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Syntheses and Evaluation of Pyridazine and Pyrimidine Containing Bioisosteres of (±)-Pyrido[3.4-b]homotropane and Pyrido-[3.4-b]tropane as Novel nAChR Ligands

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Abstract—Bioisosteric replacement of the pyridine pharmacophoric element in (±)-pyrido[3.4-b]homotropane (PHT) and pyrido[3.4-b]tropane with the pyridazine and pyrimidine nucleus resulted in hitherto unknown nAChR ligands such as **5**–**8**. Inverse type Diels–Alder reactions constitute the key steps in the new routes to the pyridazine- or pyrimidine-annulated bioisosteres. The enantiopure (+)-2-tropinone (**11**) from the 'chiral pool' is transformed to the ring-expanded silyl enol ether **12** and to the enamine **15**. Both proved to be highly dienophilic species in the inverse type [4+2] cycloaddition reactions with the 1,2,4,5-tetrazines **13** and **16a,b** or with the 1,3,5-triazine **19** to provide the enantiopure target compounds **5**–**7**. In the same way the racemic pyrimidine-annulated species **8** was obtained from 3-tropanone **21**. The new ligands were tested for their in vitro affinity for $(\alpha4)_2(\beta2)_3$ and α7* nAChR subtype. In comparison to PHT, well known to exhibit affinity for agonist binding sites in rat brain approximately equivalent to that of (+)-anatoxin-a (**1**), replacement of the pyridine by the bioisosteric pyridazine resulted in 30-fold lower affinity at the $(\alpha4)_2(\beta2)_3$ subtype. The annulated diazinotropanes **6**–**8**, ligands with ferruginine-like structures more or less retained the affinity of (−)-norferruginine (**3**) except of compound **7**. Remarkably, all of the novel ligands are devoid of affinity at the α7* subtype.

Introduction

(+)-Anatoxin-a (**1**) is an alkaloidal toxin from strains of the fresh bluegreen alga *Anabaena flos-aquae (Lyngb.)* de Breb., referred to as 'very fast death factor'.[1,2] Because of its unusual biological properties[3–5]—its potent binding affinity at various nicotinic acetylcholine receptor (nAChR) subtypes combined with strong agonist actions and its stereospecifity (*ent*-**1** is inactive[4c])—the alkaloid **1** provides an attractive lead for the design of novel structural analogues. The first bioisosteric and conformationally constrained variation of (+)-anatoxin-a (**1**) found to retain much of the potency of the natural compound was racemic (±)-pyrido[3,4-b]homotropane (**2**, PHT),[5,6] representing the conceptual combination of anatoxin-a and nornicotine. Additionally, the structural relationship of (−)-norferruginine (**3**)[7–9] to anatoxin-a (**1**)—in both alkaloids the acetyl moiety is a pharmacophoric element—has aroused increasing interest also in these tropane alkaloids. Thus, only recently Rapoport et al.[10] have developed an enantiospecific synthetic route to the conformationally restricted bioisosteric variant of norferruginine (**3**), the enantiomerically pure pyrido[3,4-b]tropane (**4**) together with *ent*-**4**.

In order to develop new ligands selective for distinct nAChR subtypes and possibly appropriate for the treatment of CNS disorders such as Alzheimer's and Parkinson's disease or with potent analgesic activity combined with reduced toxicity and a satisfactory safety profile,[3] we have started to synthesize novel analogues of PHT (**2**) and of the pyrido[3,4-b]tropane (**4**). In these new variants the pyridine pharmacophoric element is bioisosterically[11] replaced by other nitrogen containing heteroarenes such as 1,2- and 1,3-diazines. Herein we report a new strategy for the synthesis of novel conformationally restricted analogues of **2** and **4**, the pyridazine- or pyrimidine-annulated variants **5**–**8** utilizing the inverse electron demand [4+2] cycloaddition as the

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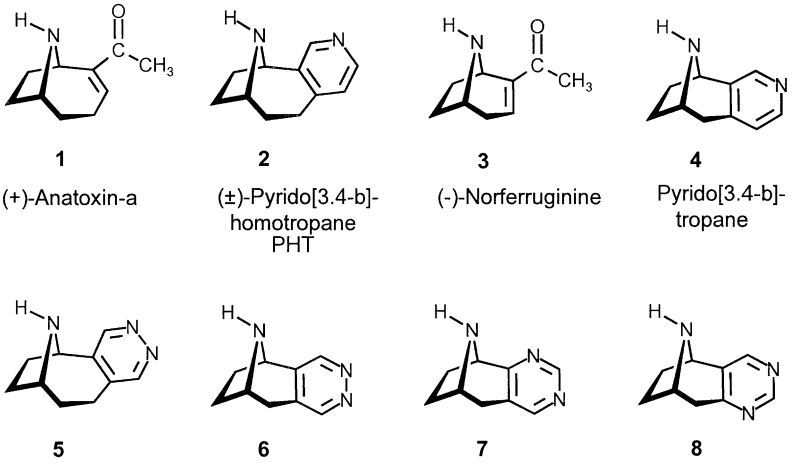
key step.[12,13] Additionally the preliminary biological profile of these potential nAChR-ligands is described (Scheme 1).

