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# BIS(BIBENZYL) ETHERS FROM *PELLIA ENDIVIIFOLIA**

TOSHIHIRO HASHIMOTO, HAZIMU SUZUKI, MOTOO TORI and YOSHINORI ASAKAWA

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

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**Key Word Index**—*Pellia endiviifolia*; Metzgeriales; Hepaticae; bis(bibenzyl) ethers; perrottetin E; perrottetin E-11′-methyl ether; 14-hydroxyperrottetin E-11′-methyl ether; synthesis; chemosystematics.

**Abstract**—Two new bis(bibenzyl) ethers, perrottetin E-11′-methyl ether and 14-hydroxyperrottetin E-11′-methyl ether were isolated from an ethyl acetate extract of the liverwort *Pellia endiviifolia* together with the previously known bis(bibenzyl) ether, perrottetin E and their structures characterized by spectroscopic methods, chemical evidence and total synthesis. The present results strongly support Schuster's phylogenic classification of the Metzgeriales and Jungermanniales.

## INTRODUCTION

Previously, we reported the isolation and structure elucidation of a new biologically active diterpene dialdehyde, sacculatal, with an intensely hot taste from the liverwort, *Pellia endiviifolia*, together with the non-pungent isosacculatal [2–5]. In pursuit of pharmacologically interesting substances found in liverworts, we have further investigated the chemical constituents of the female thallus of *P. endiviifolia* and isolated two new bis(bibenzyl) ethers, perrottetin E-11′-methyl ether (**1**), 14-hydroxyperrottetin E-11′-methyl ether (**2**), together with the previously known bis(bibenzyl) ether, perrottetin E (**3**) [6] found in the stem-leafy liverwort *Radula perrottetii* belonging to the Jungermanniales. We report on their isolation, structural characterization and synthesis of the new bibenzyls and discuss the chemosystematics of *P. endiviifolia*.

## RESULTS AND DISCUSSION

A combination of column chromatography on Sephadex LH-20 and silica gel of an ethyl acetate extract of the female thallus of *P. endiviifolia* resulted in the isolation of the two new bis(bibenzyl) ethers, perrottetin E-11′-methyl ether (**1**), 14-hydroxyperrottetin E-11′-methyl ether (**2**) and the previously known bis(bibenzyl) ether, perrottetin E (**3**) [6].

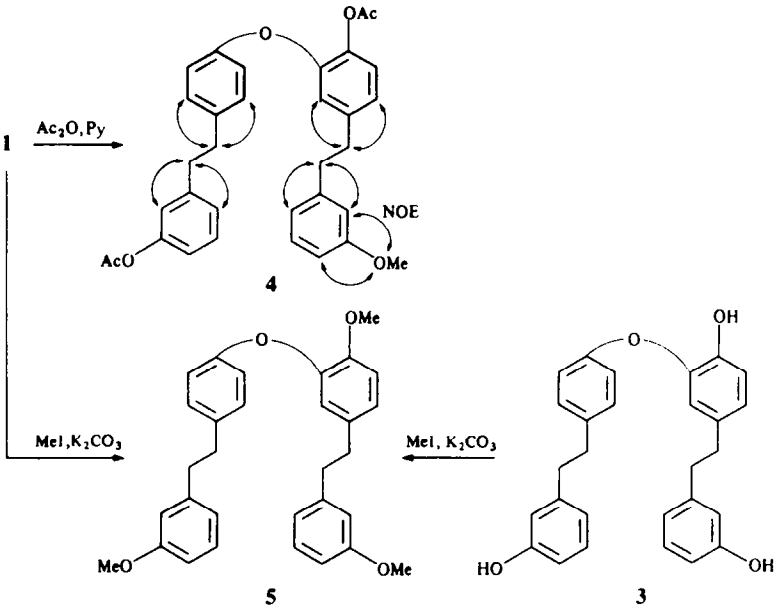
Compound **1** has the molecular formula $C_{29}H_{28}O_4$ ($[M]^+$ *m/z* 440.1991) and its IR spectrum showed the presence of a hydroxyl group (3300 $cm^{-1}$). The $^1H$ (Table 1) and $^{13}C$ NMR spectra contained the signals of one methoxyl group ($\delta_H$ 3.75; $\delta_C$ 55.1), four benzylic methylenes [$\delta_H$ 2.78, 2.86, each 4H; $\delta_C$ 36.9 (two carbon overlapped), 37.7, 37.9] and 24 benzene ring carbons. Their signal patterns were quite similar to those of perrottetin E (**3**), except for the presence of one methoxyl group, indicating that **1** is perrottetin E monomethyl ether. Acetylation of **1** with acetic anhydride–pyridine gave a diacetate (**4**) ($[M]^+$ *m/z* 524; 1760 $cm^{-1}$) (Scheme 1). Methylation of **1** with methyl iodide afforded a trimethyl ether (Scheme 1), whose spectral data were identical to those of perrottetin E trimethyl ether (**5**) ($[M]^+$ *m/z* 468; $\delta_H$ 3.76, 3.77, 3.81), supporting the above assumption. The position of one methyl group at C-11′ was confirmed by NOE (Fig. 1 and Scheme 1) between (i) H-12′ and OMe-11′ and (ii) H-10′ and OMe-11′ in **1** and **4**. The structure of **1** was further supported by the following chemical degradation. Birch reduction of triethyl ether (**6**), which was prepared from perrottetin E (**3**) with ethyl iodide, gave 3,4′-diethoxydihydrostilbene (**7**) and 3-ethoxy-4′-hydroxydihydrostilbene (**8**) (Scheme 2). The same reduction of diethyl ether (**9**) prepared from **1** gave **8** and 4-ethoxy-3′-methoxydihydrostilbene (**10**) (Scheme 3). The structure of **10** was determined by its synthesis (Scheme 4). *p*-Ethoxybenzaldehyde (**11**) and dimethyl[(3-methoxyphenyl)methyl]phosphonate (**12**) were combined by Wadsworth–Emmons olefination using potassium *tert*-butoxide in dry DMF to give the stilbene (**13**), followed by hydrogenation in the presence of 20% Pd-C to afford bibenzyl (**10**). Finally, we undertook the total synthesis of **1** by a modification of Kodama's method [7]. Ullmann coupling ($CuO$–$K_2CO_3$–pyridine) of 4-benzyloxy-3-hydroxybenzaldehyde (**14**) [6] with ethyl *p*-bromobenzoate afforded **15**. Compound **15** and diphosphonate (**12**) were combined by Wadsworth–Emmons olefination using potassium *tert*-butoxide in dry DMF at room temperature to afford the stilbene-type ether (**16**). The ester group of **16** was then reduced with lithium aluminium hydride to give an alcohol (**17**). The hydroxyl group of **17** was then oxidized with pyridinium dichromate (PDC) to give an aldehyde (**18**) (Scheme 5). Condensation of **18** and diethyl [(3-benzyloxyphenyl) methyl]phosphonate (**19**) was effected with potassium *tert*-butoxide in dry DMF to give a distilbene-type ether (**20**), followed by catalytic hydrogenation in the presence of 20% Pd-C to furnish perrottetin E-11′-methyl ether (**1**) (Scheme 6). The synthetic material was identical with the natural product (**1**) in all respects (TLC, mass spectrum, IR, $^1H$ and $^{13}C$ NMR).

