Chemical Transformation of Protoberberines. IV.\textsuperscript{1)} A Novel, Simple Synthesis of (±)-Canadaline and a Retroprotoberberine from Tetrahydroberberine\textsuperscript{2)}

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Heating of tetrahydroberberine (I) in ethyl chloroformate preferentially afforded the C\(_8\)-N bond cleavage (4) with small amounts of the C\(_8\)-N and C\(_{14}\)-N bond cleavage products (5 and 6, respectively). The urethane (4) was effectively converted to (±)-canadaline (2), a secobarbiral alkaid, and a retroprotoberberine (3).

Keywords—ethyl chloroformate; regioselective C–N bond cleavage; biomimetic conversion; protoberberine alkaloid; secobarbinal alkaloid; retroprotoberberine alkaloid; tetrahydroberberine; canadaline

Regioselective C\(_8\)-N bond cleavage of protoberberine alkaloids might be a key step for their transformation to related alkaloids such as secobarbinal, retroprotoberberine, phthalideisoquinoline, spirobenzylisoquinoline, benzindenoazepine, and rhoeadine alkaloids (Chart 1).\textsuperscript{3)} Although several methods for C\(_8\)-N and C\(_{14}\)-N bond cleavage of tetrahydroprotober-berines have so far been reported,\textsuperscript{4)} little is known concerning general and selective C\(_8\)-N bond cleavage, except for some special examples.\textsuperscript{5)} In this paper we describe an efficient C\(_8\)-N bond cleavage of tetrahydroberberine (I) using ethyl chloroformate and its application to a simple, novel synthesis of (±)-canadaline (2) and a retroprotoberberine (3).

![Diagram](chart.png)

Chart 1\textsuperscript{3)}
Knabe et al. have extensively studied C–N bond cleavage reactions of tertiary amines and alkaloids with ethyl chloroformate and found that tetrahydroberberine was inert to this reagent under Schotten–Baumann-like conditions.\(^5\) We therefore investigated the reaction of 1 with ethyl chloroformate under different conditions.

On treatment with excess ethyl chloroformate in benzene or toluene, tetrahydroberberine (1) was recovered unchanged. However, heating of 1 in ethyl chloroformate at 85°C for 9 h without solvent afforded three products, 4, 5, and 6 in 41 (59),\(^7\) 10 (14), and 8.5% (12%) yields, respectively, in addition to the starting material 1 (29.5%), after careful chromatographic separation on silica gel.\(^8\) The structures of these products were elucidated by analysis of their spectral data (see Experimental). The C\(_8\)-N bond cleavage product 4, \(m/e: 449, 447\) (M\(^+\), 1 : 3), showed a rather complicated proton nuclear magnetic resonance (PMR) spectrum at 25°C due to slow interconversion of urethane rotamers, whereas the regiosomeric C\(_8\)-N bond cleavage product 5, \(m/e: 449, 447\) (M\(^+\), 1 : 3), showed a sharp PMR spectrum. The structure of 4 was further confirmed by its conversion to the amine 7 (97% yield) by lithium aluminum hydride reduction. The PMR spectrum of 7 exhibited two singlets at 2.46 and 2.02 ppm due to the N- and C-methyls, respectively. The third product 6 was derived through C\(_{14}\)-N bond cleavage followed by elimination of hydrogen chloride. E-Configuration of 6 was established from the 200 MHz PMR spectrum, which showed the olefinic proton signals as an AB-quartet (\(J = 16.5\) Hz) at 6.66 and 6.63 ppm, though they appeared as a singlet at 100 MHz. This stereochemistry was further supported by photochemical isomerization\(^9\) of 6 to the Z-isomer (8), the PMR spectrum of which exhibited an AB-quartet (\(J = 12\) Hz) at 6.73 and 6.71 ppm due to the cis olefinic protons.

Thus, the C\(_8\)-N bond cleavage product (4) was obtained readily and directly from tetrahydroberberine (1). Next, we investigated a synthesis of (±)-canadamine and a retroprotoberberine starting from 4.