Results and Discussion

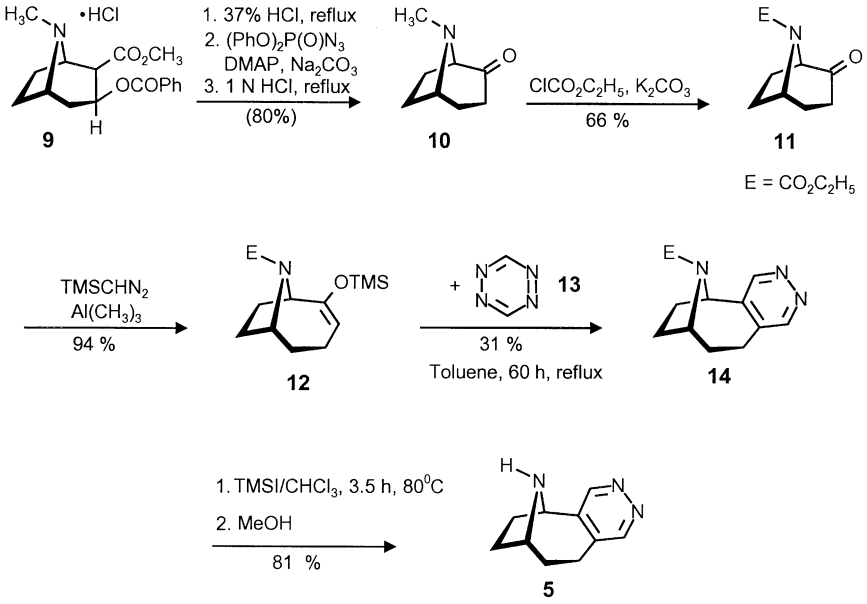
Chemistry

A particularly attractive feature for the synthesis of the enantiomerically pure target molecules **5**, **6** and **7** was the opportunity for its ready preparation from (+)-2-tropanone **10**. This represents a chiral building block with the 8-azabicyclo[3.2.1]octane ring system easily available by degradation of (−)-cocaine hydrochloride (**9**) in a high-yielding two step synthesis.[14] As illustrated in Scheme 2, *N*-demethylation of (+)-2-tropanone **10** by heating with ethyl chloroformate in the presence of K_2CO_3 afforded the *N*-protected bicyclic chiral ketone **11** in good yield.[2] Utilizing this enantiomerically pure 2-tropanone **11** as starting material the pyridazine-analogue **5** of PHT (**2**) with a semirigid 9-azabicyclo[4.2.1]-nonane skeleton was easily accessible in a three-step synthesis. This includes a ring-expansion step to form the homotropane skeleton and a [4+2] cycloaddition reaction with inverse electron demand. The one-carbon homologation of the ketone **11** was easily achieved with trimethylsilyldiazomethane ($TMSCHN_2$) promoted by the organoaluminum Lewis acid $Al(CH_3)_3$.[15] This procedure was developed only recently by us as part of an improved synthesis of natural (+)-anatoxin-a (**1**).[2] The ring-enlarged product, initially formed under the conditions employed, is the trimethylsilyl enol ether **12**, which offered a straightforward access to the pyridazine annulated target molecule **5**.

In an inverse-type Diels–Alder reaction **12** cycloadds as a highly reactive cyclic dienophile to the electron-deficient diazadiene system of the 1,2,4,5-tetrazine (**13**)[13] to



Scheme 1.



Scheme 2.

yield the carbamate-protected species **14** after [4 + 2] cycloaddition, extrusion of nitrogen and elimination of trimethylsilanol.[13] Removal of the protecting group from the carbamate **14** proceeded smoothly with fuming aqueous hydrochloric acid and subsequent flash chromatography of the resulting oily product, or advantageously by the conventional protocol with trimethylsilyliodide (TMSI) in boiling $CHCl_3$,[16] affording the target ligand **5** in more than 80% yield as an air-stable pale yellow oil. Contrary to the base **5** the hydrochloride salt of **5** is hygroscopic and must be handled with exclusion of air. Spectroscopic data analysis (MS, ^1H and ^{13}C NMR) conclusively proved the expected structure of the enantiomerically pure pyridazine bioisostere **5** of PHT (**2**).

The pyridazine annulated target molecules of type **6** should be easily accessible by inverse electron demand [4 + 2] cycloaddition reactions of enamines such as **15**, dienophiles of choice in this inverse-type Diels–Alder reactions for the activated tetrazines **16** as electron-deficient diazadienes.[13] Thus, we transformed the ketone **11** as the key chiral precursor for the new nAChR ligand **6** nearly quantitatively to the requisite enamine **15** by treatment with morpholine/p-TosOH (Scheme 3).[17]

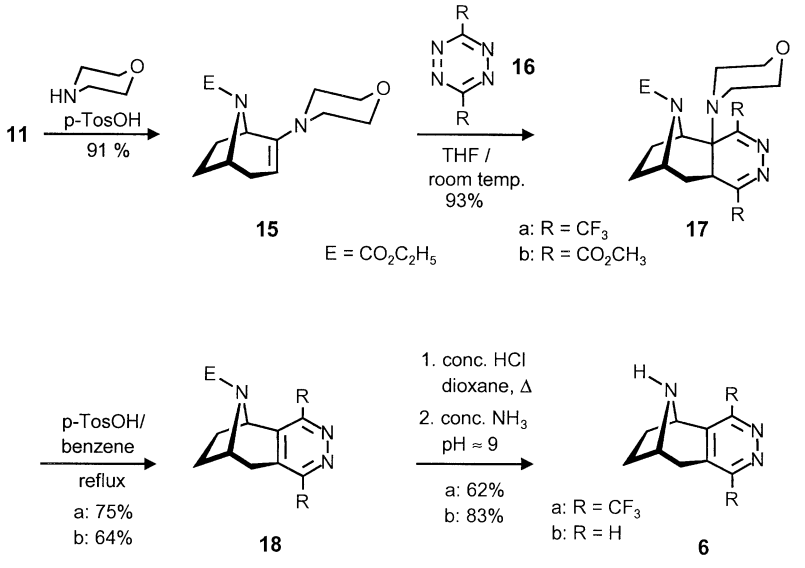
The enamine **15** indeed offers a straightforward access to the substituted pyridazine derivatives **18a,b** in a two step procedure with the initially formed 4,5-dihydropyridazines **17a,b** as isolable intermediates. Aromatization occurs easily on further treatment of **17a,b** with p-TosOH in boiling benzene, leading to the *N*-protected tricyclic pyridazines **18a,b** after elimination of morpholine. Deprotection of the carbamates **18a,b** using concd aqueous hydrochloric acid in dioxane generated the desired target molecules as the free bases **6a** and **6b** after treatment with concd aqueous ammonia. Interestingly the threefold ester **18b** suffers complete hydrolysis and decarboxylation to yield the parent compound **6b** with R = H.

Compound **6b** exhibited the expected ^1H and ^{13}C NMR, IR, and mass spectral characteristics and gave satisfactory high-resolution mass spectral data (see Experimental).

