# A Short, Chirospecific Synthesis of the Ant Venom Alkaloid (3R,5S,8S)-3,5-Dialkylpyrrolizidines

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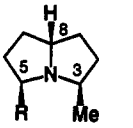
The stereospecific synthesis of both (+)-xenovenine (1) and (+)-(3R,5S,8S)-3-methyl-5-(8-nonenyl)pyrrolizidine (2), found in ant venom, is described. The stereoselective intramolecular amidomercuration of the N-alkenylurethane 3, available from D-alanine, followed by oxidative demercuration provides the trans pyrrolidine alcohol 5. Thereafter, oxidation of 5 followed by Horner–Wadsworth–Emmons elongation of the ring appendage affords the relevant bicyclic precursors 7 and 9, which are stereoselectively converted into 1 and 10, respectively, by catalytic hydrogenation. The pyrrolizidine 10 is readily transformed into 2 by elaboration of the side chain at C5.

## Introduction

Pyrrolizidine alkaloids offer attractive targets for synthesis because of their unique structures and intriguing biological activities.[1] Two are found in ant venom: xenovenine (1),[2] isolated from *Solenopsis xenoveneum*, and 3-methyl-5-(8-nonenyl)pyrrolizidine (2),[3] produced by *Monomorium antarcitum* (Chart I). Their absolute configurations and potential biological activities, however, remain unknown due to their short supply from natural sources. Consequently, the practical preparation of these rare substances is of great importance. So far, the synthesis of xenovenine (1) has been reported three times in its racemic form[2,4] and twice asymmetrically,[5] whereas the synthesis of 2 has been reported only once in racemic form.[3] Unfortunately, most of the syntheses reported are those by less selective or multistep procedures. Accordingly, we were stimulated into the development of a comprehensive synthetic program for these alkaloids. Our interest in this field has focused on the synthetic utilization of electrophile-mediated olefin heterocyclization, as employed for the stereoselective construction of nitrogen and oxygen heterocycles leading to natural products.[6,7] In this paper,[8] we disclose a short, chirospecific synthesis of 1 and 2 via stereoselective intramolecular amidomercuration of a homochiral N-alkenylurethane available from an α-amino acid as a chiral educt.[9]

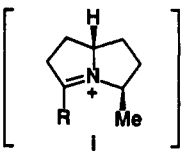



1 R= $(CH_2)_6CH_3$
2 R= $(CH_2)_7CH{=}CH_2$

Chart I

## Results and Discussion

Our design for synthesizing a pyrrolizidine (1 or 2) having the 3R,5S,8S configuration involves two critical steps ((1) 3 → 4; (2) 7 or 9 → 1 or 10). The elaboration of the trans arrangement of the C3 and C8 hydrogens is assumed on the basis of the protocol developed for the synthesis of (+)-pyrrolidine 197B, where the kinetically controlled intramolecular amidomercuration of an α-alkylated 4-pentenylcarbamate has effected the purpose.[10] The stereoselective construction of the bicyclic skeleton is presumed to be performed via catalytic hydrogenation of the iminium intermediate i, expected to arise from 7 or




i

9 via debenzyloxycarbonylation, with its least hindered side (α) attacked. Accordingly, the chirality of D-alanine, which will constitute the one at the C3 in the pyrrolizidine products 1 and 2, is expected to control completely the genesis of the two other sites C5 and C8, thereby affording a single product, namely, the enantiomer having the 3R,5S,8S configuration.

Our synthesis of 1 began with the intramolecular amidomercuration[11] of (R)-N-(benzyloxycarbonyl)-1-methyl-4-pentenylamine (3),[12] readily available from D-(−)-alanine (Scheme I). The unsaturated carbamate 3 underwent the cyclization mediated by mercuric acetate in THF followed by treatment with aqueous NaBr to afford the organomercurial 4, which was oxidatively demercurated[13] to provide only the trans diastereomer 5 in 75% yield without

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(9) Coppola, G. M.; Schuster, H. F. in *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; John Wiley: New York, 1987.

