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Chemoenzymatic Synthesis of Stannylated Metomidate as a Precursor for Electrophilic Radiohalogenations – Regioselective Alkylation of Methyl 1*H*-Imidazole-5-carboxylate [1]

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Summary. Metomidate (*ee* 99%) substituted with iodine in the phenyl ring was prepared from (*S*)-1-(4-iodophenyl)ethanol (*ee* >98%) obtained by lipase-catalysed resolution and methyl 1*H*-imidazole-5-carboxylate. The two fragments were joined highly regioselectively (alkylation only at N-1 of substituted imidazole) with inversion of configuration using the *Mitsunobu* reaction. Finally, *p*-iodometomidate was transformed into the *p*-trimethylstannyl derivative.

Keywords. Enzymes; Heterocycles; Nucleophilic substitution; Metomidate; Radiopharmaceuticals.

Introduction

Etomidate ((*R*)-(+)-ethyl 1-(1-phenylethyl)-1*H*-imidazole-5-carboxylate, **1**) is a short-acting hypnotic [2] in animals [3] and man [4] without analgesic properties. It is also a potent inhibitor of 11β-hydroxylase, a key enzyme in the biosynthesis of cortisol, corticosterone, and aldosterone in the adrenal cortex [5]. Metomidate (**2**), the corresponding methyl ester, has similar properties. Recently, [O-methyl-^{11}C] metomidate was introduced as a radiotracer for adrenal imaging with positron emission tomography [6]. We have developed a new synthesis of metomidate to introduce the radioactive label in the phenyl ring. Here, we present the synthesis of a 4-(trimethylstannyl)metomidate as a precursor for radiohalogenations (^{123}I, ^{131}I, ^{76}Br, and ^{18}F), primarily with radioiodine [7].

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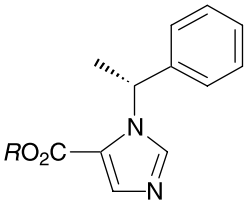


1 *R* = *Et* (etomidate)
2 *R* = *Me* (metomidate)

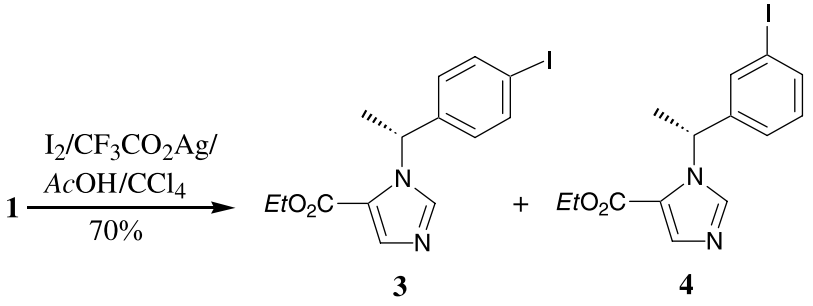
The trimethylstannyl group in a phenyl ring may be replaced easily and rapidly in high yield by electrophilic halogen, making radiohalodemetallation very attractive for the preparation of iodinated radiopharmaceuticals [8]. Substituents in the aromatic nucleus do not interfere with the halodemetallation. The stannylated precursors are derived from the corresponding bromo or iodo compounds. These are either transformed into the lithium or magnesium organometallics, which are reacted with trialkyltin chloride, or are treated with a zero-valent palladium catalyst and hexaalkyldistannane to yield the stannylated precursors. The latter method is the method of choice as it tolerates a variety of functional groups. In the case of etomidate (metomidate), the phenyl ring was selected for stannylation starting from the more reactive iodo derivative. From the three available positions the *para* position was selected for substitution.

Three approaches were considered to obtain 4-iodometomidate: 1) Synthesis of a 4-iodo-substituted derivative from commercially available etomidate or metomidate by electrophilic iodination, which would probably furnish a mixture of regioisomers [9]. 2) Another approach might be the synthesis from unknown (*R*)-1-(4-iodophenyl)ethylamine by an established, at least five step sequence, which is the standard procedure for the laboratory and also technical synthesis of the hypnotic to assemble the imidazole ring [2, 10]. However, this method is laborious and therefore not attractive. 3) We envisaged joining two fragments regioselectively, namely an appropriate alkyl imidazole carboxylate with a chiral 1-(4-iodophenyl)ethyl fragment. Additionally, alkylation at N-1 of the substituted imidazole would be desirable. This method would give access to compounds with the 1-phenylethyl group being modified.

Results and Discussions

Direct Electrophilic Iodination of Etomidate

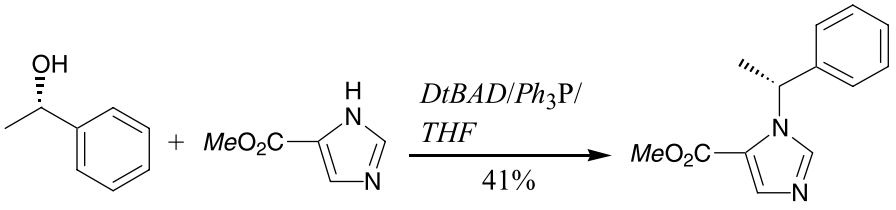
There are numerous methods for the iodination of aromatic compounds differing mainly in the way the electrophilic iodine is generated [9]. Influenced by a previous, delicate but successful iodination [11], we treated commercially available etomidate with 2 equiv. of I_2/CF_3CO_2Ag in dry CCl_4 in the presence of acetic acid at 80°C (Scheme 1). Removal of the solid silver salts, extraction, and flash chromatography furnished in 70% yield an oily mixture of the *p*-iodo derivative **3** and *m*-iodo derivative **4** in a ratio of 11:5. The structures were assigned on the basis of the ^{1}H NMR spectrum of the mixture and later verified by the spectra of the isolated compounds. The two isomeric iodides were separated by preparative HPLC on a chiral stationary phase (Chiracel OD), since flash chromatography and preparative thin layer chromatography did not separate the two isomeric



