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A New Synthesis of α-Arylglycines from Aryl Boronic Acids

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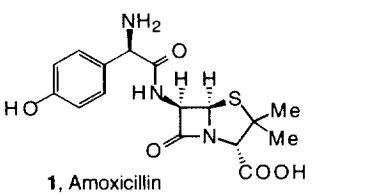
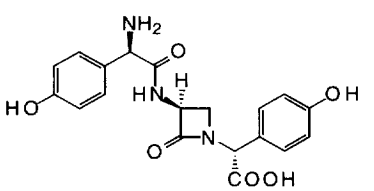
Abstract: Aryl and heteroaryl boronic acids react with the adducts of amines and glyoxylic acid to give the corresponding α-aryl and α-heteroaryl glycine derivatives. Several examples of this reaction with *m*- and *p*-substituted aryl boronic acids as well as 3-thienyl, 2-thienyl, 2-furyl, 2-benzo[b]furyl and 2-benzo[b]thienyl boronic acids are described. © 1997 Elsevier Science Ltd.

Introduction

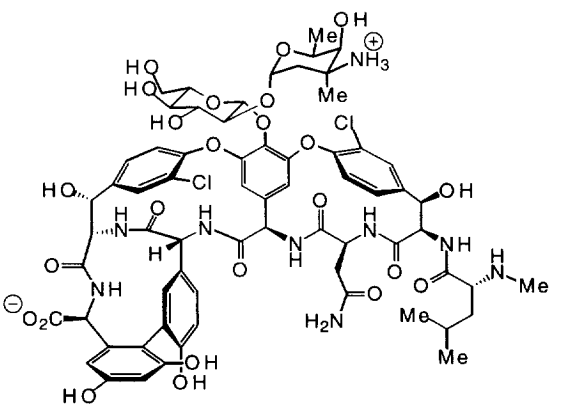
α-Arylglycines are among the most important types of non-proteinogenic amino acids.[1,2] Molecules of this type were recently shown to be potent and selective agonists or antagonists of the glutamate receptors of the central nervous system.[3,4] In addition, these compounds are key components of some of the most widely used β-lactam antibiotics including cephalexin and amoxicillin (**1**) and they are present in a number of other naturally occurring antibiotics, such as nocardicin G (**2**).[5] Moreover, the unique framework of vancomycin (**3**) and other related glycopeptide antibiotics[6] contains several structural types of α-arylglycines. Due to their novel mode of action which involves inhibition of cell wall biosynthesis,[7] vancomycin-type antibiotics have been used widely for the treatment of some of the most serious and potentially lethal infections involving staphylococci and enterococci. Not surprisingly, the remarkable crosslinked structures of these complex natural products have attracted the interest of many synthetic chemists in recent years.[8]



