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A unified approach to mesityl amino acids based on Sharpless dihydroxylation

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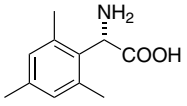
Abstract—Enantioselective syntheses of two mesityl (2,4,6-trimethylphenyl) amino acids are described. Starting from ethyl 3-mesityl-2-propenoate both enantiomeric dihydroxy esters **5** were prepared in excellent yield and enantiomeric purity (>99% ee) by Sharpless dihydroxylation. Each diol was converted into ethyl 3-azido-2-hydroxy-3-mesitylpropanoate **3** which is the common intermediate. Compound (2*S*,3*S*)-**3** was transformed into Fmoc-D-mesitylglycine D-**1** and Fmoc-L-mesitylalanine L-**2** through two four-step-sequences.

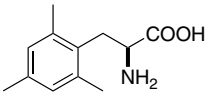
1. Introduction

Non-proteinogenic amino acids have become increasingly important due to the biological and therapeutic properties of their derivatives as drug intermediates[1] or as fragments of modified peptides.[2] One strategy to modify the biological activity of a peptide and to increase its bioavailability is to introduce conformationally restricted residues into the natural sequence.[3] In our group we have been interested in amino acids with conformational restrictions at the χ_1 and χ_2 angles.[4] Some years ago, we found that the replacement of phenyl by mesityl (2,4,6-trimethylphenyl) in several amino acids notably increased the rotational barriers without substantially changing the geometry of the lowest energy conformer.[5] Mesityl fragments moreover would notably increase the lipophilicity of the modified peptide, thus modifying their biological activity. Several examples of peptide analogues with mesitylalanine have already been described, but the synthesis was performed using racemic mesitylalanine and the final diastereomers had to be separated by chromatography.[6]

In a project devoted to the synthesis of analogues of peptidic natural hormones, we became interested in the preparation of multigram amounts of Fmoc-mesitylglycine **1** and Fmoc-mesitylalanine **2**. Although several preparations of these amino acids have been described[5,7,8] none of them report the Fmoc protection, which is very convenient for SPPS. Our previous synthesis[5] of mesityl amino acids based on Sharpless epoxidation and Sharpless aminohydroxylation had important drawbacks that made them impractical for large scale preparations, as they lead to the Boc-protected amino acids; furthermore, the Sharpless epoxidation of mesitylpropenol gives low conversion and the Sharpless aminohydroxylation affords reaction crudes that need to be chromatographed to remove the excess of reagents. We planned to use Sharpless asymmetric dihydroxylation[9] as a chirality source because this reaction is very easy to perform and usually gives high yields and enantiomeric excess with aromatic unsaturated esters. We envisaged that both Fmoc-protected amino acids **1** and **2** could be prepared from the same azido alcohol **3** as a key intermediate. This compound would arise by regioselective ring-opening of sulfite **4** derived from dihydroxyester **5**. Herein, we report a practical and reliable preparation of both Fmoc-protected mesityl amino acids **1** and **2** of any absolute configuration based on the Sharpless asymmetric dihydroxylation (Scheme 1).



L-Mesitylglycine L-**1**



L-Mesitylalanine L-**2**

2. Results and discussion

According to our retrosynthetic analysis, the synthesis started from unsaturated ester **6**, which was easily available

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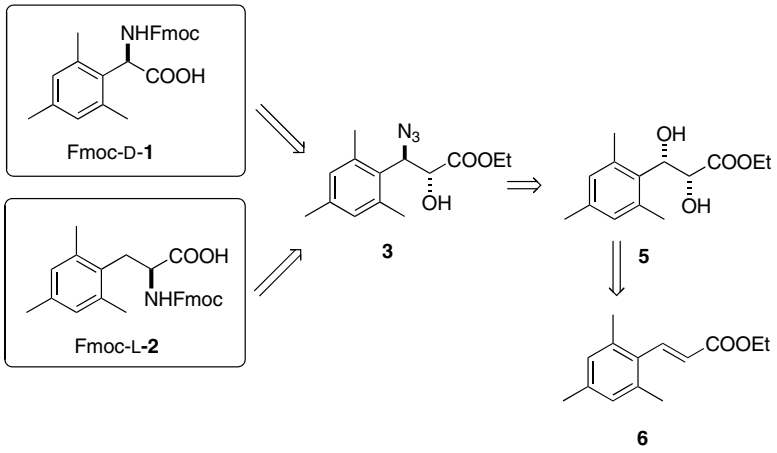


