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ORIGINAL PAPER

Synthesis of bipyridine analogues of metomidate for conjugate formation with the ^{99m}Tc(I)-tricarbonyl complex

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Abstract Ethyl 2,2′-bipyridine-5-carboxylate was converted to (2,2′-bipyridine-5-yl)methanol and (*S*)-1-(2,2′-bipyridine-5-yl)ethanol. The latter synthesis comprised five steps and resolution by HPLC on a chiral stationary phase. Both alcohols were reacted with methyl 1*H*-imidazole-5-carboxylate in a Mitsunobu reaction to give mixtures of the desired methyl 1-(2,2′-bipyridine-5-yl)alkyl-1*H*-imidazole-5-carboxylate as main product and the methyl 1-(2,2′-bipyridine-5-yl)alkyl-1*H*-imidazole-4-carboxylate as side product. The structure of (*R*)-(−)-methyl 1-(2,2′-bipyridine-5-yl)ethyl-1*H*-imidazole-4-carboxylate was determined by X-ray structure analysis.

Keywords Heterocycles · Alkylations · Resolution · Nucleophilic substitutions · X-ray structure determination

Introduction

Metomidate ((*R*)-(+)-methyl 1-(1-phenylethyl)-1*H*-imidazole-5-carboxylate, MTO, **1a** Fig. 1) and the corresponding ethyl ester etomidate (ETO, **1b**) are short-acting hypnotics [1–4] and potent inhibitors of 11β-hydroxylase in the adrenal cortex [5–9].

MTO, ETO, and structural analogues have been evaluated for their potency to inhibit specific [^{131}I]IMTO binding to rat adrenal membranes [10]. It was found that the (*R*) enantiomer of MTO is a much better ligand than the (*S*) enantiomer (IC_{50} = 3.7 vs. 492 nM). Removal of the methyl group from the benzylic carbon atom gave an achiral species, which blocked [^{131}I]IMTO binding less efficiently (IC_{50} = 28.8 nM) than the parent MTO. Furthermore, analogues containing a substituted phenyl or a pyridine-3-yl ring (IC_{50} = 20.7 nM) in place of the phenyl ring were evaluated. Recently, ^{11}C-metomidate was introduced as the first carbon-11 labeled radiotracer for PET investigations of the adrenal cortex and its tumours [11–14]. Subsequent developments include [^{18}F]FETO for PET [15, 16] and [^{123}I]IMTO for SPECT investigations [17–20]. We have synthesized 4-(trimethylstannyl)MTO as a precursor for radiohalogenations with ^{123}I, ^{131}I, ^{76}Br, and ^{18}F, primarily with radioiodine [21].

Technetium-99m forms stable coordination complexes with a variety of ligands of medicinal importance [22, 23]. The ^{99m}Tc(I)-tricarbonyl complex has been successfully used for the coupling of bidentate and tridentate ligands with the organometallic $[^{99m}Tc(CO)_3]^+$ core [24–26]. To probe the application of $^{99m}Tc(I)(CO)_3^+$ complexes of MTO for imaging of the adrenal cortex, its structure had to be modified appropriately. Thus the phenyl ring was replaced by a 2,2′-bipyridine-5-yl ring, with or without conservation of the methyl group at the stereogenic centre. The syntheses of these two bidentate ligands **2a** and **2b** are reported.

Results and discussion

We decided first to prepare the achiral compound **2a**, which is more easily accessible than the homochiral

Ilse Zolle: deceased April 8 2009.

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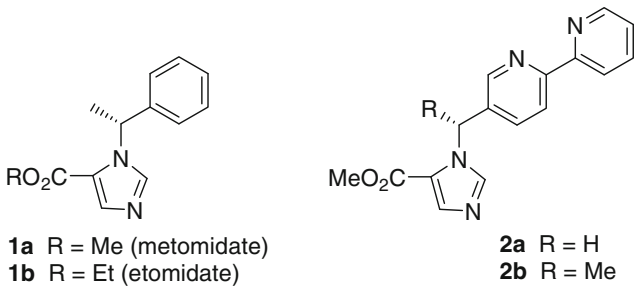
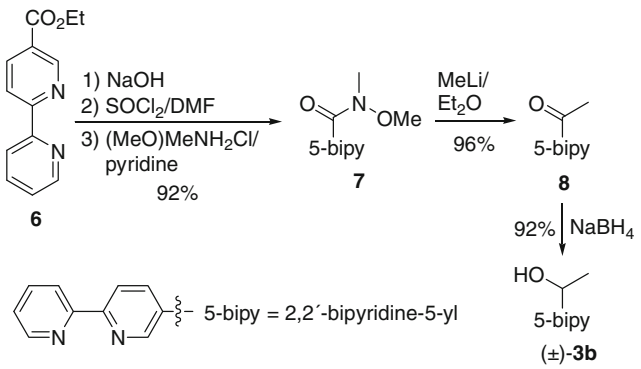


Fig. 1 Structures of metomidate, etomidate, and analogues



Scheme 2

compound **2b**, by the Mitsunobu method used previously [21], because the required alcohol **3a** is a known compound [27]. The secondary alcohol (*S*)-**3b** is unknown and we expected it to be difficult to obtain. Furthermore, we wanted to see whether the Mitsunobu reaction developed to synthesize a variety of structural analogues of MTO worked in this case also (Scheme 1).

