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Synthesis of chiral 2-(2′-pyrrolidinyl)pyridines from (*S*)- and (*R*)-proline: potential ligands of the neuronal nicotinic acetylcholine receptors

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Abstract

A new strategy for a straightforward synthesis of novel optically active nicotine analogues starting from (*S*)- and (*R*)-proline is reported utilizing as the key steps the inverse electron demand Diels–Alder reaction of, hitherto unknown, chiral 5-(2′-pyrrolidinyl)-1,2,4-triazines (*S*)- and (*R*)-**16**. These serve as appropriate precursors for the preparation of different, highly enantiomerically enriched 2-(2′-pyrrolidinyl)pyridines, modifications of natural (−)-nornicotine and (−)-nicotine and potential ligands of the neuronal nicotinic acetylcholine receptors. The multistep syntheses proceed under mild conditions, with good overall yields and with stereochemical integrity of the original stereogenic centers.

1. Introduction

Recent observation of beneficial effects following administration of (−)-nicotine **1** to humans provided evidence that drugs acting at nicotinic acetylcholine receptors (nAChRs) may have therapeutic utility in the treatment of a variety of central nervous system (CNS) disorders ranging from Alzheimer's and Parkinson's disease to Tourette's syndrome and schizophrenia.[1,2] Moreover, when (−)-epibatidine **2**,[3] an alkaloid from the skin of a South American frog, was recently shown to exhibit potent nAChR-mediated analgesic properties in rodents, these findings prompted a worldwide search for agents with cognition-enhancing properties on the one hand and antinociceptive qualities on the other.[1–4] However, this potential therapeutic usefulness of (−)-nicotine **1** and (−)-epibatidine **2** — both prototypic agonistic ligands at the nAChRs — is severely limited by side effects that are the results of activation of both cholinergic and noncholinergic pathways in the central and peripheral nervous system.

Thus, in order to optimize the potential of nAChRs as therapeutic targets, an important objective of pharmaceutical research would be the design and synthesis of novel nAChR-ligands that achieve

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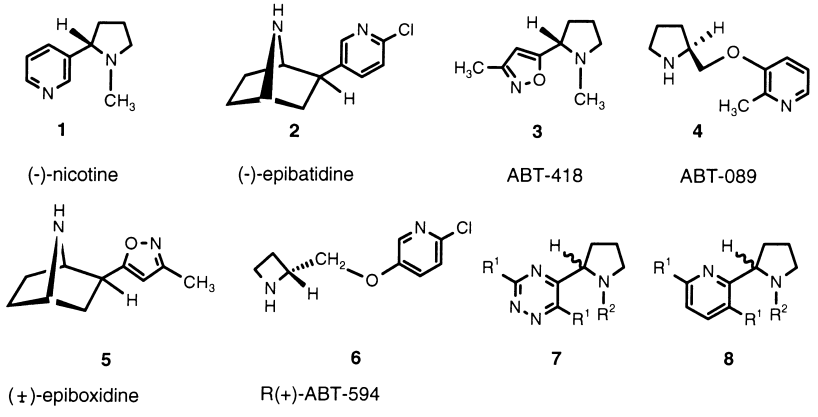
selectivity for central versus ganglionic nAChRs possibly with improved safety and pharmacokinetic and pharmacodynamic profiles over (−)-nicotine **1** and (−)-epibatidine **2**.

Recent advances in the search for novel nAChR ligands include subtype-selective nAChR ligands for the treatment of specific CNS disorders with reduced side effect liabilities, such as ABT-418 **3**[5] and ABT-089 **4**.[1a] Both these novel ligands exhibit cognition-enhancing properties and anxiolytic-like activities in animal models combined with an improved safety profile compared to that of (−)-nicotine **1** (Scheme 1). In addition, several nicotine- and epibatidine-like nAChR ligands have been reported as disclosing remarkable analgesic activity in the hot plate assay. For example, (±)-epiboxidine **5**[6] proved to be a potent central nAChR agonist in which methylisoxazole has been incorporated as a replacement for the chloropyridyl ring of (±)-epibatidine *rac*-**2**. It is approximately 10-fold less potent than (−)-epibatidine **2** as an analgesic agent but at least 10-fold less lethal in mice. A notable new member of a previously reported series of 3-pyridyl ether compounds, ABT-594 **6**[1c] was disclosed as a novel nAChR ligand which exerts potent analgesic action in models of nociceptive and persistent pain and to possess substantially reduced activity at peripheral nAChRs compared to (±)-epibatidine *rac*-**2**. Thus, ABT-594 **6** represents an attractive candidate for further evaluation as a non-opioid analgesic agent with a novel mechanism of action for management of pain states.



Scheme 1.

These new findings have generated our interest in the preparation of novel epibatidine and nicotine analogues, which may be subtype-selective nAChR ligands with potent analgesic and/or cognition-enhancing activities.

The structural requirements for the binding of (−)-nicotine **1** to central nicotine receptors remain largely uninvestigated.[7,8] Nevertheless, several pyridine- and pyrrolidine-modified analogues of nicotine have been proved to be potent ligands at the nAChRs.[1]

Since (−)-ABT-418 **3**, in which the pyridinyl moiety of (−)-nicotine **1** was replaced by a bioisosteric methylisoxazolyl ring, has been reported to be a potent nAChR ligand with cognitive enhancing, anxiolytic and antinociceptive effects in mice, we started to design and synthesize a new series of enantiomerically pure *pyridine-modified* analogues of (−)-nicotine **1**. It was anticipated that bioisosteric replacement of the pyridine moiety by other 6-membered heteroaromatic systems with one, two or three nitrogen atoms might provide compounds with subtype-selectivity at the nAChRs and perhaps better ratios of pharmacological to toxicological activity.

Herein we wish to report a new strategy for the synthesis of such novel optically active nicotine analogues utilizing as the key steps the inverse electron demand Diels–Alder reaction[9,10] with the goal to, firstly, gain hitherto unknown, chiral pyrrolidinyltriazines of type **7**. Secondly, because these are

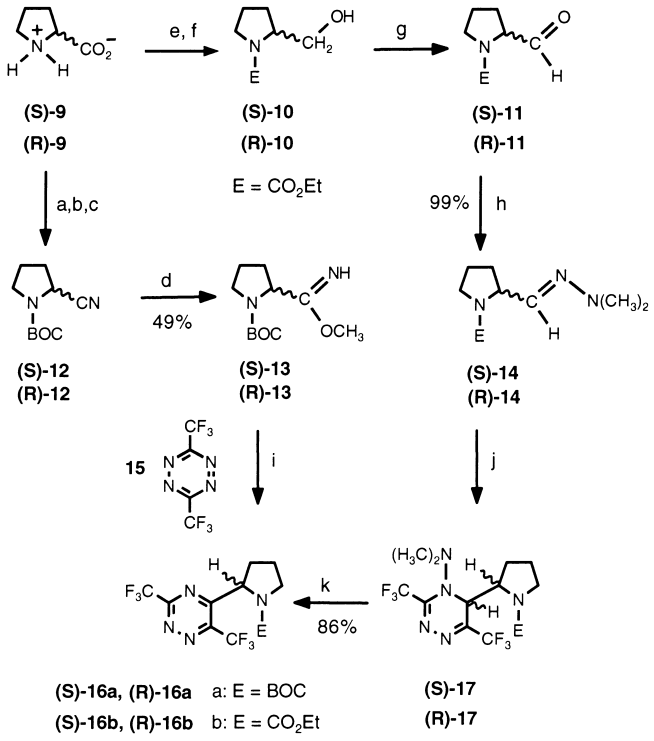
characterized by a highly reactive diazadiene moiety they should readily react with several electron-rich dienophiles to yield novel enantiomerically pure 2-(2′-pyrrolidinyl)pyridines of type **8**.

