10 mL of ether were added, the layers were separated, and the aqueous layer was extracted twice with ether. The combined extracts were dried over magnesium sulfate, the solvent was evaporated, and the residue was subjected to column chromatography on silica with chloroform/methanol (99:1) to afford **30** as a yellow foam. Recrystallization from cyclohexane yielded 234 mg (0.74 mmol, 42%) of light yellow microcrystals, mp 118–119 °C. The product is an equimolar mixture of syn and anti isomers: ^{1}H NMR ($CDCl_3$) δ 1.47 and 1.60 (2 d, both J = 6.6 Hz, 3 H, $CHOHCH_3$), 4.43 and 4.54 (2 d, J = 4.0 and 3.0 Hz, 1 H, O*H*), 4.95–5.05 (m, 1 H, $CHOHCH_3$, become two quartets with J = 6.6 Hz upon D_2O exchange), 7.06 (d, J = 7.7 Hz, 2 H, phenyl ortho H), 7.20 (t, J = 7.3 Hz, 1 H, phenyl para H), 7.42 (m, centered, 2 H, phenyl meta H), 8.55–8.75 (m, 3 H, pyrazinyl-H); FTIR (KBr) 3204, 3065, 2974, 2923, 1578, 1559, 1539, 1516, 1402, 1145, 1101, 1066, 1011, 853, 762, 693 cm^{-1}; LRMS 315 (M^+, calcd for $C_{15}H_{13}N_3OS_2$), 314 (- H), 270 (- $CHOHCH_3$), 211 (- PhNCH$^+$), 180 (- PhNCS); HRMS calcd 315.0500, found 315.0484. Anal. Calcd for $C_{15}H_{13}N_3OS_2$: C, 57.12; H, 4.15; N, 13.32; S, 20.33. Found: C, 57.15; H, 3.99; N, 13.21; S, 20.46.

2-(Phenylimino)-4-(1-hydroxyethyl)-5-(2-pivaloylpterin-6-yl)-1,3-dithiole (31). Reduction of the ketone **29** (160 mg, 0.33 mmol) was carried out with 4 mg (0.10 mmol) of sodium borohydride, as described above for the preparation of **30**. Column chromatography on silica gel with chloroform/methanol (98:2) afforded the alcohol **31** as a yellow oil. Upon addition of hexane, the compound crystallized to yield 107 mg (0.22 mmol, 67%) of a yellow crystalline powder, mp 230–235 °C dec. The product is an equimolar mixture of syn and anti isomers: ^{1}H NMR δ 1.37 and 1.39 (2 s, 9 H, both $(CH_3)_3C$), 1.50 and 1.64 (2 d, both J = 6.6 Hz, $CHOHCH_3$), 4.85–4.92 (br d, 1 H, O*H*), 5.04 and 5.13 (2 m centered, 1 H, $CHOHCH_3$, become doublets with J = 6.6 Hz upon D_2O exchange), 7.05–7.08 (m, 2 H, phenyl ortho H), 7.20 (t, J = 7.6 Hz, 1 H, phenyl para H), 7.43 (m centered, 2 H, phenyl meta H), 8.48 and 8.59 (2 br s, 1 H, tBuCON*H*), 8.78 and 8.91 (2 s, 1 H, ring C*H*), 12.46 (br s, 1 H, ring N*H*); FTIR (KBr): 3220, 2970, 2922, 1686, 1620, 1578, 1560, 1448, 1356, 1262, 1143, 961, 764, 698 cm^{-1}; LRMS 482 (M^+, calcd for $C_{22}H_{22}N_6O_3S_2$), 481 (- H), 464 (- water), 438 (- isobutene), 361, 331, 304, 135 (PhNCS); HMRS 482.1194, found 482.1167. Anal. Calcd for $C_{22}H_{22}N_6O_3S_2$: C, 54.76; H, 4.61; N, 17.42; S, 13.29. Found: C, 54.54; H, 4.61; N, 17.25; S, 13.64.

2-[Bis(methoxycarbonyl)methenyl]-4-(1-hydroxyethyl)-5-(2-pivaloylpterin-6-yl)-1,3-dithiole (35). The ketone **34** (274 mg (0.50 mmol) was reduced with 6 mg (0.15 mmol) of sodium borohydride, as described above for the preparation of **30**. Part of the product **35** precipitated directly from the reaction mixture and was collected by filtration and washed with pentane. An additional amount of product was obtained by triturating the filtrate with pentane; combined yield 246 mg (0.45 mmol, 89%) of a yellow crystalline powder: mp >260 °C; ^{1}H NMR δ 1.24 (s, 9 H, $(CH_3)_3C$, overlapping 2 t, 6 H, OCH_2CH_3), 1450 (d, J = 6.5 Hz, 3 H, $CHOHCH_3$), 4.15–4.23 (m, 4 H, OCH_2CH_3), 5.15–5.25 (m, 1 H, $CHOHCH_3$), 5.82 (br s, 1 H, O*H*), 8.90 (br s, 1 H, tBuCON*H*), 8.93 (s, 1 H, ring C*H*), 12.45 (br, 1 H, ring N*H*); IR 3420, 2980, 2930, 1710, 1630, 1540, 1495, 1445, 1410, 1290, 1160, 1035, 945, 795, 760 cm^{-1}; LRMS 549 (M^+, calcd for $C_{23}H_{27}N_5O_7S_2$), 548 (- H), 531 (- water), 502 (- EtOH), 346 (- $(EtOOC)_2C{=}C{=}S$), 304, 246 (2-pivaloylpterin-6-yl$^+$), 202, 85 (tBuCO$^+$).

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Organometallic Reactions of ω-Heterosubstituted *N*-Acyl Lactams. A New Route to γ-Keto Aldehydes from 5-Ethoxy-2-pyrrolidinone

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A new route to γ-keto aldehydes has been developed in which 5-ethoxy-2-pyrrolidinone is the key intermediate, easily available from 2-pyrrolidinone or succinimide. The lactam undergoes the selective ring opening, previous "in situ" N-acylation reaction with pivaloyl chloride or di-*tert*-butyl dicarbonate and attack of Grignard reagents or pyridyllithium compounds, whereupon the γ-keto aldehydes are produced by acidic hydrolysis. By this way the γ-keto aldehydes, which are precursors of natural compounds, such as dihydrojasmone and methyl dihydrojasmonate, a feromone component of the peach fruit moth *Carposina niponensis*, and nicotine derivatives have been prepared. A practical synthesis of pyridyl-substituted pyrroles (α- and β-nicotyrine and the nor derivatives) can be achieved without purification of the intermediates. N-Acylated 6-ethoxy-2-piperidinone is less reactive toward the organometallic attack, affording in low yields 5-phenyl-5-oxopentanal using phenylmagnesium chloride, and 2-pentylcyclohex-2-en-1-one using *n*-hexylmagnesium bromide.