1, Amoxicillin



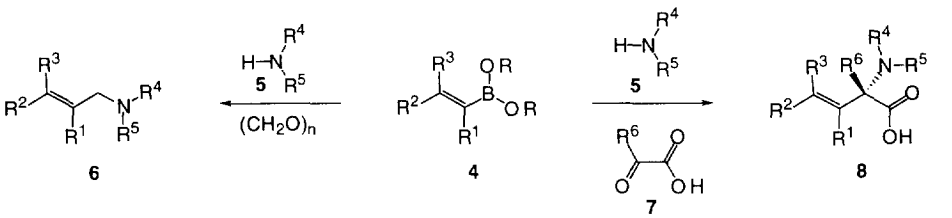
2, Nocardicin G



3, Vancomycin

As with other classes of antibacterials,[9] there is also a continuing interest in the development of semisynthetic β-lactams as well as glycopeptides.[10] Such molecules are of great significance in the fight against the emergenece of bacterial resistance to antibiotics.[11,12] For this reason, the need to synthesize new structural types of α-arylglycines is constantly increasing. Indeed, numerous approaches to this class of amino acids have been developed[2] including methods based on: Friedel-Crafts reaction of electrophilic glycine equivalents,[13,14,15] enolate azidation,[16] photolysis of chromium complexes,[17] Ugi condensation,[18] Strecker synthesis[19,20,21,22] or other reactions.[23] Although many of these methods are quite effective, they are often limited to certain substitution patterns, require multistep synthesis, involve strong Lewis acids or other highly reactive reagents, or utilize very toxic cyanides followed by harsh hydrolysis conditions. A major challenge in the synthesis of α-arylglycines is their facile base-catalyzed epimerization,[24] which makes it difficult to prepare these molecules in enantiomerically pure form. Also, some of the most effective methods for the synthesis of other types of amino acids,[1,25] such as enolate alkylation or enamine hydrogenation, are not suitable for these molecules.

Following our discovery of the boronic acid Mannich reaction[26,27] which is suitable for the synthesis of geometrically pure allylamines (**6**) from an organoboronic acid or boronate (**4**), an amine (**5**) and formaldehyde, we have recently employed this type of chemistry in a general and practical synthesis of β,γ-unsaturated α-amino acids (**8**).[28] This new approach involves a three component reaction among an alkenylboronic acid (**4**), an amine (**5**) and an α-keto acid (**7**). In addition to being highly convergent, this method can lead to enantiomerically pure derivatives via the use of chiral amines as well as isomerically or geometrically pure products, resulting from the stereospecific methodology used for the synthesis of the boronic acid precursors. Moreover, this process, which is a novel variant of the Mannich reaction,[29,30] is experimentally convenient and is directly suitable for the production of combinatorial libraries.[31]



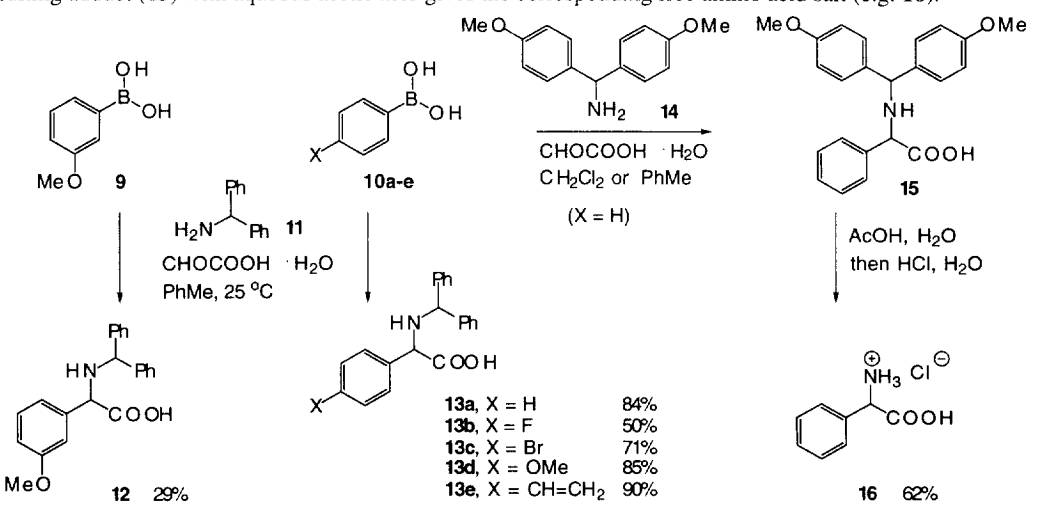
Herein, we report a related approach to α-arylglycines involving the use of aryl boronic acids. In recent years these arylboron compounds[32] have attracted increasing attention for their novel molecular recognition properties[33] and especially for their ability to participate in the Pd-catalyzed Suzuki coupling[34,35] for the synthesis of substituted aryl or biaryl derivatives.[36] They can be prepared by several methods, including the reaction of trialkylborates with arylmagnesium or aryllithium reagents,[37] and the Pd-catalyzed coupling among aryl halides and alkoxydiboron derivatives.[38] In addition to being readily available, aryl boronic acids are especially attractive for large scale synthesis, due to their relatively low toxicity and their convenient handling, resulting from their relative stability to air and water. Indeed, aryl boronic acids are increasingly used in the industrial production of pharmaceuticals[39] or novel organic materials[40,41] and a growing number of them are commercially available.

