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Stereoselective conjugate addition of lactams to nitroalkenes and formal total synthesis of indolizidine 167B

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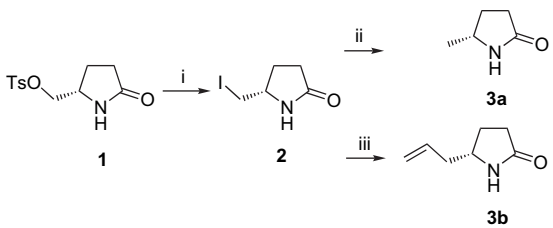
Abstract—Optically active 5-substituted pyrrolidin-2-ones underwent conjugate addition to nitroalkenes to give the corresponding adducts in a diastereoselective manner. The presence of 18-crown-6 was crucial to achieve good stereoselective addition. Addition of 6-substituted piperidin-2-ones also gave the corresponding adduct in a stereoselective manner. The adduct was readily converted into a bicyclic lactam through intramolecular nitroaldol reaction, and the formal synthesis of indolizidine 167B was achieved.

1. Introduction

Conjugate addition to nitroalkenes is one of the useful reaction to construct carbon backbones in organic synthesis.[1] So far a variety of carbon as well as heteroatom nucleophiles have been utilized for the reaction. Nitrogen nucleophiles are frequently used in the preparation of β-diamines and heterocyclic compounds.[2] Although amines act as a good nucleophile toward the reaction, the adducts, β-nitroamines, are usually labile and sometimes present serious limitation in their handling during synthesis.[3] On the other hand, β-nitroamides are usually stable enough for use in organic synthesis, while the conjugate addition of amide to nitroalkene has been quite rarely employed for the preparation.[4] Recently, we have reported that formamides work as a good nucleophile for the conjugate addition to nitroalkenes.[5] Mioskowski and his co-workers reported asymmetric conjugate addition to nitroalkenes with aza-nucleophiles using optically active oxazolidinones.[6] Their work prompted us to examine cyclic lactam as a nucleophile that should be potentially useful for the construction of bicyclic alkaloids. In this paper we report that the stereoselective addition of 5-substituted pyrrolidin-2-ones and 6-substituted piperidin-2-one to nitroalkenes to give potential precursors for the synthesis of aza-heterocyclic compounds. We also examined the application of the present method to the formal synthesis of indolizidine 167B, which was detected by Daly and his group from neotropical frog genera *Dendrobates*.[7] There have been many reports of its total synthesis[8,9] due to its interesing biological activity.

2. Results and discussion

Optically active 5-substituted pyrrolidinones **3** were prepared through the route shown in Scheme 1. Tosylpyrrolidinone **1**, which was readily available from L-pyroglutamic acid,[10] was converted to iodide **2**, which was then reduced by Bu_3SnH to give **3a**. Treatment of **2** with vinyl copper reagent afforded **3b** in good yield. Optical purity of both pyrrolidinones **3** was checked by HPLC analyses on CHIRALCEL OD-H.



Scheme 1. Preparation of optically active pyrrolidinones **3**. Reagents and conditions: (i) NaI, acetone reflux, 88%; (ii) Bu_3SnH, AIBN, toluene, 90 °C, 89% (94% ee); (iii) CH_2=CHMgBr (5.5 equiv), CuI (2.5 equiv), THF, −30 °C, 1 h, 64% (90% ee).

With chiral nucleophiles in hand, nucleophilic addition of **3a** to nitroalkene **4a** was examined under various conditions (Scheme 2). The results are summarized in Table 1.

Keywords: Michael addition; Lactams; Alkaloids; Aldol reaction.
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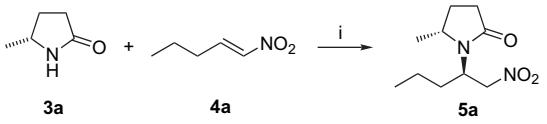


Scheme 2. Conjugate addition of **3a** to nitroalkenes **4a**. Reagents and conditions: (i) ^{t}BuOK, 18-crown-6, H_2O, THF, −50 °C then NH_4Cl aq.

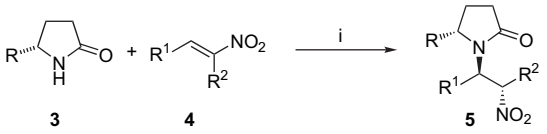
Table 1. Conjugate addition of **3a** to **4a** under various conditions

Entry	18-Crown-6 (equiv)	H_2O (equiv)	**5a** (Yield,[a] %)	dr[b]
1	0	0	61	65:35
2	1	0	42	96:4
3	0.5	0	35	86:14
4	1	1	66	89:11
5	0.5	1	53	93:3

[a] Isolated yield.
[b] Determined by GC analyses.

