Chemical Modification and Structure-activity Relationships of Pyripyropenes

1. Modification at the Four Hydroxyl Groups

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(Received for publication May 2, 1996)

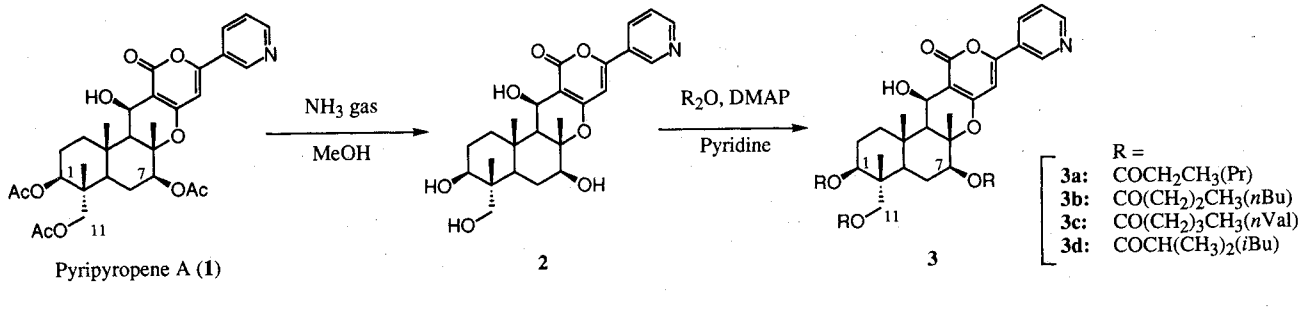
Four hydroxyl groups of pyripyropenes have been modified and evaluated for their ability to inhibit microsomal acyl-CoA : cholesterol acyltransferase (ACAT) activity *in vitro* and to lower cholesterol absorption *in vivo* in a cholesterol-fed hamster. 7-*O*-*n*-Valeryl derivative (**8c**) improved the *in vitro* ACAT inhibitory activity ($IC_{50}=13$ nM) about 7 times better than pyripyropene A. Introduction of methanesulfonyl group at 11-hydroxyl group (**17a**) increased both *in vitro* activity ($IC_{50}=19$ nM) and *in vivo* efficacy ($ED_{50}=10$ mg/kg).

The enzyme acyl-CoA : cholesterol *O*-acyltransferase (ACAT) [EC 2.3.1.26] catalyzes the intracellular esterification of cholesterol. ACAT plays a critical role in three events: absorption of dietary cholesterol in gut, lipoprotein synthesis in liver, and accumulation of oily cholesterol esters within the macrophages and smooth muscle cells of developing arterial lesions. Therefore, inhibitors of ACAT hold promise as a new type of antiatherosclerotic agents[1~3]. Most of ACAT inhibitors reported to date were synthetic compounds such as amide, urea or imidazole derivatives[4,5]. Recently, search for ACAT inhibitors from microbial origin is one of the growing areas[5]. However, inhibitory activity of most naturally occurring ACAT inhibitors[6~16] was less potent than that of synthetic inhibitors.

Recently, we have isolated pyripyropenes from the fermentation broth of *Aspergillus fumigatus* FO-1289 as potent ACAT inhibitor[17~19]. The IC_{50} value of pyripyropene A (**1**) is 89 nM, which represents the most potent naturally occurring ACAT inhibitor. Importantly, **1** proved to be orally active in hamsters with reducing cholesterol absorption. Therefore, they are expected as excellent lead compounds. The structure of pyripyropenes consists of pyridine, 2-pyrone and terpene moieties, which are categorized to the meroterpenoid[20]. Only a few structurally related natural compounds were reported[8,21~23]. We determined the absolute stereochemistry of **1** by NOE difference studies, X-ray crystallographic analysis and MOSHER's NMR method[24] and clarified the biosynthesis of **1** by feeding experiments using [^{13}C] and [^{14}C] precursors[25]. We also accomplished the first total synthesis of **1**[26].

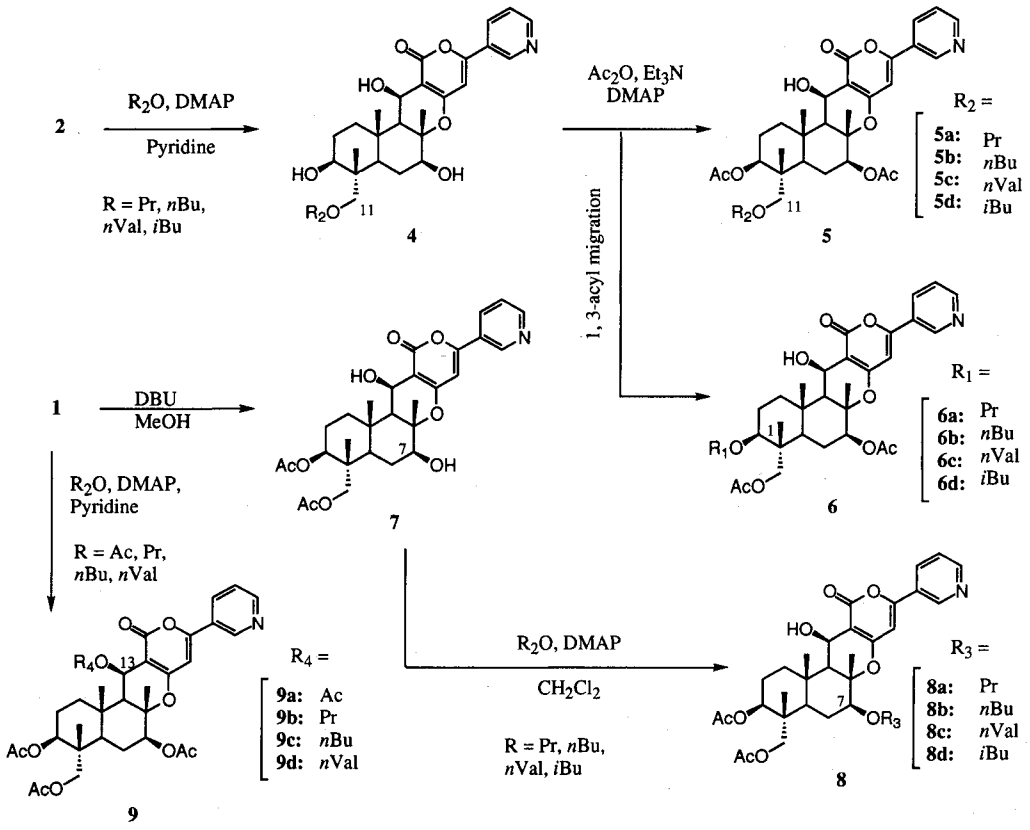
In this paper, we describe the chemical modification and structure-activity relationships of these four hydroxyl moieties of **1**[27,28].

Scheme 1.



Pyripyropene A (**1**) **2** **3**

Scheme 2.



Chemistry

First, **1** was treated with ammonia gas by bubbling into the methanol to obtain trideacetyl pyripyropene A (**2**) in a quantitative yield, subsequent acylation of 1-, 7- and 11-hydroxyl groups were carried out by acid anhydride and 4-dimethylaminopyridine (DMAP) in pyridine to give **3** (Scheme 1). 13-hydroxyl group was not acylated under this condition because of the structure hindrance.

Selective substitution of 1-, 7-, 11- and 13-hydroxyl groups was carried out as shown in Scheme 2. The primary alcohol at C-11 on **2** was selectively acylated by controlling the amount of the reagents. Then, the mono-acylated derivative **4** was acetylated with acetic anhydride, triethylamine, and DMAP in dichloromethane to give the mixture of **5** and **6** by 1, 3-acyl migration, which was separated by HPLC to obtain pure **5** and **6**. 7-Substituted derivatives (**8**) were obtained by two steps. First, selective removal of the 7-*O*-acetyl group of **1** was accomplished by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[29] in methanol, and the resultant 7-hydroxyl group of **7** was acylated to give **8**. Introduction of an acyl group to the 13-hydroxyl group required an excess amount of reagent and long reaction time to obtain **9**. Introducing a branched acyl group such as *i*-butyryl to the 13-hydroxyl group was not successful.

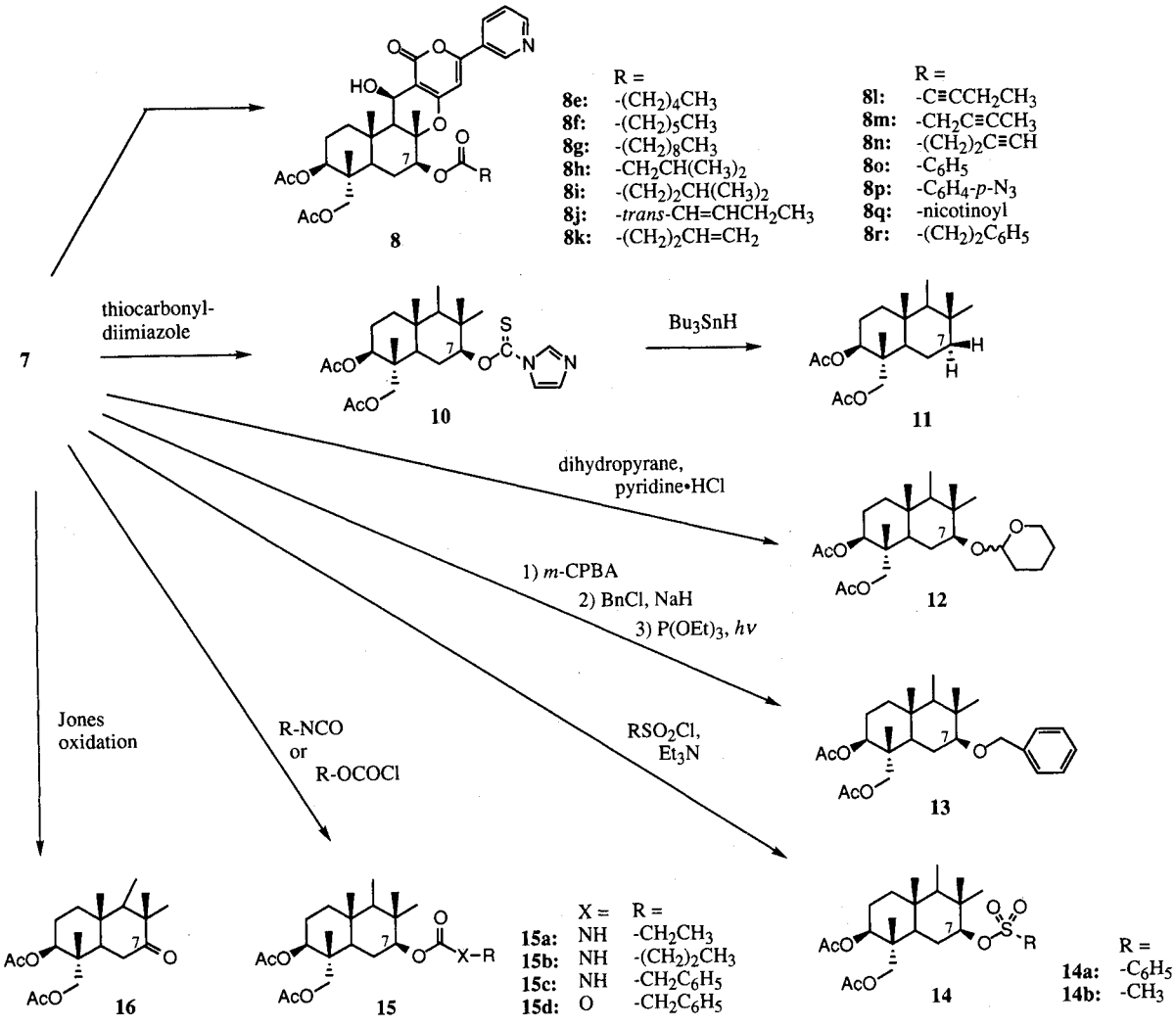
Further chemical modification of 7-hydroxyl group was accomplished as Scheme 3. Acylation of **7** was carried out by treatment with the corresponding acyl anhydride (Method A) or acyl chloride (Method B) in the presence of triethylamine and DMAP in dichloromethane, or by treatment with corresponding carboxylic acid, 1,3-dicyclohexylcarbodiimide (DCC), and DMAP in dichloromethane (Method C) to obtain **8e**~**8r**. Reaction condition of compound **8a** to **8r** are shown in Table 1.