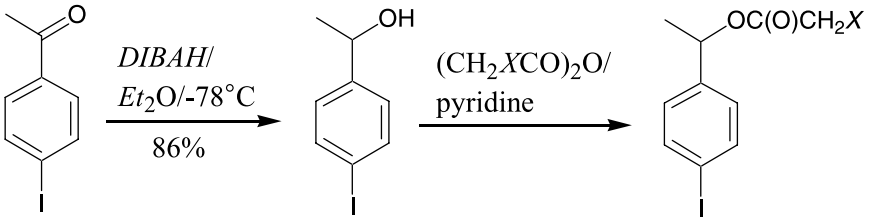
Scheme 1

compounds. Oily compound **4** has a diagnostic triplet ($J = 1.5$ Hz) at 7.43 ppm for the proton having no neighbouring *ortho*-protons. The tedious separation by HPLC and the resistance of the reaction conditions to improve the p/m-ratio, induced us to turn to the third option for the synthesis of isomerically pure *p*-stannane of metomidate on a gram scale from two easily available building blocks. We envisaged a coupling of commercially available methyl 1*H*-imidazole-5-carboxylate and (*S*)-1-(4-iodphenyl)ethanol with inversion of configuration to get the stereochemistry of metomidate, that is (*R*), followed by replacing iodine by trimethyltin. Activation of a benzyl alcohol for a S_N2 substitution may cause problems. However, the *Mitsunobu* reaction seemed to have the capabilities to activate the alcohol to generate a reactive alkoxyphosphonium salt, which reacts with the conjugate base of methyl 1*H*-imidazole-5-carboxylate [12].

To test this idea, *DtBAD* (di-*tert*-butyl azodicarboxylate) was added to a mixture of (*S*)-1-phenylethanol ((*S*)-**5**, 99% *ee*) [13], Ph_3P and methyl 1*H*-imidazole-5-carboxylate (**6**) in *THF* at room temperature (Scheme 2). Workup after 2 h gave a mixture of hydrazo ester and optically active metomidate (*R*)-**2** (41%) which could be separated by flash chromatography. Analytical HPLC on Chiracel OD-H revealed that its *ee* was 92% indicating a small amount of racemisation. The isomer of metomidate having the 1-phenylethyl group at N-3 instead of N-1 of the methyl 1*H*-imidazole-5-carboxylate could not be detected. These two experiments demonstrate that the alkylation is surprisingly regioselective (only at N-1) and proceeds with inversion of configuration, contrary in part to the results obtained with imidazole-4,5-dinitrile and ethyl 1*H*-imidazole-5-carboxylate [14]. Although the yield is medium, the simplicity of the method allows to synthesise analogues of



Scheme 2



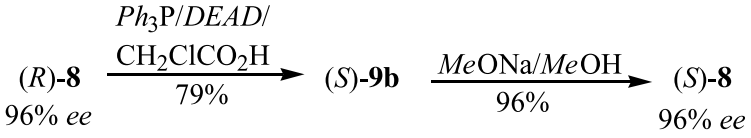
7 (±)-**8** (±)-**9a** X = H, 93%
(±)-**9b** X = Cl, 91%

Scheme 3

etomidate very quickly. The small amount of racemisation could possibly be overcome by lowering the reaction temperature.

Synthesis of (S)-1-(4-Iodophenyl)ethanol by Lipase Catalysed Enantioselective Hydrolysis

Among the many syntheses for chiral, nonracemic secondary benzyl alcohols, the method of *Laumen* and *Schneider* gives products with excellent *ee* (>98%) [13]. They found that lipase *SAM II* hydrolyses acetates and chloroacetates of secondary benzyl alcohols with high enantioselectivity. *Nakamura et al*. reported that 4-iodophenyl methyl ketone was reduced by fermenting *S. cerevisiae* to the (*S*)-alcohol with 96% *ee* in only 30% yield [15]. We decided to use the procedure of *Laumen* and *Schneider* for the resolution of racemic 1-(4-iodophenyl)ethanol [(±)-**8**], which was obtained by reduction of 4-iodophenyl methyl ketone (**7**) with *DIBAH* in 86% yield (Scheme 3). Reduction with $NaBH_4$ in ethanol caused partial deiodination. Esterification of the alcohol with acetic or chloroacetic anhydride/pyridine furnished the acetate (±)-**9a** and chloroacetate (±)-**9b** in 93 and 91% yield. First, racemic acetate (±)-**9a** (3.7 mmol) was hydrolysed with lipase *SAM II* (96 mg) in a biphasic system (phosphate buffer *pH* 7.0/*tert-Bu*O*Me*) using an autotitrator to keep *pH* constant by addition of 0.5 *N* NaOH. After 72 h, when 1.8 mmol of base had been consumed, the reaction was stopped and worked up. Alcohol (*R*)-**8** and ester (*S*)-**9a** were separated by flash chromatography and the ester was transesterified using *Me*ONa/*Me*OH to give (*S*)-**8**. The enantiomeric excesses of alcohols (*R*)- and (*S*)-**8** as determined by HPLC on Chiracel OD–H were 92 and 98%. (*R*)-Configuration was assigned to the alcohol formed by enzymatic saponification as lipase *SAM II* is known to hydrolyse the (*R*)-esters of secondary benzyl alcohols preferentially. Furthermore, iodometomidate which has (*R*)-configuration is obtained only from the alcohol of the ester not accepted as substrate by lipase *SAM II*. The long reaction time was shortened by using the more reactive chloroacetate (±)-**9b**. With 2.6 mmol of substrate and 96 mg of *SAM II*, 98% of the calculated amount of 0.5 *N* NaOH was consumed in the first 2.6 h. After another 14 h, when during the last 9 h virtually no base was consumed, the reaction was stopped. Workup and separation of alcohol (*R*)-**8** and chloroacetate (*S*)-**9b**, which was transesterified to yield (*S*)-**8**, were performed as before. The enantiomeric excess of alcohols (*R*)- and (*S*)-**8** were 98 and >98%. Alcohol (*R*)-**8**