2. Results and discussion

A particularly attractive feature for the asymmetric synthesis of enantiomerically pure nicotine analogues like **7** and **8** was the opportunity for their ready preparation from the commercially available (*S*)- and (*R*)-proline, (*S*)-**9** and (*R*)-**9**.

As outlined in Scheme 2, (*S*)- and (*R*)-proline **9** could be transformed by sequences of conventional reactions to yield the desired heterodienophilic imidates (*S*)- and (*R*)-**13**. These react with the electron-deficient diazadiene system of 1,2,4,5-tetrazine **15**[10] to yield (*R*)- and (*S*)-**16a** in fair yield after inverse [4+2] cycloaddition and elimination of nitrogen.[9] A second route to the desired 5-(2′-pyrrolidinyl)-1,2,4-triazines (*S*)- and (*R*)-**16b** started with the dienophilic hydrazones (*S*)- and (*R*)-**14**, prepared in nearly quantitative yield from the protected prolinals (*S*)- and (*R*)-**11**[11] as shown in Scheme 2. The electron-rich C=N bond of the hydrazones proved to be more reactive than those of the imidates; thus the inverse [4+2] cycloaddition with tetrazine **15**[12,13] occurred at milder reaction conditions to furnish the amine-substituted intermediates (*S*)- and (*R*)-**17** nearly quantitatively after N_2-elimination. Subsequent heating of compounds (*S*)- and (*R*)-**17** in benzene at 80°C and in the presence of *p*-TsOH as a catalyst afforded the novel 5-(2′-pyrrolidinyl)-1,2,4-triazines (*S*)- and (*R*)-**16b** in good yields. To our great disappointment, all attempts to deprotect the compounds of type **16** by conventional methods failed; possibly 5-(2′-pyrrolidinyl)-1,2,4-triazines **16** with E=H are not stable enough to be isolated because the nucleophilic pyrrolidine-NH-group attacks the electron-deficient 1,2,4-triazine leading to complex mixtures of unidentified products.

In contrast, the syntheses of the novel enantiomerically pure 2-(2′-pyrrolidinyl)pyridines of type **8** could successfully be realized starting with the triazines (*S*)- and (*R*)-**16b** (Scheme 3). The electron-deficient diazadiene system of **16** could have entered as a 4π electron component in hetero Diels–Alder reactions and reacted, as expected, with an excess of the electron-rich enolether **18** by way of a $LUMO_{diene}/HOMO_{dienophile}$-controlled cycloaddition. The reaction took 12 h in a sealed tube at 100°C for completion leading after elimination of N_2 and EtOH to the protected nicotine analogues (*S*)- and (*R*)-**19** with 86% and 95% yields, respectively. In this case removal of the protecting group[14] by $(CH_3)_3SiI$ in boiling $CHCl_3$ afforded the compounds (*S*)- and (*R*)-**20** in 91% and 58% yield, as air-stable pale yellow oils. The free NH-group of these compounds rendered possible an evaluation of the stereochemical course for the reaction sequence with (*S*)- and (*R*)-proline-**9** as the starting materials. The enantiomeric excess of (*S*)- and (*R*)-**20** was analyzed by ^1H NMR spectroscopy of the corresponding camphanic acid amides, prepared by reaction of both enantiomers with (−)-(1*S*)-camphanoyl chloride.[15] The diastereomeric camphanates gave base-line separated ^1H NMR signals; the protons in the 1′-position showed well-resolved signals which where used for e.e. determination. From these data an enantiomeric purity of >98% could be calculated for (*S*)-**20**, which is very close to that of (*S*)-proline used, demonstrating that no stereomutation accompanies the reaction sequence. In the case of (*R*)-**20** the two diastereomers were found to be clearly distinguishable indicating a 95:5 mixture. Because the enantiomeric excess of the starting (*R*)-proline was 95% the data obtained with (*R*)-**20** corroborate that no racemization occurred during the several synthetic steps. The 2-nicotine analogues (*S*)- and (*R*)-**21** could easily be obtained from nornicotines (*S*)- and (*R*)-**20** by treatment with aqueous formaldehyde and formic acid[16] (reductive alkylation with trioxane/$NaBH_3CN$ failed). Thus the described procedure demonstrating easy access to

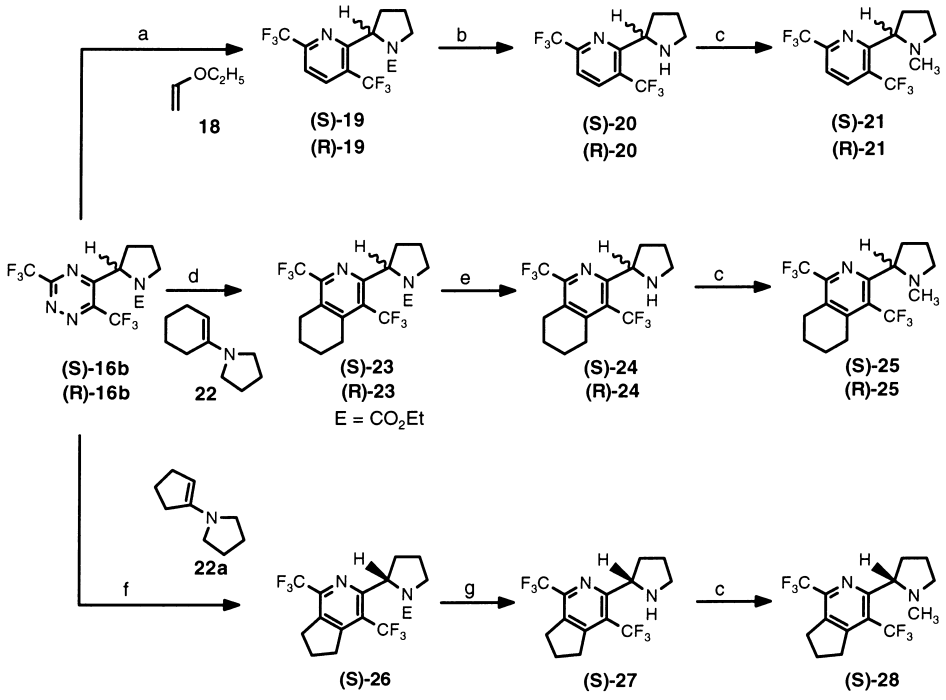


Scheme 2. Reagents and conditions: (a) BOC_2O, $N(Et)_3$, 50°C; (b) $ClCO_2Et$, NH_3, THF, −10°C; (c) $(COCl)_2$, DMSO, $N(Et)_3$, −60°C; (d) NaOMe:MeOH, 20°C; (e) MeI, $KHCO_3$, DMF, 20°C; (f) $NaBH_4$, LiCl, THF:EtOH, 12 h, 20°C; (g) $(COCl)_2$, DMSO, $N(Et)_3$; (h) $H_2N–N(Me)_2$, $MgSO_4$, CH_2Cl_2, 0−20°C, 12 h; (i) +**15**, toluene, 110°C; (j) +**15**, CH_2Cl_2, 0−20°C; (k) *p*-TsOH, benzene, 80°C

