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STEREOCONTROLLED TOTAL SYNTHESIS OF (+)-PEDERINE

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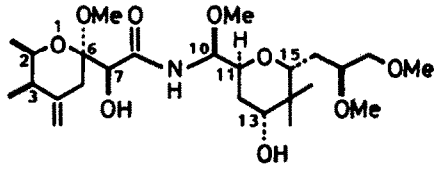
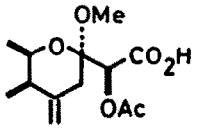
Abstract: A mild one-pot method for the synthesis of acyclic *N*-(1-methoxyalkyl)amides starting from carboxylic acid and methyl imidates has been developed and applied to the first total synthesis of (+)-pederine (1), a potent insect poison. Furthermore, the stereocontrolled total synthesis of 1 was also achieved by employing acid catalyzed double alkoxy-exchange reaction of *N*-(1-methoxylakyl)amide group as key step.

(+)-Pederine (1), a potent insect poison isolated from *Paedrus fuscipes*, exhibits remarkable physiological activities, such as inhibition of mitosis in HeLa cells and blocking protein synthesis in 80S ribosomes at concentration of 1-10 ng/ml.[3] The principle responsible for this action was first isolated independently by A. Ueta[4] and M. Pavan.[5] Detailed NMR spectral analysis[6] of the toxin, coupled with chemical evidence,[7] suggested that the structure was represented by 1 and this was confirmed by an X-ray crystallographic study.[8] The X-ray analysis also established the absolute configuration of 1.



1



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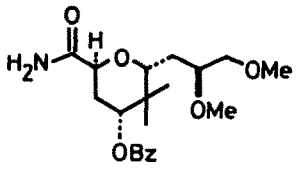


3

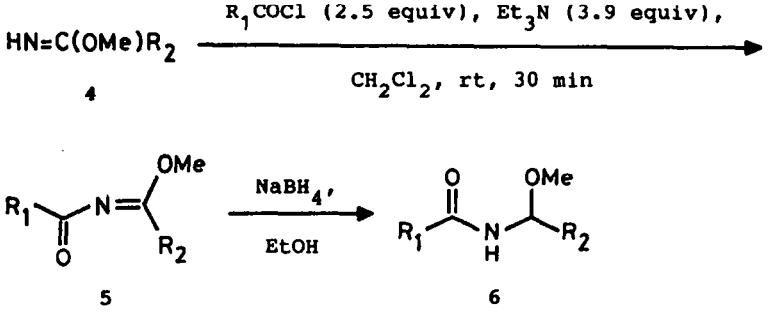
Since the natural product is not readily available, a practical chemical synthesis of 1 seemed to be an attractive problem, because of its unconventional chemical structure and physiological properties.[9-12] For the total syntheis of 1, a logical route is to connect two tetrahydropyran moieties through an *N*-(1-methoxyaklyl)amide linkage. According to this synthetic strategy, we have already achieved the total syntheses of 1. The stereoselective synthesis of the two tetrahydropyran moieties, (+)-acetylpederic acid (2) and (+)-benzoylpedamide (3) had already been reported.[9] Thus, this paper concerns with full details of devel-

opment of a new and effective synthetic method for *N*-(1-methoxyalkyl)amides, its application to the first total synthesis of **1**, and the stereocontrolled total synthesis of **1** accomplished by employing acid catalyzed double alkoxy-exchange reaction of *N*-(1-methoxyalkyl)amide group as key step.[10]

Results and Discussion

New and Effective Synthetic Method for *N*-(1-Methoxyalkyl)amides. One of the most characteristic features of **1** is the connecting functionality acyclic *N*-(1-methoxyalkyl)amide group. Since the chemistry of this class of compounds had not been well studies, a new and effective synthetic method for those compounds was necessary to the total synthesis of **1**. Preliminary experiments showed that treatment of methyl *N*-acylimidates (**5**),[13] which were prepared by the reaction of methyl imidates (**4**)[14] with acid chlorides,[15] with sodium borohydride afforded *N*-(1-methoxyalkyl)amides (**6**) in excellent yields as shown in **Table 1**. Therefore, it appeared indispensable for the total synthesis of **1** to find out an acylation method for **4** under mild conditions, because acetylpederic acid (**2**) is very unstable to acids and the corresponding pederoyl chloride was supposed to be too labile to be prepared.

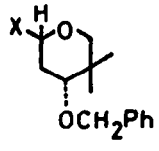
Table 1



Acid Chloride	Imidate	Reduction Conditions	Yield of **6** (%)
AcCl	HN=C(OMe)Ph	0 °C, 10 min	78[a]
MeCH(OAc)COCl	HN=C(OMe)Ph	0 °C, 10 min	81[a]
MeCH(OAc)COCl	**7**	-20 °C, 20 min	76[b]

a) From methyl benzoimidate.

b) From an amide (**8**) through a methyl imidate (**7**), which was prepared by treatment with trimethyloxonium tetrafluoroborate (CH_2Cl_2, rt, 12 h).



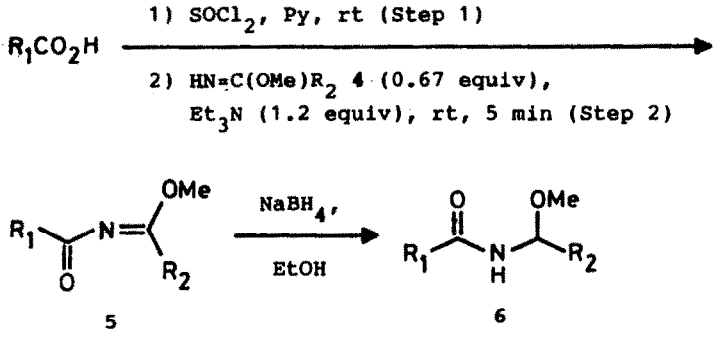
X = C(OMe)=NH **7**
X = $CONH_2$ **8**

Initially, 2-chloro-1-methylpyridinium iodide[16] seemed promising. For example, 2-acetoxypropionic acid[17] and α-acetoxyphenylacetic acid[18] acylated methyl benzoimidate by means of this reagent smoothly and almost quantitatively. However, by the use of acetylpederic acid (**2**)[9a] as an acid component, methyl imidates were scarcely acylated.

In an effort to acylate methyl imidates under mild conditions, it was found that carboxylic acids were converted into the corresponding acid chlorides very

rapidly and almost quantitatively with a nearly stoichiometric amount of thionyl chloride in the presence of pyridine in methylene chloride at room temperature. Almost quantitative formation of acid chlorides under such mild conditions was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra (at 60 MHz and 25 MHz, respectively) of a methylene chloride solution of a mixture of isobutyric acid, thionyl chloride (1.2 equiv), and pyridine (1.3 equiv) with those of methylene chloride solution of authentic isobutyryl chloride and those of a mixture of these two solutions. For the preparation of acid chlorides employing thionyl chloride and pyridine, usually a long reaction period was required.[19,20]

Table 2



5 6

Carboxylic Acid	Imidate	Step 1			Yield of 6 (%)
		$SOCl_2$ (equiv)	Py (equiv)	Time (min)	
AcOH	HN=C(OMe)Ph	1.1	1.4	2	85[a]
$^{i}PrCO_2H$	HN=C(OMe)Ph	1.2	1.3	6	85[a]
$MeCH(OAc)CO_2H$	HN=C(OMe)Ph	1.1	2.8	6	87[a]
$PhCH(OAc)CO_2H$	HN=C(OMe)Ph	1.1	2.8	2.5	88[a]
$MeCH(OAc)CO_2H$	7	1.1	2.8	6	78[b]
$PhCH(OAc)CO_2H$	7	1.1	2.8	2.5	79[b]

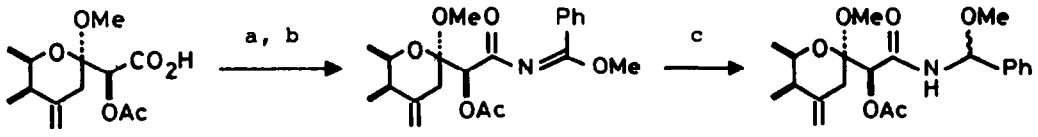
a) From methyl benzoimidate.

b) From 8.

Application of this modified activation method for carboxylic acids employing thionyl chloride and pyridine to the acylation of methyl imidates gave excellent results as shown in **Table 2**. Carboxylic acids were activated sufficiently within 6 min under moderately mild conditions (Step 1). Treatment of the resultant acid chlorides *in situ* with methyl imidates (4) employing triethylamine as a base at room temperature afforded the corresponding methyl *N*-acylimidates (5) within 5 min in high yields (Step 2). Methyl *N*-acylimidates (5) thus obtained in turn were reduced with sodium borohydride to give *N*-(1-methoxylalkyl)amides (6) in excellent yields.

In contrast, acetylpederic acid (2) required a long period of acylation reaction (rt, 10 h) to give methyl *N*-(acetylpederoyl)benzoimidate (9) in high yield (**Scheme 1**). After sodium borohydride reduction, *N*-(α-methoxybenzyl)acetylpederamide (10) was obtained in 82% overall yield from methyl benzoimidate. Upon interrupting this acylation reaction, dimethyl *N*,*N*'-sulfinyldibenzoimidate (11)[21]

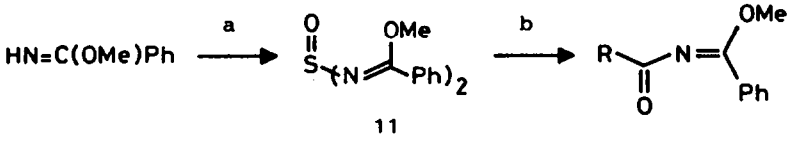
Scheme 1



2 9 10

a) $SOCl_2$ (1.5 equiv), Py (2.1 equiv), CH_2Cl_2, rt, 5 min b) HN=C(OMe)Ph (0.67 equiv), Et_3N, (1.0 equiv), CH_2Cl_2, rt, 10 h c) $NaBH_4$, EtOH, 0 °C, 10 min.

