# 3- and 4-Pyridylalkyl Adamantanecarboxylates: Inhibitors of Human Cytochrome $P450_{17\alpha}$ (17α-Hydroxylase/$C_{17,20}$-Lyase). Potential Nonsteroidal Agents for the Treatment of Prostatic Cancer

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Various 3- and 4-pyridylalkyl 1-adamantanecarboxylates have been synthesized and tested for inhibitory activity toward the 17α-hydroxylase and $C_{17,20}$-lyase activities of human testicular cytochrome $P450_{17\alpha}$. The 4-pyridylalkyl esters were much more inhibitory than their 3-pyridylalkyl counterparts. The most potent was (*S*)-1-(4-pyridyl)ethyl 1-adamantanecarboxylate (**3b**; $IC_{50}$ for lyase, 1.8 nM), whereas the (*R*)-enantiomer **3a** was much less inhibitory ($IC_{50}$ 74 nM). Nearly as potent as **3b** was the dimethylated counterpart, the 2-(4-pyridylpropan-2-yl) ester **5** ($IC_{50}$ 2.7 nM), which was also more resistant to degradation by esterases. In contrast to their 4-pyridyl analogs, the enantiomers of the 1-(3-pyridyl)ethyl ester were similarly inhibitory ($IC_{50}$ for lyase; (*R*)-isomer **8a** 150 nM , (*S*)-isomer **8b** 230 nM). Amides corresponding to the 4-pyridylmethyl ester **1** and the (*S*)-1-(4-pyridyl)ethyl ester **3b**, respectively **11** and **15b,** were much less inhibitory than their ester counterparts. On the basis of a combination of inhibitory potency and resistance to esterases, the ester **5** was the best candidate for further development as a potential nonsteroidal inhibitor of cytochrome $P450_{17\alpha}$ for the treatment of prostate cancer.

Work from this laboratory has identified a series of esters of 3- and 4-pyridylacetic acid and their α-alkylated derivatives as possessing inhibitory activity toward steroidal 17α-hydroxylase/$C_{17,20}$-lyase, a potential target enzyme for the treatment of prostate cancer.[1,2] The inhibitory activities of 4-pyridyl esters reported in the earlier of these studies[1] was in part rationalized in terms of a partial overlay of key structural elements in the active esters with the steroidal skeleton,[3] with the pyridyl nitrogen atom situated so as to coordinate with the haem iron atom of this P450 enzyme. The results of the later study[2] suggested that an investigation of individual enantiomers of compounds monosubstituted in the methylene residue adjacent to the pyridyl substituent might have markedly different inhibitory potencies.

The enantiomers of α-monoalkylated pyridyl acetic esters are not appropriate synthetic targets for investigating this prediction. Racemization at physiological pH of enantiomers of drugs which have a benzylic proton at the chiral center is well-known.[4] This problem should be circumvented, allowing the effect on enzyme inhibitory activity of chirality adjacent to the pyridyl residue to be explored, by reversal of the ester linkage to give compounds which we have termed "reverse esters". The structural relationship between such "reverse esters" and the esters of the previous studies,[1,2] which we have here termed "normal esters", is shown in Figure 1. The synthesis and evaluation of "reverse esters" with defined chirality at carbon α to a 4- or 3-pyridyl function was the principal objective of the present study. Since

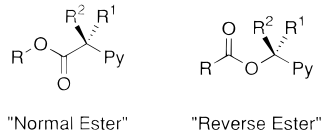


**Figure 1.**

reversal of the ester linkage might influence inhibitory potency, adversely or otherwise, a study of the effect of such reversal was an additional aim, and has revealed potent inhibitors. All the present compounds were derivatives of 1-adamantanecarboxylic acid, chosen as the acid component because of its ready availability, coupled with the generally good inhibitory properties found for adamantyl esters during previous studies.[1,2]

## Results

**Chemistry.** The target esters were prepared, as exemplified for 4-pyridylmethyl 1-adamantanecarboxylate (**1**) by reacting 1-adamantanecarbonyl chloride with the appropriate alkoxide generated from the pyridylalkanol and *n*-butyllithium (Scheme 1). The chiral 1-(4-pyridyl)ethyl esters **3a** and **3b** were prepared from the commercially available chiral alcohols **2a** and **2b**. The (*R*)-**7a** and (*S*)-**7b** enantiomers of 1-(3-pyridyl)ethanol were prepared with high enantiomeric excess (ee) (respectively 87% and 80%) by reducing 3-acetylpyridine with the enantiomers of diisopinocampheylchloroborane, an efficient chiral reducing agent[5] for aromatic prochiral ketones. A single recrystallization of the appropriate chiral 10-camphorsulfonate salts of the derived esters afforded the corresponding 1-(3-pyridyl)ethyl esters **8a** and **8b** of high enantiomeric purity (respective ee values 98% and 95%). The tertiary alcohols 2-(4-pyridyl)-propan-2-ol (**4**) and the 3-pyridyl counterpart **9** required for the preparation of the respective esters **5** and **10** were made by reacting the acetylpyridines with methyllithium (Scheme 2).

