95. Asymmetric Synthesis of the Alkaloids Mayfoline and *N*(1)-Acetyl-*N*(1)-deoxymayfoline

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The total syntheses of the spermidine alkaloids (–)-mayfoline (**11**) and (+)-*N*(1)-acetyl-*N*(1)-deoxymayfoline (**12**) are described. These macrocyclic lactams belong to the most interesting conjugates of the polyamine derivatives very commonly found in nature. The enantioselective syntheses were achieved through resolution of the methyl 3-amino-3-phenylpropanoate (**2**) by recrystallization of its (+)-L-tartrate salt. Construction of the 13-membered ring ensued through condensation, reductive ring expansion (internal bond cleavage), and finally a transamidation reaction involving a second ring expansion.

Introduction. – Our interest in polyamine chemistry originated from the isolation and characterization of putrescine, spermidine, spermine, and related polyamine alkaloids [1]. The nitrogenous bases not only occur as free bases but also as alkylated or acylated conjugates with proteins, sugars, and other cellular constituents [2]. Among the most interesting of these are the macrocyclic polyamine alkaloids, isolated from several plant families, and generally characterized by the condensation of spermidine or spermine with cinnamic- or fatty-acid units to form large ring lactam systems [3]. It was natural then that they would become targets for synthesis.

The two spermidine alkaloids mayfoline (**11**) and *N*(1)-acetyl-*N*(1)-deoxymayfoline[2]) (**12**) were isolated from *Maytenus buxifolia* (A. RICH.) GRISEB. (Celastraceae) [4] (*Scheme*). They belong to the group of medium-ring compounds involving one 3-phenylpropanoic-acid unit incorporated into the ring; therefore, the expression macrocyclic lactam.

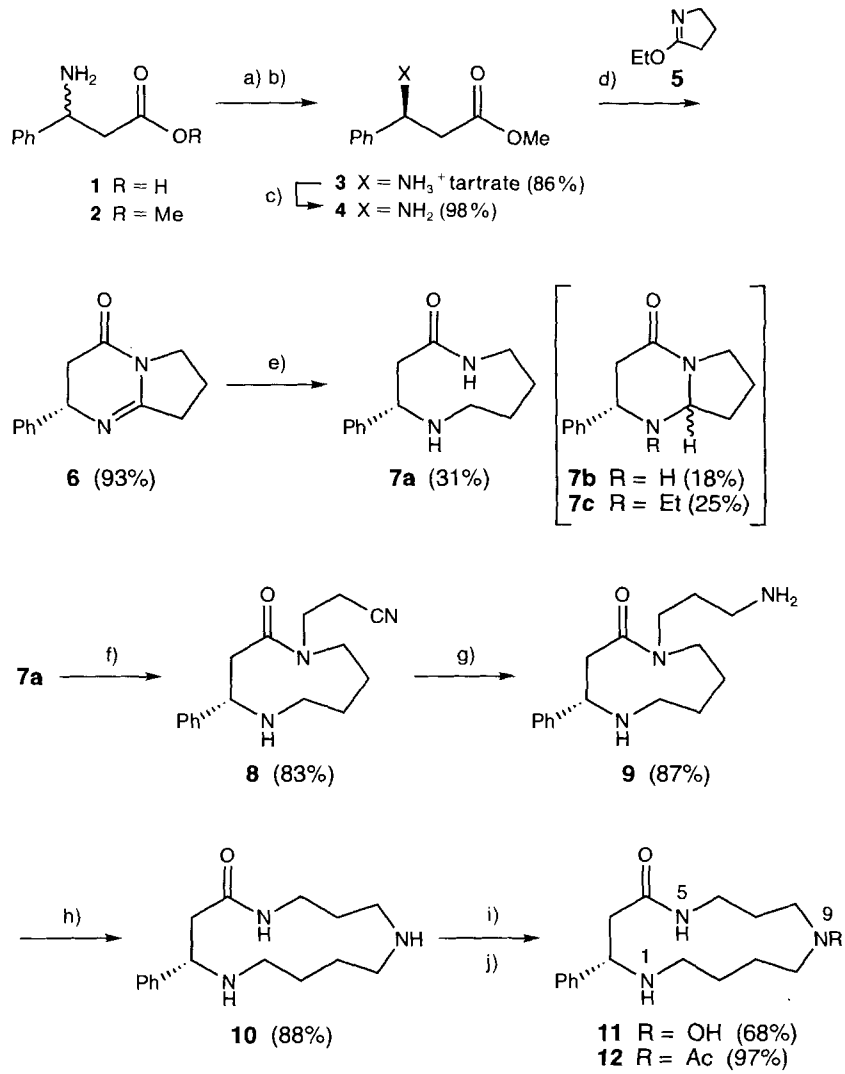
In taking the 13-membered spermidine macrocyclic skeleton as our example, there have been four general approaches to its formation. *McManis* and *Ganem* had first reported that such a ring could be achieved by a straightforward lactamization [5]. A second strategy put forth by *Wasserman et al.* involved the successive use of ring expansions [6]. A third route reported by *Yamamoto* and *Maruoka* utilized a template effect to induce long chains with α- and ω-functional groups to condense internally into large rings [7]. Most recently appearing in the literature, the fourth method relied on elaborating the 13-membered lactam *via* intramolecular iminium cyclization [8].

Results and Discussion. – We synthesized the related macrocyclic lactams **11** and **12** by the exploitation of ring expansions. This methodology required the prior preparation

[1]) Part of the planned Ph. D. thesis of *P. K.*, Universität Zürich.

[2]) Numbering of atoms in the text and *Exper. Part* follows that of the systematic nomenclature.

