Synthesis of Chiral Tetramic Acids: Preparation of (S)-5-Benzylpyrrolidine-2,4-dione from L-Phenylalanine Methyl Ester Hydrochloride

Kyle M. Lambert,* Austin W. Medley, Amy C. Jackson, Lauren E. Markham, and John L. Wood

Department of Chemistry and Biochemistry, Baylor University, One Bear Place 97348, Waco, Texas 76798, United States

Checked by Anna C. Impastato and Dirk Trauner

![Chemical reactions and products](image)
Procedure (Note 1)

A. (S)-2-[2-(Methoxycarbonyl)acetylamino]-3-phenylpropanoic acid methyl ester (2). A 1-L three-necked, round-bottomed flask (24/40) (Note 2) (Figure 1) is equipped with a Teflon-coated, oval, magnetic stir bar (2 cm x 2 cm x 4 cm) and L-phenylalanine methyl ester hydrochloride (1) (21.6 g, 0.1 mol, 1.0 equiv) (Note 3), a saturated aqueous solution of NaHCO₃ (500 mL) (Note 4), and methylene chloride (300 mL) (Note 3) (Figure 1) are added under an air atmosphere.

Figure 1. Initial reaction set-up; (A) Upon addition of 1, (B) After addition of 500 mL of saturated, aqueous NaHCO₃, (C) Upon initial addition of CH₂Cl₂, (D) Upon completion of addition of CH₂Cl₂

Magnetic stirring is commenced (Notes 5 and 6) and the reaction mixture is allowed to stir for 20 min (Note 7), at which point, methyl malonyl chloride (15.1 g, 11.8 mL, 0.11 mol, 1.1 equiv) (Notes 3 and 8) is added drop-wise via
syringe (Note 9) through the septum fitted on the central neck of the reaction flask (Note 10) (Figure 2).

Figure 2. Depiction of the reaction progress, (A) Initial addition of methyl malonyl chloride, (B) 10 Minutes into the addition (C) Rinsing of syringe upon completion of addition, (D) Upon completion of reaction, 20 minutes after addition

After completion of the addition of methyl malonyl chloride, the reaction mixture is allowed to stir for 20 min (Note 11). The reaction mixture is then transferred (Note 12) (Figure 3) to a 1-L separatory funnel, and the two phases are allowed to settle, the organic layer is removed.
The remaining aqueous layer in the separatory funnel is extracted with methylene chloride (2 x 150 mL). The organic layers are combined into a 1-L Erlenmeyer flask, dried over anhydrous sodium sulfate (~ 20 g) (Note 3) and filtered (Note 13) into a tared 1-L one-necked, round-bottomed flask. The bulk of the solvent is removed on a rotary evaporator (Note 14). Residual solvent is removed by placing the flask under high vacuum with agitation at 45 °C (Note 15), which affords (S)-2-[2-(methoxycarbonyl)acetylamino]-3-phenylpropanoic acid methyl ester (2) (27.8 g, 99%) (Notes 16, 17, 18 and 19) as a faint yellow oil (Figure 4).
B. (5S)-5-Benzyl-3-methoxycarbonyl-2,4-dioxopyrrolidine (3). To a 1-L, one-necked, round-bottomed flask (24/40) containing (S)-2-[2-(methoxycarbonyl)acetylamino]-3-phenylpropanoic acid methyl ester (2) (27.4 g, 98.1 mmol, 1.0 equiv) and a Teflon-coated, oval, magnetic stir bar (2 cm x 2 cm x 4 cm) is added 500 mL of HPLC-grade methanol (500 mL) (Note 3). The flask is capped with a septum and placed under an atmosphere of nitrogen gas with purging. Magnetic stirring is commenced (Note 20), and a 25 wt% solution of sodium methoxide in methanol (24 mL) (Note 3) (5.8 g, 108 mmol, 1.1 equiv) is added in one portion via syringe through the septum (Figure 5A).

Figure 5. Depiction of reaction progress; (A) Initial addition of 25 wt% sodium methoxide solution, (B) Upon completion of addition, (C) Reaction set-up for heating, (D) Upon completion of reaction, 10 minutes of heating
At this point, the septum is quickly removed and the reaction flask is fitted with a large Vigreux column (24/40; 16 in. length) capped with a septum, the atmosphere of nitrogen gas is restored, and the entire set-up is placed in a pre-heated aluminum block set at 65 °C (Note 21) (Figure 5C). The reaction mixture is placed in the aluminum block for 10 min (Note 22), then the heating element of the hot plate is switched off and the reaction flask is removed from the heating block by raising the clamped apparatus, and the solution is allowed to cool under the nitrogen atmosphere for 5 min. The magnetic stir bar is then removed and rinsed with methanol (5 mL). The solvent is immediately removed on a rotary evaporator (Note 23) to afford an off-white to yellow-colored solid (Figure 6).

![Crude off-white to yellow solid](image)

**Figure 6. Crude off-white to yellow solid**

To the flask containing the solid is added deionized water (500 mL) and the flask is manually swirled until full dissolution occurred. The yellow aqueous solution is transferred to a 2-L separatory funnel and washed with ethyl acetate (3 x 200 mL) (Note 24). The aqueous layers (~700 mL) are combined and added back into the separatory funnel, which is followed by addition of methylene chloride (500 mL) (Note 25). To this biphasic solution is added aqueous 1 M solution of hydrochloric acid (300 mL) (Note 26) and the separatory funnel is vigorously shaken. Upon settling of the two layers, the bottom organic layer is removed. The remaining aqueous layer is additionally extracted with methylene chloride (2 x 200 mL). The methylene chloride layers are combined in a 1-L Erlenmeyer flask, dried over 20 g of
anhydrous sodium sulfate (Note 3) and filtered (Note 27) into a tared 2-L one-necked, round-bottomed flask. The bulk of the solvent is removed on a rotary evaporator (Note 28). Residual solvent is removed by placing the flask under high vacuum (Note 29), which affords (5S)-5-benzyl-3-methoxycarbonyl-2,4-dioxopyrrolidine (3) (23.3 g, 89%) (Notes 30, 31, 32, and 33) as an off-white solid (Figure 7).

Figure 7. Title compound 3 upon isolation

C. (5S)-5-Benzylpyrrolidine-2,4-dione (4). To the 2-L one-necked, round-bottomed flask (24/40) containing (5S)-5-benzyl-3-methoxycarbonyl-2,4-dioxopyrrolidine (3) (22.6 g, 91.4 mmol, 1.0 equiv) is added a Teflon-coated, oval, magnetic stir bar (2 cm x 2 cm x 4 cm), acetonitrile (1.2 L) (Note 3) and deionized water (1.5 mL) (Note 3). The flask is swirled manually to ensure all solids are free from the flask walls, and then fitted with a large Vigreux column (24/40) capped with a septum. The flask is placed under an atmosphere of nitrogen gas and heated to reflux for 12 h in an aluminum heating block set to 85 °C (Note 34) (Figure 8). At which point, the heating element of the hot plate is switched off, the reaction flask is removed from the heating block, and the solution allowed to cool to 40 °C. The magnetic stir bar is removed and rinsed with acetonitrile (5 mL). The solvent is removed on a rotary evaporator (Note 23) to afford 17.9 g (95%) of a yellow-colored solid (Note 35). The magnetic stir bar is placed back into the 2-L flask that contain crude 4.
Using a plastic funnel (9 cm diameter) and a set of heat-resistant gloves, hot (77 °C) ethyl acetate (200 mL) (Note 3) is added to the 2-L flask (Figure 9a). The flask is swirled manually to ensure all solids are free from the flask walls (Figure 9b) and then fitted with a large Vigreux column (24/40; 16 in. length) open to air. The solution is heated to reflux (77 °C) until complete dissolution (Figure 9c). The homogenous yellow solution is then directly poured, while hot, into a 500-mL Erlenmeyer flask containing a Teflon-coated, octahedral, magnetic stir bar (5 cm x 1 cm x 1 cm) (Note 36) and ethyl acetate (50 mL) (Notes 3 and 37) (Figure 9d). Saturation of the solution is achieved by concentrating to a volume of 200 mL by gently heating the Erlenmeyer flask on the hot plate (85 °C) under a gentle stream of nitrogen gas (Figure 10a). Upon reaching a total volume of 200 mL, the magnetic stir bar is removed. The magnetic stir bar and temperature probe are each rinsed with warm (77 °C) ethyl acetate (5 mL). The flask is set aside (Figure 10b) and allowed to slowly cool to room temperature (23 °C). Crystals of 4 form within 10 min (Note 38) (Figure 10c). The flask is then placed in a −4 °C freezer for 4 h. The recrystallized product 4 is isolated via filtration (Note 39) to afford 10.0 g (60%) of the title compound 4 as a light yellow crystalline solid (Note 40). A second recrystallization is necessary to increase the enantiopurity of the final compound, thus the 10.0 g of compound 4 is transferred to a 300-mL
Figure 9. (A) Addition of hot ethyl acetate into flask, (B) Dislodgment of solid adhered to walls of flask, (C) Heating of mixture to achieve dissolution, (D) Transfer of solution into Erlenmeyer flask for recrystallization

Erlenmeyer flask, and a Teflon-coated, octahedral, magnetic stir bar (5 cm x 1 cm x 1 cm) (Note 36) is added along with ethyl acetate (150 mL) (Note 3). The flask is heated to 77 °C on a hot plate until complete dissolution is achieved, at which point, the heating element is switched off, the magnetic stir bar removed, and the flask allowed to slowly cool to room temperature (23 °C). Within 10 minutes crystals of 4 form (Note 40). The flask is then placed in a −4 °C freezer for 4 h. The recrystallized product 4 is isolated via
filtration (Note 41) to afford 6.9 g (41%) of the title compound (4) as a white crystalline solid in > 99% ee (Notes 41, 42, 43, and 44) (Figure 11).

