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A General Synthesis of Enantiopure 1,2-Aminoalcohols via Chiral Morpholinones

Fabienne Segat-Dioury, Olivier Lingibé, Bernadette Graffe, Marie-Claude Sacquet and Gérard Lhommet*

Université Pierre et Marie Curie (Paris VI), Laboratoire de Chimie des Hétérocycles (associé au C.N.R.S.), 4 Place Jussieu, F-75252 Paris Cedex 05, France

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Abstract—Eleven optically active 1,2-aminoalcohols **20a**–**i** and **26b**–**c** were prepared from D-phenylglycine via cyclic imines **7b**–**i** (or enamine **7a**). The key step of the strategy is the diastereoselective reduction of chiral oxazinones **7a**–**i**.

Introduction

Optically active 1,2-aminoalcohols play an important role in asymmetric synthesis.[1] They are frequently used as chiral synthons,[2] and as precursors of chiral auxiliaries.[3] In addition, enantiomerically pure 1,2-aminoalcohols have proven to be efficient chiral ligands in many asymmetric reactions involving achiral reagents such as Lewis acids,[4] organometallic reagents[5] or metallic hydrides.[6]

The most direct synthesis of optically active 1,2-aminoalcohols is the reduction of natural α-aminoacids or derivatives,[7] but this method is limited by the nature of lateral chains and optical antipode. Other racemic methods coupled with enzymatic[8a] or chemical[8b] resolution have thus been developed, providing a greater variety of 1,2-aminoalcohols.

Few stereoselective preparations have been reported. The synthesis of optically active 2-amino-1-phenylethanols was carried out by Salvadori et al.[9a] from mandelic acid and phenylethylamine. Akiba et al.[9b] described a more general stereoselective synthesis of 1,2-aminoalcohols by the diastereoselective addition of organometallic reagents to an α-silyloximine derived from (*S*)-ethyl lactate. Another approach was chosen by Umezawa et al.[10a] and by Senanayake et al.[10b] to prepare optically active 1,2-aminoalcohols via an oxazoline using asymmetric induction. These two groups obtained optically active oxazoline by enantioselective alkene epoxidation followed by opening of the epoxide with an appropriate amine. The first group used a microbial epoxidation while the latter used an enantioselective chemical one.

Apart from these, Lee et al.[11] described another synthesis of 1,2-aminoalcohols by addition of organometallic reagents on enantiopure aziridine-2-carboxaldehydes. These enantiopure aldehydes were obtained after separation of a diastereoisomeric mixture of corresponding esters.

So we wish to report here a convenient procedure for the synthesis of both enantiomers of 1,2-aminoalcohols from D- or L-phenylglycine via morpholinones in which the heteroatoms were the precursors of amine and alcohol functions. The retrosynthetic analysis outlined in Scheme 1 suggests two routes to morpholin-2-ones. The difference between these two routes is the step of introduction of the different R groups.

In *route A*, the introduction of R group takes place in an alkylation step of a common β-enaminoester (divergent strategy).

In *route B*, the different R substituents must be present at the early step of the synthesis and each chiral morpholinone results from the condensation of phenylglycine with different halomethylketones (linear strategy).

In each case, the use of either D- or L-phenylglycine as starting material provides access to the corresponding (*R*)- or (*S*)-enantiomer of the 1,2-aminoalcohols synthesised.

It is noteworthy that these two routes develop an 'inverse' approach to the one described by Dellaria et al.[12a] or by Harwood et al.[12b] These authors used an aminoalcohol (phenylglycinol) as chiral inductor to synthesise optically

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* Corresponding author. Tel.: +33-01-44-27-3057; fax: +33-01-44-27-30-56; e-mail: lhommet@ccr.jussieu.fr

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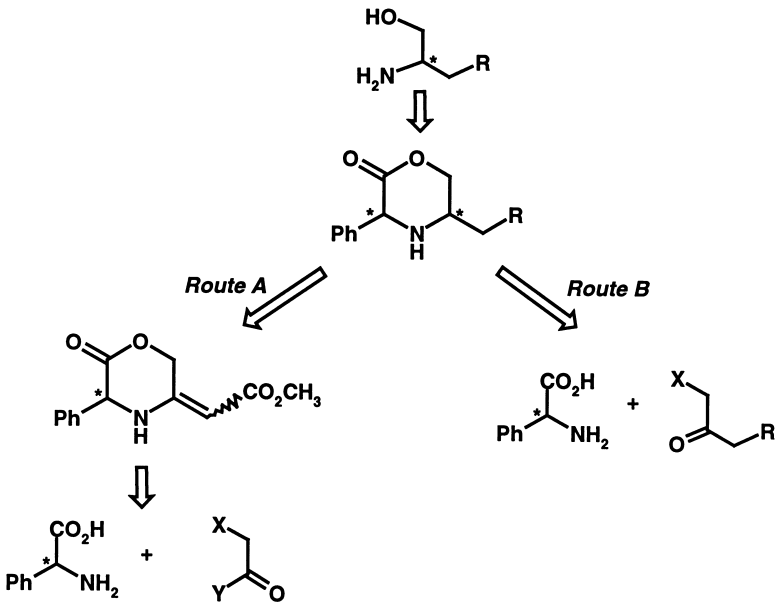


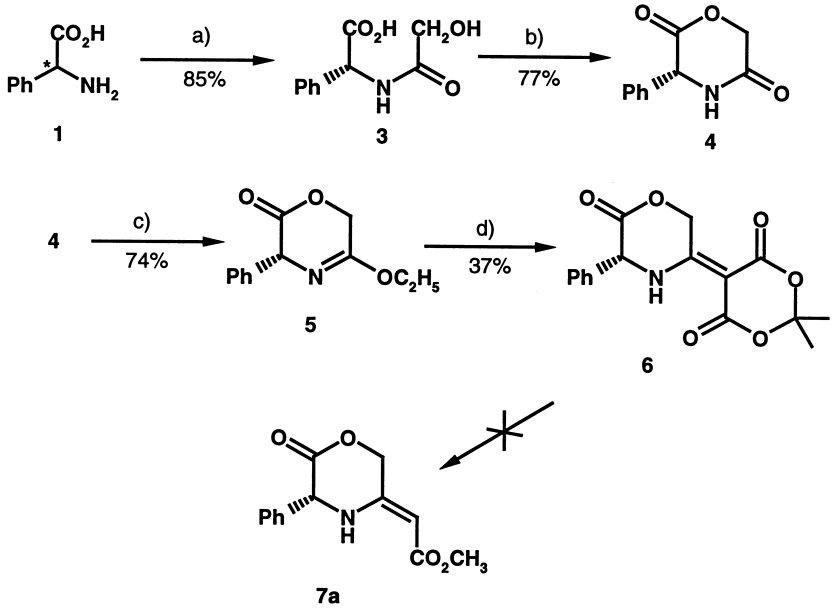
Scheme 1.

pure aminoacids via chiral oxazinone while our strategy uses an aminoacid (phenylglycine) as chiral inductor to synthesise optically pure aminoalcohols.

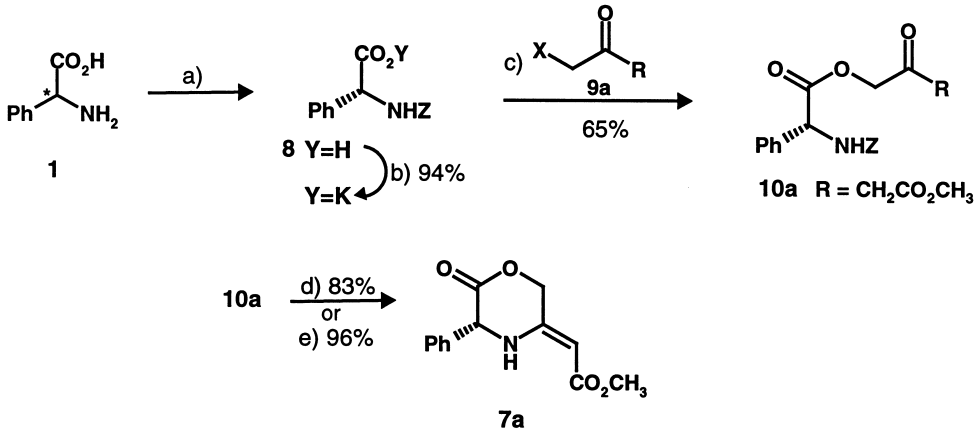
Results and Discussion

We first chose to explore the divergent strategy (*Route A*). The initial steps of the synthesis leading to the intermediate β-enamino ester **7a** are outlined in Scheme 2. Treatment of the sodium salt of (*R*)-phenylglycine **1** with the (chlorocarbonyl)methyl acetate **2** according to Schotten–Baumann's conditions[13] gave, after saponification, the hydroxyacid **3** in 85% yield. This compound, after lactonisation and activation of the lactam function, was converted to the expected β-enaminodiester **6**. The monodecarboxylating transesterification step[14] achieved by heating an ethanol solution of **6** at 230°C in an autoclave failed to give the desired enaminoester **7a** and the starting material was not recovered.

To prepare the desired compound **7a**, we thus investigated another approach in which the enamino ester **7a** would result from the cyclisation of the ω-amino-β-ketoester **10a** (Scheme 3). The potassium salt of the *N*-protected (*R*)-phenylglycine **8** was first condensed with methyl-4-chloroacetoacetate **9a** following the method developed by Caplar



Scheme 2. a) (i) NaOH aq. 0.5 mol L^{-1} (1 equiv.); (ii) $CH_3CO_2CH_2COCl$ **2** in dioxane (1 equiv.), NaOH aq. 2 mol L^{-1} (1.1 equiv.), rt, 5 h; (iii) NaOH aq. 2 mol L^{-1} (1.1 equiv.), rt; (iv) HCl aq. 6 mol L^{-1} (2.1 equiv.). b) CH_3SO_3H (0.3 equiv.), CH_3CN/PhH (6/1), molecular sieves 3 Å, reflux 48 h. c) (i) Et_3OBF_4 (2 equiv.), CH_2Cl_2, reflux 36 h; (ii) phosphate buffer, pH 7. d) Meldrum's acid (1.1 equiv.), $Ni(Acac)_2$ (3×10^{-3} equiv.), $CHCl_3$, reflux 48 h. e) CH_3OH, autoclave, 230°C, 30 min.



Scheme 3. a) (i) NaOH aq. (1 equiv.); (ii) $PhCH_2OCOCl$ (1.1 equiv.) in dioxane, NaOH aq. (1.1 equiv.); (iii) HCl aq. (1.1 equiv.). b) KOH in CH_3OH (1 equiv.), rt, 30 min. c) **9a** (X=Cl, R=$CH_2CO_2CH_3$) (1.1 equiv.), KI (0.1 equiv.), CH_3CN or DMF, rt, 15 h. d) H_2, 1 atm, 10% Pd/C, $CH_3CO_2CH_3$, rt, 6 h. e) (i) HBr (9 equiv.) in CH_3CO_2H, rt, 30 min; (ii) solid K_2CO_3.

et al.[15] (DMF, rt) and led to the expected ω-amino-β-ketoester **10a** in moderate yield (38%). However, we found that by very slow dropwise addition of the highly reactive chloroketoester **9a** to a solution of **8** containing potassium iodide (cat.) the product yield was increased to 65%. It must be emphasised that self condensation of compound **9a** (bearing both a nucleophilic site and an electrophilic site) competes with the desired condensation thus limiting the yield of the reaction.[16]

The cyclisation of the *N*-protected aminoketodiester **10a** proved to proceed spontaneously after removal of its *N*-protecting group. Indeed, under neutral catalytic hydrogenolysis conditions, the *N*-benzyloxycarbonyl group of compound **10a** was cleaved, releasing an aminoketone intermediate that cyclised to the expected enamino ester **7a** in 83% yield.[17]

Furthermore, the yield of the cyclisation was improved to 96% by treatment of the aminoketodiester **10a** with a solution of hydrobromic acid in acetic acid.[15] The stable hydrobromide intermediate was then neutralised by addition of solid potassium carbonate thus giving rise to the free aminoketone that cyclised spontaneously to enaminoester. This enaminoester was sufficiently pure to be used in the next step without purification.

The two methods of cyclisation led to the β-enamino ester **7a** with an identical optical activity. However, an attempt to purify this compound by chromatography on silica gel led to a total loss of its optical activity. It was suspected that the observed racemisation might result from the acid-catalysed equilibrium between the enamino ester (−)-**7a** and the two imino forms **12** and **13** (Scheme 4). An equilibration between two regioisomeric imines has previously been observed by Harwood and co-workers on neighbouring structures.[12b,18]

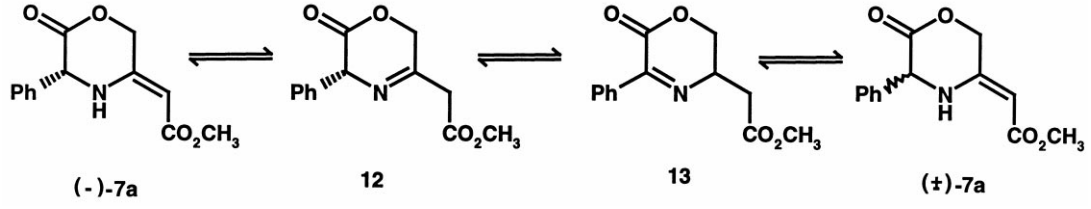
To confirm this hypothesis, we thus prepared the corresponding *N*-benzylated enamino ester **14**[19] for which such an equilibrium would not occur. This compound was obtained in good yield from *N*-benzylphenylglycine following a similar route as previously described for the preparation of enamino ester **7a**. In this way we verified that purification of *N*-benzylated enamino ester **14** by chromatography on silica gel, that acid treatment, and that prolonged stirring on silica, did not cause racemisation of compound **14**.

