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17,20-Lyase inhibitors. Part 4: Design, synthesis and structure–activity relationships of naphthylmethylimidazole derivatives as novel 17,20-lyase inhibitors

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ABSTRACT

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 of the methylcarbamoyl derivative led to the discovery of the corresponding tricyclic compound, which showed highly potent activity against human 17,20-lyase (IC_{50} 19 nM) and good selectivity (>1000-fold) for inhibition of 17,20-lyase over CYP3A4. Additional biological evaluation revealed that the tricyclic compound had potent in vivo efficacy in monkeys and favorable pharmacokinetic profiles when administered in rats. Asymmetric synthesis of the selective tricyclic inhibitor was also achieved using a chiral α-hydroxy ketone.

1. Introduction

Prostate cancer is one of the most prevalent cancers among men in the USA and Europe.[1] In most cases, growth, maintenance and progression of prostate cancer is androgen-dependent.[2,3] Therefore, the current first-line treatment for prostate cancer is hormone therapy, such as surgical castration or medical castration via administration of a luteinizing hormone-releasing hormone (LH-RH) agonist, which reduces the production of testosterone secreted by the testes. However, resistance to this therapy eventually occurs and this clinical condition is referred to as castration-resistant prostate cancer (CRPC).[4] Despite very many studies in this field, the mechanism of progression to CRPC has not been fully understood. However, recent studies have suggested that residual adrenal androgen dehydroepiandrosterone (DHEA) after surgical castration could be responsible for the development of CRPC.[5,6]

Thus one possible target for CRPC treatment is the enzyme 17,20-lyase, which plays a crucial role in androgen biosynthesis. This is because inhibition of 17,20-lyase would be expected to decrease serum androgen levels secreted not only by the testes but also by the adrenal glands.[7–9]

In recent years, several groups have reported the development of steroidal and non-steroidal inhibitors of 17,20-lyase,[10–44] such as YM-116[27] and abiraterone acetate,[11] which have been evaluated in clinical studies, and we have also disclosed the design of 17,20-lyase inhibitors such as compounds **1a**[45] and **1b** (Kaku et al., manuscript in preparation), as shown in Figure 1.

We have previously reported that the introduction of a small alkoxy group such as methoxy or ethoxy group at the 6-position of the naphthalene ring of these compounds slightly increased 17,20-lyase inhibition. Moreover, docking studies of **1a** 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 the enzyme. Unfortunately, compound **1a** was found to also be a potent inhibitor of CYP3A4, with an IC_{50} value of less than 1000 nM, as shown in Table 1. Therefore, we continued further modification of this series of compounds, aiming to improve the selectivity for 17,20-lyase over CYP3A4. In this report, we discuss the synthesis and structure–activity relationships (SAR) of novel naphthylmethylimidazole derivatives and related compounds as 17,20-lyase inhibitors. Additionally, asymmetric synthesis of the

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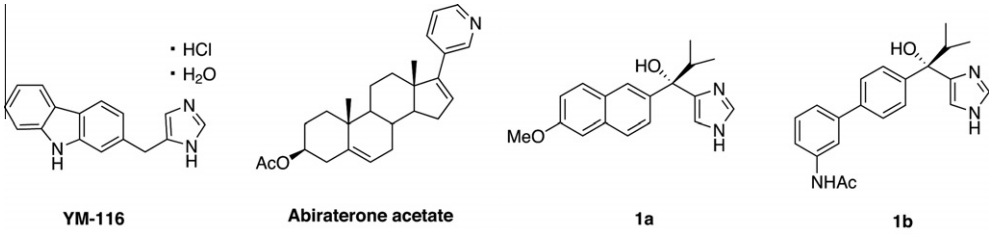
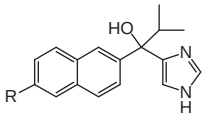


Figure 1. Chemical structures of previously developed 17,20-lyase inhibitors.

Table 1
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		
1a	OMe	21	28	<1000	<36
6	Ac	14	28	1400	50
10a	NHAc	29	39	<1000	<26
10b	NHCONHMe	11	36	<1000	<28
22	COOMe	43	24	1400	58
24b	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.

selected compound using the chiral α-hydroxy ketone was achieved and is described in detail.

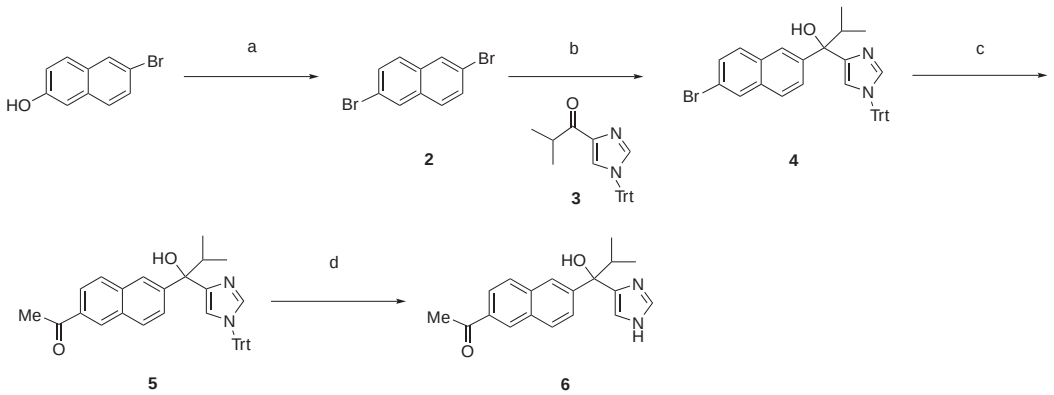
2. Chemistry

The synthesis of ketone **6** is outlined in Scheme 1. As reported previously,[46] conversion of 6-bromo-2-naphthol to dibromide **2** was achieved by treatment with triphenylphosphine (PPh_3) and bromine at 70–300 °C. Treating dibromide **2** with a sub-stoichiometric amount of *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF) followed by the addition of ketone **3**, gave bromide **4** in high yield. Sequential treatment of bromide **4** with *n*-BuLi generated the lithium dianion, to which Weinreb's amide was added at −78 °C to give a moderate yield of ketone **5**. Finally, removal of the trityl group with pyridine hydrochloride in methanol (MeOH) provided the targeted ketone **6**.

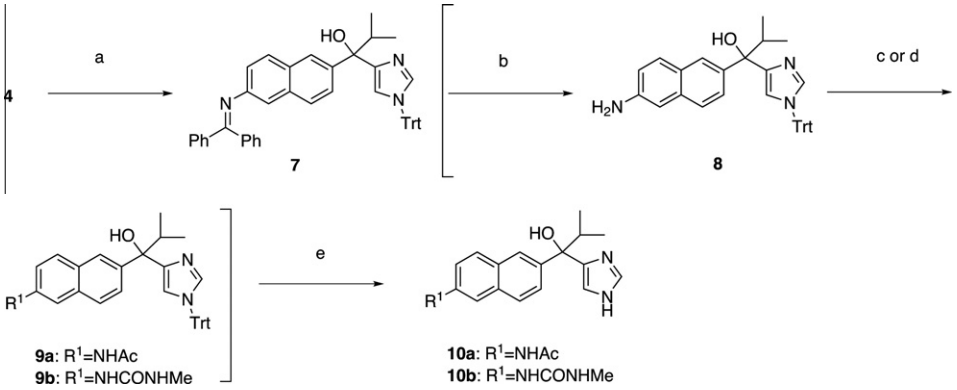
The syntheses of **10a** and **10b** are shown in Scheme 2. Conversion of bromide **4** into **7** was performed by Buchwald's method using tris(dibenzylideneactone)dipalladium ($Pd_2(dba)_2$), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), sodium *tert*-butoxide (*tert*-BuONa) and benzophenonimine, to provide good yields of **7**. The resulting imine **7** was deprotected to give **8**, which was then treated with acetic anhydride or phenyl chloroformate, followed by methylamine hydrochloride to yield **9a** and **9b**, respectively. Subsequent deprotections of **9a** and **9b** were performed by treatment with pyridine hydrochloride to give **10a** and **10b**, respectively.