The pyrimidine-bioisostere **7** of the pyrido[3,4-b]tropane (**4**) characterized by the same semirigid 8-azabicyclo[3.2.1]octane skeleton was easily accessible in a two-step synthesis. Fortunately the 1,3,5-triazine nucleus **19**, though less reactive compared with the tetrazines **16a,b**, is sufficiently electron-deficient and thus well-suited for participation in [4 + 2] cycloaddition processes with the electron-rich enamine **15**.[18] Regiospecific pyrimidine annulation occurs readily by heating the components in dioxane for 15 h at 110 °C in a sealed bottle affording the carbamate-protected nAChR ligand **20** as the sole reaction product with 89% yield after loss of hydrogen cyanide and morpholine. Removal of the protecting group by the conventional protocol with $(CH_3)_3SiI$ in boiling $CHCl_3$[16] furnished the desired pyrimido[4,5-b]tropane (**7**) in high yield (Scheme 4).

Using the same two-step regiospecific pyrimidine annulation for the preparation of the isomeric pyrimido[5,4-b]tropane (**8**) it was mandatory to choose the enamine **22** as dienophile in the inverse [4 + 2] cycloaddition with the diazadiene system of the 1,3,5-triazine **19**. The requisite key precursor **22** was prepared by treatment of the carbamate-protected 3-tropanone **21** with morpholine/p-TosOH.[17] The pivotal step, the inverse type [4 + 2] cycloaddition reaction was again carried out in a pressure bottle in dioxane at 105 °C. The reaction was complete in ca. 19 h. Chromatographic purification afforded the carbamate-protected pyrimidin-annulated tropanoid **23** with modest success in only 24% yield (Scheme 5).

Deprotection of the carbamate **23** could easily be achieved using the same strategy as that described for **7** to give **8** in 42% yield, the structure of which could be conclusively proved by spectroscopic data analysis (MS, ^1H and ^{13}C NMR, see Experimental).



Scheme 3.

In vitro receptor binding

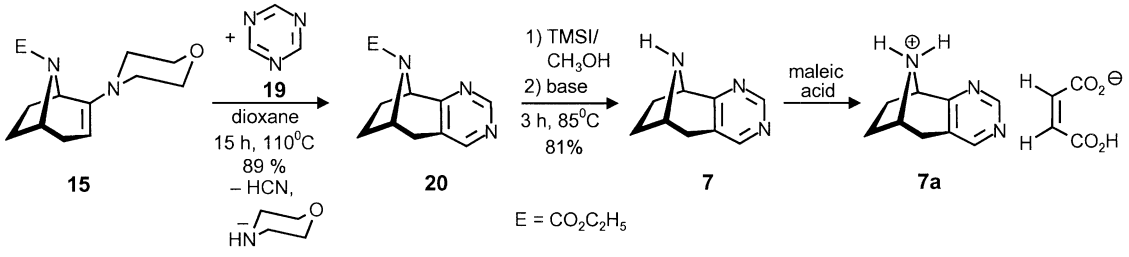
The new nAChR ligands **5**–**8** listed in Table 1 were tested for their in vitro affinity for $(\alpha4)_2(\beta2)_3$ and α7* nAChRs subtypes by radioligand binding assays. To determine the affinities for the $(\alpha4)_2(\beta2)_3$ nAChR subtype[19] a previously described competition assay was used with (±)-[^{3}H]epibatidine and P2 membrane fraction of Sprague–Dawley rat forebrain. These studies demonstrated that the specific binding of (±)-[^{3}H]epibatidine to crude synaptic membranes of rat forebrain, at concentrations up to 800 pM, is characterized by a single population of binding sites with $K_d = 8 \pm 0.3$ pM.[20] It has been previously found that the predominant receptor with high affinity for [^{3}H]nicotine, (−)-[^{3}H]cytisine, (±)-[^{3}H]epibatidine, and 5-[^{125}I]iodo-A-85380 in rat brain is composed of α4 and β2 subunits.

To characterize binding of each of the novel anatoxin-a or norferruginine variants to the α7* nAChR subtype, [^{3}H]MLA and membrane fractions isolated from the rat brain were used, [^{3}H]MLA bound to a single population of binding sites exhibited a K_d value of 1.2 ± 0.2 nM ($n = 3$). The affinity determined was in good agreement with previously published values ($K_d = 1.86$ nM). [^{3}H]MLA bound to rat brain membranes with regional distribution characteristic of α-BTX-sensitive, putative α7* subunit-containing nAChRs.[21]

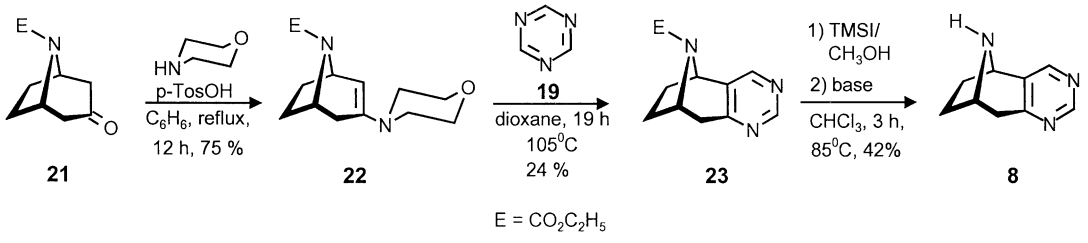
As shown in Table 1 the above characterized competition assays yielded K_i values of 0.838 nM for (−)-nicotine and 0.008 nM for (±)-epibatidine for the $(\alpha4)_2(\beta2)_3$ nAChR subunit. These findings are consistent with recently reported in vitro measurements of the natural alkaloids.[19]

