4-(Benzoylindolizinyl)butyric Acids; Novel Nonsteroidal Inhibitors of Steroid 5α-Reductase. III.[1)]

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A novel series of indolizinebutyric acids with various benzoyl substituents was synthesized to develop nonsteroidal inhibitors of steroid 5α-reductase, and the structure–activity relationships in this series were studied. We previously reported the structure–activity relationships in a series of indolebutyric acids as well as the discovery of the novel nonsteroidal 5α-reductase inhibitor, FK143. We have now made other modifications to this compound to improve *in vivo* inhibitory activity. By altering the heterocyclic nucleus and changing the benzoyl substituent we have succeeded in identifying the strongly active compound, FK687, (*S*)-4-[1-[4-[[1-(4-isobutylphenyl)butyl]oxy]benzoyl]indolizin-3-yl]butyric acid, which displays strong *in vitro* inhibitory activity against the human enzyme and *in vivo* inhibitory activity against the castrated young rat model. This compound should be a useful agent for the treatment of benign prostatic hyperplasia.

Key words 5α-reductase inhibitor; FK687; benign prostatic hyperplasia; nonsteroidal

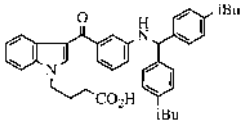
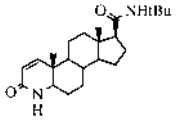
Benign prostatic hyperplasia (BPH) is a common disorder in aging males. Approximately 50% to 75% of all males over the age of 50 are known to develop this condition.[3)] This disorder is characterized by a progressive enlargement of the prostate grand, leading to an increase in pressure on the urethra; it results in obstruction of urinary flow. In light of the high incidence of this condition, it is obvious that some form of chemical therapy would be of immense potential importance in treating BPH.[4)]

Steroid 5α-reductase enzymatically converts testosterone (T) into 5α-dihydrotestosterone (DHT), which is the most active agonist for androgen receptors.[5)] An accumulation of DHT to high levels in the prostate gland or the skin is recognized as leading to various pathological conditions such as BPH, acne, female hirsutism, and male pattern baldness.[4)] Therefore, therapy with a 5α-reductase inhibitor would be expected to lead to a decrease in DHT concentration within the prostate gland or other tissues, and may be an extremely useful agent for the treatment of BPH and other diseases.

Though many laboratories have investigated 5α-reductase inhibitors,[6,7)] these efforts have predominantly concentrated on compounds with a steroidal structure, for example finasteride[6a)] (Table 1). However, due to the presence of a steroidal structure, there is the strong possibility of unwanted side-effects.[8)] We previously reported[1)] the discovery of an excellent nonsteroidal compound, FK143, 4-[3-[3-[[bis(4-isobutylphenyl)methyl]amino]benzoyl]-1*H*-indol-1-yl]butyric acid (Table 1), which displays high *in vitro* inhibitory activity against human prostatic 5α-reductase (IC_{50}=1.9 nM) and *in vivo* inhibitory activity against the castrated young rat model.[9)] In this model, the growth of ventral prostate was induced by the subcutaneous injection of testosterone propionate (TP) to castrated young rats and was reduced by administration of the inhibitor. In order to obtain a more clinically effective candidate, we have now investigated more active compounds against this *in vivo* model. We employed two types of modification, 1) altering the indole ring to other heterocyclic rings, and 2) changing the benzoyl substituent at the 3-position.

Chemistry The indolizine derivative **17** was prepared as shown in Charts 1 and 2. Friedel–Crafts acylation of indolizine was carried out with ethyl 3-(chloroformyl)propionate and aluminum chloride to obtain **1** and **2**. The ketone **1** was reduced to **3** by a borane–tetrahydrofuran (THF) complex, and **3** was acylated with 3-nitrobenzoyl chloride to obtain **8**. The catalytic reduction of **8** gave the amine **11**, which was alkylated with bis(4-isobutylphenyl)chloromethane to afford **14**. **17** was obtained by hydrolysis of the ester **14**. The indolizine derivative **18** was prepared from **2** in a similar manner to **17** (Charts 1, 2). The imidazopyridine **19** was prepared as shown in Charts 1 and 2. 1-Formylimidazo[1,5-*a*]pyridine[10)] was treated with Wittig reagent to give the β,γ-unsaturated acid **5**. Esterification and catalytic reduction of **5** afforded **7,** which was derived to **19** in a manner similar to **17**. The imidazopyridine derivative **30** was prepared as shown in Charts 3 and 4. The reaction of 2-picolylamine and glutaric anhydride yielded 4-carbamylbutyric acid **20**, which

Table 1. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by FK143 and Finasteride

Compd.	Structure	*In vitro* IC_{50} (nM)		*In vivo* (*p.o.*)[a)] 10 mg/kg (%)
		Human	Rat	
FK143		1.9	4.2	46.1##
Finasteride		1.0	5.9	48.1##

a) *In vivo* effect of FK143 and finasteride on ventral prostate weight of castrated rats (TP-treated). Prepubertal male rats were castrated, subcutaneously injected with 300 mg/kg of TP (except castrated control), and orally administered with drug suspension for 5 d. Data are expressed as percent reduction in prostate weight which was calculated as follows: 100[(prostate weight of vehicle+TP group)−(prostate weight of test comp+TP group)]/[(prostate weight of vehicle+TP group)−(prostate weight of castrated control group)]. ##$p<0.01$ *vs.* Control Dunnett *t*-test mean±S.E.

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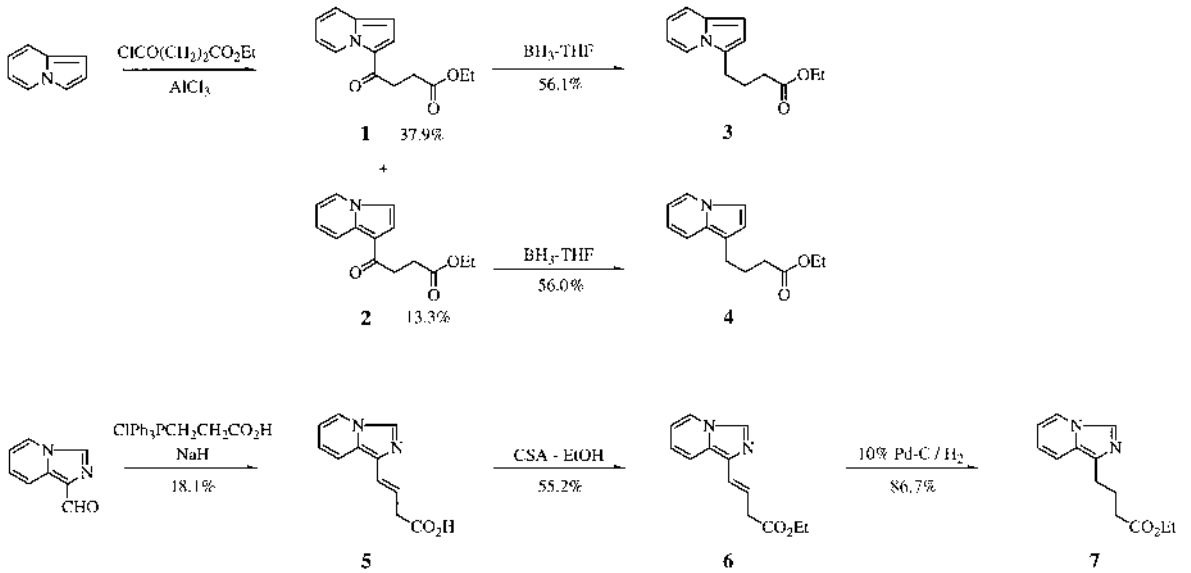


Chart 1. Preparation of **3**, **4** and **7**

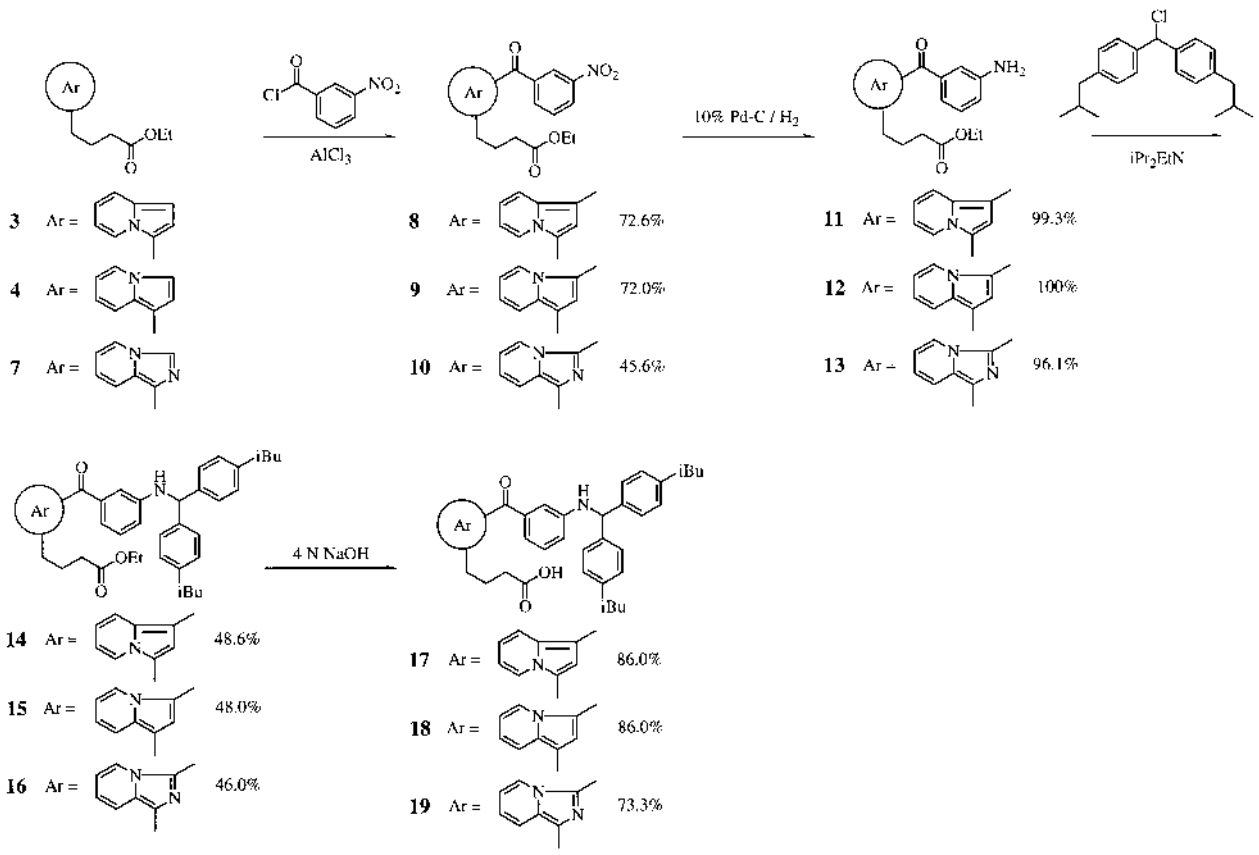


Chart 2. Preparation of Compouds **17**—**19**

was treated with ethanol and camphorsulfonic acid (CSA) to afford the ester **21**. The imidazo[1,5-*a*]pyridine **22** was prepared by cyclization of **21** with phosphorus oxychloride, and **22** was acylated under Friedel–Crafts conditions with 3-nitrobenzoyl chloride to give **23**. Hydrolysis of the ester moiety and reduction of the nitro group of **23** afforded the amine **28**, which was alkylated with bis(4-isobutylphenyl)chloromethane to obtain **30**. The azaindole derivative **31** was prepared as shown in Charts 3 and 4. 7-Azaindole was acylated with 3-nitrobenzoyl chloride to give **24**, which was alkylated with ethyl 4-bromobutyrate to afford the ester **25**. **25** was derived to **31** in a manner similar to **30**.

