Enantioselective Total Synthesis of Harmonine, a Defence Alkaloid of Ladybugs (Coleoptera: Coccinellidae)

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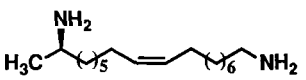
An efficient and highly enantioselective (ee > 97%) total synthesis of the ladybug defence alkaloid (17*R*,9*Z*)-1,17-diaminooctadec-9-ene [(*R*,*Z*)-**1**, harmonine] in good overall yield is described. As the key step for the generation of the stereogenic center, asymmetric C–C bond formation by nucleophilic addition of methyllithium to an aldehyde SAMP hydrazone is used.

Alkaloids, once thought to be a unique part of the richness and diversity of secondary metabolism of plants, have now been recorded to occur in a number of anthropods[1], e.g. Coccinellidae.

When disturbed or molested these insects release hemolymph, small droplets of yellow blood at their knee joints[2]. This well-described process, known as "reflex bleeding", serves as an efficient protection against certain predators[3]. Tursch et al. were the first to report that the repellent properties result from the presence of alkaloids[1,4] and are correlated with the warning coloration of ladybugs[4]. The title substance, (17*R*,9*Z*)-1,17-diaminooctadec-9-ene (**1**), termed harmonine was isolated from 500 beetles of *Harmonia leis conformis* (Coleoptera, Coccinellidae, Coccinellinae) and several other ladybug species[5]. The structure, which is unusual amongst ladybug defence alkaloids[1], was determined by a combination of spectroscopic and chemical methods[5] and confirmed by a total synthesis of racemic **1**[6]. By empirical correlation of ^{1}H-NMR/LIS data of **1** and amines of known absolute configuration it was possible to show that naturally occurring **1** has (*R*) configuration at C-17[6].

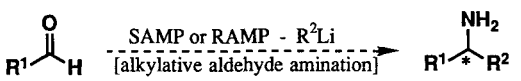


(R,Z)-1

Results and Discussion

We now report on the first highly enantioselective total synthesis of (17*R*,9*Z*)-1,17-diaminooctadec-9-ene (*R*,*Z*)-**1**, termed harmonine, a naturally occurring ladybug defence alkaloid[6].

The stereogenic center at carbon 17 is created in the last step of the synthesis employing our efficient, overall enantioselective SAMP/RAMP hydrazone method to generate α-substituted primary amines from aldehydes (Eq. 1)[7].



(1)

A further synthetic strategy was to create in one step stereoselectively the *Z* geometry of the disubstituted double bond at carbon 9 and chemoselectively the primary amino group at C-1 in the presence of a hydrazone functionality by using Lindlar's palladium catalyst[8]. For this approach a C_{17}-acetylene intermediate had to be prepared in a convergent synthesis by coupling an α,ω-disubstituted halide moiety with an ω-functionalized 1-alkyne moiety. The functional group management based on a series of key reactions which are in current use in the synthesis of unsaturated aliphatic insect pheromones was applied.

The sequence of reactions used for the total synthesis of (*R*,*Z*)-**1** is outlined in Scheme 1.

As illustrated, the 1-alkyne moiety was obtained as acetylene acetal **5** in four steps in 52% overall yield starting from 1,7-heptanediol (**2**). **2** was heated with 48% hydrobromic acid under azeotrope distillation conditions[9] to give 7-bromo-1-heptanol (**3**), which upon oxidation with pyridinium chlorochromate (PCC)[10], subsequent protection of the aldehyde function with 1,2-ethanediol, and coupling with acetylene as stable lithium acetylide–ethylenediamine (EDA) complex[11] gave the desired acetylene acetal **5**.

For the synthesis of the C_8-halide, 8-chloro-1-octanol (**6**) was mesylated, followed by treatment with lithium bromide in acetone to form 8-bromo-1-chlorooctane (**7**) in 86% yield.

To achieve the alkylation[12] of the 1-alkyne moiety **5**, the metalation was carried out with *n*-butyllithium in tetrahydrofuran (THF) at −20 to 0°C. After addition of the bishalide moiety **7** in hexamethylphosphoric triamide (HMPA) at 0°C, the disubstituted C_{17}-acetylene derivative **8** was isolated in 58% yield based on added compound **5**. The acetylene acetal **5** was recovered in 30% yield. Two different ways to synthesize the azido acetal **9** were tested. In the first one, the coupling product **8** was heated with sodium azide in *N*,*N*-dimethylformamide (DMF) to yield **9** (56% yield based on added **5**).

The other approach was to use the easily prepared 8-azido-1-bromooctane **14** (Scheme 2) as protected primary amine reagent in the alkylation of the metalated C_9-alkyne **5**. It was necessary to adjust the experimental conditions

