Nortriterpenoids from Schisandra wilsoniana

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Three new highly oxygenated nortriterpenoids, wilsonianadilactones A–C (1–3), together with twelve known ones, *i.e.*, 4–15, were isolated from the leaves and stems of *Schisandra wilsoniana*. Their structures were established by means of extensive analysis of spectroscopic data, and compound 1 was further confirmed by X-ray crystallographic diffraction. Compounds 1–3 showed weak anti-HIV-1 activity with EC_{50} values of 23.5, 55.5, and 66.4 µg/ml, respectively.

Introduction. – Plants of the genus *Schisandra* were used widely as traditional Chinese medicine. They were rich sources of bioactive lignans, which possessed various beneficial pharmacological effects such as antihepatitis, antitumor, and anti-HIV-1 activity [1-6]. In the course of our search for bioactive compounds from this genus species, we discovered a series of highly oxygenated, fused heterocyclic triterpenoids endowed with different oxygenated skeletons, such as schiartane [7], 18-norschiartane [8][9], $18(13 \rightarrow 14)$ -abeo-schiartane [10], schisanartane [11], pre-schisanartane [12] and wuweiziartane [13], and some of them exhibited modest or strong anti-HIV activities [7][14][15].

Schisandra wilsoniana A. C. SMITH, a climbing plant, is mainly distributed in Heqing, Dali, and Yulong prefectures of Yunnan province. Up to now, there were no reports about the chemical constituents of this species. In continuation of our investigation on Schisandra-genus species, we examined the chemical constituents of Schisandra wilsoniana, collected from the Heqing prefecture, which led to the isolation of three new nortriterpenoids, wilsonianadilactones $A-C^1$ (1-3), together with twelve known ones, lancifodilactones B, C, and D (4-6) [16], micrandilactone A (7) [11], micrandilactones D-F (8-10) [17], lancifodilactones I, L, and N (11-13) [18], henridilactone A (14) [19], and lancifodilactone A (15) [8]. Their structures were determined by extensive NMR spectroscopic experiments, including ¹H,¹H-COSY, HSQC, HMBC, and NOESY techniques. The structure of 1 was further confirmed by

¹⁾ Arbitrary atom numbering; for systematic names, see Exper. Part.

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X-ray crystallographic diffraction. In addition, the new compounds were tested for their anti-HIV-1 activities. The present article reports the isolation, structural elucidation, and biological evaluation of the new compounds.

Results and Discussion. – Wilsonianadilactone A (1) was obtained as optically active colorless crystals. Its molecular formula, $C_{33}H_{42}O_{11}$, was established on the basis of HR-ESI-MS analysis ($[M + Na]^+$ at m/z 637.2628) and its ¹H- and ¹³C-NMR spectra (*Tables 1* and 2). The ¹H- and ¹³C-NMR, HMBC (*Fig. 1*), ¹H,¹H-COSY (*Fig. 1*), HSQC, and ROESY data established the structure of **1**. The relative configuration of **1** was determined by a ROESY experiment and comparison of 1D-NMR data with those

