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Nonsteroidal progesterone receptor ligands (II); synthesis and SAR of new tetrahydrobenzindolone derivatives

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Abstract—The human progesterone receptor (PR) binding affinity and the PR agonistic or antagonistic potency of tetrahydronaphthofuranone derivatives were shown previously to be markedly influenced by substituents at the 6- and 7-positions. Here, we synthesized tetrahydrobenzindolones possessing a lactam ring, which enabled us to modify the 6- and 7-positions more freely, since tetrahydrobenzindolones are chemically more stable than tetrahydronaphthofuranones. The tetrahydrobenzindolone derivatives generally showed higher PR binding affinity than the corresponding tetrahydronaphthofuranones. We also succeeded in separating the agonistic and antagonistic activities by choosing suitable substituent groups at the 6- and/or 7-position(s) of the tetrahydrobenzindolone. The effects of representative agonists, **12c** (**CP8668**), and **14a** (**CP8816**), and a representative antagonist, **15f** (**CP8661**), were confirmed in in vivo tests. In this report, we mainly describe the synthesis and structure–activity relationships (SAR) of tetrahydrobenzindolone derivatives, as new nonsteroidal PR ligands.
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1. Introduction

Various medicines that control the functions of steroid hormones were developed in the 20th century and have contributed greatly to medical care. Among them, progesterone receptor PR ligands have been used as contraceptives (e.g., norethisterone) and to treat various gynecological diseases and female sex hormone-dependent tumors (e.g., medroxyprogesterone acetate (MPA)).[1] Furthermore, PR antagonists, such as Mifepristone (RU486),[2] discovered in 1980s, contributed to the great progress in understanding the PR functions and are also used in clinical available for abortion. Since the middle of 1990s, nonsteroidal PR ligands, such as LG 100128, LG 120746, and RWJ 26819, were reported and now Tanaproget,[3–6] are on the clinical trial (Fig. 1).

PF1092A, B, and C are new eremophilane-type sesquiterpenoids isolated from the fermentation broth of a rare fungus, *Penicillium oblatum*, by a group at Meiji Seika Kaisha.[7,8] They have a tetrahydronaphthofuranone skeleton, and all the methyl groups at the C-4a and C-5 positions and hydroxyl groups at the C-6 and C-7 positions have *cis*-configuration (Fig. 2). PF1092A and B have highly selective affinity for human PR, but possess a nonsteroidal skeleton.[9] We initially sought to identify the minimal pharmacophore by totally synthetic methods[10,11] and then clarified the structure–activity relationships (SAR) of tetrahydronaphthofuranone derivatives.[12] These compounds are good candidates for new PR ligands that lack the side effects induced by steroidal agents.

During the above studies, we incidentally obtained a small amount of compound (1) as a by-product during an attempt to introduce a methylamino group at the C-7 position of tetrahydronaphthofuranones. Compound (1) has a new skeleton, tetrahydrobenzindolone, containing a lactam ring, in place of the lactone ring of tetrahydronaphthofuranone. Since a lactam ring is generally more chemically stable than a lactone ring, we compared the chemical stability of compounds (**1**) and (**2**), especially in basic media. In alkaline solution at pH 11.5, the 7α-methoxytetrahydrobenzindolone compound (**1**) was sufficiently stable even after 24 h, whereas the tetrahydronaphthofuranone compound (**2**) was rapidly decomposed (Fig. 3).[13]

Keywords: Nonsteroidal progesterone receptor ligand; Tetrahydrobenzindolone; Tetrahydronaphthofuranone; PF1092.
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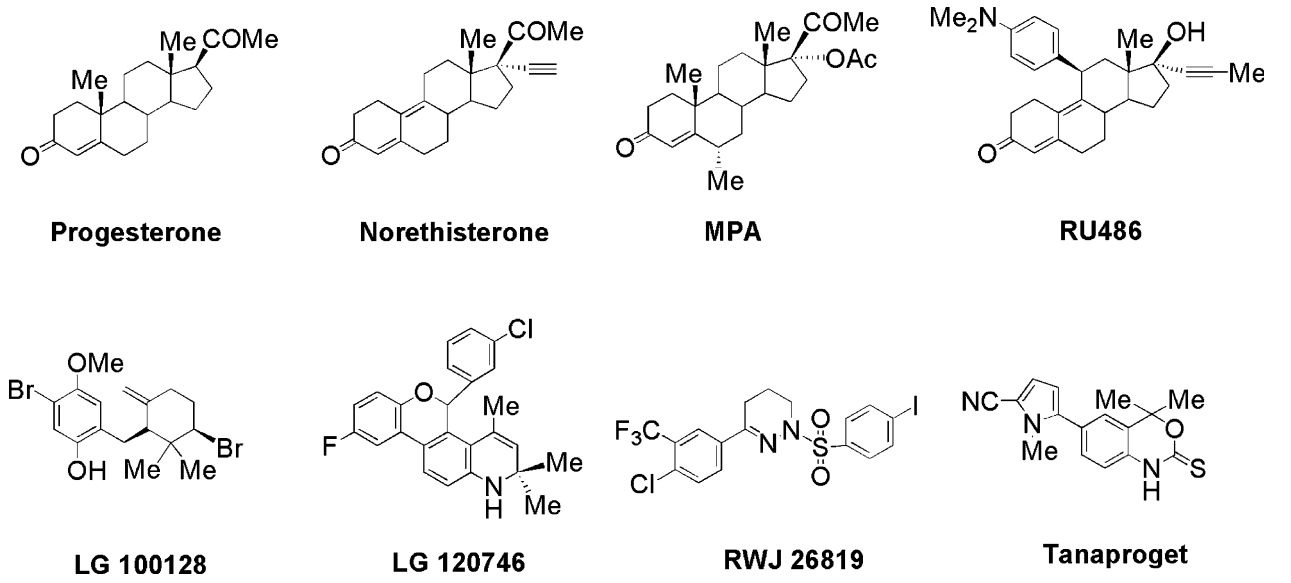


Figure 1. Progesterone receptor ligands.

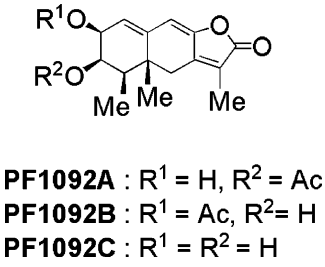


Figure 2. Structure of PF1092A, B, and C.

In view of this desirable feature of compound (**1**), we investigated the synthesis and SAR of tetrahydrobenzindolones in order to seek novel nonsteroidal PR agonists and antagonists. In this paper, we describe in detail the synthesis and SAR of tetrehydrobenzindolones as novel nonsteroidal PR agonists and antagonists.

2. Results and discussion

2.1. Synthesis of the tetrahydrobenzindolone skeleton from PF1092C

As shown in Scheme 1, the tetrahydrobenzindolone compound (**5**) was synthesized by treatment of PF1092C with methanesulfonyl chloride in the presence of diisopropylethylamine, followed by one-pot sequential reactions of lactone opening and lactam closing with methylamine, and S_N2'-type reaction with acetic acid.

The C-7 acetoxy group of compound (**5**) was confirmed to have α-configuration by comparison of the coupling constants in the ^1H NMR spectrum with those of PF1902B having the 7β-configuration.

In our SAR study of the tetrahydronaphthofuranones as candidate PR ligands, C-6 and C-7 were identified as critical positions for the PR binding affinity and for agonist and/or antagonist activities. Therefore, we aimed towards transformation at the C-7 position of tetrahydrobenzindolone in order to clarify the role of the substituent at that position.

The 7-*O*-acetyl group of compound (**5**) was especially reactive and was expected to be useful for introduction of new substituents at the 7-position. For example, treatment of compound (**5**) with alcohols (ROH) gave 7-*O*-alkyl compounds (**1a**, **c**–**f**), while the use of water in place of alcohol readily afforded compound (**1b**).

In order to obtain 7β-substituted compounds, we initially required the 7β-hydroxyl compound. First, the epoxy compound was derived from compound (**5**) by treatment with 1 N NaOH and then treatment with 1 N HCl afforded the 7α- and 7β-hydroxyl compounds as a mixture. The 7β-hydroxyl compound (**6**) was isolated by silica gel column chromatography, but this diol (**6**) was insufficiently stable and the yield was low.

The 7-deoxy compound (**8**) was next synthesized by reduction of the 6-oxo precursor (**7**). This precursor

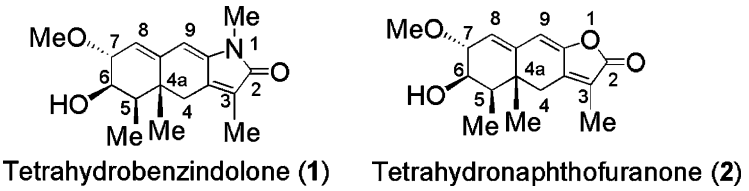
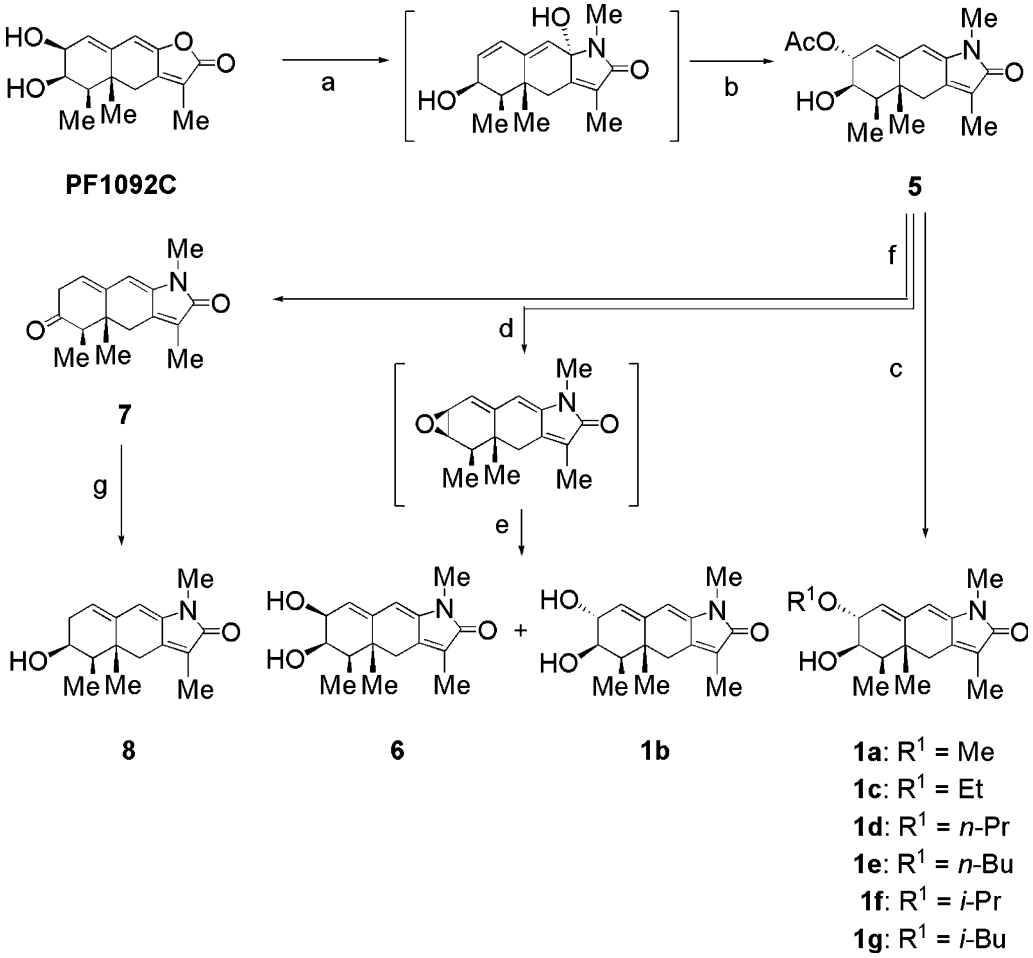


Figure 3. Structures of tetrahydrobenzindolone and tetrahydronaphthofuranone.



Scheme 1. Reagents: (a)—(i) MsCl, *i*-Pr_2NEt, CH_2Cl_2, (ii) $MeNH_2$, THF; (b) AcOH, CH_3CN; (c) R^1OH or H_2O, CH_3CN; (d) 1N NaOH; (e) 1N HCl; (f) p-TsOH, toluene; (g) $NaBH_4$, MeOH.

(**7**) was obtained by treatment of compound (**5**) with *p*-toluenesulfonic acid (*p*-TsOH). The oxo compound (**7**) was considered to be formed from an enol intermediate via elimination of the acetoxy group. Reduction of the 6-oxo precursor (**7**) with $NaBH_4$ selectively afforded the 6β-hydroxyl compound (**8**), but its stability was also unsatisfactory.

Thus, we established the basic synthetic route to tetrahydrobenzindolone and methods for its transformation at the 7-position.