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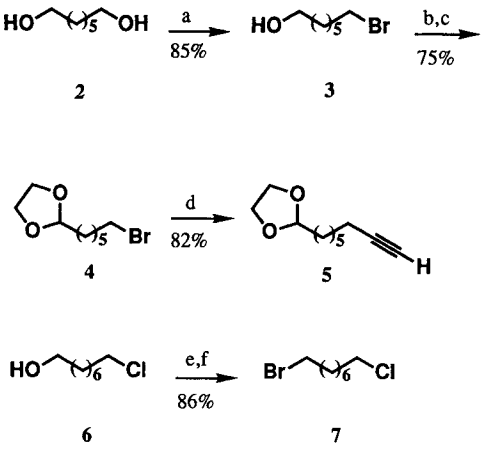
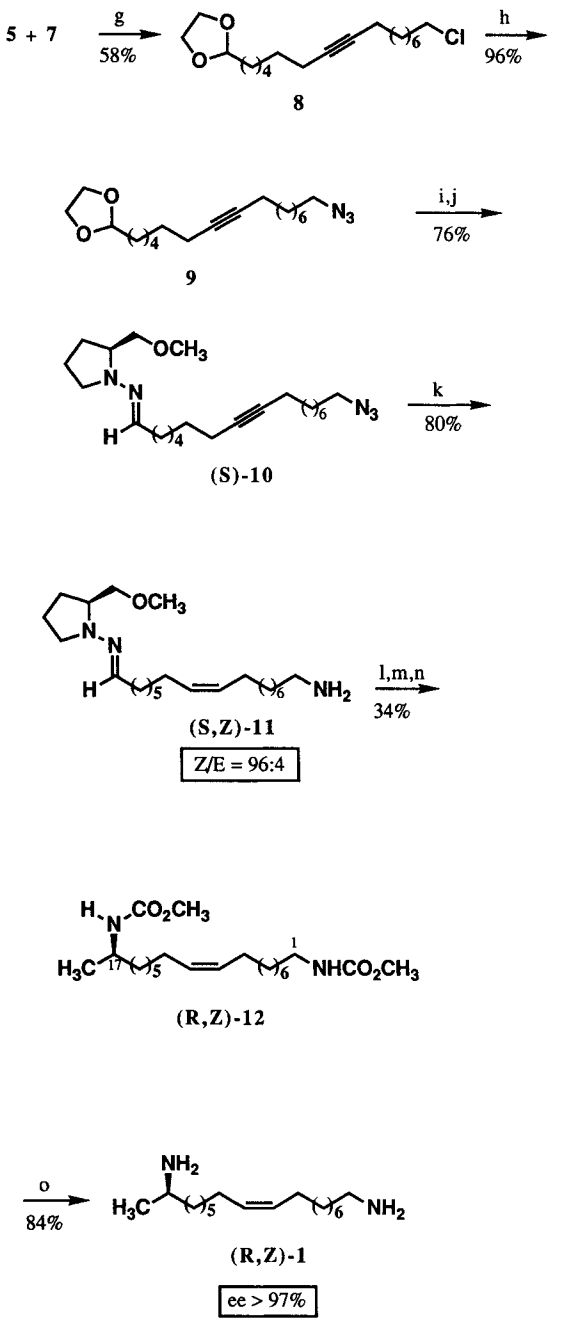
Scheme 1



carefully because the azido group was not completely inert to the lithiated carbanion species. Best results (46% yield of **9** based on added **5**) were obtained by quick addition of the lithiated 1-alkyne **5** in THF to a solution of the azido bromide **14** in HMPA. Next, the introduction of the primary amino group at carbon 17 was effected by acidic catalyst exchange dioxolanation of acetal **9** in acetone and subsequent conversion of the aldehyde to its SAMP hydrazone (*S*)-**10** with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)[13,14]. Hydrogenation of the acetylenic hydrazono azide (*S*)-**10** over Lindlar's palladium catalyst in ethanol at 20°C for 90 min gave both the required (9*Z*)-double bond and the primary amino group at C-1. The CN-double bond of the SAMP hydrazone was uneffected. According to the ^{13}C-NMR spectra, under these conditions the aminoalkene (*S,Z*)-**11** was formed with only a small amount (ca. 4%) of the (*E*)-isomer. The nucleophilic addition to the CN-double bond of the SAMP hydrazone in (*S,Z*)-**11** was carried out with methyllithium (3 equivalents) in THF at −78°C[7,15]. After quenching with methyl chloroformate[15] the protected hydrazino amine was obtained. The diastereomeric excess (de) of the diastereoface-differentiating addition could not be determined by NMR spectroscopy, because of the signal broadening due to hindered bond rotation of the amide[16]. The methoxycarbonyl group of the hydrazino function activates the N−N bond so that the reductive cleavage can proceed without epimerisation by treatment with a high excess of lithium in liquid ammonia at −33°C for 4 h[15]. The protected diamine (*R,Z*)-**12** was isolated following a three-step process in 34% chemical yield from (*S,Z*)-**11**. The recycling of the chiral auxiliary is possible by nitrosation of the (*S*)-2-(methoxymethyl)pyrrolidine (SMP) and following reduction. Finally, the methoxycarbonylcarbamate (*R,Z*)-**12** was cleaved in 84% yield by heating with trimethylsilyl iodide to 50°C for 2 h and subsequent methanolysis[23]. Chromatography affords the desired title substance (*R,Z*)-**1**. Thus, we have completed the total synthesis of harmonine in 13 steps from 1,7-heptanediol (**2**) and 8-chloro-1-octanol (**6**) (*overall yield*: 5%).

The accurate determination of the enantiomeric excess (ee) of the diamine (*R,Z*)-**1** was achieved by NMR spectroscopy

Scheme 1 *(Continued)*



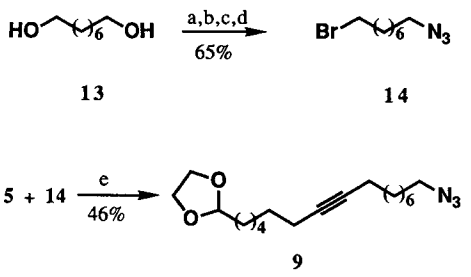
a: HBr, toluene, ΔT. – b: PCC, CH_2Cl_2, rt. – c: $HO(CH_2)_2OH$, PPTS, benzene, ΔT. – d: LiC≡CH·EDA, DMSO, 8°C → rt. – e: MsCl, NEt_3, CH_2Cl_2, 0°C. – f: LiBr, acetone, rt. – g: n-BuLi, THF/HMPA, -20°C → rt. – h: NaN_3, DMF, 60°C. – i: 1N HCl, acetone, ΔT. – j: SAMP, Et_2O, 0°C → rt. – k: H_2, Lindlar, EtOH, 20°C. – l: H_3CLi, THF, -78°C. – m: $ClCO_2CH_3$, THF, -60°C → rt. – n: Li/NH_3, -33°C. – o: $(H_3C)_3SiI$, $CHCl_3$, 50°C.

