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17,20-Lyase inhibitors. Part 3: Design, synthesis, and structure–activity relationships of biphenylylmethylimidazole derivatives as novel 17,20-lyase inhibitors

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ABSTRACT

A novel series of biphenylylmethylimidazole derivatives and related compounds were synthesized as inhibitors of 17,20-lyase, a key enzyme in the production of steroid hormones, and their biological activities were evaluated. In an attempt to identify potent and selective inhibitors of 17,20-lyase over the related CYP3A4 enzyme, a homology model for human 17,20-lyase was developed using the X-ray crystallographic structure of the mammalian CYP2C5 enzyme. With the aid of molecular modeling, optimization of the biphenyl moiety was performed to give an acetamide derivative, which was resolved by HPLC to give the active (−)-enantiomer. The obtained active enantiomer showed not only potent inhibition of both rat and human 17,20-lyase,with IC_{50} values of 14 and 26 nM, respectively, but also excellent selectivity (>300-fold) for inhibition of 17,20-lyase over CYP3A4. Moreover, the active enantiomer significantly reduced both serum testosterone and DHEA concentrations in a monkey model after single oral administration. Asymmetric synthesis of the active enantiomer was also developed via a chiral intermediate using a diastereoselective Grignard reaction.

1. Introduction

The prostate is an androgen-dependent organ and androgens are essential for growth and maintenance of prostate function. As around 80% of patients with prostate cancer respond to hormonal ablation,[1] the current standard treatment for prostate cancer is surgical castration or medical castration, which involves the administration of luteinizing hormone–releasing hormone (LH–RH) agonists[2] such as leuprorelin or goserelin. In the past decade, combination therapy of an LH–RH agonist with an anti-androgen, referred to as maximum androgen blockade (MAB), has also been used in the medical treatment of advanced prostate cancer.[3] However, unfavorable effects of anti-androgens such as anti-androgen withdrawal syndrome have been observed in some clinical cases.[4] Additionally, recent studies have suggested that residual adrenal androgens remaining after castration could be responsible for the development of castration-resistant prostate cancer.[5]

17,20-Lyase, also known as CYP17A1, is a key enzyme in androgen biosynthesis that has been proposed as an alternative therapeutic target for prostate cancer to address some of these issues.[6–8] To date, several steroidal and nonsteroidal inhibitors of 17,20-lyase[9–43] have been reported, of which a few, for example, YM-116[26] and abiraterone acetate[10] (Fig. 1), have been evaluated in clinical studies. The structural features of these inhibitors include a lipophilic moiety such as a steroidal skeleton or a steroid mimetic fused ring with a heteroaromatic ring, which may bind heme iron in the targeted enzyme.

Our previous studies found that some steroid mimetic structures such as stilbene, biphenyl, naphthalene and benzothiophene rings were suitable for lipophilic moieties of 17,20-lyase inhibitors, and several inhibitors obtained using a steroid A, C-ring mimetic approach have already been published.[44] During the same period, two studies by Hartmann et al. also reported a steroid mimetic approach using a biphenyl ring,[29,30] but our studies were continued independently.[45]

The objective of this study was to identify potent 17,20-lyase inhibitors with selectivity over the cytochrome P450 enzymes, particularly CYP3A4, a major drug-metabolizing enzyme. This is because inhibitors of the P450 family of enzymes have the potential to cause drug–drug interactions or significant systemic side effects due to poor selectivity among the P450 enzymes. Here,

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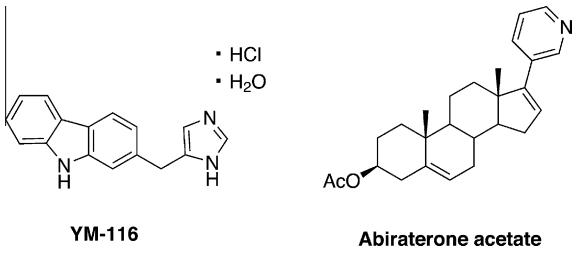


Figure 1. Structures of previously developed 17,20-lyase inhibitors.

we describe the synthesis and biological evaluations of biphenylylmethylimidazole derivatives and related compounds (**I**), focusing on the improvement of selectivity for 17,20 lyase over CYP3A4. In addition, asymmetric synthesis of the selected compound (−)-**17** using a diastereoselective Grignard reaction is described in detail.

2. Results and discussion

2.1. Molecular design

As we have previously reported, naphthylmethylimidazole derivative **1** (Fig. 2) and its related compounds, which together form a new class of 17,20-lyase inhibitor with a hydroxymethylimidazole ring that acts as a ligand for heme iron in the active site of 17,20-lyase, have shown promising in vitro activity for further development.[46] Unfortunately, compound **1** was found to be a potent inhibitor of CYP3A4, with an IC_{50} value of less than 1000 nM (Kaku and co-workers, manuscript in press). Therefore, aiming to improve the selectivity for 17,20-lyase over CYP3A4, scaffold hopping was achieved in this series of inhibitors by using a steroid A, C-ring mimetic approach to develop biphenylylmethylimidazole derivatives and related compounds (**I**) with distinct structural features in the hydroxymethylimidazole ring, as shown in Figure 2.

2.2. Chemistry

Strategies for the synthesis of biphenylylmethylimidazole derivatives and related compounds (**I**) are summarized in Figure 3. Lithiation of biphenyl derivatives **2a**–**3b** followed by addition to ketone **4**[47] gave biphenylylmethylimidazole derivatives and related compounds (**I**) (method A). Otherwise, coupling of lithium species generated from 1,3- or 1,4-dibromobenzene and *n*-butyllithium (*n*-BuLi) with tritylated ketone **9** provided the key intermediates **10a** and **10b**. The biphenylylmethylimidazole derivatives and related compounds (**I**) can be synthesized via a palladium-catalyzed Suzuki coupling reaction of bromide **10a** or **10b** with boronic acid derivatives (**11a**–**d**), followed by deprotection (method B). It was difficult to convert all the arylbromides **20a**–**e**[48] to the corresponding aryl boronic acids; hence, the conversion of **10b** to the suitable boronic acid **19** was investigated as an alternative approach to give biphenylylmethylimidazole derivatives and related compounds (**I**) (method C).

The synthesis of compounds **5**–**8** is shown in Scheme 1. Addition of lithium species generated from *n*-BuLi with commercially available **2a**–**3b** to ketone **4** gave good-to-moderate yields of **5**–**8**. Scheme 2 depicts the preparation of compounds **13**–**18**. Treating 1,3- or 1,4-dibromobenzene with a substoichiometric amount of *n*-BuLi in tetrahydrofuran (THF), followed by addition to ketone **9** gave bromide **10a** or **10b** in high yield. Compounds **13**–**18** were synthesized via a palladium-catalyzed Suzuki coupling reaction of **10a** or **10b** with the corresponding arylboronic acids **11a**–**d**, followed by detritylation using pyridine hydrochloride in methanol (MeOH). As shown in Scheme 3, in all cases in which suitable arylboronic acids were unavailable, **10b** was successfully converted to the boronic acid **19**, which was then subjected to Suzuki coupling reaction without purification to give **21a**–**e**. Deprotection of **21a**–**e** was performed by the same procedure used for **13** to give low-to-moderate yields of compounds **22**–**26**.

The synthesis of analogs of **17**, in which the isopropyl group was replaced by hydrogen or other alkyl groups, is shown in Scheme 4. Coupling of lithium species, generated from 1,4-dibromobenzene and *n*-BuLi, with N-tritylated aldehyde **27**[49] was performed in the same manner as for **10a**, followed by oxidation of **28** with manganese dioxide (MnO_2) to give ketone **29**. The ketone **29** was then subjected to Suzuki coupling reaction to give the acetamide derivative **30**, which was treated with Grignard reagent to give good-to-moderate yields of **31a**–**c**. As deprotection of **31a** or **31c** using pyridine hydrochloride in MeOH gave an unsatisfactory yield (39–59%), an alternative method using Pd/C (10%) under a hydrogen atmosphere was investigated for the deprotection of **31b** and found to give a good yield of the desired compound **33**. Otherwise, deprotection of the acetamide derivative **30** with pyridinium hydrochloride provided **35**, which was then subjected to reduction with sodium borohydride to give a good yield of the alcohol **36**.

2.3. Asymmetric synthesis of compound (−)-17

The synthetic route toward chiral (−)-**17** is shown in Scheme 5. The preparation of α-hydroxyketone **41** began from chiral silylether **38**, which was easily prepared from the known morpholine amide **37**[50] or achiral **40**. Chiral silylether **38** was treated with lithium species generated from 1,4-dibromobenzene and *n*-BuLi to yield **39**, followed by removal of the *tert*-butyldimethylsilyl (TBS) group with tetrabutylammonium fluoride (TBAF) to give α-hydroxyketone **41** in moderate chemical yield with 96% enantiomeric excess (ee) (in two steps). The enantiomeric purity of the obtained chiral compounds was determined by high-performance liquid chromatography (HPLC) on a Chiralpak AD column. Alternatively, osmium-catalyzed asymmetric dihydroxylation of the corresponding enol ethers derived from **40** gave the desired α-hydroxyketone **41** in good chemical yield with excellent ee (98% ee).

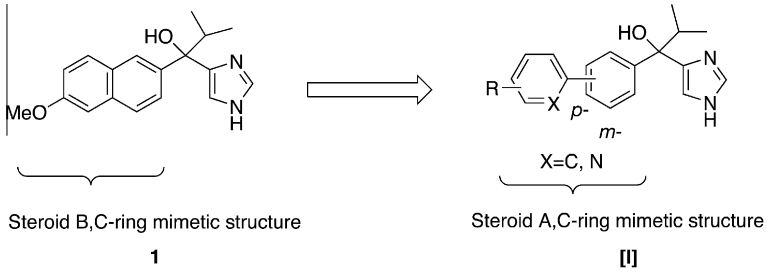


Figure 2. Molecular design of novel 17,20-lyase inhibitors.

