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Enantioselective synthesis of unsaturated amino acids using *p*-methoxybenzylamine as an ammonia equivalent

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Abstract

A versatile, non-alkylative enantioselective synthesis of unsaturated α-amino acids based on the Sharpless asymmetric epoxidation has been developed. Enantiomerically enriched *trans* epoxy alcohols bearing unsaturated substituents were prepared and submitted to regio- and stereospecific ring-opening with *p*-methoxybenzylamine as a nucleophile, leading to *anti*-3-(*p*-methoxybenzylamino)-1,2-diols which were further protected by reaction with Boc_2O. The 1,2-diol fragment was then oxidatively cleaved by a sequential treatment with sodium periodate and sodium chlorite to afford the corresponding amino acid. Using this methodology, doubly *N*-protected (*p*-methoxybenzyl and Boc) allyl glycine, 3-butenyl glycine and 4-pentenyl glycine have been prepared in three synthetic steps from the corresponding allyl alcohols. As a demonstration of the orthogonal nature of the nitrogen protection, both protecting groups have been selectively removed from the fully protected amino ester.

1. Introduction

The increasing interest of modified peptides in biological studies and as therapeutic agents[1] is fostering the research of methodologies directed to the synthesis of unnatural amino acids in enantiomerically pure form.[2] Unsaturated α-amino acids are key components in the synthesis of biologically active peptides[3] and peptide isosteres.[4] They are also useful chiral synthons[5] and, as with many other unsaturated substrates, their synthetic interest has recently increased with the advent of the ring-closing metathesis (RCM) methodologies.[6] In combination with this reaction, they have been used as precursors of dicarba analogs of macrocyclic peptides,[7] isosteric cystine dipeptide bis-amino diacids,[8] physiologically active *meso*-diaminopimelic acid derivatives,[9] unsaturated heterocycles[10] or cyclic protease inhibitors.[11]

Among the α-amino acids bearing an unsaturated alkene-type residue, allyl glycine **1a** is the most important and widely used[3–10,12] although other specimens of the same family such as 3-butenyl glycine

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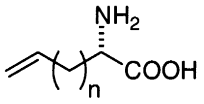
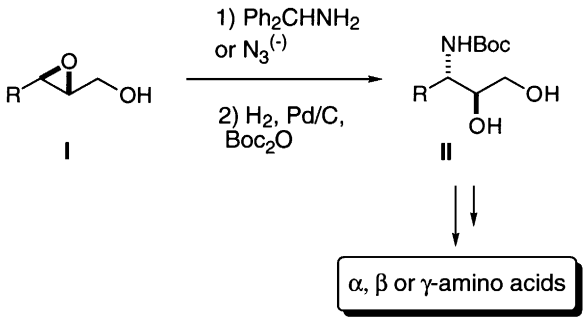
1b[13] or 4-pentenyl glycine **1c**[5e,10,11,13b,c,14] have also shown high synthetic utility. The syntheses described for these compounds include enzymatic resolutions,[3e,12b,15] alkylation of alanine synthons[13b,c,16] and asymmetric synthesis using the chiral auxiliary approach[17] but, to the best of our knowledge, no practical catalytic asymmetric synthesis[18] has been developed to date for this important type of amino acids.



1a n = 1
1b n = 2
1c n = 3

Recently, we have set out the principles of a general methodology based on the catalytic Sharpless epoxidation[19] which allows the completely stereocontrolled synthesis of amino acids of different structural types in enantiomerically pure form[20] (Scheme 1). Our method relies on the regio- and stereospecific ring-opening of epoxy alcohols **I** by a synthetic equivalent of ammonia to provide, after hydrogenation and protection, *N*-Boc-3-amino-1,2-diols **II**; until now we have used benzhydrylamine or azide reagents for this purpose. Whereas our approach has been successfully applied to the preparation of a wide range of biologically important amino acids,[20] the need of reductive protocols for the actualization of the amino function (**I**→**II**) poses some limitations to the scope of the method. Thus, amino acids containing side chains with olefinic double bonds could not be efficiently prepared by our original procedure, due to the difficulties encountered in the chemoselective reduction of the benzhydryl group and the low yields obtained in the preparation of non-aromatic unsaturated 3-azido-1,2-diols.[21]



Scheme 1. The regio- and stereospecific ring-opening of epoxy alcohols **I** by a reductively cleavable synthetic equivalent of ammonia provides *N*-Boc-3-amino-1,2-diols **II** which have been used as starting materials in the preparation of several structural types of amino acids

The failure of our early efforts[21] directed towards developing a high-yield synthesis of unsaturated *N*-Boc-3-amino-1,2-diols [**II**, R=$(CH_2)_n$-CH=CH_2] through non-hydrogenative reduction of the benzhydryl or azido groups drove our attention towards the use of an alternative amino synthon that could be unmasked by oxidative methods. *p*-Methoxybenzylamine appeared as an attractive candidate for this purpose. Although *p*-methoxybenzylamine has been used as a nitrogen source in the preparation of amides from lactones[22] and the *p*-methoxybenzyl group is a well known protecting group,[23] to the best of our knowledge *p*-methoxybenzylamine has never been used in epoxide chemistry as a vehicle for the introduction of the amino group. We report herein a new and efficient methodology for the preparation of unsaturated α-amino acids, orthogonally protected at nitrogen, based on the use of *p*-methoxybenzylamine as ammonia surrogate.

2. Results and discussion

Our initial study of the Lewis acid assisted, regioselective ring-opening of chiral epoxy alcohols by primary amines[24] already showed that *p*-methoxybenzylamine was an excellent reagent for this process, leading, under titanium tetraisopropoxide catalysis,[25] to the corresponding C-3 ring-opened products in good yields and excellent regioselectivities. According to this precedent, and bearing in mind the easy oxidative cleavage of the *p*-methoxybenzyl group[23,26] this amine was selected as a promising ammonia source for our study. *N*-Protected derivatives of (*S*)-allyl glycine **1a**, (*S*)-3-butenyl glycine **1b**, and (*S*)-4-pentenyl glycine **1c** which, as we have already mentioned, are the most representative examples of unsaturated α-amino acids, were selected as the targets.

