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Efficient asymmetric synthesis of 2,3-diamino-3-phenylpropanoic acid derivatives

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Abstract—An efficient, stereoselective synthesis of selectively-protected *anti* and *syn*, methyl 2-amino-3-(Boc-amino)-3-phenylpropanoate is described. Preparation of *syn* β-acetylamino-α-hydroxy ester was from isopropyl cinnamate via an acetamide-based Sharpless amino-hydroxylation (AA), and its *anti* isomer was obtained via C-α epimerization of the *syn* isomer. For the installation of a second amino group, two different approaches, involving substitution of the β-hydroxyl group with azide, were investigated. The first was a ring-opening reaction of *trans*-oxazoline-5-carboxylate with trimethylsilyl azide, which produced *anti* β-(acetylamino)-α-azido esters, which then transformed into the *anti* isomer; whereas the *cis*-oxazoline-5-carboxylate was found to be unreactive under this reaction condition. The second approach used the Mitsunobu reaction of *syn* and *anti* β-(Boc-amino)-α-hydroxy esters with hydrazoic acid, followed by catalytic hydrogenation, which gave both *anti* and *syn* isomers, respectively.

1. Introduction

The 2,3-diamino acid family constitutes a key structural component in a variety of antibiotics[1] and anti-fungal dipeptides[2] as well as in other biologically active molecules.[3] For example, 2,3-diaminobutanoic acids are present in peptide antibiotics such as aspartocin, lavendomycin, etc.,[4,5] while 2,3-diamino-4-phenylbutanoic acid is an important structural element of aminodeoxybestatin.[6] 2,3-Diamino-3-phenylpropanoic acid has been used as an alternative to the side chain of taxol, in order to improve the water solubility of that anticancer drug.[7]

Recently, several synthetic routes for 3-substituted 2,3-diamino acids, including 3-aryl-2,3-diamino acids, have been reported.[8] Harwood, reported that the cycloaddition reaction of (5*S*)-phenylmorpholin-2-one with aromatic imine, produced enantiomerically pure (2*S*,3*R*)-3-aryl-2,3-amino acids in 36–46% yield.[9] Lin described an efficient method for the synthesis of (2*R*,3*R*)-2,3-diamino-3-phenylpropanoic acid from optically active 2-imidazoline.[10] However, in both Harwood's and Lin's methods, only *syn* or *anti* 2,3-diamino acid can be prepared, respectively.

On the other hand, Ojima has reported that both *syn* and *anti* 2,3-diamino acids can be synthesized from 3-amino-β-lactam via acid hydrolysis.[3b,11,12] In his method, β-lactam was obtained from the chiral ketene-imine [2+2] cycloaddition process, or chiral lithium ester enolate-imine cyclocondensation.

Merino has reported that the diastereoselective addition of a Grignard reagent to α-amino nitrones derived from L-serine may afford both the *syn* and *anti* 3-substituted 2,3-diamino acids as orthogonally protected forms.[13] Recently, both the *syn* and *anti* isomers of Boc- and benzoyl-protected 3-phenyl-2,3-diamino acid were synthesized utilizing oxazolidinone, which was prepared from 1-phenylallyl alcohol via a Sharpless asymmetric epoxidation.[7]

A common route to synthesize 2,3-diamino acid, utilizes β-hydroxy-α-amino acid as a starting material.[14,15] However, in the cases of β-substituted β-hydroxy-α-amino esters, the applicability of this protocol has been hampered by β-elimination, forming dehydro amino esters.[5,8] For example, under similar Mitsunobu conditions, the Fmoc-threonine methyl ester produced only the elimination product.[5] To solve this elimination problem, the carboxylic acid of *N*-protected threonine, was protected as Boc-hydrazide,[5] or masked as TBS ether, or 2,2-dimethyl-1,3-oxazoline, after reduction to an hydroxyl group.[16] Very recently, β-hydroxy-α-amino acids, which were protected as a cyclic ortho ester to reduce the acidity of the α-proton, were converted to diamino acids via the Mitsunobu reaction, without an elimination reaction.[8]

On the other hand, β-amino-α-hydroxy acid[17] is probably a better starting point for the synthesis of 2,3-diamino acid,

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which eliminates the drawbacks found in the previous syntheses. Of note, is a method reported by Han and Janda,[18] in which *tert*-butyl crotonate was exploited as the starting material. A carbamate-based Sharpless asymmetric aminohydroxylation (AA) reaction and a regioselective ring opening of the aziridine functionality, were used for the installation of amino groups.

We report here on an efficient stereoselective synthesis of both the *syn* and *anti* isomers of selectively protected 2,3-diamino-3-phenylpropanoic acids utilizing this β-amino-α-hydroxy ester, which was prepared from isopropyl cinnamate via an acetamide-based Sharpless AA reaction. Mitsunobu reaction conditions were applied for the installation of the second amino group. We also show an efficient, and high-yielding, synthesis of *anti* β-amino-α-hydroxy ester via C-α epimerization of its *syn* isomer. It is known that only (2*R*,3*S*)- or (2*S*,3*R*)-amino alcohol (*syn* isomers) can be obtained from a Sharpless AA reaction, either by using hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$], or by using hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$].