The addition took place efficiently when **3a** was treated with 1 equiv of base, while two diastereomers of **5a** were formed in a 65:35 ratio (entry 1). To improve the diastereoselectivity, 18-crown-6 was added to the reaction mixture. Although the yield of **5a** remained at a moderate level, the stereoselectivity was dramatically improved to 96:4 (entry 2). 18-Crown-6 effectively achieved high selectivity when reduced to 0.5 equiv (entry 3). Addition of 1 equiv of water in the presence of 18-crown-6 raised the yield of **5a** to 66% (entry 4).[11]

We next examined the present reaction conditions for nucleophilic addition of **3** to various nitroalkenes (Scheme 3). The results are summarized in Table 2.



Scheme 3. Stereoselective conjugate addition of pyrrolidinones **3**. Reagents and conditions: (i) ^{t}BuOK (1 equiv), 18-crown-6 (1 equiv), H_2O (1 equiv), THF, −50 °C then NH_4Cl aq.

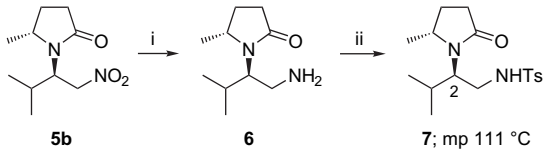
The conjugate addition proceeded smoothly, giving desired adducts **5** in good yield. For example, 3-methyl-1-nitrobutene underwent the conjugate addition of **3a** to give **5b** in 71% yield (entry 2). The stereoselectivity of the reaction was sufficiently high that **5b** was isolated as an almost single diastereomer. Purified **5b** indicated negative optical rotation. Either substituent at C5 in **3** or R^1 in **4** had very little effect on the stereoselectivity; adducts **5** were generally isolated in a similar level of high selectivity (entries 2–4). The presence of the α-substituent in nitroalkene **4** generated additional stereogenic carbon so that four diastereomers might be produced in the reaction. However, protonation of the reaction intermediate at low temperature controls the configuration at the carbon adjacent to the nitro group so that stereoselective addition would be expected.[12] In such case, protonation to the nitronate intermediate occurs from the opposite side of the heteronucleophile attacking, giving *anti*-isomer as the major adduct. Indeed, the single diastereomer of **5e** was obtained as a major isomer in the reaction of 2-methyl-2-nitrobutene with **3a** quenched at −50 °C (entry 5). The diastereomeric ratio of the four isomers was found to be 74:15:9:2 by HPLC analysis. Therefore the stereochemistry of the β-position as well as the α-position in nitroalkene **4** was well-controlled during the present addition reaction.

Table 2. Stereoselective conjugate addition of pyrrolidinones **3**

Entry	R	R^1	R^2	**5** (Yield,[a] %)	dr[b]
1	Me	Pr	H	**5a** (66)	89:11
2	Me	^{i}Pr	H	**5b** (71)	93:7
3	CH_2=$CHCH_2$	Pr	H	**5c** (58)	93:7
4	CH_2=$CHCH_2$	^{i}Pr	H	**5d** (54)	99:1
5	CH_2=$CHCH_2$	Me	Me	**5e** (45)	74:15:9:2[c]

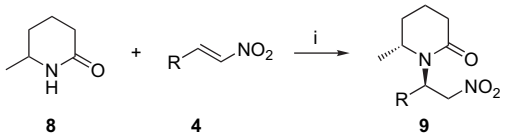
[a] Isolated yield.
[b] Determined by GC analyses.
[c] Determined by HPLC analyses.

The relative configuration of the adduct **5** was determined by using X-ray crystallographic analysis after appropriate chemical conversion (Scheme 4). The nitro group in compound **5b** was quantitatively reduced to the amino group on treatment with hydrogen in the presence of 10% Pd–C. The obtained amine **6** was tosylated under standard conditions to give crystal tosylamide **7** in 58% yield, X-ray analysis of which showed the newly formed stereogenic center at C2 to be *R*.[13] Thus, the sense of the stereoselection for the conjugate addition was the same as the reaction of chiral oxazolidinones reported by Mioskowski et al.[6]



Scheme 4. Structural determination of the conjugate adduct **5**. Reagents and conditions: (i) H_2/Pd–C, 40 atm, MeOH; (ii) TsCl, DMAP, Et_3N, 58% (2 steps).

Piperidinone **8** was examined as a nucleophile in conjugate additions to nitroalkenes (Scheme 5). The results are summarized in Table 3.



