Reactions of *N*-(Ethoxycarbonyl)-3-halo-3-(halomethyl)azetidines with DBU. The Halogen Dance

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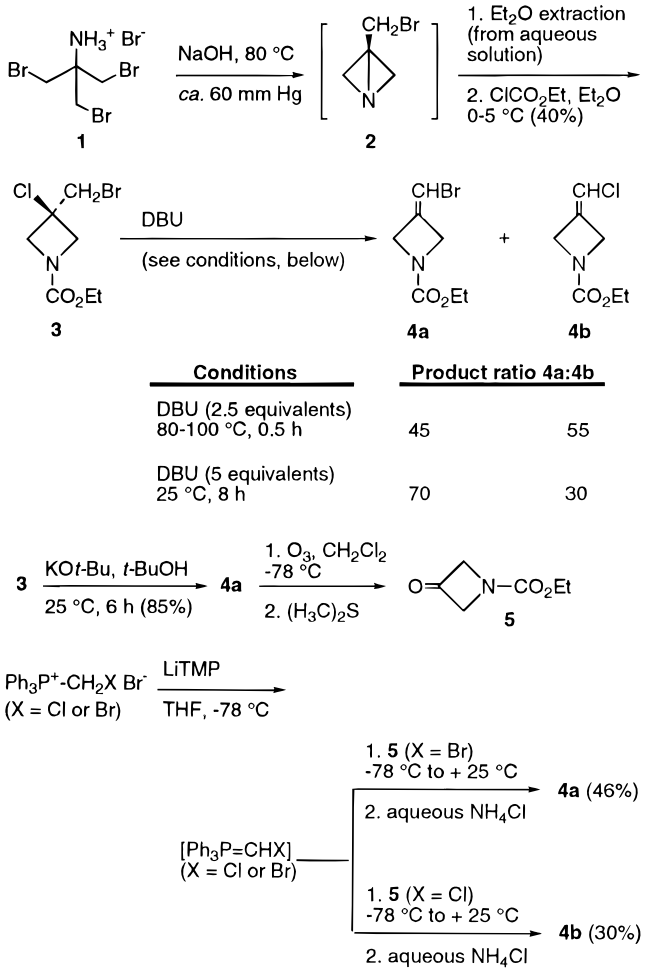
Reaction of *N*-(ethoxycarbonyl)-3-(bromomethyl)-3-chloroazetidine (**3**) with DBU results in the formation of two haloalkenes, i.e., *N*-(ethoxycarbonyl)-3-(bromomethylene)azetidine and *N*-(ethoxycarbonyl)-3-(chloromethylene)azetidine (**4a** and **4b**, respectively). The results of control experiments suggest that Cl^- is capable of promoting nucleophilic displacement of bromine in the CH_2Br groups of both **3** and *N*-(ethoxycarbonyl)-3-bromo-3-(bromomethyl)azetidine (**8**), but Br^- is incapable of displacing chlorine in the CH_2Cl groups of both *N*-(ethoxycarbonyl)-3-chloro-3-(chloromethyl)-azetidine (**7**) and *N*-carbethoxy-3-bromo-3-(chloromethyl)azetidine (**10**). Thus, it is suggested that the formation of **4b** via reaction of **3** with DBU is a result of DBU-promoted elimination of HCl from **7**, a key reaction intermediate. The observations reported herein can be explained without invoking the intermediacy of any bridged halonium ion.

Introduction

3-Substituted 1-azabicyclo[1.1.0]butanes were first synthesized in the late 1960s.[1,2] Despite their unusual and highly strained bicyclic structures, little interest was shown initially in pursuing the chemistry of compounds of this type. However, the current decade has witnessed a renaissance of interest in azabicyclo[1.1.0]butane chemistry.[3] Thus, reactions of carbenes[4] and a variety of other electrophiles[5,6] with 3-substituted 1-azabicyclo[1.1.0]-butanes have been reported recently. In addition, their use as intermediates in the synthesis of energetic materials, e.g., 1,3,3-trinitroazetidine (TNAZ) in particular, has been reported.[7] In the present study, some *N*-(ethoxycarbonyl)-3-halo-3-(halomethyl)azetidines have been synthesized, and their respective reactions with non-nucleophilic bases (e.g., DBU and DBN) have been studied.

Synthesis of *N*-(Ethoxycarbonyl)-3-(bromomethyl)-3-chloroazetidine (3) and Its Subsequent Reactions with DBU and DBN. Compound **3** was prepared in 40% overall yield via generation of 1-aza-3-(bromomethyl)-bicyclo[1.1.0]butane (**2**)[7a] and its subsequent trapping with $ClCO_2Et$ (see Experimental Section). Interestingly, when **3** was heated with DBU (2.5 equiv) at 80−100 °C for 30 min (method A), elimination of hydrogen halide occurred to afford two different haloalkenes, i.e., **4a** and **4b** (Scheme 1; ratio **4a**:**4b** = 45:55). When the reaction instead was performed at ambient temperature for 8 h in the presence of a large excess of DBU (*ca.* 5 equiv, method B) the product ratio **4a**:**4b** became 70:30. The corresponding reaction of **3** with DBN (2 equiv) at 80−100 °C for 15 min produced a 1:1 mixture of **4a** and **4b**.

Scheme 1



In contrast to these results, the corresponding reaction of **3** with KO-*t*-Bu in *t*-BuOH solvent at 25 °C for 6 h proceeded as expected, with exclusive elimination of HCl to afford **4a** as the sole reaction product in 85% yield. Ozonolysis of **4a** thereby obtained afforded *N*-(ethoxy-

