博士論文

Discovery of orteronel (TAK-700) as a highly selective 17,20-lyase inhibitor with potential utility in the treatment of prostate cancer

（前立腺癌治療薬を指向した高選択的 17,20-lyase 阻害薬 orteronel（TAK-700）の創製）

加来　智弘

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1. Introduction

1.1. Clinical course and standard treatment of prostate cancer

Prostate cancer is one of the most prevalent cancers among men in the USA.[1] For the screening and diagnosis of prostate cancer, prostate-specific antigen (PSA), a glycoprotein that is secreted by the prostate gland, has been widely used, and the PSA level in plasma is also utilized as a clinical marker to monitor the disease progression in patients who received medical treatment for prostate cancer.

In most cases of early stage disease, growth, maintenance and progression of prostate cancer is androgen-dependent.[2, 3] Therefore, the current first-line treatment for prostate cancer is hormonal therapy, which is mainly targeted to reduce the production of testosterone secreted by the testes or block the signal transduction *via* androgen receptors. However, most of these patients eventually relapse and develop castration-resistant prostate cancer (CRPC). To date, limited therapeutic options for the treatment of CRPC are available, and management of the later stages of this disease is not always successful.

The molecular mechanisms leading to the progression of CRPC are not yet fully defined, but recent studies[4-6] have suggested that residual adrenal androgens that remain after castration could be responsible for CRPC evolution. Therefore, pharmacological methods to reduce adrenal androgen production can be considered as a new therapeutic option to delay CRPC progression.

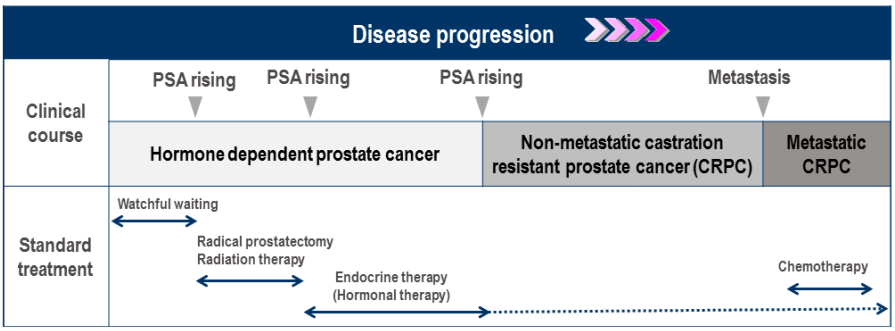


Figure 1. Standard treatment for prostate cancer.

1.2. 17, 20-Lyase as a therapeutic target

As around 80% of patients with prostate cancer respond to hormonal ablation,[7] 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[8] such as leuprorelin or

goserelin, as shown in Figure 2. However, resistance to this therapy eventually occurs during medical treatment by hormonal therapy. 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.[9] Unfortunately, unfavorable effects of anti-androgens, such as anti-androgen withdrawal syndrome, have been observed in some clinical cases.[10]

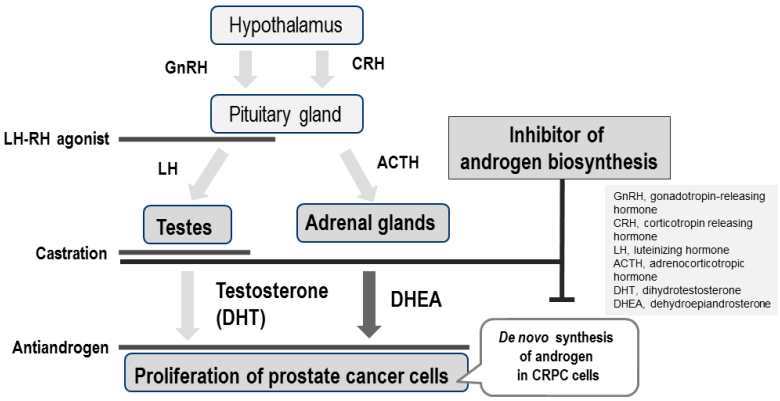


Figure 2. Current hormonal therapy options for prostate cancer.

To address these issues in the clinical treatment of advanced prostate cancer, one possible approach to decrease androgen levels in tumor and plasma is to inhibit the 17,20-lyase activity of CYP17A1, which is an enzyme known to be responsible for androgen biosynthesis in both testes and adrenal glands, as shown in Figure 3.

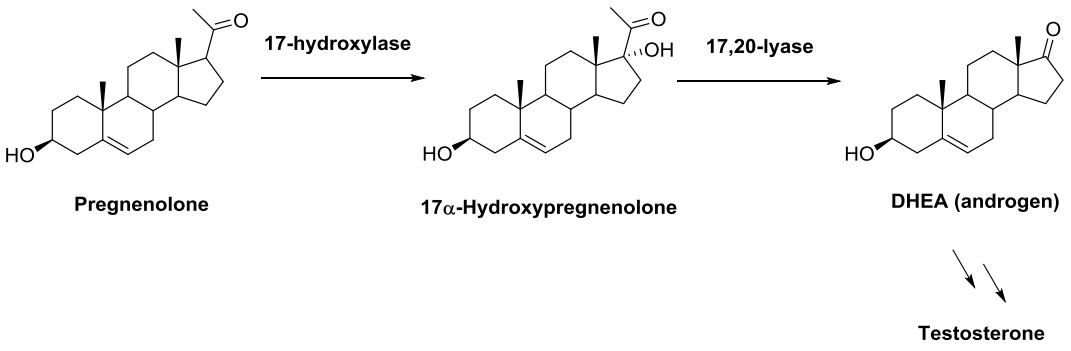


Figure 3. 17,20-Lyase as a therapeutic target.

Indeed, over the past decade, steroidal and nonsteroidal inhibitors of 17,20-lyase,[11-45] such as YM-116[28] and abiraterone acetate[12] (Figure 4), have been evaluated in clinical studies and have been found to effectively reduce circulating androgen levels. Ketoconazole (Figure 4), known as a class of

drugs to treat fungal infections, was also used clinically as an off-label drug for the treatment of prostate cancer because of its ability to inhibit androgen biosynthesis.[46] Among them, the use of abiraterone acetate (Zytiga, Janssen Biotech, Inc.) with prednisone was approved by the U.S. Food and Drug Administration for the treatment of metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy in 2011.

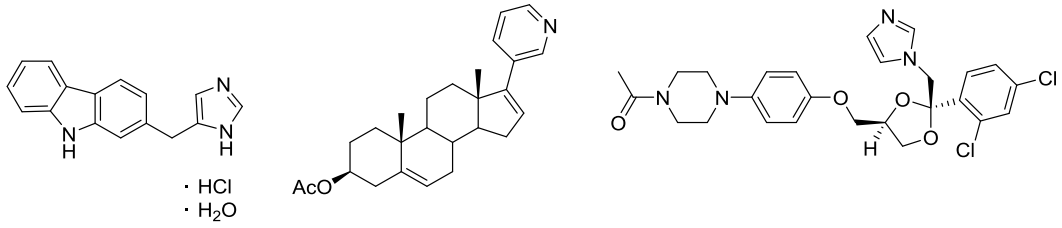


Figure 4. Structures of previously developed 17,20-lyase inhibitors.

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, as shown in Figure 4.

1.3. Background of this study

At the beginning of our study on novel nonsteroidal 17,20-lyase inhibitors, our group developed *de novo* designs based on the enzyme's substrate, 17α-hydroxypregnenolone.[47] Amongst several designed compounds, the naphthylmethyimidazole derivative **1** and its related compound **2** (Figure 5) were identified as promising lead compounds for further development. However, compound **2** was found to have hepatotoxicity risk after 5-days consecutive administration in rats. Therefore, optimization of this series of compounds was investigated to reduce the hepatotoxicity risk, mainly focused on the linker moiety between the naphthalene ring and imidazole ring, suggested by a docking study of compound **2** in the homology model of 17,20-lyase. As a result, compound ***S*-3**, with a hydroxyl group and isopropyl group in the linker moiety, showed potent 17,20-lyase inhibitory activity without hepatotoxicity risk in a 5-days consecutive administration test in rats. Therefore, further modifications based on the compound ***S*-3**, were continued to prepare a novel series of 17,20-lyase inhibitors.

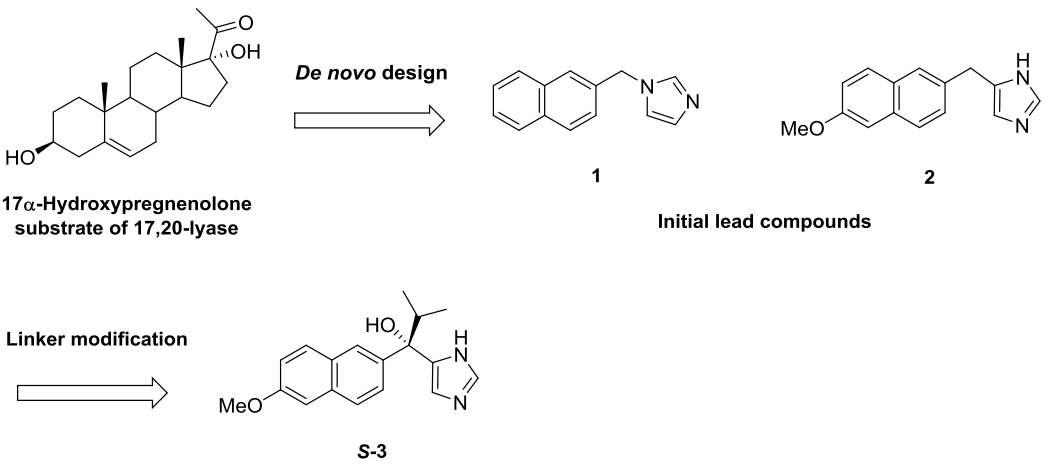


Figure 5. *De novo* design of novel 17,20-lyase inhibitors and identification of a new lead compound ***S*-3**.

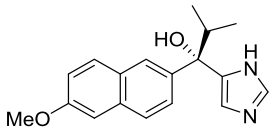
2. Synthetic study on biphenylylmethylimidazole derivatives

2.1. Molecular design

Our group has previously reported that the naphthylmethylimidazole derivative ***S*-3** (Table 1) 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, showed promising *in vitro* activity for further development.[48] Unfortunately, compound ***S*-3** was also found to be a potent inhibitor of CYP3A4, with an IC_{50} value of less than 1000 nM, as shown in Table 1.

CYP3A4 is one of the key metabolizing enzymes of the cytochrome P450 (CYP) superfamily of heme-containing monooxygenases. As the CYP family of enzymes plays important roles not only in the xenobiotic metabolism and detoxification of a large number of drugs, but also in the biosynthesis of endogenous steroids, CYP inhibitors have potential risk to induce drug–drug interactions or significant systemic side effects. Therefore, high specificity and selectivity for 17,20-lyase over the other CYPs is an important requirement for clinical use.

Table 1. Inhibitory effects of ***S*-3** on human 17,20-lyase and human CYP3A4 enzymes.



***S*-3**

Compound No.	Enzyme inhibition IC_{50} (nM)	
	human 17,20-lyase	CYP3A4
***S*-3**	28	<1000

Also, in our earlier studies, some steroid mimetic structures, such as stilbene, biphenyl and benzothiophene rings, were found to be suitable as lipophilic moieties of 17,20-lyase inhibitors, which were designed based on the structure of the substrate of 17,20-lyase, 17α-hydroxypregnenolone.[47] Therefore, aiming to improve the selectivity for 17, 20-lyase over CYP3A4 of ***S*-3**, scaffold hopping was achieved 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 6.

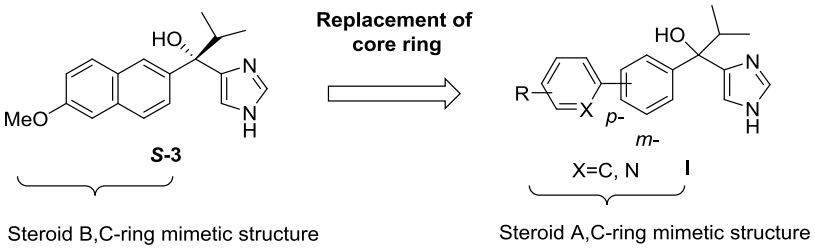


Figure 6. Molecular design of novel 17, 20-lyase inhibitors.

2.2. Chemistry

General strategies for the synthesis of biphenylylmethylimidazole derivatives and related compounds (**I**) are summarized in Figure 7. Lithiation of biphenyl derivatives **4a–5b** followed by addition to ketone **4**[49] 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 *N*-protected ketone **11** provided the key intermediates **12a** and **12b**. The biphenylylmethylimidazole derivatives and related compounds (**I**) can be synthesized *via* a palladium-catalyzed Suzuki coupling reaction of bromide **12a** or **12b** with boronic acid derivatives (**13a–d**), followed by deprotection (method B). It was difficult to convert all the arylbromides **22a–e**

[50] to the corresponding aryl boronic acids; hence, the conversion of **12b** to the suitable boronic acid **21** was investigated as an alternative approach to give biphenylylmethylimidazole derivatives and related compounds (**I**) (method C).

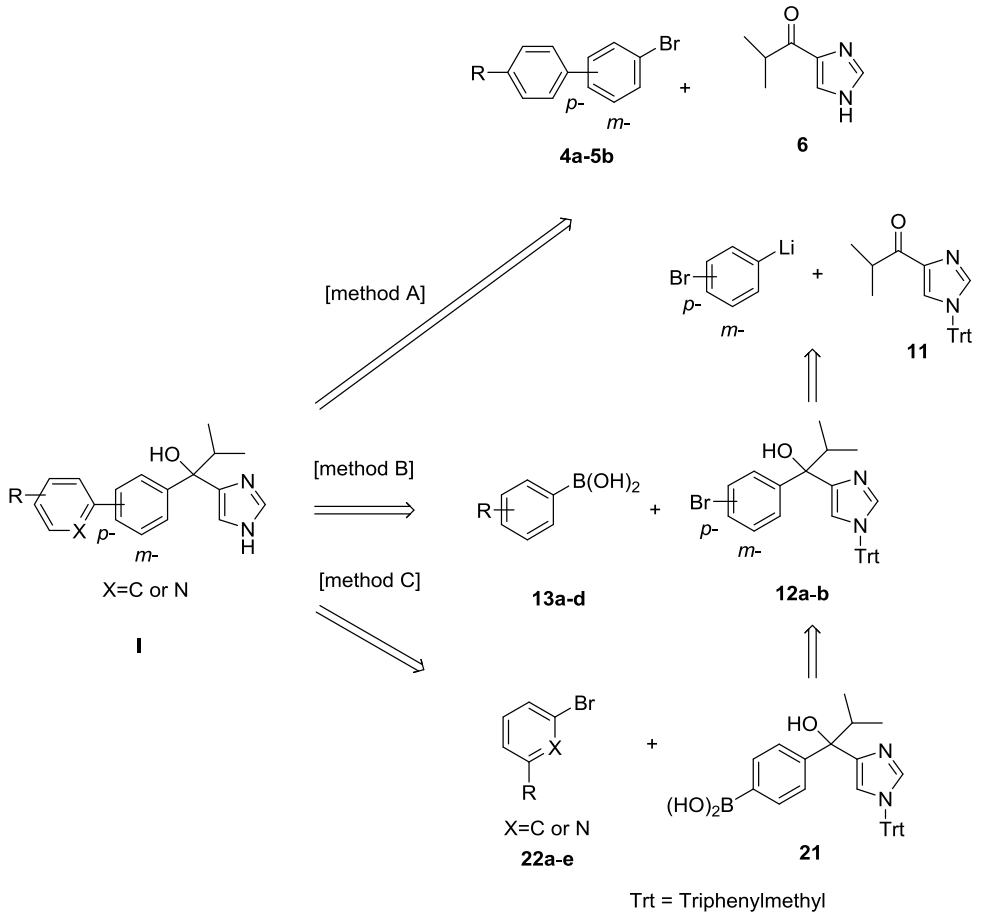
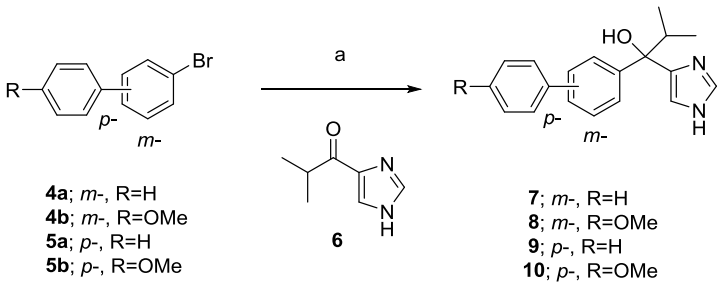


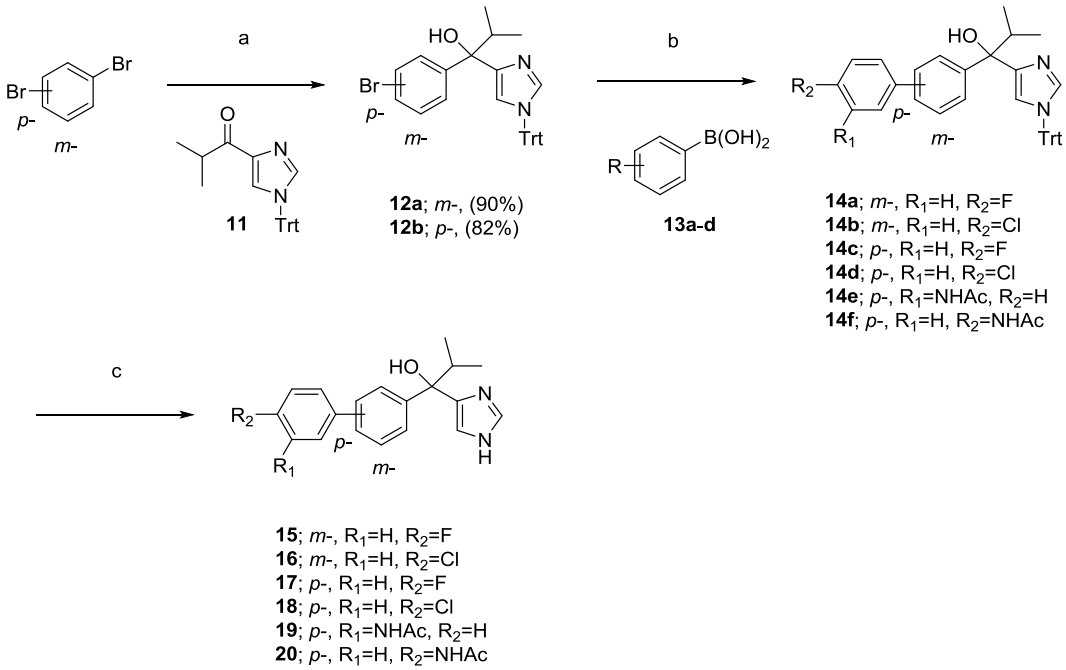
Figure 7. Retrosynthesis of novel biphenyl derivatives and related compounds as 17,20-lyase inhibitors.

The synthesis of compounds **7–10** is shown in Scheme 1. Addition of lithium species generated from *n*-BuLi with commercially available **4a**–**5b** to ketone **6** gave good-to-moderate yields of **7**–**10**. Scheme 2 depicts the preparation of compounds **15**–**20**. Treating 1,3- or 1,4-dibromobenzene with a sub stoichiometric amount of *n*-BuLi in tetrahydrofuran (THF), followed by addition to ketone **11** gave bromide **12a** or **12b** in high yield. Compounds **15**–**20** were synthesized *via* a palladium-catalyzed Suzuki coupling reaction of **12a** or **12b** with the corresponding arylboronic acids **13a**–**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, **12b** was successfully converted to the boronic acid **21**, which was then subjected to Suzuki coupling reaction without

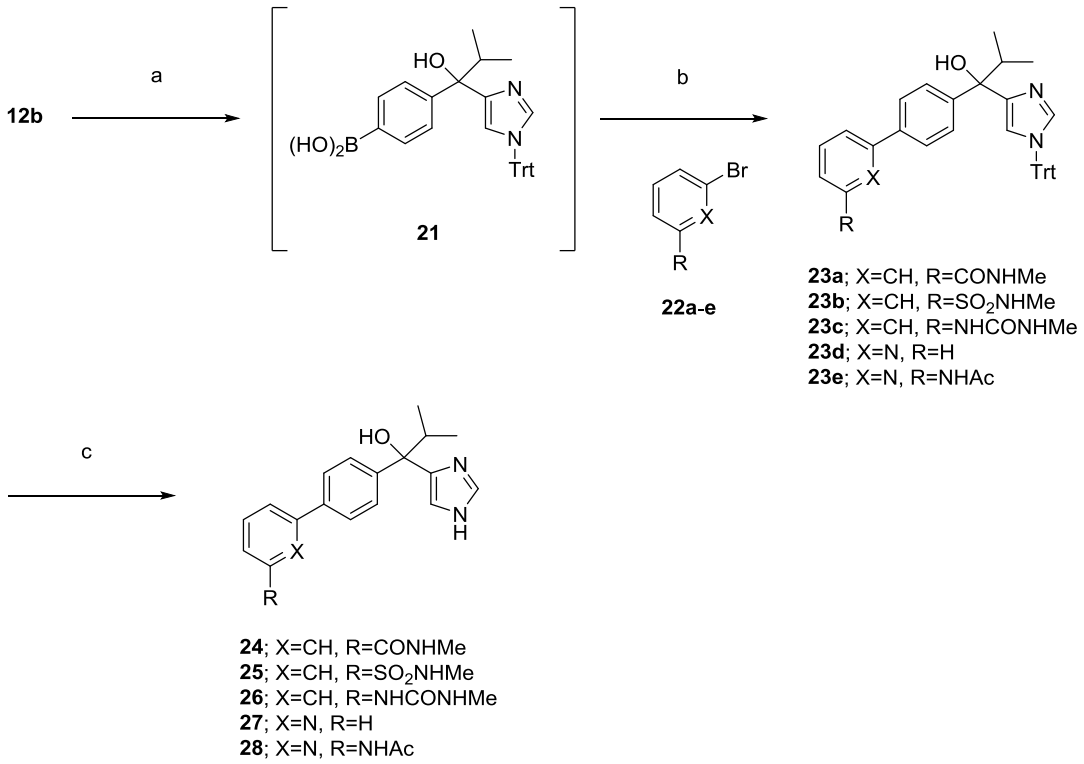
purification to give **23a–e**. Deprotection of **23a–e** was performed by the same procedure used for **15** to give low-to-moderate yields of compounds **24–28**.



Scheme 1. Reagents and conditions: (a) (1) **4a–5b**, *n*-BuLi, THF, −78°C, then (2) **6**, −78°C to rt, 39–82%.

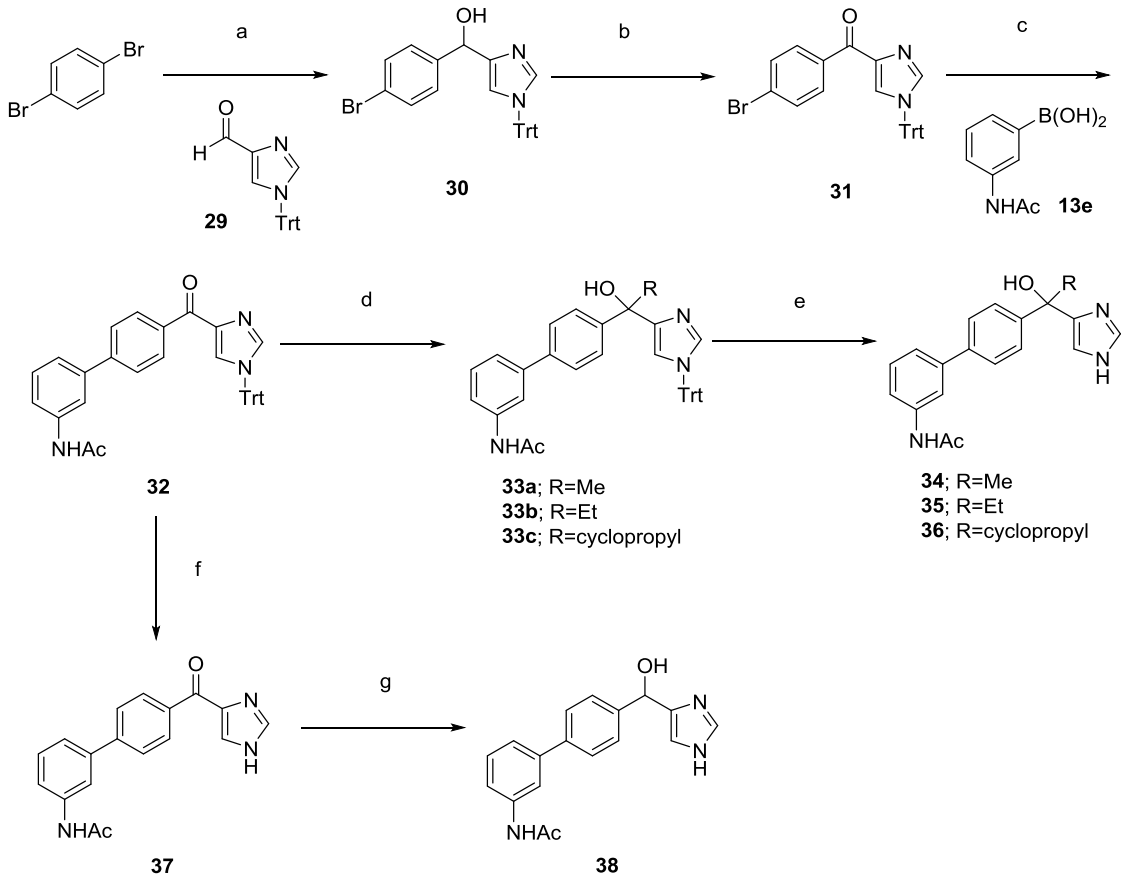


Scheme 2. Reagents and conditions: (a) (1) *n*-BuLi, Et_2O, −78°C, then (2) **11**, −78 to −50°C, 82–90%; (b) substituted phenylboronic acid **13a–d**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, reflux, 32–96%; (c) pyridine hydrochloride, MeOH, 60°C, 21–79%.



Scheme 3. Reagents and conditions: (a) (1) *n*-BuLi; (2) trimethoxyborane ($B(OMe)_3$), −78°C to rt; (3) 1 N HCl, compound **21** was not isolated; (b) substituted arylbromide **22a–e**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, reflux, 23–72%; (c) pyridine hydrochloride, MeOH, 60°C, 26–61%.

The synthesis of analogs of **19**, 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 **29**[51] was performed in the same manner as for **12a**, followed by oxidation of **30** with manganese dioxide (MnO_2) to give ketone **31**. The ketone **31** was then subjected to Suzuki coupling reaction to give the acetamide derivative **32**, which was treated with Grignard reagent to give good-to-moderate yields of **33a–c**. As deprotection of **33a** or **33c** 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 **33b** and found to give a good yield of the desired compound **35**. Otherwise, deprotection of the acetamide derivative **32** with pyridinium hydrochloride provided **37**, which was then subjected to reduction with sodium borohydride to give a good yield of the alcohol **38**.

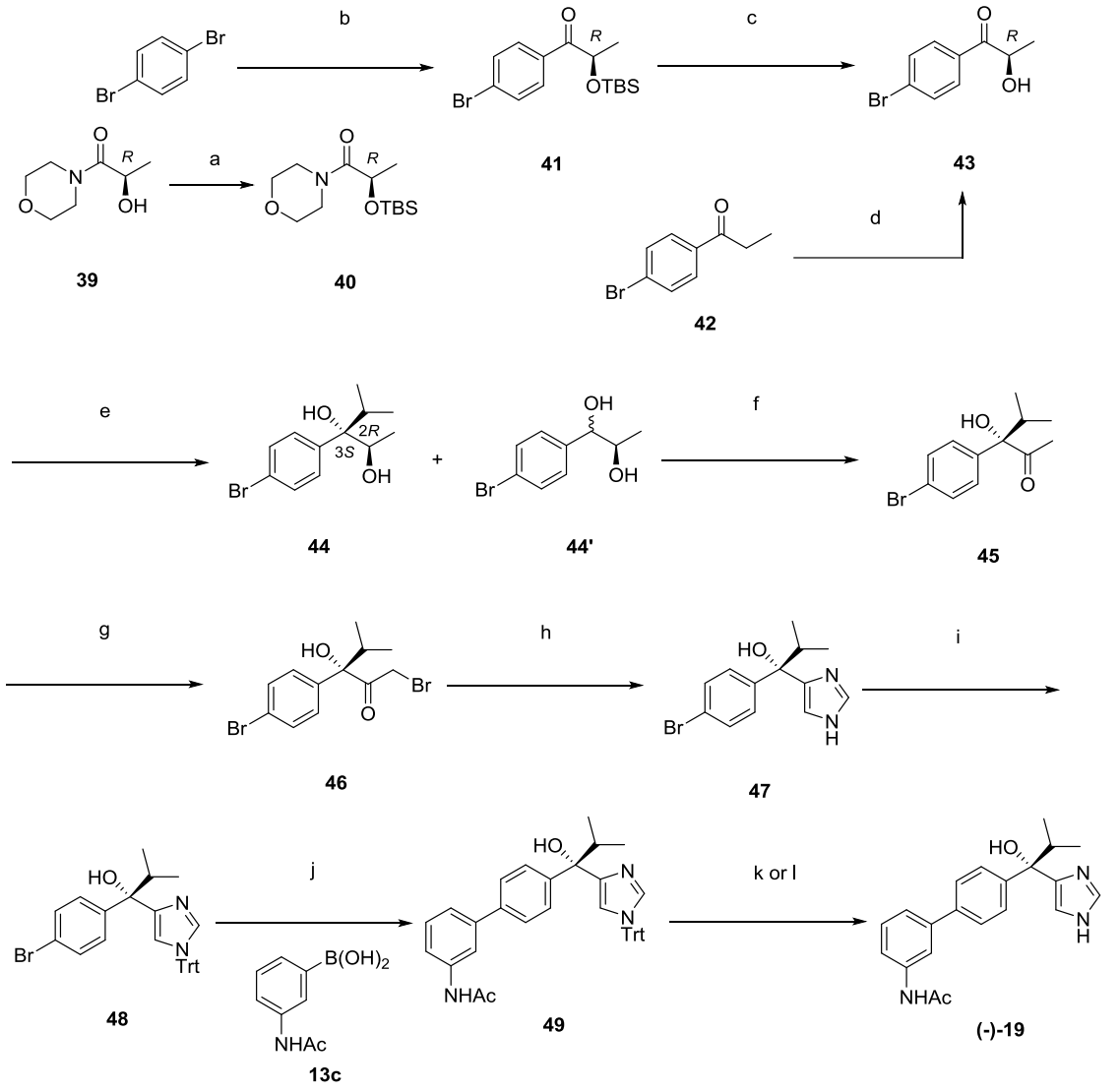


Scheme 4. Reagents and conditions: (a) (1) *n*-BuLi, THF, −78 to −50°C, then (2) **29**, 56%; (b) MnO_2, CH_2Cl_2, rt, 78%; (c) **13c**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, EtOH, reflux, 76%; (d) RMgBr, THF, 0°C, 61% to quant.; (e) For **33a, 33c**, pyridine hydrochloride, MeOH, 60°C, 39–59%, for **33b**, 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%.

2.3. Asymmetric synthesis of compound (−)-19

The synthetic route toward chiral **(−)-19** is shown in Scheme 5. The preparation of α-hydroxyketone **43** began from chiral silylether **40**, which was easily prepared from the known morpholine amide **39**[52] or achiral **42**. Chiral silylether **40** was treated with lithium species generated from 1,4-dibromobenzene and *n*-BuLi to yield **41**, followed by removal of the *tert*-butyldimethylsilyl (TBS) group with tetrabutylammonium fluoride (TBAF) to give α-hydroxyketone **43** 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 **42** gave the desired α-hydroxyketone **43** in good chemical yield with excellent ee (98% ee).



Scheme 5. Reagents and conditions: (a) TBSCl, imidazole, DMF, 0°C to rt, 98%; (b) (1) *n*-BuLi, THF, −78°C, then (2) **40**, 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% (99% ee); (j) 3-acetamidophenylboronic acid **13c**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, EtOH, reflux, 87% (99% ee);

(k) 90% formic acid, THF, reflux, 83% (92% ee); (l) H_2 (4 atm), 10% Pd/C, EtOH, 70°C, 61% (99% ee).

To construct the chiral center of compound **(−)-19**, a chelation-controlled Grignard reaction was used for the synthesis of (2*R*,3*S*)-diol **44**; compound **43** with 96% ee was treated with isopropylmagnesium bromide (*i*-PrMgBr) to give (2*R*,3*S*)-diol **44** together with some by-products, including reduction product **44'**. Isolation of **44** from the other by-products proved troublesome; therefore, optical purity of (2*R*,3*S*)-diol **44** was not determined. Swern oxidation of (2*R*,3*S*)-diol **44** gave **45**, which was then converted to bromide **46** at moderate yield. After protection of **46** with a trimethylsilyl group, imidazole ring closure was performed with formamidine acetate in saturated NH_3 solution in MeOH and THF to give **47** at good chemical yield with 90% ee. Unfortunately, the conversion of α-hydroxyketone **43** into **47** proceeded with decreased optical purity, whereas recrystallization of the *N*-tritylated imidazole **48** with 90% ee led to improved optical purity of **48**, up to 99% ee. Compound **48** was then subjected to Suzuki coupling reaction to give a good yield of the acetamide derivative **49** with 99% ee. Deprotection of compound **49** using 90% formic acid resulted in decreased enantiomeric excess; however, an alternative approach using catalytic hydrogenation of **49** was performed to give **(−)-19** without any loss of optical purity. Finally, the absolute configuration of compound **(−)-19** was confirmed to be *S* by X-ray crystallographic analysis of the precursor **48** (Figure 8).

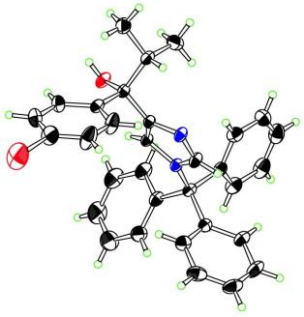


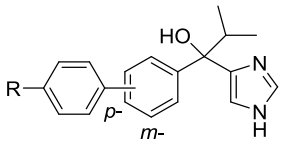
Figure 8. ORTEP drawing of **48**.

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

Results of the initial SAR study of *m*- and *p*-biphenyl compounds **7–10** and **15–18** are shown in Table 2. The unsubstituted compounds **7** and **9** 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 against CYP3A4.

Regarding the *m*-biphenyl derivatives, all 4'-substituted compounds (**8**, **15** and **16**) showed potent inhibition of rat 17,20-lyase, but insufficient selectivity between 17,20-lyase and CYP3A4 inhibition. Furthermore, the introduction of a methoxy group on to the phenyl ring led to decreased activity of human 17,20-lyase.

Table 2. Effects of meta or para substitution and R substituents on inhibition of rat and human 17,20-lyase and human CYP3A4 enzymes



Compound No.	Meta or para substitution	R	Enzyme inhibition IC_{50} (nM)			Ratio[a]
			17,20-lyase		CYP3A4	
			Rat	Human		
7	*m*-	H	15	18	1200	67
8	*m*-	OMe	10	130	2000	15
15	*m*-	F	8.3	19	2100	111
16	*m*-	Cl	19	49	2400	49
9	*p*-	H	33	33	3700	112
10	*p*-	OMe	120	54	4900	91
17	*p*-	F	28	27	5300	196
18	*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.

On the other hand, *p*-biphenyl derivatives, other than **10**, 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*)-17** 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 **17** showed potent inhibition against human 17,20-lyase with an IC_{50} value of 27 nM and both of the enantiomers of **17** are expected to have inhibitory activity against human 17,20-lyase, based on the previously reported results on compound **3** and its enantiomers.[48] The docking experiment was designed on the assumption that **(*S*)-17** should be coordinated to the heme iron *via* the nitrogen of the imidazole ring, and the proposed binding mode of **(*S*)-17** is shown in Figure 9. Results of docking studies indicated that the biphenyl ring of **(*S*)-17** 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.

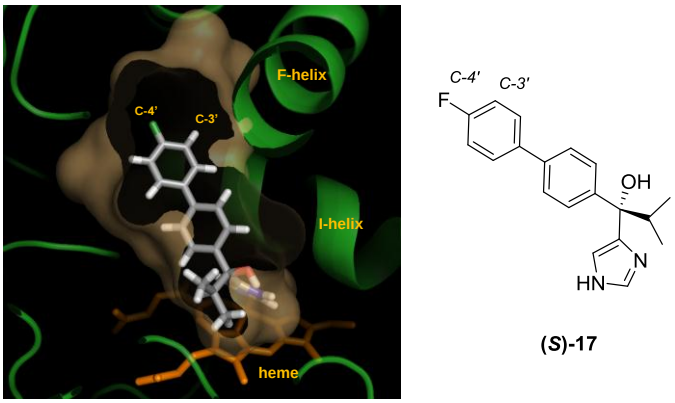


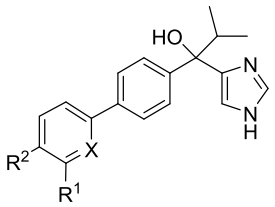
Figure 9. Docking analysis of **(*S*)-17** in the homology model of 17,20-lyase.

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 is 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 improve the selectivity for 17,20-lyase over CYP3A4 while retaining the inhibitory activity against 17,20-lyase. 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 3). As a result, compound **19** 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 similar to that observed with **18**. On the other hand, **20** 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, **27** exhibited less potent activity against human 17,20-lyase compared with **9**. In contrast, **28** 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*)-17**.