Thus, (2,2′-bipyridine-5-yl)methanol (**3a**) was coupled with methyl 1*H*-imidazole-5-carboxylate (**4**) using Ph_3P–di-*t*-butyl azodicarboxylate (D*t*BAD) in THF at 0 °C. After 3 h, the starting alcohol had been consumed and two overlapping spots of reaction products could be detected by TLC. They could be isolated by flash column chromatography in 60 and 6% yield and were assigned the structures **2a** and **5a**, anticipating later results. Surprisingly, in the previous experiments only the desired products, the methyl 1-alkyl-1*H*-imidazole-5-carboxylates, were detected when benzylic alcohols were used in place of (2,2′-bipyridine-5-yl)methanol [21].

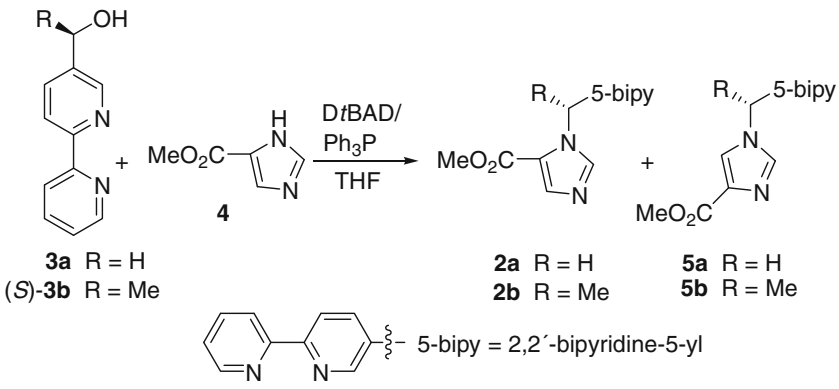
This result encouraged us to proceed to the preparation of **2b**, with a methyl substituent at the benzylic carbon atom, which was also essential for the high potency in MTO. The respective alcohol (*S*)-**3b** was accessed from the known ester **6** (Scheme 2) [27].

It was hydrolysed under basic conditions to give the corresponding sodium salt, which was converted in a one-pot reaction via the acid chloride to Weinreb amide **7** in an overall yield of 92% [28]. Smooth addition [28] of methyllithium to **7** at low temperature furnished methyl ketone **8** in 96% yield. CBS-reduction [29] could give the desired alcohol (*S*)-**3b** directly. Although the enantiomeric excesses are generally high with this method, but not ≥99%, we decided to reduce the ketone with $NaBH_4$ to (±)-**3b** and resolve it by HPLC on a chiral stationary phase (Chiralcel OD) (Scheme 3). Both enantiomers had 99% *ee* by analytical HPLC on a Chiralcel OD-H column ((−)-**3b**: t_R = 19.3 min; (+)-**3b**: t_R = 23.2 min, isopropanol–*n*-hexane 30:70). To determine the absolute configuration of the enantiomers, the alcohols (±)- and (+)-**3b** were derivatised with (*S*)-MTPACl and the ^{1}H NMR spectra of the respective (*R*) Mosher esters were recorded (Scheme 4).

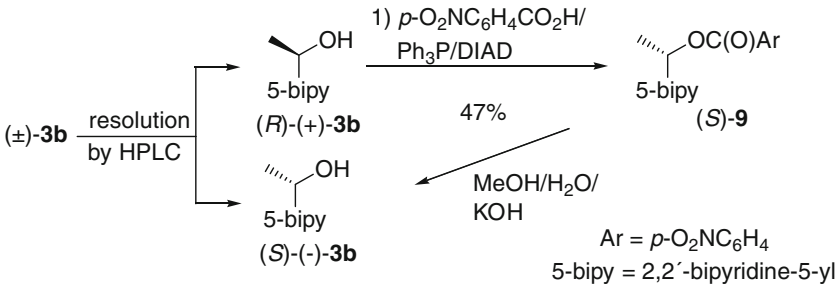
Assuming that the two diastereomers have conformations as depicted for (+)-**3b**·MTPA-(*R*) and (−)-**3b**·MTPA-(*R*) [30], the resonances of the Me and OMe groups will be shielded (lower δ values) by the aromatic substituents in the former diastereomer and deshielded (higher δ values) in the latter. This allowed assignment of the (*R*) and (*S*) configurations to (+)-**3b** and (−)-**3b**.