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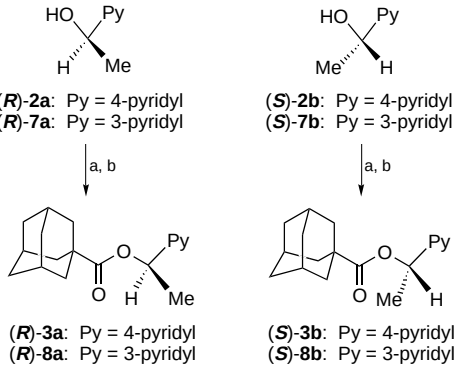
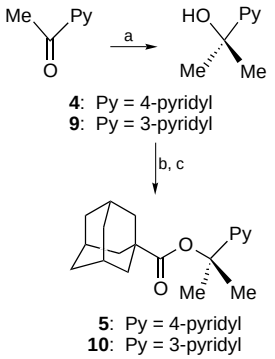
**Scheme 1**[a]




[a] (a) *n*-BuLi; (b) 1-adamantoyl chloride.

**Scheme 2**[a]

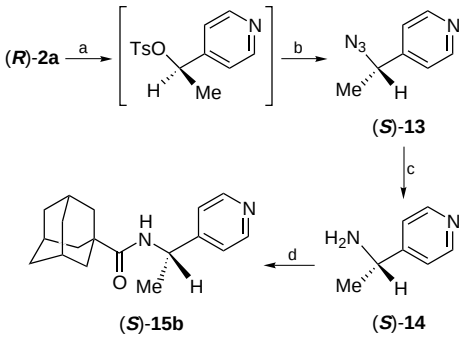



[a] (a) MeLi; (b) *n*-BuLi; (c) 1-adamantoyl chloride.

"Reverse amides" **11** and **12**, corresponding to the esters **1** and **6** and the racemic 1-(4-pyridyl)ethyl amide (**15a**) and its (*S*)-enantiomer **15b** analogous to ester **3b**, were made from the corresponding amines and 1-adamantanecarbonyl chloride. The chiral amine **14** required as precursor to **15b** had been obtained previously[6] by resolution of the racemate by multiple recrystallizations of its *d*-tartrate, but the recovery was poor (20%). Here, it was synthesized (Scheme 3) in three steps from the corresponding chiral alcohol **2a**, based on a strategy employed[7] in the synthesis of selectively deuterated (*S*)-neopentyl tosylate from the corresponding chiral neopentyl alcohol. The chiral pyridyl azide **13** was prepared, with inversion of configuration, by reacting the tosylate of **2a** with $NaN_3$ in THF containing HMPA. Catalytic hydrogenation of **13** gave the amine **14**, of 96% ee, in 49% overall yield.

**Inhibition of Human Testicular 17α-Hydroxylase and $C_{17,20}$-Lyase. Structure−Activity Relationships.** The most potent inhibitors of human testicular steroidal 17α-hydroxylase/$C_{17,20}$-lyase (Table 1) were the 4-pyridyl ester **1** and its methylated derivatives **3b** and **5**. In contrast to the situation with the "normal ester" isopinocampheyl 4-pyridylacetate ($IC_{50}$ for lyase, 5 nM; for hydroxylase, 14 nM) and its dimethylated counterpart (respective $IC_{50}$ values 10 and 26 nM),[2] dimethylation in the present "reverse ester" series gave a much more potent inhibitor (compare **1** and **5**). Indeed the potency of **5** was comparable to that of our recently described steroidal inhibitor 17-(3-pyridyl)androsta-5,16-dien-3$\beta$-ol ($IC_{50}$ for lyase, 2.9 nM; for hydroxylase, 4 nM)[8] and more potent than the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor ketoconazole (Table 1), which has been used clinically.[9] Comparison of the inhibitory activity displayed by the enantiomers of the monomethyl derivative shows that the $IC_{50}$ of (*S*)-enantiomer **3b** was 40-fold lower against the lyase and 100-fold lower against the hydroxylase than the $IC_{50}$ of the corresponding (*R*)-enantiomer **3a** and that the (*R*)-enantiomer is considerably less active than the unsubstituted compound **1**.

