Approaches to the Syntheses of Partially Reduced Imidazo[1,2-a]pyridines

Junhwa Shin,* Young Chang Nho, and Arthur S. Howard†

Advanced Radiation Technology Institute, Korea Atomic Energy Research Institute, Jeongeup, Jeonbuk 580-185, Korea
**E-mail: shinj@kaeri.re.kr*
†Department of Chemistry, Eastern Michigan University, Ypsilanti, Michigan 48179, USA
Received July 28, 2008

Two synthetic pathways to substituted hexahydroimidazo[1,2-a]pyridines, which may serve as precursors of aza-alkaloids, were investigated. The first involves the condensation of a bisnucleophilic enediaminoester and a biselectrophile. The second involves attachment to nitrogen of the carbon chain skeleton required to form the six-memberd ring, before formation of the enediaminoester. Several substituted hexahydroimidazo[1,2-a]pyridines were synthesized *via* these two approaches.

Key Words : Aza-alkaloid, Heterocyclic compounds, Indolizidine

Introduction

Alkaloids are naturally occurring organic compounds containing nitrogen atoms. Many alkaloids have important and unique pharmacological activities. Alkaloids have been isolated not only from well known sources such as plants or native drugs but also from animals, insects, marine organisms, and microorganisms. Examples of well known alkaloids include morphine, nicotine, cocaine, and quinine. The alkaloids which are related to this research are izidine alkaloids[1] which have structures containing five- or six-membered rings fused together with a nitrogen at the fusion point. Some structurally simple examples are shown in Figure 1 (A, B, and C). Of the izidine alkaloids, indolizidine alkaloids which have a fused five- and six-membered ring system with a ring junction nitrogen atom are directly related to this study.

One of many synthetic pathways to indolizidine alkaloids,[2-5] performed by Howard *et al.* uses vinylogous urethanes as the key intermediates during the synthesis of an Elaeocarpus alkaloid precursor.[5] One structural modification of indolizidine alkaloids is to replace a carbon atom in the five-membered ring with a nitrogen atom such that the two nitrogens are in a 1,3-relationship as shown in Figure 1(D). Such modification to prepare analogs of alkaloids is important to the pharmaceutical industry because side effects which the alkaloid may have may be reduced in the analogs, or they may show improved physiological properties.

The main goal of our study is the development of synthetic pathways to partially reduced imidazo[1,2-a]pyridines which may serve as precursors of aza-alkaloids. A retrosynthetic analysis of the relevant diazabicyclic compounds indicates a number of possible approaches and two of these approaches, shown in Scheme 1, have been investigated. Both involve the annulation of the six-membered ring onto the five-membered ring and differ in the timing of the attachment of the carbons that will complete the six-membered ring. The first approach (Scheme 1A) involves the formation of a bisnucleophilic enediaminoester containing an unsubstituted nitrogen atom followed by its reaction with biselectrophiles such as 1,3-dibromobutane, or acryloyl chloride. The second

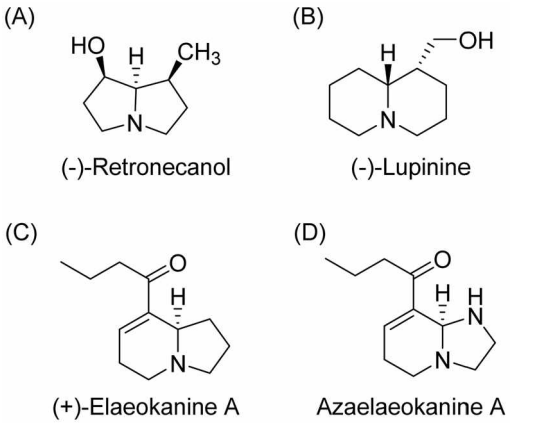
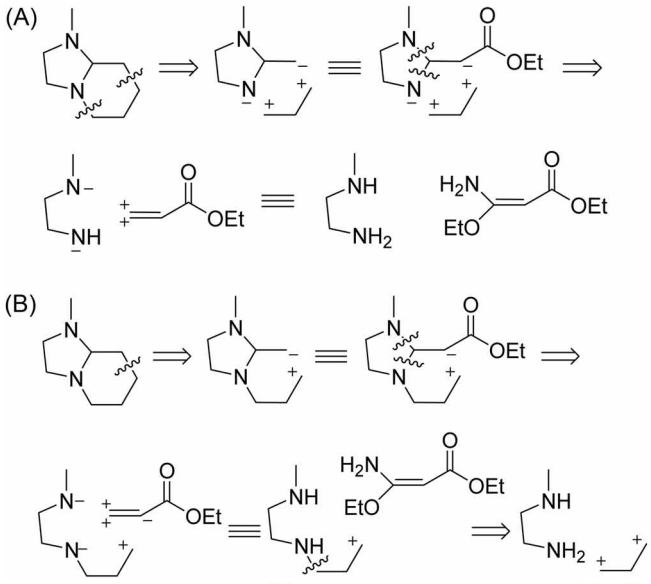
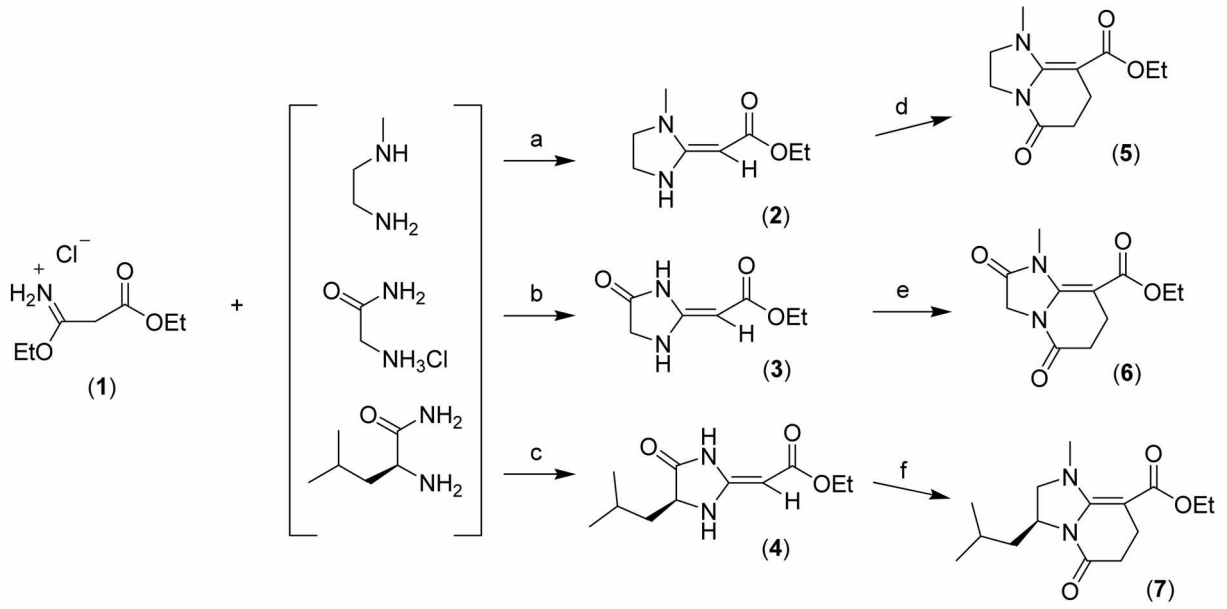


