Structural Elucidation and Chemical Conversion of Amorphispironone, a Novel Spironone from *Amorpha fruticosa*, to Rotenoids¹⁾

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To search for possible antitumor promoters, we carried out an investigation of the leaves of *Amorpha fruticosa* L. (Leguminosae). The novel spironone type rotenoid, amorphispironone (1), was isolated together with four known rotenoids, tephrosin (2), amorphigenin (3), 12a-hydroxyamorphigenin (4) and 12a-hydroxydalpanol (5). Some of these compounds were inhibitors of Epstein-Barr virus early antigen activation induced by 12-*O*-tetradecanoylphorbol-13-acetate. The structure of 1 was determined from 2D-NMR spectral data and difference NOE experiments. Amorphispironone (1) was also converted to known rotenoids in order to confirm the proposed structure.

Keywords *Amorpha fruticosa*; amorphispironone; rotenoid; Leguminosae; tephrosin; deguelin

In a primary random screening of many plants, the leaves of *Amorpha fruticosa* showed strong inhibitory activity on Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), a well-known tumor promoter.¹⁾ The crude extracts of *A. fruticosa* have also been shown to exhibit feeding deterrence along with insecticidal, antiparasitic, antimicrobial and hypotensive activities.²⁾ In addition, a plant of the same genus has traditionally been used by the American Indian as an anthelmintic, antirheumatic and analgesic for stomach pain.³⁾

Many rotenoids have been isolated from the fruit and root bark of this native North American plant.⁴⁾ In a preliminary communication, we reported that amorphispironone (1), isolated from the leaves of *A. fruticosa*, is a novel cytotoxic spironone type rotenoid.⁵⁾ In this paper, a detailed structural elucidation of amorphispironone (1) is described. Further, the chemical conversion of amorphispironone (1) to known rotenoids was performed to support this structural assignment and to suggest the biogenetic relationship of

these rotenoids.

Results and Discussion

Five rotenoids (1–5) were isolated from the leaves of *Amorpha fruticosa* using various chromatographic techniques. We identified compounds 2–5 as tephrosin (2), amorphigenin (3), 12a-hydroxyamorphigenin (4) and 12a-hydroxydalpanol (5) by comparison with reported UV, IR and ¹H-NMR spectral data.⁶⁾

The general features of the NMR spectral data also suggested a rotenoid structure for compound 1. Comparison of ¹H-NMR spectral data of 1 and deguelin (11), a compound with a typical rotenoid skeleton, showed that the C–D–E ring protons were similar but the A–B ring protons were different.⁷⁾ These data suggested that 1 was a rotenoid, structurally similar to deguelin (11) but differing in the A–B ring region. The molecular formula of 1 was determined to be C₂₃H₂₂O₇ from its high-resolution mass spectrum (HRMS). The IR spectrum (1665, 1640, 1625 cm⁻¹) and the UV spectrum (269 nm, ε: 31900)