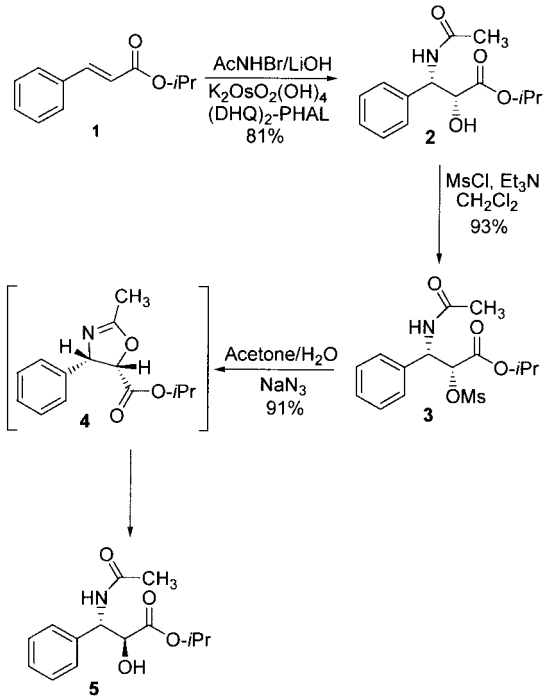
2. Results and discussion

In our synthesis route, isopropyl cinnamate **1** was first functionalized to *syn* acetylamino alcohol **2**, using $(DHQ)_2PHAL$ and *N*-bromoacetamide following a published procedure (Scheme 1).[17a] This Sharpless AA reaction gave **2** in high regioselectivity and enantioselectivity (>99% ee after a single crystallization).[19]

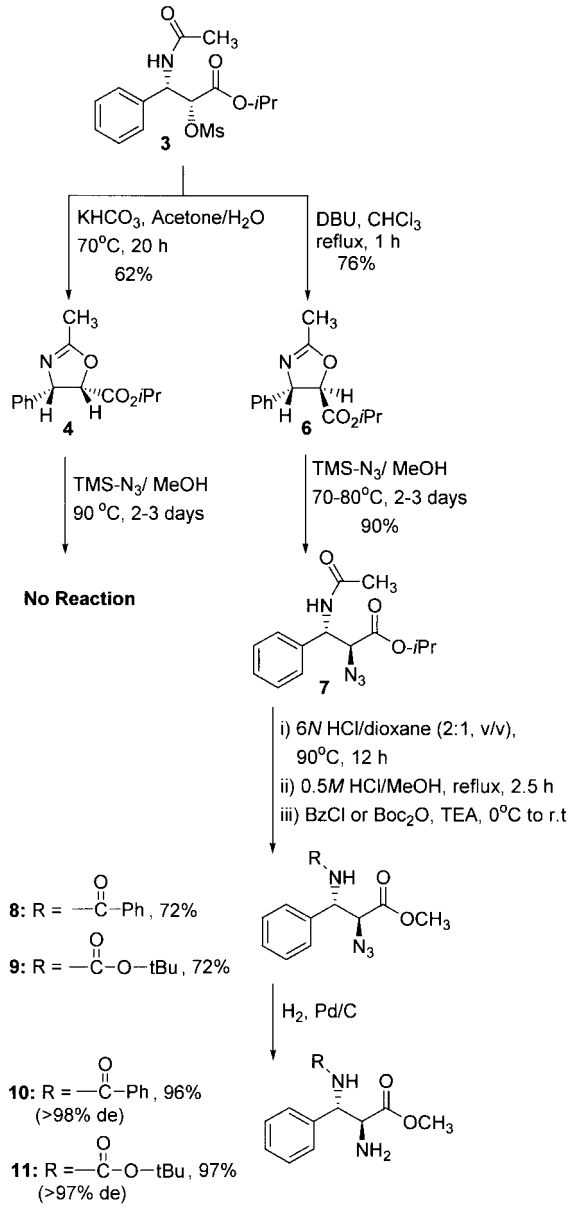
Although, either *syn* acetylamino alcohol **2**, or its methansulfonate **3**, can be considered as the synthetic equivalent of an α-cation in the preparation of *anti* α-azido species, we could not obtain any promising results from these candidates.[20]

While we were probing various reaction conditions, we found that the *anti* β-acetylamino-α-hydroxy ester could be obtained in a high yield from the methanesulfonate **3**, with clean inversion at the α-carbon, when water was used as a co-solvent. When methanesulfonate **3** was heated to 70°C for 20 h in a sealed vial (5:4 acetone/water mix) in the presence of two equivalents of sodium azide, *anti* acetylamino alcohol **5** was obtained in a 91% yield (with overall yield from *syn* amino alcohol **2** of 85%). In our case, oxazoline formation, hydrolysis, and O→N acyl migration, all occurred in the one pot under this reaction condition.[21]

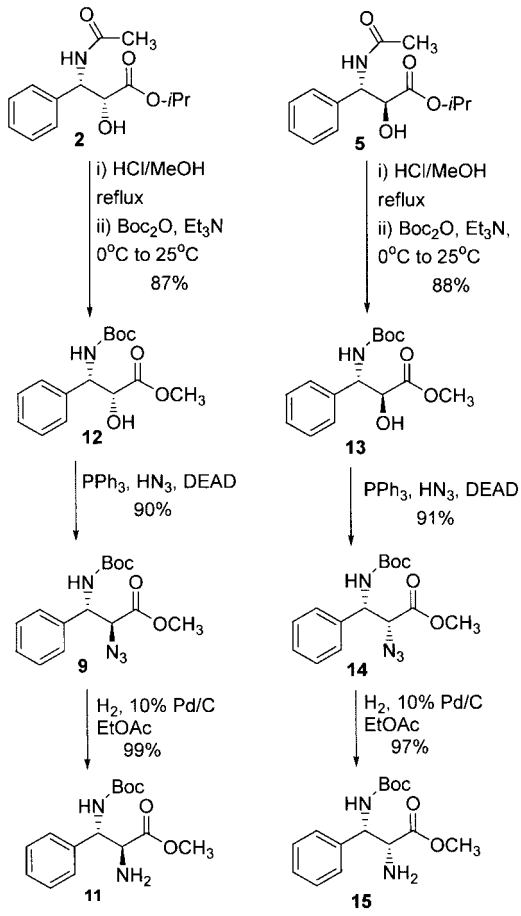
In the synthesis of 2,3-diamino acid, we have recently investigated the ring opening reactions of oxazoline-5-carboxylate, as another candidate with an equivalent



Scheme 1. Synthesis of *anti* acetylamino alcohol **5** via an oxazoline intermediate **4**.

