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Memory of Chirality of Tertiary Aromatic Amide: Application to the Asymmetric Synthesis of (*S*)-α-MethylDOPA

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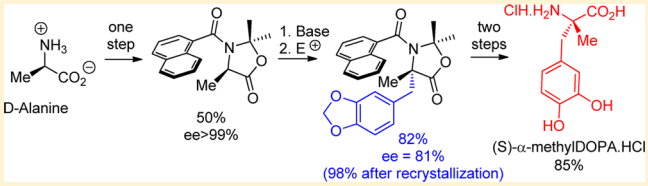
Supporting Information

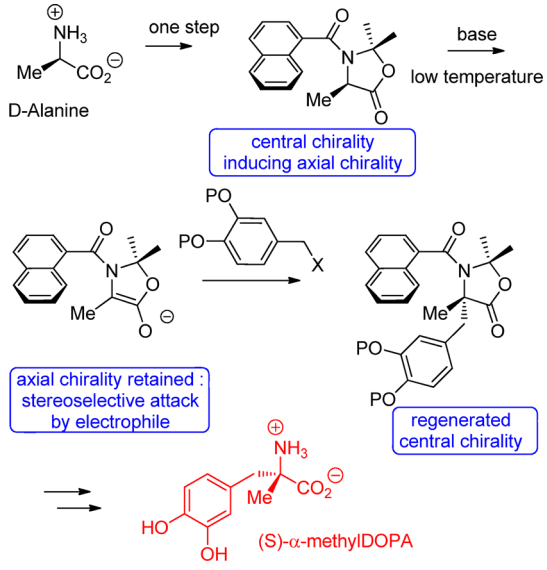
ABSTRACT: We describe an original asymmetric synthesis of (*S*)-α-methylDOPA proceeding by the concept of memory of chirality, the only source of chirality being the starting D-alanine. The initial chirality of the amino acid is temporarily transferred to a dynamic axial chirality of a tertiary aromatic amide. The (*S*)-α-methylDOPA hydrochloride is obtained after four steps with 98% ee.



A substantial amount of quaternary α-amino acids possess interesting biological activity,[1] and thus, many asymmetric syntheses have been described so far for these compounds.[2] The asymmetry can be introduced through a chiral auxiliary or a chiral catalyst, but few methods benefit from the chirality of a natural tertiary α-amino acid used as starting material. Among the self-regeneration of stereocenters developed by Seebach,[3] methods based on memory of chirality[4] have recently been explored. Almost all of these methods have been applied to the synthesis of (*S*)-α-methylDOPA, a well-known quaternary amino acid, used in the treatment of hypertension. Several total asymmetric syntheses have thus already been described, some of them using a chiral auxiliary,[5] other using a chiral catalyst[6] or simply resolution of a racemic intermediate[7] or application of the self-regeneration of stereocenters.[8] According to the concept of Memory of Chirality, the strategy could be to start from a chiral tertiary amino acid, either alanine or DOPA, and to perform an alkylation. This strategy has been applied by Kawabata starting from L-DOPA and led to a (*S*)-α-methylDOPA derivative with 80% ee.[9] We have been interested for a few years in the development of new methods to synthesize nonproteinogenic amino acids,[10] in particular, quaternary α-amino acids by memory of chirality.[11] We have applied this original methodology to model substrates, and we wanted to extend this efficiently to the total synthesis of a biologically active compound, such as (*S*)-α-methylDOPA. In this paper, we describe a four-step asymmetric total synthesis of (*S*)-α-methylDOPA hydrochloride, starting from D-alanine.

