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Immunosuppressive Decalin Derivatives from Red Yeast Rice

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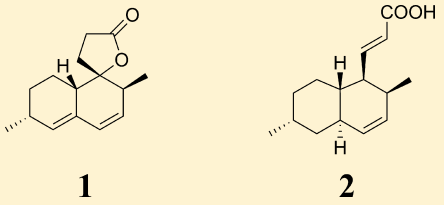
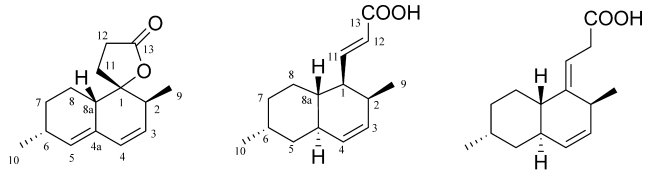
Supporting Information

ABSTRACT: Five new decalin derivatives (**1**–**5**), together with two known compounds (**6** and **7**), were isolated from the ethyl acetate extract of red yeast rice. Their structures were elucidated by means of NMR and mass spectroscopic analyses. Monascusic lactone A (**1**) is the first reported naturally occurring decalin derivative possessing a spiro lactone at the C-1 position. The immunosuppressive effects of all these isolates (**1**–**7**) on human T cell proliferation were investigated, and all, especially monascusic acids B (**2**), C (**3**), D (**4**), and A (**6**) and heptaketide (**7**), suppressed human T cell proliferation in a dose-dependent manner from 10 to 100 μM. This is the first report on the immunosuppressive activity of decalin derivatives.

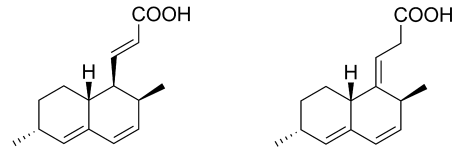


1 **2**

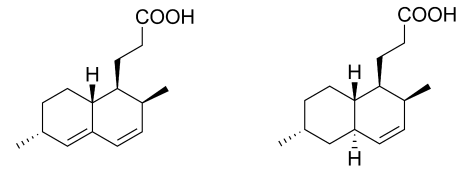
Red yeast rice, produced from the fermentation of steamed rice using the fungus *Monascus purpureus*, has been applied as traditional Chinese medicine (TCM) for improving food digestion and blood circulation in China.[1] It also has been widely used as a food preservative for maintaining color and taste, as well as to make rice wine.[2] It has been reported that *Monascus* can produce several kinds of secondary metabolites including pigments, monacolins, γ-aminobutyric acid (GABA), and unsaturated fatty acids.[3−7] Monascus pigments, called azaphilones, are derived from esterification of polyketide chromophores and β-keto acids; they include monascin and ankaflavin (yellow), monascorubrin and rubropunctatin (orange), and monascorubramine and rubropunctamine (red-purple).[2] Fourteen monacolin compounds including monacolins K, J, L, M, and X and their deriavtives have been found in red yeast rice.[8] Monacolin K, which is also known as mevinolin or lovastatin, is a potent HMG-CoA reductase inhibitor and now used clinically as a cholesterol-lowering drug. Other red yeast rice constituents such as unsaturated fatty acids and sterols are reported to have a synergistic effect on the hypolipidemic activity.[9,10] Flavonoids, phytosterols, and pyrrolonic compounds formed in red yeast rice possess the potential to reduce blood sugar and triglyceride levels while raising HDL-C.[11] GABA was reported to possess antihypertensive effects in humans.[12] Monascusic acid A (**6**) and heptaketide (**7**) are the only two decalin derivatives previously reported from red yeast rice, but no biological activity has been reported.[13] Additional metabolites from red yeast rice remained unidentified, and their biological activities are unknown. Detailed chemical analysis of red yeast rice in our laboratory led to the discovery of a series of new decalin derivatives, whose immunosuppressive effects on human T cell proliferation were further investigated. Herein we report the isolation, structural determination, and biological activity of these decalin derivatives.