Scheme



a) HCl, MeOH, reflux, 1 h. b) (+)-L-tartaric acid, MeOH. c) Basified to pH 10–12, CH_2Cl_2. d) 130°, 3 h. e) $NaBH_3CN$, AcOH, r.t., 2 h; 45°, 1 h; r.t., 22 h. f) NaOEt/EtOH, acrylonitrile, toluene. g) *Raney*-Ni, H_2, EtOH, 25% aq. NH_3, 3 atm, 14 h. h) 1N 95% EtOH NaOH soln., 55°, 11 d. i) *Davis*' reagent, CH_2Cl_2, 40 min. j) Ac_2O, pyridine, CH_2Cl_2, r.t., 2 d.

of the optically active key intermediate, the nine-membered azalactam **7a**, formed in high yields by condensation of methyl (−)-(3*S*)-3-amino-3-phenylpropanoate (**4**) with 5-ethoxy-3,4-dihydro-2*H*-pyrrole (**5**). The enantiomerically pure amino ester **4** was synthesized from 3-amino-3-phenylpropanoic acid (**1**), the latter being produced in large

quantities by condensing PhCHO, ammonium acetate, and malonic acid in EtOH while heating under reflux (*vide infra*). This was followed by a *Fischer* esterification in HCl/MeOH from which the amino ester **2**, produced in very good yields, was liberated with aqueous 1N NaOH. The ester **2** was then resolved by recrystallization of its (+)-L-tartrate salt **3** [9]. The ester **4**, obtained upon treatment of resolved **3** with aqueous base, was shown to be optically pure by the presence of a single diastereoisomeric [Eu(hfc)$_3$] complex in the 300-MHz NMR spectrum monitoring both the benzylic proton and the methyl-ester *singlet*. This result is corroborated by the measured optical rotation which agrees with the value given in literature for (−)-(*S*)-**4**, prepared by a different methodology, of purity > 99% ee [10].

Our synthetic approach to **11** and **12** is as outlined in the *Scheme*. One of two methods developed for the formation of the nine-membered lactam **7a** made use of the bicyclic ketone **6** prepared by heating **4** with **5** [9]. Reductive cleavage of (+)-(2*S*)-2-phenyl-2,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrimidin-4-one (**6**) took place by reaction with 3–4 equiv. of $NaBH_3CN$ in the presence of AcOH, followed by basic workup forming (−)-(4*S*)-4-phenyl-1,5-diazanonan-2-one (**7a**) in yields only slightly better than 30%. There is a precedent that this type of reductive cleavage does not lead to significant racemization at C(4) [11]. Other products of this reductive ring expansion were the nine-membered azalactam (−)-(2*S*)-perhydro-2-phenylpyrrolo[1,2-*a*]pyrimidin-4-one (**7b**) and (2*S*)-*N*-ethylperhydro-2-phenylpyrrolo[1,2-*a*]pyrimidin-4-one (**7c**). While the reduction/*N*-ethylation of amines with $NaBH_4$/AcOH is a well-established protocol [12], there seems to be no analogous reaction with $NaBH_3CN$. Attempts to improve the above yield by use of other liquid or solid carboxylic acids, co-solvents, and/or *Lewis* acids have been unsuccessful.

Selective alkylation of the amide NH group was achieved in good yields by treatment of **7a** with NaOEt in EtOH followed after evaporation of the solvent by the addition of acrylonitrile in dry toluene. Reduction of the nitrile **8** to amine **9** was performed catalytically with *Raney*-Ni under an atmosphere of H_2 at 50 psi in an EtOH/aqueous NH_3 solution. Transannular ring enlargement of the nine-membered diazalactam **9** to the 13-membered macrocyclic lactam **10** proved not to be troublesome and could be accomplished under both acidic [13] or basic conditions [14]. Thus, treating **9** with 0.8 equiv. of toluene-4-sulfonic acid (TsOH) in refluxing xylene for 3 h furnished **10** as a colorless solid after purification. Yields were better under basic conditions, but the required reaction times were much longer (*vide infra*). Lactam **10** was then converted to mayfoline (**11**) and *N*(1)-acetyl-*N*(1)-deoxymayfoline (**12**) by oxidation with *Davis*' reagent ((±)-*trans*-2-(butylsulfonyl)-3-phenyloxaziridine) [15] and acetylation using Ac_2O/pyridine, respectively. As expected for such compounds, the regio-/chemoselectivity shown by the hydroxylation and respective acylation was the outcome of the difference in nucleophilic character between the secondary amine in position 9 and the amine in the benzylic position [13]. However, the actual discriminatory stimulus should be attributed to steric factors.

Concluding, both synthesized products **11** and **12** were fully characterized by analyzing their physical and spectroscopic data and comparing them with corresponding values for the natural products [4] [16]. In the case of **11**, high-temperature NMR experiments (^{1}H and ^{13}C) not only allowed reasonable spectra to be recorded (showing fine structure) but also yielded correlated spectra which facilitated the assignment of some neighboring

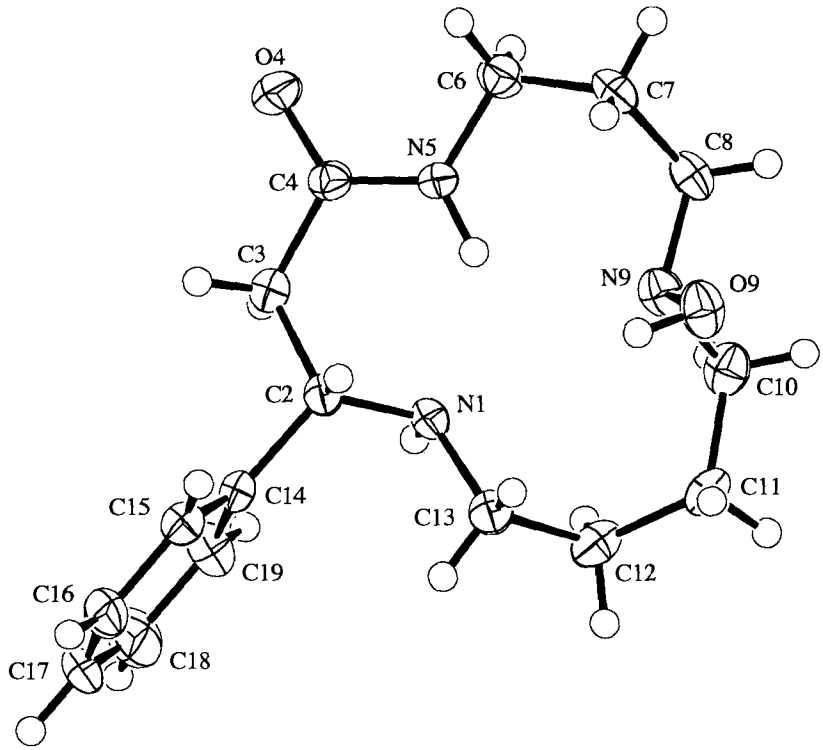


Fig. 1. *ORTEP Plot of mayfoline* (**11**; ellipsoids with 50% probability; H-atoms given arbitrary thermal parameters for clarity)

