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Chiral Brønsted Acid-Catalyzed Stereoselective Mannich-Type Reaction of Azlactones with Aldimines

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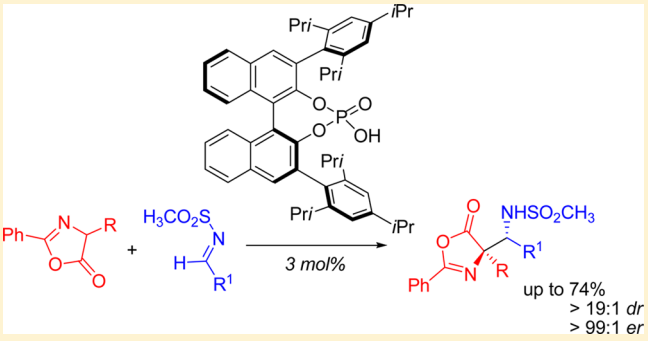
Supporting Information

ABSTRACT: A highly diastereo- and enantioselective Mannich-type reaction of azlactones with aldimines catalyzed by a chiral phosphoric acid is described. Only 3 mol % catalyst was required to prepare the Mannich adducts in good yields with high stereochemical control (up to >19:1 dr, >99:1 er). Moreover, the final product contains two consecutive stereogenic centers, one of which is quaternary.



Chiral α,β-diamino acid derivatives are very important building blocks in organic chemistry, as they possess remarkable pharmacological properties. Viso and co-workers have shown the importance of these motifs in the treatment of neurodegenerative diseases and various cancers.[1] A variety of methods for the synthesis chiral α,β-diamino acid derivatives have been reported.[1] One attractive route utilizes azlactones, as these rings are essentially protected amino acids that are readily unmasked under acidic conditions. Additionally, azlactones can easily be prepared on a preparative scale following literature protocols[2] and derivatized through Mannich-type reactions[3] mediated by transition metals or organocatalysts[4,5]

In particular, chiral gold(I) complexes have been used to catalyze enantioselective Mannich reactions of azlactones. The reaction of aliphatic mesitylsulfonimines with azlactones in the presence of a spirocyclic bisphosphine gold(I) benzoate complex (xylyl-SDP(AuOBz)$_2$) provided the desired 1,2-*anti* Mannich adducts in high yields and selectivities.[4] In contrast, organocatalytic approaches tolerate both aromatic and aliphatic imines for the synthesis of chiral α,β-diamino acid derivatives in high yields and selectivities.[5a,b] Interestingly, the major products observed in these reactions were the 1,2-*syn* diastereomers.

Since the pioneering work of Terada[6] and Akiyama[7] that demonstrated the potential of chiral phosphoric acids as organocatalysts, new applications exploiting the H-donor capacity of these catalysts have appeared in the literature.[8] In our research program,[9] we envisioned that chiral phosphoric acids could be an alternative, metal-free catalyst for the reaction between azlactones and aldimines. Moreover, we envisioned that this approach may be complementary to existing organocatalytic methods and provide access to the 1,2-*anti*-diamino acid derivatives from aromatic imines.

The azlactone and imine skeletons are both readily accessed following literature protocols.[4] To our delight, the reaction between azlactone **1a** and aldimine **2a** catalyzed with only a 3 mol % loading of commercially available (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, (*S*)-TRIP,[10] in toluene[11] gave the desired Mannich adduct **3a** in good yield (70% isolated yield) with excellent enantio- and diastereoselectivity (Table 1, entry 3). However, increasing the size of the sulfonamide led to a decrease in yield. Only traces of product were detected when dichloromethane (entry 2) was used as the solvent. While performing the reaction in THF provided the desired product in moderate yield, the diastereoselectivity of the transformation was low. A significant background reaction was observed when either acetone or chloroform was used. The catalyst loading could be decreased to 2 mol % without any loss of stereoselectivity, albeit at a lower isolated yield (50%).

