Parallel Synthesis of Novel Heteroaromatic Acromelic Acid Analogues from Kainic Acid

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A range of new C-4 heteroaromatic acromelic acid analogues has been synthesized in a parallel fashion from (−)-α-kainic acid **1**. Protection of the amine and carboxylate groups of **1** followed by ozonolysis gave methyl ketone **8**. A silyl enol ether **9**, generated regiospecifically from the methyl ketone **8** using "kinetic" conditions, was brominated in situ with phenyltrimethylammonium perbromide to give the key α-bromo ketone **10**. Parallel cyclization reactions of bromo ketone **10** with thioamides and thioureas were then performed. The aromatic heterocyclic derivatives **11a**−**d** and **19** produced were deprotected to give the new kainoid amino acids **6a**−**d** and **25** in excellent yield. Compounds **6a** and **6c** show strong binding to the kainate receptor. Reaction of **10** with alternative condensing agents was also briefly investigated.

Introduction

The kainoid family of nonproteinogenic amino acids includes (−)-α-kainic acid (**1**), (−)-domoic acid (**2**), and the acromelic acids A (**3**) and B (**4**) among its members (Figure 1).[1] This interesting class of compounds displays potent biological activity, namely insecticidal,[2] anthelmintic,[3] and most significantly, potent neuroexcitatory activity.[1,4] They act as conformationally restricted analogues of the neurotransmitter L-glutamic acid, the primary excitatory neurotransmitter in the mammalian central nervous system (CNS), which acts at a number of different receptors.[5] Kainoids show predominant activity at the kainate subclass of ionotropic glutamate receptors and new ligands that behave selectively as agonists or antagonists are highly sought after as tools for neuropharmacological research into the functioning of these receptors in the CNS.[6]

Several concise syntheses of the naturally occurring kainoids and 'unnatural' C-4 analogues (e.g., **5a**−**d**) have been carried out by others[1,7] and by us.[8] We have recently reported in preliminary form a rapid route to C-4 thiazole and aminothiazole acromelic acid analogues starting from commercially available (−)-α-kainic acid (**1**).[9] Herein, we wish to report in detail the parallel synthesis of heteroaromatic kainoid analogues **6a**−**d** and approaches to other C-4 aromatic heterocyclic kainoids.

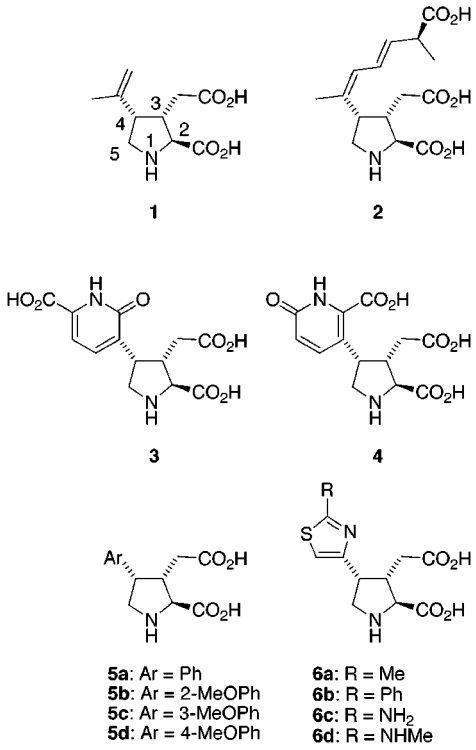

Figure 1. Kainoid family and analogues.

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(1) For a comprehensive review, see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149.

(2) Maeda, M.; Kodama, T.; Tanaka, T.; Yoshizumi, H.; Takemoto, T.; Nomoto, K.; Fujita, T. *Chem. Pharm. Bull.* **1986**, *34*, 4892.

(3) (a) Watase, H.; Tomiie, Y.; Nitta, I. *Nature (London)* **1958**, *181*, 761. (b) Daigo, K. *J. Pharm. Soc. Jpn.* **1959**, *79*, 350.

(4) (a) Meldrum, B.; Garthwaite, J. *Trends Pharmacol. Sci.* **1990**, *11*, 379. (b) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939. (c) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807. (d) Shirahama, H. In *Organic Synthesis in Japan Past, Present and Future*; Noyori, R., Ed.; Tokyo Kagaku Dozin Co. Ltd.: Tokyo, 1992; p 373.

(5) (a) Cantrell, B. E.; Zimmerman, D. M.; Monn, J. A.; Kamboj, R. K.; Hoo, K. H.; Tizzano, J. P.; Pullar, I. A.; Farrell, L. N.; Bleakman, D. *J. Med. Chem.* **1996**, *39*, 3617 and references cited therein.

(6) (a) Mayer, M. *Nature* **1997**, *389*, 542. (b) Clarke, V. R. J.; Ballyk, B. A.; Hoo, K. H.; Mandelzys, A.; Pellizzari, A.; Bath, C. P.; Thomas, J.; Sharpe, E. F.; Davies, C. H.; Ornstein, P. L.; Schoepp, D. D.; Kamboj, R. K.; Collingridge, G. L.; Lodge, D.; Bleakman, D. *Nature* **1997**, *389*, 599.

(7) Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, *62*, 2314.

(8) (a) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5233. (b) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5255. (c) Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5273. (d) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1997**, *39*, 707. (e) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1998**, *54*, 7465.

(9) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 309.

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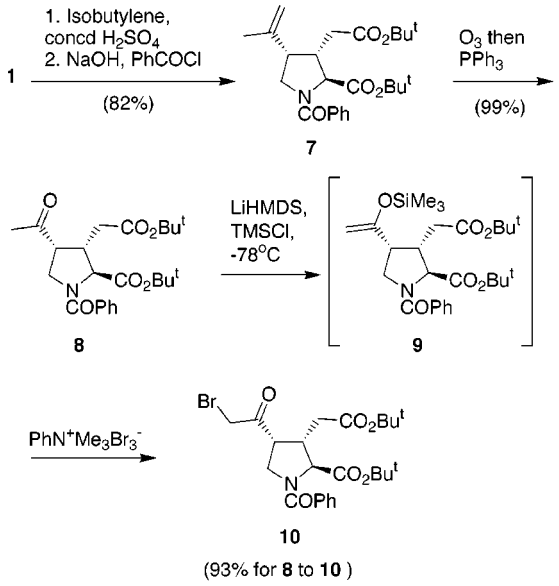
Scheme 1. Synthesis of Bromo Ketone 10

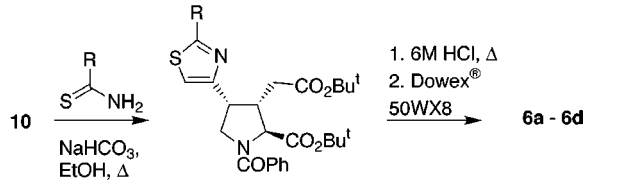


Results and Discussion

Our synthetic route uses **1** as a starting material, and our overall aim has been to convert the C-4 isopropylidine substituent into a number of different reactive groups from which libraries of substituted aromatic heterocycles can be produced by standard cyclization reactions. Typical reactive groups include 1,2-dicarbonyl, 1,3-dicarbonyl, acetylenic ketone, and α-bromo ketone functionalities that would each undergo different cyclization reactions, forming diverse families of C-4 heteroaromatic acromelic acid analogues. In the present study, an α-bromo ketone was chosen as the reactive unit for the C-4 position. Preliminary investigation of protecting group strategies revealed that subsequent chemistry was problematic with methyl esters protecting the carboxylic acids. In addition, protection of the amine as the *tert*-butyloxy carbamate was found not to fully withstand the later cyclization reactions. The more sterically hindered *tert*-butyl esters were therefore chosen to protect the carboxylic acids and the less acid-labile benzoyl group was used to protect the amine. In a one-pot procedure **1** was esterified with isobutylene and concentrated sulfuric acid in 1,4-dioxane, basified with aqueous sodium hydroxide and acylated on nitrogen using benzoyl chloride (Scheme 1). Olefin **7** was obtained in good yield and was then treated with ozone in methanol and dichloromethane at −78 °C. A reductive workup using triphenylphosphine gave a high yield of methyl ketone **8**.

Bromination of methyl ketone **8** under acidic conditions led to mixtures of brominated products and epimerization of the C-4 stereocenter. The bromination of **8** therefore had to be carried out using basic conditions under kinetic control so that bromination took place on the methyl group rather than at the C-4 ring position. Initial studies focused on generating a kinetic enolate from **8** by treatment with LiHMDS in tetrahydrofuran at −78 °C. This enolate was then quenched at −78 °C with molecular bromine or NBS giving disappointing yields of the bromo ketone **10**. Silyl enol ethers can be generated regioselectively from unsymmetrical ketones with the appropriate choice of conditions.[10] Regiospecific bromination of an unsymmetrical ketone can therefore be achieved via the bromination of a requisite silyl enol ether.[11] Treatment of **8** with lithium hexamethyldisilylamide in tetrahydrofuran at −78 °C in the presence of excess trimethylsilyl chloride gave the silyl enol ether **9**, which was not isolated but treated directly with the brominating agent. The use of NBS as brominating agent led to a mixture of brominated products from which **10** was obtained in 42% yield. It was gratifying, however, to find that treatment of **9** with phenyltrimethylammonium perbromide (PTAB) produced much better results, giving the desired bromo ketone **10** as a single isomer in 93% yield after purification by silica gel chromatography.