*Part 44 in the series 'Chemosystematics of Bryophytes'. For Part 43, see ref. [1].

Table 1. $^1$H NMR (400 MHz) spectral data of compounds **1**, **2**, **4** and **21**

| H | 1 | 2 | 4 | 21 |
|---|---|---|---|---|
| 2,6 | 6.87 *d* (8.5)* | 6.84 *d* (8.8) | 6.86 *d* (8.3) | 6.87 *d* (8.5) |
| 3,5 | 7.10 *d* (8.5) | 7.10 *d* (8.8) | 7.09 *d* (8.3) | 7.08 *d* (8.5) |
| 7,8 | 2.86 *m* | 2.85 *m* | 2.89 *m* | 2.84 *m* |
| 10 | 6.64 *dd* (2.0, 2.0) | 6.55 *d* (3.2) | 6.92 *dd* (2.0, 2.0) | 6.97 *d* (1.7) |
| 12 | 6.87 *ddd* (7.8, 2.0, 2.0) | 6.52 *dd* (8.3, 3.2) | 6.91 *ddd* (8.6, 2.0, 2.0) | 6.95 *dd* (8.3, 1.7) |
| 13 | 7.16 *dd* (7.8, 7.8) | 6.60 *d* (8.3) | 7.26 *dd* (8.1, 8.1) | 7.05 *d* (8.3) |
| 14 | 6.74 *ddd* (7.8, 2.0, 2.0) | — | 7.03 *ddd* (8.6, 2.0, 2.0) | — |
| 3′ | 6.64 *d* (2.0) | 6.63 *d* (2.0) | 6.76 *d* (2.0) | 6.78 *d* (2.0) |
| 5′ | 6.84 *dd* (8.1, 2.0) | 6.82 *d* (8.3, 2.0) | 6.91 *dd* (8.3, 2.0) | 6.92 *dd* (8.1, 2.0) |
| 6′ | 6.94 *d* (8.1) | 6.94 *d* (8.3) | 7.03 *d* (8.3) | 7.03 *d* (8.3) |
| 7′,8′ | 2.78 *m* | 2.78 *m* | 2.83 *m* | 2.80 *m* |
| 10′ | 6.66 *dd* (2.0, 2.0) | 6.65 *dd* (2.7, 2.7) | 6.64 *dd* (3.4, 3.4) | 6.71 *dd* (1.7, 1.7) |
| 12′ | 6.73 *ddd* (7.6, 2.0, 2.0) | 6.73 *ddd* (8.1, 2.7, 2.7) | 6.73 *ddd* (8.1, 3.4, 3.4) | 6.73 *ddd* (8.1, 1.7, 1.7) |
| 13′ | 7.14 *dd* (7.6, 7.6) | 7.15 *dd* (8.1, 8.1) | 7.15 *dd* (8.1, 8.1) | 7.17 *dd* (8.1, 8.1) |
| 14′ | 6.71 *ddd* (7.6, 2.0, 2.0) | 6.70 *ddd* (8.1, 2.7, 2.7) | 6.71 *ddd* (8.1, 3.4, 3.4) | 6.71 *ddd* (8.1, 1.7, 1.7) |
| OMe | 3.75 *s* | 3.75 *s* | 3.73 *s* | 3.75 *s* |
| Others | 5.05 *s* (OH) | 4.58 *s* (OH) | 2.13 *s* (OAc) | 2.16 *s* (OAc) |
| | 5.50 *s* (OH) | 4.84 *s* (OH) | 2.26 *s* (OAc) | 2.27 *s* (OAc) |
| | | 5.59 *s* (OH) | | 2.31 *s* (OAc) |

*Coupling constant ($J$ in Hz) are given in parentheses.




Scheme 1. Reactions of perrottetin E monomethyl ether (**1**).

14-Hydroxyperrottetin E-11′-methyl ether (**2**) has the molecular formula $C_{29}H_{28}O_5$ ([M]$^+$ $m/z$ 456.1862). The $^1$H (Table 1) and $^{13}$C NMR spectra indicated the presence of three phenolic hydroxyl groups ($\delta_H$ 4.58, 4.84, 5.59), a methoxyl group ($\delta_H$ 3.75; $\delta_C$ 55.1) and four methylene bearing benzene rings ($\delta_H$ 2.78, 2.85, each 4H; $\delta_C$ 32.4, 35.2, 36.9, 38.1), and their signal pattern resembled those of **1** and **3** suggested that **2** contained an additional phenolic hydroxyl group to **1**. Acetylation of **2** gave a triacetate (**21**) ([M]$^+$ $m/z$ 582; 1760 cm$^{-1}$; $\delta_H$ 2.16, 2.27, 2.31, 3H, *s*) (Scheme 7). A solution of **2** in $CHCl_3$ was allowed to stand for five days to afford *p*-quinone (**22**) indicating the presence of a *p*-hydroquinone moiety in **2** (Scheme 7). Double resonance and NOE experiments (Fig. 1 and Scheme 7) of **2** and **21** revealed that **2** is 14-hydroxyperrottetin E-11′-methyl ether. Conclusive evidence for structure **2** was obtained by total synthesis (Scheme 8). Condensation of aldehyde (**18**) and dimethyl [[(2,5-bis(benzyloxy)phenyl]methyl]phosphonate (**23**) prepared from 2,5-dihydroxybenzoic acid in four steps [7,

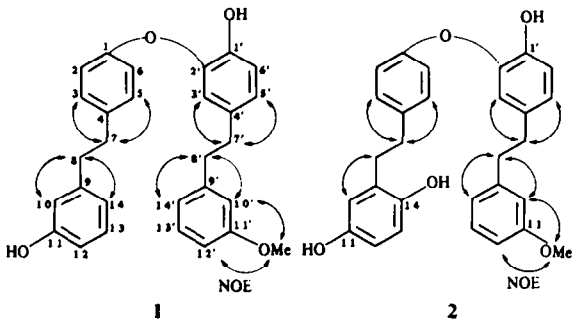
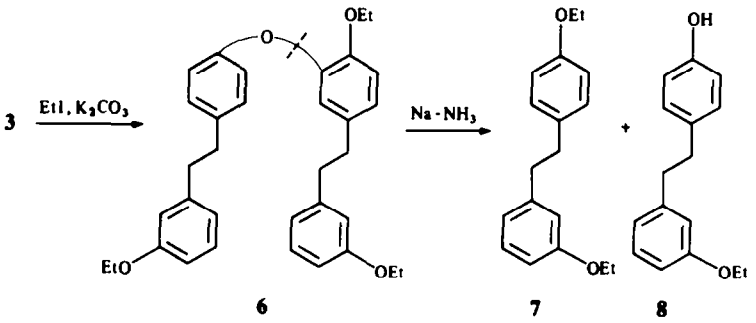


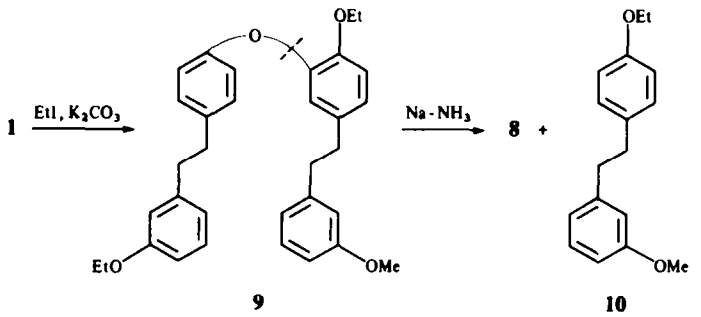

Fig. 1. NOE interactions of compounds **1** and **2**.

