Pyrrole Butyric Acid Derivatives as Inhibitors of Steroid 5α-Reductase

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A series of pyrrole butyric acid derivatives was synthesized and evaluated for inhibitory activity on human and rat steroid 5α-reductase *in vitro* and *ex vivo*. 3-Benzoyl-4-alkylpyrrole-1-butyric acids and 1-methyl-2-alkyl-3-benzoylpyrrole-5-butyric acid derivatives were effective inhibitors. Structure activity relationships were evaluated among the 37 compounds synthesized. Compound 37 (HQL-1069) shows potent inhibitory activities against both rat and human 5α-reductase.

Key words 5α-reductase inhibitor; benign prostate hypertrophy; pyrrole derivative

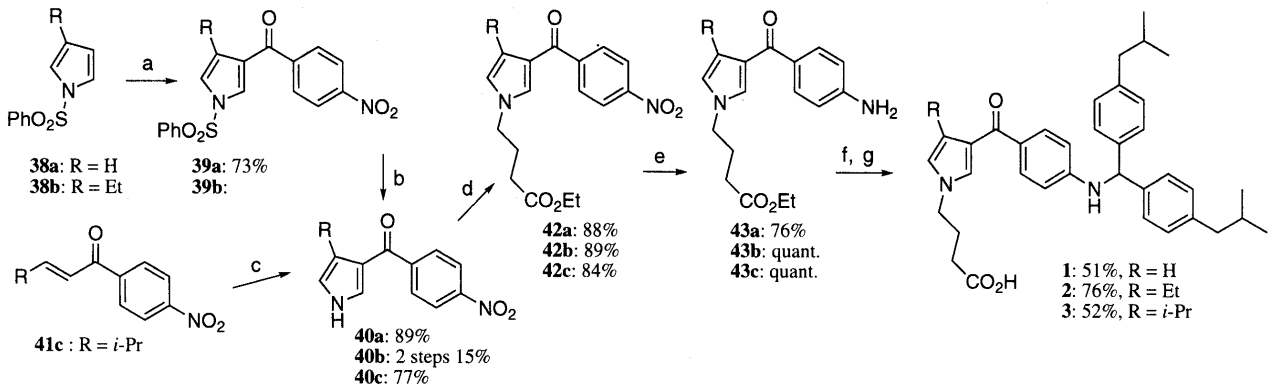
Steroid 5α-reductase is an enzyme that converts testosterone (T) into the more potent intracellular androgen 5α-dihydrotestosterone (DHT). On the basis of pathological studies of males genetically deficient in this enzyme, selective blockade of DHT biosynthesis is expected to provide a potential treatment for benign prostate hypertrophy (BPH),[1] as well as androgen related skin disorders such as acne[2] and male pattern baldness.[3] Merck (finasteride)[4] and SK & F (epristeride)[5] developed steroid 5α-reductase inhibitors, and nonsteroidal inhibitors, including ONO-3805,[6] FK-143[7] and KF-18678,[8] have also been reported. Our attention was drawn to these nonsteroidal inhibitors in view of the side effects of steroidal inhibitors, and we have searched for new nonsteroidal inhibitors of 5α-reductase.

The series of nonsteroidal inhibitors mentioned above consists of compounds having a butyric acid, either a hydroxyanilide or an indole, and a benzyloxy (or amino) benzoyl moiety. Our survey to find novel inhibitors of steroid 5α-reductase was primarily focused on compounds derived by converting the central part of these structures into various groups, including 5-membered heterocycles such as pyrrole, furan and thiophene. Among the synthesized compounds, a compound having a pyrrole nucleus (**1**) showed relatively strong inhibition of both human and rat 5α-reductase and was selected as a promising candidate. Further structural modification of **1** resulted in a series of novel 5α-reductase inhibitors. Herein we present the syntheses of these pyrrole butyric acid derivatives and we discuss the structure-activity relationships based on *in vitro* studies using human and rat 5α-reductase. The *in vivo* efficiency of the compounds is also discussed on the basis of an *ex vivo* experiment.

Chemistry

Pyrrole butyric acid derivatives **1**—**3** were synthesized *via* the routes shown in Chart 1. *N*-Phenylsulfonylpyrrole (**38a**)[9] was subjected to Friedel-Crafts acylation and subsequent removal of the directing group to give the 3-acyl pyrrole **40a**. After introduction of a butyric acid moiety, the nitro group was reduced to an amino group. Alkylation with di(isobutylphenyl)methyl chloride and successive hydrolysis afforded **1**. In the case of the 3-ethyl derivative, the resulting mixture of 3-acyl-4-ethyl and 2-acyl-3-ethyl isomers was subjected to alkaline hydrolysis and the mixture was separated by silica gel column chromatography to give **40b**. Michael addition of **41c** with tosylmethyl isocyanide (TosMIC) [10] afforded the 3-acyl-4-isopropyl pyrrole **40c**. Compounds **40b** and **40c** were converted to **2** and **3**, respectively. Compounds listed in Table 1 were also prepared as described above.

According to Charts 2—5, four regio-isomers of **2** (**12**—**16**) were synthesized through the corresponding *p*-nitrobenzoyl intermediates (**47**, **52**, **56**, **60**) prepared from



(a) RCOCl, $AlCl_3$, CH_2Cl_2; (b) 5 N NaOH; (c) TosMIC, NaH, THF; (d) $Br(CH_2)_3COOEt$, NaH, DMF; (e) H_2, Pd-C, EtOH; (f) (*p*-isobutylphenyl)$_2$CHCl, K_2CO_3, CH_2Cl_2; (g) 1 N NaOH, EtOH.

Chart 1

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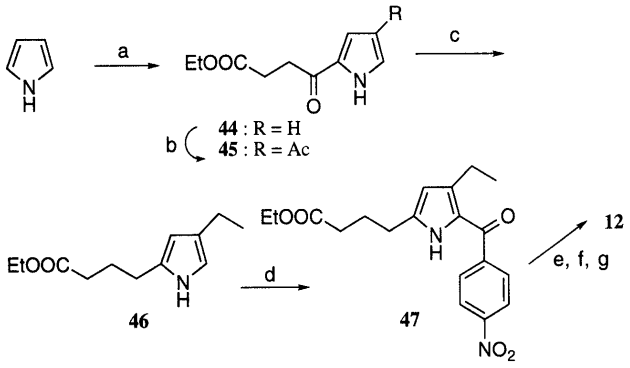
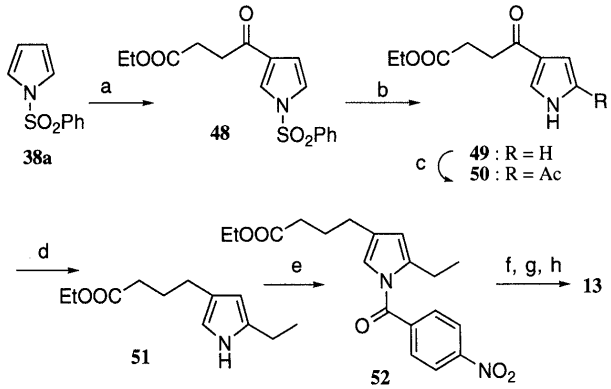


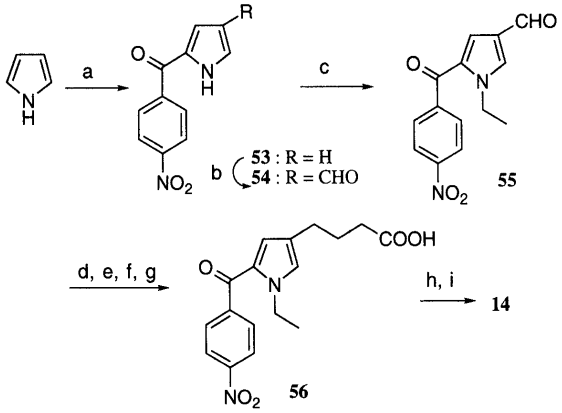
(a) $EtOOCCH_2CH_2COCl$, $AlCl_3$, CH_2Cl_2; (b) AcCl, $AlCl_3$, CH_2Cl_2, 2 steps 89%; (c) *tert*-$BuNH_2$-BH_3, THF; (d) *p*-nitrobenzoyl chloride, K_2CO_3, THF, 2 steps 34%; (e) H_2, Pd-C, EtOH; (f) (isobutylphenyl)$_2$CHCl, iso-Pr_2NEt, CH_2Cl_2; (g) NaOH, EtOH, 3 steps 39%.

Chart 2



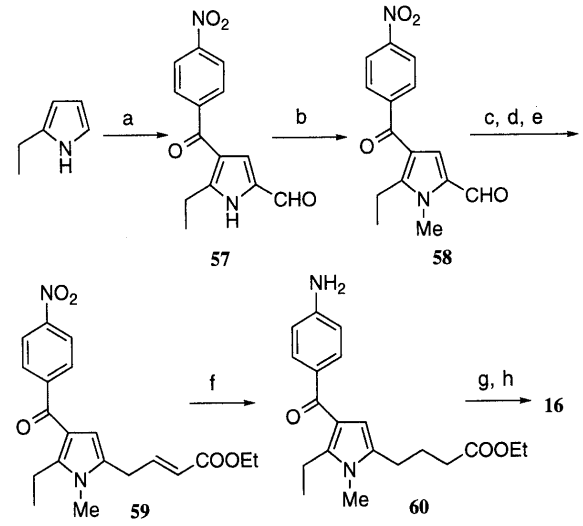
(a) $EtOOCCH_2CH_2COCl$, $AlCl_3$, CH_2Cl_2; (b) NaOEt, EtOH; (c) AcCl, $AlCl_3$, CH_2Cl_2, 3 steps 85%; (d) *tert*-$BuNH_2$-BH_3, THF, 46%; (e) phenyl *p*-nitrobenzoate, NaH, THF, 49%; (f) H_2, Pd-C; (g) (isobutylphenyl)$_2$CHCl, iso-Pr_2NEt, CH_2Cl_2; (h) NaOH, EtOH, 3 steps 18%.

Chart 3



(a) *p*-nitrobenzoyl chloride, 2,6-lutidine, 22%; (b) Cl_2CHOMe, $TiCl_4$, 19%; (c) EtI, K_2CO_3, 85%; (d) $Ph_3PCH_2CH_2CH_2OTHPBr$, *n*-BuLi, THF, 68%; (e) *p*-TsOH, 89%; (f)i) Et_3SiH, TFA; ii) *n*-Bu_4NF, quant.; (g) Jones reagent, acetone, 24%; (h) H_2, Pd-C, EtOH, 89%; (i) (isobutylphenyl)$_2$CHCl, iso-Pr_2NEt, CH_2Cl_2, 15%.