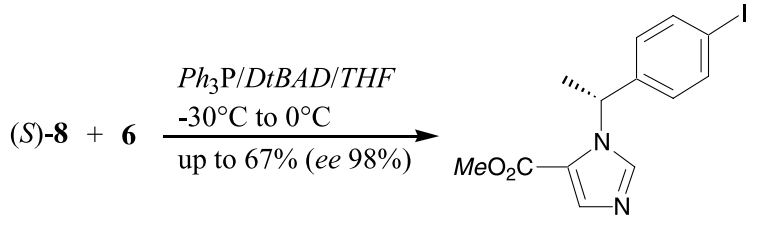


Scheme 4

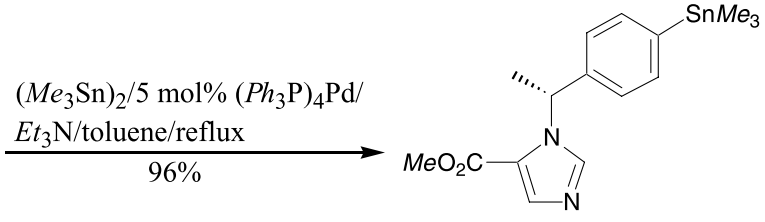
can be transformed into the (*S*)-alcohol of the same enantiomeric excess by *Mitsunobu* reaction with $Ph_3P/DEAD/CH_2ClCO_2H$ (Scheme 4). When the *ee* of the starting alcohol was high enough (98%), the chloroacetate was transesterified directly. If the *ee* is $<98\%$, the chloroacetate can be subjected to enzymatic hydrolysis by lipase *SAM II* before transesterifaction to remove the ester (*R*)-**9b** and thus increase the *ee* of the ester. The combination of lipase-catalysed resolution and *Mitsunobu* reaction allows to transform (±)-**8** into the desired alcohol (*S*)-**8** of at least 98% *ee*.

Synthesis of p-Iodo- and p-(Trimethylstannyl)metomidate

The coupling of 1-(4-iodophenyl)ethanol ((*S*)-**8**) with **6** was performed first at 0°C to minimize racemisation (Scheme 5). The iodinated metomidate (*R*)-**10** was formed in 57% yield as a crystalline product. The *ee* of 95.7% (starting alcohol had *ee* >98%) is indicating that even at that temperature some racemisation occurs. Therefore, the *Mitsunobu* reaction was also conducted at −20 and −30°C. The yields were nearly the same, 56 versus 52% and the *ee* was in both cases >98%, which contrasts with the results with the imidazole-4,5-dinitrile [14]. The *Mitsunobu* reaction at −30°C was conducted at a 4 mmol scale. Starting material could only be detected, if at all, at trace levels at the end of the reaction

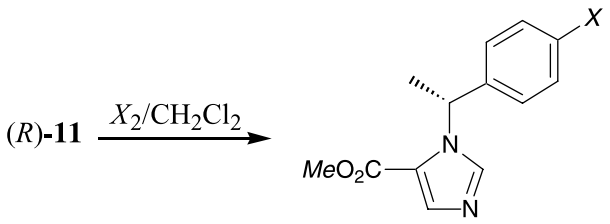


(*R*)-**10**



(*R*)-**11**

Scheme 5



(*R*)-**10** X = I, 92%

(*R*)-**12** X = Br, 99%

Scheme 6

time. Iodide (*S*)-**10** (*ee* >98%) was prepared in 56% yield by the same procedure. Stannylation of iodide (*R*)-**10** on a 3.2 mmol (5.19 mmol) scale by a standard procedure [16] furnished crystalline stannane (*R*)-**11** in 96% (87%) yield. Reductive removal of iodine was insignificant.

To test stannane (*R*)-**11** as precursor for halodemetallation, it was treated with a stoichiometric amount of iodine or bromine (Scheme 6). In both cases, the colour of the halogen was discharged immediately and the corresponding iodo and bromo compounds were formed in virtually quantitative yield. Therefore, (trimethylstannyl)metomidate is a valuable precursor for radiohalogenations.