Introduction of thiocarbonylimidazole group (**10**) to the 7-hydroxyl group of **7** followed by treatment with tributyltinhydride (Bu_3SnH) afforded 7-dehydroxyl compound (**11**).

7-*O*-Tetrahydropyranyl (THP) derivative (**12**) was obtained by treatment of **7** with dihydropyrane (DHP) and pyridine-hydrochloride salt in dichloromethane.

The 7-*O*-alkyl derivative (**13**) was prepared as following; the pyridine moiety of **1** was first protected as *N*-oxide by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA). Then, the 7-hydroxyl group was alkylated by treatment with benzyl chloride and sodium hydride in

Scheme 3.



dimethylformamide. Finally, *N*-oxide was reduced by irradiation in the presence of triethylphosphite[30] to give **13**.

7-*O*-Alkylsulfonyl derivatives (**14a** and **14b**) were obtained by treatment of **7** with the corresponding alkylsulfonyl chloride and triethylamine in dichloromethane.

7-*O*-Carbamate derivatives (**15a**~**15c**) were obtained by treatment of **7** with the corresponding alkyl isocyanate and triethylamine in dichloromethane. 7-*O*-Carbonate derivative (**15d**) was prepared from **7** by treating with benzyl chloroformate, triethylamine and DMAP in dichloromethane. Jones oxidation of **7** gave 7-keto (**16**).

Furthermore, 11-alkylsulfonyl analogs (**17a**~**17d**) were obtained by selective alkylsulfonylation of the primary 11-hydroxyl group of **2** by controlling the amount of reagent and temperature, followed by acetylation of 1- and 7-hydroxyl groups (Scheme 4).

Table 1. Reaction condition of compound **8a** to **8r**.

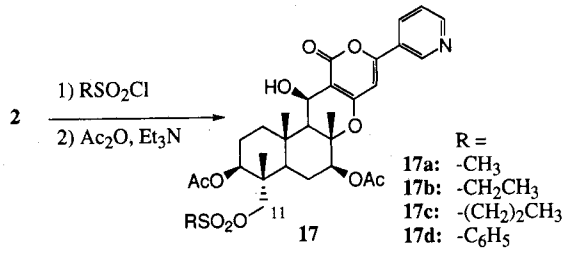
Compound	Method	Reagent	Yeild (%)
8a	A	Acetic anhydride	40
8b	A	Propionic anhydride	98
8c	A	*n*-Butiric anhydride	86
8d	A	*n*-Valeric anhydride	100
8e	A	*n*-Capric anhydride	100
8f	A	Hepatanoic anhydride	68
8g	A	*n*-Caproic anhydride	96
8h	A	*i*-Valeric anhydride	95
8i	C	*i*-Caproic acid	100
8j	C	2-Pentenoic acid	62
8k	C	4-Pentenoic acid	88
8l	C	2-Pentynoic acid	47
8m	C	3-Pentynoic acid	8
8n	C	4-Pentynoic acid	92
8o	A	Benzoic anhydride	92
8p	C	4-Azidobenzoic acid	100
8q	C	Nicotinic acid	85
8r	B	Hydrocinnamoyl chloride	18

A and B: Et_3N, DMAP; C: DCC, DMAP.

On the other hand, modification of the 13-hydroxyl group is illustrated in Scheme 5. Jones oxidation of **1** gave 13-keto compound (**18**). Elimination of the 13-hydroxyl group easily occurred by treatment of **1** with hydrochloric acid under anhydrous condition to form 5, 13-olefin derivative (**19**). For methylation of the 13-hydroxyl group, pyridine moiety was first protected as *N*-oxide to form compound **20**. Then, **20** was treated with methyl iodide and sodium hydride, followed by reduction of *N*-oxide to give 13-*O*-methyl derivative (**21**).

Analytical data of compound **2**~**21** are shown in Tables 2 to 7.

Scheme 4.



Scheme 5.

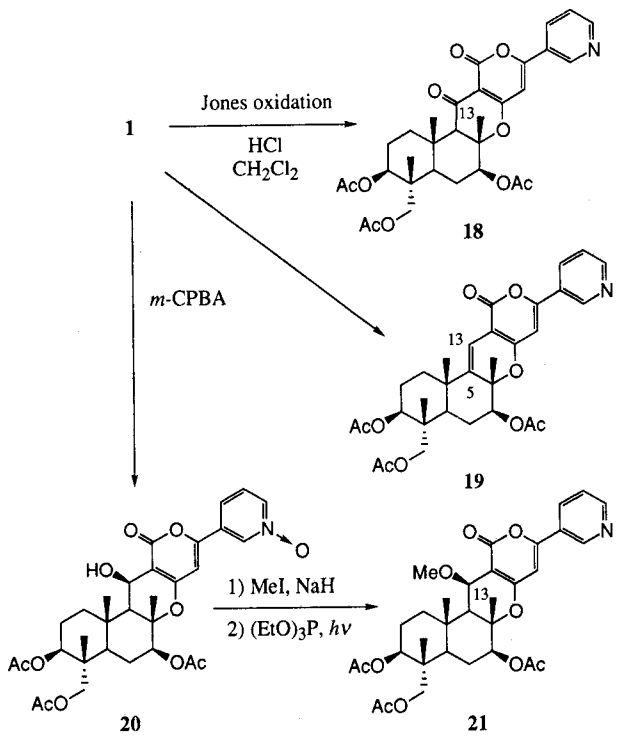


Table 2-1. Analytical data of compound **2**~**4b**.

	^{1}H NMR ($CDCl_3$)* δ (ppm)	HR-MS	IR**
2	0.73 (3H, s), 1.40 (3H, s), 1.64 (3H, s), 3.31 (1H, d, J=11.9 Hz), 3.61 (1H, d, J=10.9 Hz), 3.65 (1H, dd, J=5.3, 12.2 Hz), 3.78 (1H, dd, J=4.6, 11.2 Hz), 4.96 (1H, d, J=3.6 Hz), 6.82 (1H, s), 7.57 (1H, dd, J=4.5, 7.8 Hz), 8.27 (1H, dt, J=2.0, 8.6 Hz), 8.64 (1H, dd, J=1.5, 4.8 Hz), 9.02 (1H, d, J=1.7 Hz) [solvent: CD_3OD]	Found: (EI) 457.2090 (M^+) Calcd: 457.2100 (as $C_{25}H_{31}O_7N$)	1690, 1580
3a	0.82 (3H, s), 1.17 (9H, m), 1.37 (3H, s), 1.62 (3H, s), 2.37 (6H, m), 3.63 (1H, d, J=11.9 Hz), 3.72 (1H, d, J=11.9 Hz), 4.73 (1H, dd, J=5.0, 11.2 Hz), 4.94 (1H, d, J=4.0 Hz), 4.94 (1H, m), 6.39 (1H, s), 7.34 (1H, dd, J=4.1, 8.1 Hz), 8.03 (1H, dt, J=2.0, 8.3 Hz), 8.62 (1H, dd, J=1.5, 4.8 Hz), 8.94 (1H, d, J=1.7 Hz)	Found: (FAB) 626.2946 (M+H) Calcd: 262.2965 (as $C_{34}H_{44}O_{10}N$)	1730, 1190
3b	0.89 (3H, s), 0.96 (9H, m), 1.44 (3H, s), 1.69 (3H, s), 2.31 (6H, m), 3.67 (1H, d, J=11.9 Hz), 3.78 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, d, J=4.3 Hz), 5.01 (1H, m), 6.39 (1H, s), 7.39 (1H, ddd, J=0.7, 5.0, 7.9 Hz), 8.07 (1H, dt, J=2.0, 8.3 Hz), 8.67 (1H, dd, J=1.5, 4.8 Hz), 8.98 (1H, d, J=1.7 Hz)	Found: (FAB) 668.3422 (M+H) Calcd: 668.3434 (as $C_{37}H_{50}O_{10}N$)	1730
3c	0.90 (3H, s), 0.92 (9H, m), 1.44 (3H, s), 1.69 (3H, s), 2.32 (6H, m), 3.68 (1H, d, J=11.9 Hz), 3.78 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.1, 11.4 Hz), 5.00 (1H, d, J=4.0 Hz), 5.02 (1H, dd, J=5.3, 11.2 Hz), 6.40 (1H, s), 7.40 (1H, dd, J=4.6, 7.9 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 8.99 (1H, d, J=2.0 Hz)	Found: (FAB) 710.3888 (M+H) Calcd: 710.3904 (as $C_{40}H_{56}O_{10}N$)	1730, 1170
3d	0.91 (3H, s), 1.18 (18H, m), 1.44 (3H, s), 1.70 (3H, s), 2.58 (3H, m), 3.67 (1H, d, J=11.9 Hz), 3.76 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.6, 10.9 Hz), 4.97 (1H, m), 4.99 (1H, d, J=3.3 Hz), 6.37 (1H, s), 7.39 (1H, dd, J=4.8, 8.1 Hz), 8.07 (1H, dt, J=2.0, 8.3 Hz), 8.67 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=2.3 Hz)	Found: (FAB) 668.3442 (M+H) Calcd: 668.3434 (as $C_{37}H_{50}O_{10}N$)	1730
4a	0.84 (3H, s), 1.41 (3H, s), 1.41 (3H, t, J=7.6 Hz), 1.66 (3H, s), 2.35 (2H, q, J=7.6 Hz), 3.47 (1H, m), 3.75 (1H, d, J=11.9 Hz), 3.77 (1H, m), 4.18 (1H, d, J=11.9 Hz), 4.99 (1H, s), 6.52 (1H, s), 7.40 (1H, m), 8.10 (1H, m), 8.69 (1H, d, J=4.0 Hz), 9.01 (1H, s)	Found: (FAB) 514.2411 (M+H) Calcd: 514.2440 (as $C_{28}H_{36}O_8N$)	1700, 1580
4b	0.83 (3H, s), 0.94 (3H, t, J=7.4 Hz), 1.39 (3H, s), 1.65 (3H, s), 2.31 (2H, m), 3.41 (1H, dd, J=5.9, 10.6 Hz), 3.76 (1H, d, J=11.9 Hz), 3.77 (1H, m), 4.25 (1H, d, J=11.5 Hz), 4.98 (1H, d, J=4.0 Hz), 6.52 (1H, s), 7.41 (1H, dd, J=5.0, 7.9 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 528.2608 (M+H) Calcd: 528.2597 (as $C_{29}H_{38}O_8N$)	1700

*: Solvent of compound **2** is CD_3OD; **: IR (KBr) cm^{-1}.

Table 2-2. Analytical data of compound **4c**~**4d**.