novel optically active 2-nicotine analogues from (*S*)- and (*R*)-proline encouraged further syntheses of enantiomerically pure 2-nicotines of types **25** and **28**.

Because enamines like **22** or **22a** have been proved to be highly appropriate dienophiles in the 'inverse' electron demand cycloaddition,[9] it was anticipated that they would easily undergo Diels–Alder reaction with the s-*cis*-fixed diazadiene systems of triazines (*S*)- and (*R*)-**16b**, activated by two trifluoromethyl groups. Thus treatment of enamine **22** with the 1,2,4-triazine derivatives (*S*)- and (*R*)-**16b** in tetrahydrofuran at ambient temperature led to the corresponding Diels–Alder adducts, which spontaneously eliminate N_2 and pyrrolidine to give the protected pyrrolidinyl-isoquinolines (*S*)- and (*R*)-**23** with 78% and 67% yield. With enamine **22a** as the starting material the pyrindine-derivative (*S*)-**26** was obtained in the same fashion with 91% yield. Removal of the protecting group in all cases proceeded smoothly with $(CH_3)_3SiI$ in boiling $CHCl_3$, with yields of the nornicotine variations (*S*)- and (*R*)-**24** and (*S*)-**27**, ranging from 66–91%. Finally, we succeeded in obtaining the desired nicotine analogues (*S*)- and (*R*)-**25** and (*S*)-**28** in very good yields (ca. 90%) when corresponding nornicotine precursors were treated with aqueous formaldehyde and formic acid.

In conclusion, the synthetic protocol we have chosen for preparing chiral optically active pyridine-modified nicotine analogues from (*S*)- and (*R*)-proline seems to be convenient and versatile. The synthetic steps including [4+2] cycloaddition reactions with inverse electron demand as a rule proceeded under mild conditions and with high yields; the stereogenic centers of the precursors are not directly involved in the reactions. Consequently no racemization is observed. Each pair of enantiomers synthesized had nearly the same specific rotation value but of opposite sign and the enantiomeric purity of compounds



Scheme 3. Reagents and conditions: (a) +excess of **18**, 12 h, 100°C; (i) [4+2] cycloadd., (ii) $-N_2$, −EtOH; (b) $(CH_3)_3SiI$, $CHCl_3$, 4 h reflux; (c) HCO_2H, CH_2O, 12 h reflux; (d) +**22**, CH_2Cl_2, 4 h reflux; (i) [4+2] cycloadd., (ii) $-N_2$, −pyrrolidine; (e) $(CH_3)_3SiI$, $CHCl_3$, 4 h reflux; (f) +**22a**, CH_2Cl_2, 4 h reflux, (i) [4+2] cycloadd., (ii) $-N_2$, −pyrrolidine; (g) $(CH_3)_3SiI$, $CHCl_3$, 4 h reflux

(*S*)- and (*R*)-**20** — intermediates in the synthetic sequence — assayed by ^1H NMR spectroscopy after derivatization with (−)-(1*S*)-camphanoyl chloride was determined to be >98% and >94%, respectively.

3. 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. ^1H NMR and ^{13}C NMR: Jeol JNM-GX 400 and LA 500; δ/ppm=0 for tetramethylsilane, 7.26 for chloroform. MS: Vacuum Generators 7070 (70 eV; ^{11}B). Column chromatography: purifications were carried out on Merck silica gel 60 (70–260 or 200–400 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-60-F_{254} microcards (Riedel de Haen). Optical rotations: Mod. Dip-370 polarimeter (Jasco). UV: UV/vis scanning spectrophotometer UV-2101 PC (Shimadzu). As chiral starting materials (*S*)-proline (>98% e.e.) and (*R*)-proline (>94% e.e.) were used.

*3.1. (S)- and (R)-N-Ethoxycarbonylpyrrolidine-2-carboxaldehyde, (S)- and (R)-**11***

To a stirred solution of 2.91 g (22.9 mmol) oxalyl chloride in 30 ml of dichloromethane was added dropwise at −78°C a solution of 2.97 g (38.1 mmol) dimethyl sulfoxide in 5 ml of dichloromethane. After 5 min a solution of 1.38 g (8.00 mmol) (*S*)-**10** in 10 ml dichloromethane was added dropwise,

after 30 min at −78°C, 9 ml triethylamine and stirring continued until room temperature was reached. Then the mixture was poured into 80 ml of water and the organic layer separated. The aqueous layer was extracted with dichloromethane (3×40 ml) and the combined extracts washed sequentially with brine (30 ml), saturated sodium bicarbonate solution (30 ml) and water (30 ml) and dried with magnesium sulfate (20 g). Removal of solvent in vacuo yielded an oily residue, which was purified by column chromatography [silica gel, 30×2 cm, eluant: ethyl acetate:petroleum ether (40–60°C), 3:1; R_f=0.48]. Removal of solvent in vacuo yielded 1.29 g (94%) of aldehyde (*S*)-**11** as a dense oil, which was used without further purification. $[\alpha]_D^{20}$ −75 (c 0.10, methanol); IR (neat): ν=3438, 2982, 1785, 1710, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ: 1.18 and 1.24 (t, J=7.1 Hz, 3H), 1.79–1.90 (m, 1H), 1.92–2.18 (m, 3H), 3.41–3.60 (m, 2H), 4.11 (q, J=7.1 Hz, 2H), 4.12–4.23 (m, 1H), 9.46 and 9.54 (d, J=1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.56 and 14.66, 23.81 and 24.54, 26.61 and 27.88, 46.59 and 47.12, 61.52, 64.82 and 65.12, 154.75 and 155.61, 200.20; MS (70 eV) m/z (%) 171 (0.1, M^+); HRMS calcd for $C_7H_{12}NO_2$ (142.18) (M^+−CHO): 142.0866. Found: 142.1000. (*R*)-*N*-Ethoxycarbonylpyrrolidine-2-carboxaldehyde (*R*)-**11** was prepared by the same procedure from 1.38 g (8.00 mmol) (*R*)-**10**. Yield: 1.19 g (87%).