Figure 10. (A) Concentration of solution under N$_2$ gas, (B) Solution after complete dissolution, (C) Onset of crystallization

Figure 11. Title compound 4 upon isolation
Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include, but not necessarily be limited to, an evaluation of the potential hazards associated with phenylalanine methyl ester hydrochloride, methyl malonyl chloride, methylene chloride, sodium bicarbonate, methanol, acetonitrile, ethyl acetate, hexanes, sodium methoxide, trifluoroacetic acid, and hydrochloric acid, as well as the proper procedures for operating a vacuum pump and working with systems under negative pressure, using an aluminium heating block/oil bath to heat reactions to reflux in an open system, and working with caustic acids and bases such as 1M aqueous hydrochloric acid and sodium methoxide.

2. The three-necked flask is equipped as follows: the first side neck is fitted with an alcohol thermometer via a thermometer adapter, the central neck is fitted with a septum, and the third side neck is left open to the atmosphere to be used for addition of reagents and for ventilation. See Figure 1 for reaction set-up.

3. L-Phenylalanine methyl ester hydrochloride (>98% purity; [α]D25 = +36.7, c = 1.00, EtOH), D-phenylalanine methyl ester hydrochloride (>98% purity; [α]D25 = -36.5, c = 2.00, EtOH), and methyl malonyl chloride (97% purity) were purchased from Oakwood Chemicals. Methylene chloride (GC/MS grade/ ACS grade), methanol (HPLC grade), acetonitrile (HPLC grade), and ethyl acetate (HPLC grade/ACS grade), sodium bicarbonate (ACS grade, EMD Millipore), and sodium sulfate
(anhydrous, granular) were purchased from Fisher Scientific. Sodium methoxide as 25 weight % solution in methanol was purchased from Sigma Aldrich. Deionized water was obtained from NYU’s water purification system. ACS grade solvents were used for extractions. HPLC or GC/MS grade solvents were used for all reactions and recrystallizations. All chemicals were used as received with no further purification.

4. An aqueous saturated solution of sodium bicarbonate was prepared by adding solid sodium bicarbonate (150 g) to 1 L of deionized water at 23 °C. Upon saturation, the remaining solid was allowed to settle to the bottom of the container, and the top portion of the solution was used.

5. The magnetic stirring was conducted at a rate of 900 rpm to ensure proper mixing of the bi-phasic reaction medium occurred.

6. Upon commencing stirring, the initially milky reaction medium turns to a clear, light yellow biphasic solution. Evolution of carbon dioxide is observed from the neutralization of the hydrochloride salt of the starting material 1.

7. This is the point when carbon dioxide evolution ceased due to full neutralization. The pH of the aqueous layer was measured to be ≈ 8. This can be confirmed by stopping the stirring briefly and noting the absence of bubbles emerging from the organic layer; stirring must be commenced before proceeding to the next operation.

8. The methyl malonyl chloride was weighed in a capped, tared 12-mL plastic syringe.

9. The neat methyl malonyl chloride solution was added dropwise, by hand, at a rate of ≈ 1 mL/min over a period of ≈ 12 minutes. The submitters found that it was necessary to use a syringe for the addition of the methyl malonyl chloride as it avoided contact of the reagent with adventitious moisture. Use of a small addition funnel, even under a stream of N₂(g) resulted in partial consumption of the acid chloride with residual moisture. A syringe pump, while ideal for this task, was not used to keep the method readily accessible by avoiding the need to employ specialized equipment. The temperature of the reaction mixture increased slightly from 21 °C to 24 °C during the addition.

10. The syringe was rinsed by drawing up 12 mL of the reaction mixture through the open neck of the reaction flask.

11. At this time evolution of carbon dioxide had ceased and the reaction was deemed complete. The pH of the aqueous layer was measured to be ≈ 8.
This can be confirmed by stopping the stirring briefly and noting the absence of bubbles emerging from the organic layer.

12. The reaction flask was rinsed with a 50-mL portion of methylene chloride to ensure complete transfer to the separatory funnel.

13. The reaction mixture was gravity filtered through a plastic funnel (9 cm diameter) containing a folded, filter paper (15 cm diameter; coarse porosity; fast flow rate; Fisherbrand). The flask was rinsed with two 25-mL portions of methylene chloride.

14. The rotary evaporator was operated at 25 °C at a pressure of 350 mmHg, which was then reduced to 25 mmHg.

15. A pre-weighed Teflon-coated, oval magnetic stir bar (2 cm x 2 cm x 4 cm) of known mass was added to the 1-L flask containing compound 2 and dried under high vacuum with stirring (700 rpm) and gentle heating (1 mmHg, 45 °C) for 4 h. The mass of the stir bar was subtracted from the final obtained mass to provide the final yield of the analytically pure product.
The procedure described will afford the title compound (2) in high analytical purity. Quantitative $^1$H NMR analysis (relaxation delay of 30 sec) showed this product to be >99% purity (28.72 mg of analyte with 16.57 mg 1,3,5-trimethoxybenzene of 99.7% purity purchased from Oakwood Chemicals as a standard). An additional run of this procedure on the same scale afforded the product in an isolated yield of 98%.

The product (2) was characterized as follows: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.08 (dd, $J = 13.9, 6.4$ Hz, 1H), 3.17 (dd, $J = 13.9, 5.7$ Hz, 1H), 3.23 – 3.36 (m, 2H), 3.71 (s, 6H), 4.86 (dt, $J = 7.6, 6.1$ Hz, 1H), 7.12 (d, $J = 6.4$ Hz, 1H), 7.20 – 7.26 (m, 1H), 7.26 – 7.32 (m, 2H), 7.38 (d, $J = 7.7$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 37.9, 41.2, 52.5, 52.6, 53.6, 127.2, 128.7, 129.3, 135.9, 164.6, 169.3, 171.7. ATR-FTIR: 3318, 3029, 2953, 1737, 1652, 1531, 1497, 1435, 1346, 1274, 1169, 1118, 1079, 1016, 744 cm$^{-1}$. $[\alpha]_D^{23} = +24.1$ (c = 1.01, MeOH), HRMS (ESI) calcd. for [M+H] $^+$ C$_{14}$H$_{17}$NO$_5$ 280.1179, found: 280.1176.

Chiral HPLC analysis was conducted on a Preparative HPLC using a 1260 Infinity Agilent Technologies system coupled to a photodiode array detector (PDA) as follows: chiral column- Phenomenex Lux-3u Cellulose–2 (150 x 4.6 mm), part number = 00F-4456-E0; solvent system-isocratic flow of 30% acetonitrile containing 0.1% formic acid and 70% water containing 0.1% formic acid at a rate of 1.0 mL/min. The retention time of (S)-2 was 12.44 min (11.4 min to 14.3 min, baseline to baseline) and that of its enantiomer (R)-2 was 17.72 min (16.1 min to 21.2 min,
baseline to baseline). Integration of the diode array trace revealed that the title compound 2 was isolated in high enantiopurity (100% ee). Additional runs of this procedure provided enantiopurities of 99.9%.

19. TLC conditions were as follows: 75% EtOAc in hexanes, stained with potassium permanganate solution. \( R_f = 0.14 \) (1); 0.68 (2).

Figure 14. TLC of 1 and 2; KMnO\(_4\) stain

20. The magnetic stirring was conducted at a rate of 700 rpm. Manual swirling of the reaction mixture may be necessary if the magnetic stir bar fails to initiate.

21. It is important to pre-heat the aluminum block to 65 °C before adding the sodium methoxide solution to the reaction flask. The magnetic stirring rate was set to 700 rpm.

22. It is critical to only allow the reaction mixture to remain in the heating block for 10 min, which is just enough time to allow the reaction mixture to reach reflux. At that point, the heating element is switched off and the flask removed by raising the clamp holding the set-up so that the flask is free of the aluminum block. The reaction mixture is then allowed to cool to 40 °C outside of the aluminum block. If this step is not carefully executed, substantial epimerization of the desired product will result.

23. The rotary evaporator bath temperature was set at 40 °C and was operated at 90 rpm at an initial pressure of 250 mmHg to avoid bumping of the solution. The rotary evaporator was then adjusted to 150 rpm and a pressure of 25 mmHg during the course of the distillation (~ 40 min).

24. Each time the aqueous layer was transferred the container was rinsed with a portion of deionized water (25 mL). The ethyl acetate washings were combined and back-extracted with deionized water (100 mL). The
ethyl acetate layer was then discarded as it contained the organic impurities.

25. It is important to add the methylene chloride before the aqueous 1 M hydrochloric acid is added or else a heterogeneous emulsion will result.

26. The yellow aqueous solution will become milky upon the addition of the solution of hydrochloric acid, but upon vigorous shaking will eventually become clear.

27. The reaction mixture was gravity filtered through a plastic funnel (9 cm diameter) containing a folded, filter paper (15 cm diameter; coarse porosity; fast flow rate; Fisherbrand). The flask was rinsed with methylene chloride (2 x 25 mL).

![Figure 15. Filtration of dried organic layer into a tared 2-L flask](image)

28. The rotary evaporator bath temperature was set at 25 °C and was operated at 30 rpm and at an initial pressure of 300 mmHg to avoid bumping of the solution, after which the rotary evaporator was slowly adjusted to 50 mmHg during the course of the distillation.