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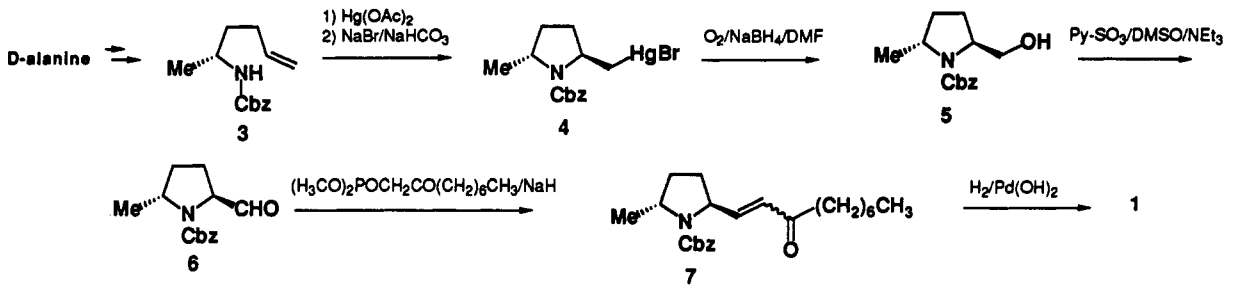
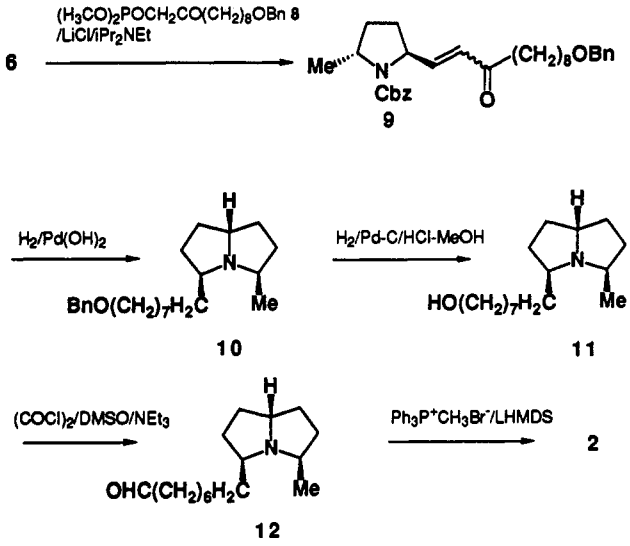
**Scheme I**




concomitant formation of the cis isomer.[14] The Parikh–Doering oxidation (DMSO/pyridine–$SO_3$ complex)[15] of **5** gave the aldehyde **6**, and subsequent Horner–Wadsworth–Emmons reaction of **6** with dimethyl (2-oxononyl)phosphonate provided the $\alpha,\beta$-unsaturated ketone **7** ($E$:$Z$ = 8:1)[16] in 49% overall yield from **5**. Enantioselectivity for pure geometrical isomer ($E$)-**7** was determined by HPLC analysis, with a Daicel AS column using a mixture of hexane/ethanol/diethylamine (95/5/0.1) as eluant, to be >98% ee.[17] Exposure of highly scalemic **7** to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ as a catalyst in MeOH caused simultaneous reduction of its double bond, debenzyloxycarbonylation, annulative imination, and reduction of the resulting iminium intermediate to give stereoselectively the desired pyrrolizidine **1** [bp 80 °C/0.6 mmHg, $[\alpha]^{24}_D$ + 11.7° ($c$ 0.695, $CHCl_3$)[18] [lit.[5a] $[\alpha]^{20}_D$ + 9° ($c$ 2.13, $CHCl_3$)]] in 58% yield after purification by column chromatography. Spectral data ($^1H$ and $^{13}C$ NMR) for **1** were completely identical with those reported.[2] Since **1** in our hands was formed as a single product with enantiomeric integrity, it can be assumed that the operations employed cause no racemization.

Having obtained these results, the synthesis of **2** was next undertaken (Scheme II). Our synthesis of **2** was initiated with the Horner–Wadsworth–Emmons reaction of the aldehyde **6** with dimethyl (10-(benzyloxy)-2-oxodecyl)phosphonate (**8**). This time the elongation of the ring appendage was performed according to the Masamune–Roush procedure[19] to afford the $\alpha,\beta$-unsaturated ketone **9**[20] in 75% yield from **5**. Construction of the bicyclic ring from **9** by catalytic hydrogenation provided the desired pyrrolizidine **10** as a single diastereomer in 65% yield. Debenzylation of **10** ($H_2$, 5% Pd/C) in an acidic medium afforded the primary alcohol **11** in 99% yield. The last step of our synthesis of **2** called for a terminal olefination at the C5 substituent in **11**. The Swern oxidation of the primary hydroxyl and subsequent olefination of the resulting aldehyde with the Wittig reaction