Results and Discussion

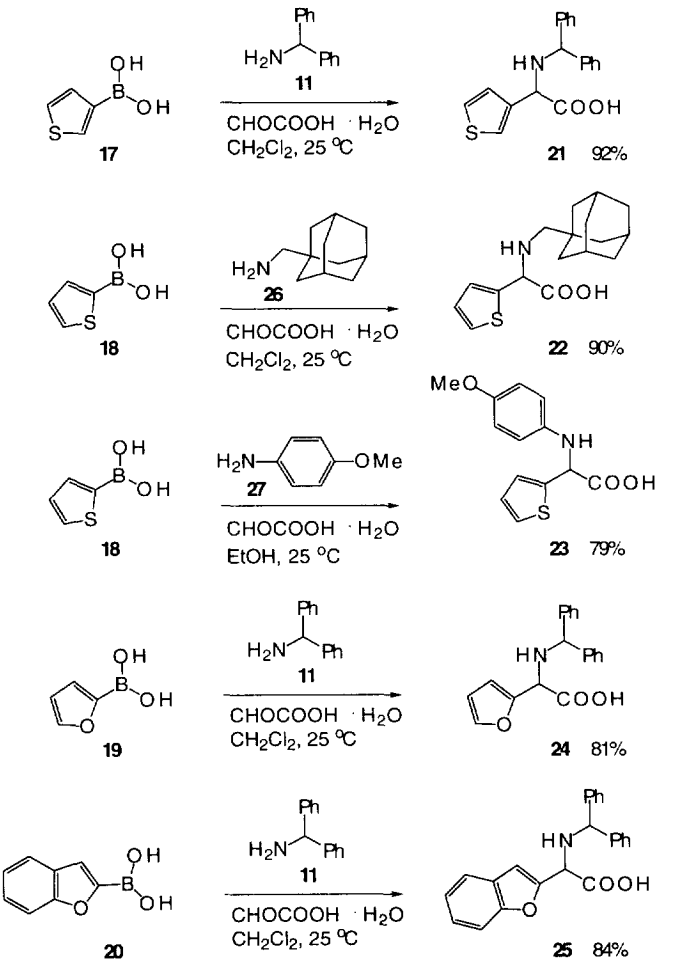
In general, aryl boronic acids are somewhat less reactive than alkenyl boronic acids. We have found, however, that many derivatives of this type (e.g. **9**, **10a-e**) can participate in the boronic acid Mannich reaction at room temperature to give the corresponding aryl amino acids in good to moderate yields. As with our synthesis of β,γ-unsaturated amino acids, the products of this reaction usually precipitate out and can be isolated by filtration, followed by recrystallization or ion-exchange chromatography.

Among the most useful amines for this reaction is aminodiphenylmethane (**11**) and the corresponding bis(*p*-methoxy) derivative (**14**). Due to their steric bulk, these primary amines do not participate readily in other potentially competing side reactions, such as a double participation in this reaction to give iminodicarboxylic acids or the formation of amides, which is known to be catalyzed by some electron-deficient aryl boronic acids.[42] Moreover, the diarylmethyl group can be subsequently cleaved by hydrogenation or hydrolysis to give the free amino acids. We have examined the reaction of **11** and **14** with several aryl boronic acids and glyoxylic acid monohydrate. Although other solvents can also be used, these reactions were typically performed in dichloromethane or toluene where the product precipitated upon stirring at room temperature over 4-48 hrs. The resulting amino acids were easily identified by their characteristic ^{13}C chemical shifts for the α-carbon in the 55-70 ppm region. In certain cases we also observed the formation of some stable intermediates which presumably result from boronic acid complexation with glyoxylic acid and/or its amine adduct.