These experiments demonstrated that the equilibrium enamine/imine (Scheme 4) was probably responsible for the racemisation of the enamino ester **7a**.

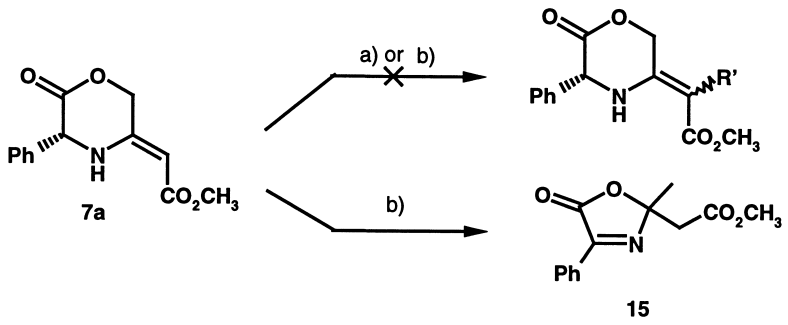
Attempts to alkylate the β-enamino ester **7a** did not afford the expected compounds under the conditions investigated (Scheme 5); either the starting material **7a** was recovered intact or it was transformed to the dihydro oxazole **15**.[20] The *C*-alkylation of the previously prepared *N*-protected enamino ester **14** also failed.

So we investigated the alkylation of the ω-amino-β-ketoester **10a**, the linear precursor of the enamino ester **7a**. Attempts to alkylate **10a** provided a mixture of the desired monoalkylated product, dialkylated and *O*-alkylated byproducts, together with the unreacted starting material.

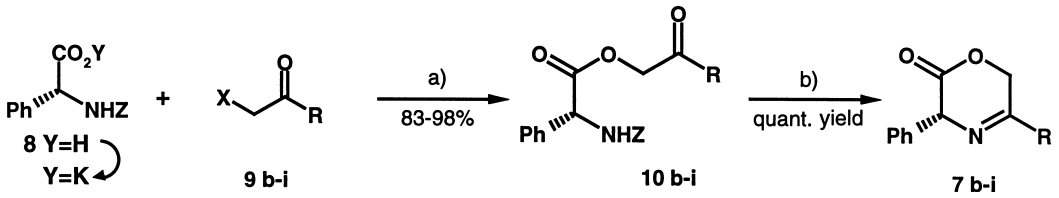
The best result was obtained when **10a** was treated with



Scheme 4.



Scheme 5. a) CH_3I, reflux, 24 h. b) (i) NaH (1.1 equiv.), $PhCH_3$, reflux, 30 min; (ii) *n*-PrI (1.3 equiv.), $PhCH_3$, reflux, 3–12 h.



Scheme 6. b: R=$(CH_2)_2CO_2CH_3$; **c**: R=$(CH_2)_3CO_2CH_3$; **d**: R=CH_3; **e**: R=C_2H_5; **f**: R=*i*-C_3H_7; **g**: R=*n*-C_4H_9; **h**: R=*i*-C_4H_9; **i**: R=*t*-C_4H_9. For a) and b) see Ref. 15.

iodomethane in the presence of potassium carbonate in acetone at room temperature,[21] the 2-methyl-3-oxo-4-[(*R*)-(phenyl)(phenylmethoxycarbonylamino)acetoxy]butyric acid methyl ester **16** was isolated in 18% yield after chromatography as an equimolar mixture of diastereoisomers.

With regard to the problems encountered for the alkylation of the enamino ester **7a** and the ω-amino-β-ketoester **10a**, we thus investigated the second envisaged approach to enantiopure 1,2-aminoalcohols (Scheme 1, *Route B*). This route (linear strategy) implies the preparation of a wide range of α-halomethylketones **9**, precursors to a variety of chiral morpholinones **7b**–**i**. The halomethylketones **9b**–**i**, prepared according to literature procedures,[22,23] were condensed with the potassium salt of (*R*)-*N*-(benzyloxycarbonyl)phenylglycine **8** in dimethylformamide as described by Caplar et al.[15] This procedure provided the desired aminoketoesters **10b**–**i** in high yield (83–98%).

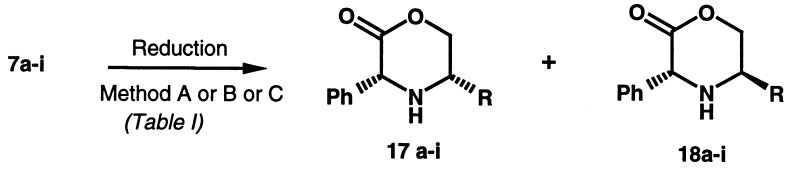
The cyclisation of aminoketoesters **10b**–**i** took place under conditions similar to those described for **10a** (hydrobromic acid in acetic acid), and led to chiral oxazinones **7b**–**i** in quantitative yields (Scheme 6). The cyclisation of **10b**–**i** thus provided imines **7b**–**i** with an endocyclic carbon–nitrogen double bond while the cyclisation of **10a** led to the conjugate enamino ester **7a**.

To prevent the racemisation observed when the enamino ester **7a** was chromatographed on silica gel, the imines **7b**–**i** were not purified, and the crude products were sufficiently pure to be used in the next step (purity=95% by NMR and GC analysis).

We have studied various diastereocontrolled reduction reactions leading to the morpholinones **17a**–**i** and/or **18a**–**i** (Scheme 7). The results are summarised in Table 1. We first examined various catalytic hydrogenation conditions. The best yields and the best diastereoselectivities were obtained when the reactions were carried out using PtO_2 as catalyst, in methanol, under atmospheric pressure of hydrogen and at room temperature (Table 1, method A).[24]

Indeed, under these conditions, the yields ranged from 73 to 89%, except for enamino ester **7a** and for iminoester **7c**. The reduction of enamino ester **7a** (entry 1, method A) afforded only a small amount (18%) of the expected morpholinone **17a**. This reduction was limited by the undesirable opening of the morpholinone ring.[25]

The reduction of the imino ester **7c** (entry 3, method A) took place but the intermediate morpholinones **17c** and **18c** spontaneously cyclised to the corresponding lactams while, under the same conditions, imino ester **7b** provided the expected morpholinones **17b** and **18b** without further cyclisation (entry 2, method A).



Scheme 7.

Table 1. Reductions of compounds **7a–i**.

Entry	Compound **7**	R	Method A[a]		Method B[b]		Method C[c]	
			Yield%[d] **17**	d.e.%[e]	Yield%[d] **17**	d.e.%[e]	Yield%[d] **17**	d.e.%[e]
1	**7a**	$CH_2CO_2CH_3$	18[f]	–	26	40	Trace	–
2	**7b**	$(CH_2)_2CO_2CH_3$	73	70	63	60	80	90
3	**7c**	$(CH_2)_3CO_2CH_3$	–[g]	–	60	60	76	92
4	**7d**	CH_3	73	82	74	64	89	>98
5	**7e**	C_2H_5	82	72	78	82	90	92
6	**7f**	iC_3H_7	84	80	73	70	93	96
7	**7g**	nC_4H_9	78	66	75	60	87	92
8	**7h**	iC_4H_9	76	70	80	80	92	92
9	**7i**	tC_4H_9	89	86	83	86	71	84

[a] Method A=H_2, 1 atm, PtO_2, CH_3OH, 4–6 h.
[b] Method B=$NaBH(OAc)_3$ (1.6 equiv.), TMSCl (1.2 equiv.), 4 h.
[c] Method C=BH_3–THF (1.4 equiv.), CH_3CN, 4 h.
[d] Yield referred to chromatographed product.
[e] Determined by ^{1}H-NMR analysis of the crude products.
[f] Methanolysis and hydrogenolysis by-products were also obtained, see Ref. 25.
[g] The morpholinones **17i** and **18i** were obtained in mixture with corresponding bicyclic lactams.

The diastereoselectivity of the catalytic hydrogenation varies from 66 to 86%, and the *cis* stereochemistry of the major diastereoisomer **17** was established unambiguously by a positive NOE experiment between hydrogens H-3 and H-5. No NOE effect was observed for the minor diasteroisomer **18**.

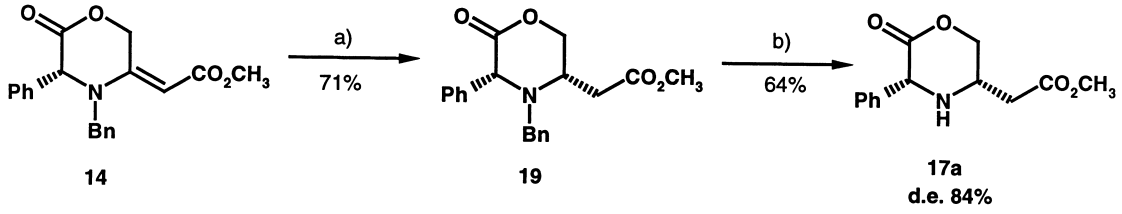
In order to improve the diastereoselectivity of the reaction, we next envisaged chemical reduction of compounds **7** (methods B and C). With potassium borohydride, in acetonitrile, reduction of imines **7b–i** or enamine **7a** did not occur, and the starting material was either decomposed (**7a**) or recovered unchanged (**7b–i**). The addition of trimethylsilylchloride according to Giannis[26] promoted the reductions, but the diastereoselectivity was modest. We found that with the more bulky metal borohydride, sodium triacetoxyborohydride, the diastereoisomeric excesses and the yields could be improved (method B). Thus the *cis* morpholinones **17b–i** were obtained with yields and diastereoisomeric excesses comparable to those obtained by catalytic hydrogenation (method A) except for the *cis* morpholinone **17a** which was formed in better yield (26%) but with only a moderate diastereoisomeric excess (40%) (entry 1, method B).

Finally, we found that the best results (except for the enamino ester **7a** which was recovered unreacted) were obtained when the reduction was performed using the borane–tetrahydrofuran complex in acetonitrile (method C). Under these conditions the imines **7b–i** were reduced into morpholinones **17b–i** with good diastereoselectivity (84–98%) and good chemical yields (71–93%). Nevertheless the *cis* morpholinone **17a** could be obtained in modest yield (23.5% after chromatography) by catalytic hydrogenation using 10% Pt/C as the catalyst.[25] We also found that the *cis* morpholinone **17a** could be prepared in higher yield from the previously prepared *N*-benzylmorpholinone **14** as depicted in Scheme 8.

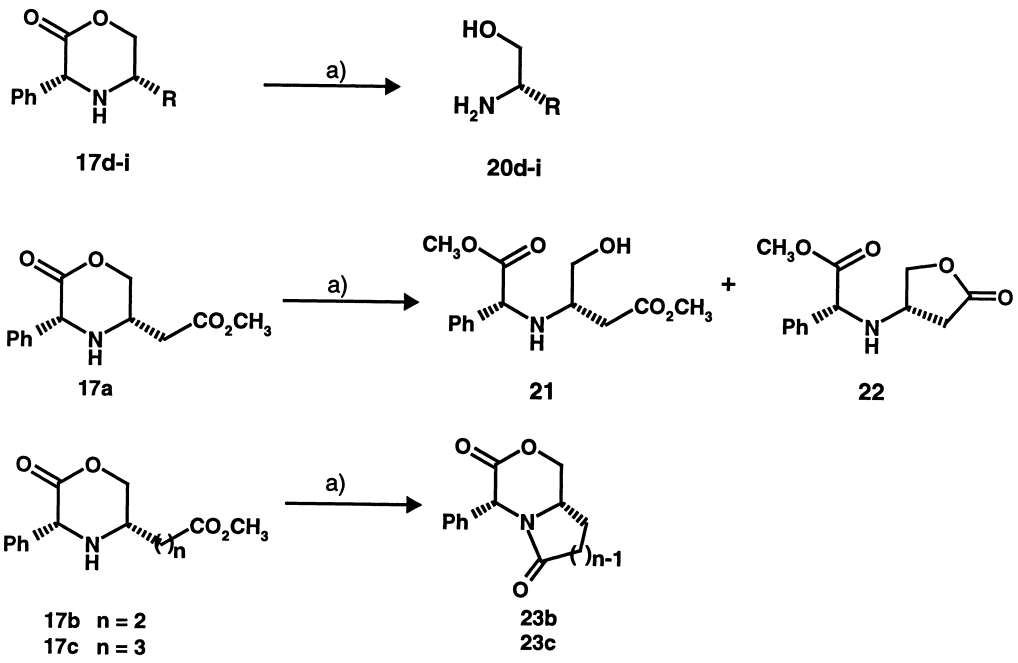
Indeed, the reduction of *N*-protected enamino ester **14** with sodium triacetoxyborohydride occurred with a good diastereoselectivity (d.e. 94%) and enabled us to isolate the *cis* product **19** in 71% yield. A subsequent deprotection by regioselective catalytic hydrogenolysis of the intermediate **19** led to the expected *cis* morpholinone **17a** in good diastereoisomeric excess (84%) and in 64% yield.