	^{1}H NMR ($CDCl_3$)* δ (ppm)	HR-MS	IR**
4c	0.83 (3H, s), 0.91 (3H, t, J=7.6 Hz), 1.39 (3H, s), 1.65 (3H, s), 2.34 (2H, m), 3.41 (1H, dd, J=5.9, 10.6 Hz), 3.75 (1H, d, J=11.9 Hz), 3.78 (1H, dd, J=4.6, 11.9 Hz), 4.25 (1H, d, J=11.9 Hz), 4.98 (1H, d, J=4.3 Hz), 6.52 (1H, s), 7.42 (1H, dd, J=4.6, 7.9 Hz), 8.11 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.7, 5.0 Hz), 9.00 (1H, d, J=1.7 Hz)	Found: (FAB) 542.2762 (M+H) Calcd: 542.2753 (as $C_{30}H_{40}O_8N$)	1700, 1580
4d	0.83 (3H, s), 1.16 (6H, d, J=6.9 Hz), 1.39 (3H, s), 1.66 (3H, s), 2.56 (1H, quint, J=6.9 Hz), 3.37 (1H, dd, J=4.3, 10.6 Hz), 3.75 (1H, m), 3.75 (1H, d, J=11.9 Hz), 4.24 (1H, d, J=11.9 Hz), 4.98 (1H, d, J=4.0 Hz), 6.49 (1H, s), 7.40 (1H, dd, J=5.0, 7.9 Hz), 8.09 (1H, d, J=8.2 Hz), 8.63 (1H, d, J=4.6 Hz), 8.98 (1H, s)	Found: (FAB) 528.2609 (M+H) Calcd: 528.2597 (as $C_{29}H_{38}O_8N$)	1700, 1580

*: Solvent of compound **2** is CD_3OD; **: IR (KBr) cm^{-1}.

Table 3. Analytical data of compound **5a**~**7**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
5a	0.89 (3H, s), 1.16 (3H, t, J=7.6 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.16 (3H, s), 2.37 (2H, q, J=7.6 Hz), 3.70 (1H, d, J=11.9 Hz), 3.79 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.1, 11.4 Hz), 4.99 (1H, m), 5.00 (1H, d, J=3.0 Hz), 6.46 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 9.01 (1H, d, J=2.3 Hz)	Found: (FAB) 598.2642 (M+H) Calcd: 598.2652 (as $C_{32}H_{40}O_{10}N$)	1730, 1240
5b	0.88 (3H, s), 0.94 (3H, t, J=7.4 Hz), 1.43 (3H, s), 1.68 (3H, s), 2.03 (3H, s), 2.15 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.79 (1H, d, J=11.9 Hz), 4.77 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, d, J=4.6 Hz), 4.99 (1H, m), 6.45 (1H, s), 7.40 (1H, dd, J=4.8, 8.1 Hz), 8.08 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.5, 4.8 Hz), 9.00 (1H, d, J=1.7 Hz)	Found: (FAB) 612.2799 (M+H) Calcd: 612.2808 (as $C_{33}H_{42}O_{10}N$)	1740, 1240
5c	0.88 (3H, s), 0.90 (3H, t, J=7.3 Hz), 1.43 (3H, s), 1.68 (3H, s), 2.03 (3H, s), 2.15 (3H, s), 3.68 (1H, d, J=11.9 Hz), 3.79 (1H, d, J=11.9 Hz), 4.77 (1H, dd, J=5.1, 11.4 Hz), 4.99 (1H, d, J=3.3 Hz), 4.99 (1H, m), 6.45 (1H, s), 7.40 (1H, dd, J=4.6, 7.9 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.5, 3.3 Hz), 9.0 ((1H, d, J=2.0 Hz)	Found: (FAB) 626.2971 (M+H) Calcd: 626.2965 (as $C_{34}H_{44}O_{10}N$)	1740, 1240
5d	0.89 (3H, s), 1.19 (3H, d, J=6.9 Hz), 1.19 (3H, d, J=6.9 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.15 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.76 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.3, 11.2 Hz), 4.97 (1H, m), 4.99 (1H, d, J=5.3 Hz), 6.46 (1H, s), 7.40 (1H, dd, J=5.0, 8.3 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, d, J=4.3 Hz), 9.00 (1H, s)	Found: (FAB) 612.2806 (M+H) Calcd: 612.2808 (as $C_{33}H_{42}O_{10}N$)	1740, 1240
6a	0.89 (3H, s), 1.13 (3H, t, J=7.6 Hz), 1.44 (3H, s), 1.70 (3H, s), 2.09 (3H, s), 2.16 (3H, s), 2.32 (1H, q, J=7.6 Hz), 3.71 (1H, d, J=11.9 Hz), 3.77 (1H, d, J=11.9 Hz), 4.81 (1H, dd, J=5.1, 11.7 Hz), 5.00 (1H, s), 5.00 (1H, m), 6.46 (1H, s), 7.41 (1H, dd, J=4.8, 7.8 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 9.01 (1H, d, J=2.0 Hz)	Found: (FAB) 598.2681 (M+H) Calcd: 598.2652 (as $C_{32}H_{40}O_{10}N$)	1740, 1240
6b	0.89 (3H, s), 0.94 (3H, t, J=7.3 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.09 (3H, s), 2.17 (3H, s), 3.71 (1H, d, J=11.9 Hz), 3.76 (1H, d, J=11.9 Hz), 4.81 (1H, dd, J=5.3, 11.2 Hz), 5.00 (1H, d, J=3.6 Hz), 5.01 (1H, m), 6.41 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.09 (1H, d, J=8.3 Hz), 8.69 (1H, d, J=3.6 Hz), 9.01 (1H, s)	Found: (FAB) 612.2814 (M+H) Calcd: 612.2808 (as $C_{33}H_{42}O_{10}N$)	1740, 1240
6c	0.89 (3H, s), 0.92 (3H, t, J=7.3 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.09 (3H, s), 2.16 (3H, s), 3.74 (1H, s), 3.74 (1H, s), 4.81 (1H, dd, J=5.1, 11.1 Hz), 5.00 (1H, d, J=5.3 Hz), 5.01 (1H, m), 6.46 (1H, s), 7.41 (1H, dd, J=5.0, 7.9 Hz), 8.10 (1H, dd, J=2.2, 6.4 Hz), 8.68 (1H, d, J=5.3 Hz), 9.01 (1H, s)	Found: (FAB) 626.2981 (M+H) Calcd: 626.2965 (as $C_{34}H_{44}O_{10}N$)	1740, 1240
6d	0.90 (3H, s), 1.15 (3H, d, J=6.9 Hz), 1.17 (3H, d, J=6.9 Hz), 1.45 (3H, s), 1.70 (3H, s), 2.09 (3H, s), 2.17 (3H, s), 2.53 (1H, quint, J=6.9 Hz), 3.74 (1H, s), 3.74 (1H, s), 4.79 (1H, dd, J=5.6, 10.9 Hz), 5.00 (1H, br s), 5.00 (1H, m), 6.46 (1H, s), 7.41 (1H, dd, J=4.8, 8.4 Hz), 8.10 (1H, dt, J=2.0, 8.6 Hz), 8.68 (1H, d, J=4.3 Hz), 9.01 (1H, d, J=1.7 Hz)	Found: (EI) 611.2702 (M^+) Calcd: 611.2730 (as $C_{33}H_{41}O_{10}N$)	1730, 1240
7	0.90 (3H, s), 1.41 (3H, s), 1.65 (3H, s), 2.04 (3H, s), 2.04 (3H, s), 3.75 (1H, d, J=11.9 Hz), 3.80 (1H, m), 3.81 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.6, 10.9 Hz), 4.98 (1H, d, J=4.0 Hz), 6.50 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (EI) 541.2288 (M^+) Calcd: 541.2311 (as $C_{29}H_{35}O_9N$)	1730, 1250

Table 4-1. Analytical data of compound **8a**~**8l**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
8a	0.89 (3H, s), 1.22 (3H, t, J=7.6 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.44 (2H, dq, J=1.8, 7.6 Hz), 3.68 (1H, d, J=11.9 Hz), 3.81 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.3, 11.2 Hz), 5.00 (1H, s), 5.01 (1H, dd, J=5.6, 10.9 Hz), 6.43 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, s), 9.01 (1H, s)	Found: (FAB) 598.2670 (M+H) Calcd: 598.2652 (as $C_{32}H_{40}O_{10}N$)	1740, 1240
8b	0.88 (3H, s), 0.99 (3H, t, J=7.6 Hz), 1.43 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.36 (2H, m), 3.68 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, d, J=4.0 Hz), 5.00 (1H, dd, J=5.9, 7.9 Hz), 6.40 (1H, s), 7.41 (1H, dd, J=5.0, 7.9 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, d, J=3.6 Hz), 8.99 (1H, s)	Found: (FAB) 612.2817 (M+H) Calcd: 612.2808 (as $C_{33}H_{42}O_{10}N$)	1730, 1250
8c	0.89 (3H, s), 0.97 (3H, t, J=7.4 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.81 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.3, 10.9 Hz), 5.00 (1H, d, J=3.0 Hz), 5.02 (1H, m), 6.40 (1H, s), 7.41 (1H, dd, J=4.8, 7.6 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.7, 5.0 Hz), 9.00 (1H, d, J=1.7 Hz)	Found: (FAB) 626.2945 (M+H) Calcd: 626.2965 (as $C_{34}H_{44}O_{10}N$)	1740, 1250
8d	0.88 (3H, s), 1.24 (6H, d, J=6.9 Hz), 1.44 (3H, s), 1.70 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.58 (1H, quint, J=6.9 Hz), 3.66 (1H, d, J=12.2 Hz), 3.82 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, d, J=4.0 Hz), 5.00 (1H, m), 6.37 (1H, s), 7.40 (1H, dd, J=5.0, 7.9 Hz), 8.08 (1H, dt, J=2.0, 7.9 Hz), 8.68 (1H, dd, J=1.5, 4.8 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 612.2806 (M+H) Calcd:612.2808 (as $C_{33}H_{42}O_{10}N$)	1730, 1250
8e	0.88 (3H, s), 0.92 (3H, m), 1.43 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.40 (2H, dt, J=2.0, 7.6 Hz), 3.67 (1H, d, J=10.9 Hz), 3.80 (1H, d, J=12.2 Hz), 4.78 (1H, dd, J=5.1, 11.1 Hz), 4.99 (1H, s), 5.01 (1H, dd, J=5.6, 14.1 Hz), 6.40 (1H, s), 7.40 (1H, dd, J=5.0, 7.9 Hz), 8.08 (1H, dt, J=2.0, 8.2 Hz), 8.68 (1H, d, J=3.6 Hz), 8.98 (1H, s)	Found: (FAB) 640.3123 (M+H) Calcd: 640.3121 (as $C_{35}H_{46}O_{10}N$)	1740, 1240
8f	0.88 (3H, s), 0.88 (3H, s), 1.43 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 2.37 (2H, m), 3.67 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.1, 11.4 Hz), 4.99 (1H, d, J=4.0 Hz), 5.01 (1H, m), 6.41 (1H, s), 7.41 (1H, dd, J=5.1, 8.1 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, d, J=4.6 Hz), 8.99 (1H, s)	Found: (FAB) 654.3262 (M+H) Calcd: 654.3278 (as $C_{36}H_{48}O_{10}N$)	1740, 1240
8g	0.85 (3H, m), 0.88 (3H, s), 1.43 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 2.40 (2H, t, J=7.4 Hz), 3.67 (1H, d, J=11.9 Hz), 3.81 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.0, 11.2 Hz), 4.99 (1H, d, J=4.0 Hz), 5.01 (1H, m), 6.40 (1H, s), 7.40 (1H, dd, J=4.8, 8.1 Hz), 8.08 (1H, d, J=7.1 Hz), 8.68 (1H, d, J=4.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 718.3572 (M+Na) Calcd: 718.3567 (as $C_{39}H_{53}O_{10}NNa$)	1710
8h	0.88 (3H, s), 0.98 (6H, d, J=6.6 Hz), 1.43 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.79 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.1, 11.1 Hz), 4.99 (1H, d, J=4.3 Hz), 5.01 (1H, dd, J=5.0, 11.2 Hz), 6.38 (1H, s), 7.42 (1H, dd, J=4.9, 7.9 Hz), 8.08 (1H, dt, J=2.0, 8.6 Hz), 8.69 (1H, d, J=3.3 Hz), 8.98 (1H, s)	Found: (FAB) 626.2957 (M+H) Calcd: 626.2965 (as $C_{34}H_{44}O_{10}N$)	1740, 1240
8i	0.88 (3H, s), 0.94 (6H, d, J=5.8 Hz), 1.44 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 3.67 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, s), 5.01 (1H, dd, J=5.6, 10.6 Hz), 6.39 (1H, s), 7.40 (1H, dd, J=5.0, 8.3 Hz), 8.08 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.3, 5.0 Hz), 8.98 (1H, d, J=2.0 Hz)	Found: (FAB) 640.3115 (M+H) Calcd: 640.3121 (as $C_{35}H_{46}O_{10}N$)	1740, 1240
8j	0.88 (3H, s), 1.11 (3H, t, J=7.4 Hz), 1.44 (3H, s), 1.72 (3H, s), 2.03 (3H, s), 2.09 (3H, s), 3.66 (1H, d, J=11.9 Hz), 3.81 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.0, 11.3 Hz), 5.00 (1H, d, J=2.0 Hz), 5.08 (1H, dd, J=5.1, 11.1 Hz), 5.89 (1H, dt, J=1.7, 15.8 Hz), 6.45 (1H, s), 7.11 (1H, dt, J=6.3, 15.8 Hz), 7.39 (1H, dd, J=4.8, 8.1 Hz), 8.08 (1H, dt, J=2.0, 7.9 Hz), 8.67 (1H, dd, J=1.5, 4.8 Hz), 8.99 (1H, d, J=2.3 Hz)	Found: (FAB) 624.2791 (M+H) Calcd: 624.2808 (as $C_{34}H_{42}O_{10}N$)	1730, 1240
8k	0.88 (3H, s), 1.43 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 3.67 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, d, J=3.3 Hz), 5.00 (1H, m), 5.04 (1H, dd, J=1.3, 10.2 Hz), 5.11 (1H, dd, J=1.7, 17.2 Hz), 5.87 (1H, m), 6.41 (1H, s), 7.40 (1H, dd, J=4.8, 8.1 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, d, J=3.6 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 624.2787 (M+H) Calcd: 624.2808 (as $C_{34}H_{42}O_{10}N$)	1740, 1240
8l	0.88 (3H, s), 1.24 (1H,), 1.43 (3H, s), 1.72 (3H, s), 2.04 (1H, ?), 2.07 (1H, ?), 2.39 (1H, ?), 3.68 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.77 (1H, dd, J=5.1, 11.4 Hz), 4.99 (1H, d, J=1.7 Hz), 5.09 (1H, m), 6.48 (1H, s), 7.42 (1H, dd, J=4.8, 8.2 Hz), 8.11 (1H, dd, J=2.0, 8.2 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 9.02 (1H, d, J=1.7 Hz)	Found: (FAB) 622.2653 (M+H) Calcd: 622.2652 (as $C_{34}H_{40}O_{10}N$)	1710, 1620, 1250

