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An Enantioselective, Stereodivergent Approach to *anti*- and *syn*-α-Hydroxy-β-amino acids from *anti*-3-Amino-1,2-diols. Synthesis of the Ready for Coupling Taxotere® Side Chain.§

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Abstract: Both *anti*- and *syn*-α-hydroxy-β-amino acids are efficiently synthesised in protected form and high enantiomeric purity from readily available *anti*-*N*-Boc-1-*tert*-butyldimethylsilyl-3-amino-1,2-diols. The preparation of the *anti* series is straightforward, and takes place by protection of the secondary hydroxyl group (1-ethoxyethyl) followed by desilylation/oxidation of the primary hydroxyl group. For the preparation of the *syn* isomers, the secondary alcohol is inverted at the beginning of the sequence by Mitsunobu methodology (*p*-nitrobenzoate). Starting from homochiral (2*S*,3*S*)-*N*-Boc-1-*tert*-butyldimethylsilyl-3-amino-3-phenylpropane-1,2-diol, the ready for coupling Taxotere® side chain has been prepared in enantiomerically pure form.

Stereodefined α-hydroxy-β-amino acids are well recognised key components for a variety of protease inhibitors[1] and other new generation pharmaceutics[2,3].

We have recently reported the enantioselective synthesis of fully protected *anti*-α-hydroxy-β-amino acids[4] from readily available *anti*-3-amino-1,2-diols.[5] Our initial approach, however, was unsuitable for the preparation of the even more interesting *syn* stereoisomers.[6] We report in the present paper a new approach which overcomes this difficulty and allows a ready enantioselective access to both diastereomeric series in stereodivergent manner from *N*-Boc-3-amino-1,2-diols. The versatility of the reported methodology is demonstrated by the development of an enantiospecific synthesis of the fully protected Taxotere® side chain, ready for coupling with 10-Deacetylbaccatin III.[2b]

ANTI DERIVATIVES

The 3-amino-2-hydroxybutyrate system was selected as a model for methodology set-up. In this way, *anti*-*N*-Boc-3-aminobutan-1,2-diol **1**, readily available in multigram amounts in both enantiomeric forms by Sharpless epoxidation and methodology developed in our laboratories,[5a,c] was the starting material of choice.

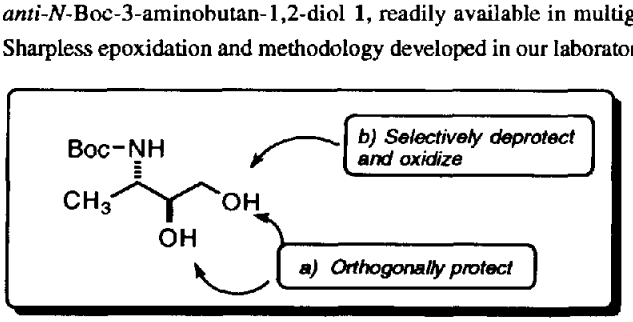
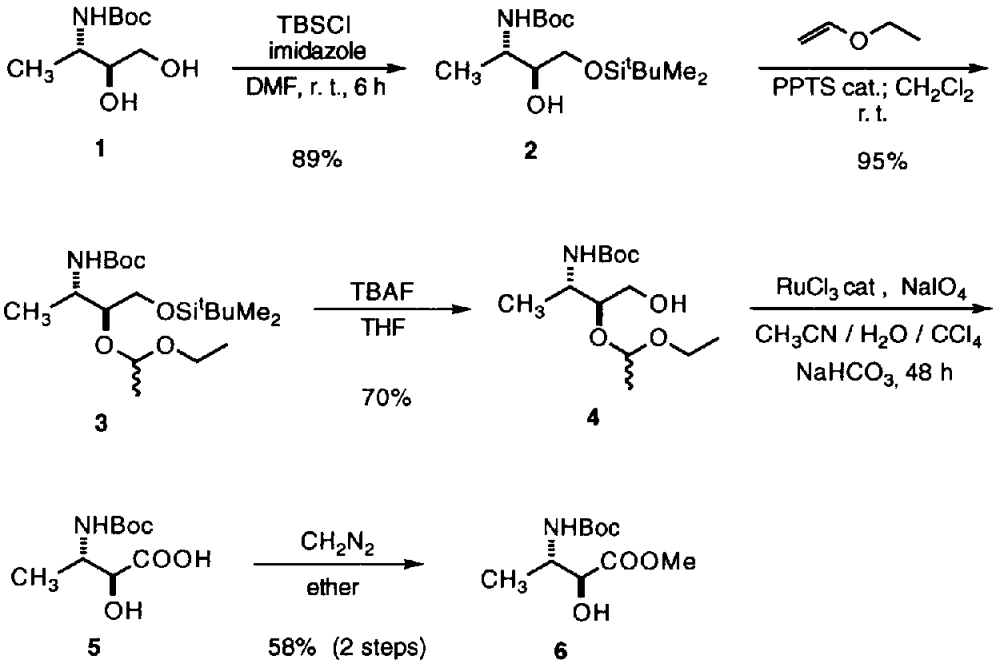


Figure 1

The simple strategy outlined in Figure 1 should allow the conversion of **1** into the target molecule.[7] The orthogonal protection of the two hydroxy groups could be easily achieved. Thus, treatment of **1** with *tert*-butyldimethylsilyl chloride (TBSCl)/imidazole in DMF afforded the primary TBS ether **2** in 89% yield. Subsequent treatment with excess ethyl vinyl ether in dichloromethane[8] provided access to the fully protected derivative **3** in 95% yield as a mixture of diastereomers at the acetal carbon (Scheme 1).



Scheme 1

Having **3** in hand, the primary hydroxy group was selectively deprotected by treatment with anhydrous tetrabutylammonium fluoride in THF, leading to the primary alcohol **4** in 70% yield. Final oxidation of **4** into the α-hydroxy-β-amino acid was performed with $RuCl_3/NaIO_4$ in $CH_3CN/CCl_4/H_2O$.[9] Although it has been reported that the 1-ethoxyethyl protecting group is compatible with these oxidising conditions[2b], deprotection occurred during the subsequent acidic work-up. To facilitate isolation and characterisation, the free acid **5** was converted into its methyl ester by treatment with diazomethane. In this way, the methyl ester **6** could be isolated in 58% yield from **4** (2 steps). Both **5** and **6** are diastereomerically pure according to high resolution NMR. Given the enantiomeric purity of the starting material and the stereochemical course of the reactions involved, the enantiomeric excess of **6** should be, at least, 90%. The preceding sequence nicely illustrated the potential of *anti* *N*-Boc-3-amino-1,2-diols as starting materials for the straightforward preparation of *anti*-α-hydroxy-β-amino acids.

Application of exactly the same methodology to *syn*-*N*-Boc-3-amino-1,2-diols should similarly provide the stereoisomeric *syn*-α-hydroxy-β-amino acids. In practice, the implementation of this methodology would

ultimately involve the epoxidation of (*Z*)-allyl alcohols and the nucleophilic regioselective ring opening of the so formed epoxy alcohol (Figure 2).

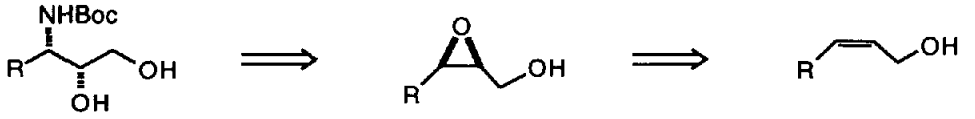


Figure 2

It is well known that, in general, Sharpless epoxidation of (*Z*)-allyl alcohols proceeds slowly and with low enantioselectivity[10]. Moreover, when the nucleophilic ring opening of *cis* epoxy alcohols was attempted, the process took place with very low yield[10]. In any case, the early intermediate **2** could play a key role in the synthesis of the corresponding *syn* stereoisomers, provided that a inversion of configuration can be performed at carbon two (Figure 3).

