PYRIPYROPENES, NOVEL INHIBITORS OF ACYL-CoA: CHOLESTEROL ACYLTRANSFERASE PRODUCED BY *Aspergillus fumigatus*

II. STRUCTURE ELUCIDATION OF PYRIPYROPENES A, B, C AND D

YOUNG KOOK KIM, HIROSHI TOMODA, HIROYUKI NISHIDA†,
TOSHIAKI SUNAZUKA, RIKA OBATA and SATOSHI ŌMURA*

Research Center for Biological Function, The Kitasato Institute,
Minato-ku, Tokyo 108, Japan

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The structures of pyripyropenes A, B, C and D, novel acyl-CoA: cholesterol acyltransferase (ACAT) inhibitors, were determined mainly by spectroscopic studies including various NMR measurements. Pyripyropenes have a common structure which consists of pyridine, α-pyrone and sesquiterpene moieties. One of the three *O*-acetyl residues in the sesquiterpene moiety of pyripyropene A is replaced with an *O*-propionyl residue in pyripyropenes B, C and D.

Pyripyropenes produced by *Aspergillus fumigatus* FO-1289 were very potent inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT)[1]. The taxonomy of the producing organism, fermentation, isolation and biological properties of pyripyropenes have been described in the preceding paper[2]. We will report herein the structure elucidation of pyripyropenes A, B, C and D.

Physico-chemical Properties of Pyripyropenes A, B, C and D

Pyripyropenes A, B, C and D were isolated as white powders. The physico-chemical properties of pyripyropenes are summarized in Table 1. The molecular formulas were determined to be $C_{31}H_{37}NO_{10}$ for pyripyropene A and $C_{32}H_{39}NO_{10}$ for pyripyropenes B, C and D by high resolution electron impact mass (HREI-MS) and fast atom bombardment mass spectra (FAB-MS). Pyripyropenes showed the same UV maxima at 231 (ε 24,300) and 320 nm (ε 13,400) in MeOH. The IR spectra of pyripyropenes suggested the presence of –OH (3550 cm^{-1}) and –CO–O– (1740 and 1702 cm^{-1}) residues.

Structure of Pyripyropene A

In the EI-MS of pyripyropene A (Fig. 1), the presence of one hydroxy and three acetoxy residues in the molecule was suggested from the fragment ion peaks at *m/z* 565 $[M-H_2O]^+$, 523 $[M-AcOH]^+$, 505 $[M-AcOH-H_2O]^+$, 463 $[M-2AcOH]^+$, 445 $[M-2AcOH-H_2O]^+$, 403 $[M-3AcOH]^+$ and 385 $[M-3AcOH-H_2O]^+$. The ^1H and ^{13}C NMR spectra of pyripyropene A (Figs. 2 and 3) showed 37 protons and 31 carbons, supporting the molecular formula. They were classified as six methyls, three methylenes, one oxy methylene, two methines, three oxy methines, three quaternary carbons, five sp^2 methines, four sp^2 quaternary carbons and four carbonyl carbons in the DEPT spectrum. The connectivity of proton and carbon atoms was assigned by ^1H-^{13}C COSY spectrum as shown in Table 2. The chemical shift values of four olefinic protons at δ 7.40 (dd, J=8.0 and 5.0 Hz), 8.09 (ddd, J=8.0, 2.0 and 1.5 Hz), 8.68 (dd, J=5.0 and 1.5 Hz) and 9.00 (d, J=2.0 Hz) exhibited a good agreement with those of 3-substituted pyridine[3] (Fig. 4C and Table 2). There was a partial overlap of signals in the high field region (δ 1.63

† Present address: Pfizer Central Research, Nagoya, Pfizer Pharmaceuticals Inc., 5-2 Taketoyo, Aichi 470-23, Japan.

Table 1. Physico-chemical properties of pyripyropenes A, B, C and D.

