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Racemic and enantiopure 4-(piperidine-2′-yl)-pyridazines: novel synthesis of anabasine-analogues with potential nicotinic acetylcholine receptor agonist activity—a new approach via Diels–Alder reaction with inverse electron demand

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Abstract—A novel multistep synthesis of anabasine analogues bearing a bioisosteric pyridazine moiety instead of a pyridine nucleus in 2-position of the piperidine ring of the alkaloid is described. Starting materials are racemic 2-hydroxymethyl-piperidine, racemic pipecolic acid or (*S*)-(−)-piperidine-1,2-dicarboxylic-acid-1-*tert*-butyl ester. Key step of this synthetic approach is a Diels–Alder cycloaddition process with inverse electron demand utilizing diverse 1,2,4,5-tetrazines as electron-deficient dienes and the new racemic or enantiopure 2-(2′-methoxyethenyl)-piperidine as electron-rich dienophile. In this [4+2]-cycloadditions 1,2,4,5-tetrazines serve as synthons for introducing the pyridazine ring in the 2-position of the piperidine moiety.

1. Introduction

(−)-Anabasine (**1**)[1,2] with a 3-(2′-piperidyl)-pyridine constitution is one of the several minor tobacco alkaloids and preferentially found in extracts of the wild tree tobacco *Nicotiana glauca Graham* (solanaceae), or of *Anabasis aphylla* L. (chenopodiaceae), poisonous plants in which **1** supplants (−)-nicotine (**3**, R=CH_3) as the chief alkaloid. Consumption of plants containing this neurotoxin led to intoxination, e.g. of cattle with symptoms of disorder in motion and skeletal growth similar to the lupine-induced 'crooked calf disease'.[3] The constitution of **1** has been elucidated by chemical degradation and by syntheses, the absolute configuration of the chiral center C-2 was established to be *S*.[1,2,4,5]

Anabaseine,[6] 3-[2′-(3,4,5,6-tetrahydropyridyl)]-pyridine (**2**)—in contrast to the plant alkaloids **1** and (−)-nicotine (**3**, R=CH_3)—is an invertebrate toxin, closely related to **1**. It differs from **1** by unsaturation in the 1,2-position of the piperidine moiety. Initially, it was known as a useful intermediate in the synthesis of anabasine (**1**).[1,2] Later it was found to be a naturally occurring toxin, first in hoplonemertine sea worms as defensive compound and then in certain species of ants.[7]

Due to their structural similarity to (−)-nornicotine (**3**, R=H) (−)-anabaseine (**1**) and anabasine (**2**)—often referred to as 'homoprolines'—were investigated extensively in pharmacological studies for potential activity at nicotinic acetylcholine receptors (nAChR).[8]

Anabaseine (**2**) is a potent agonist on muscle and neuronal α-bungarotoxin-sensitive nicotinic acetylcholine receptors (nAChRs).[7b] Derivatives of the animal toxin **2** have been shown to enhance a variety of cognitive behaviors. Most interestingly addition of a 3-substituent to **2** seems to diminish its peripheral nervous system and α4β2 stimulation without reducing central α7 stimulation. This is probably the major pharmacodynamic advantage of the 3-substituted variants over the parent toxin. One of these derivatives, DMXB-anabaseine **4** [3-(2′,4′-dimethoxybenzylidene)-anabasine], also known as GTS-21, an α7 selective agonist, is currently in clinical trials for possible treatment of Alzheimer's dementia and other cognitive deficits.[8,9]

Based upon the approach that bioisosteric alteration in the pyridine moiety of **1** and **2** might provide compounds with better ratios of neuroprotecting and memory-enhancing effects to toxic activity (i.e. an improved therapeutical index), we developed a new synthetic route to anabasine-derivatives **5** with the pyridine nucleus bioisosterically displaced by a pyridazine moiety (Scheme 1).

Furthermore our synthetic approach allows great flexibility in synthesizing racemic anabasine derivatives as well as

Keywords: NAChR ligands; anabasine; bioisosterism; inverse [4+2] cycloadditions.

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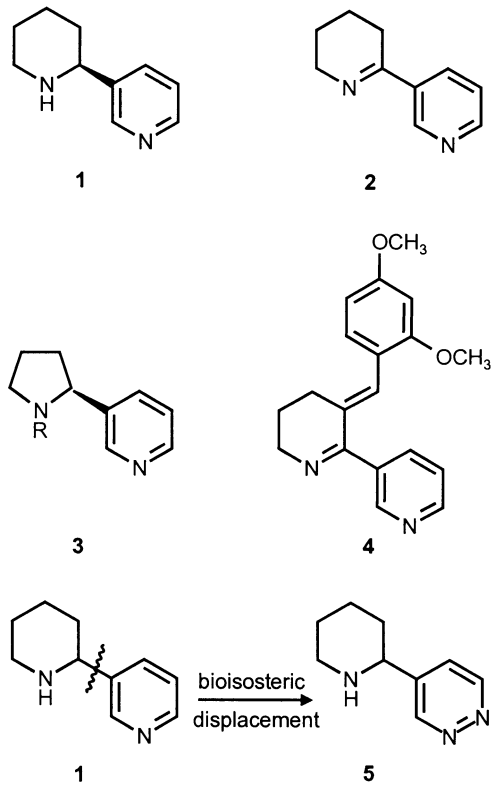
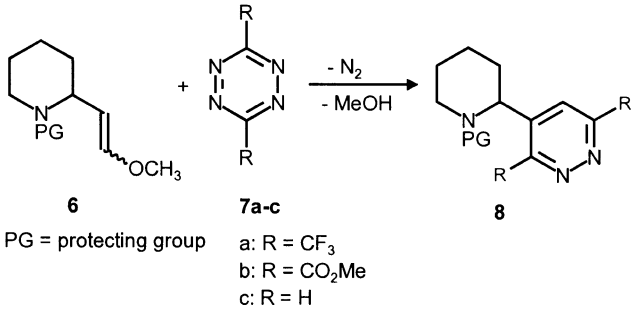


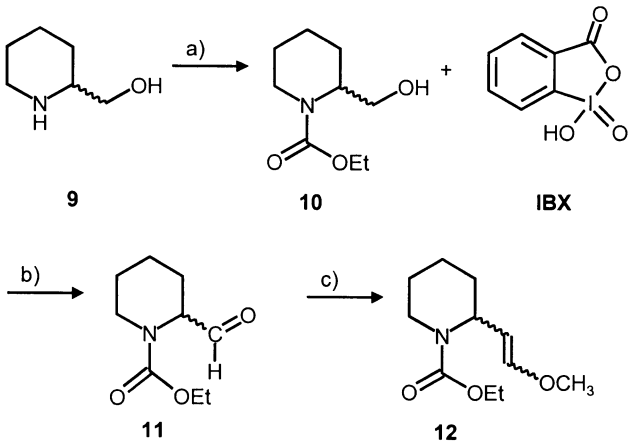
Scheme 1. (−)-Anabaseine (**1**), anabaseine (**2**), (−)-nornicotine (**3**, R=H), (−)-nicotine (**3**, R=CH_3), GTS-21 (**4**, 3-(2,4-dimethoxy-benzylidene)-anabasine).

their corresponding *R*- and *S*-enantiomers. Therefore our protocol should open up the possibility of investigating the enantioselectivity of 2*R*- and 2*S*-enantiomers at nAChRs as molecular site of action, in order to identify either the *R*- or the *S*-enantiomer of anabasine analogues **5** as dystomer or eutomer.

In the key step of our synthetic approach, the bioisosteric displacement of the pyridine nucleus in **1** by a pyridazine fragment can retrosynthetically be achieved utilizing the methodology of Diels–Alder reaction with inverse electron-demand[10] (Scheme 2). The enol ether **6** as an electron-rich dienophile is reacted with several 1,2,4,5-tetrazines as electron-deficient diazadiene-systems, to yield the target pyridazines of type **8** after [4+2] cycloaddition and subsequent expulsion of nitrogen and elimination of methanol.



Scheme 2. Inverse type Diels–Alder reaction of the electron-rich enol ether **6** with the electron-deficient 1,2,4,5-tetrazines **7a–c**.



Scheme 3. *Reagents and conditions*: (a) EtOCOCl, NEt_3, DMAP, THF, 24 h, −15⇒0°C, 84%; (b) IBX (2-iodoxybenzoic acid), DMSO, 3.5 h, rt, 86%; (c) $Ph_3PCH_2OCH_3^+Cl^-$, KO^{t}Bu, Et_2O, 24 h, −15°C⇒rt, 87%.

2. Results and discussion

The synthetic route to the novel racemic enol ether **12** originating from commercially available racemic 2-hydroxymethyl-piperidine (**9**) is outlined in Scheme 3.

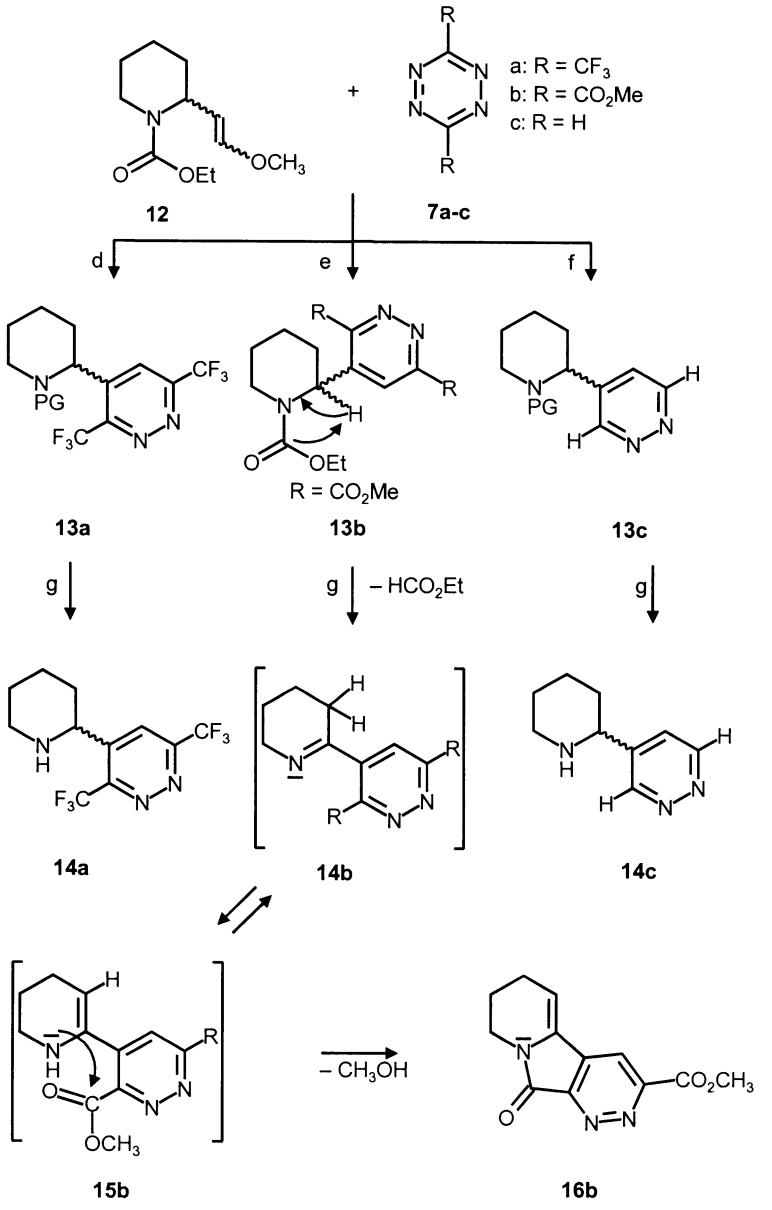
Racemic alcohol **9** can be chemoselectively protected as *N*-ethoxycarbonyl–aminoalcohol **10** by standard procedures.[11] It is important to note that alcohol **9** can be exclusively *N*-protected by performing the reaction in THF as solvent of choice at −15°C and suppressing the concurring *O*-acylation to a negligible extent (<5%). In contrast, performing the reaction in CH_2Cl_2 or MeOH leads to formation of the *O*-protected piperidine-analogue of **9** as undesired by-product.