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 ($\delta = 7.24$). ^{13}C NMR spectra (in part *J* modulated) were recorded on the above spectrometer operating at 100.61 MHz (internal reference $CDCl_3$, $\delta = 77.00$). Coupling constants, *J*, are given in Hz. IR spectra were recorded as films on a silicon disc on a Perkin-Elmer 1600 FT-IR spectrometer [17]. Optical rotations were measured at 20°C on a Perkin-Elmer 341 polarimeter in a 1 dm cell. Elemental analyses (C, H, N) were conducted using the Elemental Analyzer Perkin-Elmer 2400 CHN, their results were in good agreement (±0.2%) with the calculated values. TLC was performed on 0.25 mm thick Merck plates, silica gel 60 F_{254}. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by UV and/or with I_2 or dipping the plate into a solution of 24 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and 1 g of $Ce(SO_4)_2{\cdot}4H_2O$ in 500 cm^3 of 10% H_2SO_4 in H_2O, followed by heating with a hot gun. A Metrohm 702 SM Titrino instrument was used as an autotitrator. Lipase *SAM II* was stored at +4°C and used as supplied. *THF* was distilled from K and diethyl ether from $LiAlH_4$.

Analytical HPLC was performed on a Jasco System (PU-980 pump, UV 975 and RI 930) using a Chiracel 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 Chiracel OD column, Ø 5 cm × 50 cm.

Retention times on analytical column using 5% *iPr*OH/*n*-hexane, 1 cm^3/min, UV (254 nm); for iodoetomidates, 5°C: $t_R = 13.1$ min for *m*-isomer and 14.9 min for *p*-isomer; for 1-phenylethanol, 5°C: $t_R = 8.1$ min for (*R*) enantiomer and 10.6 min for (*S*); for 1-(4-iodophenyl)ethanol, 5°C: $t_R = 9.2$ min for (*S*) enantiomer and 9.2 min for (*R*); for metomidate, 20°C: $t_R = 14.7$ min for (*S*) enantiomer and 17.6 min for (*R*), iodometomidate, 20°C: $t_R = 13.7$ min for (*S*) enantiomer and 17.4 min for (*R*). The mixture of *m*/*p*-iodoetomidates was separated by preparative HPLC using a H_2O-cooled column, 240 cm^3/min of 3% *iPr*OH/*n*-hexane; $t_R = 17.5$ min for *m*-isomer and 19.5 min for *p*-isomer.

(R)-(+)-Ethyl 1-[1-(4-iodophenyl)ethyl]-1H-imidazole-5-carboxylate and (R)-(+)-Ethyl 1-[1-(3-iodophenyl)ethyl]-1H-imidazole-5-carboxylate (**3** and **4**, $C_{14}H_{15}IN_2O_2$)

A mixture of 0.135 g of **1** (0.55 mmol), 18 drops of acetic acid, 0.280 g of I_2 (1.10 mmol), 0.284 g of CF_3CO_2Ag (1.10 mmol), and 5 cm^3 of dry CCl_4 was heated at 80°C (bath temperature) for 16 h under Ar and protected against light. When the starting material was consumed (TLC: Et_2O:iPr_2NH = 9:1, R_f = 0.74 (**1**), 0.62 (**3** and **4**)), the mixture was filtered through Celite and washed with 3 × 10 cm^3 of CH_2Cl_2. The filtrate was washed with aqueous NH_3, $NaHSO_3$, and H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by flash chromatography (*n*-hexane:Et_2O:iPr_2NH = 60:30:1) to give 0.143 g (70%) of a mixture of **3**/**4** (*p*:*m* = 11:5 by ^1H NMR) as a colourless oil. The iodides were separated by preparative HPLC. Iodide **3** crystallised from *n*-hexane, mp 74–74°C; ^1H NMR: δ = 1.29 (t, J = 7.0, $C\underline{H}_3CH_2$), 1.80 (d, J = 7.0, $C\underline{H}_3CH$), 4.21 (*AB* part of an *ABX*$_3$ system, J_{AB} = 11.0, $J_{AX} = J_{BX}$ = 7.0, $CH_3C\underline{H}_2$), 6.26 (q, J = 7.0, $CH_3C\underline{H}$), 6.86 (d, J = 8.5, $2H_{arom}$), 7.61 (d, J = 8.5, $2H_{arom}$), 7.72 (s, H_{het}), 7.74 (d, J = 1.0, H_{het}) ppm; ^{13}C NMR: δ = 14.2, 22.1, 54.9, 60.5, 93.4, 122.6, 128.0, 137.9, 138.2, 139.4, 141.2, 160.2 ppm; IR: $\bar{\nu}$ = 2982, 1713, 1487, 1472, 1374, 1348, 1216, 1133 cm^{-1}; $[\alpha]_D^{20} = +76^\circ\ cm^{-2}\ g^{-1}$ (c = 1.12, acetone).