**Scheme 3**[a]



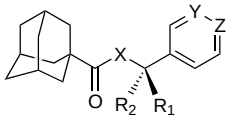

[a] (a) *n*-BuLi, tosyl chloride; (b) $NaN_3$; (c) Pd/C, $H_2$; (d) 1-adamantoyl chloride.

Compared with their analogs in the 4-pyridyl series, the 3-pyridyl derivatives **6**, **8b**, and **10** were much less potent inhibitors. In marked contrast to **3a** and **3b**, the enantiomers of the monomethylated 3-pyridyl derivatives **8a** and **8b** were almost equipotent, and both more active than the unsubstituted compound **6**. The 4−5-fold improvement in activity on dimethylation in this series (compare **6** and **10**, Table 1) was similar to that seen in the present 4-pyridyl series (compare **1** and **5**) and to that seen in 3-pyridyl analogs in the "normal ester" series. Thus, in the latter series, dimethylation converted the moderate inhibitor isopinocampheyl 3-pyridylacetate ($IC_{50}$ for lyase, 88 nM, for hydroxylase, 260 nM) into a good one (respective values 14 and 29 nM).[2]

In view of the potential lability of esters toward esterases (see below) in the body, which might hamper their further development as potential drugs, some corresponding amides were made. However, the amides **11** and **12** were each some 3 orders of magnitude less potent than their ester counterparts **1** and **6**. In an attempt to improve potency, the amide counterpart **15b** of the most potent ester, the (*S*)-enantiomer **3b** of the monomethyl derivative, as well as the corresponding racemate **15a** were made. This (*S*)-enantiomer **15b** was about twice as inhibitory as the racemate **15a**, implying that, as with its ester counterpart **3b**, this enantiomer is much the more active. However, though showing a similar improvement over its nonmethylated counterpart **11** as did the corresponding ester **3b** over **1**, the inhibitory activity of **15b** remained some 2 orders of magnitude less than that of **3b**. Hence replacement of the ester linkage in the present series of compounds by an amide linkage was markedly detrimental to inhibitory activity.

**Aromatase Inhibition.** Ideally, if an inhibitor of cytochrome $P450_{17\alpha}$ is to be used clinically, it should be selective for the target enzyme, and not inhibit other cytochrome P450 enzymes. Esters of 4-pyridylacetic acid have previously been identified as quite potent inhibitors of aromatase,[1] the most active being 1-adamantyl 4-pyridylacetate ($IC_{50}$ 0.09 $\mu$M). Aromatase is a cytochrome P450 enzyme which catalyzes the conversion of androstenedione, a product of the cytochrome $P450_{17\alpha}$ enzymic reaction, into estrone. Inhibition of

**Table 1.** Enzyme Inhibition Data




| compd | substituents X | Y | Z | $R_1$ | $R_2$ | $IC_{50}$ (nM)[a] $C_{17,20}$-lyase[b] | 17α-hydroxylase[b] | $IC_{50}$ (μM)[a] aromatase[c] |
|---|---|---|---|---|---|---|---|---|
| **1** | O | CH | N | H | H | 18 | 43 | 0.58 |
| **3a** | O | CH | N | Me | H | 74 | 340 | 16 |
| **3b** | O | CH | N | H | Me | 1.8 | 3.3 | 5.6 |
| **5** | O | CH | N | Me | Me | 2.7 | 8.8 | 20 |
| **6** | O | N | CH | H | H | 460 | 1500 | 8 |
| **8a** | O | N | CH | Me | H | 150 | 580 | 36 |
| **8b** | O | N | CH | H | Me | 230 | 840 | 4.6 |
| **10** | O | N | CH | Me | Me | 92 | 390 | 51 |
| **11** | NH | CH | N | H | H | 1600 | 7700 | 1.5 |
| **12** | NH | N | CH | H | H | 18000 | 70000 | 3.2 |
| **15a** | NH | CH | N | H or Me | Me or H | 430 | 1900 | ND |
| **15b** | NH | CH | N | H | Me | 210 | 820 | ND |
| ketoconazole | | | | | | 26 | 65 | 16 |

[a] $IC_{50}$ values >200 nM were calculated using linear regression to fit the data to the Dixon equation. Those <200 nM were calculated using nonlinear regression to fit the data to the median effect equation of Chou.[14] The regression coefficients were >0.97. [b] The standard errors for the hydroxylase and lyase $IC_{50}$ values were <12% and averaged 5% of the $IC_{50}$ value. The substrate concentration was 3 μM in both assays. [c] The standard errors for the aromatase $IC_{50}$ values were <15% and averaged 8% of the $IC_{50}$ value. The substrate concentration was 0.38 μM in the assay. [d] ND = not determined.