	Pyripyropene A	Pyripyropene B	Pyripyropene C	Pyripyropene D
Appearance	White powder	White powder	White powder	White powder
$[\alpha]_D^{18}$ (c 1.0, $CHCl_3$)	+65.8°	+62.0°	+9.4°	+64.5°
HREI-MS (m/z)				
Found:	583.2437	597.2573	597.2573	597.2573
Calcd:	583.2415 for $C_{31}H_{37}NO_{10}$	597.2576 for $C_{32}H_{39}NO_{10}$	597.2576 for $C_{32}H_{39}NO_{10}$	597.2576 for $C_{32}H_{39}NO_{10}$
EI-MS (m/z)	583 $(M)^+$, 565 $(M-H_2O)^+$, 523 $(M-AcOH)^+$, 505 $(M-AcOH-H_2O)^+$, 463 $(M-2AcOH)^+$, 445 $(M-2AcOH-H_2O)^+$, 403 $(M-3AcOH)^+$, 385 $(M-3AcOH-H_2O)^+$	597 $(M)^+$, 579 $(M-H_2O)^+$, 537 $(M-AcOH)^+$, 519 $(M-AcOH-H_2O)^+$, 477 $(M-2AcOH)^+$, 459 $(M-2AcOH-H_2O)^+$, 403 $(M-2AcOH-PrOH)^+$*, 385 $(M-2AcOH-PrOH-H_2O)^+$	597 $(M)^+$, 579 $(M-H_2O)^+$, 523 $(M-PrOH)^+$, 505 $(M-PrOH-H_2O)^+$, 463 $(M-AcOH-PrOH)^+$, 445 $(M-AcOH-PrOH-H_2O)^+$, 403 $(M-2AcOH-PrOH)^+$, 385 $(M-2AcOH-PrOH-H_2O)^+$	597 $(M)^+$, 579 $(M-H_2O)^+$, 537 $(M-AcOH)^+$, 519 $(M-AcOH-H_2O)^+$, 463 $(M-PrOH-AcOH)^+$, 445 $(M-PrOH-AcOH-H_2O)^+$, 403 $(M-2AcOH-PrOH)^+$, 385 $(M-2AcOH-PrOH-H_2O)^+$
FAB-MS (m/z)	584 $(M+H)^+$, 606 $(M+Na)^+$	598 $(M+H)^+$, 620 $(M+Na)^+$	598 $(M+H)^+$, 620 $(M+Na)^+$	598 $(M+H)^+$, 620 $(M+Na)^+$
IR $\nu_{max}^{CCl_4}$ (cm^{-1})	3550 (OH), 1740 (CO–O), 1702 (CO–O)	3550 (OH), 1740 (CO–O), 1702 (CO–O)	3550 (OH), 1740 (CO–O), 1702 (CO–O)	3550 (OH), 1740 (CO–O), 1702 (CO–O)
UV λ_{max}^{MeOH} (nm)	231, 320	231, 320	231, 320	231, 320
Solubility				
Soluble	MeOH, EtOAc, $CHCl_3$	MeOH, EtOAc, $CHCl_3$	MeOH, EtOAc, $CHCl_3$	MeOH, EtOAc, $CHCl_3$
Insoluble	H_2O, n-hexane	H_2O, n-hexane	H_2O, n-hexane	H_2O, n-hexane
Color reaction				
Positive	50% aq H_2SO_4	50% aq H_2SO_4	50% aq H_2SO_4	50% aq H_2SO_4
Negative	Ninhydrine	Ninhydrine	Ninhydrine	Ninhydrine

* PrOH: Propionic acid.

Fig. 1. EI-MS of pyripyropene A.