members. X-Ray crystallographic studies (*Fig. 1*) proved unambiguously that position N(9) was primarily oxidized by *Davis'* reagent[3]). The disparity in melting point and specific rotation between natural and synthetic material is due to the fact that the natural compound **11** was not in the form of the free base as described in [4]. Circumstantial evidence, supported by MS studies, allowed for conclusions to be drawn as to the uniformity of both materials. Though otherwise identical, the substance we had received from *Ripperger* [4] contained HCl. This fact is also supported by chemical shifts in ^{1}H-NMR spectra reported previously [4]. The three low-field signals at 10.17, 9.24, and 8.21, described also as exchangeable with D_2O, can best be explained when the sample is protonated. As to the difference in the direction and magnitude of the optical rotation, it can be assumed that salt formation is the cause. Synthetic mayfoline was constructed with a chiral building block of known absolute configuration. Racemization or partial racemization had not occurred during synthesis; the final product was found to possess a

[3]) Monitoring the chemical shift of H–C(2) also provides evidence as to where oxidation and acetylation has taken place.

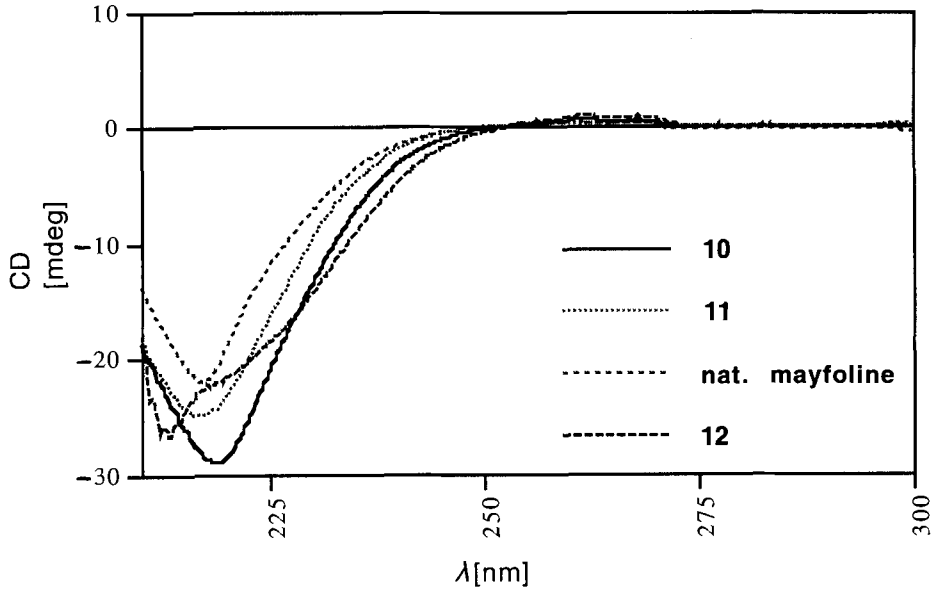


Fig. 2. *CD Spectra of* **10**–**12** *and natural mayfoline measured in EtOH*

rotation value of −52.3 ($c = 0.636$, $CHCl_3$), now believed to be its true $[\alpha]_D$[4]). When **11** was transformed into its ammonium chloride, the rotation was reduced (to −3). A similar observation of a strong reduction in specific rotation upon protonation was made by *Graf* and *Boeddeker* in 1958 in their studies of the alkaloid taxin B [17]. Final support as to the identity of the synthetic and natural materials was made available by CD spectroscopy. Shown in *Fig. 2* are the spectra of the synthetic compounds **10**–**12**, and natural mayfoline. Used as an empirical tool, the qualitative form of the spectra indicates that the skeleton of each compound is the same, and that they possess the same absolute configuration.

As for *N*(1)-acetyl-*N*(1)-deoxymayfoline (**12**), all measured physical and spectroscopic properties showed no deviation from the values cited previously [16]. The ^{13}C-NMR spectrum of **12** shows doubling of several signals due to the different conformation and/or configuration of the amide bond at N(9) and/or N(5). Similar doubling of signals has also been observed in the spectra of the 13-membered spermidine alkaloid loesenerine [18] and myricoidine [19]. To exclude the possibility of having a mixture, high-temperature NMR measurements were conducted. Especially for ^{13}C, the chemical-shift assignment was made facile and showed our sample to be homogeneous.

This work was generously supported by the *Swiss National Science Foundation*. We are also very thankful to Dr. *H. Ripperger*, Institut für Pflanzenbiochemie, Weinberg 3, Halle/Saale, for a sample of the original alkaloid mayfoline, *A. Guggisberg*, and the analytical services at our institute.

[4]) The value is negative, opposite to that of the value cited in [4] for natural mayfoline (+10.6 ($c = 0.61$, $CHCl_3$)).

Experimental Part

General. All chemicals used were of high commercial quality. Solvents used for chromatography were distilled prior to use. Column (CC) or flash (FC) chromatography: *Merck* silica gel *60* (0.04–0.06 mm) TLC: on precoated Kieselgel *60* F_{254} plates (*Merck*); spots visualized under UV light (254 nm) and by staining reagents. M.p. or dec.: *Mettler FP-5*. Optical rotation: *Perkin-Elmer 241* polarimeter. CD: *JASCO J-500A*, in EtOH. UV: *Perkin-Elmer 555* or *Perkin-Elmer Lambda 19* UV/VIS/NIR. IR: *Perkin-Elmer 781*, in $CHCl_3$ unless stated otherwise. ^{1}H-NMR: *Bruker AC-300*, *ARX-300*, or *AM-400*; ^{13}C-NMR: *Varian XL-400* or *Bruker ARX-300*; chemical shifts in ppm (δ scale) and $CDCl_3$, unless otherwise stated, as solvent and sometimes as internal standard (when not, then TMS); EI-MS: at 70 eV; CI-MS: NH_3 or isobutane as reactant gas, given are only peaks with values of $m/z \geq 40$ and with intensities $\geq 15\%$, except for M^+; *Finnigan*'s *MAT 90* or *MAT SSQ 700* and ESI: *Finnigan MAT TSQ 700*.