Oxidative transformation of alcohol **10** to aldehyde **11** can easily be achieved by Swern or Parikh-von Doering-reaction.[11,12]

Another attractive and comfortable method consists of utilizing the periodinane 2-iodoxybenzoic acid (IBX) recently gaining growing interest in oxidative processes.[13–16]

IBX itself can be prepared in multigram quantities either from 2-iodobenzoic acid and $KBrO_3$[13] or from Oxone® ($KHSO_5/KHSO_4$)[17] as oxidant, is stable to air, moisture and acid and can be stored without decomposition for months.

For our purposes (oxidation of alcohol **10** to **11**), IBX was best prepared following the 2-iodobenzoic acid/$KBrO_3$-protocol from Frigerio.[13] In our case, this procedure proved to be superior to the previously reported protocol using Oxone® as oxidant.[17] Although the latter method is less time-consuming and avoids formation of toxic bromine and tedious washing-operations, we found that aldehyde **11** is formed in significantly lower, varying yields (between 50 and 60%) and cannot be used without purification by flash chromatography in the next step, when 'Oxone–IBX' is used. In contrast, '$KBrO_3$–IBX' converts **10**



Scheme 4. *Reagents and conditions*: (d) +**7a**, toluene, 7 h, reflux, 65%; (e) +**7b**, toluene, 5 h, reflux, 56%; (f) +**7c**, without solvent, 12 h, 80°C, 80%; (g) $(CH_3)_3SiI$, $CHCl_3$, 4.5 h, reflux, then CH_3OH. Yields: **14a**: 50%; **16b**: 15%; **14c**: 50%.

reproducibly to aldehyde **11** in 86% yield within 3.5 h at room temperature in DMSO as the solvent. Obviously, 'Oxone–IBX' contains still some trace amounts of impurities being disadvantageous for the oxidation of **10**.

Aldehyde **11** can be transformed to the hitherto unknown enol ether **12** which may subsequently act as an electron-rich dienophile (Scheme 3).

In the course of our synthetic studies, high-temperature Wittig-reaction[18,19] (KO^tBu, Et_2O, $-15 \Rightarrow 20$°C) was found to be superior to the standard low-temperature procedure[20] (LDA, THF, −78°C) in each case using triphenyl-(methoxymethylene)-phosphoniumchloride as ylide precursor (Scheme 3).

We preferred the high-temperature Wittig-reaction[11,18,19] in view of the high yields obtained: with LDA in THF the enol ether **12** is obtained in only 47% yield, whereas the target molecule **12** is formed in an excellent 87% yield using *t*-BuOK in diethyl ether. As determined by ^1H NMR (400 MHz, $CDCl_3$), enol ether **12** is isolated as a mixture of *E*- and *Z*-isomers in ratio *E*/*Z*=68:32.

With racemic enol ether **12** in hands, we studied the outcome of the $LUMO_{diene}/HOMO_{dienophile}$-controlled Diels–Alder reaction[10] of the tetrazines **7a–c** as electron-deficient diazadiene-systems with enol ether **12** as electron-rich dienophile (Scheme 4). This [4+2] cycloaddition could be successfully carried out in our research group for a variety of structurally different enol ethers, starting materials for novel potent pyridazine analogues of (±)-epibatidine and chiral 2-(2′-pyrrolidinyl)-pyridines.[21,22]

The *N*-protected target compounds **13a–c** can be isolated in good to excellent yields (56–80%) after [4+2]

cycloaddition with subsequent expulsion of nitrogen and 1,2-elimination of methanol.

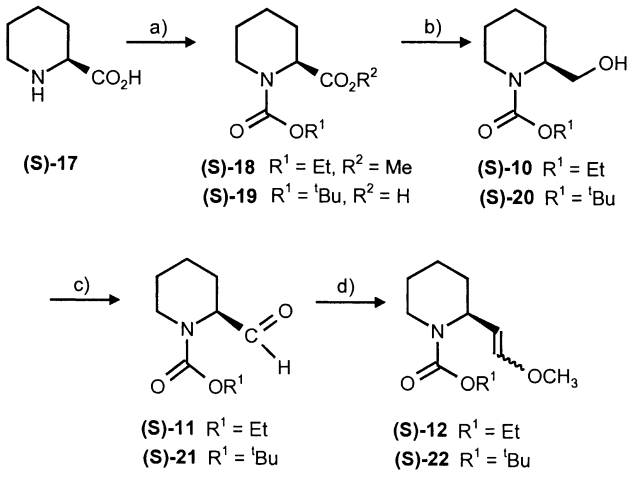
Removal of the protecting group (PG) is successfully accomplished by treatment of **13a–c** with Me_3SiI[22,23] (TMSI) in boiling trichloromethane and subsequent quenching with methanol, thus affording the desired pyridazine analogues **14a** and **14c** in satisfying yields (50%).

Surprisingly, attempted deprotection of **13b** with TMSI results in formation of the not isolable intermediate imine **14b** probably by 1,2-elimination of the protecting group as formic acid ethyl ester. Imine **14b** thus formed rapidly tautomerized to the enamine **15b**. This serves as an *N*-nucleophile attacking the neighboring ester group of the pyridazine moiety in **15b**. Subsequent elimination of MeOH generates the tricyclic lactame **16b.**

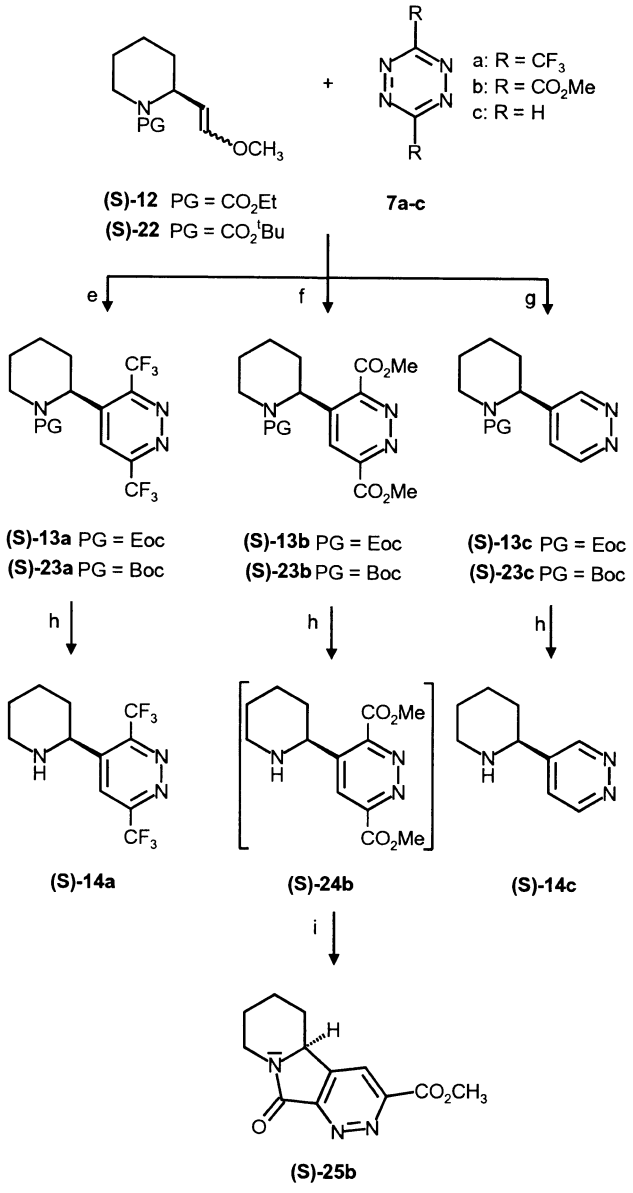
With this optimized process for the synthesis of racemic anabasine derivatives **14a** and **14c** in view, we evaluated an approach to the *R*- and *S*-enantiomers of **14a** and **14c**, starting from racemic pipecolic acid (±)-**17**. At the outset, resolution of this amino acid **17** was carried out utilizing the protocol reported by Mende[24] and Shiraiwa[25] with use of L-(+)-tartaric acid in EtOH.

The enantiomers of **17** were then transformed to the corresponding enantiopure enol ethers **12** as depicted in Scheme 5 for the *S*-enantiomer using standard procedures.[18,19,26–28]

Subsequently the enantiopure enol ethers (*R*)-**12** and (*S*)-**12** were successfully cycloadded to 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (**7a**) or to the parent 1,2,4,5-tetrazine (**7c**) in the previously reported manner (Scheme 4) yielding the enantiopure *N*-protected target compounds, e.g. (*S*)-**13a** in 69% and (*S*)-**13c** in 64% yield, respectively (Scheme 6).

