dihydroisoflavone (7e). From 0.5 g of acid **3e**, a mixture of **6e** and **7e** was obtained. Separation by silica gel chromatography resulted in 90 mg (24%) of **6e** and 210 mg (49%) of **7e**.

6e: mp 90–92 °C; IR 1630, 1600, 1570 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 266 (M^+, 100), 235 (38), 234 (10), 159 (32), 135 (44); ^1H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 3.8 (s, 3 H), 7.0–7.6 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 191.1, 163.2, 156.6, 153.28 131.7, 130.6, 128.5, 126.2, 123.9, 123.5, 121.1, 120.6, 117.7, 111.2, 110.4, 55.4, 14.3.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 76.67; H, 5.32.

7e: mp 110–111 °C; IR 1850, 1690, 1605 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 310 (M^+, 3), 266 (25), 251 (43), 235 (100); ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 3.7 (s, 3 H), 6.9–8.0 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 186.0, 169.2, 158.0, 155.4, 136.8, 130.6, 128.8, 126.9, 126.6, 122.0, 121.4, 118.9, 118.5, 110.6, 91.0, 84.0, 55.6 18.0.

β-Lactone of 2-Carboxy-3-hydroxy-2-methyl-2′,4′,7-trimethoxy-2,3-dihydroisoflavone (7f). A 0.48-g (57%) portion of **7f** was obtained from 1 g of **3f**: mp >135 °C dec; IR 1850, 1685, 1610 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 326 ($M^+ - CO_2$, 39), 312 (8), 311 (41), 295 (100); ^1H NMR ($CDCl_3$) δ 1.5 (s, 3 H), 3.6 (s, 3 H), 3.8 (s, 3 H), 3.9 (s, 3 H), 6.45–6.75 (m, 4 H), 7.4 (d, 1 H), 7.9 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 184.5, 169.5 166.6, 161.8, 160.1, 156.3, 130.6, 127.6, 114.7, 112.3, 112.2, 104.8, 101.3, 98.9, 90.9, 83.6, 55.8, 55.6, 55.4, 18.1.

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.86. Found: C, 65.35; H, 5.20.

6-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (10). A 0.5-g (1.87 mmol) portion of [(*o*-propenylphenoxy)phenyl]acetic acid was refluxed with 2.0 g (24 mmol) of sodium acetate and 15 mL (159 mmol) of acetic anhydride for 4 h. The reaction mixture was poured into a cold dilute aqueous sodium of hydroxide solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then evaporated to 0.5 g (90%) of **9**: IR, 1760, 1680, 1605, 1590, cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 292 (M^+, 13), 250 ($M^+ - 42$, 78), 235 (11), 222 (27), 221 (47), 205 (59), 194 (29), 178 (22), 165 (40), 42 (100); ^1H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.15 (s, 3 H), 3.8 (s, 1 H), 6.8–7.6 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 166.8, 162.1, 137.5, 136.2, 134.1, 128.7, 128.5, 128.2, 127.9, 125.6, 124.4, 120.6, 111.7, 93.7, 55.3, 20.6, 12.3.

Compound **9** was treated with a 50% aqueous potassium hydroxide solution containing methanol. The methanol was removed under reduced pressure and the aqueous residue extracted with ether. Upon drying the ether over anhydrous magnesium sulfate, and the ether was evaporated to yield 0.3 g (64%) of **10**. The mp and IR and ^1H and ^{13}C NMR spectra were identical with those previously reported.[1f]

Cyclization of 3d and 3e Using Perkin Reaction Conditions. A 0.5-g portion of **3d** was refluxed with 1.5 equiv of acetic anhydride and 2.0 equiv of sodium acetate in 30 mL of benzene for 24 h. The reaction mixture was cooled and filtered and an IR spectrum of the concentrated filtrate revealed a strong β-lactone peak at 1850 cm^{-1}. Rotary chromatography of the filtrate resulted in 0.1 g of **6d** (25%) and 0.08 g of **7d** (17%).

A 0.1-g portion of **3e** was treated as described above. An IR spectrum of an aliquot of the reaction mixture revealed a strong β-lactone peak at 1850 cm^{-1}. Thin layer chromatography revealed two spots with the same R_f values as characterized above for **6e** and **7e**. Preparative thin layer chromatography gave a trace of **6e** and **7e**, which were identified by IR and GC/MS.

General Procedure for Decarboxylation of β-Lactones 7d–f. A sample of the β-lactone was placed in a melting point capillary tube and heated in a melting point apparatus. When the temperature reached 135–140 °C, small bubbles began to appear. The temperature was kept at 150 °C for 5 h. The tube was broken and the contents were recovered for analysis.

2-Methylisoflavone (8d). This isoflavone was recovered as an oil: IR 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3), 7.25–8.25 (m, 9 H).

2-Methyl-2′-methoxyisoflavone (8e). This isoflavone was also recovered as an oil: IR 1645, 1600, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.8 (s, 3 H), 7.0–8.2 (m, 8 H).

2-Methyl-2′,4′,7-trimethoxyisoflavone (8f). This isoflavone was recovered as a crystalline solid: mp 185–187 °C; IR 1625, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 6.6 (m, 2 H), 6.9 (m, 2 H), 7.1 (m, 1 H), 8.1 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.2, 163.7, 163.5, 160.9, 158.3, 157.6, 132.4, 127.7, 119.4, 117.2, 114.7, 113.8, 104.7, 99.9, 99.0, 55.7, 55.6, 55.4, 19.2.

Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found: C, 69.86; H, 5.63.

Acknowledgment. We are grateful to the Robert A. Welch Foundation for support of this work.

Registry No. **1a**, 34082-43-4; **1b**, 6706-92-9; **1c**, 82362-01-4; **2a**, 34589-99-6; **2b**, 107943-61-3; **2c**, 95281-05-3; **3a**, 113180-51-1; **3b**, 103031-10-3; **3c**, 103206-86-6; **3d**, 113180-52-2; **3e**, 113180-53-3; **3f**, 113180-54-4; **6a**, 6454-01-9; **6b**, 113180-55-5; **6d**, 18703-72-5; **6e**, 93321-78-9; **7d**, 113180-56-6; **7e**, 113180-57-7; **7f**, 113180-58-8; **8a**, 574-12-9; **8b**, 7622-32-4; **8c**, 7678-84-4; **8d**, 24258-66-0; **8e**, 113180-59-9; **8f**, 70387-01-8; **9**, 113218-61-4; **10**, 99477-35-7; 2-$HO_2CCH(Ph)OC_6H_4CH{=}CHCH_3$, 99477-28-8; $MeCHBrCO_2CH_2Me$, 535-11-5; 2,2′-dihydroxy-4,4′-dimethoxybenzil, 6706-94-1; ethyl α-bromoacetate, 105-36-2.

A General Method for the Synthesis of Tetramic Acid Derivatives

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Received October 3, 1987

Fragmentation of 2,5-disubstituted isoxazolium salts resulted in the formation of highly functionalized β-keto amide derivatives. Subsequent base-catalyzed cyclization afforded 3-acyltetramic acid derivatives similar to the tetramic acid moieties found in tirandamycin A/B and streptolydigin. The scope and limitations of this methodology for the total synthesis of naturally occurring tetramic acid antibiotics is discussed.

The dienoyl tetramic acids tirandamycin A (**1**) and B (**2**)[1] streptolydigin (**3**)[2] and ikarugamycin (**4**)[3] are representative examples of the structurally diverse family of tetramic acid antibiotics. The common feature of these natural products is the 2,4-pyrrolidinedione or tetramic

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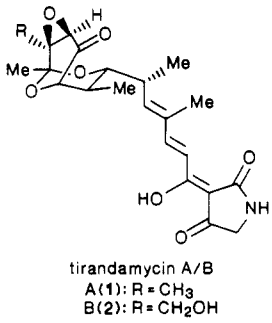
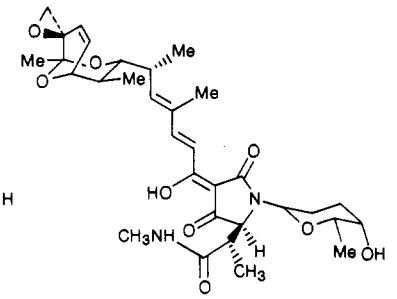
0022-3263/88/1953-1356$01.50/0

acid moiety (5).