The results of a series of in vitro and in vivo assays published by Kanne et al. have revealed that (±)-PHT (**2**, $IC_{50} = 5$ nM) possesses activity comparable to that of the highly potent agonist (±)-anatoxin-a (**1**, $IC_{50} = 8$ nM) in its binding affinity to the brain nicotinic sites.[5,6] With our methodology to determine the affinities for the $(\alpha4)_2(\beta2)_3$ nAChR subtype[22] (see above) enantiomerically pure (+)-anatoxin-a (**1**), as anticipated, was identified as a highly potent nicotinic ligand ($K_i = 1.1$ nM) consistant with recently reported in vitro measurements of racemic **1**[4c] ($K_i = 1.25$ nM). Interestingly, bioisosteric replacement of the pyridine pharmacophore in PHT (**2**) with the pyridazine nucleus resulted in an approximately 30 times less potent ligand **5**. The lower basicity of the pyridazine nitrogen of **5** can explain this difference, irrespective of the relevant inter-nitrogen distance, which in **5** is approximately equal to that of **2** and within the limits imposed by current models of the nAChR pharmacophore.[3,19,23] Compared to (−)-norferruginine (**3**), found to be a good agonist for the nAChR,[24] although only $1.2 \cdot 10^{-2}$ times as potent as (+)-anatoxin-a (**1**), the conformationally restricted bioisosteres **6**–**8** more or less retained the only moderate affinity of **3** at the $(\alpha4)_2(\beta2)_3$ subtype ($K_i = 94$ nM), except of bioisostere **7**.

The highest $(\alpha4)_2(\beta2)_3$ subtype affinity was obtained with the pyridazino[4.5-b]tropane (**6**) ($K_i = 76$ nM), nevertheless 1.5-fold more potent than the parent alkaloid **3**. Ligand **6** differentiates from the higher homologue **5** by a 2-fold lower affinity (Table 1). As expected for the pyrimidine annulated isomer **7** a dramatic decrease in affinity is observed with a K_i value higher than 10,000 nM, because of a less favorable orientation of the relevant nitrogen atoms. In contrast, the isomeric racemic pyrimidino[5.4-b]tropane **8** binds with significantly higher affinity, however 19-fold or 9-fold lower in comparison with the pyridazine annulated species **5** and **6**. Surprisingly all of the novel ligands **5**–**8** are devoid of affinity at the α7* subtype, thus disclosing high selectivity for the $(\alpha4)_2(\beta2)_3$—over the α7*-subtype.

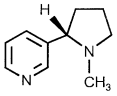
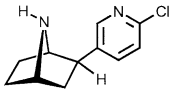
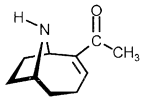
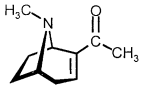
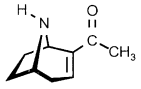
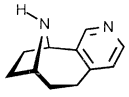
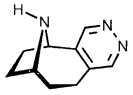
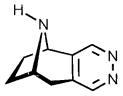
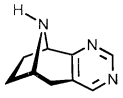
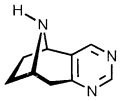


Scheme 4.



Scheme 5.

Table 1. Radioligand binding affinities of novel (+)-anatoxin-a and (−)-norferruginine variants to $(\alpha4)_2(\beta2)_3$ and α7* nAChRs in comparison with (−)-nicotine and (±)-epibatidine[a]

Structure	Compound	$(\alpha4)_2(\beta2)_3$[b] [^{3}H]epibatidine rat brain K_i (nM)	α7*[b] [^{3}H]MLA rat brain K_i(nM)
	(−)-Nicotine	0.838±0.132	127±5 [^{125}I] α-BTX
	(±)-Epibatidine	0.008±0.0002	4±0.5 [^{125}I] α-BTX
	(+)-Anatoxin-a (**1**)	1.1±0.1	90±5.4
	(−)-Ferruginine	120±2	330±23
	(−)-Norferruginine (**3**)	94±5	>100,000
	(±) PHT (**2**)	(IC_{50}=5 nM)[5,6]	Unknown
	**5**	35±3.2	No effect
	**6**	76±4.4	No effect
	**7**	>10,000	No effect
	**8**	676±26	No effect

[a]Values represent mean±S.E.M. obtained from *n* independent experiments where *n*=3–5.
[b]Naturally expressed nAChRs.[22]

Conclusion

Starting from the versatile chiral building block (−)-2-tropinone **11** or the 3-tropanone **21**, we have developed efficient syntheses of four conformationally restricted diazine bioisosteres **5**–**8** of PHT (**2**) and pyrido[3.4-b]tropane (**4**) utilizing inverse-type Diels–Alder reactions as the key step in the synthetic routes. All of the new nicotinic ligands with anatoxin-a, or ferruginine, like structures except **7** interact with the $(\alpha4)_2(\beta2)_3$ subtype with only moderate affinity. Among the compounds synthesized and tested the pyridazine analogue **5** of PHT was found to be the most active one retaining much of the affinity of the alkaloid anatoxin-a, thus proving again bioisosterism as a successful concept in SAR-studies. Surprisingly, in contrast to anatoxin-a with still moderate affinity for the α7* nAChR none of the pyridazine or pyrimidine annulated ligands possesses any affinity for this subtype, demonstrating a substantially improved selectivity ratio between the $(\alpha4)_2(\beta2)_3$ and the α7* subtype.

Experimental

General procedures

Standard vacuum techniques were used in handling of air sensitive materials. Melting points are uncorrected: ''Leitz-Heiztischmikroskop'' HM-Lux. Solvents were dried and freshly distilled before use according to literature procedures. IR: Perkin–Elmer 257, 398 and FT-IR spectrometer 510-P (Nicolet). Liquids were run as films, solids as KBr pellets. ^{1}NMR and ^{13}C NMR: Jeol JNM-GX 400 and LA 500; δ/ppm=0 for tetramethylsilane, 7.24 for chloroform. MS: Vacuum Gen-

erators 7070 (70 eV; ^{11}B). Column chromatography: purifications were carried out on Merck silica gel 40 (40–60 mesh), flash chromatography. Reactions were monitored by thin-layer chromatography (TLC) by using plates of silica gel (0.063–0.200 mm, Merck) or silicagel-60F_{254} microcards (Riedel de Haen). Optical rotations: Mod. Dip-370 polarimeter (Jasco). UV: UV–vis scanning spectrophotometer UV-2101 PC (Shimadzu).