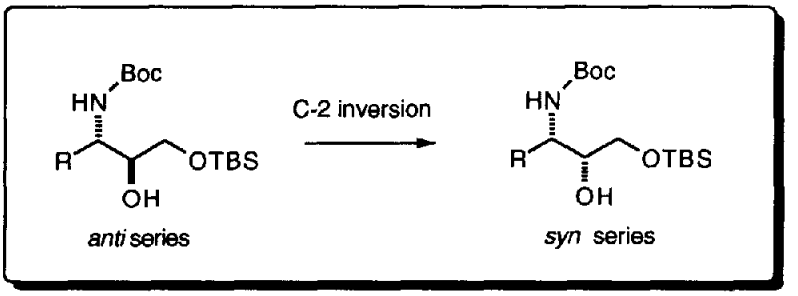


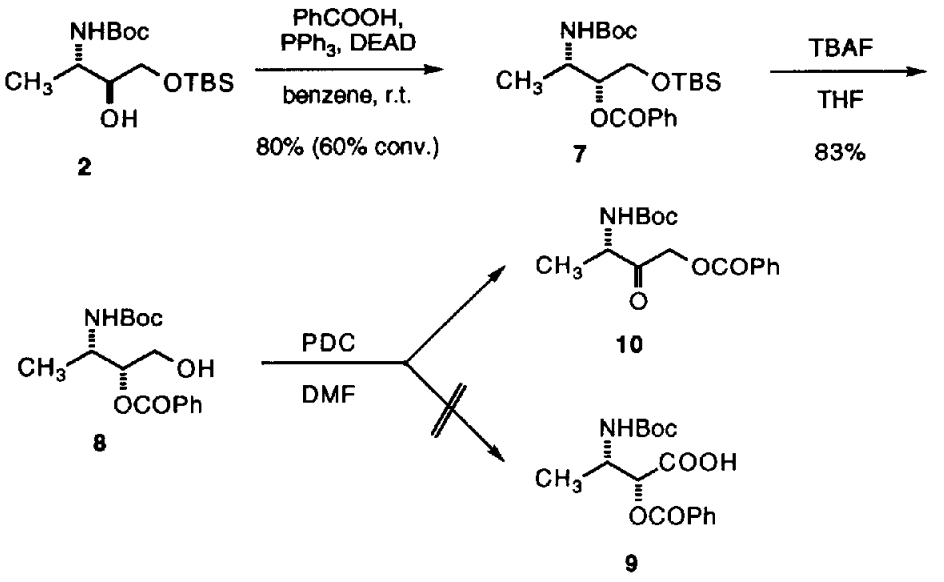
Figure 3

SYN DERIVATIVES

As in the *anti* series, the synthetic methodology was developed working on 3-aminobutane-1,2-diol derivatives (Figure 3, R=CH_3) given the availability of the starting material.[5a]

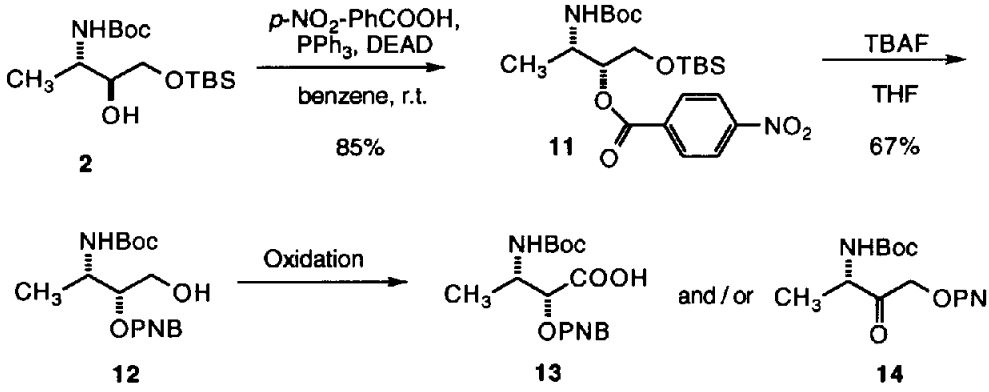
As already indicated, our synthetic strategy for the *syn* derivatives relied on the possibility of performing an inversion of configuration at C-2 on the secondary alcohol **2**. Mitsunobu methodology[11] was perfectly suited for our purposes so that **2** was treated with benzoic acid in benzene in the presence of triphenylphosphine and diethyl azodicarboxylate (Scheme 2). The inverted benzoate **7** was obtained in 80% yield (60% conversion).

Treatment of **7** with TBAF in THF afforded the deprotected primary alcohol **8** in 83% yield. Quite disappointingly, the final oxidation of **8** with PDC in DMF did not led to the expected acid **9**. Instead, the ketone **10**, arising from a transacylation/oxidation of **8**, was the main reaction product.



Scheme 2

In an attempt to circumvent this difficulty and improve the yield of the Mitsunobu reaction, *p*-nitrobenzoic acid was used as the nucleophile[12] in the first step of the sequence (Scheme 3).



Scheme 3

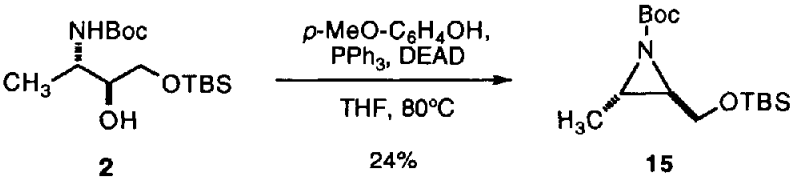
The Mitsunobu reaction took place cleanly on **2**, and the (2*R*,3*S*) *p*-nitrobenzoate **11**, already belonging to the *syn* series, was obtained in 85% yield. Again, selective deprotection of the primary alcohol could be efficiently performed with TBAF in THF, being the primary alcohol **12** obtained in 67% yield. Oxidation of **12** was attempted under a variety of reaction conditions (Table 1). Although the desired acid **13** could be isolated in yields up to 25%, the major product was always the ketone **14**, arising from a transacylation/oxidation sequence. It is worth noting that this transacylation seems to require the presence of both basic medium and

oxidising agent to proceed, since **12** remains unaffected after a treatment with base (pyridine) in the absence of oxidant.

Table 1. Oxidation of alcohol **12**

Oxidation conditions	**12**	**13**	**14**
PDC / DMF[13]	31%	25%	18%
$NaIO_4$ / $RuCl_3$[9]	35%	0%	23%
NaOCl / TEMPO[14]	-	20%	63%
H_2CrO_4 / acetone[15]	-	25%	69%

To avoid this problem, a Mitsunobu reaction with *p*-methoxyphenol as a nucleophile[16] was attempted on **2**. However, the nitrogen atom present in the molecule preferentially acted as the nucleophile in an intramolecular fashion, leading to the formation of aziridine **15** in 24% yield (Scheme 4).



Scheme 4

In view of this result, we turned back to the *p*-nitrobenzoate intermediate **11**. It was clear, however, that the functionality at C-2 had to be modified given the incompatibility of the *p*-nitrobenzoate with the oxidising conditions required in the last step of the synthesis. Our ultimate strategy for the *syn*-α-hydroxy-β-amino acids was then stablished as shown in figure 4.

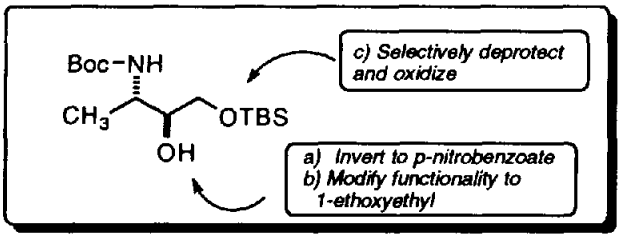
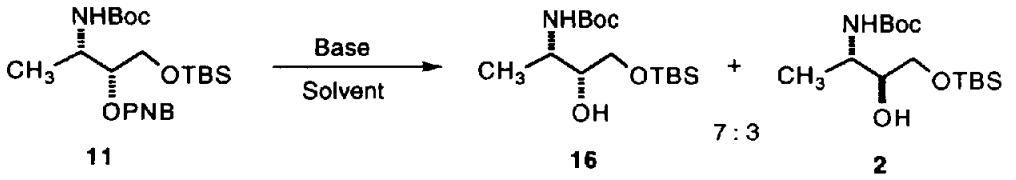


Figure 4

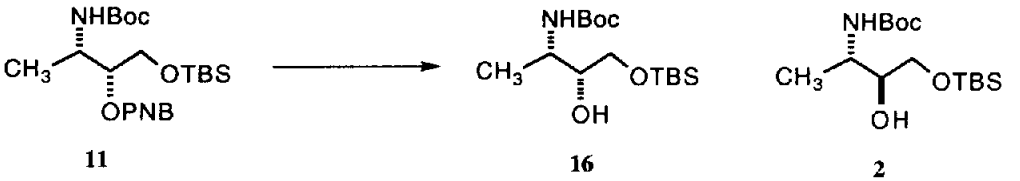
Removal of the *p*-nitrobenzoate ester from **11** was initially attempted by saponification. However, under a variety of reaction conditions (1% NaOH/MeOH, LiOH/H_2O-THF, K_2CO_3/THF-MeOH)[17] the ester hydrolysis was always accompanied by significant epimerization at C-2.



11 **16** **2**

As a more convenient alternative, a reductive removal of the *p*-nitrobenzoate ester was also performed. After screening different reducing agents (Table 2), which also induced epimerization at C-2, it was finally found that the use of DIBAL-H in dichloromethane at -20°C completely preserves the stereochemical integrity of the starting material, allowing the isolation of diastereomerically pure **16** in 73% yield.

Table 2. Reductive cleavage of *p*-nitrobenzoate **11**.