Table 1. Preparation and Deprotection Reactions of C-3 C-4 *cis*-Acromelic Acid Analogues



R	cyclized product	yield (%)	deprotected kainoid	yield (%)
Me	**11a**	99	**6a**	100
Ph	**11b**	91	**6b**	100
NH_2	**11c**	100	**6c**	97
NHMe	**11d**	100	**6d**	100

With **10** now readily available, parallel cyclization reactions were investigated. Our initial target C-4 heterocycles were thiazole and aminothiazoles, which could be accessed by reacting **10** with thioamides and thioureas (Hantzsch synthesis).[12] Typical thioamides and thioureas were chosen to demonstrate the feasibility of this route. The cyclization procedure involved heating **10** with 1 equiv of the condensing agent and 1 equiv of sodium bicarbonate in ethanol under reflux (Table 1). Cyclized products **11a**−**d** were obtained in excellent yield with little or no purification necessary. Deprotection of **11a**−**d** was achieved by heating under reflux in 6 M hydrochloric acid, and purification by ion-exchange chromatography using Dowex 50WX8 removed liberated benzoic acid, giving the free kainoid amino acids **6a**−**d** in excellent yields. Initially, problems were encountered with the deprotection of the aminothiazole derivative **11d**. If the deprotection was left on for extended periods, some epimerization at C-4 was observed, but provided the reaction time was approximately 5 h, hydrolysis of the benzamide was complete before epimerization took place. This epimerization raised concerns that the other compounds **6a**−**c** could have epimerized during the deprotection step. We therefore sought means of confirming that the C-4 stereochemistry was still correct and that epimerization had not taken place to give the more thermodynamically stable C-3, C-4 trans compounds. ^{1}H NMR NOE experiments with the deprotected compounds **6a** and **6b** indicated that the stereochemistry around the pyrrolidine ring was the desired 4*S* configuration (Figure 2).

Unfortunately, **6a**−**d** could not be recrystallized successfully for X-ray crystallographic analysis and so final

(10) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(11) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, 194.

(12) (a) Dickey, J. B.; Byers, J. R. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 31. (b) Metzger, J. V. In *Comprehnsive Heterocyclic Chemistry*, 1st ed.; Katritzky, A. R., Rees, C. W., Eds.; 1984; Vol. 6, p 294.

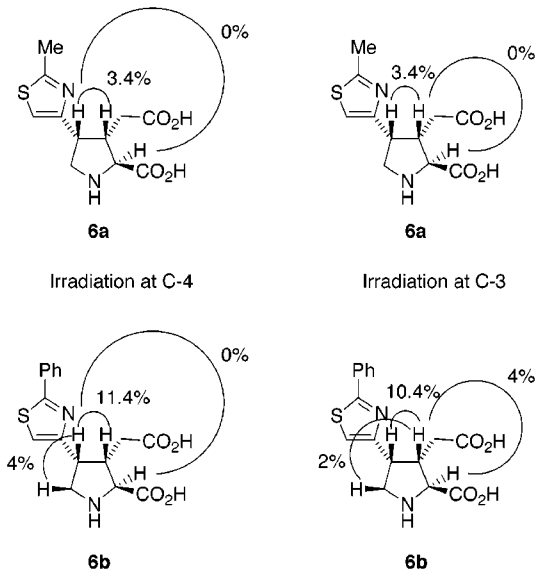
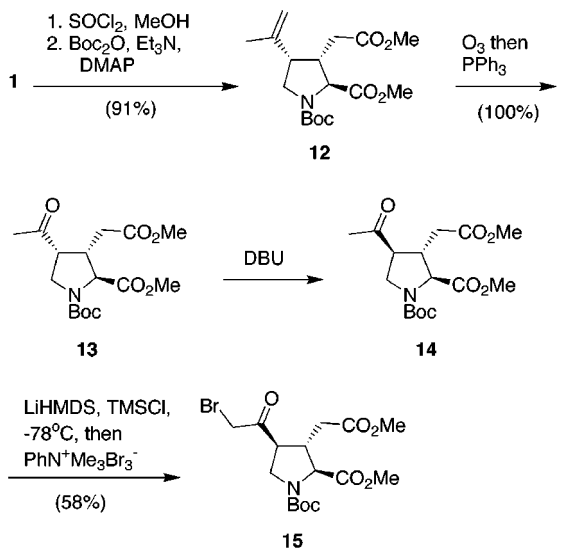


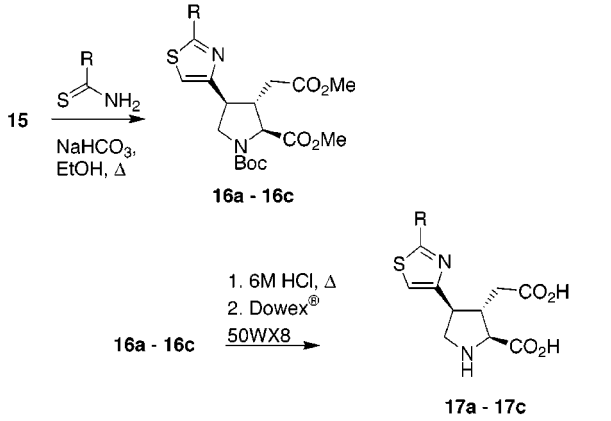
Figure 2. NOE experiments for **6a** and **6b**.

Scheme 2. Synthesis of Bromo Ketone 15



confirmation of stereochemistry was obtained by synthesising their C-4 epimers possessing the undesired 4*R* configuration. Methyl ketone **13** was in hand from our earlier protecting group investigations and was deliberately epimerized at C-4 with DBU in toluene at room temperature (Scheme 2). Complete epimerization could not be facilitated even after the reaction mixture was heated under reflux for 16 h. A 5:1 mixture of C-4 epimers was obtained in favor of the isomer with the 4*R* configuration (Note: major isomer only shown in Scheme 2 and reported in the Experimental Section). Separation of the two epimers was difficult, and so the 5:1 mixture was brominated using the same procedure as described above. The epimeric bromides produced were more readily separated by column chromatography, and bromo ketone **15** was obtained as a single isomer in a yield of 58% (two steps). Cyclization reactions of **15** with thioacetamide, thiourea, and *N*-methylthiourea were performed to give the thiazole derivatives **16a**−**c**. Deprotection was achieved as before by refluxing **16a**−**c** in 6 M hydrochloric acid, and ion-exchange chromatography using Dowex 50WX8 gave the amino acids **17a**−**c** with the 4*R* configuration (Table 2). Comparison of the ^{1}H NMR data for the two

Table 2. Preparation and Deprotection Reactions of C-3, C-4 *trans*-Acromelic Acid Analogues



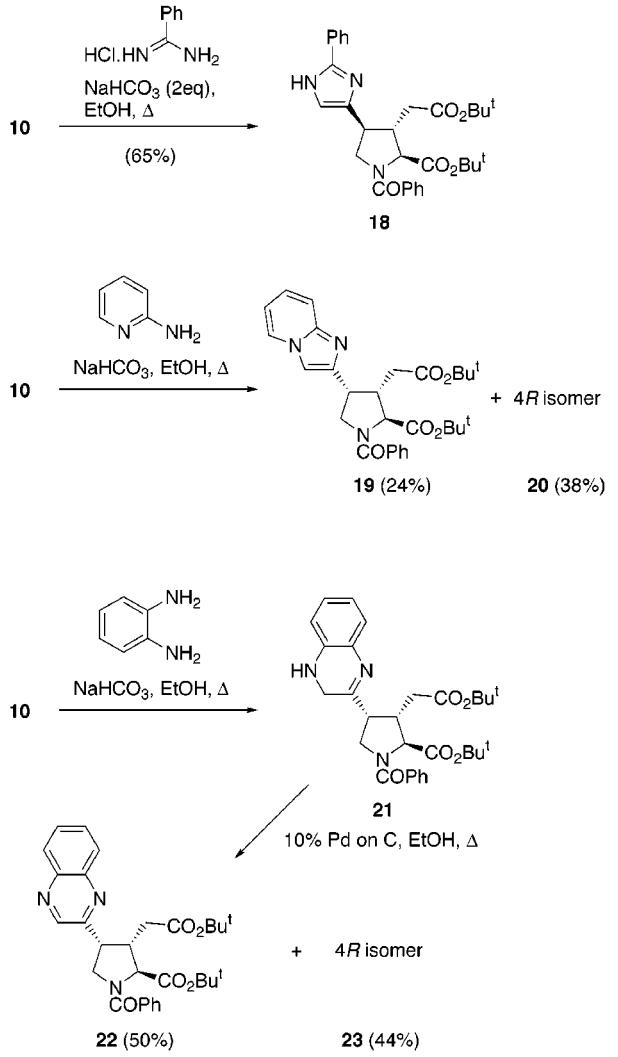
R	cyclized product	yield (%)	deprotected kainoid	yield (%)
Me	**16a**	55%	**17a**	99%
NH_2	**16b**	97%	**17b**	95%
NHMe	**16c**	93%	**17c**	96%

sets of C-4 epimers **6a**, **6c**, and **6d** and **17a**−**c** indicated that the C-4 stereochemistry of **6a**, **6c**, and **6d** was indeed correct. We have recently noted an empirical rule for assigning C-4 stereochemistry to both protected and unprotected kainoid amino acids.[13] When both C-4 epimers are available, the rule states that in the ^{1}H NMR spectra for the pair of C-4 epimers one of the methylene protons on the C-3 side chain of the correct 4*S* isomer appears at lower chemical shift than the corresponding proton for the undesired 4*R* isomer. In addition, the rule states that the difference in chemical shift between the two individual methylene protons for the 4*S* isomer is significantly greater than the corresponding difference for the 4*R* isomer. This rule was in full agreement with the pairs of epimers **6a** and **17a**, **6c** and **17b**, and **6d** and **17c**. Shirahama has also reported an empirical rule concerning the relative positions of the C-4 protons in pairs of unprotected C-4 epimers, and this rule also holds for these pairs of epimers.[14]

