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Asymmetric synthesis of 3,5-disubstituted indolizidines by intermolecular addition of an allylsilane on an *N*-acyliminium ion

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Abstract—A diastereoselective synthesis of 3,5-disubstituted indolizidines based on an intermolecular addition of an allylsilane on an acyliminium ion derived from (*S*)-pyroglutamic acid is described. The synthetic potential of this methodology is demonstrated by the enantioselective synthesis of (−)-indolizidine 195B, (−)-indolizidine 223AB, (+)-monomorine and (−)-3-butyl-5-propyl indolizidine.

1. Introduction

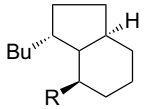
Indolizidine alkaloids constitute a very important class of compounds, which are mainly isolated from the skin extracts of neotropical frogs of the family Dendrobates.[1,2] Most of them are disubstituted by alkyl chains at the 3,5 positions. These compounds have been attractive targets for synthesis because of their potential biological activities.[3] Accordingly, novel strategies for the preparation of substituted indolizidines have received considerable attention.[4]

The allylsilyl functional group is a weak carbon nucleophile used for trapping *N*-acyliminium ions, thus providing a useful method for intramolecular carbon–carbon bond formation.[5] We have applied this methodology towards the synthesis of quinolizidine and indolizidine alkaloids.[6] More recently, an intermolecular version has been developed to access the racemic indolizidine 167B.[7]

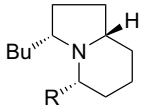
Herein, we report the enantioselective synthesis of (−)-indolizidine 195B, (+)-monomorine, (−)-indolizidine 223AB and (−)-3-butyl-5-propyl indolizidine (Fig. 1) based on the intermolecular addition of allylsilanes on an *N*-acyliminium ion starting from L-pyroglutamic acid used as the chiral precursor.

As the disconnective analysis shows, our plan for the synthesis of indolizidines **1** and **3** depends on the diastereoselectivitiy of steps A and C (Scheme 1).

Step A involves the reduction of iminium ion **5**. A literature survey shows that, whatever the reducing agent (H_2/Pd or hydrides)[4d,e] and C-3 configuration, the incoming C-5 hydrogen atom is mainly deduced to be *syn* to that of C-8a. In fact, the stereocontrol of our synthesis depends on the stereoselective addition of the allylsilyl group of alcohols **7** to the in situ generated *N*-acyliminium **6** (step C). It has been well established that π-nucleophiles give, selectively, *syn* addition to the *N*-acyliminium ion derived



1 R = Me (-)-indolizidine 195B
3 R = Pr (-)-indolizidine 223AB



2 R = Me (+)-monomorine
4 R = Pr (-)- (3*R*,5*S*,8a*S*)-3-butyl-5-propylindolizidine

Figure 1.

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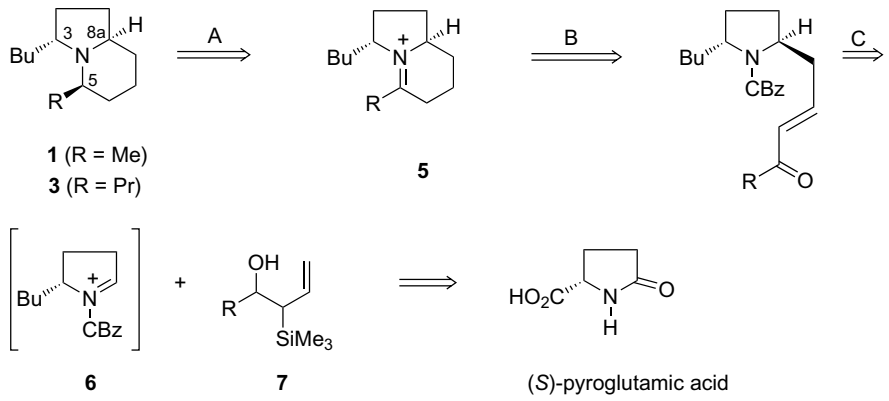


Scheme 1. Retrosynthetic analysis.

from (*S*)-proline[8] and, despite some previous examples of cis-addition of the allylsilane to substituted five-membered *N*-acyliminium ions,[9] we reasoned that the steric requirement of the *n*-butyl side chain would direct the approach of the allylsilyl moiety to the *re*-face of **6**. This selectivity was registered by Pilli during the total synthesis of (−)-indolizidine 223AB.[4e]