*3.2. (2*S*)- and (2*R*)-*N*-(tert-Butoxycarbonyl)pyrrolidine-2-carboximidic acid methyl ester, (*S*)- and (*R*)-**13**

To a stirred solution of 1.90 g (9.7 mmol) (*S*)-**12**[17] in 40 ml of dry methanol was added a solution of 0.45 g (19.0 mmol) metallic sodium in 30 ml of dry methanol and stirring was continued for 4 h. Then the solution was neutralized by adding a cation-exchange resign (Amberlyst 15, H^+-form, 20–50 mesh, Fluka, dried for 24 h at 120°C), in small portions. The resign was filtered and the obtained solution evaporated in vacuo. The residue was dissolved in 30 ml of dry diethyl ether, the solution filtered and the solvent removed in vacuo. The syrupy residue was dried in vacuo for 12 h to give 1.1 g (49%) (*S*)-**13** as a yellow oil which proved to be extremely unstable. Thus it was used without further purification and characterization by analytical data. (*R*)-**13** was obtained by the same procedure in 45% yield as a yellow, unstable syrup.

*3.3. (2*S*)- and (2*R*)-*N*-Ethoxycarbonylpyrrolidine-2-carboxaldehyde*-N,N-*dimethylhydrazone, (*S*)- and (*R*)-**14**

To a solution of 0.86 g (5 mmol) (*S*)-**11** in 20 ml dichloromethane stirred under argon at room temperature was added 0.80 g (6.7 mmol) anhydrous magnesium sulfate. The suspension was cooled to 0°C and 0.57 ml (0.45 g, 7.5 mmol) asymmetric *N,N*-dimethylhydrazine added. The mixture was allowed to warm up to room temperature and stirring continued for 12 h. After filtration removal of solvent and excess of the hydrazine in vacuo yielded hydrazone (*S*)-**14** as a viscous oil which was purified by column chromatography [silica gel, 20×2 cm, eluant: ethyl acetate:petroleum ether (40–60°C), 6:1; R_f=0.38]. Yield: 1.03 g (97%); $[\alpha]_D^{20}$ −95 (c 0.10, methanol); IR (neat): ν=2987, 2796, 1696, 1603, 1532 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, J=7.1 Hz, 3H), 1.76–1.88 (m, 2H), 1.94–2.08 (m, 2H), 2.73 (s, 6H), 3.44 (s, broad, 2H), 4.11 (q, J=7.1 Hz, 2H), 4.40 (s, broad, 1H), 6.48 and 6.62 (s, broad, 1H, rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.87, 23.52, 31.46, 43.09 (2C), 46.75, 58.91, 60.89, 137.68, 155.40; MS (70 eV) m/z (%) 213 (100, M^+); HRMS calcd for $C_{10}H_{19}N_3O_2$ (M^+): 213.1475. Found: 213.1477.

(*R*)-**14** was obtained by the same procedure from 5.90 g (34 mmol) (*R*)-**11**. Yield: 6.10 g (84%); $[\alpha]_D^{20}$ +89.3 (c 0.1, methanol).

3.4. (2′S)- and (2′R)-5-[2′-N-(tert-Butoxycarbonyl)pyrrolidinyl]-3,6-bis(trifluoromethyl)-1,2,4-triazine, (S)- and (R)-16a

To a stirred solution of 1.0 g (4.4 mmol) (*S*)-**13** in 50 ml dry toluene was added dropwise a solution of 0.96 g (4.4 mmol) tetrazine **15** in 15 ml dry toluene. The solution was refluxed for ca. 6 h until the red color of **15** disappeared. The solvent was evaporated in vacuo and the syrupy residue purified by column chromatography [silica gel, 20×2 cm, eluant: petroleum ether (40–60°C):diethyl ether, 5:1]. Removal of the solvent under reduced pressure gave (*S*)-**16a** as a yellow oil which crystallized after 3 weeks, stored at 5°C. Yield: 1.17 g (68%) yellow crystals; m.p. 87–88°C; $[\alpha]_D^{20}$ −22.5 (c 0.22, methanol); UV (methanol): λ_{max} (lg ε)=363 nm (2.56); IR (neat): ν=2980, 1680, 1540, 1150, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 1.07 and 1.37 (9H, 2s, $C(CH_3)_3$), 1.84–2.15 and 2.47–2.59 (4H, 2m, 3′-H, 4′-H), 3.58–3.62 and 3.68–3.79 (2H, 2m, 5′-H), 5.15–5.18 and 5.21–5.24 (1H, 2m, 2′-H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 23.40 and 24.21, 27.90 and 28.20, 32.78 and 34.18, 47.37, 57.86 and 57.96, 80.53 and 80.69 ($C(CH_3)_3$), 118.97 (q, CF_3, $^1J_{CF}$=276.6 Hz) and 119.08 (q, CF_3, $^1J_{CF}$=276.9 Hz), 120.85 (q, CF_3, $^1J_{CF}$=275.9 Hz) and 120.92 (q, CF_3, $^1J_{CF}$=275.9 Hz), 148.84 (q, C-6, $^2J_{CF}$=36.0 Hz), 152.55 and 154.22 (C=O), 158.49 (q, C-3, $^2J_{CF}$=39.1 Hz), 165.83 and 166.46 (C-5); MS (70 eV) m/z (%) 386 (0.2, M^+), 313 (71, M^+-73), 285 (3, M^+-101). Anal. calcd for $C_{14}H_{16}F_6N_4O_2$: C, 43.53; H, 4.17; N, 14.50. Found: C, 43.88; H, 4.30; N, 14.62. The same procedure, starting from (*R*)-**13** afforded (*R*)-**16a**, yield 0.98 g (58%) yellow crystals; m.p. 88–89°C; $[\alpha]_D^{20}$ +21.0 (c 0.1, methanol).

3.5. (2′S)- and (2′R)-5-(2′-N-Ethoxycarbonylpyrrolidinyl)-3,6-bis(trifluoromethyl)-1,2,4-triazine, (S)- and (R)-16b