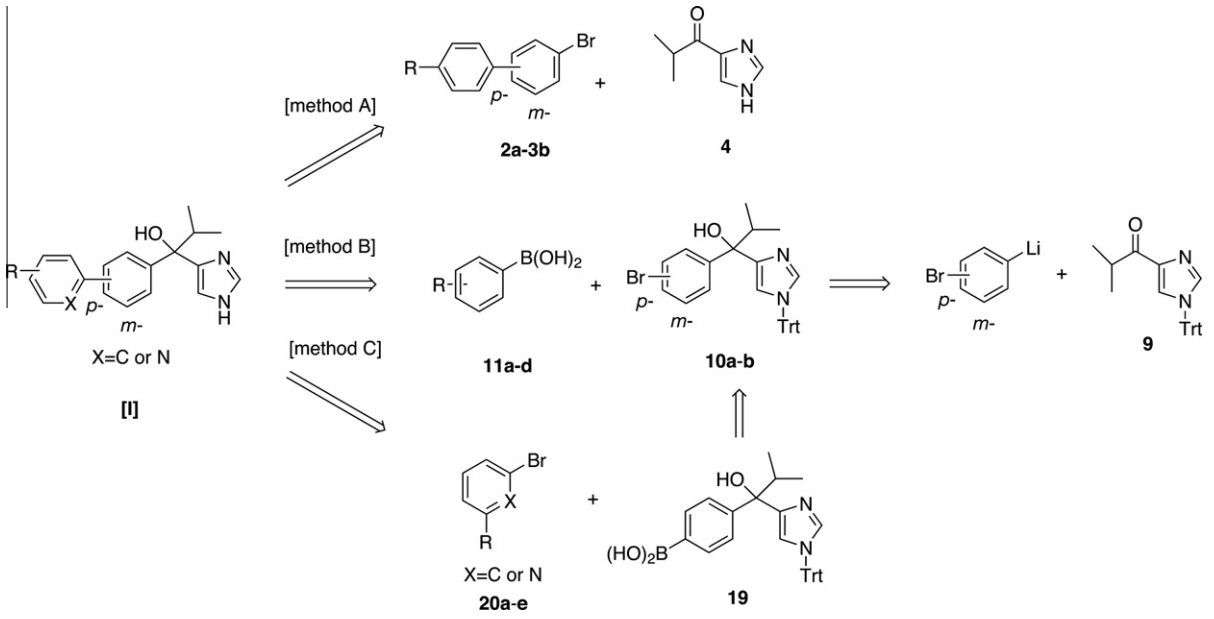
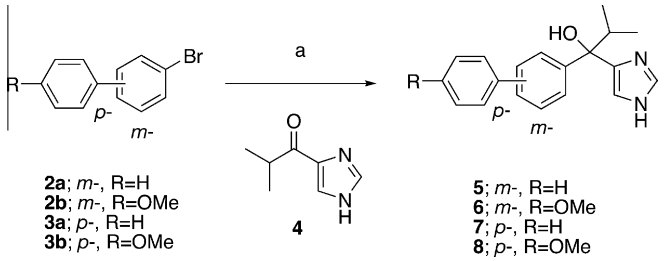
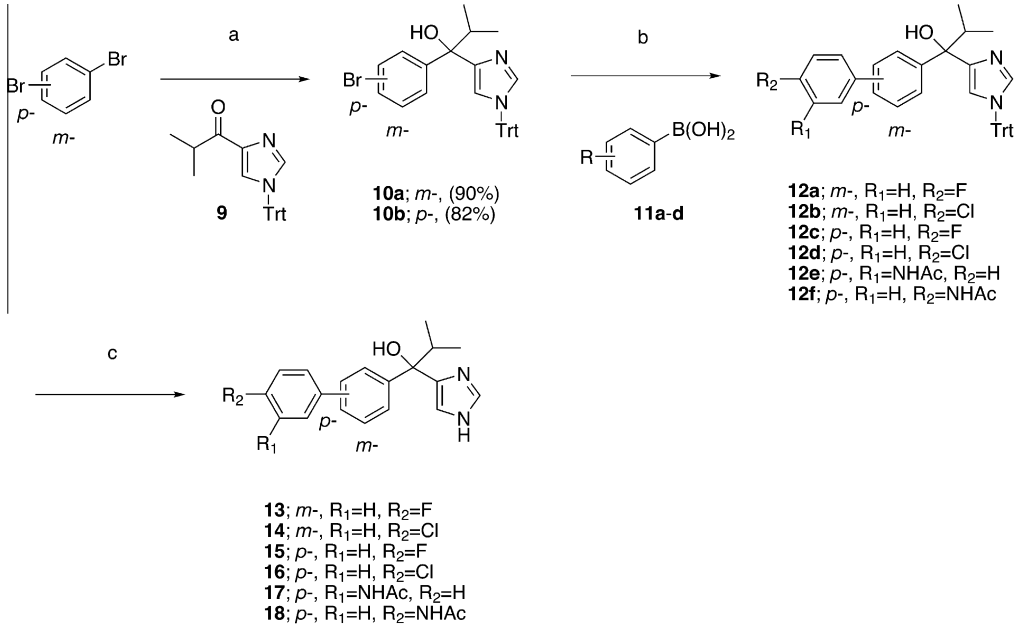


Figure 3. Retrosynthesis of novel biphenyl derivatives and related compounds as 17,20-lyase inhibitors.

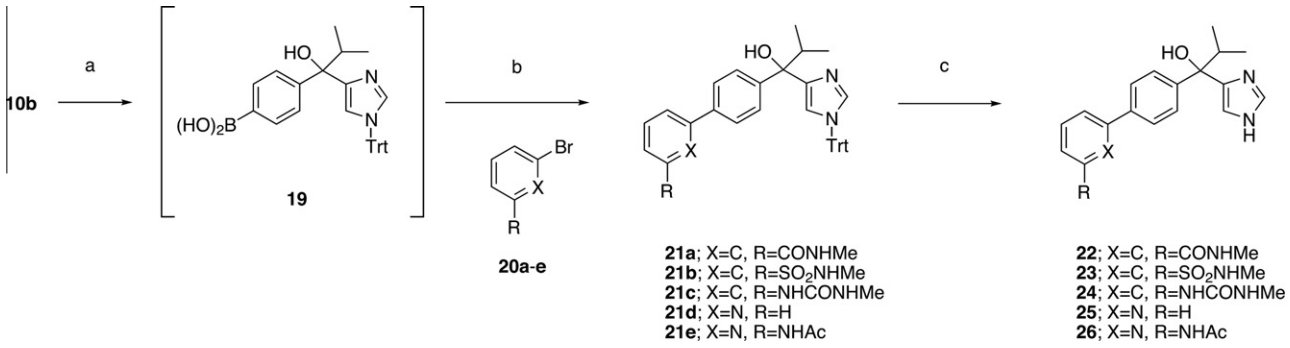


Scheme 1. Reagents and conditions: (a) (1) **2a**–**3b**, *n*-BuLi, THF, −78 °C, then (2) **4**, −78 °C to rt, 39–82%.

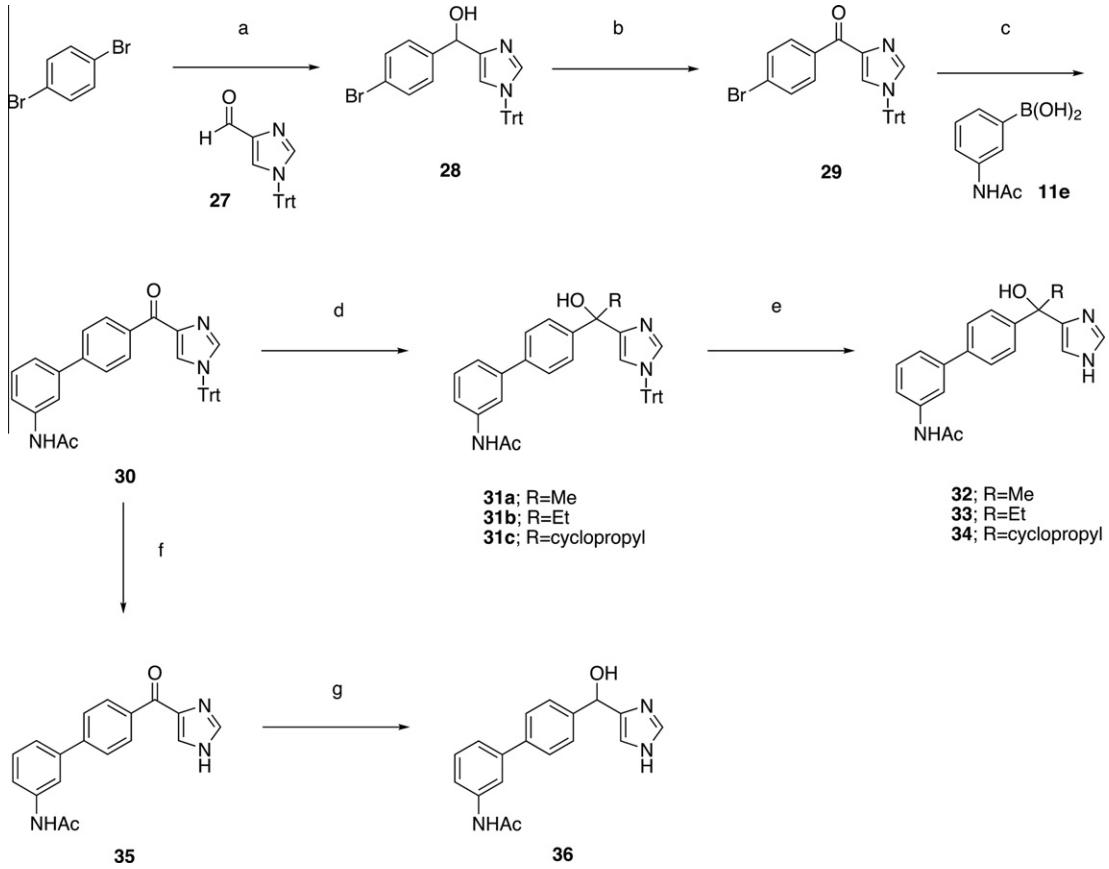
To construct the chiral center of compound (−)-**17**, a chelation-controlled Grignard reaction was used for the synthesis of (2*R*,3*S*)-diol **42**; compound **41** with 96% ee was treated with isopropylmagnesium bromide (*i*-PrMgBr) to give (2*R*,3*S*)-diol **42** together with some by-products, including reduction product **42′**. Isolation of **42** from the other by-products proved troublesome; therefore, optical purity of (2*R*,3*S*)-diol **42** was not determined. Swern oxidation of (2*R*,3*S*)-diol **42** gave **43**, which was then converted to bromide **44** at moderate yield. After protection of **44** with a trimethylsilyl group, imidazole ring closure was performed with formamidine acetate in saturated NH_3 solution in



Scheme 2. Reagents and conditions: (a) (1) *n*-BuLi, Et_2O, −78 °C, then (2) **9**, −78 to −50 °C, 82–90%; (b) substituted phenylboronic acid **11a**–**d**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, reflux, 32–96%; (c) pyridine hydrochloride, MeOH, 60 °C, 21–79%.



Scheme 3. Reagents and conditions: (a) (1) *n*-BuLi; (2) trimethoxyborane ($B(OMe)_3$), −78 °C to rt; (3) 1 N HCl, compound **19** was not isolated; (b) substituted arylbromide **20a–e**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, reflux, 23–72%; (c) pyridine hydrochloride, MeOH, 60 °C, 26–61%.



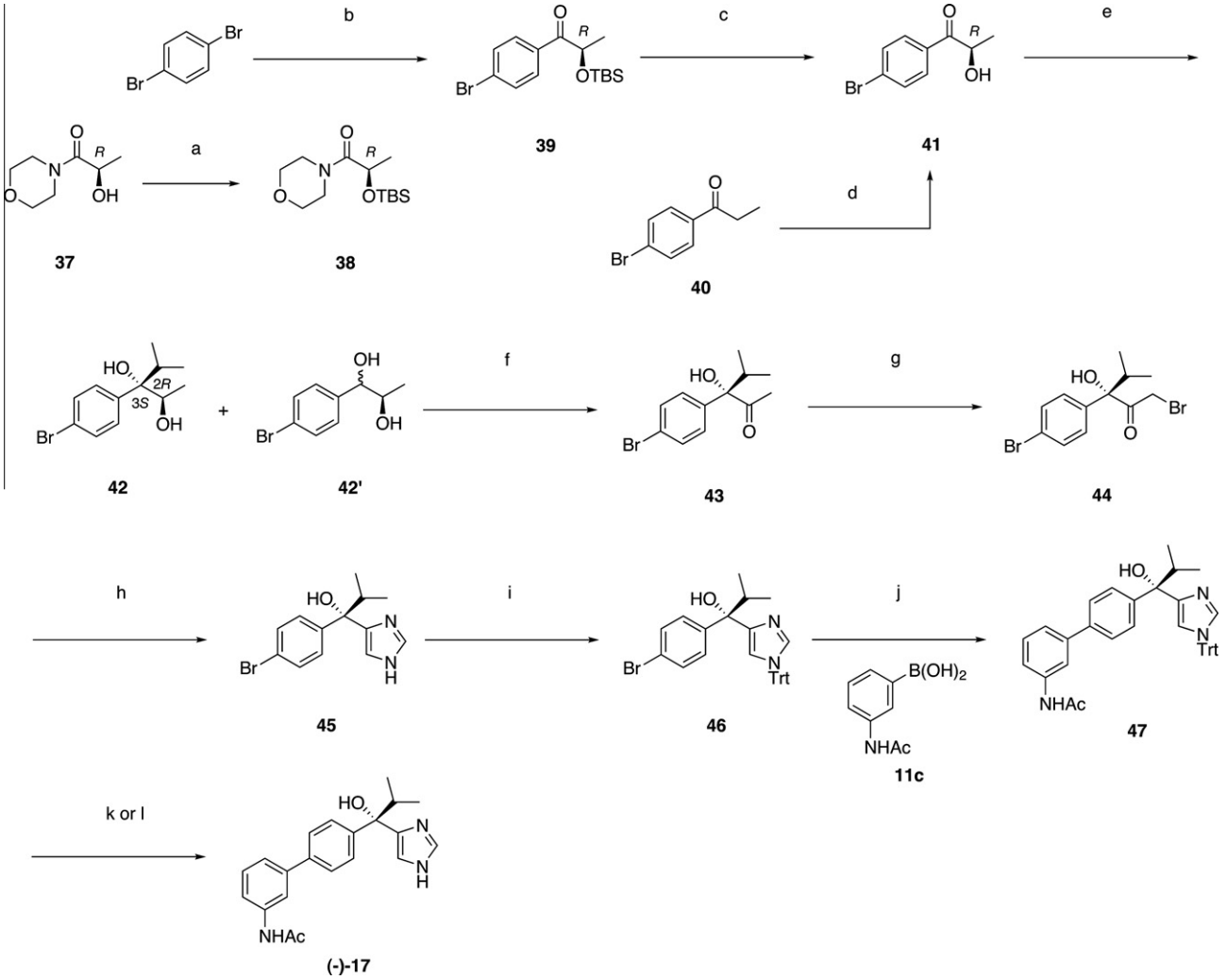
Scheme 4. Reagents and conditions: (a) (1) *n*-BuLi, THF, −78 to −50 °C, then (2) **27**, 56%; (b) MnO_2, CH_2Cl_2, rt, 78%; (c) **11c**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, EtOH, reflux, 76%; (d) RMgBr, THF, 0 °C, 61% to quant.; (e) For **31a**, **31c**, pyridine hydrochloride, MeOH, 60 °C, 39–59%, for **31b**, H_2, 10%Pd/C, 1 N HCl, EtOH, rt, 84%; (f) pyridine hydrochloride, MeOH, 60 °C, 88%; (g) $NaBH_4$, MeOH, 0 °C to rt, 76%.