8] was effected with potassium *tert*-butoxide in dry DMF to give a distilbene-type ether (**24**). Hydrogenation of **24** in the presence of 20% Pd-C afforded 14-hydroxyperrottetin E-11'-methyl ether (**2**) and *p*-quinone (**22**). The synthetic material (**2**) was identical with the natural product in all respects (TLC, mass spectrum, IR, $^1$H and $^{13}$C NMR).

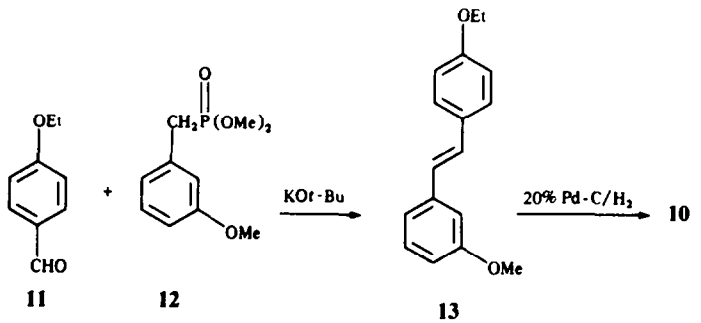
There is chemically clear evidence that the Metzgeriales and the Jungermanniales originated from a common ancestor although the present species belonging to both orders are morphologically quite different [9, 10]. Perrottetin E (**3**) and its analogues have been found in *Radula* species belonging to the Jungermanniales [6]. *Pellia endiviifolia* belonging to the Metzgeriales also elaborates



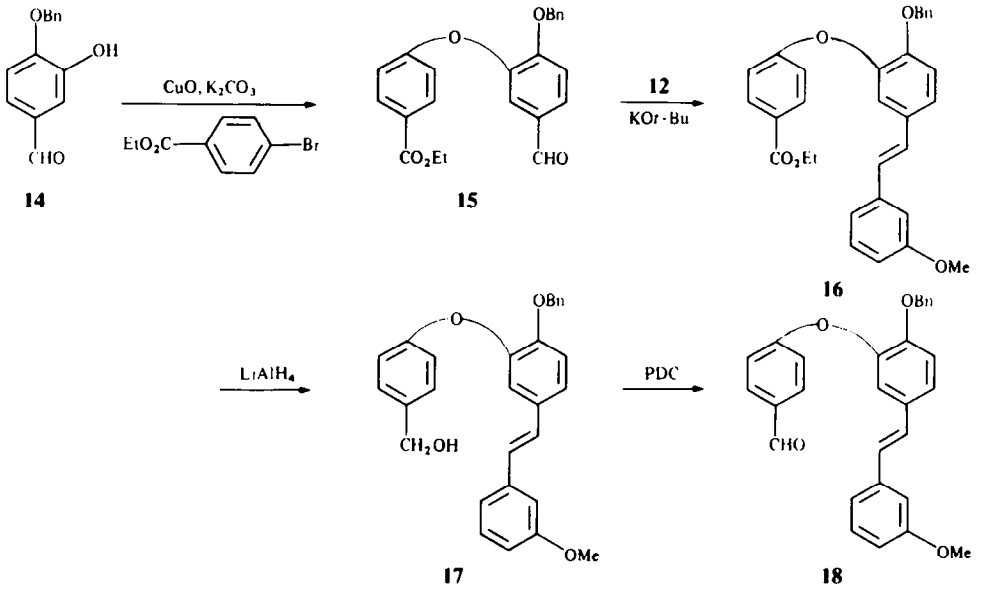

Scheme 2. Degradation of compound **3**.



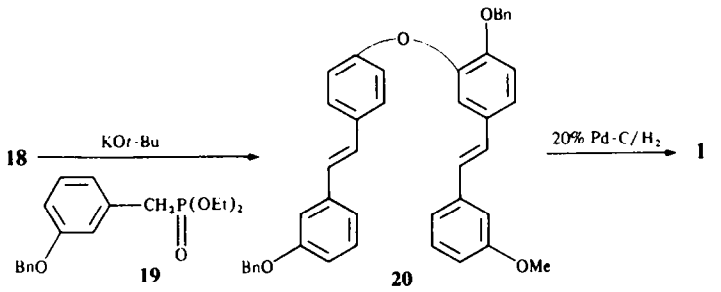

Scheme 3. Degradation of compound **1**.




Scheme 4. Synthesis of compound **10**.




Scheme 5. Synthesis of compound **18**.




Scheme 6. Synthesis of compound **1** from compound **18**.

bis(bibenzyl) ethers (**1–3**). The present new chemical evidence strongly supports Schuster's phylogenic classification of the two orders [9].

## EXPERIMENTAL

Mps: uncorr. Solvents used for spectral measurements were TMS–$CDCl_3$ [$^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz)]; EtOH (UV).

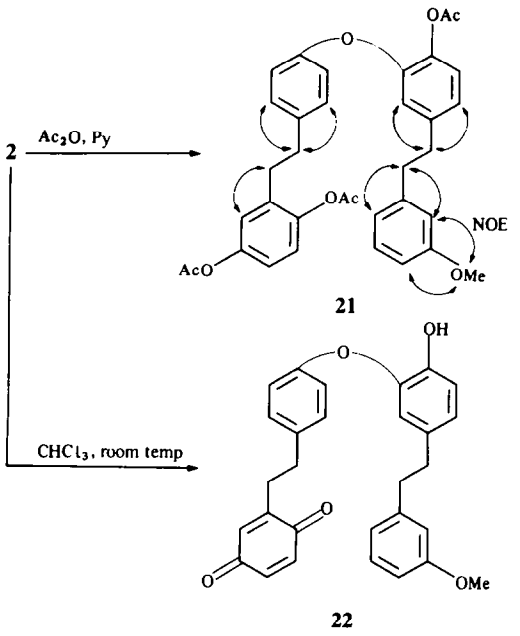
*Plant material.* *Pellia endiviifolia* (Dick.) Dum. was collected in Tokushima, Japan in October 1987 and identified by Dr M. Mizutani and Y.A. A voucher specimen is deposited at the Herbarium of the Institute of Pharmacognosy, Tokushima Bunri University.

