Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 629–646

TETRAHEDRON: *ASYMMETRY*

Totally stereocontrolled synthesis of α,β-diamino acids by addition of Grignard reagents to nitrones derived from L-serine

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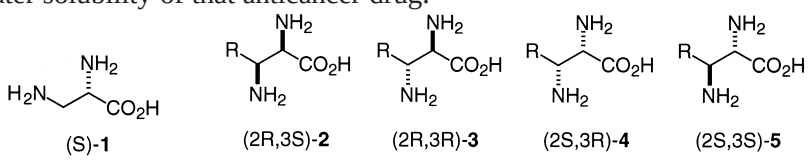
Received 11 December 1997; accepted 30 December 1997

Abstract

The asymmetric synthesis of protected (2R,3S)- and (2R,3R)-3-substituted 2,3-α-amino acids is reported. The key step in the synthesis of these compounds is the diastereoselective addition of Grignard reagents to α-amino nitrones derived from L-serine. Total stereocontrol of the addition step is achieved by changing the protecting groups in the starting material. The predominant selectivity in each case can be reasonably interpreted in terms of steric effects of the substituents.

1. Introduction

Optically active α,β-diamino acids **1**–**5** are an important class of compounds due to their presence in a variety of antibiotics and other natural products of importance.[1] In particular, 2,3-diaminopropanoic acid **1** occurs in nature both in its free form and as a constituent of cyclic peptides such as viomycin, capreomycins and tuberactinomycins with antibiotic activity.[2] Similarly, 2,3-diaminobutanoic acids **2a** and **3a** can be found in a variety of peptide antibiotics such as antrimycins, lavendomycin, amphomycin, aspartocin and glumamycin.[1a,b] (2S,3R)-2,3-Diamino-4-phenylbutanoic acid **4b** is the non-leucine part of the aminodeoxybestatin, an AP-M inhibitor equipotent to the known bestatin.[3] More recently, 2,3-diamino-3-phenylpropanoic acid **2c** has been revealed as an alternative to the side chain of Taxol for improving the water solubility of that anticancer drug.[4]



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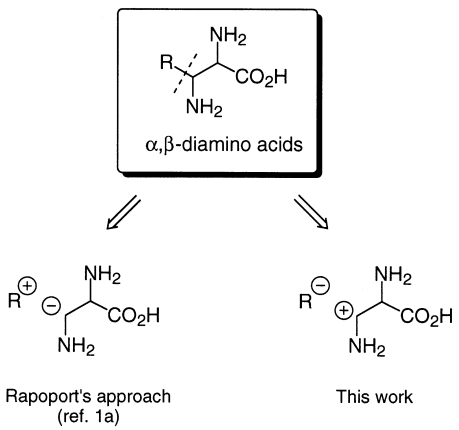
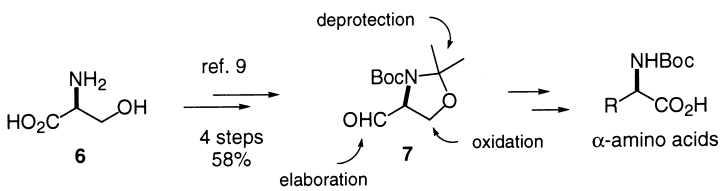
0957-4166/98/$19.00
PII: S0957-4166(98)00004-4

Because of the biological importance of the α,β-diamino acids, much effort has been directed toward their stereoselective synthesis. Specifically, synthetic approaches have been reported for preparing 2,3-diaminopropanoic[5] and 2,3-diaminobutanoic[1b,6] acids as well as other 2,3-diaminoalkanoic acids.[1a,3a,4,7] However, among these synthetic procedures it is difficult to find an approach of general applicability. This problem was pointed out by Rapoport and co-workers[1a] and prompted them to develop a general methodology for the stereoselective synthesis of 3-substituted 2,3-diamino acids via alkylation of an aspartic acid derivative. The Rapoport-type aspartate alkylation consisted of the incorporation of the C-3 substituent as a positive synthon (a halide was used as a suitable synthetic equivalent). We wish to report now[8] a complementary route to 3-substituted 2,3-diamino acids in which the incorporation of the C-3 substituent is made from a negative synthon, a Grignard derivative being the corresponding synthetic equivalent (Scheme 1).



Scheme 1.

As a source of the amino acid unit we chose L-serine **6**. Garner and Park had described the L-serine derived aminoaldehyde **7** as an equivalent of penaldic acid.[9] The use of **7** as a suitable starting material in the construction of complex amino acids by applying that equivalence has been well-demonstrated by several authors (Scheme 2).[9,10]



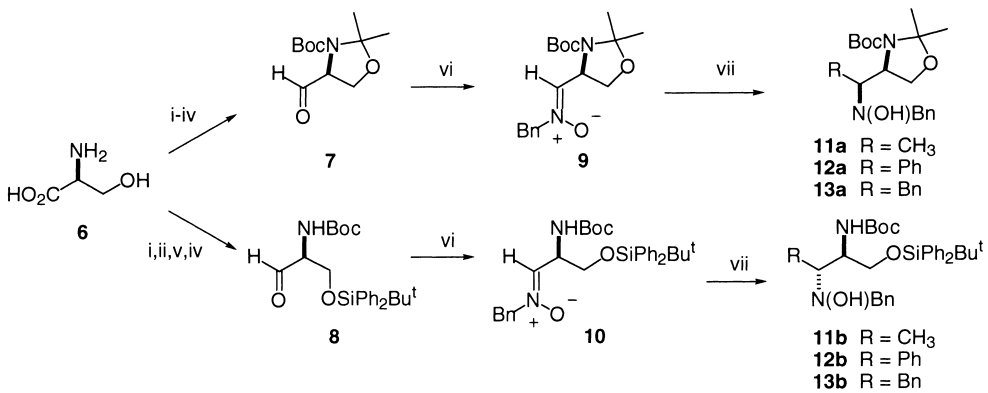
Scheme 2.

The introduction of the second nitrogen atom is made by using differentially N-protected α-amino nitrones, obtained from L-serine **6**, as key intermediates. We have experimented with the use of nitrones as electrophiles in nucleophilic additions in which a total stereocontrol of the process can be raised;[11] moreover, in the particular case of α-amino nitrones derived from L-serine, recent results obtained in our laboratory[8,12] indicated a tunable diastereofacial selectivity depending on the protecting groups arrangement of the starting nitrone. So, in addition to a general applicability, our approach allows the control of the stereochemical course of the reaction thus having access to both (2R,3S)- and (2R,3R)-3-substituted α,β-diamino acids. Also, since D-serine is available commercially the methodology described herein constitutes a formal synthesis of (2S,3R)- and (2S,3S)-α,β-diamino acids.

2. Results and discussion

α-Amino aldehydes **7** and **8** were prepared from L-serine as described.[13] The carbonyl functionality was changed to nitrone by a condensation reaction with N-benzylhydroxylamine[14] following our previously reported procedure.[15] Nitrones **8** and **9** were crystalline stable compounds and showed a Z-configuration as demonstrated by NOE experiments which established that the azomethine proton and the benzyl group were on the same side of the nitrone function.

The reaction between an excess (3.0 equivalents) of Grignard reagent and nitrones **7** and **8** took place smoothly at −50°C in THF as a solvent to give the corresponding hydroxylamines **11**–**13** (Scheme 3), which could be isolated by column chromatography. The results of these experiments are collected in Table 1.



Reagents and conditions: i, Boc_2O, dioxane, NaOH, 0 °C to r.t. ii, MeI, DMF, K_2CO_3, 0 °C to r.t. iii, DMP, p-TosOH, C_6H_6, reflux. iv, DIBALH, CH_2Cl_2, -78 °C. v, $^tBuPh_2SiCl$, DMF, imidazole, r.t. vi, $PhCH_2NHOH$, $MgSO_4$, CH_2Cl_2, r.t. vii, RMgX (3.0 equiv.), THF, -50 °C.

Scheme 3.