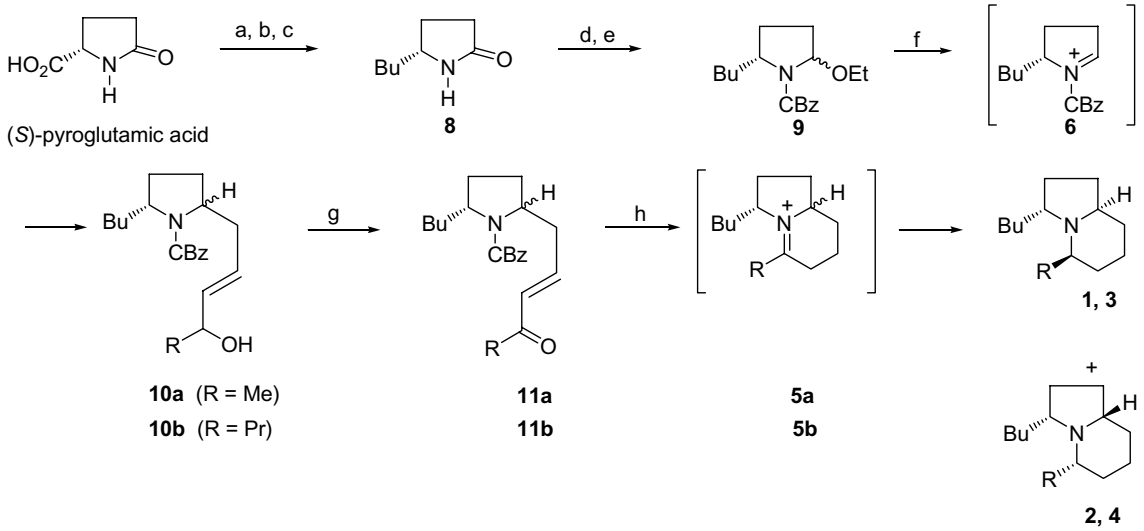
Moreover, according to the literature, additions of cuprates[10] and enol silylated ethers[4e] onto iminium ions were performed to give a majoritary of trans products. No results concerning the addition of allylsilanes on iminium ions type **5** were described except an example of addition of an allylsilane on the iminium ion derived from oxazolidinones.[11]

2. Results and discussion

The synthesis of indolizidines **1**, **2**, **3** and **4** was carried out as shown in Scheme 2. Preparation of lactam **8** was accomplished starting from the commercially available *S*-(−)-pyroglutamic acid according to a previously described procedure.[4e,12]

Next, lactam **8** was protected (*n*-BuLi, benzyl chloroformate), then converted to ethoxycarbamate **9**, isolated as a mixture of two diastereomers in 84% yield according to Hiemstra's procedure.[13] Condensation of allylsilanes **7a**[7] (R = Me) and **7b**[14] (R = Pr) onto iminium ion **6** generated in situ by treatment of **9** with stannous chloride led to compounds **10a** and **10b** in 40% and 30% yields, respectively. Compounds **10a** and **10b** were obtained as a mixture of isomers, which could not be separated. Spectroscopic data did not allow us to establish the stereochemical pattern of each isomer; their ratios were not determined at this step, but would be during the final step on the natural products possessing known configurations.

The next two steps were straightforward: oxidation (pyridinium dichromate, CH_2Cl_2) of **10a** and **10b** afforded α,β-ethylenic ketones **11a** and **11b** in 60% and 84% yields, respectively, and **11a** and **11b** were obtained as a mixture of two isomers, which could not be separated.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, $NaBH_4$; (b) TsCl, Et_3N; (c) Pr_2CuLi, ether, −20 °C; (d) *n*-BuLi, benzylchloroformate; (e) $NaBH_4$, H_2SO_4, EtOH; (f) $SnCl_4$, RCH(OH)CH($SiMe_3$)CH=CH_2 **7**; (g) PDC, CH_2Cl_2, 25 °C; (h) H_2, Pd/C, MeOH.