TABLE I. ¹H-NMR Spectral Data of 1, 2, 8–12

	1	11	8	12	9	2	10
1-H	5.02 s	6.79 s	6.84 s	8.44 s	8.37 s	6.56 s	6.66 s
4-H	5.51 s	6.46 s	6.43 s	6.54 s	6.52 s	6.49 s	6.47 s
6-H	β 4.49 dd (J=10.3, 2.7)	β 4.64 dd (J=12.0, 3.1)	β 4.62 dd (J=12.1, 3.0)	5.01 s	4.97 s	β 4.64 dd (J=12.0, 2.4)	β 4.62 dd (J=12.1, 2.3)
	α 4.64 d (J=10.3)	α 4.19 d (J=12.0)	α 4.18 d (J=12.1)			α 4.49 d (J=12.0)	α 4.49 d (J=12.1)
6a-H	5.27 dd (J=4.5, 2.7)	4.92 m	4.90 m			4.57 d (J=2.4)	4.55 d (J=2.3)
12a-H	3.44 d (J=4.5)	3.84 d (J=4.1)	3.81 br d				
10-H	6.49 d (J=8.7)	6.46 d (J=8.7)	6.44 d (J=8.8)	6.85 d (J=8.8)	6.84 d (J=8.8)	6.47 d (J=8.7)	6.46 d (J=8.8)
11-H	7.66 d (J=8.7)	7.75 d (J=8.7)	7.74 d (J=8.8)	8.03 d (J=8.8)	8.04 d (J=8.8)	7.73 d (J=8.7)	7.71 d (J=8.8)
4'-H	6.67 d (J=10.1)	6.65 d (J=10.0)	6.64 d (J=10.1)	6.76 d (J=10.3)	6.75 d (J=10.0)	6.59 d (J=10.1)	6.59 d (J=10.1)
5'-H	5.64 d (J=10.1)	5.56 d (J=10.0)	5.55 d (J=10.1)	5.71 d (J=10.3)	5.70 d (J=10.0)	5.56 d (J=10.1)	5.55 d (J=10.1)
7'-H	1.44 s ^{a)}	1.39 s ^{a)}	1.38 s ^{a)}	1.48 s	1.48 s	1.39 s ^{a)}	1.38 s ^{a)}
8'-H	1.47 s ^{a)}	1.46 s ^{a)}	1.45 s ^{a)}	1.48 s	1.48 s	1.45 s ^{a)}	1.44 s ^{a)}
OCH ₃	3.24 s, 3.83 s	3.77 s, 3.81 s	3.81 s	3.86 s, 3.94 s	3.86 s	3.73 s, 3.82 s	3.82 s

a) Assignments with the same superscripts in each column may be interchangeable.

suggested the presence of a conjugated carbonyl group in addition to the normal rotenoid skeleton. In addition, a distortionless enhancement by polarization transfer (DEPT) experiment indicated the presence of four methyl carbons, one methylene carbon, eight methine carbons, eight quaternary carbons and two ketones. A detailed structural elucidation of **1** was carried out using two dimensional (2D)-NMR spectral data and difference nuclear Overhauser effect (NOE) experiments; discussion of this data follows.

All proton and carbon signals of **1** could be assigned using ^1H - ^1H correlation spectroscopy (COSY), DEPT experiments, ^1H - ^{13}C COSY and ^1H - ^{13}C long range COSY spectral data, and they are listed in Tables I and II. The ^1H - ^{13}C long range COSY of **1** was measured in order to confirm the connectivities of the partial structure. The significant long range ^1H - ^{13}C correlations are indicated by

TABLE II. ^{13}C -NMR Spectral Data of **1**, **2**, **8**-**12**

	1	11	8	12	9	2	10
C-1a	84.12	104.77	105.95	110.56	111.46	108.64	109.89
C-1	105.53	110.43	113.15	110.01	113.10	109.40	112.10
C-2	148.35	143.88	140.12	144.12	140.58	143.97	140.11
C-3	166.25	149.48	146.76 ^{a)}	148.98	145.83 ^{a)}	151.12	147.64 ^{a)}
C-4	99.86	100.94	100.15	100.42	99.83	101.10	100.33
C-4a	198.84	147.43	146.88 ^{a)}	146.29	146.36 ^{a)}	148.40	148.41 ^{a)}
C-6	76.03	66.31	66.32	64.89	64.91	63.87	63.85
C-6a	82.74	72.45	72.37	156.18	156.33	76.27	76.18
C-12a	60.15	44.40	44.40	118.51	118.58	67.46	67.35
C-7a	156.33	157.32	156.80	151.11	151.06	156.67	156.56
C-8	109.42	109.14	109.07	109.12	109.06	109.14	109.08
C-9	160.14	160.13	159.96	157.24	157.15	160.76	160.64
C-10	111.72	111.49	111.42	114.72	114.77	111.89	111.84
C-11	127.60	128.57	128.63	126.52	126.78	128.56	128.67
C-11a	114.51	112.76	112.74	111.79	111.83	111.12	111.14
C-12	185.99	189.25	188.91	174.37	174.04	191.38	191.07
C-4'	115.66	115.77	115.81	115.43	115.29	115.42	115.47
C-5'	129.25	128.68	128.63	130.59	130.52	128.83	128.79
C-6'	77.76	77.71	77.62	77.80	77.72	78.01	77.93
C-7'	28.00 ^{a)}	28.17 ^{a)}	28.16 ^{b)}	28.14	28.12	28.30 ^{a)}	28.29 ^{b)}
C-8'	28.26 ^{a)}	28.51 ^{a)}	28.48 ^{b)}	28.14	28.12	28.54 ^{a)}	28.52 ^{b)}
OCH_3	55.14	55.86	55.92	55.95	56.01	55.87	55.92
	56.73	56.33		56.31		56.37	