To obtain more of the desired enantiomer (*S*)-(−)-**3b**, the (*R*) enantiomer was transformed into the *p*-nitrobenzoate (*S*)-**9** using a combination of the Mitsunobu reaction (S_N2 reaction; Ph_3P/*p*-$O_2NC_6H_4CO_2H$/diisopropyl azodicarboxylate (DIAD)) and base-catalyzed transesterification (overall yield 47%, Scheme 3). Alcohol (*S*)-**3b**

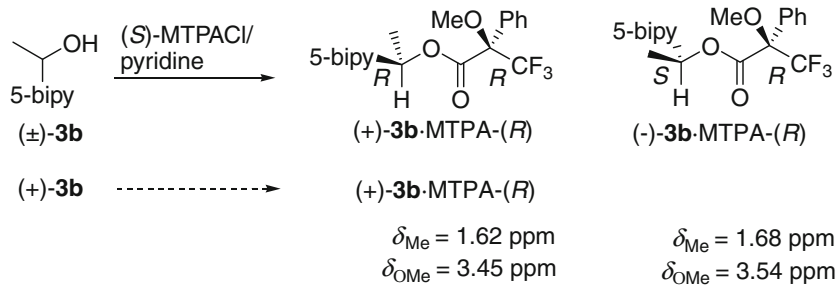
Scheme 1



Scheme 3



Scheme 4



(99% *ee*) was converted in the same way as **3a** to two isomeric imidazole derivatives, an oily major one (**2b**, 70%) and a crystalline minor one (**5b**, 11%, Scheme 1).

Careful inspection of the ^{1}H and ^{13}C NMR spectra revealed significant similarities between the spectra of the two main and two side products of the Mitsunobu coupling and significant differences between the two pairs of spectra, taking into account the changes brought about by the methyl substituent ("Experimental" section). To unequivocally assign the structures, that of the minor and crystalline MTO analogue **5b** derived from alcohol (*S*)-(−)-**3b** was determined by X-ray structure analysis (Fig. 2). The minor analogue has structure **5b** and the major one **2b**. Consequently, the minor MTO analogue derived from alcohol **3a** has structure **5a** and the major one **2a**.

In conclusion, we have prepared analogues of metomidate and its demethylated version with a 2,2′-bipyridine-5-yl substituent in place of the phenyl rings. Investigation of the ligating properties and the biological relevance of the novel systems is under way [31, 32].

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer (400.13 MHz) in $CDCl_3$ using the residual solvent peak as internal reference ($\delta = 7.24$ ppm). ^{13}C NMR spectra (in part *J* modulated) were recorded on the above spectrometer operating at 100.61 MHz (internal reference $CDCl_3$; $\delta = 77.00$ ppm). IR spectra were recorded as films on a silicon disc using a Perkin–Elmer 1600 FT-IR spectrometer [33]. Optical rotations were measured in a 1 dm cell at 20 °C on a Perkin–Elmer 341 polarimeter. Elemental analyses (C, H, N) were conducted using the Perkin–Elmer 2400 CHN elemental analyzer, and the results were in good agreement with the calculated values. TLC was performed on Merck plates coated with 0.25 mm layers of silica gel 60 F_{254}. Spots were visualized by UV and/or with iodine or by dipping the plate into a solution of 24 g $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 1 g $Ce(SO_4)_2{\cdot}4H_2O$ in 500 cm^3 10% H_2SO_4 in water, followed by heating with a heat gun. Flash chromatography was performed with

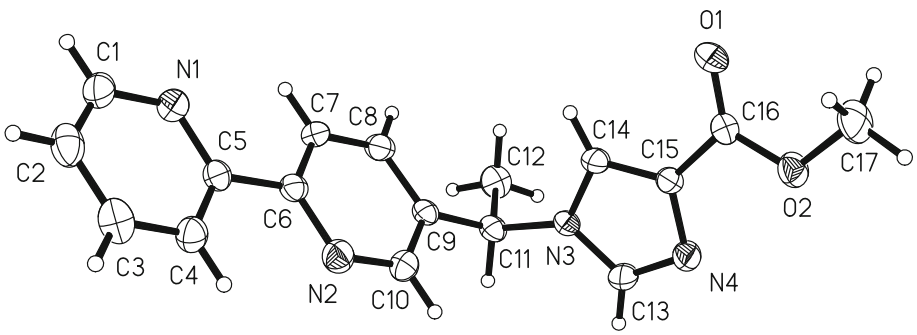


Fig. 2 Molecular structure of **5b** in the solid state. Note that the nitrogen atoms in bipyridine are here *anti*-configured