Scheme 2



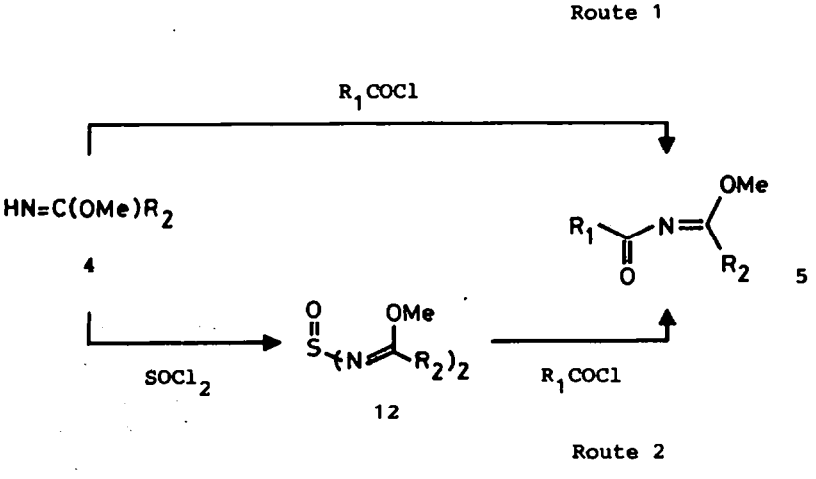
11

a) $SOCl_2$ (0.52 equiv), Et_3N (1.9 equiv), CH_2Cl_2, rt, 10 min b) AcCl or MeCH(OAc)COCl (2.1 equiv), Py (4.2 equiv), CH_2Cl_2, rt, 20 h.

was obtained along with **9**. This compound was also obtained as the major product on the reaction of methyl benzoimidate with a half equiv of thionyl chloride under comparable conditions (92%) (**Scheme 2**). Furthermore, treatment of **11** with acetyl chloride or 2-acetoxypropionyl chloride[17] in the presence of pyridine in methylene chloride at room temperature afforded the methyl *N*-acylbenzoimidates almost quantitatively.

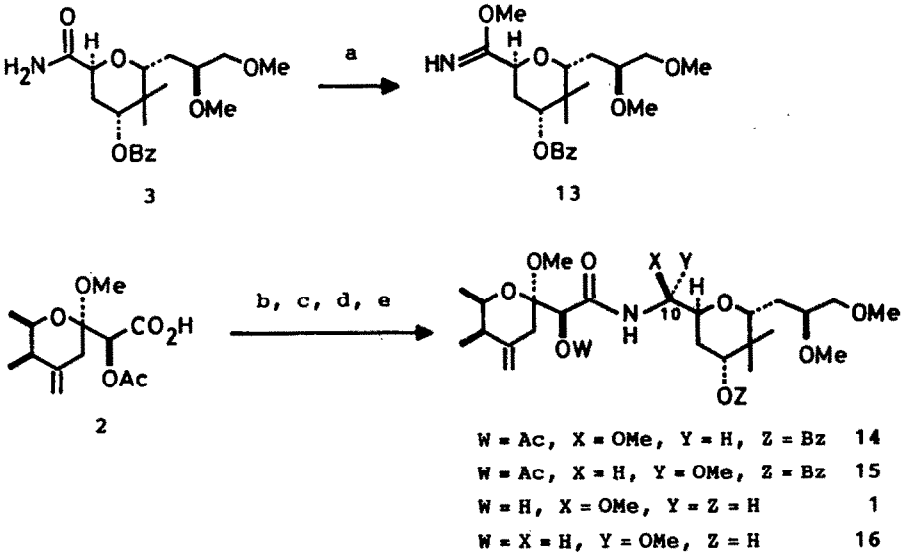
Therefore, as shown in **Scheme 3**, it is likely that in the case of sterically hindered **2** bearing three substituents at the β-position, the rate of the acylation reaction is slow and an alternative acylation (Route 2) *via* dimethyl *N,N'*-sulfinyldiimidate (**12**) proceeds concurrently with the normal acylation (Route 1). In the cases of other less hindered acids in **Table 2**, the acylation reaction takes place *via* only normal acylation route. This presumption was supported by TLC monitoring of these acylation reaction.

Scheme 3



First Total Synthesis of (+)-Pederine. Since pederine (1) and acetylpederic acid (2) are sensitive to acidic conditions, an attempt was made to apply this new and mild synthetic method to the total synthesis of 1. Methyl benzoylpedimidate (13), which was obtained from (+)-benzoylpedamide (3)[9b] by treatment with trimethyloxonium tetrafluoroborate,[14c] and (+)-2 were connected together through the *N*-(1-methoxylalkyl)amide linkage by the sequence of reactions shown in **Scheme 4**, yielding an epimeric mixture of *N*-(1-methoxylalkyl)amides (14 and 15) in 73% overall yield from 3. Deprotection and successive separation of C-10 (pederine numbering) epimers by preparative TLC afforded a 23% yield of (+)-1 and a 62% yield of (+)-10-*epi*-pederine (16) (1:16 = 1:3). The synthetic pederine was identical with natural (+)-pederine (1) in all respects (IR, ^{1}H NMR, mp, mmp, optical rotation, and TLC mobilities with several different solvent systems).

Scheme 4

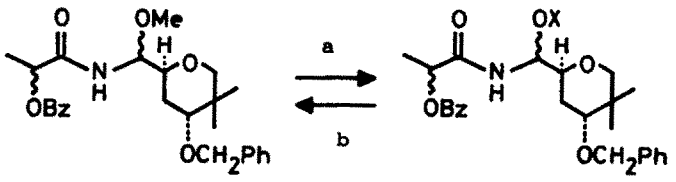


a) $Me_3O{\cdot}BF_4$, CH_2Cl_2, rt, 12 h b) $SOCl_2$ (1.4 equiv), Py (1.9 equiv), CH_2Cl_2, rt, 5 min c) 13 (0.67 equiv as 3), Et_3N (1.7 equiv), CH_2Cl_2, rt, 3 h d) $NaBH_4$, EtOH, -20 °C, 30 min e) 1M LiOH, MeOH, rt, 3 h.

Alkoxy Exchange Reaction of *N*-(1-Methoxylalkyl)amides. As described, the first total synthesis of 1 was achieved. However, the ratio of 1 to its epimer (16) was not satisfactory. To remove this default, the reactivities of *N*-(1-methoxyalkyl)-amides to various acids were investigated. In the course of preliminary investigations, it turned out that alkoxy-exchange reactions of model *N*-(1-methoxylalkyl)-amides (17, 18, and 19) took place almost quantitatively by hydrogen chloride treatment in alcoholic solvents as shown in **Scheme 5**. Furthermore, it was noted that a large alkoxy group was rapidly replaced by a methoxy group in methanol.

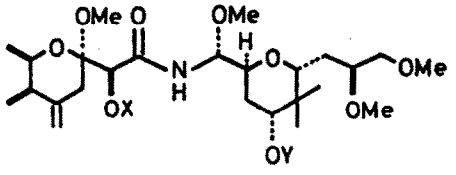
Contrary to expectation, however all attempts to achieve direct epimerization of 10-*epi*-pederine (16) itself and its derivatives (15 and 20) by hydrogen chloride treatment in methanol were fruitless because of their lability under acidic conditions. The lability seemed to be due to the presence of the *exo*-double bond. Therefore, it was planed that the *exo*-double bond was generated at a later stage of the synthesis.

Scheme 5



17 X = Et 18
X = ^{i}Pr 19

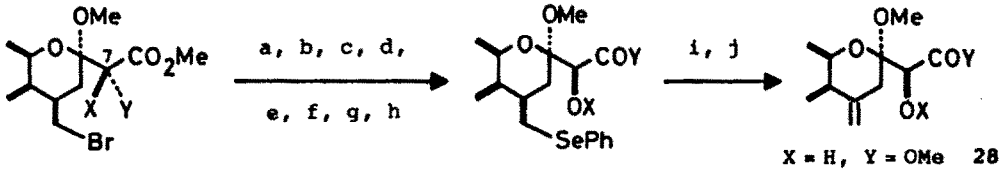
X=Et a) AcCl (0.23 M), EtOH, rt, 1.5 h, 99%
b) AcCl (0.23 M), MeOH, rt, 25 min, 98%
X=^{i}Pr a) AcCl (0.23 M), ^{i}PrOH, rt, 4 h, 97%
b) AcCl (0.23 M), MeOH, rt, 15 min, 99%



