



# A new method for the enantioselective synthesis of *N*-Boc- $\alpha,\alpha$ -disubstituted $\alpha$ -amino acids

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**Abstract**—A new method for the enantioselective synthesis of *N*-Boc- $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids has been developed. The starting materials are diastereomerically pure 3,3-disubstituted allyl alcohols, prepared by DIBAL-H reduction of the corresponding unsaturated esters derived from carbocyclization of an acetylenic ester or from Wadsworth–Emmons olefination of a ketone. Sharpless epoxidation of the allylic alcohols provided enantiomerically enriched epoxy alcohols that were submitted to nucleophilic ring-opening under Crotti's conditions ( $\text{N}_3\text{Na}/\text{LiClO}_4$ ) to give 3-azido-1,2-diols. Hydrogenation and in situ protection provided the *N*-Boc-3-amino-1,2-diols that were oxidatively cleaved to the  $\alpha,\alpha$ -disubstituted *N*-Boc- $\alpha$ -amino acids. Protected  $\alpha$ -methyl- $\alpha$ -phenylglycine and  $\alpha$ -methylisoleucine have been prepared by this methodology. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The biological activity of a given peptide is strongly linked to its lowest energy conformation. Small peptides designed to mimic a protein are conformationally more flexible and consequently less active than the parent protein due to the absence of the multiple long-range interactions present in proteins.<sup>1</sup> A usual strategy to increase both the stability, biological activity and selectivity of peptides is to restrict their available conformations by the introduction of peptide cyclizations or by the use of unnatural amino acids with conformational constraints.<sup>2,3</sup> The increasing interest of modified peptides in biological studies and as therapeutic agents<sup>4</sup> has fostered the research of methodologies directed to the synthesis of new unnatural amino acids in enantiomerically pure form.<sup>5</sup>  $\alpha,\alpha$ -Disubstituted  $\alpha$ -amino acids (quaternary amino acids) are among the most important unnatural residues able to give conformational rigidity to a peptide. Many of them have been specifically designed and synthesized in the last decade, this subject having been recently reviewed.<sup>6</sup>

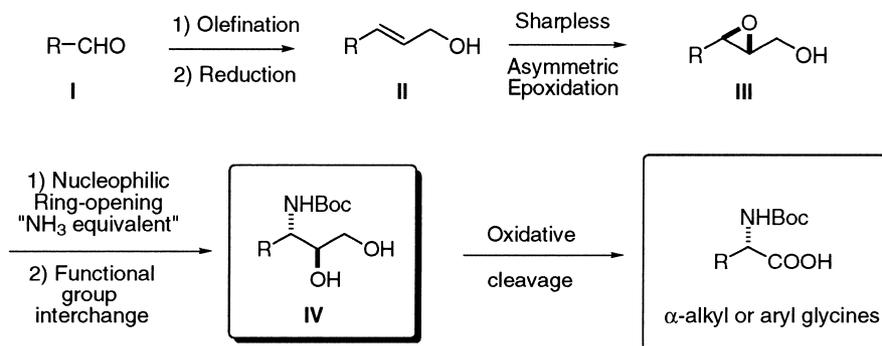
Over the last years, we have developed a general synthetic methodology which allows the stereocontrolled preparation of amino acids of different structural types in high enantiomeric purity.<sup>7–14</sup> The starting materials are allyl alcohols **II** often prepared from carbaldehydes **I** by a two-step sequence of olefination (Wittig, Wadsworth–Emmons, Knoevenagel

etc.) and reduction. The catalytic Sharpless epoxidation<sup>15</sup> of **II** reliably provides enantiomerically enriched epoxy alcohols **III** which are then submitted to a regio- and stereo-specific ring-opening using a synthetic equivalent of ammonia.<sup>16</sup> We have used several reagents as a nucleophiles in this crucial step: benzhydrylamine,<sup>7a,b,11</sup> *p*-methoxybenzylamine,<sup>7c</sup>  $\text{NaN}_3$ ,<sup>7b,8,9</sup>  $\text{Ti}(\text{N}_3)_2(\text{O}^i\text{Pr})_2$ .<sup>11,13b</sup> The reaction products have been converted into *N*-Boc-3-amino-1,2-diols **IV**. Oxidation of diol **IV** affords directly the corresponding  $\alpha$ -amino acids without any epimerization at the chiral center. This sequence has proven to be particularly useful for  $\alpha$ -alkyl or  $\alpha$ -aryl glycines<sup>7</sup> such as homophenylalanine<sup>7a</sup> and naphthylglycine<sup>7b</sup> and has been effective for the preparation of highly lipophilic amino acids such as mesityl glycine<sup>8</sup> (Scheme 1).