Extremely high syn selectivity was observed for the addition to the N,N-diprotected nitrone **9** (entries 1–3). On the other hand, the diastereoselectivity changed to anti when the addition was carried out to the N-monoprotected α-amino nitrone **10** (entries 4–6). In all cases the chemical yields of the obtained N-benzylhydroxylamines **11**–**13** were excellent. Neither the presence of Lewis acids[16] nor changing the solvent affected the stereochemical course of the reaction. This behaviour was not surprising since the same effect had already been observed by us upon the addition of metalated heterocycles such as

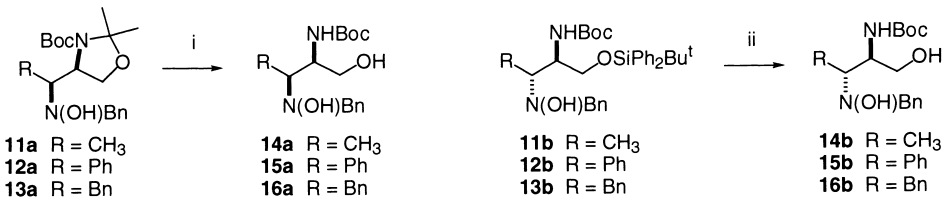
Table 1
Stereoselective addition of Grignard reagents to nitrones **9** and **10**[a]

entry	nitrone	R-MgBr[b]	hydroxylamine	*syn* : *anti*[c]	yield[d] (%)
1	**9**	MeMgBr	**11a**	≥95 : 5	88
2	**9**	PhMgBr	**12a**	≥95 : 5	91
3	**9**	BnMgBr	**13a**	≥95 : 5	88
4	**10**	MeMgBr	**11b**	9 : 91	90
5	**10**	PhMgBr	**12b**	11 : 89	87
6	**10**	BnMgBr	**13b**	8 : 92	91

[a] All reactions were carried out in THF at -50 °C. [b] 3.0 equiv. were added. [c] Measured from the intensities of ^1H NMR signals. [d] determined on isolated mixture

2-lithiothiazole[12b] and 2-lithiofuran.[17] Thus, the stereodivergency achieved by means of the different N-protection of α-amino nitrones **9** and **10** seems to become now a general applicability.[18]

The absolute configuration of the newly formed stereogenic carbons was not determined immediately. However, that a complete reversal of the selectivity had occurred was promptly confirmed by deprotecting hydroxylamines **11**–**13** to the corresponding primary alcohols **14**–**16** (Scheme 4). The physical and spectroscopic properties of compounds **14a**–**16a** were clearly different to those of their epimers **14b**–**16b**.



Reagents and conditions: i, p-TosOH, MeOH, reflux. ii, Bu_4NF, THF, r.t.

Scheme 4.

The absolute configuration of hydroxylamines **12a** and **12b** was determined by chiroptical methods.[19] For that purpose the CD spectra of compounds **15a** and **15b** were recorded (Fig. 1). According to the Smith's sector rule for the benzene chromophore,[20] the observed positive Cotton effect in the range 250–270 nm for **15a** (Fig. 1) is consistent with the (S)-configuration in the asymmetric center bearing the phenyl group. As expected, the epimeric compound **15b** showed a negative Cotton effect in the same range of wavelength corresponding to an (R)-configuration.

These results are in excellent agreement with those reported by us for other phenylmethyl hydroxylamines,[15] thus confirming the validity of the circular dichroic method for the stereochemical assignment of N-benzyl hydroxylamines α-phenyl substituted.[21]

The configurational assignments of hydroxylamines **11** and **13** was made on the basis of our previous observations about the conformational preferences of β-(tert-butoxycarbonylamino) hydroxylamines.[15] According to these observations, an intramolecular hydrogen bond interaction between the hydrogen atom of the hydroxylamino group and the carbonyl oxygen of the tert-butoxycarbonylamino group fixes the two nitrogenated functionalities to be in a gauche conformation.[22] As a consequence, the relative syn–anti stereochemistry can be determined by the chemical shift at ^{13}C of the carbon atom in the β-position of the hydroxylamino functionality, the δ of the syn isomer always being lower than the anti one.

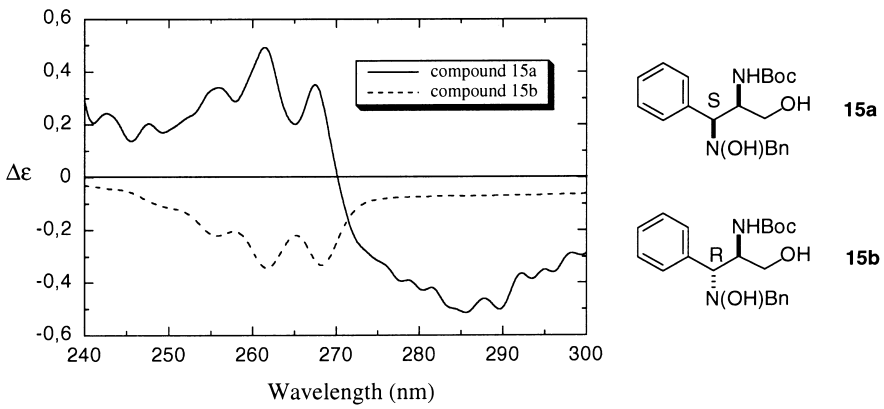
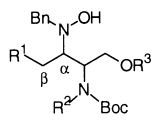


Fig. 1. CD spectra of compounds **15a** and **15b**

Table 2
Selected NMR data of hydroxylamines

	syn adducts[a] ($\delta_{C\beta}$)[b]	anti adducts[a] ($\delta_{C\beta}$)[b]
11	8.4	9.6
13	29.6	36.0
14	8.5	10.0
16	29.7	35.7

[a] syn and anti compounds are referred by **a** and **b** series, respectively. [b] data in ppm.



11a R^1 = Me; R^2,R^3 = CMe_2
11b R^1 = Me; R^2 = H; R^3 = TBDPS
13a R^1 = Ph; R^2,R^3 = CMe_2
13b R^1 = Ph; R^2 = H; R^3 = TBDPS
14a,b R^1 = Me; R^2 = R^3 = H
16a,b R^1 = Ph; R^2 = R^3 = H

The same relationship was found in the corresponding deprotected compounds **14** and **16** thus confirming the above-mentioned empirical rule (Table 2).

Moreover, definitive stereochemical assignments to the obtained hydroxylamines **11a** and **11b** were made on the basis of characteristic spectroscopic data and comparisons of further derivatives reported earlier (see below).

2.1. Mechanistic considerations

The asymmetric induction exerted by the N,N-diprotection in the nucleophilic additions of Grignard reagents to the nitrone **7** can be assumed to proceed by a model similar to the one proposed by Houk[23] for the nucleophilic additions to double bonds. In fact, the corresponding conformer that leads to such a model has been proved to be the more stable in the case of other N,N-disubstituted α-amino nitrones.[15] Accordingly, the addition process takes place preferentially on the less-hindered *si*-face of the nitrone as illustrated in model **A** (Fig. 2).

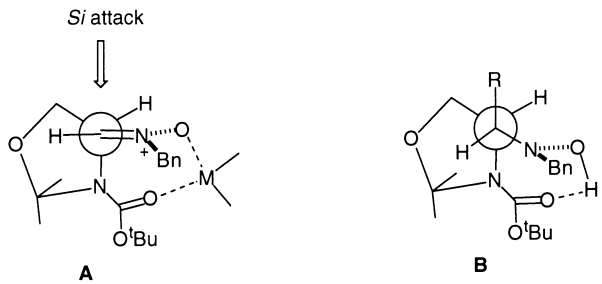


Fig. 2. Models of addition for nitrone **7**

Further support for this model arises from considering nucleophilic additions to nitrones to proceed via a product-like transition state. In this context, the X-ray structural analyses of several hydroxylamines having a tert-butoxycarbonylamino group in the α-position have shown that conformation **B** (Fig. 2) is involved in all cases studied.[24] Coordination either by the reagent or by a Lewis acid would not change the general picture as can be inferred by the presence of an intramolecular hydrogen bond in **B**. That interaction illustrates the possibility of a chelation between the nitrogen oxygen and the carbonyl group of the carbamate.[25] Conformational studies of both **A** and **B** have also been carried out by using the MOPAC (AM1) program[26] and they showed those conformations to be minima of energy. Nevertheless, the relative energies between conformers are quite close and no precise conclusions can be extracted.[27]

More intriguing appears to be the facial diastereoselectivity on varying the nature of the O-protecting group. However, some consideration concerning the tert-butyldiphenylsiloxy group allows rationalization of the anti selectivity observed with the N-monoprotected nitrone **8**. Since it is not easy, for nitrone **8**,

to decide which is the group (NHBoc or $CH_2OSiPh_2{}^tBu$) that can be considered as the larger one, two conformers **C** and **D** (Fig. 3) are considered, in principle, as possible transition state models for the reaction.