X = Ac, Y = Bz 15
X = Y = H 16
X = Y = Bz 20

Stereocontrolled Total Synthesis of (+)-Pederine. For this purpose, the synthesis of (+)-selenoacid (27) was examined at first. As shown in **Scheme 6**, the preparation of 27 was started from a 1:1 epimeric mixture of benzoates (21 and 22), which has been synthesized from (+)-(2R,3R)-2,3-epoxybutane as key intermediate for the synthesis of (+)-acetylpederic acid (2).[9a] This mixture of 21 and 22 was first converted into a keto ester (23) in 82% overall yield by methanolysis of the benzoyl group by sodium methoxide in methanol and successive Collins oxidation. Reduction of 23 with sodium borohydride proceeded stereoselectively (24:25 = 5:1)[9a] to afford the desired β-alcohol (24) in 77% yield together with a 15% yield of α-alcohol (25), which was recycled, after separation with preparative TLC. The stereochemistry at C-7 was confirmed by conversion (52% overall yield)

Scheme 6



X = OBz, Y = H 21
X = H, Y = OBz 22
X = Y = O 23
X = OH, Y = H 24
X = H, Y = OH 25

X = H, Y = OMe 26
X = Ac, Y = OH 27

X = H, Y = OMe 28
X = Ac, Y = OH 2
X = H, Y = NH_2 29

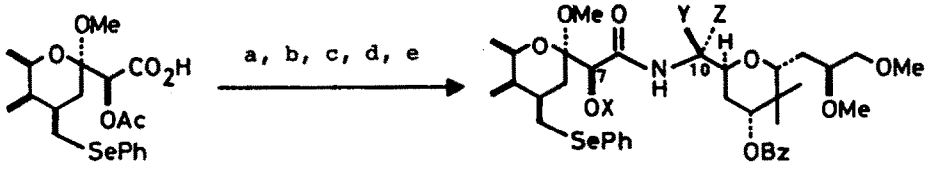
a) NaOMe, MeOH, rt, 20 min b) $CrO_3 \cdot 2Py$, CH_2Cl_2, rt, 20 min c) $NaBH_4$, EtOH, -78 °C, 30 min d) BzCl, DMAP, Py, CH_2Cl_2, rt, 12 h e) $(PhSe)_2$, $NaBH_4$, MeOH, reflux, 2 h f) Et_3N, H_2O, MeOH, rt, 12 h g) Ac_2O, Py, rt, 12 h h) $(C_6H_{11})_2NH$ i) 1M HCl j) 30% H_2O_2, THF, rt, 3 h k) Et_3N, PhH, reflux, 30 min.

of 24 into (+)-methyl pederate (28) through a selenoester (26). Methyl pederate (28) has already been converted into (+)-pederamide (29), a degradation product of 1,[9a] *via* 2.

Conversion of 24 into (+)-27 was effected in 45% overall yield through 26 by the sequence of (1) protection of the C-7 hydroxyl group as benzoate, (2) treatment with sodium benzeneselenolate, (3) hydrolysis of the methoxycarbonyl group, (4) protection of the C-7 hydroxyl group as acetate, (5) conversion of crude 27 into its DCHA (dicyclohexylammonium) salt, which was purified by simple recrystallization very easily, and (6) hydrochloric acid treatment to afford pure 27.

Methyl benzoylpedimidate (13), obtained from (+)-benzoylpedamide (3), and (+)-27 were connected together through the *N*-(1-methoxylalkyl)amide linkage by the previously described method to give epimeric mixture of *N*-(1-methoxylalkyl)amides (30 and 31) in 72% overall yield from 3 (Scheme 7). Conversion of the acetyl group into a benzoyl group afforded, after separation by preparative TLC, 18% yield of the (+)-dihydropederine derivative (32) and a 63% yield of the (+)-dihydro-10-*epi*-pederine derivative (33) (32:33 = 2:7). The C-7 acetoxy compounds (30 and 31) were labile to acidic conditions necessitated in the following step. Furthermore, the conversion into benzoates were essential for separation of the C-10 epimers. The stereochemistry at C-10 was determined by conversion of 32 into 1 as described later.

Scheme 7



27

X = Ac, Y = OMe, Z = H 30
X = Ac, Y = H, Z = OMe 31
X = Bz, Y = OMe, Z = H 32
X = Bz, Y = H, Z = OMe 33

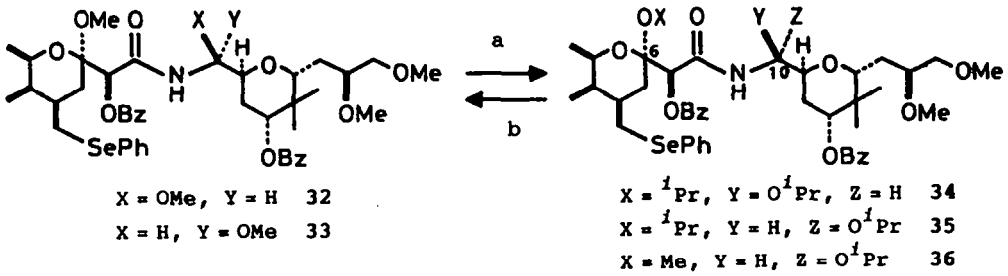
a) $SOCl_2$ (1.4 equiv), Py (1.9 equiv), CH_2Cl_2, rt, 5 min b) 13 (0.67 equiv as 3), Et_3N (1.7 equiv), CH_2Cl_2, rt, 2 h c) $NaBH_4$, EtOH, -20 °C, 30 min d) 1M LiOH, MeOH, rt, 3 h e) BzCl, DMAP, Py, rt.

The *epi*-pederine derivative (33) was treated with acetyl chloride in methanol (rt, 3 h) give an equilibrium mixture of 32 and 33. Separation of the epimers by preparative TLC gave a 23% yield of 32 and a 68% yield of 33. Therefore, 33 is thermodynamically favorable (32:33 = 1:3).

Thus, possibility of selective conversion of the *epi*-pederine derivative (33) into pederine derivative (32) under kinetically controlled conditions was next examined, by taking into account acceleration effect of the alkoxy-exchange reaction in methanol by a large alkoxy group in the model study (Scheme 5). The *epi*-pederine derivative (33) was treated first with acetyl chloride in isopropanol to afford after 7 days selectively a 6α,10α-diisopropoxy compound (35) through initial formation of a kinetically controlled product, 6α,10β-diisopropoxy compound (34) (by TLC). The product (35) was unstable and could not be isolated in a pure state. However, kinetically controlled methoxylation of 35 with acetyl chloride in methanol proceeded in a stereoselective manner to give at 50% conversion (rt, 4.5 h) a 60% isolated yield (based on consumed 35) of 32 and a 14% yield of 33

(32:33 = 4:1). The 10α-isopropoxy compound was recovered in 42% yield in the form of a 6α-methoxy compound (36). The recovered 36 in turn afforded the same mixture of 32, 33, and 36 in 37, 9, and 45% yield, respectively, by similar hydrogen chloride treatment in methanol (rt, 3 h). At 100% conversion the ratio of 32:33 was 2:3 (**Scheme 8**).

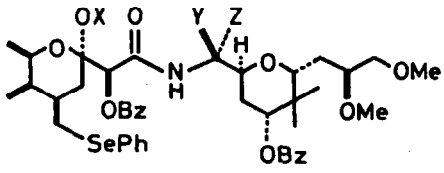
Scheme 8



X = OMe, Y = H 32
X = H, Y = OMe 33

X = ^{i}Pr, Y = O^{i}Pr, Z = H 34
X = ^{i}Pr, Y = H, Z = O^{i}Pr 35
X = Me, Y = H, Z = O^{i}Pr 36

a) AcCl (0.67 equiv), ^{i}PrOH, rt, 7 days b) AcCl (0.23 M), MeOH, rt, 4.5 h.



X = Et, Y = OEt, Z = H 37
X = Et, Y = H, Z = OEt 38
X = Me, Y = H, Z = OEt 39

Similar hydrogen chloride treatment of 32 in ethanol gave after 3 days 37 and 38 in a ratio of 1:4 at equilibrium, through initial formation of 37. Methoxylation of 38 (isolated by preparative TLC) proceeded more slowly than that of 35 (rt, 10 h) and afforded at 50% conversion 32 and 33 in 2:1 ratio and 39 was recovered. At 100% conversion the ratio of 32:33 was 1:2. Furthermore, methoxylation of 37 afforded 33 as kinetically controlled product in contrast to that of 38.

The stereochemistry at C-10 of the above described alkoxy isomers was inferred from δ values of their NH protons and their thermodynamic stabilities. As shown in **Table 3**, the NH proton of 10β-, and 10α-alkoxy compounds exhibited peaks at δ 6.6-6.8 and δ 7.7-8.0 (hydrogen bonded proton), respectively. As a rule 10α-alkoxy compounds were more stable than the corresponding 10β-alkoxy compounds.