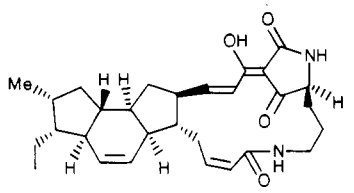
We[4] and others[5-11] have developed a variety of general strategies for the total synthesis of tetramic acid derivatives. A major focus of these studies has been the evolution of methodologies for the preparation of highly functionalized tetramic acid reagents. As depicted by structures 1–4, it is necessary to synthesize tetramic acid moieties



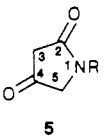
tirandamycin A/B
A(1): R = CH_3
B(2): R = CH_2OH



streptolydigin
3



ikarugamycin
4

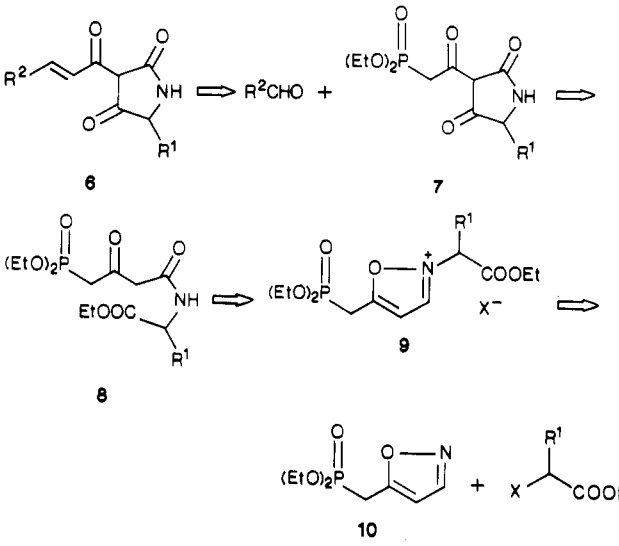


5

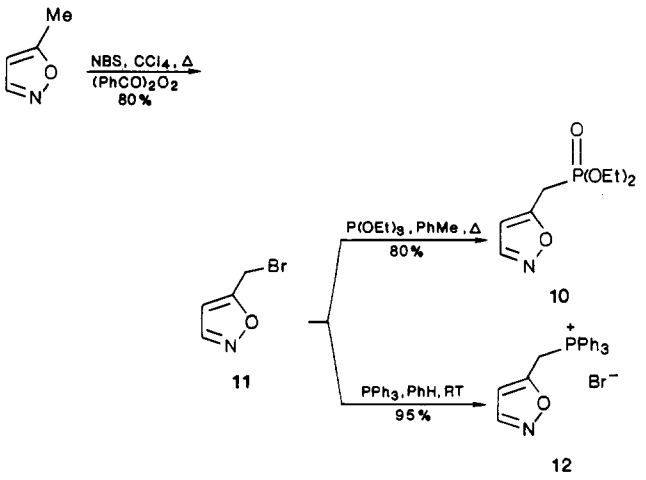
having (1) a (poly)enoyl functionality at C-3 and (2) substituents at N-1 and C-5 of the heterocyclic nucleus. Once the tetramic acid has been introduced, subsequent transformations of the molecule are restricted due to the sensitivity of this functional group; therefore, it is prudent to introduce the tetramic acid at the final stages of the total synthesis of the antibiotics.

A potential solution to this dilemma is outlined in Scheme I. The retrosynthetic strategy envisioned condensation of an aldehyde with the anion (or dianion) of phosphonate 7 to provide enoyl tetramic acid 6. This

Scheme I



Scheme II



approach was especially appealing because the tetramic acid moiety could be delivered intact at an advanced stage of a synthesis while avoiding the need for protecting groups. Secondly, acyl phosphonate anions are known to condense readily with unsaturated aldehydes,[4b,5,6b] thus polyenoyl tetramic acid derivatives would be accessible by this approach. This paper describes the scope and limitations of this approach to the synthesis of functionalized tetramic acids.

Phosphonate–tetramic acid 7 was to be prepared by alkylation of isoxazole 10 followed by fragmentation of the resulting isoxazolium salt 9 to afford β-keto amide 8. Previous studies by Rinehart,[9] Mulholland,[12] and Lacey[13] had demonstrated that β-keto amides similar to 8 underwent base-catalyzed cyclization furnishing 3-acyltetramic acid derivatives.

Phosphonate 10 and phosphonium salt 12 were prepared as depicted in Scheme II. Bromination of 5-methylisoxazole furnished 5-(bromomethyl)isoxazole (11) in 80% yield. Michaelis–Arbuzov reaction of bromide 11 with triethylphosphite yielded phosphonate 10. Alternatively, treatment of 11 with triphenylphosphine provided phosphonium salt 12. The insolubility of phosphonium salt 12

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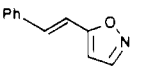
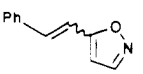
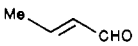
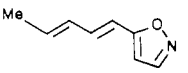
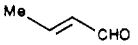
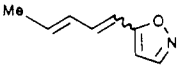
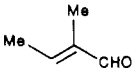
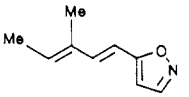
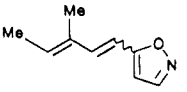
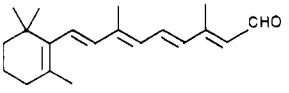
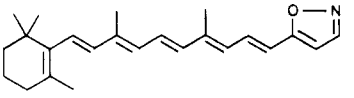
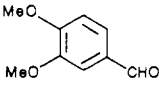
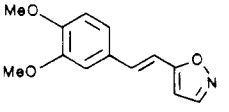
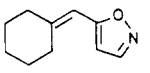
Table I. Wittig Reaction of Aldehydes with Phosphonate 10/Phosphonium Salt 12

entry	aldehyde	Wittig reagent	product	yield (%)[a]	isomer ratio (E:Z)[b]
1	PhCHO	10	 **15A**	92	*d*
2	PhCHO	12	 **15A:15B**	*c*	1.4:1.0
3		10	 **16A**	75	*d*
4		12	 **16A:16B**	*c*	2.2:1.0
5	 **13**	10	 **17A**	70	*d*
6	**13**	12	 **17A:17B**	*c*	2.7:1.0
7	 **14**	10	 **18**	54	*d*
8		10	 **19**	80	*d*
9		10	 **20**	60	*d*

[a] Yield of isolated, chromatographically homogeneous product. [b] Determined by capillary gas chromatography or ^{1}H NMR spectroscopy. [c] Isolated yield of mixture of alkenes was >60%. Optimized yields not determined. [d] *E* isomer exclusively.

in common organic solvents limited its application in the outlined approach, although it proved to be a viable Wittig olefination reagent (vide infra).

Olefination reactions of phosphonate **10** and phosphonium salt **12** were investigated and the results are summarized in Table I. For the condensation with phosphonate **10** and phosphonium salt **12**, various base/solvent combinations were evaluated and the optimum conditions employed *n*-butyllithium in tetrahydrofuran. Aromatic aldehydes such as benzaldehyde and 3,4-dimethoxybenzaldehyde (entries 1, 2, and 8) and α,β-unsaturated aldehydes (entries 3–7) were substrates in the olefination procedure. Even the extremely sensitive *trans*-retinal (**14**, entry 7) afforded an acceptable yield of homologated isoxazole (**18**) upon treatment with the phosphonate anion under optimum conditions. Also gratifying was the discovery that cyclohexanone (entry 9) was a viable substrate with the phosphonate reagent.

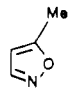
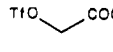
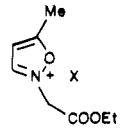
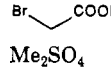
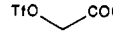
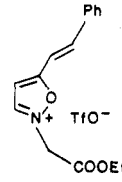
As anticipated, under these reaction conditions the condensation of aldehydes with the anion of phosphonate **10** furnished exclusively alkenes with the *E* configuration.[14] The alkene geometry was confirmed from the ^{1}H NMR spectra of the adducts which showed coupling constants of 15.2–16.4 Hz for the respective alkene resonances. This result was significant because the naturally occurring tetramic acid antibiotics always have the (*E*)-alkene configuration.

Representative olefinations with the ylide derived from phosphonium salt **12** afforded a mixture of (*E*)- and (*Z*)-alkenes, with the *E* isomer predominating (Table I). Due to the disappointing lack of stereoselectivity observed in the reactions of the phosphorane, this coupling sequence was not investigated in detail.

Phosphonate **10** and related isoxazoles **15A** and **21** were readily alkylated with electrophilic reagents to afford isoxazolium salts (Table II). In each instance, treatment of the isoxazole with 1.1 equiv of the electrophile provided

(14) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87. Wadsworth, W. S. *Org. React. (N.Y.)* **1977**, *25*, 73 and references cited therein. See also: Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318. Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1.

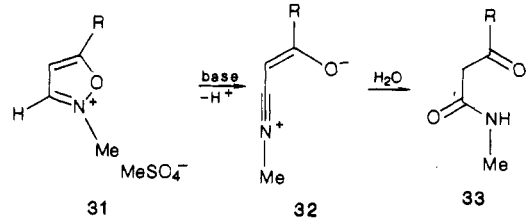
Table II. N-Alkylation of Isoxazoles

entry	isoxazole	electrophilic reagent	product	yield (%)[a]
1	 21	Me_2SO_4	24	>95
2	21	 23	 25: X=TfO^- 26: X=BF_4^-	>95
3	21			80
4	15A	Me_2SO_4	27	>95
5	15A	 23	 28	>95
6	10	Me_2SO_4	29	>95
7	10	23	30	>95

[a] Yield of isolated product.

the corresponding salt in excellent yield. The salt was identified by its characteristic ^1H NMR spectrum in which the isoxazole proton signals at δ 6.1 and 8.2 were shifted downfield to approximately δ 7.2 and 9.3, respectively, in the salt.