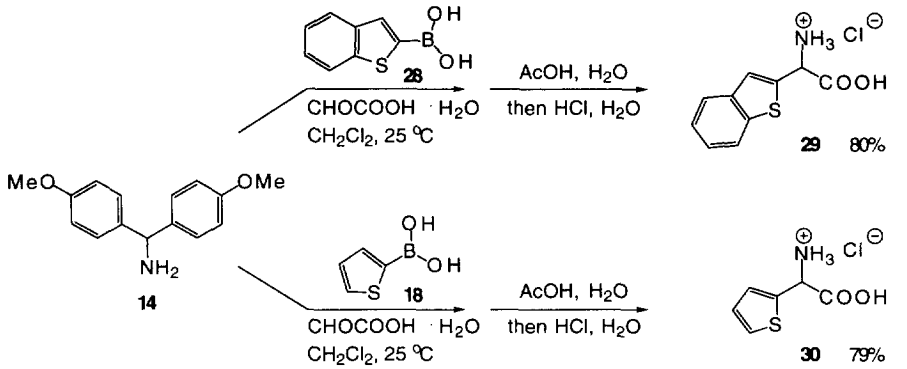
This reaction was used for the synthesis of several substituted arylglycines that have attracted previous attention, including the *p*- and *m*-methoxy derivatives (**12**, **13d**) related to **1**-**3**, as well as the *p*-fluoro- (**13b**)[43] and the *p*-vinyl- (**13e**)[44] derivatives. An important advantage of this process over acid-mediated amidoalkylation reactions is that the reaction is directed at the position of the boronic acid substituent rather than the preferred position of electrophilic aromatic substitution resulting from the substituents' directing effects. Thus, it is possible to employ this reaction for the synthesis of isomerically pure products as well as isomers that are not easily available by other methods. Also, when **14** is used as the amine component subsequent hydrolysis of the resulting adduct (**15**) with aqueous acetic acid gives the corresponding free amino acid salt (e.g. **16**).



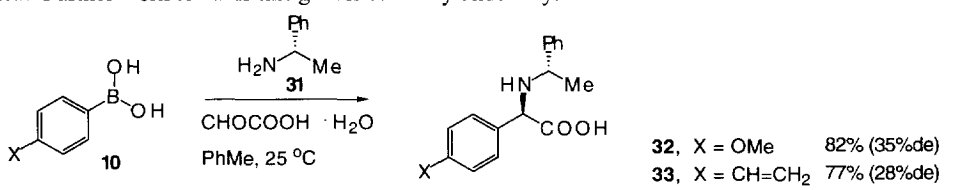
The analogous synthesis of heteroaryl amino acids from heteroaryl boronic acids was also examined. Thus, 3-thienyl (**17**), 2-thienyl (**18**), 2-furyl (**19**), 2-benzo[b]furyl (**20**), as well as 2-benzo[b]thienyl (**28**) boronic acids were found to participate readily in this reaction giving the expected amino acids (e.g. **21** - **25**). In fact, these heteroaryl derivatives were among the most reactive boronic acids for this process. In addition to **11** and **14** we found that certain alkyl amines such as the 1-adamantanemethyl amine (**26**) as well as aryl amines (e.g. **27**) can also readily participate as the amine components. Compounds of type **23**, having two aryl groups, may be useful precursors of novel polycylic amino acids by using appropriate aryl moieties followed by subsequent coupling between these groups.



