Efficient Synthesis of (2*S*,12'*R*)-2-(12'-Aminotridecyl)pyrrolidine: A Defense Alkaloid of the Mexican Bean Beetle

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Abstract: The synthesis of (2*S*,12'*R*)-2-(12'-aminotridecyl)pyrrolidine [(*S*,*R*)-**8**], a defense alkaloid of the Mexican bean beetle *Epilachna varivestis* starting from (*R*)-proline is described. The second stereogenic center is generated by nucleophilic 1,2-addition of methyllithium to an aldehyde-SAMP-hydrazone, followed by reductive N−N bond cleavage. The product is obtained in good yield and high enantiomeric and diastereomeric purity.

Key words: natural products, asymmetric synthesis, alkaloids, nucleophilic 1,2-addition, SAMP/RAMP hydrazone method, pyrrolidines

The Mexican bean beetle, *Epilachna varivestis* (Coccinellidae), protects itself from predators by discharging a blood droplet containing a variety of defense alkaloids from its knee joints.[1] Among a set of other related alkaloids, (2*S*,12'*R*)-2-(12'-aminotridecyl)pyrrolidine [(*S*,*R*)-**8**] was extracted from the bodies of adult bean beetles and characterized.[2] The determination of the absolute configuration and a diastereoselective synthesis by an "exchiral-pool" approach was reported shortly afterwards.[3] We now describe a new stereoselective synthesis of [(*S*,*R*)-**8**] starting from (*R*)-proline in which the distant stereogenic center at C-12' is created by asymmetric synthesis employing the diastereoselective 1,2-addition of methyllithium to an aldehyde-SAMP-hydrazone.[4]

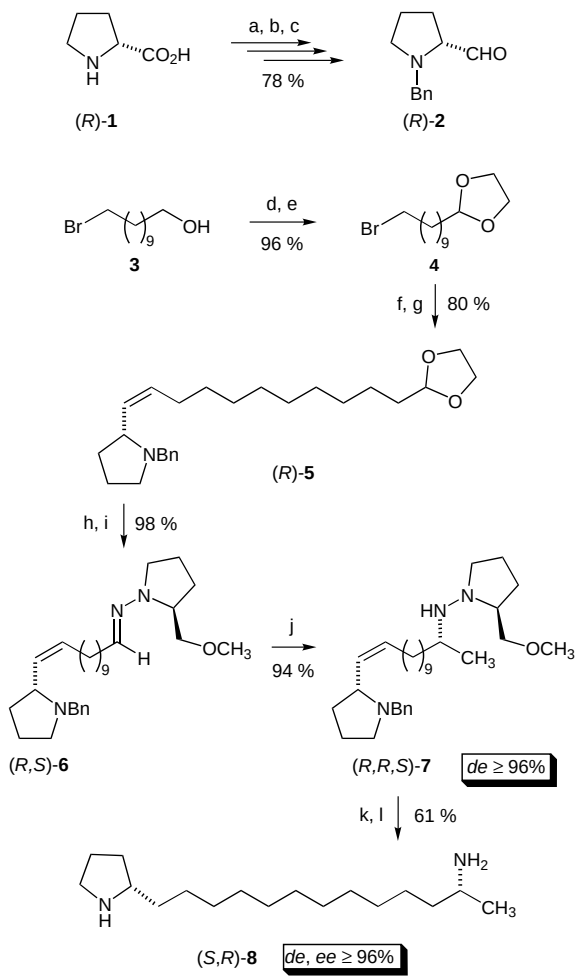
As shown in the Scheme, our synthesis starts from commercially available 11-bromoundecan-1-ol (**3**), which was transformed to acetal **4** by Swern-oxidation and subsequent reaction with ethylene glycol.[5] The bromo acetal **4** was then treated with triphenylphosphine to give a phosphonium bromide which was used in a Wittig olefination with (*R*)-*N*-benzylprolinal [(*R*)-**2**], itself being obtained from (*R*)-proline according to a literature procedure.[6] We have found that *tert*-butyllithium is necessary to ensure complete conversion of the phosphonium bromide to the corresponding ylide. The pyrrolidino acetal (*R*)-**5** was obtained in this way in 80% yield, while the yields were well below 60% when one equivalent of butyllithium was used as a base. Treatment of (*R*)-**5** with 1 M hydrogen chloride in acetone yielded the corresponding aldehyde, which was directly trapped with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) affording hydrazone (*R*,*S*)-**6**. Addition of methyllithium to the carbon-nitrogen double bond of (*R*,*S*)-**6** gave hydrazine (*R*,*R*,*S*)-**7** as a single diastereomer (de ≥ 96%).[7] It was necessary to reduce the double bond in (*R*,*R*,*S*)-**7** by hydrogenation before the N−N bond cleavage with the borane-tetrahydrofuran-complex. Because the benzyl protecting group was not essential for the next steps, conditions for the hydrogenation [$Pd(OH)_2$/charcoal, 3 bar H_2] were chosen to ensure its removal along with the reduction of the double bond.[8] The air sensitive hydrazine obtained after removal of the catalyst and the solvent was used in the final step of our synthesis without purification. Treatment with excess borane-tetrahydrofuran complex (10 equiv) gave (*S*,*R*)-**8** in 60% yield over two steps.[9] The analytical data were consistent with those reported in the literature,[3a] where it has been stated that the four stereoisomers of **8** can be distinguished by ^{1}H NMR after conversion into their MTPA diamides. Therefore, we prepared the (*R*)-MTPA diamide of (2*S*,12'*R*)-**8** with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacety chloride. As expected, the crude ^{1}H NMR spectrum was identical to that reported for the enantiomeric (*S*)-MTPA-diamide of (2*R*,12'*S*)-**8**, and no other diastereomer could be detected. The diastereomeric and enantiomeric excess was therefore determined to be greater than 96%.