On hydrogenation over palladium on carbon, **11a** gave a mixture of indolizidines **1** and **2** in an 8:2 ratio. These compounds were separated by flash column chromatography. They were identified as (−)-indolizidine 195B and (+)-monomorine, respectively, by comparison of their ^{1}H and ^{13}C NMR spectra with the literature.[15–17] The specific rotations $[\alpha]_D^{22}$ were determined to be −90.2 (*c* 0.75, MeOH) for **1** and +17.6 (*c* 0.21, hexane) for **2**. These values compare favourably with those obtained previously for synthetic samples.[10,15,17]

In the same manner, the hydrogenation of **11b** provided a mixture of isomers **3** and **4** in a 7:3 ratio. These could be separated by flash column chromatography. Spectroscopic data and the specific rotation of **3** are in agreement with those described for (−)-indolizidine 223AB.[4d] Indolizidine **4** was identified as the stereoisomer of **3**.

This reaction involved the simultaneous hydrogenolysis of the CBz group, and cyclisation to generate the iminium ion, which was reduced to give the indolizidines. It is well known that the reduction (H_2, Pd/C) of iminium ions type **5a** or **5b** leads to a single isomer, resulting from the addition of the C-5 hydrogen atom *syn* to that of C-8a.[4d,18] We have also observed this selectivity during the synthesis of indolizidine 167B.[7] Consequently, the observed ratio of indolizidine isomers results from the diastereoselectivity of the addition of the allylsilyl functional group of alcohols **7a** and **7b** onto the iminium ion **6**. This selectivity is attributed to the *n*-Bu group, which preferentially orients the addition of the allylsilyl functional group in a trans position.

3. Conclusion

We have developed a new diastereoselective method for the preparation of 3,5-dialkylindolizidines. These syntheses have been achieved starting from a common pyrrolidone **8**, which is readily available from natural (*S*)-pyroglutamic acid. Indolizidines were obtained in five steps with overall yields of about 8%.

4. Experimental

4.1. General

Commercially available materials were used without further purification. THF, which was used for moisture sensitive operations, was distilled from potassium/benzophenone under an argon atmosphere. All moisture sensitive reactions were carried out in flame-dried glassware under an argon atmosphere. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Visualisation on TLC was achieved by the use of UV light (254 nm), iodide, ninhydrin or vanillin followed by heating. Flash chromatography was performed using Merck Kieselgel 40–60 μm silica gel.

Infrared spectra were recorded on a Perkin–Elmer 881 (spectra in solution) or on a Perkin–Elmer FTIR Spectrometer Aragon 500 (film), only selected absorbances are reported. Optical rotations were measured on a Jasco DIP-370 polarimeter at 589 nm (Na D-line).

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer at operating frequencies of 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR). Chemical shifts (δ) are given in parts per million relative to residual solvent ($\delta = 7.27$ ppm for ^{1}H, $\delta = 77.1$ ppm for ^{13}C) and coupling constants (*J*) in hertz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet; the prefix br is applied when the signal in question is broadened. Microanalysis was carried out at the Laboratoire Central de Microanalyse du CNRS (Vernaison, France).

4.2. General procedure for preparation of 7

To a solution of *s*-BuLi (*c* 1.3 M, 73 mL, 95 mmol) in THF (120 mL) at −78 °C under argon was added tetramethylenethylendiamine (TMEDA) (11.04 g, 95 mmol). To this mixture, allyltrimethylsilane (10.8 g, 95 mmol) was added dropwise. The temperature was then raised to −30 °C after which the solution was stirred at this temperature for 30 min. After cooling to −78 °C, titanium(IV) isopropoxide (27 g, 95 mmol) was added and stirred for 1 h. Next, the aldehyde (0.9 equiv) was added and the solution stirred for 2 h. The mixture was poured into an aqueous solution of HCl 5% (250 mL). Ether was added and the aqueous phase extracted with ether. The organic phases were combined and dried over $MgSO_4$. The crude compound was purified by flash chromatography to afford compounds **7**.

4.2.1. 3-Trimethylsilylpent-4-en-2-ol 7a. Yield: 88%; ^{1}H NMR δ 0.05 (s, 9H), 1.23 (d, 3H, $J = 6.3$ Hz), 1.62 (dd, 1H, $J = 10.6$ and 6.9 Hz), 1.87 (s, 1H), 3.95 (m, 1H), 4.95 (dd, 1H, $J = 17.1$ and 2.0 Hz), 5.05 (dd, 1H, $J = 10.3$ and 2.0 Hz), 5.80 (td, 1H, $J = 17.1$ and 10.3 Hz); ^{13}C NMR δ 0.0, 23.4, 45.1, 67.6, 115.3, 136.6.

