47% yield was achieved under PTC conditions (see entries 11 and 7 of Table 1 and Table 2, respectively). Negligible amounts of *O*-alkylation products were detected in the reaction mixture (ca. 5% being observed with ethyl iodide) whereas more significant ratios were reported for oxazinones **1**.[16a,16c] As in the PTC alkylation reactions, different product **7** ratios were observed. Although the formation of **7** was favoured by the long reaction times, a radical dimerization mechanism can be discarded since reactions carried out in the absence of oxygen and light also gave compound **7** (entry 9 of Table 2). For electrophilic olefins, the presence of lithium iodide was necessary to achieve good yields in spite of the iodide-promoted generation of dimer **7**. The use of lithium chloride afforded a poor yield of alkylated product without any significant amounts of **7** (entry 10 of Table 2). On the basis of this result, a PTC reaction was performed in the absence of electrophilic olefin giving dimer **7** and unchanged **2**, indicating that the phase-transfer catalyst (TBAB) caused dimerization of the 2-pyrazinone. However, when the reaction was performed with tetraethylammonium chloride as catalyst, no Michael adduct was detected. Using these previous results, the synthesis of dimer **7** was optimized and **7** was obtained exclusively in 87% yield using 1,2-diiodoethane and DBU (2 mol-equiv.) in NMP for 24 h at room temperature. When the same reaction was carried out under PTC conditions (or PTC conditions using iodine), **7** was isolated in poor yields.

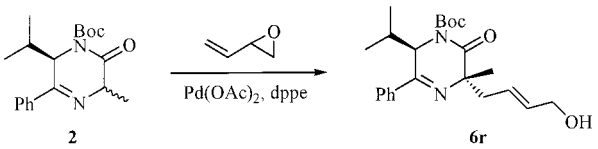
In spite of the similarity of structures **1** and **2**, 2-pyrazinones did not undergo any transformation when an activated dihalide was used in order to prepare heterocyclic α-amino acids by subsequent *C*- and *N*-alkylation, either under PTC conditions or using DBU, as occurred with oxazinones **1**.[16]

Table 2. Diastereoselective alkylation of 2-pyrazinone **2** with DBU as organic base in the presence of LiI

Entry	Electrophile	R	*t* [h][a]	Product ratio **6**/**7**[b]	**6** (%)[c]	% *de*[b]
1	EtI	Et	1	17:1[d]	(6*R*)-**6a** (84)	97
2	CH_2=$CHCH_2Cl$	CH_2CH=CH_2	20	10:1.6	(6*R*)-**6b** (77)	98
3	*n*BuBr	*n*Bu	24	10:1.5	(6*R*)-**6l** (70)	98
4	*n*BuI	*n*Bu	12	10:0.5	(6*R*)-**6l** (75)	98
5	*i*BuI	*i*Bu	24	5:1	(6*R*)-**6m** (64)	98
6	BnCl	Bn	24	> 100:1	(6*R*)-**6d** (71)	98
7	CH_2=$CHCN$	CH_2CH_2CN	24[e]	> 1:100	–	–
8	CH_2=$CHCOMe$	CH_2CH_2COMe	24[e]	30:1	(6*R*)-**6j** (69)	96
9	CH_2=$CHCO_2Me$	$CH_2CH_2CO_2Me$	24[e]	6:1[e][f]	(6*R*)-**6j** (56)	96
10	CH_2=$CHCO_2Et$	$CH_2CH_2CO_2Et$	24[e]	> 100:1	(6*R*)-**6j** (30)	96
11	CH_2=$CHCO_2Et$	$CH_2CH_2CO_2Et$	24[e]	10:1	(6*R*)-**6n** (49)	95

[a] Monitored by TLC. – [b] Determined by ^{1}H NMR (300 and 500 MHz) and HPLC analysis of the crude reaction mixture. – [c] Isolated yield after flash chromatography. – [d] 5% of *O*-alkylation product was also detected. – [e] The same results were obtained using 10 mol-% or 2 mol-equiv. of DBU. – [f] This reaction was carried out in the absence of oxygen (He) and with freshly distilled methyl acrylate.

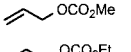
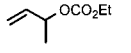
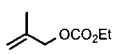
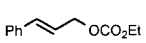
Substrate **2** was diastereoselectively allylated by using allylic carbonates and vinyloxirane[25] under mild and neutral Pd^0 catalysis.[16a,16b] Good yields and very good *de* of 2-pyrazinones **6** were achieved using $Pd(PPh_3)_4$ (2.5 mol-%) and 1,2-(diphenylphosphanoyl)ethane (dppe, 5 mol-%) or $Pd(OAc)_2$ (5 mol-%) and triphenylphosphane (10 mol-%) as catalysts, in THF at room temperature (Scheme 3 and 4 and Table 3). Mixtures of regioisomers were obtained when unsymmetrical allylic carbonates (entries 2 and 4 of Table 3) were employed and were separated by flash chromatography. Additives such LiI, introduced for improving the regioselectivity of Pd^0-catalyzed allylation reaction,[26] or other catalysts such as $[Rh(PPh_3)_3Cl]$, used for inverting the regioselectivity achieved with Pd^0 catalyst,[27] did not produce the expected results. The palladium(0)-catalyzed addition of enolate of **2** onto vinyloxirane took place under similar reaction conditions in good yields (77%) and excellent *de* (98%) (Scheme 4 and entries 5 and 6 of Table 3). The *Z*/*E* ratio of final product (determined by ^{13}C NMR and NOE experiments) depends on the palladium complex structure such as indicated in the literature.[25] While a complex comprised of $Pd(OAc)_2$ (5 mol-%) and triphenylphosphane (10 mol-%) furnished a 3:1 *Z*/*E* mixture of **6r**, the catalyst generated by $Pd(OAc)_2$ (5 mol-%) and dppe (5 mol-%) gave *E*-**6r** as the only isomer. In both examples, a regioselective nucleophilic addition of enolate to the less-hindered position of the π-allyl complex was observed.



Scheme 4

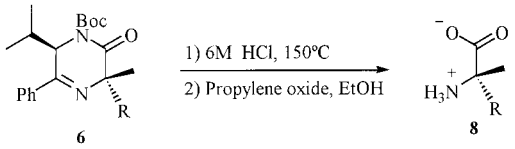
Hydrolysis of some representative alkylated 2-pyrazinones **6** was carried out with 6 M aqueous hydrochloric acid at 150 °C (pressure tube) followed by treatment with propylene oxide in refluxing ethanol for 30 min. (*S*)-AMAAs **8** were isolated by filtration in moderate to good yields and excellent *ee* (Scheme 5 and Table 4). Important (*S*)-AMAAs such as α-ethylalanine, α-methylphenylalanine, α-methylaspartic acid, α-methyltryptophan, α-methylserine and α-methylglutamic acid were thus obtained employing this methodology. These forcing hydrolysis conditions could not be applied to α-allyllic 2-pyrazinones. However, a representative example such as α-allylalanine **8b** was obtained in 62% yield after hydrolysis employing a mixture of 0.75 M hydrochloric acid, acetic acid containing Dowex 50X8–100 at

Table 3. Diastereoselective allylation of **2** under Pd^0 catalysis

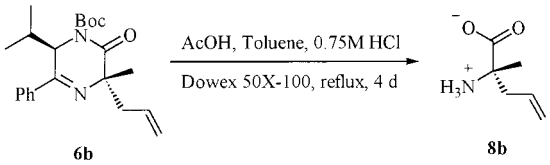
Entry	Allylic Substrate	t[d][a]	Product **6**	Yield (%)[b]	% de[c]
1		1	(6*R*)-**6b**	75	98
2		1	(6*R*)-**6o**	64[c,d]	98[f]
3		2	(6*R*)-**6p**	85	98
4		1	(6*R*)-**6q**	78[c,e]	98[g]
5		1	(6*R*)-**6r**	77[h]	98[g]
6		1[i]	(6*R*)-**6r**	77[j]	98

[a] Monitored by TLC with $Pd(OAc)_2/PPh_3$ as catalyst. – [b] Isolated yield after flash chromatography. – [c] Determined by ^{1}H NMR (300 and 500 MHz) and HPLC analysis. – [d] A 1:1 ratio of regioisomers was obtained. – [e] As a 11:1 mixture of diastereomers. – [f] Same value of *de* for each regio- and diasteroisomer. – [g] Value for the major regio- and diastereomer. – [h] A 3:1 ratio of *Z*:*E* diastereomers was detected (^{13}C NMR). – [i] $Pd(OAc)_2$/dppe as catalyst. – [j] Pure *E*-isomer (^{13}C NMR).

100 °C for 4 d[28] (Scheme 6). Unfortunately, the chiral auxiliary could not be recovered at the end of the synthesis as its amino ketone hydrochloride form **3**, because decomposition of this sensitive compound took place under both hydrolysis conditions.