Figure 1. Examples of Izidines (A, B, and C), Indolizidine (C), and Azaindolizine (D).



Scheme 1. Two retrosynthetic approaches of the relevant diazabicyclic compounds.



Scheme 2. Synthetic pathway (A) to substituted hexahydroimidazo[1,2-a]pyridines (a) Abs. EtOH, reflux, 3 h, 89% (b) Abs. EtOH, Et_3N, reflux, 0.5 h, 30% (c) Abs. EtOH, Et_3N, reflux, 4 h, 60% (d) Acryloyl chloride, CH_2Cl_2, Et_3N, r.t., 3.5 h, 70% (e) Acryloyl chloride, CH_2Cl_2, Et_3N, r.t., 1.5 h, (**6**) was obtained as a major product and uncyclized one as a minor product (f) Acryloyl chloride, CH_2Cl_2, Et_3N, r.t., 1 h, (**7**) was obtained as a minor product and uncyclized one as a minor product

approach (Scheme 1B) involves attachment to nitrogen of the carbon chain skeleton required to form the six-membered ring before formation of the enediaminoester. Several substituted hexahydroimidazo[1,2-a]pyridines were synthesized *via* these two approaches and some of the chemistry of these systems was investigated and reported in this paper.

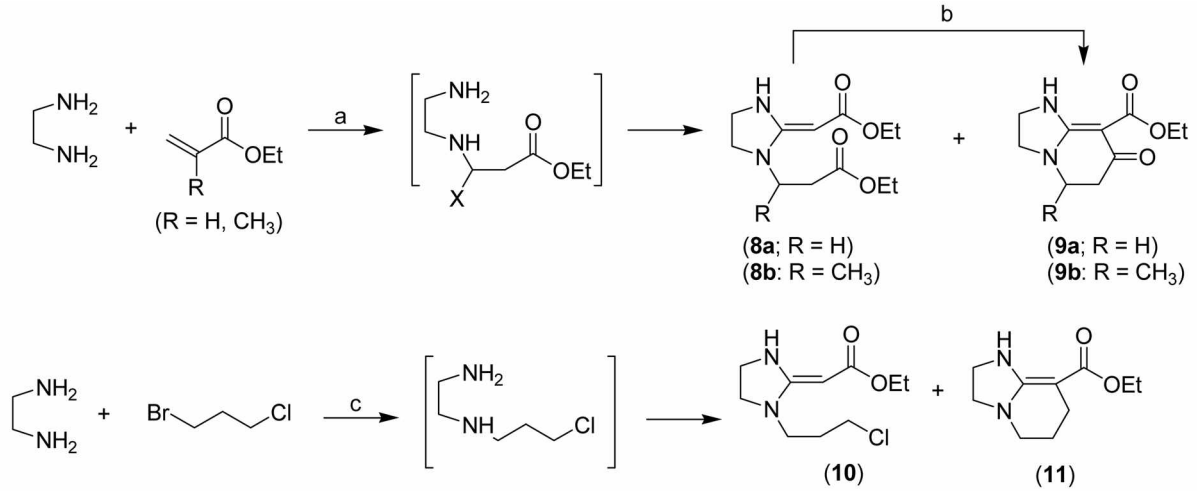
Results and Discussion

Compound (**1**), which will be referred to as the imidate hydrochloride, was prepared by bubbling hydrogen chloride gas into the reaction media containing ethyl cyanoacetate and anhydrous ethanol as described in the literature.[6] By analogy to the work of Jones,[7] *N*-methyl-1,2-diaminoethane, glycinamide hydrochloride, and L-leucinamide were condensed with imidate hydrochloride to produce respectively compounds (**2**), (**3**), and (**4**) as described in Scheme 2. A mixture of *N*-methyl-1,2-diaminoethane and imidate hydrochloride in anhydrous ethanol was refluxed for 3 h to give compound (**2**) in a yield of 89%. The melting point and ^{1}H NMR data are in agreement with previously reported data for the compound obtained *via* a different sequence.[8]

For the synthesis of compound (**3**), a mixture of glycinamide hydrochloride, imidate hydrochloride, and triethylamine in anhydrous ethanol was refluxed for 30 minutes during which time it turned red. It was expected that this reaction would be slower than the condensation of *N*-methyl-1,2-diaminoethane with imidate hydrochloride due to the lower nucleophilicity of the amide, but surprisingly the reaction was found to be at least twice as fast. After purification by chromatography, compound (**3**) was obtained in a yield of 30%. The ^{1}H NMR spectra showed it to be a single isomer but assignment of the stereochemistry of the double bond was not made. There was a large difference between the melting point found for compound (**3**) (mp 170-174 °C) and that given in the single report of the compound in the literature (mp 99-100 °C).[9] Since no other data was recorded, an attempt was made to reproduce the literature preparation in order to permit a comparison to be made. The attempt was unsuccessful. Despite this difference in the melting point the spectral data strongly suggest that compound (**3**) has the structure shown above.

Compound (**4**) was made in a yield of 60% by the condensation of L-leucinamide with imidate hydrochloride (**1**) in the presence of triethylamine. Following the procedure of Yang and Rising[10] L-leucinamide was made in a yield of 58% from L-leucine methyl ester hydrochloride by treatment with methanol saturated with ammonia. The main reason for the moderate yield is the significant solubility of L-leucinamide in water. The ^{1}H NMR spectra of L-leucinamide and of compound (**4**) each showed two doublets near $\delta = 0.9$ for the diastereotopic methyl groups resulting from the presence of the chiral center. The ^{13}C NMR spectra of the two compounds also each showed two methyl peaks near $\delta = 22$ for the same reason.