4.2.2. 3-Trimethylsilylhept-1-en-4-ol 7b. Yield: 76%; ^{1}H NMR: δ 0.04 (s, 9H), 0.85 (t, $J = 7$ Hz), 1.25 (m, 2H), 1.45 (m, 2H), 1.57 (s, 1H), 1.65 (dd, $J = 10.6$ and 5.8, 1H), 3.77 (m, 1H), 4.91 (dd, 1H, $J = 2.0$ and 17.1 Hz), 5.04 (dd, $J = 2.0$ and 10.4 Hz, 1H), 5.8 (td, $J = 10.4$ and 17.1 Hz, 1H); ^{13}C NMR δ 0.0, 14.0, 19.0, 39.5, 42.5, 71.2, 114.7, 135.9.

4.3. General procedure for the preparation of 10

To a solution of ethoxypyrrolidine **9** (1 g, 3.3 mmol) in anhydrous CH_2Cl_2 (65 mL), cooled at −78 °C under Ar, was added a solution of $SnCl_4$ in CH_2Cl_2 (*c* 1 M, 3.3 mL, 3.3 mmol) dropwise. The mixture was stirred until the complete consumption of **9**. Next, the temperature was raised to −20 °C, and then silylated alcohols **7** (1.1 equiv) were added dropwise and stirred for a further 90 min. The mixture was then poured into a saturated solution of $NaHCO_3$. The aqueous phases were extracted with CH_2Cl_2, and organic extracts were evaporated. The crude product was purified by flash chromatography to afford pure **10**.

4.3.1. *N*-(Benzyloxycarbonyl)-2-(4-hydroxypent-2-enyl)-5-butyl pyrrolidine 10a. Yield: 30%; ^{1}H NMR δ 0.83 (t, 3H, $J = 6.7$ Hz), 1.23 (d, 3H, $J = 6.2$ Hz), 1.25–1.36 (m, 8H), 1.63–1.93 (m, 5H), 3.83 (m, 2H), 4.2 (m, 1H), 5.13 (m, 2H), 5.45–5.57 (m, 2H), 7.3–7.4 (m, 5H); ^{13}C NMR δ 14.4, 14.5, 23.1, 26.9, 28.0, 29.2, 57.8, 57.9, 58.4, 58.9, 67.0, 66.9, 69.0, 69.1, 127.4, 128.9, 137.2, 137.3, 137.4, 155.0. Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05. Found: C, 73.08; H, 9.32; N, 4.11.

4.3.2. *N*-(Benzyloxycarbonyl)-2-(4-hydroxyhept-2-enyl)-5-butylpyrrolidine 10b. Yield: 40%; ^{1}H NMR δ 0.83–0.92 (m, 6H), 1.25–1.36 (m, 10H), 1.65–1.93 (m, 6H), 4.03 (m, 3H), 4.06 (m, 1H), 5.3 (m, 2H), 5.48–5.57 (m, 2H), 7.3–7.4 (m, 5H). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.75. Found: C, 74.05; H, 9.62; N, 3.95; ^{13}C NMR δ 14.4, 14.5, 19.0, 19.1, 22.9, 23.1, 28.9, 28.93, 29.1, 29.2, 32.7, 34.0, 39.8, 39.9, 57.8, 58.4, 58.5, 58.9, 66.8, 66.9, 72.9, 73.0, 128.1, 128.9, 136.2, 136.4, 137.3, 137.4, 154.7, 154.8.

4.4. General procedure for preparation of 11

A solution of alcohols **10** (0.46 mmol) was stirred with pyridinium dichromate (0.26 g, 0.66 mmol) in CH_2Cl_2 (1 mL) for 24 h at 25 °C. The mixture was diluted with a mixture of ether–pentane (1:1) and then filtered over Celite, after which it was concentrated to give final products **11**, which were purified by flash chromatography.

4.4.1. *N*-Benzyoxycarbonyl-2-(4-oxopent-2-enyl)-5-butyl pyrrolidine 11a. Yield: 60%; ^{1}H NMR δ 0.8 (m, 3H), 1.1–1.4 (m, 8H), 1.5–1.7 (m, 2H), 1.8–2.0 (m, 3H), 2.1–2.2 (m, 2H), 3.8–4.0 (m, 2H), 5.14 (m, 2H), 6.0–6.2 (m, 1H), 6.6–6.7 (m, 1H), 7.3–7.4 (m, 5H). ^{13}C NMR δ 14.8, 23.2, 23.4, 27.6, 29.3, 29.5, 33.02, 34.4, 36.8, 38.0, 57.4, 58.8, 67.4, 67.5, 128.7, 129.2, 133.8, 133.9, 137.6, 144.7, 145.4, 154.8, 155.2, 198.9, 199.2. Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.82; H, 8.65; N, 4.15.