*Extraction and isolation.* Fr. material (570 g) was extracted with EtOAc for 5 days. The resultant EtOAc extract was evapd *in vacuo* to yield a green oil (4.85 g), which was chromatographed on Sephadex LH-20 using 50% MeOH–$CHCl_3$. The crude products (1.193 g) obtained from fr. A were further chromatographed on silica gel using a $C_6H_6$–EtOAc gradient. Fr. A-1 (EtOAc $C_6H_6$, 1:9) gave perrottetin E-11′-methyl-ether (**1**) (205 mg) as an oil. Fr. A-2 (EtOAc–$C_6H_6$, 3:17) afforded perrottetin E (**3**) (221 mg) [6] as an oil. From Fr. A-3 (EtOAc–$C_6H_6$, 1:4), 14-hydroxyperrottetin E-11′-methyl ether (**2**) (38 mg) was obtained as an oil.

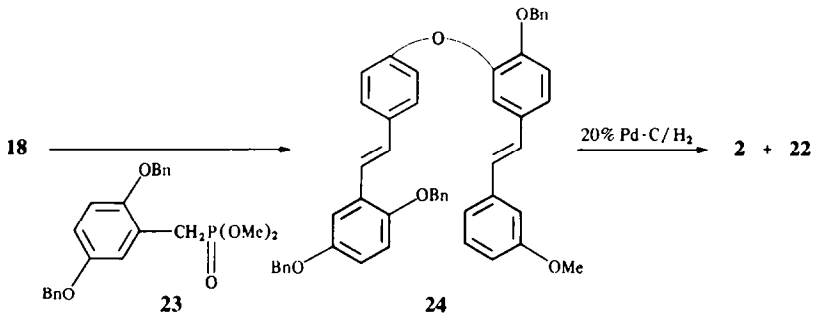
*Compound* **1**. IR $\nu_{max}^{neat}$ cm$^{-1}$: 3400, 3025, 2930, 2850, 1600, 1500, 1450, 1435, 1270, 1215, 1150, 1100, 1040. $^{13}$C NMR $\delta$: 36.9 (*t*), 37.7 (*t*), 37.9 (*t*), 55.1 (*q*), 111.3 (*d*), 114.3 (*d*), 115.5 (*d*), 117.7 (*d*), 118.8 (*d*), 120.8 (*d*), 121.0 (*d*), 124.4 (*d*), 129.2 (*d*), 129.7 (*d*), 134.2 (*s*), 136.8 (*s*), 143.1 (*s*), 143:4 (*s*), 145.4 (*s*), 154.9 (*s*), 155.6 (*s*), 159.5 (*s*). $^1$H NMR; see Table 1. HRMS: found: $[M]^+$ *m/z* 440.1991; $C_{29}H_{28}O_4$ requires: 440.1987; EIMS *m/z* (rel. int.): 440 $[M]^+$ (47), 333 (68), 320 (21), 319 (98), 225 (25), 211 (53), 199 (39), 181 (16), 121 (100), 107 (95), 105 (34), 91 (53), 77 (55).

*Compound* **2**. IR $\nu_{max}^{neat}$ cm$^{-1}$: 3350, 3010, 2925, 1590, 1500, 1440, 1270, 1210, 1160, 1100, 1040. $^{13}$C NMR $\delta$: 32.4 (*t*), 35.2 (*t*), 36.9 (*t*), 38.1 (*t*), 55.1 (*q*), 111.3 (*d*), 113.6 (*d*), 114.2 (*d*), 115.9 (*d*), 116.2 (*d*), 117.0 (*d*), 118.0 (*d*), 118.7 (*d*), 121.0 (*d*), 124.4 (*d*), 129.0 (*s*), 129.3 (*d*), 129.8 (*d*), 134.2 (*s*), 137.0 (*s*), 143.2 (*s*), 143.3 (*s*), 145.3 (*s*), 147.4 (*s*), 149.4 (*s*), 154.9 (*s*), 159.5 (*s*). $^1$H NMR; see Table 1. HRMS: found: $[M]^+$ *m/z* 456.1862; $C_{29}H_{28}O_5$ requires: 456.1937; EIMS *m/z* (rel. int.): 456 $[M]^+$ (31), 335 (18), 334 (21), 333 (69), 225 (17), 211 (100), 199 (19), 121 (44), 107 (55), 105 (31), 91 (44), 77 (36).

*Acetylation of compound* **1**. A mixt. of **1** (25 mg), $Ac_2O$ (1 ml) and pyridine (1 ml) was stirred at room temp. for 24 hr. Usual work-up afforded the diacetate (**4**) (26 mg; 87.2%) as an oil. UV $\lambda_{max}$ nm (log $\varepsilon$): 221 (4.64), 274 (3.85), 282 (3.78). IR




Scheme 7. Reactions of 14-hydroxyperrottetin E-11'-methyl ether (**2**).




Scheme 8. Synthesis of compound **2**.

$\nu_{max}^{neat}$ $cm^{-1}$: 3025, 2925, 1760, 1590, 1500, 1420, 1365, 1260, 1200, 1160, 1140, 1105, 1035, 1010. $^{13}C$ NMR $\delta$: 20.4 (*q*), 21.0 (*q*), 36.7 (*t*), 37.1 (*t*), 37.5 (*t*), 55.0 (*q*), 111.5 (*d*),114.1 (*d*), 118.1 (*d*), 119.0 (*d*), 120.2 (*d*), 120.8 (*d*), 121.4 (*d*), 123.3 (*d*), 125.8 (*d*), 129.1 (*d*), 129.2 (*d*), 129.4 (*d*), 136.2 (*s*), 139.8 (*s*), 140.7 (*s*), 143.2 (*s*), 148.2 (*s*), 150.8 (*s*), 155.2 (*s*), 159.6 (*s*), 168.7 (*s*), 169.2 (*s*). $^1H$ NMR: see Table 1. EIMS *m/z* (rel. int.): 524 $[M]^+$ (4), 483 (15), 482 (44), 361 (25), 333 (43), 319 (57), 211 (41), 121 (68), 107 (36), 105 (16), 91 (21), 77 (22).

*Methylation of compound* **1**. To a soln of **1** (20 mg) in dry $Me_2CO$ (10 ml) was added $K_2CO_3$ (2 g) and MeI (0.5 ml). The reaction mixt. was refluxed for 3 hr and filtered. The filtrate was evapd to give an oil (45 mg), which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield **5** (21 mg; 98.6%) as an oil, which was identical with the triMe ether (**5**) of perrottetin E (**3**) isolated from *Radula* species [6].