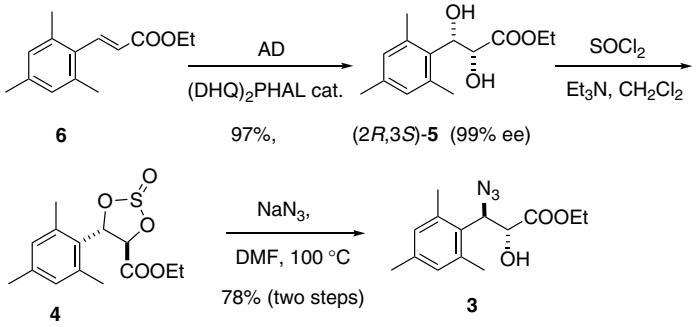
Scheme 1. Retrosynthetic analysis.

in multigram scale by Horner–Wadsworth–Emmons reaction of mesityl aldehyde. The Sharpless asymmetric dihydroxylation (AD) afforded nearly quantitative yields of both dihydroxy esters **5** in enantiomerically pure forms (>99% ee by chiral HPLC) using either $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ as ligands.[9] The absolute configuration of the dihydroxylated products **5** was assigned by the mnemonic device for predicting stereoselectivities reported by Sharpless.[10] The absolute configuration was later confirmed by the specific rotation of the hydrochloride of **11**. Although compound **5** was obtained as very dense oil, the reaction crude was pure enough to be used in the next step without any purification. The preparation of the corresponding sulfate was unsuccessful on this substrate. Consequently, we introduced the amino functionality through sulfite **4**, which was prepared by treatment with thionyl chloride in methylene chloride in quantitative yield.[11] The crude reaction of sulfite **4** without any purification was dissolved in DMF and treated with sodium azide at 100 °C. The ring-opening was completely regioselective, affording azido alcohol **3** in good yield as an oil. Using this procedure, several grams of either enantiomer of the key intermediate **3** could be easily prepared (Scheme 2).

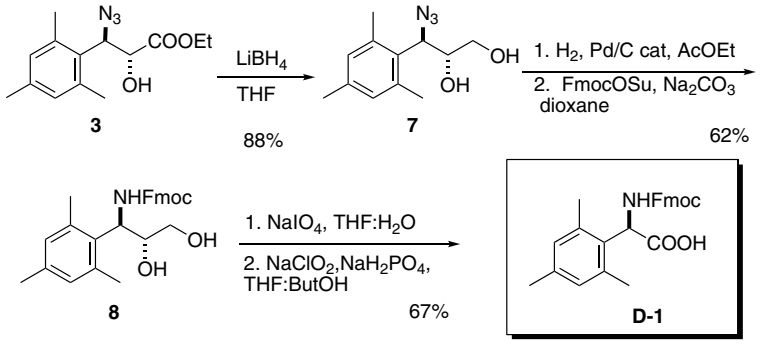
The synthesis of Fmoc-mesitylglycine D-**1** was performed as follows. The ester was reduced with $LiBH_4$ in THF to give azido diol **7** in excellent yield. Then, the azido group was hydrogenated with Pd/C in ethyl acetate to the primary amine which was protected under standard conditions to give **8**. Fmoc-protected aminodiol **8** was subsequently oxidized to the desired amino acid D-**1** in excellent yield. The enantiomeric purity was checked by chiral HPLC (>99% ee) (Scheme 3).

