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Absolute Configuration of Novel Bioactive Flavonoids from *Tephrosia purpurea*

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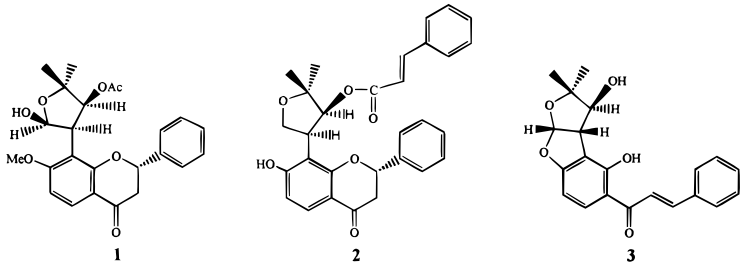
ABSTRACT



Three novel flavonoids, (+)-tephrorins A (1) and B (2) and (+)-tephrosone (3), were isolated from *Tephrosia purpurea*. Their structures were elucidated by NMR spectral analysis, and their absolute configurations were determined by Mosher ester methodology. Compounds 1 and 2 are flavanones containing an unusual tetrahydrofuran moiety. Compounds 1–3 were evaluated for their potential cancer chemopreventive properties using a cell-based quinone reductase induction assay.

The genus *Tephrosia* (Leguminosae) comprises more than 300 members found in India and the southern part of Africa, and extracts of some *Tephrosia* species have shown antibacterial,[1] antifungal,[1] and insecticidal activities.[2] In our ongoing project directed toward the discovery of novel naturally occurring cancer chemopreventive agents from plants,[3] the whole flowering and fruiting parts of *Tephrosia purpurea* Pers. were chosen for detailed investigation, since its petroleum ether- and ethyl acetate-soluble extracts significantly induced quinone reductase (QR) activity with cultured Hepa 1c1c7 (mouse hepatoma) cells.[4] Induction of Phase II drug-metabolizing enzymes such as QR is considered a major mechanism of protection against tumor initiation.[3,5] We earlier reported an initial phytochemical and biological investigation on this plant, with the isolation of several flavonoids as quinone reductase inducers.[4]

Many flavonoids have been reported from the genus *Tephrosia*, with their structures determined by spectroscopic analysis and chemical methods, but their absolute configurations typically have not been studied, with the exception of the recent reports on (+)-purpurin,[6] (−)-semiglabrin,[7] and (+)-pseudosemiglabrin.[7] Herein, we report the isolation of three additional novel flavonoids, compounds **1**−**3**, from *Tephrosia purpurea*, in addition to their absolute configurations and activity as inducers of quinone reductase.

Bioassay-guided fractionation of an EtOAc-soluble residue of *Tephrosia purpurea* involving successive silica gel and Sephadex LH-20 chromatographic steps afforded three novel

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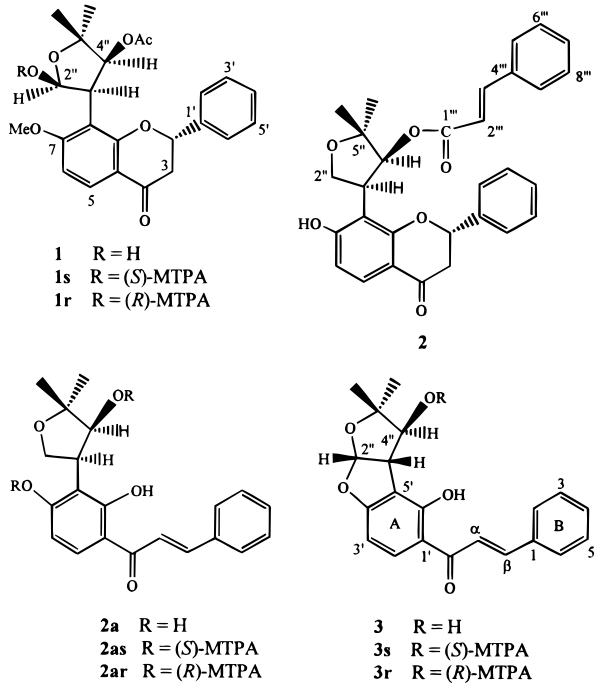
flavonoids, namely, (+)-tephrorins A (**1**) and B (**2**) and (+)-tephrosone (**3**).[8]