a, b) Assignments with the same superscripts in each column may be interchangeable.

arrows in Fig. 1. The quaternary carbon at δ 77.76 (C-6') is correlated with the methyl protons at δ 1.44 and δ 1.47 (H-7' and H-8') and with the olefinic proton at δ 6.67 (H-4'). The quaternary carbon at δ 84.12 (C-1a) is correlated with one of the methylene protons at δ 4.64 (H-6 α), the methine protons at δ 5.27 (H-6a) and δ 3.44 (H-12a) and with the olefinic proton at δ 5.51 (H-4). The quaternary carbon at δ 148.35 (C-2) is correlated with the methoxy protons at δ

Fig. 1. Correlation ($^{13}\text{C} \rightarrow ^1\text{H}$) in ^1H - ^{13}C Long-Range COSY Spectrum of Amorphispironone (**1**)

Fig. 2. Significant Enhancement of Signal Intensity by Difference NOE Experiments of Amorphispironone (**1**)

Chart 1. Structures of Rotenoids isolated from the Leaves of *A. fruticosa*

3.24 (2-OMe) and the olefinic proton at δ 5.51 (H-4). The quaternary carbon at δ 166.25 (C-3) is correlated with the methoxy protons at δ 3.83 (3-OMe) and the olefinic proton at δ 5.02 (H-1). The carbonyl carbon at δ 198.84 (C-4a) is correlated with the methine proton at δ 3.44 (H-12a) and the olefinic proton at δ 5.02 (H-1).

Further, difference NOE spectra of **1** were measured in order to confirm the relative stereochemistry of the ring systems. Some significant NOE results are indicated by arrows in Fig. 2. Irradiation at δ 5.27 (H-6a) enhanced the signal intensities of the H-12a methine proton at δ 3.44 and one of the methylene protons (H-6 β) at δ 4.49. Correspondingly, irradiation both at δ 4.49 (H-6 β) and at δ 3.44 (H-12a) enhanced the signal intensity of the H-6a methine proton at δ 5.27. Therefore, we confirmed that the stereochemical conformation of the B-C ring was *cis*-type. From these and the preceding results, the structure of the new compound isolated from *Amorpha fruticosa*, amorphispiro-1, was proposed to be a spiro-1,2-dione type rotenoid as shown by Chart 1.

To support the structural assignment of amorphispiro-1, we then tried to chemically convert this spiro-1,2-dione type rotenoid into a typical rotenoid ring system. The first attempted chemical conversion was through the reduction of **1** followed by treatment with acid. However, reduction with NaBH₄ gave a triol (**6**) accompanied by the cleavage of ring B. The structure of **6** was deduced from the spectral data of its triacetate (**7**). We next tried to recycle ring B directly using organic acid. On treatment of **1** with *p*-toluenesulfonic acid in toluene, compounds **8**, **9** and **10** were obtained. Their ¹H- and ¹³C-NMR spectral data

showed that these compounds were recycled and demethylated derivatives.^{7b,8)} Compounds **8** and **10** were methylated with CH₂N₂ to afford deguelin (**11**) and tephrosin (**2**), respectively, as identified by comparison with reported physicochemical data of the known compounds.^{7b,8)} Compounds **8** and **9**, together with their methylated derivatives, **11** and **12** (6a,12a-dehydrodeguelin), were also obtained upon treatment of **1** with *dl*-camphor-10-sulfonic acid in toluene. These structures were again confirmed by ¹H- and ¹³C-NMR spectral comparisons.^{7b,8)} These results strongly support the proposed structure of the new rotenoid, amorphispiro-1, and suggest a biogenetic relationship of these rotenoids.