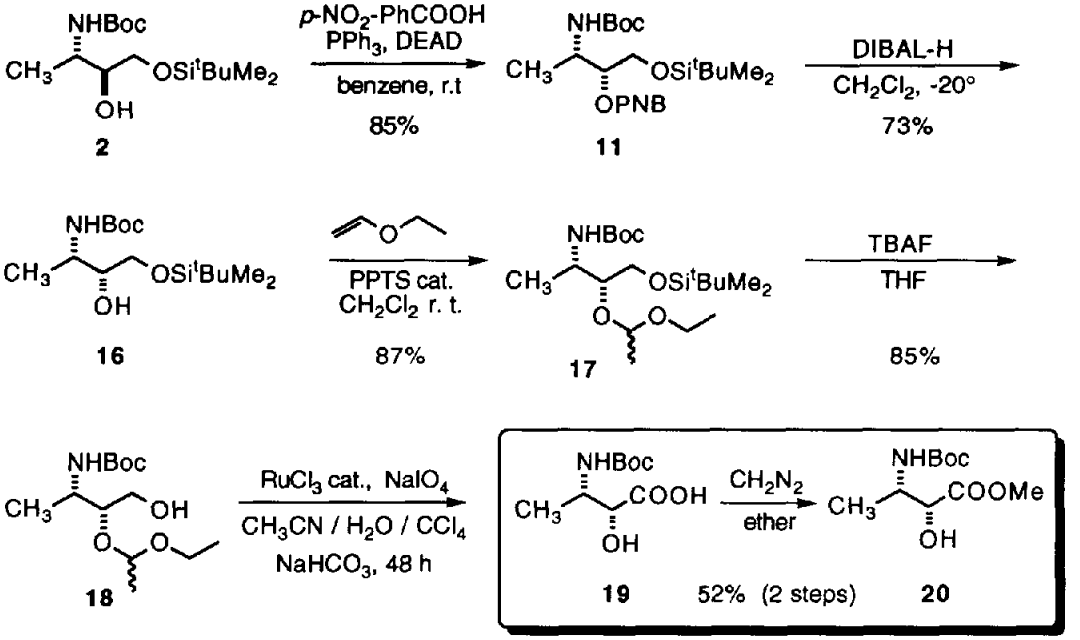


11 **16** **2**

Reducing Agent	Solvent	Reaction Conditions	Overall Yield	**16/2**
$NaBH_4$	MeOH	r.t. 3h	71%	8 : 2
$LiAlH_4$	ether	r.t, 1h	70%	8 : 2
$LiBEt_3H$	THF	0°C, 4h	79%	8 : 2
DIBAL-H	CH_2Cl_2	-20°C, 5h	73%	100 : 0

The conversion of **16** into the target *syn* α-hydroxy-β-amino acid is parallel to that of **2** into the *anti* stereoisomer **6** and has been summarised in Scheme 5 along with the initial steps of the synthesis.

The secondary hydroxy group in **16** was protected as a 1-ethoxyethyl ether (**17**, 87%) and the primary hydroxy group was then selectively deprotected with TBAF in THF to afford **18** in 85% yield. Oxidation with a catalytic amount of $RuCl_3/NaIO_4$[9] took place with concomitant deprotection of the secondary alcohol, as already observed for the *anti* stereoisomer. To facilitate isolation and characterisation, the hydroxy acid **19** was converted into the methyl ester **20** by treatment with diazomethane (52% yield from **18**). As for the *anti* stereoisomers, the enantiomeric excess of **19/20** should be at least the same as that of **1** (90%). From the TBS derivative **2**, the synthesis of the corresponding *syn* α-hydroxy-β-amino acid: (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxybutyric acid, involves only five steps and takes place in more than 25% overall yield.



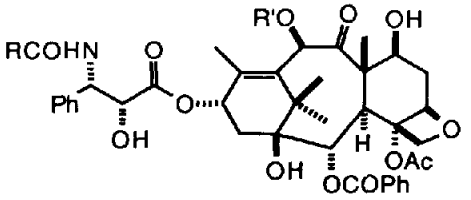
Scheme 5

Among the many biologically relevant *syn* α-hydroxy-β-amino acids, we have selected Taxotere® side chain as a touchstone for the present methodology.

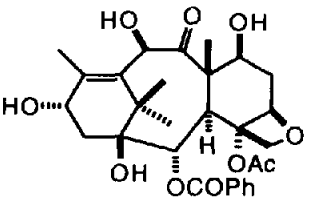
ENANTIOSELECTIVE SYNTHESIS OF THE TAXOTERE® SIDE CHAIN

Taxol and Taxotere® are probably the most powerful chemical weapons presently available for fight against some types of breast and ovarian cancer.[18] A differently functionalised phenylisoserine side chain is present in both molecules.

Although three total synthesis have been reported up to now,[19] the most practical route to both Taxol and Taxotere® is nowadays semisynthesis from 10-Deacetylbaccatin III, a readily available natural product.[20] This explains the enormous interest on the phenylisoserine moiety and the plethora of synthetic approaches reported in the last years to the Taxol and Taxotere® side chains. In the Potier-Greene semisynthesis of Taxotere®,[2b, 20] the 1-ethoxyethyl derivative **21** is directly coupled with 10-Deacetylbaccatin III.



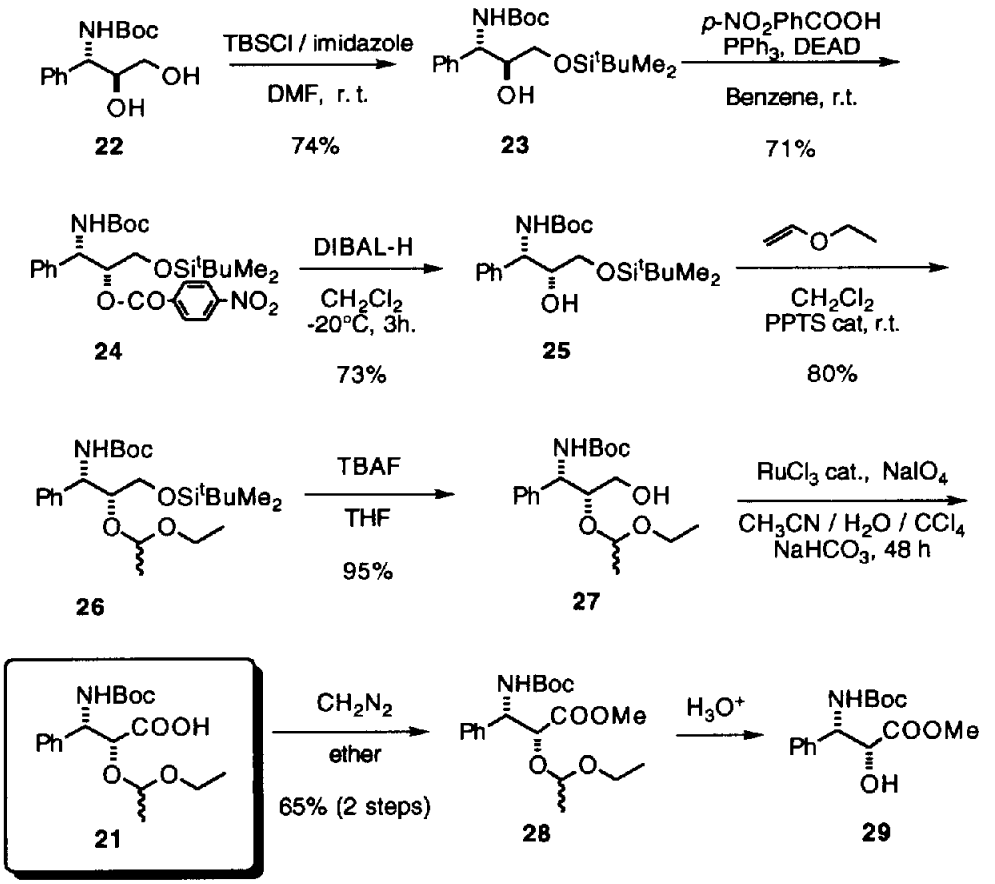
Taxol R=C_6H_5 R'=$COCH_3$
Taxotere R=Bu^tO R'=H



10-Deacetylbaccatin III

Since the methodology we have just described directly leads to *syn* α-hydroxy-β-amino acids with this protection scheme, we decided to apply it to a synthesis of **21**.