*Ethylation of compound* **3**. To a soln of **3** (62 mg) in dry $Me_2CO$ (10 ml) was added $K_2CO_3$ (2.38 g) and EtI (1.5 ml). The reaction mixt. was refluxed for 2 hr and filtered. The filtrate was evapd to give an oil (89 mg), which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield perrottetin E triEt ether (**6**) (68 mg; 91.6%) as an oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3025, 2975, 2925, 1600, 1580, 1500, 1250, 1210, 1150, 1115, 1040. $^1H$ NMR $\delta$: 1.28 (3H, *t*, $J = 6.8$ Hz, –OEt), 1.36 (3H, *t*, $J = 6.8$ Hz, –OEt), 1.38 (3H, *t*, $J = 6.8$ Hz, –OEt), 2.81 (4H, *m*, H-7', H-8'), 2.87 (4H, *m*, H-7, H-8), 4.01 (6H, *m*, 3 × OEt), 6.68–7.19 (15H, *m*, aromatic protons). $^{13}C$ NMR $\delta$: 14.7 (*q*), 14.9 (*q*), 36.9 (*t*), 37.0 (*t*), 37.9 (*t*), 38.1 (*t*), 63.3 (*t*), 64.9 (*t*), 111.9 (*d*), 115.0 (*d*), 115.1 (*d*), 117.1 (*d*), 120.8 (*d*), 121.4 (*d*), 124.3 (*d*), 129.2 (*d*), 135.0 (*s*), 135.5 (*s*), 143.1 (*s*), 143.4 (*s*), 145.7 (*s*), 148.9 (*s*), 156.5 (*s*), 159.0 (*s*). HRMS: found: $[M]^+$ *m/z* 510.2743; $C_{34}H_{38}O_4$ requires: 510.2770. EIMS *m/z* (rel. int.): 510 $[M]^+$ (64), 375 (69), 239 (30), 213 (54), 212 (25), 211 (90), 149 (24), 147 (23), 135 (96), 133 (27), 121 (43), 107 (100), 105 (25), 91 (28).

*Birch reduction of compound* **6**. To liquid $NH_3$ (*ca* 30 ml) was added Na (120 mg) and the mixt. stirred for 10 min at −70 to −80°. To the reaction mixt. was added a soln of **6** (68 mg) in $Et_2O$ (5 ml) and stirred for 1 hr. After standing at room temp. for 1 hr, $NH_4Cl$ (10 g) was added, which was partitioned between EtOAc and $H_2O$. The EtOAc layer was dried ($MgSO_4$) and evapd to give an oil (78 mg), which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield 3,4'-diethoxydihydrostilbene (**7**) (31 mg; 86.1%) and 3-ethoxy-4'-hydroxydihydrostilbene (**8**) (28 mg; 86.7%) as an oil.

*Compound* **7**. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3025, 2975, 2925, 1610, 1600, 1585, 1510, 1480, 1240, 1170, 1150, 1110, 1045. $^1H$ NMR $\delta$: 1.39 (6H, *t*, $J$ = 6.8 Hz, 2× -OEt), 2.84 (4H, *br s*, H-α, H-β), 3.99 (4H, *q*, $J$ = 6.8 Hz, 2× -OEt), 6.71 (1H, *br s*, H-2), 6.72 (1H, *br d*, $J$ = 7.6 Hz, H-4), 6.75 (1H, *br d*, $J$ = 7.6 Hz, H-6), 6.80 (2H, *d*, $J$ = 8.5 Hz, H-3', H-5'), 7.07 (2H, *d*, $J$ = 8.5 Hz, H-2', H-4'), 7.17 (1H, *dd*, $J$ = 7.6, 7.6 Hz, H-5). $^{13}C$ NMR $\delta$: 14.9 (*q*), 36.9 (*t*), 38.2 (*t*), 63.3 (*t*), 63.5 (*t*), 111.8 (*d*), 114.5 (*d*), 114.9 (*d*), 120.8 (*d*), 129.2 (*d*), 129.3 (*d*), 133.8 (*s*), 143.5 (*s*), 157.2 (*s*), 159.0 (*s*). HRMS: found: $[M]^+$ 270.1632; $C_{18}H_{22}O_2$ requires: 270.1632. EIMS *m/z* (rel. int.): 270 $[M]^+$ (32), 136 (12), 135 (100), 107 (81), 77 (13).

*Compound* **8**. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 3025, 2975, 2900, 1610, 1585, 1580, 1510, 1245, 1160, 1150, 1040. $^1H$ NMR $\delta$: 1.40 (3H, *t*, $J$ = 7.1 Hz, -OEt), 2.83 (4H, *br s*, H-α, H-β), 4.01 (2H, *q*, $J$ = 7.1 Hz, -OEt), 5.05 (1H, *br s*, -OH), 6.73 (2H, *d*, $J$ = 8.6 Hz, H-3', H-5'), 6.71–6.76 (3H, *m*, H-2, H-3, H-5), 7.03 (2H, *d*, $J$ = 8.6 Hz, H-2', H-4'), 7.17 (1H, *dd*, $J$ = 7.6, 7.6 Hz, H-4). $^{13}C$ NMR $\delta$: 14.9 (*t*), 36.9 (*t*), 38.2 (*t*), 63.4 (*t*), 111.9 (*d*), 115.0 (*d*), 115.2 (*d*), 129.2 (*d*), 129.5 (*d*), 134.0 (*s*), 143.4 (*s*), 153.7 (*s*), 158.9 (*s*). HRMS: found: $[M]^+$ *m/z* 242.1325; $C_{16}H_{18}O_2$ requires: 242.1307. EIMS *m/z* (rel. int.): 242 $[M]^+$ (20), 107 (100), 77 (19).

*Ethylation of compound* **1**. To a soln of **1** (60 mg) in dry $Me_2CO$ (10 ml) was added $K_2CO_3$ (2.38 g) and EtI (1 ml). The reaction mixt. was treated in the same manner as described above to give perrottetin E-11,1'-diethyl-11'-methyl ether (**9**) (62 mg; 91.7%) as an oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3025, 2975, 2925, 1600, 1580, 1500, 1260, 1210, 1150, 1120, 1040. $^1H$ NMR $\delta$: 1.27 (3H, *t*, $J$ = 7.1 Hz, -OEt), 1.39 (3H, *t*, $J$ = 7.1 Hz, -OEt), 2.81 (4H, *m*, H-7', H-8'), 2.86 (4H, *m*, H-7, H-8), 3.74 (3H, *s*, -OMe), 3.98 (2H, *q*, $J$ = 7.1 Hz, -OEt), 4.01 (2H, *q*, $J$ = 7.1 Hz, -OEt), 6.67–7.18 (15H, *m*, aromatic protons). $^{13}C$ NMR $\delta$: 14.8 (*q*), 36.8 (*t*), 36.9 (*t*), 37.8 (*t*), 38.0 (*t*), 55.0 (*q*), 63.2 (*t*), 64.9 (*t*), 111.3 (*t*), 111.8 (*t*), 114.2 (*d*), 114.9 (*d*), 117.0 (*d*), 120.7 (*d*), 121.4 (*d*), 124.2 (*d*), 129.2 (*d*), 134.9 (*d*), 135.4 (*s*), 143.1 (*s*), 143.3 (*s*), 145.6 (*s*), 148.8 (*s*), 156.4 (*s*), 159.0 (*s*), 159.6 (*s*). HRMS: found: $[M]^+$ *m/z* 496.2623; $C_{33}H_{36}O_4$ requires: 496.2613. EIMS *m/z* (rel. int.): 496 $[M]^+$ (18), 361 (69), 239 (13), 225 (15), 213 (25), 211 (65), 135 (37), 121 (100), 107 (66), 105 (25), 91 (40), 77 (21).

