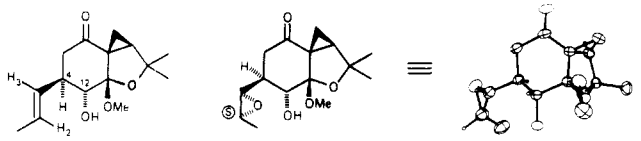
constant of 11.7 Hz, while the corresponding value for the trans isomer was 15.9 Hz.[14] Second, $J_{4,12}$ in both isomers (ca. 13 Hz) was consistent with a C(4)–C(12) trans relationship (vide infra).[8] Interestingly, when the cuprate reagent was allowed to warm to 25 °C followed by addition of enone **4a**, the isomer ratio shifted to 96:4 in favor of the cis isomer. To accommodate this improvement in stereoselectivity, in conjunction with a somewhat diminished yield, we suggest that the higher temperature promotes a more facile bimolecular coupling of the trans cuprate vs. the cis isomer.[15] Fortunately, utilization of an excess of cuprate reagent (ca. 2.5 equiv) precludes starting material recovery.

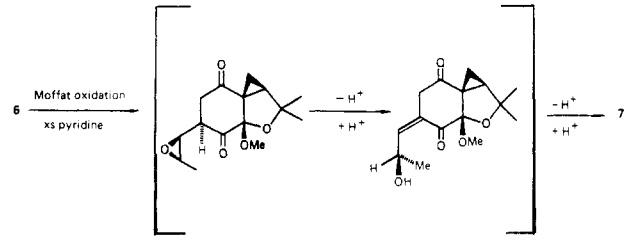
Turning next to the key epoxidation, treatment of olefin **5**[11] with *tert*-butyl hydroperoxide, $Mo(CO)_6$, and Na_2HPO_4 (1.5:0.03:0.05 equiv, respectively in benzene)[16] provided a single epoxy alcohol (**6**)[11] in 84% yield. The stereochemical outcome in this case was assigned initially by default, that is, via preparation and rigorous structural assignment of the alternative isomer (i.e., **9**); confirmation came with



8 9

completion of the gilmicolin venture (vide infra). Toward this end, epoxidation of olefin **5** with *m*-CPBA, as expected, afforded a 1:1 mixture of epoxy alcohols **6** and **9**.[11] The latter was a crystalline solid (mp 116–117 °C). Single-crystal X-ray analysis (see ORTEP) established not only the configuration at C(2) as *S* but also confirmed the stereochemical outcome of the conjugate addition [i.e., the substituents at C(4) and C(12) disposed trans].[17]

With epoxy alcohol **6** in hand, there remained only the conversion to gilmicolin methyl ether (**7**) and hydrolysis of the mixed ketal to complete the synthesis. We selected the Moffat oxidation[18] anticipating that use of excess pyridine would, after initial oxidation, effect both epoxide opening and isomerization of the resultant exo olefinic bond. In the event, treatment of **6** with 6 equiv of dicyclohexylcarbodiimide/Me_2SO and 2 equiv of pyridine afforded gilmicolin methyl ether (**7**) in 51% yield. Final



hydrolysis of the mixed methyl ketal via the Trofast–Wickberg protocol (50% HBF_4, dioxane, H_2O)[3] led to (–)-gilmicolin [$[\alpha]^{24}_D$ –25.1° (*c* 0.49, methanol); lit.[4] $[\alpha]^{24}_D$ –48 ± 2° (*c* 0.143, methanol)] in 44% yield.[19] That in fact gilmicolin was in hand was established via careful comparison of the physical and spectral properties with those derived from natural (–)-gilmicolin (**2**).[20]

In summary, the first total synthesis of (–)-gilmicolin has been achieved. The synthesis proved short (i.e., five steps from our common advanced intermediate), efficient, highly stereocontrolled, and secured for the *first* time the absolute stereochemistry of (–)-gilmicolin. Studies directed toward the synthesis of other members of this class will be reported in due course.

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(13) We thank Professor Stanley Opella and the Smith Kline Research Laboratories for obtaining the 500-MHz NMR spectra of **6** and **8**.
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(17) Unpublished results of P. Carroll of this laboratory.
(18) Pfitzner, K. E.; Moffat, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.
(19) The observed optical purity of synthetic (–)-gilmicolin is consistent with the optical purity (ca. 60% ee) of **4a** obtained via asymmetric hydroboration.
(20) We thank Professor C. Tamm, University of Zurich, for providing spectral data of natural (–)-gilmicolin.

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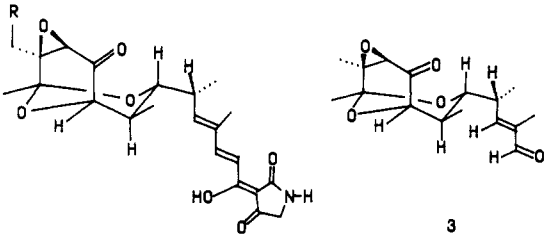
A Versatile 3-Acyltetramic Acid Reagent

Summary: The 3-acyltetramic acid derived Emmons reagent **6** undergoes smooth reaction with saturated and unsaturated aldehydes to afford easily characterized adducts which are readily debenzylated under acidic conditions.