Enantiomerically pure (2*S*,3*S*)-*N*-Boc-3-amino-3-phenylpropane-1,2-diol **22**, readily secured from (*E*)-3-phenyl-1-propanol via Sharpless epoxidation/regioselective ring opening,[5c] was treated with TBSCl/imidazole in DMF to afford with complete chemoselectivity in 74% yield the product of monosilylation at the primary alcohol **23** (Scheme 6)



Scheme 6

Mitsunobu inversion with *p*-nitrobenzoic acid as the nucleophile led to the fully protected intermediate **24** in 71% yield. Reduction of **24** with DIBAL-H, under the previously optimised conditions (see above) took place without any detectable level of epimerisation at C-2 and afforded the alcohol **25** in 73% yield. Protection of the secondary alcohol as a 1-ethoxyethyl ether and subsequent deprotection of the primary one with TBAF provided the primary alcohol **27** in 76% overall yield. Final oxidation of **27** with $RuCl_3/NaIO_4$ afforded the protected phenylisoserine derivative **21**. Careful control of the work-up conditions completely avoided the

deprotection of the secondary hydroxy group which was observed on the methyl derivative. In order to facilitate product isolation **21** was converted into its methyl ester **28** by treatment with diazomethane. The overall yield for the oxidation/esterification sequence was 65%. As a confirmation of enantiomeric purity, **28** was converted into the known hydroxy ester **29** by acidic treatment ($[\alpha]_D$=-7.6; Lit[2a]: $[\alpha]_D$=-7). The synthesis of **21** can be thus accomplished in six steps and 19-22% overall yield from the known aminodiol **22**. The Taxotere® side chain has been obtained in both diastereomerically and enantiomerically pure form and can be directly coupled with protected derivatives of 10-Deacetylbaccatin III without any additional protection/deprotection step.

CONCLUSION

In summary, we have developed a flexible, stereodivergent approach to *syn* and *anti* α-hydroxy-β-amino acids in enantioenriched or enantiomerically pure form from *anti N*-Boc-3-amino-1,2-diols. These precursors are readily available through Sharpless catalytic epoxidation of (*E*) allyl alcohols, subsequent regioselective opening with benzhydrylamine and change of the amino protecting group. Selection of the tartrate ester (D or L) employed in the epoxidation step and use of the methodologies presented here provides completely stereocontrolled access to any of the four possible α-hydroxy-β-amino acid stereoisomers from a single (*E*)-allyl alcohol (Figure 5). Moreover the present methodology offers the advantage of completely avoiding the use of azides as a nitrogen synthons, a relevant characteristic when scale-up is considered.

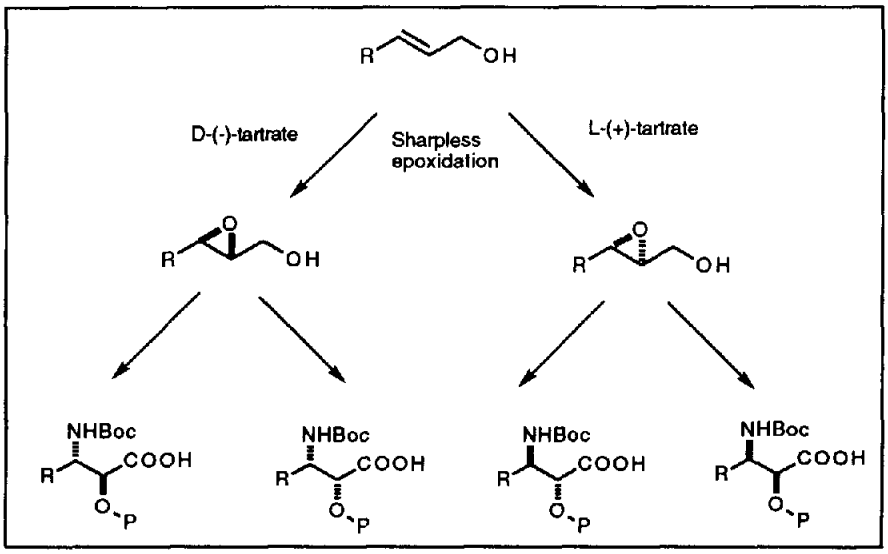


Figure 5

Given the broad scope of the Sharpless epoxidation, it is presumed that the procedures presented here can provide access to a great variety of diastereo- and enantiomerically pure α-hydroxy-β-amino acids. The synthesis of the Taxotere® side chain described here represents an initial example of application of our methodology. The synthesis of other biologically relevant α-hydroxy-β-amino acids is in progress in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. Optical rotations were measured at room temperature (23°C) on a Perkin-Elmer 241 MC automatic polarimeter (Concentration in g/100 mL). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Perkin-Elmer 681, or on a Nicolet 510 FT-IR instrument using NaCl film or KBr pellet techniques. NMR spectra were acquired on Varian XL-200 or Varian-Unity-300 instruments. ^{1}H-NMR were obtained at 200 or 300 MHz (s=singlet, d=doublet, t=triplet, q=quartet, dt= double triplet, m=multiplet and b=broad). ^{13}C-NMR were obtained at 50.3 MHz or 75.4 MHz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra were recorded on a Hewlett-Packard 5890 instrument. Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona). Chromatographic separations were carried out using NEt_3 pre-treated (2.5% v/v) SiO_2 (70-230 mesh) and eluting with hexanes/ethyl acetate mixtures of increasing polarity. Chromatographic analyses were performed on a Helwett-Packard 1050 HPLC instrument equipped with Nucleosil 120 C18 (20 cm) or a Chiralcel® ODR (25 cm) columns.

(2*S*,3*S*)-3-*tert*-butoxycarbonylamino-1,2-butanediol (1).

A solution of (2*S*,3*S*)-3-benzhydrylamino-1,2-butanediol (44.8 g, 0.16 mol) and Boc_2O (47 g, 0.21 mol, 1.3 eq.) in ethyl acetate (300 mL) was added *via* cannula to a stirred suspension of 20% $Pd(OH)_2/C$ (4.5 g) in ethyl acetate (75 mL). The mixture was hydrogenated at atmospheric pressure until no starting material could be observed by TLC, filtered through Celite and evaporated. The crude oil was crystallized from ethyl ether/hexane. 24.1 g of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-1,2-butanediol were obtained in two crops as a white solid. The mother liquor was concentrated and purified by flash chromatography affording additional 4.2 g (total yield, 84%).

$[\alpha]_D$=-5.8 (*c*=1,$CHCl_3$), mp: 74-75°C. IR (KBr) $\nu_{max.}$=3400 (b), 3360, 2970, 2940, 1680, 1530, 1370, 1320, 1250, 1170, 1050, 630 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.24 (d, J=6.7 Hz, 3H), 1.44 (s, 9H), 3.03 (b, 2H, hydroxyls), 3.3 (m, 1H), 3.64 (m, 3H), 4.7 (m, 1H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ=16.8 (CH_3), 28.3 (CH_3), 47.9 (CH), 63.2 (CH_2), 75.3 (CH), 80.0 (C), 156.5 (C) ppm. MS (EI) m/e=205 (M^+, 0.09%), 144 (M^+-$C_2H_5O_2$, 35%), 88 ($C_4H_9O_2^+$, 37%), 57 ($^tBu^+$, 100%). Anal. Calcd. for $C_9H_{19}NO_4$: C, 52.65; H, 9.13; N, 6.82. Found: C, 52.58; H, 9.43; N, 6.72.

(2*S*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol (2).

To a solution of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-1,2-butanediol **1** (1.23 g, 5.98 mmol) in dimethylformamide (28 mL) were added TBMS-Cl (0.99 g,6.58 mmol) and imidazole (0.89 g, 13.1 mmol). The reaction was monitored by TLC. After 6 hours, the mixture was diluted with ether (30 mL) and washed with saturated NH_4Cl aqueous solution. The organic layer was separated, dried over $MgSO_4$ and the solvents were evaporated *in vacuo*. The crude product was purified by chromatography yielding 1.7 g of **2** (89% yield).

$[\alpha]_D$=1.2 (*c*=3.0, $CHCl_3$). IR (film) ν_{max} =3450 (b), 2940, 2860, 1700-1730, 1515, 1370, 1260, 1180, 845, 780 cm^{-1}.^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.08 (s, 6H), 0.91 (s, 9H), 1.14 (d, J=6.8Hz, 3H), 1.44 (s, 9H), 2.3-2.4 (m, b, 1H), 3.5-3.7 (m, 4H), 4.9-5.1 (m, 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.6 (CH_3), 16.1 (CH_3), 18.1 (C), 25.8 (CH_3), 28.3 (CH_3), 48.7 (CH), 64.4 (CH_2), 73.6 (CH), 79.1 (C), 155.6 (C) ppm. MS (EI) m/e=320 (M^++1, 0.03%), 246 (20%), 206 (M^+-$C_6H_{15}Si$+2, 94%), 188 (M^+-$C_6H_{15}OSi$, 27%), 162 (76%), 145 ($C_7H_{17}OSi^+$, 100%), 144 (M^+-$C_8H_{19}O_2Si$, 45%), 115 ($C_6H_{15}Si^+$, 37%).

(2*S*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-butane (3).