Having optimized the reaction conditions, we conducted experiments to evaluate the substrate scope of this transformation (Table 2). Various aromatic imines containing either electron-withdrawing or electron-donating groups could be used in the reaction. For example, a benzaldehyde derivative containing fluorine at the *para* position worked quite well, providing the Mannich adduct **3g** in good yield with both diastereo- and enantioselectivity (>19:1 dr, 98:2 er). Phenylalanine-derivatived azlactone could also be used under the optimized reaction conditions, yielding product **3i** with >98%

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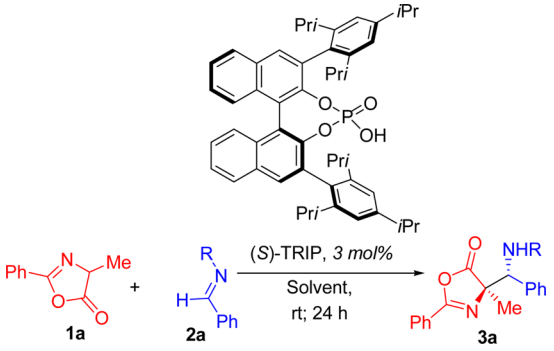
Table 1. Optimization of Reaction Conditions for the Stereoselective Mannich-Type Reaction[a]



entry	R	solvent	dr (*anti*/*syn*)[b]	er[c]	yield[d]
1	mesyl	THF	1:1	99:1	40
2	mesyl	CH_2Cl_2	1:1	n.d.[e]	traces
3	mesyl	PhMe	>19:1	>99:1	70
4	tosyl	PhMe	5:1	n.d.[e]	20
5	mesityl	PhMe	2:1	n.d.[e]	15
6[f]	mesyl	PhMe	>19:1	>99:1	55
7[g]	mesyl	PhMe	–	–	–

[a]Reactions were carried out using 0.2 mmol of **1**, 0.006 mmol of (*S*)-TRIP (3 mol %), and 0.21 mmol of **2** in PhMe (0.2 M in azlactone). [b]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]Determined by enantiodiscriminating HPLC. [d]Isolated yields. [e]Not determined. [f]Without molecular sieves. [g]No catalyst, 48 h.

ee. The relative and absolute stereochemistry (1,2-*anti*) of the Mannich adduct **3b** was determined by X-ray crystallographic analysis (Figure 1). The other products were assigned by analogy. To the best of our knowledge, this work comprises the first highly enantio- and diastereoselective Mannich-type reaction between azlactones and aldimines catalyzed by a chiral phosphoric acid. A variety of aliphatic imines were evaluated; however, all led to complex product mixtures that could not be deciphered.[12]

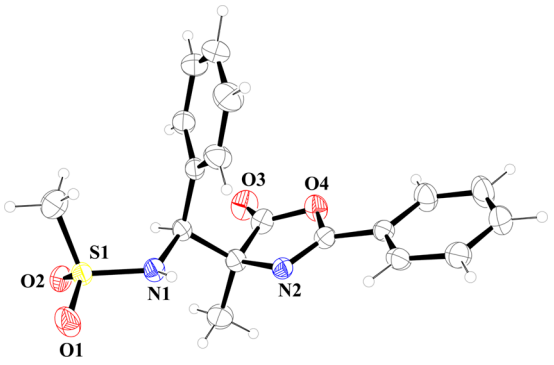
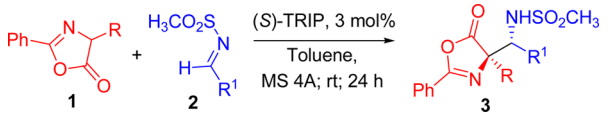
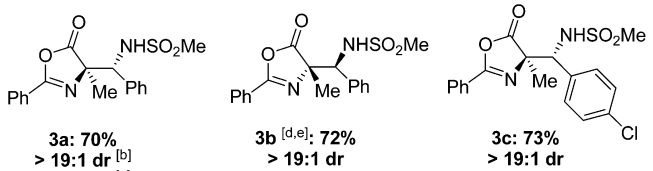


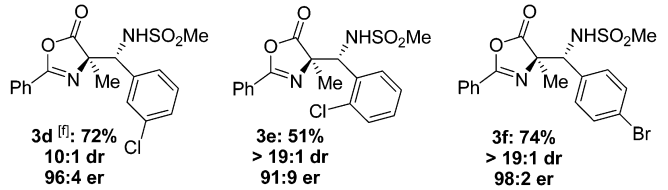
Figure 1. X-ray crystallographic structure of **3b**.