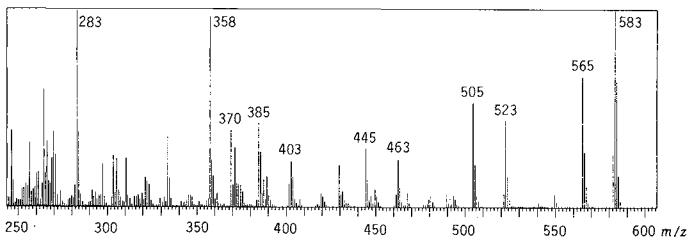


Table 2. ^{1}H and ^{13}C chemical shifts

No.	Pyripyropene A		Pyripyropene B	
	^{13}C (ppm)	^{1}H (ppm)	^{13}C (ppm)	^{1}H (ppm)
C-1	73.50	4.79 (1H, dd, 11.5, 4.8)	73.57	4.77 (1H, dd, 12.0, 5.0)
C-2	22.63	1.82, 1.90 (2H, m)	22.68	1.80, 1.88 (2H, m)
C-3	36.10	1.38, 2.16 (2H, m)	36.20	1.35, 2.14 (2H, m)
C-4	37.78		37.83	
C-5	54.60	1.54 (1H, m)	54.75	1.52 (1H, m)
C-6	83.14		83.19	
C-7	77.66	5.02 (1H, m)	77.70	4.98 (1H, m)
C-8	25.11	1.63, 1.78 (2H, m)	25.18	1.61, 1.76 (2H, m)
C-9	45.28	1.63 (1H, m)	45.42	1.61 (1H, m)
C-10	40.22		40.35	
C-11	64.76	3.71, 3.79 (2H, d, 12.0)	64.63	3.68, 3.77 (2H, d, 12.0)
C-12	17.37	1.44 (3H, s)	17.43	1.43 (3H, s)
C-13	59.97	4.99 (1H, m)	60.13	4.96 (1H, m)
13-OH		2.91 (1H, brs)		3.04 (1H, brs)
C-14	16.21	1.69 (3H, s)	16.25	1.69 (3H, s)
C-15	13.15	0.89 (3H, s)	13.23	0.88 (3H, s)
1-O-CO-*CH_3*	21.05	2.04 (3H, s)	21.12	2.02 (3H, s)
1-O-*CO*-CH_3	170.43		170.45	
1-O-CO-CH_2-*CH_3*				
1-O-CO-*CH_2*-CH_3				
1-O-*CO*-CH_2-CH_3				
7-O-CO-*CH_3*	21.15	2.15 (3H, s)	21.20	2.13 (3H, s)
7-O-*CO*-CH_3	169.98		169.96	
7-O-CO-CH_2-*CH_3*				
7-O-CO-*CH_2*-CH_3				
7-O-*CO*-CH_2-CH_3				
11-O-CO-*CH_3*	20.70	2.09 (3H, s)		
11-O-*CO*-CH_3	170.83			
11-O-CO-CH_2-*CH_3*			9.12	1.14 (3H, t, 7.5)
11-O-CO-*CH_2*-CH_3			27.52	2.35 (2H, q, 7.5)
11-O-*CO*-CH_2-CH_3			174.19	
C-2′	163.83		163.93	
C-3′	102.91		102.93	
C-4′	162.11		162.14	
C-5′	99.31	6.45 (1H, s)	99.24	6.43 (1H, s)
C-6′	157.19		157.30	
C-2″	146.67	9.00 (1H, d, 2.0)	146.78	8.99 (1H, d, 2.0)
C-3″	127.07		127.12	
C-4″	132.89	8.09 (1H, ddd, 8.0, 2.0, 1.5)	132.93	8.08 (1H, ddd, 8.0, 2.0, 2.0)
C-5″	123.56	7.40 (1H, dd, 8.0, 5.0)	123.61	7.39 (1H, dd, 8.5, 4.5)
C-6″	151.41	8.68 (1H, dd, 5.0, 1.5)	151.53	8.67 (1H, dd, 5.0, 1.5)

In $DCDl_3$.

to 1.90). Therefore, the proton sequences were determined by differential selective proton decoupling spectra as shown in Fig. 5. The irradiation at δ 2.16 (3-Hb) and 4.79 (1-H) simplified the three signals of δ 1.38 (3-Ha), 1.82 (2-Ha) and 1.90 (2-Hb) and the two signals of 1.82 (2-Ha) and 1.90 (2-Hb), respectively. These results indicated the sequence of –O–CH–CH_2–CH_2– as shown in Fig. 4G. The irradiation at δ 1.54 (5-H) and 2.91 (13-OH) gave the positive signal at δ 4.99 (13-H), showing the presence of –CH–CH–OH sequence (Fig. 4D). Furthermore, the irradiation at δ 1.63 (8-Ha) and 1.78 (8-Hb) showed the positive signals at δ 5.02 (7-H) and 1.63 (9-H), indicating the presence of –O–CH–CH_2–CH– sequence (Fig. 4H). From the results of NMR and MS measurements described above, a total of eight partial

of pyripyropenes A, B, C and D.