*N*-Boc-3-Amino-1,2-diols **IV**, key intermediates for the synthesis of alkyl and aryl glycines, are also versatile precursors for many other types of amino acids (Scheme 2).  $\beta$ -Aryl alanines, for instance, were obtained through the intermediacy of *N*-Boc-aziridines **V**, which can be readily prepared by a sequence of regioselective protection of the primary alcohol (to give **VI**), mesylation of the secondary alcohol and base-induced cyclization.<sup>8,9</sup> Regioselective hydrogenolysis of **V**, followed by deprotection and oxidation afforded directly  $\beta$ -aryl alanines. Nucleophilic ring-opening of **V** by a cuprate reagent followed by the same reaction sequence provided  $\beta$ -substituted- $\beta$ -aryl alanines. Intermediates **IV** are also suited for the synthesis of  $\alpha$ -hydroxy- $\beta$ -amino acids and  $\beta$ -hydroxy- $\gamma$ -amino acids of both diastereomeric series. The former can be prepared by simple protecting group manipulation followed by oxidation of the primary alcohol,<sup>10</sup> whereas the latter are

**Keywords:**  $\alpha$ -amino acids;  $\alpha,\alpha$ -dialkylglycines; quaternary amino acids; Sharpless epoxidation.

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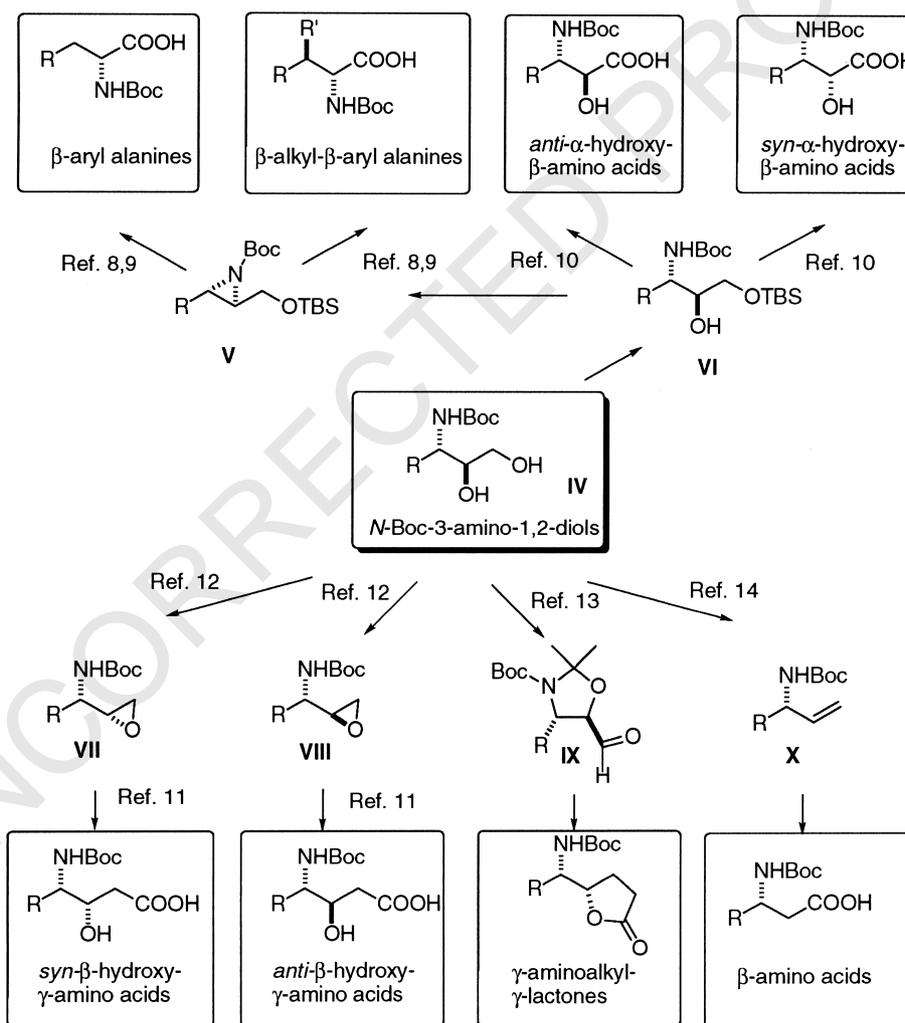


Scheme 1.

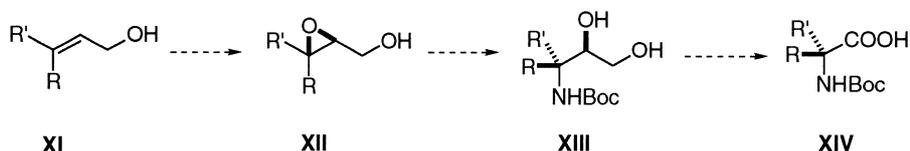
available through a sequence that involves cyanide ring-opening<sup>11</sup> of the 2-alkylamino epoxides **VII** and **VIII**.<sup>12</sup> The *syn*- and *anti*-amino epoxides **VII** and **VIII** have been respectively prepared by intramolecular Mitsunobu reaction and a three step sequence featuring protection of the primary alcohol, activation of the secondary alcohol and simultaneous deprotection with cyclization. In addition, precursors of dipeptide isosteres, such as  $\gamma$ -aminoalkyl- $\gamma$ -lactones,<sup>13</sup> are also accessible from **IV** by homologation of aldehydes **IX** following a protocol of Wittig olefination,

hydrogenation and acid treatment. Finally,  $\beta$ -alkyl  $\beta$ -amino acids<sup>14</sup> were prepared by deoxygenation of the diol fragment to provide unsaturated amines **X** that were hydroborated and oxidized.