Canadamine,\(^10\) isolated from *Hydrastis canadensis* L. is a representative secoberberine alkaloid\(^11\) and its racemate has been synthesized\(^11\) from 8-benzyltetrahydroberberine via the Hofmann degradation.\(^5\)

Treatment of 4 with silver nitrate in aqueous acetone at room temperature gave the alcohol (9) in 66% yield. Alternatively, the same product 9 was readily obtained in 92% yield, upon stirring of 4 with alumina in dichloromethane at room temperature. More conveniently, 9 was directly synthesized from 1, namely, the crude products derived from 1 with ethyl chloroformate were chromatographed on alumina to give 9 in 46% (64.5%)\(^7\) yield along with 5, 6, and 1 in 9 (13), 11 (15.5), and 28.5% yields, respectively. Reduction of 9 with lithium aluminum hydride in ether afforded the N-methyl alcohol (11), mp 107—108°C, \(m/e: 371\) (M\(^+\)), in 80% yield. It was also derived in 31% yield from 4 via 10 on treatment with sodium acetate in acetic acid followed by lithium aluminum hydride. Oxidation of 11 with pyridinium chlorochromate\(^12\) in dichloromethane in the presence of sodium acetate provided (±)-canadamine (2), mp 143—143.5°C (lit.\(^11\) mp 139—140°C), in 68% yield. The synthetic (±)-canadamine was shown to be identical with natural canadamine in PMR spectral comparison. Independently, Rönsch has recently synthesized (±)-canadamine via a reaction sequence
similar to ours using ethyl chloroformate–sodium iodide in a key step.\textsuperscript{13)}

On the other hand, retroprotoberine alkaloids,\textsuperscript{14,15} e.g., mecambridine (13) and orientalidine (14), characterized by the presence of one extra carbon on ring D, have been proposed to be biosynthesized from the corresponding protoberberine (15) through C\textsubscript{8}–N bond cleavage.\textsuperscript{5b,16} Therefore, the extra carbon should originate from C\textsubscript{8} of the precursor protoberberine. On this biogenetic assumption, we tried to convert 1 to the retroprotoberine (3).

Hydrolysis of the urethane (9) with potassium hydroxide in aqueous ethanol in a sealed tube at 140—145°C afforded the amino-alcohol (12), mp 157—158°C, in 67% yield accompanied with the starting material 9 (22% yield). The Mannich reaction of 12 with 37% aqueous formaldehyde in acetic acid furnished the retroprotoberberine (3), mp 195—196°C, m/e: 369 (M\textsuperscript{+}), in 90% yield. This simple biogenetic-type conversion of tetrahydroberberine to 3 represents a new general method for the synthesis of the retroprotoberberine alkaloids.

The present efficient C\textsubscript{8}–N bond cleavage reaction using ethyl chloroformate seems promising for the transformation of protoberberine alkaloids to the related alkaloids shown
in Chart 1. Studies on the scope and limitations of this reaction are in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. All organic extracts were dried over anhydrous Na₂SO₄. Column chromatography was carried out with silica gel (Kieselgel 60, 70–230 or 230–400 mesh, Merck) and alumina (Aluminaoxid 90, Aktivitätstufe II-III, 70–230 mesh, Merck). Preparative thin-layer chromatography (PTLC) was performed on alumina (Aluminaoxid GF₂₅₄ Typ 60/E, Merck). Infrared (IR) spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 mass spectrometer, ultraviolet (UV) spectra with a Hitachi 323 spectrometer, and PMR spectra with JEOL FX-100 and Varian XL-200 spectrometers in CDCl₃ using tetramethylsilane as an internal standard at 25°C unless otherwise stated.