(1*R*)-4,5,13-Triazatricyclo[8.2.1.0^{2,7}]trideca-2(7)-3,5-triene-13-carboxylic acid ethyl ester (14). To a solution of crude silyl enol ether **12**[2] (283 mg, 1.00 mmol) in dried toluene (10 mL) was added a solution of the tetrazine **13**[13a] (82 mg, 1.00 mmol) in dried toluene (5 mL). The solution was heated under Ar at reflux for 60 h, cooled to room temperature and after evaporation of the solvent in vacuo the residue was purified by flash chromatography on silica gel (column 20×1.5 cm, eluting with ethyl acetate) to provide **14** as a colorless oil (77 mg, 31%) which crystallized after storing for 7 days at 4 °C. Mp: 104–106 °C; R_f = 0.22 (ethyl acetate); $[\alpha]_D^{20}$ + 1.1° (c 0.36 CH_3OH); IR (film) 2978, 1702, 1451 cm^{-1}; UV (CH_3OH): λ_{max} (lgε) = 245 nm (3.09), 207 (3.67); ^1H NMR (500 MHz, $CDCl_3$, two rotamers, ratio 2:1) δ 1.05 (t, *J* = 6.9 Hz, 1H), 1.13 (t, *J* = 6.9 Hz, 2H), 1.72–1.92 (m, 4H), 2.13–2.27 (m, 1H), 2.49–2.61 (m, 1H), 2.70–2.78 (m, 1H), 3.04 (dt, *J* = 3.8 Hz, *J* = 13.1 Hz, 1H), 3.89 (q, *J* = 6.9 Hz, 0.66 H), 3.98 (q, *J* = 6.9 Hz, 1.34H), 4.48 (t, *J* = 3.9 Hz, 0.33 H), 4.54 (t, *J* = 3.9 Hz, 0.66H), 4.83 (d, *J* = 9.6 Hz, 0.66H), 4.92 (d, *J* = 9.5 Hz, 0.33H), 8.83–8.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 2 rotamers) δ (major rotamer) 14.4, 28.0, 29.3, 30.1, 30.9, 56.9, 57.5, 61.2, 138.1, 143.0, 149.8, 153.0, 153.2; (minor rotamer) 14.6, 28.2, 29.0, 29.6, 30.5, 56.6, 57.8, 61.2, 137.9, 143.0, 150.0, 153.1, 153.2; MS (70 eV) *m*/*z* (%) 247 (M^+, 100), 174 (46); Exact mass calcd for $C_{13}H_{17}N_3O_2$: 247.1321, found 247.1339.

(1*R*)-4,5,13-Triazatricyclo[8.2.1.0^{2,7}]trideca-2(7)-3,5-triene (5). Fuming aqueous hydrochloric acid (3 mL, 37%) was degassed with Ar for 5 min before a solution of carbamate **14** (70 mg, 0.28 mmol) in dioxane (0.5 mL) was added. The resulting solution was heated at reflux for 20 h under an atmosphere of Ar. After cooling to room temperature and addition of water (5 mL, degassed with Ar) the solvent was evaporated in vacuo. To the residue again water (1 mL) was added and the aqueous solution adjusted to pH = 9–10 with concentrated aqueous NH_3. The alkaline solution was extracted with $CHCl_3$/2-propanol 3:1 (4×2 mL), the combined organic phase dried with Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel (column 15×1.5 cm, eluting with CH_2Cl_2/CH_3OH/concd aqueous NH_3 95:15:0.1) affording a colorless oil (24 mg, 49%), which partly crystallized after standing at −40 °C for two weeks under an atmosphere of Argon. ^1H NMR (500 MHz, $CDCl_3$) δ 1.65–1.91 (m, 4H), 2.13–2.19 (m, 1H), 2.62–2.83 (m, 2H), 2.94–3.06 (m, 1H), 3.88–3.91 (m, 1H), 4.33 (dd, *J* = 2.3 Hz, *J* = 9.4 Hz, 1H), 8.83 (s, 1H), 8.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 29.6, 31.4, 32.1, 58.4, 59.9, 138.9, 145.0, 149.6, 152.8.

Deprotection of carbamate 14 with the TMSI/CH_3OH method. To a solution of **14** (49 mg, 0.20 mmol) in degassed $CHCl_3$ (2 mL) was added TMSI (34 μL, 0.25 mmol) and the mixture heated at 80 °C in a sealed tube for 4 h. The mixture was cooled to room temperature and the volatile components evaporated. Then HCl in diethyl ether (0.2 mL, 2M, 0.4 mmol) and CH_3OH (2 mL) were added. After evaporation of the solvent the resulting hydrochloride was purified by column chromatography on reversed phase, silica gel (RP18, ICN, column 12×1.5 cm, THF/CH_3OH 0–9%) to afford the hydrochloride salt of **5** as a pale yellow, viscous, hygroscopic oil (34 mg, 81%); R_f = 0.19 (streaking, CH_2Cl_2/CH_3OH/aq. NH_3 = 95:15:0.1); $[\alpha]_D^{25}$ + 38.6 (c 0.14, CH_3OH); IR (film) 2928, 1569, 1129 cm^{-1}; UV (CH_3OH): λ_{max} (lgε) = 252 (3.00), 220 (3.76); ^1H NMR (500 MHz, CD_3OD) δ = 1.94–2.08 (m, 1H), 2.14–2.46 (m, 4H), 2.65–2.78 (m, 1H), 2.95–3.08 (m, 1H), 3.24–3.35 (m, 1H), 4.35–4.45 (m, 1H), 5.03 (dd, *J* = 9.7 Hz, *J* = 2.6 Hz, 1H), 9.16 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 27.1, 28.5, 30.5, 31.3, 60.6, 52.3, 139.4, 141.5, 150.6, 152.9; MS (70 eV) *m*/*z* (%) 175 (M^+, 46), 68 (72), 41 (100); Exact mass calcd for $C_{10}H_{13}N_3$: 175.1109, found 175.1130.

