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$C_{17,20}$-lyase inhibitors. Part 2: Design, synthesis and structure–activity relationships of (2-naphthylmethyl)-1*H*-imidazoles as novel $C_{17,20}$-lyase inhibitors ☆

Nobuyuki Matsunaga,[a,*] Tomohiro Kaku,[a] Akio Ojida,[a,†] Toshimasa Tanaka,[a] Takahito Hara,[b] Masuo Yamaoka,[b] Masami Kusaka[b] and Akihiro Tasaka[a]

[a]*Medicinal Chemistry Research Laboratories, Pharmaceutical Research Division: Takeda Chemical Industries Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*
[b]*Pharmacology Research Laboratories I, Pharmaceutical Research Division: Takeda Chemical Industries Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*

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Abstract—A series of 1- and 4-(2-naphthylmethyl)-1*H*-imidazoles (**3** and **4**) has been synthesized and evaluated as $C_{17,20}$-lyase inhibitors. Several 6-methoxynaphthyl derivatives showed potent $C_{17,20}$-lyase inhibition, suppression of testosterone biosynthesis in rats and reduction in the weight of prostate and seminal vesicles in rats, whereas most of these compounds increased the liver weight after consecutive administrations. The effect on the liver weight was removed by incorporation of a hydroxy group and an isopropyl group at the methylene bridge, as seen in (*S*)-**28d** and (*S*)-**42**. Selectivity for $C_{17,20}$-lyase over 11β-hydroxylase is also discussed, and (*S*)-**42** was found to be a more than 260-fold selective inhibitor. Furthermore, (*S*)-**42** showed a potent suppression of testosterone biosynthesis after a single oral administration in monkeys. These data suggest that (*S*)-**42** may be a promising agent for the treatment of androgen-dependent prostate cancer.

1. Introduction

Prostate cancer is now the second leading cause of cancer death in men in the US. The prostate cancer in about 80% of these patients grows androgen-dependently and responds to first-line endocrine therapy. At present, the standard treatment includes orchidectomy and its medical equivalent, the administration of gonadotropin-releasing hormone (GnRH) analogues, which abolish the production of testosterone in the testes. However, these treatments do not inhibit adrenal androgen production and therefore are frequently combined with an androgen receptor antagonist to block the action of residual adrenal androgens.[2,3] The combination strategy is termed combined androgen blockade (CAB), although to date none of the androgen antagonists achieve effective therapeutic results due to suboptimal pharmacokinetic properties or substantial efficacy-limiting adverse effects. Furthermore, long term treatment with androgen antagonists cause the selection of androgen receptor mutations in prostate cancers, and antagonists may become agonists.[4–7]

An alternative target would be $C_{17,20}$-lyase, one of the key enzymes responsible for the biosynthesis of androgens, that catalyzes the conversion of 17α-hydroxypregnenolone and 17α-hydroxyprogesterone into the weak androgens, dehydroepiandrosterone and androstenedione, respectively, in testes and adrenal glands. Since these weak androgens are subsequently converted into more potent androgens, such as testosterone and dihydrotestosterone in prostate cancer cells, the inhibition of $C_{17,20}$-lyase could prevent initial androgen production and consequently prevent subsequent conversion to more potent androgens. Therefore, the use of $C_{17,20}$-lyase inhibitors may offer a promising therapeutic approach, either as a single agent or in combination

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☆ See Ref. 1.
* Corresponding author. Tel.: +81-6-63006909; fax: +81-6-63006306; e-mail: matsunaga_nobuyuki@takeda.co.jp
† Present address: Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 812-8581, Japan.

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with castration, for the treatment of androgen-dependent prostate cancer.[8,9] Among $C_{17,20}$-lyase inhibitors, ketoconazole has been used clinically in the treatment of patients suffering from advanced prostate cancer.[10–12] However, ketoconazole has now been withdrawn from clinical use because of significant adverse effects, due to inhibition of other P450 enzymes at clinical doses.[13] In recent years, $C_{17,20}$-lyase inhibitors have been reported,[14–34] and some of them have entered clinical trials.

We started out the de novo design based on the substrate mimic strategy, and we have previously reported that 1-[(*E*)-3-(2-naphthyl)-2-propen-1-yl]-1*H*-imidazole (**1a**) and 1-[(*E*)-3-(benzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (**1b**) are potent $C_{17,20}$-lyase inhibitors for rat and human enzymes, with suppression of testosterone biosynthesis in vivo in rats (Fig. 1).[1] A number of analogues were synthesized and evaluated, and consequently **1c** showed more potent in vivo efficacy with extended duration. In the course of our research, 1-(2-naphthylmethyl)-1*H*-imidazole (**2**) was also found to be a potent $C_{17,20}$-lyase inhibitor. The compound was attractive because it has a simple structure that allows a wide range of modification. Therefore, we decided to modify **2** as a new lead compound, to develop a novel class of $C_{17,20}$-lyase inhibitors. We herein describe the synthesis and SAR study of (2-naphthylmethyl)-1*H*-imidazoles (**3** and **4**) as $C_{17,20}$-lyase inhibitors. Selected compounds were also evaluated for suppression of testosterone biosynthesis and reduction in the weight of androgen-dependent organs in male rats. We also discuss a possible binding mode for these inhibitors in the human $C_{17,20}$-lyase model and the selectivity for $C_{17,20}$-lyase over 11β-hydroxylase.

2. Molecular design

We first performed the docking study on the homology model of human $C_{17,20}$-lyase with a intrinsic ligand, 17α-hydroxypregnenolone (Fig. 2). The docking mode suggested that the 3β-hydroxy group of 17α-hydroxypregnenolone (blue) should form a hydrogen-bond with the OH of Thr101 in the enzyme. Next, we investigated the docking mode of **2** (white) in the enzyme model, and it was suggested that the 6-position on the naphthalene ring of **2** may occupy the same regions of space as the 3β-hydroxy group of 17α-hydroxypregnenolone. We thus proposed the incorporation of a hydrogen-bond acceptor substituent at the 6-position on the naphthalene ring, which could form a hydrogen-bond with Thr101 of the enzyme. Furthermore, the model sug-

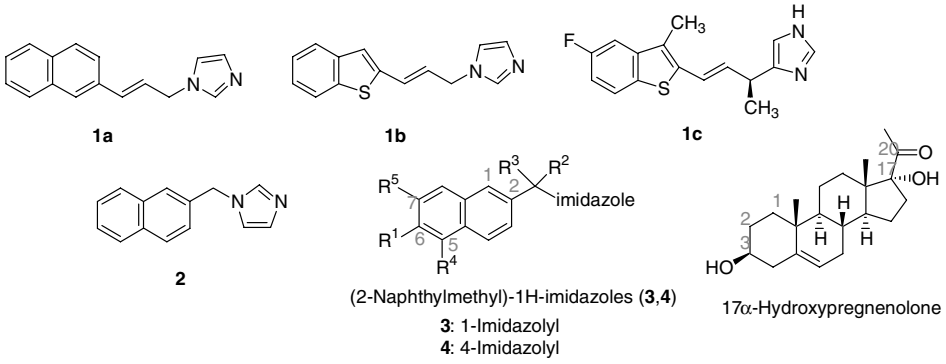


Figure 1.

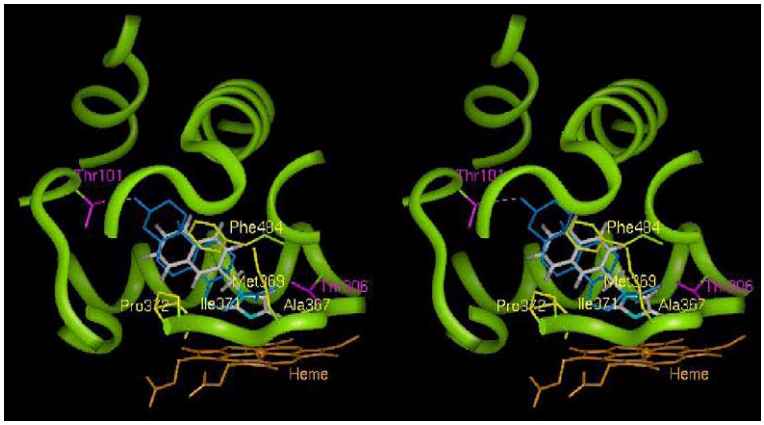


Figure 2. Proposed binding mode of **2** (white) and 17α-hydroxypregnenolone (blue) at the active site in a human $C_{17,20}$-lyase model. Selected active site residues are labeled; orange, heme; magenta, polar residues; yellow, lipophilic residues.

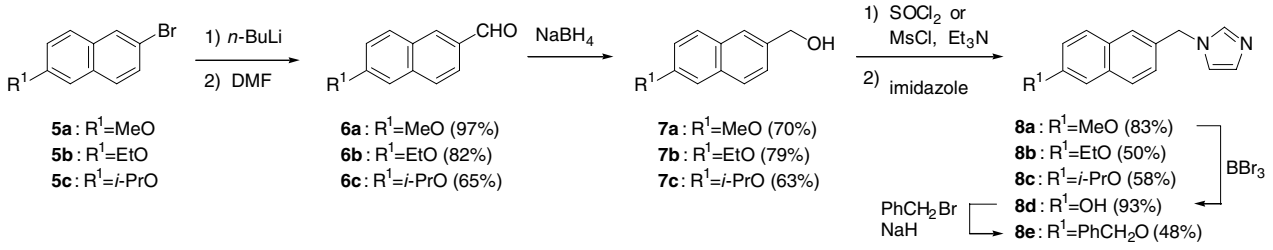
gested that Ala367, Met369, Ile371, Pro372 and Phe484 in the enzyme might construct a small lipophilic pocket near the heme, which prompted us to introduce a lipophilic group on the methylene bridge between the naphthalene and the imidazole to interact with the pocket.

3. Chemistry

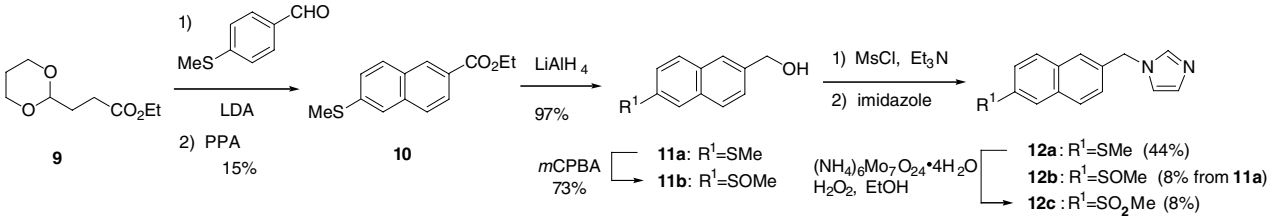
The synthesis of 1-imidazolyl compounds is shown in Schemes 1–3. The alkoxy derivatives at the 6-position on the naphthalene ring were synthesized as shown in Scheme 1. 2-Bromonaphthalenes **5a–c** were lithiated with *n*-BuLi and treated with DMF to give the aldehydes **6a–c**, which were reduced with $NaBH_4$ to afford the alcohols **7a–c**. The alcohols were converted to the 1-imidazolyl derivatives **8a–c** in twosteps; chlorination with $SOCl_2$ or methanesulfonylation with MsCl in the presence of triethylamine, followed by reaction with imidazole. Demethylation of **8a** was achieved with BBr_3 to yield the naphthol **8d**, which was treated with benzylbromide in the presence of NaH to afford the benzyl ether **8e**.

The sulfide, sulfoxide and sulfone derivatives were prepared with naphthalene ring construction[35] as shown in Scheme 2. The acetal ester **9** was treated with LDA and then reacted with 4-methylthiobenzaldehyde. The intermediate was subjected to a ring closure reaction by heating with polyphosphoric acid (PPA) at 120 °C affording the naphthoate **10**. Compound **10** was reduced by $LiAlH_4$ to give the alcohol **11a**, and the sulfide was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to yield the sulfoxide **11b**. Compounds **11a** and **11b** were mesylated and reacted with imidazole giving the 1-imidazolyl derivatives **12a** and **12b**, respectively. The sulfone **12c** was prepared by oxidation of the sulfide **12a** using ammonium heptamolybdate tetrahydrate and hydrogen peroxide.

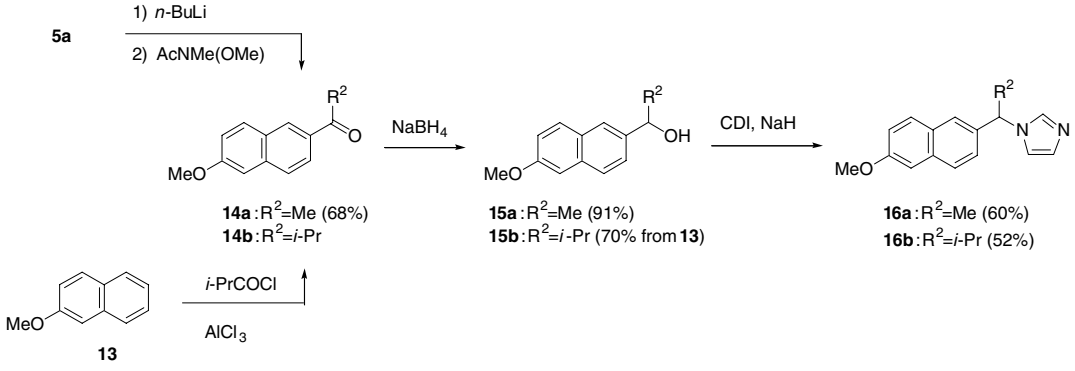
Compounds with an alkyl group (R^2) on the methylene bridge were synthesized as shown in Scheme 3. The methyl naphthyl ketone **14a** was readily prepared from **5a** via lithiation followed by addition of



Scheme 1.



Scheme 2.



Scheme 3.

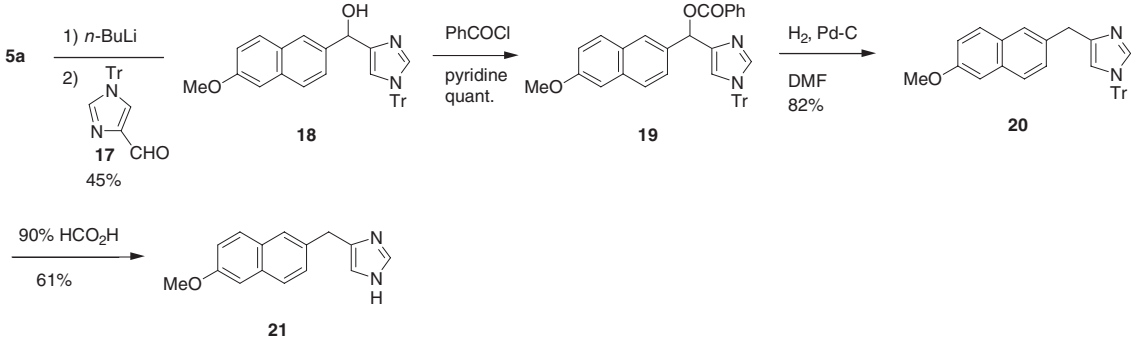
N-methoxy-*N*-methylacetamide. The isopropyl naphthyl ketone **14b** was obtained from the 2-methoxynaphthalene **13** by a Friedel–Crafts acylation. Reduction of **14a** and**14b** with $NaBH_4$ gave the alcohols **15a** and **15b**, which were converted to the imidazolyl derivatives **16a** and **16b** by treatment with carbonyldiimidazole (CDI) in the presence of a catalytic amount of NaH.

The 4-imidazolyl compounds were prepared as described in Schemes 4–9. The synthesis of compound **21** is shown in Scheme 4. Reaction of **5a** with the aldehyde **17**[36] was carried out via lithiation to give the secondary alcohol **18**. Benzoylation of the hydroxy group afforded the ester **19**, which was subjected to debenzoyloxygenation with H_2/Pd–C to yield **20**. The trityl (Tr) group in **20** was deprotected with 90% HCO_2H to furnish **21**.

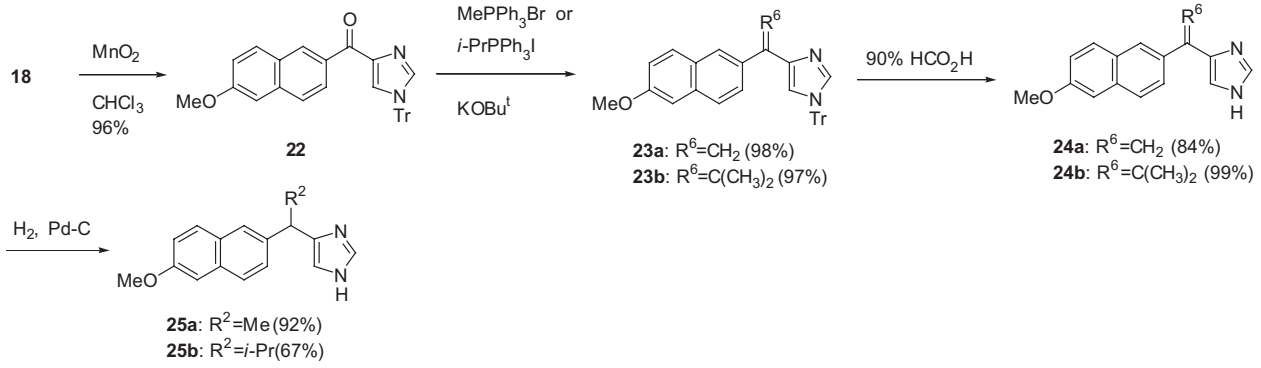
Compounds possessing an alkyl group (R^2) on the methylene bridge were synthesized as shown in Scheme 5. The alcohol **18** was oxidized with MnO_2 to provide the ketone **22**. A Wittig reaction of **22** with methyltriphenylphosphonium bromide or isopropyltriphenylphosphonium iodide gave the olefins **23a** and **23b**, which were detritylated to yield **24a** and **24b**. Catalytic hydrogenation of these olefins afforded compounds **25a** and **25b**.