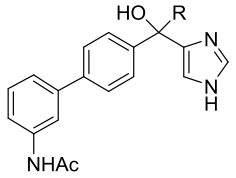
Table 3. Effects of R_1 and R_2 substituents and X on inhibition of rat and human 17,20-lyase and human CYP3A4 enzymes



Compound No.	X	R^1	R^2	Enzyme inhibition IC_{50} (nM)		
				17,20-lyase		CYP3A4
				Rat	Human	
19	C	NHAc	H	17	24	7100
20	C	H	NHAc	24	120	1000
24	C	CONHMe	H	49	44	8100
25	C	SO_2NHMe	H	71	160	3300
26	C	NHCONHMe	H	24	21	5500
27	N	H	H	210	150	5200
28	N	NHAc	H	53	36	>10000

The effects of substituents at the linker position between the biphenyl and imidazole rings are summarized in Table 4. When the isopropyl (*i*-Pr) group of **19** 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 **19** with hydrogen decreased the inhibitory activity against human 17,20-lyase. These results suggest that the introduction of a small alkyl group into the linker position was necessary to show inhibitory activity against human 17,20-lyase, and that the *i*-Pr group gives optimal potency.

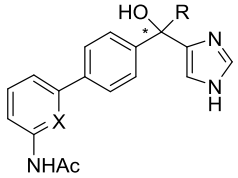
Table 4. Effects of R substituents on inhibition of rat and human 17,20-lyase and human CYP3A4 enzymes



Compound No.	R	Enzyme inhibition IC_{50} (nM)		
		17,20-lyase		CYP3A4
		Rat	Human	
19	*i*-Pr	17	24	7100
34	Me	62	38	>10,000
35	Et	25	40	>10,000
36	cyclo-Pr	81	45	5500
38	H	320	77	>10,000

Finally, we selected compounds **19**, **28**, and **35** 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 5 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.

Table 5. Inhibitory effects of **(±)-19**, **(±)-28** and **(±)-35** enantiomers on rat and human 17,20-lyase and human CYP3A4 enzymes



Compound No.	X	R	Enzyme inhibition IC_{50} (nM)		
			17,20-lyase		CYP3A4
			Rat	Human	
(−)-19	C	*i*-Pr	14	26	>10,000
(+)-19	C	*i*-Pr	770	340	6700
(−)-28	N	*i*-Pr	33	26	>10,000
(+)-28	N	*i*-Pr	>1000	92	>10,000
(−)-35	C	Et	19	22	>10,000
(+)-35	C	Et	450	240	>10,000

2.5. *In vivo* efficacy on (-)-19

Among synthesized inhibitors, the active enantiomer **(−)-19**, 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 6, single oral doses of **(−)-19** 3 mg/kg significantly decreased both serum testosterone and DHEA concentrations in male cynomolgus monkeys. These biological results indicate that **(−)-19** might be useful for the treatment of both hormone-dependent and castration-resistant prostate cancer.

Table 6. *In vivo* effects of ***S*-(−)-19** on serum testosterone and DHEA levels after single oral dosing (3 mg/kg) in monkeys

Compound No.	% 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*-(−)-19** (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).

2.6. Conclusions

The scaffold hopping approach successfully led to the discovery of novel biphenylylmethylimidazole derivatives as a new class of 17,20-lyase inhibitors. On the basis of molecular modeling, compounds **19**, **28** and **35**, 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 **(−)-19**, **(−)-28** and **(−)-35**, 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, **(−)-19** significantly reduced both serum testosterone and DHEA concentrations in a monkey model. Additionally, asymmetric synthesis of the active enantiomer **(−)-19** was also achieved *via* a chiral intermediate using a diastereoselective Grignard reaction.

3. Synthetic study on naphthylmethyimidazole derivatives part-I

3.1. Molecular design

As described in the section **2.1.**, compound ***S*-3** was found to have an issue on CYP3A4 inhibition for further development, and a scaffold hopping approach to improve the selectivity of ***S*-3** between 17,20-lyase and CYP3A4 by replacement of the naphthalene ring with a biphenyl ring was successfully investigated to discover biphenylylmethyl derivatives. In the following section, another approach to improve the selectivity between 17,20-lyase and CYP3A4 for ***S*-3** will be described and discussed.

Our previous efforts on this series of compounds revealed that the introduction of a small alkoxy group, such as methoxy or ethoxy group, at the 6-position of the naphthalene ring of naphthylmethyimidazole derivatives was well tolerated in terms of *in vitro* activity. Moreover, docking studies of ***S*-3** using a homology model for human 17,20-lyase suggested that the methoxy group at the 6-position on the naphthalene ring might form a hydrogen bond with threonine 101 (Thr101) in the active site of 17,20-lyase.

Based on these observations, one possible approach to optimize the substituent at the 6-position on the naphthalene ring was proposed and with the aim of improving the selectivity for 17,20-lyase over CYP3A4, introduction of a hydrophilic substituent at the 6-position of the naphthalene ring was initially designed and examined. Additionally, further modifications, including SAR studies at the 5-and 7-position on the naphthalene ring and ring cyclization, were also investigated, as shown in Figure 10.

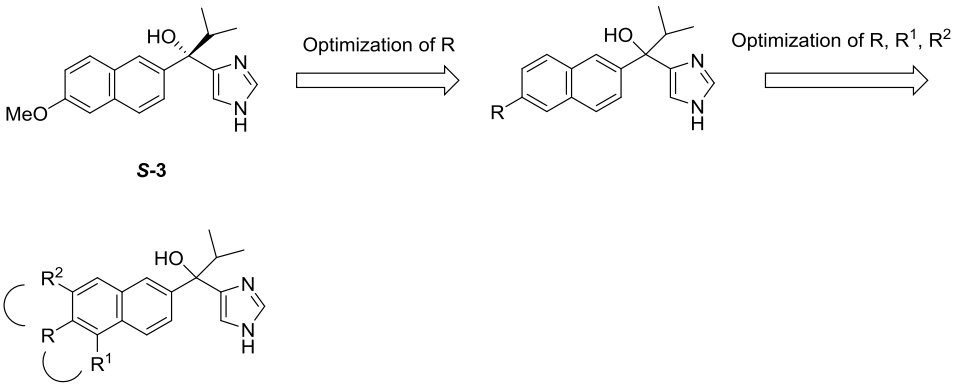
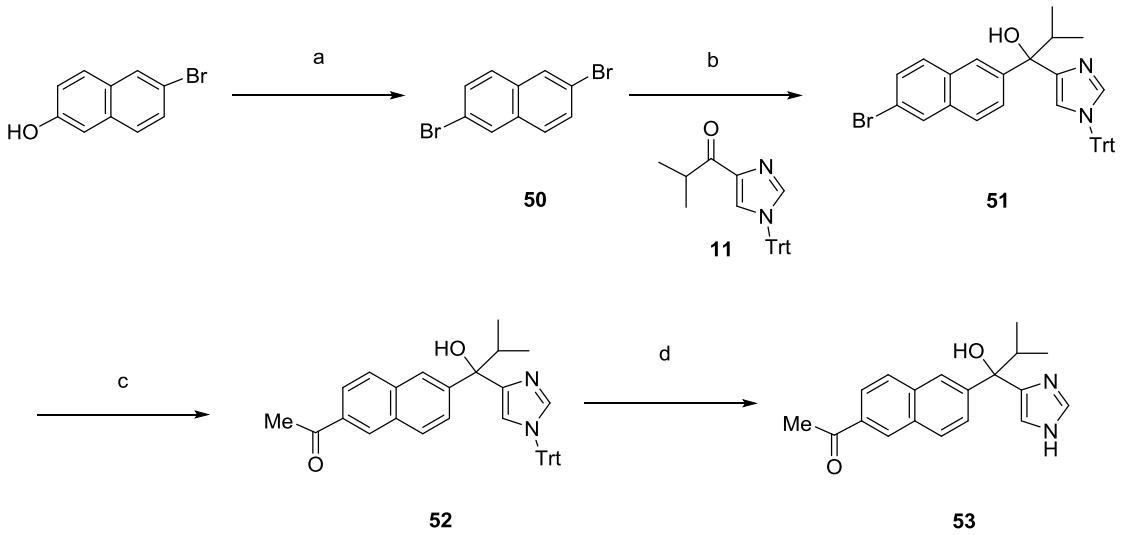


Figure 10. Molecular design of novel 17,20-lyase inhibitors.

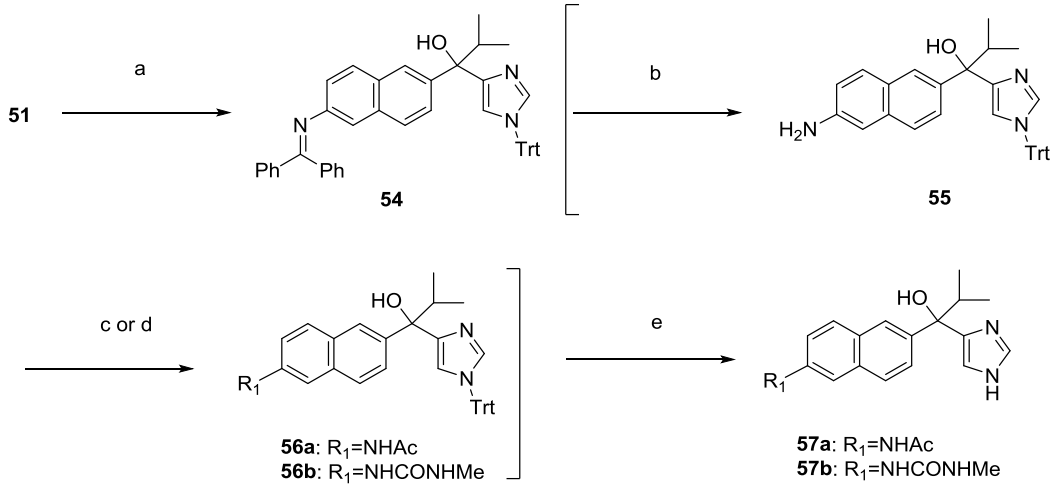
3.2. Chemistry

The synthesis of ketone **53** is outlined in Scheme 6. As reported previously,[53] conversion of 6-bromo-2-naphthol to dibromide **50** was achieved by the treatment with triphenylphosphine (PPh_3) and bromine at 70–300°C. Treating dibromide **50** with a sub-stoichiometric amount of *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF) followed by the addition of ketone **11**, gave bromide **51** in high yield. Sequential treatment of bromide **51** with *n*-BuLi generated the lithium dianion, to which Weinreb's amide was added at −78°C to give a moderate yield of ketone **52**. Finally, removal of the trityl group with pyridine hydrochloride in methanol (MeOH) provided the targeted ketone **53**.



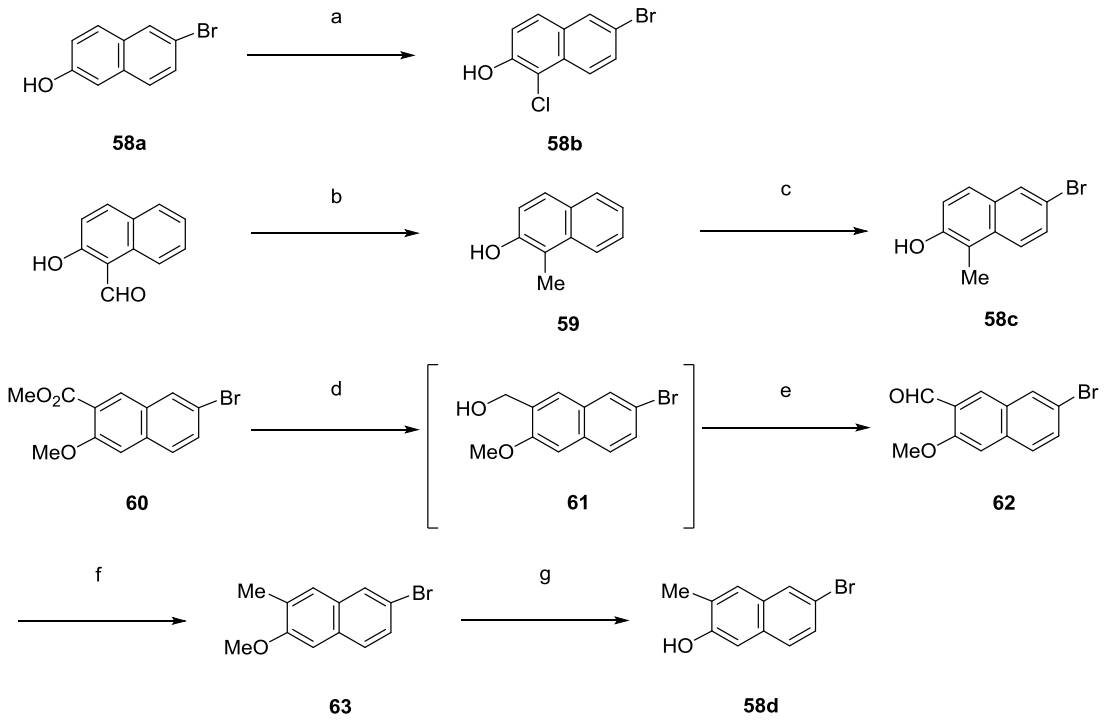
Scheme 6. Reagents and conditions: (a) (1) PPh_3, Br_2, CH_3CN, 70°C, then 300°C, 29%; (b) (1) *n*-BuLi, THF, −50°C; (2) **11**, THF, −50°C, 93%; (c) (1) *n*-BuLi, THF, −70°C; (2) *N*-methoxy-*N*-methylacetamide, THF, −70°C, 54%; (d) pyridine hydrochloride, MeOH, $CHCl_3$, 60°C, 81%.

The syntheses of **57a** and **57b** are shown in Scheme 7. Conversion of bromide **51** into **54** was performed by Buchwald's method using tris(dibenzylideneactone)dipalladium ($Pd_2(dba)_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), sodium *tert*-butoxide (*tert*-BuONa) and benzophenonimine, to provide good yields of **54**. The resulting imine **54** was deprotected to give **55**, which was then treated with acetic anhydride or phenyl chloroformate, followed by methylamine hydrochloride to yield **56a** and **56b**, respectively. Subsequent deprotections of **56a** and **56b** were performed by treatment with pyridine hydrochloride to give **57a** and **57b**, respectively.



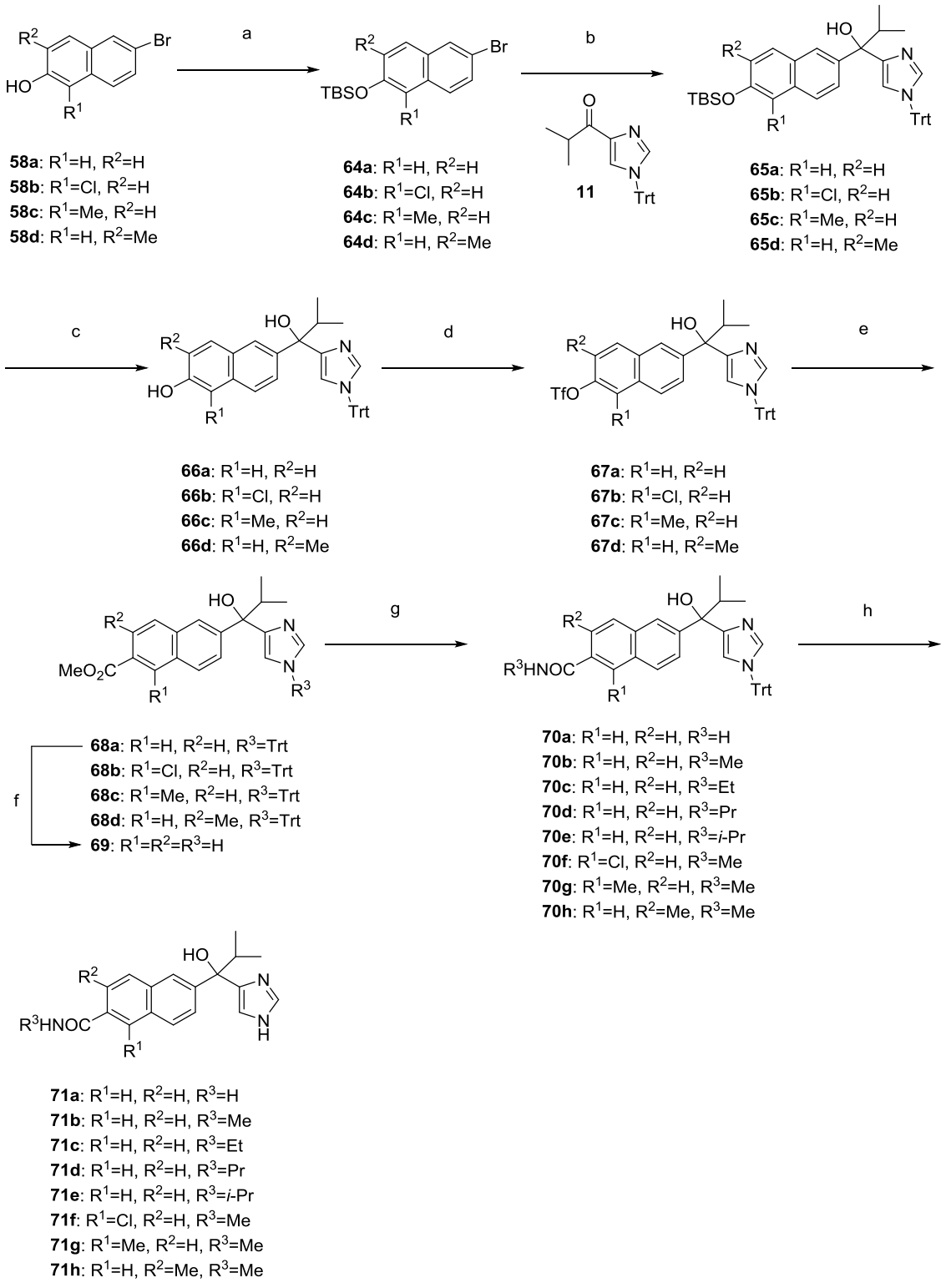
Scheme 7. Reagents and conditions: (a) benzophenoneimine, $Pd_2(dba)_2$, BINAP, *tert*-BuONa, toluene, 80°C, 87%; (b) $NH_2OH{\cdot}HCl$, AcONa, THF, MeOH, rt; (c) Ac_2O, pyridine, rt; (d) (1) phenyl chloroformate, pyridine, THF, 0°C, then (2) $MeNH_2{\cdot}HCl$, 10 N NaOH, DMSO, rt; (e) pyridine hydrochloride, MeOH, $CHCl_3$, 60°C, 31–80% in three steps.

The syntheses of the trisubstituted naphthalene derivatives **58b–d** are shown in Scheme 8. 6-Bromo-2-naphthol was chlorinated at the 1-position with sulfuryl chloride to give a moderate yield of **58b**. After Wolff–Kishner reduction of 1-formyl-2-naphthol, **59** was treated with bromine to give 6-brominated **58c** in high yield. Trimethoxyborane-catalyzed reduction of **60** with lithium borohydride gave alcohol **61**. The alcohol **61** was successively oxidized with manganese dioxide (MnO_2) to produce **62** in high yield (in two steps). After Wolff–Kishner reduction of the aldehyde **62**, conversion of the methoxy group of **63** with BBr_3 was carried out to give a high yield of phenol **58d**.



Scheme 8. Reagents and conditions: (a) SO_2Cl_2, Et_2O, 0°C to rt, 51%; (b) hydrazine monohydrate, KOH, triethyleneglycol, 170–190°C, 89%; (c) Br_2, AcOH, 10–20°C, 99%; (d) $LiBH_4$, cat.$B(OMe)_3$, THF; refluxed; (e) MnO_2, CH_2Cl_2, refluxed, 94% in two steps; (f) hydrazine monohydrate, KOH, triethyleneglycol, 160–180°C, 98%; (g) BBr_3, CH_2Cl_2, −70°C to rt, 89%.

The syntheses of **69** and **71a–71h** are shown in Scheme 9. Phenols **58a–d** were protected with *tert*-butyldimethylsilyl chloride (TBSCl), the resulting silyl ethers were treated with *n*-BuLi at −78°C, followed by addition of ketone **11** to produce excellent yields of **65a–d**, respectively. Removal of the *tert*-butyldimethylsilyl (TBS) group with tetrabutylammonium fluoride (TBAF) provided phenols **66a–d**, which were allowed to react with trifluoromethansulfonic anhydride (Tf_2O) to give **67a–d**, respectively. Methoxycarbonylation of **67a–d** using palladium(II) acetate ($Pd(OAc)_2$) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) in MeOH and *N*,*N*-dimethylformamide (DMF) under CO atmosphere gave the corresponding esters, which underwent hydrolysis, followed by treatment with diphenylphosphoryl azide (DPPA) and ammonium bicarbonate or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI·HCl) and alkylamine to provide carbamoyl derivatives **70a–h** in good yield. Deprotections of **68a** and **70a–h** were performed according to a similar method as described for **53** to give the desired compounds **69** and **71a–h**, respectively.



58a: R^1=H, R^2=H
58b: R^1=Cl, R^2=H
58c: R^1=Me, R^2=H
58d: R^1=H, R^2=Me

64a: R^1=H, R^2=H
64b: R^1=Cl, R^2=H
64c: R^1=Me, R^2=H
64d: R^1=H, R^2=Me

65a: R^1=H, R^2=H
65b: R^1=Cl, R^2=H
65c: R^1=Me, R^2=H
65d: R^1=H, R^2=Me

66a: R^1=H, R^2=H
66b: R^1=Cl, R^2=H
66c: R^1=Me, R^2=H
66d: R^1=H, R^2=Me

67a: R^1=H, R^2=H
67b: R^1=Cl, R^2=H
67c: R^1=Me, R^2=H
67d: R^1=H, R^2=Me

68a: R^1=H, R^2=H, R^3=Trt
68b: R^1=Cl, R^2=H, R^3=Trt
68c: R^1=Me, R^2=H, R^3=Trt
68d: R^1=H, R^2=Me, R^3=Trt
69: R^1=R^2=R^3=H

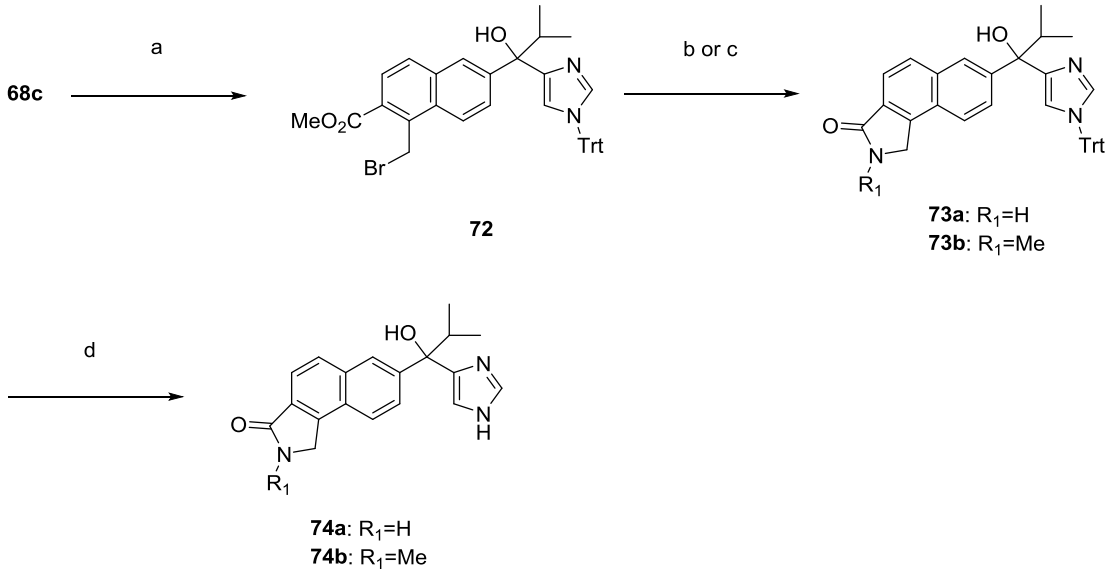
70a: R^1=H, R^2=H, R^3=H
70b: R^1=H, R^2=H, R^3=Me
70c: R^1=H, R^2=H, R^3=Et
70d: R^1=H, R^2=H, R^3=Pr
70e: R^1=H, R^2=H, R^3=*i*-Pr
70f: R^1=Cl, R^2=H, R^3=Me
70g: R^1=Me, R^2=H, R^3=Me
70h: R^1=H, R^2=Me, R^3=Me

71a: R^1=H, R^2=H, R^3=H
71b: R^1=H, R^2=H, R^3=Me
71c: R^1=H, R^2=H, R^3=Et
71d: R^1=H, R^2=H, R^3=Pr
71e: R^1=H, R^2=H, R^3=*i*-Pr
71f: R^1=Cl, R^2=H, R^3=Me
71g: R^1=Me, R^2=H, R^3=Me
71h: R^1=H, R^2=Me, R^3=Me

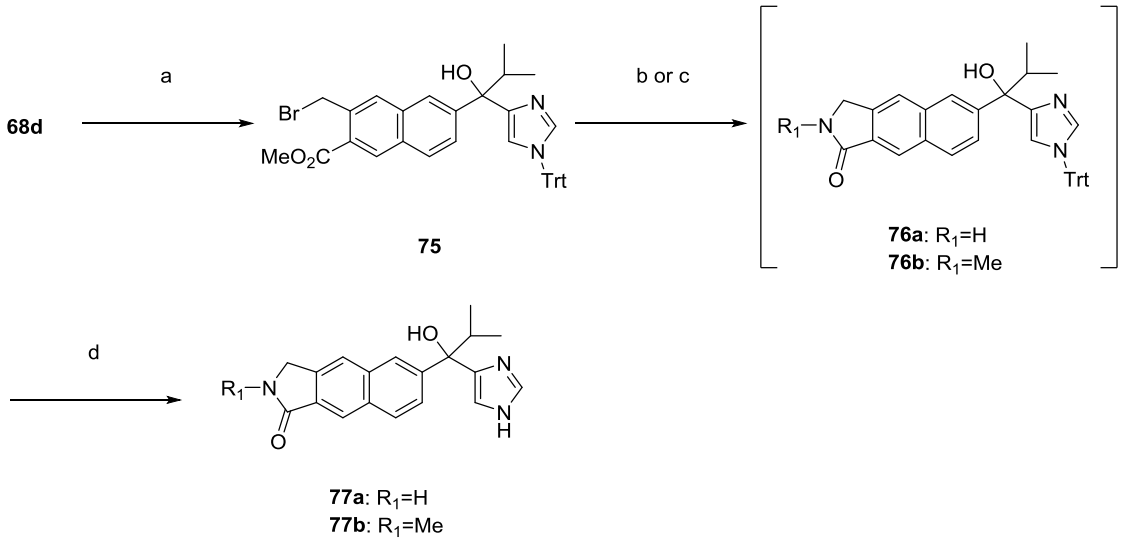
Scheme 9. Reagents and conditions: (a) TBSCl, imidazole, DMF, 0°C to rt, 85–98%; (b) (1) *n*-BuLi, THF, −70°C; (2) **11**, 84–93%; (c) TBAF, THF, 0°C to rt, 89–98%; (d) Tf_2O, pyridine, 0°C, 61–94%; (e) CO, $Pd(OAc)_2$, dppf, Et_3N, DMF, MeOH, 70°C, 81–95%; (f) pyridine hydrochloride, MeOH,

$CHCl_3$, 60°C, 94%; (g) (1) 4 N NaOH, THF, MeOH, 60°C, then (2) for **70a**, NH_4HCO_3, DPPA, Et_3N, DMF, rt, quant., for **70b–h**, R_3NH_2, EDCI·HCl, HOBt·H_2O, Et_3N, DMF, rt, 75% to quant.; (h) pyridine hydrochloride, MeOH, $CHCl_3$, 60v, 73–93%.

The syntheses of **74a** and **74b** are shown in Scheme 10. Substituted naphthalene **68c** was brominated using *N*-bromosuccinimide (NBS) and 2,2'-azobis(2-methylpropionitrile) (AIBN) to yield **72**, which was subjected to lactam cyclization to form **73a** and **73b**, respectively. Deprotections of each compound yielded the desired **74a** and **74b**. The regioisomers **77a** and **77b** were also synthesized from **68d** in a similar manner, as shown in Scheme 11.

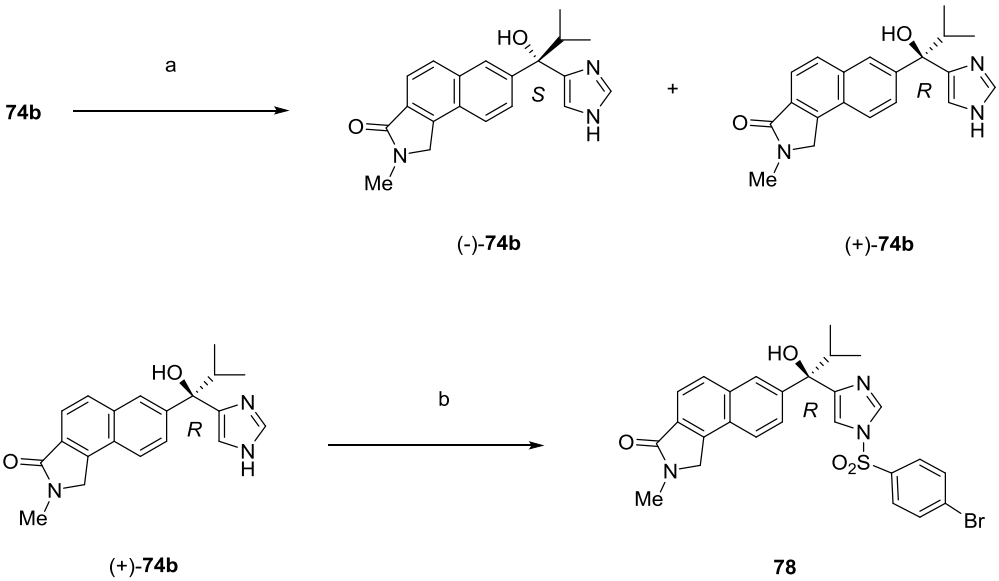


Scheme 10. Reagents and conditions: (a) NBS, AIBN, CCl_4, refluxed, 59% as a mixture of **72** and **68c** (**72**:**68c** = ca. 7:1); (b) for **73a**, saturated NH_3 in MeOH, THF, 0°C to rt, 26%; (c) for **73b**, 40% NH_2Me in MeOH, rt, quant.; (d) pyridine hydrochloride, MeOH, $CHCl_3$, 60°C, 75–90%.



Scheme 11. Reagents and conditions: (a) NBS, AIBN, CCl_4, refluxed, quant.; (b) for **76a**, saturated NH_3 in MeOH, THF, 0°C to rt; (c) for **76b**, 40% NH_2Me in MeOH, rt; (d) pyridine hydrochloride, MeOH, $CHCl_3$, 60°C, 22–64% in two steps.

To examine the stereochemical requirement at the chiral centers of these inhibitors, optical resolutions of **74a** and **74b** into **(−)-74a** and **(+)-74a**, and **(−)-74b** and **(+)-74b**, respectively, were performed using preparative HPLC with a Chiralpak AD column. Additionally, as shown in Scheme 12, **(+)-74b** was converted to the 4-bromobenzenesulfonyl derivative **78** and the absolute configuration of **(+)-74b** was confirmed to be *R* by X-ray crystallographic analysis of **78**, as shown in Figure 11.



Scheme 12. Reagents and conditions: (a) optical resolution using preparative HPLC on a Chiralpak AD column; (b) 4-bromobenzenesulfonyl chloride, Et_3N, DMF, rt, 88%.

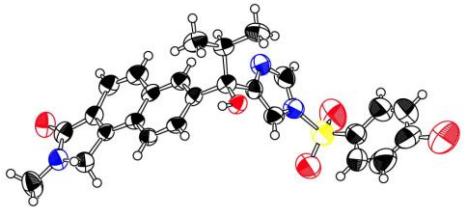
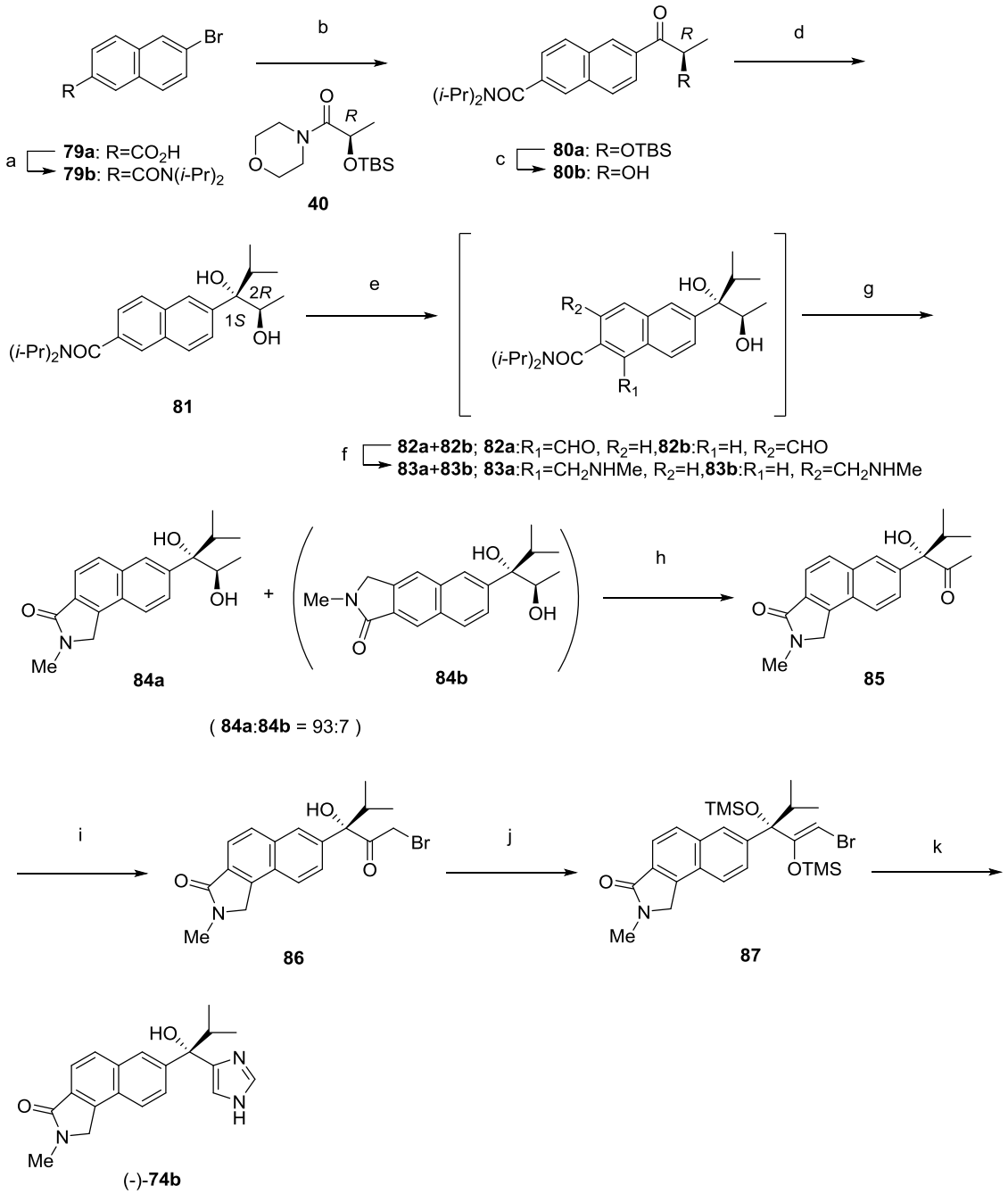


Figure 11. ORTEP drawing of **78**.

3.3. Asymmetric synthesis of compound (−)-74b

The asymmetric synthesis of **(−)-74b**, which represents the promising *in vitro* and *in vivo* profiles in the following sections **3.3.** through **3.8.**, is shown in Scheme 13. Diastereoselective Grignard reactions are versatile and effective methods for providing chiral tertiary alcohols.[54-56] Our group has previously reported the application of this method to substrates with an α-hydroxy ketone and established effective methods to synthesize chiral hydroxymethylimidazole derivatives utilizing diastereoselective Grignard reactions.[57, 58] To construct the chiral center of **(−)-74b**, we used our previously reported method using α-hydroxy ketone **80b**. The key intermediate **80b** was easily prepared from the known morpholine amide **40**.[52] The synthesized **40** was treated with lithium species generated from **79b** and *n*-BuLi to give **80a**, which was followed by deprotection of the TBS group with TBAF to afford moderate yield of the desired **80b**.



Scheme 13. Reagents and conditions: (a) (1) $SOCl_2$, DMF, THF, 60°C; (2) diisopropylamine, Et_3N, THF, 0°C –rt; 88%; (b) (1) *n*-BuLi, toluene, THF, −70°C; (2) **40**, THF, −78°C; (c) TBAF, THF, −10 to 0°C, 58% from **40**; (d) isopropylmagnesium bromide, THF, −10 to 0°C, 54%; (e) *n*-BuLi, TMEDA, DMF, THF, −70°C; (f) 2 M $MeNH_2$ in THF, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt; (g) LDA, THF, −70 to −10°C, 42% as a mixture of **84a** and **84b**; (h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −70 to −20°C, 33%; (i) pyridinium bromide perbromide, THF, 0°C to rt; (j)

N,*O*-bis(trimethylsilyl)acetamide, cat. TBAF, DMF, rt, 54% from **85**; (k) formamidine acetate, saturated NH_3 in MeOH, THF, −15°C to rt, 54%, >99% ee.

Treatment of **80b** with isopropylmagnesium bromide gave the crude (1*S*,2*R*)-diol **81** in a diastereoselective manner together with some by-products, followed by crystallization to give **81** with 95% purity; this was used without further purification in the next step. *Ortho*-lithiation of **81** followed by the addition of DMF gave a mixture of **82a** and **82b** (**82a**:**82b** = ca. 6:1), which was then treated with methylamine under reductive amination conditions to yield a mixture of **83a** and **83b**. Subsequent internal cyclization of a mixture of **83a** and **83b** using lithium diisopropylamide (LDA), followed by recrystallization gave a mixture of the regioisomers such as **84a** and **84b** (**84a**:**84b** = 93:7) in moderate yield. Swern oxidation of a mixture of **84a** and **84b**, and subsequent recrystallization of the product gave **85** with >99% purity, which was then subjected to the α-bromination condition using pyridinium bromide perbromide to give α-bromoketone **86**.