2-(Morpholin-4′-yl)-8-azabicyclo[3.2.1]oct-2-en-8-carboxylic acid ethyl ester (15). To a stirred solution of the ketone **11** (200 mg, 1.01 mmol) in benzene (60 mL) was added morpholine (0.17 mL, 2.02 mmol) and *p*-toluenesulfonic acid monohydrate (3.0 mg, 0.016 mmol) and the mixture heated at reflux in a water separator for 12 h. The solution was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (2×20 mL) and with brine (10 mL), dried over $MgSO_4$ (10 g), filtered and evaporated in vacuo. The oily residue was dried in vacuo (0.2–0.3 Torr) for 3 h to yield 245 mg (91%) of a pale yellow oil; $[\alpha]_D^{20}$ + 36.8° (c 0.02, CH_3OH); IR (film) 2975, 1700, 1420 cm^{-1}; UV (CH_3OH) λ_{max} (lgε) = 343 nm (1.63), 289 (2.25), 206 (3.01); ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.80–1.84, 2.16–2.22, 2.33–2.48, 2.85–2.92 (4m, 7H), 3.64–3.73 (m, 4H), 4.10–4.14 (m, 2H), 4.31–4.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.61, 27.45, 30.58, 32.53, 46.42, 52.81, 53.65, 60.88, 61.48, 64.10, 66.90, 67.98, 128.33, 154.17; MS (70 eV) *m*/*z* (%) 266 (M^+, 100), 221 (7), 193 (6). Exact mass calcd for $C_{14}H_{22}N_2O_3$: 266.1630, found 266.1628.

2-(Morpholin-4′-yl)-3,6-bis(trifluoromethyl)-4,5,12-triazatricyclo[7.2.1.0^{2,7}]dodeca-3,5-dien-12-carboxylic acid ethyl ester (17a). To a solution of the enamine **15** (0.22 g, 0.82 mmol) in dry THF (30 mL) was added dropwise at room temperature under argon a solution of the tetrazine **16a** (0.17 g, 0.80 mmol) in THF (20 mL). The red solution was stirred at room temperature for ca. 3 h, until the red color of **16a** disappeared. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica gel (column 15×3 cm with petrol ether/diethyl ether 2:1) to provide **17a** as a yellow oil (0.35 g, 93%); $[\alpha]_D^{20}$ + 41.6 (c 0.01, CH_3OH); UV (CH_3OH) λ_{max} (lgε) = 314 nm (2.63), 250 (3.10), 209 (3.80); IR (film) 2980, 2860, 1710, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 and 1.24 (2t, *J* = 7.1 Hz, 3H),

1.61–1.65, 1.73–1.90, 2.01–2.06, 2.14–2.22 (4m, 7H), 2.31–2.48, 2.58–2.61 (2m, 4H), 3.54–3.63 (m, 4H), 4.09 (q, $J=7.1$ Hz, 2H), 4.74 (s, broad, 1H), 5.24 (s, broad, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.27, 26.89, 30.46, 32.49, 34.15, 47.63, 52.44, 52.72, 54.44, 61.45, 62.14, 67.21, 120.02 (q, $J=278.1$ Hz), 120.39 (q, $J=278.9$ Hz), 155.94, 156.12 (q, $J=34$ Hz), 157.68 (q, $J=33.2$ Hz); MS (70 eV, 100 °C) *m/z* (%) 456 (M^+, 14). Exact mass calcd for $C_{18}H_{22}F_6N_4O_3$: 456.1529, found 456.1596.

2-(Morpholin-4′-yl)-3,6-bis(methoxycarbonyl)-4,5,12-triazatricyclo[7.2.1.0^{2,7}]dodeca-3,5-dien-12-carboxylic acid ethyl ester (17b). Utilizing the same protocol as described for **17a** compound **17b** was obtained after heating the reaction mixture in THF for 12 h at reflux. The raw material was purified by flash chromatography on silica gel (column 20×2 cm with petrol ether/ethyl acetate 1:4) to provide **17b** as a yellow oil (0.31 g, 72%); $[\alpha]_D^{20}+38.8$ (c 0.02, CH_3OH); UV (CH_3OH): λ_{max} (lgε) = 318 nm (2.53), 307 (2.55), 214 (3.96); IR (film): 2955, 1735, 1700, 1440, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (t, $^3J_{H,H}=7.1$ Hz, 3H), 1.63–1.68, 1.74–1.93, 1.99–2.24 (3m, 7H), 2.47–2.52, 2.62–2.67 (2m, 4H), 3.48–3.60 (m, 4H), 3.84 (s, 3H), 3.92 (s, 3H), 4.08 (q, $^3J_{H,H}=7.1$ Hz, 2H), 4.32–4.35 (m, 1H), 5.05 (d, $^3J_{1,11}=6.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.12, 14.43, 24.04, 26.91, 29.99, 33.50, 48.86, 51.70, 53.13, 53.57, 54.82, 60.30, 61.76, 67.55 (2C), 155.25, 155.80, 157.82, 163.83 (2 C); MS (70 eV, 100 °C) *m/z* (%) 436 (M^+, 17). Exact mass calcd for $C_{20}H_{28}N_4O_7$: 436.1964, found 436.1958.

3,6-Bis(trifluoromethyl)-4,5,12-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-12-carboxylic acid ethyl ester (18a). To a solution of **17a** (300 mg, 0.65 mmol) in benzene (40 mL) was added *p*-toluenesulfonic acid monohydrate (0.37 g, 1.97 mmol). The mixture was heated at reflux for 4 h, cooled to room temperature and then aqueous NaOH (150 mL, 1 M) added. The organic phase was separated and the aqueous phase extracted with benzene (3×20 mL). The combined organic phase was washed with aqueous Na_2CO_3-solution (30 mL, 10%) and brine (20 mL) dried over $MgSO_4$ (5 g), filtered and the solvent was evaporated in vacuo. The pale yellow, oily residue was purified by column chromatography on silica gel (column 2×20 cm, eluent petrolether/ethyl acetate = 4:1) to furnish **18a** as colorless oil (180 mg, 75%); $[\alpha]_D^{20}=+37.5$ (c 0.02, CH_3OH); IR (film) 2985, 1705, 1560 cm^{-1}; UV (CH_3OH) λ_{max} (lgε) = 313 nm (2.55), 213 (3.63); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, $^3J_{H,H}=7.1$ Hz, 3H), 1.73–1.78, 2.02–2.06 (2m, 2H), 2.39–2.49 (m, 2H), 2.86 (d, $^2J_{8a,8b}=18.8$ Hz, 1H), 3.55 (bs, 1H), 4.12 (q, $^3J_{H,H}=7.1$ Hz, 2H), 4.74 (bs, 1H), 5.47 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.28, 29.22, 31.89, 35.24, 51.24, 52.56, 62.02, 121.30 (q, CF_3, $^1J_{C,F}=277.4$ Hz), 121.35 (q, CF_3, $^1J_{C,F}=276.9$ Hz), 135.42, 141.84, 148.46 (q, C-3 or C-6, $^2J_{C,F}=36.4$ Hz), 152.91 (q, C-3 or C-6, $^2J_{C,F}=37.1$ Hz), 153.68; MS (70 eV, 30 °C) *m/z* (%) 369 (M^+, 100); Exact mass calcd for $C_{14}H_{13}F_6N_3O_2$: 369.0912, found 369.0911. Anal. calcd for $C_{14}H_{13}F_6N_3O_2$ (369.26): C, 45.54; H, 3.55; N 11.38; found C, 45.56; H, 3.37; N 11.05.

