Diastereoselective Syntheses of *N*-Protected Derivatives of 1α,5α,6β-6-Amino-3-azabicyclo[3.1.0]hexane; A Route to Trovafloxacin 6β-Diastereomer

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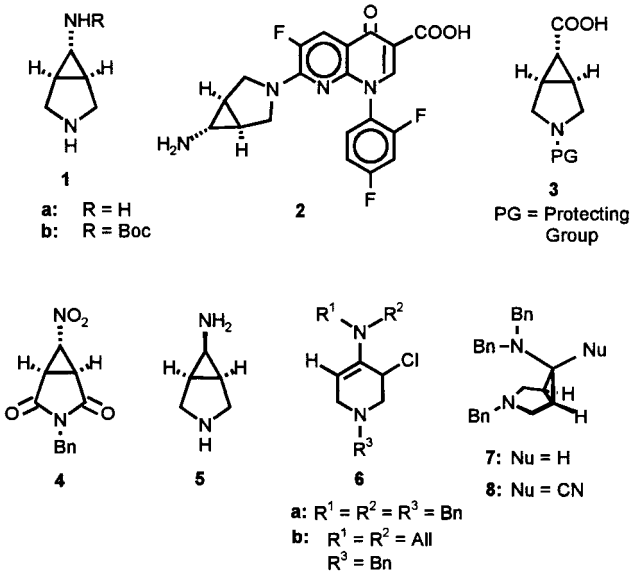
Abstract: *N*-Protected derivatives **12**, **13** and **17** of 1α,5α,6β-6-amino-3-azabicyclo[3.1.0]hexane **5** were synthesized via chloroenamines **6a** or **6b**. The specific *N*-protection was realized either by using a chloroenamine **6b** with different protecting groups or by selective removal of identical protecting groups at the bicyclic target molecule **7**. Dibenzylamino compound **13** allowed the preparation of naphthyridine derivative **25** which represents the 6β-diastereomer of trovafloxacin mesylate, a potent Gyrase inhibitor.

Key words: trovafloxacin 6β-diastereomer, synthesis, chloroenamines, *N*-protected 1α,5α,6β-6-amino-3-azabicyclo[3.1.0]hexanes

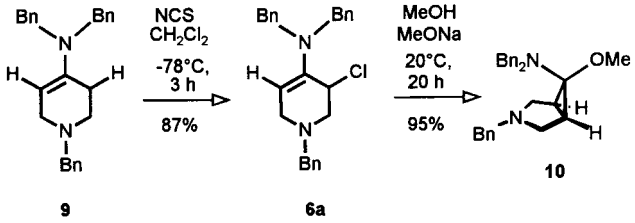
1α,5α,6α-6-Amino-3-azabicyclohexane **1a** represents the amino moiety in trovafloxacin[1] (**2**) which is strongly active against Gram-negative and Gram-positive bacteria as well as anaerobes and penicillin-resistant Streptococcus pneumoniae pathogens.[2, 3]



6α-Amine **1a** was synthesized as Boc-protected compound **1b** via carboxylic acid **3**[1, 4, 5] or nitro derivative **4**[6] both by multistep procedures. The 6-amino moiety at the cyclopropane system, thereby, is generated by a Curtius degradation[1, 4, 5] or the reduction of the nitro moiety.[6] Predominantly or exclusively 6α-isomers were obtained in all sequences. On the other hand, amino-chloroenamines of type **6** proved to be simple starting materials for the synthesis of 6-amino-3-azabicyclo[3.1.0]hexane derivatives[7–15] leading mostly to 6β-isomers. The applicability of chloroenamines[11] for the preparation of azabicyclohexane derivatives such as **1a** or **5** with an unsubstituted amino function in 6-position, however, was strongly doubted in the literature.[6] We investigated, therefore, stereoselective ways to *N*-protected species of 6β-isomer **5** on the basis of chloroenamines. The chloroenamine way to 6β-amino-3-azabicyclohexane derivatives requires non-deactivating substituents at N(3) (see ref 11) and at the enamino-N-atom. Consequently, only allyl and benzyl groups are suitable candidates within the family of various *N*-protecting groups.[16, 17] Realization of a specific *N*-protection pattern was intended either by starting from a chloroenamine with different protecting groups (e.g. **6b**) or by regioselective removal of identical protecting groups at a bicyclic derivative (e.g. 7) as shown already successfully for selective N(3) debenzylation of bicyclic carbonitrile **8**.[12] The results of these investigations and a new synthesis of the 6β-diastereomer of trovafloxacin are reported in this paper.

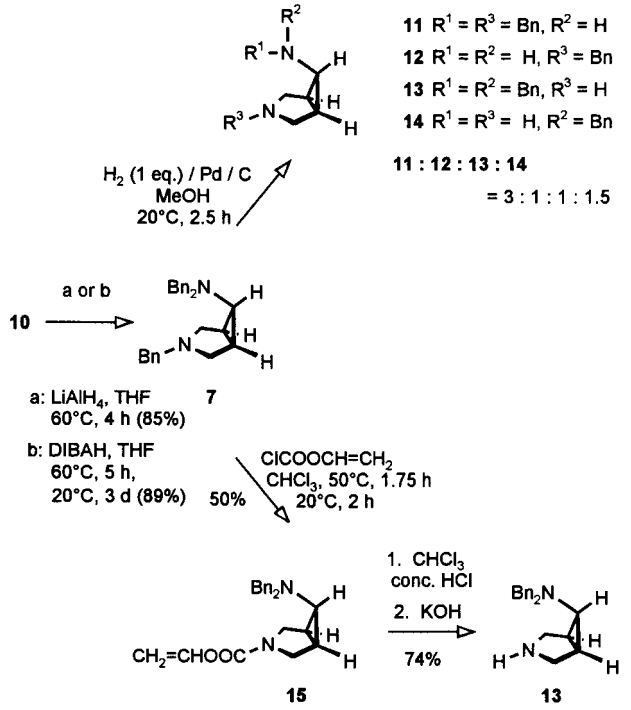
Synthesis of Bicyclic Tribenzyl Derivative 7 and Its Selective Debenzylation

Chloroenamine **6a** as starting material is accessible in 87% yield by NCS chlorination of tribenzylenamine **9** as described in ref 12. Reaction of chloroenamine **6a** with sodium methoxide in methanol gave 6α-*N*,*O*-acetal **10** (95% yield) (Scheme 1).



