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Preparation of 2,3-Diamino Acids: Stereocontrolled Synthesis of an Aminated Analog of the Taxol Side Chain

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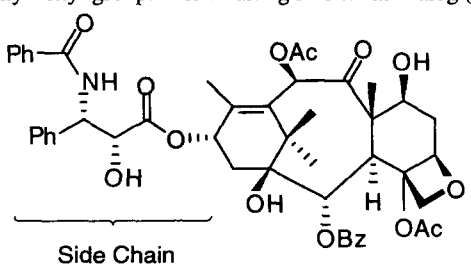
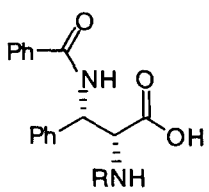
Abstract: A method for the preparation of 2,3-diamino acids is presented, and applied to the synthesis of a β-benzoylamino-phenylalanine (**2b**), an analog of the taxol side chain. Differentially protected *erythro* and *threo* diamines were prepared from a common, optically active, precursor. Copyright © 1996 Elsevier Science Ltd

Because of its profound antitumor activity and its unique mode of action, the diterpene taxol (**1**) has attracted considerable attention in both the chemical literature and the popular press.[1] Although a promising drug for the treatment of ovarian and other cancers,[2-4] the low water solubility of taxol can be problematic.[2,5,6] Previous attempts to improve water solubility have relied on either the conversion of an acetate group on the taxane nucleus to a hydroxyl group, the preparation of water soluble prodrugs, which are converted to taxol under physiological conditions, or novel drug formulations.[5-8] An alternative method of increasing water solubility would be to replace one of the hydroxyl groups of taxol with an amino group; salts of the resulting amine would have improved water solubility. Because the taxol side chain is less structurally complex than the taxane ring system and can be coupled to it,[9] an amino group is most easily introduced by replacement of the side chain hydroxyl group. The resulting side chain analog (**2a**) is a differentially protected vicinal diamine.



Taxol (**1**)



2a R = H
2b R = Boc

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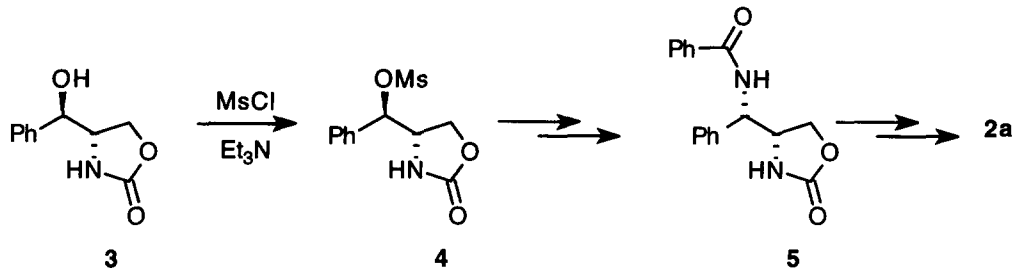
Scheme 1