Compounds **1** and **2** exhibited inhibitory effects on EBV-EA activation and on the two-stage carcinogenesis test.¹⁾

Experimental

General Experimental Procedures IR spectra were measured on a Shimadzu IR-408 spectrometer in CHCl₃. ¹H- and ¹³C-NMR spectra were recorded on a Varian XL-300 spectrometer in CDCl₃ using tetramethylsilane (TMS) as an internal standard. 2D-NMR and difference NOE spectra were recorded on a JEOL JNM GX-400 spectrometer. MS and HRMS were taken under electron impact (EI) conditions using a Hitachi M-80 mass spectrometer at 20 eV having a direct inlet system. UV spectra were obtained on a Shimadzu UV-240 spectrophotometer in MeOH. Preparative HPLC was carried out on a Japan Analytical Industry SD-8 with a hydrophobic column [JAIGEL-1H (20 × 600 mm)–2H (20 × 600 mm)] using CHCl₃ (3.0 ml/min) as an eluent and detected with RI and UV (254 nm) detectors. Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 27°. Silica gel (Merck, Kieselgel 60, 230 mesh and 70–230 mesh) was used for column and for flask chromatography, and silica gel plates (Merck, Kieselgel 60 F-254, 0.25 mm) were used for analytical TLC. Compounds were detected by UV light and by spraying

with a 10% H_2SO_4 solution containing anisaldehyde followed by heating.

Plant Material The leaves of *A. fruticosa* were collected at Fort Sill Military Reservation, Oklahoma, U.S.A. in August, 1990. Herbarium specimens are deposited in the herbarium of Kyoto Pharmaceutical University.

Extraction The fresh leaves of *A. fruticosa* (1176 g) were air-dried, cut and exhaustively extracted with *n*-hexane. The solvent was removed *in vacuo* to afford a dark green residue (34.0 g). Then, leaves were completely extracted with hot MeOH. After the solvent was removed *in vacuo*, the concentrated extract was suspended into H_2O and extracted with CH_2Cl_2 several times. The aqueous layer was extracted with EtOAc and *n*-BuOH saturated with H_2O , successively. Each organic layer was evaporated *in vacuo* to give an oily residue (CH_2Cl_2 45.5 g, EtOAc 15.6 g, *n*-BuOH 35.0 g).

Isolation The isolation process was guided throughout by the results of the assay of EBV-EA activation. Therefore, both the *n*-hexane and CH_2Cl_2 extract were fractionated by column chromatography on silica gel, respectively. When the *n*-hexane extract was chromatographed on a column of silica gel using benzene and benzene containing increasing amounts of CHCl_3 as eluents, elution with 100% benzene afforded tephrosin (**2**) (200 mg, 0.017% of dried leaves), and elution with 30% CHCl_3 in benzene afforded amorphispironone (**1**) (300 mg, 0.026%). On the other hand, when the CH_2Cl_2 extract was chromatographed on a column of silica gel using *n*-hexane and *n*-hexane containing increasing amounts of EtOAc as eluents, elution with 20% EtOAc in *n*-hexane afforded amorphispironone (**1**) (800 mg, 0.068%), elution with 30% EtOAc in *n*-hexane afforded amorphigenin (**3**) (15 mg, 0.0013%) and 12a-hydroxydalpanol (**5**) (220 mg, 0.019%), and elution with 40% EtOAc in *n*-hexane afforded 12a-hydroxyamorphigenin (**4**) (80 mg, 0.0068%). Purification of these compounds was carried out by repeated flash chromatography [adsorbent silica gel (Merck, Kieselgel 60, 230 mesh); pressure 1.2 kg/cm² (N_2 gas flow)], preparative-TLC and -HPLC. Compounds **2**–**5** were identified by comparison with previously reported data.⁶⁾