According to the planned strategy (Fig. 1), these amino acids would come from *N*-protected 3-amino-1,2-diols **2** which, in turn, would arise from epoxy alcohols **3**, readily accessible by Sharpless epoxidation of allyl alcohols **4**.

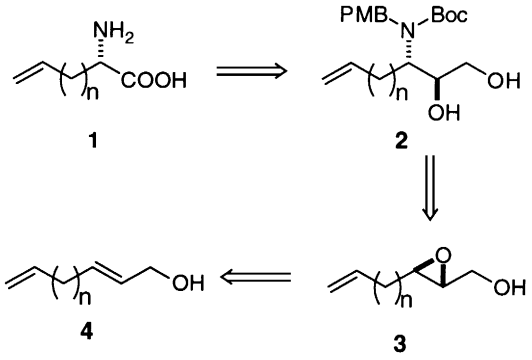
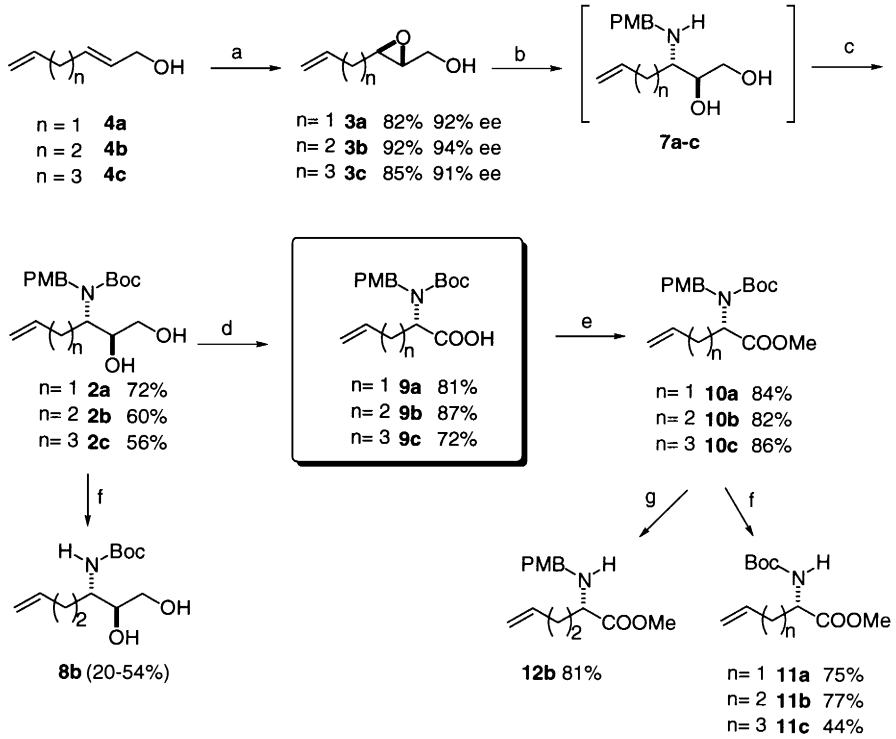


Fig. 1. Retrosynthetic analysis of unsaturated amino acids

Whereas the synthesis and even the asymmetric epoxidation of (*E*)-2,5-hexadien-1-ol **4a**[27] and (*E*)-2,7-octadien-1-ol **4c**[28,29] were already described in the literature, (*E*)-2,6-heptadien-1-ol **4b** was previously unknown. Nevertheless, it could be prepared in multigram scale from commercially available 4-penten-1-ol **5** by a sequence of Swern oxidation, Wittig olefination and DIBALH reduction, to provide diastereomerically pure **4b** in 66% overall yield.

The catalytic Sharpless epoxidation of **4a**–**c** took place uneventfully, leading to **3a**–**c** in good yield. The enantiomeric excess of these epoxy alcohols was determined to be 91–94% by HPLC analysis of the corresponding *p*-toluenesulfonates (Scheme 2). Optimization of conditions for the ring-opening process and nitrogen protecting group manipulation was performed with readily available epoxy alcohol **3b**. Thus, treatment of this epoxy alcohol with 2 equivalents of *p*-methoxybenzylamine and 3 equivalents of titanium tetraisopropoxide in methylene chloride at reflux afforded *p*-methoxybenzylaminodiol **7b** in 80% yield, although the removal of excess of *p*-methoxybenzylamine proved to be very troublesome. Significantly, and contrary to what happened with 3-benzhydrylamino-1,2-diols,[30] the nucleophilicity of the amino group in **7b** allowed its further protection with a *tert*-butoxycarbonyl group. In effect, when a solution of compound **7b** in methanol was sonicated in the presence of Boc_2O and $NaHCO_3$,[31] the orthogonally protected aminodiol **2b** was obtained in 80% yield (Scheme 2). The difficulties encountered in the purification of **7b** could be overcome by submitting the reaction crude (still containing some *p*-methoxybenzylamine) to the Boc protection conditions. In this way, **2b** was obtained in 60% overall yield. When the same optimized experimental protocol was applied to epoxy alcohols **3a** and **3c**, the doubly protected aminodiols **2a** and **2c** were obtained in good overall yields.



Scheme 2. Reaction conditions: (a) *tert*-Butyl hydroperoxide, D-(−)-DIPT (cat), $Ti(O^iPr)_4$ (cat), 4 Å sieves, −20°C. (b) *p*-Methoxybenzylamine, $Ti(O^iPr)_4$, CH_2Cl_2, reflux. (c) $(Boc)_2O$, $NaHCO_3$, MeOH, sonication. (d) (i) $NaIO_4$, THF, H_2O; (ii) $NaClO_2$, Bu^tOH, 2-methyl-2-butene. (e) MeI, DMF, $KHCO_3$. (f) Ceric ammonium nitrate (CAN), CH_3CN, H_2O. (g) HCl, THF

On the way to the target amino acids, removal of the PMB protection could in principle be performed at the stage of aminodiols **2a**–**c**, since all of the remaining operations are compatible with the presence of the terminal double bond. Unfortunately, however, the oxidative deprotection of **2b**, using ceric ammonium nitrate (CAN), gave *N*-Boc-3-amino-5-hepten-1,2-diol **8b** in low and poorly reproducible yields (Scheme 2). The failure of this reaction was probably due to the presence of the oxidatively labile 1,2-diol functionality; to avoid this problem, we decided to proceed to the orthogonally protected unsaturated amino acids before cleavage of the PMB group.