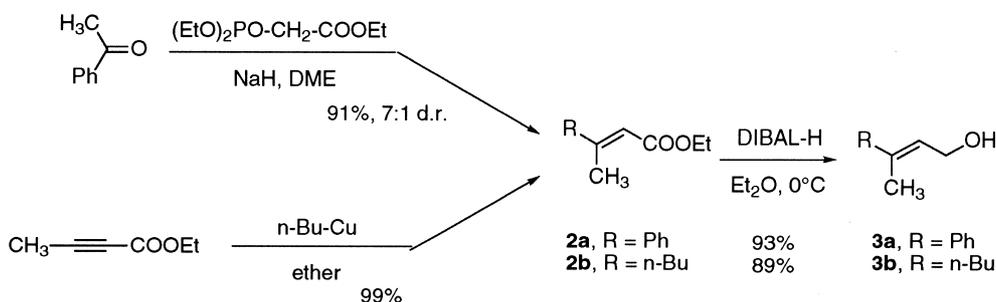
The increasing importance of  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids as components in biologically active peptides prompted us to attempt their preparation by appropriate modification of our basic synthetic sequence. We describe herein our methodology for the enantioselective synthesis of



Scheme 2.

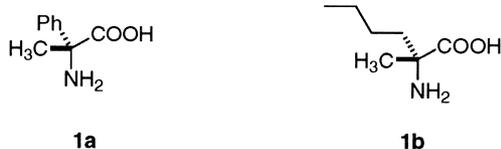


Scheme 3.



Scheme 4.

two targets:  $\alpha$ -methyl- $\alpha$ -phenylglycine (**1a**) as an example possessing an aromatic residue and  $\alpha$ -methylisoleucine (**1b**) as a representative of  $\alpha,\alpha$ -dialkyl glycine residue.  $\alpha$ -Methyl- $\alpha$ -phenylglycine (**1a**) has been synthesized in enantiomerically pure form<sup>17</sup> and used for a variety of biological purposes.<sup>18</sup>  $\alpha$ -Methylisoleucine (**1b**) has been previously synthesized by routes featuring alkylation of chiral glycine equivalent<sup>19</sup> and by microbial resolution.<sup>20</sup>



## 2. Results and discussion

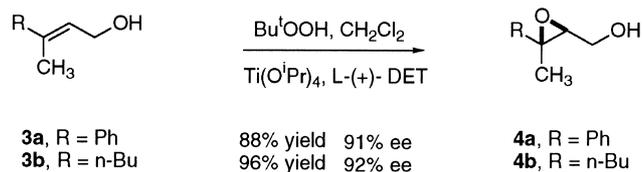
Experience from our previous work indicated several difficulties that needed to be overcome to reach our target (Scheme 3). First of all, stereochemically pure allyl alcohol **XI** had to be prepared because each diastereomer would lead to the opposite enantiomeric product. Two additional issues to be addressed were the enantioselectivity of the Sharpless epoxidation and the regioselectivity of the nucleophilic ring-opening of the epoxy alcohol **XII**, both of which may diminish with the increased steric bulk at carbon 3 and the tertiary nature of the carbocationic intermediate. Finally, the oxidative cleavage of the *N*-Boc-aminodiols **XIII** was expected to provide the desired amino acid.

The first step in the planned syntheses was the preparation of the unsaturated esters (*E*)-**2a** and (*E*)-**2b** for reduction to the starting allylic alcohols (Scheme 4). The preparation of ethyl 3-phenylbutanoate (*E*)-**2a** had already been described by the Reformatsky reaction on benzophenone<sup>21</sup> as well as by conjugate addition of lithium diphenylcuprate to ethylbutynoate.<sup>22</sup> In our hands, however, the carbocupration reaction was difficult to reproduce and the Reformatsky reaction gave only moderate yields. Consequently, we decided to explore other reactions conditions. Whereas the