The syntheses of the trisubstituted naphthalene derivatives **11b–d** are shown in Scheme 3. 6-Bromo-2-naphthol was chlorinated at the 1-position with sulfuryl chloride to give a moderate yield of **11b**. After Wolff–Kishner reduction of 1-formyl-2-naphthol, **12** was treated with bromine to give 6-brominated **11c** in high yield. Trimethoxyborane-catalyzed reduction of **13** with lithium borohydride gave alcohol **14**. The alcohol **14** was successively oxidized with manganese dioxide (MnO_2) to produce **15** in high yield (in two steps). After Wolff–Kishner reduction of the aldehyde **15**, conversion of the methoxy group of **16** with BBr_3 was carried out to give a high yield of phenol **11d**.

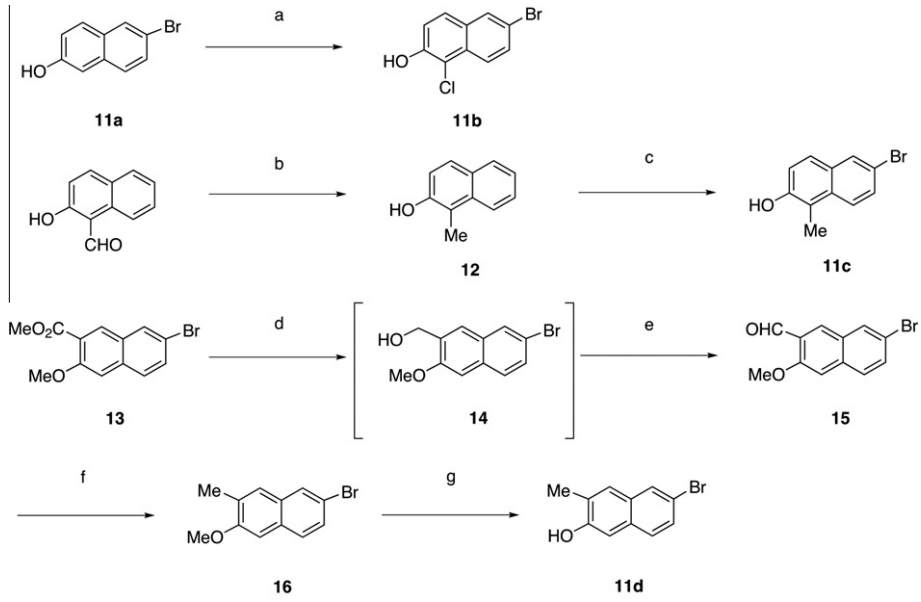
The syntheses of **22** and **24a–24h** are shown in Scheme 4. Phenols **11a–d** were protected with *tert*-butyldimethylsilyl chloride (TBSCl), the resulting silyl ethers were treated with *n*-BuLi at −78 °C, followed by addition of ketone **3** to produce excellent yields of **18a–d**, respectively. Removal of the *tert*-butyldimethylsilyl (TBS) group with tetrabutylammonium fluoride (TBAF) provided phenols **19a–d**, which were allowed to react with trifluoromethansulfonic anhydride (Tf_2O) to give **20a–d**, respectively. Methoxycarbonylation of **20a–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)



Scheme 1. 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) **3**, 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%.



Scheme 2. 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.



Scheme 3. 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%.

carbodiimide hydrochloride (EDCI·HCl) and alkylamine to provide carbamoyl derivatives **23a**–**h** in good yield. Deprotections of **21a** and **23a**–**h** were performed according to a similar method as described for **6** to give the desired compounds **22** and **24a**–**h**, respectively.

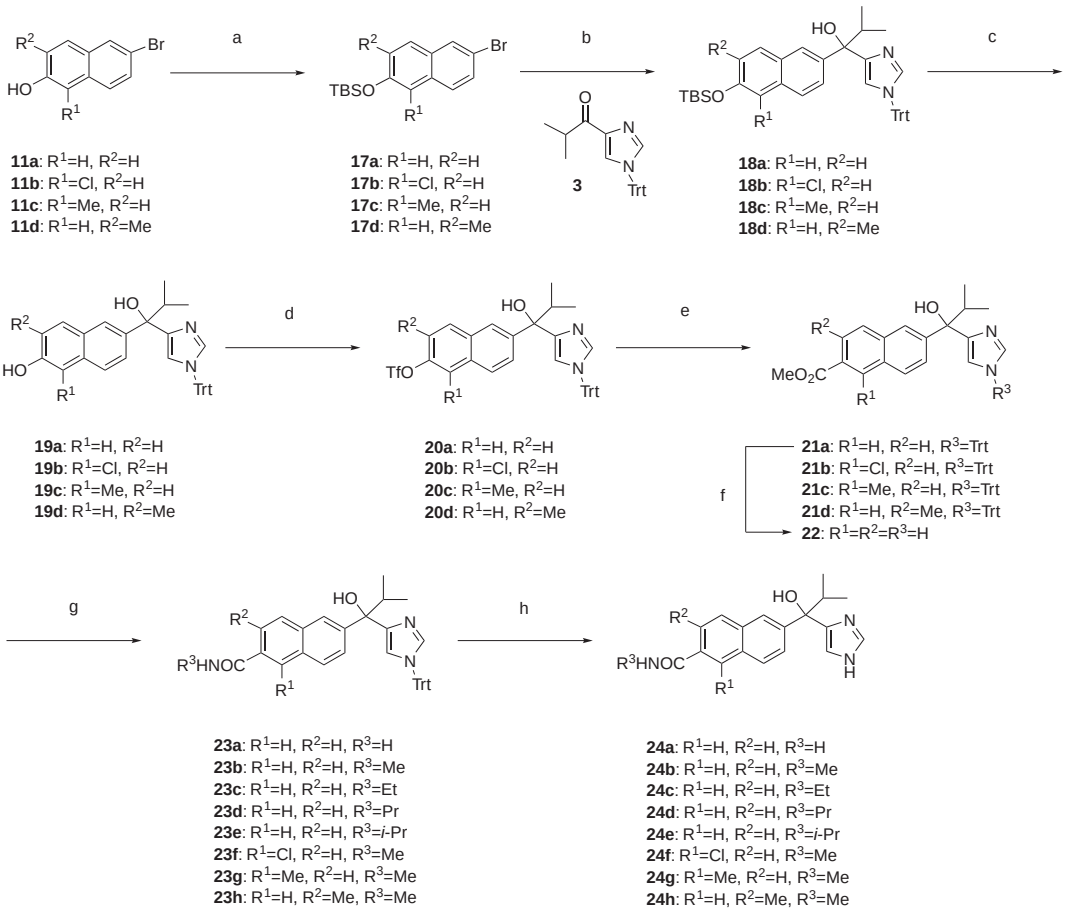
The syntheses of **27a** and **27b** are shown in Scheme 5. Substituted naphthalene **21c** was brominated using *N*-bromosuccinimide (NBS) and 2,2′-azobis(2-methylpropionitrile) (AIBN) to yield **25**, which was subjected to lactam cyclization to form **26a** and **26b**, respectively. Deprotections of each compound yielded the desired **27a** and **27b**. The regioisomers **30a** and **30b** were also synthesized from **21d** in a similar manner, as shown in Scheme 6.

To examine the stereochemical requirement at the chiral centers of these inhibitors, optical resolutions of **27a** and **27b** into **(−)-27a** and **(+)-27a**, and **(−)-27b** and **(+)-27b**, respectively, were performed using preparative HPLC with a Chiralpak AD column. Additionally, as shown in Scheme 7, **(+)-27b** was converted to the 4-bromobenzenesulfonyl derivative **31** and the absolute configuration of **(+)-27b** was confirmed to be *R* by X-ray crystallographic analysis of **31**, as shown in Figure 2.