Scheme 5. Stereoselective conjugate addition of piperidinone **8**. Reagents and conditions: (i) ^{t}BuOK (1 equiv), 18-crown-6 (1 equiv), H_2O (1 equiv), THF, −50 °C.

Basic treatment of piperidinone **8** also resulted in the smooth formation of adduct **9a** in moderate yield. Absence of

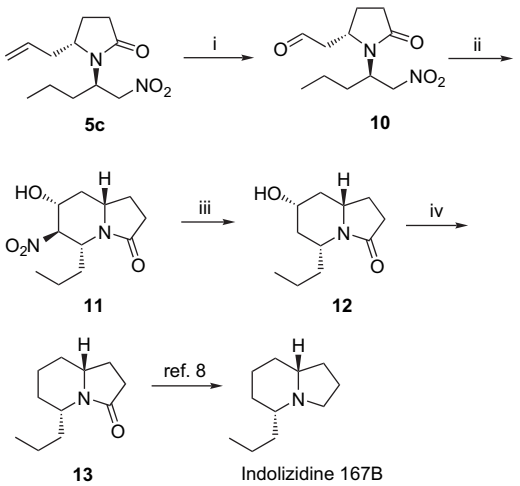
Table 3. Stereoselective conjugate addition of piperidinone **8**

Entry	R	18-crown-6 (equiv)	**9** (Yield,[a] %)	dr[b]
1	Pr	0	**9a** (48)	57:43
2	Pr	1	**9a** (49)	84:16
3	^{i}Pr	1	**9b** (47)	71:29

[a] Isolated yield.
[b] Determined by GC analyses.

18-crown-6 gave a 1:1 mixture of two possible isomers of **9a** (entry 1), but the presence of 18-crown-6 improved the diastereoselectivity to 84:16 (entry 2). Unfortunately, the present selectivity was spoiled when a sterically bulky substituent occupied at the β-position of nitroalkenes (entry 3).

We then examined the application of the present method to the formal synthesis of indolizidine 167B (Scheme 6). Our synthesis started from compound **5c** prepared from 1-nitro-1-pentene. The vinyl group in adduct **5c** was converted to aldehyde by treatment with OsO_4 and NMO followed by $NaIO_4$ and compound **10** was isolated in 60% yield. The formyl group then underwent an intramolecular nitroaldol reaction by basic treatment to give indolizidinone **11** in good yield. Compound **11** was isolated as a white solid that contained a single diastereomer so that we assumed that the aldol reaction took place in a stereoselective manner. The stereochemistry of **11** was unambiguously determined by X-ray crystallographic analysis.[14] Both of the nitro and the hydroxyl groups in compound **11** occupy pseudo-equatorial positions so that the stereoselectivity of the present intramolecular nitroaldol reaction could be thermodynamically controlled. Following removal of the nitro[15] and the hydroxyl groups of **11** was achieved through radical reduction to give **13**. The spectral data and negative value of optical rotation of compound **13**, which was previously converted to indolizidine 167B, were identical to the reported ones.[8] Thus, we finished the formal synthesis of indolizidine 167B. Since the present procedure is regarded to be useful for the preparation of the analogous alkaloids such as indolizidine 209D,[16] our present method provides a new procedure for general synthesis of these alkaloids containing bicyclic structure.



Scheme 6. Formal total synthesis of indolizidine 167B. Reagents and conditions: (i) OsO_4/NMO then $NaIO_4$, 60%; (ii) DBU/CH_3CN, 62%; (iii) Bu_3SnH, AIBN, toluene, reflux, 58%; (iv) $Im_2C{=}S$, DMAP then Bu_3SnH, AIBN, 79%.

In conclusion, we have succeeded in providing the stereoselective conjugate addition of a nitrogen nucleophile in 5-membered and 6-membered lactams to nitroalkenes. The reaction takes place smoothly and the addition of 18-crown-6 to the reaction mixture improves the diastereoselectivity of the reaction. The adducts of the reaction are potential precursors for aza-heterocyclic compounds. The present method will provide a new strategy for the construction of such optically active heterocyclic compounds. Further research on the present methodology is now underway in our laboratory.

3. Experimental section

3.1. General

All ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 and recorded on JEOL EX-270 (270 MHz for ^1H and 67.5 MHz for ^{13}C) or Brucker Advance 500 (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer. All the reactions in this paper were performed under nitrogen atmosphere unless otherwise mentioned. Dichloromethane and toluene were dried over CaH_2 and sodium, respectively, and distilled under nitrogen before use. Anhydrous ether and THF were purchased from Kanto Chemical Co. Ltd. Optical rotations were measured on HORIBA SEPA-200 Digital Polarimeter at room temperature, using the sodium D line. Elemental analyses and high resolution mass spectra (HRMS) were measured at Integrated Center for Sciences, Ehime University, Matsuyama, Japan.