rt = room temperature

of the corresponding 3,3,3-trifluoro-2-(methoxyphenyl)propionamide (MTPA)[17]. The asymmetric induction was shown to be virtually complete (ee ≥ 97%) by observation of a single diastereomer in the ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra. Supporting evidence for the (*R*) configuration at carbon 17 in (*R,Z*)-**1** by polarimetry was not possible due to the

absence of any optical rotation value in the literature. The assignment of the (*R*) configuration (obtained via SAMP) can be made by analogy with earlier asymmetric aldehyde aminations using SAMP/RAMP hydrazones[15], which allows the prediction of the absolute configuration of the major enantiomer with a great reliability.

Scheme 2



a: HBr, toluene, ΔT. – b: NaN_3, MeOH, ΔT. – c: MsCl, NEt_3, CH_2Cl_2, 0°C. – d: LiBr, acetone, rt. – e: n-BuLi, THF/HMPA, -20°C → rt.

rt = room temperature

In summary, the enantioselective total synthesis of the natural ladybug defence alkaloid harmonine described above shows the synthetic utility of the enantioselective alkylative amination of aldehydes using the SAMP/RAMP hydrazone method.

This work was supported by the *Fonds der Chemischen Industrie*. We thank *Degussa AG* [(*S*)-proline] and *BASF AG* (8-chloro-1-octanol) for providing us with chemicals.

Experimental

Optical rotations: Perkin-Elmer P 241 polarimeter. – Elemental analyses: Heraeus CHN-O-Rapid. – IR Spectra: Beckman Acculab 4 and Perkin-Elmer FTIR 1750. – ^{1}H-NMR (300 MHz), ^{13}C-NMR (75 MHz), ^{19}F-NMR spectra (282 MHz): Varian VXR 300 (TMS as internal standard for ^{1}H and ^{13}C and CD_2F_2 as external standard for ^{19}F). – Mass spectra: Varian MAT 212 (70 eV). – Analytical GC: Siemens Sichromat 2 or 3 equipped with an OV-1-CB or SE-54-CB column. – All solvents were dried by conventional methods and destilled for metalations under argon. The chiral auxiliary (*S*)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) was synthesized from (*S*)-proline according to earlier reported procedures[13,14].

Synthesis of the 1-Alkyne Moiety 2-(7-Octinyl)-1,3-dioxolane (**5**)

7-Bromo-1-heptanol (**3**): According to ref.[9] 39.7 g (300 mmol) of 1,7-heptanediol (**2**) was monobrominated in toluene. The resultant residue was purified by filtration on silica gel. The first fraction with pentane/ether (10:1) as eluent afforded 7.3 g (9%) of 1,7-dibromoheptane. Then with pentane/ether (1:2) the monobromo derivative **2** was eluted as a pale yellow liquid (49.9 g, 85% yield). – The spectroscopic data of **2** correspond to those given in ref.[9].

2-(6-Bromohexyl)-1,3-dioxolane (**4**): In a 500-ml round-bottom flask fitted with a reflux condenser, 46.6 g (216 mmol) of pyridinium chlorochromate was suspended in 290 ml of dichloromethane according to ref.[10]. 28.1 g (144 mmol) of bromoalcohol **3** in 29 ml of dichloromethane was then added in one portion to the stirred suspension. After 1.5 h, 250 ml of ether was added and the supernant liquid was decanted from a black gum. The insoluble residue was washed with ether. The combined organic solution was passed through a short pad of silica gel and concentrated. 27.4 g (98%) of the crude aldehyde was obtained as a pale green liquid. – IR (film): $\tilde{\nu}$ = 3420 cm^{-1}, 2930 (CH_2), 2860 (CH_2), 2720 (CHO), 1720 (C=O), 1460, 1440, 1430, 1410, 1390, 1255, 730, 645.

To a solution of 27.4 g (144 mmol) of crude aldehyde in 1.1 l of benzene were added 32.2 ml (576 mmol) of 1,2-ethanediol and 1.7 g (7 mmol) of pyridinium *p*-toluenesulfonate (PPTS)[18]. The mixture was heated at reflux with water separation by a Dean-Stark trap (ca. 12 h). Excess solvent was then removed in vacuo, ether was added, and the mixture was washed with satd. $NaHCO_3$ solution and brine. The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by filtration on silica gel (pentane/ether, 1:1), yield 25.6 g (75% for two steps) of bromo acetal **4**, pale violet liquid. – IR (film): $\tilde{\nu}$ = 2930 cm^{-1} (CH), 2850 (CH), 2760, 1460, 1430, 1410, 1360, 1255, 1235, 1210, 1135 (br.), 1030 (br.), 940 (sh), 730, 640. – ^{1}H NMR ($CDCl_3$): δ = 1.25–1.55 [complex signal, 6H, $(CH_2)_3$], 1.58–1.71 (m, 2H, CH_2), 1.85 (quint, *J* = 7 Hz, 2H, CH_2CH_2Br), 3.38 (t, *J* = 7 Hz, CH_2Br), 3.76–4.00 (m, 4H, 2 CH_2O), 4.83 (t, *J* = 4.7 Hz, 1H, OCHO). – ^{13}C NMR ($CDCl_3$): δ = 23.81 (C-2′), 28.05, 28.64 (C-3′,4′), 32.66 (C-6′), 33.75 (C-1′, C-5′), 64.79 (C-4, C-5), 104.46 (C-2). – GC-MS (70 eV): *m/z* (%) = 239 (0.03) [M^+ + 1], 238/236 (0.18/0.17) [M^+], 237/235 (1.62/1.57) [M^+ – 1], 74 (8), 73 (100) [$C_3H_5O_2^+$], 55 (6), 45 (28), 41 (9).