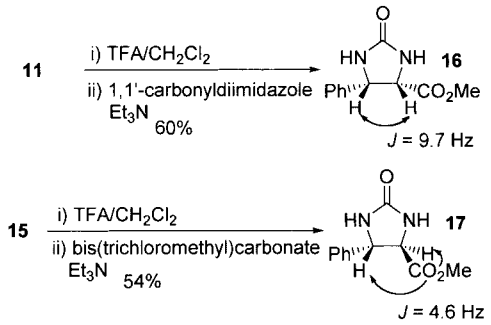


Scheme 2. Syntheses of selectively protected 2,3-diamino esters (**10**, **11**) through ring-opening reactions of *trans*-oxazoline-5-carboxylate **6**.



Scheme 3. Syntheses of the *anti* and *syn* isomers of selectively protected 2,3-diamino esters (**11**, **15**).

α-cation (Scheme 2).[22] Methanesulfonate **3** was successfully transformed to *cis*-oxazoline **4** with a clean inversion of configuration at the α-center with potassium bicarbonate in acetone-water. On the other hand, the DBU-induced cyclization proceeds via initial epimerization, prior to cyclization. When trimethylsilyl azide was used as an azide source in the synthesis of the 2,3-diamino acid derivative, we found that there were huge differences in reactivity between the *trans*-, and *cis*-oxazoline compounds (**6**,**4**). The treatment of *trans*-oxazoline **6**, with trimethylsilyl azide in methanol at 70–80°C, led to the *anti* azide **7** in 90% yield. However, even at a higher reaction temperature, or in the presence of an additional Lewis acid, such as boron trifluoride diethyl etherate ($Et_2O{\cdot}BF_3$), or trimethylsilyl triflate (TMSOTf), only unreacted *cis*-oxazoline **4** was recovered in the attempt to open this oxazoline ring with trimethylsilyl azide. After sequential hydrolysis, esterification, appropriate *N*-protection, and catalytic hydrogenation, selectively-protected *anti* diamino esters (**10**,**11**) could be obtained. As shown in Scheme 2, we could obtain only *anti* isomers, and less than 2% epimers were detected. These epimers were probably produced during heating (90°C) in acidic solution.



Scheme 4. Syntheses of *cis*- and *trans*-imidazolidinones (**16**, **17**).

To obtain the *syn* isomer, we attempted a Mitsunobu reaction of *anti* β-acetylamino-α-hydroxy ester **5**, as an α-cation equivalent, with hydrazoic acid. However, we could not get the desired *syn* azide isomer: instead, only *trans*-oxazoline **6** was obtained under this reaction condition.

So, we employed a rather labile, and useful, *N*-protecting group, the Boc group, instead of the acetyl group, in order to avoid easy oxazoline ring formation under Mitsunobu conditions. We re-investigated the synthesis of the *anti* and *syn* diamino esters from the corresponding Boc-protected β-amino-α-hydroxy ester (**12**, **13**) under Mitsunobu reaction conditions (Scheme 3).

The *N*-acetyl group was removed under relatively mild conditions, (refluxed in 0.5 M methanolic HCl for 10 h (twice)), and was then protected by a Boc group, using Boc_2O and triethylamine. In this step, concomitant transesterification of the isopropyl ester to the methyl ester also occurred. Then, the standard Mitsunobu reaction afforded the *anti* and *syn* azide compounds (**9**,**14**) with a clean inversion of the configuration at the α-carbon in 90 and 91% yields, respectively. Finally, the catalytic hydrogenation of the azide group gave (2*S*,3*S*)- and (2*R*,3*S*)-isomers of methyl 2-amino-3-(Boc-amino)-3-phenylpropanoate (**11**, **15**).

The overall yields of these compounds in our synthesis were very good (>50%) for both the (2*S*,3*S*)-isomer **11** and the (2*R*,3*S*)-isomer **15**. These compounds have a free α-amino group, a Boc-protected β-amino group, and a methyl ester group, which can be easily derivatized for further uses.

To confirm the stereochemistry of our products, *cis*-imidazolidinone **16** and *trans*-imidazolidinone **17** were synthesized from our products (**11**, **15**), using 1,1′-carbonyldiimidazole (CDI), or triphosgene, after removing the protection of the Boc group (Scheme 4). The ^1H NMR coupling constant between H-4 and H-5 for the *cis*-imidazolidinone **16** was 9.7 Hz, and for the *trans*-imidazolidinone **17** was 4.6 Hz. These results are consistent with similar reported results,[7,23] and provide supporting evidence for the stereochemistry of our *anti* and *syn* products (**11**,**15**). Although the above chemistry relates to the (2*S*,3*S*)- and (2*R*,3*S*)-isomers, our chemistry can be extended in the same manner to the remaining two enantiomers, the (2*R*,3*R*)- and (2*S*,3*R*)-isomers, utilizing (2*S*,3*R*)-acetylamino alcohol, which can be obtained from the Sharpless AA reaction using $(DHQD)_2PHAL$.