The molecular formula of compound **1** was determined to be $C_{24}H_{26}O_7$ by positive-ion HRFABMS. Comparison of its ^{1}H and ^{13}C NMR data with the previously reported known compound, (+)-purpurin,[4] indicated that **1** was a flavanone in which ring B was unsubstituted.[4,9]

Hydroxyl (IR, ν_{max} 3426 cm^{-1}), acetate (δ_C 170.8 and 21.3; δ_H 1.96), methoxyl (δ_H 3.93 s), and *gem*-dimethyl (ν_{max} 1368−1236 cm^{-1}; δ_C 27.6 and 24.3; δ_H 1.08 and 1.37) functionalities were present. The ^{1}H and ^{13}C NMR data for **1** are shown in Table 1. The remaining portion of the molecule of **1** was established as consisting of one furan ring, by spectral data comparison with (+)-tepurindiol.[10] This inference was supported by a HMBC experiment in which correlations were observed for the resonances at δ_H 5.63 (H-4″) with the signals of δ_C 113.5 (C-8), 170.8 (OAc-4″), 81.8 (C-5″), 27.6 and 24.3 (Me_2-5″), and 47.9 (C-3″). Additional HMBC correlations observed are summarized in Table 1. The relative stereochemistry of compound **1** in the pairs H-2″/H-3″ and H-3″/H-4″ was established as *cis* by their coupling constants and from a 1D NOE experiment. In the ^{1}H NMR spectrum of **1**, a doublet of doublets (J = 9.4, 5.7 Hz) at δ_H 4.16 (H-3″), a doublet (J = 5.7 Hz) at δ_H 5.74 (H-2″), and a doublet (J = 9.4 Hz) at δ_H 5.63 (H-4″) were observed as an ABX system. In the 1D NOE experiment, irradiation at OCH_3-7 (δ_H 3.93) gave enhancements of H-2″ and H-6, whereas irradiation at H-3″ (δ_H 4.16) gave an enhancement of H-2″.

The absolute configuration of the stereogenic centers in **1** was determined using Mosher ester methodology.[11,12] Compound **1** was treated with (*R*)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride to obtain the mono-(*S*)- (**1s**) and mono-(*R*)-ester (**1r**) C-2″ analogues.[11] The negative values ($\Delta\delta_{S-R}$) obtained for the methyls in C-5″ and the positive difference for H-3″ (Table 2) showed that the absolute stereochemistry of the chiral center at C-2″ was *S*. Hence, the absolute stereochemistry for C-3″ and C-4″ was deduced as *R* and *S*, respectively, and C-2 is assigned as *S* based on biogenetic analogy.[9] Thus, (+)-tephrorin A (**1**) was assigned as (2*S*)-8-[(2*S*,3*R*,4*S*)-4-(acetyloxy)tetrahydro-2-hydroxy-5,5-dimethyl-3-furanyl]-2,3-dihydro-7-methoxy-2-phenyl-4*H*-1-benzopyran-4-one.