The indole derivatives **39** and **40** were prepared as shown in Chart 6. Indole was acylated under Friedel–Crafts conditions to give **35a**, **b**, which were alkylated with ethyl 4-bromobutyrate to afford the ester **36a**, **b**. Hydrolysis and the catalytic reduction of **36a**, **b** afforded **38a**, **b**, which were alkylated with 1-(4-isobutylphenyl)ethyl bromide to obtain **39**

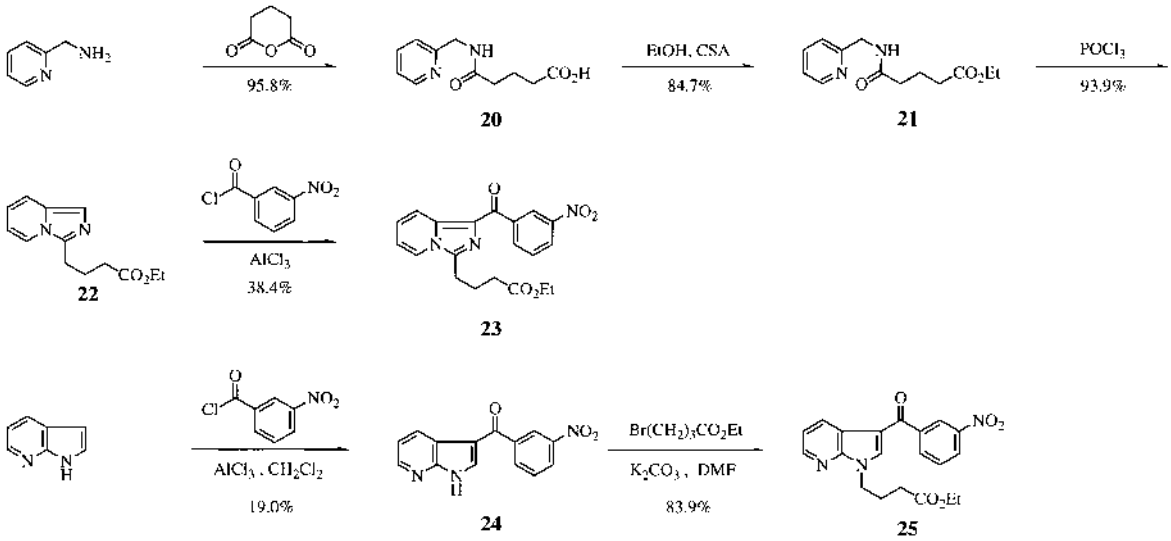


Chart 3. Preparation of **23** and **25**

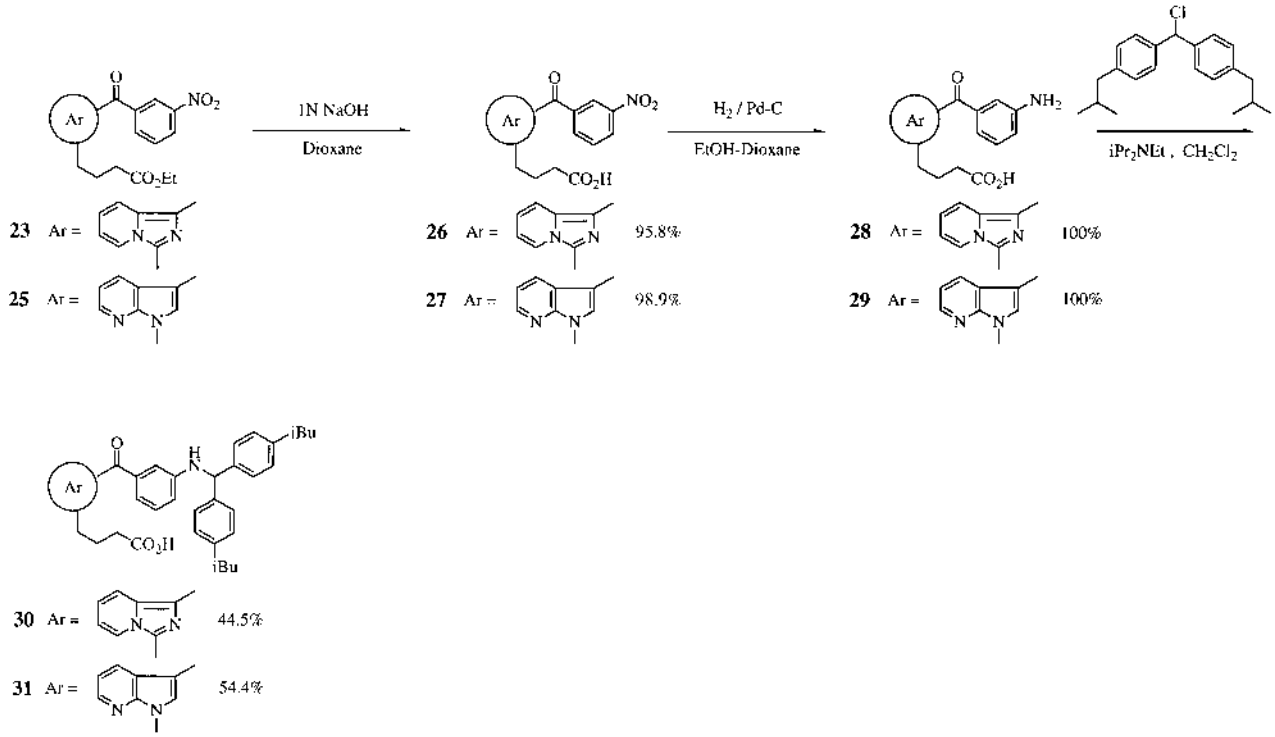


Chart 4. Preparation of **30** and **31**

and **40**.

The indole derivatives **45a**—**g** were prepared as shown in Chart 7. Indole was acylated with 4-methoxybenzoyl chloride to give **41**, which was alkylated with ethyl 4-bromobutyrate to afford the ester **42**. Demethylation of the methoxy group of **42** was carried out with aluminum chloride and ethanethiol to afford the phenol **43**. *O*-Alkylation of **43** was achieved with the benzyl bromides **34a**—**g** and potassium carbonate to obtain **44a**—**g**, which were hydrolyzed to afford **45a**—**g**. The chiral indole derivatives **50a**—**d** and **51a**—**d** were prepared as shown in Chart 8. The phenol **43** was reacted with the chiral *R* alcohols **46a**—**d**, obtained by reduction of the ketones **32a**—**d** with (+)-*B*-chlorodiisopinocampheylborane ((+)-DIP-chloride),[11] under Mitsunobu conditions, to give the *S* ethers **48a**—**d**, which were hydrolyzed with 1 N NaOH to afford **50a**—**d**. **51a**—**d** were prepared in a similar manner to **50a**—**d**. The indolizine derivatives **55b**—**f** were prepared as shown in Chart 9. The indolizinebutyric acid ethyl ester **3** was acylated by 4-acetoxybenzoyl chloride to afford **52**, which was deacetylated to obtain the phenol **53**. *O*-Alkylation of **53** with the benzyl bromides **34b**—**f** gave **54b**—**f**, which were hydrolized with 1 N NaOH to afford **55b**—**f**. The chiral indolizine derivatives FK687 and **59** were prepared as shown in Chart 10. **56** was alkylated by the chiral alcohol **46c** under Mitsunobu conditions to give **57**, which was hydrolyzed by 1 N NaOH to afford FK687. **59** was ob-

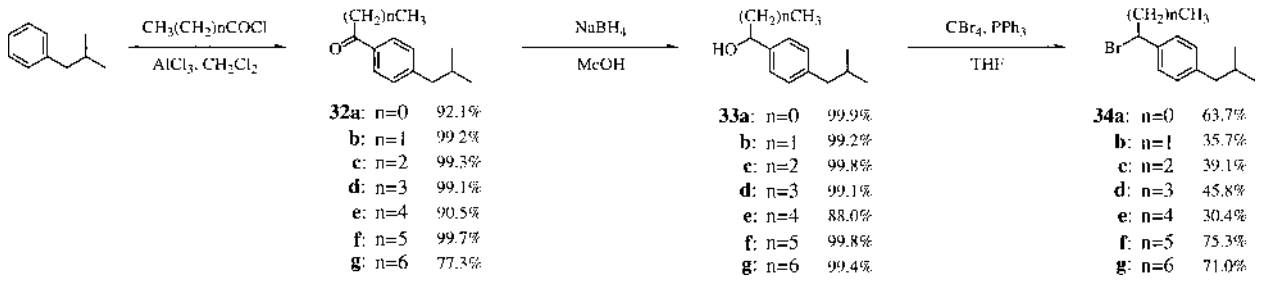


Chart 5. Preparation of **34a**—**g**

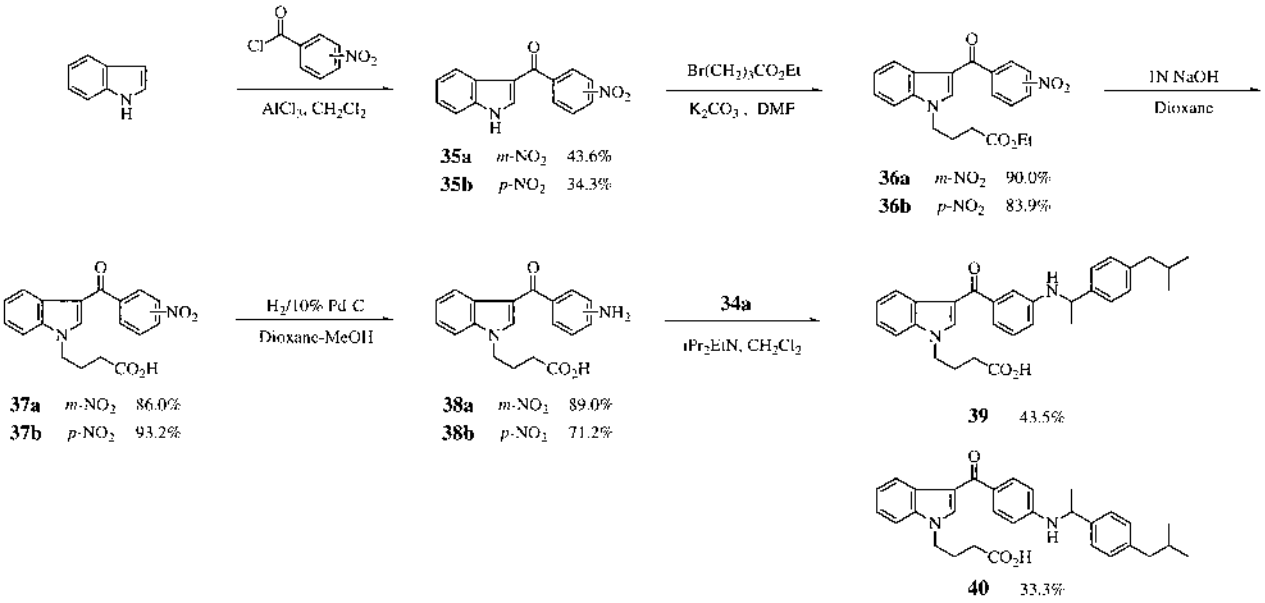


Chart 6. Preparation of **39** and **40**

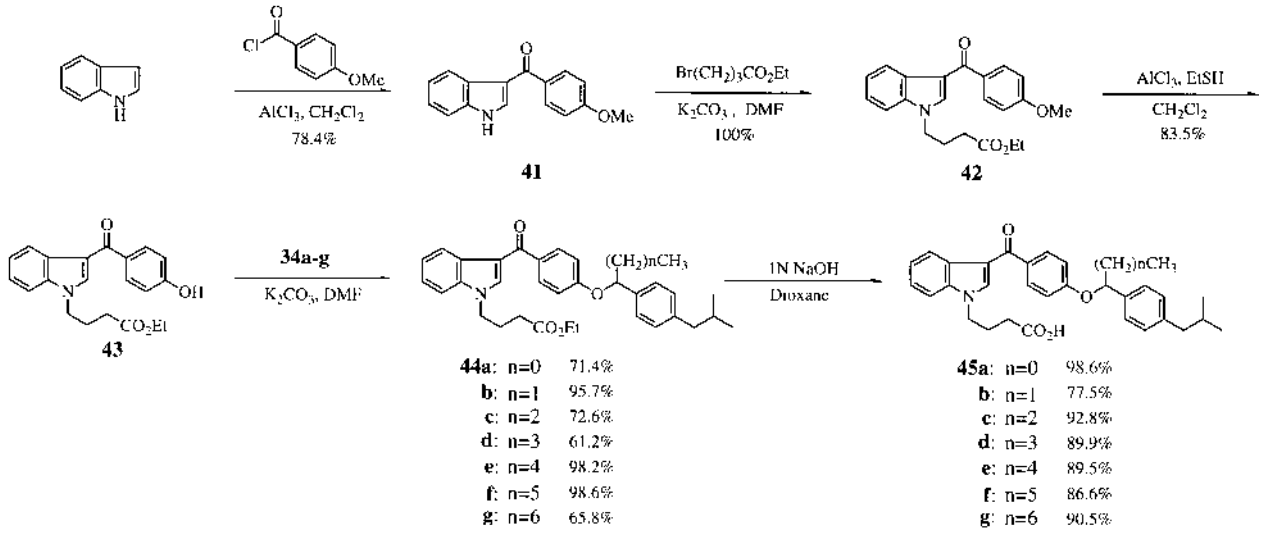
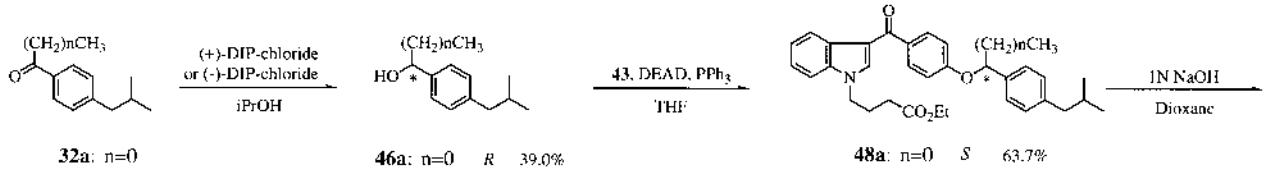


Chart 7. Preparation of **45a**—**g**

tained in a similar manner to FK687.

