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Homosecoiridoids from the Flower Buds of *Lonicera japonica*

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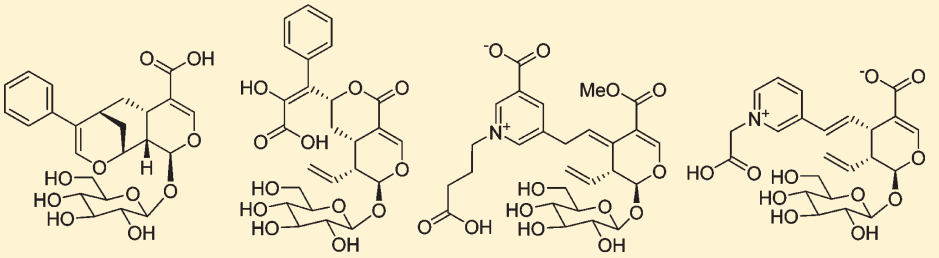
Supporting Information

ABSTRACT:



1 2 9 12

Homosecoiridoids (**1**−**15**) were isolated from the flower buds of *Lonicera japonica*. Compounds **1**−**4**, designated as loniphenyruviridosides A−D, possess unprecedented skeletons featuring phenylpyruvic acid derived moieties coupled with an iridoid or a secoiridoid nucleus. Compounds **5**−**15** (lonijaposides D−N) are additional examples of the unusual pyridinium alkaloid-coupled secoiridoids (lonijaposides A−C). The validity of the CD data to determine the configuration of the secoiridoid derivatives is discussed on the basis of detailed CD data analysis and semisynthesis of **2** and **3** with the co-occurring secologanic acid. The configuration of secologanic acid was determined by a single-crystal X-ray crystallographic analysis using anomalous scattering of Cu Kα radiation. Biosynthetic pathways of the homosecoiridoids were postulated. Compounds **1**−**4** inhibited STAT-3 activity of HELF cells, and lonijaposides F (**7**), H (**9**), I (**10**), and K (**12**) showed activity against the release of glucuronidase in rat polymorphonuclear leukocytes induced by platelet-activating factor.

Lonicera japonica Thunb. (Caprifoliaceae) is widely cultivated in Shandong and Henan Provinces of China. Its flower buds and stems are used in traditional Chinese medicine for the treatment of various diseases and are among the most common ingredients of formulations used for treating influenza, cold, fever, and infections.[1,2] Chemical and pharmacological studies resulted in characterization of constituents with different structural features and biological activities from the flower buds of *L. japonica*, including caffeoyl quinic acids, secoiridoids, flavonoids, saponins, cerebrosides, and polyphenols.[3,4] As part of a program to assess the chemical and biological diversity of traditional Chinese medicines,[5] three pyridinium alkaloid-coupled secoiridoids (lonijaposides A−C) with an unusual skeleton of an *N*-substituted nicotinic acid nucleus coupled with a secoiridoid, together with seven known iridoid derivatives, were reported from a water extract of the flower buds of *L. japonica*.[6] Focusing our continuing investigation on the minor components of the extract, 15 new homosecoiridoids (**1**−**15**) have been isolated. Compounds **1**−**4**, named loniphenyruviridosides A−D, possess unprecedented skeletons featuring phenylpyruvic acid derived moieties coupled with an iridoid or a secoiridoid nucleus, and compounds **5**−**15** (lonijaposides D−N) are analogues of lonijaposides A−C.[6] We report herein the isolation, structure determination, and biological activity of the new isolates. In addition, the validity of the CD data to determine the configuration of the secoiridoid derivatives is discussed on the basis of systematic comparison of the CD data combined with a single-crystal X-ray crystallographic analysis of the co-occurring secologanic acid using anomalous scattering of Cu Kα radiation.

RESULTS AND DISCUSSION

Loniphenyruviridoside A (**1**) showed IR absorptions for hydroxy, carboxylic, conjugated double bond, and aromatic ring functional groups. Its molecular formula, $C_{24}H_{28}O_{10}$, was indicated by HR-ESIMS combined with NMR data (Table 1 and Experimental Section). The NMR spectra of **1** showed resonances (Table 1) attributable to two trisubstituted double bonds, two methylenes, and five methines (two oxygen-bearing), in addition to diagnostic resonances for phenyl and β-glucopyranosyl moieties. These data indicated that **1** was an unusual

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Table 1. NMR Data for Compounds 1−4, 2a, and 3a in Methanol-d_4[a]

	1		2		2a		3		3a		4	
no.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	5.66 s	97.3	5.40 d (4.8)	98.1	5.42 d (4.8)	97.9	5.50 d (4.8)	98.1	5.51 d (4.8)	98.0	5.27 d (4.2)	97.3
3	7.14 s	151.9	7.44 s	153.6	7.44 s	153.8	7.41 s	153.5	7.40 s	153.6	6.94 s	146.7
4		112.8		112.8		111.9		111.3		110.9		119.2
5	3.02 ddd (6.6, 6.6, 1.8)	24.5	3.19 ddd (5.4, 4.2, 4.2)	31.0	3.19 ddd (5.4, 4.2, 4.2)	30.8	3.26 m	29.9	3.26 m	29.8	3.23 ddd (5.4, 4.8, 4.8)	31.4
6a	2.87 dd (13.8, 1.8)	30.4	2.23 ddd (14.4, 4.2, 1.8)	37.6	2.24 ddd (14.4, 4.2, 1.8)	37.1	2.05 m	35.4	2.04 m	35.4	2.24 ddd (14.4, 4.8, 1.8)	37.5
6b	1.73 dd (13.8, 6.6)		1.43 ddd(14.4, 9.6, 4.2)		1.43 ddd(14.4, 8.4, 4.2)		1.92 m		1.93 m		1.33 ddd (14.4, 10.2, 5.4)	
7	2.78 m	28.2	5.68 dd(9.6, 1.8)	81.6	5.61 dd(8.4, 1.8)	N.D.	5.45 dd(10.2, 1.8)	78.1	5.45 dd(10.2, 1.8)	78.2	5.72 dd(10.2, 1.8)	82.2
8	4.57 m	72.2	5.57 ddd(16.8, 10.2, 7.8)	135.8	5.54 ddd(16.8, 10.2, 7.8)	135.4	5.74 ddd(16.8, 11.4, 9.6)	136.4	5.75 ddd(16.2, 11.4, 9.6)	136.0	5.59 ddd(17.4, 10.2, 9.6)	136.6
9	2.23 d (6.6)	44.6	2.72 ddd (7.8, 5.4, 4.8)	46.8	2.74 ddd (7.8, 5.4, 4.8)	46.3	2.92 ddd (9.6, 4.8, 4.8)	44.9	2.91 ddd (9.6, 4.8, 4.8)	44.7	2.74 ddd (9.6, 4.8, 4.2)	47.1
10a	1.91 m	31.6	5.17 d (16.8)	120.5	5.18 d (16.8)	120.4	5.46 d (16.8)	120.8	5.45 d (16.2)	120.6	5.16 d (17.4)	120.1
10b	1.90 m		5.13 d (10.2)		5.12 d (10.2)		5.36 d (11.4)		5.35 d (10.2)		5.08 d (10.2)	
11		171.9		171.6		N.D.		171.5		169.0		176.3
1′	4.59 d (8.4)	99.4	4.61 d (8.4)	100.3	4.61 d (7.8)	100.1	4.61 d (7.8)	100.2	4.61 d (7.8)	100.1	4.59 d (7.8)	99.9
2′	3.11 dd (9.0, 8.4)	74.6	3.16 dd (9.0, 8.4)	75.0	3.16 dd (9.0, 7.8)	74.6	3.25 dd (9.0, 7.8)	74.9	3.25 dd (9.0, 7.8)	74.6	3.25 dd (9.0, 7.8)	75.1
3′	3.28 dd (9.0, 9.0)	78.0	3.30 dd (9.0, 9.0)	78.3	3.30 dd (9.0, 9.0)	78.0	3.31 dd (9.0, 9.0)	78.2	3.31 dd (9.0, 9.0)	78.0	3.30 dd (9.0, 9.0)	78.0
4′	3.21 dd (9.0, 9.0)	71.6	3.21 dd (9.0, 9.0)	71.9	3.21 dd (9.0, 9.0)	71.6	3.30 dd (9.0, 9.0)	71.8	3.30 dd (9.0, 9.0)	71.5	3.32 dd (9.0, 9.0)	71.9
5′	3.26 m	78.2	3.22 m	78.6	3.22 m	78.4	3.29 m	78.6	3.29 m	78.4	3.28 m	78.5
6′a	3.86 dd (12.0, 2.4)	62.8	3.81 dd (12.0, 1.2)	63.0	3.81 dd (12.0, 1.2)	62.7	3.84 dd (12.0, 1.8)	63.0	3.84 dd (12.0, 1.8)	62.8	3.81 d (10.8)	63.0
6′b	3.61 dd (12.0, 6.0)		3.58 dd (12.0, 5.4)		3.58 dd (12.0, 5.4)		3.62 dd (12.0, 5.4)		3.62 dd (12.0, 5.4)		3.60 dd (10.8, 5.4)	
1″		140.1		132.3		132.6		132.2		132.8		132.8
2″	7.22 d (7.8)	125.7	7.66 d (7.2)	129.0	7.66 d (7.2)	128.3	7.57 d (7.8)	128.9	7.59 d (7.8)	128.3	7.71 d (7.8)	128.9
3″	7.14 dd (7.8, 7.2)	129.6	7.35 t (7.2)	129.9	7.33 t (7.2)	129.5	7.34 t (7.8)	129.8	7.31 t (7.8)	129.5	7.34 dd (7.8)	129.9
4″	7.01 t (7.2)	126.3	7.26 t (7.2)	129.9	7.23 t (7.2)	129.3	7.26 t (7.8)	129.9	7.21 t (7.8)	129.0	7.21 t (7.8)	129.3
5″	7.14 dd (7.8, 7.2)	129.6	7.35 t (7.2)	129.9	7.33 t (7.2)	129.5	7.34 t (7.8)	129.8	7.31 t (7.8)	129.5	7.34 dd (7.8)	129.9
6″	7.22 d (7.8)	125.7	7.66 d (7.2)	129.0	7.66 d (7.2)	128.3	7.57 d (7.8)	128.9	7.59 d (7.8)	128.3	7.71 d (7.8)	128.9
7″		116.9		132.1		N.D.		132.4		N.D.		131.4
8″	6.58 s	144.5		139.4		N.D.		139.1		N.D.		140.6
9″				171.6		169.4		171.5		169.0		172.8
OMe					3.69 s	51.9			3.58 s	51.7		

[a] Data were recorded at 600 MHz (^{1}H) and 125 MHz (^{13}C). Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT, ^{1}H−^{1}H COSY, gHSQC, and HMBC experiments.