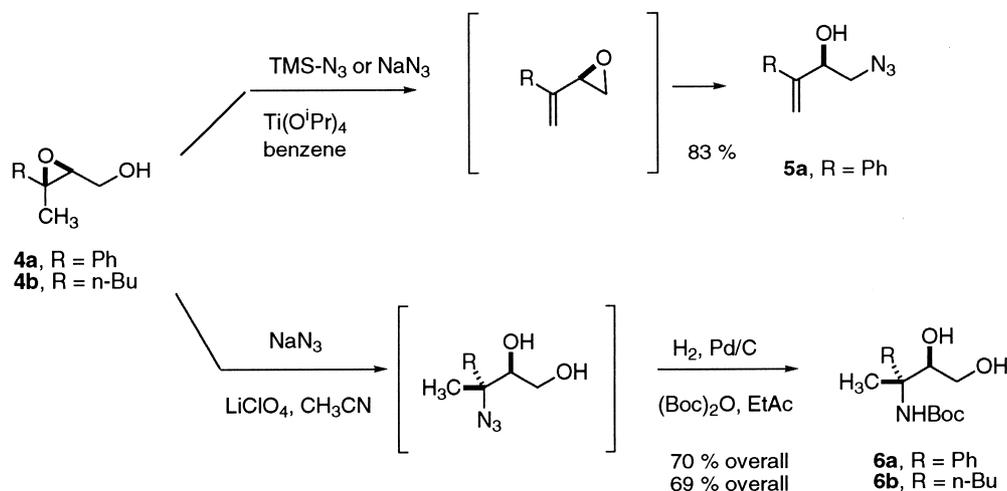
Peterson olefination<sup>23</sup> gave excellent yields but low diastereoselectivities, the Wadsworth–Emmons reaction<sup>24</sup> gave the best combination of yield and selectivity. On the contrary, in order to obtain diastereomerically pure (*E*)-**2b**, we found that carbocupration<sup>25</sup> of ethyl butynoate was the most convenient procedure. Following the protocol described by Henrick,<sup>26</sup> the conjugate addition of a polymeric organocopper complex prepared from *n*-butyl lithium took place in a completely diastereoselective manner affording (*E*)-**2a** in quantitative yield. The reduction of both unsaturated esters with DIBAL-H took place uneventfully providing the corresponding allylic alcohols (*E*)-**3a** and (*E*)-**3b**<sup>27</sup> in excellent yield (Scheme 4).

Alcohols **3a** and **3b** were subsequently submitted to the Sharpless catalytic epoxidation procedure<sup>15</sup> using L-(+)-DIPT to generate the catalyst (Scheme 5). Epoxy alcohols **4a** and **4b** were obtained in good yields and the enantiomeric excesses of 83–84%<sup>28</sup> as determined by <sup>19</sup>F NMR of their corresponding Mosher's esters.<sup>29</sup> The enantiomeric excesses of **4a** and **4b** were increased up to 91–92% ee by using L-(+)-DET in the preparation of the catalyst.

Nucleophilic ring-opening of epoxy alcohol **4a** proved to be difficult due to the steric hindrance at C-3 and to the stability of the putative carbocationic-like intermediate. We first used the complex Ti(N<sub>3</sub>)<sub>2</sub>(O<sup>i</sup>Pr)<sub>2</sub> in benzene,<sup>16a</sup> conditions that usually give excellent results with sterically hindered substrates,<sup>11,13b</sup> however, a complex mixture of products was observed by TLC and the desired azidodiols could not be isolated. The Caron–Sharpless conditions<sup>30</sup> for the nucleophilic ring opening with azide ion (TMS-N<sub>3</sub>, Ti(O<sup>i</sup>Pr)<sub>4</sub>, benzene) gave the unexpected allyl alcohol **5a**



Scheme 5.

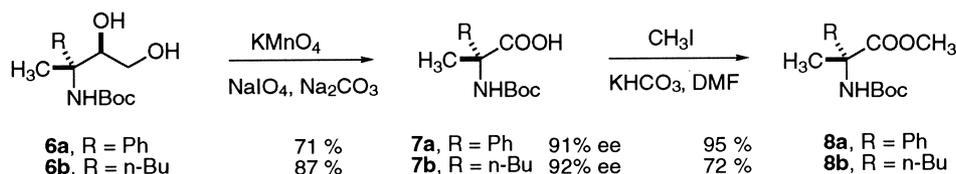


Scheme 6.

in good yield (Scheme 6). Other conditions using Ti(O<sup>i</sup>Pr)<sub>4</sub> as a Lewis acid (NaN<sub>3</sub>, Ti(O<sup>i</sup>Pr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>) also afforded the undesired alcohol **5a** which is presumed to have arisen from a terminal epoxide formed on rearrangement and dehydration of **4a** (Scheme 6). An analogous allylic alcohol was obtained using benzhydrylamine as ammonia synthetic equivalent (Ph<sub>2</sub>CHNH<sub>2</sub>, Ti(O<sup>i</sup>Pr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>).<sup>31</sup> These results prompted us to explore milder Lewis acids. We were pleased to find that under Crotti's conditions<sup>32</sup> the reaction took place cleanly providing a single isomer of azidodiols that was immediately submitted to catalytic hydrogenation in the presence of (Boc)<sub>2</sub>O to give *N*-Boc-3-phenyl-3-aminobutane-1,2-diol **6a**. When the same reaction sequence was applied to epoxy alcohol **4b**, after hydrogenation and *N*-Boc-protection of the crude, *N*-Boc-aminodiols **6b** was isolated in good yield.