**Scheme II**




($Ph_3P^+CH_3Br^-$, LHMDS) gave **2**, in 58% yield, which exhibited an $^1H$ NMR spectrum identical with that provided by Jones. The optical rotation $[\alpha]^{24}_D$ was determined to be +11.3° ($c$ 2.255, $CHCl_3$), which corresponded to that for **1**.[21]

In summary, starting from the homochiral $N$-alkenylurethane **3**, available from D-alanine, both 3,5-dialkylpyrrolidines (**1** and **2**) found in ant venom were chirospecifically prepared in five steps in an overall yield of 21.3% and in eight steps in an overall yield of 21.0%, respectively. This synthesis is short and economical, requiring no extra procedures to ensure the required stereochemistry. Further application of our procedure to the preparation of other scarce, chiral pyrrolizidines and indolizidines are under study, and the results will be described in due course.

## Experimental Section

Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a JASCO A 102 spectrophotometer or Perkin-Elmer 1600 series FTIR spectrophotometer. Proton magnetic resonance ($^1H$ NMR) spectra were recorded either at 60 MHz on a JEOL PMX-60 instrument or at 270 MHz on a JEOL-FX270 instrument with tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a Varian XL-200 or a JEOL-FX270 instrument with tetramethylsilane as an internal standard unless otherwise specified. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. High-performance liquid chromatography (HPLC) was performed on a Chiralcel AS column (Daicel Chemical Industries) by using a Waters pump and

(14) No C5 methyl peak of the cis isomer was detected by $^1H$ NMR at 270 MHz. Selectivity is >20:1 by this criterion.

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(16) A ratio of $E$:$Z$ was determined by the integral values of vinyl protons (6.63 and 6.66 ppm for $E$ and 6.00–6.18 ppm for $Z$) in the crude **7** in $^1H$ NMR spectra at 270 MHz, which are sufficient to differentiate and quantitate the geometrical isomers.

(17) For determination of the enantiomeric excess (ee), *ent*-**7** was prepared from L-alanine in this way. The retention times ($t_R$) for ($E$)-**7** and its enantiomer by HPLC showed 6.3 min and 7.1 min, respectively. Only one peak (6.3 min) for ($E$)-**7** was detected. Selectivity is >100:1 (>98% ee) by this criterion.

(18) The value of specific rotation for *ent*-**1** prepared from L-alanine showed $[\alpha]^{24}_D$ −11.5° ($c$ 0.51, $CHCl_3$).

(19) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamume, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(20) Enantioselectivity for ($E$)-**9** was determined by HPLC (Daicel/AS column) ($t_R$ 43.5 min for ($E$)-**9** and 49.7 min for ent-($E$)-**9** prepared from L-alanine by the method described for **9**) to exhibit >98% ee.

(21) Unfortunately, none of the ant-derived pyrrolizidines has been isolated in enough quantity to determine its optical rotation.

a flow rate of 1 mL/min or 0.25 mL/min. Column chromatography was performed on silica gel (Fuji-Davision BW-200 or Merck 60 (no. 9385) with a medium pressure apparatus and a mixture of ethyl acetate/hexane was used as eluant unless otherwise specified. The extracts were dried over $Na_2SO_4$ unless otherwise specified.