Scheme 1

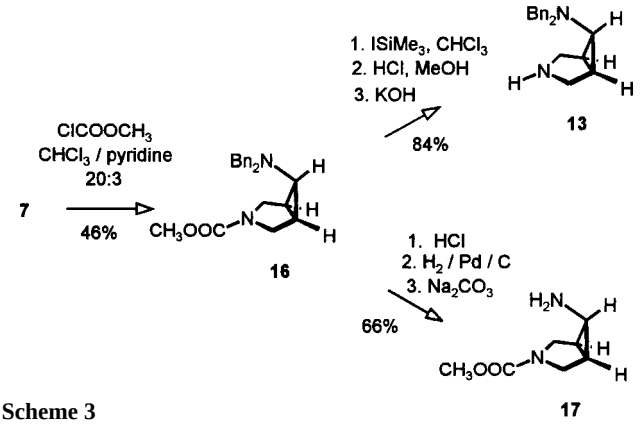
The methoxy moiety in **10** can be replaced with complete retention of configuration by hydrogen by reaction with lithium aluminum hydride or with diisobutylaluminum hydride to give the tribenzylic diamine **7**. The resulting 6β-stereoisomer **7** is expected as consequence of the attack of the hydride nucleophile to the intermediate azabicyclo[3.1.0]hexan-6-iminium ion from the sterically less hindered *exo*-side. Treatment of **7** with one equivalent of hydrogen in methanol and a palladium charcoal catalyst led to a mixture of debenzylated products **11–14**. The missing selectivity in the hydrogenolytic debenzylation of **7** with respect to the analogous reaction of carbonitrile **8**



Scheme 2

should be the consequence of the absence of a deactivating group at C(6) in the case of diamine **7** (Scheme 2).

A selective debenzylation, however, could be achieved with vinyl chloroformate[18] in chloroform at 50 °C to give carbamate **15** besides benzyl chloride. Dibenzylamine hydrochloride was formed as a byproduct in small amounts from a partial decomposition of the azabicyclohexane system. Carbamate **15** was isolated in 50% yield by distillation; its subsequent decomposition by hydrogen chloride in chloroform produced diamine **13**. The latter can be regarded as selective N–C(6) protected derivative of 6β-6-amino-3-azabicyclo[3.1.0]hexane (**5**).

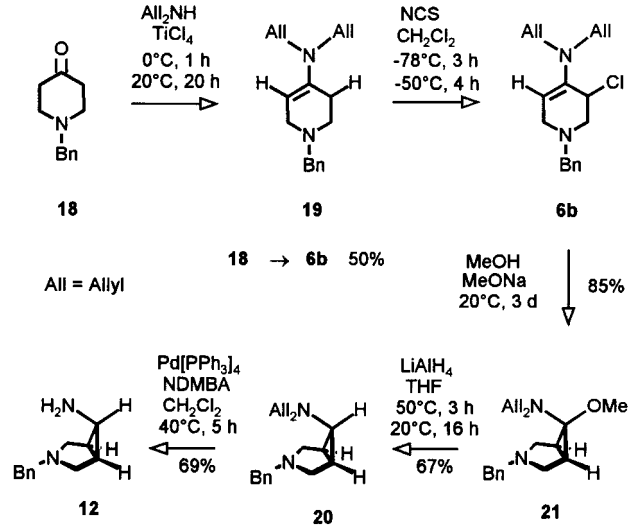


Scheme 3

Methyl chloroformate can also be used for the debenzylation of **7**. Chloroform/pyridine (20:3) at 50 °C gave the best results. The two different protecting groups in the resulting carbamate **16** were removed either by hydrogen or by iodotrimethylsilane[19] leading to the selectively protected diamines **17** and **13**, respectively (Scheme 3).

Synthesis of Benzyl Derivative 12 Using an Orthogonally Protected Chloroenamine

Chloroenamine **6b** with an N(3) benzyl residue and a diallylamino moiety was selected for an alternative way to an orthogonally protected derivative of 6β-amine **5**. The corresponding enamine **19** was prepared from *N*-benzylpiperidone **18** with diallylamine in the presence of titanium tetrachloride according to the Weingarten method.[20] Chlorination of **19** by NCS gave chloroenamine **6b** in 50% yield (based on **18**) which was transformed into bicyclic *N*,*O*-acetal **21** by interaction with sodium methoxide in methanol (85% yield). Reaction of *N*,*O*-acetal **21** with lithium aluminum hydride caused a displacement of the methoxy moiety by hydrogen to give **20** (67% yield) which could be deallylated to monobenzyldiamine **12** (69% yield) in the presence[21] of tetrakis(triphenylphosphine)palladium and *N*,*N*′-dimethylbarbituric acid (NDMBA) (Scheme 4).