3-Amino-3-phenylpropionic Acid (=*β-Phenyl-β-alanine*, **1**). A mixture of ammonium acetate (154.2 g, 2.00 mol), malonic acid (104.1 g, 1.00 mol), and PhCHO (106.1 g, 1.00 mol) in EtOH (250 ml) was heated under reflux for 6.5 h. From the cooled mixture, the precipitate was collected, pressed, washed with Et_2O and EtOH, and finally dried *in vacuo* yielding 102.8 g (62%). M.p. 227.4–228.5° (dec.). The crude material was recrystallized according to *Steiger* [20].

The amino acid **1** was dissolved in 16 times its weight of boiling H_2O followed by the addition of abs. EtOH (46 ml per g of amino acid). The soln. was stirred mechanically while being cooled in an ice-water bath. After 3 h, the colorless crystalls were collected, washed with 95% EtOH in small portions, and then dried *in vacuo*. The recovery of **1** (colorless powder) was 92.8 g (56%). M.p. 231.8–232.9° (dec.). IR (KBr): 3410*w* (br.), 3020–2600*s* (br.), 2200*m*, 1620*s*, 1580*s*, 1510*s*, 760*m*, 695*s*. ^{1}H-NMR (D_2O): 7.53–7.43 (*m*, 5 arom. H); 4.66 (*dd*, J = 8.0, 6.6, H–C(3)); 2.92 (*dd*, J = 16.0, 8.0, H_a–C(2)); 2.85 (*dd*, J = 16.0, 6.6, H_b–C(2)). ^{13}C-NMR (D_2O): 177.12 (*s*, C(1)); 135.91 (*s*, 1 arom. C); 129.16, 126.81 (2*d*, 5 arom. C); 52.63 (*d*, C(3)); 40.32 (*t*, C(2)). EI-MS: 165 (5, M^+), 106 (100, $[M - C_2H_3O_2]^+$), 104 (16), 79 (37), 77 (28). Anal. calc. for $C_9H_{11}O_2$ (165.19): C 65.44, H 6.71, N 8.48; found: C 65.20, H 6.58, N 8.31.

Methyl 3-Amino-3-phenylpropanoate (**2**). *Fischer* esterification was performed by passing gaseous HCl through a soln. of **1** (5.00 g, 30.3 mmol) in abs. MeOH (250 ml). Following workup, the concentrated raw material was distilled (bulb-to-bulb) at 90°/10^{-2} Torr to give **2** (5.26 g, 97%) as a colorless oil. IR (film): 3370*w*, 3055*w*, 3020*w*, 2995*w*, 2945*w*, 1735*s*, 1635*w*, 1600*w*, 760*m*, 700*m*. ^{1}H-NMR: 7.33–7.16 (*m*, 5 arom. H); 4.35 (*dd*, J = 7.0, 6.7, H–C(3)); 3.61 (*s*, MeO); 2.59 (*d*, J = 6.7, 2 H–C(2)); 1.68 (br. *s*, NH_2). ^{13}C-NMR: 172.40 (*s*, C(1)); 144.63 (*s*, 1 arom. C); 128.59, 127.36, 126.10 (3*d*, 5 arom. C); 52.56 (*q*, MeO); 51.59 (*d*, C(3)); 43.95 (*t*, C(2)). CI-MS: 359 (34, $[2M + H]^+$), 180 (100, $[M + H]^+$).

(+)-(1S)-[2-(Methoxycarbonyl)-1-phenylethyl]ammonium L-*Tartrate* (**3**). A soln. of **2** (28.1 g, 0.157 mol) in MeOH (157 ml) was added to a refluxing soln. of (+)-L-tartaric acid (23.5 g, 0.157 mol) in MeOH (157 ml). The product crystallized overnight at −20° and was filtered off. Recrystallization from MeOH (157 ml) furnished **3** (22.2 g, 86%)[5]) as a colorless powder. M.p. 165.3–166.8°. Further recrystallization of the salt from MeOH (100 ml) gave colorless crystals whose physical and spectroscopic properties were in accordance with the literature [9]. M.p. 170.6–171.6°. $[\alpha]_D^{22} = +18.5$ (c = 7.60, H_2O). IR (KBr): 3450*m*, 3400*m*, 3310*m*, 3260*m*, 2910*m* (br.), 1730*m*, 1600*m* (br.), 1550*m*, 1520*m*, 1500*m*, 700*m*, 670*m*. CI-MS: 180 ($[M + H - C_4H_6O_6]^+$). Anal. calc. for $C_{14}H_{19}NO_8$ (329.31): C 51.06, H 5.82, N 4.25; found: C 51.27, H 6.06, N 4.45.

Methyl (−)-(3S)-3-Amino-3-phenylpropanoate (**4**). A soln. of **4** (20.0 g, 0.616 mol) in 1N aq. NaOH soln. (*ca.* 2 equiv.) was extracted with $CHCl_3$ (3×). The org. layer was dried (Na_2SO_4) and concentrated. Bulb-to-bulb distillation by 85–90°/10^{-2} Torr delivered **4** (10.8 g, 98%) as a colorless oil. $[\alpha]_D^{22} = -20.3$ (c = 1.53, $CHCl_3$). IR: 3370*w*, 2990*w*, 2950*w*, 1730*vs*, 1585*w*, 700*m*. ^{1}H-NMR: 7.48–7.16 (*m*, 5 arom. H); 4.35 (*dd*, J = 7.2, 6.5, H–C(3)); 3.61 (*s*, MeO); 2.59 (*d*, J = 7.2, H_a–C(2)); 2.58 (*d*, J = 6.7, H_b–C(2)); 1.67 (br. *s*, NH_2). ^{13}C-NMR: 172.36 (*s*, C(1)); 144.55 (*s*, 1 arom. C); 128.56, 127.34, 126.07 (3*d*, 5 arom. C); 52.53 (*q*, MeO); 51.56 (*d*, C(3)); 43.87 (*t*, C(2)). CI-MS: 180 (100, $[M + H]^+$), 106 (37). Anal. calc. for $C_{10}H_{13}NO_2$ (179.22): C 67.02, H 7.31, N 7.82; found: C 67.33, H 7.03, H 8.15.