Scheme 5



Scheme 6

Conclusions

A new strategy for the synthesis of enantiomerically pure 3,5,6-trisubstituted 1,2,3,6-tetrahydro-2-pyrazinones has been developed. The diastereoselective α-alkylation or α-allylation under very mild conditions occurs in higher yields (up to 86%) than those obtained from oxazinones **1**, because pyrazinones are more stable compounds in aqueous media and no decomposition was observed after purification. The diastereomeric excesses are similar or even slightly better than the reported ones for oxazinones. Another advantage of this chiral template, relative to oxazinones **1**, represents the possibility of Michael additions with electrophilic olefins as well as additions to reactive and unreactive organic halides using catalytic or stoichiometric amounts of DBU as base. Finally, (*S*)-AMAAs can be obtained through two complementary procedures of hydrolysis, depending on the sensitivity of the resulting amino acid.

Experimental Section

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

Synthesis of (2*R*)-2-Amino-3-methyl-1-phenyl-1-butanone Hydrochloride (3)[19] − Method A: Sodium bicarbonate (1.68 g, 20 mmol), di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) and dioxane (15 mL) were added to a stirred suspension of (*R*)-valine (1.17 g, 10 mmol) in water (15 mL). The mixture was heated at reflux for 12 h and the solvent was then evaporated. The residue was extracted with ethyl acetate (20 mL) and a saturated aqueous solution of potassium bisulfate (20 mL) was added. The organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo affording the protected valine (2.17 g) in a near-quantitative yield. This compound was then dissolved in acetonitrile (30 mL) together with TBTU (3.22 g, 10 mmol) and dimethylamine chlorohydrate (4.10 g, 50 mmol). The mixture was cooled to −20 °C, and triethylamine (9.7 mL, 70 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue dissolved in ethyl acetate (25 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo giving the corresponding dimethylamide (2.44 g) in a near-

Table 4. Synthesis of (*S*)-AMAAs **8**

Entry	Starting (6*R*)-**6**	R^1	Product **8** (Yield %)[a]	R^2	% ee[b]
1	(6*R*)-**6a**	Et	(*S*)-**8a** (71)	Et	99
2	(6*R*)-**6b**	CH_2=$CHCH_2$	(*S*)-**8b** (62)[c]	CH_2=$CHCH_2$	98
3	(6*R*)-**6d**	Bn	(*S*)-**8d** (72)	Bn	99
4	(6*R*)-**6e**	EtO_2CCH_2	(*S*)-**8e** (77)	HO_2CCH_2	98
5	(6*R*)-**6g**		(*S*)-**8g** (40)[d]		98
6	(6*R*)-**6h**	$HOCH_2$	(*S*)-**8h** (64)	$HOCH_2$	80
7	(6*R*)-**6k**	$EtO_2CCH_2CH_2$	(*S*)-**8k** (91)	$HO_2CCH_2CH_2$	96

[a] Based on compound (6*R*)-**6**, after recrystallization. − [b] Determined by comparison with [α] values reported in the literature. − [c] Dowex 50X-100, AcOH, toluene, 0.75 M HCl, reflux 4 d instead of 6 M HCl at 150 °C was used. − [d] A partial decomposition was observed in the crude reaction mixture.

quantitative yield. Phenylmagnesium bromide (1 M solution in THF, 30 mL, 30 mmol) was added to a stirred solution of dimethylamide (2.44 g, 10 mmol) in THF (20 mL) at 0 °C and stirring was continued at room temperature for 1 d. A saturated solution of ammonium chloride (100 mL) was added dropwise at 0 °C, followed by ethyl acetate (20 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated. The resulting residue was treated with a solution of hydrogen chloride in ethyl acetate (3 M, 80 mL) and stirred at room temperature for 30 min. The solvent was evaporated in vacuo and the remaining solid was washed with hot *n*-hexane to afford ketone hydrochloride **3** (2.95 g, 70% overall yield from valine). − **Method B:** Pivaloyl chloride (1.23 mL, 10 mmol) was added dropwise to a solution of *N*-Boc-protected valine (2.17 g, 10 mmol) and triethylamine (2.02 g, 10 mmol) in THF (60 mL) at 0 °C, and the resulting suspension was stirred for 1 h at the same temperature. Pyrrolidine (1.40 g, 20 mmol) was added and the resulting mixture was stirred for 6 h. The solvent was evaporated and the residue dissolved in ethyl acetate (25 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo to give the corresponding amide (2.40 g) in a near-quantitative yield. Phenylmagnesium bromide (1 M solution in THF, 30 mL, 30 mmol) was added to a stirred solution of dimethylamide (2.44 g, 10 mmol) in THF (20 mL) at 0 °C and stirring was continued at room temperature for 1 d. A saturated solution of ammonium chloride (100 mL) was added dropwise at 0 °C, followed by ethyl acetate (20 mL) . The organic phase was separated, dried (Na_2SO_4) and concentrated. The resulting residue was treated with a solution of hydrogen chloride in ethyl acetate (3 M, 80 mL) and stirred at room temperature for 30 min. The solvent was evaporated in vacuo and the remaining solid washed with hot *n*-hexane to afford ketone **3** hydrochloride (2.95 g, 69% overall yield from valine) as a colourless solid, m.p. 206−208 °C from ethyl acetate (ref.[19] 205−207 from MeOH/EtOAc). − $[\alpha]_D^{25} = -61.4$ (c = 0.65, H_2O). − IR (KBr): $\tilde{\nu}$ = 3000−2750, 1680 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.84, 1.12 [2 d, J = 7.3 Hz, 6 H, $(CH_3)_2CH$], 2.45 [m, 1 H, $CH(CH_3)_2$], 5.14 (d, J = 3.7 Hz, 1 H, CHN), 7.35−8.03 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 21.9, 24.9 [$(CH_3)_2CH$], 36.1 [$CH(CH_3)_2$], 67.2 (CHN), 132.1, 134.5, 135.3, 141.8 (ArC), 204.7 (CO). − MS (EI); *m*/*z* (%): 178 (0.01) [M^+ − Cl], 105 (11), 77 (24), 72 (100), 57 (16), 56 (21), 55 (59), 51 (12), 43 (26).

Synthesis of *N*-1-[(1*R*)-1-Benzoyl-2-methylpropyl]-(2*S*)-2-(*N*-Boc-amino)propanamide (4): Compound **3** (2.13 g, 10 mmol) was added to a suspension of freshly prepared *N*-Boc-(*S*)-alanine-pivalic acid mixed anhydride[29] (10 mmol) containing triethylamine (4.17 mL, 30 mmol) at 0 °C and the reaction mixture stirred at room temperature for 3 h. Water (40 mL) and ethyl acetate (30 mL) were added, the organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. The residue was washed with hot *n*-hexane, yielding ketone **4** (3.31 g, 95%) as colourless sticky oil. − $C_{19}H_{28}N_2O_4$ (348.4): calcd. C 65.5, H 8.05, N 8.05; found C 65.4, H 8.0, N 7.8. − $[\alpha]_D^{25}$ = −67.4 (c = 1.07, CH_2Cl_2). − TLC: R_f = 0.43 (hexane/ethyl acetate, 3/2). − IR (film): $\tilde{\nu}$ = 3400−3200, 1700−1600 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.78, 1.02 [2 d, J = 6.7 Hz, 6 H, $(CH_3)_2CH$], 1.39 (d, J = 7.3 Hz, 3 H, CH_3CHN), 1.45 [s, 9 H, $(CH_3)_3C$], 2.21 [m, 1 H, $CH(CH_3)_2$], 4.34 (m, 1 H, $CHCH_3$), 5.49 (br. s, 1 H, NHBoc), 5.59 (dd, J = 8.5, 4.5 Hz, 1 H, CHCOAr), 8.02−7.01 (m, 6 H, ArH, NHCOCH). − ^{13}C NMR (75 MHz): δ = 16.5, 18.4 [$(CH_3)_2CH$], 19.8 (CH_3CH), 28.1 [$(CH_3)_3C$], 31.5 [$CH(CH_3)_2$], 57.7 ($CHCH_3$, CHN), 81.7 [$(CH_3)_3C$], 125.5, 128.6, 133.5, 135.1 (ArC), 155.2, 172.9 (2 × NCO), 198.9 (ArCO). − MS (ESI); *m*/*z* (%): 349 (34) [M^+ + 1].

Synthesis of (3*S*,6*R*)-6-Isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (5): A solution of ketone **4** (3.84 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, the residue dissolved in hydrochloric acid (0.1 M, 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 concentrated affording pure pyrazinone **5**. When cyclization 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 **5** was obtained (1.98 g, 86%) as a pale yellow oil. − $C_{14}H_{18}N_2O$ (230.2): calcd. C 73.05, H 7.8, N 12.15; found C, 73.5, H 7.9, N 11.8. − $[\alpha]_D^{25} = -76.5$ (c = 1.60, CH_2Cl_2). − TLC: R_f = 0.51 (ethyl acetate). − IR (film): $\tilde{\nu}$ = 3500−3200, 1670−1660 cm^{-1}. − ^1H NMR (300 MHz): δ (major diastereomer) = 0.78, 1.02 [2 d, J = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 1.68 [d, J = 7.6 Hz, 3 H, CH_3CHCO], 2.08 [m, 1 H, $CH(CH_3)_2$], 4.21 (qd, J = 7.3, 2.8 Hz, 1 H, CHCO), 4.71 (m, 1 H, CHN), 7.71−7.18 (m, 5 H, ArH), 8.15 (br. s, 1 H, NH). − ^{13}C NMR (75 MHz): δ (major diastereomer) = 15.7, 19.1 [$(CH_3)_2CH$)], 19.5 [CH_3CHCO], 32.5 [$CH(CH_3)_2$], 56.1 (CHN), 60.2 (CH_3CHCO), 126.7, 128.5, 129.3, 136.8 (ArC), 164.1 (C=N), 172.7 (CO). − MS (ESI); *m*/*z* (%): 231 (27) [M^+ + 1].