Chart 4



(a) i) $(COCl)_2$, DMF, CH_2Cl_2, ii) *p*-nitrobenzoyl chloride, $AlCl_3$, 73%; (b) MeI, K_2CO_3, DMF, 84%; (c) $MeOCH_2PPh_3Cl$, *tert*-BuOK, THF; (d) HCl-dioxane, THF; (e) $Ph_3P{=}CHCO_2Et$, DMF, 3 steps 71%; (f) H_2, Pd-C, EtOH, quant.; (g) (isobutylphenyl)$_2$CHCl, iso-Pr_2NEt, CH_2Cl_2; (h) NaOH, EtOH, 2 steps 74%.

Chart 5

pyrrole *via* regioselective Friedel-Crafts acylation. Pyrrole was acylated in 2 steps to afford the 2,4-diacylpyrrole **45**, which was reduced to give the 2,4-dialkylpyrrole **46**. Acylation of **46** was performed with potassium carbonate to afford **47**, which was converted to **12** in 3 steps.

For the synthesis of **13**, **38a** was converted to the 3,5-diacylpyrrole **50** by Friedel-Crafts acylation, and the 3,5-dialkylpyrrole derivative **51** was obtained by reduction. *N*-Acylation of **51** was performed using *p*-nitrobenzoic acid *p*-nitrophenylester to yield the *p*-nitrobenzoyl amide **52**, a precursor of **13**.

The 2,4-diacylpyrrole derivative **55** was synthesized by the same methods as used for the preparation of **45**. Three-carbon homologation by Wittig reaction and removal of the THP group gave an unsaturated alcohol, which afforded **56** after hydrogenation of the double bond with Et_3SiH, and oxidation by Jones reagent. Further elaboration gave **14**.

Compound **16** was prepared according to the schemes in Chart 5.

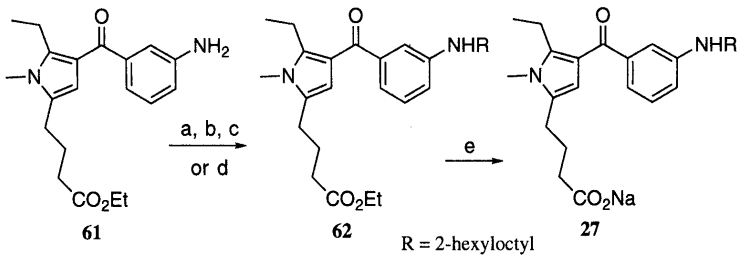
Derivatives listed in Tables 5 and 6 were synthesized similarly. The case of **27** is shown in Chart 6. Required alkyl halides for the preparation of **26**—**36** were obtained by one-carbon homologation once or twice using the Wittig reaction and subsequent conversion into the corresponding halides, as shown in Chart 7.

Compound **27** was also obtained by reductive alkylation (Chart 6). Calcium salts (**37**) were prepared by cation exchange (See Experimental).

Results and Discussion

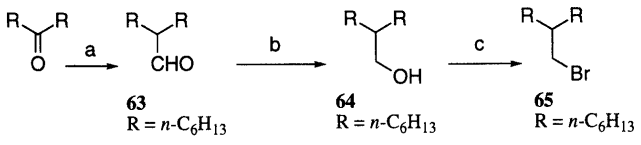
We found that pyrrole butyric acid derivatives show rather strong inhibition of rat steroid 5α-reductase, and so the effect of substituents in the pyrrole ring on the inhibitory activity was investigated.

In the case of *para*-aminobenzoyl pyrrole, introduction of an ethyl (**2**) or isopropyl group (**3**) at C-4 increased the inhibitory activity against the human 5α-reductase, while the presence of a carboxyl (**4**) or an ethoxycarbonyl group (**5**) at C-4 decreased it. The presence of an ethyl (**8**) or isopropyl group (**10**) at C-4 of the pyrrole ring markedly increases the inhibitory activity in the case of *meta*-derivatives. The benzoylpyrrole is probably in a planar



(a) ZCl, iso-Pr_2EtN, DMF, quant.; (b) $(C_6H_{13})_2CHCH_2Br$, NaH, DMF, 62%; (c) H_2, Pd-C, EtOH, 91%; (d) $(C_6H_{13})_2CHCHO$, BH_3-THF, THF; (e) 1N NaOH, EtOH, 95%.

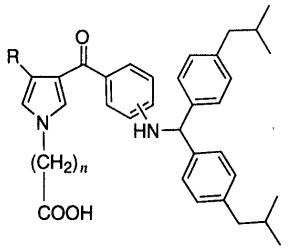
Chart 6



(a) i) $MeOCH_2PPh_3Cl$, *tert*-BuOK, THF, ii) 4 N HCl/dioxane, THF, 93%; (b) $NaBH_4$, MeOH, 96%; (c) CBr_4, Ph_3P, THF, 69%.

Chart 7

Table 1. Effects of Pyrrole Ring Substituents on the Inhibitory Activities of Pyrrole Butyric Acid Derivatives against 5α-Reductase



Compd.	R	*n*	p[a]	IC_{50}, nM	
				Rat	Human
1	H	3	*p*	26	280
2	CH_2CH_3	3	*p*	7.0	32
3	$CH(CH_3)_2$	3	*p*	25	9.2
4	COOH	3	*p*	500	>100
5	$COOCH_2CH_3$	3	*p*	200	>100
6	$CH(CH_3)_2$	4	*p*	580	>100
7	$CH(CH_3)_2$	2	*p*	22	>100
8	CH_2CH_3	3	*m*	210	4.6
9	$(CH_2)_2CH_3$	3	*m*	>1000	18
10	$CH(CH_3)_2$	3	*m*	60	3.2
11	$C(CH_3)_3$	3	*m*	790	23

a) Position of di(isobutylphenyl)methylamino substituent on the benzoyl ring.

form due to conjugation between the carboxyl group and the aromatic rings, so that the compounds have two possible conformers, an extended form and a folded form (Fig. 1). In the case of **1**, two forms are possible, whereas the compound having a substituent at C-4 is inclined to be in a folded form (**3b**) because of steric hindrance in the extended form (**3a**), as shown in Fig. 1. These findings imply that the inhibitors containing a pyrrole ring bind more tightly to the human enzyme in the folded form than in the extended form. The finding that a bulkier group than ethyl or isopropyl at C-4 reduced the activity

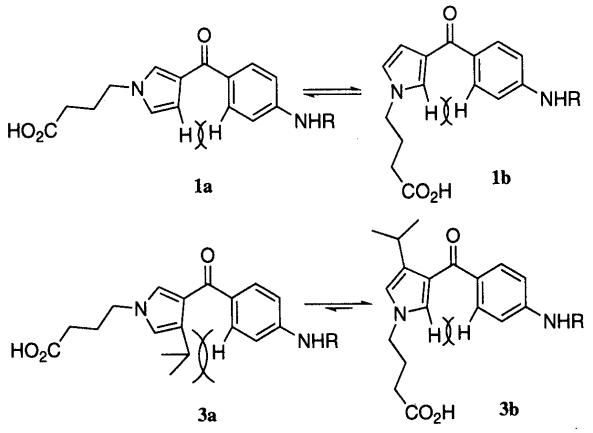
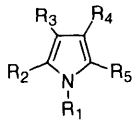


Fig. 1. Plausible Conformers of **1** and **3**

showed that there is a steric restriction in the binding site on the enzyme. The most favorable distance between the pyrrole ring and carboxylic acid was estimated to be three methylenes (compare **3** with **6** and **7**). Among these compounds, *meta*-aminobenzoyl pyrroles (**8**, **10**) were slightly stronger inhibitors of the human enzyme than the *para*-isomers (**2**, **3**).

We examined the effect of the position of nitrogen in pyrrole butyric acid on the inhibitory activity. Compound **2**, having an ethyl group and a *para*-aminobenzoyl moiety on the pyrrole ring, was selected. Four regio-isomers of **2** are listed in Table 2, and **16** is an *N*-methyl derivative of **15**. Among them, **16** was the most effective inhibitor. The *meta*-isomer **17** inhibited human 5α-reductase more strongly than **16**, indicating that the position of pyrrolic nitrogen is important for the inhibition of enzyme activity. This was also supported by the finding that the derivatives in which the pyrrole ring of **16** is converted into furan or thiophene scarcely inhibited the human 5α-reductase.[11] Five compounds that inhibit the human 5α-reductase with an IC_{50} value of below 5 nM were obtained. To estimate the *in vivo* effects of these compounds, an *ex vivo* assay method for prostatic 5α-reductase activity in rats was used. Table 3 shows the percent inhibition of prostatic enzyme activity in male rats killed at 6 and 24 h after single oral administration of the compounds. Compound **16** showed the strongest inhibition in the rat prostatic tissues and the dosage of 10 mg/kg completely inhibited the enzyme activity. However, further study of **16** revealed a tendency for suppression of body weight gain in a one-week toxicity study in rats. Further study of **16** was abandoned.

Table 2. Effects of the Position of Nitrogen on the Inhibitory Activities of Pyrrole Butyric Acids



p-ABz=*p*-[di(isobutylphenyl)methylamino]benzoyl
m-ABz=*m*-[di(isobutylphenyl)methylamino]benzoyl
BuA=carboxypropyl

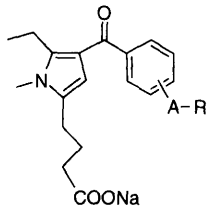
Compd.	R_1	R_2	R_3	R_4	R_5	IC_{50}, nM	
						Rat	Human
2	BuA	H	CH_2CH_3	*p*-ABz	H	7.0	32
12	H	BuA	H	CH_2CH_3	*p*-ABz	260	>100
13	*p*-ABz	H	BuA	H	CH_2CH_3	110	>100
14	CH_2CH_3	*p*-ABz	H	BuA	H	40	34
15	H	CH_2CH_3	*p*-ABz	H	BuA	22	27
16	CH_3	CH_2CH_3	*p*-ABz	H	BuA	15	4.4
17	CH_3	CH_2CH_3	*m*-ABz	H	BuA	290	3.2

Table 3. Prostatic *ex Vivo* 5α-Reductase Inhibitory Activities in Rats

Compd.	Dose (mg/kg)	Inhibitory activities (%)[a]	
		6 h[b]	24 h[b]
8	10	54	51
10	10	63	56
16	10	100	98
17	10	56	64
16	1	12	25
16	3	41	73

a) Percent inhibition of enzyme activities with respect to the control. *b*) Time after administration.