MeOH and THF to give **45** at good chemical yield with 90% ee. Unfortunately, the conversion of α-hydroxyketone **41** into **45** proceeded with decreased optical purity, whereas recrystallization of the N-tritylated imidazole **46** with 90% ee led to improved optical purity of **46**, up to 98.8% ee. Compound **46** was then subjected to Suzuki coupling reaction to give a good yield of the acetamide derivative **47** with 99.1% ee. Deprotection of compound **47** using 90% formic acid resulted in decreased enantiomeric excess; however, an alternative approach using catalytic hydrogenation of **47** was performed to give (−)-**17** without any loss of optical purity. Finally, the absolute configuration of compound (−)-**17** was confirmed to be *S* by X-ray crystallographic analysis of the precursor **46** (Fig. 4).

2.4. Structure–activity relationships (SARs) for 17,20-lyase and CYP3A4 inhibitors

All compounds synthesized as racemates were tested in vitro for inhibition of rat 17,20-lyase, recombinant human 17,20-lyase and CYP3A4. Selected compounds were resolved by HPLC and the resulting optical isomers were tested using the same in vitro assay.

Results of the initial SAR study of *m*- and *p*-biphenyl compounds **5**–**8** and **13**–**16** are shown in Table 1. The unsubstituted compounds **5** and **7** demonstrated promising potency against 17,20-lyase, with IC_{50} values of 15 and 33 nM, respectively, for rat enzymes, and 18 and 33 nM, respectively, for human enzymes. However, these compounds also showed potent inhibitory activity



Scheme 5. Reagents and conditions: (a) TBSCl, imidazole, DMF, 0 °C to rt, 98%; (b) (1) *n*-BuLi, THF, −78 °C, then (2) **38**, 92%; (c) TBAF, THF, 0 °C, 82% (96%ee); (d) (1) NaHMDS, TBSCl, THF, −70 °C to rt, then; (2) AD-mix-β, $CH_3SO_2NH_2$, *tert*-BuOH, H_2O, 5 °C to rt, 87% (98%ee); (e) *i*-PrMgBr, THF, 0 °C, 59%; (f) oxalylchloride $(COCl)_2$, DMSO, triethylamine (Et_3N), CH_2Cl_2, −70 °C to rt, 84%; (g) pyridinium bromide perbromide, THF, rt, 65%; (h) (1) TMSOTf, 2,6-lutidine, THF, 0 °C to rt, then (2) formamidine acetate, satd NH_3, MeOH, THF, rt, 74% (90% ee); (i) (1) trityl chloride, Et_3N, DMF, 0 °C to rt; (2) recrystallization from hexane–AcOEt, 63% (98.8% ee); (j) 3-acetamidophenylboronic acid **11c**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, EtOH, reflux, 87% (99.1% ee); (k) 90% formic acid, THF, reflux, 83% (91.7% ee); (l) H_2 (4 atm), 10% Pd/C, EtOH, 70 °C, 61% (99.0% ee).

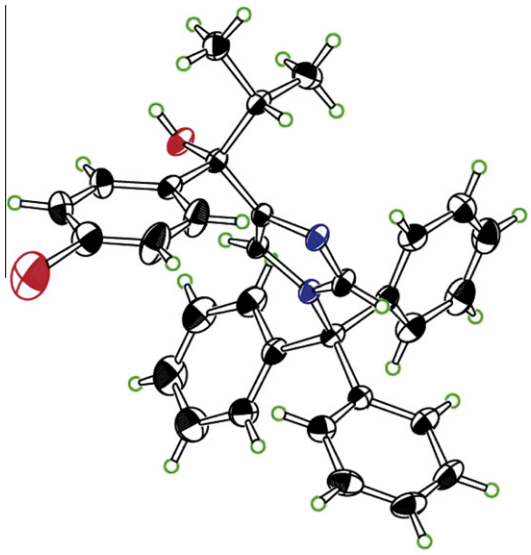


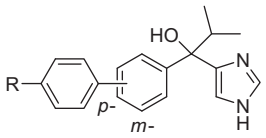
Figure 4. ORTEP drawing of **46**.

against CYP3A4. Regarding the *m*- biphenyl derivatives, all 4′-substituted compounds (**6**, **13** and **14**) showed potent inhibition of rat 17,20-lyase, but insufficient selectivity between 17,20-lyase and CYP3A4 inhibition. Furthermore, the introduction of a large substituent, such as a methoxy group, on to the phenyl ring led to decreased activity of human 17,20-lyase.

On the other hand, *p*-biphenyl derivatives, other than **8**, exhibited potent inhibitory activities against both rat and human 17,20-lyase and the introduction of an appropriate substituent into the benzene ring was tolerated. Additionally, as a general trend, *p*-biphenyl derivatives showed improved selectivity of 17,20-lyase over CYP3A4 inhibition compared with the corresponding *m*-biphenyl derivatives. These results encouraged us to focus on further modification of the *p*-biphenyl derivatives.

To increase the inhibitory activities of *p*-biphenyl derivatives, a homology model of human 17,20-lyase was developed using the X-ray crystallographic structure of the mammalian CYP2C5 enzyme. Among several inhibitors, we selected (*S*)-**15** as one of the representative compound that was used in the docking study in the homology model of human 17,20-lyase. This was because the racemate **15** showed potent inhibition against human 17,20-lyase with an IC_{50} value of 27 nM and both of the enantiomers of **15** are

Table 1
Effects of meta or para substitution and R substituents on inhibition of rat and human 17,20-lyase and human CYP3A4 enzymes



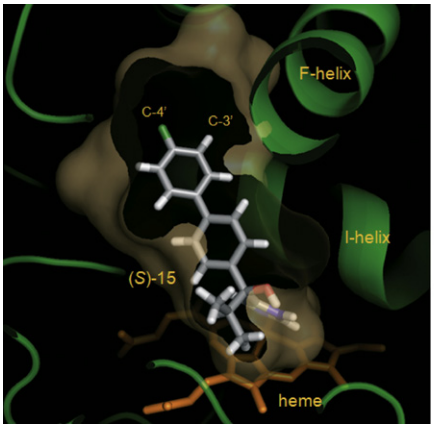
Compound	Meta or para substitution	R	Enzyme inhibition IC_{50} (nM)			Ratio[a]
			17,20-Lyase		CYP3A4	
			Rat	Human		
5	*m*-	H	15	18	1200	67
6	*m*-	OMe	10	130	2000	15
13	*m*-	F	8.3	19	2100	111
14	*m*-	Cl	19	49	2400	49
7	*p*-	H	33	33	3700	112
8	*p*-	OMe	120	54	4900	91
15	*p*-	F	28	27	5300	196
16	*p*-	Cl	29	28	7600	271

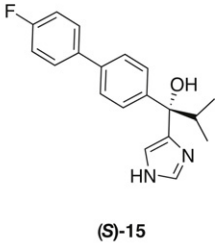
[a] Ratio is given by IC_{50} value of CYP3A4 inhibition/IC_{50} value of human 17,20-lyase inhibition.

expected to have inhibitory activity against human 17,20-lyase, based on the previously reported results on compound **1** and its enantiomers.[46] The docking experiment was designed on the assumption that (*S*)-**15** should be coordinated to the heme iron via the nitrogen of the imidazole ring, and the proposed binding mode of (*S*)-**15** is shown in Figure 5. Results of docking studies indicated that the biphenyl ring of (*S*)-**15** occupied a hydrophobic region in the active site of the enzyme and there was still enough space between the I-helix and the F-helix to introduce an appropriate substituent at the C-3′ or C-4′ position of the benzene ring of the inhibitor.

Additionally, it was postulated that reducing the lipophilicity of inhibitors would improve the selectivity for 17,20-lyase over CYP3A4. That is because, in general, the CYP family of enzymes are known to favor lipophilic molecules as substrates or inhibitors.

Based on the observations, the introduction of a polar substituent at the C-3′ or C-4′ position on the benzene ring or replacement of the benzene ring with pyridine ring in this series of inhibitors seems to be a promising strategy to enhance inhibitory activity against 17,20-lyase and improve the selectivity for 17,20-lyase over CYP3A4. Therefore, the effects of polar substituents on the benzene ring and replacement of the benzene ring with pyridine ring in *p*-biphenyl derivatives were investigated (Table 2). As a result, compound **17** with an acetamide group at C-3′ position, showed potent activity against both rat and human 17,20-lyase and the selectivity for inhibition of 17,20 lyase over CYP3A4 was

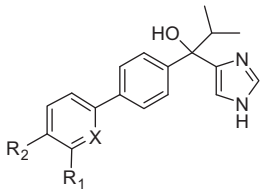




(S)-15

Figure 5. Docking analysis of (*S*)-**15** in the homology model of 17,20-lyase.

Table 2
Effects of R_1 and R_2 substituents and X on inhibition of rat and human 17,20-lyase and human CYP3A4 enzymes

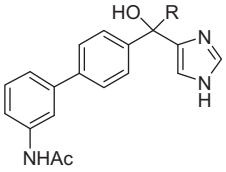


Compound	X	R_1	R_2	Enzyme inhibition IC_{50} (nM)		
				17,20-Lyase		CYP3A4
				Rat	Human	
17	C	NHAc	H	17	24	7100
18	C	H	NHAc	24	120	1000
22	C	CONHMe	H	49	44	8100
23	C	SO_2NHMe	H	71	160	3300
24	C	NHCONHMe	H	24	21	5500
25	N	H	H	210	150	5200
26	N	NHAc	H	53	36	>10000

similar to that observed with **16**. On the other hand, **18** with an acetamide group at the C-4′ position, exhibited less potent activity against human 17,20-lyase and decreased selectivity for 17,20-lyase versus CYP3A4. Among the various substituent groups at the C3′-position, the acetamide group provides optimal inhibitory activity against 17,20-lyase and selectivity for the inhibition of 17,20-lyase over CYP3A4. Furthermore, **25** exhibited less potent activity against human 17,20-lyase compared with **7**. In contrast, **26** bearing an acetamide group on the pyridine ring showed potent inhibition of human 17,20-lyase and reduced CYP3A4 inhibition. In summary, the introduction of an appropriate polar substituent such as an acetamide group on the benzene or pyridine rings of the inhibitor was tolerated, as predicted by results of the docking study of (*S*)-**15**.

