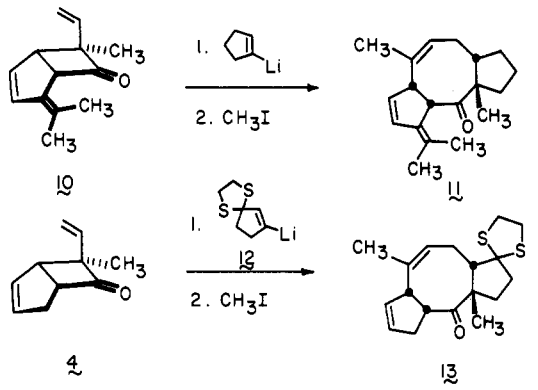
accepted values. Tables containing the final X-ray parameters may be found in the supplementary material.

The synthetic scheme outlined above is subject to ready modification. For example, analogous processing of **10**, an



10 **11** **4** **12** **13**

adduct of methyl vinyl ketene and dimethylfulvene,[9b] results in straightforward preparation of **11** (65%). This compound provides the opportunity for ring-A functionalization. Similarly, **4** condenses rapidly with 3-lithiocyclopentenone dithioketal **12**[17] to furnish **13** (56%). The "unwanted" carbonyl group in **13** is nicely differentiated from that which is protected. Following reductive removal of the oxygen atom, hydrolysis of the dithioketal function is expected to be accompanied by α epimerization in ring C as required for ophiobolin construction (see **1**).[18] Realization of these goals and overall application of this two-step procedure to the total synthesis of ophiobolane sesterterpenes are subjects of current investigation.

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Supplementary Material Available: Experimental details for synthesis and properties of compounds **7**, **8**, **9a**, **9b**, **11**, and **13** as well as fractional coordinates and temperature parameters, bond distances, and angles for **8** (8 pages). Ordering information is given on any current masthead page.

(17) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825.

(18) Relatively facile epimerization at this center may already have been foreshadowed by the ease with which **7** experiences this equilibration in ring A.

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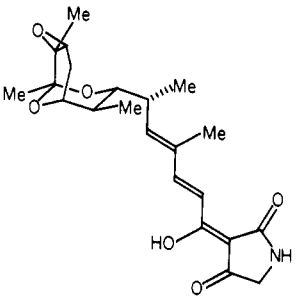
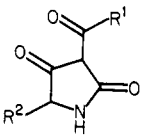
Methodology for the Synthesis of 3-Acyltetramic Acids

Summary: A general method for the preparation of 3-acyltetramic acids is described. The methodology can be extended to produce 3-enoyl or 3-dienoyl substituents via a Wadsworth–Emmons olefination sequence.

Sir: During the course of studies directed toward the total synthesis of tirandamycin (**1**)[1] and related natural products, it became obvious that a general method for the preparation of 3-enoyl or 3-dienoyl tetramic acids was required. Earlier studies by Rinehart[2] demonstrated that the methodology available for the preparation of simple 3-acyltetramic acids (**2**) could not be successfully extended to unsaturated derivatives **3**. A complicating factor was that the new methodology must also allow us to introduce a substituent at C-5 of the tetramic acid since this position is substituted in many tetramic acid containing natural products. This report describes a general method for the preparation of 3-acyltetramic acids. The method can be modified to introduce 3-enoyl or 3-dienoyl substituents via a Wadsworth–Emmons olefination sequence.



1



2, $R^1 = R^2$ = alkyl

3, R^1 =  ; R^2 = alkyl

In 1966, Woodward and Olofson[3] reported that isoxazolium salts (**5**) could be fragmented in dilute base solution to produce β-keto amides in excellent yield. Since β-keto amides such as **6** had been cyclized to 3-acyltetramic acids (**2**) with ethoxide in ethanol,[4] we anticipated that the process outlined in Scheme I would allow the preparation of a variety of 3-acyltetramic acids.

Treatment of 5-methylisoxazole (**4a**) or 5-phenylisoxazole (**4b**) with ethyl bromoacetate in nitromethane containing 1 equiv of $AgBF_4$ at 75 °C for 4-12 h resulted in formation of **5a** and **5b**, respectively, in high yield (>95%).[5] Although the salts could be purified by chromatography on ion-exchange resins or LH-20, pure material was routinely obtained by filtration of the precipitated AgBr and passage of the filtrate through LH-20 with CH_2Cl_2. In analogous fashion, **5c**[5] was prepared from **4a** and ethyl bromopropionate. Isoxazolium salt **5d**[5] was produced in quantitative yield by alkylation of **4a** with carbethoxy methyl trifluoromethanesulfonate (X = OSO_2CF_3)[6] in nitromethane. The triflate procedure was the preferred method for the preparation of this salt since the alkylation proceeds rapidly at reflux and it was not necessary to subject the crude product to further purification.

