was warmed to −15 °C for 2 h and quenched with 0.5 mL of water, and a solution of 7 mL of pyridine in 6 mL of ether was added, followed by a solution of 1.9 mL of benzoyl chloride in 7 mL of ether, and the solution was stirred overnight. Extractive workup with chloroform provided a yellow solid which was chromatographed on a medium-pressure silica gel column using 20% ethyl acetate in hexane as eluant to provide 0.76 g (90%) of analytically pure *N*-phenylbenzamide as a white solid, mp 161.5–163 °C (lit.[8] mp 163 °C).

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Registry No. Methoxyamine, 67-62-9; methyllithium, 917-54-4; ethyllithium, 811-49-4; butyllithium, 109-72-8; (1-methylpropyl)lithium, 598-30-1; (1,1-dimethylethyl)lithium, 594-19-4; phenyllithium, 591-51-5; (2-methoxyphenyl)lithium, 31600-86-9; (phenylmethyl)-lithium, 766-04-1; dibenzothiophene-4-yllithium, 75288-58-3; 1-bromobutane, 109-65-9; bromobenzene, 108-86-1; *N*-methylbenzamide, 613-93-4; *N*-ethylbenzamide, 614-17-5; *N*-butylbenzamide, 2782-40-3; *N*-(1-methylpropyl)benzamide, 879-71-0; *N*-(1,1-dimethylethyl)benzamide, 5894-65-5; *N*-phenylbenzamide, 93-98-1; *N*-(2-methoxyphenyl)benzamide, 5395-00-6; *N*-(phenylmethyl)benzamide, 1485-70-7; 4-dibenzothiophenamine, 72433-66-0.

(8) "Handbook of Chemistry of Physics", 45th ed.; Weast, R. C., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1964; p C-181.

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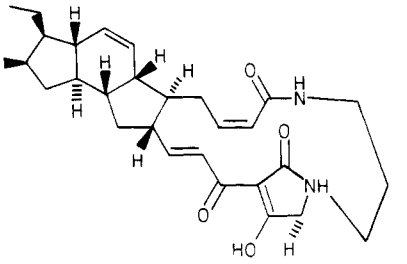
Methodology for the Synthesis of Phosphorus-Activated Tetramic Acids: Applications to the Synthesis of Unsaturated 3-Acyltetramic Acids[1]

Summary: A general method is described for the preparation of phosphonate-activated 3-acetyltetramic acids from a variety of α-amino esters, which can serve as precursors of enoyl and dienoyl tetramic acids which are found in a number of natural products.

Sir: As part of a research program directed toward the synthesis of tetramic acid containing natural products such as ikarugamycin (**1**)[2] and tirandamycin (**2**),[3] we required a general method for construction of unsaturated 3-acyltetramic acids which would fulfill several requirements. Among these requirements were the following: (1) the use of α-amino acids as starting materials in order to take advantage of this pool of optically active starting materials, (2) the use of mild conditions to prevent racemization, (3) the specific activation of the terminal acetyl methyl for



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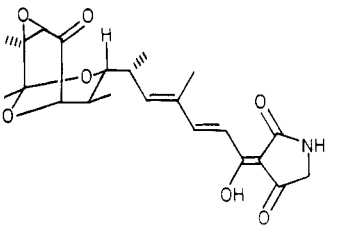
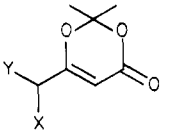
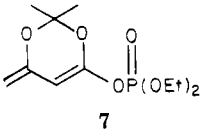


2

olefin formation prior to generation of the heterocyclic nucleus, (4) sufficiently high reactivity of the activated derivative permitting olefination under mild conditions. These restrictions were deduced in part from the studies of Rinehart who demonstrated that direct acylation of unsaturated acid fluorides and chlorides was not feasible nor was functionalization (halogenation) or condensation (with aldehydes) of the intact tetramic acids.[4,5] Furthermore, construction of the heterocycle after olefination was not feasible due to the severity of the conditions required for condensation of the unsaturated β-keto esters with amino esters.[5]

Given these considerations, we sought to prepare a protected β-keto ester already activated for olefin formation, which would have sufficient reactivity utilizing weak acid catalysis, to condense with a variety of α-amino esters to afford the corresponding β-keto amide. Two such substances which appeared to fulfill these requirements were the phosphonate **3** and phosphorane **4**.





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3, X = H; Y = P(=O)(OEt)$_2$
4, X = Y = PPh$_3$
5, X = Y = H
6, X = H; Y = Br
8, X = H; Y = Cl

We hoped to prepare these substances from the readily available unsubstituted system **5** obtained from diketene and acetone (91%).[6] Our initial attempt involved conversion to bromide **6** with NBS (CCl_4/$h\nu$/peroxide) in 83% yield. Bromide **6** underwent smooth conversion to phosphorane **4** upon treatment with triphenylphosphine in benzene followed by exposure to aqueous base (~90% overall). Phosphorane **4** reacts with aldehydes as expected, but the difficulties associated with isolation and manipulation of the ylide products led us to carry on our explorations in the phosphonate series.