$C_9H_{17}BrO_2$ (237.14) Calcd. C 45.57 H 7.23
Found C 45.61 H 7.25

The synthesis of **4** in another way is outlined in ref.[19].

2-(7-Octinyl)-1,3-dioxolane (**5**): A flask was flushed with argon and charged with 4.4 g (47 mmol) of lithium acetylide–ethylenediamine complex[11]. Then 21 ml of dry dimethyl sulfoxide were added to make the solution (slurry) ca. 2 M in complex. The mixture was stirred and cooled to 8°C. 9.2 g (39 mmol) of bromo acetal **4** was then added dropwise over a period of 1 h with the temperature maintained by external cooling. When the addition was complete, the reaction mixture was permitted to warm up to room temp. and stirred for 1 h. The reaction mixture was hydrolysed with a two-fold amount of water and extracted several times with ether. The combined ethereal extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel, pentane/ether, 3:1) to provide 5.8 g (82%) of 1-alkyne **5** as a colorless liquid. – IR (film): $\tilde{\nu}$ = 3295 cm^{-1} (≡CH), 2930 (CH), 2850 (CH), 2760, 2120 (C≡C), 1460, 1430, 1405, 1360, 1330, 1220 (br.), 1135 (br.), 1105, 1085, 1030 (br.), 940 (sh), 630 (br.). – ^{1}H NMR ($CDCl_3$): δ = 1.25–1.70 [complex signal, 10H, $(CH_2)_5$], 1.91 (t, *J* = 2.7 Hz, 1H, ≡CH), 2.17 (td, *J* = 7 Hz, *J* = 2.7 Hz, 2H, CH_2C≡), 3.75–4.00 (m, 4H, 2 CH_2O), 4.83 (t, *J* = 4.7 Hz, 1H, OCHO). – ^{13}C NMR ($CDCl_3$): δ = 18.40 (C-6′), 23.97 (C-2′), 28.64, 28.71, 29.11 (C-3′,4′,5′), 33.95 (C-1′), 64.84 (C-4, C-5), 68.28 (C-8′), 84.38 (C-7′), 104.65 (C-2). – GC-MS (70 eV): *m/z* (%) = 181 (1.26) [M^+ – 1], 74 (3), 73 (100) [$C_3H_5O_2^+$], 45 (10), 41 (3).

$C_{11}H_{18}O_2$ (182.26) Calcd. C 72.49 H 9.95
Found C 72.20 H 9.89

Synthesis of the Halide Moieties

8-Bromo-1-chlorooctane (**7**): According to ref.[20], to a solution of 9.6 g (58 mmol) of 8-chloro-1-octanol (**6**) and 16.8 ml (122 mmol) of triethylamine in 300 ml of dichloromethane, 7.7 ml (99 mmol) of methanesulfonyl chloride was added dropwise at 0°C. After stirring for 1 h at 0°C, the mixture was extracted with ice-cold water, satd.

NH_4Cl solution, satd. $NaHCO_3$ solution, and brine. After evaporation of the solvent in vacuo the organic phase yielded a residue of 13.2 g (94%) of the mesylated product as a yellow oil, which was pure according to TLC analysis.

To a solution of the mesylate in 100 ml of dry acetone was added 20.1 g (232 mmol) of lithium bromide, and the mixture was stirred at room temp. for 16 h. After concentration it was diluted with ether and washed with brine. Evaporation of the solvent in vacuo and distillation [b.p. 135–140°C/10 Torr (ref.[21] b.p. 92–94°C/1.5 Torr)] of the residue yielded 11.3 g (86%) of **7** as a colorless liquid.

1-Azido-8-bromooctane (**14**): According to ref.[9], 43.8 g (300 mmol) of 1,8-octanediol (**13**) was monobrominated in toluene. The resultant residue was purified by filtration on silica gel. The first fraction with ether/pentane (1:10) as eluent afforded 7.6 g (9%) of 1,8-dibromooctane. Then with pentane/ether (1:2) the desired 8-bromo-1-octanol was eluted as a pale yellow liquid (53.3 g, 85% yield). – Spectroscopic data correspond with those given in ref.[6,9].

To a solution of 15.0 g (72 mmol) of 8-bromo-1-octanol in 250 ml of methanol was added a slurry of 6.5 g (100 mmol) of sodium azide in 9.0 ml of water according to ref.[22]. The mixture was heated at reflux for 8 h, the methanol removed by evaporation and the residue diluted with water. The resultant oil was extracted several times with ether, and the combined ethereal extracts were dried ($MgSO_4$). After evaporation of the ether in vacuo, 11.6 g (94%) of pure 8-azido-1-octanol was obtained by distillation, b.p. 108–110°C/1.5 Torr. – IR (film): $\tilde{\nu}$ = 3350 cm^{-1} (br., OH), 2930 (CH_2), 2860 (CH_2), 2100 (N_3), 1460 (sh), 1350 (m), 1300–1255 (br.), 1055 (br., sh), 895 (br.), 725. – ^1H NMR ($CDCl_3$): δ = 1.28–1.42 [complex signal, 8H, $(CH_2)_4$], 1.57 (complex signal, 4H, CH_2CH_2O, $CH_2CH_2N_3$), 1.87 (s, 1H, OH), 3.25 (t, *J* = 6.9 Hz, 2H, CH_2N_3), 3.62 (t, *J* = 6.7 Hz, 2H, CH_2O). – ^{13}C NMR ($CDCl_3$): δ = 25.73 (C-3), 26.72 (C-6), 28.89, 29.17, 29.33 (C-4,5,7), 32.78 (C-2), 51.52 (C-8), 62.88 (C-1).