1 **2** **3**



4 **5**



6 **7**

RESULTS AND DISCUSSION

Seven decalin derivatives (**1**–**7**) were isolated from the ethyl acetate extract of red yeast rice by repeated column chromatographies; **6** and **7** were identified as the known compounds monascusic acid A[13] and heptaketide,[14] respectively, by comparison of their NMR and HRESIMS data with those published.

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds 1−5 (δ in ppm)[a]

	1[b,d]		2[c,d]		3[c,e]		4[c,d]		5[c,d]	
position	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	89.1, C		45.6, CH	2.35, td (11.0, 6.0)	145.3, C		46.1, CH	2.18	143.2, C	
2	41.7, CH	2.37	34.9, CH	2.20, m	32.6, CH	3.00	35.0, CH	2.25	32.4, CH	3.19
3	128.6, CH	5.63, dd (10.0, 5.2)	131.9, CH	5.57, ddd (10.0, 4.5, 3.0)	131.2, CH	5.51, dt (9.5, 3.0)	132.4, CH	5.72, dd (9.6, 5.6)	131.2, CH	5.64, dd (10.0, 5.6)
4	128.3, CH	6.00, d (9.6)	130.8, CH	5.32, d (10.0)	131.0, CH	5.33, d (9.5)	127.8, CH	5.91, d (9.6)	127.7, CH	5.92, d (9.6)
4a	132.5, C		35.5, CH	1.90, t (11.0)	36.6, CH	1.83, t (11.5)	134.9, C		135.4, C	
5α	133.6, CH	5.61	31.4, CH_2	1.50	38.7, CH_2	1.29, td (13.0, 4.5)	130.6, CH	5.45, d (4.0)	129.5, CH	5.42, m
5β						1.53				
6	28.9, CH	2.36	26.9, CH	2.00, m	26.7, CH	2.00, m	28.4, CH	2.32	28.4, CH	2.33, m
7α	29.0, CH_2	1.64	38.0, CH_2	1.25	31.2, CH_2	1.59	28.6, CH_2	1.47	28.5, CH_2	1.58
7β		1.79, m		1.47				1.70, m		1.79, m
8α	18.0, CH_2	1.44, m	24.7, CH_2	1.03	21.9, CH_2	1.41	23.4, CH_2	1.03, m	20.3, CH_2	1.56
8β		1.61		1.27		1.50		1.46		1.70, m
8a	39.4, CH	2.47, m	38.3, CH	1.17	41.7, CH	1.68, t (11.0)	32.7, CH	2.20	36.0, CH	2.92, m
9	17.1, CH_3	1.07, d (7.0)	16.0, CH_3	0.89, d (7.0)	20.9, CH_3	1.00, d (7.0)	15.0, CH_3	0.93, d (7.0)	20.2, CH_3	1.07, d (7.0)
10	21.0, CH_3	1.01, d (7.0)	17.9, CH_3	0.96, d (7.0)	17.6, CH_3	0.95, d (7.0)	21.1, CH_3	0.94, d (7.0)	20.7, CH_3	0.97, d (7.0)
11	28.8, CH_2	2.18, m	149.9, CH	6.71, dd (15.5, 10.5)	112.0, CH	5.19, brs	148.5, CH	6.70, dd (15.5, 9.2)	112.2, CH	5.30, td (7.6, 2.0)
12	29.8, CH_2	2.61, m	123.3, CH	5.79, d (15.5)	32.7, CH_2	2.99	124.8, CH	5.83, d (15.5)	32.5, CH_2	3.01, m
13	176.7, C		167.0, C		173.4, C		167.6, C		172.9, C	

[a]Overlapped signals are reported without designating multiplicity. [b]Measured in $CDCl_3$. [c]Measured in DMSO-d_6. [d]^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. [e]^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz.

Compound **1** was obtained as a white powder with a molecular formula of $C_{15}H_{20}O_2$ by HRESIMS, bearing six degrees of unsaturation. Two were attributed to two conjugated double bonds based on the UV absorptions at λ_{max} 230 (2.14), 236 (2.13), and 245 (1.93) nm, as well as four olefin carbon signals (δ_C 128.6, 128.3, 132.5, and 133.6) in the ^{13}C NMR spectrum (Table 1). The IR absorption at 1762 cm^{-1} and the carbonyl signal at δ_C 176.7 in the ^{13}C NMR spectrum revealed an ester carbonyl in **1**. The remaining three unsaturation degrees indicated a tricyclic structure of **1** since no more unsaturated carbon signals were observed in the ^{13}C NMR spectrum.