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	1	2	3	12		1	2	3	12
C(1)	83.0 (<i>d</i>)	80.3 (<i>d</i>)	80.3 (d)	81.5 (d)	C(18)	26.7 (q)	27.8(q)	26.8(q)	26.0(q)
C(2)	41.8 (t)	35.8 (t)	35.6 (t)	35.4 (t)	C(19)	34.2 (t)	44.5 (t)	44.8 (t)	42.6 (t)
C(3)	171.4 (s)	174.6 (s)	174.2 (s)	175.5 (s)	C(20)	44.9 (d)	40.0(d)	74.6 (s)	40.3(d)
C(4)	89.0 (s)	84.3 (s)	84.1 (s)	83.9 (s)	C(21)	14.4(q)	15.1(q)	25.8(q)	14.9(q)
C(5)	135.5 (s)	53.6 (d)	53.7 (d)	58.5(d)	C(22)	40.2(d)	44.0(d)	41.4(d)	44.6(d)
C(6)	30.5 (t)	31.5 (t)	31.4 (t)	36.4 (t)	C(23)	74.9(d)	74.7(d)	73.5(d)	73.2 (d)
C(7)	69.1 (d)	63.0(d)	63.1 (<i>d</i>)	67.9 (d)	C(24)	69.1(d)	73.2(d)	72.1(d)	75.1 (d)
C(8)	55.1 (d)	56.2 (d)	55.2 (d)	60.2(d)	C(25)	42.8(d)	76.6 (s)	41.8(d)	76.8 (s)
C(9)	85.2 (s)	80.6 (s)	81.2 (s)	81.4 (s)	C(26)	177.6 (s)	177.2 (s)	177.7 (s)	177.5 (s)
C(10)	128.7(s)	97.0 (s)	96.8 (s)	95.8 (s)	C(27)	8.3(q)	18.0(q)	8.2(q)	17.5(q)
C(11)	41.8 (t)	36.4 (t)	36.5 (t)	41.9 (t)	C(29)	26.3(q)	27.8(q)	27.7(q)	27.8(q)
C(12)	30.5 (t)	33.8 (t)	33.7 (t)	31.3 (t)	C(30)	28.5(q)	21.0(q)	21.0(q)	20.9(q)
C(13)	49.7 (s)	49.9 (s)	50.0 (s)	50.2 (s)	AcO	20.9(q)			
C(14)	45.1 (d)	44.5(d)	44.3 (d)	45.0(d)		169.7			
C(15)	99.7 (s)	99.1 (s)	98.5 (s)	99.1 (s)	EtO	14.6(q)			
C(16)	210.0(s)	208.6(s)	208.6(s)	209.5 (s)		60.6 (t)			
C(17)	220.0 (s)	220.0 (s)	220.1 (s)	220.4 (s)					

Table 1. ¹³C-NMR Data of Wilsonianadilactones A - C (1-3) and Lancifodilactone L (12)^a)¹)

^a) Data were recorded in C₅D₅N; chemical shifts δ in ppm.



Fig. 1. Selected 2D-NMR correlations of compounds 1 and 2. Bond in bold indicates ¹H,¹H-COSY, arrow indicates HMBC.

of lancifodilactone C (5) [16], and finally determined by an X-ray crystallographic analysis (*Fig. 2*).

The ¹H-NMR spectrum of **1** exhibited the presence of seven Me groups. Analysis of the ¹H- and ¹³C-NMR, HSQC, and HMBC data revealed the presence of one EtO group, one Ac group, and additional 29 C-atoms, including two ester groups, two CO groups, five Me, five CH₂, and nine CH groups (including four oxygenated ones), and six quaternary C-atoms (including two olefinic and three oxygenated C-atoms). Comparison of the ¹³C-NMR spectra of **1** with those of lancifodilactone C (**5**) [16] showed that the obvious differences were the appearance of a C=C bond, an EtO group, and an AcO group, and the lack of a CH group and an oxygenated quaternary C-atom in **1**. Combinative analysis of 1D- and 2D-NMR data revealed that **1** possessed the same rings D-H as **5**. In the HMBC spectrum