According to the synthesis of 8-bromo-1-chlorooctane (**7**), to a solution of 10.0 g (58 mmol) of 8-azido-1-octanol and 16.9 ml (123 mmol) of triethylamine in 300 ml of dichloromethane, 7.8 ml (99 mmol) of methanesulfonyl chloride was added dropwise at 0°C.

To the solution of the mesylate in 150 ml of dry acetone was added 20.3 g (234 mmol) of lithium bromide. After drying ($MgSO_4$) and concentration of the mixture the crude product was filtered through silica gel to afford 11.1 g (82% yield relative to 8-azido-1-octanol) of **14** as a colorless liquid. – IR (film): $\tilde{\nu}$ = 2940 cm^{-1} (CH_2), 2860 (CH_2), 2100, 1465, 1350, 1320–1240 (br.), 730, 650. – ^1H NMR ($CDCl_3$): δ = 1.27–1.51 [complex signal, 8H, $(CH_2)_4$], 1.60 (quint, *J* = 7 Hz, 2H, $CH_2CH_2N_3$), 1.85 (quint, *J* = 7 Hz, 2H, CH_2CH_2Br), 3.25 (t, *J* = 7 Hz, 2H, CH_2N_3), 3.39 (t, *J* = 7 Hz, 2H, CH_2Br). – ^{13}C NMR ($CDCl_3$): δ = 26.68 (C-3), 28.10, 28.67, 28.87, 29.01 (C-2,4,5,6), 32.82 (C-8), 33.69 (C-7), 51.46 (C-1).

$C_8H_{16}BrN_3$ (234.14) Calcd. C 41.04 H 6.89 N 17.94
Found C 41.27 H 6.93 N 17.43

Alkylation of the 1-Alkyne Moiety **5** *with the Halide Moiety* **7** *and Further Synthesis of (17R,9Z)-1,17-Diaminooctadec-9-ene*

2-(16-Chloro-7-hexadecynyl)-1,3-dioxolane (**8**): To a stirred solution of 4.7 g (26 mmol) of **5** in 21 ml of anhydrous THF was added according to ref.[12] 17.5 ml (27 mmol) of a 1.6 M solution of *n*-butyllithium in *n*-hexane at –30°C. The yellow reaction solution was allowed to warm to 0°C by exchanging the cooling medium for an ice bath. After 30 min at 0°C, 6.2 g (27 mmol) of **7** in 36 ml of HMPA was added dropwise while maintaining the temperature at 0°C. The reaction mixture was worked up after 45 min by pouring it into a large volume of ice/water and extracting twice with ether. The organic layer was washed once with water, once with brine, and dried ($MgSO_4$). Evaporation of the solvent yielded 11.2 g of crude product. By kugelrohr distillation (100°C/0.2 Torr) the crude oil was separated from **5** and the elimination products of **7**. After column chromatography (silica gel, pentane/ether, 5:1) of the distillate 1.0 g (30%) of **5** was recovered. The filtration (silica gel, pentane/ether, 1:1) of 7.9 g of the distillation residue gave 4.9 g (58% based on added **5**) of **8** as a colorless oil. – IR (film): $\tilde{\nu}$ = 2920 cm^{-1} (CH_2), 2850 (CH_2), 2760, 1460, 1430, 1410, 1360, 1330, 1305, 1285, 1210 (sh), 1135 (COC), 1100, 1090, 1030 (sh, COC), 940, 725, 650. – ^1H NMR ($CDCl_3$): δ = 1.27–1.53 [complex signal, 18H, $(CH_2)_4$, $(CH_2)_5$], 1.60–1.70 (m, 2H, CH_2CH_2O), 1.71–1.83 (m, 2H, CH_2CH_2Cl), 2.13 (m, 4H, $CH_2C{\equiv}CCH_2$), 3.52 (t, *J* = 6.7 Hz, 2H, CH_2Cl), 3.75–4.00 (m, 4H, 2 CH_2O), 4.84 (t, *J* = 4.7 Hz, 1H, OCHO). – ^{13}C NMR ($CDCl_3$): δ = 18.73 (C-6′,9′), 23.99 (C-2′), 26.86 (C-14′), 28.73, 28.74, 28.81, 28.99, 29.03 (C-3′,4′,11′,12′,13′), 29.09 (C-5′,10′), 32.65 (C-15′), 33.89 (C-1′), 45.06 (C-16′), 64.83 (C-4,5), 80.13, 80.15 (C-7′,8′), 104.64 (C-2). – GC-MS (70 eV): *m/z* (%) = 331 (0.04) [M^+ + 1], 330/328 (0.21/0.55) [M^+], 329/327 (0.25/0.51) [M^+ – 1], 285 (1) [M^+ – 56], 181 (1), 73 (100) [$C_3H_5O_2^+$], 67 (4), 55 (4), 45 (6), 41 (6).

$C_{19}H_{33}ClO_2$ (328.92) Calcd. C 69.53 H 10.11
Found C 69.22 H 10.31

2-(16-Azido-7-hexadecynyl)-1,3-dioxolane (**9**): A solution of 4.4 g (13 mmol) of **8** and 4.2 g (65 mmol) of sodium azide in 50 ml of dry DMF was heated at 60°C for 6 h. The reaction solution was diluted with the same amount of water and extracted with petroleum ether. After removal of the solvent in vacuo, 4.2 g (96%) of pure **9** as a pale yellow oil was obtained.

