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An Efficient Route to Chiral *trans*-2,5-Dialkylpyrrolidines via Stereoselective Intramolecular Amidomercuration

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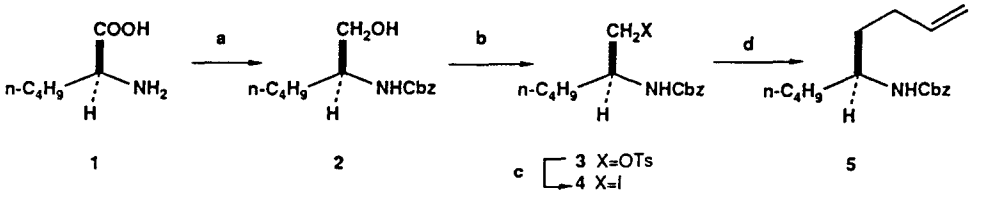
Abstract: An intramolecular amidomercuration of α-butylated 4-pentenylcarbamate **5** predominantly provided *trans*-2,5-disubstituted pyrrolidine **6**, which was elaborated to chiral *trans*-5-butyl-2-alkylpyrrolidines **10** and **13**, constituents of ant venoms.

trans-2,5-Disubstituted pyrrolidines are known as constituents of fire ant venom of the genera *Solenopsins* and *Monomorium*.[1] Due to a broad range of physiological activities, a number of syntheses in the racemic mode have been reported.[2] Recent attention is focussed on their asymmetric synthesis.[3] However, the *trans* selectivity between 2 and 5 positions in the earlier synthesis is not so high.[3] In connection with our study on electrophilic olefin heterocyclization in organic synthesis,[4] we disclose here a highly *trans*-selective synthesis of chiral 2,5-dialkylpyrrolidines (constituents of fire ant venom and poison frog) by an intramolecular amidomercuration of 4-pentenylcarbamate.

Diastereoselective electrophilic heterocyclization reactions which proceed with asymmetric induction are commonly employed to control relative stereochemistry in cyclic compounds and increasingly recognized as an attractive protocol for the stereoselective synthesis of biologically active heterocycles.[5] Recently, Harding suggests that the observed stereoselectivity (1,3-asymmetric induction) in the intramolecular amidomercuration of α-methyl-δ-alkenylcarbamate critically depends on the reaction conditions which prescribe kinetic (*trans* selectivity) versus thermodynamic (*cis* selectivity) control. [6] Accordingly, we examined the kinetically controlled amidomercuration of α-alkylated 4-pentenylcarbamates derived from α-amino acid as a chiral educt.[7]

The α-butylated 4-pentenylcarbamate **5** was prepared in five steps from commercially available L-(+)-norleucine (**1**) according to the analogous procedure[8] reported for α-methylated 4-pentenylcarbamate as shown in Scheme I. Reduction of **1** with lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF) followed by treatment with benzyl chloroformate (CbzCl) and NaOH gave the alcohol **2** in 85% yield. Tosylation of **2** with toluenesulfonyl chloride and pyridine in CH_2Cl_2 followed by iodination with NaI in acetone afforded the iodide **4** in 63% yield. The CuI-mediated coupling reaction of **3** with allyl magnesium chloride provided the desired **5** in 74% yield.

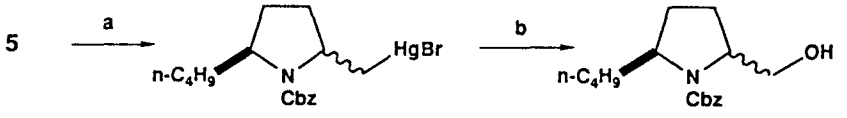
Scheme I



a, (1) $LiAlH_4$; (2) CbzCl/NaOH; b, TsCl/NEt_3; c, NaI/acetone; d, allyl magnesium chloride/CuI

The 4-pentenylcarbamate **5** underwent the cyclization mediated by mercuric acetate (THF/room temp./18 h) followed by treatment with aq. NaBr to provide the organomercurial bromide **6**, which was reductively oxygenated (O_2/$NaBH_4$/DMF)[9] to give a 25:1 (*trans*:*cis*) mixture[10] of diastereomeric 2,5-disubstituted pyrrolidines **7**. The pure diastereomer *trans*-**7** [$[\alpha]_D^{27}$ +53.3° (*c* 1.05, $CHCl_3$)]was isolated by chromatography in 56% yield from **5**.