29. Residual solvent was removed under high vacuum (0.7 mmHg, 35 °C) for 1 h.
The procedure described will afford the title compound (3) in fair analytical purity. Quantitative $^1$H NMR analysis (relaxation delay of 30 sec) showed this product to be of 93% purity (28.4 mg of analyte with 15.0 mg 1,3,5-trimethoxybenzene of 99.7% purity purchased from Oakwood Chemicals as a standard). The quantitative $^1$H NMR analysis should be taken upon isolation since the title compound (3) very slowly converts to compound 4 upon standing. A second run of the procedure on the same scale afforded an isolated yield of 88%.

The product was characterized as follows: mp 152–156 °C (DCM; uncorrected); $^1$H NMR (400 MHz, CDCl$_3$) δ: 2.77 (dd, $J = 13.8, 8.7$ Hz, 1H), 3.27 (dd, $J = 14.1, 4.1$ Hz, 1H), 3.89 (s, 3H), 4.36 (dd, $J = 9.0, 4.0$ Hz, 1H), 6.11 (s, 1H), 7.16 – 7.23 (m, 2H), 7.20 – 7.34 (m, 3H), 11.20 (br s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 38.2, 52.6, 57.5, 99.2, 127.7, 129.1, 129.5, 135.6, 168.0, 168.2, 187.8; ATR-FTIR: 3377, 2865, 2534, 1643, 1589, 1496, 1441, 1423, 1394, 1224, 1296, 1116, 1093, 1061, 983, 908, 846, 795, 759, 743 cm$^{-1}$; $[\alpha]_D^{23.5} = -72.43$ (c = 1.00, MeOH); HRMS (APCI) calcd. for C$_{13}$H$_{13}$NO$_4$ [M+H]$^+$ 248.0917, found 248.0917; calcd. for C$_{13}$H$_{13}$NO$_4$ [M+Na]$^+$ 270.0737, found 270.0741.

Chiral HPLC analysis was conducted on a Preparative HPLC using a 1260 Infinity Agilent Technologies system coupled to a photodiode array detector (PDA) as follows: chiral column- Phenomenex Lux-3u Cellulose-2 (150 x 4.6 mm), part number = 00F-4456-E0; solvent system-isocratic flow of 40% acetonitrile containing 0.1% formic acid and 60%
water containing 0.1% formic acid at a rate of 1.2 mL/min. The retention time of (S)-3 was 39.30 min (37.1 min to 46.2 min, baseline to baseline) and that of its enantiomer (R)-3 was 50.91 min (49.5 min to 61.8 min, baseline to baseline). Integration of the diode array trace revealed that the title compound 3 was isolated in modest enantiopurity (60% ee). See attached data for chromatograph. Additional runs of this procedure provided enantiopurities of 54%. Runs by the submitting authors provided enantiopurities of 64, 73 and 74%.

33. TLC conditions were as follows: 10% MeOH in methylene chloride, stained with potassium permanganate solution. $R_f = 0.76$ (2); 0.16 (3).

Figure 17. TLC of 2 and 3; UV Light and KMnO$_4$ Stain

34. The cloudy solution was magnetically stirred at a rate of 700 rpm and upon reaching reflux full dissolution of the precipitate was observed; see Figure 8.

35. The crude material obtained was of high analytical purity 92%, however it had only modest enantiopurity (65% ee). Additional runs of this procedure provided enantiopurities of 64%.

36. The magnetic stirring was conducted at a rate of 200 rpm.

37. The flask was rinsed with ethyl acetate (50 mL) to ensure complete transfer.

38. The solution was allowed to stand for 2 h at 23 °C.

39. The reaction mixture was vacuum filtered (ca. 40 mmHg) through a ceramic Büchner funnel (10 cm diameter) containing a filter paper (9 cm diameter; medium porosity; fast flow rate; Whatman) fitted to a 1-L filter flask. The collected precipitate was rinsed with cold ethyl acetate (2 x
100 mL (Note 3), which was chilled in a dry-ice acetone bath (−78 °C) prior to use. The precipitate was dried by pulling air through the filter-set-up for 20 min. The final product was placed under high vacuum (0.7 mmHg; 25 °C) for 1 h to remove any residual solvent.

Figure 18. Vacuum filtration setup to isolate recrystallized product 4

This material obtained was of high analytical purity >98% and had good enantiopurity (97% ee). Additional runs of this procedure provided enantiopurities of 98%.

Figure 19. Isolation of recrystallized product 4
41. The procedure described will afford the title compound (4) in high analytical purity. Quantitative $^1$H NMR analysis (relaxation delay of 30 sec) showed this product was of 98% purity (21.17 mg of analyte with 21.30 mg 1,3,5-trimethoxybenzene of 99.7% purity purchased from Oakwood Chemicals as a standard). Additional runs of this procedure afforded isolated yields of 39%.

42. The product was characterized as follows: mp 161–163 °C (EtOAc, uncorrected); $^1$H NMR (400 MHz, CDCl$_3$) δ: 2.69 (dd, $J = 22.2$, 1.6 Hz, 1H), 2.85 (dd, $J = 13.9$, 8.0 Hz, 1H), 2.91 (d, $J = 22.2$ Hz, 1H), 3.14 (dd, $J = 22.2$ Hz, 1H), 4.23 (ddd, $J = 8.1$, 4.1, 1.5 Hz, 1H), 6.76 (s, 1H), 7.10–7.18 (m, 2H), 7.23–7.28 (m, 1H), 7.28–7.34 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 38.5, 41.0, 65.2, 127.5, 129.0, 129.4, 135.2, 171.0, 206.6; ATR-FTIR: 3209, 3029, 2919, 1765, 1666, 1625, 1278, 766, 703, 571 cm$^{-1}$; [$\alpha$]$_D^{24.1}$ = −44.77 (c = 1.02, MeOH); HRMS (APCI): calcd. for C$_{11}$H$_{11}$NO$_2$ [M+H]$^+$ 190.0863, found 190.0860.

43. Chiral HPLC analysis was conducted on a Preparative HPLC was performed on a 1260 Infinity Agilent Technologies system coupled to a photodiode array detector (PDA) as follows: chiral column-Phenomenex Lux-3u Cellulose–2 (150 x 4.6 mm), part number = 00F-4456-E0; solvent system-isocratic flow of 15% acetonitrile containing 0.1% formic acid and 85% water containing 0.1% formic acid at a rate of 1.2 mL/min. The retention time of (S)-4 was 15.49 min (14.5 min to 17.5 min, baseline to baseline) and that of its enantiomer (R)-4 was 12.93 min (11.9 min to 14.4 min, baseline to baseline). Integration of the diode array trace revealed that the title compound 4 was isolated in high enantiopurity (>99% ee). See attached data for chromatograph. Additional runs of this procedure provided enantiopurities of >99%.

44. TLC conditions were as follows: 10% MeOH in methylene chloride, stained with potassium permanganate solution. $R_f = 0.16$ (3); 0.16 (4).
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Discussion

An Overview of Tetramic Acid-Containing Natural Products and their Biological Properties

The tetramic acid (pyrrolidine-2,4-dione) scaffold can be found embedded within a plethora of natural products which exhibit a wide range of bioactivities, including powerful antibiotic, antiviral, cytotoxic, and fungicidal properties, as well as inhibition of tumor growth. The molecular complexity of tetramic acid-containing natural products is quite diverse as exemplified in Figure 21. Tenuazonic acid (5) was one of the first tetramic acid natural products isolated and its identification as an antitumor, antiviral, and antibiotic agent spurred the interest in the isolation and development of syntheses to access tetramic acid natural products. Not long after, more structurally complex tetramic acid natural products such as tirandamycin A (6), streptolydigin (8) and tirandalydigin (7), which contain 2,6-dioxabicyclononane skeletons, were isolated and found to function as potent antibiotics due to their inhibition of bacterial DNA-directed RNA polymerase. The toxic alkaloid cyclopiazonic acid (11) is an indole-based tetramic acid that was isolated as a fungal secondary metabolite from samples of commercially stored grain and cereal products that had accumulated mold. It is also common to find the tetramic acid scaffold embedded within complex macrocyclic core structures such as those found within aburatubolactam A (9), macrocidin A (10), and cylindramide A (12), which exhibited inhibitory properties towards superoxide generation, herbicidal properties, and cytotoxicity towards B16 melanoma cells, respectively. Tetrapetalone A (12) which was isolated by Hirota and co-workers is a modest lipoxygenase inhibitor and further exemplifies the diversity present in tetramic acid natural products as it features a fused tetramic acid-azepine core, a central para-quinol, a β-linked rhodinose sugar, and lastly, a unique C3 methylation that is atypical of tetramic acid natural products which typically feature a C3 acylation (i.e. 5-12). More recently, aspergilline A (14), a highly oxygenated cyclopiazonic acid derivative,
Figure 21. Selected natural products containing a tetramic acid
along with four other congeners was isolated in 2014 from the fungus *Aspergillus versicolor* by Hu and Gao\(^1\) and was found to exhibit cytotoxicity against a number of human cancer cell lines (NB4 promyelocytic leukemia, A549 lung epithelial carcinoma, SHSY5Y neuroblastoma, PC3 prostate cancer, and MCF7 breast adenocarcinoma) at concentrations in the range of 1.2-3.6 \(\mu\)M. Aside from its interesting biological activity, it features a unique rigid, hexacyclic indole-tetrahydrofuran-tetramic acid scaffold. The tetramic acid portion of 14 is oxidized at the C3 position and the C4 carbonyl is tied-up as a hemiacetal that forms the central fused tetrahydrofuran ring. Given the wide-ranging biological activities and molecular diversity present in tetramic acid natural products, there is a great interest in developing synthetic methodologies that allow for a modular and facile construction of this privileged motif.

Given the interest in tetramic acids both from a biological and synthetic perspective, the chemistry to access these motifs and their biological properties has been the subject of extensive reviews.\(^2\) This discussion is aimed at providing a general overview of tetramic acid chemistry and highlighting the utility of developed synthetic methodologies aimed at the construction of the pyrrolidine-2,4-dione core as well as the challenges encountered when applying these methods towards more complex systems.

