Enantioselective Syntheses of Conformationally Rigid, Highly Lipophilic Mesityl-Substituted Amino Acids

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Three *N*-Boc-protected amino acids substituted with a mesityl (=2,4,6-trimethylphenyl) group were synthesized in enantiomerically pure form, either by asymmetric epoxidation or by aminohydroxylation as the source of chirality. The 3-mesityloxirane-2-methanol **7**, easily available in high enantiomer purity by *Sharpless* epoxidation, was converted into 3-{[(*tert*-butoxy)carbonyl]amino}-3-mesitylpropane-1,2-diol **9** by a regio- and stereoselective ring opening with an ammonia equivalent (sodium azide or benzhydrylamine), followed by hydrogenation and *in situ* treatment with $(Boc)_2O$ (Boc = [(*tert*-butoxy)carbonyl]) (*Scheme 3*). Oxidative cleavage of the diol fragment in **9** afforded *N*-[(*tert*-butoxy)carbonyl]-α-mesitylglycine **1** of > 99% ee. This amino acid was also prepared in enantiomerically pure form starting from 2,4,6-trimethylstyrene (**11**) by a regioselective *Sharpless* asymmetric aminohydroxylation, followed by a 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO)-catalyzed oxidation (*Scheme 4*). On the other hand, 1-[(*tert*-butoxy)carbonyl]-2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-3-mesitylaziridine **14** was prepared from **9** by a sequence involving selective protection of the primary alcohol (as a silyl ether), activation of the secondary alcohol as a mesylate, and base-induced (NaH) cyclization (*Scheme 5*). The reductive cleavage of the aziridine ring (H_2, Pd/C), followed by alcohol deprotection (Bu_4NF/THF) and oxidation (pyridinium dichromate (PDC)/DMF or (TEMPO)/NaClO) provided, in high yield and enantiomeric purity, *N*-[(*tert*-butoxy)carbonyl]-β-mesitylalanine **2**. Alternatively, the regioselective ring opening of the aziridine ring of **14** with lithium dimethylcuprate, followed by silyl-ether cleavage and oxidation lead to *N*-[(*tert*-butoxy)carbonyl]-β-mesityl-β-methylalanine **3**. A conformational study of the methyl esters of the *N*-Boc-protected amino acids **1** and **3** carried out by variable-temperature ^{1}H-NMR and semi-empirical (AM1) calculations shows the strong rotational restriction imposed by the mesityl group.

1. Introduction. – Peptides and proteins are mediators of multiple biological processes, their activity being usually coupled to a given conformation. In the field of small peptides, the absence of the multiple long-range interactions that stabilize protein conformations has fostered the preparation of a myriad of synthetic analogues designed to modify their conformational behavior and, consequently, their biological activity [1]. These modified peptides are finding increasing importance both as drugs (see, *interalia*, [2]), and in structure-activity relationship studies [3]. One of the simplest approaches to these modified peptides is the substitution of one or several amino acids by unnatural residues [1–6][1]), and this strategy has also been applied in protein-structure/function studies [7] by site-specific amino acid incorporation techniques [8].

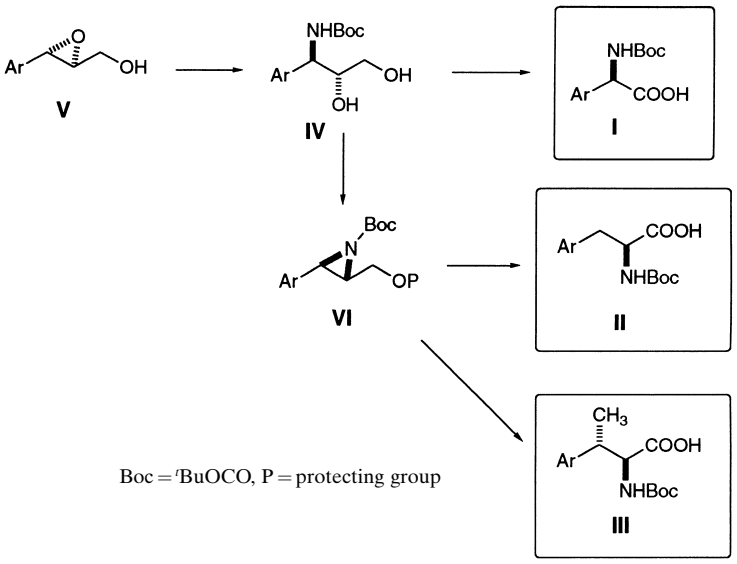
The need for specifically designed amino acids as constituents of modified peptides and proteins has stimulated the development of new synthetic methodologies for their preparation in enantiomerically pure form [9], asymmetric synthesis being the most

[1]) For some examples of conformationally restricted peptides with unnatural amino acids, see [4]; for some examples of modified peptides with hydrophobic amino acids, see [5].

practical and economical approach, especially in the case of very hydrophobic side-chain residues, where the enzymatic resolution fails [10].

In recent years, we have been involved in the development of enantioselective syntheses of several important types of *N*-Boc-amino acids [11–14]. Among them, arylglycines **I** [11], arylalanines **II** [12], and β-aryl-β-methylalanines **III** [12–13] can be prepared in a very straightforward and practical way from the corresponding intermediates, the enantiomerically pure *N*-Boc-3-amino-1,2-diol **IV**. Compounds of type **IV** are readily available by a regio- and stereospecific ring opening with an ammonia synthetic equivalent [11–15] of the corresponding epoxy alcohols of type **V** which, in turn, can be prepared with full stereochemical control from allyl alcohols by *Sharpless* epoxidation [16] (*Scheme 1*).

Scheme 1



Boc = ^{t}BuOCO, P = protecting group

The substitution of a phenyl by another aromatic group with different electronic or steric characteristics is a well-established strategy in the synthesis of peptide or protein analogues [4–7]. In this context, amino acids containing in their side chain a 2,4,6-trimethylphenyl (mesityl) group could be very useful in the preparation of more hydrophobic and conformationally restricted analogues. Up to now, however, the use of such residues has been rare, probably because of the difficulties encountered in the preparation of enantiomerically pure amino acids that contain this group in the side chain [17]. Whereas (2,4,6-trimethylphenyl)glycine (= α-mesitylglycine) has not been described up to now, all attempts of enzymatic resolution of 3-(2,4,6-trimethylphenyl)alanine (= β-mesitylalanine) have been reported to fail [17]. Notwithstanding, several peptide analogues with very promising biological activity have been prepared in which a phenylalanine is replaced by a β-mesitylalanine residue; however, the racemic amino acid had to be introduced and the deprotected diastereoisomeric peptides separated by HPLC [17][18]. On the other hand, several conformationally restricted

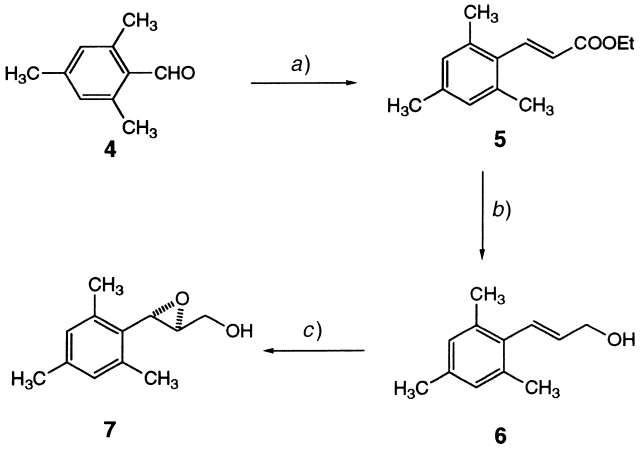
β-aryl-β-methylalanines have been used in structure-activity studies of biologically important peptides [6][19], but whether the β-mesityl-β-methylalanine is a potentially useful amino acid is still unknown.

We wish to report herein the successful enantioselective synthesis of three important *N*-Boc-protected amino acids bearing a mesityl residue, *i.e.*, *N*-[(*tert*-butoxy)carbonyl]-α-mesitylglycine **1** (**I**, Ar = mesityl), *N*-[(*tert*-butoxy)carbonyl]-β-mesitylalanine **2** (**II**, Ar = mesityl), and *N*-[(*tert*-butoxy)carbonyl] β-mesityl-β-methylalanine **3** (**III**, Ar = mesityl), using a catalytic asymmetric reaction (*Sharpless* epoxidation or aminohydroxylation) to introduce chirality. Moreover, the role of the mesityl residue as a conformational lock (*i.e.*, by increasing barriers for conformer interconversion) in these amino acids was demonstrated by a combined NMR and theoretical (AM1) conformational study of the methyl esters of compounds **1** and **3**.

2. Results and Discussion. – 2.1. *Enantioselective Synthesis of* N-*Boc-Protected* α-*Mesitylglycine* **1**. The synthesis of *N*-Boc-protected α-mesitylglycine **1** was initially planned to make use of our previously described methodology for the preparation of α-arylglycines [11b]. First of all, commercially available mesitaldehyde (=2,4,6-trimethylbenzaldehyde; **4**) was converted into mesitylpropenol **6** by the standard sequence of *Wittig* olefination (→**5**) followed by diisobutylaluminium hydride (DIBAL-H) reduction (*Scheme 2*). Subsequent catalytic asymmetric *Sharpless* epoxidation [16] with diisopropyl L-tartrate afforded (2*S*,3*S*)-3-mesityloxirane-2-methanol (**7**) in 63% yield and 88% ee. The high crystallinity of this epoxy alcohol allowed the enantiomer excess to be increased up to 99% by repeated recrystallization from hexanes.