*Birch reduction of compound* **9**. To liquid $NH_3$ (*ca* 30 ml) was added Na (110 mg) and the mixt. stirred for 5 min at −70 to −80°. To the reaction mixt. was added a soln of **9** (50 mg) in $Et_2O$ (2 ml) and stirred for 30 min. After standing at room temp. for 2 hr, the reaction mixt. was poured into cooled 1 M HCl and extracted with $Et_2O$. The $Et_2O$ layer was washed with brine, dried ($MgSO_4$) and the solvent evapd to afford an oil (69 mg), which was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to yield 3-ethoxy-4'-hydroxydihydrostilbene (**8**) (20 mg, 82.0%) and 4-ethoxy-3'-methoxydihydrostilbene (**10**) (22 mg, 85.3%) as an oil.

*Compound* **10**. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3030, 2975, 2925, 1610, 1600, 1585, 1510, 1240, 1150, 1110, 1045. $^1H$ NMR $\delta$: 1.39 (3H, *t*, $J$ = 7.1 Hz, -OEt), 2.85 (4H, *br s*, H-α, H-β), 3.77 (3H, *s*, -OMe), 4.00 (2H, *q*, $J$ = 7.1 Hz, -OEt), 6.72 (1H, *br s*, H-2'), 6.73 (1H, *br d*, $J$ = 7.6 Hz, H-4'), 6.75 (1H, *br d*, $J$ = 7.6 Hz, H-6'), 6.79 (2H, *d*, $J$ = 8.5 Hz, H-3, H-5), 7.07 (2H, *d*, $J$ = 8.5 Hz, H-2, H-4), 7.19 (1H, *dd*, $J$ = 7.6, 7.6 Hz, H-5'). $^{13}C$ NMR $\delta$: 14.9 (*q*), 36.9 (*t*), 38.2 (*t*), 55.1 (*t*), 63.5 (*t*), 111.3 (*d*), 114.3 (*d*), 114.4 (*d*), 120.9 (*d*), 129.3 (*d*), 133.7 (*s*), 143.5 (*s*), 157.2 (*s*), 159.7 (*s*). HRMS: found: $[M]^+$ *m/z* 256.1478; $C_{17}H_{20}O_2$ requires: 256.1464. EIMS *m/z* (rel. int.): 256 $[M]^+$ (28), 135 (100), 121 (16), 107 (97), 91 (13).

*Wadsworth–Emmons olefination of compound* **11**. To an ice-cooled soln of dimethyl [(3-methoxyphenyl)methyl]phosphonate (**12**) (2.42 g) in dry DMF (30 ml) under Ar was added KO*t*-Bu (1.23 g) in one portion. After stirring for 15 min at 0–5°, a soln of *p*-ethoxybenzaldehyde (**11**) (1.0 g) in dry DMF (20 ml) was added to the resulting yellow soln over 30 min. After stirring at room temp. for 2 hr, the reaction mixt. was poured into ice-$H_2O$, acidified to pH 4 with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent evapd to give an oil (2.38 g), which was chromatographed on Sephadex LH-20 with $CHCl_3$–MeOH (1:1) to afford 4-ethoxy-3'-methoxystilbene (**13**) (1.238 g; 73.1%) as needles. Mp 86.0–87.0°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2975, 2925, 1600, 1580, 1510, 1290, 1250, 1158, 1118, 1040, 970. $^1H$ NMR $\delta$: 1.42 (3H, *t*, $J$ = 7.1 Hz, -OEt), 3.84 (3H, *s*, -OMe), 4.05 (2H, *q*, $J$ = 7.1 Hz, -OEt), 6.79 (1H, *ddd*, $J$ = 8.1, 1.7, 1.7 Hz, H-4'), 6.88 (2H, *d*, $J$ = 8.5 Hz, H-3, H-5), 7.02 (1H, *dd*, $J$ = 1.7, 1.7 Hz, H-2'), 7.05 (1H, *d*, $J$ = 8.1 Hz, -CH=CH-), 7.08 (1H, *dd*, $J$ = 8.1, 1.7 Hz, H-6'), 7.26 (1H, *dd*, $J$ = 8.1, 8.1 Hz, H-5'), 7.44 (2H, *d*, $J$ = 8.5 Hz, H-2, H-6). $^{13}C$ NMR $\delta$: 14.8 (*q*), 55.1 (*q*), 63.4 (*t*), 111.5 (*d*), 112.8 (*d*), 114.7 (*d*), 119.0 (*d*), 126.4 (*d*), 127.7 (*d*), 128.6 (*d*), 129.5 (*d*), 129.9 (*s*), 139.1 (*s*), 158.7 (*s*), 159.9 (*s*). EIMS *m/z* (rel. int.): 256 $[M]^+$ (64), 136 (53), 135 (97), 121 (51), 108 (31), 107 (100), 91 (45), 78 (52), 77 (59); (Found: C, 80.64; H, 7.13; calcd for $C_{19}H_{18}O_2$: C, 80.28; H, 7.13).

*Hydrogenation of* **13**. Compound **13** (200 mg) in EtOAc (30 ml) was hydrogenated in the presence of 20% Pd-C (200 mg) at room temp. Catalyst was filtered off and the filtrate concd to afford 4-ethoxy-3'-methoxydihydrostilbene (**12**) (188 mg, 93.3%) as an oil.

*Coupling of* **14** *with ethyl* p-*bromobenzoate*. To a soln of 3-hydroxy-4-benzyloxybenzaldehyde (**14**) (10.14 g) and ethyl *p*-bromobenzoate (9.22 g) in dry pyridine (80 ml) under Ar were added dry $K_2CO_3$ (16.7 g) and CuO (6.4 g). The mixt. was heated under reflux for 24 hr with vigorous stirring. After pyridine was evapd *in vacuo*, $CHCl_3$ (200 ml) was added to the residue. The ppt. was filtered over Celite and washed with $CHCl_3$. The combined filtrates were washed with brine, dried ($MgSO_4$) and the solvent evapd to afford an oil (18.50 g), which was chromatographed on silica gel using a *n*-hexane EtOAc gradient. The eluant with 20% EtOAc–*n*-hexane was evapd to yield ethyl 4-(2-benzyloxy-5-formylphenoxy)benzoate (**15**) (11.85 g; 81.3%). Mp 98.0–99.5° ($Et_2O$–*n*-hexane). UV $\lambda_{max}$ nm (log ε): 212 (4.55), 292.5 (4.53), 322.5 (4.48). IR $\nu_{max}^{KBr}$ cm $^{-1}$: 1710, 1680, 1610, 1590, 1500, 1280, 1230, 1110, 1100, 1020. $^1H$ NMR $\delta$: 1.39 (3H, *t*, $J$ = 7.1 Hz, -OEt), 4.37 (2H, *q*, $J$ = 7.1 Hz, -OEt), 5.15 (2H, *s*, $-OCH_2\phi$), 6.94 (2H, *d*, $J$ = 8.8 Hz, H-3, H-5), 7.12 (5H, *m*, $-\phi$), 7.14 (1H, *d*, $J$ = 8.3 Hz, H-3'), 7.65 (1H, *d*, $J$ = 2.0 Hz, H-6'), 7.71 (1H, *dd*, $J$ = 8.3, 2.0 Hz, H-4'), 8.01 (2H, *d*, $J$ = 8.8 Hz, H-2, H-6), 9.86 (1H, *s*, -CHO). $^{13}C$ NMR $\delta$: 14.2 (*q*), 60.6 (*t*), 70.6 (*t*), 114.0 (*d*), 115.9 (*d*), 122.3 (*d*), 124.8 (*d*), 126.8 (*d*), 128.0 (*d*), 128.4 (*d*), 128.8 (*d*), 130.5 (*s*), 131.4 (*d*), 135.3 (*s*), 144.4 (*s*), 155.6 (*s*), 161.5 (*s*), 165.9 (*s*), 189.8 (*d*). EIMS *m/z* (rel. int.): 376 $[M]^+$ (9), 331 (3), 240 (2), 104 (2), 91 (100), 76 (3); (found: C, 73.59; H, 5.36; calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36).