Table 4. Inhibitory Activities of Alkyl and Alkenyl Derivatives

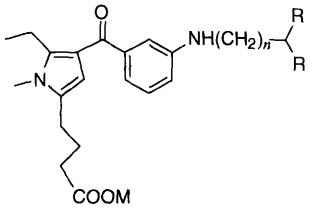


Compd.	R	A	IC_{50}, nM	
			Rat	Human
18	Butyl	*m*-NH	90	29
19	Hexyl	*m*-NH	16	4.0
20	Heptyl	*m*-NH	4.6	1.9
21	Octyl	*m*-NH	4.2	0.78
22	Octyl	*p*-O	74	70
23	Octyl	*m*-O	110	15
24	Geranyl	*m*-NH	11	0.78
25	Geranyl	*p*-NH	22	17
26	2-Ethyloctyl	*m*-NH	6.2	1.2
27	2-Hexyloctyl	*m*-NH	4.0	0.54
28	3-Hexylnonyl	*m*-NH	6.4	2.4

Next, transformation of the two isobutylphenyl groups in **16** into other substituents was attempted.

Various alkyl chains were examined (Table 4). Compound **21**, which has an octylaminobenzoyl moiety, inhibits human 5α-reductase with an IC_{50} as low as 0.78 nM. Replacement of the *para*-octylamino group in **21** with a *para*- or *meta*-octyloxy group resulted in a decrease in the inhibitory activity (**22**, **23**). Although a *meta*-geranylamino group showed adequate inhibition, this group at the *para*-position showed reduced activity. Compound **27**, having a 2-hexyloctylamino group, was the strongest inhibitor among the compounds, and others showed moderately strong inhibitory activities. These findings led us to speculate that an alkylated amino or ether group attached to the benzoyl group is not essential for the inhibitory activity, but is important for binding in the active site of such enzymes, and that a reasonably long alkyl chain is favorable.

Table 5. Inhibitory Activities of Derivatives of Compound **27**



Compd.	R	*n*	M	IC_{50}, nM	
				Rat	Human
27	Hexyl	1	Na	4.0	0.54
29	Phenethyl	1	Na	2.8	0.43
30	4-Methylphenethyl	1	Na	7.8	0.42
31	4-Methoxylphenethyl	1	Na	35	1.1
32	4-Chlorophenethyl	1	Na	17	1.3
33	4-Hydroxyphenethyl	1	H	92	35
34	Phenylpropyl	1	Na	5.0	0.58
35	4-Methylphenylpropyl	1	H	36	1.6
36	Phenylpropyl	0	H	7.2	0.093
37	Hexyl	1	1/2Ca	5.8	0.6

As **27** appeared interesting, we continued further optimization. Phenylalkyl amino groups were examined instead of the 2-hexyloctyl amino group in **27**. The results are shown in Table 5. Though **29** and **30** exhibited potent inhibitory activity, **33** with a hydrophilic group showed reduced inhibition. Both **34** and **35** were moderately strong inhibitors. A product **36** which was derived from **30** by modifying the branching position in the alkylated amino moiety inhibited the human 5α-reductase at an extremely

Table 6. Prostatic *ex Vivo* 5α-Reductase Inhibitory Activities in Rats

Compd.	Dose (mg/kg)	Inhibitory activities (%)[a]	
		6 h[b]	24 h[b]
16	5	74	89
21	5	47	0
24	5	28	0
27	5	75	34
29	5	63	11
30	5	71	19
34	5	60	24
36	5	67	40
37	5	83	21

a) Percent inhibition of enzyme activities with respect to the control. *b*) Time after administration.

low concentration (IC_{50} was 0.093 nM).

Seven compounds that inhibit the human enzyme at low concentrations ($\leq$ 1 nM) were further examined in *ex vivo* experiments. The results in Table 6 indicated that the compounds having a non-branched straight alkyl chain or less bulky alkyl chain such as **21** and **24** are poorly absorbed orally, and those with an alkyl chain that branches at the β-carbon to aniline nitrogen are better absorbed. HQL-940 (**27**) appeared to be very favorable, but its physical properties were undesirable in some respects: crystallization was unsuccessful and the foamy solid prepared by freeze drying was highly hygroscopic. Therefore the calcium salt (**37**) was employed. As shown in Tables 5 and 6, **37** showed essentially the same inhibitory activity as **27** in *in vitro* and *ex vivo* experiments.

As described above, HQL-1069 (**37**) showed potent inhibitory activity against rat and human 5α-reductase and had satisfactory absorbability. Further investigation of the biological and pharmaceutical properties of HQL-1069 is in progress.

Experimental

Chemistry Melting points were determined on a Mettler FR62 melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on a JEOL JNM-EX270 spectrometer, and chemical shifts were reported in δ units with tetramethylsilane as an internal standard. Mass spectra were taken on a JEOL AX505H instrument. Combustion analyses were performed on a Perkin-Elmer 2400II instrument. Chromatography was conducted on Kieselgel 60 (70—230 mesh for column chromatography and 230—400 mesh for flash column chromatography) supplied by E. Merck. All solvents for chromatography were of reagent grade.

Physical properties and spectral data for synthesized compounds are summarized in Table 7. All compounds for biological assay were purified by column chromatography.

1-Benzenesulfonyl-3-(4-nitrobenzoyl)-1*H*-pyrrole (39a) *p*-Nitrobenzoyl chloride (1.02 g) was added to a suspension of $AlCl_3$ (0.8 g) in CH_2Cl_2 (10 ml) at room temperature and the mixture was stirred for 10 min. A solution of 1-benzensulfonyl-1*H*-pyrrole (1.04 g) in CH_2Cl_2 (2 ml) was then added slowly and the whole was stirred for 2.5 h. The reaction was quenched with ice-water. The aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue, which was chromatographed over silica gel (1 : 2 EtOAc/hexane) to furnish **39a** (1.31 g). EI-MS *m/z*: 356 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.36 (2H, d, *J*=8 Hz), 7.96—7.90 (4H, m), 7.72—7.55 (4H, m), 7.25 (1H, br s), 6.80 (1H, br s).

3-(4-Nitrobenzoyl)-1*H*-pyrrole (40a) A 5 N NaOH aqueous solution (10 ml) was added to a dioxane solution (10 ml) containing **39a** (1.13 g) and the mixture was stirred at room temperature for 17 h. The usual work-up afforded **40a** (0.61 g). EI-MS *m/z*: 216 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.70 (1H, br s), 8.33 (2H, d, *J*=8 Hz), 7.97 (2H, d, *J*=8 Hz), 7.38 (1H, quint, *J*=2 Hz), 6.92—6.88 (1H, m), 6.77—6.74 (1H, m).

Ethyl 4-[3-(4-Nitrobenzoyl)-1*H*-pyrrol-1-yl]butyrate (42a) A solution of **40a** (460 mg) in dimethylformamide (DMF) (5 ml) was added to a suspension of 60% NaH (160 mg) in DMF (2 ml) at room temperature and the mixture was stirred for 10 min. A solution of ethyl 4-bromobutyrate (415 mg) in DMF (2 ml) was added slowly and the whole was stirred for 1.5 h. The reaction was quenched with ice-water, and extracted twice with ethyl acetate. Usual work-up and purification by silica gel chromatography (1 : 2 EtOAc/hexane) furnished **42a** (625 mg). EI-MS *m/z*: 330 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.22 (2H, d, *J*=8 Hz), 7.97 (2H, d, *J*=8 Hz), 7.24 (1H, t, *J*=2 Hz), 6.70—6.64 (2H, m), 4.13 (2H, q, *J*=7 Hz), 4.00 (2H, t, *J*=7 Hz), 2.32 (2H, t, *J*=7 Hz), 2.13 (2H, quint, *J*=7 Hz), 1.26 (3H, t, *J*=7 Hz).

Ethyl 4-[3-(4-Aminobenzoyl)-1*H*-pyrrol-1-yl]butyrate (43a) A mixture of **42a** (850 mg) in ethanol (20 ml) and 10% Pd-C (500 mg) was hydrogenated at 2 kg/cm^2 in a Parr apparatus for 30 min. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The resulting oil was chromatographed over silica gel (1 : 3 : 9 EtOH/EtOAc/hexane) to furnish **43a** (584 mg). EI-MS *m/z*: 300 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.76 (2H, d, *J*=8 Hz), 7.22 (1H, t, *J*=2 Hz), 6.68—6.64 (4H, m), 4.13 (2H, q, *J*=7 Hz), 3.98 (2H, t, *J*=7 Hz), 2.31 (2H, t, *J*=7 Hz), 2.10 (2H, quint, *J*=7 Hz), 1.26 (3H, t, *J*=7 Hz).

4-[3-(4-{[Bis(4-isobutylphenyl)methyl]amino}benzoyl)-1*H*-pyrrol-1-yl]butyric Acid (1) *N*,*N*,-Diisopropylethylamine (37 mg) was added to a solution of **43a** (85 mg), bis(4-isobutylphenyl)methyl chloride (89 mg) in CH_2Cl_2 (20 ml) and the mixture was heated at reflux for 1 d. The reaction was quenched with ice-water, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. Usual work-up and purification with silica gel chromatography (1 : 2 EtOAc/hexane) furnished ethyl 4-[3-(4-{[bis(4-isobutylphenyl)methyl]amino}benzoyl)pyrrol-1-yl]butyrate (118 mg); EI-MS *m/z*: 578 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.72 (2H, d, *J*=8 Hz), 7.24—7.17 (2H, m), 7.22 (4H, d, *J*=8 Hz), 7.09 (4H, d, *J*=8 Hz), 6.62 (1H, br s), 6.55 (2H, d, *J*=8 Hz), 5.53 (1H, d, *J*=4 Hz), 4.63 (1H, d, *J*=4 Hz), 4.13 (2H, q, *J*=7 Hz), 3.96 (2H, t, *J*=7 Hz), 2.45 (4H, d, *J*=7 Hz), 2.28 (2H, t, *J*=7 Hz), 2.10 (2H, quint, *J*=7 Hz), 1.86 (2H, sept, *J*=7 Hz), 1.24 (3H, t, *J*=7 Hz), 0.93 (12H, d, *J*=7 Hz). A solution of the above ester (118 mg) in ethanol (10 ml) was treated with aqueous 1 N NaOH (2 ml) and the mixture was stirred at room temperature for 15 h. The reaction mixture was acidified with HCl, and extracted with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue which was chromatographed over silica gel (1 : 10 MeOH/$CHCl_3$) to give **1** (79 mg).