Enantiomerically pure oxiranemethanol **7** was treated under *Sharpless* conditions [20] ($Ti(O^iPr)_4/CH_2Cl_2$) using benzhydrylamine (=(diphenylmethyl)amine) as an

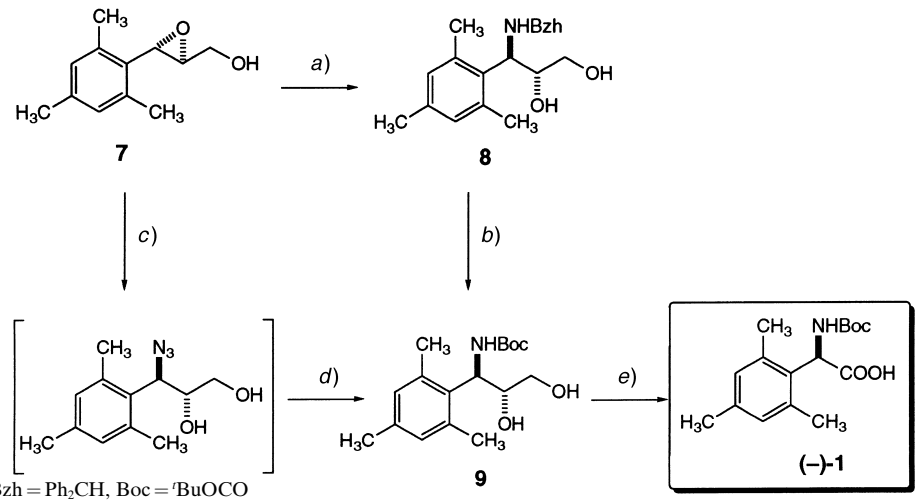
Scheme 2



a) $Ph_3PCHCOOEt$, CH_2Cl_2; 97%. *b*) DIBAL-H, Et_2O; 86%. *c*) ^tBuOOH, diisopropyl L-tartrate, $Ti(O^iPr)_4$, CH_2Cl_2, −30°, 63%.

ammonia surrogate but, quite unexpectedly, without success. In our hands, this is the first epoxy alcohol that does not provide the corresponding aminodiol by treatment with an amine and titanium tetraisopropoxide [11][14c][15]. Quite gratifyingly, however, a totally regio- and stereospecific oxirane-ring opening took place with the same amine but under *Crotti*'s conditions [21] ($LiClO_4$/MeCN) to afford (2*R*,3*R*)-3-(benzhydrylamino)-3-mesityl-1,2-diol **8** in 97% yield (*Scheme 3*). Catalytic hydrogenolysis ($Pd(OH)_2$/C) of **8** with *in situ* protection (Boc_2O) afforded in 68% yield the *N*-Boc-protected 3-amino-3-mesityl propane-1,2-diol **9**, which is the key intermediate in our approach to the synthesis of mesityl-substituted amino acids. An alternative preparation of this key intermediate was performed using NaN_3 as a synthetic equivalent of ammonia. Thus, ring opening of the oxiranemethanol **7** under *Crotti*'s conditions gave the corresponding azido diol, which was immediately hydrogenated and protected to provide **9** in 62% overall yield (*Scheme 3*). The oxidative cleavage ($KMnO_4$/$NaIO_4$) of the diol moiety of **9** led to the desired *N*-Boc-protected α-mesitylglycine (−)-**1** in 72% yield. The enantiomer purity was checked by HPLC (*Chiralcel OD*) after reduction to (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-2-mesitylethanol (−)-**10**); the determined >99% ee was in good agreement with that of the starting epoxy alcohol.

Scheme 3



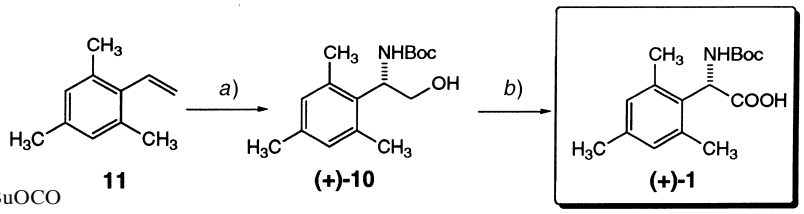
Bzh = Ph_2CH, Boc = ^{t}BuOCO

a) Ph_2CHNH_2, $LiClO_4$, MeCN; 97%. *b*) H_2, $Pd(OH)_2$/C, $(Boc)_2O$, AcOEt; 68%. *c*) NaN_3, $LiClO_4$, MeCN. *d*) H_2, Pd/C, $(Boc)_2O$, MeOH; 62%, two steps. *e*) $NaIO_4$, $KMnO_4$, Na_2CO_3, dioxane, H_2O; 72%.

Although these methodologies proved to highly reliably lead to enantiomerically pure *N*-Boc-protected α-mesitylglycine, the synthesis of α-arylglycines recently described by *Reddy* and *Sharpless* [22], based on the asymmetric aminohydroxylation [23], would be an even shorter approach. Literature precedents, however, were not encouraging since 2,4,6-trimethylstyrene (**11**) was not among the examples prepared by *Reddy* and *Sharpless* and, more significantly, a recent report [24] described that this reaction was sluggish, yielding, after 7.5 h, only 21% of *N*-Boc-protected (*S*)-2-amino-

2-mesitylethanol (+)-**10** in a poor 56% ee. Nevertheless, we decided to perform the aminohydroxylation of 2,4,6-trimethylstyrene (**11**) with *tert*-butyl carbamate as a N-source and bis(dihydroquininyl) phthalazine-1,4-diyl diether ($(DHQ)_2PHAL$) as a ligand. In our hands, the aminohydroxylation reaction worked reasonably well[2]), affording the amino alcohol (+)-**10** in 44% yield as the predominant component of a 4:1 mixture of regioisomers. The unwanted minor regioisomer was removed by chromatography, and the initial 88% ee could be increased to 99% by crystallization from Et_2O. The 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO)-catalyzed oxidation [25] of alcohol (+)-**10** provided the *N*-Boc-protected (*S*)-α-mesitylglycine (+)-**1** in 82% yield and with no decrease in optical purity.

Scheme 4



Boc = ^{t}BuOCO

a) ^{t}BuOCONH$_2$, ^{t}BuOCl, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$; 44%. *b*) TEMPO, NaClO, KBr, acetone; 82%.

Remarkably enough, both approaches reported here for the preparation of **1** allow the synthesis of both enantiomers, the final configuration being determined simply by the ligand used in the catalytic asymmetric epoxidation or aminohydroxylation.

2.2. *Synthesis of* N-*Boc-Protected* β-*Mesitylalanines* **2** *and* **3**. The syntheses of the *N*-Boc-protected β-mesitylalanine **2** and of β-mesityl-β-methylalanine **3** were envisaged to proceed *via* the intermediacy of (2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl] 2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-3-mesitylaziridine (**14**). The latter was readily prepared from the enantiomerically pure *N*-Boc-protected aminodiol **9** by a sequence involving the protection of the primary-alcohol function as a *tert*-butyldimethylsilyl ether ($\rightarrow$**12**), mesylation of the secondary-alcohol function ($\rightarrow$ **13**), and treatment with NaH in THF (*Scheme 5*). Hydrogenolytic cleavage of aziridine **14** was completely regioselective at the benzylic position, leading almost quantitatively to *N*-Boc-protected (2*S*)-1-{[(*tert*-butyl)dimethylsilyl]oxy]–3-mesitylpropan-2-amine **15**. Bu_4NF-Mediated cleavage of the silyl ether ($\rightarrow$**16**) followed by oxidation of the primary alcohol afforded *N*-Boc-protected β-mesitylalanine (–)-**2** in excellent yield. The final oxidation step could be performed either with pyridinium dichromate (PDC)/DMF [26] (92% yield) or with sodium hypochlorite, TEMPO, and KBr [25] (95% yield). The optical purity of (–)-**2** was checked by chiral HPLC of the corresponding methyl ester and, in good agreement with the optical purity of the starting epoxy alcohol, was >99%, irrespective of the oxidation protocol employed.

The synthesis of the sterically hindered *N*-Boc-protected amino acid (–)-**3** was planned to involve the ring opening of aziridine **14** by an appropriate C-nucleophile. This could be achieved by treatment with lithium dimethylcuprate, although the target

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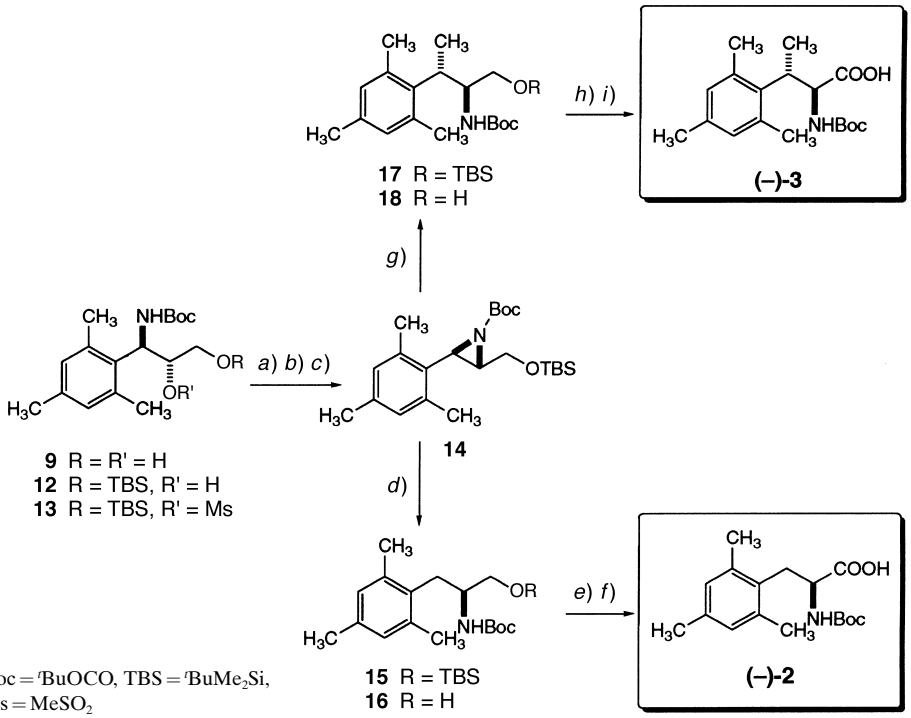
[2]) We found that the *Sharpless* aminohydroxylation is extremely sensitive to the purity of the reagents.