It has been recently reported by one of us[1] that five- to eight-membered lactams **1** (X = H), through their *N*-pivaloyl and *N*-Boc derivatives **2**, undergo regioselective ring-opening reaction with organometallic reagents, affording in good yields the N-substituted ω-amino ketones **3** (Scheme I). In the case of *N*-Boc derivatives, the cyclic imines **4** can be obtained by treatment with trifluoroacetic acid. Aiming to develop a new route to synthetically useful ω-keto aldehydes **5**, we have examined the possibility to perform the same synthetic sequence starting from ω-heterosubstituted lactams **1** (X = hetero group).

Preparation of ω-Heterosubstituted Lactams. The ethoxy lactams **8a,b** are easily prepared by the anodic oxidation of *N*-hydro lactams **6a,b** in ethanol[2] or by the reduction of cyclic imides **7a,b** with sodium borohydride in ethanol at controlled pH, followed by treatment with ethanolic solution of hydrochloric acid[3] (Scheme II). The benzyloxy and ethylthio lactams **9b** and **10b** were obtained by the reaction of the ethoxy lactam **8b** with benzyl alcohol

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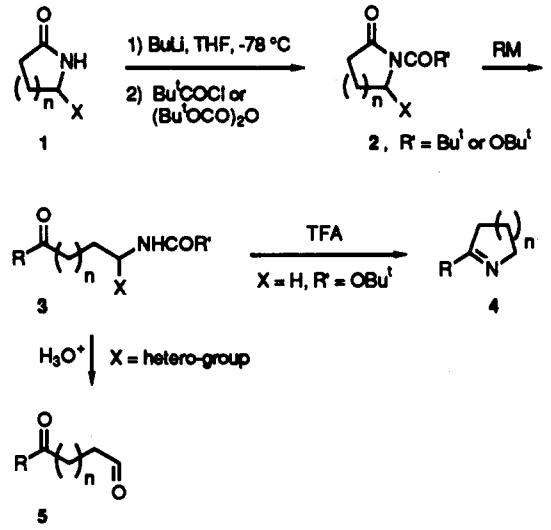
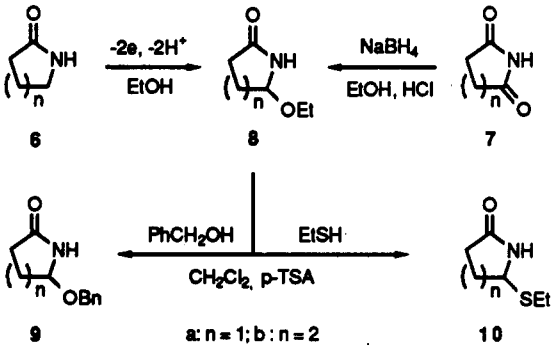
0022-3263/91/1956-1822$02.50/0

Scheme I



Scheme II

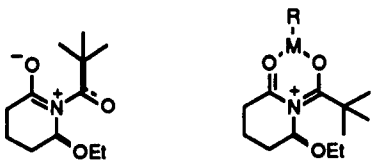


or ethyl mercaptan in methylene chloride in the presence of catalytic amount of *p*-toluenesulfonic acid (Scheme II).

Preparation and Organometallic Reactions of *N*-Pivaloyl and *N*-Boc ω-Heterosubstituted Lactams. Synthesis of γ-Keto Aldehydes. As was described for the unsubstituted lactams,[1] the γ-ethoxy lactam **8a** was easily and quantitatively acylated by treatment with an equivalent amount of *n*-butyllithium in dry tetrahydrofuran at −78 °C and successive addition of pivaloyl chloride or di-*tert*-butyl dicarbonate (Scheme III). The *N*-pivaloyl- or *N*-Boc-ω-ethoxy lactams **11a** and **12a** were isolated in quantitative yield by quenching the reaction mixtures with saturated aqueous ammonium chloride and usual workup, so we considered it more convenient to perform the organometallic reactions on **11a,b** formed "in situ". In fact, following this procedure from the γ-lactam **8a**, upon addition of Grignard reagents the γ-keto aldehydes **14a**, **15a**, and **16a** were obtained in more than 60% yields after quenching with hydrochloric acid and stirring the reaction mixtures at reflux for 30 min.[4] When the corresponding reaction sequence was performed starting from the δ-lactam **8b** the results were less satisfactory: by using phenylmagnesium chloride, **16b** was isolated in only 22% yield; furthermore, by using *n*-hexylmagnesium bromide, **14b** could not be isolated, since it cyclized in the acidic medium to 2-pentylcyclohex-2-en-1-one (**17**, 33% yield).

The synthetic sequence involving the *N*-Boc lactams **12a,b** is even more efficient, as ascertained by comparing the yields of **15**[5] and **16b** by the two alternative methods

Chart I



I II

(Scheme III). Pyridyl-substituted γ-keto aldehydes **18** and **19** could be prepared by a slightly modified procedure, owing to the necessity of preparing 2- and 3-pyridyllithium reagents at low temperature from 2- and 3-bromopyridine (butyllithium, tetrahydrofuran, −78 °C).[1] The *N*-Boc γ-lactam **12a** (crude isolated compound) was added to the organolithium reagents, quenching with 6 N hydrochloric acid and vigorous stirring at room temperature, and then basic treatment and extraction afforded **18** and **19** in 64 and 58% yield, respectively (based on **8a**), after flash chromatography (Scheme III).