Synthesis of (3*S*,6*R*)-*N*-1-Boc-6-Isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (2): Di-*tert*-butyl dicarbonate (2.64 g, 11 mmol) dissolved in THF (6 mL) was added to a stirred solution of **5** (2.30 g, 10 mmol) and 4-(dimethylamino)pyridine (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 in vacuo and the residue purified by chromatography (SiO_2) eluting with *n*-hexane yielding **2** (2.77 g, 84%) as a pale yellow oil. − $C_{19}H_{26}N_2O_3$ (330.3): calcd. C 69.0, H 7.6, N 4.1; found C, 69.1, H 7.9, N 4.5. − TLC: R_f = 0.62 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 1780−1700 cm^{-1}. − ^1H NMR (300 MHz): δ (major diastereomer) = 0.85, 0.97 [2 d, J = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 1.59 [s, 9 H, $(CH_3)_3C$], 1.72 (d, J = 7.3 Hz, 3 H, CH_3CHCO), 2.21 [m, 1 H, $(CH_3)_2CH$)], 4.33 (q, J = 7.3 Hz, 1 H, CH_3CHCO), 5.63 (d, J = 8.5 Hz, 1 H, CHN), 7.85−7.42 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ (major diastereomer) = 18.3, 19.4 [$(CH_3)_2CH$)], 20.4 [CH_3CHCO], 27.8 [$(CH_3)_3C$], 31.5 [$(CH_3)_2CH$)], 58.6 (CHN), 61.0 (CH_3CHCO), 83.7 [$(CH_3)_3C$], 126.8, 128.6, 130.6, 137.2 (ArC), 152.1, 167.8, 170.2 (2 × C=O and C=N). − MS (ESI); *m*/*z* (%): 331 (21) [M^+ + 1]. −MS (EI); *m*/*z* (%): 330 (3) [M^+], 230 (37), 215 (46), 91 (14), 77 (15), 44 (100). − HRMS calcd. for $C_{19}H_{26}N_2O_3$: 330.1943; found 330.1948.

Diastereoselective Alkylation of 2 under PTC Conditions. − General Procedure: A suspension of pyrazinone **2** (0.33 g, 1 mmol), tetra-*n*-butylammonium chloride (32 mg, 0.1 mmol), potassium carbonate (0.414 g, 3 mmol) and the electrophile (1.5 mmol) in acetonitrile (5 mL) was stirred at room temperature for times depicted in Table 1. The solvent was evaporated and the residue purified by chromatography (SiO_2) eluting with mixtures of *n*-hexane/ethyl acetate giving product **6** in yields and *de*'s shown in Table 1. Physical and analytical data follow.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-ethyl-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6a): Pale yellow oil. − $[\alpha]_D^{25} = -151.7$ (c = 1.03, CH_2Cl_2). −TLC: R_f = 0.76 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 1712−1655 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.74 (t, J = 7.6 Hz, 3 H, CH_3CH_2), 0.81, 0.86 [2 d, J = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.55 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 1.97 [m, 1 H, $(CH_3)_2CH$], 1.94, 2.12 (2 m, 2 H, CH_2), 5.52 (d, J = 5.5 Hz, 1 H, CHN), 7.76, 7.42 (m, 5 H, ArH). − ^{13}C NMR

(75 MHz): δ = 18.5 (CH_3CH_2), 18.9, 19.8 [$(CH_3)_2CH$)], 26.6 (CH_3CCO), 28.0 [$(CH_3)_3C$], 34.7 [$(CH_3)_2CH$)], 37.4 (CH_2), 61.5 (CHN), 66.1 (CH_3CCO), 83.3 [$(CH_3)_3C$], 127.1, 128.6, 130.2, 138.1 (ArC), 151.8 (C=N), 163.8 (CO_2tBu), 175.7 (CH_3CCON). − MS (EI); *m/z* (%): 357 (1) [M^+ − 1], 230 (1), 117 (13), 91 (70), 77 (51), 43 (100). − HRMS calcd. for $C_{21}H_{30}N_2O_3$: 358.2256; found 358.2255.

(3*S*,6*R*)-3-Allyl-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6b): Pale yellow oil. − $[\alpha]_D^{25}$ = −88.9 (*c* = 0.80, CH_2Cl_2). − TLC: R_f = 0.77 (*n*-hexane/ethyl acetate, 3:2). − IR (film): ṽ = 3075, 1651, 981, 1802, 1631 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.78, 0.86 [2 d, *J* = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 1.54 [s, 9 H, $(CH_3)_3C$], 1.58 (s, 3 H, CH_3CCO), 1.98 [m, 1 H, $(CH_3)_2CH$)], 2.64 (dd, *J* = 13.4, 6.7 Hz, 1 H, CH_2CH=C), 2.73 (dd, *J* = 13.4, 8.6 Hz, 1 H, CH_2CH=C), 4.98 (d, *J* = 10.4 Hz, 1 H, CH=CH_2), 5.04 (d, *J* = 17.7 Hz, 1 H, CH=CH_2), 5.55 (d, *J* = 4.9 Hz, 1 H, CHN), 5.59 (m, 1 H, CH=CH_2), 7.76−7.20 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.7, 19.6 [$(CH_3)_2CH$)], 26.2 [CH_3CCO], 28.0 [$(CH_3)_3C$], 34.5 [$(CH_3)_2CH$)], 48.1 (CH_2CH=C), 61.5 (CHN), 66.3 (CH_3CCO), 83.2 [$(CH_3)_3C$], 118.7 (CH=CH_2), 127.1, 128.6, 130.2, 132.6, 137.9 (ArC, CH=CH_2), 151.6, 163.3, 174.9 (2 × C=O, C=N). − MS (EI); *m/z* (%): 270 (9) [M^+ − 100], 229 (100), 213 (15), 199 (2), 91 (4), 77 (5), 44 (11). − HRMS calcd. for $C_{22}H_{30}N_2O_3$: 370. 2256; found 370.2260.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-3-(2-propynyl)-1,2,3,6-tetrahydro-2-pyrazinone (6c): Pale yellow oil. − $[\alpha]_D^{25}$ = −194.5 (*c* = 0.96, CH_2Cl_2). − TLC: R_f = 0.29 (*n*-hexane/ethyl acetate, 4:1). − IR (film): ṽ = 3250, 1716,1662 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.79, 0.88 [2 d, *J* = 6.9 Hz, 6 H, $(CH_3)_2CH$)], 1.56 [s, 9 H, $(CH_3)_3C$], 1.61 (s, 3 H, CH_3CCO), 1.90 (t, *J* = 2.6 Hz, 1 H, C≡CH), 1.98 [m, 1 H, $(CH_3)_2CH$)], 2.75, 2.90 (2 dd, *J* = 16.1, 2.6 Hz, 2 H, CH_2), 5.67 (d, *J* = 4.9 Hz, 1 H, CHN), 7.78−7.20 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.5, 19.6 [$(CH_3)_2CH$)], 25.9 (CH_3CCO), 28.0 [$(CH_3)_3C$], 34.1 (CH_2), 34.3 [$(CH_3)_2CH$)], 61.6 (CHN), 65.2 (CH_3CCO), 70.8 (C≡CH), 79.6 (C≡CH), 83.5 [$(CH_3)_3C$], 127.2, 128.6, 130.4, 137.8 (ArC), 151.6, 164.4, 173.5 (2 × C=O and C=N). − MS (EI); *m/z* (%): 369 (5) [M^+ + 1], 253 (13), 229 (3), 213 (6), 77 (6), 44 (100). − HRMS calcd. for $C_{22}H_{28}N_2O_3$: 368.2099; found 368.2101.