The effects of substituents at the linker position between the biphenyl and imidazole rings are summarized in Table 3. When the isopropyl (*i*-Pr) group of **17** was replaced with other alkyl groups or hydrogen at the linker position, small alkyl substituents such as methyl, ethyl, and cyclopropyl (*cyclo*-Pr) groups were shown to maintain inhibitory activity against human 17,20-lyase. On the other hand, replacement of the *i*-Pr group of **17** with hydrogen decreased the inhibitory activity against human 17,20-lyase.

Table 3
Effects of R substituents on inhibition of rat and human 17,20-lyase and human CYP3A4 enzymes



Compound	R	Enzyme inhibition IC_{50} (nM)		
		17,20-Lyase		CYP3A4
		Rat	Human	
17	*i*-Pr	17	24	7100
32	Me	62	38	>10,000
33	Et	25	40	>10,000
34	*cyclo*-Pr	81	45	5500
36	H	320	77	>10,000

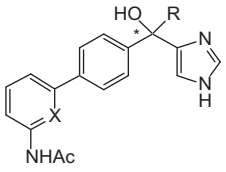
These results suggest that the introduction of a small alkyl group into the linker position was necessary to increase the inhibitory activity against human 17,20-lyase, and that the *i*-Pr group gives optimal potency.

Finally, we selected compounds **17**, **26**, and **33** as candidates for chiral resolution by HPLC, to evaluate whether the interaction with enzymes such as 17,20-lyase and CYP3A4 by these inhibitors is stereospecific. Table 4 shows the biological activities of the obtained optical isomers. Interestingly, each enantiomer had different inhibitory activity against 17,20-lyase and all of the (−)-enantiomers had potent activity against both rat and human 17,20 lyase, with greater than 300-fold selectivity for the inhibition of 17,20-lyase over CYP3A4. These findings suggest that the chiral configuration at the linker position between the biphenyl and imidazole rings plays an important role in inhibition of 17,20-lyase and the selectivity of 17,20-lyase over CYP3A4 inhibition.

2.5. In vivo efficacy

Among synthesized inhibitors, the active enantiomer (−)-**17**, which showed potent inhibitory activity against human 17,20-lyase in vitro, was selected as a representative for the evaluation of in vivo activity. In a monkey model, both testicular androgen testosterone and adrenal androgen dehydroepiandrosterone (DHEA) concentrations were investigated. As shown in Table 5, single oral doses of (−)-**17** 3 mg/kg significantly decreased both serum testosterone and DHEA concentrations in male cynomolgus monkeys. These biological results indicate that (−)-**17** might be useful for the treatment of both hormone-dependent and castration-resistant prostate cancer.

Table 4
Inhibitory effects of (±)-**17**, (±)-**26** and (±)-**33** enantiomers on rat and human 17,20-lyase and human CYP3A4 enzymes



Compound	X	R	Enzyme inhibition IC_{50} (nM)		
			17,20-Lyase		CYP3A4
			Rat	Human	
(−)-**17**	C	*i*-Pr	14	26	>10,000
(+)-**17**	C	*i*-Pr	770	340	6700
(−)-**26**	N	*i*-Pr	33	26	>10,000
(+)-**26**	N	*i*-Pr	>1000	92	>10,000
(−)-**33**	C	Et	19	22	>10,000
(+)-**33**	C	Et	450	240	>10,000

Table 5
In vivo effects of S-(−)-**17** on serum testosterone and DHEA levels after single oral dosing (3 mg/kg) in monkeys

Compound	% of average 0 h values, mean ± SD			
	Serum testosterone		Serum DHEA	
	2 h	5 h	2 h	5 h
Vehicle	110 ± 29	98 ± 33	116 ± 95	148 ± 53
S-(−)-**17** (3 mg/kg)	52 ± 8[a]	23 ± 5	23 ± 9	13 ± 6[b]

n = 3.
[a] P <0.05 versus vehicle (t-test).
[b] P <0.05 versus vehicle (Welch test).

3. Conclusion

We have reported the synthesis and SAR of a new class of 17,20-lyase inhibitors. On the basis of molecular modeling, compounds **17**, **26** and **33**, bearing an acetamide group on the benzene or pyridine rings, were synthesized and their biological activities were evaluated. Optical resolution of these inhibitors by HPLC gave the biologically active enantiomers (−)-**17**, (−)-**26** and (−)-**33**, respectively, which showed potent activities against both rat and human 17,20-lyase, with excellent selectivity (>300-fold) for the inhibition of 17,20-lyase over CYP3A4. Among these enantiomers, (−)-**17** significantly reduced both serum testosterone and DHEA concentrations in a monkey model. From the data presented here, we concluded that the *p*-biphenyl derivatives and related compounds, as well as the naphthalene derivative **1**, showed promising profiles for further development.[46] Further investigation of this series should provide further insights to the selectivity for 17,20-lyase over the cytochrome P450 enzymes.

4. Experimental

Melting points were determined using a BUCHI Melting Point B-545 apparatus and are uncorrected. Infrared (IR) spectra were recorded using a SHIMADZU FT-IR-8200PC spectrometer. ^{1}H NMR spectra were recorded using a Varian Gemini-200 or Varian Mercury-300 spectrometer; chemical shifts are given in ppm with tetramethylsilane as an internal standard, and coupling constants (J) are measured in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. Reactions were followed by thin-layer chromatography (TLC) on Silica Gel 60 F_{254} precoated TLC plates (Merck, Darmstadt, Germany). Column chromatography was performed using Silica Gel 60 (Merck, Darmstadt, Germany). Compounds **2a–b**, **3a–b**, **11a–d**, **20a–b**, **20d–e**, **40** were commercially available, compounds **4**,[47] **20c**,[48] **27**,[49] and **37**[50] were prepared in the same manner as described previously, and compound **9** was easily prepared from compound **4** and trityl chloride in the usual manner.

4.1. General procedure for method A and 1-[1,1′-biphenyl]-3-yl-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (5)

n-BuLi in hexane (1.6 M; 6.4 mL, 10.2 mmol) was added to a cooled (−78 °C) solution of **2a** (2.11 g, 9.05 mmol) in THF (30 mL) and the mixture was stirred at −78 °C for 1 h. A solution of **4** (400 mg, 2.89 mmol) in THF (10 mL) was added to the mixture and the solution was allowed to warm to rt. The reaction was quenched with aqueous NH_4Cl solution and the aqueous phase was extracted with AcOEt. The extract was dried over $MgSO_4$ and

concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 20:1) and recrystallized from AcOEt–hexane to give **5** (450 mg, 1.54 mmol, 53%) as a colorless powder. Melting point (mp) 180–183 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.83 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 2.55–2.73 (1H, m), 6.97 (1H, d, J = 1.0 Hz), 7.28–7.50 (7H, m), 7.54–7.62 (2H, m), 7.72–7.77 (1H, m). IR (KBr): 3200, 1005, 799 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.84; H, 6.86; N, 9.36. Compounds **6–8** were prepared in the same manner as described for the preparation of **5**.

4.2. 1-(1*H*-Imidazol-4-yl)-1-(4′-methoxy-[1,1′-biphenyl]-3-yl)-2-methyl-1-propanol (6)

Yield 74%. Mp 74–77 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.82 (3H, d, J = 6.9 Hz), 0.98 (3H, d, J = 6.9 Hz), 2.50–2.74 (1H, m), 3.83 (3H, s), 6.89–6.99 (3H, m), 7.26–7.55 (6H, m), 7.71–7.76 (1H, m). IR (KBr): 2969, 1516, 1480, 1248, 1181 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.45; H, 7.17; N, 8.40.

4.3. 1-[1,1′-Biphenyl]-4-yl-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (7)

Yield 83%. Mp 182–183 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.83 (3H, d, J = 6.8 Hz), 0.99 (3H, d, J = 6.8 Hz), 2.57–2.74 (1H, m), 6.98 (1H, d, J = 1.2 Hz), 7.30–7.47 (3H, m), 7.50–7.65 (7H, m). IR (KBr): 3142, 2965, 1487, 826, 762 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O{\cdot}0.1H_2O$: C, 77.57; H, 6.92; N, 9.52. Found: C, 77.57; H, 6.95; N, 9.61.

4.4. 1-(1*H*-Imidazol-4-yl)-1-(4′-methoxy[1,1′-biphenyl]-4-yl)-2-methyl-1-propanol (8)

Yield 39%. Mp 200–201 °C (AcOEt). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.83 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 2.52–2.76 (1H, m), 3.85 (3H, s), 6.92–7.02 (3H, m), 7.38–7.62 (7H, m). IR (KBr): 3218, 1497, 1252, 1038, 1007, 816 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.64; H, 6.89; N, 8.53.

4.5. General procedure for method B and 1-(3-bromophenyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (10a)

n-BuLi (1.6 M; 50 mL, 80 mmol) was added to a cooled (−78 °C) solution of 1,3-dibromobenzene (29.02 g, 123 mmol) in diethylether (250 mL) and the mixture was stirred at −78 °C for 30 min. A solution of **9** (20.0 g, 53 mmol) in THF (100 mL) was added and the solution was allowed to warm to −50 °C. After stirring at −50 °C for a further 30 min, the reaction was quenched with aq NH_4Cl solution. The mixture was extracted with AcOEt and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from AcOEt–hexane to give **10a** (25.30 g, 47 mmol, 90%) as a colorless powder. Mp 164–165 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.72 (3H, d, J = 6.8 Hz), 0.90 (3H, d, J = 6.8 Hz), 2.22–2.44 (1H, m), 3.65 (1H, s), 6.73 (1H, d, J = 1.6 Hz), 7.06–7.19 (7H, m), 7.26–7.39 (11H, m), 7.46 (1H, dt, J = 7.8, 1.3 Hz), 7.59 (1H, t, J = 1.8 Hz). IR (KBr): 1493, 1472, 1445, 702 cm^{-1}. Anal. Calcd for $C_{32}H_{29}N_2OBr$: C, 71.51; H, 5.44; N, 5.21. Found: C, 71.43; H, 5.60; N, 5.38. Compound **10b** was prepared in the same manner as described for the preparation of **10a**.

4.6. 1-(4-Bromophenyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (10b)

Yield 82%. Mp 145–146 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.71 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), 2.30–2.44 (1H, m), 3.50 (1H, s), 6.72 (1H, d, J = 1.2 Hz), 7.09–7.16 (6H, m), 7.30–7.38 (14H, m). IR (KBr): 1489, 1445, 1159, 1009, 909, 812, 747, 735, 702, 660 cm^{-1}. Anal. Calcd for $C_{32}H_{29}N_2OBr$: C, 71.51; H, 5.44; N, 5.21. Found: C, 71.54; H, 5.48; N, 5.20.

4.7. 1-(4′-Fluoro-[1,1′-biphenyl]-3-yl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (12a)

Under N_2 atmosphere, a mixture of **10a** (1.01 g, 1.88 mmol), 4-fluorophenylboronic acid (413 mg, 2.95 mmol) and $Pd(PPh_3)_4$ (0) (190 mg, 0.16 mmol) in dimethyloxyethane (DME)/2 M Na_2CO_3 (20 mL/8 mL) was refluxed for 18 h. The resulting mixture was extracted with AcOEt and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 4:1) and recrystallized from AcOEt–hexane to give **12a** (705 mg, 1.28 mmol, 68%) as a pale yellow powder. Mp 141–143 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.75 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.8 Hz), 2.35–2.52 (1H, m), 3.70 (1H, s), 6.78 (1H, d, J = 1.0 Hz), 7.04–7.18 (8H, m), 7.22–7.38 (12H, m), 7.44–7.55 (3H, m), 7.63 (1H, s). IR (KBr): 1512, 1480, 1233, 1159 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2OF$: C, 82.58; H, 6.02; N, 5.07. Found: C, 82.43; H, 5.83; N, 4.91. Compounds **12b–f** were prepared in the same manner as described for the preparation of **12a**.

4.8. 1-(4′-Chloro[1,1′-biphenyl]-3-yl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (12b)

Yield 70%. Mp 157 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.75 (3H, d, J = 6.7 Hz), 0.94 (3H, d, J = 6.7 Hz), 2.35–2.55 (1H, m), 3.70 (1H, s), 6.78 (1H, d, J = 1.4 Hz), 7.05–7.60 (23H, m), 7.65 (1H, s). IR (KBr): 1493, 1476, 1445, 909 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2OCl{\cdot}H_2O$: C, 79.94; H, 5.86; N, 4.91. Found: C, 79.85; H, 5.85; N, 4.80.