	Table 2. ¹ H-NMR Assign	uments of Wilsonianadilactones $A-C$	C(1-3) and Lancifodilactone L (12)) ^a) ¹)
	1	2	3	12
H-C(1)	$5.21 \ (dd, J = 3.4, 7.4)$	$4.29 \ (d, J = 4.3)$	$4.14 \ (d, J = 4.7)$	4.22 (d, J = 6.4)
$CH_2(2)$	2.55 (dd, J = 7.4, 13.2),	$2.82 (d, J = 14.3, H_a),$	2.81 $(d, J = 14.5, H_a)$,	$3.03 (dd, J = 6.0, 18.1, H_a),$
	$2.87 \ (dd, J = 3.4, 13.2)$	$3.21 \ (dd, J = 4.3, 14.3, H_{\beta})$	$3.18 \ (dd, J = 4.7, 14.5, H_{\beta})$	2.72 $(d, J = 18.1, H_{\beta})$
H-C(5)		2.95 (br. $d, J = 10.5$)	2.93 (br. $d, J = 10.3$)	$2.48 \ (dd, J = 3.9, 13.2)$
$CH_2(6)$	$2.53 \ (dd, J = 8.5, 12.0)$	$1.82 - 1.86 \ (m, H_a),$	$1.84 - 1.90 \ (m, H_a),$	$2.04 - 2.10 \ (m, H_a),$
		$1.54 - 1.60$ (m, H_{eta})	$1.56 - 1.62 \ (m, H_{eta})$	$2.20-2.26 \ (m, H_{\beta})$
H-C(7)	5.78 (dd, J = 8.5, 9.2)	4.49 - 4.55 (m)	4.50-1.56(m)	$4.56 \ (dd, J = 9.4, 9.7)$
H-C(8)	3.06 (d, J = 9.2)	4.12 $(d, J = 7.5)$	4.12 $(d, J = 7.4)$	$2.89 \ (d, J = 9.7)$
$CH_2(11)$	$1.92 - 1.96 (H_a)^b),$	$2.00-2.05 \ (m, H_a),$	$2.08 - 2.13 (m, H_a),$	$1.90 - 1.96 \ (m, H_a),$
	$1.70 - 1.75 \ (m, H_{eta})$	$1.69 - 1.74 \ (m, { m H}_eta)$	$1.65 - 1.71 \ (m, H_{\beta})$	$1.61 - 1.67 \ (m, { m H}_{eta})$
$CH_{2}(12)$	$1.90 - 1.96 (H_a)^b),$	1.82 - 1.87 (m, H _a),	$1.84 - 1.90 \ (m, H_a),$	$1.78 - 1.63$ (m, H_a) ,
	$1.48 - 1.53 \ (m, H_{eta})$	$1.55 - 1.60 \ (m, H_{eta})$	$1.72 - 1.77 \ (m, H_{B})$	$1.52 - 1.57 \ (m, { m H}_{eta})$
H-C(14)	$2.72 - 2.77^{b}$	$2.82 - 2.88^{b}$	2.92 $(d, J = 7.0)$	2.84 (d, J = 7.1)
Me(18)	0.92(s)	0.94~(s)	(s) 600	0.92(s)
$CH_{2}(19)$	$2.68 - 2.76^{b}$)	1.90 $(AB, J = 13.5, H_{\alpha})$,	1.91 $(AB, J = 13.3, H_a)$,	$2.40(AB, J = 15.4, H_a),$
		2.50 $(AB, J = 13.5, H_{\beta})$	2.45 $(AB, J = 13.3, H_{\beta})$	2.29 $(AB, J = 15.4, H_{\beta})$
H - C(20)	$2.77 - 2.83^{b}$)	2.88-2.94 (m)		2.85 - 2.90 (m)
Me(21)	$1.24 \ (d, J = 6.4)$	$1.24 \ (d, J = 7.0)$	1.56(s)	1.02 (d, J = 7.1)
H - C(22)	$2.78 - 2.82^{b}$)	$2.81 - 2.86^{b}$)	3.15 (br. d, J = 7.8)	2.63 - 2.68 (m)
H - C(23)	$4.66 (\mathrm{br.}s)$	$5.17 ({\rm br.}s)$	4.87 (br. s)	5.15 (br. s)
H - C(24)	4.73 (br. s)	4.73 (br. s)	4.83 (br. s)	5.17 (br. s)
H-C(25)	3.09 - 3.15 (m)		$3.05 - 3.10 \ (m)$	
Me(27)	$1.31 \ (d, J = 6.7)$	1.82(s)	$1.20 \ (d, J = 7.2)$	1.68(s)
Me(29)	1.28(s)	1.07(s)	1.09(s)	1.24(s)
Me(30)	1.36(s)	1.29(s)	1.23(s)	1.05(s)
AcO	3.03(s)			
EtO	1.13 $(t, J = 7.1)$,			
	$4.12 - 4.16 \ (m)$			
^a) Data were reco	rded in C_5D_5N ; chemical shifts δ	in ppm; J in Hz. ^b) Overlapped.		

