# Solid-Phase Synthesis of Substituted Tetramic Acids

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## Introduction

The synthesis of structurally diverse, nonpeptidic compounds by the solid-phase approach has garnered considerable attention in the past few years.[1] In particular, the synthesis of various heterocycles with potentially desirable pharmacological properties has received much of the attention.[2]

In general, our group, as well as many others, has paid particular attention to the synthesis of heterocycles which contain three points of diversity in search of leads by utilizing automated high-throughput biological screening (HTS).[3] As in our previous publication,[3b] we were interested in synthesizing linear molecules on the solid support, which when treated with base, would cyclize to form nitrogen-containing heterocycles and concomitantly cleave from the solid support.

Herein we focus our attention toward the synthesis of 1,3,5-trisubstituted tetramic acids, which until now have remained unexplored by using solid-phase technology. There are numerous examples in the literature utilizing standard solution phase chemistry in which chiral amino acids are reacted either with Meldrum's acid or ethyl hydrogen malonate followed by a Dieckman condensation step to provide the targeted tetramic acids.[4] Primarily, these tetramic acids served as intermediates which were further manipulated to generate chiral N-substituted statine and its congeners, which have been widely used as transition state isosteres in aspartic protease inhibitors, as well as analogues of penicillins and cephalosporins.[4] Also, there are a number of biologically active compounds which contain the tetramic acid nucleus. For example, antimicrobials, such as, streptolydigin and tirandamycin,[5] contain a 3-acyl moiety, and 5-oxotetramic acids are known inhibitors of glycolic acid oxidase.[6] Although the synthetic route to prepare tetramic acids as well as the overall yields of the aforementioned procedures have been improved greatly over the years, diversity at the C-3 carbon of the tetramic acid nucleus has rarely been explored. Using a solid-phase approach allows us to take maximum advantage of the versatility and wealth of commercially available starting materials; i.e., amino acids, aldehydes, and either malonic acids or aryl acetic acids.

Described herein is the three-step solid-phase synthesis of diverse libraries of 1,3,5-trisubstituted tetramic acids: (1) Reductive alkylation of a resin-bound α-amino acid with aldehydes; (2) acylation of the secondary amine with either malonic acids or aryl acetic acids; (3) base-promoted cyclization of the acyclic tertiary amide precursor to the tetramic acid nucleus with concomitant cleavage of the desired compounds cleanly from the resin.

## Results and Discussion

The preparation of the tetramic acid skeleton is outlined in Scheme 1. Our approach to the synthesis of trisubstituted tetramic acids **1**, **2**, and **3** features a reductive amination step of the primary amine **5** (deprotected in the first step) of an α-amino acid linked to Wang resin, using variations of previously reported strategies.[3b,7] While only reductive alkylations with aryl benzaldehydes to provide $R_1$ are reported, aliphatic aldehydes could provide nonaryl $R_1$ substituents.[3b] For each resin-bound intermediate, the structures were verified by cleaving a small sample of resin with 90% TFA/$H_2O$. Analysis of NMR and mass spectroscopy data confirmed that only monoalkylation of the primary amine occurred.

The secondary amine intermediate **6** was then acylated using standard acylation procedures with either ethyl hydrogen malonate (route a), phenyl malonic acid monobenzyl ester (route b), or aryl acetic acids (route c) to provide resin intermediates **7**, **8**, and **9**, respectively, as indicated in Scheme 1. Again, cleavage of a small sample of resin under acidic conditions followed by spectroscopic analysis confirmed complete acylation of intermediate **6**.

Similar to our previous work[3b] and that of Dressman,[8] base-promoted cyclization of our acyclic intermediates **7**, **8**, and **9** with 2 equiv of base, accompanied by spontaneous cleavage of the targeted compounds from the resin support, provides tetramic acid compounds **1**, **2**, and **3** in quantitative yields.