The synthesis of Fmoc-mesitylalanine **2** from the common intermediate **3** required the rearrangement of the amino function from C3 to C2. Following our previous work in which we used *N*-Boc aziridines in the preparation of aryl alanines,[12] we planned to use aziridines as intermediates, as we predicted that their hydrogenation would be regioselective at the benzylic position. Since our aim was to protect the amino group with Fmoc, the unprotected aziridine would be the most suitable for our purpose. Thus, by treating azido alcohol **3** with triphenylphosphine under Staudinger[13] conditions, aziridine **9** was obtained in moderate yield but in enantiomerically pure form (>99% ee by chiral HPLC). After some experimentation, hydrogenation of **9** took place in quantitative yield with complete regioselectivity using Pd/C as a catalyst. The best reaction conditions included the addition of acetic acid and working at high hydrogen pressure. The amino acid could be obtained by hydrolysis of ester **10** either in basic or acidic media. Hydrolysis of the ester was carefully studied to minimize racemization (Table 1, Scheme 4).

The hydrolysis in acidic media (Table 1, entry 1) provided the hydrochloride of **11** but with some loss of enantiomeric purity {$[\alpha]_D = +51.8$ (*c* 1.0, CH_3OH); lit.[8a] $[\alpha]_D = +64.6$ (*c*



Scheme 2. Preparation of the key intermediate.



Scheme 3. Synthesis of Fmoc-mesitylglycine from **3**.

Table 1. Hydrolysis of **10** to **11**

Entry	Conditions	Time (h)	ee (%)	Yield (%)
1	Concd HCl at reflux	6	93	99[a]
2	20% NaOH/EtOH, 65 °C	2	95	64
3	20% LiOH/EtOH, 65 °C	2	94	74
4	20% LiOH/dioxane, rt	24	99	80

ee was measured by chiral HPLC.
[a] The yield corresponds to the hydrochloride.

0.5, CH_3OH)}. Gratifyingly, basic hydrolysis using 20% aq LiOH in dioxane (Table 1, entry 4) yielded mesitylalanine **11** in enantiomerically pure form (>99% ee by chiral HPLC). This result confirmed the absolute configuration of **11**. Finally, protection under standard conditions afforded the desired Fmoc-L-**2** (Scheme 4).

3. Conclusion

In conclusion, we have developed enantioselective syntheses of two amino acids with a mesityl (2,4,6-trimethylphenyl) fragment using Sharpless dihydroxylation as a source of chirality. Starting from ethyl 3-mesityl-2-propenoate, both enantiomeric dihydroxy esters **5** were prepared in excellent yield and enantiomeric purity (>99% ee). These diols were converted into methyl 3-azido-2-hydroxy-3-mesitylpropanoate **3**, which is the common intermediate for the synthesis of Fmoc-mesitylglycine **1** and Fmoc-mesitylalanine **2**.

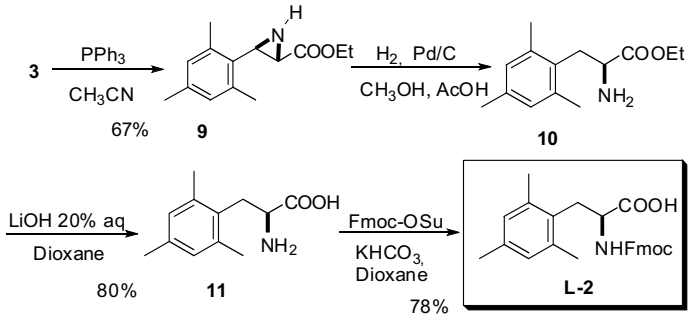
4. Experimental

4.1. General

Optical rotations were measured at room temperature on a Perkin–Elmer 241MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded on a Nicolet 510FT-IR instrument using NaCl film or KBr pellet techniques. NMR spectra were acquired on a 400 MHz instrument. ^{1}H NMR were obtained at 400 MHz (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet and br = broad) ^{13}C NMR were obtained at 100 MHz. ^{1}H chemical shifts are quoted relative to TMS and ^{13}C shifts relative to solvent signals. Signals marked with an asterisk correspond to rotamers.