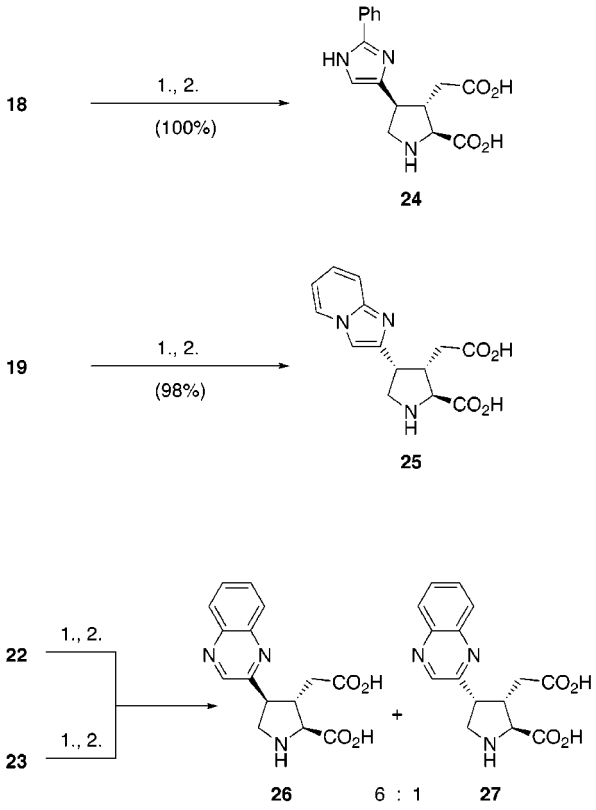
It was our aim to prepare other heterocycles from bromo ketone **10** in addition to thiazoles and aminothiazoles. Cyclization reactions of **10** with benzamidine, 2-aminopyridine, and 1,2-phenylenediamine were thus investigated (Scheme 3). Unfortunately, benzamidine cyclized significantly more slowly with **10** than the reactions involving thioamides and thioureas and proved to be too basic (pK_a 11.6 in water at 20 °C).[15] This caused epimerization at C-4, giving the imidazole derivative **18** in 65% yield. The cyclization with 2-aminopyridine (pK_a 6.82 in water at 20 °C)[15] was more promising, producing the [1,2-*a*]imidazopyridine **19** in 24% yield. Some C-4 epimerization also occurred, however, and the undesired epimer **20** was isolated in 38% yield, although surprisingly, this epimer was unstable and suffered decomposition before it could be fully characterized. Finally, cyclization of **10** with 1,2-phenylenediamine (pK_a 4.47 in water at 20 °C)[15] proceeded as planned, giving the dihydroquinoxaline derivative **21** without any epimer-

(13) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2597.
(14) Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem.* **1996**, *61*, 4685.
(15) Perrin, D. D. In *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965.

Scheme 3. Reactions of 10 with Diamines



Scheme 4. Deprotection of Nitrogen Heterocyclics[a]



[a] Reagents: (1) 6 M HCl (aq), Δ; (2) Dowex 50WX8 ion-exchange.

ization at C-4. Oxidation to the desired quinoxaline **22** did not occur under the reaction conditions but was achieved by an aerial oxidation using 10% palladium on carbon in refluxing ethanol. The oxidation process did, however, cause epimerization at C-4, and the undesired quinoxaline epimer **23** was also obtained.

Deprotection of **18**, **19**, **22**, and **23** was carried out as before followed by ion-exchange chromatography on Dowex 50WX8 (Scheme 4). The C-4 imidazole derivative **24** with the undesired 4*R* isomer was obtained quantitatively from **18**, and its structure was confirmed by X-ray crystallography.[16] [1,2-*a*]Imidazopyridine kainoid analogue **25** was produced in 98% yield, but deprotection of the pair of quinoxalines **22** and **23** gave the same 6:1 ratio of C-4 epimers **26**, **27** in each case (in favor of the undesired 4*R* isomer). The epimerization in this particular deprotection reaction was presumably taking place as a consequence of the inherent weak basicity of the quinoxaline substituent (the pK_a of quinoxaline itself is 0.7 in water at 20 °C).[15]

Biological Data

With our target C-4 thiazole and aminothiazole acromelic acid analogues in hand, initial biological assessment was undertaken. Compounds **6a**−**d** were screened against the kainate receptor for K_i values, and compounds **5a**−**d** were also screened for comparison. The results are summarized in Table 3.

Table 3. K_i Values in μM for Compounds 6a−d and 5a−d

compd	K_i (μM)	compd	K_i (μM)
6a	0.006	**5a**	0.1
6b	0.29	**5b**	0.01
6c	0.005	**5c**	0.04
6d	0.016	**5d**	1.3

It can be seen that compounds **6a**, **6c**, and **6d** all show strong binding to the kainate receptor. Compounds **6a** and **6d** show a stronger binding than **5b**, which was previously reported as the most active compound. The route, reported in this paper, thus allows chemists and neuropharmacologists to access a range of very active acromelic acid analogues easily.

Summary

A parallel synthesis of new C-4 heteroaromatic kainoid amino acids has been investigated. The route focused on a key bromo ketone **10**, which was efficiently synthesized in three steps from commercially available (−)-α-kainic acid **1**. New C-4 thiazole and aminothiazole acromelic acid analogues **6a**−**d** were produced by standard cyclization reactions of thioamides and thioureas with **10** followed by deprotection. This process should allow the rapid preparation of a number of related thiazole and aminothiazole kainoid amino acids, which will be valuable as neuropharmacological probes. New kainoids **6a**−**d** are currently undergoing further biological evaluation, and initial results have shown that compounds **6a** and **6c** are twice as active as **5b** and are thus the most

(16) Full structure refinement was not carried out; a copy of the structure is given in the Supporting Information.

potent neuroexcitatory kainoids known. Synthesis of other C-4 heterocycles from bromo ketone **10** was also investigated but problems with epimerization at C-4 were encountered due to the basicity of the condensing agents employed. The new [1,2-*a*]imidazopyridine kainoid analogue **25** was synthesized by this route but not as efficiently as the thiazoles and aminothiazoles. Further work toward synthesising other reactive units at C-4 from which other heterocycles can be produced is currently in progress. We are also studying the use of alternative protecting groups in the system so that milder deprotection conditions can be employed to obtain the kainoid amino acids without C-4 epimerization. The results of these studies will be reported in due course.

Experimental Section

General Methods. All solvents and reagents were purified by standard techniques reported in *Purification of Laboratory Chemicals* (Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988) or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a water or dry ice condenser as necessary. Flash chromatography was carried out using Sorbsil C60 (40−63 mm, 230−40 mesh) silica gel as stationary phase. Thin-layer chromatography was carried out on aluminum plates precoated with Merck silica gel 60 F_{254} which were visualized by quenching of UV fluorescence or by staining with 10% w/v ammonium molybdate in 2 M sulfuric acid (followed by heat) as appropriate. Other general experimental information and spectroscopic instrumentation used have been described in ref 8e. ^{13}C NMR in D_2O are referenced internally to 1,4-dioxane.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-isopropylidenylpyrrolidine (7). To a solution of **1** monohydrate (300 mg, 1.29 mmol) in 1,4-dioxane (3 mL) at 0 °C with stirring was added concentrated sulfuric acid (0.612 mL) dropwise. Isobutylene (4.5 mL (excess)) was added, and the reaction was sealed and allowed to warm to room temperature for 62 h. After being cooled to 0 °C, the reaction vessel was opened and a solution of sodium hydroxide (785 mg, 19.6 mmol) in water (4 mL) was added dropwise with vigorous stirring. Benzoyl chloride (302 μL, 2.60 mmol) was added, and stirring continued for 22 h at room temperature. After removal of the solvent in vacuo, the residue was taken up into chloroform and the organics were washed with water. The aqueous phase was extracted with chloroform, and the combined organics were washed with saturated brine. The organics were dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (9:1 v/v) to give **7** (455 mg, 82%) as a white crystalline solid: mp 114−116 °C; $[\alpha]^{22}_D$ −39.0 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1728s, 1630s; ^1H NMR (200 MHz; $CDCl_3$) mixture of rotamers; δ 1.35, 1.37, 1.47, 1.52 (18H, 4 × s), 1.65, 1.77 (3H, 2 × s), 1.93−2.51 (2H, complex), 2.69−3.17 (2H, complex), 3.43−3.96 (2H, complex), 4.21, 4.32 (1H, 2 × d, J = 6, 3 Hz), 4.55−5.02 (2H, complex), 7.29−7.63 (5H, complex); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers; δ 21.92, 22.61, 27.64, 27.78, 27.93, 28.29, 34.20, 34.45, 41.29, 43.03, 44.56, 46.72, 47.03, 52.34, 64.25, 66.58, 81.00, 81.75, 82.16, 113.39, 114.15, 126.86, 127.28, 128.53, 129.94, 130.42, 136.24, 136.79, 140.69, 142.17, 169.84, 170.78, 171.32, 171.44; MS (APCI+) *m*/*z* 430 (MH^+, 100). Anal. Calcd for $C_{25}H_{35}NO_5$: C, 69.89; H, 8.22; N, 3.26. Found: C, 69.54; H, 8.24; N, 3.12.