### An Overview of Tetramic Acid Properties that Influence their Chemical Reactivity

The simplest member of the tetramic acids is pyrrolidine-2,4-dione (15; Scheme 1), known colloquially as “tetramic acid”; a term first coined in 1909 by Anschütz in order to describe the nitrogen counterpart of tetronic acid.\(^2\) While tetramic acid (15) was named in 1909 and tetramic acid derivatives such as 5 and 11 were isolated and identified in the 1960s, the parent compound itself (15) did not exist until 1972 when it was prepared by Mulholland and co-workers.\(^1\) Some years earlier, in 1954 Lacey prepared a number of 3-acyltetramic acid derivatives via an intramolecular Dieckmann condensation facilitated by the use of sodium methoxide in methanol,\(^6\) as exemplified by the conversion of 16 to 17 shown below in Scheme 2. This procedure is the principle method used to prepare tetramic acids and their
derivatives as it is operationally simple and a wide range of tetramic acids with varying substitutions (i.e. $R_1$, $R_2$, and $R_3$) can be constructed. Of note, a number of tetramic acids can be prepared in enantiomerically enriched form using the Lacey-Dieckmann cyclization since the acyclic precursors are easily prepared from a variety of chiral amino acid esters (such as 2); which are commercially available as their hydrochloride salts (i.e. 1). These acyclic starting materials possess an asymmetric center which becomes established at the C5 position of the tetramic acid (Scheme 1) upon base-catalyzed cyclization. Surprisingly, these chiral materials can be subjected to strongly basic conditions (i.e. sodium methoxide, potassium tert-butoxide, etc.) for short periods of time without complete racemization, even though the asymmetric center is adjacent to the C4 ketone of the tetramic acid.

Scheme 2. An example of the Lacey-Dieckmann condensation

The presence of an asymmetric center at C5 is common among tetramic acid natural products (i.e. 5, 8-14; Figure 21), and is unusual given tetramic acids are known to exist as a mixture of keto-enol tautomers in solution.
(Scheme 1). Unsubstituted tetramic acid (15) could theoretically exist as a mixture of five possible keto-enol tautomers (15, 15a, 15b, 15c, and 15d; Scheme 1), although only the keto form 15 and enol form 15a are observed by NMR spectroscopy. Moloney and Jeong computationally and experimentally investigated by NMR spectroscopy the tautomeric behavior of 15 as well as several N1 and C5 substituted tetramic acids. It was found computationally, at the B3LYP (6-31G*) level, that relative to the keto form of 15, the enol form of 15a was 11.2 kcal/mol higher in energy in the gas phase. In comparison, enol forms 15b and 15c were computed at the same level in the gas phase to be 17.7 and 18.6 kcal/mol higher in energy than the keto form 15, respectively. Addition of an acyl substituent to N1 of the tetramic acid was found to lower this difference in relative energies between tetramic acids of keto-type 15 and enol-type 15b to the range of 4.6–12.9 kcal/mol still favoring keto-type 15. The existence of an aromatic pyrrole tautomer (15d), formed from a second enolization of either 15a or 15b, was not considered in Moloney and Jeong’s study. This possibility was investigated in a semiempirical SCF-MO study at the AM1 level of 3-acyl tetramic acids by Broughton and Woodward and they concluded that the heats of formation of pyrrole tautomers such as 15d were too high (~16–19 kcal/mol) to be formed under normal conditions. Quite simply put, the stereointegrity of the asymmetric center commonly found at C5 of tetramic acid natural products is upheld because the enol-forms (15c and 15d) are too high in energy to be formed under the standard biological conditions in which such natural products exist. Synthetically, the C5 position of the tetramic acid is prone to racemization under certain conditions, and for this reason, a number of methodologies have been developed to circumvent this challenge; a topic that warrants further discussion below.

While these DFT calculations provide some insight into the keto-enol tautomeric behavior of tetramic acids in the gas phase, they do not account for external solvent effects which are present in the context of synthetic methods involving tetramic acids. Thus, in solution 15 and 15a were found to exist as nearly a 1:1 mixture in DMSO-D6, resulting in a negligible energy difference between the two forms of 0.05 kcal/mol at 298K. However, this tautomeric ratio is solvent dependent as demonstrated by the N1 Boc-protected derivative of tetramic acid 15 (R1=Boc). In CDCl3 solvent at 298K, the observed tautomeric ratio is 55:45 (15; R1=Boc:15a; R1=Boc) corresponding to a small energy difference of ~0.12 kcal/mol that slightly favors 15 (R1=Boc). On the contrary, the tautomeric preference reverses in CD3OD solvent at 298K, affording an observed ratio of 1:99 (15; R1=Boc:15a; R1=Boc), which
corresponds to a relative energy difference of ~2.7 kcal/mol favoring the enol form 15a (R₁=Boc). This tautomerism arises, as one might expect, due to the enhanced acidity of the hydrogens on the C3 position of the tetramic acid, hence its namesake.

Scheme 3. Keto-enol tautomerism observed in 3-acyl tetramic acid

Tetramic acids with no substitution at the C3 position generally have pKa values in the range of 4–6. The addition of an acyl or alkoxycarbonyl substituent to C3 of the tetramic acid core further increases the acidity of the C3 hydrogen and these compounds generally have pKa values in the ranges of 3–3.5 and 2.3–2.5 respectively. The introduction of a third carbonyl at C3 theoretically allows for nine possible keto-enol tautomers; however, similar to the unsubstituted case, not all are present in solution. In fact, only two pairs of rapidly converting internal keto-enol tautomers, such as 18/18a and 18b/18c (Scheme 3), are observed spectroscopically. This internal conversion proceeds through a fast exchange of the hydroxy proton along an intramolecular hydrogen bond (Scheme 3), which is faster than the NMR time scale, and thus, the observable chemical shifts and coupling constants represent the weighted population averages of these two internal tautomers. The interconversion of external tautomers, such as 18/18a into 18b/18c (Scheme 3), occurs more slowly as it requires a C-C bond rotation and this behavior is observable on the NMR time scale. The predominant keto-enol form observed in both solution and the solid state for 3-acylated tetramic acids is the exo-enol form, exemplified in 18. When the C3 position contains an alkoxycarbonyl substituent, such as compound 3 prepared in the
above procedure, the major tautomer observed tends to be the internal enol form, similar to 18c (as depicted for 3 in the above procedure).

This high degree of tautomerism in 3-acyl and 3-alkoxycarbonyl tetramic acids allows for the facile chelation with a number of metals, an important implication for their transport across the membranes of biological systems. Complexes of tetramic acids with Na, Mg, Ca, Cu, Ni, and Fe have all been isolated and characterized. From a synthetic perspective, during the work-up of reactions involving tetramic acids, the careful choice of drying agent is often necessary to prevent loss of the desired tetramic acid due to chelation to the metal. For example, in the above described procedure the use of magnesium sulfate (generally a preferred drying agent), instead of the described use of sodium sulfate to dry the final organic layer in the preparation of compound 3, resulted in lower isolated yields of product. While the above procedure avoids the use of column chromatography, the chelating ability of tetramic acids combined with their polar nature can make such separations difficult to accomplish. Commercial samples of silica gel used for chromatographic separations contain variable quantities of trace metals such as Fe, Cu, and Ca that can affect the quality of separations involving tetramic acids. The presence of these trace metals frequently leads to streaking along with the development of a colored band during the course of the separation (usually light pink-red in color, but can vary). This is due to the scrubbing of the trace metals from the silica gel by the tetramic acid substrate resulting in colored metal complexes. The presence of even small quantities of these inadvertently formed metal complexes can complicate NMR analysis, resulting in broadened peaks and seemingly “messy” spectra. However, if this problem arises, it can be resolved by shaking the collected fractions that contain the desired tetramic acid with a quantity of 5 wt% aqueous HCl in a separatory funnel and drying the collected organic layer with sodium sulfate; this effectively “frees” the tetramic acid substrate from the unwanted metal complex. If the substrate is tolerant to acidic media, the addition of a small quantity of acetic or formic acid to the solvent system used for the chromatographic separation may help to proactively alleviate these difficulties.
Synthetic Methods to Prepare Functionalized Tetramic Acids

Lacey-Dieckmann approach:

\[
\begin{align*}
R_1 & \quad \text{HCl} \\
\text{N} & \quad \text{O} \\
+ & \quad R_5 \\
\text{H} & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{Sat. NaHCO}_3 & \quad \\
\text{DCM} & \quad R_3 \\
\text{N} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{R}_1 & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{饱和} & \quad \text{NaHCO}_3 \\
\text{DCM} & \quad R_3 \\
\text{N} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{R}_1 & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{EtOAc} & \quad -\text{CO}_2 \quad \text{acetone} \\
\text{cat. H}_2\text{O} & \quad \text{MeCN} \quad \text{reflux} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{R}_1 & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{MeOH} & \quad \text{NaOMe} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} \\
\text{MeCN} & \quad \text{reflux} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{R}_1 & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{EtOAc} & \quad -\text{CO}_2 \quad \text{acetone} \\
\text{cat. H}_2\text{O} & \quad \text{MeCN} \quad \text{reflux} \\
\end{align*}
\]