Fifteen carbon singals were displayed in the ^{13}C NMR and DEPT spectra of **1** (Table 1), including two methyls, four methylenes, six methines, and three quaternary carbons. Detailed analyses of the ^{1}H−^{1}H COSY and HSQC spectra disclosed three partial structure units as shown by heavy lines in Figure 1. The HMBC correlations (Figure 1) between H-2 (δ_H 2.37) and C-8a (δ_C 39.4), H-3 (δ_H 5.63) and C-4a (δ_C 132.5), H-4 (δ_H 6.00) and C-8a (δ_C 39.4), H-4 (δ_H 6.00) and C-5 (δ_C 133.6), H-5 (δ_H 5.61) and C-8a (δ_C 39.4), and H-6 (δ_H 2.36) and C-4a (δ_C 132.5) connected these partial structural units, demonstrating that compound **1** possesses a skeleton of 3,4a(5)-diene decalin. Furthermore, the HMBC correlations between H_3-9 (δ_H 1.07) and C-1 (δ_C 89.1) and C-3 (δ_C 128.6), as well as between H_3-10 (δ_H 1.01) and C-5 (δ_C 133.6) and C-7 (δ_C 29.0), indicated that two methyl groups were located at C-2 and C-6 of the decalin skeleton, respectively. The third ring unit was deduced to be a five-membered lactone structure based on the molecular formula, C-13 (δ_C 176.7), and IR absorption at 1762 cm^{-1}. This five-membered lactone was shown to be attached to C-1, which was further clarified by the HMBC correlations (Figure 1) between H-3 (δ_H 5.63) and C-1 (δ_C 89.1), H_3-9 (δ_H 1.07) and C-1 (δ_C 89.1), and H-12 (δ_H 2.61) and C-1 (δ_C 89.1). Therefore, compound **1** was characterized as a decalin derivative having a spiro lactone at C-1.

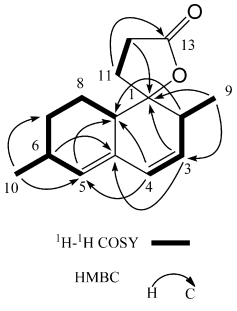

Figure 1. ^{1}H−^{1}H COSY and key HMBC correlations (from H to C) of monascusic lactone A (**1**).

The relative configuration of compound **1** was determined on the basis of the NOE correlations in its NOESY spectrum (Figure 2). The NOE correlations between H-7β and H-8a, H-8β and H-8a, H-8a and H_3-9, and H_3-9 and both H-11α and H-11β indicated the β-orientation for H-8a, H_3-9, and C-11. Similarly, the NOE correlations between H-8α and H_3-10 suggested that C-10 should be α-oriented. Therefore, the relative stereochemistry of compound **1** was established as shown in Figure 2. Compound **1**, named monascusic lactone A, is the first example of a decalin derivative in nature possessing a spiro lactone at the C-1 position.

Compound **2** was obtained as a white powder, with a molecular formula of $C_{15}H_{22}O_2$ by HRESIMS. Comparison of the ^{1}H and ^{13}C NMR (Table 1) data revealed large similarities

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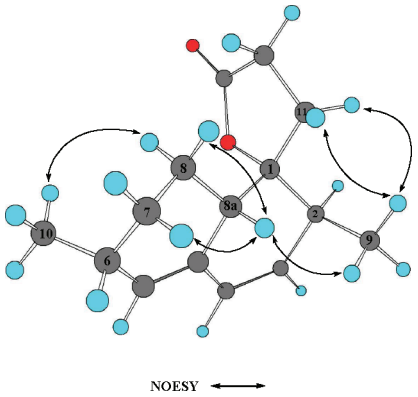


Figure 2. Key NOESY correlations of monascusic lactone A (**1**).