The *N*-Boc-3-amino-1,2-diols **6a** and **6b** were somewhat unstable, probably due to the easy hydrolysis of the carbamate. To convert them into the target amino acids, they were each submitted to oxidation with KMnO<sub>4</sub>/NaIO<sub>4</sub>/Na<sub>2</sub>CO<sub>3</sub> in dioxane/water<sup>33</sup> (Scheme 7) Purification and characterization of the *N*-Boc-amino acids, was facilitated by conversion to the respective methyl esters. The enantiomeric purity of **8a** was ascertained by HPLC analysis on a chiral stationary phase (Chiracel OD) which indicated the same enantiomeric excess as the starting epoxy alcohol **4a**. The absence of a chromophore in **8b** forced us to prepare the amino acid protected as a benzyloxycarbamate methyl ester<sup>34</sup> which also exhibited the same enantiomeric excess as the starting epoxy alcohol **4b**.

In summary, we have developed a new methodology for the synthesis of  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids from epoxy



Scheme 7.

alcohols. As representative examples of this interesting class of compounds we have described the preparation of two enantiomerically enriched *N*-Boc-protected  $\alpha$ -disubstituted glycines from the corresponding allyl alcohols. Because our methodology relies on the Sharpless catalytic epoxidation for enantioselective introduction of chirality, it may be applicable to amino acids of both enantiomeric series possessing a variety of side chains. Moreover, taking into account the synthetic versatility of *N*-Boc-3-amino-1,2-diols, which have been converted into many types of biologically active compounds, the new 3,3-disubstituted-3-amino-1,2-diols may exhibit a similarly broad synthetic potential. In addition, a serendipitous discovery has provided an efficient synthesis of enantiomerically enriched vinyl azido alcohols **5** has been developed. The synthetic potential of these intermediates is currently being studied in our laboratory.

### 3. Experimental

#### 3.1. General

Specific rotations were recorded at room temperature (23°C, Concentration in g/100 mL). <sup>1</sup>H NMR spectra were obtained at 200 and 300 MHz (s=singlet, d=doublet, t=triplet, q=quartet, dt=doublet triplet, m=multiplet, brs=broad signal). <sup>13</sup>C NMR spectra were obtained at 50.3 or 75.4 MHz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Low-resolution mass spectra were recorded in CI mode using ammonia. High-resolution mass spectra (CI) were performed by the 'Unidade de Espectrometria de Masas, Universidad de Santiago de

Compostela'. Dichloromethane was distilled from CaH<sub>2</sub> under nitrogen prior to use. Chromatographic separations were carried out using Net<sub>3</sub> pre-treated (2.5% v/v) SiO<sub>2</sub> (70–230 mesh). (*E*)-3-Methyl-2-heptenoic acid ethyl ester was prepared according to the described procedure<sup>26</sup> and used without purification in the next step.

**3.1.1. (*E*)-3-Phenyl-2-butenic acid ethyl ester (2a).** To a solution of sodium hydride (0.2 g, 8.33 mmol) in anhydrous dimethoxyethane (16 mL) at room temperature, triethyl phosphonoacetate (1.64 mL, 8.33 mmol) and a solution of acetophenone (970 μL, 8.33 mmol) in anhydrous dimethoxyethane (5 mL) were sequentially added, dropwise and with stirring. After 3–4 h, the reaction mixture was partitioned between water (5 mL) and diethyl ether (15 mL). The aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine and dried (MgSO<sub>4</sub>). Solvent was removed in vacuo and the residual oil (7:1 diastereomeric ratio) was purified by column chromatography eluting with hexanes/ethyl acetate mixtures yielding 1.35 g of pure *trans* isomer (85% yield) as a colorless oil. The spectral data were identical to those from the literature.<sup>21c</sup>

**3.1.2. (*E*)-3-Phenyl-2-buten-1-ol (3a).** To a solution of **2a** (335 mg, 1.76 mmol) in diethyl ether (4 mL) at 0°C, DIBALH (3.52 mL, 1 M in hexanes) was added slowly. The reaction mixture was allowed to warm to room temperature, and stirred for 1.5 h, diluted with diethyl ether (13 mL), cooled to 0°C and quenched with careful addition of brine (10 mL). Then, 4 M HCl was added dropwise under stirring until two clear phases were formed (ca. 10 mL). The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with brine, dried (sodium sulfate) and evaporated. The residue was purified by column chromatography eluting with hexanes/ethyl acetate mixtures yielding 243 mg of **3a** (93% yield) as a colorless oil. The spectral data was identical to those from the literature.<sup>21c</sup>

**3.1.3. (*E*)-3-Methyl-2-heptenen-1-ol (3b).** Following the procedure described for the preparation of **3a**, alcohol **3b** (1.04 g, 89% overall yield from ethyl butynoate) was synthesized from **2b** (1.5 g, 8.8 mmol) and obtained as an oil. The spectral data were identical to those from the literature.<sup>27</sup>