Scheme 5

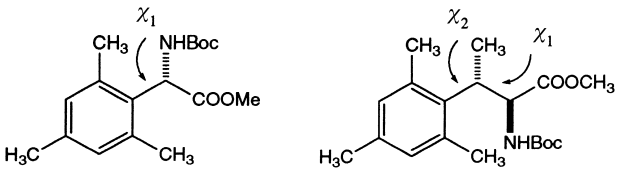


a) ^{t}BuMe$_2$SiCl, DMF, 1*H*-imidazole; 91% (**12**). *b*) MsCl, CH_2Cl_2, 4-(dimethylamino)pyridine (DMAP); 82% (**13**). *c*) NaH, THF; 94% (**14**). *d*) H_2, Pd/C, AcOEt; quant. (**15**). *e*) Bu_4NF, THF; 82% (**16**). *f*) NaClO, TEMPO, acetone 95% (**2**). *g*) Me_2CuLi, Et_2O; 48% (**17**). *h*) Bu_4NF, THF; 86% (**18**). *i*) NaClO, TEMPO, KBr, acetone 91% (**3**).

O-protected amino alcohol was formed with moderate regioselectivity (2 : 1), probably due to the high steric shielding exerted by the two *ortho*-Me groups. The minor regioisomer could be separated by chromatography, and the desired silyl ether **17** was deprotected with Bu_4NF in good yield (→ **18**). TEMPO-Catalyzed oxidation of **18** took place uneventfully as in the previous cases, leading to the *N*-Boc-protected (2*S*,3*S*)-β-mesityl-β-methylalanine (–)-**3** in excellent yield (*Scheme 5*).

2.3. *Conformational Behavior of α-Mesitylglycine and β-Mesityl-β-methylalanine.* The usefulness of incorporating amino acids with conformational restrictions into peptides as a method to study structure-function relationships has been stressed mainly by *Hruby* and co-workers [6][19][27][3]). Before including the new amino acids α-mesitylglycine and β-mesityl-β-methyl-alanine in the toolkit for the construction of modified peptides, it is important to know their conformational behavior in comparison with that of their phenyl-substituted analogues. This can provide a clue as to how the conformation of peptide chains will be modified by the inclusion of these amino acids. To gather this knowledge, we decided to perform a conformational study of the

[3]) For asymmetric syntheses of β-aryl-β-methylalanines and tyrosines, see [28].



corresponding methyl esters **19** and **20**, which were easily prepared from **1** and **3**, respectively, by treatment with MeI/$KHCO_3$ in DMF.

In α-mesitylglycine derivatives, the only relevant dihedral angle is the one corresponding to the rotation around the C–C bond between the aromatic ring and the methine moiety (χ_1). The conformational hypersurface of *N*-Boc-protected α-mesitylglycine methyl ester **19** was explored with the RHF version of the semi-empirical SCF-MO procedure AM1 [29] as implemented in the SPARTAN package of programs [30]. In the minimum-energy conformer (see *Fig. 1*), the mesityl ring is eclipsed with the methine C–H bond to avoid the repulsions of the *ortho*-Me groups with the methoxycarbonyl and Boc-amino groups. The dihedral angle χ_1 in the minimum-energy conformation is 11°. The rotation around the dihedral χ_1 was studied by stepwise variation of this parameter (10° increments) with full optimization of all other geometrical parameters. The resulting energetic profile (see *Fig. 2*) exhibits a maximum around 90°. Although the transition state corresponding to the rotation could not be characterized, it is clear that, in the energetic maximum, the position of the aromatic ring is perpendicular to the C–H bond, and its energy is *ca.* 7.7 kcal mol^{-1} above the minimum.

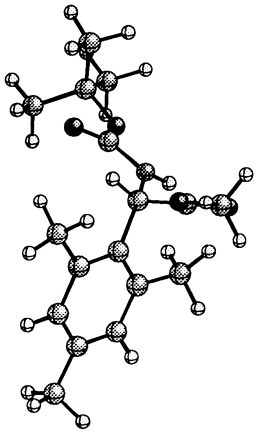


Fig. 1. *AM1-Optimized structure of the minimum-energy conformer of* N-*Boc-protected* α*-mesitylglycine methyl ester* **19**

The energy barrier associated with this rotation in **19** was measured by a variable-temperature ^{1}H-NMR experiment in CD_2Cl_2. Whereas at room temperature both *ortho*-Me groups gave only one resonance at 2.36 ppm, this signal started broadening on lowering the temperature (*Fig. 3*) and finally split into two resonances (at −90°, 2*s* at δ 2.11 and 2.47). The coalescence temperature was −66.5°. According to well-

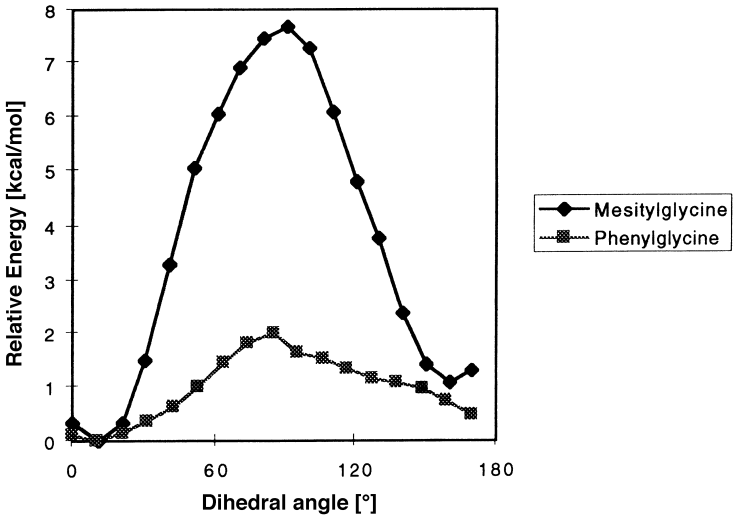


Fig. 2. *Relative energies of* N-*Boc-protected* α-*mesitylglycine methyl ester* **19** *and* N-*Boc-protected* α-*phenylglycine methyl ester as a function of the dihedral angle* χ_1

known equations of dynamic NMR [31], this temperature was used to calculate the activation free energy for the rotation: $\Delta G^{\ddagger} = -9.7$ kcal mol^{-1}; this value is in good agreement with the energetic barrier found by the coordinate driving at the semi-empirical AM1 level.

For comparison, an analogous coordinate driving was performed at the same level of theory for the α-phenylglycine methyl ester[4]). As it can be seen in *Fig. 2*, the shape of the curve is fairly similar, both the minimum and the maximum being very close, from the geometrical point of view, to the mesityl compound. The size of the barrier, however, is much lower: only 2.0 kcal mol^{-1}. It can thus be concluded that the effect of the two *ortho*-Me groups is almost exclusively an increase of the rotational barrier. Thus, using α-mesitylglycine instead of α-phenylglycine would induce an important conformational restriction in the side chain making the peptide topographically much more constrained.

The conformational analysis of β-mesityl-β-methylalanine methyl ester **20** is more complex since two significant dihedral angles χ_1 and χ_2 should be taken into account. A systematic conformational search around the corresponding C–C bonds led to the characterization of three staggered conformers **I**–**III** arising from the rotation of the dihedral angle χ_1 (see *Fig. 4*). The most stable conformer **I** has the two H-atoms *anti*-periplanar ($\chi_1 = 169.4°$), although the energy difference between this conformer **I** and the two synclinal ones is only 1.4–1.6 kcal mol^{-1}. Quite interestingly, in all conformers **I**–**III**, the aromatic ring was eclipsed to the benzylic C–H bond, the χ_2 dihedral angle being in all cases close to 0°. The arrangement of the mesityl ring is thus analogous to the one found in the conformational analysis of α-mesitylglycine (*Fig. 5*).

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[4]) The conformational rigidity of *N*-([*tert*-butoxy)carbonyl]-α-phenylglycine has allowed its use as an efficient auxiliary reagent for the assignment of the absolute configuration of chiral primary amines by ^{1}H-NMR [32].