4.4.2. *N*-Benzyloxycarbonyl-2-(4-oxohept-2-enyl)-5-butyl pyrrolidine 11b. Yield: 84%; ^{1}H NMR δ 0.8 (m, 6H), 1.1–1.4 (m, 6H), 1.5–1.7 (m, 4H), 1.8–2.0 (m, 4H), 2.3–2.5 (m, 2H), 3.8 (m, 1H), 4.0 (m, 1H), 5.14 (m, 2H), 6.0–6.2 (m, 1H), 6.6–6.8 (m, 1H), 7.3 (m, 5H); ^{13}C NMR δ 14.6, 14.8, 18.4, 23.2, 23.4, 29.3, 29.5, 34.3, 37.9, 42.8, 57.1, 57.5, 58.8, 59.4, 67.4, 67.5, 128.7, 129.2, 132.9, 133.2, 137.6, 143.5, 144.1, 154.8, 155.1, 201.0, 201.3. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.52; H, 9.23; N, 3.94.

4.4.3. Indolizidines 1, 2, 3 and 4. To a solution of **11** (0.258 mmol) in anhydrous methanol was added Pd/C 10% (0.096 g, 0.089 mmol). The resultant mixture was stirred under 3 atm of hydrogen for 5 h at room temperature. The mixture was filtered over Celite and rinsed with methanol. The solvent was then evaporated in vacuo. The crude product was purified by flash chromatography.

Compound **1**: 36% yield; $[\alpha]_D^{22} = -90.2$ (*c* 0.75, MeOH); lit.[10] $[\alpha]_D^{22} = -99$ (*c* 0.21, MeOH). ^{1}H NMR δ 0.9 (t, 3H), 1.1 (d, 3H), 1.15–1.6 (m, 12H), 1.75–1.9 (m, 4H), 2.4 (m, 1H), 2.55 (m, 1H), 3.3 (br s, 1H); ^{13}C NMR δ 14.3, 20.5, 23.1, 24.8, 25.9, 26.4, 29.4, 30.1, 32.4, 34.5, 52.1, 58.9, 59.0.

Compound **2**: 7% yield; $[\alpha]_D^{22} = +17.6$ (*c* 0.21, hexane); lit.[17] $[\alpha]_D^{22} = +29$ (*c* 0.80, hexane). ^{1}H NMR δ 0.9 (t, 3H), 1.15 (d, 3H), 1.2–1.8 (m, 16H), 2.05–2.25 (m, 2H), 2.5 (br t, 1H); ^{13}C NMR δ 14.25, 20.4, 22.9, 24.9, 29.4, 29.8, 30.4, 31.0, 35.9, 38.8, 60.3, 62.9, 67.3.

Compound **3**: 34% yield; $[\alpha]_D^{22} = -98$ (*c* 2.1, MeOH); lit.[4d] $[\alpha]_D^{22} = -103$ (*c* 1.12, hexane). ^{1}H NMR δ 0.9 (t and d, 6H), 1.1–1.5 (m, 16H), 1.6–1.75 (m, 4H), 2.1–2.35 (m, 2H), 2.5 (br t, 1H); ^{13}C NMR δ 14.2, 14.5, 19.6, 23.1, 24.9, 28.8, 30.5, 31.0, 31.9, 32.3, 38.1, 39.9, 65.9, 67.5.

Compound **4**: 13% yield; $[\alpha]_D^{22} = -87.5$ (*c* 0.83, MeOH); ^{1}H NMR δ 0.9 (m, 6H), 1.1–1.5 (m, 16H), 1.6–1.7 (m, 16H), 2.4 (m, 2H), 3.25 (br t, 1H); ^{13}C NMR δ 14.2, 14.5, 19.3, 22.9, 24.7, 25.0, 25.1, 26.4, 29.4, 30.9, 32.4, 35.9, 56.7, 58.6, 59.1. Anal. Calcd for $C_{15}H_{29}N$: C, 80.62; H, 13.11; N, 6.27. Found: C, 80.93; H, 13.58; N, 6.52.

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