this enzyme would reduce the level of circulating estrogens which would stimulate the production of gonadotrophins, which in turn would stimulate the testicular production of androgens.[10] For these reasons, the inhibition of human placental aromatase by the "reverse esters" was studied. The reverse ester counterpart **1** of 1-adamantyl 4-pyridylacetate was much less inhibitory (Table 1), and all other compounds studied were even less so. The decrease in potency progressing from the α-unsubstituted compounds (e.g. **1**, $IC_{50}$ 0.58 μM) to their dimethylated counterparts (e.g. **5**, $IC_{50}$ 20 μM) has been noted for "normal ester" counterparts[1−3] and has been ascribed to the occupancy by one of the methyl groups of a region, the position occupied by C(2) of the steroid substrate, intolerant of steric bulk.[11] Compound **5** has comparable inhibitory activity toward aromatase to ketoconazole (Table 1), but has much less activity against aromatase relative to its activity against cytochrome $P450_{17\alpha}$.

**Resistance to Hydrolysis by Esterase.** Esters of the present study are intrinsically susceptible to hydrolysis by esterases *in vivo*. A combination of good inhibitory activity toward the target enzyme and high resistance to esterases is essential if a compound is to be a candidate for further preclinical development. A rat liver microsomal preparation was used as a source of esterase for preliminary evaluation of the effect of methylation α to the ester linkage on the susceptibility of esters to hydrolysis or to oxidative cleavage.[12] Selected compounds were studied in more detail for their stability toward mouse hepatic microsomal esterase and in blood from mouse, rat, and human.

The 4-pyridylmethyl ester **1** and both enantiomers (**3a**,**b**) of the 1-(4-pyridyl)ethyl ester were rapidly hydrolyzed by the rat microsomes (Table 2). The corresponding ester **5** of the tertiary alcohol **4** was resistant, being unaffected after 1 h. In further studies, **5** also proved completely resistant to hydrolysis in rat and human blood, though minor degradation was detected by mouse microsomes (13−15%) and in mouse blood (2%). The ester **1** was completely hydrolyzed by the animal test systems, but proved less labile in human blood, with 45% being metabolized in 1 h. 3-Pyridyl derivatives were not examined, since hydrolysis rates by esterases had been previously found[2] to be similar for analogous 3- and 4-pyridyl derivatives.

**Table 2.** Comparative Rates of Hydrolysis of Selected Esters by Rat Liver Microsomal Esterase at 37 °C

| compd | hydrolysis $t_{1/2}$ (min) |
|---|---|
| **1** | <1[a] |
| **3a** | 0.5 |
| **3b** | 0.5 |
| **5** | >60[b] |

[a] No substrate detectable at 1 min. [b] No hydrolysis at 60 min.

**Table 3.** Extent of Hydrolysis of Selected Esters by Rat and Mouse Liver Microsomes and by Blood from Rat, Mouse, and Human at 37 °C

| | % substrate metabolized at 1 h | | | | |
|---|---|---|---|---|---|
| | rat | | mouse | | |
| compd | microsomes | blood | microsomes | blood | human blood |
| **1** | 100[a] | 100[b] | 100[c] | 100[b] | 45 |
| **5** | 0 | 0 | 13 | 2 | 0 |

[a] No substrate detectable at 5 min. [b] 97% substrate hydrolyzed at 10 min. [c] 97% substrate hydrolysed at 2 min.

**Conclusions.** This study set out to investigate the importance to the inhibitory activity of chirality at the position α to the 3- and 4- pyridyl substituents, by utilizing derivatives not susceptible to racemization. The study has identified several potent inhibitors of cytochrome $P450_{17\alpha}$ and confirmed what features are necessary for resistance to esterase activity. The ester **5**, on the basis of high inhibitory potency and resistance to degradation, merits further assessment as a potential nonsteroidal inhibitor of cytochrome $P450_{17\alpha}$ for use against prostatic cancer.

## Experimental Section

**Chemical Methods.** $^1H$ NMR spectra (250 MHz) (internal $Me_4Si$ = δ 0) were determined in $CDCl_3$ (unless otherwise indicated) using a Bruker AC 250 spectrometer. Infrared

spectra were determined with a Perkin-Elmer 1720X spectrometer. Mass spectra (electron impact, 70 eV) were obtained by direct insertion with a VG 7070H spectrometer and VG 2235 data system. Melting points were determined with a Reichert micro hot stage apparatus and are uncorrected. Chromatography refers to column chromatography on silica gel (Merck Art. 15111) with solvent indicated applied under positive pressure. Petroleum ether refers to the fraction with bp 60−80 °C. Elemental analyses were determined by CHN Analysis Ltd., South Wigston, Leicester, England.