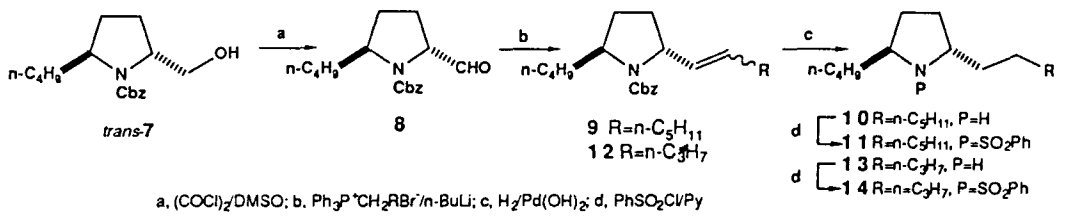
Scheme II



a, $Hg(OAc)_2$/THF; b, O_2/$NaBH_4$/DMF

The synthesis of *trans*-2-butyl-5-heptylpyrrolidine (**10**), an active and major component of the repellent venom of the ant *Solenopsis fugax*,[11] from *trans*-**7** was achieved as outlined in Scheme III. The Swern oxidation of *trans*-**7** provided the aldehyde **8**. Without purification, the aldehyde **8** was subjected to the Wittig reaction using n-hexylidenetriphenylphosphorane, generated *in situ* from the appropriate phosphonium bromide and n-butyllithium (n-BuLi) in THF, to afford the olefin **9** in 69% yield from *trans*-**7**. Finally, **9** underwent simultaneously hydrogenation and hydrogenolysis over palladium hydroxide in an atmosphere of hydrogen to give the desired **10** in 92% yield. The optical purity of **10** could not be determined by simple measurement of the optical rotation since such measurement gave erratic results[12] (values from +9.2° to +16.5° were obtained) and two published optical rotations differ considerably from each other (+60.1° and +7.5°). Instead, the corresponding phenysulfonamide **11** prepared was found to have high optical purity: $[\alpha]_D^{26}$ +62.0 (*c* 1.79, CH_2Cl_2):[(lit. values: +59.7° (*c* 1.8, CH_2Cl_2),[3e] +58° (*c* 1.1, CH_2Cl_2),[3c] and -62.0° (*c* 1.1, CH_2Cl_2)[3a] for (-)-enantiomer].

Scheme III



a, $(COCl)_2$/DMSO; b, $Ph_3P^+CH_2RBr^-$/n-BuLi; c, H_2/$Pd(OH)_2$; d, $PhSO_2Cl$/Py

Next, *trans*-2-butyl-5-pentylpyrrolidine (**13**), a component of the venom of *Solenopsis punctaticeps*[13] and a constituent (pyrrolidine 197B) of the position frog *Dendrobates histrionicus* [14] was synthesized from

trans-7 in a similar manner to that described above. The Wittig reaction of **8** with n-butylidenetriphosphorane provided **12** in 60% yield. Treatment of **12** with $Pd(OH)_2$ under hydrogen gave **13**[15] [$[\alpha]_D^{26}$ +8.8 (*c* 1.05, MeOH)] in 88% yield. The enantiomeric excess of **13** was determined on the basis of 400 MHz ^1H NMR analysis for the corresponding (+)-α-methoxy-α-trifluorophenyl acetic acid (MTPA) ester, which indicated the optical purity to be 98%ee. The optical rotation of the corresponding phenylsufonamide **14** gave a value of $[\alpha]_D^{26}$ +42.1 (*c* 0.405, CH_2Cl_2).

In summary, an effective avenue to optically pure *trans*-5-butyl-2-alkylpyrrolidines **10** and **13**, constituents of ant venoms or dendrobates alkaloids, via highly *trans*-selective intramolecular amidomercuration has been developed. This method would be applied to the synthesis of a variety of chiral *trans*-2,5-dialkylpyrrolidines by using α-amino acids as chiral educts.

Experimental Section

Melting points were determined with a Yanaco micro melting point apparatus and are not corrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a JASCO A 102 spectrophotometer. Proton magnetic resonance (^1H NMR) were recorded either at 60 MHz on a JEOL PMX-60 instrument or at 270 MHz on a JEOL-FX270 instrument or at 400 MHz on a JEOL-FX400 instrument with tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a Varian XL-200 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. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Davision BW-200, Merck 60 (No 9385) , or Nakarai 60) 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.