Meldrum’s acid approach:

\[
\begin{align*}
R_1 & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{OH} & \quad R_3 \\
\text{H}_{2}	ext{C} & \quad \text{CH}_3 \\
\text{H}_{2}	ext{C} & \quad \text{CH}_3 \\
\text{IPCF} & \quad \text{DMAP} \\
\text{EtOAc} & \quad \text{reflux} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{R}_1 & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{EtOAc} & \quad -\text{CO}_2 \quad \text{acetone} \\
\text{cat. H}_2\text{O} & \quad \text{MeCN} \quad \text{reflux} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad R_5 \\
\text{R}_1 & \quad \text{O} \\
\text{O} & \quad R_3 \\
\text{EtOAc} & \quad -\text{CO}_2 \quad \text{acetone} \\
\text{cat. H}_2\text{O} & \quad \text{MeCN} \quad \text{reflux} \\
\end{align*}
\]

Scheme 4. Two common synthetic approaches to tetramic acids

The procedure described above was prepared to serve as a detailed and general method to access tetramic acids through a Lacey-Dieckmann cyclization approach (a generalized scheme is shown in Scheme 4). The Lacey-Dieckmann cyclization, aside from being the first methodology developed to access substituted tetramic acids, is still one of the most operationally simple methods available. As exemplified above, the preparation of acyclic precursors such as 2 can be accomplished in high yield under Schotten-Baumann conditions\(^\text{\textsuperscript{21}}\) from commercially available amino acid ester derivatives (i.e. 1) akin to the Fischer peptide synthesis.\(^\text{\textsuperscript{22}}\) While the above procedure furnished compounds 2, 3, and 4 with excellent isolated
yields (98%, 96%, and 99%; respectively), a slight epimerization (~15-20%) occurs during the cyclization of 3 in 4. This material with optical purity in the range of 65–74% ee could be purified by two simple recrystallizations to afford 4 as essentially a single enantiomer (>98% ee) in 53% over three synthetic steps with no required chromatography.

The epimerization at C5 of the tetramic acid (generally 10–30%) due to the strongly basic conditions used in the Lacey-Dieckmann cyclization has been found to be dependent on the overall reaction time, the identity of the substrate, and the base employed in the reaction. A notable methodology by Jouin, Nisato, and Castro was developed to address this synthetic drawback of the Lacey-Dieckmann cyclization. Their method (Scheme 4) relies on the acylation of Meldrum’s acid with a protected chiral amino acid (23). This is accomplished by employing isopropylchloroformate (IPCF) to generate a mixed anhydride of 23 that undergoes acylation with Meldrum’s acid in the presence of 4-dimethyaminopyridine (DMAP) to form an acylated derivative of general structure 24. Upon heating 24 in refluxing ethyl acetate, carbon dioxide is expelled along with a molecule of acetone resulting in the formation of an intermediate ketene which is captured via intramolecular attack by the nitrogen of the amino acid to produce nitrogen-protected tetramic acids of general form 22. The conditions employed preclude the epimerization of the C5 as no base is necessary. The experimental procedure needs to be stringently followed as slight changes in the stoichiometry or reversal of addition of the reagents resulted in lower yields of product. A subsequent improvement to this methodology using N,N′-dicyclohexylcarbodiimide (DCC) to accomplish the sensitive acylation was developed, but often difficulties arose in separating the final product away from the urea by-product; this problem was solved by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) which results in a water-soluble urea by-product that is easily removed by an extractive work-up. The one drawback of the Meldrum’s acid approach is that the nitrogen of the amino acid must be protected and the yields can vary greatly based on nature of this protecting group with tert-butyloxycarbonyl (Boc), carboxybenzyl (Cbz), fluorenylmethoxycarbonyl (Fmoc), and alkyl groups most commonly used. These two methods (Scheme 4) have found wide applications in the preparation of synthetic tetramic acids and in total synthesis.

As eluded to above, the tetramic acid core structure is unique in its ability to maintain a chiral center at C5, it possesses fairly acidic hydrogens at C3, and the cyclic lactam is extraordinarily stable allowing exposure to strong basic and strongly acidic conditions without opening. As such, tetramic
acids are extremely important building blocks for synthesis as they not only serve as core structures for a number of bioactive natural products, but they function as intermediates en route to other natural products.

![Figure 22. Tetramic acids as versatile building blocks](image)

Some of the common functionalizations that are possible with tetramic acids are shown in Figure 22. Due to their acidic nature, anions of tetramic acids are not particularly nucleophilic, thus, C3 alkylation and acylation can be particularly difficult as O-alkylation and O-acylation is favored at C4. The work of Jones and co-workers circumvents this problem by using a Lewis acid-catalyzed acylation of tetramic acids with acyl chlorides to afford isolable boron difluoride complexes which can be decomposed by acidic work-up to 3-acyl tetramic acids (Scheme 5).

![Scheme 5. Methods to accomplish C3 acylation of tetramic acids](image)
More recently, Jeong and Moloney\textsuperscript{32} have developed a milder approach to C3-acylated tetramic acids (30) (Scheme 5) that proceeds \textit{via} O-acylation of the parent tetramic acid (28) with the desired carboxylic acid in the presence of DCC and a catalytic amount of DMAP affording 27. By adding additional DMAP to a solution of this O-acylated tetramic acid (27) they were able to promote an acyl rearrangement to afford C3-acylated tetramic acids (30); initially adding a stoichiometric excess of DMAP affords 30 directly. These two synthetic methods provide a convenient way to introduce saturated acyl groups onto the 3-position of tetramic acids.

**Direct Acylation of Tetramic Acids with Unsaturated Systems and Synthetic Methodologies that Arose from the Total Syntheses of Tirandamycin (6)**

\begin{center}
\textbf{Scheme 6. Methodologies to access phosphorous-activated tetramic acids}
\end{center}
The direct acylation of tetramic acids with unsaturated acid chlorides or acid fluorides is of particular interest as this functionality is often found in natural products (i.e., 5–12; Figure 21). Unfortunately, this sort of transformation is problematic as O-acylation predominates and the attempted C3-acyl migration of these unsaturated systems results in complex mixtures of products.\textsuperscript{32,33} The installation of unsaturated acyl systems can be accomplished through either a late-stage Lacy-Dieckmann cyclization of a pre-functionalized, acyclic, unsaturated \( \beta \)-ketoamide to prepare the tetramic acid\textsuperscript{33} or through a Horner-Wadsworth-Emmons (HWE) olefination\textsuperscript{34} of a prepared tetramic acid containing a phosphonate ester. Boeckman and Thomas\textsuperscript{35} as well as Deshong and co-workers\textsuperscript{36} were pioneers in the area of developing methodologies to access phosphorous-activated tetramic acids (Scheme 6). Boeckman and Thomas prepared a Meldrum’s acid like phosphonate ester\textsuperscript{31,35b} that could be opened up under slightly acid conditions by glycine methyl ester to afford\textsuperscript{32} 32. Treatment of 32 with one equivalent of sodium methoxide cleanly affords the functionalized tetramic acid 33 via a Lacey-Dieckmann cyclization. Furthermore, it was shown that the phosphorous-activated tetramic acid 33 when exposed to two equivalents of lithium diisopropylamine (LDA) could undergo condensation with aldehydes to give 3-enoyl tetramic acids\textsuperscript{34} \textit{via} a HWE olefination. Deshong and co-workers prepared the same phosphorous-activated tetramic acid 33 from isooxazole\textsuperscript{35} through generating an isooxazolium salt (36) which then underwent base-induced fragmentation to give 37, and finally, treatment of 37 with one equivalent of sodium ethoxide cleanly affords the functionalized tetramic acid 33 also via a Lacey-Dieckmann cyclization. The \( N \)-2,4-dimethoxybenzyl (DMB) analogue (45) of 33 was used extensively to introduce the tetramic acid into the natural product tirandamycin A (6) in three separate total syntheses by Schlessinger,\textsuperscript{37} Deshong,\textsuperscript{38} Boeckman,\textsuperscript{39} and their co-workers (Scheme 7). A fourth total synthesis of 6 was accomplished by Bartlett and co-workers\textsuperscript{40} and uses a penultimate Lacey-Dieckmann cyclization of a DMB-protected \( \beta \)-ketoamide 47 followed by deprotection to afford 6. Tirandamycin A (6), unlike compound 5 and compounds 8-14, does not contain an asymmetric center at C5 of the tetramic acid, thus the strongly basic conditions needed for the HWE olefination as well as for the Lacey-Dieckmann cyclization precludes the use of such an approach to access these natural products.
Scheme 7. Synthetic approaches and key steps toward tirandamycin A (6)
Scheme 8. Ley’s mild approach to enantiopure 3-enoyl tetramic acids

An alternative approach that uses phosphonate esters to build functionalized tetramic acids without epimerization was developed by Ley and co-workers (Scheme 8).²⁵ By starting with t-buty1 4-diethylphosphono-3-oxobutanthioate (48) and conducting an HWE olefination with requisite aldehydes first generates the unsaturated 3-oxobutanthioate intermediate 49. Introduction of the chiral amino acid methyl ester (50) onto 49 with silver (I) trifluoroacetate affords 51 under mild conditions that prevents unwanted epimerization. After extensive screening of various bases, they identified that tetrabutylammonium fluoride (TBAF) was an optimal base to conduct the Lacey-Dieckmann cyclization of 51 and that by limiting the reaction time (~5 min) and conducting the reaction at room temperature little to no epimerization of the C5 asymmetric center was observed affording 3-enoyl tetramic acids 52 in high enantiopurity. Importantly, the short exposure of 51 to potassium tert-butoxide under the same conditions also affords 52 in high enantiopurity. One shortcoming of using TBAF as a base is that cyclizations of unprotected β-ketoamides, such as 2, are slow and generally require 24 h and reflux conditions in order to proceed in low yield. The Ley modification to the Lacey-Dieckmann cyclization was employed in the final sequence of the attempted total synthesis of tirandalydigin (7) by Miyashita and co-workers⁴¹ (Scheme 9); a testament to its utility in advanced systems. They envisaged that 7 could arise from the late-stage formation of the tetramic acid moiety via Lacey-Dieckmann condensation. In order to build the key β-ketoamide precursor (57), they treated streptolic acid (53) with thionyl chloride followed by the addition of trimethylsilyl 3-(tert-butythio)-3-oxopropanoate (54) and sodium hydride in THF solvent to afford 55 in a
respectable 79% yield over the two steps. Then using Ley's procedure,\textsuperscript{25} which employs thiophilic silver (I) trifluoroacetate under anhydrous conditions to promote the facile reaction of amines with β-ketothioesters to afford β-ketoamides, they treated 55 with N-2,4-dimethoxybenzyl glycine ethyl ester (56) to access key intermediate 57 in 95% yield. The Lacey-Dieckmann cyclization was conducted using TBAF in THF to afford N-2,4-dimethoxybenzyl tirandalydigin (58) in an excellent overall yield of 9.8% over 37 synthetic steps. Unfortunately, the DMB protecting group could not be removed as the vinyl epoxide was sensitive to the acidic conditions (neat TFA) necessary for deprotection, impeding the total synthesis of 7.