Compound **9** was also prepared by a coupling reaction: To a stirred solution of 5.3 g (29.0 mmol) of **5** in 60 ml of anhydrous THF was added according to ref.[12] 20.3 ml (30.5 mmol) of a 1.6 M solution of *n*-butyllithium in *n*-hexane at –30°C. The yellow reaction solution was allowed to warm to 0°C by exchanging the cooling medium for an ice bath. After 30 min at 0°C, this solution was quickly added through a double-ended needle to a solution of 7.1 g (30.5 mmol) of **14** in 45 ml of HMPA at 0°C. The reaction mixture was worked up and purified as for **8** to give 4.5 g (46% based on added **5**) of azido acetal **9**. – IR (film): $\tilde{\nu}$ = 2920 cm^{-1} (CH_2), 2850 (CH_2), 2760, 2090 (N_3), 1460, 1430, 1410, 1350 (sh), 1330, 1310–1240 (br.), 1135 (COC), 1100, 1090, 1030 (sh, COC), 940, 725. – ^1H NMR ($CDCl_3$): δ = 1.25–1.53 [complex signal, 18H, $(CH_2)_4$, $(CH_2)_5$], 1.53–1.70 (complex signal, 4H, CH_2CH_2O, $CH_2CH_2N_3$), 2.13 (m, 4H, $CH_2C{\equiv}CCH_2$), 3.25 (t, *J* = 7 Hz, 2H, CH_2N_3), 3.75–4.00 [m, 4H, $O(CH_2)_2O$], 4.84 (t, *J* = 4.7 Hz, 1H, CH). – ^{13}C NMR ($CDCl_3$): δ = 18.75 (C-6′,9′), 24.01 (C-2′), 26.72 (C-14′), 28.74, 28.76, 28.86, 29.03, 29.05, 29.09 (C-3′,4′,11′,12′,13′,15′), 29.15 (C-5′,10′), 33.91 (C-1′), 51.48 (C-16′), 64.83 (C-4,5), 80.13, 80.16 (C-8′,7′), 104.65 (C-2). – GC-MS (70 eV): *m/z* (%) = 335 (0.31) [M^+], 334 (0.32) [M^+ – 1], 307 (0.17) [M^+ – N_2], 293 (0.18) [M^+ – N_3], 262 (1), 164 (1), 134 (1), 119 (1), 110 (1), 105 (1), 99 (3), 73 (100) [$C_3H_5O_2^+$], 67 (5), 55 (5), 45 (10), 41 (8).

$C_{19}H_{33}N_3O_2$ (335.49) Calcd. C 68.02 H 9.91 N 12.52
Found C 67.82 H 9.95 N 12.47

(2S)-(–)-1-(17-Azido-8-heptadecynylidenamino)-2-(methoxymethyl)pyrrolidine [(*S*)-**10**]: 5.4 g (16 mmol) of acetal **9** was dissolved in 80 ml of acetone and 8 ml of 1 N HCl was added. The reaction mixture was heated at 50–60°C for 3.5 h. The solution was cooled to room temp., neutralized with pH 7 buffer, concentrated to about one third of the original volume, and extracted several times with ether. The combined ethereal layers were washed with satd. $NaHCO_3$ solution and brine and dried ($MgSO_4$). After

cooling to 0°C, 2.1 ml (16 mmol) of SAMP was added. The mixture was stirred at room temp. for 3 h. The solvent was removed by evaporation and the resultant residue was purified by column chromatography (silica gel, pentane/ether, 5:1 then 3:1). The first fractions contained 1.1 g (20%) of unconverted **9**. Further elution afforded 4.9 g (76% yield over two steps based on added **9**) of the desired hydrazone (*S*)-**10** as a pale yellow oil. – $[\alpha]_D^{24.5}$ (neat) = −64.52. – IR (film): $\tilde{\nu}$ = 2920 cm^{-1} (CH), 2850 (CH), 2100 (N_3), 1605 (C=N), 1460 (sh), 1340 (sh), 1310–1240 (br.), 1195, 1120 (br.), 970, 900 (br.), 725. – ^1H NMR ($CDCl_3$): δ = 1.27–1.51 [complex signal, 18H, $(CH_2)_4$), $(CH_2)_5$], 1.51–1.65 (m, 2H, $CH_2CH_2N_3$), 1.70–2.00 (complex signal, 4H, 2 βCH_2), 2.12 (m, 4H, $CH_2C{\equiv}CCH_2$), 2.10–2.25 (m, 2H, $CH_2C{=}N$), 2.69 (m, 1H, CHHN), 3.25 (t, *J* = 7 Hz, 2H, CH_2N_3), 3.36 (s, 3H, OCH_3), 3.30–3.50 (complex signal, 3H, OCH_2, CHHN), 3.56 (m, 1H, CHN), 6.63 (t, *J* = 5.5 Hz, 1H, HC=N). – ^{13}C NMR ($CDCl_3$): δ = 18.74 (C-7′,10′), 22.17 (C-3), 26.62, 26.69 (C-4,15′), 27.76 (C-3′), 28.71[d], 28.75, 28.86, 29.00, 29.07 (C-4′,5′,12′,13′,14′,16′), 29.09 (C-6′,11′), 33.08 (C-2′), 50.41 (C-5), 51.44 (C-17′), 59.12 (OCH_3), 63.51 (C-2), 74.88 (OCH_2), 80.06, 80.13 (C-8′,9′), 138.92 (C-1′); [d] denotes doubled signal intensity. – MS (70 eV): *m/z* (%) = 404 (1.69) [M^+ + 1], 403 (6.01) [M^+], 359 (25) [$M^+ + 1 - CH_2OCH_3$], 358 (100) [$M^+ - CH_2OCH_3$], 170 (23), 155 (19), 127 (17), 95 (10), 83 (10), 81 (12), 79 (13), 70 (34) [$C_4H_8N^+$], 69 (19), 68 (10), 67 (20), 57 (11), 56 (14), 55 (22), 45 (19) [$CH_2{=}OCH_3^+$], 43 (29), 41 (33) [$CH_2{=}C{=}NH^+$].