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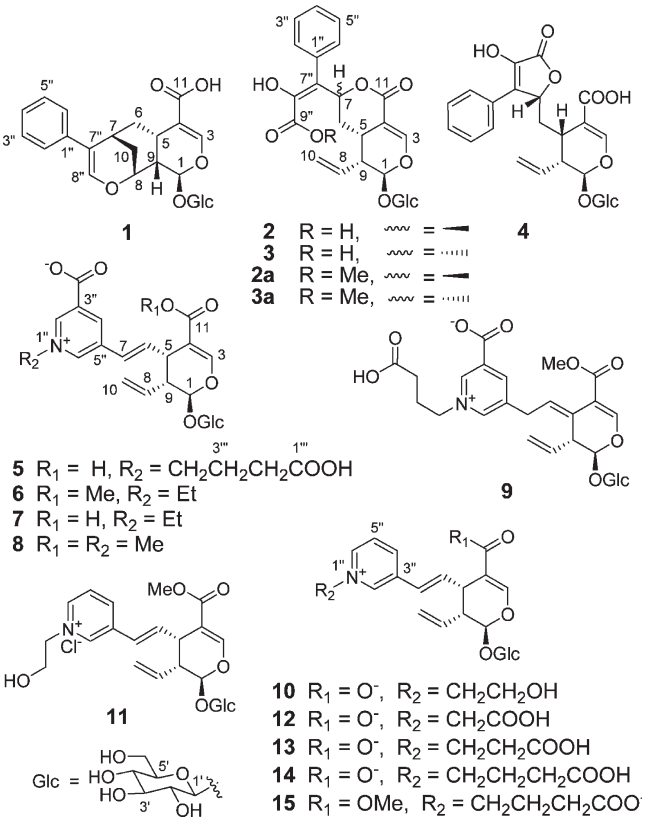
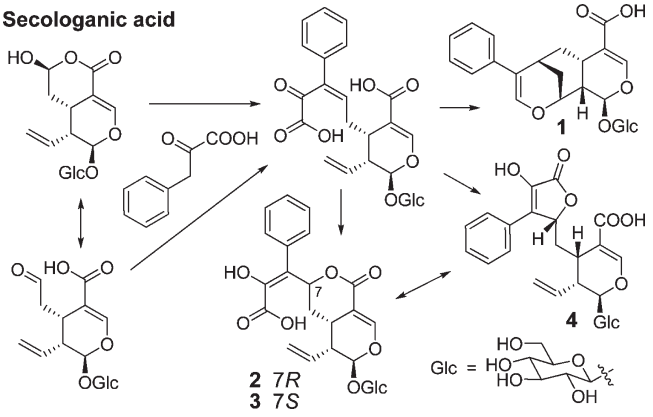


analogue of the co-occurring secoiridoids[6] having an additional trisubstituted double bond and phenyl units. The presence of a β-glucopyranosyl unit was confirmed by enzymatic hydrolysis of **1** with β-glucosidase, which produced glucose, identified by TLC comparison with an authentic sugar sample. The glucose isolated from the hydrolysate gave a positive optical rotation, $[\alpha]^{20}_{D}$ +41.1 (*c* 0.06, H_2O), indicating that it was β-D-glucose.[7] The structure of the aglycone moiety of **1** was finalized by 2D NMR data analysis (Supporting Information, Figures S8−S10). The proton and protonated carbon resonances in the NMR spectra were assigned by the gHSQC data. $^1H-^1H$ gCOSY cross-peaks of H-9/H-5/H_2-6/H-7/H_2-10/H-8/H-9 indicated the presence of a 1,2,3,5-tetrasubstituted cyclohexane ring in **1**. HMBC correlations of H-1/C-3, C-5, and C-1′; H-3/C-1, C-4, C-5, and C-11; H-5/C-3, C-4, and C-9; H-9/C-1, C-4, and C-5; and H-1′/C-1, in combination with their shifts, revealed a 3-carboxy-6-β-glucopyranosyl-4,5-dihydro-[6*H*]-pyrano moiety sharing C-5 and C-9 with the cyclohexane ring. This was supported by gCOSY cross-peaks of H-1/H-9 and H-3/H-5 (a long-range *W*-type coupling) and gHMBC correlations of H-1/C-8, H-5/C-6, C-7, and C-8, H-8/C-5, and H_2-10/C-6, C-7, and C-9. In addition, gHMBC correlations of H-2″ and H-6″/C-4″ and C-7″; H-3″ and H-5″/C-1″; and H-8″/C-1″ and C-7″, together with the shifts of H-8″ and C-8″ and the quaternary nature of C-7″, indicated the occurrence of a 3-phenyl-4,5-dihydro-[6*H*]-pyrano moiety in **1**. Meanwhile, gHMBC correlations of H-8/C-8″, H-8″/C-7 and C-8, and H_2-10/C-7″, combined with the molecular composition, demonstrated a connection of C-7 and C-7″ and an oxygen bridge between C-8 and C-8″. Accordingly, the planar structure of **1** was elucidated as shown. In the NOE difference spectrum of **1**, irradiation of H-6b gave enhancements of H-5, H-7, H-9, and H-10a (*endo*); in turn, when H-9 was irradiated H-5, H-6b, H-8, and H-10a were enhanced. These

Scheme 1. Plausible Biosynthetic Pathways of 1−4



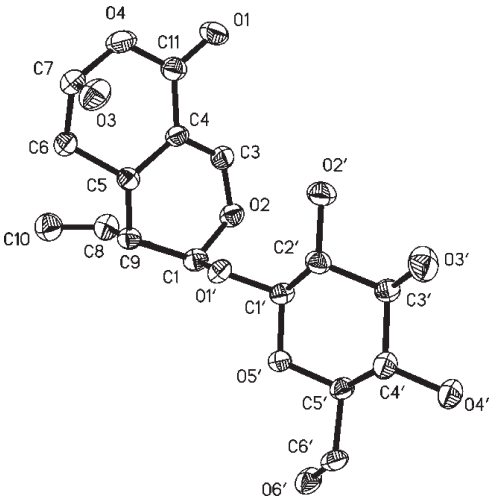


Figure 1. ORTEP diagram of secologanic acid.

NOE enhancements, combined with coupling constants of the vicinal protons, indicated that these protons were cofacial on the cyclohexane ring. The coupling constant for $J_{1,9}$ and $J_{8,9}$ (≈0.0 Hz) in the ^1H NMR spectrum indicated that the torsion angles between H-1 and H-9 and between H-8 and H-9 were around 90°. This suggested that H-1 was oriented on the other side of the *cis*-fused ring system based on molecular modeling. The CD spectrum of **1** displayed positive Cotton effects at 272 nm and negative at 227 and 244 nm, arising from the ^1L_b band of the styrene chromophore[8] of the 3-phenyl-4,5-dihydro-[6*H*]-pyrano moiety and an overlap of the $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions of the 3-carboxy-4,5-dihydro-[6*H*]-pyrano chromophore,[9] respectively. On the basis of the empirical helicity rule for the styrenes,[8] in combination with the relative configuration and lowest energy conformation analysis (MM2), the longer wavelength Cotton effect predicts the 7*R*,8*R* configuration for **1**. When applying the octant rule to the conjugated carbonyl chromophore[10] and the helicity rule to the 3-carboxy-4,5-dihydro-[6*H*]-pyrano chromophore,[9] the shorter wavelength Cotton effects predict the 1*S*,5*S*,9*S* configuration. The predicted configuration is consistent with that based on a biogenetic postulation of **1** (Scheme 1) combined with the above NOE enhancements. The configuration of the proposed biosynthetic precursor, the co-occurring secologanic

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Table 2. ^{1}H NMR Spectroscopic Data (δ) for Lonijaposides D−N (5−15)[a]