Enediaminoesters (**2**), (**3**), and (**4**) can react with a wide variety of organic compounds to give different kinds of fused heterobicyclic compounds.[11] Compound (**5**) was prepared by the annulation of compound (**2**) using acryloyl chloride in the presence of triethylamine in a yield of 70%. A mixture of compound (**3**), acryloyl chloride, and triethylamine was stirred at room temperature for 1.5 h under nitrogen. After attempted purification by flash chromatography the residue was still a mixture. The ^{1}H NMR spectrum was not readily interpreted but on the basis of the ^{13}C NMR spectrum the desired compound (**6**) was the major product. It



Scheme 3. Synthetic pathway (B) to substituted hexahydroimidazo[1,2-a]pyridines (a) Abs. EtOH, reflux, 18-20 h, 25% (**8a**), 26% (**9a**), 31% (**8b**), 9% (**9b**) (b) Abs. EtOH NaOEt, reflux, 1-3.5 h, 54% (**9a**), 82% (**9b**) (c) Abs. EtOH, Et_3N, reflux, 3.5 h, 10% (**10**), 17% (**11**).

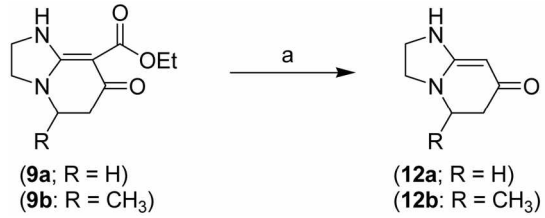
was contaminated with some of the acylated but uncyclized compound as shown by the presence of peaks at 124.5 and 137.0 in the ^{13}C NMR spectrum and multiplets between δ = 5.4 and 7.3 in the ^1H NMR spectrum. Compound (**4**) was treated with 1.2 equivalents of each of acryloyl chloride and triethylamine, and stirred at room temperature for 2 h. Purification by column chromatography gave an uncyclized compound as the major product and a cyclized compound (**7**) as a minor product. The ^{13}C NMR spectrum of the uncyclized compound, which showed only one spot in TLC using several solvent system, showed many sets of two peaks with similar chemical shifts. This suggested that the uncyclized compound existed as a mixture of tautomers.

This synthetic pathway shown in Scheme 3 differs from that previously discussed in Scheme 2 in that the carbon atoms destined to become C5 to C7 of the imidazo[1,2-a]pyridine ring are attached to the nitrogen before formation of the five-membered ring. This requires differentiation of the two nitrogens in the acyclic precursor. Selective mono-substitution of simple diamines is not easily achieved but the ready availability and low cost of the starting materials made this worthy of investigation.

A mixture of 1,2-diaminoethane and 1 equivalent of ethyl acrylate was stirred at 35 °C for 1 h. Analysis of the reaction mixture by ^1H NMR showed that it was a mixture of un-, mono-, and disubstituted amines. Of the three compounds only the monosubstituted compound is of value in the next step, the condensation with imidate hydrochloride (**1**). The efforts to separate these compounds were unsuccessful. Partitioning between water and dichloromethane failed due to the surprisingly high solubility of the monosubstituted compound in water. Column chromatography was also not successful because the mobility of the three compounds was too similar in several solvent systems. Attempted separation using the solubilities of the hydrochloride salts also failed. In an attempt to improve the yield of the monosubstituted compound the reaction was performed at low temperature by reacting 1,2-diaminoethane with ethyl acrylate in a freezer. No significant improvement was observed. Because of these difficulties, the sequence was continued without separation. The mixture of un-, mono-, and disubstituted compounds was combined with 1.3 equivalents of imidate hydrochloride (**1**) in anhydrous ethanol and refluxed for 20 h. After purification by column chromatography a monocyclic compound (**8a**) and a bicyclic compound (**9a**) were obtained in yields of 25% and 26% respectively as shown in Scheme 3. Attempts to cyclize compound (**8a**) to compound (**9a**) were made by treatment with 0.5 M NaOH followed by acetic anhydride, by reaction with sodium hydride, sodium ethoxide, or by refluxing in ethanol. Only the attempt using sodium ethoxide solution and refluxing for 1 h was successful (yield 54%).

In a sequence similar to the synthesis of compound (**9a**), ethyl crotonate was mixed with one equivalent of 1,2-diaminoethane and stirred at 45 °C for 2 h. The total crude reaction mixture was combined with 1.4 equivalents of imidate hydrochloride (**1**) in anhydrous ethanol and then refluxed for 18 h. Separation by column chromatography gave an uncyclized compound (**8b**) and a cyclized compound (**9b**) in yields of 31% and 9% respectively. The compound (**8b**) was treated with sodium ethoxide and refluxed for 3.5 h to give the compound (**9b**) in a yield of 82%.

1-Bromo-3-chloropropane was mixed with one equivalent of 1,2-diaminoethane in anhydrous ethanol and the mixture stirred at 40 °C for 40 h. This reaction sequence was continued without the separation of the un-, mono-, and disubstituted compounds for the same reasons mentioned previously. The reaction mixture was combined with one equivalent of imidate hydrochloride (**1**) and two equivalents of triethylamine in anhydrous ethanol and refluxed for 3.5 h to give a byproduct from the reaction of 1,2-diaminoethane with imidate hydrochloride, a monocyclic compound (**10**), and the bicyclic compound (**11**) in yields of 15%, 10%, and 17% respectively. The melting point and ^{13}C NMR data for compound (**11**) are in agreement with previously reported



(**9a**; R = H) (**12a**; R = H)
(**9b**: R = CH_3) (**12b**: R = CH_3)

Scheme 4. Decarbalkoxylation of the *C*8 ester group in substituted hexahydroimidazo[1,2-a]pyridines (a) 1 M KOH in EtOH, reflux, 3 h. 100% (**12a**), 68% (**12b**).

data.[12,13]