(3*S*,6*R*)-3-Benzyl-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6d): Pale yellow oil. − $[\alpha]_D^{25}$ = −74.2 (*c* = 0.50, CH_2Cl_2). − TLC: R_f = 0.56 (*n*-hexane/ethyl acetate, 3/2). − IR (film): ṽ = 1772, 1661 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.66, 0.77 [2 d, *J* = 6.9 Hz, 6 H, $(CH_3)_2CH$)], 1.48 [s, 9 H, $(CH_3)_3C$], 1.71 (s, 3 H, CH_3CCO), 1.88 [m, 1 H, $(CH_3)_2CH$)], 3.18, 3.31 (2 d, *J* = 12.7 Hz, 2 H, CH_2), 5.04 (d, *J* = 4.3 Hz, 1 H, CHN), 7.61−6.99 (m, 10 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.8, 19.1 [$(CH_3)_2CH$)], 26.8 (CH_3CCO), 27.9 [$(CH_3)_3C$], 34.4 [$(CH_3)_2CH$)], 50.0 (CH_2), 61.5 (CHN), 66.9 (CH_3CCO), 83.0 [$(CH_3)_3C$], 126.5, 126.8, 127.5, 128.5, 130.0, 130.4, 136.1, 138.4 (ArC), 151.0, 162.9, 173.7 (2 × C=O and C=N). − MS (EI); *m/z* (%): 320 (7) [M^+ − 100], 229 (100), 213 (14), 199 (2), 91 (34), 77 (9), 44 (20). − HRMS calcd. for $C_{26}H_{32}N_2O_3$: 420.2413; found 420.2421.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-(ethoxycarbonyl)methyl-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6e): Pale yellow oil. − $[\alpha]_D^{25}$ −124.9 (*c* = 1.03, CH_2Cl_2). − TLC: R_f = 0.59 (*n*-hexane/ethyl acetate, 3:2). − IR (film): ṽ = 1770, 1738, 1670 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.85, 0.87 [2 d, *J* = 4.6 Hz, 6 H, $(CH_3)_2CH$)], 1.09 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3) 1.58 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 1.97 [m, 1 H, $(CH_3)_2CH$)], 2.90, 3.33 (2 d, *J* = 16.2 Hz, 2 H, CH_2CO), 3.94, 4.00 (2 dq, *J* = 10.8, 7.2 Hz, 2 H, CH_2O), 5.63 (d, *J* = 5.8 Hz, 1 H, CHN), 7.72−7.28 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 14.0 (CH_2CH_3), 19.0, 20.2 [$(CH_3)_2CH$)], 27.2 (CH_3CCO), 27.9 [$(CH_3)_3C$], 34.8 [$(CH_3)_2CH$)], 47.8 (CH_2CO), 60.2 (CH_2O), 61.2 (CHN), 62.8 (CH_3CCO), 83.6 [$(CH_3)_3C$], 127.0, 128.5, 130.2, 138.3 (ArC), 152.1, 164.3, 179.0, 172.6 (3 × C=O and C=N). − MS (EI); *m/z* (%): 316 (5) [M^+ − 100], 229 (15), 213 (12), 185 (11), 104 (100), 91 (84), 77 (41), 44 (83). − HRMS calcd. for $C_{23}H_{32}N_2O_5$: 416.2311; found 416.2313.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-3-[(*E*)-3-methyloxycarbonyl-2-propenyl]-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6f): Pale yellow oil. − $[\alpha]_D^{25}$ = −117.2 (*c* = 1.70, CH_2Cl_2). − TLC: R_f = 0.58 (*n*-hexane/ethyl acetate, 3:2). − IR (film): ṽ = 3059, 1659, 985, 1772, 1725, 1659, 1291, 1155 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.81, 0.84 [2 d, *J* = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.53 [s, 9 H, $(CH_3)_3C$], 1.61 (s, 3 H, CH_3CCO), 1.98 [m, 1 H, $(CH_3)_2CH$)], 2.80 (ddd, *J* = 13.3, 6.9, 1.5 Hz, 1 H, CH_2), 2.87 (ddd, *J* = 13.3, 8.6, 1.2 Hz, 1 H, CH_2), 3.66 (s, 3 H, OCH_3), 5.49 (d, *J* = 5.8 Hz, 1 H, CHN), 5.84 (dm, *J* = 15.9 Hz, 1 H, CH=$CHCO_2CH_3$), 6.74 (ddd, *J* = 15.9, 8.6, 6.9 Hz, 1 H, CH=$CHCO_2CH_3$), 7.78−7.28 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 19.0, 19.7 [$(CH_3)_2CH$)], 26.4 (CH_3CCO), 27.8 [$(CH_3)_3C$], 34.4 [$(CH_3)_2CH$)], 46.1 (CH_2), 51.2 (OCH_3), 61.3 (CHN), 65.9 (CH_3CCO), 83.4 [$(CH_3)_3C$], 124.3, 127.1, 128.5, 130.4, 137.6, 142.9 (ArC, C=C), 151.6, 164.2, 166.2 and 174.3 (3 × C=O, C=N). − MS (EI); *m/z* (%): 328 (4) [M^+ − 100], 313 (1), 297 (1), 229 (100), 213 (14), 185 (18), 91 (10), 77 (11), 44 (9). − HRMS calcd. for $C_{24}H_{32}N_2O_5$: 428.2311; found 428.2307.

***tert*-Butyl [3-(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-2-oxo-5-phenyl-1,2,3,6-tetrahydropyrazinylmethyl]-1*H*-1-indolecarboxylate (6g):** Light brown oil. − $C_{33}H_{41}N_3O_5$ (559.6): calcd. C 70.82, H 7.38, N 7.51; found C 71.00, H 7.41, N 7.80. − $[\alpha]_D^{25}$ = −43.7 (*c* = 3.00, CH_2Cl_2). − TLC: R_f = 0.68 (*n*-hexane/ethyl acetate, 3:2). − IR (film): ṽ = 3055, 1661, 1769−1721 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.71, 0.78 [2 d, *J* = 7.3 Hz, 6 H, $(CH_3)_2CH$)], 1.34, 1.56 [2 × s, 18 H, $(CH_3)_3C$], 1.52 (s, 3 H, CH_3CCO), 1.88 [m, 1 H, $(CH_3)_2CH$)], 3.28, 3.45 (2 × d, *J* = 14.0 Hz, 2 H, CH_2), 5.16 (d, *J* = 4.9 Hz, 1 H, CHN), 6.86 (t, *J* = 7.6 Hz, 1 H, C=CHN), 8.02−7.10 (m, 9 H, ArH). − ^{13}C NMR (75 MHz): δ = 19.1, 19.5 [$(CH_3)_2CH$)], 26.9 (CH_3CCO), 28.1 [$(CH_3)_3C$], 34.7 [$(CH_3)_2CH$)], 39.7 (CH_2), 61.1 (CHN), 66.8 (CH_3CCO), 83.2 [2 × $(CH_3)_3C$], 114.6 (CH=CN), 115.5 (CH=CN), 120.8, 122.1, 123.8, 125.0, 127.0, 128.4, 130.1, 138.3 (ArC), 151.3 (C=N), 163.4 (CO_2tBu) and 173.9 (CH_3CCON). − MS (EI); *m/z* (%): 228 (100), 213 (30), 185 (74), 77 (25).

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-hydroxymethyl-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6h): Pale yellow oil. − $[\alpha]_D^{25}$ = −107.5 (*c* = 2.1, CH_2Cl_2). − TLC: R_f = 0.50 (*n*-hexane/ethyl acetate, 3:2). − IR (film): ṽ = 3400, 1770, 1700 and 1600 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.83, 0.86 [2 d, *J* = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 1.52 (s, 3 H, CH_3CCO), 1.55 [s, 9 H, $(CH_3)_3C$], 1.96 [m, 1 H, $(CH_3)_2CH$)], 3.78, 3.90 (2 d, *J* = 10.4 Hz, 2 H, CH_2), 5.55 (d, *J* = 6.7 Hz, 1 H, CHN), 7.76−7.41 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 19.2, 20.2 [$(CH_3)_2CH$)], 25.9 (CH_3CCO), 28.0 [$(CH_3)_3C$], 34.0 [$(CH_3)_2CH$)], 61.1 (CHN), 66.0 (CH_3CCO), 71.2 (CH_2), 83.7 [$(CH_3)_3C$], 127.2, 128.7, 130.7, 137.7 (ArC), 151.8 (C=N), 166.3 (CO_2tBu), 173.8 (CH_3CCON). − MS (EI); *m/z* (%): 260 [M^+ − 100], 229 (100), 215 (10), 213 (17), 187 (18), 117 (8), 104 (13), 91 (11), 77 (16), 72 (20), 44 (15) and 41 (34). − HRMS calcd. for $C_{20}H_{28}N_2O_4$: 360.2049; found 360.2048.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-(2-cyanoethyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6i): Light yellow