no.	5	6	7	8	9	10	11	12	13	14	15
1	5.47 d (7.8)	5.58 d (7.8)	5.45 d (7.2)	5.56 d (7.8)	5.73 d (7.0)	5.41 d (7.0)	5.58 d (7.5)	5.47 d (7.2)	5.45 d (6.5)	5.46 d (6.5)	5.58 d (7.8)
3	7.40 s	7.77 s	7.33 s	7.75 s	7.43 s	7.30 s	7.78 s	7.40 s	7.33 s	7.37 s	7.77 s
5	3.74 dd (7.8, 7.2)	3.74 dd (7.8, 7.2)	3.72 dd (7.8, 7.2)	3.73 dd (7.8, 7.2)		3.68 dd (7.5, 7.0)	3.73 dd (7.5, 7.0)	3.71 dd (7.2, 6.0)	3.71 dd (7.5, 6.5)	3.70 dd (6.5, 7.5)	3.75 dd (7.8, 7.2)
6	6.72 dd (15.6, 7.8)	6.70 dd (16.2, 7.8)	6.70 dd (15.6, 7.2)	6.68 dd (16.2, 7.8)	6.56 t (7.5)	6.64 dd (16.0, 7.5)	6.68 dd (16.5, 7.5)	6.67 dd (15.6, 7.2)	6.66 dd (16.0, 7.5)	6.67 dd (16.0, 7.5)	6.67 dd (16.2, 7.8)
7	6.58 d (15.6)	6.63 d (16.2)	6.57 d (15.6)	6.63 d (16.2)	3.81 d (7.5)	6.51 d (16.0)	6.62 d (16.5)	6.55 d(15.6)	6.53 d (16.0)	6.54 d (16.0)	6.60 d (16.2)
8	5.81 ddd (17.4 10.8, 7.8)	5.79 ddd (17.4, 10.8, 7.8)	5.81 ddd (17.4, 10.8, 7.8)	5.77 ddd (17.4, 11.4, 7.8)	5.78 ddd (17.5, 11.0, 7.5)	5.76 ddd (17.5, 10.5, 7.5)	5.80 ddd (17.0 10.5, 7.5)	5.81 ddd (16.8 10.8, 7.2)	5.81 ddd (17.0, 11.0, 7.5)	5.80 ddd (17.0, 10.0, 8.0)	5.79 ddd (17.4, 10.8, 7.8)
9	2.85 dt (7.2, 7.8)	2.86 dt (7.2, 7.8)	2.85 dt (7.2, 7.8)	2.84 dt (7.2, 7.8)	3.83 dd (7.0, 7.5)	2.86 dt (7.5, 7.0)	2.87 dt (7.0, 7.5)	2.85 dt (6.0, 7.2)	2.85 dt (7.5, 6.5)	2.85 dt (8.0, 6.5)	2.86 dt (7.2, 7.8)
10a	5.37 d (17.4)	5.38 d (17.4)	5.36 d (17.4)	5.36 d (17.4)	5.18 d(11.0)	5.32 d (17.5)	5.39 d (17.0)	5.36 d(16.8)	5.36 d (17.0)	5.36 d(17.0)	5.38 d(17.4)
10b	5.32 d (10.8)	5.33 d (10.8)	5.31 d (10.8)	5.31 d (11.4)	5.15 d(17.5)	5.27 d (10.5)	5.34 d (10.5)	5.31 d (10.8)	5.30 d (11.0)	5.31 d(10.0)	5.34 d(10.8)
1′	4.88 d (8.4)	4.90 d (8.4)	4.87 d (7.8)	4.88 d (8.4)	4.80 d (7.8)	4.82 d (8.0)	4.92 d (8.0)	4.88 d (7.8)	4.88 d (8.0)	4.87 d (8.0)	4.91 d(8.0)
2′	3.34 dd (8.4, 9.0)	3.34 dd (8.4, 9.0)	3.34 dd (7.8, 9.0)	3.32 dd (8.4, 9.0)	3.26 dd (7.8, 9.0)	3.31 dd (8.0, 9.0)	3.35 dd (8.0, 9.0)	3.34 dd (9.0, 7.8)	3.35 dd (9.0, 8.0)	3.34 dd (8.0, 9.0)	3.35 dd (8.0, 9.0)
3′	3.53 t (9.0)	3.53 t (9.0)	3.53 t (9.0)	3.52 t (9.0)	3.48 t (9.0)	3.49 t (9.0)	3.53 t (9.0)	3.53 t (9.0)	3.54 t (9.0)	3.53 t (9.0)	3.54 t (9.0)
4′	3.41 t (9.0)	3.40 t (9.0)	3.41 t (9.0)	3.39 t (9.0)	3.37 t (9.0)	3.37 t (9.0)	3.42 t (9.0)	3.41 t (9.0)	3.41 t (9.0)	3.41 t (9.0)	3.41 t (9.0)
5′	3.49 m	3.49 m	3.49 m	3.48 m	3.46 m	3.45 m	3.50 m	3.49 m	3.49 m	3.49 m	3.50 m
6′a	3.91 dd (12.0, 2.4)	3.90 dd (12.0, 2.4)	3.90 dd (12.0, 2.4)	3.88 dd (12.0, 2.4)	3.91 dd(12.0, 2.4)	3.89 brd (12.0)	3.92 brd (12.0)	3.91 brd(10.8)	3.91 brd (12.0)	3.91 brd (12.0)	3.91 brd (12.0)
6′b	3.71 dd (12.0, 6.0)	3.70 dd (12.0, 6.0)	3.70 dd (12.0, 6.0)	3.68 dd (12.0, 6.0)	3.70 dd (12.0, 6.0)	3.66 dd (12.0, 6.0)	3.71 dd (12.0, 6.0)	3.71 dd (10.8, 5.4)	3.71 dd (12.0, 6.0)	3.71 dd (12.0, 6.0)	3.70 dd (12.0, 6.0)
2″	8.99 s	9.01 s	8.98 s	8.92 s	9.04 s	8.77 s	8.80 s	8.73 s	8.82 s	8.81 s	8.81 s
4″	8.83 s	8.81 s	8.81 s	8.75 s	8.74 s	8.52 d (8.5)	8.56 d (8.5)	8.54 d (8.4)	8.51 d (8.0)	8.51 d (7.5)	8.51 d (7.8)
5″						7.95 dd (8.5, 6.0)	8.02 dd (8.5, 6.0)	7.99 dd (8.4, 4.8)	7.95 dd (8.0, 6.0)	7.96 dd (5.5, 7.5)	7.98 dd (7.8, 6.0)
6″	8.86 s	8.84 s	8.85 s	8.78 s	8.77 s	8.62 d (6.0)	8.69 d (6.0)	8.57 d (4.8)	8.67 d (6.0)	8.65 d (5.5)	8.69 d (6.0)
1‴		4.67 q (7.2)	4.66 q (7.2)	4.39 s		4.05 t (7.0)	4.10 t (7.0)				
2‴	2.33 t (7.0)	1.66 t (7.2)	1.65 t (7.2)		2.25 m	4.66 t (7.0)	4.72 t (7.0)	5.20 s	2.92 t (7.0)	2.27−2.30 m	2.27−2.32 m
3‴	2.28 m				2.26 m				4.78 t (7.0)	2.27−2.30 m	2.27−2.32 m
4‴	4.64 t (7.0)				4.64 t (7.0)					4.59 t (7.0)	4.61 t (7.2)
OMe		3.74 s		3.72 s	3.74 s		3.75 s				3.74 s

[a] Data were measured in D_2O at 500 MHz for **10**, **11**, **13**, and **14** and at 600 MHz for **5**−**9**, **12**, and **15**, respectively. Coupling constants (J) in Hz are given in parentheses. The assignments were based on DEPT, ^{1}H−^{1}H COSY, gHSQC, and HMBC experiments, while the data are presented as calculated using solvent peak (δ 4.80 ppm) as the reference.

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Table 3. ^{13}C NMR Spectroscopic Data (δ) for Lonijaposides D (5), E (6), and H−N (9−15)[a]

no.	5	6	9	10	11	12	13	14	15
1	99.8	100.2	100.3	99.6	100.1	99.7	99.7	99.7	100.2
3	N.D.	157.3	154.3	151.5	157.2	152.5[b]	151.6	151.7	157.3
4	115.8[b]	109.9	111.4	116.0	109.9	115.4	116.1	116.1	110.0
5	41.2	40.9	128.7	40.8	40.7	41.0	41.0	41.0	40.9
6	141.6	140.3	127.8	141.4	140.2	141.1	141.3	141.3	140.1
7	128.0	128.4	32.3	127.8	128.4	128.0	128.1	128.0	128.6
8	136.7	136.1	135.4	136.6	136.0	136.6	136.7	136.7	136.1
9	47.8	47.4	44.4	47.7	47.4	47.7	47.8	47.8	47.5
10	122.5	122.8	121.0	122.3	122.8	122.4	122.4	122.4	122.8
11	N.D.	172.2	171.3	177.8	172.2	177.7[b]	177.6[b]	177.4[b]	172.3
1′	101.9	102.1	101.6	101.7	102.0	101.8	101.8	101.8	102.1
2′	75.5	75.4	75.2	75.4	75.4	75.4	75.5	75.5	75.5
3′	78.5	78.5	79.0	78.4	78.5	78.4	78.5	78.5	78.6
4′	72.5	72.4	72.2	72.4	72.3	72.4	72.5	72.5	72.4
5′	79.2	79.2	78.3	79.1	79.2	79.1	79.2	79.2	79.3
6′	63.5	63.5	63.5	63.5	63.5	63.5	63.5	63.5	63.5
2″	145.5	145.3	143.0	144.9	144.9	145.7	144.9	144.8	144.7
3″	139.8	139.9	137.2	141.0	140.7	140.7	141.0	141.2	140.9
4″	144.0	143.8	145.3	144.6	144.7	144.5	144.5	144.5	144.5
5″	141.0	140.7	142.1	130.4	130.6	130.3	130.5	130.6	130.8
6″	145.6	145.2	144.6	145.0	145.3	145.7	144.8	144.8	145.1
7″	N.D.	170.8	170.6						
1‴	N.D.	60.5	180.0[b]	63.1	63.1	173.7[b]	179.7[b]	180.2[b]	183.2
2‴	36.4	18.5	36.3	66.3	66.4	66.2	26.2	36.5	36.1
3‴	30.3		30.2				61.7	30.3	30.1
4‴	64.4		64.1					63.5	64.3
OMe		54.8	54.8		54.8				54.9

[a] Data were measured in D_2O at 125 MHz for **6**, **9**, **10**, **11**, **13**, and **14** and at 150 for **5**, **12**, and **15**, respectively. The assignments were based on DEPT, ^{1}H−^{1}H COSY, HSQC, HMQC, and HMBC experiments, while the data are presented as calculated using C-6′ (δ 63.5 ppm) as the reference. "N.D." means that the carbon resonance was not observed in the spectrum. [b] The resonance data were obtained from the HMBC spectrum.

acid, was determined by a single-crystal X-ray crystallographic analysis using anomalous scattering of Cu Kα radiation. An ORTEP drawing with the atom-numbering indicated is shown in Figure 1. Therefore, the structure of compound **1** was determined and designated as loniphenyruviridoside A.