We performed the above described sequence of reactions on the benzyloxy and ethylthio lactams **9b** and **10b**, since the ring-opened products, obtained by avoiding the acidic quenching, should be converted to the desired δ-keto aldehydes by hydrogenolysis or mercuric chloride mediated hydrolysis, respectively. The *N*-pivaloyl derivatives of δ-lactams **9b** and **10b**, prepared "in situ", were treated with 1 equiv of *n*-propylmagnesium bromide at −78 °C, but no reaction was observed, even after allowing the temperature to rise overnight to 0 °C. The reaction with the more reactive allylmagnesium chloride (1 equiv) gave only a partial conversion of the intermediate *N*-pivaloyl lactam (about 40%, by GC–MS) after prolonged reaction duration. After addition of another equivalent of allylmagnesium chloride, two products were isolated and identified by spectroscopic means (GC–MS, IR, and NMR) as the tertiary alcohols (**20** and **21** from **9b**, and **22** and **21** from **10b**), deriving from the double organometallic addition on both the exocyclic and endocyclic carbonyl groups of the *N*-pivaloyl lactams (Scheme IV). For sake of comparison, we performed the same reaction sequence starting from the γ-lactam **8a**, and unexpectedly we observed by GC–MS analysis that only **21** was produced, accompanied by unreacted *N*-pivaloyl lactam (**11a**).

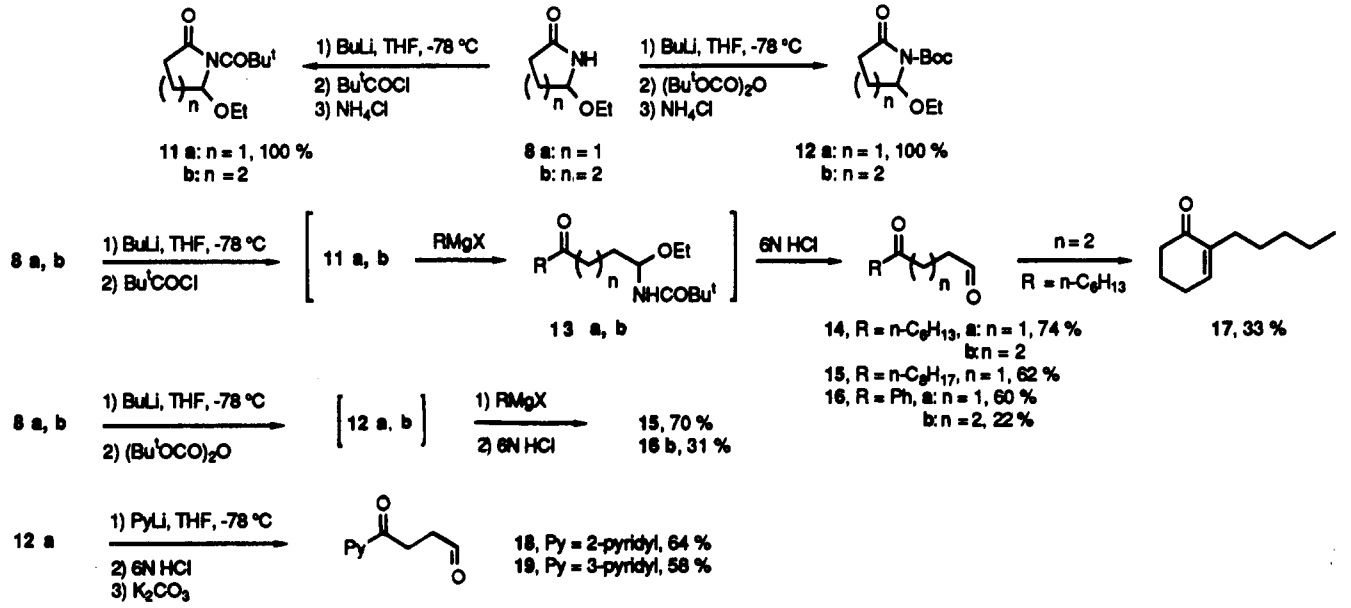
The quite lower reactivity of the N-acylated δ-heterosubstituted δ-lactams can be plausibly explained as follows. The most stable conformation for N-acylated ω-substituted lactams should have a transoid orientation of the carbonyl groups, as depicted in Chart I by structure I (relative to compound **11b**) to minimize the repulsion of carbonyl dipoles and the steric interaction between the ring and the nitrogen substituents. Furthermore, the exocyclic carbonyl group should not be coplanar with the lactam N–CO moiety.[6] In this transoid conformation neither the endocyclic carbonyl (for resonance stabilization) nor the exocyclic carbonyl (for steric reasons) are reactive toward the nucleophilic attack. We believe that the organometallic reaction can take place only if a cisoid chelated conformation II (Chart I) is attained by the interaction with the organometallic reagent, probably facilitating the resonance

(4) When the reaction mixtures were quenched with saturated aqueous ammonium chloride, after usual workup and column chromatography the γ-keto *N*-acylamino acetals **13a** were isolated and fully identified by spectroscopic means and elemental analyses.

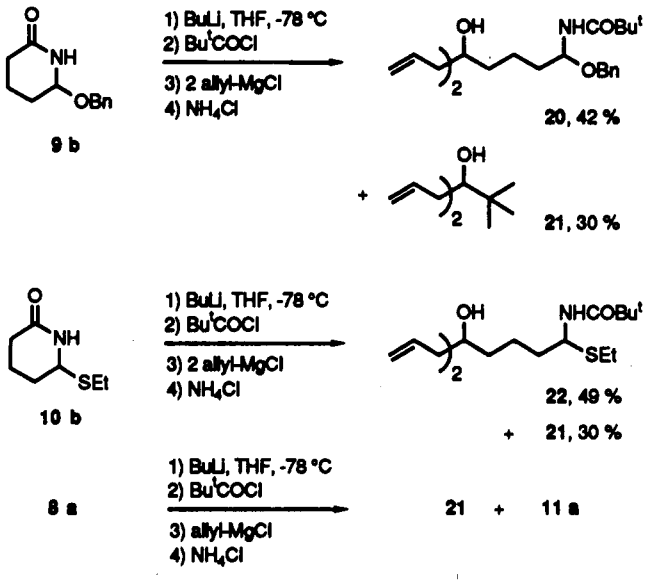
(5) After the acidic hydrolysis of the reaction mixture coming from **12a**, the crude compound **15** was accompanied by a discrete amount (8–10%) of 1-ethoxydodec-2-en-4-one, identified by the GC–MS analysis (M^+ = 226), but not isolated by flash chromatography.

(6) It has been shown by UV studies that in 1-phenyl-2-piperidinone the phenyl group is substantially deflected out of the plane of the NCO group, whereas coplanarity of 1-phenyl-2-pyrrolidinone appears feasible: Manhas, M. S.; Jeng, S.; Bose, A. K. *Tetrahedron* **1968**, *24*, 1237.