During the synthesis of tetramic acid **2**, it should be noted that the intermediate resin **8**, when heated with

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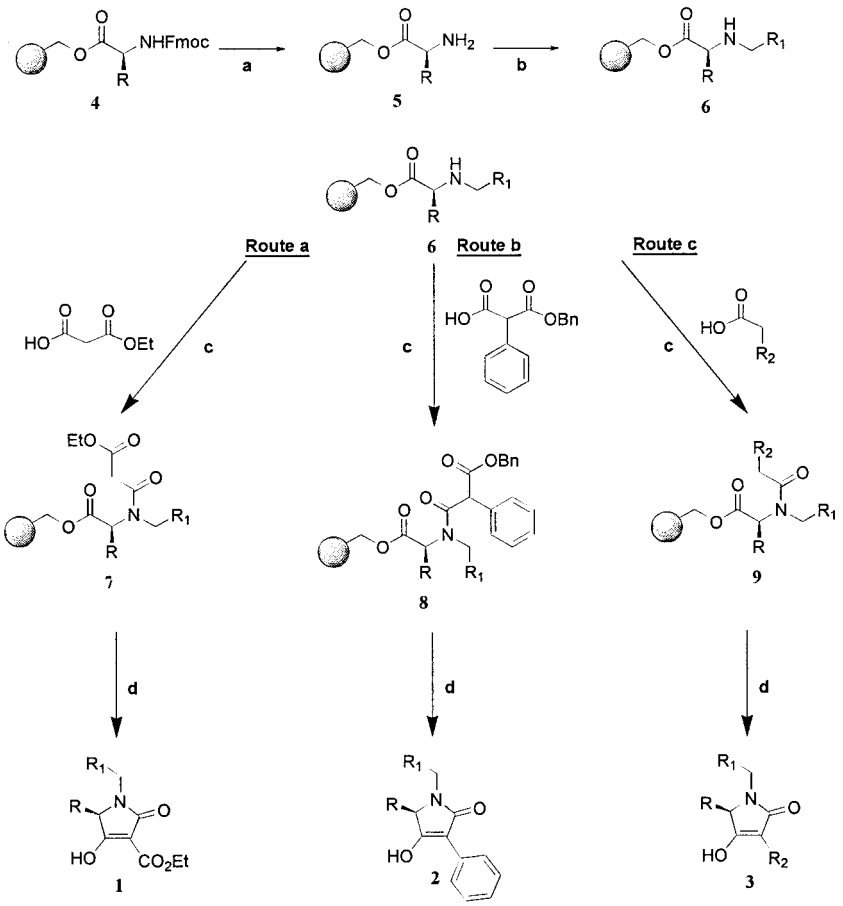
**Scheme 1**[a]




[a] (a) 20% piperidine/DMF, 1 h, rt; (b) $R_1CHO$, TMOF, $NaBH_3CN$/TMOF, 1% HOAc, rt; (c) DMF, DIC; (d) 0.1 M NaOEt.

0.1 M NaOEt, not only cyclized and cleaved from the solid-support, but also decarboxylated to generate product **2**.

Unfortunately, phenyl malonic acid is the only α-substituted malonic acid commercially available. Furthermore, the preparation of half-acid malonate esters is not a trivial process.[9] Typically, the syntheses are multistep, and the yields are modest at best. Also, to generate greater molecular diversity for HTS-screening, the synthesis of a number of the half-acid malonate esters in solution would be necessary, which slows the process of high-throughput organic synthesis. Thus, we explored the reactions of other starting materials which contain an active methylene which could potentially cyclize to a tetramic acid under base-catalyzed conditions. Route c of Scheme 1 outlines one such example. We found that coupling of aryl acetic acids with **6**, followed by base-promoted cyclization/cleavage does provide **3** in excellent yields and purity, thus offering an alternate avenue by which to prepare compounds with expanded diversity at the C-3 position.

