Structural Elucidation and Chemical Conversion of Amorphispironone, a Novel Spironone from *Amorpha fruticosa*, to Rotenoids[1)]

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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 derermined 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 ^{1}H-NMR spectral data.[6)]

The general features of the NMR spectral data also suggested a rotenoid structure for compound **1**. Comparison of ^{1}H-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 $C_{23}H_{22}O_7$ 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. ^{1}H-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 ^{1}H–^{1}H correlation spectroscopy (COSY), DEPT experiments, ^{1}H–^{13}C COSY and ^{1}H–^{13}C long range COSY spectral data, and they are listed in Tables I and II. The ^{1}H–^{13}C long range COSY of **1** was measured in order to confirm the connectivities of the partial structure. The significant long range ^{1}H–^{13}C correlations are indicated by 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-6α), 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

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.

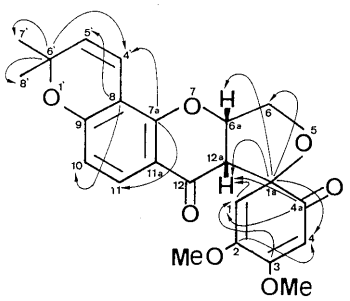


Fig. 1. Correlation ($^{13}C \rightsquigarrow {}^{1}H$) in ^{1}H–^{13}C Long-Range COSY Spectrum of Amorphispironone (**1**)

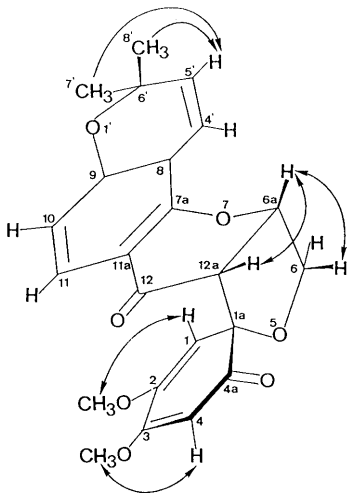
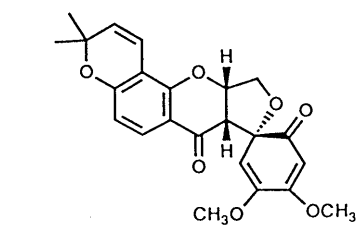
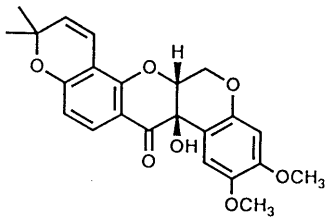


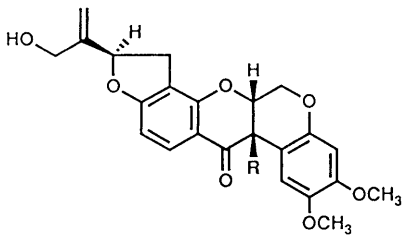
Fig. 2. Significant Enhancement of Signal Intensity by Difference NOE Experiments of Amorphispironone (**1**)



1



2



3 : R=H
4 : R=OH

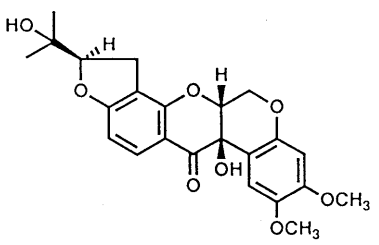


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Chart 1. Structures of Rotenoids isolated from the Leaves of *A. fruticosa*