By HR-ESIMS and NMR data (Table 1 and Experimental Section) compound **2** had the molecular formula $C_{25}H_{28}O_{12}$ with an additional CO_2 unit compared to **1**. The NMR data of **2** (Table 1) indicated that it consisted of 7-substituted secologanic acid[6] and 7″,8″-disubstituted phenylpropenoic acid moieties, as verified by 2D NMR data analysis (Supporting Information, Figures S20−S22). In the gHMBC spectrum, long-range correlations of H-6b/C-7″; H-7/C-1″, C-7″, and C-8″; and H-2″ and H-6″/C-7″, together with their shifts, revealed that the two moieties were connected via a carbon bond between C-7 and C-7″, while correlations of H-7/C-11 and their shifts confirmed the presence of the oxygen bridge between C-7 and C-11 forming a lactone ring in the 7-substituted secologanic acid moiety. In the NOE difference spectrum of **2**, irradiation of H-7 enhanced H-5 and H-6a, and irradiation of H-9 gave enhancement of H-5. In addition, H-1 and H-6b were enhanced upon irradiation of H-8. These enhancements indicated that H-5, H-6a, H-7, and H-9, opposite of H-8 and H-1, were cofacial. In the NOE difference spectrum of methyl ester **2a**, irradiation of H-2″ and/or H-6″ did not enhance the COOCH_3 (Supporting Information, Figure S29), indicating an *E* geometry of the C-7″−C-8″ double bond that was supported by absorptions at 1678 and 1635 cm^{-1} in the IR spectrum of **2**.[11] The CD spectrum of **2** displayed positive Cotton effects at 281 nm and negative at 232 nm, resulting from the ^1L_b band of the phenylpropenoic chromophore[12] and the $\pi\rightarrow\pi^*$ transition of the 4,5-dihydro-[6*H*]-pyrano chromophore.[9] The shorter wavelength Cotton effect predicts the 1*S*,5*S*,9*S* configuration by application of the helicity rule to the 4,5-dihydro-[6*H*]-pyrano chromophore.[9] With this information and the knowledge of relative configuration, the absolute configuration at C-7 could be determined as *R*. The absolute configuration was confirmed by semisynthesis of **2** using the co-occurring secologanic acid and the commercially available phenylpyruvic acid (Experimental Section). Thus, the structure of compound **2** was determined and designated as loniphenyruviridoside B.

The spectroscopic data of compound **3** (Table 1 and Experimental Section) indicated that it was an isomer of **2**. Comparison of the NMR data of **2** and **3** indicated that H-6a and H-7 and C-6 and C-7 in **3** were shielded, whereas H-1, H-5, H-8, H-9, and H_2-10 were deshielded. This suggested that **3** was a C-7 epimer of **2** and was proved by 2D NMR, NOE difference, and CD data (Supporting Information, Figures S40−S44), as well as by semisynthesis of **3** (Experimental Section). Particularly, the CD spectrum of **3** displayed a negative Cotton effect at 282 nm, opposite that of **2**, suggesting the 7*S* configuration (Supporting Information, Figure S44). Therefore, the structure of compound **3** was assigned for loniphenyruviridoside C, as confirmed by semisynthesis with the co-occurring secologanic acid (Experimental Section).

Compound **4** was another isomer of **2**, as indicated by spectroscopic data (Table 1 and Experimental Section). Comparison of the NMR data of **2** and **4** indicated that H-3 and C-3 of **4** were shielded by $\Delta\delta_H$ −0.50 and $\Delta\delta_C$ −6.9 ppm, respectively, whereas C-4, C-11, and C-9″ were deshielded by $\Delta\delta_C$ +6.4, +4.7, and +1.2 ppm. This suggested that **4** resulted from intramolecular *trans*-esterification of **2** with the lactone formed between C-9″ and C-7. This was confirmed by 2D NMR data of **4** (Supporting Information, Figures S59−S61), particularly, by gHMBC correlations of H-7/C-7″, C-8″, and C-9″. In the NOE difference spectrum of **4**, irradiation of H-7 enhanced H-5 and H-2″/H-6″, and irradiation of H-2″/H-6″ gave enhancements of H-5, H-6a, and H-7. In addition, H-1 and H-6b were enhanced upon irradiation of H-8. These enhancements demonstrated that free rotation about the C-5−C-6−C-7 bonds in **4** was limited in the solution state and that the configuration at C-1, C-5, and C-9 of **4** was identical to that of **2**. The CD spectrum of **4** showed a positive Cotton effect at 282 nm attributed to the ^1L_b band of the phenylpropenoic chromophore[12] (Supporting Information, Figure S64), which was similar to that of **2** but opposite that of **3**. This suggested the 7*R* configuration for **4**. Therefore, the structure of compound **4** was defined for loniphenyruviridoside D.

Compound **5**, molecular formula $C_{26}H_{31}NO_{13}$ by HR-ESIMS and NMR data, showed IR absorptions for hydroxy and carboxylic groups (Tables 2 and 3 and Experimental Section). The ^{1}H NMR data of **5** (Table 2) were similar to those of lonijaposide A[6] except for the absence of the methyl moiety of the ester group and a shielded shift of H-3 ($\Delta\delta_H$ −0.37 ppm) in **5**.

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This suggested that **5** was demethyl lonijaposide A, which was verified by the HMBC data (Supporting Information, Figure S70), as well as by alkaline hydrolysis of lonijaposide A that produced **5**. Thus, the structure of compound **5** was determined and designated as lonijaposide D.

Compound **6**, molecular formula $C_{25}H_{31}NO_{11}$ by HR-ESIMS and NMR data, exhibited spectroscopic data (Tables 2 and 3 and Experimental Section) similar to those of lonijaposide B.[6] Comparison of the NMR data of **6** with those of lonijaposide B indicated that the *N*-(2-hydroxyethyl) unit in lonijaposide B was replaced by an *N*-ethyl group in **6**, as verified by 2D NMR data (Supporting Information, Figures S78−S80). In the HMBC spectrum of **6**, correlations of H-3 and CH_3OCO/C-11; H-2″ and H-6″/C-1‴; and H_2-1‴/C-2″, C-6″, and C-2‴, together with their shifts, confirmed the presence of the methoxycarbonyl and *N*-ethyl units in **6**. Therefore, the structure of compound **6** was assigned for lonijaposide E.

Compound **7** had the molecular formula $C_{24}H_{29}NO_{11}$ with one less CH_2 unit than **6** (HR-ESIMS and NMR data). The ^{1}H NMR spectrum of **7** (Table 2) was similar to that of **6** except for the absence of the methyl group and a shielded shift of H-3 ($\Delta\delta_H$ −0.44 ppm) in **7**. This revealed that **7** was the 11-carboxylic acid analogue of **6**, which was proved by alkaline hydrolysis of **6** that gave **7**. Thus, the structure of compound **7** was assigned for lonijaposide F.

Comparison of the ^{1}H NMR data of compounds **8** and **6** (Table 2) indicated replacement of the *N*-ethyl in **6** by an *N*-methyl (δ_H 4.39) group in **8**. This was supported by HR-ESIMS of **8** (Experimental Section). Although the ^{13}C NMR resonances were not obtained because of the limited sample amount, the gHMBC spectrum of **8** (Supporting Information, Figure S92) showed correlations from COOCH_3 to a carbon resonance at δ_C 172 (C-11) and from both *N*-CH_3 and H-4″ to a carbon resonance at δ_C 145 (C-2″/C-6″). This combined with the chemical shift of H-3 confirmed the presence of the methoxycarbonyl and *N*-methyl groups in **8**. Accordingly, the structure of compound **8** was assigned for lonijaposide G.

The spectroscopic data of compound **9** (Tables 2 and 3 and Experimental Section) showed that it was an isomer of lonijaposide A.[6] Comparison of the NMR data with that of lonijaposide A indicated that the disubstituted C-6−C-7-*trans* double bond in lonijaposide A was replaced by a trisubstituted double bond in **9**. In addition, the methine (CH-5) in lonijaposide A was substituted by a methylene (CH_2-7) group in **9**. This suggested the presence of the C-5−C-6 double bond in **9**, which was proved by the 2D NMR data. A gCOSY cross-peak of H-6/H_2-7 (Supporting Information, Figure S100) and gHMBC correlations of H-6/C-4, C-7, C-9, and C-5″; H_2-7/C-5, C-6, and C-4″; and H-4″ and H-6″/C-7 (Supporting Information, Figure S102), in combination with their shifts, confirmed the location of the trisubstituted double bond in **9**. In addition, gHMBC correlations of H-2″ and H-6″/C-4‴; H-4‴/C-2″ and C-6″; and COOCH_3/C-11 demonstrated the presence of the *N*-(3-carboxypropyl) and methoxycarbonyl units. In the NOE difference spectrum of **9** (Supporting Information, Figure S103), irradiation of H-6 gave enhancements of H-4″, H-6″, and COOCH_3, demonstrating an *E* configuration for the trisubstituted double bond. The CD spectrum of **9** displayed positive Cotton effects at 277 nm and negative at 247 and 232 nm, probably resulting from the ^1L_b band of the *N*-substituted nicotinic chromophore and the n→π^* and π→π^* transitions of the conjugated carbonyl and 4-methylene-4,5-dihydro-[6*H*]-pyrano chromophores (Supporting Information, Figure S104), respectively. When applying the helicity rule to the 4-methylene-4,5-dihydro-[6*H*]-pyrano chromophore,[9] the recorded negative Cotton effect (232 nm) predicts the 1*S*,9*R* configuration for **9**, which is consistent with that of the reported natural glycosidic secoiridoids.[9,13,14] Therefore, the structure of compound **9** was assigned for lonijaposide H.

Compound **10** had the molecular formula $C_{23}H_{29}NO_{10}$, indicated by HR-ESIMS and NMR data. Comparison of the NMR data of **10** (Tables 2 and 3) and lonijaposide B[6] showed the presence of a 3-substituted pyridine ring in **10** replacing the 3,5-disubstituted nicotinic acid unit in lonijaposide B. This was verified by gCOSY cross-peaks of H-4″/H-5″/H-6″ (Supporting Information, Figure S111) and gHMBC correlations of H-2″/C-4″, C-6″, and C-7; H-4″/C-2″, C-6″, and C-7; H-5″/C-3″ and C-6″; and H-6″/C-2″, C-4″, and C-5″ (Supporting Information, Figure S113). Meanwhile, a COSY cross-peak of H_2-1‴/H_2-2‴ and HMBC correlations of H-2″ and H-6″/C-1‴ and H-1‴/C-2″ and C-6″ confirmed the presence of the *N*-(2-hydroxyethyl) in **10**. Hence, the structure of compound **10** was assigned for lonijaposide H.