A stirred solution of 0.80 g (1.98 mmol) (*S*)-**17** and 1.03 g (5.94 mmol) *p*-toluenesulfonic acid was refluxed for 4 h under argon. After cooling to room temperature a solution of 50 ml 1 N NaOH was added, the organic layer separated and the aqueous layer extracted with 30 ml of benzene. The combined organic extracts were washed sequentially with saturated sodium bicarbonate solution (30 ml) and brine (30 ml) and dried with anhydrous magnesium sulfate (20 g). After filtration removal of solvent in vacuo yielded an oily residue which was purified by column chromatography [silica gel, 20×2 cm, petroleum ether (40–60°C):ethyl acetate, 6:1, R_f=0.8]. Removal of the solvent in vacuo yielded 0.61 g (86%) (*S*)-**16b** as colorless crystals; m.p. 86–88°C; $[\alpha]_D^{20}$ −42 (c 0.92, methanol); IR (KBr): ν=2986, 2889, 2835, 1700, 1548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 0.82 and 1.21 (each t, J=7.1 Hz, 3H), 1.88–2.08 (m, 2H), 2.10–2.21 (m, 1H), 2.48–2.60 (m, 1H), 2.63–2.84 (m, 2H), 3.87 and 4.05 (each q, J=7.1 Hz, 2H), 5.21–5.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.1 and 14.6, 23.5 and 24.4, 32.9 and 34.0, 47.2 and 47.7, 57.6 and 58.2, 61.5 and 61.8, 118.4 (q, $^1J_{CF}$=275.3 Hz), 119.2 (q, $^1J_{CF}$=276.8 Hz), 149.0 (q, $^2J_{CF}$=33.0 Hz), 158.3 (q, $^2J_{CF}$=35.3 Hz), 153.4 and 154.9, 165.4 and 165.8; MS (70 eV) m/z (%) 358 (11, M^+). Anal. calcd for $C_{12}H_{12}F_6N_4O_2$: C, 40.23; H, 3.38; N, 15.64. Found: C, 40.55; H, 3.49; N, 15.38. The same procedure, starting from 2.3 g (5.7 mmol) (*R*)-**17** afforded 1.9 g (93%) *R*-**16b**; m.p. 82–84°C; $[\alpha]_D^{20}$ +40.0 (c 1.0, methanol).

3.6. (2′S)- and (2′R)-4-Dimethylamino-4,5-dihydro-5-(2′-N-ethoxycarbonylpyrrolidinyl)-3,6-bis(trifluoromethyl)-1,2,4-triazine, (S)- and (R)-17

To a solution of 1.02 g (4.8 mmol) (*S*)-**14** in 20 ml of dry dichloromethane, cooled to 0°C and stirred under argon, was added dropwise a violet solution of 0.88 g (4.0 mmol) tetrazine **15** in 15 ml of dry dichloromethane. Stirring was continued for 30 min, then the mixture allowed to warm up

to room temperature. The violet solution was kept at ambient temperature for ca. 3 h until the violet color disappeared. The solvent was evaporated in vacuo and the oily residue worked up by column chromatography [silica gel, 30×3 cm, eluant: petroleum ether (40–60°C):ethyl acetate, 1:6; R_f=0.78]. Removal of the solvent in vacuo yielded (*S*)-**17** as a pale yellow oil, which crystallized, stored for 3 d at 4°C. Yield: 1.85 g (96%) colorless crystals; m.p. 91–92°C; IR (KBr): ν=2987, 2890, 2835, 1700, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 1.24 and 1.32 (each t, J=7.1 Hz, 3H), 1.30–1.48 (m, 1H), 1.67–1.87 (m, 3H), 2.32 (s, 3H), 2.50 (s, 3H), 3.29–3.50 (m, 2H), 3.89–3.97 and 3.99–4.07 (each m, 1H), 4.11–4.28 (m, 2H), 4.97 and 5.33 (each d, J=3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.5 and 14.7, 23.2 and 24.2, 26.1 and 27.0, 42.7 and 43.5, 45.0 and 45.2, 47.0 (NCH_3) and 47.7 (NCH_3), 58.3 and 59.7, 61.6 and 61.9, 118.8 (q, $^1J_{CF}$=275.3 Hz), 119.6 (q, $^1J_{CF}$=276.8 Hz), 142.9 (q, $^2J_{CF}$=33.0 Hz), 145.4 (q, $^2J_{CF}$=35.3 Hz), 154.8 and 155.8; MS (70 eV) m/z (%) 403 (1, M^+). Anal. calcd for $C_{14}H_{19}F_6N_5O_2$: C, 41.69; H, 4.75; N, 17.36. Found: C, 41.74; H, 4.80; N, 17.20. The same procedure, starting from 2.8 g (13 mmol) (*R*)-**14** afforded 3.1 g (76%) (*R*)-**17**.

*3.7. (2′S)- and (2′R)-2-(2′-N-Ethoxycarbonylpyrrolidinyl)-3,6-bis(trifluoromethyl)pyridine, (S)- and (R)-**19***

A solution of 179 mg (0.5 mmol) (*S*)-**16b** in 8 ml of ethyl vinyl ether **18** was heated for 12 h at 100°C (oil bath) in a sealed tube and allowed to cool to ambient temperature. Excess ethyl vinyl ether was evaporated in vacuo and the yellow oily residue purified by column chromatography [silica gel, 10×2 cm, eluant: petroleum ether (40–60°C):ethyl acetate, 6:1; R_f=0.83]. Yield: 154 mg (87%) pale yellow oil; $[\alpha]_D^{20}$ −35 (c 0.03, methanol); IR (neat): ν=2984, 2883, 1701, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 0.81 and 1.21 (each t, J=7.1 Hz, 3H), 1.81–2.02 (m, 2H), 2.12–2.23 (m, 1H), 2.36–2.47 (m, 1H), 3.32–3.64 (m, 1H), 3.59–3.73 (m, 1H), 3.75–3.93 (m, 1H), 4.00–4.19 (m, 1H), 5.28 and 5.34 (each m, 1H), 7.64 (m, 1H), 8.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.1 and 14.7, 23.1 and 23.8, 33.0 and 34.1, 47.3 and 47.7, 58.5 and 59.0, 60.7 and 61.1, 118.1, 121.8 (q, $^1J_{CF}$=275.3 Hz), 122.9 (q, $^1J_{CF}$=276.8 Hz), 135.6 and 135.7, 150.5 (q, $^2J_{CF}$=33.0 Hz), 161.3 (q, $^2J_{CF}$=35.3 Hz), 154.2 and 155.0, 162.9 and 163.4; MS (70 eV) m/z (%) 356 (11, M^+); HRMS calcd for $C_{14}H_{14}F_6N_2O_2$ (M^+): 356.0926. Found: 356.0959.

Compound (*R*)-**19** was obtained by the same procedure from 750 mg (2.1 mmol) (*R*)-**16b** and 30 ml of **18**. Yield: 710 mg (95%) pale yellow oil; $[\alpha]_D^{20}$ +36 (c 0.03, methanol). Anal. calcd for $C_{14}H_{14}F_6N_2O_2$: C, 47.20; H, 3.96; N, 7.86. Found: C, 47.16; H, 4.12; N, 7.65.