N-Methylation of isoxazoles **10**, **15A**, and **21** with neat dimethyl sulfate produced the respective isoxazolium salts in nearly quantitative yield. Similarly, treatment of these isoxazoles with carbethoxymethyl triflate (**23**) in nitromethane at 0 °C according to the method of Vedejs[15] afforded salts **25**, **28**, and **30**, respectively (entries 2, 5, and 7). Alternatively, tetrafluoroborate salt **26** (entry 3) was prepared by alkylation of isoxazole **21** with ethyl bromoacetate in refluxing acetonitrile containing silver tetrafluoroborate; however, the harsh reaction conditions necessary to effect N-alkylation with the bromo ester limited the generality of this method. The isoxazolium salts were stable for weeks when stored at 0 °C under an inert atmosphere but underwent partial hydrolysis to give β-keto amides (vide infra) when exposed to adventitious moisture.



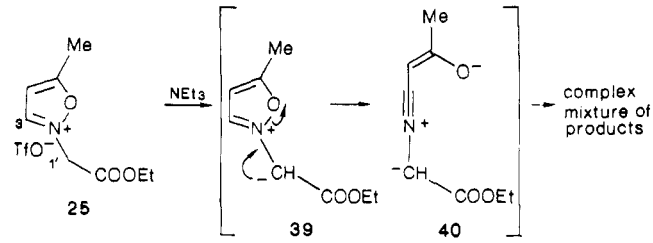
31 32 33

Fragmentation of isoxazolium salts to yield β-keto amide derivatives had been investigated previously by Woodward and Olofson.[16] They demonstrated that deprotonation of isoxazolium salt **31** at C-3 affected cleavage of the

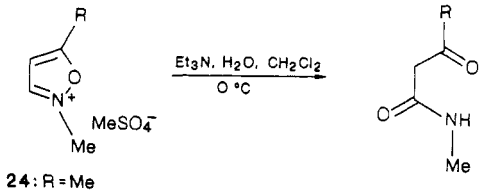
(15) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

(16) Woodward, R. B.; Olofson, R. A. *Tetrahedron, Suppl.* **1966**, *7*, 415. Woodward, R. B.; Olofson, R. A. *J. Am. Chem. Soc.* **1961**, *83*, 1007. Woodward, R. B.; Olofson, R. A.; Mayer, H. *Ibid.* **1961**, *83*, 1010.

Scheme III



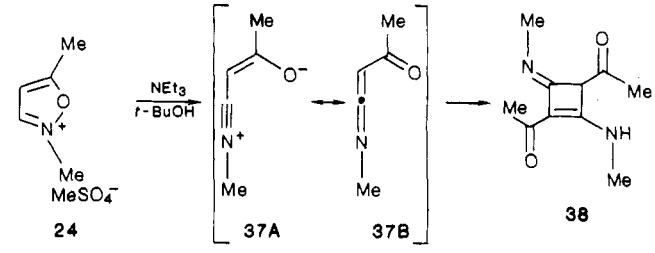
N,O-bond and afforded nitrilium ion **32**. Subsequent capture of the nitrilium ion by water gave β-keto amide **33**. Using a modified Woodward–Olofson protocol for isoxazolium salt fragmentation, β-keto amides were obtained from cleavage of the salts depicted in Table II. In the modified protocol, a two-phase system of the isoxazolium salt in CH_2Cl_2–H_2O was treated with triethylamine to give the β-keto amides in excellent yield. For example, isoxazolium salt **24** was cleaved to afford a 90% yield of *N*-methylacetoacetamide.



24: R = Me
27: R = CH=CHPh
29: R = $CH_2PO(OEt)_2$

34: R = Me
35: R = CH=CHPh
36: R = $CH_2PO(OEt)_2$

An anomalous product was obtained from the cleavage of isoxazolium salt **24** with triethylamine in *tert*-butyl alcohol. In the absence of a nucleophilic solvent, nitrilium ion **37A** underwent head-to-tail dimerization to furnish cyclobutene **38** in 85% yield. The dimerization could have occurred by nucleophilic attack of the enolate of one molecule onto the nitrilium ion of the second. Alternatively, cyclobutene **38** may have arisen by [2 + 2] cycloaddition of ketimine **37B**.[16]

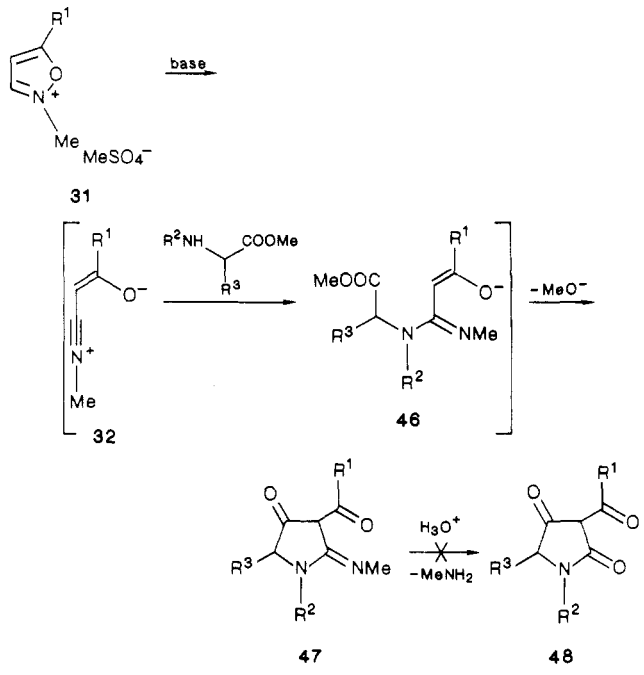


24 37A 37B 38

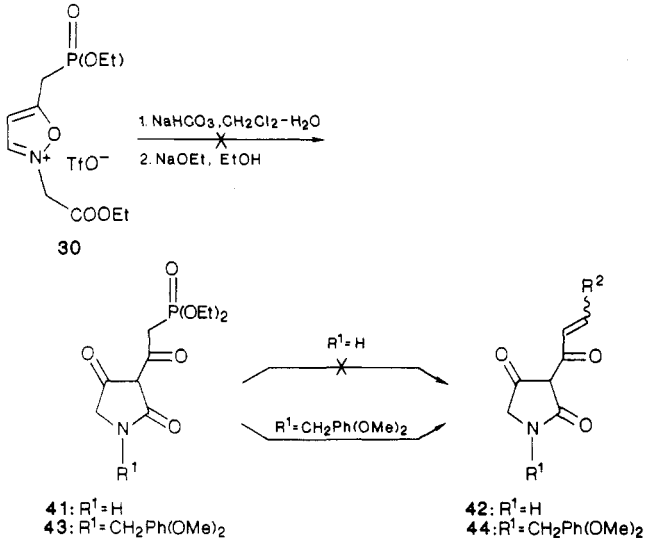
Carbethoxymethyl isoxazolium salts **25**, **26**, **28**, and **30** (Table II), unlike the *N*-methyl analogues, were cleaved under basic conditions to provide an array of products from which the β-keto amide was not isolated. One possible explanation for this anomolous behavior is the presence of an electron-withdrawing group attached to the N-2 substituent of the salt. Under basic conditions, the kinetic acidity of the protons attached to C-1′ may be greater than C-3 and thus ylide formation (**39**/**40**) results either prior to or after isoxazolium ring fragmentation. The ylide must have reaction pathways available which are not common to the methyl isoxazolium fragmentation analogues (Scheme III).

The failure of the fragmentation of isoxazolium salts **25**, **26**, **28**, and **30** to afford β-keto amides is a major limitation of this approach for the preparation of functionalized tetramic acids. For example, treatment of phosphonate **30** with 1 equiv of triethylamine in CH_2Cl_2–H_2O at 0 °C followed by cyclization with sodium ethoxide in ethanol

Scheme IV



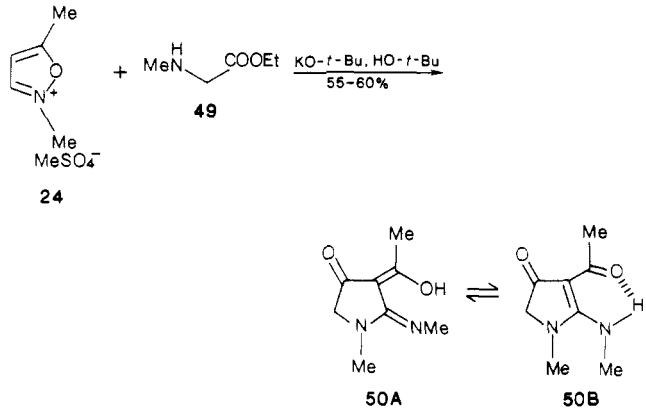
gave phosphonate–tetramic acid **41**. However, the yield of tetramic acid was generally low (<20%) and irreproducible.