Merck silica gel 60 (230–400 mesh). THF was distilled from potassium and Et_2O from $LiAlH_4$. Analytical HPLC was performed with a Jasco System (PU-980 pump, UV 975, and RI 930) using a Chiralcel OD-H column, Ø 0.46 cm × 25 cm. Preparative HPLC was performed on a Dynamix Model SD-1 equipped with a Model UV-1 absorbance detector using a Chiralcel OD column, Ø 5 cm × 50 cm.

Methyl 1-[(2,2′-bipyridine-5-yl)methyl]-1H-imidazole-5-carboxylate and methyl 1-[(2,2′-bipyridine-5-yl)methyl]-1H-imidazole-4-carboxylate (**2a** and **5a**, $C_{16}H_{14}N_4O_2$)

At 0 °C and under Ar a solution of 0.279 g (2,2′-bipyridine-5-yl)methanol (**3a**, 1.5 mmol) in 3 cm^3 dry THF was added to a stirred suspension of 0.465 g Ph_3P (1.77 mmol, 1.18 equiv.) and 0.189 g methyl 1*H*-imidazole-4-carboxylate (**4**, 1.5 mmol, 1.0 equiv.) in 2 cm^3 dry THF. After addition of 0.414 g D*t*BAD (1.8 mmol, 1.2 equiv.) dissolved in 3 cm^3 dry THF the reaction mixture was stirred for 3 h at 0 °C (TLC, MeOH–Et_2O 1:5, no starting material detectable). The solvent was removed under reduced pressure and the resulting viscous oil was stirred for 2 h with 5 cm^3 Et_2O. After filtration, the mother liquor was concentrated in vacuo; 5 cm^3 water and 5 cm^3 HCl (2 M) were added and the mixture was extracted twice with CH_2Cl_2 to remove impurities. After addition of 10 cm^3 NaOH (2 M), the products were extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (MeOH–Et_2O 1:100, then 1:5; TLC on silica: Et_2O–MeOH 5:1, **2a** and **5a** overlap, with streaking; TLC on aluminium oxide: CH_3CN–toluene–conc. NH_3 50:50:1, **2a**: $R_f = 0.7$, **5a**: $R_f = 0.6$) to give 0.265 g (60%) **2a**, m.p. 125–126 °C (CH_2Cl_2–*n*-hexane), and 25 mg (6%) **5a**, m.p. 130–131 °C (CH_2Cl_2–*n*-hexane).

2a: ^{1}H NMR (400.13 MHz): $\delta = 8.63$ (ddd, $J = 4.8$, 1.7, 0.8 Hz, 1H, H_{ar}), 8.53 (d, $J = 2.3$ Hz, 1H, H_{ar}), 8.34 (d with unresolved couplings, $J \sim 8.1$ Hz, 2H, H_{ar}), 7.77 (dt, $J = 7.7$, 1.7 Hz, 1H, H_{ar}), 7.76 (d, $J = 1.0$ Hz, 1H, H_{het}), 7.69 (d, $J = 1.0$ Hz, 1H, H_{het}), 7.57 (dd, $J = 8.3$, 2.3 Hz,1H, H_{ar}), 7.27 (ddd, $J = 7.7$, 4.8, 1.2 Hz, 1H, H_{ar}), 5.56 (s, 2H, NCH_2), 3.78 (s, 3H, OCH_3) ppm; ^{13}C NMR (100.61 MHz): $\delta = 160.5$ (CO), 156.1 (C_{ar}), 155.5 (C_{ar}), 149.2 (HC_{ar}), 148.2 (HC_{ar}), 142.1 (HC_{het}), 138.3 (HC_{het}), 136.9 (HC_{ar}), 135.9 (HC_{ar}), 131.8 (C_{ar}), 123.9 (HC_{ar}), 122.3 (C_{het}), 121.1 (HC_{ar}), 121.0 (HC_{ar}), 51.6 (OCH_3), 47.5 (NCH_2) ppm; IR (Si): $\bar{\nu} = 2,951$, 1,715, 1,462, 1,437, 1,365, 1,126, 1,112 cm^{-1}.