The spectroscopic data of compound **11** (Tables 2 and 3 and Experimental Section) indicated that it was the methyl ester of **10**. This was supported by a deshielded shift of H-3 ($\Delta\delta_H$ +0.48 ppm) in **11** when compared with that of **10** and confirmed by correlations from both H-3 and COOCH_3 to C-11 in the HMBC spectrum of **11** (Supporting Information, Figure S121). Compound **11** was proposed to be a chloride salt based on the isotope cluster of quasi-molecular ions at *m/z* 528/530/532 (3:2:1) $[M - H]^-$ by negative ESIMS and a peak at *m/z* 494.2029 $[M - Cl]^+$ (494.2021 calcd for $C_{24}H_{32}NO_{10}$) by positive HR-ESIMS. In addition, a quasi-molecular ion peak for the acetate salt of **11**, at *m/z* 552 $[M - H]^-$, was also indicated by the negative ESIMS (Supporting Information, Figure S118); however, it was an artifact formed in the isolation procedure by acetic acid used in the HPLC separation. Therefore, the structure of compound **11** was assigned for lonijaposide J.

Compound **12** was the analogue of **10** with an *N*-(carboxymethyl) replacing the *N*-(2-hydroxyethyl), which was demonstrated by comparison of the spectroscopic data of **12** and **10** (Tables 2 and 3 and Experimental Section). In the HMBC spectrum of **12** (Supporting Information, Figure S128), correlations of H-2‴/C-1‴, C-2″, and C-6″ and H-2″ and H-6″/C-2‴ combined with shifts of these proton and carbon resonances verified the presence of the *N*-(carboxymethyl) moiety. In addition, the shift of C-11 (δ_C 177.7) in **12** was in agreement with that of **10**, supporting that the inner salt was formed via the 11-carboxylate. Accordingly, the structure of compound **12** was assigned for lonijaposide K.

The HR-ESIMS of compound **13** indicated that it was a homologue of **12** having the molecular formula $C_{24}H_{29}NO_{11}$. Comparison of the NMR data of **13** and **12** (Tables 2 and 3) revealed the presence of an *N*-(2-carboxyethyl) in **13** replacing the *N*-(carboxymethyl) in **12**. Although resonances for the carboxylic carbons (C-11 and C-1‴) were not observed in the ^{13}C NMR spectrum of **13**, their shifts were assigned by correlations from H-3 to a carbon resonance at δ_C 177.6 (C-11) and from H_2-2‴ to a carbon resonance at δ_C 179.7 (C-1‴), respectively, in the HMBC spectrum (Supporting Information, Figure S134). In addition, HMBC correlations of H_2-3‴/C-1‴, C-2‴, C-2″, and C-6″ and H-2″ and H-6″/C-3‴ confirmed the presence of the *N*-(2-carboxyethyl) moiety in **13**. Thus, the structure of compound **13** was assigned for lonijaposide L.

The spectroscopic data of compound **14** (Tables 2 and 3 and Experimental Section) demonstrated that it was a homologue of **13** with an *N*-(3-carboxypropyl) unit substituting the *N*-(2-carboxyethyl) unit. This was confirmed by correlations of H-2″ and H-6″/C-4‴ and H_2-4‴/C-2″ and C-6″ in the HMBC spectrum of **14** (Supporting Information, Figure S142). Hence, the structure of compound **14** was defined for lonijaposide M.

Compound **15** was the methyl ester of **14**, as indicated by comparison of the spectroscopic data of **15** and **14** (Tables 2 and 3 and Experimental Section) and confirmed by the HMBC data of **15** (Supporting Information, Figure S148) displaying a correlation from $COOCH_3$ to C-11. The carboxylate inner salt was supported by the deshielded shift of C-1‴ (δ_C 183.2) in **15**. Therefore, the structure of compound **15** was assigned for lonijaposide N and further confirmed by alkaline hydrolysis of **15** to produce **14**.

The acids (lonijaposide C[6] and compounds **1**−**5**, **7**, **10**, and **12**−**14**) and methyl esters (lonijaposides A and B[6] and compounds **6**, **8**, **9**, **11**, and **15**) were considered to be natural products since hydrolysis of the esters and methylation of the acids were unlikely to occur in the isolation procedure and under simulated conditions, heating H_2O solutions of the esters or MeOH solutions of the acids, either with or without SP-700 resin, silica gel, Pharmadex LH-20, or reversed C_{18} silica gel at 45 °C for 48 h.

The biosynthetic precursors of **1**−**4** are proposed to be the co-occurring secologanic acid and/or secologanin. A plausible pathway to compounds **1**−**4** is postulated in Scheme 1. Condensation of secologanic acid with phenylpyruvic acid by an aldol-like reaction would yield a key conjugated enone intermediate.[15] The intermediate may be cyclized through a sequentially or simultaneously intramolecular hetero-Diels−Alder addition and decarboxylation to yield **1**, while it undergoes *re*- and *si*-1,4-additions of the conjugated enone with the carboxylic alcohols to generate **2**−**4**, respectively. In addition, an enzyme-catalyzed intramolecular ester exchange of **2**−**4** would be an alternative for their formation. The biosynthetic pathway of **5**−**15** would be similar to that postulated for lonijaposides A−C.[6] Compounds **5**−**9** may be derived from an enzyme-catalyzed coupling between nicotinic acid with γ-hydroxy/γ-aminobutyric acid (**5** and **9**), ethanol/ethylamine (**6** and **7**), or methanol/methylamine (**8**) and the co-occurring secologanic acid (**5** and **7**) or secologanin (**6**, **8** and **9**), and compounds **10**−**15** from coupling between pyridine with 2-aminoethanol/1,2-ethandiol (**10** and **11**), 2-hydroxy/2-amino acetic acid (**12**), 3-hydroxy/3-amino propionic acid (**13**), or γ-hydroxy/γ-amino butyric acid (**14** and **15**) and the co-occurring secologanic acid (**10** and **12**−**14**) or secologanin (**11** and **15**). An enzyme-catalyzed methylation or demethylation would be an alternative for the mutual conversion between the 11-carboxylic acids and the methyl 11-carboxylates.

In the preliminary in vitro assays, compounds **1**−**4**, at 10 μM, inhibited STAT-3 (signal transducers and activators of transcription 3, which has been reported to play critical roles of regulating tyrosine kinase correlative cytokine signaling pathways in the pathogenesis of autoimmune and inflammation diseases and cancer[16]) activity in human embryonic lung fibroblast (HELF) cells. As compared with the blank, control compounds **1**−**4** showed 45.7 ± 12.5%, 25.8 ± 2.0%, 30.9 ± 1.8%, and 48.8 ± 8.7% inhibition, respectively. Lonijaposides F (**7**), H (**9**), I (**10**), and K (**12**), at 10 μM, showed inhibitory activity against the release of glucuronidase in rat polymorphonuclear leukocytes induced by platelet-activating factor with 87.6 ± 1.6%, 68.6 ± 2.8%, 72.1 ± 2.6%, and 54.6 ± 2.3% inhibition rates, respectively, while other isolates exhibited inhibition rates lower than 30%. The positive control (ginkgolide B) gave an inhibition rate of 84.3 ± 3.3% at the same concentration.[6,17] In addition, these compounds were also assessed for their activities against several human cancer cell lines,[18] neuroprotective activity against glutamate-induced neurotoxicity in cultures of PC12 cells,[19] and antioxidant activity in Fe^{2+}-cystine-induced rat liver microsomal lipid peroxidation,[20] as well as the inhibitory activity against HIV-1 replication[21] and protein tyrosine phosphatase 1B (PTP1B),[20] but all were inactive at a concentration of 10 μM.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a PE model 343. UV and CD spectra were measured on a JASCO J-810 spectropolarimeter. IR spectra were recorded on a Nicolet 5700 FT-IR microscope spectrometer (FT-IR microscope transmission). 1D- and 2D-NMR spectra were obtained at 500 or 600 MHz for ^1H and 125 or 150 MHz for ^{13}C, respectively, on INOVA 500 MHz or SYS 600 MHz spectrometers with solvent peaks as references (unless otherwise noted). ESIMS data were measured with a Q-Trap LC/MS/MS (Turbo ionspray source) spectrometer. HR-ESIMS data were, in turn, measured on an AccuToFCS JMS-T100CS spectrometer. Column chromatography was performed with silica gel (200−300 mesh, Qingdao Marine Chemical Inc., Qingdao, People's Republic of China) and Pharmadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden). HPLC separation was performed on an instrument with a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector on an Prevail (250 × 10 mm i.d.) semipreparative column packed with C_{18} (5 μm). Glass precoated silica gel GF254 plates were used for TLC. Spots were visualized under UV light or by spraying with 7% H_2SO_4 in 95% EtOH followed by heating.

Plant Material. See ref 6.