4.2. Ethyl (2*R*,3*S*)-dihydroxy-3-mesitylpropanoate 5

To a mixture of $(DHQ)_2PHAL$ (790 mg, 1.0 mmol), $K_3Fe(CN)_6$ (100 g, 302 mmol), K_2CO_3 (41.7 g, 302 mmol) in $H_2O/^tBuOH$ (1:1, 1 L) was added $K_2OsO_4(OH)_4$ (149 mg, 0.403 mmol) followed by methanesulfonamide (9.5 g, 100 mmol). After stirring for 15 min, ethyl 3-mesityl-2-propenoate **6** (22.0 g, 100 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 48 h and then quenched with sodium sulfite (180 g). The stirring was continued for 2 h and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was washed with 2 M KOH, dried over $MgSO_4$ and evaporated to give (2*R*,3*S*)-**5** as a yellow oil (24.3 g, 97% yield). $[\alpha]_D = -24.7$ (*c* 0.98, $CHCl_3$). IR (film):



Scheme 4. Synthesis of Fmoc-mesitylalanine from **3**.

ν_{max} 3441 (b), 2978, 1733, 1611, 1190 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 5.18 (d, 1H, $J = 6.4$ Hz), 4.51 (d, 1H, $J = 6.4$ Hz), 4.04 (q, 2H, $J = 7$ Hz), 3.18 (br, 1H), 2.86 (br, 1H), 2.40 (s, 6H), 2.24 (s, 3H), 1.00 (t, 3H, $J = 7$ Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 173.0 (CO), 137.4 (C), 136.8 (C), 131.8 (C), 130.3 (CH), 73.8 (CH), 73.7 (CH), 61.9 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 13.7 (CH_3). MS (CI–NH_3) *m/z*: 270.1 [$(M+18)^+$, 100%], 252.1 [$(M)^+$, 60%]. HRMS (CI+): calcd for $C_{14}H_{20}O_4$, 252.1361; found, 252.1357. HPLC: Chiralpack-AD. Hexane/*i*-PrOH 98:2, 1 mL/min, $\lambda = 254$ nm, t_R (*S*,*R*) = 44 min and t_R (*R*,*S*) = 41 min. The same procedure using $(DHQD)_2PHAL$ as catalyst gave (2*S*,3*R*)-**5** in 95% yield. The enantiomeric purity of (2*R*,3*S*)-**5** and (2*S*,3*R*)-**5** was >99% ee.

4.3. (4*R*,5*S*)-4-Ethoxycarbonyl-5-mesityl-1,3,2-dioxathiolane-2-oxide 4

To a solution of diol **5** (23.5 g, 93 mmol) in CH_2Cl_2 (1.4 L) was added NEt_3 (38.9 mL, 279 mmol). The reaction mixture was cooled at 0 °C and stirred for 5 min. $SOCl_2$ (9.5 mL, 130.4 mmol) was added dropwise, and after stirring for 15 min at 0 °C, Et_2O (370 mL) and water (370 mL) were added. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic layer washed with brine, dried over $MgSO_4$ and evaporated, yielding 27.0 g of **4** (quantitative yield) as an oil. $[\alpha]_D = -18.8$ (*c* 1.00, $CHCl_3$). IR (film): ν_{max} 2979, 1742, 1216, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 2H), 6.89* (s, 2H), 6.61 (d, 1H, $J = 8$ Hz), 5.95* (d, 1H, $J = 10$ Hz), 5.35* (d, 1H, $J = 10$ Hz), 4.96 (d, 1H, $J = 8$ Hz), 4.30 (dq, 2H, $J = 20$ and 7 Hz), 4.22* (m, 2H), 2.45* (s, 6H), 2.37* (s, 6H), 2.28 (s, 6H), 1.31 (t, 3H, $J = 7$ Hz), 1.22* (t, 3H, $J = 7$ Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 168.0 (CO), 166.2 (CO), 139.9 (C), 139.8 (C), 138.4 (C), 138.2 (C), 131.0 (CH), 130.9 (CH), 125.6 (C), 122.6 (C), 84.9 (CH), 80.6 (CH), 80.3 (CH), 76.0 (CH), 62.8 (CH_2), 21.07 (CH_3), 21.06 (CH_3), 20.5 (CH_3), 20.2 (CH_3), 14.2 (CH_3), 14.0 (CH_3). MS (CI–NH_3) *m/z*: 315.6 [$(M+17)^+$, 100%]. HRMS (CI+): calcd for $C_{14}H_{18}O_5S$, 298.0875; found, 298.0876.