Scheme 9. Miyashita’s total synthesis of N-2,4-DMB tirandalydigin (58)
A Brief Discussion of the Optimization of Part B of this Organic Syntheses Procedure

Table 1. Optimization of the cyclization of 2 to 3

<table>
<thead>
<tr>
<th>base</th>
<th>solvent</th>
<th>temperature (°C)</th>
<th>time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOMe</td>
<td>MeOH</td>
<td>–78</td>
<td>2 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>NaOMe (2 equiv)</td>
<td>MeOH</td>
<td>0</td>
<td>10 min</td>
<td>34% conversion, 38% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>THF/ t-BuOH</td>
<td>–40</td>
<td>1 h</td>
<td>6% conversion, &lt;95% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>THF/ t-BuOH</td>
<td>0</td>
<td>20 min</td>
<td>61% conversion, 64% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>THF/ t-BuOH</td>
<td>0</td>
<td>1.5 h</td>
<td>85% conversion, 60% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>23</td>
<td>1 h</td>
<td>70% conversion, 94% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>40</td>
<td>30 min</td>
<td>89% conversion, 74% ee</td>
</tr>
<tr>
<td>t-BuOK(sublimed)</td>
<td>t-BuOH</td>
<td>40</td>
<td>4 h</td>
<td>91% conversion, 82% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>50</td>
<td>10 min</td>
<td>100% conversion, 74% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>23</td>
<td>20 min</td>
<td>12% conversion, 90% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>23</td>
<td>45 min</td>
<td>97% conversion, 80% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>40</td>
<td>4 h</td>
<td>78% conversion, 92% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>MTBE</td>
<td>23</td>
<td>20 min</td>
<td>74% conversion, 85% ee</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>t-BuOH</td>
<td>23</td>
<td>20 min</td>
<td>100% conversion, 74% ee</td>
</tr>
<tr>
<td>DBU</td>
<td>THF</td>
<td>70</td>
<td>30 min</td>
<td>100% conversion, 78% ee</td>
</tr>
<tr>
<td>1M NaOH</td>
<td>Water/ DCM</td>
<td>23</td>
<td>30 min</td>
<td>31% conversion, 58% ee</td>
</tr>
<tr>
<td>sat’d K₂CO₃</td>
<td>Water/ DCM</td>
<td>23</td>
<td>30 min</td>
<td>no reaction</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>THF</td>
<td>–78</td>
<td>2 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>NaHMDS (0.5 equiv)</td>
<td>THF</td>
<td>0</td>
<td>20 min</td>
<td>61% conversion, 86% ee</td>
</tr>
<tr>
<td>TBAF (2 equiv)</td>
<td>THF</td>
<td>23</td>
<td>1 h</td>
<td>25% conversion, &gt;99% ee</td>
</tr>
<tr>
<td>TBAF (2 equiv)</td>
<td>THF</td>
<td>23</td>
<td>2 h</td>
<td>44% conversion, &gt;99% ee</td>
</tr>
<tr>
<td>TBAF (2 equiv)</td>
<td>THF</td>
<td>23</td>
<td>8 h</td>
<td>64% conversion, &gt;99% ee</td>
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<tr>
<td>TBAF (2 equiv)</td>
<td>THF</td>
<td>23</td>
<td>11 h</td>
<td>67% conversion, &gt;99% ee</td>
</tr>
</tbody>
</table>

*Conditions were screened on 1 mmol scale with 1 equivalent of base (unless otherwise denoted) at a concentration of 0.5 M in the given solvent system and the percent conversion and enantiomeric excess of the reaction was determined via chiral UHPLC analysis with the conditions developed in Note 32 above.

In the above described procedure, the conditions reported by Ley²₅ were attempted in order to cyclize 2 into 3 without racemization (Table 1). Extensive screening of reaction conditions was conducted on 1 mmol scale using various bases, solvents, and temperatures. Aliquots of the test reactions were taken at various time points and evaluated by UHPLC analysis (Note 32) to determine the enantiomeric excess of 3, as well as, the overall
percent conversion from 2 to 3. In general, the trends identified parallel those observed by Ley and coworkers,\textsuperscript{25} that is, lower temperatures and shorter reaction times limited epimerization and the use of TBAF as a base was superior in terms of suppressing the epimerization. However, when TBAF was used for the cyclization of 2 into 3 the reactions stalled around 70% conversion at room temperature; the addition of greater equivalencies of TBAF did not help progress the reactions further and often led to partial racemization. In addition, the purification of the 3 away from the excess TBAF was difficult to accomplish requiring multiple chromatographic separations as the two co-elude even under the best conditions (20% MeOH/DCM; TBAF R\textsubscript{f} = 0.3, 3 R\textsubscript{f} = 0.25) due to the polar nature of the product 3. Attempts to carry the crude mixture onto the final step were unsuccessful as the excess TBAF precluded the decarboxylation to provide 4, and decomposition of 3 \textit{via} competitive aldol processes\textsuperscript{17} was observed.

![Scheme 10. Evaluation of a TBAF-mediated Lacey-Dieckmann cyclization of 59 to afford 4](image)

The use of 3,4-DMB-protected \( \beta \)-ketoamide 59 to access enantiopure 4 using a TBAF-mediated cyclization (Scheme 10) was not successful. In the event, 2.5 molar equivalents of TBAF was used with mild heating to 35 °C, and after one hour, the reaction reached >90% conversion. Owing to its less polar nature, compound 59 could be chromatographically separated away from the excess TBAF by passage through a short plug of silica gel rinsing with copious amounts of 60% EtOAc/hexanes as an eluent. The decarboxylation event proceeded smoothly to afford 61. Cleavage of the DMB group was accomplished in neat trifluoroacetic acid (TFA) in the presence of thioanisole and heating the mixture to 110°C in a microwave reactor for two
hours to afford 4. Chiral UHPLC analysis (Note 44) revealed that 4 had an enantiomeric excess of 68%, thus ~16% epimerization had occurred. Separately, a scaled-up procedure of the cyclization of 2 to 3 (100 mmol) was conducted with potassium tert-butoxide in tert-butanol; nearly identical results to those obtained when sodium methoxide was used were observed (~13% epimerization; 4 had an enantiopurity of 74% ee). Thus, a more operationally simple procedure employing sodium methoxide as the base was chosen for scale-up. The use of sodium methoxide avoids the required sublimation of commercial potassium tert-butoxide to remove trace amounts of potassium hydroxide, results in the full conversion of 2 to 3 after 10 minutes at 65 °C, results in only slight epimerization of the asymmetric center at C5 (~10-17%), allows for an expedient extractive work-up, avoids any column chromatography, and lastly, affords analytically pure 3.

The Application of Tetramic Acids and the Lacey-Dieckmann Cyclization to Total Synthesis

Tetramic acids are not only moieties found directly within natural products (5-14), but are valuable functional handles given the diversity of manipulations that can performed on the pyrrolidine 2,4-dione scaffold (Figure 22). A unique functionalization of the tetramic acid core is the installation of a diazo moiety onto the C3 position, which can allow for the formation of a metal carbenoid species, effectively reversing the C3 position from weakly nucleophilic to strongly electrophilic (Scheme 11). These isolable 3-diazotetramic acids (i.e. 67-71) were prepared, in a similar manner to the above described procedure for 3, from ethyl glycinate.42 The addition of a catalytic amount of Rh₂(OAc)₄ (10 mol%) to the 3-diazotetramic acids (67-71) dissolved in a degassed solution of pinacolone facilitates the formation of a reactive rhodium carbenoid which undergoes an addition with biindole 72 upon heating to 120 °C in a sealed tube for 8 hours to produce indolocarbazoles 73-77. The reaction proceeds in a step-wise manner where one of the indoles in 72 adds into the carbenoid, this intermediate then undergoes an electrocyclization/elimination to furnish the indolocarbazoles (73-77). It is clear from the isolated yields of 73-77 that this reaction sequence is sensitive towards the protecting group on the amide nitrogen of the
Scheme 11. Wood and co-workers’ use of 3-diazotetramic acids in the total synthesis of indolocarbazole natural products.
diazotetramic acid. It was found that diazotetramic acid 69 with a 3,4-DMB protecting group was the most efficient substrate for the sequence; resulting in the formation of indolocarbazole 75 in 68% yield, whereas, the unprotected tetramic acid 67 only resulted in a 25% yield of K252c (73). The identification of a latent tetramic acid moiety in the indolocarbazole backbone and the development of this easily accessible route to 75, enabled the total syntheses of (−)-K252a (78) in 12-steps, (+)-K252a (79) in 12 steps, (+)-RK-286c (80) in 17-steps, (+)-MLR-52 (81) in 19-steps, (+)-staurosporine (82) in 19-steps, and (−)-TAN-1030a (83) in 18-steps (Scheme 11). More recently, 3-aryltetramic acids have been used to construct synthetic benzocarbazoles and indolocarbazoles by Pelkey and co-workers (Scheme 12). They developed a Lewis acid-mediated arylation reaction between 3-aryltetramic acids (i.e. 84) and N-methylindole (85) to afford 3,4-bis-arylated tetramic acids (i.e. 86). These 3,4-bis-arylated tetramic acids were found to be to undergo a Scholl-type oxidative cyclization in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) and a Lewis acid at –40 °C to afford the fused carbazoles (i.e. 87) in decent yield (69%).