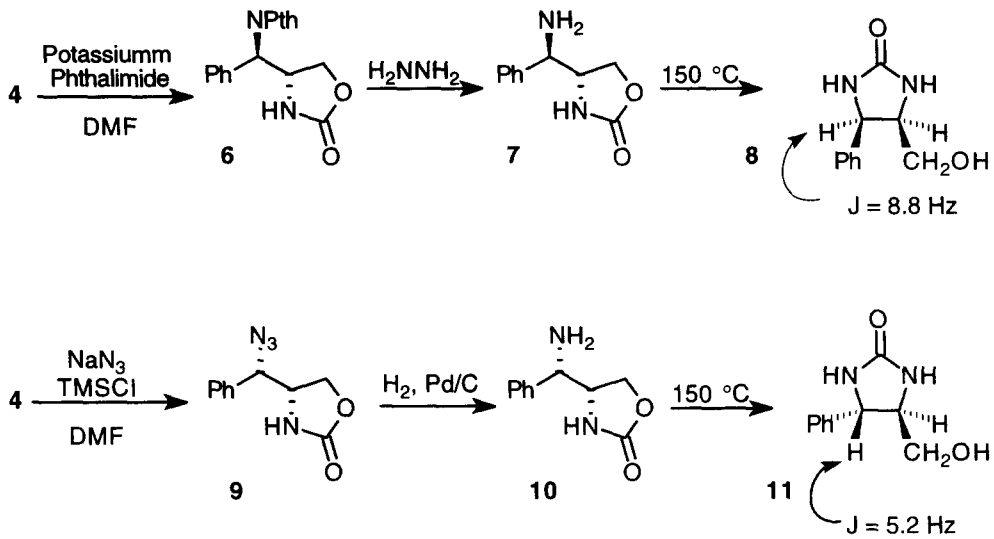
RESULTS AND DISCUSSION

Although vicinal amines have a number of applications[10,11] few good methods are available for the stereocontrolled synthesis of such compounds.[12-17] Available methodology was not applicable to the preparation of compounds, such as **2a** and **2b**, with two differentially protected primary amino groups. Our strategy, as outlined in Scheme 1, was to make use of oxazolidinone **3**, which can be synthesized as either enantiomer from a chiral epoxy alcohol, prepared via Sharpless asymetric epoxidation.[18,19] The hydroxyl group of **3** is activated as the methanesulfonate ester. Displacement with a nitrogen containing nucleophile, followed by functional group transformation gives intermediate **5**. The desired amino acid **2a** is prepared by hydrolysis of the oxazolidinone ring and oxidation of the resulting primary hydroxyl group.

We originally envisioned utilizing a Gabriel synthesis to introduce the benzylic amino group of **5**, as outlined in Scheme 2. The sulfonate ester group of **4** was displaced with potassium phthalimide to give **6**. Deprotection of the phthalimide without destruction of the oxazolidinone ring was achieved by treating **6** with dilute hydrazine to give amine **7**.

The stereochemical outcome of the Gabriel synthesis was initially unknown, since participation of the oxazolidone nitrogen in the displacement mechanism was possible.[20,21] Lipshutz and Miller observed that neighboring group participation in β-amino alcohol systems was dependent on the nature of the amino protecting group.[22] Although the authors found no participation by amino groups when they were protected as acyclic urethanes, it is nevertheless possible that the more nucleophilic nitrogen of the cyclic oxazolidinone could displace the mesylate. The relative configuration of the stereocenters present in **7** was determined by thermal isomerization of the oxazolidinone to the conformationally restricted cyclic urea **8**. In its proton NMR spectrum, the resonance corresponding to the benzylic proton of **8** was observed as a doublet with a coupling constant of 8.8 Hz. This is consistent with *cis* -ring substitution and indicates that the S_N2 reaction, undesirably, had occurred with net retention of configuration. The stereochemistry of amine **7** was confirmed by X-ray crystallographic analysis.