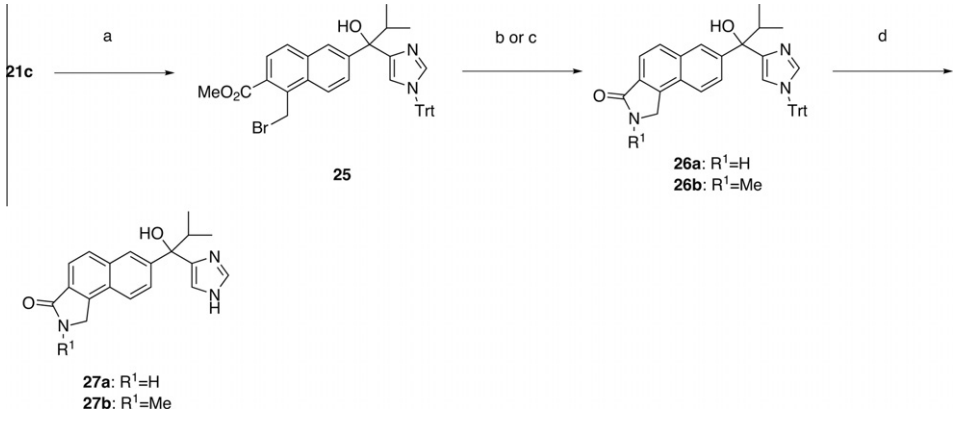
2.1. Asymmetric synthesis of compound (−)-27b

The asymmetric synthesis of **(−)-27b** is shown in Scheme 8. Diastereoselective Grignard reactions are versatile and effective methods for providing chiral tertiary alcohols.[47–49] 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.[50,51] To construct the chiral center of **(−)-27b**, we used our previously reported method using α-hydroxy ketone **34b**. The key intermediate **34b** was easily prepared from the known morpholine amide **33**.[52] The synthesized **33** was treated with lithium species generated from **32b** and *n*-BuLi to give **34a**, which was followed by deprotection of the TBS group with TBAF to afford moderate yield of the desired **34b**.

Treatment of **34b** with isopropylmagnesium bromide gave the crude (1*S*,2*R*)-diol **35** in a diastereoselective manner together with some by-products, followed by crystallization to give (1*S*,2*R*)-diol **35** with 95% purity; this was used without further purification in the next step. *ortho* lithiation of **35** followed by the addition of



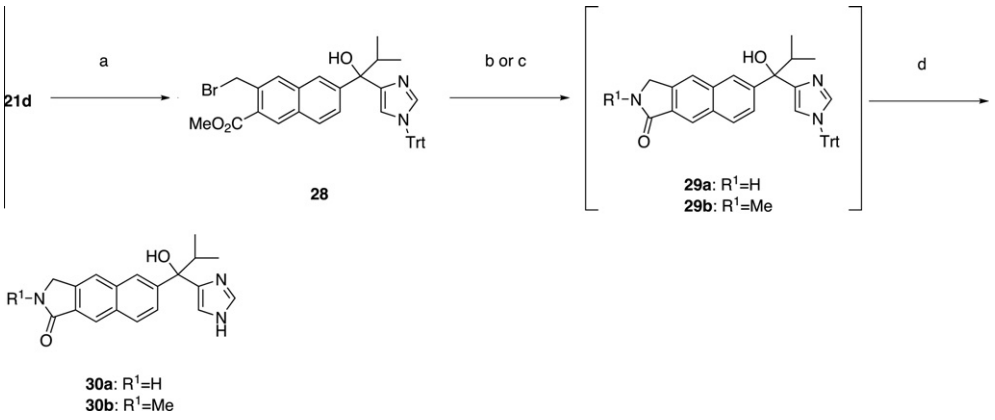
Scheme 4. Reagents and conditions: (a) TBSCl, imidazole, DMF, 0 °C to rt, 85–98%; (b) (1) *n*-BuLi, THF, −70 °C; (2) **3**, 84–93%; (c) TBAF, THF, 0 °C to rt, 89–98%; (d) Tf_2O, pyridine, 0 °C, 61–94%; (e) CO, $Pd(OAc)_2$, dppf, Et_3N, DMF, MeOH, 70 °C, 81–95%; (f) pyridine hydrochloride, MeOH, $CHCl_3$, 60 °C, 94%; (g) (1) 4 N NaOH, THF, MeOH, 60 °C, then (2) for **23a**, NH_4HCO_3, DPPA, Et_3N, DMF, rt, quant., for **23b**–**h**, R^3NH_2, EDCI·HCl, HOBt·H_2O, Et_3N, DMF, rt, 75% to quant.; (h) pyridine hydrochloride, MeOH, $CHCl_3$, 60 °C, 73–93%.



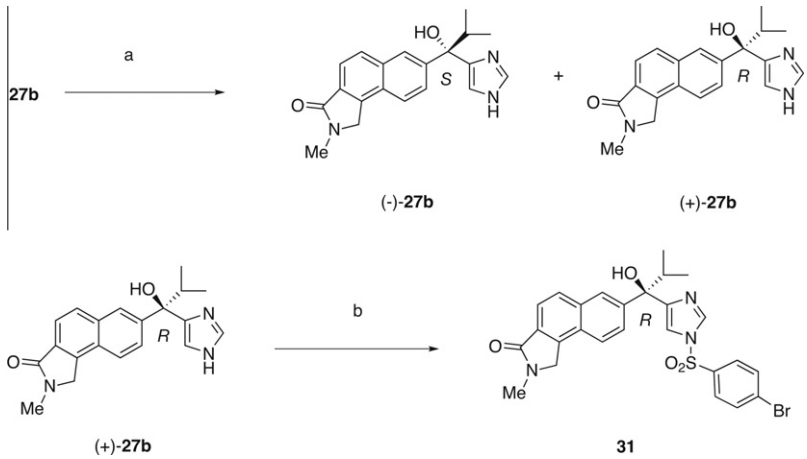
Scheme 5. Reagents and conditions: (a) NBS, AIBN, CCl_4, refluxed, 59% as a mixture of **25** and **21c** (**25**:**21c** = ca. 7:1); (b) for **26a**, saturated NH_3 in MeOH, THF, 0 °C to rt, 26%; (c) for **26b**, 40% NH_2Me in MeOH, rt, quant.; (d) pyridine hydrochloride, MeOH, $CHCl_3$, 60 °C, 75–90%.

DMF gave a mixture of **36a** and **36b** (**36a**:**36b** = ca. 6:1), which was then treated with methylamine under reductive amination conditions to yield a mixture of **37a** and **37b**. Subsequent internal cyclization of a mixture of **37a** and **37b** using lithium diisopropylamide (LDA), followed by recrystallization gave a mixture of the regioisomers such as **38a** and **38b** (**38a**:**38b** = 93:7) in moderate yield. Swern oxidation of a mixture of **38a** and **38b**, and subsequent recrystallization of the product gave **39** with >99% purity, which was then subjected to the α-bromination condition using pyridinium bromide perbromide to give α-bromoketone **40**.

Since the direct conversion from **40** to **(−)-27b** gave insufficient yield of **(−)-27b** with 2% (not shown in Scheme 8), imidazole ring closure was performed after protection of **40** with a trimethylsilyl group by *N*,*O*-bis(trimethylsilyl)acetamide. The obtained **41** was



Scheme 6. Reagents and conditions: (a) NBS, AIBN, CCl_4, refluxed, quant.; (b) for **29a**, saturated NH_3 in MeOH, THF, 0 °C to rt; (c) for **29b**, 40% NH_2Me in MeOH, rt; (d) pyridine hydrochloride, MeOH, $CHCl_3$, 60 °C, 22–64% in two steps.