The free amino acid salts (e.g. **29**, **30**) could be prepared in good yields by using di(*p*-anisyl)methyl amine (**14**) as the amine component followed by hydrolysis of the resulting adduct with aqueous acetic acid.[45]



Finally, we have examined the use of chiral amines in this process in order to develop an asymmetric synthesis of α-arylglycines. We have found that α-methylbenzyl amine (**31**) can indeed participate in the reaction, but the resulting products (**32, 33**) have only modest diastereoselectivities. As mentioned above, the facile epimerization of α-arylglycines makes it harder to identify conditions for a more efficient asymmetric approach. Further work towards this goal is currently underway.



In summary, we have shown that aryl as well as heteroaryl boronic acids can participate in a one-step three-component synthesis of the corresponding α-aryl- and α-heteroaryl-glycines. These results extend the utility of our boron-mediated amino acid synthesis, which we continue to explore.

Experimental

General: Reactions were monitored by TLC using precoated glass-backed silica gel plates (Merck 60 F-254, 0.25 mm). Spots were visualized with UV light or were developed with a solution of ninhydrin or phosphomolybdic acid followed by heating. ^{1}H NMR spectra were recorded on a Bruker 250 MHz or 360 MHz spectrometer. Signals are abbreviated as follows: s=singlet; d=doublet; dd=doublet of doublets; t=triplet; q=quartet; m=multiplet. ^{13}C NMR spectra were recorded at 63 MHz or 90 MHz on the same instruments. Mass spectra were obtained at the Southern California Mass Spectrometry Facility, University of California, Riverside and elemental analyses at Galbraith Laboratories.

(±)-N-(Diphenylmethyl)-α-phenylglycine (**13a**). To a stirred solution of glyoxylic acid monohydrate (92 mg, 1 mmol) in dichloromethane (7 mL) was added aminodiphenylmethane (183 mg, 1 mmol), followed by phenylboronic acid (122 mg, 1 mmol). After the flask was purged with argon and sealed, the reaction mixture was stirred vigorously at room temperature for 48 h. The resulting precipitate was isolated by filtration, washed with dichloromethane (10 mL) and purified by ion-exchange chromatography (Dowex 50W-X8) to give pure **13a** (266 mg, 84 % yield). ^{1}H-NMR (360 MHz, DMSO-d_6) δ 7.0-7.8 (m, 15H), 4.78 (s, 1H), 4.17 (s, 1H);

^{13}C-NMR (90 MHz, DMSO-d_6) δ 172.8, 142.4, 133.6, 129.6, 128.1, 127.5, 127.1, 126.9, 126.7, 63.6, 62.2. Anal. calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41; found: C, 79.48; H, 6.17; N, 4.32.

(±)-N-(Diphenylmethyl)-α-(4-fluorophenyl)glycine (**13b**). Prepared similarly to **13a** (50% yield). ^{1}H-NMR (250 MHz, DMSO-d_6) δ 7.15-7.92 (m, 14H), 4.72 (s, 1H), 4.12 (s, 1H); ^{13}C-NMR (63 MHz, DMSO-d_6) δ 173.2, 163.3, 159.7, 143.3, 143.2, 134.7, 129.3, 129.2, 128.3, 128.2, 127.0, 115.2, 114.9, 63.9, 61.8; ^{19}F-NMR (339 MHz, DMSO-d_6) δ -114.6 (br).

(±)-N-(Diphenylmethyl)-α-(4-bromophenyl)glycine hydrochloride (**13c**). Prepared similarly to **13a** (71% yield). ^{1}H-NMR (250 MHz, DMSO-d_6) δ 7.71 (d, J=8.28 Hz, 2H), 7.53 (d, J=8.28 Hz, 2H), 7.45-7.32 (m, 10H), 5.75 (s, 1H), 5.66 (s, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) 164.75, 155.51, 142.70, 138.07, 136.20, 134.21, 133.75, 130.38, 128.92, 128.52, 127.36, 127.20, 124.13, 75.92, 56.93.