No.	Pyripyropene C		Pyripyropene D	
	^{13}C (ppm)	^{1}H (ppm)	^{13}C (ppm)	^{1}H (ppm)
C-1	73.56	4.78 (1H, dd, 12.0, 5.0)	73.31	4.78 (1H, dd, 12.0, 4.8)
C-2	22.71	1.80, 1.88 (2H, m)	22.74	1.80, 1.88 (2H, m)
C-3	36.17	1.35, 2.14 (2H, m)	36.17	1.35, 2.14 (2H, m)
C-4	37.87		37.88	
C-5	54.70	1.52 (1H, m)	54.71	1.52 (1H, m)
C-6	83.39		83.28	
C-7	77.47	5.02 (1H, m)	77.74	5.02 (1H, m)
C-8	25.25	1.61, 1.76 (2H, m)	25.20	1.61, 1.76 (2H, m)
C-9	45.37	1.69 (1H, m)	45.37	1.69 (1H, m)
C-10	40.33		40.39	
C-11	64.87	3.67, 3.81 (2H, d, 12.0)	64.85	3.67, 3.81 (2H, d, 12.0)
C-12	17.48	1.43 (3H, s)	17.45	1.43 (3H, s)
C-13	60.18	4.99 (1H, m)	60.14	4.99 (1H, m)
13-OH		2.91 (1H, br s)		2.92 (1H, br s)
C-14	16.31	1.68 (3H, s)	16.27	1.68 (3H, s)
C-15	13.22	0.88 (3H, s)	13.28	0.88 (3H, s)
1-O-CO-*CH_3*	21.14	2.02 (3H, s)		
1-O-*CO*-CH_3	170.54			
1-O-CO-CH_2-*CH_3*			9.14	1.12 (3H, t, 7.5)
1-O-CO-*CH_2*-CH_3			27.84	2.31 (2H, q, 7.5)
1-O-*CO*-CH_2-CH_3			173.84	
7-O-CO-*CH_3*			21.24	2.13 (3H, s)
7-O-*CO*-CH_3			170.10	
7-O-CO-CH_2-*CH_3*	9.17	1.21 (3H, t, 7.5)		
7-O-CO-*CH_2*-CH_3	27.86	2.43 (2H, q, 7.5)		
7-O-*CO*-CH_2-CH_3	173.43			
11-O-CO-*CH_3*	20.82	2.07 (3H, s)	20.80	2.08 (3H, s)
11-O-*CO*-CH_3	170.98		170.93	
11-O-CO-CH_2-*CH_3*				
11-O-CO-*CH_2*-CH_3				
11-O-*CO*-CH_2-CH_3				
C-2′	163.98		163.98	
C-3′	102.98		103.02	
C-4′	162.21		162.22	
C-5′	99.48	6.43 (1H, s)	99.50	6.43 (1H, s)
C-6′	157.24		157.19	
C-2″	146.64	8.99 (1H, br s)	146.55	8.99 (1H, d, 1.8)
C-3″	127.25		127.28	
C-4″	133.15	8.08 (1H, ddd, 8.2, 2.0, 2.0)	133.21	8.10 (1H, ddd, 8.2, 2.0, 2.0)
C-5″	123.73	7.39 (1H, dd, 8.5, 4.7)	123.76	7.40 (1H, dd, 8.2, 4.8)
C-6″	151.34	8.68 (1H, br d, 4.0)	151.24	8.66 (1H, dd, 4.5, 1.0)

structures are proposed as shown in Fig. 4. The connection of these partial structures was determined by heteronuclear multiple-bond correlation spectroscopy (HMBC) experiments (Fig. 6). First, the presence of 3,4-disubstituted 6-(3-pyridyl)-α-pyrone was shown because the methine proton of δ 6.45 (5′-H) was coupled to the four carbons of δ 102.91 (C-3′), 127.07 (C-3″), 157.19 (C-6′) and 162.11 (C-4′). The partial structure was supported by a good agreement of the ^{1}H and ^{13}C chemical shifts with those of unsaturated heterocyclic rings and oxalicine A reported previously[3]. Second, the structure of the sesquiterpene moiety was suggested by the following evidences; the respective three methyl protons of δ 0.89 (15-H_3), 1.44 (12-H_3) and 1.69 (14-H_3) had four coupling carbons of δ 40.22 (C-10), 45.28 (C-9), 64.76 (C-11) and 73.50