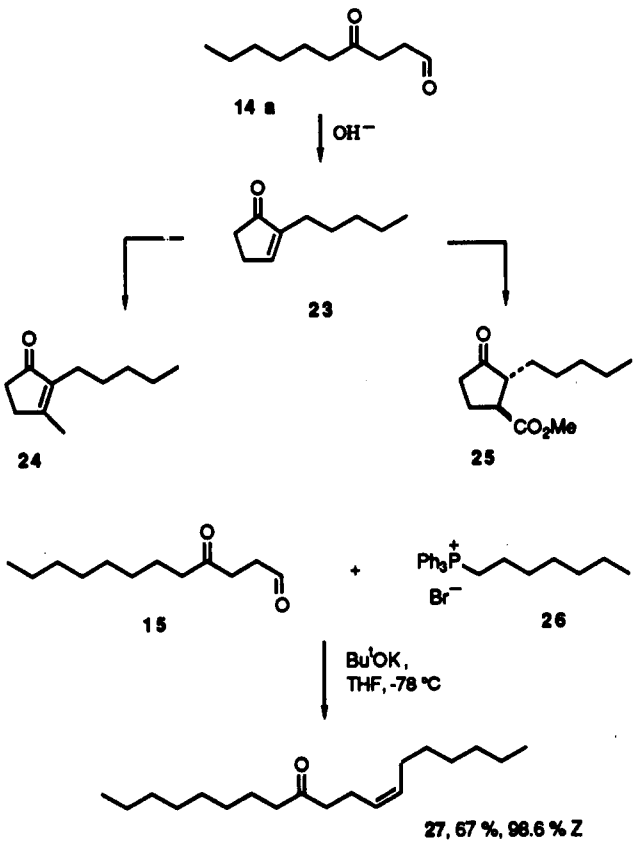
Scheme III



Scheme IV



Scheme V



delocalization of the nitrogen electron pair on the exocyclic carbonyl, and directing the organometallic addition toward the less sterically hindered endocyclic carbonyl.

An examination of stereochemical models shows that such cisoid conformation can be easily attained by the five-membered ring, whereas for the six-membered ring considerable steric interaction of the ethoxy substituent and the pivaloyl group impedes rotation around the exo N–CO bond. Such steric interaction should be even more important with ω-benzyloxy and ω-ethylthio substituents and for seven- and eight-membered lactams. The observation that the corresponding *N*-Boc lactams are slightly more reactive than the *N*-pivaloyl lactams is also consistent with this view.

Applications of γ-Keto Aldehydes to the Synthesis of Natural Compounds. The γ-keto aldehydes prepared from γ-ethoxy lactams were selected as they are known precursors of natural compounds. 4-Oxodecanal (**14a**) has been converted by basic treatment to 2-pentylcyclopent-2-en-1-one (**23**), from which dihydrojasmone (**24**)[7] and methyl dihydrojasmonate (**25**),[8] important materials for perfume industry, have been in turn prepared (Scheme V). On the other hand Wittig olefination of 4-oxododecanal (**15**) with the ylide prepared from triphenylheptylphosphonium bromide (**26**) yields (*Z*)-7-nonadecen-11-one (**27**),[9] which is a component of the pheromone of the peach

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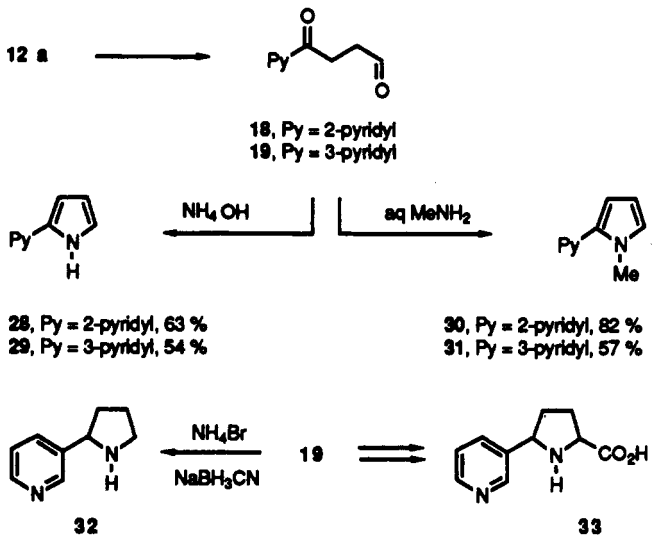
Scheme VI



fruit moth *Carposina niponensis* (Scheme V). Two different procedures have been described for this transformation. In one case an excess of the ylide was prepared from the phosphonium salt **26** and butyllithium, and the olefination on the aldehyde was performed in benzene at 5 °C, affording **27** in 40% yield (*Z*/*E* 9:1).[9a] Alternatively, sodium amide in benzene was used to obtained the "salt-free" ylide, which afforded almost pure *Z*-**27** (the yield was not given, but the olefination of the homologue 4-oxotridecanal was accomplished with 54% yield).[9b] By repeating the olefination of **15** in the reported conditions[9a] (BuLi, 5 °C), we could isolate by column chromatography of the reaction mixture a discrete amount of 8-octyl-7,11-octadecadiene (13% yield based on **15**), which comes from the olefination of both the carbonyl groups, followed by the desired product **27** (42% yield, 85% *Z*). To get an improved chemoselectivity, we treated **26** with butyllithium in tetrahydrofuran and then added **15** to the ylide (1.1 equiv) at −78 °C, so obtaining **27** in 55% yield (*Z*/*E* 85:15). Good yield (67%) and excellent stereoselectivity (98.6% *Z*) were finally achieved by using potassium *tert*-butoxide as the base and carrying out the olefination with the stoicheiometric ratio of the reagents in tetrahydrofuran at −78 °C (Scheme V).

The γ-keto aldehyde **19**,[10,11] containing the 3-pyridyl substituent, is also a precursor of natural compounds. For example, it affords nornicotine (**32**) by the reaction with ammonium bromide and sodium cyanoborohydride in methanol,[11] and 5'-carboxynornicotine (**33**) by a sequence of reactions[10] (Scheme VI).