The oxidative cleavage of the 1,2-diol fragment in the presence of two oxidatively sensitive groups, like the double bond and the *p*-methoxybenzylamino substituent, required a careful selection of reaction conditions. After some experimentation on **2a**, we found an appropriate protocol: the 1,2-diol fragment was first cleaved with sodium periodate to the corresponding aldehyde,[32] which was immediately oxidized by sodium chlorite[33] to the PMB/Boc protected amino acid **9a** in 81% yield. This sequence was also applied to **2b** and to **2c** which afforded the doubly *N*-protected (*S*)-butenyl glycine **9b** and (*S*)-pentenyl glycine **9c**, respectively, also in good yields.

Given the intermediacy of a labile α-amino aldehyde in the synthetic sequence, special attention was paid to the control of stereochemical integrity of the stereogenic center along the sequence. In practice, the periodate oxidation was performed quickly, and the intermediate aldehyde was submitted to chlorite oxidation without purification. In order to check the enantiomeric purity of **9a**–**c**, the methyl ester derivatives were prepared by treatment with MeI/$KHCO_3$ in DMF, providing **10a**–**c** in good yields (82–86%). HPLC analysis of these compounds (Chiralcel OD column) showed ee values essentially identical to those of the starting epoxy alcohols (91, 93 and 94% ee, respectively) although we could

confirm by analysis of a sample that was stored overnight, that the intermediate aldehyde racemized on standing.

As a demonstration of the orthogonal nature of the nitrogen protection, all three amino acids were esterified and both protecting groups were selectively removed. The cleavage of the *p*-methoxybenzyl group in **10a**–**c** took place cleanly with CAN, affording the Boc-amino esters **11a**–**c**, in good yields (Scheme 2). On the other hand, the Boc group in **10b** could be readily removed with HCl/MeOH, leading to the PMB-protected (*S*)-butenyl glycine methyl ester **12b** in 81% yield

In summary, we have developed a new methodology for the synthesis of unsaturated α-amino acids from epoxy alcohols using *p*-methoxybenzylamine as an ammonia equivalent. As representative examples of this interesting class of compounds we have described the preparation of enantiomerically enriched, fully protected, allyl, butenyl and pentenyl glycines in only three separate steps from the corresponding allyl alcohols. The intrinsic characteristics of our methodology, which uses a Sharpless catalytic epoxidation as the sole source of chirality, make it extendable to amino acids of both enantiomeric series bearing carbon–carbon double bonds at the side chain. Moreover, the protection of the amino function with two orthogonal groups (*p*-methoxybenzyl and Boc) confers to the intermediates in the sequence a great potential as synthetic intermediates. Results on the evaluation of this potential will be reported in due course.

3. Experimental

3.1. General

Optical rotations were recorded at room temperature (23°C) (concentration in g/100 mL. Infrared spectra were recorded using film NaCl technique. ^{1}H NMR were obtained at 200 or 300 MHz (s=singlet, d=doublet, t=triplet, q=quartet, dt=double triplet, m=multiplet, b=broad and bd=broad doublet). ^{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. Low resolution mass spectra were recorded in CI mode using ammonia. High-resolution mass spectra (CI) were performed by the Servicio de Espectrometría de Masas, Universidad de Córdoba using methane. Elemental analyses were performed by the 'Servei d'Anàlisis Elementals del CSIC de Barcelona'. Dichloromethane was distilled from CaH_2 under nitrogen prior to use. Chromatographic separations were carried out using NEt_3 pre-treated (2.5% v/v) SiO_2 (70–230 mesh). (*E*)-2,5-Hexadien-1-ol **4a**[27] and (*E*)-2,7-octadien-1-ol **4c**[28] were prepared according to the procedures described in the literature.

*3.2. (*E*)-2,6-Heptadienoic acid methyl ester **6***

To a solution of oxalyl chloride (4.2 mL) in anhydrous dichloromethane (90 mL) at −60°C were sequentially added, dropwise and under stirring, dimethyl sulfoxide (7.1 mL) in anhydrous dichloromethane (22.5 mL) and a solution of 4-penten-1-ol **5** (3.5 g, 40.7 mmol) in anhydrous dichloromethane (37.7 mL). After 15–20 min, triethylamine (28.6 mL) was added dropwise and stirring was continued at the same temperature. After 20–25 min, the reaction mixture was allowed to warm to room temperature. Then, water (188 mL) was added and phases were separated. The aqueous layer was extracted with dichloromethane and the combined organic phases were washed with 5% hydrochloric acid and brine, dried over magnesium sulfate and concentrated (to ca. 100 mL) under reduced pressure without heating. To this solution (containing mainly 4-pentenal), was added methyl triphenylphosphoranylacetate (15 g,

44.8 mmol) with stirring and the mixture was heated at reflux for 2 h. The solvent was removed in vacuo and the residual oil extracted with hexanes. The hexane solution was evaporated and the resulting oil purified by column chromatography eluting with hexanes:ethyl acetate (95:5) to afford 4.56 g of **6** (80% yield) as an oil. IR (NaCl) ν 3090, 1730, 1660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 6.95 (m, 1H), 5.9–5.7 (m, 2H), 5.1–4.95 (m, 2H), 3.73 (s, 3H), 2.26 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.0 (C), 148.6 (CH), 137.0 (CH), 121.2 (CH), 115.5 (CH_2), 51.4 (CH_3), 32.0 (CH_2), 31.4 (CH_2).