*Wadsworth–Emmons olefination of compound* **15**. To an ice-cooled soln of dimethyl [(3-methoxyphenyl)methyl]phosphonate (**12**) (2.06 g) in dry DMF (50 ml) under Ar was added KO*t*-Bu (0.95 g) in one portion. After stirring for 15 min at 0–5°, a soln of **15** (2 g) in dry DMF (30 ml) was added to the resulting yellow soln over 30 min. After stirring at room temp. for 4 hr, the reaction mixt. was poured into ice-$H_2O$, acidified to pH 4 with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evapd to give an oil, which was chromatographed on silica gel using a *n*-hexane–EtOAc gradient. The eluant with 30% EtOAc–*n*-hexane was evapd to yield **16** (1.98 g; 77.6%) as an oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3025, 2975, 2925, 1710, 1600, 1590, 1500, 1270, 1160, 1110, 1010. $^1H$ NMR $\delta$: 1.39 (3H, *t* $J$ = 7.1 Hz, -OEt), 3.83 (3H, *s*, -OMe), 4.36 (2H, *q*, $J$ = 7.1 Hz, -OEt), 5.07 (2H, *s*, $-OCH_2\phi$), 6.92 (1H, *d*, $J$ = 16.6 Hz, -CH=CH-), 6.99 (1H, *d*, $J$ = 16.6 Hz, -CH=CH-), 6.79–7.33 (14H, *m*, aromatic protons), 8.00 (2H, *d*, $J$ = 9.0 Hz, H-2, H-6). $^{13}C$ NMR $\delta$: 14.3 (*q*), 55.1 (*q*), 60.6 (*t*), 70.7 (*t*), 111.7 (*d*), 113.2 (*d*), 115.1 (*d*), 115.7 (*d*), 119.0 (*d*), 120.2 (*d*), 124.3 (*s*), 124.4 (*d*),

126.9 (*d*), 127.5 (*d*), 127.7 (*d*), 128.3 (*d*), 129.5 (*d*), 131.4 (*d*), 136.3 (*s*), 138.6 (*s*), 144.1 (*s*), 150.2 (*s*), 159.9 (*s*), 162.2 (*s*), 166.0 (*s*). EIMS *m/z* (rel. int.): 480 $[M]^+$ (30), 467 (17), 389 (30), 275 (26), 316 (41), 224 (12), 153 (11), 152 (11), 91 (100).

*Reduction of* **16** *with* $LiAlH_4$. To an ice-cooled suspension of $LiAlH_4$ (0.48 g) in dry $Et_2O$ (30 ml) under Ar was added a soln of **16** (1.78 g) in dry $Et_2O$ (20 ml) over 30 min with stirring at room temp. After stirring for 4 hr, EtOAc was added to the reaction mixt. The mixt. was then poured into ice-$H_2O$, acidified with 1 M HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and evapd. The residue (1.82 g) was recrystallized from EtOAc–*n*-hexane to give **17** (1.61 g; 99.1%) as needles. Mp 79.0–81.0° ($Et_2O$–*n*-hexane). UV $\lambda_{max}$ nm (log $\varepsilon$): 212.5 (4.36), 290.5 (4.20), 322.0 (4.13). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3250, 1590, 1500, 1270, 1210, 1130, 1110, 1020. $^1H$ NMR ($\delta$): 3.81 (3H, *s*, –OMe), 4.64 (2H, *s*, $-CH_2OH$), 5.09 (2H, *s*, $-OCH_2\phi$), 7.00–7.35 (18H, *m*, aromatic protons). $^{13}C$ NMR $\delta$: 55.1 (*q*), 64.7 (*t*), 70.9 (*t*), 111.6 (*d*), 113.1 (*d*), 115.4 (*d*), 116.8 (*d*), 119.0 (*d*), 119.5 (*d*), 123.4 (*d*), 127.0 (*d*), 127.7 (*d*), 127.8 (*d*), 128.3 (*d*), 128.4 (*d*), 129.5 (*d*), 131.4 (*s*), 134.9 (*s*), 136.6 (*s*), 138.7 (*s*), 145.4 (*s*), 150.1 (*s*), 157.7 (*s*), 159.8 (*s*). EIMS *m/z* (rel. int.): 438 $[M]^+$ (100), 408 (11), 347 (61), 329 (25), 317 (85), 224 (34), 196 (17), 181 (21), 165 (14), 91 (92); (found; C, 79.67; H, 5.98; calcd for $C_{29}H_{26}O_4$ requires: C, 79.43; H, 5.98).

*Oxidation of* **17** *with PDC*. To a suspension of pyridinium dichromate (PDC) (1.74 g) in dry $CH_2Cl_2$ (50 ml) under Ar was added a soln of **17** (0.60 g) in dry $CH_2Cl_2$ (30 ml) over 30 min with stirring. After stirring for 12 hr, the reaction mixt. was filtered over Celite. The filtrate was evapd to afford an oil (0.695 g), which was chromatographed on silica gel with a 20% *n*-hexane–EtOAc gradient. The eluant with 20% EtOAc–*n*-hexane was evapd to yield **18** (0.568 g; 95.1%) as needles. Mp 78–80° (*n*-hexane). UV $\lambda_{max}$ nm (log $\varepsilon$): 213.5 (4.69), 225 (4.65), 255.5 (4.66), 325 (3.73). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1690, 1595, 1580, 1500, 1260, 1230, 1160, 1110. $^1H$ NMR $\delta$: 3.92 (3H, *s*, –OMe), 5.14 (2H, *s*, $-CH_2\phi$), 7.02 (1H, *d*, $J = 16.3$ Hz, –CH=CH–), 7.10 (1H, *d*, $J = 16.3$ Hz, –CH=CH–), 6.89–7.44 (14H, *m*, aromatic protons), 7.92 (2H, *d*, $J = 8.8$ Hz, H-2′, H-6′), 9.91 (1H, *s*, –CHO). $^{13}C$ NMR $\delta$: 55.1 (*q*), 70.7 (*t*), 111.8 (*d*), 113.2 (*d*), 115.1 (*d*), 116.3 (*d*), 119.1 (*d*), 120.4 (*d*), 124.8 (*d*), 126.9 (*d*), 127.5 (*d*), 127.8 (*d*), 128.0 (*d*), 128.3 (*d*), 129.6 (*d*), 131.0 (*s*), 131.6 (*d*), 131.7 (*d*), 136.2 (*s*), 138.6 (*s*), 143.6 (*s*), 150.2 (*s*), 159.9 (*s*), 163.6 (*s*), 190.6 (*d*). HRMS: (found: $[M]^+$ *m/z* 436.1664; $C_{29}H_{24}O_4$ requires: 436.1675. EIMS *m/z* (rel. int.): 436 $[M]^+$ (76), 345 (84), 317 (16), 224 (24), 209 (7), 196 (17), 165 (9), 153 (13), 91 (100); (found; C, 79.51; H, 5.57; calcd for $C_{29}H_{24}O_4$ requires: C, 79.79; H, 5.54).