5a: ^{1}H NMR (400.13 MHz): $\delta = 8.63$ (ddd, $J = 4.8$, 1.8, 0.7 Hz, 1H, H_{ar}), 8.54 (br. d, $J = 2.0$ Hz, 1H, H_{ar}), 8.39 (d, $J = 8.4$ Hz, 1H, H_{ar}), 8.35 (ddd, $J = 7.7$, 1.1, 0.7 Hz, 1H, H_{ar}), 7.78 (dt, $J = 7.7$, 1.8 Hz, 1H, H_{ar}), 7.58 (d, $J = 1.3$ Hz, 1H, H_{het}), 7.57 (d, $J = 1.3$ Hz, 1H, H_{het}), 7.57 (dd, $J = 8.4$, 2.0 Hz, 1H, H_{ar}), 7.29 (ddd, $J = 7.7$, 4.8, 1.1 Hz, 1H, H_{ar}), 5.18 (s, 2H, NCH_2), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (100.61 MHz): $\delta = 162.9$ (CO), 156.8 (C_{ar}), 155.1 (C_{ar}), 149.2 (HC_{ar}), 148.2 (HC_{ar}), 137.9 (HC_{het}), 137.0 (HC_{ar}), 136.1 (HC_{ar}), 134.5 (C_{het}), 130.4 (C_{ar}), 125.0 (HC_{het}), 124.1 (HC_{ar}), 121.3 (HC_{ar}), 121.2 (HC_{ar}), 51.7 (OCH_3), 48.7 (NCH_2) ppm; IR (Si): $\bar{\nu} = 2,949$, 1,723, 1,549, 1,461, 1,438, 1,381, 1,231, 1,201 cm^{-1}.

N-Methoxy-N-methyl 2,2′-bipyridine-5-carboxamide (**7**, $C_{13}H_{13}N_3O_2$)

A mixture of 0.82 g ester **6** (3.59 mmol), 0.172 g NaOH (4.30 mmol, 1.2 equiv.), 19 cm^3 water, and 8.2 cm^3 EtOH was stirred and heated under reflux until the starting material was consumed (30 min, TLC, AcOEt). The solution was concentrated under reduced pressure and the residue was dried in a vacuum desiccator over KOH for 18 h. $SOCl_2$ (20 cm^3) and 0.04 cm^3 DMF were added to the residue. The mixture was stirred and heated under reflux for 1 h. After cooling the $SOCl_2$ was removed under reduced pressure (3 mm Hg); 41 cm^3 dry CH_2Cl_2 and 0.419 g *N*,*O*-dimethylhydroxylamine hydrochloride (4.30 mmol, 1.2 equiv.) were added to the residue. The stirred mixture was cooled to 0 °C and 1.16 cm^3 dry pyridine (1.136 g, 14.36 mmol, 4 equiv.) was added dropwise. After stirring for 2.5 h at room temperature, the mixture was concentrated under reduced pressure. Brine was added and the mixture was extracted three times with AcOEt. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to leave a residue which was purified by flash chromatography (TLC: AcOEt, $R_f = 0.37$) to give 0.807 g (92%) amide **7** as a yellow oil. ^{1}H NMR (400.13 Hz): $\delta = 8.98$ (dd, $J = 2.1$, 0.8 Hz, 1H, H_{ar}), 8.65 (ddd, $J = 4.8$, 2.0, 0.8 Hz, 1H, H_{ar}), 8.42 (dd, $J = 8.3$, 0.8 Hz, 1H, H_{ar}), 8.40 (ddd ≈ dt, $J = 7.8$, 1.0, 0.8 Hz, 1H, H_{ar}), 8.12 (dd, $J = 8.3$, 2.1 Hz, 1H, H_{ar}), 7.78 (ddd ≈ td, $J = 7.8$, 7.4, 2.0 Hz, 1H, H_{ar}), 7.29 (ddd, $J = 7.4$, 4.8, 1.0 Hz, 1H, H_{ar}), 3.53 (s, 3H, OCH_3), 3.36 (s, 3H, NCH_3) ppm; ^{13}C NMR (100.63 MHz): $\delta = 167.4$, 157.5, 155.2, 149.3, 148.9, 137.1, 136.9, 129.4, 124.1, 121.5, 120.1, 61.2, 33.2 ppm; IR (Si): $\bar{\nu} = 2,936$, 2,971, 1,644, 1,589, 1,457, 1,435, 1,418, 1,384 cm^{-1}.