Fig. 2. ^{1}H NMR spectra of pyripyropenes A, B, C and D.

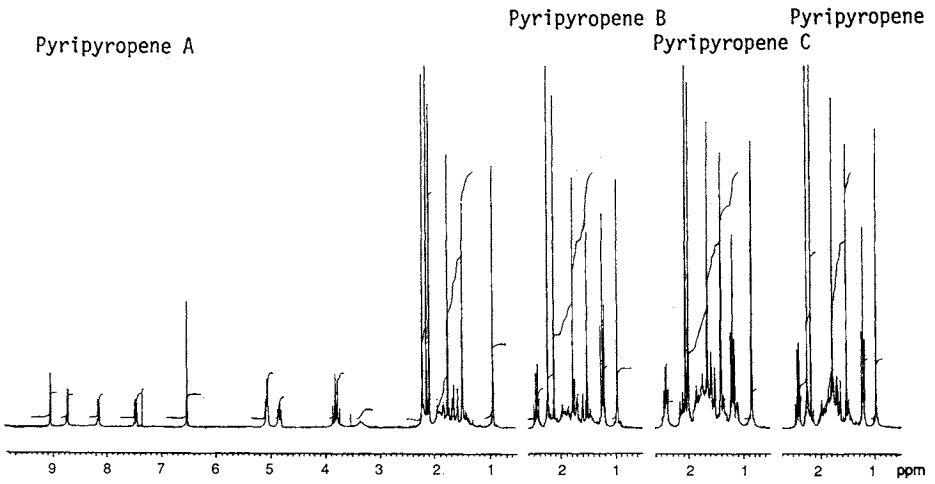
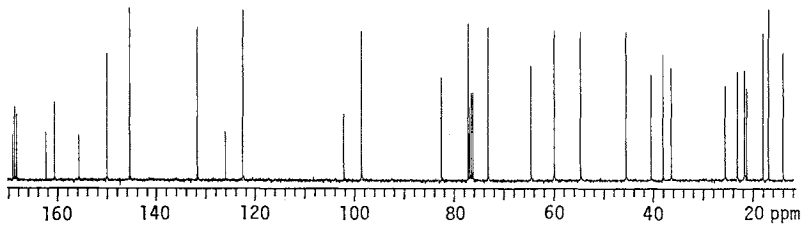


Fig. 3. ^{13}C NMR spectra of pyripyropene A.



(C-1), four ones of δ 36.10 (C-3), 37.78 (C-4), 45.28 (C-9) and 54.60 (C-5) and three ones of δ 54.60 (C-5), 77.66 (C-7) and 83.14 (C-6). Furthermore, the oxymethine proton observed at δ 4.99 (13-H) was coupled to the three carbons of C-2′, C-3′ and C-4′, suggesting the connection of α-pyrone and sesquiterpene moieties as shown in Fig. 6. The three acetoxy positions were determined by long range selective proton decoupling (LSPD) experiments. The individual irradiation of the two oxymethine protons at δ 4.79 (1-H) and 5.02 (7-H) and the oxymethylene protons at δ 3.71~3.79 (11-H_2) simplified the carbonyl carbons of δ 170.43, 169.98, 170.83, respectively, showing the acetoxy positions at C-1, C-7 and C-11. To confirm the acetoxy positions the ^{1}H NMR spectrum of the trideacetyl derivative of pyripyropene A prepared by the treatment with MeONa - MeOH was also analyzed. Although the chemical shift of 13-H moved slightly (from δ 4.99 to 4.94), the chemical shifts of two oxymethine (1-H and 7-H) and one oxymethylene (11-H_2) protons of trideacetylpyripyropene A exhibited high field shifts from δ 4.79 to 3.65, from δ 5.02 to 3.77, and from δ 3.80~3.74 to 3.53~3.32, respectively, supporting that the deacetylation occured at these positions. On the basis of the results described above, the plane structure of pyripyropene A was deduced to be a pentacyclic alkaloidal sesquiterpene as shown in Fig. 7.