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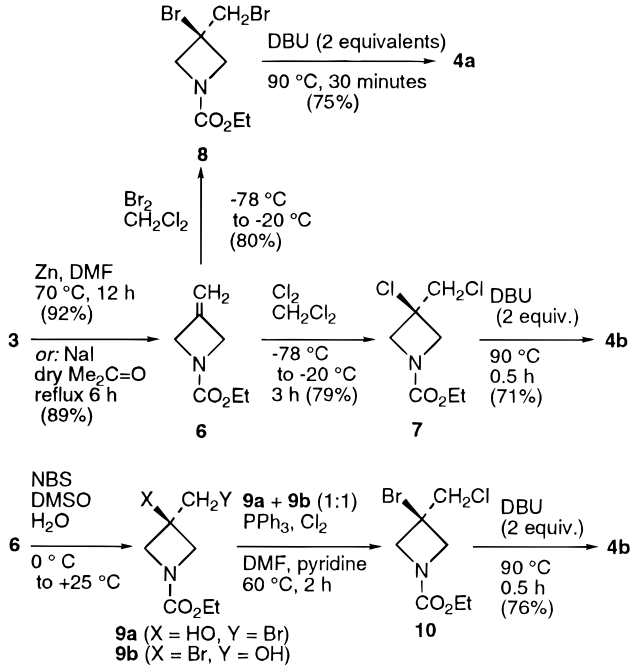
Scheme 2



carbonyl)azetidin-3-one (**5**, Scheme 1). Subsequent Wittig reaction of **5** with $Ph_3P{=}CHX$ (X = Br or Cl) afforded **4a** (46%) and **4b** (30%), thereby providing independent verification of the assigned structures of **4a** and **4b**.

Whereas DBU-promoted elimination of HCl from **3** to afford **4a** certainly had been expected, the fact that this occurred concomitant with the formation of **4b** was indeed surprising. Accordingly, a study was undertaken in an effort to determine the detailed mechanism of formation of **4b** in this reaction.

First, we sought to prepare samples of pure **4a** and pure **4b**; this was accomplished by using the procedures shown in Scheme 2. Thus, thermal reaction of **3** with either (i) Zn−DMF at 70 °C for 12 h or (ii) NaI−dry acetone at reflux for 6 h afforded *N*-(ethoxycarbonyl)-3-methyleneazetidine (**6**) in excellent yield (89−92%). Subsequent reaction of **6** with Cl_2 and with Br_2 produced **7** and **8**, respectively. DBU-promoted elimination of HCl from **7** afforded **4b**, while the corresponding DBU-promoted elimination of HBr from **8** produced **4a** (Scheme 2).

Next, it was of interest to prepare *N*-(ethoxycarbonyl)-3-bromo-3-(chloromethyl)azetidine (**10**) in order to study DBU-promoted elimination in this system (which is isomeric with **3**). This was done by using the method shown in Scheme 2. Thus, reaction of **6** with *N*-bromosuccinimide (NBS) in aqeuous dimethyl sulfoxide (DMSO) afforded an inseparable 1:1 mixture of two isomeric halo alcohols, **9a** and **9b**. This product mixture was characterized spectrally (^1H and ^{13}C NMR) and then used as obtained in the next synthetic step (*vide infra*).

Subsequent reaction of the mixture of **9a** and **9b** thereby obtained with Ph_3PCl_2[8] in DMF−pyridine mixed solvent produced **10** in 80% isolated yield (Scheme 2). In our hands, thermal reaction of **10** with DBU resulted exclusively in elmination of HBr, thereby affording **4b** as the sole reaction product (Scheme 2). The behavior of **10** toward DBU thus contrasts with the corresponding behavior of **3**, since it was noted above (Scheme 1) that

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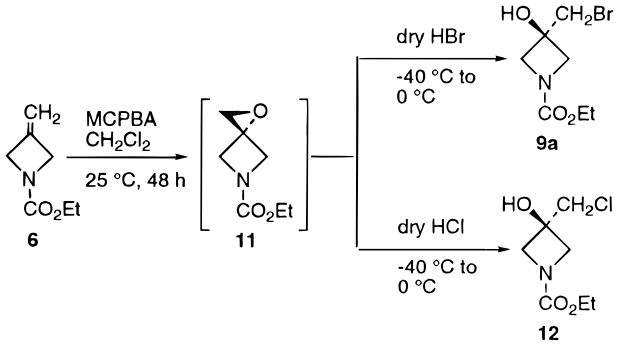
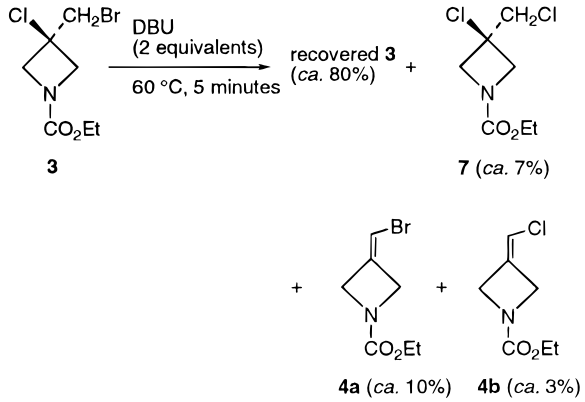
Scheme 3



Scheme 4



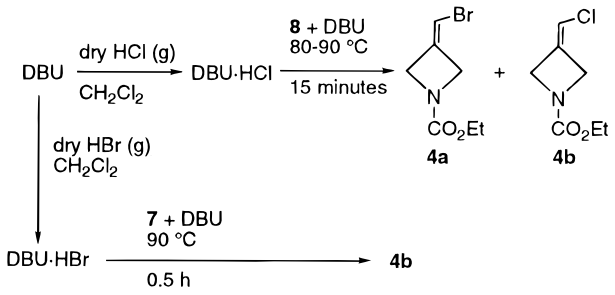
DBU reacts with **3** under comparable conditions with concomitant elimination of both HCl and HBr to produce a mixture of **4a** and **4b**.

The reaction sequence depicted in Scheme 3 was employed to further characterize the mixture of halo alcohols **9a** and **9b** obtained via reaction of **6** with NBS−DMSO. Comparison of the ^1H and ^{13}C NMR spectra of **9a**, produced via the method shown in Scheme 3, with the corresponding spectra obtained for the mixture of **9a** and **9b** obtained previously permitted specific resonance signals in NMR spectra of the isomeric mixture to be assigned to the individual isomers, **9a** and **9b**.