Selective monosubstitution utilizing some amino amides (*e.g.* glycinamide and L-leucinamide) instead of diamines is considered as an efficient alternative synthetic method since the nucleophilic character of the two nitrogens is clearly very different and preparations of the appropriately monosubstituted derivatives can be expected to be more readily achieved. A potentially very useful aspect of sequences starting from amino acid derivatives is the introduction at what will eventually be C3 in the bicyclic system, of a substituent of known absolute stereochemistry. It is, however, true the carbonyl group at the C2 position will render C3 prone to racemization. Several *N*-monosubstituted amino amides were prepared by the reaction of amino amides (glycinamide and L-leucinamide) and electrophiles such as ethyl acrylate, ethyl crotonate, and 1-bromo-3-chloropropane. Attempts to react the previously prepared *N*-substituted amino amides with imidate hydrochloride in the presence of triethylamine or with separately generated imidate were carried out in refluxing ethanol or by heating without solvent. No reaction occurred as shown by TLC except for the reaction of *N*-(3-chloropropyl) L-leucinamide with imidate by heating without solvent. This gave a glass-like material which could not be further purified.

Several azabicyclic compounds have been synthesized by the two routes discussed previously. These compounds all have an ester group at *C*8. This group is potentially useful in cases such as azaelaeokanine derivatives, but other azaalkaloids such as azamonomorines are not substituted at *C*8. Therefore, we investigated the decarbalkoxylation of *C*8 ester group in compounds (**9a**) and (**9b**) by treatment with 1 M KOH in 95% ethanol and refluxing for 3 h. The work-up procedure used was found to be critical. Attempts to isolate the products *via* extractive procedures failed. Instead the total reaction mixture was adsorbed directly onto silica which after drying was loaded onto a column and developed. This led to the isolation of compounds (**12a**) and (**12b**) in 100% and 68% yields respectively (Scheme 4).

Decarbalkoxylations of compound (**5**) were also attempted several times using different reaction conditions of solvent, time, temperature, pH, and work-up procedures. Yields were very low and no desired product was obtained. The ^{13}C NMR data on some of these crude products showed the disappearance of the absorption for the *C*5 amide at $\delta = 154$ while the absorptions between $\delta = 165$ and $\delta = 175$ for the enediamino carbonyl group were still present. Therefore, it is considered that the undesirable ring-opening reaction is at least competitive with the desired decarbalkoxylation.

In this study, several substituted hexahydroimidazo[1,2-a]pyridines, which may serve as precursors of aza-alkaloids, were prepared *via* two synthetic pathways as proposed in Scheme 1. The versatility and usefulness of these two synthetic approaches can be applied for the synthesis of various structural analogs of indolizidine alkaloids.

Experimental Section

Proton and carbon 13 nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 250 MHz Spectrometer and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Where necessary, DEPT, COSY, and HETCOR spectra were used to assign ^1H and ^{13}C signals. Infrared spectra (IR) were obtained on a BIO-RAD FTS-7 FT-IR Spectrometer and recorded as films between sodium chloride plates, in chloroform solution using a 0.1 mm cell, or as KBr pellets. Band positions are reported in reciprocal centimeters (cm^{-1}) and the following abbreviations are used; s = strong; m = medium; w = weak; br = broad; sh = shoulder. Mass spectra were recorded at the University of Michigan, on a Finnigan 4021 GC/EI-CI mass spectrometer. Molecular ions were reported as exact mass and other ion peaks as m/z (relative abundance) for all those of greater than 15% relative abundance. Melting points were determined in a capillary tube using a micro hot stage apparatus (MEL-TEMP II) and are uncorrected.

Ethyl ethoxycarbonylethanimidate hydrochloride (1): Hydrogen chloride gas (8.37 g, 230 mmol) was bubbled slowly into anhydrous diethyl ether (20 mL) containing ethyl cyanoacetate (20.0 g, 176.8 mmol) and anhydrous ethanol (9.26 g, 200 mmol) maintained at 0 °C. The reaction solution was placed in a freezer for 2 days. A white solid precipitated was filtered off, washed with anhydrous diethyl ether (4 × 25 mL), and dried with a stream of nitrogen (27 g, 77%). The percent yields ranged from 53% to 82%. The melting point was 104-106 °C (Lit.[6]: mp 99-101 °C). ^1H NMR ($CDCl_3$): 12.50 (br, 1H), 11.80 (br, 1H), 4.65 (q, J = 7.0, 2H), 4.16 (q, J = 7.0, 2H). 3.85 (s, 2H), 1.43 (t, J = 7.0, 3H), 1.21 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 172.2, 164.4, 71.6, 62.5, 39.2, 13.9, 13.5.

Ethyl (*E*)-(1-methyl-2-imidazolidinylidene)acetate (2): *N*-Methyl-1,2-diaminoethane (0.53 g, 7.16 mmol) in anhydrous ethanol (5 mL) was added to a solution of imidate hydrochloride (**1**) (1.40 g, 7.16 mmol) in anhydrous ethanol (35 mL). The reaction solution was heated at reflux for 3 hours. After removal of the solvent, the viscous oily residue was partitioned between dichloromethane (30 mL) and saturated sodium bicarbonate solution (10 mL). The extraction with dichloromethane was repeated (2 × 10 mL). The organic extracts were combined and dried to leave a white solid (**2**) (1.1 g, 89%. mp 96-98 °C). The product was recrystallized from acetone (mp 99-101 °C, Lit.[8]: mp 101-102 °C from ether). ^1H NMR ($CDCl_3$): 7.38 (br, 1H), 4.05 (q, J = 7.0, 2H), 3.98 (s, 1H), 3.49 (t, J = 7.5, 2H), 3.35 (t, J =

7.5, 2H), 2.72 (s, 3H), 1.22 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 171.1, 164.3, 60.2, 58.0, 50.5, 41.9, 32.5, 14.8. IR (KBr): 3365 (s), 2985 (m), 2905 (m), 1637 (s), 1582 (s), 1530 (m), 1490 (m), 1426 (m), 1295 (m), 1160 (s), 1133 (s), 1060 (s), 1005 (m), 950 (m), 774 (m).