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Fig. 2. ORTEP Drawing of 1

(*Fig. 1*), the geminal Me groups, Me(29) and Me(30), showed strong HMBC correlations to C(4) and an olefinic C-atom (δ (C) 135.5), and the signals of H–C(1) (δ (H) 5.21) and H–C(2) (δ (H) 2.55 and 2.87) exhibited strong correlations to another olefinic C-atom (δ (C) 128.7), which suggested a C=C bond between C(5) and C(10). The position of the EtO group at C(3) was established by a HMBC correlation from the H-atom signals of the oxygenated CH₂ (δ (C) 60.6) to C(3). Moreover, an CH–O signal at δ (H) 5.78 was assigned to H–C(7) based on a ¹H,¹H-COSY correlation with H–C(8) and the HMBC correlations with C(5), C(6), C(9), and C(16) (*Fig. 1*). In addition, HMBC correlation of H–C(7) with the CO C-atom of the AcO group indicated that the AcO group was located at C(7). Thus, the constitutional formula of **1** was established as shown. The strong ROESY correlation CH₂(2)/Me(29) determined that the CH₂(2) group is α -oriented. Accordingly, H–C(1) is β -oriented. H–C(7) was deduced to be α -oriented by the large coupling constant with H–C(8) (J=9.2 Hz), which was similar to that of **5** (J=9.6 Hz). The Me(21) group was deduced to be in β -orientation by the ROESY correlation Me(21)/H–C(14). All of the other chiral centers of **1**, which were identical with those of **5**, were established by pivotal ROESY correlations and X-ray crystallographic analysis.

The molecular formula of **2** was deduced as $C_{29}H_{36}O_{10}$ from its HR-ESI-MS ([M + Na]⁺ at m/z 583.2304) and ¹³C-NMR spectrum, which is the same as that of lancifodilactone L (**12**) [18]. The ¹H- and ¹³C-NMR data were analogous to those of **12** (*Tables 1* and 2). Analysis of the ¹H, ¹H-COSY and HMBC data (*Fig. 1*) showed that **2** possessed the same constitution as **12**. The coupling constant J(7,8) and the ROESY correlations (*Fig. 3*) established the α -position of OH–C(7) in **2**, instead of its β -position in **12**.

The significant chemical-shift differences observed in the NMR spectra of **2** and **12** were associated with the signals of the moieties C(5) to C(8) and C(11) (*Tables 1* and 2). HMBC Cross-peaks H-C(5)/C(7), H-C(6)/C(7) and C(8), and H-C(8)/C(7), C(11), C(16), and C(19), and the ¹H,¹H-COSY cross-peaks of H-C(5), H-C(6), H-C(7), and H-C(8) fully corroborated that the OH group is located at C(7) in **2**. This suggested that the differences between **2** and **12** were the relative configurations in the C(5) to C(8) moiety. A ROESY correlation (*Fig. 3*) between Me(29) and H-C(5) established that the configuration at C(5) is the same in both compounds. The ROESY correlation between $H_{\beta}-C(19)$ and H-C(8) suggested that H-C(8) is β -oriented. The coupling constant between H-C(7) and H-C(8) in **2** (J=7.5 Hz) is much smaller than that in **12** (J=9.7 Hz; *Table 2*), suggesting that OH-C(7) may be α -



Fig. 3. Computer-generated molecular model showing key ROESY correlations of compound 2

oriented in 2, instead of β -oriented as in 12. This deduction was further supported by the downfield chemical shift of H-C(5) from δ (H) 2.48 in 12 to δ (H) 2.95 in 2 due to the deshielding effect of the β -positioned OH-C(7) in 2. In addition, the absence of a ROESY correlation between H-C(5) and H-C(7) also supported the above deduction. The remaining chiral centers of 2 were established to have the same relative configuration as those of 12 by the observed ROESY correlations and comparison of 1D-NMR data of 2 and 12.

HR-ESI-MS Analysis of compound **3** demonstrated that it had the same molecular formula $C_{29}H_{36}O_{11}$ as **2**. The ¹H- and ¹³C-NMR spectra were very similar to that of **1**. Analysis of the HSQC, ¹H,¹H-COSY, and HMBC data of **3** showed that obvious chemical-shift differences resulted from the C(20) being oxygenated in **3**, instead of C(25) in **2**. The structure of **3** was confirmed by the HMBC and ROESY data.

The oxygenation of C(20) of **3** was supported by the HMBC cross-peaks Me(21) (δ (H) 1.56)/C(17) (δ (C) 220.1), C(20) (δ (C) 74.6), and C(22) (δ (C) 41.4), and Me(27) (δ (H) 1.20)/C(24) (δ (C) 72.1), C(25) (δ (C) 41.8), and C(26) (δ (C) 177.7). The β -orientation of Me(27) was deduced by the ROESY correlation Me(27)/H–C(22).