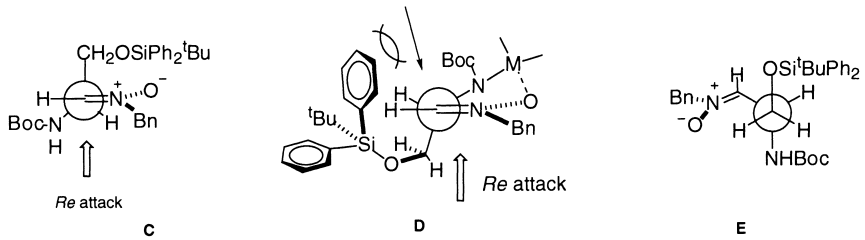
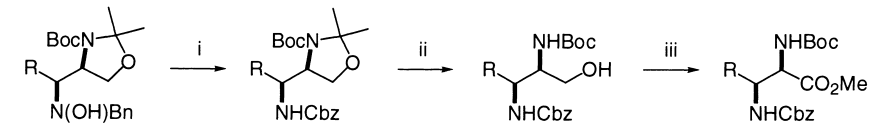


Fig. 3. Models for addition to nitrone **8**

In the absence of any chelating agent, it is possible to assume model **C** as we have proposed for the addition of lithiated heterocycles.[12b] However, model **D** becomes a more plausible explanation if we consider the possibility of chelation with the Grignard reagent in a similar way to that proposed by us for other N-monoprotected α-amino nitrones.[15] In such a case it becomes necessary to consider the relative position of the tert-butyldiphenylsiloxy group, too. In this respect, semiempirical calculations (AM1) for model **D** showed the alternative conformation depicted in Fig. 3 (model **E**) as the most stable.[27] According to this result, the tert-butyldiphenylsiloxy group is placed in such a way that the *si* face is completely hindered (Fig. 3, **D**) and, as a consequence, a *re* attack remains the only possibility for model **D**.

2.2. Synthesis of 2,3-diamino acids

Having a stereodivergent route to syn- and anti-N-benzylhydroxylamines in hand we set out to explore the necessary functional and protecting group transformations in order to prepare the targeted 2,3-diamino acids. Starting from hydroxylamines **11a**–**13a** only two transformations were required to provide diamines **17a**–**19a**: (i) reduction of the hydroxylamine functionality, and (ii) N-benzyloxycarbonylation (Scheme 5).



11a R = CH_3 **17a** R = CH_3 **20a** R = CH_3 **23a** R = CH_3
12a R = Ph **18a** R = Ph **21a** R = Ph **24a** R = Ph
13a R = Bn **19a** R = Bn **22a** R = Bn **25a** R = Bn

Reagents and conditions: i, H_2, $Pd(OH)_2$-C, 70 psi, r.t. then CbzCl, $NaHCO_3$ (aq), THF, r.t. ii, p-TosOH (cat.), MeOH, reflux. iii, $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, r.t. then CH_2N_2, Et_2O, 0 °C

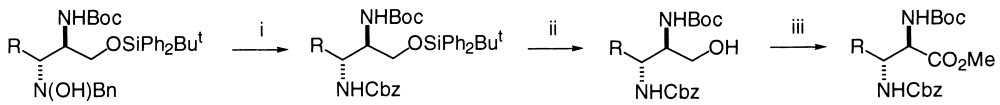
Scheme 5.

Concomitant deoxygenation and debenzylation was achieved by catalytic hydrogenation at 75 psi, using $Pd(OH)_2$ on charcoal as a catalyst and methanol as a solvent. The complete reduction to the corresponding primary amines was shown to be slow and three days were required to obtain a quantitative reaction. The resulting primary amines were then protected as the N-benzyloxycarbonyl derivatives **17a**–**19a** in a high overall yield from **11a**–**13a**, respectively.

The terminal carboxyl group was unmasked in a sequence requiring two steps. Initial cleavage of the acetonide in **17a**–**19a** was accomplished with catalytic p-toluenesulfonic acid in refluxing methanol,

the corresponding aminoalcohols **20a**–**22a** being obtained in excellent yields. For compound **20a** the physical and spectroscopic properties of the obtained compound were compared with those described in the literature[1b] (see Experimental) thus supporting the stereochemical assignment. Further oxidation of **20a**–**22a** to the corresponding carboxylic acids was accomplished with ruthenium trichloride with acetonitrile–carbon tetrachloride–water as cosolvents and added sodium periodate as a reoxidant. Esterification of the carboxylic acids with excess diazomethane provided the methyl esters in good overall yields from **11a**–**13a**.

In a similar way, hydroxylamines **11b**–**13b** were transformed into the corresponding N-(benzyloxycarbonyl) derivatives **17b**–**19b** (Scheme 6). Deprotection of these compounds with tetrabutylammonium fluoride in anhydrous tetrahydrofuran gave anti aminoalcohols **20b**–**22b** which were oxidized as their epimers (see above) to afford the corresponding anti-2,3-diaminoacids. Also in the case of the methyl derivative **20b** the physical and spectroscopic properties of the obtained compound were compared with those described in the literature[1b] (see Experimental). Esterification of the obtained α,β-amino acids with excess diazomethane afforded the corresponding methyl esters **23b**–**25b**.



11b R = CH_3
12b R = Ph
13b R = Bn

17b R = CH_3
18b R = Ph
19b R = Bn

20b R = CH_3
21b R = Ph
22b R = Bn

23b R = CH_3
24b R = Ph
25b R = Bn

Reagents and conditions: i, H_2, $Pd(OH)_2$-C, 70 psi, r.t. then CbzCl, $NaHCO_3$ (aq), THF, r.t. ii, Bu_4NF, THF, r.t. iii, $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, r.t. then CH_2N_2, Et_2O, 0 °C

Scheme 6.

3. Conclusions

An assessment was made of the tunable selectivity by means of protecting groups of the nucleophilic additions to nitrones derived from serine. Whereas the N,N-diprotected α-amino nitrone expressed a high syn selectivity, the N-monoprotected α-amino nitrone showed an anti selectivity. The present reaction was successfully applied to the synthesis of (2S,3R)- and (2S,3S)-2,3-diaminobutanoic acids and (2S,3R)- and (2S,3S)-2,3-diamino-3-phenylpropanoic acids. The use of commercially available serine (both in D- and L- forms) for asymmetric induction provides a practical, useful method for the synthesis of optically active 3-substituted 2,3-diamino acids.

4. Experimental

4.1. General methods

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[28] and were freshly distilled prior to use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300 Varian Unity spectrometer in $CDCl_3$ at room temperature unless otherwise specified. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured using a Perkin–Elmer 214 polarimeter with a thermally jacketed 10 cm cell at 25°C (concentration C given as g/100 mL) and

CD spectra on a Jasco J-710 spectrometer. IR spectra were recorded in chloroform and measured in cm^{-1}, using a Perkin–Elmer 1600 FT-IR infrared spectrophotometer; only representative bands are given. Elemental analyses were performed on a 1106 Microanalyzer Carlo Erba. All reactions were monitored by TLC on silica gel plates (Merck Kiesel gel 60 F254) and visualized by spraying with either 1 M aqueous $KMnO_4$ or a solution of 2,4-dinitrophenylhydrazine in methanolic sulfuric acid and heated. Flash column chromatography was performed on silica gel 60 F254.[29] Methylmagnesium bromide and phenylmagnesium bromide were used in THF from 1.0 M commercial solutions. Benzylmagnesium bromide was prepared from benzyl bromide as described.[30] N-Boc-L-Serinal acetonide **7** and N-Boc-O-(tert-butyldiphenylsilyl)-L-serinal **8** were prepared as described.[13]

*4.2. (Z)-N-[(4R)-3-(tert-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-ylidene]benzylamine N-oxide **9***

To a well-stirred solution of N-Boc-L-serinal acetonide **7** (4.59 g, 20 mmol) in dichloromethane (200 ml), anhydrous magnesium sulfate (3.61 g, 30 mmol) and N-benzylhydroxylamine[14] (2.46 g, 20 mmol) were added sequentially and the resulting mixture was stirred at 20°C for 4 h. The reaction mixture was filtered and the filtrate rotatory evaporated to yield the crude product which was purified by column chromatography on silica gel (hexane:diethyl ether=9:1) to yield the pure nitrone **9** (5.62 g, 84%) as a white solid: mp 57–59°C; $[\alpha]_D$ −46.6 (c 1.8, $CHCl_3$); IR ν 1599 cm^{-1}; ^{1}H NMR (55°C) δ 1.38 (s, 9H), 1.42 (s, 3H), 1.51 (s, 3H), 4.01 (dd, 1H, J=2.5, 9.5 Hz), 4.18 (dd, 1H, J=6.6, 9.5 Hz), 4.81 (s, 2H), 4.92 (ddd, 1H, J=2.5, 4.7, 6.6 Hz), 6.88 (d, 1H, J=4.7 Hz), 7.28–7.36 (m, 5H); ^{13}C NMR (55°C) δ 23.1, 26.4, 28.3, 55.0, 66.4, 69.0, 80.4, 94.4, 128.9, 129.1, 129.2, 132.4, 140.2, 151.5. Anal. calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.53; H, 8.02; N, 9.09.