*5-Ethoxy-3,4-dihydro-2*H*-pyrrole* (**5**). Under an inert atmosphere, a 1M soln. of triethyloxonium tetrafluoroborate (50.0 g, 0.260 mol) was added dropwise to pyrrolidin-2-one (22.4 g, 0.260 mol) while stirring. The faintly yellow soln. was refluxed for 4 h and left overnight without stirring at r.t. The mixture was then made alkaline with a 5N soln. of K_2CO_3 under ice-cooling. The CH_2Cl_2 layer was separated and the aq. layer extracted with CH_2Cl_2 (2×). The combined org. extracts were dried (K_2CO_3), evaporated, and finally purified by bulb-to-bulb distillation (130–140°/400 Torr) yielding **5** (26.7 g, 90%) as a colorless liquid. IR (CH_2Cl_2): 3650*w*, 3270*w*, 3020*m*, 2955*s*,

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[5]) Yield determination took only the single (desired) antipode in consideration.

1640*vs*. ^{1}H-NMR: 4.12 (*q*, *J* = 7.1, MeCH_2O); 3.59 (*t*, *J* = 7.0, 2 H–C(2)); 2.38 (*t*, *J* = 8.4, 2 H–C(4)); 2.03–1.88 (*m*, 2 H–C(3)); 1.24 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 172.98 (*s*, C(5)); 63.67 (*t*, MeCH_2O); 55.05, 31.05, 23.04 (3*t*, 3 C); 14.39 (*q*, 1 C). CI-MS: 114 (100, $[M + H]^+$), 103 (23), 86 (51).

*(+)-(2S)-2,6,7,8-Tetrahydro-2-phenyl-3*H*-pyrrolo[1,2-a]pyrimidin-4-one* (**6**). Modifying the procedure of *Bormann* [21], a mixture of **4** (1.81 g, 0.101 mol) and **5** (1.25 g, 0.111 mol) was heated under N_2 to 125–135° (oil bath) for 2.5–3 h. On cooling, a single product crystallized. Isolation of the solid material and purification of the oily reaction residue by CC furnished (combined) **6** (1.99 g, 93%) as a colorless crystalline mass. R_f (Et_2O/hexane/MeOH/25% aq. NH_3 75:20:5:1) 0.23. M.p. (cyclohexane) 110.7–111.0°. $[\alpha]_D^{22} = +80.6$ (*c* = 2.50, $CHCl_3$). IR: 3350*w* (br.), 2990*m*, 2960*m*, 2900*w*, 2460*w*, 1865*vs*, 1370*s*, 700*m*. ^{1}H-NMR: 7.47–7.18 (*m*, 5 arom. H); 4.74–4.66 (*m*, H–C(2)); 3.81–3.66 (*m*, 2 H); 2.80–2.60 (*m*, 3 H); 2.40 (*dd*, *J* = 16.8, 13.1, H–C(3)); 2.06–1.96 (*quint.*, *J* = 7.5, 2, H–C(7)). ^{13}C-NMR: 167.98 (*s*, C(4)); 158.81 (*s*, C(9)); 142.39 (*s*, 1 arom. C); 128.64, 127.26, 126.39 (3*d*, 5 arom. C); 59.07 (*d*, C(2)); 44.37, 37.16, 31.02, 19.53 (4*t*, 4 C). CI-MS: 215 ($[M + H]^+$). Anal. calc. for $C_{13}H_{14}N_2O$ (214.27): C 72.87, H 6.59, N 13.07; found: C 73.09, H 6.42, N 12.80.

(−)-(4S)-4-Phenyl-1,5-diazacyclononan-2-one (**7a**). To a soln. of **6** (4.28 g, 0.020 mol) in glacial AcOH (50 ml) was added $NaBH_3CN$ (5.04 g, 0.068 mol) in portions at r.t. under N_2. The mixture was stirred at r.t. for 2 h, warmed to 50° for 1 h, then stirred for *ca.* 23 h again at r.t. After cooling (0°), H_2O (60 ml) was added, the soln. made strongly basic by addition of a 50% aq. NaOH, and extracted with CH_2Cl_2 (3×). The combined org. fractions were washed with a sat. NaCl soln., dried (K_2CO_3), and concentrated *in vacuo* to leave a yellow oil. Pure **7a** (1.35 g, 31%) was obtained by CC on silica gel. R_f (Et_2O/cyclohexane/MeOH/25% aq. NH_3 70:25:5:1) 0.26. M.p. (CH_2Cl_2/hexane) 85.7–86.2°. $[\alpha]_D^{21} = -151$ (*c* = 0.936, $CHCl_3$). IR: 3350*w* (br.), 3060*w*, 2990*m*, 2930*m*, 2850*w*, 1665*vs*, 1550*m*, 690*m*. ^{1}H-NMR: 7.32–7.11 (*m*, 5 arom. H); 6.91 (br. *d*, *J* = 9.4, CONH); 3.75–3.60 (*m*, 1 H); 3.50 (*dd*, *J* = 11.9, 2.7, 1 H); 2.88–2.75 (*m*, 2 H); 2.69 (*td*, *J* = 11.7, 3.1, 1 H); 2.44 (*t*, *J* = 11.9, 1 H); 2.29 (*dd*, *J* = 11.9, 2.7, 1 H); 1.91–1.26 (*m*, 5 H). ^{13}C-NMR: 175.30 (*s*, C(2)); 143.61 (*s*, 1 arom. C); 128.11, 126.61, 124.82 (3*d*, 5 arom. C); 60.51 (*d*, C(4)); 50.48, 45.25, 39.32, 28.23, 24.75, (5*t*, 5 C). EI-MS: 218 (33, M^+), 146 (57), 132 (30), 119 (32), 118 (100), 106 (46), 105 (30), 104 (85), 103 (21), 91 (34), 77 (28), 56 (31), 42 (59).