2.2. Comparison of PR binding affinity of tetrahydronaphthofuranone and tetrahydrobenzindolone

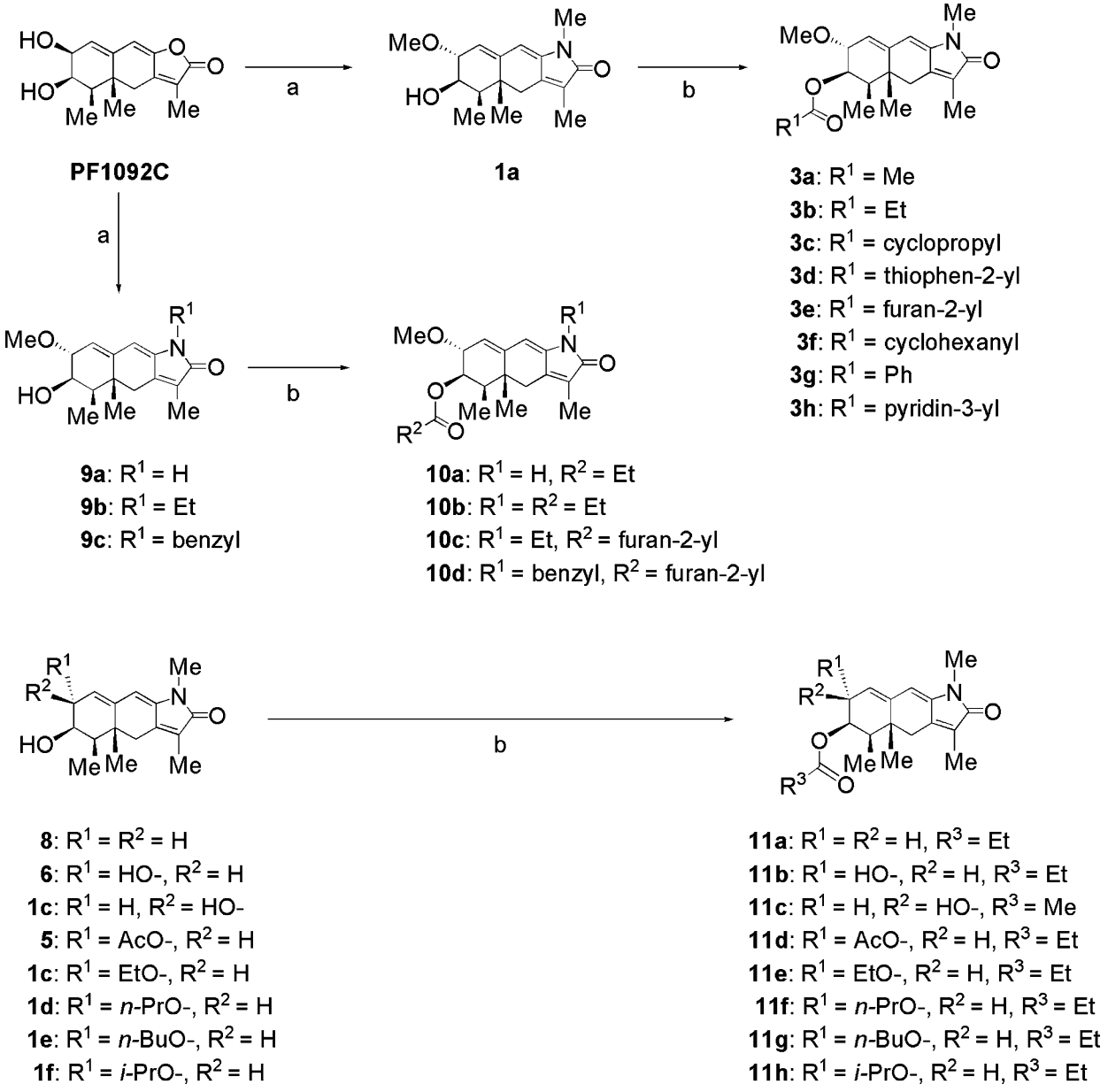
To evaluate the PR binding affinity of the new skeleton, tetrahydrobenzindolone, compared with that of the corresponding tetrahydronaphthofuranone, 6-*O*-acyl derivatives (**3a**–**e**) were prepared from compound (**1a**) by treatment with various acyl halides in the presence of pyridine (Scheme 2).

The PR binding affinities of tetrahydrobenzindolone derivatives (**3a**–**e**) and tetrahydronaphthofuranone derivatives (**4a**–**e**) possessing the same substituent groups at the 6- and 7-positions were compared in terms of the relative binding affinity (RBA), that is, the ratio obtained by dividing IC_{50} of progesterone (32 nM) by IC_{50} of a test compound at the human progesterone receptor (thus, a large value of RBA indicates high PR binding affinity). The tetrahydrobenzindolone derivatives showed substantially higher (2.4- to 21-fold) PR binding affinity than the tetrahydronaphthofuranone derivatives. Surprisingly, one of them (**3c**) showed 2.3-fold higher PR-binding affinity than progesterone itself (Table 1).

The improved chemical stability and high PR binding affinity of the tetrahydrobenzindolone derivatives indicated that they would be promising lead compounds. We therefore started to search for new PR ligands based on the tetrahydrobenzindolone skeleton.

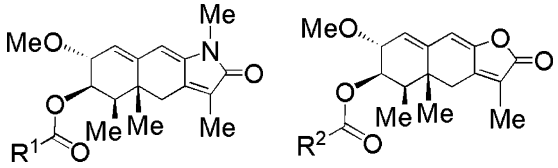
2.3. Selection of lead compound

In the beginning of our SAR investigation, we started with optimization of the substituent at the 1-position, so the derivatives (**10a**–**d**) were synthesized in addition to **3b** and **3e**. The derivatives (**10a**–**d**, **3b**, and **3e**), with hydrogen, methyl, ethyl or benzyl at the 1-position, were obtained by acylation of compound (**9**) in the same manner as described for compound (**1a**) (Scheme 2).



Scheme 2. Reagents: (a) (i) MsCl, *i*-Pr_2NEt, CH_2Cl_2; (ii) R^1NH_2, THF; (iii) AcOH, CH_3CN; (iv) MeOH; (b) RCOCl or RCO_2O, pyridine.

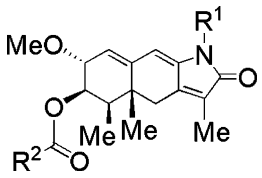
Table 1. Relative PR-binding affinities of the compounds



Compound	R^1	RBA[a]	Compound	R^2	RBA[a]
3a	Me	16	**4a**	Me	5
3b	Et	34	**4b**	Et	4
3c	Cyclopropyl	230	**4c**	Cyclopropyl	11
3d	Thiophen-2-yl	57	**4d**	Thiophen-2-yl	10
3e	Furan-2-yl	94	**4e**	Furan-2-yl	40
Progesterone		100			

[a] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.

Table 2. Relative PR-binding affinities of the compounds



Compound	R^1	R^2	RBA[a]
10a	H	Et	4
3b	Me	Et	34
10b	Et	Et	2
3e	Me	Furan-2-yl	91
10c	Et	Furan-2-yl	8
10d	Benzyl	Furan-2-yl	<5

[a] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.

The methyl derivatives (**3b**, **e**) showed the highest PR binding affinity among these compounds, and the binding affinity decreased as the side chain became larger. Compound (**10a**), with hydrogen at the 1-position, showed very low PR binding affinity. Thus, the methyl group was selected for the 1-position (Table 2).

Next, to examine the SAR at the 7-position, we modified the derivatives possessing a propionyl group at the 6-position by the method shown in Scheme 2 (except compound (**11c**)).

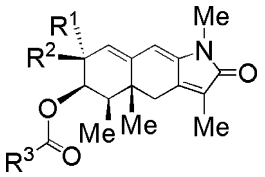
The new derivatives were subjected not only to PR binding affinity assay, but also to an exogenous luciferase (LUC) assay using a T47D human breast cancer cell line to determine whether their activities were agonistic or antagonistic.[9] Agonistic activity represented the relative activity to 1 nM progesterone as 100%. Antagonistic activity represented the relative activity to 1 nM progesterone as 0%. A full agonist (i.e., progesterone) and a pure antagonist (i.e., RU486) have 100% corresponding activity, whereas our derivatives generally did not show 100% agonistic or antagonistic activity. We therefore classified the derivatives into four types according to their pattern of agonistic and antagonistic activities, as follows:

Type a: agonist <10% and antagonist ⩾90%,
Type b: agonist 11–25% and antagonist 75–89%,
Type c: agonist 26–74% and antagonist 74–26%,
Type d: agonist >75% and antagonist ⩽25%.

The 7-deoxy derivative (**11a**) did not show high PR binding affinity, whereas the 7β-hydroxyl derivative (**11c**) showed high affinity. The 7α-hydroxyl derivative (**11b**) showed the highest PR binding affinity. The 7α-methoxy derivative (**3b**) showed relatively high PR binding affinity, whereas among other 7α-alkyloxy derivatives (**11e–h**), the PR binding affinity decreased with increasing size of the alkyl moiety. In LUC assay, these compounds were generally classified as type-c agonists (Table 3).

In the selection of the lead compound, the 7-deoxy derivative or 7β-hydroxyl derivative was regarded as unsuitable, because of its insufficient chemical stability and low yield, although the 7β-hydroxyl derivative (**11c**) showed relatively satisfactory PR binding affinity. On the other hand, the 7α-methoxytetrahydrobenzindolone skeleton offers a good balance of high PR binding affinity, good chemical stability, good yield, and ease of derivatization. We therefore selected the 7α-methoxy-1-methyl derivative (**1a**) as the preferred lead compound, even though the 7α-hydroxyl derivative showed higher PR binding affinity.

Table 3. Relative PR-binding affinities and LUC assay of the compounds



Compound	R^1	R^2	R^3	RBA[a]	LUC assay
11a	H	H	Et	17	c
11b	HO	H	Et	178	c
11c	H	HO	Me	59	N.T.[b]
11d	AcO	H	Et	12	c
3b	MeO	H	Et	34	c
11e	EtO	H	Et	20	c
11f	*n*-PrO	H	Et	13	c
11g	*n*-BuO	H	Et	8	c
11h	*i*-PrO	H	Et	6	b

[a] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.
[b] Not tested.

2.4. Screening of agonistic ligands

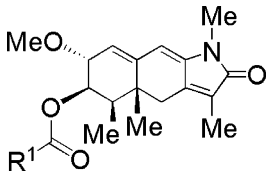
As most of the 6-*O*-propionyl derivatives were type-c agonists in LUC assay, 6-*O*-acyl derivatives were synthesized to clarify the role of acyl substituents at the 6-position. The 6-*O*-acyl derivatives (**3f–h**) were prepared from compound (**1a**) by treatment with various acyl halides in the presence of pyridine (Scheme 2).

The derivatives possessing the carbonyl group generally showed high PR binding affinity. The cyclopropyl carbonyl derivative (**3c**) showed the highest affinity, while the acetyl and cyclohexyl carbonyl derivatives (**3a**, **3f**) showed lower affinity. Moreover, they were type-c agonists in LUC assay (Table 4).

To find compounds with superior agonistic activity, we focused on the carbonyl group of 6-*O*-acyl derivatives. The 6-*O*-carbamoyl derivatives (**12a–f**) were obtained via 6-*O*-imidazolyl intermediates, which were generated by treatment of compound (**1a**) with carbonyl diimidazole (CDI) in methylene chloride, followed by substitution of an appropriate amine. Further, the 6-propyl carbamoyl derivatives (**13a–e**) and dialkyl carbamates (**14a–f**) were similarly synthesized to study their SAR (Scheme 3).

The series of 6-*O*-carbamoyl derivatives (**12–14**) showed generally high PR binding affinity and had a type-c ago-

Table 4. Relative PR-binding affinities and LUC assay of the compounds



Compound	R^1	RBA[a]	LUC assay
3a	Me	15	c
3b	Et	33	c
3c	Cyclopropyl	230	c
3d	Thiophen-2-yl	56	c
3e	Furan-2-yl	91	c
3f	Cyclohexanyl	17	c
3g	Ph	47	c
3h	Pyridin-3-yl	86	c

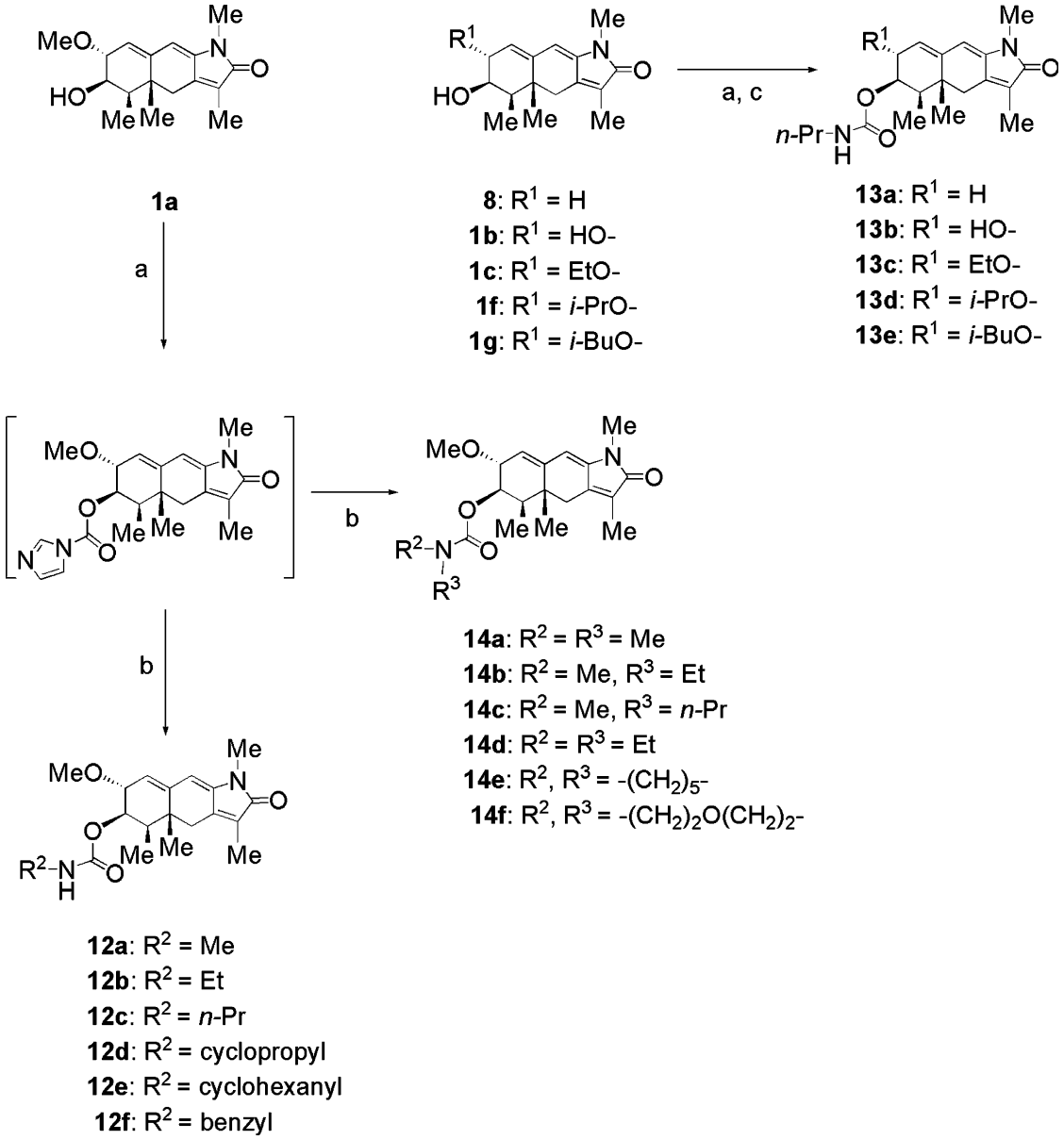
[a] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.

nistic profile in LUC assay. Compounds (**12a**, **12b**, **12c**, **13a**, **14a**, and **14f**) in particular showed 1.1- to 1.9-fold higher PR binding affinity than progesterone. Among the series of 6-*O*-carbamoyl derivatives (**12c**, **13a**–**e**), the result for compound (**12c**), which showed the highest PR binding affinity among the other derivatives, indicated that the best substituent at the 7-position of 6-*O*-carbamoyl derivatives was the α-methoxy group (Table 5).