Scheme 7. Reagents and conditions: (a) optical resolution using preparative HPLC on a Chiralpak AD column; (b) 4-bromobenzenesulfonyl chloride, Et_3N, DMF, rt, 88%.

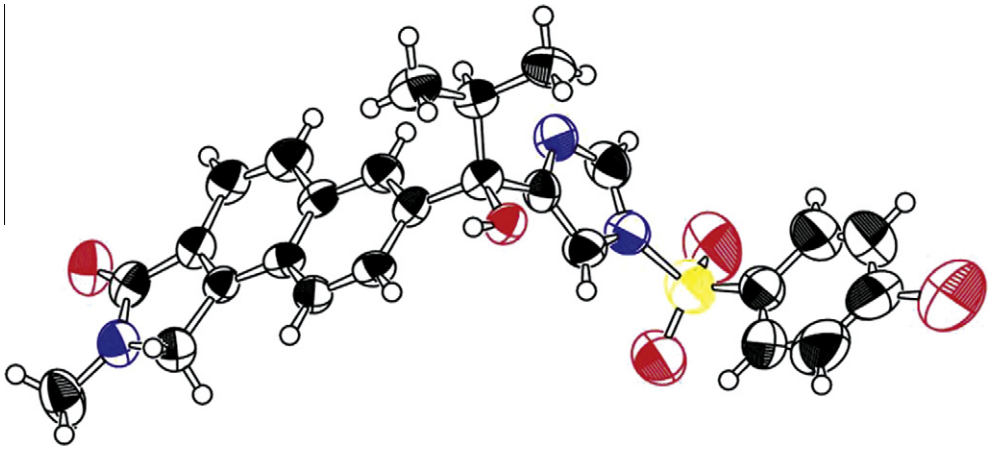


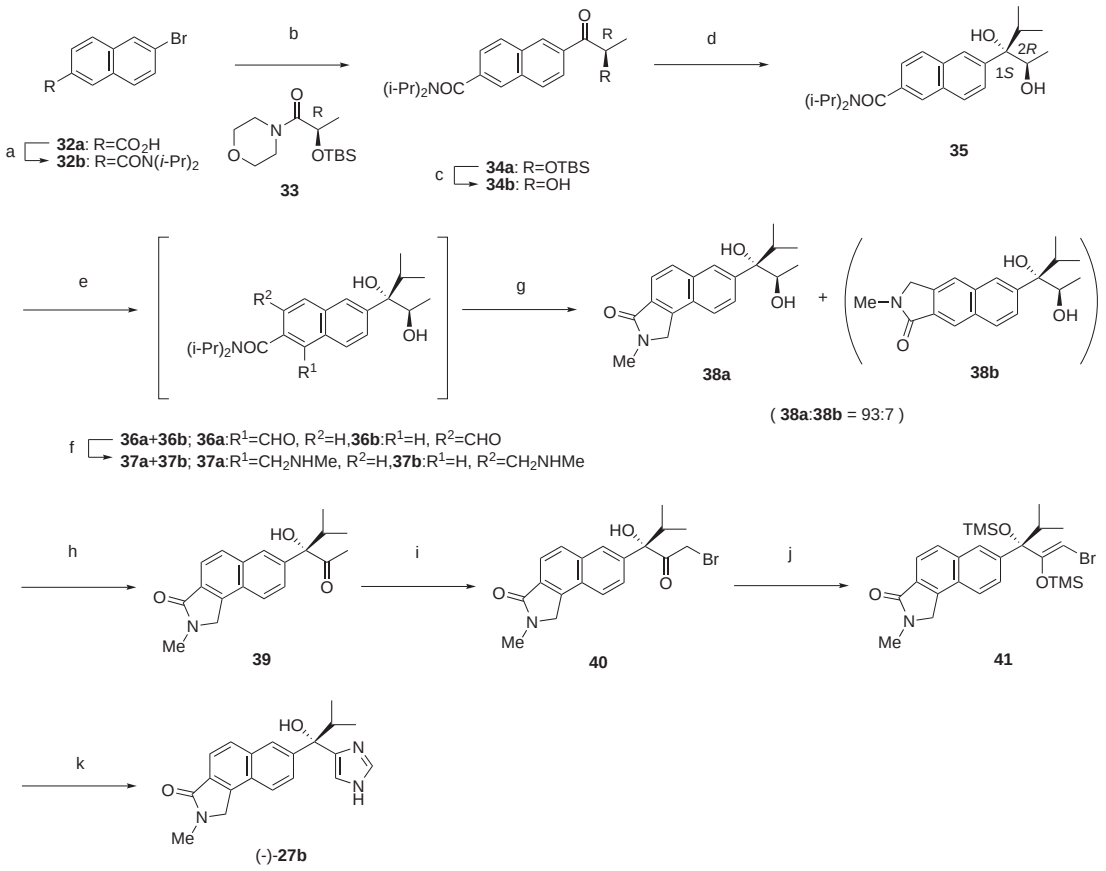
Figure 2. ORTEP drawing of **31**.

then subjected to the reaction conditions using formamidine acetate in saturated NH_3 solution, shown in Scheme 8 to give **(−)-27b** in moderate chemical yield with excellent ee (>99%ee). In summary, an 11-step method was developed for asymmetric synthesis of the selected **(−)-27b** from 6-bromo-2-naphthoic acid **32a** using the diastereoselective Grignard reaction as a key step to construct the chiral center of **(−)-27b**.

3. Results and discussion

3.1. SARs for 17,20-lyase, CYP3A4, and 11-hydroxylase

All compounds synthesized as racemates were tested in vitro for inhibition of rat 17,20-lyase, human 17,20-lyase and CYP3A4. Selected compounds were resolved by HPLC and the resultant



Scheme 8. 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) **33**, THF, −78 °C; (c) TBAF, THF, −10 to 0 °C, 58% from **33**; (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 **38a** and **38b**; (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 **39**; (k) formamidine acetate, saturated NH_3 in MeOH, THF, −15 °C to rt, 54%, >99% ee.

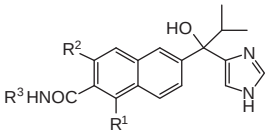
optical isomers were further examined in vitro for inhibition of rat 11-hydroxylase, which is responsible for the biosynthesis of glucocorticoid and mineralocorticoid.

As previously described,[45] 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 the enzyme. 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 1. On the basis of a docking study of **1a**, hydrogen bond acceptors were examined as replacements for the methoxy group of compound **1a**. Although replacing the methoxy group (**1a**) with an acetyl group (**6**) or a methoxycarbonyl group (**22**) 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 (**1a**) with an acetamide group (**10a**) or a methylureido group (**10b**) 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 (**1a**) with a methylcarbamoyl group (**24b**), 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.

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 2. Replacement of the methylcarbamoyl group (**24b**) with a carbamoyl (**24a**) or other small alkyl carbamoyl group (**24c**, **24d** and **24e**) 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 (**24f**) at the 5-position resulted in a decrease in potency of more than an order of magnitude when com-

Table 2
Effect of R^1, R^2, R^3 substituents on inhibition of rat and human 17,20-lyase and human CYP3A4



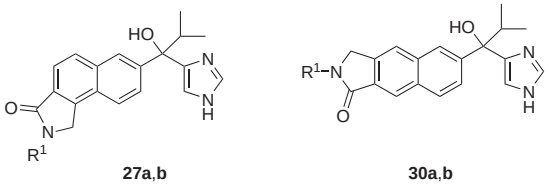
Compound No.	R^1	R^2	R^3	Enzyme inhibition IC_{50} (nM)		
				17,20-Lyase		CYP3A4
				Rat	Human	
24a	H	H	H	<10	30	3700
24b	H	H	Me	6	16	3600
24c	H	H	Et	11	46	5700
24d	H	H	Pr	13	38	3400
24e	H	H	*i*Pr	12	75	9300
24f	Cl	H	Me	91	200	>10000
24g	Me	H	Me	200	160	>10000
24h	H	Me	Me	12	39	3600

pared with the unsubstituted **24b**. Even a relatively small methyl group (**24g**) 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 (**24h**) resulted in only a slight decrease in inhibition of human 17,20-lyase and no change in inhibition of CYP3A4 compared with **24b**. These results suggested that the methylcarbamoyl group (**24b**) 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.