3. Conclusions

In conclusion, we have shown a simple and practical synthesis

route of both enantiomerically pure *syn* and *anti* isomers of selectively-protected 2,3-diamino-3-phenylpropanoic acid in high yields, which were derived from the readily available starting material, isopropyl cinnamate. Also, we have shown a convenient and high-yielding method for the C-α epimerization of the *syn* β-amino-α-hydroxy ester. Furthermore, in principle, our synthetic route can be applied to the synthesis of other 2,3-diamino acid derivatives by simply varying the starting olefin.

4. Experimental

4.1. General methods

The HN_3 in CH_2Cl_2 solution was prepared according to a literature procedure,[24] and titrated before use. NMR spectra were recorded using a JEOL JNM-LA 300 spectrometer at 300 MHz (for ^1H NMR) and at 75 MHz (for ^{13}C NMR). Chemical shifts were obtained in ppm, using TMS as an internal standard. Mass spectra were obtained using a JEOL JMS AX505WA spectrometer. Melting points were determined in open capillaries, and are uncorrected. Optical rotations were determined at the sodium D line using a JASCO DIP 1000 polarimeter. Infrared spectra were recorded using a JASCO FT/IR-200 spectrometer. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Thin layer chromatography was carried out using Merck 60 F_{254} plates with a 0.25-mm thickness. The $CHCl_3$, CH_2Cl_2, and MeOH were distilled from CaH_2, and THF was distilled from sodium-benzophenone ketyl.

4.1.1. Isopropyl (2*R*,3*S*)-3-(acetylamino)-2-hydroxy-3-phenylpropionate (2). This compound was prepared in 81% yield, according to the reported acetamide-based Sharpless aminohydroxylation protocol:[17a] mp 111–112°C; $[\alpha]_D^{18}=+28.3°$ (c=1, $CHCl_3$); IR (KBr) 3377, 3283, 1715, 1652, 1542 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, J=6.2 Hz, 3H), 1.31 (d, J=6.2 Hz, 3H), 2.01 (s, 3H), 3.26 (d, J=3.8 Hz, 1H), 4.48 (dd, J=2.0, 3.8 Hz, 1H), 5.11 (sept, J=6.2 Hz, 1H), 5.56 (dd, J=2.0, 9.2 Hz, 1H), 6.30 (br d, J=9.2 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.48, 21.65, 23.14, 54.31, 70.79, 73.25, 126.86, 127.74, 128.58, 138.88, 169.28, 172.40; HRMS (CI) m/z=266.1400 $(M+H)^+$, calcd for $C_{14}H_{20}N_1O_4$=266.1392.

4.1.2. Isopropyl (2*R*,3*S*)-3-(acetylamino)-2-(methanesulfonyloxy)-3-phenylpropionate (3). MsCl (645 mg, 5.65 mmol) in CH_2Cl_2 (5 ml) was added drop-wise to a stirred solution of **2** (1 g, 3.77 mmol) and Et_3N (1.05 ml, 7.54 mmol) in CH_2Cl_2 (25 ml) at 0°C under N_2. After being stirred for 1 h at 0°C, the reaction mixture was stirred for an additional 2 h at room temperature. The reaction mixture was then passed through a short silica gel plug (~10 cm^3), and further eluted with EtOAc (100 ml). The combined filtrate was then concentrated under reduced pressure, and the crude product was recrystallized from EtOAc/hexane to afford **3** (1.2 g, 3.49 mmol, 93%) as a pale yellow solid: mp 116–117°C; $[\alpha]_D^{18}=+5.5°$ (c=1, $CHCl_3$); IR (KBr) 3254, 1735, 1645, 1541 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, J=6.2 Hz, 3H), 1.30 (d, J=6.2 Hz, 3H), 2.05 (s, 3H), 2.75 (s, 3H), 5.11 (sept, J=6.2 Hz, 1H), 5.18 (d, J=2.8 Hz, 1H), 5.81 (dd, J=2.8, 9.4 Hz, 1H), 6.34 (br d, J=9.4 Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.33, 21.56, 22.94, 38.40, 53.41, 70.90, 80.78, 126.60, 128.32, 128.82, 136.91, 166.17, 169.40; HRMS (FAB) m/z=344.1175 $(M+H)^+$, calcd for $C_{15}H_{22}N_1O_6S_1$=344.1168.

4.1.3. Isopropyl (2*S*,3*S*)-3-(acetylamino)-2-hydroxy-3-phenylpropionate (5). Compound **3** (500 mg, 1.46 mmol) and NaN_3 (190 mg, 2.91 mmol), were dissolved in an acetone-water mixture (10 ml, 5:4). The resulting mixture was heated to 70°C for 20 h, with occasional swirling. The reaction mixture was then allowed to cool to room temperature, and the solvent was evaporated to dryness. The residue was treated with EtOAc (4×10 ml) and passed through a short silica gel plug (~5 cm^3). The combined filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (EtOAc/hexane, 2:1) afforded **5** (351 mg, 1.32 mmol, 91%) as a white crystalline solid: mp 112.5–113.5°C; $[\alpha]_D^{18}=+49.4°$ (c=1, $CHCl_3$); IR (KBr) 3469, 3358, 1716, 1648, 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, J=6.2 Hz, 3H), 1.22 (d, J=6.2 Hz, 3H), 2.03 (s, 3H), 3.11 (d, J=6.1 Hz, 1H), 4.53 (dd, J=3.5, 6.1 Hz, 1H), 4.93 (sept, J=6.2 Hz, 1H), 5.41 (dd, J=3.5, 8.8 Hz, 1H), 6.50 (br d, J=8.8 Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.62, 21.74, 23.40, 54.84, 70.50, 72.81, 127.89, 128.28, 128.41, 136.61, 169.24, 171.31; HRMS (CI) m/z=266.1395 $(M+H)^+$, calcd for $C_{14}H_{20}N_1O_4$=266.1392.