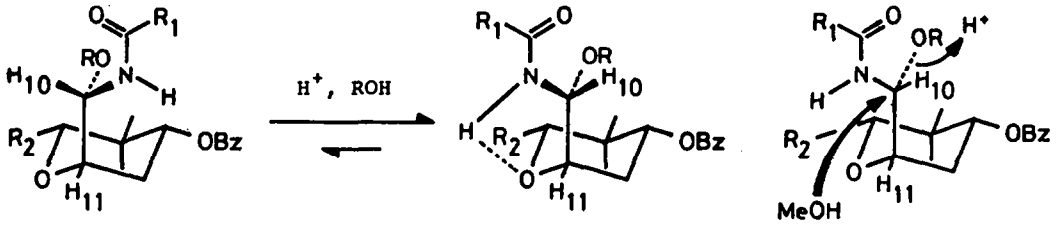
The small J_{10-11} values for diacyl derivatives of 10β- and 10α-alkoxy pederine series (**Table 3**) indicated that in both series H_{10} and H_{11} are arranged in a gauche form. Taking into account difference in steric hindrance between alkoxyl and acylamino groups, partial conformation (**40**), in which smaller alkoxyl group is situated upon the ring, was assumed to be preferred out of two possible H/H gauche conformations for 10β-alkoxy compounds (**Scheme 9**). This assumption is further supported by the fact that conformation (**40**) of bis(*p*-bromobenzoyl)pederine in crystalline state has already been demonstrated by X-ray.[8] Similarly, partial conformation (**41**) was presumed to be favorable in the case of 10α-alkoxy compounds. Consideration of these conformations (**40** and **41**) and chemical shifts of amide protons (**Table 3**) concluded the presence of a hydrogen bond between NH and O atom of the tetrahydropyran ring in 10α-alkoxy compounds. Increased thermodynamic stability of 10α-alkoxy compounds over the corresponding 10β-alkoxy compound may

Table 3

Compound		δ_{NH}	J_{NH-10} (Hz)	J_{10-11} (Hz)
10β-OR	30	6.61	9.8	4.2
	32	6.69	9.6	3.7
	37	6.76	9.6	4.2
	43	6.77	9.8	4.4
10α-OR	31	7.73	9.4	3.9
	33	7.80	9.8	3.4
	36	7.94	9.6	3.7
	38	7.81	9.4	3.7
	39	7.88	9.6	3.4

The spectral data were obtained at 400 MHz in $CDCl_3$.

Scheme 9



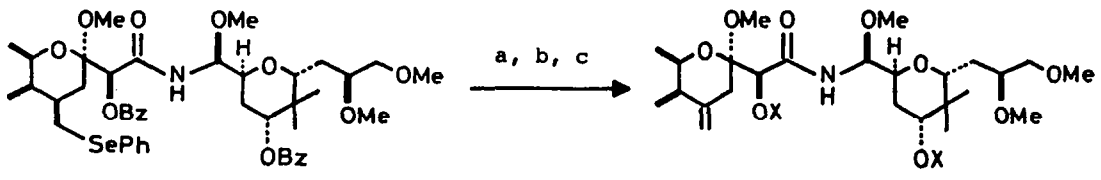
40 41 42

R = Me, Et, ^{i}Pr

be understood by ascribing it to the presence of the similar hydrogen bond in alcoholic solvents in the former compounds. On the basis of the preferred conformation (**41**), kinetically controlled conversion of 10α-alkoxy compounds (**35**, **36**, **38**, and **39**) into 10β-alkoxy compound (**32**) may be are rationalized by assuming the transition state (**42**), in which the substrate takes the similar conformation to **41** and methanol attacks from the less hindered site in a concerted manner.

The dihydropederine derivative (**32**) thus obtained was converted into (+)-pederine (**1**) through (+)-dibenzoylpederine (**43**) in three steps and 75% overall yield by (1) oxidation by sodium periodate, (2) elimination of benzeneseleninic acid in a mixture of benzene and triethylamine, and (3) debenzoylation (**Scheme 10**). The synthetic pederine and its dibenzoate were identical with natural (+)-

Scheme 10



32

X = Bz 43

X = H 1

a) $NaIO_4$, MeOH, rt, 1 h b) Et_3N, PhH, reflux, 30 min c) 1M LiOH, MeOH, rt, 3 h.

pederine (1) and authentic (+)-dibenzoate (43), prepared from 1, respectively, in all respect (400 MHz ^{1}H NMR, IR, mp, mmp, optical rotations, and TLC mobilities with several different solvent systems).

Experimental

Melting points were determined in open gcapillaries and were uncorrected. Optical rotations were determined on a JASCO DIP-SL instrument. IR spectra were recorded on a JASCO IR-S instrument and were calibrated with 1603 cm^{-1} absorption of polystyrene. ^{1}H NMR spectra were measured at 60 MHz on a Hitachi R20B instrument and 400 MHz on a JEOL JNM-FX 400 instrument. Chemical shifts were reported in δ units relative to TMS as internal standard. Low resolution mass spectra were run on a Hitachi RMS-6U instrument (EI-MS) and JEOL-OISG-2 instrument (FD-MS). High resolution mass spectra were taken by a JEOL JMS-OISG-2 instrument. Elemental analyses were performed at Laboratory for Instrumental Analysis of Hokkaido University.

(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-carboxamide (8). To a stirred solution of 2-(2-hydroxy-1,1-dimethyl-4-pentenyl)-1,3-dioxolane[9b] (2.0 g, 11 mmol) and NaO^{t}Am (2.4 g, 22 mmol) in DMSO (15 ml) was added $PhCH_2Cl$ (1.6 g, 13 mmol) at rt under an Ar atmosphere. After stirring at rt for 2 h, brine (100 ml) was added and the mixture was extracted with ether. The ethereal extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a crude product. Column chromatography of the crude product (SiO_2, hexane-AcOEt, 97:3) gave 2.6 g (88%) of 2-[2-(benzyloxy)-1,1-dimethyl-4-pentenyl]-1,3-dioxolane.

To a solution of the dioxolane (2.6 g, 9.4 mmol) in acetone (150 ml) was added 3M HCl (32 ml) at rt. The reaction mixture was heated at reflux for 2 h. After cooling to rt, the acetone was removed off *in vacuo* and the mixture was extracted with ether. The combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a crude product, which was purified by column chromatography (SiO_2, hexane-AcOEt, 97:3) to yield 2.0 g (92%) of 3-(benzyloxy)-2,2-dimethyl-5-hexenal.

To a stirred solution of the aldehyde (2.0 g, 8.6 mmol) in EtOH (40 ml) cooled at 0 °C was added solid $NaBH_4$ (1.0 g, 26 mmol). The stirring was continued at 0 °C for 10 min and the excess hydride was destroyed by the addition of AcOH. After evaporation of the solvent *in vacuo*, brine was added and the mixture was extracted with ether. The ethereal extracts were combined, washed with brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 1.9 g (94%) of 3-(benzyloxy)-2,2-dimethyl-5-hexen-1-ol.

To a solution of the alcohol (1.9 g, 8.1 mmol) in CH_2Cl_2 (40 ml) was added solid *m*CPBA (85%, 2.1 g, 10 mmol) at rt. The reaction mixture was stirred at rt for 12 h. To the mixture was added ether (300 ml) and the solution was washed successively with 2M NaOH and brine and dried over Na_2SO_4. After evaportation of the solvent *in vacuo*, column chromatography of the residual oil (SiO_2, PhH-AcOEt, 90:10) gave 1.7 g (84%) of [4-(benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]-methanol as a mixture of diastereoisomers.

A solution of the THP derivative (1.7 g, 6.8 mmol) in acetone (70 ml) was cooled at 0 °C and treated with Jones reagent by portions until the faint red color persisted. After stirring at rt for 12 h, the excess Jones reagent was destroyed by the addition of ^{i}PrOH. The precipitate was filtered off and washed with AcOEt. The combined filtrates were concentrated *in vacuo* and the residue was extracted with AcOEt. The extracts were combined and dried over Na_2SO_4. Removal of the solvent *in vacuo* left 4-(benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-carboxylic acid, which was dissolved in CH_2Cl_2 (25 ml). To the solution was added $SOCl_2$ (4.0 g, 34 mmol) and DMF (250 mg, 3.4 mmol) at rt. The reaction mixture was then heated at reflux for 3 h. After cooling, the solvent and excess $SOCl_2$ were removed off *in vacuo*. To the residue was added CH_2Cl_2 (25 ml) and the solution was cooled at 0 °C. Gaseous NH_3 was bubbled through the solution at 0 °C for 30 min. The solution was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the crude oil (SiO_2, PhH-AcOEt, 80:20) and successive recrystallization from ether gave 550 mg (31%) of diastereoisomerically pure **8**: mp 105-106 °C; IR (Nujol) 3340, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88, 0.99

(each 3H, s), 1.76 (1H, ddd, 4, 11, and 15 Hz), 2.25 (1H, dt, 15 and 4 Hz), 3.25 (1H, t, 4 Hz), 3.27, 3.65 (each 1H, d, 12 Hz), 4.11 (1H, dd, 4 and 11 Hz), 4.34, 4.62 (each 1H, d, 12 Hz), 6.67, 6.85 (each 1H, brs), 7.23 (5H, s); EI-MS m/z 263 (M^+). *Anal.* Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32%. Found: C, 68.28; H, 7.94; H, 5.28%.

$NaBH_4$ Reduction of Methyl *N*-Acylimidates. General procedures are illustrated by the synthesis of *N*-(α-methoxybenzyl)acetamide and *N*-[[(2R*,4S*)-4-(benzyloxy)-tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide.

***N*-(α-Methoxybenzyl)acetamide.** To a stirred solution of methyl benzoimidate[14b] (30 mg, 0.22 mmol) and Et_3N (87 mg, 0.86 mmol) in CH_2Cl_2 (1.0 ml) was added AcCl (44 mg, 0.56 mmol) at rt under an Ar atmosphere. After stirring at rt for 30 min, the solvent was removed off under reduced pressure. To the resulting residue (methyl *N*-acetylbenzoimidate) was added at 0 °C a suspension of $NaBH_4$ (200 mg, 5.3 mmol) in EtOH (5.0 ml) cooled at 0 °C. After stirring at 0 °C for 10 min, the reaction was quenched by the addition of brine (25 ml) and the mixture was extracted with $CHCl_3$. The combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a crude product, which was purified by column chromatography (SiO_2, PhH-AcOEt, 80:20) to yield 31 mg (78%, from methyl benzoimidate) of *N*-(α-methoxybenzyl)acetamide: mp 84-85 °C; IR (Nujol) 3340, 1660, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95, 3.37 (each, 3H, s), 6.07 (1H, d, 10 Hz), 6.76 (1H, brd, 10 Hz), 7.32 (5H, s); EI-MS m/z 164 (M^+-Me), 148 (M^+-MeO). *Anal.* Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%. Found: C, 67.12; H, 7.29; N, 7.87%.