4: Oil; ^1H NMR: δ = 1.30 (t, J = 7.0, $C\underline{H}_3CH_2$), 1.82 (d, J = 7.0, $C\underline{H}_3CH$), 4.21 (*AB* part of an *ABX*$_3$ system, J_{AB} = 10.5, $J_{AX} = J_{BX}$ = 7.0, $CH_3C\underline{H}_2$), 6.29 (q, J = 7.0, $CH_3C\underline{H}$), 7.04 (t, J = 7.5, H_{arom}), 7.09 (dt, J = 1.5, 7.5, H_{arom}), 7.43 (t, J = 1.5, H_{arom}), 7.60 (dt, J = 1.5, 7.5, H_{arom}), 7.72 (s, H_{het}), 7.77 (d, J = 1.0, H_{het}) ppm; ^{13}C NMR: δ = 14.2, 22.1, 54.6, 60.5, 94.7, 122.6, 125.5, 130.5, 135.2, 137.1, 138.2, 139.5, 143.6, 160.2 ppm; IR: $\bar{\nu}$ = 2979, 2926, 2853, 1711, 1373, 1348, 1215, 1131, 1108 cm^{-1}; $[\alpha]_D^{20} = +40.1^\circ\ cm^{-2}\ g^{-1}$ (c = 2.26, acetone).

(±)-1-(4-Iodophenyl)ethanol ((±)-**8**)

A solution of *DIBAH* (16.45 cm^3, 24.67 mmol, 1.5 *M*, in toluene) was added dropwise to a stirred mixture of 5.08 g of 4-iodoacetophenone (20.65 mmol) in 50 cm^3 of dry Et_2O at −78°C under Ar. After stirring for 2 h at −78°C, 2 cm^3 of *Me*OH were added and stirring was continued for 30 min at room temperature before 10 cm^3 of H_2O were added cautiously and 30 min later, the formed aluminium hydroxide was dissolved in 50 cm^3 of 2*N* HCl under cooling with ice. The organic phase was separated, washed with H_2O and a sat. aqu. solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane:CH_2Cl_2 = 1:2, R_f = 0.20) and bulb to bulb distillation (90–95°C/0.2 mm) to give 3.91 g (86%) of (±)-**8**; mp 47–49°C (Ref. [18] 50.5–51.5°C); ^1H NMR: δ = 1.40 (d, J = 6.5, $C\underline{H}_3CH$), 1.75 (br s, OH), 4.78 (q, J = 6.5, $CH_3C\underline{H}$), 7.06 (d, J = 8.5, $2H_{arom}$), 7.60 (d, J = 8.5, $2H_{arom}$) ppm; ^{13}C NMR: δ = 25.6, 70.3, 93.1, 127.8, 137.9, 145.9 ppm.

(±)-1-(4-Iodophenyl)ethyl acetate ((±)-**9a**)

A mixture of 1.70 g of (±)-**8** (6.85 mmol), 3 cm^3 of dry pyridine, and 3 cm^3 of Ac_2O was stirred for 1 h at 50°C. After cooling, 50 cm^3 of CH_2Cl_2 and 20 cm^3 of H_2O were added and stirring was continued for 10 min. The organic phase was separated, washed with 25 cm^3 of 2*N* HCl, 25 cm^3 of H_2O, and 25 cm^3 of a sat. aqu. solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by bulb to bulb distillation (85–90°C/0.3 mm) (Ref. [19] 114°C/1.1 mm) to give 1.86 g (93%) of (±)-**9a** as a colourless liquid; ^1H NMR: δ = 1.48 (d, J = 6.5, $C\underline{H}_3CH$), 2.05 (s, CH_3CO), 5.78 (q, J = 6.5, $CH_3C\underline{H}$), 7.08 (d, J = 8.0, $2H_{arom}$), 7.65 (d, J = 8.0, $2H_{arom}$) ppm; ^{13}C NMR: δ = 21.3, 22.1, 71.7, 93.3, 128.0, 137.6, 141.4, 170.2 ppm.

(±)-1-(4-Iodophenyl)ethyl chloroacetate ((±)-**9b**, $C_{10}H_{10}ClIO_2$)

Dry pyridine (6.0 cm^3) and 6.2 g of $(CH_2ClCO)_2O$ (36.26 mmol) were added to a stirred solution of 5.95 g of (±)-**8** (24.0 mmol) in 100 cm^3 of dry CH_2Cl_2 at 0°C under Ar. When the reaction was

finished (2 h, TLC: *n*-hexane:CH_2Cl_2 = 3:2, R_f = 0.35 for (±)-**9b**), 40 cm^3 of H_2O and 3.6 cm^3 of conc. HCl were added. After stirring for 10 min, the organic phase was separated and the aqueous phase was extracted with 3 × 15 cm^3 of CH_2Cl_2. The combined organic phases were washed with 50 cm^3 of H_2O and 25 cm^3 of a sat. aqu. solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane:CH_2Cl_2 = 3:2) and bulb to bulb distillation (105°C/0.1 mm) to give 7.09 g (91%) of (±)-**9b**; mp 50–51°C; ^{1}H NMR: δ = 1.54 (d, J = 7.0, C<u>H</u>$_3$CH), 4.03 (*AB* system, J = 14.8, CH_2Cl), 5.90 (q, J = 7.0, CH_3C<u>H</u>), 7.08 (d, J = 8.5, $2H_{arom}$), 7.68 (d, J = 8.0, $2H_{arom}$) ppm; ^{13}C NMR: δ = 21.8, 41.0, 73.8, 93.9, 128.9, 137.8, 140.3, 166.5 ppm; IR: $\tilde{\nu}$ = 2983, 1756, 1591, 1488, 1285, 1176, 1063, 1007 cm^{-1}.