The positive-ion HRFABMS of compound **2** showed a molecular ion peak at *m*/*z* 485.1957 indicating a molecular formula of $C_{30}H_{28}O_6$. Hydroxyl (ν_{max} 3422 cm^{-1}) and *gem*-dimethyl groups (ν_{max} 1365−1261 cm^{-1}; δ_C 27.1 and 26.6; δ_H 1.24) were observed. The ^{1}H and ^{13}C NMR spectra of compound **2** (Table 1) were quite similar to those of **1**, except for the absence of acetate and methoxyl moieties in **2**, and additional signals appeared for a pair of methylene protons at δ_H 4.87 and 4.66 (H-2″). Moreover, additional signals at δ_H 6.24 (d, J = 16.0 Hz, 1H), δ_H 7.45 (d, J = 16.0 Hz, 1H), and δ_H 7.36−7.46 (m, 5H) supported the presence of a *trans*-cinnamic acid group. The location of this cinnamic group at the C-4″ position was confirmed by HMBC NMR spectral observations, with a cross-peak observed between H-4″ and 166.3 (C-1‴), and additional correlations were observed as summarized in Table 2. The relative stereochemistry of the pair H-3″/H-4″ was established as *cis* from the H-4″ coupling constant (δ 5.10, J = 6.3 Hz, Table 1). To determine the absolute configuration of the stereogenic centers in compound **2** using the Mosher ester methodology, a hydrolysis reaction was considered necessary. Treatment of compound **2** under mild alkaline conditions[13] afforded a semisynthetic novel chalcone (**2a**)[13] and cinnamic acid, which is consistent

(8) Physical and spectroscopic data. For **1**: yellowish oil; $[\alpha]^{20}_D$ +26° (*c* 0.5, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 239 (4.2), 281 (4.2), 314 (3.8) nm; IR ν_{max} (film) 3426, 2974, 2931, 1736, 1680, 1596, 1435, 1368, 1273, 1236, 1094 cm^{-1}; FABMS *m*/*z* (rel int. %) $[M + 1]^+$ 427 (100), 349 (95), 305 (27), 245 (99), 217 (32), 163 (21), 131 (27); HRFABMS (positive-ion mode) *m*/*z* $[M + H]^+$ 427.1759 (calcd for $C_{24}H_{27}O_7$, 427.1749). For **2**: yellowish oil; $[\alpha]^{20}_D$ +28° (*c* 0.6, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 220 (4.7), 243 (4.5), 280 (4.7) nm; IR ν_{max} (film) 3422, 2983, 1710, 1681, 1632, 1604, 1449, 1365, 1334, 1305, 1261, 1167, 1097, 1063 cm^{-1}; FABMS *m*/*z* (rel int. %): $[M + H]^+$ 485 (37), 337 (10), 265 (39), 186 (67), 161 (60), 131 (100); HRFABMS (positive-ion mode) *m*/*z* $[M + H]^+$ 485.1957 (calcd for $C_{30}H_{29}O_6$, 485.1956). For **3**: yellow needles, mp 164 °C; $[\alpha]^{20}_D$ +26° (*c* 0.23, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 207 (4.1), 229 (3.8), 339 (4.0) nm; IR ν_{max} (film) 3438, 2982, 2932, 1639, 1598, 1566, 1485, 1440, 1356, 1305, 1243, 1089 cm^{-1}; EIMS *m*/*z* (rel int. %) $[M]^+$ 352 (100), 334 (89), 291 (67), 230 (64), 208 (95), 131 (80), 103 (75); HREIMS *m*/*z* $[M]^+$ 352.1305 (calcd for $C_{21}H_{20}O_5$, 352.1306).

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(11) Preparation of (*S*)- and (*R*)-MTPA ester derivatives of compounds **1**, **2a** (see ref 13), and **3**. To a solution of **1**, **2a**, or **3** (1.5 mg in 0.5 mL of $CHCl_3$) were added sequentially pyridine (100 μL), 4-(dimethylamino)-pyridine (0.5 mg), and (*R*)-(−)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (10 mg). Each mixture was heated at 50 °C for 4 h under N_2 and then passed through a disposable pipet (0.6 × 5 cm) packed with silica gel and eluted with 5 mL of $CHCl_3$. The solvent was removed in vacuo, to obtain the mono-*S*-Mosher ester **1s** and residues from **2a** and **3**. These residues were subjected to preparative TLC to give the purified mono-*S*-Mosher ester **3s** or the purified di-*S*-Mosher **2as**, respectively. Treatment of **1**, **2a**, or **3** (1.5 mg with (*S*)-(+)α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride as described above yielded the mono-*R*-Mosher esters **1r** or **2ar** and the di-*R*-Mosher **3r**, respectively (^{1}H NMR data, Table 2).[12]