Further materials isolated from the reaction mixture: *(−)-(2S)-Perhydro-2-phenylpyrrolo[1,2-a]pyrimidin-4-one* (**7b**). Obtained as a colorless oil in 18% yield. R_f (as above) 0.09. M.p. (Et_2O/AcOEt/pentane) 77.0. $[\alpha]_D^{22} = -30.75$ (*c* = 1.42, $CHCl_3$). IR: 3660*w*, 3380*m* (br.), 3055*w*, 2980*m*, 2880*w*, 2460*w*, 1625*s*, 1485*s*, 1470*s*, 1410*m*, 695*m*. ^{1}H-NMR: 7.34–7.20 (*m*, 5 arom. H); 4.51 (*dd*, *J* = 10.0, 5.0, PhC*H*); 4.12 (*dd*, *J* = 11.3, 5.3, 1 H); 3.71–3.61 (*m*, 1 H); 3.48 (*m*, 1 H); 2.70 (*dd*, *J* = 17.7, 5.3, 1 H); 2.37 (*dd*, *J* = 17.7, 11.3, 1 H); 2.00–1.65 (*m*, 3 H); 1.64–1.49 (*m*, 1 H). ^{13}C-NMR: 167.11 (*s*, CO); 141.52 (*s*, arom. C); 128.69, 127.64, 125.96 (3*t*, 4 arom. C); 73.75 (*d*, C(4)); 56.96 (*d*, C(6)); 43.48, 38.36, 32.68 (3*t*, 3 C); 20.29 (*t*, 1 C). EI-MS: 216 (100, M^+), 188 (27), 131 (25), 121 (23), 111 (32), 106 (125), 104 (98), 103 (19), 85 (18), 83 (51), 77 (17), 70 (24). Anal. calc. for $C_{13}H_{16}N_2O$ (216.29): C 72.19, H 7.46, N 12.95; found: C 72.52, H 7.01, N 13.22.

*(2S)-*N*-Ethylperhydro-2-phenylpyrrolo[1,2-a]pyrimidin-4-one* (**7c**). Obtained as a colorless amorphous solid in 25% yield. R_f (as above) 0.17. IR: 3370*w* (br.), 2970*m*, 2870*w*, 2800*w*, 1710*w*, 1630*s*, 700*w*. ^{1}H-NMR: 7.51–7.41 (*m*, 5 arom. H); 4.44 (*dd*, *J* = 9.0, 4.6, 1 H); 4.03 (*dd*, *J* = 9.5, 5.9, 1 H); 3.87–3.71 (*m*, 2 H); 2.90–2.66 (*m*, 4 H); 2.42–2.36 (*m*, 1 H); 2.30–2.10 (*m*, 1 H); 2.09–1.90 (*m*, 2 H); 0.99 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR: 166.92 (*s*, C(4)); 141.39 (*s*, 1 arom. C); 128.59, 127.65 (2*d*, 5 arom. C); 76.54 (*d*); 62.49 (*d*, C(2)); 44.37, 42.46, 40.18, 32.58, 20.95 (5*t*, 5 C); 9.66 (*q*, 1 C). ESI-MS: 267 ($[M + Na]^+$), 245 ($[M + H]^+$).

3-[(4S)-2-Oxo-1,5-diazacyclononan-1-yl]propanenitrile (**8**). Na (287 mg, 12.5 mmol) was dissolved in abs. EtOH (10 ml). Part of the soln. (5.2 ml, containing 6.50 mmol of NaOEt) was evaporated to dryness, and dry toluene (40 ml) and **7a** (1.30 g, 5.96 mmol) were added. The suspension was heated under Ar, until a pale-orange-yellow soln. was obtained. The soln. was left to cool to r.t., then acrylonitrile (6 equiv.), dissolved in toluene, was added very slowly (over 3 h) and left stirring for an additional 2 h. The mixture at the end was evaporated and the residue purified by FC (CH_2Cl_2/hexane/MeOH 85:14:1), dried, and concentrated yielding **8** (1.34 g, 83%) as a pale-yellow viscous oil. R_f (CH_2Cl_2/hexane/MeOH 85:14:1) 0.21. IR: 3400*w* (br.), 2990*m*, 2930*m*, 2240*w* (CN), 1620*s*, 700*m*. ^{1}H-NMR: 7.30–7.16 (*m*, 5 arom. H); 4.87 (*td*, *J* = 13.4, 4.0, 1 H); 3.95–3.87 (*m*, 1 H); 3.68 (*d*, *J* = 9.6, 1 H); 3.37–3.30 (*ddd*, *J* = 14.2, 5.3, 1.7, 1 H); 3.16–3.01 (*m*, 2 H); 2.93–2.67 (*m*, 3 H); 2.58–2.49 (*m*, 2 H); 1.91–1.81 (*m*, 1 H); 1.58–1.50 (br. *m*, 2 H); 1.39–1.27 (br. *m*, 2 H). ^{13}C-NMR: 174.24 (*s*, C(2)); 146.09 (*s*, 1 arom. C); 128.81, 127.09, 125.29 (3*d*, 5 arom. C); 118.35 (*s*, CN); 60.89 (*d*, C(4)); 49.32 (*t*, C(3)); 48.80 (*t*, CH_2CH$_2$CN); 46.31 (*t*, C(9)); 41.13 (*t*, C(6)); 26.19 (*t*, C(8)); 21.61 (*t*, C(7)); 15.8 (*t*, CH$_2$CH_2CN). CI-MS: 272 ($[M + H]^+$).