1-(2,2′-Bipyridine-5-yl)ethanone (**8**, $C_{12}H_{10}N_2O$)

A solution of 1.09 cm^3 MeLi (1.74 mmol, 1.6 M in Et_2O, 0.4% LiCl) was added dropwise to a stirred mixture of 0.384 g Weinreb amide **7** (1.58 mmol) in 18 cm^3 dry THF under argon at −55 °C. The stirred reaction mixture was allowed to warm up slowly in the cooling bath from −55 °C until the starting material was consumed (TLC, when −40 °C after 50 min). Water (10 cm^3) was added and the mixture was extracted three times with AcOEt. The

combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt, $R_f = 0.64$) to give 0.300 g (96%) ketone **8** as a crystalline solid, m.p. 112–114 °C (*n*-hexane with some CH_2Cl_2). ^{1}H NMR (400.1 MHz): $\delta = 9.18$ (dd, $J = 2.3$, 0.8 Hz, 1H, H_{ar}), 8.68 (ddd, $J = 4.7$, 1.8, 1.0 Hz, 1H, H_{ar}), 8.50 (dd, $J = 8.3$, 0.8 Hz, 1H, H_{ar}), 8.45 (dt, $J = 8.0$, 2 × 1.0 Hz, 1H, H_{ar}), 8.31 (dd, $J = 8.3$, 2.3 Hz, 1H, H_{ar}), 7.82 (ddd, $J = 8.0$, 7.6, 1.8 Hz, 1H, H_{ar}), 7.33 (ddd, $J = 7.6$, 4.7, 1.0 Hz, 1H, H_{ar}), 2.64 (s, 3H, CH_3) ppm; ^{13}C NMR (100.6 MHz): $\delta = 196.5$, 159.5, 155.0, 149.5, 149.4, 137.0, 136.5, 131.9, 124.5, 121.9, 120.8, 26.8 ppm; IR (Si): $\bar{\nu} = 1,682$, 1,588, 1,383, 913 cm^{-1}.

(±), (R)-(+), and (S)-(−)-1-(2,2′-bipyridine-5-yl)ethanol ((±)-**3b**, (*R*)-(+)-**3b**, and (*S*)-(−)-**3b**, $C_{12}H_{12}N_2O$)

$NaBH_4$ (0.054 g, 1.43 mmol) was added to a stirred solution of 0.283 g ketone **8** (1.43 mmol) in 17 cm^3 dry EtOH at 0 °C. After stirring for 10 min at 0 °C and 15 min at room temperature, 1 cm^3 acetone and 5 cm^3 water were added. The mixture was extracted three times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt, $R_f = 0.33$) to give 0.263 g (92%) alcohol (±)-**3b** as a crystalline solid, m.p. 62–64 °C (*n*-hexane with some CH_2Cl_2). ^{1}H NMR (400.13 Hz): $\delta = 8.63$ (ddd, $J = 4.8$, 1.8, 1.0 Hz, 1H, H_{ar}), 8.57 (dt, $J = 2.3$, 2 × 0.7 Hz, 1H, H_{ar}), 8.31 (ddd ≈ dt, $J = 7.8$, 1.2, 1.0 Hz, 1H, H_{ar}), 8.27 (dd, $J = 8.1$, 0.7 Hz, 1H, H_{ar}), 7.80–7.75 (m, 2H, H_{ar}), 7.26 (ddd, $J = 7.6$, 4.8, 1.2 Hz, 1H, H_{ar}), 4.98 (q, $J = 6.6$ Hz, 1H, CHO), 2.81 (br. s, 1H, OH), 1.51 (d, $J = 6.6$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100.63 MHz): $\delta = 155.9$, 155.3, 149.1, 146.9, 141.1, 137.0, 134.1, 123.6, 121.1, 120.9, 67.9, 25.1 ppm; IR (Si): $\bar{\nu} = 3,356$, 2,973, 1,591, 1,576, 1,559, 1,462, 1,437, 1,098, 1,075 cm^{-1}; analytical HPLC: Chiralcel OD-H (5 °C, 0.3 cm^3/min, isopropanol–*n*-hexane 30:70), (−)-**3b**: $t_R = 19.3$ min, (+)-**3b**: $t_R = 23.2$ min.

Preparative HPLC of 0.331 g (±)-**3b** on a chiral stationary phase (Chiralcel OD, water-cooled: 10 °C, 240 cm^3/min, isopropanol–*n*-hexane 30:70) gave 0.143 g less polar enantiomer (−)-**3b** (*ee* by HPLC 99%, $[\alpha]_{20}^{D} = -46.7°cm^2g^{-1}$ ($c = 0.60$, acetone); m.p. 60–61 °C (*n*-hexane with some CH_2Cl_2)) and 0.165 g more polar (+)-**3b** (*ee* by HPLC 99%).

