# NEW SUBSTITUTED BIBENZYLS OF FRULLANIA BRITTONIAE SUBSP. TRUNCATIFOLIA

YOSHINORI ASAKAWA,\*† KAZUAKI TANIKAWA‡ and TAKAAKI ARATANI‡ † Laboratoire de Chimie Organique des Substances Naturelles, associé au CNRS, Institut de Chimie, Université Louis Pasteur, 1 rue Blaise Pascal, 67008 Strasbourg, France; ‡ Interdisciplinary Studies of Natural Environment, Faculty of Integrated Arts and Sciences, Hiroshima University, 730 Hiroshima, Japan

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**Abstract**—The two dihydrostilbenes, Brittonin A and Brittonin B, have been isolated from *Frullania brittoniae* subsp. *truncatifolia* (*F. muscicola*). They were identified as 3,4,5,3',4',5'-hexamethoxybibenzyl and 3,4,5,3'-tetramethoxy-4',5',-methylenedioxybibenzyl respectively.

### INTRODUCTION

In preceding papers [1a-d], dealing with the examination of the allergy-inducing components of European Frullania we have reported the isolation, structure and allergenic properties (contact dermatitis) of new eudesmanolides and eremophilanolides and a new sesquiterpene aldehyde. We have now investigated the constituents of the Japanese species Frullania brittoniae subsp. truncatifolia (F. muscicola) and report the isolation and characterisation of two new bibenzyl derivatives.

## **RESULTS AND DISCUSSION**

Air-dried material was extracted with ether and the crude extract after chromatography on silica gel using a *n*-hexane-ethyl acetate gradient furnished brittonin A (1) and brittonin B (2).



Brittonin A (1). The spectral properties summarized in the Experimental suggested structure (1) for this substance and it was further confirmed by synthesis. A Wittig condensation of 3,4,5-trimethoxybenzaldehyde with 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (3) gave cis- and trans-3,4,5,3',4',5'-hexamethoxystilbenes (4) which were hydrogenated in the presence of Pd–C to a dihydrostilbene, the physical, chromatographic and spectroscopic properties of which were completely identical to those of the natural brittonin A (1).



Brittonin B (2).  $C_{19}H_{22}O_6$  (M<sup>+</sup> 346). The IR and UV spectra of the compound closely resembled those of brittonin A. The PMR spectrum showed the presence of 22 protons: four OMe groups (3.83 ppm, s, 9H and 3.87 ppm, s, 3H), four protons (2.80 ppm, s), assignable to two methylenes of a bibenzyl group, methylenedioxy protons (5.88 ppm, s), one pair of aromatic protons (6.26 ppm, d, J = 1 Hz and 6.33 ppm, d, J = 1 Hz) and another pair of aromatic protons (6.33 ppm, s, 2H). The PMR signal pattern of the aromatic region was similar to that of authentic 3,4-methylenedioxy-5-methoxyallylbenzene. The base peak at m/e 181 and the intense peak at m/e 165 in the MS showed that three of the four OMe groups were located on one benzene ring, while the second benzene ring was substituted by one OMe and one methylenedioxy group. On the basis of the above spectral properties and the probable biogenetic relationship with (1), structure (2) was deduced for brittonin B; it was confirmed by synthesis. A Wittig condensation of 3,4,5,-trimethoxybenzyltriphenylphosphonium bromide (3) with 3-methoxy-4,5-methylenedioxybenzaldehvde (5) derived from vanillin through three steps, gave the stilbene mixture (6), which was hydrogenated in the presence of Pd-C, to a dihydrostilbene. This corresponded in all respects with brittonin B (2).

In the genus Frullania, F. tamarisci [1a, b], F. tamarisci subsp. obscura [1d], F. dilatata [1c], F. usamiensis [3] and F. nisquallensis [4], so far examined, contain sesquiterpene lactones and these lactones are major components in each species. F. dilatata and F. brittoniae subsp. truncatifolia are closely related species [5]. However, contrary to our expectation, no sesquiterpene lac-

<sup>\*</sup>Present address: Department of Chemistry, Faculty of Science, Hiroshima University, 730 Hiroshima, Japan.



tones were detectable by TLC and GLC in the extracts of our samples of F. *brittoniae* subsp. *truncatifolia*; in agreement with this absence, the extract of the present species had no allergenic activity [4].