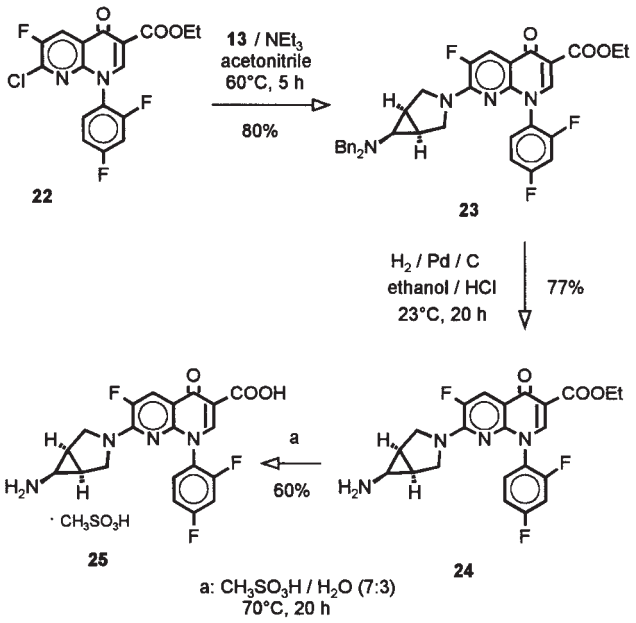
Scheme 4

Synthesis of Mesylate 25 of Trovafloxacin 6β-Diastereomer

Compound **25**, the 6β-diastereomer of trovafloxacin mesylate, can be prepared from ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**22**) and the dibenzylamino derivative **13**, subsequent debenzylation of the resulting compound **23** and saponification of the ester **24** with aqueous methanesulfonic acid (Scheme 5).

Structure of the 6-Amino-3-azabicyclo[3.1.0]hexane Derivatives 7, 10–17, 20, 21, and 23–25

The new compounds **7**, **10–17**, **20** and **21** were identified by ^{1}H and ^{13}C NMR spectroscopy (see experimental section). The 3-azabicyclo[3.1.0]hexane skeleton, thereby, is indicated unequivocally by the ^{13}C NMR data. The mixture of diamines **11–14** from the hydrogenolytic debenzy-



Scheme 5

lation of **7** was analyzed by the ^{1}H NMR spectrum: 5 benzyl ^{1}H NMR signals at δ = 3.53, 3.55, 3.59, 3.79, and 3.80 were observed for the mixture. Diamines **12** (δ = 3.59) and **13** (δ = 3.55) were identified by comparison with the data of the pure compounds. The main component (about threefold excess) corresponds to the signals at δ = 3.53 and 3.80 both of equal intensity. Thus, structure **11** with two different benzyl moieties is indicated for this compound. The remaining benzyl ^{1}H NMR signal at δ = 3.79 finally must be assigned to monobenzyl derivative **14**. The naphthyridine derivatives **23–25** were characterized by their ^{1}H NMR spectra and by mass spectrometry.

The 6β-structure of all 6-H compounds can be deduced ^{1}H NMR spectroscopically by the $^3J_{HH}$ coupling of C(6)–H: the observed values of 6.6–7.3 Hz correspond clearly to *syn* neighboring hydrogen atoms at the cyclopropane unit[8, 11, 13] (**20**: 6.6 Hz; **7**: 6.7 Hz; **14**, **15**, **16**: 6.8 Hz; **13**, **24**: 6.9 Hz; **11**: 7.1 Hz; **12**: 7.2 Hz; **23**, **25**: 7.3 Hz). Presence of an ester moiety at N(3) as in **15–17** leads to unsymmetrical compounds due to hindrance of O=C–N(3) rotation. In these cases, the azabicyclohexane ^{1}H NMR signals appear as ABCDXYZ spin system instead of the typical AA′BB′XX′Y pattern which is obtained for the symmetric compounds **7**, **10–14**, **20**, and **21**. The azabicyclohexane skeleton of the threefold substituted compounds **7**, **10**, **20**, and **21** adopts a chair conformation as indicated by the clear detectable AX coupling (J_{AX} = 2.4–2.8 Hz). The missing of this coupling in the ^{1}H NMR spectra of derivatives **11–14** establishes the presence of a boat conformation for the azabicyclohexane ring system in these cases (J_{AX} < 0.6–0.9 Hz, the upper limit value is deduced from the half line width of the $H_A/H_{A'}$ signal; see refs 9, 12, 14, 22).

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AMX 400, DPX 400 and DRX 500 spectrometer (TMS as internal standard). Microanalyses were performed using a Perkin–Elmer 2400 Elemental Analyzer. Reactions with $TiCl_4$, NCS, vinyl chloroformate, methyl chloroformate, iodotrimethylsilane, $LiAlH_4$ or DIBAH were run under N_2. A pressure tube and argon were used for the deallylation reaction.

1-Benzyl-3-chloro-4-(dibenzylamino)-1,2,3,6-tetrahydropyridine (6a):

A solution of NCS (4.14 g, 31.0 mmol) in CH_2Cl_2 (200 mL) was added dropwise at –78 °C over 2 h to a stirred solution of enamine[12] **9** (11.42 g, 31.0 mmol) in CH_2Cl_2 (50 mL). Stirring was continued for 1 h at –78 °C and under warming to –30 °C for 2 h. Then the solvent was removed in vacuo. Extraction of the residue with pentane (5 × 150 mL) and cooling of the pentane solution gave chloroenamine **6a** as colorless solid; yield: 10.9 g (87%); mp 57 °C.