Therefore, fixing the angle of the carbamoyl group seemed to be a promising strategy for further development, and tricyclic compounds such as **27a**, **27b**, **30a** and **30b** 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 **24b**, but maintained activity against 17,20-lyase, shown in Table 3. Among them, **27b** had the best selectivity for 17,20-lyase over CYP3A4 by more than 400-fold.

Further investigations regarding the stereochemical requirement at the chiral center of these inhibitors were performed using optical isomers such as **(−)-27a**, **(+)-27a**, **(−)-27b**, and **(+)-27b**, respectively, as shown in Table 4. 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.

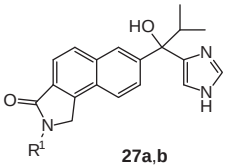
Table 3
Effect of R^1 substituent on inhibition of rat and human 17,20-lyase and human CYP3A4



27a,**b** **30a**,**b**

Compound No.	R^1	Enzyme inhibition IC_{50} (nM)		
		17,20-Lyase		CYP3A4
		Rat	Human	
27a	H	<10	18	6700
27b	Me	15	22	>10000
30a	H	42	36	>10000
30b	Me	70	19	5400

Table 4
Stereochemical requirement for inhibitory activities of **(±)-27a** and **(±)-27b** against rat and human 17,20-lyase, rat 11-hydroxylase and human CYP3A4 enzymes



27a,**b**

Compound No.	R^1	Enzyme inhibition IC_{50} (nM)			
		17,20-Lyase		11-Hydroxylase	CYP3A4
		Rat	Human		
(−)-**27a**	H	<10	15	13	>10000
(+)-**27a**	H	180	60	220	7400
(−)-**27b**	Me	<10	19	>1000	>10000
(+)-**27b**	Me	110	270	>1000	>10000

Table 5
Inhibitory effect of **(−)-27b** 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
(−)-**27b**	<10	19	28000	<3000	>30000	27000

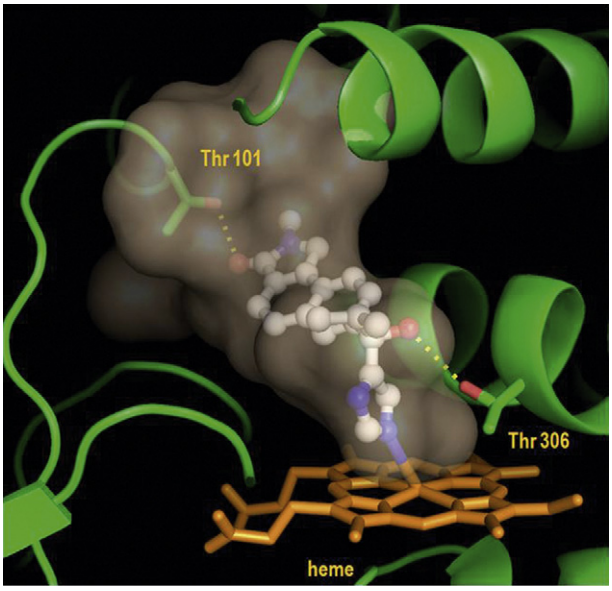


Figure 3. Docking of **(−)-27b** in the 17,20-lyase homology model.

Compounds **(−)-27a**, **(+)-27a**, **(−)-27b**, and **(+)-27b** were also tested for their ability to inhibit rat 11-hydroxylase. Compounds **(−)-27a** and **(+)-27a** showed highly potent inhibitory activity against 11-hydroxylase, while **(−)-27b** and **(+)-27b** showed low levels of 11-hydroxylase inhibition at concentrations of up to 1000 nM.

3.2. Enzyme selectivity

During a series of in vitro studies, **(−)-27b** 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.[53–56] As shown in Table 5, **(−)-27b** 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 6
In vivo effects of **(−)-27b** on serum testosterone and DHEA levels after single oral dosing (1 mg/kg) in monkeys

Compound	% 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
(−)-**27b** (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).

Table 7
Selected pharmacokinetic data for compound **(−)-27b** after oral or intravenous (IV) administration in rats

Dosage route	Dose (mg/kg)	T_{max} (h)	C_{max} (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.

3.3. Docking experiments

The docking of **(−)-27b** was studied using a homology model of 17,20-lyase. In the docking experiment it was postulated that **(−)-27b** should be connected to the catalytic heme iron via the nitrogen of the imidazole ring moiety, and the proposed binding mode of **(−)-27b** is shown in Figure 3. Results of docking studies indicated that the tricyclic ring of **(−)-27b** 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 **1a**.[45] Furthermore, an additional hydrogen bond between the hydroxyl group at the linker position between the tricyclic and imidazole rings of **(−)-27b** with Thr306 was also observed in this model.

3.4. In vivo efficacy

Based on the in vitro profiles, **(−)-27b** 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 **(−)-27b**. As shown in Table 6, **(−)-27b** 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 **(−)-27b** could be useful for the treatment of both hormone-dependent and castration-resistant prostate cancer.

3.5. Pharmacokinetics

Pharmacokinetic studies of **(−)-27b** were performed in rats (not evaluated in monkeys). As shown in Table 7, **(−)-27b** demonstrated good pharmacokinetic profiles with large oral AUC and excellent bioavailability values; these results are encouraging for the further development of **(−)-27b** as a therapeutic agent.

4. Conclusions

We have successfully synthesized a new class of potent and selective 17,20-lyase inhibitors. Replacement of the substituent at the 6-position of the naphthalene ring showed that a methylcarbamoyl group was optimal in terms of potency and selectivity. Further modifications aimed at fixing the orientation of the carbonyl group of the inhibitor yielded tricyclic compounds **27a** and **27b** that were potent and selective human 17,20-lyase inhibitors. Among them **(−)-27b** 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 **(−)-27b** exhibited potent in vivo efficacy at an oral dose of 1 mg/kg in monkeys and showed favorable pharmacokinetic profiles when administered to rats. Further evaluation on this series is ongoing, with the aim of identifying a new potent and highly selective 17,20-lyase inhibitor.

5. Experimental

Melting points were determined using a BUCHI Melting Point B-545 apparatus and are uncorrected. Infrared (IR) spectra were taken 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 **3** (Kaku, T. et al., manuscript in preparation) and **13**[57] were prepared in the same manner as described previously.

5.1. 2,6-Dibromonaphthalene (2)

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 (iPr$_2$O), successively, to give **2** (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.

5.2. 1-(6-Bromo-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (4)

n-BuLi (1.6 M; 59.0 mL, 94.4 mmol) was added dropwise to a cooled (−50 °C) solution of **2** (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 **3** (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 **4** (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.

5.3. 1-{6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-2-naphthyl}-1-ethanone (5)

n-BuLi (1.6 M; 16.4 mL, 26.2 mmol) was added dropwise to a cooled (−70 °C) solution of **4** (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 **5** (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.

5.4. 1-{6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthyl}-1-ethanone (6)

A mixture of **5** (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 **6** (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 $C_{19}H_{20}N_2O_2$·0.1AcOEt: C, 73.46; H, 6.61; N, 8.83. Found: C, 73.29; H, 6.57; N, 8.84.

5.5. 1-[6-[(Diphenylmethylene)amino]-2-naphthyl]-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (7)

A mixture of **4** (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 **7** (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.