Ethyl (4-oxo-2-imidazolidinylidene)acetate (3): To a solution of 2-aminoacetamide monohydrochloride (332 mg, 3,00 mmol) in anhydrous ethanol (20 mL), triethylamine (910 mg, 9.01 mmol) and imidate hydrochloride (**1**) (587 mg, 3.00 mmol) in anhydrous ethanol (10 mL) were added. The reaction solution was heated at reflux for 30 minutes during which time it turned red. The solvent and excess of triethylamine were removed under vacuum. The residue was extracted with dichloromethane (3 × 25 mL), filtered, concentrated under vacuum, and purified by flash chromatography to give (**3**) (brown solid, 0.16 g, 30%. mp 170-174 °C, Lit.[9]: mp 99-100 °C). ^{1}H NMR (DMSO): 10.90 (br, 1H), 7.80 (br, 1H), 4.15 (s, 1H), 3.95 (q, J = 7.0, 2H), 3.91 (s, 2H), 3.36 (H_2O in DMSO), 1.12 (t, J = 7.0, 3H). ^{13}C NMR (DMSO): 173.0, 169.0, 159.0, 65.3, 57.4, 47.7, 14.5. IR (KBr): 3179 (br), 2977 (m), 2924 (m), 1728 (s), 1691 (s), 1593 (s), 1501 (m), 1443 (m), 1267 (s), 1164 (s), 1070 (s), 897 (s), 735 (m), 673 (m).

L-Leucinamide: Ammonia gas was slowly bubbled for 5 minutes into methanol (80 mL) containing L-leucine methyl ester hydrochloride (5.00 g, 27.5 mmol). The reaction solution was stirred at room temperature for 10 days with supplementary amounts of ammonia gas supplied every day. After removal of the solvent and excess ammonia, the residual white solid was partitioned between dichloromethane (50 mL + 2 × 30 mL) and aqueous sodium hydroxide (25 mL). The organic extracts were combined, dried, and the solvent removed to leave a white solid (1.580 g, mp 90-93 °C). The pH of the aqueous solution was adjusted to 7 by adding concentrated HCl. The aqueous solution was concentrated, basified by adding sodium hydroxide, and extracted with dichloromethane (30 mL + 20 mL) to yield more product (0.49 g, mp 92-95 °C). The total yield was 58%. The product was recrystallized from benzene (mp 98-100 °C, Lit.[14]: mp 101-102 °C, $[\alpha]_D^{22}$ −34.8 (c, 1.27 in chloroform)). ^{1}H NMR ($CDCl_3$): 7.06 (br, 1H), 6.15 (br, 1H), 3.34 (dd, J = 10.0, 3.5, 1H), 1.75-1.57 (m, 2H), 1.42 (br, 2H), 1.38-1.28 (m, 1H), 0.91 (d, J = 6.5, 3H), 0.88 (d, J = 6.0, 3H). ^{13}C NMR ($CDCl_3$): 179.1, 53.4, 44.0, 24.8, 23.4, 21.2.

(*S*)-Ethyl (4-isobutyl-5-oxo-2-imidazolidinylidene)-acetate (4): L-Leucinamide (520 mg, 4.00 mmol) in anhydrous ethanol (10 mL) and triethylamine (1.212 g, 12.0 mmol) were added to a solution of imidate hydrochloride (**1**) (1.173 g, 6.00 mmol) in anhydrous ethanol (40 mL). After 3 h refluxing, imidate HCl (430 mg, 2.20 mmol) and triethylamine (470 mg, 4.65 mmol) were added to the reaction solution and refluxing continued for a further 4 h. After removal under vacuum of the solvent and excess of triethylamine, the residual yellow solid was dissolved in dichloromethane (30 mL), and washed with distilled water (3 × 6 mL). The dichloromethane was dried and concentrated to leave a yellow solid (1.055 g). A white solid (**4**) was obtained by trituration with a 1:1 mixture of acetone and hexane. Further material was obtained by flash chromatography of the soluble material (acetone:hexane 1:3) (Total yield 0.54 g, 60%. mp = 156-159 °C). The product was recrystallized from acetone (mp 159-161 °C). ^{1}H NMR (DMSO): 10.93 (br, 1H); 7.93 (br, 1H), 4.15 (s, 1H), 4.06 (t, J = 6.5, 1H), 3.97 (q, J = 7.0, 2H), 3.36 (H_2O in DMSO), 1.76 (n, J = 6.5, 1H), 1.63-1.39 (m, 2H), 1.13 (t, 3H), 0.88 (d, J = 6.5, 3H), 0.87 (d, J = 7.0, 3H). ^{13}C NMR (DMSO): 175.4, 168.7, 157.5, 65.4, 57.6, 56.2, 40.6, 24.2, 22.7, 22.2, 14.6. IR (10% chloroform solution): 3320 (br), 2961 (m), 1751 (s), 1675 (s), 1610 (s), 1486 (m), 1267 (s), 1146 (s), 1094 (m), 1052 (m), 668 (m). MS (EI) Calculated for $C_{11}H_{18}N_2O_3$: (M^-) 226.1317, found: 226.1313 m/z = 227 (MH^-, 18.3%), 226 (M^-, 49.2), 184 (17.5), 183 (100.0), 181 (49.7), 170 (37.1), 169 (17.4), 155 (26.0), 154 (66.6), 140 (20.7), 137 (34.1), 124 (29.1), 123 (68.5), 111 (23.5), 98 (17.0), 97 (32.2), 96 (15.0), 86 (40.6), 70 (18.0), 68 (44.8), 44 (23.5), 43 (39.1), 42 (24.1), 41 (34.0).

Ethyl 1-methyl-5-oxo-1,2,3,5,6,7-hexahydroimidazo-[1,2-a]pyridine-8-carboxylate (5): Acryloyl chloride (710 mg, 7.5 mmol) in anhydrous dichloromethane (3 mL) and triethylamine (730 mg, 7.2 mmol) were added to a solution of compound (**2**) (1.02 g, 6.00 mmol) in anhydrous dichloromethane (45 mL) under nitrogen, and stirred under nitrogen at room temperature for 3.5 h. After removal of solvent, the residue was extracted with anhydrous diethyl ether (6 × 10 mL). After removal of ether, a white solid (**5**) (0.95 g, 70%. mp 77-81 °C) was obtained. The product was recrystallized from hexane (mp 83-85 °C). ^{1}H NMR ($CDCl_3$): 4.08 (q, J = 7.0, 2H), 3.77 (t, J = 8.0, 2H), 3.50 (t, J = 8.0, 2H), 3.02 (s, 3H), 2.62 (t, J = 7.5, 2H), 2.40 (t, J = 7.5, 2H), 1.22 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 171.0, 167.0, 154.0, 75.1, 59.2, 51.6, 40.8, 39.5, 31.8, 21.5, 14.6. IR (KBr): 2976 (s), 2906 (s), 2847 (s), 1672 (s), 1586 (s), 1480 (s), 1440 (s), 1388 (s), 1310 (s), 1280 (s), 1240 (s), 1203 (s), 1170 (s), 1114 (s), 1050 (s), 1000 (m), 830 (w), 755 (m), MS (EI) Calculated for $C_{11}H_{16}N_2O_3$: (M^+) 224.1162, found: 224.1154 m/z = 224 (M^-, 12.0%), 151 (59.0), 84 (19.2), 58 (21.4), 57 (35.0), 49 (29.1), 44 (100.0).