4.4. Ethyl (2*S*,3*S*)-3-azido-2-hydroxy-3-mesitylpropanoate 3

To a solution of **4** (18.6 g, 62.95 mmol) in DMF (386 mL), NaN_3 (8.2 g, 125.9 mmol) was added and heated at 100 °C for 18h. The solvent was removed and the crude was dissolved in Et_2O (310 mL) and 20% H_2SO_4 (310 mL) and stirred at room temperature overnight. An excess of saturated $NaHCO_3$ was added and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude was purified by flash chromatography (hexanes/AcOEt) yielding 13.6 g (78% yield) of **3** as a yellow oil. $[\alpha]_D = -126$ (*c* 0.79, $CHCl_3$). IR (film): ν_{max} 3468 (b), 2924, 2105, 1737, 1610, 1257 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 2H), 5.19 (d, 1H, $J = 8.8$ Hz), 4.45 (dd, 1H, $J = 7$ and 9 Hz), 4.33 (m, 2H), 2.52 (d, 1H, $J = 7$ Hz), 2.43 (s, 6H), 2.26 (s, 3H), 1.36 (t, 3H, $J = 7$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0 (CO), 138.4 (C), 137.6 (C), 130.66 (CH), 130.56 (CH), 128.6 (C), 72.1 (CH), 64.1 (CH), 62.4 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 14.2 (CH_3). MS (CI–NH_3) *m/z*: 295.3 [$(M+18)^+$, 90%]. HRMS (ESI): calcd for $C_{14}H_{19}N_3O_3Na$, 300.1315; found, 300.1318.

4.5. (2*R*,3*R*)-3-Azido-3-mesitylpropane-1,2-diol 7[5]

To a solution of **3** (10.0 g, 36.06 mmol) in dry THF (100 mL) was added $LiBH_4$ (1.1 g, 50.48 mmol) in portions. The mixture was stirred 2.5 h at room temperature, quenched with ammonium chloride and 2 M HCl (1:1, 326 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give **7** (7.5 g, 88% yield) as a yellow solid. Mp 72–74 °C. $[\alpha]_D = -183$ (*c* 1, $CHCl_3$). IR (film): ν_{max} 3392, 2956, 2101, 1760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (s, 2H), 5.20 (d, 1H, $J = 10$ Hz), 4.04 (m, 1H), 3.94 (m, 1H), 3.78 (m, 1H), 2.42 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6 (C), 138.1 (C), 130.8 (C), 128.8 (CH), 128.6 (C), 72.0 (CH), 64.1 (CH_2), 62.1 (CH), 21.3 (CH_3), 21.0 (CH_3). MS (CI–NH_3) *m/z*: 253 [$(M+18)^+$, 100%]. Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N 17.86. Found C, 61.59; H, 7.61; N 17.45.