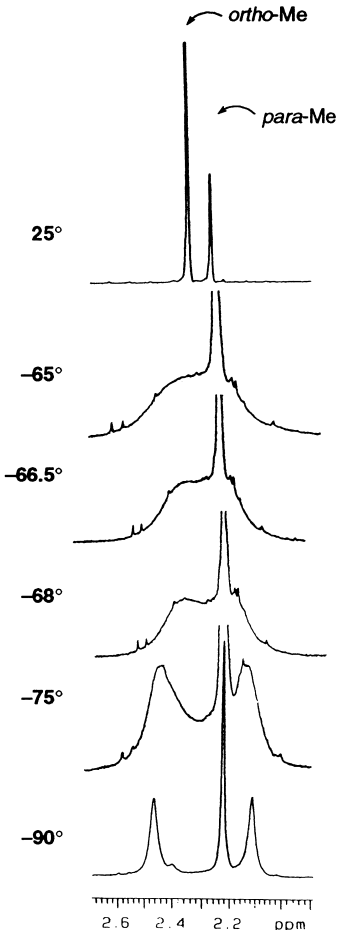

Fig. 3. *Variable-temperature ^{1}H-NMR spectrum of* **19** *in CD_2Cl_2*

For each of the conformers **I**–**III**, a coordinate driving was performed by a stepwise change of the dihedral-angle value χ_2, with optimization of all other parameters, as described for **19** (see *Fig. 6*). Interestingly enough, the value of χ_2 is very similar for all three maxima, being *ca.* 90–110°, and the energies of all three maxima are also very

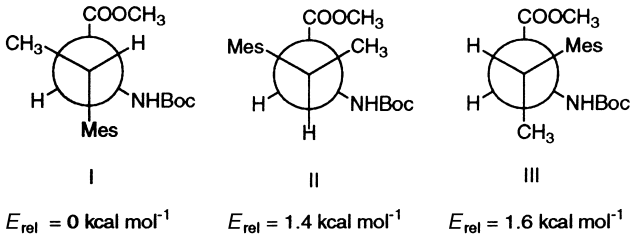

Fig. 4. *AM1-Calculated relative energies of the staggered conformers* **I**–**III** (dihedral angle χ_1) *of* N-*Boc-protected β-mesityl-β-methylalanine methyl ester* **20**

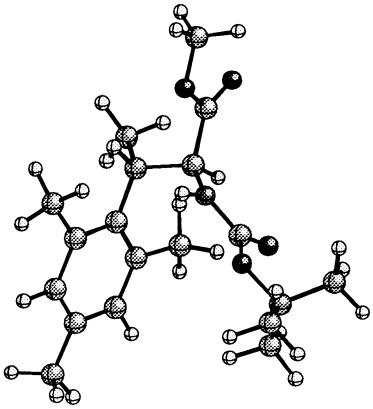

Fig. 5. *AM1-Optimized structure of the minimum-energy conformer of* N-*Boc-protected β-mesityl-β-methylalanine methyl ester* **20**

similar, differing by less than 0.5 kcal mol^{-1} [5]). An inspection of the geometry of these maxima indicate that both *ortho*-Me groups simultaneously contribute to hinder the rotation of the mesityl group: while one of them is interacting with the β-Me group, the other interacts with the amino moiety. It is now easy to understand why the absence of one of these *ortho*-Me groups gives rise to much lower energy barriers [28]. The energy barrier of 14.8 kcal · mol^{-1} was again estimated as the energy difference between the minimum and the highest point of the plot (*Fig. 6*). The ^{1}H-NMR spectrum ($CDCl_3$) of

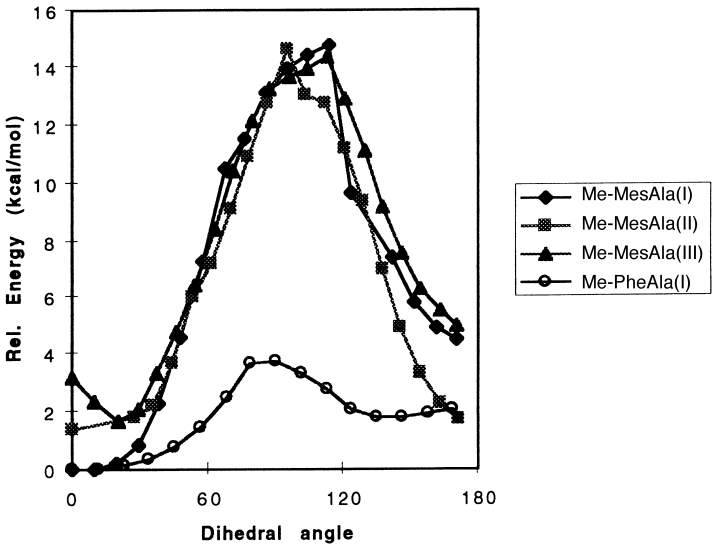

Fig. 6. *Relative energies of* N-*Boc-protected-β-mesityl-β-methylalanine methyl ester* **20** (starting from the three staggered conformers **I**–**III** of χ_1) *and of* N-*Boc-protected β-methyl-β-phenylalanine methyl ester* (conformer **I**, χ_1 (H–C–C–H) = 180°) *as the function of the dihedral angle* χ_2

[5]) During the increase of χ_2 in the coordinate driving of conformer **I**, the dihedral angle χ_1 changed to a synclincal conformation of type **II**. As a consequence, the final energy and geometry after a 180° rotation are not the initial ones.

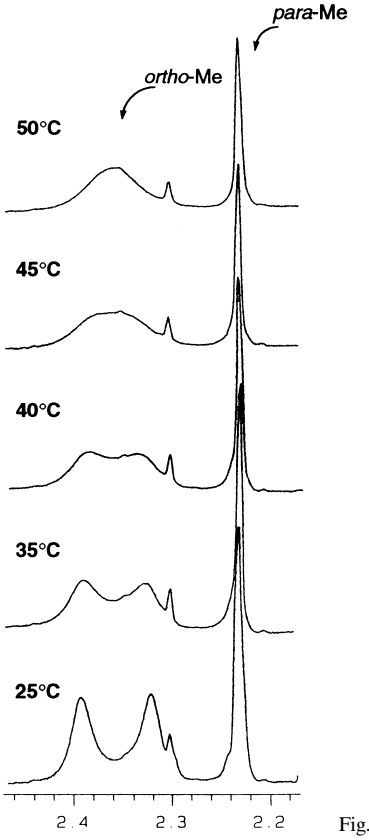

Fig. 7. *Variable-temperature ^{1}H-NMR spectrum of* **20** *in* $CDCl_3$

methyl ester **20** exhibited already at room temperature two signals for the *ortho*-Me groups (*Fig. 7*). On temperature increase, both signals smeared between 40 and 50°, the coalescence temperature being 45°, which resulted in an activation free energy ($\Delta G^{\neq} =$ 16.2 kcal mol^{-1}) in excellent agreement with the calculated value. These values are in the same range as those observed for β,2′,6′-trimethyltyrosines [28], which have been synthesized and incorporated into peptides for conformational and biological studies.

3. Conclusions. – In summary, we have developed the first enantioselective synthesis of *N*-Boc-protected α-mesitylglycines and β-mesitylalanines **1**–**3** using *Sharpless* asymmetric epoxidation and aminohydroxylation methodologies. Our approach to β-mesitylalanines *via N*-Boc-protected 2-mesityl-3-[(silyloxy)methyl]aziridine **14** offers the additional advantage of allowing the preparation of configurationally completely defined β-methyl-substituted analogues. According to variable-temperature ^{1}H-NMR studies and semi-empirical AM1 calculations, the conformation of the mesityl group in these amino acids is very similar to that of the phenyl group in α-phenylglycine and β-phenylalanine analogues, but the barriers to rotation around the C(α/β)–C(aryl) bond are much higher in the mesityl derivatives. Thus, the incorporation of the *N*-Boc-protected-α-mesitylglycine **1**, β-mesitylalanine **2**, and β-mesityl-β-

methylalanine **3** into modified peptides should represent, besides an important increase in lipophilicity, the introduction of a highly local constraint in the peptide conformation without a significant change in the geometry of the minimum-energy conformer.

Experimental Part

General. THF and Et_2O were distilled over Na/benzophenone and DMF and CH_2Cl_2 were distilled over CaH_2. The 2-ethenyl-1,3,5-trimethylbenzene (=2,4,6-trimethylstyrene; **11**) was prepared by *Wittig* olefination of mesitaldehyde (**4**), yielding a product spectroscopically identical to the one described in [33]. Column chromatography (CC): Et_3N-pretreated (2.5% *v*/*v*) SiO_2 (70–230 mesh). Anal HPLC: *Chiralcel® OD* (25 cm) or *Chiralcel® ODR* (25 cm) column; t_R in min. $[\alpha_D]$: at r.t. (23°); *c* in g/100 ml. M.p.: open capillary tubes; uncorrected. IR Spectra: NaCl film or KBr pellet; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: at 200 or 300 MHz (^1H) and 50.3 or 75.4 MHz (^{13}C); ^{13}C-multiplicities by DEPT; δ in ppm rel. to $SiMe_4$, *J* in Hz. MS: electron ionization (EI) or chemical ionization (CI); in *m*/*z* (rel. %). High-resolution chemical ionization (CI) MS were performed by the Servicio de Espectrometría de Masas, Universidad de Córdoba. Elemental analyses were performed by the Servei d'Anàlisis Elementals del CSIC de Barcelona.