*Wadsworth–Emmons olefination of* **18**. To an ice-cooled soln of diethyl [(3-benzyloxyphenyl)methyl]phosphonate (**19**) (140 mg) in dry DMF (10 ml) under Ar was added KO*t*-Bu (77 mg) in one portion. After stirring for 15 min at 0–5°, a soln of **18** (100 mg) in dry DMF (10 ml) was added to the resulting yellow soln over 10 min. The reaction mixt. was treated in the same manner as described in the synthesis of **16** to give **20** (75 mg; 53.1%) as needles. Mp 110–111.5° (from *n*-hexane–$Et_2O$). UV $\lambda_{max}$ nm (log $\varepsilon$): 211.0 (4.51), 325.5 (4.56). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3025, 2925, 1600, 1590, 1500, 1450, 1430, 1280, 1250, 1220, 1150, 1050, 1020, 960. $^1H$ NMR $\delta$: 3.81 (3H, *s*, –OMe), 5.09 (4H, *s*, $2 \times -CH_2\phi$), 6.91–7.50 (29H, *m*, aromatic protons and $2 \times$ –CH=CH–); HRMS: found: $[M]^+$ *m/z* 616.2632; $C_{43}H_{36}O_4$ requires; 616.2613.

*Hydrogenation of* **20**. Compound **20** (49.0 mg) in EtOAc (30 ml) was hydrogenated in the same manner as described above. The reaction mixt. was treated in the same manner as described in the synthesis of **10** to give **1** (28 mg; 80.7%) as an oil. This compound was identical with perrottetin E-11′-methyl ether (**1**) isolated from the liverwort.

*Acetylation of* **2**. A mixt. of **2** (15 mg), $Ac_2O$ (1 ml) and pyridine (1 ml) was stirred at room temp. for 24 hr. Usual work-up afforded the triacetate (**21**) (16 mg; 83.8%) as an oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3025, 2940, 1760, 1595, 1500, 1410, 1365, 1260, 1190, 1110, 1040, 1010, 910, 900. EIMS *m/z* (rel. int.): 582 $[M]^+$ (1), 542 (65), 499 (16), 419 (33), 377 (42), 375 (24), 335 (48), 334 (31), 333 (100), 228 (18), 225 (31), 213 (34), 212 (24), 211 (78), 199 (29), 121 (49), 107 (31), 105 (20), 91 (20). $^1H$ NMR: see Table 1.

*Preparation of* **22**. A soln of **2** (10 mg) in $CHCl_3$ (5 ml) was allowed to stand for 5 days. The soln was concd *in vacuo* to give an oil (11 mg) which was purified by prep. TLC ($C_6H_6$–EtOAc, 4:1) to give *p*-quinone (**22**) (5 mg; 50.2%) as a light yellow oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3530, 2900, 1650, 1590, 1490, 1260, 1200, 1160. $^1H$ NMR $\delta$: 2.74–2.82 (8H, *m*, $4 \times -CH_2$), 3.76 (3H, *s*, OMe), 5.43 (1H, *br s*, OH), 6.51–7.18 (14H, *m*, aromatic protons). EIMS *m/z* (rel. int.): 454 $[M]^+$ (41), 334 (15), 333 (61), 212 (21), 211 (100), 121 (20), 107 (14), 105 (11), 91 (13).

*Wadsworth–Emmons olefination of* **18**. To an ice-cooled soln of dimethyl [[2,5-bis(benzyloxy)phenyl]methyl]phosphonate (**23**) (530 mg) in dry DMF (30 ml) under Ar was added KO*t*-Bu (154 mg) in one portion. After stirring for 15 min at 0–5°, a soln of **18** (200 mg) in dry DMF (10 ml) was added to the resulting yellow solution over 20 min. The reaction mixt. was treated in the same manner as described in the synthesis of **16** to yield **24** (225 mg; 67.9%) as needles. Mp 127.5–129° (from $Et_2O$–*n*-hexane). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3025, 2925, 1590, 1580, 1500, 1270, 1220, 1170, 1120, 1020, 960. $^1H$ NMR $\delta$: 3.82 (3H, *s*, –OMe), 5.06 (2H, *s*, $-OCH_2\phi$), 5.08 (2H, *s*, $-CH_2\phi$), 5.10 (2H, *s*, $-CH_2\phi$), 6.78–7.46 (33H, *m*, aromatic protons and –CH=CH–). $^{13}C$ NMR $\delta$: 55.1 (*q*), 70.6 (*t*), 70.8 (*t*), 71.5 (*t*), 111.6 (*d*), 112.9 (*d*), 113.2 (*d*), 114.4 (*d*), 115.2 (*d*), 117.0 (*d*), 119.1 (*d*), 119.6 (*d*), 121.9 (*d*), 123.6 (*d*), 127.0 (*d*), 127.3 (*d*), 127.4 (*d*), 127.7 (*d*), 128.2 (*d*), 128.3 (*d*), 128.5 (*d*), 128.9 (*d*), 129.5 (*d*), 131.4 (*s*), 132.2 (*s*), 136.6 (*s*), 137.2 (*s*), 138.7 (*s*), 145.3 (*s*), 150.2 (*s*), 150.7 (*s*), 153.3 (*s*), 157.9 (*s*), 159.9 (*s*). EIMS *m/z* (rel. int.): 726 $[M]^+$ (3), 604 (17), 514 (15), 513 (35), 181 (37), 91 (100), 65 (46); (Found; C, 82.45; H, 6.32; calcd for $C_{50}H_{46}O_5$; C, 82.62; H, 6.38).

*Hydrogenation of* **24**. Compound **24** (92 mg) in EtOAc (30 ml) was hydrogenated in the same manner as described above to furnish **2** (38 mg; 65.4%) and *p*-quinone (**22**) (8 mg; 13.8%) as an oil. Compound **2** was identical with 14-hydroxyperrottetin E-11′-methyl ether isolated from the liverwort.

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