Structures of Pyripyropenes B, C and D

The molecular formulas of pyripyropenes B, C and D were determined to be all $C_{32}H_{39}NO_{10}$ by HREI-MS. They all had the same fragment ion peaks at m/z 385 and 403 in EI-MS, suggesting that they

Fig. 4. Partial structures for pyripyropene A.

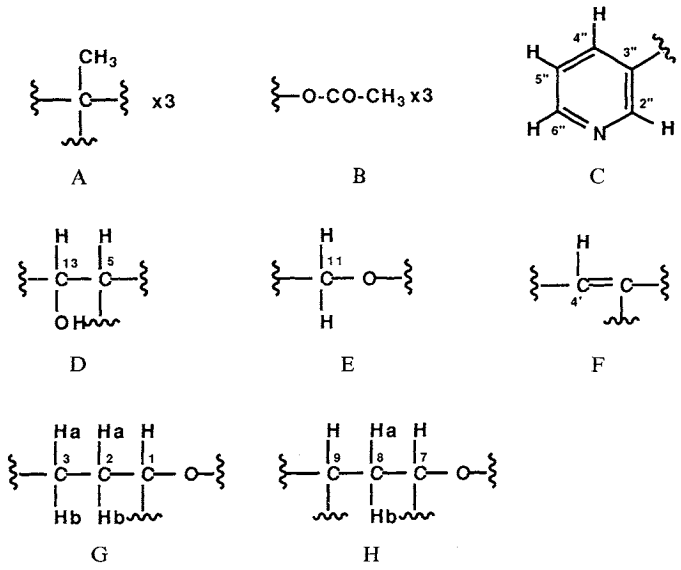


Fig. 5. Differential selective proton decoupling spectra of pyripyropene A.