Stilbene derivatives have been found mainly in the higher plants [6] and some of them possess fungitoxic activity [7]. However, bibenzyl derivatives are less usual natural products and hydroxy- and methoxy-substituted bibenzyls have been isolated from only a few higher plants [8]. However, recently, several bibenzyl derivatives have also been found in the liverworts *Lunularia cruciata* [9, 10], *Pellia epiphylla* [11], and *Marchantia polymorpha* [12]. Among them, lunularic acid (7) has been characterized as an endogenous growth inhibitor of the lower plants, algae and liverworts [9, 10].



#### **EXPERIMENTAL**

All mp's are uncorrected. Analytical and preparative TLC were carried out on Si gel 60  $F_{254}$  plates using the solvent *n*-hexane-C<sub>6</sub>H<sub>6</sub>-EtOAc (5:14:6). The compounds were detected by UV light (254 and 360 nm) and by heating after spraying 50% H<sub>2</sub>SO<sub>4</sub>. Bibenzyls showed intense reddish orange spots with the H<sub>2</sub>SO<sub>4</sub> reagent. MS were recorded under the following conditions: chamber volt., 70 V; total emission, 8  $\mu$ A; ion chamber temp, 150°; target current, 50  $\mu$ A; direct inlet system. IR spectra were recorded in CHCl<sub>3</sub> soln and UV spectra in EtOH. PMR spectra were measured at 60 MHz using CDCl<sub>3</sub> as solvent and TMS as internal standard.

Extraction and isolation. Fresh material (60 g) was collected in October, 1974 in Hiroshima Prefecture, Japan and washed with H<sub>2</sub>O for several times. After being air-dried for one week, the ground material (30 g) was extracted with Et2O and the crude extract (1.31g) chromatographed on Si gel using a n-hexane-EtOAc gradient. From the n-hexane-EtOAc (4:1) fraction, brittonin A (1) was separated. Recrystallization from n-hexane gave white crystals, (30 mg), mp 142-143°; M<sup>+</sup> m/e 362 (rel. intensity, 16%), 182 (9), 181 (100), 148 (6), 85 (8), 83 (4),  $\lambda_{max}$  217 (log  $\epsilon$  4.37), 270 (3.20) and 279 nm (3.03); 3005, 2945, 2845, 1595, 1505, 1460, 1418, 1335, 1241, 1130, 1005, 970 and 830 cm<sup>-1</sup>. A viscous oil was obtained from the n-hexane-EtOAc (2:3) fraction. Purification in preparative-TLC furnished brittonin B (2), amorphous, (15 mg), M<sup>+</sup>m/e 346 (30), 181 (100), 165 (88), 148 (16), 136 (15), 120 (16);  $\lambda_{max}$  276 nm (log  $\epsilon$  3.27);  $\nu_{max}$  1635, 1593, 1510, 1465, 1330, 1130, 1095, 1040, 1005, 925, 830 cm<sup>-1</sup>.

Synthesis of Brittonin A (1). 3,4,5-Trimethoxybenzylalcohol (2.34 g) in  $C_6H_6$  (10 ml) was treated with 47% HBr (0.76 ml) with stirring for 2 hr at room temp. Work-up in the usual manner gave 3,4,5-trimethoxybenzyl bromide (88%), mp