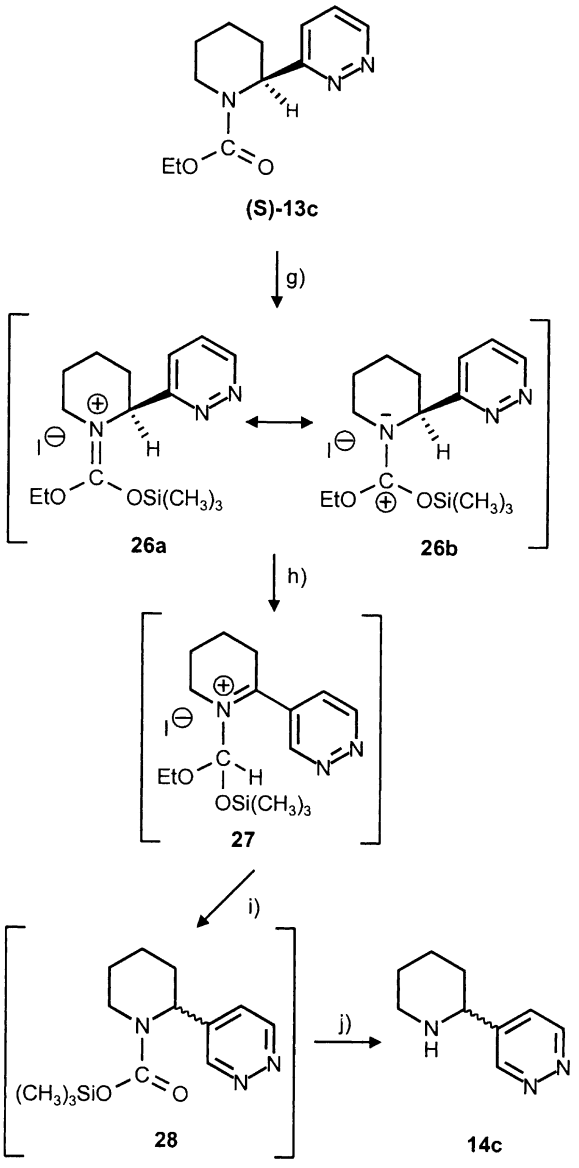


Scheme 5. *Reagents and conditions* for R^1=Et and R^2=Me starting from (*S*)-**17**: (a) K_2CO_3, MeOH, then EtOCOCl, 0°C⇒rt, **3d**, 90% from (*S*)-**17**; (b) DIBAL-H, toluene, −40°C⇒rt, 12 h, 88% from (*S*)-**18**; (c) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2, −78°C, 0.5 h, 83% from (*S*)-**10**; (d) $Ph_3PCH_2OCH_3{}^+Cl^-$, KO^{t}Bu, Et_2O, −15°C⇒rt, 24 h, 89% from (*S*)-**11**. *Reagents and conditions* for R^1=^{t}Bu and R^2=H starting from (*S*)-**19**; (e) $BH_3{\times}Me_2S$, THF, −15°C⇒rt, 15 h, 96% from (*S*)-**19**;[37] (f) IBX (2-iodoxybenzoic acid), DMSO, 4.5 h, rt, 87% from (*S*)-**20**; (g) $Ph_3PCH_2OCH_3{}^+Cl^-$, KO^{t}Bu, Et_2O, −15°C⇒rt, 24 h, 83% from *S*-**21**.



Scheme 6. *Reagents and conditions* for PG=Boc starting from (*S*)-**22**: (e) +**7a**, toluene, 24 h, reflux, 72%; (f) +**7b**, toluene, 28 h, reflux, 81%; (g) +**7c**, trichloromethane, 30 h, reflux, 95%;[41] (h) CF_3CO_2H, CH_2Cl_2, −15°C⇒rt; (i) $-CH_3OH$.

To our disappointment intense efforts to remove the protecting group from the carbamate *S*-**13c** without racemization were not successful. All attempts to deprotect (*S*)-**13c** by conventional methods with TMSI in boiling $CHCl_3$ or with dioxane/aqueous hydrochloric acid (37%) furnished racemic **14c** as determined in NMR-experiments with (*R*)-(−)-1,1′-Binaphthyl-2,2′-diylphosphoric acid as shift reagent.[29–31] A comprehensive and plausible mechanism for the unprecedented racemization is outlined in Scheme 7. We suppose that the carbamate (*S*)-**13c** reacts with TMSI under the conditions employed to yield the resonance stabilized carbenium–iminium cation [**26a**⇔**26b**] as intermediate. Obviously the neighboring iminium group together with the electron-attracting character of the pyridazine moiety in [**26a**⇔**26b**] enhances the acidity of the adjacent CH-bond giving rise to the formation of **27** via a fast



Scheme 7. *Reagents and conditions*: (g) $(CH_3)_3SiI$, $CHCl_3$, 4.5 h, reflux; (h) prototropic 1,3-H-shift; (i) –EtI; (j) CH_3OH, $-(CH_3)_3SiOCH_3$, $-CO_2$.

1,3-tautomerism. This explains the observed racemization at the chiral center C-2.

In view of these results, we decided to substitute the Eoc-protecting group for suitable alternative carbamate groups, i.e. the Cbz- or Boc-group.

In contrast to the Eoc-group, Cbz-moieties can be easily cleaved under mild reducing conditions, for example by hydrogenolysis, transfer catalytic hydrogenation or by dissolving metal reduction.[32]

Previous work in our research group elucidated that these conditions were not compatible with the sensitivity of the pyridazine nucleus towards reducing agents. When deprotecting *O*-benzyl-derivatives[33,34] or *N*-Cbz-derivatives[31] the pyridazine nucleus did not withstand reducing conditions resulting in decomposition of the corresponding educts.

Due to the outstanding role of the Boc-carbamate-group for N-protecting chiral substrates in peptide chemistry[35] we anticipated that this group could be removed from anabasine analogues (i.e. **8** with PG=Boc) without racemization at chiral C-2 of (*S*)-**8**. This rationale is supported by recent investigations of Hwu and co-workers[36] and Garvey et al.[37] Hwu[36] introduced a new method of removing Boc-groups from enantiopure amino acid esters without racemization utilizing ceric ammonium nitrate (CAN) as one-electron-oxidant and -reductant under pH-neutral conditions.

Garvey[37] succeeded in cleaving Boc-groups from enantiopure (*R*)-proline- and (*R*)-pipecolic-acid derivatives without racemization at C-2 by employing a modified trifluoroacetic-acid protocol.

With these encouraging aspects in mind, we focused our interest on commercially available enantiopure (*S*)-(−)-piperidine-1,2-dicarboxylic-acid-1-*tert*-butyl ester (*S*)-(**19**) (Scheme 5). Our choice was the *S*-enantiomer (*S*)-**19**, because it has been shown,[38,39] that the *S*-enantiomer of (−)-nicotine (**3**, R=CH_3) is more active at nAChRs (and therefore the eutomer at these receptors) than the *R*-enantiomer, a tendency also established for many analogues like anabasine (**1**), epibatidine and anatabine.[39]

Our efforts were now directed to the construction of enantiopure, Boc-protected *S*-enol ether (*S*)-**22** serving as dienophile in the above mentioned Diels–Alder reaction. This intermediate was synthesized in three steps from enantiopure Boc-protected *S*-pipecolic acid (*S*)-**19** (Scheme 5).

Enantiopure Boc-aminoalcohol (*S*)-**20** could be obtained in nearly quantitative yield from (*S*)-**19** following the protocol of Garvey et al.[37] (96% yield, $[\alpha]_D^{20}=-40.4°$, $c=1.02$, trichloromethane; literature:[12] $[\alpha]_D^{20}=-40.5°$, $c=1.0$, trichloromethane). Alcohol (*S*)-**20** was successfully transformed to known, enantiopure aldehyde (*S*)-**21** by employing the above described IBX-methodology (87% yield, $[\alpha]_D^{20}=-77.9°$, $c=1.49$, trichloromethane; literature:[12] $[\alpha]_D^{20}=-77.4°$, $c=1.4$, trichloromethane, enantiopurity determined by g.l.c.).

The good agreement of optical rotation of (*S*)-**21** with the value reported by Sanchez-Sancho[12] indicates that no racemization at C-2 of alcohol (*S*)-**20** occurred during IBX-mediated oxidation. Hence, IBX serves as a mild and chemoselective oxidant tolerating protected and unprotected amine functionalities[40] in the alcohol molecule and reacts without racemization. Aldehyde (*S*)-**21** could be routinely carried on to *E*/*Z*-*S*-enol ether (*S*)-**22** via high-temperature-Wittig-methoxyolefination as described above for the Eoc-series (83% yield, $[\alpha]_D^{20}=-46.3°$, $c=1.17$, trichloromethane, see Schemes 3 and 5).

Subsequently, enol ether (*S*)-**22** was cycloadded to substituted tetrazines **7a** and **7b** and parent compound **7c** in good to excellent yields (72–95%, Scheme 6).

In comparison to the Eoc-series (Schemes 4 and 6) cycloadditions to Boc-protected dienophile (*S*)-**22** are

characterized by decreased reaction rates, but increased yields. Furthermore, in contrast to Eoc enol ether **12**, an excess of tetrazines **7a–c** (1.3–3.7 equiv. **7a–c** pro equiv. (*S*)-**22**) is necessary in order to perform cycloadditions without severely decreased reaction rates. Presumably, the increased steric bulk of the Boc-group compared to Eoc-carbamate causes increased steric hindrance of the dienophilic C-2-double bond of (*S*)-**22** towards the approach of the diazadienes **7a–c** therefore making it necessary to accelerate this process kinetically by an excess of tetrazine.

With cycloadducts (*S*)-**23a–c** in hands, the stage was set for the crucial, enantiospecific deprotection of *N*-Boc-protected anabasine-analogues to the corresponding free bases (*S*)-**14a**, (*S*)-**14c** and (*S*)-**24b** (compare Scheme 6).

Efforts to remove the Boc-group by use of 0.2 equiv. CAN in refluxing CH_3CN or CH_3CN/MeOH-mixtures[36] were not successful: we observed no cleavage of the protecting group at all. After standard work-up, the Boc-protected piperidines (*S*)-**23a–c** could be recycled in nearly quantitative yield.

Therefore we investigated the standard method of cleaving Boc-groups with the help of trifluoroacetic acid (TFA) in dichloromethane.[32,37]

When subjecting *N*-Boc-pyridazines (*S*)-**23a** and (*S*)-**23c** to the mild acidic conditions of TFA in dichloromethane at room temperature clean removal of the carbamate group was observed within 2.5–4.5 h (yields 84%).

Interestingly, the steric demand of the 3- and 6-positioned CF_3-substituents of (*S*)-**23a** significantly decreased the reaction rate (4.5 h) compared to the deprotection (2.5 h) of unsubstituted pyridazine (*S*)-**23c**.

In the case of *N*-Boc-protected diester-pyridazine (*S*)-**23b** cleavage of the Boc-group was followed by spontaneous cyclization of the intermediate free base (*S*)-**24b** to tricyclic, enantiopure lactame (*S*)-**25b**. This domino process renders novel pyridazine (*S*)-**25b** in an optimized 77% yield. According to ^{1}H NMR spectroscopic investigations (500 MHz, $CDCl_3$ and [D_6]DMSO) cyclization of (*S*)-**24b** to lactame (*S*)-**25b** already occurs under the reaction conditions of deprotection and therefore does not result from subsequent basic work-up.