4-Ethyl-3-(4-nitrobenzoyl)-1*H*-pyrrole (40b) *p*-Nitrobenzoyl chloride (1.00 g) was added to a stirred suspension of $AlCl_3$ (1.53 g) in CH_2Cl_2 (10 ml) at room temperature and the mixture was stirred for 10 min. A solution of 1-benzenesulfonyl-3-ethyl-1*H*-pyrrole (450 mg) in CH_2Cl_2 (5 ml) was added slowly and the whole was stirred for 1 d. The reaction was quenched with ice-water, and subsequent work-up gave acylated pyrroles including **39b**. This crude material was dissolved in dioxane (5 ml), then 5 N NaOH aqueous solution (5 ml) was added, and the mixture was stirred at 50 °C for 1 d. It was diluted with water, and extracted with ethyl acetate. Usual work-up and purification by silica gel chromatography (1 : 3 EtOAc/hexane) furnished **40b** (71 mg) along with the regio-isomer 3-ethyl-2-(4-nitrobenzoyl)-1*H*-pyrrole (53 mg). **40b**; EI-MS *m/z*: 244 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.42 (1H, br s), 8.29 (2H, d, *J*=8 Hz), 7.88 (2H, d, *J*=8 Hz), 7.05 (1H, br s), 6.69 (1H, br s), 2.88 (2H, q, *J*=7 Hz), 1.25 (3H, t, *J*=7 Hz).

4-Isopropyl-3-(4-nitrobenzoyl)-1*H*-pyrrole (40c) A stirred suspension of 60% NaH (140 mg) in tetrahydrofuran (THF) (20 ml) was cooled to 0 °C under nitrogen. A solution of 4-methyl-1-(4-nitrophenyl)pent-2-en-1-one (**41c**, 640 mg) and TosMIC (570 mg) in THF-dimethylsulfoxide (DMSO) (3 : 1, 12 ml) was added dropwise and the mixture was stirred for 5 min. The reaction mixture was quenched with aqueous NH_4Cl solution containing ice, and extracted twice with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue, which was purified by recrystallization from EtOAc–hexane to afford **40c** (583 mg) as a pale yellow powder, mp 161—165 °C. EI-MS *m/z*: 258 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.43 (1H, br s), 8.29 (2H, d, *J*=9 Hz), 7.89 (2H, d, *J*=9 Hz), 7.03 (1H, dd, *J*=2, 3 Hz), 6.72 (1H, t, *J*=2 Hz), 3.54 (1H, m), 1.27 (6H, d, *J*=7 Hz).

Table 7. Physical Properties, MS and ^{1}H-NMR Data for Pyrrole Butyric Acid Derivatives

Compd.	mp (°C) (Recryst. solv.)	MS *m/z*	^{1}H-NMR δ (ppm)
1[a]	Oil	550 (M^+)	7.72 (2H, d, J=8 Hz), 7.22 (4H, d, J=8 Hz), 7.20—7.05 (2H, m), 7.09 (4H, d, J=8 Hz), 6.58 (1H, br s), 6.52 (2H, d, J=8 Hz), 5.54 (1H, br s), 3.93 (2H, br s), 2.44 (4H, d, J=7 Hz), 2.29 (2H, br s), 2.05 (2H, br s), 1.81 (2H, m), 0.88 (12H, d, J=7 Hz)
2[a]	81—83[e] ($EtOH-H_2O$)	578 (M^+)	7.66 (2H, d, J=8 Hz), 7.22 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 6.92 (1H, br s), 6.52 (2H, d, J=8 Hz), 6.45 (1H, br s), 5.55 (1H, s), 3.87 (2H, t, J=7 Hz), 2.76 (2H, q, J=7 Hz), 2.43 (4H, d, J=7 Hz), 2.31 (2H, t, J=7 Hz), 2.06 (2H, quint, J=7 Hz), 1.82 (2H, m), 1.18 (3H, t, J=7 Hz), 0.91 (12H, d, J=7 Hz)
3[a]	76—80[f] ($EtOH-H_2O$)	592 (M^+)	7.66 (2H, d, J=8 Hz), 7.22 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 6.88 (1H, s), 6.52 (2H, d, J=8 Hz), 6.45 (1H, s), 5.54 (1H, s), 3.88 (2H, t, J=7 Hz), 3.46 (1H, m), 2.45 (4H, d, J=7 Hz), 2.32 (2H, t, J=7 Hz), 2.06 (2H, tt, J=7, 7 Hz), 1.84 (1H, m), 1.18 (6H, d, J=7 Hz)
4[a]	Oil	594 (M^+)	7.65 (2H, d, J=9 Hz), 7.64 (1H, d, J=2 Hz), 7.22 (4H, d, J=8 Hz), 7.18 (1H, d, J=2 Hz), 7.12 (4H, d, J=8 Hz), 6.58 (2H, d, J=9 Hz), 5.58 (1H, s), 4.02 (2H, t, J=7 Hz), 2.46 (4H, d, J=7 Hz), 2.38 (2H, t, J=7 Hz), 2.13 (2H, quint, J=7 Hz), 1.87 (2H, sept, J=7 Hz), 0.89 (12H, d, J=7 Hz)
5[a]	Oil	622 (M^+)	7.66 (2H, d, J=9 Hz), 7.29 (1H, d, J=2 Hz), 7.20 (4H, d, J=8 Hz), 7.09 (4H, d, J=8 Hz), 6.90 (1H, d, J=2 Hz), 6.48 (2H, d, J=9 Hz), 5.55 (1H, s), 4.01—3.93 (4H, m), 2.44 (4H, d, J=7 Hz), 2.35 (2H, t, J=7 Hz), 2.11 (2H, quint, J=7 Hz), 1.83 (2H, sept, J=7 Hz), 0.92 (3H, t, J=7 Hz), 0.88 (12H, d, J=7 Hz)
6[a]	Oil	606 (M^+)	7.66 (2H, d, J=8 Hz), 7.23 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 6.89 (1H, d, J=2 Hz), 6.53 (2H, d, J=8 Hz), 6.45 (1H, d, J=2 Hz), 5.54 (1H, s), 3.81 (2H, t, J=7 Hz), 3.47 (1H, m), 2.45 (4H, d, J=7 Hz), 2.35 (2H, t, J=7 Hz), 1.91—1.74 (4H, m), 1.66—1.55 (2H, m), 1.19 (6H, d, J=7 Hz), 0.89 (12H, d, J=7 Hz)
7[a]	Oil	578 (M^+)	7.65 (2H, d, J=9 Hz), 7.25 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 6.92 (1H, d, J=2 Hz), 6.52 (2H, d, J=9 Hz), 6.47 (1H, d, J=2 Hz), 5.54 (1H, s), 4.12 (2H, t, J=7 Hz), 3.44 (1H, m), 2.80 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 1.84 (2H, m), 1.17 (6H, d, J=7 Hz), 0.89 (12H, d, J=7 Hz)
8[a]	79—81[g] ($EtOH-H_2O$)	578 (M^+)	7.22 (4H, d, J=8 Hz), 7.20—7.05 (2H, m), 7.08 (4H, d, J=8 Hz), 6.98 (1H, br s), 6.84 (1H, br s), 6.63 (1H, br d, J=8 Hz), 6.42 (1H, br s), 5.50 (1H, s), 3.81 (2H, t, J=7 Hz), 2.80 (2H, q, J=7 Hz), 2.42 (4H, d, J=7 Hz), 2.29 (2H, t, J=7 Hz), 2.02 (2H, m), 1.80 (2H, m), 1.18 (3H, t, J=7 Hz), 0.88 (12H, d, J=7 Hz)
9[a]	Oil	592 (M^+)	7.23 (4H, d, J=8 Hz), 7.18—7.03 (2H, m), 7.07 (4H, d, J=8 Hz), 6.97 (1H, br s), 6.84 (1H, d, J=2 Hz), 6.65 (1H, br d, J=8 Hz), 6.43 (1H, d, J=8 Hz), 5.50 (1H, s), 3.85 (2H, t, J=7 Hz), 2.85 (2H, t, J=7 Hz), 2.44 (4H, d, J=7 Hz), 2.30 (2H, t, J=7 Hz), 2.08—1.99 (2H, m), 1.92—1.75 (3H, m), 1.66—1.52 (2H, m), 0.96 (3H, t, J=7 Hz), 0.88 (12H, d, J=7 Hz)
10[a]	70—72[h] ($EtOH-H_2O$)	592 (M^+)	7.22 (4H, d, J=8 Hz), 7.15—7.03 (2H, m), 7.08 (4H, d, J=8 Hz), 6.98 (1H, br s), 6.84 (1H, d, J=2 Hz), 6.64 (1H, br d, J=8 Hz), 6.42 (1H, br s), 5.50 (1H, s), 3.81 (2H, t, J=7 Hz), 3.50 (1H, sept, J=7 Hz), 2.43 (4H, d, J=7 Hz), 2.29 (2H, t, J=7 Hz), 2.04 (2H, quint, J=7 Hz), 1.82 (2H, m), 1.20 (6H, d, J=7 Hz), 0.88 (12H, d, J=7 Hz)
11[a]	Oil	606 (M^+)	7.22 (4H, d, J=8 Hz), 7.15—6.97 (3H, m), 7.08 (4H, d, J=8 Hz), 6.82 (1H, d, J=2 Hz), 6.62 (1H, br d, J=8 Hz), 6.45 (1H, br s), 5.50 (1H, s), 3.80 (2H, t, J=7 Hz), 2.43 (4H, d, J=7 Hz), 2.30 (2H, t, J=7 Hz), 2.03 (2H, quint, J=7 Hz), 1.82 (2H, m), 1.38 (9H, s), 0.87 (12H, d, J=7 Hz)
12[b]	Oil	579 ($[M+H]^+$)	8.70 (1H, br s), 7.52 (2H, d, J=9 Hz), 7.22 (2H, d, J=8 Hz), 7.10 (2H, d, J=8 Hz), 6.51 (2H, d, J=9 Hz), 5.94 (1H, s), 5.56 (1H, s), 2.73 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.32—2.46 (4H, m), 1.75—2.05 (4H, m), 1.03 (3H, t, J=7 Hz), 0.89 (12H, d, J=7 Hz)
13[a]	Oil	578 (M^+)	7.57 (2H, d, J=9 Hz), 7.22 (4H, d, J=8 Hz), 7.12 (4H, d, J=8 Hz), 6.61 (1H, s), 6.54 (2H, d, J=9 Hz), 5.95 (1H, s), 5.55 (1H, d, J=5 Hz), 4.72 (1H, d, J=5 Hz), 2.89 (2H, q, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.42 (2H, t, J=7 Hz), 2.36 (2H, t, J=7 Hz), 1.81—1.90 (4H, m), 1.20 (3H, t, J=7 Hz), 0.90 (12H, d, J=8 Hz)
14[a]	Oil	578 (M^+)	7.68 (2H, d, J=9 Hz), 7.23 (4H, d, J=8 Hz), 7.11 (4H, d, J=8 Hz), 6.73 (1H, d, J=2 Hz), 6.54 (2H, d, J=9 Hz), 6.50 (1H, d, J=2 Hz), 5.55 (1H, s), 4.32 (2H, q, J=7 Hz), 2.49 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.37 (2H, t, J=7 Hz), 1.85 (2H, tt, J=7, 7 Hz), 1.38 (3H, t, J=7 Hz), 0.89 (12H, d, J=7 Hz)
15[a]	Oil	578 (M^+)	8.33 (1H, br s), 7.69 (2H, d, J=9 Hz), 7.22 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 6.52 (2H, d, J=9 Hz), 6.10 (1H, s), 5.54 (1H, s), 2.93 (2H, q, J=7 Hz), 2.59 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.38 (2H, t, J=7 Hz), 2.00—1.75 (4H, m), 1.23 (3H, t, J=7 Hz), 0.89 (12H, d, J=7 Hz)
16[a]	83—85[i] ($EtOH-H_2O$)	592 (M^+)	7.69 (2H, d, J=9 Hz), 7.23 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 6.53 (2H, d, J=9 Hz), 6.08 (1H, s), 5.55 (1H, s), 3.47 (3H, s), 2.95 (2H, q, J=7 Hz), 2.59 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.44 (2H, t, J=7 Hz), 2.01—1.75 (4H, m), 1.20 (3H, t, J=7 Hz), 0.89 (12H, d, J=7 Hz)
17[a]	Oil	592 (M^+)	7.25—7.02 (3H, m), 7.23 (4H, d, J=8 Hz), 7.08 (4H, d, J=8 Hz), 6.62 (1H, d, J=8 Hz), 6.04 (1H, s), 5.51 (1H, s), 3.46 (3H, s), 2.97 (2H, q, J=7 Hz), 2.56 (2H, t, J=7 Hz), 2.43 (4H, d, J=7 Hz), 2.42 (2H, t, J=7 Hz), 1.93—1.75 (4H, m), 1.18 (3H, t, J=7 Hz), 0.88 (12H, d, J=7 Hz)
18[c]	Oil	393 ($[M+H]^+$)	7.15 (1H, t, J=8 Hz), 6.83—6.65 (3H, m), 5.92 (1H, s), 5.78 (1H, t, J=5 Hz), 3.48 (3H, s), 3.04—2.85 (4H, m), 2.54 (2H, m), 1.91 (2H, t, J=7 Hz), 1.72—1.30 (6H, m), 1.10 (3H, t, J=7 Hz), 0.91 (3H, t, J=7 Hz)