Disappointingly, attempts to condense anions derived from phosphonate **41** with aldehydes such as benzaldehyde, heptanal, and tiglaldehyde failed to afford tetramic acid derivatives under a variety of reaction conditions. Subsequent investigations in our[4b] and Professor Schlessinger's[5] laboratory have indicated that the presence of a hydrogen atom on the tetramic acid nitrogen is responsible for the unsatifactory condensation sequence. Replacement of the hydrogen of **41** by an alkyl group such as 3,4-dimethoxybenzyl gave a phosphonate derivative (**43**) which upon treatment with 2 equiv of potassium *tert*-butoxide according to the Schlessinger protocol[5] condensed with aldehydes to furnish *N*-alkyltetramic acid **44**.[4b]

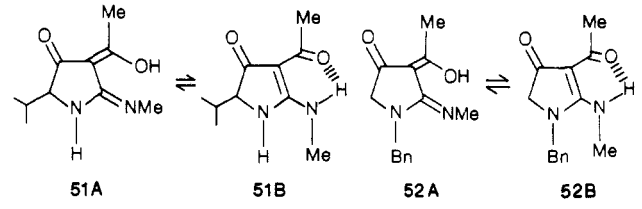
The isoxazolium salt strategy outlined in Scheme I was not applicable to the preparation of *N*-alkyltetramic acid derivatives such as **43**. Because the presence of an *N*-alkyl substituent was required for subsequent effective coupling of the tetramic acid derivatives, an alternative strategy was implemented (Scheme IV). Base-induced fragmentation of isoxazolium salt **31** afforded nitrilium salt **32** which, under anhydrous conditions, reacted with α-amino ester **45** to provide amidine **46**. Subsequent base-catalyzed cyclization then afforded tetramic acid analogue, amidine **47**. Hydrolysis of the amidine was expected to yield *N*-alkyltetramic acid **48**.

In practice, this strategy was successful with simple isoxazole derivatives. For example, heating a solution of isoxazolium salt **24** and sarcosine ethyl ester (**49**) with potassium *tert*-butoxide in *tert*-butyl alcohol gave amidine **50A/50B** in 55–60% yield. Amidine **50A** was initially obtained along with its tautomer **50B**. Recrystallization of the mixture from methanol afforded exclusively tautomer **50B**.



The structure of the recrystallized tautomer was assigned as **50B** from spectral data. In particular, the ^{1}H NMR spectrum showed a one-proton, broad singlet at δ 9.89 for the vinylogous amide proton, and a three-proton doublet at δ 3.20 with a coupling constant of 5.6 Hz for the *N*-methyl group.

Employing analogous methodology, the amidine analogue of erythroskyrine[17] (**51**) was prepared in 64% yield from isoxazolium salt **24** and L-valine ethyl ester, and amidine **52** was obtained in 60% yield from the reaction of **24** and *N*-benzylglycine ethyl ester. Interestingly, amidine **52** was isolated as the vinylogous amide tautomer **52B**, whereas **51** was isolated in amidine form **51A**.

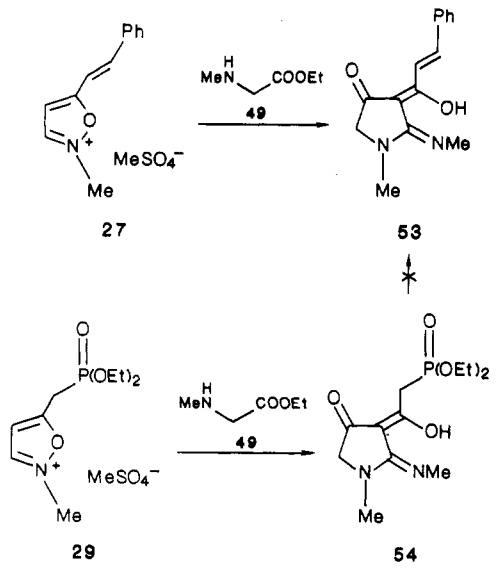


Reaction of the functionalized isoxazolium salts **27** and **29** with ethyl sarcosinate (**49**) under the basic conditions provided the amidines **53** and **54** in 60% and 55%, respectively. No tautomerization was noted in these substances and the amidine was the sole product in each instance (Scheme V).

It was anticipated that acid or base hydrolysis of the amidine moiety would provide the corresponding tetramic acid derivative. Close inspection of the literature, however, suggested that precautions had to be taken in this reaction because acid hydrolysis of 3-acyltetramic acid derivatives often resulted in liberation of the 3-acyl substituent.[18] Indeed, hydrolysis of amidines **50A** and **51–54** under a variety of acidic conditions failed to furnish the 3-acyl-

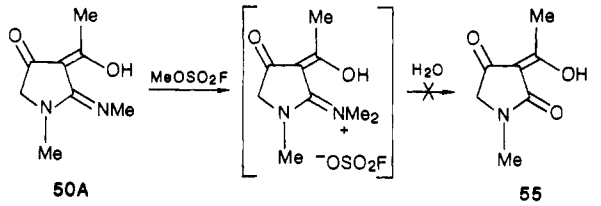
(17) Shoji, J.; Shibata, S.; Sankawa, U.; Taguchi, H.; Shibanuma, Y. *Chem. Pharm. Bull. (Tokyo)* **1965**, *13*, 1240.
(18) Stickings, C. E. *Biochem. J.* **1959**, *72*, 332.

Scheme V



tetramic acid derivative, respectively.

Attempts to enhance hydrolysis of the amidine by initial alkylation of the amidine with methyl fluorosulfonate followed by hydrolysis afforded complex reaction mixtures in which the desired tetramic acid (**55**) was not detected.



The inability to affect hydrolysis of the amidine–tetramic acid derivatives meant that this promising strategy for the synthesis of 3-acyltetramic acid derivatives had to be abandoned.

Experimental Section

Melting points were taken in Kimax soft-glass capillary tubes on a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406 K) equipped with a calibrated thermometer.

Proton magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker WP-200 or WM-360 Super Con spectrometer. Proton chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (J values) are given in hertz (Hz) and spin multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). The deuteriated NMR solvent contained 99.0–99.8% deuterium in the indicated position. Infrared spectra were recorded on a Perkin-Elmer Model 281B diffraction grating spectrophotometer. Peak positions are given in reciprocal centimeters (cm^{-1}) and are listed as very strong (vs), strong (s), medium (m), weak (w), broad (b). Mass spectral data were obtained on a Kratos MS-950 double-focusing high-resolution spectrometer or on a Finnigan 3200 twin EI and CI quadrupole mass spectrometer equipped with a Finnigan 6000 computer. The chemical ionization carrier gas was methane.

Thin-layer chromatography (TLC) was performed on 0.25-mm Merck silica gel coated glass plates with the compounds being identified in one or more of the following ways: UV light (254 nm), iodine, sulfuric acid, vanillin, ninhydrin, cerium(IV) sulfate, and/or molybdenum–phosphoric acid charring. Flash chromatography was performed on thick-walled glass columns and "medium pressure" silica gel (Merck 32–63 μm). The solvent systems used are reported in each experimental.

All solvents were distilled from $CaCl_2$ unless otherwise noted. Ethyl ether, benzene, and tetrahydrofuran were distilled from sodium/benzophenone ketyl. The reaction solvents (i.e., methylene chloride, toluene, carbon tetrachloride, nitromethane, and *tert*-butyl alcohol) were distilled from CaH_2. *n*-Butyllithium was titrated against diphenylacetic acid (used as titrant and indicator) in THF at 23 °C.[19] All reactions were carried out in glassware that had been dried in an oven for a minimum of 8 h at 120 °C and were assembled while hot under N_2.

Preparation of 5-(Bromomethyl)isoxazole (11). *N*-Bromosuccinimide (2.14 g, 12.0 mmol) and freshly distilled 5-methylisoxazole (0.98 mL, 12 mmol) were combined in CCl_4 (30.0 mL) under N_2. Benzoyl peroxide (0.291 g, 1.20 mmol) was added and the mixture was heated to 80 °C for 6 h. The reaction mixture was cooled to 0 °C and filtered, the filtrate was evaporated in vacuo, and the resultant residue was vacuum distilled to yield 1.55 g (80%) of 5-(bromomethyl)isoxazole (**11**) as a clear liquid: bp 58–62 °C/0.5 mm; IR (CCl_4) 3135 (m), 2960 (m), 1780 (m), 1585 (s), 1460 (vs), 1420 (s), 1330 (vs), 1220 (vs), 1185 (vs), 1165 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.26 (b s, 1 H), 6.39 (b s, 1 H), 4.55 (s, 2 H); mass spectrum, m/z (relative intensity) 163 (M^+, 11), 161 (M + 2, 11), 82 (100), 40 (10), 28 (16).