Compound 1: Colorless crystals, mp 152–152.5°C. $[\alpha]_{\text{D}}^{20}$ –317.4° ($c=0.73$, CHCl_3), –383.2° ($c=0.24$, MeOH). IR ν_{max} cm^{–1}: 3010, 2970, 1665, 1640, 1625, 1575. UV λ_{max} nm (ϵ): 209 (13400), 269 (31900), 316 (9000). MS m/z : 410 (M^+ , 58%), 395 ($\text{M}^+ - \text{CH}_3$, 51%), 193 (base peak). HRMS Found 410.1364, Calcd for $\text{C}_{23}\text{H}_{22}\text{O}_7$, 410.1367. ¹H- and ¹³C-NMR: Tables I and II.

Reduction of 1 with NaBH_4 To a solution of 50 mg of amorphispironone in 20 ml of MeOH was added 50 mg of NaBH_4 under ice-cooling, and the mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*, poured into ice-water, and extracted with CH_2Cl_2 . The extract was washed with water and evaporated. Purification of the residue was carried out by flash chromatography to afford 24 mg of the triol (**6**). IR ν_{max} cm^{–1}: 3600–3450, 3100–3450, 2900. UV λ_{max} nm (ϵ): 207 (19100), 231 (24000), 274 (8400), 290 (8300). MS m/z : 414 (M^+ , 23%), 397 ($\text{M}^+ - \text{OH}$, 19%), 365 (base peak).

Acetylation of 6 25 mg of compound **6** in 1 ml dry pyridine was acetylated with 0.5 ml acetic anhydride for one night. The solution was poured into ice-water and extracted with ether. The extract was washed successively with 1% HCl, 3% NaHCO_3 and water, and dried over anhydride MgSO_4 . The solvent was removed and the residue was purified by preparative-TLC to afford 19 mg of compound **7**. IR ν_{max} cm^{–1}: 3000–2900, 1770–1700. UV λ_{max} nm (ϵ): 206 (25100), 231 (32200), 279 (8600). MS m/z : 540 (M^+ , 32%), 525 ($\text{M}^+ - \text{CH}_3$, 34%), 365 (base peak). ¹H-NMR (CDCl_3) δ : 1.38, 1.46 (3H, s, 7'-, 8'- CH_3), 1.98, 2.09, 2.30 (3H, each s, COCH_3), 3.48, 3.81 (3H, s, OCH_3), 3.94 (1H, dd, $J=2.6, 6.9$ Hz, 12a-CH), 4.04 (1H, dd, $J=11.6, 5.0$ Hz, 6- CH_2), 4.17 (1H, dd, $J=11.6, 7.4$ Hz, 6- CH_2), 4.72 (1H, m, 6a-CH), 5.61 (1H, d, $J=10.1$ Hz, 5'-CH), 6.18 (1H, d, $J=6.9$ Hz, 12-CH), 6.48 (1H, d, $J=8.4$ Hz, 10-CH), 6.52 (1H, s, 4-CH), 6.66 (1H, d, $J=10.1$ Hz, 4'-CH), 6.67 (1H, s, 1-CH), 6.98 (1H, d, $J=8.4$ Hz, 11-CH). ¹³C-NMR (CDCl_3) δ : 20.8 $\times$ 2, 21.1 (COCH_3), 27.4, 27.8 (C-7', -8'), 33.1 (C-12a), 55.3, 55.8 (OCH_3), 64.4 (C-6), 68.6 (C-12), 75.1 (C-6a), 76.0 (C-6'), 105.9 (C-4), 109.5 (C-8), 110.2 (C-10), 111.6 (C-1), 112.6 (C-11a), 116.2 (C-4'), 117.1 (C-1a), 126.9 (C-11), 129.8 (C-5'), 143.7 (C-4a), 146.5 (C-2), 148.2 (C-3), 149.3 (C-7a), 153.6 (C-9), 169.7, 170.6, 171.5 (COCH_3).