4.6. (2*R*,3*R*)-3-Fmoc-amino-3-mesitylpropan-1,2-diol 8

To a solution of **7** (3.18 g; 13.55 mmol) in ethyl acetate (260 mL) was added Pd–C (318 mg, 10% Pd) and the stirred suspension was hydrogenated at atmospheric pressure (balloon) for 3 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give 2.83 g (quantitative yield) of amino diol as yellow solid that was directly used in the next step. To a solution of this oil in 10% Na_2CO_3 (36 mL), cooled to 0 °C, a solution of Fmoc-OSu (6.07 g, 18.0 mmol) in dioxane (36 mL) was slowly added. The reaction was stirred for 36 h. Then, water was added and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The crude was purified by flash chromatography (hexanes/AcOEt) yielding 1.72 g (62% yield) of **8** as a brown oil. $[\alpha]_D = -14.5$ (*c* 1.02, $CHCl_3$). IR (film): ν_{max} 3419 (b), 2949, 2916, 1703, 1450, 1254 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, 2H, $J = 8$ Hz), 7.54 (d, 2H, $J = 6$ Hz), 7.38 (m, 2H), 7.29 (m, 2H), 6.86 (s, 2H), 5.28 (m, 2H), 4.48 (dd, 1H, $J = 4$ and 7 Hz), 4.38 (dd, 1H, $J = 4$ and 6 Hz), 4.17 (t, 1H, $J = 7$ Hz), 4.02 (m, 1H), 3.73 (m, 2H), 3.21 (m, 1H), 2.41 (s, 6H), 2.24 (s, 3H) 2.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (CO), 143.6 (C), 141.3 (C), 137.5 (C), 131.7 (CH), 127.7 (CH), 127.0 (CH), 124.8 (CH), 119.9 (CH), 72.8 (CH), 67.0 (CH_2), 63.3 (CH_2), 52.3 (CH), 47.2 (CH), 21.2 (CH_3), 21.0 (CH_3), 20.7 (CH_3). MS (CI–CH_4) *m/z*: 432.4 [$(M+1)^+$, 1%], 178.1 [$(M-235)^+$, 100%]. HRMS: calcd for $C_{27}H_{30}N_2O_4$, 432.2175; found, 432.2183.

4.7. Fmoc-D-mesitylglycine D-1

To a solution of diol **8** (3.2 g, 7.41 mmol) in THF/H_2O (60 mL, 1:3) was added $NaIO_4$ (2.37 g, 11.12 mmol). After 2 h stirring at room temperature, ethyl acetate (20 mL) and water (20 mL) were added. The aqueous layer was ex-

tracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated. To the crude aldehyde dissolved in THF/^{t}BuOH (66 mL; 1:1.5) were added 2-methyl-2-butene (3.2 mL) and a solution of $NaClO_2$ (873 mg; 9.64 mmol) and NaH_2PO_4 (1.1 g; 8.89 mmol) in water (108 mL). The mixture was stirred 24 h at room temperature, the solvent was evaporated and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude was purified by chromatography (hexanes/AcOEt) yielding 7.3 g of D-**1** (67% yield) as a white solid. Mp 97–98 °C. $[\alpha]_D = -62.9$ (*c* 0.80, $CHCl_3$). IR (film): ν_{max} 3266 (b), 2956, 1725, 1665, 1450, 1051, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.55 (m, 3H), 7.38–7.26 (m, 3H), 7.13–7.03 (m, 2H), 6.87 (s, 2H), 5.8 (m, 1H), 4.45–4.10 (m, 3H), 2.40, 2.43, 2.26 (s, 9H) ppm. ^{13}C NMR (100MHz, $CDCl_3$): δ 175.5 (CO), 173.9 (CO)*, 157.4 (CO), 155.8 (CO)*, 144.0 (C), 143.8 (C)*, 143.6 (C), 141.4 (C), 141.2 (C), 138.3 (C), 137.7 (C)*, 137.1 (C), 131.0 (C), 130.6 (C)*, 130.5 (CH), 130.2 (CH)*, 127.8 (CH), 127.2 (CH)*, 125.2 (CH), 125.1 (CH)*, 124.8 (CH), 120.1 (CH), 68.3 (CH_2), 67.3 (CH_2)*, 54.1 (CH), 53.5 (CH)*, 47.3 (CH), 47.0 (CH)*, 21.1 (CH_3), 20.4 (CH_3) ppm. MS (CI–CH_4) *m*/*z*: 179.0 [(M−236)$^+$, 100%], 192.0 [(M)$^+$, 61%], 416.0 [(M+1)$^+$, 1%]. HRMS: calcd for $C_{26}H_{25}NO_4$, 415.1784; found, 415.1771. HPLC: Chiralpack-AD. Heptane/*i*-PrOH/TFA 90:10:0.2, 1 mL/min, $\lambda = 254$ nm, t_R (D) = 14 min and t_R (L) = 22 min. The enantiomeric purity of D-**1** was >99% ee.