Reaction of ethyl (4-oxo-2-imidazolidinylidene)acetate (3) with acryloyl chloride: Triethylamine (79 mg, 0.782 mmol) in anhydrous dichloromethane (2 mL) was added to a solution of reddish compound (**3**) (111 mg, 0.653 mmol) in anhydrous dichloromethane (15 mL). Acryloyl chloride (71 mg, 0.784 mmol) in anhydrous dichloromethane (2 mL) was added dropwise to the reaction solution at room temperature during 5 minutes, followed by stirring at room temperature for 1.5 h. After removal of solvent, a reddish solid was partitioned between dichloromethane (25 mL) and 10% sodium bicarbonate solution (10 mL). The organic layer was washed with water (10 mL), dried, and concentrated to leave a reddish oil (0.11 g). Purification by flash chromatography (chloroform:methanol 5:1) gave a reddish oil (0.079 g). ^{1}H NMR ($CDCl_3$): 10.60 (br), 9.60 (br), 7.25-7.13 (m), 6.16-6.06 (m), 5.50-5.45 (m), 4.26-3.96 (m), 3.70-3.61 (m), 3.40 (s), 2.68-2.48 (m), 2.80-2.00 (br), 1.32-1.15 (m). ^{13}C NMR

($CDCl_3$): 168.5, 168.0, 167.5, 147.0, 137.0, 125.0, 124.5, 82.0, 60.6, 60.5, 58.5, 46.1, 30.5, 18.6, 18.5, 14.4, 14.3.

Reaction of (S)-ethyl (4-isobutyl-5-oxo-2-imidazolidinylidene)acetate (4) with Acryloyl chloride: Acryloyl chloride (133 mg, 1.41 mmol) in anhydrous dichloromethane (2 mL) and triethylamine (700 mg, 6.93 mmol) were added to a solution of compound (**4**) (170 mg, 0.752 mmol) in anhydrous dichloromethane (20 mL) under nitrogen. The reaction mixture was stirred under nitrogen for 1 h at room temperature. After removal of the solvent and excess of triethylamine under vacuum, the residue was extracted with anhydrous diethyl ether (20 mL). The residue from the ether extract was purified by flash chromatography (chloroform: methanol 30:1) to leave a yellow oil (0.080 g). ^{1}H NMR ($CDCl_3$): 9.50 (br), 4.40 (t), 4.28-4.05 (m), 2.80-2.50 (m), 2.01 (s), 1.95-1.78 (m), 1.62 (s), 1.35-1.20 (m), 0.93 (d), 0.91 (d). ^{13}C NMR ($CDCl_3$): 171.5, 168.0, 167.0, 147.0, 137.0, 126.0, 125.0, 82.0, 60.5, 56.6, 39.2, 31.1, 24.3, 23.0, 22.5, 18.4, 14.4.

Ethyl 3-(2-ethoxycarbonylmethylenimidazolidine-1-yl)propanoate (8a) and ethyl 7-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (9a): Ethyl acrylate (3.4 g, 34 mmol) was added dropwise to 1,2-diaminoethane (2.04 g, 34 mmol) contained in a 10-mL flask at 0 °C. The reaction mixture was stirred at 35 °C for 1 h, and then mixed with imidate hydrochloride (**1**) (8.5 g, 43 mmol) in anhydrous ethanol (150 mL). After refluxing for 20 hr it was cooled, filtered, and concentrated under vacuum. The crude product was partitioned between 3 M Na_2CO_3 (9 mL) and dichloromethane (40 mL + 3 × 10 mL). The organic layer was dried and concentrated to give a reddish viscous oil (8.1 g). This was purified by flash chromatography (chloroform:methanol 15:1) to give compound (**8a**) (2.2 g, 25%, mp 37-39 °C), compound (**9a**) (1.8 g, 26%, mp 145-148 °C), and the mixture of the two compounds (0.84 g). Compound (**8a**) was recrystallized from hexane (mp 47-49 °C) and compound (**9a**) from acetone (mp 154-156 °C).

Compound (8a): ^{1}H NMR ($CDCl_3$): 7.40 (br, 1H), 4.09 (q, J = 7.0, 2H), 4.03 (q, J = 7.0, 2H), 3.98 (s, 1H), 3.51-3.34 (m, 4H), 3.37 (t, J = 7.0, 2H), 2.51 (t, J = 7.0, 2H), 1.21 (t, J = 7.0, 3H), 1.19 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 172.0, 171.0, 164.0, 60.8, 60.5, 58.1, 48.5, 42.1, 41.5, 32.3, 14.9, 14.1. IR (NaCl) 3373 (m), 2979 (s), 2942 (m), 2889 (m), 2363 (w), 1736 (s), 1652 (s), 1583 (s), 1501 (m), 1463 (m), 1377 (m), 1281 (m), 1151 (s), 1096 (s), 1058 (s), 957 (w), 856 (w), 773 (m), 602 (w). MS (EI) Calculated for $C_{12}H_{20}N_2O_4$: (M^+) 256.1424, found: 256.1419 m/z = 257 (MH^+, 17.1%), 256 (M^+, 17.1), 255 (40.4), 211 (100.0), 184 (53.1), 183 (87.7), 169 (63.6), 156 (28.0), 155 (38.6), 139 (19.9), 137 (23.6), 127 (60.6), 123 (32.7), 112 (39.3), 111 (28.9), 109 (27.0), 84 (92.6), 81 (20.5), 70 (24.0), 56 (78.0), 55 (30.2), 54 (29.1), 53 (15.0), 42 (25.3).