Extraction and Isolation. For extraction and preliminary fractionation of the extract, see ref 6. Fraction B_3-10 (22.1 g) was separated by MPLC over RP silica gel, eluting with a gradient of EtOH (0−50%) in H_2O to give subfractions B_3-10-1−B_3-10-13. B_3-10-6 (1.9 g) was further separated by flash chromatography over RP silica gel, eluting with a gradient of CH_3CN (0−30%) in H_2O to obtain fractions B_3-10-6-1−B_3-10-6-6. B_3-10-6-3 (28 mg) was subjected to RP-HPLC, using CH_3CN−H_2O (5:95) containing 0.5% HOAc as the mobile phase, to afford **6** (6 mg, 0.00005%), **7** (1 mg, 0.0000083%), and **8** (0.8 mg, 0.0000067%). Fraction B_3-11 (4.6 g) was separated by flash chromatography over RP silica gel, eluting with a gradient of EtOH (0−50%) in H_2O to give subfractions B_3-11-1−B_3-11-4. B_3-11-1 (62 mg) and B_3-11-4 (42 mg) were subjected separately to RP-HPLC, using CH_3CN−H_2O (7:93) containing 0.5% HOAc as the mobile phase, from B_3-11-1 to yield **5** (1.2 mg, 0.00001%), **9** (5.4 mg, 0.000045%), and **15** (8.8 mg, 0.000073%) and from B_3-11-4 to obtain **10** (5.6 mg, 0.000047%) and **11** (2.1 mg, 0.000018%). Fraction B_3-13 (7.6 g) was separated by flash chromatography over RP silica gel, eluting with a gradient of EtOH (0−50%) in H_2O, to give subfractions B_3-13-1−B_3-13-15. B_3-13-6 (16 mg) and B_3-13-8 (2860 mg) were subjected separately to RP-HPLC, for B_3-13-6 using CH_3CN−H_2O (3:97) containing 0.5% HOAc as the mobile phase to afford **12** (3.9 mg, 0.000033%) and **13** (5 mg, 0.000042%) and for B_3-13-8 using CH_3CN−H_2O (7:93) containing 0.5% HOAc as the mobile phase to afford **14** (370.2 mg, 0.0031%). Subfraction B_4 (86 g) was chromatographed over a RP silica gel column, eluting with a gradient of EtOH (0−100%) in H_2O, to yield subfractions B_4-1−B_4-7, of which subfraction B_4-7 (1.4 g) was further separated by flash chromatography over RP silica gel, eluting with a gradient of MeOH (0−50%) in H_2O to give subfractions (B_4-7-1−B_4-7-4). B_4-7-3 (76 mg) and B_4-7-4 (108 mg) were separately subjected to RP-HPLC,

for B_4-7-3 using CH_3OH-H_2O (1:1) containing 0.5% HOAc as the mobile phase, to afford **1** (5 mg, 0.000042%) and **2** (22 mg, 0.00018%), and for B_4-7-4 using CH_3OH-H_2O (6:4) with 0.1% HOAc as the mobile phase, to afford **3** (16 mg, 0.00013%) and **4** (4.5 mg, 0.000038%).

Loniphenyruviridoside A (***1***): white, amorphous powder; $[\alpha]^{20}_D$ −72.1 (*c* 0.14, MeOH); UV (MeOH) λ_{max} (log ε) 202 (4.42), 220 (4.13, sh), 274 (3.71, sh) nm; CD (MeOH) 244 ($\Delta\varepsilon$ −8.59), 272 ($\Delta\varepsilon$ +6.91); IR (KBr) ν_{max} 3330, 2921, 2851, 1732, 1641, 1588, 1499, 1402, 1277, 1195, 1156, 1063, 985, 930, 761, 698 cm^{-1}; ^1H NMR (methanol-d_4, 600 MHz), see Table 1; ^{13}C NMR (methanol-d_4, 125 MHz), see Table 1; negative ESIMS *m/z* 475 $[M - H]^-$; negative HR-ESIMS *m/z* 475.1603 $[M - H]^-$ (calcd for $C_{24}H_{27}O_{10}$, 475.1610).

Loniphenyruviridoside B (***2***): white, amorphous powder; $[\alpha]^{20}_D$ −50.2 (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ε) 202 (4.42), 220 (4.09, sh), 284 (3.86) nm; CD (MeOH) 232 ($\Delta\varepsilon$ − 8.26), 281 ($\Delta\varepsilon$ + 8.93); IR (KBr) ν_{max} 3361, 2920, 2850, 1740, 1678, 1635, 1541, 1500, 1395, 1307, 1279, 1163, 1074, 1020, 927, 882, 768, 696 cm^{-1}; ^1H NMR (methanol-d_4, 600 MHz), see Table 1; ^{13}C NMR (methanol-d_4, 125 MHz), see Table 1; negative ESIMS *m/z* 519 $[M - H]^-$; negative HR-ESIMS *m/z* 519.1490 $[M - H]^-$ (calcd for $C_{25}H_{27}O_{12}$, 519.1508).

Loniphenyruviridoside C (***3***): white, amorphous powder; $[\alpha]^{20}_D$ −52 (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ε) 202 (4.48), 220 (4.22, sh), 284 (4.12) nm; CD (MeOH) 214 ($\Delta\varepsilon$ −10.45), 244 ($\Delta\varepsilon$ +2.06), 282 ($\Delta\varepsilon$ −17.15); IR (KBr) ν_{max} 3329, 2920, 2852, 1741, 1676, 1628, 1541, 1499, 1395, 1311, 1281, 1158, 1073, 940, 873, 766, 695 cm^{-1}; ^1H NMR (methanol-d_4, 600 MHz), see Table 1; ^{13}C NMR (methanol-d_4, 125 MHz), see Table 1; negative ESIMS *m/z* 519 $[M - H]^-$; positive HR-ESIMS *m/z* 521.1664 $[M + H]^+$ (calcd for $C_{25}H_{29}O_{12}$, 521.1654).

Loniphenyruviridoside D (***4***): white, amorphous powder; $[\alpha]^{20}_D$ −209.5 (*c* 0.4, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.52), 220 (4.19, sh), 283 (3.89) nm; CD (MeOH) 211 ($\Delta\varepsilon$ −9.85), 244 ($\Delta\varepsilon$ + 1.16), 282 ($\Delta\varepsilon$ +11.81); IR (KBr) ν_{max} 3337, 2955, 2919, 2851, 1737, 1642, 1598, 1548, 1499, 1396, 1073, 1019, 927, 883, 771, 721, 699 cm^{-1}; ^1H NMR (methanol-d_4, 600 MHz), see Table 1; ^{13}C NMR (methanol-d_4, 125 MHz), see Table 1; negative ESIMS *m/z* 519 $[M - H]^-$; positive HR-ESIMS *m/z* 521.1652 $[M + H]^+$ (calcd for $C_{25}H_{29}O_{12}$, 521.1654).

Lonijaposide D (***5***): beige, amorphous solid; $[\alpha]^{20}_D$ −117.2 (*c* 0.05, H_2O); UV (H_2O) λ_{max} (log ε) 205 (4.23, sh) nm, 230 (3.97, sh) nm, 264 (3.74, sh) nm, 307(3.42, sh) nm; CD (H_2O) 201 ($\Delta\varepsilon$ −4.59), 212 ($\Delta\varepsilon$ −1.73), 226 ($\Delta\varepsilon$ −3.91), 244 ($\Delta\varepsilon$ −1.95), 265 ($\Delta\varepsilon$ −3.02); IR (KBr) ν_{max} 3383, 2958, 2918, 2851, 1728, 1598, 1543, 1360, 1288, 1121, 1074, 1041, 833, 796, 742, 611 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; ^{13}C NMR (D_2O, 150 MHz) data, see Table 3; positive ESIMS *m/z* 566 $[M + H]^+$; negative ESIMS *m/z* 564 $[M - H]^-$; positive HR-ESIMS *m/z* 566.1862 $[M + H]^+$ (calcd for $C_{26}H_{32}NO_{13}$, 566.1868).

Lonijaposide E (***6***): beige, amorphous solid; $[\alpha]^{20}_D$ −169.2 (*c* 0.2, H_2O); UV (H_2O) λ_{max} (log ε) 207 (4.41, sh) nm, 231 (4.34, sh) nm, 261 (4.19, sh) nm, 306 (3.67) nm; CD (H_2O) 197 ($\Delta\varepsilon$ −2.17), 205 ($\Delta\varepsilon$ −0.54), 215 ($\Delta\varepsilon$ −0.38), 229 ($\Delta\varepsilon$ −2.39), 240 ($\Delta\varepsilon$ −2.11), 267 ($\Delta\varepsilon$ −6.13); IR (KBr) ν_{max} 3363, 2922, 1700, 1638, 1612, 1592, 1437, 1385, 1303, 1261, 1165, 1076, 1046, 938, 894, 788, 770, 681 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; positive ESIMS *m/z* 522 $[M + H]^+$, 544 $[M + Na]^+$, and 560 $[M + K]^+$; negative ESIMS *m/z* 520 $[M - H]^-$, 556 $[M + Cl]^-$; positive HR-ESIMS *m/z* 522.1978 $[M + H]^+$ (calcd for $C_{25}H_{32}NO_{11}$, 522.1970).

Lonijaposide F (***7***): beige, amorphous solid; $[\alpha]^{20}_D$ −105.4 (*c* 0.04, H_2O); UV (H_2O) λ_{max} (log ε) 229 (4.03, sh), 263 (3.82), 305 (3.54) nm; CD (H_2O) 197 ($\Delta\varepsilon$ −1.63), 212 ($\Delta\varepsilon$ −0.47), 225 ($\Delta\varepsilon$ −1.04), 246 ($\Delta\varepsilon$ −0.21), 269 ($\Delta\varepsilon$ −1.07); IR (KBr) ν_{max} 3397, 2958, 2917, 2851, 1731, 1578, 1542, 1512, 1469, 1423, 1381, 1288, 1262, 1199, 1183, 1118, 1074, 1028, 802, 742, 718 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; negative ESIMS *m/z* 506 $[M - H]^-$; positive HR-ESIMS *m/z* 508.1816 $[M + H]^+$ (calcd for $C_{24}H_{30}NO_{11}$, 508.1813).

Lonijaposide G (***8***): beige, amorphous solid; $[\alpha]^{20}_D$ −103.4 (*c* 0.04, H_2O); UV (H_2O) λ_{max} (log ε) 205 (4.12, sh), 230 (3.97, sh), 261 (3.81, sh), 3.06 (3.41) nm; CD (H_2O) 196 ($\Delta\varepsilon$ −0.75), 213 ($\Delta\varepsilon$ + 0.04), 227 ($\Delta\varepsilon$ −0.80), 238 ($\Delta\varepsilon$ −0.57), 247 ($\Delta\varepsilon$ −0.65), 266 ($\Delta\varepsilon$ −1.71); IR (KBr) ν_{max} 3391, 2959, 2922, 2852, 1730, 1668, 1577, 1543, 1465, 1420, 1381, 1264, 1121, 1073, 1038, 958, 863, 801, 743, 704 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; positive ESIMS *m/z* 530 $[M + Na]^+$; positive HR-ESIMS *m/z* 508.1812 $[M + H]^+$ (calcd for $C_{24}H_{30}NO_{11}$, 508.1813).