*3.3. (*E*)-2,6-Heptadien-1-ol **4b***

To a solution of **6** (2.6 g, 18 mmol) in diethyl ether (24 mL) at 0°C, DIBALH (46.3 mL, 1 M in hexanes) was added dropwise. The reaction mixture was allowed to warm up to room temperature, and stirred for 1.5 h, diluted with diethyl ether (77 mL), cooled to 0°C and quenched with careful addition of brine (60 mL). Then, 4 M HCl was added dropwise under stirring until two clear phases were formed (ca. 46 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 1.7 g of **4b** (82% yield) as an oil. IR (NaCl) ν 3332, 3079, 1642 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.9–5.6 (m, 3H), 5.0 (m, 2H), 4.07 (d, ^3J(H,H)=4.4 Hz, 2H), 2.2–2.1 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0 (CH), 132.1 (CH), 129.3 (CH), 114.7 (CH_2), 63.4 (CH_2), 32.2 (CH_2), 31.4 (CH_2).

*3.4. (2*R,*3*R*)-2,3-Epoxy-5-hexen-1-ol **3a***

In a 250 mL round-bottomed flask were placed anhydrous powdered 4 Å molecular sieves (1.1 g) and anhydrous dichloromethane (107 mL) under nitrogen. After cooling to −20°C (CO_2/CCl_4 bath) the following reagents were introduced sequentially via cannula under stirring: D-(−)-diisopropyl tartrate (1.0 g, 4.3 mmol) in dichloromethane (1 mL), titanium tetraisopropoxide (1.07 mL, 3.55 mmol) and a 2.78 M solution of *tert*-butyl hydroperoxide in isooctane (25.8 mL, 94.6 mmol). The mixture was stirred for 1 h at –20°C and a solution of **4a** (3.5 g, 35.7 mmol) (previously distilled and stored for 24 h over 4 Å molecular sieves) in dichloromethane (18 mL) was added dropwise. After 3.5 h stirring at that temperature, the reaction was quenched by addition of 10% NaOH solution saturated with NaCl (2.86 mL) and diethyl ether (17 mL). The mixture was then allowed to warm up to 10°C, and anhydrous $MgSO_4$ (2.86 g) and Celite (0.36 g) were added. After 15 min stirring 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 removed by azeotropic distillation with toluene. The crude product was then purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield 3.33 g of **3a** (82% yield) as an oil. $[\alpha]_D^{23}$=+35.4 (*c*=1.2, $CHCl_3$); [lit.[27] $[\alpha]_D^{23}$=+23.2 (*c*=10, CH_3OH)]. ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.2–5.0 (m, 2H), 3.95 (d, ^3J(H,H)=12 Hz), 3.65 (d, ^3J(H,H)=12 Hz, 1H), 3.0 (m, 2H), 2.37 (m, 2H), 1.8 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=132.8 (CH), 117.7 (CH_2), 61.7 (CH_2), 58.2 (CH), 54.8 (CH), 35.6 (CH_2). The enantiomeric excess was determined to be 92% by HPLC analysis of its *p*-toluenesulfonate ester. HPLC (Chiralcel® OD column; 25 cm): 30°C, 254 nm; 0.5 mL/min; hexane 90%/isopropyl alcohol 10%; t_R (2*R*,3*R*)=17.37 min; t_R (2*S*,3*S*)=18.58 min.

*3.5. (2*R,*3*R*)-2,3-Epoxy-6-hepten-1-ol **3b***

Following the procedure described for the preparation of **3a** but starting from **4b** (5.3 g, 47.3 mmol), 5.57 g of **3b** (92% yield) were obtained as an oil. Bp 125°C/18 torr.[34] $[\alpha]_D^{23}$=+34.5 (*c*=2, $CHCl_3$). IR

(NaCl) ν 3423, 2981, 2929, 1642 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.9 (m, 1H), 5 (m, 2H), 3.9 (m, 1H), 3.63 (m, 1H), 2.95 (m, 2H), 2.2 (m, 2H), 1.8–1.6 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.3 (CH), 115.2 (CH_2), 61.7 (CH_2), 58.7 (CH), 55.4 (CH), 30.8 (CH_2), 30.0 (CH_2). MS (CI-NH_3): *m/z* (%): 163 (33) $[M+35]^+$, 146 (100) $[M+18]^+$. The enantiomeric excess was determined to be 94% by HPLC analysis of its *p*-toluenesulfonate. HPLC (Chiralcel® OD column; 25 cm): 30°C, 254 nm; 0.5 mL/min; hexane 90%/isopropyl alcohol 10%; t_R (2*R*,3*R*)=17.37 min; t_R (2*S*,3*S*)=18.70 min.

*3.6. (2*R,*3*R*)-2,3-Epoxy-7-octen-1-ol **3c***

Following the procedure described for the preparation of **3a** but starting from **4c** (6.4 g, 50 mmol), 6.1 g of **3c** (85% yield) were obtained as an oil. $[\alpha]_D^{23}$=+38.6 (*c*=1.8, $CHCl_3$). IR (NaCl) ν 3425, 2979, 2935, 1642 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5 (m, 2H), 3.89 (m, 1H), 3.58 (m, 1H), 3 (m, 3H), 2.1 (m, 2H), 1.6 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.9 (CH), 114.7 (CH_2), 61.7 (CH_2), 58.6 (CH), 55.8 (CH), 33.2 (CH_2), 30.8 (CH_2), 25.0 (CH_2). The enantiomeric excess was determined to be 91% by HPLC analysis of its *p*-toluenesulfonate. HPLC (Chiralcel® OD column; 25 cm): 30°C, 254 nm; 0.5 mL/min; hexane 90%/isopropyl alcohol 10%; t_R (2*R*,3*R*)=16.48 min; t_R (2*S*,3*S*)=17.94 min.