For all of the *N*-Boc-compounds (*S*)-**23a–c**, it is not necessary to add *tert*-butyl-cation scavengers (i.e. anisole, phenol, benzenethiol[32]) to the reaction mixture as this is the case for more electron-rich hetarenes like indoles (e.g. tryptophanes[32]) and 1,4-diazines.[42]

This result is supported by our rationale of the electron-deficient character of the pyridazine nucleus of (*S*)-**14a**, (*S*)-**14c** and (*S*)-**24b** (especially (*S*)-**14a** and (*S*)-**24b** with R=CF_3, CO_2Me) which are not activated towards Friedel–Crafts alkylation by Me_3C-cations meantime released in the course of deprotection.

To our delight, ^{1}H NMR-experiments (500 MHz, $CDCl_3$ and [D_6]DMSO) with (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl-phosphoric acid as shift reagent indicated that deprotection of (*S*)-**23a–c** was not accompanied by racemization at chiral center C-2 as judged from the single set of signals for (*S*)-**14a**, (*S*)-**25b** and (*S*)-**14c** in the presence of this shift reagent.

In accordance to these NMR-results the enantiopurity of pyridazines (*S*)-**14a**, (*S*)-**25b** and (*S*)-**14c** is estimated ≥96%. Hence we were able to circumvent racemization occurring at C-2 of piperidine (*S*)-**13c** in the course of the TMSI-mediated deprotection (Scheme 7) by introducing the Boc-group instead of the Eoc-carbamate group.

3. Conclusion

Bioisosterism is an important concept in drug design of novel nAChR ligands and serves as a valuable tool in QSAR. Following the idea, that bioisosteric alteration in the heteroaromatic moiety of anabasine (**1**) might provide compounds with better ratios of pharmacological to toxicological activity compared to anabasine, we synthetically replaced the pyridine pharmacophoric element of **1** by different substituted pyridazines.

A key step of our new and efficient synthesis was the Diels–Alder reaction with inverse electron demand employing the electron-rich enol ethers (*S*)-**12** and (*S*)-**22** and the electron-deficient diazadiene system of several substituted 1,2,4,5-tetrazines as starting materials. The lead compounds of type **5** were prepared for the first time with satisfying to good yields of the racemic or enantiopure species **14a** and **14c**.

At the outset of our synthetic plan, one important goal of our investigation to identify either the *R*- or the *S*-enantiomer of the novel bioisosteres of anabasine as dystomer or eutomer could not be realized with the Eoc-group protecting the N-terminus. Employing standard procedures for Eoc-group cleavage from enantiomerically pure precursors (e.g. (*S*)-**13a** or (*S*)-**13c**) resulted in complete racemization. By substituting Eoc-carbamate for the Boc-protecting group we have now accomplished an efficient enantioselective and highyielding synthesis of anabasine analogues with a pyridazine nucleus in 2-position. Investigations concerning the biological activity of these potential nAChR ligands are in progress.

4. Experimental

4.1. General experimental procedures

Standard vacuum techniques were used in handling of air sensitive materials. Melting points were determined on a 'Leitz–Heiztischmikroskop' HM-Lux and are uncorrected. Solvents were dried and freshly distilled before use according to literature procedures. IR spectra were recorded on a Perkin–Elmer 257, 398 and a Nicolet FT-IR spectrometer 510-P; liquids were run as films, solids as KBr pellets. ^{1}H and ^{13}C NMR were recorded on Jeol JNM-GX 400 or Jeol Lambda 500 and δ values are given in ppm relative to tetramethylsilane as internal standard (J values in Hz). The symbols s (singlet), d (dublet), t (triplet) and q (quartet)

in ^{13}C NMR spectroscopic data refer to the signal multiplicities of carbons (i.e. –C, –CH, CH_2– and –CH_3) as estimated by ^{13}C NMR-DEPT-measurements (DEPT: distortionless enhancement by polarization transfer). Mass spectra were measured with a Fisons Instruments VG 70–70 E spectrometer at 70 eV ionizing voltage (EI). Column chromatography was carried out on Merck silica gel 40 (40–60 mesh, flash chromatography) or Merck silica 60, 70–230 mesh. 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 were determined on a Jasco DIP-370 polarimeter. 2-Iodoxybenzoic acid (IBX) was prepared according to the procedure reported by Frigerio.[13] Racemic 2-hydroxymethyl-piperidine (**9**), racemic pipecolic acid (±)-**17** and (*S*)-(−)-piperidine-1,2-dicarboxylic-acid-1-*tert*-butyl-ester (*S*)-**19** (98% ee) were purchased from Aldrich Chemical Company. Resolution of (±)-**17** was carried out according to the protocol of Mende[24] and Shiraiwa.[25] (*S*)-2-Hydroxymethyl-piperidine-1-carboxylic-acid-*tert*-butyl ester (*S*)-(**20**) was synthesized as described by Garvey.[37] Enantiopurities (% ee) of (*S*)-**14a**, (*S*)-**25b** and (*S*)-**14c** were determined by ^1H NMR experiments (500 MHz) utilizing (*R*)-(−)-1,1′-binaphthyl-2,2′-diylphosphoric acid employing the following concentrations of bases and shift reagent in $CDCl_3$- or [D_6]DMSO-solutions: for determining the enantiopurity of (*S*)-**14a**, 30.0 mg (~0.10 mmol) (*S*)-**14a** and 61.2 mg (0.18 mmol) shift reagent were dissolved in $CDCl_3$ (2.0 mL). In an analogous manner, enantiopurities of (*S*)-**25b** and (*S*)-**14c** were determined with the help of a solution of 25.0 mg (~0.10 mmol) (*S*)-**25b** and 35.0 mg (~0.10 mmol) shift reagent in [D_6]DMSO (2.0 mL) or a solution of 16.0 mg (~0.10 mmol) (*S*)-**14c** and 35.0 mg (~0.10 mmol) shift reagent in [D_6]DMSO (1.5 mL).

4.1.1. (*RS*)-2-Hydroxymethyl-piperidine-1-carboxylic acid ethyl ester (10). To a solution of 2-hydroxymethyl-piperidine (**9**) (3.86 g, 33.5 mmol) in anhydrous THF (100 mL) were added triethylamine (4.67 mL, 33.5 mmol) and DMAP (50 mg). The mixture was cooled to −15°C. Ethylchloroformate (3.19 mL, 33.5 mmol) was slowly added within a period of 10 min and the colorless suspension was gradually warmed to room temperature over a period of 3 h. The mixture was stirred for another 24 h at ambient temperature. Concentration in vacuo was followed by partitioning the residue between dichloromethane (100 mL) and saturated aqueous NaCl-solution (100 mL). The aqueous phase was separated and extracted with dichloromethane (4×100 mL). The combined organic extracts were washed with saturated aqueous NaCl-solution (3×100 mL) and dried with magnesium sulfate (25 g). Removal of the solvent in vacuo yielded a yellowish oily residue (6.50 g), which was purified by flash chromatography (silica gel, 25×6 cm^2, eluant: ethyl acetate/cyclohexane, 2:1; R_f=0.52). Removal of the solvent in vacuo yielded alcohol (*RS*)-**10** (5.31 g, 84%) as a colorless oil. IR (neat): ν=3418, 2939, 1674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, J=7.1 Hz, 3H), 1.30–1.70 (m, 6H), 2.85 (t, 1H), 3.58 (dd, 1H), 3.75 (t, 1H), 3.90 (d, 1H), 4.07 (q, J=7.1 Hz, 2H), 4.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.59, 19.54, 25.15, 25.18, 39.95, 52.59, 61.14, 61.31, 156.09; MS (70 eV) *m/z* (%) 187 (0.1, M^+); HRMS calcd for $C_8H_{14}NO_2$ (156.20) (M^+-CH_2OH): 156.1025. Found: 156.1005.

4.1.2. (*RS*)-2-Formyl-piperidine-1-carboxylic acid ethyl ester (11). 2-Iodoxybenzoic acid[13] (IBX, 5.80 g, 20.7 mmol) was dissolved in anhydrous DMSO (40 mL, dissolution required routinely 10–15 min) at ambient temperature. To this solution was added a solution of **10** (2.97 g, 15.9 mmol) in anhydrous DMSO (15 mL) within a period of 10 min. After completion of addition, the solution was stirred for 3.5 h at room temperature (reaction was monitored by TLC: silica gel, eluant: ethyl acetate/cyclohexane, 1:1). The colorless suspension was subsequently poured into ice-water (150 mL), the resulting colorless precipitate was removed by filtration and washed with dichloromethane (2×100 mL). The filtrates were collected and the aqueous phase of the filtrates was separated and extracted with dichloromethane (4×75 mL). The combined organic extracts were thoroughly washed with saturated aqueous NaCl-solution (5×100 mL), dried with magnesium sulfate (20 g) and concentrated in vacuo, yielding a yellow oil (2.82 g, 96%). The crude product was purified by flash chromatography (silica gel, 26×4 cm^2, eluant: ethyl acetate/cyclohexane, 1:1; R_f=0.67). Removal of the solvent in vacuo yielded aldehyde (*RS*)-**11** (2.53 g, 86%) as a dense, colorless oil. IR (neat): ν=2943, 2884, 1750, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (m, 3H), 1.26–1.68 (m, 5H), 2.20 (m, 2H), 2.80–3.00 (m, 1H), 4.00–4.20 (m, 3H), 4.72 (m, 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.59, 20.85, 23.46, 24.74, 42.50, 60.97, 61.82, 156.0 and 157.0, 201.2; MS (70 eV) *m/z* (%) 185 (0.3, M^+); HRMS calcd for $C_8H_{14}NO_2$ (156.20) (M^+-CHO): 156.1025. Found: 156.1031.