*3.8. (2′S)- and (2′R)-2-(2′-Pyrrolidinyl)-3,6-bis(trifluoromethyl)pyridine, (S)- and (R)-**20***

To a solution of 300 mg (0.84 mmol) (*S*)-**19** in 5 ml dry chloroform stirred under argon at ambient temperature was added dropwise 0.34 ml (2.52 mmol) iodotrimethylsilane. The flask was sealed by a septum and the reaction mixture heated for 4 h at 75–80°C in an oil bath. The mixture was cooled to ambient temperature and 1.5 ml methanol was added dropwise. After gas evolution had ceased the solvent was evaporated in vacuo and the residue poured onto 8 ml water. Concentrated aqueous ammonia was added until pH=10 was reached. The mixture was extracted with chloroform (3×15 ml), the combined organic layers washed with brine (2×50 ml), dried with anhydrous $MgSO_4$ (10 g), filtered and evaporated to yield a pale yellow oil which was purified by column chromatography (silica gel, 20×2 cm, eluant: dichloromethane:methanol:conc. aqueous ammonia, 97:3:1; R_f=0.46). Removal of solvent in vacuo yielded 217 mg (91%) (*S*)-**20** as a pale yellow oil. $[\alpha]_D^{20}$ −40.0 (c 0.20, methanol); IR (neat): ν=2983, 2879, 1590, 1436, 1313, 1118 cm^{-1}; MS (70 eV) m/z (%) 284 (58, M^+); for spectroscopic

characterization (*S*)-**20** was transformed to the corresponding pyrrolidinium oxalate (*S*)-**20a**: to a solution of 217 mg (0.76 mmol) (*S*)-**20** in 6 ml of acetone stirred under argon and heated to 40°C was added dropwise a solution of 72 mg (0.76 mmol) oxalic acid monohydrate in 4 ml of acetone. The mixture was refluxed for 10 min, cooled to ambient temperature and stored for 12 h at 4°C. The precipitated solid (*S*)-**20a** was collected by filtration and washed with a small amount of acetone. The mother liquor was concentrated and stored at 4°C affording a second crop of crystals. Total yield after drying in vacuo 264 mg (93%) of colorless crystals with m.p. 192–193°C; $[\alpha]_D^{20}$ −36 (c 0.18, methanol); IR (KBr): ν=3084, 2988, 1735, 1658, 1312, 1122 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 2.03–2.11 (m, 1H), 2.17–2.28 (m, 2H), 2.58–2.64 (m, 1H), 3.53–3.60 (m, 1H), 3.64–3.71 (m, 1H), 5.24 (pseudo-t, J=7.6 Hz, 1H), 8.09 (d, J=8.2 Hz, 1H), 8.53 (d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 24.98, 33.69, 47.77, 60.95, 120.9 (q, $^1J_{CF}$=275.3 Hz), 121.6 (q, $^1J_{CF}$=276.8 Hz), 122.23, 127.94 (q, $^2J_{CF}$=33.0 Hz), 139.49, 151.51 (q, $^2J_{CF}$=35.3 Hz), 156.02; MS (70 eV) m/z (%) 284 (58, $M^+-H_2C_2O_4$). Anal. calcd for $C_{13}H_{12}F_6N_2O_4$: C, 41.72; H, 3.23; N, 7.49. Found: C, 41.82; H, 3.41; N, 7.44. Compound (*R*)-**20** was obtained by the same procedure from 0.50 g (1.4 mmol) (*R*)-**19** and 0.60 ml (4.2 mmol) iodotrimethylsilane. Yield: 230 mg (58%) brownish oil; $[\alpha]_D^{20}$ +37.8 (c 0.1, methanol). Anal. calcd for $C_{11}H_{10}F_6N_2$: C, 46.49; H, 3.55; N, 9.86. Found: C, 46.52; H, 3.74; N, 9.52.

*3.9. (2′S)- and (2′R)-2-(2′-N-Methyl-pyrrolidinyl)-3,6-bis(trifluoromethyl)pyridine, (S)- and (R)-**21***

To a solution of 70 mg (1.3 mmol) aqueous formic acid (85%) and 50 mg (0.6 mmol) aqueous formaldehyde (37%) was added dropwise a solution of 74 mg (0.3 mmol) (*R*)-**20** in 5 ml chloroform at 5°C under argon. Then the solution was heated under reflux for 12 h, cooled and basified with 50% aqueous NaOH. The mixture was extracted with diethyl ether (3×15 ml), the combined organic phases dried with anhydrous $MgSO_4$ (10 g), filtered and evaporated to yield a brownish oil which was purified by column chromatography (silica gel, 20×2 cm, eluant: dichloromethane:methanol:conc. aqueous ammonia, 97:3:1). Removal of the solvent in vacuo yielded 64 mg (83%) (*R*)-**21** as a brownish oil; $[\alpha]_D^{20}$ +41.6 (c 0.05, methanol); IR (neat): ν=2970, 2780, 1700, 1585 cm^{-1}; UV (methanol): λ_{max} (lg ε)=353 nm (1.24), 324 (1.82), 272 (3.22); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.83–2.17 (m, 4H, 3′-H and 4′-H), 2.16 (s, 3H, NCH_3), 2.40 (dt, 1H, 5′-H_a, ^2J=8.4 Hz, ^3J=8.6 Hz), 3.26–3.30 (m, 1H, 5′-H_b), 3.75–3.79 (m, 1H, 2′-H), 7.59 (d, 1H, 4-H or 5-H, ^3J=8.2 Hz), 8.04 (d, 1H, 4-H or 5-H, ^3J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.3 (C-4′), 33.7 (C-3′), 40.1 (NCH_3), 56.8 (C-5′), 66.9 (C-2′), 118.2 (C-5), 120.9 (q, CF_3, $^1J_{CF}$=275.6 Hz), 123.3 (q, CF_3, $^1J_{CF}$=272.9 Hz), 127.7 (q, C-3, $^2J_{CF}$=31.6 Hz), 135.6 (C-4), 151.2 (q, C-6, $^2J_{CF}$=34.0 Hz), 162.8 (C-2); MS (70 eV) m/z (%) 298 (30, M^+). HRMS calcd for $C_{12}H_{12}F_6N_2$ (M^+): 298.0904. Found: 298.0882. Compound (*S*)-**21** was obtained by the same procedure from 10 mg (0.035 mmol) (*S*)-**20** yielding 8 mg (76%) of a yellowish oil; $[\alpha]_D^{20}$ −39.3 (c 0.01, methanol).

*3.10. (2′S)- and (2′R)-5,6,7,8-Tetrahydro-3-(2′-N-ethoxycarbonylpyrrolidinyl)-1,4-bis(trifluoromethyl)-isoquinoline, (S)- and (R)-**23***

To a solution of 850 mg (2.37 mmol) (*S*)-**16b** in 30 ml dry dichloromethane stirred under argon was added dropwise a solution of 450 mg (2.98 mmol) of **22** in 5 ml dry dichloromethane. When gas evolution had ceased the mixture was refluxed for 4 h and cooled to ambient temperature. The solvent was evaporated in vacuo and the syrupy residue purified by column chromatography [silica gel, 20×2 cm, eluant: petroleum ether (40–60°C):diethyl ether, 4:1]. Removal of the solvent gave (*S*)-**23** as a pale yellow oil. Yield: 0.76 g (78%); $[\alpha]_D^{20}$ −58 (c 0.1, methanol); UV (methanol): λ_{max} (lg ε)=349 nm (2.84), 341