To a solution of (2*S*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol **2** (0.59 g, 1.85 mmol) in CH_2Cl_2 (9.5 mL) were added ethyl vinyl ether (1.7 mL, 17.8 mmol) and pyridinium *p*-toluenesulfonate (15 mg). The reaction was stirred at room temperature under nitrogen atmosphere until no starting material could be detected by TLC. The solution was washed with water and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated, yielding an oil that was purified by chromatograpy yielding 0.73 g (95% yield) of **3** as a mixture of diastereomeric acetals.
IR (film) $\nu_{max.}$=3350, 2970, 2950, 2930, 2880, 2860, 1720, 1510, 1475, 1465, 1450, 1390, 1365, 1250, 1170, 1125, 1080, 1055, 840, 775 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.02 (2s, 6H), 0.84 γ 0.85 (2s, 9H), 0.99-1.3 (complex signal, 9H), 1.38 (s, 9H), 3.3-4 (complex signal, 6H), 4.66 γ 4.75 (2 q, J=5.1Hz, 1H), 5.1-5.3 γ 5.7-5.9 (2 m, 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.6 (CH_3), 14.9 (CH_3), 15.1 (CH_3), 15.2 (CH_3), 20.1 (CH_3), 20.4 (CH_3), 25.8 (CH_3), 28.4 (CH_3), 46.7 (CH), 60.8 (CH_2), 61.7 (CH_2), 63.8 (CH_2), 64.0 (CH_2), 99.6 (CH), 101.5 (CH) ppm.

(2*S*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-1-butanol (4).

To a solution of (2*S*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-butane **3** (0.14g, 0.35 mmol) in THF (1.5 mL) was added tetrabutylammonuim fluoride (0.18 g, 0.68 mmol). The reaction was monitored by TLC. After 15 minutes, the solution was washed with water and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography yielding 67 mg (70% yield) of **4**.
IR (film) ν_{max} = 3400, (broad), 2990, 2960, 2890, 1690, 1510, 1455, 1395, 1370, 1250, 1170, 1135, 1100, 1070, 1055, 1015 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1-1.4 (complex signal, 9H γ 9H), 1.44 (s, 9H γ 9H), 3.4-3.9 (complex signal, 6H γ 6H), 4.7 (m, 1H), 4.8 (q, J=5.3Hz, 1H), 5.4 (m, 1H γ 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=14.9 (CH_3), 15.6 (CH_3), 15.9 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 28.2 (CH_3), 46.5 (CH), 46.9 (CH), 60.5 (CH_2), 61.5 (CH_2), 62.3 (CH_2), 62.9 (CH_2), 80 (C), 80.0 (CH), 82.3 (CH), 100.1 (CH); 101.1 (CH), 156 (C) ppm.

(2*S*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxybutanoic acid (5).

To a suspension of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-1-butanol **4** (55 mg, 0.20 mmol) in 1.5 mL of a mixture of $CH_3CN/CCl_4/H_2O$ (1/1/1.5) were added $NaHCO_3$ (0.11g, 1.29 mmol), of $NaIO_4$ (0.23 g, 1.09 mmol) and $RuCl_3$ (catalytic amounts). The reaction was stirred at room temperature 48 hours. When no starting material could be detected by TLC, water (1mL) was added. The organic layer was separated. The aqueous phase was washed with ether, acidified with hydrochloric acid and extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated yielding 32 mg of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxybutanoic acid **5**.

Methyl (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxybutanoate (6).

A solution of diazomethane in ethyl ether was added dropwise to a solution of acid **5** (28 mg) in ether until the yellow color of the diazomethane solution was mantained during several minutes. The solution was then concentrated *in vacuo* and purified by chromatography yielding 23 mg of **6** (58% yield from **4**).

IR (film) ν_{max} = 3360 (broad), 2980, 2960, 2940, 1740, 1720, 1505, 1445, 1385, 1360, 1340, 1240, 1210, 1160, 1065, 1020 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.38 (d, J=7.2 Hz, 3H), 1.45 (s, 9H), 3.75 (s, 3H), 3.6-3.9 (m,1H), 4.2-4.4 (m, 1H), 5-5.1 (m, 1H) ppm.

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-phenylcarbonyloxybutane (7).

To a solution of (2*S*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol **2** (0.12 g, 0.39 mmol) in benzene (2 mL) were added triphenylphosphine (0.05 g, 0.43 mmol), diethyl azodicarboxylate (0.08 mL, 0.49 mmol) and benzoic acid (0.05 g, 0.43 mmol) in 1.5 mL of benzene . The reaction was stirred at room temperature 12 hours. The mixture was concentrated *in vacuo*. The residue was purified by flash chromatography yielding 43 mg of **2** (65% conversion) and 86 mg of **7** (80% yield), as an oil.
IR (film) ν_{max} = 3480, 2975, 2940, 2900, 2870, 1730, 1715, 1510, 1460, 1375, 1275, 1175, 1120, 1100, 845, 785, 720 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.22 (d, J=6.8Hz, 3H), 1.39 (s, 9H), 3.8 (d, 2H), 4.1-4.2 (m, 1H), 4.8-4.9 (m, 1H), 5.1-5.2 (d t, 1H), 7.3-7.4 (m, 3H), 8.05 (d, J=7Hz, 2H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.6 (CH_3), 17.7 (CH_3), 25.7 (CH_3), 28.3 (CH_3), 46.6 (CH), 62.0 (CH_2), 76.5 (CH), 79 (C), 128.3 (CH), 129.7(CH), 130.0 (CH), 156 (C), 166 (C) ppm.

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-phenylcarbonyloxy-1-butanol (8).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonilamino-2-phenylcarbonyloxybutane **7** (0.15 g, 0.35 mmol) in THF (2 mL) was added tetrabutylammonium fluoride trihydrate (0.19 g, 0.72 mmol). The reaction mixture was stirred 45 min. When no starting material could be detected by TLC, water was added and the organic layer was separated. The aqueous phase was extracted with methylene chloride. The combined organic phases were dried over $MgSO_4$ and concentrated, yielding 0.22 g of crude that was purified by chromatography eluting with ethyl acetate/hexane mixtures. 92 mg of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-phenylcarbonyloxy-1-butanol **8** was obtained as an oil (83% yield).
IR (film) ν_{max} =3400 (broad), 2990, 2940, 1725, 1690, 1520, 1455, 1370, 1275, 1255, 1170, 1020, 715 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.27 (d, J=6.8Hz, 3H), 1.45 (s, 9H), 3.8-4 (m, 2H), 4.35-4.45 (m, 2H), 4.8-4.9 (m, 1H) 7.4-7.6 (m, 3H), 8.05 (d, J=7Hz, 2H) ppm.

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutane (11).

To a solution of **2** (0.56g, 1.75mmol) in benzene (30 mL) were added PPh_3 (2.27 g, 8.6 mmol), *p*-nitrobenzoic acid (1.29 g, 7.7 mmol) and diethyl azodicarboxylate (1.4 mL, 8.6 mmol). The reaction was stirred at room temperature 12 hours. The mixture was concentrated *in vacuo*. The residue was purified by flash chromatogrphy yielding 0.7 g of **11** (85% yield).
$[\alpha]_D$=0.84 (*c*=1.7, $CHCl_3$). IR (film) ν_{max} = 3400 (b), 2970, 2940, 2885, 2860, 1730, 1610, 1540, 1370, 1350, 1280, 1170, 1120, 1105, 840, 770, 720 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=-0.02 (s, 3H), 0 (s, 3H), 0.81 (s, 9H), 1.21 (d, J=6.8Hz, 3H), 1.33 (s, 9H), 3.7-3.9 (m, 2H), 4.06-4.22 (m, 1H), 4.7-4.8 (m, 1H), 5.10 (d t J=5.3Hz, J=2.6Hz, 1H), 8.24 (d, 2H), 8.26 (d, 2H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.6 (CH_3), 17.7 (CH_3), 17.9 (C), 26.0 (CH_3), 28.2 (CH_3), 46.5 (CH), 62.0 (CH_2), 78.0 (CH), 79.2 (C), 123.4 (CH), 130.8 (CH), 135.3 (C), 150.5 (C), 155.1 (C), 162 (C) ppm. MS (EI) m/e=355 (M^+-

SiC_6H_{15}+2, 0.26%), 224 (43%), 188 (M^+-$C_6H_{15}Si$+1-$C_7H_4NO_4$, 100%), 150 ($C_7H_4NO_3^+$, 89%), 144 (M^+-$C_7H_{17}OSi$-$C_8H_5NO_4$, 98%), 115 ($C_6H_{15}Si^+$, 10%), 104 (M^+-$C_5H_9O_2$-$C_7H_4NO_3$+1-SiC_6H_{15}+1, 52%).