^{1}H NMR ($CDCl_3$): δ = 2.67 (H_{B1}, 1H), 2.95 (H_{B2}, 1H), 3.08 (H_{A1}, 1H), 3.39 (H_{A2}, 1H), 4.68 (H_{X1}, H_{X2}, 2H) (2 ABX systems, H_{A1B1} = 12.5 Hz, $J_{A1X1} = J_{B1X1}$ = 2.7 Hz; J_{A2B2} = 15.5 Hz, J_{A2X2} = 4.8 Hz, $J_{B2X2} \approx$ 2.6 Hz), 3.52 (H_{B3}, 1H), 3.82 (H_{A3}, 1H) (AB system, J_{AB} = 13.2 Hz), 4.10 (H_{B4}, 2H), 4.43 (H_{A4}, 2H) (AB system, J_{AB} = 16.1 Hz), 7.15–7.45 (m, 15H).

^{13}C NMR ($CDCl_3$): δ = 141.1 (s), 138.7 (s), 137.6 (s), 128.9 (d), 128.3 (d), 128.2 (d), 127.3 (d), 127.0 (d), 126.8 (d), 101.1 (d), 61.5 (t), 57.4 (t), 54.3 (d), 52.49 (t), 52.46 (t).

Anal. Calcd for $C_{26}H_{27}ClN_2$: C, 77.50; H, 6.75; N, 6.95. Found: C, 77.23; H, 6.77; N, 6.90.

1α,5α,6β-3-Benzyl-6-(dibenzylamino)-3-azabicyclo[3.1.0]hexane (7):

Method A: A solution of *N*,*O*-acetal **10** (2.10 g, 5.27 mmol) in THF (25 mL) was added slowly to a suspension of $LiAlH_4$ (0.25 g, 6.59 mmol) in THF (5 mL). The mixture was stirred for 4 h at 60 °C. Then the solvent was removed in vacuo and the residue hydrolyzed under ice-cooling by addition of 2 M aq KOH (30 mL). The resulting solid was separated by centrifugation. Diamine **7** was obtained by extraction of the solid and of the aqueous solution with Et_2O (1 × 20 mL and 4 × 20 mL, respectively), evaporation of the Et_2O and crystallization from pentane; yield: 1.65 g (85%); mp 75 °C.

Method B: 1 M DIBAH in THF (1.88 mL, 1,88 mmol) was added to a solution of *N*,*O*-acetal **10** (0.5 g, 1.25 mmol) in THF (30 mL). The solution was stirred for 5 h at 60 °C and a further 3 d at r.t. and then poured into a mixture of ice (20 g), water (40 mL) and 95–97% H_2SO_4 (1 mL). Subsequent addition of 3 M aq KOH (30 mL) under ice-cooling and extraction with Et_2O (5 × 25 mL) gave crude diamine **7** which was distilled in a Kugelrohr apparatus (130 °C/10^{-3} Torr) and crystallized from pentane; yield: 0.4lg (89%); mp 75 °C.

^{1}H NMR ($CDCl_3$): δ = 1.73 (H_X, $H_{X'}$, 2H), 2.01 (H_Y, 1H), 2.42 (H_A, $H_{A'}$, 2H), 2.95 (H_B, $H_{B'}$, 2H) (AA′BB′XX′Y system, $J_{AB} = J_{A'B'}$ = 9.5 Hz, $J_{AX} = J_{A'X'} \approx$ 2.8 Hz, $J_{BX} = J_{B'X'}$ = 6.1 Hz, $J_{XY} = J_{X'Y'}$ = 6.7 Hz), 3.59 (s, 4H), 3.68 (s, 2H), 7.19–7.37 (m, 15H).

^{13}C NMR ($CDCl_3$): δ = 139.6 (s), 137.5 (s), 129.6 (d), 128.8 (d), 128. l (d), 127.9 (d), 126.8 (d), 126.7 (d), 59.4 (t), 56.1 (t), 51.8 (t), 47.5 (d, $^1J_{CH}$ = 163 Hz), 25.8 (d, $^1J_{CH}$ = 170 Hz).

Anal. Calcd for $C_{26}H_{28}N_2$: C, 84.74; H, 7.66; N, 7.60. Found: C, 84.58; H, 7.77; N, 7.43.

1α,5α,6α-3-Benzyl-6-(dibenzylamino)-6-methoxy-3-azabicyclo[3.1.0]hexane (10):

Chloroenamine **6a** (3.83 g, 9.50 mmol) was added to a methanolic solution of MeONa which was prepared from sodium (0.87 g, 37.84 mmol) and MeOH (90 mL). The mixture was stirred at 20 °C for 20 h. Then the solvent was removed in vacuo. Extraction of the residue with Et_2O (4 × 50 mL) gave *N*,*O*-acetal **10** as colorless oil which crystallized at –15 °C; yield: 3.59 g (95%); mp 69 °C.

^{1}H NMR ($CDCl_3$): δ = 1.90 (H_x, $H_{x'}$, 2H), 2.37 (H_{A1}, $H_{A'1}$, 2H), 2.71 (H_{B1}, $H_{B'1}$, 2H) (AA′BB′XX′ system, $J_{AB} = J_{A'B'}$ = 9.9 Hz, $J_{AX} = J_{A'X'} \approx$ 2.4 Hz, $J_{BX} = J_{B'X'}$ = 6.0 Hz), 3.33 (s, 3H), 3.59 (s, 2H), 3.93 (H_{B2},

2H), 4.12 (H_{A2}, 2H) (AB system, J_{AB} = 13.8 Hz), 7.19–7.29, 7.39–7.41(m, 15H).
^{13}C NMR ($CDCl_3$): δ = 139.1 (s), 138.5 (s), 129.1(d), 128.4 (d), 127.7 (d), 127.4 (d), 126.4 (d), 126.3 (d), 85.0 (s), 59.4 (t), 55.3 (t), 55.0 (q), 52.9 (t), 32.7 (d, $^1J_{CH}$ = 169 Hz).
Anal. Calcd for $C_{27}H_{30}N_2O$: C, 81.37; H, 7.59; N, 7.03. Found: C, 81.18; H, 7.59; N, 6.92.