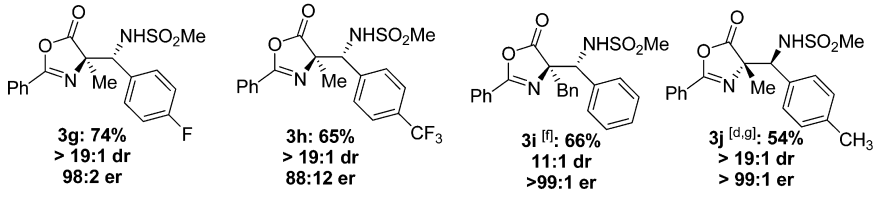
Yamanaka and Akiyama have proposed that the Mannich-type reaction of a special hydroxyaldimine catalyzed by a chiral phosphoric acid proceeds through coordination of both oxygen atoms of the chiral phosphoric acid to the aldimine.[13] Terada and co-workers have shown a chiral phosphoric acid-catalyzed enantioselective addition of azlactones to 3-vinylindoles; in this case, the chiral phosphoric acid activates both the enol intermediate of the azlactone and the vinyl double-bond system.[14] Thus, a plausible transition state for the reaction of imines and azlactones in the presence of TRIP is proposed.[15] We hypothesize that the phosphoric acid can stabilize the enol

Table 2. Diastereo- and Enantioselective Mannich-Type Addition of Azlactones to Aldimines[a]









[a]Reactions were carried out using 0.2 mmol of **1**, 0.006 mmol of (*S*)-TRIP (3 mol %), and 0.21 mmol of **2** in PhMe (0.2 M in azlactone). [b]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]Determined by chiral HPLC. [d](*R*)-TRIP was used as the catalyst. [e]The relative and absolute stereochemistries of **3b** were determined by X-ray crystallography, and those of the other products were assigned by analogy. [f]Only the major diastereomer was isolated. [g]5 mol % catalyst.

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intermediate of the azlactone and also activate the imine through protonation of the nitrogen lone pair, providing the Mannich adducts with high selectivities (Figure 2).

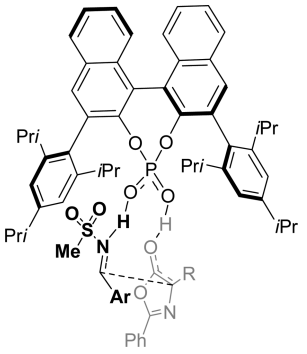
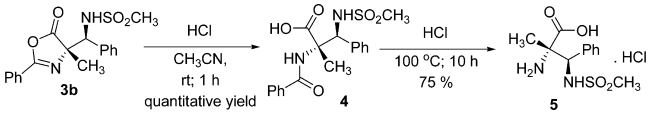


Figure 2. Plausible activation mode for the stereoselective reaction between azlactones and aldimines catalyzed by a phosphoric acid.

To probe the reversibility of the reaction, the enantioenriched Mannich addition product **3b** was resubjected to the catalytic reaction conditions in the presence of racemic camphorsulfonic acid, (±)-CSA, following the general procedure for the Mannich reaction. After 24 h at room temperature, the product was reisolated with >99% ee (eq 1), suggesting that the C−C σ-bond formation step is irreversible.

Ring opening of the enantioenriched Mannich addition product **3b** followed by amide deprotection in the presence of a mineral acid provided amino acid **5** in two steps in 75% overall yield (Scheme 1).

Scheme 1. Preparation of Amino Acid 5



In summary, a Brønsted acid-catalyzed highly diastereo- and enatioselective Mannich-type addition of azlactones with aldimines has been presented. Only a 3 mol % loading of the commercially available phosphoric acid TRIP was needed to provide protected 1,2-*anti*-diamino acid derivatives in moderate to good yields with nearly perfect control of both diastereo- and enantioselectivity (up to >19:1 dr and >99:1 er). Besides the formation of the new C−C σ bond, two stereogenic centers are created, one of them quaternary.