71-72°; δ 3.85 ppm (s, 9H), 4.43 (s, 2H) and 6.60 ppm (s, 2H). To triphenylphosphine (2.77 g) in DMF (50 ml) was added 3,4,5-trimethoxybenzyl bromide (2.83 g) and the mixture was refluxed at 155° for 3 hr. Evaporation of the excess solvent gave a yellow mass, which was crystallized from C<sub>6</sub>H<sub>6</sub>-CHCl<sub>3</sub> (1:1) to give 3.4,5-trimethoxybenzyltriphosphonium bromide (3) (68%), mp 222–223  $\lambda_{\rm max}$  262 (log  $\epsilon$  3.85), 269 (3.84), 276  $(3.76); \ \nu_{max} \ 1590, \ 1503, \ 1463, \ 1435, \ 1240, \ 1125, \ 995, \ 970.$ 840 cm<sup>-1</sup>;  $\delta$  3.50 (s, 6H), 3.76 (s. 3H), 5.31 (d, J = 14 Hz. 2H), 6.46 (bs, 2H) and 7.6 (m, 15H). The mixture of the phosphonium salt (3) (2.56 g) and 3,4,5-trimethoxybenzaldehvde (1.06 g) was refluxed with NaOMe (0.34 g) in EtOH (40 ml) for 9 hr. The reaction mixture was treated in the usual manner to give crude cis- and trans-stilbenes (4) (98%), which were chromatographed on Si gel using n-hexane-EtOAc (4:1) to give pure cis- and trans-3,4,5,3',4',5'-hexamethoxystilbene. cis-*Isomer* (8.2 mg) mp 119–120°;  $C_{20}H_{24}O_6$  (M<sup>+</sup> m/e 360, 100%), 346 (22), 345 (64);  $\lambda_{max}$  306 nm (log 4.08);  $v_{max}$  1585, 1505, 1465, 1420, 1130, 1000, 860 cm<sup>-1</sup>;  $\delta$  3.70 (s. 12H, 4 × OMe), 380 (s, 6H,  $2 \times OMe$ ), 6.50 ppm (s. 6H), and trans-Isomer (330 mg), mp 211–212 ;  $C_{20}H_{24}O_6$  (M<sup>+</sup> m/e 360, 100%), 346 (46), 345 (48);  $\lambda_{max}$  316 (log  $\epsilon$  4.53), 327 (4.57), 344 (4.38);  $\nu_{max}$ 1585, 1500, 1460, 1418, 1350, 1130, 1000, 955, 830 cm<sup>-1</sup>;  $\delta$ 3.85 (s, 6H, 2  $\times$  OMe), 3.88 (s, 12H, 4  $\times$  OMe), 6.70 (s, 4H), 6.90 (s, 2H). cis- and trans-Stilbenes (4) (64 mg) in MeOH (10 ml) were hydrogenated in the presence of  $5^{\circ}_{10}$  Pd-C to give 3,4,5,3',4',5'-hexamethoxybibenzyl (57 mg), with physical, spectral and chromatographic properties identical with those of the natural product (1).