3.1.1. Preparation of (5*S*)-5-(*p*-toluenesulfonyloxy)methylpyrrolidin-2-one [1]. To a solution of L-(*S*)-pyroglutamic acid (32.20 g, 250.2 mmol) in ethanol (300 mL) was added $SOCl_2$ (10 mL, 150 mmol) at room temperature slowly and the resulting solution was allowed to stir for 1 h. Saturated $NaHCO_3$ aq was added to adjust pH of the solution to 8. Ethanol was removed in vacuo and the resulting water phase was extracted with CH_2Cl_2 (3×80 mL). The organic phase was combined and dried over Na_2SO_4. Filtration and evaporation gave crude ester of 40.57 g, which was used for next step without further purification. The ester (40.57 g) was dissolved in EtOH (200 mL) and $NaBH_4$ (22.02 g, 582.1 mmol) was added portionwise over 2 h. The reaction mixture was allowed to stir at room temperature for additional 20 h. HCl (12 M, 30 mL) was added to the reaction mixture and the resulting mixture was filtered. The filtrate was concentrated in vacuo to give crude alcohol of 34.63 g, which was used for the next step. The crude alcohol was dissolved in CH_2Cl_2 (15 mL) and Et_3N (60 mL, 433 mmol) and DMAP (1 g) was added. To the solution, TsCl (52.43 g, 275 mmol) was added slowly at 0 °C. The reaction mixture was allowed to stir at room temperature for 24 h. HCl (1 M, 100 mL) was added and the organic layer was separated. The water phase was extracted with CH_2Cl_2 (3×80 mL). The organic phase was combined and dried over Na_2SO_4. Filtration and evaporation yielded crude **1**, which was purified through flash column chromatography (silica gel, hexane–EtOAc 5:1 then 1:4 v/v) to give compound **1** in 43% yield (29.24 g, 108.7 mmol).

White solid; mp 125 °C; $[\alpha]_D$ −20.2 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.70–1.86 (m, 1H), 2.18–2.36 (m, 3H), 2.47 (s, 3H), 3.86 (dd, 1H, *J*=6.9, 8.4 Hz), 3.92–3.98 (m, 1H), 4.07 (dd, 1H, *J*=3.4, 9.4 Hz), 6.11 (br, 1H), 7.37 (d, 2H, *J*=8.4 Hz), 7.79 (d, 2H, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.7, 29.2, 52.7, 71.9, 127.9, 130.0, 132.3, 143.3, 145.4, 177.9.

3.1.2. Preparation of (5*S*)-5-iodomethylpyrrolidin-2-one [2]. Compound **1** (7.13 g, 26.5 mmol) was added to a solution of NaI (11.9.4 g, 79.4 mmol) in acetone (100 mL) and the reaction mixture was heated under refluxing conditions for 5 h. After cooling, acetone was removed in vacuo and water was added to the residue. The resulting water phase was extracted with CH_2Cl_2 (3×50 mL). The organic phase was combined and dried over Na_2SO_4. Filtration and evaporation gave compound **2** in 93% yield (5.522 g, 24.5 mmol).

Pale yellow solid; mp 78 °C; $[\alpha]_D$ +11.6 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.76–1.89 (m, 1H), 2.29–2.57 (m, 3H), 3.20 (dd, 1H, *J*=6.4, 9.9 Hz), 3.25 (dd, 1H, *J*=5.9, 10.3 Hz), 3.82–3.91 (m, 1H), 6.50 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.4, 27.3, 30.2, 55.1, 178.2. Anal. Calcd for C_5H_8INO: C, 20.69; H, 3.58; N, 6.22. Found: C, 26.70; H, 3.49; N, 6.12.

3.1.3. Preparation of (5*R*)-5-methylpyrrolidin-2-one [3a]. A solution of compound **2** (0.893 g, 4.0 mmol), Bu_3SnH (3.3 mL, 12.0 mmol), and AIBN (0.412 g, 2.5 mmol) in toluene (815 mL) was allowed to heat at 110 °C for 2 h. The crude product was purified through flash column chromatography (silica gel, hexane–EtOAc, 5:1 then 1:3 v/v) to give **3a** in 89% yield (0.351 g, 3.5 mmol).

Pale yellow oil; 94% ee (CHIRALCEL OD-H, hexane–2-propanol 95:5); $[\alpha]_D$ −8.2 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23 (d, 3H, *J*=5.9 Hz), 1.60–1.71 (m, 1H), 2.21–2.45 (m, 3H), 3.79 (m, 1H), 6.10 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 22.9, 29.5, 31.1, 49.8, 177.2; IR (film) 1277, 1379, 1424, 1697, 2876, 2930, 2967, 3237 cm^{-1}.