Since the direct conversion from **86** to **(−)-74b** gave insufficient yield of **(−)-74b** with 2% (not shown in Scheme 8), imidazole ring closure was performed after protection of **86** with a trimethylsilyl group by *N*,*O*-bis(trimethylsilyl)acetamide. The obtained **87** was then subjected to the reaction conditions using formamidine acetate in saturated NH_3 solution, shown in Scheme 8 to give **(−)-74b** in moderate chemical yield with excellent ee (>99%ee). In summary, an 11-step method was developed for asymmetric synthesis of the selected **(−)-74b** from 6-bromo-2-naphthoic acid **79a** using the diastereoselective Grignard reaction as a key step to construct the chiral center of **(−)-74b**.

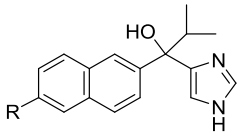
3.4. Structure–activity relationships (SARs) for 17,20-lyase, CYP3A4 and 11-hydroxylase

As previously described,[48] we have shown that the substituents at the 6-position of the naphthalene ring are likely to have an important role in hydrogen bond formation with Thr101 in 17,20-lyase. Therefore, a number of modifications to optimize the substituent at the 6-position of the naphthalene ring were investigated.

The results of a SAR study on replacement of the substituent at the 6-position of the naphthalene ring are shown in Table 7. On the basis of a docking study of ***S*-3**, hydrogen bond acceptors were examined as replacements for the methoxy group of compound ***S*-3**. Although replacing the methoxy group (***S*-3**) with an acetyl group (**53**) or a methoxycarbonyl group (**69**) had little effect on potency against human 17,20-lyase with slightly improved selectivity between human 17,20-lyase and CYP3A4, replacing the methoxy group (***S*-3**) with an acetamide group (**57a**) or a methylureido group (**57b**) led to slightly decreased inhibitory activity against human 17,20-lyase without improved selectivity between human 17,20-lyase and CYP3A4. Replacement of the methoxy group (***S*-3**) with a methylcarbamoyl group (**71b**), on the other hand, resulted in both increased inhibitory activity

against human 17,20-lyase and a promising improvement in selectivity between the two enzymes. These results indicate that the methylcarbamoyl group on the naphthalene ring is optimal in terms of both inhibition of 17,20-lyase and selectivity between 17,20-lyase and CYP3A4.

Table 7. Effect of R substituent on inhibition of rat and human 17,20-lyase and human CYP3A4

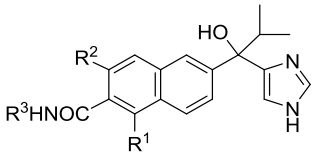


Compound No.	R	Enzyme inhibition IC_{50} (nM)			Ratio[a]
		17,20-lyase		CYP3A4	
		Rat	Human		
S-3	OMe	21	28	<1000	<36
53	Ac	14	28	1400	50
57a	NHAc	29	39	<1000	<26
57b	NHCONHMe	11	36	<1000	<28
69	COOMe	43	24	1400	58
71b	CONHMe	6	16	3600	225

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

We then focused on modification of the methylcarbamoyl group and the introduction of a substituent at the 5- or 7-position of the naphthalene ring. The results are shown in Table 8. Replacement of the methylcarbamoyl group (**71b**) with a carbamoyl (**71a**) or other small alkyl carbamoyl group (**71c**, **71d** and **71e**) resulted in a 2–5-fold loss in potency against human 17,20-lyase and a 2–3-fold decrease in selectivity for human 17,20-lyase over CYP3A4. The introduction of a substituent at the 5-position of the naphthalene ring also resulted in decreased potency. For example, incorporation of a chlorine substitution (**71f**) at the 5-position resulted in a decrease in potency of more than an order of magnitude when compared with the unsubstituted **71b**. Even a relatively small methyl group (**71g**) led to marked reductions in potency against human 17,20-lyase. On the other hand, introduction of a methyl group at the 7-position of the naphthalene ring (**71h**) resulted in only a slight decrease in inhibition of human 17,20-lyase and no change in inhibition of CYP3A4 compared with **71b**. These results suggested that the methylcarbamoyl group (**71b**) was optimum in size and the bulkiness at the 5- or 7-position may have some effect on fixing the conformation of the carbamoyl group.

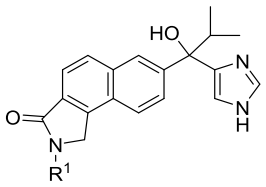
Table 8. Effect of R_1, R_2, R_3 substituents on inhibition of rat and human 17,20-lyase and human CYP3A4



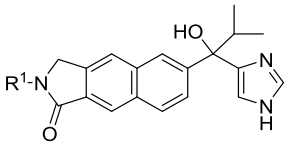
Compound No.	R^1	R^2	R^3	Enzyme inhibition IC_{50} (nM)		
				17,20-lyase		CYP3A4
				Rat	Human	
71a	H	H	H	<10	30	3700
71b	H	H	Me	6	16	3600
71c	H	H	Et	11	46	5700
71d	H	H	Pr	13	38	3400
71e	H	H	iPr	12	75	9300
71f	Cl	H	Me	91	200	>10000
71g	Me	H	Me	200	160	>10000
71h	H	Me	Me	12	39	3600

Therefore, fixing the angle of the carbamoyl group seemed to be a promising strategy for further development, and tricyclic compounds such as **74a**, **74b**, **77a** and **77b** were prepared to make the conformation of the carbonyl group more rigid. As a result, all of these tricyclic compounds had reduced inhibitory activity against CYP3A4 compared with **71b**, but maintained activity against 17,20-lyase, shown in Table 9. Among them, **74b** had the best selectivity for 17,20-lyase over CYP3A4 by more than 400-fold.

Table 9. Effect of R^1 substituent on inhibition of rat and human 17,20-lyase and human CYP3A4



74a,**b**

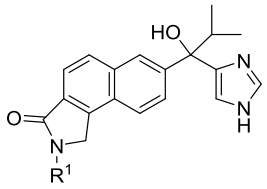


77a,**b**

Compound No.	R^1	Enzyme inhibition IC_{50} (nM)		
		17,20-lyase		CYP3A4
		Rat	Human	
74a	H	<10	18	6700
74b	Me	15	22	>10000
77a	H	42	36	>10000
77b	Me	70	19	5400

Further investigations regarding the stereochemical requirement at the chiral center of these inhibitors were performed using optical isomers such as **(−)-74a**, **(+)-74a**, **(−)-74b**, and **(+)-74b**, respectively, as shown in Table 10. As expected, each isomer exhibited markedly different potencies against 17,20-lyase, as well as selectivity between 17,20-lyase and CYP3A4. Each (−)-isomer had potent inhibitory activity against 17,20-lyase and selectivity by more than 500-fold for 17,20-lyase over CYP3A4. These data indicate that the orientation of the isopropyl group at the benzyl moiety may be critical for binding to targeted 17,20-lyase.

Table 10. Stereochemical requirement for inhibitory activities of **(±)-74a** and **(±)-74b** against rat and human 17,20-lyase, rat 11-hydroxylase and human CYP3A4 enzymes



74a,**b**

Compound No.	R^1	Enzyme inhibition IC_{50} (nM)			
		17,20-lyase		11-hydroxylase	CYP3A4
		Rat	Human		
(−)-74a	H	<10	15	13	>10000
(+)-74a	H	180	60	220	7400
(−)-74b	Me	<10	19	>1000	>10000
(+)-74b	Me	110	270	>1000	>10000

Compounds **(−)-74a**, **(+)-74a**, ***S*-(−)-74b**, and ***R*-(+)-74b** were also tested for their ability to inhibit rat 11-hydroxylase, which belongs to the CYP family of enzymes. Because this enzyme is known to play an important role in the biosynthesis of both glucocorticoid and mineralocorticoid, and high specificity for 17,20-lyase over 11-hydroxylase should be considered for further development. Compounds **(−)-74a** and **(+)-74a** showed highly potent inhibitory activity against 11-hydroxylase, while **(−)-74b** and **(+)-74b** showed low levels of 11-hydroxylase inhibition at concentrations of up to 1000 nM. In summary, selected **(−)-74b** showed promising *in vitro* profiles such as potent inhibitory activity against 17,20-lyase and excellent selectivity for the inhibition of 17,20-lyase over 11-hydroxylase and CYP3A4.

3.5. Inhibitory effect of (-)-74b on CYP isoform-specific activity

During a series of *in vitro* studies, **(−)-74b** was further investigated against other P450 enzymes such as CYP2D6, CYP2C8, and CYP2C9, which have been identified as important P450 enzymes involved in drug metabolism.[59-62] As shown in Table 11, **(−)-74b** demonstrated specific inhibition of CYP2C9 versus CYP2C8, CYP2D6, and CYP3A4; however, it also showed good selectivity (>1000-fold) for inhibition of human 17,20-lyase over CYP2C8, CYP2D6 and CYP3A4.

Table 11. Inhibitory effect of ***S*-(−)-74b** on marker enzyme activities in microsomes expressing human CYP isoforms.

Compound No.	Enzyme inhibition IC_{50} (nM)					
	17,20-lyase		Human CYP isoforms			
	Rat	Human	CYP2C8	CYP2C9	CYP2D6	CYP3A4
***S*-(−)-74b**	<10	19	28000	<3000	>30000	27000

3.6. Docking experiments

The docking of **(−)-74b** was studied using a homology model of 17,20-lyase. In the docking experiment it was postulated that **(−)-74b** should be connected to the catalytic heme iron *via* the nitrogen of the imidazole ring moiety, and the proposed binding mode of **(−)-74b** is shown in Figure 12. Results of docking studies indicated that the tricyclic ring of **(−)-74b** occupied a hydrophobic region in the active site of the enzyme and the carbonyl moiety on the lactam ring formed a hydrogen bond with Thr101. These findings are consistent with our previous results on the docking study of ***S*-3**.[48] Furthermore, an additional hydrogen bond between the hydroxyl group at the linker position between the tricyclic and imidazole rings of **(−)-74b** with Thr306 was also observed in this model.

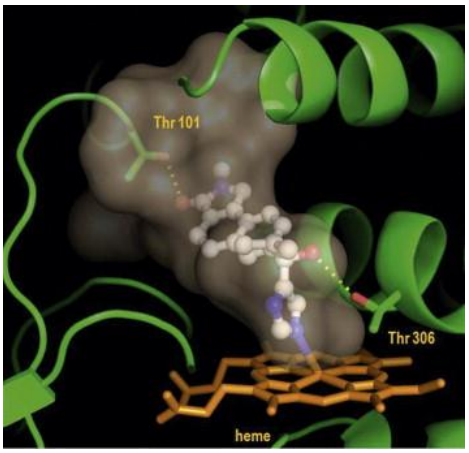


Figure 12. Docking of **(−)-74b** in the 17,20-lyase homology model.

3.7. *In vivo* efficacy on (-)-74b

Based on the *in vitro* profiles, **(−)-74b** was selected for further biological investigation. In a monkey model both testicular androgen testosterone and adrenal androgen DHEA levels were examined to evaluate *in vivo* potency of **(−)-74b**. As shown in Table 12, **(−)-74b** markedly reduced serum testosterone and DHEA levels at 4 and 8 h after administration of an oral dose (1 mg/kg) in

monkeys. These results indicate that compound **(−)-74b** could be useful for the treatment of both hormone-dependent and castration-resistant prostate cancer.

Table 12. *In vivo* effects of **(−)-74b** on serum testosterone and DHEA levels after single oral dosing (1 mg/kg) in monkeys

Compound No.	% of average 0 h values, mean ± SD			
	Serum testosterone		Serum DHEA	
	4 h	8 h	4 h	8 h
Vehicle	89.1 ± 15.6	68.5 ± 27.3	105.7 ± 4.2	38.5 ± 18.4
(−)-74b (1 mg/kg)	13.2 ± 7.5[b]	9.8 ± 4.9[a]	16.8 ± 7.0[c]	7.7 ± 4.3[a]

n = 3. [a]P <0.05 versus vehicle (Dunnett test). [b]P <0.005 versus vehicle (Dunnett test). [c]P <0.001 versus vehicle (Dunnett test).

3.8. Pharmacokinetics of (-)-74b

Pharmacokinetic studies of **(−)-74b** were performed in rats (not evaluated in monkeys). As shown in Table 13, **(−)-74b** demonstrated good pharmacokinetic profiles with large oral AUC and excellent bioavailability values; these results are encouraging for the further development of **(−)-74b** as a therapeutic agent.

Table 13. Selected pharmacokinetic data for compound **(−)-74b** after oral or intravenous (IV) administration in rats

Dosage route	Dose (mg/kg)	Tmax (h)	Cmax (μg/mL)	AUC[a] (μg h/mL)	Bioavailability (%)
Oral	10	0.42 ± 0.14	2.943 ± 0.611	7.315 ± 2.148	127.7 ± 38.1
IV	1			0.573 ± 0.030	

Mean ± SD (n = 3). [a]0–24 h.

3.9. Conclusions

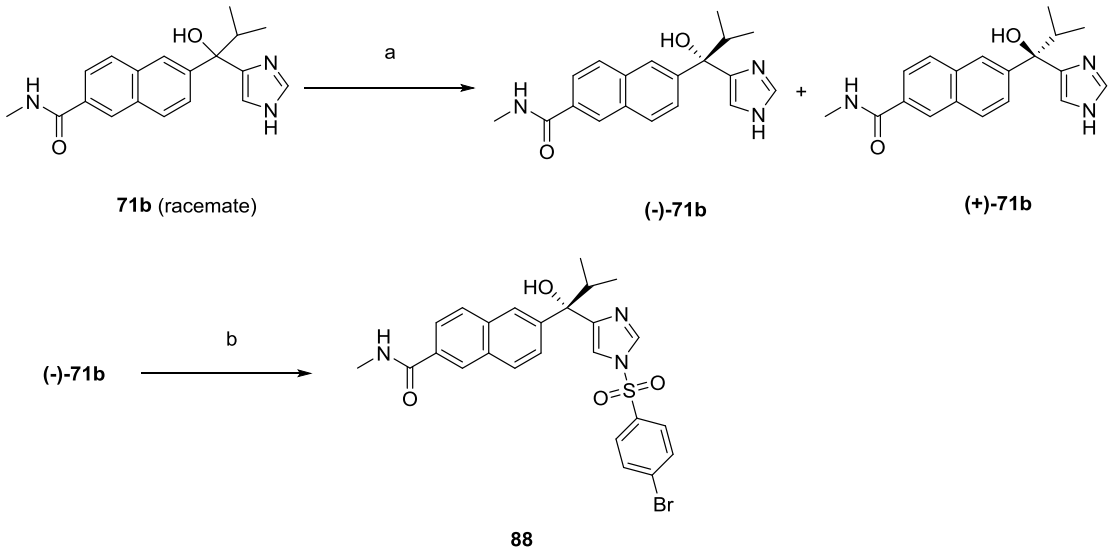
A novel series of naphthylmethylimidazole derivatives and related compounds have been investigated as selective 17,20-lyase inhibitors. Optimization of the substituent at the 6-position on the naphthalene ring was performed to yield a methylcarbamoyl derivative, which exhibited potent inhibitory activity against human 17,20-lyase and promising selectivity (>200-fold) for 17,20-lyase over CYP3A4. Further modifications aimed at fixing the orientation of the carbonyl group of the

inhibitor yielded tricyclic compounds **74a** and **74b** that were potent and selective human 17,20-lyase inhibitors. Among them **(−)-74b** showed good selectivity (>1000-fold) for the inhibition of 17,20-lyase over CYP3A4, while showing potent inhibitory activity against 17,20-lyase. Additional biological evaluation revealed that **(−)-74b** exhibited potent *in vivo* efficacy at an oral dose of 1 mg/kg in monkeys and showed favorable pharmacokinetic profiles when administered to rats. Additionally, asymmetric synthesis of **(−)-74b** was also achieved using a chiral α-hydroxy ketone. In summary, selected **(−)-74b** represents a selective 17,20-lyase inhibitor for the inhibition of 17,20-lyase over CYP3A4, with a potent *in vivo* efficacy in a monkey model.

4. Synthetic study on naphthylmethylimidazole derivatives part-II

4.1. Molecular design

As discussed in section **3.4.**, racemic **71b** showed potent inhibitory activity against 17,20-lyase with modest selectivity for the inhibition of 17,20-lyase over CYP3A4, therefore, optical resolution of **71b** was conducted using preparative HPLC on a Chiralpak AD column, as shown in Scheme 14. The absolute configuration of the obtained enantiomer **(-)-71b** was determined to be *S* by X-ray crystallographic analysis of the sulfonyl derivative **88**, as shown in Figure 13. The biological evaluation revealed that **(-)-71b** showed potent human 17,20-lyase inhibition with an IC_{50} value of 5.5 nM, along with relatively potent CYP3A4 inhibition (IC_{50} value of 7800 nM). Therefore, we continued to further modify this series of compounds, with the aim of improving selectivity to 17,20-lyase over other CYP enzymes.



Scheme 14. Reagents and conditions: (a) optical resolution using preparative HPLC on a Chiralpak AD column, **(-)-71b** (>99.9% ee) and **(+)-71b** (99.8% ee), respectively; (b) 4-bromobenzenesulfonyl chloride, Et_3N, DMF, room temperature, 79%.

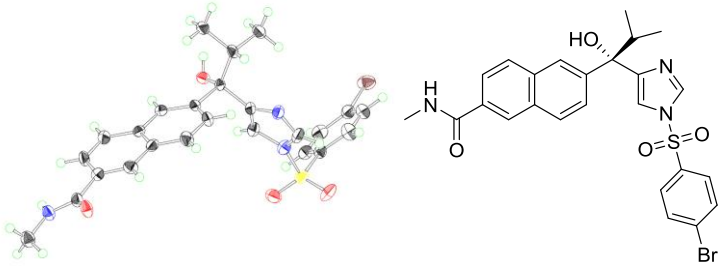


Figure 13. ORTEP drawing of **88**.

To understand the binding mode of **(-)-71b**, we conducted a docking study of the compound using a homology model of the catalytic domain of 17,20-lyase, which was constructed based on the mammalian CYP2C5 X-ray crystal structure.[63] In the docking experiment it was postulated that **(-)-71b** should be coordinated to the heme iron *via* the nitrogen of the imidazole ring moiety; the results of the docking study of **(-)-71b** are illustrated in Figure 14. The docking study suggested that: (a) **(-)-71b** formed two hydrogen bonds with the enzyme (the carbamoyl moiety of **(-)-71b** with Thr101, and the hydroxyl group of **(-)-71b** with Thr306; (b) the naphthalene ring occupied a hydrophobic region surrounded by Ala113, Phe114, Ile205, Ala302 and Ile371; and (c) the isopropyl group was located in a small hydrophobic pocket created by Val483, Phe484 and Leu485.

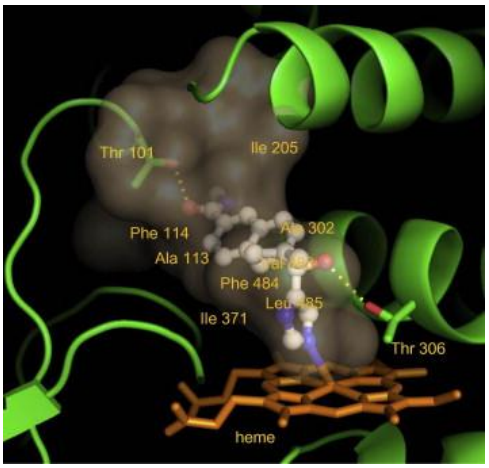


Figure 14. Docking study of **(-)-71b** in a homology model of 17,20-lyase.

In the docking experiment, both the hydrogen bonds with Thr101 and Thr306 and the coordinated bond to the heme iron seem to contribute to the *in vitro* inhibitory activity of **(-)-71b**. Therefore, further modifications were mainly focused on the conversion of the isopropyl moiety of **(-)-71b**. Due to the limited space around the isopropyl group, we developed a new class of 17,20-lyase inhibitors with a fused imidazole ring system, as shown in Figure 15.

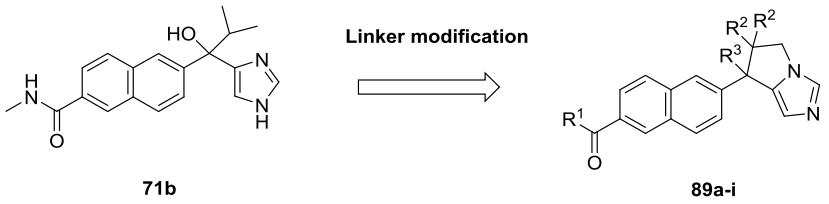
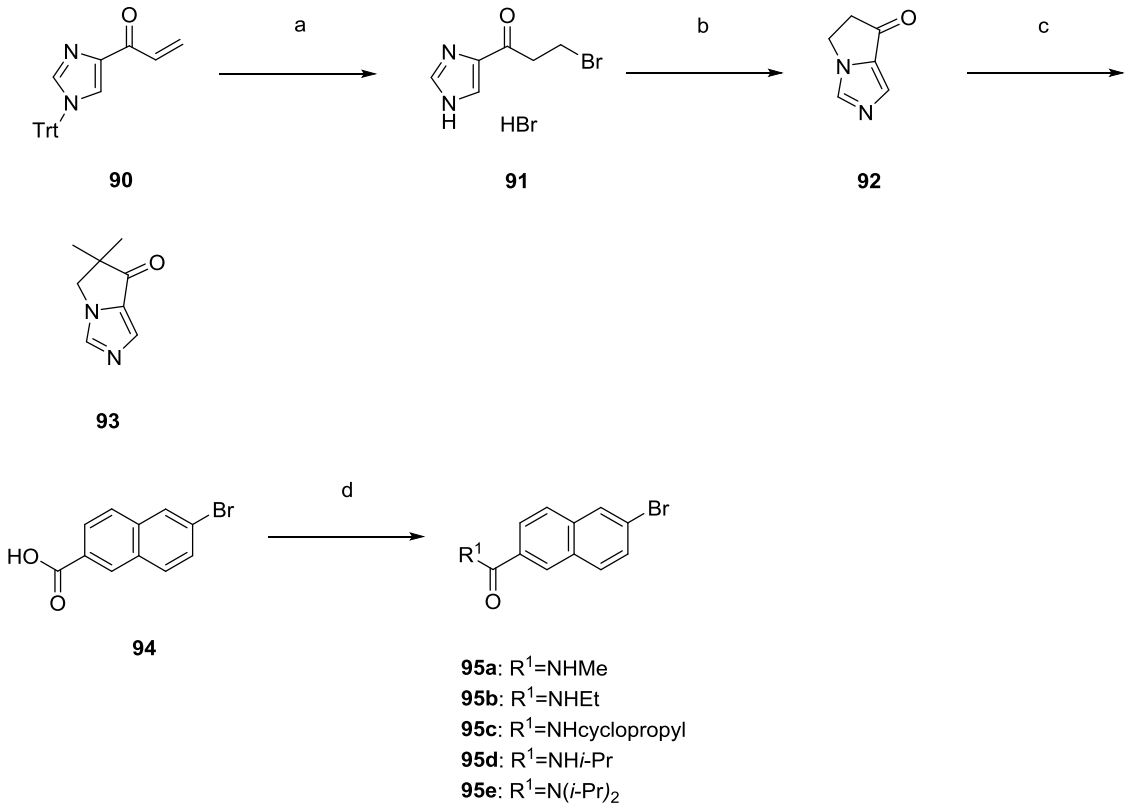


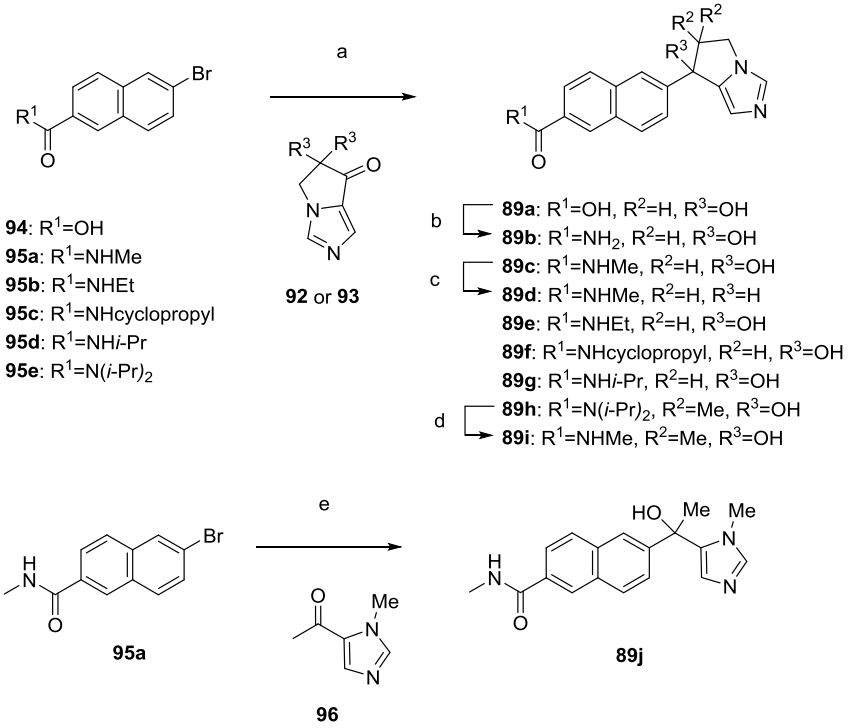
Figure 15. Molecular design of novel 17,20-lyase inhibitors.

4.2. Chemistry

The preparations of key intermediates **92**, **93** and **95a–e** are shown in Scheme 15. The synthesis of cyclic ketone **92** from compound **90** was achieved by a modification of the procedure reported by Christine *et al*.[64] Compound **90** was converted to **91**, using hydrogen bromide (HBr) in acetic acid (AcOH), and isolated as HBr salt. Subsequent cyclization of **91** was performed effectively in the presence of Et_3N, to produce **92** in moderate yield. Dimethylation of **92** using methyl iodide (MeI) afforded **93** with moderate yield. Coupling of commercially available carboxylic acid **94** with alkylamine was performed by using EDCI·HCl and 1-hydroxybenzotriazole (HOBt) or by conversion of carboxylic acid **94** into the corresponding acid chloride to give good to moderate yields of **95a–e**, respectively. The designed fused imidazole derivatives and related compounds were prepared as shown in Scheme 16. The addition of lithium species, generated from **94** and **95a–e** with *n*-butyllithium (*n*-BuLi), to ketone **92** or **93** gave moderate to low yields of the desired alcohols **89a**, **89c**, **89e–h**, respectively. Coupling of **89a** with ammonium salt of HOBt was performed in the same manner as described for **95a–d** to afford **89b** in low yield. Removal of hydroxyl group of **89c** by using Pd/C under a hydrogen atmosphere was carried out to give **89d** in good yield. Diisopropylcarbamoyl derivative **89h** was treated with lithium amides, generated from methylamine with *n*-BuLi, to give the desired **89i** in low yield. Compound **95a** was subjected to coupling reaction with **96** [65] to form **89j** in moderate yield.

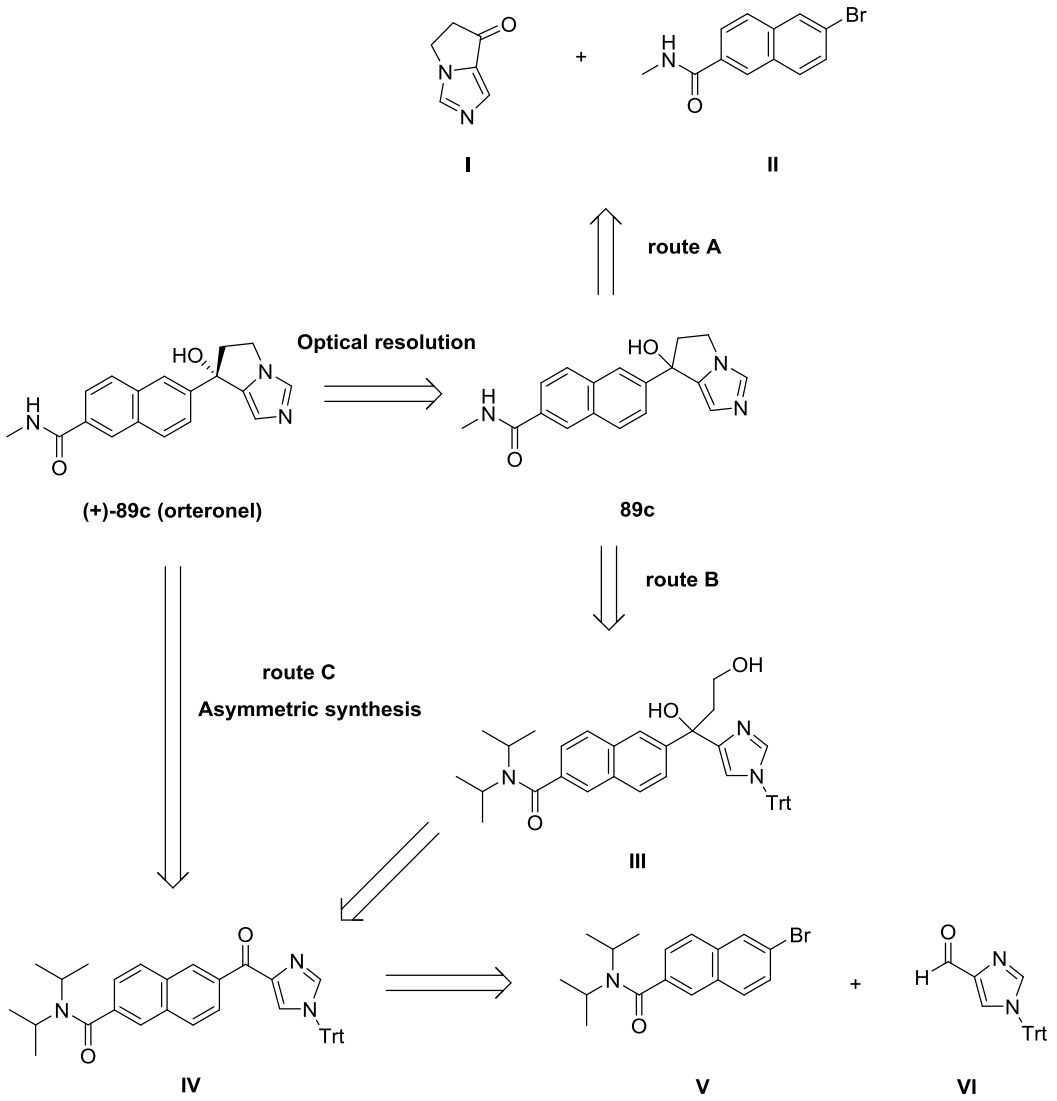


Scheme 15. Reagents and conditions: (a) 25% HBr, AcOH, 0°C to room temperature, quant.; (b) Et_3N, CH_3CN, 70°C, 61%; (c) MeI, *t*-BuOK, THF, 43%; (d) for **95a–d**, EDCI·HCl, HOBt, (*i*-Pr)$_2$NEt, R^1H, DMF, 0°C to room temperature, 60–82%; for **95e**, (i) $SOCl_2$, DMF, THF, 60°C, (ii) *N*,*N*-diisopropylamine, Et_3N, THF, 0°C to room temperature, 88%.



Scheme 16. Reagents and conditions: (a) for **89a**, (i) **94**, *n*-BuLi, THF, −100 to −80°C, (ii) **92**, THF, −70°C, 12%, for **89c**, **89e–h**, (i) **95a–e**, *n*-BuLi, THF, −70°C, (ii) **92** or **93**, THF, −70°C, 26–37%; (b) EDCI·HCl, ammonium salt of HOBt, $(i\text{-Pr})_2$NEt, DMF, 0°C to room temperature, 12%; (c) H_2 (3–4 atom), Pd/C, 1 N HCl, MeOH, room temperature, 72%; (d) *n*-BuLi, $MeNH_2$, THF, −70°C to room temperature, 33%; (e) *n*-BuLi, THF, −65 to 60°C, 38%.

We next focused on the preparation and asymmetric synthesis of **(+)-89c** as a candidate for further development. The synthetic strategy toward racemic **89c** and **(+)-89c** is outlined in Scheme 17 as a retrosynthetic analysis. Initially, we adopted two approaches, routes A and B, to prepare racemic **89c**, which could be efficiently resolved by high-performance liquid chromatography (HPLC) or diastereomeric salt formation to obtain optically pure **(+)-89c**. Route A is a convergent synthetic method *via* cyclic ketone **I**,[64] whereas route B represents a linear synthetic method *via* diol **III** and ketone **IV**. Otherwise, we developed an asymmetric synthesis of **(+)-89c** using a newly developed stereocontrolled Reformatsky reaction (route C).[66]

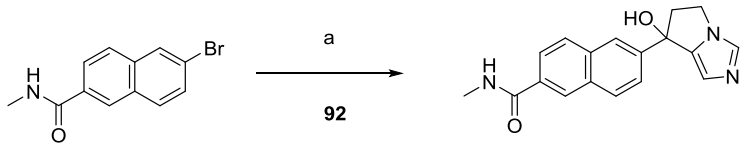


Scheme 17. Retrosynthesis of compounds **(+)-89c** and **89c**.

4.3. Improved method for the synthesis of racemic 89c and preparation of (+)-89c *via* optional resolution of racemic 89c

The improved method for the synthesis of racemic **89c** is illustrated in Scheme 18 (route A). As described above, the coupling reaction of lithium species, generated from **95a** with *n*-BuLi to ketone **92** resulted in 26% yield, therefore, the reaction condition using lithium species from **95a** and cyclic ketone **92** was optimized. As a result, the use of 1 equivalent of *o*-trifluoromethylphenyl lithium gave improved yield of desired product **89c**. That is, the addition of lithium species, generated from 2-bromobenzotrifluoride with *n*-BuLi to **95a** gave lithium salt, which was allowed to react with

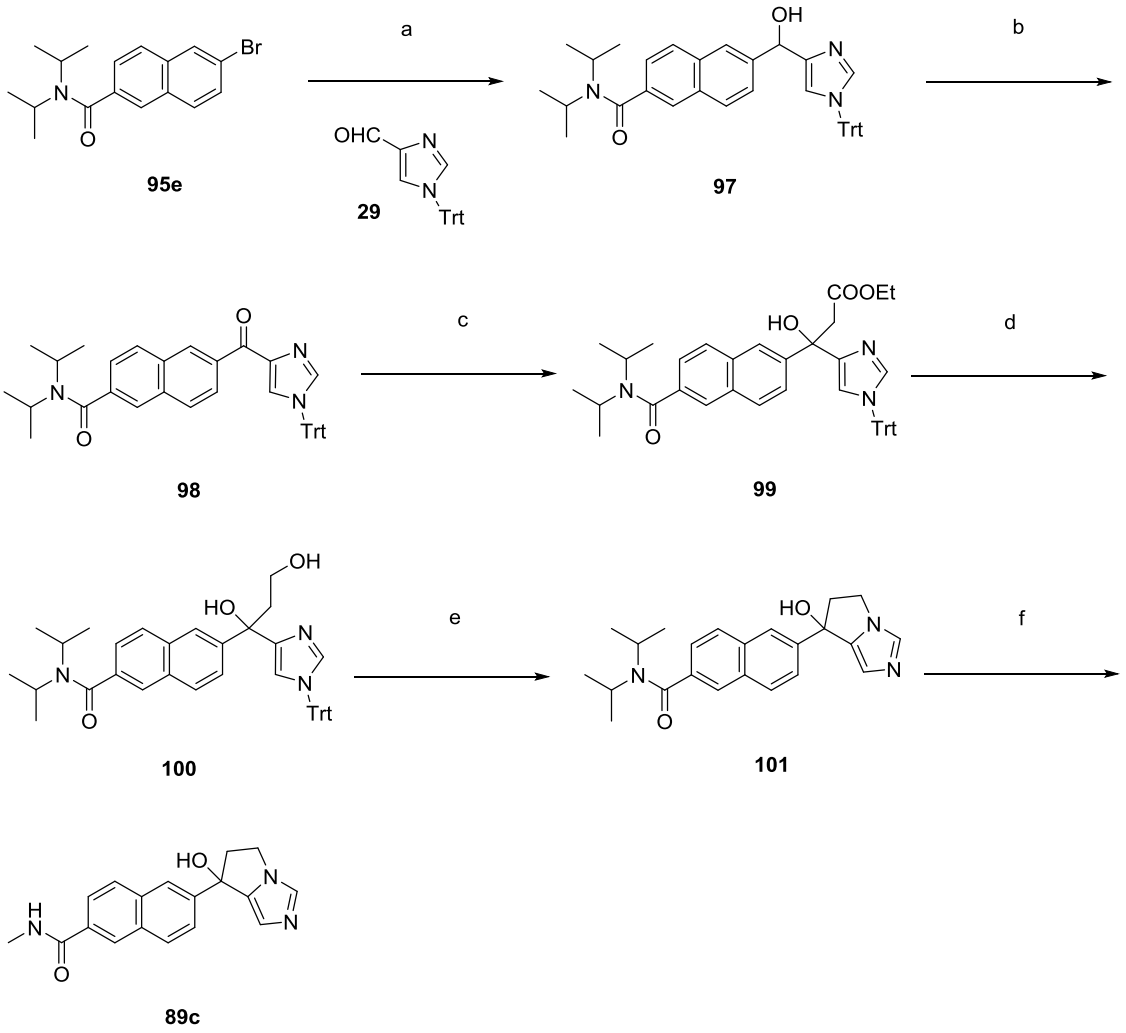
n-BuLi to afford dilithium salt in the reaction vessel. The obtained dilithium salt was then subjected to a coupling reaction with cyclic ketone **92** to produce in 45% yield of racemic **89c**.