(±)-N-(Diphenylmethyl)-α-(4-methoxyphenyl)glycine (**13d**). Prepared similarly to **13a** in toluene (85% yield). ^{1}H-NMR (250 MHz, acetone-d_6) δ 7.16-7.45 (m, 12H), 6.89-6.92 (m, 2H), 4.80 (s, 1H), 4.20 (s, 1H) 3.78 (s, 3H); ^{13}C-NMR (63 MHz, acetone-d_6) δ 174.2, 160.3, 144.6, 131.4, 129.7, 129.5, 129.3, 129.2, 128.2, 127.9, 127.8, 114.7, 114.6, 65.1, 62.8, 55.5.

(±)-N-(Diphenylmethyl)-α-(4-vinylphenyl)glycine (**13e**). Prepared similarly to **13a** in toluene (90% yield). ^{1}H-NMR (360 MHz, methanol-d_4) δ 7.31-7.58 (m, 14H), 6.77 (dd, J=17.8 Hz, 11.0 Hz, 1H), 5.91 (dd, J=17.8 Hz. 0.9 Hz, 1H), 5.38 (s, 1H), 5.34 (dd, J=11 Hz, 0.9 Hz, 1H), 4.74 (s, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 173.8, 143.7, 138.5, 137.0, 136.6, 129.3, 128.8, 128.1, 127.4, 126.6, 114.8, 64.2, 62.7.

(±)-α-Phenylglycine hydrochloride (**16**). To a stirred solution of glyoxylic acid monohydrate (184 mg, 2 mmol) in toluene (10 mL) was added di(*p*-anisyl)methyl amine (486 mg, 2 mmol), followed by phenylboronic acid (244 mg, 2 mmol). After the flask was purged with argon and sealed, the reaction mixture was stirred vigorously at room temperature for 48 h. Upon evaporation of the solvent the resulting crude product (**15**) was dissolved in 70 % aqueous acetic acid (10 mL) and heated under reflux at 80 °C for 40 min. After cooling to room temperature the reaction mixture was further acidified with 3N aqueous HCl (5 mL) and extracted with diethyl ether (3x20 mL). Evaporation of the aqueous layer gave a solid, which was washed with dichloromethane and dried to give **16** (233 mg, 62 % yield). ^{1}H-NMR (250 MHz, methanol-d_4) δ 7.41-7.51 (br, 5H), 5.18 (s, 1H); ^{13}C-NMR (63 MHz, methanol-d_4) δ 170.7, 131.0, 130.5, 129.7, 129.1, 57.6; HRMS-CI calcd for $C_8H_9NO_2$ (M^+ + 1) 152.0633, obsd 152.0591.

(±)-N-(Diphenylmethyl)-α-(3-methoxyphenyl)glycine (**12**). Prepared similarly to **13a** in toluene (29 % yield). ^{1}H-NMR (360 MHz, DMSO-d_6) δ 7.15-7.41 (m, 11H), 6.86-6.96 (m, 3H), 4.76 (s, 1H), 4.07 (s, 1H), 3.73 (s, 3H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 173.20, 159.36, 158.60, 143.04, 129.63, 128.54, 127.19, 127.39, 119.79, 119.01, 115.79, 113.23, 113.12, 63.96, 62.60, 55.06.

(±)-N-(Diphenylmethyl)-α-(3-thienyl)glycine (**21**). Prepared similarly to **13a** over 8 h (92% yield). ^{1}H-NMR (360 MHz, DMSO-d_6) δ 7.20-7.75 (m, 13 H), 4.77 (s, 1H), 4.15 (s, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 173.3, 143.6, 143.2, 139.2, 122.7, 128.4, 127.1, 127.0, 126.8, 126.3, 64.1, 58.7.