Synthesis of Brittonin B (2). Vanillin (7 g) in HOAc (50 ml) was treated with  $Br_2$  (3 ml) to give 5-bromovanillin (94%), mp 164-165°;  $\delta$  4.00 (s, 3H), 6.54 (bs, 1H), 7.40 (d, J = 1 Hz, 1H), 7.70 (d, J = 1 Hz, 1H), 9.75 ppm (s, 1H). A mixture of 5-bromovanillin (10 g) and 8% NaOH soln (180 ml) was heated in the presence of Cu-bronze (3g) in a rotatory autoclave at 220° for 3 hr. Work-up in the usual manner gave 3.4-dihydroxy-5-methoxybenzaldehyde (44%), mp 131-132 (lit. [13]  $132-133^{\circ}$ );  $\delta$  3.93 (s, 3H), 7.06 (d, J = 1 Hz, 1H), 7.13 (d, J = 1Hz, 1H), 9.75 ppm (s, 1H), which was refluxed with MeI (4.1 g) in the presence of CuO (0.4 g), K<sub>2</sub>CO<sub>3</sub> (5.7 g) and DMF (40 ml) for 4 hr at 135°. The reaction mixture was extracted with Et<sub>2</sub>O, washed successively with 3% HCl, 3% NaOH and  $H_2O$ , to give 3-methoxy-4,5-methylenedioxybenzaldehyde (86%), mp 130-131° (lit. [14] 129-130°). A mixture of the phosphonium salt (3) (1.83 g) and 3-methoxy-4,5-methylenedioxybenzaldehyde (5) (3 g) was refluxed for 6 hr in the manner described above, to obtain the stilbene mixture (6)  $(53^{\circ})$ , which was chromatographed on Si gel using n-hexane-EtOAc to yield the cis- and trans-3.4.5-3'-tetramethoxy-4'.5'-methylenedioxystilbenes (6). cis-Isomer (5 mg),  $M^+ m/e$  344 (100%). amorphous,  $\lambda_{max}$  310 nm (log  $\epsilon$  3.68);  $v_{max}$  1620, 1580, 1505, 1460, 1455, 1425, 1330, 1130, 1090, 1040, 1000, 925, 860 cm δ 3.70 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 5.90 (s, 2H), 6.4-6.5 (m, 4H), 6.66 (bs, 1H). 6.85 (bs. 1H) and trans-isomer (280 mg). mp 113–114°, M + m/e 344 (100%),  $\lambda_{max}$  312 (log  $\epsilon$  4.00), 331 (4.04), 346 nm (3.91);  $v_{max}$  1620, 1585, 1505, 1465, 1450, 1430, 1130, 1090, 1040, 1000, 955, 930,  $830 \text{ cm}^{-1}$ ,  $\delta$  3.85, 3.90, 3.95 (s. 12H,  $4 \times OMe$ ), 5.98 (s. 2H), 6.66 (m. 2H), 6.70 (s. 2H), 6.88 ppm (s, 2H). The catalytic hydrogenation of the stilbene mixture (140 mg) in the manner described above gave a bibenzyl (60 mg), with chromatographic, physical and spectral data identical with those of the natural product (2).

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#### REFERENCES

- (a) Knoche, H., Ourisson, G., Perold, G. W., Foussereau, J. and Maleville, J. (1969) Science 166, 239. (b) Perold, G. W., Muller, J.-C. and Ourisson, G. (1972) Tetrahedron 28, 5797. (c) Asakawa, Y., Muller, J.-C., Ourisson, G., Foussereau, J. and Ducoms, C. in press. (d) Asakawa, Y., Ourisson G. and Aratani, T. in press.
- Connolly, J. D. and Thornton, I. M. S. (1973) *Phytochemistry* 12, 631.
- 3. Asakawa, Y., Ourisson, G. and Aratani, T. unpublished results.

- Mitchell, J. C., Fritig, B., Singh, B. and Towers, G. H. N. (1970) J. Invest. Derm. 54, 233.
- Hattori, S. (1975) Miscellanea Bryologica et Lichenologica, 7, 27.
- Billek, G. (1964) Fortschr. Chem. Org. Naturst. 22, 115. Asakawa, Y. (1971) Bull. Chem. Soc. Japan 44, 2761.
- 7. Frykholm, K. O. (1945) Nature 155, 454.
- Lindstedt, G. (1950) Acta Chem. Scand. 4, 1246. Letcher, R. M., Nhamo, L. R. M. and Gumiro, I. T. (1972) J. Chem. Soc. Perkin 1, 206. Letcher, R. M. and Nhamo, L. R. M. (1972) J. Chem. Soc. Perkin 1, 2941. Hashimoto, T., Hasegawa, K., Yamaguchi, H., Saito, M. and Ishimoto, S. (1974) Phytochemistry 13, 2849.
- Valio, I. F. M., Burdon, R. S. and Schwabe, W. W. (1969) Nature 223, 1176.
- 10. Pryce, R. J. (1972) Phytochemistry 11, 1759.
- 11. Benešová, V. and Herout, V. (1970) Coll. Czech. Chem. Commun. 35, 1926.
- 12. Hopkins, B. J. and Perold, G. W. (1974) J. Chem. Soc. Perkin 1, 32.
- Bradley, W., Robinson R. and Schwarzenbach, G. (1930) J. Chem. Soc. 793.
- 14. Tomita, M. and Aoyagi, Y. (1968) Chem. Pharm. Bull. 16, 523.