Lonijaposide H (***9***): beige, amorphous solid; $[\alpha]^{20}_D$ −140 (*c* 0.1, H_2O); UV (H_2O) λ_{max} (log ε) 193 (4.57), 210 (4.27, sh), 265 (4.03) nm; CD (H_2O) 200 ($\Delta\varepsilon$ −2.74), 206 ($\Delta\varepsilon$ −2.58), 213 ($\Delta\varepsilon$ −3.05), 227 ($\Delta\varepsilon$ −0.92), 239 ($\Delta\varepsilon$ −0.89), 247 ($\Delta\varepsilon$ −1.16), 277 ($\Delta\varepsilon$ + 1.21), 308 ($\Delta\varepsilon$ + 0.21); IR (KBr) ν_{max} 3420, 2128, 1644, 1564, 1414, 1299, 1077, 1020, 932, 657 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; negative ESIMS *m/z* 578 $[M - H]^-$; positive HR-ESIMS *m/z* 580.2039 $[M + H]^+$ (calcd for $C_{27}H_{34}NO_{13}$, 580.2025).

Lonijaposide I (***10***): beige, amorphous solid; $[\alpha]^{20}_D$ −237.2 (*c* 0.05, H_2O); UV (H_2O) λ_{max} (log ε) 227 (4.18), 252 (3.95, sh), 302 (3.54) nm; CD (H_2O) 197 ($\Delta\varepsilon$ −2.15), 215 ($\Delta\varepsilon$ −0.80), 228 ($\Delta\varepsilon$ −1.70), 243 ($\Delta\varepsilon$ −0.77), 265 ($\Delta\varepsilon$ −2.72); IR (KBr) ν_{max} 3349, 2928, 1643, 1538, 1412, 1346, 1189, 1160, 1075, 1045, 1022, 951, 796, 659, 617 cm^{-1}; ^1H NMR (D_2O, 500 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; positive ESIMS *m/z* 480 $[M + H]^+$, 502 $[M + Na]^+$; negative ESIMS *m/z* 478 $[M - H]^-$; positive HR-ESIMS *m/z* 480.1873 $[M + H]^+$ (calcd for $C_{23}H_{30}NO_{10}$, 480.1864).

Lonijaposide J (***11***): beige, amorphous solid; $[\alpha]^{20}_D$ −219.2 (*c* 0.05, H_2O); UV (H_2O) λ_{max} (log ε) 229 (4.08), 252 (3.93, sh), 299 (3.46) nm; CD (H_2O) 206 ($\Delta\varepsilon$ + 0.01), 221 ($\Delta\varepsilon$ −1.91), 235 ($\Delta\varepsilon$ −5.64), 244 ($\Delta\varepsilon$ −4.36), 260 ($\Delta\varepsilon$ −11.63); IR (KBr) ν_{max} 3352, 2920, 2851, 1691, 1631, 1567, 1414, 1306, 1253, 1200, 1164, 1076, 1045, 947, 771, 720, 656, 621 cm^{-1}; ^1H NMR (D_2O, 500 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; positive ESIMS *m/z* 494 $[M - Cl]^+$; negative ESIMS *m/z* 528/530/532 (3:2:1) $[M - H]^-$; positive HR-ESIMS *m/z* 494.2029 $[M - Cl]^+$ (calcd for $C_{24}H_{32}NO_{10}$, 494.2021).

Lonijaposide K (***12***): beige, amorphous solid; $[\alpha]^{20}_D$ −81 (*c* 0.32, H_2O); UV (H_2O) λ_{max} (log ε) 230 (4.15), 257 (3.93), 299 (3.39) nm; IR (KBr) ν_{max} 3360, 2925, 1636, 1546, 1507, 1381, 1190, 1162, 1074, 1042, 942, 795, 716, 670, 613 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; ^{13}C NMR (D_2O, 150 MHz) data, see Table 3; positive ESIMS *m/z* 494 $[M + H]^+$; positive HR-ESIMS *m/z* 494.1675 $[M + H]^+$ (calcd for $C_{23}H_{28}NO_{11}$, 494.1662).

Lonijaposide L (***13***): beige, amorphous solid; $[\alpha]^{20}_D$ −68 (*c* 0.47, H_2O); UV (H_2O) λ_{max} (log ε) 226 (3.85), 257 (3.61), 299 (3.09) nm; IR (KBr) ν_{max} 3366, 2955, 2199, 2164, 2094, 1641, 1562, 1411, 1248, 1162, 1103, 1073, 952, 929, 840, 802, 687, 652, 619 cm^{-1}; ^1H NMR (D_2O, 500 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; positive ESIMS *m/z* 508 $[M + H]^+$; negative ESIMS *m/z* 506 $[M - H]^-$, 542 $[M + Cl]^-$; positive HR-ESIMS *m/z* 508.1819 (calcd for $C_{24}H_{30}NO_{11}$, 508.1819).

Lonijaposide M (***14***): beige, amorphous solid; $[\alpha]^{20}_D$ −169 (*c* 0.24, H_2O); UV (H_2O) λ_{max} (log ε) 227 (4.26), 257 (4.04), 296 (3.53) nm; IR (KBr) ν_{max} 3408, 2936, 1643, 1560, 1401, 1188, 1159, 1075, 1042, 941, 800, 683 cm^{-1}; ^1H NMR (D_2O, 500 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; positive ESIMS *m/z* 522 $[M + H]^+$, 544 $[M + Na]^+$; negative ESIMS *m/z* 520 $[M - H]^-$; positive HR-ESIMS *m/z* 522.1958 $[M + H]^+$ (calcd for $C_{25}H_{32}NO_{11}$, 522.1975).

Lonijaposide N (***15***): beige, amorphous solid; $[\alpha]^{20}_D$ −218.4 (*c* 0.25, H_2O); UV (H_2O) λ_{max} (log ε) 229 (4.50), 250 (4.35, sh), 300 (3.78, sh) nm; CD (H_2O) 207 ($\Delta\varepsilon$ −0.40), 219 ($\Delta\varepsilon$ −1.21), 235 ($\Delta\varepsilon$ −3.73), 244 ($\Delta\varepsilon$ −2.75), 263 ($\Delta\varepsilon$ −8.81); IR (KBr) ν_{max} 3386, 2920, 1701, 1632, 1574, 1507, 1439, 1400, 1304, 1249, 1199, 1162, 1077, 1047, 938,

891, 822, 795, 771, 686, 637 cm^{-1}; ^1H NMR (D_2O, 600 MHz) data, see Table 2; ^{13}C NMR (D_2O, 125 MHz) data, see Table 3; positive ESIMS m/z 536 $[M + H]^+$; negative ESIMS m/z 534 $[M - H]^-$; positive HR-ESIMS m/z 536.2137 $[M + H]^+$ (calcd for $C_{26}H_{34}NO_{11}$, 536.2126).

Enzymatic Hydrolysis of Compound ***1***. A solution of compound **1** (3 mg) in H_2O (1 mL) was treated with β-glucosidase from almonds (Fluka) (5 mg) at 37 °C for 24 h. The reaction mixture was extracted with EtOAc (2 × 3 mL). The aqueous phase of the hydrolysate was dried using a stream of N_2 and then subjected to column chromatography over silica gel, eluting with CH_3CN-H_2O (8:1) to yield glucose (0.6 mg). It gave a positive specific rotation, $[\alpha]^{20}_D$ +41.1 (*c* 0.06, H_2O). The solvent system CH_3CN-H_2O (6:1) was used for TLC identification of glucose (R_f = 0.34).

X-ray Crystallography of Secologanic Acid. $C_{16}H_{22}O_{10}$, M = 374.34, orthorhombic, $P2_12_12_1$, a = 8.460(2) Å, b = 11.033(1) Å, c = 18.202(1) Å, $\alpha = \beta = \gamma = 90°$, V = 1699.0(1) $Å^3$, Z = 4, D_{calcd} = 1.463 g cm^{-3}, 2966 reflections independent, R = 0.0682, wR_2 = 0.1612, S = 1.043.

The data were collected on a MACDIP-2030K diffractometer with Cu Kα radiation by using the ω and κ scan technique to a maximum 2θ value of 141.74°. The crystal structures were solved by direct methods by using SHELXS-97, and all non-hydrogen atoms were refined anisotropically using the least-squares method. All hydrogen atoms were positioned by geometric calculation and difference Fourier overlapping calculation. The absolute configuration was determined on the basis of the Flack parameter, 0.2(4). Crystallographic data for the structure of secologanic acid have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 786003. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Methylation of Compounds ***2*** *and* ***3***. To a solution of **2** (3 mg) or **3** (4 mg) in anhydrous MeOH (5 mL) were added EDCI (5 mg) and DMAP (2.5 mg). After the solution was stirred for 20 min at rt, H_2O (5 mL) was added and evaporated under reduced pressure to give a residue. The residue was subjected to RP-HPLC, using CH_3CN-H_2O (3:10) containing 1% HOAc as the mobile phase, to afford **2a** (1.9 mg) from **2** and **3a** (2.3 mg) from **3**, respectively. **2a**: white, amorphous powder; ^1H NMR (methanol-d_4, 600 MHz) and ^{13}C NMR (methanol-d_4, 150 MHz), see Table 1. **3a**: white, amorphous powder; ^1H NMR (methanol-d_4, 600 MHz) and ^{13}C NMR (methanol-d_4, 150 MHz) data, see Table 1.