Ethyl (2E)-3-(2,4,6-Trimethylphenyl)prop-2-enoate (**5**). To a soln. of ethyl (triphenylphosphoranyl)acetate (26.4 g, 76 mmol) in CH_2Cl_2 (50 ml), mesitaldehyde (**4**; 10.2 g, 69 mmol) in CH_2Cl_2 (50 ml) was added. The mixture was stirred under reflux for 24 h. After evaporation, the residual oil was submitted to CC (hexane/AcOEt): 14.7 g (97%) of **5**. M.p. 33–35° ([34]: 36–37°). IR (NaCl): 2981, 2867, 1717. ^1H-NMR (200 MHz, $CDCl_3$): 1.33 (*t*, *J* = 7.0, 3 H); 2.26 (*s*, 3 H); 2.31 (*s*, 6 H); 4.26 (*q*, *J* = 7.0, 2 H); 6.04 (*d*, *J* = 16.6, 1 H); 6.87 (*s*, 2 H); 7.84 (*d*, *J* = 16.6, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.2 (*q*); 20.88 (*q*); 20.95 (*q*); 60.3 (*t*); 123.0 (*d*); 129.0 (*d*); 130.8 (*s*); 136.7 (*s*); 138.1 (*s*); 143.0 (*d*); 166.9 (C=O). EI-MS: 218 (34, M^+), 203 (11, $C_{13}H_{15}O_2^+$, $[M-CH_3]^+$), 173 (100, $C_{12}H_{13}O_2^+$), 144 (74). Anal. calc. for $C_{14}H_{18}O_2$: C 77.03, H 8.48; found: C 77.10, H 8.31.

(2E)-3-(2,4,6-Trimethylphenyl)prop-2-en-1-ol (**6**). To a soln. of **5** (6.0 g, 27.5 mmol) in Et_2O (35 ml) at 0°, 1M DIBALH in hexanes (55 ml, 55 mmol) was added. After 5 h stirring at r.t., the mixture was diluted with Et_2O (65 ml), cooled to 0°, and quenched by careful addition of brine (65 ml). Then, 4M HCl (65 ml) was added dropwise. The aq. layer was extracted with Et_2O (3 × 150 ml) and the combined org. phase dried ($MgSO_4$) and evaporated. The residue was submitted to CC (hexane/AcOEt): 4.2 g (86%) of **6**. White solid. M.p. 58–59°. IR (KBr): 3375, 2939, 1660, 1609, 1478, 1376. ^1H-NMR (200 MHz, $CDCl_3$): 1.77 (br. *s*, OH); 2.27 (*s*, 9 H); 4.32 (*dd*, *J* = 5.6, 1.4, 2 H); 5.86 (*dt*, *J* = 16.4, 5.6, 1 H); 6.56 (*dt*, *J* = 16.4, 1.4, 1 H); 6.86 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.8 (*q*); 64.0 (*t*); 128.5 (*d*); 128.7 (*d*); 133.3 (*d*); 133.3 (*s*); 135.8 (*s*); 136.2 (*s*). EI-MS: 176 (66, M^+), 158 (24), 161 (15), 143 (87), 133 (100). Anal. calc. for $C_{12}H_{16}O$: C 81.77, H 9.15; found: C 81.61, H 9.20.

(2S,3S)-3-(2,4,6-Trimethylphenyl)oxirane-2-methanol (**7**). Dry powdered 4-Å molecular sieves (0.87 g) and anh. CH_2Cl_2 (120 ml) under N_2 was cooled to −30° (CO_2/anisole bath). Then the following reagents were introduced sequentially *via* cannula under stirring: (+)-diisopropyl L-tartrate (285 mg, 1.22 mmol) in CH_2Cl_2 (10 ml), titanium tetraisopropoxide (0.24 ml, 0.81 mmol), and 2.8M *tert*-butyl hydroperoxide in isooctane (12 ml, 33.6 mmol). The mixture was stirred 1 h at −30°, and a soln. of **6** (2.86 g, 16.25 mmol; previously recrystallized in hexanes and stored for 24 h over 4-Å molecular sieves) in CH_2Cl_2 (5 ml) was added. After 8 h stirring at −30°, the reaction was quenched by addition of 10% NaOH soln. saturated with NaCl (1.3 ml) and Et_2O (16 ml). The mixture was allowed to warm to 10°, and anh. $MgSO_4$ (1.26 g) and *Celite®* (160 mg) were added. After 15 min stirring at r.t., the mixture was filtered through a short *Celite®* pad. The solvents were evaporated and the excess of *tert*-butyl hydroperoxide removed by azeotropic distillation with toluene (3 × 100 ml). The crude was then submitted to CC (hexanes/AcOEt): 1.98 g (63%) of **7** as a white solid of 88% ee. Three recrystallizations from hexane afforded 0.8 g (26%) of enantiomerically pure **7**. HPLC (*Chiralcel OD-R*, 0.5M aq. $NaClO_4$/MeOH 3:7, flow 0.5 ml/min; t_R (2*R*,3*R*) 21.68 and t_R (2*S*,3*S*) 26.44): 99% ee. M.p. 104–105°. $[\alpha]_D = +18.0$ (*c* = 1, $CHCl_3$). IR (KBr): 3380, 3310, 2954, 1611, 1455, 1380. ^1H-NMR (300 MHz, $CDCl_3$): 1.80 (*dd*, *J* = 7.6, 5.4, OH); 2.27 (*s*, 3 H); 2.35 (*s*, 6 H); 3.16 (*m*, 1 H); 3.88 (*ddd*, *J* = 12.8, 7.4, 4.2, 1 H); 3.97 (*d*, *J* = 2.2, 1 H); 4.12 (*ddd*, *J* = 12.8, 5.4, 2.6, 1 H); 6.83 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.6 (*q*, *Me*–C(2), *Me*–C(6)); 20.9 (*q*); 54.4 (*d*); 59.7 (*d*); 61.5 (*t*); 128.7 (*d*, C(3), C(5)); 130.2 (*s*, C(1)); 136.9 (*s*, C(2), C(6)); 137.4 (*s*, C(4)). EI-MS: 192 (56, M^+), 161 (6), 147 (87), 132 (49), 117 (100). Anal. calc. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.90, H 8.34.

(2R,3R)-3-[(Diphenylmethyl)amino]-3-(2,4,6-trimethylphenyl)propane-1,2-diol (**8**). To a soln. of **7** (0.10 g, 0.52 mmol) in MeCN (1.3 ml), $LiClO_4$ (0.86 g, 8.0 mmol) was added. After 10 min stirring, benzhydrylamine (0.91 ml, 5.2 mmol) was added and the mixture heated at 65° for 24 h under N_2. The mixture was then treated with H_2O (5 ml) and extracted with CH_2Cl_2 (3 × 4 ml). The combined org. phase was dried ($MgSO_4$) and

evaporated. To a soln. of the crude in Et_2O, solid CO_2 was added, and the precipitate was filtered off and washed with more Et_2O saturated with CO_2. The solvent was evaporated and the crude submitted to CC (hexanes/AcOEt): 0.19 g (97%) of **8**. $[\alpha]_D = -25.6$ (*c* 1, $CHCl_3$). IR (NaCl): 3411, 2921, 1609, 1453, 1030, 702. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.7 (*s*, 3 H); 2.3 (*s*, 3 H); 2.5 (*s*, 3 H); 3.8–4.2 (complex *m*, 6 H); 4.5 (*s*, 1 H); 6.9 (*s*, 1 H); 6.95 (*s*, 1 H); 7.2–7.3 (*m*, 10 H). ^{13}C-NMR (50 MHz, $CDCl_3$); 20.8 (*q*); 20.9 (*q*); 21.06 (*q*); 59.9 (*d*); 64.4 (*d*); 66.4 (*t*); 72.5 (*d*); 127.0 (*d*); 127.2 (*d*); 127.3 (*d*); 127.5 (*d*); 128.5 (*d*); 128.7 (*d*); 129.7 (*d*); 131.3 (*s*); 131.4 (*d*); 135.8 (*s*); 136.9 (*s*); 139.8 (*s*); 142.2 (*s*). CI-MS (CH_4): 376 (100, $[M+1]^+$). HR-CI-MS: 376.2273 ($C_{25}H_{30}NO_2^+$, $[M+1]^+$; calc. 376.2277).

*(2*R*,3*R*)-3-{[(*tert*-Butoxy)carbonyl]amino}-3-(2,4,6-trimethylphenyl)propane-1,2-diol* (**9**). *From* **8**. A suspension of **8** (189 mg, 0.5 mmol), di(*tert*-butyl) dicarbonate (143 mg, 0.65 mmol) and 15% $Pd(OH)_2$/C (28 mg) in MeOH (1.8 ml) was hydrogenated at r.t. and 1 atm until no starting material could be observed by TLC (*ca.* 2 days). The mixture was filtered and the filtrate evaporated. The residue was submitted to CC (hexanes/AcOEt): 105 mg (68%) of **9**.

From **7**. To a soln. of **7** (0.5 g, 2.60 mmol) in MeCN (13 ml), $LiClO_4$ (6.9 g) was added. After 10 min stirring, NaN_3 (0.85 g, 13 mmol) was added and the mixture heated at 65° for 24 h under N_2. The mixture was treated with H_2O (75 ml) and extracted with Et_2O (3 × 60 ml). The combined org. phase was dried ($MgSO_4$) and evaporated. The residue, composed mainly of (2*R*,3*R*)-3-azido-3-(2,4,6-trimethylphenyl)propane-1,2-diol (0.59 g), was immediately dissolved in AcOEt (6 ml). This soln. was added to a suspension of di(*tert*-butyl) dicarbonate (0.75 g, 3.43 mmol) and 10% Pd/C (59 mg) in AcOEt (1.2 ml) and hydrogenated at 1 atm until no starting material could be observed by TLC (*ca.* 24 h). The mixture was filtered, the filtrate evaporated, and the residue submitted to CC (hexanes/AcOEt): 0.5 g (62%) of **9**. $[\alpha]_D = -61.3$ ($c = 1$, $CHCl_3$). IR (NaCl): 3384, 2977, 1696, 1366, 853, 765. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.41 (*s*, 9 H); 2.28 (*s*, 3 H); 2.4 (*s*, 6 H); 3.2–3.9 (*m*, 4 H); 5.14 (*m*, 2 H); 6.84 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.7 (*q*); 21.2 (*q*); 28.2 (*q*); 51.3 (*d*); 63.0 (*t*); 73.0 (*d*); 80.4 (*s*); 130.3 (*d*); 132.2 (*s*); 137.2 (*s*, 2 C); 156.9 (*s*, C=O). CI-MS (NH_3): 310 (100, $[M+1]^+$), 254 (59), 210 (2). HR-CI-MS: 310.2029 ($C_{17}H_{28}NO_4^+$, $[M+1]^+$; calc. 310.2018).