*Enzymatic Hydrolysis of Acetate (±)-**9a** and Chloroacetate (±)-**9b***

Acetate (±)-**9a** (1.08 g, 3.7 mmol), 4 cm^3 of *tert-BuOMe*, 17 cm^3 of phosphate buffer (50 mmol, sterile), and 96 mg of lipase *SAM II* were stirred vigorously at room temperature. The *pH* was kept at 7.0 by addition of 0.5 *N* NaOH using an autotitrator. The reaction was stopped after 72 h (the last 10 h the consumption of base was negligible; 3.6 cm^3 of base had been consumed) by bringing the *pH* to about 2.0 using 2 *N* HCl. 100 cm^3 of H_2O were added and (*S*)-**9a** and (*R*)-**8** were extracted with 3 × 200 cm^3 of CH_2Cl_2. The combined organic layers were washed with 50 cm^3 each of H_2O and a sat. aqu. solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to leave a residue which was purified by flash chromatography (*n*-hexane:CH_2Cl_2 = 3:2 for (*S*)-**9a**, R_f = 0.30, R_f = 0.06 for (*R*)-**8**; *n*-hexane:CH_2Cl_2 = 1:2 for (*R*)-**8**, R_f = 0.10] to give 0.491 g (46%, *ee* 91% after chemical hydrolysis) of (*S*)-**9a** as an oil and 0.393 g (43%, *ee* 98%) of (*R*)-**8** as a crystalline solid.

Chloroacetate (±)-**9b** (0.835 g, 2.57 mmol) was hydrolysed using the same procedure (17 cm^3 of buffer, 4 cm^3 of *tert-BuOMe*, 96 mg of lipase *SAM II*). 98% of the calculated amount of base was consumed in 2.6 h. The reaction was stopped after another 14 h. Virtually no base was consumed during the last 9 h. Flash chromatography (*n*-hexane:CH_2Cl_2 = 3:2 for (*S*)-**9b**, R_f = 0.35; *n*-hexane:CH_2Cl_2 = 1:2 for alcohol (*R*)-**8**, R_f = 0.20] gave 0.367 g (44%, $[\alpha]_D^{20} = -83°\ cm^{-2}\ g^{-1}$ (c = 2.57, acetone), *ee* ≥98% and $[\alpha]_D^{20} = -36°\ cm^{-2}\ g^{-1}$ (c = 2.04, acetone) after chemical hydrolysis) of (*S*)-**9b** as a liquid and 0.393 g (43%, $[\alpha]_D^{20} = +36°\ cm^{-2}\ g^{-1}$ (c = 1.96, acetone), *ee* 98% before crystallisation from *n*-hexane/CH_2Cl_2, afterwards $[\alpha]_D^{20} = +36°\ cm^{-2}\ g^{-1}$ (c = 2.0, acetone), mp 48–49°C) of (*R*)-**8** as a crystalline solid.

Similarly, chloroacetate (±)-**9b** was hydrolysed on a larger scale (5.67 g (17.47 mmol), 40 cm^3 of phosphate buffer, 17 cm^3 of *tert-BuOMe*, 510 mg of lipase *SAM II*, stoichiometric amount of base, 22 h). After the addition of HCl, the reaction mixture was filtered through Celite before extraction with *EtOAc*.

*Chemical Hydrolysis of Acetate (S)-**9a** and Chloroacetate (S)-**9b***

Acetate (S)-**9a** (0.491 g, 1.69 mmol) was dissolved in 17 cm^3 of *Me*OH/*Me*ONa (obtained by dissolving 69 mg of Na in 30 cm^3 of dry *Me*OH). After 1 h, a few drops of H_2O were added, the solution was concentrated under reduced pressure, and 30 cm^3 of water and 15 cm^3 of CH_2Cl_2 were added. The organic layer was separated and the aqueous phase was extracted with 2 × 15 cm^3 of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to leave a residue, which was purified by flash chromatography (*n*-hexane:CH_2Cl_2 = 1:2, R_f = 0.17) to give 0.380 g (91%, *ee* 91%) of (*S*)-**8** as a crystalline solid.

Chloroacetate (*S*)-**9b** was hydrolysed by means of the same procedure in 10 min (yield >90%).

*Synthesis of Chloroacetate (S)-**9b** from Alcohol (R)-**8** by Mitsunobu Reaction*

A solution of 0.706 g of (*R*)-**8** (2.85 mmol, $[\alpha]_D^{20} = +36°\ cm^{-2}\ g^{-1}$ (c = 2.05, acetone), *ee* 96%) in 6 cm^3 of dry *THF* was added dropwise to a stirred solution of 0.894 g of Ph_3P (3.41 mmol) and 0.322 g of CH_2ClCO_2H (3.41 mmol) in 8 cm^3 of dry *THF* at −78°C under an atmosphere of argon, followed by

0.594 g (0.54 cm^3) of *DEAD* (3.41 mmol). The reaction mixture was allowed to warm up to 0°C within 2.5 h and was then concentrated under reduced pressure. The residue was diluted with 5 cm^3 of Et_2O and stirred for 2 h at room temperature. The crystalline precipitate was collected and washed with Et_2O. The mother liquor was concentrated under reduced pressure and the residue was purified by flash chromatography (*n*-hexane:CH_2Cl_2 = 2:1, R_f = 0.38) to give 0.726 g (79%) of (*S*)-**9b**, $[\alpha]_D^{20} = -79° \text{ cm}^{-2} \text{ g}^{-1}$ (c = 1.50, acetone). Chemical hydrolysis of 51 mg of (*S*)-**9b** (0.16 mmol) furnished 0.038 g (96%, *ee* 96%) of (*S*)-**8** as crystalline solid.