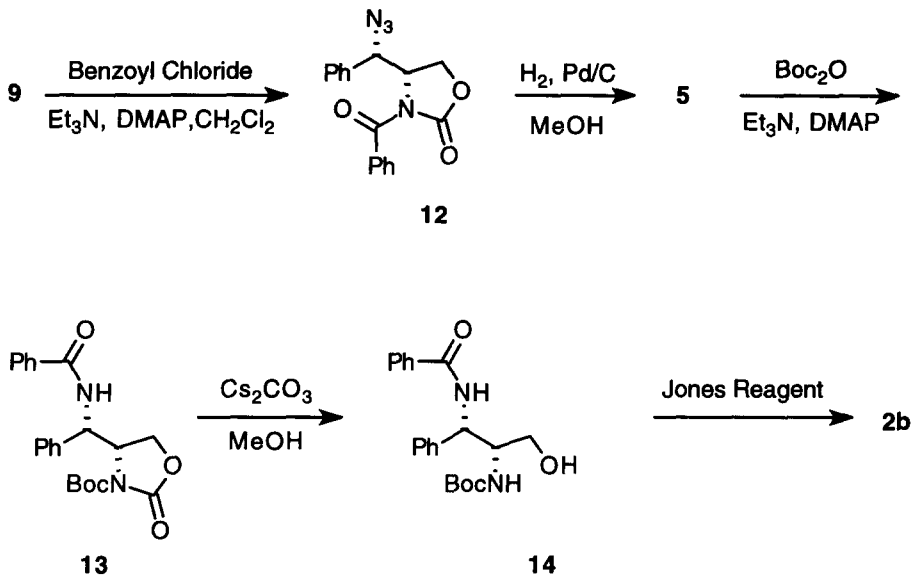
Scheme 2



Based on the observation that treatment of **3** with benzoic acid under Mitsunobu reaction conditions gave a mixture of diastereomers,[23] we believed that neighboring group participation might be reduced by the utilization of a more acidic nitrogen source. When mesylate **5** was treated with sodium azide, a 2:1 mixture of diastereomers was isolated. Unfortunately, the mixture was difficult to purify. The major product was, however, obtained exclusively if the oxazolidinone was first silylated *in situ* with chlorotrimethylsilane, and then treated with sodium azide. Reduction of the resulting azide (**9**) gave amine **10**, which was spectroscopically different from the previously isolated amine **7**. Heating **10** resulted in its isomerization to cyclic urea **11**. The proton NMR resonance corresponding to the benzylic proton of **11** was observed as a doublet with a coupling constant of 5.2 Hz, indicating the ring had a *trans*-substitution pattern, and that the S_N2 reaction had proceeded with inversion. Thus, both *erythro* and *threo* diastereomers (**7** and **10**) were prepared from a common precursor.

Synthesis of the taxol side chain analog continued, as outlined in Scheme 3, with the benzoylation of the oxazolidinone nitrogen of azide **9** to give **12**. Reduction of the azide with hydrogen over Pd/C, accompanied by spontaneous benzoyl transfer gave benzamide **4**. The oxazolidinone ring was activated with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine at 0 °C to give Boc protected oxazolidinone **13**, which was treated with cesium carbonate in methanol[24] to give the N-Boc-amino alcohol **14**. Although nonacidic ruthenium based oxidations [25,26] failed to give the corresponding carboxylic acid, the desired oxidation of amino alcohol **14** was achieved with Jones reagent to give **2b**.

Scheme 3



CONCLUSIONS

A method for the preparation of optically active vicinal diamino acids was developed. The stereochemical course of the key transformation in the sequence, the introduction of the benzylic nitrogen, is dictated by the reaction conditions and the nature of the nitrogen containing nucleophile. Nucleophilic displacement with phthalimide occurs with retention of configuration, giving the *erythro* product. The neighboring group participation of the oxizolidinone nitrogen can be eliminated if it is first allowed to react with chlorotrimethylsilane. Subsequent treatment with azide results in the formation of the *threo* product. Thus, both diastereomers can be prepared from a common synthetic intermediate. The differentially protected diamine was elaborated into an analog of the taxol side chain.

EXPERIMENTAL

General. Proton NMR spectra were obtained at 200 MHz on a Varian XL-200 spectrometer or at 400 MHz on a Varian XL-400 spectrometer as specified. Carbon-13 NMR were obtained at 100 MHz on a Varian XL-400 spectrometer. High resolution mass spectra were recorded at the University of Illinois at Urbana-Champaign Mass Spectrometry facility. Optical rotations were taken with a Perkin-Elmer 241 Polarimeter. Single crystal X-ray diffraction data were collected on a Syntex P21 diffractometer. THF was distilled from potassium and benzophenone; methylene chloride and pyridine were distilled from CaH_2; DMF was dried over CaH_2, filtered, distilled at reduced pressure and stored over 4Å molecular sieves. Other solvents and all reagents

were used as received from the manufacturer. Thin layer chromatography (TLC) was performed using pre-coated silica gel plates (Baker IB2-F) and flash chromatography was performed using silica gel (Krackeler Scientific, 230-400 mesh). All reactions were carried out under inert atmosphere (argon or nitrogen) unless otherwise noted.

4(S)-[(R)-(Methanesulphonyloxy)phenylmethyl]-1,3-oxazolidin-2-one (4). Methanesulfonyl chloride (0.46 mL, 5.9 mmol) and triethylamine (0.83 mL, 5.9 mmol) were added to a solution of oxazolidinone alcohol **3** (0.99 g, 5.1 mmol, prepared from (2R,3R)-(+)-3-phenylglycidol[18]) dissolved in methylene chloride (25 mL). After 1 h the reaction mixture was concentrated and the residue chromatographed (hexanes/ethyl acetate 1:2) to yield 1.20 g (89%) of **5**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 3 H), 4.21 - 4.26 (m, 1 H), 4.32 - 4.40 (m, 2 H), 5.59 (d, 1 H, J = 4.9 Hz), 6.5 (br s, 1 H), 7.26 - 7.43 (m, 5 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 38.8, 56.1, 65.7, 82.3, 126.6, 129.1, 129.6, 133.6, 159.2; HRFAB-MS calcd for $C_{11}H_{14}NO_5S$ (M + H$^+$) 272.0593, obsd 272.0592; $[\alpha]^{23}_D$ = -48° (c = 1.6, $CHCl_3$).