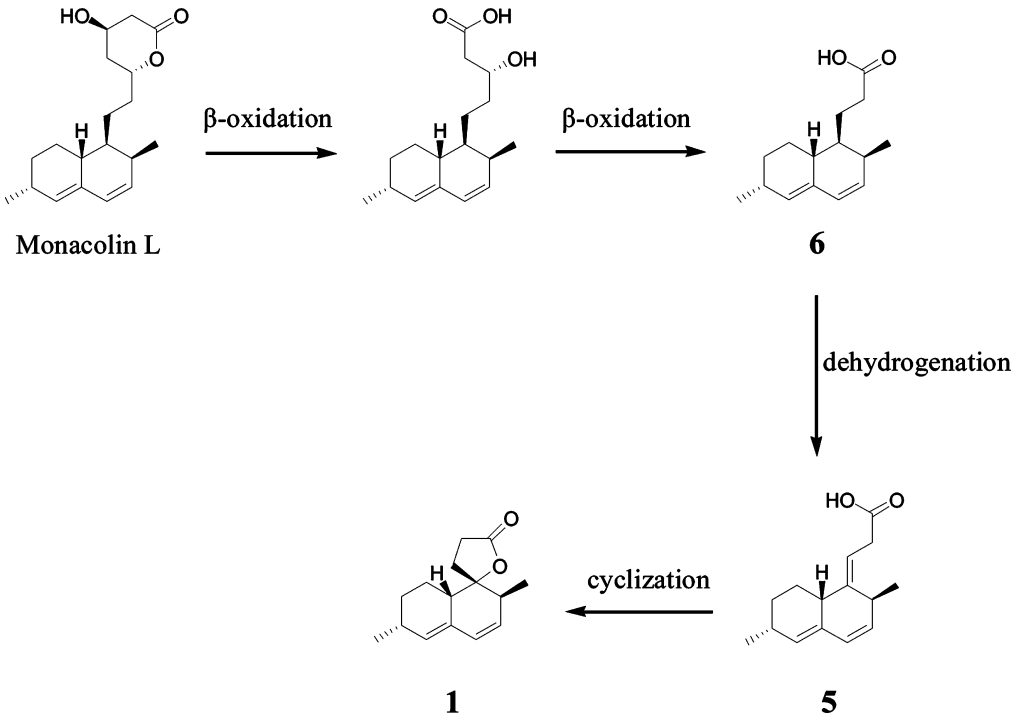
between **2** and heptaketide (**7**),[14] indicating that they shared the same decalin skeleton with only one double bond, at C_3–C_4; the only difference between **2** and **7** were signals derived from the propionic acid moiety attached to C-1. Because two more olefinic signals (δ_H 6.71, 5.79; δ_C 149.9, 123.3) were observed in the ^1H and ^{13}C NMR spectra of **2**, one double bond was deduced to be at C-11 and C-12 of the propionic acid moiety. This was supported by the molecular formula that was two hydrogen atoms less than that of **7**, as well as the ^1H–^1H COSY correlations of H-1/H-11/H-12 and HMBC correlations from H-11 to C-2, C-8a, and C-13. The *E* geometry of the Δ^{11} was elucidated from the large coupling constant of H-11 (J = 15.5 Hz). The NOE correlations of H-1/H-4a/H_3-10 and H-8a/H_3-9 observed in the NOESY spectrum were in agreement with the α-orientation of H-1, H-4a, and H_3-10 and the β-orientation of H-8a and H_3-9. On the basis of the data above, compound **2** was concluded to be 3-(2,6-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)propenoic acid and named monascusic acid B.

Monascusic acid C (**3**) has the same molecular formula, $C_{15}H_{22}O_2$, as **2**. ^1H and ^{13}C (Table 1) NMR data of **3** are similar to those of **2**, except for those of the double bond (δ_H 5.19; δ_C 145.3, 112.0) at the propionic acid moiety. The position of this double bond was determined to be located between C-1 and C-11, based on the HMBC correlations from H-11 to C-8a/C-2 and H-3/H_3-9 to C-1, as well as the ^1H–^1H COSY correlations of H-11/H-12. The NOE correlations between H-4a and H_3-10, as well as between H-8a and H_3-9, indicated an α-orientation of H-4a and H_3-10 and the β-orientation of H-8a and H_9-10. Compound **3** was therefore determined to be 3-(2,6-dimethyl-2,4a,5,6,7,8,8a-septahydronaphthalen-1-ylidene)propanoic acid.