In conclusion, we have synthesised a defense alkaloid of the Mexican bean beetle employing (*R*)-proline as a pyrrolidine building block and by 1,2-addition of methyllithium to an aldehyde-SAMP-hydrazone as a key step in good yield and excellent diastereomeric and enantiomeric purity.

All reagents were of commercial quality used from freshly opened containers. Solvents were dried and purified by conventional methods prior to use. Petroleum ether used had bp 40-60 °C. THF was freshly distilled from sodium/lead alloy under Ar. *t*-BuLi (1.6 M in hexane), MeLi (1.5 M in Et_2O) were purchased from Merck, Darmstadt. $Pd(OH)_2$ (20% on C) was purchased from Acros Organics. Borane-tetrahydrofuran-complex (1 M in THF) was purchased from Aldrich. Preparative column chromatography: Merck silica gel 60, particle size 0.040−0.063 mm (230−400 mesh, flash). Analytical TLC: Silica gel 60 F_{254} plates, Merck, Darmstadt. Optical rotation values were measured using a Perkin-Elmer P 241 polarimeter, solvents used were of Merck UVASOL quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID element analyzer. Mass spectra: Varian MAT 212 (EI 70 eV) with DIE ionization. IR spectra: Perkin-Elmer FT/IR 1750. ^{1}H NMR spectra (300 and 400 MHz), ^{13}C NMR (75 and 100 MHz): Varian VXR 300, Gemini 300 or Varian Inova 400 (solvent $CDCl_3$, TMS as internal standard).

2-(10-Bromodecyl)-1,3-dioxolane (4)

To a solution of oxalyl chloride (4.1 mL, 45 mmol) in CH_2Cl_2 (25 mL) at −78 °C was slowly added a solution of DMSO (4.4 mL, 60 mmol) in CH_2Cl_2 (45 mL). After stirring for 15 min at −78 °C, a solution of 11-bromoundecan-1-ol (7.47 g, 30 mmol) in CH_2Cl_2 (60 mL) was added slowly and the mixture was stirred for 30 min, fol-



Reagents and conditions: (a) BzCl/NaOH, H_2O, 0°C, 2 h; (b) $LiAlH_4$/THF, reflux, 16 h; (c) $(COCl)_2$/DMSO/Et_3N, −40 → 25 °C; (d) $(COCl)_2$/DMSO/Et_3N, −78 → 25 °C; (e) $HOCH_2CH_2OH$/*p*-TsOH/toluene, reflux, 16 h; (f) Ph_3P/MeCN, reflux, 72 h; (g) *t*-BuLi/THF, −78 → 25 °C, 2 h; (*R*)-**2**/THF, −78 → 25 °C, 15 h; (h) 1 M HCl/acetone, 25 °C, 14 h; (i) SAMP, 0 → 25 °C, 30 min; (j) MeLi/THF, −78 → 25 °C, 15 h; (k) H_2/Pd(OH)$_2$-C/MeOH, 25 °C, 6 h; (l) BH_3•THF (excess), reflux, 4h