**3.1.4. (2*S*,3*S*)-2,3-Epoxy-3-phenyl-butan-1-ol (4a).** In a 250 mL round-bottomed flask, anhydrous powdered 4 Å molecular sieves (0.636 g) and anhydrous CH<sub>2</sub>Cl<sub>2</sub> (102 mL) were placed under nitrogen. After cooling the flask to –20°C, the following reagents were introduced sequentially via cannula with stirring: L-(+)-diethyl tartrate (173 mg, 0.84 mmol) in dichloromethane (1 mL), titanium tetraisopropoxide (170 μL, 0.55 mmol) and a 2.5 M solution of *tert*-butyl hydroperoxide in isooctane (8.9 mL, 22.25 mmol). The mixture was stirred for 1 h at –20°C and treated dropwise with a solution of **3a** (1.67 g, 11.3 mmol—previously distilled and stored for 24 h over 4 Å molecular sieves) in dichloromethane (7 mL). After stirring for 4 h at –20°C, the reaction was quenched by addition of 10% NaOH solution saturated with NaCl (0.9 mL) and diethyl ether (6 mL). The mixture was then allowed to warm to

10°C, and anhydrous MgSO<sub>4</sub> (0.9 g) and Celite™ (0.12 g) were added. After stirring for 15 min at room temperature, the mixture was filtered through a short pad of Celite™. The solvents were evaporated in vacuo and the excess of *tert*-butyl hydroperoxide was removed by azeotropic distillation with toluene. The crude product was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield 1.63 g of **4a** (88% yield) as a colorless oil. [α]<sub>D</sub><sup>23</sup> = –19.2 (c 1.0, CHCl<sub>3</sub>). IR (NaCl) ν: 3422, 1725, 1653, 1603, 1447, 1259, 1068 cm<sup>–1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.42–7.34 (m, 5H), 4.01 (dd, *J*=8.9, 4.4 Hz, 1H), 3.88 (dd, *J*=8.9, 6.6 Hz, 1H), 3.61 (brs, 1H), 3.18 (dd, *J*=6.6, 4.4 Hz, 1H), 1.75 (s, 3H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 141.85 (C), 128.18 (CH), 127.31 (CH), 124.89 (CH), 66.03 (CH), 60.96 (CH<sub>2</sub>), 60.71 (C), 17.59 (CH<sub>3</sub>) ppm. MS (CI–NH<sub>3</sub>). *m/z* (%): 165 (100) [M+1]<sup>+</sup>, 182 (12) [M+18]<sup>+</sup>. The enantiomeric excess was determined to be 91% by <sup>19</sup>F NMR and <sup>1</sup>H NMR of the corresponding MTPA ester. When the reaction was performed using L-(+)-diisopropyl tartrate, the enantiomeric excess was determined to be 83% by the same method.

**3.1.5. (2*S*,3*S*)-2,3-Epoxy-3-methyl-heptan-1-ol (4b).** Employing **3b** (0.6 g, 4.69 mmol) in the procedure described for the preparation of **4a**, **4b** (0.65 g, 96% yield) was obtained as an oil. IR (NaCl) ν: 3855, 3426, 2959, 2936, 2863 cm<sup>–1</sup>. [α]<sub>D</sub><sup>23</sup> = –7.0 (c 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.82 (dd, *J*=4.2, 12 Hz, 1H), 3.65 (dd, *J*=6.6, 12 Hz, 1H), 2.95 (dd, *J*=4.5, 6.6 Hz, 1H), 2.62 (brs, 1H), 1.62 (m, 1H), 1.31 (m, 8H), 0.90 (t, *J*=7 Hz, 3H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 63.0 (CH), 61.4 (C), 61.3 (CH<sub>2</sub>), 38.2 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 16.6 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>) ppm. MS (CI–NH<sub>3</sub>). *m/z* (%): 145 (26.5) [M+1]<sup>+</sup>, 127 (55.7) [M–18]<sup>+</sup>, 108 (100) [M–36]<sup>+</sup>. HRMS calcd for MH<sup>+</sup>, C<sub>8</sub>H<sub>17</sub>O<sub>2</sub>: 145.1228, found 145.1230. The enantiomeric excess was determined to be 92% by <sup>19</sup>F NMR and <sup>1</sup>H NMR of the corresponding MTPA ester. When the reaction was performed using L-(+)-diisopropyl tartrate, the enantiomeric excess was determined to be 83% by the same method.

**3.1.6. (2*R*,3*R*)-3-*tert*-Butoxycarbonylamino-3-phenylbutan-1,2-diol (6a).** To a solution of **4a** (0.5 g, 3.05 mmol) in acetonitrile (15 mL), LiClO<sub>4</sub> (8 g, 75.2 mmol) and sodium azide (0.99 g, 15.2 mmol) were added under nitrogen. The reaction mixture was then heated at 65°C with stirring for 24 h, allowed to cool to room temperature and quenched by addition of water and diethyl ether. The aqueous layer was extracted with diethyl ether and the combined organic phases were dried (MgSO<sub>4</sub>) and evaporated. The crude product was directly used in the next step.