*4.3. (Z)-N-[(2R)-2-(tert-Butoxycarbonyl)-3-(tert-butyldiphenylsiloxy)propylidene]benzylamine N-oxide **10***

The α-amino aldehyde **8** (8.55 g, 20 mmol) was treated as described above for the preparation of **4**. Column chromatography (hexane:diethyl ether=1:4) of the crude product gave 8.52 g (80%) of **10** as a white solid: mp 110–112°C; $[\alpha]_D$ +2.5 (c 1.70, $CHCl_3$); IR ν 1603; ^{1}H NMR δ 1.02 (s, 9H), 1.39 (s, 9H), 3.93 (dd, 1H, J=5.4, 9.9 Hz), 4.00 (dd, 1H, J=4.7, 9.9 Hz), 4.72 (dddd, 1H, J=4.7, 5.4, 5.8, 8.0 Hz), 4.82 (s, 2H), 5.61 (d, 1H, J=8.0 Hz), 6.74 (d, 1H, J=5.8 Hz), 7.32–7.45 (m, 11H), 7.69–7.82 (m, 4H); ^{13}C NMR δ 19.3, 26.9, 28.4, 50.7, 62.8, 69.8, 79.7, 127.8 (2C), 129.0 (2C), 129.4, 129.9, 132.7, 133.2, 133.3, 135.5 (2C), 135.6, 136.7, 155.3. Anal. calcd for $C_{31}H_{40}N_2SiO_4$: C, 69.89; H, 7.57; N, 5.26. Found: C, 69.72; H, 7.70; N, 5.30.

4.4. Addition of Grignard reagents to nitrones. General procedure

To a cold solution (−50°C) of the corresponding nitrone (5 mmol) in THF (30 ml), a solution of Grignard reagent (15 mmol, 15 ml of a 1.0 M solution in THF) was added under Ar atmosphere. The rate of the addition was adjusted so as to keep the temperature of the mixture below −50°C. The reaction mixture was stirred at −50°C for 2 h, then saturated aqueous ammonium chloride (30 ml) was added, and the mixture was allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was extracted with diethyl ether (2×25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel gave pure hydroxylamines **11**–**13** (eluent is given in brackets for each compound).

4.5. 1,1-Dimethylethyl-(R)-4-[(S)-1-(N-benzylhydroxyamino)ethyl]-2,2-dimethyl-3-oxazolidine-carboxylate ***11a***

1.54 g, 88%; oil; (hexane:diethyl ether=80:20): $[\alpha]_D=-5.9$ (c 0.47, $CHCl_3$); ^1H NMR (55°C) δ 1.12 (d, 3H, J=6.2 Hz), 1.41 (s, 3H), 1.49 (s, 3H), 1.51 (s, 9H), 2.73 (dq, 1H, J=3.5, 6.2 Hz), 3.70 (d, 1H, J=13.7 Hz), 3.76 (dt, 1H, J=3.5, 8.3 Hz), 3.91 (m, 2H), 4.00 (d, 1H, J=13.7 Hz), 6.9 (bs, 1H), 7.10–7.38 (m, 5H); ^{13}C NMR (55°C) δ 8.4, 24.8, 27.3, 28.5, 60.0, 60.5, 61.1, 65.7, 80.7, 93.5, 126.8, 128.0, 128.6, 139.1, 154.4. Anal. calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.24; H, 8.54; N, 7.71.

4.6. (2R,3R)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-1-O-(tert-butyldiphenylsilyl)-1-butanol ***11b***

2.25 g, 82%; oil; (hexane:diethyl ether=90:10): $[\alpha]_D=-1.1$ (c 0.41, $CHCl_3$); ^1H NMR δ 1.07 (s, 9H), 1.13 (d, 3H, J=6.6 Hz), 1.45 (s, 9H), 3.0 (dq, 1H, J=6.0, 6.6 Hz), 3.70 (d, 1H, J=13.5 Hz), 3.75 (dd, 1H, J=5.1, 10.3 Hz), 3.89 (dd, 1H, 4.1, 10.3 Hz), 4.00 (ddd, 1H, J=4.1, 5.1, 6.0 Hz), 4.02 (d, 1H, J=13.6 Hz), 4.87 (d, 1H, J=9.0 Hz), 5.60 (bs, 1H), 7.23–7.50 (m, 11H), 7.67–7.79 (m, 4H); ^{13}C NMR δ 9.6, 19.3, 27.0, 28.5, 54.3, 60.5, 62.2, 63.8, 79.3, 126.9, 127.7, 127.8, 128.2, 128.9, 129.8, 133.3, 133.4, 135.6, 135.7 (2C), 138.8, 156.2. Anal. calcd for $C_{32}H_{44}N_2O_4Si$: C, 70.03; H, 8.08; N, 5.10. Found: C, 70.36; H, 7.86; N, 5.23.

4.7. 1,1-Dimethylethyl-(R)-4-[(S)-(N-benzylhydroxyamino)phenylmethyl]-2,2-dimethyl-3-oxazolidinecarboxylate ***12a***

1.88 g, 91%; oil; (hexane:diethyl ether=80:20): $[\alpha]_D=+10.2$ (c 0.62, $CHCl_3$); ^1H NMR (55°C) δ 1.54 (s, 6H), 1.60 (s, 9H), 3.44 (d, 1H, J=9.1 Hz), 3.61 (dd, 1H, J=1.5, 10.6 Hz), 3.64 (d, 1H, J=13.8 Hz), 3.69 (d, 1H, J=13.8 Hz), 3.77 (ddd, 1H, J=1.5, 5.3, 9.1 Hz), 4.60 (dd, 1H, J=5.3, 10.6 Hz), 7.50–7.13 (m, 9H), 7.60–7.70 (m, 2H); ^{13}C NMR (55°C) δ 16.4, 24.7, 27.6, 58.6, 60.4, 65.7, 70.7, 81.0, 94.1, 126.8, 127.24, 127.9, 128.7, 129.6, 130.7, 135.9, 138.7, 154.6. Anal. calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.74; H, 7.89; N, 6.54.

4.8. (2R,3R)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-1-O-(tert-butyldiphenylsilyl)-3-phenyl-1-propanol ***12b***

2.35 g, 77%; oil; (hexane:diethyl ether=85:15): $[\alpha]_D=-8.7$ (c 0.31, $CHCl_3$); ^1H NMR δ 1.00 (s, 9H), 1.58 (s, 9H), 3.41 (dd, 1H, J=2.2, 10.4 Hz), 3.68 (dd, 1H, J=2.6, 10.4 Hz), 3.70 (s, 2H), 3.83 (d, 1H, J=10.5 Hz), 4.23 (tt, 1H, J=2.4, 10.1 Hz), 5.19 (d, 1H, J=9.7 Hz), 6.8 (s, 1H), 7.26–7.49 (m, 16H), 7.70–7.77 (m, 4H); ^{13}C NMR δ 19.3, 26.9, 28.4, 53.3, 60.4, 63.6, 70.2, 80.0, 127.3, 127.6, 127.8, 127.9, 128.1, 128.5, 129.7, 129.9, 132.7, 132.9, 135.4, 135.5, 135.6, 135.6, 138.8 (2C), 158.2. Anal. calcd for $C_{37}H_{46}N_2O_4Si$: C, 72.75; H, 7.59; N, 4.59. Found: C, 72.84; H, 7.75; N, 4.43.