4.9. 1-(4′-Fluoro-[1,1′-biphenyl]-4-yl)-1-(1-trityl-1*H*-imidazol-4-yl)-2-methyl-1-propanol (12c)

Yield 80%. Mp 213–214 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.77 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 2.42–2.49 (1H, m), 3.53 (1H, s), 6.78 (1H, s), 7.06–7.15 (7H, m), 7.337.57 (17H, m). IR (KBr): 1493, 1445, 1223, 1159, 818, 748, 733, 702 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2OF$: C, 81.52; H, 6.08; N, 5.00. Found: C, 81.58; H, 6.08; N, 4.92.

4.10. 1-(4′-Chloro-[1,1′-biphenyl]-4-yl)-1-(1-trityl-1*H*-imidazol-4-yl)-2-methyl-1-propanol (12d)

Yield 85%. Mp 211–212 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.76 (3H, d, J = 7.0 Hz), 0.92 (3H, d, J = 7.0 Hz), 2.42–2.49 (1H, m), 3.53 (1H, s), 6.78 (1H, s), 7.13–7.15 (6H, m), 7.32–7.59 (18H, m). IR (KBr): 1485, 1445, 1094, 1005, 909, 812, 747, 733, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2OCl$: C, 79.69; H, 5.88; N, 4.89. Found: C, 79.48; H, 6.14; N, 4.72.

4.11. *N*-{4′-[1-Hydroxy-2-methyl1-(1-trityl-1*H*-imidazol-4-yl)-propyl][1,1′-biphenyl]-3-yl}acetamide (12e)

Yield 96%. ^{1}H NMR ($CDCl_3$) δ: 0.76 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 2.20 (3H, s), 2.38–2.56 (1H, m), 3.55 (1H, s), 6.77 (1H, d, J = 1.2 Hz), 7.06–7.20 (6H, m), 7.24–7.76 (18H, m). IR (KBr): 3063, 1674, 1557, 1483, 1445 cm^{-1}. FAB-MS m/z: 592.2935 (calcd for $C_{40}H_{38}N_3O_2$: 592.2964).

4.12. *N*-{4′-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl][1,1′-biphenyl]-4-yl}acetamide (12f)

Yield 32%. Mp 244–248 °C (AcOEt). ^{1}H NMR ($CDCl_3$) δ: 0.77 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6 Hz), 2.20 (3H, s), 2.30–2.56 (1H, m), 3.53 (1H, s), 6.77 (1H, d, J = 1.4 Hz), 7.08–7.14 (6H, m), 7.27–7.38 (10H, m), 7.43–7.58 (8H, m). IR (KBr): 2971, 1671, 1535, 1493 cm^{-1}. Anal. Calcd for $C_{40}H_{37}N_3O_2$: C, 81.19; H, 6.30; N, 7.10. Found: C, 81.01; H, 6.37; N, 6.99.

4.13. 1-(4′-Fluoro[1,1′-biphenyl]-3-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (13)

A mixture of **12a** (620 mg, 1.12 mmol) and pyridine hydrochloride (270 mg, 2.34 mmol) in MeOH (20 mL) was stirred at 60 °C for 4 h. The mixture was made alkaline with aq $NaHCO_3$ solution and concentrated under reduced pressure. The resulting mixture was extracted with AcOEt and the combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 40:1) and recrystallized from AcOEt–hexane to give **13** (274 mg, 0.88 mmol, 79%) as a colorless powder. Mp 154–156 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.82 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz), 2.40–2.80 (1H, m), 6.70–7.16 (3H, m), 7.30–7.59 (6H, m), 7.72 (1H, s). IR (KBr): 3187, 1514, 1236, 1005, 795 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_2OF$: C, 73.53; H, 6.17; N, 9.03. Found: C, 73.48; H, 5.94; N, 9.02. Compounds **14**–**18** were prepared in the same manner as described for the preparation of **13**.

4.14. 1-(4′-Chloro[1,1′-biphenyl]-3-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (14)

Yield 76%. Mp 169 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.82 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz), 2.50–2.78 (1H, m), 6.99 (1H, d, J = 1.0 Hz), 7.33–7.44 (4H, m), 7.45–7.56 (4H, m), 7.78 (1H, s). IR (KBr): 2969, 1476, 1092, 1013 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_2OCl$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.98; H, 5.98; N, 8.50.

4.15. 1-(4′-Fluoro[1,1′-biphenyl]-4-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (15)

Yield 69%. Mp 198–199 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.85 (3H, d, J = 7.0 Hz), 1.00 (3H, d, J = 7.0 Hz), 2.60–2.74 (1H, m), 3.42 (1H, br s), 7.02–7.16 (3H, m), 7.48–7.66 (7H, m), 9.16 (1H, br s). IR (KBr): 3241, 1493, 1397, 1242, 1009, 814, 781, 762, 623, 511 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_2OF$: C, 75.53; H, 6.17; N, 9.03. Found: C, 73.43; H, 6.09; N, 9.03.

4.16. 1-(4′-Chloro[1,1′-biphenyl]-4-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (16)

Yield 76%. Mp 197–198 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, d, J = 7.0 Hz), 0.98 (3H, d, J = 7.0 Hz), 2.58–2.75 (1H, m), 3.38 (1H, br s), 7.00 (1H, s), 7.37 (2H, d, J = 8.4 Hz), 7.48–7.64 (7H, m), 9.24 (1H, br s). IR (KBr): 3200, 1485, 1364, 1190, 1094, 1028, 1005, 808, 781 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_2OCl$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.80; H, 5.85; N, 8.65.

4.17. *N*-{4′-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl][1,1′-biphenyl]-3-yl}acetamide (17)

Yield 48%. ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.82 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz), 2.17 (3H, s), 2.51–2.74 (1H, m), 6.96 (1H, d, J = 1.0 Hz), 7.25–7.39 (3H, m), 7.42–7.56 (5H, m), 7.68 (1H, s). IR (KBr): 3210, 2971, 1672, 1557, 1483 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.75\ H_2O$: C, 69.50; H, 6.80; N, 11.58. Found: C, 69.12; H, 6.91; N, 11.45. FAB-MS m/z: 350.1825 (calcd for $C_{21}H_{24}N_3O_2$: 350.1869).

4.18. *N*-{4′-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl][1,1′-biphenyl]-4-yl}acetamide (18)

Yield 21%. Mp 199–201 °C (AcOEt). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.82 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz), 2.17 (3H, s), 2.49–2.70 (1H, m), 6.96 (1H, d, J = 0.8 Hz), 7.44–7.60 (9H, m). IR (KBr): 3173, 1667, 1534, 1499 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.1$AcOEt: C, 71.75; H, 6.70; N, 11.73. Found: C, 71.70; H, 6.65; N, 11.90.

4.19. General procedure for method C and 4-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl] phenylboronic acid (19)

n-BuLi (1.6 M; 14 mL, 23 mmol) was added to a cooled (−78 °C) solution of 1,4-dibromobenzene (5.10 g, 22 mmol) in diethylether (30 mL) and THF (40 mL) and the mixture was stirred at −78 °C for 15 min. A solution of **10b** (6.50 g, 17 mmol) in THF (30 mL) was added dropwise to the mixture. After stirring at −78 °C for 15 min, *n*-BuLi (1.6 M; 20 mL, 33 mmol) was added dropwise. The resulting mixture was further stirred at −78 °C for 15 min and trimethoxyborane (15 mL, 134 mmol) was added. The mixture was allowed to warm to rt and further stirred for 1 h. HCl (1 N) was added to the reaction mixture and the solution was extracted with AcOEt. The combined organic layers were concentrated under reduced pressure. The residue was redissolved in AcOEt and the solution was washed with 1 N NaOH and brine, before being dried over $MgSO_4$. Concentration of the solvent under reduced pressure gave crude **19** (4.00 g) as a colorless amorphous solid. This compound was used for the next step without further purification.

4.20. 4′-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-methyl[1,1′-biphenyl]-3-carboxamide (21a)

Under N_2 atmosphere a mixture of crude **19** (3.44 g), 3-bromophenyl-*N*-methylcarboxamide **20a** (1.10 g, 5.14 mmol) and $Pd(PPh_3)_4$ (0) (210 mg, 0.18 mmol) in DME (20 mL) and 2 M Na_2CO_3 solution (20 mL) was refluxed for 16 h. The resulting mixture was extracted with AcOEt and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 1:2) to give **21a** (1.00 g, 1.69 mmol, 33%) as a pale yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ: 0.76 (3H, d, J = 6.7 Hz), 0.93 (3H, d, J = 6.7 Hz), 2.30–2.54 (1H, m), 3.02 (3H, d, J = 4.8 Hz), 3.58 (1H, s), 6.33 (1H, br s), 6.78 (1H, d, J = 1.4 Hz), 7.04–7.20 (6H, m), 7.22–7.38 (9H, m), 7.39–7.76 (8H, m), 7.98 (1H, t, J = 1.4 Hz). IR (KBr): 3295, 2969, 1644, 1549, 1121 cm^{-1}. FAB-MS m/z: 592.2999 (calcd for $C_{40}H_{38}N_3O_2$:592.2964). Compounds **21b**–**e** were prepared in the same manner as described for the preparation of **21a**.

4.21. 4′-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-*N*-methyl[1,1′-biphenyl]-3-sulfonamide (21b)

Yield 24%. Mp 148–149 °C (AcOEt). ^{1}H NMR ($CDCl_3$) δ: 0.76 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.8 Hz), 2.36–2.58 (1H, m), 2.69 (3H, d, J = 5.6 Hz), 3.57 (1H, s), 4.38–4.50 (1H, m), 6.79 (1H, s), 7.08–7.20 (6H, m), 7.28–7.40 (10H, m), 7.48–7.65 (5H, m), 7.80 (2H, d, J = 8.0 Hz), 8.07 (1H, s). IR (KBr): 2969, 1495, 1472, 1445, 1327, 1161 cm^{-1}. Anal. Calcd for $C_{39}H_{37}N_3O_3S$: C, 74.61; H, 5.94; N, 6.69. Found: C, 74.71; H, 6.00; N, 6.69.

4.22. *N*-{4′-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl][1,1′-biphenyl]-3-yl}-*N*′-methylurea (21c)

Yield 34%. ^{1}H NMR ($CDCl_3$) δ: 0.75 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.7 Hz), 2.38–2.56 (1H, m), 2.78 (3H, d, J = 4.6 Hz), 3.52 (1H, s), 5.00–5.20 (1H, m), 6.79 (1H, d, J = 1.0 Hz), 6.90 (1H, br s), 7.06–7.18 (6H, m), 7.22–7.39 (14H, m), 7.42 (2H, d, J = 8.6 Hz), 7.51 (2H, d, J = 8.6 Hz). IR (KBr): 2967, 1669, 1557 cm^{-1}. Anal. Calcd for $C_{40}H_{38}N_4O_2$·0.2AcOEt: C, 78.48; H, 6.39; N, 8.97. Found: C, 78.45; H, 6.53; N, 8.99.

4.23. 2-Methyl-1-[4-(2-pyridinyl)phenyl]-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (21d)

Yield 72%. Mp 226–227 °C (chloroform–MeOH–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.75 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.4 Hz), 2.39–2.53 (1H, m), 3.60 (1H, s), 6.78 (1H, d, J = 1.4 Hz), 7.10–7.35 (17H, m), 7.58–7.63 (2H, m), 7.71–7.78 (2H, m), 7.89–7.93 (2H, m), 8.66–8.69 (1H, m). IR (KBr): 1588, 1491, 1466, 1447, 1435, 1003, 781, 747, 702 cm^{-1}.