5.6. 1-(6-Amino-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (8)

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 **8** (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.

5.7. *N*-{6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-2-naphthyl}acetamide (9a)

Pyridine (5.0 mL, 61.2 mmol) and acetic anhydride (3.9 mL, 40.8 mmol) were added to a crude mixture of **8** 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 **9a** (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 $C_{38}H_{35}N_3O_2$·0.3AcOEt: C, 79.51; H, 6.37; N, 7.10. Found: C, 79.50; H, 6.47; N, 7.28.

5.8. *N*-{6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthyl}acetamide (10a)

Compound **10a** was prepared in the same manner as described for the preparation of **6**. 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.

5.9. *N*′-{6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthyl}-*N*-methylurea (10b)

Phenyl chloroformate (0.50 mL, 4.01 mmol) was added dropwise to a cooled (0 °C) solution of **8** (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 **9b** (984 mg) as a pale yellow powder, which contained a small amount of impurities. **9b** (850 mg) was used as a starting material. Using the same procedure as described for the synthesis of **6**, **10b** (278 mg, 31% from **8**) 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.

5.10. 6-Bromo-1-chloro-2-naphthol (11b)

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 **11b** (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.

5.11. 1-Methyl-2-naphthol (12)

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 **12** (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.

5.12. 6-Bromo-1-methyl-2-naphthol (11c)

A solution of bromine (16.1 g, 101 mL) in AcOH (30 mL) was added dropwise to a cooled (10 °C) solution of **12** (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 **11c** (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.

5.13. (7-Bromo-3-methoxy-2-naphthyl)methanol (14)

Trimethoxyborane (1.60 mL, 13.6 mmol) was added dropwise to a solution of lithium borohydride (2.96 g, 136 mmol) and **13**[56] (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 **14** 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.

5.14. 7-Bromo-3-methoxy-2-naphthaldehyde (15)

A suspension of **14** 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 **15** (33.9 g, 94% from **13**) 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.

5.15. 6-Bromo-2-methoxy-3-methylnaphthalene (16)

A mixture of **15** (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 **16** (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.

5.16. 6-Bromo-3-methyl-2-naphthol (11d)

BBr_3 (1 M solution in CH_2Cl_2; 55.0 mL) was added dropwise to a cooled (−70 °C) solution of **16** (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 **11d** (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.

5.17. 2-Bromo-6-(*tert*-butyldimethylsilyloxy)naphthalene (17a)

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 **17a** (71.3 g, 94%) as colorless plates. ^1H 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 **17b–d** were prepared using the same method as described for the preparation of **17a**.

5.18. 6-Bromo-2-[(*tert*-butyldimethylsilyl)oxy]-1-chloronaphthalene (17b)

Yield 98%, pale yellow oil. ^1H 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}.

5.19. 6-Bromo-2-[(*tert*-butyldimethylsilyl)oxy]-1-methylnaphthalene (17c)

Yield 85%, pale yellow plates. ^1H 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.

5.20. 6-Bromo-2-[(*tert*-butyldimethylsilyl)oxy]-3-methylnaphthalene (17d)

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.

5.21. 1-(6-*tert*-Butyldimethylsilyloxy-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (18a)

n-BuLi (1.6 M; 55.6 mL, 88.9 mmol) was added dropwise to a cooled (−70 °C) solution of **17a** (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 **3** (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 **18a** (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 **18b–d** were prepared using the same method as described for the preparation of **18a**.

5.22. 1-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-chloro-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (18b)

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}.

5.23. 1-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-methyl-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (18c)

Yield 89%, colorless powder. ^1H 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.

5.24. 1-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-methyl-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-1-propanol (18d)

Yield 93%, pale yellow powder. ^1H 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.

5.25. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-2-naphthol (19a)

Tetrabutylammonium fluoride (1 M in THF; 100 mL) was added to a cooled (0 °C) solution of **18a** (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 **19a** (28.3 g, 98%) as a colorless powder. The analytical sample was obtained by recrystallization from THF–hexane (colorless powder). ^1H 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 **19b–d** were prepared using the same method as described for the preparation of **19a**.

5.26. Chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthol (19b)

Yield 89%, colorless powder. ^1H 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.

5.27. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-1-methyl-2-naphthol (19c)

Yield 95%, colorless powder. ^1H 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.

5.28. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-3-methyl-2-naphthol (19d)

Yield 98%, colorless plates. ^1H 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.

5.29. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-2-naphthyl trifluoromethanesulfonate (20a)

Trifluoromethanesulfonic anhydride (9.1 mL, 54.1 mmol) was added dropwise to a cooled (0 °C) solution of **19a** (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 **23** (26.1 g, 77%) as a colorless powder. The mother liquor was concentrated, and the residue was recrystallized from i-Pr_2O to give **20a** (3.54 g, 10%) as a colorless powder. ^1H 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 **20b–d** were prepared using the same method as described for the preparation of **20a**.

5.30. 1-Chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthyl trifluoromethanesulfonate (20b)

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.

5.31. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-1-methyl-2-naphthyl trifluoromethanesulfonate (20c)

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.

5.32. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-3-methyl-2-naphthyl trifluoromethanesulfonate (20d)

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.

5.33. Methyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (21a)

A degassed solution of **20a** (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 **21a** (12.3 g, 95%) as a light brown powder. ^1H 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 **21b–d** were prepared using the same method as described for the preparation of **21a**.

5.34. Methyl-1-chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (21b)

Yield 89%, colorless powder. ^1H 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.

5.35. Methyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-1-methyl-2-naphthoate (21c)

Yield 81%, colorless powder. ^1H 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.

5.36. Methyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-3-methyl-2-naphthoate (21d)

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.

5.37. Methyl 6-[1-hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthoate (22)

Compound **21a** (1.40 g, 2.47 mmol) was used as a starting material. Using the same procedure described for the synthesis of **6**, **22** (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.

5.38. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-2-naphthamide (23a)

A solution of **21a** (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 **23a** (1.96 g, quant.) as a colorless powder. The analytical sample was obtained by recrystallization from THF–hexane (colorless powder). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 0.74 (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 $C_{37}H_{33}N_3O_2$·1.0THF: C, 78.94; H, 6.62; N, 6.74. Found: C, 78.83; H, 6.57; N, 6.94.

5.39. 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 (23b)

Using the same procedure as described for the synthesis of **23a**, **21a** (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·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 **23b** (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 $C_{38}H_{35}N_3O_2$·0.3THF: C, 80.03; H, 6.58; N, 7.14. Found: C, 79.81; H, 6.46; N, 7.05. Compounds **23c–h** were prepared using the same method as described for the preparation of **23b**.

5.40. *N*-Ethyl-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-2-naphthamide (23c)

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 $C_{39}H_{37}N_3O_2$·0.1AcOEt: C, 80.41; H, 6.47; N, 7.14. Found: C, 80.26; H, 6.54; N, 7.09.

5.41. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-*N*-propyl-2-naphthamide (23d)

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.

5.42. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-*N*-isopropyl-2-naphthamide (23e)

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 $C_{40}H_{39}N_3O_2$·0.25H_2O: C, 81.30; H, 6.65; N, 7.02. Found: C, 80.33; H, 6.68; N, 6.88.

5.43. 1-Chloro-6-[1-hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propyl]-*N*-methyl-2-naphthamide (23f)

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.

5.44. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-*N*,1-dimethyl-2-naphthamide (23g)

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.

5.45. 6-[1-Hydroxy-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)-propyl]-*N*,3-dimethyl-2-naphthamide (23h)

Yield 86%, colorless powder. ^{1}H 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 **24a–h** were prepared using the method as described for the preparation of **6**.

5.46. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthamide (24a)

Yield 88%, a colorless amorphous solid. ^{1}H 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.

5.47. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl-2-naphthamide (24b)

Yield 88%, colorless powder. Mp 217.0–219.0 °C. ^{1}H 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.