4.1.4. (4*S*,5*S*)-5-(Isopropoxycarbonyl)-2-methyl-4-phenyl-2-oxazoline (4). Compound **3** (300 mg, 0.874 mmol) and $KHCO_3$ (175 mg, 1.75 mmol) were dissolved in a mixture of acetone (8 ml) and water (3.2 ml). The resulting mixture was heated to 70°C for 20 h, with occasional swirling. The reaction mixture was then allowed to cool to room temperature, and the solvent was evaporated to dryness. The residue was treated with EtOAc (4×10 ml), and passed through a short silica gel plug (~3 cm^3). The combined filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane/EtOAc, 4:3) afforded **4** (135 mg, 0.546 mmol, 62%) as a colorless oil: $[\alpha]_D^{20}=-52.6°$ (c=1, $CHCl_3$); IR ($CHCl_3$) 1746, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.60 (d, J=6.4 Hz, 3H), 1.00 (d, J=6.4 Hz, 3H), 2.21 (d, J=1.5 Hz, 3H), 4.52 (sept, J=6.4 Hz, 1H) 5.13 (d, J=10.8 Hz, 1H), 5.48 (dd, J=1.5, 10.8 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.83, 20.70, 21.47, 69.04, 73.13, 80.80, 127.96, 128.05, 128.12, 136.97, 165.77, 167.66; HRMS (FAB) m/z=248.1284 $(M+H)^+$, calcd for $C_{14}H_{18}N_1O_3$=248.1287.

4.1.5. (4*S*,5*R*)-5-(Isopropoxycarbonyl)-2-methyl-4-phenyl-2-oxazoline (6). DBU (333 mg, 2.18 mmol) was added to a stirred solution of compound **3** (500 mg, 1.46 mmol) in dry $CHCl_3$ (15 ml) at room temperature, and the resulting solution was heated under reflux for 1 h. After being cooled to room temperature, the reaction mixture was then passed through a short silica gel plug (~5 cm^3) and further eluted with EtOAc (50 ml). The combined filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane/EtOAc, 3:1) afforded **6** (274 mg, 1.11 mmol, 76%) as a colorless oil:

$[\alpha]_D^{20}=-139.3°$ ($c=1$, $CHCl_3$); IR ($CHCl_3$) 1747, 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, $J=6.2$ Hz, 3H), 1.33 (d, $J=6.2$ Hz, 3H), 2.19 (d, $J=1.5$ Hz, 3H), 4.67 (d, $J=6.8$ Hz, 1H), 5.10–5.25 (m, 2H), 7.20–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.84, 21.70, 69.58, 74.38, 83.12, 126.27, 127.86, 128.75, 141.20, 165.14, 169.69; HRMS (FAB) $m/z=248.1283$ $(M+H)^+$, calcd for $C_{14}H_{18}N_1O_3=248.1287$.

4.1.6. Isopropyl (2*S*,3*S*)-3-(acetylamino)-2-azido-3-phenylpropionate (7). TMS-N_3 (0.8 ml) was quickly added to a solution of **6** (178 mg, 0.720 mmol) in dry MeOH (0.8 ml) in a 6-ml vial at 0°C. The vial was then closed tightly with a teflon disk lid, and the reaction mixture was heated to 70°C for 1 day, and then to 80°C for 1.5 day, with occasional swirling. The solvent was then removed under reduced pressure, and the residue purified by flash chromatography (hexane/EtOAc, 2:1) to afford **7** (188 mg, 0.648 mmol, 90%) as a colorless oil: $[\alpha]_D^{20}=+3.4°$ ($c=1$, $CHCl_3$); IR ($CHCl_3$) 3295, 2116, 1734, 1661, 1526 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (d, $J=6.2$ Hz, 3H), 1.17 (d, $J=6.2$ Hz, 3H), 2.05 (s, 3H), 4.49 (d, $J=5.0$ Hz, 1H), 4.95 (sept, $J=6.2$ Hz, 1H), 5.53 (dd, $J=5.0$, 8.4 Hz, 1H), 6.39 (br d, $J=8.4$ Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.39, 21.57, 23.35, 53.76, 64.41, 70.30, 127.53, 128.50, 128.69, 136.53, 167.52, 169.41; HRMS (FAB) $m/z=291.1462$ $(M+H)^+$, calcd for $C_{14}H_{19}N_4O_3=291.1457$.