Reaction of Tetrahydroberberine (1) with Ethyl Chloroformate—A solution of tetrahydroberberine (1, 594 mg) in ethyl chloroformate (50 ml) was heated at 85°C for 9 h with stirring. The excess ethyl chloroformate was removed in vacuo and the residue was taken up in CHCl₃. The organic layer was washed with aqueous K₂CO₃ and brine, dried, and concentrated in vacuo to leave an oily residue, which was chromatographed on SiO₂ with CH₂Cl₂. The first fraction afforded ethyl 3-[(2-chloroethyl)-4,5-methylenedioxyphenyl]-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline-2-carboxylate [5, 78.6 mg, 10% (14% based on the consumed starting material)] as a pale brown oil. IR ν_max cm⁻¹: 1680 (CO). MS m/e: 449 (M⁺, 1:3), 164 (base peak). High resolution MS m/e: Caled for C₂₃H₂₆ClNO₄: 449.142, 447.145. Found: 449.146, 447.146. PMR δ: 6.83, 6.82 (2H, AB q, J = 8.5 Hz, C₆₋ and C₇₋), 6.66, 6.48 (each 1H, s, C₈₋ and C₉₋), 5.85 (2H, s, OCH₂O), 5.39 (1H, t, J = 5 Hz, C₁₋), 5.09, 4.18 (2H, AB q, J = 17 Hz, C₁₋), 4.13 (2H, q, J = 7 Hz, OCH₂CH₃), 3.86 (6H, s, OCH₃ x 2), 3.68 (2H, t, J = 7 Hz, CH₂Cl), 3.20, 2.84 (2H, AB q, J = 16; 5 Hz, C₇₋), 3.11 (2H, t, J = 7 Hz, CH₂CH₂Cl), 1.22 (3H, t, J = 7 Hz, OCH₂CH₃). The second fraction afforded ethyl 1-[(2-chloromethyl)-4,5-methylenedioxyphenyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-2-carboxylate [3, 424.4 mg, 41% (59% based on consumed starting material)] as a pale brown oil. IR ν_max cm⁻¹: 1680 (CO). MS m/e: 449, 447 (M⁺, 1:3), 248 (base peak). High resolution MS m/e: Caled for C₂₃H₂₆ClNO₄: 447.145. Found: 447.144, 447.146. PMR δ: 6.78 (2H, t-like, C₆₋ and C₇₋), 6.60 (1H, s, C₈₋), 6.41, 5.95 (1H, each s, C₉₋ and C₁₀₋), 5.89 (2H, br s, OCH₂O), ca. 5.2 (1H, m, C₁₋), 4.8–4.6 (2H, CH₂Cl), 4.2–4.0 (2H, OCH₂CH₃), 3.93, 3.90 (3H, each s, OCH₃), 3.84 (3H, s, OCH₃), 1.26, 1.05 (3H, each t, J = 7 Hz, OCH₃CH₂), δ (80°C): 6.76, 6.72 (2H, AB q, J = 8 Hz, C₆₋ and C₇₋), 6.57 (1H, s, C₈₋), 6.20 (1H, br s, C₉₋), 5.85 (2H, s, OCH₂O), 5.20 (1H, t, J = 7 Hz, C₁₀₋), 4.8–4.4 (2H, CH₂Cl), 4.2–4.0 (2H, OCH₂CH₃), 3.90, 3.83 (each 3H, s, OCH₃ x 2), 1.14 (3H, t, J = 7 Hz, OCH₂CH₃). The third fraction afforded ethyl (E)-5,6,7,8-tetrahydro-3,4-dimethoxy-10,11-methylenedioxybenzo[c]glaucicene-6-carboxylate [5, 61.4 mg, 8.5% (12% based on consumed starting material)] as colorless crystals. Recrystallization from MeOH afforded colorless needles, mp 186–187°C. IR ν_max cm⁻¹: 1685 (CO). MS m/e: 411 (M⁺, base peak). PMR δ: 6.99, 6.87 (2H, AB q, J = 8.5 Hz, C₁₋ and C₂₋), 6.75, 6.67 (each 1H, s, C₈₋ and C₁₀₋), 6.65 (2H, s, C₁₁₋ and C₁₂₋), 5.93 (2H, s, OCH₂O), 4.56 (2H, s, C₃₋), 3.85 (6H, s, OCH₃ x 2), 4.1–3.8 (2H, OCH₂CH₃), 1.3–0.9 (3H, OCH₃CH₂), 79°C: 6.96, 6.84 (2H, AB q, J = 8.5 Hz, C₁₋ and C₂₋), 6.73, 6.65 (each 1H, s, C₈₋ and C₁₀₋), 6.64 (2H, s, C₁₁₋ and C₁₂₋), 5.90 (2H, s, OCH₂O), 4.54 (2H, s, C₃₋), 4.01 (2H, q, J = 7 Hz, OCH₂CH₃), 3.91, 3.86 (each 3H, s, OCH₃ x 2), 3.61 (2H, t, J = 5.5 Hz, C₉₋), 3.01 (2H, t, J = 5.5 Hz, C₁₀₋), 1.01 (3H, t, J = 7 Hz, OCH₃CH₂), δ (200 MHz): 7.01, 6.84 (2H, AB q, J = 8.5 Hz, C₁₋ and C₂₋), 6.74, 6.66 (each 1H, s, C₈₋ and C₁₀₋), 6.68, 6.63 (2H, AB q, J = 16.5 Hz, C₁₁₋ and C₁₂₋), 5.92 (2H, s, OCH₂O), 4.55 (2H, s, C₃₋), 3.99 (2H, br s, OCH₂CH₃), 3.87 (6H, s, OCH₃ x 2), 3.7–3.6 (2H, br s, C₁₋ and C₂₋), 1.31–2.9 (2H, br s, C₈₋ and C₁₀₋), 1.21, 1.02 (3H, each t-like, OCH₂CH₃). Anal. Caled for C₂₃H₂₇N₄O₅: C, 55.78; H, 4.83; N, 9.59. Found: C, 55.70; H, 4.71; N, 9.54.