Furthermore, we devised a new preparation of α- and β-nicotyrine (**30** and **31**, respectively),[12] alkaloids having insecticidal properties, and their nor derivatives **28** and **29**[13,14] (Scheme VI). Aiming to prepare **28**/**29**, the γ-keto aldehydes **18**/**19** were isolated, although not purified, before the reaction with aqueous ammonia. On the other hand, the 1-methylpyrroles **30**/**31** were conveniently prepared by a one-flask procedure, quenching the organometallic reaction with hydrochloric acid and then adding excess aqueous methylamine.

Experimental Section

General Information. Spectral data were recorded on the following instruments: ^{1}H NMR, Varian EM390 (90 MHz, $CDCl_3$, TMS); ^{13}C NMR, Varian FT 80A ($CDCl_3$, TMS); IR, Perkin-Elmer PE682; GC–MS, Hewlett-Packard HP 5890-5970B (70 eV). Melting points were determined on a Büchi 510 apparatus and are not corrected. Chromatographic separations were performed by using 70–230-mesh silica gel (flash chromatography) or 230–400-mesh silica gel (Merck). Capillary gas chromatography was performed on a Carlo Erba HRGC 5300 Mega Series apparatus using an OV1 column (15 m, 0.1-μm film thickness) or a Supelcowax column (30 m, 0.25-μm film thickness). TLC analyses were carried out by using Merck plastic sheets coated with silica gel 60 F_{254} (layer thickness: 0.2 mm). Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under an argon atmosphere before use. 2-Pyrrolidinone (**6a**), 2-piperidinone (**6b**), succinimide (**7a**), glutarimide (**7b**), pivaloyl chloride, di-*tert*-butyl dicarbonate, 2-bromopyridine, 3-bromopyridine, phenylmagnesium chloride (2.0 M in THF), allylmagnesium chloride (2.0 M in THF), and *n*-butyllithium (2.5 M in hexane) were purchased from Aldrich or Fluka.

Preparation of ω-Ethoxy Lactams 8a,b. 5-Ethoxy-1-azacyclopentan-2-one (**8a**) and 6-ethoxy-1-azacyclohexan-2-one (**8b**) have been prepared with minor modifications following the procedures reported in the literature, i.e. by the anodic oxidation of 2-pyrrolidinone and 2-piperidinone (**6a**,**b**)[2] and by reduction of succinimide and glutarimide (**7a**,**b**).[3] Constant current (0.25 A) electrolysis were carried out in 50–75-mmol scale in ethanol solution (75 mL), containing tetraethylammonium tetrafluoroborate as supporting electrolyte in a thermostated undivided cell (100 mL) equipped with platinum electrodes (surface area: about 3 cm^2) and conventional instrumentation: an Amel (Milan) Model 552 potentiostat, AMEL Model 568 programmable function generator, and AMEL Model 731 integrator. The reduction of the imides was performed by a procedure simplified on respect to the one reported, i.e. by using about half the amount of ethanol (solvent) and especially avoiding the periodic addition of hydrochloric acid to control the pH. By these procedures the yields of ethoxy lactams **8a**,**b** from **6a**,**b** and **7a** are generally 60–70%. The ethoxy lactams were purified by flash chromatography on silica gel, eluting with ethyl acetate.

Preparation of 6-(Benzyloxy)-1-azacyclohexan-2-one (9b). A solution of 6-ethoxy-1-azacyclohexan-2-one (**8b**) (2.1 g, 15 mmol) in methylene chloride (15 mL) is added dropwise to a mixture of benzylic alcohol (3.1 mL, 30 mmol) and *p*-toluenesulfonic acid (30 mg) with magnetic stirring. After 24 h the solvent is removed by evaporation, and the residue is flash chromatographed on silica gel, eluting with ethyl acetate, to give pure **9b** (1.85 g, 60%) as a white solid: mp 89–90 °C (ether–ethyl acetate); IR 3200, 3020, 1660 cm^{-1}; ^{1}H NMR δ 8.50 (s, 1 H, NH), 7.32 (m, 5 H, Ph), 4.68 (m, 1 H, NCHO), 4.70 and 4.47 (AB, J = 12 Hz, OCH_2), 1.5–2.5 ppm (m, 6 H); MS *m*/*e* (relative intensity) 97 (M^+ − BnOH, 100), 43 (68), 68 (50), 54 (45), 79 (13), 108 (9), 91 (3). Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.49; H, 7.38; N, 6.84.

Preparation of 6-(Ethylthio)-1-azacyclohexan-2-one (10b). Ethyl mercaptan (0.74 mL, 10 mmol) and *p*-toluenesulfonic acid (30 mg) are added to a solution of 6-ethoxy-1-azacyclohexan-2-one (**8b**, 1.43 g, 10 mmol) in methylene chloride (10 mL) with magnetic stirring. After 3 h the solvent is evaporated to give an oily residue (1.54 g). Simple filtration through a small plug of silica gel affords **10b** (1.45 g, 91%): mp 79–81 °C (ether); IR 3180, 1650 cm^{-1}; ^{1}H NMR δ 7.50 (s, 1 H, NH), 4.53 (m, 1 H, CHN), 2.69 (q, 2 H, SCH_2), 2.40 (m, 2 H, $CH_2C{=}O$), 1.6–2.3 (m, 4 H), 1.30 ppm (t, 3 H, Me); MS *m*/*e* (relative intensity) 159 (M^+, 3), 98 (100), 55 (74), 70 (13), 100 (3). Anal. Calcd for $C_7H_{13}NOS$: C, 52.80; H, 8.23; N, 8.80; S, 20.13. Found: C, 52.74; H, 8.22; N, 8.80; S, 20.16.

General Procedure for the Preparation of *N*-Pivaloyl and *N*-Boc ω-Ethoxy Lactams. In a three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet is dissolved the lactam (30 mmol) in anhydrous THF (100 mL). The solution is cooled to −78 °C, and then *n*-butyllithium (2.5 M, 30

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(11) (a) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 399. (b) Leete, E.; Isaacson, H. V.; Durst, H. D. *J. Labelled Compd.* **1971**, *7*, 313.
(12) Mullen, G. B.; Georgiev, V. St. *J. Org. Chem.* **1989**, *54*, 2476.
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(14) Firl, J. *Chem. Ber.* **1968**, *101*, 218.

mmol) is added dropwise with stirring. After 15 min a solution of pivaloyl chloride or di-*tert*-butyl dicarbonate (30 mmol) in THF (30 mL) is added dropwise, and the reaction mixture is stirred at −78 °C for 3 h and then quenched with saturated aqueous ammonium chloride (40 mL). The organic phase is extracted with diethyl ether (3 × 50 mL), dried over sodium sulfate and concentrated to leave the crude product in quantitative yield, almost pure by TLC and GC analyses.