*3.7. (2*S,*3*S*)-3-[*tert*-Butoxycarbonyl-(4-methoxybenzyl)-amino]hex-5-en-1,2-diol **2a***

To a solution of freshly distilled **3a** (1.0 g, 9 mmol) in anhydrous dichloromethane (12 mL), titanium tetraisopropoxide (9.3 mL, 31.3 mmol) was added. The mixture was briefly stirred and a solution of *p*-methoxybenzylamine (2.87 g, 20.9 mmol, freshly distilled) in anhydrous dichloromethane (12 mL) was added via cannula. The reaction mixture was then heated at reflux with stirring for 24 h, allowed to cool down to room temperature and quenched by addition of 10% NaOH solution saturated with NaCl (36.2 mL). The mixture was stirred for 5 h, filtered through a short pad of Celite and washed thoroughly with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organic phases were dried ($MgSO_4$) and evaporated. The crude product (a mixture of (2*S*,3*S*)-3-(4-methoxybenzylamino)-5-hexene-1,2-diol and *p*-methoxybenzylamine) was directly used in the next step.

To a solution of the previously obtained reaction crude in MeOH (105 mL), Boc_2O (5.92 g, 27.2 mmol), and $NaHCO_3$ (5.22 g) were added. The suspension was sonicated in a cleaning bath until the evolution of CO_2 ceased (ca. 4 h). The solids were then filtered and the solvent evaporated. Addition of 105 mL of ether provoked the precipitation of small quantities of salts that were also filtered off. Evaporation of the solvent afforded a crude product that was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield 2.26 g of **2a** (72% overall yield). $[\alpha]_D^{23}$=+3.2 (*c*=1.5, $CHCl_3$). IR (NaCl) ν 3419, 3076, 1665, 1613 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.16 (d, ^3J(H,H)=8.5 Hz, 2H), 6.83 (d, ^3J(H,H)=8.5 Hz, 2H), 5.7 (m, 1H), 5.1–4.9 (m, 2H), 4.29 (m, 2H), 3.78 (s, 3H), 4.1–3.0 (m, 4H), 2.57 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.9 (C), 156.5 (C), 135.4 (CH), 130.4 (C), 129.1 (CH), 116.9 (CH_2), 113.8 (CH), 80.8 (C), 73.8 (CH), 63.4 (CH_2), 59.4 (CH), 55.1 (CH_3), 50.3 (CH_2), 31.7 (CH_2), 28.3 (CH_3). MS (CI-NH_3): *m/z* (%): 352 (100) $[M+1]^+$, 369 (1) $[M+18]^+$, 296 (3), 297 (1). HRMS calcd for $C_{19}H_{29}NO_5$: 351.2030, found 351.2046.

*3.8. (2*S,*3*S*)-3-[(4-Methoxybenzyl)amino]hept-5-en-1,2-diol **7b***

To a solution of freshly distilled **3b** (4.9 g, 38.3 mmol) in anhydrous dichloromethane (44 mL), titanium tetraisopropoxide (34.5 mL, 115 mmol) was added. The mixture was stirred for several

minutes, a solution of *p*-methoxybenzylamine (10.5 g, 76.5 mmol, freshly distilled) in anhydrous dichloromethane (44 mL) was added via cannula and the mixture was heated to reflux. After 48 h reflux, the reaction mixture was allowed to cool down to room temperature, quenched (5 h stirring) with 10% NaOH solution saturated with NaCl (134 mL), filtered through a short pad of Celite and thoroughly washed with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organic phases were extracted with 0.1N HCl. The organic phase was dried ($MgSO_4$) and evaporated to afford 1.58 g of pure **7b**. The combined aqueous layers were brought to pH 9 with 2N NaOH and extracted with dichloromethane. The organic phase was dried ($MgSO_4$), concentrated in vacuo, and the residue dissolved in diethyl ether. To this solution, solid CO_2 was added to precipitate the excess *p*-methoxybenzylamine as the carbonate. The precipitate was filtered off and washed with ether saturated with CO_2. Evaporation of this ether solution afforded 8.43 g of crude **7b** (containing 23% of *p*-methoxybenzylamine) that was used in the next step without further purification. The estimated overall yield was 80%. $[\alpha]_D^{23}$=+10.2 (*c*=2.1, $CHCl_3$). IR (NaCl) ν 3361, 2935, 1640, 1613 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.22 (d, ^3J(H,H)=8.5 Hz, 2H), 6.87 (d, ^3J(H,H)=8.5 Hz, 2H), 5.8 (m, 1H), 5.1–4.95 (m, 2H), 3.8 (s, 3H), 3.8–3.6 (m, 5H), 2.8 (m, 1H), 2.1 (m, 2H), 1.6 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7 (C), 137.8 (CH), 131.9 (C), 129.3 (2CH), 115.2 (CH_2), 113.8 (2CH), 71.4 (CH), 64.3 (CH_2), 59.9 (CH), 55.2 (CH_3), 51.7 (CH_2), 30.2 (CH_2), 29.6 (CH_2). MS (CI-NH_3): *m/z* (%): 266 (100) $[M+1]^+$, 204 (3). HRMS calcd for $C_{15}H_{24}NO_3$: 266.1756, found 266.1713.

*3.9. (2*S*,3*S*)-3-[*tert*-Butoxycarbonyl-(4-methoxybenzyl)amino]hept-5-en-1,2-diol **2b***

From pure **7b**: A mixture of **7b** (100 mg, 0.38 mmol), Boc_2O (100 mg, 0.456 mmol), and $NaHCO_3$ (94 mg) in MeOH (1.9 mL) was sonicated in a cleaning bath until the evolution of CO_2 ceased (ca. 4 h). The solids were then filtered off, and the solvent evaporated. The crude product was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford 110 mg of **2b** (80% yield).