**4-Pyridylmethyl 1-Adamantanecarboxylate (1).** To 4-pyridylmethanol (1.2 g, 11.0 mmol) in THF (40 mL) at −18 °C was added *n*-butyllithium (2.5 M, 4.2 mL, 10.5 mmol) in hexane dropwise with stirring. After 10 min a solution of 1-adamantanecarbonyl chloride (2.0 g, 10.0 mmol) in THF (10 mL) was added, and stirring continued at room temperature for 30 min. The mixture was poured into water, basified with saturated aqueous $NaHCO_3$, and extracted with $Et_2O$. The $Et_2O$ extracts were combined, dried ($Na_2CO_3$), and concentrated. Chromatography, on elution with petroleum ether−$Et_2O$−$Et_3N$, 100:50:1, gave **1** (0.95 g, 35%): mp 57−58 °C (petroleum ether); IR $\upsilon_{max}$ 1730 $cm^{-1}$; NMR $\delta$ 1.74 and 1.96 (2s, 12, adamantyl $CH_2$), 2.05 (s, 3, adamantyl CH), 5.12 (s, 2, $OCH_2$), 7.24 (d, 2, $J$ = 5.7 Hz, pyridyl H-3, H-5), 8.60 (d, 2, pyridyl H-2, H-6). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

***(R)*-(+)-1-(4-Pyridyl)ethyl 1-Adamantanecarboxylate (3a).** The method followed that described for **1**, but using (*R*)-(+)-1-(4-pyridyl)ethanol (**2a**, >99% ee, Fluka Chemie AG, Buchs, Switzerland, 369 mg, 3.0 mmol) in THF (12 mL), *n*-butyllithium (2.5 M, 1.2 mL, 3.0 mmol) in hexane, and 1-adamantanecarbonyl chloride (656 mg, 3.3 mmol) in THF (3 mL). Chromatography, on elution with petroleum ether−$Et_2O$−$Et_3N$ 200:50:1, afforded **3a** (754 mg, 88%): $[\alpha]_D$ +25.8° (*c* 1, $CHCl_3$); IR $\upsilon_{max}$ 1730 $cm^{-1}$; NMR $\delta$ 1.50 (d, 3, $J$ = 6.6 Hz, $CHCH_3$), 1.73 and 1.93 (2s, 12, adamantyl $CH_2$), 2.04 (s, 3, adamantyl CH), 5.80 (q, 1, $J$ = 6.6 Hz, OCH), 7.23 (d, 2, $J$ = 6.1 Hz, pyridyl H-3, H-5), 8.58 (d, 2, pyridyl H-2, H-6); MS $m/z$ 285 ($M^+$). The hydrochloride of **3a** was obtained by passing HCl gas through a solution in $Et_2O$: mp 164−166 °C. Anal. ($C_{18}H_{24}NO_2Cl$) C, H, N; Cl: found, 10.50; required, 11.02.

***(S)*-(−)-1-(4-Pyridyl)ethyl 1-Adamantanecarboxylate (3b).** The method was the same as for **3a**, but using (*S*)-(−)-1-(4-pyridyl)ethanol (**2b**, Fluka AG, 369 mg, 3.0 mmol), and provided **3b** (774 mg, 90%): $[\alpha]_D$ −24.4° (*c* 1, $CHCl_3$); IR, NMR, and MS data were the same as for **3a**. The hydrochloride of **3b** had mp 164−166 °C. Anal. ($C_{18}H_{24}NO_2Cl$) H, N, Cl; C: found, 67.89; required, C, 67.17.

**2-(4-Pyridyl)propan-2-ol (4).** A solution of methyllithium (1.4 M; 30 mL, 42 mmol) in $Et_2O$ was added dropwise to a stirred solution of 4-acetylpyridine (4.65 mL, 42 mmol) in dry THF (100 mL) at −76 °C, and the deep blue solution was allowed to reach ambient temperature. After 24 h the mixture was partitioned between $Et_2O$ and saturated aqueous $NaHCO_3$, and the $Et_2O$ phase was concentrated. Chromatography, on elution with EtOAc−$CH_2Cl_2$−$Et_3N$, 60:40:1, gave **4** (2.59 g, 45%) as an oil: NMR $\delta$ 1.58 (s, 6, $CMe_2$), 7.40 (d, 2, $J$ = 6.2 Hz, pyridyl H-3, H-5), 8.55 (d, 2, pyridyl H-2, H-6); MS $m/z$ 137 ($M^+$).