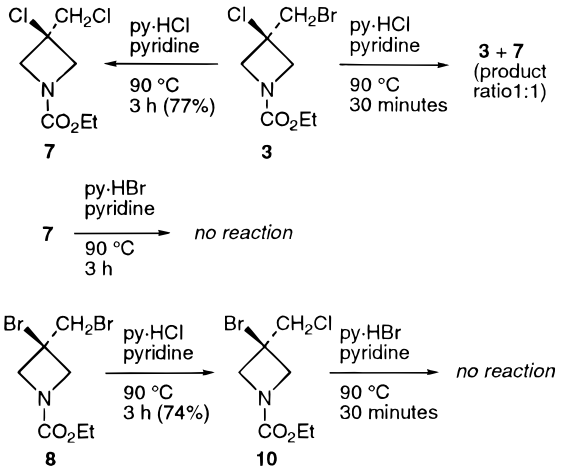
Control Experiments. 1. Short Reaction Time. In an effort to detect the presence of potentially isolable intermediates in the reaction of DBU with **3**, control reactions were run at short reaction time (i.e., 5 min). Under the conditions shown in Scheme 4 (method C), several compounds could be detected and identified via careful analysis of the ^1H and ^{13}C NMR spectra of the mixture of products thereby obtained. The presence of **7** among the products of this reaction suggested that nucleophilic displacement of bromine in **3** by Cl^- occurs concomitant with DBU-promoted elimination of HBr in **3** (it is this latter process that leads to the formation of **4a**, another reaction product). Importantly, no trace of **8**, which might have been formed by nucleophilic displacement of chlorine by Br^- in **3**, was observed in the control reaction shown in Scheme 4.

2. Effect of Added Solvent. The DBU-promoted elimination reactions described above were performed in the absence of added solvent. In an effort to determine if solvent might play a role in this reaction, a control study was undertaken in which a benzene solution of **3** (1 equiv) and DBU (2 equiv) was refluxed for 30 h (method D). Under these conditions, an inseparable 1:1 mixture of **4a** and **4b** was obtained, as determined by

Scheme 5



Scheme 6



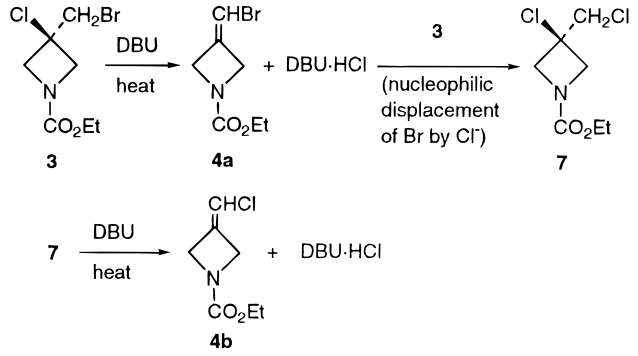
integration of the ^{1}H NMR spectrum of the reaction product after purification by column chromatography (see Experimental Section). When this same reaction was performed by refluxing for 18 h (instead of 30 h), a mixture of **4a**, **4b**, and **7** (product ratio 4:4:1) was obtained (method E).

3. Effect of Added Nucleophiles. The fact that **7** is formed in the control study shown in Scheme 4 provides a possible explanation for our prior observation that DBU reacts with **3** to afford both **4a** and **4b** (Scheme 1). Thus, while **3** reacts directly with DBU to form **4a** (via elimination of HCl), competitive reaction of Cl^- with **3** affords **7**, which subsequently undergoes DBU-promoted elimination of HCl to afford the other observed elimination product, **4b**. In order to test this hypothesis, we sought reaction conditions to promote nucleophilic displacement(s) in **3** both with and without concomitant elimination.

The experimental conditions shown in Scheme 5 [i.e., reactions of DBU·HX (X = Cl or Br) in the presence of excess DBU with **7** and **8**] provide both a source of nucleophile ($X:^-$) and a base that is capable of promoting elimination of HX in the substrates. The results shown in Scheme 5 clearly indicate that Cl^- is capable of displacing bromine in the CH_2Br group in **8**, whereas Br^- is incapable of displacing chlorine in the CH_2Cl group in **7**. This result is consistent with the corresponding results of the control experiment shown in Scheme 4 and also with the fact that **8** was not found among the products of the reaction shown in Scheme 4.

By way of contrast, the experimental conditions shown in Scheme 6 [i.e., reactions of pyridine·HX (X = Cl or Br) in the presence of excess pyridine with **3** and **10**] provide a source of nucleophile ($X:^-$) in the presence of a base that is incapable of promoting elimination of HX in the substrates. The results shown in Scheme 6 again are consistent with those cited above, i.e., Cl^- is capable of displacing bromine in **3** but Br^- is incapable of displacing chlorine in **10**.

Scheme 7



Some Thoughts on the Mechanism of DBU-Promoted Elimination of HX from *N*-(Ethoxycarbonyl)-3-halo-3-(halomethyl)azetidines. A plausible mechanism that is consistent with all of the experimental results cited above is shown in Scheme 7. Importantly, this mechanism accounts for the following facts: (i) reaction of DBU with **3** affords both **4a** and **4b**; (ii) Cl^- is capable of promoting nucleophilic displacement of bromine in the CH_2Br groups of both **3** and **8** but Br^- is incapable of displacing chlorine in the CH_2Cl groups of both **7** and **10**. The observations reported herein can be explained without invoking the intermediacy of any bridged halonium ion.

Experimental Section

Melting points are uncorrected. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ. High-resolution mass spectral data for **4a** were obtained at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin, by using a ZAB-E double-sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. High-resolution electron impact mass spectral data for **4b** were obtained by personnel at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. Low-resolution mass spectra were obtained by using a Varian Saturn 3 ion trap GC/MS system that was operated at 70 eV.

***N*-(Ethoxycarbonyl)-3-(bromomethyl)-3-chloroazetidine (3).** Compound **2**, i.e., 3-(bromomethyl)-1-azabicyclo-[1.1.0]butane, was prepared by using a modification of a previously published procedure.[7a] Thus, a solution of NaOH (40 g, 1 mol) in water (200 mL) was placed in a 500 mL three-neck boiling flask. The reaction vessel was fitted with a pressure-equalized dropping funnel and a distillation condenser, and the reaction vessel was connected to a water aspirator. A solution of **1** (19.5 g, 50 mmol) in 1% aqueous $NaHCO_3$ (50 mL) was placed in the dropping funnel, and a vacuum was applied to the system via water aspirator. The contents of the reaction flask were heated to 80 °C, and the contents of the dropping funnel were added dropwise during 10 min. During this time, the distillate was collected in a receiving flask which was cooled externally to −78 °C via application of an external dry ice−acetone bath. The distillation was continued for 1.5 h after all of the aqueous $NaHCO_3$ solution had been added. The receiving flask was removed from the distillation apparatus and then was placed in an ice−water bath and allowed to warm gradually to 0 °C. The distillate was extracted with ether (2 × 100 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo* to a net volume of 60 mL.