(2*S*,3*S*,4*S*)-Acetyl-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-pyrrolidine (8). A solution of **7** (666 mg, 1.55 mmol) in methanol (15 mL) and dichloromethane (10 mL) was cooled to −78 °C, and ozone was bubbled through this solution for 45 min. Triphenylphosphine (447 mg, 1.71 mmol) was added, and the reaction was warmed to room temperature and stirred for 1 h. The reaction was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (9:1 v/v) to give **8** (660 mg, 99%) as a white crystalline solid: mp 135−137 °C; $[\alpha]^{22}_D$ −12.6 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1720s, 1634s; ^1H NMR (200 MHz; $CDCl_3$) mixture of rotamers; δ 1.28, 1.39, 1.46, 1.52 (18H, 4 × s), 2.15, 2.25 (3H, 2 × s), 2.21−2.57 (2H, complex), 2.78−3.02 (1H, m), 3.45−3.65 (1H, m), 3.67−4.13 (2H, complex), 4.22, 4.40 (1H, 2 × d, J = 5, 5 Hz), 7.29−7.60 (5H, complex); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers; δ 27.58, 27.90, 30.46, 30.72, 34.50, 34.76, 40.85, 42.97, 46.78, 49.82, 50.06, 51.65, 64.90, 66.54, 81.37, 81.47, 82.04, 82.45, 127.06, 127.35, 128.53, 130.12, 130.49, 135.91, 136.39, 170.09, 170.62, 170.96; MS (APCI+) *m*/*z* 432 (MH^+, 100).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-4-(bromoacetyl)-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethylpyrrolidine (10). To a 1 M solution of lithium hexamethyldisilylamide (365 μL, 0.37 mmol) at −78 °C under an argon atmosphere was added chlorotrimethylsilane (320 μL, 2.44 mmol) dropwise. A cold (−78 °C) solution of **8** (105 mg, 0.24 mmol) in tetrahydrofuran (1.2 mL) was then added dropwise. After being stirred for 25 min at −78 °C, the reaction mixture was warmed to 0 °C and phenyltrimethylammonium tribromide (93 mg, 0.25 mmol) was added. The reaction was stirred at 0 °C for 30 min and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (9:1 v/v) to give **10** (115 mg, 93%) as a white crystalline solid: mp 159−160 °C; $[\alpha]^{22}_D$ +23.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1732s, 1638s; ^1H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.29, 1.40, 1.44, 1.52 (18H, 4 × s), 2.30−2.56 (2H, complex), 2.82−3.04 (1H, m), 3.71−4.26 (5H, complex), 4.42, 4.43 (1H, 2 × d, J = 5, 5 Hz), 7.30−7.61 (5H, complex); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 27.64, 27.95, 34.63, 34.80, 41.18, 43.35, 47.75, 47.92, 48.19, 48.63, 50.17, 50.52, 65.16, 66.75, 81.65, 82.14, 82.55, 126.90, 127.09, 128.34, 129.98, 130.35, 135.50, 136.00, 169.66, 170.01, 170.62, 170.88, 200.21, 200.80; MS (APCI+) *m*/*z* 512, 510 (MH^+, 19 and 34); HRMS *m*/*z* calcd for $C_{24}H_{33}{}^{81}BrNO_6$ (MH^+) 512.1471, obsd 512.1471; HRMS *m*/*z* calcd for $C_{24}H_{33}{}^{79}BrNO_6$ (MH^+) 510.1491, obsd 510.1491.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2′-methylthiazol-4′-yl)pyrrolidine (11a). To a stirred solution of **10** (19.0 mg, 0.037 mmol) in ethanol (1 mL) were added thioacetamide (2.8 mg, 0.037 mmol) and sodium bicarbonate (3.1 mg, 0.037 mmol). The reaction was heated under reflux for 2 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (9:1 v/v) to give **11a** (18.0 mg, 99%) as a white crystalline solid: mp 163−165 °C; $[\alpha]^{22}_D$ −36.9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1732s, 1630s; ^1H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.29, 1.35, 1.44, 1.52 (18H, 4 × s), 1.90−2.57 (2H, complex), 2.64, 2.71 (3H, 2 × s), 2.90−3.09 (1H, m), 3.63−4.12 (3H, complex), 4.33, 4.36 (1H, 2 × d, J 5, 9 Hz), 6.64, 6.85 (1H, 2 × s), 7.31−7.62 (5H, complex); ^{13}C NMR (100.6 MHz; $CDCl_3$) mixture of rotamers δ 19.28, 19.33, 27.74, 27.91, 28.06, 34.63, 34.85, 40.69, 42.55, 42.75, 44.72, 49.78, 54.20, 63.81, 66.19, 80.72, 80.81, 81.63, 82.09, 114.32, 114.63, 126.88, 127.24, 128.24, 128.29, 129.70, 130.10, 136.20, 153.22, 153.61, 165.90, 169.84, 170.61, 170.75, 170.85, 171.01; MS (APCI+) *m*/*z* 487 (MH^+, 100); HRMS *m*/*z* calcd for $C_{26}H_{35}SN_2O_5$ (MH^+) 487.2267, obsd 487.2267.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2′-phenylthiazol-4′-yl)pyrrolidine (11b). To a stirred solution of **10** (37.0 mg, 0.073 mmol) in ethanol (2 mL) were added thiobenzamide (10.0 mg, 0.073 mmol) and sodium bicarbonate (6.1 mg, 0.073 mmol). The reaction was heated under reflux for 4 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium

bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (19:1 v/v) to give **11b** (36.0 mg, 91%) as a white crystalline solid: mp 110−112 °C; $[\alpha]^{22}_D$ −80.0 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1732brs, 1631s; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers, major rotamer only assigned δ 1.43, 1.54 (2 × 9H, 2 × s), 2.05 (1H, ca. dd, *J* = 17, 11 Hz), 2.62 (1H, ca. dd, *J* = 17, 8 Hz), 2.93−3.13 (1H, m), 3.72−3.91 (2H, complex), 4.06−4.15 (1H, m), 4.51 (1H, d, *J* = 10 Hz), 6.84 (1H, s), 7.32−7.63 (8H, complex), 7.92−7.99 (2H, complex); ^{13}C NMR (100.6 MHz; $CDCl_3$) mixture of rotamers, major rotamer assigned only; δ 27.94, 28.07, 34.68, 42.70, 42.96, 54.67, 63.73, 80.72, 81.62, 114.92, 126.44, 127.37, 128.22, 128.93, 130.11, 133.36, 136.27, 155.05, 168.46, 169.91, 170.92, 171.17; MS (APCI+) *m*/*z* 549 (MH^+, 27); HRMS *m*/*z* calcd for $C_{31}H_{37}SN_2O_5$ (MH^+) 549.2423, obsd 549.2423.