4.9. 1,1-Dimethylethyl-(R)-4-[(S)-1-(N-benzylhydroxyamino)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate ***13a***

1.88 g, 88%; oil; (hexane:diethyl ether=80:20): $[\alpha]_D=-44.6$ (c 1.94, $CHCl_3$); ^1H NMR (55°C) δ 1.45 (s, 3H), 1.49 (s, 3H), 1.51 (s, 9H), 2.60–2.71 (m, 1H), 3.06–3.12 (m, 1H), 3.60–3.64 (m, 1H), 3.70 (d, 1H, J=13.6 Hz), 3.78–3.88 (m, 2H), 3.99 (d, 1H, J=13.6 Hz), 4.12 (dd, 1H, J=5.8, 9.5 Hz), 6.95 (bs, 1H),

7.28–7.36 (m, 10H); ^{13}C NMR (55°C) δ 24.8, 27.3, 28.5, 29.6, 60.4, 61.2, 65.7, 67.4, 80.8, 93.6, 126.0, 126.4, 127.9, 128.7, 128.8, 129.2, 139.9, 140.1, 154.8. Anal. calcd for $C_{25}H_{34}N_2O_4$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.50; H, 7.89; N, 7.94.

4.10. (2R,3R)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-1-O-(tert-butyldiphenylsilyl)-4-phenyl-1-butanol ***13b***

2.62 g, 84%; oil; (hexane:diethyl ether=90:10): $[\alpha]_D=-35.6$ (c 0.26, $CHCl_3$); ^{1}H NMR (55°C) δ 1.04 (s, 9H), 1.50 (s, 9H), 2.72–2.82 (m, 1H), 3.02–3.11 (m, 1H), 3.49–3.53 (m, 1H), 3.70–3.91 (m, 4H), 4.09 (d, 1H, J=13.5 Hz), 5.20 (bs, 1H), 6.50 (d, 1H, J=9.0 Hz), 7.18–7.39 (m, 16H), 7.46–7.58 (m, 4H); ^{13}C NMR (55°C) δ 19.2, 26.9, 28.5, 36.0, 54.8, 61.6, 63.6, 65.4, 79.3, 127.7 (2C), 128.2, 128.3, 128.4, 128.6, 128.9 (2C), 129.2, 129.7, 130.0, 130.4, 133.3, 135.3, 135.5, 135.6, 156.80. Anal. calcd for $C_{38}H_{48}N_2O_4Si$: C, 73.04; H, 7.74; N, 4.48. Found: C, 73.35; H, 7.66; N, 4.59.

4.11. (2R,3S)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-1-butanol ***14a***

A solution of hydroxylamine **11a** (0.2 g, 0.57 mmol) in MeOH (15 mL) at room temperature was treated with catalytic p-TosOH (4.1 mg, 2% w/w). The resulting solution was warmed to reflux where it was maintained until all starting material disappeared (TLC, 1 h). The mixture was allowed to cool to room temperature, at which time the solvent was removed under reduced pressure. The crude product was then partitioned between CH_2Cl_2 (15 mL) and saturated aqueous $NaHCO_3$ (15 mL), the layers were separated, and the aqueous layer extracted with additional portions of CH_2Cl_2 (3×10 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the crude product on silica gel (hexane:ethyl acetate=80:20) gave 0.168 g (95%) of diaminoalcohol **14a** as a white solid: mp 126–128°C; $[\alpha]_D=-9.2$ (c 1.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O) δ 1.20 (d, 3H, J=6.5 Hz), 1.44 (s, 9H), 2.98 (m, 1H), 3.59 (m, 1H), 3.69 (dd, 1H, J=3.4, 11.3 Hz), 3.71 (d, 1H, J=13.3 Hz), 3.75 (dd, 1H, J=3.6, 11.2 Hz), 3.98 (d, 1H, J=13.3 Hz), 5.40 (d, 1H, J=5.9 Hz), 7.31–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$+D_2O) δ 8.5, 28.4, 55.1, 60.8, 61.1, 64.0, 79.7, 127.2, 128.3, 128.9, 138.0, 157.4. Anal. calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.64; H, 8.17; N, 9.00.

4.12. (2R,3S)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-3-phenyl-1-propanol ***15a***

The hydroxylamine **12a** (0.2 g, 0.48 mmol) was treated as described above for the preparation of **14a**. Column chromatography on silica gel (hexane:ethyl acetate=80:20) of the crude product gave 0.172 g (96%) of **15a** as a sticky foam: $[\alpha]_D=-9.6$ (c 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O) δ 1.50 (s, 9H), 3.30 (dd, 1H, J=3.5, 10.9 Hz), 3.58 (dd, 1H, J=3.2, 10.9 Hz), 3.59 (d, 1H, J=13.4 Hz), 3.61 (d, 1H, J=13.4 Hz), 3.65 (d, 1H, J=10.3 Hz), 4.21 (dddd, 1H, J=3.2, 3.5, 9.3, 10.3 Hz), 5.29 (d, 1H, J=9.3 Hz), 7.28–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$+D_2O) δ 28.5, 53.4, 60.6, 62.5, 70.8, 80.14, 126.8, 127.9, 128.0, 128.3, 128.5, 130.1, 135.9, 138.6, 158.1. Anal. calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.49; H, 7.52; N, 7.41.

4.13. (2R,3S)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-4-phenyl-1-butanol ***16a***

The hydroxylamine **13a** (0.2 g, 0.47 mmol) was treated as described above for the preparation of **14a**. Column chromatography on silica gel (hexane:ethyl acetate=85:15) of the crude product gave 0.171 g (94%) of **16a** as an oil: $[\alpha]_D$ −24.9 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O) δ 1.45 (s, 9H), 2.90 (dd,

1H, J=9.5, 13.8 Hz), 3.11 (dd, 1H, J=4.0, 13.8 Hz), 3.29 (m, 1H), 3.50 (m, 2H), 3.71 (m, 1H), 3.95 (d, 1H, J=12.8 Hz), 4.12 (d, 1H, J=12.8 Hz), 5.84 (d, 1H, J=7.5 Hz), 7.19–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$+D_2O) δ 28.4, 29.7, 52.3, 62.0, 65.0, 67.5, 79.4, 126.3, 127.7, 128.6, 128.7, 129.1, 129.2, 136.8, 139.4, 156.5. Anal. calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.26; H, 7.90; N, 7.41.

*4.14. (2R,3R)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-1-butanol **14b***

A solution of hydroxylamine **11b** (0.3 g, 0.55 mmol) in THF (20 mL) at ambient temperature was treated with 0.7 mL (0.7 mmol) of a 1.0 M solution of Bu_4NF in anhydrous THF. After 2 h the reaction was quenched by the addition of saturated $NaHCO_3$, and the resulting mixture partitioned between Et_2O (20 mL) and H_2O (30 mL). The layers were separated, and the aqueous solution was extracted with Et_2O (3×20 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting oil was chromatographed on silica gel (hexane:ethyl acetate=80:20) to afford diamino alcohol **14b** (0.154 g, 90%) as a sticky oil: $[\alpha]_D$=−49.8 (c 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O) δ 1.40 (s, 9H), 1.55 (d, 3H, J=6.9 Hz), 3.70 (m, 3H), 4.18 (d, 1H, J=11.9 Hz), 4.66 (m, 1H), 5.25 (d, 1H, J=11.9 Hz), 5.56 (d, 1H, J=6.8 Hz), 7.45–7.53 (m, 5H); ^{13}C NMR ($CDCl_3$+D_2O) δ 10.0, 28.3, 54.8, 56.8, 60.7, 62.4, 79.5, 127.3, 128.2, 128.9, 137.6, 155.0. Anal. calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.96; H, 8.64; N, 9.27.

*4.15. (2R,3R)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-3-phenyl-1-propanol **15b***

The hydroxylamine **12b** (0.3 g, 0.49 mmol) was treated as described above for the preparation of **14b**. Column chromatography on silica gel (hexane:ethyl acetate=80:20) of the crude product gave 0.157 g (86%) of **15b** as an oil: $[\alpha]_D$=−14.3 (c 0.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O) δ 1.42 (s, 9H), 3.54 (dd, 1H, J=5.8, 10.8 Hz), 3.75 (s, 2H), 3.90 (dd, 1H, J=1.8, 10.8 Hz), 4.32 (dddd, 1H, J=1.8, 5.8, 6.6, 8.1 Hz), 5.51 (d, 1H, J=6.6 Hz), 6.08 (d, 1H, J=8.1 Hz), 7.30–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$+D_2O) δ 28.2, 54.7, 55.4, 58.9, 62.7, 80.0, 127.3, 127.6, 128.5, 128.7, 129.0, 129.5, 130.0, 139.9, 156.5. Anal. calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.70; H, 7.35; N, 7.32.