Results and Discussion

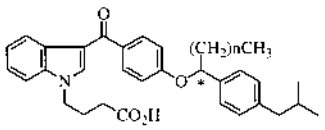
Modification of the Indole Ring The prepared compounds were evaluated for their ability to inhibit human and rat prostatic 5α-reductases, and inhibitory activities were expressed as the IC_{50} value. Two isozymes of human 5α-reductase, type 1 and type 2, have been isolated,[12] and the type 2



32a: n=0
b: n=1
c: n=2
d: n=3

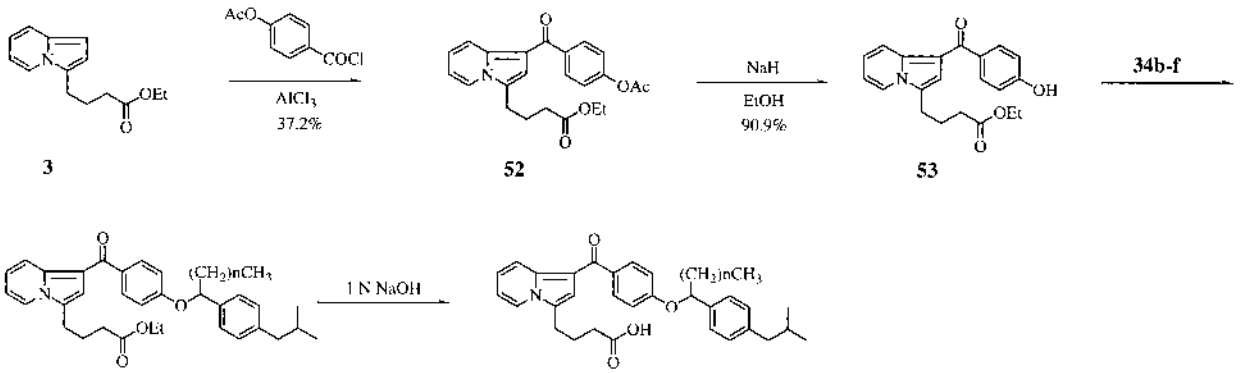
46a: n=0	*R*	39.0%	
b: n=1	*R*	86.0%	
c: n=2	*R*	84.0%	
d: n=3	*R*	30.0%	
47a: n=0	*S*	84.0%	
b: n=1	*S*	77.2%	
c: n=2	*S*	60.0%	
d: n=3	*S*	55.0%	

48a: n=0	*S*	63.7%	
b: n=1	*S*	42.8%	
c: n=2	*S*	49.0%	
d: n=3	*S*	84.0%	
49a: n=0	*R*	58.0%	
b: n=1	*R*	46.6%	
c: n=2	*R*	49.0%	
d: n=3	*R*	67.0%	



50a: n=0	*S*	83.0%
b: n=1	*S*	89.2%
c: n=2	*S*	92.0%
d: n=3	*S*	84.0%
51a: n=0	*R*	94.2%
b: n=1	*R*	89.2%
c: n=2	*R*	100%
d: n=3	*R*	65.0%

Chart 8. Preparation of **50a**—**d** and **51a**—**d**

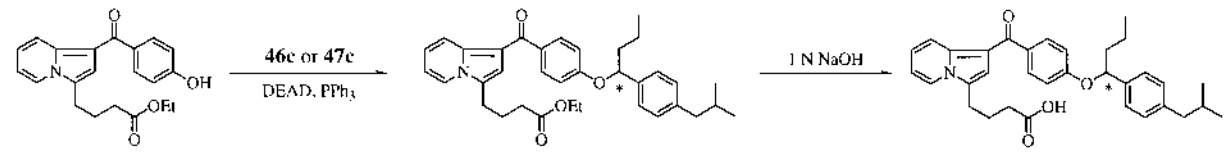


3 **52** **53**

54b: n=1		87.5%
c: n=2		88.3%
d: n=3		75.9%
e: n=4		93.5%
f: n=5		90.9%

55b: n=1		91.3%
c: n=2		79.2%
d: n=3		86.0%
e: n=4		91.9%
f: n=5		89.8%

Chart 9. Preparation of **55b**—**f**

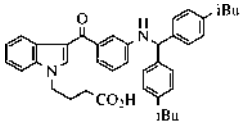
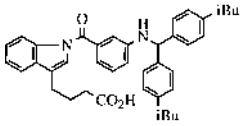
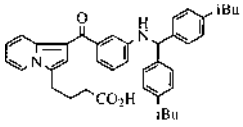
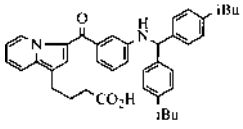
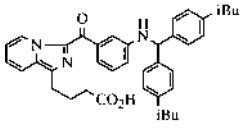
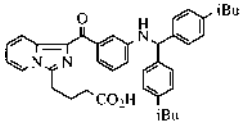
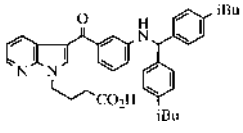


56

57	*R*	56.2%	
58	*S*	60.5%	
FK687	*S*	75.9%	
59	*R*	84.1%	

Chart 10. Preparation of FK687 and **59**

Table 2. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by FK143, **60**, **17**—**19**, **30** and **31**

Compd. No.	Structure	*In vitro* IC_{50} (nM)		*In vivo* (*p.o.*)[a]	
		Human	Rat	3.2	1 mg/kg (%)
FK143		1.9	4.2	33.8###	8.3
60		38	75	N.T.[b]	
17		0.53	1.1	17.5##	−9.8
18		0.60	2.9	22.7##	11.7
19		15	5.3	N.T.[b]	
30		59	5.0	N.T.[b]	
31		37	1.5	N.T.[b]	

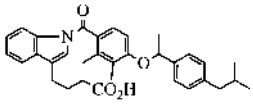
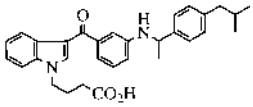
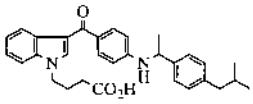
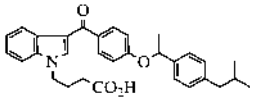
a) *In vivo* effect of FK143, **60**, **17**, **18**, **19**, **30**, and **31** on ventral prostate weight of castrated rats (TP-treated). See the footnotes of Table 1. *b*) Not tested. ##$p<0.01$, ###$p<0.001$ *vs.* Control Dunnett *t*-test mean±S.E.

isozyme participates in the growth of the prostate. Since type 2 isozyme is predominantly expressed in the prostate, we used the enzymes from the human and rat prostate for *in vitro* assay. *In vivo* inhibitory activities of these compounds in the castrated young rat model were measured and expressed as a percentage of the reduction of ventral prostate weight (Table 1).

We previously reported[1] that FK143 displayed ten times stronger *in vitro* inhibitory activity against human prostatic 5α-reductase than **60**, 4-[1-[3-[[bis(4-isobutylphenyl)methyl]-amino]benzoyl]-1*H*-indol-3-yl]butyric acid (Table 2), in which the two substituents on the indole ring are at opposite positions to those of FK143. This suggests that alteration of the nucleus may lead to improvement of the *in vitro* inhibitory activity. Thus, we first exchanged the indole nucleus of FK143 to other heterocyclic rings, such as indolizine (**17**, **18**), imidazopyridine (**19**, **30**) and azaindole (**31**), keeping the substituents constant (Table 2). Among these compounds, the indolizine derivatives (**17**, **18**) had stronger inhibitory activity against the human enzyme than FK143; the IC_{50} value of **17** was 0.53 nM and that of **18** was 0.60 nM. These compounds (**17**, **18**) also displayed significant *in vivo* inhibitory activity against the castrated young rat model (Table 2). However, these inhibitory activities were not so potent, thus other modifications were necessary to improve the *in vivo* inhibitory activity.

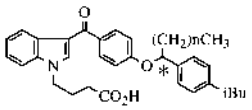
Modification of the Benzoyl Substituent We next investigated the benzoyl substituent on the indole moiety. We considered that a bis(4-isobutylphenyl)methyl group was too lipophilic for *in vivo* inhibitory activity. Indeed, we previously reported[1] that compound **61**, which has a 1-(4-isobutylphenyl)ethyl group at the benzoyl substituent instead of a bis(4-isobutylphenyl)methyl group, had strong *in vivo* inhibitory activity in the castrated young rat model (Table 3). Thus, the 1-(4-isobutylphenyl)ethyl group was introduced to the benzoyl substituent of various indolebutyric acids (**39**, **40**, **45a**) (Table 3). Among these compounds, **45a** had clearly stronger *in vivo* inhibitory activity than FR143. However, re-

Table 3. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by **61**, **39**, **40** and **45a**

Compd. No.	Structure	*In vitro* IC_{50} (nM)		*In vivo* (%)[a]	
		Human	Rat	3.2	1 mg/kg (*p.o.*)
FK143		1.9	4.2	33.8$^{\#\#\#}$	8.3
61		320	2.5	55.0$^{\#\#\#}$	14.4
39		89	7.5	20.8$^{\#}$	2.4
40		45	1.8	28.2$^{\#}$	20.8$^{\#}$
45a		38	3.1	44.6$^{\#\#\#}$	38.0$^{\#\#\#}$

a) *In vivo* effect of FK143, **61**, **39**, **40**, and **45a** on ventral prostate weight of castrated rats (TP-treated). See the footnotes of Table 1. $^{\#}p<0.1$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ *vs.* Control Dunnett *t*-test mean±S.E.

Table 4. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by **45a**—**g**



Compd. No.	*n*	*	*In vitro* IC_{50} (nM)		*In vivo* (%)[a]		
			Human	Rat	3.2	1.0	0.32 mg/kg (*p.o.*)
45a	0	*RS*	33	3.1	44.6$^{\#\#\#}$	38.0$^{\#\#\#}$	
45b	1	*RS*	47	0.78	60.4$^{\#\#\#}$	46.7$^{\#\#\#}$	50.0$^{\#\#\#}$
45c	2	*RS*	14	1.5	55.4$^{\#\#}$	51.8$^{\#\#}$	20.1
45d	3	*RS*	3.3	0.66	52.7$^{\#\#\#}$	29.3$^{\#}$	11.9
45e	4	*RS*	4.8	7.5	42.5$^{\#\#}$	−3.2	
45f	5	*RS*	7.4	1.7	−5.2	−16.3	
45g	6	*RS*	8.5	7.7	−4.5	−7.5	

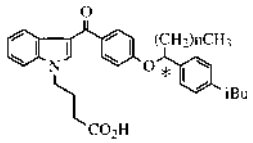
a) *In vivo* effect of **45a**—**g** on ventral prostate weight of castrated rats (TP-treated). See the footnotes of Table 1. $^{\#}p<0.1$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ *vs.* Control Dunnett *t*-test mean±S.E.

garding *in vitro* inhibitory activity against the human enzyme, **45a** was not so strong; its IC_{50} value was 38 nM. It was thus considered that a larger group was necessary at the benzoyl substituent for strong *in vitro* inhibitory activity against the human enzyme, and we introduced longer alkyl groups at the benzoyl substituent instead of the methyl group; *i.e.* 1-(4-isobutylphenyl)propyl, 1-(4-isobutylphenyl)-butyl, 1-(4-isobutylphenyl)pentyl, and so on, were introduced instead of 1-(4-isobutylphenyl)ethyl (**45b**—**g**) (Table 4). As expected, among these compounds, compounds with larger substituents (**45d**—**g**) had stronger *in vitro* inhibitory activities against the human enzyme. On the other hand, the *in vivo* inhibitory activities of compounds with smaller substituents (**45a**—**d**) were stronger.

These compounds are racemic since they have an asymmetric center in the benzoyl moiety. Optical isomers often do not have the same physiological activities, thus we compared the activities of both enantiomers (**50a**—**d**, **51a**—**d**) (Table 5). The *S* isomers of these compounds had stronger *in vitro* inhibitory activity against human and rat enzymes than the *R* isomers, and among them, **50d** had the strongest inhibitory activity; its IC_{50} value was 4.8 nM against the human enzyme and 0.8 nM against the rat enzyme. The *in vivo* inhibitory activity of **50d** was also stronger than its *R* isomer, **51d**.

Next, we introduced these benzoyl substituents to the indolizine moiety of 4-(indolizin-3-yl)butyric acid (**55b**—**f**) (Table 6). These indolizine derivatives showed the same tendencies for *in vitro* inhibition as the indole derivatives, and compounds with a larger substituent (**55c**—**f**) had stronger *in vitro* inhibitory activity against the human enzyme with

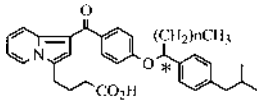
Table 5. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by **50a**—**d** and **51a**—**d**



Compd. No.	n	*	ee (%)	*In vitro* IC_{50} (nM)		*In vivo* (%)[a]		
				Human	Rat	3.2	1.0	0.32 mg/kg (*p.o.*)
50a	0	*S*	87.1	58	0.29	48.8$^{\#\#}$	43.8$^{\#}$	20.4
50b	1	*S*	93.9	47	0.68	54.1$^{\#\#}$	50.3$^{\#\#}$	18.0
50c	2	*S*	95.6	54	0.73	57.8$^{\#\#\#}$	51.5$^{\#\#}$	46.5$^{\#\#\#}$
50d	3	*S*	95.1	4.8	0.8	70.6$^{\#\#}$	49.4$^{\#\#}$	9.0
51a	0	*R*	90.0	440	1.4	10.3	19.5	4.4
51b	1	*R*	91.1	470	2.7	36.1$^{\#}$	12.5	23.4
51c	2	*R*	94.8	490	1.3	30.5$^{\#\#}$	18.8	23.5
51d	3	*R*	96.0	62	1.8	20.3	11.0	14.7

a) *In vivo* effect of **50a**—**d** and **51a**—**d** on ventral prostate weight of castrated rats (TP-treated). See the footnotes of Table 1. $^{\#}p<0.1$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ *vs.* Control Dunnett *t*-test mean±S.E.

Table 6. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by **55b**—**f**, **59** and FK687



Compd. No.	n	*	ee (%)	*In vitro* IC_{50} (nM)		*In vivo* (%)[a]		
				Human	Rat	3.2	1.0	0.32 mg/kg (*p.o.*)
55b	1	*RS*		12	0.55	47.6$^{\#\#\#}$	47.2$^{\#\#\#}$	
55c	2	*RS*		3.6	2.2	43.4$^{\#\#\#}$	49.5$^{\#\#\#}$	10.5
55d	3	*RS*		5.0	1.8	45.7$^{\#\#}$	17.3	
55e	4	*RS*		3.4	1.6	38.0$^{\#\#}$	13.4	−1.9
55f	5	*RS*		5.3	6.4	10.3		
59	2	*R*	97.6	120	1.2	15.4	10.1	2.4
FK687	2	*S*	96.0	4.6	1.7	60.1$^{\#\#}$	47.0$^{\#\#}$	42.6$^{\#\#}$
FK143				1.9	4.2	33.8$^{\#\#\#}$	8.3	

a) *In vivo* effect of **13b**—**f**, **14**, FK687 and FK143 on ventral prostate weight of castrated rats (TP-treated). See the footnotes of Table 1. $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ *vs.* Control Dunnett *t*-test mean±S.E.

nanomolar IC_{50} values. Amongst those compounds, **55c** had the strongest *in vivo* inhibitory activity. The *S* isomer of **55c**, FK687, had stronger *in vitro* inhibitory activity than the *R* isomer (**59**); its IC_{50} value was 4.6 nM against the human enzyme. FK687 also had very strong *in vivo* inhibitory activity, and that activity was clearly stronger than that of FK143 in the castrated young rat model.