In a 50 mL round-bottomed flask, palladium on activated charcoal (109 mg, 10% mol) was added to ethyl acetate (5 mL). Air was removed in vacuo from the flask which was purged with nitrogen, evacuated and refilled with nitrogen three times. The mixture was briefly stirred for 15 min and treated with a solution of the previously obtained reaction crude with Boc<sub>2</sub>O (0.76 g, 3.48 mmol) in 4 mL ethyl acetate. After purging with hydrogen, the reaction mixture was stirred at room temperature under dry hydrogen. After 5 h, the mixture was filtered through

a short pad of Celite™. The solvent was evaporated in vacuo and the resulting oil was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford **6a** (0.6 g, 70% overall yield from **3**) as an oil.  $[\alpha]_D^{23} = -24.3$  (*c* 0.9, CHCl<sub>3</sub>) IR (NaCl)  $\nu$ : 3415, 1694, 1497, 1252, 1169 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.29–7.36 (m, 5H), 5.78 (brs, 1H), 3.88 (brs, 1H), 3.62 (dd, *J*=7.6, 3.4 Hz, 1H), 3.43 (dd, *J*=11.4, 3.4 Hz, 1H), 3.27 (dd, *J*=11.4, 7.6 Hz, 1H) 2.82 (brs, 1H), 1.78 (s, 3H), 1.26 brs, 9H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  156.1 (C), 142.8 (C), 128.5 (CH), 127.9 (CH), 126.5 (CH), 79.9 (C), 69.6 (C), 62.3 (CH<sub>3</sub>) 60.6 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 23.3 (CH<sub>3</sub>) ppm. MS (CI–NH<sub>3</sub>). *m/z* (%): 282 (100) [M+1]<sup>+</sup>, 299 (40) [M+18]<sup>+</sup>.

**3.1.7. (2R,3R)-3-tert-Butoxycarbonylamino-3-methylheptan-1,2-diol (6b).** Employing **4b** (0.20 g, 1.38 mmol) in the procedure described for the preparation of **4a**, **6b** (0.11 g, 69% yield) was obtained as an oil.  $[\alpha]_D^{23} = +3.4$  (*c* 0.5, CHCl<sub>3</sub>) IR (NaCl)  $\nu$ : 3361, 2960, 2937, 2875, 1690 cm<sup>-1</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.10 (bs, 1H), 4.60 (s, 1H), 2.51–2.75 (m, 3H), 1.62 (m, 2H), 1.49 (s, 3H), 1.47 (s, 9H), 1.25–1.37 (m, 4H), 0.96 (t, *J*=6.6 Hz, 3H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  156.2 (C), 79.7 (C), 73.5 (CH), 62.8 (CH<sub>2</sub>), 57.4 (C), 36.7 (CH<sub>2</sub>), 36.3\* (CH<sub>2</sub>), 28.0 (CH<sub>3</sub>), 27.9\* (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>) 25.1\* (CH<sub>2</sub>), 23.0 (CH<sub>2</sub>), 22.8\* (CH<sub>2</sub>), 21.0 (CH<sub>3</sub>), 13.7 (CH<sub>3</sub>), 13.6\* (CH<sub>3</sub>) ppm. Signals marked with an asterisk correspond to a rotamer.

**3.1.8. (2R)-1-Azido-3-phenyl-but-3-en-2-ol (5a).** To a solution of **4a** (50 mg, 0.30 mmol) in benzene (3 mL) under nitrogen, titanium tetraisopropoxide (0.12 mL, 0.37 mmol) and TMS-N<sub>3</sub> (85  $\mu$ L, 0.61 mmol) were added dropwise. The reaction mixture was stirred for 2 h at room temperature and quenched by addition of 10% NaOH solution saturated with NaCl (2 mL). The mixture was stirred for 5 h, filtered through a short pad of Celite and washed thoroughly with diethyl ether. The aqueous layer was extracted with diethyl ether and the combined organic phases were dried (MgSO<sub>4</sub>) and evaporated. The crude product was then purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield 53 mg of **5a** (83% yield) as an oil.  $[\alpha]_D^{23} = -7.8$  (*c* 1, CHCl<sub>3</sub>) IR (NaCl)  $\nu$ : 3390, 2101, 1725, 1684, 1601, 1065 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.36 (m, 5H), 5.43 (d, *J*=8 Hz, 2H), 4.77 (dd, *J*=4.8, 2 Hz, 1H), 3.65 (dd, *J*=7.6, 2 Hz, 1H), 3.48 (dd, *J*=7.6, 4.8 Hz, 1H), 2.85 (bd, 1H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  148.1 (C), 139.3 (C), 128.5 (CH) 128.4 (CH), 127.9 (CH), 113.8 (CH<sub>2</sub>), 73.8 (CH), 65.9 (CH<sub>2</sub>) ppm. MS (CI–NH<sub>3</sub>): *m/z* (%): 147 (15%), 190 (M+1, 100%), 197 (40%).

**3.1.9. 2-tert-Butoxycarbonylamino-2-phenyl-propionic acid methyl ester (8a).** A solution of **4a** (75 mg, 0.27 mmol) in dioxane (0.57 mL) and water (0.25 mL) was treated with Na<sub>2</sub>CO<sub>3</sub> (14 mg, 0.13 mmol), NaIO<sub>4</sub> (231 mg, 1.35 mmol) and KMnO<sub>4</sub> (9 mg, 10% mol) at room temperature and stirred overnight. Then, the mixture was made alkaline with a solution of NaOH 1N until pH 8. The aqueous layer was extracted with EtOAc. The aqueous layer was carefully acidified<sup>35</sup> with a solution of HCl 2N and extracted with EtOAc. Evaporation of the solvent afforded a

crude product which was used without further purification in the next step.