Workup of the crude, final compounds **1**, **2**, and **3** involves the elution of the sodium salt of the final compounds through a carboxylic acid ion-exchange column[10] to convert excess sodium ethoxide to ethanol and protonate the sodium salt of the tetramic acids. The absence of ethanol (sodium ethoxide) in the $^1H$ NMR spectra of the crude, final compounds confirmed the complete quenching of sodium ethoxide.

In general, the final compounds in the libraries were >95% pure, with an occasional impurity due to hydroxide cleavage of intermediate **7**, **8**, and **9** from the resin. This impurity presumably arises from the presence of trace amounts of water in the cyclization/cleavage reaction. The results are not unusual since Wang resin is susceptible to cleavage in the presence of nucleophiles and heat. All the yields were based on the manufacturer's loading of the Wang resins, and the LC traces obtained were of the isolated, crude material.[11]

## Experimental Section

**General.** The Fmoc-(L)-Phe Wang resin (0.87 and 0.51 mmol/g) and the Fmoc-(L)-Val Wang resin (0.68 mmol/g) were purchased from NovaBiochem. Proton NMR spectra were obtained in $CD_3OD$. Chemical shifts are expressed in units (ppm) downfield from TMS. Purity was determined utilizing a Hewlett-Packard LC system (YMC column, 4 mm × 50 mm, 4 mm $C_{18}$, 220, 260, and 280 nm; 1.0 mL/min, 7 min gradient from 95% $H_2O$ (0.1% TFA) to 95% $CH_3CN$ (0.1% TFA)). Melting points are uncorrected. Unless otherwise noted, reactions were mixed on a Gyrotory Shaker-Model G2 at 300 rpm.

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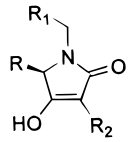
(10) Carboxylic acid ($CO_2H$) ion-exchange cartridges were purchased from Applied Separations.

(11) Literature precedent suggests that the configuration at the α-carbon of the starting amino acids are retained in the tetramic acid products after the reaction of the acyclic intermediates with sodium ethoxide in the presence of heat.[4d] The entiomeric purity of the final products prepared on the solid phase will be addressed in a future publication.

**Table 1.**



**I**

| product | R | $R_1$ | $R_2$ | %yield/ %purity[a] |
|---|---|---|---|---|
| **1a** | $CH_2Ph$ | Ph | $CO_2Et$ | 100/100 |
| **1b** | $CH_2Ph$ | 3,4-$(Cl)_2C_6H_3$ | $CO_2Et$ | 100/100 |
| **1c** | $CH_2Ph$ | 3,5-$(CF_3)_2C_6H_3$ | $CO_2Et$ | 100/90 |
| **1d** | *i*-Pr | Ph | $CO_2Et$ | 100/100 |
| **1e** | *i*-Pr | 3,4-$(Cl)_2C_6H_3$ | $CO_2Et$ | 100/100 |
| **1f** | *i*-Pr | 3,5-$(CF_3)_2C_6H_3$ | $CO_2Et$ | 100/100 |
| **2a** | *i*-Pr | Ph | Ph | 67/97 |
| **2b** | *i*-Pr | 3,4-$(Cl)_2C_6H_3$ | Ph | 79/93 |
| **2c** | *i*-Pr | 3,5-$(CF_3)_2C_6H_3$ | Ph | 83/90 |
| **3a** | $CH_2Ph$ | 4-$(Ph)C_6H_4$ | (4-$CF_3$) $C_6H_4$ | 100/100 |
| **3b** | $CH_2Ph$ | 4-$(Ph)C_6H_4$ | 2-thienyl | 100/95 |
| **3c** | $CH_2Ph$ | 4-$(Ph)C_6H_4$ | 3,5-$(CF_3)_2$ $C_6H_3$ | 100/100 |
| **3d** | $CH_2Ph$ | 4-$(Ph)C_6H_4$ | 5-Cl-3-Me-2-benzo[*b*]thienyl | 100/100 |

[a] All yields were on crude material after eluting through an ion-exchange cartridge. The purity of the crude products was determined by HPLC analysis at three wavelengths (220, 260, and 280 nm).