Synthesis of the compounds with a hydroxyl group on the methylene bridge, is shown in Scheme 6. The compound **26** was prepared from **18** by detritylation with 90% HCO_2H. Compounds **28a**,**d**,**i**–**k** were obtained from the ketone **22** in two-steps. The addition of the appropriate aryl lithium reagents, or Grignard reagents, to **22** provided the tertiary alcohols **27a**,**d**,**i**–**k** and removal of the Tr group gave **28a**,**d**,**i**–**k** (Method A). Compounds **28b**,**c**,**e**–**h** were synthesized by the reverse two-step procedures. Namely, treatment of **22** with 90% HCO_2H gave **29**, which were reacted with the corresponding Grignard reagent to yield **28b**,**c**,**e**–**h** (Method B). Optical resolution of the racemic compound **28d** was accomplished by HPLC using Chiralpak® AD to give the enantiomers (*S*)-**28d** and (*R*)-**28d**. Stereochemistry of these enantiomers was determined by a single-crystal X-ray analysis of (*R*)-**28d** (Fig. 3).

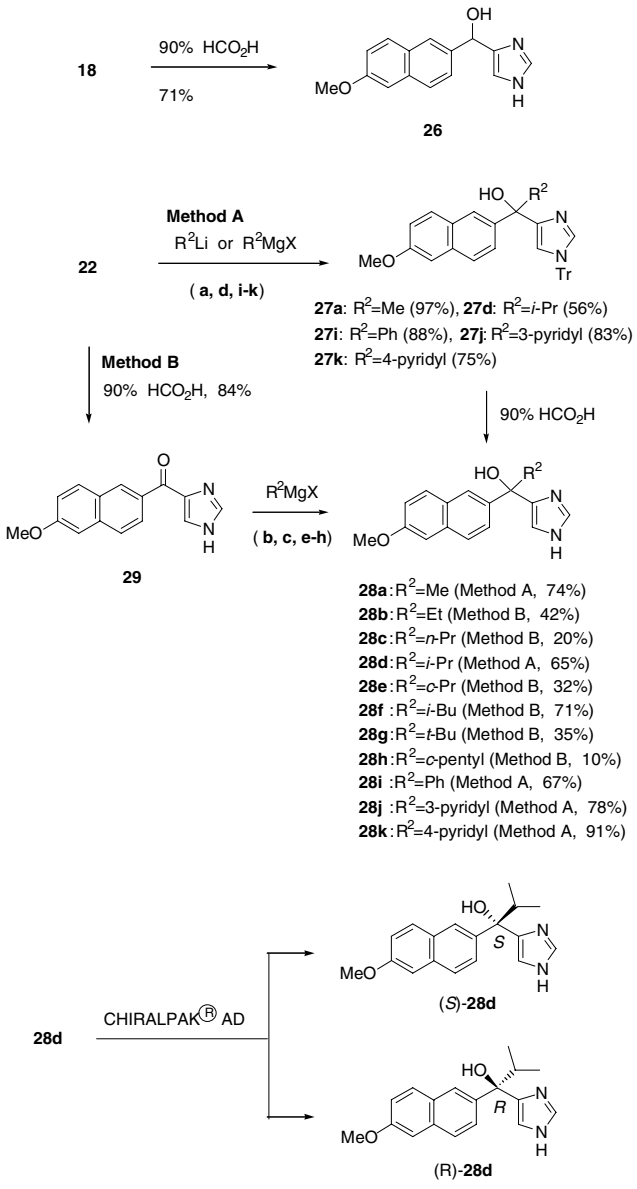
The compounds with an additional substituent on the naphthalene ring were synthesized as described in Scheme 7. Introduction of a formyl group at the 5-position of **5a** was achieved by Vilsmeier reaction to afford the aldehyde **30**. Reduction of the formyl group using $NaBH_4$ yielded the alcohol **31**, and the hydroxyl group was converted to the methyl group by methanesulfonylation, iodination and reduction to provide the 5-methylnaphthalene **32**. Baeyer–Villiger reaction of **30** using *m*-CPBA gave the formate **33**, followed by hydrolysis with LiOH and methylation of the resulting hydroxyl group to yield the 5,6-dimethoxynaphthalene **34**. The naphthalenes **32** and **34** were lithiated and reacted with the imidazolyl isopropyl ketone **35**[37] to give **36a** and **36b**, respectively. The aldehyde **37** was subjected to naphthalene ring construction as described above, with some modification, to provide **38**. The ester was reduced using



Scheme 4.



Scheme 5.



Scheme 6.

$LiAlH_4$ to afford the alcohol **39**, which was oxidized with MnO_2 to yield the aldehyde **40**. Then **40** was treated with 1,4-dilithioimidazole, which was prepared from 4-bromoimidazole and *t*-BuLi by Katritzky's procedure,[38] to provide the imidazolyl naphthyl ketone **41**. In this reaction, the product was not the corresponding alcohol but the ketone as Katritzky obtained. Grignard reaction of **41** with isopropylmagnesium chloride furnished **42**. Optical resolution of **42** was accomplished by HPLC using Chiralpak® AD to give (*S*)-**42** and (*R*)-**42**, respectively, which were crystallized as the fumarate salts. Stereochemistry of these enantiomers was determined by a single-crystal X-ray analysis of (*S*)-**42** as the salt with (−)-(4*S*)-5,5-dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide [(−)-CPA][39,40] (Fig. 4).

The 1,2-dihydronaphtho[2,1-*b*]furan derivative **47** was synthesized via the key intermediate **46** as shown in Scheme 8. Allylation of **43** followed by a Claisen rearrangement at 190 °C gave the 1-allyl-2-naphthol **44**. Ozonolysis of **44** followed by treatment with $NaBH_4$ afforded the diol **45** and intramolecular dehydration under acidic conditions provided **46**. Lithiation of **46** and then addition to **35** furnished **47**.

The 2,3-dihydronaphtho[2,3-*b*]furan derivative **56** was synthesized as shown in Scheme 9. Bromination of 2,3-dihydro-1-benzofuran (**48**) followed by formylation gave the aldehyde **50**, which was converted to the imidazolyl naphthyl ketone **55** by the similar method described for **42**. Since Katritzky's imidazole introduction into **53** afforded the alcohol **54**, additional oxidation with MnO_2 was employed to obtain **55**. A Grignard reaction of **55** with *i*-PrMgCl provided **56**.

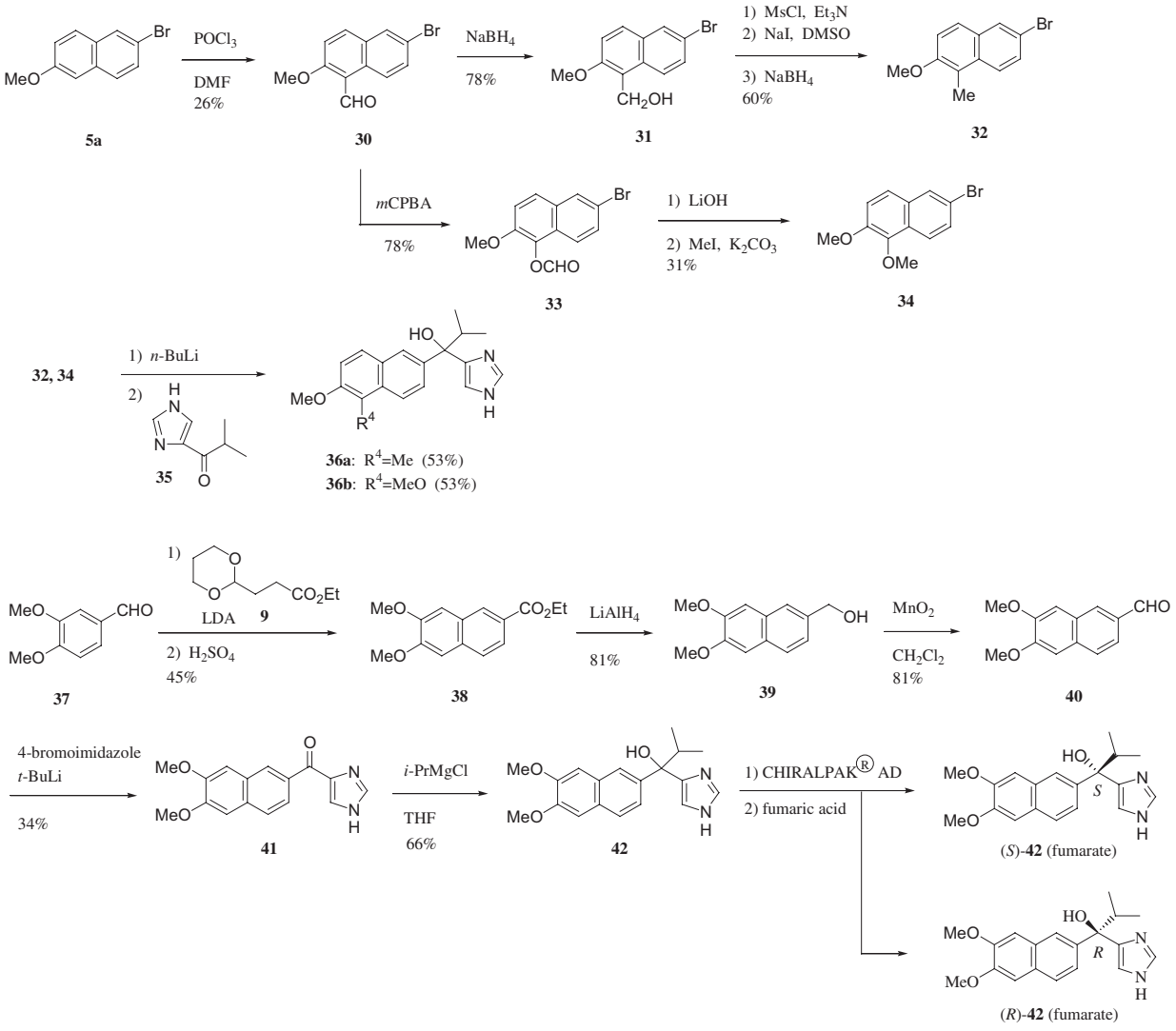
4. Results and discussion

4.1. Enzyme inhibitory activity (in vitro study)

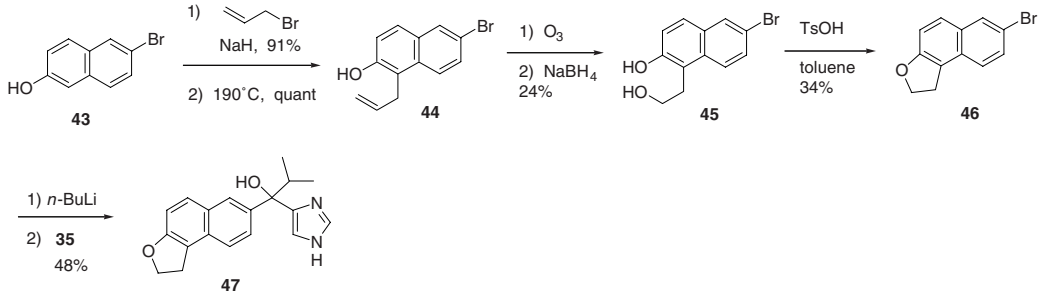
Test compounds were evaluated in vitro for the inhibition of rat and human $C_{17,20}$-lyase using the radiometric assay described in our previous paper.[1] The source of the rat and human enzymes were testicular microsomes and a recombinant enzyme,[1,41] respectively.

The pharmacological activities of 1-imidazolyl and 4-imidazolyl series are shown in Tables 1 and 2, respectively. In the 1-imidazolyl derivatives, small alkoxy substituents for R^1, such as in **8a** and **8b**, slightly increased the inhibitory activity towards rat and human enzymes compared to the unsubstituted compound **2** (Table 1). The isopropoxy compound **8c** led to an increase in the activity only against the rat enzyme. The benzyloxy group, as in **8e**, resulted in significantly less inhibition than the other alkoxy compounds. The methylsulfide **12a** showed potent activity, while the methylsulfoxide and methylsulfone (**12b** and **12c**) led to a modest decrease in the inhibition. Alkyl groups for R^2, such as in **16a** and **16b**, resulted in the same level of activity as for **8a**.

Next, we investigated 4-imidazolyl compounds and found that the orientation of the 4-imidazolyl group corresponded with the potency of the corresponding 1-imidazolyl compounds (comparison of **21** and **8a**, **25a** and **16a**, **25b** and **16b**). Alkyl substituents for R^2 had a negligible effect on the enzyme inhibition, as did 1-imidazolyl compounds. The structure–activity relationships regarding incorporation of a hydroxy group at R^3 and an alkyl group at R^2 were interesting. The hydroxy group at R^3 tended to lower the inhibitory activity, but the activity depended on the size of R^2. The isopropyl group was found to be optimum for R^2 in a rat enzyme inhibition assay. Both smaller and larger alkyl groups decreased the activity (comparison of **26** and **28a**–**h**). For the human enzyme, methyl to propyl R^2 groups were appropriate size for the optimum enzyme inhibition. An aromatic group for R^2, such as in **28i**–**k**, led to reduced activity. These results suggest a possible



Scheme 7.



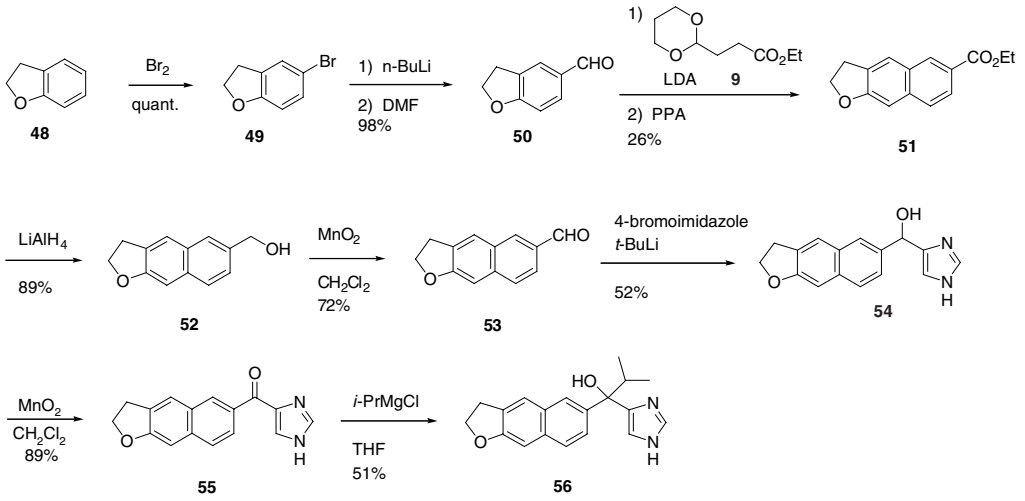
Scheme 8.

interaction with the enzyme and will be discussed in the modeling section.

4.2. Suppression of testosterone biosynthesis in rats (in vivo study)

Selected compounds with an IC_{50} of <50 nM towards the rat enzyme were evaluated in vivo for the suppression of testosterone biosynthesis. Test compounds were orally administrated to male rats ($n = 5$) at a dose of 25 mg/kg. After 2 and 5 h, the serum concentration of testosterone was measured by a specific radioimmunoassay and expressed as the percentage of the control.

The 1-imidazolyl compounds with a methoxy group at R^1 (**8a**, **16a** and **16b**), dramatically reduced the serum testosterone concentration to 4–5% and 1% of the con-



Scheme 9.

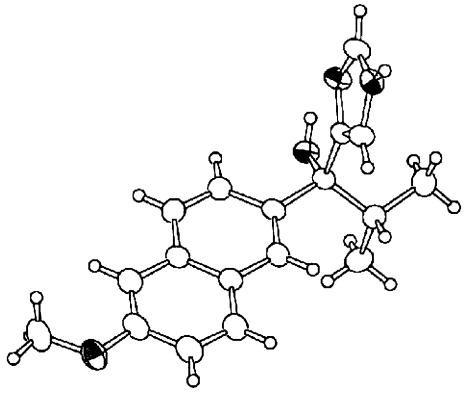


Figure 3. Crystal structure of (*R*)-**28d**.

trol at 2 and 5 h after treatment, respectively. These three compounds obviously had more potent in vivo effects than the lead compound **2**. Ethoxy or isopropoxy derivatives (**8b** and **8c**) showed a potent reduction in the serum testosterone concentration at 2 h after treatment, while the duration of action was insufficient at 5 h after treatment. The methoxy and methylthio groups at R^1 were the key structural determinants for the in vivo effects with extended duration.