(*S*)-2-Benzyloxycarbonylamino-1-hexanol (2). To a suspension of $LiAlH_4$ (1.7 g, 44.8 mmol) in THF (85 mL) was added L-norleucine (2.9 g, 22.1 mmol) in portions with ice cooling. After addition, the reaction mixture was refluxed for 12 h. After cooling, 2N NaOH (20 mL) was added to the mixture . After stirring, the mixture was filtered and the solids were washed with THF (25 mL). The solids were suspended in THF (35 mL) , and the resulting mixture was refluxed for 1 h. The solution was filtrated the solids washed with THF (20 mL). To the combined THF solutions was added aqueous 2N NaOH (45 mL) and benzyl chloroformate (8.41 g, 49.3 mmol). After stirring 16 h, biphasic system was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layer was dried and evaporated to give a solid, which was recrystallized with a mixture of THF-n-hexane to provide **2** (4.7 g, 85%). Mp 93-94 °C; $[\alpha]^{26}_D$ - 19.5 (*c* 1.04, $CHCl_3$); IR (nujol) 3325, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67-1.67 (9 H, m), 2.33 (1 H, br s), 3.50-3.83 (3 H, m), 5.10 (2 H, s), 7.33 (5 H, s); MS *m/z* 251 (M^+); Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.66; H, 8.36; N, 5.48.

(*S*)-2-Benzyloxycarbonylamino-1-hexyl p-Toluenesulfonate (3). To a solution of **2** (2.7 g, 10.7 mmol) in pyridine (5 mL) was added p-toluenesulfonyl chloride (2.8 g, 14.7 mmol) at 0 °C and the reaction mixture was stirred for 16 h. Ether (50 mL) was added to the mixture . The mixture was filtered and the solid was washed with ether (25 mL). The combined organic layer was washed with 0.5N H_2SO_4, aq. 5% $NaHSO_3$ and brine, and dried. Evaporation of the organic layer afforded the crude **3**, which was purified by column chromatography to yield **3** (3.29g, 76%). Mp 72-74 °C (n-hexane); $[\alpha]_D^{26}$ -20.0 (*c* 1.04, $CHCl_3$); IR (nujol) 3420, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67-1.67 (9 H, m), 2.47 (3 H, s), 3.93-4.12 (3 H, m), 5.00 (2

H, s), 7.36 (7 H, s), 7.56-7.87 (2 H, m). Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.32; H, 6.66; N, 3.35.

(*S*)-2-Benzyloxycarbonylamino-1-iodohexane (4). A mixture of **3** (2.79 g, 6.87 mmol) and sodium iodide (12.8 g, 85.4 mmol) in acetone (30 mL) was stirred at room temperature for 69 h . After evaporation, ethyl acetate was added to the residue. The mixture was filtered. The filtrate was washed with water, 5% $Na_2S_2O_3$ and brine, and dried. After concentration of the organic layer, the resulting residue was purified by column chromatography to yield **4** (2.05 g, 83%). Mp 66-67 °C; $[\alpha]_D^{28}$ - 22.2 (*c* 0.885, $CHCl_3$), IR (nujol) 3325, 1685 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.67-1.67 (9 H, m), 3.10-3.60 (3 H, br s), 5.10 (2 H, s), 7.40 (5 H, s). Anal Calcd for $C_{14}H_{20}INO_2$: C, 46.55; H, 5.58; N, 3.87. Found: C, 46.58; H, 5.68; N, 3.78.

(*S*)-5-Benzyloxycarbonylamino-1-nonene (5). To a solution of copper (I) iodide (1.32 g, 6.93 mmol) in THF (30 mL) was dropwise added 2M allylmagnesium chloride in THF (6.93 mL, 13 mmol) at -78 °C. The reaction mixture was gradually raised to - 35 °C and stirred for 5 min. After cooling at - 78 °C, a solution of **4** (1.65 g, 4.57 mmol) in THF (7 mL)was added to the mixture. The reaction mixture was stirred for 6.5 h at -30 °C and quenched with aq. NH_4Cl. After evaporation, ether was added to the residue. The mixture was filtered and the solid was washed with ether. The combined organic solvents were washed with brine, 10% NH_3, and brine and dried. After evaporation of the solvent, the residue was purified by chromatography to yield **5** (0.93 g, 74%). Mp 62-63 °C; $[\alpha]_D^{28}$ -4.60 (*c* 1.0, $CHCl_3$); IR (KBr) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63-2.33 (14 H, m), 3.27-3.80 (1 H, m), 4.23-4.87 (2 H, m), 5.07 (2 H, s), 5.30-6.00 (1 H, m), 7.30 (5 H, s); MS *m/z* 276 (M^++1). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.03; H, 9.13; N, 5.12.