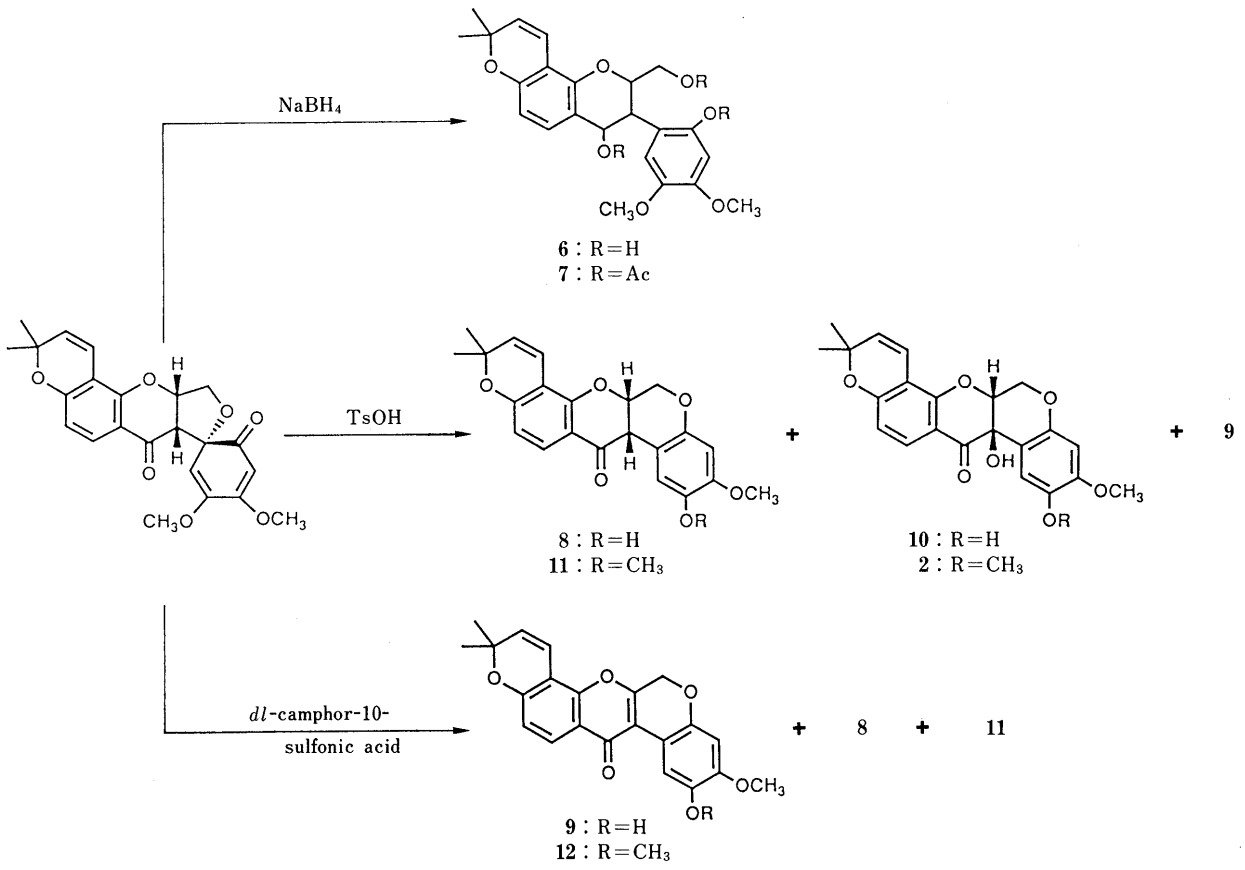

Chart 2

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-6β) at δ 4.49. Correspondingly, irradiation both at δ 4.49 (H-6β) 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*, amorphispironone (**1**), was proposed to be a spironone type rotenoid as shown by Chart 1.

To support the structural assignment of amorphispironone (**1**), we then tried to chemically convert this spironone 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 $NaBH_4$ 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 recyclize ring B directly using organic acid. On treatment of **1** with *p*-toluenesulfonic acid in toluene, compounds **8**, **9** and **10** were obtained. Their ^{1}H- and ^{13}C-NMR spectral data showed that these compounds were recyclized and demethylated derivatives.[7b,8] Compounds **8** and **10** were methylated with CH_2N_2 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 ^{1}H- and ^{13}C-NMR spectral comparisons.[7b,8] These results strongly support the proposed structure of the new rotenoid, amorphispironone (**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 $CHCl_3$. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian XL-300 spectrometer in $CDCl_3$ 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 $CHCl_3$ (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/cm^2 (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. $[\alpha]_D$ −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 (M^+-CH_3, 51%), 193 (base peak). HRMS Found 410.1364, Calcd for $C_{23}H_{22}O_7$, 410.1367. ^{1}H- and ^{13}C-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 (M^+-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 prepalative-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 (M^+-CH_3, 34%), 365 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.38, 1.46 (3H, s, 7′-, 8′-CH_3), 1.98, 2.09, 2.30 (3H, each s, $COC\underline{H}_3$), 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). ^{13}C-NMR ($CDCl_3$) δ: 20.8 × 2, 21.1 ($CO\underline{C}H_3$), 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 ($\underline{C}OCH_3$).

Treatment of 1 with *p*-Toluenesulfonic Acid To a solution of 100 mg of amorphispirone 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). ^{1}H- and ^{13}C-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 (M^+-CH_3, 56%). HRMS Found 378.1096, Calcd for $C_{22}H_{18}O_6$, 378.1091. ^{1}H- and ^{13}C-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 $C_{22}H_{20}O_7$, 396,1228. ^{1}H- and ^{13}C-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_2N_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). ^{1}H- and ^{13}C-NMR: Tables I and II.

Compound **2**: $[\alpha]_D$ −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). ^{1}H- and ^{13}C-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*-camphar-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 (M^+-CH_3, 29%). HRMS Found 392.1282, Calcd for $C_{23}H_{20}O_6$, 392.1305. ^{1}H- and ^{13}C-NMR: Tables I and II.

References and Notes

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