Conclusions

We set out to produce 5α-reductase inhibitors with a non-steroidal structure, beginning with the indole nucleus of FK143. By introducing a benzoyl substituent with an (*S*)-1-phenylbutoxy group and by changing the indole nucleous to indolizine we have succeeded in producing the strongly active compound, FK687, which displays high *in vitro* inhibitory activity against human prostatic 5α-reductase and, significantly, very strong *in vivo* inhibitory activity against the castrated young rat model. FK687 therefore has great potential to be an extremely useful agent for the treatment of BPH.[13]

Experimental

Chemistry Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker AM200 (200 MHz) spectrometer, and chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as an internal standard (TMS, δ 0.00). Mass spectra (MS) were obtained on a VG Platform. Optical rotations were obtained on a JASCO DIP-370 operating at 589 nm. Enantiomeric excess (ee) was determined by chiral HPLC on a Chiralpak AS (25 cm×4.6 mm) from Daicel.[14]

Ethyl 4-(Indolizin-3-yl)-4-oxobutyrate (1) and Ethyl 4-(Indolizin-1-yl)-4-oxobutyrate (2) To a mixture of ethyl 3-chloroformylpropionate (1.65 g, 10.0 mmol) and $AlCl_3$ (1.78 g, 13.4 mmol) in CH_2Cl_2 (20 ml) was added a solution of indolizine (977 mg, 7.97 mmol) in CH_2Cl_2 (5 ml) at room temperature (r.t.) After being stirred for 1 h, the reaction was quenched by the addition of ice and the mixture was extracted with $CHCl_3$. The extract was washed with sat. $NaHCO_3$ and brine, then dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane : EtOAc=3 : 2) to give **1** (0.74 g, 37.9%) and **2** (0.26 g, 13.3%). **1**: ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 2.79 (2H, t, J=7 Hz), 3.29 (2H, t, J=7 Hz), 4.18 (2H, q, J=7 Hz), 6.51 (1H, d, J=5 Hz), 6.84 (1H, dt, J=2, 6 Hz), 7.12 (1H, m), 7.52 (1H, m), 7.58 (1H, d, J=6 Hz), 9.83 (1H, dd, J=2, 6 Hz). **2**: ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 2.78 (2H, t, J=7 Hz), 3.25 (2H, t, J=7 Hz), 4.17 (2H, q, J=7 Hz), 6.77 (1H, dt, J=2, 7 Hz), 7.12 (1H, m), 7.22 (2H, m), 8.03 (1H, dt, J=7, 2 Hz), 8.44 (1H, dt, J=9, 2 Hz).

Ethyl 4-(Indolizin-3-yl)butyrate (3) To a solution of **1** (556 mg,

Table 7. NMR Data for **32a**—**g** and **33a**—**g**

Compd.	^{1}H-NMR ($CDCl_3$), δ (ppm)
32a	0.91 (6H, d, J=7 Hz), 1.90 (1H, m), 2.53 (2H, d, J=7 Hz), 7.23 (2H, d, J=8 Hz), 7.88 (2H, d, J=8 Hz)
32b	0.92 (6H, d, J=7 Hz), 1.21 (3H, d, J=7 Hz), 1.90 (1H, m), 2.53 (2H, d, J=7 Hz), 3.00 (3H, q, J=7 Hz), 7.23 (2H, d, J=8 Hz), 7.90 (2H, d, J=8 Hz)
32c	0.86—1.07 (9H, m), 1.67—2.01 (3H, m), 2.53 (2H, d, J=7 Hz), 2.93 (3H, t, J=7 Hz), 7.22 (2H, d, J=8 Hz), 7.88 (2H, d, J=8 Hz)
32d	0.85—1.00 (9H, m), 1.31—1.51 (2H, m), 1.67—2.01 (3H, m), 2.53 (2H, d, J=7 Hz), 2.95 (2H, t, J=7 Hz), 7.22 (2H, d, J=8 Hz), 7.88 (2H, d, J=8 Hz)
32e	0.84—0.98 (9H, m), 1.30—1.43 (4H, m), 1.60—2.01 (3H, m), 2.53 (2H, d, J=7 Hz), 2.94 (2H, t, J=7 Hz), 7.22 (2H, d, J=8 Hz), 7.88 (2H, d, J=8 Hz)
32f	0.82—0.97 (9H, m), 1.18—1.47 (6H, m), 1.55—2.01 (3H, m), 2.53 (2H, d, J=7 Hz), 2.94 (2H, t, J=7 Hz), 7.22 (2H, d, J=8 Hz), 7.88 (2H, d, J=8 Hz)
32g	0.82—0.98 (9H, m), 1.20—1.46 (8H, m), 1.63—2.01 (3H, m), 2.53 (2H, d, J=7 Hz), 2.95 (2H, t, J=7 Hz), 7.22 (2H, d, J=8 Hz), 7.88 (2H, d, J=8 Hz)
33a	0.85 (6H, d, J=7 Hz), 1.30 (2H, d, J=6 Hz), 1.80 (1H, m), 2.41 (2H, d, J=7 Hz), 4.67 (1H, m), 7.08 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz)
33b	0.88 (6H, d, J=7 Hz), 0.89 (3H, t, J=7 Hz), 1.60—2.00 (3H, m), 2.47 (2H, d, J=7 Hz), 4.57 (1H, t, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz)
33c	0.86—0.98 (9H, m), 1.16—1.97 (5H, m), 2.47 (2H, d, J=7 Hz), 4.63 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.26 (2H, d, J=8 Hz)
33d	0.82—0.95 (9H, m), 1.17—1.48 (4H, m), 1.60—1.97 (3H, m), 2.47 (2H, d, J=7 Hz), 4.63 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz)
33e	0.83—0.96 (9H, m), 1.16—1.40 (6H, m), 1.60—1.96 (3H, m), 2.48 (2H, d, J=7 Hz), 4.64 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz)
33f	0.80—0.97 (9H, m), 1.16—1.50 (8H, m), 1.58—1.97 (3H, m), 2.47 (2H, d, J=7 Hz), 4.63 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz)
33g	0.80—0.97 (9H, m), 1.16—1.50 (10H, m), 1.60—1.97 (3H, m), 2.47 (2H, d, J=7 Hz), 4.63 (1H, t, J=7 Hz), 7.12 (2H, d, J=8 Hz), 7.26 (2H, d, J=8 Hz).

Table 8. NMR Data for Compounds **34a**—**g**

Compd.	^{1}H-NMR ($CDCl_3$), δ (ppm)
34a	0.90 (6H, d, J=7 Hz), 1.85 (1H, m), 2.04 (3H, d, J=7 Hz), 2.40 (2H, d, J=7 Hz), 5.22 (1H, q, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.34 (2H, d, J=8 Hz)
34b	0.90 (6H, d, J=7 Hz), 1.01 (3H, t, J=7 Hz), 1.70—2.00 (1H, m), 2.00—2.40 (2H, m), 2.45 (2H, d, J=7 Hz), 4.89 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz)
34c	0.84—1.00 (9H, m), 1.18—2.38 (5H, m), 2.46 (2H, d, J=7 Hz), 4.99 (1H, t, J=7 Hz), 7.10 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz)
34d	0.80—0.94 (9H, m), 1.15—1.55 (4H, m), 1.60—1.97 (3H, m), 2.46 (2H, d, J=7 Hz), 4.96 (1H, t, J=7 Hz), 7.10 (2H, d, J=8 Hz), 7.29 (2H, d, J=8 Hz)
34e	0.82—0.97 (9H, m), 1.20—1.60 (6H, m), 1.74—1.97 (1H, m), 2.00—2.38 (2H, m), 4.96 (1H, t, J=7 Hz), 7.10 (2H, d, J=8 Hz), 7.29 (2H, d, J=8 Hz)
34f	0.81—0.97 (9H, m), 1.16—1.55 (8H, m), 1.73—1.98 (1H, m), 2.03—2.35 (2H, m), 4.96 (1H, t, J=7 Hz), 7.10 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz)
34g	0.82—0.96 (9H, m), 1.18—1.55 (10H, m), 1.72—1.96 (1H, m), 2.08—2.30 (2H, m), 4.97 (1H, t, J=7 Hz), 7.10 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz)

2.27 mmol) in THF (5 ml) was added a 1 M solution of borane in THF (3.6 ml) at 0 °C. After being stirred for 10 min at r.t., the reaction was quenched by the addition of aq. KH_2PO_4 at 0 °C, and the mixture was extracted with ether 2 times. The extracts were combined, washed with water, sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on Al_2O_3 (hexane : CH_2Cl_2=1 : 1) to give **3** (294 mg, 56.1%). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.08 (2H, m), 2.43 (2H, t, J=7 Hz), 2.79 (2H, t, J=7 Hz), 4.14 (2H, q, J=7 Hz), 6.3—6.7 (4H, m), 7.37 (1H, dt, J=9, 2 Hz), 7.78 (1H, dt, J=6, 2 Hz).

Ethyl 4-(Indolizin-1-yl)butyrate (4) Yield: 56.0%. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 1.98 (2H, m), 2.34 (2H, t, J=7 Hz), 2.79 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 6.37 (1H, dt, J=2, 7 Hz), 6.56 (1H, m), 6.62 (1H, d, J=3 Hz), 7.21 (1H, d, J=3 Hz), 7.29 (1H, d, J=9 Hz), 7.84 (1H, d, J=7 Hz).

***trans*-4-(Imidazo[1,5-*a*]pyridin-1-yl)-3-butenoic Acid (5)** To a solution of (2-carboxyethyl)triphenylphosphonium chloride (6.87 g, 18.5 mmol) in dimethylformamide (DMF) (20 ml) was added NaH (60% in mineral oil, 1.48 g, 37 mmol) at 20 °C. After 20 min, 1-formylimidazo[1,5-*a*]pyridine[10] (2.46 g, 16.8 mmol) was added, and the mixture was stirred at 30 °C for 1 h. The reaction was quenched by the addition of ice and the mixture was made acidic by 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel (10% MeOH in $CHCl_3$) to give **5** (613 mg, 18.1%). ^{1}H-NMR (DMSO-d_6) δ: 3.20 (2H, dd, J=2, 7 Hz), 6.32 (1H, dt, J=16, 7 Hz), 6.74 (1H, d, J=16 Hz), 6.78 (1H, m), 7.65 (1H, d, J=9 Hz), 8.27 (1H, d, J=7 Hz), 8.33 (1H, s).

Ethyl *trans*-4-(Imidazo[1,5-*a*]pyridin-1-yl)-3-butenate (6) To a suspension of **5** (1.91 g, 9.46 mmol) in EtOH (100 ml) was added CSA (2.4 g), and the mixture was refluxed for 2 h, then water was removed by 3 Å molecular sieves. After evaporation of the solvent, the residue was chromatographed on silica gel (EtOAc) to give **6** (1.20 g, 55.2%). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 3.30 (2H, dd, J=2, 7 Hz), 4.18 (2H, q, J=7 Hz), 6.40—6.60 (2H, m), 6.65—6.80 (2H, m), 7.49 (1H, d, J=9 Hz), 7.85 (1H, d, J=7 Hz), 8.04 (1H, s).

Ethyl 4-(Imidazo[1,5-*a*]pyridin-1-yl)butyrate (7) To a solution of **6** (1.2 g, 5.22 mmol) in a mixture of dioxane (5 ml) and EtOH (5 ml) was added 10% palladium on activated carbon (10% Pd–C) (200 mg), and the mixture was hydrogenated under H_2 (4 atm) for 2 h. After removal of the catalyst by filtration, the filtrate was evaporated to give **7** (1.05 g, 86.7%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz), 2.10 (2H, m), 2.36 (2H, t, J=7 Hz), 2.94 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 6.50 (1H, dt, J=2, 7 Hz), 6.63 (1H, m), 7.38 (1H, d, J=9 Hz), 7.87 (1H, d, J=7 Hz), 8.12 (1H, s).