(2.86), 274 (3.46); IR (neat): ν=2980, 2955, 2875, 1705, 1655, 1565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 0.84 and 1.18 (each t, J=7.2 Hz, 3H), 1.65–1.74 and 1.81–1.99 (each m, 4H), 2.04–2.13 and 2.29–2.38 (each m, 4H), 2.85–3.05 (m, 4H), 3.52–3.64 and 3.71–3.79 (each m, 2H), 3.81–3.91 and 4.00–4.09 (each m, 2H), 5.27–5.29 and 5.33–5.36 (each m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.20 and 14.76, 20.95, 21.38 and 21.47, 22.80 and 23.35, 24.37, 27.43, 32.88 and 33.77, 46.95 and 47.43, 60.01 and 60.06, 60.45 and 60.82, 121.77 (q, $^1J_{CF}$=276.7 Hz), 124.51 (q, $^2J_{CF}$=30.0 Hz), 124.62 (q, $^1J_{CF}$=276.7 Hz), 130.82 and 131.07, 146.87 (q, $^2J_{CF}$=30.0 Hz), 149.22 and 149.50, 154.34 and 155.12, 157.50 and 158.20; MS (70 eV) m/z (%) 410 (53, M^+). Anal. calcd for $C_{18}H_{20}F_6N_2O_2$: C, 52.69; H, 4.91; N, 6.83. Found: C, 52.52; H, 5.00; N, 6.77. (*R*)-**23** was obtained by the same procedure from 850 mg (2.37 mmol) (*R*)-**16b** and 450 mg (2.98 mmol) of **22**. Yield: 650 mg (67%); $[\alpha]_D^{20}$ +55.7 (c 0.05, methanol).

*3.11. (2′S)- and (2′R)-3-(2′-Pyrrolidinyl)-5,6,7,8-tetrahydro-1,4-bis(trifluoromethyl)isoquinoline, (S)- and (R)-**24***

To a solution of 700 mg (1.70 mmol) (*S*)-**23** in 10 ml dry chloroform stirred under argon at ambient temperature was added dropwise 0.73 ml (5.1 mmol) iodotrimethylsilane. The flask was sealed by a septum and the reaction mixture heated for 4 h at 75–80°C in an oil bath. After cooling to ambient temperature 3.2 ml methanol was added, the solvent evaporated in vacuo and the brownish residue mixed with 17 ml water and 4.2 ml conc. aqueous ammonia. Then the mixture was extracted with chloroform (3×15 ml), the combined organic layers washed with brine (2×50 ml), dried with anhydrous sodium sulfate, filtered and evaporated in vacuo to yield a brownish oil which was purified by column chromatography (silica gel, 20×2 cm, eluant: dichloromethane:methanol:conc. aqueous ammonia, 97:3:1). Removal of solvent in vacuo yielded 0.38 g (66%) of a brownish oil, which crystallizes after storing for 14 d, m.p. 47–49°C. $[\alpha]_D^{20}$ −39.8 (c 0.17, methanol); UV (methanol): λ_{max} (lg ε)=341 nm (2.14), 338 (2.16), 325 (2.26); IR (neat): ν=3330, 2950, 2875, 1570, 1455, 1435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.55–1.64 (m, 1H), 1.69–1.88 (m, 6H), 2.18–2.26 (m, 1H), 2.88–2.98 (m, 5H), 3.21 (s, broad, 1H), 3.27–3.33 (m, 1H), 4.54 (dt, ^3J=7.4 Hz, ^2J=1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.97, 21.48, 24.40, 26.67, 27.58, 34.57, 47.67, 61.04, 121.82 (q, $^1J_{CF}$=276.1 Hz), 125.16 (q, $^2J_{CF}$=30.0 Hz), 127.30 (q, $^1J_{CF}$=276.8 Hz), 131.39, 146.77 (q, $^2J_{CF}$=31.7 Hz), 150.20, 157.38; MS (70 eV) m/z (%) 338 (40, M^+). Anal. calcd for $C_{15}H_{16}F_6N_2$: C, 53.25; H, 4.77; N, 8.28. Found: C, 53.08; H, 4.94; N, 8.10.

(*R*)-**24** was obtained by the same procedure from 700 mg (1.7 mmol) (*R*)-**23** and 0.73 ml (5.1 mmol) $(CH_3)_3SiI$. Yield: 490 mg (86%); $[\alpha]_D^{20}$ +38.0 (c 0.1, methanol).

*3.12. (2′S)- and (2′R)-3-(2′-N-Methyl-pyrrolidinyl)-5,6,7,8-tetrahydro-1,4-bis(trifluoromethyl)isoquinoline, (S)- and (R)-**25***

To a solution of 160 mg (2.9 mmol) aqueous formic acid (85%) and 120 mg (1.5 mmol) aqueous formaldehyde (37%) was added a solution of 200 mg (0.59 mmol) (*S*)-**24** in 5 ml $CHCl_3$ at 5°C under argon. Then the solution was heated under reflux for 12 h, cooled to ambient temperature and basified with 50% aqueous NaOH. The mixture was extracted with diethyl ether (3×15 ml), the combined organic layers dried with anhydrous $MgSO_4$ (10 g), filtered and evaporated to yield a syrup which was purified by column chromatography (silica gel, 20×2 cm, eluant: dichloromethane:methanol:conc. aqueous ammonia, 97:3:1). Removal of the solvent in vacuo yielded 190 mg (91%) (*S*)-**25** as a brownish oil; $[\alpha]_D^{20}$ −48.1 (c 0.07, methanol); IR (neat): ν=2950, 2870, 2780, 1555, 1455 cm^{-1}; UV (methanol): λ_{max} (lg ε)=354 nm (2.40), 272 (3.41), 215 (3.94); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.69–1.88 and

1.95–2.18 (2m, 8H, 3′-H, 4′-H, 6-H, 7-H), 2.21 (s, 3H, NCH_3), 2.47 (dt, 1H, 5′-H_a, ^2J=8.9 Hz, ^3J=7.8 Hz), 2.89–3.02 (m, 4H, 5-H, 8-H), 3.26–3.31 (m, 1H, 5′-H_b), 3.91–3.96 (m, 1H, 2′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.00, 21.63, 23.53, 24.46, 27.81, 33.22, 40.12, 56.59, 66.95, 121.95 (q, CF_3, $^1J_{CF}$=278.0 Hz), 124.86 (q, CF_3, $^1J_{CF}$=277.5 Hz), 125.93 (q, C-4, $^2J_{CF}$=31.2 Hz), 130.78, 147.73 (q, C-1, $^2J_{CF}$=32.0 Hz), 148.92, 158.13; HRMS calcd for $C_{16}H_{18}F_6N_2$ (M^+): 352.1374. Found: 352.1328. Anal. calcd for $C_{16}H_{18}F_6N_2$: C, 54.54; H, 5.15; N, 7.95. Found: C, 54.78; H, 5.09; N, 7.89. Compound (*R*)-**25** was obtained by the same procedure from 200 mg (1.2 mmol) (*R*)-**24**. Yield: 180 mg (88%) brownish oil; $[\alpha]_D^{20}$ +46.2 (c 0.1, methanol). Anal. calcd for $C_{16}H_{18}F_6N_2$: C, 54.54; H, 5.15; N, 7.95. Found: C, 54.62; H, 5.25; N, 7.78.