Since some of the nortriterpenoids from the *Schisandra* genus species exhibited modest to strong anti-HIV activities [7][14][15], the three new compounds 1-3 were tested for their potencies in preventing the cytopathic effects of HIV-1 in C8166 cells and for cytotoxicity measured in parallel with the determination of antiviral activity, by using AZT (3'-azido-3'-deoxythymidine) as a positive control ($EC_{50} = 0.0045 \ \mu g/ml$ and $CC_{50} > 200 \ \mu g/ml$). Compounds 1-3 showed weak anti-HIV-1 activities with EC_{50} values of 23.5, 55.5, and 66.4 $\mu g/ml$, respectively, and all exerted minimal cytotoxicity

against C8166 cells ($CC_{50} > 200 \ \mu g \ /ml$). The therapeutic-index (TI) values (CC_{50} / EC_{50}) of **1**-**3** were more than 8.51, 3.60, and 3.01, respectively.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO₂; 200–300 mesh, Qingdao Marine Chemical, Inc., Qingdao, China). Prep. HPLC: Agilent-1100 liquid chromatograph; Zorbax-SB-C₁₈ column (9.4 mm × 25 cm); TLC monitoring with visualization by heating SiO₂ plates sprayed with 10% H₂SO₄ in EtOH. M.p.: XRC-1 micro-melting-point apparatus; uncorrected. Optical rotations: Horiba-SEPA-300 polarimeter. UV Spectra: Shimadzu-UV-2401A spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: Tenor-27 spectrophotometer; KBr pellets; in cm⁻¹. 1D- and 2D-NMR Spectra: Bruker AM-400 and DRX-500 spectrometers; unless otherwise specified, chemical shifts δ in ppm with reference to the solvent signals, J in Hz. MS: VG-Autospec-3000 spectrometer; at 70 eV; in m/z.

Plant Material. The leaves and stems of *S. wilsoniana* were collected in Heqing Prefecture of Yunnan Province, China, in August 2006. The specimen was identified by Prof. *Xi-Wen Li*, and a voucher specimen (No. KIB 2008-08-12) is deposited with the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The dried leaves and stems of *S. wilsoniana* (5.5 kg) were powdered and extracted with 70% aq. Me₂CO (4×81) for 24 h at r.t. and filtrated. The filtrate was concentrated and partitioned with AcOEt. The AcOEt part (79.0 g) was subjected to CC (SiO₂, CHCl₃/MeOH 1:0, 9:1, 8:2, 2:1, 1:1, and 0:1): *Fractions I–VI. Fr. II* (14.4 g) was repeatedly subjected to CC (SiO₂ (200–300 mesh) and *Sephadex LH-20*), then purified by prep. HPLC (MeOH/H₂O 43:57 and 40:60, and MeOH/MeCN/H₂O 10:40:50 and 15:35:50): **1** (7 mg), **3** (5 mg), **4** (10 mg), **7** (9 mg), **8** (15 mg), **9** (16 mg), **11** (11 mg), and **14** (8 mg). *Fr. III* (14.5 g) was further subjected to CC (SiO₂, CHCl₃/Me₂CO 10:1, 5:1, 2:1, and 1:1): *Fr. IIIA – IIID. Subfr. Fr. IIIA* (4.8 g) was purified by repeated CC (SiO₂, *RP-18*, and *Sephadex LH-20* (MeOH)), followed by prep. HPLC (MeOH/H₂O 40:60 and MeOH/MeCN/H₂O 20:25:55): **2** (6 mg), **5** (4 mg), **6** (12 mg), and **12** (4 mg). Similarly, *Fr. IIIB* (2.5 g) was purified with all kinds of chromatography methods mentioned above, to yield **10** (10 mg), **13** (7 mg), and **15** (8 mg).