Preparation of Diethyl (5-Isoxazolylmethyl)phosphonate (10). Freshly distilled triethyl phosphite (3.40 mL, 19.8 mmol) was added to a stirred solution of 5-(bromomethyl)isoxazole (**11**) (3.21 g, 19.8 mmol) in 5.0 mL of toluene under N_2 at 0 °C. The reaction mixture was allowed to warm to room temperature over the course of 4 h and was then heated at reflux for 24 h. After cooling, the solvent was evaporated in vacuo, and the resultant residue was vacuum distilled to yield 3.48 g (80%) of phosphonate **10** as a clear, viscous liquid: bp 110–115 °C/0.35 mm; IR (CCl_4) 3150 (w), 2990 (vs), 2940 (s), 2910 (s), 1725 (s), 1595 (s), 1470 (vs), 1445 (s), 1395 (vs), 1370 (s), 1345 (s), 1270 (b vs), 1180 (s), 1160 (s), 1020 (b vs) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.27 (b s, 1 H), 6.33 (b s, 1 H), 4.17 (dq, J = 7.0, 7.0 Hz, 4 H), 3.45 (d, J = 21.4 Hz, 2 H), 1.36 (t, J = 7.0 Hz, 6 H); mass spectrum, m/z relative intensity) 219 (M^+, 31), 192 (44), 163 (42), 136 (23), 109 (100), 83 (78).

Preparation of (5-Isoxazolylmethyl)triphenylphosphonium Bromide (12). Triphenylphosphine (1.58 g, 6.00 mmol) was dissolved in 15.0 mL of benzene under N_2. Bromoisoxazole **11** (0.973 g, 6.00 mmol) dissolved in 3.0 mL of benzene was added to the phosphine solution and the reaction mixture was allowed to stir at 23 °C for 20 h. The reaction mixture was centrifuged and the solvent decanted leaving a light yellow solid. The solid was dispersed in CH_2Cl_2 and the centrifugation–decantation process was repeated until no color was evident in the CH_2Cl_2 washings. Phosphonium bromide **12** (2.43 g, 95%) was obtained as a white solid: mp 225–226 °C; IR (Nujol) 2940–2880 (b vs), 2840 (vs), 1460 (s), 1360 (m), 1120 (w), 1080 (w) cm^{-1}. Anal. Calcd for $C_{22}H_{19}ONPBr$: C, 62.28; H, 4.51. Found: C, 61.98; H, 4.49.

General Procedure for the Horner–Emmons Olefinations with Phosphonate 10. Diethyl (5-isoxazolylmethyl)phosphonate (**10**, 1.0 equiv) was dissolved in THF (10 mL/mmol isoxazole) and cooled to 0 °C. Freshly titrated *n*-BuLi (1.5–2.5 M in hexanes, 1.0 equiv) was slowly added. Upon completion of addition, the neat aldehyde (1.1 equiv) was added. The reaction mixture was allowed to warm to 23 °C and was quenched by addition of H_2O after 5 h. The resultant solution was extracted thrice with CH_2Cl_2. The extracts were combined, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated in vacuo. The resultant residue was purified by flash chromatography to give alkenes **15–20** in the indicated yields.

(*E*)-5-(2-Phenylethenyl)isoxazole (15A) was prepared according to the general procedure from isoxazole **10** (0.219 g, 1.00 mmol), *n*-BuLi (0.45 mL, 2.24 M, 1.0 mmol), and benzaldehyde (0.11 mL, 1.1 mmol) in 10 mL of THF. Flash chromatography with ethyl acetate–hexane (1:5) afforded **15A** (R_f 0.36) as a yellow solid. Recrystallization from ethyl acetate–hexane gave 0.157 g (92%) of yellow needles: mp 33–34 °C; IR (CCl_4) 3160 (m), 3040 (s), 1950 (m), 1880 (m), 1810 (m), 1780 (m), 1745 (s), 1710 (s), 1645 (vs), 1470 (vs), 1350 (vs), 1170 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 1.8 Hz, 1 H), 7.50 (m, 2 H), 7.37 (m, 4 H), 6.98 (d, J = 16.4 Hz, 1 H), 6.25 (d, J = 1.8 Hz, 1 H); mass spectrum, m/z (relative intensity) 171 (M^+, 100), 144 (46), 103 (40), 77 (40). Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30. Found: C, 77.28; H, 5.61.

(19) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(*E,E*)-5-(1,3-Pentadienyl)isoxazole (16A) was prepared according to the general procedure from isoxazole **10** (0.219 g, 1.00 mmol), *n*-BuLi (0.45 mL, 2.24 M, 1.0 mmol), and crotonaldehyde (0.090 mL, 1.1 mmol) in 10 mL of THF. Flash chromatography with CH_2Cl_2 afforded 0.101 g (75%) of **16A** (R_f 0.52) as a yellow oil: IR (CCl_4) 3040 (s), 2980 (s), 2940 (s), 2860 (m), 1685 (m), 1650 (vs), 1465 (vs), 1450 (vs), 1350 (s), 1180 (s), 900 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, J = 1.7 Hz, 1 H), 6.93 (dd, J = 15.7, 10.3 Hz, 1 H), 6.30 (d, J = 15.7 Hz, 1 H), 6.18 (m, 1 H), 6.11 (d, J = 1.7 Hz, 1 H), 5.99 (m, 1 H), 1.83 (d, J = 6.5 Hz, 3 H); mass spectrum, m/z (relative intensity) 135 (M^+, 100), 120 (15), 106 (54), 92 (14), 79 (87), 67 (38), 51 (25), 39 (66).

(*E,E*)-5-(3-Methyl-1,3-pentadienyl)isoxazole (17A) was prepared according to the general procedure from isoxazole **10** (0.219 g, 1.00 mmol), *n*-BuLi (0.45 mL, 2.24 M, 1.0 mmol), and tiglaldehyde (0.11 mL, 1.1 mmol) in 10 mL of THF. Flash chromatography with ethyl acetate–hexane (1:5) afforded 0.104 g (70%) of **17A** (R_f 0.46) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 8.14 (d, J = 1.7 Hz, 1 H), 6.99 (d, J = 16.1 Hz, 1 H), 6.30 (d, J = 16.1 Hz, 1 H), 6.11 (d, J = 1.7 Hz, 1 H), 5.85 (m, 1 H), 1.78 (b s, 6 H); mass spectrum, m/z (relative intensity) 149 (M^+, 48), 137 (49), 122 (64), 106 (28), 94 (45), 79 (82), 66 (36), 53 (27), 43 (68), 28 (100).

(*all-E*)-5-[4,8-Dimethyl-10-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9-decapentaenyl]isoxazole (18) was prepared according to the general procedure from isoxazole **10** (0.219 g, 1.00 mmol), *n*-BuLi (0.45 mL, 2.24 M, 1.0 mmol), and *trans*-retinal (**14**, 0.313 g, 1.10 mmol) in 10 mL of THF. Flash chromatography with CH_2Cl_2 afforded **18** (R_f 0.54) as an orange solid. Recrystallization from hexane gave 0.190 g (54%) of deep metallic orange crystals: mp 122–123 °C; IR (CCl_4) 3050 (s), 2970 (vs), 2930 (vs), 2870 (vs), 1625 (s), 1455 (vs), 1360 (s), 1150 (s) cm^{-1}; UV (EtOH) 397 nm; ^1H NMR ($CDCl_3$) δ 8.16 (d, J = 1.6 Hz, 1 H), 7.35 (dd, J = 15.2, 11.8 Hz, 1 H), 6.76 (dd, J = 15.2, 11.8 Hz, 1 H), 6.38 (m, 2 H), 6.16 (m, 5 H), 2.04 (s, 3 H), 1.97 (s, 3 H), 1.70 (s, 3 H), 1.59 (m, 4 H), 1.45 (m, 2 H), 1.01 (s, 6 H); mass spectrum, m/z (relative intensity) 349 (M^+, 100), 281 (15), 119 (26), 105 (25). Anal. Calcd for $C_{24}H_{31}NO$: C, 82.48; H, 8.94. Found: C, 82.75; H, 9.29.

(*E*)-5-[2-(3,4-Dimethoxyphenyl)ethenyl]isoxazole (19) was prepared according to the general procedure from isoxazole **10** (0.219 g, 1.00 mmol), *n*-BuLi (0.45 mL, 2.24 M, 1.0 mmol), and 3,4-dimethoxybenzaldehyde (0.015 g, 0.090 mmol). Flash chromatography with CH_2Cl_2 afforded **19** (R_f 0.32) as a yellow solid. Recrystallization from ethyl acetate–hexane gave 0.185 g (80%) of **19** as white needles: mp 71–72 °C; IR (CCl_4) 2990 (w), 2940 (w), 2920 (w), 2820 (w), 1635 (m), 1575 (m), 1500 (m), 1455 (s), 1260 (vs), 1120 (s), 1010 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 1.7 Hz, 1 H), 7.28 (d, J = 16.4 Hz, 1 H), 7.06 (m, 2 H), 6.86 (d, J = 8.1 Hz, 1 H), 6.85 (d, J = 16.4 Hz, 1 H), 6.22 (d, J = 1.7 Hz, 1 H), 3.39 (s, 3 H), 3.90 (s, 3 H); mass spectrum, m/z (relative intensity) 231 (M^+, 100), 216 (7), 191 (6), 161 (6).