The reaction we developed according to the concept of memory of chirality was based on the dynamic axial chirality of tertiary aromatic amides.[12] The strategy, applied to the synthesis of (*S*)-α-methylDOPA, is depicted below (Scheme 1): initial central chirality of the starting natural α-amino acid should temporarily be transferred to a tertiary aromatic amide (in our case, a naphthoyl amide), and induce an axial chirality; this retained axial chirality should then lead to stereoselective deprotonation/alkylation, even though the initial central chirality is lost during deprotonation. As we previously

Scheme 1. Strategy for the (*S*)-α-MethylDOPA Synthesis



observed[11a] that alkylation occurs always with retention of configuration, we thus planned to start from D-alanine to obtain the (*S*)-α-methylDOPA.

The first step, preparation of oxazolidinone **1**, was achieved as previously described.[11a] Compound **1** was obtained with 50% yield without racemization (Scheme 2).

For the second step, deprotonation/alkylation, our previous studies had shown that for alanine derivative the best solvent was THF, without the presence of toluene (removed from the commercial solution of KHMDS). We tried to optimize the reaction by changing the base, the leaving group of the

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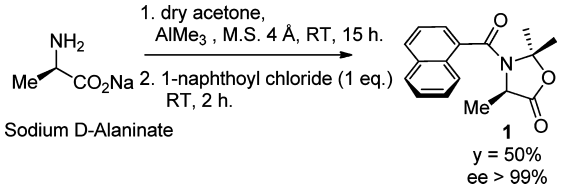
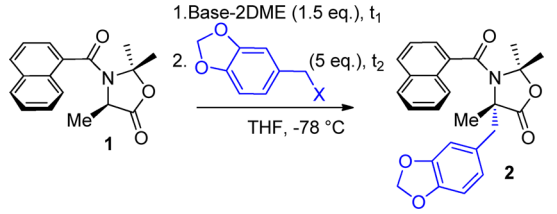
Scheme 2. Synthesis of Oxazolidinone 1



electrophile, and the reaction time. The results obtained are gathered in Table 1.

Table 1. Alkylation of Oxazolidinone 1[a]



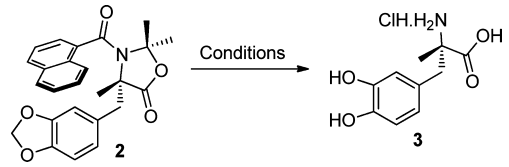
entry	base	X	t_1/t_2 (min)	conv[b] (%)	ee[b] (%)	yield[c] (%)
1	KHMDS	Br	3/10	100	81 (98[d])	82
2	NaHMDS[e]	Br	3/10	85	72[f]	
3	KHMDS	Br	1/10	100	80[f]	
4	KHMDS[g]	Br	0/10	95	82[f]	
5	KHMDS[h]	Br	3/10	100	79	84
6	KHMDS	I	1/10	100	61[f]	
7	KHMDS	I	1/2	100	56[f]	
8	KHMDS	Cl	3/10	0		
9	KHMDS	Cl	3/180	0		

[a]General procedure: KHMDS (1.5 equiv, 0.5 M in THF) diluted in DME (3 equiv) at −78 °C was added via canula to a solution of **1** in THF (1.2 mL) at −78 °C (0.32 mmol); after t_1 (min), electrophile (5 equiv) diluted in THF (1.2 mL) was rapidly added and after t_2 (min) at −78 °C, the reaction was quenched with acetic acid. [b]Determined by HPLC using a chiral stationary phase. [c]After purification by chromatography. [d]ee after recrystallization (yield = 69%). [e]Commercial solution in THF (C = 2 M). [f]Determined on the crude material. [g]In situ reaction: a mixture of DME, THF, base, and electrophile was directly canulated on compound **1**. [h]Reaction on 1.77 mmol of compound **1**.

Replacing KHMDS by NaHMDS (entry 2) induced a lower enantiomeric excess, and reducing the deprotonation time (entries 3 and 4) did not improve the results. Surprisingly, going from piperonyl bromide[13] to piperonyl iodide was deleterious for the enantiomeric excess. This could be related to the unexpected results we observed for the reaction of valine oxazolidinone enolate with benzyl iodide:[11b] in that case, the results (yield and enantiomeric excess) were not reproducible, perhaps due to competitive single electron transfer reaction or to degradation of the electrophile. Thus, the best results were obtained when KHMDS was used as a base and piperonyl bromide as the electrophile. Recrystallization from ethyl acetate by pentane diffusion led to compound **2** with 98% ee and 69% yield (in that case, the mother liquor was enantioenriched and isolated).