Table 7. (continued)

Compd.	mp (°C) (Recryst. solv.)	MS *m/z*	^{1}H-NMR δ (ppm)
19[c]	Oil	421 ($[M+H]^+$)	7.13 (1H, t, J=7 Hz), 6.83 (1H, s), 6.78 (1H, d, J=7 Hz), 6.68 (1H, d, J=7 Hz), 5.91 (1H, s), 3.48 (3H, s), 2.99 (2H, t, J=7 Hz), 2.91 (2H, q, J=7 Hz), 2.46 (2H, t, J=7 Hz), 1.90 (2H, t, J=7 Hz), 1.70—1.22 (10H, m), 1.10 (3H, t, J=7 Hz), 0.87 (3H, t, J=7 Hz)
20[c]	Oil	435 ($[M+H]^+$)	7.13 (1H, t, J=7 Hz), 6.82 (1H, s), 6.78 (1H, d, J=7 Hz), 6.68 (1H, d, J=7 Hz), 5.91 (1H, s), 3.48 (3H, s), 2.98 (2H, t, J=7 Hz), 2.91 (2H, q, J=7 Hz), 2.47 (2H, t, J=8 Hz), 1.91 (2H, t, J=7 Hz), 1.70—1.21 (12H, m), 1.10 (3H, t, J=7 Hz), 0.86 (3H, t, J=7 Hz)
21[c]	Oil	449 ($[M+H]^+$)	7.13 (1H, t, J=7 Hz), 6.82 (1H, s), 6.78 (1H, d, J=7 Hz), 6.68 (1H, d, J=7 Hz), 5.91 (1H, s), 3.48 (3H, s), 2.98 (2H, t, J=7 Hz), 2.91 (2H, q, J=7 Hz), 2.50 (2H, t, J=7 Hz), 1.91 (2H, t, J=7 Hz), 1.72—1.18 (14H, m), 1.10 (3H, t, J=7 Hz), 0.85 (3H, t, J=7 Hz)
22[c]	Oil	450 ($[M+H]^+$)	7.60 (2H, d, J=9 Hz), 6.76 (2H, d, J=9 Hz), 6.03 (1H, s), 3.88 (2H, t, J=7 Hz), 3.17 (3H, s), 2.56 (2H, q-like), 2.24 (2H, t-like), 2.08 (2H, t-like), 1.93—1.20 (14H, m), 0.95 (3H, t, J=7 Hz), 0.87 (6H, d, J=7 Hz)
23[c]	Oil	450 ($[M+H]^+$)	7.37 (1H, t, J=8 Hz), 7.20 (1H, d, J=7 Hz), 7.12 (1H, br s), 7.07(1H, dd, J=8, 3 Hz), 5.89 (1H, s), 3.99 (2H, t, J=7 Hz), 3.50 (3H, s), 2.93 (2H, q, J=7 Hz), 2.48 (2H, t, J=8 Hz), 1.91 (2H, t, J=7 Hz), 1.76—1.58 (4H, m), 1.48—1.20 (10H, m), 1.11 (3H, t, J=7 Hz), 0.86 (3H, t, J=7 Hz)
24[c]	Oil	473 ($[M+H]^+$)	7.14 (1H, t, J=8 Hz), 6.84 (1H, s), 6.80 (1H, d, J=8 Hz), 6.68 (1H, d, J=8 Hz), 5.91 (1H, s), 5.24 (1H, t-like), 5.07 (1H, t-like), 3.63 (2H, t-like), 3.48 (3H, s), 2.91 (2H, q, J=7 Hz), 2.46 (2H, t, J=7 Hz), 2.10—1.56 (8H, m), 1.67 (3H, s), 1.61 (3H, s), 1.55 (3H, s), 1.10 (3H, t, J=7 Hz)
25[c]	Oil	473 ($[M+H]^+$)	7.53 (2H, d, J=9 Hz), 6.53 (2H, d, J=9 Hz), 5.90 (1H, s), 5.25 (1H, t-like), 5.08 (1H, t-like), 3.67 (2H, d, J=6 Hz), 3.46 (3H, s), 2.85 (2H, q, J=7 Hz), 2.47 (2H, t, J=7 Hz), 2.10—1.90 (6H, m), 1.77—1.56 (2H, m), 1.68 (3H, s), 1.62 (3H, s), 1.56 (3H, s), 1.09 (3H, t, J=7 Hz)
26[c]	Oil	477 ($[M+H]^+$)	7.10 (1H, t, J=8 Hz), 6.82 (1H, br s), 6.77 (1H, d, J=8 Hz), 6.68 (1H, br d, J=8 Hz), 5.90 (1H, s), 3.48 (3H, s), 3.31 (2H, d, J=8 Hz), 2.97—2.88 (4H, m), 2.47 (2H, t, J=8 Hz), 1.89 (2H, t, J=8 Hz), 1.70—1.22 (16H, m), 1.10 (3H, t , J=8 Hz), 0.83 (6H, br t, J=8 Hz)
27[c]	Oil[j]	533 ($[M+H]^+$)	7.12 (1H, t, J=7 Hz), 6.86 (1H, d, J=2 Hz), 6.77 (1H, d, J=8 Hz), 6.68 (1H, dd, J=8, 2 Hz), 5.92 (1H, s), 6.64 (1H, t, J=8 Hz), 3.49 (3H, s), 2.95—2.88 (4H, m), 2.48 (2H, t, J=7 Hz), 1.92 (2H, t, J=7 Hz), 1.66 (2H, quint, J=7 Hz), 1.62—1.55 (1H, m), 1.37—1.22 (20H, m), 1.11 (3H, t, J=7 Hz), 0.85 (6H, t, J=7 Hz)
28[c]	Oil	547 ($[M+H]^+$)	7.12 (1H, t, J=8 Hz), 6.82 (1H, br s), 6.77 (1H, d, J=8 Hz), 6.68 (1H, br d, J=8 Hz), 5.90 (1H, s), 5.73 (1H, br s), 3.48 (3H, s), 3.03—2.86 (4H, m), 2.46 (2H, t, J=8 Hz), 1.88 (2H, t, J=8 Hz), 1.70—1.42 (3H, m), 1.31—1.21 (22H, m), 1.10 (3H, t , J=8 Hz), 0.85 (6H, t, J=8 Hz)
29[c]	Oil	573 ($[M+H]^+$)	7.27—7.07 (11H, m), 6.89 (1H, s), 6.78 (1H, d, J=9 Hz), 6.69 (1H, d, J=9 Hz), 5.92 (1H, s), 3.48 (3H, s), 3.28 (2H, s), 3.10—2.85 (4H, m), 2.60 (4H, t, J=7 Hz), 2.50—2.40 (2H, m), 1.88 (2H, t, J=7 Hz), 1.75—1.58 (6H, m), 1.10 (3H, t, J=7 Hz)
30[c]	Oil	601 ($[M+H]^+$)	7.12 (1H, t, J=8 Hz), 7.05 (8H, s), 6.88 (1H, s), 6.77 (1H, d, J=8 Hz), 6.70 (1H, d, J=8 Hz), 5.91 (1H, s), 5.84 (1H, t-like), 3.48 (3H, s), 3.03 (2H, m), 2.91 (2H, q, J=7 Hz), 2.55 (4H, t, J=7 Hz), 2.46 (2H, t, J=7 Hz), 2.24 (6H, s), 1.90 (2H, t, J=7 Hz), 1.73—1.58 (7H, m), 1.10 (3H, t, J=7 Hz)
31[c]	Oil	632 ($[M+H]^+$)	7.12 (1H, t, J=8 Hz), 7.09 (4H, d, J=8 Hz), 6.89 (1H, s), 6.80 (4H, d, J=8 Hz), 6.78 (1H, br s), 6.69 (1H, d, J=8 Hz), 5.92 (1H, s), 3.70 (6H, s), 3.47 (3H, s), 3.02 (2H, m), 2.91 (2H, q, J=7 Hz), 2.57—2.42 (6H, m), 1.90 (2H, t, J=7 Hz), 1.73—1.57 (7H, m), 1.10 (3H, t, J=7 Hz)
32[c]	Oil	640 ($[M+H]^+$)	7.31—7.12 (9H, m), 6.89 (1H, s), 6.79 (1H, d, J=8 Hz), 6.67 (1H, d, J=8 Hz), 5.90 (2H, m), 3.48 (3H, s), 3.10 (2H, s), 3.05 (2H, br s), 2.91 (2H, q, J=9 Hz), 2.60 (4H, m), 2.46 (2H, t, J=7 Hz), 1.90 (2H, t, J=7 Hz), 1.76—1.55 (6H, m), 1.10 (3H, t, J=9 Hz)
33[a]	Oil	582 (M^+)	7.17 (1H, t, J=8 Hz), 7.02 (1H, d, J=8 Hz), 6.96 (1H, s), 6.93 (4H, d, J=8 Hz), 6.71 (4H, d, J=8 Hz), 6.65 (1H, d, J=8 Hz), 6.10 (1H, s), 3.48 (3H, s), 3.10 (2H, br s), 3.04—2.85 (2H, m), 2.59 (6H, br s), 2.34 (1H, t, J=7 Hz), 1.90 (2H, quint, J=7 Hz), 1.80—1.60 (5H, m), 1.23 (3H, t, J=9 Hz)
34[c]	Oil	601 ($[M+H]^+$)	7.30—7.10 (11H, m), 6.85 (1H, s), 6.78 (1H, d, J=8 Hz), 6.69 (1H, d, J=8 Hz), 5.92 (1H, s), 5.79 (1H, t-like), 3.46 (3H, s), 2.98—2.87 (4H, m), 2.67—2.42 (6H, m), 1.97 (2H, t, J=7 Hz), 1.72—1.21 (11H, m), 1.10 (3H, t, J=7 Hz)
35[c]	Oil	629 ($[M+H]^+$)	7.13 (1H, t, J=8 Hz), 7.03 (8H, s), 6.84 (1H, s), 6.77 (1H, d, J=8 Hz), 6.67 (1H, d, J=8 Hz), 5.91 (1H, s), 5.77 (1H, t-like), 3.47 (3H, s), 2.92—2.83 (4H, m), 2.53—2.41 (6H, m), 2.24 (6H, s), 1.90 (2H, t, J=7 Hz), 1.70—1.20 (11H, m), 1.10 (3H, t, J=7 Hz)
36[c]	Oil	564 ($[M+H]^+$)	7.28—7.06 (11H, m), 6.82 (1H, br s), 6.73—6.65 (2H, m), 5.88 (1H, s), 5.55 (1H, d, J=8 Hz), 3.46 (3H, s), 3.39—3.31 (3H, m), 2.92 (2H, q, J=7 Hz), 2.58—2.42 (4H, m), 1.90 (2H, t, J=7 Hz), 1.71—1.40 (12H, m), 1.10 (3H, t, J=7 Hz)
37[d]	225—235[k] (H_2O)	1060 ($[M+H]^+$)	7.14 (1H, t, J=8 Hz), 6.88 (1H, d, J=2 Hz), 6.86 (1H, d, J=8 Hz), 6.74 (1H, dd, J=8, 2 Hz), 6.06 (1H, s), 3.52 (3H, s), 2.99 (2H, d, J=7 Hz), 2.99 (2H, q, J=7 Hz), 2.57 (2H, t, J=7 Hz), 2.24 (2H, t, J=7 Hz), 1.86 (2H, quint, J=7 Hz), 1.70—1.58 (1H, m), 1.42—1.22 (20H, m), 1.17 (3H, t, J=7 Hz), 0.87 (6H, t, J=7 Hz)