1-(2,2-Dimethylpropanoyl)-5-ethoxy-1-azacyclopentanone (11a): IR 3260, 1740, 1690 cm^{-1}; ^{1}H NMR δ 5.76 (m, 1 H, NCHO), 3.60 (m, 2 H, CH_2O), 1.8–3.1 (m, 4 H, CH_2C=O), 1.37 (s, 9 H, *t*-Bu), 1.18 ppm (t, 3 H, Me); MS *m/e* (relative intensity) 168 (M^+ − OEt, 10), 84 (100), 57 (80), 158 (38), 113 (35), 128 (21), 198 (3). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.01; H, 9.0; N, 6.58.

1-(*tert*-Butoxycarbonyl)-5-ethoxy-1-azacyclopentan-2-one (12a): IR 1785, 1755, 1715 cm^{-1}; ^{1}H NMR δ 5.45 (m, 1 H, NCHO), 4.67 (m, 2 H, OCH_2), 1.88–3.0 (m, 4 H), 1.52 (s, 9 H, *t*-Bu), 1.15 ppm (t, 3 H, Me); MS *m/e* (relative intensity) 156 (M^+ − *t*-BuO, 8), 84 (100), 57 (92), 129 (40), 173 (8), 110 (7). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.42; H, 8.36; N, 6.10.

Organometallic Ring-Opening Reaction of ω-Heterosubstituted Lactams. General Procedure. The heterosubstituted lactam (8–10, 30 mmol) is converted to the *N*-pivaloyl or *N*-Boc derivative as described above. To that solution in THF at −78 °C is added the Grignard reagent in THF solution dropwise, and the reaction mixture is stirred for 3 h and then quenched with 6 N hydrochloric acid (40 mL). The heterogeneous mixture is allowed to reach room temperature, heated for 30 min at reflux with vigorous stirring, cooled to room temperature and neutralized with sodium hydrogen carbonate. Most of the THF is evaporated, and the organic phase is extracted with ether (3 × 60 mL) or with cyclohexane (the use of hydrocarbon solvents is necessary to separate the aldehyde from pivalamide, when the *N*-pivaloyl lactam is the intermediate) and dried over sodium sulfate. The solvent is distilled at reduced pressure, and the crude product is purified by flash chromatography on silica gel, eluting with cyclohexane–ether.

4-Oxodecanal (14a):[7,8] IR 2720, 1720 cm^{-1}; ^{1}H NMR δ 9.78 (s, 1 H, CHO), 2.76 (s, 4 H, CH_2CH_2C=O), 2.48 (t, 2 H, CH_2C=O), 1.1–2.0 (m, 8 H), 0.88 ppm (t, 3 H, Me); MS *m/e* 170 (M^+).

4-Oxododecanal (15a):[9] IR 2720, 1720 cm^{-1}; ^{1}H NMR δ 9.78 (s, 1 H, CHO), 2.76 (s, 4 H, CH_2CH_2C=O), 2.48 (t, 2 H, CH_2C=O), 1.1–1.9 (m, 12 H), 0.88 ppm (t, 3 H, Me); MS *m/e* (relative intensity) 198 (M^+, 4%), 79 (100), 141 (96), 100 (94), 41 (70), 79 (73), 57 (45).

4-Phenyl-4-oxobutanal (16a):[12,15] IR 2820, 2720, 1715, and 1680 cm^{-1}; ^{1}H NMR δ 9.82 (s, 1 H, CHO), 7.89 (m, 2 H, Ph), 7.38 (m, 3 H, Ph), 3.20 (m, 2 H, CH_2C=O), 2.75 ppm (m, 2 H, CH_2C=O); MS *m/e* (relative intensity) 162 (M^+, 3), 105 (100), 77 (82), 134 (37), 51 (32), 120 (17), 74 (5).

5-Phenyl-5-oxopentanal (16b):[16] IR 2720, 1730, 1690 cm^{-1}; ^{1}H NMR δ 9.72 (s, 1 H, CHO), 7.90 (m, 2 H, Ph), 7.45 (m, 3 H, Ph), 3.01 (t, 2 H, CH_2C=O), 2.54 (t, 2 H, CH_2C=O), 2.06 ppm (m, 2 H); MS *m/e* (relative intensity 176 (M^+, 3), 105 (100), 77 (55), 51 (18), 120 (18), 148 (13), 158 (5).

2-Pentylcyclohex-2-en-1-one (17):[17] IR 1675 cm^{-1}; ^{1}H NMR δ 6.68 (t, 1 H, C=CH), 1.75–2.60 (m, 8 H), 1.30 (m, 6 H), 0.85 ppm (t, 3 H, Me); MS *m/e* (relative intensity) 166 (M^+, 32), 41 (100), 57 (92), 137 (46), 81 (56), 95 (47).

***N*-(1-(Benzyloxy)-5-hydroxy-5-(2-propenyl)-7-octenyl)-2,2-dimethylpropanamide (20)**: IR 3450, 3350, 3065, 3025, 1650 cm^{-1}; ^{1}H NMR δ 7.28 (m, 5 H, Ph), 6.16 (d, 1 H, NH), 4.90–6.10 (m, 6 H, C=CH), 5.35 (m, 1 H, NCHO), 4.53 (s, 2 H, PhCH_2), 2.20 (d, 4 H, allylic), 1.30–1.80 (m, 6 H), 1.20 ppm (s, 9 H, t-Bu); MS *m/e* (relative intensity) 57 (100), 122 (42), 224 (18), 85 (13), 102 (12), 140 (8). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.85; H, 9.46; N, 3.76.

***N*-(1-(Ethylthio)-5-hydroxy-5-(2-propenyl)-7-octenyl)-2,2-dimethylpropanamide (22)**: IR 3440, 3340, 3070, 1640 cm^{-1}; ^{1}H NMR δ 4.90–6.20 (m, 6 H, C=CH), 5.95 (d, 1 H, NH), 5.28 (m, 1 H, NCHS), 2.58 (m, 2 H, CH_2S), 2.27 (d, 4 H, allylic), 1.25 (s, 9 H, t-Bu), 0.80 ppm (m, 3 H, Me); MS *m/e* (relative intensity) 57 (100), 122 (38), 224 (21), 85 (12), 102 (12), 140 (8). Anal. Calcd for $C_{18}H_{33}NO_2S$: C, 66.01; H, 10.16; N, 4.28; S, 9.79. Found: C, 66.20; H, 10.14; N, 4.28; S, 9.80.