The next step was deprotection, and our first experiments were performed directly on compound **2** (Table 2). We first tried the previously optimized conditions that are heating in concentrated HBr or HCl (entries 1 and 2). In those cases, the

Table 2. Direct Hydrolysis of Compound 2



entry	conditions	results
1	HBr (47%), 130 °C, overnight	mixture including Pictet−Spengler cyclization
2	HCl 6 N, 135 °C, 5 days	**2** recovered (org layer) + mixture (aq layer)
3	(i) concd HCl, AcOH, reflux, 2 h; (ii) $TMSCHN_2$, MeOH, THF, 0.5 h	no reaction, **2** recovered
4	(i) concd HCl, AcOH, reflux, 24 h; (ii) $TMSCHN_2$, MeOH, THF, 0.5 h	degradation
5	CsOH (5 equiv), EtOH, H_2O, sealed tube, 95 °C, 2 h, then H^+	oxazolidinone hydrolysis (compound **4**)
6	CsOH (5 equiv), EtOH, H_2O, sealed tube, 95 °C, 24 h, then H^+	oxazolidinone hydrolysis (compound **4**)
7	6 N HCl, AcOH (3 equiv), PhOH (3 equiv), 110 °C, 7 h	no reaction, **2** recovered

major product in the aqueous layer was a tetrahydroisoquinoleine arising from Pictet−Spengler cyclization on the acetone−iminium intermediate.[14] We tried also various other conditions (entries 3, 4, and 7), but either no reaction occurred or degradation was observed. Basic hydrolysis led only to hydrolysis of the oxazolidinone ring (entries 5 and 6).

To avoid the Pictet−Spengler reaction, we then decided to first hydrolyze the oxazolidinone ring. This was achieved under basic conditions with 92% yield. Hydrolysis of the amide and the acetal were then studied (Table 3). Use of iodhydric acid led to degradation products (entry 1).[15,5a] Application of reductive conditions, with the Schwartz reagent,[16,10a] gave access to the expected methyl ester but with a low yield (entry 2). We observed degradation when the reaction was heated under acidic conditions at high temperature for a prolonged time (entries 3 and 8). Performing the reaction in a sealed tube in the presence of acetic acid[17] (or formic acid) improved the reaction, but the catechol function was not deprotected (entries 4−7, 9, and 10). Full deprotection was ensured by addition of phenol (entries 11−13).[6a] We have thus found two different conditions to obtain either compound **3** or compound **5**.[18] In the best conditions (entry 13) the expected chlorhydrate of (*S*)-α-methylDOPA was obtained in 92% yield. This was also performed on the compound with 98% ee. Measurement of the optical rotation confirmed that the final compound possess the (*S*) absolute configuration.[6a] The free base could be released after heating in propylene oxide (yield = 86%), but the compound was photosensitive.

To conclude, we have performed an original four-step synthesis of (*S*)-α-methylDOPA with 81% enantiomeric excess and 24% overall yield according to the principle of Memory of Chirality (the ee of the product was enhanced to 98% by recrystallization). The only source of chirality is the starting D-alanine, despite this initial chiral center is temporarily destroyed during the alkylation reaction. We have thus shown that the methodology we previously developed is easily applied to the total synthesis of a biologically active compound.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were conducted in oven-dried glassware under an atmosphere of dry argon