Table 4-2. Analytical data of compound **8m**~**8r**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
8m	0.89 (3H, s), 1.44 (3H, s), 1.70 (3H, s), 1.86 (3H, t, J=2.3 Hz), 2.05 (3H, s), 2.09 (3H, s), 3.35 (2H, quint, J=2.3 Hz), 3.65 (1H, d, J=11.9 Hz), 3.84 (1H, d, J=12.2 Hz), 4.78 (1H, dd, J=5.1, 11.4 Hz), 5.01 (1H, s), 5.03 (1H, m), 6.47 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.7, 5.0 Hz), 9.01 (1H, d, J=1.7 Hz)	Found: (FAB) 622.2673 (M+H) Calcd: 622.2652 (as $C_{34}H_{40}O_{10}N$)	1740, 1250
8n	0.96 (3H, s), 1.43 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 3.67 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.3, 11.2 Hz), 4.99 (1H, d, J=2.0 Hz), 5.03 (1H, m), 6.43 (1H, s), 7.39 (1H, dd, J=5.0, 8.1 Hz), 8.08 (1H, dt, J=2.0, 8.6 Hz), 8.68 (1H, dd, J=1.3, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 622.2628 (M+H) Calcd: 622.2652 (as $C_{34}H_{40}O_{10}N$)	1740, 1250
8o	0.91 (3H, s), 1.50 (3H, s), 1.86 (3H, s), 2.05 (3H, s), 2.14 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.85 (1H, d, J=12.2 Hz), 4.64 (1H, dd, J=5.3, 11.2 Hz), 5.04 (1H, d, J=4.3 Hz), 5.28 (1H, dd, J=4.8, 11.1 Hz), 6.45 (1H, s), 7.41 (1H, m), 7.47 (3H, m), 8.10 (1H, m), 8.70 (1H, d, J=3.3 Hz), 9.00 (1H, d, J=1.7 Hz)	Found: (FAB) 646.2662 (M+H) Calcd: 646.2652 (as $C_{36}H_{40}O_{10}N$)	1720, 1250
8p	0.90 (3H, s), 1.48 (3H, s), 1.83 (3H, s), 2.04 (3H, s), 2.12 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.83 (1H, d, J=12.2 Hz), 4.81 (1H, d, J=5.3, 11.2 Hz), 5.02 (1H, d, J=4.0 Hz), 5.24 (1H, dd, J=5.0, 10.9 Hz), 6.41 (1H, s), 7.11 (1H, d, J=2.3, 8.6 Hz), 7.39 (1H, d, J=4.8, 8.1 Hz), 8.07 (1H, m), 8.09 (1H, d, J=2.0, 8.6 Hz), 8.66 (1H, d, J=3.6 Hz), 8.96 (1H, d, J=1.6 Hz)	Found: (FAB) 622.2653 (M+H) Calcd: 688.2744 (as $C_{36}H_{40}O_{10}N_4$)	2130, 1720, 1270
8q	0.91 (3H, s), 1.49 (3H, s), 1.85 (3H, s), 3.71 (1H, d, J=11.9 Hz), 3.82 (1H, d, J=11.9 Hz), 4.82 (1H, dd, J=5.1, 11.4 Hz), 5.03 (1H, d, J=4.0 Hz), 5.28 (1H, dd, J=4.8, 11.3 Hz), 6.42 (1H, s), 7.39 (1H, dd, J=5.0, 7.9 Hz), 7.47 (1H, dd, J=5.0, 7.6 Hz), 8.08 (1H, dt, J=2.0, 8.6 Hz), 8.38 (1H, dt, J=2.0, 8.3 Hz), 8.66 (1H, d, J=3.6 Hz), 8.83 (1H, d, J=3.3 Hz), 8.97 (1H, s), 9.30 (1H, s)	Found: (FAB) 647.2601 (M+H) Calcd: 647.2605 (as $C_{35}H_{39}O_{10}N_2$)	1730, 1250
8r	0.87 (3H, s), 1.42 (3H, s), 1.64 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 2.69 (2H, m), 2.97 (2H, m), 3.65 (1H, d, J=11.9 Hz), 3.80 (1H, d, J=11.9 Hz), 4.77 (1H, m), 4.98 (1H, d, J=4.0 Hz), 4.99 (1H, m), 6.32 (1H, s), 7.27 (5H, m), 7.32 (1H, m), 8.10 (1H, d, J=7.9 Hz), 8.69 (1H, d, J=5.0 Hz), 9.00 (1H, d, J=2.0 Hz)	Found: (FAB) 674.2976 (M+H) Calcd: 674.2965 (as $C_{38}H_{44}O_{10}N$)	1740, 1240

Table 5-1. Analytical datas of compound **9a**~**11**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
9a	0.84 (3H, s), 1.11 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.09 (3H, s), 2.09 (3H, s), 2.17 (3H, s), 3.72 (1H, s), 3.72 (1H, s), 4.79 (1H, dd, J=4.6, 11.6 Hz), 5.00 (1H, dd, J=5.1, 10.7 Hz), 6.37 (1H, d, J=3.3 Hz), 6.41 (1H, s), 7.39 (1H, dd, J=5.0, 8.3 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.5, 4.8 Hz), 8.99 (1H, d, J=2.3 Hz)	Found: (FAB) 626.2609 (M+H) Calcd: 626.2601 (as $C_{33}H_{40}O_{11}N$)	1740, 1230
9b	0.84 (3H, s), 1.10 (3H, s), 1.17 (3H, t, J=7.6 Hz), 1.70 (3H, s), 2.03 (3H, s), 2.10 (3H, s), 2.17 (3H, s), 3.72 (1H, s), 3.72 (1H, s), 4.79 (1H, dd, J=4.8, 11.6 Hz), 5.00 (1H, dd, J=5.0, 10.9 Hz), 6.38 (1H, d, J=3.6 Hz), 6.41 (1H, s), 7.39 (1H, dd, J=5.3, 7.9 Hz), 8.09 (1H, dt, J=2.0, 8.6 Hz), 8.67 (1H, dd, J=1.5, 3.1 Hz), 8.99 (1H, d, J=2.0 Hz)	Found: (FAB) 640.2744 (M+H) Calcd: 640.2758 (as $C_{34}H_{42}O_{11}N$)	1740, 1230
9c	0.84 (3H, s), 0.97 (3H, t, J=7.4 Hz), 1.09 (3H, s), 1.69 (3H, s), 2.03 (3H, s), 2.09 (3H, s), 2.17 (3H, s), 3.72 (1H, s), 3.72 (1H, s), 4.79 (1H, dd, J=4.6, 11.6 Hz), 5.00 (1H, dd, J=4.3, 10.2 Hz), 6.37 (1H, d, J=3.3 Hz), 6.42 (1H, s), 7.41 (1H, dd, J=5.1, 7.8 Hz), 8.12 (1H, dt, J=2.0, 8.6 Hz), 8.67 (1H, d, J=3.3 Hz), 9.00 (1H, s)	Found: (FAB) 654.2892 (M+H) Calcd: 654.2914 (as $C_{35}H_{44}O_{11}N$)	1740, 1230
9d	0.91 (3H, t, J=7.3 Hz), 1.11 (3H, s), 1.70 (3H, s), 2.04 (3H, s), 2.10 (3H, s), 2.17 (3H, s), 2.33 (3H, s), 3.73 (1H, s), 3.73 (1H, s), 4.80 (1H, dd, J=4.8, 11.7 Hz), 5.01 (1H, dd, J=4.8, 10.4 Hz), 6.38 (1H, d, J=3.3 Hz), 6.41 (1H, s), 7.40 (1H, dd, J=4.8, 8.1 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.5, 4.8 Hz), 9.00 (1H, d, J=2.0 Hz)	Found: (FAB) 668.3065 (M+H) Calcd: 668.3071 (as $C_{36}H_{46}O_{11}N$)	1740, 1230
10	0.90 (3H, s), 1.50 (3H, s), 1.86 (3H, s), 2.05 (3H, s), 2.11 (3H, s), 3.74 (1H, s), 3.74 (1H, s), 4.82 (1H, dd, J=5.0, 11.6 Hz), 5.04 (1H, d, J=4.3 Hz), 5.66 (1H, dd, J=4.6, 10.9 Hz), 6.46 (1H, s), 7.08 (1H, dd, J=0.7, 1.7 Hz), 7.38 (1H, ddd, J=0.7, 5.0, 8.3 Hz), 7.67 (1H, t, J=1.5 Hz), 8.06 (1H, dt, J=2.0, 7.9 Hz), 8.38 (1H, d, J=1.0 Hz), 8.67 (1H, dd, J=1.7, 5.0 Hz), 8.98 (1H, d, J=1.7 Hz)	Found: (FAB) 652.2349 (M+H) Calcd: 652.2328 (as $C_{33}H_{38}O_9NS$)	1720, 1250
11	0.90 (3H, s), 1.41 (3H, s), 1.66 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.75 (1H, d, J=11.9 Hz), 3.83 (1H, d, J=11.9 Hz), 4.81 (1H, dd, J=5.6, 10.6 Hz), 4.99 (1H, s), 6.46 (1H, s), 7.41 (1H, dd, J=5.1, 7.8 Hz), 8.11 (1H, dt, J=2.0, 8.3 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 9.00 (1H, d, J=1.7 Hz)	Found: (FAB) 526.2441 (M+H) Calcd: 526.2440 (as $C_{29}H_{36}O_8N$)	1740, 1700, 1250