Synthesis of 2-Pyridyl- and 3-Pyridyl-4-oxobutanal (18 and 19). General Procedure. To a solution of 2- or 3-bromopyridine (2.40 mL, 24 mmol) in anhydrous THF (80 mL) under argon atmosphere is added *n*-butyllithium (2.5 M, 9.6 mL, 24 mmol) at −78 °C with stirring. After 20 min a solution of the *N*-Boc lactam **12a** (4.60 g, 20 mmol) in THF (30 mL) is slowly added, and the mixture is stirred at −78 °C for 3 h, quenched with 6 N hydrochloric acid (30 mL), and vigorously stirred at room temperature for 2.5 h. The aqueous phase is separated, washed with ether (2 × 30 mL), and then poured into a vigorously stirred mixture of saturated aqueous solution of potassium carbonate (100 mL) and chloroform (100 mL) (this procedure is necessary to avoid the substantial conversion of the γ-keto aldehydes to the corresponding pyrroles during the neutralization). The chloroform phase is separated, the aqueous phase is extracted with chloroform (2 × 50 mL), and the combined chloroform phases are washed with brine and dried over sodium sulfate. The solvent is evaporated at reduced pressure at a temperature below to 40 °C, and the obtained oil is purified by flash chromatography on silica gel by eluting with a cyclohexane–ethyl acetate (4:6) mixture.

4-(2-Pyridyl)-4-oxobutanal (18): IR 2820, 2720, 1710, 1690 cm^{-1}; ^{1}H NMR δ 9.87 (s, 1 H, CHO), 8.67 (m, 1 H, Py), 7.89 (m, 2 H, Py), 7.47 (m, 1 H, Py), 3.58 (m, 2 H, CH_2C=O), 2.89 ppm (m, 2 H, CH_2C=O); MS *m/e* (relative intensity) 134 (M^+ − CHO, 38), 78 (100), 51 (41), 106 (35), 135 (24). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.46; H, 5.57; N. 8.60.

4-(3-Pyridyl)-4-oxobutanal (19):[10,11] IR 2820, 2720, 1690 cm^{-1}; ^{1}H NMR δ 9.87 (s, 1 H, CHO), 9.17 (m, 1 H, Py), 8.74 (m, 1 H, Py), 8.25 (m, 1 H, Py), 7.43 (m, 1 H, Py), 3.37 (t, 2 H, CH_2C=O), 3.37 ppm (m, 2 H, CH_2C=O); MS *m/e* (relative intensity) 134 (M^+ − CHO), 78 (100), 106 (100), 121 (47), 135 (43), 51 (37).

Synthesis of Pyridyl-Substituted Pyrroles. (A) 1-Hydropyrroles. The γ-keto aldehydes 18 and 19 are prepared as previously described. The crude reaction product is treated with methanol (20 mL) and 30% aqueous ammonia (20 mL), and the mixture is stirred for 2.5 h at room temperature, excess ammonia and methanol are then evaporated, potassium carbonate is added to pH 10, and the organic bases are extracted with chloroform. The collected chloroform extracts are washed with brine and dried over sodium sulfate. The solvent is removed at reduced pressure, and the residue is purified by flash chromatography on silica gel, eluting with cyclohexane–ethyl acetate (4:6).

2-(Pyrrol-2-yl)pyridine (28):[13,14] 96% pure by GC analysis; mp 87–89 °C (ether) (lit.[14] mp 92 °C); IR 3460, 1590, 1560 cm^{-1}; ^{1}H NMR δ 10.4 (br s, 1 H, NH), 8.44 (m, 1 H), 7.55 (m, 2 H), 7.0 (m, 1 H), 6.87 (m, 1 H), 6.73 (m, 1 H), 6.28 ppm (m, 1 H); MS *m/e* (relative intensity) 144 (M^+, 100), 143 (27), 117 (26), 104 (25), 89 (18), 90 (17), 78 (15), 63 (14), 51 (14).

3-(Pyrrol-2-yl)pyridine (29):[13,14] 92‰ pure by GC analysis; mp 96–98 °C (ether) (lit.[14] mp 102 °C); IR 3150, 1600, 1530 cm^{-1}; ^{1}H NMR δ 10.7 and 4.4 (1 H, NH), 8.79 (s, 1 H), 8.25 (m, 1 H), 7.72 (m, 1 H), 7.10 (m, 1 H), 6.83 (m, 1 H), 6.53 (m, 1 H), 6.27 ppm (m, 1 H); MS *m/e* (relative intensity 144 (M^+, 100), 117 (45), 90 (32), 89 (28), 143 (26), 63 (20), 116 (18), 118 (16).

(B) 1-Methylpyrroles. The experimental procedure above described for the preparation of 18 and 19 is followed until quenching of the organometallic reaction mixture with 6 N hydrochloric acid. At this point the aqueous phase containing **18–19** as chlorhydrates is washed with ether, 35% aqueous methylamine is added to basic pH, and the mixture is vigorously stirred for 2.5 h (this procedure affords products free from little amounts of 1*H*-pyrroles (**28–29**) which are generally produced when **18–19** are isolated as previously described). Excess amine and solvent are removed at reduced pressure, potassium carbonate is added to pH 10, and the organic base is extracted with chloroform. The organic phase is washed with brine and dried over sodium sulfate. The solvent is evaporated at reduced pressure at a temperature below 40 °C, and the residue is purified by flash chromatography

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on silica gel, eluting with cyclohexane–ethyl acetate (4:6).

2-(1-Methylpyrrol-2-yl)pyridine (α-Nicotyrine) (30):[12] 97% pure by GC analysis; IR 1585, 1560, 1540 cm^{-1}; ^1H NMR δ 8.48 (m, 1 H), 7.47 (m, 2 H), 6.95 (m, 1 H), 6.67 (m, 1 H), 6.53 (m, 1 H), 6.14 (m, 1 H), 3.95 ppm (s, 3 H, Me); MS *m/e* (relative intensity) 158 (M^+, 50), 157 (100), 130 (20), 78 (18), 51 (10).