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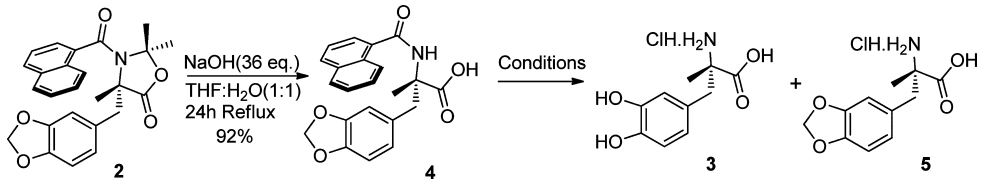
Table 3. Basic Hydrolysis of Compound 2, Followed by Hydrolysis of Compound 4



entry	conditions	results (yield, %)
1	HI (47%), reflux, 24 h	degradation
2	(i) $TMSCHN_2$, MeOH, THF; (ii) Cp_2ZrHCl, CH_2Cl_2, −20 °C	methyl ester of **5** (31)
3	concd HCl, AcOH, reflux, 24 h	degradation
4	concd HCl, AcOH, EtOH, sealed tube, 95 °C, 4 h	mixture of ethyl esters of **3** and **5** (80)
5	concd HCl, AcOH, 1,4-dioxane, sealed tube, 95 °C, 2 h	traces of **5**
6	concd HCl, AcOH, 1,4-dioxane, sealed tube, 95 °C, 5 h	**5** (86)
7	concd HCl, AcOH, THF, sealed tube, 95 °C, 4 h	**5** + THF degradation
8	6 N HCl, AcOH, 1,4-dioxane, reflux, 15 h	**5** (24) + compound **4** + degradation
9	concd HCl, HCO_2H, 1,4-dioxane, sealed tube, 95 °C, 4 h	**5** (75)
10	6 N HCl, AcOH, 1,4-dioxane, sealed tube, 95 °C, 5 h	**5** (54)
11	6 N HCl, AcOH (3 equiv), PhOH (3 equiv), 110 °C, 15 h	**3** (74)
12	6 N HCl, AcOH (3 equiv), PhOH (3 equiv), 120 °C, 16 h	**3** (91)
13	6 N HCl, AcOH (3 equiv), PhOH (3 equiv), sealed tube, 115 °C, 4 h	**3** (92)

gas. THF was double distilled, first over sodium/benzophenone and then over $LiAlH_4$/triphenylmethane under argon. Acetone was purchased with water <50 ppm. All other reagents were used as received. Potassium bis(trimethylsilyl)amide was purchased as a toluene solution (0.5 or 0.7 M). Flash chromatography was performed on Kieselgel 60 (35−70 μm) silica gel. Infrared spectra were recorded as thin films on NaCl plates using an FT-IR spectrophotometer. ^1H NMR were measured at 250, 300, or 360 MHz using $CDCl_3$ or D_2O as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision with coupling constants reported to 0.1 Hz precision using residual solvent as an internal reference. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet. ^{13}C NMR were measured at 62.5, 75, or 90 MHz using $CDCl_3$, D_2O as solvent. Chemical shifts are reported in δ units to 0.1 ppm precision using residual solvent as an internal reference. The mass analyzer type used for the HRMS measurements is a quadrupole-TOF. The HPLC instrument is principally composed of gradient pump, Peltier effect column oven and Diodes array detector. All enantiomerics excesses were determinated by normal-phase HPLC analyses with column Chiralpak AD-H (250 mm × 4.6 mm i.d.); part. size: 5 μm.

(*R*)-3-(1-Naphthoyl)-2,2,4-trimethyloxazolidin-5-one (1). To a stirred suspension of sodium D-alaninate (1.59 g, 14.38 mmol) and oven-activated 4 Å molecular sieves in extra-dry acetone (40 mL) at 0 °C under argon atmosphere was slowly added a solution of trimethylaluminium in toluene (7.19 mL, 14.38 mmol). The mixture was stirred for 5 min at 0 °C and 15 h at room temperature. Then, 1-naphthoyl chloride (2.16 mL, 14.38 mmol) was added, and the reaction mixture was stirred for 2 h. The final mixture was filtered through Celite, and molecular sieves were washed with ether (2 × 20 mL). Solvents were evaporated, and the resulting solid was dried under high vacuum for 1 h and then purified by flash column chromatography on silica gel (cyclohexane/EtOAc: 80/20 with 1% triethylamine) to give the oxazolidinone **1** in 50% yield as white solid.