Scheme 12. Construction synthetic indolocarbazoles from 3-aryltetramic acids
The use of the classic Lacey-Dieckmann cyclization conditions (sodium alkoxide base in alcohol solvent) in total synthesis is not limited to the preparation of simplified tetramic acid building blocks but has also been used late-stage in a number of syntheses to install the tetramic acid moiety directly. In Laschat and co-workers’ 18-step enantioselective total synthesis of (+)-cylindramide A (12) (Scheme 13), they used sodium methoxide in methanol in the final step to convert β-ketoamide 88 to 12 in 49% yield; fifty years after Lacey’s original report. Shortly thereafter, Philips and Hart in their 19-step enantioselective total synthesis of (+)-cylindramide A (12) (Scheme 13) used a 2,4-DMB protecting group on their β-ketoamide 89 to improve the Lacey-Dieckmann cyclization process (90%) to afford 12 in 59% yield from 89 over the two-step process involving cyclization and DMB removal. Philips and Henderson would also use a similar tactic in their 23-step total synthesis of aburatubolactam A (9) (Scheme 13) to cyclize N-methyl-β-ketoamide 90 to the desired tetramic acid this was followed by a macrolactonization event and protecting group removal to furnish 9. More recently Pfaltz, Suzuki, and co-workers completed a 17-step total synthesis of macrocidin A (10) (Scheme 13). The antepenultimate step in the synthesis involved a potassium tert-butoxide catalyzed Lacey-Dieckmann cyclization of N-p-azidobenzyl (PAB) protected 91 to afford PAB-protected 10 in 87% yield. The reason for the unusual protecting group choice is that the epoxide in 10 was found to be susceptible to the conditions necessary for deprotection of more standard protecting groups (i.e. benzyl, 2,4-DMB, and 3,4-DMB) similarly to the difficulties faced by Miyashita et al. in their attempted synthesis of tirandalydigin (7). The PAB protecting group can be removed from the amide by facile reduction to the 4-aminobenzyl moiety, which under mild oxidative conditions (2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and water in THF solvent at room temperature for 30 minutes) is cleaved to afford 10 from PAB-10 in 78% yield over the two deprotection steps. The total syntheses of these macrocyclic tetramic acid natural products (9, 10 and 12) exemplify the utility of the Lacey-Dieckmann cyclization, which allows for the preparation of tetramic acid moieties in advanced intermediates. It also illustrates that the use of electron rich amide protecting groups such as (2,4-DMB, 3,4-DMB, and PAB) helps improve the overall yield of the cyclization process, but careful consideration needs to be taken into account as the potentially harsh conditions necessary for their removal can be problematic.
Scheme 13. Late-stage application of the Lacey-Dieckmann cyclization in the total synthesis of tetramic acid natural products.
Recent Approaches to Unusual Tetramic Acid Containing Natural Products

The tetrapetalone family of natural products were isolated in 2003 by Hirota and co-workers\(^1\) in their efforts to identify novel lipoxygenase inhibitors. The tetrapetalones, such as Tetrapetalone A (13), have a number of structural features which are unique and make them intriguing and challenging synthetic targets. In particular, a stereogenic para-quinol moiety, a trisubstituted olefin found within the fused azepine ring, a β-linked rhodinose moiety, and a reactive C3-methylated tetramic acid moiety need to be considered. The C3 tetramic acid moiety in the tetrapetalones is a rare substitution pattern for tetramic acid natural products, and a number of new methodologies have arisen that develop this C3 methylated tetramic acid moiety. In terms of developing a viable synthetic approach to the tetrapetalones, this reactive tetramic acid portion either needs to be developed late within the synthetic route or masked to avoid unwanted reactivity. This portion of the discussion will focus on the construction and manipulation of the tetramic acid portion of the tetrapetalone scaffold synthetic efforts of various groups that address this issue. In late 2017, Wood and coworkers completed the first total synthesis of (+)-tetrapetalone A (13) and (−)-tetrapetalone C in 18 and 19 steps respectively (Scheme 14).\(^4\) One crucial aspect that was required for the successful completion of 13 was masking the acidity and reactivity of the C3 methyl tetramic acid moiety as a C3 quaternary ethoxycarbonyl moiety (see 92 in Scheme 14) which could be easily removed by decarboxylation in the presence of LiOH to afford 13. This ethoxycarbonyl masked tetramic acid was constructed early on in the synthesis before the azepine formation to afford intermediate 97 and carried throughout the rest of the synthesis which required cyclopentanol formation to afford 94, an intermediate that was prepared in 12% overall yield over 12 steps, a stereospecific glycosolation between 94 and 95, installation of the para-quinol through oxidative dearomatization of 93, and finally unmasking of the tetramic acid to afford (+)-tetrapetalone A (13). The construction of the masked tetramic acid moiety 98 is shown in Scheme 15. Beginning with 3-hydroxyaniline (101) the β-ketoamide (100) is prepared in 3-steps involving amination, TIPS protection of the phenol, and amidation. A modified Lacey-Dieckmann cyclization catalyzed by DBU under anhydrous conditions (4 Å MS) in THF at reflux is used to afford 99. This was followed exposure of 99 to NaHMDS to initiate C5 deprotonation, then mixing with methacrolein pre-complexed with the bulky Lewis acid aluminum tris(2,6-
Scheme 14. Wood and co-worker’s retrosynthetic analysis of 13

diphenylphenoxide); this was done to suppress 1,2-addition and preferentially affords the 1,4-addition product. The in situ addition of elemental bromine to the enolate completes the sequence and affords masked tetramic acid 98. This route to the C3 methyl tetramic acid moiety renders the tetramic acid inert to the conditions employed in the remainder of the synthesis as both protons adjacent to the reactive C4 carbonyl are now removed.

Prior to the successful development of a total synthesis to tetrapetalones A and C, there were a number of innovative approaches reported to access their unique architecture. A common theme that arises when surveying these efforts is the masking of the acidity of the tetramic acid moiety.
The first efforts towards the tetrapetalone family of natural products were reported by Wang and Porco in 2005. They surmised that given the similarities of the tetracyclic core of tetrapetalone and the ansamycin family of macrocyclic antibiotics, that an approach involving transannular [4+3] cyclization of a pre-assembled macrocycle (106 → 105) would allow facile access to the tetracycle (Scheme 16). They envisioned that from the nearly complete protected aglycon 105 they would be able to access 13 after glycosylation of the β-rhodinose moiety. The reactivity of the tetramic acid portion of the molecule is masked one oxidation state lower by a methoxymethyl ether (MOM)-protected alcohol (Scheme 16). Porco and co-workers efficiently assembled the macrocycle 106 in eight linear steps and implemented their envisioned approach by exposure of 106 to PhI(OAc)₂ to oxidize the hydroquinone moiety surmising that the intermediate oxonium ion would be trapped by the transannular olefin initiating the [4+3] cyclization. In their original report they assigned the structure of the product to that of desired 105 (Scheme 16), however corrected their structural assignment shortly thereafter to the macrocyclic quinone 107 (Scheme 16).
In 2010, Marcus and Sarpong reported a synthesis of the tetracyclic core of the tetrapetalones enabled by a reductive alkylation of a pyrrole (Scheme 17). The core of the tetracycle (110) was formed in a two-step process. The terminal olefin in 111 was hydroborated and subjected to oxidative work-up to afford a primary alcohol. Oxidation of the alcohol intermediate after the addition of Dess-Martin periodinane (DMP) afforded an intermediate aldehyde, which underwent intramolecular attack by the pyrrole and further oxidation to afford the tetracycle 110 (see 111 → 110; Scheme 17). Intermediate 110 was further elaborated to an α,β-unsaturated lactam 109, which served as a way to mask the tetramic acid moiety. The tetramic acid 108 was installed in four synthetic steps from 109 by exposure to LDA and methylation with MeI, followed by conjugate edition of a boron pinacolato ester, oxidation of the boronic ester adduct, and Swern oxidation of the alcohol to furnish tetramic acid 108. Compound 108 is just shy of the aglycon portion of the tetrapetalones; it lacks the tri-substituted olefin of the azepine ring and the para-quinol moiety.