**General Procedure for the Deprotection of the Fmoc-Protected Amino Acids (5a and 5b).** To the Fmoc-Wang resins (5.0 g) was added 20% piperidine/DMF solution (35 mL), and the suspension was orbitally mixed at room temperature for 30 min. The resin was filtered and washed several times with DMF, MeOH, $CH_2Cl_2$, and MeOH (3 × 25 mL each). The resin was dried in vacuo overnight.

**General Procedure for the Preparation of Intermediates 7, 8, and 9**. To the appropriate resin **5** (0.284 mmol), swelled in trimethyl orthoformate (6 mL), was added the appropriate benzaldehyde (5.68 mmol), and the reaction was vigorously mixed at room temperature for 20 h. $NaCNBH_3$ (5.68 mmol) dispersed in trimethyl orthoformate (3 mL) was added followed by HOAc (0.060 mL), and the reaction was vigorously mixed for an additional 20 h. The reaction was filtered and the resin washed with DMF, MeOH, $CH_2Cl_2$, and MeOH (3 × 10 mL each). The resin was dried in vacuo to provide intermediate resin **6**. To resin **6** (0.108 mmol), swelled in anhydrous DMF (2 mL), was added the appropriate malonic acid (for **7** and **8**) (1.08 mmol) or aryl acetic acid (for **9**) followed by 1,3-diisopropylcarbodiimide (1.08 mmol), and the reaction was orbitally mixed at room temperature overnight. The resin was filtered and subsequently washed, alternating with DMF, MeOH (3 × 10 mL), 10% HOAc/ $CH_2Cl_2$, MeOH (1 × 10 mL), 10% TEA/ $CH_2Cl_2$, MeOH (1 × 10 mL), $CH_2Cl_2$, MeOH (3 × 10 mL), and dried in vacuo to provide intermediate resins **7**, **8**, and **9**. To resins **7**, **8**, and **9** (0.108 mmol) was added 0.1 M sodium ethoxide (2.1 mL, 0.216 mmol), and the reactions were heated with vigorous shaking at 85 °C for 24 h. The reactions were cooled to room temperature and filtered, and the resins were washed with ethanol and $CH_2Cl_2$ several times (3 × 3 mL). The combined washings were evaporated, and the crude residue was dissolved in MeOH (2 mL) and eluted through a $CO_2H$ ion-exchange column (preequilibrated with MeOH) with MeOH.[10] The fractions were combined and evaporated to provide the desired products as white and tan solids or an oil.

**(*S*)-5-Benzyl-1-(3,4-dichlorobenzyl)-3-(ethoxycarbonyl)-4-hydroxypyrrolidin-2-one (1b)**: 19.6 mg (100%); HPLC $t_R$ 5.62 min; mp 66−68 °C; $^1$H NMR ($CD_3OD$) $\delta$ 1.25−1.29 (t, $J$ = 7 Hz, 3H), 2.81−2.88 (dd, 1H), 3.19−3.24 (dd, 1H), 3.62−3.65 (q, 1H), 3.80−3.85 (d, $J$ = 15 Hz, 1H), 4.10−4.22 (m, 2H), 6.85−6.88 (dd, 1H), 6.98 (s, 1H), 7.12−7.35 (m, 5H), 7.41−7.44 (d, $J$ = 8 Hz, 1H); ESI MS $m/z$ 486 ($M - H^+$).

**1-Benzyl-(5*S*)-isopropyl-3-(ethoxycarbonyl)-4-hydroxypyrrolidin-2-one (1d)**: 11.6 mg (100%); HPLC $t_R$ 5.16 min; $^1$H NMR ($CD_3OD$) $\delta$ 0.795−0.977 (dd, $J$ = 7 Hz, 6H), 1.27−1.32 (t, $J$ = 7 Hz, 3H), 2.15−2.22 (m, 1H), 3.30 (s, 1H), 4.03−4.08 (d, $J$ = 15 Hz, 1H), 4.13−4.28 (m, 2H), 5.12−5.17 (d, $J$ = 15 Hz, 1H), 7.18−7.33 (m, 5H); ESI MS $m/z$ 302 ($M - H^+$).