Table 5-2. Analytical datas of compound **12**~**14b**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
12	0.89 (3H, s), 1.40 (3H, s), 1.69 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 3.68 (1H, d, J=11.9 Hz), 3.76 (1H, m), 3.85 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.6, 11.2 Hz), 4.97 (1H, d, J=2.0 Hz), 6.40 (1H, s), 7.40 (1H, dd, J=5.0, 7.9 Hz), 8.09 (1H, m), 8.67 (1H, d, J=5.0 Hz), 8.99 (1H, d, J=2.0 Hz)	Found: (FAB) 626.2972 (M+H) Calcd: 626.2965 (as $C_{34}H_{44}O_{10}N$)	1730, 1250
13	0.87 (3H, s), 1.36 (3H, s), 1.75 (3H, s), 2.04 (6H, s), 3.74 (1H, d, J=11.9 Hz), 3.76 (1H, m), 3.81 (1H, d, J=11.9 Hz), 4.74 (1H, dd, J=4.6, 11.5 Hz), 4.80 (1H, d, J=11.6 Hz), 4.97 (1H, d, J=2.6 Hz), 5.04 (1H, d, J=11.2 Hz), 6.48 (1H, s), 7.34 (5H, m), 7.42 (1H, dd, J=5.0, 8.3 Hz), 8.12 (1H, dt, J=2.0, 8.6 Hz), 8.69 (1H, dd, J=1.7, 5.0 Hz), 9.01 (1H, d, J=1.7 Hz)	Found: (FAB) 632.2864 (M+H) Calcd: 632.2860 (as $C_{36}H_{42}O_9N$)	1740, 1250
14a	0.91 (3H, s), 1.44 (3H, s), 1.71 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 3.18 (3H, s), 3.76 (1H, d, J=12.2 Hz), 3.82 (1H, d, J=12.2 Hz), 4.68 (1H, dd, J=5.3, 11.9 Hz), 4.76 (1H, dd, J=5.1, 11.4 Hz), 5.00 (1H, d, J=2.3 Hz), 6.41 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.09 (1H, dt, J=2.0, 8.6 Hz), 8.69 (1H, dd, J=1.5, 4.8 Hz), 9.00 (1H, d, J=1.7 Hz)	Found: (FAB) 620.2147 (M+H) Calcd: 620.2166 (as $C_{30}H_{38}O_{11}NS$)	1720, 1250
14b	0.85 (3H, s), 1.39 (3H, s), 1.63 (3H, s), 2.03 (3H, s), 2.12 (3H, s), 3.52 (1H, d, J=11.9 Hz), 3.81 (1H, d, J=12.2 Hz), 4.61 (1H, dd, J=6.3, 10.9 Hz), 4.72 (1H, dd, J=5.1, 11.4 Hz), 4.92 (1H, d, J=2.3 Hz), 5.86 (1H, s), 7.42 (1H, dd, J=4.9, 7.9 Hz), 8.06 (1H, dt, J=2.0, 8.2 Hz), 8.70 (1H, dd, J=1.5, 4.8 Hz), 8.91 (1H, d, J=2.3 Hz)	Found: (FAB) 704.2134 (M+H) Calcd: 704.2142 (as $C_{35}H_{40}O_{11}NS$)	1720, 1260

Table 6. Analytical datas of compound **15**~**17**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
15a	0.88 (3H, s), 1.42 (3H, s), 1.62 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 3.20 (2H, dd, J=5.9, 13.2 Hz), 3.65 (1H, d, J=11.6 Hz), 3.85 (1H, d, J=11.9 Hz), 4.75 (1H, t, J=5.6 Hz), 4.77 (1H, dd, J=5.3, 11.2 Hz), 4.92 (1H, m), 4.98 (1H, s), 6.45 (1H, s), 7.39 (1H, dd, J=5.0, 7.9 Hz), 8.08 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.7, 4.6 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 627.2911 (M+H) Calcd: 627.2918 (as $C_{33}H_{43}O_{10}N_2$)	1720, 1250
15b	0.88 (3H, s), 0.96 (3H, t, J=7.1 Hz), 1.62 (3H, s), 1.65 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 3.24 (2H, dd, J=6.4, 13.0 Hz), 3.64 (1H, d, J=11.5 Hz), 3.85 (1H, d, J=11.9 Hz), 4.73 (1H, t, J=5.3 Hz), 4.77 (1H, dd, J=5.3, 11.2 Hz), 4.92 (1H, m), 4.98 (1H, s), 6.45 (1H, s), 7.40 (1H, ddd, J=0.7, 5.0, 7.9 Hz), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.7, 4.6 Hz), 8.99 (1H, dd, J=0.7, 2.3 Hz)	Found: (FAB) 663.2908 (M+H) Calcd: 663.2967 (as $C_{34}H_{45}O_{10}N_2$)	1720, 1250
15c	0.89 (3H, s), 1.43 (3H, s), 1.65 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.68 (1H, d, J=11.9 Hz), 3.86 (1H, d, J=12.2 Hz), 4.44 (2H, t, J=5.1 Hz), 4.79 (1H, dd, J=5.3, 11.2 Hz), 4.96 (1H, m), 4.98 (1H, s), 5.09 (1H, t, J=5.9 Hz), 6.43 (1H, s), 7.37 (5H, m), 7.41 (1H, m), 8.09 (1H, d, J=8.3 Hz), 8.70 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 697.2721 (M+H) Calcd: 697.2737 (as $C_{37}H_{43}O_{10}N_2$)	1720, 1250
15d	0.89 (3H, s), 1.43 (3H, s), 1.70 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.71 (1H, d, J=11.9 Hz), 3.82 (1H, d, J=11.9 Hz), 4.79 (1H, dd, J=5.4, 11.4 Hz), 4.86 (1H, dd, J=5.3, 11.5 Hz), 4.99 (1H, d, J=3.0 Hz), 6.38 (1H, s), 7.37 (5H, m), 7.42 (1H, m), 8.09 (1H, dt, J=2.0, 8.3 Hz), 8.70 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 698.2573 (M+Na) Calcd: 698.2577 (as $C_{37}H_{41}O_{11}NNa$)	1740, 1250
16	0.06 (1H, m), 0.95 (3H, s), 1.58 (3H, s), 1.58 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 3.58 (1H, d, J=11.9 Hz), 3.88 (1H, d, J=11.9 Hz), 4.78 (1H, m), 5.05 (1H, s), 6.61 (1H, s), 7.42 (1H, m), 8.09 (1H, m), 8.70 (1H, s), 9.03 (1H, s)	Found: (FAB) 498.2486 (M+H) Calcd: 498.2491 (as $C_{28}H_{36}O_7N$)	1730, 1240
17a	0.88 (3H, s), 1.42 (3H, s), 1.68 (3H, s), 2.03 (3H, s), 2.13 (3H, s), 3.04 (3H, s), 3.80 (1H, s), 3.84 (1H, s), 4.78 (1H, m), 4.96 (1H, s), 4.99 (1H, m), 6.44 (1H, s), 7.39 (1H, m), 8.07 (1H, d, J=7.9 Hz), 8.66 (1H, s), 8.98 (1H, s)	Found: (FAB) 620.2173 (M+H) Calcd: 620.2166 (as $C_{30}H_{38}O_{11}NS$)	1730, 1240
17b	0.84 (3H, s), 1.37 (3H, t, J=7.3 Hz), 1.38 (3H, s), 1.63 (3H, s), 2.00 (3H, s), 2.10 (3H, s), 3.10 (2H, dd, J=7.3, 14.8 Hz), 3.78 (1H, d, J=10.6 Hz), 3.83 (1H, d, J=10.6 Hz), 4.73 (1H, dd, J=4.6, 11.6 Hz), 5.00 (1H, m), 6.39 (1H, s), 7.34 (1H, dd, J=4.8, 8.1 Hz), 8.03 (1H, dt, J=2.0, 8.3 Hz), 8.62 (1H, dd, J=1.5, 4.8 Hz), 8.94 (1H, d, J=2.3 Hz)	Found: (FAB) 656.2107 (M+Na) Calcd: 656.2141 (as $C_{31}H_{39}O_{11}NSNa$)	1730, 1240
17c	1.03 (3H, s), 1.20 (3H, t, J=7.4 Hz), 1.56 (3H, s), 1.81 (3H, s), 2.18 (3H, s), 2.28 (3H, s), 3.20 (2H, m), 3.95 (1H, d, J=4.6 Hz), 3.99 (1H, d, J=5.0 Hz), 4.88 (1H, dd, J=5.0 Hz), 5.13 (2H, m), 6.58 (1H, s), 7.51 (1H, d, J=4.6 Hz), 8.21 (1H, d, J=7.3 Hz), 8.81 (1H, d, J=4.0 Hz), 9.12 (1H, d, J=4.3 Hz)	Found: (FAB) 648.2476 (M+H) Calcd: 648.2479 (as $C_{32}H_{42}O_{11}NS$)	1730, 1240
17d	0.84 (3H, s), 1.40 (3H, s), 1.66 (3H, s), 1.91 (3H, s), 2.17 (3H, s), 3.67 (2H, s), 4.73 (1H, dd, J=4.6, 11.9 Hz), 4.95 (1H, d, J=4.3 Hz), 5.07 (1H, dd, J=5.3, 10.9 Hz), 6.47 (1H, s), 7.53 (1H, s), 7.56 (4H, m), 7.92 (2H, d, J=7.3 Hz), 8.14 (1H, d, J=7.9 Hz), 8.69 (1H, s), 9.03 (1H, s)	Found: (FAB) 682.2331 (M+H) Calcd: 682.2322 (as $C_{35}H_{40}O_{11}NS$)	1740, 1240

Table 7. Analytical datas of compound **18**~**21**.