EXPERIMENTAL SECTION

Representative Procedure for the Enantio- and Diastereoselective Mannich-Type Addition of Azlactones to Aldimines. To a flamed screw-cap vial with molecular sieves (50 mg) was added 0.2 mmol of azlactone under a nitrogen atmosphere, after which toluene was cannulated to a concentration of 0.2 mol·L^{-1} in azlactone. To this solution was added 0.006 mmol of phosphoric acid (3 mol %) followed by 0.21 mmol of imine. The reaction mixture was kept at room temperature under a nitrogen atmosphere for 24 h, diluted with CH_2Cl_2 (10 mL), and washed with a saturated solution of sodium bicarbonate (5 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. An aliquot was taken to the NMR spectrometer, and the diastereoisomeric ratio was measured by ^{1}H NMR analysis. The crude reaction mixture was then purified through silica gel chromatography using ethyl acetate/hexanes (up to 2:1) as the solvent. The major diastereomers were submitted to chiral HPLC analysis and then fully characterized by conventional elemental analysis.

Characterization Data for the Mannich Adducts 3a–j. ***3a.*** The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3a** (50.1 mg, 70%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.86 (d, 2H, J = 7.1 Hz), 7.58−7.55 (m, 1H), 7.49−7.43 (m, 2H), 7.22−7.19 (m, 5H), 5.71 (d, 1H, J = 10 Hz), 4.87 (d, 1H, J = 10 Hz), 2.56 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (63 MHz) δ: 177.5, 161.5, 135.5, 133.1, 129.1, 128.8, 128.7, 128.0, 127.6, 125.1, 73.7, 61.9, 41.9, 22.1. HRMS: calcd for $[C_{18}H_{18}N_2O_4S]^+$ ([M + H]$^+$) m/z 359.1066, found 359.1079. HPLC Chiralpak IA column (Hex/*i*PrOH 95:05, 0.7 mL/min): t_R 26.6 min (major), 28.7 min (minor), >99:1 er. See ref 4.

3b. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3b** (51.6 mg, 72%). ^{1}H NMR (250 MHz, $CDCl_3$) and ^{13}C NMR (63 MHz): identical to those for **3a**. HPLC Chiralpak IA column (Hex/*i*PrOH 95:05, 0.7 mL/min): t_R 26.8 min (minor), 29.3 min (major), >99:1 er. See ref 4.

3c. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3c** (57.2 mg, 73%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.88−7.85 (m, 2H), 7.60−7.45 (m, 3H), 7.26−7.14 (m, 4H), 5.75 (d, 1H, J = 9.8 Hz), 4.86 (d, 1H, J = 9.8 Hz), 2.61 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.5, 162.0, 135.4, 134.6, 133.6, 129.4, 129.3, 128.3, 125.1, 78.8, 61.5, 42.4, 22.4. HRMS: calcd for $[C_{18}H_{17}N_2O_4SCl]^+$ ([M + H]$^+$) m/z 393.0676, found 393.0707. HPLC Chiralpak IA column (Hex/*i*PrOH 90:10, 0.5 mL/min): t_R 26.0 min (major), 30.4 min (minor), 99:1 er.

3d. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was 10:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3d** (56.5 mg, 72%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.85−7.57 (m, 2H), 7.56−7.26 (m, 3H), 7.22−7.12 (m, 5H), 5.70 (d, 1H, J = 9.8 Hz), 4.85 (d, 1H, J = 9.9 Hz), 2.64 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.4, 162.0, 138.0, 135.0, 133.6, 130.3, 129.6, 129.2, 128.2, 128.1, 126.0, 125.1, 73.7, 61.6, 42.4, 22.3. HRMS: calcd for $[C_{18}H_{17}N_2O_4SCl]^+$ ([M + H]$^+$) m/z 393.0676, found 393.0677. HPLC Chiralpak IA column (Hex/*i*PrOH 90:10, 0.5 mL/min): t_R 19.6 min (major), 22.4 min (minor), 96:4 er.