a) Mass spectra were measured by the EI method and ^{1}H-NMR spectra were taken in $CDCl_3$ solution. *b*) Data from FAB-MS and ^{1}H-NMR spectra in $CDCl_3$. *c*) Data from FAB-MS and ^{1}H-NMR spectra in DMSO-d_6. *d*) Data from FAB-MS and ^{1}H-NMR spectra in CD_3OD_3. *e*) A colorless powder. *Anal.* Calcd for $C_{38}H_{46}N_2O_3 \cdot 1/4H_2O$: C, 78.25; H, 8.03; N, 4.80. Found: C, 78.45; H, 8.08; N, 4.65. *f*) A colorless powder. *Anal.* Calcd for $C_{39}H_{48}N_2O_3 \cdot 1/4H_2O$: C, 78.42; H, 8.18; N, 4.69. Found: C, 78.35; H, 8.30; N, 4.75. *g*) A colorless powder. *Anal.* Calcd for $C_{38}H_{46}N_2O_3$: C, 78.86; H, 8.01; N, 4.84. Found: C, 78.98; H, 8.11; N, 4.78. *h*) A pale yellow powder. *Anal.* Calcd for $C_{39}H_{48}N_2O_3 \cdot 1/4H_2O$: C, 78.42; H, 8.18; N, 4.69. Found: C, 78.27; H, 8.13; N, 4.60. *i*) A pale yellow powder. *Anal.* Calcd for $C_{39}H_{48}N_2O_3$: C, 79.02; H, 8.16; N, 4.73. Found: C, 78.81; H, 8.23; N, 4.64. *j*) *Anal.* Calcd for $C_{32}H_{49}N_2O_3Na \cdot H_2O$: C, 69.79; H, 9.33; N, 5.09. Found: C, 69.87; H, 9.27; N, 5.13. *k*) A colorless powder. *Anal.* Calcd for $C_{64}H_{98}N_4O_6Ca \cdot 1/2H_2O$: C, 71.94; H, 9.33; N, 5.24. Found: C, 71.95; H, 9.49; N, 5.27.

Ethyl 4-(1*H*-Pyrrol-2-yl)-4-oxobutyrate (44) Ethyl succinyl chloride (9.05 g) was added to a stirred suspension of $AlCl_3$ (8.0 g) in CH_2Cl_2 (100 ml) at room temperature and the mixture was stirred for 10 min, then cooled to 0 °C. A solution of pyrrole (3.35 g) in CH_2Cl_2 (50 ml) was added slowly. After additional stirring for 1 h, usual work-up and purification by silica gel chromatography (1 : 3 EtOAc/hexane) furnished **44** (4.71 g) and 1.47 g of ethyl 4-(1*H*-pyrrole-3-yl)-4-oxobutyrate. **44**: EI-MS *m/z*: 195 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.81 (1H, br s), 7.04 (1H, m), 6.98 (1H, m), 6.28 (1H, m), 4.15 (2H, q, J=7 Hz), 3.15 (2H, t, J=7 Hz), 2.73 (2H, t, J=7 Hz), 1.25 (3H, t, J=7 Hz).

Ethyl 4-(4-Acetyl-1*H*-pyrrol-2-yl)-4-oxobutyrate (45) A suspension of $AlCl_3$ (13.7 g) in CH_2Cl_2 was treated with acetyl chloride (7.3 ml) at room temperature and the mixture was stirred for 30 min. A solution of **44** (2.0 g) in CH_2Cl_2 was added slowly and the whole was stirred for 1 h. The reaction was quenched with ice-water, and usual work-up and purification by silica gel chromatography (1 : 1 EtOAc/hexane) furnished **45** (2.16 g). EI-MS *m/z*: 237 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.84 (1H, s), 7.63 (1H, d, J=1 Hz), 7.40 (1H, d, J=1 Hz), 4.15 (2H, q, J=7 Hz), 3.16 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 2.47 (3H, s), 1.25 (3H, t, J=7 Hz).

Ethyl 4-(4-Ethyl-1*H*-pyrrol-2-yl) butyrate (46) *tert*-Butylamine-borane complex (7.34 g) and a trace of methanol was added to a stirred solution of **45** (1.0 g) in toluene (80 ml). The resulting mixture was stirred at 100 °C overnight, then cooled and quenched with ice-water. Usual work-up and purification by silica gel chromatography (1 : 8 EtOAc/hexane) furnished **46** (408 mg). FAB-MS *m/z*: 210 ($[M+H]^+$). ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, s), 6.44 (1H, s), 5.81 (1H, s), 4.13 (2H, q, J=7 Hz), 2.61 (2H, t, J=7 Hz), 2.47 (2H, q, J=7 Hz), 2.35 (2H, t, J=7 Hz), 1.93 (2H, tt, J=7 Hz), 1.26 (3H, t, J=7 Hz), 1.18 (3H, t, J=7 Hz).

Ethyl 4-[5-(4-Nitrobenzoyl)-4-ethyl-1*H*-pyrrol-2-yl]butyrate (47) A solution of **46** (200 mg) in $CHCl_3$ (1 ml) was added to a suspension of *p*-nitrobenzoyl chloride (222 mg) and potassium carbonate (661 mg) in $CHCl_3$ (2 ml) at 50 °C. The resultant mixture was stirred at 50 °C for 2 h, then cooled to room temperature, and the precipitates were filtered off. The filtrate was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue, which was chromatographed over silica gel (1 : 3 EtOAc/hexane) to furnish **47** (123 mg). EI-MS *m/z*: 358 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.18 (1H, br s), 8.32 (2H, d, J=9 Hz), 7.77 (2H, d, J=9 Hz), 6.02 (1H, d, J=7 Hz), 4.15 (2H, q, J=7 Hz), 2.69 (2H, t, J=7 Hz), 2.37 (2H, t, J=7 Hz), 2.24 (2H, q, J=7 Hz), 2.00 (2H, tt, J=7 Hz), 1.27 (3H, t, J=7 Hz), 1.03 (3H, t, J=7 Hz).