Monascusic acid D (**4**) was obtained as a white powder, with a molecular formula of $C_{15}H_{20}O_2$ by HRESIMS. Its ^1H and ^{13}C (Table 1) NMR data closely resembled those of monascusic acid A (**6**),[13] which indicated that they share the same decalin skeleton. The only difference between **4** and **6** was found in the propionic acid moiety. A pair of additional olefinic signals (δ_H 6.70, 5.83, J = 15.5 Hz; δ_C 148.5, 124.8) of one double bond were observed in the ^1H and ^{13}C NMR spectra of **4**, which was deduced to be at C-11 and C-12 of the propionic acid moiety. The location of the olefin at the propionic acid moiety of **4** was also supported by the connectivities of H-1/H-11/H-12 in the ^1H–^1H COSY spectrum. Furthermore, comparison of its NMR data with those of **2** revealed that compound **2** is a hydrogenation product of compound **4**, sharing the same propionic acid moiety as **2**. Thus compound **4** was shown to be 3-(2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl)-propenoic acid.

Monascusic acid E (**5**) has the same molecular formula, $C_{15}H_{20}O_2$, as **4**. ^1H and ^{13}C (Table 1) NMR data of **5** are similar to those of **4**, except for those of the double bond (δ_H 5.30; δ_C 143.2, 112.2) at the propionic acid moiety. The position of this double bond was determined to be between C-1

Scheme 1. Biogenesis of Monascusic Lactone A (1)



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and C-11, based on the correlations from H_3-9 to C-1 in the HMBC spectrum and $^1H-^1H$ COSY correlation between H-11 and H-12. Moreover, comparison of its ^1H and ^{13}C (Table 1) NMR data with those of **3** revealed that the propionic acid moiety was the same as that of **3**. Therefore, compound **5** was determined to be 3-(2,6-dimethyl-2,6,7,8,8a-pentahydronaphthalen-1-ylidene)propanoic acid.

From these results, the biogenesis of these decalin derivatives could be proposed. Compound **1** is biosynthetically related to monacolin L. First, cascades of β-oxidation of monacolin L yield monascusic acid A (**6**). This is followed by dehydrogenation to produce monascusic acid E (**5**) and then terminated by cyclization to produce **1** (Scheme 1). Monacolin L is one of the monacolins produced during the fermentation of red yeast rice,[8] which is also considered to be an intermediate in the biosynthesis of monacolin K.[14] The ubiquitous occurrence of β-oxidation in fungi[15,16] and coexistence of **5** and **6** in red yeast rice further support the proposed biogenetic pathway (Scheme 1). Likewise, other decalin derivatives (**2**, **3**, **4**, and **7**) were also presumed to be formed by β-oxidation and dehydrogenation from monacolin L analogues.

The immunosuppressive effects of these decalin derivatives (**1**–**7**) on human T cell proliferation were investigated, mediated by PMA–ionomycin (P/I). Lovastatin and simvastatin, which were reported to be capable of inhibiting T cell proliferation and autoimmunity,[17–19] were used as positive controls in the bioassay. The results (Figure 3) demonstrated

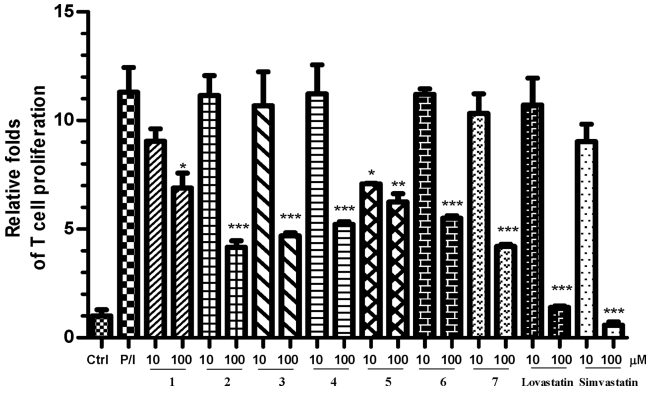

Figure 3. Inhibition effects of decalin derivatives (**1**–**7**) on human T cell proliferation (n = 3; Ctrl: T cells, P/I: T cells stimulated by PMA–ionomycin; positive controls: lovastatin and simvastatin; significance of differences shown as $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