**(2S,5R)-1-(Benzyloxycarbonyl)-2-(hydroxymethyl)-5-methylpyrrolidine (5).** To a solution of **3** (1.59 g, 6.42 mmol) in THF (117 mL) was added mercuric acetate (3.07 g, 9.63 mmol), and the reaction mixture was stirred for 18 h at room temperature. Saturated $NaHCO_3$ was added to the mixture with ice cooling. After 30 min of stirring, saturated KBr (4.58 g, 38.5 mmol) was added to the mixture. After 2 h of stirring, the THF layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried. After evaporation, the resulting residue was purified by column chromatography to yield the organomercurial bromide **4** (87%) as an oil. Oxygen ($O_2$) was bubbled into a suspension of $NaBH_4$ (114 mg, 3.0 mmol) in DMF (27 mL) for 1 h, and to this was dropwise added a solution of **4** (1.09 g, 2.12 mmol) in DMF (90 mL) over 3 h with continuous introduction of $O_2$. The bubbling of $O_2$ into the mixture was continued for 1 h, and ether was added. The reaction mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The residue was chromatographed to yield **5** (354 mg, 67%) as an oil: $[\alpha]^{24}_D$ + 45.8° (*c* 3.895, $CHCl_3$); IR (neat) 3424, 3033, 1674, 1455, 1412 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (3 H, d, $J$ = 6.0 Hz), 1.45–1.55 (1 H, m), 1.66–1.69 (1 H, m), 2.00–2.16 (2 H, m), 2.96 (1 H, br s), 3.55–3.78 (2 H, m), 4.02–4.15 (2 H, m), 5.09–5.16 (2 H, m), 7.36 (5 H, s). Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.11; H, 7.86; N, 5.58.

**(2R,5S)-1-(Benzyloxycarbonyl)-2-methyl-5-(3-oxo-1-decenyl)pyrrolidine (7).** A solution of sulfur trioxide–pyridine complex (556 mg, 3.45 mmol) in DMSO (3.1 mL) was added to a solution of **5** (307 mg, 1.17 mmol) and triethylamine (487 $\mu$L, 3.50 mmol) in $CH_2Cl_2$ (3.1 mL) with ice cooling. The reaction mixture was stirred at room temperature for 2 h and then diluted with ether. A 10% citric acid solution was added to the mixture with the acidity adjusted to pH 4. The organic phase was separated, and the aqueous phase was extracted with ether three times. The organic layer and extracts were combined, washed with brine, dried, and evaporated to leave a crude product (**5**) as an oil. To a suspension of sodium hydride (56 mg, 1.40 mmol) in THF (4.2 mL) was added dimethyl (2-oxononyl)phosphonate (bp 140 °C/3 mmHg) (310 $\mu$L, 1.40 mmol, prepared by the reaction of methyl octanoate with dimethyl methylphosphonate in the presence of *n*-BuLi according to Dauben's method)[22] over 5 min at 0 °C. After being stirred for 15 min, a solution of **6** (1.17 mmol) was added to the mixture, and the whole mixture was stirred for 2 h at 0 °C. Saturated $NH_4Cl$ (3 mL) was added to the reaction mixture. After separation of organic layer, the aqueous phase was extracted with ether three times. The organic layer and extracts were combined, washed with brine, dried, and evaporated to give an oil, which was chromatographed to afford **7** (210 mg, 48.5%) (*E*:*Z* = 8:1) as an oil. (*E*)-**7**: $[\alpha]^{24}_D$ -74.0° (*c* 0.94, $CHCl_3$); HPLC (AS) ($t_R$ 6.3 min); IR (neat) 2928, 1700, 1636, 1498, 1458, 1405 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3 H, t, $J$ = 6.8 Hz), 1.16–127 (11 H, m), 1.52–1.57 (3 H, m), 1.67–1.74 (1 H, m), 2.02–2.05 (1 H, m), 2.23–2.26 (1 H, m), 4.48–4.68 (1 H, m), 4.59–5.19 (2 H, m), 5.93 (0.55 H, d, $J$ = 15.6 Hz), 6.05 (0.45 H, d, $J$ = 15.6 Hz), 6.63 (0.45 H, t, $J$ = 15.6 Hz), 6.66 (0.55 H, t, $J$ = 15.6 Hz), 7.28–7.35 (5 H, m). Anal. Calcd for $C_{23}H_{33}O_3N$: C, 74.41; H, 8.96; N, 3.77. Found: C, 74.10; H, 9.30; N, 3.87.