*Transformation of (R)-(+)-**3b** into (S)-(−)-**3b** via Mitsunobu reaction followed by saponification*

DIAD (0.41 cm^3, 0.433 g, 2.14 mmol, 1.2 equiv.) was added, under argon, to a stirred mixture of 0.356 g (*R*)-(+)-**3b** (1.78 mmol), 0.560 g Ph_3P (2.14 mmol, 1.2 equiv.), 0.357 g *p*-$O_2NC_6H_4CO_2H$ (2.14 mmol, 1.2 equiv.), and 6 cm^3 dry THF cooled to −30 °C. The reaction mixture was allowed to warm slowly to +10 °C within 3 h and then concentrated after addition of 1 cm^3 water. The residue was purified by flash chromatography (AcOEt) to give a mixture of hydrazo ester and 1.017 g *p*-nitrobenzoate (*S*)-**9**. KOH (2 M, in MeOH–H_2O 4:1, 10 cm^3) was added and the mixture was stirred for 18 h at room temperature. The solution was concentrated under reduced pressure. Water (5 cm^3) was added and the mixture was extracted three times with AcOEt. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to give 0.166 g (47%) (*S*)-(−)-**3b**, $[\alpha]_{20}^{D} = -46.9°cm^2\ g^1$ ($c = 1.21$, acetone), *ee* 99% by HPLC, m.p. 57–59 °C before crystallisation from *n*-hexane containing a few drops of CH_2Cl_2, afterwards 60–61 °C.

*(R)-Mosher esters of (±)-**3b** and (+)-**3b***

A solution of 0.015 g (±)-**3b** (0.075 mmol) and 0.20 cm^3 solution of (*S*)-MTPA-Cl (0.16 mmol, in dry CH_2Cl_2: 200 mg/cm^3) in 0.5 cm^3 dry CH_2Cl_2 and 1 cm^3 dry pyridine was left at room temperature for 18 h. Water (5 cm^3) was added and after stirring for 5 min the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with 5 cm^3 HCl (2 M), then with a saturated aqueous solution of $NaHCO_3$, dried, and concentrated under reduced pressure. The residue was flash chromatographed (AcOEt, $R_f = 0.69$) to give 0.031 g (quantitative) of a mixture of (+)-**3b**·MTPA-(*R*) and (−)-**3b**·MTPA-(*R*) as an oil. The (*R*)-Mosher ester of (+)-**3b** was prepared similarly. ^{1}H NMR (400.13 MHz) of (*R*)-Mosher ester of (+)-**3b** (only diagnostic signals are given): $\delta = 3.45$ (q, $J = 1.0$ Hz, OCH_3), 1.62 (d, $J = 6.8$ Hz, CH_3) ppm; of (−)-**3b**: 3.54 (q, $J = 1.0$ Hz, OCH_3), 1.68 (d, $J = 6.6$ Hz, CH_3) ppm.

(R)-Methyl 1-[1-(2,2′-bipyridine-5-yl)ethyl]-1H-imidazole-5-carboxylate and (R)-Methyl 1-[1-(2,2′-bipyridine-5-yl)-ethyl]-1H-imidazole-4-carboxylate

(**2b** and **5b**, $C_{17}H_{16}N_4O_2$)

Solutions of 0.115 g (*S*)-(−)-**3b** (0.57 mmol, dissolved in 2 cm^3 dry THF) and 0.170 g di-*t*-butyl azodicarboxylate (0.74 mmol, 1.3 equiv., dissolved in 2 cm^3 dry THF) were added to a stirred mixture of 0.193 g Ph_3P (0.74 mmol, 1.3 equiv.) and 0.079 g methyl 1*H*-imidazole-5-carboxylate (0.63 mmol, 1.1 equiv.) in 2 cm^3 dry THF at −30 °C under Ar. The reaction mixture was allowed to warm to room temperature in the cooling bath within 2 h (TLC, MeOH–Et_2O 1:5); three drops of water were added and the reaction mixture was concentrated under reduced pressure; 4 cm^3 water and 3 cm^3 HCl (2 M) were added to the residue and the mixture was extracted twice with CH_2Cl_2. The aqueous phase was adjusted to pH 8–9 by use of NaOH (1 M) then extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and

concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH–Et_2O 1:10; TLC in MeOH–Et_2O 1:5 $R_f = 0.58$ for **2b**, $R_f = 0.06$ for **5b**) to give 0.124 g (70%) **2b** as a viscous oil and 0.020 g (11%) **5b** as a crystalline solid, m.p. 140-141 °C (CH_2Cl_2–*n*-hexane).