**2-(4-Pyridyl)propan-2-yl 1-Adamantanecarboxylate (5).** The method followed that described for **1**, but using 2-(4-pyridyl)propan-2-ol (**4**, 0.69 g, 5.0 mmol) in THF (20 mL), *n*-butyllithium (2.5 M; 2.0 mL, 5.0 mmol) in hexane, and 1-adamantanecarbonyl chloride (1.09 g, 5.5 mmol) in THF (6 mL). Chromatography, on elution with $Et_2O$−petroleum ether−$Et_3N$, 150:50:1, gave **5** (1.06 g, 71%) as an oil: IR $\upsilon_{max}$ 1730 $cm^{-1}$; NMR $\delta$ 1.71 (s, 6, $CMe_2$), 1.71 and 1.90 (2s, 12, adamantyl $CH_2$), 2.02 (s, 3, adamantyl CH), 7.23 (d, 2, $J$ = 6.1 Hz, pyridyl H-3, H-5), 8.56 (d, 2, $J$ = 6.1 Hz, pyridyl H-2, H-6). Anal. ($C_{19}H_{25}NO_2$) C, H, N.

**3-Pyridylmethyl 1-Adamantanecarboxylate (6).** The method followed that described for **1**, but using 3-pyridylcarbinol (240 mg, 2.2 mmol) in THF (10 mL), *n*-butyllithium (2.5 M; 0.84 mL, 2.1 mmol) in hexane, and 1-adamantanecarbonyl chloride (397 mg, 2.0 mmol) in THF (2 mL). Chromatography, on elution with petroleum ether−$Et_2O$−$Et_3N$, 200:50:1, gave **6** (422 mg, 78%) as an oil: IR $\upsilon_{max}$ 1728 $cm^{-1}$; NMR $\delta$ 1.71 and 1.91 (2s, 12, adamantyl $CH_2$), 2.02 (s, 3, adamantyl CH), 5.11 (s, 2, $OCH_2$), 7.30 (m, 1, pyridyl H-5), 7.66 (m, 1, pyridyl H-4), 8.56 (m, 1, pyridyl H-6), 8.61 (m, 1, pyridyl H-2). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

***(R)*-(+)-1-(3-Pyridyl)ethyl 1-Adamantanecarboxylate (8a).** The method followed that described for **1**, but using (*R*)-(+)-1-(3-pyridyl)ethanol [**7a**, 87% ee; prepared by asymmetric reduction of 3-acetylpyridylridine with (1*S*)-(+)-*B*-chlorodiisopinocampheylborane[5]] (0.62 g, 5.0 mmol) in THF (20 mL), *n*-butyllithium (2.5 M; 2.0 mL, 5.0 mmol) in hexane, and 1-adamantanecarbonyl chloride (1.09 g, 5.5 mmol) in THF (5 mL). Chromatography, on elution with $Et_2O$−petroleum ether−$Et_3N$, 100:50:1, gave **8a** (1.16 g, 81%) as an oil: $[\alpha]_D$ +29.9° (*c* 2, MeOH), 87% ee. Recrystallization of the (1*R*)-(−)-10-camphorsulfonate salt from EtOAc, and reliberation of the free base, afforded **8a** with 98% ee: $[\alpha]_D$ +33.7° (*c* 2, MeOH): IR $\upsilon_{max}$ 1728 $cm^{-1}$; NMR $\delta$ 1.54 (d, 3, $J$ = 6.5 Hz, $CHCH_3$), 1.72 and 1.90 (2s, 12, adamantyl $CH_2$), 2.03 (s, 3, adamantyl CH), 5.88 (q, 1, $J$ = 6.5 Hz, $CHCH_3$), 7.30 (m, 1, pyridyl H-5), 7.65 (m, 1, pyridyl H-4), 8.56 (m, 1, pyridyl H-6), 8.63 (m, 1, pyridyl H-2); MS $m/z$ 285 ($M^+$). Anal. ($C_{18}H_{23}NO_2$) C, H, N.

***(S)*-(−)-1-(3-Pyridyl)ethyl 1-Adamantanecarboxylate (8b).** The method followed that described for **1**, but using (*S*)-(−)-1-(3-pyridyl)ethanol [**7b**, 80% ee; prepared by asymmetric reduction of 3-acetylpyridine with (1*R*)-(−)-*B*-chlorodiisopinocampheylborane[5]] (0.49 g, 4.0 mmol) in THF (16 mL), *n*-butyllithium (2.5 M; 1.6 mL, 4.0 mmol) in hexane, and 1-adamantanecarbonyl chloride (0.87 g, 4.4 mmol) in THF (4 mL). Chromatography, as described for **8a**, gave **8b** (0.92 g, 81%) as an oil: $[\alpha]_D$ −27.6° (*c* 2, MeOH), 80% ee. Recrystallization of the (1*S*)-(+)-10-camphorsulfonate salt, and reliberation of the free base, afforded **8b** with 95% ee, $[\alpha]_D$ −32.7° (*c* 2, MeOH). IR, NMR, and MS data were the same as for **8a**.