The 4-imidazolyl compounds **21**, **25a** and **25b** showed strong reduction in the serum testosterone level, as did the corresponding 1-imidazolyl analogues (comparison of **21** and **8a**, **25a** and **16a**, **25b** and **16b**). It should be noted that suppression of testosterone biosynthesis was diminished by $R^3 = OH$ (e.g. **28b** and **28c**), but incorporation of a hydroxy group and an isopropyl group at R^2 and R^3 (compound **28d**) resulted in preferable serum testosterone reduction, to 4% and 13% of the control at 2 and 5 h after treatment, respectively.

4.3. Effects on the weight of prostate and seminal vesicles in rats (in vivo study)

Selected compounds were orally administrated to male rats ($n = 5$) at a dose of 50 mg/kg, twice a day, 9 times in total. After the final administration, the effects of the test compounds on the weight of androgen-dependent organs, such as prostate and seminal vesicles, were evaluated. These organ weights are shown as the % of the control values, which were calculated by the equation;

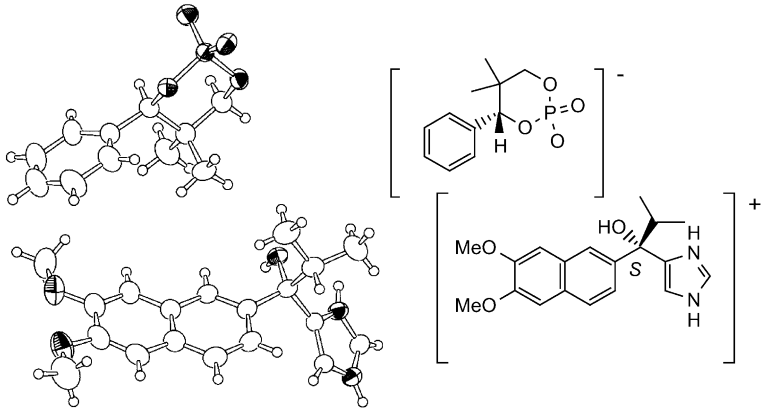
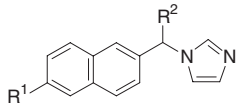


Figure 4. Crystal structure of (*S*)-**42** as the salt with (−)-(4*S*)-5,5-dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide.

Table 1. Pharmacological activities of 1-imidazolyl derivatives



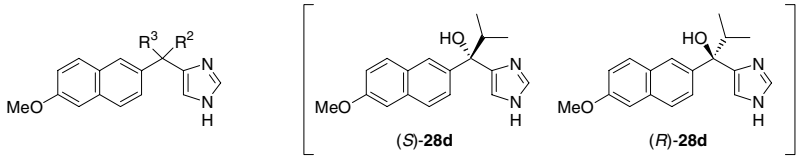
2, 8, 12, 16

Com-No.	R^1	R^2	$C_{17,20}$-lyase inhibition IC_{50} (nM)		T concn (in vivo)[a] % of control	
			Rat	Human	2 h	5 h
2	H	H	53	43	13	55
8a	MeO	H	27	27	5	1
8b	EtO	H	26	23	8	15
8c	*i*-PrO	H	24	46	8	31
8e	$PhCH_2O$	H	670	230	Nt	Nt
12a	MeS	H	18	20	7	1
12b	MeSO	H	270	240	Nt	Nt
12c	$MeSO_2$	H	230	200	Nt	Nt
16a	MeO	Me	22	21	4	1
16b	MeO	*i*-Pr	26	24	5	1

Nt: not tested.

[a] Test compounds were administrated orally at a dose of 25 mg/kg to male rats ($n = 5$). After 2 and 5 h, the serum testosterone (T) concentration was measured by radioimmunoassay and shown as the % values of that of control.

Table 2. Pharmacological activities of 4-imidazolyl derivatives



(*S*)-**28d** (*R*)-**28d**

Com-No.	R^2	R^3	$C_{17,20}$-lyase inhibition IC_{50} (nM)		T concn (in vivo)[a] % of control	
			Rat	Human	2 h	5 h
21	H	H	13	18	1	6
25a	Me	H	28	23	3	1
25b	*i*-Pr	H	22	30	6	6
26	H	OH	170	63	Nt	Nt
28a	Me	OH	130	35	Nt	Nt
28b	Et	OH	41	27	17	62
28c	*n*-Pr	OH	43	36	18	109
28d	*i*-Pr	OH	33	32	4	13
28e	*c*-Pr	OH	64	35	Nt	Nt
28f	*i*-Bu	OH	85	41	Nt	Nt
28g	*t*-Bu	OH	160	83	Nt	Nt
28h	*c*-Pentyl	OH	48	42	Nt	Nt
28i	Ph	OH	230	110	Nt	Nt
28j	3-Pyridyl	OH	420	270	Nt	Nt
28k	4-Pyridyl	OH	240	54	Nt	Nt
(*S*)-**28d**	(*S*)-*i*-Pr	OH	21	28	3	20
(*R*)-**28d**	(*R*)-*i*-Pr	OH	52	54	24	211

Nt: not tested.

[a] 25 mg/kg (po).

$100 \times (X - B)/(A - B)$, where A, B and X are the organ weights for intact, castrated and treated groups, respectively.

Compounds **8a**, **12a**, **16a**, **16b** and **28d** decreased the weight of the prostate and seminal vesicles to 23–42% and 6–48% of the controls, respectively (Table 3). Especially, the effects of **16b** and **28d** on seminal vesicle weight were almost comparable to those induced by castration. Unfortunately **8a**, **12a**, **16a** and **16b** increased the liver weight, while **28d** did not have this adverse effect. The crucial element to remove the effect on the liver weight seems to be the hydroxyl group, which may suitably adjust the molecular lipophilicity. In addition, the 4-imidazolyl orientation is also an important because it allows the introduction of the hydroxyl group

Table 3. Effects of $C_{17,20}$-lyase inhibitors on the weights of prostate and seminal vesicles in male rats after nine times consecutive oral administration (50 mg/kg/day, bid)

Com-no.	Tissue weight (% of control[a])	
	Prostate	Seminal vesicles
8a	32	43
12a	23	48
16a	37	34
16b	32	4
28d	42	6
(*S*)-**28d**	43	−1
(*S*)-**42**[b]	65	47

[a] The organ weights in castrated and intact groups were set to 0% and 100%, respectively. The % of control values $= 100 \times (X - B)/(A - B)$, where A, B and X are the organ weights in intact, castrated and treatment groups, respectively.
[b] Fumarate.

into the methylene bridge. Compound **21**, **25a** and **25b** showed acute toxicity and therefore the examination was not completed.

The enantiomers of **28d** were examined to establish which enantiomer was responsible for the pharmaceutical activity. No definite difference of enzyme inhibition was observed between the enantiomers (Table 2, IC_{50}s: (*S*)-**28d**; rat 21 nM, human 28 nM, (*R*)-**28d**; rat 52 nM, human 54 nM). However, the suppressive effects on the testosterone biosynthesis revealed that (*S*)-**28** was more active than (*R*)-**28d** (Table 2, testosterone concentration: (*S*)-**28d**; 3% at 2 h, 20% at 5 h, (*R*)-**28d**; 24% at 2 h, 211% at 5 h). The less active enantiomer (*R*)-**28d** led to an increase in the serum testosterone concentration, compared to the control, at 5 h after treatment. The increase was probably due to cancellation of the negative feedback control, caused by transient suppression of the testosterone levels, as previously reported.[1] Compound (*S*)-**28d** significantly decreased the weight of the prostate and seminal vesicles without an increase in the liver weight after consecutive administrations (Table 3).

4.4. Molecular modeling

A molecular modeling study of the human $C_{17,20}$-lyase using a homology model helps us to understand the in vitro structure–activity relationships (Fig. 5). According to the docking mode, the methoxy oxygen of (*S*)-**28d**, as expected, forms a hydrogen bond with the hydroxyl group of Thr101 in the enzyme. The docking mode suggests no interaction between the hydroxy group of (*S*)-**28d** and the enzyme. Furthermore, the mode suggests that the isopropyl group of (*S*)-**28d** fits into the lipophilic pocket, which is constructed by Ala367, Met369, Ile371, Pro372 and Phe484 in the enzyme. As mentioned in the enzyme inhibitory activity section, a hydroxy group at the methylene bridge tends to lower the inhibitory activity, while the activity was affected by the arrangement of the hydroxy group and the other substituents. The fit of the isopropyl group into the pocket may account for the fact that incorporation of both an isopropyl group and a hydroxyl group produced the optimum enzyme inhibition.

4.5. Selectivity for $C_{17,20}$-lyase and steroid 11β-hydroxylase

Compound (*S*)-**28d** was subjected to further evaluation as a candidate. However, it was revealed that (*S*)-**28d** showed relatively potent inhibitory activity for the rat steroid 11β-hydroxylase, which is a P450 enzyme and responsible for the production of corticosterone and cortisol, with an IC_{50} value of 140 nM. Thus, more selective inhibitors were required. As preliminary data, insertion of a methyl group at the 5-position on the naphthalene ring provided a more selective inhibitor (Table 4, selectivity for rat $C_{17,20}$-lyase over rat 11β-hydroxylase: **36a**; 39 vs (*S*)-**28d**; 6.7), and the substituent on the naphthalene ring was thus thought to be important for a high selectivity. Derivatives modified at the 5- or 7-position on the naphthalene ring, such as **36b**, **42**, **47** and **56**, were designed and these compounds showed equipotent $C_{17,20}$-lyase inhibition to (*S*)-**28d** and changed the selectivity as predicted. A methoxy group at the 5- or 7-position on the naphthalene increased the selectivity, as did a 5-methyl group (selectivity: **36b**; 30, **42**; >100). The tricyclic inhibitor **56** was 17-fold more selective, while **47** had poor selectivity. Compounds **36a**,**b** and **42**, which showed more than about 30-fold selectivity, suppressed testosterone biosynthesis at a dose of 50 mg/kg in rats, and the best results were achieved in **42** (4% and 9% of the control at 2 and 5 h after treatment, respectively). From the data for rat $C_{17,20}$-lyase inhibition, the active enantiomer was identified to be the (*S*)-form as well as **28**, and (*S*)-**42** showed the most potent activity ($IC_{50} = 3.8$ nM), with more than 260-fold selectivity for $C_{17,20}$-lyase over 11β-hydroxylase. In addition, (*S*)-**42** decreased the weight of prostate and seminal vesicles without an increase in the liver weight (Table 3). Biosynthesis of androgens in primates is somewhat different from that in rodents, so (*S*)-**42** was studied in male cynomolgus monkeys to determine the efficacy for testosterone suppression. When (*S*)-**42** was orally administrated at a dose of 1 mg/kg to monkeys, the serum testosterone level was reduced to the castration level at 8 h after treatment.

5. Conclusions

We have synthesized 1- and 4-(2-naphthylmethyl)-1*H*-imidazoles as $C_{17,20}$-lyase inhibitors. These compounds were tested for enzyme inhibitory activities, suppressive effects on testosterone biosynthesis in rats, and reduction in the weight of prostate and seminal vesicles in rats. Several 6-methoxynaphthyl compounds achieved potent enzyme inhibition and strong suppression of testosterone biosynthesis in rats, while most of these compounds increased the liver weight after consecutive administrations. The best results were achieved by the incorporation of a hydroxy group and an isopropyl group, as described for (*S*)-**28d** and (*S*)-**42**, which was effective in expressing pharmacological activities and

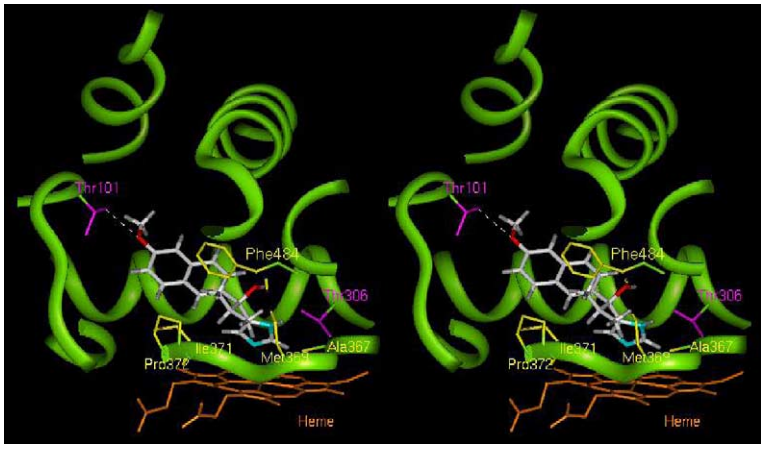
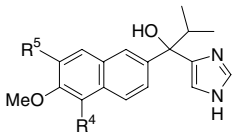
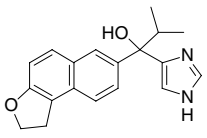


Figure 5. Proposed binding mode of (*S*)-**28d** at the active site in a human $C_{17,20}$-lyase model. Selected active site residues are labeled; orange, heme; magenta, polar residues; yellow, lipophilic residues. White dotted line shows a hydrogen bond.

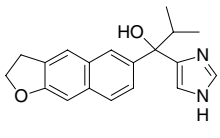
Table 4. Pharmacological activities of 4-imidazolyl derivatives



36, 42



47



56

Com-No.	R^4	R^5	Enzyme inhibition; IC_{50} (nM)			Selectivity[b]	T concn (in vivo, po) % of control	
			$C_{17,20}$-lyase		11β-Hydroxylase			
			Rat	Human	Rat		2 h	5 h
(*S*)-**28d**	H	H	21	28	140	6.7	3	20 (25 mg/kg)
36a	Me	H	13	28	500	39	12	13 (50 mg/kg)
36b	MeO	H	26	29	780	30	18	19 (50 mg/kg)
42	H	MeO	9.5	29	>1000	>100	4	9 (50 mg/kg)
47	See structure		26	25	77	3.0	Nt	Nt
56	See structure		21	23	350	17	Nt	Nt
(*S*)-**42**[a]			3.8	11	>1000	>260	Nt	Nt
(*R*)-**42**[a]			78	39	>1000	>13	Nt	Nt

Nt: not tested.
[a] Fumarate.
[b] Rat 11β-hydroxylase/rat C17,20-lyase.

removing the effect of liver weight. Through the examination of selectivity for $C_{17,20}$-lyase over 11β-hydroxylase, (*S*)-**42** was found to be a more than 260-fold selective inhibitor. Finally, compound (*S*)-**42** showed a potent suppression of testosterone biosynthesis after a single oral administration in monkeys. These data suggest that (*S*)-**42** may be a promising agent for the treatment of androgen-dependent prostate cancer.

6. Experimental

6.1. Chemistry

Melting points were determined on a Yanaco MP-500V micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Shimadzu FTIR-8200PC spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, br s = broad singlet. Column chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck).

6.2. 2-Bromo-6-ethoxynaphthalene (5b)

To a suspension of NaH (60% oil dispersion, 2.10 g, 52.5 mmol) in DMF (50 mL) was added 6-bromo-2-naphthol (11.2 g, 50.0 mmol) with ice-cooling, and the stirring was continued at room temperature for 0.5 h. Ethyl iodide (8.19 g, 52.5 mmol) was added and the

reaction was stirred at room temperature for an additional 16 h. The mixture was diluted with water and Et_2O, and the organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was suspended in hexane and collected by filtration to give **5b** (10.9 g, 87%) as a colourless powder. ^{1}H NMR ($CDCl_3$) δ: 1.48 (3H, t, $J = 7.0$ Hz), 4.13 (2H, q, $J = 7.0$ Hz), 7.08 (1H, d, $J = 2.6$ Hz), 7.16 (1H, dd, $J = 9.0$, 2.6 Hz), 7.48 (1H, dd, $J = 8.8$, 1.8 Hz), 7.58 (1H, d, $J = 9.0$ Hz), 7.64 (1H, d, $J = 8.8$ Hz), 7.91 (1H, d, $J = 1.8$ Hz).

6.3. 2-Bromo-6-isopropoxynaphthalene (5c)

Prepared from 6-bromo-2-naphthol and 2-iodopropane by the procedure described for the synthesis of **5b** in 85% yield. Mp 79 °C. IR (KBr): 2980, 1590, 1391, 1211 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.40 (6H, d, $J = 6.0$ Hz), 4.06–4.80 (1H, m), 7.06–7.20 (2H, m), 7.47 (1H, dd, $J = 8.8$, 1.8 Hz), 7.57 (1H, d, $J = 8.8$ Hz), 7.64 (1H, d, $J = 8.8$ Hz), 7.90 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{13}H_{13}BrO$: C, 58.89; H, 4.94. Found: C, 58.86; H, 4.98.