4.1.7. Methyl (2*S*,3*S*)-2-azido-3-(benzoylamino)-3-phenylpropionate (8): Procedure A. Compound **7** (150 mg, 0.517 mmol) in a 6-ml vial, was treated with a solution of 6 *N* HCl/dioxane (4.5 ml, 2:1). The vial was closed tightly with a teflon disk lid, and the reaction mixture was then heated to 90°C for 12 h, with occasional swirling. The reaction mixture was then transferred into a single-necked round bottom flask (25 ml), and the solvent was evaporated to dryness. The resulting white solid was treated with 0.5M HCl in MeOH (15 ml) and heated under reflux for 2.5 h. After removal of the solvent under reduced pressure, the residue was redissolved in fresh MeOH (2×15 ml) and re-evaporated. To this residue, dry CH_2Cl_2 (15 ml) was added, and it was cooled to 0°C. To this suspension, Et_3N (288 μl, 2.07 mmol) in CH_2Cl_2 (1 ml) and then BzCl (80 mg, 0.568 mmol) in CH_2Cl_2 (1 ml) was added dropwise. The reaction mixture was then stirred for 1 h at 0°C, and for a further hour at room temperature. The reaction mixture was then passed through a short silica gel plug (~3 cm^3), and further eluted with EtOAc (50 ml). The combined filtrate was then concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane/EtOAc, 3:1) afforded **8** as a white solid. This was further purified by recrystallization (EtOAc/hexane) yielding **8** (120 mg, 0.370 mmol, 72%) as a white crystalline solid: mp 123–124°C; $[\alpha]_D^{20}=-11.6°$ ($c=1$, $CHCl_3$); IR (KBr) 3331, 2104, 1740, 1642, 1531 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3H), 4.65 (d, $J=4.7$ Hz, 1H), 5.75 (dd, $J=4.7$, 8.2 Hz, 1H), 7.09 (br d, $J=8.2$ Hz, 1H), 7.28–7.60 (m, 8H), 7.75–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.80, 54.42, 64.61, 127.10, 127.31, 128.65, 128.71, 128.90, 131.94, 133.80, 136.51, 166.82, 168.70; HRMS (FAB) $m/z=325.1298$ $(M+H)^+$, calcd for $C_{17}H_{17}N_4O_3=325.1301$.

4.1.8. Methyl (2*S*,3*S*)-2-azido-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (9) (Scheme 2). Application of procedure A to 163 mg (0.561 mmol) of **7**, 196 μl of Et_3N (1.41 mmol), and 184 mg of Boc_2O (0.842 mmol), gave 129 mg of **9** (0.403 mmol, 72%) as white needles, after flash chromatography (hexane/EtOAc, 6:1) and recrystallization (hexane): mp 93–94°C; $[\alpha]_D^{20}=-2.8°$ ($c=1$, $CHCl_3$); IR (KBr) 3368, 2104, 1743, 1690, 1524 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 9H), 3.69 (s, 3H), 4.50 (br d,$J=4.1$ Hz, 1H), 5.23 (br s, 1H), 5.38 (br s, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.32, 52.66, 55.67, 65.22, 80.42, 127.23, 128.51, 128.75, 136.83, 154.78, 168.48; HRMS (FAB) $m/z=321.1564$ $(M+H)^+$, calcd for $C_{15}H_{21}N_4O_4=321.1562$.

4.1.9. Methyl (2*S*,3*S*)-2-amino-3-(benzoylamino)-3-phenylpropionate (10): Procedure B. A 10% Pd/C catalyst (20 mg) was added to a stirred solution of **8** (100 mg, 0.303 mmol) in EtOAc (12 ml). The mixture was then hydrogenated under atmospheric H_2 (balloon) at room temperature for 30 h, and filtered through a short silica gel plug (~3 cm^3). After removal of the solvent under reduced pressure, the residue was purified using flash chromatography (hexane/EtOAc, 1:5) to afford **10** (88 mg, 0.295 mmol, 96%) as a white solid: mp 114.5–117°C; $[\alpha]_D^{20}=-40.6°$ ($c=1$, $CHCl_3$); IR (KBr) 3414, 3372, 3308, 1741, 1649, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75 (br s, 2H), 3.70 (s, 3H), 3.94 (d, $J=4.4$ Hz, 1H), 5.65 (dd, $J=4.4$, 8.4 Hz, 1H), 7.20–7.60 (m, 8H), 7.69 (br d, $J=8.4$ Hz, 1H), 7.80–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.16, 54.76, 58.23, 126.85, 127.07, 128.08, 128.59, 128.62, 131.62, 134.26, 137.46, 166.35, 173.50; HRMS (FAB) $m/z=299.1392$ $(M+H)^+$, calcd for $C_{17}H_{19}N_2O_3=299.1396$.

4.1.10. Methyl (2*S*,3*S*)-2-amino-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (11) (Scheme 2). Application of procedure B to 110 mg of **9** (0.343 mmol) and 22 mg of 10% Pd/C catalyst gave 98 mg of **11** (0.333 mmol, 97%) as a white solid, after flash chromatography (hexane/EtOAc, 1:1): mp 97–98°C; ^1H NMR ($CDCl_3$, 300 MHz, 50°C) δ 1.40 (s, 9H), 1.47 (br s, 2H), 3.66 (s, 3H), 3.81 (d, $J=4.6$ Hz, 1H), 5.08 (br s, 1H), 5.76 (br d, $J=6.8$ Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.29, 51.96, 56.07, 58.51, 79.59, 126.70, 127.80, 128.42, 137.88, 155.01, 173.58; HRMS (FAB) $m/z=295.1657$ $(M+H)^+$, calcd for $C_{15}H_{23}N_2O_4=295.1658$.