$C_{23}H_{41}N_5O$ (403.60) Calcd. C 68.44 H 10.24 N 17.35
Found C 68.23 H 10.04 N 17.23

(2S,8Z)-(−)-1-(17-Amino-8-heptadecenylidenamino)-2-(methoxymethyl)pyrrolidine [(*S,Z*)-**11**]: According to ref.[8] a solution of 1.7 g (4.2 mmol) of acetylenic hydrazono azide (*S*)-**10** in 50 ml of dry ethanol was stirred with 0.28 g (17% by weight) of Lindlar catalyst under hydrogen at 20°C and the progress of the reaction was followed by TLC until all the azide was consumed. When the reaction was complete after 1.5 h, the catalyst was removed by filtration through Celite. After concentration of the filtrate, the crude product was purified by filtration through silica gel (ether before methanol) to yield 1.3 g (80%) of the amino alkene (*S,Z*)-**11** as a pale yellow oil. – $[\alpha]_D^{25.5}$ (neat) = −44.94, $[\alpha]_D^{24.5}$ = −43.37 (*c* = 1.03, $CHCl_3$). – *Z*:*E* = 96:4, determined by ^{13}C NMR from the C=C signals 130 (*E*), 129 (*Z*) and $=CCH_2$ signals 32 (*E*), 27 (*Z*). – IR (film): $\tilde{\nu}$ = 3360 cm^{-1}, 3300 (NH_2), 3000 (=CH), 2920 (CH), 2850 (CH), 1660 (C=C), 1605 (br., NH_2, C=N), 1460 (br.), 1370, 1340, 1300, 1280, 1195, 1120 (br.), 970, 905 (sh), 730 [m, $(Z){=}CCH_2$]. – ^1H NMR ($CDCl_3$): δ = 1.27–1.51 [complex signal, 20H, $(CH_2)_4$, $(CH_2)_6$], 1.60 (s, br., 2H, NH_2), 1.70–2.10 (complex signal, 8H, 2 βCH_2, 2 $CH_2C{=}$), 2.18 (m, 2H, $CH_2C{=}N$), 2.67 (t, *J* = 7 Hz, 2H, CH_2NH_2), 2.69 (m, 1H, CHHN), 3.36 (s, 3H, OCH_3), 3.30–3.50 (complex signal, 3H, OCH_2, CHHN), 3.56 (m, 1H, CHN), 5.33 (m, 2H, HC=CH), 6.63 (t, *J* = 5.5 Hz, 1H, HC=N). – ^{13}C NMR ($CDCl_3$): δ = 22.14 (C-3), 26.59 (C-4), 26.91 (C-15′), 27.17, 27.19 (C-7′,10′), 27.80 (C-3′), 29.12[d], 29.24, 29.49, 29.53, 29.67, 29.75 (C-4′,5′,6′,11′,12′,13′,14′), 33.09 (C-2′), 33.87 (C-16′), 42.26 (C-17′), 50.38 (C-5), 59.10 (OCH_3), 63.48 (C-2), 74.87 (OCH_2), 129.75, 129.81 (C-8′,9′), 138.98 (C-1′); [d] denotes doubled signal intensity. – MS (70 eV): *m/z* (%) = 379 (0.92) [M^+], 334 (4) [$M^+ - CH_2OCH_3$], 293 (11), 265 (12), 250 (14), 249 (28), 234 (13), 220 (10), 208 (38), 206 (18), 192 (10), 164 (14), 154 (10), 153 (11), 152 (13), 150 (15), 140 (13), 138 (20), 136 (18), 126 (13), 125 (10), 124 (10), 123 (15), 122 (24), 114 (57), 112 (17), 111 (10), 110 (31), 109 (12), 105 (16), 98 (23), 97 (21), 96 (84), 95 (14), 85 (100) [$C_6H_{13}^+$], 84 (47), 83 (21), 82 (35), 81 (23), 79 (12), 77 (10), 71 (14), 70 (58) [$C_4H_8N^+$], 69 (26), 68 (30), 67 (32), 58 (23), 57 (26), 56 (54), 55 (51), 54 (14), 53 (10), 45 (10) [$CH_2{=}OCH_3^+$], 44 (30), 43 (26), 42 (19), 41 (75) [$C_3H_5^+$, $CH_2{=}C{=}NH^+$], 39 (17).

(17R,9Z)-1,17-bis(methoxycarbonylamino)octadec-9-ene [(*R,Z*)-**12**]: According to ref.[15], 15.3 ml (23 mmol) of 1.7 M methyllithium in ether was diluted with 24 ml of anhydrous THF and cooled to −78°C. To this suspension was slowly added a solution of (*S,Z*)-**11** (2.6 g, 6.8 mmol) in 8 ml of anhydrous THF at −78°C. The heterogeneous mixture was allowed to slowly warm to room temp. with stirring (ca. 12 h). The resulting amber solution was then cooled to −60°C. After the addition of 3.9 ml (50 mmol) of methyl chloroformate the resulting clear orange solution was stirred for 3.5 h in an ice bath and was then quenched with satd. aqueous NH_4Cl and extracted once with ether. The ethereal extract was dried ($MgSO_4$) and concentrated to yield 4.0 g of the crude protected amino hydrazine as a viscous amber oil.