Treatment of 1 with *p*-Toluenesulfonic Acid To a solution of 100 mg of amorphispironone in 30 ml of toluene was added 30 mg of *p*-toluenesulfonic acid under heating with reflux for 1 h. The solution was poured into water and extracted with benzene. The solvent was evaporated and the residue was purified by flash chromatography and preparative-TLC to afford 38, 5 and 10 mg of compounds **8**, **9** and **10**, respectively.

Compound 8: IR ν_{max} cm^{–1}: 3600–3500, 3050–2800, 1670, 1630, 1600, 1580. UV λ_{max} nm (ϵ): 207 (20100), 251 (17500), 269 (21300), 301 (8100). MS m/z : 380 (M^+ , 30%), 178 (base peak). ¹H- and ¹³C-NMR: Tables I and II.

Compound 9: IR ν_{max} cm^{–1}: 3550–3500, 3000–2900, 1630. UV λ_{max} nm (ϵ): 258 (20300), 314 (8800). MS m/z : 378 (M^+ , base peak), 363 ($\text{M}^+ - \text{CH}_3$, 56%). HRMS Found 378.1096, Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_6$, 378.1091. ¹H- and ¹³C-NMR: Tables I and II.

Compound 10: IR ν_{max} cm^{–1}: 3600–3500, 2900, 1670, 1630, 1600, 1580. UV λ_{max} nm (ϵ): 207 (16800), 251 (15000), 270 (17400), 301 (6300). MS m/z : 396 (M^+ , 18%), 194 (base peak). HRMS Found 396.1218, Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_7$, 396.1228. ¹H- and ¹³C-NMR: Tables I and II.

Methylation of the Compounds 8 and 10 Solutions of 40 mg and 20 mg of compounds **8** and **10** were methylated with CH_3N_2 in ether, respectively, and each reaction mixture stood for 48 h at room temperature. The solvent was removed and the residue was purified by preparative-TLC to afford 12 and 4 mg of compounds **11** and **2**, respectively.

Compound 11: IR ν_{max} cm^{–1}: 2900, 1660, 1595, 1575. UV λ_{max} nm (ϵ): 206 (21200), 239 (14800), 250 (15400), 270 (19700), 300 (7100), 314 (6600). MS m/z : 394 (M^+ , 22%), 192 (base peak). ¹H- and ¹³C-NMR: Tables I and II.

Compound 2: $[\alpha]_{\text{D}}^{20}$ –81.8° ($c=1.25$, CHCl_3). IR ν_{max} cm^{–1}: 3600–3400, 3000–2900, 1660, 1630, 1600, 1580. UV λ_{max} nm (ϵ): 206 (18600), 239 (13800), 251 (14800), 270 (18400), 302 (6200), 315 (6200). MS m/z : 410 (M^+ , 20%), 208 (base peak). ¹H- and ¹³C-NMR: Tables I and II.

Treatment of 1 with *dl*-Camphor-10-sulfonic Acid To a solution of 100 mg of amorphispironone in 30 ml of toluene was added 50 mg of *dl*-camphor-10-sulfonic acid under heating. The mixture was then refluxed for 4 h. The solution was poured into water and extracted with benzene. The solvent was evaporated and the residue was purified by flash chromatography and preparative-TLC to afford 4, 3, 3 and 5 mg of compounds **8**, **9**, **11** and **12**, respectively.

Compound 12: IR ν_{max} cm^{–1}: 3000–2850, 1630. UV λ_{max} nm (ϵ): 235 (11600), 260 (13700), 314 (6200). MS m/z : 392 (M^+ , base peak), 377 ($\text{M}^+ - \text{CH}_3$, 29%). HRMS Found 392.1282, Calcd for $\text{C}_{23}\text{H}_{20}\text{O}_6$, 392.1305. ¹H- and ¹³C-NMR: Tables I and II.

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