3,6-Bis(trifluoromethyl)-4,5,12-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (6a). To a solution of **18a** (130 mg, 0.35 mmol) in dioxane (5 mL) was added aqueous HCl (4 mL, 32%) and the mixture heated at reflux for 24 h. The solution was cooled to room temperature, washed with diethyl ether (2×10 mL) and concd aqueous ammonia was added until the pH of 9 was reached. The mixture was extracted with CH_2Cl_2 (3×10 mL), the combined organic phase was dried over $MgSO_4$ (5 g), filtered and the solvent was evaporated in vacuo. The pale yellow, oily residue was purified by column chromatography on silica gel (column 1×15 cm, eluent CH_2Cl_2/CH_3OH/concd aqueous NH_3 97:3:1) to furnish **6a** (65 mg, 62%) as a colorless oil, which crystallized after storing for one week at room temperature; mp 105–106 °C; $[\alpha]_D^{20}+31.9°$ (c 0.01, CH_3OH); IR (KBr) 3290, 1700, 1685, 1645 cm^{-1}; UV (CH_3OH) λ_{max} (lgε) = 313 nm (2.57), 250 (3.06), 211 (3.65); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64–1.70, 1.99–2.07, 2.13–2.28 (3m, 5H), 2.77–2.83 (m, 1H), 3.34 (dd, $J=18.9$ Hz, $J=5.3$ Hz, 1H), 4.04 (t, $J=6.1$ Hz, 1H), 4.69–4.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.12, 33.93, 36.65, 52.08, 53.41, 121.43 (q, $J=276.7$ Hz), 121.50 (q, $J=276.7$), 135.54, 143.78, 147.95 (q, $J=33.8$ Hz), 152.65 (q, $J=33.0$ Hz); MS (70 eV, 100 °C) *m/z* (%) 297 (22, M^+), 268 (100). Anal. calcd for $C_{11}H_9F_6N_3$: C, 44.46; H, 3.05; N, 14.14; found: C, 44.27; H, 3.16; N, 14.04.

3,6-Bis(methoxycarbonyl)-4,5,12-triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-12-carboxylic acid ethyl ester (18b). Utilizing the same protocol as described for the synthesis of **18a** compound **18b** was obtained as a yellow oil (100 mg, 64%) from **17b** (200 mg, 0.45 mmol) and *p*-toluenesulfonic acid monohydrate (0.26 g, 1.37 mmol); $[\alpha]_D^{20}$ +36.3° (c 0.01, CH_3OH); IR (film): 2980, 1735, 1705 cm^{-1}; UV (CH_3OH): λ_{max} (lgε) = 310 nm (2.58), 222 (3.75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.29 (m, 3H), 1.63–1.70, 2.05–2.11, 2.24–2.45 (3m, 4H), 2.94 (d, $^2J_{8a,8b}=19.0$ Hz, 1H), 3.54 (bs, 1H), 4.01 (s, 3H), 4.07 (s, 3H), 4.05–4.11 (m, 2H), 4.66 (bs, 1H), 5.58 (d, $^3J_{1,11}=6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.46, 29.27, 33.86, 35.23, 51.48, 53.22, 53.41, 53.49, 61.63, 136.00, 142.82, 153.82 (2C), 153.84, 164.41, 164.53; MS (70 eV) *m/z* (%) 349 (43, M^+), 321 (76, M^+-N_2), 304 (10, M^+-OEt), 276 (19, $M^+-COOEt$), 248 (100, M^+-N_2,–COOEt). Anal. calcd for $C_{16}H_{19}N_3O_6$ (349.34): C, 55.01; H, 5.70; N, 12.03, found C, 54.90; H, 5.48; N, 11.66.

4,5,12-Triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (6b). To a solution of **18b** (60 mg, 0.17 mmol) in dioxane (5 mL) was added concd aqueous HCl (4 mL, 32%). After heating the solution at reflux for 48 h, the mixture was cooled to room temperature, washed with diethyl ether (2×10 mL) and concd aqueous ammonia was added until the pH of 9 was reached. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), the combined organic phase dried over $MgSO_4$ (5 g) filtered and the solvent evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (column 1×15 cm, eluent CH_2Cl_2/CH_3OH/concd aqueous NH_3 90:10:1) to afford **6b** (15 mg, 83%) as a pale yellow oil;

$[\alpha]_D^{20}$ + 35.0° (c 0.2, CH_3OH); IR (film) 3290, 3245, 2950, 1655, 1575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.62, 1.90–1.94, 2.12–2.19 (3m, 4H), 2.53 (d, J = 17.8 Hz, 1H), 2.94 (s, broad, NH), 3.12 (dd, J = 17.8 Hz, J = 4.8 Hz, 1H), 4.17 (t, J = 5.9 Hz, 1H), 4.27 (d, J = 5.7 Hz, 1H), 8.80 (s, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.54, 34.60, 36.50, 52.73, 54.87, 132.97, 141.58, 148.03, 152.88; MS (70 eV, 25 °C) m/z (%) 161 (37, M^+), 132 (100). Exact mass calcd for $C_9H_{11}N_3$: 161.0952, found 161.0952.