Thus, we identified several new compounds with agonistic activity in in vitro assay, that is, **3c**, **12a**, **12b**, **12c**, **13a**, **14a**, and **14f**, based on the 7α-methoxytetrahydrobenzindolone skeleton.

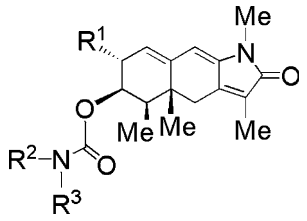
2.5. Screening of antagonistic ligands

In our previous study, the 6-hydroxyl group of tetrahydronaphthofuranone could not be alkylated due to its poor chemical stability under basic conditions, but it



Scheme 3. Reagents: (a) CDI, CH_2Cl_2; (b) various amines, THF; (c) *n*-$PrNH_2$.

Table 5. Relative PR-binding affinities and LUC assay of the compounds



Compound	R^1	R^2	R^3	RBA[a]	LUC assay
12a	MeO	Me	H	139	c
12b	MeO	Et	H	145	c
12c	MeO	*n*-Pr	H	119	c
12d	MeO	Cyclopropyl	H	38	c
12e	MeO	Cyclohexanyl	H	14	c
12f	MeO	Benzyl	H	21	c
13a	H	*n*-Pr	H	107	c
13b	HO	*n*-Pr	H	48	c
13c	EtO	*n*-Pr	H	78	c
13d	*i*-PrO	*n*-Pr	H	11	b
13e	*i*-BuO	*n*-Pr	H	7	c
14a	MeO	Me	Me	188	c
14b	MeO	Me	Et	80	c
14c	MeO	Me	*n*-Pr	89	c
14d	MeO	Et	Et	43	c
14e	MeO	$-(CH_2)_5-$		59	c
14f	MeO	$-(CH_2)_2O(CH_2)_2-$		107	c

[a] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.

was possible to alkylate the hydroxyl group at the 6-position of the 7-methoxytetrahydrobenzindolone skeleton. Several kinds of 6-*O*-alkyl derivatives of tetrahydrobenzindolone were synthesized, to investigate the influence of the linkage at the 6-position. The 6-*O*-alkyl derivatives (**15a**–**h**) were obtained by treatment of compound (**1a**) with alkyl halides in the presence of sodium hydride (NaH) in DMF solution (Scheme 4).

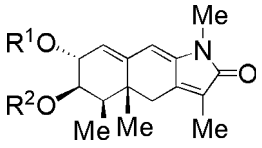
The PR binding affinities of the 6-*O*-alkyl derivatives (**15a**–**h**) were generally lower than those of the 6-*O*-carbamoyl derivatives. All the derivatives, except for compound (**15f**), showed a type-b profile; compound (**15f**), however, had a type-a profile (Table 6).

Interestingly, the derivatives (**11h**) and (**13d**), which possess a 7α-isopropyloxy group, showed a type-b profile in LUC assay, although other derivatives were agonistic ligands with a type-c profile (Tables 3 and 5). We speculated that it might be possible to synthesize antagonistic PR ligands by choosing an appropriate substituent at the 7-position.

To examine the substituent effect at the 7-position, the 7α-isopropyloxy derivatives (**16a**–**e**) were synthesized by alkylation of compound (**1f**) (Scheme 4).

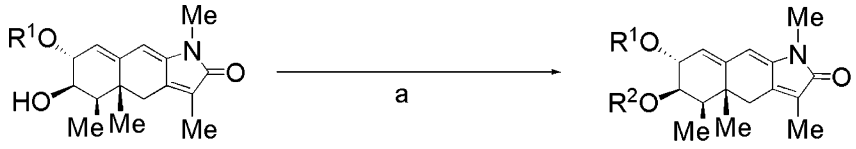
All the 7α-isopropyloxy derivatives obtained showed a type-a profile in LUC assay, although they did not always have high PR binding affinity (Table 6).

Table 6. Relative PR-binding affinities and LUC assay of the compounds



Compound	R^1	R^2	RBA[a]	LUC assay
15a	Me	Me	3	b
15b	Me	Et	8	b
15c	Me	*n*-Pr	14	b
15d	Me	$CH_2{=}CH_2CH_2-$	10	b
15e	Me	*n*-Bu	20	b
15f	Me	$(CH_3)_2CH(CH_2)_2-$	8	a
15g	Me	Cyclopropylmethyl	46	b
15h	Me	Benzyl	6	b
16a	*i*-Pr	Et	6	a
16b	*i*-Pr	*n*-Pr	8	a
16c	*i*-Pr	*n*-Bu	2	a
16d	*i*-Pr	$(CH_3)_2CH(CH_2)_2-$	1	a
16e	*i*-Pr	Cyclopropylmethyl	5	a

[a] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.



1a: R^1 = Me
1f: R^1 = *i*-Pr

15a: R^1 = R^2 = Me
15b: R^1 = Me, R^2 = Et
15c: R^1 = Me, R^2 = *n*-Pr
15d: R^1 = Me, R^2 = $CH_2{=}CH_2CH_2$-
15e: R^1 = Me, R^2 = *n*-Bu
15f: R^1 = Me, R^2 = $(CH_3)_2CH(CH_2)_2$-
15g: R^1 = Me, R^2 = cyclopropylmethyl
15h: R^1 = Me, R^2 = benzyl

16a: R^1 = *i*-Pr, R^2 = Et
16b: R^1 = *i*-Pr, R^2 = *n*-Pr
16c: R^1 = *i*-Pr, R^2 = *n*-Bu
16d: R^1 = *i*-Pr, R^2 = $(CH_3)_2CH(CH_2)_2$-
16e: R^1 = *i*-Pr, R^1 = cyclopropylmethyl

Scheme 4. Reagents: (a) NaH, RX, DMF.

This result indicated that we would be able to separate agonistic and antagonistic activities by choosing an appropriate substituent at the 7-position.

2.6. In vivo study

In the selection of agonists, an endogenous alkaline-phosphatase assay using T47D cell was employed as a functional assay to evaluate the effects of compounds on PR-dependent enzyme expression[9] in addition to LUC assay. We selected **12c** (**CP8668**) and **14a** (**CP8816**) as agonists on the basis of the endogenous alkaline-phosphatase assay. We examined their in vivo effect using the Clauberg–McPhail assay, in which the in vivo progestational activity is evaluated in terms of a rabbit endometrial transformation.[14,15] In the Clauberg–McPhail assay, the compounds showed good progestational activity after sc and po administration, and their efficacy after sc administration was similar to that of progesterone.[14,15]

To select antagonistic ligands, we also used the endogenous alkaline-phosphatase assay. Compound **15f** (**CP8661**) was confirmed to possess pure PR antagonistic activity in this assay, and in the Clauberg–McPhail assay, it showed potent anti-progestational effects. This compound was inactive in the agonist format of the rabbit endometrial transformation test at the same dosage.[16]

The affinity of the agonistic ligands, **12c** (**CP8668**) and **14a** (**CP8816**), and the antagonistic ligand **15f** (**CP8661**) for other steroidal receptors was examined, and these compounds exhibited selective affinity for the progesterone receptor. The selectivity of **12c** (**CP8668**) and **14a** (**CP8816**) was especially high.[14–16]

3. Conclusion

We have developed a new lead compound, tetrahydrobenzindolone, possessing a lactam ring, which shows sufficient stability for easy modification at the 6- and/or 7-positions. We have investigated the SAR of tetrahydrobenzindolones as PR ligands. As representative active compounds, we identified the 6-*O*-carbamoyl derivatives **12c** (**CP8668**) and **14a** (**CP8816**) as agonists, and the 6-*O*-alkyl derivative **15f** (**CP8661**) as an antagonist by means of in vitro and in vivo assays. Our results indicate that PR ligands with agonistic or antagonistic activity, as required, can be derived from a tetrahydrobenzindolone core structure by choosing an appropriate linkage type and suitable substituents at the 6- and 7-positions. We expect that these compounds will be good candidate drugs for the treatment of various PR-related diseases.

4. Experimental

4.1. Biological method

4.1.1. Materials. Progesterone was purchased from Junsei Chemical. RU486 (11β-[4-dimethylamino]phenyl-17β-hydroxy-17-[1-propynyl]estra-4,9-diene-3-one) was purchased from Sigma. [1,2,6,7-^{3}H(N)]Progesterone (specific activity: 3848 GBq/mmol) was purchased from NEN™ Life Science Products.

4.1.2. Cell cultures. T47D human breast carcinoma cells were purchased from the American Type Culture Collection (ATCC). The T47D line was cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum. This cell line was cultured at 37 °C with 5% CO_2.

4.1.3. PR binding assay. The measurements of the binding affinity of compounds for the PR were performed as described earlier.[9] Unless otherwise specified, the following procedures were conducted at temperatures of 0–4 °C. Collected T47D cells were sonicated with a Branson Sonifier 450 in a buffer consisting of 5 mM KH_2PO_4 (pH 7.4), 30% glycerol, 0.1% α-thioglycerol, and 25 μg/ml leupeptin, followed by centrifugation at 100,000*g* for 30 min. The resulting supernatant (cytosol) was stored at −80 °C prior to its use as a source of progesterone receptors for the binding assays.

A reaction mixture (100 μl) containing 50 mM KH_2PO_4 (pH 7.4), 10% glycerol, 0.1% α-thioglycerol, 25 μg/ml leupeptin, 1 mM EDTA, [1,2,6,7-^{3}H(N)]progesterone (final concentration of 1.4 nM), T47D cytosol (0.8 mg protein/ml), and a test sample was incubated for 1 h at 4 °C. After incubation, 100 μl of Dextran-coated charcoal solution consisting of 0.5% Norit A (Nacalai Tesque) and 0.05% Dextran T-70 (Pharmacia Fine Chemicals) was added to the incubation mixture, and incubation was continued for 10 min at 4 °C. The mixture was then centrifuged at 1800 rpm for 5 min. The radioactivity of 100 μl of the supernatant was measured in 2 ml of Aquasol-2 (Packard) with a liquid scintillation counter (Beckman LS6500). Non-specific binding was defined as the binding observed when 10 μM of cold progesterone was added to the reaction mixture. Sigmoid fitting curves of the results expressed as inhibitory effects of the test compounds were obtained using KaleidaGraph software (Synergy Software). IC_{50} values were determined from the sigmoid fitting curve parameters. Relative binding affinity (RBA) was calculated by the comparison of IC_{50} values of the test compounds and progesterone.

4.1.4. Progesterone-dependent exogenous luciferase expression assay. The progesterone-dependent modulation of gene transcription was examined using the luciferase assay with stable transfected T47D-pMAMneo-LUC cells. The assay was performed as previously described.[9] In brief, the growth medium for T47D-pMAMneo-LUC cells was replaced with phenol red-free DMEM containing 5% fetal bovine serum treated with dextran-coated charcoal. After 24 h of cultivation, the cells were plated in 96-well plates at 50,000 cells/well. After 8 h of cultivation, the test compounds were added to each well to achieve the appropriate compound concentration. After 16 h of cultivation, 100 μl of Luc Lite (Packard) solution was added to each well and mixed. After 15 min of incubation at room temperature, lumi-

nescence was measured using either the LUMIstar (BMG Labtechnologies) luminometer or the ARVO (Perkin-Elmer) luminometer.