1α,5α,6β-6-(Dibenzylamino)-3-(vinyloxycarbonyl)-3-azabicyclo[3.1.0]hexane (15):
A solution of vinyl chloroformate (0.5 mL, 5.88 mmol) in $CHCl_3$ (5 mL) was added dropwise at 50 °C over 15 min to a solution of tribenzyldiamine **7** (1.95 g, 5.29 mmol) in $CHCl_3$ (80 mL). The mixture was stirred at 50 °C for 1.75 h and at r.t. for 2 h. Then the solvent was removed in vacuo and the residue was distilled in a Kugelrohr apparatus (140–180 °C/10^{-3} Torr). Carbamate **15** was separated from the additional formed dibenzylammonium chloride (0.36 g) by extraction of the distillate with pentane (4 × 20 mL) and redistilled at l35 °C/l0^{-3} Torr to give a colorless oil; yield: 0.93 g (50%).
^{1}H NMR ($CDCl_3$): δ = 1.70 (H_X, H_Y, 2H), 2.09 (Hz, 1H), 3.39 (H_A, 1H), 3.49 (H_C, 1H), 3.51 (H_B, 1H), 3.56 (H_D, 1H) (ABCDXYZ system, J_{AB} = 11.2 Hz, J_{AX} < 0.8 Hz, J_{BX} = 5.0 Hz, J_{CD} = 10.7 Hz, J_{CY} < 0.9 Hz, J_{DY} = 4.9 Hz, J_{XZ} = J_{YZ} = 6.8 Hz), 3.60 (s, 4H), 4.45 (dd, 1H), 4.76 (dd, 1H), 7.20–7.36 (m, 11H).
^{13}C NMR ($CDCl_3$): δ = 150.9 (s), 142.4 (d), 137.2 (s), 129.4 (d), 128.1 (d), 127.0 (d), 94.7 (dd), 57.7 (t), 46.0 (t), 45.2 (t), 43.4 (d), 23.2 (d, $^1J_{CH}$ = 171 Hz), 22.4 (d, $^1J_{CH}$ = 170 Hz).
Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83 ; H, 6.94; N, 8.04. Found: C, 75.80; H, 7.00; N, 7.98.

1α,5α,6β-6-(Dibenzylamino)-3-(methoxycarbonyl)-3-azabicyclo[3.1.0]hexane (16):
A solution of methyl chloroformate (0.16 mL, 2.07 mmol) in $CHCl_3$ (5 mL) was added dropwise at 50 °C over 15 min to a solution of tribenzyldiamine **7** (0.5 g, 1.36 mmol) in $CHCl_3$ (15 mL) and pyridine (3 mL). The mixture was stirred at 50 °C for 4 h. Then again methyl chloroformate (0.02 mL, 0.26 mmol) was added and stirring was continued for 30 min at 50 °C. Removal of the solvent in vacuo and distillation of the residue in a Kugelrohr apparatus (220 °C/10^{-3} Torr) gave carbamate **16** which was separated from the additional formed dibenzylammonium chloride (0.07 g) by extraction of the distillate with Et_2O (4 × 20 mL). Redistillation at 145 °C/10^{-3} Torr led to a colorless oil; yield: 0.21 g (46%).
^{1}H NMR ($CDCl_3$): δ = 1.70 (H_X, H_Y, 2H), 2.09 (H_Z, 1H), 3.37 (H_A, 1H), 3.46 (H_B, 1H), 3.52 (H_C, 1H), 3.55 (H_D, 1H) (ABCDXYZ system, J_{AB} = 11.2 Hz, J_{AX} < 0.8 Hz, J_{BX} = 4.8 Hz, J_{CD} = 11.3 Hz, J_{CY} < 0.7 Hz, J_{DY} = 4.5 Hz, J_{XZ} = J_{YZ} = 6.8 Hz), 3.61 (s, 4H), 3.74 (s, 3H), 7.22–7.34 (m, 10H).
^{13}C NMR ($CDCl_3$): δ = 154.5 (s), 137.3 (s), 129.5 (d), 128.1 (d), 127.0 (d), 57.3 (t), 52.1 (q), 46.0 (t), 45.2 (t), 43.2 (d), 23.4 (d, $^1J_{CH}$ = l70 Hz), 22.7 (d, $^1J_{CH}$ = 170 Hz).
Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.85; H, 7.09; N, 8.56.

1α,5α,6β-6-(Dibenzylamino)-3-azabicyclo[3.1.0]hexane (13):
Method A: 37% aq HCl (7 mL) was added to solution of carbamate **15** (0.93 g, 2.67 mmol) in $CHCl_3$ (30 mL); the mixture was stirred 14 h at r.t. Then water (20 mL) was added, the $CHCl_3$ was removed in vacuo and the aqueous solution extracted with Et_2O (20 mL). Addition of 5 M aq KOH (25 mL) under ice-cooling and extraction with Et_2O (80 mL) in a Kutscher–Steudel apparatus for 5 d gave diamine **13** which was purified by distillation in a Kugelrohr apparatus (105 °C/10^{-3} Torr) and by crystallization from pentane to give colorless crystals; yield: 0.55 g (74%); mp 86 °C.