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Table 1. ^{1}H and ^{13}C NMR Data and HMBC Correlations for Compounds **1** and **2** (300, 75 MHz, $CDCl_3$, ppm)

	1			**2**		
^{1}H no.	δ_H (mult)	δ_C	HMBC[a]	δ_H (mult)	δ_C	HMBC[a]
2	5.53 dd (4.0, 12.2)	80.8 d	1′, 4, 2′/6′	5.42 dd (3.2, 12.6)	80.8 d	1′, 4, 2′/6′
3	2.83 m	44.7 t	2, 1′, 4	2.83 m	44.7 t	2, 1′, 4
4		191.5 s			190.7 s	
4a		116.1 s			115.9 s	
5	7.90 d (8.9)	128.9 d	6, 4a, 8a, 7, 4	7.83 d (8.6)	131.1 d	4a, 8a, 7, 4
6	6.68 d (8.9)	105.9 d	8, 4a, 7, 3″	6.57 d (8.6)	105.9 d	8, 4a, 7
7		164.3 s			168.9 s	
8		113.5 s			114.0 s	
8a		161.3 s			159.5 s	
1′		139.2 s			138.9 s	
2′/6′	7.46 m	126.1 d	2, 3′, 4′	7.46 m	126.0 d	2, 3′, 4′
3′/5′	7.36 m	129.1 d	1′, 2′	7.36 m	128.6 d	1′, 2′
4′	7.36 m	129.4 d	3′, 5′, 2′/6′	7.36 m	130.7 d	3′, 5′, 2′/6′
				4.87 dd (9.3, 2.6)		
2″	5.74 d (5.7)	99.3 d	4″, 3″, 8		78.5 t	4″, 3″, 8
				4.66 dd (9.3, 8.5)		
3″	4.16 dd (5.7, 9.4)	47.9 d	4″, 2″, 8, 7, 8a	4.07 m	40.6 d	4″, 5″, 8, 7, 2″
4″	5.63 d (9.4)	80.1 d	Me_2−5″, 3″, 5″, 8	5.10 d (6.3)	80.1 d	Me_2−5″, 3″, 5″, 8, 1‴
5″		81.8 s			72.9 s	
OCH_3	3.93 s		7			
Me_2	1.37 s	27.6 q			26.6 q	
	1.08 s	24.3 q		1.24 s	27.1 q	5″, 6″, 7″
1‴					166.3 s	
2‴				6.24 d (16.0)	117.4 d	C-1‴, C-3‴
3‴				7.45 d (16.0)	146.0 d	C-1‴, C-2‴
4‴					134.2 s	
5‴/9‴				7.36 m	129.1 d	
6‴/8‴				7.46 m	129.3 d	
7‴				7.36 m	131.1 d	
AcO	1.96 s	170.8, 21.3				

[a] C to H correlations.

with the structure proposed. The di-Mosher esters of the chalcone (**2as** and **2ar**) indicated the *S* configuration at C-4″, because of the negative difference values for H-3″, H-2a″, and H-2b″ and the positive differences for the methyls in C-5″ (Table 2). The absolute stereochemistry at C-3″ was determined as *S* accordingly with the *cis* arrangements of the pair H-3″/H-4″. Therefore, (+)-tephrorin B (**2**) was assigned as (3*S*,4*S*)-4-[(2*S*)-3,4-dihydro-7-hydroxy-4-oxo-2-phenyl-2*H*-1-benzopyran-8-yl]tetrahydro-2,2-dimethyl-3-furanyl (2*E*)-3-phenyl-2-propenoate.