that all these decalin derivatives could inhibit human T cell proliferation, especially compounds **2**, **3**, **4**, **6**, and **7**. To confirm the effects of these compounds on human T lymphocyte proliferation are not derived from their cytotoxic effects, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assays were conducted to examine their cytotoxicity on human T lymphocytes. The results clearly demonstrated that these compounds showed no cytotoxicity on human T lymphocytes, suggesting that compounds **1**–**7** suppressed the proliferation of T lymphocytes through inhibiting cell reproduction rather than reducing the viability of the cells. This is the first report on the immunosuppressive activity of decalin derivatives.

EXPERIMENTAL SECTION

General Experimantal Procedures. Optical rotations were measured with a JASCO P-1010 polarimeter. UV spectra were recorded on a JASCO V-530 UV/vis spectrophotometer. IR spectra were obtained on a PerkinElmer Spectrum One Fourier transform infrared (FTIR) spectrometer (KBr). NMR spectra were recorded on a Bruker Avance-III NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in ppm, and coupling constants (J) in Hz. HRESIMS spectra were measured with a Bruker MicrOTOFQ mass spectrometer. Column chromatography was performed on silica gel (40–63 μm, Grace, USA) and Bondapak C_{18} (37–55 μm, Waters, USA). Semipreparative HPLC was performed on an Alltima C_{18} (250 × 22 mm, 10 μm) semipreparative column. Precoated Kieselgel 60 F_{254} plates (0.2 mm thick, Merck KGaA) were used for thin-layer chromatography (TLC).

Material. Red yeast rice powder was purchased from Zhejiang Sanhe Bio-Tech Co. Ltd. (Quzhou, China) in March 2010. This commercial product was made by fermenting the fungus *Monascus purpureus* on steamed rice. A voucher specimen was deposited in School of Chinese Medicine, Hong Kong Baptist University.

Extraction and Isolation. Red yeast rice powder (2.0 kg) was extracted with EtOAc (20 L × 3) at room temperature with sonication. The extract was combined and evaporated under reduced pressure to afford a brownish residue (ca. 150 g). The residue was subjected to silica gel column chromatography (CC) eluted with petroleum ether–$CHCl_3$ (100:0 → 0:100) and then $CHCl_3$–MeOH (100:0 → 65:35) to obtain 16 major fractions (Fr.1–Fr.16). Fr.6 (42 g) was chromatographed on silica gel eluted with petroleum ether–EtOAc (100:0 → 0:100) to give 13 fractions (Fr.6-1–6-13). Fr.6-4 (6 g) was recrystallized by EtOAc to give a colorless powder (2 g). The material was loaded on an ODS column eluting with CH_3CN–0.1% formic acid in H_2O (50:50 → 70:30) and purified by semipreparative HPLC using CH_3CN–0.1% formic acid in H_2O (65:35) to give compounds **6** (58 mg), **7** (550 mg), **3** (19 mg), and **2** (42 mg). The rest of Fr.6-4 (4 g) after recrystallization was subjected to silica gel CC eluted with *n*-hexane–EtOAc (95:5 → 80:20) and an ODS column eluted with CH_3CN–0.1% formic acid in H_2O (50:50 → 65:35) and finally purified by semipreparative HPLC using CH_3CN–0.1% formic acid in H_2O (65:35) to give compound **4** (14 mg). Fr.6-7 (4 g) was chromatographed on silica gel eluted with petroleum ether–EtOAc (95:5 → 50:50) and then purified on semipreparative HPLC using CH_3CN–0.1% formic acid in H_2O (50:50) to give compound **5** (2 mg). Fr.6-8 (300 mg) was subjected to CC on ODS eluted with MeOH–H_2O (50:50 → 70:30) to give compound **1** (6 mg).

Cell Culture. Human peripheral blood T lymphocytes were isolated from buffy coat blood, based on the method described previously.[20] In brief, the buffy coat blood obtained from the Red Cross Association of Hong Kong was mixed with normal saline and then transferred to Ficoll-Pague (Amersham Biosciences) in 50 mL tubes. The mixture was centrifuged at 400g for 35 min to separate the blood into layers. The layer of the nonadherent mononuclear cells was collected, from which the macrophages were removed by adherence to obtain T lymphocytes. The nonadherent cells containing predominantly T lymphocytes were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum.