95a **89c**

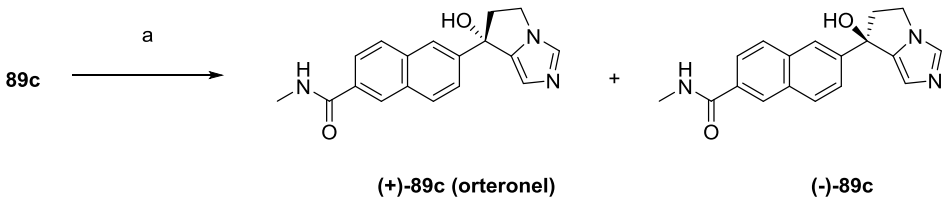
Scheme 18. Improved method for the synthesis of racemic **89c**. Reagents and conditions: (a) (i) 2-bromobenzotrifluoride, *n*-BuLi, THF, −65°C, (ii) **95a**, THF, −55°C, then (iii) *n*-BuLi, THF, −65°C, (iv) **92**, THF, −65°C, 45%.

An alternative method to synthesize racemic **89c** is shown in Scheme 19 (route B). Coupling of lithium species, generated from amide **95e** and *n*-BuLi, to aldehyde **29** gave alcohol **97**. Oxidation of the obtained alcohol **97** was conducted using manganese (IV) oxide (MnO_2) to give ketone **98** with moderate yield in two steps. Addition of lithium enolates, formed by ethyl acetate (AcOEt) in the presence of lithium diisopropylamide (LDA), to **98** gave **99**. The alcohol **99** was then reduced using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) to provide the diol **100** with good yield in two steps. The diol **100** was allowed to react with methanesulfonyl chloride (MsCl) and the resulting mesylate underwent cyclization under basic conditions to produce the cyclized compound **101** in good yield. Subsequent coupling of **101** with lithium amides, generated from methylamine ($MeNH_2$) with *n*-BuLi, gave the desired racemic **89c** in good yield.



Scheme 19. Reagents and conditions: (a) (i) *n*-BuLi, toluene/THF, −70°C, (ii) **29**, THF, −70°C; (b) MnO_2, CH_2Cl_2, room temperature, 60% in 2 steps; (c) AcOEt, LDA, THF, −70°C to −30°C; (d) Red-Al, toluene, −15°C to 0°C, 98% in 2 steps; (e) (i) MsCl, $(i\text{-Pr})_2$NEt, THF, 0–10°C, (ii) CH_3CN, 70°C, (iii) $(i\text{-Pr})_2$NEt, MeOH, CH_3CN, 70°C, 87%; (f) *n*-BuLi, $MeNH_2$, THF, −78°C to room temperature, 79%.

Successively, optical resolution of racemic **89c** obtained above was performed by preparative HPLC using a Chiralpack AD column to yield **(+)-89c** and **(−)-89c** with 99.8% ee, respectively, as shown in Scheme 20.



Scheme 20. Optical resolution of racemic **89c**. Reagents and conditions: (a) optical resolution using preparative HPLC on a Chiralpak AD column, **(+)-89c** (99.8% ee) and **(−)-89c** (99.8% ee), respectively.

4.4. Optical resolution of racemic 89c by diastereomeric salt formation with (2*S*,3*S*)-(−)-tartranilic acid

To prepare optically active **(+)-89c** by an alternative method using diastereomeric salt formation, we screened a number of optically active acid derivatives. As a result, it was found that 1 equivalent of **(+)-89c** efficiently formed poorly soluble crystals with 2 equivalent of (2*S*,3*S*)-(−)-tartranilic acid in ethanol (EtOH). In fact, recrystallization of the obtained diastereomeric salts gave optically purified (99% de) salts, which were subjected to neutralization with 1 N NaOH, followed by recrystallization to yield free **(+)-89c** with >99% ee.

4.5. X-ray crystallographic analysis of (+)-89c with (2*S*,3*S*)-(−)-tartranilic acid

To determine the absolute configuration of **(+)-89c**, the crystal structure of the diastereomeric salt of **(+)-89c** with (2*S*,3*S*)-(−)-tartranilic acid was analyzed. The crystal contained one molecule of **(+)-89c** and two molecules of (2*S*,3*S*)-(−)-tartranilic acid in the asymmetric unit. The absolute configuration of **(+)-89c** was determined to be *S* using the absolute stereochemistry of (2*S*,3*S*)-(−)-tartranilic acid as an internal reference (Figure 16).

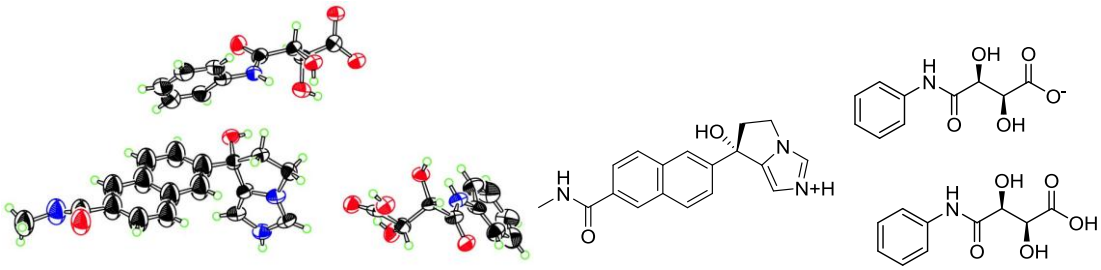
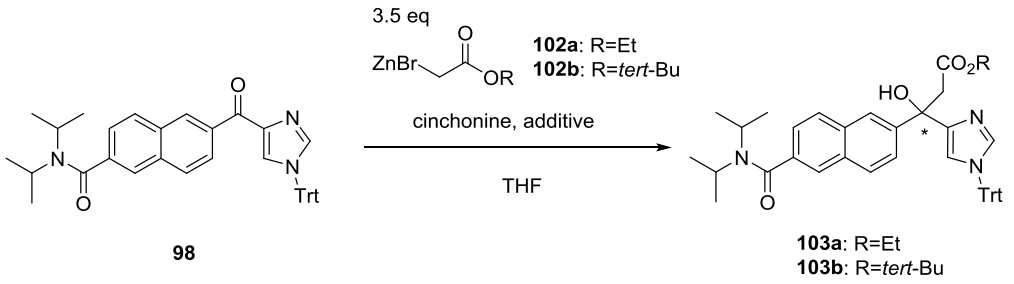


Figure 16. ORTEP drawing of **(+)-89c** with (2*S*,3*S*)-(−)-tartranilic acid.

4.6. Asymmetric synthesis of (+)-89c

To establish an efficient and practical asymmetric synthesis of **(+)-89c**, we focused on development of the coupling reaction from ketone **98** to **99**, as shown in Scheme 19, for the application of a chelation-assisted enantioselective Reformatsky reaction.[45] Asymmetric Reformatsky reactions are versatile and effective methods for providing chiral β-hydroxy esters and, to date, several asymmetric Reformatsky reactions have been reported by several groups.[67-79] In most of the reported cases, 1,2-aminoalcohols were used as chiral ligands to give high enantioselectivity in the asymmetric Reformatsky reactions. More recently, our group reported chelation-assisted enantioselective Reformatsky reactions of ketones, using cinchona alkaloids as chiral ligands.[66] We have previously analyzed a selection of chiral ligands and the effect of additives such as pyridine, as well as the effect of reaction temperature on the enantioselectivity in the Reformatsky reaction. Table 14 summarizes the selected results for the asymmetric Reformatsky reaction with ketone **98** using zinc reagents (**102a** and **102b**) generated from ethyl or *tert*-butyl bromoacetate and activated zinc. The enantioselectivity of the obtained tertiary alcohol **103a** was improved by reduction of the reaction temperature (entry 1 vs 3), the addition of an excess amount of pyridine (entry 1 vs 4) and the addition of a slight excess of cinchonine with an excess amount of pyridine (entry 4 vs 5), respectively in this reaction. Additionally, the use of Reformatsky reagent with *tert*-butyl ester (**102b**, entries 2 and 6) gave a slightly improved enantioselectivity, up to 95% ee, when compared with the corresponding reagent with ethyl ester (**102a**, entries 1 and 5) under the same reaction conditions. The chiral tertiary alcohol of **103b** with 71% ee obtained in entry 2 was successfully converted to **(+)-89c** with 69% ee as a similar manner shown in Scheme 19, and the configuration of **103b** obtained in this reaction using cinchonine as a chiral ligand was determined to be *S*.

Table 14. Reaction conditions of newly developed asymmetric Reformatsky reaction using ketone **98** and zinc reagents **102a** and **102b**



98

103a: R=Et
103b: R=*tert*-Bu

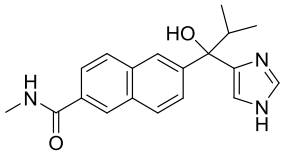
Entry	zinc reagent	Temp (°C)	Additive (eq.)	Cinchonine (eq.)	ee (%)	Yield[a] (%)
1	**102a**	0	None	1	67	Quant.
2	**102b**	0	None	1	71[b]	Quant.
3	**102a**	−42	None	1	76	97
4	**102a**	−42	Pyridine (3)	1	85	98
5[c]	**102a**	−42	Pyridine (4)	1.25	90	99
6[d]	**102b**	−42	Pyridine (4)	1.25	95 (92)[e]	Quant. (97)[e]

[a]Determined by HPLC. [b]The absolute configuration of **103b** was determined to be *S* after the conversion to **(+)-89c**. [c]4 eq. of Reformatsky reagent **102a** was used. [d]4 eq. of Reformatsky reagent **102b** was used. [e]Isolated yield and enantiomeric excess.

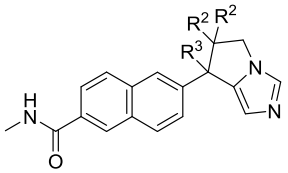
4.7. Structure–activity relationships (SARs) for 17,20-lyase, CYP3A4 and 11-hydroxylase

The impact of fused imidazole derivatives and related compound **89j** on inhibition of rat and human 17,20-lyase, 11-hydroxylase and CYP3A4 are shown in Table 15 and 16. The cyclized compound **89c** demonstrated both promising inhibitory activity against human 17,20-lyase with IC_{50} value of 38 nM and selectivity between human 17,20-lyase and the other CYPs (vs 11-hydroxylase and CYP3A4). On the contrary, *gem*-dimethyl derivatives **89i** with fused imidazole ring exhibited decreased inhibitory activity against human 17,20-lyase with lower selectivity between human 17,20-lyase and the other CYPs, compared with **89c**. The results were consistent with our previous docking experiment of **(-)-71b**, and they suggested that the bulkyness near the coordinated site should give some negative impact on inhibitory activity against 17,20-lyase. Additionally, for better understanding of excellent selectivity between human 17,20-lyase and the other CYPs of **89c**, a few analogues of **89c** were also investigated.

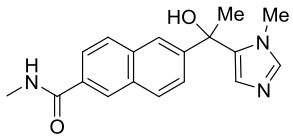
Table 15. Inhibitory effect of compounds **71b**, **89c–d**, **89i–j** on rat and human 17,20-lyase, 11-hydroxylase and CYP3A4



71



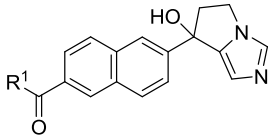
89c-d, 89i



89j

Compound No.	R^2	R^3	Enzyme inhibition IC_{50} (nM)			
			17, 20-lyase		11-hydroxylase	CYP3A4
			Rat	Human		
71b	—		6.1	16	>1000	3600
89c	H	OH	54	38	>1000	>10,000
89i	Me	OH	110	88	520	3200
89d	H	H	15	13	290	<1000
89j	—		>1000	410	>1000	6900

Table 16. Inhibitory effect of compounds **89b–c**, **89e–g** on rat and human 17,20-lyase, 11-hydroxylase and CYP3A4



89b-c, 89e-g

Compound No.	R^1	Enzyme inhibition IC_{50} (nM)			
		17, 20-lyase		11-hydroxylase	CYP3A4
		Rat	Human		
89c	NHMe	54	38	>1000	>10,000
89b	NH_2	24	29	100	>10,000
89e	NHEt	110	190	>1000	>10,000
89f	NHcyclopropyl	100	290	>1000	>10,000
89g	NH*i*-Pr	160	400	>1000	>10,000

As a result, the removal of hydroxyl group (**89d**) of **89c** led to considerably decreased selectivity between human 17,20-lyase and the other CYPs while keeping the potent inhibitory activity against

human 17,20-lyase. The cleaved derivatives (**89j**) of fused imidazole ring on **89c** was also investigated to result in both decreased inhibitory activity against 17,20-lyase and selectivity between 17,20-lyase and CYP3A4. These results indicated that both hydroxyl group and fused ring structure of **89c** may have the responsibility for its selectivity between 17,20-lyase and CYP3A4.

The effect of substitution of carbamoyl group on inhibition of rat and human 17,20-lyase, 11-hydroxylase and CYP3A4 was summarized in Table 16. Replacement of methylcarbamoyl group of **89c** with carbamoyl group (**89b**) had little effect on inhibitory activity against human 17,20-lyase and selectivity between 17,20-lyase and CYP3A4, but led to decreased selectivity between 17,20-lyase and 11-hydroxylase. Replacing the methyl group of **89c** with small alkyl groups such as ethyl (**89e**), cyclopropyl (**89f**) and *i*-propyl (**89g**) groups resulted in 5–11-fold weaker inhibitory activity against human 17,20-lyase. These results suggested that the methylcarbamoyl group (**89c**) was optimal in terms of both inhibitory activity against human 17,20-lyase and selectivity between 17,20-lyase and the other CYPs.

The enantiomers, **(+)-89c** and **(−)-89c**, both exhibited potent inhibitory activity against human 17,20-lyase and promising selectivity between human 17,20-lyase and CYP3A4, as shown in Table 17. In particular, the inhibitory effect on CYP3A4 of **(+)-89c** was hardly detectable at 10,000 nM. Therefore, **(+)-89c** was identified as a highly selective inhibitor with a greater than 500-fold selectivity between 17,20-lyase and CYP3A4. The enantiomers were also assessed for the inhibition of 11-hydroxylase, and both **(+)-89c** and **(−)-89c** exhibited low probability of inhibition against 11-hydroxylase below 1000 nM.

Table 17. Inhibitory effect of **(+)-89c** and **(−)-89c** on rat and human 17,20-lyase, 11-hydroxylase and CYP3A4

Compound No.	Enzyme inhibition IC_{50} (nM)			
	17, 20-lyase		11-hydroxylase	CYP3A4
	Rat	Human		
(+)-89c	48	19	>1000	>10,000
(−)-89c	180	48	>1000	>10,000

4.8. A preliminary study in cynomolgus monkeys

In addition to the *in vitro* studies, the ability of **(+)-89c** and **(−)-89c** to reduce serum androgen concentrations were examined in a preliminary study using cynomolgus monkeys, and in these studies both testicular androgen testosterone and adrenal androgen dehydroepiandrosterone (DHEA) levels were measured. As a result, **(+)-89c** administered orally at a dose of 1 mg/kg reduced serum testosterone and DHEA levels 8 h after administration (Table 18). In contrast, **(−)-89c** had a smaller

effect on these parameters. This difference in *in vivo* efficacy between **(+)-89c** and **(−)-89c** may reflect differences in *in vitro* inhibitory activities and the pharmacokinetic profiles of the two compounds, but additional investigations would be required to examine these possibilities. In summary, these biological evaluations revealed that **(+)-89c** had a promising profile for further development in terms of both *in vitro* inhibitory activity and *in vivo* potency with exploitable selectivity between 17,20-lyase and CYP3A4.

Table 18. *In vivo* effects of **(+)-89c** and **(−)-89c** on serum testosterone and DHEA levels after single oral dosing (1 mg/kg) in cynomolgus monkeys

Compound No.	% of average 0 h values, mean ± SD	
	Serum testosterone	Serum DHEA
	8 h	8 h
Vehicle for **(+)-89c**	101 ± 54	54 ± 25
(+)-89c (1 mg/kg)	30 ± 23	12 ± 8.0
Vehicle for **(−)-89c**	296 ± 277	25 ± 6.2
(−)-89c (1 mg/kg)	258 ± 302	91 ± 126

4.9. *In vivo* efficacy on (+)-89c

In a monkey model, both testosterone and DHEA levels were investigated at different time points (2, 5 and 10 h) after dosing to evaluate *in vivo* potency of **(+)-89c**, as shown in Table 19. When given orally to monkeys at a dose of 1 mg/kg, **(+)-89c** markedly reduced serum testosterone and DHEA at 5 h after administration. This finding suggested that **(+)-89c** should be useful for the clinical treatment of both hormone-dependent prostate cancer and CRPC.

Table 19. *In vivo* effects of **(+)-89c** on serum testosterone and DHEA levels after single oral dosing (1 mg/kg) in cynomolgus monkeys

Compound No.	% of pre-treatment average [a], mean ± SD					
	Serum testosterone			Serum DHEA		
	2 h	5 h	10 h	2 h	5 h	10 h
Vehicle	90.0 ± 16.6	63.0 ± 19.2	269.8 ± 94.5	97.9 ± 22.3	88.6 ± 4.4	7.2 ± 0.99
(+)-89c (1 mg/kg)	75.9 ± 50.0	14.2 ± 3.2	55.6 ± 18.7	61.1 ± 15.1	32.8 ± 11.1	7.6 ± 1.8

[a] Mean serum testosterone and DHEA levels on three consecutive days prior to treatment.

4.10. Inhibitory effect of (+)-89c on CYP isoform-specific activity

In a series of *in vitro* studies, the possible inhibitory effect of the selected compound **(+)-89c** on CYP-specific activities was investigated using microsomes expressing human CYP isoforms. As shown in Table 20, **(+)-89c** inhibited the specific activities of CYP2C19; however, the IC_{50} values for all the CYP-specific activities were greater than 10,000 nM. Inhibitory effects on CYP2A6, CYP2B6 and CYP3A4 were hardly detectable with IC_{50} values of up to 30,000 nM. Compound **(+)-89c** was shown to exhibit greater inhibitory effects on 17,20-lyase compared with the other CYP isoforms, thus indicating that **(+)-89c** is a selective 17,20-lyase inhibitor.

Table 20. Inhibitory effect of **(+)-89c** on human 17,20-lyase (CYP17A1) and marker enzyme activities of microsomes expressing human CYP isoforms

	Enzyme inhibition IC_{50} (nM)									
	CYP isoforms									
17A1 (17,20-lyase)	1A2	2A6	2B6	2C8	2C9 (Arg)	2C9 (Cys)	2C19	2D6	2E1	3A4
19	28,000	>30,000	>30,000	>30,000	>30,000	>30,000	14,000	>30,000	>30,000	>30,000

Marker enzyme activities are as follows; CYP1A2: 7-ethoxyresorufin O-deethylation; CYP2A6: coumarin 7-hydroxylation; CYP2B6: ethoxycoumarin O-deethylation; CYP2C8, 2C9(Arg), 2C9(Cys): tolbutamide hydroxylation; CYP2C19: (*S*)-mephenytoin 4'-hydroxylation; CYP2D6: (+)-bufuralol 1'-hydroxylation; CYP2E1: 4-nitrophenol hydroxylation; CYP3A4: testosterone 6β-hydroxylation.

4.11. Docking experiments

To determine the binding mode of **(+)-89c**, a docking study was conducted using a homology model for the catalytic domain of 17,20-lyase. In the docking experiment, it was postulated that **(+)-89c** was coordinated to the catalytic heme iron *via* the nitrogen of the imidazole ring moiety.
The results of the docking study are shown in Figure 17, and suggest that the naphthalene ring of **(+)-89c** is contained in a hydrophobic pocket surrounded by Ala 113, Phe 114, Ile 205, Ala 302 and Ile 371. In addition, the carbamoyl oxygen of **(+)-89c** was shown to form a hydrogen bond with Thr 101, while the hydroxy group formed a hydrogen bond with Thr 306. These results were consistent with our previous experiments on **(-)-71b**. Moreover, the superimposition of **(+)-89c** with 17α-hydroxypregnenolone, a known substrate of 17,20-lyase, demonstrated that the naphthalene ring of **(+)-89**c and the B and C rings of the steroidal skeleton of 17α-hydroxypregnenolone are located in a similar position (Figure 18).

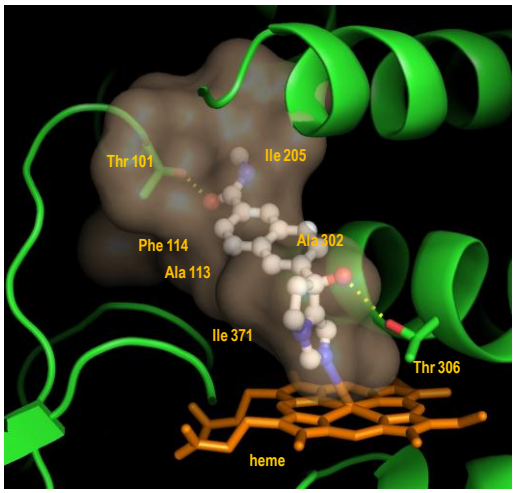


Figure 17. Docking study of **(+)-89c** in the homology model of 17,20-lyase.

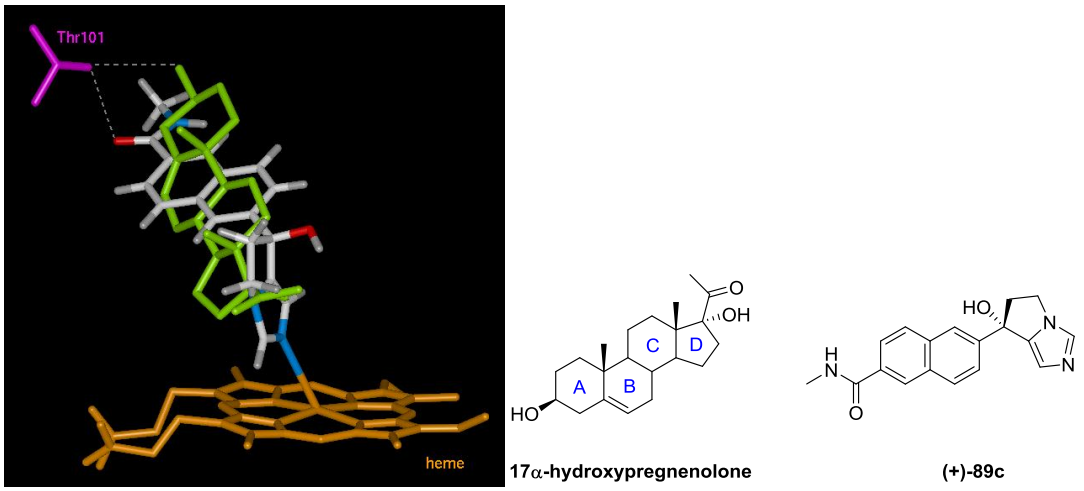


Figure 18. Overlay of **(+)-89c** (white) with 17α-hydroxypregnenolone (green) in the homology model of 17,20-lyase.

4.12. Conclusions

A novel naphthylmethylimidazole derivative **(-)-71b** and its related compounds were identified as 17,20-lyase inhibitors. Based on the structure‑activity relationship around the naphthalene scaffold and the results of a docking study of **(-)-71b** in the homology model of 17,20-lyase, the 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole derivative **(+)-89c** was synthesized and identified as a potent and highly selective 17,20-lyase inhibitor. Biological evaluation of **(+)-89c** at a dose of 1 mg/kg in a male monkey model revealed marked reductions in both serum testosterone and dehydroepiandrosterone concentrations. Furthermore, asymmetric synthesis of **(+)-89c** has been

established by developing the novel chelation-assisted enantioselective Reformatsky reaction using cinchona alkaloids as a chiral ligand.

5. Conclusions

As discussed in the previous sections **2** through **4**, **(-)-19**, **(-)-74b** and **(+)-89c** were identified as promising candidates for further development. The Figure 19 summarizes the selected flow of representative compounds, **(-)-19**, **(-)-74b** and **(+)-89c**, and their biological profiles. In terms of *in vivo* activity in a monkey model and selectivity between 17,20-lyase and the other CYP family enzymes, **(+)-89c** was identified as a potent and highly selective inhibitor of 17,20-lyase.

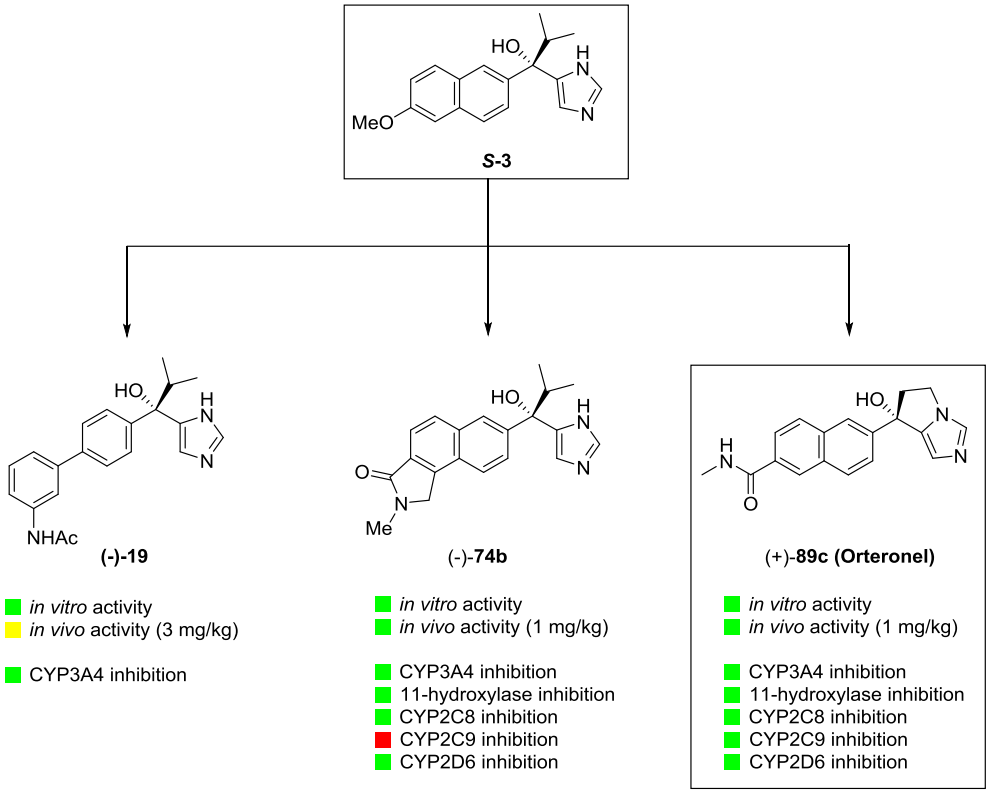


Figure 19. Summary of biological profiles for selected compounds, **(-)-19**, **(-)-74b** and **(+)-89c (orteronel)**.

To rationalize the characteristic properties of **(+)-89c** identified as a highly selective 17,20-lyase inhibitor over the other CYPs, a homology model for the catalytic domain of CYP3A4 was also investigated and the docking experiment of **(+)-89c** was conducted. First, the impact of conformational change as a factor contributing to enzyme selectivity was examined for two different inhibitors, compounds **(-)-71b** (CYP3A4 IC_{50} = 7800 nM) and **(+)-89c** (CYP3A4 IC_{50} = >30,000 nM) (Figure 20). In the homology model, it was shown that when **(-)-71b** is bound to the active site of CYP3A4, the naphthyl group is located in the pocket, as shown in Figure 20. However, in the case of **(+)-89c**, owing to the high rigidity of the molecule, it was difficult to superimpose **(+)-89c** with

(-)-71b for this model. Furthermore, we determined that when **(+)-89c** was coordinated to the heme iron *via* the nitrogen of the fused imidazole ring moiety, a part of the naphthyl group appeared to be out of the pocket, shown as a red dotted circle in Figure 20. Based on these observations and previously discussed SAR study in Table 15, the conformational rigidity of the fused imidazole ring moiety of **(+)-89c** may contribute to its selectivity of 17,20-lyase over CYP3A4.

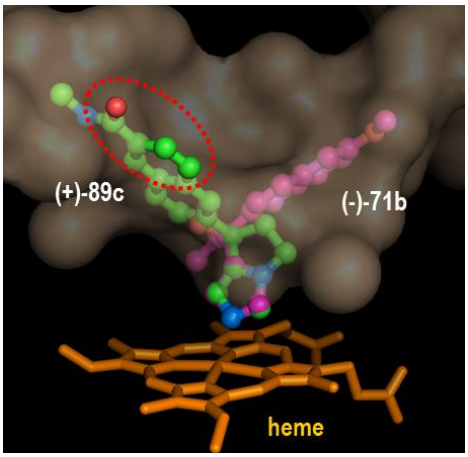


Figure 20. Docking study of **(-)-71b** (magenta) with **(+)-89c** (green) in the homology model of CYP3A4.

Another potential factor that may affect enzyme selectivity is the lipophilicity of the inhibitors. As described above, CYP family of enzymes is known to prefer lipophilic molecules as substrates or inhibitors. Therefore, an index such as Clog P, which represents the lipophilicity of a molecule, may, at least in part, provide helpful information on enzyme selectivity. The Clog P values of compounds **(-)-71b** and **(+)-89c** were 1.5 and 0.3, respectively, and the correlation between the potency of inhibition for CYP3A4 and Clog P values of these two inhibitors were as expected; **(+)-89c** with a lower Clog P value showed less potent inhibition against CYP3A4 than **(-)-71b** with a higher Clog P value. Based on these data, the decreased inhibition of CYP3A4 by **(+)-89c** seemed to be partly due to a decrease in lipophilicity of the molecule. However, regarding the inhibition of 17,20-lyase, **(+)-89c** shows potent inhibition with a lower Clog P value; therefore, additional contributions such as hydrogen bond interactions proposed by docking experiments should be considered for further discussion. In summary, these observations suggested that two main factors, namely conformational rigidity of the fused imidazole ring moiety and the low Clog P value of **(+)-89c**, may account for the observed selectivity for 17,20-lyase versus CYP3A4.

In general, ring systems such as imidazole and pyridine rings are known to be good ligands for heme iron, which is a component of CYP family enzymes. Therefore, difficulties are often encountered when developing CYP inhibitors with these rings, owing to their ability to bind

nonselectively to heme iron found in the CYP enzymes. The author believes that these findings regarding the selectivity of **(+)-89c** over the CYPs could be applied to other series of CYP inhibitors and the author's approach to **(+)-89c** may provide a new methodology in this field. Finally, **(+)-89c** (termed orteronel [TAK-700]) was selected as a candidate for further development, and clinical evaluation of orteronel has been investigated for the potential treatment of metastatic CRPC.

In conclusion, this study provides an excellent example of medicinal chemistry effort with a novel strategy that is able to achieve high specificity for the inhibition of 17,20-lyase over the other CYP enzymes, and the following new insights were obtained throughout this study.

1. SARs for the novel series of biphenylylmethylimidazole derivatives and naphthylmethylimidazole derivatives as 17,20-lyase inhibitors were explored and compounds **(-)-19**, **(-)-74b** and orteronel as selective and orally active 17,20-lyase inhibitors were discovered by the novel approach using the homology model of 17,20-lyase.

2. Asymmetric synthesis of **(-)-19**, **(-)-74b** and orteronel were examined, and especially, enantioselective Reformatsky reaction using cinchonine as a chiral ligand was developed in the case of orteronel.

3. Orteronel was identified as a potent, highly selective and nonsteroidal inhibitor of 17,20-lyase and selected as a candidate for clinical evaluation.

6. 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, Varian Mercury-300 spectrometer, or a Bruker AVANCE-300 spectrometer. ^{13}C NMR spectra were recorded using a Bruker AVANCE-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. LCMS was performed on the Agilent1200Sl and Agilent6130MS apparatus with 5 mM aqueous $AcONH_4$ solution/acetonitrile mobile phase. Reactions were followed by TLC on Silica Gel 60 F_{254} precoated TLC plates (Merck, Darmstadt, Germany). Column chromatography was performed using Silica Gel 60 (E. Merck, Darmstadt, Germany). Compounds **4a–b, 5a–b, 13a–d, 22a–b, 22d–e, 42** were commercially available, compounds **6**, [49] **22c**, [50] **29**, [51] , **39** [52] and **60** [80] were prepared in the same manner as described previously, and compound **11** was easily prepared from compound **6** and trityl chloride in the usual manner.

6.1.1. General procedure for method A and 1-[1,1'-biphenyl]-3-yl-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (7)

n-BuLi in hexane (1.6 M; 6.4 mL, 10.2 mmol) was added to a cooled (−78°C) solution of **4a** (2.11 g, 9.05 mmol) in THF (30 mL) and the mixture was stirred at −78°C for 1 h. A solution of **6** (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 **7** (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 **8–10** were prepared in the same manner as described for the preparation of **7**.

6.1.2. 1-(1*H*-Imidazol-4-yl)-1-(4'-methoxy-[1,1'-biphenyl]-3-yl)-2-methyl-1-propanol (8)

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.

6.1.3. 1-[1,1'-Biphenyl]-4-yl-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (9)

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.

6.1.4. 1-(1*H*-Imidazol-4-yl)-1-(4'-methoxy[1,1'-biphenyl]-4-yl)-2-methyl-1-propanol (10)

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.

6.1.5. General procedure for method B and 1-(3-bromophenyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (12a)

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 **11** (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 **12a** (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 **12b** was prepared in the same manner as described for the preparation of **12a**.

6.1.6. 1-(4-Bromophenyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (12b)

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.

6.1.7. 1-(4'-Fluoro-[1,1'-biphenyl]-3-yl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (14a)

Under N_2 atmosphere, a mixture of **12a** (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 **14a** (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 **14b–f** were prepared in the same manner as described for the preparation of **14a**.

6.1.8. 1-(4'-Chloro[1,1'-biphenyl]-3-yl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (14b)

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 $C_{38}H_{33}N_2OCl·H_2O$: C, 79.94; H, 5.86; N, 4.91. Found: C, 79.85; H, 5.85; N, 4.80.

6.1.9. 1-(4'-Fluoro-[1,1'-biphenyl]-4-yl)-1-(1-trityl-1*H*-imidazol-4-yl)-2-methyl-1-propanol (14c)

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), 7.33–7.57

(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.

6.1.10. 1-(4'-Chloro-[1,1'-biphenyl]-4-yl)-1-(1-trityl-1*H*-imidazol-4-yl)-2-methyl-1-propanol (14d)

Yield 85%. Mp 211–212°C (AcOEt–hexane). ^1H 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.

6.1.11. *N*-{4'-[1-Hydroxy-2-methyl1-(1-trityl-1*H*-imidazol-4-yl)propyl][1,1'-biphenyl]-3-yl} acetamide (14e)

Yield 96%. ^1H 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).

6.1.12. *N*-{4'-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl][1,1'-biphenyl]-4-yl} acetamide (14f)

Yield 32%. Mp 244–248°C (AcOEt). ^1H 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.

6.1.13. 1-(4'-Fluoro[1,1'-biphenyl]-3-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (15)

A mixture of **14a** (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 **15** (274 mg, 0.88 mmol, 79%) as a colorless powder. Mp 154–156°C (AcOEt–hexane). ^1H 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 **16–20** were prepared in the same manner as described for the preparation of **15**.

6.1.14. 1-(4'-Chloro[1,1'-biphenyl]-3-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (16)

Yield 76%. Mp 169°C (AcOEt–hexane). ^1H 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.

6.1.15. 1-(4'-Fluoro[1,1'-biphenyl]-4-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (17)

Yield 69%. Mp 198–199°C (AcOEt–hexane). ^1H 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.

6.1.16. 1-(4'-Chloro[1,1'-biphenyl]-4-yl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol (18)

Yield 76%. Mp 197–198°C (AcOEt–hexane). ^1H 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.

6.1.17. *N*-{4'-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl][1,1'-biphenyl]-3-yl}acetamide (19)

Yield 48%. ^1H 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).

6.1.18. *N*-{4'-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl][1,1'-biphenyl]-4-yl}acetamide (20)

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 $C_{21}H_{23}N_3O_2$·0.1AcOEt: C, 71.75; H, 6.70; N, 11.73. Found: C, 71.70; H, 6.65; N, 11.90.

6.1.19. General procedure for method C and 4-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl] phenylboronic acid (21)

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 **12b** (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 **21** (4.00 g) as a colorless amorphous solid. This compound was used for the next step without further purification.

6.1.20. 4'-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-methyl[1,1'-biphenyl]-3-carboxamide (23a)

Under N_2 atmosphere a mixture of crude **21** (3.44 g), 3-bromophenyl-*N*-methylcarboxamide **22a** (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 **23a** (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 **23b–e** were prepared in the same manner as described for the preparation of **23a**.

6.1.21. 4'-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-methyl[1,1'-biphenyl]-3-sulfonamide (23b)

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.

6.1.22. *N*-{4'-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl][1,1'-biphenyl]-3-yl}-*N*'-methylurea (23c)

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.

6.1.23. 2-Methyl-1-[4-(2-pyridinyl)phenyl]-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (23d)

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}.

6.1.24. *N*-{6-(4-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]phenyl)-2-pyridinyl} acetamide (23e)

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 $C_{39}H_{36}N_4O_2 \cdot 1.1AcOEt$: C, 75.58; H, 6.55; N, 8.12. Found: C, 75.52; H, 6.46; N, 8.17. Compounds **24–28** were prepared in the same manner as described for the preparation of **15**.

6.1.25. 4'-[1-Hydroxy1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl[1,1'-biphenyl]-3-carboxamide (24)

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 $C_{21}H_{23}N_3O_2 \cdot 0.75H_2O$: C, 69.50; H, 6.80; N, 11.58. Found: C, 69.53; H, 7.16; N, 11.28.

6.1.26. 4'-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl[1,1'-biphenyl]-3-sulfonamide (25)

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 $C_{20}H_{23}N_3O_3S \cdot 0.5H_2O$: C, 60.89; H, 6.13; N, 10.65. Found: C, 61.10; H, 6.31; N, 10.78.