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxy-1-butanol (12).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonilamino-2-*p*-nitrophenylcarbonyloxibutane **11** (0.2 g, 0.42 mmol) in THF (2 mL) was added tetrabutylammonium fluoride trihydrate (0.27 g, 0.84 mmol). The reaction mixture was stirred 45 min. When no starting material could be detected by TLC, water was added and the organic layer was separated. The aqueous phase was extracted with methylene chloride. The combined organic phases were dried over $MgSO_4$ and concentrated, yielding 0.22 g of crude that was purified by chromatography eluting with ethyl acetate/hexane mixtures. 0.15 g of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxy-1-butanol **12** were obtained as a white solid (67% yield). $[\alpha]_D$=-12.4 (*c*=1.1, $CHCl_3$). IR (KBr) ν_{max} = 3440, 3420, 3000, 2980, 1735, 1670, 1620, 1540, 1460, 1400, 1370, 1350, 1300, 1250, 1170, 1130, 1120, 1100, 1070, 880, 850, 720 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.28 (d, J=6.8Hz, 3H), 1.45 (s, 9H), 2.9-3.1 (m, broad, 1H), 3.8-4.0 (m, 2H), 4.3-4.5 (m, 2H), 4.7-4.9 (m, 1H), 8.25 (d, 2H), 8.28 (d, 2H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=17.9 (CH_3), 28.3 (CH_3), 48.2 (CH), 67.7 (CH_2), 72.9 (CH), 80 (C), 123.5 (CH), 130.8 (CH) ppm. EM (EI) m/e=150 ($C_7H_4NO_3^+$, 100%), 144 (M^+-CH_3O-$C_7H_4NO_4$, 96%), 104 (M^+-$C_7H_4NO_3$+1-$C_5H_9O_2$, 65%). Anal. Calcd. for $C_{16}H_{22}N_2O_7$. C, 54.22, H 6.26, N, 7.91.Found: C, 54.23, H, 6.26, N, 7.93.

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutanoic acid (13).

To a solution of **12** (0.13 g, 0.38 mmol) in methylene chloride (0.5 mL) were added a solution of Aliquat 336 (7 mg, 0.05 eq.) in methylene chloride (0.25 mL), a 0.5 M solution of KBr (0.75 mL) and a solution of 4-methoxy-2,2,6,6-tetramethylpiperidinaloxyl (TEMPO) (0.1mg, < 0.001 eq.) in methylene chloride (0.25 mL). The mixture was cooled to 0°C and 2.7 mL of 0.35 M solution of NaOCl (pH 8.6) were added under stirring. After 40 min. the reaction mixture was basified to pH>12 with 2M NaOH. Water was added and the aqueous layer was extracted with ether. The combined organic phases were dried under $MgSO_4$ and concentrated yielding 84 mg of ketone **14**. The aqueous phase was carefully acidified with HCl and extracted with ether. The ethereal phases were dried under $MgSO_4$ and evaporated affording 27 mg of acid **13** as a white solid (20% yield).

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutanoic acid **13**. IR (KBr) ν_{max} = 3380, 3120 (broad), 3000, 1750, 1685, 1615, 1550, 1525, 1395, 1375, 1355, 1315, 1275, 1245, 1170, 1125, 1115, 1020, 880, 860, 725 cm^{-1}. ^{1}H-RMN (200 MHz, CD_3OD, $TMS_{int.}$) δ=1.40 (d, J=7.1 Hz, 3H), 1.52 (s, 9H), 4.4-4.6 (m, 1H), 5.24 (d, J=4.04, 2H), 8.34-8.54 (m, 4H) ppm. Anal. Calcd. for $C_{16}H_{20}N_2O_8$: C, 52.16, H, 5.47, N, 7.61. Found: C, 51.81, H, 5.37, N, 7.60.

(3*S*)-3-*tert*-butoxycarbonylamino-2-oxabutyl *p*-nitrobenzoate **14.** IR (film) ν_{max} = 3380, 2990, 2940, 1740, 1720, 1620, 1540, 1375, 1355, 1285, 1255, 1175, 740 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.43 (d, J=7.5 Hz, 3H), 1.46 (s, 9H), 4.4-4.5 (m, 1H), 5-5.1 (m, 1H), 5.15 (s, 2H), 8.28 (d, 2H), 8.30 (d, 2H) ppm. ^{13}C-RMN (75 MHz, $CDCl_3$) δ=17.2 (CH_3), 28.3 (CH_3), 52.7 (CH), 67.0 (CH_2), 80.5 (C), 123.6 (CH), 131.0 (CH), 134.5 (C), 150.8 (C), 164.0 (C), 202.4 (C) ppm.

Saponification of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutane 11.

Method A. To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutane **11** (0.26 g, 0.56 mmol) in MeOH (26mL) were added 0.26 g of NaOH. The reaction was monitored by TLC. After 17 hours at room temperature and 3 hours at 60ºC, the solvent was evaporated *in vacuo*. Water (10mL) was addded to the mixture and was extracted with ether. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*, yielding 0.12 g of 1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol. The product is a 7:3 mixture of the epimers **16** and **2**, respectively (yield, 68%).

Method B. To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutane **11** (0.12 g, 0.26 mmol) in THF (10mL) were added 2mL of 2N LiOH aqueous solution. The reaction was monitored by TLC. After 3 hours at 65ºC, the solvent was evaporated *in vacuo*. Water was addded to the mixture and was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*, yielding 0.1 g of an oil that was purified by chromatography. 1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol was obtained (74 mg, 91% yield), as a 7:3 mixture of epimers **16** and **2**, respectively.

Method C. To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutane **11** (0.21 g, 0.45 mmol) in a mixture of THF (2 mL) and MeOH (2 mL) were added 4 mg of K_2CO_3. The reaction was monitored by TLC. After 29 hours at room temperature the solvent was evaporated *in vacuo*. Water was added to the mixture and was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*, yielding an oil that was purified by chromatography. 1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol was obtained (135 mg, 94% yield), as a 7:3 mixture of the epimers **16** and **2**, respectively.

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol (16).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxybutane **11** (0.6 g, 0.13 mmol) in CH_2Cl_2 (1 mL) at -20ºC was added DIBAL-H (0.5 mL, 0.49 mmol, 20% in hexanes). The reaction was monitored by TLC. After 5 hours at -20ºC, methanol was added, the solution was washed with water and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 30 mg (yield, 73%) of (2*R*,3*S*) 1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol **16**.

$[\alpha]_D$=-9.6 (*c*=1.5, $CHCl_3$). ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.07 (s, 6H), 0.90 (s, 9H), 1.22 (d, J=6.8Hz, 3H), 1.44 (s, 9H), 2.7-2.8 (m, b, 1H), 3.4-3.7 (m, 4H), 4.8-4.9 (m, 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.4 (CH_3), 18.2 (C), 18.5 (CH_3), 25.8 (CH_3), 28.3 (CH_3), 47.1 (CH), 64.8 (CH_2), 74.3 (CH), 79 (C), 156 (C) ppm.

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-butane (17).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-butanol **16** (0.11 g, 0.34 mmol) in CH_2Cl_2 (2 mL) were added ethyl vinyl ether (0.32mL, 3.4 mmol) and pyridinium tosylate (catalytic amounts). The reaction was stirred at room temperature under nitrogen until no starting product could

be detected by TLC (4 hours). The solution was washed with water and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated, yielding an oil that was purified by chromatography to give 0.12 g (87% yield) of **17**.

IR (film) $\nu_{max.}$=3350, 2970, 2950, 2930, 2880, 2860, 1720, 1510, 1475, 1465, 1450, 1390, 1365, 1250, 1170, 1125, 1080, 1055, 840, 775 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.06 (s, 6H), 0.9 (s, 9H), 1.1-1.4 (complex signal, 9H), 1.43 (s, 9H), 3.4-4 (complex signal, 6H), 4.75 γ 4.83 (2 q, J=5.3Hz, 1H), 5-5.2 (m, 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.7 (CH_3), 15.2 (CH_3), 16.8 (CH_3), 17.7 (CH_3), 18.1 (C), 20.5 (CH_3), 25.8 (CH_3), 28.3 (CH_3), 46.8 (CH), 47.0 (CH), 61.0 (CH_2), 61.1 (CH_2), 62.6 (CH_2), 63.4 (CH_2), 77.6 (CH), 78.2 (CH), 79 (C), 100.0 (CH), 100.8 (CH) ppm. MS (CI-CH_4) m/e=392 (M^++1, 0.6%), 346 (3.0%), 314 (7.8%), 298 (2.8%), 281 (2.3%), 136 (100%).

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-1-butanol (18).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-butane **16** (0.11g, 0.29 mmol) in tetrahydrofuran (2.5 mL) were added 0.5 mL of tetrabutylammonuim fluoride (1.1M solution in THF). The reaction was monitored by TLC. After 20 minutes, the solution was washed with water and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue (0.22g) was purified by chromatography to afford 69 mg (85% yield) of **18**.