The resulting ethereal solution was cooled to 0 °C via application of an external ice−water bath. Ethyl chlorofor-

mate (4.32 g, 40 mmol) was added dropwise, whereupon an exothermic reaction ensued. After all of the $ClCO_2Et$ had been added, the reaction mixture was stirred at 0−10 °C for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified via column chromatography on silica gel by eluting with 15% EtOAc−hexane. Pure *N*-(ethoxycarbonyl)-3-(bromomethyl)-3-chloroazetidine (**3**) (5.10 g, 40%) was thereby obtained as a colorless oil: bp 150 °C (2 mmHg); IR (film) 2980 (vs), 1710 (vs), 765 (vs), 660 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7.3 Hz, 3 H), 3.63−3.74 (m, 2 H), 3.90−4.29 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 38.7 (t), 60.2 (s), 61.4 (t), 62.3 (t), 156.0 (s); mass spectrum (70 eV) m/z (relative intensity) 222 (11.6), 221 (1.3), 220 (12.2), 150 (39.9), 148 (41.5), 97 (30.5), 69 (21.1), 68 (100.0), 56 (13.7), 54 (12.8), 42 (12.4), 41 (61.7), 40 (9.7), 39 (52.7). Anal. Calcd for $C_7H_{11}BrClNO_2$: C, 32.78; H, 4.32. Found: C, 32.80, 33.00; H, 4.50, 4.57.

DBU-Promoted Dehydrohalogenation of 3. Method A. To neat **3** (300 mg, 1.17 mmol) under argon was added dropwise DBU (456 mg, 3.0 mmol), and the resulting mixture was stirred at 80−100 °C during 0.5 h. A colorless precipitate formed during this period. The resulting suspension was extracted with Et_2O (2 × 50 mL), and the remaining solid residue was discarded. The combined ethereal extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. An inseparable mixture of **4a** and **4b** (45:55, as determined by careful integration of the product mixture) was thereby obtained as a colorless oil (150 mg): IR (film) 3086 (m), 2960 (vs), 1710 (vs), 835 (w), 723 (w), 690 (s), 763 cm^{-1} (vs); ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 3.92−4.15 (m, 2 H), 4.35−4.50 (m, 4 H), 5.88−6.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 56.2 (t), 56.7 (t), 57.1 (t), 58.5 (t), 61.1 (t), 98.5 (d), 110.8 (d), 131.2 (s), 134.3 (s), 156.5(s).

Method B. To neat **3** (300 mg, 1.17 mmol) under argon was added dropwise DBU (760 mg, 5.00 mmol), and the resulting mixture was stirred at ambient temperature during 8 h. A colorless precipitate formed during this period. Workup of the reaction mixture was performed by using the method described in method A (*vide supra*). An inseparable mixture of **4a** and **4b** (70:30, as determined by careful integration of the product mixture) was thereby obtained as a colorless oil (160 mg). The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained agreed with the corresponding spectra obtained in method A, above, for a mixture of **4a** and **4b**.

Method C. A mixture of **3** (256 mg, 1.0 mmol) and DBU (304 mg, 2.0 mmol) was heated with stirring at 60 °C for 5 min. The reaction was quenched by addition of ice (5 g), and the resulting aqueous suspension was extracted with Et_2O (2 × 50 mL). The combined ethereal extracts were washed sequentially with water (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc−hexane. Careful analysis and integration of the ^1H NMR spectrum of the material thereby obtained (170 mg) revealed that it consisted of an inseparable mixture of products as follows: recovered **3** (*ca*. 80%), **7** (*ca*. 7%), **4a** (*ca*. 10%), and **4b** (*ca*. 3%). The presence of a sharp singlet at δ 3.80 in the ^1H NMR spectrum and a methylene resonance at δ 49.7 in the corresponding ^{13}C NMR spectrum of the crude product is diagnostic of the presence of **7** (*vide infra*).

Method D. To a solution of **3** (300 mg, 1.17 mmol) in benzene (10 mL) under argon was added DBU (711 mg, 4.68 mmol), and the resulting mixture was refluxed for 30 h. The reaction mixture was allowed to cool to ambient temperature, and water (10 mL) then was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed sequentially with water (20 mL), 20% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. An inseparable mixture of **4a** and **4b** (product ratio **4a**:**4b** = 1:1 as determined by careful integration of the ^1H NMR spectrum of the product mixture) was thereby obtained as a colorless oil (200 mg). The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained agreed with the corresponding spectra obtained in method A, above, for a mixture of **4a** and **4b**.

Method E. To a solution of **3** (300 mg, 1.17 mmol) in benzene (10 mL) under argon was added DBU (711 mg, 4.68 mmol), and the resulting mixture was refluxed for 18 h. Workup of the reaction mixture was performed by using the method described in method D (*vide supra*). Analysis of the ^1H and ^{13}C NMR spectra of the residue thereby obtained (prior to chromatographic purification) indicated that the crude product consisted of three compounds, i.e., **4a**, **4b**, and **7** (product ratio **4a**:**4b**:**7** = 4:4:1 as determined by careful integration of the ^1H NMR spectrum of the product mixture). The presence of a sharp singlet at δ 3.80 in the ^1H NMR spectrum and a methylene resonance at δ 49.7 in the corresponding ^{13}C NMR spectrum of the crude product is diagnostic of the presence of **7** (*vide infra*).

DBN-Promoted Dehydrohalogenation of 3. To neat **3** (300 mg, 1.17 mmol) under argon was added dropwise DBN (290 mg, 2.34 mmol), and the resulting mixture was stirred at 90 °C during 15 min. The resulting suspension was allowed to cool gradually to room temperature. Water (30 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. An inseparable mixture of **4a** and **4b** (50:50, as determined by careful integration of the product mixture) was thereby obtained as a colorless oil (150 mg). The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained agreed with the corresponding spectra obtained previously for a mixture of **4a** and **4b** (*vide supra*).