From crude **7b**: Following the procedure described above but starting from 2 g of crude **7b** containing 23% of *p*-methoxybenzylamine, 1.6 g of **2b** (75% yield) were obtained as an oil. $[\alpha]_D^{23}$=−8.9 (*c*=1.6, $CHCl_3$). IR (NaCl) ν 3423, 1663, 1613, 1586 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.19 (d, ^3J(H,H)=8.5 Hz, 2H), 6.84 (d, ^3J(H,H)=8.5 Hz, 2H), 5.7 (m, 1H), 5.0–4.9 (m, 2H), 4.3 (s, 2H), 3.78 (s, 3H), 3.8–3.2 (m, 4H), 2.1–1.8 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8 (C), 157.2 (C), 137.8 (CH), 130.4 (C), 129.1 (CH), 114.9 (CH_2), 113.8 (CH), 80.9 (C), 73.5 (CH), 63.2 (CH_2), 58.4 (CH), 55.2 (CH_3), 49.0 (CH_2), 30.6 (CH_2), 28.4 (CH_3), 26.4 (CH_2). MS (CI-NH_3): *m/z* (%): 366 (100) $[M+1]^+$, 383 (3) $[M+18]^+$. Anal. calcd for $C_{20}H_{31}NO_5$: C 65.73, H 8.55, N 3.83; found C 65.64, H 8.63, N 3.91.

*3.10. (2*S*,3*S*)-3-[*tert*-Butoxycarbonyl-(4-methoxybenzyl)amino]oct-7-en-1,2-diol **2c***

Following the procedure described for the preparation of **2a**, but starting from **3c** (6.0 g, 42.2 mmol), 9.0 g of **2c** (56% yield) were obtained as an oil. $[\alpha]_D^{23}$=–10.5 (*c*=1.9, $CHCl_3$). IR (NaCl) ν 3419, 1663, 1613, 1586 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.18 (d, ^3J(H,H)=8.5 Hz, 2H), 6.84 (d, ^3J(H,H)=8.5 Hz, 2H), 5.75 (m, 1H), 5 (m, 2H), 4.3 (m, 3H), 3.8 (s, 3H), 3.7–3 (m, 3H), 2.1–1.8 (m, 4H), 1.5 (s, 9H), 1.3 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8 (C), 157.3 (C), 138.4 (CH), 130.5 (C), 129.1 (CH), 114.6 (CH_2), 113.8 (CH), 81.1 (C), 73.5 (CH), 63.1 (CH_2), 58.8 (CH), 55.2 (CH_3), 49.0 (CH_2), 33.6 (CH_2), 28.5 (CH_3), 26.6 (CH_2), 26.0 (CH_2). HRMS calcd for $C_{21}H_{34}NO_5$ (M+1): 380.2437, found 380.2436.

3.11. (2S,3S)-3-[(tert-Butoxycarbonyl)amino]-5-hepten-1,2-diol **8b**

To a solution of **2b** (200 mg, 0.55 mmol) in CH_3CN:H_2O (3:1) (2.2 mL), ceric ammonium nitrate (600 mg, 1.1 mmol) was added. After 0.5 h, the mixture was diluted with dichloromethane (82 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (41 mL). The combined organic phases were dried with $MgSO_4$ and evaporated. The crude product was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford 72 mg of **8b** (54% yield). $[\alpha]_D^{23}$=–6.4 (c=3.1, $CHCl_3$). IR (NaCl) ν 3355, 1684 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.1–4.9 (m, 2H), 3.75 (b, 1H), 3.9–3.2 (m, 4H), 2.3–1.8 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.1 (C), 137.6 (CH), 115.2 (CH_2), 80.2 (C), 74.5 (CH), 63.1 (CH_2), 51.9 (CH), 30.2 (CH_2), 28.3 (CH_3), 26.4 (CH_2).

3.12. (2S)-2-[tert-Butoxycarbonyl-(4-methoxybenzyl)amino]-4-pentenoic acid **9a**

To a solution of **2a** (675 mg, 1.9 mmol), in 7.5 mL THF:H_2O (1:3) was added $NaIO_4$ (616 mg, 2.9 mmol). After 2 h stirring at room temperature, the solution was diluted with water and dichloromethane until two clear phases formed. The aqueous layer was extracted with dichloromethane and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo without heating. The crude product (557 mg) was placed in a pressure tube, immediately dissolved in ^{t}BuOH (8.9 mL) and a solution of 2-methyl-2-butene (0.38 mL, 6.63 mmol) in THF (1.4 mL) and a solution of sodium chlorite (80% purity, 257 mg, 2.28 mmol) and NaH_2PO_4 (252 mg, 2.1 mmol) in H_2O (2.2 mL) were sequentially added to this solution. The reaction flask was hermetically sealed and the mixture was vigorously stirred at 25°C for 15 h. Then, it was extracted with dichloromethane (2×61 mL) and the organic phase was washed with 0.1 M $NaHSO_4$ (41 mL) and water (28 mL). Solvent evaporation in vacuo afforded 518 mg of acid **9a** (81% yield). $[\alpha]_D^{23}$=–28.0 (c=2, $CHCl_3$). IR (NaCl) ν 3080, 1744, 1700, 1613 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.21 (bd, 2H), 6.84 (d, ^3J(H,H)=8.8 Hz, 2H), 5.6 (m, 1H), 5.0 (m, 2H), 4.7–4.0 (m, 3H), 3.79 (s, 3H), 2.67 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.9–175.6* (C), 158.9 (C), 134.3 (CH, C), 120.0 (CH), 129.0 (CH), 117.9 (CH_2), 113.7 (CH), 81.3 (C), 64.4–59.1* (CH), 55.2 (CH_3), 51.4 (CH_2), 34.7–33.7* (CH_2), 28.3 (CH_3) (signals marked with an asterisk correspond to a rotamer). HRMS calcd for $C_{18}H_{25}NO_5$: 335.1716, found 335.1733.