**(3R,5S,8S)-5-Heptyl-3-methylpyrrolizidine (Xenovenine, 1).** A suspension of **7** (92 mg, 0.248 mmol) and palladium hydroxide (18 mg) in methanol (5 mL) was stirred under a hydrogen atmosphere for 20 h. The insoluble materials were removed by filtration and the filtrate was evaporated to give a residue, which was chromatographed using ether as eluant to yield **1** (25.1 mg, 58%) as an oil: bp 80 °C/0.6 mmHg (Kugelrohr); $[\alpha]^{24}_D$ +11.7° (*c* 0.695, $CHCl_3$); IR (neat) 3567, 2954, 2924, 2856, 1458, 1374 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.86 (3 H, t, $J$ = 7.1 Hz), 1.10 (3 H, d, $J$ = 6.4 Hz), 1.28–1.55 (16 H, m), 1.95 (4 H, m), 2.62 (1 H, m), 2.77 (1 H, m), 3.60 (1 H, m); $^{13}C$ NMR ($C_6D_6$) $\delta$ 11.73, 14.32, 22.50, 23.08, 27.35, 29.89, 30.42, 32.28, 32.51, 35.03, 37.45, 61.81, 65.02, 66.38; MS 223, 222, 208, 194, 180, 166, 152, 139, 138, 125, 124, 110; HRMS calcd for $C_{15}H_{29}N$ 223.2313, found 223.2334.

**(2S,5R)-1-(Benzyloxycarbonyl)-2-(11-(benzyloxy)-3-oxo-1-undecenyl)-5-methylpyrrolidine (9).** To a stirred suspension of LiCl (84 mg, 1.99 mmol) in $CH_3CN$ (20 mL) at room temperature were added phosphonate **8** (738 mg, 1.99 mmol) (prepared by the reaction of methyl 9-(benzyloxy)nonanoate with dimethyl methylphosphonate in the presence of *n*-BuLi),[22] *N*,*N*-diisopropylethylamine (289 $\mu$L, 1.66 mmol), and finally a solution of the aldehyde (**6**, 1.66 mmol) prepared from **5** in $CH_3CN$ (3 mL). The reaction mixture was stirred for 21 h at room temperature. Saturated $NH_4Cl$ was added to the mixture, and the solvent was removed under reduced pressure. The residue was extracted with ether. The extracts were combined, washed with brine, dried, and evaporated to leave an oil, which was chromatographed to yield **9** (609 mg, 75%) (*E*:*Z* = 8:1) as an oil. (*E*)-**9**: $[\alpha]^{24}_D$ -58.3° (*c* 2.255, $CHCl_3$); HPLC (AS) ($t_R$ 43.5 min); IR (neat) 1701, 1631 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.16–1.29 (11 H, m), 1.43–1.74 (6 H, m), 1.97–2.28 (2 H, m), 2.32–2.54 (2 H, m), 3.46 (2 H, t, $J$ = 6.6 Hz), 4.04–4.15 (1 H, m), 4.50 (2 H, s), 4.54–4.57 (1 H, m), 4.96–5.20 (2 H, m), 5.93 (0.55 H, d, $J$ = 15.4 Hz), 6.05 (0.45 H, d, $J$ = 15.4 Hz), 6.64 (1 H, td, $J$ = 15.4, 5.8 Hz), 7.26–7.36 (10 H, m); $^{13}C$ NMR ($CDCl_3$) (two conformations) $\delta$ 19.47 ($CH_3$), 20.59 ($CH_3$), 23.96 ($CH_2$), 26.15 ($CH_2$), 28.13 ($CH_2$), 29.11 ($CH_2$), 29.20 ($CH_2$), 29.32 ($CH_2$), 29.55 ($CH_2$), 29.75 ($CH_2$), 30.04 ($CH_2$), 30.47 ($CH_2$), 40.60 ($CH_2$), 40.86 ($CH_2$), 53.39 (CH), 53.94 (CH), 58.14 (CH), 58.34 (CH), 66.66 ($COOCH_2$), 66.90 ($COOCH_2$), 70.47 ($OCH_2$), 72.86 ($OCH_2$), 127.45 (aromatic CH), 127.60 (aromatic CH), 127.97 (aromatic CH), 128.12 (aromatic CH), 128.32 (aromatic CH), 128.40 (aromatic CH), 128.52 (aromatic CH), 128.75 (aromatic CH), 136.64 (aromatic C), 136.76 (aromatic C), 138.74 (aromatic C), 144.76 (vinyl CH), 145.34 (vinyl CH), 154.09 (NC=O), 154.32 (NC=O), 200.22 (C=O), 200.51 (C=O); HRMS calcd for $C_{31}H_{41}NO_4$ 491.3035, found 491.3057.