***N*-[[(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide.** To a solution of **8** (29 mg, 0.11 mmol) in CH_2Cl_2 (2.5 ml) was added solid $Me_3O{\cdot}BF_4$[14c] (147 mg, 0.99 mmol) at rt under an Ar atmosphere. After stirring at rt for 12 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 ml). The mixture was extracted with ether. The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a methyl imidate (**7**), which was dissolved in CH_2Cl_2 (1.2 ml). To the stirred solution of **7** was added successively Et_3N (44 mg, 0.43 mmol) and 2-actoxypropionyl chloride[17] (41 mg, 0.27 mmol) at rt under an Ar atmosphere. After stirring at rt for 30 min, the solvent was removed off under reduced pressure. To the resulting residue was added at -20 °C a suspension of $NaBH_4$ (100 mg, 2.6 mmol) in EtOH (2.5 ml) cooled at -20 °C. After stirring at -20 °C for 20 min, the reaction mixture was processed as above to give a crude product, which was purified with column chromatography (SiO_2, PhH-AcOEt, 80:20) to yield 33 mg (76%, from **8**) of *N*-[[(2R*,3S*)-4-(benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide (a mixture of diastereoisomers): IR (neat) 3360, 1750, 1690, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88, 0.97, 1.03, 1.05 (total 6H, each s), 1.47, 1.50, 1.53 (total 3H, each d, 7 Hz), 2.08 (3H, s), 3.30, 3.33 (total 3H, each s), 4.35, 4.58 (each 1H, d, 12 Hz), 4.96 (1H, brd, 10 Hz), 5.13, 5.15 (total 1H, each q, 7 Hz), 6.81 (1H, brd, 10 Hz), 7.23 (5H, s); EI-MS m/z 361 (M^+-MeOH). *Anal.* Calcd. for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56%. Found: C, 64.18; H, 7.87; N, 3.57%.

***N*-(α-Methoxybenzyl)-2-acetoxypropionamide** (a mixture of epimers): IR (Nujol) 3300, 1750, 1675, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50, 1.53 (total 3H, each d, 7 Hz), 2.07, 2.09 (total 3H, each s), 3.45, 3.48 (total 3H, each s), 5.16, 5.21 (total 1H, each q, 7 Hz), 6.16 (1H, d, 10 Hz), 6.62 (1H, brd, 10 Hz), 7.36 (5H, s); EI-MS m/z 236 (M^+-Me), 220 (M^+-MeO). *Anal.* Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57%. Found: C, 62.01; H, 6.79; N, 5.55%.

Synthesis of *N*-(1-Methoxyalkyl)amides from Less Hindered Carboxylic Acids and Methyl Imidates. General procedures are illustrated by the synthesis of *N*-(α-methoxybenzyl)acetamide and *N*-[[(2R*,4S*)-4-(benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide.

***N*-(α-Methoxybenzyl)acetamide.** To a stirred solution of AcOH (25 mg, 0.42 mmol) and pyridine (47 mg, 0.59 mmol) in CH_2Cl_2 (1.0 ml) was added $SOCl_2$ (54 mg, 0.45 mmol) at rt under an Ar atmosphere. After stirring at rt for 2 min, a solution of methyl benzoimidate (38 mg, 0.28 mmol) and Et_3N (50 mg, 0.49 mmol) in CH_2Cl_2 (0.5 ml) was added at rt. Stirring was continued at the same temperature for 5 min, then the solvent was removed off under reduced pressure. To the resulting residue was added at 0 °C a suspension of $NaBH_4$ (200 mg, 5.3 mmol) in EtOH (5.0 ml) cooled

at 0 °C. After stirring at 0 °C for 10 min, similar treatment as before afforded 43 mg (85%, from methyl benzoimidate, isolated yield by column chromatography) of *N*-(α-methoxybenzyl)acetamide.

***N*-[[(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide.** To a stirred solution of 2-acetoxypropionic acid[17] (19 mg, 0.14 mmol) and pyridine (32 mg, 0.40 mmol) in CH_2Cl_2 (0.5 ml) was added $SOCl_2$ (19 mg, 0.16 mmol) at rt under an Ar atmosphere. After stirring at rt for 6 min, a solution of **7** [prepared from **8** (25 mg, 0.095 mmol) by similar treatment with $Me_3O{\cdot}BF_4$ (127 mg, 0.86 mmol) in CH_2Cl_2 (2.0 ml) as before] and Et_3N (17 mg, 0.17 mmol) in CH_2Cl_2 (0.4 ml) was added at rt. Stirring was continued at the same temperature for 5 min, and the solvent was removed off under reduced pressure. To the resulting residue was added at -20 °C a suspension of $NaBH_4$ (100 mg, 2.6 mmol) in EtOH (2.5 ml) cooled at -20 °C. After stirring at -20 °C, similar treatment as before afforded 29 mg (79%, from **8**, isolated yield by column chromatography) of *N*-[[(2R*,4S*)-4-(benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide as a mixture of diastereoisomers.

***N*-(α-Methoxybenzyl)isobutyramide:** mp 109-119 °C; IR (Nujol) 3280, 1655, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17, 1.21 (each 3H, d, 7 Hz), 2.41 (1H, heptet, 7 Hz), 3.42 (3H, s), 6.17 (2H, brs), 7.34 (5H, s); EI-MS m/z 192 (M^+-Me), 176 (M^+-MeO). *Anal.* Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%. Found: C, 69.56; H, 8.39; N, 6.80%. As a solvent for $NaBH_4$, MeOH was employed instead of EtOH.

***N*-(α-Methoxybenzyl)-α-acetoxyphenylacetamide** (a mixture of epimers): IR (Nujol) 3280, 1745, 1665, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02, 2.05 (total 3H, each s), 3.28, 3.36 (total 3H, each s), 5.98, 6.02 (total 1H, each s), 6.09, 6.11 (total 1H, each d, 10 Hz), 6.88 (1H, brd, 10 Hz), 7.22 (5H, s), 7.28, 7.33 (total 5H, each s); EI-MS m/z 282 (M^+-MeO). *Anal.* Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47%. Found: C, 69.00; H, 6.11; N, 4.39%.

***N*-[[(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-α-acetoxyphenylacetamide** (a mixture of diastereoisomers): IR (neat) 3340, 1745, 1680, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81, 0.84, 0.86, 0.98, 1.03 (total 6H, each s), 2.12, 2.14, 2.16 (total 3H, each s), 3.23 (3H, s), 4.33, 4.54 (each 1H, d, 12 Hz), 4.96 (1H, brd, 10 Hz), 5.98, 6.00 (total 1H, each s), 6.85 (1H, brd, 10 Hz), 7.23 (5H, s), 7.31 (5H, brs); EI-MS m/z 423 (M^+-MeOH). *Anal.* Calcd. for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.08%. Found: C, 68.40; H, 7.34; N, 3.08%.

***N*-(α-Methoxybenzyl)acetylpederamide (10).** To a stirred solution of $SOCl_2$ (26 mg, 0.22 mmol) and pyridine (24 mg, 0.30 mmol) in CH_2Cl_2 (0.4 ml) was added dropwise a solution of (+)-acetylpederic acid (**2**)[9a] (39 mg, 0.14 mmol) in CH_2Cl_2 (0.5 ml) at rt under an Ar atmosphere for 3 min. The stirring was continued at rt for additional 2 min. A solution of methyl benzoimidate (13 mg, 0.096 mmol) and Et_3N (15 mg, 0.15 mmol) in CH_2Cl_2 (0.2 ml) was added at rt. The stirring was continued at the same temperature for 10 h and the solvent was removed off under reduced pressure. To the resulting residue was added at 0 °C a suspension of $NaBH_4$ (100 mg, 2.6 mmol) in EtOH (2.5 ml) cooled at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was processed as above to give a crude product, which was purified by preparative TLC (SiO_2, PhH-AcOEt, 90:10) to yield 14 mg (37%, from methyl benzoimidate) of the less polar epimer of **10** and 17 mg (45%) of the more polar epimer of **10**.

Less polar epimer of **10**: $[\alpha]_D^{20}$ +104° (1.50, $CHCl_3$); IR (neat) 3380, 1760, 1695, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (6H, d, 7 Hz), 2.22 (3H, s), 2.28 (1H, dq, 3 and 7 Hz), 2.48 (2H, brs), 3.15, 3.48 (each 3H, s), 3.99 (1H, dq, 3 and 7 Hz), 4.79, 4.88 (each 1H, brs), 5.39 (1H, s), 6.06 (1H, d, 10 Hz), 7.15 (1H, brd, 10 Hz), 7.38 (5H, s); EI-MS m/z 359 (M^+-MeOH). *Anal.* Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.24%. Found: C, 64.41; H, 7.42; N, 3.30%.

More polar epimer of **10**: $[\alpha]_D^{20}$ +29.1° (1.50, $CHCl_3$); IR (neat) 3360, 1755, 1690, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.36, 0.89 (each 3H, d, 7 Hz), 2.20 (3H, s), 2.23 (1H, dq, 3 and 7 Hz), 2.32 (2H, brs), 3.14, 3.46 (each 3H, s), 3.85 (1H, dq, 3 and 7 Hz), 4.75 (2H, brs), 5.27 (1H, s), 6.13 (1H, d, 10 Hz), 6.83 (1H, brd, 10 Hz), 7.37 (5H, s); EI-MS m/z 359 (M^+-MeOH). *Anal.* Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.24%. Found: C, 64.66; H, 7.55; N, 3.34%.