(±)-N-(1-Adamantanemethyl)-α-(2-thienyl)glycine (**22**). Prepared similarly to **13a** over 12 h (90% yield). ^{1}H-NMR (360 MHz, DMSO-d_6) δ 7.46 (d, J=4.8 Hz, 1H), 7.15 (d, J=3.2 Hz, 1H), 7.00 (dd, J=4.8 Hz, 3.2 Hz, 1H), 4.52 (s, 1H), 1.31-2.52 (m, 17H); ^{13}C-NMR (90 MHz, DMSO-d6) δ 170.2, 126.8, 126.7, 126.3,

126.0, 61.3, 58.6, 39.6, 36.4, 32.6, 27.6; HRMS-CI calcd for $C_{17}H_{23}NO_2S$ (M^+ + 1) 306.1449, obsd 306.1493.

(±)-N-(p-Anisyl)-α-(2-thienyl)glycine (**23**). Prepared similarly to **13a** in ethanol over 12 h (79% yield). ^{1}H-NMR (250 MHz, DMSO-d_6) δ 7.42 (d, J=5.2 Hz, 1H), 7.17 (d, J=3.5 Hz, 1H), 6.98 (dd, J=5.2 Hz, J=3.5 Hz, 1H), 6.65 (br, 4H), 5.29 (s, 1H), 3.61 (s, 3H); ^{13}C-NMR (63 MHz, DMSO-d_6) δ 172.7, 151.9, 142.4, 141.2, 127.1, 126.2, 125.8, 114.8, 114.7, 56.9, 55.5.

(±)-N-(Diphenylmethyl)-α-(2-furyl)glycine (**24**). Prepared similarly to **13a** over 4 h (81% yield). ^{1}H-NMR (250 MHz, DMSO-d_6) δ 7.18-7.61 (m, 11H), 6.43 (br, 1H), 6.34 (br, 1H), 4.76 (s, 1H), 4.16 (s, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 171.5, 151.3, 143.3, 143.1, 142.6, 128.5, 127.0, 126.9, 110.5, 107.8, 63.9, 56.8; HRMS-CI calcd for $C_{19}H_{17}NO_3$ (M^+ + 1) 308.1208, obsd 308.1242.

(±)-N-α-(2-Benzo[b]furyl)glycine hydrochloride (**25**). Prepared similarly to **13a** over 4 h (84% yield). ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.14-7.61 (m, 14H), 6.85 (s, 1H), 4.86 (s, 1H), 4.33 (s, 1H); ^{13}C-NMR (90 MHz, DMSO-d_6) δ 171.1, 154.5, 154.2, 143.3, 143.1, 128.5, 128.4, 127.8, 127.1, 127.0, 124.3, 122.9, 121.1, 111.1, 104.8, 64.0, 57.3; HRMS-CI calcd for $C_{23}H_{19}NO_3$ (M^+ + 1) 358.1365, obsd 358.1427.

(±)-N-α-(2-Benzo[b]thienyl)glycine hydrochloride (**29**). Prepared similarly to **16** in dichloromethane over 12 h (80% yield). ^{1}H NMR (360 MHz, DMSO-d_6) δ 7.35-8.21 (m, 5H), 5.55 (s, 1H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 168.6, 139.4, 138.5, 135.2, 125.6, 125.4, 125.0, 124.2, 122.7, 51.7; HRMS-CI calcd for $C_{10}H_9NO_2S$ (M^+ + 1) 208.0354, obsd 208.0387.

(±)-N-α-(2-Thienyl)glycine hydrochloride (**30**). Prepared similarly to **16** in dichloromethane over 12 h (79% yield). ^{1}H-NMR (360 MHz, DCl / D_2O) δ 6.48 (d, J=4.8 Hz, 1H), 6.21 (d, J=3.7 Hz, 1H), 5.99 (dd, J=4.8 Hz, J=3.7 Hz, 1H), 4.50 (s, 1H); ^{13}C-NMR (90 MHz, DCl / D_2O) δ 169.9, 131.6, 130.5, 129.8, 128.4, 52.0; HRMS-CI calcd for $C_6H_7NO_2S$ (M^+ + 1) 158.0197, obsd 158.0199.

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