In order to obtain the desired aminoalcohols **20** it was necessary to cleave the morpholine ring of **17**. For this, two routes were envisaged: the intramolecular hydrogenolysis of the *N*-benzyl bond followed by the hydrolysis of the ester, or the initial lactone opening followed by the hydrogenolysis of the *N*-benzyl bond.

Examining the first route, compounds **17d–i** were treated under classical hydrogenolysis conditions. Under atmospheric pressure of hydrogen, over Pd/C or $Pd(OH)_2$ as catalyst, at room temperature or at reflux, under neutral or acidic conditions, no hydrogenolysis occurred even after prolonged reaction time (6 days). This result was predictable from the experiments using PtO_2 to prepare these morpholinones **17d–i** (see Table 1, method A). When the reaction was carried out in methanol for a long time, only



Scheme 8. a) (i) $NaBH_4$ (6 equiv.), CH_3CO_2H (60 equiv.), CH_3CN, 10°C; (ii) chromatography on SiO_2. b) H_2, 1 atm, 10% Pd/C, (1 equiv. in weight), $CH_3CO_2CH_3$, rt, 1 day.



Scheme 9. a) H_2, 150 atm, 10% Pd/C, CH_3OH.

lactone methanolysis took place. Attempted hydrogenolysis with ammonium formate over Pd/C also failed.

Finally, when the morpholinones **17d**–**i** were submitted to high hydrogen pressure (150 atm) in methanol, over Pd/C, the chiral inductor moiety was cleaved by simultaneous *N*-benzyl bond hydrogenolysis and lactone methanolysis (Scheme 9). The (*S*)-aminoalcohols **20d**–**i** were directly obtained with good yields (78–89%).

When we applied the same conditions to the functionalised morpholinones **17a**–**c**, these compounds proved to be resistant to hydrogenolysis: the morpholinone **17a** was only methanolysed and gave a mixture of aminoalcohol diester **21** and butyrolactone **22**, whereas the morpholinones **17b** and **17c** were converted to the corresponding bicyclic lactams **23b** and **23c**.[27]

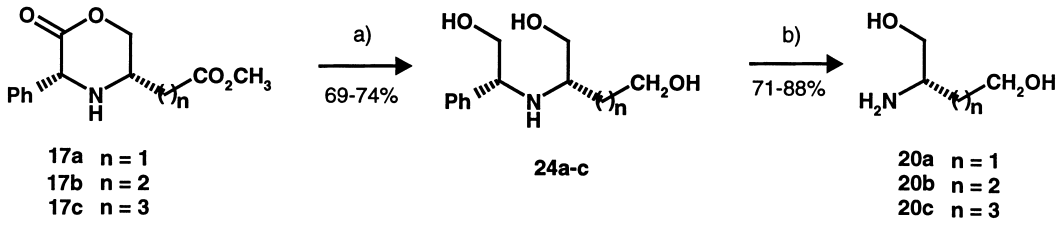
Since the first protocol failed to transform the morpholinones **17a**–**c** to the expected amino alcohol esters we decided to examine the second route leading to aminodiols **20a**–**c**.

Cleavage of the lactone ring, in morpholinones **17a**–**c**, was achieved by treatment with lithium aluminium hydride in tetrahydrofuran at room temperature (Scheme 10). The aminotriols **24a**–**c** thus obtained in 69–74% yield were submitted to catalytic hydrogenolysis conditions. At room temperature, even under high hydrogen pressure, the cleavage of the *N*-benzyl bond failed. However, hydrogenolysis of the *N*-benzyl bond succeeded under atmospheric pressure of hydrogen, in methanol at 50°C. Under these conditions the aminotriols **24a**–**c** gave enantiopure (*S*)-aminodiols **20a**–**c** in 71–88% yield. Furthermore, this second route also provided access to the cyclic aminoalcohols prolinol **26b** and pipecolinol **26c** from bicyclic lactams **23b** and **23c** following the sequence of reactions outlined in Scheme 11.

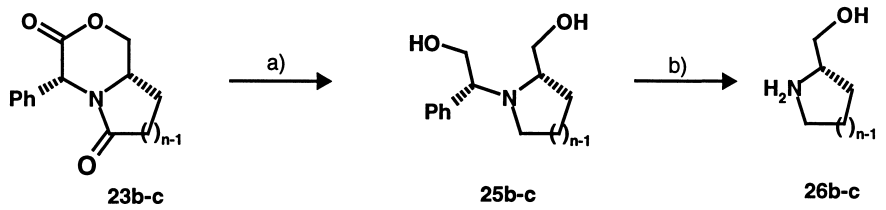
The simultaneous reduction of lactone and lactam functions were realised with the borohydride–tetrahydrofuran complex and provided the cyclic aminodiols **25b**–**c** (yield 88–90%) which were *N*-deprotected by hydrogenolysis at room temperature in methanol to give (*S*)-prolinol **26b** and (*S*)-pipecolinol **26c**.

Conclusion

The strategy described here, involving the use of phenylglycine as the chiral inductor, gave access to both the (*R*) and (*S*) optical antipodes of the targeted 1,2-aminoalcohols.



Scheme 10. a) $LiAlH_4$, THF, rt, 5 h. b) H_2, 1 atm, 10% Pd/C, CH_3OH, 50°C, 4 h.



Scheme 11. a) BH_3–THF, rt, 3 h (88% of **25b** and 90% of **25c**). b) H_2, 1 atm, 10% Pd/C, rt, 2 h (90%).

Moreover, the chiral induction step proceeds with high diastereoselectivity, thus providing an efficient route to 1,2-aminoalcohols which are tools of great interest for asymmetric synthesis. Application of this methodology enabled us to prepare a variety of enantiomerically pure 1,2-aminoalcohols (linear and cyclic) and aminodiols.

Experimental

The melting points were measured with a Büchi 535 apparatus. Infrared spectra were recorded on a Philips PU 9706 instrument. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker ARX 250 instrument, chemical shifts are expressed in ppm (δ) from TMS for ^{1}H spectra and from $CDCl_3$ (77.7 ppm) for ^{13}C spectra. Optical rotations were measured with a Perkin–Elmer 241 polarimeter (589 nm).

(−)-(*R*)-[((2-Hydroxy)acetyl)amino][phenyl] acetic acid (3). To a cooled and vigorously stirred solution of 50.0 mmol of (*R*)-phenylglycine (7.55 g) in 100 mL of aqueous sodium hydroxide 0.5 mol L^{-1} (50.0 mmol; 1.0 equiv.), 6.82 g of (chlorocarbonyl)methyl acetate **2** (500 mmol; 1.0 equiv.) in 25 mL of dioxane and 27.5 mL of 2 mol L^{-1} aqueous sodium hydroxide (55.0 mmol; 1.1 equiv.) were simultaneously added dropwise. After completion of the additions, the resulting mixture was vigorously stirred at room temperature for 2 h. The resulting mixture was acidified with 17.5 mL of 6 mol L^{-1} aqueous solution of HCl (105 mmol; 2.1 equiv.) and then extracted with ethylacetate (4×50 mL). The organic extracts were combined, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The solid residue was recrystallised in water to give 8.88 g of **3** (42.5 mmol). Mp 180–182°C. Yield 85%. $[\alpha]_D^{20}$ −220.0 (*c* 0.25; C_2H_5OH). IR ($CHBr_3$) ν cm^{-1} 3340 (NH); 3200–2500 (OH); 1720 (C=O_{acid}); 1610 (C=O_{amide} and C=C_{ar}). ^{1}H NMR (DMSO-d_6) δ 3.90 (s, 2H, CH_2); 5.40 (d, 1H, *J*=7.5, CH); 5.50–5.75 (br s, 2H, OH); 7.40 (s, 5H, H_{ar}); 8.10 (d, 1H, *J*=7.5, NH). ^{13}C NMR (DMSO-d_6) δ 55.5 (CH); 61.2 (CH_2); 127.4 and 137.5 (C_{ar}); 171.3 and 171.7 (2×CO). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found C, 57.94; H, 5.42; N, 6.80.

(−)-(3*R*)-Phenylmorpholine-2,5-dione (4). To a solution of 7.80 g of (*R*)-[((2-hydroxy)acetyl)amino][phenyl] acetic acid **3** (37.3 mmol) in 375 mL of anhydrous acetonitrile and 65 mL of anhydrous benzene, 1.10 g of methanesulfonic acid (11.4 mmol; 0.3 equiv.) were added. The mixture was stirred and refluxed in a Soxhlet apparatus (cartridge filled with 3 Å molecular sieves)[28] until completion of the reaction (monitored by TLC, about 2 days). The solvent was then removed under reduced pressure. The resulting solid was dissolved in 300 mL of dichloromethane. The solution was washed with a phosphate buffer (pH 7; NaH_2PO_4/Na_2HPO_4 1/2.7) (2×50 mL). The organic layer was dried over anhydrous sodium sulphate then concentrated under reduced pressure to give a solid that was recrystallised in cyclohexane/ethylacetate (1/1) to obtain 5.49 g of (3*R*)-(−)-phenylmorpholine-2,5-dione 4 (28.7 mmol) as a white solid. Mp 167–169°C. Yield 77%. $[\alpha]_D^{20}$ −83.0 (*c* 1.00; CH_3OH). IR (Nujol) ν cm^{-1} 3320 (NH); 1720 (C=$O_{lactone}$); 1675 (C=$O_{lactame}$). ^{1}H NMR (DMSO-d_6) δ 4.89 (s, 2H, H-6); 5.47 (s, 1H, H-3); 7.40–7.55 (m, 5H, H_{ar}); 9.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 56.9 (C-3); 67.7 (C-6); 127.4, 128.7, 128.9 and 136.3 (C_{ar}); 165.4 and 166.7 (2×CO). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found C, 62.84; H, 4.76; N, 7.35.

(−)-(3*R*)-5-Ethoxy-3-phenyl-3,6-dihydro-1,4-oxazin-2-one (5). A freshly prepared solution of trimethyloxonium fluoroborate[29] in dichloromethane (51.0 mmol; 1.9 equiv.) was added dropwise to a suspension of 5 g (26.2 mmol) of dione **4** in 90 mL of anhydrous dichloromethane. The mixture was stirred and refluxed until complete consumption of starting dione (monitored by TLC, about 1.5 days). The resulting iminium salt was rapidly filtered on Büchner under a nitrogen flow and dissolved in 100 mL of dichloromethane. The organic solution was washed with a phosphate buffer (pH 7; NaH_2PO_4/Na_2HPO_4 1/2.7) (2×50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a solid that was purified by chromatography on silica gel (chloroform) to obtain 4.25 g of **5** as a white solid (19.4 mmol). Mp 80–81°C. Yield 74%. $[\alpha]_D^{20}$ −89.0 (*c* 7.55; $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 1745 (C=O); 1675 (C=N). ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 3H, *J*=7.1, CH_3); 4.33 (q, 2H, *J*=7.1, C$H_2$$CH_3$); 4.82 (s, 2H, CH_2); 5.44 (s, 1H, CH); 7.32–7 40 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) 14.6 (CH_3); 61.1 (CH); 63.3 and 65.7 (2×CH_2); 127.4, 128.6, 129.2 and 136.6 (C_{ar}); 161.1 and 168.6 (CO and CN). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found C, 65.78; H, 6.01; N, 6.32.

(−)-2,2-Dimethyl-5-[(6-oxo-5-(*R*)-phenyl)morpholin-3-yliden]-1,3-dioxan-4,6-dione (6). To a stirred solution of 2.45 g of lactim ether **5** (11.2 mmol) in 15 mL of chloroform, 1.80 g of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid; 12.5 mmol; 1.1 equiv.) and 9 mg of nickel acetylacetonate (0.035 mmol; 0.003 equiv.) were added. The reaction mixture was stirred and refluxed until complete consumption of starting lactim ether (monitored by TLC, about 2 days). The resulting reddish mixture was concentrated under reduced pressure to give a red solid that was triturated with ether and filtered on Büchner to give a pink

flaky solid. This solid was recrystallised in *n*-hexane/tetrahydrofuran (1/4) to obtain 1.29 g (4.08 mmol) of **6**. Mp 192–193°C. Yield 37%. $[\alpha]_D^{20}$ −1.5 (*c* 3.00; $CHCl_3$). IR (Nujol) ν cm^{-1} 3100 (NH); 1735, 1700 and 1650 (C=O); 1590 (C=C). ^1H NMR ($CDCl_3$) δ 1.75 (s, 6H, 2×CH_3); 5.46 (s, 1H, CH); 5.57 (d, 1H, *J*=18.2, CH_2); 5.97 (d, 1H, *J*=18.2, CH_2); 7.33–7.47 (m, 5H, H_{ar}); 11.58 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 27.2 and 27.7 (2×CH_3); 58.0 (CH); 67.3 (CH_2); 105.0 (O–C–O); 130.4, 130.5 and 132.6 (C_{ar}); 162.7, 165.4, 166.6 and 167.2 (CO and C=C). Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.56; H, 4.77; N, 4.41. Found C, 60.65; H, 4.77; N, 4.25.