Method B: A solution of iodotrimethylsilane (0.21 mL, 1.48 mmol) and carbamate **16** (100 mg, 0.30 mmol) in $CHCl_3$ (5 mL) was stirred at 60 °C for 6.5 h. Then concd methanolic HCl (2 mL) was added at r.t.; stirring was continued for 10 min. The solution was basified with a solution of MeONa (0.65 g, 12.0 mmol) in MeOH (20 mL). Removal of the solvent in vacuo and addition of 2M aq KOH (10 mL) gave diamine **13** which was extracted with Et_2O (5 × 20 mL) and purified by distillation in a Kugelrohr apparatus (105 °C/10^{-3} Torr); yield: 70 mg (84%).
^{1}H NMR ($CDCl_3$): δ = 1.45 (H_X, $H_{X'}$, 2H), 1.98 (H_Y, 1H), 2.52 (H_A, $H_{A'}$, 2H), 2.78 (H_B, $H_{B'}$, 2H) (AA′BB′XX′Y system, J_{AB} = 12.2 Hz, J_{AX} = $J_{A'X'}$ < 0.8 Hz, J_{BX} = $J_{B'X'}$ ≈ 2.7 Hz, J_{XY} = $J_{X'Y}$ = 6.9 Hz), 1.85 (s (broad), 1H), 3.55 (s, 4H), 7.22–7.35 (m, 10 H).
^{13}C NMR ($CDCl_3$): δ = 138.2 (s), 129.5 (d), 128.2 (d), 127.1 (d), 59.7 (t), 48.3 (t), 45.0 (d), 24.5 (d, $^1J_{CH}$ = 167 Hz).
MS: *m/z* (%) = 278 (M^+,10), 249 (25), 187 (45), 158 (56), 91 (100).
Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.66; H, 8.08; N, 9.96.

1α,5α,6β-6-Amino-3-(methoxycarbonyl)-3-azabicyclo[3.1.0]hexane (17):
Carbamate **16** (0.13 g, 0.39 mmol) in $Et_2O/CHCl_3$ (1:1, 14 mL) was treated with gaseous HCl. Then the solvent was evaporated; the resulting salt was triturated with Et_2O (2 × 10 mL) and dried in vacuo. 10% Pd/C (100 mg) was added to a solution of the salt (0.14 g, 0.38 mmol) in MeOH (30 mL); the mixture was saturated with H_2 for 16 h. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated with Na_2CO_3 (0.65 g, 6.13 mmol) and distilled in a Kugelrohr apparatus at 150 °C/10^{-3} Torr. Sublimation of the distillate at 70 °C/10^{-3} Torr gave pure monoprotected diamine **17**; yield: 40 mg (66%); mp 76 °C.
^{1}H NMR ($CDCl_3$): δ = 1.60 (H_X, H_Y, 2H), 2.48 (Hz, 1H), 3.46, 3.53 (H_A/H_C, 2H), 3.56, 3.62 (H_B/H_D, 2H), (ABCDXYZ system, J_{AB} = J_{CD} = 11.2 Hz, J_{AX} = J_{CY} ≈ 1.6 Hz, J_{BX} = J_{DY} = 6.0 Hz, J_{XZ} = J_{YZ} = 7.1 Hz), 3.68 (s, 3H).
^{13}C NMR ($CDCl_3$): δ = 154.6 (s), 52.2 (q), 44.9 (t), 44.3 (t), 31.4 (d), 21.3 (d, $^1J_{CH}$ = 170 Hz), 20.4 (d, $^1J_{CH}$ = 173 Hz).
Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83 ; H, 7.74; N, 17.94. Found: C, 53.67; H, 7.55; N, 17.99.

1-Benzyl-3-chloro-4-(diallylamino)-1,2,3,6-tetrahydropyridine (6b):
$TiCl_4$ (4.5 mL, 40.9 mmol) in toluene (15 mL) was added at 0 °C to a solution of diallylamine (41.84 mL, 338.9 mmol) and 1-benzylpiperidin-4-one (**18**) (15 mL, 84.7 mmol) in toluene (200 mL). The mixture was stirred for 1 h at 0 °C and 20 h at r.t. Removal of the solid by suction, evaporation of the solvent in vacuo and distillation at 130–150 °C/10^{-3} Torr gave enamine **19** as light yellow oil [13.03 g, 55% yield; purity 96% (4% ketone **18**)]. A solution of NCS (6.22 g, 46.6 mmol) in CH_2Cl_2 (160 mL) was added dropwise at –78 °C over 2 h to a stirred solution of enamine **19** (13.03 g of 96% purity, 46.6 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 1 h at –78 °C and under warming to –50 °C for 4 h. Then the solvent was removed in vacuo. Extraction of the residue with pentane (7 × 50 mL) and cooling of the pentane solution gave chloroenamine **6b** as colorless solid; yield: 12.92 g (50% based on ketone **18**); mp 34 °C.
^{1}H NMR ($CDCl_3$): δ = 2.64 (H_{B1}, 1H), 2.94 (H_{B2}, 1H), 3.07 (H_{A1}, 1H), 3.44 (H_{A2}, 1H), 4.55 (H_{X1}, 1H), 4.62 (H_{X2}, 1H) (2 ABX systems, J_{A1B1} = 12.6 Hz, J_{A1X1} = J_{B1X1} = 3.1 Hz; J_{A2B2} = 15.6 Hz, J_{A2X2} = 4.9 Hz, J_{B2X2} ≈ 2.6 Hz), 3.52 (H_{B3}, 1H), 3.79 (H_{A3}, 1H) (AB system, J_{AB} = 13.4 Hz), 3.58 (H_Y, 2H), 3.78 (H_{X3}, 2H), 5.10 (H_M, 2H), 5.13 (H_N, 2H), 5.78 (H_{A4}, 2H) (AMNXY system, J_{AX} = J_{AY} = 5.6 Hz, J_{AM} = 10.4 Hz, J_{AN} = 17.2 Hz, J_{XY} = 16.2 Hz), 7.22–7.43 (m, 5H).
^{13}C NMR ($CDCl_3$): δ = 140.5 (s), 137.5 (s), 134.7 (d), 128.6 (d), 127.9 (d), 126.8 (d), 116.1 (t), 99.3 (d), 61.3 (t), 57.2 (t), 54.0 (d), 52.4 (t), 51.0 (t).
Anal. Calcd for $C_{18}H_{23}ClN_2$: C, 71.39; H, 7.65; N, 9.25. Found: C, 70.83; H, 7.34; N, 9.22.