3.1.4. Preparation of (5*S*)-5-allylpyrrolidin-2-one [3b]. To a mixture of compound **2** (0.222 g, 0.97 mmol) and CuI (0.475 g, 2.5 mmol) in THF (2 mL) was added vinylmagnesium bromide in THF (1 M, 5.5 mL, 5.5 mmol) at −30 °C and the reaction mixture was allowed to stir for 18 h at the same temperature. NH_4Cl aq (20 mL) and water (10 mL) were added to the mixture and the water phase was extracted with CH_2Cl_2 (3×20 mL). The organic phase was combined and dried over Na_2SO_4. Filtration and evaporation gave crude compound **3b**, which was purified through flash column chromatography (silica gel, hexane–EtOAc 5:1 then 1:3 v/v) to give **3b** in 64% yield (0.078 g, 0.62 mmol).

Oil; 90% ee (CHIRALCEL OD-H, hexane–2-propanol 98:2); $[\alpha]_D$ −61.0 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.71–1.84 (m, 1H), 2.14–2.38 (m, 5H), 3.72 (m, 1H), 5.11–5.18 (m, 2H), 5.75 (dddd, 1H, *J*=6.0, 7.9, 9.9, 13.9 Hz), 5.87 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 26.5, 30.2, 40.9, 53.7, 118.3, 133.6, 178.3; IR (film) 916, 997, 1288, 1385, 1425, 1643, 1694, 2926, 2976, 3078, 3223 cm^{-1}.

3.2. General procedures for the conjugate addition of pyrrolidinone 3 to nitroalkenes 4

3.2.1. Preparation of (5*R*)-5-methyl-1-((1*R*)-1-nitromethylbutyl)-pyrrolidin-2-one [5a]. To a solution of ^{t}BuOK (0.0673 g, 0.60 mmol) and 18-crown-6 (0.159 g, 0.10 mmol) in anhydrous THF (4 mL) at 0 °C were added 5-methylpyrrolidin-2-one **3a** (0.0530 g, 0.53 mmol) and water (10.8 μL, 0.60 mmol). The solution was cooled to −50 °C and nitroalkene **4a** (0.0747 g, 0.65 mmol) was added. The reaction mixture was allowed to stir at the same temperature until starting materials disappeared for 1 h. The reaction mixture was poured into NH_4Cl aq (10 mL) and the water layer was extracted with EtOAc (3×20 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure to give crude product, which was purified through flash column chromatography (silica gel, hexane–EtOAc 10:1 then 2:1 v/v) to give **5a** in 66% yield (0.075 g, 0.35 mmol).

Colorless oil; $[\alpha]_D$ −46.6 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J*=6.9 Hz), 1.17 (d, 3H, *J*=6.4 Hz), 1.24–1.44 (m, 2H,), 1.55–1.67 (m, 3H), 2.05 (ddd, 1H, *J*=5.2, 9.4, 13.4 Hz), 2.14–2.49 (m, 2H), 3.67 (m, 1H, *J*=6.4 Hz) 3.97 (m, 1H, *J*=5.5 Hz), 4.54 (dd, 1H, *J*=4.7, 11.9 Hz), 5.21 (dd, 1H, *J*=9.1, 11.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.6, 20.2, 27.4, 30.4, 32.1, 53.0, 55.7, 76.4, 175.9; IR (film) 1281, 1364, 1381, 1424, 1553, 1696, 2874, 2934, 2965 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.07. Found: C, 55.87; H, 8.40; N, 12.93.

3.2.2. (5*R*)-5-Methyl-1-((1*R*)-2-methyl-1-nitromethylpropyl)-pyrrolidin-2-one [5b]. Colorless oil; $[\alpha]_D$ −48.2 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (d, 3H, *J*=6.4 Hz), 1.01 (d, 3H, *J*=6.4 Hz), 1.14 (d, 3H, *J*=6.4 Hz), 1.55–1.69 (m, 1H), 2.16–2.53 (m, 4H), 3.51 (dt, 1H, *J*=3.5, 9.4 Hz), 3.66 (m, 1H), 4.62 (dd, 1H, *J*=4.0, 11.9 Hz), 5.32 (dd, 1H, *J*=9.9, 11.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.7, 19.9, 20.0, 27.4, 29.0, 30.4, 56.5, 59.8, 75.4, 175.7; IR (film) 1283, 1360, 1381, 1424, 1553, 1686, 2876, 2934, 2970 cm^{-1}. HRMS (FAB^+ M+1) *m/z* 215.1395 calcd for $C_{10}H_{19}N_2O_3$ 215.1396.