1.80 g (3.4 mmol) of crude methoxycarbonyl-activated hydrazine was dissolved in 15 ml of dry ether and slowly added to a vigorously stirred heterogeneous solution of lithium wire (0.70 g, 100.0 mmol in 100 ml of liquid ammonia) at −65°C. The reaction mixture was warmed to about −33°C, stirred for 4 h, cooled to −50°C, and carefully treated with methanol unitl complete decoloration. After about 12 h the solvent was evaporated through a KOH-filled drying tube. The syrupy residue was dissolved in water. The resulting mixture was extracted with ether, the ethereal extract dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, pentane/ether, 4:1, 2:1, 1:1) afforded 0.10 g (6%) of unconverted protected amino hydrazine and 0.49 g (34% yield over three steps) of the desired (*R,Z*)-**12** as a colorless solid; m.p. 44–52°C; $[\alpha]_D^{23.5}$ = +0.54 (*c* = 4.49, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3345 cm^{-1}, 3005 (=CH), 2980, 2930 (CH), 2860 (CH), 1790 (C=O), 1550 (br.), 1470, 1455, 1345, 1260 (br.), 1195, 1120, 1100, 1050, 1030, 780, 725, 710, 660 (br.). – ^1H NMR ($CDCl_3$): δ = 1.13 (d, *J* = 6.7 Hz, 3H, CH_3), 1.20–1.60 [complex signal, 22H, $(CH_2)_5$, $(CH_2)_6$], 2.01 (m, 4H, 2 $CH_2C{=}$), 3.14 (m, 2H, CH_2N), 3.69 (m, 7H, 2 OCH_3, CH), 4.78 (m, br., 1H, CHNH), 5.05 (s, br., 1H, CH_2NH), 5.33 (m, 2H, HC=CH). – ^{13}C NMR ($CDCl_3$): δ = 21.27 (C-18), 25.98, 26.75 (C-3,15), 27.18 (C-8,11), 29.20[d], 29.29, 29.43[d], 29.69, 29.71 (C-4,5,6,7,12,13,14), 30.03 (C-2), 37.17 (C-16), 41.12 (C-1), 46.79 (C-17), 51.85 (2 OCH_3), 129.80, 129.86 (C-9,10), 156.51, 157.15 (2 C=O); [d] denotes doubled signal intensity, signal broadening. – MS (70 eV): *m/z* (%) = 399 (3.02) [M^+ + 1], 398 (9.18) [M^+], 366 (10) [$M^+ - 32$], 279 (11), 255 (25), 211 (27), 209 (12), 197 (11), 167 (15), 154 (11), 149 (30), 125 (10), 114 (15), 110 (48), 109 (21), 105 (19), 102 (31), 97 (13), 96 (10), 95 (12), 91 (12), 85 (61), 84 (14), 83 (24), 82 (24), 81 (14), 80 (13), 78 (16), 77 (24), 76 (14), 70 (95), 69 (21), 68 (22), 67 (22), 66 (26), 65 (20), 59 (12), 57 (38), 56 (17), 55 (43), 54 (13), 53 (12), 49 (14), 45 (32), 44 (16), 43 (100) [$C_2H_3O^+$], 42 (27), 41 (73), 39 (42), 38 (10).

$C_{22}H_{42}N_2O_4$ (398.59) Calcd. C 66.29 H 10.62 N 7.03
Found C 66.22 H 10.64 N 7.06

(17R,9Z)-1,17-Diaminooctadec-9-ene [harmonine, (*R,Z*)-**1**]: According to the procedure of Jung et al.[23] a solution of 0.15 g (0.37 mmol) of (*R,Z*)-**12** in 0.20 ml of chloroform, sealed in a reaction vessel under argon, was added to 0.13 ml (0.98 mmol) of trimethylsilyl iodide via a syringe. The mixture was then heated at 50°C for 2 h after which time TLC analysis showed complete consumption of the starting material. The solution was cooled to room temp., then 0.18 g (2.7 mmol) of methanol pretreated with gaseous HCl was added and the volatile components were then removed under reduced pressure. The residue was taken up in methanol and 0.06 g (1.1 mmol) of freshly prepared sodium methoxide was added. The volatile components were again removed under reduced pressure. Filtration of the residue through Celite and concentration of the

filtrate gave 0.088 g (84%) of harmonine [(*R*,*Z*)-**1**] as a yellow oil, whose spectroscopic data corresponded to those reported in ref.[6]; $[\alpha]_D^{23} = -3.95$ ($c = 1.04$, C_6H_6); ee $\geq$ 97% determintated by ^{19}F-NMR spectra of Mosher's derivative of (*R*,*Z*)-**1**.

CAS Registry Numbers

1: 133576-26-8 / **2**: 629-30-1 / **3**: 10160-24-4 / **4**: 22374-56-7 / **5**: 133497-17-3 / **6**: 23144-52-7 / **7**: 28598-82-5 / **8**: 133497-18-4 / **9**: 133497-19-5 / **10**: 133497-20-8 / **11**: 133522-84-6 / **12**: 133497-21-9 / **13**: 629-41-4 / **14**: 133497-22-0 / 1,8-dibromooctane: 4549-32-0 / 8-bromo-1-octanol: 50816-19-8 / 8-azido-1-octanol: 57395-46-7 / 7-bromoheptanal: 54005-84-4

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