IR (film) ν_{max} = 3400, (b), 2990, 2960, 2890, 1690, 1510, 1455, 1395, 1370, 1250, 1170, 1135, 1100, 1070, 1055, 1015 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.15-1.32 (complex signal, 9H), 1.44 (s, 9H), 3.4-4.1 (complex signal, 6H), 4.63 γ 4.7 (2q, J=5.2Hz, 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=15.1 (CH_3), 17.9 (CH_3), 20.1 (CH_3), 20.5 (CH_3), 28.3 (CH_3), 45.9 (CH), 46.4 (CH), 61.0 (CH_2), 61.5 (CH_2), 61.9 (CH_2), 62.4 (CH_2), 77.2 (CH), 79.7 (C), 79.8 (C), 82.3 (CH), 99.4 (CH), 102.1 (CH) ppm.

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxybutanoic acid (19).

To a solution of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-1-butanol **18** (67 mg, 0.24 mmol) in 1.75 mL of a mixture 1/1/1.5 of $CH_3CN/CCl_4/H_2O$ were added $NaHCO_3$ (0.14g, 1.62 mmol), $NaIO_4$ (0.29 g, 1.37 mmol) and $RuCl_3$ (catalytic amounts). The reaction was stirred at room temperature 48 hours. When no starting material could be detected by TLC, water (1mL) was added. The organic layer was separated. The aqueous phase was washed with ether, acidified with diluted hydrochloric acid and extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated yielding 57 mg of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxybutanoic acid **19**.[21] To facilitate isolation, the crude acid was treated with a solution of diazomethane in ethyl ether until the yellow color of the diazomethane solution was mantained during several minutes. The solution was then concentrated *in vacuo* and purified by chromatography yielding 29 mg of **20** (52% yield from **18**).

20. IR (film) ν_{max} =3360, 2960, 2915, 1735, 1705, 1500, 1445, 1385, 1360, 1340, 1240, 1210, 1160, 1125, 1045, 1025, 1005 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.25 (d, J=4.8 Hz, 3H), 1.42 (s, 9H), 3.80 (s, 3H), 4.1-4.3 (m, 2H), 4.7-4.8 (m, 1H) ppm. ^{13}C-RMN (75 MHz, $CDCl_3$) δ=17.9 (CH_3), 28.3 (CH_3), 48.7 (CH), 52.8 (CH_3), 73.3 (CH), 80 (C), 155.1 (C), 173.9 (C) ppm. MS (CI-NH_3) m/e=251 (M^++18, 49%), 234 (M^++1, 35%), 195(M^++18-C_4H_8, 100%).

(2*S*,3*S*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-propanediol (22).

A solution of (2*S*,3*S*)-3-benzhydrylamino-3-phenyl-1,2-butanediol[5a,5c] (0.29 g, 0.9 mmol) and Boc_2O (0.24 g, 1.1 mmol) in ethyl acetate (1.6 mL) was added *via* cannula to a stirred suspension of 20% $Pd(OH)_2/C$ (23.4 mg) in ethyl acetate (0.4 mL). The mixture was hydrogenated at atmospheric pressure until no starting material could be observed by TLC, filtered through Celite and evaporated. The crude oil was crystallized from ethyl ether/hexane. 0.19 g of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-propanediol were obtained in two crops as a white solid. The mother liquor was concentrated and purified by flash chromatography affording additional 18 mg (total yield, 89%).

$[\alpha]_D$=52.7 (*c*=1, $CHCl_3$). mp: 109-116°C. IR (KBr) ν_{max} =3520, 3380, 3060, 2980, 2880, 1680, 1520, 1170, 890, 760, 720, 630 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.43 (s, 9H), 2.4 (d, J=7.6Hz, 1H), 3.5 (m b), 3.65-3.9 (m, 3H), 4.58 (t, J= 7.9Hz, 1H), 5.15 (m, 1H), 7.3-7.5 (m, 5H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=28.2 (CH_3), 56.6 (CH), 63.0 (CH_2), 74.1 (CH), 80.4 (C), 127.3 (CH), 127.9 (CH), 128.0 (CH), 128.9 (C) ppm. MS (EI) m/e=206 (M^+-$C_2H_5O_2$, 11%), 194 (M^+-C_4H_9O, 2%), 150 (M^+-$C_2H_5O_2$-C_4H_8, 58%), 106 (M^+-$C_2H_5O_2$-C_4H_8-CO_2, 72%), 57 (^{t}Bu, 100%). Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90, H, 7.92, N, 5.24. Found: C, 62.54, H, 7.70, N, 5.15.

(2*S*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-3-phenyl-2-propanol (23).

To a solution of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-propanediol **22** (0.88 g, 3.28 mmol) in dimethylformamide (17 mL) were added TBMS-Cl (0.54 g, 3.61. mmol) and imidazole (0.49 g, 2.22 mmol). The reaction was monitored by TLC. After 12 hours, 30 mL of ether were added to the reaction. The mixture was washed with saturated NH_4Cl aqueous solution. The organic layer was separated, dried over $MgSO_4$ and the solvents were evaporated *in vacuo*. The crude product was purified by chromatography yielding 0.87 g of **23** (89% yield) and 84 mg of starting material (96% conversion).

$[\alpha]_D$=25.9 (*c*=0.21, $CHCl_3$). mp: 43.5-45.5 °C. IR (film) ν_{max} =3410, 2960, 2940, 2870, 1700, 1500, 1375, 1210, 1175, 845, 785, 705 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.04 (s, 3H), 0.06 (s, 3H), 0.92 (s, 9H), 1.41 (s, 9H), 3.44 (d d, J=10.4Hz, J=4.2Hz, 1H), 3.57 (d d, J=10.4Hz, J=3.8Hz, 1H), 3.86 (m, 1H), 4.7-4.9 (m, 1H), 5.9-6.1 (m, 1H), 7.15-7.35 (s,b, 5H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.6 (CH_3), 18.0 (C), 25.8 (CH_3), 28.3 (CH_3), 58.1 (CH), 63.9 (CH_2), 72.9 (CH), 79.3 (C), 126.9 (CH), 127.3 (CH), 128.1 (CH), 139.4 (C), 155.5 (C) ppm. MS (EI) m/e=382 (M^++1, 0.02%), 207 (39%), 206 (M^+-$C_8H_{19}O_2Si$, 6%), 150 (M^+-$C_8H_{19}O_2Si$-C_4H_8, 100%), 106 (M^+-$C_8H_{19}O_2Si$-C_4H_8-CO_2, 88%). Anal. Calcd. for $C_{20}H_{35}NO_4Si$: C, 62.95, H, 9.25, N, 3.67. Found: C, 63.14, H, 9.23, N, 3.62.

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxy-3-phenylpropane (24).

To a solution of **23** (0.46 g, 1.21 mmol) in benzene (17 mL) were added 1.59 g of PPh_3 (6.06 mmol), *p*-nitrobenzoic acid (0.9 g, 4.4 mmol) and diethyl azodicarboxylate (0.95 mL, 6.03 mmol). The reaction was stirred at room temperature 12 hours. The mixture was concentrated *in vacuo*. The residue was purified by flash chromatography yielding 0.45 g of **24** (71% yield).

$[\alpha]_D$=37.4 (*c*=1.5, $CHCl_3$). IR (film) ν_{max} =3370 (broad), 2940, 2920, 2820, 1720, 1700, 1605, 1525, 1270, 1165, 1110, 835, 720 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.01 (s, 6H), 0.88 (s, 9H), 1.32 (s, 9H), 3.6-3.8 (two d d, 2H), 5.1-5.3 (m, 1H), 5.3-5.5 (m, 2H), 7.35 (s, b, 5H), 8.23 (d, 2H), 8.31 (d,

2H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5 (CH_3), 19 (C), 25.7 (CH_3), 28.1 (CH_3), 55.0 (CH), 61.6 (CH_2), 77.4 (CH), 79 (C), 123.5 (CH), 127.0 (CH), 127.9 (CH), 128.7 (CH), 130.8 (CH), 136 (C), 139 (CH), 151 (C), 155 (C), 160 (C) ppm. MS (EI) m/e=417 (M^+-$C_6H_{15}Si$+2, 14%), 250 (15%), 224 (27%), 207 (48%), 206 (M^+-$C_7H_{17}OSi$-$C_8H_5NO_4$, 28%), 150 ($C_7H_4NO_3^+$, 100%), 132 (49%), 106 (M^+-$C_7H_{17}OSi$-$C_8H_5NO_4$-C_4H_8-CO_2, 53%)

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-3-phenyl-2-propanol (25).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-*p*-nitrophenylcarbonyloxy-3-phenylpropane **24** (0.45 g, 0.85 mmol) in CH_2Cl_2 (7 mL) at -20ºC was added DIBAL-H (3.5 mL, 3.42 mmol, 20% in hexanes) The reaction was monitored by TLC. After 3 hours at -20ºC, methanol was added, the solution was washed with water and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatogrphy yielding 0.24 g (yield, 73%) of (2*R*,3*S*) 1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-3-phenyl-2-propanol **25**.