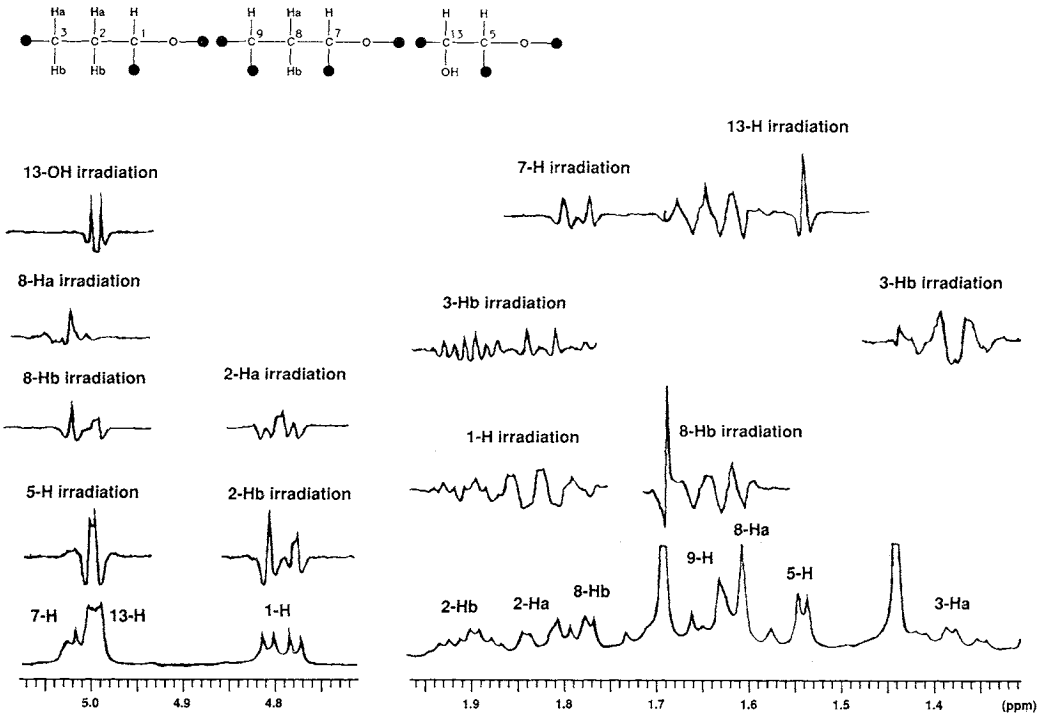


Fig. 6. ^{1}H-^{1}H coupling, LSPD and HMBC experiments of pyripyropene A.

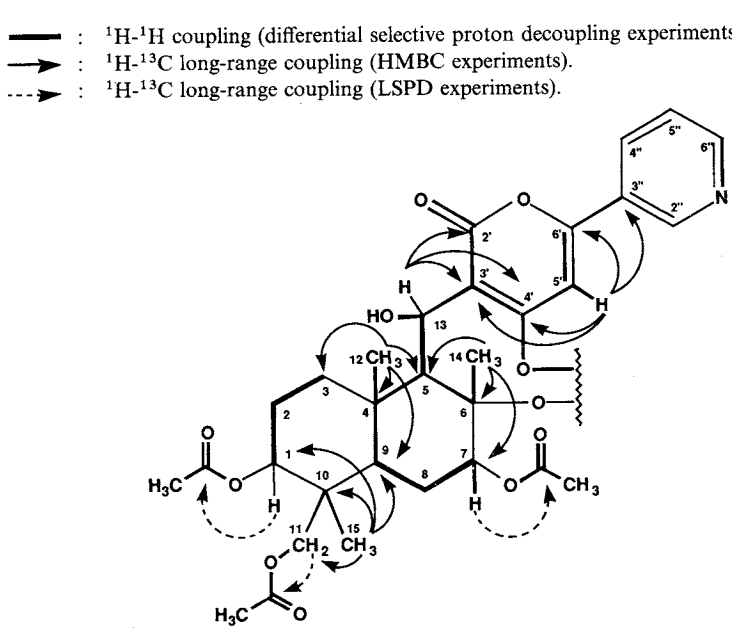
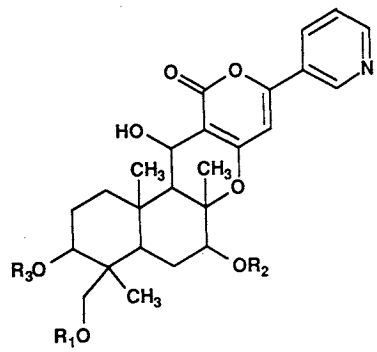


Fig. 7. Structures of pyripyropenes A, B, C and D.



	R_1	R_2	R_3
Pyripyropene A	$-COCH_3$	$-COCH_3$	$-COCH_3$
B	$-COCH_2CH_3$	$-COCH_3$	$-COCH_3$
C	$-COCH_3$	$-COCH_2CH_3$	$-COCH_3$
D	$-COCH_3$	$-COCH_3$	$-COCH_2CH_3$

have a common skeleton of trideacetylpyripyropene A. The ^{1}H and ^{13}C NMR spectra of pyripyropenes B, C and D (Fig. 2 and Table 2) are very similar to those of pyripyropene A except for the presence of one propionyl signal instead of one of the three acetyl signals for pyripyropene A. These results indicate that one of the three acetyl residues in pyripyropene A is replaced with a propionyl residue in pyripyropenes B, C and D. The positions of the propionyl residues were determined by comparison with the ^{1}H and ^{13}C chemical shifts of pyripyropene A. As summarized in Table 2, one of the three acetyl signals (δ 2.04