Sir: In conjunction with synthetic efforts aimed at the construction of the natural products tirandamycin A (**1**) and tirandamycin B (**2**),[1] we became mired in the tactical problem of coupling aldehyde **3** onto a 3-acyltetramic acid residue. At the time we had reached this juncture, others,



tirandamycin-A(1); R=H
tirandamycin-B(2); R=OH

3

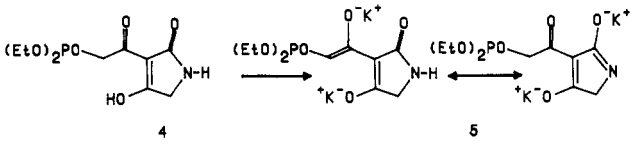
namely, Rinehart,[2] Boeckman,[3] and DeShong,[4] had addressed this situation. Unfortunately, the methodology described by these authors proved inappropriate for our

(1) Reusser, F. In "Antibiotics: Mechanism of Action of Antibacterial Agents"; Hahn, F. E., Ed.; Springer-Verlag: New York, 1979; Vol. V, Part I, p 361, and references cited therein.

0022-3263/85/1950-1344$01.50/0

needs. However, we felt that some promise was held by the Emmons reagent **4**, first described by Boeckman.[3]

The dianion of **4** reacted reasonably with saturated aldehydes but only poorly and under harsh conditions with unsaturated aldehydes.[3] It was our opinion that this unfortunate behavior stemmed from a lack of regiodefinition of the dianion **5** generated from **4**. This phenomenon

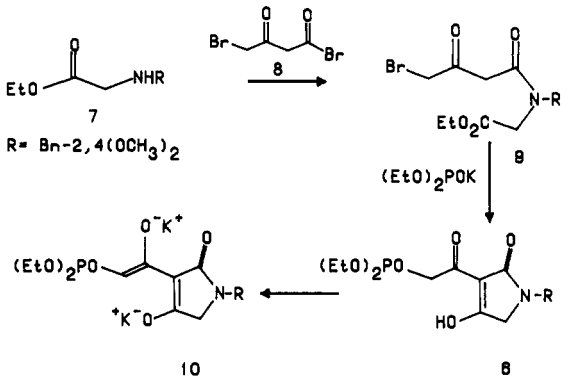


4 **5**

could account for the sluggish reactivity of the dianion **5**, particularly toward unsaturated aldehydes. A logical experimental response to this situation would be increasing both reaction time and temperature, but, unfortunately, conditions of this sort also enhance the basicity of most nucleophiles. With a base-sensitive aldehyde as the reaction partner, this could present serious experimental difficulties.

Motivated not only by our aforementioned synthetic effort on the natural products **1** and **2** but also by the realization that 3-acyltetramic acids are heterocyclic residues usually possessed of considerable biological activity, we set out to develop a more versatile form of the reagent **4**. It occurred to us that a nitrogen-protected derivative of **4** might serve to ameliorate its reactivity problem by virtue of defining its dianion analogue. However, the subsequent removal of this group had vexing potential, particularly when viewed within the context of substances like **1** and **2**.

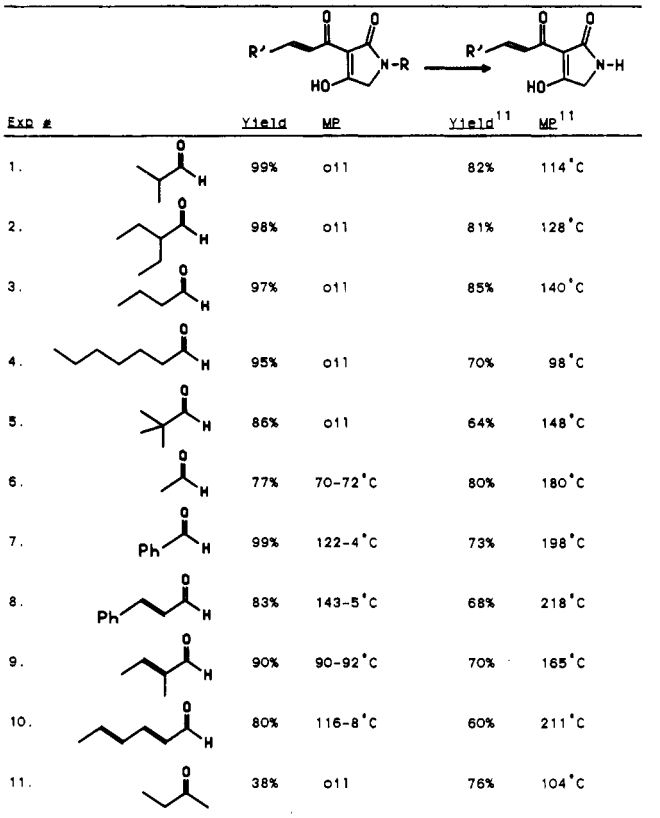
After some study, we elected to prepare the nitrogen-protected Emmons reagent **6**, the hope being that the 2,4-dimethoxybenzyl residue present on the lactam nitrogen atom could be removed either under mild oxidative or acidic conditions.[5] The preparation of **6** proved remarkably expeditious starting from the glycine derivative **7**.[6] Acylation of **7** (1 equiv) with the acid bromide **8**[7] (1