(2*S*,5*R*)-1-Benzyloxycarbony-2-butyl-5-(hydroxymethyl)pyrrolidine (*trans*-7). To a solution of **5** (0.6 g, 2.2 mmol) in THF (40 mL) was added mercuric acetate (1.05 g, 3.29 mmol), and the reaction mixture was stirred for 18 h at room temperature. Sat. $NaHCO_3$ was added to the mixture. After being stirred for 15 min., sat. potassium bromide was added to the mixture. After being stirred for 3 h, the THF layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried. After evaporation, the resulting residue was purified by column chromatography to yield the organomercurial bromide **6** (1.07 g, 88%) as an oil. Oxygen (O_2) was bubbled into a suspension of sodium borohydride (0.097 g, 2.56 mmol) in DMF (30 mL)for 1 h. A solution of **6** in DMF (5 mL) was added dropwise to the mixture over 4 h with continuous introduction of O_2 and the bubbling of O_2 into the mixture was continued for 1 h. Ether was added to the reaction mixture. The precipitate was removed by filtration through celite and the filtrate was evaporated *in vacuo*. The residue was purified by chromatography to yield *trans*-**7** (355 mg, 56%) as an oil; $[\alpha]_D^{27}$ +53.3 (*c* 1.05, $CHCl_3$); IR (neat) 3425, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, t, *J*=7.1 Hz), 1.10-2.20 (10 H, m), 5.10, 5.19 (each 1 H, ABq, *J*=12.4 Hz), 7.36 (5 H, s); HRMS calcd for $C_{17}H_{25}NO_3$ 291.1835. found 291.1877.

(2*S*,5*R*)-1-Benzyloxycarbonyl-2-butyl-5-(1-heptenyl)pyrrolidine (9). To a solution of oxalyl chloride (0.064 mL, 0.73 mmol) in CH_2Cl_2 (1 mL) was added dropwise a mixture of DMSO (0.069 mL, 0.97 mmol) in CH_2Cl_2 (0.5 mL) of -78 °C. After being stirred at -60 °C for 10 min, a solution of *trans*-**7** (0.145 g, 0.490 mmol) in CH_2Cl_2 (3 mL) was added to the mixture . After being stirred at -60 °C for 25 min, triethylamine (0.2 mL, 1.44 mmol) added to the mixture. The resulting mixture was warmed to room temperature and then quenched with water. The mixture was successively washed with 20% $KHSO_4$, saturated $NaHCO_3$, and brine. The organic layer washed was dried and evaporated to yield the crude aldehyde **8**. To a

solution of n-hexyltriphenylphosphonium bromide (0.26 g, 0.61 mmol) in THF (5 mL) was added n-BuLi (1.6 M in hexane) (0.41 mL) at -78 °C. The reaction mixture was gradually warmed to room temperature and stirred for 30 min. After being cooled at -78 °C, a solution of the crude **8** in THF (5 mL) was added to the mixture. The resulting mixture was gradually warmed to room temperature and then stirred for 12 h. The mixture was quenched with water at 0 °C and extracted with ether. The organic phase was dried and evaporated. The residue was purified by chromatography to yield **9** (0.12 g, 69%) as an oil, $[\alpha]_D^{27}$ -50.0 (*c* 1.54, $CHCl_3$); IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76-0.92 (6 H, m), 1.10-2.20 (18 H, m), 3.86 (1 H, br s), 4.55-4.70 (1 H, m), 5.08 (2 H, s), 5.15-5.47 (2 H, m), 7.20-7.40 (5 H, m).

(2*S*,5*S*)-2-Butyl-5-heptylpyrrolidine (10). A solution of **9** (140 mg, 0.39 mmol) in CH_3OH (7 mL) was stirred in the presence of $Pd(OH)_2$ (19 mg) and hydrogen at atmospheric pressure for 3 h. The catalyst was removed by filtration through celite and the filtrate was evaporated. The residue was distilled under reduced pressure to give **10** (80.6 mg, 92%) as an oil, bp 77-80 °C/0.7 mmHg; IR (neat) 3350, 2950, 2925, 2850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85-0.91 (6 H, m), 1.27-1.98 (23 H, m), 3.00-3.20 (2 H, m). ^{13}C NMR ($CDCl_3$) δ 14.12, 22.70, 22.90, 27.36, 29.35, 29.55, 29.77, 31.88, 32.56, 36.92, 37.26, 58.03. Anal. Calcd for $C_{15}H_{31}N$: C, 79.92; H, 13.86; N, 6.21. Found: 79.37; H, 13.91; N, 6.05.