Potassium *tert*-Butoxide Promoted Dehydrohalogenation of 3. To a solution of **3** (400 mg, 1.56 mmol) in *t*-BuOH (15 mL) under argon was added portionwise with stirring KO-*t*-Bu (2.1 g, 1.9 mmol), and the resulting mixture was stirred at ambient temperature for 8 h. The reaction mixture was extracted with Et_2O (2 × 50 mL), and the combined organic extracts were washed sequentially with water (2 × 25 mL) and brine (2 × 25 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. Pure **4a** (300 mg, 85%) was thereby obtained as a colorless oil: IR (film) 3086 (s), 2955 (vs), 1715 (vs), 767 (vs), 686 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 4.05 (q, J = 7.1 Hz, 2 H), 4.38 (d, J = 1.8 Hz, 4 H), 5.96−6.03 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 57.2 (t), 58.5 (t), 61.2 (t), 98.5 (d), 134.4 (s), 156.5 (s); mass spectrum (70 eV) m/z (relative intensity) 222 (42.6), 221 (14.5), 220 (47.3), 219 (11.7), 192 (21.0), 190 (21.5), 148 (20.7), 146 (22.7), 119 (23.4), 68 (93.5), 39 (100.0); HRMS calcd for $C_7H_{10}BrNO_2$ $[M_r + H]^+$ 219.9973, found (high-resolution chemical ionization mass spectrometry) $[M_r + H]^+$ 219.9976.

***N*-(Ethoxycarbonyl)azetidin-3-one (5).** A solution of **4a** (220 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C via application of an external dry ice−acetone bath. Ozone gas was passed through the solution until the presence of **4a** could no longer be detected by TLC analysis (*ca*. 3 h). Argon was bubbled through the reaction mixture to purge excess ozone, and the reaction was quenched via addition of $(CH_3)_2S$ (4 mL). The external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature. The reaction mixture was concentrated *in vacuo*, and the residue was purified via column chromatography on silica gel by eluting with 30% EtOAc−hexane. Pure **5** (100 mg, 70%) was thereby obtained as a colorless microcrystalline solid: mp 45−47 °C; IR (KBr) 2975 (vs), 1710 cm^{-1} (vs); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.68 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 61.8 (t), 71.1 (t), 156.6 (s), 195.9(s). Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34. Found: C, 50.60; H, 6.19.

Thermolysis of 3 (Control Experiment). Neat **3** (256 mg, 1 mmol) was heated under argon at 130−150 °C for 6 h. Thin-layer chromatographic and NMR spectral analyses of the

resulting material revealed that only unreacted starting material had been recovered.

***N*-(Ethoxycarbonyl)-3-(bromomethylene)azetidine (4a).** A solution of (bromomethyl)triphenylphosphonium bromide (1.31 g, 3.0 mmol) in dry THF (15 mL) was cooled to −78 °C via application of an external dry ice−acetone bath. A solution of lithium 2,2,6,6-tetramethylpiperidide (LiTMP, 3.0 mmol) in dry THF was prepared via dropwise addition of *n*-BuLi (1.3 mL of a 2.5 M solution in hexane, 3.2 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (423 mg, 3 mmol) in dry THF (10 mL) at 0 °C, and the resulting solution was added dropwise with stirring to the cold reaction mixture. After all of the base had been added, the resulting orange suspension was stirred at −78 °C for 1 h. A solution of **5** (215 mg, 1.5 mmol) in dry THF (5 mL) was added dropwise with stirring to the reaction mixture. After all of the azetidinone had been added, the external cold bath was removed, and the stirred reaction mixture was allowed to warm gradually to ambient temperature during 3 h and then stirred at that temperature for an additional 4 h. The resulting mixture was poured into saturated aqueous NH_4Cl (50 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (20 mL). The combined organic layer and Et_2O extract were washed sequentially with water (20 mL) and brine (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. Pure **4a** (150 mg, 46%) was thereby obtained as a colorless, viscous oil. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with the corresponding spectra obtained for **4a** which had been prepared previously via KO-*t*-Bu-promoted dehydrohalogenation of **3** (*vide supra*).

***N*-(Ethoxycarbonyl)-3-(chloromethylene)azetidine (4b).** A solution of (chloromethyl)triphenylphosphonium bromide (1.04 g, 3.0 mmol) in dry THF (15 mL) was cooled to −78 °C via application of an external dry ice−acetone bath. A solution of lithium 2,2,6,6-tetramethylpiperidide (LiTMP, 3.0 mmol) in dry THF was prepared via dropwise addition of *n*-BuLi (1.3 mL of a 2.5 M solution in hexane, 3.2 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (423 mg, 3 mmol) in dry THF (10 mL) at 0 °C, and the resulting solution was added dropwise with stirring to the cold reaction mixture. After all of the base had been added, the resulting orange suspension was stirred at −78 °C for 1 h. A solution of **5** (215 mg, 1.5 mmol) in dry THF (5 mL) was added dropwise with stirring to the reaction mixture. After all of the azetidinone had been added, the external cold bath was removed, and the stirred reaction mixture was allowed to warm gradually to ambient temperature during 3 h and then stirred at that temperature for an additional 6 h. Workup of the reaction mixture was performed as described previously for the corresponding synthesis of **4a** (*vide supra*). The crude product was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. Pure **4b** (72 mg, 30%) was thereby obtained as a colorless, viscous oil: IR (film) 3086 (s), 2955 (vs), 1710 (vs), 1130 (vs), 770 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 4.05 (q, J = 7.1 Hz, 2 H), 4.45 (d, J = 1.8 Hz, 4 H), 5.70−5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 56.3 (t), 56.8 (t), 61.2 (t), 110.9 (d), 131.3 (s), 156.6 (s); mass spectrum (70 eV) *m*/*z* (relative intensity) 177 (8.2), 176 (9.4), 175 (27.4), 148 (15.4), 146 (47.7), 102 (26.1), 77 (14.0), 75 (46.1), 68 (73.3), 56 (37.1), 41 (40.7), 39 (94.4), 28 (100.0); HRMS calcd for $C_7H_{10}ClNO_2$ M_r^+ 175.0400, found (high-resolution electron impact mass spectrometry) M_r^+ 175.0402. The ^{1}H and ^{13}C NMR spectral data of **4b** thereby obtained corresponded to one component of the mixture of **4a** and **4b** that previously had been obtained via DBU-promoted dehydrohalogenation of **3** at 80−100 °C (*vide supra*).