4.2. Chemistry

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter. ^{1}H NMR (300 MHz) spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts are reported in δ value (ppm) with tetramethylsilane (TMS) as the internal standard (NMR peak description: s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet; and br, broad peak). Elemental analyses were within ±0.4% of the theoretical values for the elements indicated, unless otherwise noted. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-700. All commercial reagents and solvents were used as received. PF1092C was prepared according to described procedure.[7]

4.2.1. (4a*R*,5*R*,6*R*,7*R*)-7-Acetoxy-6-hydroxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (5). To a solution of PF1092C (200 mg = 0.76 mmol) in CH_2Cl_2 (4 ml) were added methanesulfonyl chloride (88 μl = 1.15 mmol) and diisopropylethylamine (266 μl = 1.53 mmol). The reaction was maintained at −15 °C until complete consumption of the starting material was observed as determined by TLC analysis. The mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. This residue was used in the following step with no further purification. The residue was diluted in 2 M solution methylamine in THF (2.29 ml) and stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was used in the following step with no further purification. To a solution of the residue (100 mg = 0.36 mmol) in CH_3CN(5 ml) was added acetic acid (200 μl = 3.30 mmol). The mixture was stirred at room temperature for 20 h. This mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 85 mg (74%) of the title compound (5) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, s, 4a-CH_3), 1.20 (3H, d, J = 7.2 Hz, 5-CH_3), 1.88 (3H, d, J = 2.0 Hz, 3-CH_3), 1.90 (1H, dq, J = 7.2, 2.9 Hz, 5-H), 2.06 (3H, s, $OCOCH_3$), 2.16 (1H, br d, J = 16.0 Hz, 4-H), 2.82 (1H, d, J = 16.0 Hz, 4-H), 3.10(3H, s, N-CH_3), 3.84 (1H, m, 6-H), 5.20 (1H, dd, J = 4.8, 1.7 Hz, 7-H), 5.70 (1H, d, J = 4.8 Hz, 8-H), 5.75 (1H, s, 9-H); $[\alpha]_D^{18}$ −608 (*c* 1.0, MeOH); mp 50–55 °C; MS (EI) *m*/*z* 317 $(M)^+$; HRMS (FAB) ($C_{18}H_{24}O_4N$) calcd 318.1706, obsd 318.1710.

4.2.2. (4a*R*,5*R*,6*R*,7*R*)-6-Hydroxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (1a). A solution of compound (**5**) (100 mg = 0.32 mmol) in MeOH (10 ml) was stirred at 50 °C for 3 h. The solvent was removed under reduced pressure. Preparative TLC of this residue provided 90 mg (100%) of the title compound (**1a**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, s, 4a-CH_3), 1.19 (3H, d, J = 7.3 Hz, 5-CH_3), 1.86 (3H, d, J = 2.0 Hz, 3-CH_3), 1.91 (1H, dq, J = 7.3, 2.6 Hz, 5-H), 2.13 (1H, br d, J = 16.0 Hz, 4-H), 2.78 (1H, d, J = 16.0 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.43 (3H, s, OCH_3), 3.70 (1H, dd, J = 4.8, 1.9 Hz, 7-H), 3.91 (1H, br s, 6-H), 5.74 (1H, s, 9-H), 5.82 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −584 (*c* 0.8, MeOH); mp 165–170 °C; MS (EI) *m*/*z* 289 $(M)^+$; HRMS (FAB) ($C_{17}H_{24}O_3N$) calcd 290.1757, obsd 290.1753.

4.2.3. (4a*R*,5*R*,6*R*,7*R*)-6-Acetoxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (3a). To a solution of compound (**1a**) (20 mg = 0.07 mmol) in pyridine (1 ml) was added acetyl chloride (15 μl = 0.21 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 12 mg (53%) of the title compound (**3a**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, s, 4a-CH_3), 1.08 (3H, d, J = 7.2 Hz, 5-CH_3), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 2.06 (3H, s, $OCOCH_3$), 2.08 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.12 (1H, br d, J = 15.9 Hz, 4-H), 2.79 (1H, d, J = 15.9 Hz, 4-H), 3.09 (3H, s,N-CH_3),3.49 (3H, s, O-CH_3), 3.60 (1H, dd, J = 4.8, 1.3 Hz, 7-H), 5.08 (1H, m, 6-H), 5.72 (1H, s, 9-H), 5.74 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −291 (*c* 1.0, MeOH); MS (EI) *m*/*z* 331 $(M)^+$.

4.2.4. (4a*R*,5*R*,6*R*,7*R*)-6,7-Dihydroxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (1b). A solution of compound (**5**) (100 mg = 0.32 mmol) in CH_3CN (5 ml)–H_2O (5 ml) was stirred at room temperature for 20 h. The solvent was removed under reduced pressure. Preparative TLC of this residue provided 63 mg (71%) of the major compound (**1b**) as a colorless solid and 10 mg (11%) of the minor compound (**6**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, s, 4a-CH_3), 1.20 (3H, d, J = 7.2 Hz, 5-CH_3), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 1.94 (1H, dq, J = 7.2, 2.5 Hz, 5-H), 2.08 (1H, br d, J = 15.9 Hz, 4-H), 2.80 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.87 (1H, m, 6-H), 4.17 (1H, dd, J = 4.8, 1.9 Hz, 7-H), 5.73 (1H, s, 9-H), 5.80 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{20}$ −455 (*c* 0.2, MeOH); MS (EI) *m*/*z* 275 $(M)^+$.

4.2.5. (4a*R*,5*R*,6*R*,7*S*)-6,7-Dihydroxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (6). ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, s, 4a-CH_3), 1.21 (3H, d, J = 7.2 Hz, 5-CH_3), 1.78 (1H, dq, J = 7.2, 2.5 Hz, 5-H), 1.85 (3H, d, J = 1.9 Hz, 3-CH_3), 2.08 (1H, br d, J = 15.9 Hz, 4-H), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.98 (1H, m, 6-H), 4.39 (1H, m, 7-H), 5.67 (1H, br s, 8-H), 5.70 (1H, s, 9-H); MS (EI) *m*/*z* 275 $(M)^+$.

4.2.6. (4a*R*,5*R*)-6-Oxo-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (7). A solution of compound (**5**) (20 mg = 0.07 mmol) in toluene (4 ml) was added methanesulfonic acid (4.5 μl = 0.07 mmol). This mixture was heated at reflux for 20 min. The reaction mixture was cooled, and the mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 6 mg (36%) of the title compound (**7**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, s, 4a-CH_3), 1.15 (3H, d, J = 6.7 Hz, 5-CH_3), 1.91 (3H, d, J = 2.2 Hz, 3-CH_3), 2.45 (1H, br d, J = 15.9 Hz, 4-H), 2.77(1H, d,

J = 15.9 Hz, 4-H), 2.82 (1H, q, J = 6.7 Hz, 5-H), 3.01 (1H, dd, J = 23.3, 4.1 Hz, 7-H), 3.14 (3H, s, N-CH_3), 3.17 (1H, dd, J = 23.3, 4.1 Hz, 7-H), 5.77 (1H, br t, J = 4.1 Hz, 8-H), 5.79 (1H, s, 9-H); MS (EI) m/z 257 $(M)^+$.

4.2.7. (4a*R*,5*R*,6*S*)-6-Hydroxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (8). A solution of compound (**7**) (215 mg = 0.84 mmol) in MeOH (4 ml) was added sodium borohydride (63 mg = 1.67 mmol). The reaction mixture was stirred at 0 °C until complete consumption of the starting material was observed as determined by TLC analysis. H_2O was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 190 mg (88%) of the title compound (**8**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, s, 4a-CH_3), 1.18 (3H, d, J = 7.0 Hz, 5-CH_3), 1.74 (1H, dq, J = 7.0, 2.7 Hz, 5-H), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 2.09 (1H, br d, J = 16.0 Hz, 4-H), 2.40 (1H, br dd, J = 20.5, 4.2 Hz, 7-H), 2.58 (1H, br ddd, J = 20.5, 4.2 Hz, 7-H), 2.71 (1H, d, J = 16.0 Hz, 4-H), 3.09 (3H, s, N-CH_3), 4.01 (1H, m, 6-H), 5.68 (1H, br t, J = 4.2 Hz, 8-H), 5.74 (1H, s, 9-H); MS (EI) m/z 259 $(M)^+$; HRMS (FAB) ($C_{16}H_{22}O_2N$) calcd 260.1651, obsd 260.1656.

4.2.8. (4a*R*,5*R*,6*R*,7*R*)-6,7-Dimethoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15a). A solution of compound (**1a**) (20 mg = 0.07 mmol) in DMF (400 μl) was gradually added 60% sodium hydride (NaH) (7 mg = 0.18 mmol) under ice cooling. Methyl iodide (22 μl = 0.35 mmol) was added into the mixture after foaming subsided. The reaction mixture was stirred at room temperature for 2 h. H_2O was gradually added to the reaction mixture. The mixture was extracted with CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 13 mg (62%) of the title compound (**15a**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, s, 4a-CH_3), 1.16 (3H, d, J = 7.1 Hz, 5-CH_3), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 1.89 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.09 (1H, br d, J = 15.9 Hz, 4-H), 2.77 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.28 (1H, m, 6-H), 3.40 (3H, s, O-CH_3), 3.43 (3H, s, OCH_3), 3.74 (1H, dd, J = 4.8, 1.4 Hz, 7-H), 5.72 (1H, s, 9-H), 5.81 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −340 (c 1.0, MeOH); MS (EI) m/z 303 $(M)^+$.

4.2.9. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (3b). Reaction of **1a** gave **3b** in 30% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, J = 7.2 Hz, 5-CH_3), 1.09 (3H, s, 4a-CH_3), 1.14 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.87 (3H, d, J = 1.9 Hz, 3-CH_3), 2.08 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.13 (1H, br d, J = 15.9 Hz, 4-H), 2.34 (2H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.79 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.50 (3H, s, OCH_3), 3.60 (1H, dd, J = 4.8, 1.3 Hz, 7-H), 5.09 (1H, m, 6-H), 5.73 (1H, s, 9-H), 5.75 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −280 (c 0.6, MeOH); MS (FAB) m/z 346 $(M+H)^+$.

4.2.10. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylcarbonyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (3c). Reaction of **1a** gave **3c** in 100% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.83–1.04 (4H, m, OCO-cyclopropane), 1.09 (3H, d, J = 7.2 Hz, 5-CH_3), 1.10 (3H, s, 4a-CH_3), 1.57 (1H, m, OCO-cyclopropane), 1.87 (3H, d, J = 1.9 Hz, 3-CH_3), 2.07 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.14 (1H, br d, J = 15.9 Hz, 4-H), 2.80 (1H, d, J = 15.9 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.49 (3H, s, OCH_3), 3.60 (1H, dd, J = 4.7, 1.3 Hz, 7-H), 5.07 (1H, m, 6-H), 5.73 (1H, s, 9-H), 5.75 (1H, d, J = 4.7 Hz, 8-H); $[\alpha]_D^{20}$ −196 (c 1.0, MeOH); MS (EI) m/z 357 $(M)^+$.

4.2.11. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethyl-6-(2-thiophenecarbonyloxy)benz[*f*]indol-2(4*H*)-one (3d). Reaction of **1a** gave **3d** in 89% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 7.2 Hz, 5-CH_3), 1.22 (3H, s, 4a-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.17 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.18 (1H, br d, J = 15.9 Hz, 4-H), 2.83 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.55 (3H, s, OCH_3), 3.76 (1H, br d, J = 4.8 Hz, 7-H), 5.27 (1H, m, 6-H), 5.75 (1H, s, 9-H), 5.77 (1H, d, J = 4.8 Hz, 8-H), 7.10 (1H, dd, J = 4.9, 3.8 Hz, $OCOC_4H_3S$), 7.55 (1H, dd, J = 4.9, 1.3 Hz, $OCOC_4H_3S$), 7.77 (1H, dd, J = 3.8, 1.3 Hz, $OCOC_4H_3S$); $[\alpha]_D^{18}$ +36 (c 1.0, MeOH); mp 148–153 °C; MS (EI) m/z 399 $(M)^+$.

4.2.12. (4a*R*,5*R*,6*R*,7*R*)-6-(2-Furancarbonyloxy)-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (3e). Reaction of **1a** gave **3e** in 75% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J = 7.2 Hz, 5-CH_3), 1.21 (3 H, s, 4a-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.17 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.17 (1H, br d, J = 15.9 Hz, 4-H), 2.83 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.54 (3H, s, O-CH_3), 3.73 (1H, dd, J = 4.8, 1.3 Hz, 7-H), 5.30 (1H, m, 6-H), 5.75 (1H, s, 9-H), 5.77 (1H, d, J = 4.8 Hz, 8-H), 6.49 (1H, dd, J = 3.5, 1.7 Hz, $OCOC_4H_3O$), 7.10 (1H, dd, J = 3.5, 0.8 Hz, $OCOC_4H_3O$), 7.57 (1H, dd, J = 1.7, 0.8 Hz, OCO-C_4H_3O); $[\alpha]_D^{18}$ 0 (c 1.0, MeOH); mp 155–158 °C; MS (FAB) m/z 384 $(M+H)^+$.

4.2.13. (4a*R*,5*R*,6*R*,7*R*)-6-(2-Cyclohexylcarbonyloxy)-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]-indol-2(4*H*)-one (3f). Reaction of **1a** gave **3b** in 52% yield as a colorless solid by a similar procedure to **3f**: ^{1}H NMR ($CDCl_3$) δ 1.06 (3H, d, J = 7.2 Hz, 5-CH_3), 1.09 (3H, s, 4a-CH_3), 1.14–1.66 (11H, m, OCO-cyclohexane), 1.85 (3H, d, J = 1.9 Hz, 3-CH_3), 2.07 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.13 (1H, br d, J = 15.9 Hz, 4-H), 2.28 (1H, m, OCO-cyclohexane), 2.77 (1 H, d, J = 15.9 Hz, 4-H), 3.08 (3 H, s, N-CH_3), 3.48 (3 H, s, OCH_3), 3.53 (1 H, dd, J = 4.8, 1.3 Hz, 7-H), 5.06 (1H, m, 6-H), 5.72 (1H, s, 9-H), 5.73 (1H, br d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −152 (c 2.0, MeOH); MS (FAB) m/z 400 $(M+H)^+$; HRMS (FAB) ($C_{24}H_{34}O_4N$) calcd 400.2488, obsd 400.2514.