(−)-(4S)-1-(3-Aminopropyl)-4-phenyl-1,5-diazacyclononan-2-one (**9**). Substrate **8** (1.27 g, 4.68 mmol), 95% EtOH (100 ml), 25% aq. NH_3 (20 ml), and *Raney*-Ni (0.960 g) were all placed in a bottle for use on a *Parr* apparatus. The mixture was then subjected to a H_2 atmosphere of 50 p.s.i. for 14 h. The catalyst could be captured by filtering the soln. through *Celite*; the filtrate was then evaporated and the residue purified by CC (CH_2Cl_2/

MeOH/25% aq. NH_3 95:5:0.5) yielding **10** (1.12 g, 87%) as a colorless oil. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 90:10:1) 0.25. IR: 3630*w*, 3370*m*, 3000*s*, 2940*s*, 2860*m*, 1615v*s* 700*m*. ^{1}H-NMR: 7.35–7.21 (*m*, 5 arom. H); 4.73 (*td*, *J* = 13.1, 3.6, H–C(8)); 3.93 (*dt*, *J* = 13.6, 7.1, 1 H); 3.79 (*d*, *J* = 10.1, 1 H); 3.29–3.22 (*m*, 1 H); 3.16 (*dd*, *J* = 12.6, 10.4, 1 H); 2.99–2.92 (*m*, 2 H); 2.82–2.72 (*m*, 2 H); 2.20 (br. *s*, NH_2, NH); 1.99–1.81 (*m*, 1 H); 1.79–1.75 (*m*, 2 H); 1.60–1.39 (*m*, 3 H). ^{13}C-NMR: 174.11 (*s*, C(2)); 146.37 (*s*, C(1)); 128.86, 127.09, 125.52 (3*d*, 5 arom. C); 61.06 (*d*, C(4)); 49.30, 47.30, 46.22, 40.95, 39.11, 30.09, 26.15, 22.04 (8*t*, 8 C). CI-MS: 276 ($[M + H]^+$).

(−)-(4S)-4-Phenyl-1,5,9-triazacyclotridecan-2-one (**10**). *Method 1*: Preparation of **10** was accomplished by placing **9** (0.920 g, 3.34 mmol) in a 1N NaOH ethanolic soln. (95% EtOH, 30 ml) and stirring the mixture at 55° for 11 d. The solvent was evaporated and the residue taken up with H_2O and extracted with CH_2Cl_2. After workup, CC on silica gel with CH_2Cl_2/MeOH/25% aq. NH_3 (first 85:14:1, then 78:19:3, lastly 7:3:1) gave **10** (0.810 g, 88%) as a colorless amorphous solid.

Method 2: Amidation under acidic conditions was achieved by placing **9** (200 mg, 0.726 mmol) in a soln. of TsOH (110 mg, 0.581 mmol) in xylene (10 ml) and heating under reflux for 3 h. Upon cooling, the mixture was basified, extracted with CH_2Cl_2, dried (Na_2SO_4), evaporated *in vacuo*, and chromatographed (CH_2Cl_2/MeOH/25% aq. NH_3 7:3:1) to afford **10** (114 mg, 57%) as a colorless amorphous solid. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 7:3:1) 0.18. M.p. (CH_2Cl_2/hexane) 117.3–118.4°. $[\alpha]_D^{22} = -41.2$ (*c* = 0.612, $CHCl_3$). IR: 3440*w*, 3210*m* (br.), 3000*s*, 2930*s*, 2850*m*, 1640*s* (br.), 1525*s*, 700*m*. ^{1}H-NMR: 8.55 (br. *s*, CONH); 7.36–7.20 (*m*, 5 arom. H); 3.93 (*dd*, *J* = 8.7, 5.5, H–C(4)); 3.65 (*dt*, *J* = 19.1, 5.8, CONHCH_a); 3.29–3.19 (*m*, CONHCH_b); 2.94–2.87 (*m*, 1 H); 2.82–2.53 (*m*, 2 H); 2.51–2.44 (*m*, 2 H); 2.36 (*td*, *J* = 9.0, 2.1, 1 H); 2.14 (br. *s*, 2 NH); 1.79–1.36 (*m*, 8 H). ^{13}C-NMR: 171.4 (*s*, C(2)); 143.1 (*s*, 1 arom. C); 128.5, 127.1, 126.3 (3*d*, 5 arom. C); 60.0 (*d*, C(4)); 49.9, 48.8, 45.9, 44.8, 39.8, 28.6, 27.6, 27.2 (8*t*, 8 C). CI-MS: 276 (36, $[M + H]^+$), 259 (100).

(−)-(2S)-9-Hydroxy-2-phenyl-1,5,9-triazacyclotridecan-4-one (= *Mayfoline*, **11**). To a soln. of **10** (100 mg, 0.363 mmol) in CH_2Cl_2 (4 ml) was added under N_2 (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (104 mg, 1.1 equiv.) in portions, followed by monitoring of the reaction by TLC. After 40 min, the mixture was concentrated *in vacuo* to give the crude product which was purified by CC to yield **11** (71.8 mg, 68%) as a colorless foam. Recrystallization from benzene/hexane gave crystals, unfortunately containing solvent molecules in a 2:1 ratio with **11** (mayfoline/MeOH). R_f (Et_2O/hexane/MeOH/25% aq. NH_3 6:3:1:0.1) 0.22. $[\alpha]_D^{21} = -52.3$ (*c* = 0.636, $CHCl_3$). UV (EtOH): λ_{max} 267 (sh, 2.16), 263.4 (2.34), 2.57 (2.49), 2.51 (2.60). IR: 3280*m* (br.), 3000*m*, 2930*m*, 2870*m*, 2840*m*, 1655*s*, 1530*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO, 363 K): 8.12 (br. *s*, H–N(5)); 7.35–7.27 (*m*, 4 arom. H); 7.23–7.16 (*m*, 1 arom. H); 3.94 (*dd*, *J* = 11.0, 2.8, H–C(2)); 3.46–3.38 (*m*, H_a–C(6)); 3.19–3.10 (*m*, H_b–C(6)); 2.83–2.63 (*m*, 5 H); 2.52–2.33 (*m*, 4 H, underneath H_a–C(3)); 2.22 (*dd*, *J* = 14.4, 2.8, H_b–C(3)); 1.84–1.36 (*m*, 6 H). ^{13}C-NMR ((D$_6$)DMSO, 363 K): 170.79 (*s*, C(4)); 144.98 (*s*, 1 arom. C); 128.51, 126.91 (2*d*, 5 arom. C); 60.41 (*t*, 1 C); 60.09 (*d*, C(2)); 58.32, 45.91, 45.61, 38.31, 27.45, 25.89, 24.82 (7*t*, 7 C). EI-MS: 292 (100, $M^{+\cdot}$), 274 (64), 160 (50), 110 (23), 104 (22), 100 (40), 91 (29), 84 (24), 70 (48), 56 (24).