***N*-(Ethoxycarbonyl)-3-methyleneazetidine (6). Method A.** A mixture of **3** (600 mg, 2.3 mmol) and powdered Zn (1.6 g, 25 mmol) in dimethylformamide (DMF, 30 mL) was stirred at 70 °C for 12 h. The reaction mixture was allowed to cool gradually to ambient temperature, and Et_2O (200 mL) was added to the reaction mixture. The resulting mixture was washed sequentially with water (3 × 40 mL) and brine (2 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% Et_2O−pentane. Pure **6** (310 mg, 92%) was thereby obtained as a colorless, viscous oil: IR (film) 3092 (w), 2937 (s), 1713 (s), 1116 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3 H), 4.03 (q, J = 7.6 Hz, 2 H), 4.44 (t, J = 2.4 Hz, 4 H), 4.90−4.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 58.2 (t), 60.9 (t), 107.2 (t), 137.3 (s), 156.7 (s); mass spectrum (70 eV) *m*/*z* (relative intensity) 142 (100.0), 141 (25.9), 112 (33.1), 96 (13.7), 82 (21.7), 69 (12.8), 68 (66.3), 42 (11.9), 41 (18.3), 39 (64.0). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85. Found: C, 59.15; H, 7.59.

Method B. A mixture of **3** (600 mg, 2.3 mmol) and NaI (6.0 g, 40 mmol) in dry acetone (50 mL) was refluxed for 6 h. The reaction mixture was allowed to cool to ambient temperature, Et_2O (200 mL) was added, and the resulting mixture was washed sequentially with 20% aqueous $NaHSO_3$ (2 × 30 mL), water (3 × 40 mL), and brine (2 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by eluting with 20% Et_2O−pentane. Pure **6** (293 mg, 89%) was thereby obtained as a colorless, viscous oil whose IR, ^{1}H NMR, and ^{13}C NMR spectra were identical to the corresponding spectra obtained for authentic **6** which had been prepared previously via method A (*vide supra*).

***N*-(Ethoxycarbonyl)-3-chloro-3-(chloromethyl)azetidine (7).** A solution of **6** (200 mg, 1.42 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C via application of an external dry ice−acetone bath. Chlorine gas was bubbled through the cold reaction mixture until the greenish-yellow color of Cl_2 persisted. The external dry ice−acetone bath was replaced with a dry ice−CCl_4 cold bath, and the reaction mixture was allowed to warm gradually to −20 °C with stirring and then was stirred at −20 °C for 3 h. The reaction then was quenched by pouring into a mixture of ice (100 g) and 20% aqueous $NaHSO_3$ (40 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer and CH_2Cl_2 extracts were washed successively with water (30 mL), 10% aqueous $NaHCO_3$ (2 × 30 mL), water (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc−hexane. Pure **7** (240 mg, 79%) was thereby obtained as a colorless oil: IR (film) 2968 (s), 1707 (s), 766 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3 H), 3.83 (s, 2 H), 4.02−4.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 49.7 (t), 60.3 (t), 61.3 (t), 61.4 (s), 156.2 (s); mass spectrum (70 eV) *m*/*z* (relative intensity) 214 (3.5), 212 (5.0), 178 (23.3), 176 (71.7), 106 (19.1), 104 (59.7), 96 (26.6), 77 (12.8), 75 (41.7), 69 (16.2), 68 (100.0), 56 (27.6), 49 (16.1), 42 (36.3), 41 (22.9), 39 (53.3). Anal. Calcd for $C_7H_{11}Cl_2NO_2$: C, 39.64; H, 5.23. Found: C, 39.35; H, 5.21.

DBU-Promoted Dehydrohalogenation of 7. A mixture of **7** (150 mg, 0.71 mmol) and DBU (230 mg, 1.5 mmol) was heated at 90 °C for 30 min. The reaction mixture was allowed to cool gradually to ambient temperature. Diethyl ether (100 mL) was added, and the resulting mixture was washed with water (2 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% Et_2O−pentane. Pure **4b** (80 mg, 71%) was thereby obtained as a viscous, colorless oil. The IR, ^{1}H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with that of **4b** which had been prepared previously via Wittig reaction of **5** with $Ph_3P{=}CHCl$ (*vide supra*).

***N*-(Ethoxycarbonyl)-3-bromo-3-(bromomethyl)azetidine (8).** A solution of **6** (150 mg, 1.06 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C via application of an external dry ice−acetone bath. To this cooled solution was added dropwise with stirring Br_2 (320 mg, 2.0 mmol). The external dry ice−acetone bath was replaced with a dry ice−CCl_4 cold bath, and the reaction mixture was allowed to warm gradually to −20 °C with stirring and then was stirred at −20 °C for 3 h. The

reaction mixture then was poured into a mixture of ice (100 g) and 20% aqueous $NaHSO_3$ (40 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed sequentially with water (30 mL), $NaHCO_3$ (2 × 30 mL), water (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc−hexane. Pure **8** (250 mg, 80%) was thereby obtained as a colorless oil: IR (film) 2951 (s), 1712 (s), 773 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 3.84 (s, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 4.32−4.49 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 39.3 (t), 50.7 (s), 61.5 (t), 63.2 (t), 156.1 (s); mass spectrum (70 eV) *m/z* (relative intensity) 302 (1.6), 222 (35.4), 220 (36.7), 150 (35.9), 148 (36.9), 121 (16.1), 119 (17.6), 97 (26.3), 82 (27.5), 69 (100.0), 56 (20.7), 39 (73.0). Anal. Calcd for $C_7H_{11}Br_2NO_2$: C, 27.93; H, 3.68. Found: C, 28.12; H, 3.51.