*3.13. (2′S)-6,7-Dihydro-3-(2′-N-ethoxycarbonylpyrrolidinyl)-1,4-bis(trifluoromethyl)-5H-2-pyridine, (S)-**26***

To a solution of 1.20 g (3.35 mmol) (*S*)-**16b** in 40 ml dry dichloromethane stirred under argon at ambient temperature was added dropwise a solution of 570 mg (4.15 mmol) enamine **22a** in 5 ml dry dichloromethane. When gas evolution had ceased the mixture was refluxed for 4 h and cooled to ambient temperature. The solvent was evaporated in vacuo and the syrupy residue purified by column chromatography [silica gel, 20×2 cm, eluant: petroleum ether, (40–60°C):diethyl ether, 4:1]. Removal of the solvent gave (*S*)-**26** as a pale yellow oil. Yield: 1.21 g (91%). $[\alpha]_D^{20}$ −45.3 (c 0.1, methanol); UV (methanol): λ_{max} (lg ε)=271 nm (3.55); IR (neat): ν=2980, 2885, 1705, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ: 0.83 and 1.18 (each t, 3H, OCH_2CH_3, ^3J=7.1 Hz), 1.79–1.93, 2.07–2.24 and 2.29–2.40 (3m, 6H, 3′-H, 4′-H, 6-H), 3.04–3.18 (m, 4H, 5-H, 7-H), 3.52–3.65 and 3.72–3.80 (each m, 2H, 5′-H), 3.82–3.89 and 3.95–4.07 (each m, 2H, OCH_2CH_3), 5.25 and 5.30 (each d, 1H, 2′-H, $^2J_{2',3'a}$=8 Hz, $^2J_{2',3'b}$=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ: 14.20 and 14.75, 22.83 and 23.58, 24.44, 29.73, 33.01, 33.93, 47.08 and 47.51, 58.66 and 59.27, 60.53 and 60.86, 121.64 (q, CF_3, $^1J_{CF}$=275.5 Hz), 122.70 (q, C-4, $^2J_{CF}$=30.4 Hz), 124.38 (q, CF_3, $^1J_{CF}$=275.5 Hz), 137.55 and 137.71, 144.76 (q, C-1, $^2J_{CF}$=35.1 Hz), 154.35 and 155.07, 156.10 and 156.36, 159.64 and 160.15; HRMS calcd for $C_{17}H_{18}F_6N_2O_2$ (M^+): 396.1272. Found: 396.1303. Anal. calcd for $C_{17}H_{18}F_6N_2O_2$: C, 51.52; H, 4.57; N, 7.07. Found: C, 51.60; H, 4.70; N, 7.12.

*3.14. (2′S)-6,7-Dihydro-3-(2′-pyrrolidinyl)-1,4-bis(trifluoromethyl)-5H-2-pyridine, (S)-**27***

The compound (*S*)-**27** was prepared following the procedure for (*S*)-**24**, starting from 600 mg (1.50 mmol) (S)-**26** and 0.64 ml (4.50 mmol) $(CH_3)_3SiI$. The crude product obtained was purified by column chromatography (silica gel, 20×2 cm, eluant: dichloromethane:methanol:conc. aqueous ammonia, 97:3:1). Yield: 450 mg (91%) of a brownish oil. $[\alpha]_D^{20}$ −38.0 (c 0.15, methanol); UV (methanol): λ_{max} (lg ε)=354 nm (1.76), 342 (1.87), 324 (2.15); IR (neat): ν=3320, 2970, 1590, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.55–1.64 (m, 1H, 3′-H_a), 1.82–1.90 (m, 2H, 6-H), 2.12–2.33 (m, 3H, 3′-H_b, 4′-H), 2.90 and 2.93 (2t, 1H, 5′-H_a, $^3J_{4'a,5'a}$=$^3J_{4'b,5'a}$=7.5 Hz), 3.09–3.13 and 3.14–3.20 (2m, 5H, 5-H, 7-H, NH), 3.31 and 3.34 (2t, 1H, 5′-H_b, $^3J_{4'a,5'b}$=$^3J_{4'b,5'b}$=6.4 Hz), 4.50 (dt, 1H, 2′-H, $^3J_{2',3'}$=7.3 Hz, $^3J_{2',NH}$=1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.52, 26.80, 29.81, 33.18, 34.82, 47.84, 60.49, 121.58 (q, CF_3, $^1J_{CF}$=274.8 Hz), 123.48 (q, C-4, $^2J_{CF}$=32.4 Hz), 124.25 (q, CF_3, $^1J_{CF}$=276.0 Hz), 138.02, 144.60 (q, C-1, $^2J_{CF}$=35.9 Hz), 156.86, 159.33; HRMS calcd for $C_{14}H_{14}F_6N_2$ (M^+): 324.1061. Found: 324.1041. Anal. calcd for $C_{14}H_{14}F_6N_2$: C, 51.85; H, 4.35; N, 8.64. Found: C, 51.96; H, 4.52; N, 8.33.

3.15. (2′S)-6,7-Dihydro-3-(N-methyl-2′-pyrrolidinyl)-1,4-bis(trifluoromethyl)-5H-2-pyridine, (S)-28

The compound (*S*)-**28** was prepared following the procedure for (*S*)-**21**, starting from 400 mg (1.20 mmol) (*S*)-**27**. Yield: 400 mg (96%) of a brownish oil. $[\alpha]_D^{20}$ −36.4 (c 0.1, methanol); UV (methanol): λ_{max} (lg ε)=352 nm (2.40), 271 (3.41), 215 (3.94); IR (neat): ν=2970, 2780, 1590, 1435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.70–1.88, 1.96–2.02, 2.05–2.12 and 2.14–2.18 (4m, 6H, 3′-H, 4′-H, 6-H), 2.21 (s, 3H, NCH_3), 2.48 (dt, 1H, 5-H_a, $^2J_{5'a,5'b}$=8.6 Hz, $^3J_{4',5'a}$=8 Hz), 2.89–3.04 (m, 4H, 5-H, 7-H), 3.26–3.33 (m, 1H, 5′-H_b), 3.91–3.96 (m, 1H, 2′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.21, 24.32, 29.81, 33.37, 33.45, 39.95, 56.59, 66.67, 121.60 (q, CF_3, $^1J_{CF}$=275.9 Hz), 124.43 (q, CF_3, $^1J_{CF}$=275.2 Hz), 124.48 (q, C-4, $^2J_{CF}$=31.5 Hz), 137.55, 145.56 (q, C-1, $^2J_{CF}$=36.1 Hz), 155.71, 159.60; MS (70 eV) m/z (%)=338 (100, M^+). Anal. calcd for $C_{15}H_{16}F_6N_2$: C, 53.26; H, 4.77; N, 8.28. Found: C, 53.19; H, 4.78; N, 8.03.

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