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A radical approach towards indolizidine 167B

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Abstract—The alkaloids (+)- and (−)-indolizidine 167B were synthesized via radical addition of a carbon radical to a chiral acrylamide. Further cyclization in the presence of BBr_3, treatment with 'nickel boride' and stereospecific hydrogenation over palladium/carbon in acetic acid were other key steps in this synthesis.

Indolizidine alkaloids isolated as trace amounts from the skin of neotropical frogs display a wide range of biological activity.[1] Several asymmetric syntheses towards these alkaloids have been developed in the last decade, some of them to obtain the (−)-indolizidine 167B (**1**) (Fig. 1).[2] Despite the studies involving chiral auxiliaries to control the stereochemistry in radical reactions,[3] there are only a few examples of radical stereocontrol involved in indolizidine alkaloid synthesis.[2h,4]

We report herein a new synthesis towards indolizidine 167B where the stereocontrol is achieved by a stereoselective addition of a carbon radical onto an optically pure acrylamide. After the conversion of the α-amino acid DL-norvaline onto a pyrrole derivative by condensation with tetrahydro-2,5-dimethoxyfuran in acidic medium, the resulting carboxylic acid (**2**) was converted into the corresponding Barton ester (**4**) by DCC and *N*-hydroxy-2-thiopyridone (**3**) (Scheme 1).[5]

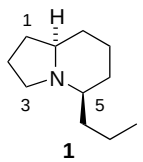

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Figure 1. (−)-Indolizidine 167B (**1**).

Low temperature irradiation† of **4** in dichloromethane yielded the corresponding carbon radical which, in the presence of an excess of chiral acrylates or acrylamides (**5**), prepared by the reaction of an optically pure alcohol or amine[6] with acryloyl chloride, gave rise to the addition products **6**.[7] The stereocontrol on the C-4 center was only achieved when an acrylamide was used (**5d–e**). Experiments performed with chiral acrylic esters derived from (1*R*,2*S*,5*R*)-(−)-menthol (**5a**), [(1*S*)-*endo*]-(−)-borneol (**5b**) and [(1*R*)-*endo*]-(+)-fenchol (**5c**) provided a good chiral induction at the C-2 center (32, 24 and 29% d.e., respectively) but lack induction at the C-4 stereogenic center on the addition product (**6a–c**). These addition products (**6a–c**) yielded 38–58% from **2**. When using (*S*)-*N*-(1-phenylethyl)acrylamide (**5d**), we obtained the *N*-(1-phenylethyl)-2-(2-pyridinylsulfanyl)-4-(1*H*-pyrrol-1-yl) heptanamide (**6d**) in 53% yield, with low chiral induction in the new stereogenic center C-4 close to pyrrole ring (53:47 of *S*/*R* ratio) and 32% of chiral induction at C-2. The herein C-4 configuration was established by the ^{13}C NMR data and the specific optical rotation on the latter compound (+)-**1**,[2m] since this stereocenter does not change along the synthetic pathway. When acetonitrile was used as solvent the (4*R*)-**6d** was the major stereoisomer formed in 16% d.e. If we use the hindered acrylamide, (*S*)-*N*-isopropyl-*N*-(1-phenylethyl) acrylamide (**5e**), a lower yield of addition product **6e** (12%) was achieved and with the bulky (*S*)-*N*-neopentyl-*N*-(1-phenylethyl)acrylamide (**5f**) no addition product was formed (Table 1).

The low yields obtained by the addition of carbon radicals to acrylamides have previously been reported

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† Phillips high pressure mercury vapour lamp with internal reflector, 125 HPR.