6.1.27. *N*-{4'-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl][1,1'-biphenyl]-3-yl}-*N*'-methylurea (26)

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 $C_{20}H_{24}N_4O_2 \cdot 0.5AcOEt$: C, 66.65; H, 7.12; N, 14.13. Found: C, 66.89; H, 7.00; N, 14.28.

6.1.28. 1-(1*H*-Imidazol-4-yl)-2-methyl-1-[4-(2-pyridinyl)phenyl]-1-propanol (27)

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 $C_{18}H_{19}N_3O \cdot 0.4H_2O$: C, 71.93; H, 6.64; N, 13.98. Found: C, 71.69; H, 6.55; N, 13.98.

6.1.29. *N*-{6-(4-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]phenyl)-2-pyridyl}acetamide (28)

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.

6.1.30. 4-Bromophenyl(1-trityl-1*H*-imidazol-4-yl)methanol (30)

Compound **30** was prepared in the same manner as described for the preparation of **12a**. 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.

6.1.31. 4-Bromophenyl(1-trityl-1*H*-imidazol-4-yl)methanone (31)

A mixture of **30** (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 **31** (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}.

6.1.32. *N*-[4'-[(1-Trityl-1*H*-imidazol-4-yl)carbonyl][1,1'-biphenyl]-3-yl]acetamide (32)

Compound **32** was prepared in the same manner as described for the preparation of **14a**. 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.

6.1.33. *N*-[4'-[1-Hydroxy-1-(1-trityl-1*H*-imidazol-4-yl)ethyl][1,1'-biphenyl]-3-yl]acetamide (33a)

Methylmagnesium bromide (1.0 M in THF, 4.4 mL, 4.38 mmol) was added dropwise to a cooled (0°C) solution of **32** (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 **33a** (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 $C_{38}H_{33}N_3O_2 \cdot 0.5$AcOEt: C, 79.05; H, 6.14; N, 6.91. Found: C, 79.13; H, 6.33; N, 6.71. Compounds **33b,c** were prepared in the same manner as described for the preparation of **33a**.

6.1.34. *N*-[4'-[1-Hydroxy-1-(1-trityl-1*H*-imidazol-4-yl)propyl][1,1'-biphenyl]-3-yl]acetamide (33b)

Yield 86%. ^{1}H 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 $C_{39}H_{35}N_3O_2 \cdot 0.5$AcOEt: C, 79.20; H, 6.32; N, 6.76. Found: C, 79.23; H, 6.40; N, 6.93.

6.1.35. *N*-[4'-[Cyclopropyl(hydroxy)(1-trityl-1*H*-imidazol-4-yl)methyl][1,1'-biphenyl]-3-yl] acetamide (33c)

Yield 61%. Mp 230–231°C (AcOEt–MeOH–hexane). ^{1}H 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 **34, 36,** and **37** were prepared in the same manner as described for the preparation of **15**.

6.1.36. *N*-[4'-[1-Hydroxy-1-(1*H*-imidazol-4-yl)ethyl][1,1'-biphenyl]-3-yl]acetamide (34)

Yield 59%. ^{1}H 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.

6.1.37. *N*-[4'-[Cyclopropyl(hydroxy)-1*H*-imidazol-4-ylmethyl][1,1'-biphenyl]-3-yl]acetamide (36)

Yield 39%. ^{1}H 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.

6.1.38. *N*-[4'-(1*H*-Imidazol-4-ylcarbonyl)[1,1'-biphenyl]-3-yl]acetamide (37)

Yield 88%. Mp 253–254°C (AcOEt–MeOH–hexane). ^{1}H 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.

6.1.39. *N*-[4'-[1-Hydroxy-1-(1*H*-imidazol-4-yl)propyl][1,1'-biphenyl]-3-yl]acetamide (35)

Under H_2 atmosphere, a mixture of **33b** (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 **35** (640 mg, 1.91 mmol, 84%) as a colorless amorphous solid. ^{1}H 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.

6.1.40. *N*-[4'-[1-Hydroxy(1*H*-imidazol-4-yl)methyl][1,1'-biphenyl]-3-yl]acetamide (38)

Sodium borohydride ($NaBH_4$) (172 mg, 4.55 mmol) was added to a cooled (0°C) solution of **37** (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 **38** (461 mg, 1.50 mmol, 76%) as a colorless powder. Mp 227–228°C (AcOEt–diethylether–hexane). ^{1}H 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.

6.1.41. Optical resolution of 19

Optical resolution of **19** (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 **(−)-19** (970 mg, >99.9% ee) and **(+)-19** (920 mg, 99.9% ee), respectively. The HPLC retention time of **(−)-19** was 10.8 min and that of **(+)-19** 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). [**(−)-19**: Anal. Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.5H_2O \cdot 0.1$AcOEt: C, 69.99; H, 6.81; N, 11.44. Found: C, 70.22; H, 7.13; N, 11.27. **(+)-19**: 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).

6.1.42. Optical resolution of 28

Optical resolution of **28** (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 **(−)-28** (1410 mg, 99.8% ee) and **(+)-28** (1180 mg, >99.9% ee), respectively. The HPLC retention time of **(−)-28** was 8.6 min and that of **(+)-28** 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). **(−)-28**: $[\alpha]_D^{20}$ = −8.3 (c 0.362, MeOH). **(+)-28**: $[\alpha]_D^{20}$ = +6.9 (c 0.376, MeOH).

6.1.43. Optical resolution of 35

Optical resolution of **35** (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 **(−)-35** (53 mg, >99.9% ee) and **(+)-35** (67 mg, 99.6% ee), respectively. The HPLC retention time of **(−)-35** was 43.0 min and that of **(+)-35** 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). **(−)-35**: $[\alpha]_D^{20}$ = −2.24 (c 1.03, EtOH). **(+)-35**: $[\alpha]_D^{20}$ = +1.69 (c 1.06, EtOH).

6.1.44. 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 (40)

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 **39** (24.09 g, 151.3 mmol)[49] 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 **40** (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).

6.1.45. (2*R*)-1-(4-Bromophenyl)-2-[[*tert*-butyl(dimethyl)silyl]oxy]propan-1-one (41)

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 **40** (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 **41** (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}.

6.1.46. (2*R*)-1-(4-Bromophenyl)-2-hydroxypropan-1-one (43)

Tetrabutylammonium fluoride (21.5 g, 21.5 mmol) was added to a cooled (0°C) solution of **41** (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 **43** (14.1 g, 61.6 mmol, 82%) as a pale yellow oil. The optical purity of the obtained **43** was 96% ee as determined by HPLC using a Chiralpak AD column with hexane/EtOH = 85:15 as an eluent. ^{1}H 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}.

6.1.47. Alternative method for (2*R*)-1-(4-bromophenyl)-2-hydroxypropan-1-one (43); 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 **42** (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 **43** (468 mg, 2.04 mmol, 87%) as a pale yellow oil. The optical purity of the obtained **43** was 98% ee as determined by HPLC (Chiralpak AD).

6.1.48. (2*R*,3*S*)-3-(4-Bromophenyl)-4-methylpentane-2,3-diol (44)

Solution **43** (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 **44** (70.8 mg, 0.6 mmol, 59%) with some by-products. This compound was used without further purification in the next step. ^{1}H 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}.

6.1.49. (3*S*)-3-(4-Bromophenyl)-3-hydroxy-4-methylpentane-2-one (45)

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 **43** (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 **45** (8.72 g, 32.2 mmol, 84%) as a pale yellow amorphous solid. ^{1}H 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.

6.1.50. (3*S*)-1-Bromo-3-(4-bromophenyl)-3-hydroxy-4-methylpentane-2-one (46)

Pyridinium bromide perbromide (11.2 g, 34.9 mmol) was added to a stirred solution of **45** (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 **46** (6.58 g, 18.8 mmol, 65%) as a pale yellow powder. ^{1}H 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}.

6.1.51. (1*S*)-1-(4-Bromophenyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (47)

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (8.01 mL, 44.3 mmol) was added dropwise to a cooled (0°C) solution of **46** (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 **47** (3.89 g, 13.2 mmol, 74%) as a pale yellow amorphous solid. The optical purity of the obtained **47** was 90% 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}.

6.1.52. (1*S*)-1-(4-Bromophenyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (48)

Trityl chloride (1.00 g, 3.59 mmol) was added to a cooled (0°C) mixture of **47** (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 **48** (1.16 g, 2.16 mmol, 63%) as a colorless powder. The optical purity of the obtained **48** was 99% ee as determined by HPLC (Chiralpak AD). Recrystallization of **48** with 99% ee from hexane–AcOEt provided needle crystals with 99.5% ee for X-ray crystallographic analysis. The spectral data of **48** were identical to those of the racemate **12b** 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).

6.1.53. *N*-[4'-[(1*S*)-1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-1,1'-biphenyl-3-yl]acetamide (49)

Compound **49** was prepared from **48** (300 mg, 0.56 mmol, 99% 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 **14a**. The optical purity of **49** was 99% ee as determined by HPLC (Chiralpak AD). The spectral data of **49** were identical to those of the racemate **14e** except for optical rotation. $[\alpha]_D^{20}$ = +46.6 (c 0.49, MeOH).

6.1.54. *N*-[4'-[(1*S*)-1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-1,1'-biphenyl-3-yl] acetamide (S-(−)-19)

A solution of **49** (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 **(−)-19** (30.7 mg, 0.088 mmol, 61%) as a colorless amorphous solid. The optical purity of the obtained **(−)-19** was 99% ee as determined by HPLC (Chiralpak AD). The spectral data of **(−)-19** were identical to those of the racemate **19** 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).

6.2.1. 2,6-Dibromonaphthalene (50)

Bromine (78.8 g, 493 mmol) was added dropwise to a cooled (0°C) solution of triphenylphosphine (129 g, 493 mmol) in anhydrous CH_3CN (200 mL) and the solution was stirred for 30 min at rt. A solution of 6-bromo-2-naphthol (100 g, 448 mmol) in anhydrous acetonitrile (CH_3CN) (200 mL) was added, and the reaction mixture was stirred for a further 2 h at 70°C. After removal of the solvent (bath temp was increased to 140°C), the residue was heated to 300°C for 1 h. After being cooled to 100°C, the black tar was dissolved in toluene (100 mL), and cooled to rt while stirring. The resulting solution was washed with 1 N NaOH and water, followed by drying over $MgSO_4$. The solvent was removed in vacuo and the residue was dissolved in MeOH (50 mL). The precipitate was filtered and washed with MeOH (200 mL) and diisopropylether (*i*Pr_2O), successively, to give **50** (37.2 g, 29%) as a grey powder. The analytical sample was obtained by recrystallization from AcOEt (light brown plates). ^{1}H NMR ($CDCl_3$) δ: 7.51–7.62 (4H, m), 7.94 (2H, s). IR (KBr): 1568, 1481, 1175, 1134, 1065, 885, 853, 816 cm^{-1}. Anal. Calcd for $C_{10}H_6Br_2$: C, 42.00; H, 2.11. Found: C, 42.28; H, 2.18.

6.2.2. 1-(6-Bromo-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (51)

n-BuLi (1.6 M; 59.0 mL, 94.4 mmol) was added dropwise to a cooled (−50°C) solution of **50** (27.0 g, 94.4 mmol) in anhydrous THF (1300 mL) , and the solution was stirred for 20 min at −50°C. A solution of **11** (23.9 g, 62.9 mmol) in anhydrous THF (200 mL) was added dropwise over 20 min, and the reaction mixture was stirred for 20 min at −50°C. After dilution with water, the organic phase was separated. The aqueous phase was extracted with AcOEt. The extracts were washed with brine and dried over $MgSO_4$, and then concentrated in vacuo. The residue was washed with hot AcOEt to give **51** (34.4 g, 93%) as a light brown powder. The analytical sample was obtained by recrystallization from THF–hexane (colorless powder). ^{1}H NMR ($CDCl_3$) δ: 0.72 (3H, d, *J* = 6.7 Hz), 0.95 (3H, d, *J* = 6.7 Hz), 2.45–2.58 (1H, m), 3.75 (1H, s), 6.80 (1H, d, *J* = 1.4 Hz), 7.10–7.15 (6H, m), 7.29–7.35 (10H, m), 7.50 (1H, dd, *J* = 1.8, 8.7 Hz), 7.57 (1H, dd, *J* = 1.8, 8.8 Hz), 7.63–7.69 (2H, m), 7.94 (1H, d, *J* = 1.8 Hz), 8.02 (1H, s). IR (KBr): 3241, 2967, 1493, 1445, 1169, 1017, 826, 812, 756, 747, 700 cm^{-1}. Anal. Calcd for $C_{36}H_{31}N_2OBr$: C, 73.59; H, 5.32; N, 4.77. Found: C, 73.89; H, 5.11; N, 4.63.

6.2.3. 1-{6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthyl}-1-ethanone (52)

n-BuLi (1.6 M; 16.4 mL, 26.2 mmol) was added dropwise to a cooled (−70°C) solution of **51** (7.0 g, 11.9 mmol) in anhydrous THF (150 mL) , and the solution was stirred for 20 min at −70°C. A solution of *N*-methoxy-*N*-methylacetamide (2.45 g, 23.8 mmol) in anhydrous THF (10 mL) was added, and the reaction mixture was stirred for 20 min at −70°C. After dilution with water, the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/THF = 6:1–3:1) to give **52**(3.53 g, 54%) as a colorless powder. The analytical sample was obtained by recrystallization from *i*-Pr_2O (colorless powder). ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 2.48–2.61 (1H, m), 2.72 (3H, s), 3.75 (1H, br s), 6.83 (1H, d, *J* = 1.4 Hz), 7.10–7.17 (6H, m), 7.30–7.37 (10H, m), 7.65 (1H, dd, *J* = 1.6, 8.8 Hz), 7.84 (1H, d, *J* = 8.8 Hz), 7.87 (1H, d, *J* = 8.8 Hz), 8.01 (1H, dd, *J* = 1.6, 8.8 Hz), 8.07 (1H, s), 8.42 (1H, s). IR (KBr): 3519, 2963, 1671, 1275, 1231, 1140, 747, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{34}N_2O_2$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.96; H, 6.17; N, 5.37.

6.2.4. 1-{6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthyl}-1-ethanone (53)

A mixture of **52** (350 mg, 0.64 mmol) and pyridine hydrochloride (148 mg, 1.28 mmol) in MeOH (4 mL) and $CHCl_3$ (2 mL) was stirred at 60°C for 3 h. The mixture was diluted with aq $NaHCO_3$ solution and the resulting mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$. After removing the solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1–10:1) to give **53** (159 mg, 81%) as a colorless powder. The analytical sample was obtained by recrystallization from AcOEt as a colorless powder. Mp 180.0–182.0°C. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.81 (3H, d, *J* = 6.7 Hz), 1.02 (3H, d, *J* = 6.7 Hz), 2.73–2.86 (4H, m), 7.05 (1H, d, *J* = 1.1 Hz), 7.56 (1H, d, *J* = 1.1 Hz), 7.73 (1H, dd, *J* = 1.7, 8.7 Hz), 7.89 (1H, d, *J* = 8.7 Hz), 7.92 (1H, d, *J* = 8.7 Hz), 7.99 (1H, dd, *J* = 1.7, 8.7 Hz), 8.11 (1H, s), 8.46 (1H, s). IR (KBr): 3235, 2969, 1672, 1306, 1289, 1044, 895, 824, 789 cm^{-1}. LCMS (API): *m/z* 309.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_2 \cdot 0.1$AcOEt: C, 73.46; H, 6.61; N, 8.83. Found: C, 73.29; H, 6.57; N, 8.84.

6.2.5. 1-[6-[(Diphenylmethylene)amino]-2-naphthyl]-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (54)

A mixture of **51** (14.0 g, 23.8 mmol), benzophenoneimine (5.18 g, 28.6 mmol), *tert*-BuONa (5.72 g, 59.5 mmol), $Pd_2(dba)_3$ (440 mg, 0.48 mmol), and *R*-(+)-BINAP (872 mg, 1.40 mmol) in anhydrous toluene (140 mL) was heated at 80°C for 18 h under Ar atmosphere. After dilution with AcOEt, the resulting mixture was passed through Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/THF = 1:1) and recrystallized from AcOEt–hexane (×2) to give **54** (14.3 g, 87%) as a yellow powder. ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, *J* = 6.7 Hz), 0.93 (3H, d, *J* = 6.7 Hz), 2.42–2.56 (1H, d), 3.65 (1H, br s), 6.79 (1H, d, *J* = 1.4 Hz), 6.87 (1H, dd, *J* = 2.0, 8.6 Hz), 7.10–7.57 (28H, m), 7.76 (1H, d, *J* = 2.0 Hz), 7.80 (1H, d, *J* = 1.4 Hz), 7.86 (1H, s). IR (KBr): 3453, 2969, 1493, 1445, 1256, 1163, 1005, 812, 748 cm^{-1}. Anal. Calcd for $C_{49}H_{41}N_3O·0.3THF$: C, 84.98; H, 6.17; N, 5.92. Found: C, 84.87; H, 6.27; N, 5.74.

6.2.6. 1-(6-Amino-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (55)

Sodium acetate (4.02 g, 49.0 mmol) and hydroxylamine hydrochloride (2.52 g, 36.3 mmol) were added to a solution of **7** (14.0 g, 20.4 mmol) in anhydrous THF (100 mL) and MeOH (100 mL) and the mixture was stirred for 40 min at rt. After concentration in vacuo, the residue was diluted with 0.2 N NaOH, and the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine and dried over $MgSO_4$ followed by concentration in vacuo to give **55** (orange-colored oil), which was used in the next reaction without further purification. The analytical sample was obtained by recrystallization from AcOEt (pale yellow powder). ^{1}H NMR ($CDCl_3$) δ: 0.75 (3H, d, *J* = 6.8 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 2.44–2.57 (1H, m), 3.62 (1H, br s), 6.79 (1H, d, *J* = 1.4 Hz), 6.89–6.94 (2H, m), 7.11–7.18 (6H, m), 7.29–7.36 (10H, m), 7.44 (1H, dd, *J* = 1.8, 8.8 Hz), 7.50 (1H, d, *J* = 8.8 Hz), 7.61 (1H, d, *J* = 8.4 Hz), 7.86 (1H, d, *J* = 1.2 Hz). IR (KBr): 3370, 3092, 2963, 1634, 1485, 1445, 760, 747, 700 cm^{-1}. Anal. Calcd for $C_{36}H_{33}N_3O·0.2AcOEt$: C, 81.66; H, 6.44; N, 7.76. Found: C, 81.55; H, 6.51; N, 7.66.

6.2.7. *N*-{6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthyl}acetamide (56a)

Pyridine (5.0 mL, 61.2 mmol) and acetic anhydride (3.9 mL, 40.8 mmol) were added to a crude mixture of **55** in anhydrous CH_2Cl_2 (100 mL) and stirred for 40 min at rt. After dilution with saturated $NaHCO_3$ (200 mL), the mixture was extracted with CH_2Cl_2 (×3). The combined organic

layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from AcOEt to give **56a** (10.9 g, 95% from **7**) as a pale yellow powder. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.75 (3H, d, *J* = 6.7 Hz), 0.95 (3H, d, *J* = 6.7 Hz), 2.20 (3H, s), 2.57–2.71 (1H, m), 6.87 (1H, d, *J* = 1.4 Hz), 7.10–7.15 (6H, m), 7.32–7.54 (12H, m), 7.68–7.77 (2H, m), 7.92 (1H, s), 8.15 (1H, s), 9.60 (1H, br s). IR (KBr): 3058, 2969, 1686, 1493, 1298, 1011, 747, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{35}N_3O_2 \cdot 0.3AcOEt$: C, 79.51; H, 6.37; N, 7.10. Found: C, 79.50; H, 6.47; N, 7.28.

6.2.8. *N*-{6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthyl}acetamide (57a)

Compound **57a** was prepared in the same manner as described for the preparation of **53**. Yield 84%, colorless powder. Mp 186.0–188.0°C. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.79 (3H, d, *J* = 6.8 Hz), 1.0 (3H, d, *J* = 6.8 Hz), 2.17 (3H, s), 2.63–2.76 (1H, m), 6.99 (1H, s), 7.43–7.54 (3H, m), 7.65–7.74 (2H, m), 7.91 (1H, s), 8.11 (1H, s). IR (KBr): 3248, 2971, 1669, 1557, 1495, 1391, 1296, 818 cm^{-1}. LCMS (API): *m/z* 324.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.58; H, 6.90; N, 12.94.

6.2.9. *N'*-{6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthyl}-*N*-methylurea (57b)

Phenyl chloroformate (0.50 mL, 4.01 mmol) was added dropwise to a cooled (0°C) solution of **55** (1.40 g, 2.67 mmol) and pyridine (0.65 mL, 8.01 mmol) in anhydrous THF (10 mL) and stirred for 30 min at 0°C. After pouring into phosphate buffer (pH 7.0), the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine and dried over $MgSO_4$, followed by concentrating in vacuo to give the carbamate (red viscous oil) which was used for the next reaction without further purification. Methylamine hydrochloride (360 mg, 5.34 mmol) and 10 N NaOH (0.54 mL, 5.4 mmol) were added to a stirred solution of the carbamate in DMSO (5 mL), and the reaction mixture was stirred for 1 h at rt. After dilution with 0.5 N NaOH, the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine and dried over $MgSO_4$ followed by concentrating in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:2–1:4) to give **56b** (984 mg) as a pale yellow powder, which contained a small amount of impurities. **56b** (850 mg) was used as a starting material. Using the same procedure as described for the synthesis of **53, 57b** (278 mg, 31% from **55**) was obtained as colorless amorphous solid. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.79 (3H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.9 Hz), 2.74–2.87 (1H, m), 2.79 (3H, s), 7.03 (1H, s), 7.38 (1H, dd, *J* = 2.2, 8.8 Hz), 7.55–7.66 (3H, m), 7.72 (1H, d, *J* = 9.0 Hz), 7.87 (1H, d, *J* = 2.0 Hz), 7.94 (1H, s). IR (KBr): 3320,

2971, 1655, 1555, 1493, 1248 cm^{-1}. LCMS (API): *m/z* 339.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{22}N_4O_2 \cdot H_2O$: C, 64.03; H, 6.79; N, 15.72. Found: C, 64.06; H, 6.72; N, 15.63.

6.2.10. 6-Bromo-1-chloro-2-naphthol (58b)

Sulfuryl chloride (6.48 mL, 80.7 mmol) was added dropwise to a cooled (0°C) solution of 6-bromo-2-naphthol (15.0 g, 67.2 mmol) in anhydrous Et_2O (80 mL) and stirred for 1 h at rt. After removal of the solvent in vacuo, the residue was diluted with AcOEt. The solution was washed with water and brine, and then dried over $MgSO_4$. After concentration in vacuo, the residue was recrystallized from *i*-Pr_2O–hexane (×2) to give **58b** (8.89 g, 51%) as a light brown powder. ^{1}H NMR ($CDCl_3$) δ: 5.90 (1H, s), 7.27 (1H, d, *J* = 9.0 Hz), 7.61 (1H, d, *J* = 9.0 Hz), 7.63 (1H, dd, *J* = 2.2, 9.0 Hz), 7.92 (1H, d, *J* = 9.0 Hz), 7.94 (1H, d, *J* = 2.2 Hz). IR (KBr): 3491, 3432, 1589, 1200, 1184, 939, 806 cm^{-1}. Anal. Calcd for $C_{10}H_6OBrCl$: C, 46.64; H, 2.35. Found: C, 46.44; H, 2.35.

6.2.11. 1-Methyl-2-naphthol (59)

A mixture of 2-hydroxy-1-naphthaldehyde (20.0 g, 116 mmol), hydrazine monohydrate (16.9 mL, 348 mmol) and KOH (20 g) in triethyleneglycol (150 mL) was slowly heated to 170°C in a round-bottomed flask equipped with Dean-Stark apparatus. The mixture was then heated at 170°C for 90 min and at 190°C for a further 20 min. After cooling to rt, the mixture was poured into water and acidified with concentrated HCl. The precipitate was filtered, washed with water, and dried in vacuo to give **59** (16.3 g, 89%) as a pale yellow powder. The analytical sample was obtained by recrystallization from *i*-Pr_2O–hexane (colorless needles). ^{1}H NMR ($CDCl_3$) δ: 2.52 (3H, s), 4.91 (1H, br s), 7.04 (1H, d, *J* = 8.8 Hz), 7.29–7.37 (1H, m), 7.44–7.52 (1H, m), 7.60 (1H, d, *J* = 8.8 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.4 Hz). IR (KBr): 3295, 1514, 1354, 1227, 1213, 806, 742 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.55; H, 6.46.

6.2.12. 6-Bromo-1-methyl-2-naphthol (58c)

A solution of bromine (16.1 g, 101 mL) in AcOH (30 mL) was added dropwise to a cooled (10°C) solution of **59** (16.0 g, 101 mmol) in AcOH (50 mL); the temperature of the solution was maintained at 10–20°C. After stirring for 15 min at 15–20°C, the mixture was poured into water. The precipitate was filtered, washed with water, and dried in vacuo to give **58c** (23.7 g, 99%) as a reddish powder. ^{1}H NMR ($CDCl_3$) δ: 2.49 (3H, s), 4.94 (1H, s), 7.05 (1H, d, *J* = 8.8 Hz), 7.50 (1H, d, *J* = 8.8 Hz), 7.52 (1H, dd, *J* = 2.2, 9.0 Hz), 7.76 (1H, d *J* = 9.0 Hz), 7.89 (1H, d, *J* = 2.2 Hz). IR (KBr): 3245,

1591, 1497, 1356, 1341, 1198, 1080, 893, 878, 810 cm^{-1}. Anal. Calcd for $C_{11}H_9OBr$: C, 55.72; H, 3.83. Found: C, 55.70; H, 3.81.

6.2.13. (7-Bromo-3-methoxy-2-naphthyl)methanol (61)

Trimethoxyborane (1.60 mL, 13.6 mmol) was added dropwise to a solution of lithium borohydride (2.96 g, 136 mmol) and **60**[62] (40.0 g, 136 mmol) in anhydrous THF (150 mL), and the solution was refluxed for 90 min. After cooling to 0°C, water was carefully added, and the mixture was acidified with 6 N HCl followed by extraction with AcOEt (×2). The combined organic layers were washed with 1 N NaOH (×2) and brine, and then dried over $MgSO_4$. The solvent was removed in vacuo to give **61** as a colorless powder, which was used for the next reaction without further purification. The analytical sample was obtained by recrystallization from AcOEt–hexane (colorless needles). ^{1}H NMR ($CDCl_3$) δ: 3.97 (3H, s), 4.82 (2H, s), 7.09 (1H, s), 7.49 (1H, dd, *J* = 1.8, 8.8 Hz), 7.60 (1H, d, *J* = 8.8 Hz), 7.65 (1H, s), 7.91 (1H, d, *J* = 1.8 Hz). IR (KBr): 3239, 1497, 1248, 1215, 1065, 1049, 839 cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_2Br$: C, 53.96; H, 4.15. Found: C, 53.76; H, 3.93.

6.2.14. 7-Bromo-3-methoxy-2-naphthaldehyde (62)

A suspension of **61** and MnO_2 (200 g) in CH_2Cl_2 (600 mL) was refluxed for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give **62** (33.9 g, 94% from **60**) as a yellow powder. The analytical sample was obtained by recrystallization from AcOEt–hexane (colorless plates). ^{1}H NMR ($CDCl_3$) δ: 4.01 (3H, s), 7.13 (1H, s), 7.58 (2H, s), 7.98 (1H, s), 8.20 (1H, s), 10.55 (1H, s). IR (KBr): 2882, 1680, 1620, 1250, 1157 cm^{-1}. Anal. Calcd for $C_{12}H_9O_2Br$: C, 54.37; H, 3.42. Found: C, 54.41; H, 3.46.

6.2.15. 6-Bromo-2-methoxy-3-methylnaphthalene (63)

A mixture of **62** (13.0 g, 49.0 mmol), hydrazine monohydrate (7.13 mL, 147 mmol) and KOH (13.0 g) in triethyleneglycol (100 mL) was slowly heated to 160°C in a round-bottomed flask equipped with Dean-Stark apparatus. Evolution of N_2 gas started at 100°C. The mixture was heated at 160°C for 20 min and then at 180°C for a further 10 min. After cooling to rt, the mixture was poured into water. The precipitate was washed with water and dried in vacuo to give **63** (12.1 g, 98%) as pale yellow plates. The analytical sample was obtained by recrystallization from AcOEt–hexane (colorless plates). ^{1}H NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.91 (3H, s), 7.01 (1H, s), 7.40–7.45 (2H, m), 7.56 (1H, d, *J* = 8.4 Hz), 7.82 (1H, s). IR (KBr): 2978, 1590, 1490, 1256, 1157, 1119, 1019, 903, 851 cm^{-1}. Anal. Calcd for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42. Found: C, 57.27; H, 4.47.

6.2.16. 6-Bromo-3-methyl-2-naphthol (58d)

BBr_3 (1 M solution in CH_2Cl_2; 55.0 mL) was added dropwise to a cooled (−70°C) solution of **63** (11.5 g, 45.8 mmol) in anhydrous CH_2Cl_2 (120 mL), and the mixture was slowly heated to rt. After stirring for 2 h at rt, the reaction was quenched with water at 0°C. The resulting mixture was extracted with CH_2Cl_2 (×2). The combined organic layers were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 2:1) and washed with hexane to give **58d** (9.67 g, 89%) as a pale yellow powder. The analytical sample was obtained by recrystallization from AcOEt–hexane (pale yellow prisms). ^{1}H NMR ($CDCl_3$) δ: 2.40 (3H, s), 5.12 (1H, s), 7.02 (1H, s), 7.40 (1H, dd, *J* = 1.8, 8.8 Hz), 7.46–7.50 (2H, m), 7.82 (1H, s). IR (KBr): 3562, 1589, 1512, 1232, 1186, 1153, 1103, 920, 905, 860 cm^{-1}. Anal. Calcd for $C_{11}H_9OBr$: C, 55.72; H, 3.83. Found: C, 55.65; H, 3.63.

6.2.17. 2-Bromo-6-(*tert*-butyldimethylsilyloxy)naphthalene (64a)

TBSCl (37.0 g, 246 mmol) was added to a cooled (0°C) solution of 6-bromo-2-naphthol (50.0 g, 224 mmol) and imidazole (22.9 g, 336 mmol) in DMF (200 mL), and the solution was stirred for 2 h at rt. After dilution with water, the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was recrystallized from MeOH (20 mL) to give **64a** (71.3 g, 94%) as colorless plates. ^{1}H NMR ($CDCl_3$) δ: 0.24 (6H, s), 1.01 (9H, s), 7.08 (1H, dd, *J* = 2.4, 8.8 Hz), 7.15 (1H, d, *J* = 2.4 Hz), 7.46 (1H, dd, *J* = 1.8, 8.8 Hz), 7.54 (1H, d, *J* = 8.8 Hz), 7.61 (1H, d, *J* = 8.8 Hz), 7.90 (1H, d, *J* = 1.8 Hz). IR (KBr): 2957, 2930, 2857, 1256, 874, 797, 783 cm^{-1}. Anal. Calcd for $C_{16}H_{21}OBrSi$: C, 56.97; H, 6.27; Br, 23.69. Found: C, 56.94; H, 6.26. Compounds **64b–d** were prepared using the same method as described for the preparation of **64a**.

6.2.18. 6-Bromo-2-[(*tert*-butyldimethylsilyl)oxy]-1-chloronaphthalene (64b)

Yield 98%, pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.27 (6H, s), 1.07 (9H, s), 7.14 (1H, d, *J* = 8.8 Hz), 7.56 (1H, d, *J* = 8.8 Hz), 7.60 (1H, dd, *J* = 2.0, 9.0 Hz), 7.93 (1H, d, *J* = 2.0 Hz), 8.07 (1H, d, *J* = 9.0 Hz). IR (KBr): 2930, 1588, 1487, 1352, 1271, 1246, 960, 839 cm^{-1}.

6.2.19. 6-Bromo-2-[(*tert*-butyldimethylsilyl)oxy]-1-methylnaphthalene (64c)

Yield 85%, pale yellow plates. ^{1}H NMR ($CDCl_3$) δ: 0.23 (6H, s), 1.05 (9H, s), 2.49 (3H, s), 7.07 (1H, d, *J* = 8.8 Hz), 7.48 (1H, d, *J* = 8.8 Hz), 7.51 (1H, dd, *J* = 2.2, 9.2 Hz), 7.77 (1H, d, *J* = 9.2 Hz),

7.89 (1H, d, *J* = 2.2 Hz). IR (KBr): 2926, 1460, 1258, 928, 841, 781 cm^{-1}. Anal. Calcd for $C_{17}H_{23}OBrSi$: C, 58.11; H, 6.60; Br, 22.74. Found: C, 57.97; H, 6.56.

6.2.20. 6-Bromo-2-[(*tert*-butyldimethylsilyl)oxy]-3-methylnaphthalene (64d)

Yield 98%, pale yellow powder. ^1H NMR ($CDCl_3$) δ: 0.28 (6H, s), 1.04 (9H, s), 2.35 (3H, s), 7.05 (1H, s), 7.40 (1H, dd, *J* = 2.0, 8.6 Hz), 7.48–7.52 (2H, m), 7.81 (1H, d, *J* = 1.8 Hz). IR (KBr): 2928, 2856, 1587, 1460, 1254, 840, 781 cm^{-1}. Anal. Calcd for $C_{17}H_{23}OBrSi$: C, 58.11; H, 6.60; Br, 22.74. Found: C, 58.23; H, 6.64.

6.2.21. 1-(6-*tert*-Butyldimethylsilyloxy-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (65a)

n-BuLi (1.6 M; 55.6 mL, 88.9 mmol) was added dropwise to a cooled (−70°C) solution of **64a** (30.0 g, 88.9 mmol) in anhydrous THF (300 mL), and the solution was stirred for 20 min at −70°C. A solution of **11** (22.6 g, 59.3 mmol) in anhydrous THF (150 mL) was added dropwise over 30 min, and the reaction mixture was stirred for 20 min at −70°C. After dilution with water, the organic phase was separated and the aqueous phase was extracted with AcOEt. The extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) and recrystallized from iPr_2O–hexane to give **65a** (34.8 g, 92%) as a colorless powder. ^1H NMR ($CDCl_3$) δ: 0.23 (6H, s), 0.75 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 1.02 (9H, s), 2.45–2.59 (1H, m), 3.66 (1H, s), 6.80 (1H, d, *J* = 1.4 Hz), 7.04 (1H, dd, *J* = 2.4, 8.8 Hz), 7.11–7.16 (6H, m), 7.30–7.34 (11H, m), 7.49 (1H, dd, *J* = 1.6, 8.6 Hz), 7.60 (1H, d, *J* = 8.6 Hz), 7.68 (1H, d, *J* = 8.8 Hz), 7.94 (1H, s). IR (KBr): 3158, 2955, 2930, 1601, 1480, 1260, 843, 700 cm^{-1}. Anal. Calcd for $C_{42}H_{46}N_2O_2Si$: C, 78.95; H, 7.26; N, 4.38. Found: C, 79.05; H, 7.26; N, 4.47. Compounds **65b–d** were prepared using the same method as described for the preparation of **65a**.

6.2.22. 1-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-chloro-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (65b)

Yield 84%, colorless powder. ^1H NMR ($CDCl_3$) δ: 0.25 (6H, s), 0.74 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 1.07 (9H, s), 2.45–2.59 (1H, m), 3.70 (1H, s), 6.80 (1H, d, *J* = 1.2 Hz), 7.07–7.16 (7H, m), 7.29–7.34 (10H, m), 7.59 (1H, dd, *J* = 1.8, 8.8 Hz), 7.61 (1H, d, *J* = 8.8 Hz), 7.99 (1H, d, *J* = 1.8 Hz), 8.07 (1H, d, *J* = 8.8 Hz). IR (KBr): 3155, 2957, 1599, 1474, 1360, 1252, 1020, 964, 841, 700 cm^{-1}.

6.2.23. 1-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-methyl-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (65c)

Yield 89%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.22 (6H, s), 0.75 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 1.05 (9H, s), 2.44–2.60 (4H, m), 3.64 (1H, s), 6.80 (1H, d, *J* = 1.2 Hz), 7.03 (1H, d, *J* = 8.8 Hz), 7.10–7.16 (6H, m), 7.28–7.34 (10H, m), 7.55 (1H, d, *J* = 8.8 Hz), 7.56 (1H, dd, *J* = 1.8, 9.0 Hz), 7.81 (1H, d, *J* = 9.0 Hz), 7.92 (1H, d, *J* = 1.8 Hz). IR (KBr): 3200, 2961, 1472, 1242, 839, 702 cm^{-1}. Anal. Calcd for $C_{43}H_{48}N_2O_2Si$: C, 79.10; H, 7.41; N, 4.29. Found: C, 79.11; H, 7.44; N, 4.40.

6.2.24. 1-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-methyl-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (65d)

Yield 93%, pale yellow powder. ^{1}H NMR ($CDCl_3$) δ: 0.27 (6H, s), 0.75 (3H, d, *J* = 6.6 Hz), 0.94 (3H, d, *J* = 6.6 Hz), 1.05 (9H, s), 2.35 (3H, s), 2.45–2.58 (1H, m), 3.67 (1H, s), 6.80 (1H, d, *J* = 1.2 Hz), 7.06 (1H, s), 7.11–7.15 (6H, m), 7.30–7.7.33 (10H, m), 7.44 (1H, dd, *J* = 1.8, 8.6 Hz), 7.53–7.57 (2H, m), 7.86 (1H, s). IR (KBr): 3198, 1472, 1445, 1250, 1163, 1124, 914, 700 cm^{-1}. Anal. Calcd for $C_{43}H_{48}N_2O_2Si$: C, 79.10; H, 7.41; N, 4.29. Found: C, 79.12; H, 7.39; N, 4.44.