*(2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-2-(2,4,6-trimethylphenyl)ethanol* ((+)-**10**). A soln. of *tert*-butyl carbamate (363 mg, 3.1 mmol) in PrOH (3 ml) was sequentially treated with NaOH (122 mg, 3.05 mmol) in H_2O (7.5 ml) and ^{t}BuOCl (0.35 ml, 0.33 g, 3.05 mmol). After 5 min stirring, the soln. was cooled to 0°, and a soln. of $(DHQ)_2PHAL$ (0.040 g, 0.05 mmol, 5 mol-%) in PrOH (3.5 ml) was added (homogeneous mixture). Then 2,4,6-trimethylstyrene (**11**) (146 mg, 1 mmol) was added, followed by $K_2OsO_2(OH)_4$ (14.8 mg, 0.04 mmol, 4 mol-%). The mixture was stirred for 3 h at 0° (light green soln. → light yellow), and the reaction was quenched with sat. aq. $NaHSO_3$ soln. (10 ml). The aq. phase was extracted with AcOEt (2 × 10 ml), the combined org. phase washed with brine (25 ml), dried ($MgSO_4$), and evaporated to afford a crude product composed mainly of a regioisomer mixture (4:1) of amino alcohols and *tert*-butyl carbamate. The crude was submitted to CC (hexanes/AcOEt), yielding 123 mg (44%) of (+)-**10** as a white solid of 88% ee. Crystallization from Et_2O provided enantiomerically pure (+)-**10**. HPLC (*Chiralcel® OD*, 30°, hexane ^{i}PrOH 98:2, flow 1 ml/min; t_R(2*S*) 17.83 and t_R(2*R*) 20.37): >99% ee. M.p. 76–77°. $[\alpha]_D = +19.2$ ($c = 1$, $CHCl_3$). IR (KBr): 3284, 2971, 1684, 1368, 1057. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.42 (*s*, 9 H); 2.24 (*s*, 3 H); 2.4 (*s*, 6 H); 3.8 (*m*, 2 H); 4.1 (br. *s*, 1 OH); 5.05 (br. *s*, 1 H); 5.2 (br. *s*, NH); 6.8 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.7 (*q*); 21.2 (*q*); 28.3 (*q*); 55.0 (*d*); 65.9 (*t*); 80.0 (*s*); 130.2 (*d*); 132.0 (*s*); 136.0 (*s*, 2 C); 156.9 (*s*, C=O). CI-MS (NH_3): 298 (5, $[M+18]^+$), 280 (100, $[M+1]^+$). Anal. calc. for $C_{16}H_{25}NO_3$: C 68.79, H 9.02, N 5.01; found: C 68.95, H 9.06, N 4.85.

*2-{[(*tert*-Butoxy)carbonyl]amino}-2-(2,4,6-trimethylphenyl)acetic Acid (=*N*-[(*tert*-Butoxy)carbonyl]-α-mesitylglycine*, **1**). *(2*R*)-Enantiomer* (−)-**1** *from* **9**. A mixture of **9** (110 mg, 0.35 mmol), Na_2CO_3 (19 mg, 0.18 mmol), $NaIO_4$ (304 mg, 1.42 mmol), and $KMnO_4$ (11 mg, 0.07 mmol) in dioxane (1.5 ml) and H_2O (0.65 ml) was vigorously stirred at r.t. until no starting material could be observed by TLC (*ca.* 17 h). AcOEt (10 ml) was added, and the mixture was acidified by addition of 2M HCl. The org. phase was washed with brine, dried, and evaporated. The crude was dissolved in 1M $NaHCO_3$ and the aq. phase washed with AcOEt, acidified, and extracted again with AcOEt. The org. phase was then dried and evaporated: 75 mg (72%) of (−)-**1**. White solid.

*(2*S*)-Enantiomer (+)-***1** *from (+)-***10**. A soln. of (+)-**10** (84 mg, 0.3 mmol) in acetone (2.3 ml) was added to a 5% $NaHCO_3$ soln. (0.8 ml). This magnetically stirred heterogeneous mixture was cooled to 0° and treated sequentially with KBr (3.6 mg, 0.03 mmol) and TEMPO (50 mg, 0.33 mmol). Then, 0.63M NaClO (0.6 ml, 0.38 mmol) was added dropwise while the mixture was vigorously stirred and maintained at 0°. After 1 h, additional 0.63M NaClO (0.23 ml, 0.15 mmol) was added, and stirring was continued for 1 h at 0°. Then, 5% $NaHCO_3$ soln. (1.2 ml) was added, and the acetone was evaporated. The aq. layer was washed twice with Et_2O,

acidified to pH 3 with 2M HCl, and extracted with AcOEt. The combined org. phase was washed with H_2O and brine, dried ($MgSO_4$), and evaporated: 72 mg (82%) of (+)-**1**. White solid.

*Data of (−)-***1**. M.p. 55–56°. $[\alpha]_D = -142.4$ ($c = 1$, MeOH). IR (KBr): 3293, 2979, 1729, 1657, 1368. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.4 (*s*, 9 H); 2.2 (*s*, 6 H); 2.4 (*s*, 3 H); 5.6 (br. *s*, 1 H); 8.3 (br. *s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.2 (*q*); 20.8 (*q*); 27.9 (*q*); 54.0 (*d*); 81.5 (*s*); 129.9 (*d*); 136.9 (*s*); 137.0 (*s*); 157.5 (*s*); 173.6 (*s*). CI-MS (NH_3): 294 (12, $[M+1]^+$), 311 (100, $[M+18]^+$). Anal. calc. for $C_{16}H_{23}NO_4$: C 65.50, H 7.90, N 4.77; found: C 65.37, H 7.90, N 4.81.

*Methyl (2*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-2-(2,4,6-trimethylphenyl)acetate* (=*(2*S*)*-N-*[(*tert*-Butoxy)carbonyl]-α-mesitylglycine Methyl Ester*; **19**). (2*S*)-Enantiomer (+)-**1** (63 mg, 0.21 mmol) was dissolved in DMF (0.35 ml), and $KHCO_3$ (43 mg, 0.43 mmol) and MeI (21 ml, 1.16 mmol) were added. The mixture was stirred at r.t. for 16 h, H_2O was added, and the org. layer was extracted with Et_2O (3×3 ml). The combined org. phase was washed successively with H_2O (2×2 ml), sat. Na_2SO_3 soln. and brine, dried ($MgSO_4$), and evaporated and the crude purified by CC (hexane/AcOEt): 48 mg (73%) of **19**. Oil. IR (NaCl): 3442, 2977, 1742, 1719, 1613, 1393, 1368, 1161, 852. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.4 (*s*, 9 H); 2.25 (*s*, 3 H); 2.4 (*s*, 6 H); 3.7 (*s*, 3 H); 5.4 (br. *s*, 1 H); 5.8 (br. *d*, 1 H); 6.8 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.2 (*q*); 20.8 (*q*); 28.3 (*q*); 52.7 (*q*); 52.8 (*d*); 79.9 (*s*); 129.8 (*d*); 131.3 (*s*); 136.7 (*s*, 2 C); 137.6 (*s*); 155.5 (*s*); 172.5 (*s*). CI-MS (NH_3): 325 (95, $[M+18]^+$), 308 (100, $[M+1]^+$), 269 (24). HR-CI-MS: 307.1777 ($C_{17}H_{25}NO_4^+$, M^+; calc. 307.1784).

*(1*R*,2*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-1-{[(*tert*-butoxy)carbonyl]amino}-1-(2,4,6-trimethylphenyl)-propan-2-ol* (**12**). To a soln. of **9** (0.99 g, 3.20 mmol) in DMF (17.8 ml), (*tert*-butyl)chlorodimethylsilane (0.53 g, 3.52 mmol) and 1*H*-imidazole (0.48 g, 7.04 mmol) were added. The mixture was stirred at r.t. and monitored by TLC. After 24 h, H_2O (20 ml) was added and the aq. phase extracted with Et_2O (3×15 ml). The combined org. phase was washed with sat. aq. NH_4Cl soln., dried ($MgSO_4$), and evaporated. The crude product was purified by CC (0–15% AcOEt/hexane): 1.23 g (91%) of **12**. Oil. $[\alpha]_D = -5.4$ ($c = 1$, $CHCl_3$). IR (NaCl): 3421, 2931, 1700, 1366, 837. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.18 (*s*, 6 H); 1.0 (*s*, 9 H); 1.4 (*s*, 9 H); 2.3 (*s*, 3 H); 2.5 (*s*, 6 H); 2.9 (br. *s*, OH); 3.5–4 (*m*, 3 H); 5.3 (br. *d*, 1 H); 5.6 (br. *d*, NH); 6.9 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −5.4 (*q*); 18.2 (*s*); 20.7 (*q*); 21.2 (*q*); 25.9 (*q*); 28.4 (*q*); 53.8 (*d*); 64.9 (*t*); 72.5 (*d*); 130.2 (*d*); 132.7 (*s*); 136.6 (*s*); 155.1 (*s*). CI-MS (NH_3): 424 (15, $[M+1]^+$), 368 (32), 192 (100, $C_{12}H_{19}NO^+$), 324 (19). HR-CI-MS: 424.2899 ($C_{23}H_{42}NO_4Si^+$, $[M+1]^+$; calc. 424.2883).