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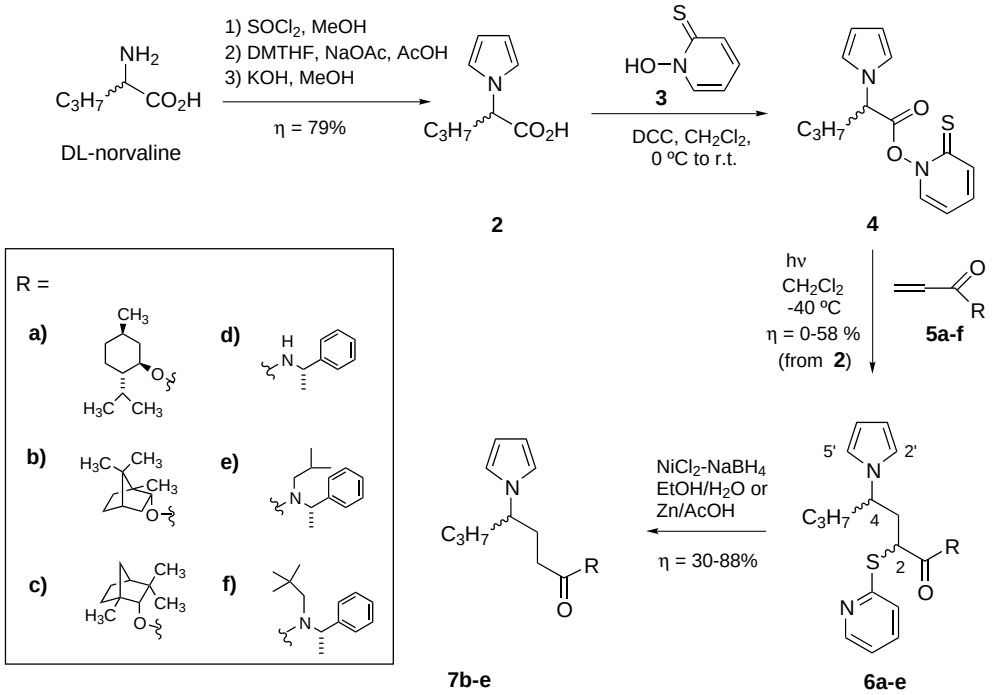


Scheme 1.

Table 1. Chemical yields of compounds **6** from **2** and **7** (%)

		a	b	c	d	e
6[a]	(4*R*)	21	29	15	25	5
7	(4*R*)	–	21[b]	15[b]	38[c]	31[c]
6[a]	(4*S*)	21	29	15	28	7
7	(4*S*)	–	21[b]	15[b]	42[c]	40[c]

[a] Both epimers at C-2 (2*S*,2*R*).
[b] Zn/acetic acid method.
[c] $NiCl_2$–$NaBH_4$ method.

by Barton and Liu.[8] All of the diastereomeric amide pairs (**6d–e**), *R* and *S* at C-2 and C-4 were resolved by TLC. This observation was important because it means that the addition products **6d–e** could be purified by column chromatography and the diastereomeric pure samples obtained (Scheme 1). Removal of the thiopyridyl group from **6** yielded **7**.[7] When the transformation is performed on the diastereomers (4*S*)-**6d** or (4*R*)-**6d**, the *N*-[(1*S*)-1-phenylethyl]-4-(1*H*-pyrrol-1-yl)heptanamides, (4*S*)-**7d** and (4*R*)-**7d**, are obtained, respectively (Table 2).

Treatment of **6d** with boron tribromide yielded the cyclic ketone **8** with concomitant removal of the chiral auxiliary (Scheme 2). Albeit this is a known reaction in ester derivatives[9] this is the first example involving the less reactive amide analogues. The thiopyridyl group bound to the C-2 center in **6d** plays an important role during ring closure. Its removal by the combination of nickel(II) chloride and sodium borohydride ('nickel boride'[8]) in aqueous ethanol solution or by zinc in acetic acid,[5] led to compounds **7b–e**. Treatment of **7d** by boron tribromide for 1 week led to the cyclic ketone **9**[7] in poor yield (18%). When the same reaction was performed in a pure diastereomer of **6d**, epimerization of the carbon center holding the thiopyridyl group was observed. It seems that the thiopyridyl group favours the amine elimination during ring closure, which yielded the desired cyclic ketone **8**[7] in 72%.

Removal of the thiopyridyl group by treatment with 'nickel boride' and catalytic stereospecific hydrogenation of the resulting ketone **9**, over palladium/carbon (10%) in acetic acid[9] yielded 74% of the desired indolizidine 167B (**1**) (Scheme 2, Table 2).

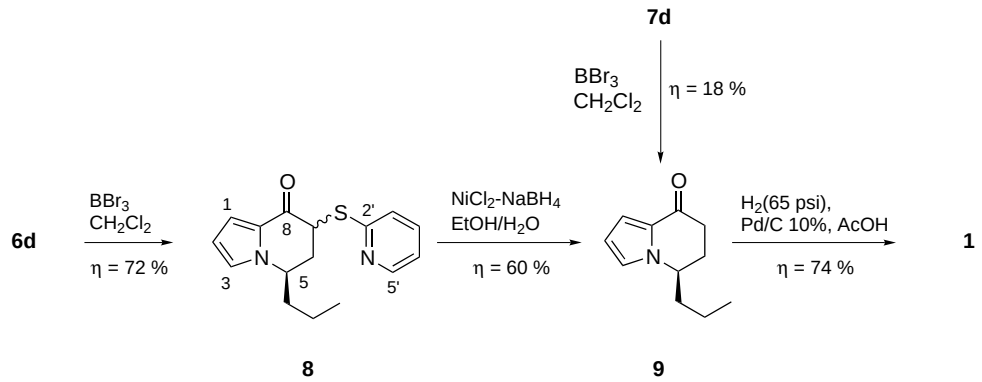
The enantiomer of **1** (+)-(5*S*,8a*S*)-indolizidine 167B, $[\alpha]_D^{25}=+101$ (*c* 0.44, CH_2Cl_2)[10] was achieved from the pure diastereomer (4*S*)-**6d** in 32% yield. A mixture of **6d** diastereomers (4*S* and 4*R*) yielded the (−)-(5*R*,8a*R*)-indolizidine 167B (**1**) mixed with the (+) enantiomer. The specific optical rotation value, $[\alpha]_D^{25}=-27.5$ (*c* 0.30, CH_2Cl_2),[11] agrees with the 4*S*/4*R* ratio calculated from the ^1H NMR spectrum.