Scheme

lowed by addition of Et_3N (12 mL). The mixture was slowly warmed to r.t. and H_2O (30 mL) was added. The organic phase was separated and the aqueous phase was extracted three times with a total of 300 mL of CH_2Cl_2 and the combined organic layers were washed with 1 M HCl, sat. of $NaHCO_3$ and brine. After drying ($MgSO_4$) and evaporation of the solvent, the crude aldehyde was obtained as a colourless oil, which was added to a solution of *p*-toluenesulfonic acid (50 mg) and ethylene glycol (9.3 g, 150 mmol) in anhyd toluene (150 mL) and refluxed for 16 h. Et_2O (200 mL) was added and the mixture was washed with sat. $NaHCO_3$ and brine. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel; petroleum ether/Et_2O, 10:1) afforded **4** as a colourless oil; yield: 8.4 g (96%). The analytical data were consistent with the literature data.[3a]

(2*R*,11*Z*)-1-Benzyl-2-{[11-(1,3-dioxolane)-2-yl]undec-1-enyl}pyrrolidine [(*R*)-5]

A solution of Ph_3P (6.55 g, 25 mmol) and **4** (7.32 g, 25 mmol) in anhyd MeCN (50 mL) was heated under reflux for 72 h. The solvent was removed under reduced pressure and the residue was washed with Et_2O (30 mL) until it crystallized. The colourless solid phosphonium bromide obtained in this way (13.35 g, 98%) was used without any further purification in the next reaction. To a suspension of the crude phosphonium bromide (8.40 g, 15.4 mmol) in anhyd THF (80 mL) under argon was slowly added a solution of *t*-BuLi (1.6 M in hexane, 9.63 mL, 15.4 mmol) at −78 °C. After 15 min of stirring at this temperature, the suspension was allowed to warm to r.t. and stirred for an additional 30 min, during which the solid disappeared. The dark red solution was cooled to −78 °C and a solution of **2** (1.96 g, 10.4 mmol) in THF (20 mL) was added slowly. The mixture was allowed to warm to r.t. over a period of 15 h after which it was treated with H_2O (25 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were dried ($MgSO_4$). After removal of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel; petroleum ether/EtOAc, 4:1), **5** was obtained as a greenish oil; yield: 3.20 g (80%); $[\alpha]_D^{25}$ +37.8 (*c* = 1.01, $CHCl_3$).

IR (film): ν = 2925, 2854, 2785, 1454, 1141, 1126, 1030, 700 cm^{-1}.

^1H NMR (300 MHz): δ = 1.25−1.48 [m, 14 H, CH=CHCH_2(CH_2)$_7$], 1.48−1.96 [m, 6 H, CH_2CH(OCH$_2$CH_2O), NCHHCH_2CH_2], 2.02−2.14 (m, 3 H, NCH*H*CH=CHCH_2), 2.92 (m, 1 H, NC*H*H), 3.03 (d, 1 H, *J* = 12.7 Hz, C_6H_5C*H*HN), 3.12 (m, 1 H, C*H*N), 3.87 (m, 4 H, OCH$_2$CH$_2$O), 4.01 (d, 1 H, *J* = 12.7 Hz, C_6H_5CH*H*N), 4.83 [t, 1 H, *J* = 4.9 Hz, C*H*(OCH$_2$CH$_2$O)], 5.34 (ddt, 1 H, *J* = 10.8, 8.8, 1.4 Hz, C*H*=CHCH$_2$), 5.54 (dtd, 1 H, *J* = 10.8, 7.2, 0.7 Hz, CH$_2$=C*H*CH$_2$), 7.17−7.31 (m, 5 H, C_6H_5CHHN).

^{13}C NMR (75 MHz): δ = 22.09 (NCH$_2$CH$_2$*C*H$_2$), 24.08, 27.77, 29.30−29.87 [(*C*H$_2$)$_7$, *C*H$_2$*C*H(OCH$_2$CH$_2$O), NCH$_2$*C*H$_2$], 31.39 (CH=CH*C*H$_2$), 33.94 [*C*H$_2$CH(OCH$_2$CH$_2$O)], 53.18 (NCH$_2$), 58.36 (N*C*H$_2$C$_6$H$_5$), 61.81 (N*C*HCH=CH), 64.80 (OCH$_2$CH$_2$O), 104.70 [*C*H(OCH$_2$CH$_2$O)], 126.69, 128.07, 129.00 (C_{arom}), 132.25, 132.49 (CH=CH), 139.65 (C_{arom}).

MS: *m*/*z* (%) = 385 (M^+, 43), 294 ($M^+ - C_7H_7$, 11), 160 (52), 91 (100).

Anal. calcd. for $C_{25}H_{39}NO_2$ (385.6): C 77.87, H 10.19, N 3.63. Found: C 77.41, H 10.31, N 4.08.