In 2014, Frontier and co-workers pushed synthetic efforts toward the construction of the aglycon even further when they completed a synthesis of the tetrapetalone A-Me aglycon (Scheme 19). However, the methyl enol ether used to mask the tetramic acid was never reported to be successfully removed by Frontier and co-workers, and this sort of difficulty has thwarted previous generations of Wood and co-worker’s attempts at the tetrapetalones.
Scheme 17. Sarpong and co-worker’s retrosynthetic analysis and envisioned construction of 13

The approach by Frontier and co-workers began with the implementation of their trademark Nazarov cyclization chemistry to afford bromide 119 from 120; setting two of the five stereogenic centers in the aglycon of 13. Compound 119 was elaborated to triene 118 which was successfully engaged in a ring closing metathesis after extensive catalyst optimization. The tetramic acid was installed from 117 by treatment with Stryker’s reagent followed by Swern oxidation to give the C3 chlorinated tetramic acid 116. Intermediate 116 was dechlorinated with zinc and acetic acid to furnish a C3-methyl tetramic acid, that was then masked as the methyl enol ether using trimethylsilyl diazomethane. Deprotection of the TIPS-protected phenol and phenolic oxidation to the para-quinol afforded 115 in six synthetic steps from 116.
Following the reported total synthesis of tetrapetalones A and C by Wood and co-workers, Bai and Pettus disclosed their own efforts toward the tetrapetalones. Their synthetic approach, like Frontier’s masks the tetramic acid moiety as a methyl enol ether (Scheme 19). In contrast to Frontier and co-worker’s approach, Bai and Pettus begin their efforts by first preparing the C3 tetramic acid moiety (126) and constructing the tetracycle around this masked tetramic acid. Employing the method of Jones and co-worker’s they construct 126 in three steps from iodoaniline 127 and allylic bromide 128. Using their developed vinylogous aldol reaction of tetramic acids, they were able to quickly construct tricycle 125. Isomerization of the cyclic olefin and installation of the cyclopentanol ring in 13 additional synthetic steps affords 122, a methyl and a hydride short of an intermediate prepared by Frontier and co-workers.

Pettus and Bai’s synthetic approach focused on the early installation of the tetramic acid moiety, and as such, has led to their development of a notable method to prepare the rarely encountered C3 methyl tetramic acid moiety (Scheme 20). Starting with chiral amino acid ester derivatives such
as 1 used above, they developed a samarium diiodide-mediated cyclization approach with Cbz-protected bromo amides such as 130 (Scheme 20). Similar to the above described method, a slight epimerization was observed affording Cbz-protected tetramic acids such as 131 with 80% enantiomeric excess. After Cbz deprotection, a single recrystallization afforded material with enantiomeric purities >99%. This SmI$_2$ method compliments the few methods$^{56}$ to access C3-methyl tetramic acids. As exemplified in this discussion, the tetrapetalones have led to the development of a number of synthetic strategies to access and functionalize tetramic acids from pyrroles,$^{50}$ aldol reactions,$^{51,54}$ a samarium diiodide initiated cyclization,$^{55}$ and modified Lacy-Dieckmann cyclization conditions.$^{48}$

Scheme 20. Pettus and co-worker’s methodology to C3-methyl tetramic acids
More recently, a key step in Nakhla and Wood’s 16-step total synthesis of (±)-Aspergilline A (14) (Scheme 21) featured a very unique construction of a tetramic acid moiety from a formal [3+2] cycloaddition with cyclopropenone.  

Scheme 21. Wood and Nakhla’s retrosynthetic analysis and construction of 14

The details of the two-step installation of the tetramic acid moiety are shown below in Scheme 22. In the event, O-methyl imidate 133, was exposed to cyclopropenone with gentle heating (50 °C) in acetonitrile solvent to afford formal [3+2] cycloaddition product 137. Oxidation of 137 with oxone in acetonitrile/water solvent at 0 °C resulted in hydrolysis of the O-methyl aminal and the desired oxidation furnishing tetramic acid 132.  

Scheme 22. Wood and Nakhla’s formal [3+2] cycloaddition / oxidation sequence for construction of tetramic acid 132
Concluding Remarks

The total synthetic endeavors included within this Discussion serve to highlight the utility of the above described Organic Syntheses procedure and the Lacey-Dieckmann cyclization in advanced systems, and a look into other recent approaches to tetramic acid-containing natural products. It is clear that given the bioactivity and structural diversity of tetramic acid-containing natural products much progress has been made in understanding tetramic acid chemistry, but despite these advancements, development in this area of synthetic chemistry is far from over. The above described Organic Syntheses procedure was developed to be used as a general method to build the tetramic acid core in an efficient, enantioselective manner from commercially available amino acid esters using the Lacey-Dieckmann cyclization without the need for chromatographic separation.

References

1. Department of Chemistry and Biochemistry, Baylor University, One Bear Place 97348, Waco, Texas 76798, United States. Email address: kyle_lambert@baylor.edu (ORCID: 0000-0002-8230-2840). We gratefully acknowledge financial support from Baylor University, the Welch Foundation (Chair, AA-006), the Cancer Prevention and Research Institute of Texas (CPRIT, R1309), the National Science Foundation (NSF, CHE-1764240), and the National Institutes of Health (NIH, K.M.L. NRSA postdoctoral fellowship F32GM129969).


24. For an example of substrate dependence see the following dissertation: Petsch, D. T. Ph. D. Dissertation, Yale University, 1999.


Appendix

Chemical Abstracts Nomenclature (Registry Number)

(S)-2-[2-(Methoxycarbonyl)acetylamino]-3-phenylpropanoic acid methyl ester: L-phenylalanine, N-(3-methoxy-1,3-dioxopropyl)-, methyl ester; (308277-48-7)

(5S)-5-Benzyl-3-methoxyacrylonitrile, 1 H-Pyrrole-3-carboxylic acid, 2,5-dihydro-4-hydroxy-2-oxo-5-(phenylmethyl)-, methyl ester, (5S)-; (128892-60-4)

Org. Synth. 2019, 96, 528-585

DOI: 10.15227/orgsyn.096.0528
(5S)-5-Benzylpyrrolidine-2,4-dione: 2,4-Pyrrolidinedione, 5-(phenylmethyl)-, (5S); (69358-30-1)
L-Phenylalanine methyl ester hydrochloride: L-Phenylalanine, methyl ester, hydrochloride; (7524-50-7)
D-Phenylalanine methyl ester hydrochloride: D-Phenylalanine, methyl ester, hydrochloride; (13033-84-6)
Methyl malonyl chloride: Methyl 3-chloro-3-oxopropionate; (37517-81-0)
25 wt% sodium methoxide in methanol: Methanol, sodium salt; (124-41-4)
Sodium sulfate: Sulfuric acid disodium salt; (7757-82-6)
Trifluoroacetic acid: Acetic acid, trifluoro-; (76-05-1)
Hydrochloric acid: Hydrochloric acid; (7647-01-0)

Kyle Lambert received dual B.S. degrees summa cum laude in chemistry and forensic science from the University of New Haven in 2012. He obtained his Ph.D. in 2017 from University of Connecticut under the direction of William F. Bailey. Kyle’s doctoral research involved the exploration of oxoammonium salts as selective oxidants as well as conformational studies of saturated heterocycles. Currently he is a NIH NRSA postdoctoral fellow completing his postdoctoral studies in Prof. John Wood’s group at Baylor University in the area of natural product total synthesis. He plans to pursue an academic position upon completion of his postdoctoral studies.

Austin Medley is an undergraduate student studying finance and chemistry at Baylor University. He is currently an undergraduate researcher in Prof. John Wood’s organic synthesis research group at Baylor, and hopes to pursue a Ph.D. in synthetic organic chemistry after graduation.
Amy C. Jackson received her B.S. degree in Chemistry in 2018 at San Diego State University. She is currently a first-year chemistry graduate student, working in natural products synthesis at Baylor University under the supervision of Dr. John L. Wood.

Lauren Markham was born in Texas in 1998. She will graduate from Baylor University with a B.S. in Chemistry in May 2019. She is currently an undergraduate researcher in Prof. John L. Wood’s organic synthesis research group at Baylor. In July of 2019 she will begin her graduate studies in chemistry at Dartmouth College, with research interests in organic synthesis.
John L. Wood received a B.A. degree from the University of Colorado in 1985 and a Ph.D. from the University of Pennsylvania in 1991 under the direction of Amos B. Smith, III. In 1991 he moved to Harvard University as an American Cancer Society postdoctoral fellow and continued studying natural products synthesis in the laboratories of Stuart Schreiber. He joined the faculty at Yale University in 1993 as an Assistant Professor and was promoted to Full Professor in 1998. In 2006, Professor Wood joined the faculty at Colorado State University as the Albert I. Meyers Professor of Chemistry and in 2013 moved to Baylor University as the Robert A. Welch Distinguished Professor of Chemistry and Cancer Prevention Research Institute of Texas Scholar. A major focus of Professor Wood’s research is synthetic organic chemistry. Of primary emphasis is the design of innovative solutions to problems in natural product synthesis. Professor Wood is the *Tetrahedron Letters* associate editor for the Americas and is on the board of editors for *Organic Syntheses*.

Anna C. Impastato received her B.A. in Chemistry from Boston University in 2015. After, she did post-bachelorette work at AstraZeneca as part of the Graduate Program in Innovative Medicines and Early Development. Currently, Anna is a third-year graduate student at New York University under the supervision of Professor Dirk Trauner, working on the design and synthesis of photoswitchable small molecules to study cancer pathways.
16.57 mg x 279.3 g/mol x (0.35/1H)/(1.00/3H) x 0.997 x 100 = 100%

28.72 mg x 168.2 g/mol
16.4 mg x 247.3 g/mol x (0.23/1H)/(1.00/3H) x 0.997 x 100 = 92.7%

17.9 mg x 168.2 g/mol

\[ \frac{16.4 \text{ mg} \times 247.3 \text{ g/mol} \times (0.23/1H)/(1.00/3H) \times 0.997 \times 100}{17.9 \text{ mg} \times 168.2 \text{ g/mol}} = 92.7\% \]
$21.3 \text{ mg} \times 189.2 \text{ g/mol} \times \frac{(0.29/1\text{H})}{(1.00/3\text{H})} \times 0.997 \times 100 = 98.2\%$

$21.17 \text{ mg} \times 168.2 \text{ g/mol} \times \frac{(0.29/1\text{H})}{(1.00/3\text{H})} \times 0.997 \times 100 = 98.2\%$