4.24. *N*-{6-(4-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]phenyl)-2-pyridinyl}acetamide (21e)

Yield 23%. Mp 137 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, J = 6.8 Hz), 0.92 (3H, d, J = 6.8 Hz), 2.20 (3H, s), 2.34–2.58 (1H, m), 3.60 (1H, s), 6.77 (1H, d, J = 1.4 Hz), 7.06–7.20 (6H, m), 7.28–7.42 (10H, m), 7.44 (1H, dd, J = 0.8, 7.9 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.75 (1H, t, J = 7.9 Hz), 7.83 (2H, d, J = 8.4 Hz), 8.05–8.16 (2H, m). IR (KBr): 2969, 1732, 1690, 1447 cm^{-1}. Anal. Calcd for $C_{39}H_{36}N_4O_2$·1.1AcOEt: C, 75.58; H, 6.55; N, 8.12. Found: C, 75.52; H, 6.46; N, 8.17. Compounds **22**–**26** were prepared in the same manner as described for the preparation of **13**.

4.25. 4′-[1-Hydroxy1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl[1,1′-biphenyl]-3-carboxamide (22)

Yield 42%. ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.81 (3H, d, J = 6.9 Hz), 0.98 (3H, d, J = 6.9 Hz), 2.40–2.80 (1H, m), 3.00 (3H, s), 6.96 (1H, s), 7.30 (1H, d, J = 1.4 Hz), 7.38–7.60 (5H, m), 7.60–7.74 (2H, m), 7.93 (1H, s). IR (KBr): 3277, 2969, 1645, 1547 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O_2$·0.75H_2O: C, 69.50; H, 6.80; N, 11.58. Found: C, 69.53; H, 7.16; N, 11.28.

4.26. 4′-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl[1,1′-biphenyl]-3-sulfonamide (23)

Yield 52%. ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.81 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 2.20–2.70 (4H, m), 6.98 (1H, d, J = 1.2 Hz), 7.48–7.65 (6H, m), 7.74–7.83 (2H, m), 8.04 (1H, t, J = 1.9 Hz). IR (KBr): 3287, 2971, 1474, 1308, 1161 cm^{-1}. Anal. Calcd for $C_{20}H_{23}N_3O_3S$·0.5H_2O: C, 60.89; H, 6.13; N, 10.65. Found: C, 61.10; H, 6.31; N, 10.78.

4.27. *N*-{4′-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl][1,1′-biphenyl]-3-yl}-*N*′-methylurea (24)

Yield 61%. ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.77 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz), 2.40–2.70 (1H, m), 2.71 (3H, s), 6.89 (1H, s), 7.02–7.50 (9H, m). IR (KBr): 3260, 1665, 1557 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_4O_2$·0.5AcOEt: C, 66.65; H, 7.12; N, 14.13. Found: C, 66.89; H, 7.00; N, 14.28.

4.28. 1-(1*H*-Imidazol-4-yl)-2-methyl-1-[4-(2-pyridinyl)phenyl]-1-propanol (25)

Yield 26%. ^{1}H NMR ($CDCl_3$) δ: 0.82 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.6 Hz), 2.57–2.70 (1H, m), 6.95 (1H, d, J = 1.2 Hz), 7.18–7.24 (1H, m), 7.49 (1H, d, J = 1.2 Hz), 7.62–7.79 (4H, m), 7.91 (2H, d, J = 8.4 Hz), 8.66 (1H, d, J = 4.8 Hz). IR (KBr): 1590, 1468, 1435, 829, 781, 733 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_3O$·0.4H_2O: C, 71.93; H, 6.64; N, 13.98. Found: C, 71.69; H, 6.55; N, 13.98.

4.29. *N*-{6-(4-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]phenyl)-2-pyridyl}acetamide (26)

Yield 42%. Mp 206–208 °C (AcOEt–MeOH). ^{1}H NMR ($CDCl_3$+CD_3OD) δ: 0.81 (3H, d, J = 6.7 Hz), 0.98 (3H, d, J = 6.7 Hz), 2.22 (3H, s), 2.52–2.74 (1H, m), 6.97 (1H, d, J = 1.0 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.52 (1H, d, J = 1.0 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.76 (1H, t, J = 7.8 Hz), 7.83 (2H, d, J = 8.4 Hz), 8.09 (1H, d, J = 7.8 Hz). IR (KBr): 3177, 2967, 1651, 1559, 1451 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_4O_2$·0.3AcOEt: C, 67.57; H, 6.53; N, 14.87. Found: C, 67.39; H, 6.63; N, 14.89.

4.30. 4-Bromophenyl(1-trityl-1*H*-imidazol-4-yl)methanol (28)

Compound **28** was prepared in the same manner as described for the preparation of **10a**. Yield 56%. Mp 214–215 °C (AcOEt–MeOH–THF–hexane). ^{1}H NMR ($CDCl_3$) δ: 3.56 (1H, br s), 5.71 (2H, d, J = 4.4 Hz), 6.58 (1H, s), 7.07–7.13 (7H, m), 7.25–7.44 (12H, m). IR (KBr): 1493, 1445, 1128, 1011, 909, 747, 733, 702 cm^{-1}. Anal. Calcd for $C_{29}H_{23}N_2OBr$: C, 70.31; H, 4.68; N, 5.65. Found: C, 69.93; H, 4.86; N, 5.31.

4.31. 4-Bromophenyl(1-trityl-1*H*-imidazol-4-yl)methanone (29)

A mixture of **28** (30.0 g, 60.6 mmol) and MnO_2 (52.6 g, 606 mmol) in CH_2Cl_2 (1000 mL) was stirred at rt for 26 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was recrystallized from AcOEt–Et_2O–hexane to give **29** (23.3 g, 47.2 mmol, 78%) as a colorless powder. Mp 145–146 °C (AcOEt–Et_2O–hexane). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.19 (6H, m), 7.31–7.41 (9H, m), 7.52 (1H, d, J = 1.4 Hz), 7.68 (2H, d, J = 8.4 Hz), 7.77 (1H, d, J = 1.4 Hz), 8.21 (2H, d, J = 8.4 Hz). IR (KBr): 1644, 1520, 1213, 887, 756, 747, 702 cm^{-1}.

4.32. *N*-[4′-[(1-Trityl-1*H*-imidazol-4-yl)carbonyl][1,1′-biphenyl]-3-yl]acetamide (30)

Compound **30** was prepared in the same manner as described for the preparation of **12a**. Yield 76%. Mp 198–199 °C (AcOEt–hexane). ^{1}H NMR ($CDCl_3$) δ: 2.20 (3H, s), 7.14–7.21 (6H, m), 7.36–7.44 (12H, m), 7.54–7.77 (6H, m), 8.33 (2H, d, J = 8.4 Hz). IR (KBr): 1671, 1645, 1603, 1553, 1524, 756, 702 cm^{-1}. Anal. Calcd for $C_{37}H_{29}N_3O_2$: C, 81.15; H, 5.34; N, 7.67. Found: C, 80.89; H, 5.58; N, 7.45.

4.33. *N*-[4′-[1-Hydroxy-1-(1-trityl-1*H*-imidazol-4-yl)ethyl][1,1′-biphenyl]-3-yl]acetamide (31a)

Methylmagnesium bromide (1.0 M in THF, 4.4 mL, 4.38 mmol) was added dropwise to a cooled (0 °C) solution of **30** (800 mg, 1.46 mmol) in THF (14 mL). After being stirred for 20 min at 0 °C, the reaction was quenched with saturated NH_4Cl solution. The resulting mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was recrystallized from AcOEt–MeOH–hexane to give **31a** (823 mg, 1.46 mmol, quant.) as a colorless powder. Mp 157–158 °C (AcOEt–MeOH–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.81 (3H, s), 2.20 (3H, s), 3.37 (1H, s), 6.79

(1H, d, J = 1.4 Hz), 7.12–7.20 (8H, m), 7.31–7.52 (16H, m), 7.65 (1H, br s). IR (KBr): 1672, 1553, 1483, 1445, 909, 747, 733, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_3O_2 \cdot 0.5AcOEt$: C, 79.05; H, 6.14; N, 6.91. Found: C, 79.13; H, 6.33; N, 6.71. Compounds **31b**,**c** were prepared in the same manner as described for the preparation of **31a**.

4.34. *N*-[4′-[1-Hydroxy-1-(1-trityl-1*H*-imidazol-4-yl)propyl][1,1′-biphenyl]-3-yl]acetamide (31b)

Yield 86%. ^1H NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 7.6 Hz), 2.12–2.20 (5H, m), 3.35 (1H, s), 6.77 (1H, s), 7.13–7.22 (6H, m), 7.26–7.48 (18H, m), 7.66 (1H, s). IR (KBr): 1674, 1609, 1557, 1485, 1445, 747, 733, 702 cm^{-1}. Anal. Calcd for $C_{39}H_{35}N_3O_2 \cdot 0.5AcOEt$: C, 79.20; H, 6.32; N, 6.76. Found: C, 79.23; H, 6.40; N, 6.93.

4.35. *N*-[4′-[Cyclopropyl(hydroxy)(1-trityl-1*H*-imidazol-4-yl)methyl][1,1′-biphenyl]-3-yl]acetamide (31c)

Yield 61%. Mp 230–231 °C (AcOEt–MeOH–hexane). ^1H NMR ($CDCl_3$) δ: 0.41–0.49 (4H, m), 1.47–1.55 (1H, m), 2.20 (3H, s), 3.26 (1H, s), 6.82 (1H, d, J = 1.4 Hz), 7.11–7.41 (19H, m), 7.50–7.53 (5H, m), 7.65 (1H, s). IR (KBr): 1671, 1591, 1559, 1483, 1445, 731, 702 cm^{-1}. Anal. Calcd for $C_{40}H_{35}N_3O_2$: C, 81.47; H, 5.98; N, 7.13. Found: C, 81.25; H, 6.01; N, 6.92. Compounds **32**, **34**, and **35** were prepared in the same manner as described for the preparation of **13**.

4.36. *N*-[4′-[1-Hydroxy-1-(1*H*-imidazol-4-yl)ethyl][1,1′-biphenyl]-3-yl]acetamide (32)

Yield 59%. ^1H NMR ($CDCl_3$+CD_3OD) δ: 1.89 (3H, s), 2.16 (3H, s), 6.89 (1H, s), 7.27–7.52 (8H, m), 7.69 (1H, s). IR (KBr): 3031, 1672, 1609, 1591, 1559, 1483, 1397, 1312, 791 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 0.3H_2O$: C, 69.83; H, 6.05; N, 12.86. Found: C, 69.98; H, 6.05; N, 12.61.

4.37. *N*-[4′-[Cyclopropyl(hydroxy)-1*H*-imidazol-4-ylmethyl][1,1′-biphenyl]-3-yl]acetamide (34)

Yield 39%. ^1H NMR ($CDCl_3$+CD_3OD) δ: 0.47–0.60 (4H, m), 1.57–1.64 (1H, m), 2.17 (3H, s), 7.00 (1H, s), 7.36–7.58 (8H, m), 7.71 (1H, s). IR (KBr): 3148, 1667, 1591, 1555, 1485, 831, 791 cm^{-1}. Anal. Calcd for $C_{21}H_{21}N_3O_2 \cdot 0.5CHCl_3 \cdot 0.7H_2O$: C, 61.53; H, 5.50; N, 10.01. Found: C, 61.46; H, 5.67; N, 9.81.

4.38. *N*-[4′-(1*H*-Imidazol-4-ylcarbonyl)[1,1′-biphenyl]-3-yl]-acetamide (35)

Yield 88%. Mp 253–254 °C (AcOEt–MeOH–hexane). ^1H NMR ($CDCl_3$+CD_3OD) δ: 2.19 (3H, s), 7.34–7.47 (2H, m), 7.47–7.59 (1H, m), 7.72–7.84 (5H, m), 8.04 (2H, d, J = 8.4 Hz). IR (KBr): 1671, 1638, 1599, 1559, 1437, 1399, 1345, 768 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.72; H, 4.70; N, 13.58.