4.2.14. (4a*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (3g). Reaction of **1a** gave **3g** in 87% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, d, J = 7.2 Hz, 5-CH_3), 1.25 (3H, s, 4a-CH_3), 1.89 (3H, d,

J = 1.9 Hz, 3-CH_3), 2.20 (1H, br d, J = 15.9 Hz, 4-H), 2.21 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.85 (1H, d, J = 15.9 Hz, 4-H), 3.11 (3H, s, N-CH_3), 3.57 (3H, s, OCH_3), 3.75 (1H, dd, J = 4.7, 1.3 Hz, 7-H), 5.36 (1H, m, 6-H), 5.76 (1H, s, 9-H), 5.79 (1H, d, J = 4.7 Hz, 8-H), 7.40–8.00 (5H, m, $OCOC_6H_5$); $[\alpha]_D^{20}$ +12 (*c* 1.0, MeOH); MS (FAB) *m*/*z* 394 $(M+H)^+$.

4.2.15. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(3-pyridinecarbonyloxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (3h). Reaction of **1a** gave **3h** in 54% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, d, J = 7.1 Hz, 5-CH_3), 1.23 (3H, s, 4a-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.20 (1H, br d, J = 15.9 Hz, 4-H), 2.23 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.85 (1H, d, J = 15.9 Hz, 4-H), 3.11 (3H, s, N-CH_3), 3.57 (3H, s, OCH_3), 3.76 (1H, dd, J = 4.7, 1.4 Hz, 7-H), 5.38 (1H, m, 6-H), 5.75 (1H, s, 9-H), 5.78 (1H, d, J = 4.7 Hz, 8-H), 7.40–8.76(4H, m, $OCOC_5H_4N$); $[\alpha]_D^{20}$ −7 (*c* 1.0, MeOH); MS (EI) *m*/*z* 363 $(M)^+$.

4.2.16. (4a*R*,5*R*,6*R*,7*R*)-7-methoxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylbenz[*f*]indol-2(4*H*)-one (10a). Reaction of PF1092C with NH_3 gave **9a** in 16% by a similar procedure to **5**. Reaction of **9a** gave **10a** in 74% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, d, J = 7.3 Hz, 5-CH_3), 1.12 (3H, s, 4a-CH_3), 1.16 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.89 (3H, d, J = 1.9 Hz, 3-CH_3), 2.08 (1H, dq, J = 7.3, 2.7 Hz, 5-H), 2.17 (1H, br d, J = 15.9 Hz, 4-H), 2.35 (2H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.81 (1H, d, J = 15.9 Hz, 4-H), 3.51 (3H, s, OCH_3), 3.60 (1H, dd, J = 4.8, 1.7 Hz, 7-H), 3.61 (2H, m, N-CH_2CH_3), 5.11 (1H, m, 6-H), 5.73 (1H, d, J = 4.8 Hz, 8-H), 5.84 (1H, s, 9-H); MS (FAB) *m*/*z* 332 $(M+H)^+$; HRMS (FAB) ($C_{19}H_{26}O_4N$) calcd 332.1862, obsd 332.1852.

4.2.17. (4a*R*,5*R*,6*R*,7*R*)-1-Ethyl-7-methoxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylbenz[*f*]indol-2(4*H*)-one (10b). Reaction of PF1092C with $EtNH_2$ gave **9b** in 47% by a similar procedure to **5**. Reaction of **9b** gave **10b** in 30% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, J = 7.3 Hz, 5-CH_3), 1.09 (3H, s, 4a-CH_3), 1.14 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.15 (3H, t, J = 7.2 Hz, N-CH_2CH_3), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 2.08 (1H, dq, J = 7.3, 2.7 Hz, 5-H), 2.14 (1H, br d, J = 15.9 Hz, 4-H), 2.34 (2H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.80 (1H, d, J = 15.9 Hz, 4-H), 3.50 (3H, s, OCH_3), 3.60 (1H, dd, J = 4.8, 1.7 Hz, 7-H), 3.61 (2H, m, N-CH_2CH_3), 5.09 (1H, m, 6-H), 5.73 (1H, s, 9-H), 5.74 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −228 (*c* 1.0, MeOH); MS (EI) *m*/*z* 359 $(M)^+$.

4.2.18. (4a*R*,5*R*,6*R*,7*R*)-1-Ethyl-6-(2-furancarbonyloxy)-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylbenz[*f*]indol-2(4*H*)-one (10c). Reaction of **9b** gave **10c** in 85% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J = 7.3 Hz, 5-CH_3), 1.16 (3H, t, J = 7.2 Hz, N-CH_2CH_3), 1.87 (3H, d, J = 1.9 Hz, 3-CH_3), 1.21 (3H, s, 4a-CH_3), 2.17 (1H, dq, J = 7.3, 2.7 Hz, 5-H), 2.18 (1 H, br d, J = 15.9 Hz, 4-H), 2.83 (1H, d, J = 15.9 Hz, 4-H), 3.55 (3H, s, OCH_3), 3.59 (1H, dq, J = 7.0, 7.2 Hz, N-CH_2CH_3), 3.66 (1H, dq, J = 7.0, 7.2 Hz, N-CH_2CH_3), 3.73 (1H, br d, J = 4.8 Hz, 7-H), 5.29 (1H, br s, 6-H), 5.75 (1H, s, 9-H), 5.76 (1H, d, J = 4.8 Hz, 8-H), 6.49 (1H, dd, J = 3.5, 1.7 Hz, OCO-C_4H_3O), 7.11 (1 H, dd, J = 3.5, 0.8 Hz, $OCOC_4H_3O$), 7.57 (1H, dd, J = 1.7, 0.8 Hz, $OCOC_4H_3O$); $[\alpha]_D^{18}$ −17 (*c* 1.0, MeOH); MS (EI) *m*/*z* 397 $(M)^+$.

4.2.19. (4a*R*,5*R*,6*R*,7*R*)-1-Benzyl-6-(2-furancarbonyloxy)-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylbenz[*f*]indol-2(4*H*)-one (10d). Reaction of PF1092C with $PhCH_2NH_2$ gave **9c** in 32% by a similar procedure to **5**. Reaction of **9c** gave **10d** in 100% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.19 (3H, s, 4a-CH_3), 1.93 (3H, d, J = 1.8 Hz, 3-CH_3), 2.14 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.19 (1H, br d, J = 15.9 Hz, 4-H), 2.85 (1H, d, J = 15.9 Hz, 4-H), 3.52 (3H, s, OCH_3), 3.68 (1H, dd, J = 4.7, 1.1 Hz, 7-H), 4.69 (1H, d, J = 15.9 Hz, N-$CH_2C_6H_5$), 4.91 (1H, d, J = 15.9 Hz, N-$CH_2C_6H_5$), 5.27 (1H, m, 6-H), 5.65 (1H, s, 9-H), 5.66 (1H, d, J = 4.8 Hz, 8-H), 6.49 (1H, dd, J = 3.5, 1.7 Hz, $OCOC_4H_3O$), 7.09 (1H, dd, J = 3.5, 0.8 Hz, $OCOC_4H_3O$), 7.17–7.32 (5H, m, N-$CH_2C_6H_5$), 7.56 (1H, dd, J = 1.7, 0.8 Hz, OCO-C_4H_3O); $[\alpha]_D^{20}$ −30 (*c* 1.0, MeOH); MS (EI) *m*/*z* 459 $(M)^+$.

4.2.20. (4a*R*,5*R*,6*S*)-6-Propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11a). Reaction of **8** gave **11a** in 58% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, d, J = 7.0 Hz, 5-CH_3), 1.11 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.13 (3H, s, 4a-CH_3), 1.87 (3H, d, J = 2.0 Hz, 3-CH_3), 1.88 (1H, dq, J = 7.0, 2.7 Hz, 5-H), 2.11 (1H, br d, J = 16.0 Hz, 4-H), 2.31 (2H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.52 (1H, br dd, J = 20.5, 4.2 Hz, 7-H), 2.72 (1H, br ddd, J = 20.5, 4.2 Hz, 7-H), 2.78 (1H, d, J = 16.0 Hz, 4-H), 3.09 (3H, s, N-CH_3), 5.13 (1H, m, 6-H), 5.63 (1H, br t, J = 4.2 Hz, 8-H), 5.73 (1H, s, 9-H); MS (EI) *m*/*z* 315 $(M)^+$.

4.2.21. (4a*R*,5*R*,6*R*,7*R*)-7-Hydroxy-6-propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11b). A solution of **1b** (200 mg = 0.73 mmol) in DMF (10 ml) were added *t*-butyldimethylsilyl chloride (TBDMSCl) (650 mg = 4.31 mmol) and imidazole (500 mg = 7.34 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was dissolved in AcOEt and washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography on silica gel of this residue provided (282 mg, 100%) of the 7-*O*-TBDMS-compound. To a solution of 7-*O*-TBDMS-compound (25 mg = 0.06 mmol) in CH_2Cl_2 (1 ml) were added propionyl chloride (28 μl = 0.28 mmol) and pyridine (52 μl = 0.64 mmol). The reaction mixture was stirred at room temperature for 17 h. The mixture was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. This residue was used in the following step with no further purification. The residue was diluted in THF (1 ml) and added 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (50 μl = 0.05 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was dissolved in AcOEt and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 1.4 mg (34%) of the title

compound (**11 b**) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, s, 4a-CH_3), 1.11 (3H, d, J = 7.1 Hz, 5-CH_3), 1.15 (3H, t, J = 7.6 Hz, $OCOCH_2CH_3$), 1.89 (3H, d, J = 2.0 Hz, 3-CH_3), 2.16 (1H, br d, J = 15.0 Hz, 4-H), 2.16 (1H, dq, J = 7.1, 3.1 Hz, 5-H), 2.35 (1H, q, J = 7.6 Hz, $OCOCH_2CH_3$), 2.36 (1H, q, J = 7.6 Hz, $OCOCH_2CH_3$), 2.82 (1H, d, J = 15.0 Hz, 4-H), 3.12 (3H, s, N-CH_3), 4.14 (1H, dd, J = 4.6, 1.2 Hz, 7-H), 4.96 (1H, m, 6-H), 5.74 (1H, s, 9-H), 5.77 (1H, d, J = 4.6 Hz, 8-H); MS (TSP) m/z 332 $(M+H)^+$.

4.2.22. (4a*R*,5*R*,6*R*,7*S*)-7-Acetoxy-6-hydroxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11c). Reaction of **6** gave **11c** in 42% yield as a colorless solid by a similar procedure to **11b**: ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, d, J = 7.2 Hz, 5-CH_3), 1.15 (3H, s, 4a-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 1.99 (1 H, dq, J = 7.2, 2.5 Hz, 5-H), 2.12 (1H, br d, J = 15.9 Hz, 4-H), 2.15 (3H, s, $COCH_3$), 2.81 (1H, d, J = 15.9 Hz, 4-H), 3.12 (3H, s, N-CH_3), 4.56 (1H, m, 7-H), 5.30 (1H, m, 6-H), 5.60 (1H, s, 8-H), 5.74 (1H, s, 9-H); MS (EI) m/z 317 $(M)^+$; HRMS (FAB) ($C_{13}H_{24}O_6N_3$) calcd 318.1665, obsd 318.1694.

4.2.23. (4a*R*,5*R*,6*R*,7*R*)-7-Acetoxy-6-propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11d). Reaction of **5** gave **11d** in 30% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, d, J = 7.2 Hz, 5-CH_3), 1.11 (3H, s, 4a-CH_3), 1.14 (3H, t, J = 7.6 Hz, $OCOCH_2CH_3$), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.05 (3H, s, $OCOCH_3$), 2.10 (1H, dq, J = 7.2, 2.8 Hz, 5-H), 2.17 (1H, br d, J = 15.9 Hz, 4-H), 2.34 (2H, q, J = 7.6 Hz, $OCOCH_2CH_3$), 2.83 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 5.08 (1H, m, 6-H), 5.13 (1H, dd, J = 4.7, 1.6 Hz, 7-H), 5.73 (1H, s, 9-H), 5.76 (1H, d, J = 4.7 Hz, 8-H); $[\alpha]_D^{20}$ −291 (c 1.0, MeOH); MS (FAB) m/z 374 $(M+H)^+$.

4.2.24. (4a*R*,5*R*,6*R*,7*R*)-7-Ethoxy-6-propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11e). Reaction of **5** with EtOH gave **1c** in 85% by a similar procedure to **1a**. Reaction of **1c** gave **11e** in 44% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, J = 7.1 Hz, 5-CH_3), 1.09 (3H, s, 4a-CH_3), 1.13 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.20 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 2.11 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.15 (1H, br d, J = 15.9 Hz, 4-H), 2.33 (2H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.62 (1H, dq, J = 7.0, 2.4 Hz, OCH_2CH_3), 3.68 (1H, dd, J = 4.8, 1.5 Hz, 7-H), 3.83 (1H, dq, J = 7.0, 2.4 Hz, OCH_2CH_3), 5.06 (1H, m, 6-H), 5.72 (1H, s, 9-H), 5.73 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −267 (c 1.0, MeOH); MS (EI) m/z 359 $(M)^+$.