(+)-(2S)-9-Acetyl-2-phenyl-1,5,9-triazacyclotridecan-4-one (= *(+)-N(1)-Acetly-N(1)-deoxymayfoline*, **12**). To a soln. of **10** (100 mg, 0.363 mmol) in CH_2Cl_2 (5 ml) were added under cooling (0°) pyridine (1.1 equiv.) and Ac_2O (1.1 equiv.). After addition, the ice bath was removed and the mixture allowed to stir for 48 h at r.t. The mixture was made then alkaline with 25% aq. NH_3, evaporated *in vacuo*, and purified by CC (CH_2Cl_2/MeOH/25% aq. NH_3) to furnish **12** (112 mg, 97%) as a colorless powder. Recrystallization from AcOEt delivered colorless crystals. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 95:5:1 and 97:3:0.5) 0.29 and 0.18, resp. M.p. 177.4–178°. $[\alpha]_D^{21} = +17.4$ (*c* = 1.01, $CHCl_3$). UV (MeOH): λ_{max} 268 (sh, 2.01), 264 (2.21), 258 (2.35), 252 (2.35). IR (KBr): 3370*s*, 3280*m*, 3080*w*, 3020*w*, 2960*m*, 2935*m*, 2880*m*, 2850*m*, 2820*m*, 1635v*s* (br.), 1585*m*, 1560*s*. ^{1}H-NMR ((D$_6$)DMSO, 388 K): 7.61 (br. *s*, NHCO); 7.37–7.26 (*m*, 4 arom. H); 7.25–7.15 (*m*, 1 arom. H); 3.99 (*dd*, *J* = 11.3, 3.5, H–C(2)); 3.46–3.15 (*m*, 5 H); 3.04–2.93 (*m*, 1 H); 2.63–2.55 (*m*, 1 H); 2.45–2.26 (*m*, 3 H); 1.95 (br. *s*, Me); 1.94–1.24 (*m*, 7 H). ^{13}C-NMR ((D$_6$)DMSO, 388 K): 171.27 (*s*, C(4)); 169.12 (*s*, CO); 144.74 (*s*, C(1′)); 128.57 (*d*, 2 arom. C); 126.90 (*d*, C(4′)); 126.70 (*d*, 2 arom. C); 60.61 (*d*, C(2)); 45.82 (br. *t*, 2 C); 45.43, 43.80, 36.52, 28.92, 25.11, 24.73, (6*t*, 6 C); 21.00 (*t*, 1 C). EI-MS: 317 (31, $M^{+\cdot}$), 274 (19, $[M - Ac]^+$), 189 (36), 176 (27), 171 (35), 160 (49), 159 (39), 158 (22), 146 (100) 132 (33), 131 (29), 129 (21), 119 (29), 105 (24), 104 (50), 100 (47), 98 (39), 91 (41), 84 (50), 70 (91), 69 (36). Anal. calc. for $C_{18}H_{27}N_3O_2$ (317.43): C 68.11, H 8.57, N 13.24; found: C 68.01, H 8.29, N 13.58.

Crystal-Structure Determination of **11**[6]. All measurements were conducted at low temp. on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ = 0.71069 Å) and a 12-kW rotating anode

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[6]) Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-10/2. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: teched@chemcrys.cam.ac.uk).

generator. The intensities were collected using $\omega/2\theta$ scans. Three standard reflections measured every 150 reflections showed negligible variation in intensity. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods using SHELXS86 [22] which revealed the positions of all non-H-atoms.

The asymmetric unit contains two molecules of the substrate plus one molecule of solvent (benzene). One of the molecules is disordered in the region around the N-atom nearest to the Ph substituent. Two positions were defined for this N-atom and the site occupation factors refined to a ratio of 0.63:0.37. The non-H-atoms were refined anisotropically. All of the amine and hydroxy H-atoms were placed in the positions indicated by difference electron-density map and, except for that bonded to O(29), their positions were allowed to refine together with individual isotropic temp. factors. The H-atoms bonded to C-atoms were fixed in geometrically calculated positions with a C–H distance of 0.95 Å and they were assigned fixed isotropic temp. factors with a value of 1.2 U_{eq} of the parent C-atom. Refinement of the structure was carried out on F using full-matrix least-squares procedures. A correction for secondary extinction was applied. The data collection and refinement parameters are listed in the *Table*.

Table. *Crystallographic Data for Compound* **11**

Crystallized from	benzene/hexane	D_x [g cm^{-3}]	1.202
Empirical formula	$C_{16}H_{25}N_3O_2 \cdot \frac{1}{2} C_6H_6$	μ (MoK_α) [mm^{-1}]	0.0787
Formula weight	330.45	Scan type	$\omega/2\theta$
Crystal color, habit	colorless, prism	$2\theta_{(max)}$ [°]	55
Crystal dimension [mm]	0.25 × 0.38 × 0.42	Total reflections measured	5441
Temp. [K]	173 (1)	Symmetry-independent reflections	5294
Crystal system	orthorhombic		
Space group	$P2_12_12_1$	Reflections used [$I > 2\sigma(I)$]	3512
Z	8	Parameters refined	463
Unit cell parameters		Final R	0.0485
a [Å]	15.482 (4)	wR	0.0417
b [Å]	23.336 (3)	Goodness of fit	1.600
c [Å]	10.110 (4)	Final Δ_{max}/σ	0.01
V [Å^3]	3652 (2)	$\Delta\rho$ (max; min) [e Å^{-3}]	0.39; –0.25
Reflections for cell determination	25		
2θ range for cell determination [°]	26–39		

Neutral atom scattering factors for non-H-atoms were taken from [23], and the scattering factors for H-atoms were taken from [24]. Anomalous dispersion effects were included in F_{calc} [25]; the values for $\Delta f'$ and $\Delta f''$ were those from [26]. All calculations were performed using the TEXSAN crystallographic software package [27].

The two independent molecules differ in that the configuration at N(9) [N–OH] is inverted when the lone pair is also taken into consideration.

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