4.39. *N*-[4′-[1-Hydroxy-1-(1*H*-imidazol-4-yl)propyl][1,1′-biphenyl]-3-yl]acetamide (33)

Under H_2 atmosphere, a mixture of **31b** (1.31 g, 2.27 mmol) and 10% Pd/C (1.31 g) in 1 N HCl (2.3 mL) and EtOH (22 mL) was vigorously stirred at rt for 8.5 h. The mixture was made alkaline with $NaHCO_3$ (210 mg) and filtered through Celite. After removal of the solvent in vacuo, the residue was chromatographed on silica gel ($CHCl_3$/MeOH = 10:1 to 4:1) to give **33** (640 mg, 1.91 mmol, 84%) as a colorless amorphous solid. ^1H NMR ($CDCl_3$+CD_3OD) δ: 0.89 (3H, t, J = 7.6 Hz), 2.17–2.32 (5H, m), 6.91 (1H, s), 7.30–7.53 (8H, m), 7.69 (1H, s). IR (KBr): 3148, 1667, 1609, 1591, 1557, 1485, 831, 791 cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 0.4H_2O$: C, 70.11; H, 6.41; N, 12.26. Found: C, 70.43; H, 6.48; N, 12.01.

4.40. *N*-[4′-[1-Hydroxy(1*H*-imidazol-4-yl)methyl][1,1′-biphenyl]-3-yl]acetamide (36)

Sodium borohydride ($NaBH_4$) (172 mg, 4.55 mmol) was added to a cooled (0 °C) solution of **35** (500 mg, 1.97 mmol) in MeOH (40 mL) and the mixture was stirred at rt for 3 h. The mixture was diluted with H_2O and the aqueous phase was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 10:1 to 4:1) and recrystallized from AcOEt–diethylether–hexane to give **36** (461 mg, 1.50 mmol, 76%) as a colorless powder. Mp 227–228 °C (AcOEt–diethylether–hexane). ^1H NMR ($CDCl_3$+CD_3OD) δ: 2.17 (3H, s), 5.85 (1H, s), 6.74 (1H, s), 7.38–7.59 (8H, m), 7.74 (1H, s). IR (KBr): 1667, 1651, 1607, 1561, 1485, 1325, 793, 775 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3O_2 \cdot 0.3H_2O$: C, 69.13; H, 5.67; N, 13.44. Found: C, 69.21; H, 5.81; N, 13.21.

4.41. Optical resolution of 17

Optical resolution of **17** (2.00 g) was performed using preparative HPLC on a Chiralpak AD column (Daicel Chemical Industries, 50 mmID × 500 mmL, eluent: hexane/EtOH = 50:50, flow rate: 70 mL/min, temperature: 25 °C) to yield (−)-**17** (970 mg, >99.9% ee) and (+)-**17** (920 mg, 99.9% ee), respectively. The HPLC retention time of (−)-**17** was 10.8 min and that of (+)-**17** was 26.3 min under the analytical condition (Chiralpak AD column, 4.6 mmID × 250 mmL, eluent: hexane/EtOH = 50:50, flow rate: 0.5 mL/min, temperature: rt). [(−)-17: Anal. Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.5H_2O \cdot 0.1AcOEt$: C, 69.99; H, 6.81; N, 11.44. Found: C, 70.22; H, 7.13; N, 11.27. (+)-**17**: Anal. Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.75H_2O$: C, 69.50; H, 6.80; N, 11.58. Found: C, 69.68; H, 7.00; N, 11.43. $[\alpha]_D^{20}$ = +16.5 (c 0.912, MeOH).

4.42. Optical resolution of 26

Optical resolution of **26** (3.00 g) was performed using preparative HPLC on a Chiralpak AD column (50 mmID × 500 mmL, eluent: hexane/EtOH = 30:70, flow rate: 70 mL/min, temperature: 25 °C) to yield (−)-**26** (1410 mg, 99.8% ee) and (+)-**26** (1180 mg, >99.9% ee), respectively. The HPLC retention time of (−)-**26** was 8.6 min and that of (+)-**26** was 23.9 min under the analytical condition (Chiralpak AD column, 4.6 mmID × 250 mmL, eluent: hexane/EtOH = 30:70, flow rate: 0.5 mL/min, temperature: rt). (−)-**26**: $[\alpha]_D^{20}$ = −8.3 (c 0.362, MeOH). (+)-**26**: $[\alpha]_D^{20}$ = +6.9 (c 0.376, MeOH).

4.43. Optical resolution of 33

Optical resolution of **33** (280 mg) was performed using preparative HPLC on a Chiralpak AD column (50 mmID × 500 mmL, eluent: hexane/EtOH/diethylamine = 85:15:0.1, flow rate: 60 mL/min, temperature: 25 °C) to yield (−)-**33** (53 mg, >99.9% ee) and (+)-**33** (67 mg, 99.6% ee), respectively. The HPLC retention time of (−)-**33** was 43.0 min and that of (+)-**33** was 59.2 min under the analytical condition (Chiralpak AD column, 4.6 mmID × 250 mmL, eluent: hexane/EtOH = 85:15, flow rate: 1.0 mL/min, temperature: rt). (−)-**33**: $[\alpha]_D^{20}$ = −2.24 (c 1.03, EtOH). (+)-**33**: $[\alpha]_D^{20}$ = +1.69 (c 1.06, EtOH).

4.44. Asymmetric synthesis of *N*-[4′-[(1*S*)-1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-1,1′-biphenyl-3-yl]acetamide ((−)-17): synthesis of 4-[(2*R*)-2-(*tert*-butyldimethylsilyloxy)-propanoyl]morpholine (38)

Imidazole (12.26 g, 180.1 mmol) was added dropwise to a cooled (0 °C) solution of (2*R*)-2-hydroxy-1-(morpholin-4-yl)

propan-1-one **37** (24.09 g, 151.3 mmol)[47] in *N*,*N*-dimethylformamide (DMF) (150 mL), followed by *tert*-butyldimethylsilyl chloride (TBSCl) (23.06 g, 153.0 mmol) and the mixture was stirred at 0 °C for 30 min, allowed to warm to rt and stirred for a further 16 h. The reaction mixture was poured into water and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with water and brine, dried over $MgSO_4$ and evaporated to give **38** (40.70 g, 98%) as a pale yellow oil. This compound was used without purification in the next step. IR (KBr): 1651, 1119, 831 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.11 (6H, s), 0.91 (9H, s), 1.41 (3H, d, J = 6.6 Hz), 3.60–4.00 (8H, m), 4.57 (1H, q, J = 6.6 Hz).

4.45. (2*R*)-1-(4-Bromophenyl)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-propan-1-one (39)

n-BuLi (1.6 M; 62.9 mL, 101 mmol) was added to a cooled (−78 °C) solution of 1,4-dibromobenzene (25.6 g, 109 mmol) in THF (350 mL) and the mixture was stirred at −78 °C for 20 min. A solution of **38** (22.0 g, 80.5 mmol) in THF (50 mL) was added to the mixture and the solution was stirred at −78 °C for 45 min. The reaction was quenched with aq NH_4Cl and the mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane/AcOEt = 40:1) to give **39** (25.3 g, 73.7 mmol, 92%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ: 0.02 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 1.50 (3H, d, J = 7.0 Hz), 4.84 (1H, q, J = 7.0 Hz), 7.56–7.61 (2H, m), 7.94–8.00 (2H, m). IR (KBr): 1684, 1586, 1256, 1146, 1071, 920, 835, 777 cm^{-1}.

4.46. (2*R*)-1-(4-Bromophenyl)-2-hydroxypropan-1-one (41)

Tetrabutylammonium fluoride (21.5 g, 21.5 mmol) was added to a cooled (0 °C) solution of **39** (25.7 g, 74.9 mmol) in THF (250 mL) and the mixture was stirred at 0 °C for 15 min. The mixture was diluted with satd aq NH_4Cl solution and the aqueous phase was extracted with diisopropylether. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane/AcOEt = 4:1) to give **41** (14.1 g, 61.6 mmol, 82%) as a pale yellow oil. The optical purity of the obtained **41** was 96.3% ee as determined by HPLC using a Chiralpak AD column with hexane/EtOH = 85:15 as an eluent. ^1H NMR ($CDCl_3$) δ: 1.44 (3H, d, J = 7.0 Hz), 3.70 (1H, d, J = 6.6 Hz), 5.05–5.18 (1H, m), 7.64–7.69 (2H, m), 7.77–7.82 (2H, m). IR (KBr): 1717, 1485, 1402, 1358, 1175, 1073, 1011, 824 cm^{-1}.

4.47. Alternative method for (2*R*)-1-(4-bromophenyl)-2-hydroxypropan-1-one (41); asymmetric oxidation with AD-mix-β™

40% sodium bis(trimethylsilyl)amide solution (NaHMDS) in THF–cumene (2.46 g, 4.70 mmol) at −70 °C was added to a solution of 1-(4-bromophenyl)propan-1-one **40** (500 mg, 2.35 mmol) in THF (10 mL) and stirred for 30 min. A solution of TBSCl (429 mg, 2.84 mmol) in hexane (2 mL) was added to the mixture and stirred at −70 °C for 30 min, allowed to warm to rt, and stirred for an additional 100 min. The mixture was diluted with water and the aqueous phase was extracted with AcOEt. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The remaining residue was dissolved in *tert*-butanol (*tert*-BuOH) (15 mL) and H_2O (12 mL) and the mixture was cooled to 5 °C, followed by the addition of methanesulfonamide (226 mg, 2.37 mmol) and AD-mix-β (3.32 g, 2.37 mmol). After being stirred at 5 °C for 22 h and at rt for a further 15 h, sodium sulfite (2.35 g, 18.6 mmol) was added. The mixture was stirred for an additional 2 h and diluted with water. The aqueous phase was extracted with AcOEt and the extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (hexane/AcOEt = 10:1 to 4:1) to give **41** (468 mg, 2.04 mmol, 87%) as a pale yellow oil. The optical purity of the obtained **41** was 98.0% ee as determined by HPLC (Chiralpak AD).

4.48. (2*R*,3*S*)-3-(4-Bromophenyl)-4-methylpentane-2,3-diol (42)

Solution **41** (100 mg, 0.44 mmol; 96.3% ee) in THF (3 mL) was added dropwise to a cooled (0 °C) solution of *i*-PrMgBr (0.75 M in THF; 2.9 mL, 2.2 mmol) and the mixture was stirred at 0 °C for 4.5 h. The reaction was quenched with satd aq NH_4Cl and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt = 3:1) to give **42** (70.8 mg, 0.6 mmol, 59%) with some by-products. This compound was used without further purification in the next step. ^1H NMR ($CDCl_3$) δ: 0.82 (3H, d, J = 7.0 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 6.2 Hz), 1.57 (1H, s), 2.23–2.36 (1H, m), 2.41 (1H, s), 4.25 (1H, dt, J = 6.2, 6.2 Hz), 7.22–7.27 (2H, m), 7.44–7.51 (2H, m). IR (KBr): 2975, 1489, 1393, 1076, 1009, 986, 882, 818 cm^{-1}.

4.49. (3*S*)-3-(4-Bromophenyl)-3-hydroxy-4-methylpentane-2-one (43)

Dimethyl sulfoxide (DMSO) (10.9 mL, 154 mmol) was added dropwise to a cooled (−70 °C) solution of oxalyl chloride (6.71 mL, 38.4 mmol) in CH_2Cl_2 (150 mL). After stirring for 10 min, a solution of **41** (10.5 g, 38.4 mmol) in CH_2Cl_2 (100 mL) was added dropwise, and the reaction mixture was stirred at a temperature of −50 to −40 °C for 30 min. The mixture was then cooled to −70 °C, and triethylamine (53.5 mL, 384 mmol) was added dropwise, and the solution was allowed to warm to rt. The resulting mixture was diluted with satd aq NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane/AcOEt = 10:1) to give **43** (8.72 g, 32.2 mmol, 84%) as a pale yellow amorphous solid. ^1H NMR ($CDCl_3$) δ: 0.88 (6H, d, J = 6.6 Hz), 2.14 (3H, s), 2.69–2.82 (1H, m), 4.44 (1H, s), 7.40–7.45 (2H, m), 7.47–7.53 (2H, m). IR (KBr): 2971, 1709, 1487, 1358, 1169, 1142, 1009, 816 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2Br$: C, 53.15; H, 5.58; N, 0.00; Br, 29.47. Found: C, 52.94; H, 5.59; N, 0.07.