Haloketones (9)

1-Halo-2-alkanones (9a–i). 1-Chloromethylketones **9a** and **9d** were purchased from Aldrich and distilled before use; **9b**, **9c**, **9e**, **9g**, and **9h** were prepared according to the literature procedures[22] from methyl 2-chloro-3-oxoalkanoates. 1-Bromomethylketones **9f** and **9i** were prepared according to the literature procedure.[23]

5-Chloro-4-oxopentanoic acid methyl ester (9b). Bp 81°C (0.01 mmHg). Lit. 100°C (0.2 mmHg).[30] Yield 76%. IR (neat) ν cm^{-1} 1735, 1720. ^1H NMR ($CDCl_3$) δ 2.65 (t, 2H, H-2); 2.90 (t, 2H, H-2); 3.65 (s, 3H, OCH_3); 4.10 (s, 2H, H-5). ^{13}C NMR ($CDCl_3$) δ 27.7 (C-2); 34.3 (C-3); 48.1 (C-5); 51.8 (OCH_3); 172.7 (C-1); 201.1 (C-4).

6-Chloro-5-oxohexanoic acid methyl ester (9c). Bp 81°C (0.01 mmHg). Yield 80%. IR (neat) ν cm^{-1} 1740, 1725. ^1H NMR ($CDCl_3$) δ 1.95 (m, 2H, H-3); 2.4 (t, 2H, H-2); 2.70 (t, 2H, H-4); 3.70 (s, 3H, OCH_3); 4.10 (s, 2H, H-6). ^{13}C NMR ($CDCl_3$) δ 18.7 (C-3); 32.7, 38.5 (C-2, C-4); 48.1 (C-6); 51.6 (OCH_3); 172.4 (C-1); 202.8 (C-5). Anal. Calcd for $C_7H_{11}ClO_3$: C, 47.06; H, 6.16. Found: C, 47.11; H, 6.12.

1-Chlorobutan-2-one (9e). Bp 78°C (80 mmHg). Yield 86%. IR (neat) ν cm^{-1} 1730. ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, H-4); 2.60 (q, 2H, H-3); 4.10 (s, 2H, H-1). ^{13}C NMR ($CDCl_3$) δ 7.5 (C-4); 33.0 (C-3); 47.9 (C-1); 203.0 (C-2).

1-Bromo-3-methylbutan-2-one (9f). Bp 60–62°C (13 mmHg). Lit. 83–86°C (54 mmHg).[23] Yield 85%. IR (neat) ν cm^{-1} 1720. ^1H NMR ($CDCl_3$) δ 1.16 (d, 6H, 2×CH_3); 3.00 (m, 1H, H-3); 4.00 (s, 2H, H-1). ^{13}C NMR ($CDCl_3$) δ 16.5 (2×CH_3); 33.1 (C-1); 38.3 (C-3); 205.3 (C-2).

1-Chlorohexan-2-one (9g). Bp 73°C (16 mmHg). Lit. 73°C (20 mmHg).[31] Yield 94%. IR (neat). ν cm^{-1} 1730. ^1H NMR ($CDCl_3$) δ 0.80 (t, 3H, CH_3); 1.10–2.15 (m, 4H, H-4 and H-5); 2.60 (t, 2H, H-3); 4.20 (s, 2H, H-1). ^{13}C NMR ($CDCl_3$) δ 13.7 (C-6); 22.2, 25.7 (C-4 and C-5); 48.1 (C-3); 52.4 (C-1); 202.7 (C-2).

1-Chloro-4-methylpentan-2-one (9h). Bp 79–80°C (35 mmHg). Lit. 55–59°C (11 mmHg).[22] Yield 95%. IR (neat) ν cm^{-1} 1730. ^1H NMR ($CDCl_3$) δ 0.90 (d, 6H, 2×CH_3); 2.20 (m, 1H, H-4); 2.50 (d, 2H, H-3); 4.10 (s, 2H, H-1). ^{13}C NMR ($CDCl_3$) δ 22.5 (2×CH_3); 24.6 (C-4); 48.5, 48.7 (C-1 and C-3); 202.2 (C-2).

1-Bromo-3,3-dimethylbutan-2-one (9i). Bp 81°C (23 mmHg). Lit. 72°C (15 mmHg).[32] Yield 83%. IR (neat) ν cm^{-1} 1720. ^1H NMR ($CDCl_3$) δ 1.24 (s, 9H, 3×CH_3); 4.23 (s, 2H, H-1). ^{13}C NMR ($CDCl_3$) δ 26.5 (3×CH_3); 31.9 (C-1); 44.0 (C-3); 205.6 (C-2).

Aminoketo esters (10)

(*R*)-(Phenyl)(phenylmethoxycarbonylamino)acetic esters (10)

(−)-3-Oxo-4-[(*R*)-(phenyl)(phenylmethoxycarbonylamino)acetoxy]butanoic acid methyl ester (10a). This product was obtained according to a modified procedure of Caplar et al.[15] A solution of methyl 4-chloroacetoacetate **9a** (0.10 mmol; 1.0 equiv.) in 65 mL of dimethylformamide or acetonitrile was added dropwise very slowly (about 12 h) to a solution of the potassium salt of *N*-protected amino acid **8** in 65 mL of dimethylformamide (or 130 mL of acetonitrile) containing 1.66 g of potassium iodide (0.01 mol; 0.1 equiv.). The reaction mixture was stirred for 5 h at room temperature then concentrated under reduced pressure. The crude brownish residue was dissolved in 125 mL of dichloromethane, washed with water until neutrality, dried over anhydrous sodium sulphate then concentrated under reduced pressure. The residue obtained was filtered on silica gel (cyclohexane/ethylacetate: 8/2) leading to compound **10a** as an oil that crystallised. Mp 55–56°C. Yield 65%. $[\alpha]_D^{20}$ −73.5 (*c* 3.26, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3400 (N–H); 1750, 1720 (C=O). ^1H NMR ($CDCl_3$) δ 3.40 (s, <2H, COCH_2CO); 3.70, 3.73 (enol) (2s, 3H, CH_3); 4.81 (s, 2H, OCH_2CO); 5.12 (d, 2H, *J*=12.1, OCH_2Ph); 5.49 (d, 1H, *J*=7.1, CHN); 5.76 (d, 1H, *J*=7.1 NH); 7.31–7.43 (m, 10H, H_{ar}); 12.0 (s, <1H, OH_{enol}). ^{13}C NMR ($CDCl_3$) δ 46.1 (COCH_2CO); 52.1 (CH_{3enol}); 53.2 (CH_3); 58.6 (CHN); 63.4 (OCH_2CO_{enol}); 67.8 (OCH_2Ph); 69.2 (OCH_2CO); 89.6 (C=CH_{enol}); 128.0, 128.8, 129.1, 129.5, 129.7, 136.3, 136.6 (C_{ar}); 156.0 (NCOO); 167.2, 170.7 (COO); 196.6 (CO); Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found C, 63.12; H, 5.27; N, 3.51.

The addition of halomethylketones **9b–i** to the potassium salt of (*R*)-(phenyl)(phenylmethoxycarbonylamino)acetic acid **8** was performed according to the procedure previously described by Caplar et al.[15]

(−)-4-Oxo-5-[(*R*)-(phenyl)(phenylmethoxycarbonylamino)acetoxy]pentanoic acid methyl ester (10b). The product could be obtained pure by recrystallisation (ethylacetate/*n*-hexane: 1/1). Mp 74–76°C. Yield 94%. $[\alpha]_D^{20}$ −80.0 (*c* 2.45, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3410 (N–H); 1740, 1715 (C=O). ^1H NMR ($CDCl_3$) δ 2.60–2.65 (2s, 4H, 2×CH_2CO); 3.65 (s, 3H, OCH_3); 4.70 (s, 2H, OCH_2CO); 5.10 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 6.60 (d, 1H, NH); 7.20–7.60 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 26.8, 32.8 (2×CH_2CO); 51.5 (OCH_3); 57.8 (CHN) 66.6 (OCH_2Ph); 68.4 (OCH_2CO); 127.0, 127.8, 128.0, 128.3, 135.7 and 135.9 (C_{ar}); 155.3 (NCOO); 169.9 (*C*OOC); 172.3 (*C*OOCH$_3$); 201.6 (CO). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.57; N, 3.39. Found C, 63.92; H, 5.51; N, 3.37.

(−)-5-Oxo-6-[(*R*)-(phenyl)(phenylmethoxycarbonylamino)acetoxy]hexanoic acid methyl ester (10c). The product could be obtained pure by recrystallisation (ethylacetate/*n*-hexane: 1/1). Mp 82–83°C. Yield 98%. $[\alpha]_D^{20}$ −70.0 (*c* 1.35, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3400 (N–H) 1750, 1720 (C=O). ^1H NMR ($CDCl_3$) δ 1.85 (m, 2H, $CH_2CH_2COOCH_3$); 2.30 (m, 4H, CH_2COOCH_3 and CH_2CH_2CO); 3.65 (s, 3H, OCH_3); 4.60 (s, 2H, OCH_2CO); 5.10 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 5.80 (d, 1H, NH); 7.20–7.40 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 18.2 ($CH_2CH_2COOCH_3$); 32.7, 37.5 (CH_2COOCH_3, CH_2CO); 51.6 (OCH_3); 58.0 (CHN); 67.3 (OCH_2Ph); 68.8 (OCH_2CO); 127.5, 128.2, 128.6, 128.9, 129.1, 134.9 and 136.1 (C_{ar}); 155.3 (NCOO); 170.3 (COOC); 173.3 ($COOCH_3$); 202.7 (CO). Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.64; H, 5.85; N, 3.28. Found C, 64.65; H, 5.95; N, 3.16.

(−)-(*R*)-(Phenyl)(phenylmethoxycarbonylamino)acetic acid 2-oxo-propyl ester (10d). The product could be obtained pure by recrystallisation (ethylacetate/*n*-hexane: 1/2). Mp 99°C. Yield 98%. $[\alpha]_D^{20}$ −90.6 (*c* 3.00, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3420, 3320 (N–H); 1745, 1715 (C=O). ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3); 4.65 (s, 2H, OCH_2CO); 5.10 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 5.80 (d, 1H, NH); 7.35 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_3); 58.3 (CHN); 67.4 (OCH_2Ph); 69.3 (OCH_2CO); 127.5, 128.2, 128.3, 128.6, 129.0, 129.1 and 136.3 (C_{ar}); 155.0 (NCOO); 170.3 (COO); 200.9 (CO). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.10. Found C, 66.90; H, 5.53; N, 4.05.

(−)-(*R*)-(Phenyl)(phenylmethoxycarbonylamino)acetic acid 2-oxo-butyl ester (10e). The product could be obtained pure by recrystallisation (ethylacetate/*n*-hexane: 2/1). Mp 94–96°C. Yield 98%. $[\alpha]_D^{20}$ −30.5 (*c* 2.47, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3420, 3320 (N–H); 1745, 1715 (C=O). ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, CH_3); 2.27 (q, 2H, CH_2CO); 4.66 (s, 2H, OCH_2CO); 5.10 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 5.65 (d, 1H, NH); 7.35 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 7.0 (CH_3); 32.0 (CH_2CO); 58.0 (CHN); 67.2 (OCH_2Ph); 68.6 (OCH_2CO); 127.5, 128.2, 128.6, 128.7, 129.0 and 136.1 (C_{ar}); 155.4 (NCOO); 170.3 (COO); 203.9 (CO). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.60; H, 5.91; N, 3.94. Found C, 67.66; H, 5.97; N, 3.97.

(−)-(*R*)-(Phenyl)(phenylmethoxycarbonylamino)acetic acid 3-methyl-2-oxo-butyl ester (10f). The product could be obtained pure by recrystallisation (ethylacetate/*n*-hexane: 1/20). Mp 67–68°C. Yield 92%. $[\alpha]_D^{20}$ −81.2 (*c* 3.00, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3400 (N–H); 1745, 1715 (C=O). ^1H NMR ($CDCl_3$) δ 1.05 (d, 6H, 2×CH_3); 2.50 (m, 1H, $CH(CH_3)_2$); 4.50 (s, 2H, OCH_2CO); 5.05 (s, 2H, OCH_2Ph); 5.45 (d, 1H, CHN); 5.80 (d, 1H, NH); 7.35 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 17.8 (2×CH_3); 37.5 ($CH(CH_3)_2$); 58.3 (CHN); 67.3, 67.5 (OCH_2CO and OCH_2Ph); 127.5, 128.2, 128.3, 128.6, 128.8, 129.1, 133.5 and 136.4 (C_{ar}); 155.2 (NCOO); 170.3 (COO); 206.2 (CO). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found C, 68.00; H, 6.27; N, 3.61.