HPLC analysis: Chiralpak AD-H, hexane/ethanol 95/05, 1 mL/min, T = 25 °C, λ = 281 nm; retention times of racemic mixture: 28.4 min and 31.3 min. (*R*). ^1H NMR (360 MHz, 300 K, $CDCl_3$) (δ, ppm): 0.96 (s, 3H), 2.01 (s, 3H), 2.06 (s, 3H) 4.18 (bs, 1H), 7.44−7.58 (m, 4H), 7.80−7.93 (m, 3H). ^{13}C NMR (90 MHz, 300 K, $CDCl_3$) (δ, ppm): 20.2, 26.3, 27.7, 54.0, 98.5, 124.2, 125.1, 126.9, 128.0, 128.9, 130.5, 133.7, 167.8, 171.6. IR (cm^{-1}): 665, 787, 969, 1057, 1131, 1265, 1378, 1409, 1593, 1650, 1790, 2937, 2985, 3057. Mp (*R*): 130−132 °C. HRMS (electrospray, Na^+): calcd for $C_{17}H_{17}NO_3Na$ 306.1106, found 306.1091. Optical rotation (product with ee >99%): $[\alpha]^{23}_D$ = −202.6 (c = 1.00, CH_2Cl_2)

(*S*)-3-(1-Naphthoyl)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2,2,4-trimethyloxazolidin-5-one (2). To a stirred solution of starting *N*-(1-naphthoyl)-oxazolidinone (**1**) (91 mg, 0.321 mmol) in THF (1.2 mL) at −78 °C was added by canulation a −78 °C precooled solution of potassium bis(trimethylsilyl)amide in THF (680 μL, 0.482 mmol, c = 0.7 M, 1.5 equiv) and 1,2-dimethoxyethane (100 μL; 0.963 mmol, 3 equiv). The mixture was stirred 3 min at −78 °C. Then a solution of piperonyl bromide (345 mg, 1.606 mmol, 5 equiv) in THF (1.2 mL) was injected rapidly, and stirring was maintained for 10 min at −78 °C. Acetic acid (0.7 mL) was finally added, and the resultant mixture was diluted in diethyl ether (10 mL) and then washed with a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried with magnesium sulfate, filtered, and then concentrated to give the crude alkylated oxazolidinone, which was then purified by flash column chromatography on silica gel (cyclohexane/EtOAc 80/20) to yield oxazolidinone **2** in 82% yield as a white solid with 81% enantiomeric excess (ee = 98% after crystallization from EtOAc and pentane by diffusion, the mother liquor was isolated in 69% yield).