In summary, we have developed a method for obtaining indolizidine 167B from racemic norvaline using a stereoselective addition of a carbon radical onto an optically pure acrylamide. This strategy involves the use of a Barton ester as the carbon radical precursor. The further application of this method to the synthesis of other indolizidine alkaloids is being pursued (Scheme 2).

Table 2. Specific optical rotation and ^{1}H and ^{13}C NMR spectroscopic data of compounds (4*S*)-**7d**, (4*R*)-**7d** and (5*S*)-**9**

	$[\alpha]_D^{25}$	^{1}H NMR δ (400 MHz, $CDCl_3$)	^{13}C NMR δ (100 MHz, $CDCl_3$)
7d (4*S*)	−41.4°[a]	7.30 (m, 5H, H_{arom}), 6.50 (d, 2H, J=1.6 Hz, H(2′), H(5′)), 6.10 (d, 2H, J=1.6 Hz, H(3′), H(4′)), 5.55 (brd, 1H, J=7.2 Hz, N-H), 5.09 (quint, 1H, J=7.2 Hz, C$\underline{H}$CH$_3$), 3.74 (m, 1H, H(4)), 2.10 (m, 1H, H(2)), 1.98 (m, 1H, H(3)), 1.84 (m, 2H, H(3), H(2)), 1.67 (m, 2H), 1.42 (d, 3H, J=6.8 Hz, CHC$\underline{H}_3$), 1.12 (m, 2H), 0.82 (t, 3H, J=7.2 Hz, CH$_2$C$\underline{H}_3$)	171.0, 143.7, 128.5, 127.3, 126.0, 118.8, 107.5, 59.1, 48.5, 38.8, 32.6, 31.9, 21.4, 19.2, 13.5
7d (4*R*)	−65.3°[b]	7.32 (m, 5H, H_{arom}), 6.62 (s, 2H, $\underline{H}$(2′), H(5′)), 6.13 (s, 2H, H(3′), H(4′)), 5.54 (d, 1H, J=6.0 Hz, N-H), 5.09 (quint, 1H, J=6.8 Hz, C$\underline{H}$CH$_3$), 3.84 (m, 1H, H(4)), 2.18 (m, 1H, H(2)), 1.90 (m, 3H, H(3), H(2)), 1.71 (m, 2H), 1.46 (d, 3H, J=6.8 Hz, CHC$\underline{H}_3$), 1.16 (m, 2H), 0.85 (t, 3H, J=7.2 Hz, CH$_2$C$\underline{H}_3$)	171.0, 143.0, 128.5, 127.2, 126.0, 118.8, 107.6, 59.2, 48.6, 38.8, 32.6, 31.8, 21.6, 19.3, 13.6
9 (5*S*)	+13.2°[c]	7.02 (dd, 1H, J=4.0, 1.2 Hz, H(3)), 6.92 (m, 1H, H(1)), 6.24 (dd, 1H, J=4.0, 2.4 Hz, H(2)), 4.18 (m, 1H, H(5)), 2.67 (m, 1H, H(7)), 2.52 (m, 1H, H(7)), 2.37 (m, 1H, H(6)), 2.12 (m, 1H, H(6)), 1.90 (m, 1H, C$\underline{H}_2$CH$_2$CH$_3$), 1.76 (m, 1H, C$\underline{H}_2$CH$_2$CH$_3$), 1.44 (m, 2H, CH$_2$C$\underline{H}_2$CH$_3$), 0.99 (t, 3H, J=7.4 Hz, CH$_2$C$\underline{H}_3$)	187.4, 130.3, 125.1, 114.3, 110.1, 54.4, 38.8, 33.1, 27.5, 19.1, 13.7

[a] c 8.20, $CHCl_3$.
[b] c 1.05, $CHCl_3$.
[c] c 0.63, $CHCl_3$.