6.2.25. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthol (66a)

Tetrabutylammonium fluoride (1 M in THF; 100 mL) was added to a cooled (0°C) solution of **65a** (35.0 g, 54.8 mmol) in anhydrous THF (100 mL), and the reaction mixture was stirred for 1 h at rt. After removal of the solvent in vacuo, the residue was diluted with water. The precipitate was filtered, washed with water and AcOEt, and then dried in vacuo (100°C) to give **66a** (28.3 g, 98%) as a colorless powder. The analytical sample was obtained by recrystallization from THF–hexane (colorless powder). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.76 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 2.27–2.71 (1H, m), 6.86 (1H, d, *J* = 1.4 Hz), 7.05–7.17 (7H, m), 7.31–7.38 (11H, m), 7.48 (1H, dd, *J* = 1.8, 8.6 Hz), 7.58 (1H, d, *J* = 8.8 Hz), 7.67 (1H, d, *J* = 8.6 Hz), 7.85 (1H, s). IR (KBr): 3598, 2965, 1603, 1445, 1250, 1223, 1171, 702 cm^{-1}. LCMS (API): *m/z* 523.1 $[M-H]^-$. Anal. Calcd for $C_{36}H_{32}N_2O_2 \cdot 0.5H_2O \cdot 0.5THF$: C, 80.11; H, 6.55; N, 4.92. Found: C, 80.27; H, 6.55, N, 4.92. Compounds **66b–d** were prepared using the same method as described for the preparation of **66a**.

6.2.26. Chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthol (66b)

Yield 89%, colorless powder. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.73 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 2.48–2.61 (1H, m), 6.86 (1H, d, *J* = 1.4 Hz), 6.90 (1H, d, *J* = 9.2 Hz), 7.12–7.17 (6H, m), 7.31–7.47 (12H, m), 7.85 (1H, s), 7.94 (1H, d, *J* = 9.2 Hz). IR (KBr): 3533, 2971, 1485, 1350, 1310, 1001, 758, 702 cm^{-1}. LCMS (API): *m/z* 557.1 $[M-H]^-$. Anal. Calcd for $C_{36}H_{31}N_2O_2Cl$·0.5THF: C, 76.69; H, 5.93; N, 4.71. Found: C, 76.51; H, 5.92; N, 4.62.

6.2.27. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-1-methyl-2-naphthol (66c)

Yield 95%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.69 (3H, d, *J* = 6.6 Hz), 1.03 (3H, d, *J* = 6.6 Hz), 2.30–2.43 (1H, m), 2.43 (3H, s), 3.89 (1H, s), 6.04 (1H, d, *J* = 8.8 Hz), 6.49 (1H, d, *J* = 8.8 Hz), 6.85–6.93 (2H, m), 7.21–7.25 (6H, m), 7.37–7.48 (10H, m), 7.55 (1H, d, *J* = 8.8 Hz), 7.56 (1H, d, *J* = 1.0 Hz). IR (KBr): 3511, 2976, 1485, 1445, 1348, 1169, 1001, 758, 702 cm^{-1}. LCMS (API): *m/z* 539.1 $[M+H]^+$. Anal. Calcd for $C_{37}H_{34}N_2O_2$·0.5THF: C, 81.50; H, 6.66; N, 4.87. Found: C, 81.54; H, 6.67; N, 4.82.

6.2.28. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-3-methyl-2-naphthol (66d)

Yield 98%, colorless plates. ^{1}H NMR (DMSO-d_6) δ: 0.61 (3H, d, *J* = 6.8 Hz), 0.71 (3H, d, *J* = 6.6 Hz), 2.27 (3H, s), 2.54–2.64 (1H, m), 5.04 (1H, s), 6.83 (1H, d, *J* = 1.4 Hz), 7.03–7.08 (6H, m), 7.29 (1H, d, *J* = 1.4 Hz), 7.33–7.41 (10H, m), 7.45–7.50 (2H, m), 7.69 (1H, dd, *J* = 1.4, 8.8 Hz), 7.84 (1H, s), 9.26 (1H, br s). IR (KBr): 3603, 2966, 1670, 1447, 1244, 1159, 760, 748, 704 cm^{-1}. Anal. Calcd for $C_{37}H_{34}N_2O_2$·0.6DMF: C, 80.00; H, 6.61; N, 6.25. Found: C, 80.03; H, 6.59; N, 6.19.

6.2.29. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthyl trifluoromethanesulfonate (67a)

Trifluoromethanesulfonic anhydride (9.1 mL, 54.1 mmol) was added dropwise to a cooled (0°C) solution of **66a** (27.0 g, 51.5 mmol) in anhydrous pyridine (200 mL) and stirred for 1 h at 0°C. After dilution with water, the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) and recrystallized from *i*-Pr_2O to give **70** (26.1 g, 77%) as a colorless powder. The mother liquor was concentrated, and the residue was recrystallized from *i*-Pr_2O to give **67a** (3.54 g, 10%) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 2.47–2.60 (1H, m), 3.72 (1H, br s),

6.82 (1H, d, *J* = 1.4 Hz), 7.10–7.17 (6H, m), 7.30–7.35 (11H, m), 7.65 (1H, dd, *J* = 1.7, 8.6 Hz), 7.70 (1H, d, *J* = 2.6 Hz), 7.77 (1H, d, *J* = 8.6 Hz), 7.88 (1H, d, *J* = 9.0 Hz), 8.11 (1H, s). IR (KBr): 3164, 2965, 1431, 1412, 1242, 1211, 1142, 909, 897, 748, 702 cm^{-1}. Anal. Calcd for $C_{37}H_{31}N_2O_4SF_3$: C, 67.67; H, 4.76; N, 4.27. Found: C, 67.75; H, 4.51; N, 4.34. Compounds **67b–d** were prepared using the same method as described for the preparation of **67a**.

6.2.30. 1-Chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthyl trifluoromethanesulfonate (67b)

Yield 94%, colorless powder. ^1H NMR ($CDCl_3$) δ: 0.72 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 2.48–2.61 (1H, m), 3.75 (1H, s), 6.82 (1H, d, *J* = 1.6 Hz), 7.09–7.16 (6H, m), 7.30–7.37 (10H, m), 7.40 (1H, d, *J* = 9.2 Hz), 7.75 (1H, dd, *J* = 1.8, 8.8 Hz), 7.81 (1H, d, *J* = 9.2 Hz), 8.15 (1H, d, *J* = 1.8 Hz), 8.19 (1H, d, J = 8.8 Hz). IR (KBr): 3194, 2965, 1422, 1221, 1134, 828, 702 cm^{-1}. Anal. Calcd for $C_{37}H_{30}N_2O_4SClF_3$: C, 64.30; H, 4.37; N, 4.05. Found: C, 64.03; H, 4.19; N, 4.03.

6.2.31. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-1-methyl-2-naphthyl trifluoromethanesulfonate (67c)

Yield 61%, colorless powder. ^1H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 2.48–2.63 (1H, m), 2.67 (3H, s), 3.70 (1H, s), 6.82 (1H, d, *J* = 1.4 Hz), 7.10–7.16 (6H, m), 7.29–7.35 (11H, m), 7.69–7.74 (2H, m), 7.95 (1H, d, *J* = 8.8 Hz), 8.07 (1H, d, *J* = 1.8 Hz). IR (KBr): 3208, 2973, 1408, 1219, 1140, 897, 702 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2O_4SF_3$: C, 68.05; H, 4.96; N, 4.18. Found: C, 68.22; H, 4.97; N, 4.19.

6.2.32. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-3-methyl-2-naphthyl trifluoromethanesulfonate (67d)

Yield 74%, yellow powder. ^1H NMR ($CDCl_3$) δ: 0.72 (3H, d, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 2.46–2.59 (1H, m), 2.51 (3H, s), 3.72 (1H, s), 6.80 (1H, d, *J* = 1.6 Hz), 7.09–7.16 (6H, m), 7.29–7.36 (10H, m), 7.56 (1H, dd, *J* = 1.8, 8.6 Hz), 7.67–7.73 (3H, m), 8.02 (1H, s). IR (KBr): 3219, 2966, 1408, 1215, 1140, 1055, 895, 748, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2O_4SF_3$: C, 68.05; H, 4.96; N, 4.18. Found: C, 68.16; H, 4.98; N, 4.01.

6.2.33. Methyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (68a)

A degassed solution of **67a** (15.0 g, 22.8 mmol) and triethylamine (6.36 mL, 45.6 mmol) in anhydrous DMF (90 mL) and MeOH (30 mL) was added to $Pd(OAc)_2$ (256 mg, 1.14 mmol) and dppf (632 mg, 1.14 mmol), and vigorously stirred for 14 h at 70°C under CO atmosphere (1 atm). After dilution with water, the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (hexane/THF = 1:2) and recrystallized from hexane–AcOEt to give **68a** (12.3 g, 95%) as a light brown powder. ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 2.47–2.61 (1H, m), 3.75 (1H, s), 3.97 (3H, s), 6.82 (1H, d, *J* = 1.2 Hz), 7.10–7.16 (6H, m), 7.29–7.35 (10H, m), 7.62 (1H, dd, *J* = 1.8, 8.6 Hz), 7.81 (1H, d, *J* = 3.2 Hz), 7.85 (1H, d, *J* = 3.2 Hz), 8.02 (1H, dd, *J* = 1.8 Hz, 8.6 Hz), 8.07 (1H, s), 8.55 (1H, s). IR (KBr): 3542, 2965, 1707, 1441, 1279, 1231, 747, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{34}N_2O_3$·0.1AcOEt: C, 80.41; H, 6.09; N, 4.87. Found: C, 80.07; H, 6.06; N, 4.95. Compounds **68b–d** were prepared using the same method as described for the preparation of **68a**.

6.2.34. Methyl-1-chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (68b)

Yield 89%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.72 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 6.0 Hz), 2.44–2.61 (1H, m), 3.79 (1H, s), 3.98 (3H, s), 6.82 (1H, d, *J* = 1.4 Hz), 7.09–7.14 (6H, m), 7.31–7.38 (10H, m), 7.70 (1H, dd, *J* = 1.8, 9.0 Hz), 7.75 (s, 2H), 8.09 (1H, d, *J* = 1.4 Hz), 8.34 (1H, d, *J* = 9.2 Hz). IR (KBr): 3162, 1732, 1240, 1012, 747, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_2O_3Cl$: C, 75.92; H, 5.53; N, 4.66. Found: C, 75.88; H, 5.58; N, 4.65.

6.2.35. Methyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-1-methyl-2-naphthoate (68c)

Yield 81%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, *J* = 7.0 Hz), 0.76 (3H, d, *J* = 6.0 Hz), 2.48–2.62 (1H, m), 2.91 (3H, s), 3.74 (1H, s), 3.94 (3H, s), 6.82 (1H, d, *J* = 1.4 Hz), 7.10–7.15 (6H, m), 7.30–7.34 (10H, m), 7.64–7.70 (2H, m), 7.80 (1H, d, *J* = 8.8 Hz), 8.02 (1H, d, *J* = 1.4 Hz), 8.08 (1H, d, *J* = 9.2 Hz). IR (KBr): 3162, 2969, 1719, 1445, 1240, 1173, 747, 700 cm^{-1}. Anal. Calcd for $C_{39}H_{36}N_2O_3$: C, 80.66; H, 6.25; N, 4.82. Found: C, 80.47; H, 6.26; N, 4.72.

6.2.36. Methyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-3-methyl-2-naphthoate (68d)

Yield 88%, pale yellow powder. ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 2.45–2.59 (1H, m), 2.71 (3H, s), 3.73 (1H, s), 3.94 (3H, s), 6.80 (1H, d, *J* = 1.6 Hz), 7.10–7.16 (6H, m), 7.29–7.36 (10H, m), 7.54 (1H, dd, *J* = 1.6, 8.6 Hz), 7.61 (1H, s), 7.76 (1H, d, *J* = 8.6 Hz), 7.96 (1H, s), 8.44 (1H, s). IR (KBr): 3223, 2968, 1724, 1445, 1283, 1267, 748, 700 cm^{-1}. Anal. Calcd for $C_{39}H_{36}N_2O_3$·0.4AcOEt: C, 79.17; H, 6.41; N, 4.55. Found: C, 79.17; H, 6.23; N, 4.61.

6.2.37. Methyl 6-[1-hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthoate (69)

Compound **68a** (1.40 g, 2.47 mmol) was used as a starting material. Using the same procedure described for the synthesis of **53, 69** (751 mg, 94%) was obtained as a pale yellow powder after recrystallization from AcOEt. Mp 167.0–169.0°C. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.80 (3H, d, *J* = 7.0 Hz), 1.02 (3H, d, *J* = 6.6 Hz), 2.69–2.82 (1H, m), 3.97 (3H, s), 7.02 (1H, d, *J* = 1.2 Hz), 7.52 (1H, d, *J* = 1.2 Hz), 7.68 (1H, dd, *J* = 1.0, 8.4 Hz), 7.87 (2H, d, *J* = 8,4 Hz), 8.01 (1H, dd, *J* = 1.0, 8.4 Hz), 8.08 (1H, s), 8.55 (1H, s). IR (KBr): 3542, 2965, 1707, 1441, 1279, 1231, 747, 700 cm^{-1}. LCMS (API): *m/z* 325.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{20}N_2O_3$·0.2AcOEt: C, 69.54; H, 6.37; N, 8.19. Found: C, 69.53; H, 6.43; N, 8.26.

6.2.38. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthamide (70a)

A solution of **68a** (2.0 g, 3.53 mmol) in THF (20 mL) and MeOH (4 mL) and 4 N NaOH (4 mL) was stirred for 2 h at 60°C. After cooling to 0°C, the solution was neutralized with concentrated HCl and extracted with AcOEt (×2). The combined organic layers were washed with brine and concentrated in vacuo. The residue was dried with toluene azeotropically (×2) to give the carboxylate as a light brown powder, which was used for the next reaction without further purification. A mixture of the carboxylate, ammonium bicarbonate (558 mg, 7.06 mmol), DPPA (0.91 mL, 4.24 mmol) and triethylamine (0.98 mL, 7.06 mmol) in anhydrous DMF (10 mL) was stirred for 12 h at rt. After dilution with water, the mixture was extracted with AcOEt (×2). The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (hexane/THF = 1:2) and washed with hexane–AcOEt to give **70a** (1.96 g, quant.) as a colorless powder. The analytical sample was obtained by recrystallizaion from THF–hexane (colorless powder). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.74 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 7.0 Hz), 2.55–2.68 (1H, m), 6.86 (1H, d, *J* = 1.2 Hz), 7.09–7.14 (6H, m), 7.27–2.38 (10H, m), 7.63 (1H, d, *J* = 1.7,

8.5 Hz), 7.82–7.85 (3H, m), 8.04 (1H, s), 8.33 (1H, s). IR (KBr): 3407, 3189, 2965, 1644, 1443, 748, 700 cm^{-1}. Anal. Calcd for $C_{37}H_{33}N_3O_2 \cdot 1.0THF$: C, 78.94; H, 6.62; N, 6.74. Found: C, 78.83; H, 6.57; N, 6.94.

6.2.39. General procedure for the synthesis of the carbamoyl derivatives: 6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-methyl-2-naphthamide (70b)

Using the same procedure as described for the synthesis of **70a, 68a** (8.0 g, 14.1 mmol) was hydrolyzed to give the carboxylate (light brown powder). A solution of the carboxylate, methylamine (2 M solution in THF; 8.45 mL), EDCI·HCl (3.24 g, 16.9 mmol), $HOBt \cdot H_2O$ (2.59 g, 16.9 mmol) and triethylamine (2.36 mL, 16.9 mmol) in anhydrous DMF (80 mL) was stirred for 12 h at rt. After dilution with water, the mixture was extracted with AcOEt (×2). The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was washed with AcOEt to give **70b** (8.0 g, quant.) as a pale yellow powder. The analytical sample was obtained by recrystallization from THF–hexane (pale yellow powder). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.75 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 7.0 Hz), 2.60–2.74 (1H, m), 3.01 (3H, d, *J* = 4.4 Hz), 6.89 (1H, s), 7.10–7.14 (6H, m), 7.27–7.38 (10H, m), 7.65 (1H, dd, *J* = 1.4, 8.8 Hz), 7.82–7.86 (3H, m), 8.03 (1H, s), 8.28 (1H, s). IR (KBr): 3345, 2969, 1657, 1443, 1302, 1011, 747, 700 cm^{-1}. Anal. Calcd for $C_{38}H_{35}N_3O_2 \cdot 0.3THF$: C, 80.03; H, 6.58; N, 7.14. Found: C, 79.81; H, 6.46; N, 7.05. Compounds **70c–h** were prepared using the same method as described for the preparation of **70b**.

6.2.40. *N*-Ethyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthamide (70c)

Yield 83%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 3.3 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 1.28 (3H, t, *J* = 7.2 Hz), 2.47–2.60 (1H, m), 3.48–3.61 (2H, m), 3.79 (1H, s), 6.32 (1H, t, *J* = 5.5 Hz), 6.82 (1H, d, *J* = 1.4 Hz), 7.09–7.16 (6H, m), 7.28–7.34 (10H, m), 7.61 (1H, dd, *J* = 1.8, 8.8 Hz), 7.75–7.84 (3H, m), 8.05 (1H, s), 8.23 (1H, s). IR (KBr): 3308, 2967, 1638, 1535, 1308, 1009, 747, 700 cm^{-1}. Anal. Calcd for $C_{39}H_{37}N_3O_2 \cdot 0.1AcOEt$: C, 80.41; H, 6.47; N, 7.14. Found: C, 80.26; H, 6.54; N, 7.09.

6.2.41. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-propyl-2-naphthamide (70d)

Yield 92%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 1.02 (3H, t, *J* = 7.2 Hz), 1.60–1.78 (2H, m), 2.53 (1H, quintet, *J* = 6.8 Hz), 3.48 (2H, q, *J* = 7.2 Hz), 3.76 (1H, s), 6.28 (1H, t, *J* = 7.2 Hz), 6.81 (1H, d, *J* = 1.4 Hz), 7.07–7.20 (6H, m), 7.28–7.37 (10H, m), 7.62 (1H, dd, *J* = 1.8, 8.6 Hz), 7.75–7.86 (3H, m), 8.06 (1H, s), 8.23 (1H, s). IR (KBr): 3326, 2967, 1642, 1599, 1541, 1445, 1308, 1157 cm^{-1}. Anal. Calcd for $C_{40}H_{39}N_3O_2$: C, 80.91; H, 6.62; N, 7.08. Found: C 80.84; H, 6.86; N, 7.08.

6.2.42. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-isopropyl-2-naphthamide (70e)

Yield 91%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 1.31 (6H, d, *J* = 6.6 Hz), 2.53 (1H, quintet, *J* = 6.8 Hz), 3.76 (1H, s), 4.27–4.43 (1H, m), 6.06 (1H, d, *J* = 7.4 Hz), 6.81 (1H, d, *J* = 1.4 Hz), 7.07–7.18 (6H, m), 7.28–7.38 (10H, m), 7.61 (1H, dd, *J* = 1.8, 8.6 Hz), 7.74–7.85 (3H, m), 8.06 (1H, s), 8.22 (1H, s). IR (KBr): 3301, 2971, 1640, 1601, 1537, 1447, 1289, 1171 cm^{-1}. Anal. Calcd for $C_{40}H_{39}N_3O_2 \cdot 0.25H_2O$: C, 81.30; H, 6.65; N, 7.02. Found: C, 80.33; H, 6.68; N, 6.88.

6.2.43. 1-Chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-methyl-2-naphthamide (70f)

Yield 75%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.71 (3H, d, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 2.46–2.60 (1H, m), 3.07 (3H, d, *J* = 4.8 Hz), 3.81 (1H, s), 6.24 (1H, d, *J* = 4.8 Hz), 6.82 (1H, d, *J* = 0.6 Hz), 7.09–7.14 (6H, m), 7.31–7.34 (10H, m), 7.57 (1H, d, *J* = 8.4 Hz), 7.69–7.73 (2H, m), 8.05 (1H, s), 8.22 (1H, d, *J* = 8.8 Hz). IR (KBr): 3376, 2969, 1634, 1157, 1134, 702 cm^{-1}. Anal. Calcd for $C_{38}H_{34}N_3O_2Cl$: C, 76.05; H, 5.71; N, 7.00. Found: C, 75.87; H, 5.71; N, 6.97.

6.2.44. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*,1-dimethyl-2-naphthamide (70g)

Yield 95%, colorless powder. ^{1}H NMR ($CDCl_3$) δ: 0.72 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 2.47–2.61 (1H, m), 2.70 (3H, s), 3.02 (3H, d, *J* = 4.8 Hz), 3.75 (1H, s), 5.89 (1H, br s), 6.81 (1H, d, *J* = 1.2 Hz), 7.09–7.14 (6H, m), 7.28–7.35 (10H, m), 7.59–7.68 (2H, m), 7.93–7.99 (2H, m). IR

(KBr): 3407, 3250, 2971, 1634, 1495, 1157, 816, 702 cm^{-1}. Anal. Calcd for $C_{39}H_{37}N_3O_2$: C, 80.80; H, 6.43; N, 7.25. Found: C, 80.41; H, 6.33; N, 7.18.

6.2.45. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*,3-dimethyl-2-naphthamide (70h)

Yield 86%, colorless powder. ^1H NMR ($CDCl_3$ + CD_3OD) δ: 0.72 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 2.54 (3H, s), 2.52–2.65 (1H, m), 2.99 (3H, d, *J* = 4.0 Hz), 6.85 (1H, d, *J* = 1.6 Hz), 7.10–7.15 (6H, m), 7.32–7.38 (10H, m), 7.53 (1H, dd, *J* = 1.6, 8.6 Hz), 7.58 (1H, s), 7.69 (1H, d, *J* = 8.6 Hz), 7.78 (1H, s), 7.89 (1H, s). IR (KBr): 3412, 3277, 2966, 1645, 1011, 746, 702 cm^{-1}. Anal. Calcd for $C_{39}H_{37}N_3O_2$·0.1AcOEt: C, 80.41; H, 6.47; N, 7.14. Found: C, 80.36; H, 6.31; N, 7.14. Compounds **71a–h** were prepared using the method as described for the preparation of **53**.

6.2.46. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthamide (71a)

Yield 88%, a colorless amorphous solid. ^1H NMR ($CDCl_3$ + CD_3OD) δ: 0.78 (3H, d, *J* = 6.6 Hz), 1.00 (3H, d, *J* = 7.0 Hz), 2.66–2.80 (1H, m), 7.00 (1H, d, *J* = 1.0 Hz), 7.49 (1H, d, *J* = 1.0 Hz), 7.63 (1H, d, *J* = 1.8, 8.8 Hz), 7.77–7.81 (3H, m), 8.04 (1H, s), 8.29 (1H, s). IR (KBr): 3200, 2969, 1659, 1393, 816 cm^{-1}. LCMS (API): *m/z* 310.1 $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}N_3O_2$·H_2O: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.65; H, 6.45; N, 12.86.

6.2.47. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl-2-naphthamide (71b)

Yield 88%, colorless powder. Mp 217.0–219.0°C. ^1H NMR ($CDCl_3$ + CD_3OD) δ: 0.78 (3H, d, *J* = 7.0 Hz), 1.01 (3H, d, *J* = 6.6 Hz), 2.67–2.80 (1H, m), 3.00 (3H, s), 7.00 (1H, d, *J* = 1.2 Hz), 7.49 (1H, d, *J* = 1.0 Hz), 7.63 (1H, dd, *J* = 1.8, 8.8 Hz), 7.74–7.79 (2H, m), 7.83 (1H, d, *J* = 8.4 Hz), 8.03 (1H, s), 8.22 (1H, s). ^{13}C NMR (DMSO-d_6) δ: 16.7, 17.4, 26.3, 36.6, 77.4, 112.0, 123.1, 123.8, 125.9, 126.7, 127.5, 127.9, 130.6, 131.1, 133.6, 134.2, 147.2, 147.5, 166.7. IR (KBr): 3565, 3351, 3318, 2973, 1638, 1628, 1549, 1308, 993, 812 cm^{-1}. LCMS (API): *m/z* 324.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.46; H, 6.67; N, 12.87.

6.2.48. *N*-Ethyl-6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthamide (71c)

Yield 92%, pale yellow amorphous solid. ^1H NMR ($CDCl_3$ + CD_3OD) δ: 0.77 (3H, d, *J* = 7.0 Hz), 1.00 (3H, d, *J* = 7.0 Hz), 1.26 (3H, t, *J* = 7.2 Hz), 2.63–2.77 (1H, m), 3.42–3.56 (2H, m), 6.98 (1H, d, *J* = 1.2 Hz), 7.22 (1H, t, *J* = 5.5 Hz), 7.44 (1H, d, *J* = 1.2 Hz), 7.59 (1H, dd, *J* = 1.6, 8.6 Hz), 7.70–

7.76 (3H, m), 8.01 (1H, s), 8.19 (1H, s). IR (KBr): 3310, 2971, 1638, 1561, 1306, 1146, 816 cm^{-1}. LCMS (API): *m/z* 338.2 $[M+H]^+$. Anal. Calcd for $C_{20}H_{23}N_3O_2 \cdot 0.75H_2O$: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.62; H, 7.08; N, 11.93.

6.2.49. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-propyl-2-naphthamide (71d)

Yield 77%, colorless amorphous powder solid. ^1H NMR ($CDCl_3$) δ: 0.78 (3H, d, *J* = 6.6 Hz), 1.00 (3H, t, *J* = 7.2 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 1.58–1.77 (2H, m), 2.68 (1H, quintet, *J* = 7.2 Hz), 3.40–3.52 (2H, m), 3.49 (1H, s), 6.44 (1H, t, *J* = 5.5 Hz), 6.99 (1H, s), 7.45 (1H, s), 7.59–7.80 (4H, m), 8.05 (1H, s), 8.1 7 (1H, s). IR (KBr): 3400–3100, 2967, 1640, 1601, 1539, 1464, 1308, 1144 cm^{-1}. LCMS (API): *m/z* 352.3 $[M+H]^+$. Anal. Calcd for $C_{21}H_{25}N_3O_2 \cdot 0.2H_2O$: C, 71.04; H, 7.21; N, 11.83. Found: C, 70.83; H, 7.29; N, 11.78.

6.2.50. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-isopropyl-2-naphthamide (71e)

Yield 73%, colorless amorphous solid. ^1H NMR ($CDCl_3$) δ: 0.77 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.29 (6H, d, *J* = 6.6 Hz), 2.67 (1H, quintet, *J* = 6.8 Hz), 3.48 (1H, s), 4.26–4.42 (1H, m), 6.23 (1H, d, *J* = 7.8 Hz), 6.97 (1H, d, *J* = 1.2 Hz), 7.41 (1H, d, *J* = 1.2 Hz), 7.57–7.80 (4H, m), 8.04 (1H, s), 8.14 (1H, s). IR (KBr): 3400–3100, 2973, 1626, 1601, 1537, 1456, 1294, 1173 cm^{-1}. LCMS (API): *m/z* 352.3 $[M+H]^+$. Anal. Calcd for $C_{21}H_{25}N_3O_2 \cdot 0.15H_2O$: C, 71.22; H, 7.20; N, 11.87. Found: C, 71.05; H, 7.34; N, 11.81.

6.2.51. 1-Chloro-6-[1-hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl-2-naphthamide (71f)

Yield 93%, pale yellow amorphous solid. ^1H NMR ($CDCl_3$ + CD_3OD) δ: 0.76 (3H, d, *J* = 6.6 Hz), 0.99 (3H, d, *J* = 6.6 Hz), 2.64–2.78 (1H, m), 3.01 (3H, d, *J* = 1.4 Hz), 6.98 (1H, s), 7.41 (1H, dd, *J* = 1.4, 8.6 Hz), 7.42 (1H, s), 7.69 (1H, d, *J* = 7.8 Hz), 7.72 (1H, dd, *J* = 1.4, 7.8 Hz), 8.01 (1H, s), 8.19 (1H, d, *J* = 8.6 Hz). IR (KBr): 3242, 2970, 1630, 1553, 1333, 824 cm^{-1}. LCMS (API): *m/z* 358.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{20}N_3O_2 \cdot 0.5H_2O$: C, 62.21; H, 5.77; N, 11.45. Found: C, 62.10; H, 5.84; N, 11.37.

6.2.52. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*,1-dimethyl-2-naphthamide (71g)

Yield 91%, colorless amorphous solid. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.78 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 6.6 Hz), 2.65 (3H, s), 2.65–2.78 (1H, m), 2.98 (3H, s), 6.97 (1H, d, *J* = 1.2 Hz), 7.31 (1H, d, *J* = 8.4 Hz), 7.42 (1H, d, *J* = 1.2 Hz), 7.61–7.67 (2H, m), 7.93–7.97 (2H, m). IR (KBr): 330, 2975, 1634, 1559, 1410, 1159, 822 cm^{-1}. LCMS (API): *m/z* 338.2 $[M+H]^+$. Anal. Calcd for $C_{20}H_{23}N_3O_2 \cdot 0.75H_2O$: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.20; H, 7.15; N, 11.83.

6.2.53. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*,3-dimethyl-2-naphthamide (71h)

Yield 84%, pale yellow amorphous solid. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.77 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 6.6 Hz), 2.48 (3H, s), 2.61–2.74 (1H, m), 2.98 (3H, d, *J* = 3.0 Hz), 6.95 (1H, d, *J* = 1.2 Hz), 7.37 (1H, d, *J* = 1.2 Hz), 7.50 (1H, dd, *J* = 1.8, 8.8 Hz), 7.54 (1H, s), 7.64 (1H, d, *J* = 8.8 Hz), 7.72 (1H, s), 7.88 (1H, s). IR (KBr): 3192, 2968, 1643, 1539, 1408, 1304, 1155, 908, 818 cm^{-1}. LCMS (API): *m/z* 338.2 $[M+H]^+$. Anal. Calcd for $C_{20}H_{23}N_3O_2 \cdot 0.75H_2O$: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.56; H, 7.12; N, 11.79.

6.2.54. Methyl-1-(Bromomethyl)-6-[1-hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (72)

A mixture of **68c** (34.61 g, 59.6 mmol), *N*-bromosuccinimide (12.28 g, 69.0 mmol) and 2,2'-azobisisobutyronitrile (0.99 g, 6.0 mmol) in CCl_4 (800 mL) was refluxed for 21 h. After removing the solvent, the mixture was diluted with aq $NaHCO_3$ solution. The resulting mixture was extracted with AcOEt–THF and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt) to give a crude mixture of **68c** and **72** (**68c:72** = 1:7, 23.1 g, 59%). The analytical sample was obtained by recrystallization from THF–AcOEt as a colorless powder. Mp 195°C decomp. ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 2.55 (1H, septet, *J* = 6.8 Hz), 3.78 (1H, s), 3.99 (3H, s), 5.43 (1H, d, *J* = 9.8 Hz), 5.47 (1H, d, *J* = 9.8 Hz), 6.82 (1H, d, *J* = 1.4 Hz), 7.10–7.35 (16H, m), 7.72 (1H, dd, *J* = 8.8, 1.8 Hz), 7.81 (1H, d, *J* = 8.8 Hz), 7.92 (1H, d, *J* = 8.8 Hz), 8.10 (1H, d, *J* = 1.8 Hz), 8.18 (1H, d, *J* = 8.8 Hz). IR (KBr): 1725, 1238, 702 cm^{-1}. Anal. Calcd for $C_{39}H_{35}N_2O_3Br$: C, 71.01; H, 5.35; N, 4.25; Br, 12.11. Found: C, 70.86; H, 5.42; N, 4.19.

6.2.55. 7-[1-Hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (73a)

A solution of saturated NH_3 in MeOH (50 mL) was added to a cooled (0°C) solution of **72** (5.58 g, crude 8.5 mmol) in THF (50 mL), and stirred for 1 h at rt. After removal of the solvent, the residue was diluted with aq $NaHCO_3$ solution. The resulting mixture was extracted with AcOEt–THF and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt/MeOH = 20:1) to give **73a** (1.22 g, 26%) as a colorless powder. Mp 250°C decomp. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.74 (3H, d, *J* = 6.6 Hz), 0.98 (3H, d, *J* = 6.6 Hz), 2.59 (1H, septet, *J* = 6.6 Hz), 4.73 (2H, s), 6.85 (1H, s), 7.10–7.38 (16H, m), 7.78–7.90 (4H, m), 8.11 (1H, s). IR (KBr): 1690, 745, 702 cm^{-1}. Anal. Calcd for $C_{38}H_{33}N_3O_2 \cdot 0.5H_2O$: C, 79.69; H, 5.98; N, 7.34. Found: C, 79.57; H, 6.27; N, 7.07.

6.2.56. 7-[1-Hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (73b)

Using **72** (0.80 g, 1.2 mmol) was used as the starting material and the same procedure described for the synthesis of **73a** with 40% methylamine solution, **73b** (0.77 g, quant.) was obtained as a colorless powder. The analytical sample was obtained by recrystallization from THF as a colorless powder. Mp 250°C decomp. ^{1}H NMR ($CDCl_3$) δ: 0.74 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 2.56 (1H, septet, *J* = 6.6 Hz), 3.29 (3H, s), 3.69 (1H, br s), 4.68 (2H, s), 6.83 (1H, d, *J* = 1.4 Hz), 7.10–7.36 (16H, m), 7.76 (2H, s), 7.83 (2H, s), 8.11 (1H, s). IR (KBr): 3409, 1680, 704 cm^{-1}. Anal. Calcd for $C_{39}H_{35}N_3O_2$: C, 81.08; H, 6.11; N, 7.27. Found: C, 80.69; H, 6.11; N, 7.12.

6.2.57. 7-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (74a)

Compound **73a** (1.17 g, 2.1 mmol) was used as a starting material. Using the same procedure described for the synthesis of **53, 74a** (0.50 g, 75%) was obtained as a colorless powder. The analytical sample was obtained by recrystallization from EtOH–H_2O as a colorless powder. Mp 230°C decomp. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.79 (3H, d, *J* = 6.6 Hz), 1.02 (3H, d, *J* = 6.6 Hz), 2.76 (1H, septet, *J* = 6.6 Hz), 4.68 (2H, s), 7.04 (1H, s), 7.55 (1H, s), 7.70–7.77 (3H, m), 7.88 (1H, d, *J* = 8.4 Hz), 8.15 (1H, s). IR (KBr): 1684, 1472, 747 cm^{-1}. LCMS (API): *m/z* 322.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.76; H, 6.04; N, 12.78.

6.2.58. 7-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*] isoindol-3-one (74b)

Using **73b** was used as the starting material and the same procedure as described for the synthesis of **74a, 74b** (0.28 g, 90%) was obtained as a colorless powder. The analytical sample was obtained by recrystallization from THF–MeOH (colorless powder). Mp 250°C decomp. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.80 (3H, d, *J* = 7.0 Hz), 1.02 (3H, d, *J* = 7.0 Hz), 2.78 (1H, septet, *J* = 7.0 Hz), 3.29 (3H, s), 4.73 (2H, s), 7.04 (1H, d, *J* = 1.2 Hz), 7.54 (1H, d, *J* = 1.2 Hz), 7.76–7.94 (4H, m), 8.17 (1H, s). ^{13}C NMR (DMSO- d_6) δ: 16.7, 17.4, 29.0, 36.7, 50.6, 77.4, 112.0, 119.0, 122.5, 124.3, 125.9, 126.5, 128.6, 129.0, 133.9, 134.2, 140.5, 147.1, 147.7, 168.1. IR (KBr): 3193, 1667, 1003 cm^{-1}. LCMS (API): *m/z* 336.2 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 0.1H_2O$: C, 71.24; H, 6.34; N, 12.46. Found: C, 71.09; H, 6.48; N, 12.23.

6.2.59. Methyl-3-(bromomethyl)-6-[1-hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (75)

Using **68d** (5.93 g, 10.2 mmol) as the starting material and the same procedure as described for the synthesis of **72**, crude **75** (6.70 g, quant.) was obtained as a brown amorphous solid. ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 2.53 (1H, septet, *J* = 6.6 Hz), 3.74 (1H, s), 4.00 (3H, s), 5.12 (1H, d, *J* = 10.4 Hz), 5.15 (1H, d, *J* = 10.4 Hz), 6.81 (1H, d, *J* = 1.0 Hz), 7.09–7.38 (16H, m), 7.65 (1H, dd, *J* = 8.4, 1.6 Hz), 7.78–7.84 (2H, m), 8.02 (1H, s), 8.50 (1H, s). IR (KBr): 2969, 1717, 1287, 702 cm^{-1}. Anal. Calcd $C_{39}H_{35}N_2O_3Br \cdot 2H_2O$: C, 67.34; H, 5.65; N, 4.03; Br, 12.11.Found: C, 67.38; H, 5.50; N, 4.34.

6.2.60. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2,3-dihydro-1*H*-benzo[*f*]isoindol-1-one (77a)

Using **75** (5.00 g, 7.3 mmol) as the starting material and the same procedure as described for the synthesis of **74a, 77a** (1.46 g, 64%) was obtained as a colorless power. The analytical sample was obtained by recrystallization from EtOH as a colorless powder. Mp 204.0–208.0°C. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.80 (3H, d, *J* = 7.0 Hz), 1.02 (3H, d, *J* = 7.0 Hz), 2.76 (1H, septet, *J* = 7.0 Hz), 4.56 (2H, s), 7.03 (1H, d, *J* = 1.2 Hz), 7.53 (1H, d, *J* = 1.2 Hz), 7.65 (1H, dd, *J* = 8.4, 1.6 Hz), 7.90–7.96 (2H, m), 8.13 (1H, s), 8.31 (1H, s). IR (KBr): 3208, 1671 cm^{-1}. LCMS (API): *m/z* 322.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot C_2H_5OH$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.30; H, 6.84; N, 11.29.