*4.16. (2R,3R)-3-(N-Benzylhydroxyamino)-2-(tert-butoxycarbonylamino)-4-phenyl-1-butanol **16b***

The hydroxylamine **13b** (0.3 g, 0.48 mmol) was treated as described above for the preparation of **14b**. Column chromatography on silica gel (hexane:ethyl acetate=85:15) of the crude product gave 0.163 g (88%) of **16b** as an oil: $[\alpha]_D$ −48.5 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O) δ 1.44 (s, 9H), 3.10 (dd, 1H, J=4.6, 13.8 Hz), 3.61 (dd, 1H, J=6.3, 10.9 Hz), 3.74 (m, 2H), 3.81 (m, 1H), 3.88 (d, 1H, J=12.9 Hz), 4.10 (d, 1H, J=12.9 Hz), 6.00 (d, 1H, J=7.0 Hz), 7.29–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$+D_2O) δ 28.3, 35.7, 54.1, 62.5, 69.3, 75.5, 79.7, 126.9, 128.4, 128.9, 129.2, 129.6, 130.7, 136.9, 138.8, 156.4. Anal. calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 8.03; N, 7.19.

*4.17. 1,1-Dimethylethyl-(R)-4-[(S)-1-(benzyloxycarbonylamino)ethyl]-2,2-dimethyl-3-oxazolidine-carboxylate **17a***

A mixture of the hydroxylamine **11a** (0.175 g, 0.5 mmol) and 20% palladium hydroxide on activated charcoal (Pearlman's catalyst) (10 mg) in MeOH (8 mL) was degassed under vacuum and saturated with hydrogen three times. The resulting suspension was stirred in a Parr hydrogenation apparatus at ambient temperature for 3 days under 70 psi, then filtered through a plug of Celite, and concentrated.

The residue containing the crude primary amine was taken up in 1,4-dioxane (8 mL) and treated with 7% aqueous sodium bicarbonate (3 mL). The resulting solution was stirred at 0°C for 10 min and then treated with benzyl chloroformate (0.1 mL, 0.70 mmol). After the reaction had been stirred at 0°C for 20 min, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (hexane:diethyl ether=70:30) to afford 0.159 g (84%) of pure **17a** as a colourless oil: $[\alpha]_D=-4.3$ (c 0.72, MeOH); ^{1}H NMR (55°C) δ 1.10 (d, 3H, J=6.3 Hz), 1.45 (s, 3H), 1.46 (s, 9H), 1.52 (s, 3H), 3.60–3.72 (m, 1H), 3.81–4.02 (m, 3H), 5.03 (d, 1H, J=12.4 Hz), 5.07 (d, 1H, J=12.4 Hz), 5.80 (bs, 1H), 7.22–7.31 (m, 5H); ^{13}C NMR (55°C) δ 18.9, 24.0, 27.1, 28.0, 50.6, 60.7, 66.0, 66.4, 80.7, 93.7, 126.7, 127.1, 128.2, 136.6, 154.1, 156.1. Anal. calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.51; H, 7.89; N, 7.73.

*4.18. 1,1-Dimethylethyl-(R)-4-[(S)-(benzyloxycarbonylamino)phenylmethyl]-2,2-dimethyl-3-oxazolidinecarboxylate **18a***

The hydroxylamine **12a** (0.2 g, 0.48 mmol) was treated as described above for the preparation of **17a**. Column chromatography on silica gel (hexane:diethyl ether=75:25) of the crude product gave 0.182 g (86%) of **18a** as a yellowish oil: $[\alpha]_D=+32.7$ (c 1.89, $CHCl_3$); ^{1}H NMR (55°C) δ 1.43 (s, 3H), 1.51 (s, 9H), 1.54 (s, 3H), 3.62–3.79 (m, 2H), 4.28 (dd, 1H, J=5.3, 10.7 Hz), 4.74 (dd, 1H, J=7.7, 10.7 Hz), 4.90 (d, 1H, J=12.5 Hz), 5.09 (d, 1H, J=12.5 Hz), 6.80 (d, 1H, J=8.4 Hz), 7.25–7.35 (m, 10H); ^{13}C NMR (55°C) δ 24.2, 27.6, 28.2, 60.1, 60.6, 65.1, 66.2, 81.3, 94.4, 127.5, 127.7, 127.8, 127.9, 128.3, 128.8, 136.9, 140.7, 154.9, 156.2. Anal. calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 67.89; H, 7.60; N, 6.04.

*4.19. 1,1-Dimethylethyl-(R)-4-[(S)-1-(benzyloxycarbonylamino)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate **19a***

The hydroxylamine **13a** (0.19 g, 0.45 mmol) was treated as described above for the preparation of **17a**. Column chromatography on silica gel (hexane:diethyl ether=70:30) of the crude product gave 0.168 g (82%) of **19a** as an oil: $[\alpha]_D=-16.6$ (c 1.12, $CHCl_3$); ^{1}H NMR (55°C) δ 1.44 (s, 3H), 1.46 (s, 9H), 1.48 (s, 3H), 2.72 (dd, 1H, J=6.2, 14.6 Hz), 2.91 (dd, 1H, J=4.4, 14.6 Hz), 3.62–3.73 (m, 1H), 3.80 (dd, 1H, J=7.0, 8.6 Hz), 3.94 (dd, 1H, J=5.5, 8.6 Hz), 4.10–4.21 (m, 1H), 5.00 (s, 2H), 7.01 (d, 1H, J=7.9 Hz), 7.29–7.46 (m, 10H); ^{13}C NMR (55°C) δ 27.8, 28.1, 28.2, 38.8, 65.3, 65.7, 66.3, 66.4, 80.7, 94.3, 127.6, 128.3, 128.7, 128.8, 129.2, 129.4, 137.2, 137.4, 156.1, 156.8. Anal. calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.92; H, 7.45; N, 6.29.

*4.20. (2R,3S)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-1-butanol **20a***

The compound **17a** (0.15 g, 0.4 mmol) was treated as described above for the preparation of **14a**. Column chromatography on silica gel (hexane:diethyl ether=60:40) of the crude product gave 0.118 g (88%) of **20a** as a white solid: mp 110–112°C; $[\alpha]_D=-26.8$ (c 1.32, MeOH) [lit.[1b] $[\alpha]_D=-25.4$ (c 1.60, MeOH)]; ^{1}H NMR δ 1.35 (d, 3H, J=7.1 Hz), 1.40 (s, 9H), 1.84 (bs, 1H), 3.48–3.50 (m, 1H), 3.51–3.54 (m, 2H), 3.90–4.02 (m, 1H), 4.90 (bs, 1H), 5.10 (s, 2H), 5.71 (bs, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR δ 18.5, 28.3, 47.6, 56.6, 62.6, 67.1, 79.9, 127.6, 128.2, 128.5, 136.4, 156.5, 157.2. Anal. calcd for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.20; H, 7.59; N, 8.37.

4.21. (2R,3S)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-3-phenyl-1-propanol ***21a***

The compound **18a** (0.16 g, 0.36 mmol) was treated as described above for the preparation of **14a**. Column chromatography on silica gel (hexane:diethyl ether=65:35) of the crude product gave 0.123 g (85%) of **21a** as a white solid: mp 132–134°C; $[\alpha]_D$=+17.2 (c 1.85, $CHCl_3$); ^{1}H NMR (55°C) δ 1.41 (s, 9H), 2.88 (bs, 1H), 3.35–3.50 (m, 2H), 3.82–3.99 (m, 1H), 4.82–4.86 (m, 1H), 5.00 (d, 1H, J=12.5 Hz), 5.10 (d, 1H, J=12.5 Hz), 5.41 (d, 1H, J=8.1 Hz), 6.06 (d, 1H, J=7.8 Hz), 7.23–7.40 (m, 10H); ^{13}C NMR (55°C) δ 28.3, 56.0, 57.3, 61.7, 66.8, 80.0, 127.2, 128.0, 128.4 (2C), 128.8 (2C), 136.3, 139.8, 156.7, 157.2. Anal. calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.90; H, 7.12; N, 7.15.