4.2.25. (4a*R*,5*R*,6*R*,7*R*)-6-Propionyloxy-7-propoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11f). Reaction of **5** with ^{n}PrOH gave **1d** in 85% by a similar procedure to **1a**. Reaction of **1d** gave **11f** in 59% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.5, $OCH_2CH_2CH_3$), 1.07 (3H, d, J = 7.3 Hz, 5-CH_3), 1.08 (3H, s, 4a-CH_3), 1.13 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.57 (2H, sep, J = 7.2 Hz, $OCH_2CH_2CH_3$), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 2.09 (1H, dq, J = 7.3, 2.6 Hz, 5-H), 2.15 (1H, br d, J = 16.0 Hz, 4-H), 2.32 (1H, q, J = 7.5, $OCOCH_2CH_3$), 2.33 (1H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.77 (1H, d, J = 16.0 Hz, 4-H), 3.07 (3H, s, N-CH_3), 3.53 (1H, dt, J = 9.4, 6.5 Hz, $OCH_2CH_2CH_3$), 3.67 (1H, m, 7-H), 3.70 (1H, dt, J = 9.4, 6.5 Hz, $OCH_2CH_2CH_3$), 5.05 (1H, m, 6-H), 5.71 (1H, s, 9-H), 5.72 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 374 $(M+H)^+$; HRMS (FAB) ($C_{22}H_{32}O_4N$) calcd 374.2331, obsd 374.2309.

4.2.26. (4a*R*,5*R*,6*R*,7*R*)-7-Butoxy-6-propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11g). Reaction of **5** with ^{n}BuOH gave **1e** in 85% by a similar procedure to **1a**. Reaction of **1e** gave **11g** in 42% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz, $OCH_2CH_2CH_2CH_3$), 1.07 (3H, d, J = 7.3 Hz, 5-CH_3), 1.08 (3H, s, 4a-CH_3), 1.13 (3H, t, J = 7.5 Hz, $OCOCH_2CH_3$), 1.36 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.54 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 2.09 (1H, dq, J = 7.3, 2.6 Hz, 5-H), 2.15 (1H, br d, J = 16.0 Hz, 4-H), 2.32 (1H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.33 (1H, q, J = 7.5 Hz, $OCOCH_2CH_3$), 2.79 (1H, d, J = 16.0 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.57 (1H, dt, J = 6.4, 9.4 Hz, $OCH_2CH_2CH_2CH_3$), 3.66 (1H, dd, J = 5.2, 1.4 Hz, 7-H), 3.76 (1H, dt, J = 6.4, 9.4 Hz, $OCH_2CH_2CH_2CH_3$), 5.05 (1H, br s, 6-H), 5.71 (1H, s, 9-H), 5.72 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 388 $(M+H)^+$; HRMS (FAB) ($C_{23}H_{34}O_4N$) calcd 388.2488, obsd 388.2494.

4.2.27. (4a*R*,5*R*,6*R*,7*R*)-7-(1-Methylethoxy)-6-propionyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (11h). Reaction of **5** with ^{i}PrOH gave **1f** in 85% by a similar procedure to **1a**. Reaction of **1f** gave **11h** in 31% yield as a colorless solid by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, J = 7.1 Hz, 5-CH_3), 1.09 (3H, s, 4a-CH_3), 1.14 (3H, t, J = 7.6 Hz, $OCOCH_2CH_3$), 1.16 (3H, d, J = 6.1 Hz, $OCH(CH_3)_2$), 1.19 (3H, d, J = 6.1 Hz, $OCH(CH_3)_2$), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 2.13 (1H, dq, J = 7.1, 2.7 Hz, 5-H), 2.16 (1H, br d, J = 15.9 Hz, 4-H), 2.34 (2H, q, J = 7.6 Hz, $OCOCH_2CH_3$), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.75 (1H, dd, J = 4.8, 1.4 Hz, 7-H), 3.97 (1H, sep, J = 6.1 Hz, $OCH(CH_3)_2$), 4.96 (1H, m, 6-H), 5.67 (1H, d, J = 4.8 Hz, 8-H), 5.72 (1H, s, 9-H); $[\alpha]_D^{28}$ −304 (c 0.5, MeOH); MS (FAB) m/z 374 $(M+H)^+$.

4.2.28. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-methylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (12a). A solution of **1a** (100 mg = 0.35 mmol) in CH_2Cl_2 (3 ml) was added 1,1′-carbonyldiimidazole (204 mg = 1.26 mmol). The reaction mixture was stirred at room temperature for 17 h. The reaction mixture was added CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The organic layer was dried ($MgSO_4$), filtered, and concentrated. This residue was used in the following step with no further purification. The residue was diluted in toluene and added 1 M methylamine of THF solution (0.7 ml). The reaction mixture was stirred at room temperature until complete consumption of the starting material was observed as determined by TLC analysis. The mixture was washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided 103 mg (85%) of the title compound (**12a**) as a colorless solid: ^{1}H NMR

($CDCl_3$) δ 0.97 (3H, s, 4a-CH_3), 1.10 (3H, d, J = 7.1 Hz, 5-CH_3), 1.84 (3H, br s, 3-CH_3), 2.03 (1H, dq, J = 7.1, 2.6 Hz, 5-H), 2.11 (1H, br d, J = 16.3 Hz, 4-H), 2.77 (1H, d, J = 16.3 Hz, 4-H), 2.82 (3H, d, J = 4.7 Hz, $OCONHCH_3$), 3.06 (3H, s, N-CH_3), 3.51 (3H, s, OCH_3), 3.67 (1H, br d, J = 4.8 Hz, 7-H), 4.97 (1H, m, 6-H), 5.11 (1H, m, $OCONHCH_3$), 5.70 (1H, s, 9-H), 5.75 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 347 $(M+H)^+$; HRMS (FAB) ($C_{19}H_{27}O_4N_2$) calcd 347.1971, obsd 347.1977.

4.2.29. (4a*R*,5*R*,6*R*,7*R*)-6-Ethylcarbamoyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (12b). Reaction of **1a** gave **12b** in 97% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.02 (3H, s, 4a-CH_3), 1.12 (3H, d, J = 7.1 Hz, 5-CH_3), 1.16 (3H, t, J = 6.9 Hz, $OCONHCH_2CH_3$), 1.86 (3H, br s, 3-CH_3), 2.05 (1H, dq, J = 7.1, 1.9 Hz, 5-H), 2.13 (1H, br d, J = 16.0 Hz, 4-H), 2.79 (1H, d, J = 16.0 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.25 (2H, br q, J = 6.9 Hz, $OCONHCH_2CH_3$), 3.52 (3H, s, OCH_3), 3.69 (1H, br d, J = 4.7 Hz, 7-H), 4.49 (1H, m, $OCONHCH_2CH_3$), 4.97 (1H, m, 6-H), 5.72 (1H, s, 9-H), 5.76 (1H, d, J = 4.7 Hz, 8-H); MS (FAB) m/z 361 $(M+H)^+$.

4.2.30. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-propylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (12c). Reaction of **1a** gave **12c** in 88% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.2 Hz, $OCONHCH_2CH_2CH_3$), 0.99 (3H, s, 4a-CH_3), 1.11 (3H, d, J = 6.8 Hz, 5-CH_3), 1.54 (2H, seq, J = 7.2 Hz, $OCONHCH_2CH_2CH_3$), 1.85 (3H, br s, 3-CH_3), 2.04 (1H, dq, J = 6.8, 1.9 Hz, 5-H), 2.11 (1H, br d, J = 16.3 Hz, 4-H), 2.77 (1H, d, J = 16.3 Hz, 4-H), 3.06 (3H, s, N-CH_3), 3.15 (2H, br dt, J = 7.2 Hz, $OCONHCH_2CH_2CH_3$), 3.51 (3H, s, OCH_3), 3.67 (1H, br d, J = 4.9 Hz, 7-H), 4.97 (1H, m, 6-H), 5.08 (1H, m, $OCONHCH_2CH_2CH_3$), 5.71 (1H, s, 9-H), 5.75 (1H, d, J = 4.9 Hz, 8-H); MS (FAB) m/z 375 $(M+H)^+$; HRMS (FAB) ($C_{21}H_{30}O_4N_2$ Na) calcd 397.2103, obsd 397.2074.

4.2.31. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylcarbamoyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (12d). Reaction of **1a** gave **12d** in 68% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 0.52–0.74 (4H, m, $OCONHC_3H_5$), 1.00–1.22 (6H, m, 4a-CH_3, 5-CH_3), 1.87 (3H, d, J = 1.7 Hz, 3-CH_3), 2.10 (1H, m, 5-H), 2.14 (1H, br d, J = 15.9 Hz, 4-H), 2.61 (1H, m, $OCONHC_3H_5$), 2.80 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.54 (3H, s, OCH_3), 3.71 (1H, br d, J = 4.4 Hz, 7-H), 5.00 (1H, m, 6-H,), 5.73 (1H, s, 9-H), 5.76 (1H, d, J = 4.4 Hz, 8-H); MS (FAB) m/z 373 $(M+H)^+$; HRMS (FAB) ($C_{21}H_{29}O_4N_2$) calcd 373.2121, obsd 373.2124.

4.2.32. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclohexylcarbamoyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (12e). Reaction of **1a** gave **12e** in 52% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.08 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.2 Hz, 5-CH_3), 1.10–2.10 (11H, m, $OCONHC_6H_{11}$), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.07 (1H, dq, J = 7.2, 3.0 Hz, 5-H), 2.14 (1H, br d, J = 16.1 Hz, 4-H), 2.80 (1H, d, J = 16.1 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.50 (1H, m, $OCONHC_6H_{11}$), 3.53 (3H, s, OCH_3), 3.70 (1H, br d, J = 4.9 Hz, 7-H), 4.97 (1H, m, 6-H), 5.73 (1H, s, 9-H), 5.77 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 415 $(M+H)^+$; HRMS (FAB) ($C_{24}H_{35}O_4N_2$) calcd 415.2596, obsd 415.2600.

4.2.33. (4a*R*,5*R*,6*R*,7*R*)-6-Benzylcarbamoyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (12f). Reaction of **1a** gave **12f** in 64% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.03 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.86 (3H, d, J = 1.7 Hz, 3-CH_3), 2.08 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.13 (1H, br d, J = 15.7 Hz, 4-H), 2.79 (1H, d, J = 15.7 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.54 (3H, s, OCH_3), 3.72 (1H, br d, J = 4.6 Hz, 7-H), 4.40 (2H, m, $OCONHCH_2C_6H_5$), 5.04 (1H, m, 6-H), 5.16 (1H, m, $OCONHCH_2C_6H_5$), 5.72 (1H, s, 9-H), 5.77 (1H, d, J = 4.6 Hz, 8-H), 7.27-7.35 (5H, m, $OCONHCH_2C_6H_5$); MS (FAB) m/z 423 $(M+H)^+$; HRMS (FAB) ($C_{25}H_{31}O_4N_2$) calcd 423.2284, obsd 423.2291.

4.2.34. (4a*R*,5*R*,6*S*)-6-Propylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (13a). Reaction of **9b** gave **13a** in 74% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.1 Hz, $OCONHCH_2CH_2CH_3$), 1.03 (3H, s, 4a-CH_3), 1.09 (3H, d, J = 7.0 Hz, 5-CH_3), 1.53 (2H, seq, J = 7.1 Hz, $OCONHCH_2CH_2CH_3$), 1.83 (1H, br q, J = 6.9 Hz, 5-H), 1.85 (3H, br s, 3-CH_3), 2.10 (1H, br d, J = 16.0 Hz, 4-H), 2.45 (1H, dd, J = 20.4, 4.5 Hz, 7-H), 2.56 (1H, br dd, J = 20.4, 4.5 Hz, 7-H), 2.77 (1H, d, J = 16.0 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.14 (2H, br dt, J = 7.1 Hz, $OCONHCH_2CH_2CH_3$), 4.99 (1H, m, $OCONHCH_2CH_2CH_3$), 5.04 (1H, m, 6-H), 5.65 (1H, m, 8-H), 5.71 (1H, s, 9-H); MS (FAB) m/z 343 $(M-H)^+$.

4.2.35. (4a*R*,5*R*,6*R*,7*R*)-7-Hydroxy-6-propylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (13b). Reaction of **1b** gave 7-*O*-TBDMS-compound by a procedure to **11b**. Reaction of 7-*O*-TBDMS-compound gave **13b** in 34% by a similar procedure to **12a**, followed by deprotection of the TBDMS group with TBAF: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz, $OCONHCH_2CH_2CH_3$), 1.04 (3H, s, 4a-CH_3), 1.12 (3H, d, J = 7.0 Hz, 5-CH_3), 1.53 (2H, seq, J = 7.3 Hz, $OCONHCH_2CH_2CH_3$), 1.88 (3H, br s, 3-CH_3), 2.14 (1H, dq, J = 7.0, 2.8 Hz, 5-H), 2.15 (1H, br d, J = 16.3 Hz, 4-H), 2.80 (1H, d, J = 16.3 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.15 (2H, br dt, J = 7.3 Hz, $OCONHCH_2CH_2CH_3$), 4.21 (1H, m, 7-H), 4.83 (1H, m, 6-H), 4.83 (1H, m, $OCONHCH_2CH_2CH_3$), 5.74 (1H, s, 9-H), 5.78 (1H, d, J = 4.5 Hz, 8-H); MS (FAB) m/z 361 $(M+H)^+$; HRMS (FAB) ($C_{20}H_{29}O_4N_2$) calcd 361.2128, obsd 361.2122.