$[\alpha]_D$=2.65 (*c*=1.1, $CHCl_3$). ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.07 (s, 6H), 0.91 (s, 9H), 1.40 (s, 9H), 2.5-2.7 (m b, 1H), 3.52 (d d J=10.1Hz, J=6.8Hz, 1H), 3.67 (d d J=4.7Hz, J=2.0Hz, 1H), 4.8-4.9 (m,1H), 4.6-4.8 (m,1H), 5.4-5.6 (m, 1H), 7.2-7.4 (s, ample, 5H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=-5.5 (CH_3), 18.2 (C), 25.8 (CH_3), 28.3 (CH_3), 55.7 (CH), 64.2 (CH_2), 74.5 (CH), 79.5 (C), 126.7 (CH), 127.3 (CH), 128.4 (CH), 141 (C), 155.7 (C) ppm.

(2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenylpropane (26).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-3-phenyl-2-propanol **25** (0.05 g, 0.13 mmol) in CH_2Cl_2 (2 mL) were added ethyl vinyl ether (0.12 mL, 1.3 mmol) and catalytic amounts of pyridinium *p*-toluenesulfonate. The reaction was stirred at room temperature under nitrogen atmosphere until no starting product could be detected by TLC. The solution was washed with water and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated, yielding an oil that was purified by chromatography to give 47 mg (80% yield) of **26**.

IR (film) ν_{max} =3450, 3070, 3040, 2980, 2960, 2940, 2890, 2860, 1730, 1490, 1390, 1365, 1255, 1170, 1120, 1075, 1055, 940, 840, 780, 700 cm^{-1}. ^{1}H-RMN (200 MHz, CDCl3, $TMS_{int.}$) δ=0.06 γ 0.08 (2s, 6H), 0.92 γ 0.94 (2s, 9H), 0.9-1.3 (complex signal, 6H), 1.42 (s, 9H), 2.9-4 (complex signal, 5H), 4.3 γ 4.7 (2m, 1H), 4.8-4.9 γ 4.9-5.1 (2m, 1H), 5.6-5.9 (m, 1H), 7.2-7.4 (complex signal, 5H) ppm. ^{13}C-RMN (50 MHz, CDCl3) δ=-5.6 (CH_3), 15.0 (CH_3), 15.2 (CH_3), 20.0 (CH_3), 20.4 (CH_3), 25.9 (CH_3), 28.3 (CH_3), 54.2 (CH), 54.9 (CH), 60.6 (CH_2), 62.8 (CH_2), 79.1 (CH), 80.1 (CH), 99.8 (CH), 101.1 (CH), 126.5 (CH), 126.6 (CH), 126.9 (CH), 128.1 (CH) ppm. MS (EI) m/e=206 (M^+-$C_5O_2H_{10}$-C_7OSiH_{17}, 37%), 150 (M^+-$C_5O_2H_{10}$-C_7OSiH_{17}-C_4H_8, 100%), 106 (82%).

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenyl-1-propanol (27).

To a solution of (2*R*,3*S*)-1-*tert*-butyldimethylsilyloxy-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenylpropane **26** (0.13g, 0.30 mmol) in tetrahydrofuran (2.5 mL) were added 0.55 mL (0.6 mmol) of tetrabutylammonuim fluoride (1.1M in THF). The reaction was monitored by TLC. After 15 minutes, the

solution was washed with water and the organic layer extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography to give 93 mg (95% yield) of **27**.

IR (film) ν_{max} =3430, (b), 3050, 3020, 2970, 2920, 2870, 1700, 1600, 1585, 1495, 1450, 1390, 1365, 1340, 1290, 1250, 1170, 1130, 1080, 1050, 950, 900, 870, 750, 700 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.9-1.3 (complex signal, 6H), 1.43 (s, 9H), 3-4.1 (complex signal, 5H), 4.5-4.7 (m, 1H), 4.8-5 (m, 1H), 5.3-5.5 γ 5.5-5.7 (2m, 1H) 7.1-7.4 (complex signal, 5H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=14.9 (CH_3), 15.1 (CH_3), 19.8 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 54.4 (CH), 54.7 (CH), 61.1 (CH_2), 61.5 (CH_2), 62.3 (CH_2), 63.2 (CH_2), 78.6 (CH), 79.7 (C), 80 (C), 83.6 (CH), 99.5 (CH), 102.1 (CH), 126.4 (CH), 126.7 (CH), 127.1 (CH), 127.3 (CH), 128.3 (CH), 140 (C), 156 (C) ppm. MS (EI) m/e=206 (M^+-$C_5O_2H_{10}$-C_7OSiH_{17}, 29%), 150 (100%), 106 (98%). Anal. Calcd. for $C_{18}H_{29}NO_5$: C, 63.74, H, 8.56, N, 4.13. Found: C, 63.61, H, 8.72, N, 4.05.

(2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenylpropanoic acid (21).

To a solution of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenyl-1-propanol **27** (0.13 g, 0.39 mmol) in 3 mL of a mixture of $CH_3CN/CCl_4/H_2O$ (1/1/1.5) were added $NaHCO_3$ (0.21g, 2.53 mmol), $NaIO_4$ (0.46 g, 2.17 mmol) and $RuCl_3$ (catalytic amount). The reaction was stirred at room temperature 48 hours. When no starting material could be detected by TLC, water (1mL) was added. The organic layer was separated. The aqueous phase was washed with ether, acidified with a phosphate solution of pH=5.6 and extracted with ether. The combined organic phases were dried over $MgSO_4$ and concentrated yielding 0.1 g of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenylpropanoic acid **21** (75% crude yield). In order to facilitate isolation and characterization, crude acid **21** was treated with a solution of diazomethane in ethyl ether until the yellow color of the diazomethane solution was mantained during several minutes. The solution was then concentrated *in vacuo* and purified by chromatography yielding 90 mg of **28** (65% yield from **27**).

Methyl (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-(1-ethoxyethoxy)-3-phenylpropanoate **28.** IR ($CHCl_3$) ν_{max} = 3410, 2980, 1730, 1700, 1360, 1155, 1100, 1040, 1020, 920 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=0.78 (t, J=7Hz, 3H), 0.95 (t, J=7Hz, 3H), 1.09 (d, J=5.4Hz, 3H), 1.16 (d, J=5.4Hz, 3H), 1.41 (s, 18H), 2.6-2.8 (m, 1H), 3.1-3.4 (m, 3H), 3.76 (s, 6H), 4.3-4.5 (m, 3H), 4.73 (q, J=5.4, 1H), 5.2 (m, 1H), 5.6 (m, 1H), 7.2-7.4 (complex signal, 5H) ppm. ^{13}C-RMN (75 MHz, $CDCl_3$) δ=14.9 (CH_3), 19.2 (CH_3), 28.3 (CH_3), 52.1 (CH), 56.2 (CH), 53.0 (CH_3), 58.9 (CH_2), 61.1 (CH_2), 73.5 (CH), 76 (CH), 80 (C), 98.7 (CH), 100.7 (CH), 126.5 (C), 126.6 (CH), 126.7 (CH), 127.3 (C) 127.5 (C), 128.2 (CH), 128.3 (CH), 128.6 (CH), 155 (C) ppm. Anal. Calcd. for $C_{19}H_{29}NO_6$: C, 62.11, H, 7.96, N, 3.81. Found: C, 63.10, H, 8.03, N, 3.79.

Acid hydrolisis of acetal **28** afforded quantitatively methyl (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-phenylpropanoate **29.**

$[\alpha]_D$=-7.6 (*c*=1.5, $CHCl_3$), lit.[2a]: $[\alpha]_D$=-7 (*c*=1.2, $CHCl_3$). m.p.: 128°C. IR (KBr) ν_{max} = 3500, 3375, 3015, 3000, 2965, 2920, 1730, 1680, 1505, 1440, 1380, 1355, 1295, 1240, 1165, 1095, 1045, 1020, 935, 920, 895, 700 cm^{-1}. ^{1}H-RMN (200 MHz, $CDCl_3$, $TMS_{int.}$) δ=1.41 (s, 9H), 3.1-3.2 (m, 1H), 3.8 (s, 3H), 4.4-4.5 (m, 1H), 5.2 (m, 1H), 5.4 (m, 1H) ppm. ^{13}C-RMN (50 MHz, $CDCl_3$) δ=28.2 (CH_3), 53.1 (CH_3), 56.0 (CH), 73.5 (CH), 79.9 (C), 126.7 (CH), 127.7 (CH), 128.6 (CH), 140 (C), 155.1 (C), 174 (C) ppm.

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[§]Dedicated to our teacher and friend, Fèlix Serratosa, *in memoriam.*

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21.- Even very careful acidic treatments at the work-up stage afford mixtures of α-hydroxy acid **19** and its 1-ethoxy ethoxy acetal.

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