Compound (9a): ^{1}H NMR ($CDCl_3$): 8.30 (br, 1H), 4.17 (q, J = 7.0, 2H), 3.70 (t, J = 8.5, 2H), 3.47 (t, J = 8.5, 2H), 3.24 (t, J = 7.0, 2H), 2.51 (t, J = 7.0, 2H), 1.26 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 186.0, 168.3, 167.6, 86.7, 59.5, 49.7, 43.4, 43.1, 36.5, 14.4. IR (KBr): 3505 (m), 3364 (s), 3271 (m), 2974 (m), 2891 (m), 2623 (w), 1651 (s), 1605 (s), 1560 (s), 1474 (m), 1391 (m), 1301 (m), 1236 (m), 1138 (s), 1033 (m), 790 (m), 584 (m). MS (EI) Calculated for $C_{10}H_{14}N_2O_3$: (M^+) 210.1005, found : 210.0995 m/z = 210 (M^+, 51.0%), 181 (21.0), 166 (32.7), 165 (67.6), 164 (16.6), 163 (38.7), 153 (17.9), 138 (100.0), 137 (20.3), 111 (23.3), 110 (28.0), 109 (26.7), 84 (12.6), 81 (17.6), 80 (19.1), 56 (18.4), 49 (15.1), 42 (20.4).

Cyclization of ethyl 3-(2-ethoxycarbonylmethylenimidazolidine-1-yl)propanoate (8a) to ethyl 7-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (9a). Compound (**8a**) (256 mg, 1.00 mmol) was dissolved in anhydrous ethanol (5 mL). Sodium ethoxide solution (25.4 mg Na/1.07 mL ethanol, 1.1 mmol) was added dropwise to the reaction solution which was kept under nitrogen and refluxed for 1 h. Three drops of saturated NH_4Cl solution were added to the reaction mixture, which was then concentrated and extracted with dichloromethane (13 mL). The organic layer was dried, concentrated, and purified by flash chromatography (chloroform:methanol 5:1) to give a white solid (**9a**) (0.11 g, 54%, mp 145-148 °C).

Ethyl 3-(2-ethoxycarbonylmethylenimidazolidine-1-yl)butanoate (8b) and ethyl 5-methyl-7-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (9b). Ethyl crotonate (2.38 g, 20 mmol) was added dropwise to 1,2-diaminoethane (1.2 g, 20 mmol) contained in a 10-mL flask at 0 °C. The reaction mixture was stirred at 45 °C for 2 h and then mixed with imidate hydrochloride (**1**) (5.37 g, 27.5 mmol) in anhydrous ethanol (80 mL). The reaction mixture was then refluxed for 18 h during which time it turned reddish in color. After removal of the solvent, the crude mixture was partitioned between saturated $NaHCO_3$ (20 mL) and CH_2Cl_2 (3 × 30 mL). The organic extracts were dried and the solvent removed to give a reddish oil (3.80 g), a portion (0.5 g) of which was purified by flash chromatography (chloroform:methanol 15:1) to give compound (**8b**) (0.22 g, 31%) and compound (**9b**) (0.050 g, 9%).

Compound (8b): ^{1}H NMR ($CDCl_3$): 7.54 (br), 4.13-3.98 (m), 3.57-3.29 (m), 2.58-2.36 (m), 1.24-1.10 (m). ^{13}C NMR ($CDCl_3$): 170.7, 162.8, 128.7, 60.9, 60.7, 58.1, 46.7, 42.3, 41.8, 39.0, 17.0, 14.8, 14.1.

Compound (9b): ^{1}H NMR ($CDCl_3$): 8.40 (br, 1H), 4.17 (q, J = 7.0, 2H), 3.70 (m, 3H), 3.40 (m, 1H), 3.30 (m, 1H), 2.50 (dd, J = 16.0, 5.0, 1H), 2.30 (dd, J = 16.0, 10.0, 1H), 1.27 (t, J = 7.0, 3H), 1.18 (d, J = 6.0, 3H). ^{13}C NMR ($CDCl_3$): 186.3, 168.4, 167.3, 86.5, 59.6, 49.8, 46.9, 44.8, 42.8, 18.5, 14.5. IR (KBr): 3342 (s), 2978 (s), 2962 (s), 2892 (s), 1626 (s), 1566 (s), 1519 (s), 1465 (m), 1371 (s), 1306 (s), 1235 (m), 1149 (s), 1093 (m), 1032 (m), 829 (s), 794 (m), 659 (m), 591 (m).

Cyclization of ethyl 3-(2-ethoxycarbonylmethylenimidazolidine-1-yl)butanoate (8b) to ethyl 5-methyl-7-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (9b). Compound (**8b**) (80 mg, 0.30 mmol) was dissolved in anhydrous ethanol (2 mL). A sodium ethoxide solution (7 mg Na/0.3 mL ethanol, 0.3 mmol) was added dropwise to the reaction solution maintained under nitrogen. The reac-

tion mixture was refluxed for 3.5 h. Saturated NH_4Cl solution (3 drops) was added to the reaction mixture which was concentrated, and extracted with dichloromethane (10 mL). The organic layer was dried and the solvent removed to give a white solid (**9b**) (0.055 g, 82%. mp 142-145 °C).

Ethyl 1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (11). 1-Bromo-3-chloropropane (1.57 g, 10.0 mmol) in anhydrous ethanol (10 mL) was added dropwise to a solution of 1,2-diaminoethane (0.60 g, 10.0 mmol) in anhydrous ethanol (50 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 40 h. Triethylamine (2.02 g, 20.0 mmol) and imidate hydrochloride (**1**) (1.955 g, 10.0 mmol) were added to the reaction mixture at room temperature which was then refluxed for 3.5 h. After removal of solvent, a yellow oil was partitioned between dichloromethane (30 mL) and 10% $NaHCO_3$ (20 mL). The organic layer was dried, and the solvent removed to give a solid (1.221 g). The solid was then treated with ether and then the organic layer was concentrated to give a mixture of solid and oil (895 mg). A portion (292 mg) was purified by flash chromatography (chloroform:methanol 30:1) to give an oily liquid (**10**) (0.073 g, 10%), a solid (**11**) (0.11 g, 17%. mp 62-68 °C), and a mixture of the two compounds (0.009 g). Compound (**11**) was recrystallized from hexane (mp 84-87 °C, Lit.[12]: mp 89-92 °C).