Examination of the Effects of Compounds 1–7 on Human T Cell Proliferation. T lymphocyte proliferation was assessed by 5-bromo-2′-deoxyuridine (BrdU, Roche) assay as described previously.[21] In brief, the isolated human T lymphocytes (10^5 cells/well) were cultured in triplicate in a 96-well flat-bottomed plate (Costar, Corning Incorporated, Corning, NY, USA) in 100 μL of RPMI 1640 medium supplemented with 10% FBS and then co-stimulated with PMA–ionomycin in the presence or absence of these compounds (10–100 μM) for 72 h. BrdU was added to the cells 14 h before the end of stimulation at a final concentration of 10 μM. BrdU can be incorporated into DNA of growing cells during the labeling period; the amount of BrdU incorporated into the DNA can be quantified as an indicator of cell proliferation. In this experiment, BrdU was determined by ELISA according to the manufacturer's instructions.

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Lovastatin and simvastatin were used as positive controls. Results are expressed as means ± SEM. One-way ANOVA was used to determine the significance of difference.

Cytotoxity of Compounds 1−7 on Human T Lymphocytes. Cytotoxicity of **1**−**7** was examined by MTT assay, as described previously.[22] Briefly, the isolated human T lymphocytes (1×10^5/well), cultured in 100 μL of RPMI 1640 medium plus 10% FBS in a 96-well plate ($n = 3$), were treated by **1**−**7** from 10 to 100 μM for 72 h. MTT (5 mg/mL) was added for 4 h incubation, and then a solvent (10% sodium dodecyl sulfate (SDS), 50% *N*,*N*-dimethyl formamide, pH 7.2) was added to dissolve the purple precipitate. The absorbance from each well was determined at 570 nm. The percentage of cell viability was calculated using the following formula: Cell viability (%) = $A_{treated}/A_{control} \times 100$.

*Monascusic lactone A (**1**):* white powder; $[\alpha]^{22}_D$ = +164.7 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 230 (2.14), 236 (2.13), 245 (1.93) nm; IR (KBr) γ_{max} 2960, 2927, 1762, 1456, 1384, 1281, 1212, 1045, 995, 955, 927, 875, 760, 651 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS 233.1535 ($[M + H]^+$, $C_{15}H_{21}O_2$, calcd 233.1536).

*Monascusic acid B (**2**):* white powder; $[\alpha]^{22}_D$ = +110.5 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) end absorption. IR (KBr) γ_{max} 3421, 2961, 2917, 1693, 1647, 1426, 1309, 1288, 996, 876, 725, 601 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS 235.1688 ($[M + H]^+$, $C_{15}H_{23}O_2$, calcd 235.1692).

*Monascusic acid C (**3**):* white powder; $[\alpha]^{22}_D$ = +55.6 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) end absorption; IR (KBr) γ_{max} 3421, 2960, 2914, 1701, 1409, 1378, 1291, 943, 841, 718, 621 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS 235.1693 ($[M + H]^+$, $C_{15}H_{23}O_2$, calcd 235.1692).

*Monascusic acid D (**4**):* white powder; $[\alpha]^{22}_D$ = +284.0 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 233 (4.27); IR (KBr) γ_{max} 3385, 2959, 2926, 1700, 1638, 1413, 1304, 1275, 993, 862, 755, 626 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HRESIMS 233.1531 ($[M + H]^+$, $C_{15}H_{21}O_2$, calcd 233.1536).

*Monascusic acid E (**5**):* white powder; $[\alpha]^{22}_D$ = +6.8 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 230 (3.25), 238 (3.16), 246 (3.11) nm; ^1H and ^{13}C NMR, Table 1; HRESIMS 233.1535 ($[M + H]^+$, $C_{15}H_{21}O_2$, calcd 233.1536).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D and 2D NMR spectra of compounds **1**−**5**. Results of cytotoxicity assays of compounds **1**−**7** on human T lymphocytes. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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