6.4. 6-Methoxy-2-naphthaldehyde (6a)

To a solution of **5a** (42.27 g, 0.178 mol) in THF (600 mL) was added *n*-BuLi (1.65 M solution in hexane; 125 mL, 0.199 mol) at −78 °C, and the stirring was continued for 0.5 h. Then DMF (28 mL, 0.381 mol) was added and the mixture was warmed up to room temperature, diluted with aqueous NH_4Cl, and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated to give **6a** as crystals (32.31 g, 97%). Mp 56–60 °C (hexane). IR (KBr): 2841, 1686, 1624, 1480, 1269, 1028, 856 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.96 (3H, s), 7.15–7.30 (2H, m), 7.75–7.97 (3H, m), 8.26 (1H, s), 10.10 (1H, s). Anal. Calcd for $C_{12}H_{10}O_2$: C, 76.66; H, 5.47. Found: C, 76.64; H, 5.48.

6.5. 6-Ethoxy-2-naphthaldehyde (6b)

Yield 82%. ^{1}H NMR ($CDCl_3$) δ: 1.51 (3H, t, $J = 7.0$ Hz), 4.19 (2H, q, $J = 7.0$ Hz), 7.17 (1H, d, $J = 2.4$ Hz), 7.23 (1H, dd, $J = 8.8$, 2.4 Hz), 7.79 (1H, d, $J = 8.8$ Hz), 7.89 (1H, d, $J = 8.8$ Hz), 7.92 (1H, dd, $J = 8.8$, 1.6 Hz), 8.25 (1H, d, $J = 1.6$ Hz), 10.08 (1H, s).

6.6. 6-Isopropoxy-2-naphthaldehyde (6c)

Yield 65%. Mp 50–51 °C. IR (KBr): 2975, 1686, 1275, 1169 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.43 (6H, d, $J = 6.0$ Hz), 4.76 (1H, m), 7.14–7.25 (2H, m), 7.77 (1H, d, $J = 8.6$ Hz), 7.85–7.93 (2H, m), 8.24 (1H, s), 10.09 (1H, s). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.31; H, 6.68.

6.7. (6-Methoxy-2-naphthyl)methanol (7a)

To a solution of **6a** (3.90 g, 21.0 mmol) in MeOH (60 mL) was added $NaBH_4$ (0.50 g, 13.2 mmol) with ice-cooling, and the mixture was stirred at room temperature for 1 h and concentrated. The residue was partitioned between AcOEt and water, and the organic layer was separated, dried over $MgSO_4$, and concentrated to give **7a** (2.77 g, 70%) as colourless crystals. Mp 116–118 °C (AcOEt–*i*-Pr_2O). IR (KBr): 1633, 1608, 1487, 1269, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.68 (1H, br), 3.93 (3H, s), 4.83 (2H, d, $J = 5.2$ Hz), 7.08–7.25 (3H, m), 7.46 (1H, d, $J = 8.8$ Hz), 7.68–7.80 (3H, m). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.23.

6.8. (6-Ethoxy-2-naphthyl)methanol (7b)

Yield 79%. ^{1}H NMR ($CDCl_3$) δ: 1.48 (3H, t, $J = 7.0$ Hz), 4.16 (2H, q, $J = 4.8$ Hz), 4.82 (2H, s), 7.13 (1H, s), 7.16 (1H, dd, $J = 8.4$, 2.4 Hz), 7.45 (1H, dd, $J = 8.4$, 1.7 Hz), 7.73 (2H, d, $J = 8.4$ Hz), 7.73 (1H, s).

6.9. (6-Isopropoxy-2-naphthyl)methanol (7c)

Yield 63%. Mp 60–64 °C. IR (KBr): 3252, 2971, 1605, 1481, 1271 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.40 (6H, d, $J = 6.0$ Hz), 1.73 (1H, br s), 4.70 (1H, m), 4.81 (2H, s), 7.08–7.17 (2H, m), 7.44 (1H, dd, $J = 8.6$, 1.6 Hz), 7.66–7.77 (3H, m). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.58; H, 7.43.

6.10. 1-[(6-Methoxy-2-naphthyl)methyl]-1*H*-imidazole (8a)

To a solution of **7a** (3.76 g, 20.0 mmol) in CH_2Cl_2 (40 mL) was added $SOCl_2$ (2.92 mL, 40.0 mmol) with ice-cooling, and the mixture was stirred at 0 °C for 1 h and concentrated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$, and the organic layer was separated, dried over $MgSO_4$ and concentrated to give 6-chloromethyl-2-methoxy-naphthalene. This compound was stirred at room temperature for 18 h with imidazole (6.81 g, 100 mmol) in DMF (40 mL) and the mixture was poured into water and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (10:1) as an eluent. The product was recrystallized from AcOEt to give **8a** (2.92 g, 61%) as colourless needles. Mp 129–132 °C. IR (KBr): 3092, 1609, 1507, 1227 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.92 (3H, s), 5.24 (2H, s), 6.94 (1H, s), 7.09–7.16 (2H, m), 7.19 (1H, d, $J = 2.6$ Hz), 7.22 (1H, dd, $J = 8.8$, 1.8 Hz), 7.54 (1H, s), 7.60 (1H, s), 7.69 (1H, d, $J = 8.8$ Hz), 7.73 (1H, d, $J = 8.2$ Hz). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.42; H, 5.85; N, 11.68.

6.11. 1-[(6-Ethoxy-2-naphthyl)methyl]-1*H*-imidazole (8b)

Prepared from **7b** by the procedure described for the synthesis of **8a** in 50% yield. Mp 133.5 °C. IR (KBr): 2986, 1609, 1507, 1227 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.48 (3H, t, $J = 7.0$ Hz), 4.15 (2H, q, $J = 7.0$ Hz), 5.24 (2H,

s), 6.94 (1H, s), 7.10–7.15 (3H, m), 7.22 (1H, dd, $J = 9.2$, 2.6 Hz), 7.53 (1H, s), 7.60 (1H, s), 7.69 (1H, d, $J = 9.2$ Hz), 7.71 (1H, d, $J = 8.4$ Hz). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.10; H, 6.57; N, 11.12.

6.12. 1-[(6-Isopropoxy-2-naphthyl)methyl]-1*H*-imidazole (8c)

To a mixture of **7c** (1.42 g, 6.57 mmol) and Et_3N (2.7 mL, 20.3 mmol) in THF (50 mL) was added methanesulfonyl chloride (0.66 mL, 8.53 mmol) with ice-cooling. The mixture was stirred at 0 °C for 3 h and imidazole (0.75 g, 11.0 mmol) was added. The reaction was stirred at room temperature for an additional 9 h and concentrated, and the residue was partitioned between AcOEt and water. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using AcOEt–MeOH = 30:1 as an eluent. The product was recrystallized from hexane–AcOEt to give **8c** (1.01 g, 58%). Mp 96 °C. IR (KBr): 2975, 1609, 1507, 1225 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40 (6H, d, $J = 6.2$ Hz), 4.70 (1H, m), 5.23 (2H, s), 6.93 (1H, t, $J = 1.3$ Hz), 7.67–7.25 (4H, m), 7.50–7.73 (4H, m). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.66; H, 6.56; N, 10.35.

6.13. 6-(1*H*-Imidazol-1-ylmethyl)-2-naphthol (8d)

To a solution of boron tribromide (4.81 g, 19.2 mmol) in CH_2Cl_2 (10 mL) was added **8a** (1.91 g, 8.0 mmol) with ice-cooling. The mixture was stirred at room temperature for 4 h and poured onto ice. The aqueous phase was separated, neutralized with $NaHCO_3$ and extracted with THF–AcOEt. The extract was dried over Na_2SO_4 and concentrated, and the residue was recrystallized from THF to give **8d** (1.67 g, 93%) as colourless prisms. Mp 208.5 °C. IR (KBr): 3112, 2548, 1508, 1451, 1306 cm^{-1}. ^1H NMR (DMSO-d_6+D_2O) δ: 5.29 (2H, s), 6.93 (1H, br s), 7.10 (1H, dd, $J = 9.8$, 2.2 Hz), 7.12 (1H, s), 7.24 (1H, br s), 7.31 (1H, d, $J = 8.0$ Hz), 7.67 (1H, d, $J = 8.0$ Hz), 7.69 (1H, s), 7.74 (1H, d, $J = 9.8$ Hz), 7.87 (1H, br s). Anal. Calcd for $C_{14}H_{12}N_2O{\cdot}0.25H_2O$: C, 73.50; H, 5.51; N, 12.25. Found: C, 73.32; H, 5.34; N, 12.18.

6.14. 1-[(6-Benzyloxy-2-naphthyl)methyl]-1*H*-imidazole (8e)

Prepared from **8d** and benzyl bromide by a similar procedure to that described for the synthesis of **5b** in 48% yield. Mp 146 °C. IR (KBr): 3106, 1607, 1508, 1223 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.18 (2H, s), 5.24 (2H, s), 6.94 (1H, s), 7.11 (1H, s), 7.20–7.28 (4H, m), 7.33–7.60 (6H, m), 7.71 (2H, d, $J = 8.6$ Hz). Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.16; H, 5.57; N, 9.07.

6.15. Ethyl 6-(methylthio)-2-naphthoate (10)

To a solution of LDA (0.6 mol/L in THF, 215 mL) was added **9**[35] (20.0 g, 0.106 mol) dropwise at −78 °C, and the mixture was stirred for 1 h. A solution of 4-methylthiobenzaldehyde (16.43 g, 0.108 mol) in THF (30 mL) was added, and the reaction was warmed up to room temperature and then quenched with water. After the separation of the layers, the aqueous phase was further extracted with AcOEt, and the organic layers were combined, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using hexane–AcOEt = 2:1 as an eluent to give an oil. (21.2 g). A mixture of the oil (9.11 g) and polyphosphoric acid (27.3 g) in toluene (100 mL) was heated at 100 °C for 0.5 h, poured into ice water and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using hexane–AcOEt = 8:1 as an eluent to give **10** (1.73 g, 15%) as colourless crystals. Mp 57 °C. IR (KBr): 2990, 1705, 1267, 1227 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (3H, t, $J = 7.1$ Hz), 2.60 (3H, s), 4.43 (2H, q, $J = 7.1$ Hz), 7.41 (1H, dd, $J = 8.8$, 1.8 Hz), 7.57 (1H, s), 7.75 (1H, d, $J = 8.8$ Hz), 7.83 (1H, d, $J = 8.8$ Hz), 8.06 (1H, dd, $J = 8.8$, 1.8 Hz), 8.53 (1H, s). Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.27; H, 5.63.

6.16. [6-(Methylthio)-2-naphthyl]methanol (11a)

To a suspension of $LiAlH_4$ (0.52 g, 13.8 mmol) in THF (50 mL) was added **10** (1.56 g, 6.33 mmol) portionwise with ice-cooling, and the stirring was continued for 0.5 h. After the reaction was quenched by the addition of water, AcOEt and 1 N HCl were added. The organic layer was separated, dried over $MgSO_4$ and concentrated and the residue was recrystallized from hexane–AcOEt to give **11a** (1.27 g, 97%) as colourless crystals. Mp 114 °C (AcOEt–hexane). IR (KBr): 3175, 1593, 1026, 872 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.59 (3H, s), 4.84 (2H, d, $J = 5.6$ Hz), 7.38 (1H, dd, $J = 8.6$, 2.0 Hz), 7.47 (1H, dd, $J = 8.6$, 1.6 Hz), 7.60 (1H, d, $J = 2.0$ Hz), 7.69–7.79 (3H, s). Anal. Calcd for $C_{12}H_{12}OS$: C, 70.55; H, 5.92. Found: C, 70.47; H, 5.97.

6.17. [6-(Methylsulfinyl)-2-naphthyl]methanol (11b)

To a solution of **11a** (401 mg, 1.96 mmol) in CH_2Cl_2 (30 mL) was added a solution of 3-chloroperoxybenzoic acid (649 mg, 3.76 mmol) in CH_2Cl_2 (10 mL) with ice-cooling. The mixture was stirred for 2 h and then diluted with saturated aqueous $NaHCO_3$. The separated organic layer was dried over $MgSO_4$ and concentrated. The product was suspended in AcOEt and collected by filtration to give **11b** (317 mg, 73%) as colourless crystals. Mp 217–221 °C. IR (KBr): 3399, 1022, 901, 824 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.80 (3H, s), 4.91 (2H, d, $J = 4.8$ Hz), 7.54–7.64 (2H, m), 7.85–7.99 (3H, m), 8.17 (1H, s). Anal. Calcd for $C_{12}H_{12}O_2S{\cdot}0.1H_2O$: C, 64.90; H, 5.54. Found: C, 64.73; H, 5.59.

6.18. 1-{[6-(Methylthio)-2-naphthyl]methyl}-1*H*-imidazole (12a)

Prepared from **11a** by the procedure described for the synthesis of **8c** in 44% yield. Mp 112 °C (AcOEt–hex-

ane). IR (KBr): 3090, 1595, 1507, 1235, 1067 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.58 (3H, s), 5.25 (2H, s), 6.92–6.96 (1H, m), 7.12 (1H, s), 7.24 (1H, dd, $J = 8.6$, 1.6 Hz), 7.39 (1H, dd, $J = 8.4$, 2.0 Hz), 7.53 (1H, s), 7.54–7.62 (2H, m), 7.64–7.76 (2H, m). Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01. Found: C, 70.75; H, 5.47; N, 11.07.

6.19. 1-{[6-(Methylsulfinyl)-2-naphthyl]methyl}-1*H*-imidazole (12b)

Prepared from **11b** by the procedure described for the synthesis of **8c** in 8% yield. Mp 114–115 °C. IR (KBr): 3102, 1505, 1069, 1038 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.80 (3H, s), 5.33 (2H, s), 6.97 (1H, br s), 7.15 (1H, br s), 7.38 (1H, d, $J = 8.4$ Hz), 7.52–7.70 (3H, m), 7.94 (2H, d, $J = 8.8$ Hz), 8.22 (1H, s). Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.42; H, 5.06; N, 10.27.

6.20. 1-{[6-(Methylsulfonyl)-2-naphthyl]methyl}-1*H*-imidazole (12c)

To a solution of hexaammonium heptamolybdate tetrahydrate (136 mg, 0.11 mmol) in water (0.1 mL) was added 30% H_2O_2 (0.4 mL) with ice-cooling. This mixture was stirred for 10 min and then added to a (0 °C) solution of **12a** (227 mg, 0.89 mmol) in EtOH (2 mL). The stirring was continued at room temperature for 16 h, and the mixture was diluted with AcOEt and THF. After the catalyst was filtered off, the filtrate was washed with water, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using AcOEt–MeOH = 15:1 as an eluent, and the product was suspended in diisopropylether and collected by filtration to give **12c** (20 mg, 8%) as colourless crystals. Mp 139–140 °C. IR (KBr): 3000, 1304, 1142, 1125, 1074 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.13 (3H, s), 5.35 (2H, s), 6.97 (1H, br s), 7.16 (1H, br s), 7.42 (1H, dd, $J = 8.6$, 2.0 Hz), 7.63 (2H, s), 7.88–7.04 (3H, m), 8.52 (1H, s). Anal. Calcd for $C_{15}H_{14}N_2O_2S{\cdot}0.3H_2O$: C, 61.75; H, 5.04; N, 9.60. Found: C, 61.71; H, 5.21; N, 9.32.

6.21. (6-Methoxy-2-naphthyl) methyl ketone (14a)

To a solution of **5a** (10.0 g, 42.2 mmol) in THF (200 mL) was added *n*-BuLi (1.6 M solution in hexane, 31.7 mL, 50.6 mmol) dropwise at −78 °C, and the stirring was continued for 30 min. A solution of *N*-methoxy-*N*-methylacetamide (4.79 g, 46.4 mmol) in THF (30 mL) was added dropwise, and the mixture was stirred at −70 °C for 1 h and then poured into 1N HCl (300 mL). After the separation of the layers, the aqueous phase was further extracted with AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was recrystallized from cyclohexane to give **14a** (5.77 g, 68%) as colourless crystals. Mp 108–109 °C. IR (KBr): 1674, 1622, 1480, 1360, 1277, 1202, 1022, 860, 822 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.70 (3H, s), 3.95 (3H, s), 7.15–7.24 (2H, m), 7.77 (1H, d, $J = 8.8$ Hz), 7.86 (1H, d, $J = 8.8$ Hz), 8.01 (1H, dd, $J = 8.6$, 1.8 Hz), 8.39 (1H, s). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.97; H, 6.17.

6.22. 1-(6-Methoxy-2-naphthyl)ethanol (15a)

To a solution of **14a** (5.71 g, 28.5 mmol) in THF–EtOH (1:10, 44 mL) was added sodium borohydride (1.08 g, 28.5 mmol) with ice-cooling. The mixture was stirred at room temperature for 3 h, diluted with water and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was purified by column chromatography on silica gel using hexane–AcOEt = 5:1 to 1:1 as an eluent to give **15a** (5.26 g, 91%) as colourless crystals. Mp 114–115 °C (AcOEt–hexane). IR (KBr): 3337, 1634, 1607, 1487, 1464, 1267, 1219, 1163, 1076, 1030, 893, 855, 816 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.57 (3H, d, $J = 6.6$ Hz), 1.90 (1H, br s), 3.92 (3H, s), 5.03 (1H, q, $J = 6.6$ Hz), 7.12–7.18 (2H, m), 7.47 (1H, dd, $J = 8.6$, 1.8 Hz), 7.70–7.75 (3H, m). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.30; H, 7.12.