**3-(Ethoxycarbonyl)-4-hydroxy-(5*S*)-isopropyl-1-(3,5-bis-(trifluoromethyl)benzyl)pyrrolidin-2-one (1f)**: 15.6 mg (100%); HPLC $t_R$ 5.72 min; mp 89−90 °C; $^1$H NMR ($CD_3OD$) $\delta$ 0.835−0.858 (d, $J$ = 7 Hz, 3H), 0.955−0.978 (d, $J$ = 7 Hz, 3H),1.27−1.32 (t, $J$ = 7 Hz, 3H), 2.14−2.18 (m, 1H), 3.40 (d, $J$ = 2 Hz, 1H), 4.15−4.26 (m, 2H), 4.48−4.54 (d, $J$ = 2H), 1.99−2.03 (m, 1H), 4.02−4.03 (d, 1H), 4.36−4.41 (d, $J$ = 15.3 Hz, 1H), 4.91−4.96 (d, $J$ = 15.3 Hz, 1H), 7.32−7.51 (m, 10H); ESI MS $m/z$ 323 ($M + H^+$).

**(*S*)-5-Benzyl-4-hydroxy-1-(4-phenylbenzyl)-3-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (3a)**: 36.1 mg (100%); HPLC $t_R$ 4.49 min; mp 221−223 °C; $^1$H NMR ($CD_3OD$) $\delta$ 2.97−3.04 (dd, 1H), 3.35−3.36 (dd, 1H), 3.68 (s, 0.5H), 3.91−3.96 (m, 1H), 4.01 (s, 0.5H), 5.14−5.20 (d, $J$ = 15 Hz, 1H), 7.12−7.59 (m, 14H), 8.08−8.10 (d, $J$ = 8 Hz, 2H); ESI MS $m/z$ 498 ($M - H^+$).

**(*S*)-5-Benzyl-4-hydroxy-1-(4-phenylbenzyl)-3-(3,5-bis(trifluoromethyl)phenyl)pyrrolidin-2-one (3c)**: 43.0 mg (100%); HPLC $t_R$ 4.85 min; mp 228−230 °C; $^1$H NMR ($CD_3OD$) $\delta$ 2.98−3.05 (dd, 1H), 3.31−3.38 (dd, 1H), 3.94−4.03 (m, 2H), 5.15−5.20 (d, $J$ = 15 Hz, 1H), 7.12−7.90 (m, 15H), 8.68 (s, 1H); ESI MS $m/z$ 566 ($M - H^+$).

**(*S*)-5-Benzyl-3-(5-chloro-3-methylbenzo[*b*]thiophene)-4-hydroxy-1-(4-(phenyl)benzyl)pyrrolidin-2-one (3d)**: 42.2 mg (100%); HPLC $t_R$ 4.67 min; mp 198−200 °C; $^1$H NMR ($CD_3OD$) $\delta$ 1.98 (s, 3H), 3.05−3.11 (dd, 1H), 3.32−3.37 (dd, 1H), 4.09−4.12 (t, $J$ = 4 Hz, 1H), 4.18−4.23 (d, $J$ = 15 Hz, 1H), 5.17−5.23 (d, $J$ = 15 Hz, 1H), 7.20−7.34 (m, 10H), 7.39−7.44 (t, $J$ = 7 Hz, 2H), 7.57−7.61 (m, 4H), 7.69−7.71 (d, $J$ = 8 Hz, 1H); ESI MS $m/z$ 534 ($M - H^+$).

**Supporting Information Available:** $^1$H NMR spectra, low-resolution mass spectra, and LC spectra available for all compounds (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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