Ethyl (Z)-5,6,7,8-tetrahydro-3,4-dimethoxy-10,11-methylenedioxybenzo[c]glaucicene-6-carboxylate (8)—A mixture of the Z-glaucicene (6, 54.2 mg) in benzene (150 ml) and rose bengal (10 mg) in MeOH (20 ml) was irradiated with a 250 W high-pressure mercury lamp with a Pyrex filter in an N₂ atmosphere for 2 h at room temperature. The organic solvents were evaporated off in vacuo and the residue was purified by PTLC (Al₂O₃, CHCl₃) to give the Z-glaucicene (8, 17 mg, 32%) as a colorless oil. IR ν_max cm⁻¹: 1680 (CO). MS m/e: 541 (M⁺, base peak). High resolution MS m/e: Caled for C₂₃H₂₇N₄O₅: 541.168. Found: 541.168. PMR δ: 6.73 (2H, br s, C₁₁₋ and C₁₂₋), 6.71 (2H, s, C₁₋ and C₂₋), 6.6–6.4 (2H, C₉₋ and C₁₀₋), 5.86 (2H, s, OCH₂O), 4.53, 4.44 (2H, each s, C₁₋ and C₂₋), 4.3–4.0 (2H, OCH₂CH₃), 3.79 (3H, s, OCH₃), 3.70, 3.67 (3H, each s, OCH₃), 1.4–1.1 (3H, OCH₂CH₃). δ (70°C): 6.73, 6.71 (2H, AB q, J = 12 Hz, C₁₁₋ and C₁₂₋), 6.69, 6.68 (2H, AB q, J = 8.5 Hz, C₁₋ and C₂₋), 6.50, 6.45 (each 1H, s, C₈₋ and C₉₋).
(9) /—1] A solution of AgNO₃ (300 mg) in water (10 mL) was added to a stirred solution of 4 (300 mg) in Me₆CO (10 mL) and stirring was continued for 40 h at room temperature. The organic solvent was evaporated off in vacuo and water was added to the residue. The aqueous layer was extracted with CHCl₃. The extract was washed with water, dried, and concentrated in vacuo. The residue was purified by column chromatography (Al₂O₃, CHCl₃) to afford 9 (191 mg, 66%) as a pale brown oil. IR ν(CHCl₃) cm⁻¹: 3400 (OH), 1670 (CO). MS m/e: 429 (M⁺), 248 (base peak). High resolution MS m/e: Calculated for C₂₃H₂₃NO₅: 429.179. Found: 429.179. PMR δ: 6.65 (2H, s, C₂-H), 6.5 (1H, s, C₃-H), 6.3 (1H, m, C₂-H), 5.82 (2H, s, OCH₂O), 5.1 (1H, m, C₂-H), 4.57 (2H, brs, CH₂OH), 3.84, 3.79 (each 3H, s, OCH₃ × 2), 3.03 (2H, d, J = 7 Hz, C₃-H₂), 1.3–0.9 (3H, OCH₃CH₃). δ (80 °C): 6.73, 6.70 (2H, ABq, J = 8.5 Hz, C₂-H and C₃-H), 6.57 (1H, s, C₃-H), 6.31 (1H, s, C₂-H), 5.85 (2H, s, OCH₂O), 5.21 (1H, t, J = 7 Hz, C₂-H), 4.68 (2H, s, CH₂OH), 3.95, 3.87 (each 3H, s, OCH₃ × 2), 3.07 (2H, d, J = 7 Hz, C₃-H₂), 1.13 (3H, t, J = 7 Hz, OCH₃CH₃).