**(3R,5S,8S)-5-(8-(Benzyloxy)octyl)-3-methylpyrrolizidine (10).** A suspension of **9** (290 mg, 0.590 mmol) and palladium hydroxide (58 mg) in methanol (10 mL) was stirred under a hydrogen atmosphere for 20 h. The insoluble materials were removed by filtration, and the filtrate was evaporated to give the residue, which was chromatographed using ether as eluant to yield **10** (138 mg, 65%) as an oil: $[\alpha]^{24}_D$ +9.3° (*c* 1.285, $CHCl_3$); IR (neat) 2926, 2855, 1452 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.10 (3 H, d, $J$ = 6.3 Hz), 1.23–1.61 (18 H, m), 1.88–2.04 (4 H, m), 2.56–2.67 (1 H, m), 2.69–2.82 (1 H, m), 3.46 (2 H, t, $J$ = 6.7 Hz), 3.54–3.66 (1 H, m), 4.50 (2 H, s), 7.27–7.35 (5 H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 22.00 ($CH_3$), 26.21 ($CH_2$), 27.21 ($CH_2$), 29.46 ($CH_2$), 29.63 ($CH_2$), 29.78 ($CH_2$), 29.86 ($CH_2$), 31.73 ($CH_2$), 32.11 ($CH_2$), 32.43 ($CH_2$), 34.47 ($CH_2$), 37.18 ($CH_2$), 61.65 (CH), 64.97 (CH), 66.61 (CH), 70.52 ($OCH_2$), 72.86 ($OCH_2$), 127.43 (aromatic CH), 127.60 (aromatic CH), 128.32 (aromatic CH), 138.74 (aromatic C); HRMS calcd for $C_{24}H_{39}NO$ 357.3032, found 357.3054.

**(3S,5R,8S)-3-(8-Hydroxyoctyl)-5-methylpyrrolizidine (11).** A suspension of **10** (165 mg, 0.462 mmol) and 5% palladium on carbon (165 mg) in 2% HCl–methanol (16 mL) was stirred under a hydrogen atmosphere for 20 h. The insoluble materials were removed by filtration, and the filtrate was neutralized with a 1 N NaOH solution and extracted with $CH_2Cl_2$. The extract was dried and evaporated to give a residue, which was chromatographed using ether as eluant to yield **11** (115 mg, 99%) as an oil: $[\alpha]^{24}_D$ +10.7° (*c* 4.145, $CHCl_3$); IR (neat) 3384, 2926, 2855, 1459 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.10 (3 H, d, $J$ = 6.4 Hz), 1.30–1.56 (18 H, m), 1.85–2.03 (4 H, m), 2.55–2.70 (1 H, m), 2.70–2.83 (1 H, m), 2.70–2.83 (1 H, m), 3.55–3.64 (3 H, m); HRMS calcd for $C_{16}H_{31}NO$ 253.2406, found 253.2422. Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 75.43; H, 12.56; N, 5.74.

**(3R,5S,8S)-3-Methyl-5-(8-nonenyl)pyrrolizidine (2).** A solution of $Me_2S$ (44 $\mu$L, 0.62 mmol) in $CH_2Cl_2$ (410 $\mu$L) was slowly added to a solution of oxalyl chloride (39 $\mu$L, 0.45 mmol) in $CH_2Cl_2$ (410 $\mu$L) at -78 °C. After 10 min of stirring, a solution of **11** (83 mg, 0.328 mmol) in $CH_2Cl_2$ (2.5 mL) was added to the mixture at -78 °C. After 30 min of stirring, triethylamine (193 $\mu$L, 1.39 mmol) was added to the mixture at the same temperature. After being stirred for 2 h, the reaction mixture was quenched with a 20% $KHSO_4$ solution (1.5 mL) and extracted with $CH_2Cl_2$ three