(2*R*)-[(11*Z*)-12-(1-Benzylpyrrolidin-2-yl)dodec-11-en-1-ylidene]-(2*S*)-(2-methoxymethylpyrrolidin-1-yl)amine[(*R*,*S*)-6]

To a solution of **5** (2.89 g, 7.5 mmol) in acetone (100 mL) was added HCl (1 M, 30 mL) and the mixture was stirred for 18 h under argon. After removal of the solvent, the residue was saturated with solid K_2CO_3 and extracted with Et_2O (3 × 100 mL). Drying ($MgSO_4$) of the combined organic extracts and removal of the solvent yielded a pale red oil that was used directly in the next reaction. The crude aldehyde prepared this way was treated with SAMP (0.99 g, 7.6 mmol) under argon at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 30 min, before Et_2O (150 mL) was added. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (silica gel; petroleum ether/EtOAc, 2:1, containing 1% Et_3N) yielded **6** as a pale yellow oil; yield: 3.33 g (98%); $[\alpha]_D^{25}$ −18.7 (*c* = 1.19, $CHCl_3$).

IR (film): ν = 2924, 2875, 1605, 1454, 1197, 1120, 737, 699 cm^{-1}.

^1H NMR (400 MHz): δ = 1.25−1.38 [m, 12 H, CH=CHCH_2(CH_2)$_6$], 1.41−1.49 (m, 2 H, CH_2CH$_2$CH=N), 1.50−1.84 (m, 4 H, NCHHCH_2CH_2), 1.85−1.98 (m, 4 H, NNCHHCH_2CH_2), 2.05−2.13 (m, 3 H, NCH*H*, CH=CHCH_2), 2.20 (m, 2 H, CH_2CH=N), 2.70 (m, 1 H, NNCH*H*), 2.92 (m, 1 H, NC*H*H), 3.07 (d, 1 H, *J* = 12.8 Hz,

C_6H_5CHHN), 3.12 (m, 1 H, CHN), 3.33−3.45 (m, 6 H, $CH_3OCHHCH$, $NNCHH$), 3.56 (dd, 1 H, J = 8.5, 3.3 Hz, CH_3OCHH), 4.01 (d, 1 H, J = 12.7 Hz, C_6H_5CHHN), 5.40 (m, 1 H, CH=$CHCH_2$), 5.55 (m, 1 H, CH=$CHCH_2$), 6.65 (t, 1 H, J = 5.6 Hz, CH=N), 7.18−7.32 (m, 5 H, C_6H_5CHHN).

^{13}C NMR (100 MHz): δ = 22.01, 22.17, 26.58, 27.77, 27.87, 29.25−29.86 [($NCH_2CH_2CH_2$, $NNCH_2CH_2CH_2$, CH=$CHCH_2(CH_2)_7$], 31.32 (CH=$CHCH_2$), 33.15 (CH_2CH=N), 50.57 ($NNCH_2$), 53.16 (NCH_2), 58.34 ($NCH_2C_6H_5$), 59.20 (OCH_3), 61.82 ($NCHCH$=CH), 63.52 ($NNCHCH_2O$), 74.88 (CH_2O), 126.70, 128.10, 129.06 (C_{arom}), 132.10, 132.60 (CH=$CHCH_2$), 139.50 (C_{arom}), 139.69 (CH=N).

MS: *m*/*z* (%) = 408 (M^+ − CH_2OCH_3, 10), 339 (52), 160 (44), 91 ($C_7H_7^+$, 100).

Anal calcd for $C_{29}H_{47}N_3O$ (453.4): C 76.77, H 10.44, N 9.26. Found: C 76.66, H 10.93, N 9.26.

(2*R*)-[(12*Z*)-13-(2*R*)-(1-Benzylpyrrolidin-2-yl)tridec-12-en-2-yl]-(2*S*)-(2-methoxymethylpyrrolidin-1-yl)amine [(*R*,*R*,*S*)-7]

To a solution of MeLi (1.5 M in Et_2O, 7.3 mL, 11 mmol) under argon in anhyd THF (10 mL) at −78 °C was slowly added a solution of **6** (2.27 g, 5 mmol) in THF (5 mL). The mixture was allowed to warm to r.t. over a period of 15 h and quenched with sat. aq $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (20 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel; EtOAc/petroleum ether, 1:1) afforded **7** as a colourless oil; yield: 2.20 g (94%); $[\alpha]_D^{26}$ −14.6 (*c* = 1.03, $CHCl_3$).