(1) These studies were performed in part at Wayne State University, Department of Chemistry and form part of a dissertation submitted to Wayne State University by A.J.T. in partial fulfillment of the requirements for the Ph.D.

(2) (a) Ito, S.; Hirata, Y. *Bull. Soc. Chem. Jpn.* **1977**, *50*, 227. (b) *Ibid.* **1977**, *50*, 1813.

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(6) Carroll, M. F.; Bader, A. R. *J. Am. Chem. Soc.* **1953**, *75*, 5400.

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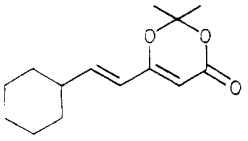
Somewhat surprisingly, bromide **6** did not afford the expected phosphonate **3** upon exposure to hot triethyl phosphite, but rather reductive dehalogenation took place, providing **5**. It was not ascertained whether this occurred via a Perkow process and hydrolysis of the resulting vinyl phosphonate **7** or by direct reductive dehalogenation.

The desired phosphonate **3** was subsequently obtained by conversion of **5** to its anion with LDA (1.3 equiv) in THF (−78 °C) and chlorination with hexachloroethane (1.76 equiv) in THF, using inverse quenching at −48 °C, affording chloride **8** in 76% yield.[7-9] Treatment of **8** with the sodium salt of diethyl phosphite (NaH/ether–DMF (12:1), 2.0 equiv) at room temperature (~1 h) and acidic workup (HCl) afforded **3** (88%) after filtration chromatography.[9,10]

The anion derived from phosphonate **3** (NaH/THF) behaves normally in its reaction with a variety of aldehydes. Treatment with cyclohexanecarboxaldehyde and tiglic aldehyde affords the protected Nazarov-type reagents **9** and **10** in excellent yields (84% and 78% respectively).[9]



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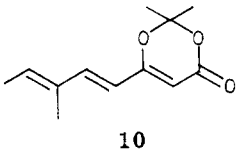

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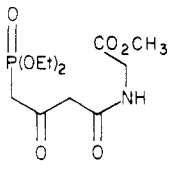

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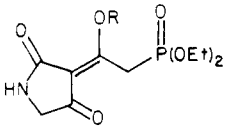
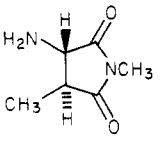


12, R = H
13, R = Na

Reaction of **3** with glycine methyl ester under mild acid catalysis ($PyH^+ {}^-OTs$) in refluxing THF provides the desired N-functionalized amide **11** in 67% yield. Conversion of **11** to the activated tetramic acid **12** (74%) proceeds smoothly upon exposure to $NaOCH_3$ (1.005 equiv) in CH_3OH/PhH at room temperature (12 h) and acidification.[9] **12** is conveniently isolated and stored in the form of its sodium salt **13**.

Similarly, (*S*)-ω-*N*-(carbobenzyloxy)ornithine methyl ester and racemic imide **14**[5b] have been converted to the activated tetramic acids **15** and **16** in yields of 67% and 72%.[9,11] Tetramic acid **16** may serve as a useful intermediate toward streptolydigan.[3b,13] In these instances, where reactivity of **3** with the α-amino ester was slower due to steric effects and amino ester dimerization was slow, dropwise addition of **3** to a refluxing solution of the amino ester and catalyst was required to avoid degradation of **3**.



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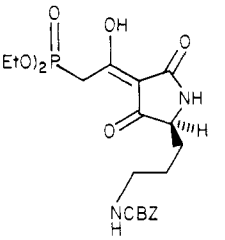

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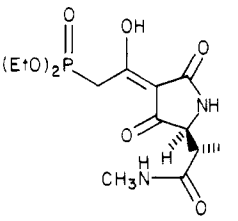

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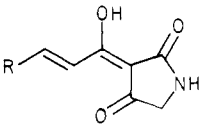
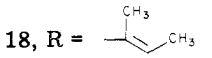


17, R =



18, R =

The activated tetramic acids function as expected in their reactions with carbonyl compounds. For example, treatment of **12** (1 equiv) with 2 equiv of LDA in THF at −78 °C followed by cyclohexanecarboxaldehyde (1 equiv) at −78 °C (0.5 h) and then warming to room temperature (12 h) followed by acidic workup afforded the desired enoyl tetramic acid **17** in 72% yield.[9] Reactivity with tiglic aldehyde is somewhat lower, requiring use of somewhat more vigorous conditions (THF/40 °C/24 h), but affords the dienoyl system **18** (mp 177–178 °C) in good yield (64%).[9]

With the previously discussed convenient preparation of a variety of these activated systems from α-amino acids in hand, we are in a position now to approach the synthesis of the physiologically active, naturally occurring systems such as **1**, **2**, related compounds, and analogue structures. We are also investigating the chemistry of this interesting class of masked dicarbonyl compounds, for example **3** and **5**, with respect to their potential for asymmetric synthesis.