*(1*R*,2*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-1-{[[(*tert*-butyl)dimethylsilyl]oxy}methyl]-2-(2,4,6-trimethylphenyl)ethyl Methanesulfonate* (**13**). To a soln. of **12** (0.60 g, 1.42 mmol) in CH_2Cl_2 (1.8 ml) at −15°, Et_3N (0.22 ml, 1.56 mmol), 4-(dimethylamino)pyridine (9 mg, 0.07 mmol), and methanesulfonyl chloride (0.12 ml, 1.56 mmol) were added. The mixture was allowed to warm to r.t. under stirring, and the reaction progress was monitored by TLC. After *ca.* 5 h (no starting material detectable), CH_2Cl_2 (5 ml) was added, the org. phase washed sequentially with cold 10% aq. HCl soln., sat. $NaHCO_3$ soln., and H_2O, dried ($MgSO_4$), and evaporated, and the crude product purified by CC (hexanes/AcOEt): 0.58 g (82%) of **13**. White solid. M.p. 95–96°. $[\alpha]_D = +5.0$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3267, 2931, 1702, 1366, 1177. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.0–0.02 (*s*, 6 H); 0.83 (*s*, 9 H); 1.26 (*s*, 9 H); 2.10 (*s*, 3 H); 2.22 (*s*, 6 H); 2.32 (*s*, 3 H); 3.85 (*d*, $J = 4$, 2 H); 4.76 (*m*, 1 H); 5.32 (*m*, 1 H); 5.62 (br. *d*, NH); 6.70 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −5.6 (*q*); 18.1 (*s*); 20.7 (*q*); 20.8 (*q*); 25.7 (*q*); 28.2 (*q*); 37.5 (*q*); 52.0 (*d*); 63.8 (*t*); 79.6 (*s*); 82.0 (*d*); 130.2 (*d*); 131.7 (*s*); 137.2 (*s*); 155.0 (*s*). CI-MS (NH_3): 502 (88, $[M+1]^+$), 446 (100). HR-CI-MS: 444.1894 ($C_{20}H_{34}NO_6SSi^+$, $[M - C_4H_8 + 1]^+$; calc. 444.1876).

*(2*S*,3*R*)-1-[(*tert*-Butoxy)carbonyl]-2-{[[(tert-butyl)dimethylsilyl]oxy}methyl]-3-(2,4,6-trimethylphenyl)aziridine* (**14**). To a suspension of NaH (7.5 mmol; from 300 mg of a 55–60% dispersion in paraffin, washed with anh. hexane under N_2) in THF (4 ml), a soln. of **13** (1.25 g, 2.5 mmol) in THF (7.7 ml) was added. After 3 h stirring at r.t., the crude was carefully treated with H_2O/AcOEt 1:1. The aq. phase was extracted with AcOEt (3×12 ml) and the combined org. phase dried ($MgSO_4$) and evaporated. Purification of the crude by CC (AcOEt/hexanes) gave 0.96 g (94%) of **14**. White solid. M.p. 46–47°. $[\alpha]_D = -143.4$ ($c = 1.1$, $CHCl_3$). IR (NaCl): 2931, 1719, 1254, 1159, 837. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.0–0.01 (*s*, 6 H); 0.82 (*s*, 9 H); 1.40 (*s*, 9 H); 2.14 (*s*, 3 H); 2.3 (*s*, 6 H); 2.43 (*m*, 1 H); 3.40 (br. *d*, 1 H); 3.86 (*dd*, $J = 11.5$, 3.6, 1 H); 4.10 (*dd*, $J = 11.5$, 2.6, 1 H); 6.7 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −5.4 (*q*); −5.3 (*q*); 18.4 (*s*); 20.0 (*q*); 20.8 (*q*); 25.9 (*q*); 28.2 (*q*); 39.1 (*d*); 46.0 (*d*); 59.7 (*t*); 80.7 (*s*); 128.8 (*d*); 130.3 (*s*); 136.5 (*s*); 137.4 (*s*); 159.9 (*s*). CI-MS (NH_3): 406 (16, $[M+1]^+$), 367 (97), 350 (100). HR-CI-MS: 406.2812 ($C_{23}H_{40}NO_3Si^+$, $[M+1]^+$; calc. 406.2777). Anal. calc. for $C_{23}H_{39}NO_3Si$: C 68.10, H 9.69, N 3.45; found: C 68.19, H 9.95, N 3.45.

*(2*S*)-*N*-[(*tert*-Butoxy)carbonyl]-1-{[(*tert*-butyl)dimethylsilyl]oxy}-3-(2,4,6-trimethylphenyl)propan-2-amine* (**15**). A soln. of **14** (124 mg, 0.30 mmol) in AcOEt (1.5 ml) was added to a stirred suspension of 10% Pd/C (15 mg) in AcOEt (0.6 ml) under H_2: The mixture was hydrogenated at 1 atm (H_2 balloon) for *ca.* 12 h (TLC monitoring). Then, the suspension was filtered through *Celite*® and the latter washed thoroughly with AcOEt.

Evaporation yielded 122 mg (quant.) of crude, spectroscopically pure **15**. $[\alpha]_D = -30.7$ ($c = 1.0$, $CHCl_3$). IR (NaCl): 3456, 2931, 1719, 1366, 1173, 837. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.0–0.01 (*s*, 6 H); 0.86 (*s*, 9 H); 1.33 (*s*, 9 H); 2.17 (*s*, 3 H); 2.28 (*s*, 6 H); 2.80 (*m*, 2 H); 3.42 (*dd*, $J = 9.8$, 2.2, 1 H); 3.52 (*dd*, $J = 9.8$, 3.6, 1 H); 3.74 (*m*, 1 H); 4.78 (br. *d*, NH); 6.76 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −5.5 (*q*); −5.3 (*q*); 18.3 (*s*); 20.2 (*q*); 20.8 (*q*); 25.9 (*q*); 28.3 (*q*); 31.3 (*t*); 51.5 (*d*); 63.2 (*d*); 78.9 (*s*); 128.8 (*d*); 132.1 (*s*); 135.3 (*s*); 137.0 (*s*); 155.1 (*s*). CI-MS (NH_3): 408 (37, $[M+1]^+$), 407 (100, M^+), 352 (36), 308 (11). HR-CI-MS: 408.2917 ($C_{23}H_{41}NO_3Si^+$, $[M+1]^+$; calc. 408.2934).

*(2*S*)-2-[[(*tert*-Butoxy)carbonyl]amino]-3-(2,4,6-trimethylphenyl)propan-1-ol* (**16**). To a soln. of **15** (120 mg, 0.30 mmol) in THF (1.4 ml) at 0°, a soln. of $Bu_4NF \cdot H_2O$ (0.14 g, 0.54 mmol) in THF (0.8 ml) was added. The mixture was stirred at r.t. and monitored by TLC. After 60 min, the soln. was washed with H_2O and the org. layer extracted with Et_2O. The combined org. phase was dried ($MgSO_4$) and evaporated and the residue purified by CC (AcOEt/hexanes): 70 mg (82%) of **16**. White solid. M.p. 127–129°. $[\alpha]_D = -51.8$ ($c = 1.0$, $CHCl_3$). IR (NaCl): 3363, 1688, 1532, 1175, 1005. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.4 (*s*, 9 H); 2.24 (*s*, 3 H); 2.33 (*s*, 6 H); 2.8 (*m*, 2 H); 3.54 (*dd*, $J = 10.7$, 5.3, 1 H); 3.66 (*dd*, $J = 10.7$, 3.5, 1 H); 3.81 (*m*, 1 H); 6.83 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$); 20.3 (*q*); 20.8 (*q*); 28.3 (*q*); 31.4 (*t*); 52.9 (*d*); 64.5 (*t*); 79.5 (*s*); 129.1 (*d*); 132.0 (*s*); 135.6 (*s*); 136.8 (*s*); 157.0 (*s*). CI-MS (NH_3): 294 (100, $[M+1]^+$), 238 (59), 194 (15). Anal. calc. for $C_{17}H_{27}NO_3$: C 69.59, H 9.28, N 4.77; found: C 69.44, H 9.46, N 4.72.

*(2*S*)-2-[[(*tert*-Butoxy)carbonyl]amino]-3-(2,4,6-trimethylphenyl)propanoic Acid* (= N-*[(*tert*-Butoxy)carbonyl]-β-mesityl*-L-*alanine;* (−)-**2**). *Method A:* A soln. of PDC (295 mg, 0.78 mmol) in DMF (0.6 ml) was added to **16** (46 mg, 0.16 mmol) at r.t. under N_2. After 24 h stirring, H_2O (5 ml) and Et_2O (5 ml) were added. The aq. phase was extracted with Et_2O (3 × 3 ml) and the combined org. phase dried ($MgSO_4$) and evaporated. The crude was taken up with AcOEt and extracted with sat. $NaHCO_3$ soln., the aq. layer washed with AcOEt, then acidified with 2N HCl, and extracted with AcOEt, and the combined org. phase dried ($MgSO_4$) and evaporated: 44 mg (92%) of (−)-**2**. White solid.