DBU-Promoted Dehydrohalogenation of 8. A mixture of **8** (200 mg, 0.67 mmol) and DBU (202 mg, 1.33 mmol) was heated at 90 °C for 30 min. The reaction mixture was allowed to cool gradually to ambient temperature. Diethyl ether (100 mL) was added, and the resulting mixture was washed sequentially with water (2 × 30 mL) and brine (20 mL). The organic organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% Et_2O−pentane. Pure **4a** (110 mg, 75%) was thereby obtained as a viscous, colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with that of **4a** which had been prepared previously via Wittig reaction of **5** with $Ph_3P{=}CHBr$ (*vide supra*).

Reaction of *N*-(Ethoxycarbonyl)-3-methyleneazetidine with *N*-Bromosuccinimide in Aqueous DMSO. A solution of **6** (700 mg, 5.0 mmol) in DMSO (60 mL) under argon was cooled to 0 °C via application of an external ice−water bath. To this cooled solution under argon were added sequentially with stirring water (180 mg, 10 mmol) and *N*-bromosuccinimide (NBS, 1.78 g, 10 mmol). After the addition of reagents had been completed, the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature during 2 h and then stirred at that temperature for an additional 1 h. A solution of EtOAc (100 mL) in Et_2O (150 mL) was added to the reaction mixture, and the resulting mixture was washed sequentially with water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 40% EtOAc−hexane. An inseparable mixture of **9a** and **9b** (900 mg, 76%, ratio **9a**:**9b** = 50:50, as determined by careful integration of the ^1H NMR spectrum of the product mixture) was thereby obtained as a colorless oil: IR (neat) 3390 (br, s), 2966 (s), 1700 (vs), 904 (m), 769 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.14−1.26 (m, 6 H), 3.62 (s, 2 H), 3.83 (s, 2 H), 3.88−3.93 (m, 5 H), 3.98−4.12 (m, 4 H), 4.21−4.42 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 14.5 (q), 39.9 (t), 54.0 (s), 60.2 (2 C, t), 61.4 (2 C, t), 61.5 (2 C, t), 67.9 (t), 69.3 (s), 156.6 (s), 156.9 (s). Anal. Calcd for $C_7H_{12}BrNO_3$: C, 35.31; H, 5.08. Found: C, 35.12; H, 5.27. This mixture of **9a** and **9b** was used as obtained in the next synthetic step without further purification or characterization (*vide infra*).

***N*-(Ethoxycarbonyl)-3-bromo-3-(chloromethyl)azetidine (10).** To a 1:1 mixture of **9a** and **9b** (900 mg, 3.8 mmol) in DMF (20 mL) under argon was added pyridine (0.4 mL, 5 mmol). To the resulting solution under argon was added with stirring a solution of freshly prepared Ph_3PCl_2[8] (1.33 g, 4.0 mmol) in DMF (10 mL), and the resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature, and Et_2O (100 mL) was added. The resulting ethereal solution was washed sequentially with water (30 mL) and brine (2 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc−hexane. Pure **10** (390 mg, 80%) was thereby obtained as a colorless oil: IR (neat) 2988 (vs), 1715 (vs), 1445 (vs), 781 (vs), 714 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 3.89 (s, 2 H), 3.99−4.12 (m, 2 H), 4.35 (dd, J = 10.1, 13.5 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 50.3 (t), 51.0 (s), 61.3 (t), 62.1 (t), 156.0 (s). Anal. Calcd for $C_7H_{11}BrClNO_2$: C, 32.78; H, 4.32. Found: C, 32.90; H, 4.55.

***N*-(Ethoxycarbonyl)-3-(bromomethyl)azetidin-3-ol (9a).** A solution of **6** (700 mg, 5.0 mmol) and MCPBA (1.54 g, 9.0 mmol) in CH_2Cl_2 (70 mL) under argon was stirred at ambient temperature for 2 days. The resulting mixture was cooled to −40 °C by application of an external dry ice−CH_3CN cold bath, and dry HBr (g) was bubbled through the cold reaction mixture for 10 min. The external cold bath was replaced by an external ice−water bath, and the reaction mixture was allowed to warm gradually to 0 °C during 1 h. Dichloromethane (100 mL) was added to the reaction mixture, and the resulting solution was washed successively with 10% aqueous $NaHCO_3$ (2 × 20 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by eluting with 40% EtOAc−hexane. Pure **9a** (650 mg, 55%) was thereby obtained as a colorless oil: IR (film) 3385 (br, s), 2970 (s), 1700 (vs), 855 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 3.62 (s, 2 H), 3.91 (s, 4 H), 4.02−4.15 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.6 (q), 40.2 (t), 60.2 (t), 61.4 (t), 69.3 (s), 156.8 (s). Anal. Calcd for $C_7H_{12}O_3BrN$: C, 35.31; H, 5.08. Found: C, 35.53; H, 5.11.

***N*-(Ethoxycarbonyl)-3-(chloromethyl)azetidin-3-ol (12). Method A.** A solution of **6** (600 mg, 4.26 mmol) and MCPBA (1.30 g, 6.24 mmol) in CH_2Cl_2 (70 mL) under argon was stirred at ambient temperature for 2 days. The resulting mixture was cooled to −40 °C via application of an external dry ice−CH_3CN cold bath, and dry HCl(g) was bubbled through the cold reaction mixture for 10−15 min. The external cold bath was replaced by an external ice−water bath, and the reaction mixture was allowed to warm gradually to 0 °C during 1 h. Dichloromethane (100 mL) was added to the reaction mixture, and the resulting solution was washed successively with 10% aqueous $NaHCO_3$ (2 × 20 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by eluting with 40% EtOAc−hexane. Pure **12** (467 mg, 57%) was thereby obtained as a colorless oil: IR (film) 3387 (br, s), 2975 (s), 1700 (vs), 1445 (s), 775 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 3.69 (s, 2 H), 3.83−4.12 (m, 6 H), 4.48 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 50.0 (t), 59.7 (t), 61.4 (t), 69.6 (s), 156.9 (s). Anal. Calcd for $C_7H_{12}O_3ClN$: C, 43.42; H, 6.25. Found: C, 43.18; H, 6.22.