HPLC analysis: Chiralpak AD-H, hexane/ethanol: 90/10, 1 mL/min, T = 25 °C, λ = 222 nm; retention times of racemic mixture: 11.9 min and 14.5 min. (*S*). ^1H NMR (250 MHz, 300 K, $CDCl_3$) two conformers major = *M*, minor = *m*; ratio *M*:*m* = 10:2.3 (δ, ppm): 0.52 (s, 3H*m*), 0.68 (s, 3H*M*), 1.00 (s, 3H*M*), 1.48 (s, 3H*m*), 1.95 (s, 3H*m*), 2.01 (s, 3H*M*) 3.19 (d, J = 14.4 Hz, 1H*M*), 3.33 (d, J = 14.4 Hz, 1H*m*), 3.95 (d, J = 14.4 Hz, 1H*M*), 4.01 (d, J = 14.4 Hz, 1H*m*), 5.97 (m, 2H*M* + *m*), 6.81−6.89 (m, 3H*M* + *m*), 7.20 (d, J = 7.8 Hz, 1H*M*), 7.30−7.34 (m, 1H*m*), 7.38−7.55 (m, 3H*M* + 4H*m*), 7.74 (d, J = 7.8 Hz, 1H*M*), 7.85 (m, 2H*M* + *m*). ^{13}C NMR (75.5 MHz, 300 K, $CDCl_3$): (δ, ppm): 23.9*m*, 24.1*M*, 28.5*m*, 28.8*M*, 30.1*M*, 30.8*m*, 40.9*M*, 42.7*m*, 68.1*M* + *m*, 96.5*m*, 96.6*M*, 101.2*M* + *m*, 108.5*m*, 108.6*M*, 110.8*M*, 111.1*m*, 123.5*M*, 123.7*m*, 124.3*M* + *m*, 124.8*M*, 125.0*M*, 125.9*m*, 126.1*m*, 126.8*M*, 127.0*m*, 127.5*M*+*m*, 128.5*m*, 128.7*M*, 130.0*M* + *m*, 130.4*M*, 130.5*m*, 130.7*M* + *m*, 133.5*M* + *m*, 134.2*M*, 134.8*m*,147.2*M* + *m*, 148.1*M* + *m*, 168.6*M*, 168.9*m*, 174.0*M*, 174.5*m*. IR (cm^{-1}): 665, 732, 781, 1038, 1085, 1250, 1361, 1373, 1404, 1445, 1489, 1504, 1637, 1788, 2924, 2982. Mp (*S*, ee = 98%): 127−129 °C. HRMS (electrospray, Na^+): calcd for $C_{25}H_{23}NO_5Na$ 440.1468, found 440.1456. Optical rotation (product with ee = 98%): $[\alpha]^{22.5}_D$ = +64.8 (c = 1.00, CH_2Cl_2).

(*S*)-2-(1-Naphthamido)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanoic Acid (4). To a solution of **2** (100 mg, 0.24 mmol, ee = 98%) in a 1/1 mixture of water (3 mL) and THF (3 mL) was added NaOH (36 equiv, 8.6 mmol, 344.8 mg) and the resulting solution

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refluxed for 24 h. After complete consumption of starting oxazolidinone by TLC, the solution was allowed to cool and washed with ether. The aqueous layer was acidified with 2N HCl and then extracted with dichloromethane, dried over $MgSO_4$, filtered, and evaporated to give the crude (*S*)-2-(1-naphthamido)-3-(benzo[*d*]-[1,3]dioxol-5-yl)-2-methylpropanoic acid (**4**) (83 mg, ee = 98%, 92% yield). ^{1}H NMR (360 MHz, 300 K, $CDCl_3$) (δ, ppm): 1.77 (s, 3H), 3.37 (d, J = 13.8 Hz, 1H), 3.56 (d, J = 13.8 Hz, 1H), 5.87 (s, 2H), 6.63−6.72 (m, 4H), 7.38 (t, J = 15.2 Hz, 1H), 7.45−7.52 (m, 3H), 7.80−7.83 (m, 1H), 7.86 (d, J = 8.1 Hz, 1H), 8.01 (bs, 1H), 8.22−8.25 (m, 1H). ^{13}C NMR (90 MHz, 300 K, $CDCl_3$) (δ, ppm): 23.3, 41.0, 61.8, 101.1, 108.4, 110.6, 123.5, 124.8, 125.3, 125.5, 126.6, 127.4, 128.5, 129.8, 130.2, 131.1, 133.8, 133.9, 146.8, 147.7, 167.8, 177.9. IR (cm^{-1}): 666, 1040, 1073, 1098, 1249, 1443, 1489, 1517, 1591, 1637, 1647, 1654, 1717, 2927, 3368, 3583. HRMS (electrospray, Na^+): calcd for $C_{22}H_{19}NO_5Na$ 400.1161, found 400.1142. Optical rotation (product with ee = 98%): $[\alpha]^{25}_D$ = +43.25 (c = 0.47, CH_2Cl_2)