Table 2. Partial ^{1}H NMR Data of the (*S*)- and (*R*)-Mosher Ester Derivatives of Compounds **1**, **2a**, and **3**[a]

	δ_H			δ_H			δ_H		
proton	**1s**	**1r**	$\Delta\delta_{S-R}$	**2as**	**2ar**	$\Delta\delta_{S-R}$	**3s**	**3r**	$\Delta\delta_{S-R}$
2″	6.60	6.62	*S*[b]	4.84	4.90	−0.06	6.39	6.42	−0.03
				4.64	4.69	−0.05			
3″	4.49	4.42	+0.07	4.13	4.16	−0.03	3.79	3.92	−0.13
4″	5.72	5.72	∼0	5.27	5.31	*S*[b]	5.43	5.46	*S*[b]
6″	1.17	1.20	−0.03	1.31	1.25	+0.06	1.27	1.25	+0.02
7″	1.17	1.30	−0.13	1.21	1.10	+0.11	1.26	1.17	+0.09

[a] Obtained in $CDCl_3$ at 300 MHz. [b] Absolute configuration.

Compound **3** was shown to possess a molecular formula of $C_{21}H_{20}O_5$ by HREIMS. Its IR spectrum showed a hydroxyl group (3438 cm^{-1}), a conjugated carbonyl absorption (1639 cm^{-1}; δ_C 192.7), and a *gem*-dimethyl group (1356−1243 cm^{-1}). The ^{1}H and ^{13}C NMR spectra of **3** (Table 3) exhibited signals at δ_H 7.91 (d, 15.5 Hz); δ_C 145.2, δ_H 7.58 (d, 15.5 Hz); δ_C 120.6, and δ_C 192.7, consistent with the presence of a chalcone unit in which ring B was unsubstituted.[9]

The remaining portion of the molecule was established as consisting of two substituted fused furan rings, by compari-

(13) Alkaline hydrolysis of **2** to **2a**. (+)-Tephrorin B (**2**) (12 mg) was treated with 5 mL of 0.25% KOH in MeOH, and the mixture was refluxed for 4 h. The resultant solution was adjusted to pH 8.0 and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo to yield 6 mg of **2a**. The aqueous phase was acidified with 1 N HCl to pH 3.0 and extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo to give cinnamic acid (2 mg), for which the obtained IR and ^{1}H and ^{13}C NMR data were consistent with literature values.[15] Compound (**2a**): yellowish needles, mp 162 °C; $[\alpha]^{20}_D$ +70° (*c* 0.08, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 215 (3.9), 345 (4.2) nm; IR ν_{max} (film) 3400, 2962, 1640, 1566, 1480, 1440, 1356, 1310, 1242, 1095 cm^{-1}; FABMS positive mode *m*/*z* (rel int. %) $[M + 1]^+$ 355 (72), 265 (31), 251 (45), 233 (36), 186 (98), 161 (100), 115 (40).

Table 3. ^{1}H and ^{13}C NMR Data for Compounds **3** and **2a** and HMBC Correlations for Compound **3** (300, 75 MHz, $CDCl_3$, ppm)

	3			**2a**	
^{1}H no.	δ_H (mult)	δ_C	HMBC[a]	δ_H (mult)	δ_C
1		135.0 s			134.9 s
2	7.66 m	128.9 d		7.65 m	129.2 d
3	7.44 m	129.4 d	1, 5, 4	7.44 m	128.8 d
4	7.44 m	130.9 d	6, 5	7.44 m	131.1 d
5	7.44 m	129.4 d	4, 3, 1	7.44 m	128.8 d
6	7.66 m	128.9 d		7.66 m	129.2 d
1′		114.1 s			114.8 s
2′	7.87 d (8.7)	132.8 d	6′, 4′, 1′	7.87 d (8.7)	133.0 d
3′	6.47 d (8.7)	102.8 d	2′, 4′	6.51 d (8.7)	103.5 d
4′		165.9 s			169.4 s
5′		115.5 s			113.9 s
6′		161.8 s			161.9 s
2″	6.57 d (6.4)	113.1 d	3″, 4″, 5″, 4′	4.74 m	78.8 t
3″	4.04 d (6.4)	55.5 d	4″, 5′, 5″, 6′, 4′	3.85 m	42.5 d
4″	4.34 s	80.4 d	5″	3.54 br s	81.5 d
5″		88.5 s			72.7 s
a	7.58 d (15.5)	120.6 d	β′-C=O, 1	7.57 d (15.4)	120.3 d
b	7.91 d (15.5)	145.2 d	β′-C=O, 1, 6, 2	7.90 d (15.4)	145.2 d
β′-C=O		192.7 s			192.5 s
Me_2	1.07 s, 1.40 s	23.4 q, 27.8 q	5″, 4″, 27.8, 23.4	1.29 s, 1.42 s	26.5 q
OH	13.6 s		6′, 1′, 5′	14.7 s	