**2-(3-Pyridyl)propan-2-ol (9).** The method followed that for **4**, but using methyllithium (1.4 M; 14 mL, 20 mmol) in $Et_2O$ and 3-acetylpyridine (2.2 mL, 20 mmol) in dry THF (40 mL). Chromatography, on elution with $Et_2O$−petroleum ether−$Et_3N$, 30:10:1, afforded **9** (1.26 g, 46%) as an oil: NMR $\delta$ 1.58 (s, 6, $CMe_2$), 7.22 (m, 1, pyridyl H-5), 7.85 (m, 1, pyridyl H-4), 8.32 (m, 1, pyridyl H-6), 8.65 (m, 1, pyridyl H-2); MS $m/z$ 137 ($M^+$).

**2-(3-Pyridyl)propan-2-yl 1-Adamantanecarboxylate (10).** The method followed that for **5**, but using 2-(3-pyridyl)propan-2-ol (**9**, 0.69 g, 5.0 mmol), and provided **10** (1.06 g, 71%) as an oil: IR $\upsilon_{max}$ 1730 $cm^{-1}$; NMR $\delta$ 1.71 (s, 6, $CMe_2$), 1.77 and 1.94 (2s, 12, adamantyl $CH_2$), 2.02 (s, 3, adamantyl CH), 7.25 (m, 1, pyridyl H-5), 7.65 (m, 1, pyridyl H-4), 8.48 (m, 1, pyridyl H-6), 8.63 (m, 1, pyridyl H-2). Anal. ($C_{19}H_{25}NO_2$) C, H, N.

**4-Pyridylmethyl Adamantanecarboxamide (11).** To a solution of 4-(aminomethyl)pyridine (1.08 g, 10 mmol) in dry THF (25 mL) was added 1-adamantanecarbonyl chloride (1.987 g, 10 mmol). After stirring for 3 h at room temperature, the reaction mixture was added to $H_2O$, treated with saturated aqueous $NaHCO_3$, extracted with $Et_2O$ and EtOAc, dried ($Na_2CO_3$), and concentrated. Chromatography, on elution with petroleum ether−$Et_2O$−$Et_3N$, 20:20:1, gave **11** (1.9 g (70%): mp 177−178 °C (from toluene); IR $\upsilon_{max}$ 3332 $cm^{-1}$ (NH str), 1635 (C═O str); MS $m/z$ 270 ($M^+$). Anal. ($C_{17}H_{22}NO$) C, H, N.

**3-Pyridylmethyl Adamantanecarboxamide (12).** By the foregoing procedure, but using 3-(aminomethyl)pyridine (1.08 g, 10 mmol), compound **12** was prepared: mp 129−130 °C (from toluene). Anal. ($C_{17}H_{22}NO$) C, H, N.

***(S)*-(−)-1-(4-Pyridyl)ethyl Azide (13).** To a solution of (*R*)-(+)-1-(4-pyridyl)ethanol (**2a**, 369 mg, 3.0 mmol) in THF (10 mL) at 0 °C was added *n*-butyllithium (1.6 M in hexane, 1.88 mL, 3.0 mmol), followed after 5 min by *p*-toluenesulfonyl chloride (572 mg, 3.0 mmol). After stirring for a further 30 min at 0 °C, a suspension of $NaN_3$ (585 mg, 9.0 mmol) in hexamethylphosphoramide (HMPA) (Aldrich Chemical Co., Gillingham, Dorset, U.K.) (6 mL) was added and the mixture allowed to attain room temperature. After 1 h, it was poured into $H_2O$ (50 mL) and extracted with $Et_2O$ (2 × 50 mL), and the extracts were dried ($Na_2CO_3$) and concentrated. Chroma-

tography on elution with hexane−$Et_2O$−$Et_3N$, 100:50:1, gave **13** (333 mg, 75%) as an oil: $[\alpha]_D$ −65.7° (*c* 1.0, $CHCl_3$); IR $\upsilon_{max}$ 2096 $cm^{-1}$ ($N_3$); NMR $\delta$ 1.55 (d, 3, $J$ = 6.8 Hz, $CHCH_3$), 4.63 (q, 1, $CHCH_3$), 7.26 (d, 2, $J$ = 6.1 Hz, pyridyl H-2, H-6), 8.63 (d, 2, pyridyl H-3, H-5).