oil. − $[\alpha]_D^{25}$ = −111.5 (*c* =1.00, CH_2Cl_2). − TLC: R_f = 0.50 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 2247, 1731, 1715 and 1644 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.84, 0.88 [2 d, *J* = 7.3 Hz, 6 H, $(CH_3)_2CH$)], 1.57 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 1.98 [m, 1 H, $(CH_3)_2CH$)], 2.25, 2.47 [2 m, 4 H, $(CH_2)_2CN$], 5.49 (d, *J* = 6.1 Hz, 1 H, CHN), 7.77−7.40 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 12.7 (CH_2CN), 19.3, 20.3 [$(CH_3)_2CH$)], 26.5 (CH_3CCO), 28.0 [$(CH_3)_3C$], 35.2 [$(CH_3)_2CH$)], 38.8 (CH_2CH_2CN), 61.3 (CHN), 64.2 (CH_3CCO), 84.3 [$(CH_3)_3C$], 119.2 (CN), 127.2, 128.7, 130.8, 137.4 (ArC), 151.8, 165.8, 173.6 (2 × C=O, C=N). − MS (EI); *m*/*z* (%): 283 (17) [M^+ − 100], 268 (12), 243 (6), 230 (17), 229 (100), 213 (17), 91 (9), 77 (19), 44 (13). − HRMS calcd. for $C_{29}H_{29}N_3O_3$: 383.2210; found 383.2211.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-3-(3-oxobutyl)-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6j): Pale yellow oil. − $[\alpha]_D^{25}$ = −137.9 (*c* = 0.72, CH_2Cl_2). − TLC: R_f = 0.58 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 1770, 1732, 1715, 1651 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.85 [d, *J* = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.57 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 2.02 (s, 3 H, CH_3CO), 2.58−1.95 [m, 5 H, $(CH_3)_2CH$, $(CH_2)_2CO$], 5.50 (d, *J* = 6.1 Hz, 1 H, CHN), 7.77−7.28 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 19.1, 20.0 [$(CH_3)_2CH$)], 26.5 (CH_3CCO), 28.0 [$(CH_3)_3C$], 29.7 (CH_3CO), 34.9 [$(CH_3)_2CH$)], 37.9, 38.8 [$(CH_2)_2CO$], 61.3 (CHN), 64.6 (CH_3CCO), 83.6 [$(CH_3)_3C$], 127.1, 128.6, 130.5, 137.7 (ArC), 151.9, 164.3, 174.9 (CON, CO_2tBu, ArC=N), 207.7 (CH_3CO). − MS (EI); *m*/*z* (%): 302 (3) [M^+ + 2 − 100], 284 (3), 269 (8), 229 (3), 91 (6), 77 (11), 44 (89), 43 (100). − HRMS calcd. for $C_{23}H_{32}N_2O_4$: 400.2362; found 400.3366.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-3-(2-methoxycarbonyl)ethyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6k): Pale yellow oil. − $[\alpha]_D^{25}$ = −109.2 (*c* = 0.70, CH_2Cl_2). − TLC: R_f = 0.29 (*n*-hexane/ethyl acetate, 4:1). − IR (film): $\tilde{\nu}$ = 1770, 1727, 1650 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.84 [d, *J* = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 1.56 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 1.98 [m, 1 H, $(CH_3)_2CH$)], 2.29 [m, 4 H, $(CH_2)_2CO_2CH_3$], 3.48 [s, 3 H, $(CH_2)_2CO_2CH_3$], 5.50 (d, *J* = 6.1 Hz, 1 H, CHN), 7.76−7.22 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 19.2, 20.1 [$(CH_3)_2CH$)], 26.7 (CH_3CCO), 28.2 [$(CH_3)_3C$], 29.6 ($CH_2CH_2CO_2CH_3$), 35.1 [$(CH_3)_2CH$)], 39.0 ($CH_2CH_2CO_2CH_3$), 51.7 (OCH_3), 61.7 (CHN), 65.2 (CH_3CCO), 84.2 [$(CH_3)_3C$], 127.9, 129.3, 131.3, 138.6 (ArC), 152.8, 165.4, 174.4, 175.9 (3 × C=O, C=N). − MS (EI); *m*/*z* (%): 316 (3) [M^+ − 100], 285 (1), 229 (15), 91 (100), 77 (6), 44 (73). − HRMS calcd. for $C_{23}H_{32}N_2O_5$: 416.2311; found 416.2316.

***C*-3 Dimer of (6*R*)-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (7):** Pale yellow oil. − $C_{38}H_{50}N_4O_6$ (658.6): calcd. C 69.3, H 7.6, N 8.5; found C 69.0, H 7.7, N 8.9. − $[\alpha]_D^{25}$ = −151.7 (*c* = 0.50, CH_2Cl_2). − TLC: R_f = 0.43 (*n*-hexane/ethyl acetate, 4:1). − IR (film): $\tilde{\nu}$ = 1800, 1714, 1645 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.59, 0.75 [2 d, *J* = 7.0 Hz, 12 H, 2 × $(CH_3)_2CH$)], 1.52 [s, 18 H, 2 × $(CH_3)_3C$], 1.78 (s, 6 H, 2 × CH_3CCO), 1.85 [m, 2 H, 2 × $(CH_3)_2CH$)], 5.55 (d, *J* = 3.7 Hz, 2 H, 2 × CHN) and 7.78−7.20 (m, 10 H, 2 × ArH). − ^{13}C NMR (75 MHz): δ = 18.5, 19.1 [2 × $(CH_3)_2CH$)], 21.8 (2 × CH_3CCO), 28.1 [2 × $(CH_3)_3C$], 34.1 [2 × $(CH_3)_2CH$)], 61.3 (2 × CHN), 71.6 (2 × CH_3CCO), 82.4 [2 × $(CH_3)_3C$], 126.8, 128.2, 130.2, 137.7 (ArC), 151.2, 163.1, 172.3 (4 × C=O, 2 × C=N). − MS (EI); *m*/*z* (%): 662 (0.6) [M^+ + 4], 648 (0.6), 329 (5), 274 (13), 229 (31), 187 (55), 186 (100), 158 (42), 157 (12), 117 (11), 116 (29), 104 (11), 90 (10), 89 (18), 77 (10), 57 (94), 43 (17), 41 (35).

Diastereoselective Alkylation of 2 under Organic Base Conditions. − General Procedure: A solution of pyrazinone **2** (0.33 g, 1 mmol), lithium iodide (133 mg, 1 mmol), DBU (0.284 mL, 2 mmol or 0.015, 0.1 mmol, see text and Table 2) and the electrophile (1.5 mmol) in NMP (5 mL) was stirred at room temperature for times depicted in Table 2. The solvent was evaporated and the residue purified by chromatography (SiO_2) eluting with mixtures of *n*-hexane/ethyl acetate giving product **6** in yields shown in Table 2. Physical and analytical data follow.

(3*S*,6*R*)-3-Butyl-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6l): Pale yellow oil. − $[\alpha]_D^{25}$ = −29.0 (*c* = 3.00, CH_2Cl_2). − TLC: R_f = 0.69 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 1800−1716. − ^1H NMR (300 MHz): δ = 0.80, 0.85 [2 × d, *J* = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 0.81 (t, *J* = 6.7 Hz, 3 H, CH_3CH_2), 1.51 (s, 3 H, CH_3CCO), 1.55 [s, 9 H, $(CH_3)_3C$], 2.16−1.66 [m, 7 H, $(CH_2)_3$, $(CH_3)_2CH$], 5.52 (d, *J* = 5.5 Hz, CHN), 7.75−7.18 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 14.0 (CH_3CH_2), 18.9, 19.8 [$(CH_3)_2CH$)], 22.7 (CH_3CH_2), 26.3 ($CH_3CH_2CH_2$), 26.9 (CH_3CCO), 28.1 [$(CH_3)_3C$], 34.7, [$(CH_3)_2CH$)], 44.3 (CH_2CCO), 61.6 (CHN), 65.8 (CH_3CCO), 83.3 [$(CH_3)_3C$], 127.1, 128.6, 130.2, 138.1 (ArC), 151.9 (C=N), 163.8 (CO_2tBu), 175.9 (CH_3CCON). − MS (EI); *m*/*z* (%): 286 (9) [M^+ − 100], 229 (100), 213 (13), 187 (7), 91 (6), 77 (6), 41 (23). − HRMS calcd. for $C_{23}H_{34}N_2O_3$: 386.2570; found 386.2573.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-isobutyl-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6m): Pale yellow oil. − $[\alpha]_D^{25}$ = −71.3 (*c* =1.05, CH_2Cl_2). − TLC: R_f = 0.58 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 1800−1716, 1395, 1370 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.86−0.74 (m, 12 H, 2 × $(CH_3)_2CH$)], 1.51 (s, 3 H, CH_3CCO), 1.54 [s, 9 H, $(CH_3)_3C$], 1.86 (dd, *J* = 14.0, 6.1 Hz, 1 H, CH_2), 1.95 [m, 2 H, 2 × $(CH_3)_2CH$], 2.08 (dd, *J* = 14.0, 6.4 Hz, 1 H, CH_2), 5.53 (d, *J* = 6.1 Hz, 1 H, CHN), 7.75−7.19 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 19.1, 20.0, 23.5, 24.8 [2 × $(CH_3)_2CH$)], 27.9 (CH_3CCO), 28.1 [$(CH_3)_3C$], 34.2, 34.9 [2 × $(CH_3)_2CH$)], 52.7 (CH_2), 61.3 (CHN), 65.8 (CH_3CCO), 83.4 [$(CH_3)_3C$], 126.9, 127.0, 128.7, 130.1 (ArC), 151.8 (C=N), 162.8 (CO_2tBu), 175.5 (CH_3CCON). − MS (EI); *m*/*z* (%): 286 (9) [M^+ − 100], 229 (100), 213 (12), 187 (13), 41 (28). − HRMS calcd. for $C_{23}H_{34}N_2O_3$: 386.2569; found 386.2568.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-(2-ethoxycarbonylethyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6n): Pale yellow oil. − $[\alpha]_D^{25}$ = −122.6 (*c* = 2.80, CH_2Cl_2). − TLC: R_f = 0.68 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 1765, 1719, 1640 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.83, 0.84 [2 × d, *J* = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.13 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.58 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 1.95 [m, 1 H, $(CH_3)_2CH$)], 2.43−2.21 (m, 4 H, 2 × CH_2), 3.94 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 5.49 (d, *J* = 6.1 Hz, 1 H, CHN) and 7.76−7.41 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 14.1 (OCH_2CH_3), 19.1, 20.1 [$(CH_3)_2CH$)], 26.5 (CH_3CCO), 28.0 [$(CH_3)_3C$], 29.7 ($CH_2CH_2CO_2Et$), 35.0 [$(CH_3)_2CH$)], 38.8 ($CH_2CH_2CO_2Et$), 61.3 (CHN), 64.8 (CH_3CCO), 83.7 [$(CH_3)_3C$], 127.2, 128.6, 130.5, 137.7 (ArC), 151.9, 165.4, 172.8, 176.0 (3 × C=O and C=N). − MS (EI); *m*/*z* (%): 330 (10) [M^+ − 100], 285 (7), 230 (17), 229 (100), 91 (5), 77 (5), 44 (5). − HRMS calcd. for $C_{24}H_{34}N_2O_5$: 430.2468; found 430.2462.