[a] C to H correlations.

son with (+)-purpurin.[4,9] This observation was supported by an HMBC experiment, as summarized in Table 3.

In addition, the location of the chelated OH proton (δ_H 13.6 s) at C-6′ of **3** showed correlations with the signals of δ_C 161.8 (C-6′), 114.1 (C-1′), and 115.5 (C-5′). The H-2″ and H-3″ protons were mutually coupled (J = 6.4 Hz) and supported their occurrence in a *cis* configuration. Moreover, the H-4″ proton was observed as a singlet, suggesting that it was at an opposite position relative to H-2″ and H-3″.[4] The absolute configuration at C-2″ of **3** was also determined by analysis of the ^{1}H NMR data of the (*S*)- and (*R*)-mono-Mosher ester derivatives **3s** and **3r**, respectively (Table 2), in a manner similar to the procedure described for **1**. Analysis of the $\Delta\delta_H(_{S-R})$ data for compound **3** (Table 2) indicated a negative difference in chemical shift for H-2″ and H-3″ and a positive difference for the methyls at C-5″. Thus, the absolute configuration at C-4″ was established as *S*.

Accordingly, the absolute configuration at C-3″ and C-2″ was deduced as *S* and *R*, respectively, because of the *trans* configuration of H-4″/H-3″ and the *cis* relationship of H-3″/H-2″. Venkata Rao and Ranga Raju[9] reported a similar compound obtained from alkaline hydrolysis from (+)-purpurin without determination of its absolute configuration. Recent work which established the absolute configuration of (+)-purpurin as 2*S*,2″*R*,3″*S*,4*S*[7] also supported the stereochemical assignments made for this part of the molecule of **3**. Thus, the structure of **3** was determined to be (+)-(2″*R*,3″*S*,4″*S*)-[2″,3″-*b*]dihydrofurano-5″,5″-dimethyl[4′,5′-*h*]-6′-hydroxy-4″-tetrahydrofuranohydroxychalcone, to which we have accorded the trivial name (+)-tephrosone.

In conclusion, three novel compounds of the flavonoid class (**1**−**3**) have been isolated from *Tephrosia purpurea* in this investigation. Compounds **1** and **2** bear a novel tetrahydrofurano ring as a side chain at the C-8 position, and in **2** an unusual cinnamic acid moiety occurs at the C-4″ position. It is interesting to note that the C-4″ substituent is in the *S* configuration in **1**−**3**, as in the case also of (+)-purpurin[6] and (+)-pseudosemiglabrin.[7]

Biological Activity. Compounds **1**−**3** were evaluated for their potential as quinone reductase inducers in cultured mouse Hepa 1c1c7 cells, according to established protocols.[4,5,14] Compounds with CD (concentration to double enzyme induction) values of <10 μg/mL are considered active.[4,5] Each IC_{50} value (μg/mL) (half-maximal inhibitory concentrations of cell viability) was divided by the CD value to obtain a chemopreventive index, CI, IC_{50}/CD.[14] Compound **2** was inactive (CD value >10 μg/mL), whereas compounds **1**, **2a**, and **3** significantly induced QR activity, with the observed CD values being 4.0, 5.9, and 3.1 μM, respectively. The CI values of these compounds were 11.8, 5.5, and 6.2, respectively. The presence of the bulky cinnamic acid group at C-4″ in **2** may affect its biological activity.

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