A solution of the crude acid (0.059 g, 0.192 mmol) in 1 mL of anhydrous DMF was treated with KHCO<sub>3</sub> (0.036 g, 0.39 mmol) and methyl iodide (0.03 mL, 0.49 mmol) at room temperature and stirred overnight. After the addition of 1 mL of NH<sub>4</sub>Cl, the aqueous phase was extracted with ethyl acetate. The combined organics layers were washed with brine and then dried with MgSO<sub>4</sub>. The solvent was removed in vacuo to give 0.055 g of crude ester that was purified by chromatography (SiO<sub>2</sub>/Et<sub>3</sub>N, 5% EtOAc in hexanes as the eluant) to afford pure **8a** (0.05 g, 68% overall yield from **4a**) as an oil.  $[\alpha]_D^{23} = +40.6$  (*c* 1.3, CHCl<sub>3</sub>) IR (NaCl)  $\nu$ : 2979, 1721.1, 1704, 1451, 1279, 1167, 1057 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.31–7.43 (m, 5H), 5.82 (brs, 1H), 3.69 (s, 3H), 1.99 (s,3H), 1.36 (s, 9H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  173.5 (C), 154.0 (C), 140.3 (C), 128.5 (CH), 127.7 (CH), 126.5 (CH), 64.8 (C), 61.8 (C), 53.0 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 23.2 (CH<sub>3</sub>) ppm. MS (CI–NH<sub>3</sub>). *m/z* (%): 280 (17) [M+1]<sup>+</sup>, 297 (100) [M+18]<sup>+</sup>. HRMS calcd for C<sub>15</sub>H<sub>21</sub>NO<sub>4</sub>: 279.1471, found 279.1483. The enantiomeric excess was determined to be 91% by HPLC analysis on a Chiralcel<sup>®</sup> OD column (25 cm) at 30°C with the detector centered at 254 nm using a flow rate of 0.5 mL min<sup>-1</sup> and an eluant of hexane/isopropyl alcohol 95/5: *t*<sub>R</sub> (2R,2R)=10.17 min; *t*<sub>R</sub> (2S,2S)=11.12 min.

**3.1.10. (2R,2R)-2-tert-Butoxycarbonylamino-2-methylhexanoic acid methyl ester (8b).** Following the procedure described for the preparation of **8a**, starting from **6b** (0.10 g, 0.38 mmol), **8a** (0.071 g, 72% yield) was obtained as an oil. IR (film)  $\nu$ : 3432, 3380, 2959, 2875, 1719 cm<sup>-1</sup>.  $[\alpha]_D^{23} = -7.3$  (*c* 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.22 (br, 1H), 3.77 (s, 3H), 1.95–2.16 (m, 1H), 1.65–1.82 (m, 1H), 1.56 (s, 3H), 1.46 (s, 9H), 1.2–1.4 (m, 2H), 1.15 (m, 2H), 0.91 (t, *J*=6.6 Hz, 3H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  175.1 (C), 154.3 (C), 79.4 (C), 59.6 (C), 52.4 (CH<sub>3</sub>), 37.0 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 26.1 (CH<sub>2</sub>), 23.3 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>) ppm. MS (CI–NH<sub>3</sub>). *m/z* (%): 260 (100) [M+1]<sup>+</sup>, 160 (74) [M–Boc]<sup>+</sup>. HRMS calcd for C<sub>13</sub>H<sub>26</sub>NO<sub>4</sub>: 260.1862, found 260.1859. The enantiomeric excess was determined to be 83% by HPLC analysis of the corresponding benzyloxycarbamate methyl ester, prepared by the same reaction sequence<sup>34</sup> from a sample of epoxide **4b** of 83% ee. HPLC performed as described for **8a**: *t*<sub>R</sub> (2R,2R)=22.4 min; *t*<sub>R</sub> (2S,2S)=29.7 min.

## Acknowledgements

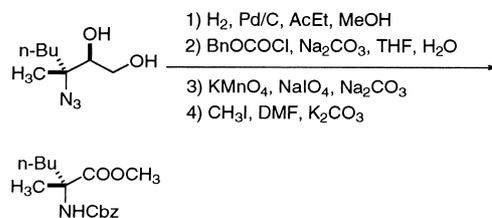
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- 910 34. The known benzyloxycarbamate methyl ester<sup>19e,20</sup> was  
911 prepared without characterizing the intermediates by the  
912 following sequence:  
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- 946 35. The *N*-Boc-protected amino acids **7a** and **7b** as well as the  
947 *N*-Boc-aminodiols **6a** and **6b** are more sensitive to acid  
948 hydrolysis than usual, easily affording the deprotected  
949 products, probably due to the steric hindrance near the  
950 nitrogen atom.