Ethyl 4-[1-(4-Nitrobenzoyl)indolizin-3-yl]butyrate (8) To a solution of 3-nitrobenzoyl chloride (314 mg, 1.69 mmol) in CH_2Cl_2 (20 ml) was added $AlCl_3$ (305 mg, 2.29 mmol) at room temperature (r.t.) After the reac-

Table 9. NMR Data for Compounds **44a**—**g**

Compd.	^{1}H-NMR ($CDCl_3$), δ (ppm)
44a	0.90 (6H, d, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.67 (2H, d, J=6 Hz), 1.85 (m, 2H), 2.18 (2H, quintet J=7 Hz), 2.30 (2H, t, J=7 Hz), 2.45 (2H, d, J=7 Hz), 4.09 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.38 (1H, q, J=6 Hz), 6.94 (2H, d, J=9 Hz), 7.13 (2H, d, J=9 Hz), 7.26—7.40 (5H, m), 7.54 (1H, s), 7.75 (2H, d, J=9 Hz), 8.35 (1H, m)
44b	0.89 (6H, d, J=7 Hz), 1.02 (3H, t, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.70—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.09 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.09 (1H, t, J=7 Hz), 6.93 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
44c	0.88 (6H, d, J=7 Hz), 0.97 (3H, t, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.30—2.10 (7H, m), 2.10—2.40 (4H, m), 2.45 (2H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.17 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.52 (1H, s), 7.73 (2H, d, J=9 Hz), 8.36 (1H, m)
44d	0.80—1.00 (9H, m), 1.20 (3H, t, J=7 Hz), 1.30—1.65 (4H, m), 1.75—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
44e	0.80—0.95 (9H, m), 1.15—1.65 (9H, m), 1.70—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.09 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.14 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
44f	0.80—0.95 (9H, m), 1.15—1.65 (11H, m), 1.70—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.14 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
44g	0.80—0.95 (9H, m), 1.15—1.65 (13H, m), 1.70—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)

Table 10. Spectral Data for Compounds **45a**—**g**

Compd.	ESI-MS m/z:	^{1}H-NMR ($CDCl_3$), δ (ppm)
45a	496 $(M-H)^-$	0.90 (6H, d, J=7 Hz), 1.66 (3H, d, J=6 Hz), 1.84 (1H, m), 2.20 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 2.45 (2H, d, J=7 Hz), 4.25 (2H, t, J=7 Hz), 5.37 (1H, q, J=6 Hz), 6.95 (2H, d, J=9 Hz), 7.13 (2H, d, J=9 Hz), 7.25—7.40 (5H, m), 7.75 (2H, d, J=9 Hz), 8.32 (1H, m)
45b	510 $(M-H)^-$	0.88 (6H, d, J=7 Hz), 1.00 (3H, t, J=7 Hz), 1.70—2.30 (5H, m), 2.30—2.50 (4H, m), 4.24 (2H, t, J=7 Hz), 5.09 (1H, t, J=7 Hz), 6.73 (2H, d, J=9 Hz), 7.11 (2H, d, J=9 Hz), 7.25—7.45 (5H, m), 7.53 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
45c	524 $(M-H)^-$	0.88 (6H, d, J=7 Hz), 0.96 (3H, t, J=7 Hz), 1.20—2.30 (7H, m), 2.38 (2H, t, J=7 Hz), 2.44 (2H, d, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.16 (1H, dd, J=5, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.73 (2H, d, J=9 Hz), 8.33 (1H, m)
45d	538 $(M-H)^-$	0.80—1.00 (9H, m), 1.25—1.60 (4H, m), 1.75—2.30 (5H, m), 2.37 (2H, d, J=7 Hz), 2.43 (2H, d, J=7 Hz), 4.24 (2H, t, J=7 Hz), 5.14 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.54 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
45e	552 $(M-H)^-$	0.80—0.95 (9H, m), 1.20—1.65 (6H, m), 1.70—2.30 (5H, m), 2.36 (2H, d, J=7 Hz), 2.44 (2H, d, J=7 Hz), 4.22 (2H, t, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.54 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
45f	566 $(M-H)^-$	0.80—0.95 (9H, m), 1.15—1.65 (8H, m), 1.70—2.30 (5H, m), 2.32—2.50 (4H, m), 4.23 (2H, t, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.54 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
45g	580 $(M-H)^-$	0.80—0.95 (9H, m), 1.15—1.65 (10H, m), 1.70—2.28 (5H, m), 2.32—2.50 (4H, m), 4.24 (2H, t, J=7 Hz), 5.15 1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.54 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)

tion mixture was stirred at r.t. for 10 min, a solution of **3** (297 mg, 1.28 mmol) in CH_2Cl_2 (3 ml) was added thereto. After 1 h, the reaction was quenched by the addition of ice and the mixture was extracted with $CHCl_3$. The extract was washed with water, sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane : EtOAc=2 : 3) to give **8** (353 mg, 72.6%). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 2.08 (2H, m), 2.46 (2H, t, J=7 Hz), 2.93 (2H, t, J=7 Hz), 4.13 (2H, q, J=7 Hz), 6.80 (1H, s), 6.98 (1H, dt, J=1, 7 Hz), 7.30 (1H, m), 7.69 (1H, t, J=8 Hz), 8.10 (1H, d, J=7 Hz), 8.16 (1H, m), 8.39 (1H, m), 8.53 (1H, dt, J=9, 1 Hz), 8.57 (1H, m).

Ethyl 4-[3-(3-Nitrobenzoyl)indolizin-1-yl]butyrate (9) Yield: 72.0%. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 2.01 (2H, m), 2.37 (2H, t, J=7 Hz), 2.81 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 7.02 (1H, dt, J=2, 7 Hz), 7.11 (1H, s), 7.28 (1H, dt, J=2, 8 Hz), 7.62 (1H, dt, J=8, 2 Hz), 7.69 (1H, t, J=7 Hz), 8.12 (1H, m), 8.38 (1H, m), 8.63 (1H, m), 9.98 (1H, d, J=7 Hz).

Ethyl 4-[3-(3-Nitrobenzoyl)imidazo[1,5-*a*]pyridin-1-yl]butyrate (10) Yield: 45.6%. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.19 (2H, m), 2.48 (2H, t, J=7 Hz), 3.04 (2H, t, J=7 Hz), 4.14 (2H, q, J=7 Hz), 7.11 (1H, dt, J=7, 2 Hz), 7.28 (1H, m), 7.70 (1H, t, J=8 Hz), 7.76 (1H, m), 8.51 (1H, m), 8.79 (1H, dt, J=2, 8 Hz), 9.41 (1H, m), 9.89 (1H, dt, J=7, 2 Hz).

Ethyl 4-[1-(4-Aminobenzoyl)indolizin-3-yl]butyrate (11) To a solution of **8** (350 mg, 0.921 mmol) in a mixture of dioxane (5 ml) and EtOH (5 ml) was added 10% palladium on activated carbon (10% Pd–C) (210 mg), and the mixture was hydrogenated under H_2 (4 atm) for 4 h. After removal of the catalyst by filtration, the filtrate was evaporated to give **11** (320 mg, 99.3%). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 2.05 (2H, m), 2.43 (2H, t, J=7 Hz), 2.88 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 6.90 (1H, m), 6.91 (1H, s), 7.10—7.40 (5H, m), 8.10 (1H, d, J=7 Hz), 8.48 (1H, dt, J=8, 1 Hz).

Ethyl 4-[3-(3-Aminobenzoyl)indolizin-1-yl]butyrate (12) Yield: 100%. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 1.98 (2H, m), 2.33 (2H, t, J=7 Hz), 2.78 (2H, t, J=7 Hz), 4.25 (2H, q, J=7 Hz), 6.80—7.00 (2H, m), 7.10—7.30 (6H, m), 7.54 (1H, dt, J=8, 2 Hz), 9.94 (1H, d, J=7 Hz).

Ethyl 4-[3-(3-Aminobenzoyl)imidazo[1,5-*a*]pyridin-1-yl]butyrate (13) Yield: 96.1%. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.17 (2H, m), 2.47 (2H, t, J=7 Hz), 3.03 (2H, t, J=7 Hz), 4.15 (2H, q, J=7 Hz), 6.89 (1H, m),

Table 11. NMR Data for Compounds **46a**—**d**, **47a**—**d**, **48a**—**d** and **49a**—**d**

Compd.	^{1}H-NMR ($CDCl_3$), δ (ppm)
46a, **47a**	0.90 (6H, d, J=7 Hz), 1.51 (1H, d, J=7 Hz), 1.81 (1H, m), 2.47 (2H, d, J=7 Hz), 4.88 (1H, q, J=7 Hz), 7.13 (2H, d, J=8 Hz), 7.28 (2H, d, J=8 Hz)
46b, **47b**	0.85—1.00 (9H, m), 1.60—1.90 (4H, m), 2.47 (2H, d, J=7 Hz), 4.57 (1H, t, J=7 Hz), 7.12 (2H, d, J=8 Hz), 7.26 (2H, d, J=8 Hz)
46c, **47c**	0.86—0.98 (9H, m), 1.16—1.97 (5H, m), 2.47 (2H, d, J=7 Hz), 4.65 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.26 (2H, d, J=8 Hz)
46d, **47d**	0.82—0.95 (9H, m), 1.17—1.48 (4H, m), 1.60—1.97 (3H, m), 2.47 (2H, d, J=7 Hz), 4.63 (1H, t, J=7 Hz), 7.11 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz)
48a, **49a**	0.88 (6H, d, J=7 Hz), 1.21 (3H, t, J=7 Hz), 1.67 (3H, d, J=7 Hz), 1.85 (1H, m), 2.10—2.40 (4H, m), 2.46 (2H, d, J=7 Hz), 4.11 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.39 (1H, q, J=7 Hz), 6.94 (2H, d, J=9 Hz), 7.12 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.75 (2H, d, J=9 Hz), 8.36 (1H, m)
48b, **49b**	0.89 (6H, d, J=7 Hz), 1.02 (3H, t, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.70—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.09 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.09 (1H, t, J=7 Hz), 6.93 (2H, d, J=9 Hz), 7.12 (2H, d, J=9 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
48c, **49c**	0.88 (6H, d, J=7 Hz), 0.97 (3H, t, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.30—2.10 (7H, m), 2.10—2.40 (4H, m), 2.45 (2H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.16 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.52 (1H, s), 7.73 (2H, d, J=9 Hz), 8.36 (1H, m)
48d, **49d**	0.89 (6H, d, J=7 Hz), 0.80—0.95 (3H, m), 1.20 (3H, t, J=7 Hz), 1.30—1.65 (4H, m), 1.75—2.35 (7H, m), 2.45 (2H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.74 (2H, d, J=9 Hz), 8.34 (1H, m)

Table 12. Spectral Data for Compounds **50a**—**d** and **51a**—**d**

Compd.	$[\alpha]_D^{25}$	ESI-MS m/z:	^{1}H-NMR ($CDCl_3$), δ (ppm)
50a	−56.1° (c=0.5, $CHCl_3$)	496 $(M-H)^-$	0.90 (6H, d, J=7 Hz), 1.66 (3H, d, J=6 Hz), 1.84 (1H, m), 2.20 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 2.45 (2H, d, J=7 Hz), 4.25 (2H, t, J=7 Hz), 5.37 (1H, q, J=6 Hz), 6.95 (2H, d, J=9 Hz), 7.13 (2H, d, J=9 Hz), 7.25—7.40 (5H, m), 7.75 (2H, d, J=9 Hz), 8.32 (1H, m)
50b	−71.2° (c=0.5, $CHCl_3$)	510 $(M-H)^-$	0.88 (6H, d, J=7 Hz), 1.00 (3H, t, J=7 Hz), 1.70—2.30 (5H, m), 2.30—2.50 (4H, m), 4.24 (2H, t, J=7 Hz), 5.09 (1H, t, J=7 Hz), 6.73 (2H, d, J=9 Hz), 7.11 (2H, d, J=9 Hz), 7.25—7.45 (5H, m), 7.53 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
50c	−66.8° (c=0.5, $CHCl_3$)	524 $(M-H)^-$	0.88 (6H, d, J=7 Hz), 0.96 (3H, t, J=7 Hz), 1.20—2.30 (7H, m), 2.38 (2H, t, J=7 Hz), 2.44 (2H, d, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.16 (1H, dd, J=5, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.73 (2H, d, J=9 Hz), 8.33 (1H, m)
50d	−59.6° (c=0.5, $CHCl_3$)	538 $(M-H)^-$	0.80—1.00 (9H, m), 1.25—1.60 (4H, m), 1.75—2.30 (5H, m), 2.37 (2H, d, J=7 Hz), 2.43 (2H, d, J=7 Hz), 4.24 (2H, t, J=7 Hz), 5.14 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.54 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
51a	+60.3° (c=0.5, $CHCl_3$)	496 $(M-H)^-$	0.90 (6H, d, J=7 Hz), 1.66 (3H, d, J=6 Hz), 1.84 (1H, m), 2.20 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 2.45 (2H, d, J=7 Hz), 4.25 (2H, t, J=7 Hz), 5.37 (1H, q, J=6 Hz), 6.95 (2H, d, J=9 Hz), 7.13 (2H, d J=9 Hz), 7.25—7.40 (5H, m), 7.75 (2H, d, J=9 Hz), 8.32 (1H, m)
51b	+70.2° (c=0.5, $CHCl_3$)	510 $(M-H)^-$	0.88 (6H, d, J=7 Hz), 1.00 (3H, t, J=7 Hz), 1.70—2.30 (5H, m), 2.30—2.50 (4H, m), 4.24 (2H, t, J=7 Hz), 5.09 (1H, t, J=7 Hz), 6.73 (2H, d, J=9 Hz), 7.11 (2H, d, J=9 Hz), 7.25—7.45 (5H, m), 7.53 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)
51c	+65.3° (c=0.5, $CHCl_3$)	524 $(M-H)^-$	0.88 (6H, d, J=7 Hz), 0.96 (3H, t, J=7 Hz), 1.20—2.30 (7H, m), 2.38 (2H, t, J=7 Hz), 2.44 (2H, d, J=7 Hz), 4.23 (2H, t, J=7 Hz), 5.16 (1H, dd, J=5, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.11 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.53 (1H, s), 7.73 (2H, d, J=9 Hz), 8.33 (1H, m)
51d	+62.4° (c=0.5, $CHCl_3$)	538 $(M-H)^-$	0.80—1.00 (9H, m), 1.25—1.60 (4H, m), 1.75—2.30 (5H, m), 2.37 (2H, d, J=7 Hz), 2.43 (2H, d, J=7 Hz), 4.24 (2H, t, J=7 Hz), 5.14 (1H, dd, J=2, 7 Hz), 6.92 (2H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.20—7.45 (5H, m), 7.54 (1H, s), 7.73 (2H, d, J=9 Hz), 8.30—8.40 (1H, m)