4.50. (3*S*)-1-Bromo-3-(4-bromophenyl)-3-hydroxy-4-methylpentane-2-one (44)

Pyridinium bromide perbromide (11.2 g, 34.9 mmol) was added to a stirred solution of **43** (7.89 g, 29.1 mmol) in THF (150 mL) and the mixture was stirred at rt for 12 h. The reaction mixture was diluted with aqueous sodium thiosulfate solution and the aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane/AcOEt = 10:1) to give **44** (6.58 g, 18.8 mmol, 65%) as a pale yellow powder. ^1H NMR ($CDCl_3$) δ: 0.78 (3H, d, J = 7.0 Hz), 0.95 (3H, d, J = 7.0 Hz), 2.72–2.85 (1H, m), 4.11 (1H, d, J = 14.2 Hz), 4.19 (1H, d, J = 14.2 Hz), 7.37–7.44 (2H, m), 7.48–7.55 (2H, m). IR (KBr): 2969, 1726, 1487, 1076, 1026, 1009, 814 cm^{-1}.

4.51. (1*S*)-1-(4-Bromophenyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (45)

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (8.01 mL, 44.3 mmol) was added dropwise to a cooled (0 °C) solution of **44**

(6.20 g, 17.7 mmol) and 2,6-lutidine (6.18 mL, 53.1 mmol) in anhydrous THF (50 mL), and the reaction mixture was stirred at 0 °C for 30 min and allowed to warm to rt. After stirring for a further 90 min, the mixture was diluted with 1 N HCl followed by extraction with AcOEt. The combined organic layers were washed with satd $NaHCO_3$ solution followed by brine, before drying over $MgSO_4$. The solution was concentrated in vacuo to give crude (3*S*)-1-bromo-3-(4-bromophenyl)-4-methyl-3-[(trimethylsilyl)oxy]pentane-2-one as a colorless amorphous solid. This material, without further purification, was mixed with THF (6 mL) and formamidine acetate (2.95 g, 28.3 mmol) and added to a saturated ammonia solution in MeOH (30 mL); the resulting mixture was stirred at rt for 22 h. After removing excess NH_3 and MeOH, the residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 50:1 to 10:1) to give **45** (3.89 g, 13.2 mmol, 74%) as a pale yellow amorphous solid. The optical purity of the obtained **45** was 90.0% ee as determined by HPLC (Chiralpak AD). ^{1}H NMR ($CDCl_3$) δ: 0.78 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 7.0 Hz), 2.50–7.64 (1H, m), 6.95 (1H, d, J = 1.2 Hz), 7.43 (4H, s), 7.55 (1H, d, J = 1.2 Hz). IR (KBr): 2971, 1485, 1395, 1009, 814, 733 cm^{-1}.

4.52. (1*S*)-1-(4-Bromophenyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (46)

Trityl chloride (1.00 g, 3.59 mmol) was added to a cooled (0 °C) mixture of **45** (1.01 g, 3.42 mmol, 90.0% ee) and triethylamine (0.715 mL, 5.13 mmol) in DMF (10 mL), and the reaction mixture was stirred at rt for 2.5 h. After being diluted with H_2O, the mixture was extracted with AcOEt. The combined organic layers were washed with H_2O and brine successively, followed by drying over $MgSO_4$. The solution was concentrated in vacuo and the obtained residue was recrystallized from hexane–AcOEt to give **46** (1.16 g, 2.16 mmol, 63%) as a colorless powder. The optical purity of the obtained **46** was 98.8% ee as determined by HPLC (Chiralpak AD). Recrystallization of **46** with 98.8% ee from hexane–AcOEt provided needle crystals with 99.5% ee for X-ray crystallographic analysis. The spectral data of **46** were identical to those of the racemate **10b** except for elemental analysis and optical rotation. Anal. Calcd for $C_{32}H_{29}N_2OBr$: C, 71.51; H, 5.44; N, 5.21; Br, 14.87. Found: C, 71.45; H, 5.66; N, 5.02. $[\alpha]_D^{20}$ = +34.6 (*c* 1.00, MeOH).

4.53. *N*-[4′-[(1*S*)-1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-1,1′-biphenyl-3-yl]acetamide (47)

Compound **47** was prepared from **46** (300 mg, 0.56 mmol, 98.8% ee) and 3-acetamidephenylboronic acid (130 mg) and $Pd(PPh_3)_4$ (0) (32 mg, 0.028 mmol) as a colorless amorphous solid (288 mg, 0.49 mmol, 87%) using the same method described for the preparation of **12a**. The optical purity of **47** was 99.1% ee as determined by HPLC (Chiralpak AD). The spectral data of **47** were identical to those of the racemate **12e** except for optical rotation. $[\alpha]_D^{20}$ = +46.6 (*c* 0.49, MeOH).

4.54. *N*-[4′-[(1*S*)-1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-1,1′-biphenyl-3-yl]acetamide (S-(−)-17)

A solution of **47** (86.3 mg, 0.143 mmol) and 10% Pd/C (85 mg) in EtOH (10 mL) was vigorously stirred at 70 °C for 9 h under H_2 (4 atm) atmosphere. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 10:1) to give (−)-**17** (30.7 mg, 0.088 mmol, 61%) as a colorless amorphous solid. The optical purity of the obtained (−)-**17** was 99.0% ee as determined by HPLC (Chiralpak AD). The spectral data of (−)-**17** were identical to those of the racemate **17** except for optical rotation. $[\alpha]_D^{20}$ = −15.7 (*c* 1.10, MeOH). FAB-MS *m*/*z*: 350.1834 (calcd for $C_{21}H_{24}N_3O_2$:350.1869).

4.55. Inhibition of rat 17,20-lyase activity in vitro

Inhibition of rat enzymes was determined according to a previously described method,[51] with some modifications. Testes excised from 13-week-old male Sprague–Dawley (SD) rats were homogenized, and testicular microsomes were prepared by a series of centrifugation. The reaction mixture contained 75 mM phosphate buffer (pH 7.4), 7 μg microsome protein, 10 nM [1,2-^{3}H]-17α-hydroxyprogesterone (NEN), 5 mM NADPH (Oriental Yeast), and 1–1000 nM test compound in a total volume of 20 μL. The concentration of reagents was expressed as the final concentration in the reaction mixture. The test compounds were serially diluted with dimethylformamide, and then diluted fivefold with distilled water before 5 μL were added to the reaction mixture. The reaction was terminated by the addition of 40 μL of ethyl acetate after 15 min incubation at 37 °C, then vortexing for 30 s and brief centrifugation; 30 μL of the organic phases were applied to silica gel TLC plates (Whatman, LHPK). The substrate and the products androstenedione and testosterone were separated using the toluene–acetone (7:2) solvent system. Detection of the spots and measurement of the radioactivity as PSL were performed using a BAS2000 Bio-image analyzer (FUJIX). The concentrations of the test compounds necessary to reduce the concentration of the products by 50% (IC_{50}) were calculated.

4.56. Inhibition of human 17,20-lyase activity in vitro

Inhibition of human enzymes was determined as described above for rat enzymes. The reaction mixture contained 75 mM phosphate buffer (pH 7.4), 1 mM magnesium chloride, 0.5 pmol of recombinant P450c17 (Biotechnology Laboratories, Takeda Pharmaceutical Company Limited), 0.5 pmol recombinant cytochrome b5 (Pan Vera), 20.8 ng recombinant NADPH-cytochrome P450 reductase (Pan Vera), 10 nM [1,2-^{3}H]-17α-hydroxypregnenolone (Amersham), 5 mM NADPH (Oriental Yeast), and 1–1000 nM test compounds in a total volume of 20 μL. Dilution of test compounds and termination of the reaction were performed as described above for rat 17,20-lyase assays. Organic phases (30 μL) were applied to silica gel thin-layer chromatography plates (Whatman, LHPK). The substrate and the product, DHEA, were separated using the cyclohexane–ethyl acetate (3:2) solvent system.

4.57. Inhibition of CYP3A4 activity in vitro

The reaction mixture contained 50 mM phosphate buffer (pH 7.4), 10 pmol/mL recombinant CYP3A4 (Gentest), 100 μM testosterone, NADPH regenerating system (0.5 mM NADP (Oriental Yeast)), 5 mM glucose-6-phosphate (Oriental Yeast), 1 mM $MgCl_2$, 1.5 unit/mL G-6-P dehydrogenase (Oriental Yeast)), and 1 or 10 μM test compound in a total volume of 200 μL. The total microsome protein content was adjusted by control microsome protein (Gentest). The reaction mixture was incubated for 30 min at 37 °C and terminated by adding 200 μL of acetonitrile. After addition of 400 μL water, the reaction mixture was centrifuged at 14,000 rpm for 10 min. The 6-hydroxytestosterone contents in the supernatants were determined using a HPLC system (Shimadzu LC-10, column: Inertsil ODS-3 [4.6 × 150 mm] GL Sciences).

4.58. Homology modeling

Multiple alignment using the amino acid sequences of human CYP enzymes was performed using ClustalW and revised by hand. According to the alignment, side chains of the CYP2C5 crystal

structure obtained from the Protein Data Bank (PDB code 1DT6) were replaced by the corresponding residues of CYP17 using the homology module of Insight II (v2000, Accelrys Inc.). Using the Search-Loop function of Insight II, conformations of the insertions and deletions in the alignment were created. After some manual adjustments to remove large steric hindrances, the whole structure was subjected to energy minimization for 1000 steps with steepest descent minimization and, subsequently, 5000 steps with conjugate gradient minimization, using the Discover-ESFF force field (v98.0, Accelrys Inc.). During the minimization procedure, the dielectric constant was set to $4*r$, where r is the distance between two interacting atoms, and the force constant of tethering constraints for the backbone of structurally conserved regions and heme was set to 40 kcal/Å^2 to prevent large movements from the initial positions.

4.59. Docking modes of compound (*S*)-15

After connecting the (*S*)-**15** to the heme Fe, its binding modes were investigated by systematic analysis around the rotatable bonds in the ligands (torsion driving). During this procedure, energy values were estimated based on the Discover ESFF force field. The most stable binding mode of (*S*)-**15** was energy minimized with the CYP17 model using the Discover force field. All computational procedures were performed on O_2/R10000 workstations (Silicon Graphics, Inc).

4.60. X-ray crystallographic analysis of compound 46

A single crystal (0.50 × 0.20 × 0.16 mm) of **46** was obtained by recrystallization from AcOEt. The reflection data were collected using a Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation. The structure was determined by direct methods (SIR92), and refined by the full-matrix least-squares techniques (SHELXL-97) with anisotropic temperature factors for the non-hydrogen atoms. Hydrogen atoms were included using a riding model. The absolute configuration was determined by the Flack parameter of 0.00 (2). Crystal data: $C_{32}H_{29}BrN_2O$; M = 537.50; orthorhombic; space group $P2_12_12_1$ (#19); cell constants a = 11.040 (2) Å, b = 46.207 (3) Å, c = 10.827 (4) Å, V = 5523 (2) Å^3; Z = 4; Dc = 1.293 g/cm^3; unique reflections, 9,330; observed reflections [$I > 2\sigma(I)$], 6,988; $R1$ = 0.048, $wR2$ = 0.124. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 781830).

4.61. Effects of (−)-17 on serum testosterone and DHEA levels in male cynomolgus monkeys

Adult male cynomolgus monkeys, housed in a temperature-controlled room (23 ± 2 °C) with a 12:12-h light/dark cycle (illumination from 7:00 am to 7:00 pm), were used for the single dosing experiments. All procedures were performed according to protocols approved by the Institutional Animal Care and Use Committee of the Pharmaceutical Research Division, Takeda. The test compound (−)-**17** was suspended in 0.5% methylcellulose and orally administered at a dose of 3 mg/kg. Blood samples were collected just before, and 2 and 5 h after dosing. Serum was stored at −30 °C until assayed by radioimmunoassay. Concentrations of testosterone were determined using a Testosterone I-125 kit (Dia Sorin s.r.l., Italy), according to the manufacturer's instructions.

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