Dimethyl *N*,*N*'-Sulfinyldibenzoimidate (11). To a stirred solution of methyl benzoimidate (50 mg, 0.37 mmol) and Et_3N (72 mg, 0.71 mmol) in CH_2Cl_2 (1.0 ml) was added $SOCl_2$ (23 mg, 0.19 mmol) at rt under an Ar atmosphere. After stirring at rt

for 10 min, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5.0 ml) and the product was extracted with $CHCl_3$. The extracts were combined, washed with brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a crude product. Column chromatography of the crude product (SiO_2, PhH-AcOEt, 70:30) gave 54 mg (92%) of **11**: mp 116-118 °C; IR (Nujol) 1605, 1585, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (6H, s), 7.25 (10H, s); EI-MS m/z 316 (M^+), 182 [M^+-N=C(OMe)Ph]. *Anal.* Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85; S, 10.13%. Found: C, 60.64; H, 5.27; N, 8.62; S, 10.20%.

Pederine (1) and 10-*epi*-Pederine (16). To a stirred solution of $SOCl_2$ (26 mg, 0.22 mmol) and pyridine (24 mg, 0.30 mmol) in CH_2Cl_2 (0.4 ml) was added dropwise a solution of (+)-**2** (43 mg, 0.16 mmol) in CH_2Cl_2 (0.5 ml) at rt under an Ar atmosphere for 3 min. The stirring was continued at rt for additional 2 min. To the resulting mixture was added a solution of methyl benzoylpedimidate (**13**) [prepared from (+)-benzoylpedamide (**3**)[9b] (40 mg, 0.11 mmol) by similar treatment with $Me_3O^+BF_4^-$ (141 mg, 0.95 mmol) in CH_2Cl_2 (2.5 ml) as before] and Et_3N (26 mg, 0.26 mmol) in CH_2Cl_2 (0.4 ml) at rt. After stirring at the same temperature for 3 h, the solvent was removed off under reduced pressure. To the resulting residue was added at -20 °C a suspension of $NaBH_4$ (100 mg, 2.6 mmol) in EtOH (2.5 ml) cooled at -20 °C. After stirring at -20 °C for 30 min, the reaction mixture was processed as above to give a crude product, which was purified by column chromatography (SiO_2, PhH-AcOEt, 70:30) to yield 50 mg (73%, from **3**) of an epimeric mixture of *N*-(1-methoxyalkyl)amides (**14** and **15**).

To a solution of the mixture (50 mg, 0.077 mmol) in MeOH (1.0 ml) was added 1M LiOH (1.0 ml) at rt. The reaction mixture was stirred at rt for 3 h. The mixture was extracted with $CHCl_3$ and the combined extracts were dried over Na_2SO_4 and evaporated *in vacuo*. Preparative TLC of the residue (SiO_2, AcOEt) gave 8.9 mg (23%) of **1** (less polar epimer) and 24 mg (62%) of **16** (more polar epimer). The synthetic pederine was identical with the natural product in all respects (mp, mmp, optical rotation, IR, ^1H NMR, and TLC mobilities with several different solvent systems).

Pederine (**1**): mp 112-113 °C; $[\alpha]_D^{20}$ +86.8° (1.00, $CHCl_3$); IR (Nujol) 3460, 3380, 1670, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89, 0.95 (each 3H, s), 1.04, 1.21 (each 3H, d, 7 Hz), 2.40 (2H, brs), 3.33, 3.39 (each 6H, s), 4.31 (1H, s), 4.73, 4.85 (each 1H, brs), 5.37 (1H, dd, 8 and 10 Hz), 7.16 (1H, brd, 10 Hz).

10-*epi*-Pederine (**16**): $[\alpha]_D^{20}$ +69.9° (1.00, $CHCl_3$); IR (neat) 3400, 3070, 1680, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91, 1.00 (each 3H, s), 1.03, 1.20 (each 3H, d, 7 Hz), 2.34 (2H, brs), 3.31 (3H, s), 3.37 (6H, s), 3.42 (3H, s), 4.21 (1H, s), 4.75, 4.85 (each 1H, brs), 5.27 (1H, dd, 6 and 10 Hz), 7.43 (1H, brd, 10 Hz).

***N*-[[(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-(benzoyloxy)propionamide (17).** To a solution of *N*-[[(2R*,4S*)-4-(benzyloxy)-tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-2-acetoxypropionamide (a mixture of diastereoisomers, 54 mg, 0.14 mmol) in MeOH (2.0 ml) was added 1M LiOH (2.0 ml) at rt. The reaction mixture was stirred at rt for 3 h. The product was extracted with $CHCl_3$ and the combined extracts were dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a deacetyl product, which was dissolved in pyridine (1.0 ml) and treated with BzCl (360 mg, 2.7 mmol) and DMAP (5.0 mg, 0.041 mmol) at rt for 5 h. To the mixture was added MeOH (0.5 ml) and the solvent was removed off *in vacuo*. The residue was diluted with AcOEt and the solution was washed successively with 1M HCl, saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. After evaporation *in vacuo*, column chromatography of the crude product (SiO_2, PhH-AcOEt, 90:10) gave 54 mg (86%) of **17** (a mixture of diastereoisomers): IR (neat) 3300, 1720, 1690, 1605, 1585, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58, 0.61, 0.78, 0.84, 0.90, 1.06 (total 6H, eash s), 1.62, 1.64, 1.67 (total 3H, each d, 7 Hz), 3.33, 3.34, 3.39, 3.41 (total 3H, each s), 5.05 (1H, brd, 10 Hz), 5.43, 5.46, 5.48 (total 1H, each q, 7 Hz), 7.10 (1H, brd, 10 Hz), 7.10-7.75 (3H, m), 7.23, 7.25 (total 5H, each s), 7.90-8.20 (2H, m); EI-MS m/z 423 (M^+-MeOH). *Anal.* Calcd. for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.08%. Found: C, 68.51; H, 7.45; N, 3.09%.

Alkoxy-Exchange Reaction of Model *N*-(1-Alkoxyalkyl)amides. A typical experiment is shown by the conversion of the *N*-(1-methoxyalkyl)amide (**17**) into an *N*-(1-ethoxyalkyl)amide (**18**).

***N*-[[(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]ethoxymethyl]-**

-(benzoyloxy)propionamide (18). A solution of 17 (50 mg, 0.11 mmol) in EtOH (1.0 ml) was treated with AcCl (18 mg, 0.23 mmol) at rt under an Ar atmosphere for 1.5 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5.0 ml) and the product was extracted with ether. The ethereal extracts were combined, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave 51 mg (99%) of 18 (a mixture of diastereoisomers): IR (neat) 3320, 1730, 1690, 1605, 1585, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.57, 0.61, 0.78, 0.84, 0.91, 1.06 (total 6H, each s), 1.19, 1.23 (total 3H, each t, 7 Hz), 1.62, 1.65 (total 3H, each d, 7 Hz), 5.12 (1H, brd, 10 Hz), 5.43, 5.48 (total 1H, each q, 7 Hz), 7.07 (1H, brd, 10 Hz), 7.10-7.75 (3H, m), 7.25, 7.27, 7.29 (total 5H, each s), 7.90-8.20 (2H, m); EI-MS m/z 423 (M^+-EtOH). *Anal.* Calcd. for $C_{27}H_{35}NO_6$: C, 69.06; H, 7.51; N, 2.98%. Found: C, 68.90; H, 7.68; N, 3.07%.

***N*-[[(2R*,4S*)-4-(Benzyloxy)tetrahydro-5,5-dimethyl-2H-pyran-2-yl]isopropoxy-methyl]-2-(benzoyloxy)propionamide (19)** (a mixture of diastereoisomers): IR (neat) 3310, 1725, 1690, 1605, 1585, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60, 0.65, 0.78, 0.85, 0.92, 1.07 (total 6H, each s), 1.20, 1.23, 1.25 (total 6H, each d, 7 Hz), 1.62, 1.64, 1.66 (total 3H, each d, 7 Hz), 5.18 (1H, brd, 10 Hz), 5.44, 5.46, 5.48 (total 1H, each q, 7 Hz), 7.08 (1H, brd, 10 Hz), 7.10-7.75 (3H, m), 7.27, 7.28 (total 5H, each s), 7.90-8.20 (2H, m); EI-MS m/z 423 (M^+-^{i}PrOH). *Anal.* Calcd. for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90%. Found: C, 69.69; H, 7.63; N, 2.88%.

Methyl (αS,2R,4R,5R,6R)-4-(Bromomethyl)tetrahydro-α-hydroxy-2-methoxy-5,6-dimethyl-2H-pyran-2-acetate (24). To a solution of NaOMe [prepared from metallic Na (55 mg, 2.4 mmol) and MeOH (6.0 ml) at rt under an Ar atmosphere] was added a solution of a 1:1 epimeric mixture of benzoates (21 and 22)[9a] (275 mg, 0.64 mmol) in MeOH (6.0 ml) at rt. The stirring was continued at rt for 20 min and the reaction was quenched by the addition of AcOH (160 mg, 2.7 mmol). After removal of the solvent *in vacuo*, the residue was diluted with AcOEt. The solution was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give 200 mg (96 mg) of a 1:1 epimeric mixture of 24 and 25.