5.48. *N*-Ethyl-6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-naphthamide (24c)

Yield 92%, pale yellow amorphous solid. ^{1}H 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 $C_{20}H_{23}N_3O_2$·0.75H_2O: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.62; H, 7.08; N, 11.93.

5.49. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-propyl-2-naphthamide (24d)

Yield 77%, colorless amorphous powder solid. ^{1}H 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 $C_{21}H_{25}N_3O_2$·0.2H_2O: C, 71.04; H, 7.21; N, 11.83. Found: C, 70.83; H, 7.29; N, 11.78.

5.50. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-isopropyl-2-naphthamide (24e)

Yield 73%, colorless amorphous solid. ^{1}H 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 $C_{21}H_{25}N_3O_2$·0.15H_2O: C, 71.22; H, 7.20; N, 11.87. Found: C, 71.05; H, 7.34; N, 11.81.

5.51. 1-Chloro-6-[1-hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*-methyl-2-naphthamide (24f)

Yield 93%, pale yellow amorphous solid. ^{1}H 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 $C_{19}H_{20}N_3O_2$·0.5H_2O: C, 62.21; H, 5.77; N, 11.45. Found: C, 62.10; H, 5.84; N, 11.37.

5.52. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*,1-dimethyl-2-naphthamide (24g)

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 $C_{20}H_{23}N_3O_2$·0.75H_2O: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.20; H, 7.15; N, 11.83.

5.53. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-*N*,3-dimethyl-2-naphthamide (24h)

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_2·0.75H_2O: C, 68.45; H, 7.04; N, 11.97. Found: C, 68.56; H, 7.12; N, 11.79.

5.54. Methyl-1-(Bromomethyl)-6-[1-hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (25)

A mixture of **21c** (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 **21c** and **25** (**21c**:**25** = 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.

5.55. 7-[1-Hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (26a)

A solution of saturated NH_3 in MeOH (50 mL) was added to a cooled (0 °C) solution of **25** (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 **26a** (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.

5.56. 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 (26b)

Using **25** (0.80 g, 1.2 mmol) was used as the starting material and the same procedure described for the synthesis of **26a** with 40% methylamine solution, **26b** (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.

5.57. 7-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (27a)

Compound **26a** (1.17 g, 2.1 mmol) was used as a starting material. Using the same procedure described for the synthesis of **6**, **27a** (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.

5.58. 7-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (27b)

Using **26b** was used as the starting material and the same procedure as described for the synthesis of **27a**, **27b** (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.

5.59. Methyl-3-(bromomethyl)-6-[1-hydroxy-2-methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)propyl]-2-naphthoate (28)

Using **21d** (5.93 g, 10.2 mmol) as the starting material and the same procedure as described for the synthesis of **25**, crude **28** (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.

5.60. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2,3-dihydro-1*H*-benzo[*f*]isoindol-1-one (30a)

Using **28** (5.00 g, 7.3 mmol) as the starting material and the same procedure as described for the synthesis of **27a**, **30a** (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.

5.61. 6-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2-methyl-2,3-dihydro-1*H*-benzo[*f*]isoindol-1-one (30b)

Using **28** (0.99 g, 1.5 mmol) as the starting material and the same procedure as described for the synthesis of **27a**, **30b** (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.

5.62. Optical resolution of 27a

Optical resolution of **27a** (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 **(−)-27a** (5.27 g, 99.9% enantiomeric excess [ee]) as a colorless powder and **(+)-27a** (5.39 g, 99.7% ee) as colorless amorphous solid. **(−)-27a**: 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). **(+)-27a**: The spectral data of **(+)-27a** were identical to those of the **(−)-27a** except for elemental analysis and optical rotation. LCMS (API): m/z 322.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_3O_2{\cdot}1.25H_2O{\cdot}0.25$AcOEt: 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).

5.63. Optical resolution of 27b

Optical resolution of **27b** (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 **(−)-27b** (1.10 g, 99.9% ee) as a colorless powder and **(+)-27b** (1.00 g, 99.8% ee) as a colorless powder. **(−)-27b**: 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 **(−)-27b** was identical to those of the **27b**. 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). **(+)-27b**: The spectral data of **(+)-27b** were identical to those of the **(−)-27b** 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).

5.64. 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 (31)

4-Bromobenzenesulfonyl chloride (460 mg, 1.8 mmol) was added to a solution of **(+)-27b** (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 **31** (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 (CDCl3) 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.

5.65. 6-Bromo-*N*,*N*-diisopropyl-2-naphthamide (32b)

A solution of 6-bromo-2-naphthoic acid **32a** (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 **32b** (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.

5.66. 6-[(2*R*)-2-(*tert*-Butyldimethylsilyloxy)propanoyl]-*N*,*N*-diisopropyl-2-naphthamide (34a)

Solution **32b** (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 **33** (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 **34a** as a pale yellow oil. This compound was directly used without further purification in the next step. ^{1}H 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}.

5.67. 6-[(2*R*)-2-Hydroxypropanoyl]-*N*,*N*-diisopropyl-2-naphthamide (34b)

TBAF (41.01 g, 157 mmol) was added to a cooled (−10 °C) solution of **34a** (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 **34b** (24.00 g, 58% from **33**) as a colorless solid. Mp 174 °C. $[\alpha]_D^{20} = +38.2$ (c 0.726, MeOH). ^{1}H 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.

5.68. 6-[(1*S*,2*R*)-1,2-Dihydroxy-1-isopropylpropyl]-*N*,*N*-diisopropyl-2-naphthamide (35)

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 **34b** (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 **35** (12.35 g, 54%) as a colorless solid. The purity of the obtained **35** 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.

5.69. 7-[(1*S*,2*R*)-1,2-Dihydroxy-1-isopropylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (38a)

n-BuLi (1.6 mol/L, 103.8 mL, 166 mmol) was added dropwise to a cooled (−70 °C) solution of **35** (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 **36a** and **36b** (**36a**:**36b** = ca. 6:1) as amorphous solid. The crude product of **36a** and **36b** 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 **37a** and **37b**.

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 **37a** and **37b** 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 **38a** and **38b** (4.33 g, 42%, **38a**:**38b** = 93:7) as a colorless solid. The ratio of the obtained **38a** and **38b** was determined by HPLC using Chiralpak AD column. ^1H 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 $C_{19}H_{23}NO_3 \cdot 0.1AcOEt$: C, 72.32; H, 7.45; N, 4.35. Found: C, 72.37; H, 7.61; N, 4.32.

5.70. 7-[(1*S*)-1-Acetyl-1-hydroxy-2-methylpropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (39)

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 **38a** (4.00 g, 12.8 mmol, **38a**:**38b** = 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 **39** (3.10 g, 33% from **35**) as a colorless solid. The purity of the obtained **39** was >99% as determined by HPLC using a Chiralpak AD column. Mp 171 °C. $[\alpha]_D^{20} = -22.9$ (*c* 0.615, MeOH). ^1H 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 $C_{19}H_{21}NO_3 \cdot 0.6AcOEt$: C, 70.57; H, 7.14; N, 3.85. Found: C, 70.60; H, 7.16; N, 4.12.

5.71. 7-[(1*S*)-3-Bromo-1-hydroxy-1-isopropyl-2-oxopropyl]-2-methyl-1,2-dihydro-3*H*-benzo[*e*]isoindol-3-one (40)

Pyridinium bromide perbromide (3.17 g, 9.9 mmol) was added to a cooled (0 °C) solution of **39** (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 **40** (2.97 g, 85%) including starting material **39** as a colorless solid. This compound was used without further purification in the next step. ^1H 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}.

5.72. 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 (41)

TBAF (1 M solution in THF, 32 mL, 0.032 mmol) was added to a solution of **40** (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 **41** (0.55 g, 54% from **39**) as colorless amorphous solid. ^1H 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 $[M+H]^+$.