3,5,12-Triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-12-carboxylic acid ethyl ester (20). To a solution of the enamine **15** (400 mg, 1.5 mmol) in dry dioxane (1.5 mL) in a pressure bottle was added under argon the 1,3,5-triazine **19** (122 mg, 1.5 mmol). The pressure bottle was sealed and heated for 15 h at 110 °C. The mixture was cooled to room temperature, the solvent evaporated in vacuo and the residue purified by flash chromatography on silica gel (column 2×25 cm with *n*-hexane/ethyl acetate 1:1) to provide **20** as a pale yellow oil (311 mg, 89%); $[\alpha]_D^{20}$ + 11.0° (c 0.2, CH_2Cl_2); IR (film) 2981, 1700, 1588, 1554 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18–1.23 (m, 3H), 1.58–1.61, 1.92–1.96, 2.25–2.29 (3m, 4H), 2.52 (d, J = 16.7 Hz, 1H), 3.32 (bs, 1H), 4.06–4.13 (m, 2H), 4.65–5.00 (2bs, 2H), 8.41 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5, 28.7, 32.4, 34.3, 52.2, 58.8, 61.4, 126.3, 154.2, 156.3, 157.7, 161.6; MS (70 eV, RT) m/z (%) 233 (M^+, 36), 145 (100); exact mass calcd for $C_{12}H_{15}N_3O_2$: 233.1164, found 233.1180.

3,5,12-Triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene maleate (7a). To a solution of the carbamate **20** (233 mg, 1.0 mmol) in dry chloroform (5 mL) was added TMSI (156 μL, 1.1 mmol) and the mixture heated at 85 °C for 3 h in a pressure bottle. After cooling to room temperature the volatile components were evaporated in vacuo for 30 min, then a mixture of dry CH_3OH (3 mL) and HCl in diethyl ether (1.0 mL, 2M, 1.0 mmol) was added and the resulting solution stirred for 10 min at ambient temperature. After evaporation of the solvent in vacuo water (3 mL) was added to the residue and the aqueous phase extracted with CH_2Cl_2 (5×2 mL). The organic phase was rejected, the aqueous phase made basic with aqueous NH_3 up to pH = 9, extracted with CH_2Cl_2 (5×2 mL) and the organic phase dried over $MgSO_4$. After filtration the solvent was removed and the residue dried in vacuo to afford the free base **7** (130 mg, 81%). This was dissolved in butanone (2 mL), the solution heated to 70 °C and a solution of maleic acid (116 mg, 1.0 mmol) in butanone (2 mL) added. The immediately formed white precipitant was collected to yield the corresponding maleate of **7** (130 mg, 58%). Mp 155–158 °C; $[\alpha]_D^{20}$ = + 41.7 (c 0.002, CH_3OH); IR (KBr): 3401, 2925, 1698, 1631, 1567, 1485 cm^{-1}; ^1H NMR (500 MHz, MeOH) δ 1.77–1.84 (m, 1H), 2.08–2.14 (m, 1H), 2.27–2.34 (m, 2H), 2.86 (d, J = 17.9 Hz, 1H), 3.28 (dd, J = 4.1 Hz, J = 17.9 Hz, 1H), 4.35 (s, 1H), 4.66 (d, J = 5.3 Hz, 1H), 6.09 (s, 2H), 8.56 (s, 1H), 8.87 (s, 1H); ^{13}C NMR (125 MHz, MeOH) δ 28.3, 32.3, 33.8, 55.7, 60.8, 126.3, 136.8, 158.2, 159.8, 164.0, 171.0; MS (70 eV, 25 °C) m/z (%) 161 [54, M^+ (base)], 132 (100); Exact mass calcd for $C_9H_{11}N_3$: 161.0953, found 161.0953.

(±)3-(Morpholin-4′-yl)-8-azabicyclo[3.2.1]oct-2-en-8-carboxylic acid ethyl ester (22). Utilizing the same protocol as described for the synthesis of the enamine **15** compound **22** was obtained as a colorless oil, yield 808 mg (75%), which was used without further purification in the following Diels–Alder reaction with the triazine **19**.

(±)-4,6,12-Triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-12-carboxylic acid ethyl ester (23). Utilizing the same protocol as described for the synthesis of compound **20**, the pyrimidine annulated species **23** was obtained as a pale yellow oil, 170 mg (24%). IR (film) 2982, 1704, 1582, 1553, 1418 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21–1.28 (m, 3H), 1.67–1.73 (m, 1H), 1.86–1.90 (m, 1H), 2.21–2.35 (m, 2H), 2.72 (d, J = 18.4 Hz, 1H), 3.39 (bs, 1H), 4.10 (q, J = 7.1 Hz, 2H), 4.65 (s, 1H), 5.05 (s, 1H), 8.40 (s, 1H), 8.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 29.8, 35.6, 40.0, 52.3, 54.2, 61.7, 134.6, 152.5, 152.6, 154.2, 157.8; MS (70 eV, 180 °C) m/z (%) 233 (53, M^+), 205 (100); exact mass calcd for $C_{12}H_{15}N_3O_2$: 233.1164, found 233.1205.

(±)-4,6,12-Triazatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene·acetone (8). Utilizing the same protocol as described for the preparation of **5** (TMSI/CH_3OH method) the free base **8** was obtained in 42% yield; after crystallization from acetone **8** was obtained crystallizing with one molecule of acetone; mp 233–235 °C; IR (KBr): 3473, 2950, 1700, 1586, 1559 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 2.12–2.17 (m, 1H), 2.33–2.34 (m, 6H), 2.38–2.44 (m, 1H), 2.52–2.62 (m, 2H), 3.27 (d, J = 19.5 Hz, 1H), 3.67 (dd, J = 5 Hz, J = 19.5 Hz, 1H), 4.69 (t, J = 5 Hz, J = 6.2 Hz, 1H), 5.21 (d, J = 6 Hz, 1H), 8.79 (s, 1H), 9.17 (s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 27.4, 30.8, 33.6, 37.9, 54.7, 55.7, 130.3, 154.8, 158.3, 161.6, 215.9; MS (70 eV, 160 °C) m/z (%) 161 (20, M^+-base), 133 (100); Exact mass calcd for $C_9H_{11}N_3$: 161.0952; found 161.0934

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