Method B. A solution of **6** (550 mg, 3.9 mmol) and MCPBA (1.20 g, 5.7 mmol) in CH_2Cl_2 (70 mL) under argon was stirred at ambient temperature for 2 days. Dichloromethane (100 mL) was added to the reaction mixture, and the resulting solution was washed successively with 10% aqueous $NaHCO_3$ (2 × 20 mL), water (20 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo* to a total volume of 40 mL. The concentrated solution was cooled to 0 °C by application of an external ice−water bath. To this cooled solution was added dropwise with stirring a solution of freshly prepared Ph_3PCl_2[8] (1.3 g, 4.0 mmol) in CH_2Cl_2 (30 mL). The external ice−water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature during 2 h. The reaction mixture then was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel by eluting with 40% EtOAc−hexane. Pure **12** (330 mg, 44%) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical to the corresponding spectra obtained for authentic **12** that had been prepared previously via method A, above.

DBU-Promoted Dehydrohalogenation of 10. A mixture of **10** (100 mg, 0.39 mmol) and DBU (120 mg, 0.78 mmol) was heated at 90 °C for 30 min. The reaction mixture was allowed to cool gradually to ambient temperature. Diethyl ether (100 mL) was added, and the resulting mixture was washed sequentially with water (2 × 30 mL) and brine (20 mL). The organic organic layer was dried ($MgSO_4$) and filtered, and the

filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% Et_2O−pentane. Pure **4b** (48 mg, 76%) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with the corresponding spectra obtained previously for **4b**.

Effect of Added Br^- on the Course of the Reaction of DBU with 7. A solution of DBU (395 mg, 2.6 mmol) in Et_2O (30 mL) was cooled to 0 °C via application of an external ice−water bath. Dry HBr gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and DBU (395 mg, 2.6 mmol) was added under argon to the residue. Compound **7** (275 mg, 1.3 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 30 min. The reaction mixture was allowed to cool gradually to ambient temperature. Water (10 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. Pure **4b** (140 mg, 68%) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with the corresponding spectra obtained previously for **4b**.

Effect of Added Cl^- on the Course of the Reaction of DBU with 8. A solution of DBU (395 mg, 2.6 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C via application of an external ice−water bath. Dry HCl gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and DBU (395 mg, 2.6 mmol) was added under argon to the residue. Compound **8** (400 mg, 1.33 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 30 min. The reaction mixture was allowed to cool gradually to ambient temperature. Water (50 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 30% Et_2O−pentane. An inseparable mixture of **4a** and **4b** (200 mg, 74%, ratio **4a**:**4b** = 80:20, as determined by careful integration of the ^1H NMR spectrum of the product mixture) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with the corresponding spectra obtained previously for **4a** and **4b**.

Reaction of 3 with Pyridine Hydrochloride. Method A. Short Reaction Time (30 min). A solution of pyridine (160 mg, 2.0 mmol) in Et_2O (30 mL) under argon was cooled to 0 °C via application of an external ice−water bath. Dry HCl gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and pyridine (160 mg, 2.0 mmol) was added under argon to the residue. Compound **3** (256 mg, 1.0 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 30 min. The reaction mixture was allowed to cool to ambient temperature. Water (10 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc−hexane. An inseparable mixture of **3** and **7** (220 mg, 92%, ratio **3**:**7** = 50:50, as determined by careful integration of the ^1H NMR spectrum of the product mixture) was thereby obtained as a colorless oil. Absorbances in the IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained could be accounted for via comparison with the corresponding spectra obtained previously for **3** and **7**.

Reaction of 3 with Pyridine Hydrochloride. Method B. Longer Reaction Time (3 h). A solution of pyridine (160 mg, 2.0 mmol) in Et_2O (30 mL) under argon was cooled to 0 °C via application of an external ice−water bath. Dry HCl gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and pyridine (160 mg, 2.0 mmol) was added under argon to the residue. Compound **3** (256 mg, 1.0 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 3 h. The reaction mixture was allowed to cool to ambient temperature. Water (10 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc−hexane. Pure **7** (163 mg, 77%) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with the corresponding spectra obtained previously for **7**.

Reaction of 8 with Pyridine Hydrochloride. A solution of pyridine (160 mg, 2.0 mmol) in Et_2O (30 mL) under argon was cooled to 0 °C via application of an external ice−water bath. Dry HCl gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and pyridine (160 mg, 2.0 mmol) was added under argon to the residue. Compound **8** (300 mg, 1.0 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 3 h. The reaction mixture was allowed to cool to ambient temperature. Water (10 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc−hexane. Pure **10** (190 mg, 74%) was thereby obtained as a colorless oil. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained are identical in all respects with the corresponding spectra obtained previously for **10**.

Reaction of 7 with Pyridine Hydrobromide. A solution of pyridine (160 mg, 2.0 mmol) in Et_2O (30 mL) under argon was cooled to 0 °C via application of an external ice−water bath. Dry HBr gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and pyridine (160 mg, 2.0 mmol) was added under argon to the residue. Compound **7** (212 mg, 1.0 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 3 h. The reaction mixture was allowed to cool to ambient temperature. Water (10 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra of the starting material (i.e., **7**, 180 mg, 85% recovery).

Reaction of 10 with Pyridine Hydrobromide. A solution of pyridine (160 mg, 2.0 mmol) in Et_2O (15 mL) under argon was cooled to 0 °C via application of an external ice−water bath. Dry HBr gas was bubbled through the cooled solution for 10 min. The reaction mixture was concentrated *in vacuo*, the reaction vessel was purged with argon, and pyridine (160 mg, 2.0 mmol) was added under argon to the residue. Compound **10** (256 mg, 1.0 mmol) then was added, and the resulting suspension was heated under argon at 90 °C for 30 min. The reaction mixture was allowed to cool to ambient temperature. Water (10 mL) was added, and the resulting aqueous suspension was extracted with Et_2O (2 × 30 mL). The organic layer was washed sequentially with water (20 mL), 10% aqueous $NaHCO_3$ (30 mL), and brine (30

mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The IR, ^1H NMR, and ^{13}C NMR spectra of the material thereby obtained were essentially identical with the corresponding spectra of the starting material (i.e., **10**, 240 mg, 94% recovery).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **4a** and **4b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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