Wilsonianadilactone A (=(1\$,3aR,3b\$,4\$,5a\$,7a\$,9R,13\$,13aR,14a\$,14b\$,15aR)-13-(Acetyloxy)-1,3a,3b,4,5,5a,6,7,9,11,12,13,13a,14,14b,15a-hexadecahydro-1,4,5a,11,11-pentamethyl-2,5,14-trioxo-2H,8H-7a,14a-epoxy-3,10,15-trioxaazuleno[6',5':5,6]cyclooct[1,2,3-cd]-as-indacene-9-acetic Acid Ethyl Ester; **1**): White crystals. M.p. 177–178°. $[a]_{25}^{25} = +85.9$ (c = 0.41, MeOH). UV (MeOH): 204 (3.68). IR (KBr): 3035, 2948, 2921, 2880, 1771, 1726, 1622, 1460, 1382, 1167, 1078, 1021, 879. ¹H- and ¹³C-NMR: *Tables 1* and 2. ESI-MS (pos.): 637 ($[M + Na]^+$). HR-ESI-MS: 637.2628 ($[M + Na]^+$, $C_{33}H_{42}NaO_{11}^+$; calc. 637.2625).

 $\label{eq:wisonianadilactone B (= (1R, 3aR, 3bS, 4S, 5aS, 7aS, 8aR, 11aR, 13aS, 15R, 15aR, 16aS, 16bS, 17aS) - Tetradecahydro-1, 15-dihydroxy-1, 4, 5a, 13, 13-pentamethyl-2H, 8H-7a, 16a-epoxy-10H-3, 9, 12, 17-tetraoxacyclopent[3', 3'a]azuleno[6', 5': 5, 6]cyclooct[1, 2, 3-cd]-as-indacene-2, 5, 10, 16(1H, 13H)-tetrone; 2): White powder. [a]_{D}^{25} = + 61.1 (c = 0.13, MeOH). UV (MeOH): 205 (3.30). IR (KBr): 3437, 2925, 1789, 1741, 1632, 1373, 1234, 1120, 1019, 588. ¹H- and ¹³C-NMR: Tables 1 and 2. ESI-MS (pos.): 583 ([M+Na]^+). HR-ESI-MS: 583.2302 ([M+Na]^+, C_{29}H_{36}NaO_{11}^+; calc. 583.2307).$

Wilsonianadilactone C (=(1\$,3aR,3b\$,4R,5a\$,7a\$,8aR,11aR,13a\$,15R,15aR,16a\$,16b\$,17aR)-Tetradecahydro-4,15-dihydroxy-1,4,5a,13,13-pentamethyl-2H,8H-7a,16a-epoxy-10H-3,9,12,17-tetraoxacyclopent[3',3'a]azuleno[6',5':5,6]cyclooct[1,2,3-cd]-as-indacene-2,5,10,16(1H,13H)-tetrone; **3**. White powder. $[a]_{D}^{26} = +64.3 (c = 0.20, MeOH). UV (MeOH): 205 (3.34). IR (KBr): 3440, 2950, 2931, 1786, 1735, 1630, 1380, 1117, 1035, 1015, 590. ¹H- and ¹³C-NMR: Tables 1 and 2. ESI-MS (pos.): 583 ([M + Na]⁺). HR-ESI-$ MS: 583.2304 ([M + Na]⁺, C₂₉H₃₆NaO⁺₁₁; calc. 583.2307). *Crystallographic data of* **1**. $C_{33}H_{42}O_{11}$, M_r 614.69, orthorhombic, space group $P2_12_12_1$; a = 12.221(1) Å, b = 16.033(1) Å, c = 17.673(1) Å, V = 3462.8 (4) Å³, Z = 4, d = 1.214 g/cm³, crystal dimensions $0.50 \times 0.60 \times 0.80$ mm; measured on a *MAC-DIP-2030K* diffractometer with a graphite monochromator (ω scans, $2\theta_{max} = 50.0^\circ$), MoK_a radiation. The total number of independent reflections measured was 3554, of which 3113 were observed ($|F|^2 \ge 2\sigma |F|^2$). Final indices: $R_1 = 0.0612$, $wR_2 = 0.1713$, S = 1.039. The crystal structure was solved by direct methods with SHELX-97 [20a] and expanded with difference *Fourier* techniques, refined by the program and method *NOMCSDP* [20b] and full-matrix least-squares calculations. CCDC-683430 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif from the *Cambridge Crystallographic Data Centre*.

Anti-HIV-1 Assay. The cytotoxicity assay against C8166 cells (CC_{50}) was assessed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) method, and the anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50}) [21].

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