(2*S*,3*S*,4*S*)-4-(2′-Aminothiazol-4′-yl)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethylpyrrolidine (11c). To a stirred solution of **10** (50.0 mg, 0.098 mmol) in ethanol (2.5 mL) was added thiourea (7.5 mg, 0.098 mmol) and sodium bicarbonate (8.2 mg, 0.098 mmol). The reaction was heated under reflux for 1 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$), the solvent was removed in vacuo to give **11c** (56.0 mg, 100%) as a colorless gum: $[\alpha]^{22}_D$ −30.7 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1732brs, 1626brs; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.29, 1.36, 1.44, 1.52 (18H, 4 × s), 2.05−2.19 (1H, m), 2.53 (1H, ca. dd, *J* = 17, 5 Hz), 2.82−3.02 (1H, m), 3.53−3.73, 3.93−4.05 (3H, complex), 4.32, 4.40 (1H, 2 × d, *J* = 3, 9 Hz), 5.09, 5.12 (2H, 2 × brs), 6.03, 6.22 (1H, 2 × s), 7.35−7.60 (5H, complex); ^{13}C NMR (100.6 MHz; $CDCl_3$) mixture of rotamers δ 27.73, 27.91, 28.06, 34.51, 40.65, 42.49, 42.70, 44.57, 48.51, 53.98, 64.10, 66.22, 80.68, 81.58, 104.58, 126.86, 127.24, 128.25, 129.74, 130.11, 136.14, 149.91, 167.85, 170.01, 170.77, 171.18; MS (APCI+) *m*/*z* 488 (MH^+, 100); HRMS *m*/*z* calcd for $C_{25}H_{34}SN_3O_5$ (MH^+) 488.2219, obsd 488.2219.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2′-(methylamino)thiazol-4′-yl)-pyrrolidine (11d). To a stirred solution of **10** (51.0 mg, 0.10 mmol) in ethanol (1.5 mL) were added *N*-methylthiourea (9.0 mg, 0.10 mmol) and sodium bicarbonate (8.4 mg, 0.10 mmol). The reaction was heated under reflux for 0.5 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the combined organics washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (1:1 v/v) to give **11d** (50.0 mg, 100%) as a white crystalline solid: mp 203−204 °C; $[\alpha]^{22}_D$ −39.9 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1732brm, 1626m; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.27, 1.36, 1.44, 1.51 (18H, 4 × s), 2.04−2.18 (1H, m), 2.53 (1H, ca.. dd, *J* 17, 5 Hz), 2.83−2.99 (1H, m), 2.91, 2.93 (3H, 2 × s), 3.54−3.71 (2H, complex), 3.93−4.05 (1H, m), 4.32, 4.41 (1H, 2 × d, *J* = 5, 9 Hz), 5.09, 5.29 (1H, m), 5.99, 6.20 (1H, 2 × s), 7.31−7.61 (5H, complex); ^{13}C NMR (100.6 MHz; $CDCl_3$) mixture of rotamers δ 27.73, 27.94, 28.07, 31.94, 32.14, 34.58, 40.85, 42.62, 42.79, 44.64, 54.24, 64.02, 66.28, 80.59, 81.47, 102.49, 126.92, 127.33, 128.20, 128.28, 129.71, 130.06, 136.30, 150.45, 169.84, 170.51, 170.98, 171.28; MS (APCI+) *m*/*z* 502 (MH^+, 40); HRMS *m*/*z* calcd for $C_{26}H_{36}SN_3O_5$ (MH^+) 502.2376, obsd 502.2376.

(2*S*,3*S*,4*S*)-3-Methylenecarboxy-4-(2′-methylthiazol-4′-yl)pyrrolidine-2-carboxylic Acid (6a). To **11a** (18 mg, 0.037 mmol) was added 6 M hydrochloric acid (2 mL), and the reaction was heated under reflux for 16 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give **6a** (10 mg, 100%) as a white waxy solid. Free amino acid; $[\alpha]^{25}_D$ +44.7 (c 0.6, H_2O); IR (KBr disk) ν_{max} 3600−2450brs, 1700brs, 1652brs; ^{1}H NMR (500 MHz; D_2O) δ 1.89 (1H, dd, *J* = 16, 10 Hz), 2.48 (1H, dd, *J* = 16, 5 Hz), 2.58 (3H, s), 2.93−2.99 (1H, m), 3.55, 3.57 (1H, dd, *J* = 12, 6 Hz), 3.71, 3.74 (1H, dd, *J* = 12, 7 Hz), 3.86 (1H, dd, *J* = 14, 7 Hz), 3.96 (1H, d, *J* = 8 Hz), 7.02 (1H, s); ^{13}C NMR (125.8 MHz; D_2O) δ 18.32, 35.66, 41.95, 43.73, 49.03, 65.06, 117.21, 150.88, 169.23, 173.77, 177.52; MS (electrospray, positive ion) *m*/*z* 271 (MH^+, 100).

(2*S*,3*S*,4*S*)-3-Methylenecarboxy-4-(2′-phenylthiazol-4′-yl)pyrrolidine-2-carboxylic Acid (6b). To **11b** (32.0 mg, 0.058 mmol) was added 6 M hydrochloric acid (2 mL), and the reaction was heated under reflux for 8 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL), and the resulting solution was evaporated in vacuo to give **6b** (19.5 mg, 100%) as a white solid. Free amino acid: mp 161−165 °C; $[\alpha]^{25}_D$ −9.9 (*c* 0.4, 1 M HCl (aq)); IR (KBr disk) ν_{max} 3700−2000brs, 1721m, 1704s, 1652s; ^{1}H NMR (200 MHz; D_2O) δ 1.73 (1H, dd, *J* = 17, 10 Hz), 2.46 (1H, dd, *J* = 17, 5 Hz), 2.79−2.95 (1H, m), 3.49, 3.55 (1H, dd, *J* = 12, 4 Hz), 3.64, 3.70 (1H, dd, *J* = 12, 7 Hz), 3.79−3.89 (1H, m), 4.00 (1H, d, *J* = 9 Hz), 7.10 (1H, s), 7.31−7.37 (3H, complex), 7.73−7.78 (2H, complex); ^{13}C NMR (125.8 MHz; D2O) δ 35.67, 42.77, 44.09, 49.96, 65.35, 118.37, 127.27, 129.95, 131.35, 133.46, 153.43, 170.32, 173.92, 177.37; MS (electrospray, positive ion) *m*/*z* 333 (MH^+, 100).

(2*S*,3*S*,4*S*)-4-(2′-Aminothiazol-4′-yl)-3-methylenecarboxypyrrolidine-2-carboxylic Acid (6c). To **11c** (26 mg, 0.046 mmol) was added 6 M hydrochloric acid (2 mL), and the reaction was heated under reflux for 12h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give **6c** (14 mg, 97%) as a beige waxy solid. Free amino acid: $[\alpha]^{25}_D$ +9.5 (*c* 0.4, H_2O); IR (KBr disk) ν_{max} 3700−2400brs, 1634brs; ^{1}H NMR (200 MHz; D_2O) δ 1.75 (1H, dd, *J* = 17, 10 Hz), 2.35 (1H, dd, *J* = 17, 5 Hz), 2.64−2.82 (1H, m), 3.31−3.48 (1H, m), 3.49−3.61 (2H, complex), 3.84 (1H, d, *J* 8 Hz), 6.22 (1H, s); ^{13}C NMR (125.8 MHz; D_2O) δ 36.77, 42.07, 44.20, 48.92, 65.54, 106.64, 145.31, 170.90, 174.23, 179.00; MS (electrospray, positive ion) *m*/*z* 272 (MH^+, 100).

(2*S*,3*S*,4*S*)-4-(2′-(Methylamino)thiazol-4′-yl)-3-methylenecarboxypyrrolidine-2-carboxylic Acid (6d). To **11d** (37 mg, 0.074 mmol) was added 6 M hydrochloric acid (2 mL), and the reaction was heated under reflux for 5 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL), and the resulting solution was evaporated in vacuo to give **6d** (21 mg, 100%) as a white waxy solid. Free amino acid: $[\alpha]^{25}_D$ −30.6 (*c* 0.6, H_2O); IR (KBr disk) ν_{max} 3700−2100brs, 1726m, 1708m; ^{1}H NMR (500 MHz; D_2O) δ 2.07 (1H, dd, *J* 16, 10 Hz), 2.51 (1H, dd, *J* 16, 5 Hz), 2.93 (3H, s), 2.95−3.04 (1H, m), 3.59, 3.62 (1H, dd, *J* 11, 5 Hz), 3.70−3.79 (2H, complex), 4.04 (1H, d, *J* 7 Hz), 6.47 (1H, s); ^{13}C NMR (125.8 MHz; D_2O) δ 32.18, 36.94, 41.98, 44.27, 48.75, 65.63, 104.89, 144.60, 172.56, 174.15, 179.17; MS (electrospray, positive ion) *m*/*z* 286 (MH^+, 100).