(2*S*,5*S*)-1-Benzenesulfonyl-2-butyl-5-heptylpyrrolidine (11). According to the procedure described by Rapoport,[3e] 20% NaOH (0.043 mL) was added to a solution of **10** (24 mg, 0.106 mmol) in $CHCl_3$ (1 mL) at 0 °C. To the resulting mixture was added a solution of benzenesulfonyl chloride (0.014 mL) in $CHCl_3$ (0.3 mL) and then the reaction mixture was stirred at 0 °C for 1 h. After being stirred at room temperature for 3 h, the mixture was diluted with CH_2Cl_2 (20 mL). The mixture was successively washed with water (5 mL), saturated NH_4Cl, and brine, dried, and evaporated. The residue was purified by chromatography to yield **11** (36 mg, 93%) as an oil, $[\alpha]_D^{26}$ +62.0 (*c* 1.79, CH_2Cl_2); IR (neat) 3065, 2956, 2923, 2857, 1446, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76-0.95 (6 H, m), 1.0-2.05 (22 H, m), 3.75-3.92 (2 H, m), 7.40-7.58 (3 H, m), 7.78-7.90 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.07, 22.62, 26.48, 28.02, 28.60, 29.26, 29.47, 31.80, 33.69, 33.93, 61.03, 126.82, 131.92, 143.05. HRMS calcd for $C_{21}H_{35}NO_2S$ 365.2387. found 365.2355.

(2*S*,5*R*)-1-Benzyloxycarbonyl-2-butyl-5-(1-pentenyl)pyrrolidine (12). According to the procedure described for **9**, treatment of **7** (430 mg, 1.48 mmol) with oxallyl chloride (0.193 mL, 2.2 mmol), DMSO (0.21 mL, 3 mmol), and triethylamine (1.2 mL, 8.64 mmol) in CH_2Cl_2 (8 mL) gave the crude aldehyde **8**. The Wittig reaction of **8** in THF (15 mL) with n-butyltriphenylphosphonium bromide (1.26 g, 3.15 mmol) and n-BuLi (1.9 mL, 3 mmol) in THF (15 mL) yield **12** (291 mg, 60%) as an oil, $[\alpha]_D^{26}$ -43.8 (*c* 1.15, $CHCl_3$); IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76-0.95 (6 H, m), 1.12-2.24 (14 H, m), 3.79-3.93 (1 H, m), 4.53-4.73 (1 H, m), 5.06 (2 H, s), 5.00-5.48 (2 H, m), 7.26-7.40 (5 H, m).

(2*S*,5*S*)-2-Butyl-5-pentylpyrrolidine (13). According to the procedure described for **10**, treatment of **12** (291 mg, 0.88 mmol) with $Pd(OH)_2$ (28 mg) under an H_2 atmosphere in CH_3OH (8 mL) gave **13** (154 mg, 88%) as an oil; bp 70-80 °C/0.1 mmHg; $[\alpha]_D^{26}$ +8.8 (*c* 1.05, CH_3OH); IR (neat); 3350, 2960, 2924, 2856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79-1.00 (6 H, m), 1.15-2.00 (19 H, m), 3.02-3.20 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.66, 22.90, 27.03, 29.55, 32.04, 32.52, 36.93, 37.18, 58.03. HRMS calcd for $C_{13}H_{27}N$ 197.2142. found 197.2097.

(2*S*,5*S*)-1-Benzenesufonyl-2-butyl-5-pentylpyrrolidine (14). According to the procedure described for **11**, treatment of **13** (6.8 mg) with benzenesulfonyl chloride (0.04 mL) in the presence of 20%

NaOH (0.012 mL) in $CHCl_3$ (1.3 mL) gave **14** (8.1 mg). $[\alpha]_D^{26}$ + 42.1 (*c* 0.405, CH_2Cl_2); IR (neat) 3066, 2957, 2928, 2859, 1447, 1380, 1335 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 0.82-0.88 (6 H, m), 1.19-1.94 (18 H, m), 3.84 (2 H, m), 7.45-7.76 (3 H, m), 7.82-8.02 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.01, 22.57, 26.09, 27.98, 28.09, 28.57, 31.63, 33.63, 33.70, 33.87, 60.97, 126.78, 126.98, 128.74, 129.69, 131.86, 143.01. HRMS calcd for $C_{19}H_{31}NO_2S$ 337.2070. found 337.2059.

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