IR (film): ν = 2925, 2853, 1673, 1462, 1197, 1124, 755, 684 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.01 (d, 3 H, J = 6.0 Hz, $NHCHCH_3$) 1.25−1.38 [m, 16 H, CH=$CHCH_2(CH_2)_8$], 1.48−1.98 (m, 8 H, $NCHHCH_2CH_2$, $NNCHHCH_2CH_2$), 2.03−2.19 (m, 4 H, NCH*H*, NNCH*H*, CH=$CHCH_2$), 2.56 (m, 1 H, $NNCHH$), 2.80 (m, 1 H, $CHCH_3$), 2.92 (m, 1 H, $NCHH$), 3.02 (d, 1 H, J = 12.8 Hz, C_6H_5CHHN), 3.12 (m, 1 H, CHN), 3.30−3.45 (m, 5 H, $CH_3OCHHCH$), 3.54 (dd, 1 H, J = 9.0, 3.8 Hz, CH_3OCHH), 4.01 (d, 1 H, J = 12.8 Hz, C_6H_5CHHN), 5.39 (m, 1 H, CH=$CHCH_2$), 5.56 (dt, 1 H, J = 11.0, 7.4 Hz, CH=$CHCH_2$), 7.18−7.32 (m, 5 H, C_6H_5CHHN).

^{13}C NMR (100 MHz): δ = 20.17 ($NCHCH_3$), 21.03, 22.03, 22.12, 26.22, 27.77, 29.30−29.91 [$NCH_2CH_2CH_2$, $NNCH_2CH_2CH_2$, CH=$CHCH_2(CH_2)_7$], 31.34 (CH=$CHCH_2$), 35.90 (CH_2NCHCH_3), 53.18 (NCH_2), 54.06 ($NCHCH_3$), 57.56 ($NNCH_2$), 58.36 ($NCH_2C_6H_5$), 59.07 (OCH_3), 61.82 ($NCHCH$=CH), 65.75 ($NNCHCH_2O$), 75.07 (CH_2O), 126.71, 128.10, 129.04 (C_{arom}), 132.16, 132.57 (CH=$CHCH_2$), 139.56 (C_{arom}).

MS: *m*/*z* (%) = 469 (M^+, 24), 424 (M^+ − CH_2OCH_3, 100), 339 (42), 91 (36).

HRMS: *m*/*z* calcd for $C_{30}H_{51}N_3O^+$: 469.40321. Found: 469.40314.

(2*S*,12'*R*)-2-(12'-Aminotridecyl)pyrrolidine [(*S*,*R*)-8]

Hydrazine **7** (1.41 g, 3 mmol) was dissolved in MeOH (30 mL) and hydrogenated over $Pd(OH)_2$/C (0.3 g) under 3 bar pressure for 6 h. The residue obtained after filtration and evaporation of the solvent from the filtrate was dissolved in anhyd THF (15 mL). After addition of borane-tetrahydrofuran complex (1 M in THF, 30 mL, 30 mmol), the mixture was stirred under reflux under argon (balloon) for 4 h. After it had reached r.t., 10% HCl (15 mL) was added very slowly and the mixture was stirred for 2 h at r.t.. The solvent was removed under reduced pressure and the residue was extracted with Et_2O (2 × 25 mL). It was then saturated with solid K_2CO_3 and extracted three times with a total of 150 mL of CH_2Cl_2. The residue obtained after removal of the solvent was purified by column chromatography (silica gel; CH_2Cl_2/MeOH/NH_4OH, 6:4:0.3) to afford the final product **8**; yield: 0.49 g (61%); $[\alpha]_D^{25}$ +8.8 (*c* = 2.21, $CDCl_3$). {Lit.[3a] $[\alpha]_D^{22}$ +9.3 (*c* = 0.15, $CDCl_3$); Lit.[3b] $[\alpha]_D^{22}$ +9.8 (*c* = 0.25, $CDCl_3$)}. MS, IR, ^{1}H NMR and ^{13}C NMR analyses were consistent with those given in the literature.[3a]

HRMS: *m*/*z* calcd for $C_{17}H_{36}N_2^+$: 268.287849. Found: 268.287818.

The (*R*)-MTPA diamide of **8** was prepared by dissolving **8** (0.052g, 0.2 mmol) in anhyd CH_2Cl_2 (2 mL) and adding a solution of (*S*)-MTPA chloride (0.101 g, 0.4 mmol) in anhyd CH_2Cl_2 (1 mL) at −78°C. The mixture was allowed to warm to r.t. and sat. NH_4Cl (2 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2 × 4 mL) and the combined organic phases where dried ($MgSO_4$). The residue obtained after removal of the solvent (120 mg) was used for ^{1}H NMR analysis.

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