3e. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3e** (39.9 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, 1H, J = 7.8 Hz), 7.67−7.62 (m, 2H), 7.56−7.32 (m, 5H), 5.60 (d, 1H, J = 11.1 Hz), 5.27 (d, 1H, J = 11.1 Hz), 2.66 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (75 MHz) δ: 179.4, 162.4, 135.1, 134.5, 133.7, 130.3, 130.1, 129.2, 129.0, 128.5, 128.0, 125.5, 73.7, 57.3, 41.5, 21.0. HRMS: calcd for $[C_{18}H_{17}N_2O_4SCl]^+$ ([M + H]$^+$) m/z 393.0676, found 393.0681. HPLC Chiralpak IA column (Hex/*i*PrOH 96:4, 0.45 mL/min): t_R 59.4 min (major), 67.9 min (minor), 91:9 er.

3f. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3f** (64.5 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90−7.87 (m, 2H), 7.66−7.60 (m, 1H), 7.53−7.48 (m, 2H), 7.41−7.37 (m, 2H), 7.12−7.10 (m, 2H), 5.67 (d, 1H, J = 9.9 Hz), 4.86 (d, 1H, J = 9.9 Hz), 2.63 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.5, 162.0, 135.1, 133.6, 132.2, 129.5, 129.2, 128.3, 125.1, 123.7, 73.7, 61.5, 42.5, 22.5. HRMS: calcd for $[C_{18}H_{17}N_2O_4SBr]^+$ ([M +

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H]$^+$) m/z 437.0171, found 437.0181. HPLC Chiralpak IB column (Hex/*i*PrOH 97:3, 0.8 mL/min): t_R 44.9 min (major), 54.3 min (minor), 98:2 er.

3g. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3g** (55.6 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90−7.88 (m, 2H), 7.65−7.60 (m, 1H), 7.52−7.47 (m, 2H), 7.28−7.22 (m, 2H), 6.98−6.92 (m, 2H), 5.93 (d, 1H, J = 9.9 Hz), 4.90 (d, 1H, J = 9.9 Hz), 2.63 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.6, 163.4 (d, J = 207 Hz), 162.0, 161.5, 133.6, 131.9, 131.8, 129.8, 129.7, 129.2, 128.3, 125.1, 116.1 (d, J = 22 Hz), 74.0, 61.5, 42.3, 22.3. HRMS: calcd for $[C_{18}H_{17}N_2O_4SF]^+$ ([M + H]$^+$) m/z 377.0971, found 377.0991. HPLC Chiralpak IB column (Hex/*i*PrOH 97:3, 0.8 mL/min): t_R 38.4 min (major), 47.4 min (minor), 98:2 er.

3h. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1 to 2:1) to afford product **3h** (55.4 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89−7.87 (m, 2H), 7.64−7.61 (m, 1H), 7.54−7.49 (m, 4H), 7.39−7.37 (m, 2H), 5.86 (d, 1H, J = 9.8 Hz), 4.98 (d, 1H, J = 9.8 Hz), 2.67 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (125 MHz) δ: 177.2, 161.8, 133.5, 131.3 (q, J = 32.7 Hz), 129.0, 128.1, 128.0 125.7 (q, J = 3.8 Hz), 123.6 (q, J = 270.6 Hz), 73.5, 61.4, 42.3, 22.3. HRMS: calcd for $[C_{19}H_{17}N_2O_4SF_3]^+$ ([M + H]$^+$) m/z 427.0939, found 427.0951. HPLC Chiralpak IB column (Hex/*i*PrOH 97:3, 0.8 mL/min): t_R 41.8 min (major), 52.2 min (minor), 88:12 er.