3-(1-Methylpyrrol-2-yl)pyridine (β-Nicotyrine) (31):[13] 96% pure by GC analysis; IR 1590, 1565, 1535 cm^{-1}; ^1H NMR δ 8.65 (s, 1 H), 8.46 (m, 1 H), 7.60 (m, 1 H), 7.20 (m, 1 H), 6.67 (m, 1 H), 6.20 (m, 2 H), 3.57 ppm (s, 3 H, Me); MS *m/e* (relative intensity) 158 (M^+, 100), 157 (56), 130 (31), 42 (17), 63 (17), 51 (15), 116 (13), 117 (12), 89 (11), 90 (10).

Synthesis of (*Z*)-7-Nonadecen-11-one (27). Potassium *tert*-butoxide (0.42 g, 3.75 mmol) is added to a suspension of triphenylheptylphosphonium bromide (**26**, 1.75 g, 4 mmol) in anhydrous THF (10 mL), with stirring at 0 °C, under an argon atmosphere. After 30 min the mixture is cooled to −78 °C, and a solution of 4-oxodecanal (**15**, 0.75 g, 3.75 mmol) in THF (5 mL) is added dropwise. The reaction mixture is stirred at −78 °C for 3 h and then allowed to reach room temperature overnight with stirring. After quenching with saturated aqueous solution of sodium chloride (10 mL) the organic phase is extracted with ether (3 × 20 mL) and dried over sodium sulfate. The residue is purified by flash chromatography on silica gel, eluting with cyclohexane, to give 1.38 g (67%) of pure **27**: IR 1720 cm^{-1}; ^1H NMR δ 5.37 (m, 2 H), 2.40 (m, 6 H), 2.05 (m, 20 H), 0.89 ppm (t, 3 H); MS *m/e* 280 (M^+); the *Z*:*E* ratio of 98.6:1.4 was determined by GLC on glass capillary Supelcowax column (30 m, 0.33 mm, 0.25 μm) at 130 °C: retention times, 37.38 min (*Z* isomer) and 39.26 min (*E* isomer).

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Registry No. **8a**, 39662-63-0; **8b**, 39662-64-1; **9b**, 131684-94-1; **10b**, 131684-95-2; **11a**, 131684-96-3; **12a**, 131684-97-4; **13a** (R = n-C_6H_{13}), 131685-01-3; **13a** (R = n-C_8H_{17}), 131685-02-4; **13a** (R = Ph), 131685-03-5; **14a**, 43160-78-7; **15a**, 56268-03-2; **16a**, 56139-59-4; **16b**, 75424-63-4; **17**, 25435-63-6; **18**, 131684-98-5; **19**, 76014-80-7; **20**, 131684-99-6; **21**, 10202-74-1; **22**, 131685-00-2; **26**, 13423-48-8; (*Z*)-**27**, 63408-45-7; **28**, 17285-54-0; **29**, 494-98-4; **30**, 525-75-7; **31**, 487-19-4; n-hexylmagnesium, 3761-92-0; phenylmagnesium chloride, 100-59-4; 2-bromopyridine, 109-04-6; 3-bromopyridine, 626-55-1; 1-ethoxydodec-2-en-4-one, 131685-04-6.

Cyano Phosphate: An Efficient Intermediate for the Chemoselective Conversion of Carbonyl Compounds to Nitriles[1]

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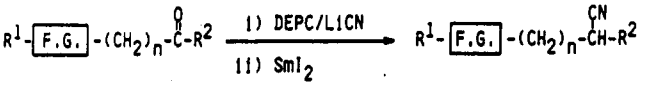
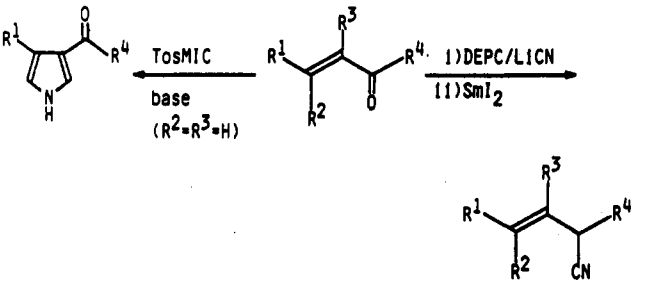
Cyanohydrin diethyl phosphates, readily obtained from various ketones and aldehydes by reaction with diethyl phosphorocyanidate and lithium cyanide, reacted chemoselectively with samarium(II) iodide in THF to give the corresponding nitriles in excellent yields. This method was also found applicable to α,β-unsaturated carbonyl compounds via cyano phosphates to give β,γ-unsaturated nitriles, not obtainable by standard methods, without isomerization of the double bonds.

The conversion of carbonyl groups into nitriles is important for one-carbon homologation in organic synthesis.[2] Cyanation with tosylmethyl isocyanide (TosMIC), developed by van Leusen,[3] is widely used for the one-pot conversion of ketones to nitriles and is frequently used for cyanation in organic synthesis. However, it involves the use of *t*-BuOK and generally gives low yields in the case of aliphatic and α,β-unsaturated aldehydes.[4] α,β-Unsaturated ketones[5] generally give only 3-acylpyrroles by this procedure without generation of nitriles. There is the alternative method for the cyanation of carbonyl groups using 2,4,6-triisopropylbenzenesulfonohydrazide (TPSH)[6] followed by refluxing of the hydrazones with excess potassium cyanide in methanol. In spite of these efforts to convert carbonyl compounds to nitriles, no general method for the chemoselective cyanation of carbonyl compounds bearing various functional groups is presently available. Reported here is a novel and efficient method for the

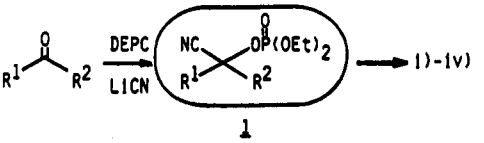
Scheme I



F.G. = alcohol, ether, epoxide, acetal, ester, amine, carbamate, amide, sulfonylamide, alkene, alkyne



Scheme II



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chemoselective conversion of carbonyl compounds into nitriles via cyanohydrin *O,O'*-diethyl phosphates (cyano phosphates). By this method, the conversion of α,β-unsaturated carbonyl compounds into the corresponding

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