3.2.3. (5*S*)-5-Allyl-1-((1*R*)-1-nitromethylbutyl)-pyrrolidin-2-one [5c]. Colorless oil; $[\alpha]_D$ −71.4 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (t, 3H, *J*=6.9 Hz), 1.29–1.42 (m, 2H), 1.54–1.67 (m, 1H), 1.73–1.85 (m, 1H), 1.99–2.49 (m, 6H), 3.59 (tt, 1H, *J*=4.0, 7.9 Hz), 3.97 (tt, 1H, *J*=5.5, 8.9 Hz), 4.64 (dd, 1H, *J*=6.0, 12.4 Hz), 5.12–5.20 (m, 3H), 5.62–5.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.6, 24.1, 30.3, 32.2, 38.2, 53.3, 59.7, 76.5, 118.9, 132.7, 176.1; IR (film) 920, 1288, 1366, 1383, 1424, 1553, 1641, 1682, 2874, 2934, 2961 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.68; H, 8.36; N, 11.28.

3.2.4. (5*S*)-5-Allyl-1-((1*R*)-2-methyl-1-nitromethylpropyl)-pyrrolidin-2-one [5d]. Colorless oil; $[\alpha]_D$ −75.9 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (d, 3H, *J*=6.9 Hz), 1.00 (d, 3H, *J*=6.4 Hz), 1.74–1.85 (m, 1H), 1.99–2.53 (m, 6H), 3.51–3.61 (m, 2H), 4.68 (dd, 1H, *J*=4.4, 12.4 Hz), 5.14 (d, 1H, *J*=10.4 Hz), 5.16 (d, 1H, *J*=16.3 Hz), 5.30 (dd, 1H, *J*=8.9, 12.4 Hz), 5.60–5.75 (m, 1H) ^{13}C NMR ($CDCl_3$) δ 19.9, 24.0, 29.4, 30.2, 37.7, 59.9, 60.6, 75.7, 118.8, 132.8, 176.0; IR (film) 922, 997, 1290, 1364, 1383, 1425, 1553, 1641, 1688, 2876, 2936, 2969 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.89; H, 8.34; N, 11.50.

3.2.5. (5*S*)-5-Allyl-1-((1*R*)-1-methyl-2-nitropropyl)pyrrolidin-2-one [5e]. Colorless oil; $[\alpha]_D$ −79.1 (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (d, 3H, *J*=6.6 Hz), 1.51 (d, 3H, *J*=6.6 Hz), 1.77–1.91 (m, 1H), 2.10–2.60 (m, 5H), 3.59 (tt, 1H, *J*=4.3, 8.2 Hz), 3.83 (qd, 1H, *J*=6.6, 9.6 Hz),

5.19 (d, 1H, J=10.9 Hz), 5.20 (d, 1H, J=16.5 Hz), 5.40 (qd, 1H, J=6.6, 9.3 Hz), 5.66–5.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.6, 24.4, 30.1, 38.9, 52.5, 57.7, 85.3, 119.1, 132.5, 176.0; IR (film) 922, 993, 1290, 1354, 1381, 1422, 1549, 1641, 1686, 2942, 2980 cm^{-1}. HRMS (FAB$^+$ M+1) m/z 227.1394 calcd for $C_{11}H_{19}N_2O_3$ 227.1396.

3.2.6. 6-Methyl-1-(1-nitromethylbutyl)piperidin-2-one [9a]. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J=7.4 Hz), 1.23 (d, 3H, J=6.3 Hz), 1.23–1.69 (m, 2H), 1.79–1.90 (m, 4H), 2.07–2.18 (m, 2H), 2.21–2.37 (m, 2H), 3.47 (m, 1H), 3.64–3.74 (m, 1H) 4.81 (dd, 1H, J=6.3, 12.4 Hz), 4.99 (dd, 1H, J=5.9, 12.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 16.3, 19.7, 19.9, 29.8, 32.6, 32.7, 55.4, 59.5, 78.6, 170.9; IR (film) 1184, 1298, 1368, 1381, 1420, 1474, 1551, 1640, 2874, 2938, 2961 cm^{-1}. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.85; H, 8.82; N, 12.11.

3.2.7. 6-Methyl-1-(2-methyl-1-nitromethylpropyl)piperidin-2-one [9b]. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, J=6.9 Hz), 0.96 (d, 3H, J=6.9 Hz), 1.21 (d, 3H, J=6.4 Hz), 1.61–1.92 (m, 4H), 2.34–2.39 (m, 2H), 2.51–2.62 (m, 1H), 3.28 (m, 1H), 3.44–3.53 (m, 1H), 4.82 (dd, 1H, J=5.0, 13.4 Hz), 5.05 (dd, 1H, J=5.9, 13.4 Hz); ^{13}C NMR ($CDCl_3$) δ 16.3, 19.6, 19.8, 19.9, 29.5, 29.8, 32.5, 56.3, 66.2, 78.4, 170.6; IR (film) 1184, 1294, 1366, 1381, 1418, 1474, 1551, 1640, 2876, 2967 cm^{-1}. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.61; H, 8.81; N, 12.05.