(−)-(*R*)-(Phenyl)(phenylmethoxycarboxylamino)acetic acid 2-oxo-hexyl ester (10g). The product could be obtained pure by recrystallisation (diethylether/*n*-pentane: 2/1). mp 85–86°C. Yield 88%. $[\alpha]_D^{20}$ −82.6 (*c* 3.00, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3420, 3320 (N–H); 1750, 1715 (C=O). ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, CH_3); 1.25–1.50 (m, 4H, 2×CH_2); 2.25 (t, 2H, CH_2CO); 4.60 (s, 2H, OCH_2CO); 5.10 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 5.80 (d, 1H, NH); 7.35 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3); 22.2, 25.2 (2×CH_2); 38.5 (CH_2CO); 58.1 (CHN); 67.2 (OCH_2CO); 127.5, 128.3, 128.6, 128.9, 129.1 and 136.1 (C_{ar}); 155.3 (NCOO); 170.3 (COO); 203.5 (CO). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.93; H, 6.53; N, 3.65. Found C, 68.94; H, 6.50; N, 3.62.

(−)-(*R*)-(Phenyl)(phenylmethoxycarbonylamino)acetic acid 4-methyl-2-oxo-pentyl ester (10h). The product could be obtained pure by recrystallisation (diethylether/*n*-pentane: 1/1). Mp 67–69°C. Yield 83%. $[\alpha]_D^{20}$ −67.9 (*c* 3.00, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3420, 3330 (N–H) 1745, 1720 (C=O). ^1H NMR ($CDCl_3$) δ 0.85 (d, 6H, 2×CH_3); 1.95-2.20 (m, 3H, $CH(CH_3)_2$ and CH_2CO); 4.60 (s, 2H, OCH_2CO); 5.10 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 5.80 (d, 1H, NH); 7.35 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.5 (2×CH_3); 24.3 ($CH(CH_3)_2$); 47.8 (CH_2CO); 58.0 (CHN); 67.3 (OCH_2Ph); 69.3 (OCH_2CO); 127.5, 128.3, 128.6, 128.9, 129.1 and 136.1 (C_{ar}); 155.3 (NCOO); 170.3 (COO); 202.5 (CO). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.93; H, 6.53; N, 3.65. Found C, 68.89; H, 6.55; N, 3.62.

(−)-(*R*)-(Phenyl)(phenylmethoxycarbonylamino)acetic acid 3,3-dimethyl-2-oxo-butyl ester (10i). The product could be obtained pure by recrystallisation (ethylacetate/*n*-hexane; 1/60). Mp 70–71°C. Yield 90%. $[\alpha]_D^{20}$ −76.9 (*c* 1.30, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 3420, (N–H); 1745, 1715 (C=O). ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H, 3×CH_3); 4.80 (s, 2H, OCH_2CO); 5.05 (s, 2H, OCH_2Ph); 5.50 (d, 1H, CHN); 6.00 (d, 1H, NH); 7.35 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 25.9 (3×CH_3); 42.6 ($C(CH_3)_3$); 57.8 (CHN); 65.3 (OCH_2Ph); 66.9 (OCH_2CO); 127.4, 128.0, 128.3, 128.4, 128.7, 136.0 and 136.2 (C_{ar}); 155.3 (NCOO); 170.3 (COO); 206.5 (CO). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.93; H, 6.53; N, 3.65. Found C, 68.66; H, 6.62; N, 3.68.

Oxazinones (7) and (14)

General procedure for the preparation of imines or enamine (7). Compounds **7** were prepared from halomethylketones **9** following a similar procedure to that used by Caplar et al.[15] In our methodology, hydrobromides were not isolated and were neutralised by addition of solid potassium carbonate. The purity of oxazinones **7** is superior to 95% based on NMR and GC analyses.

(−)-(*Z*)-[(6-Oxo-5*R*-phenyl)morpholin-3-yliden]acetic acid methyl ester (7a). Yield 96%. $[\alpha]_D^{20}$ −453.4 (*c* 1.01, $CHCl_3$). IR (Nujol) ν cm^{-1} 3320 (NH); 1765 (C=O). ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H, CH_3); 4.71 (dd, 2H, *J*=14.8 and 21.1, H-2); 4.80 (s, 1H, C=CH); 5.32 (d, 1H, H-5); 7.43 (m, 5H, H_{ar}); 8.80 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 51.4 (CH_3); 58.2 (C-5); 67.7 (C-2); 83.2 (C=CH); 126.8, 128.0, 129.6, 130.0 and 134.7 (C_{ar}); 152.7, 168.2, 170.9 (2×COO and *C*=CH).

3-(6-Oxo-5*R*-phenyl-5,6-dihydro-2*H*-[1,4]oxazin-3-yl)-propanoic acid methyl ester (7b). Yield 94%. IR ($CHBr_3$) ν cm^{-1} 1735, 1720 (C=O); 1675 (C=N). ^1H NMR ($CDCl_3$) δ 2.60–2.80 (m, 4H, $CH_2CO_2CH_3$ and CH_2CN); 3.65 (s, 3H, OCH_3); 4.90 (d, 2H, J=1.7, H-2); 5.45 (s, 1H, H-5); 7.25–7.40 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 28.5, 29.2 (2×CH_2); 51.3 (OCH_3); 62.0 (C-5); 68.9 (C-2); 126.8, 127.7, 128.2 and 135.1 (C_{ar}); 166.6, 167.3 (2×COO); 172.5 (CN).

4-(6-Oxo-5*R*-phenyl-5,6-dihydro-2*H*-[1,4]oxazin-3-yl)butanoic acid methyl ester (7c). Yield 95%. IR ($CHBr_3$) ν cm^{-1} 1750, 1740 (C=O); 1675 (C=N). ^1H NMR ($CDCl_3$) δ 2.00 (m, 2H, CH_2CH_2COO); 2.40 (t, 2H, $CH_2CO_2CH_3$); 2.50 (t, 2H, CH_2CN); 3.70 (s, 3H, OCH_3); 4.80 (d, 2H, J=1.5, H-2); 5.40 (s, 1H, H-5); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 20.4 ($CH_2CH_2CH_2$); 32.9, 34.6 ($CH_2CO_2CH_3$ and CH_2CN); 51.6 (OCH_3); 62.8 (C-5); 69.0 (C-2); 127.3, 128.1, 128.7 and 135.5 (C_{ar}); 166.1, 167.8 (2×COO); 173.4 (CN).

5-Methyl-3*R*-phenyl-3,6-dihydro-[1,4]oxazin-2-one (7d). Quantitative yield. IR (neat) ν cm^{-1} 1735 (C=O), 1670 (C=N). ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H, CH_3); 4.80 (s, 2H, H-6); 5.30 (s, 1H, H-3); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.6 (CH_3); 62.9 (C-3); 69.7 (C-6) 127.4, 128.3, 128.9 and 135.6 (C_{ar}); 165.8, 167.5 (CN, COO).

5-Ethyl-3*R*-phenyl-3,6-dihydro-[1,4]oxazin-2-one (7e). Quantitative yield. IR (neat) ν cm^{-1} 1735 (C=O); 1670 (C=N). ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, CH_3); 2.40 (q, 2H, CH_2CH_3); 4.75 (s, 2H, H-6); 5.35 (s, 1H, H-3); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 19.5 (CH_3); 28.7 (CH_2CH_3); 62.4 (C-3); 68.6 (C-6), 127.1, 127.8, 128.4 and 135.5 (C_{ar}); 167.9, 169.7 (CN, COO).

5-(Methylethyl)-3*R*-phenyl-3,6-dihydro-[1,4]oxazin-2-one (7f). Quantitative yield. IR (neat) ν cm^{-1} 1740 (C=O); 1665 (C=N). ^1H NMR ($CDCl_3$) δ 1.20 (d, 6H, 2×CH_3); 2.70 (m, 1H, $CH(CH_3)_2$); 4.80 (s, 2H, H-6); 5,30 (s, 1H, H-3); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 19.4 and 19.5 (2×CH_3); 35.1 ($CH(CH_3)_2$); 62.8 (C-3); 67.7 (C-6); 127.2, 128.2, 128.8 and 135.3 (C_{ar}); 168.4 (CN); 173.5 (COO).

5-Butyl-3*R*-phenyl-3,6-dihydro-[1,4]oxazin-2-one (7g). Quantitative yield. IR (neat) ν cm^{-1} 1740 (C=O); 1660 (C=N). ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, CH_3); 1.10–1.80 (m, 4H, CH_2CH_3 and $CH_2CH_2CH_2$); 2.40 (t, 2H, CH_2CN); 4.80 (s, 2H, H-6); 5.40 (s, 1H, H-3); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 13.5 (CH_3); 22.1 and 27.5 (CH_2CH_3 and $CH_2CH_2CH_2$); 35.6 (CH_2CN); 62.6 (C-3); 68.7 (C-6); 127.2, 127.8, 128.4 and 135.5 (C_{ar}); 167.8, 169.1 (COO and CN).

5-(2-Methylpropyl)-3*R*-phenyl-3,6-dihydro-[1,4]oxazin-2-one (7h). Quantitative yield. IR (neat) ν cm^{-1} 1740 (C=O), 1665 (C=N). ^1H NMR ($CDCl_3$) δ 1.00 (d, 6H, 2×CH_3); 2.10 (m, 1H, $CH(CH_3)_2$); 2.30 (d, 2H, CH_2CH); 4.80 (s, 2H, H-6); 5.40 (s, 1H, H-3); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.5 (2×CH_3); 26.0 ($CH(CH_3)_2$); 44.9 (CH_2CH); 62.9 (C-3); 69.1 (H-6); 127.3, 128.0, 128.6 and 135.7 (C_{ar}); 167.9, 168.7 (COO and CN).

5-(1,1-Dimethylethyl)-3*R*-phenyl-3,6-dihydro-[1,4]oxazin-2-one (7i). Quantitative yield. IR (neat) ν cm^{-1} 1735 (C=O); 1670 (C=N). ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H, 3×CH_3); 4.80 (s, 2H, H-6); 5.30 (s, 1H, H-3); 7.30 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 26.1, 27.2 (3×CH_3 and $C(CH_3)_3$); 62.9 (C-3); 65.8 (C-6); 127.2, 128.0, 128.7 and 135.1 (C_{ar}); 168.7 (CN); 175.6 (COO).

Preparation of enamine (7a) by cyclisation with H_2 over Pd/C. To a solution of 27.5 mmol of 3-oxo-4-[(*R*)-(phenyl)(phenylmethoxycarbonylamino) acetoxy]butanoic acid methyl ester **10a** in 170 mL of methyl acetate, 10% Pd/C (0.6 equiv. in weight) was added. The mixture was stirred under H_2 (1 atm) until completion of the reaction (monitored by TLC, 4–6 h), then filtered over Celite®, concentrated under reduced pressure giving rise to 22.8 mmol of (−)-(*Z*)-[(6-oxo-5*R*-phenyl)morpholin-3-yliden]acetic acid methyl ester **7a** as a yellow oil that crystallised.

Preparation of *N*-benzylated enamine (14)

(−)-3-Oxo-4-[(*R*)-(phenyl)((phenylmethoxycarbonyl)-(phenylmethyl)amino)acetoxy] butanoic acid methyl ester. Using the same procedure as for **10a**, the methyl 4-chloroacetoacetate **9a** was condensed with the potassium salt of (−)-(*R*)-(phenyl)[(phenylmethoxycarbonyl)(phenylmethyl)amino]acetic acid to give a colourless oil after chromatography. Yield 66%. $[\alpha]_D^{20}$ −17.9 (*c* 3.72, $CHCl_3$). IR (neat) ν cm^{-1} 1750–1690 (C=O). ^1H NMR ($CDCl_3$) δ 3.47 (s, <2H, $COCH_2CO$); 3.71 and 3.75 (enol) (2s, 3H, CH_3); 4.23 (d, 1H, J=16.0, PhCH*H*N); 4.40–4.95 (m, 3H, OCH_2CO+PhC*H*HN); 5.21 (s, 2H, OCH_2Ph); 5.85 (br s, 1H, CHN); 6.91 (br s, 2H, H_{ar}); 7.14–7.30 (m, 13H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 46.1 ($COCH_2CO$); 49.6 (NCH_2Ph); 52.0 (CH_{3enol}); 53.0 (CH_3); 63.9 (CHN); 68.4 (OCH_2Ph); 69.0 (OCH_2CO); 89.7 ($C=CH_{enol}$); 127.3, 127.6, 128.6, 129.0, 129.1, 129.3 130.3, 133.9, 136.6 and 138.5 (C_{ar}); 157.5 (NCOO); 167.2 and 170.4 (2×COO); 197.0 (CO). Anal. Calcd for $C_{28}H_{27}NO_7$: C, 68.70; H, 5.56; N, 2.86. Found C, 68.57; H, 5.71; N, 2.80.