4(R)-[(R)-Phenyl(phthaloylamino)methyl]-1,3-oxazolidin-2-one (6). Potassium phthalimide (0.60 g, 3.24 mmol) was added to a solution of **5** (0.22 g, 0.82 mmol) dissolved in DMF (10 mL). After stirring vigorously for 13 h, the suspension was taken up in methylene chloride and washed with water. The aqueous phase was washed twice with methylene chloride, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography of the residue (hexanes/ethyl acetate 2:1, followed by 7:5) gave 0.21 g of **6** (79%). mp 132-134 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.20 (dd, 1 H, J = 1.1 Hz, 3.9 Hz), 4.54 (m, 1 H), 5.15 - 5.25 (m, 2 H), 5.29 (br s, 1 H), 7.3-7.6 (m, 5 H), 7.7-7.9 (m, 4 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 52.6, 58.9, 67.8, 123.7, 128.9, 129.2, 129.2, 131.3, 134.5, 135.5, 158.2, 168.1; CIMS 323.3 (M + H$^+$), 237.2; HRMS(EI) calcd for $C_{18}H_{14}N_2O_4$ (M$^+$) 322.0954, obsd 322.0950; $[\alpha]^{24}_D$ = +62° (c = 1.8, $CHCl_3$)

4(R)-[(R)-Aminophenylmethyl]-1,3-oxazolidin-2-one (7). Hydrazine monohydrate (60 μL, 1.2 mmol) was added to a solution of **6** (61 mg, 0.19 mmol) dissolved in absolute ethanol (25 mL). The reaction mixture was heated to 60 °C. After 30 h, the reaction mixture was cooled and a white, gel like precipitate formed. The reaction mixture was filtered, concentrated and chromatographed (hexanes/ethyl acetate 1:2 followed by methylene chloride/methanol/NH_4OH 300:20:1) to yield 26 mg (72%) of **7**. Crystallization of **7** from ethanol gave crystals suitable for X-ray crystallographic analysis. mp 132-133 °C; ^{1}H-NMR (200 MHz, CD_3OD) δ 3.95 (d, 1 H, J = 5.9 Hz), 4.1 (m, 1 H), 4.4 (m, 2 H), 7.35 (~s, 5 H); ^{13}C-NMR (100 MHz, CD_3OD) δ 59.3, 59.6, 68.5, 128.3, 129.7, 129.8, 142.0, 162.1; CIMS 193.2 (M + H$^+$), 106.1; HRMS(EI) calcd for $C_{10}H_{12}N_2O_2$ (M$^+$) 192.0899, obsd 192.0893; $[\alpha]^{25}_D$ = + 4.0° (c = 1.2, methanol).

4(R)-Hydroxymethyl-5(R)-phenyl-imidazolidin-2-one (8). Amine **7** (20 mg, 0.10 mmol) was heated to 150 °C for 15 min. The residue was crystalized from methanol to give 5 mg of **8** (25%). The mother liquor was chromatographed (methylene chloride/methanol/NH_4OH 100:10:1) to give an additional 2 mg of **8** for a total yield of 35%. mp= 159-161 °C; ^{1}H-NMR (300 MHz, CD_3OD) δ 3.02 (m, 2H), 4.03-4.11 (m, 1H), 4.99 (d, J=8.8 Hz, 1H), 7.24-7.56 (m, 5H); ^{13}C-NMR (100 MHz, CD_3OD) δ 166.5, 139.2, 129.6, 129.2, 128.2, 63.7, 59.6, 59.5; HRMS(EI) calc for $C_{10}H_{12}O_2N_2$ (M$^+$) 192.0899, obsd 192.0893; $[\alpha]^{25}_D$ = -99.9° (c=0.73, CH_3OH).

4(R)-[(S)-Azidophenylmethyl]-1,3-oxazolidin-2-one (9). Chlorotrimethylsilane (0.50 mL, 3.94

mmol) was added to a solution of **5** (0.467 g, 1.72 mmol) in DMF. The reaction mixture was stirred for 1 h and sodium azide (0.455 g, 7.00 mmol) was added. After 19 h, the reaction mixture was taken up in methylene chloride, washed with water, dried with $MgSO_4$ and concentrated. Chromatography of the resulting residue (hexane/ethyl acetate 2:3) gave 0.240 g of **9** (64%) as a crystalline solid. mp 78 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.96 - 4.05 (m, 2 H), 4.13 - 4.23 (m, 1 H), 4.49 (d, 1 H, J = 8.0 Hz), 6.3 (br s, 1 H), 7.27 - 7.46 (m, 5 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.5, 66.5, 69.2, 127.6, 129.5, 129.7, 134.2, 158.9. HRFAB-MS calcd for $C_{10}H_{11}N_4O_2$ (M + H$^+$) 219.0882, obsd 219.0872; IR(thin film) 3256, 2092, 1752; $[\alpha]^{25}_D$ = +185° (c = 1.5, $CHCl_3$).