(*S*)-2-Amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic Acid Hydrochloride (3). (*S*)-2-(1-Naphthamido)-3-(benzo[*d*][1,3]-dioxol-5-yl)-2-methylpropanoic acid (**4**) (70 mg, 0.185 mmol), phenol (52.3 mg, 0.556 mmol, 3 equiv), acetic acid (32 μL, 0.556 mmol, 3 equiv), and 6 M HCl (2.6 mL) were heated to 115 °C in a sealed tube covered with a foil for 4 h. The solution was washed with EtOAc 3 × 5 mL, and the aqueous phase was concentrated to yield (*S*)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid as its hydrochloride salt as a pale orange solid (43 mg, 92% yield). ^{1}H NMR (360 MHz, 300 K, D_2O) (δ, ppm): 1.55 (s, 3H), 2.89 (d, J = 15.3 Hz, 1H), 3.18 (d, J = 15.3 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 6.70 (s, 1H), 6.82 (d, J = 8.1 Hz, 1H). ^{13}C NMR (90 MHz, 300 K, D_2O) (δ, ppm): 21.5, 41.5, 60.9, 116.4, 117.5, 122.4, 125.5, 143.7, 144.0, 173.8. HRMS (electrospray, H^+): calcd for $C_{10}H_{14}NO_4$ 212.0917, found 212.0926. Optical rotation (product with ee = 98%): $[\alpha]^{20}_D$ = −2.9 (c = 1.00, 0.1 M HCl)

(*S*)-2-Amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic Acid. (*S*)-2-Amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid hydrochloride (**3**) (65 mg, 0.26 mmol) was refluxed with propylene oxide (0.5 mL) in ethanol (1 mL) for 3 h. The resulting white precipitate was then filtered and washed once with ethanol to give the α- methylDOPA in 86% yield (46 mg). ^{1}H NMR (360 MHz, 300 K, $CDCl_3$) (δ, ppm): 1.52 (s, 3H), 2.83 (d, J = 14.7 Hz, 1H), 3.18 (d, J = 14.7 Hz, 1H), 6.68 (dd, J = 8.3 Hz, 2.3 Hz, 1H), 6.70 (d, J = 2.3 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H).

(*S*)-2-Amino-3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanoic Acid Hydrochloride (5). (*S*)-2-(1-Naphthamido)-3-(benzo[*d*][1,3]-dioxol-5-yl)-2-methylpropanoic acid (**4**) (40 mg, 0.106 mmol), acetic acid (0.5 mL), and concd HCl (1.2 mL) in 1 mL of 1,4-dioxane were heated to 95 °C in a sealed tube covered with a foil for 5 h. The solution was partitioned with ethyl acetate (5 mL) and water (5 mL), and the aqueous layer was washed with ethyl acetate (2 × 5 mL), and the aqueous phase was concentrated to yield (*S*)-2-amino-3-(benzo-[*d*][1,3]dioxol-5-yl)-2-methylpropanoic acid as its hydrochloride salt as a white solid (22 mg, 86% yield). ^{1}H NMR (250 MHz, 300 K, D_2O) (δ, ppm): 1.56 (s, 3H), 2.96 (d, J = 14.5 Hz, 1H), 3.25 (d, J = 14.5 Hz, 1H), 5.9 (s, 2H), 6.72 (d, J = 7.5 Hz, 1H), 6.74 (s, 1H), 6.85 (d, J = 7.5 Hz, 1H). ^{13}C NMR (62.9 MHz, 300 K, D_2O) (δ, ppm): 21.8, 42.1, 61.4, 101.3, 108.8, 110.2, 123.6, 127.2, 146.9, 147.5, 174.6. HRMS (electrospray, H^+): calcd for $C_{11}H_{14}NO_4$ 224.0917, found 224.0916.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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