Method B: As described for (+)-**1**, with **16** (30 mg, 0.10 mmol): 30 mg (95%) of (−)-**2**, spectroscopically identical to the product obtained by *Method A*.

Data of (−)-**2**: M.p. 140–142°. $[\alpha]_D = -20.2$ ($c = 1.0$, $CHCl_3$). IR (NaCl): 3311, 1721, 1659, 1167, 756. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.4 (*s*, 9 H); 2.24 (*s*, 3 H); 2.34 (*s*, 6 H); 3.06–3.16 (*m*, 2 H); 4.52 (*m*, 1 H); 5.01 (br. *d*, NH); 6.83 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.3 (*q*); 20.5 (*q*); 27.5 (*q*); 34.1 (*d*); 54.0 (*t*); 81 (*s*); 129.0 (*d*); 130.5 (*s*); 136.0 (*s*); 138.0 (*s*); 156.5 (*s*); 175.0 (*s*) ppm. CI-MS (NH_3): 325 (55, $[M+18]^+$), 308 (41, $[M+1]^+$), 269 (100). HR-CI-MS: 206.1118 ($C_{17}H_{25}NO_4^+$, $[M - C_5H_9O_2]^+$; calc. 206.1028).

Enantiomer Purity of (−)-**2**: To a mixture of (−)-**2** (33 mg, 0.11 mmol) and $KHCO_3$ (22 mg, 0.21 mmol) in DMF (0.3 ml), MeI (27 µl, 0.43 mmol) was added by syringe. After 24 h stirring, H_2O (2 ml) was added and the aq. phase extracted with Et_2O (3 × 3 ml). The combined org. phase was washed with H_2O (2 × 2 ml), 5% aq. Na_2SO_3 soln. (2 × 2 ml), and brine (2 × 2 ml), dried ($MgSO_4$), and evaporated. The crude was chromatographed (0–5% AcOEt/hexanes): 27 mg (78%) of N-*[(*tert*-butoxy)carbonyl]-β-mesityl*-L-*alanine methyl ester*. HPLC (*Chiralcel® OD*, 30°, hexane/^{i}PrOH 9:1, flow 1 ml/min, λ 254 nm): only one peak at t_R 5.18; >99% ee; *cf.* racemic sample: t_R (2*R*) 4.20 and t_R (2*S*) 5.19.

*(2*S*,3*S*)-1-[[(*tert*-Butyl)dimethylsilyl]oxy]-2-[(*tert*-butoxy)carbonyl]-3-(2,4,6-trimethylphenyl)butan-2-amine* (**17**). A soln. of lithium dimethylcuprate was prepared by addition of 1.6M MeLi (4.4 mmol) in Et_2O to a stirred slurry of CuI (422 mg, 2.2 mmol) in anh. Et_2O (7.5 ml) at 0° and stirring at 0° for a few minutes. To this soln. was added *via* cannula a soln. of **14** (300 mg, 0.74 mmol) in Et_2O (7.5 ml). The mixture was stirred under N_2 at 0°, and sat. aq. NH_4Cl soln. (8 ml) and NH_4OH soln. (2 ml) were added. Then the org. layer was extracted with more Et_2O (3 × 6 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue submitted to CC (hexanes/AcOEt): 150 mg of **17** (48%) and 75 mg (24%) of its regioisomer. **17**: Colorless oil. $[\alpha]_D = -40.0$ ($c = 0.5$, $CHCl_3$). IR (NaCl): 3457, 2931, 1717, 1366, 1175, 835. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.0–0.01 (*s*, 6 H); 0.84 (*s*, 9 H); 1.2 (*s*, 9 H); 1.2 (*d*, $J = 7.2$, 3 H); 2.12 (*s*, 3 H); 2.19 (*s*, 3 H); 2.28 (*s*, 3 H); 3.50 (*m*, 1 H); 3.70 (*m*, 1 H); 3.95 (*m*, 2 H); 4.3 (br. *d*, NH); 6.69 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −5.43 (*q*); −5.39 (*q*); 16.7 (*q*); 18.3 (*s*); 20.6 (*q*); 21.2 (*q*); 21.8 (*q*); 26.0 (*q*); 28.2 (*q*); 33.5 (*d*); 54.8 (*d*); 62.6 (*t*); 78.6 (*s*); 128.8 (*d*); 130.9 (*d*); 135.0 (*s*); 136.7 (*s*); 137.1 (*s*); 155.0 (*s*). HR-CI-MS 422.3098 ($C_{24}H_{44}NO_3Si$, $[M+1]^+$; calc. 422.3090).

*(2*S*,3*S*)-2-[[(*tert*-Butoxy)carbonyl]amino]-3-(2,4,6-trimethylphenyl)butan-1-ol* (**18**). As described for **16**, with **17** (70 mg, 0.17 mmol): 44 mg (86%) of **18**. Colorless oil. $[\alpha]_D = -13.2$ ($c = 1$, $CHCl_3$). IR (NaCl): 3457, 2931, 1717, 1366, 1175, 835. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.30 (*s*, 9 H); 1.34 (*d*, $J = 7$, 3 H); 2.23 (*s*, 3 H); 2.29 (*s*, 3 H); 2.35 (*s*, 3 H); 3.3–3.6 (*m*, 1 H); 3.7–3.8 (*m*, 1 H); 3.9–4.1 (*m*, 2 H); 4.35 (br. *s*, 1 H); 6.8 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 16.9 (*q*); 20.6 (*q*); 21.2 (*q*); 21.6 (*q*); 28.2 (*q*); 34.5 (*d*); 56.5 (*d*); 64.7 (*t*); 79.6 (*s*);

129.3 (*d*); 131.2 (*d*); 135.5 (*s*); 135.7 (*s*); 138 (*s*); 155.9 (*s*); 178.0 (*s*). EI-MS: 325 (8, $[M+18]^+$), 308 (100, $[M+1]^+$). HR-CI-MS: 307.2137 ($C_{18}H_{29}NO_3^+$, M^+; calc. 307.2147).

*(2*S*,3*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(2,4,6-trimethylphenyl)butanoic Acid* (=*(3*S*)*-N-*{(*tert*-*Butoxy)carbonyl}-β-mesityl-β-methyl*-L-*alanine*; (−)-**3**). As described for (−)-**2** (*Method B*), with **18** (45 mg, 0.15 mmol): 43 mg (91%) of (−)-**3**. Colorless oil. $[\alpha]_D = -23.6$ ($c = 2$, $CHCl_3$). IR (NaCl): 3745, 3313, 2929, 1719, 1654, 1457, 835. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.3 (*s*, 9 H); 1.41 (*d*, $J = 5$, 3 H); 2.24 (*s*, 3 H); 2.34 (*s*, 6 H); 2.38 (*s*, 6 H); signal of a rotamer; 3.4–3.8 (*m*, 1 H); 4.4–4.8 (*m*, 1 H); 6.9 (*s*, 2 H). ^{13}C-NMR (75 MHz, C_7D_8; signals marked with an asterisk correspond to a rotamer; the other signals are slightly split): 16.5 (*q*); 20.6 (*q*); 21.4 (*q*); 21.8 (*q*); 27.7 (*q*); 28.1 (*q*)*; 36.6 (*d*); 38.1 (*d*)*; 57.7 (*d*); 80.1 (*s*); 80.2 (*s*)*; 129.3 (*d*); 131.4 (*d*); 134.1 (*s*); 135.0 (*s*); 136.2 (*s*); 136.6 (*s*); 155.8 (*s*); 156.0 (*s*)*; 176.0 (*s*)*, 178 (*s*)*. EI-MS: 283 (100, $[M+18]^+$), 322 (47, $[M+1]^+$), 266 (6), 283 (78).

*Methyl (2*S*,3*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-(2,4,6-trimethylphenyl)butanoate* (=*(3*S*)*-N-*{(*tert*-*Butoxy)carbonyl}-β-mesityl-β-methyl*-L-*alanine Methyl Ester*; **20**). As described for **19**, (−)-**3** (39 mg, 0.12 mmol): 27 mg (68%) of **20**. Oil. IR (KBr): 3379, 1746, 1717, 1495, 1167. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.3 (*s*, 9 H); 1.35 (*d*, 3 H); 2.30 (*s*, 3 H); 2.32 (*s*, 3 H); 2.39 (*s*, 3 H); 3.4–3.6 (br. *m*, 1 H); 3.8 (*s*, 3 H); 4.4–4.6 (br., 2 H); 6.8 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 16.5 (*q*); 20.2 (*q*); 21.1 (*q*); 21.6 (*q*); 28.1 (*q*); 30.9 (*q*); 52.0 (*d*); 57.3 (*d*); 79.9 (*s*); 129.40 (*s*); 129.44 (*d*); 131.5 (*d*); 134.1 (*s*); 136.2 (*s*); 136.8 (*s*); 155.5 (*s*); 174.2 (*s*). CI-MS (NH_3): 353 (24, $[M+18]^+$), 336 (100, $[M+1]^+$). HR-CI-MS: 336.2147 ($C_{19}H_{30}NO_4^+$, $[M+1]^+$; calc. 336.2175).

Financial support from *DGICYT* (PB98-1246 and PB97-0939) and from *CIRIT* (1998SGR 00005) is gratefully acknowledged. *E.M.* thanks Universitat de Barcelona for a predoctoral fellowship.

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Received January 21, 2000