6.2.61. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-methyl-2,3-dihydro-1*H*-benzo[*f*] isoindol-1-one (77b)

Using **75** (0.99 g, 1.5 mmol) as the starting material and the same procedure as described for the synthesis of **74a, 77b** (0.11 g, 22%) was obtained as a colorless power. The analytical sample was obtained by recrystallization from EtOH (colorless powder). Mp 260°C decomp. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.81 (3H, d, *J* = 6.6 Hz), 1.02 (3H, d, *J* = 6.6 Hz), 2.70–2.90 (1H, m), 3.27 (3H, s), 4.59 (2H, s), 7.04 (1H, s), 7.54 (1H, s), 7.65–7.73 (1H, m), 7.92–7.96 (2H, m), 8.14 (1H, s), 8.27 (1H, s). ^{13}C NMR (DMSO- d_6) δ: 16.7, 17.4, 29.1, 36.6, 51.1, 77.4, 112.0, 121.8, 121.9, 123.4, 125.5, 128.0, 130.0, 130.8, 134.1, 134.1, 134.2, 136.5, 147.2, 147.4, 167.1. IR (KBr): 3167, 1663, 1400, 1150, 810, 625 cm^{-1}. LCMS (API): *m/z* 336.2 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.22; H, 6.61; N, 12.46.

6.2.62. Optical resolution of 74a

Optical resolution of **74a** (13.1 g) was performed using preparative HPLC on a Chiralpak AD column (50 mmID × 500 mmL, eluent: hexane/EtOH/diethylamine = 85:15:0.1, flow rate: 80–100 mL/min, temperature: 35°C) to yield **(−)-74a** (5.27 g, 99.9% enantiomeric excess [ee]) as a colorless powder and **(+)-74a** (5.39 g, 99.7% ee) as colorless amorphous solid. **(−)-74a**: Mp 220.0–222.0°C. ^{1}H NMR (DMSO- d_6) δ : 0.66 (3H, d, *J* = 6.8 Hz), 0.75–0.97 (3H, m), 2.67–2.86 (1H, m), 4.71 (2H, s), 5.18 (1H, br s), 7.02 (1H, br s), 7.56 (1H, br s), 7.64 (1H, d, *J* = 8.3 Hz), 7.82–8.10 (3H, m), 8.25 (1H, br s), 8.58 (1H, s), 11.82 (1H, br s). IR (KBr): 3185, 2976, 1686 cm^{-1}. LCMS (API): *m/z* 322.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 0.5H_2O$: C, 69.07; H, 6.10; N, 12.72. Found: C, 69.37; H, 6.11; N, 12.68. $[\alpha]_D^{20}$ =-41.2 (c 0.9520, MeOH). **(+)-74a**: The spectral data of **(+)-74a** were identical to those of the **(−)-74a** except for elemental analysis and optical rotation. LCMS (API): *m/z* 322.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 1.25H_2O \cdot 0.25AcOEt$: C, 65.65; H, 6.47; N, 11.48. Found: C, 65.40; H, 6.68; N, 11.36. $[\alpha]_D^{20}$ =+35.4 (c 1.0085, MeOH).

6.2.63. Optical resolution of 74b

Optical resolution of **74b** (2.40 g) was performed using preparative HPLC on a Chiralpak AD column (50 mmID × 500 mmL, eluent: hexane/EtOH = 40:60, flow rate: 60 mL/min, temperature: rt) to yield **(−)-74b** (1.10 g, 99.9% ee) as a colorless powder and **(+)-74b** (1.00 g, 99.8% ee) as a colorless powder. **(−)-74b**: Mp 207.0–209.0°C. ^{1}H NMR (DMSO- d_6) δ : 0.65 (3H, d, *J* = 6.6 Hz),

0.83 (3H, d, *J* = 6.6 Hz), 2.65–2.87 (1H, m), 3.14 (3H, s), 4.78 (2H, s), 5.17 (1H, s), 7.04 (1H, s), 7.42–7.76 (2H, m), 7.80–8.08 (3H, m), 8.26 (1H, s), 11.83 (1H, br s). The ^{13}C NMR spectral data of **(−)-74b** was identical to those of the **74b**. IR (KBr): 3148, 2971, 1669 cm^{-1}. LCMS (API): *m/z* 336.2 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 0.75H_2O$: C, 68.85; H, 6.50; N, 12.04. Found: C, 68.71; H, 6.38; N, 11.99. $[\alpha]_D^{20}$ =-33.4 (c 0.226, MeOH). **(+)-74b**: The spectral data of **(+)-74b** were identical to those of the **(−)-74b** except for elemental analysis and optical rotation. Mp 207.0–209.0°C. LCMS (API): *m/z* 336.1 $[M+H]^+$. Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 0.75H_2O$: C, 68.85; H, 6.50; N, 12.04. Found: C, 68.99; H, 6.45; N, 11.95. $[\alpha]_D^{20}$ =+34.5 (c 0.258, MeOH).

6.2.64. 7-[(1*R*)-1-{1-[(4-Bromophenyl)sulfonyl]-1*H*-imidazol-4-yl}-1-hydroxy-2-methylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (78)

4-Bromobenzenesulfonyl chloride (460 mg, 1.8 mmol) was added to a solution of **(+)-74b** (503 mg, 1.5 mmol) in DMF (12 mL) and the mixture was stirred at rt for 3 h. The mixture was poured into water and the aqueous phase extracted with AcOEt. The combined organic layer was washed with 10% citric acid solution, H_2O and brine, dried over $MgSO_4$ and evaporated. The residue was crystallized from AcOEt–*i*-Pr_2O to give **78** (730 mg, 88%). Analytical sample was obtained by recrystallization from THF–MeOH. Mp 170°C. IR (KBr): 3345, 1671, 745, 635 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.76 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.6 Hz), 2.79 (1H, septet, *J* = 6.6 Hz), 2.96 (1H, s), 3.27 (3H, s), 4.66 (2H, s), 7.31 (1H, d, *J* = 1.4 Hz), 7.64–7.88 (8H, m), 7.94 (1H, d, *J* = 1.4 Hz), 8.14 (1H, s). Anal. Calcd for $C_{26}H_{24}BrN_3O_4S \cdot MeOH$: C, 55.29; H, 4.81; N, 7.13. Found: C, 55.48; H, 4.75; N, 6.98.

6.2.65. 6-Bromo-*N*,*N*-diisopropyl-2-naphthamide (79b)

A solution of 6-bromo-2-naphthoic acid **79a** (100 g, 398 mmol), thionylchloride (37.7 mL, 517 mmol) and DMF (0.5 mL) in THF (1000 mL) was stirred at 60°C for 90 min. After cooling to rt, the solvent and excess amount of thionylchloride was evaporated. The resulting residue was dissolved in dry THF (400 mL) and the solution was added dropwise to a cooled (0°C) solution of diisopropylamine (112 mL, 799 mmol) and triethylamine (112 mL, 804 mmol) in THF (800 mL). After being stirred at rt for 1 h, about 50% of the solvent was evaporated. Then the mixture was diluted with AcOEt and the organic phase was washed with H_2O, 1 N NaOH solution and brine, dried over $MgSO_4$ and evaporated. The residue was washed with *i*-Pr_2O to give **79b** (117 g, 88%) as a colorless crystal. ^{1}H NMR ($CDCl_3$) δ: 1.36 (12H, br s), 3.71 (2H, br s), 7.44 (1H, dd, *J* = 1.2 Hz,

8.6 Hz), 7.58 (1H, dd, *J* = 2.2 Hz, 8.8 Hz), 7.70–7.79 (3H, m), 8.01 (1H, d, *J* = 1.2 Hz). IR (KBr): 2968, 1620, 1435, 1369, 1333, 895, 814 cm^{-1}. LCMS (API): *m/z* 334.1 $[M+H]^+$. Anal. Calcd for $C_{17}H_{20}NOBr$: C, 61.09; H, 6.03; N, 4.19; Br, 23.91. Found: C, 61.22; H, 6.08; N, 4.12.

6.2.66. 6-[(2*R*)-2-(*tert*-Butyldimethylsilyloxy)propanoyl]-*N*,*N*-diisopropyl-2-naphthamide (80a)

Solution **79b** (46.80 g, 140.0 mmol) in THF (400 mL) was added dropwise to a cooled (−70°C) solution of *n*-BuLi (1.6 mol/L in hexane; 96.3 mL, 154 mmol) in toluene (900 mL) and the mixture was stirred at −70°C for 30 min. A solution of **40** (34.45 g, 126.0 mmol) in toluene (50 mL) was added to the mixture and the solution was stirred at −78°C for 30 min. The reaction was quenched with aq NH_4Cl and the mixture was warmed to rt. After extraction with AcOEt, the combined organic layers were dried over $MgSO_4$ and evaporated to give **80a** as a pale yellow oil. This compound was directly used without further purification in the next step. ^1H NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.12 (3H, s), 0.91 (9H, s), 1.10–1.60 (12H, m), 1.60 (3H, d, *J* = 7.0 Hz), 3.50–4.00 (2H, br m), 5.04 (1H, q, *J* = 7.0 Hz), 7.50 (1H, dd, *J* = 8.4, 1.4 Hz), 7.83 (1H, s), 7.91 (1H, d, *J* = 8.4 Hz), 7.99 (1H, d, *J* = 8.4 Hz), 8.14 (1H, d, *J* = 8.4, 1.4 Hz), 8.72 (1H, s). IR (KBr): 1694, 1630, 1441, 1335, 835 cm^{-1}.

6.2.67. 6-[(2*R*)-2-Hydroxypropanoyl]-*N*,*N*-diisopropyl-2-naphthamide (80b)

TBAF (41.01 g, 157 mmol) was added to a cooled (−10°C) solution of **80a** (25.7 g, 74.9 mmol) in THF (900 mL) and the mixture was stirred at 0°C for 1 h. The mixture was diluted with brine 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 = 2:1–2:3) and washed with diethylether to give **80b** (24.00 g, 58% from **40**) as a colorless solid. Mp 174°C. $[\alpha]_D^{20}$ =+38.2 (c 0.726, MeOH). ^1H NMR ($CDCl_3$) δ: 1.10–1.70 (12H, br m), 1.52 (3H, d, *J* = 6.9 Hz), 3.40–3.90 (2H, br), 3.84 (1H, d, *J* = 6.9 Hz), 5.32 (1H, quint, *J* = 6.9 Hz), 7.52 (1H, dd, *J* = 8.4, 1.8 Hz), 7.84 (1H, s), 7.95 (1H, d, *J* = 8.4 Hz), 8.00–8.04 (2H, m), 8.45 (1H, s). IR (KBr): 3493, 1678, 1628, 1117, 826 cm^{-1}. LCMS (API): *m/z* 328.1 $[M+H]^+$. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.24; H, 7.60; N, 4.21.

6.2.68. 6-[(1*S*,2*R*)-1,2-Dihydroxy-1-isopropylpropyl]-*N*,*N*-diisopropyl-2-naphthamide (81)

A solution of *i* -propylmagnesium bromide (0.7 M in THF; 500 mL, 350 mmol) was added dropwise over 2 h to a cooled (−10°C) solution of **80b** (20.08 g, 61.3 mmol) in THF (300 mL) and

the mixture was stirred at 0°C for 1 h. The reaction was quenched with satd aq NH_4Cl and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was crystallized from *i* -Pr_2O to give **81** (12.35 g, 54%) as a colorless solid. The purity of the obtained **81** was >95% as determined by HPLC using a Chiralpak AD column. The analytical sample was obtained by recrystallization from AcOEt. Mp 200°C. $[\alpha]_D^{20}$ =+19.9 (c 0.545, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 1.06 (3H, d, *J* = 6.6 Hz), 1.00–1.70 (12H, br m), 1.65 (1H, d, *J* = 4.2 Hz), 2.45 (1H, septet, *J* = 6.6 Hz), 2.61 (1H, s), 3.50–4.00 (2H, br), 4.37 (1H, dq, *J* = 4.2, 6.6 Hz), 7.41 (1H, dd, *J* = 8.4, 1.8 Hz), 7.48 (1H, dd, *J* = 8.4, 1.8 Hz), 7.77–7.90 (4H, m). IR (KBr): 3511, 2971, 1617, 1443, 1372, 1341 cm^{-1}. LCMS (API): *m/z* 372.2 $[M+H]^+$. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.39; H, 8.77; N, 3.73.

6.2.69. 7-[(1*S*,2*R*)-1,2-Dihydroxy-1-isopropylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (84a)

n-BuLi (1.6 mol/L, 103.8 mL, 166 mmol) was added dropwise to a cooled (−70°C) solution of **81** (12.35 g, 33.2 mmol) and tetramethylethylenediamine (TMEDA) (60 mL) in THF (250 mL) and the mixture was stirred at −70°C for 2.5 h. To the mixture, DMF (25 mL) was added dropwise, and the reaction mixture was further stirred at −70°C for 1 h. After diluting with aq NH_4Cl solution, the aqueous layer was extracted with AcOEt. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$. Removal of the solvent in vacuo gave a crude product of **82a** and **82b** (**82a:82b** = ca. 6:1) as amorphous solid. The crude product of **82a** and **82b** was dissolved in CH_2Cl_2 (250 mL) and methylamine (2 M in THF, 67.5 mL, 135 mmol) was added. After adjusting the pH of the reaction mixture to 6–7 with acetic acid (ca. 9 mL), $NaBH(OAc)_3$ (59.3 g, 280 mmol) was added dropwise to the reaction mixture, which was then stirred at rt for 62 h. After being diluted with 2 N HCl, the aqueous layer was washed with AcOEt. The aqueous layer was then made alkaline with 10 N NaOH solution and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a crude product of **83a** and **83b**.

n-BuLi (1.6 M in hexane; 104 ml, 166 mmol) was added dropwise to a cooled (−60°C) solution of diisopropylamine (24.5 mL, 175 mmol) in THF (250 mL) and the mixture was stirred at −70°C for 10 min to prepare the LDA solution. A solution of the crude product of **83a** and **83b** in THF (70 mL) was then added dropwise, and the reaction mixture was allowed to warm to 0°C over 2 h. After being diluted with aq NH_4Cl solution, the aqueous layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (AcOEt) and crystallized from THF–AcOEt to yield a mixture of **84a**

and **84b** (4.33 g, 42%, **84a:84b** = 93:7) as a colorless solid. The ratio of the obtained **84a** and **84b** was determined by HPLC using Chiralpak AD column. ^{1}H NMR ($CDCl_3$) δ: 0.89 (3H, d, *J* = 6.9 Hz), 0.95 (3H, d, *J* = 6.9 Hz), 1.07 (3H, d, *J* = 6.3 Hz), 1.82 (1H, d, *J* = 6.3 Hz), 2.46 (1H, septet, *J* = 6.9 Hz), 2.69 (1H, s), 3.29 (3H, s), 4.41 (1H, quint, *J* = 6.3 Hz), 4.70 (2H, s), 7.61 (1H, dd, *J* = 8.7, 1.8 Hz), 7.80–7.97 (3H, m), 8.01 (1H, d, *J* = 1.8 Hz). IR (KBr): 3420, 1686, 826, 747 cm^{-1}. LCMS (API): *m/z* 314.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{23}NO_3 \cdot 0.1$AcOEt: C, 72.32; H, 7.45; N, 4.35. Found: C, 72.37; H, 7.61; N, 4.32.

6.2.70. 7-[(1*S*)-1-Acetyl-1-hydroxy-2-methylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (85)

Dimethyl sulfoxide (DMSO) (3.63 mL, 51.1 mmol) was added dropwise to a cooled (−70°C) solution of oxalylchloride (2.22 mL, 25.5 mmol) in CH_2Cl_2 (40 mL) and the mixture was stirred at −70°C for 1 h. A solution of **84a** (4.00 g, 12.8 mmol, **84a:84b** = 93:7) in CH_2Cl_2/DMSO (1:1, 12 mL) was added dropwise, and the reaction mixture was warmed to −20°C over 1 h. After cooling to −70°C, triethylamine (10.7 mL, 76.6 mmol) was added dropwise to the mixture and the solution was allowed to warm to rt and stirred for a further 2 h. The resulting mixture was diluted with H_2O and the combined organic layers were washed with H_2O and dried over $MgSO_4$. After removal of the solvent in vacuo, the resulting solid was washed with *i* -Pr_2O and recrystallized from AcOEt to give **85** (3.10 g, 33% from **81**) as a colorless solid. The purity of the obtained **85** was >99% as determined by HPLC using a Chiralpak AD column. Mp 171°C. $[\alpha]_D^{20}$ =-22.9 (c 0.615, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.94 (3H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 6.9 Hz), 2.20 (3H, s), 2.97 (1H, septet, *J* = 6.9 Hz), 3.29 (3H, s), 4.63 (1H, s), 4.70 (2H, s), 7.77 (1H, dd, *J* = 8.7, 1.8 Hz), 7.84–7.92 (3H, m), 8.17 (1H, d, *J* = 1.8 Hz). IR (KBr): 3335, 1705, 1667, 1171, 748 cm^{-1}. LCMS (API): *m/z* 312.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}NO_3 \cdot 0.6$AcOEt: C, 70.57; H, 7.14; N, 3.85. Found: C, 70.60; H, 7.16; N, 4.12.

6.2.71. 7-[(1*S*)-3-Bromo-1-hydroxy-1-isopropyl-2-oxopropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (86)

Pyridinium bromide perbromide (3.17 g, 9.9 mmol) was added to a cooled (0°C) solution of **85** (2.80 g, 9.0 mmol) in THF (35 mL) and the mixture was stirred at rt for 66 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 10% aq citric acid solution and aq $NaHCO_3$ solution, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was

chromatographed on silica gel (hexane/AcOEt = 1:1–1:2) to give **86** (2.97 g, 85%) including starting material **85** as a colorless solid. This compound was used without further purification in the next step. ^{1}H NMR ($CDCl_3$) δ: 0.80 (3H, d, *J* = 6.6 Hz), 1.04 (3H, d, *J* = 6.6 Hz), 2.99 (1H, septet, *J* = 6.6 Hz), 3.28 (3H, s), 3.97 (1H, s), 4.27 (1H, d, *J* = 15.0 Hz), 4.34 (1H, d, *J* = 15.0 Hz), 4.68 (2H, s), 7.72–7.91 (4H, m), 8.19 (1H, d, *J* = 1.4 Hz). IR (KBr): 1670 cm^{-1}.

6.2.72. 7-{(1*S*,2*Z*)-3-Bromo-1-isopropyl-1,2-bis[(trimethylsilyl)oxy]prop-2-enyl}-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (87)

TBAF (1 M solution in THF, 32 mL, 0.032 mmol) was added to a solution of **86** (0.63 g, 1.6 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (2.4 mL, 9.7 mmol) in DMF (8 mL) and the reaction mixture was stirred at rt for 16 h. After being diluted with AcOEt, the mixture was washed with H_2O, followed by brine, before drying over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (hexane/AcOEt = 13:7–7:13) to give **87** (0.55 g, 54% from **85**) as colorless amorphous solid. ^{1}H NMR ($CDCl_3$) δ: −0.14 (9H, s), 0.09 (9H, s), 0.85 (3H, d, *J* = 6.9 Hz), 1.00 (3H, d, *J* = 6.9 Hz), 2.59 (1H, septet, *J* = 6.9 Hz), 3.31 (3H, s), 4.72 (2H, s), 5.90 (1H, s), 7.64 (1H, dd, *J* = 9.0, 4.8 Hz), 7.78–7.94 (4H, m). IR (KBr): 1690, 1252, 843 cm^{-1}. LRMS (FAB): *m/z* 534 $[M+H]^+$.

6.2.73. 7-[(1*S*)-1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one [(−)-74b]

Saturated ammonia solution in MeOH (1.5 mL) and formamidine acetate (31 mg, 0.3 mmol) was added to a cooled (−15°C) solution of **87** (160 mg, 0.30 mmol) in THF (0.5 mL) and the resulting mixture was stirred at −15°C for 30 min. The reaction mixture was allowed to warm to rt over 3 h and stirred at rt for a further 90 h. After removing excess NH_3 and MeOH, the residue was diluted with brine. The aqueous layer was extracted with AcOEt/THF (1:1) and the combined organic layer was dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 30:1–6:1) to give **(−)-74b** (54 mg, 54%). The optical purity of the obtained **(−)-74b** was >99% ee as determined by HPLC using a Chiralpak AD column.

6.3.1. Optical resolution of 1 using preparative HPLC

Compound **71b** (12.7 g, 39.3 mmol) was subjected to optical resolution by preparative HPLC using a Chiralpak AD column (50 mm × 500 mm) using hexane/ethanol (85/15) as an eluent, detected at 254 nm, to afford **(-)-71b** (6.09 g, 18.8 mmol, 48%) as a first elution and **(+)-71b** (6.02 g, 18.6 mmol, 47%) as a second elution. **(-)-71b**: $[\alpha]_D^{25}$ = −55.7 (c 0.908, MeOH); t R = 17.1 min (Chiralpak AD 4.6 mmID × 250 mmL, hexane/ethanol = 85/15, 0.8 mL/min, at 254 nm); >99.9% ee. Compound **(+)-71b**: $[\alpha]_D^{25}$ = +56.1 (c 0.924, MeOH); tR = 29.0 min (Chiralpak AD 4.6 mmID × 250mmL, hexane/ethanol = 85/15, 0.8 mL/min, at 254 nm); 99.8% ee.

6.3.2. 6-[(1*S*)-1-{1-[(4-Bromophenyl)sulfonyl]-1*H*-imidazol-4-yl}-1-hydroxy-2-ethylpropyl]-*N*-methylnaphthalene-2-carboxamide (88)

To a solution of **(-)-71b** (210 mg, 0.65 mmol) and Et_3N (0.226 mL, 1.62 mmol) in DMF (5 mL) was added dropwise 4-bromobenzenesulfonyl chloride (166 mg, 0.65 mmol) and the mixture was stirred at room temperature for 16 h. After being diluted with aqueous $NaHCO_3$ solution, the appeared solid was filtered off, washed with H_2O and dried in air. The obtained solid was recrystallized from AcOEt and tetrahydrofuran (THF) to give **88** (278 mg, 0.512 mmol, 79%) as a colorless powder. ^{1}H NMR (DMSO-d_6) δ : 0.62 (3H, d, *J* = 6.8 Hz), 0.73 (3H, d, *J* = 6.8 Hz), 2.64–2.78 (1H, m), 2.82 (3H, d, *J* = 4.5 Hz), 5.55 (1H, s), 7.49 (1H, d, *J* = 1.5 Hz), 7.80–7.94 (6H, m), 7.96–8.04 (2H, m), 8.09 (1H, s), 8.33 (1H, s), 8.37 (1H, d, *J* = 1.5 Hz), 8.54 (1H, q, *J* = 4.6 Hz). $[\alpha]_D^{25}$ = +57.6 (c 0.187, MeOH).

6.3.3. 3-Bromo-1-(1*H*-imidazol-4-yl)-1-propanone hydrogen bromide (91)

25% hydrogen bromide in acetic acid (100 mL) was added dropwise to a cooled (10°C) solution of **90** (29.0 g, 80.0 mmol) in acetic acid (130 mL) and the mixture was stirred for 2 h at room temperature. After being diluted with diisopropylether (*i*-Pr_2O) the precipitate was collected by filtration and washed with *i*-Pr_2O to give **91** (22.3 g, quant.) as a pale yellow powder. ^{1}H NMR (CD_3OD) δ: 3.54–3.81 (4H, m), 8.50 (1H, d, *J* = 1.2 Hz), 9.15 (1H, d, *J* = 1.2 Hz).

6.3.4. 5,6-Dihydro-7*H*-pyrrolo[1,2-*c*]imidazol-7-one (92)

A solution of Et_3N (15.3 mL, 110 mmol) in CH_3CN (25 mL) was added dropwise to a hot (70°C) suspension of **91** (28.5 g, 100 mmol) in CH_3CN (1100 mL) and the mixture was stirred at 70°C for 2 h. Triethylamine (25 mL, 179 mmol) was then added to the mixture, and the solution was stirred at 70°C for a further 30 min. After cooling to room temperature, the insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the insoluble material was again filtered off. The filtrate was concentrated under reduced pressure and the resulting residue was separated by chromatography on silica gel (CH_2Cl_2/5% ammonia in MeOH = 10:1) to give **92** (6.67 g, 61%) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ: 3.24 (2H, t, *J* = 6.5 Hz), 4.41 (2H, t, *J* = 6.5 Hz), 7.60 (1H, s), 7.74 (1H, s). IR(KBr): 3121, 1713, 1537, 1489, 1412, 1319, 1204, 1109 cm^{-1}.

6.3.5. 6,6-Dimethyl-5,6-dihydro-7*H*-pyrrolo[1,2-*c*]imidazol-7-one (93)

Potassium *tert*-butoxide (*t*-BuOK) (3.14 g, 28.0 mmol) was added dropwise to a cooled (0°C) solution of **92** (1.71 g, 14.0 mmol) in anhydrous tetrahydrofuran (THF) (60 mL), and the solution was stirred for 15 min at 0°C. To the mixture, MeI (1.74 ml, 28.0 mmol) was added dropwise, and the whole was stirred for 2 h at 0°C. After dilution with 20% aqueous ammonium chloride solution and addition of sodium chloride, the aqueous phase was extracted with THF and the extracts were dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (AcOEt) to give **93** (0.90 g, 43%) as a colorless powder. Mp 87°C (*i*-Pr_2O). IR (KBr): 3112, 2971, 1713, 1535, 1211, 1113, 841, 654 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.37 (6H, s), 4.15 (2H, s), 7.63 (1H, s), 7.71 (1H, s). Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.09; H, 6.98; N, 18.81.

6.3.6. 6-Bromo-*N*-methyl-2-naphthamide (95a)

Under an argon atmosphere, to a cooled (0°C) solution of **94** (60.26 g, 240 mmol), EDCI·HCl (55.21 g, 288 mmol), HOBt·H_2O (44.1 g, 288 mmol) and *N*,*N*-diisopropylethylamine ((*i*-$Pr)_2$NEt) (37.23 g, 288 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (960 mL) was added dropwise to a solution of $MeNH_2$ (2 M solution in THF; 192 mL, 384 mmol) and the whole was stirred at room temperature for 18 h. After dilution with water, the precipitate was filtered off, washed with H_2O and *i*-Pr_2O and dried under the reduced pressure to give **95a** (60.6 g, 82%) as a colorless powder. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 3.04 (3H, s), 7.60 (1H, dd, *J* = 1.8 Hz, 8.6 Hz), 7.78 (2H, d, *J* = 8.6 Hz), 7.85 (1H, dd, *J* = 1.8 Hz, 8.6 Hz), 8.03 (1H, d, *J* = 1.8 Hz), 8.25 (1H, s). IR (KBr): 3274, 1638, 1622,

1559, 1495, 1408, 1316, 1159 cm^{-1}. Anal. Calcd for $C_{12}H_{10}NOBr.0.1H_2O$: C, 54.20; H, 3.87; N, 5.27; Br, 30.25. Found: C, 54.03; H, 3.72; N, 5.24. Compounds **95b–d** were prepared in the same manner as described for the preparation of **95a**.

6.3.7. 6-Bromo-*N*-ethyl-2-naphthamide (95b)

Yield 60%. ^1H NMR ($CDCl_3$) δ:1.30 (3H, t, *J* = 7.3 Hz), 3.56 (2H, dq, *J* = 5.6 Hz, 7.3 Hz), 6.29 (1H, br s), 7.60 (1H, dd, *J* = 2.0 Hz, 8.8 Hz), 7.77 (2H, d, *J* = 8.8 Hz), 7.85 (1H, dd, *J* = 2.0 Hz, 8.8 Hz), 8.03 (1H, d, *J* = 2.0 Hz), 8.24 (1H, s). IR (KBr): 3275, 2976, 1638, 1620, 1555, 1460, 1314, 1186 cm^{-1}. Anal. Calcd for $C_{13}H_{12}NOBr.0.25H_2O$: C, 55.24; H, 4.46; N, 4.96; Br, 28.73. Found: C, 55.54; H, 4.16; N, 4.80.

6.3.8. 6-Bromo-*N*-cyclopropyl-2-naphthamide (95c)

Yield 70%. ^1H NMR ($CDCl_3$) δ: 0.64–0.73 (2H, m), 0.87–0.97 (2H, m), 2.90–3.02 (1H, m), 6.42 (1H, br s), 7.60 (1H, dd, *J* = 2.0 Hz, 8.8 Hz), 7.77 (2H, d, *J* = 8.8 Hz), 7.82 (1H, dd, *J* = 2.0 Hz, 8.8 Hz), 8.03 (1H, d, *J* = 2.0 Hz), 8.21 (1H, d, *J* = 2.0 Hz). IR (KBr): 3254, 3061, 1632, 1618, 1541, 1491, 1318, 1138 cm^{-1}. Anal. Calcd for $C_{14}H_{12}NOBr$: C, 57.95; H, 4.17; N, 4.83; Br, 27.54. Found: C, 57.71; H, 4.12; N, 4.79.

6.3.9. 6-Bromo-*N*-isopropyl-2-naphthamide (95d)

Yield 70%. ^1H NMR ($CDCl_3$) δ:1.31 (6H, d, *J* = 6.6 Hz), 4.27–4.44 (1H, m), 6.09 (1H, d, *J* = 7.8 Hz), 7.60 (1H, dd, *J* = 1.8 Hz, 8.8 Hz), 7.78 (2H, d, *J* = 8.8 Hz), 7.84 (1H, dd, *J* = 1.8 Hz, 8.8 Hz), 8.03 (1H, d, *J* = 1.8 Hz), 8.22 (1H, s). IR (KBr):3262, 2973, 1634, 1620, 1557, 1468, 1352, 1186 cm^{-1}. Anal. Calcd for $C_{14}H_{14}NOBr$: C, 57.55; H, 4.83; N, 4.79; Br, 27.35. Found: C, 57.40; H, 4.65; N, 4.83.

6.3.10. 6-Bromo-*N*,*N*-diisopropyl-2-naphthamide (95e)

A solution of 6-bromo-2-naphthoic acid **94** (100 g, 398 mmol), thionylchloride ($SOCl_2$) (37.7 mL, 517 mmol) and DMF (0.5 mL) in THF (1000 mL) was stirred at 60°C for 90 min. After cooling to room temperature, the solvent and excess thionylchloride were evaporated. The resulting residue was dissolved in dry THF (400 mL) and the solution was added dropwise to a cooled (0°C) solution of diisopropylamine (112 mL, 799 mmol) and Et_3N (112 mL, 804 mmol) in THF (800 mL). After stirring at room temperature for 1 h, about half the amount of solvent was evaporated. The mixture

was then diluted with AcOEt and the organic phase was washed with H_2O, 1 N NaOH solution and brine, dried over $MgSO_4$ and evaporated. The residue was washed with *i*-Pr_2O to give **95e** (117 g, 88%) as a colorless crystal. ^{1}H NMR ($CDCl_3$) δ: 1.36 (12H, br s), 3.71 (2H, br s), 7.44 (1H, dd, *J* = 1.2 Hz, 8.6 Hz), 7.58 (1H, dd, *J* = 2.2 Hz, 8.8 Hz), 7.70–7.79 (3H, m), 8.01 (1H, d, *J* = 1.2 Hz). IR (KBr) : 2968, 1620, 1435, 1369, 1333, 895, 814 cm^{-1}. Anal. Calcd for $C_{17}H_{20}NOBr$: C, 61.09; H, 6.03; N, 4.19; Br, 23.91. Found: C, 61.08; H, 5.88; N, 4.11.

6.3.11. 6-(7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-2-naphthoic acid (89a)

Under an argon atmosphere, **94** (1.51 g, 6.0 mmol) was dissolved in dry THF (50 mL) and the solution was cooled to −100°C in a liquid N_2 and diethylether bath. A *n*-BuLi hexane solution (1.6 M: 7.88 mL, 12.6 mmol) was added dropwise over 5 min with stirring and the mixture was stirred at the same temperature for 30 min and at −80°C for 10 min. After cooling to −100°C, a solution of **92** (610 mg, 6.0 mmol) in dry THF (11 mL) was added dropwise over 5 min and the whole was stirred at the same temperature for 30 min. After being warmed up to −70°C over 30 min, the reaction was quenched with saturated aqueous ammonium chloride solution. The mixture was diluted with AcOEt and the organic layer was separated. The aqueous phase was concentrated to dryness under reduced pressure. The resulting residue was chromatographed on silica gel ($CHCl_3$/MeOH/H_2O = 65:25:4) and concentrated under the reduced pressure. The residue was dissolved in MeOH and concentrated again under the reduced pressure. The appeared precipitates were washed with diethylether to give **89a** (180 mg, 12%) as a colorless powder. Mp >250°C decomp (Et_2O–MeOH). ^{1}H NMR (CD_3OD) δ: 2.87–3.13 (2H, m), 4.28–4.50 (2H, m), 6.94 (1H, s), 7.65 (1H, dd, *J* = 1.6 Hz, 8.6 Hz), 7.90 (1H, d, *J* = 8.4 Hz), 7.99 (1H, d, *J* = 8.6 Hz), 8.01 (1H, s), 8.06 (1H, dd, *J* = 1.4 Hz, 8.4 Hz), 8.09 (1H, s), 8.57 (1H, s). IR (KBr): 3500–3000, 1698, 1609, 1551, 1480, 1397, 1325, 1086 cm^{-1}. FAB-Ms MH+ 295.

6.3.12. 6-(7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-2-naphthamide (89b)

To a cooled (0°C) solution of **89a** (449 mg, 1.53 mmol), EDCI·HCl (321 mg, 1.67 mmol), ammonium salt of HOBt (301 mg, 1.98 mmol) in anhydrous DMF (7.6 mL) was added dropwise (*i*-Pr)$_2$NEt (216 mg, 1.67 mmol) and the mixture was stirred at room temperature for 18 h. After being concentrated under the reduced pressure with silica gel (3 g), the residue was purified by column chromatography on silica gel ($CHCl_3$/7%NH_3 in MeOH = 19:1) and recrystallized from EtOH to give **89b** (53 mg, 12%). Mp >186°C decomp ($CHCl_3$–MeOH). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 2.94–3.00 (2H, m), 4.15–4.40 (2H, m), 6.82 (1H, s), 7.58 (1H, s), 7.66 (1H, dd, *J* = 1.8 Hz, 8.6 Hz), 7.90 (2H, s), 7.95 (1H, d, *J* = 8.6 Hz), 8.07 (1H, s), 8.40 (1H, s). IR (KBr): 3345, 1663, 1618,

1599, 1493, 1414, 1080 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O_2 \cdot 1.0H_2O$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.63; H, 5.50; N, 13.73.

6.3.13. 6-(7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*-methyl-2-naphthamide (89c)

Under an argon atmosphere, **95a** (436 mg, 1.65 mmol) was dissolved in dry THF (30 mL) and the mixture was cooled to −65°C in a dry ice acetone bath. A *n*-BuLi hexane solution (1.6 M: 2.28 mL, 3.63 mmol) was added with stirring and the mixture was stirred at the same temperature for 1.5 h. After stirring, a solution of **92** (183 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise and the whole was stirred at the same temperature for 1.5 h. After dilution with saturated aqueous ammonium chloride solution, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethanol and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure and the resulting residue was chromatographed on silica gel ($CHCl_3$/7% ammonia in MeOH = 19:1) and crystallized from $CHCl_3$ and diethylether to give **89c** (121 mg, 26%) as a colorless powder. Mp >185°C decomp ($CHCl_3$ + diethylether). ^1H NMR ($CDCl_3$ + CD_3OD) δ: 2.89–3.02 (2H, m), 3.04 (3H, s), 4.12–4.25 (1H, m), 4.27–4.43 (1H, m), 6.79 (1H, s), 7.20 (1H, q, *J* = 4.6 Hz), 7.54 (1H, s), 7.63 (1H, dd, *J* = 1.8 Hz, 8.6 Hz), 7.83 (2H, s), 7.89 (1H, d, *J* = 8.6 Hz), 8.03 (1H, s), 8.28 (1H, s). IR (KBr): 3500–3000, 1644, 1605, 1559, 1497, 1464, 1318, 1082 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3O_2 \cdot 0.1CHCl_3$: C, 68.09; H, 5.40; N, 13.16. Found: C, 68.14; H, 5.20; N, 12.94. Compounds **89e–h** and **89j** were prepared in the same manner as described for the preparation of **89c**.

6.3.14. *N*-Ethyl-6-(7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-2-naphthamide (89e)

Yield 29%. Mp 157–8°C ($CHCl_3$–MeOH). ^1H NMR ($CDCl_3$ + CD_3OD) δ: 1.29 (3H, t, *J* = 7.2 Hz), 2.85–3.06 (2H, m), 3.46–3.60 (2H, m), 4.10–4.24 (1H, m), 4.27–4.41 (1H, m), 6.88 (1H, s), 6.89 (1H, t, *J* = 5.2 Hz), 7.50 (1H, s), 7.62 (1H, dd, *J* = 1.6 Hz, 8.6 Hz), 7.81 (2H, s), 7.87 (1H, d, *J* = 8.6 Hz), 8.02 (1H, s), 8.26(1H, s). IR (KBr): 3283, 1642, 1605, 1557, 1495, 1447, 1316, 1080 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 0.25H_2O$: C, 70.03; H, 6.03; N, 12.89. Found: C, 69.94; H, 6.12; N, 12.74.

6.3.15. *N*-Cyclopropyl-6-(7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-2-naphthamide (89f)

Yield 30%. Mp 146–7°C ($CHCl_3$–MeOH). ^{1}H NMR (DMSO-d_6) δ: 0.58–0.79 (4H, m), 2.75–3.00 (3H, m), 4.12–4.32 (2H, m), 6.17 (1H, s), 6.66 (1H, s), 7.63 (1H, dd, *J* = 1.4 Hz, 8.8 Hz), 7.64 (1H, s), 7.90 (1H, dd, *J* = 1.4 Hz, 8.6 Hz), 7.98 (2H, d, *J* = 8.6 Hz), 8.05 (1H, s), 8.39 (1H, s), 8.61 (1H, d, *J* = 4.4 Hz). IR (KBr): 3258, 1644, 1630, 1603, 1541, 1495, 1316, 1080 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_3O_2 \cdot 0.75H_2O$: C, 69.25; H, 5.96; N, 12.11. Found: C, 69.35; H, 6.22; N, 12.15.