6.23. 1-(6-Methoxy-2-naphthyl)-2-methylpropanol (15b)

To a mixture of 2-methoxynaphthalene (**13**, 10.0 g, 63.2 mmol) and $AlCl_3$ (12.6 g, 94.8 mmol) in CH_2Cl_2 (150 mL) was added isobutyryl chloride (7.95 mL, 75.8 mmol) dropwise with ice-cooling. The reaction mixture was stirred for 1 h, poured into ice water and extracted with several portions of CH_2Cl_2. The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated give (6-methoxy-2-naphthyl) isopropyl ketone (**14b**, 14.6 g) as a pale yellow oil, which was used for the next step without further purification. To a solution of **14b** in EtOH (100 mL) was added sodium borohydride (2.42 g, 64.0 mmol) portionwise with ice-cooling. The mixture was stirred overnight at room temperature, diluted with water, and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was purified by column chromatography on silica gel using hexane–AcOEt = 6:1 as an eluent to give **15b** (10.2 g, 70%) as a colourless oil. IR (KBr): 3334, 2955, 1607, 1485, 1466, 1265, 1233, 1175, 1032, 856 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.81 (3H, d, $J = 6.6$ Hz), 1.04 (3H, d, $J = 6.6$ Hz), 1.94–2.14 (2H, m), 3.92 (3H, s), 4.48 (1H, d, $J = 7.0$ Hz), 7.13–7.18 (2H, m), 7.42 (1H, dd, $J = 1.6$, 8.4 Hz), 7.68–7.75 (3H, m).

6.24. 1-[1-(6-Methoxy-2-naphthyl)ethyl]-1*H*-imidazole (16a)

A mixture of **15a** (4.0 g, 19.8 mmol), carbonyldiimidazole (3.53 g, 21.8 mmol) and NaH (60% oil dispersion, 80 mg, 2.0 mmol) in THF (10 mL) was refluxed for 3 h. The reaction mixture was diluted with water and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was purified by column

chromatography on silica gel using $CHCl_3$–MeOH = 40:1 as an eluent to give **16a** (2.99 g, 60%) as colourless crystals. Mp 113–114 °C (AcOEt–hexane). IR (KBr): 1609, 1507, 1487, 1265, 1221, 1032, 855, 820, 665 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.93 (3H, d, $J = 7.0$ Hz), 3.91 (3H, s), 5.46 (1H, q, $J = 7.0$ Hz), 6.94 (3H, s), 7.08–7.23 (4H, m), 7.52 (1H, s), 7.63 (1H, s), 7.68 (1H, d, $J = 4.0$ Hz), 7.72 (1H, d, $J = 3.9$ Hz). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.01; H, 6.28; N, 11.16.

6.25. 1-[1-(6-Methoxy-2-naphthyl)-2-methylpropyl]-1*H*-imidazole (16b)

Prepared from **15b** by the procedure described for the synthesis of **16a** in 52% yield. A pale yellow oil. IR (KBr): 2963, 1634, 1607, 1507, 1485, 1269, 1223, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.91 (3H, d, $J = 6.6$ Hz), 0.96 (3H, d, $J = 6.6$ Hz), 2.58–2.77 (1H, m), 3.91 (3H, s), 4.75 (1H, d, $J = 10.2$ Hz), 7.05–7.19 (4H, m), 7.37 (1H, dd, $J = 1.9$, 8.5 Hz), 7.65–7.74 (4H, m). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.01; H, 7.48; N, 10.20.

6.26. (6-Methoxy-2-naphthyl)-(1-trityl-1*H*-imidazol-4-yl)methanol (18)

To a solution of **5a** (15.6 g, 66.0 mmol) in THF (200 mL) was added *n*-BuLi (1.6 M solution in hexane, 49.5 mL, 79.2 mmol) dropwise at −70 °C, and the stirring was continued for 30 min. A solution of **17**[37] (20.6 g, 60.0 mmol) in THF (300 mL) was added dropwise, and the reaction mixture was stirred for 1.5 h at 0 °C and poured into 5% citric acid. After the separation of the layers, the aqueous phase was further extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated and the residue was purified by column chromatography on silica gel using AcOEt as an eluent to give **18** (13.5 g, 45%) as colourless crystals. Mp 206–207 °C (THF–hexane). IR (KBr): 3166, 1603, 1478, 1451, 1260, 1171, 1128, 754, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.90 (3H, s), 5.89 (1H, s), 6.60 (1H, d, $J = 1.4$ Hz), 7.08–7.15 (8H, m), 7.26–7.34 (9H, m), 7.42–7.47 (2H, m), 7.63–7.69 (2H, m), 7.78 (1H, s). Anal. Calcd for $C_{34}H_{28}N_2O_2$: C, 82.23; H,5.68; N, 5.64. Found: C, 82.16; H,5.68; N, 5.55.

6.27. (6-Methoxy-2-naphthyl)-(1-trityl-1*H*-imidazol-4-yl)methyl benzoate (19)

To a solution of **18** (12.5 g, 25.2 mmol) in pyridine (100 mL) was added benzoylchloride (3.5 mL, 30.2 mmol) dropwise with ice-cooling. The mixture was stirred at room temperature for 3 h and concentrated. Saturated aqueous $NaHCO_3$ (150 mL) was added, and the resulting mixture was stirred vigorously. The precipitate was filtered, washed with water and Et_2O successively, and dried to give **19** (15.3 g, quantitative yield) as colourless crystals. Mp 192–194 °C (THF–hexane). IR (KBr): 1709, 1262, 1173, 1103, 1028, 860, 774, 704 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.89 (3H, s), 6.90 (1H, s), 7.10–7.74 (25H, m), 7.91 (1H, s), 8.08 (1H, d, $J = 1.6$ Hz), 8.12 (1H, s). Anal. Calcd for $C_{41}H_{32}N_2O_3 \cdot 0.2H_2O$: C, 81.49; H, 5.40; N, 4.64. Found: C, 81.50; H, 5.61; N, 4.64.

6.28. 4-[(6-Methoxy-2-naphthyl)methyl]-1-trityl-1*H*-imidazole (20)

A solution of **19** (15.0 g, 25.0 mmol) and 10% Pd–C (1.50 g) in DMF (200 mL) was vigorously stirred under H_2 atmosphere at room temperature. The mixture was stirred at room temperature for 12 h and the catalyst was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel using AcOEt as a eluent. The eluate was washed with 1 M K_2CO_3, dried over $MgSO_4$ and concentrated to give **20** (9.79 g, 82%) as pink crystals. Mp 144–145 °C (THF–hexane). IR (KBr): 3058, 1605, 1491, 1443, 1262, 1229, 1175, 1032, 750, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.89 (3H, s), 4.03 (2H, s), 6.57 (1H, d, $J = 1.4$ Hz), 7.08–7.18 (8H, m), 7.25–7.40 (11H, m), 7.59–7.66 (3H, m). Anal. Calcd for $C_{34}H_{28}N_2O$: C, 84.97; H, 5.87; N,5.83. Found: C, 84.73; H, 5.86; N, 5.79.

6.29. 4-[(6-Methoxy-2-naphthyl)methyl]-1*H*-imidazole (21)

A mixture of **20** (6.02 g, 12.5 mmol) and 90% formic acid (50 mL) was stirred at 50 °C for 3 h and concentrated. The residue was dissolved in AcOEt–THF (2:1) and washed with saturated aqueous $NaHCO_3$. The organic layer was extracted with 2 N HCl, and the aqueous phase was made alkaline with aqueous $NaHCO_3$ and extracted with AcOEt–THF (2:1). The extract was dried and concentrated, and the residue was recrystallized from MeOH to give **21** as colourless crystals (1.81 g, 61%). Mp 199 °C. IR (KBr): 2820, 2635, 1605, 1480, 1238 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6) δ: 3.90 (3H, s), 4.05 (2H, s), 6.73 (1H, s), 7.10 (1H, d, $J = 9.6$ Hz), 7.11 (1H, s), 7.35 (1H, d, $J = 7.8$ Hz), 7.51 (1H, s), 7.60–7.68 (3H, m). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.53; H, 5.93; N, 11.73.

6.30. (6-Methoxy-2-naphthyl)-(1-trityl-1*H*-imidazol-4-yl)ketone (22)

A mixture of **18** (6.00 g, 12.1 mmol) and MnO_2 (24.8 g) in $CHCl_3$ (120 mL) was refluxed for 6 h. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was recrystallized from Et_2O–hexane to give **22** (5.71 g, 96%) as colourless crystals. Mp 202–203 °C (AcOEt–hexane). IR (KBr): 1620, 1520, 1493, 1480, 1445, 1265, 1196, 1179, 909, 872, 747, 733, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.94 (3H, s), 7.15–7.23 (8H, m), 7.34–7.40 (9H, m), 7.58 (1H, d, $J = 1.3$ Hz), 7.77 (1H, d, $J = 1.3$ Hz), 7.78 (1H, d, $J = 8.6$ Hz), 7.86 (1H, d, $J = 9.6$ Hz), 8.26 (1H, dd, $J = 8.6$, 1.6 Hz), 8.95 (1H, s). Anal. Calcd for $C_{34}H_{26}N_2O_2$: C,82.57; H, 5.30; N, 5.66. Found: C, 82.30; H,5.40; N, 5.75.

6.31. 4-[1-(6-Methoxy-2-naphthyl)vinyl]-1-trityl-1*H*-imidazole (23a)

To a suspension of methyltriphenylphosphonium bromide (7.22 g, 20.2 mmol) in THF (150 mL) was added *t*-BuOK (2.49 g, 22.2 mmol) portionwise with ice-cooling. The stirring was continued for 10 min, and **22** (5.0 g, 10.1 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 1 h. Then methyltriphenylphosphonium bromide (3.61 g, 10.1 mmol), *t*-BuOK (1.25 g, 11.1 mmol) and THF (50 mL) were added and the mixture was stirred at room temperature for an additional 1 h. After removal of the solvent, the residue was diluted with water and extracted with several portions of AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was concentrated to ca. 50 mL, and then the precipitate was collected by filtration to give **23a** (3.45 g, 70%) as colourless crystals. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane–AcOEt = 1:1 as an eluent to give additional **23a** (1.38 g, 28%) as colourless crystals. Mp 212–213 °C (AcOEt–hexane). IR (KBr): 1632, 1601, 1489, 1445, 1391, 1262, 1229, 1196, 1182, 1128, 1117, 1034, 907, 855, 747, 733, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.90 (3H, s), 5.32 (1H, d, $J = 1.6$ Hz), 5.99 (1H, d, $J = 1.6$ Hz), 6.70 (1H, d, $J = 1.4$ Hz), 7.09–7.21 (8H, m), 7.27–7.35 (9H, m), 7.45–7.52 (2H, m), 7.58–7.65 (2H, m), 7.75 (1H, d, $J = 1.2$ Hz). Anal. Calcd for $C_{35}H_{28}N_2O$: C, 85.34; H, 5.73; N, 5.69. Found: C, 85.29; H, 5.67; N, 5.76.

6.32. 4-[1-(6-Methoxy-2-naphthyl)-2,2-dimethylvinyl]-1-trityl-1*H*-imidazole (23b)

To a suspension of isopropyltriphenylphosphonium iodide (13.1 g, 30.3 mmol) in THF (100 mL) was added *t*-BuOK (3.40 g, 30.3 mmol) portionwise with ice-cooling. The stirring was continued for 10 min, and **22** (10.0 g, 20.2 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, diluted with water and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated, and the residue was purified by column chromatography on silica gel using hexane–AcOEt = 2:1 to 1:1 as an eluent to give **23b** (10.2 g, 97%) as a pale yellow powder. IR (KBr): 1603, 1493, 1483, 1445, 1264, 1177, 1159, 1136, 1034, 851, 747, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.76 (3H, s), 2.08 (3H, s), 3.89 (3H, s), 6.50 (1H, d, $J = 1.4$ Hz), 7.08–7.19 (9H, m), 7.23–7.31 (10H, m), 7.42 (1H, d, $J = 1.6$ Hz), 7.56 (1H, d, $J = 1.2$ Hz), 7.62 (1H, d, $J = 2.8$ Hz), 7.66 (1H, d, $J = 4.2$ Hz).

6.33. 4-[1-(6-Methoxy-2-naphthyl)vinyl]-1*H*-imidazole (24a)

Prepared from **23a** by the procedure described for the synthesis of **21** in 84% yield. Colourless crystals. Mp 198–200 °C (THF–hexane). IR (KBr): 2625, 1603, 1466, 1260, 1217, 1026, 891, 839, 814 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.94 (3H, s), 4.31 (1H, br s), 5.33 (1H, s), 5.73 (1H, s), 6.88 (1H, s), 7.12–7.17 (2H, m), 7.53 (1H, dd, $J = 8.5$, 1.7 Hz), 7.63 (1H, s), 7.71 (1H, s), 7.75 (1H, s), 7.83 (1H, s). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.57; H, 5.73; N, 11.26.

6.34. 4-[1-(6-Methoxy-2-naphthyl)-2,2-dimethylvinyl]-1*H*-imidazole (24b)

Prepared from **23b** by the procedure described for the synthesis of **21** in 99% yield. A pale yellow amorphous powder. IR (KBr): 2908, 1632, 1603, 1499, 1481, 1264, 1225, 1177, 1032, 851 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.77 (3H, s), 2.06 (3H, s), 3.90 (3H, s), 6.89 (1H, s), 7.10–7.20 (2H, m), 7.35 (1H, m), 7.51 (1H, s), 7.63–7.69 (3H, m).

6.35. 4-[1-(6-Methoxy-2-naphthyl)ethyl]-1*H*-imidazole (25a)

A mixture of **24a** (1.20 g, 4.8 mmol) and 10% Pd–C (0.12 g) in DMF (15 mL) was vigorously stirred at room temperature for 12 h under a H_2 atmosphere. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel using $CHCl_3$–MeOH = 10:1 as an eluent. The product was recrystallized from THF–hexane to give **25a** (1.11 g, 92%) as colourless needles. Mp 193–194 °C. IR (KBr): 3056, 2907, 1603, 1264, 1225, 1117, 1032, 851 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 1.67 (3H, d, $J = 7.2$ Hz), 3.91 (3H, s), 4.09 (1H, s), 4.22 (1H, q, $J = 7.2$ Hz), 6.75 (1H, s), 7.09–7.15 (2H, m), 7.32 (1H, dd, $J = 8.4$, 1.9 Hz), 7.51 (1H, d, $J = 1.2$ Hz), 7.59 (1H, s), 7.65–7.70 (2H, m). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.03; H, 6.07; N, 11.05.

6.36. 4-[1-(6-Methoxy-2-naphthyl)-2-methylpropyl]-1*H*-imidazole (25b)

Prepared from **24b** by the procedure described for the synthesis of **25a** in 67% yield. Colourless crystals. Mp 153–154 °C (AcOEt). IR (KBr): 2953, 1605, 1483, 1464, 1264, 1227, 1034, 856, 839, 818 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.83 (3H, d, $J = 6.6$ Hz), 1.00 (3H, d, $J = 6.6$ Hz), 2.40–2.58 (1H, m), 3.68 (1H, d, $J = 9.6$ Hz), 3.89 (3H, s), 5.64 (1H, br s), 6.90 (1H, s), 7.08–7.13 (2H, m), 7.40 (1H, dd, $J = 8.4$, 1.6 Hz), 7.47 (1H, s), 7.63–7.67 (3H, m). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.92; H, 6.99; N, 10.01.

6.37. (1*H*-Imidazol-4-yl)-(6-methoxy-2-naphthyl)methanol (26)

A solution of **18** (424 mg, 0.85 mmol) in 90% HCO_2H (3 mL) was stirred for 45 min at 50 °C. The mixture was diluted with 1 N HCl and the precipitate was filtered off. The aqueous filtrate was washed with Et_2O, neutralized with K_2CO_3 and extracted with several portions of $CHCl_3$–MeOH (10:1). The combined

organic layers were concentrated and the residue was purified by column chromatography on silica gel using $CHCl_3$–MeOH = 5:1 as an eluent to give **26** (153 mg, 71%) as colourless crystals. Mp 162.5–163.5 °C (THF–hexane). IR (KBr): 3106, 2998, 1611, 1264, 1198, 1161, 1032, 847 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 1.94 (1H, s), 3.92 (3H, s), 5.94 (1H, s), 6.69 (1H, s), 7.11–7.17 (2H, m), 7.48 (1H, dd, $J = 8.5$, 1.7 Hz), 7.56 (1H, d, $J = 1.0$ Hz), 7.70 (1H, s), 7.75 (1H, d, $J = 1.8$ Hz), 7.84 (1H, s). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.77; H, 5.49; N, 10.76.