3i. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was 11:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1) to afford product **3i** (57.3 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70−7.68 (m, 2H), 7.56−7.53 (m, 1H), 7.44−7.40 (m, 2H), 7.29−7.26 (m, 5H), 7.17−7.12 (m, 5H), 5.82 (d, 1H, J = 10.0 Hz), 5.06 (d, 1H, J = 10.0 Hz), 3.85 (d, 1H, J = 13.2 Hz), 3.43 (d, 1H, J = 13.2 Hz), 2.58 (s, 3H). ^{13}C NMR (125 MHz) δ: 176.1, 161.7, 133.5, 133.0, 130.3, 129.2, 128.9, 128.7, 128.2, 127.80, 127.75, 127.3, 124.9, 78.8, 61.7, 42.0, 41.7. HRMS: calcd for $[C_{24}H_{22}N_2O_4S]^+$ ([M + H]$^+$) m/z 435.1379, found 435.1385. HPLC Chiralpak IA column (Hex/*i*PrOH 95:5, 0.5 mL/min): t_R 38.8 min (major), 45.8 min (minor), >99:1 er.

3j. The diastereoisomeric ratio from ^{1}H NMR analysis of the crude reaction mixture was >19:1 (*anti*/*syn*). The product was purified by column chromatography on silica gel (hexanes/AcOEt 3:1) to afford product **3i** (47.5 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91−7.87 (m, 2H), 7.64−7.58 (m, 1H), 7.51−7.46 (m, 2H), 7.11−7.02 (m, 4H), 5.74 (d, 1H, J = 10.0 Hz), 4.84 (d, 1H, J = 10.0 Hz), 2.56 (s, 3H), 2.25 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.8, 161.7, 139.2, 133.3, 132.8, 129.7, 129.1, 128.2, 127.7, 125.4, 74.0, 61.9, 42.2, 22.4, 21.3. HRMS: calcd for $[C_{19}H_{20}N_2O_4S]^+$ ([M + H]$^+$) m/z 373.1222, found 373.1240. HPLC Chiralpak IA column (Hex/*i*PrOH 95:5, 0.5 mL/min): t_R 41.1 min (minor), 53.4 min (major), >99:1 er.

Procedure for Azlactone Opening/Amide Deprotection of Mannich Adduct 3b. To a solution of **3b** (35.0 mg, 0.098 mmol) in 2 mL of CH_3CN was added HCl (12 mol·L^{-1}, 0.04 mL, 0.56 mmol). The mixture was stirred for 1 h at rt, and then the volatile materials were removed under reduced pressure to give intermediate **4**. To the crude product was added 2 mL of concentrated HCl, and the reaction was stirred at 100 °C for 10 h. The resulting mixture was concentrated under reduced pressure, diluted with water (5 mL), and washed three times with ethyl acetate (3 mL each one). Amino acid **5** (22.5 mg, 0.072 mmol, 75% yield) was obtained by purification through Amberlite IR 120 resin (HCl).

4. ^{1}H NMR (500 MHz, CD_3OD) δ: 8.06 (d, 1H, J = 10.0 Hz), 7.94 (br, 1H), 7.68−7.66 (m, 2H), 7.56−7.53 (m, 1H), 7.49−7.45 (m, 4H), 7.35−7.32 (m, 2H), 7.30−7.27 (m, 1H), 5.06 (d, 1H, J = 9.5 Hz), 2.60 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ: 172.8, 166.6, 138.0, 134.1, 131.6, 128.4, 128.2, 128.0, 127.8, 127.1, 62.5, 61.2, 41.3, 19.5. HRMS: calcd for $[C_{18}H_{20}N_2O_5S]^+$ ([M + Na]$^+$) m/z 399.0991, found 399.0982.

5. ^{1}H NMR (500 MHz, D_2O) δ: 7.50−7.46 (m, 5H), 2.68 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, D_2O + dioxane) δ: 173.4, 135.7, 131.8, 131.3, 130.4, 74.2, 64.1, 42.6, 20.8. HRMS: calcd for $[C_{11}H_{17}ClN_2O_4S]^+$ ([M − Cl]$^+$) m/z 273.0909, found 273.0897.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra and HPLC traces and X-ray crystallographic details (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1005467 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor Fernando Coelho in recognition of his outstanding contributions to Brazilian chemistry.

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