2b: $[\alpha]_D^{20} = +66.7°cm^2g^{-1}$ ($c = 0.73$, acetone); ^1H NMR (400.13 Hz): $\delta = 8.64$ (ddd, $J = 4.8$, 1.8, 1.0 Hz, 1H, H_{ar}), 8.52 (br. d, $J = 2.4$ Hz, 1H, H_{ar}), 8.37–8.34 (m, 2H, H_{ar}), 7.82 (d, $J = 0.8$ Hz, 1H, H_{het}), 7.79 (td, $J = 7.6$, 1.8 Hz, 1H, H_{ar}), 7.78 (d, $J = 0.8$ Hz, 1H, H_{het}), 7.55 (ddd, $J = 8.3$, 2.4, 0.5 Hz, 1H, H_{ar}), 7.29 (ddd, $J = 7.6$, 4.8, 1.0 Hz, 1H, H_{ar}), 6.42 (q, $J = 7.3$ Hz, 1H, C*H*CH_3), 3.77 (s, 3H, OCH_3), 1.92 (d, $J = 7.3$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100.63 MHz): $\delta = 160.6$ (CO), 155.9 (C_{ar}), 155.5 (C_{ar}), 149.2 (HC_{ar}), 147.4 (HC_{ar}), 139.4 (HC_{het}), 138.5 (HC_{het}), 136.9 (HC_{ar}), 136.8 (C_{ar}), 134.5 (HC_{ar}), 123.9 (HC_{ar}), 122.3 (C_{het}), 121.09 (HC_{ar}), 121.0 (HC_{ar}), 53.4 (CHN), 51.5 (OCH_3), 22.0 (CH_3) ppm; IR (Si): $\bar{\nu} = 2,951$, 1,714, 1,461, 1,437, 1,362, 1,219, 1,133, 1,113, 2,948, 1,725, 1,546, 1,460, 1,437, 1,218, 1,197 cm^{-1}.

5b: $[\alpha]_D^{20} = -18.0°cm^2\ g^{-1}$ ($c = 0.70$, acetone); ^1H NMR (400.13 Hz): $\delta = 8.65$ (ddd, $J = 4.8$, 1.8, 1.0 Hz, 1H, H_{ar}), 8.53 (br. d, $J = 2.3$ Hz, 1H, H_{ar}), 8.39 (dd, $J = 8.3$, 0.5 Hz, 1H, H_{ar}), 8.35 (td, $J = 7.7$, 1.0 Hz, 1H, H_{ar}), 7.79 (ddd $\approx$ td, $J = 7.5$, 1.8 Hz, 1H, H_{ar}), 7.66 (d, $J = 1.4$ Hz, 1H, H_{het}), 7.61 (d, $J = 1.4$ Hz, 1H, H_{het}), 7.54 (ddd, $J = 8.3$, 2.3, 0.5 Hz, 1H, H_{ar}), 7.30 (ddd, $J = 7.3$, 4.8, 1.0 Hz, 1H, H_{ar}), 5.46 (q, $J = 7.1$ Hz, 1H, C*H*CH_3), 3.85 (s, 3H, OCH_3), 1.93 (d, $J = 7.1$ Hz, 3H, CH_3) ppm; ^{13}C NMR (100.63 MHz): $\delta = 162.0$ (CO), 156.5 (C_{ar}), 155.1 (C_{ar}), 149.2 (HC_{ar}), 147.1 (HC_{ar}), 137.1 (HC_{ar}), 136.8 (HC_{het}), 135.8 (C_{ar}), 134.5 (HC_{ar}), 134.2 (C_{het}), 124.1 (HC_{ar}), 123.7 (HC_{het}), 121.3 (HC_{ar}), 121.2 (HC_{ar}), 55.0 (HCN), 51.7 (OCH_3), 21.7 (CH_3) ppm; IR (Si): $\bar{\nu} = 2,985$, 2,948, 1,725, 1,546, 1,460, 1,437, 1,218, 1,197 cm^{-1}.

Crystal structure of ***5b***

Crystal data: $C_{17}H_{16}N_4O_2$, FW = 308.34, $T = 297(2)$ K, monoclinic, space group $P2_1$, $a = 7.767(3)$ Å, $b = 7.597(2)$ Å, $c = 13.479(4)$ Å, $\beta = 102.745(8)°$, $V = 775.8(4)$ $Å^3$, $Z = 2$, $D_c = 1.320$ g cm^{-3}, $\mu = 0.090$ mm^{-1}, Bruker AXS Smart APEX CCD 3-axis diffractometer, λ(MoKα) = 0.71073 Å, colourless plate of 0.54 × 0.27 × 0.07 mm^3 from ethanol by evaporation. Of 9,733 reflections measured, 3,794 were unique. Refinement of F^2 using program SHELXTL (version 2006; Bruker AXS, Madison, WI, USA) concluded with $R1 = 0.0460$ and $wR2 = 0.0828$ for 208 parameters and 1,671 data with $I > 2\sigma(I)$. CCDC 756617 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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