7 R = Bn-2,4(OCH$_3$)$_2$ **8** **9** **10** **6**

equiv, 0.5 M, CH_2Cl_2, −40 °C) containing triethylamine (1.5 equiv) gave the amide **9** (oil) in 97% yield after chromatography.[8] Treatment of **9** (1 equiv) with the potassium salt of diethyl phosphite[9] (2.2 equiv, 0.5 M, THF, 22 °C, 12 h) resulted both in formulation of the β-keto phosphonate residue and in ring-closure providing the tetramic acid **6** (red oil) in an overall yield of 85% after acid–base extraction.[10]

Table I



Exp #	Yield	MP	Yield[11]	MP[11]
1.	99%	oil	82%	114 °C
2.	98%	oil	81%	128 °C
3.	97%	oil	85%	140 °C
4.	95%	oil	70%	98 °C
5.	86%	oil	64%	148 °C
6.	77%	70–72 °C	80%	180 °C
7.	99%	122–4 °C	73%	198 °C
8.	83%	143–5 °C	68%	218 °C
9.	90%	90–92 °C	70%	165 °C
10.	80%	116–8 °C	60%	211 °C
11.	38%	oil	76%	104 °C

The conversion of **6** into its dianion **10** could be easily accomplished by addition of potassium *tert*-butoxide (2.1 equiv) in THF, at 0 °C, to a solution of **6** (1 equiv) also in THF. The resulting bright red mixture (0.5 M in THF) was reacted with a variety of aldehydes for 12 h at 0 °C. Chromatographic isolation of the adducts gave good yields in all cases except for 2-butanone, where a low yield of adducts (2.5:1 mixture of olefin isomers) was obtained (Table I). Removal of the 2,4-dimethoxybenzyl residue from the foregoing Emmons adducts was best accomplished by using trifluoroacetic acid (neat, 0.1 M, 22 °C, 30 min). In all cases, aqueous workup of these reactions

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(8) Satisfactory physical data were obtained for new compounds.
(9) For examples of the reaction of the sodium salt of this compound, see: Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, *31*, 2340.
(10) Compound **4** can be prepared by the method outlined for **6** by using ethyl glycinate, the acid bromide **8**, and the potassium salt of diethyl phosphite in 60% overall yield. Spectral data for **6** are as follows: IR ($CHCl_3$) 2999, 1710, 1640, 1616, 1292, 1031, 909 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 6 H, J = 7.1 Hz), 3.43 (d, 2 H, J = 23.2 Hz), 3.55 (s, 2 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 3.99 (q, 4 H, J = 7.1 Hz), 4.42 (s, 2 H), 6.33 (d, 2 H, J = 5.8 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 10.38 (bs, 1 H); ^{13}C NMR ppm CH_3 16.38/16.32 (J_{CP} = 4.5 Hz), 55.46, CH_2 62.92/62.84 (J_{CP} = 6.0 Hz), 55.84, 40.24, 32.76/31.04 (J_{CP} = 129.8 Hz), CH 131.34, 104.57, 98.60, C 191.42, 176.76, 172.67, 161.17, 158.69, 131.48, 115.61; MS, *m/e* (relative intensity) 426 (89), 291 (39), 290 (30), 289 (56), 274 (32), 248 (89), 178 (32), 166 (75), 152 (70), 151 (100), 121 (100), 99 (48), 91 (52), 81 (39), 43 (43).

followed by extraction with CH_2Cl_2 afforded the crude tetramic acid products.[11]

The method described herein has been successfully applied to the total synthesis of 1.[12]

(11) These materials were purified either by acid-base extraction or by chromatography of their corresponding sodium salts on Merck 7734 silica gel. Melting points are uncorrected.

(12) Manuscript in press. Professor P. DeShong has also used the reagent 6 to complete a total synthesis of 1.

(13) Merck and Company postdoctorate fellow.

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Recent Reviews. 15

Reviews are listed in order of appearance in the sources indicated. In multidisciplinary review journals, only those reviews which fall within the scope of this Journal are included. Sources are listed alphabetically in three categories: regularly issued review journals and series volumes, contributed volumes, and monographs. Titles are numbered serially, and these numbers are used for references in the index.

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This installment of Recent Reviews covers the second half of the 1984 literature. Previous installment: *J. Org. Chem.* **1984**, *49*, 4103. For regularly issued journals and series volumes, the coverage in this installment continues from the last items included in Recent Reviews 14.

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