**(2*S*,3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-isopropylidenylpyrroli-

dine (12). To methanol (5 mL) at 0 °C was added thionyl chloride (0.63 mmol, 8.66 mmol) dropwise. After the addition was complete, **1** monohydrate (500 mg, 2.16 mmol) was added, and the reaction was heated at 60 °C for 16 h. After removal of the solvent in vacuo, the white solid was recrystallized from chloroform/diethyl ether to give (2*S*,3*S*,4*S*)-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-isopropylidenylpyrrolidine hydrochloride as a white crystalline solid. To a solution of (2*S*,3*S*,4*S*)-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-isopropylidenylpyrrolidine hydrochloride (950 mg, 3.41 mmol) in dichloromethane (6 mL) was added triethylamine (804 μL, 5.76 mmol) at room temperature under an atmosphere of argon. A solution of di-*tert*-butyl dicarbonate (990 mg, 4.54 mmol) in dichloromethane (6 mL) was then added dropwise, and the reaction was stirred at room temperature for 3 h. 4-(Dimethylamino)pyridine (10 mg) was then added, and stirring was continued for 1 h. After removal of the solvent in vacuo, the residue was taken up into dichloromethane and the organics were washed with 1 M aqueous citric acid, saturated aqueous sodium bicarbonate, and saturated brine. The organics were dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (12:1 v/v) to give **12** (0.671 g, 91%) as a colorless syrup: $[\alpha]^{23}_D$ −17.8 (*c* 1.2, $CHCl_3$); (lit.[17] $[\alpha]^{25}_D$ −12.7 (*c* 2.1, $CHCl_3$)); IR ($CHCl_3$) ν_{max} 1737s, 1690s; ^{1}H NMR (300 MHz; $CDCl_3$) mixture of rotamers δ 1.38, 1.45 (9H, 2 × s), 1.67 (3H, s), 2.18−2.38 (2H, complex), 2.74−2.87 (1H, m), 2.93−3.03 (1H, m), 3.35−3.48 (1H, m), 3.60−3.72 (1H, m), 3.68, 3.74 (2 × 3H, 2 × s), 4.04, 4.14 (1H, 2 × d, *J* = 4, 3 Hz), 4.67, 4.90 (2 × 1H, 2 × s); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 22.07, 22.17, 27.82, 28.05, 28.22, 32.77, 40.74, 41.72, 45.10, 45.84, 47.45, 47.71, 51.72, 52.00, 52.13, 52.27, 63.58, 63.92, 80.18, 113.28, 113.53, 141.42, 141.55, 153.86, 154.51, 172.54, 172.65, 172.93; MS (APCI+) *m*/*z* 364 (M + Na^+, 88); HRMS *m*/*z* calcd for $C_{17}H_{31}N_2O_6$ (MNH_4^+) 359.2182, obsd 359.2182.

(2*S*,3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-acetylpyrrolidine (13). A solution of **12** (1.200 g, 3.52 mmol) in methanol (20 mL) and dichloromethane (10 mL) was cooled to −78 °C and ozone was bubbled through the solution for 30 min. Triphenylphosphine (0.93 g, 3.52 mmol) was then added, and the reaction was warmed to room temperature and stirred for 1.5 h. The reaction was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (9:1 v/v) to give **13** (1.208 g, 100%) as a colorless syrup: $[\alpha]^{23}_D$ +6.42 (c 1.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1740s, 1710s, 1694s; ^{1}H NMR (300 MHz; $CDCl_3$) mixture of rotamers δ 1.37, 1.43 (9H, 2 × s), 2.18 (3H, s), 2.45−2.68 (2H, complex), 2.78−2.87 (1H, m), 2.89−2.99 (1H, m), 3.41−3.52 (1H, m), 3.58−3.77 (1H, m), 3.67, 3.73 (2 × 3H, 2 × s), 4.13, 4.21 (1H, 2 × d, *J* 6, 4 Hz); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 27.86, 28.03, 28.18, 30.34, 32.56, 33.07, 40.68, 41.94, 46.34, 46.99, 50.34, 51.43, 51.43, 52.20, 52.46, 63.84, 80.55, 153.72, 154.40, 172.15, 172.35, 172.53, 172.89; MS (APCI+) *m*/*z* 366 (M + Na^+, 100); HRMS *m*/*z* calcd for $C_{16}H_{29}N_2O_7$ (MNH_4^+) 361.1975, obsd 361.1975.

(2*S*,3*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-acetylpyrrolidine (14). To a solution of **13** (412 mg, 1.20 mmol) in toluene (7.5 mL) was added DBU (270 μL, 1.80 mmol), and the reaction was stirred under an atmosphere of argon for 14 h. A further portion of DBU (270 μL, 1.80 mmol) was then added, and the reaction was heated under reflux for 1.5 h. The solvent was removed in vacuo, and the residue was taken up into ethyl acetate. The organics were washed sequentially with saturated aqueous sodium bicarbonate, water, and saturated brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give a 5:1 mixture of **14** and **13** (403 mg, 98%) as a colorless syrup which was used in the next reaction without further purification. Limited spectroscopic data obtained for the major isomer **14**: IR (thin film) ν_{max} 1746brs, 1698brs; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.36, 1.44 (9H, 2 × s), 2.18 (3H, s), 2.38−2.70 (2H, complex), 2.90−3.13 (2H, complex), 3.18−3.52 (1H, m), 3.59−3.76 (1H, m), 3.65, 3.71 (2 × 3H, 2 × s), 3.93−4.02 (1H, m); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 28.02, 28.17, 29.13, 30.31, 36.01, 36.48, 40.74, 41.54, 47.98, 51.76, 52.13, 52.30, 54.06, 55.07, 63.39, 63.71, 80.52, 80.66, 153.46, 171.68, 172.08, 172.31, 172.42; MS (Probe CI (NH_3)) *m*/*z* 344 (MH^+, 2); HRMS *m*/*z* calcd for $C_{16}H_{26}NO_7$ (MH^+) 344.1709, obsd 344.1709.

(2*S*,3*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(bromoacetyl)pyrrolidine (15). To a 1 M solution of lithium hexamethyldisilylamide (1.75 mL, 1.75 mmol) at −78 °C under an argon atmosphere was added chlorotrimethylsilane (1.53 mL, 11.66 mmol) dropwise. A cold (−78 °C) solution of **14** (400 mg, 1.17 mmol) in tetrahydrofuran (4.4 mL) was then added dropwise. After being stirred for 25 min at −78 °C, the reaction was warmed to 0 °C, and then phenyltrimethylammonium perbromide (461 mg, 1.23 mmol) was added. After being stirred at 0 °C for 0.5 h, the reaction was concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (12:1 v/v) to give **15** (285 mg, 58%) as a colorless syrup: $[\alpha]^{23}_D$ −30.0 (*c* 1.5, $CHCl_3$); IR (thin film) ν_{max} 1734brs, 1694brs; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.39, 1.41, 1.45 (9H, 3 × s), 2.42−2.78 (2H, complex), 2.94−3.12 (1H, m), 3.33−3.55 (2H, complex), 3.66, 3.74 (2 × 3H, 2 × s), 3.88−4.10 (3H, complex), 4.15 (1H, d, *J* 3 Hz); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 28.02, 28.13, 34.03, 36.01, 36.45, 41.99, 42.49, 42.79, 48.02, 48.81, 49.40, 50.78, 51.12, 51.70, 51.92, 52.24, 52.39, 63.38, 63.75, 80.79, 153.26, 171.77, 171.90, 172.24, 199.87; MS (probe CI (NH_3)) *m*/*z* 424, 422 (MH^+, 23, 23); HRMS *m*/*z* calcd for $C_{16}H_{25}{}^{81}BrNO_7$ (MH^+) 424.0794, obsd 424.0794; HRMS *m*/*z* calcd for $C_{16}H_{25}{}^{79}BrNO_7$ (MH^+) 422.0814, obsd 422.0814.

(2*S*,3*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2′-methylthiazol-4′-yl)pyrrolidine (16a). To a stirred solution of **15** (48.0 mg, 0.11 mmol) in ethanol (1.5 mL) were added thioacetamide (8.5 mg, 0.11 mmol) and sodium bicarbonate (9.6 mg, 0.11 mmol). The reaction was heated under reflux for 4 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$), the solvent was removed in vacuo to give a residue which was purified by flash chromatography on silica gel (eluting with 4:1 v/v dichloromethane/ethyl acetate) to give **16a** (25 mg, 55%) as a pale yellow gum: $[\alpha]^{23}_D$ −21.4 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1737s, 1691s; ^{1}H NMR (400 MHz; $CDCl_3$) mixture of rotamers δ 1.41, 1.45 (9H, 2 × s), 2.52−2.69 (2H, complex), 2.67 (3H, s), 2.93−2.98 (1H, m), 3.24−3.32 (1H, m), 3.57 (3H, s), 3.63−3.77 (1H, m), 3.73, 3.75 (3H, 2 × s), 3.91−4.00 (1H, m), 4.05, 4.11 (1H, 2 × d, *J* 9, 9 Hz), 6.88 (1H, s); ^{13}C NMR (100.6 MHz; $CDCl_3$) mixture of rotamers δ 19.16, 28.20, 28.32, 35.33, 35.57, 44.74, 44.99, 45.59, 45.99, 50.99, 51.72, 51.60, 52.02, 52.21, 63.92, 64.35, 80.33, 114.41, 114.53, 152.78, 153.02, 153.56, 166.11, 171.48, 172.54; MS (APCI+) *m*/*z* 421 (M + Na^+, 32), 399 (MH^+, 20); HRMS *m*/*z* calcd for $C_{18}H_{27}SN_2O_6$ (MH^+) 399.1590, obsd 399.1590.