Scheme 2.

Acknowledgements

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7. The new compounds gave satisfactory spectral and high resolution mass data: (1*S*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl-2-(2-pyridinylsulfanyl)-4-(1*H*-pyrrol-1-yl)heptanoate (**6a**): MALDI-FTMS HRMS (DHB): *m*/*z*: 465.2536 [M+Na$^+$] calcd for $C_{26}H_{38}N_2O_2S$ 465.2546; (2*R*)-4,7,7-trimethylbicyclo[2.2.1]hep-2-yl-2-(2-pyridinylsulfanyl)-4-(1*H*-pyrrol-1-yl)heptanoate (**6b**): MALDI-FTMS HRMS (DHB): *m*/*z*: 441.2571 [M+H$^+$] calcd for $C_{26}H_{36}N_2O_2S$ 441.2570; (2*S*)-1,3,3-trimethylbicyclo-[2.2.1]hept-2-yl-2-(2-pyridinylsulfanyl)-4-(1*H*-pyrrol-1-yl)-heptanoate (**6c**): MALDI-FTMS HRMS (DHB): *m*/*z*: 441.2579 [M+H$^+$] calcd for $C_{26}H_{36}N_2O_2S$ 441.2570; *N*-((1*S*)-1-phenylethyl)-2-(2-pyridinylsulfanyl)-4-(1*H*-pyrrol-1-yl)heptanamide (**6d**): MALDI-FTMS HRMS (DHB): *m*/*z*: 430.1942 [M+Na$^+$] calcd for $C_{24}H_{29}N_3OS$ 430.1924; *N*-isobutyl-*N*-[(1*S*)-phenylethyl]-2-(2-pyridinylsulfanyl)-4-(1H-pyrrol-1-yl)heptanamide (**6e**): MALDI-FTMS HRMS (DHB): *m*/*z*: 486.2570 [M+Na$^+$] calcd for $C_{28}H_{37}N_3OS$ 486.2550; *N*-[(1*S*)-1-phenylethyl]-4-(1*H*-pyrrol-1-yl)heptanamide (**7d**): MALDI-FTMS HRMS (DHB): *m*/*z*: 299.2104 [M+H$^+$] calcd for $C_{19}H_{26}N_2O$ 299.2118; 5-propyl-7-(2-pyridinylsulfanyl)-6,7-dihydro-8(5*H*)-indolizinone (**8**): oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, 1H, J=4.4 Hz, H(5′)), 7.50 (t, 1H, J=7.6 Hz, H(3′)), 7.27 (s, 1H, H(3)), 7.09 (m, 1H, H(4′)), 7.02 (d, 1H, J=4.4 Hz, H(2′)), 7.00 (d, 1H, J=5.6 Hz, H(2′)), 6.93 (s, 1H, H(1)), 6.31 (m, 1H, H(2)), 6.28 (m, 1H, H(2)), 5.15 (dd, 1H, J=9.4, 5.3 Hz, H(5)), 5.06 (dd, 1H, J=12.3, 4.7 Hz, H(5)), 4.34 (t, 1H, J=4.7 Hz, H(7)), 2.60 (m, 2H, H(6)), 2.65 (m, 2H, H(6)), 2.32 (q, 2H, J=11.6 Hz, $C\underline{H}_2CH_2CH_3$), 1.96 (q, 2H, J=7.6 Hz, $C\underline{H}_2CH_2CH_3$), 1.51 (m, 2H, $CH_2C\underline{H}_2CH_3$), 1.02 (t, 3H, J=7.3 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.4, 156.1, 149.3, 125.3, 123.6, 122.9, 122.8, 119.9, 119.7, 116.6, 115.5, 115.4, 110.8, 55.3, 54.1, 48.5, 45.4, 36.8, 36.5, 35.9, 35.1, 19.3, 18.0, 13.9; MALDI-FTMS HRMS (DHB): *m*/*z*: 287.1212 [M+H$^+$] calcd for $C_{16}H_{18}N_2OS$ 287.1213; 5-propyl-6,7-dihydro-8(5*H*)-indolizinone (**9**): MALDI-FTMS HRMS (DHB): *m*/*z*: 178.1220 [M+H$^+$] calcd for $C_{11}H_{15}NO$ 178.1226.
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11. Previously described values for (−)-(5*R*,8a*R*)-indolizidine 167B (1): $[\alpha]_D^{20}=-106.9$ (*c* 1.10, CH_2Cl_2)[2c] and references cited therein.