Table 13. NMR Data for Compounds **54b**—**f**

Compd.	^{1}H-NMR ($CDCl_3$), δ (ppm)
54b	0.88 (6H, d, J=7 Hz), 1.01 (3H, t, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.72—2.17 (5H, m), 2.35—2.50 (4H, m), 2.87 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 5.10 (1H, t, J=7 Hz), 6.79—6.97 (4H, m), 7.07—7.32 (5H, m), 7.73 (2H, d, J=9 Hz), 7.96 (1H, d, J=7 Hz), 8.44 (1H, d, J=9 Hz)
54c	0.80—1.05 (9H, m), 1.24 (3H, t, J=7 Hz), 1.30—1.65 (2H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.87 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 5.17 (1H, dd, J=2, 7 Hz), 6.80—6.94 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, J=9 Hz), 7.98 (1H, d, J=7 Hz), 8.44 (1H, d, J=9 Hz)
54d	0.80—1.00 (9H, m), 1.20—1.65 (7H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.88 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.73 (2H, d, J=9 Hz), 7.99 (1H, d, J=7 Hz), 8.44 (1H, d, J=9 Hz)
54e	0.80—0.95 (9H, m), 1.26—1.65 (9H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.87 (2H, t, J=7 Hz), 4.13 (2H, q, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.80—6.97 (4H, m), 7.07—7.31 (5H, m), 7.72 (2H, d, J=9 Hz), 7.98 (1H, d, J=7 Hz), 8.43 (1H, d, J=9 Hz)
54f	0.80—1.00 (9H, m), 1.20—1.65 (11H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.88 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 5.15 (1H, dd, J=2, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.74 (2H, d, J=9 Hz), 7.98 (1H, d, J=7 Hz), 8.43 (1H, d, J=9 Hz)

Table 14. Spectral Data for Compounds **55b**—**f**

Compd.	ESI-MS *m/z*:	^{1}H-NMR ($CDCl_3$), δ (ppm)
55b	496 $(M-H)^-$	0.88 (6H, d, *J*=7 Hz), 1.01 (3H, t, *J*=7 Hz), 1.72—2.17 (5H, m), 2.40—2.55 (4H, m), 2.88 (2H, t, *J*=7 Hz), 5.08 (1H, t, *J*=7 Hz), 6.79—6.98 (4H, m), 7.07—7.32 (5H, m), 7.73 (2H, d, *J*=9 Hz), 7.94 (1H, d, *J*=7 Hz), 8.42 (1H, d, *J*=9 Hz)
55c	510 $(M-H)^-$	0.80—1.05 (9H, m), 1.30—1.65 (2H, m), 1.70—2.15 (5H, m), 2.40—2.55 (4H, m), 2.88 (2H, t, *J*=7 Hz), 5.16 (1H, dd, *J*=2, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, *J*=9 Hz), 7.96 (1H, d, *J*=7 Hz), 8.42 (1H, d, *J*=9 Hz)
55d	524 $(M-H)^-$	0.80—1.00 (9H, m), 1.20—1.65 (7H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.88 (2H, t, *J*=7 Hz), 4.12 (2H, q, *J*=7 Hz), 5.15 (1H, dd, *J*=2, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.73 (2H, d, *J*=9 Hz), 7.99 (1H, d, *J*=7 Hz), 8.44 (1H, d, *J*=9 Hz)
55e	538 $(M-H)^-$	0.80—0.95 (9H, m), 1.23—1.65 (6H, m), 1.70—2.15 (5H, m), 2.38—2.55 (4H, m), 2.88 (2H, t, *J*=7 Hz), 5.14 (1H, dd, *J*=2, 7 Hz), 6.78—6.97 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, *J*=9 Hz), 7.94 (1H, d, *J*=7 Hz), 8.43 (1H, d, *J*=9 Hz)
55f	552 $(M-H)^-$	0.80—1.00 (9H, m), 1.20—1.65 (8H, m), 1.70—2.15 (5H, m), 2.40—2.55 (4H, m), 2.89 (2H, t, *J*=7 Hz), 5.15 (1H, dd, *J*=2, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.73 (2H, d, *J*=9 Hz), 7.95 (1H, d, *J*=7 Hz), 8.43 (1H, d, *J*=9 Hz)

7.01 (1H, dt, *J*=2, 7 Hz), 7.16 (1H, m), 7.29 (1H, t, *J*=8 Hz), 7.60—7.90 (3H, m), 9.92 (1H, dt, *J*=7, 2 Hz).

Ethyl 4-[1-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]indolizin-3-yl]butyrate (14) To a solution of **11** (320 mg, 0.913 mmol) in CH_2Cl_2 (10 ml) were added chlorobis(4-isobutylphenyl)methane (340 mg, 1.07 mmol) and iso-Pr_2NEt (0.22 ml) at r.t. After being stirred overnight at r.t., the reaction mixture was evaporated and the residue was partitioned between ether and 0.1 N HCl. The organic layer was washed with water and brine, then dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (CH_2Cl_2 : EtOAc=20 : 1) to give **14** (279 mg, 48.6%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (12H, d, *J*=7 Hz), 1.28 (3H, t, *J*=7 Hz), 1.87 (2H, m), 2.08 (2H, m), 2.40—2.55 (6H, m), 2.88 (2H, t, *J*=7 Hz), 4.25 (2H, q, *J*=7 Hz), 5.56 (1H, s), 6.70 (1H, m), 6.86 (1H, s), 6.90 (1H, dt, *J*=1, 7 Hz), 7.00—7.40 (12H, m), 8.02 (1H, d, *J*=7 Hz), 8.50 (1H, d, *J*=9 Hz).

Ethyl 4-[3-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]indolizin-1-yl]butyrate (15) Yield: 48.0%. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (12H, d, *J*=7 Hz), 1.22 (3H, t, *J*=7 Hz), 1.70—2.05 (4H, m), 2.32 (2H, t, *J*=7 Hz), 2.43 (4H, d, *J*=7 Hz), 2.73 (2H, t, *J*=7 Hz), 4.10 (2H, q, *J*=7 Hz), 5.52 (1H, s), 6.68 (1H, m), 6.88 (1H, dt, *J*=2, 7 Hz), 7.00—7.30 (13H, m), 7.52 (1H, dt, *J*=8, 2 Hz), 9.92 (1H, d, *J*=7 Hz).

Ethyl 4-[3-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]imidazo-[1,5-*a*]pyridin-1-yl]butyrate (16) Yield: 46.0%. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (12H, d, *J*=7 Hz), 1.20 (3H, t, *J*=7 Hz), 1.81 (2H, m), 2.03 (2H, m), 2.32 (2H, t, *J*=7 Hz), 2.41 (4H, d, *J*=7 Hz), 3.04 (2H, t, *J*=7 Hz), 4.08 (2H, q, *J*=7 Hz), 5.51 (1H, s), 6.80—7.20 (4H, m), 7.06 (4H, d, *J*=8 Hz), 7.28 (4H, d, *J*=8 Hz), 7.43 (1H, t, *J*=9 Hz), 7.52 (1H, t, *J*=9 Hz), 7.79 (1H, t, *J*=9 Hz), 7.92 (1H, s), 8.43 (1H, d, *J*=9 Hz), 9.60 (1H, d, *J*=9 Hz).

4-[1-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]indolizin-3-yl]butyric Acid (17) To a solution of **14** (279 mg, 0.443 mmol) in EtOH (10 ml) was added 4 N NaOH (0.44 ml). After being stirred at 40 °C for 1 h, the reaction mixture was evaporated *in vacuo*, then an aq. solution of KH_2PO_4 (300 mg) and 1 N HCl (26 ml) were added. The mixture was extracted with EtOAc and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (EtOAc) to give **17** (229 mg, 86.0%). ^{1}H-NMR $CDCl_3$) δ: 0.87 (12H, d, *J*=7 Hz), 1.83 (2H, m), 2.22 (2H, m), 2.40—2.50 (6H, m), 2.85 (2H, t, *J*=7 Hz), 5.51 (1H, s), 6.69 (1H, m), 6.82 (1H, s), 6.84 (1H, dt, *J*=1, 7 Hz), 7.00—7.30 (12H, m), 7.94 (1H, d, *J*=7 Hz), 8.46 (1H, d, *J*=9 Hz). Electrospray ionization (ESI)-MS *m/z*: 599 $(M-H)^-$.

4-[3-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]indolizin-1-yl]butyric Acid (18) Yield: 86.0%. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (12H, d, *J*=7 Hz), 1.70—2.05 (4H, m), 2.38 (2H, t, *J*=7 Hz), 2.43 (4H, d, *J*=7 Hz), 2.76 (2H, t, *J*=7 Hz), 5.52 (1H, s), 6.71 (1H, m), 6.88 (1H, dt, *J*=2, 7 Hz), 7.00—7.30 (13H, m), 7.49 (1H, dt, *J*=8, 2 Hz), 9.91 (1H, d, *J*=7 Hz). ESI-MS *m/z*: 599 $(M-H)^-$.

4-[3-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]imidazo[1,5-*a*]pyridin-1-yl]butyric Acid (19) Yield: 73.3%. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (12H, d, *J*=7 Hz), 1.82 (2H, m), 2.05 (2H, m), 2.40 (2H, t, *J*=7 Hz), 2.42 (4H, d, *J*=7 Hz), 3.06 (2H, t, *J*=7 Hz), 5.51 (1H, s), 6.68 (1H, m), 7.08 (4H, d, *J*=8 Hz), 7.10—7.30 (3H, m), 7.25 (4H, d, *J*=7 Hz), 7.42 (1H, t, *J*=9 Hz), 7.51 (1H, t, *J*=9 Hz), 7.78 (1H, t, *J*=9 Hz), 7.92 (1H, s), 8.41 (1H, d, *J*=9 Hz), 9.59 (1H, d, *J*=9 Hz). ESI-MS *m/z*: 600 $(M-H)^-$.

4-[*N*-(2-Pyridylmethyl)carbamoyl]butyric Acid (20) To a solution of 2-(aminomethyl)pyridine (1.74 g, 15.9 mmol) in pyridine (5 ml) was added glutaric anhydride (1.84 g, 16.1 mmol) at r.t., and the mixture was stirred for 2 h. The resulting solid was treated with CH_2Cl_2 and the crystals were filtered to give **20** (3.38 g, 95.8%). ^{1}H-NMR (DMSO-d_6) δ: 1.55 (2H, m), 2.15—2.30 (4H, m), 4.32 (2H, d, *J*=6 Hz), 7.15—7.30 (2H, m), 7.75 (1H, dt, *J*=2, 8 Hz), 8.35—8.55 (2H, m).

Ethyl 4-[*N*-(2-Pyridylmethyl)carbamoyl]butyrate (21) Following the procedure described above for **6**, **21** (3.22 g, 84.7%) was prepared from **20** (3.38 g). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, *J*=7 Hz), 2.01 (2H, m), 2.30—2.50 (4H, m), 4.13 (2H, q, *J*=7 Hz), 4.59 (2H, d, *J*=2 Hz), 6.95 (1H, m), 7.20—7.40 (2H, m), 7.75 (1H, dt, *J*=1, 7 Hz), 8.57 (1H, m).

Ethyl 4-(Imidazo[1,5-*a*]pyridin-3-yl)butyrate (22) A mixture of **21** (692 mg, 2.76 mmol) and $POCl_3$ (1.4 ml) in benzene (5 ml) was refluxed for 5 h. The reaction was quenched by the addition of the water, and the mixture was made basic by sat. $NaHCO_3$ and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo.* The residue was chromatographed on silica gel (EtOAc) to give **22** (638 mg, 93.9%). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, *J*=7 Hz), 2.26 (2H, m), 2.48 (2H, t, *J*=7 Hz), 3.11 (2H, t, *J*=7 Hz), 4.14 (2H, q, *J*=7 Hz), 6.55—6.80 (2H, m), 7.48 (1H, s), 7.43 (1H, dt, *J*=9, 2 Hz), 7.88 (1H, dd, *J*=2, 7 Hz).

Ethyl 4-[1-(3-Nitrobenzoyl)imidazo[1,5-*a*]pyridin-3-yl]butyrate (23) Following the procedure described above for **8**, **23** (240 mg, 38.4%) was prepared from **22** (405 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J*=7 Hz), 2.24 (2H, m), 2.59 (2H, t, *J*=7 Hz), 3.14 (2H, t, *J*=7 Hz), 4.16 (2H, q, *J*=7 Hz), 6.99 (1H, dt, *J*=2, 7 Hz), 7.32 (1H, m), 7.68 (1H, t, *J*=8 Hz), 8.16 (1H, m), 8.38 (1H, m), 8.55 (1H, dt, *J*=2, 8 Hz), 8.72 (1H, m), 9.43 (1H, m).

3-(3-Nitrobenzoyl)-1*H*-pyrrolo[2,3-*b*]pyridine (24) Following the procedure described above for **8**, **24** (430 mg, 19.0%) was prepared from 1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g) and 3-nitrobenzoyl chloride (1.88 g). ^{1}H-NMR (DMSO-d_6) δ: 7.36 (1H, dd, *J*=5, 8 Hz), 7.87 (1H, t, *J*=7 Hz), 8.26 (1H, d, *J*=7 Hz), 8.35—8.66 (5H, m).