(2*S*,3*S*,4*R*)-4-(2′-Aminothiazol-4′-yl)-*N*-*tert*-butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethylpyrrolidine (16b). To a stirred solution of **15** (49.0 mg, 0.12 mmol) in ethanol (1.5 mL) were added thiourea (8.8 mg, 0.12 mmol) and sodium bicarbonate (9.8 mg, 0.12 mmol). The reaction was heated under reflux for 1 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$), the solvent was removed in vacuo to give **16b** (45.0 mg, 97%) as a colorless

(17) Papaioannou, D.; Sivas, M.; Kouvelas, E.; Francis, G. W.; Aksnes, D. W. *Acta Chem. Scand.* **1994**, *48*, 831.

gum: $[\alpha]^{23}_D$ −26.1 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3496w, 3397w, 1734s, 1690brs; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.41, 1.44 (9H, 2 × s), 2.38−2.63 (2H, complex), 2.72−2.93 (1H, m), 2.93−3.12 (1H, m), 3.54−3.93 (2H, complex), 3.59, 3.60, 3.74, 3.76 (2 × 3H, 4 × s), 3.93−4.06 (1H, m), 6.04 (1H, brs), 6.19, 6.20 (1H, 2 × s), 6.24 (1H, brs); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 28.14, 28.24, 35.28, 35.45, 44.67, 45.06, 45.47, 45.90, 50.73, 51.40, 51.67, 52.13, 52.39, 63.85, 64.20, 80.37, 80.44, 104.16, 104.29, 148.52, 153.42, 154.15, 169.36, 169.58, 171.87, 173.73; MS (APCI+) *m*/*z* 400 (MH^+, 33); HRMS *m*/*z* calcd for $C_{17}H_{26}SN_3O_6$ (MH^+) 400.1542, obsd 400.1542.

(2*S*,3*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2′-(*N*-methylamino)thiazol-4′-yl)pyrrolidine (16c). To a stirred solution of **15** (53.0 mg, 0.13 mmol) in ethanol (1.5 mL) were added *N*-methylthiourea (11.3 mg, 0.13 mmol) and sodium bicarbonate (10.6 mg, 0.13 mmol). The reaction was heated under reflux for 30 min and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$), the solvent was removed in vacuo to give **16c** (48.0 mg, 93%) as a colorless gum: $[\alpha]^{23}_D$ −22.2 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3432w, 1738s, 1690s; ^{1}H NMR (200 MHz; $CDCl_3$) mixture of rotamers δ 1.40, 1.42, 1.44, 1.46 (9H, 4 × s), 2.41−2.72 (2H, complex), 2.78−3.13 (2H, 2 × m), 2.94 (3H, d, *J* 5 Hz), 3.52−3.96 (2H, complex), 3.59, 3.67, 3.72, 3.73 (2 × 3H, 4 × s), 4.01 (1H, d, *J* 9 Hz), 5.49 (1H, brs), 6.22 (1H, s); ^{13}C NMR (50.3 MHz; $CDCl_3$) mixture of rotamers δ 28.12, 28.24, 32.06, 35.24, 35.46, 44.54, 45.04, 45.50, 45.89, 50.64, 51.37, 51.61, 51.98, 52.18, 64.00, 64.43, 80.20, 80.34, 102.64, 149.64, 153.50, 154.12, 171.55, 171.95, 172.82, 173.07; MS (APCI+) *m*/*z* 414 (MH^+, 63); HRMS *m*/*z* calcd for $C_{18}H_{28}SN_3O_6$ (MH^+) 414.1699, obsd 414.1699.

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-(2′-methylthiazol-4′-yl)pyrrolidine-2-carboxylic Acid (17a). To **16a** (20 mg, 0.048 mmol) was added 2 M hydrochloric acid (3 mL), and the reaction was heated under reflux for 14 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give **17a** (13 mg, 99%) as a beige waxy solid. Free amino acid: $[\alpha]^{23}_D$ −29.3 (*c* 0.5, H_2O); IR (KBr disk) ν_{max} 3700−2200brs, 1724m; ^{1}H NMR (500 MHz; D_2O) δ 2.44 (1H, dd, *J* = 16, 8 Hz), 2.54 (3H, s), 2.68 (1H, dd, *J* = 16, 5 Hz), 2.71−2.77 (1H, m), 3.42−3.49 (2H, complex), 3.61−3.66 (1H, m), 3.89 (1H, d, *J* = 10 Hz), 7.10 (1H, s); ^{13}C NMR (125.8 MHz; D_2O) δ 18.47, 38.43, 45.82, 46.09, 49.91, 65.45, 117.36, 151.01, 169.85, 173.82, 177.98; MS (APCI+) *m*/*z* 271 (MH^+, 100).

(2*S*,3*S*,4*R*)-4-(2′-Aminothiazol-4′-yl)-3-methylenecarboxypyrrolidine-2-carboxylic Acid (17b). To **16b** (44.0 mg, 0.11 mmol) was added 2 M hydrochloric acid (3 mL), and the reaction was heated under reflux for 14 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give **17b** (28.5 mg, 95%) as a beige waxy solid. Free amino acid: $[\alpha]^{23}_D$ −46.7 (*c* 0.8, H_2O); IR (KBr disk) ν_{max} 3600−2300brs, 3427s, 3191s, 1700s; ^{1}H NMR (200 MHz; D_2O) δ 2.29 (1H, ca. dd, *J* 16, 8 Hz), 2.52 (1H, ca.dd, *J* 16, 4 Hz), 2.59−2.73 (1H, m), 3.13−3.41 (2H, complex), 3.50, 3.57 (1H, ca. dd, *J* 12, 8 Hz), 3.84 (1H, d, *J* 9 Hz), 6.34 (1H, s); ^{13}C NMR (125.8 MHz; D_2O) δ 39.85, 45.42, 45.86, 49.66, 65.55, 106.31, 146.82, 171.19, 174.08, 179.44; MS (APCI+) *m*/*z* 272 (MH^+, 100).

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-(2′-(methylamino)-thiazol-4′-yl)pyrrolidine-2-carboxylic Acid (17c). To **16c** (47 mg, 0.11 mmol) was added 2 M hydrochloric acid (3 mL), and the reaction was heated under reflux for 16 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give **17c** (31 mg, 96%) as a beige waxy solid. Free amino acid: $[\alpha]^{23}_D$ −48.9 (*c* 1.1, H_2O); IR (KBr disk) υ_{max} 3700−2000brs, 1651s; ^{1}H NMR (200 MHz; D_2O) δ 2.26 (1H, ca.dd, *J* 15, 8 Hz), 2.48 (1H, ca.dd, *J* 15, 4 Hz), 2.57−2.73 (1H, m), 2.70 (3H, s), 3.13−3.38 (2H, complex), 3.47, 3.53 (1H, ca.dd, *J* 11, 8 Hz), 3.79 (1H, d, *J* 8 Hz), 6.28 (1H, s); ^{13}C NMR (125.8 MHz; D_2O) δ 32.13, 39.97, 45.33, 45.62, 49.57, 65.63, 104.25, 146.69 and 146.86, 173.21 and173.27, 173.99, 179.45;[18] MS (APCI+) *m*/*z* 286 (MH^+, 100).

(2*S*,3*S*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2′-phenylimidazol-4′-yl)pyrrolidine (18). To a stirred solution of **10** (37.0 mg, 0.073 mmol) in ethanol (2.5 mL) were added benzamidine hydrochloride (11.4 mg, 0.073 mmol) and sodium bicarbonate (12.2 mg, 0.145 mmol). The reaction was heated under reflux for 24 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (2:1 v/v) to give **18** (25.0 mg, 65%) as a white crystalline solid: mp 89−91 °C; $[\alpha]^{22}_D$ −17.2 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3691w, 3462w, 1728brs, 1631s; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.39, 1.51 (2 × 9H, 2 × s), 2.51−2.73 (2H, complex), 2.81−3.04 (1H, m), 3.20−3.41 (1H, m), 3.75−4.01 (2H, complex), 4.43 (1H, d, *J* = 9 Hz), 6.88 (1H, s), 7.27−7.63 (8H, complex), 7.79−7.84 (2H, complex); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 28.00, 29.65, 36.37, 42.60, 44.27, 55.17, 64.63, 81.11, 81.95, 125.35, 127.42, 128.30, 128.85, 130.45, 135.40, 146.59, 169.43, 170.75; MS (APCI+) *m*/*z* 532 (MH^+, 53), 476 (100); HRMS *m*/*z* calcd for $C_{31}H_{38}N_3O_5$ (MH^+) 532.2811, obsd 532.2861.

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(imidazo[1′,2′-a]pyrid-2′-yl)pyrrolidine (19). To a stirred solution of **10** (72.0 mg, 0.073 mmol) in ethanol (2.5 mL) were added 2-aminopyridine (13.3 mg, 0.141 mmol) and sodium bicarbonate (11.9 mg, 0.141 mmol). The reaction was heated under reflux for 5.5 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (1:1 v/v) to give **19** (17.0 mg, 24%) as a beige crystalline solid: mp 203 °C; $[\alpha]^{25}_D$ −50.0 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1728s; ^{1}H NMR (400 MHz; $CDCl_3$) mixture of rotamers δ 1.32, 1.35, 1.43, 1.53 (2 × 9H, 4 × s), 2.03−2.46 (2H, complex), 3.02−3.17 (1H, m), 3.81−4.22 (3H, complex), 4.37, 4.44 (1H, 2 × d, *J* = 7, 3 Hz), 6.73−6.80 (1H, m), 7.12−7.20 (1H, m), 7.25−7.64 (7H, complex), 8.01, 8.08 (1H, 2 × d, *J* = 7, 7 Hz); ^{13}C NMR (100.6 MHz; $CDCl_3$) mixture of rotamers δ 27.80, 27.86, 28.06, 35.02, 38.66, 40.88, 42.78, 44.51, 48.89, 53.89, 64.24, 66.50, 80.70, 81.69, 82.15, 109.48, 110.02, 112.27, 117.26, 117.36, 124.48, 124.78, 125.38, 125.59, 126.84, 127.29, 128.29, 129.72, 130.17, 136.10, 136.80, 144.31, 144.93, 169.92, 170.69, 170.98; MS (APCI+) *m*/*z* 506 (MH^+, 100); HRMS *m*/*z* calcd for $C_{29}H_{36}N_3O_5$ (MH^+) 506.2655, obsd 506.2655.