6.38. Introduction of alkyl or aryl group into 22. 1-(6-Methoxy-2-naphthyl)-1-(1-trityl-1*H*-imidazol-4-yl)ethanol (27a)

To a solution of **22** (2.50 g, 5.1 mmol) in THF (20 mL) was added methylmagnesium bromide (3.0 M solution in Et_2O, 3.4 mL, 10.1 mmol) dropwise with ice-cooling. The mixture was stirred for 20 min, diluted with saturated NH_4Cl and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated to give **27a** (2.51 g, 97%) as colourless crystals. Mp 169–170 °C (AcOEt–hexane). IR (KBr): 3150, 1605, 1493, 1445, 1264, 1177, 1165, 909, 747, 733, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.85 (3H, s), 3.62 (1H, br s), 3.90 (3H, s), 6.77 (1H, d, $J = 1.4$ Hz), 7.09 (1H, s), 7.13–7.21 (7H, m), 7.30–7.36 (9H, m), 7.41 (1H, d, $J = 1.4$ Hz), 7.45 (1H, dd, $J = 8.7$, 1.8 Hz), 7.62–7.69 (2H, m), 7.80 (1H, d, $J = 1.6$ Hz). Anal. Calcd for $C_{35}H_{30}N_2O_2$: C, 82.33; H, 5.92; N, 5.49. Found: C, 82.18; H, 5.89; N, 5.39.

6.39. 1-(6-Methoxy-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (27d)

Prepared from **22** and isopropylmagnesium bromide (2.0 M solution in THF) by a similar procedure to that described for the synthesis of **27a** in 56% yield. Mp 186–187 °C (ether). IR (KBr): 1605, 1483, 1445, 1264, 1223, 1167, 909, 747, 733, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.74 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.6$ Hz), 1.90 (1H, br s), 2.46–2.59 (1H, m), 3.91 (3H, s), 6.80 (1H, d, $J = 1.4$ Hz), 7.09–7.17 (8H, m), 7.29–7.37 (10H, m), 7.53 (1H, dd, $J = 8.7$, 1.7 Hz), 7.62–7.71 (2H, m), 7.93 (1H, d, $J = 1.2$ Hz). Anal. Calcd for $C_{37}H_{34}N_2O_2$: C, 82.50; H, 6.36; N, 5.20. Found: C, 82.29; H, 6.34; N, 5.22.

6.40. (6-Methoxy-2-naphthyl)(phenyl)(1-trityl-1*H*-imidazol-4-yl)methanol (27i)

To a solution of bromobenzene (0.85 mL, 8.1 mmol) in Et_2O (20 mL) was added *n*-BuLi (1.6 M solution in hexane, 5.1 mL, 8.1 mmol) dropwise at −78 °C. The stirring was continued for 20 min and a solution of **22** (1.0 g, 2.0 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min, quenched with water and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was purified by column chromatography on silica gel using AcOEt–hexane = 3:1 to 1:1 as an eluent to give **27i** (1.04 g, 88%) as colourless crystals. Mp 120–121 °C (AcOEt). IR (KBr): 3167, 1742, 1609, 1485, 1447, 1265, 1165, 1132, 1030, 889, 849, 756, 700 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 3.85 (3H, s), 6.49 (1H, s), 6.83 (1H, d, $J = 1.4$ Hz), 7.11–7.15 (7H, m), 7.25 (1H, d, $J = 1.4$ Hz), 7.37–7.43 (13H, m), 7.67–7.74 (3H, m), 8.44–8.47 (2H, m). Anal. Calcd for $C_{40}H_{32}N_2O_2 \cdot 0.4H_2O$: C, 82.85; H, 5.70; N, 4.83. Found: C, 82.82; H, 5.74; N, 4.67.

6.41. (6-Methoxy-2-naphthyl)-3-pyridyl-(1-trityl-1*H*-imidazol-4-yl)methanol (27j)

Prepared from **22** and 3-bromopyridine by a similar procedure to that described for the synthesis of **27i** in 83% yield. Colourless crystals. Mp 170 °C decomp (AcOEt–hexane). IR (KBr): 3216, 1609, 1485, 1443, 1385, 1269, 1171, 1067, 1028, 878, 849, 748, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.90 (3H, s), 6.40 (1H, d, $J = 1.4$ Hz), 7.09–7.23 (9H, m), 7.27–7.41 (10H, m), 7.50 (1H, d, $J = 1.6$ Hz), 7.57–7.65 (3H, m), 7.70–7.76 (1H, m), 8.47 (1H, dd, $J = 4.8$, 1.6 Hz), 8.54 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{39}H_{31}N_3O_2 \cdot 0.3H_2O$: C, 80.89; H, 5.50; N, 7.26. Found: C, 80.82; H, 5.50; N, 7.04.

6.42. (6-Methoxy-2-naphthyl)-4-pyridyl-(1-trityl-1*H*-imidazol-4-yl)methanol (27k)

Prepared from **22** and 4-bromopyridine by a similar procedure to that described for the synthesis of **27i** in 75% yield. Colourless crystals. IR (KBr): 1605, 1483, 1447, 1265, 1223, 1169, 1130, 1063, 1036, 762, 748, 702 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 3.85 (3H, s), 6.49 (1H, s), 6.83 (1H, d, $J = 1.4$ Hz), 7.11–7.15 (7H, m), 7.25 (1H, d, $J = 1.4$ Hz), 7.37–7.43 (13H, m), 7.67–7.74 (3H, m), 8.44–8.47 (2H, m). Anal. Calcd for $C_{39}H_{31}N_3O_2$: C, 81.65; H, 5.45; N, 7.32. Found: C, 81.55; H, 5.35; N, 7.28.

6.43. Deprotection of the trityl group

Compounds **28a**,**i**,**j**,**k** and **29** were prepared from **27a**,**i**,**j**,**k** and **22**, respectively, by the procedure described for the synthesis of **26**.

6.44. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-ethanol (28a)

Yield 74%. Colourless crystals. Mp 159–160 °C (THF–hexane). IR (KBr): 3200, 1609, 1485, 1453, 1264, 1173, 1115, 1034, 905, 893, 847, 802 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 1.94 (3H, s), 3.92 (3H, s), 6.88 (1H, s), 7.11–7.16 (2H, m), 7.46 (1H, dd, $J = 8.5$, 1.9 Hz), 7.53 (1H, d, $J = 1.0$ Hz), 7.67 (1H, d, $J = 3.4$ Hz), 7.72 (1H, d, $J = 5.2$ Hz), 7.82 (1H,

d, $J = 1.2$ Hz). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.44; H, 5.79; N, 10.39.

6.45. 1*H*-Imidazol-4-yl-(6-methoxy-2-naphthyl)(phenyl) methanol (28i)

Yield 67%. Colourless crystals. Mp 180 °C decomp (AcOEt). IR (KBr): 3362, 2838, 1607, 1389, 1264, 1221, 1167, 1034, 862, 756 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 3.91 (3H, s), 6.41 (1H, s), 7.08–7.13 (2H, m), 7.25–7.39 (5H, m), 7.44 (1H, dd, $J = 8.7$, 1.7 Hz), 7.59 (1H, d, $J = 1.2$ Hz), 7.63–7.64 (2H, m), 7.68 (1H, d, $J = 2.6$ Hz). Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.21; H, 5.30; N, 8.40.

6.46. (1*H*-Imidazol-4-yl)-(6-methoxy-2-naphthyl)-3-pyridylmethanol (28j)

Yield 78%. Colourless crystals. Mp180 °C decomp (THF). IR (KBr): 3058, 2840, 1422, 1265, 1167, 1152, 1034, 891, 851, 806 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 3.92 (3H, s), 6.44 (1H, s), 7.12–7.16 (2H, m), 7.25–7.29 (1H, m), 7.43 (1H, dd, $J = 8.5$, 1.7 Hz), 7.64–7.71 (4H, m), 7.80 (1H, dd, $J = 8.0$. 1.6 Hz), 8.44 (1H, dd, $J = 3.4$. 1.2 Hz), 8.54 (1H, d, $J = 2.4$ Hz). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.34; H, 5.04; N, 12.44.

6.47. (1*H*-Imidazol-4-yl)-(6-methoxy-2-naphthyl)-4-pyridylmethanol (28k)

Yield 91%. Colourless crystals. Mp 153–155 °C (AcOEt–hexane). IR (KBr): 3067, 2840, 1601, 1414, 1265, 1167, 893, 866, 853 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 3.92 (3H, s), 6.50 (1H, d, $J = 1.4$ Hz), 7.10–7.16 (2H, m), 7.39–7.44 (3H, m), 7.64–7.72 (4H, m), 8.67 (2H, dd, $J = 4.6$, 1.6 Hz). Anal. Calcd for $C_{20}H_{17}N_3O_2 \cdot 0.3H_2O$: C, 71.33; H, 5.27; N, 12.48. Found: C, 71.31; H, 5.35; N, 12.17.

6.48. (1*H*-Imidazol-4-yl)-(6-methoxy-2-naphthyl)ketone (29)

Prepared from **22** by the procedure described for the synthesis of **26** in 84% yield. Colourless crystals. Mp 200 °C decomp ($CHCl_3$–MeOH–AcOEt). IR (KBr): 3146, 2649, 2579, 1636, 1624, 1481, 1346, 1264, 1169, 860 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 3.97 (3H, s), 7.21–7.26 (2H, m), 7.78 (1H, s), 7.82–7.91 (3H, m), 7.99 (1H, dd, $J = 8.5$, 1.7 Hz), 8.49 (1H, s). Anal. Calcd for $C_{15}H_{12}N_2O_2 \cdot 0.2H_2O$: C, 70.41; H, 4.88; N, 10.95. Found: C, 70.32; H, 4.62; N, 10.69.

6.49. Introduction of alkyl group into 29. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methylpropan-1-ol (28d)

To a solution of **29** (1.50 g, 6.0 mmol) in THF (30 mL) was added isopropylmagnesium bromide (2.0 M solution in THF, 8.9 mL, 17.9 mmol) dropwise at −10 °C. The mixture was stirred for 30 min, diluted with saturated NH_4Cl and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was purified by column chromatography on silica gel using $CHCl_3$–MeOH = 20:1 to 10:1 as an eluent. The product was recrystallized from AcOEt to give **28d** (1.14 g, 65%) as colourless crystals. Mp 171–172 °C. IR (KBr): 3140, 2984, 2957, 1464, 1222, 1028, 856, 806, 652 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 0.81 (3H, d, $J = 6.8$ Hz), 1.00 (3H, d, $J = 6.8$ Hz), 2.64–2.78 (1H, m), 3.91 (3H, s), 7.00 (1H, d, $J = 1.0$ Hz), 7.09–7.15 (2H, m), 7.51–7.56 (2H, m), 7.65–7.75 (2H, m), 7.91 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C,72.95; H, 6.80; N, 9.45. Found: C, 72.77; H, 6.79; N, 9.31. Compounds **28b**,**c** and **28e**–**h** were prepared from **29** using the corresponding Grignard reagent by a similar procedure to that described for the synthesis of **28d**.

6.50. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)propan-1-ol (28b)

Yield 42%. Colourless crystals. Mp 168–169 °C (THF–AcOEt). IR (KBr): 3160, 2971, 1607, 1483, 1265, 1223, 1169, 1032, 853 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 0.87 (3H, t, $J = 7.3$ Hz), 2.19–2.41 (2H, m), 3.92 (3H, s), 6.91 (1H, d, $J = 1.2$ Hz), 7.11–7.16 (2H, m), 7.42 (1H, dd, $J = 8.8$, 1.2 Hz), 7.54 (1H, d, $J = 1.2$ Hz), 7.66–7.75 (2H, m), 7.86 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.18; H, 6.24; N, 9.82.

6.51. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-butan-1-ol (28c)

Yield 20%. Colourless crystals. Mp 164–165 °C (AcOEt). IR (KBr): 2955, 1605, 1505, 1483, 1265, 1221, 1167, 1032, 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.89 (3H, t, $J = 7.3$ Hz), 1.10–1.30 (1H, m), 1.37–1.55 (1H, m), 2.20–2.30 (2H, m), 3.91 (3H, s), 6.90 (1H, s), 7.10–7.15 (2H, m), 7.45 (1H, dd, $J = 8.6$, 1.8 Hz), 7.50 (1H, s), 7.65–7.73 (2H, m), 7.91 (1H, s). Anal. Calcd for $C_{18}H_{20}N_2O_2 \cdot 0.1$AcOEt: C, 72.42; H, 6.87; N, 9.18. Found: C, 72.45; H, 6.78; N, 9.02.

6.52. Cyclopropyl-(1*H*-imidazol-4-yl)-(6-methoxy-2-naphthyl)methanol fumarate (28e)

Yield 32%. Isolated as the fumarate salt. Colourless crystals. Mp 167–168 °C (MeOH). IR (KBr): 3117, 1609, 1265, 1227, 1179, 1163, 1063, 851 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.32–0.62 (4H, m), 1.62–1.76 (1H, m), 2.49–2.52 (1H, m), 3.86 (3H, s), 6.61 (2H, s), 7.04 (1H, d, $J = 1.2$ Hz), 7.12 (1H, dd, $J = 8.8$, 2.4 Hz), 7.25 (1H, d, $J = 2.4$ Hz), 7.52 (1H, dd, $J = 8.7$, 1.7 Hz), 7.65–7.79 (3H, m), 7.89 (1H, s). Anal. Calcd for $C_{18}H_{18}N_2O_2 \cdot C_4H_4O_4$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.33; N, 6.86.

6.53. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-3-methylbutan-1-ol (28f)

Yield 71%. Colourless crystals. Mp 172–174 °C (AcOEt-*i*-Pr_2O). IR (KBr): 2953, 1607, 1505, 1483, 1466, 1389, 1265, 1219, 1169, 1032, 853 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.72 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.8$ Hz), 1.63–1.82 (1H, m), 2.20 (2H, d, $J = 5.8$ Hz), 3.90 (3H, s), 6.82 (1H, s), 7.10–7.14 (2H, m), 7.38 (1H, s), 7.42 (1H, dd, $J = 8.4$, 1.8 Hz), 7.63–7.72 (2H, m), 7.93 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.34; H, 7.35; N, 8.83.

6.54. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2,2-dimethylpropan-1-ol fumarate (28g)

Yield 35%. Isolated as the fumarate salt. Pale yellow crystals. Mp 168–170 °C (EtOH). IR (KBr): 3416, 3152, 2976, 1535, 1391, 1271, 1215, 1167, 899, 851 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.06 (9H, s), 3.89 (3H, s), 6.71 (2H, s), 7.62 (1H, dd, $J = 8.8$, 2.0 Hz), 7.69–7.70 (2H, m), 7.80 (1H, d, $J = 1.2$ Hz), 7.93 (1H, s), 8.50 (1H, s). Anal. Calcd for $C_{19}H_{22}N_2O_2 \cdot C_4H_4O_4$: C, 64.78; H, 6.14; N, 6.57. Found: C, 64.65; H, 6.07; N, 6.50.

6.55. Cyclopentyl-(1*H*-imidazol-4-yl)-(6-methoxy-2-naphthyl)methanol (28h)

Yield 10%. Colourless crystals. Mp 177–178 °C (AcOEt). IR (KBr): 2959, 1607, 1483, 1265, 1221, 1169, 1032, 851 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.72–1.34 (8H, m), 2.92–3.06 (1H, m), 3.90 (3H, s), 7.02 (1H, s), 7.09–7.14 (2H, m), 7.51–7.56 (2H, m), 7.63–7.74 (2H, m), 7.97 (1H, s). Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot 0.1H_2O$: C, 74.09; H, 6.90; N, 8.64. Found: C, 73.97; H, 6.76; N, 8.66.

6.56. Optical resolution of 28d

Separation of **28d** into its enantiomers was carried out by HPLC using Chiralpak® AD (20 mm id ×250 mm) with detection at 254 nm. Elution with a mixture of *n*-hexane–EtOH (70:30) at a flow rate of 8 mL/min at 30 °C gave (*S*)-**28d** and (*R*)-**28d**, respectively.

6.57. (−)-(*S*)-1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methylpropan-1-ol [(*S*)-28d]

Retention time = 9.26 min (Chiralpak® AD (4.6 mm id ×250 mm), detection at 254 nm, elution with *n*-hexane–EtOH (80:20), flow rate of 0.8 mL/min). $[\alpha]_D^{23}$ −48.4 (*c* 0.5, MeOH). Mp 179–181 °C (AcOEt).

6.58. (+)-(*R*)-1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methylpropan-1-ol [(*R*)-28d]

Retention time = 24.84 min (the same conditions for the analysis of (*S*)-**28d**). $[\alpha]_D^{23}$ +46.7 (*c* 0.5, MeOH).