Ethyl 4-(1*H*-Pyrrol-3-yl)-4-oxobutyrate (49) Ethyl 4-[1-(phenylsulfonyl)pyrrole-3-yl)-4-oxobutyrate (**48**) was prepared from pyrrole by a literature procedure.[12] A stirred solution of **48** (2.5 g) in EtOH (30 ml) was treated with sodium ethoxide and the mixture was stirred for 1 d. The reaction was quenched with ice-water and ammonium chloride, and the whole was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave **49** (1.38 g). EI-MS *m/z*: 195 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.88 (1H, br s), 7.44 (1H. s). 6.77 (1H, s), 6.67 (1H, s), 4.15 (2H, q, J=7 Hz), 3.12 (2H, t, J=7 Hz), 2.72 (2H, t, J=7 Hz), 1.23 (3H, t, J=7 Hz).

Ethyl 4-(5-Acetyl-1*H*-pyrrol-3-yl)-4-oxobutyrate (50) Essentially the same procedure described above for the preparation of **45** afforded **50** from **49**. EI-MS *m/z*: 237 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.70 (1H, br s), 7.68 (1H, m), 7.36 (1H, s), 4.16 (2H, q, J=7 Hz), 3.14 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 2.49 (3H, s), 1.27 (3H, t, J=7 Hz).

Ethyl 4-(5-Ethyl-1*H*-pyrrol-3-yl)butyrate (51) Essentially the same procedure as described above for the preparation of **46** afforded **51** from **50**. EI-MS *m/z*: 209 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, br s), 6.44 (1H, s), 5.78 (1H, s), 4.12 (2H, q, J=7 Hz), 2.59 (2H, q, J=7 Hz), 2.4 (2H, t, J=7 Hz), 2.34 (2H, t, J=7 Hz), 1.89 (2H, tt, J=7, 7 Hz), 1.25 (3H, t, J=7 Hz), 1.22 (3H, t, J=7 Hz).

Ethyl 4-[1-(4-Nitrobenzoyl)-5-ethyl-1*H*-pyrrol-3-yl]butyrate (52) A solution of **51** (100 mg) in THF (1 ml) was added to a suspension of 60% NaH (29 mg) in THF (1 ml) at room temperature. The resultant mixture was stirred at room temperature for 15 min and then a solution of *p*-nitrobenzoyl chloride (175 mg) in THF (2 ml) was added. The whole was stirred for an additional 15 min and quenched with ice-water. Usual work-up and purification by silica gel chromatography (1 : 8 EtOAc/hexane) furnished **52** (84 mg). EI-MS *m/z*: 358 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.34 (2H, d, J=9 Hz), 7.85 (2H, d, J=9 Hz), 6.93 (1H, s), 6.84 (1H, s), 4.11 (2H, q, J=7 Hz), 2.98 (2H, q, J=7 Hz), 2.39 (2H, t, J=7 Hz), 2.30 (2H, t, J=7 Hz), 1.84 (2H, quint, J=7 Hz), 1.27 (3H, t, J=7 Hz), 1.24 (3H, t, J=7 Hz).

2-(4-Nitrobenzoyl)-1*H*-pyrrole (53) A solution of pyrrole (1.8 g) and 2,6-lutidine (3.15 g) in $CHCl_3$ (14 ml) was added dropwise to a refluxing solution of *p*-nitrobenzoyl chloride (5.47 g) in $CHCl_3$ (14 ml) over a period of 30 min. The resulting mixture was stirred at reflux for an additional 1.5 h. The mixture was cooled to room temperature and quenched with ice-water. Usual work-up afforded **53** (1.27 g). EI-MS *m/z*: 216 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.50 (1H, br s), 8.36 (2H, d, J=8 Hz), 8.03 (2H, d, J=8 Hz), 7.22 (1H, m), 6.87 (1H, m), 6.40 (1H, m).

2-(4-Nitrobenzoyl)-1*H*-pyrrole-4-carboxaldehyde (54) $TiCl_4$ (3.0 ml) was added slowly to a stirred solution of **53** (1.2 g) and dichloromethyl methyl ether (2.5 ml) in CH_2Cl_2 (20 ml) cooled to 0 °C and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with ice-water, and usual work-up and purification by silica gel chromatography (1 : 2 EtOAc/hexane) furnished **54** (252 mg) and the starting material (550 mg). EI-MS *m/z*: 244 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.85 (1H, s), 8.38 (2H, d, J=9 Hz), 8.04 (2H, d, J=9 Hz), 7.80 (1H, d, J=1 Hz), 7.26 (1H, d, J=1 Hz).

1-Ethyl-5-(4-nitrobenzoyl)-1*H*-pyrrole-3-carboxaldehyde (55) A solution of **54** (250 mg) in DMF (4 ml) at room temperature was treated with K_2CO_3 (283 mg) and ethyl iodide (0.12 ml). The resultant mixture was stirred at room temperature for 2 h. The reaction was quenched with ice-water and extracted with EtOAc. Usual work-up and purification by silica gel chromatography (1 : 2 EtOAc/hexane) furnished **55** (260 mg). EI-MS *m/z*: 272 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.80 (1H, s), 8.35 (2H, d, J=9 Hz), 7.95 (2H, d, J=9 Hz), 7.67 (1H, d, J=2 Hz), 7.14 (1H, d, J=2 Hz), 4.52 (2H, q, J=7 Hz), 1.54 (3H, t, J=7 Hz).

4-[1-Ethyl-5-(4-nitrobenzoyl)-1*H*-pyrrol-3-yl]-butyric Acid (56) A solution of 1.6 N *n*-BuLi in hexane (0.55 ml) was added dropwise to a suspension of [3-(tetrahydropyran-2-yloxy)propyl]triphenylphosphonium bromide (454 mg) in THF (2.5 ml) at 0 °C. The mixture was stirred at this temperature for 30 min and then a solution of **55** (84 mg) in THF (2.0 ml) was added. Stirring was continued for 30 min at room temperature, then usual work-up and purification by silica gel chromatography (1 : 5 EtOAc/hexane) furnished 1-ethyl-5-(4-nitrobenzoyl)-3-(4-tetrahydropyranyloxy-1-butenyl)-1*H*-pyrrole (104 mg). To a solution of this intermediate (104 mg) in MeOH (10 ml) was added *p*-TsOH (10 mg), and the mixture was stirred at room temperature overnight. The reaction was quenched with water, and the whole was extracted with EtOAc. Usual work-up and purification by silica gel chromatography (1 : 2 EtOAc/hexane) furnished 1-ethyl-5-(4-nitrobenzoyl)-3-(4-hydroxy-1-butenyl)-1*H*-pyrrole (73 mg). A solution of the deprotected alcohol (70 mg) in CH_2Cl_2 (1 ml) was treated with triethylsilane (0.11 ml) and trifluoroacetic acid (TFA) (0.3 ml), and the mixture was stirred at room temperature overnight. The reaction was quenched with ice-water and usual work-up gave the crude silyl ether, which was dissolved in THF (3 ml) and treated with tetrabutyl ammonium fluoride. After having been stirred for 1 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was chromatographed over silica gel (2 : 1 ethyl acetate/hexane) to furnish 4-[1-ethyl-5-(4-nitrobenzoyl)-1*H*-pyrrole-3-yl] butanol (73 mg). The obtained pyrrolylbutanol (65 mg) was oxidized with Jones reagent in acetone and the crude product was chromatographed over silica gel (20 : 1 $CHCl_3$/MeOH) to furnish **56** (16 mg). EI-MS *m/z*: 330 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.31 (2H, d, J=9 Hz), 7.89 (2H, d, J=9 Hz), 6.90 (1H, d, J=2 Hz), 6.49 (1H, d, J=2 Hz), 4.41 (2H, q, J=7 Hz), 2.50 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 1.88 (2H, tt, J=7, 7 Hz), 1.45 (3H, t, J=7 Hz).

5-Ethyl-4-(4-nitrobenzoyl)-1*H*-pyrrole-2-carboxaldehyde (57) A solution of oxalyl chloride (5.1 ml) in CH_2Cl_2 (10 ml) was added to a cooled solution of DMF (4.27 g) in CH_2Cl_2 (10 ml) at 0 °C over a period of 20 min. The suspension of white solid thus obtained was stirred at room temperature for 15 min. The suspension was cooled in an ice bath and a solution of 2-ethylpyrrole (5.0 g) in CH_2Cl_2 (7 ml) was added over 20 min. The light orange solution obtained was stirred for 15 min at room temperature. *p*-Nitrobenzoyl chloride (10.8 g) in CH_2Cl_2 (40 ml) was added to a suspension of $AlCl_3$ (15.6 g) in CH_2Cl_2 (40 ml), and the mixture was stirred at room temperature for 30 min. Then the Vilsmeier complex prepared above was added. The reaction mixture was stirred at room temperature for 3 h, then poured into ice-water, and the whole was stirred overnight. The precipitates were collected and washed with aqueous 5% NaOH, water and diethyl ether to yield **57** (10.4 g). A pale yellow powder, mp 202—204 °C. EI-MS *m/z*: 272 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.41 (1H, s), 8.36 (2H, d, J=8 Hz), 7.93 (2H, d, J=8 Hz), 7.08 (1H, s), 3.12 (2H, q, J=8 Hz), 1.37 (3H, t, J=8 Hz).

5-Ethyl-1-methyl-4-(4-nitrobenzoyl)-1*H*-pyrrole-2-carboxaldehyde (58)

A solution of **57** (6.7 g) in DMF (100 ml) was treated with K_2CO_3 (5.1 g) and methyl iodide (3.1 ml). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (300 ml), then filtered. The filtrate was washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave a crude solid, which was recrystallized from diisopropyl ether to furnish **58** (6.0 g). A colorless powder, mp 144—145 °C. EI-MS *m/z*: 286 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.50 (1H, s), 8.34 (2H, d, J=9 Hz), 7.91 (2H, d, J=9 Hz), 7.00 (1H, s), 4.01 (3H, s), 3.11 (2H, q, J=8 Hz), 1.30 (3H, t, J=8 Hz).