	^{1}H NMR ($CDCl_3$) δ (ppm)	HR-MS	IR
18	0.83 (3H, s), 1.19 (3H, s), 1.53 (3H, s), 1.99 (3H, s), 2.07 (3H, s), 2.13 (3H, s), 3.67 (1H, d, J=12.2 Hz), 3.73 (1H, d, J=12.2 Hz), 4.74 (1H, dd, J=5.3, 11.2 Hz), 5.18 (1H, d, J=3.3 Hz), 5.20 (1H, dd, J=5.0, 11.2 Hz), 6.48 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 8.13 (1H, dt, J=2.0, 8.3 Hz), 8.70 (1H, s), 9.01 (1H, s), 8.70 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 582.2350 (M+H) Calcd: 582.2339 (as $C_{31}H_{36}O_{10}N$)	1740, 1540, 1240
19	0.87 (3H, s), 1.25 (3H, s), 1.58 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.15 (3H, s), 3.73 (1H, d, J=12.2 Hz), 3.79 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=4.6, 11.2 Hz), 5.22 (1H, dd, J=5.0, 11.6 Hz), 6.35 (1H, s), 6.52 (1H, s), 7.41 (1H, dd, J=4.8, 7.8 Hz), 8.12 (1H, d, J=7.9 Hz), 8.67 (1H, s), 9.01 (1H, s), 8.70 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 566.2388(M+H) Calcd: 566.2390 (as $C_{31}H_{36}O_9N$)	1740, 1240
20	0.88 (3H, s), 1.43 (3H, s), 1.68 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 2.15 (3H, s), 3.69 (1H, d, J=11.9 Hz), 3.78 (1H, d, J=11.9 Hz), 4.78 (1H, dd, J=5.2, 11.1 Hz), 4.97 (1H, d, J=4.3 Hz), 4.98 (1H, m), 6.42 (1H, s), 7.36 (1H, m), 7.66 (1H, m), 8.27 (1H, d, J=6.6 Hz), 8.63 (1H, s), 8.70 (1H, dd, J=1.7, 5.0 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 600.2462 (M+H) Calcd: 600.2445 (as $C_{31}H_{38}O_{11}N$)	1730, 1250
21	0.88 (3H, s), 1.37 (3H, s), 1.71 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 2.16 (3H, s), 3.61 (3H, s), 3.71 (1H, s), 3.76 (1H, s), 4.68 (1H, d, J=3.3 Hz), 4.78 (1H, m), 4.92 (1H, m), 6.39 (1H, s), 7.39 (1H, dd, J=4.6, 7.9 Hz), 8.10 (1H, dt, J=2.0, 8.3 Hz), 8.68 (1H, dd, J=1.7, 4.6 Hz), 9.00 (1H, d, J=1.7 Hz), 8.99 (1H, d, J=1.7 Hz)	Found: (FAB) 598.2652 (M+H) Calcd: 598.2652 (as $C_{32}H_{40}O_{10}N$)	1740, 1240

Biological Activity

Synthetic derivatives prepared in this study were evaluated *in vitro* ACAT inhibitory activity according to our established method[15]. Their IC_{50} values are shown in Tables 8 to 12.

The importance of the three acetyl groups of **1** was demonstrated since **2**, which has no acetyl groups, lost the inhibitory activity completely (Table 8). Tri-*O*-propionyl (**3a**) showed 10 times less potent inhibitory activity than **1**. Other tri-acyl derivatives with *n*-butyryl (**3b**), *n*-valeryl (**3c**) or *i*-butyryl (**3d**) groups also showed weak activity. Substitution of the three hydroxyl groups with bigger acyl groups did not improve the activity.

Next, each of these three acetyl groups was substituted separately with other acyl groups, and the 13-hydroxyl group was modified with an acyl group (Table 9). Substitution with a longer acyl group at the 11-hydroxyl group (**5a**~**5d**) or introduction of acyl group to the 13-hydroxyl group (**9a**~**9d**) significantly reduced the activity, except **5a**. The substituent of the 11-position should be a small group. And the free 13-hydroxyl group might be very important for inhibitory activity. As for 1-substituted derivatives propionyl (**6a**), *i*-butyryl (**6b**) or *n*-butyryl (**6d**) analogs showed similar inhibitory activity although *n*-valeryl analog (**6c**) weakened the activity.

Interestingly, substitution by a longer acyl group at the 7-hydroxyl group appeared to improve the inhibitory activity (**1** *vs.* **8a**~**8c**, Tables 8 and 9). The seven fold increase in the activity of **8c** in comparison with that of **1** led us to study further modification of 7-substituted derivatives (Table 10).

As for derivatives substituting a linear acyl group (**8a**~**8c** and **8e**~**8g**) for the 7-position, longer acyl derivatives with 1- to 5-carbon length showed potent inhibitory activity, and derivatives with more than 6 carbon length decreased the inhibitory activity. As the result, *n*-valeryl derivative (**8c**) showed the most potent inhibitory activity among this series of derivatives. Branched acyl analogs (**8d**, **8h** and **8i**) were less potent than the corresponding linear acyl analogs (**8a**, **8b** and **8c**, respectively).

Derivatives with a terminal alkene (**8k**), non-terminal *trans*-alkene (**8j**), and terminal alkyne (**8n**) group at the 7-hydroxyl group showed potent inhibitory activity, but derivatives with a non-terminal alkyne (**8l** and **8m**) groups were less potent. Benzoyl (**8o**) and thiocarbonyl imidazole (**10**) analogs showed potent activity, but *p*-azidobenzoyl (**8p**) and nicotinoyl (**8q**) analogs were less potent. And phenylpropionyl ester (**8r**) showed potent inhibitory activity. These results indicated that at the β~δ positions of the acyl chain, structurally similar substituents as normal chain alkane, such as **8j** and **8k** showed potent inhibitory activity. In contrast, compounds containing branched chain (**8d**, **8h**) or fixed structure which is different to alkane (**8l** and **8m**) at these positions were less active. However, the terminal position can be different structure as alkyne or branched chain (**8i**, **8n**

and **8r**).

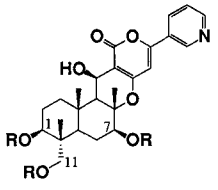
Furthermore, the benzoyl derivative (**8o**) and **1** showed almost the same inhibitory activity, but benzyl (**13**), phenylsulfonyl (**14a**) and methanesulfonyl (**14b**) derivatives decreased the activity, indicating that the carbonyl moiety at the 7-position is important for ACAT inhibition. Among the carbamate analogs (**15a**~**15c**), **15b**, with the same chain length as **8c** showed the best activity. By comparing with **15c**, **15d** and **8r**, the order of inhibitory activity depended upon the β atom, that is, $CH_2 > O > NH$. 7-Hydroxyl derivative (**7**) lost the inhibitory activity, and ketone (**16**) and deoxy derivatives (**11**) were less potent but better than **7**. Hydrophobic substituents were preferred at the 7-position to hydrophilic ones.

Structure and inhibitory activity of 11-alkylsulfonyl derivatives are shown in Table 11. Methanesulfonyl analog (**17a**) showed 5 times more potent inhibitory activity than **1**. But derivatives with a longer alkyl chain (**17c** and **17d**) decreased the inhibitory activity dramatically.

As shown in Table 12, derivatives lacking the free 13-hydroxyl group decreased inhibitory activity. This result suggested that the 13-hydroxyl group is essential for potent ACAT inhibitory activity.

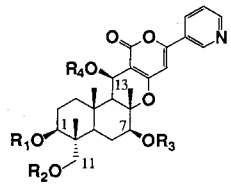
The *in vivo* efficacy of **8c** and **17a** was tested with a hamster model[17,28]. The cholesterol absorption was inhibited 57±9% by **8c** at 67 mg/kg dose, which was almost the same inhibitory activity as **1**. Remarkably, **17a** showed dose-dependent inhibition with an ED_{50} value of about 10 mg/kg, showing that **17a** is ten-fold more potent than **1**.

Table 8. Structure and *in vitro* ACAT inhibitory activity of 1,7,11-*tri*-*O*-substituted derivatives.



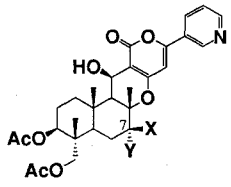
Compound	Structure R=	IC_{50} (μM)
1	$COCH_3$	0.089
2	H	>150
3a	$COCH_2CH_3$	0.78
3b	$CO(CH_2)_2CH_3$	0.62
3c	$CO(CH_2)_3CH_3$	0.84
3d	$COCH_2(CH_3)_2$	0.34

Table 9. Structure and *in vitro* ACAT inhibitory activity of 1,7,11,13-*O*-acylated derivatives.



Compound	Structure				IC_{50} (μM)
	R_1=	R_2=	R_3=	R_4=	
5a	$COCH_3$	$COCH_2CH_3$	$COCH_3$	H	0.27
5b	$COCH_3$	$CO(CH_2)_2CH_3$	$COCH_3$	H	4.2
5c	$COCH_3$	$CO(CH_2)_3CH_3$	$COCH_3$	H	>8.0
5d	$COCH_3$	$COCH_2(CH_3)_2$	$COCH_3$	H	5.9
6a	$COCH_2CH_3$	$COCH_3$	$COCH_3$	H	0.14
6b	$CO(CH_2)_2CH_3$	$COCH_3$	$COCH_3$	H	0.20
6c	$CO(CH_2)_3CH_3$	$COCH_3$	$COCH_3$	H	0.62
6d	$COCH_2(CH_3)_2$	$COCH_3$	$COCH_3$	H	0.13
8a	$COCH_3$	$COCH_3$	$COCH_2CH_3$	H	0.067
8b	$COCH_3$	$COCH_3$	$CO(CH_2)_2CH_3$	H	0.038
8c	$COCH_3$	$COCH_3$	$CO(CH_2)_3CH_3$	H	0.013
8d	$COCH_3$	$COCH_3$	$COCH_2(CH_3)_2$	H	0.13
9a	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_3$	5.1
9b	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_2CH_3$	23
9c	$COCH_3$	$COCH_3$	$COCH_3$	$CO(CH_2)_2CH_3$	2.4
9d	$COCH_3$	$COCH_3$	$COCH_3$	$CO(CH_2)_3CH_3$	16

Table 10. Structure and *in vitro* ACAT inhibitory activity of 7-substituted derivatives.



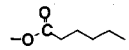
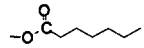
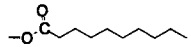
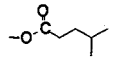
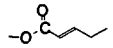
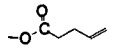
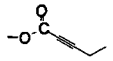
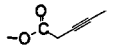
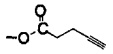
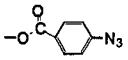
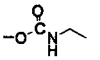
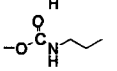
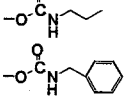
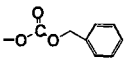
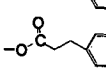
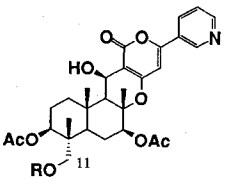
Compound	Structure X=	Structure Y=	IC_{50} (μM)
8e		H	0.019
8f		H	0.17
8g		H	0.12
8h		H	0.21
8i		H	0.039
8j		H	0.030
8k		H	0.080
8l		H	0.55
8m		H	0.37
8n		H	0.054
8o		H	0.085
8p		H	0.28
8q		H	0.40
10		H	0.14
12		H	1.0
13		H	7.4
14a		H	3.1
14b		H	1.7
15a		H	1.2
15b		H	0.59
15c		H	1.2
15d		H	0.41
8r		H	0.050
7	OH	H	57
16	=O		7.0
11	H	H	1.4

Table 11. Structure and *in vitro* ACAT inhibitory activity of 11-*O*-alkylsulfonyl derivatives.



Compound	Structure R=	IC_{50} (μM)
17a	SO_2CH_3	0.019
17b	$SO_2CH_2CH_3$	0.28
17c	$SO_2(CH_2)_2CH_3$	110
17d	$SO_2C_6H_5$	>150

Table 12. *In vitro* ACAT inhibitory activity of derivatives modified at the 13 hydroxyl group.

Compound	*In vitro* ACAT inhibitory activity (IC_{50}, μM)
18	1.2
19	3.3
21	23

Conclusion

We have investigated the chemical modification at the 1-, 7-, 11- and 13-hydroxyl groups of pyripyropenes, novel ACAT inhibitors. Clear structure-activity relationships of this series of derivatives has been shown as follows: 1) A substituent at the 7-position was essential for potent activity, that is, a) hydrophobicity was desirable, b) the best length was as long as *n*-valeryl, c) carbonyl moiety at the β position of the chain was necessary, d) structure at the $\beta \sim \delta$ position should be similar to straight-chain alkane, and e) alkane carbon at α-atom of carbonyl was better than O or NH. 2) Acetyl group at the 1-position showed better activity than other acyl groups, but difference of acyl did not critically relate to the activity. 3) A small substituent such as acetyl or mesyl groups at the 11-position was important for potent inhibitory activity. 4) Free hydroxyl group at the 13-position is essential for potent activity.