Diastereoselective Allylation of 2 under Neutral Palladium(0)-Catalyzed Conditions. − General Procedure: A solution of pyrazinone **2** (0.33 g, 1 mmol), and palladium catalyst (a) triphenylphosphane (27 mg, 0.1 mmol), palladium acetate (8 mg, 0.05 mmol) or (b) dppe (20 mg, 0.05 mmol), palladium acetate (8 mg, 0.05 mmol) or (c) dppe (20 mg, 0.05 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and the corresponding allylic carbonate or vinyloxirane (1.1 mmol) in THF (5 mL) was stirred at room temperature for times depicted in

Table 3. The solvent was evaporated and the residue purified by chromatography (SiO_2) eluting with mixtures of *n*-hexane/ethyl acetate giving product **6** in yields shown in Table 3. Physical and analytical data follow.

(3*S*,6*R*)-3-[(*E*)-2-Butenyl]-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6o): Pale yellow oil. − $[\alpha]_D^{25}$ = −96.6 (*c* = 2.10, CH_2Cl_2). − TLC: R_f = 0.53 (*n*-hexane/ethyl acetate, 8:1). − IR (film): $\tilde{\nu}$ = 3028, 1658, 981, 1715 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.70, 0.78 [2 d, *J* = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.48 [s, 12 H, $(CH_3)_3C$, CH_3CCO], 1.49 (d, *J* = 2.8 Hz, 3 H, $CH_3CH{=}C$), 1.90 [m, 1 H, $(CH_3)_2CH$], 2.48 (dd, *J* = 13.1, 6.7 Hz, 1 H, $CH_2CH{=}CH$), 2.59 (dd, *J* = 13.1, 8.3 Hz, 1 H, $CH_2CH{=}CH$), 5.14, 5.37 (2 m, 2 H, CH=CH), 5.44 (d, *J* = 4.9 Hz, CHN), 7.68−7.35 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.1 ($CH_3CH{=}C$), 18.8, 19.6 [$(CH_3)_2CH$], 26.1 (CH_3CCO), 28.0 [$(CH_3)_3C$], 34.5 [$(CH_3)_2CH$)], 47.1 ($CH_2CH{=}C$), 61.6 (CHN), 66.4 (CH_3CCO), 83.0 [$(CH_3)_3C$], 124.9, 129.4 (CH=CH), 127.0, 128.6, 130.2, 138.1 (ArC), 151.7, 163.1, 175.1 (2 × C=O and C=N). − MS (EI); *m*/*z* (%): 284 (5) [M^+ − 100], 229 (100), 213 (15), 185 (18), 91 (7), 77 (10), 55 (27), 44 (64). − HRMS calcd. for $C_{23}H_{32}N_2O_3$: 384.2413; found 384.2413.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-3-[1-methyl-2-propenyl)-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6o): Pale yellow oil. − $[\alpha]_D^{25}$ = −131.4 (*c* = 0.85, CH_2Cl_2). − TLC: R_f = 0.63 (*n*-hexane/ethyl acetate). − IR (film): $\tilde{\nu}$ = 3070, 1650, 920, 1724 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.78, 0.79 [2 d, *J* = 6.9 Hz, 6 H, $(CH_3)_2CH$)], 1.48−1.43 [m with s at δ = 1.45, 12 H, $(CH_3)_3C$, CH_3CCO], 1.89 (d, *J* = 7.0 Hz, 3 H, CH_3CH), 1.90 [m, 1 H, $(CH_3)_2CH$], 2.73 (m, 1 H, CH_3CH), 4.99 (dd, *J* = 4.7, 2.2 Hz, 1 H, $CH{=}CH_2$), 4.97−5.06 (m, 2 H, $CH{=}CH_2$), 5.43 (d, *J* = 6.4 Hz, 1 H, CHN), 5.92 (ddd, *J* = 19.2, 10.1, 9.2 Hz, 1 H, $CH{=}CH_2$), 7.74−7.35 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 15.7 (CH_3CH), 19.1, 20.1 [$(CH_3)_2CH$)], 25.3 (CH_3CCO), 28.0 [$(CH_3)_3C$], 35.0 [$(CH_3)_2CH$)], 50.0 (CH_3CH), 60.7 (CHN), 67.5 (CH_3CCO), 83.3 [$(CH_3)_3C$], 116.1 ($CH{=}CH_2$), 127.1, 128.4, 130.2, 137.9 (ArC), 139.9 ($CH{=}CH_2$), 151.8, 163.4, 175.8 (2 × C=O, C=N). − MS (EI); *m*/*z* (%): 284 (4) [M^+ − 100], 229 (100), 213 (16), 187 (32), 185 (13), 91 (6), 77 (7), 55 (13), 44 (9). − HRMS calcd. for $C_{23}H_{32}N_2O_3$: 384.2413; found 384.2414.

(3*S*,6*R*)-3-(2-Methylallyl)-*N*-1-(*tert*-butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (6p): Colourless oil. − $[\alpha]_D^{25}$ = −96.2 (*c* = 1.05, CH_2Cl_2). − TLC: R_f = 0.34 (*n*-hexane/ethyl acetate, 8:1). − IR (film): $\tilde{\nu}$ = 3070, 1650, 900, 1721 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.71, 0.79 [2 d, *J* = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.31 (s, 3 H, CH_3CCO), 1.48 [s, 12 H, $(CH_3)_3C$, $CH_3C{=}CH_2$], 1.91 [m, 1 H, $(CH_3)_2CH$], 2.53, 2.74 (2 d, *J* = 12.8 Hz, 2 H, $CH_2C{=}CH_2$), 4.61, 4.67 (2s, 2 H, $C{=}CH_2$), 5.47 (d, *J* = 4.9 Hz, 1 H, CHN), 7.71,7.27 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.9, 19.6 [$(CH_3)_2CH$)], 24.3 ($CH_3C{=}CH_2$), 27.2 (CH_3CCO), 28.0 [$(CH_3)_3C$], 34.6 [$(CH_3)_2CH$)], 51.1 ($CH_2C{=}CH_2$), 61.2 (CHN), 66.8 (CH_3CCO), 83.2 [$(CH_3)_3C$], 114.9 ($CH_2C{=}CH_2$), 127.0, 128.5, 130.1, 138.1 (ArC), 141.2 ($CH_2C{=}CH_2$), 151.8, 162.7, 174.4 (2 × C=O, C=N). − MS (EI); *m*/*z* (%): 284 (6) [M^+ − 100], 229 (100), 213 (16), 185 (17), 91 (9), 77 (9), 55 (14), 44 (10). − HRMS calcd. for $C_{23}H_{32}N_2O_3$: 384.2413; found 384.2420.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-6-isopropyl-3-methyl-5-phenyl-3-[(*E*)-3-phenyl-2-propenyl]-1,2,3,6-tetrahydro-2-pyrazinone (6q): Pale yellow oil. − $[\alpha]_D^{25}$ = −93.3 (*c* = 0.70, CH_2Cl_2). − TLC: R_f = 0.65 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 3026, 1653, 980 and 1720 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.77, 0.85 [2 d, *J* = 6.9 Hz, 6 H, $(CH_3)_2CH$)], 1.37 [s, 9 H, $(CH_3)_3C$], 1.63 (s, 3 H, CH_3CCO), 1.97 [m, 1 H, $(CH_3)_2CH$], 2.81 (ddd, *J* = 13.1, 6.7, 1.2 Hz, 1 H, $CH_2CH{=}CH$), 2.89 (ddd, *J* = 13.1, 8.5, 0.9 Hz, 1 H, $CH_2CH{=}CH$), 5.47 (d, *J* = 4.9 Hz, CHN), 5.98 (m, 1 H, $CH_2CH{=}CH$), 6.38 (d, *J* = 15.8 Hz, 1 H, $CH_2CH{=}CH$), 7.75−7.13 (m, 10 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.9, 19.6 [$(CH_3)_2CH$)], 26.3 (CH_3CCO), 27.7 [$(CH_3)_3C$], 34.7 [$(CH_3)_2CH$)], 47.4 ($CH_2CH{=}C$), 61.6 (CHN), 66.6 (CH_3CCO), 83.2 [$(CH_3)_3C$], 123.1, 124.0, 126.2, 127.1, 128.3, 128.6, 130.3, 133.8, 137.4, 138.1 (ArC, CH=CH), 151.6, 163.6, 174.9 (2 × C=O, C=N). − MS (EI); *m*/*z* (%): 346 (1) [M^+ − 100], 229 (100), 213 (11), 187 (22), 117 (16), 91 (9), 77 (5), 43 (8). − HRMS calcd. for $C_{28}H_{34}N_2O_3$: 446.2569; found 446.2571.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-[(*Z*)-4-hydroxy-2-butenyl]-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (*Z*-6r): Pale yellow oil. − TLC: R_f = 0.35 (hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 3600−3200 (OH), 3020, 1650, 928, 1722 cm^{-1}. − ^1H NMR (300 MHz): δ (major diastereomer) = 0.83 [2 d, *J* = 7.0 Hz, 6 H, $(CH_3)_2CH$)], 1.57 [s, 9 H, $(CH_3)_3C$], 1.60 (s, 3 H, CH_3CCO), 1.95 [m, 1 H, $(CH_3)_2CH$], 2.73 (dd, *J* = 13.1, 7.3 Hz, 1 H, CH_2CN), 3.01 (dd, *J* = 13.1, 8.9 Hz, 1 H, CH_2CN), 3.98 (m, 2 H, CH_2OH), 4.64 (s, 1 H, OH), 5.33 (m, 1 H, $CH{=}CHCH_2OH$), 5.51 (d, *J* = 6.1 Hz, CHN), 5.73 (m, 1 H, $CH{=}CHCH_2OH$), 7.75−7.19 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ (major diastereomer) = 19.1, 20.1 [$(CH_3)_2CH$)], 27.0 (CH_3CCO), 28.0 [$(CH_3)_3C$], 35.1 [$(CH_3)_2CH$)], 41.6 ($CH_2C{=}C$), 57.8 (CH_2OH), 61.1 (CHN), 66.4 (CH_3CCO), 84.2 [$(CH_3)_3C$], 127.1, 128.8 (CH=CH), 126.7, 128.7, 130.8, 137.5 (ArC), 151.4, 165.1, 174.7 (2 × C=O, C=N). − MS (EI); *m*/*z* (%): 400 (1) [M^+], 262 (100), 228 (4), 183 (92), 108 (46), 91 (2), 77 (6), 44 (7). − HRMS calcd. for $C_{23}H_{32}N_2O_4$: 400.2362; found 400.2384.