4.1.11. Methyl (2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropionate (12): Procedure C. Compound **2** (420 mg, 1.58 mmol) was treated with 0.5 M HCl in MeOH (42 ml), and heated under reflux for 10 h. After removal of the solvent under reduced pressure, the residue was again treated with 0.5 M HCl in MeOH (42 ml) and heated under reflux for an additional 10 h. After removal of the solvent under reduced pressure, the residue was redissolved in fresh MeOH (2×30 ml) and re-evaporated. To this residue, dry CH_2Cl_2 (15 ml) was added and it was then cooled to 0°C. To this suspension, Et_3N (0.53 ml, 3.80 mmol) in CH_2Cl_2 (2 ml) was added, followed by Boc_2O (518 mg, 2.375 mmol) in CH_2Cl_2 (2 ml), and the reaction mixture was stirred for 30 min at 0°C and then for a day at room temperature. The reaction

mixture was then passed through a short silica gel plug (~5 cm^3), and further eluted with EtOAc (50 ml). The combined filtrate was then concentrated under reduced pressure, and the residue was recrystallized from hexane to afford **12** (406 mg, 1.38 mmol, 87%) as a white crystalline solid: mp 128–129°C; $[\alpha]_D^{20}=-7.3°$ (c=1, $CHCl_3$); ^{25}IR (KBr) 3508, 3380, 1734, 1690, 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 3.20 (d, J=4.4 Hz, 1H), 3.84 (s, 3H), 4.47 (br s, 1H), 5.22 (br d, J=9.3 Hz, 1H), 5.42 (br d, J=9.5 Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.22, 52.05, 55.03, 72.50, 78.91, 125.70, 126.71, 127.59, 138.09, 154.11, 172.39; HRMS (FAB) m/z=296.1499 $(M+H)^+$, calcd for $C_{15}H_{22}N_1O_5$=296.1498.

4.1.12. Methyl (2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-hydroxy-3-phenylpropionate (13). Application of procedure C to 360 mg of **5** (1.36 mmol) gave 352 mg of **13** (1.19 mmol, 88%) as a white crystalline solid, after recrystallization (from hexane): mp 134.5–135.5°C; $[\alpha]_D^{20}=+28.6°$ (c=1, $CHCl_3$); IR (KBr) 3366, 1719, 1695, 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 2.85 (br s, 1H), 3.71 (s, 3H), 4.61 (br d, J=2.8 Hz, 1H), 5.11 (br dd, J=3.2, 8.6 Hz, 1H), 5.60 (br d, J=8.1 Hz, 1H), 7.15–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.85, 51.06, 55.28, 71.86, 78.47, 125.82, 126.66, 126.99, 135.41, 153.54, 170.83; HRMS (FAB) m/z=296.1496 $(M+H)^+$, calcd for $C_{15}H_{22}N_1O_5$=296.1498.

4.1.13. Methyl (2*S*,3*S*)-2-azido-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (9) (Scheme 3): Procedure D. Compound **12** (295 mg, 1.00 mmol) and PPh_3 (315 mg, 1.20 mmol) were dissolved in dry THF (15 ml), and the resulting mixture cooled to 0°C. To this stirred mixture, HN_3 (1 M solution in CH_2Cl_2, 2 ml, 2.00 mmol) was added drop-wise, followed by diethyl azodicarboxylate (209 mg, 1.20 mmol) in THF (3 ml) via syringe. The reaction mixture was then stirred for 1 h at 0°C, and for a further hour at room temperature. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane/EtOAc, 4:1) to afford **9** (288 mg, 0.899 mmol, 90%) as a white solid.

4.1.14. Methyl (2*R*,3*S*)-2-azido-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (14). Application of procedure D to 315 mg of **13** (1.07 mmol) gave 311 mg of **14** (0.971 mmol, 91%) as a white solid after flash chromatography (hexane/EtOAc, 4:1): mp 133–134°C; $[\alpha]_D^{20}=+16.5°$ (c=1, $CHCl_3$); IR (KBr) 3388, 2094, 1741, 1683, 1526 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 3.81 (s, 3H), 4.38 (br s, 1H), 5.34 (br s, 2H), 7.25–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.19, 52.95, 55.18, 66.71, 80.21, 126.51, 128.09, 128.71, 138.27, 154.78, 168.62; HRMS (FAB) m/z=321.1564 $(M+H)^+$, calcd for $C_{15}H_{21}N_4O_4$=321.1562.

4.1.15. Methyl (2*S*,3*S*)-2-amino-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (11) (Scheme 3). Application of procedure B to 233 mg of **9** (0.727 mmol) and 23 mg of 10% Pd/C catalyst gave 212 mg of **11** (0.720 mmol, 99%) as a white solid, after flash chromatography ($CHCl_3$/MeOH, 20:1): mp 97–98°C; $[\alpha]_D^{20}=+26.7°$ (c=1, $CHCl_3$); IR (KBr) 3370, 1725, 1694, 1517 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, 90°C) δ 1.34 (s, 9H), 1.77 (br s, 2H), 3.59 (s, 3H), 3.70 (d, J=6.2 Hz, 1H), 4.77 (dd, J=6.2, 9.2 Hz, 1H), 6.79 (br d, J=9.2 Hz, 1H), 7.20–7.31 (m, 5H).

4.1.16. Methyl (2*R*,3*S*)-2-amino-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (15). Application of procedure B to 311 mg of **14** (0.971 mmol) and 33 mg of 10% Pd/C catalyst gave 276 mg of **15** (0.938 mmol, 97%) as a white solid, after flash chromatography ($CHCl_3$/MeOH, 20:1): mp 74–75°C; $[\alpha]_D^{20}=-23.7°$ (c=1, $CHCl_3$); IR (KBr) 3398, 1734, 1689, 1516 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, 90°C) δ 1.35 (s, 9H), 1.87 (br s, 2H), 3.53 (s, 3H), 3.67 (d, J=5.5 Hz, 1H), 4.84 (dd, J=5.5, 9.2 Hz, 1H), 6.87 (br d, J=9.2 Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.30, 52.43, 56.36, 58.54, 79.61, 126.39, 127.51, 128.62, 139.94, 155.29, 173.01; HRFABMS m/z=295.1666 $(M+H)^+$, calcd for $C_{15}H_{23}N_2O_4$=295.1658.