(*E*)-[(6-Oxo-5*R*-phenyl-4-phenylmethyl)morpholin-3-yliden]acetic acid methyl ester (14). The (−)-3-oxo-4-[(*R*)-(phenyl)((phenylmethoxycarbonyl)(phenylmethyl)-amino) acetoxy]butanoic acid methyl ester was cyclised to enaminoester **14** using the same procedure as for **7a**. Crude yield 96%. IR ($CHBr_3$) ν cm^{-1} 1750 (C=O); 1680 (C=C); 1600 (C=C_{ar}). ^1H NMR ($CDCl_3$) δ 3.66 (s, 3H, CH_3); 4.23 (d, 1H, J=15.9, PhC*H*HN); 4.77 (d, 1H, J=15.9, CH*H*O); 4.83 (d, 1H, J=15.9, PhCH*H*N); 5.08 (s, 1H, C=CH); 5.22 (s, 1H, H-5); 6.53 (d, 1H, J=15.9, C*H*HO); 7.15–7.50 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 51.4 (CH_3); 54.2 ($PhCH_2N$); 64.2 (C-5); 65.0 (C-2); 86.6 (C=*C*H); 126.3, 127.6, 128.9, 129.7, 129.8, 130.2, 133.2 and 134.5 (C_{ar}); 153.4 (*C*=CH); 167.8 and 168.8 (2×COO).

Morpholinones (17)

Method A. To a stirred solution of freshly prepared oxazinone **7** (10 mmol) in methanol (30 mL), 0.4 mmol of platinum oxide (hydrate) (0.04 equiv.) was added. The suspension was stirred under H_2 (1 atm.) at room temperature until completion of the reaction (monitored by TLC, 4–6 h). The mixture was then filtered through Celite® and the

filtrate was concentrated under reduced pressure. The major *cis* morpholinone **17** was isolated after chromatography on silica gel (chloroform/acetone) as a yellow oil (for yields see Table 1).

Method B. To a stirred mixture of freshly prepared oxazinone **7** (5 mmol) in acetonitrile (35 mL) and sodium triacetoxyborohydride (8 mmol, 1.70 g, 1.6 equiv.), chlorotrimethylsilane (6 mmol) was added. The suspension was stirred at room temperature until completion of the reaction (monitored by TLC, about 4 h). The mixture was then filtered through Celite® and the filtrate was concentrated. The crude oily residue was diluted with 30 mL of dichloromethane, washed with a saturated aqueous solution of sodium hydrogenocarbonate (2×30 mL) and then with brine (30 mL). The organic layer was dried over anhydrous sodium sulphate. The major *cis* diasteroisomer was isolated after chromatography on silica gel (chloroform/acetone) as a yellow oil (for yields see Table 1).

Method C. To a stirred solution of freshly prepared oxazinone **7** (10 mmol) in acetonitrile (40 mL), 14 mL of a 1 mol L^{-1} solution of borane–tetrahydrofuran complex (BH_3–THF) (14 mmol, 1.4 equiv.) were added. The solution was stirred at room temperature until completion of the reaction (monitored by TLC, about 3 h). The reaction was quenched with methanol (5 mL) and concentrated under reduced pressure. The crude residue was diluted with 50 mL of dichloromethane, washed with brine (2×50 mL) then dried over anhydrous sodium sulphate. The major *cis* diastereoisomer was isolated after chromatography on silica gel (chloroform/acetone) as a yellow oil (for yields see Table 1).

(−)-3-[(3*S*,5*R*)-6-Oxo-5-phenylmorpholin-3-yl]propanoic acid methyl ester (17b). Yield 80% (method C). $[\alpha]_D^{20}$ −1.4 (*c* 3.20, $CHCl_3$). IR (neat) ν cm^{-1} 3320 (NH); 1730 (C=O). ^1H NMR ($CDCl_3$) δ 1.60–2.00 (m, 2H, C*H*$_2$$CH_2CO_2CH_3$); 1.90 (br s, 1H, NH); 2.45 (t, 2H, C*H*$_2$$CO_2CH_3$); 3.35 (m, 1H, H-3); 3.70 (s, 3H, OCH_3); 4.15 (t, 1H, *J*=10.7, H-2); 4.35 (dd, 1H, *J*=3.6 and 10.7, H-2); 4.75 (s, 1H, H-5); 7.20–7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 26.5 (*C*$H_2CH_2CO_2CH_3$); 29.8 (*C*$H_2CO_2CH_3$); 51.1, 51.5 (CH_3 and C-3); 62.7 (C-5); 73.1 (C-2); 127.9, 128.3 and 138.1, (C_{ar}); 168.9 and 173.1 (2×COO). Anal. Calcd for $C_{14}H_{17}NO_4$:C, 63.89; H, 6.46; N, 5.32. Found C, 64.05; H, 6.38; N, 5.45.

(−)-4-[(3*S*,5*R*)-6-Oxo-5-phenylmorpholin-3-yl]butanoic acid methyl ester (17c). Yield 76% (method C). $[\alpha]_D^{20}$ −1.8 (*c* 3.00, $CHCl_3$). IR (neat) ν cm^{-1} 3330 (NH); 1740, 1725 (C=O). ^1H NMR ($CDCl_3$) δ 1.50–2.00 (m, 4H, C*H*$_2$C*H*$_2$$CH_2CO_2CH_3$); 2.00 (br s, 1H, NH); 2.40 (t, 2H, C*H*$_2$$CO_2CH_3$); 3.20–3.40 (m, 1H, H-3); 3.70 (s, 3H, OCH_3); 4.20 (t, 1H, *J*=10.6, H-2); 4.40 (dd, 1H, *J*=3.6 and 10.6, H-2); 4.75 (s, 1H, H-5); 7.20–7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 20.6 (*C*$H_2CH_2CO_2CH_3$); 30.6, 33.4 (*C*H_2CH_2*C*$H_2CO_2CH_3$); 51.7 (C-3); 51.8 (OCH_3); 63.6 (C-5); 74.0 (C-2); 128.2, 128.5 and 137.9 (C_{ar}); 169.2 and 173.5 (2×COO). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.28; H, 6.86; N, 5.05. Found C, 64.63; H, 6.70; N, 5.23.

(−)-(3*R*,5*S*)-5-Methyl-3-phenylmorpholin-2-one (17d). Yield 89% (method C). $[\alpha]_D^{20}$ −9.5 (*c* 3.00, $CHCl_3$). IR (neat) ν cm^{-1} 1735 (C=O). ^1H NMR ($CDCl_3$) δ 1.10 (d, 3H, CH_3); 1.90 (br s, 1H, NH); 3.40 (m, 1H, H-5); 4.10 (t, 1H, *J*=10.5, H-6); 4.25 (dd, 1H, *J*=3.7 and 10.5, H-6); 4.70 (s, 1H, H-3); 7.25–7.45 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 16.6 (CH_3); 48.0 (C-5); 64.0 (C-3); 75.4 (C-6); 128.3, 128.5 and 138.3 (C_{ar}); 168.6 (CO). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.30. Found C, 69.08; H, 6.84; N, 7.30.

(−)-(3*R*,5*S*)-5-Ethyl-3-phenylmorpholin-2-one (17e). Yield 90% (method C). $[\alpha]_D^{20}$ −66.1 (*c* 3.75, $CHCl_3$). IR (neat) ν cm^{-1} 1735 (C=O). ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3); 1.50 (m, 2H, C*H*$_2$$CH_3$); 2.05 (br s, 1H, NH); 3.10 (m, 1H, H-5); 4.10 (t, 1H, *J*=10.7, H-6); 4.20 (dd, 1H, *J*=3.4 and 10.7, H-6); 4.70 (s, 1H, H-3); 7.25-7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 9.9 (CH_3); 24.9 (*C*H_2CH_3); 53.7 (C-5); 63.7 (C-3); 74.1 (C-6); 128.4, 128.5, 128.7 and 136.4 (C_{ar}); 169.1 (CO). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found C, 70.24; H, 7.29; N, 6.88.

(−)-(3*R*,5*S*)-5-Methylethyl-3-phenylmorpholin-2-one (17f). Yield 93% (method C). $[\alpha]_D^{20}$ −38.4 (*c* 3.15, $CHCl_3$). IR (neat) ν cm^{-1} 1740 (C=O). ^1H NMR ($CDCl_3$) δ 0.97 (d, 3H, *J*=6.8 CH_3); 1.00 (d, 3H, *J*=6.8 CH_3); 1.70 (m, 1H, C*H*$(CH_3)_2$); 1.90 (br s, 1H, NH); 3.00 (m, 1H, H-5); 4.20 (t, 1H, *J*=10.7, H-6); 4.40 (dd, 1H, *J*=3.9 and 10.7, H-6); 4.70 (s, 1H, H-3); 7.25–7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 18.7, 18.9 (2×CH_3); 30.2 (*C*H$(CH_3)_2$); 58.0 (C-5); 63.5 (C-3); 72.8 (C-6); 128.2, 128.3, 128.6 and 138.5 (C_{ar}); 169.3 (CO). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 6.85; N, 6.39. Found C, 71.26; H, 6.84; N, 6.50.

(−)-(3*R*,5*S*)-5-Butyl-3-phenylmorpholin-2-one (17g). Yield 87% (method C). $[\alpha]_D^{20}$ −15.2 (*c* 3.00, $CHCl_3$). IR (neat) ν cm^{-1} 1735 (C=O). ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3); 1.10–1.55 (m, 6H, 3×CH_2); 1.90 (br s, 1H, NH); 3.30 (m, 1H, H-5); 4.20 (t, 1H, *J*=10.7, H-6); 4.40 (dd, 1H, *J*=3.5 and 10.7, H-6); 4.70 (s, 1H, H-3); 7.30–7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3); 22.7, 22.8, 31.4 (3×CH_2); 52.6 (C-5); 64.0 (C-3); 74.5 (C-6); 128.4, 128.6, 129.5, 129.6, 130.6 and 138.4 (C_{ar}); 170.5 (CO). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found C, 72.18; H, 8.17; N, 6.12.

(−)-(3*R*,5*S*)-5-(2-Methylpropyl)-3-phenylmorpholin-2-one (17h). Yield 92% (method C). $[\alpha]_D^{20}$ −1.2 (*c* 3.70, $CHCl_3$). IR (neat) ν cm^{-1} 1735 (C=O). ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J*=4.0, CH_3); 0.95 (d, 3H, *J*=4.0, CH_3); 1.30 (m, 2H, C*H*$_2$$CH(CH_3)_2$); 1.70 (m, 1H, C*H*$(CH_3)_2$); 1.90 (br s, 1H, NH); 3.30 (m, 1H, H-5); 4.10 (t, 1H, *J*=10.2, H-6); 4.30 (dd, 1H, *J*=3.5 and 10.2, H-6); 4.70 (s, 1H, H-3); 7.30–7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.4, 23.1 (2×CH_3); 24.5 (*C*$H_2CH(CH_3)_2$); 40.5 (*C*H$(CH_3)_2$); 50.4 (C-5); 63.9 (C-3); 74.7 (C-6); 128.3, 128.6 and 138.4 (C_{ar}); 169.0 (CO). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found C, 72.10; H, 8.15; N, 6.11.

(−)-(3*R*,5*S*)-5-(1,1-Dimethylethyl)-3-phenylmorpholin-2-one (17i). Yield 89% (method A). $[\alpha]_D^{20}$ −5.7 (*c* 3.00, $CHCl_3$). IR (neat) ν cm^{-1} 1735 (C=O). ^1H NMR ($CDCl_3$) δ 1.00 (s, 9H, 3×CH_3); 1.90 (br s, 1H, NH); 3.00 (m, 1H, H-5); 4.30 (t, 1H, *J*=10.2, H-6); 4.40 (dd, 1H, *J*=3.5 and 10.2,

H-6); 4.70 (s, 1H, H-3); 7.25-7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 26.4 (3×CH_3); 32.7 ($C(CH_3)_3$); 61.1, 63.6 (C-3 and C-5); 71.2 (C-6); 128.3, 128.6 and 138.7 (C_{ar}); 169.4 (CO). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found C, 72.02 H, 8.21; N, 6.05.

Preparation of (17a) from (7a). (−)-2-[(3*S*,5*R*)-6-Oxo-5-phenylmorpholin-3-yl]acetic acid methyl ester (17a). To a stirred solution of 4.98 g of (−)-(*Z*)-[(6-oxo-5*R*-phenyl)-morpholin-3-yliden]acetic acid methyl ester **7a** (20.2 mmol) in 60 mL of dry tetrahydrofuran was added 1.50 g of 10% Pt/C (0.3 equiv. in weight). The mixture was stirred at room temperature under H_2 (1 atm) until completion of the reaction (monitored by TLC, about 18 h). The mixture was then filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was chromatographed on silica gel (cyclohexane/ethylacetate 8/2) to lead to 0.91 g (3.65 mmol) of (−)-2-[(3*S*,5*R*)-6-oxo-5-phenylmorpholin-3-yl]acetic acid methyl ester **17a** as a white solid. Yield 18%. $[\alpha]_D^{20}$ −96.9 (*c* 1.50, $CHCl_3$). IR (Nujol) ν cm^{-1} 3330 (NH); 1720 (C=O). ^1H NMR ($CDCl_3$) δ 2.48–2.51 (m, 2H, C*H*$_2CO_2CH_3$); 2,63 (br s, 1H, NH); 3.69–3.80 (m, 4H, CH_3 and H-3); 4.21 (t, 1H, *J*=10.6, H-2); 4.37 (dd, 1H, *J*=3.7 and 10.6, H-2); 4.81 (s, 1H, H-5); 7.35–7.51 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 36.4 (*C*$H_2CO_2CH_3$); 49.3, 52.5 (CH_3 and C-3); 63.4 (C-5); 73.0 (C-2); 127.8, 128.6, 128.8, 129.0 and 138.6 (C_{ar}); 169.3 and 171.7 (2×COO). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found C, 62.61; H, 6.06; N, 5.54.