(1-*O*-Ac), 2.09 (11-*O*-Ac) and 2.15 (7-*O*-Ac)) observed in pyripyropene A disappeared in pyripyropenes B (δ 2.02 (1-*O*-Ac) and 2.13 (7-*O*-Ac)), C (δ 2.02 (1-*O*-Ac) and 2.07 (11-*O*-Ac)) and D (δ 2.08 (11-*O*-Ac) and 2.13 (7-*O*-Ac)). In turn, one of the three carbonyl carbon signals (δ 169.98 (7-*O*-Ac), 170.43 (1-*O*-Ac) and 170.83 (11-*O*-Ac)) observed in pyripyropene A was shifted to lower field in pyripyropenes B (δ 169.96 (7-*O*-Ac), 170.45 (1-*O*-Ac) and 174.19 (11-*O*-Pr)), C (δ 174.43 (7-*O*-Pr), 170.54 (1-*O*-Ac) and 170.98 (11-*O*-Ac)) and D (δ 170.10 (7-*O*-Ac), 173.84 (1-*O*-Pr) and 170.93 (11-*O*-Ac)). From the results described above, their structures were elucidated as shown in Fig. 7. The respective acetyl residue at 11-, 7- and 1-*O*-positions in pyripyropene A is replaced with a propionyl residue in pyripyropenes B, C and D.

Discussion

The structure elucidation described in this paper revealed that all pyripyropenes consist of common three parts, pyridine, α-pyrone and sesquiterpene moieties, to form a steroid-like skeleton. The three acetoxy positions were determined by LSPD experiments (Fig. 6) and comparison of ^{1}H and ^{13}C chemical shifts between pyripyropene A and its trideacetyl derivative. A similar observation was reported for structure determination of aphidicolin[4]. Furthermore, from comparison of the chemical shifts, it was concluded that one of the three acetyl residues at 11-, 7- and 1-*O*-positions in pyripyropene A is substituted by a propionyl residue in pyripyropenes B, C and D, respectively (Fig. 7). To confirm the pyrone structure of pyripyropene A, the $^1J_{C,H}$ coupling constant at C-5′ position (172 Hz) was compared with those of α- and γ-pyrones[5], also supporting the α-pyrone structure. Thus, pyripyropenes with a unique pentacyclic alkaloidal skeleton comprising pyridine, α-pyrone and sesquiterpene moieties are expected to be a new type of lead compounds for potent ACAT inhibitors. The sesquiterpene moiety appears to be synthesized from drimane-related compounds such as macrophorins[6] and sesquiterpene alcohol[7]. The biosynthesis and determination of the absolute configurations of pyripyropenes are now in progress.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-400 spectrometer, and HMBC was recorded on a JEOL JNM-GX-500 spectrometer. MS spectra were measured on a JEOL model DX-300 spectrometer. UV and IR spectra were recorded on a Shimadzu model UV-240 spectrophotometer and a Jasco model A-102 infrared spectrophotometer, respectively.

Preparation of Trideacetyl Derivative of Pyripyropene A

Pyripyropene A (20 mg) was dissolved in MeONa - MeOH and stirred for 1 hour at room temperature to obtain trideacetylpyripyropene A (16 mg): UV_{max} 320 nm; EI-MS *m/z* (M+) 457; ^{1}H NMR (CD_3OD) δ 0.72 (3H, s), 1.39 (3H, s), 1.63 (3H, s), 3.32 (1H, d, J=11.5 Hz), 3.53 (1H, d, J=11.5 Hz), 3.65 (1H, dd, J=5.3 and 11.2 Hz), 3.77 (1H, dd, J=5.0 and 11.2 Hz), 4.94 (1H, d, J=3.6 Hz), 6.81 (1H, s), 7.59 (1H, ddd, J=0.8, 5.0 and 8.1 Hz), 8.26 (1H, ddd, J=1.7, 2.3 and 8.0 Hz), 8.63 (1H, dd, J=1.7 and 5.0 Hz), 9.02 (1H, d, J=2.3 Hz); ^{13}C NMR (CD_3OD) δ 12.74, 15.97, 17.99, 27.31, 28.87, 37.68, 39.15, 43.32, 46.29, 55.67, 60.41, 66.32, 72.74, 78.36, 86.97, 101.18, 104.36, 125.50, 129.30, 134.88, 147.33, 151.91, 158.04, 164.69, 165.61.

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