4.1.17. (4*S*,5*S*)-4-(Methoxycarbonyl)-5-phenyl-2-imidazolidinone (16). Compound **11** (160 mg, 0.544 mmol) was treated with 10 ml of TFA–CH_2Cl_2 (1:1), and the resulting solution stirred for 1 h at room temperature. After removal of the solvent under reduced pressure, the residue was redissolved in fresh CH_2Cl_2 (3×10 ml) and re-evaporated. To this residue, dry THF (10 ml) was added, and the mixture cooled to 0°C. To this stirred solution, Et_3N (0.758 ml, 5.44 mmol) in THF (1 ml) was added drop-wise, and then 1,1′-carbonyldiimidazole (132 mg, 0.815 mmol) in THF (1 ml). The reaction mixture was then stirred for 30 min at 0°C, and for 2 h at room temperature. After removal of the solvent under reduced pressure, the residue was treated with EtOAc (3×30 ml) and passed through a short silica gel plug (~10 cm^3). The combined filtrate was concentrated under reduced pressure, and the residue was recrystallized from EtOAc to afford **16** (72 mg, 0.327 mmol, 60%), as a white crystalline solid: mp 203–205°C (dec.); $[\alpha]_D^{20}=+123.2°$ (c=1, MeOH); IR (KBr) 3409, 3255, 1707 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 3.15 (s, 3H), 4.64 (d, J=9.7 Hz, 1H), 5.21 (d, J=9.7 Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 52.02, 60.07, 61.65, 128.28, 129.30, 129.51, 138.89, 166.06, 171.83; HRMS (FAB) m/z=221.0919 $(M+H)^+$, calcd for $C_{11}H_{13}N_2O_3$=221.0926.

4.1.18. (4*R*,5*S*)-4-(Methoxycarbonyl)-5-phenyl-2-imidazolidinone (17). Compound **15** (160 mg, 0.544 mmol) was treated with 10 ml of TFA–CH_2Cl_2 (1:1), and the resulting solution stirred for 1 h at room temperature. After removal of the solvent under reduced pressure, the residue was redissolved in fresh CH_2Cl_2 (3×10 ml) and re-evaporated. To this residue, dry CH_2Cl_2 (10 ml) was added, and the mixture cooled to 0°C. To this stirred solution Et_3N (0.758 ml, 5.44 mmol) in CH_2Cl_2 (2 ml) was added drop-wise, and then bis(trichloromethyl) carbonate (81 mg, 0.273 mmol) in CH_2Cl_2 (1 ml). The reaction mixture was then stirred for 1 h at 0°C, and for a further hour at room temperature. After removal of the solvent under reduced pressure, the residue was treated with EtOAc (4×20 ml), and passed through a short silica gel plug (~10 cm^3). The combined filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (EtOAc/hexane, 5:1) afford **17** (65 mg, 0.295 mmol, 54%) as a off-white solid: mp 206–209°C (dec.); $[\alpha]_D^{20}=-101.7°$ (c=1, MeOH); IR (KBr) 3401, 3246,

1715, 1686 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 3.81 (s, 3H), 4.10 (d, J=4.6 Hz, 1H), 4.87 (d, J=4.6 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 53.13, 60.52, 63.83, 126.99, 129.36, 129.95, 143.13, 165.00, 173.30; HRMS (FAB) m/z=221.0919 $(M+H)^+$, calcd for $C_{11}H_{13}N_2O_3$=221.0926.

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19. Enantiomeric excess was determined by HPLC using Chiralcel OD column and isopropyl alcohol/hexane (1:9) as a mobile phase. The retention time was 37.4 min for (2*R*,3*S*) isomer and 18.7 min for (2*S*,3*R*) isomer, repectively.
20. *anti* Azide **7** was accessible from *syn* acetylamino alcohol **2** using the Mitsunobu reaction conditions (DEAD, PPh_3, hydrazoic acid). However, the desired product was not easily separated from diethyl hydrazodicarboxylate by column chromatography. When methanesulfonate **3** reacted with sodium azide in anhydrous DMF, an unseparable mixture of *cis*-oxazoline **4** and *anti* azide **7** (1.6–1.8:1, based on ^1H NMR) was produced.
21. Initial attempt was made to displace the mesylate of **3** with azide. Obviously, sodium azide didn't act as a nucleophile. We believe that HN_3 generated in situ could open the oxazoline ring **4** as a general acid. In a separate experiment, we could isolate this *cis*-oxazoline intermediate **4** in 62% yield after chromatography when methanesulfonate **3** was heated in acetone–water with potassium bicarbonate instead of sodium azide. *anti* Acetylamino alcohol **5** could be also obtained nearly quantitatively when *cis*-oxazoline **4** was heated to 70°C for 3 h in acetone–water containing methanesulfonic acid (1 equiv.) and sodium azide (2 equiv.). Related examples for the inversion of the alcohol stereocenter were reported via oxazoline formation, using the Mitsunobu condition,[21a] thionyl chloride,[21b] or Tf_2O,[21c] and subsequent acid hydrolysis. (a) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2385. (b) Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287. (c) Cabri, W.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **1996**, *37*, 4785.
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