5.73. 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 [(−)-27b]

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 **41** (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 **(−)-27b** (54 mg, 54%). The optical purity of the obtained **(−)-27b** was >99% ee as determined by HPLC using a Chiralpak AD column.

5.74. Homology modeling

Homology models of 17,20-lyase (CYP17) were constructed based on the crystal structure of mammalian CYP2C5 (PDB code:1DT6) using the Insight II homology module (v2000, Accelrys Inc.). Using the Search/Generate-Loops function of Insight II, conformations of the insertions and deletions in the alignment were obtained with reference to the known 3-D structures. After some

manual adjustments to remove large steric hindrances, the structure was subjected to 1000 steps of energy minimization with the steepest descent minimizer, followed by 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 (v980, Accelrys Inc.). During the minimization procedure, the dielectric constant was set to $4 * r$, where r is the distance between two interacting atoms, and the force constant of tethering constraints for the backbone of structurally conserved regions and heme was set to 40 kcal/Å^2 to prevent a large movement from the initial positions.

5.75. Docking of inhibitors

Covalent bonding models of imidazole were constructed by full energy minimization using the Discover-ESFF force field. The residual parts of compounds were connected to the imidazole. Using the Search—Compare module of Insight II, the stable binding mode of each compound was investigated by systematic bond rotation within the ligand, including of some side chains around the ligand. Energy minimization was continued using the Discover-ESFF force field. The energy minimization conditions were the same as those used for the homology modeling.

5.76. X-ray crystallographic analysis of compound 31

A single crystal (0.40 × 0.40 × 0.16 mm) of **31** 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 (SIR92), 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 (**31**) 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).

5.77. Inhibition of rat 17,20-lyase in vitro

Inhibitory activity against rat enzymes was determined according to a previously described method[58] with some modifications. Testes excised from 13-week-old male Sprague-Dawley (SD) rats were homogenized and testicular microsomes were prepared by centrifugation. The reaction mixture consisted of 75 mM phosphate buffer (pH 7.4), 7 μg the microsome protein, 10 nM [1,2-^{3}H]-17α-hydroxyprogesterone (NEN), 5 mM NADPH (Oriental Yeast), and 1–1000 nM test compound in a total volume of 20 μL. The concentration of reagents was expressed as the final concentration in the reaction mixture. The test compounds were serially diluted with dimethylformamide, and then diluted fivefold with distilled water before 5 μL samples were added to the reaction mixture. The reaction was terminated with the addition of 40 μL of ethyl acetate after 15 min (17,20-lyase) incubation at 37 °C, followed by vortexing for 30 s and a brief centrifugation. Samples (30 μL) of the organic phase were applied to silica gel TLC plates (Whatman, LHPK). The substrate and products, androstenedione and testosterone, were separated using the toluene–acetone (7:2) solvent system. Detection of the spots and measurement of the radioactivity as PSL were performed using a BAS2000 Bio-image analyzer (FUJIX). The concentrations of the test compounds required to reduce the concentration of the products by 50% (IC_{50}) were calculated.

5.78. Inhibition of human 17,20-lyase in vitro

Inhibition of human enzymes was determined as above. The reaction mixture consisted of 75 mM phosphate buffer (pH 7.4), 1 mM magnesium chloride, 0.5 pmol recombinant P450c17 (Biotechnology Laboratories, Takeda), 0.5 pmol recombinant cytochrome b5 (Pan Vera), 20.8 ng recombinant NADPH-cytochrome P450 reductase (Pan Vera), 10 nM [1,2-^{3}H]-17α-hydroxypregnenolone (Amersham), 5 mM NADPH (Oriental Yeast), and 1–1000 nM test compound in a total volume of 20 μL. The test compounds were serially diluted with dimethylformamide, and then diluted fivefold with distilled water before 5 μL of the solution was added to the reaction mixture. The reaction was terminated by the addition of 40 μL of ethyl acetate after 15 min (17,20-lyase) incubation at 37 °C, then vortexing for 30 s and briefly centrifuging. Organic phases (30 μL) were applied to silica gel thin layer chromatography plates (Whatman, LHPK). The substrate and product DHEA were separated using the cyclohexane–ethyl acetate (3:2) solvent system.

5.79. Screening for the inhibition of CYP3A4 in vitro (Tables 1–4)

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

5.80. Inhibition of rat 11-hydroxylase in vitro

Adrenal glands excised from SD rats were homogenized, and the mitochondrial fraction was prepared through a series of centrifugation steps. Rat 11-hydroxylase activity was measured according to the method described for side-chain cleavage activity by Uzgiris et al.[59] 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 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 compound in a total volume of 150 μL. The test compounds were serially diluted with dimethylformamide, and 1.5 μL samples were directly added to the reaction mixture. The concentration of reagents was expressed as the final concentration in the reaction mixture. The reaction was terminated by the addition of 400 μL ethyl acetate and 100 μL distilled water after 30 min incubation at 37 °C, followed by vortexing for 30 s and a brief centrifugation. Organic phase (300 μL) was transferred to a new tube, and evaporated until dry with nitrogen gas. The steroids were dissolved with 30 μL ethyl acetate. The whole volume was applied to silica gel TLC plates (Whatman, LHPK). The sub-

strate and the products, 11-deoxycortisol and cortisol, were separated using the toluene–acetone (7:2) solvent system.

5.81. Effect of (−)-27b on metabolic activities of CYP-expressing microsomes (Table 5)

The effect of **(−)-27b** on CYP isoforms was assessed by incubating a marker substrate with the microsomes expressing each human CYP isoform in the presence of 3, 10, and 30 μmol/L of **(−)-27b**. 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 2C9, 80 mmol/L Tris–HCl buffer (pH 7.4) was used instead of phosphate buffer. After preincubation of **(−)-27b** and CYP isoform-specific substrate in the mixture at 37 °C for 5 min, the reaction was initiated by the addition of microsomes derived from specific CYP-expressing human B-lymphoblastoid cells. The concentration of the substrates was referenced from the data sheet from GENTEST Corp. [(±)-bufuralol 1′-hydroxylation for CYP2D6 and testosterone 6β-hydroxylation activity for CYP3A4] or published reports (tolbutamide hydroxylation for CYP2C8 and 2C9)[60,61] with slight modifications.

The marker reactions specific for CYP isoforms except for CYP3A4, were measured by published analytical methods[60,62–66] with slight modifications. Testosterone 6β-hydroxylation activity for CYP3A4 was analyzed under the following HPLC conditions: Inertsil ODS-2 column (150 × 4.6 mm I.D.; GL Science, Tokyo, Japan), detection wavelength 254 nm, flow rate 1.0 mL/min, column temperature 50 °C, and mobile phase 10 mmol/L acetate buffer (pH4.3)/acetonitrile = 7/3. Control marker enzymatic activities were measured for the preincubation samples in the presence of methanol alone without **(−)-27b**.

5.82. Effects of (−)-27b on serum testosterone and DHEA concentrations in male cynomolgus monkeys

Adult male cynomolgus monkeys housed in a temperature-controlled room (23 ± 2 °C) with a 12:12 h light/dark cycle (illumination from 7:00 am to 7:00 pm) were used for the single dosing experiments. All procedures were performed according to protocols approved by the Institutional Animal Care and Use Committee of Pharmaceutical Research Division, Takeda. The test compound **(−)-27b** was suspended in 0.5% methylcellulose and orally administered at a dose of 1 mg/kg. Blood samples were collected just before dosing, and 4 and 8 h after the dosing. Serum was stored at −30 °C until assayed by radioimmunoassay (RIA). Concentrations of testosterone were determined using a Testosterone I-125 kit (Dia Sorin s.r.l., Italy), according to the manufacturer's directions.

5.83. Pharmacokinetic studies

Compound **(−)-27b** 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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