4.22. (2R,3S)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-4-phenyl-1-butanol ***22a***

The compound **19a** (0.14 g, 0.31 mmol) was treated as described above for the preparation of **14a**. Column chromatography on silica gel (hexane:diethyl ether=60:40) of the crude product gave 0.110 g (86%) of **22a** as a yellow oil: $[\alpha]_D$=−41.3 (c 0.75, $CHCl_3$); ^{1}H NMR (55°C) δ 1.44 (s, 9H), 2.60 (bs, 1H), 2.75 (dd, 1H, J=5.7, 16.2 Hz), 2.96 (dd, 1H, J=4.8, 16.2 Hz), 3.40–3.51 (m, 1H), 3.60 (dd, 1H, J=3.9, 8.1 Hz), 3.71–3.80 (m, 1H), 4.11–4.19 (m, 1H), 4.90 (bs, 1H), 5.00 (s, 2H), 5.61 (bs, 1H), 7.19–7.30 (m, 10H); ^{13}C NMR (55°C) δ 28.3, 38.6, 54.8, 62.2, 62.8, 67.0, 79.9, 126.7, 127.8, 128.1, 128.4, 128.6, 129.0, 136.2, 136.4, 156.1, 157.3. Anal. calcd for $C_{23}H_{30}N_2O_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.60; H, 7.42; N, 6.70.

4.23. Methyl (2R,3S)-3-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino) butanoate ***23a***

To a well-stirred mixture of CH_3CN (1.3 mL), CCl_4 (1.3 mL) and H_2O (2 mL) were added $NaIO_4$ (0.265 g, 1.24 mmol) and $RuCl_3 \cdot H_2O$ (9.7 mg, 0.043 mmol) sequentially. The resulting yellowish mixture was allowed to stir for 30 min, at which time it was poured into a flask containing pure **20a** (0.254 g, 0.75 mmol). The resulting mixture turned black and additional $NaIO_4$ (0.133 mg, 0.62 mmol) was added. After 5 min the reaction mixture was partitioned between ethyl acetate (25 mL) and water (25 mL), the layers were separated, and the aqueous layer was extracted with additional portions of ethyl acetate (5×10 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered through a short plug of Florisil, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid. This crude material was dissolved in Et_2O and treated with an ethereal solution of diazomethane to give, after purification by column chromatography on silica gel (hexane:diethyl ether=80:20) the ester **23a** (0.220 g, 80%) as a colourless oil: $[\alpha]_D$=−26.3 (c 0.56, $CHCl_3$); ^{1}H NMR δ 1.9 (d, 3H, J=6.6 Hz), 1.42 (s, 9H), 3.72 (s, 3H), 4.19 (ddq, 1H, J=4.1, 6.6, 9.1 Hz), 4.30 (dd, 1H, J=4.1, 8.4 Hz), 4.81 (d, 1H, J=8.4 Hz), 5.06 (s, 2H), 5.20 (d, 1H, J=9.1 Hz), 7.30–7.40 (m, 5H); ^{13}C NMR δ 18.4, 28.2, 49.5, 52.2, 57.5, 67.0, 81.4, 128.1, 128.2, 128.5, 136.8, 155.7, 156.3, 172.1. Anal. calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.83; H, 7.29; N, 7.46.

4.24. Methyl (2R,3S)-3-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-3-phenyl propanoate ***24a***

The compound **21a** (0.3 g, 0.75 mmol) was treated as described above for the preparation of **23a**. Column chromatography on silica gel (hexane:diethyl ether=80:20) of the crude product gave 0.260 g (81%) of **24a** as a white solid: mp 94–96°C; $[\alpha]_D$=−40.1 (c 1.50, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 9H), 3.57 (s, 3H), 3.62–3.69 (m, 1H), 4.73–4.86 (m, 1H), 5.10 (s, 2H), 5.25 (bs, 1H), 5.90 (bs, 1H), 7.26–7.30 (m,

10H); ^{13}C NMR δ 28.2, 52.5, 57.5, 58.0, 67.0, 80.4, 126.7, 128.12 (2C), 128.5, 128.7 (2C), 136.2, 137.9, 155.4, 155.8, 170.6. Anal. calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.42; H, 6.88; N, 6.30.

4.25. Methyl (2R,3S)-3-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-4-phenyl butanoate ***25a***

The compound **22a** (0.3 g, 0.72 mmol) was treated as described above for the preparation of **23a**. Column chromatography on silica gel (hexane:diethyl ether=80:20) of the crude product gave 0.252 g (79%) of **25a** as an oil: $[\alpha]_D=-49.7$ (c 0.55, $CHCl_3$); ^{1}H NMR δ 1.44 (s, 9H), 2.78 (dd, 1H, J=8.4, 15.7 Hz), 2.95 (dd, 1H, J=5.7, 15.7 Hz), 3.68 (s, 3H), 4.35 (dddd, 1H, J=3.8, 5.7, 8.4, 8.8 Hz), 4.45 (dd, 1H, J=3.8, 8.4 Hz), 4.80 (d, 1H, J=8.4 Hz), 4.96 (s, 2H), 5.28 (d, 1H, J=8.8 Hz), 7.26–7.39 (m, 10H); ^{13}C NMR δ 28.2, 31.8, 52.3, 54.9, 56.6, 66.8, 80.3, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 136.4, 137.0, 155.7, 155.8, 171.1. Anal. calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.07; H, 6.99; N, 6.14.

4.26. (2R,3R)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-1-O-(tert-butyldiphenylsilyl)-1-butanol ***17b***

The hydroxylamine **11b** (0.34 g, 0.62 mmol) was treated as described above for the preparation of **17a**. Column chromatography on silica gel (hexane:diethyl ether=90:10) of the crude product gave 0.272 g (76%) of **17b** as an oil: $[\alpha]_D=-24.0$ (c 0.11, $CHCl_3$); ^{1}H NMR δ 1.02 (d, 3H, J=6.6 Hz), 1.07 (s, 9H), 1.42 (s, 9H), 3.57–3.61 (m, 2H), 3.97–4.03 (m, 2H), 4.24 (d, 1H, J=12.1 Hz), 4.56 (d, 1H, J=12.1 Hz), 4.70 (bs, 1H), 5.11 (bs, 1H), 7.18–7.40 (m, 11H), 7.57–7.61 (m, 4H); ^{13}C NMR δ 9.5, 19.3, 27.1, 28.4, 49.5, 54.8, 63.8, 67.3, 79.3, 126.9, 127.0, 127.6, 127.8, 127.9, 128.1, 128.4, 128.5, 129.8, 135.7, 136.8, 138.9, 155.8, 156.0. Anal. calcd for $C_{33}H_{44}N_2O_5Si$: C, 68.72; H, 7.69; N, 4.86. Found: C, 68.92; H, 7.93; N, 4.82.

4.27. (2R,3R)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-1-O-(tert-butyldiphenylsilyl)-3-phenyl-1-propanol ***18b***

The hydroxylamine **12b** (0.38 g, 0.62 mmol) was treated as described above for the preparation of **17a**. Column chromatography on silica gel (hexane:diethyl ether=85:15) of the crude product gave 0.314 g (79%) of **18b** as an oil: $[\alpha]_D=+6.4$ (c 1.59, $CHCl_3$); ^{1}H NMR δ 1.11 (s, 9H), 1.45 (s, 9H), 3.40 (dd, 1H, J=3.3, 10.6 Hz), 3.61 (dd, 1H, J=3.8, 10.6 Hz), 3.96 (dddd, 1H, J=3.3, 3.7, 7.4, 9.3 Hz), 4.92 (dd, 1H, J=8.7, 9.3 Hz), 5.01 (d, 1H, J=12.5 Hz), 5.12 (d, 1H, J=12.5 Hz), 5.48 (d, 1H, J=8.7 Hz), 6.00 (d, 1H, J=7.4 Hz), 7.24–7.40 (m, 16H), 7.55–7.62 (m, 4H); ^{13}C NMR δ 19.3, 27.0, 28.3, 56.2, 57.8, 63.2, 66.6, 79.9, 126.9, 127.3, 127.5, 127.7, 127.8, 128.3 (2C), 128.4 (2C), 128.6, 129.8, 129.9, 132.9, 133.0, 135.5 (2C), 156.2, 156.6. Anal. calcd for $C_{38}H_{46}N_2O_5Si$: C, 71.44; H, 7.26; N, 4.38. Found: C, 71.72; H, 7.18; N, 4.27.