(3*S*,6*R*)-*N*-1-(*tert*-Butoxycarbonyl)-3-[(*E*)-4-hydroxy-2-butenyl]-6-isopropyl-3-methyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone (*E*-6r): Pale yellow oil. − $[\alpha]_D^{25}$ = − 43.0 (*c* = 1.50, CH_2Cl_2) − TLC: R_f = 0.35 (*n*-hexane/ethyl acetate, 3:2). − IR (film): $\tilde{\nu}$ = 3600−3200, 3020, 1670, 928, 1731 cm^{-1}. − ^1H NMR (300 MHz): δ = 0.78, 0.84 [2 d, *J* = 6.7 Hz, 6 H, $(CH_3)_2CH$)], 1.57 [s, 9 H, $(CH_3)_3C$], 1.60 (s, 3 H, CH_3CCO), 1.95 [m, 1 H, $(CH_3)_2CH$], 2.60−2.77 (m, 2 H, $CH_2C{=}C$), 3.96−4.14 (m, 3 H, CH_2OH), 5.46 (d, *J* = 4.9 Hz, 1 H, CHN), 5.49−5.89 (m, 2 H, CH=CH), 7.19−7.75 (m, 5 H, ArH). − ^{13}C NMR (75 MHz): δ = 18.8, 19.7 [$(CH_3)_2CH$)], 26.1 (CH_3CCO), 28.0 [$(CH_3)_3C$], 34.7 [$(CH_3)_2CH$)], 46.4 ($CH_2C{=}C$), 61.7 (CHN), 63.4 (CH_2OH), 66.3 (CH_3CCO), 83.6 [$(CH_3)_3C$], 123.5, 126.5, 127.1, 128.7, 130.4, 137.8 (ArC, C=C), 151.7, 163.7, 174.8 (2 × C=O, C=N). − MS (EI); *m*/*z* (%): 400 (1) [M^+], 300 (3) [M^+ − 100], 230 (18), 229 (100), 228 (32), 213 (20), 187 (17), 185 (22), 91 (8), 77 (12), 44 (10), 41 (20). − HRMS calcd. for $C_{23}H_{32}N_2O_4$: 400.2362; found 400.2357.

General Procedure for the Synthesis of (*S*)-AMAAs 8 Using 6 M HCl: A mixture of hydrochloric acid (6 M, 5 mL) and 2-pyrazinone **6** (1 mmol) was placed in a sealed tube and heated at 150 °C for 3 d. The aqueous phase was extracted with ethyl acetate (10 mL), and the water layer was separated, concentrated in vacuo and the resulting residue dissolved in ethanol (5 mL). Propylene oxide (2 mL) was added, and the resulting solution was heated at reflux for 30 min. The mixture was cooled, and the precipitate was filtered and washed with ethyl acetate and acetone, giving AMAAs **8** in yields shown in Table 4.

(*S*)-α-Ethylalanine (8a): $[\alpha]_D^{25}$ = +10.1 (*c* = 1, H_2O), ref.[16a] $[\alpha]_D^{20}$ = −10.3 (*c* = 1, H_2O).

(*S*)-α-Methylphenylalanine (8d): − $[\alpha]_D^{25}$ = −22.1 (*c* = 1, H_2O), ref.[16a] $[\alpha]_D$ = −22.1 (*c* = 1, H_2O).

(*S*)-α-Methylaspartic acid (8e): $[\alpha]_D^{25} = +52.5$ ($c = 1$, H_2O), ref.[16a] $[\alpha]_D = -52.9$ ($c = 1$, H_2O).

(*S*)-α-Methyltryptophan (8g): $[\alpha]_D^{25} = -11.3$ ($c = 1.1$, H_2O), ref.[30] for (*R*) isomer $[\alpha]_D^{20} = +11.6$ ($c = 1.1$, H_2O).

(*S*)-α-Methylserine (8h): $[\alpha]_D^{25} = +5.1$ ($c = 1$, H_2O), ref.[16a] $[\alpha]_D = +6.3$ ($c = 1$, H_2O).

(*S*)-α-Methylglutamic acid (8k): $[\alpha]_D^{25} = +22.1$ ($c = 2.6$, 6 M HCl), ref.[16a] $[\alpha]_D = +22.0$ ($c = 2.7$, 6 M HCl).

Hydrolysis of Compound (6*R*)-6b: A suspension of cation-exchange resin Dowex 50X-100 (3.5 mL) and HCl (0.75 M, 3 mL, prepared in deionised water) was added to a solution of (6*R*)-**6b** (370 mg, 1 mmol) in acetic acid (0.8 mL) and toluene (1.2 mL). The resulting mixture was heated at reflux for 4 d, and then cooled at room temperature and transferred to a column. The resin was washed with water until neutral pH was obtained, 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 **8b** (80 mg, 62%).

(*S*) α-Allylalanine (8b)·HCl: $[\alpha]_D^{25} = -14.1$ ($c = 1.3$, D_2O), ref.[16a] $[\alpha]_D^{20} = -14.4$ ($c = 1.3$, D_2O).

Acknowledgments

This work was supported by the Dirección General de Enseñanza Superior e Investigación Científica (Projects PB94−1515 and PB97−0123). T. A. thanks E. Lilly S. A. for a grant and J. M. S. thanks the Spanish Ministerio de Educación y Cultura (MEC) for a contract under the program Acciones para la Incorporación a España de Doctores y Tecnólogos.

[1] For reviews see: [1a] C. Cativiela, M. D. Díaz-de Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. − [1b] Highlights of the chemistry of AMAAs: T. Wirth, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225−277. − [1c] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708−2748. − [1d] M. North, *Contemp. Org. Synth.* **1996**, 323−343. − [1e] R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1540−1650. − [1f] H. Heimgartner, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238−264. − [1g] R. M. Williams, *Synthesis of Optically Active Amino Acids*, Pergamon Press, Oxford, **1989**.

[2] For some examples see: [2a] D. C. Horwell, G. S. Ratcliffe, E. Roberts, *Bioorg. Med. Chem. Lett.* **1991**, *1*, 169−171. − [2b] W. H. J. Boesten, B. H. N. Dassen, J. C. S. Kleijans, B. van Agen, S. van der Wal, N. K. de Vries, H. E. Shoenmaker, E. M. Meijer, *J. Agric. Food Chem.* **1991**, *39*, 154−159. − [2c] A. Khosla, K. Stachowiak, R. R. Sunby, F. G. Bumpus, F. Pirion, K. Lintner, S. Fernandjian, *Proc. Nat. Acad. Sci. U.S.A.* **1981**, *78*, 757−760.