Thus, several derivatives were found as more potent ACAT inhibitors than **1**. Especially, 7-*O*-*n*-valeryl (**8c**) and 11-*O*-methanesulfonyl (**17a**) derivatives showed significant *in vitro* ACAT inhibition with IC_{50} values of 13 and 19 nM, respectively. Furthermore, **17a** showed *in vivo* efficacy in inhibiting cholesterol absorption in cholesterol-fed hamsters (ED_{50}: 10 mg/kg, more than 10-fold potent than pyripyropene A).

Experimental

Reagents were obtained from commerical suppliers and were used without purification, unless otherwise noted. Column chromatography was carried out on sillica gel (Merck, Kieselgel 60, 230~400 mesh). And for preparative TLC (PTLC), Kiesel gel 60 F-254 (Merck) was used. Mass spectra were obtained by using a JEOL model DX-300 mass spectrometer. ^1H (270 MHz) and ^{13}C NMR (76.5 MHz) spectra were aquired on a JEOL-EX270 spectrophotometer. Chemical shifts are given in ppm with solvent peak ($CHCl_3$: 7.26 ppm, CD_3OD: 3.60 ppm) as the standard, and coupling constants (J) are given as Hz. Abbreviations of ^1H NMR signal patterns are following: s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, dt = double triplet, q = quartet, m = multiplet, br s = broad singlet. IR spectra were taken with a Horiba model FT-210 spectrophotometer.

Trideacetyl Pyripyropene A (2)

1 (250 mg) was dissolved in MeOH (10 ml) and ammonia gas was bubbled into the solution at room temperature for 4 days. The reaction mixture was cooled with ice-water bath. The precipitate was washed with cooled MeOH and dried *in vacuo* to give **2** (154.9 mg, 79%) as colorless powder.

General Method of 1,7,11-*tri*-*O*-Acylation

Trideacetyl-1,7,11-*tri*-*O*-propyonyl Pyripyropene A (**3a**):

To the solution of **2** (6.6 mg) in dry THF (0.6 ml) was added propyonic anhydride (10 μl), Et_3N (14 μl) and DMAP (2 mg), and stirred at room temperature for 6 hours. The reaction mixture was dried up *in vacuo* and diluted with CH_2Cl_2. The organic layer was washed with water and dried over anhrdr sodium sulfide (Na_2SO_4), then filtered off. The filtrate was concentrated *in vacuo* and the residue was purified by PTLC (10 × 20 cm, 0.25 mm thick, CH_2Cl_2 : MeOH = 10 : 1) to afford **3a** (3.5 mg, 39%) as colorless solid.

In the similar manner, **2** was treated with *n*-butiric anhydride, *n*-valeric anhydride and *i*-butiric anhydride individually to afford **3b**, **3c** and **3d** (10, 8 and 15%, respectively).

General Method of 11-*mono*-*O*-Acylation

Trideacetyl-11-*O*-propyonyl Pyripyropene A (**4a**):

To the solution of **2** (19 mg) in dry pyridine (1 ml) was added propyonic anhydride (40 μl) and DMAP (2 mg), and stirred at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (i.d. 1 × 15 cm, CH_2Cl_2 : MeOH = 20 : 1) to obtain **4a** (7 mg, 33%) as colorless powder.

In a similar manner, **2** was treated with *n*-butiric anhydride, *n*-valeric anhydride and *i*-butiric anhydride individually to afford **4b**, **4c** and **4d** (61, 43 and 19%, respectively).

General Method of Acetylation of 11-*O*-Acyl Pyripyropene A

11-*O*-propyonyl Pyripyropene A (**5a**) and 1-*O*-Propyonyl Pyripyropene A (**6a**):

To the solution of **4a** (7 mg) in dry CH_2Cl_2 (2 ml) was added acetic anhydride (Ac_2O, 3 μl), Et_3N (10 μl) and DMAP (2 mg), and stirred at room temperature for 20 hours. The reaction mixture was washed with water and dried over anhrdr Na_2SO_4, then filtered off. The filtrate was concentrated *in vacuo* to give a mixture of **5a** and **6a**, which was separated by HPLC (column: SenshuPak ODS-4251-N, eluant: 40% acetonitril-water) to obtain **5a** (2.3 mg, 28%) and **6a** (1.2 mg, 15%), respectively.

In the similar manner, **4b**, **4c** and **4d** were acetylated individually to afford **5b** and **6b** (60 and 7%), **5c** and **6c** (39 and 24%), and **5d** and **6d** (44 and 29%), respectively.

7-Deacetyl Pyripyropene A (7)

Compound **1** (291 mg) was hydrolyzed with DBU (75 μl) in 80% MeOH aq (10 ml). After stirred at room temperature for 10 minutes, the reaction mixture was added AcOH (0.1 ml) and EtOAc (5 ml), and azeotroped with MeOH. The residue was purified with column chromatography (i.d. 1 × 18 cm, CH_2Cl_2 : MeOH = 50 : 1 ~ 7 : 1) to afford **7** (140.6 mg, 52%) as colorless powder.

General Method of 7-*O*-Acylation of 7

Method A: Acyl Anhydride

7-*O*-Propyonyl Pyripyropene A (**8a**):

To the solution of **7** (9 mg) in dry CH_2Cl_2 (1 ml) was added propionic anhydride (80 μl), Et_3N (60 μl) and DMAP (1 mg), and stirred at room temperature. Additional amount of propionic anhydride (20 μl) and Et_3N (20 μl) were added at 4th and 6th days respectively, and the reaction mixture was heated to 80 °C for 1 hour. After stirring for 14 hours at room temperature, the mixture was cooled to 0°C and additional amount of DMAP (2 mg) was added and stirred at 0°C for 2 hours, then MeOH (1 ml) was added and dried up. The residue was diluted with EtOAc (2 ml) and washed with water (1 ml × 3), satd NaCl, respectively. The organic phase was dried over anhrdr Na_2SO_4 then filtered off. The filtrate was concentrated *in vacuo* to give pale yellow oil, which was purified by PTLC (10 × 20 cm, 0.25 mm thick, CH_2Cl_2 : MeOH = 20 : 1) to give **8a** (4 mg, 40%).

Method B: Acyl Chloride

7-*O*-Hydroxycinnanmoil Pyripyropene A (**8r**):

To the solution of **7** (11 mg) in dry CH_2Cl_2 (2 ml) was added hydrocinnamoyl chloride (4 μl) and Et_3N (8 μl), and stirred at room temperature for 15 hours. The reaction mixture was added additional amount of hydrocinnamoyl chloride (6, 15, 15 and 20 μl portions) and DMAP (1 mg), during 4 days. The reaction mixture was worked up in a similar manner to **6a** and purified

by PTLC to give **8r** (2.5 mg, 18%).

Method C: Carboxylic Acid

7-*O*-*i*-Capryl Pyripyropene A (**8i**):

To the solution of **7** (16 mg) in dry CH_2Cl_2 (1 ml) was added *i*-caproic acid (4 μl), DCC (10 mg) and DMAP (1.2 mg), and stirred at room temperature for 20 hours. Additional amount of DCC(6 mg) was added and stirred for 6 hours, then dried up. The residue was dissolved in cooled EtOAc, and the insoluble residue was filtered off and was washed with cooled EtOAc. The filtrate and the washing were combined and washed with water, satd NaCl respectively, then dried over anhrdr Na_2SO_4 and filtered off. The filtrate was purified by column chromatography (i.d. 1 × 8 cm, CH_2Cl_2 : MeOH = 50 : 1 ~ 25 : 1) to afford **8i** (19 mg, 100%).

3-Pentynoic Acid:

3-Pentyn-1-ol (1.2 ml) was dissolved in acetone (25 ml) and Jones reagent (3 M CrO_3 in aq. H_2SO_4, 6 ml) was added. After stirring at room temperature for 3 hours, the precipitated chloride was filtered off and the filtrate was concentrated *in vacuo* to give pale green solid (851 mg), which was purified with column chromatography (i.d. 1.5 × 30 cm, CH_2Cl_2 : MeOH = 50 : 1 ~ 40 : 1) to obtain 3-pentynoic acid (393 mg, 31%) as colorless oil.

General Method of 13-*O*-Acylation

13-*O*-Acetyl Pyripyropene A (**9a**):

To the solution of **1** (5 mg) in dry THF (0.1 ml) was added Ac_2O (14 μl), Et_3N (14 μl) and DMAP (4 mg), and stirred at room temperature for 17 hours. The reaction mixture was treated in a similar manner to **3a** to give **9a** (4 mg, 74%).

In the similar manner, **1** was treated with propionic anhydride, *n*-butyric anhydride and *n*-valeric anhydride individually to afford **9b**, **9c** and **9d** (56, 93 and 92%, respectively).

7-*O*-Thiocarbonylimidazoyl Pyripyropene A (**10**)

A mixture of **7** (16 mg) and thiocarbomate (5 mg) in dry THF (2 ml) was refluxed at 80°C for 3 hours. Toluene (1 ml) was added to the reaction mixture and was refluxed at 120°C for 1 hour. The reaction was quenched by adding water and extracted with EtOAc. The organic layer was treated in a similar manner to **8a** to give **10** (13.3 mg, 69%).

7-Dehydroxyl Pyripyropene A (**11**)

To the solution of Bu_3SnH (5 μl) in toluene (1 ml) was added **10** (7.5 mg in 1 ml toluene) during 2 minutes at 120°C, and stirred for 3 hours. The reaction mixture was concentrated *in vacuo* to give pale yellow solid, which was purified by PTLC (10 × 20 cm, 0.25 mm thick, CH_2Cl_2 : MeOH = 10 : 1) to give **11** (1 mg, 17%) as colorless powder.

7-*O*-Tetrahydropyranyl Pyripyropene A (**12**)

To the solution of **7** (9 mg) in dry CH_2Cl_2 (1 ml) was added DHP (50 μl) and pyridinium hydrochloride (5 mg), and stirred at room temperature for 2 days. The reaction mixture was treated in a similar manner to compound **8r** to give **12** (9.2 mg, 89%).

7-*O*-Benzyl Pyripyropene A (**13**)

To the solution of **7** (80 mg) in dry CH_2Cl_2 (5 ml) was added *m*-CPBA (40 mg). After stirring at room temperature for 3 hours, the reaction mixture was washed with satd $Na_2S_2O_4$ and water, respectively. The organic phase was purified in the similar manner as compound **3a** to give 7-deacetyl pyripyropene A-*N*-oxide (82 mg, 100%). $C_{29}H_{35}O_{10}N$; HR FAB-MS 558.2355 (M+1) Calcd: 558.2339 (as $C_{29}H_{36}O_{10}N$); IR (KBr) cm^{-1} 1730, 1250; ^1H NMR ($CDCl_3$) δ 0.90 (3H, s), 1.41 (3H, s), 1.65 (3H, s), 2.05 (6H, s), 3.8 (1H, m), 3.8 (2H, s), 4.77 (1H, dd, J = 5.9, 10.6 Hz), 4.9 (1H, d, J = 3.6 Hz), 6.48 (1H, s), 7.39 (1H, t, J = 7 Hz), 7.65 (1H, d, J = 8.3 Hz), 8.26 (1H, d, J = 6.9 Hz), 8.65 (1H, s). Prepared 7-deacetyl pyripyropene A-*N*-oxide (22 mg) was dissolved in a mixed solution (THF : DMSO = 1 : 1, 1 ml) and sodium hydride (NaH, 5 mg) was added at 0°C and stirred for 5 minutes. Benzyl bromide (5 μl) was added to the mixture and stirred at 0°C for 40 minutes. Reaction was quenched by adding satd ammonium chloride and extracted with chloroform. The organic layer was purified in the similar manner as **3a** to give 7-deacetyl-7-*O*-benzyl-pyripyropene A-*N*-oxide (2.6 mg, 10%). $C_{36}H_{41}O_{10}N$; HR FAB-MS 648.2833 (M+1) Calcd: 648.2808 (as $C_{36}H_{42}O_{10}N$); IR (KBr) cm^{-1} 1720, 1250; ^1H NMR ($CDCl_3$) δ 0.87 (3H, s), 1.61 (3H, s), 2.04 (3H, s), 3.74 (1H, d, J = 11.6 Hz), 3.77 (1H, m), 3.8 (1H, d, J = 11.9 Hz), 4.78 (2H, d, J = 11.2 Hz), 4.82 (1H, dd, J = 5.0, 11.2 Hz), 4.95 (1H, d, J = 3.0 Hz), 5.02 (2H, d, J = 11.5 Hz), 6.43 (1H, s), 7.32 (5H, m), 7.38 (1H, dd, J = 6.3, 7.9 Hz), 7.65 (1H, dd, J = 1.3, 8.3 Hz), 8.24 (1H, dd, J = 1.3, 6.6 Hz), 8.6 (1H, s). To the solution of 7-deacetyl-7-*O*-benzyl-pyripyropene A-*N*-oxide (9 mg) in $CDCl_3$ (0.5 ml) was added triethyl phosphite (20 μl), and irradiated with a Hg lamp (Ushio, UM-102) for 6.5 hours. The reaction mixture was dried up and the residue was purified by PTLC (20 × 20 cm, 0.25 mm thick, CH_2Cl_2 : MeOH = 10 : 1) to give **13** (0.2 mg, 2%).