(2*S*,3*S*,4*S*)-3-Methylenecarboxy-4-(imidazo[1′,2′-a]pyrid-2′-yl)pyrrolidine-2-carboxylic Acid (25). To **19** (16.0 mg, 0.032 mmol) was added 6 M hydrochloric acid (3 mL), and the reaction was heated under reflux for 7 h. The solution was

(18) Two carbon signals seen for C-2 and C-4, of 2-methylaminothiazole group, due to restricted rotation.

cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give **25** (9.0 mg, 98%) as a beige gum. Free amino acid: $[\alpha]^{25}_D$ +39.4 (*c* 0.3, H_2O); IR (KBr disk) ν_{max} 3700−2100brs, 1738m, 1716m, 1694s; ^{1}H NMR (500 MHz; D_2O) δ 2.03, 2.06 (1H, dd, *J* 15, 9 Hz), 2.41, 2.45 (1H, dd, *J* 15, 6 Hz), 3.16−3.22 (1H, m), 3.73, 3.77 (1H, m), 3.97, 4.00 (1H, dd, *J* 12, 8 Hz), 4.04−4.07 (1H, m), 4.09 (1H, d, *J* 6 Hz), 7.19−7.22 (1H, m), 7.65−7.71 (2H, complex), 7.87 (1H, s), 8.48 (1H, d, *J* 7 Hz); ^{13}C NMR (125.8 MHz; D_2O) δ 37.26, 38.76, 44.35, 48.20, 66.10, 113.51, 114.12, 116.14, 128.60, 131.58, 136.73, 143.15, 173.70, 179.21; MS (electrospray, positive ion) *m*/*z* 290 (MH^+, 100).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(quinoxal-2′-yl)pyrrolidine (22) and (2*S*,3*S*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(quinoxal-2′-yl)pyrrolidine (23). To a stirred solution of **10** (51.0 mg, 0.073 mmol) in ethanol (2.5 mL) were added phenylenediamine (10.8 mg, 0.10 mmol) and sodium bicarbonate (8.4 mg, 0.10 mmol). The reaction was heated under reflux for 7 h and then concentrated in vacuo. The residue was taken up into ethyl acetate, and the organics were washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate, and the combined organics were washed with water and saturated brine. After drying ($MgSO_4$) and removal of the solvent in vacuo, the residue was redissolved in ethanol (3 mL) and 10% palladium on charcoal (30 mg) was added. The reaction was heated under reflux for 3 h, and the catalyst was then filtered off and the solvent removed in vacuo. Purification by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (1:1 v/v) gave two close running fractions. Fraction 1 contained **22** (26.0 mg, 50%) as a white crystalline solid: mp 195−197 °C; $[\alpha]^{25}_D$ −46.3 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1728s; ^{1}H NMR (400 MHz; $CDCl_3$) mixture of rotamers, major rotamer assigned only δ 1.35, 1.54 (2 × 9H, 2 × s), 2.04 (1H, ca. dd, *J* = 16, 4 Hz), 2.27 (1H, ca. dd, *J* = 16, 4 Hz), 3.15−3.21 (1H, m), 3.95−4.00, 4.11−4.16 (3H, complex), 4.55 (1H, d, *J* = 9 Hz), 7.34−8.12 (9H, complex), 8.61 (1H, s); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 27.89, 28.06, 34.45, 43.26, 45.28, 53.85, 64.22, 81.19, 81.90, 127.23, 128.28, 128.38, 129.30, 129.53, 129.75, 130.22, 136.15, 141.52, 142.13, 145.36, 154.53, 170.07, 170.66, 170.80; MS (APCI+) *m*/*z* 518 (MH^+, 91), 406 (100); HRMS *m*/*z* calcd for $C_{30}H_{36}N_3O_5$ (MH^+) 518.2655, obsd 518.2655. Fraction 2 contained **23** (23.0 mg, 44%) as a pale yellow gum: $[\alpha]^{25}_D$ +13.2 (*c* 1.125, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1725brs; ^{1}H NMR (400 MHz; $CDCl_3$) mixture of rotamers, major rotamer assigned only δ 1.23, 1.55 (2 × 9H, 2 × s), 2.54−2.59 (1H, m), 2.63−2.68 (1H, m), 3.23−3.31 (1H, m), 3.71−3.79 (1H, m), 3.92−3.96 (1H, m), 4.23 (1H, t, *J* = 11 Hz), 4.56 (1H, d, *J* = 10 Hz), 7.36−7.44 (3H, complex), 7.63−7.65 (2H, complex), 7.72−7.80 (2H, complex), 8.06−8.09 (2H, complex), 8.73 (1H, s); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 27.89, 28.06, 34.45, 43.26, 45.28, 53.85, 64.22, 81.19, 81.90, 127.23, 128.28, 128.38, 129.30, 129.53, 129.75, 130.22, 136.15, 141.52, 142.13, 145.36, 154.53, 170.07, 170.66, 170.80; MS (APCI+) *m*/*z* 518 (MH^+, 91), 406 (100); HRMS *m*/*z* calcd for $C_{30}H_{36}N_3O_5$ (MH^+) 518.2655, obsd 518.2655.

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-(2′-phenylimidazol-4′-yl)pyrrolidine-2-carboxylic Acid (24). To **18** (16.0 mg, 0.030 mmol) was added 6 M hydrochloric acid (2 mL), and the reaction was heated under reflux for 9 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL), and the resulting solution was evaporated in vacuo to give **24** (9.5 mg, 100%) as a white solid. Free amino acid: mp 240 °C dec; $[\alpha]^{25}_D$ −30.0 (*c* 0.2, 1 M HCl (aq)); IR (KBr disk) ν_{max} 3650−2400brs, 1652brs; ^{1}H NMR (200 MHz; D_2O) δ 2.35, 2.43 (1H, dd, *J* 15, 8 Hz), 2.59, 2.67 (1H, dd, *J* 15, 4 Hz), 2.72−2.92 (1H, m), 3.40−3.58 (2H, complex), 3.65−3.80 (1H, m), 3.95 (1H, d, *J* 8 Hz), 7.14 (1H, s), 7.41−7.44 (3H, complex), 7.62−7.65 (2H, complex); ^{13}C NMR (125.8 MHz; D_2O) δ 38.85, 40.22, 45.18, 49.00, 65.02, 117.51, 123.49, 126.80, 129.73, 131.54, 132.25, 145.73, 172.78, 177.89; MS (electrospray, positive ion) *m*/*z* 316 (MH^+, 100).

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-(quinoxal-2′-yl)pyrrolidine-2-carboxylic Acid (26). To **22** (19 mg, 0.037 mmol) was added 6 M hydrochloric acid (2 mL), and the reaction was heated under reflux for 5 h. The solution was cooled to room temperature and concentrated in vacuo, and the solid residue was dissolved in water (10 mL) and loaded onto a preactivated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After the column was flushed with water (100 mL), the compound was eluted with 2 M ammonia solution (50 mL) and the resulting solution was evaporated in vacuo to give a 6:1 mixture of **26** and **27** (11 mg, 99%) as a beige gum. Limited spectroscopic data was obtained for the major isomer **26**: IR (KBr disk) ν_{max} 3700−2100brs, 1738m, 1716m, 1694s; ^{1}H NMR (200 MHz; D_2O) δ 2.62 (1H, dd, *J* 15, 9 Hz), 2.84 (1H, dd, *J* 15, 4 Hz), 2.97−3.15 (1H, m), 3.83−3.93 (3H, complex), 4.09 (1H, d, *J* 9 Hz), 7.72−7.90 (2H, complex), 7.90−8.09 (2H, complex), 8.78 (1H, s); ^{13}C NMR (50.3 MHz; D_2O) δ 36.42, 45.56, 48.77, 50.18, 64.26, 128.42, 128.85, 131.73, 132.05, 140.96, 142.11, 145.15, 154.20, 171.60, 175.42; MS (APCI+) *m*/*z* 302 (MH^+, 37), 208 (100).

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Supporting Information Available: Copies of the ^{1}HNMR or ^{13}CNMR spectra for compounds **12**, **13**, **8**, **10**, **11a**−**d**, **6a**−**d**, **15**, **16a**−**c**, **17a**−**c**, **18**, **24**, **25**, **22**, **23**, **19**, and **26/27**, as well as an X-ray structure for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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