[3] For some examples see: [3a] M. Tanaka, N. Imakawa, M. Kurihara, H. Suemune, *Helv. Chim. Acta* **1999**, *82*, 494−510. − [3b] A. I. Jiménez, C. Cativiela, M. París, J. M. Peregrina, A. Avenoza, A. Aubry, M. Marrand, *Tetrahedron Lett.* **1998**, *39*, 7841−7844. − [3c] A. Polese, F. Formaggio, M. Crisma, G. Valle, C. Toniolo, G. M. Bonora, Q. B. Broxterman, J. Kamphuis, *Chem. Eur. J.* **1996**, *2*, 1104−1111. − [3d] D. Obrecht, M. Altolfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* **1996**, *61*, 4080−4086. − [3e] D. Obrecht, U. Bohdal, J. Daly, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* **1995**, *51*, 10883−10900. − [3f] D. Obrecht, C. Lehmann, R. Ruffieux, P. Schönholzer, K. Müller, *Helv. Chim. Acta* **1995**, *78*, 1567−1587. − [3g] C. Bisang, C. Weber, J. Inglis, C. A. Schiffer, W. F. van Gunsteren, I. Jelesarov, H. R. Bosshard, J. A. Robinson, *J. Am. Chem. Soc.* **1995**, *117*, 7904−7915.

[4] D. Becker, M. Kiess, H. Brückner, *Liebigs Ann.* **1997**, 767−772, and references cited therein.

[5] C. Yuan, R. M. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 11777−11784.

[6] H. Yano, S. Nakanishi, Y. Ikuina, K. Ando, M. Yoshida, Y. Saitoh, Y. Matsuda, C. Bando, *J. Antibiot.* **1997**, *50*, 992−997, 998−1008.

[7] B. G. M. Burgand, D. C. Horwell, A. Padova, M. C. Pritchard, *Tetrahedron* **1996**, *52*, 13035−13050, and references cited therein.

[8] Naturally occurring antibiotics such as lactacistin, conagenin, altemicidin, myomicin and sphingofungins are structurally complex AMAAs. − [8a] B. M. Trost, C. B. Lee, *J. Am. Chem. Soc.* **1998**, *120*, 6818−6819. − [8b] N. Chida, J. Takeoka, K. Ando, N. Tsutsumi, S. Ogawa, *Tetrahedron* **1997**, *53*, 16287−16298. − [8c] A. Kovács-Kulyassa, P. Herczegh, F. Sztaricskai, *Tetrahedron* **1997**, *53*, 13883−13896. − [8d] S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi, H. Irie, *J. Org. Chem.* **1997**, *62*, 2275−2279. − [8e] S. Kobayashi, M. Matsumara, T. Furuta, T. Hayashi, S. Iwamoto, *Synlett* **1997**, 301−303; S. Kobayashi, T. Furuta, *Tetrahedron* **1998**, *54*, 10275−10294.

[9] [9a] Y. Aoyagi, R. M. Williams, *Synlett* **1998**, 1099−1100. − [9b] J. C. Stinson, *Chem. Eng. News* **1992**, *70*(39), 46−79.

[10] [10a] D. Ma, H. Tian, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3493−3496. − [10b] E. Ndzié, P. Cardinael, A. R. Schoofs, G. Coquerel, *Tetrahedron: Asymmetry* **1997**, *8*, 2913−2920. − [10c] D. Ma, Z. Ma, J. Jian, Z. Yang, C. Zheng, *Tetrahedron: Asymmetry* **1997**, *8*, 889−893.

[11] C. Cativiela, M. D. Díaz-de Villegas, J. A. Gálvez, Y. Lapeña, *Tetrahedron* **1997**, *53*, 5891−5898.

[12] [12a] A. B. Smith III, A. B. Benowitz, M. C. Guzmán, P. A. Sprengeler, R. Hirschmann, *J. Am. Chem. Soc.* **1998**, *120*, 12704−12705. − [12b] P. Wipf, S. Venkatraman, *Synlett* **1997**, 1−10. − [12c] H. Cheng, P. Keitz, J. B. Jones, *J. Org. Chem.* **1994**, *59*, 7671−7676. − [12d] U. Koert, *Nachr. Chem. Tech. Lab.* **1995**, *43*, 347−354.

[13] T. Abellán, R. Chinchilla, N. Galindo, G. Guillena, C. Nájera, J. M. Sansano, *Eur. J. Org. Chem.*, in press.

[14] [14a] Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, V. S. Parmár, R. Kumar, H. B. Kagan, *Tetrahedron: Asymmetry* **1998**, *9*, 851−857. − [14b] Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, S. Vyskocyl, H. B. Kagan, *Tetrahedron: Asymmetry* **1999**, *10*, 1723−1728.

[15] [15a] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. − [15b] E. J. Corey, F. Xu, M. Noe, *Tetrahedron* **1998**, *39*, 5347−5350. − [15c] B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595−8598. − [15d] T. Ooi, M. Kameda, K. Maruoka. *J. Am. Chem. Soc.* **1999**, *121*, 6519−6520. − [15e] E. V. Dehmlow, S. Wagner, A. Müller. *Tetrahedron* **1999**, *55*, 6335−6346. − [15f] M. Horikawa, J. Busch-Petersen, E. J. Corey. *Tetrahedron Lett*. **1999**, *40*, 3843−3846. − [15g] B. Lygo, J. Crosby, Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671−8674. − [15h] M. J. O′Donnell, S. Wu, *Tetrahedron:Asymmetry* **1992**, *3*, 591−594.

[16] [16a] R. Chinchilla, N. Galindo, C. Nájera, *Synthesis* **1999**, 704−717. − [16b] R. Chinchilla, L. R. Falvello, N. Galindo, C. Nájera, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 995−997. − [16c] R. Chinchilla, N. Galindo, C. Nájera, *Tetrahedron: Asymmetry* **1999**, *9*, 2769−2772.

[17] For preliminary communication see: T. Abellán, C. Nájera, J. M. Sansano, *Tetrahedron: Asymmetry* **1998**, *9*, 2211−2214.

[18] To our knowledge, the only reported example of these kinds of heterocycles is the case of 1,2,3,6-tetrahydro-6,6-dimethyl-5-phenyl-2-pyrazinone, prepared by the reaction of 2,2-dimethyl-3-phenyl-2*H*-azirine with glycine ethyl ester: G. Alvernhe, A. Laurent, A. Masroua, *Tetrahedron Lett.* **1983**, *24*, 1153−1156.

[19] The chiral amino ketone was recently prepared from N-Cbz-(*S*)-valine *N*-methoxy-*N*-methyl amide, but no experimental yield and analytical data were reported: P. Edwards, D. J. Wolanin, D. W. Andisik, M. W. Davis, *J. Med. Chem.* **1995**, *38*, 76−85.

[20] The racemic compound was also reported: A. Guzmán, C. Quintero, J. M. Muchowski. *Can. J. Chem.* **1991**, *69*, 2059−2063, and references cited therein.

[21] Hyperchem from Hypercube was used for these calculations.

[22] T. Gan, R. Liu, P. Yu, S. Khao, J. M. Cook, *J. Org. Chem.* **1997**, *62*, 9298−9304.

[23] Y. N. Belokon', N. I. Chernoglazova, A. S. Batsanov, N. S. Garbalinskaya, V. I. Bakhmutov, Y. T. Struchkov, V. M. Belikov, *Izv. Akad. Nauk SSSR, Ser.Khim.* **1987**, *4*, 852−857; *Chem. Abstr.* **1988**, *108*, 801, 132255v.

[24] [24a] M. J. O'Donnell, F. Delgado, C. Hostettler, R. Schwesinger, *Tetrahedron Lett.* **1998**, *39*, 8775−8788. − [24b] M. J. O'Donnell, C. W. Lugar, R. S. Pottorf, C. Zhou, W. L. Scott, C. L. Cwi, *Tetrahedron Lett.* **1997**, *38*, 7163−7166. − [24c] R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435−2454, and references cited therein.

[25] The palladium(0)-catalyzed addition of benzophenone imine of α-aminoacetonitrile to vinyloxiranes has been previously described: A. Mazón, C. Nájera, J. Ezquerra, C. Pedregal, *Tetrahedron Lett.* **1997**, *38*, 2167−2170.

[26] M. Kawatsura, Y. Uazumi, T. Hayashi, *Chem. Commun.* **1998**, 217−218.

[27] P. A. Evans, J. D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581−5582.

[28] A. Mazón, C. Nájera. *Tetrahedron: Asymmetry* **1997**, *8*, 1855−1859.

[29] A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc.* **1997**, *119*, 656−673.

[30] L. Zhang, J. M. Finn, *J. Org. Chem.* **1995**, *60*, 5719−5720.

Received January 23, 2000
[O00041]