Acknowledgment. This investigation was supported by research grants CHE-78-07525 and CHE-80-05176 from the National Science Foundation to whom we are extremely grateful.

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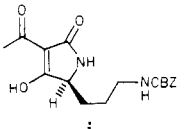
(8) Smith, A. B., III; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, 4193. We observed only products derived from γ chlorination where Smith observed both α and γ alkylation.

(9) Partial spectral data: (**3**) NMR ($CDCl_3$) δ 5.37 (d, *J* = 4 Hz, 1), 4.10 (m, 4), 2.77 (d, *J* = 23 Hz, 2), 1.70 (s, 6), 1.33 (s, 6); (**8**) NMR ($CDCl_3$) δ 5.56 (s, 1), 4.03 (s, 2), 1.72 (s, 6); (**9**) NMR ($CDCl_3$) δ 6.49 (dd, J_1 = 16.5 Hz, J_2 = 6.5 Hz, 1), 5.78 (d, *J* = 16 Hz, 1), 5.24 (s, 1), 2.30–0.82 (m, 11), 1.70 (s, 6); (**10**) NMR ($CDCl_3$) δ 6.91 (d, *J* = 16 Hz, 1), 6.15–5.75 (m, 1), 5.84 (d, *J* = 16 Hz, 1), 5.27 (s, 1), 1.83 (d, *J* = 6 Hz, 3), 1.78 (s, 3), 1.70 (s, 6); (**11**) NMR ($CDCl_3$) δ 4.16 (m, 4), 4.07 (d, *J* = 14 Hz, 2), 3.79 (s, 3), 3.66 (s, 2), 3.32 (d, *J* = 22 Hz, 2), 1.41–1.28 (m, 6); (**12**) NMR ($CDCl_3$) δ 9.77–8.80 (m, 2), 4.36–3.97 (m, 4), 3.85 (s, 2), 3.61 (d, *J* = 22.5 Hz, 2), 1.48–1.13 (m, 6); (**15**) NMR ($CDCl_3$) δ 7.27 (s, 5), 5.03 (s, 2), 4.36–3.90 (m, 4), 3.70 (s, 1), 3.53–3.06 (m, 4), 2.10–1.04 (m, 10); (**16**) NMR ($CDCl_3$) δ 9.51–9.06 (m, 1), 7.43–7.20 (m, 1), 6.93–6.66 (m, 1), 4.37–3.93 (m, 4), 3.68 (br s), 3.58 (d, *J* = 23 Hz, 2), 3.17–2.60 (m, 4), 1.34 (t, *J* = 7 Hz, 6), 1.04 (d, *J* = 7.5 Hz, 3); (**17**) NMR ($CDCl_3$) δ 9.63 (m, 1), 7.15 (dd, J_1 = 16 Hz, J_2 = 6.8 Hz, 1), 7.10 (d, 16 Hz, 1), 5.95 (m, 1), 3.89 (s, 2), 2.29 (m, 1), 1.83–1.19 (m, 10); (**18**) NMR ($CDCl_3$) δ 9.42 (s, 1), 7.55 (d, *J* = 16 Hz, 1), 7.12 (d, *J* = 16 Hz, 1), 6.18 (q, *J* = 6.5 Hz, 1), 5.96 (m, 1), 3.81 (s, 2), 1.89 (s, 3), 1.88 (d, *J* = 6.5 Hz, 3).

(10) Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, 2340.

(11) As evidence that partial racemization does not occur during the formation of **15**, we prepared the unactivated analogue i by the identical



i

procedure (an adaptation of that of Lacey[12]). This material was degraded to optically pure ornithine by the procedure developed for ikarugamycin;[2] therefore, by analogy no racemization of **15** had occurred. Use of optically active shift reagents to determine the optical purity of i and **15** directly was not possible due to line broadening.

(12) Lacey, R. N. *J. Chem. Soc.* **1954**, 850.

(13) Rinehart, K. L., Jr.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. *J. Am. Chem. Soc.* **1963**, *85*, 4038.

(14) (a) Fellow of the A. P. Sloan Foundation (1976–1980). (b) Career Development Awardee (1976–1981) from the National Cancer Institutes of NIH (CA-00702).

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