2) A solution of 4 (137.7 mg) in CH₂Cl₂ (10 mL) was stirred with Al₂O₃ (Aluminaoxoid 90 Aktivitätsstufe II–III, Merck, 10 g) for 48 h at room temperature. Al₂O₃ was filtered off and washed thoroughly with CHCl₃–MeOH (95:5). The filtrate and washings were concentrated in vacuo to afford 9 (121 mg, 92%) as a pale brown oil, which was identical with an authentic specimen obtained in 1).

3) A solution of tetrahydroborazine (1, 547 mg) in ethyl chlorofomate (50 mL) was treated as described above to give an oil residue, which was chromatographed on Al₂O₃ with CHCl₃. The first fraction gave a mixture which was further separated by PTLC to afford 5 [56.9 mg, 9.1% (12.7% based on consumed starting material)] as an upper fraction and 6 [73.3 mg, 11% (15.5% based on consumed starting material)] as a lower fraction. The second fraction afforded uncharget tetrahydroborazine 1 (155.8 mg, 28.5%). The third fraction, eluted with CH₂Cl₂–MeOH (98:2), afforded 9 [320.8 mg, 46% (64.5% based on consumed starting material)], which was identical with an authentic specimen.

1,2,3,4-Tetrahydro-1-(2-hydroxymethyl-3,4-dimethoxyphenylmethyl)-2-methyl-6,7-methylenedioxyisouquinoline (11) — A mixture of the urethane (9, 137 mg) and LiAlH₄ (53 mg) in anhyd. Et₂O (20 mL) was heated under reflux for 8 h with stirring. Work-up as usual gave 11 (94.5 mg, 80%) as an oil, which soon solidified. Recrystallization from MeOH gave colorless plates, mp 107–108 °C. IR ν(CHCl₃) cm⁻¹: 3350 (OH). MS m/e: 371 (M⁺), 190 (base peak). PMR δ: 6.83 (2H, s, C₂-H and C₃-H), 6.69, 6.54 (each 1H, s, C₂-H and C₃-H), 5.92 (2H, s, OCH₂O), 4.76, 4.48 (2H, ABq, J = 11.5 Hz, CH₂OH), 3.89, 3.85 (each 3H, s, OCH₃ × 2), 2.20 (3H, s, NCH₃). Anal. Calcd for C₂₁H₂₂NO₅: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.18; H, 6.97; N, 3.94.

2) A mixture of 4 (70 mg) and Ac₂O (30 mg) in AcOH (10 mL) was heated under reflux for 40 h. The organic solvent was evaporated off in vacuo and water was added to the residue. The aqueous layer was extracted with CHCl₃. The extract was washed with water, dried, and concentrated to leave crude 10 [54 mg, IR ν(CHCl₃) cm⁻¹: 1725 (OAc), 1675 (NCO)], which was used for the next step without further purification. A mixture of 10 (54 mg) and LiAlH₄ (20 mg) in anhyd. tetrahydrofuran (THF) (5 mL) was heated under reflux for 5.5 h with stirring. Work-up as usual followed by column chromatography (Al₂O₃, CHCl₃) gave 7 (18 mg, 31% from 4), which was identical with an authentic specimen.