***(S)*-(−)-1-(4-Pyridyl)ethylamine (14).** A solution of the azide **13** (400 mg, 2.7 mmol) in MeOH (5 mL) containing 5% Pd/C (60 mg) was stirred under $H_2$ for 30 min, then filtered, and concentrated. Chromatography on elution with $CH_2Cl_2$−EtOAc−$Et_3N$, 300:50:1 → 100:50:1, gave **14** (214 mg, 65%): bp 98 °C at 4.0 mmHg: $[\alpha]_D$ −24.9° (*c* 1.5, EtOH) of 96% ee (lit.[6] $[\alpha]_D$ −26.6° for homochiral **14**); NMR $\delta$ 1.39 (d, 3, $J$ = 6.8 Hz, $CHCH_3$), 1.65 (s, 2, $NH_2$), 4.10 (1, q, $CHCH_3$), 7.27 (d, 2, $J$ = 6.1 Hz, pyridyl H-3, H-5), 8.54 (d, 2, pyridyl H-2, H-6).

***(R,S)*-1-(4-Pyridyl)ethyl 1-Adamantanecarboxamide (15a).** To a stirred solution of (*R,S*)-1-(4-pyridyl)ethylamine (85 mg, 0.70 mmol; prepared as for **14** but from (*R,S*)-1-(4-pyridyl)ethanol) in $CH_2Cl_2$ (4 mL) was added pyridine (0.2 mL) and then 1-adamantanecarbonyl chloride (278 mg, 1.4 mmol). After 1 h, the mixture was concentrated. Chromatography, on elution with hexane−EtOAc−$Et_3N$, 100:50:1, gave **15a** as white crystals (181 mg, 91%): mp 201−203 °C (from cyclohexane); IR $\upsilon_{max}$ 1633 $cm^{-1}$; NMR $\delta$ 1.46 (d, 3, $J$ = 6.9 Hz, $CHCH_3$), 1.74 (s, 6, adamantyl $CH_2$), 2.07 (s, 3, adamantyl CH), 5.08 (q, 1, $CHCH_3$), 5.80 (s, 1, NH), 7.21 (d, 2, $J$ = 6.0 Hz, pyridyl H-3, H-5), 8.55 (d, 2, pyridyl H-2, H-6); MS *m/z* 284 ($M^+$). Anal. ($C_{18}H_{24}N_2O$) C, H, N.

***(S)*-(−)-1-(4-Pyridyl)ethyl 1-Adamantanecarboxamide (15b).** By the foregoing method, but using (*S*)-(−)-1-(4-pyridyl)ethylamine **(14**, 85 mg, 0.70 mmol), **15b** (185 mg, 93%) was obtained as a white solid, mp 159−160 °C (from cyclohexane), $[\alpha]_D$ −35.7° (c 0.6, MeOH), having IR, NMR, and MS data identical with those of **15a**.

**Enzyme Inhibitory Activities.** The hydroxylase and lyase assays were carried out as described previously[2] using 3 $\mu$M [$^3$H]progesterone or 3 $\mu$M [$^3$H]-17α-hydroxyprogesterone as substrate. The enzyme concentration was estimated to be ≤4 nM. Under the conditions used, the $K_m$ values (±SE) were 0.2 ± 0.05 and 2.2 ± 0.15 $\mu$M, respectively. The reagents and conditions for the assays for inhibition of aromatase enzyme from the microsomal fraction of human placenta were as previously described.[13] The $K_m$ (±SE) for the substrate, androstenedione, was 38 ± 5 nM.

**Hydrolysis of Esters by Microsomal and Blood Esterases.** Esters were incubated with, and extracted from, liver microsomal preparations as described previously[2] and extracts subjected to HPLC (see below). The stability of the esters was also assessed in mouse, rat, and human blood. Thus esters (0.25 mg) were incubated at 37 °C with blood (4.5 mL) and aliquots (0.5 mL) removed at various times up to 1 h. An internal standard (25 $\mu$g) was added before deproteinization of the sample with acetonitrile (0.5 mL); for example, for compounds **3a** and **3b**, the internal standard was compound **1**. Aliquots (100 $\mu$L) of the supernatant obtained after centrifugation were analyzed by HPLC. The HPLC system consisted of a 15 cm Apex column containing 5 $\mu$m of C18 stationary phase with a mobile phase comprising 10 mM sodium phosphate buffer, pH 6.8, and acetonitrile (44:56). Esters were detected by their UV absorption at 229 and 254 nm. No hydrolysis was observed when the esters were incubated in the presence of the esterase inhibitor phenylmethylsulfonyl fluoride (0.1 mM). Half-lives were derived from the plots of the natural log of % ester remaining against time.

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