4.1.3. *E*- and *Z*-(*RS*)-2-(2′-Methoxyethenyl)-piperidine-1-carboxylic acid ethyl ester (*E*-) and (*Z*)-(12). Potassium *tert*-butanolate (2.37 g, 21.1 mmol) was added over a period of 0.5 h via a side-arm addition funnel under argon atmosphere to a suspension of (methoxymethyl)-triphenylphosphonium chloride (7.23 g, 21.10 mmol) in anhydrous diethyl ether (60 mL) at −15°C. The reaction mixture was stirred at −15°C for 1 h, then a solution of aldehyde (*RS*)-**11** (1.95 g, 10.5 mmol) in anhydrous diethyl ether (20 mL) was added over a period of 20 min at this temperature. Stirring at room temperature was continued for 24 h. The reaction mixture was hydrolyzed with water (40 mL), and the organic and aqueous phases were separated. The aqueous phase was extracted with diethyl ether (2×70 mL) and petroleum ether (40–60°C, 4×70 mL), and the combined organic layers were dried with magnesium sulfate (15 g). Cooling of the organic phase to −30°C resulted in crystallization of triphenylphosphine oxide, which was separated by decantation. Concentration in vacuo yielded an orange oil (3.35 g), which was purified by flash chromatography (silica gel, 30×5.5 cm^2, eluant: diethyl ether/petroleum ether (40–60°C), 1:1; R_f=0.52 (*Z*-**12**), 0.62 (*E*-**12**). Removal of the solvent in vacuo yielded a separable mixture of *E*- and *Z*-**12** in the ratio 70:30 (1.95 g, 87%). IR (neat): ν=2937, 2863, 1694, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *E*-isomer, rotamers) δ: 1.25 (t, J=7.2 Hz, 3H), 1.40–1.85 (m, 6H), 2.88 (td, J=2.6, 12.9 Hz, 1H), 3.53 (s, 3H), 3.95 (m, 1H), 4.05 and 4.14 (q, J=7.2 Hz, 2H), 4.79 (t, J=6.8 Hz, 1H), 4.95 (dd, J=7.7 Hz, ^3J=12.6 Hz, 1H), 6.47 (d,

^3J=12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.65, 19.25, 25.49, 30.39, 39.52, 49.35, 56.00, 61.02, 100.33, 149.65, 155.62; ^{1}H NMR (400 MHz, $CDCl_3$, *Z*-isomer, rotamers) δ: 1.21 (t, *J*=7.0 Hz, 3H), 1.40–1.71 (m, 6H), 2.81 (td, *J*=2.8, 13.0 Hz, 1H), 3.55 (s, 3H), 3.95 (m, 1H), 4.08 and 4.10 (q, *J*=7.0 Hz, 2H), 4.50 (dt, ^3J=6.5 Hz, ^3J=7.2 Hz, 1H), 5.15 (m, 1H), 5.86 (dd, ^4J=1.5 Hz, ^3J=6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.76, 19.77, 25.65, 30.36, 39.89, 47.05, 59.86, 60.98, 104.42, 146.75, 155.76; MS (70 eV) *m/z* (%) 213 (25, M^+); HRMS calcd for $C_{11}H_{19}NO_3$ (213.28) (M^+): 213.1365. Found: 213.1363.

4.1.4. (*RS*)-2-(3′,6′-Bis-trifluoromethyl-pyridazine-4′-yl)-piperidine-1-carboxylic acid ethyl ester (13a). To a solution of **12** (702 mg, 3.29 mmol) in anhydrous toluene (10 mL) was added a solution of tetrazine **7a** (718 mg, 3.29 mmol) in anhydrous toluene (10 mL) at room temperature. The mixture was refluxed under an atmosphere of argon for 7 h until the deep orange color of **7a** disappeared. The solvent was evaporated in vacuo and the syrupy residue (1.42 g) purified by column chromatography (silica gel, 24×3 cm^2, eluant: ethyl acetate/cyclohexane, 1:2; R_f=0.49). Removal of the solvent in vacuo yielded pyridazine (*RS*)-**13a** (794 mg, 65%) as a colorless solid, mp 93–95°C. IR (neat): ν=3073, 2958, 2870, 1709, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (t, *J*=7.2 Hz, 3H), 1.65 (m, 1H), 1.83 (m, 2H), 2.09 (m, 1H), 3.61 (m, 1H), 3.95 (m, 1H), 4.01 (q, *J*=7.2 Hz, 2H), 5.18 (m, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.20, 19.03, 22.89, 30.68, 42.33, 52.67, 62.17, 121.01 (q, $^1J_{CF}$=276.7 Hz), 122.08, 122.10 (q, $^1J_{CF}$=275.2 Hz), 147.38, 149.80 (q, $^2J_{CF}$=33.8 Hz), 153.55 (q, $^2J_{CF}$=35.3 Hz), 156.38; MS (70 eV) *m/z* (%) 371 (1, M^+); HRMS calcd for $C_{14}H_{15}F_6N_3O_2$ (371.28) (M^+): 371.1038. Found: 371.1069.

4.1.5. (*RS*)-2-(3′,6′-Bis-methoxycarbonyl-pyridazine-4′-yl)-piperidine-1-carboxylic acid ethyl ester (13b). To a solution of **12** (619 mg, 2.90 mmol) in anhydrous toluene (10 mL) was added a solution of the tetrazine **7b** (575 mg, 2.90 mmol) in anhydrous toluene (10 mL) at room temperature. The mixture was refluxed under an atmosphere of argon for 5 h until the deep red color of **7b** disappeared. The solvent was evaporated in vacuo and the syrupy residue (1.19 g) purified by column chromatography (silica gel, 24×3 cm^2, eluant: ethyl acetate/cyclohexane, 2:1; R_f=0.37). Removal of the solvent in vacuo yielded pyridazine (*RS*)-**13b** (571 mg, 56%) as a colorless oil. IR (neat): ν=2954, 2870, 1731, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, *J*=7.1 Hz, 3H), 1.45 (m, 1H), 1.66 (m, 3H), 1.90 (m, 1H), 2.12 (m, 1H), 3.17 (td, *J*=5.4, 6.2 Hz, 1H), 4.04 (s, 3H), 4.07 (m, 1H), 4.10 (s, 3H), 4.12 (q, *J*=7.1 Hz, 2H), 5.60 (m, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.41, 19.08, 24.74, 28.57, 41.79, 51.90, 52.81, 53.46, 61.99, 125.79, 144.30, 151.71, 153.37, 156.15, 164.20, 165.25; MS (70 eV) *m/z* (%) 351 (48, M^+); HRMS calcd for $C_{16}H_{21}N_3O_6$ (351.36) (M^+): 351.1428. Found: 351.1430.

4.1.6. (*RS*)-2-(Pyridazine-4′-yl)-piperidine-1-carboxylic acid ethyl ester (13c). *E*- and *Z*-enol ether **12** (820 mg, 3.84 mmol) and tetrazine **7c** (315 mg, 3.84 mmol) were heated at 80°C without solvent for 12 h under an atmosphere of argon in a pressure bottle. The residue (1.15 g) was purified by column chromatography (silica gel, 24×3 cm^2, eluant: dichloromethane/methanol, 80:6; R_f=0.46). Evaporation of the solvent in vacuo yielded pyridazine **13c** (714 mg, 80%) as a colorless oil. IR (neat): ν=2940, 2855, 1694, 1583 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t overlapped by m, *J*=7.2 Hz, 4H), 1.50–1.75 (m, 3H), 2.09 (m, 1H), 2.37 (d, *J*=7.3 Hz, 1H), 2.74 (dt, *J*=3.5 Hz, 12.6, 1H), 4.20 (m, 3H), 5.52 (s, 1H), 7.32 (m, 1H), 9.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.64, 19.31, 24.96, 27.28, 40.64, 51.33, 62.05, 124.49, 140.23, 150.79, 151.07, 156.11; MS (70 eV) *m/z* (%) 235 (26, M^+); HRMS calcd for $C_{12}H_{17}N_3O_2$ (235.29) (M^+): 235.1309. Found: 235.1321.

4.1.7. (*RS*)-4-(Piperidin-2′-yl)-(3,6-bis-trifluoromethyl)-pyridazine (14a). To a solution of the carbamate **13a** (500 mg, 1.35 mmol) in trichloromethane (6 mL) under an argon atmosphere at room temperature was added within a period of 10 min trimethylsilyliodide (0.57 mL, 4.04 mmol). Subsequently the reaction mixture was heated at 75–80°C for 4 h. After cooling to ambient temperature anhydrous methanol (2.0 mL) was added over a period of 5 min and the mixture kept at room temperature for 30 min. The solvent was removed in vacuo and the residue resolved in (10 mL) of water. Concentrated aqueous ammonia was added until pH=10. The resulting mixture was extracted with trichloromethane (6×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$- and NaCl-solution (each 2×15 mL), dried with magnesium sulfate (5 g) and concentrated in vacuo, leaving a brown oil (363 mg, 90%). The crude product was purified by column chromatography (silica gel, 20×2 cm^2, eluant: dichloromethane/methanol, 97:3; R_f=0.60), yielding pyridazine **14a** (201 mg, 50%) as a colorless oil. IR (neat): ν=3322, 3080, 2946, 2850, 2790, 1424 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15–1.90 (m, 6H), 2.77 (dt, *J*=2.6, 11.6 Hz, 1H), 3.15 (m, 1H), 4.00 (d, ^3J=10.8 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.76, 25.00, 35.25, 47.10, 55.31, 121.04 (q, $^1J_{CF}$=275.2 Hz), 121.50 (q, $^1J_{CF}$=276.0 Hz), 124.62, 147.19, 150.20 (q, $^2J_{CF}$=34.6 Hz), 154.15 (q, $^2J_{CF}$=35.4 Hz); MS (70 eV) *m/z* (%) 299 (12, M^+); HRMS calcd for $C_{11}H_{11}F_6N_3$ (299.21) (M^+): 299.0826. Found: 299.0857.

4.1.8. 9-Oxo-6,7,8,8a-tetrahydro-1,2,8a-triaza-fluoren-3-carboxylic acid methyl ester (16b). Using the same procedure as described for **13a**, **16b** (15 mg, 15%) was obtained from **13b** (149 mg, 0.42 mmol). Purification was accomplished by column chromatography (silica gel, 20×2 cm^2, eluant: dichloromethane/methanol/conc. ammonia, 97:3:1; R_f=0.40). IR (neat): ν=3077, 2950, 2931, 2895, 1712, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.03 (m, 2H), 2.56 (m, 2H), 3.91 (m, 2H), 4.06 (s, 3H), 6.33 (t, *J*=6.9 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.85, 22.77, 38.88, 53.72, 113.97, 118.44, 130.43, 131.06, 151.33, 151.41, 160.68, 164.50; MS (70 eV) *m/z* (%) 245 (58, M^+); HRMS calcd for $C_{12}H_{11}N_3O_3$ (245.24) (M^+): 245.0800. Found: 245.0756.

4.1.9. (*RS*)-4-(Piperidin-2′-yl)-pyridazine (14c). Using the same procedure as described for **13a**, **14c** (139 mg, 50%) was obtained from **13c** (400 mg, 1.70 mmol). Purification

was accomplished by column chromatography (silica gel, 20×3 cm^2, eluant: dichloromethane/methanol/conc. ammonia, 80:12:1; R_f=0.49). IR (neat): ν=3407, 3270, 2925, 1690, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.34–2.05 (m, 7H), 2.75 (dt, J=2.8, 11.8 Hz, 1H), 3.17 (m, 1H), 3.63 (dd, J=2.5, 10.9 Hz, 1H), 7.46 (dd, ^3J=5.3 Hz, ^4J=2.0 Hz, 1H), 9.05 (dd, ^3J=4.8 Hz, ^4J=1.9 Hz, 1H), 9.14 (d, ^3J=5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.84, 25.41, 34.49, 47.09, 58.59, 123.80, 144.41, 151.02, 151.29; MS (70 eV) m/z (%) 163 (17, M^+); HRMS calcd for $C_9H_{13}N_3$ (163.22) (M^+): 163.1121. Found: 163.1109.