Preparation of (17a) from (19). (−)-2-[(3*S*,5*R*)-6-Oxo-5-phenyl-4-phenylmethylmorpholin-3-yl]acetic acid methyl ester (19). 0.80 g of sodium borohydride (21.0 mmol) was added portionwise to 12 mL of stirred and cooled glacial acetic acid (210 mmol; 60 equiv.). The mixture was then diluted with 3 mL of anhydrous acetonitrile. A solution of 1.18 g of (*E*)-[(6-oxo-5*R*-phenyl-4-phenylmethyl)morpholin-3-yliden]acetic acid methyl ester **14** (3.50 mmol) in acetonitrile (3 mL) was added to the previously prepared reductive solution. The mixture was stirred at 10°C until complete consumption of **14** (monitored by TLC, 4–6 h). After addition of 30 mL of water and 20 mL of dichloromethane, the reaction mixture was neutralised with solid sodium carbonate. The aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and then concentrated under reduced pressure giving rise to an oil that crystallised. The major *cis* morpholine **19** (d.e. 94%) was isolated as a white solid after chromatography on silica gel (cyclohexane/ethylacetate: 9/1). Mp 94–96°C. Yield 71%. $[\alpha]_D^{20}$ −58.5 (*c* 3.05; $CHCl_3$). IR (Nujol) ν cm^{-1} 1770 and 1740 (C=O). ^1H NMR ($CDCl_3$) δ 2.37 (dd, 1H, *J*=7.8 and 15.8, C*H*HCOO); 2.53 (dd, 1H, *J*=5.7 and 15.8, CH*H*COO); 3.45–3.56 (m, 1H, H-3); 3.60 (s, 3H, CH_3); 3.77 (d, 1H, *J*=13.5, NC*H*HPh); 3.87 (d, 1H, *J*=13.5, NCH*H*Ph); 3.91 (dd, 1H, *J*=9.1 and 11.8, C*H*HO); 4.25 (dd, 1H, *J*=4.6 and 11.8, CH*H*O); 4.49 (s, 1H, H-5); 7.19–7.36 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 38.1 (*C*H_2COOCH_3); 52.3 (CH_3); 55.7 (C-3); 60.9 (N*C*H_2Ph); 65.0 (C-5); 68.1 (C-2); 127.4, 128.3, 128.6, 128.8, 129.1, 129.3, 129.7, 137.5 and 136.7 (C_{ar}); 171.0 and 171.6 (2×COO). Anal. Calcd for $C_{20}H_{21}NO_4$:C, 70.78; H, 6.24; N, 4.13. Found C, 70.88; H, 6.25; N, 4.25.

(−)-2-[(3*S*,5*R*)-6-Oxo-5-phenylmorpholin-3-yl]acetic acid methyl ester (17a). To a stirred solution of 0.14 g of **19** (0.413 mmol) in 4.5 mL of methylacetate was added 0.14 g of 10% Pd/C (1 equiv. in weight). The mixture was stirred at room temperature under H_2 (1 atm) until completion of the reaction (monitored by TLC, about 20 h). The mixture was then filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude product was chromatographed on silica gel (cyclohexane/ethylacetate 1/1) to lead to 0.065 g (0.26 mmol) of (−)-2-[(3*S*,5*R*)-6-oxo-5-phenylmorpholin-3-yl]acetic acid methyl ester **17a**. Yield 64%.

Aminoalcohols (20d–i)

General procedure for preparation of aminoalcohols (20d–i) from morpholinones (17). To a stirred solution of 4 mmol of morpholinone **17** in methanol (20 mL), 0.6 equiv. in weight of palladium (10% Pd/C) was added. The mixture was stirred under 150 atm of H_2 for 72 h. The catalyst was then removed by filtration through Celite®. The filtrate was concentrated under reduced pressure and the oily residue was dissolved in chloroform (20 mL). The solution was extracted with an aqueous solution of 3 mol L^{-1} hydrochloric acid (3×20 mL). Solid sodium carbonate was added to the combined aqueous extracts until saturation and the solution was then extracted with chloroform (5×20 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated. The oily residue thus obtained was distilled under reduced pressure with a Kugelrohr apparatus.

(+)-(2*S*)-Aminopropan-1-ol (20d). Yield 89%. $[\alpha]_D^{20}$ +18.2 (neat). Lit.[33] $[\alpha]_D^{20}$ +15.2 (neat).

(+)-(2*S*)-Aminobutan-1-ol (20e). Yield 84%. $[\alpha]_D^{20}$ +10.2 (neat). Lit.[33] $[\alpha]_D^{20}$ +9.8 (neat).

(+)-(2*S*)-Amino-3-methylbutan-1-ol (20f). Yield 88%. $[\alpha]_D^{20}$ +17.1 (*c* 11.00, C_2H_5OH). Lit.[34] $[\alpha]_D^{25}$ +17.0 (*c* 11.53, C_2H_5OH).

(+)-(2*S*)-Aminohexan-1-ol (20g). Yield 78%. $[\alpha]_D^{20}$ +12.2 (*c* 1.00, $CHCl_3$). Lit.[8a] $[\alpha]_D^{22}$ +12.3 (*c* 0.60, $CHCl_3$).

(+)-(2*S*)-Amino-4-methylpentan-1-ol (20h). Yield 86%. $[\alpha]_D^{20}$ +1.2 (neat). Lit.[35] $[\alpha]_D^{20}$ +1.2 (neat).

(+)-(2*S*)-Amino-3,3-dimethylbutan-1-ol (20i). Yield 82%. $[\alpha]_D^{20}$ +37.2 (*c* 3.00, C_2H_5OH). Lit.[36] $[\alpha]_D^{22}$ +35.3 (*c* 3.00, C_2H_5OH).

Cyclic aminoalcohols (26)

Lactamisation of oxazinones (17b) and (17c). Oxazinone **17b** or **17c** (2.5 mmol) was dissolved in toluene (20 mL). The mixture was stirred at reflux for 10–20 h (reaction monitored by TLC). Toluene was evaporated and the residue obtained was chromatographed on silica gel (ethylacetate/chloroform: 4/1).

(−)-(4*R*,8a*S*)-4-Phenyltetrahydropyrrolo-[2,1-*c*][1,4]-oxazin-3,6-dione (23b). The oily product was crystallised

in ethylacetate/*n*-hexane (2/1). Mp 124°C. Yield 85%. $[\alpha]_D^{20}$ −14.9 (*c* 0.70, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 1730 (OC=O); 1680 (NC=O). ^1H NMR ($CDCl_3$) δ 1.80–2.00 (m, 1H, H-8); 2.25–2.40 (m, 1H, H-8); 2.50–2.60 (m, 2H, H-7); 4.00–4.15 (m, 1H, H-8a); 4.40 (d, 1H, *J*=10.6, H-1); 4.50 (dd, 1H, *J*=3.6 and 10.6, H-1); 5.6 (s, 1H, H-4); 7.30–7.45 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.6 (C-8); 31.6 (C-7); 54.1 (C-8a); 59.8 (C-4); 70.9 (C-1); 126.6, 128.8, 129.1 and 134.4 (C_{ar}); 166.8 (COO); 173.1 (CON). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.52; H, 5.71; N, 6.02.

(−)-(4*R*,9a*S*)-4-Phenyltetrahydropyrido-[2,1-c][1,4]-oxazin-3,6-dione (23c). The oily product was crystallised in ethylacetate/*n*-hexane (1/1). Mp 137–139°C. Yield 92%. $[\alpha]_D^{20}$ −0.5 (*c* 2.80, $CHCl_3$). IR ($CHBr_3$) ν cm^{-1} 1740 (OC=O); 1640 (NC=O). ^1H NMR ($CDCl_3$) δ 1.70 (m, 1H, H-8); 1.95 (m, 1H, H-8); 2.05 (m, 1H, H-9); 2.15 (m, 1H, H-9); 2.55–2.65 (m, 2H, H-7); 3.80–3.95 (m, 1H, H-9a); 4.20 (d, 2H, *J*=6.8, H-1); 6.10 (s, 1H, H-4); 7.25–7.40 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 19.8 and 24.7 (C-8 and C-9); 31.4 (C-7); 54.3 (C-9a); 58.7 (C-4); 68.9 (C-1); 125.8, 128.4, 129.1 and 134.9 (C_{ar}); 167.7, 169.4 (COO and CON). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.54; H, 6.17; N, 5.66.

Cyclic aminodiols (25). To a stirred 1 mol L^{-1} solution of borane–tetrahydrofuran complex (10 mmol, 2.5 equiv.) in tetrahydrofuran (10 mL), a solution of lactolactam **23b** or **23c** (4 mmol) in 30 mL of tetrahydrofuran was added. The mixture was stirred at room temperature for 3 h (monitored by TLC) and then concentrated under reduced pressure. The oily residue was dissolved in chloroform (30 mL), washed with brine (30 mL), dried over anhydrous sodium sulphate and then concentrated. The crude residue was purified by chromatography on silica gel (ethylacetate then ethylacetate/methanol: 1/1) to provide the corresponding cyclic aminodiol as an oily product.

(−)-(2*R*)-[(2*S*)-Hydroxymethyl)pyrrolidin-1-yl]-2-phenylethanol (25b). Yield 88%. $[\alpha]_D^{20}$ −8.5 (*c* 4.00, $CHCl_3$). IR (neat) ν cm^{-1} 3350. ^1H NMR ($CDCl_3$) δ 1.45–1.80 (m, 4H, 2×CH_{2pyr}); 2.35 (m, 1H, C*H*HN); 2.75 (br s, 2H, 2×OH); 2.95 (m, 1H, C*H*HN); 3.05 (m, 1H, NC*H*CH_2O); 3.50 (dd, 1H, *J*=4.5 and 11.5, C*H*HO); 3.70–3.90 (m, 2H, 2×C*H*HO); 4.00 (m, 2H, C*H*HO and C*H*Ph); 7.15–7.45 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 23.4, 27.5 (2×CH_{2pyr}); 47.4 (CH_2N); 60.3 (N*C*HCH_2OH); 62.7, 63.4 (2×CH_2OH); 64.7 (Ph*C*HN); 127.7, 128.2, 129.1 and 136.4 (C_{ar}). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60; N, 6.33. Found: C, 70.41; H, 8.52; N, 6.42.

(−)-(2*R*)-[(2*S*)-Hydroxymethyl)piperidin-1-yl]-2-phenylethanol (25c). Yield 90%. $[\alpha]_D^{20}$ −13.6 (*c* 2.10, $CHCl_3$). IR (neat) ν cm^{-1} 3350. ^1H NMR ($CDCl_3$) δ 1.10–1.70 (m, 6H, 3×CH_{2pip}); 1.85 (t, 1H, C*H*HN); 2.50 (br s, 2H, 2×OH); 2.60 (m, 1H, NC*H*CH_2OH); 2.90 (m, 1H, C*H*HN); 3.65 (m, 1H, C*H*HO); 3.70 (m, 1H, C*H*HO); 4.05 (d, 1H, *J*=10.2, C*H*HO); 4.10 (dd, 1H, *J*=3.6 and 10.2, C*H*HO); 4.40 (dd, 1H, *J*=4.9 and 10.2, NC*H*Ph); 7.15–7.50 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 23.6, 25.6, 29.5 (3×CH_{2pip}); 45.2 (CH_2N); 58.7, 61.2 (2×CH_2O); 60.4 (N*C*HCH_2OH); 63.6 (Ph*C*HN); 127.6, 128.2, 128.9 and 136.3 (C_{ar}). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.49; H, 8.93; N, 5.96. Found: C, 71.86; H, 8.75; N, 5.77.

General procedure for debenzylation of aminodiols (25b) and (25c). To a stirred solution of aminodiol **25b** or **25c** (4.52 mmol) in methanol (25 mL), 1 equiv. in weight of palladium (10% Pd/C) was added. The mixture was stirred under 1 atm of H_2 at room temperature for about 2 h (monitored by TLC). The catalyst was removed by filtration through Celite® and the filtrate was concentrated. The oily residue was dissolved in chloroform (20 mL) and then extracted with a solution of hydrochloric acid, 3 mol L^{-1} (3×20 mL). The combined aqueous extracts were neutralised by addition of solid sodium carbonate and then extracted with chloroform (5×20 mL). The latter organic extracts were combined, dried over anhydrous sodium sulphate, concentrated and the residue was distilled with a Kugelrohr apparatus.

(+)-(2*S*)-Hydroxymethylpyrrolidine (26b). Yield 90%. $[\alpha]_D^{21}$ +30.4 (*c* 1.00, $PhCH_3$). Lit.[37] $[\alpha]_D^{23}$ +30.9 (*c* 1.10, PhH).

(+)-(2*S*)-Hydroxymethylpiperidine (26c). Yield 90%. $[\alpha]_D^{21}$ +15.9 (*c* 2.50, C_2H_5OH). Lit.[38] $[\alpha]_D^{21}$ +16.0 (*c* 2.34, C_2H_5OH).