4.2.36. (4a*R*,5*R*,6*R*,7*R*)-7-Ethoxy-6-propylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (13c). Reaction of **1c** gave **13c** in 56% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR

($CDCl_3$) δ 0.92 (3H, t, J = 7.1 Hz, $OCONHCH_2CH_2CH_3$), 1.01 (3H, s, 4a-CH_3), 1.11 (3H, d, J = 7.2 Hz, 5-CH_3), 1.21 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.54 (2H, seq, J = 7.1 Hz, $OCONHCH_2CH_2CH_3$), 1.85 (3H, br s, 3-CH_3), 2.08 (1H, dq, J = 7.2, 2.6 Hz, 5-H), 2.14 (1H, br d, J = 15.8 Hz, 4-H), 2.77 (1H, d, J = 15.8 Hz, 4-H), 3.07 (3H, s, N-CH_3), 3.16 (2H, br dt, J = 7.1 Hz, $OCONHCH_2CH_2CH_3$), 3.64 (1H, dq, J = 9.4, 7.0 Hz, OCH_2CH_3), 3.77 (1H, br d, J = 4.9 Hz, 7-H), 3.87 (1H, dq, J = 9.4, 7.0 Hz, OCH_2CH_3), 4.99 (1H, m, $OCONHCH_2CH_2CH_3$), 4.95 (1H, m, 6-H), 5.74 (1H, d, J = 4.9 Hz, 8-H), 5.71 (1H, s, 9-H); MS (FAB) m/z 389 $(M+H)^+$; HRMS (FAB) ($C_{22}H_{33}O_4N_2$) calcd 389.2441, obsd 389.2425.

4.2.37. (4a*R*,5*R*,6*R*,7*R*)-7-(1-Methylethoxy)-6-propylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz-[*f*]indol-2(4*H*)-one (13d). Reaction of **1f** gave **13d** in 43% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz, $OCONHCH_2$ CH_2CH_3), 1.03 (3H, s, 4a-CH_3), 1.12 (3H, d, J = 7.0 Hz, 5-CH_3), 1.18 (3H, d, J = 6.5 Hz, $OCH(CH_3)_2$), 1.21 (3H, d, J = 6.5 Hz, $OCH(CH_3)_2$), 1.55 (2H, seq, J = 7.3 Hz, $OCONHCH_2CH_2CH_3$), 1.86 (3H, br s, 3-CH_3), 2.12 (1H, br q, J = 7.1 Hz, 5-H), 2.16 (1H, br d, J = 16.6 Hz, 4-H), 2.78 (1H, d, J = 16.6 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.16 (2H, br dt, J = 7.3 Hz, $OCONHCH_2CH_2$ CH_3), 3.84 (1H, m, 7-H), 4.03 (1H, sep, J = 6.5 Hz, $OCH(CH_3)_2$), 4.09 (1H, m, $OCONHCH_2$ CH_2CH_3), 4.86 (1H, m, 6-H), 5.69 (1H, d, J = 4.5 Hz, 8-H), 5.72 (1H, s, 9-H); MS (FAB) m/z 403 $(M+H)^+$; HRMS (FAB) ($C_{23}H_{35}O_4N_2$) calcd 403.2596, obsd 403.2599.

4.2.38. (4a*R*,5*R*,6*R*,7*R*)-7-(2-Methyl-1-propoxy)-6-propylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (13e). Reaction of **5** gave **1g** in 52% by a similar procedure to **1a**. Reaction of **1g** gave **13e** in 34% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 0.91 (3H, d, J = 6.6 Hz, OCH_2 $CH(CH_3)_2$), 0.92 (3H, d, J = 6.6 Hz, $OCH_2CH(CH_3)_2$), 0.95 (3H, t, J = 7.0 Hz, $OCONHCH_2CH_2CH_3$), 1.03 (3H, s, 4a-CH_3), 1.12 (1H, m, $OCH_2CH(CH_3)_2$), 1.12 (3H, d, J = 7.0 Hz, 5-CH_3), 1.55 (2H, seq, J = 7.0 Hz, $OCONHCH_2CH_2CH_3$), 1.87 (3H, br s, 3-CH_3), 2.09 (1H, dq, J = 7.0, 2.3 Hz, 5-H), 2.16 (1H, br d, J = 16.2 Hz, 4-H), 2.79 (1H, d, J = 16.2 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.17 (2H, br dt, J = 7.0 Hz, $OCONHCH_2CH_2$ CH_3), 3.40 (3H, dd, J = 9.2, 6.8 Hz, $OCH_2CH(CH_3)_2$), 3.53 (3H, dd, J = 9.2, 6.8 Hz, $OCH_2CH(CH_3)_2$), 3.76 (1H, br d, J = 4.7 Hz, 7-H), 4.89 (1H, m, $OCONHCH_2$ CH_2CH_3), 4.95 (1H, m, 6-H), 5.74 (1H, s, 9-H), 5.77 (1H, d, J = 4.7 Hz, 8-H); MS (FAB) m/z 417 $(M+H)^+$; HRMS (FAB) ($C_{24}H_{37}O_4N_2$) calcd 417.2753, obsd 417.2756.

4.2.39. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-*N*,*N*-dimethylcarbamoyloxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz-[*f*]indol-2(4*H*)-one (14a). Reaction of **1a** gave **14a** in 82% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.11 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.10 (1H, dq, J = 7.1, 2.6 Hz, 5-H), 2.16 (1H, br d, J = 16.3 Hz, 4-H), 2.82 (1H, d, J = 16.3 Hz, 4-H), 2.86 (3H, s, $OCON(CH_3)_2$), 2.95 (3H, s, $OCON(CH_3)_2$), 3.11 (3H, s, N-CH_3), 3.55 (3H, s, OCH_3), 3.71 (1H, br d, J = 4.8 Hz, 7-H), 4.98 (1H, m, 6-H), 5.74 (1H, s, 9-H), 5.76 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 361 $(M+H)^+$; HRMS (FAB) ($C_{20}H_{29}O_4N_2$) calcd 361.2127, obsd 361.2123.

4.2.40. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(*N*-ethyl-*N*-methylcarbamoyloxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (14b). Reaction of **1a** gave **14b** in 54% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.06 (3H, t, $OCO(CH_3)N(CH_2CH_3)$), 1.10 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.10 (1H, dq, J = 7.1, 2.6 Hz, 5-H), 2.16 (1H, br d, J = 16.3 Hz, 4-H), 2.81 (1H, d, J = 16.3 Hz, 4-H), 2.83 and 2.93 (3H, s, $OCO(CH_3)N(CH_2CH_3)$), 3.28 (2H, m, $OCO(CH_3)N(CH_2CH_3)$), 3.11 (3H, s, N-CH_3), 3.55 (3H, s, OCH_3), 3.70 (1H, br s, 7-H), 4.99 (1H, br s, 6-H), 5.74 (1H, s, 9-H), 5.77 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 375 $(M+H)^+$, HRMS (FAB) ($C_{21}H_{31}$ O_4N_2) calcd 375.2284, obsd 375.2276.

4.2.41. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(*N*-methyl-*N*-propylcarbamoyloxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (14c). Reaction of **1a** gave **14c** in 52% yield as a colorless solid by a similar procedure to **12a**:^1H NMR ($CDCl_3$) δ 0.80 & 0.88 (3H, each t, $OCO(CH_3)N(CH_2CH_2CH_3)$), 1.09 (3H, s, 4a-CH_3), 1.13 (3H, d, J = 7.1 Hz, 5-CH_3), 1.51 (2H, m, $OCO(CH_3)$ $N(CH_2CH_2CH_3)$), 1.87 (3H, d, J = 1.9 Hz, 3-CH_3), 2.09 (1H, dq, J = 7.1, 2.6 Hz, 5-H), 2.15 (1H, br d, J = 16.3 Hz, 4-H), 2.81 (1H, d, J = 16.3 Hz, 4-H), 2.82 and 2.92 (3H, each s, $OCO(CH_3)N(CH_2CH_2CH_3)$), 3.09 (3H, s, N-CH_3), 3.18 (2H, m, $OCO(CH_3)N(CH_2CH_2$ CH_3)), 3.18 (2H, m, $OCO(CH_3)N(CH_2CH_3)$), 3.55 (3H, s, OCH_3), 3.68 (1H, m, 7-H), 4.98 (1H, br s, 6-H), 5.73 (1H, s, 9-H), 5.74 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 389 $(M+H)^+$; HRMS (FAB) ($C_{22}H_{33}O_4N_2$) calcd 389.2440, obsd 389.2435.

4.2.42. (4a*R*,5*R*,6*R*,7*R*)-6-(*N*,*N*-Diethylcarbamoyloxy)-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (14d). Reaction of **1a** gave **14d** in 70% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.07–1.17 (6H, m, $OCON(CH_2CH_3)_2$), 1.10 (3H, s, 4a- CH_3), 1.16 (3H, d, J = 7.2 Hz, 5-CH_3), 1.88 (3H, d, J = 1.7 Hz, 3-CH_3), 2.12 (1H, dq, J = 7.2, 3.0 Hz, 5-H), 2.17 (1H, br d, J = 15.9 Hz, 4-H), 2.82 (1H, d, J = 15.9 Hz, 4-H), 3.11 (3H, s, N-CH_3), 3.18–3.53 (4H, m, $OCON(CH_2CH_3)_2$), 3.55 (3H, s, OCH_3), 3.70 (1H, br d, J = 4.7 Hz, 7-H), 5.00 (1H, m, 6-H), 5.75 (1H, s, 9-H), 5.77 (1H, d, J = 4.7 Hz, 8-H); MS (FAB) m/z 387 $(M+H)^+$; HRMS (FAB) ($C_{22}H_{33}O_4N_2$) calcd 389.2440, obsd 389.2435.

4.2.43. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(piperidin-1-ylcarbamoyloxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (14e). Reaction of **1a** gave **14e** in 85% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.10 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.2 Hz, 5-CH_3), 1.49–1.59 (6H, m, $OCOC_5H_{10}N$), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.10 (1H, dq, J = 7.2, 3.0 Hz, 5-H), 2.16 (1H, br d, J = 16.1 Hz, 4-H), 2.82 (1H, d, J = 16.1 Hz, 4-H), 3.11 (3H, s, N-CH_3), 3.32–3.47 (4H, m, $OCOC_5H_{10}N$), 3.55

(3H, s, OCH_3), 3.72 (1H, dd, J = 4.8, 1.2 Hz, 7-H), 5.02 (1H, m, 6-H), 5.75 (1H, s, 9-H), 5.77 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 401 $(M+H)^+$; HRMS (FAB) ($C_{23}H_{33}O_4N_2$) calcd 401.2440, obsd 401.2436.

4.2.44. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(morpholin-4-yl-carbamoyloxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (14f). Reaction of **1a** gave **14f** in 74% yield as a colorless solid by a similar procedure to **12a**: ^1H NMR ($CDCl_3$) δ 1.07 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.88 (3H, d, J = 1.9 Hz, 3-CH_3), 2.12 (1H, dq, J = 7.1, 3.0 Hz, 5-H), 2.17 (1H, br d, J = 15.8 Hz, 4-H), 2.82 (1H, d, J = 15.8 Hz, 4-H), 3.11 (3H, s, N-CH_3), 3.40–3.66 (8H, m, $OCOC_4H_8NO$), 3.54 (3H, s, OCH_3), 3.71 (1H, br d, J = 4.8 Hz, 7-H), 5.04 (1H, m, 6-H), 5.74 (1H, s, 9-H), 5.77 (1H, d, J = 4.8 Hz, 8-H); MS (FAB) m/z 403 $(M+H)^+$; HRMS (FAB) ($C_{22}H_{31}O_5N_2$) calcd 403.2233, obsd 403.2234.

4.2.45. (4a*R*,5*R*,6*R*,7*R*)-6-Ethoxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15b). Reaction of **1a** gave **15b** in 36% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 1.06 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.17 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 1.87 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.09 (1H, br d, J = 15.9 Hz, 4-H), 2.77 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.38 (1H, m, 6-H), 3.42 (1H, dq, J = 7.0, 2.3 Hz, OCH_2CH_3), 3.42 (3H, s, O-CH_3), 3.66 (1H, dq, J = 7.0, 2.3 Hz, OCH_2CH_3), 3.70 (1H, dd, J = 4.8, 1.4 Hz, 7-H), 5.72 (1H, s, 9-H), 5.81 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −300 (c 1.0, MeOH); MS (EI) m/z 317 $(M)^+$.

4.2.46. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-propoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15c). Reaction of **1a** gave **15c** in 24% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 6.4 Hz, $OCH_2CH_2CH_3$), 1.07 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.55 (2H, seq, J = 6.4 Hz, $OCH_2CH_2CH_3$), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 1.87 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.09 (1H, br d, J = 15.9 Hz, 4-H), 2.77 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.30 (1H, dt, J = 9.0, 6.4 Hz, $OCH_2CH_2CH_3$), 3.37 (1H, m, 6-H), 3.42 (3H, s, OCH_3), 3.57 (1H, dt, J = 9.0, 6.4 Hz, $OCH_2CH_2CH_3$), 3.70 (1H, dd, J = 4.8, 1.4 Hz, 7-H), 5.72 (1H, s, 9-H), 5.80 (1H, d, J = 4.8 Hz, 8-H); $[\alpha]_D^{18}$ −309 (c 1.0, MeOH); MS (EI) m/z 331 $(M)^+$.

4.2.47. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(2-propenyloxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15d). Reaction of **1a** gave **15d** in 69% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 1.08 (3H, s, 4a-CH_3), 1.15 (3H, d, J = 7.1 Hz, 5-CH_3), 1.85 (3H, d, J = 2.0 Hz, 3-CH_3), 1.90 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.10 (1H, br d, J = 15.9 Hz, 4-H), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.41 (3H, s, OCH_3), 3.46 (1H, m, 6-H), 3.72 (1H, dd, J = 4.8, 1.4 Hz, 7-H), 3.94 (1H, ddt, J = 13.1, 5.6, 1.5 Hz, $OCH_2CH{=}CH_2$), 4.15 (1H, ddt, J = 13.1, 5.6, 1.5 Hz, $OCH_2CH{=}CH_2$), 5.20 (2H, m, $OCH_2CH{=}CH_2$), 5.72 (1H, s, 9-H), 5.80 (1H, d, J = 4.8 Hz, 8-H), 5.89 (1H, m, $OCH_2CH{=}CH_2$); $[\alpha]_D^{18}$ −272 (c 1.0, MeOH); MS (EI) m/z 329 $(M)^+$.