4.1.10. (*R*)-Piperidine-1,2-dicarboxylic acid-1-ethyl-2-methyl ester (*R*)-(18). A mixture of (*R*)-pipecolic acid **17**[24,25] (6.00 g, 46.0 mmol) and potassium carbonate (6.42 g, 46.0 mmol) in anhydrous methanol (50 mL) was stirred at room temperature for 5 min and subsequently cooled to 0°C. Ethylchloroformate (14.0 mL, 147 mmol) was added within a period of 20 min and the mixture was stirred for 3 h at 0°C. After stirring for additional 3 d at ambient temperature, the solid was filtered off and the solvent was evaporated in vacuo. The resulting residue was partitioned between trichloromethane (150 mL) and saturated aqueous NaCl-solution (80 mL). The organic layer was separated, washed with saturated aqueous NaCl-solution (80 mL) and dried with magnesium sulfate. After concentration in vacuo the residual oil was purified by distillation (boiling point 110°C/0.1 Torr), yielding 9.16 g (93%) enantiopure ester (*R*)-**18** as a colorless liquid. $[\alpha]_D^{20}$=+49.4° (c=0.45, trichloromethane); IR (neat): ν=3471, 2929, 2863, 1751, 1693, 1538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 1.22–1.75 (t overlapped by m, J=7.1 Hz, 8H), 2.22 (bs, 1H), 3.02 (m, 1H), 3.73 (s, 3H), 4.00 (m, 1H), 4.08 and 4.19 (q, J=7.1 Hz, 2H), 4.81 and 4.93 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.62, 20.79, 24.61 and 24.77, 26.78, 41.55 and 41.75, 52.14, 54.17 and 54.54, 61.63, 156.01, 172.26; MS (70 eV) m/z (%) 215 (2, M^+). Anal. calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.57; H, 7.89; N, 6.85.

(*S*)-**18** was prepared by the same procedure from (*S*)-pipecolic acid (*S*)-(**17**)[24,25] (7.50 g, 57.5 mmol). Yield: 11.1 g (90%), $[\alpha]_D^{20}$=−52.2° (c 0.36, trichloromethane).

4.1.11. (*R*)-Hydroxymethyl-piperidine-1-carboxylic acid ethyl ester (*R*)-(10). To a solution of (*R*)-**18** (10.0 g, 46.5 mmol) in anhydrous toluene (100 mL) at −40°C was slowly added a solution of DIBAL-H (17.0 mL, 100 mmol) in anhydrous toluene (40 mL). The reaction mixture was allowed to come to ambient temperature gradually with stirring for additional 12 h. Subsequently, the mixture was hydrolyzed with diluted hydrochloric acid at −15°C until gas evolution ceased. After separation of the organic layer the aqueous phase was extracted with toluene (4×80 mL). The combined organic layers were dried with magnesium sulfate (30 g), evaporated in vacuo and purified by flash chromatography (silica gel, 30×6 cm^2, eluant: ethyl acetate/*n*-hexane, 2:1; R_f=0.52), yielding (*R*)-**10** (6.37 g, 73%) as a colorless liquid. $[\alpha]_D^{20}$=+36.5° (c 0.41, trichloromethane).

(*S*)-**10** was prepared by the same procedure from ester (*S*)-**18** (8.05 g, 37.4 mmol). Yield: 6.15 g (88%), $[\alpha]_D^{20}$=−36.6° (c 0.40, trichloromethane). Further analytical data of the enantiomers correspond to those of the racemate.

4.1.12. (*R*)-2-Formyl-piperidine-1-carboxylic acid ethyl ester (*R*)-(11). To a stirred solution of oxalyl chloride (3.70 mL, 43.0 mmol) in anhydrous dichloromethane (40 mL) was added dropwise at −78°C a solution of anhydrous DMSO (5.10 mL, 70.0 mmol) in anhydrous dichloromethane (10 mL). After 5 min a solution of alcohol (*R*)-**10** (2.78 g, 14.8 mmol) in anhydrous dichloromethane (15 mL) was added dropwise, after 30 min triethylamine (18 mL, 129 mmol) and stirring continued until room temperature was reached. Subsequently, the mixture was poured into water (80 mL) and the organic layer separated. The aqueous layer was extracted with dichloromethane (4×50 mL) and the combined extracts washed sequentially with saturated aqueous NaCl-solution (50 mL), saturated aqueous $NaHCO_3$-solution (50 mL) and water (40 mL) and dried with magnesium sulfate (15 g). Removal of solvent in vacuo yielded an oily residue which was purified by flash chromatography (silica gel, 26×4 cm^2, eluant: ethyl acetate/cyclohexane, 1:1; R_f=0.67). Removal of the solvent in vacuo yielded aldehyde *(R)*-**11** (2.63 g, 96%) as a dense, colorless oil. $[\alpha]_D^{20}$=+29.6° (c 0.24, trichloromethane).

(*S*)-**11** was prepared by the same procedure from alcohol (*S*)-**10** (5.91 g, 31.5 mmol). Yield: 4.88 g (83%), $[\alpha]_D^{20}$=−30.0° (c 0.26, trichloromethane). Further analytical data of the enantiomers correspond to those of the racemate.

4.1.13. (*R*)-2-(2′Methoxyethenyl)-piperidine-1-carboxylic acid ethyl ester (*R*)-(12). Using the same procedure as described for aldehyde (*RS*)-**11**, enol ether (*R*)-**12** (3.11 g, 82%) was obtained as a mixture of *E*- and *Z*-isomers with the ratio 68:32 from (*R*)-**11** (3.29 g, 17.8 mmol). $[\alpha]_D^{20}$=+29.3° (c 0.28, trichloromethane).

(*S*)-**12** was prepared by the same procedure from aldehyde (*S*)-**11** (4.70 g, 25.4 mmol). Yield: 4.82 g (89%), $[\alpha]_D^{20}$=−30.1° (c 0.27, trichloromethane). Further analytical data of the enantiomers correspond to those of the racemate.

4.1.14. (*R*)-2-(3′,6′-Bis-trifluoromethyl-pyridazine-4′-yl)-piperidine-1-carboxylic acid ethyl ester (*R*)-(13a). Using the same cycloaddition procedure as described for enol ether (*RS*)-**12** and tetrazine **7a**, (*R*)-**13a** (705 mg, 83%) was obtained from (*R*)-**12** (500 mg, 2.34 mmol) and tetrazine **7a** (610 mg, 2.80 mmol). $[\alpha]_D^{20}$=+18.6° (c 0.42, trichloromethane). (*S*)-**13a** was prepared by the same procedure from enol ether (*S*)-**12** (500 mg, 2.34 mmol) and tetrazine **7a** (612 mg, 2.80 mmol). Yield: 601 mg (69%), $[\alpha]_D^{20}$=−18.3° (c 0.44, trichloromethane). Further analytical data of the enantiomers correspond to those of the racemate.

4.1.15. (*R*)-2-(Pyridazine-4′-yl)-piperidine-1-carboxylic acid ethyl ester (*R*)-(13c). Using the procedure as described for enol ether (*RS*)-**12** and tetrazine **7c**, (*R*)-**13c** (300 mg, 54%) was obtained from (*R*)-**12** (500 mg, 2.34 mmol) and tetrazine **7c** (222 mg, 2.71 mmol). $[\alpha]_D^{20}$=+28.3° (c 0.47, trichloromethane). *(S)*-**13c** was prepared by the same

procedure from enol ether *(S)*-**12** (502 mg, 2.34 mmol) and tetrazine **7a** (222 mg, 2.71 mmol). Yield: 350 mg (64%), $[\alpha]_D^{20}=-28.6°$ (*c* 0.44, trichloromethane). Further analytical data of the enantiomers correspond to those of the racemate.

4.1.16. (*S*)-2-Formyl-piperidine-1-carboxylic acid-*tert*-butyl ester (*S*-21). Using the same procedure as described for alcohol (*RS*)-**10**, aldehyde (*S*)-**21** (1.91 g, 87%) was obtained within 4.5 h at room temperature from (*S*)-**20** (2.22 g, 10.3 mmol) and 2-Iodoxybenzoic acid (4.52 g, 16.1 mmol). Purification was accomplished by flash-chromatography (silica gel, 25×3 cm^2, eluant: ethylacetate/cyclohexane, 1:1; R_f=0.69). $[\alpha]_D^{20}=-77.9°$ (*c*=1.49, trichloromethane), literature:[12] $[\alpha]_D^{20}=-77.4°$ (*c*=1.4, trichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ: 1.20 (m, 1H), 1.40 (bs, 9H, OC(CH_3)$_3$), 1.52 (m, 1H), 1.60–1.65 (m, 3H), 2.11 (m, 1H), 2.79 and 2.90 (bs, 1H), 3.83 and 3.97 (bs, 1H), 4.45 and 4.55 (bs, 1H), 9.52 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$, rotamers): δ: 20.99, 23.68, 24.80, 28.38 (q, OC(CH_3)$_3$), 41.87 and 43.02, 60.60 and 61.53, 80.46 (s, O*C*(CH_3)$_3$), 155.65 and 155.73 (s, Boc-C=O), 201.39 (d, CHO); MS (70 eV) *m/z* (%) 213 (0.1, M^+), 184 (52, M^+-CHO).