4.8. Ethyl (2*R*,3*S*)-3-mesityl-aziridine-2-carboxylate 9

To a solution of **3** (13.0 g, 46.72 mmol) in acetonitrile (282 mL), PPh_3 (12.2 g, 46.72 mmol) was added. The mixture was stirred 1 h at room temperature and refluxed for 6 h. Then, the solvent was evaporated and the crude was purified by flash chromatography (hexanes/AcOEt) yielding 7.32 g (67% yield) of **9** as a yellow oil. $[\alpha]_D = -131$ (*c* 0.79, $CHCl_3$). IR (film): ν_{max} 3281, 2978, 2922, 1726, 1218, 1201 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 2H), 4.31 (m, 2H), 3.16 (d, 1H, $J = 2$ Hz), 2.57 (d, 1H, $J = 2$ Hz), 2.39 (s, 6H), 2.26 (s, 3H), 1.78 (br, 1H), 1.36 (t, 3H, $J = 7$ Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 172.8 (CO), 137.8 (C), 137.3 (C), 129.0 (CH), 61.8 (CH_2), 38.9 (CH), 37.8 (CH), 20.9 (CH_3), 20.0 (CH_3), 14.4 (CH_3). MS (CI–NH_3) *m*/*z*: 233.0 [(M)$^+$, 25%], 146.0 [(M−87)$^+$, 100%]. HRMS (CI+): calcd for $C_{14}H_{19}NO_2$, 233.1416; found, 233.1418. HPLC: Chiralpack-IA. Heptane/*i*-PrOH 95:5, 1 mL/min, $\lambda = 254$ nm, t_R (*S*,*R*) = 19 min and t_R (*R*,*S*) = 14 min. The enantiomeric purity of (2*R*,3*S*)-**9** was >99% ee. The same sequence starting from (2*S*,3*R*)-**5** afforded (2*S*,3*R*)-**9** also in >99% ee.

4.9. (2*S*)-Mesitylalanine ethyl ester 10

Aziridine **9** (9.9 g; 42.42 mmol) was hydrogenated at 40 bar of hydrogen over a catalytic amount of Pd–C (990 mg, 10% Pd/C) in methanol (300 mL) and acetic acid (10 mL, 84.84 mmol) for 48 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give 10.0 g (quantitative yield) of **10** as a yellow solid. Mp 81–83 °C. $[\alpha]_D = -26.7$ (*c* 1.00, $CHCl_3$). IR (film): ν_{max} 2918, 1742, 1612, 1483, 1225. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 2H), 5.61 (br, 1H), 4.14 (m, 2H), 3.77 (dd, 1H, $J = 6.4$ and 7.6 Hz), 3.08 (m, 2H), 2.94 (m, 2H), 2.31 (s, 6H), 2.25 (s, 3H), 1.18 (t, 3H, $J = 7$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (CO), 137.1 (C), 136.3 (C), 131.1 (C), 129.5 (CH), 129.5 (CH), 129.2 (C), 61.4 (CH2), 54.1 (CH), 34.6 (CH_2), 24.9 (CH_3), 21.0 (CH_3), 19.8 (CH_3), 14.2 (CH_3). MS (ESI+) *m*/*z*: 236.2 [(M+H)$^+$, 100%]. HRMS (ESI+): calcd for $C_{14}H_{22}NO_2$, 236.1645; found, 236.1637.