5-(Cyclohexylidenemethyl)isoxazole (20) was prepared according to the general procedure from isoxazole **10** (0.219 g, 1.00 mmol), *n*-BuLi (0.45 mL, 2.24 M, 1.0 mmol), and cyclohexanone (0.11 mL, 1.1 mmol) in 10 mL of THF. Flash chromatography with CH_2Cl_2 afforded 0.0978 g (60%) of **20** (R_f 0.52) as a yellow oil: IR (CCl_4) 2940 (vs), 2860 (vs), 1660 (vs), 1465 (vs), 1450 (vs), 1380 (s), 1345 (s), 1170 (s), 900 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (s, 1 H), 6.06 (s, 1 H), 6.01 (s, 1 H), 2.60 (m, 2 H), 2.27 (m, 2 H), 1.64 (m, 6 H); mass spectrum, m/z (relative intensity) 163 (M^+, 39), 96 (100), 81 (33).

General Procedure for the Wittig Olefinations with Triphenylphosphonium Bromide 12. The procedure is identical with that for the olefinations with phosphonate **10** (preceding section). After workup, TLC inspection of the reaction residue showed two overlapping spots, one corresponding to the *E* isomer, the other being the *Z* isomer. Column chromatography of the residue failed to completely separate the mixtures. GC analysis of the fractions obtained from chromatography enabled determination of the relative amount of each isomer present when correlated to TLC.

(*Z*)-5-(2-Phenylethenyl)isoxazole (15B) was prepared as a mixture with *E* isomer **15A** according to the general procedure from isoxazole **12** (0.426 g, 1.00 mmol), *n*-BuLi (0.47 mL, 2.14 M, 1.0 mmol), and benzaldehyde (0.11 mL, 1.0 mmol) in 10 mL of THF. Examination of the reaction mixture by GC indicated the *E*:*Z* isomer ratio to be 1.4:1.0. A pure sample of the *Z* isomer was isolated by flash chromatography with ethyl acetate–hexane (1:5): IR (CCl_4) 3140 (w), 3050 (s), 3020 (s), 1945 (m), 1875 (w), 1800 (m), 1780 (m), 1635 (vs), 1455 (vs), 1340 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (b s, 1 H), 7.37 (m, 5 H), 6.91 (d, J = 12.4 Hz, 1 H), 6.55 (d, J = 12.4 Hz, 1 H), 6.01 (b s, 1 H); mass spectrum, m/z (relative intensity) 171 (M^+, 62), 131 (100), 103 (54), 77 (32).

(*E,Z*)-5-(1,3-Pentadienyl)isoxazole (16B) was prepared as a mixture with the *E,E* isomer **16A** according to the general procedure from isoxazole **12** and crotonaldehyde. Examination of the reaction mixture by GC indicated the ratio of **16A**:**16B** was 2.2:1.0. A pure sample of **16B** could not be obtained.

(*E,Z*)-5-(3-Methyl-1,3-pentadienyl)isoxazole (17B) was prepared as a mixture with the *E,E* isomer **17A** according to the general procedure from isoxazole **12** and tiglaldehyde. Examination of the reaction mixture by GC indicated the ratio of **17A**:**17B** was 2.7:1.0. A pure sample of **17B** could not be obtained.

***CAUTION*! N-Alkylation of Isoxazoles May Result in Explosive Mixtures!** Previous studies by Woodward and Olofson[16] indicated that N-alkylation reactions of isoxazoles had the propensity to detonate when heated too quickly. While our experiments never produced explosions (even when the reactions were performed neat), it is necessary to mention that use of the stronger methylating reagent, "Magic Methyl" (methyl fluorosulfonate) produced a vigorous, exothermic reaction. The methylating agent must be added dropwise to avoid overheating the reaction mixture.

Preparation of 2,5-Dimethylisoxazolium Methyl Sulfate (24). 5-Methylisoxazole (**21**, 8.65 mL, 106 mmol) and freshly distilled dimethyl sulfate (10.00 mL, 106 mmol) were combined neat under N_2. The mixture was slowly heated to 60 °C. After 2 h at 60 °C, the reaction was heated to 80 °C for 5 h. The resultant liquid residue (22.17 g, 100%) did not require further purification and could be stored under N_2 at 0 °C for weeks without undergoing significant decomposition: IR (neat) 3110 (s), 3040 (s), 2940 (m), 1600 (s), 1540 (vs), 1460 (s), 1310 (b vs), 1040 (vs), 990 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.45 (d, J = 2.5 Hz, 1 H), 6.88 (d, J = 2.5 Hz, 1 H), 4.28 (s, 3 H), 3.40 (s, 3 H), 2.52 (s, 3 H). Due to the low volatility of the salt, mass spectral data could not be obtained.

Preparation of 2-Methyl-(*E*)-5-(2-phenylethenyl)isoxazolium Methyl Sulfate (27). (*E*)-5-(2-Phenylethenyl)isoxazole (**15A**) (0.171 g, 1.00 mmol) was dissolved in 1.0 mL of THF under N_2. Dimethyl sulfate (9.5 mL, 100 mmol) was added and the mixture was gradually heated to 60 °C and held at that temperature for 8 h. After cooling, the solvent was evaporated in vacuo and the resultant yellow semisolid (0.297 g, 100%) did not require further purification and could be stored under N_2 at 0 °C for weeks without undergoing significant decomposition: IR (CCl_4) 2940–2880 (b vs), 2840 (b vs), 1630 (w), 1575 (w), 1515 (w), 1460 (s), 1365 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.53 (b s, 1 H), 7.55 (m, 3 H), 7.29 (m, 4 H), 7.04 (d, J = 16.8 Hz, 1 H), 4.44 (b s, 3 H), 3.66 (s, 3 H). Due to the low volatility of the salt, mass spectral data could not be obtained.

Preparation of 5-[(Diethoxyphosphinyl)methyl]-2-methylisoxazolium Methyl Sulfate (29). Isoxazole **10** (1.25 g, 5.70 mmol) and dimethyl sulfate (0.54 mL, 5.7 mmol) were combined neat under N_2. The mixture was gradually heated to 60 °C and held at that temperature for 8 h. The resultant residue (1.97 g, 100%) did not require further purification and could be stored under N_2 at 0 °C for weeks without undergoing significant decomposition: IR (CCl_4) 2960 (s), 2910 (s), 2840 (s), 1740 (w), 1670 (w), 1460 (m), 1435 (m), 1395 (m), 1380 (m), 1230 (s), 1175 (s), 1090 (s), 1005 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.74 (d, J = 2.5 Hz, 1 H), 7.10 (d, J = 2.5 Hz, 1 H), 4.43 (b s, 3 H), 4.10 (dq, J = 7.0, 7.0 Hz, 4 H), 3.64 (d, J = 21.7 Hz, 2 H), 3.65 (b s, 3 H), 1.26 (t, J = 7.0 Hz, 6 H). Due to the low volatility of the salt, mass spectral data could not be obtained.

General Procedures for the Preparation of 2-(2-Ethoxy-2-oxoethyl)isoxazolium Trifluoromethyl Sulfates. Freshly distilled trifluoromethanesulfonic acid (1.0 equiv) was dissolved in nitromethane (0.3 mL/mmol) under N_2 at 0 °C. Ethyl diazoacetate (1.0 equiv) was slowly added dropwise to this solution. After addition was complete, the reaction mixture was allowed to stir for 1 h at 0 °C until N_2 evolution had ceased. In a separate flask, the isoxazole (1.0 equiv) was dissolved in nitromethane (0.2

mL/mmol), cooled to 0 °C, and then transferred by cannula into the cold triflate solution. The resultant solution was allowed to stir for 15 h while warming to 23 °C. Removal of the solvent in vacuo gave the crude isoxazolium salt which did not require further purification and could be stored under N_2 at 0 °C for weeks without undergoing significant decomposition. Due to the low volatility of the salts, mass spectral data could not be obtained.

2-(2-Ethoxy-2-oxoethyl)-5-methylisoxazolium trifluoromethyl sulfate (25) was prepared according to the general procedure from trifluoromethanesulfonic acid (0.16 mL, 1.8 mmol), ethyl diazoacetate (0.19 mL, 1.8 mmol), and 5-methylisoxazole (0.15 mL, 1.8 mmol) in 0.9 mL of nitromethane. Evaporation of the solvent in vacuo gave isoxazolium salt **25** (0.575 g, 100%) as a pale yellow oil: IR (CCl_4) 2970 (w), 1760 (b s), 1120 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.47 (b s, 1 H), 7.01 (b s, 1 H), 5.60 (s, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 2.72 (s, 3 H), 1.29 (t, J = 7.2 Hz, 3 H).