Aminodiols (20a–c)

Aminotriols (24). To a cooled (0°C) and stirred solution of morpholinone **17a**, **17b** or **17c** (4 mmol) in tetrahydrofuran (50 mL), 20 mmol (760 mg) of lithium aluminium hydride were added portionwise. The mixture was stirred at room temperature until completion of the reaction (monitored by TLC, about 2 h). After successive dropwise additions, via syringe, of 0.76 mL of water, 0.76 mL of an aqueous solution of sodium hydroxide (15%) and again 2.28 mL of water, the mixture was stirred until formation of a white solid that was removed by filtration through Celite®. The solid was washed several times with tetrahydrofuran. The organic solution was concentrated under reduced pressure. The oily residue was then purified by chromatography on silica gel (chloroform then chloroform/methanol: 8/2).

(2*S*)-[(2-Hydroxy-(1*R*)-phenyl)ethylamino]butan-1,4-diol (24a). Yield 38%. IR (neat) ν cm^{-1} 3500–3000. ^1H NMR ($CDCl_3$) δ 1.51–1.97 (m, 2H, H-3); 2.67–2.80 (m, 1H, H-2); 3.00–4.10 (m, 11H, 3×CH_2O, C*H*Ph, 3×OH and NH); 7.27–7.37 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 34.7 (C-3); 56.5 (C-2); 62.1 and 62.5 (2×CH_2O); 62.2 (*C*HPh); 67.9 (CH_2O); 128.1, 128.3, 128.6, 129.5, 130.1 and 140.1 (C_{ar}).

(2*S*)-[(2-Hydroxy-(1*R*)-phenyl)ethylamino]pentan-1,5-diol (24b). Yield 69%. IR (neat) ν cm^{-1} 3500–3000. ^1H NMR ($CDCl_3$) δ 1.45–1.80 (m, 4H, H-3 and H-4); 2.50 (m, 1H, H-2); 3.30–3.80 (m, 6H, 3×CH_2O); 4.00 (m, 1H, C*H*Ph); 4.35 (br s, 4H, 3×OH and NH); 7.10–7.40 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 29.3, 29.9 (C-3, C-4); 55.6 (C-2); 61.2, 62.3 (2×CH_2O); 61.8 (*C*HPh); 66.6 (CH_2O); 127.7, 127.8, 128.6 and 139.5 (C_{ar}).

(2*S*)-[(2-Hydroxy-(1*R*)-phenyl)ethylamino]hexan-1,6-diol (24c). Yield 74%. IR (neat) ν cm^{-1} 3500–3000. ^1H NMR ($CDCl_3$) δ 1.20–1.60 (m, 6H, H-3, H-4, H-5); 2.45 (br s, 4H, 3×OH and NH); 2.60 (m, 1H, H-2); 3.25–3.65 (m, 6H, 3×CH_2O); 3.90 (m, 1H, C*H*Ph); 7.25–7.45 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 22.0, 29.9, 31.8 (C-3, C-4, C-5); 55.8 (C-2); 61.4, 61.6 (2×CH_2O); 61.8 (*C*HPh); 66.9 (CH_2O); 127.3, 127.5, 128.5 and 140.7 (C_{ar}).

General procedure for debenzylation of aminotriols (24). A mixture of aminotriol **24a**, **24b** or **24c** (4 mmol) and catalyst (10% Pd/C, 0.6 equiv. in weight) in methanol (20 mL) was stirred at 50–60°C under dihydrogen (1 atm) until completion of the reaction (monitored by TLC, about 1 h) The catalyst was then removed by filtration through Celite®. The filtrate was concentrated and the oily residue was chromatographed on silica gel (methanol, then methanol/aqueous ammonia solution: 100/3).

(2*S*)-Aminobutan-1,4-diol (20a). The product could be obtained pure by distillation with a Kugelrohr apparatus. Bp 180–200°C (1 mmHg). Yield 71%. $[\alpha]_D^{20}$ +4.1 (*c* 1.85, CH_3CO_2H).[39] Lit.[40a] $[\alpha]_D^{22}$ −2.1 (*c* 2, H_2O),[40b] $[\alpha]_D^{22}$ +6.6 (*c* 1.2, CH_3CO_2H).

(2*S*)-Aminopentan-1,5-diol (20b). The product could be obtained pure by distillation with a Kugelrohr apparatus. Bp 160°C (0.1 mmHg). Lit.[41] 125–135°C (0.05 mmHg). Yield 71%. $[\alpha]_D^{21}$ −1.9 (*c* 1.97, CH_3OH).[39]

(2*S*)-Aminohexan-1,6-diol (20c). The product could be obtained pure by distillation with a Kugelrohr apparatus. Bp 165°C (0.1 mmHg). Lit.[42] 135–145°C (0.1 mmHg). Yield 88%. $[\alpha]_D^{20}$ +14.7 (*c* 1.00, C_2H_5OH). IR (neat) ν cm^{-1} 3300. ^1H NMR ($CDCl_3$) δ 1.20–1.70 (m, 6H, 3×CH_2); 2.85 (m, 1H, H-2); 3.40 (m, 1H, H-1); 3.55–3.65 (m, 3H, H-1, H-6). ^{13}C NMR ($CDCl_3$) δ 23.4 (C-4); 33.6, 34.3 (C-3, C-5); 53.8 (C-2); 62.7, 67.3 (C-1, C-6).

Side-products and other products

Compounds **21** and **22** are obtained when the morpholinone **17a** is subjected to the general procedure used for **17d–i** reduction (H_2, 150 atm, 10% Pd/C, CH_3OH).

4-Hydroxy-3-[((*R*)-methoxycarbonylphenylmethyl)amino]-butanoic acid methyl ester (21). IR (Nujol) ν cm^{-1} 3600–3200 (OH, NH); 1740 (C=O). ^1H NMR ($CDCl_3$) δ 2.48 (d, 2H, *J*=6.4, H-2); 3.02–3.10 (m, 1H, H-3); 3.35–3.45 (m, 1H, H-4); 3.53–3.74 (m, 7H, 2×CH_3 and H-4); 4.51 (s, 1H, C*H*Ph); 7.26–7.31 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 37.4 (C-2); 52.0, 52.8 (2×CH_3); 54.6 (C-3); 63.5 (*C*HPh); 63.7 (C-4); 128.0, 128.7, 129.2 and 138.5 (C_{ar}); 172.9 and 174.2 (2×CO). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found C, 59.71; H, 6.77; N, 4.94.

(*R*)-[(5-Oxo-tetrahydrofuran-3*S*-yl)amino]phenylacetic acid methyl ester (22). IR (neat) ν cm^{-1} 3310 (NH); 1770 (C=O lactone); 1730 (C=O ester). ^1H NMR ($CDCl_3$) δ 2.33 (dd, 1H, *J*=5.1 and 17.3, C*H*HCO); 2.26–2.34 (br s, 1H, NH); 2.57 (dd, 1H, *J*=7.1 and 17.3, CH*H*CO); 3.53–3.67 (m, 1H, NC*H*CH_2O); 3.72 (s, 3H, CH_3); 4.13 (dd, 1H, *J*=4.3 and 9.5, CH*H*O); 4.36 (dd, 1H, *J*=5.8 and 9.5, C*H*HO); 4.40 (s, 1H, NC*H*Ph); 7.35–7.38 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 36.4 (*C*H_2CO); 52.7 (N*C*HCH_2O); 53.2 (CH_3); 63.8 (N*C*HPh); 73.6 (CH_2O); 128.0, 129.2, 129.6 and 137.8 (C_{ar}); 173.4 and 176.3 (2×CO). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found C, 62.30; H, 6.10; N, 5.57.

[(2-Methyl-5-oxo-4-phenyl-2,5-dihydrooxazol-2-yl]acetic acid methyl ester (15). To a stirred solution of (*Z*)-[(6-oxo-5*R*-phenyl)morpholin-3-yliden]acetic acid methyl ester **7a** (6.09 mmol) in toluene (40 mL), 0.16 g (6.67 mmol, 1.1 equiv.) of sodium hydride was added portionwise. The mixture was refluxed for 4 h. After cooling to room temperature, water (50 mL) and dichloromethane (100 mL) were added. The mixture was then neutralised by addition of an aqueous solution of hydrochloric acid. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulphate and the oily residue was chromatographed on silica gel (cyclohexane/ethylacetate: 3/1) to give 0.54 g of **15** as a colourless oil. Yield 36%. IR (neat) ν cm^{-1} 1780 and 1740 (C=O); 1620 (C=N). ^1H NMR ($CDCl_3$) δ 1.77 (s, 3H, CH_3); 3.00 (d, 1H, *J*=16.3, C*H*HCO); 3.08 (d, 1H, *J*=16.3, CH*H*CO); 3.64 (s, 3H, CH_3O); 7.50–7.56 (m, 3H, H_{ar}); 8.36–8.40 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 26.1 (CH_3); 41.6 (*C*H_2CO); 52.4 (CH_3O); 102.3 (C-2); 129.0, 129.2, 129.3 and 133.1 (C_{ar}); 157.8, 164.8 and 168.6 (2×CO and C-4). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found C, 63.25; H, 5.32; N, 5.52.

2-(*R*,*S*)-Methyl-3-oxo-4-[(*R*)-(phenyl)(phenylmethoxycarbonylamino)acetoxy]butyric acid methyl ester (16). To a stirred solution of 5 mmol of 3-oxo-4-[(*R*)-(phenyl)-(phenylmethoxycarbonylamino)acetoxy]butyric acid methyl ester **10a** in 20 mL of freshly distilled acetone, 1.38 g of anhydrous solid potassium carbonate (10 mmol; 2.0 equiv.) were added. The mixture was stirred for 30 min at room temperature (a reddish colour appeared) and 0.35 mL of iodomethane (5.6 mmol; 1.1 equiv.) was then added. The mixture was stirred at room temperature until complete consumption of starting material (monitored by TLC, about 1 day) then concentrated under reduced pressure. The dark residue was dissolved in 40 mL of dichloromethane. The solution was washed with water until neutrality. The organic layer was dried over anhydrous sodium sulphate, concentrated and the residue was chromatographed on silica gel (cyclohexane/ethylacetate: 8/2) to give 0.37 g of **16** (as an equimolecular mixture of diastereoisomers) as a colourless oil. Yield 18%. IR ($CHBr_3$) ν cm^{-1} 3420–3320 (NH); 1750–1720 (C=O). ^1H NMR ($CDCl_3$) δ 1.32 and 1.33 (2d, 3H, *J*=7.1, CH_3); 3.48–3.61 (m, 1H, H-2); 3.67 and 3.71 (2s, 3H, CH_3O); 4.85 (d, 2H, *J*=17.3, O*C*H_2CO); 5.12 (d, 2H, *J*=12.5, O*C*H_2Ph); 5.50 (br d, 1H, *J*=7.4, CHN); 5.75 and 5.80 (2 br d, 1H, *J*=7.4, NH); 7.35–7.41 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ 12.8 (CH_3); 49.8 (C-2); 53.3 (CH_3O); 58.6 (N*C*HPh); 67.9 (O*C*H_2Ph); 68.7 (O*C*H_2CO); 128.1, 128.8, 129.2, 129.7 and 136.7 (C_{ar}); 156.1 (NCOO); 170.7 (2×COO); 199.4 (CO). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found C, 63.91; H, 5.74; N, 3.40.

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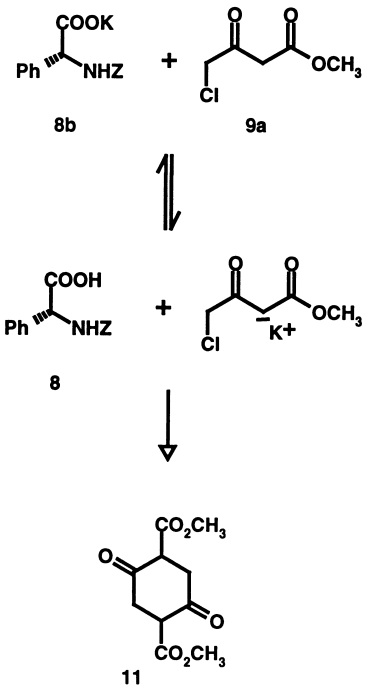
16. Unreacted aminoacid **8** and side product **11** were always isolated from the crude materials. The side product **11** may arise from the following acido-basic equilibrium followed by anionic condensation:



17. The *Z*-isomer of **7a** is only formed as it is highly stabilised by an intramolecular hydrogen bond between the hydrogen on the nitrogen atom and the ester carbonyl group, see Célérier, J. P.; Deloisy-Marchalant, E.; Lhommet, G. *J. Heterocycl. Chem.* **1633**, *21*, 1984.
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19. Unlike enaminoester **7a** only the *E*-isomer of **14** is formed. This structure was elucidated by ^{1}H NMR.
20. If the alkylating agent was not added, the dihydro oxazole **15** was isolated in 36% yield after chromatography. In prolonged reflux of toluene (without sodium hydride) or at room temperature with sodium hydride, the dihydro oxazole **15** was not formed, the enaminoester **7a** was entirely recovered.
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