4.1.17. *E*- and *Z*-(*S*)-2-(2′-Methoxyethenyl)-piperidine-1-carboxylic acid-*tert*-butyl ester *E*- and *Z*-(*S*)-(22). Using the same procedure as described for aldehyde (*RS*)-**11**, 1.70 g (83%) enol ether (*S*)-**22** was obtained as an inseparable mixture of *E*- and *Z*-isomers with the ratio 68:32 from 1.81 g (8.49 mmol) (*S*)-**21**, 6.54 g (19.1 mmol) (methoxymethyl)-triphenyl-phosphonium-chloride and 2.14 g (19.1 mmol) potassium *tert*-butanolate. Purification was accomplished by flash-chromatography (silica gel, 27×5.5 cm^2, eluant: ethylacetate/cyclohexane, 1:5; R_f=0.53, 0.60). $[\alpha]_D^{20}=-46.3°$ (*c* 1.17, trichloromethane); IR (neat): ν=2937, 1696, 1650, 1454, 1272, 1208, 1139 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, *E*-isomer) δ: 1.25 (m, 1H), 1.31 (s, 9H, OC(CH_3)$_3$), 1.40–1.44 (m, 4H), 1.56 (m, 1H), 2.68 (td, *J*=2.7 Hz, *J*=13.1 Hz, 1H), 3.38 (s, 3H, OCH_3), 3.76 (m, 1H), 4.60 (m, 1H), 4.77 (dd, $^3J_{H\text{-}1',\ H\text{-}2'}$=12.6 Hz, $^3J_{H\text{-}1',\ H\text{-}2}$=7.6 Hz, 1H, 1′-H), 6.29 (d, $^3J_{H\text{-}1',\ H\text{-}2'}$=12.6 Hz, 1H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.28, 25.51, 28.44 (q, OC(CH_3)$_3$), 30.43, 39.35, 49.26, 55.95 (q, OCH_3), 79.11 (s, O*C*(CH_3)$_3$), 100.55 (d, C-1′), 149.38 (d, C-2′), 154.92 (s, Boc-C=O); ^{1}H NMR (500 MHz, $CDCl_3$, *Z*-isomer) δ: 1.25 (m, 1H), 1.30 (s, 9H, OC(CH_3)$_3$), 1.40–1.44 (m, 4H), 1.56 (m, 1H), 2.64 (td, *J*=2.5, 12.9 Hz; 1H), 3.44 (s, 3H, OCH_3), 3.76 (m, 1H), 4.39 (dd, $^3J_{H\text{-}1',\ H\text{-}2'}$=6.5 Hz, $^3J_{H\text{-}1',\ H\text{-}2}$=6.8 Hz; 1H, 1′-H), 5.00 (m, 1H, 2-H), 5.73 (dd, $^3J_{H\text{-}1',\ H\text{-}2'}$=6.5 Hz, $^4J_{H\text{-}2',\ H\text{-}2}$=1.5 Hz, 1H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.69, 25.57, 28.40 (q, OC(CH_3)$_3$), 30.30, 39.55, 46.83, 59.65 (q, OCH_3), 78.79 (s, O*C*(CH_3)$_3$), 104.50 (d, C-1′), 146.39 (d, C-2′), 154.92 (s, Boc-C=O); MS (70 eV) *m/z* (%) 241 (6, M^+), 185 (81, $M^+-C_4H_8$); HRMS calcd for $C_{13}H_{23}NO_3$ (241.33) (M^+), 241.1678. Found: 241.1673.

4.1.18. (*S*)-2-(3′,6′-Bis-trifluoromethyl-pyridazine-4′-yl)-piperidine-1-carboxylic acid-*tert*-butyl ester (*S*)-(23a). To a solution of *S*-enol ether (*S*)-**22** (880 mg, 3.65 mmol) in anhydrous toluene (12 mL) was added a solution of tetrazine **7a** (795 mg, 3.65 mmol) in anhydrous toluene (17 mL) at room temperature. The mixture was refluxed under an atmosphere of argon for 8 h before a second portion of **7a** (300 mg, 1.38 mmol) was added to the reaction mixture at room temperature. Stirring at reflux was continued for 16 h (reaction was monitored by TLC: silica gel, eluant: ethylacetate/cyclohexane=1:2). The solvent was evaporated in vacuo and the oily residue (1.47 g) purified by flash-chromatography (silica gel, 30×3 cm^2, eluant: ethylacetate/cyclohexane, 1:3; R_f=0.61). Removal of the solvent in vacuo yielded pyridazine (*S*)-**23a** (1.05 g, 72%) as a colorless solid, mp 50–53°C. $[\alpha]_D^{20}=-45.3°$ (*c* 1.23, trichloromethane); IR (neat): ν=3058, 2945, 1704, 1654, 1401, 1167 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.18 (s, 9H, OC(CH_3)$_3$), 1.56–1.65 (m, 3H), 1.77–1.83 (m, 2H), 2.07 (m, 1H), 3.57 (m, 1H), 3.81 (m, 1H), 5.07 (m, 1H), 7.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.22, 22.94, 27.96 (q, OC(CH_3)$_3$), 30.90, 42.20, 52.76, 81.53 (s, O*C*(CH_3)$_3$), 120.46 (q, $^1J_{CF}$=275.1 Hz, CF_3), 121.91 (q, $^1J_{CF}$=273.8 Hz, CF_3), 122.02, 147.97, 149.75 (q, $^2J_{CF}$=33.4 Hz, C-3 or C-6), 153.51 (q, $^2J_{CF}$=34.3 Hz, C-3 or C-6), 155.28 (s, Boc-C=O); MS (70 eV) *m/z* (%)=399 (0.8, M^+), 344 (22, $M^+-C_4H_7$); HRMS calcd for $C_{16}H_{19}N_3O_2F_6$ (399.34) (M^+): 399.1381. Found: 399.1375.

4.1.19. (*S*)-2-(3′,6′-Bis-methoxycarbonyl-pyridazine-4′-yl)-piperidine-1-carboxylic acid-*tert*-butyl ester (*S*)-(23b). To a suspension of tetrazine **7b** (738 mg, 3.72 mmol) in anhydrous toluene (15 mL) was added a solution of *S*-enol ether (*S*)-**22** (691 mg, 2.86 mmol) in anhydrous toluene (10 mL) at room temperature. The mixture was refluxed under an atmosphere of argon for 28 h (reaction was monitored by TLC: silica gel, eluant: ethylacetate/cyclohexane=1:3). The solvent was removed in vacuo and the oily residue (1.53 g) purified by flash-chromatography (silica gel, 31×4 cm^2, eluant: ethylacetate/cyclohexane, 1:1; R_f=0.48). Removal of the solvent in vacuo yielded pyridazine (*S*)-**23b** (880 mg, 81%) as colorless oil. $[\alpha]_D^{20}=-51.0°$ (*c* 1.11, trichloromethane); IR (neat): ν=3342, 2870, 1726, 1692, 1258 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (s, 9H, OC(CH_3)$_3$), 1.40 (m, 1H), 1.58–1.71 (m, 3H), 1.80–1.87 (m, 1H), 2.04 (m, 1H), 3.14 (td, *J*=10.9 Hz, *J*=2.7 Hz, 1H), 3.96 (m, 1H), 4.02 (s, 3H, CO_2CH_3), 4.08 (s, 3H, CO_2CH_3), 5.51 (t, *J*=5.6 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.18, 23.51, 28.22 (q, OC(CH_3)$_3$), 28.74, 41.64, 51.87, 53.48 (q, CO_2CH_3), 53.70 (q, CO_2CH_3), 80.91 (s, O*C*(CH_3)$_3$), 125.72, 151.61, 153.20, 153.68, 155.01 (s, Boc-C=O), 164.04 (s, CO_2CH_3), 165.00 (s, CO_2CH_3); MS (70 eV) *m/z* (%)=379 (0.4, M^+), 279 ($M^+-C_4H_8-CO_2$); HRMS calcd for $C_{18}H_{25}N_3O_6$ (379.41) (M^+): 379.1743. Found: 379.1754.

4.1.20. (*S*)-2-(Pyridazin-4′-yl)-piperidine-1-carboxylic acid-*tert*-butyl ester (*S*)-(23c). To a solution of *S*-enol ether (*S*)-**22** (757 mg, 3.14 mmol) in anhydrous trichloromethane (10 mL) was added a solution of tetrazine **7c** (947 mg, 11.5 mmol) in anhydrous trichloromethane at room temperature. The deep red solution was refluxed under an atmosphere of argon for 30 h (reaction was monitored by TLC: silica gel, eluant: ethylacetate/cyclohexane=1:3). After removal of solvent in vacuo the sirupy residue (1.03 g) was purified by flash-chromatography (silica gel, 24.5×3 cm^2, eluant: ethylacetate; R_f=0.41)

yielding pyridazine (*S*)-**23c** (785 mg, 95%) as colorless oil. $[\alpha]_D^{20}=-103.6°$ (*c* 1.00, methanol); IR (neat): ν=3054, 2866, 1698, 1273, 1034, 982 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.19 (m, 1H), 1.40 (s, 9H, $OC(CH_3)_3$), 1.42–1.58 (m, 2H), 1.64 (m, 1H), 1.91 (m, 1H), 2.19 (bd, *J*=14.5 Hz, 1H), 2.63 (td, *J*=13.1, 3.5 Hz, 1H), 4.03 (bd, *J*=14.1 Hz, 1H), 5.38 (m, 1H), 7.26 (m, 1H), 9.03 (m, 1H), 9.07 (dd, *J*=1.2, 5.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.22, 24.85, 27.28, 28.26 (q, $OC(CH_3)_3$), 40.46, 51.12, 80.54 (s, $OC(CH_3)_3$), 124.46, 140.73, 150.74, 150.92, 155.15 (s, Boc-C=O); MS (70 eV) *m/z* (%)=264 (4, M^++1), 263 (23, M^+), 208 (19, $M^+-C_4H_7$); HRMS calcd. for $C_{14}H_{21}N_3O_2$ (263.34) (M^+): 263.1634. Found: 263.1638.

4.1.21. (*S*)-4-(Piperidin-2′-yl)-(3,6-bis-trifluoromethyl)-pyridazine (*S*)-(14a). To a solution of the *N*-Boc-protected pyridazine (*S*)-**23a** (300 mg, 0.75 mmol) in anhydrous dichloromethane (18 mL) under an argon atmosphere at −15°C was added within a period of 10 min freshly distilled trifluoroacetic acid (2.00 mL, 26.0 mmol). The yellow solution was stirred at −15°C for 30 min. The mixture was allowed to come to ambient temperature gradually with stirring for additional 2.25 h. After addition of a second portion of trifluoroacetic acid (1.00 mL, 13.0 mmol) at 0°C within 5 min stirring at room temperature was continued for 2.25 h (reaction was monitored by TLC: silica gel, eluant: ethylacetate/cyclohexane=1:5). Concentration of the mixture in vacuo (30°C) was followed by partitioning the residue between dichloromethane (50 mL) and ice-cooled, saturated aqueous K_2CO_3-solution (30 mL). The organic phase was separated and washed with ice-cooled saturated aqueous K_2CO_3-solution (3×20 mL), the combined aqueous phase was extracted with dichloromethane (5×30 mL). The combined organic phase was dried with sodium sulfate (30 g). Removal of the solvent in vacuo yielded a yellowish oil (226 mg), which was purified by flash-chromatography (silica gel, 14.5×2 cm^2, eluant: ethylacetate/cyclohexane, 1:1; R_f=0.70). Removal of eluant in vacuo yielded pyridazine (*S*)-**14a** (189 mg, 84%) as a colorless oil. $[\alpha]_D^{20}=-71.79°$ (*c* 1.04, trichloromethane); further analytical data of (*S*)-**14a** correspond to those of the racemate (*RS*)-**14a**.