The alkylations could be conveniently monitored by ^1H NMR. The two proton signals of the isoxazole ring that

(1) Duchamp, D. J.; Branfman, A. R.; Bratton, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077 and references therein.

(2) Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225. Cartwright, D.; Lee, V. J.; Rinehart, K. L., Jr. *Ibid.* **1978**, *100*, 4237.

(3) Woodward, R. B.; Olofson, R. A. *Tetrahedron* Suppl. **1966**, *No. 7*, 415.

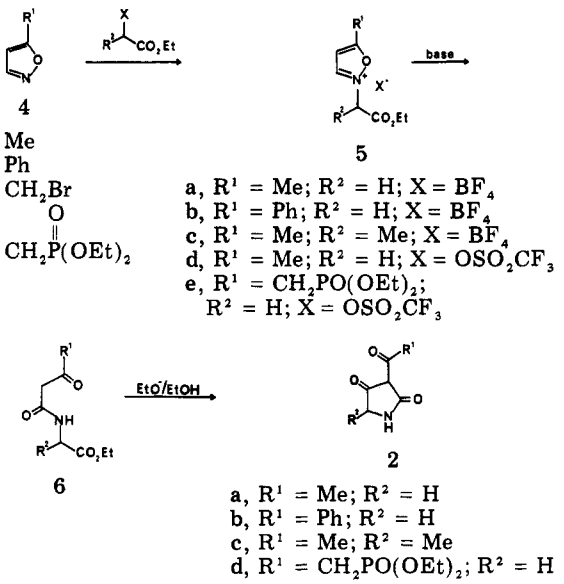
(4) Lacey, R. N. *J. Chem. Soc.* **1954**, 850. Sticklings, C. E.; Townsend, R. J. *Biochem. J.* **1961**, *78*, 412. Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2121.

(5) Spectral data for all intermediates are given in the supplemental material.

(6) Vedejs, E.; Enger, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

0022-3263/83/1948-1149$01.50/0

Scheme I



appear at δ 6.0 and 8.0 are shifted downfield to δ 7.0 and 9.3 upon formation of the isoxazolium salt.

Base-induced fragmentation of **5** could be accomplished with a variety of bases (NaOH, Triton B, Na_2CO_3, $NaHCO_3$) at room temperature in 15–30 min, but the procedure that consistently resulted in the best yield of **6** involved adding **5** to a two-phase system of CH_2Cl_2/H_2O containing 1 equiv of $NaHCO_3$ at 0 °C. The unstable β-keto amide esters **6** could be obtained in 50–60% yield after chromatography on silica. The low purified yield is a consequence of difficulty associated with the chromatography of **6** and not the fragmentation reaction. The ^1H NMR spectrum of the crude reaction mixture from treatment of **5a** (or **5d**) under the above conditions showed that **6a** had been formed in high yield.

The sequence outlined above could also be employed to prepare tetramic acid phosphonate **2d**, which we had designated as the crucial intermediate for introduction of unsaturation into the 3-acyl side chain. Bromination of 5-methylisoxazole (**4a**) with NBS/CCl_4 gave the extremely reactive bromide **4c**.[5] Due to the potent lachrymatory properties of **4c**, it was converted into phosphonate **4d** without purification ($(EtO)_3P$, $PhCH_3$ reflux, ~80% overall). Alkylation of the isoxazole nitrogen with carbethoxymethyl trifluoromethanesulfonate in refluxing nitromethane gave 90% of the salt **5e**. As before, **5e** was cleaved with bicarbonate to give **6d** (55%) and cyclized with ethoxide to produce tetramic acid phosphonate **2d** (50%).

Tetramic acid phosphonate **2d** underwent condensation with aldehydes to produce 3-enoyl tetramic acids. Boeckman has recently prepared **2d** by a different method and has shown that it will couple with aldehydes in an analogous fashion.[7] Application of this methodology to the total synthesis of tirandamycin and other natural products is currently in progress.

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Supplementary Material Available: Spectral data of intermediates and experimental procedure for **5** and **6** (3 pages). Ordering information is given on any current masthead page.

(7) Phosphonate **2d** has been prepared by Boeckman and Thomas (Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823) by an alternate procedure. They have coupled the anion of **2d** with cyclohexanecarboxaldehyde and tiglaldehyde, respectively.

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