4(R)-[(S)-Aminophenylmethyl]-1,3-oxazolidin-2-one (10). Pd/C catalyst (10%, 15 mg) was added to a solution of azide **9** (0.150 g, 0.69 mmol) dissolved in methyl alcohol (10 mL). The mixture was shaken in an atmosphere of hydrogen (35 psi) for 14 h. The catalyst was removed by filtration. Evaporation of solvent gave 0.119 g (90%) of **10** as a crystalline solid. mp 116-118 °C; ^{1}H-NMR (250 MHz, CD_3OD) δ 3.86 (d, J=6.6 Hz, 1H), 4.04-4.18 (m, 3H), 7.29-7.38 (m, 5H); ^{13}C-NMR (60 MHz, CD_3OD) δ 59.8, 60.7, 68.5, 128.4, 129.1, 129.8, 141.8; HRMS(EI) calc for $C_{10}H_{12}O_2N_2$ (M$^+$) 192.0899, odsd 192.0905; $[\alpha]^{25}_D$ = +18° (c=1.1, CH_3OH)

4(R)-Hydroxymethyl-5(S)-phenyl-imidazolidin-2-one (11). Amine **10** (100 mg, 0.52 mmol) was heated to 150 °C for 15 min. The residue was chromatographed with CH_2Cl_2/MeOH/NH_4OH (100:10:1) to give 85 mg (85%) of **11**. ^{1}H-NMR (250 MHz, CD_3OD) δ 3.38-3.54 (m, 3H), 4.48 (d, J=5.2 Hz, 1H), 7.17-7.27 (m, 5H); ^{13}C-NMR (60 MHz, CD_3OD) δ 59.6, 64.4, 64.7, 127.2, 129.0, 129.8, 143.9, 165.5; IR(thin film) 3321, 2927, 1699; HRMS(EI) calc for $C_{10}H_{12}O_2N_2$ (M$^+$) 192.0899, obsd 192.0895; $[\alpha]^{25}_D$ = -30.8° (c=0.92, CH_3OH)

4(R)-[(S)-Azidophenylmethyl]-1-benzoyl-1,3-oxazolidin-2-one (12). 4-Dimethylaminopyridine (0.140 g, 1.10 mmol), triethylamine (1.6 mL, 11 mmol), and benzoyl chloride (2.2 mL, 19 mmol) were added sequentially to a solution of oxazolidinone azide **9** (0.82 g, 3.8 mmol) dissolved in methylene chloride (55 mL). After 30 min, the excess benzoyl chloride was quenched with 5 mL of methanol, the solvent was removed, and the residue chromatographed (hexanes/ethyl acetate 3:1) to yield 1.10 g (92%) of **12**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.37 (t, 1 H, J = 9.2 Hz), 4.45 (dd, 1 H, J = 4.5 Hz, 9.7 Hz), 4.99 - 5.04 (m, 1 H), 5.37 (d, 1 H, J = 5.8 Hz), 7.29 - 7.55 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.6, 62.9, 63.6, 127.5, 127.8, 129.1, 129.3, 129.6, 132.4, 132.6, 133.1, 152.5, 169.9; HRFAB-MS calcd for $C_{17}H_{15}N_4O_3$ (M + H$^+$) 323.1144, obsd 323.1158; $[\alpha]^{25}_D$ = -51° (c = 1.6, $CHCl_3$).

24(R)-[(S)-(Benzoylamino)phenylmethyl]-1,3-oxazolidin-2-one (5). A solution of azide **12** (1.10 g, 3.4 mmol) in methanol (250 mL) was hydrogenated over 10% palladium on activated carbon (0.34 g) at 30 psi for 10 h. The reaction mixture was filtered, concentrated, and chromatographed (hexanes/ethyl acetate 1:2) to yield 0.65 mg (64%) of **4**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.15 (d, 1 H), 4.32 (m, 2 H), 5.32 (dd, 1 H, J = 2.4 Hz, 8.9 Hz), 6.33 (br s, 1 H), 7.2-7.6 (m, 9 H), 7.75 (d, 2 H, J = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 55.7, 56.8, 67.6, 126.7, 127.2, 127.4, 128.5, 129.3, 131.9, 133.6, 137.7, 159.7, 168.2; HRFAB-MS calcd for $C_{17}H_{17}N_2O_3$ (M + H$^+$) 297.1236, obsd 297.1239 ; $[\alpha]^{24}_D$ = +13° (c = 1.2, $CHCl_3$).