4.10. (2*S*)-Mesitylalanine 11[7,8]

To a solution of **10** (2.0 g; 8.50 mmol) in dioxane (57 mL) was added 20% aq LiOH (70 mL). The mixture was stirred at room temperature for 24 h. Then, the solvent was evaporated and the remaining aqueous phase was cooled and acidified to pH 7 with hydrochloric acid 1 M. The resulting crystals were collected by filtration and dried in vacuo. The product was obtained as an off-white solid (1.3g, 80%). Mp 318–320 °C. $[\alpha]_D = -80$ (*c* 1.00, CH_3OH). IR (film): ν_{max} 3300, 2973, 1730, 1608, 1409 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 2H), 3.27 (t, 1H, $J = 7.2$ Hz), 2.88 (m, 1H), 2.65 (m, 1H), 2.12 (s, 6H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8 (CO), 137.8 (C), 136.4 (C), 132.2 (C), 128.9 (CH), 56.2 (CH), 34.3 (CH_2), 19.9 (CH_3), 19.4 (CH_3). MS (CI+) *m*/*z*: 208.3 [(M+H)$^+$, 100%]. HRMS (CI+): calcd for $C_{12}H_{18}NO_2$, 208.1337; found, 208.1330. Anal. Calcd for $C_{27}H_{27}NO_4$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.36; H, 8.69; N, 6.39.

4.11. Fmoc-L-mesitylalanine L-2

To a suspension of **11** (1.08 g, 5.22 mmol) in 16 mL of 10% Na_2CO_3 was added at 0 °C a solution of Fmoc-OSu (2.64 g, 7.83 mmol) in 24 mL of dioxane. The mixture was stirred for 20 h at room temperature, diluted with water (20 mL) and extracted with hexane (3 × 20 mL). The remaining aqueous phase was cooled and acidified to pH 2 with 1 M hydrochloric acid and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude was purified by chromatography (hexanes/AcOEt) yielding 1.5 g (68% yield) of L-**2** as a white solid. Mp 187–188 °C. $[\alpha]_D = -26.0$ (*c* 1.00, $CHCl_3$). IR (film): ν_{max} 3321, 2962, 1713, 1450, 1265 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.74 (d, 2H, $J = 7.6$ Hz), 7.51 (t, 2H, $J = 7.6$ Hz), 7.40 (t, 2H, $J = 7.6$ Hz), 7.30 (t, 2H, $J = 7.6$ Hz), 6.83 (s, 2H), 5.25 (d, 1H, $J = 8$ Hz), 4.60 (dd, 1H, $J = 8.0$ and 8.4 Hz), 4.30 (m, 1H), 4.14 (m, 1H), 3.18 (m, 2H), 2.32 (s, 6H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7 (CO), 156.08 (CO), 144.0 (C), 141.5 (C), 137.2 (C), 136.6 (C), 130.0 (C), 129.6 (C), 129.5 (CH), 127.9 (CH), 127.3 (CH), 125.3 (CH), 120.2 (CH), 67.4 (CH_2), 53.7 (CH_2), 47.3 (CH), 32.5 (CH_2), 21.3 (CH_3), 20.4 (CH_3). MS (CI–NH3) *m*/*z*: 206.09 [(M−233)$^+$, 82%], 430.2 [(M+H)$^+$, 5%]. HRMS (CI+): calcd for $C_{27}H_{28}NO_4$, 430.2029; found, 430.2018. Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 74.94; H, 6.21; N, 3.41. Chiralcel-AD. Heptane/EtOH/TFA 95:5:0.2, 1 mL/min, $\lambda = 254$ nm, t_R (D) = 20 min and t_R (L) = 26 min. The enantiomeric purity

of L-**2** was >99% ee. The same sequence starting from (2*S*,3*R*)-**5** afforded D-**2** also in >99% ee.

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