4.28. (2R,3R)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-1-O-(tert-butyldiphenylsilyl)-4-phenyl-1-butanol ***19b***

The hydroxylamine **13b** (0.36 g, 0.58 mmol) was treated as described above for the preparation of **17a**. Column chromatography on silica gel (hexane:diethyl ether=90:10) of the crude product gave 0.289g

(76%) of **19b** as an oil: $[\alpha]_D=-11.5$ (c 1.3, $CHCl_3$); ^{1}H NMR δ 1.03 (s, 9H), 1.41 (s, 9H), 2.66 (dd, 1H, J=6.6, 15.8 Hz), 2.86 (dd, 1H, J=4.7, 15.8 Hz), 3.70–3.83 (m, 2H), 3.93–3.97 (m, 1H), 4.15–4.21 (m, 1H), 4.88 (bs, 1H), 5.01 (s, 2H), 5.21 (bs, 1H), 7.11–7.39 (m, 16H), 7.61–7.70 (m, 4H); ^{13}C NMR δ 19.2, 27.3, 28.3, 38.3, 53.3, 54.7, 64.0, 66.5, 79.5, 126.5, 127.5, 127.6, 127.8, 127.9 (2C), 128.4 (2C), 129.3, 129.8, 133.0, 134.7, 135.6 (2C), 136.6, 137.6, 156.1, 156.4. Anal. calcd for $C_{39}H_{48}N_2O_5Si$: C, 71.74; H, 7.41; N, 4.29. Found: C, 71.80; H, 7.65; N, 4.33.

4.29. (2R,3R)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-1-butanol ***20b***

The compound **17b** (0.26 g, 0.45 mmol) was treated as described above for the preparation of **14b**. Column chromatography on silica gel (hexane:diethyl ether=60:40) of the crude product gave 0.117 g (77%) of **20b** as a sticky foam: $[\alpha]_D=+9.8$ (c 0.60, MeOH) [Lit.[1b] $[\alpha]_D=+10.1$ (c 0.50, MeOH)]; ^{1}H NMR δ 1.36 (d, 3H, J=6.7 Hz), 1.40 (s, 9H), 1.76 (bs, 1H), 3.33 (dq, 1H, J=3.2, 6.7 Hz), 3.41–3.56 (m, 2H), 4.22–4.30 (m, 1H), 4.82 (bs, 1H), 5.14 (s, 2H), 5.22 (bs, 1H), 7.19–7.33 (m, 5H); ^{13}C NMR δ 15.5, 28.3, 46.4, 54.1, 61.8, 68.0, 79.4, 127.1, 128.2, 128.5, 136.0, 155.8, 158.1. Anal. calcd for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.11; H, 7.65; N, 8.48.

4.30. (2R,3R)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-3-phenyl-1-propanol ***21b***

The compound **18b** (0.27 g, 0.42 mmol) was treated as described above for the preparation of **14b**. Column chromatography on silica gel (hexane:diethyl ether=60:40) of the crude product gave 0.129 g (76%) of **21b** as a white solid: mp 125–127°C; $[\alpha]_D=-4.6$ (c 1.41, $CHCl_3$); ^{1}H NMR (55°C) δ 1.40 (s, 9H), 2.60 (bs, 1H), 3.44 (dd, 1H, J=3.8, 11.2 Hz), 3.51 (dd, 1H, J=4.4, 11.2 Hz), 3.94 (dddd, 1H, J=3.8, 4.4, 7.6, 8.7 Hz), 4.86 (dd, 1H, J=8.7, 9.1 Hz), 5.01 (d, 1H, J=12.4 Hz), 5.10 (d, 1H, J=12.4 Hz), 5.21 (d, 1H, J=9.1 Hz), 5.90 (d, 1H, J=7.6 Hz), 7.20–7.30 (m, 10H); ^{13}C NMR (55°C) δ 28.2, 56.0, 57.3, 61.8, 66.9, 80.1, 128.0, 128.2, 128.4, 128.5, 128.7, 128.8, 136.3, 137.8, 156.7, 157.1. Anal. calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 66.18; H, 7.14; N, 6.86.

4.31. (2R,3R)-3-(Benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-4-phenyl-1-butanol ***22b***

The compound **19b** (0.27 g, 0.41 mmol) was treated as described above for the preparation of **14b**. Column chromatography on silica gel (hexane:diethyl ether=60:40) of the crude product gave 0.137 g (80%) of **22b** as an oil: $[\alpha]_D=-62.5$ (c 0.85, $CHCl_3$); ^{1}H NMR (55°C) δ 1.43 (s, 9H), 1.60 (bs, 1H), 2.80 (dd, 1H, J=8.6, 14.3 Hz), 2.93 (dd, 1H, J=6.1, 14.3 Hz), 3.49 (dd, 1H, J=7.0, 10.6 Hz), 3.61 (dd, 1H, J=5.1, 10.6 Hz), 3.65–3.80 (m, 1H), 4.10–4.29 (m, 1H), 4.90 (bs, 2H), 5.02 (s, 2H), 7.11–7.40 (m, 10H); ^{13}C NMR (55°C) δ 28.4, 38.8, 53.1, 55.1, 63.0, 67.2, 80.1, 126.7, 127.9, 128.2, 128.6, 128.7, 129.2, 136.5, 137.6, 156.4, 157.4. Anal. calcd for $C_{23}H_{30}N_2O_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.80; H, 7.21; N, 6.59.

4.32. Methyl (2R,3R)-3-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino) butanoate ***23b***

The compound **20b** (0.254 g, 0.75 mmol) was treated as described above for the preparation of **23a**. Column chromatography on silica gel (hexane:diethyl ether=80:20) of the crude product gave 0.228 g (83%) of **23b** as an oil: $[\alpha]_D=-19.8$ (c 0.28, $CHCl_3$); ^{1}H NMR δ 1.22 (d, 3H, J=6.8 Hz), 1.43 (s, 9H), 3.68 (s, 3H), 4.19–4.21 (m, 1H), 4.25–4.32 (m, 1H), 4.88 (bs, 1H), 5.08 (s, 2H), 5.51 (d, 1H, J=8.6 Hz), 7.31–7.42 (m, 5H); ^{13}C NMR δ 18.6, 28.2, 49.2, 53.1, 55.6, 67.0, 80.2, 127.7, 128.1, 128.5, 136.3, 155.8,

156.0, 172.6. Anal. calcd for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.83; H, 7.29; N, 7.46.

4.33. Methyl (2R,3R)-3-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-3-phenyl propanoate ***24b***

The compound **21b** (0.3 g, 0.75 mmol) was treated as described above for the preparation of **23a**. Column chromatography on silica gel (hexane:diethyl ether=80:20) of the crude product gave 0.264 g (82%) of **24b** as an oil: $[\alpha]_D=-48.8$ (c 0.96, $CHCl_3$); ^{1}H NMR δ 1.39 (s, 9H), 3.60 (s, 3H), 3.62–3.64 (m, 1H), 4.60–4.64 (m, 1H), 4.99 (d, 1H, J=12.3 Hz), 5.09 (d, 1H, J=12.3 Hz), 5.30 (bs, 1H), 5.84 (bs, 1H), 7.28–7.36 (m, 10H); ^{13}C NMR δ 28.2, 52.4, 56.2, 57.9, 67.0, 80.6, 126.7 (2C), 128.2, 128.5, 128.7, 129.2, 136.7 (2C), 155.8, 156.0, 170.3. Anal. calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.42; H, 6.88; N, 6.30.

4.34. Methyl (2R,3R)-3-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)-4-phenyl butanoate ***25b***

The compound **22b** (0.3 g, 0.72 mmol) was treated as described above for the preparation of **23a**. Column chromatography on silica gel (hexane:diethyl ether=80:20) of the crude product gave 0.255 g (80%) of **25b** as an oil: $[\alpha]_D=-34.5$ (c 0.80, $CHCl_3$); ^{1}H NMR δ 1.44 (s, 9H), 2.75 (dd, 1H, J=8.5, 14.3 Hz), 2.95 (dd, 1H, J=5.9, 14.3 Hz), 3.61 (s, 3H), 3.63–3.66 (m, 1H), 4.38–4.41 (m, 1H), 4.85 (d, 1H, J=9.5 Hz), 4.97 (s, 2H), 5.32 (d, 1H, J=8.7 Hz), 7.11–7.40 (m, 10H); ^{13}C NMR δ 28.3, 38.6, 52.5, 54.8, 56.7, 66.9, 80.4, 126.8, 127.9, 128.0, 128.5, 128.6, 129.3, 136.5, 137.1, 155.7, 155.9, 177.2. Anal. calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.23; H, 6.88; N, 6.19.

Acknowledgements

Financial support from DGICYT (MEC, Madrid, Project PB94-0598) is gratefully acknowledged. One of us (A. L.) thanks DGA (Aragon, Spain) for a grant.

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