Ethyl 4-[5-Ethyl-1-methyl-4-(4-nitrobenzoyl)-1*H*-pyrrol-2-yl]crotonate (59) A solution of potassium *tert*-butoxide (4.7 g) in THF (30 ml) was added to a cooled suspension of methoxymethyltriphenylphosphonium chloride (14.4 g) in THF (60 ml) at 0 °C over 20 min. Stirring was continued for another 20 min, then a solution of **58** (3.0 g) in THF (50 ml) was added dropwise during 15 min. Stirring was continued for 20 min at room temperature, the mixture was poured into ice-water, and the whole was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a crude enol ether. This crude product was dissolved in THF (36 ml) and 4 N HCl-dioxane (36 ml) was added. After having been stirred for 30 min, the reaction mixture was poured into ice-water, and neutralized with aqueous saturated $NaHCO_3$. The mixture was extracted with ethyl acetate, and the extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a crude aldehyde. This crude aldehyde was dissolved in DMF (30 ml) and (carboethoxymethylene)triphenylphosphorane (2.6 g) was added to the solution. After stirring for 90 min at room temperature, the mixture was poured into ice-water, and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue, which was chromatographed over silica gel (1 : 2 EtOAc/hexane) to furnish **59** (1.5 g). A pale yellow powder, mp 107—108 °C (EtOAc). EI-MS *m/z*: 370 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.29 (2H, d, J=9 Hz), 7.88 (2H, d, J=9 Hz), 7.01 (1H, dt, J=16, 6 Hz), 6.02 (1H, s), 5.77 (1H, d, J=16 Hz), 4.19 (2H, q, J=7 Hz), 3.49 (3H, s), 3.47 (2H, d, J=7 Hz), 3.06 (2H, q, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.25 (3H, t, J=7 Hz).

Ethyl 4-[4-(4-Aminobenzoyl)-5-ethyl-1-methyl-1*H*-pyrrol-2-yl]butyrate (60) Compound **59** (1.48 g) was hydrogenated in the same manner as described for compound **43a** to give **60** (1.37 g). EI-MS *m/z*: 342 (M^+). ^{1}H-NMR (CDCl3) δ: 7.71 (2H, d, J=9 Hz), 6.66 (2H, d, J=9 Hz), 6.12 (1H, s), 4.12 (2H, q, J=7 Hz), 3.48 (3H, s), 2.97 (2H, q, J=7 Hz), 2.60 (2H, t, J=7 Hz), 2.38(2H, t, J=7 Hz), 1.93 (2H, quint, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.25 (3H, t, J=7 Hz).

Ethyl 4-[4-(3-aminobenzoyl)-5-ethyl-1-methyl-1*H*-pyrrol-2-yl]butyrate (61) Compound **61** was prepared in the same manner as described for compound **60**. EI-MS *m/z*: 342 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.19 (1H, t, J=8 Hz), 7.15 (1H, br d, J=8 Hz), 7.09 (1H, br s), 6.80 (1H, dd, J=8, 2 Hz), 6.10 (1H, s), 4.11 (2H, q, J=7 Hz), 3.74 (2H, br s), 3.50 (3H, s), 3.01 (2H, q, J=7 Hz), 2.58 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 1.92 (2H, quint, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.22 (3H, t, J=7 Hz).

Ethyl 4-[5-Ethyl-4-[3-(2-hexyloctylamino)benzoyl]-1-methyl-1*H*-pyrrol-2-yl] butyrate (62) A solution of **61** (14.6 g), *N,N*-diisopropylethylamine (11.04 g), and benzyloxycarbonyl chloride (10.94 g) in CH_2Cl_2 (200 ml) was stirred at room temperature for 1.5 h. Usual work-up furnished 20.3 g of the Z-amide. To a solution of this Z-amide (564 mg) and 7-bromomethyltridecane (**65**, 656 mg) in DMF (8 ml) was slowly added 60% NaH (95 mg), and the mixture was stirred at room temperature for 1 d. The reaction was quenched with ice-water, and usual work-up and purification by silica gel chromatography (1 : 5 EtOAc/hexane) furnished the *N*-alkylated Z-amide (490 mg). A mixture of the above intermediate (374 mg) in ethanol (15 ml) and 10% Pd-C (100 mg) was hydrogenated routinely to give **62** (272 mg). EI-MS *m/z*: 538 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.20 (1H, t, J=7 Hz), 7.07 (1H, d, J=8 Hz), 7.01 (1H, t, J=2 Hz), 6.72 (1H, dd, J=8, 2 Hz), 6.13 (1H, s), 4.13 (2H, q, J=7 Hz), 3.72 (1H, br s), 3.52 (3H, s), 3.05 (2H, t, J=7 Hz), 3.02 (2H, q, J=7 Hz), 2.58 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 1.92 (2H, quint, J=7 Hz), 1.62 (1H, br s), 1.37—1.20 (26H, m), 0.93 (6H, t, J=7 Hz).

Reductive Alkylation of **61**: A cooled stirred solution of **61** (13.0 g) and **63** (16.1 g) in THF was treated with 1 M borane-THF complex (42 ml) under a nitrogen atmosphere. The reaction mixture was stirred overnight, poured into ice-water and extracted twice with ethyl acetate. Usual work-up gave **62** (17.4 g).

2-Hexyloctanal (63) A solution of potassium *tert*-butoxide (90.4 g) in THF (200 ml) was added to a cooled suspension of methoxymethyltriphenylphosphonium chloride (276 g) in THF (400 ml) at 0 °C over a period of 10 min under a nitrogen atmosphere, and the mixture was stirred for a further 30 min. The resultant phosphorane solution was dropped into a cooled stirred solution of 7-tridecanone (100 g) in THF (400 ml) over 30 min under nitrogen. Stirring was continued for 1 h at room temperature, then work-up gave a crude enol ether. The enol ether was dissolved in THF (700 ml) and treated with 4 N HCl-dioxane (630 ml) to furnish the crude aldehyde, which was distilled *in vacuo* (97—102 °C, 0.2 mmHg) to give **63** (99.1 g). EI-MS *m/z*: 212 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.55 (1H, d, J=3 Hz), 2.28—2.17 (1H, m), 1.68—1.27 (20H, m), 0.88 (6H, t, J=7 Hz).

2-Hexyloctanol (64) **63** (5.02 g) in methanol (100 ml) was treated with $NaBH_4$ (894 mg) in a usual manner to afford **64** (4.85 g). EI-MS *m/z*: 214 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.53 (2H, d, J=5 Hz), 1.49—1.40 (1H, m), 1.40—1.21 (20H, m), 0.88 (6H, t, J=7 Hz).

7-Bromomethyltridecane (65) A cooled solution of **64** (4.85 g) and CBr_4 (14.9 g) in THF (50 ml), was treated with Ph_3P (11.8 g), with stirring. Stirring was continued for 30 min at room temperature, then the mixture was concentrated *in vacuo*. Removal of triphenylphosphine oxide by silica gel column chromatography gave the crude bromide, which was purified by distillation under reduced pressure (0.15 mmHg). The fraction that was distilled at 106—109 °C gave **65** (4.34 g). EI-MS *m/z*: 278, 276 (M^+). ^{1}H-NMR (CDCl3) δ: 3.45 (2H, d, J=5 Hz), 1.62—1.56 (1H, m), 1.43—1.24 (20H, m), 0.89 (6H, t, J=7 Hz).

4-[5-Ethyl-4-[3-(2-hexyloctylamino)-benzoyl]-1-methyl-1*H*-pyrrol-2-yl]-butyric Acid Calcium Salt (37) An aqueous solution of **27** (18 g/400 ml) was added dropwise to a stirred aqueous solution of calcium chloride (3.9 g/300 ml), and the whole was stirred for 2 d. The resultant precipitate was collected, washed well with water and dried to give **37** (15.3 g, 84%)

Biology. Inhibitory Effects on Rat Prostatic Steroid 5α-Reductase *in Vitro* Rat prostatic nuclear fraction was prepared from 9-week-old male SD: Crj rats according to Moore and Wilson[13] and used as rat prostatic steroid 5α-reductase. Samples were dissolved in EtOH (2 μl) and incubated for 15 min at 37 °C with 100 μl of 40 mM potassium phosphate buffer (pH 6.5) containing 1 mM dithiothreitol, 1 mM NADPH, 1 μM ^{14}C-testosterone and prostatic nuclear fraction. The enzyme reaction was quenched by extraction with 500 μl of $CHCl_3$ and MeOH (2 : 1) containing 30 μg of cold DHT. The layers were separated by centrifugation at 14000 rpm and the organic layer was evaporated to dryness. The residue was dissolved in 25 μl of CH_2Cl_2 and subjected to silica gel TLC (Kiesel gel 60F_{254}, Merck) with cyclohexane/EtOAc (1 : 1) as a developing solvent. The spot corresponding to DHT was visualized with iodine vapor and radioactivity in the spot was measured with a liquid scintillation counter (LSA-2500T, Hewlett Packard). Steroid 5α-reductase activity was expressed as pmol of DHT formed/min/mg of protein.

Inhibitory Effects on Human Steroid 5α-Reductase *in Vitro* Human genital skin fibroblast cell line Hs27(ATCC/CRL1634) was obtained from American Type Culture Collection and cultured in Dulbecco's modified MEM containing 10% heat-inactivated fetal bovine serum, 100 unit/ml of penicillin and 100 μg/ml of streptomycin. When cells reached confluence, the cell monolayer was washed 3 times with PBS(−) and cells were released from the culture flask by using 0.2% trypsin and 0.02% EDTA. The cells were collected by centrifugation and washed 3 times with PBS(−). The cell pellet was suspended in 10 mM Tris–HCl buffer pH7.4 containing 1 mM EDTA, homogenized in a Teflon homogenizer and sonicated for 30 s. The cell homogenate was stored at −80 °C until use.

Samples were dissolved in EtOH (2 μl) and incubated for 30 min at 37 °C with 100 μl of 100 mM Tris–citrate buffer (pH 5.5) containing 1 mM dithiothreitol, 0.5 mM NADPH, 1 μM ^{3}H-testosterone and Hs27 cell homogenate. DHT was separated and measured by the same method as described above. Steroid 5α-reductase activity was expressed as pmol of DHT formed/min/mg of protein.

Prostatic *ex Vivo* 5α-Reductase Inhibitory Activity in Rats The assay of prostatic *ex vivo* 5α-reductase inhibitory activity in rats was conducted mostly according to the method described by Blohm *et al.*[14] Five-week-old male Wistar rats were purchased from Charles River Japan. Two animals per group were orally given test compounds, and 6 and 24 h after dosing, they were killed under ether anesthesia and the ventral prostates were quickly removed. Tissue slices (2 mg) of ventral prostates were pre-incubated for 10 min at 37 °C in 90 μl of Krebs-Ringer phosphate buffer, pH 7.4. Then 10 μl of 20 nM ^{3}H-testosterone was added to the

mixture as a substrate, and incubation was continued for 30 min at 37 °C. Enzyme reactions were then quenched with 500 μl of $CHCl_3$/MeOH (2 : 1). The DHT formed was extracted and measured as described above. 5α-Reductase activity was expressed in units of fmol DHT formed per 30 min per mg tissue. In control runs, rats were treated with the vehicle only. In the tables, values of relative percentage of inhibitory activity versus the control are presented.

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