3.13. (2S)-2-[tert-Butoxycarbonyl-(4-methoxybenzyl)amino]-4-pentenoic acid methyl ester **10a**

To a solution of **9a** (518 mg, 1.55 mmol) in dimethylformamide (1.5 mL), were added under nitrogen $KHCO_3$ (317 mg, 3.1 mmol) and methyl iodide (150 mL, 2.4 mmol). The mixture was stirred for 16 h at room temperature and then the reaction was quenched by addition of water (6.2 mL). The product was extracted with (1:1) benzene:ethyl acetate mixtures. The combined organic phases were successively washed with water, 5% Na_2SO_3 and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography eluting with hexanes:ethyl acetate (95:5) to afford 458 mg of **10a** (84% yield). $[\alpha]_D^{23}$=–44.2 (c=1.8, $CHCl_3$). IR (NaCl) ν 2979, 1744, 1698, 1613, 1588 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.22 (bd, 2H), 6.84 (d, ^3J(H,H)=8.5 Hz, 2H), 5.8–5.5 (m, 1H), 5.0 (m, 2H), 4.6–4.3 (m, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 2.8–2.4 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.5 (C), 158.7 (C), 152.1 (C), 134.4 (CH, C), 129.9 (CH), 128.8 (CH), 117.5 (CH_2), 113.5 (CH), 80.5 (C), 59.1* (CH), 55.2 (CH_3), 51.8 (CH_3), 51.0–49.8* (CH_2), 34.9–33.9* (CH_2), 28.3 (CH_3) (signals marked with an asterisk correspond to a rotamer). MS (CI-NH_3): m/z (%): 367 (10) $[M+18]^+$, 350 (100) $[M+1]^+$, 311 (11), 294 (11). HRMS calcd for $C_{19}H_{27}NO_5$: 349.1889, found 349.1895. The enantiomeric excess was

determined to be 91% by HPLC (Chiralcel® OD column; 25 cm): 30°C; 254 nm; 0.5 mL/min; hexane 99%/isopropyl alcohol 1%; t_R (2*R*)=25.35 min; t_R (2*S*)=27.65 min.

3.14. (2S)-2-[tert-Butoxycarbonyl-(4-methoxybenzyl)amino]-5-hexenoic acid **9b**

Following the procedure described for the preparation of **9a** but starting from **2b** (527 mg, 1.44 mmol), 437 mg of **9b** (87% yield) were obtained. $[\alpha]_D^{23}$=–32 (*c*=1.1, $CHCl_3$). IR (NaCl) ν 3250, 1700, 1613, 1586 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.21 (bd, 2H), 6.85 (d, ^3J(H,H)=8.8 Hz, 2H), 5.65 (m, 1H), 5.1–4.8 (m, 2H), 4.55 (b, 1H), 4.5–4.1 (m, 2H), 3.8 (s, 3H), 2.2–1.6 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.0 (C), 159.0 (C), 157.0 (C), 137.2 (CH), 130.0 (CH, C), 115.6 (CH_2), 113.8 (CH), 81.3 (C), 59 (CH), 55.3 (CH_3), 51.1 (CH_2), 30.5 (CH_2), 29.7 (CH_2), 28.3 (CH_3). HRMS calcd for $C_{19}H_{27}NO_5$: 349.1896, found 349.1889.

3.15. (2S)-2-[tert-Butoxycarbonyl-(4-methoxybenzyl)amino]-5-hexenoic acid methyl ester **10b**

Following the procedure described for the preparation of **10a** but starting from **9b** (437 mg, 1.25 mmol), 372 mg of **10b** (82% yield) were obtained. $[\alpha]_D^{23}$=–49.7 (*c*=1.8, $CHCl_3$). IR (NaCl) ν 1744, 1698, 1613 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.22 (bd, 2H), 6.84 (d, ^3J(H,H)=8.8 Hz, 2H), 5.7 (m, 1H), 5.1–4.8 (m, 2H), 4.4 (m, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 2.2–1.7 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1 (C), 158.8 (C), 155.6 (C), 137.4 (CH), 129.7 (CH, C), 115.3 (CH_2), 113.6 (CH), 80.5 (C), 58.4 (CH), 55.2 (CH_3), 51.8 (CH_3), 50.3 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 28.3 (CH_3). MS (CI-NH_3): *m/z* (%): 381 (10) $[M+18]^+$, 364 (100) $[M+1]^+$, 325 (11%). Anal. calcd for $C_{20}H_{29}NO_5$ C 66.09, H 8.04, N 3.85; found: C 66.05, H 8.12, N 4.10. The enantiomeric excess was determined to be 93% by HPLC (Chiralcel® OD column; 25 cm): 30°C; 254 nm; 0.5 mL/min; hexane 99%/isopropyl alcohol 1%; t_R (2*R*)=23.11 min; t_R (2*S*)=24.13 min.

3.16. (2S)-2-[tert-Butoxycarbonyl-(4-methoxybenzyl)amino]-5-heptenoic acid **9c**

Following the procedure described for the preparation of **9a** but starting from **2c** (802 mg, 2.12 mmol), 556 mg of **9c** (72% yield) were obtained. $[\alpha]_D^{23}$=–24.6 (*c*=2.1, $CHCl_3$). IR (NaCl) ν 3078, 1698, 1613, 1588 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.2 (bd, 2H), 6.84 (d, ^3J(H,H)=8.8 Hz, 2H), 5.8–5.5 (m, 1H), 5.0–4.8 (m, 2H), 4.6–4.1 (m, 3H), 3.79 (s, 3H), 2.1–1.6 (m, 4H), 1.45 (s, 9H), 1.4–1.2 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.2–177.5* (C), 158.8 (C), 155.6 (C), 138.0 (CH), 129.8 (CH, C), 128.8 (CH), 114.7 (CH_2), 113.7 (CH), 81.2 (C), 60.3–59.1* (CH), 55.2 (CH_3), 50.8 (CH_2), 33.2 (CH_2), 29.7 (CH_2), 28.3 (CH_3), 25.7 (CH_2) (signals marked with an asterisk correspond to a rotamer). HRMS calcd for $C_{20}H_{29}NO_5$ (M^+): 363.2046, found 363.2045.