4.1.22. 9-Oxo-5,5a,6,7,8,8a-hexahydro-1,2,8a-triaza-fluoren-3-carboxylic acid methyl ester (*S*)-(25b). To a solution of *N*-Boc-protected pyridazine (*S*)-**23b** (344 mg, 0.91 mmol) in anhydrous dichloromethane (20 mL) under an argon atmosphere at −15°C was added within a period of 10 min freshly distilled trifluoroacetic acid (2.41 mL, 31.3 mmol). The yellow solution was stirred at −15°C for 50 min. The mixture was allowed to come to ambient temperature gradually with stirring for additional 3.5 h. After addition of a second portion of trifluoroacetic acid (1.20 mL, 15.6 mmol) at 0°C within 5 min stirring at room temperature was continued for 1.5 h (reaction was monitored by TLC: silica gel, eluant: ethylacetate/cyclohexane=2:1). Concentration of the mixture in vacuo (30°C) was followed by partitioning the residue between dichloromethane (50 mL) and ice-cooled, saturated aqueous K_2CO_3-solution (40 mL). The organic phase was separated and washed with ice-cooled, saturated aqueous K_2CO_3-solution (3×30 mL), the combined aqueous phase was extracted with dichloromethane (5×40 mL). The combined organic phase was dried with sodium sulfate (30 g). Removal of the solvent in vacuo yielded a yellowish oil (202 mg), which was purified by flash-chromatography (silica gel, 14.5×2 cm^2, eluant: trichloromethane/methanol, 7:1; R_f=0.65). Evaporation of the eluant in vacuo yielded lactame (*S*)-**25b** (173 mg, 77%) as a yellowish solid with mp 142–145°C. $[\alpha]_D^{20}=-68.9°$ (*c* 1.12, trichloromethane); IR (neat): ν=3057, 1751, 1700, 1653, 1251, 1215, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.15 (qd, *J*=3.5, 14.3 Hz, 1H), 1.35–1.42 (m, 1H), 1.63–1.72 (m, 1H), 1.85 (m, 1H), 2.00–2.08 (m, 1H), 2.41 (dd, *J*=3.0, 12.8 Hz, 1H), 3.00 (td, *J*=3.5, 11.3 Hz, 1H), 4.05 (s, 3H, OCH_3), 4.41 (dd, *J*=3.8, 12.3 Hz, 1H), 4.55 (dd, *J*=13.5, 5.0 Hz, 1H), 8.24 (d, *J*=0.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.14, 24.57, 30.48, 40.16, 53.54, 56.65 (q, CO_2CH_3), 121.75, 142.37, 151.00, 154.84, 160.95 (s, CO_2CH_3), 164.20 (s, N–C=O); MS (70 eV) *m/z* (%)=248 (8, M^++1), 247 (48, M^+); HRMS calcd for $C_{12}H_{13}N_3O_3$ (247.25) (M^+): 247.0957. Found: 247.0962.

4.1.23. (*S*)-4-(Piperidin-2′-yl)-pyridazine (*S*)-(14c). To a solution of *N*-Boc-protected pyridazine (*S*)-**23c** (733 mg, 2.78 mmol) in anhydrous dichloromethane (25 mL) under an argon atmosphere at −15°C was added within a period of 15 min freshly distilled trifluoroacetic acid (7.36 mL, 95.6 mmol). After stirring at −15°C for 50 min the yellowish reaction mixture was allowed to come to room temperature gradually with stirring for additional 2.5 h (reaction was monitored by TLC: silica gel, eluant: ethylacetate). Concentration of the mixture in vacuo (30°C) was followed by partitioning the residue between dichloromethane (50 mL) and ice-cooled, saturated aqueous K_2CO_3-solution (50 mL). The organic phase was separated and washed with ice-cooled, saturated aqueous K_2CO_3-solution (3×70 mL), the combined aqueous phase was extracted with dichloromethane (6×50 mL). The combined organic phase was dried with sodium sulfate (35 g). Removal of the solvent in vacuo yielded a brown oil (496 mg), which was purified by flash-chromatography (silica gel, 21×3.5 cm^2, eluant: trichloromethane/methanol, 6:1; R_f=0.43). Evaporation of the eluant yielded pyridazine (*S*)-**14c** (382 mg, 84%) as a yellowish oil which solidifies upon storing at −10°C. $[\alpha]_D^{20}=-84.0°$ (*c* 1.05, trichloromethane); further analytical data of (*S*)-**14c** correspond to those of the racemate (*RS*)-**14c**.

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References

1. (a) Späth, E.; Kuffner, F. *Fortsch. Chem. Org. Naturstoffe* **1939** (II), 248–300. (b) Marion, L. *The Alkaloids*; Manske, R. H. F., Homes, H. L., Eds.; Academic: New York, 1950; Vol. 1, pp 228–253. (c) Eiden, F. *Pharm. Unserer Zeit* **1976**, *5*, 1–18.

2. (a) Ehrenstein, M. *Arch. Pharm.* **1931**, *269*, 627–635. (b) Späth, E.; Kesztler, F. *Chem. Ber.* **1937**, *70*, 704–709.
3. Panter, K. E.; James, L. F.; Gardner, D. R. *J. Nat. Toxins* **1999**, *8*, 117–134.
4. For asymmetric syntheses of (*S*)-anabasine see: (a) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4262–4263. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749–1760. (c) Felpin, F.-X.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Synlett* **2000**, 1646–1648.
5. For conformationally restricted anabasine analogues see: (a) Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291–2293. (b) Sarkar, T. K.; Basak, S.; Ghosh, S. K. *Tetrahedron Lett.* **2000**, *41*, 759–762. (c) Vernier, J. M.; Holsenbach, H.; Cosford, N. D. P.; Whitten, C. J. P.; Menzaghi, F.; Reid, R.; Rao, T. S.; Sacaan, A. J.; Lloyd, G. K.; Suto, C. M.; Chavez-Noriéga, L. F.; Washburn, M. S.; Urrutia, A.; McDonald, I. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2173–2178. (d) Klimek, C.; Seitz, G. *Sci. Pharm.* **1996**, *64*, 497–502.
6. For syntheses of anabasine see: (a) Alberici, G. F.; Adam, G.; Plat, M. M. *Tetrahedron Lett.* **1983**, *24*, 1937–1940. (b) Mundy, B. P.; Larsen, B. R. *Synth. Commun.* **1972**, *2*, 197–200. (c) Späth, E.; Mamoli, L. *Chem. Ber.* **1936**, *69*, 1082–1087. (d) Leete, E. *J. Org. Chem.* **1979**, *44*, 165–168. (e) Zoltewics, J. A.; Cruski, Jr., M. P. *Org. Prep. Proced. Int.* **1995**, *27*, 510–513.
7. (a) Kem, W. R. *Invertebr. Neurosci.* **1997**, *3*, 251–259. (b) Kem, W. R.; Mahnir, V. M.; Papke, R. L.; Lingle, C. J. *J. Pharmcol. Exp. Ther.* **1997**, *283*, 979–992. (c) Segelken, R. *Cornell Chron.* **1998**, *29*, 1. (d) Attygalle, A. B.; Kern, F.; Huang, Q.; Meinwald, J. *Naturwissenschaften* **1998**, *85*, 38–41.
8. (a) Lloyd, G. K.; Williams, M. J. *Pharmacol. Exp. Ther.* **2000**, *292*, 461–467 and the references cited therein. (b) Schmitt, J. D., Bencherif, M., Eds.; *Annual Reports in Medicinal Chemistry*; Academic: New York, 2000; Vol. 35, pp 41–52. (c) Gispen, W. H., Bruinwels, J., Nijkamp, P., Versteeg, D. H. G., Eds. *Eur. J. Pharmacol.* **2000**, *393* (1–3), 1–340. (d) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169–4194. (e) Papke, R. L.; Meyer, E.; Nutter, T.; Uteshev, V. V. *Eur. J. Pharmacol.* **2000**, *393*, 179–195. (f) Lin, N.-H.; Meyer, M. D. *Exp. Opin. Ther. Pat.* **1998**, *8*, 991–1015.
9. Decker, M. W.; Brioni, J. C.; Bannon, A. W. *Life Sci.* **1995**, *56*, 545–570.
10. (a) Sauer, J. 1,2,4,5-Tetrazines. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1997; Vol. 6, pp 901–957. (b) Boger, D. L.; Weinreb, S. M. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic: New York, 1987; pp 335–357. (c) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885–2896. (d) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342–4346.
11. (a) Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040–6043. (b) Iwanowitz, E. J.; Poss, M. A.; Lin, J. *Synth. Commun.* **1993**, *23*, 1443–1445.
12. Sanchez-Sancho, F.; Herradon, B. *Tetrahedron: Asymmetry* **1998**, *9*, 1951–1965.
13. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
14. Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 622–625.
15. Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597.
16. Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S.; Vega, J. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2525–2529.
17. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
18. Clive, L. J.; Bergstra, R. J. *J. Org. Chem.* **1990**, *55*, 1786–1792.
19. Novák, J.; Salemink, C. A. *Tetrahedron Lett.* **1981**, *22*, 1063–1064.
20. Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404–1409.
21. Che, D.; Siegl, J.; Seitz, G. *Tetrahedron: Asymmetry* **1999**, *10*, 573–585.
22. Che, D.; Wegge, T.; Stubbs, M. T.; Seitz, G.; Meier, H.; Methfessel, C. *J. Med. Chem.* **2001**, *44*, 47–57.
23. Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495–496.
24. Mende, F. *Chem. Ber.* **1896**, *29*, 2887–2889.
25. Shiraiwa, T.; Shinjo, K.; Kurokawa, H. *Bull. Chem. Soc. Jpn* **1991**, *64*, 3251–3255.
26. Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149–153.
27. Hassner, A.; Maurya, R. *J. Org. Chem.* **1991**, *56*, 2775–2781.
28. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
29. Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
30. Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, *54*, 5826–5828.
31. Schulz, K. Dissertation, Marburg 2000.
32. Kociensky, P. J. *Protecting Groups*; Georg Thieme: Stuttgart, 1994.
33. Richter, M. Dissertation, Marburg 1992.
34. Lachmann, J. Dissertation, Marburg 2000.
35. Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543–5546.
36. Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035–2038.
37. Garvey, D. S.; Wasicak, J. T.; Chung, J. Y.-L.; Shue, Y.-K. *J. Med. Chem.* **1992**, *35*, 1550–1557.
38. Aceto, M. D.; Martin, B. R.; Uwaydah, J. M.; May, E. L. *J. Med. Chem.* **1979**, *22*, 174–177.
39. Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J. *J. Org. Chem.* **2001**, *66*, 6305–6312.
40. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276.
41. Seifert, S. Personal communication.
42. von Hagel, P. Dissertation, Marburg 1999.