6.59. X-ray structure of (*R*)-28d

An analytical sample of (*R*)-**28d** for X-ray analysis was obtained by recrystallization from AcOEt. The X-ray measurement was preformed on a Rigaku AFC5R diffractometer with Cu-Kα radiation. Crystal data for (*R*)-**28d**: $C_{18}H_{20}N_2O_2$, $M = 296.4$, monoclinic, space group $P2_1$ (#4), $a = 6.601(2)$ Å, $b = 7.323(3)$ Å, $c = 16.053(2)$ Å, $\beta = 95.07(2)°$, $V = 773.0(4)$ Å^3, $D_{calc} = 1.273$ gcm^{-3}, $Z = 2$; Final *R*-values were $R1 = 0.032$ for 2056 reflections with $Fo > 4\sigma$ (Fo), $wR2 = 0.093$ for all the 2297 reflections. The absolute configuration was supported by the Flack parameter[42] of 0.04(28). Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 230602).

6.60. 6-Bromo-2-methoxy-1-naphthaldehyde (30)

Phosphorous oxychloride (32.83 g, 0.214 mol) was added to DMF (50 mL) with ice-cooling and the mixture was stirred at room temperature for 0.5 h. Then **5a** (21.10 g, 89 mmol) was added, and the reaction mixture was stirred at 100 °C for 7 h, cooled to room temperature, and poured into ice water. The precipitate was filtered, washed with water and EtOH and recrystallized from diisopropylether to give **30** (6.20 g, 26%) as colourless crystals. Mp 107 °C. IR (KBr): 1665, 1501, 1269, 1154 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.06 (3H, s), 7.33 (1H, d, $J = 9.2$ Hz), 7.66 (1H, dd, $J = 2.2$, 9.2 Hz), 7.93 (1H, d, $J = 2.2$ Hz), 7.96 (1H, d, $J = 9.2$ Hz), 9.18 (1H, d, $J = 9.2$ Hz). Anal. Calcd for $C_{12}H_9BrO_2$: C, 54.37; H, 3.42. Found: C, 54.22; H, 3.38.

6.61. (6-Bromo-2-methoxy-1-naphthyl)methanol (31)

To a solution of **30** (4.07 g, 15.4 mmol) in MeOH (50 mL) was added $NaBH_4$ (1.30 g, 34.4 mmol) with ice-cooling. The mixture was stirred at room temperature for 0.5 h and concentrated. The residue was partitioned between AcOEt and water and the organic layer was separated, dried over $MgSO_4$ and concentrated to give **31** as colourless crystals (3.20 g, 78%). Mp 117 °C (hexane). IR (KBr): 3330, 1589, 1503, 1267, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.98 (3H, s), 5.14 (2H, s), 7.30 (1H, d, $J = 9.2$ Hz), 7.57 (1H, dd, $J = 2.2$, 9.2 Hz), 7.74 (1H, d, $J = 9.2$ Hz), 7.95 (1H, d, $J = 2.2$ Hz), 7.99 (1H, d, $J = 9.2$ Hz). Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 54.26; H, 4.05.

6.62. 6-Bromo-2-methoxy-1-methyl naphthalene (32)

To a mixture of **31** (2.05 g, 7.67 mmol) and Et_3N (3.2 mL, 23.0 mmol) in THF (20 mL) was added methanesulfonyl chloride (0.9 mL, 11.6 mmol) with ice-cooling. The mixture was stirred at room temperature for 1 h and concentrated. The residue was partitioned between AcOEt and water and the separated organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in DMSO (20 mL) and the solution was stirred

at room temperature for 1 h with NaI (1.49, 9.90 mmol). Then $NaBH_4$ (1.09 g, 28.8 mmol) was added and the mixture was stirred at room temperature for an additional 1 h, poured into water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel using hexane as an eluent to give **32** (1.16 g, 60%) as colourless crystals. Mp 71–72 °C. IR (KBr): 1588, 1499, 1264, 1250, 1103, 883 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.52 (3H, s), 3.94 (3H, s), 7.25 (1H, d, $J = 9.0$ Hz), 7.52 (1H, dd, $J = 1.8$, 9.0 Hz), 7.61 (1H, d, $J = 9.0$ Hz), 7.81 (1H, d, $J = 9.0$ Hz), 7.92 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{12}H_{11}BrO$: C, 57.39; H, 4.42. Found: C, 57.67; H, 4.38.

6.63. 6-Bromo-2-methoxy-1-naphthyl formate (33)

To a solution of **30** (1.15 g, 4.3 mmol) in CH_2Cl_2 (100 mL) was added 3-chloroperoxybenzoic acid (1.70 g, 9.9 mmol) with ice-cooling, and the stirring was continued for 2 h. The mixture was diluted with aqueous $NaHCO_3$, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated and the residue was washed with AcOEt to give **33** (0.96 g, 78%) as colourless crystals. Mp 149 °C (hexane). IR (KBr): 1728, 1591, 1499, 1281, 1177, 1140, 1084 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.96 (3H, s), 7.36 (1H, d, $J = 9.0$ Hz), 7.56 (1H, dd, $J = 1.8$, 8.8 Hz), 7.68 (1H, d, $J = 9.0$ Hz), 7.72 (1H, d, $J = 8.8$ Hz), 7.97 (1H, d, $J = 1.8$ Hz), 8.42 (1H, s). Anal. Calcd for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23. Found: C, 50.97; H, 3.30.

6.64. 6-Bromo-1,2-dimethoxynaphthalene (34)

A mixture of **33** (757 mg, 2.69 mmol), $LiOH{\cdot}H_2O$ (176 mg, 4.19 mmol), ethanol (8 mL) and water (4 mL) was stirred at 60 °C for 2 h. After removal of the solvent, the residue was dissolved in DMF (10 mL) and K_2CO_3 (483 mg, 3.49 mmol) and MeI (0.5 mL, 8.03 mmol) were added. The mixture was stirred at room temperature for 6 h, diluted with water and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using hexane–AcOEt = 20:1 as an eluent to give **34** (223 mg, 31%) as colourless needles. Mp 57 °C. IR (KBr): 1588, 1354, 1273, 1069 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.98 (3H, s), 3.99 (3H, s), 7.29 (1H, d, $J = 8.8$ Hz), 7.49 (1H, d, $J = 8.8$ Hz), 7.51 (1H, dd, $J = 1.8$, 8.8 Hz), 7.92 (1H, d, $J = 1.8$ Hz), 7.99 (1H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 53.79; H, 4.13.

6.65. 1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-5-methyl-2-naphthyl)-2-methylpropan-1-ol (36a)

To a solution of **32** (0.95 g, 3.8 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in hexane, 3.0 mL, 4.8 mmol) at −78 °C, and the stirring was continued for 1 h. A solution of **35**[37] (0.16 g, 1.1 mmol) in THF (10 mL) was added and the mixture was stirred at −78 °C for 1 h, diluted with aqueous NH_4Cl and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH = 15:1 as an eluent to give **36a** (0.18 g, 53%) as colourless crystals. Mp 156–160 °C. IR (KBr): 2967, 1267, 1254, 1105, 816 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.81 (3H, d, $J = 6.8$ Hz), 1.01 (3H, d, $J = 6.8$ Hz), 2.52 (3H, s), 2.60–2.80 (1H, m), 3.92 (3H, s), 6.98 (1H, d, $J = 1.0$ Hz), 7.24 (1H, d, $J = 9.2$ Hz), 7.48 (1H, d, $J = 1.0$ Hz), 7.59 (1H, dd, $J = 2.0$, 9.0 Hz), 7.69 (1H, d, $J = 9.2$ Hz), 7.87 (1H, d, $J = 9.0$ Hz), 7.97 (1H, d, $J = 2.0$ Hz). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.46; H, 7.26; N, 8.94.

6.66. 1-(5,6-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (36b)

Prepared from **34** and **35** by a similar procedure to that described for the synthesis of **36a** in 53% yield. Mp 103–108 °C. IR (KBr): 2969, 1360, 1270, 1100, 1061, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.80 (3H, d, $J = 6.8$ Hz), 1.00 (3H, d, $J = 6.8$ Hz), 2.60–2.80 (1H, m), 3.96 (3H, s), 6.97 (1H, d, $J = 1.1$ Hz), 7.24 (1H, d, $J = 8.8$ Hz), 7.46 (1H, d, $J = 1.1$ Hz), 7.56 (1H, dd, $J = 1.8$, 8.8 Hz), 7.98 (1H, d, $J = 1.8$ Hz), 8.02 (1H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{19}H_{22}N_2O_3{\cdot}0.1H_2O$: C, 69.53; H, 6.82; N, 8.54. Found: C, 69.34; H, 6.84; N, 8.63.

6.67. Ethyl 6,7-dimethoxy-2-naphthoate (38)

To a solution of LDA (0.57 M in THF, 70 mL) was added **9** (5.71 g, 30 mmol) dropwise at −78 °C and the stirring was continued for 1 h. A solution of 3,4-dimethoxybenzaldehyde (**37**, 4.98 g, 30 mmol) in THF (10 mL) was added, and the mixture was allowed to warm to room temperature, quenched with water, extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated and the residue was dissolved in EtOH (30 mL). This solution was added to refluxing 20% H_2SO_4 (300 mL), and the reflux was continued for an additional 2 h. The reaction mixture was cooled to room temperature and extracted with several portions of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using hexane–AcOEt (4:1) as an eluent. The product was recrystallized from hexane–AcOEt to give **38** (3.53 g 45%) as colourless crystals. Mp 109 °C. IR (KBr): 2978, 1713, 1489, 1238 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (3H, t, $J = 7.2$ Hz), 4.01 (3H, s), 4.02 (3H, s), 4.42 (2H, q, $J = 7.2$ Hz), 7.14 (1H, s), 7.21 (1H, s), 7.70 (1H, d, $J = 8.5$ Hz), 7.94 (1H, dd, $J = 8.5$, 1.8 Hz), 8.45 (1H, m). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.31; H, 6.33.

6.68. (6,7-Dimethoxy-2-naphthyl)methanol (39)

To a suspension of $LiAlH_4$ (2.77 g, 73.0 mmol) in THF (200 mL) was added **38** (14.30 g, 54.9 mmol) portionwise with ice-cooling. The mixture was stirred for 0.5 h, and the reaction was quenched by the addition of

water. Then AcOEt and 1 N HCl were added, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was recrystallized from hexane–AcOEt to give **39** (9.73 g, 81%) as colourless crystals. Mp 111–112 °C (*i*-Pr_2O–AcOEt). IR (KBr): 3299, 1514, 1497, 1262, 1161, 856 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.99 (3H, s), 4.00 (3H, s), 4.80 (2H, s), 7.10 (1H, s), 7.11 (1H, s), 7.33 (1H, dd, $J = 8.4$, 1.8 Hz), 7.60–7.72 (2H, m). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.57; H, 6.42.

6.69. 6,7-Dimethoxy-2-naphthaldehyde (40)

A mixture of **39** (9.26 g, 42.5 mmol) and MnO_2 (9.37 g) in CH_2Cl_2 (100 mL) was stirred at room temperature for 48 h. The mixture was filtered through Celite, and the filtrate was concentrated to give **40** as colourless crystals (7.40 g, 81%). Mp 95–97 °C (AcOEt–hexane–*i*-Pr_2). IR (KBr): 1688, 1487, 1211, 1157 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.04 (6H, s), 7.17 (1H, s), 7.26 (1H, s), 7.76 (1H, d, $J = 8.4$ Hz), 7.83 (1H, dd, $J = 8.4$, 1.6 Hz), 8.19 (1H, m). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.20; H, 5.72.

6.70. (6,7-Dimethoxy-2-naphthyl)(1*H*-imidazol-4-yl)-methanone (41)

To a solution of 4-bromoimidazole (2.01 g, 13.7 mmol) in THF (35 mL) was added *t*-BuLi (1.7 M in pentane, 22.0 mL, 37.4 mmol) at −78 °C. The mixture was allowed to warm to 0 °C and stirred for 1.5 h. Then the mixture was cooled to −78 °C, and a solution of **40** (3.84 g, 17.8 mmol) in THF (20 mL) was added dropwise. The mixture was warmed to room temperature, stirred for an additional 16 h, quenched with aqueous NH_4Cl, and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated, and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (20:1) as an eluent to give **41** (1.31 g, 34%) as colourless crystals. Mp 232 °C. IR (KBr): 3088, 1636, 1508, 1489, 1260, 1159, 883 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.93 (3H, s), 3.94 (3H, s), 7.39 (1H, s), 7.53 (1H, s), 7.80–8.03 (5H, m), 8.72 (1H, br s). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.96; H, 4.74; N, 9.88.

6.71. 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (42)

To a solution of **41** (0.80 g, 2.9 mmol) in THF (20 mL) was added isopropylmagnesium chloride (2.0 M in THF, 6 mL, 12.0 mmol) dropwise at −30 °C. The mixture was warmed up to room temperature, diluted with saturated aqueous NH_4Cl, and made alkaline with 1 N NaOH. The layers were separated, and the aqueous layer was further extracted with AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (20:1) as an eluent to give **42** (0.61 g, 66%) as colourless crystals. Mp 162–163 °C (AcOEt–hexane). IR (KBr): 3322, 2965, 1510, 1254, 1163, 731 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.81 (3H, d, $J = 6.6$ Hz), 1.00 (3H, d, $J = 6.6$ Hz), 2.60–2.78 (1H, m), 3.96 (3H, s), 3.97 (3H, s), 6.98 (1H, d, $J = 1.0$ Hz), 7.07 (1H, s), 7.11 (1H, s), 7.41–7.49 (2H, m), 7.61 (1H, d, $J = 8.4$ Hz), 7.89 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.83; H, 6.76; N, 8.42.

6.72. Optical resolution of 42

Separation of **42** into its enantiomers was carried out by HPLC using Chiralpak® AD (50 mm id × 500 mm) with detection at 254 nm. Elution with a mixture of *n*-hexane–EtOH (85:15) at a flow rate of 60 mL/min at 40 °C gave (*S*)-**42** and (*R*)-**42**, respectively.

6.73. (−)-(*S*)-1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol [(*S*)-42]

An amorphous solid. Retention time = 14.9 min (Chiralpak® AD (4.6 mm id × 250 mm), detection at 254 nm, elution with *n*-hexane–EtOH (85:15), flow rate of 1.0 mL/min).

6.74. (+)-(*R*)- 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol [(*R*)-42]

An amorphous solid. Retention time = 29.3 min (the same conditions for the analysis of (*S*)-**42**).

6.75. (*S*)-42 Fumarate

To a solution of (*S*)-**42** (8.5 mmol) in methanol (10 mL) was added fumaric acid (8.6 mmol). The mixture was concentrated to ca half its volume, and then diluted with AcOEt (10 mL). The crystals that separated out of the solution were collected by filtration to give (*S*)-**42** fumarate (69%). Mp 116–120 °C. $[\alpha^{20}]_D$ −35.3 (*c* 1.01, MeOH). Anal. Calcd for $C_{19}H_{22}N_2O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$: C, 61.19; H, 6.03; N, 6.20. Found: C, 61.01; H, 5.99; N, 6.19.

Similarly, (*R*)-**42** fumarate was obtained.

6.76. X-ray structure of (*S*)-42

An analytical sample of (*S*)-**42** as the salt with (−)-(4*S*)-5,5-dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide for X-ray analysis was obtained by recrystallization from MeOH. The X-ray measurement was preformed on a Rigaku AFC5R diffractometer with Cu-Kα radiation. Crystal data for this salt: $[C_{19}H_{23}N_2O_3]^+[C_{11}H_{14}O_4P]^- \cdot 2CH_3OH$, $M = 632.7$, monoclinic, space group $C2$ (#5), $a = 36.232(3)$ Å, $b = 6.604(2)$ Å, $c = 15.732(2)$ Å, $\beta = 114.619(9)°$, $V = 3422.3(9)$ Å^3, $D_{calc} = 1.228$ gcm^{-3}, $Z = 4$; Final *R*-values

were $R1 = 0.043$ for 4216 reflections with Fo>4σ (Fo), $wR2 = 0.116$ for all the 5888 reflections. The absolute configuration was determined by the Flack parameter[42] of 0.00(3). Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 231387).

6.77. 1-Allyl-6-bromo-2-naphthol (44)

To a solution of NaH (60% oil dispersion, 4.97 g, 124 mmol) in DMF (150 mL) was added **43** (20.09 g, 90.1 mmol) with ice-cooling, and the stirring was continued at room temperature for 0.5 h. Then 3-bromo-1-propene (12.0 mL, 138.7 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h and then poured into water and Et_2O. The organic layer was separated, dried over $MgSO_4$ and concentrated and the residue was washed with *n*-hexane to give 2-(allyloxy)-6-bromonaphthalene (21.67 g, 91%) as colourless crystals. Mp 65 °C (hexane). IR (KBr): 2901, 1591, 1499, 1458, 1262, 1022 cm^{-1}. ^1H NMR ($CDCl_3$): 4.60–4.70 (2H, m), 5.26–5.54 (2H, m), 6.00–6.23 (1H, m), 7.10 (1H, d, $J = 2.6$ Hz), 7.19 (1H, dd, $J = 2.6$, 8.9 Hz), 7.49 (1H, dd, $J = 1.8$, 8.9 Hz), 7.59 (1H, d, $J = 8.9$ Hz), 7.65 (1H, d, $J = 8.9$ Hz), 7.92 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21. Found: C, 59.41; H, 3.98.