2-(2-Ethoxy-2-oxoethyl)-(*E*)-5-(2-phenylethenyl)isoxazolium trifluoromethyl sulfate (28) was prepared according to the general procedure from trifluoromethanesulfonic acid (0.16 mL, 1.8 mmol), ethyl diazoacetate (0.19 mL, 1.8 mmol), and isoxazole **15A** (0.308 g, 1.8 mmol) in 0.9 mL of nitromethane. Evaporation of the solvent in vacuo gave isoxazolium salt **28** (0.733 g, 100%) as a pale yellow oil: IR (CCl_4) 3150 (vs), 2950 (b vs), 1760 (vs), 1630 (s), 1460 (s), 1360 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.43 (d, J = 2.6 Hz, 1 H), 7.71 (d, J = 16.8 Hz, 1 H), 7.57 (m, 1 H), 7.39 (m, 4 H), 7.21 (d, J = 2.6 Hz, 1 H), 7.04 (d, J = 16.8 Hz, 1 H), 5.63 (s, 2 H), 4.28 (q, J = 7.1 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H).

5-[(Diethoxyphosphinyl)methyl]-2-(2-ethoxy-2-oxoethyl)isoxazolium trifluoromethyl sulfate (30) was prepared according to the general procedure from trifluoromethanesulfonic acid (0.16 mL, 1.8 mmol), ethyl diazoacetate (0.19 mL, 1.8 mmol), and isoxazole **10** (0.395 mL, 1.8 mmol) in 0.9 mL of nitromethane. Evaporation of the solvent in vacuo gave isoxazolium salt **30** (0.820 g, 100%) as a pale yellow oil: IR (CCl_4) 2960 (vs), 2920 (vs), 2860 (s), 1750 (vs), 1460 (s), 1375 (s), 1280 (s), 1130 (vs), 1010 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.59 (b s, 1 H), 7.17 (b s, 1 H), 5.62 (s, 2 H), 4.14 (m, 6 H), 3.67 (d, J = 21.3 Hz, 2 H), 1.30 (t, J = 7.0 Hz, 9 H).

2-(Carbethoxymethyl)-5-methylisoxazolium Tetrafluoroborate (26). Ethyl bromoacetate (1.67 g, 10.0 mmol) and 5-methylisoxazole (0.831 g, 10.0 mmol) were combined in the presence of silver tetrafluoroborate (2.14 g, 11.0 mmol) in a nitromethane solution and heated to 75 °C for 3 h. Filtration of silver bromide and evaporation of the solvent at reduced pressure gave 2.44 g (95%) of tetrafluoroborate salt **26** as a gum: IR (CH_2Cl_2) 3140 (m), 2900 (w), 1755 (vs), 1590 (m), 1520 (s) 1325 (m), 1140–980 (br, vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.22 (br, 1 H), 7.04 (br s, 1 H), 5.50 (s, 2 H), 4.27 (q, J = 7.0 Hz, 2 H), 2.70 (s, 3 H), 1.29 (t, J = 7.0 Hz, 3 H).

General Procedure for the Fragmentation of Isoxazolium Salts. The N-substituted isoxazolium salt (1.0 equiv) was stirred with CH_2Cl_2 (2 mL/mmol isoxazolium salt) and H_2O (1 mL/mmol isoxazolium salt) at 23 °C under N_2. Triethylamine (1.0 equiv) was added and the two-phase system was stirred vigorously for 5 h. The layers were separated (except for **34**, as noted) and the aqueous layer was extracted with CH_2Cl_2 (3 × $^1/_2$ aqueous volume). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. The resultant residue was chromatographed on silica gel with the solvent system indicated for each compound.

***N*-Methyl-3-oxobutanamide (34)** was prepared according to the general procedure from isoxzolium methyl sulfate **24** (0.523 g, 2.50 mmol), triethylamine (0.35 mL, 2.5 mmol), 5.0 mL of CH_2Cl_2, and 2.5 mL of H_2O. Due to the high solubility of the product in H_2O, the entire reaction mixture was evaporated in vacuo and the residue was chromatographed with CH_2Cl_2–MeOH (18:1) to yield 0.273 g (95%) of **34** (R_f 0.36) as a clear liquid: IR (CCl_4) 3380 (w), 2940 (w), 1710 (s), 1680 (vs), 1500 (m), 1410 (m), 1350 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (s, 2 H), 2.74 (d, J = 4.8 Hz, 3 H), 2.20 (s, 3 H); mass spectrum, m/z (relative intensity) 115 (M^+, 69), 73 (37), 58 (53), 43 (100).

(*E*)-*N*-Methyl-3-oxo-5-phenyl-4-pentenamide (35) was prepared according to the general procedure from isoxazolium salt **27** (0.743 g, 2.50 mmol), triethylamine (0.35 mL, 2.5 mmol), 5.0 mL of CH_2Cl_2, and 2.5 mL of H_2O. Flash chromatography with CH_2Cl_2–MeOH (20:1) afforded **35** (R_f 0.46) as a yellow solid. Recrystallization from MeOH gave 0.458 g (90%) of a yellow powder: mp 95–96 °C; IR (CCl_4) 3480 (w), 3350 (b w), 2930 (m), 2860 (m), 1675 (vs), 1645 (vs), 1600 (b vs), 1445 (m), 1405 (m), 1250 (s), 1095 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (m, 3 H), 7.37 (m, 3 H), 6.77 (d, J = 16.2 Hz, 1 H), 3.65 (s, 2 H), 2.84 (d, J = 4.7 Hz, 3 H); mass spectrum, m/z (relative intensity) 203 (M^+, 32), 173 (8), 145 (19), 131 (100), 103 (42), 77 (26).

Diethyl [4-(methylamino)-2,4-dioxobutyl]phosphonate (36) was prepared according to the general procedure from isoxazolium salt **29** (0.863 g, 2.50 mmol), triethylamine (0.35 mL, 2.5 mmol), 5.0 mL of CH_2Cl_2, and 2.5 mL of H_2O. Flash chromatography with CH_2Cl_2–MeOH (15:1) yielded 0.558 g (89%) of **36** (R_f 0.40) as a clear, viscous liquid: IR (CCl_4) 3460 (w), 3300 (m), 2970 (s), 1740 (m), 1715 (s), 1675 (vs), 1645 (s), 1640–1605 (b m), 1410 (m), 1385 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (b s, 1 H), 4.04 (dq, J = 7.1, 7.1 Hz, 4 H), 3.50 (s, 2 H), 3.19 (d, J = 22.5 Hz, 2 H), 2.71 (d, J = 4.8 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 6 H); mass spectrum, m/z (relative intensity) 251 (M^+, 83), 221 (34), 194 (79), 179 (80), 152 (67), 123 (100), 109 (66).

Preparation of (*E*)-1,1′-[2-(Methylamino)-4-(methylimino)-1-cyclobutene-1,3-diyl]bis[ethanone] (38). Isoxazolium methyl sulfate **24** (0.418 g, 2.00 mmol) was dissolved in 4 mL of *t*-BuOH under N_2. Triethylamine (0.28 mL, 2.0 mmol) was added and the mixture was stirred for 5 h. The solvent was evaporated in vacuo and the residue was chromatographed with CH_2Cl_2–MeOH (20:1) to give a dark yellow solid (R_f 0.41) which was recrystallized from ethyl acetate–hexane to yield 0.165 g (85%) of **38** as beige needles: mp 173–174 °C; IR (CCl_4) 1645 (vs), 1625 (vs), 1400 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.63 (s, 1 H), 3.39 (s, 3 H), 2.90 (d, J = 5.1 Hz, 3 H), 2.64 (s, 3 H), 2.29 (s, 3 H); mass spectrum, m/z (relative intensity) 194 (M^+, 34), 179 (100), 56 (26). Anal. Calcd for $C_{10}H_{14}O_2N_2$: C, 61.84; H, 7.27. Found: C, 61.61; H, 7.24.

General Procedure for Preparation of Cyclic Amidines. The N-substituted ethyl ester derivative of the amino acid (2.0 equiv) was dissolved in distilled *t*-BuOH under N_2. Highest yields were obtained when the reaction concentration was 0.030 M in isoxazolium salt. Therefore, 70% of the required amount of solvent was used to dissolve the amino acid derivative, and the remaining solvent was used to complete the transfer of the other reagents. Solid potassium *tert*-butoxide (*t*-BuOK, 3.0 equiv) was added to this solution. (When the hydrochloride salt of the amino acid was used, 4.0 equiv of *t*-BuOK were required). After 2 min, the isoxazolium salt (1.0 equiv) dissolved in *t*-BuOH was added and the reaction mixture was heated to 80 °C for 5 h. The reaction mixture was cooled to 23 °C and quenched by addition of H_2O ($^1/_2$ reaction volume). The resultant solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × $^1/_2$ reaction volume). The extracts were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. Chromatography of the residue in the solvent systems indicated gave the amidines. The amidines were usually visible on TLC as bright red spots after exposure to iodine vapors.