(+)–Canadine (2) — PCC (193 mg) and NaOAc (73 mg) were added to a stirred solution of the alcohol 11 (221 mg) in CH₂Cl₂ (10 mL) and stirring was continued for 7.5 h at room temperature. PCC (60 mg) and NaOAc (24 mg) were again added to the reaction mixture and stirring was continued for another 2 h. The reaction mixture was passed through a short column packed with Florisil and the column was thoroughly washed with CHCl₃. The elute was concentrated in vacuo to leave (+)–canadine (2, 150 mg, 68%). Recrystallization from MeOH afforded colorless prisms, mp 143–145.5 °C. IR ν(CHCl₃) cm⁻¹: 1680 (CO). MS m/e: 369 (M⁺). PMR δ: 10.20 (1H, s, CHO), 6.86, 6.68 (2H, ABq, J = 8 Hz, C₂-H and C₃-H), 6.40 (2H, s, C₂-H and C₃-H), 5.76 (2H, s, OCH₂O), 3.86, 3.82 (each 3H, s, OCH₃ × 2), 2.32 (3H, s, NCH₃). UV λₘ₅₀ nm (log e): 232 (4.13), 288 (3.85). Anal. Calcd for C₁₂H₁₄NO₃: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.99; H, 6.24; N, 4.07.

1,2,3,4-Tetrahydro-1-(2-hydroxymethyl-3,4-dimethoxyphenylmethyl)-6,7-methylenedioxyisouquinoline (12) — A solution of 9 (116 mg) and 10% aqueous KOH (5 mL) in EtOH (2 mL) was heated in a sealed tube at 140 °C for 46 h in N₂ atmosphere. The organic solvent was evaporated off in vacuo and the residue was extracted with CHCl₃. The extract was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on SiO₂ with CHCl₃–MeOH (97:3). The first fraction afforded the unchanged starting material 9 (25.3 mg 22%). The second fraction afforded the amine 12 [64.9 mg, 67% (86% based on consumed starting material)] as colorless prisms, mp 157–158 °C (MeOH). IR ν(CHCl₃) cm⁻¹: 3300, 3125 (NH and OH). MS m/e: 357 (M⁺). PMR δ: 7.01, 6.86 (2H, ABq, J = 8.5 Hz, C₂-H and C₃-H), 6.80 (1H, s, C₃-H), 6.56 (1H, s, C₂-H), 5.93 (2H, s, OCH₂O), 4.84, 4.47 (2H, ABq, J = 11.5 Hz, CH₂OH), 3.90, 3.87 (each 3H, s, OCH₃ × 2). Anal. Calcd for C₂₉H₂₃NO₅: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.93; H, 6.52; N, 3.88.

5,8,13,13a-Tetrahydro-12-hydroxymethyl-10,11-dimethoxy-2,3-methylenedioxy-6H-dibenzo[a]quinoline (3)—Aqueous formaldehyde (37%, 2 mL) was added to a solution of the amine 12 (27 mg) in AcOH (1 mL) and the
mixture was heated at 100 °C for 3.5 h. The solvent was evaporated off in vacuo and the residue was taken up in CHCl₃. The organic layer was washed with aqueous K₂CO₃ and brine, and then dried. Evaporation of the solvent left the crude product, which was purified by column chromatography [Al₂O₃, CHCl₃-MeOH (98:2)] to afford 3 (25.2 mg, 90%) as colorless needles, mp 195—196 °C (MeOH). IR νmax cm⁻¹: 3350 (OH). MS m/e: 369 (M⁺). PMR δ: 6.78, 6.60, 6.58 (each 1H, s, C₁−, C₂−, and C₄−H), 5.92 (2H, s, OCH₂O), 4.73 (2H, br s, CH₂OH), 3.86, 3.85 (each 3H, s, OCH₃ x 2). Anal. Calcd for C₁₁H₂₂NO₃: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.98; H, 6.31; N, 3.86.

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References and Notes

2) A part of this work was published in preliminary communications: a) M. Hanaoka, K. Nagami, and T. Imanishi, Heterocycles, 12, 497 (1979); b) M. Hanaoka, M. Inoue, S. Yasuda, and T. Imanishi, ibid., 14, 1791 (1980).
3) Oxygenated substituents on rings A and D are omitted.
7) The yield calculated on the basis of consumed starting material is shown in parentheses.
8) In a preliminary communication we reported a single product (81% yield based on consumed starting material) assigned as 4, but we found it to be a mixture of three products after careful examination. The complicated PMR spectrum of the mixture had been assumed to be due to the presence of rotamers.