Ethyl 4-[3-(3-Nitrobenzoyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]butyrate (25) A mixture of **24** (400 mg, 1.43 mmol), ethyl 4-bromobutyrate (0.257 ml, 1.80 mmol) and K_2CO_3 (620 mg, 4.49 mmol) in DMF (10 ml) was stirred at 50 °C for 4 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo.* The residue was chromatographed on silica gel (EtOAc : hexane=1 : 4) to give **25** (480 mg, 83.9%). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, *J*=8 Hz), 2.20—2.44 (2H, m), 2.38 (2H, t, *J*=8 Hz), 4.08 (2H, q, *J*=8 Hz), 4.48 (2H, t, *J*=8 Hz), 7.35 (1H, dd, *J*=5, 8 Hz), 7.73 (1H, s), 7.74 (1H, t, *J*=7 Hz), 8.18 (1H, dd, *J*=1, 7 Hz), 8.40—8.52 (2H, m) , 8.65—8.72 (2H, m).

4-[1-(3-Nitrobenzoyl)imidazo[1,5-*a*]pyridin-3-yl]butyric Acid (26) To a solution of **23** (719 mg, 1.89 mmol) in EtOH (10 ml) was added 4 N NaOH (1.9 ml). After being refluxed for 40 min, the reaction mixture was evaporated *in vacuo*, and the resulting aqueous solution was made acidic with sat. KH_2PO_4. The mixture was extracted with EtOAc and the extract was washed with brine, then dried over Na_2SO_4. Evaporation of the solvent gave **26** (638 mg, 95.8%). ^{1}H-NMR (DMSO-d_6) δ: 2.05 (2H, m), 2.48 (2H, t, *J*=7 Hz), 3.13 (2H, t, *J*=7 Hz), 7.17 (1H, dt, *J*=2, 7 Hz), 7.52 (1H, dd,

J=7, 9 Hz), 7.84 (1H, t, J=8 Hz), 8.30—8.50 (2H, m), 8.59 (1H, d, J=7 Hz), 8.78 (1H, m) , 9.28 (1H, m).

4-[3-(3-Nitrobenzoyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]butyric Acid (27) Yield: 98.9%. ^{1}H-NMR (DMSO-d_6) δ: 2.00—2.40 (2H, m), 2.26 (2H, t, J=8 Hz), 4.38 (2H, t, J=8 Hz), 7.38 (1H, dd, J=5, 8 Hz), 7.88 (1H, t, J=8 Hz), 8.28 (1H, dd, J=2, 8 Hz), 8.42 (1H, s), 8.44—8.56 (3H, m), 8.58 (1H, dd, J=2, 8 Hz).

4-[1-(3-Aminobenzoyl)imidazo[1,5-*a*]pyridin-3-yl]butyric Acid (28) Following the procedure described above for **11**, **28** (86 mg, 100%) was prepared from **26** (93 mg). ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 2.23 (2H, m), 2.56 (2H, t, J=7 Hz), 3.13 (2H, t, J=7 Hz), 6.96 (1H, m), 7.05—7.50 (3H, m), 7.80 (1H, m), 7.92 (1H, m), 8.13 (1H, m), 8.42 (1H, d, J=9 Hz).

4-[3-(3-Aminobenzoyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]butyric Acid (29) Yield: 100%. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 2.20—2.32 (2H, m), 2.38 (2H, t, J=8 Hz), 4.42 (2H, t, J=8 Hz), 6.90—7.40 (5H, m), 7.86 (1H, s), 8.40 (1H, dd, J=1, 5 Hz), 8.65 (1H, dd, J=1, 8 Hz).

4-[1-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]imidazo[1,5-*a*]pyridin-3-yl]butyric Acid (30) To a solution of **28** (93 mg, 0.288 mmol) in CH_2Cl_2 (6 ml) were added chlorobis(4-isobutyphenyl)methane (109 mg, 0.35 mmol) and iso-Pr_2NEt (0.12 ml) at r.t. After stirring overnight at r.t., the reaction mixture was evaporated and partitioned between EtOAc and 0.1 N HCl. The organic layer was washed with water and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by thin layer silica gel chromatography (EtOAc) to give **30** (77 mg, 44.5%). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (12H, d, J=7 Hz), 1.81 (2H, m), 2.18 (2H, m), 2.52 (4H, d, J=7 Hz), 2.54 (2H, t, J=7 Hz), 3.10 (2H, t, J=7 Hz), 5.52 (1H, s), 6.70—6.90 (2H, m), 7.00—7.85 (10H, m), 7.60—7.70 (2H, m), 7.98 (1H, d, J=7 Hz), 8.40 (1H, d, J =8 Hz). ESI-MS m/z: 600 $(M-H)^-$.

4-[3-[3-[[Bis(4-isobutylphenyl)methyl]amino]benzoyl]-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl]butyric Acid (31) Yield: 54.4%. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (12H, d, J=8 Hz), 1.72—1.95 (2H, m), 2.14—2.28 (2H, m), 2.38 (2H, d, J=8 Hz), 2.42 (4H, d, J=8 Hz), 4.36 (2H, t, J=8 Hz), 5.51 (1H, s), 6.74 (1H, dd, J=2, 8 Hz), 7.00—7.34 (12H, m), 7.60 (1H, s), 8.40 (1H, dd, J=2, 5 Hz), 8.68 (1H, dd, J=2, 8 Hz). ESI-MS m/z: 600 $(M-H)^-$.

4-Isobutylacetophenone (32a) Acetyl chloride (6.43 g, 81.9 mmol) was added to a suspension of $AlCl_3$ (10.9 g, 81.9 mmol) in CH_2Cl_2 (100 ml) at 0 °C. After the mixture was stirred at 0 °C for 30 min, isobutylbenzene (10 g, 74.6 mmol) was added at 0 °C. After stirring at 0 °C for 1 h, the mixture was poured into a mixture of CH_2Cl_2 and ice water. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was distilled (96 °C/0.8 mmHg) to give **32a** (12.1 g, 92.1%) as an oil.

1-(4-isobutylphenyl)-1-ethanol (33a) $NaBH_4$ (2.58 g, 68.3 mmol) was added to a solution of **32a** (10 g, 56.8 mmol) in methanol (100 ml) at 0 °C. The mixture was stirred for 1 h at r.t. and poured into ice water. The mixture was acidified with 6 N HCl to pH 3 and extracted with ether. The extract was washed with water and brine, then dried over $MgSO_4$. Evaporation of the solvent afforded **33a** (10.1 g, 99.9%) as a colorless oil.

1-Bromo-1-(4-isobutylphenyl)ethane (34a) To a mixture of **33a** (20.2 g, 113 mmol) and CBr_4 (75.25 g, 227 mmol) in THF (250 ml) was added PPh_3 (59.5 g, 227 mmol) at 0 °C, and the mixture was stirred at r.t. for 5 h. The precipitate was removed by filtration and the filtrate was evaporated *in vacuo.* The residue was triturated with hexane and the precipitate was filtered off. The filtrate was evaporated *in vacuo* and the residue was distilled (77—80 °C/0.3 mmHg) to give **34a** (17.4 g, 63.7%) as a colorless oil.

3-(3-Nitrobenzoyl)-1*H*-indole (35a) Following the procedure described above for **8**, **35a** (495 mg, 43.6%) was prepared from indole (500 mg). ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 7.21—7.35 (2H, m), 7.42—7.55 (1H, m), 7.68—7.79 (2H, m), 8.13 (1H, dd, J=1, 8 Hz), 8.24—8.35 (1H, m), 8.40 (1H, dd, J=1, 8 Hz).

3-(4-Nitrobenzoyl)-1*H*-indole (35b) Yield: 34.3%. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 7.20—7.45 (2H, m), 7.50—7.60 (2H, m), 7.72 (2H, d, J=8 Hz), 8.20—8.30 (1H, m), 8.31 (2H, d, J=8 Hz).

Ethyl 4-[3-(3-Nitrobenzoyl)-1*H*-indol-1-yl]butyrate (36a) Following the procedure described above for **25**, **36a** (630 mg, 90.0%) was prepared from **35a** (490 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 2.12—2.40 (4H, m), 4.10 (2H, q, J=7 Hz), 4.30 (2H, t, J=7 Hz), 7.30—7.50 (3H, m), 7.58 (1H, s), 7.70 (1H, t, J=8 Hz), 8.27 (1H, dd, J=1, 8 Hz), 8.35—8.48 (2H, m), 8.68 (1H, d, J=1 Hz).

Ethyl 4-[3-(4-Nitrobenzoyl)-1*H*-indol-1-yl]butyrate (36b) Yield: 83.9%. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 2.20—2.40 (4H, m), 4.10 (2H, q, J=7 Hz), 4.27 (2H, t, J=7 Hz), 7.35—7.50 (3H, m), 7.52 (1H, s), 7.95 (1H, t, J=8 Hz), 8.35 (2H, d, J=8 Hz), 8.40—8.50 (1H, m).

4-[3-(3-Nitrobenzoyl)-1*H*-indol-1-yl]butyric Acid (37a) Following the procedure described above for **26**, **37a** (1.28 g, 86.0%) was prepared from **36a** (1.60 g). ^{1}H-NMR (CD_3Cl : CD_3OD=1 : 1) δ: 2.10 (2H, m), 2.35 (2H, t, J=7 Hz), 4.30 (2H, t, J=7 Hz), 7.30—7.55 (3H, m), 7.60 (1H, s), 7.72 (1H, t, J=8 Hz), 8.16 (1H, dd, J=2, 8 Hz), 8.31—8.48 (2H, m), 8.65 (1H, d, J=2 Hz).

4-[3-(4-Nitrobenzoyl)-1*H*-indol-1-yl]butyric Acid (37b) Yield: 93.2%. ^{1}H-NMR (CD_3Cl : CD_3OD=1 : 1) δ: 1.80—2.00 (2H, m), 2.15 (2H, t, J=7 Hz), 4.12 (2H, t, J=7 Hz), 7.10—7.25 (2H, m), 7.45—7.55 (1H, m), 7.81 (1H, s), 7.85 (2H, d, J=8 Hz), 8.10—8.15 (1H, m), 8.18 (2H, d, J=8 Hz).

4-[3-(3-Aminobenzoyl)-1*H*-indol-1-yl]butyric Acid (38a) Following the procedure described above for **11**, **38a** (982 mg, 89.0%) was prepared from **37a** (1.20 g). ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 2.15—2.45 (4H, m), 4.32 (2H, t, J=7 Hz), 6.97 (1H, m), 7.15—7.60 (6H, m), 7.72 (1H, s), 8.45 (1H, m).

4-[3-(4-Aminobenzoyl)-1*H*-indol-1-yl]butyric Acid (38b) Yield: 71.2%. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 2.20 (2H, quintet, J=7 Hz), 2.33 (2H, t, J=7 Hz), 4.36 (2H, t, J=7 Hz), 6.75 (2H, d, J=8 Hz), 7.20—7.40 (2H, m), 7.50 (1H, dd, J=2, 8 Hz), 7.65—7.80 (1H, m), 7.70 (2H, d, J=8 Hz), 8.25 (1H, dd, J=2, 8 Hz).

4-[3-[3-[[1-(4-Isobutylphenyl)ethyl]amino]benzoyl]-1*H*-indol-1-yl]butyric Acid (39) Following the procedure described above for **30**, **39** (420 mg, 43.5%) was prepared from **38a** (600 mg). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.51 (3H, d, J=7 Hz), 1.70—2.00 (1H, m), 2.10—2.30 (2H, m), 2.35 (1H, m), 2.43 (2H, d, J=7 Hz), 4.20 (2H, m), 4.52 (1H, q, J=7 Hz), 6.67 (1H, d, J=8 Hz), 7.00—7.40 (10H, m), 7.45 (1H, s), 8.43 (1H, m). ESI-MS m/z: 495 (M−H).

4-[3-[4-[[1-(4-Isobutylphenyl)ethyl]amino]benzoyl]-1*H*-indol-1-yl]butyric Acid (40) Yield: 33.3%. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H, d, J=7 Hz), 1.60 (3H, d, J=7 Hz), 1.70—2.00 (1H, m), 2.35 (2H, m), 2.45 (2H, d, J=7 Hz), 4.23 (2H, m), 4.56 (1H, q, J=7 Hz), 6.50—6.70 (2H, m), 7.10 (2H, d, J=8 Hz), 7.20—7.50 (5H, m), 7.51 (1H, s), 7.70 (2H, d, J=8 Hz), 8.30 (1H, m). ESI-MS m/z: 495 $(M-H)^-$.

3-(4-Methoxybenzoyl)-1*H*-indole (41) Following the procedure described above for **8**, **41** (8.38 g, 78.4%) was prepared from indole (5.0 g) and 4-methoxybenzoyl chloride (7.29 g). mp 203—205 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, s), 6.93 (2H, d, J=8 Hz), 7.00—7.19 (2H, m), 7.30—7.44 (1H, m), 7.67 (2H, d, J=8 Hz), 7.31 (1H, s), 8.02—8.15 (1H, m).

Ethyl 4-[3-(4-Methoxybenzoyl)-1*H*-indol-1-yl]butyrate (42) A mixture of **41** (4.0 g, 15.9 mmol), ethyl 4-bromobutyrate (3.42 g, 17.5 mmol) and K_2CO_3 (6.60 g, 47.8 mmol) in DMF (60 ml) was stirred at 20 °C for 14 h. The mixture was partitioned between EtOAc and 1 N HCl, and the organic layer was washed with water and brine, then dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel ($CHCl_3$) to give **42** (5.81 g, 100%) as an orange oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 2.08—2.38 (4H, m), 3.38 (3H, s), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 6.99 (2H, d, J=8 Hz), 7.28—7.48 (3H, m), 7.58 (1H, s), 7.85 (2H, d, J=8 Hz), 8.32—8.45 (1H, m).