Compound (10): ^{1}H NMR ($CDCl_3$): 7.49 (br, 1H), 4.05 (q, J = 7.0, 2H), 4.01 (s, 1H), 3.54 (t, J = 7.0, 2H), 3.52 (t, J = 7.0, 2H), 3.42 (t, J = 7.0, 2H), 3.25 (t, J = 7.0, 2H), 2.00 (p, J = 6.5, 2H), 1.22 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 171.0, 164.0, 60.5, 58.2, 48.8, 43.1, 42.0, 30.0, 14.8.

Compound (11): ^{1}H NMR ($CDCl_3$): 7.12 (br, 1H), 4.03 (q, J = 7.0, 2H), 3.44 (t, J = 7.5, 2H), 3.28 (t, J = 7.5, 2H), 3.02 (t, J = 6.0, 2H), 2.26 (t, J = 6.5, 2H), 1.78 (t, J = 6.0, 2H), 1.19 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$): 169.5, 159.9, 69.6, 57.9, 49.3, 44.9, 41.7, 22.1, 20.0, 14.8. IR (NaCl): 3379 (s), 2948 (s), 2844 (m), 1659 (s), 1584 (s), 1502 (m), 1444 (m), 1402 (m), 1379 (m), 1288 (s), 1263 (s), 1160 (m), 1106 (s), 1041 (m), 950 (w), 921 (w), 849 (w), 769 (m). MS (EI) Calculated for $C_{10}H_{16}N_2O_2$: (M^-) 196.1213, found: 196.1206 m/z = 196 (M^+, 57.8%), 195 (16.0), 167 (34.2), 151 (49.1), 149 (31.1), 124 (38.1), 123 (100.0), 121 (16.8), 56 (16.4).

Decarbalkoxylation of ethyl 7-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (9a). Compound (**9a**) (210 mg, 1.00 mmol) was dissolved in 1.0 M KOH in 95% ethanol (4 mL) and refluxed for 3 h. Silica gel (0.50 g) was added to the reaction mixture and the solvent removed. The silica gel containing adsorbed product was loaded on a column filled with silica gel and solvent mixture (chloroform:methanol 5:1). The column was developed to give a solid (**12a**) (0.14 g, 100%). Compound (**12a**) was recrystallized from a mixture of ethanol and acetone (mp 106-111 °C). ^{1}H NMR (DMSO): 7.55 (br, 1H), 4.30 (s, 1H), 3.41 (t, J = 7.5, 2H), 3.27 (t, J = 7.5, 2H), 3.15 (t, J = 7.0, 2H), 2.18 (t, J = 7.0, 2H). ^{13}C NMR (DMSO): 186.8, 167.0, 78.3, 49.5, 45.0, 42.5, 35.1. IR (KBr): 3164 (br), 2860 (s), 1612 (s), 1665 (s), 1526 (s), 1481 (s), 1375 (m), 1291 (m), 1211 (s), 1127 (m), 1047 (m), 829 (s), 790 (s). MS (EI) Calculated for $C_7H_{10}N_2O$: (M^-) 138.0794, found: 138.0800 m/z = 138 (M^+, 100.0%), 137 (28.3), 110 (18.8), 109 (54.6), 81 (63.5), 68 (15.9), 54 (17.9), 53 (24.5), 49 (16.3), 42 (23.2).

Decarbalkoxylation of ethyl 5-methyl-7-oxo-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-8-carboxylate (9b). Compound (**9b**) (200 mg, 0.893 mmol) was dissolved in 1.0 M KOH in 95% ethanol (4 mL) and refluxed for 3 h. Silica gel (0.50 g) was added to the reaction mixture and the solvent removed. The silica gel containing adsorbed product was loaded on a column filled with silica gel and solvent mixture (chloroform:methanol 5:1). The column was developed to give a solid (**12b**) (0.10 g, 68%. mp 98-105 °C). Compound (**12b**) was recrystallized from ethanol and acetone (mp 118-122 °C). ^{1}H NMR (DMSO): 7.50 (br, 1H), 4.28 (s, 1H), 3.5 (m, 1H), 3.4 (m, 1H), 3.37 (H_2O in DMSO), 3.30 (m, 1H), 3.20 (m, 1H), 3.00 (m, 1H), 2.12 (dd, J = 16.0, 5.0, 1H), 2.00 (dd, J = 16.0, 11.0, 1H), 1.14 (d, J = 6.0, 3H). ^{13}C NMR (DMSO): 186.6, 166.5, 78.1, 51.3, 46.7, 43.4, 41.8, 18.6. IR (KBr): 3242 (br), 3144 (br), 2994 (m), 2911 (m), 1612 (s), 1555 (s), 1520 (s), 1475 (s), 1440 (m), 1360 (m), 1290 (m), 1244 (m), 1196 (m), 1140 (m), 1084 (m), 1020 (w), 851 (s), 775 (m), 639 (m).

References

1. Hesse, M. *Alkaloid Chemistry*; John Wiley & Sons: New York, 1981; p 47.
2. Kim, G.; Shim, J. H.; Kim, J. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1832.
3. Lee, Y. S.; Kim, D. W.; Lee, J. Y.; Jeong, K. S.; Park, H. *Bull. Korean Chem. Soc.* **1998**, *19*, 814.
4. Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S, C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979.
5. Howard, A. S.; Gerrans, G. C.; Meerholz, C. A. *Terrahedron Lett.* **1980**, *21*, 1373.
6. Glickman, S. A.; Cope, A. C. *J. Am. Chem. Soc.* **1945**, *67*, 1019.
7. Anderson, M. W.; Begley, M. J.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Perkins Trans. 1* **1984**, 2599.
8. Huang, Z.; Tzai, L. *Chem. Ber.* **1986**, *119*, 2208.
9. Satzinger, G. *Justus Liebigs Ann. Chem.* **1978**, 473.
10. Yang, P. S.; Rising, M. M. *J. Am. Chem. Soc.* **1931**, *53*, 3183.
11. Jones, R. C. F.; Smallridge, M. J. *Terrahedron Lett.* **1988**, *29*, 5005.
12. Merck *U.S. Patent 3 987 183*, **1976**, *Chem. Abstr.* **1976**, *86*, 140045.
13. Wamhoff, H.; Lamers, W. *Synthesis* **1993**, 111.
14. Davis, A. C.; Levy, A. L. *J. Am. Chem. Soc.* **1951**, *73*, 2419.