1α,5α,6α-3-Benzyl-6-(diallylamino)-6-methoxy-3-azabicyclo[3.1.0]hexane (21):
Chloroenamine **6b** (4.00 g, 13.2 mmol) was added to a methanolic solution of MeONa which was prepared from sodium (0.91 g, 39.6 mmol) and MeOH (80 mL). The mixture was stirred at 20°C for 3 d. Then the solvent was removed in vacuo. Extraction of the residue with pentane (4 × 50 mL) and distillation of the extract in a Kugelrohr apparatus at 130 °C/10^{-3} Torr gave *N,O*-acetal **21** as colorless oil; yield: 3.35 g (85%).
^{1}H NMR ($CDCl_3$): δ = 2.01 (H_{X1}, $H_{X'1}$, 2H), 2.32 (H_{A1}, $H_{A'1}$, 2H), 3.07 (H_{B1}, $H_{B'1}$, 2H) (AA′BB′XX′ system, $J_{AB} = J_{A'B'}$ = 9.8 Hz, $J_{AX} = J_{A'X'} \approx$ 2.6 Hz, $J_{BX} = J_{B'X'}$ = 6.1 Hz), 3.29 (s, 3H), 3.58 (s, 2H), 3.50 (H_{X2}, 4H), 5.14 (H_M, 2H), 5.16 (H_N, 2H), 5.89 (H_{A2}, 2H) (AMNX_2 system, J_{AX} = 6.4 Hz, J_{AM} = 10.4 Hz, J_{AN} = 17.0 Hz, J_{MX} = 1.0 Hz, J_{NX} = 1.5 Hz, J_{MN} = 2.2 Hz), 7.22–7.31 (m, 5H).
^{13}C NMR ($CDCl_3$): δ = 139.1 (s), 136.1 (d), 128.3 (d), 127.8 (d), 126.4 (d), 116.5 (t), 87.2 (s), 58.9 (t), 54.5 (q), 53.28 (t), 53.18 (t), 33.7 (d, $^1J_{CH}$ = 169 Hz).
Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.23; H, 8.59; N, 9.29.

1α,5α,6β-3-Benzyl-6-(diallylamino)-3-azabicyclo[3.1.0]hexane (20):
A solution of *N,O*-acetal **21** (5.00 g, 16.8 mmol) in THF (70 mL) was added slowly to a suspension of $LiAlH_4$ (2.54 g, 66.9 mmol) in THF (20 mL). The mixture was stirred for 3 h at 50 °C and for a further 16 h at r.t. Then the solvent was removed in vacuo and the residue hydrolyzed under ice-cooling by addition of 4 M aq KOH (130 mL). The resulting solid was separated by centrifugation. Diamine **20** was obtained by extraction of the solid and of the aqueous solution with Et_2O (1 × 30 mL and 5 × 40 mL, respectively), evaporation of the Et_2O and distillation in a Kugelrohr apparatus; bp 115 °C/10^{-3} Torr; yield: 3.01 g (67%).
^{1}H NMR ($CDCl_3$): δ = 1.72 (H_X, $H_{X'}$, 2H), 2.11 (H_Y, 1H), 2.35 (H_A, $H_{A'}$, 2H), 3.10 (H_B, $H_{B'}$, 2H) (AA′BB′XX′Y system, $J_{AB} = J_{A'B'}$ = 9.7 Hz, $J_{AX} = J_{A'X'} \approx$ 2.7 Hz, $J_{BX} = J_{B'X'}$ = 6.2 Hz, $J_{XY} = J_{X'Y}$ = 6.6 Hz), 3.61 (s, 2H), 3.16 (H_{X2}, 4H), 5.15 (H_M, 2H), 5.18 (H_N, 2H), 5.92 (H_{A2}, 2H) (AMNX_2 system, J_{AX} = 6.4 Hz, J_{AM} = 10.1 Hz, J_{AN} = 17.2 Hz, J_{MX} = 1.0 Hz, J_{NX} = 1.5 Hz, J_{MN} = 2.2 Hz), 7.20–7.35 (m, 5H).
^{13}C NMR ($CDCl_3$): δ = 139.7 (s), 134.7 (d), 128.4 (d), 127.9 (d), 126.4 (d), 117.1 (t), 58.7 (t), 55.1 (t), 51.8 (t), 46.9 (d, $^1J_{CH}$ = 165 Hz), 25.6 (d,$^1J_{CH}$ = 170 Hz).
Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.18; H, 8.62; N, 10.35.