3.17. (2S)-2-[tert-Butoxycarbonyl-(4-methoxybenzyl)amino]-5-hexenoic acid methyl ester **10c**

Following the procedure described for the preparation of **10a** but starting from **9c** (395 mg, 1.09 mmol), 397 mg of **10c** (86% yield) were obtained. $[\alpha]_D^{23}$=–38.0 (*c*=2.0, $CHCl_3$). IR (NaCl) ν 1744, 1698, 1613 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.2 (bd, 2H), 6.84 (d, ^3J(H,H)=8.4 Hz, 2H), 5.8–5.5 (m, 1H), 5.0–4.8 (m, 2H), 4.6–4.2 (m, 3H), 3.79 (s, 3H), 3.58 (s, 3H), 2.0–1.6 (m, 4H), 1.45 (s, 9H), 1.5–1.2 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172 (C), 158.5 (C), 156 (C), 138.1 (CH), 129.8 (CH, C), 128.7 (CH), 114.6 (CH_2), 113.5 (CH), 80.5 (C), 59.1–58.5* (CH), 55.2 (CH_3), 51.8 (CH_3), 50.4–49.1* (CH_2), 33.3 (CH_2), 29.7 (CH_2), 28.3 (CH_3), 25.6 (CH_2) (signals marked with an asterisk correspond to

a rotamer). HRMS calcd for $C_{21}H_{32}NO_5$ ($M+1^+$): 378.2280, found, 378.2294. The enantiomeric excess was determined to be 94% by HPLC (Chiralcel® OD column; 25 cm): 30°C; 254 nm; 0.42 mL/min; hexane 99%/isopropyl alcohol 1%; t_R (2*R*)=26.71 min; t_R (2*S*)=29.08 min.

3.18. (2S)-2-[(tert-Butoxycarbonyl)amino]-4-pentenoic acid methyl ester ***11a***

To a solution of **10a** (425 mg, 1.22 mmol) in CH_3CN:H_2O (3:1) (4.9 mL), ceric ammonium nitrate (1.34 mg, 2.44 mmol) was added. After 20–30 min stirring, dichloromethane (182 mL) was added and the organic layer was washed with saturated aqueous $NaHCO_3$ (91 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford 269 mg of **11a** (75% yield). $[\alpha]_D^{23}$=–7.9 (*c*=1.3, MeOH) (lit.[13b] $[\alpha]_D^{23}$=–9 (*c*=2, MeOH), ee>95%). IR (NaCl) ν 3367, 1748, 1719 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.67 (m, 1H), 5.1 (m, 2H), 4.35 (m, 1H), 3.71 (s, 3H), 2.5 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4 (C), 155.0 (C), 132.2 (CH), 119.0 (CH_2), 79.8 (C), 52.8 (CH), 52.2 (CH_3), 36.7 (CH_2), 28.3 (CH_3). MS (CI-NH_3): *m/z* (%): 247 (100) $[M+18]^+$, 230 (71) $[M+1]^+$, 191 (28), 174 (10).

3.19. (2S)-2-[(tert-Butoxycarbonyl)amino]-5-hexenoic acid methyl ester ***11b***

Following the procedure described for the preparation of **11a** but starting from **10b** (324 mg, 0.89 mmol), 168 mg of **11b** (77% yield) were obtained. $[\alpha]_D^{23}$=–14.5 (*c*=1.2, MeOH) (lit.[13b,c] $[\alpha]_D^{23}$=–17 (*c*=1.2, MeOH), ee>95%). IR (NaCl) ν 3367, 1717, 1642 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.1–5.0 (m, 2H), 4.3 (m, 1H), 3.73 (s, 3H), 2.1 (m, 2H), 2–1.6 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.1 (C), 155.2 (C), 136.8 (CH), 115.6 (CH_2), 79.8 (C), 52.9 (CH), 52.2 (CH_3), 31.9 (CH_2), 29.4 (CH_2), 28.3 (CH_3).

3.20. (2S)-2-[(tert-Butoxycarbonyl)amino]-5-heptenoic acid methyl ester ***11c***

Following the procedure described for the preparation of **11a** but starting from **10c** (182 mg, 0.48 mmol), 54 mg of **11c** (44% yield) were obtained. $[\alpha]_D^{23}$=–10.6 (*c*=1.3, $CHCl_3$). IR (NaCl) ν 3367, 1719, 1642 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.9–5.6 (m, 1H), 5.1–4.9 (m, 2H), 4.4–4.2 (m, 1H), 3.74 (s, 3H), 2.07 (m, 2H), 1.9–1.2 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3 (C), 155.2 (C), 137.9 (CH), 115.0 (CH_2), 79.8 (C), 53.3 (CH), 52.2 (CH_3), 33.2 (CH_2), 32.2 (CH_2), 28.3 (CH_3), 24.5 (CH_2).

3.21. (2S)-2-[(4-Methoxybenzyl)amino]-5-hexenoic acid methyl ester ***12b***

A solution of **10b** (60 mg, 0.165 mmol), in 2.78 M HCl in MeOH (3 mL) was stirred for 6 h. The solvent was removed in vacuo and the crude was dissolved in saturated $NaHCO_3$. Then the solution was extracted with diethyl ether and the combined organic phases were dried over $MgSO_4$ and evaporated to afford 35 mg of **12b** (81% yield). $[\alpha]_D$=–24.9 (*c*=1.1, $CHCl_3$). IR (NaCl) ν 3332, 3078, 2931, 2838, 1737, 1613 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J=8.7 Hz, 2H), 6.78 (d, J=8.7 Hz, 2H), 5.7 (m, 1H), 4.9 (m, 2H), 3.72 (s, 3H), 3.67 (d, J=12.6 Hz, 1H), 3.65 (s, 3H), 3.48 (d, J=12.6, 1H), 3.2 (t, J=7 Hz, 1H), 2.1 (m, 2H), 1.7 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 (C), 158.7 (C), 137.7 (CH), 132.0 (C), 129.4 (CH), 115.2 (CH_2), 113.8 (CH), 60.0 (CH), 55.3 (CH_3), 51.6 (CH_3, CH_2), 32.7 (CH_2), 30.0 (CH_2) ppm.

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