General Procedure for the Mitsunobu Reaction of 1-Phenylethanols with Methyl 1H-Imidazole-5-carboxylate

A solution of **5** or **8** (1.1 mmol) in 2 cm^3 of dry *THF* was added dropwise to a stirred solution of 0.139 g of **6** (1.1 mmol) and 0.345 g of Ph_3P (1.3 mmol) in 3 cm^3 of dry *THF* under Ar at ambient temperature, 0, −20, or −30°C. Then, a solution of 0.304 g of di-*tert*-butyl azodicarboxylate (1.32 mmol) in 2 cm^3 of dry *THF* was added and the reaction mixture was stirred for 20 h at room temperature (2 h at 0°C, warming up from −20 to −5°C within 2 h, warming up from −30 to 0°C within 2.5 h). No alcohol could by detected by TLC (Et_2O:iPr_2NH = 10:1). The reaction mixture was concentrated under reduced pressure. The residue was mixed with 5 cm^3 of Et_2O and stirred for 2 h. The crystals (Ph_3PO and hydrazo ester) were collected and washed with 3 × 2 cm^3 of Et_2O. The filtrate was evaporated under reduced pressure to leave a residue, which was purified by flash chromatography (*n*-hexane:Et_2O:iPr_2NH = 60:30:1; TLC: Et_2O:iPr_2NH = 10:1, R_f = 0.44 for **10**, 0.54 for **2**) to give **2** as a viscous oil or **10** as a crystalline solid.

(R)-(+)-Methyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate ((*R*)-**2**)

Alcohol (*S*)-**5** (0.126 g, 1.0 mmol, *ee* 99%) was transformed by the general procedure for the *Mitsunobu* reaction at room temperature (reaction time of 2 h, with di-*tert*-butyl azodicarboxylate) into 0.095 g (41%, *ee* 92%) of (*R*)-**2** as a viscous oil; $[\alpha]_D^{20} = +74° \text{ cm}^{-2} \text{ g}^{-1}$ (c = 0.77, acetone). The spectroscopic data were identical with those of an authentic sample.

(R)-(+)- and (S)-(−)-Methyl 1-[1-(4-iodophenyl)ethyl]-1H-imidazole-5-carboxylate ((*R*)- and (*S*)-**10**, $C_{13}H_{13}IN_2O_2$)

Transformation of 0.272 g of (*S*)-**8** (1.1 mmol, *ee* >98%) into 0.232 g (57%, *ee* 96%) of (*R*)-**10** by the general procedure for the *Mitsunobu* reaction at 0°C (with di-*tert*-butyl azodicarboxylate) and 0.992 g of (*S*)-**8** (4.0 mmol, *ee* >98%) yielded at −30°C 0.767 g (52%, *ee* >98%) of (*R*)-**10**; mp 72–74°C (*n*-hexane); $[\alpha]_D^{20} = +81° \text{ cm}^{-2} \text{ g}^{-1}$ (c = 1.05, acetone). Likewise, 1.98 g of (*S*)-**8** (7.98 mmol) gave 1.91 g (67%, *ee* 99%) of (*R*)-**10** at –30°C; $[\alpha]_D^{20} = +76° \text{ cm}^{-2} \text{ g}^{-1}$ (c = 1.09, acetone). When the transformation was carried out with 0.248 g of (*R*)-**8** (1.0 mmol; *ee* ≥98%) at −20°C, 0.208 g (56%, ee >98%) of (*S*)-**10** were obtained; the *ee* was >98% before and after crystallisation from *n*-hexane; mp 73–74°C; $[\alpha]_D^{20} = -82° \text{ cm}^{-2} \text{ g}^{-1}$ (c = 1.03, acetone).

(*R*)-**10**: ^{1}H NMR: δ = 1.81 (d, J = 7.5, C<u>H</u>$_3$CH), 3.77 (s, OCH_3), 6.26 (q, J = 7.5, CH_3C<u>H</u>), 6.88 (d, J = 8.5, 2H_{arom}), 7.63 (d, J = 8.5, 2H_{arom}), 7.73 (s, H_{het}), 7.75 (d, J = 1.0, H_{het}) ppm; ^{13}C NMR: δ = 22.1 (<u>C</u>H$_3$CH), 51.5 (OCH_3), 55.0 (CH_3<u>C</u>H), 93.5 (IC_{arom}), 122.3 (C_{arom}), 128.0 (2HC_{arom}), 137.9 (2C_{arom}), 138.4 (HC_{het}), 139.5 (HC_{het}), 141.1 (<u>C</u>CO), 160.6 (CO) ppm; IR: $\bar{\nu}$ = 2981, 2947, 1712, 1487, 1437, 1363, 1220, 1134, 1111, 1006 cm^{-1}.