3.2.8. (5*R)-5-methyl-((1*R**)-1-*p*-toluenesulfonamidomethyl-2-methylpropyl)-pyrrolidin-2-one [7].** To a solution of racemic **5b** (0.428 g, 2.0 mmol) and AcOH (0.11 mL) in MeOH (15 mL) was added 10% Pd–C (0.246 g) and the reaction mixture was shaken in autoclave (50 mL) under hydrogen atmosphere at 30 atm for 12 h. The reaction mixture was filtered on Celite and the filtrate was concentrated in vacuo to give crude **6** (0.759 g), which was used next step without purification. The crude **6** (0.184 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and Et_3N (0.29 mL, 2.1 mmol) was added. To the solution, *p*-TsCl (0.209 g, 1.10 mmol) was added at 0 °C and the reaction mixture was allowed to stir at room temperature for 24 h. HCl aq (10 mL) was added to the solution and the water phase was extracted with EtOAc (3×20 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, the filtrated was concentrated and the residue was purified through flash column chromatography (silica gel, hexane–EtOAc 10:1 then 1:2 v/v) to give **7** in 58% yield (0.195 g, 0.58 mmol).

White solid; mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3H, J=6.9 Hz), 0.91 (d, 3H, J=6.9 Hz), 1.15 (d, 3H, J=5.9 Hz), 1.23–33 (m, 1H), 1.53–1.60 (m, 1H), 2.17–2.28 (m, 1H), 2.31–2.45 (m, 2H), 2.42 (s, 3H), 2.87–2.99 (m, 2H), 3.49–3.67 (m, 2H), 6.16–6.20 (m, 1H), 7.30 (d, 2H, J=7.9 Hz), 7.73 (d, 2H, J=7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 20.1, 20.5, 21.4, 27.1, 27.5, 30.5, 44.0, 57.3, 61.0, 126.9, 129.4, 136.9, 142.9, 176.4. Anal. Calcd for $C_{17}H_{26}N_2O_3S$: C, 60.33; H, 7.74; N, 8.28. Found: C, 60.44; H, 7.81; N, 8.24.

3.2.9. (5*S*)-5-Formylmethyl-1-((1*R*)-1-nitromethylbutyl)-pyrrolidin-2-one [10]. To a solution of NMO (0.882 g, 7.51 mmol) in acetone–water (1:3 v/v, 20 mL) were added compound **5c** (1.640 g, 6.82 mmol) and OsO_4 (5 mg), and the resulting solution was allowed to stir at room temperature for 20 h. The reaction mixture was filtered on hyflo super-cel and the filtrate was neutralized by adding dil H_2SO_4 aq. Acetone was removed in vacuo and the residue was acidified to pH 2 by adding dil H_2SO_4 aq The water phase was extracted with 1-butanol (5×15 mL). The organic phase was combined and washed with brine (20 mL). After concentration, crude diol was isolated and used for the next step without purification. The crude diol was dissolved in CH_2Cl_2 (10 mL) and the solution was slowly added to a biphasic mixture of silica gel (10 g) and $NaIO_4$ (0.979 g, 4.45 mmol) in water (10 mL)/CH_2Cl_2 (80 mL). The resulting mixture was stirred vigorously for 30 min. Silica gel was removed by filtration and the organic phase was separated and dried over Na_2SO_4. After filtration, the filtrate was concentrated and the residue was purified through flash column chromatography (silica gel, hexane–EtOAc 10:1 then 1:3 v/v) to give aldehyde **10** in 60% yield (0.991 g, 4.09 mmol).

Colorless oil; $[\alpha]_D$ −89.9 (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.4 Hz), 1.38 (m, 2H, J=7.4 Hz), 1.55–1.70 (m, 2H), 1.96–2.48 (m, 1H), 2.27–2.48 (m, 3H), 2.61 (dd, 1H, J=8.4, 18.8 Hz), 2.85 (dd, 1H, J=4.5, 18.3 Hz), 3.77–3.84 (m, 1H), 4.03–4.16 (m, 1H), 4.44 (dd, 1H, J=4.0, 12.4 Hz), 5.42 (dd, 1H, J=9.9, 12.4 Hz), 9.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.4, 25.6, 30.2, 31.7, 48.1, 53.8, 54.6, 75.8, 176.0, 199.4; IR (film) 1287, 1368, 1381, 1424, 1551, 1686, 1721, 2874, 2934, 2961 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.72; H, 7.55; N, 11.37.