Ethyl 4-[3-(4-Hydroxybenzoyl)-1*H*-indol-1-yl]butyrate (43) $AlCl_3$ (3.29 g, 24.7 mmol) was added to a solution of **42** (3.0 g, 8.21 mmol) in a mixture of CH_2Cl_2 (10 ml) and ethanethiol (10 ml) at 0 °C. After being stirred at 20 °C for 1 h, the mixture was cooled to 0 °C, and $AlCl_3$ (1.64 g, 12.3 mmol) and ethanethiol (5 ml) were added. The mixture was stirred at 20 °C for 30 min and evaporated *in vacuo.* 1 N HCl was added to the residue and the mixture was extracted with EtOAc 2 times. The extracts were combined, washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was crystallized (EtOAc–hexane) to obtain **43** (2.41 g, 83.5%) as colorless crystals, mp 129—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 2.08—2.40 (4H, m), 4.10 (2H, q, J=7 Hz), 4.25 (2H, t, J=7 Hz), 6.91 (2H, d, J=8 Hz), 7.25—7.50 (3H, m), 7.60 (1H, s), 7.75 (2H, d, J=8 Hz), 8.30—8.42 (1H, m).

Ethyl (±)-4-[3-[4-[[1-(4-Isobutylphenyl)ethyl]oxy]benzoyl]-1*H*-indol-1-yl]butyrate (44a) A mixture of **43** (0.50 g, 1.42 mmol), **34a** (0.35 g, 1.57 mmol) and K_2CO_3 (0.59 g, 4.27 mmol) in DMF (10 ml) was stirred overnight at r.t. The precipitates were filtered off and the filtrate was evaporated *in vacuo.* The residue was partitioned between EtOAc and 0.5 N HCl, and the organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography (EtOAc : hexane=1 : 4) to give **44a** (520 mg, 71.4%) as an oil.

(±)-4-[3-[4-[[1-(4-Isobutylphenyl)ethyl]oxy]benzoyl-1*H*-indol-1-yl]butyric Acid (45a) To a solution of **44a** (500 mg, 0.949 mmol) in THF (3 ml) were added 1 N NaOH (1.5 ml) and MeOH (1.5 ml), and the mixture was stirred at r.t. for 4 h. The mixture was diluted with water and washed with

ether. The aqueous layer was acidified with 1 N HCl and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo.* The residue was purified by silica gel chromatograpy with 5% MeOH in $CHCl_3$ to give **45a** (466 mg, 98.6%) as an oil.

(*R*)-1-(4-Isobutylphenyl)ethanol (46a) A solution of **32a** (1.86 g, 10.6 mmol) in THF was added to a solution of (+)-DIP-chloride (3.90 g, 12.1 mmol) in THF (8 ml) at −20 °C. After being stirred at the same temperature for 3.5 h, the mixture was quenched by acetaldehyde (0.2 ml) and evaporated *in vacuo.* The residue was dissolved in ether (40 ml), and diethanolamine (2.5 ml) was added to the solution, then the mixture was stirred for 2 h. The precipitates were filtered and washed with ether. The filtrate and washings were combined and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2) to give **46a** (616 mg, 39.0%). $[\alpha]_D^{22}=+27.8°$ ($c=1$, MeOH).

(*S*)-1-(4-Isobutylphenyl)ethanol (47a) Following the procedure described above for **46a**, **47a** (1.69 g, 84.0%) was prepared from 4-isobutylacetophenone (2.0 g, 11.4 mmol) and (−)-DIP-chloride (4.39 g, 13.7 mmol) as an oil. $[\alpha]_D^{22}=-30.6°$ ($c=1$, MeOH). (Ref. $[\alpha]_D^{20}=-30°$ ($c=1$, MeOH)).[15]

Ethyl (*S*)-4-[3-[4-[[1-(4-Isobutylphenyl)ethyl]oxy]benzoyl-1*H*-indol-1-yl]butyrate (48a) To a mixture of **43** (375 mg, 1.03 mmol), **46a** (200 mg, 1.12 mmol) and triphenylphosphine (294 mg, 1.12 mmol), in a mixture of THF (2 ml) and toluene (8 ml), was added diethyl azodicarboxylate (DEAD) (0.177 ml, 1.12 mmol) at −20 °C under N_2. The mixture was stirred at −20 °C for 1 h and AcOH (0.05 ml) was added. The mixture was warmed up to 20 °C and the solvent was evaporated off. The residue was partitioned between EtOAc and water and the organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (EtOAc : hexane = 1 : 2) to give **48a** (349 mg, 63.7%) as an oil.

(*S*)-4-[3-[4-[[1-(4-Isobutylphenyl)ethyl]oxy]benzoyl-1*H*-indol-1-yl]butyric Acid (49a) Following the procedure described above for **45a**, **50a** (270 mg, 83.0%, 87.1% ee)[14] was prepared from **48a** (345 mg) as a powder.

Ethyl 4-[1-(4-Acetoxybenzoyl)indolizin-3-yl]butyrate (52) 4-Acetoxybenzoyl chloride (53.6 g, 269 mmol) was added to a suspension of $AlCl_3$ (36.5 g, 723 mmol) in CH_2Cl_2 (500 ml). After the mixture was stirred for 20 min at r.t., a solution of **3** (57.8 g, 250 mmol) in CH_2Cl_2 (50 ml) was added. The mixture was stirred for 2 h at r.t., and the solvent was evaporated off. The residue was partitioned between EtOAc and water. The organic layer was separated and 3-(dimethylamino)propylamine (20 ml) was added. The mixture was stirred for 15 min and washed with 1 N HCl, water, sat. $NaHCO_3$, and brine, successively, and dried over $MgSO_4$. After evaporation of the solvent, the crystalline residue was washed with diisopropyl ether (IPE) to give **52** (36.5 g, 37.2%) as a yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz), 2.00—2.20 (2H, m), 2.35 (3H, s), 2.43 (2H, t, $J=7$ Hz), 2.90 (2H, t, $J=7$ Hz), 4.12 (2H, q, $J=7$ Hz), 6.85—7.00 (2H, m), 7.15—7.30 (1H, m), 7.25 (2H, d, $J=8$ Hz), 7.88 (2H, d, $J=8$ Hz), 8.03 (1H, d, $J=7$ Hz), 8.52 (1H, d, $J=9$ Hz).

Ethyl 4-[1-(4-Hydroxybenzoyl)indolizin-3-yl]butyrate (53) NaH (60% dispersion in mineral oil, 4.38 g, 110 mmol) was added to an ice cooled solution of **52** (36.1 g, 91.9 mmol) in a mixture of EtOH (200 ml) and THF (200 ml). The mixture was stirred for 20 min at 0 °C and the solvent was evaporated off. The residue was poured into a mixture of dil. HCl and ice, then extracted with 10% MeOH in $CHCl_3$. The extract was washed with sat. $NaHCO_3$ and brine, then dried over $MgSO_4$. After evaporation of the solvent, the crystalline residue was washed with EtOAc and ether to give **53** (29.3 g, 90.9%) as a yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz), 2.00—2.20 (2H, m), 2.45 (2H, t, $J=7$ Hz), 2.89 (2H, t, $J=7$ Hz), 4.15 (2H, q, $J=7$ Hz), 6.80—7.00 (4H, m), 7.18 (1H, t, $J=9$ Hz), 7.78 (2H, d, $J=8.5$ Hz), 8.00 (1H, d, $J=5.5$ Hz), 8.50 (1H, d, $J=9$ Hz).

Ethyl (±)-4-[1-[4-[1-(4-Isobutylphenyl)propyloxy]benzoyl]indolizin-3-yl]butyrate (54b) Following the procedure described above for **48a**, **54b** (80 mg, 87.5%) was prepared from **53** (53 mg) and **34b** (53 mg, 0.27 mmol) as an oil.

(±)-4-[1-[4-[[1-(4-Isobutylphenyl)propyl]oxy]benzoyl]indolizin-3-yl]butyric Acid (55b) Following the procedure described above for **45a**, **55b** (64 mg, 91.3%) was prepared from **54b** (74 mg).

Ethyl (*S*)-4-[1-[4-[[1-(4-Isobutylphenyl)butyl]oxy]benzoyl]indolizin-3-yl]butyrate (57) Following the procedure described above for **48a**, **57** (48.6 g, 56.2%) was prepared from **56** (55 g, 157 mmol) and **46c** (32.3 g, 157 mmol) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.05 (9H, m), 1.24 (3H, t, $J=7$ Hz), 1.30—1.65 (2H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.87 (2H, t, $J=7$ Hz), 4.12 (2H, q, $J=7$ Hz), 5.17 (1H, dd, $J=2$, 7 Hz), 6.80—6.94 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, $J=9$ Hz), 7.98 (1H, d, $J=7$ Hz), 8.44 (1H, d, $J=9$ Hz).

Ethyl (*R*)-4-[1-[4-[[1-(4-Isobutylphenyl)butyl]oxy]benzoyl]indolizin-3-yl]butyrate (58) Yield: 60.5% as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.05 (9H, m), 1.24 (3H, t, $J=7$ Hz), 1.30—1.65 (2H, m), 1.70—2.15 (5H, m), 2.35—2.50 (4H, m), 2.87 (2H, t, $J=7$ Hz), 4.12 (2H, q, $J=7$ Hz), 5.17 (1H, dd, $J=2$, 7 Hz), 6.80—6.94 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, $J=9$ Hz), 7.98 (1H, d, $J=7$ Hz), 8.44 (1H, d, $J=9$ Hz).

(*S*)-4-[1-[4-[[1-(4-Isobutylphenyl)butyl]oxy]benzoyl]indolizin-3-yl]butyric Acid (FK687) Following the procedure described above for **45a**, FK687 (36.1 g, 75.9%, 97.6 ee)[14] was prepared from **57** (48.6 g) as a powder, mp 94.5—96.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.05 (9H, m), 1.30—1.65 (2H, m), 1.70—2.15 (5H, m), 2.40—2.55 (4H, m), 2.88 (2H, t, $J=7$ Hz), 5.16 (1H, dd, $J=2$, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, $J=9$ Hz), 7.96 (1H, d, $J=7$ Hz), 8.42 (1H, d, $J=9$ Hz). $[\alpha]_D^{25}$ −82.8° ($c=1.0$, $CHCl_3$). ESI-MS *m/z*: 524 $(M-H)^-$.

(*R*)-4-[1-[4-[[1-(4-Isobutylphenyl)butyl]oxy]benzoyl]indolizin-3-yl]butyric Acid (59) Yield: 84.1%, 96.0% ee[14] as a powder. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.05 (9H, m), 1.30—1.65 (2H, m), 1.70—2.15 (5H, m), 2.40—2.55 (4H, m), 2.88 (2H, t, $J=7$ Hz), 5.16 (1H, dd, $J=2$, 7 Hz), 6.80—6.95 (4H, m), 7.05—7.30 (5H, m), 7.72 (2H, d, $J=9$ Hz), 7.96 (1H, d, $J=7$ Hz), 8.42 (1H, d, $J=9$ Hz). $[\alpha]_D^{25}$ +79.8° ($c=0.5$, $CHCl_3$). ESI-MS *m/z*: 524 $(M-H)^-$.

Biological Data Preparation of Prostatic Enzyme: Rat ventral prostates, removed from 10—20 week old male Wistar rats, dissected free of their capsules, were washed with saline, and stored at −80 °C. Human prostatic tissues from BPH patients who received transurethral prostatectomy were kindly provided by Dr M. Tachibana at Keio University Hospital, and stored at −80 °C. Prostatic enzyme fractions were prepared as previously described in the literature.[16] Frozen tissues were thawed on ice and minced with scissors. Unless specified, all of the following procedures were carried out at 4 °C. The tissues were homogenized with a Polytron homogenizer in 3—4 tissue volumes of medium A (0.32 M sucrose, 0.1 mM dithiothreitol (DTT), and 20 mM sodium phosphate buffer, pH 6.5). The homogenates were centrifuged at 1500 ***g*** for 20 min, and the nuclear membrane fractions were precipitated. The pellets were then resuspended in medium A and filtered with gauze. The suspension (3—10 mg/ml) was stored at −80 °C until use.

5α-Reductase Assay: 5α-Reductase activities were assayed as previously described in the literature.[17] The reaction mixture contained in a final volume of 200 μl: 1 mM DTT, 40 mM of sodium phosphate buffer, 0.1 mM NADPH, 2 nM [1,2,6,7-^{3}H]T, and the rat prostatic enzyme fraction. The amount of the prostatic enzyme fraction was adjusted to set the rate of conversion of T into DHT at around 30% at pH 6.5. The reaction, in duplicate, was started by adding the enzyme fraction, followed by incubation at 37 °C for 60 min, and stopped by mixing it with 200—300 μl of ethyl acetate containing cold 500 μg/ml T and 300 μg/ml of DHT as UV markers (245 nm for T, 305 nm for DHT). 50 μl of ethyl acetate was spotted on Kieselgel 60 F254 plates, and T and DHT were chromatographed using ethyl acetate: cyclohexane (1 : 1) as the developing solvent. The plate was air dried, sprayed with primuline solution (10 mg/400 ml in acetone: water (4 : 1)), and the T and DHT were located under UV light. Androgen containing areas were cut and the strips soaked in 5 ml of aquasol-2. Radioactivities were counted in a scintillation counter.

Effects in Castrated Young Rats: Four-week-old prepubertal male Wistar rats were anesthetized by pentobarbital and castrated. From the incised abdomen vas deferens, the testicular artery and vein were fastened and the testes were cut out.[18] After 3 d, oral administration of 5 ml/kg of drug solution was started once daily for 5 consecutive days. Drugs were dissolved in sesame oil. 300 μg/kg of TP in sesame oil was subcutaneously injected to the rats at the same time as the drug administration. Rats were sacrificed with CO_2 gas about 6 h after the last dosing, and ventral prostates and seminal vesicles were removed and weighed.

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