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times. The extracts were washed with brine, dried, and evaporated to give a crude aldehyde (12). To a suspension of methyltriphenylphosphonium bromide (161 mg, 0.452 mmo) in THF (600 μL) was added 1 M lithium bis(trimethylsilyl)amide in THF (434 μL, 0.434 mmol) at -20 °C. After being stirred for 15 min, the mixture was gradually warmed to room temperature. After being stirred for 15 min, the mixture was cooled to -20 °C, and a solution of 12 (0.328 mmol) in THF (360 μL) was added. The reaction mixture was warmed to room temperature, stirred for 2 h, and quenched with saturated $NH_4Cl$. The mixture was extracted with ether three times. The extracts were washed with brine, dried, and evaporated to give an oil, which was chromatographed on alumina to yield 2 (47 mg, 58%) as an oil: bp 75 °C/0.4 mmHg (Kugelrohr); $[\alpha]^{24}_D$ +11.3° (c 2.255, $CHCl_3$); IR (neat) 2925, 2855 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.10 (3 H, d, J = 6.4 Hz), 1.29-1.63 (16 H, m), 1.88-2.02 (6 H, m), 2.56-2.67 (1 H, m), 2.71-2.83 (1 H, m), 3.54-3.65 (1 H, m), 4.89-5.03 (2 H, m), 5.72-5.89 (1 H, m); $^{13}C$ NMR ($CDCl_3$) δ 22.00 ($CH_3$), 27.27 ($CH_2$), 28.97 ($CH_2$), 29.14 ($CH_2$), 29.55 ($CH_2$), 29.89 ($CH_2$), 31.76 ($CH_2$), 32.14 ($CH_2$), 32.45 ($CH_2$), 33.84 ($CH_2$), 34.50 ($CH_2$), 37.18 ($CH_2$), 61.71 (CH), 64.99 (CH), 66.64 (CH), 114.12 (=$CH_2$), 139.23 (CH=); MS 249, 248, 234, 220, 180, 166, 152, 138, 125, 124; HRMS calcd for $C_{17}H_{31}N$ 249.2457, found 249.2462. Anal. Calcd for $C_{17}H_{31}N$: C, 81.86; H, 12.53; N, 5.62. Found: C, 81.62; H, 12.66; N, 5.80.

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**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR spectra for compounds 1, 2, 9, and 10 (8 pages). This material is contained in many 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.

# Dirhodium Tetraacetate Catalyzed Carbon-Hydrogen Insertion Reaction in N-Substituted α-Carbomethoxy-α-diazoacetanilides and Structural Analogues. Substituent and Conformational Effects[1]

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A series of acyclic α-carbomethoxy-α-diazoacetanilides with different N-substituents, **5a-k**, was prepared and the rhodium(II) acetate catalyzed reactions studied. It was found that the rhodium carbenoid reaction with these compounds occurred only at the N-substituent; when the N-substituent is a propargyl group, rhodium carbenoid addition to the triple bond is favored, resulting, ultimately, in the formation of a bicyclic furan derivative **8**. With an *N*-(*tert*-butyloxycarbonyl)methyl substituent, interception of the rhodium carbenoid by the ester carbonyl oxygen occurred preferentially to give, eventually, 1,4-oxazine derivatives **9** and **9'**. For *N*-alkyl substituents, rhodium carbenoid carbon-hydrogen (C-H) insertion into the alkyl group to give 2-azetidinone and/or 2-pyrrolidinone derivatives was observed. The chemoselectivity of the rhodium carbenoid C-H insertion can be altered by the use of the α-acetyl and α-phenylsulfonyl substituents. In these cases, exclusive C-H insertion at the *N*-aryl moiety resulted to give 2(3*H*)-indolinone products. However, the α-substituent effect on the chemoselectivity of the insertion reaction is easily overridden by conformational effects about the amide N-C(O) bond as revealed by the insertion reactions of the conformationally rigid compounds **20a-c**. The α-substituent effects are reestablished when conformational rigidity is removed, as exemplified by the rhodium carbenoid insertion reactions of compounds **29a,b**.

## Introduction

Reactions caused by the dirhodium tetraacetate catalyzed reaction of α-diazo carbonyl compounds are facile, efficient processes that have been the subject of extensive investigations recently.[2] A synthetically useful reaction is the intramolecular rhodium carbenoid mediated carbon-hydrogen (C-H) insertion reaction, and its use in carbocyclic[3] and heterocyclic[4] ring synthesis is well documented.[2a,c] Some characteristics of the reaction are evident, particularly in the area of carbocyclic ring formation. It has been shown that the intramolecular reaction exhibits a strong preference for five-membered ring formation,[3a,i] and more importantly, electronic[3c,f,4c,g] as well as steric and conformational factors[3b,f] can influence the site selectivity of the reaction.

The rhodium(II) acetate catalyzed intramolecular C-H insertion reaction in diazo amides has been shown to be an effective method for the preparation of 2-azetidi-

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