3.2.10. (5*R*,6*R*,7*R*,8a*S*)-7-Hydroxy-6-nitro-5-propylhexahydroindolizin-3-one [11]. To a solution of **10** (0.1265 g, 0.52 mmol) in CH_3CN (2.5 mL) was added DBU (12.0 mg, 0.08 mmol) and the reaction mixture was allowed to stand at room temperature for 10 h. The mixture was diluted with EtOAc (50 mL), washed with 1 M HCl (10 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo and the crude **11** was purified through flash column chromatography (silica gel, hexane–EtOAc 1:7 v/v) to give **11** in 62% yield (0.0780 g, 0.32 mmol) as a white crystal. This material was obtained as a single isomer, which was further purified by recrystallization from EtOAc.

White solid; mp 198 °C; $[\alpha]_D$ +158.0 (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=6.9 Hz), 1.23–1.76 (m, 5H), 2.15–2.31 (m, 2H), 2.41–2.50 (m, 2H), 2.53–2.63 (m, 2H), 3.42–3.59 (m, 2H), 4.27–4.41 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 14.0, 20.5, 24.1, 30.4, 32.4, 40.0, 59.1, 59.5, 71.8, 93.9, 177.5; IR (KBr) 1288, 1354, 1377, 1424, 1549, 1667, 2874, 2936, 2961, 3333 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.40; H, 7.33; N, 11.56.

3.2.11. (5*R*,7*S*,8a*S*)-7-Hydroxy-5-propylhexahydroindolizin-3-one [12]. A solution of compound **11** (33.9 mg, 0.14 mmol), Bu_3SnH (81.5 mg, 0.28 mmol), AIBN (8.2 mg) in toluene (7 mL) was heated to 110 °C for 30 min. The reaction mixture was subjected through flash chromatography (silica gel, hexane–EtOAc 20:1 then 1:7 v/v) to give compound **12** in 58% yield as a single diastereoisomer (16.0 mg, 0.081 mmol).

Colorless oil; $[\alpha]_D$ −48.2 (*c* 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J*=7.5 Hz), 1.17–1.44 (m, 4H), 1.60–1.67 (m, 2H), 1.84 (qd, 1H, *J*=7.6, 13.8 Hz), 1.97 (m, 1H), 2.05–2.30 (m, 2H), 2.38 (dt, 1H, *J*=3.0, 7.9 Hz), 2.47 (m, 1H), 3.03–3.14 (m, 1H), 3.39 (dddd, 1H, *J*=3.0, 5.0, 7.6, 11.8 Hz), 3.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.1, 24.1, 32.0, 34.0, 40.2, 41.5, 55.6, 58.4, 68.5, 174.6; IR (film) 1049, 1260, 1296, 1424, 1456, 1667, 2870, 2835, 2956, 3302 cm^{-1}. HRMS (EI M^+) *m/z* 197.1415 calcd for $C_{11}H_{19}NO_2$ 197.1416.

3.2.12. (5*R*,8a*R*)-5-Propylhexahydroindolizin-3-one [13]. A solution of compound **12** (80.0 mg, 0.406 mmol), thiocarbonyldiimidazole (213.9 mg, 1.2 mmol) and DMAP (1 mg) in toluene (5 mL) was allowed to heat to 110 °C for 2 h. After cooling to room temperature, a solution of Bu_3SnH (345.3 mg, 1.2 mmol) and AIBN (32.6 mg, 0.2 mmol) in toluene (10 mL) was added to the reaction mixture and the resulting solution was allowed to heat to 110 °C for 2.5 h. The mixture was subjected to flash chromatography (silica gel, hexane–EtOAc 50:1 then 1:1 v/v) to give compound **13** in 79% yield (58.0 mg, 0.32 mmol).

Colorless oil; $[\alpha]_D$ −27.0 (*c* 1.00, CH_2Cl_2), lit.[8] −27.6 (*c* 0.021, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J*=6.9 Hz), 1.25–1.87 (m, 10H), 2.10 (m, 1H), 2.30–2.39 (m, 3H), 3.14–3.19 (m, 1H), 3.34–3.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.9, 22.6, 24.9, 29.4, 31.7, 31.8, 34.4, 57.3, 59.6, 174.2; IR (film) 1250, 1286, 1309, 1334, 1354, 1423, 1456, 1685, 2870, 2931, 2957 cm^{-1}. HRMS (EI M^+) *m/z* 181.1467 calcd for $C_{11}H_{19}NO$ 181.1467.

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