4(R)-[(S)-(Benzoylamino)phenylmethyl]-1-Boc-1,3-oxazolidin-2-one (13). 4-Dimethylamino-

pyridine (62 mg, 0.51 mmol), triethylamine (0.31 mL, 230 mg, 2.2 mmol), and Boc anhydride (0.5 mL, 480 mg, 2.2 mmol) were added to a solution of **5** (630 mg, 2.1 mmol) in methylene chloride (65 mL). After 2 h, the solvent was removed and the residue chromatographed (hexanes/ethyl acetate 3:2) to yield 790 mg (2.0 mmol, 94%) of **13**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 9 H), 4.14 (m, 2 H), 4.82 (ddd, 1 H, J = 2.5 Hz, 7.0 Hz, 9.8 Hz), 5.28 (dd, 1 H, J = 3.0 Hz, 7.3 Hz), 7.3-7.5 (m, 8 H), 7.8 (m, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.8, 57.2, 57.9, 64.7, 85.5, 127.0, 127.7, 128.4, 128.7, 129.2, 131.7, 133.3, 137.8, 151.1, 152.3, 166.5; HRFAB-MS calcd for $C_{22}H_{25}N_2O_5$ (M + H$^+$) 397.1763, obsd 397.1773; $[\alpha]^{24}_D$ = +31° (c = 1.5, $CHCl_3$).

2(R), 3(S)-2-Benzoylamino-2-(*tert*-butyloxycarbonyl)amino-3-phenyl-propan-1-ol (14). Oxazolidinone **13** (770 mg, 1.9 mmol) was dissolved in methanolic cesium carbonate (0.06 M, 67 mL, 4 mmol) and extra methanol (17 mL) was added to solubilize **13**. The solution was stirred for 5 h, concentrated and chromatographed (hexanes/ethyl acetate 1:1) to yield 640 mg (1.7 mmol, 89%) of **14**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 9 H), 2.6 (br s, 1 H), 3.54 (m, 2 H), 4.04 (m, 1 H), 5.42 (dd, 1 H, J = 8.3 Hz, 9.9 Hz), 5.74 (d, 1 H, 7.8 Hz), 7.2-7.5 (m, 8 H), 7.79 (d, 2 H, J = 7.3 Hz), 8.02 (d, 1 H, 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.2, 56.1, 56.8, 61.1, 80.1, 127.2, 127.6, 127.8, 128.4, 128.8, 131.6, 133.5, 140.1, 158.0, 167.5; HRFAB-MS calcd for $C_{21}H_{27}N_2O_4$ (M + H$^+$) 371.1971, obsd 371.1963; $[\alpha]^{24}_D$ = -3.7° (c = 1.8, acetone).

2(R),3(S)-3-Benzoylamino-2-(*tert*-butoxlcarbonylamino)-3-phenylpropionic Acid (2b). Jones' Reagent[27] (5.6 mL, 7.0 mmol of CrO_3) was added to a solution of **14** (620 mg, 1.7 mmol) dissolved in acetone (550 mL). After 4 h, 10% aqueous Na_2CO_3 (18 mL) was added, the reaction mixture was filtered, concentrated, and the residue was chromatographed (hexanes/ethyl acetate 1:1, followed by hexanes/ethyl acetate/HOAc 5:5:1) to yield 470 mg (1.2 mmol, 72%) of **2b**. ^{1}H-NMR (400 MHz, CD_3OD) δ 1.34 (~s, 9 H), 4.64 (d, 1 H, J = 5.3 Hz), 5.70 (d, 1 H, J = 5.2 Hz), 7.24-7.55 (m, 8 H), 7.84 (d, 2 H, J = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.6, 56.4, 59.5, 80.6, 128.2, 128.5, 128.5, 129.4, 129.6, 132.9, 135.5, 140.1, 157.8, 169.8, 174.5; FAB-MS 385.1 (MH$^+$), 329.0, 285.1; HRFAB-MS calcd for $C_{21}H_{25}N_2O_5$ (M + H$^+$) 385.1763, obsd 385.1774; $[\alpha]^{25}_D$ = -66.4° (c = 1.1, MeOH).

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