1α,5α,6β-6-Amino-3-benzyl-3-azabicyclo[3.1.0]hexane (12):
A solution of diallylamino compound **20** (1.86 g, 6.9 mmol) in CH_2Cl_2 (9 mL) was added to a mixture of Pd[PPh_3]$_4$ (160 mg, 0.14 mmol) and *N,N′*-dimethylbarbituric acid (3.49 g, 22.4 mmol) and stirred at 40 °C for 5 h. Then the solvent was evaporated; sat. aq Na_2CO_3 (40 mL) was added to the residue. The mixture was extracted with Et_2O (3 × 40 mL). The ethereal extract was acidified with 2 M aq HCl (35 mL). Removal of the Et_2O and extraction of the aqueous solution with EtOAc (3 × 30 mL) led to an aqueous solution of pure hydrochloride of diamine **12**. The free base was obtained as colorless oil by addition of solid Na_2CO_3 (10.6 g, 0.1 mol), extraction with Et_2O (5 × 30 mL) and distillation in a Kugelrohr apparatus (70 °C/10^{-3} Torr); yield: 900 mg (69%).
^{1}H NMR ($CDCl_3$): δ = 1.37 (Hx, $H_{X'}$, 2H), 2.35 (H_Y, 1H), 2.65 (H_B, $H_{B'}$, 2H), 3.05 (H_A, $H_{A'}$, 2H), (AA′BB′XX′Y system, J_{AB} = 9.3 Hz, $J_{AX} = J_{A'X'} <$ 0.6 Hz, $J_{BX} = J_{B'X'} \approx$ 3.6 Hz, $J_{XY} = J_{X'Y}$ = 7.2 Hz), 1.92 (s (broad), 2H), 3.59 (s, 2H), 7.20–7.31 (m, 5H).
^{13}C NMR ($CDCl_3$): δ = 139.4 (s), 128.2 (d), 128.1 (d), 126.7 (d), 59.8 (t), 52.5 (t), 34.5 (d,$^1J_{CH}$ = 167 Hz), 19.9 (d,$^1J_{CH}$ = 168 Hz).
Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.47; H, 8.67; N, 15.2.

Ethyl 7-[1α,5α,6β-6-(Dibenzylamino)-3-azabicyclo[3.1.0]hex-3-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (23):
Ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**22**) (896.5 mg, 2.5 mmol) was suspended in acetonitrile (80 mL). Then NEt_3 (9.5 mL) and **13** (632.5 mg, 2.5 mmol) were added and the mixture was heated to 60 °C for 5 h. The resulting solution was evaporated at 60 °C/15 Torr, the residue was treated with water, the precipitated solid was filtered off by suction, washed with water and dried at 70 °C in vacuo to yield 1.3 g of the title compound, which was purified by column chromatography [100 g silica gel (Amicon, 60A 35–70 μm), CH_2Cl_2/MeOH 95:5]; yield: 1.24 g (80%); mp 178–179 °C (dec).
^{1}H NMR (400 MHz, CF_3CO_2D): δ = 1.52 (t, *J* = 7.3 Hz, 3H), 2.20 (m, 2H), 3.06 (t, *J* = 7.3 Hz, 1H), 3.16–3.29 (m, 1H), 3.29–3.41 (m, 1H), 3.65–3.83 (m, 2H), 4.54 (d, *J* = 12.9 Hz, 2H), 4.71 (q, *J* = 7.3 Hz, 2H), 4.72–4.83 (m, 2H), 7.23 (t, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.45–7.73 (m, 11H), 8.31 (d, *J* = 10.7 Hz, 1H), 9.14 (s, 1H).
FAB/MS: *m/z* = 625 ([M+H]$^+$).

Ethyl 7-(1α,5α,6β-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (24):
A solution of **23** (1.2 g, 1.92 mmol) in EtOH (200 mL) and concd HCl (1 mL) was hydrogenated for 20 h at 23 °C under atmospheric pressure using gaseous H_2 and 5 % Pd/C (100 mg) as the catalyst. The insoluble reaction product was filtered off together with the catalyst and was dissolved in a mixture of CH_2Cl_2/MeOH/17% aq NH_3 (30:8:1). The catalyst was removed by filtration and the filtrate concentrated in vacuo to yield a residue, which was purified by column chromatography [silica gel (Amicon, 60A 35–70μm), CH_2Cl_2/MeOH/17% aq NH_3 30:8:1]; yield: 660 mg (77%); mp 216–218 °C (dec).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (broad, 2H), 1.40 (t, *J* = 7.5 Hz, 3H), 1.66 (broad, 2H), 2.49 (t, *J* = 6.9 Hz, 1H), 3.45–3.85 (broad, 4H), 4.38 (q, *J* = 7.5 Hz, 2H), 7.04 (m, 2H), 7.37 (m, 1H), 8.04 (d, *J* = 12.9 Hz, 1H), 8.36 (s, 1H).
FAB/MS: *m/z* = 445 ([M+H]$^+$).

7-(1α,5α,6β-6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid Methanesulfonic Acid Salt (25):
A suspension of **24** (400 mg, 0.9 mmol) in water (8 mL) and 70 % aq CH_3SO_3H (2.8 mL) was heated to 70 °C for 20 h. The resulting suspension was cooled with ice and the solid was isolated by filtration, washed with water and dried at 80 °C in vacuo; yield: 276 mg (60%); mp 244–247 °C (dec).
^{1}H NMR (500 MHz, CF_3CO_2D): δ = 2.38 (broad, 2H), 3.1 (s, 3H), 3.28 (t, *J* = 7.3 Hz 1H), 3.7–4.8 (broad, 4H), 7.26 (m, 2H), 7.61 (m, 1H), 7.82 (m, 1H), 7.96 (broad, 3H), 8.27 (d, *J* = 12.4 Hz, 1H), 9.21 (s, 1H).
FAB/MS: *m/z* = 417 ([M+H]$^+$).

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