6.3.16. 6-(7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*-isopropyl-2-naphthamide (89g)

Yield 37%. Mp >165°C decomp ($CHCl_3$–MeOH). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.31 (6H, d, *J* = 6.4 Hz), 2.87–3.06 (2H, m), 4.12–4.26 (1H, m), 4.27–4.44 (1H, m), 6.56 (1H, d, *J* = 7.8 Hz), 6.78 (1H, s), 7.52 (1H, s), 7.64 (1H, dd, *J* = 1.8 Hz, 8.8 Hz), 7.82 (2H, s), 7.89 (1H, d, *J* = 8.8 Hz), 8.03 (1H, s), 8.25 (1H, s). IR (KBr): 3277, 1640, 1628, 1603, 1557, 1493, 1350, 1080 cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 0.75H_2O$: C, 68.85; H, 6.50; N, 12.04. Found: C, 68.75; H, 6.43; N, 12.09.

6.3.17. *N,N*-Diisopropyl-6-(7-hydroxy-6,7-dihydro-6,6-dimethyl-5*H*-pyrrolo[1,2-*c*] imidazol-7-yl)-2-naphthamide (89h)

Yield 29%. Mp 250°C decomp (AcOEt). ^{1}H NMR ($CDCl_3$) δ: 0.8 (3H, s), 1.34 (3H, s), 1.00–1.80 (6H, br), 3.50–4.00 (2H, br), 3.79 (1H, d, *J* = 10.2 Hz), 4.14 (1H, d, *J* = 10.2 Hz), 6.89 (1H, s), 7.41–7.46 (2H, m), 7.72–7.86 (4H, m), 8.05 (1H, s). IR (KBr): 2965, 1630, 1335 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_2 \cdot 0.25H_2O$: C,72.32; H, 7.26; N, 11.00. Found: C, 72.56; H, 7.32; N, 10.72.

6.3.18. 6-[1-Hydroxy-1-(1-methyl-1*H*-imidazol-5-yl)ethyl]-*N*-methylnaphthalene-2-carboxamide (89j)

Yield 38%. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.95 (3H, s), 3.04 (3H, s), 3.25 (3H, s), 7.14 (1H, s), 7.35 (1H, s), 7.41 (1H, dd, *J* = 1.8, 8.8 Hz), 7.80–7.90 (3H, m), 7.93 (1H, s), 8.28 (1H, s). IR (KBr): 3241, 3048, 2975, 1640, 1622, 1603, 1553, 1505, 1410, 1321, 1271, 1248, 1167, 1117, 1073 cm^{-1}. Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.75; H, 6.19; N, 13.49.

6.3.19. 6-(6,7-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*-methyl-2-naphthamide (89d)

Under a hydrogen atmosphere (3–4 atom), a mixture of **89c** (77 mg, 0.25 mmol), 1 N HCl (0.5 ml) and 10% palladium carbon (Pd/C) (39 mg) was dissolved in MeOH (5 mL) and the mixture was vigorously stirred at room temperature for 12 h. After the filtration of the catalyst, the filtrate was neutralized with aqueous potassium carbonate solution (0.25 M, 1 mL, 0.25 mmol), the mixture was concentrated under reduced pressure. The resulting residue was chromatographed on silica gel ($CHCl_3$/7% ammonia in MeOH = 19:1) and recrystallized from $CHCl_3$–Et_2O to give **89d** (53 mg, 72%) as a colorless powder. Mp 174–5°C ($CHCl_3$–Et_2O). ^{1}H NMR ($CDCl_3$) δ: 2.55–2.74 (1H, m), 3.07 (3H, d, *J* = 5.0 Hz), 3.04–3.26 (1H, m), 4.01–4.27 (2H, m), 4.57 (1H, t, *J* = 7.6 Hz), 6.62 (1H, q, *J* = 5.0 Hz), 6.79 (1H, s), 7.39 (1H, dd, *J* = 1.6 Hz, 8.4 Hz), 7.55 (1H, s), 7.70 (1H, s), 7.77–7.95 (3H, m), 8.29 (1H, s). IR (KBr): 3210, 1644, 1605, 1553, 1489, 1410, 1321 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3O \cdot 0.25H_2O$: C, 73.08; H, 5.96; N, 14.20. Found: C, 72.99; H, 6.07; N, 13.99.

6.3.20. 6-(7-Hydroxy-6,7-dihydro-6,6-dimethyl-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*-methyl-2-naphthamide (89i)

n-BuLi (1.6 M in hexane; 3.3 mL, 5.28 mmol) was added dropwise to a cooled (−70°C) solution of methylamine (2 M in THF; 2.65 mL, 5.30 mmol) in anhydrous THF (4 mL) and the solution was stirred for 20 min at −70°C. This solution was transferred to a cooled (0°C) suspension of **89h** (500 mg, 1.23 mmol) in anhydrous THF (10 mL) and the reaction mixture was stirred for 16 h at room temperature. After dilution with brine (200 mL) and water (100 mL), the mixture was extracted with AcOEt and THF (1:1). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from AcOEt to give **89i** (137 mg, 33%) as a colorless powder. Mp 250°C decomp (AcOEt). ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s), 1.33 (3H, s), 3.08 (3H, d, *J* = 4.8 Hz), 3.78 (1H, d, *J* = 10.2 Hz), 4.14 (1H, d, *J* = 10.2 Hz), 6.55 (1H, br), 6.72 (1H, s), 7.45 (1H, s), 7.68–7.82 (4H, m), 8.00 (1H, s), 8.26 (1H, s). IR (KBr): 3241, 1640, 810 cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.18; H, 6.38; N, 12.21. Found: C, 71.08; H, 6.28; N, 12.23.

6.3.21. Synthesis of 6-(7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*-methyl-2-naphthamide (89c) by improved method of route A

Under an argon atmosphere, 2-bromobenzotrifluoride (33.05 g, 147 mmol) was dissolved in dry THF (600 mL) and the mixture was cooled to −65°C in a dry ice acetone bath. A *n*-BuLi hexane solution (1.6 M: 93.7 mL, 150 mmol) was added with stirring and the mixture was stirred at the same temperature for 30 min. After stirring, a cooled (10°C) solution of **95a** (38.03 g, 144 mmol) in

dry THF (2.88 L) was added at not more than −55°C and the mixture was stirred for 20 min. An additional *n*-BuLi hexane solution (1.6 M: 94.5 mL, 151 mmol) was added at not more than −65°C and the mixture was further stirred for 30 min. To the mixture, a solution of **92** (14.66 g, 120 mmol) in a dry THF solution (240 mL) was added dropwise and the resulting solution was stirred at the same temperature for 1.5 h. After dilution with saturated aqueous ammonium chloride solution, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethanol and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure and the resulting residue was chromatographed on silica gel ($CHCl_3$/7% ammonia in MeOH = 19:1 to 9:1) and recrystallized from MeOH to give **89c** (16.44 g, 45%) as a colorless powder. The spectral data were identical to those of the authentic sample.

6.3.22. *N,N*-Diisopropyl-6-[hydroxy(1-trityl-1*H*-imidazol-4-yl)methyl]-2-naphthamide (97)

A solution of **95e** (50.0 g, 150 mmol) in anhydrous THF (250 mL) was added dropwise to a cooled (−70°C) solution of *n*-BuLi (1.6 M in hexane; 98.3 mL, 158 mmol) in anhydrous toluene (1000 mL) over a 30 min period while the temperature of the reaction mixture was maintained at under −60°C. After stirring for 20 min at −70°C, a solution of **29** (38.9 g, 115 mmol) in anhydrous THF (200 mL) was added dropwise over a 20-min period, before stirring for 20 min at −70°C. After dilution with water, the organic layer was separated and the aqueous layer was extracted with AcOEt (×2). The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude mixture of **97** as a yellow viscous oil. This material was used for the next reaction without further purification. The analytical sample was obtained by recrystallization from MeOH (colorless powder). ^{1}H NMR ($CDCl_3$) δ: 1.28 (12H, br s), 3.73 (2H, br s), 4.73 (1H, s), 5.93 (1H, s), 6.59 (1H, d, *J* = 0.8 Hz), 7.06–7.13 (6H, m), 7.27–7.33 (9H, m), 7.36 (1H, dd, *J* = 1.5, 8.5 Hz), 7.42 (1H, d, *J* = 1.4 Hz), 7.48 (1H, dd, *J* = 1.7, 8.7 Hz), 7.71–7.79 (3H, m), 7.88 (1H, s); IR (KBr) 3177, 2964, 1630, 1445, 1337, 1126, 710, 702 cm^{-1}. Anal. Calcd for $C_{40}H_{39}N_3O_2$·0.3MeOH: C, 80.22; H, 6.72; N, 6.96. Found: C, 80.38; H, 6.53; N, 7.05.

6.3.23. *N,N*-Diisopropyl-6-[(1-trityl-1*H*-imidazol-4-yl)carbonyl]-2-naphthamide (98)

A suspension of a crude mixture of **97** and MnO_2 (150 g) in CH_2Cl_2 (300 mL) was stirred for 90 min at room temperature. The mixture was filtered through Celite, and the solid was washed with THF. The filtrate was concentrated, and the residue was recrystallized from EtOH to give **98** (41.0 g, 60% two steps) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ: 1.26–1.82 (12H, br d), 3.72 (2H, br s), 7.13–7.22 (6H, m), 7.34–7.42 (9H, m), 7.45 (1H, dd, *J* = 1.4, 8.4 Hz), 7.58 (1H, d, *J* = 1.4 Hz), 7.79–7.80 (2H, m), 7.90 (1H, d, *J* = 8.8 Hz), 7.98 (1H, d, *J* = 8.4 Hz), 8.29 (1H, dd, *J* = 1.6, 8.8 Hz), 8.98

(1H, s); IR (KBr) 2972, 1643, 1624, 1520, 1443, 1371, 1333, 1175, 756, 704 cm^{-1}. Anal. Calcd for $C_{40}H_{37}N_3O_2$: C, 81.19; H, 6.30; N, 7.10. Found: C, 81.04; H, 6.26; N, 7.11.

6.3.24. Ethyl 2-{6-[(diisopropylamino)carbonyl]-2-naphthyl}-2-hydroxy-2-(1-trityl-1*H*-imidazol-4-yl) acetate (99)

Ethyl acetate (14.9 mL, 152 mmol) was added dropwise to a cooled (−70°C) solution of LDA (freshly prepared from diisopropylamine [21.3 mL, 152 mmol] and *n*-BuLi [1.6 M in hexane, 95.0 mL, 152 mmol]) in anhydrous THF (600 mL). After stirring for 30 min, a solution of **98** (60.0 g, 101 mmol) in anhydrous THF (150 mL) was added dropwise. The reaction mixture was stirred for 30 min at −70°C and then allowed to warm to −30°C. After cooling to −50°C, the reaction mixture was diluted with water and the organic phase was separated. The aqueous phase was extracted with THF–toluene (1:1). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give **99** as a pale yellow oil. This material was used for the next reaction without further purification. The analytical sample was obtained by recrystallization from toluene (colorless powder): ^{1}H NMR ($CDCl_3$) δ: 1.14 (3H, t, *J* = 7.0 Hz), 1.34 (12H, br s), 3.17 (1H, d, *J* = 16.2 Hz), 3.50 (1H, d, *J* = 16.2 Hz), 3.72 (2H, br s), 3.08 (2H, q, *J* = 7.0 Hz), 5.15 (1H, s), 6.84 (1H, d, *J* = 1.4 Hz), 7.07–7.14 (6H, m), 7.26–7.34 (9H, m), 7.37 (1H, d, *J* = 1.4 Hz), 7.38 (1H, dd, *J* = 1.7, 8.3 Hz), 7.68 (1H, dd, *J* = 1.8, 8.8 Hz), 7.74–7.84 (3H, m), 8.03 (1H, d, *J* = 1.0 Hz); IR (KBr) 3454, 2968, 1705, 1636, 1371, 1337, 1213, 746, 704 cm^{-1}. Anal. Calcd for $C_{44}H_{45}N_3O_4$: C, 77.73; H, 6.67; N, 6.18. Found: C, 77.69; H, 6.67; N, 6.12.

6.3.25. 6-[1,3-Dihydroxy-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*,*N*-diisopropyl-2-naphthamide (100)

Red-Al (65% in toluene; 110 mL, 355 mL) was added dropwise to a cooled (−15°C) solution of **99** in anhydrous toluene (600 mL) over a 30-min period. The reaction mixture was stirred for 2.5 h at −10 to −0°C. The reaction was quenched with the addition of water (12 mL). After dilution with THF (300 mL), aqueous 15% NaOH solution (12 mL) and water (36 mL) were added, and the mixture was stirred until the suspension turned to a clear solution. After the addition of Celite (120 g), the suspension was stirred for 10 min, and the solid was then filtered and washed with THF. The filtrate was concentrated (ca. 60% of the solvent was evaporated), and the solution was washed with 10% citric acid solution, water, saturated $NaHCO_3$, and brine followed by drying over $MgSO_4$. After removal of the solvent in vacuo, the residue was recrystallized from hexane–AcOEt to give **100** (63.7 g, 98%) as a colorless powder: ^{1}H NMR ($CDCl_3$) δ: 1.34 (12H, br s), 2.27–2.40 (1H, m), 2.48–2.61 (1H, m), 3.70 (2H, t, *J* = 5.0 Hz), 3.83 (3H, br s), 4.54 (1H, s), 6.78 (1H, d, *J* = 1.6 Hz), 7.08–

7.17 (6H, m), 7.28–7.40 (11H, m), 7.51 (1H, dd, *J* = 1.8, 8.4 Hz), 7.71–7.81 (3H, m), 7.97 (1H, s); IR (KBr) 3497, 3200, 2964, 1634, 1445, 1335, 748, 702 cm^{-1}. Anal. Calcd for $C_{42}H_{43}N_3O_3$: C, 79.09; H, 6.80; N, 6.59. Found: C, 78.83; H, 6.71; N, 6.59.

6.3.26. 6-(7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*,*N*-diisopropyl-2-naphthamide (101)

Methanesulfonyl chloride (9.21 mL, 119 mmol) was added dropwise to a cooled (0°C) solution of **100** (63.0 g, 98.8 mmol) and (*i*-Pr)$_2$NEt (34.5 mL, 198 mmol) in anhydrous THF (400 mL) while keeping the temperature of the solution below 10°C. After stirring for 30 min, water was added and the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude mixture of the mesylate as a pink amorphous powder. The mesylate was dissolved in CH_3CN (300 mL), and the solution was heated at 70°C for 20 min, during which time the spot of the mesylate disappeared on TLC. After the addition of MeOH (100 mL) and (*i*-Pr)$_2$NEt (34.5 mL, 198 mmol), the mixture was heated at 70°C for 6 h. The mixture was concentrated in vacuo (about half of the solvent was evaporated), diluted with water, and extracted with AcOEt (×3). The combined organic layers were washed with brine (×2) and concentrated in vacuo. The remaining solid was filtered and washed with AcOEt to give **101** (32.5 g, 87%) as a colorless powder. The analytical sample was obtained by recrystallization from EtOH and AcOEt (colorless powder): ^{1}H NMR ($CDCl_3$) δ: 1.18–1.50 (12H, br d), 2.78–2.97 (2H, m), 3.69–3.77 (2H, br d), 4.01–4.09 (1H, m), 4.18–4.28 (1H, m), 6.58 (1H, s), 7.26 (1H, s), 7.36 (1H, dd, *J* = 1.2, 5.6 Hz), 7.59 (1H, dd, *J* = 1.2, 5.8 Hz), 7.72–7.78 (3H, m), 7.99 (1H, s); IR (KBr) 3275, 2964, 1611, 1487, 1450, 1371, 1342, 800 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_2 \cdot 0.1EtOH$: C, 72.93; H, 7.28; N, 11.00. Found: C, 72.73; H, 7.10; N, 11.05.

6.3.27. 6-(7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)-*N*-methyl-2-naphthamide (89c) by route B

n-BuLi (1.6 M in hexane; 199 mL, 318 mmol) was added dropwise over 30 min to a cooled (−70°C) solution of methylamine (2 M in THF; 159 mL, 318 mmol) in anhydrous THF (300 mL) and the solution was stirred for 20 min at −70°C. This solution was transferred to a cooled (0°C) suspension of **101** (30 g, 79.5 mmol) in anhydrous THF (450 mL) *via* a Teflon needle, and **101** was completely dissolved. The reaction mixture was stirred for 16 h at room temperature. After dilution with brine (200 mL) and water (100 mL), the mixture was stirred for 10 min, and the precipitated compound **89c** was separated by filtration. The organic layers of the filtrate were separated, and the aqueous layer was extracted with AcOEt and THF (1:1, ×2). The combined organic layers were dried

over $MgSO_4$ and concentrated in vacuo. The residue was filtered and washed with AcOEt to give an additional amount of compound **89c**. The two separately obtained portions of compound **89c** were combined and dissolved in hot EtOH (150 mL) and MeOH (10 mL). The insoluble material was filtered, and the filtrate was concentrated, followed by recrystallization from EtOH and AcOEt to give **89c** (19.2 g, 79%) as a colorless powder. The spectral data were identical to those of the authentic sample.

6.3.28. Optical resolution of 89c using preparative HPLC

Compound **89c** (12.8 g, 41.6 mmol) was subjected to optical resolution by preparative HPLC using a Chiralpak AD column (50 mm × 500 mm) using hexane/ethanol (1/1) as an eluent, detected at 254 nm, to afford **(−)-89c** (6.40 g, 20.8 mmol, 50%) as a first elution and **(+)-89c** (6.32 g, 20.6 mmol, 49%) as a second elution. The spectral data were identical to those of the racemic **89c** except for optical rotation.

Compound **(−)-89c**: $[\alpha]_D^{25}$ = −82.7 (c 0.526, MeOH); t R = 9.9 min (Chiralpak AD 4.6 mmID × 250mmL, hexane/ethanol = 1/1, 0.5 mL/min, at 254 nm); 99.8% ee. Compound **(+)-89c**: $[\alpha]_D^{25}$ = +83.8 (c 0.474, MeOH); tR = 19.1 min (Chiralpak AD 4.6 mmID × 250 mmL, hexane/ethanol = 1/1, 0.5 mL/min, at 254 nm); 99.8% ee.

6.3.29. Preparation of Reformatsky reagent (102a)

A catalytic amount of chlorotrimethylsilane (ca. 0.1 mL) was added to a suspension of zinc powder (1.04 g, 16.0 mmol) in anhydrous THF (8 mL), and the suspension was stirred for 20 min at room temperature, in which time the zinc powder a formed sponge-like precipitate. Ethyl bromoacetate (1.77 mL, 16.0 mmol) in anhydrous THF (20 mL) was added to the solution dropwise over a 20 min period while ensuring that the temperature of the solution remained below 30°C. The solution was stirred for a further 20 min to give **102a** as a yellow solution. This solution was immediately used for the next reaction after acid-alkaline titration (0.50 M).

6.3.30. Preparation of Reformatsky reagent (102b)

A catalytic amount of chlorotrimethylsilane (ca. 0.1 mL) was added to a suspension of zinc powder (1.04 g, 16.0 mmol) in anhydrous THF (8 mL) and the suspension was stirred for 20 min at room temperature, in which time the zinc powder formed a spongy precipitate. After heating at 50°C,

tert-butyl bromoacetate (2.36 mL, 16.0 mmol) in anhydrous THF (20 mL) was added to the solution dropwise over a 20 min period while ensuring that the temperature of the solution was kept below 60°C. The solution was stirred for a further 20 min and then allowed to cool to room temperature to give **102b** as a yellow solution. This solution was used for the next reaction after acid-alkaline titration (0.35–0.50 M).

6.3.31. Titration of Reformatsky reagent

A THF solution of Reformatsky reagent (1.0 mL), 0.10 N HCl (20 mL), together with a few drops of aqueous Methyl Orange solution was added to a distilled water (10 mL). After stirring for 10 min at room temperature, the solution was titrated with 0.10 N NaOH solution. The concentration of Reformatsky reagent was calculated with the following equation: Reformatsky reagent (M) = (20 − X) × 0.1 (where X is a amount of 0.10 N NaOH consumed).

6.3.32. General procedure for asymmetric Reformatsky reaction

Synthesis of *tert*-Butyl 2-{6-[(diisopropylamino)carbonyl]-2-naphthyl}-2(*S*)-hydroxy-2-(1-trityl-1*H*-imidazol-4-yl)acetate (**103b**, entry 2 in Table 14).

Cinchonine (142 mg, 0.42 mmol) was added to a cooled (0°C) solution of **102b** (1.47 mmol), and the solution was stirred for 20 min at 0°C. After cooling to the appropriate temperature, a solution of **98** (250 mg, 0.42 mmol) in anhydrous THF (2.5 mL) was added dropwise over a 5 min period, and the mixture was stirred until completion of the reaction (checked by HPLC). The optical purity of **103b** was determined by HPLC using a chiral column (Chiralpak AD, 4.6 mmID × 250 mmL). The analytical conditions were as follows: mobile phase; hexane/EtOH = 85/15, flow rate; 0.8 mL/min, temperature; 25 to 35°C, detection; UV (254 nm), retention time (t/min); **(*R*)-103b** (13.0 min), **(*S*)-103b** (18.4 min), **98** (21.2 min). The yield of **103b** was determined by the rate of the peak intensity of **103b** (ε at 254 nm in EtOH = 12,700) and **98** (ε at 254 nm in EtOH = 32,000).

The reaction of **98** with **102a** to produce **103a** was conducted in a similar manner as described above.

6.3.33. Large scale preparation of 103b (entry 6 in Table 14)

A solution of **102b** (0.35 M; 48.2 mL, 16.9 mmol) and pyridine (1.37 mL, 17.0 mmol) was added dropwise to a cooled (0°C) solution of cinchonine (1.55 g, 5.28 mmol) in anhydrous THF (10 mL), and the solution was stirred for 20 min at 0°C. After cooling to −42°C, a solution of **98** (2.50 g, 4.22 mmol) in anhydrous THF (20 mL) was added dropwise over 10 min, and the mixture was stirred for

4 h at −42°C. The mixture was diluted with 1 N HCl, and then diluted with AcOEt. The resulting solution was successively washed with 1 N HCl (×2), water, saturated $NaHCO_3$ solution, and brine followed by drying over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 3:1 to 2:1) to give **103b** (2.9 g, 97%, 92% ee) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ: 1.31 (9H, s), 1.0–1.6 (12H, br d), 3.12 (1H, d, *J* = 16.0 Hz), 3.40 (1H, d, *J* = 16.0 Hz), 3.69 (2H, br s), 5.26 (1H, s), 6.86 (1H, d, *J* = 1.8 Hz), 7.07–7.12 (6H, m), 7.25–7.32 (9H, m), 7.36–7.39 (2H, m), 7.70 (1H, dd, *J* = 1.8, 8.7 Hz), 7.73–7.78 (2H, m), 7.82 (1H, d, *J* = 8.4 Hz), 8.03 (1H, s); IR (KBr) 3462, 2972, 1732, 1705, 1634, 1445, 1369, 1337, 1159 cm^{-1}.

6.4.1. Alignment of amino acid sequences

The amino acid sequences of CYP3A4 and 17,20-lyase (CYP17) were taken from the ExPASy web site (http://tw.expasy.org/). The amino acid sequences for which three-dimensional (3D) structures were available at the time (*Pseudomonas putida* P450CAM, *Pseudomonas sp.* P450TERP, *Saccharopolyspora erythraea* P450eryF, *Fusarium oxysporum* P450NOR, *Bacillus megaterium* P450BM3, and *mammalian* CYP2C5) were aligned according to their 3D structures using the homology module of Insight II (ver. 2000, Accelrys Inc.). Subsequently, amino acid sequences of human CYPs were aligned by sequence homology using ClustalW. The combined alignments were manually modified so there were no insertions or deletions in the portions corresponding to probable secondary structures. The following four characteristic motifs of CYPs were aligned: WXXXR (where W is tryptophan, R is arginine, and X is any amino acid) in the alpha-helix C; EXXR (where E is glutamate, R is arginine, and X is any amino acid) in the alpha-helix K; ZXXPXXZXPXXZ (where P is proline, Z is an aromatic amino acid, and X is any amino acid) after the alpha-helix K; and FXXGXXXCXG (where F is phenylalanine, G is glycine, C is cysteine, and X is any amino acid) before the alpha-helix L.

6.4.2. Homology modeling

According to the alignment, homology models of CYP3A4 and 17,20-lyase (CYP17) were constructed based on the crystal structure of mammalian CYP2C5 (PDB code: 1DT6) using the homology module of Insight II. Using the search/generate loops function of Insight II, conformations of the insertion and deletion sections in the alignment were obtained according to the known 3D structures. After making some manual adjustments to remove large steric hindrances, the whole structure was subjected to energy minimization for 1000 steps with the steepest descent minimizer, and subsequently 5000 steps with the conjugate gradient minimizer, to a maximum gradient of 0.1 kcal/mol^{-1} Å^{-1}, using the Discover-ESFF force field (ver 980, Accelrys Inc.). During the minimization procedure, the dielectric constant was set to 4 * *r*, where *r* is the distance between two interacting atoms. 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 movement from the initial positions.

6.4.3. Docking of Inhibitors

Covalent bonding models of imidazole were constructed by full energy minimization using the Discover-ESFF force field (v980, Accelrys Inc.). The residual parts of compounds were then

connected to the imidazole. After connecting the compounds to the heme Fe in the 17,20-lyase model, its binding modes were explored by systematic analysis around the rotatable bonds within the ligands and protein side chains within 4 Å of the ligand (torsion driving). During this procedure, energy values were estimated based on the Discover-ESFF force field. The most stable binding mode of compounds was energy minimized with the 17,20-lyase model using the Discover-ESFF force field. In the minimization procedure, heme and the backbone of the protein was fixed. All computational procedures were carried out on O2/R10000 workstations of Silicon Graphics Inc.

6.4.4. Determination of the absolute configuration of 48

A single crystal (0.50 × 0.20 × 0.16 mm) of **48** 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; R_1 = 0.048, wR_2 = 0.124. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 781830).

6.4.5. Determination of the absolute configuration of 78

A single crystal (0.40 × 0.40 × 0.16 mm) of **78** was obtained by recrystallization from THF/MeOH. Reflection data were collected using a Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation. The structure was determined by direct methods ($_{SIR}$92), and refined using the full-matrix least-squares techniques ($_{SHELXL}$-97) with anisotropic temperature factors for the non-hydrogen atoms. Hydrogen atoms were included using a riding model. The crystal contained two host (**78**) molecules and two methanol molecules in the asymmetric unit. The absolute configuration was determined by the Flack parameter of −0.03 (3). Crystal data: $C_{26}H_{24}BrN_3O_4S{\cdot}CH_3OH$; M = 586.50; monoclinic; space group $P2_1$ (#4); cell constants a = 14.684(2) Å, b = 10.318(1) Å, c = 18.927(2) Å, β = 112.256(7)°, V = 2653.9(5) Å^3; Z = 4; Dc = 1.468 g/cm^3; unique reflections, 9180; observed reflections [$I > 2\sigma(I)$], 5158; R_1 = 0.072, wR_2 = 0.241. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 781827).

6.4.6. Determination of the Absolute Configuration of 88

A colorless platelet (0.15 × 0.15 × 0.05 mm^3) of **88** was obtained by re-crystallization from AcOEt and THF. A diffractometer Rigaku RAXIS RAPID was used with graphite monochromated Cu-Kα radiation to obtain the following crystal data: $C_{25}H_{24}BrN_3O_4S$, $0.5C_4H_8O$, crystal system monoclinic, space group P21 (#4), lattice parameters a = 14.3835(3) Å, b = 10.6353(2) Å, c = 17.6165(3) Å, α = 90°, β = 110.3646(7)°, γ = 90°, V = 2526.41(8) $Å^3$, Z = 4, T = 100 K. Of the 25,453 reflections collected, 8673 were unique (R_{int} = 0.054). The refinement converged with R_1 = 0.059 and wR_2 = 0.138 for 7131 reflections with $I > 2\sigma(I)$. The absolute configuration of **88** was established as *S* based on the Flack parameter,[81] 0.03(2), refined using 3806 Friedel pairs. The crystal contained two molecules of **88** and a molecule of THF in the asymmetric unit. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (CCDC deposition number: 794848).

6.4.7. Determination of the absolute configuration of (+)-89c (orteronel)

A colorless platelet of **(+)-89c** with (2*S*,3*S*)-(-)-tartranilic acid (0.35 × 0.10 × 0.01 mm^3) was obtained by re-crystallization of MeOH/*i*-Pr_2O/THF. A diffractometer Rigaku RAXIS RAPID was used with graphite monochromated Cu-Kα radiation to obtain the following crystal data: $C_{18}H_{17}N_3O_2$, $2C_{10}H_{11}NO_5$, crystal system monoclinic, space group C2 (#5), lattice parameters a = 28.9799(6) Å, b = 5.4377(1) Å, c = 26.0080(6) Å, α = 90°, β = 103.338(1)°, γ = 90°, V = 3987.9(2) $Å^3$, Z = 4, T = 173 K. Of the 22,522 reflections collected, 7029 were unique (R_{int} = 0.065). The refinement converged with R_1=0.127 and wR_2 = 0.388 for 2903 reflections with $I > 2\sigma(I)$. The absolute configuration of **(+)-89c** was established as *S* using the absolute stereochemistry of (2*S*,3*S*)-(-)-tartranilic acid as an internal reference. The crystal contained one molecule of **(+)-89c** and two molecules of tartranilic acid in the asymmetric unit. There were two tunnel-shaped solvent domains along the b-axis in a unit cell. Although several peaks originating from the crystallization solvent were observed in these solvent domains, they were disordered. Therefore, the solvent peaks were excluded from the structure refinement process. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (CCDC deposition number: 781831).

6.4.8. Inhibitory activity on rat steroid 17,20-lyase *in vitro*

Inhibitory activity against rat enzymes was determined according to a method described previously[82] with some modifications. Testes excised from 13-week-old male SD rats were homogenized, and testicular microsomes were prepared by centrifugation. The reaction mixture contained 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 1–1000 nM test compounds in a total volume of 20 μL at room temperature. 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 of the diluted solution was added to the reaction mixture. After incubating for 15 min at 37°C the reaction was terminated by the addition of 40 μL of ethyl acetate, then vortexed for 30 s and briefly centrifuged. Thirty microliters 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 with a BAS2000 Bio-image analyzer (FUJIX). The concentration of the test compounds needed to reduce the concentration of the products by 50% (the concentration of the control group in which no test compound is added is taken as 100%) was calculated.

6.4.9. Inhibitory activity on human steroid 17,20-lyase *in vitro*

Inhibitory activity on human enzymes was determined as described above. The reaction mixture contained 75 mM phosphate buffer (pH 7.4), 1 mM magnesium chloride, 0.5 pmol of recombinant P450c17 (Biotechnology Laboratories, Takeda), 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 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 of the diluted solution was added to the reaction mixture. After incubating for 15 min incubation at 37°C the reaction was terminated by the addition of 40 μL of ethyl acetate, then vortexed for 30 s and briefly centrifuged. Thirty microliters of the organic phases were applied to silica gel TLC plates (Whatman, LHPK). The substrate and the product DHEA were separated using the cyclohexane–ethyl acetate (3:2) solvent system.

6.4.10. Inhibitory activity on rat 11-hydroxylase *in vitro*

Adrenal glands excised from SD rats were homogenized, and the mitochondrial fraction was prepared at room temperature by serial centrifugation. Rat 11-hydroxylase activity was measured according to a method described for side-chain cleavage activity previously[83] with some modifications. The reaction mixture contained 200 mM mannitol, 4.5 mM HEPES, 2.3 mM potassium phosphate (pH 7.4), 0.1 mM EDTA·2 K, 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 1–1000 nM test compounds in a total volume of 150 μL. The concentrations of reagents were expressed as the final concentration in the reaction mixture. The test compounds were serially diluted with dimethylformamide, and 1.5 μL was added directly to the reaction mixture. After 30 min incubation at 37°C the reaction was terminated by addition of 400 μL of ethyl acetate and 100 μL of distilled water, then vortexed for 30 s and briefly centrifuged. Three hundred microliters of the organic phase was transferred to a new tube and evaporated until dry using nitrogen gas. The steroids were dissolved with 30 μL of ethyl acetate and the whole volume was applied to silica gel TLC plates (Whatman, LHPK). The substrate and the products (11-deoxycortisol and cortisol) were separated in the toluene–acetone (7:2) solvent system.

6.4.11. Inhibitory activity on CYP3A4 *in vitro* for screening (Table 1-5, 7-10 and 15-17)

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 compounds in a total volume of 200 μL. The total microsome protein content was adjusted by control microsome protein (Gentest). The concentration of reagents was expressed as the final concentration in the reaction mixture. The reaction mixture was incubated for 30 min at 37°C and terminated by the addition of 200 μL of acetonitrile. After addition of 400 μL of 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).

6.4.12. Effect of (−)-74b and (+)-89c on metabolic activities of CYP-expressing microsomes (Table 11 and 20)

The effect of **(−)-74b** and **(+)-89c** on CYP isoforms was assessed by incubating a marker substrate with the microsomes expressing each human CYP isoform in the presence of 3, 10, 30 and 100 μmol/L of each test compound. The incubation mixture contained 10 mmol/L $MgCl_2$, 3.2 mg/mL glucose-6-phosphate, 0.8 mg/mL β-NADP+ and 4 units/mL glucose-6-phosphate dehydrogenase in 80 mmol/L phosphate buffer (pH 7.4). In the case of CYP2A6, 2B6 and 2C9, 80 mmol/L Tris–HCl buffer (pH 7.4) was used instead of the phosphate buffer. After preincubation of each test compound and CYP isoform-specific substrate mixture at 37°C for 5 min, the reaction was initiated by adding microsomes derived from specific CYP-expressing human B-lymphoblastoid cells. The concentration of the substrate was referenced from the data sheet from GENTEST Corp. (7-ethoxyresorufin *O*-deethylation for CYP1A2, coumarin 7-hydroxylation for CYP2A6, *S*-(+)-mephenytoin 4'-hydroxylation for CYP2C19, (±)-bufuralol 1'-hydroxylation for CYP2D6, 4-nitrophenol hydroxylation for CYP2E1 and testosterone 6β-hydroxylation activity for CYP3A4) or the published reports (ethoxycoumarin *O*-deethylation for CYP2B6 and tolbutamide hydroxylation for CYP2C8 and 2C9) [84, 85] with slight modifications.

The marker reactions specific for CYP isoforms other than CYP3A4 were measured according to published analytical methods[84, 86-90] with slight modifications. Testosterone 6β-hydroxylation activity for CYP3A4 was analyzed using the following HPLC conditions: column, Inertsil ODS-2 (150 × 4.6 mm I.D.; GL Science, Tokyo, Japan); detection wavelength, 254 nm; flow rate, 1.0 mL/min; column temperature, 50°C; mobile phase, 10 mmol/L acetate buffer (pH 4.3)/acetonitrile = 7/3. Control marker enzymatic activities were measured for the preincubation samples in the presence of methanol alone without each test compound.

6.4.13. Effect of (−)-19, (−)-74b, (+)-89c and (−)-89c in male cynomolgus monkeys (Table 6, 12, 18 and 19)

Adult male cynomolgus monkeys (Keari, Wakayama, Japan) 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. The care and use of animals and the experimental protocol used in this study were approved by the Experimental Animal Care and Use Committee of Takeda Pharmaceutical Company Ltd. The test compounds **(−)-19**, **(−)-74b, (+)-89c** and **(−)-89c** were suspended in 0.5% methylcellulose and administered orally at a dose of 3 mg/kg for **(−)-19 and** 1 mg/kg for **(−)-74b, (+)-89c** and **(−)-89c**. Blood samples were collected just before dosing, and 2 h and 8h for **(−)-19**, 4 h and 8 h for **(−)-74b**, 8 h for a preliminary study of **(+)-89c** and **(−)-89c** or 2, 5

and 10 h for **(+)-89c** after dosing. Serum was stored at −30°C until assayed by radioimmunoassay (RIA). Concentrations of testosterone and DHEA were determined using a Testosterone I-125 kit (Dia Sorin s.r.l., Italy) and a DHEA RIA kit (Diagnostics System Laboratories, USA), respectively, according to the manufacturer's instructions.

Serum steroid concentrations are highly variable among individuals, show circadian variation, and are affected by stress. Thus, serum steroid concentrations were expressed as percentages of the mean pretreatment values (the mean concentrations in sera collected 48 and 24 h and just before treatment) in the single administration experiments.

6.4.14. Pharmacokinetic studies (Table 13)

Compound **(−)-74b** was administered to non-fasted Crl:CD(SD)IGS rats (male, 8 weeks old, n = 3) intravenously at a dose of 1 mg/kg and orally at a dose of 10 mg/kg. Blood samples were collected at 5, 10, 15, and 30 min and 1, 2, 4, 8, 24 h after intravenous administration, or at 15 and 30 min and 1, 2, 4, 8, 24 h after oral administration. The blood samples were centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with acetonitrile. After centrifugation, the supernatant was dried under N_2. The residue was reused with HPLC mobile phase (A:B = 90:10) and analyzed by HPLC. The analytical conditions using HPLC were: column, L-column ODS (4.6 mm × 250 mm); mobile phase, (A) 0.01 mol/L ammonium acetate:(B) acetonitrile = 78:22; flow rate, 1.0 mL/min; column temperature, 40°C.

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9. List of publications

1. Kaku, T., Tsujimoto, S., Matsunaga, N., Ojida, A., Tanaka, T., Hara, T., Yamaoka, M., Kusaka, M. and Tasaka, A. 17,20-Lyase inhibitors. Part 3: Design, synthesis, and structure–activityrelationships of biphenylylmethylimidazole derivatives as novel 17,20-lyase inhibitors. *Bioorg. Med. Chem.* 19, 2428-2442, 2011.
2. Kaku, T., Matsunaga, N., Ojida, A., Tanaka, T., Hara, T., Yamaoka, M., Kusaka, M. and Tasaka, A. 17,20-Lyase Inhibitors. Part 4: Design, synthesis and structure–activity relationships of naphthylmethylimidazole derivatives as novel 17,20-lyase inhibitors. *Bioorg. Med. Chem.* 19, 1751-1770, 2011.
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