To a stirred suspension of Collins reagent [prepared from anhydrous CrO_3 (740 mg, 7.4 mmol) and pyridine (1.2 g, 15 mmol) in CH_2Cl_2 (15 ml) at rt under an Ar atmosphere for 15 min] and Celite (1.5 g) was added a solution of the mixture (200 mg, 0.62 mmol) in CH_2Cl_2 (15 ml) at rt. The reaction mixture was stirred at rt for 20 min. The mixture was diluted with ether (300 ml) and filtered through a pad of Celite and the filtrates were washed successively with saturated aqueous $CuSO_4$ and brine, dried over Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the residual oil (SiO_2, PhH-AcOEt, 90:10) gave 169 mg (85%) of a keto ester (23).

To a stirred suspension of $NaBH_4$ (30 mg, 0.79 mmol) in EtOH (2.0 ml) cooled at -78 °C was added dropwise a solution of 23 (169 mg, 0.52 mmol) in EtOH (1.0 ml). The stirring was continued at -78 °C for 30 min and the reaction was quenched by the addition of AcOH. After evaporation of the solvent *in vacuo*, water was added and the mixture was extracted with $CHCl_3$. The extracts were combined, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Preparative TLC of the residue (SiO_2, PhH-AcOEt, 80:20) gave 26 mg (15%) of 25 (less polar epimer) and 130 mg (77%) of 24 (more polar epimer).

β-Alcohol (24): IR (neat) 3500, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66, 1.18 (each 3H, d, 7 Hz), 3.25 (2H, d, 7 Hz), 3.29, 3.80 (each 3H, s), 3.87 (1H, dq, 2 and 7 Hz), 4.30 (1H, s); EI-MS m/z 295, 293 (M^+-MeO). *Anal.* Calcd. for $C_{12}H_{21}O_5Br$: C, 44.32; H, 6.51; Br, 24.57%. Found: C, 44.36; H, 6.61; Br, 24.34%.

α-Alcohol (25): IR (neat) 3500, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75, 1.20 (each 3H, d, 7 Hz), 3.28 (2H, d, 7 Hz), 3.30, 3.78 (each 3H, s), 3.89 (1H, dq, 2 and 7 Hz), 4.38 (1H, s); EI-MS m/z 295, 293 (M^+-MeO). *Anal.* Calcd. for $C_{12}H_{21}O_5Br$: C, 44.32; H, 6.51; Br, 24.57%. Found: C, 44.10; H, 6.32; Br, 24.66%.

(αS,2R,4R,5R,6R,)-α-Acetoxytetrahydro-2-methoxy-5,6-dimethyl-4-[(phenylseleno)-methyl]-2H-pyran-2-acetic Acid (27). To a solution of 24 (130 mg, 0.40 mmol), pyridine (127 mg, 1.6 mmol), and DMAP (5.0 mg, 0.041 mmol) in CH_2Cl_2 (3.0 ml) was added BzCl (169 mg, 1.2 mmol) at rt. After stirring at rt for 12 h, MeOH (0.5 ml) was added and the solvent was removed off *in vacuo*. The residue was diluted with $CHCl_3$ and the solution was washed successively with 1M HCl and brine and dried over Na_2SO_4. After evaporation *in vacuo*, the crude product was chromatographed (SiO_2, PhH-AcOEt, 90:10) to give 161 mg (94%) of 21.

To a solution of NaSePh [prepared from $(PhSe)_2$ (141 mg, 0.45 mmol) and $NaBH_4$ (170 mg, 4.5 mmol) in MeOH (16 ml) at rt under an Ar atmosphere] was added a solution of **21** (161 mg, 0.38 mmol) in MeOH (1.6 ml) at rt. The reaction mixture was heated at reflux for 2 h. After cooling to rt, the solvent was removed off *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed successively with 1M HCl and brine, dried over Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the crude product (SiO_2, PhH-AcOEt, 80:20) gave 115 mg (74%) of a selenoester (**26**).

To a solution of **26** (115 mg, 0.28 mmol) in MeOH (2.5 ml) were added water (7.5 ml) and Et_3N (2.5 ml) at rt. The stirring was continued at rt for 12 h and the solvent was removed off *in vacuo*. The residual oil was dissolved in pyridine (2.5 ml) and treated with Ac_2O (43 mg, 41 mmol) at rt for 12 h. To the mixture was added $(C_6H_{11})_2NH$ (56 mg, 0.31 mmol) and the solvent was removed off *in vacuo*. The residue was recrystallized from AcOEt to give 125 mg (74%) of a DCHA (dicyclohexylammonium) salt of **27**.

A solution of the DCHA salt (125 mg, 0.20 mmol) in AcOEt (15 ml) was washed successively with 1M HCl and brine and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave 77 mg (88%) of **27**: IR (neat) 3080, 1750, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71, 1.20 (each 3H, d, 7 Hz), 2.16, 3.17 (each 3H, s), 3.92 (1H, dq, 2 and 7 Hz), 5.32 (1H, s), 8.41 (1H, brs); EI-MS m/z 401, 399, 397, 396, 395 (M^+-OMe). DCHA salt of **27**: mp 163-164 °C; $[\alpha]_D^{22}$ +90.4° (1.00, $CHCl_3$); IR (Nujol) 1755, 1625, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75, 1.16 (each 3H, d, 7 Hz), 2.09, 3.18 (each 3H, s), 3.83 (1H, dq, 2 and 7 Hz), 5.00 (1H, s), 9.65 (2H, bs). *Anal.* Calcd. for $C_{31}H_{49}NO_6Se$: C, 60.76; H, 8.09; N, 2.29%. Found: C, 60.89; H, 8.24; N, 2.35%.

(αS,2R,4R,5R,6R)-*N*-[(S)-[(2S,4R,6R)-4-(Benzoyloxy)-6-[(S)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-α-(benzoyloxy)tetrahydro-2-methoxy-5,6-dimethyl-4-[(phenylseleno)methyl]-2H-pyran-2-acetamide (32) and (αS,2R,4R,5R,6R)-*N*-[(R)-[(2S,4R,6R)-4-(Benzoyloxy)-6-[(S)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2H-pyran-2-yl]methoxymethyl]-α-(benzoyloxy)tetrahydro-2-methoxy-5,6-dimethyl-4-[(phenylseleno)methyl]-2H-pyran-2-acetamide (33). To a stirred solution of $SOCl_2$ (16 mg, 0.13 mmol) and pyridine (14 mg, 0.18 mmol) in CH_2Cl_2 (0.4 ml) was added dropwise a solution of (+)-**27** (40 mg, 0.093 mmol) at rt under an Ar atmosphere for 3 min. The stirring was continued at rt for additional 2 min. To the resulting mixture was added a solution of methyl benzoylpedimidate (**13**) [prepared from (+)-benzoylpedamide (**3**) (24 mg, 0.063 mmol) by similar treatment with $Me_3O{\cdot}BF_4$ (84 mg, 0.57 mmol) in CH_2Cl_2 (1.5 ml) at rt]. After stirring at the same temperature for 2 h, the solvent was removed off under reduced pressure. To the resulting residue was added at -20 °C a suspension of $NaBH_4$ (60 mg, 1.6 mmol) in EtOH (1.5 ml) cooled at -20 °C. The stirring was continued at -20 °C for 30 min and the reaction mixture was processed as above to give a crude product. The product was purified by column chromatography (SiO_2, PhH-AcOEt, 95:5) to yield 37 mg (72%, from **3**) of an epimeric mixture of *N*-(1-methoxyalkyl)amides (**30** and **31**).

To a solution of the mixture of **30** and **31** (37 mg, 0.046 mmol) in MeOH (0.7 ml) was added 1M LiOH (0.7 ml) at rt. The reaction mixture was stirred at rt for 3 h. The mixture was extracted with $CHCl_3$ and the combined extracts were dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded an epimeric mixture of deprotected *N*-(1-methoxyalkyl)amides, which was dissolved in pyridine (0.7 ml) and treated with BzCl (129 mg, 0.92 mmol) and DMAP (1.7 mg, 0.014 mmol) at rt for 5 h. The reaction mixture was processed as above and the crude product was purified by preparative TLC (SiO_2, PhH-AcOEt, 97:3) to give 25 mg (63%) of **33** (less polar epimer) and 7.2 mg (18%) of **32** (more polar epimer).

Dihydropederine Derivative (**32**): $[\alpha]_D^{20}$ +42.6° (1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.69 (3H, d, 6.8 Hz, C_3-Me), 1.00, 1.01 (each 3H, s, C_{14}-Me_2), 1.10 (3H, d, 6.5 Hz, C_2-Me), 2.80 (1H, dd, 9.8 and 12.2 Hz, C*H*SePh), 2.90 (1H, dd, 6.3 and 12.2 Hz, C*H*SePh), 3.22, 3.37, 3.38, 3.44 (each 3H, s, OMe x 4), 3.90 (1H, dq, 2.2 and 6.5 Hz, C_2-H), 5.16 (1H, dd, 4.2 and 7.6 Hz, C_{13}-H), 5.30 (1H, dd, 3.7 and 9.6 Hz, C_{10}-H), 5.44 (1H, s, C_7-H), 6.69 (1H, d, 9.6 Hz, NH)[22]; FD-MS m/z 871, 869, 867, 866, 865 (M^+). Exact Mass. Calcd. for $C_{45}H_{59}NO_{11}Se$: 869.3253. Found: 869.3241.