(*E*)-4-(1-Hydroxyethylidene)-1-methyl-5-(methylimino)-3-pyrrolidinone (50A) was prepared according to the general procedure from sarcosine ethyl ester hydrochloride (0.307 g, 2.00 mmol), *t*-BuOK (0.449 g, 4.00 mmol), and isoxazolium methyl sulfate **24** (0.209 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (19:1) afforded 0.101 g (60%) of **50** (R_f 0.38) as a pale red oil. This reaction product was a mixture of tautomers **50A** and **50B**. Recrystallization from cold MeOH gave clear plates (mp 165–166 °C) of tautomer **50A** (40% overall yield): IR (CCl_4) 2910 (w), 1755 (w), 1675 (m), 1610 (s), 1435 (w), 1410 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.89 (b s, 1 H), 3.74 (s, 2 H), 3.26 (s, 3 H), 3.20 (d, J = 5.6 Hz, 3 H), 2.41 (s, 3 H); mass spectrum, m/z (relative intensity) 168 (M^+, 100), 153 (88), 82 (66), 44 (48).

(*E*)-4-(1-Hydroxyethylidene)-2-isopropyl-5-(methylimino)-3-pyrrolidinone (51A) was prepared according to the general procedure from (*S*)-valine methyl ester hydrochloride (0.335 g, 2.00 mmol), *t*-BuOK (0.449 g, 4.00 mmol), and isoxazolium methyl sulfate **24** (0.209 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with ethyl acetate–hexane (3:2) afforded **51A** (R_f 0.30) as a white solid. Recrystallization from MeOH gave 0.135 g (64%) of white powder: mp 91–92 °C; IR (CCl_4) 3260 (w), 2950

(m), 1750 (vs), 1635 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.38 (b s, 1 H), 4.94 (s, 1 H), 3.95 (d, J = 4.0 Hz, 1 H), 3.01 (s, 3 H), 2.20 (m, 1 H), 2.11 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H); mass spectrum, m/z (relative intensity) 196 (M^+, 74), 181 (51), 153 (100), 82 (37).

(*E*)-4-(1-Hydroxyethylidene)-5-(methylimino)-1-(phenylmethyl)-3-pyrrolidinone (52A) was prepared according to the general procedure from *N*-benzylglycine ethyl ester (0.386 g, 2.00 mmol), *t*-BuOK (0.337 g, 3.00 mmol), and isoxazolium methyl sulfate **24** (0.209 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (15:1) afforded 0.146 g (60%) of **52B** (R_f 0.47) as a pale red oil: IR (CCl_4) 3050 (w), 2980 (m), 1755 (w), 1680 (s), 1620 (vs), 1420 (s), 1260 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.12 (b s, 1 H), 7.29 (m, 5 H), 4.79 (s, 2 H), 3.77 (s, 2 H), 3.10 (d, J = 5.6 Hz, 3 H), 2.45 (s, 3 H); mass spectrum, m/z (relative intensity) 244 (M^+, 81), 91 (100), 82 (40).

(*E*)-4-[Hydroxy[1(*E*)-2-phenylethenyl]methylene]-1-methyl-5-(methylimino)-3-pyrrolidinone (53) was prepared according to the general procedure from sarcosine ethyl ester hydrochloride (0.307 g, 2.00 mmol), *t*-BuOK (0.449 g, 4.00 mmol), and isoxazolium methyl sulfate **27** (0.297 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (18:1) gave amidine **53** (R_f 0.40) as a light red solid. Recrystallization from ethyl acetate–hexane gave 0.154 g (60%) of a pink powder: mp 82–83 °C; IR (CCl_4) 3020 (w), 2900 (m), 1750 (vs), 1650 (s), 1600 (b vs), 1485 (vs), 1390 (s), 1080 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (m, 3 H), 7.35 (m, 3 H), 6.82 (d, J = 15.9 Hz, 1 H), 4.96 (s, 1 H), 4.02 (s, 2 H), 3.30 (s, 3 H), 3.10 (s, 3 H); mass spectrum, m/z (relative intensity) 265 (M^+, 100), 239 (26), 165 (12), 153 (32), 82 (59).

Diethyl (*E*)-[2-hydroxy-2-[1-methyl-2-(methylimino)-4-oxo-3-pyrrolidinylidene]ethyl]phosphonate (54) was prepared according to the general procedure from sarcosine ethyl ester hydrochloride (0.307 g, 2.00 mmol), *t*-BuOK (0.449 g, 4.00 mmol), and isoxazolium methyl sulfate **29** (0.345 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (9:1) afforded 0.167 g (55%) of **54** (R_f 0.47) as a light yellow oil: IR (CCl_4) 2970 (m), 2910 (m), 1750 (s), 1645 (s), 1615 (s), 1495 (s), 1405 (s), 1225 (s), 1005 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.79 (s, 1 H), 3.96 (dq, J = 7.0, 7.0 Hz, 4 H), 3.84 (s, 2 H), 3.06 (b s, 3 H), 2.88 (s, 3 H), 2.83 (d, J = 22.0 Hz, 2 H), 1.15 (t, J = 7.0 Hz, 6 H); mass spectrum, m/z (relative intensity) 304 (M^+, 15), 290 (8), 153 (100), 126 (62), 82 (39).

Acknowledgment. We thank the National Institutes of Health (AI 20066 and 23688) and the Research Corporation for generous financial support. We also thank Dr. Robert Minard (MS), Greg Hancock (MS), Alan Freyer (NMR), and Dr. Varadaraj Elango (NMR) for help in obtaining spectral data, and Robert Waltermire, Dr. Grady Lamb, and Dr. V. Elango for helpful discussions.

A New Stereoselective Method of Synthesis of Pyrrolizidines and Indolizidines[1]

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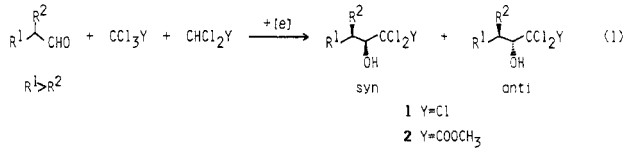
Received February 3, 1987

The addition of electrogenerated dichloro(methoxycarbonyl)methyl anions to some *N*-(methoxycarbonyl)-α-amino aldehydes prepared from α-amino acids was found to show about 100% diastereoselectivity. Some alkaloid-type compounds containing pyrrolizidine and indolizidine skeletons were synthesized from the adducts.

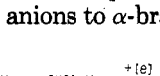
Recently we have found an anionic chain reaction induced by cathodic reduction.[2] In this reaction, electrogenerated trichloromethyl or dichloro(methoxycarbonyl)methyl (DMM) anion attacks an aldehyde to give 1,1,1-trichloro-2-alkanol **1** or methyl 2,2-dichloro-3-hydroxyalkanoate **2** in a high current efficiency and a good yield. We have also reported the diastereoselective addition of these anions to α-branching aldehydes (eq 1)[3] and



(1)

the application of the adducts to the stereoselective elongation of carbohydrates.[3,4] We report herein the stereoselective addition of the electrogenerated DMM anion to *N*-(carbomethoxy)-α-amino aldehydes **4** and the application of this reaction to the stereoselective synthesis of some optically active compounds containing a pyrrolizidine or indolizidine skeleton. Although a number of methods for the synthesis of racemic pyrrolizidine and indolizidine derivatives have already been reported, only a few methods have been known for the practical synthesis of optically active ones.[5]

Table I. Yields of 5 and 6 and Isomeric Ratios of 6

3			5	6	
R_1		R_2	yield (%)[a]	yield (%)[b]	trans/cis[c]
a	$-(CH_2)_3-$		66	68	>99/1
b			39	74	>99/1
c	$-(CH_2)_4-$		50	54	>99/1
d	$(CH_3)_2CH$	H	46	65	>99/1
e	$(CH_3)_2CHCH_2$	H	40	66	87/13
f	$C_6H_5CH_2$	H	40	68	60/40
g	p-$CH_3OC_6H_4CH_2$	H	44	65	57/43

[a] Isolated yield from **3**. [b] Isolated yield from **5**. [c] See ref 6.

(1) Electroorganic Chemistry. 100.
(2) Shono, T.; Kise, N.; Masuda, M.; Suzumoto, T. *J. Org. Chem.* **1985**, *50*, 2527.
(3) Shono, T.; Kise, N.; Suzumoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 259.
(4) Shono, T.; Ohmizu, H.; Kise, N. *Tetrahedron Lett.* **1982**, *23*, 4801.
(5) Some recent reports synthesizing optically active pyrrolizidine and indolizidine alkaloids are as follows. (a) Hart, D. J.; Yang, T. *J. Org. Chem.* **1985**, *50*, 235. (b) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *Ibid.* **1985**, *50*, 420. (c) Chamberlin, A. R.; Chung, J. Y. L. *Ibid.* **1985**, *50*, 4425. (d) Nishiyama, Y.; Kondo, S.; Umezawa, H. *Ibid.* **1985**, *50*, 5210.

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