(R)-(+)-Methyl 1-[1-(4-trimethylstannylphenyl)ethyl]-1H-imidazole-5-carboxylate ((*R*)-**11**, $C_{16}H_{22}N_2O_2Sn$)

To a stirred solution of 0.368 g of (*R*)-**10** (1.03 mmol, *ee* >98%) 0.645 g (6.5 cm^3 of a solution of 1.0 g of (Me_3Sn)$_2$ in 10 cm^3 of dry toluene) of hexamethylditin (3.2 mmol), 58 mg of (Ph_3P)$_4$Pd (5 mol%)

and 1.6 cm^3 of dry Et_3N (11.6 mmol) were added under Ar and refluxed (bath temperature 135°C) for 17 h. The cooled solution was concentrated under reduced pressure and the residue was purified by flash chromatography (*n*-hexane:Et_2O:iPr_2NH = 60:30:1; TLC: Et_2O:iPr_2NH = 10:1, R_f = 0.71 for (*R*)-**11**, R_f = 0.50 for (*R*)-**10**) to give 0.377 g (96%) of (*R*)-**11** as a crystalline solid, mp 77–79°C (*n*-hexane); $[\alpha]_D^{20} = +82°\ cm^{-2}\ g^{-1}$ (c = 2.06, acetone).

Analogously, 1.85 g of (*R*)-**10** (5.19 mmol) were transformed into (*R*)-**11**. The crude product was purified by flash chromatography (80.0 g of silica gel) eluting first with *n*-hexane: Et_2O:iPr_2NH = 60:30:1, then *n*-hexane:Et_2O:iPr_2NH = 30:15:1 for (*R*)-**11** (1.784 g, 87%); mp 78–79°C (*n*-hexane); ^1H NMR: δ = 0.25 [s, $^{117/119}Sn$ satellites, 2d, J = 53.2, 55.2, $(CH_3)_3Sn$], 1.82 (d, J = 7.0, $C\underline{H}_3CH$), 3.77 (s, OCH_3), 6.30 (q, J = 7.0, $CH_3C\underline{H}$), 7.13 (d, J = 8.0, $^{117/119}Sn$ satellites, d, J = 9.0, $2H_{arom}$), 7.43 (d, J = 8.0, $^{117/119}Sn$ satellites, d, J = 42.7, $2H_{arom}$), 7.71 (s, H_{het}), 7.74 (s, H_{het}) ppm; ^{13}C NMR: δ = −9.6 [$(CH_3)_3Sn$], 22.2 ($\underline{C}H_3CH$), 51.4 (OCH_3), 55.3 ($CH_3\underline{C}H$), 122.3 (C_{arom}), 125.8 ($^{117/119}Sn$ satellites, d, J = 45.9, $2HC_{arom}$), 136.3 ($^{117/119}Sn$ satellites, d, J = 36.8, $2HC_{arom}$), 138.2 (HC_{het}), 139.8 (HC_{het}), 141.00 (C_{arom}), 142.2 ($\underline{C}CO$), 160.7 (CO) ppm; IR: $\bar{\nu}$ = 2981, 1715, 1437, 1362, 1218, 1133, 1110, 1049 cm^{-1}; $[\alpha]_D^{20} = +83°\ cm^{-2}\ g^{-1}$ (c = 1.05, acetone).

*Halodestannylation of (R)-**11** with Bromine and Iodine*

*Preparation of (R)-(+)-Methyl 1-[1-(4-bromophenyl)ethyl]-1H-imidazole-5-carboxylate ((R)-**12**)*

A solution of 0.097 g of Br_2 (0.604 mmol) in 1 cm^3 of dry CH_2Cl_2 was added dropwise to a solution of 0.237 g of (*R*)-**11** (0.604 mmol) in 2 cm^3 of dry CH_2Cl_2. The colour of the Br_2 disappeared immediately. The solution was evaporated under reduced pressure to leave an oil, which was purified by flash chromatography (*n*-hexane:Et_2O:iPr_2NH = 60:30:1) to give 0.185 g (99%) of (*R*)-**12** as a viscous oil; ^1H NMR: δ = 1.82 (d, J = 7.0, $C\underline{H}_3CH$), 3.77 (s, OCH_3), 6.28 (q, J = 7.0, $CH_3C\underline{H}$), 6.96 (d, J = 8.5, $2H_{arom}$), 7.38 (d, J = 8.5, $2H_{arom}$), 7.73 (s, H_{het}), 7.75 (s, H_{het}) ppm; ^{13}C NMR: δ = 22.1 ($\underline{C}H_3CH$), 51.5 (OCH_3), 54.9 ($CH_3\underline{C}H$), 121.9 (C_{arom}), 122.3 (C_{arom}), 127.8 (2C, HC_{arom}), 132.0 (2C, HC_{arom}), 138.4 (HC_{het}), 139.6 (HC_{het}), 140.4 ($\underline{C}CO$), 160.6 (CO) ppm; IR: $\bar{\nu}$ = 2983, 2950, 1713, 1490, 1436, 1362, 1219, 1134, 1111, 1011 cm^{-1}; $[\alpha]_D^{20} = +74°\ cm^{-2}\ g^{-1}$ (c = 0.75, acetone).

*Iododestannylation of Stannane (R)-**11***

A solution of 30 mg of (*R*)-**11** (0.076 mmol) and 20.0 mg of I_2 (0.079 mmol) in 2 cm^3 of dry CH_2Cl_2 was stirred at room temperature for 45 min. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (*n*-hexane:Et_2O:iPr_2NH = 10:10:1, TLC in same solvent, R_f = 0.30) to give 25 mg (92%) of (*R*)-**10**.

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