Dihydro-10-*epi*-pederine Derivative (**33**): $[\alpha]_D^{20}$ +74.5° (1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75 (3H, s, 7.3 Hz, C_3-Me), 1.03, 1.04 (each 3H, s, C_{14}-Me_2),

1.19 (3H, d, 6.5 Hz, C_2-Me), 2.86 (1H, dd, 9.5 and 12.1 Hz, C*H*SePh), 2.95 (1H, dd, 6.4 and 12.1 Hz, C*H*SePh), 3.24, 3.36, 3.46, 3.48 (each 3H, s, OMe x 4), 3.95 (1H, dq, 2.2 and 6.5 Hz, C_2-H), 5.16 (1H, dd, 3.4 and 9.8 Hz, C_{10}-H), 5.34 (1H, dd, 3.4 and 8.3 Hz, C_{13}-H), 5.36 (1H, s, C_7-H), 7.80 (1H, d, 9.8 Hz, NH)[22]; FD-MS m/z 869, 867, 866, 865 (M^+). Exact Mass. Calcd. for $C_{45}H_{59}NO_{11}Se$: 869.3253. Found: 869.3262.

Equilibration of Dihydro-*epi*-pederine Derivative (33). A solution of **33** (60 mg, 0.069 mmol) in MeOH (1.5 ml) was treated with AcCl (79 mg, 1.0 mmol) at rt under an Ar atmosphere for 3 h. The reaction was quenched by the addition of Et_3N (0.4 ml). After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$. The solution was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Preparative TLC of the crude oil (SiO_2, PhH-AcOEt, 97:3) yielded 41 mg (68%) of **33** and 14 mg (23%) of **32**.

Selective Conversion of Dihydro-*epi*-pederine Derivative (33) into Dihydropederine Derivative (32) by Double Alkoxy-Exchange Reaction and Formation of (αS,2R,4R,5R,6R)-*N*-[(R)-[(2S,4R,6R)-4-(Benzoyloxy)-6-[(S)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2H-pyran-2-yl]isopropoxymethyl]-α-(benzoyloxy)tetrahydro-2-methoxy-5,6-dimethyl-4-[(phenylseleno)methyl]-2H-pyran-2-acetamide (36). A solution of **33** (112 mg, 0.12 mmol) in ^{i}PrOH (2.8 ml) was treated with AcCl (147 mg, 1.9 mmol) at rt under an Ar atmosphere for 7 days. After removal of the solvent under reduced pressure, the residue [6α,10α-diisopropoxy compound (**34**)] was dissolved in MeOH (2.8 ml). The solution was treated with AcCl (51 mg, 0.65 mmol) at rt under an Ar atmosphere for 4.5 h. Similar treatment as before afforded a crude product, which was purified by preparative TLC (SiO_2, PhH-AcOEt, 97:3) to give 47 mg (42%) of **36**, 9.0 mg (8%) of **33**, and 38 mg (35%) of **32**.

6α-Methoxy-10α-isopropoxy compound (**36**): $[\alpha]_D^{20}$ +28.8° (1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74 (3H, d, 6.8 Hz, C_3-Me), 0.97, 1.07 (each 3H, s, C_{14}-Me_2), 1.18 (3H, d, 6.8 Hz, C_2-Me), 1.25, 1.26 (each 3H, d, 6.3 Hz, OCHMe_2), 2.87 (1H, dd, 9.3 and 12.1 Hz, C*H*SePh), 2.96 (1H, dd, 6.1 and 12.1 Hz, C*H*SePh), 3.24, 3.37, 3.49 (each 3H, s, OMe x 3), 5.33 (1H, s, C_7-H), 5.36 (1H, dd, 3.7 and 9.6 Hz, C_{10}-H), 5.51 (1H, dd, 5.1 and 9.0 Hz, C_{13}-H), 7.94 (1H, d, 9.6 Hz, NH)[22]; FD-MS m/z 899, 897, 894, 893 (M^+). Exact Mass. Calcd. for $C_{47}H_{63}NO_{11}Se$: 897.3566. Found: 897.3576.

HCl Treatment of 6α-Methoxy-10α-isopropoxy Compound (36). A solution of **36** (47 mg, 0.052 mmol) in MeOH (1.2 ml) was treated with AcCl (22 mg, 0.28 mmol) at rt under an Ar atmosphere for 3.5 h. The reaction mixture was processed as above to give 21 mg (45%, isolated yield by preparative TLC) of **36**, 4.1 mg (9%) of **33**, and 17 mg (37%) of **32**.

Pederine (1). To a solution of **32** (55 mg, 0.063 mmol) in MeOH (0.5 ml) was added a solution of $NaIO_4$ (27 mg, 0.13 mmol) in MeOH (0.5 ml) at rt. After stirring at rt for 1 h, the solvent was removed off *in vacuo*. The residue was dissolved in a mixture of PhH (1.5 ml) and Et_3N (1.5 ml), and the resulting solution was heated at reflux for 30 min. After removal of the solvent *in vacuo*, the residue was diluted with $CHCl_3$. The solution was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the crude product (SiO_2, PhH-AcOEt, 95:5) gave 38 mg (84%) of Dibenzoylpederine (**43**), which was identical with an authentic sample prepared from the natural pederine (**1**) in all respects (IR, 400 MHz ^{1}H NMR, optical rotation, FD-MS, and TLC mobilities with several different solvent systems).

To a solution of **43** (38 mg, 0.053 mmol) in MeOH (0.7 ml) was added 1M LiOH (0.7 ml) at rt. The reaction mixture was stirred at rt for 3 h. The product was extracted with $CHCl_3$ and the combined extracts were dried over Na_2SO_4. After evaporation of the solvent *in vacuo*, column chromatography of the crude product (SiO_2, AcOEt) gave 24 mg (89%) of **1**. The synthetic pederine was identical with the natural product in all respects (IR, 400 MHz ^{1}H NMR, mp, mmp, optical rotation, and TLC mobilities with several different solvent systems).

Pederine (**1**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87, 0.94 (each 3H, s, C_{14}-Me_2), 1.11 (3H, d, 7.2 Hz, C_3-Me), 1.20 (3H, d, 6.6 Hz, C_2-Me), 1.78 (1H, ddd, 6.3, 11.2 and 13.2 Hz, C_{12ax}-H), 2.05 (1H, ddd, 2.4, 4.4, and 13.2 Hz, C_{12eq}-H), 2.26 (1H, dq, 2.7 and 7.2 Hz, C_3-H), 2.34 (1H, dt, 14.4 and 1.7 Hz, C_{5ax}-H), 2.44 (1H, d, 14.4 Hz, C_{5eq}-H), 3.33, 3.34, 3.39, 3.40 (each 3H, s, OMe x 4), 3.79 (1H, ddd, 2.4, 6.3, and 8.1 Hz, C_{11}-H), 3.92 (1H, d, 2.9 Hz, C_7-OH), 4.01 (1H, dq, 2.7 and 6.6

Hz, C_2-H), 4.32 (1H, d, 2.9 Hz, C_7-H), 4.75, 4.86 (each 1H, t, 1.7 Hz, C_4=CH_2), 5.39 (1H, dd, 8.1 and 9.8 Hz, C_{10}-H), 7.16 (1H, d, 9.8 Hz, NH).[22]

Dibenzoylpederine (**43**): $[\alpha]_D^{20}$ +63.9° (1.00, $CHCl_3$); IR (neat) 3320, 1730, 1695, 1605, 1585, 1535 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (3H, d, 7.1 Hz, C_3-Me), 0.99, 1.01 (each 3H, s, C_{14}-Me_2), 1.12 (3H, d, 6.4 Hz, C_2-Me), 1.82 (1H, ddd, 6.0, 7.8, and 13.8 Hz, C_{12ax}-H), 2.17 (1H, ddd, 4.3, 6.0, and 13.8 Hz, C_{12eq}-H), 2.22 (1H, dq, 2.4 and 7.1 Hz, C_3-H), 2.51, 2.76 (each 1H, d, 14.7 Hz, C_5-H_2), 3.25, 3.36, 3.37, 3.46 (each 3H, s, OMe x 4), 3.96 (1H, dt, 4.4 and 6.0 Hz, C_{11}-H), 3.98 (1H, dq, 2.4 and 6.4 Hz, C_2-H), 4.80, 4.87 (each 1H, s, C_4=CH_2), 5.15 (1H, dd, 4.3 and 7.8 Hz, C_{13}-H), 5.35 (1H, dd, 4.4 and 9.8 Hz, C_{10}-H), 5.52 (1H, s, C_7-H), 7.77 (1H, d, 9.8 Hz, NH)[22]; FD-MS m/z 711 (M^+), 679 (M^+-MeOH). Exact Mass. Calcd. for $C_{39}H_{53}NO_{11}$: 711.3619. Found: 711.3603.

Dibenzoylpederine (43). A solution of natural **1** (20 mg, 0.040 mmol) in pyridine (0.4 ml) was treated with BzCl (112 mg, 0.80 mmol) and DMAP (1.5 mg, 0.012 mmol) at rt for 5 h. To the mixture was added MeOH (0.2 ml) and the solvent was removed off *in vacuo*. The residue was diluted with AcOEt and the solution was washed successively with 1M HCl, saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After evaporation *in vacuo*, the crude product was chromatographed (SiO_2, PhH-AcOEt, 95:5) to give 26 mg (92%) of authentic **43**: $[\alpha]_D^{25}$ +62.7° (1.00, $CHCl_3$).

References and Notes

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22) Assignments of peaks are indicated according to pederine numbering.