This compound (19.95 g, 76 mmol) was heated at 190 °C for 3 h and cooled to room temperature to give **44** (19.78 g, quantitative yield) as colourless crystals. Mp 86–87 °C. IR (KBr): 3314, 1590, 1497, 1346, 1204, 878 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.79 (2H, dt, $J = 5.4$, 1.6 Hz), 4.95–5.16 (3H, m), 5.92–6.16 (1H, m), 7.10 (1H, d, $J = 9.1$ Hz), 7.52 (1H, dd, $J = 8.8$, 2.2 Hz), 7.57 (1H, d, $J = 9.1$ Hz), 7.76 (1H, d, $J = 8.8$ Hz), 7.92 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21. Found: C, 59.63; H, 4.19.

6.78. 6-Bromo-1-(2-hydroxyethyl)-2-naphthol (45)

Ozone gas was introduced into a cooled (−78 °C) solution of **44** (3.29 g, 12.5 mmol) in MeOH (80 mL) and the reaction mixture was stirred at −78 °C for 4 h. Then $NaBH_4$ (1.00 g, 26.4 mmol) was added, and the whole mixture was allowed to warm to room temperature, concentrated and then partitioned between AcOEt and water. The organic layer was separated, dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using hexane–AcOEt = 3:1 as an eluent. The product was recrystallized from hexane–AcOEt to give **45** (0.81 g, 24%) as colourless crystals. Mp 144 °C. IR (KBr): 3196, 1519, 1501, 1348, 1038, 812 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.32 (1H, br s), 3.30 (2H, t, $J = 5.4$ Hz), 4.09 (2H, t, $J = 5.4$ Hz), 7.20 (1H, d, $J = 8.8$ Hz), 7.51 (1H, dd, $J = 2.2$, 9.2 Hz), 7.58 (1H, d, $J = 8.8$ Hz), 7.70 (1H, d, $J = 9.2$ Hz), 7.78 (1H, br s), 7.93 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 53.79; H, 4.40.

6.79. 7-Bromo-1,2-dihydronaphtho[2,1-*b*]furan (46)

A mixture of **45** (30.2 g, 113 mmol), *p*-toluenesulfonic acid (0.49 g, 2.57 mmol) and toluene (500 mL) was refluxed for 2 h. After removal of the solvent, the residue was partitioned between AcOEt and water. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated, and the residue was chromatographed on silica gel using hexane–CH_2Cl_2 = 2:1 as an eluent to give **46** (8.12 g, 34%) as colourless crystals. Mp 64 °C. IR (KBr): 2922, 1510, 1348, 1244, 970, 878 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45 (2H, t, $J = 9.0$ Hz), 4.75 (2H, t, $J = 9.0$ Hz), 7.11 (1H, d, $J = 8.8$ Hz), 7.43 (1H, d, $J = 8.8$ Hz), 7.47–7.60 (2H, m), 7.93 (1H, d, $J = 1.9$ Hz). Anal. Calcd for $C_{12}H_9BrO$: C, 57.86; H, 3.64. Found: C, 57.92; H, 3.37.

6.80. 1-(1,2-Dihydronaphtho[2,1-*b*]furan-7-yl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (47)

Prepared from **46** and **35** by a similar procedure to that described for the synthesis of **36a** in 48% yield. Mp 177–178 °C (AcOEt). IR (KBr): 3125, 2967, 1470, 1244, 970, 909, 731 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.81 (3H, d, $J = 6.6$ Hz), 1.00 (3H, d, $J = 6.6$ Hz), 2.61–2.78 (1H, m), 3.45 (2H, t, $J = 9.0$ Hz), 4.74 (2H, t, $J = 9.0$ Hz), 6.98 (1H, t, $J = 0.8$ Hz), 7.08 (1H, t, $J = 8.8$ Hz), 7.46–7.78 (4H, m), 7.99 (1H, d, $J = 1.6$ Hz). Anal. Calcd for $C_{19}H_{20}N_2O_2 \cdot 0.2H_2O$: C, 73.15; H, 6.59; N, 8.98. Found: C, 73.26; H, 6.46; N, 8.78.

6.81. 2,3-Dihydro-1-benzofuran-5-carbaldehyde (50)

To a solution of **49**[45] (38.86 g, 195 mmol) in THF (300 mL) was added *n*-BuLi (1.6M in hexane, 160 mL, 256 mmol) at −78 °C, and the stirring was continued for 0.5 h. Then DMF (40 mL) was added, and the mixture was allowed to warm to room temperature. The reaction was quenched by the addition of water, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried over $MgSO_4$ and concentrated to give **50** as an oil (28.47 g, 98%). ^1H NMR ($CDCl_3$) δ: 3.27 (2H, t, $J = 8.8$ Hz), 4.69 (2H, t, $J = 8.8$ Hz), 6.87 (1H, d, $J = 8.4$ Hz), 7.62–7.71 (1H, m), 7.74 (1H, d, $J = 1.2$ Hz), 9.83 (1H, s).

6.82. Ethyl 2,3-dihydronaphtho[2,3-*b*]furan-6-carboxylate (51)

To a solution of LDA (0.70 M in THF, 310 mL) was added a solution of **9** (30.50 g, 162 mmol) in THF (50 mL) dropwise at −78 °C, and the stirring was continued for 1 h. A solution of **50** (25.85 g, 174.5 mmol) in THF (50 mL) was added, and the mixture was allowed to warm to room temperature and diluted with water. The layers were separated, and the aqueous layer was further extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated, and the residue was heated at 100 °C with polyphosphoric acid (141 g) in toluene (500 mL) for 0.5 h. The mixture was

poured onto crushed ice and extracted with AcOEt. The extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated and the residue was chromatographed on silica gel using CH_2Cl_2–hexane (1:1) as an eluent to give **51**(10.15 g, 26%) as colourless crystals. Mp 115 °C (AcOEt–hexane). IR (KBr): 2982, 1703, 1466, 1285, 1204, 1096, 868 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.43 (3H, t, $J = 7.2$ Hz), 3.38 (2H, dt, $J = 1.0$, 8.5 Hz), 4.42 (2H, q, $J = 7.2$ Hz), 4.68 (2H, t, $J = 8.5$ Hz), 7.11 (1H, s), 7.68 (1H, d, $J = 9.2$ Hz), 7.72 (1H, s), 7.96 (1H, dd, $J = 1.4$, 9.2 Hz), 8.46 (1H, m). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.39; H, 5.54.

6.83. 2,3-Dihydronaphtho[2,3-*b*]furan-6-ylmethanol (52)

Prepared from **51** by the procedure described for the synthesis of **39** in 89% yield. Mp 177 °C. IR (KBr): 3322, 2901, 1478, 1240, 1034, 988, 866 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.35 (2H, dt, $J = 1.4$, 8.3 Hz), 4.63 (2H, t, $J = 8.3$ Hz), 4.75 (2H, s), 7.07 (1H, s), 7.37 (1H, dd, $J = 1.6$, 8.6 Hz), 7.57–7.70 (3H, m). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.99; H, 6.14.

6.84. 2,3-Dihydronaphtho[2,3-*b*]furan-6-carbaldehyde (53)

Prepared from **52** by the procedure described for the synthesis of **40** in 72% yield. Mp 158 °C (AcOEt). IR (KBr): 1698, 1464, 1175, 988, 868 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.41 (2H, t, $J = 8.7$ Hz), 4.71 (2H, t, $J = 8.7$ Hz), 7.14 (1H, s), 7.60–7.90 (3H, m), 8.20 (1H, s), 10.07 (1H, s). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.47; H, 5.09.

6.85. 2,3-Dihydronaphtho[2,3-*b*]furan-6-yl(1*H*-imidazol-4-yl)methanol (54)

Prepared from **53** by the procedure described for the synthesis of **41** in 52% yield. Mp 220 °C (decomp). IR (KBr): 3069, 1460, 1229, 1028, 886, 839 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 3.33 (2H, t, $J = 8.2$ Hz), 4.59 (2H, t, $J = 8.2$ Hz), 5.79 (1H, s), 6.79 (1H, s), 7.07 (1H, s), 7.40 (1H, d, $J = 8.8$ Hz), 7.57 (1H, s), 7.65 (1H, d, $J = 8.8$ Hz), 7.70 (1H, s), 7.76 (1H, s). Anal. Calcd for $C_{16}H_{12}N_2O_2 \cdot 0.25$AcOEt: C, 71.32; H, 4.93; N, 9.78. Found: C, 71.17; H, 5.24; N, 10.17.

6.86. 2,3-Dihydronaphtho[2,3-*b*]furan-6-yl(1*H*-imidazol-4-yl)methanone (55)

Prepared from **54** by the procedure described for the synthesis of **40** in 89% yield. Mp 219–222 °C. IR (KBr): 2892, 1632, 1458, 1171, 1148, 880 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 3.85 (2H, t, $J = 8.1$ Hz), 4.67 (2H, t, $J = 8.1$ Hz), 7.21 (1H, s), 7.80 (1H, d, $J = 8.7$ Hz), 7.91 (1H, s), 7.94 (2H, s), 8.00 (1H, d, $J = 8.7$ Hz), 8.71 (1H, s). Anal. Calcd for $C_{16}H_{12}N_2O_2 \cdot 0.2H_2O$: C, 71.74; H, 4.67; N, 10.46. Found: C, 71.89; H, 4.54; N, 10.45.

6.87. 1-(2,3-Dihydronaphtho[2,3-*b*]furan-6-yl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (56)

Prepared from **55** by the procedure described for the synthesis of **42** in 51% yield. Mp 186 °C (AcOEt). IR (KBr): 2973, 1460, 1219, 990, 853 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.80 (3H, d, $J = 6.7$ Hz), 0.99 (3H, d, $J = 6.7$ Hz), 2.56–2.77 (1H, m), 3.34 (2H, t, $J = 8.1$ Hz), 4.62 (2H, t, $J = 8.1$ Hz), 6.98 (1H, s), 7.04 (1H, s), 7.44 (1H, d, $J = 8.8$ Hz), 7.50 (1H, s), 7.55–7.66 (2H, m), 7.85 (1H, s). Anal. Calcd for $C_{19}H_{20}N_2O_2 \cdot 0.1H_2O$: C, 73.57; H, 6.56; N, 9.03. Found: C, 73.28; H, 6.77; N, 8.83.

6.88. Molecular modeling

The amino acid sequence of $C_{17,20}$-lyase was aligned to those of six P450s (CYP2C5, P450cam, P450BM-3, P450terp, P450eryF and P450nor), which had been aligned based on their three-dimensional structures. According to the alignment, a homology model of $C_{17,20}$-lyase was constructed based on the crystal structure of CYP2C5[43] and P450BM-3.[44] The modeling procedure was performed using the Homology module of the Insight II program (ver. 2000, Molecular Simulation Inc. San Diego, CA, USA). After connecting the imidazole nitrogen to the heme iron, a docking mode of (*S*)-**28d** was explored by systematic analysis around the rotatable bonds in the inhibitor. During that procedure energy values were estimated based on the Discover CVFF force field (ver. 98.0, Molecular Simulation Inc. San Diego, CA, USA). A hydrogen bond between the inhibitor and the enzyme was then displayed when following two criteria were satisfied. The distance between the proton on the donor atom and the heavy atom acceptor must be less than a specified distance, and the heavy atom donor, the proton and the heavy atom acceptor must be a minimum angle of 120° and linear.

6.89. Assay of inhibitory activity on rat $C_{17,20}$-lyase

Inhibitory activity against rat $C_{17,20}$-lyase was determined by the method described previously.[1] Testes excised from 13-week old, male SD rats were homogenized and testicular microsomes were prepared by a series of centrifugations. The reaction mixture contains 75 mM phosphate buffer (pH 7.4), 7 μg of the microsome protein, 10 nM [1,2-^{3}H]-17α-hydroxyprogesterone (NEN), 5 mM NADPH (Oriental Yeast) and test compounds in a total volume of 20 μL. The test compounds were serially diluted with dimethylformamide, and then 5-fold diluted with distilled water. Test compound solution, 5 μL, was added to the reaction mixture. The reaction was terminated by addition of 40 μL of ethyl acetate after 15 min incubation at 37 °C, then vortexed for 30 s and briefly centrifuged. The organic phase, 30 μL, was applied to silica gel thin layer chromatography plates (Whatman, LHPK). The substrate and the products (androstenedione and testosterone) were separated in the toluene–acetone (7:2) solvent system. Detection of the spots and measurement of the radioactivity as PSL were performed with a BAS2000 Bio-

image analyzer (FUJIX). The concentration of the test compounds necessary to reduce the concentration of the products by 50% (The concentration in the control group in which no test compound is added is set to 100%.) was calculated.

6.90. Assay of inhibitory activity on human $C_{17,20}$-lyase

Human $C_{17,20}$-lyase was expressed in *E. Coli* with *N*-terminal sequence modification (MALLLAVF) as described previously.[41] The vector pCWori$^+$ was obtained as a generous gift from Dr. F. W. Dahlquist (University of Oregon). The membrane fraction prepared from *E. Coli* expressing human $C_{17,20}$-lyase was used for the following assay.

The reaction mixture contains 75 mM phosphate buffer (pH 7.4), 1 mM magnesium chloride, 0.5 pmol of recombinant $C_{17,20}$-lyase, 0.5 pmol of recombinant cytochrome b5 (Pan Vera), 20.8 ng of recombinant NADPH-cytochrome P450 reductase (Pan Vera), 10 nM [1,2-^{3} H]-17α-hydroxypregnenolone (Amersham), 5 mM NADPH (Oriental Yeast), and test compounds in a total volume of 20 μL. The reaction was terminated by addition of 40 μL of ethyl acetate after 15 min incubation at 37 °C, then vortexed for 30 s and briefly centrifuged. The organic phase, 30 μL, was applied to silica gel thin layer chromatography plates (Whatman, LHPK). The substrate and the product (DHEA) were separated in the cyclohexane–ethyl acetate (3:2) solvent system. The following procedures were the same as the assay of rat enzyme inhibitory activity described above, and IC_{50} value was determined.

6.91. Assay of suppressive effects on testosterone biosynthesis in rats

Test compounds were suspended in 0.5% methylcellulose and orally administered to 9 or 10-week old, male SD (Sprague–Dawley) rats at a dose of 25 mg/kg. The rats in the control group received 0.5% methylcellulose. Blood samples were obtained 2 and 5 h after the administration. The serum testosterone concentrations were determined by a specific radioimmunoassay kit (Dia Sorin srl, Italy). The percentage of the testosterone concentration of the group of rats, which received test compounds to that of the control group was calculated (T/C, %), and regarded as the inhibitory activity.

6.92. Effects on weight of prostate, seminal vesicles and liver in rat

Test compounds were suspended in 0.5% methylcellulose and orally administered to 9 or 10-week old, male SD (Sprague–Dawley) rats at a dose of 50 mg/kg, twice a day (9 am and 5 pm), 9 times in total ($n = 5$). The rats in control group received 0.5% methylcellulose (vehicle). Five rats were castrated just before the initiation of the administration (castration group). Blood samples were obtained 2 and 5 h after the final administration (9 am). The serum testosterone concentration was measured by a radioimmunoassay kit (CIS Diagnostics). Five hours after the final administration, the rats were sacrificed by exsanguination under ether anesthesia. Dorsal and ventral prostates, seminal vesicles and liver were excised and weighed. The suppressive effects of test compounds on the prostate and seminal vesicle weight were expressed as the relative potency to castration. The effect on the liver weight was expressed as the percent values of those of intact rats.

6.93. Assay of inhibitory activity on rat steroid 11β-hydroxylase

Adrenals excised from SD rats were homogenized, and mitochondria fraction were prepared by a series of centrifugation. Rat 11-hydroxylase activity was measured according to the method described for side-chain cleavage activity by Uzgiris[46] with some modifications. The reaction mixture contains 200 mM mannitol, 4.5 mM HEPES, 2.3 mM potassium phosphate (pH 7.4), 0.1 mM EDTA·2K, 0.03% BSA (crystallized, Miles), 4.5 mM NADPH (Oriental Yeast), 11 mM calcium chloride, 4 μg of mitochondria protein, 10 nM [1,2-^{3}H]-hydroxy-11-deoxycorticosterone (11-deoxycortisol, NEN, dissolved in 0.02% Tween-80) and test compounds in a total volume of 150 μL. The test compounds were serially diluted with dimethylformamide and 1.5 μL of them was directly added to the reaction mixture. The reaction was terminated by addition of 400 μL of ethyl acetate and 100 μL of distilled water after 30 min incubation at 37 °C, then vortexed for 30 s and briefly centrifuged. The organic phase, 300 μL, were transferred to new tubes, and evaporated to the dryness with nitrogen gas. The steroids were dissolved with 30 μL of ethyl acetate. The whole volume was applied to silica gel thin layer chromatography plates (Whatman, LHPK). The substrate and the products (11-deoxycortisol and cortisol) were separated in the toluene–acetone (7:2) solvent system.

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