Semisynthesis of Compounds ***2*** *and* ***3***. A solution of secologanic acid (30 mg) and phenylpyruvic acid (20 mg) in $CH_3CN-C_5H_5N$ (9:1, 10 mL) was stirred under reflux while monitored by TLC and HPLC-DAD. After refluxing for 96 h, the solution was evaporated under reduced pressure to give a residue, which was dissolved in 1 mL of 50% aqueous CH_3CN and separated by RP semipreparative HPLC using 30% aqueous CH_3CN containing 0.5% HOAc as the mobile phase to yield **S2** (1.4 mg) and **S3** (1.6 mg), respectively, while secologanic acid (16.2 mg) was recovered. The ESIMS, NMR, and CD data of **S2** and **S3** were identical to those of the natural products **2** and **3**, respectively (Supporting Information, Figures S30−S33 and S49−S52).

Alkaline Hydrolysis of Lonijaposide A, Secologanic Acid, and Compounds ***6*** *and* ***15***. Lonijaposide A, secologanic acid, and compounds **6** and **15** (0.2−1.0 mg) were dissolved separately in H_2O (0.5 mL), NaOH(aq) (0.5 mL, 1.0 mol/L) was added to each, and the mixture was stirred at rt for 24 h. The reaction solutions were neutralized with HCl(aq) (1.0 mol/L) and evaporated separately under reduced pressure to dryness. TLC indicated production of compound **5** from lonijaposide A [$CHCl_3$−MeOH (1:1), R_f = 0.4], secologanoside from secologanic acid [$CHCl_3$−MeOH (4:1), R_f = 0.5], compound **7** from **6** [$CHCl_3$−MeOH (8:5), R_f = 0.4], and **14** from **15** [$CHCl_3$−MeOH (7:5), R_f = 0.4].

STAT-3 Reporter Activity Assay (ref 21*).* Human embryonic lung fibroblast (HELF) cells were grown in DMEM supplemented with 10% FCS and maintained in a 5% CO_2 humidified atmosphere. The cells were transfected with pSTAT-3-TA-luc luciferase reporter plasmid by lipofectamine 2000 reagent according to previous reports. After 24 h, the cells were treated in 5% FBS with chemicals at varying concentrations or DMSO for 24 h. The STAT-3 luciferase activity was measured in cell lysates by a microplate luminometer using the firefly luciferase assay kit (Promega, Madison, WI, USA). The STAT-3 inhibition activity of the treated cells is reported relative to pSTAT-3-TA-luc transfected cells treated with DMSO arbitrarily set at 100%.

Anti-inflammatory Activity Assay. See refs 6 and 17.

Cells, Culture Conditions, and Cell Proliferation Assay. See ref 18.

Neuroprotective Activity Assay. See ref 19.

Antioxidative and PTP1B Inhibition Assays. See ref 20.

HIV-1 Replication Inhibition Assay. See ref 21.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Copies of UV, IR, MS, 1D and 2D NMR, and CD spectra for compounds **1**−**15**; copies of spectra of **2a**, **3a**, **S2**, and **S3**; X-ray crystallographic data of secologanic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Jiangsu New Medical College. *Dictionary of Traditional Chinese Medicine*; Shanghai Science and Technology Publishing House: Shanghai, 1977; pp 1403−1405. (b) Xu, Y. B.; Oliverson, B. G.; Simmons, D. L. *J. Ethnopharmacol.* **2007**, *111*, 667–670. (c) Yoo, H. J.; Kang, H. J.; Song, Y. S.; Park, E. H.; Lim, C. J. *J. Pharm. Pharmacol.* **2008**, *60*, 779–786.

(2) (a) Wang, Y.; Wang, Z. M.; Lin, L. M.; Gao, H. M.; Liu, T. S. *Zhongguo Zhongyao Zazhi* **2008**, *38*, 968–972. (b) Ma, S. C.; Liu, Y.; Bi, P. X.; Yang, Y.; Huang, R. C.; Lee, S. H.; Lee, S. F.; Lu, J.; Lin, R. C. *Yaowu Fenxi Zazhi* **2006**, *26*, 1039–1042.

(3) (a) Teng, R. W.; Wang, D. Z.; Chen, C. X. *Chin. Chem. Lett.* **2000**, *11*, 337–340. (b) Kakuda, R.; Imai, M.; Yaoita, Y.; Machida, K.; Kikuchi, M. *Phytochemistry* **2000**, *55*, 879–881. (c) Kumar, N.; Singh, B.; Bhandari, P.; Gupta, A. P.; Uniyal, S. K.; Kaul, V. K. *Phytochemistry* **2005**, *66*, 2740–2744. (d) Kumar, N.; Singh, B.; Gupta, A. P.; Kaul, V. K. *Tetrahedron* **2006**, *62*, 4317–4322. (e) Bi, Y. F.; Tian, Y.; Pei, S. S.; Liu, H. M. *Chin. Tradit. Herb. Drugs* **2008**, *39*, 18–21.

(4) (a) Yu, D. Q.; Chen, R. Y.; Huang, L. J.; Xie, F. Z.; Ming, D. S.; Zhou, K.; Li, H. Y.; Tong, K. M. *J. Asian Nat. Prod. Res.* **2008**, *10*, 851–856. (b) Lin, L. M.; Zhang, X. G.; Zhu, J. J.; Gao, H. M.; Wang, Z. M.; Wang, W. H. *J. Asian Nat. Prod. Res.* **2008**, *10*, 925–929. (c) Lee, E. J.; Lee, J. Y.; Kim, J. S.; Kang, S. S. *Nat. Prod. Sci.* **2010**, *16*, 32–38.

(5) Wang, S. J.; Lin, S.; Zhu, C. G.; Yang, Y. C.; Li, S.; Zhang, J. J.; Chen, X. G.; Shi, J. G. *Org. Lett.* **2010**, *12*, 1560–1563.

(6) Song, W. X.; Li, S.; Wang, S. J.; Wu, Y.; Zi, J. C.; Gan, M. L.; Zhang, Y. L.; Liu, M. T.; Lin, S.; Yang, Y. C.; Shi, J. G. *J. Nat. Prod.* **2008**, *71*, 922–925.
(7) Hudson, C. S.; Dale, J. K. *J. Am. Chem. Soc.* **1917**, *39*, 320–328.
(8) Legrand, M.; Rougier, M. J. In *Stereochemistry Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. 2, Chapter 3, pp 86−89.
(9) (a) Snatzke, G. *Pure Appl. Chem.* **1979**, *51*, 769–785. (b) Ferreira, D.; Marais, J. P. J.; Slade, D.; Walker, L. A. *J. Nat. Prod.* **2004**, *67*, 174–178.
(10) Legrand, M.; Rougier, M. J. In *Stereochemistry Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. 2, Chapter 4, pp 130−135.
(11) Hanai, K.; Kuwae, A.; Kawai, S.; Ono, Y. *J. Phys. Chem.* **1989**, *93*, 6013–6016.
(12) Ross, S. A.; Sultana, G. N. N.; Burandt, C. L.; EISohly, M. A.; Marais, J. P. J.; Ferreira, D. *J. Nat. Prod.* **2004**, *67*, 88–90.
(13) (a) Masaki, N.; Hirabayashi, M.; Fuji, K.; Osaki, K.; Inouye, H. *Tetrahedron Lett.* **1967**, *8*, 2367–2370. (b) Inouye, H.; Yoshida, T.; Tobita, S. *Tetrahedron Lett.* **1968**, *9*, 2945–2950. (c) Inouye, H.; Yoshida, T.; Nakamura, Y.; Tobita, S. *Tetrahedron Lett.* **1968**, *9*, 4429–4432. (d) Battersby, A. R.; Hall, E. S.; Southgate, R. *J. Chem. Soc. C* **1969**, 721–728. (e) Souzu, I.; Mitsuhashi, H. *Tetrahedron Lett.* **1970**, *11*, 191–192. (f) Inouye, H.; Yoshida, T.; Tobita, S.; Tanaka, K.; Nishioka, T. *Tetrahedron Lett.* **1970**, *11*, 2459–2464. (g) Büchi, G.; Carlson, J. A.; Powell, J. E., Jr.; Tietze, L. F. *J. Am. Chem. Soc.* **1973**, *95*, 540–545. (h) Bianco, A.; Passacantilli, P. *Phytochemistry* **1981**, *20*, 1873–1876.
(14) (a) Plouvier, V.; Favre-Bonvin, J. *Phytochemistry* **1971**, *10*, 1697–1722. (b) El-Naggar, L. J.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 649–707. (c) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1990**, *53*, 1055–1147. (d) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1173–1246.
(15) (a) Itoh, A.; Oya, N.; Kawaguchi, E.; Nishio, S.; Tanaka, Y.; Kawachi, E.; Akita, T.; Nishi, T.; Tanahashi, T. *J. Nat. Prod.* **2005**, *68*, 1434–1436. (b) Tietze, L. F.; Bärtels, C. *Liebigs Ann. Chem.* **1991**, 155–160.
(16) Yoshiyuki, M.; Masako, S.; Shigeru, T.; Lkuya, T.; Hidetoshi, T.; Hajime, K. *Nature* **2007**, *448*, 1058–1063.
(17) Nie, Z. G.; Wang, W. J. *Acta Pharm. Sin.* **2003**, *38*, 98–102.
(18) Mo, S. Y.; Wang, S. J.; Zhou, G. X.; Yang, Y. C.; Li, Y.; Chen, X. G.; Shi, J. G. *J. Nat. Prod.* **2004**, *67*, 823–828.
(19) Gan, M. L.; Zhang, Y. L.; Lin, S.; Liu, M. T.; Song, W. X.; Zi, J. C.; Yang, Y. C.; Fan, X. N.; Shi, J. G.; Hu, J. F.; Sun, J. D.; Chen, N. H. *J. Nat. Prod.* **2008**, *71*, 647–654.
(20) Wang, Y.; Shang, X. Y.; Wang, S. J.; Mo, S. Y.; Li, S.; Yang, Y. C.; Ye, F.; Shi, J. G.; He, L. *J. Nat. Prod.* **2007**, *70*, 296–299.
(21) Fan, X. N.; Zi, J. C.; Zhu, C. G.; Xu, W. D.; Cheng, W.; Yang, S.; Guo, Y.; Shi, J. G. *J. Nat. Prod.* **2009**, *72*, 1184–1190.