4.2.48. (4a*R*,5*R*,6*R*,7*R*)-6-Butoxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15e). Reaction of **1a** gave **15e** in 31% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz, $OCH_2CH_2CH_2CH_3$), 1.08 (3H, s, 4a-CH_3), 1.16 (3H, d, J = 7.2 Hz, 5-CH_3), 1.38 (2H, m, $OCH_2CH_2CH_2$ CH_3), 1.54 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.87 (3H, d, J = 2.0 Hz, 3-CH_3), 1.89 (1H, dq, J = 7.2, 2.7 Hz, 5-H), 2.11 (1H, br d, J = 15.9 Hz, 4-H), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.10 (3H, s, N-CH_3), 3.36 (1H, dt, J = 9.0, 6.3 Hz, $OCH_2CH_2CH_2CH_3$), 3.38 (1H, m, 6-H), 3.44 (3H, s, OCH_3), 3.62 (1H, dt, J = 9.0, 6.3 Hz, $OCH_2CH_2CH_2CH_3$), 3.72 (1H, br d, J = 4.4 Hz, 7-H), 5.74 (1H, s, 9-H), 5.82 (1H, d, J = 4.4 Hz, 8-H); MS (TSP) m/z 346 $(M+H)^+$.

4.2.49. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(3-methylbutoxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15f). Reaction of **1a** gave **15f** in 19% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 0.88 (3H, d, J = 6.7 Hz, $OCH_2CH_2CH(CH_3)_2$), 0.88 (3H, d, J = 6.7 Hz, $OCH_2CH_2CH(CH_3)_2$), 1.06 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz,5-CH_3), 1.43 (2H, m, OCH_2CH_2CH $(CH_3)_2$), 1.70 (1H, m, OCH_2CH_2CH $(CH_3)_2$), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 1.87 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.09 (1H, br d, J = 15.9 Hz, 4-H), 2.77 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.36 (1H, m, 6-H), 3.36 (1H, dt, J = 9.1, 6.3 Hz, OCH_2CH_2 $CH(CH_3)_2$), 3.43 (3H, s, OCH_3), 3.63 (1H, dt, J = 9.1, 6.3 Hz, OCH_2CH_2 $CH(CH_3)_2$), 3.71 (1H, dd, J = 4.7, 1.4 Hz, 7-H), 5.72 (1H, s, 9-H), 5.81 (1H, d, J = 4.7 Hz, 8-H); $[\alpha]_D^{20}$ −157 (c 1.0, MeOH); MS (EI) m/z 359 $(M)^+$; HRMS (FAB) ($C_{22}H_{34}O_3N$) calcd 360.2538, obsd 360.2540.

4.2.50. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylmethoxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15g). Reaction of **1a** gave **15g** in 40% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 0.20-0.48 (4H, m, $OCH_2C_3H_5$), 1.02 (1H,m, $OCH_2C_3H_5$), 1.09 (3H, s, 4a-CH_3), 1.16 (3H, d, J = 7.1 Hz, 5-CH_3), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 1.88 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.10 (1H, br d, J = 15.9 Hz, 4-H), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.27 (1H, dd, J = 10.1, 6.4 Hz, $OCH_2C_3H_5$), 3.42 (3H, s, OCH_3), 3.43 (1H, m, 6-H), 3.46 (1H, dd, J = 10.1, 6.4 Hz, $OCH_2C_3H_5$), 3.71 (1H, dd, J = 4.7, 1.4 Hz, 7-H), 5.73 (1H, s, 9-H), 5.82 (1H, d, J = 4.7 Hz, 8-H); $[\alpha]_D^{20}$ −264 (c 1.0, MeOH); MS (EI) m/z 343 $(M)^+$.

4.2.51. (4a*R*,5*R*,6*R*,7*R*)-6-Benzyloxy-7-methoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (15h). Reaction of **1a** gave **15h** in 70% yield as a colorless oil by a similar procedure to **15a**: ^1H NMR ($CDCl_3$) δ 1.13 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.86 (3H, d, J = 2.0 Hz, 3-CH_3), 1.92 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.11 (1H, br d, J = 15.9 Hz, 4-H), 2.78 (1H, d, J = 15.9 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.40 (3H, s, OCH_3), 3.55 (1H, m, 6-H), 3.78 (1H, dd, J = 4.8, 1.4 Hz, 7-H), 4.51 (1H, d, J = 12.0 Hz, $OCH_2C_6H_5$), 4.69 (1H, d, J = 12.0 Hz,

$OCH_2C_6H_5$), 5.72 (1H, s, 9-H), 5.80 (1H, d, J = 4.8 Hz, 8-H), 7.25–7.37 (5H, m, $OCH_2C_6H_5$); $[\alpha]_D^{18}$ −198 (*c* 1.0, MeOH); MS (EI) *m*/*z* 379 $(M)^+$.

4.2.52. (4a*R*,5*R*,6*R*,7*R*)-6-Ethoxy-7-(1-methylethoxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (16a). Reaction of **1f** gave **16a** in 49% yield as a colorless oil by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, s, 4a-CH_3), 1.15 (3H, d, J = 7.1 Hz, 5-CH_3), 1.18 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.19 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.19 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.86 (3H, d, J = 2.0 Hz, 3-CH_3), 1.93 (1H, dq, J = 7.1, 2.7 Hz, 5-H), 2.12 (1H, br d, J = 15.9 Hz, 4-H), 2.77 (1H, d, J = 15.9 Hz, 4-H), 3.08 (3H, s, N-CH_3), 3.30 (1H, m, 6-H), 3.40 (1H, dq, J = 9.2, 7.0 Hz, OCH_2CH_3), 3.67 (1H, dq, J = 9.2, 7.0 Hz, OCH_2CH_3), 3.86 (1H, br d, J = 4.1 Hz, 7-H), 3.75 (1H, sep, J = 6.0 Hz, $OCH(CH_3)_2$), 5.72 (1H, s, 9-H), 5.73 (1H, d, J = 4.1 Hz, 8-H); MS (EI) *m*/*z* 345 $(M)^+$.

4.2.53. (4a*R*,5*R*,6*R*,7*R*)-7-(1-Methylethoxy)-6-propoxy-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (16b). Reaction of **1f** gave **16b** in 34% yield as a colorless oil by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.4 Hz, $OCH_2CH_2CH_3$), 1.08 (3H, s, 4a-CH_3), 1.16 (3H, d, J = 7.1 Hz, 5-CH_3), 1.19 (3H, d, J = 6.1 Hz, $OCH(CH_3)_2$), 1.20 (3H, d, J = 6.1 Hz, $OCH(CH_3)_2$), 1.57 (2H, m, $OCH_2CH_2CH_3$), 1.86 (3H, d, J = 1.9 Hz, 3-CH_3), 1.94 (1H, dq, J = 7.1, 2.7 Hz, 5-H), 2.12 (1H, br d, J = 15.9 Hz, 4-H), 2.77 (1H, d, J = 15.9 Hz, 4-H), 3.09 (3H, s, N-CH_3), 3.29 (1H, dt, J = 8.8, 6.4 Hz, $OCH_2CH_2CH_3$), 3.29 (1H, m, 6-H), 3.58 (1H, dt, J = 8.8, 6.4 Hz, $OCH_2CH_2CH_3$), 3.87 (1H, dd, J = 5.2, 1.3 Hz, 7-H), 3.76 (1H, sep, J = 6.1 Hz, $OCH(CH_3)_2$), 5.72 (1H, d, J = 5.2 Hz, 8-H), 5.73 (1H, s, 9-H); MS (EI) *m*/*z* 359 $(M)^+$.

4.2.54. (4a*R*,5*R*,6*R*,7*R*)-6-Butoxy-7-(1-methylethoxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (16c). Reaction of **1f** gave **16c** in 19% yield as a colorless oil by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.10 (3H, t, J = 7.2 Hz, $OCH_2CH_2CH_2CH_3$), 1.05 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.18 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.19 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.37 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.52 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.85 (3H, d, J = 1.9 Hz, 3-CH_3), 1.92 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.11 (1H, br d, J = 15.9 Hz, 4-H), 2.75 (1H, d, J = 15.9 Hz, 4-H), 3.07 (3H, s, N-CH_3), 3.27 (1H, m, 6-H), 3.32 (1H, dt, J = 8.9, 6.2 Hz, $OCH_2CH_2CH_2CH_3$), 3.60 (1H, dt, J = 8.9, 6.2 Hz, $OCH_2CH_2CH_2CH_3$), 3.75 (1H, sep, J = 6.0 Hz, $OCH(CH_3)_2$), 3.85 (1H, dd, J = 5.2, 1.4 Hz, 7-H), 5.71 (1H, d, J = 5.2 Hz, 8-H), 5.71 (1H, s, 9-H); $[\alpha]_D^{20}$ −308 (*c* 1.0, MeOH); MS (EI) *m*/*z* 373 $(M)^+$; HRMS (FAB) ($C_{23}H_{36}O_3N$) calcd 374.2695, obsd 374.2702.

4.2.55. (4a*R*,5*R*,6*R*,7*R*)-6-(3-Methylbutoxy)-7-(1-methylethoxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (16d). Reaction of **1f** gave **16d** in 11% yield as a colorless oil by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, d, J = 6.6 Hz, $OCH_2CH_2CH(CH_3)_2$), 0.88 (3H, d, J = 6.6 Hz, $OCH_2CH_2CH(CH_3)_2$), 1.05 (3H, s, 4a-CH_3), 1.14 (3H, d, J = 7.1 Hz, 5-CH_3), 1.18 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.19 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.43 (2H, m, $OCH_2CH_2CH(CH_3)_2$), 1.70 (1H, m, OCH_2CH_2 $CH(CH_3)_2$), 1.85 (3H, d, J = 1.9 Hz, 3-CH_3), 1.92 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.11 (1H, br d, J = 15.9 Hz, 4-H), 2.75 (1H, d, J = 15.9 Hz, 4-H), 3.07 (3H, s, N-CH_3), 3.27 (1H, m, 6-H), 3.34 (1H, dt, J = 9.1, 6.3 Hz, OCH_2CH_2CH $(CH_3)_2$), 3.62 (1H, dt, J = 9.1, 6.3 Hz, $OCH_2CH_2CH(CH_3)_2$), 3.75 (1H, sep, J = 6.0 Hz, $OCH(CH_3)_2$), 3.85 (1H, dd, J = 5.2, 1.4 Hz, 7-H), 5.71 (1H, d, J = 5.2 Hz, 8-H), 5.71 (1H, s, 9-H); $[\alpha]_D^{20}$ −289 (*c* 1.0, MeOH); MS (EI) *m*/*z* 387 $(M)^+$; HRMS (FAB) ($C_{24}H_{38}O_3N$) calcd 388.2852, obsd 388.2881.

4.2.56. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylmethoxy-7-(1-methylethoxy)-4a,5,6,7-tetrahydro-1,3,4a,5-tetramethylbenz[*f*]indol-2(4*H*)-one (16e). Reaction of **1f** gave **16e** in 22% yield as a colorless oil by a similar procedure to **3a**: ^{1}H NMR ($CDCl_3$) δ 0.10–0.54 (4H, m, $OCH_2C_3H_5$), 1.00 (1H, m, $OCH_2C_3H_5$), 1.07 (3H, s, 4a-CH_3), 1.15 (3H, d, J = 7.1 Hz, 5-CH_3), 1.17 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.18 (3H, d, J = 6.0 Hz, $OCH(CH_3)_2$), 1.85 (3H, d, J = 1.9 Hz, 3-CH_3), 1.92 (1H, dq, J = 7.1, 2.8 Hz, 5-H), 2.11 (1H, br d, J = 15.9 Hz, 4-H), 2.76 (1H, d, J = 15.9 Hz, 4-H), 3.07 (3H, s, N-CH_3), 3.23 (1H, dd, J = 10.2, 6.6 Hz, $OCH_2C_3H_5$), 3.33 (1H, m, 6-H), 3.47 (1H, dd, J = 10.2, 6.6 Hz, $OCH_2C_3H_5$), 3.73 (1H, sep, J = 6.0 Hz, OCH $(CH_3)_2$), 3.84 (1H, dd, J = 5.2, 1.4 Hz, 7-H), 5.71 (1H, s, 9-H), 5.72 (1H, d, J = 5.2 Hz, 8-H); $[\alpha]_D^{20}$ −515 (*c* 1.0, MeOH); MS (EI) *m*/*z* 371 $(M)^+$; HRMS (FAB) ($C_{23}H_{34}O_3N$) calcd 372.2539, obsd 372.2533.

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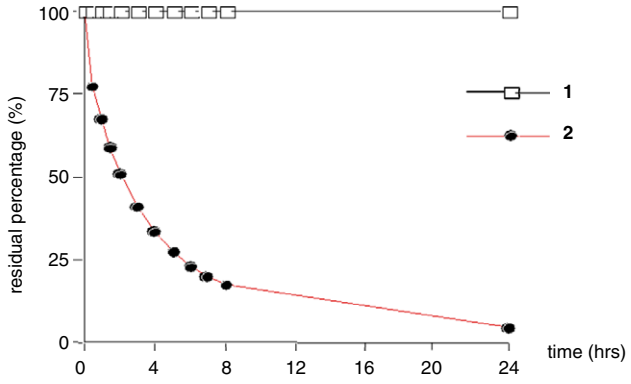
13. Figure of Stability at pH 11.5.



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