General Method of 7-*O*-Alkylsunfonylation

7-*O*-Methanesulfonyl Pyripyropene A (**14a**):

To the solution of **7** (32 mg) in dry pyridine (0.6 ml) was added methanesulfonyl chloride (7 μl), and stirred at 0°C for 1 hour and the bath was removed and stirred at room temperature for 1 hour. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was treated in the similar manner to **3a** to give **14a** (21.3 mg, 58%).

In the similar manner to **14a**, **7** was treated with benzenesulfonyl chloride to give **14b** (42%).

General Method of 7-*O*-Alkylcarbamateion

7-*O*-Propylcarbamate Pyripyropene A (**15a**):

To the solution of **7** (10.8 mg) in dry CH_2Cl_2 (0.2 ml) was added propyl isocyanate (2.4 μl) and Et_3N (4.0 μl), and stirred at room temperature. Reaction mixture was quenched by adding satd ammonium chloride and extracted with chloroform. The organic layer was treated in the similar manner to compound **3a** to give **15a** (4.2 mg, 34%).

In the similar manner to **15a**, **7** was treated with *n*-butyl isocyanate and benzyl isocyanate individually to afford **15b** and **15c** (24 and 25%, respectively).

7-*O*-Benzocarbonate Pyripyropene A (**15d**)

To the solution of **7** (10.8 mg) in dry CH_2Cl_2 (0.2 ml) was added carbobenzyl chloride (14.8 mg) and Et_3N (4 μl), and stirred at room temperature for 20 hours. An additional amount of carbobenzyl chloride (14.8 mg) and Et_3N (4 μl) was added 2 times, at 20 hours and 48 hours, respectively. The reaction mixture was treated in the similar manner to **15a** to give **15d** (8.5 mg, 63%).

7-Keto Pyripyropene A (**16**)

To the solution of **7** (47 mg) in acetone (2 ml) was added Jones reagent (40 μl), and stirred at room temperature for 6 hours. The precipitated chloride was filtered off and the filtrate was washed with acetone. The filtrate and washing were combined and dried up. Residue was treated in the similar manner to **3a** to give **16** (16.8 mg, 36%).

General Method of 11-*O*-Alkylsulfonylation

11-*O*-Methanesulfonyl Pyripyropene A (**17a**):

To the solution of **2** (158 mg) in dry pyridine (2 ml) was added methanesulfonyl chloride (60 μl), and stirred at 0°C for 30 minutes. The reaction mixture was charged on the ODS column chromatography (i.d. 1.5 × 23 cm), and eluted with 20~50% MeOH-water to give trideacetyl-11-*mono*-*O*-methanesulfonyl pyripyropene A (85.1 mg, 46%). $C_{26}H_{33}O_9NS$; HR-MS 536.1969 (M+H) Calcd: 536.1954 (as $C_{26}H_{34}O_9NS$); IR (KBr) cm^{-1} 1700, 1170; ^1H NMR δ 0.82 (3H, s), 1.41 (3H, s), 1.65 (3H, s), 3.65 (1H, t, J=8.4 Hz), 3.88 (1H, dd, J=5, 11.6 Hz), 3.96 (1H, d, J=10.2 Hz), 4.22 (1H, d, J=10.2 Hz), 4.97 (1H, d, J=4.3 Hz), 6.5 (1H, s), 7.41 (1H, dd, J=4.8, 8.1 Hz), 7.59 (3H, t, J=7.3 Hz), 7.69 (2H, t, J=7.3 Hz), 7.92 (2H, d, J=7.3 Hz), 8.1 (1H, dt, J=2, 8.3 Hz), 8.68 (1H, d, J=3.6 Hz). To the solution of afforded trideacetyl-11-*mono*-*O*-methanesulfonyl pyripyropene A (113 mg) in dry pyridine (2 ml) was added Ac_2O (0.1 ml), and stirred at room temperature for 17 hours. The reaction mixture was treated in a similar manner as **10** to give **17a** (129.4 mg, 99%).

In a similar method as above, **2** was treated with ethanesulfonyl chloride, propanesunfonyl chloride and phenylsulfonyl chloride individually, to obtain trideacetyl-11-*O*-ethanesunfonyl pyripyropene A (42%), trideacetyl-11-*O*-propanesunfonyl pyripyropene A (32%) and trideacetyl-11-*O*-phenylsulfonyl pyripyropene A (38%), respectively. Each compounds were acetylated to give **17b** (90%), **17c** (72%) and (86%). Trideacetyl-11-*O*-ethanesunfonyl pyripyropene A: $C_{26}H_{33}O_9NS$; HR-MS 550.2108 (M+H) Calcd: 550.2111 (as $C_{27}H_{36}O_9NS$); IR (KBr) cm^{-1} 1700, 1640, 1580; ^1H NMR δ 0.75 (3H, s), 1.33 (3H, s), 1.37 (3H, t, J=7.3 Hz), 1.59 (3H, s), 2.08 (2H, d, J=13.2 Hz), 3.10 (2H, dd, J=7.6, 14.8 Hz), 3.59 (1H, t, J=8.1 Hz), 3.81 (1H, dd, J=4.8, 11.4 Hz), 3.90 (1H, d, J=10.2 Hz), 4.14 (1H, d, J=10.6 Hz), 4.91 (1H, s), 6.45 (1H, s), 7.35 (1H, dd, J=4.8, 8.1 Hz), 8.04 (1H, dt, J=1.9, 8.6 Hz), 8.61 (1H, dd, J=1.5, 4.8 Hz), 8.93 (1H, d, J=1.6 Hz). Trideacetyl-11-*O*-propanesulfonyl pyripyropene A: $C_{26}H_{33}O_9NS$; HR-MS 564.2252 (M+H) Calcd: 564.2267 (as $C_{28}H_{38}O_9NS$); IR (KBr) cm^{-1} 1700, 1640, 1570; ^1H NMR δ 0.73 (3H, s), 1.01 (3H, t, J=7.3 Hz), 1.34 (3H, s), 1.56 (3H, s), 2.03 (2H, d, J=9.2 Hz), 3.15 (2H, m), 3.50 (1H, m), 3.68 (1H, m), 3.93 (1H, d, J=9.9 Hz), 4.07 (1H, d, J=9.9 Hz), 4.87 (1H, s), 6.73 (1H, s), 7.49 (1H, dd, J=4.9, 8.2 Hz), 8.19 (1H, d, J=7.6 Hz), 8.56 (1H, t, J=4.1 Hz), 8.94 (1H, s). Trideacetyl-11-*O*-phenylsulfonyl-pyripyropene A: $C_{31}H_{35}O_9NS$; HR FAB-MS 598.2109 (M+H) Calcd: 598.2111 (as $C_{31}H_{36}O_9NS$); IR (KBr) cm^{-1} 1700, 1190; ^1H NMR ($CDCl_3$) 0.73 (3H, s), 1.35 (3H, s), 1.76 (3H, s), 3.63 (1H, t, J=8 Hz), 3.7 (1H, d, J=10.1 Hz), 3.8 (1H, dd, J=5.3, 10.6 Hz), 4.02 (1H, d, J=9.9 Hz), 4.96 (1H, d, J=4 Hz), 6.53 (1H, s), 7.44 (1H, dd, J=4.8, 8.1 Hz), 7.59 (3H, t, J=7.3 Hz), 7.69 (2H, t, J=7.3 Hz), 7.92 (2H, d, J=7.3 Hz), 8.14 (1H, d, J=8.2 Hz), 8.69 (1H, d, J=3.5 Hz), 9.02 (1H, s).

13-Keto Pyripyropene A (**18**)

To the solution of **1** (64 mg) in acetone (40 ml) and water (2 ml) was added Jones reagent (0.5 ml), and stirred at room temperature for 3 hours. The reaction mixture was quenched with 2-propanol (0.5 ml), and the precipitate was filtered off. The filtrate was dried up and diluted with EtOAc, and washed with water for 2 times, satd Na_2SO_4, respectively. The organic layer was treated in the similar method to **3a** to give **18** (64 mg, 100%).

5-Olefin Pyripyropene A (**19**)

To the solution of **1** (10 mg) in dry benzene (0.1 ml) was added TFA (1 μl), and stirred at room temperature for 4 hours. The reaction mixture was treated in the similar method to **3a** to give **19** (7 mg, 72%).

Pyripyropene A-*N*-Oxide (**20**)

To the solution of **1** (58 mg) in dry CH_2Cl_2 (1 ml) was added *m*-CPBA (30 mg), and stirred at room temperature for 3 hours. The reaction mixture was treated in a similar manner to **8r** to give **20** (53 mg, 89%).

13-*O*-Methyl Pyripyropene A (**21**)

To the solution of **20** (29 mg) in dry DMF (1 ml) was added NaH (4 mg) and methyl iodide (50 μl), and stirred at 0°C for 10 minutes and at room temperature for 4

hours. The reaction mixture was treated in a similar manner to compound 7-*O*-benzyl-pyripyropene A-*N*-oxide to give 13-*O*-methyl-pyripyropene A-*N*-oxide (14.6 mg, 49%). $C_{32}H_{39}O_{11}N$; HR FAB-MS 614.2026 (M+1) Calcd: 614.2601 (as $C_{32}H_{40}O_{11}N$); IR (KBr) cm^{-1} 1740, 1240; ^1H NMR 0.88 (3H, s), 1.37 (3H, s), 1.70 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 2.15 (3H, s), 3.59 (3H, s), 3.71 (1H, d, J=11.9 Hz), 3.83 (1H, d, J=13.5 Hz), 4.65 (1H, d, J=3.0 Hz), 4.78 (1H, dd, J=5.0, 11.2 Hz), 4.94 (1H, m), 6.34 (1H, s), 7.35 (1H, dd, J=6.5, 8.1 Hz), 7.62 (1H, dd, J=2.0, 7.7 Hz), 8.24 (1H, dd, J=2.0, 6.3 Hz), 8.60 (1H, s). Prepared 13-*O*-methyl-pyripyropene A-*N*-oxide was irradiated in the similar manner to **13** to give **21** (3.5 mg, 36%).

Acknowledgment

This work was supported in part by Grant-in-aid for Scientific Research from Ministry of Education, Science and Culture of Japan, and Japan Keirin Association. We are grateful to Dr. HESS, Pfizer Inc. at Groton for kindly providing us with pyripyropene A, and arranging *in vivo* assay.

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