Synthesis of Phytuberin[1]

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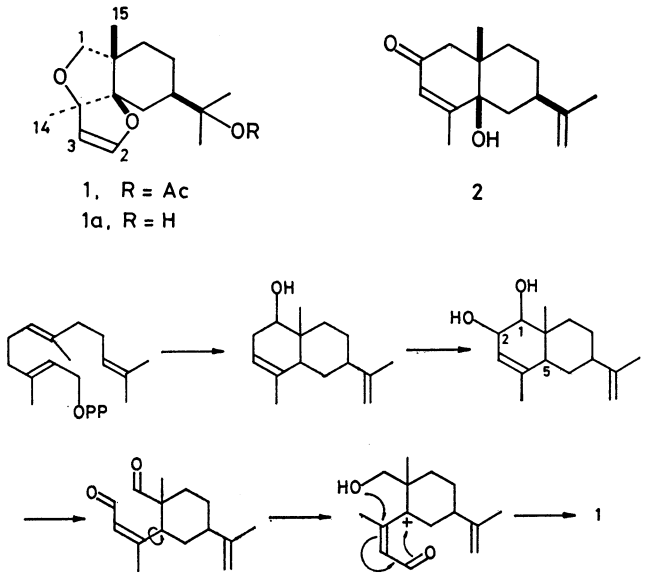
The first synthesis of phytuberin, which mimics the proposed biogeneses in critical stages, is described. The synthesis also establishes the absolute configuration.

The title compound, phytuberin (**1**), is a potential substance for an effective resistance in diseased potatoes[2] and a representative phytoalexin together with rishitin[3] in the genus *Solanum*. The sesquiterpene was first isolated in 1970 by Varns and Kuć[4] from infected potato tuber tissues (*Solanum tuberosum*), and the structure and relative configuration were determined in 1974 on the basis of the X-ray crystallographic analysis of dihydrophytuberin by Coxon and coworkers.[5] In view of the novel structure characterized by the presence of two hydrofuran rings and the biological importance, **1** is believed to be a subject of intense synthetic investigation. In a preliminary communication[6,7] we reported the synthesis of the compound, which mimics the proposed biogeneses[5,8] (*e.g.*, Scheme 1) in critical stages. The present paper describes details of the transformation of β-rotunol (**2**) into **1**, which, coupled with the synthesis[1] of **2**, completes the synthesis of the title compound.

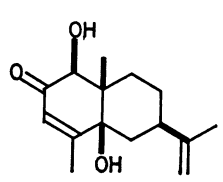


Scheme 1.

Results and Discussion

The proposed biogeneses[5,8] suggested that phytuberin (**1**) would probably be biosynthesized *via* formation of a C-5 and C-1 and/or C-2 oxygenated eudesmane from farnesyl pyrophosphate and subsequent cleavage of the C-1–C-2 bond followed by recyclization. β-Rotunol (**2**) is an eudesmane with oxo- and hydroxyl groups at C-2 and C-5 and hence a starting material suitable for the relevant cleavage and recyclization. Transformation of **2** into **1** was commenced by oxygenation at C-1; namely, **2** was oxidized under the Vedejs conditions[9] to give 1β,5β-diol (**3**) in 57% yield as a single product. Configuration of the hydroxyl group at C-1 was deduced from the formation of acetonide (**4**) by treatment with acetone in the presence of Amberlyst 15 at room temperature for 1 h. Contrary to the expectation, all attempted oxidative cleavage ($NaIO_4$ in aq THF, $Pb(OAc)_4$ in pyridine, or HIO_4 in aq THF) of the α-ketol (**3**) failed, the isopropenyl group being not left intact. Considering the lability of the isopropenyl group under the conditions, **4** was first converted into the corresponding 11,12-epoxide (**5**) by treatment with *m*-chloroperbenzoic acid in a heterogeneous mixture of 5% aqueous sodium hydrogencarbonate and dichloromethane. Reduction of the epoxy group of **5** with hydride reagents was examined under various conditions. The aimed reduction was achieved by treatment of **5** with lithium aluminium hydride (LAH) in a 5 : 2 mixture of 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF) *in an inverse addition manner*, giving tetrahydroxyeudesmane (**6**) in 56% yield from **3**. Smooth oxidative cleavage of the 1,2-diol system was accomplished by treatment of **6** with lead(IV) acetate in dry pyridine at room temperature. The reaction proceeded as expected to afford the relevant formyl γ-lactone (**7**) in a single step in 80% yield. The structure of **7** was assigned clearly on the basis of the spectral data. The mass spectrum displayed parent and fragmentation peaks at *m/e* 266 and 248 (M^+-H_2O). The IR spectrum (2710, 1755, 1720, and 1630 cm^{-1}) revealed the presence of a five-membered lactone and a formyl group. The NMR spectrum exhibited a six-proton singlet at δ 1.19, two three-proton singlets at δ 1.35 and 2.16, and a one-proton singlet at δ 9.36, which were readily assignable to the protons at 12-, 13-, 15-, 14-, and 1-carbon atoms,[10] respectively. Formation of **7** would involve oxidation of an hemiacetal intermediate (**8**) with excess lead(IV) acetate.

The final and most serious problem for the construction of phytuberin skeleton consisted in stereoselective formation of the A and B rings. Owing to difficulty of regioselective reduction of only the hindered formyl group, it was undertaken to reduce simultaneously both the formyl and lactone carbonyl groups. Treatment of the formyl γ-lactone (**7**) with diisobutylaluminium hydride (DIBAH) (3.5 mol equiv.) in DME followed by usual work-up effected reduction of the two relevant carbonyl groups followed by cyclization to two hydrofuran rings, giving alcohol, oil and $[\alpha]_D$ −40.6°, in a single step in 83% yield. The alcohol was converted smoothly into the acetate, oil and $[\alpha]_D$ −38.8°, in 84% yield by treatment with acetic anhydride and triethylamine in the presence of 4-(dimethylamino)pyridine at



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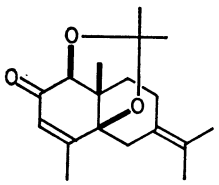

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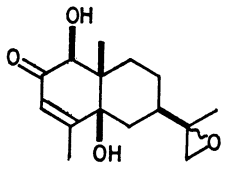

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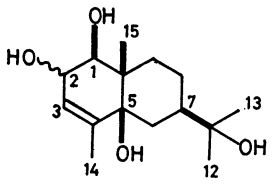

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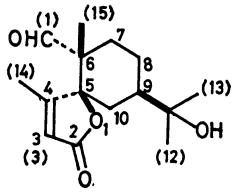

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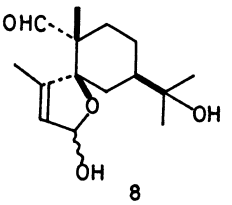

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room temperature. The alcohol and acetate were identified as phytuberol (**1a**) and phytuberin (**1**), respectively, by direct comparison of the synthetic and natural samples. The result constitutes the first synthesis of phytuberin, and also establishes the undecided absolute configuration of these sesquiterpenes.

Experimental

All the melting points were uncorrected. The homogeneity of each compound was always checked by TLC over silica gel (Wakogel B-5) with various solvent systems, the spots being developed with cerium(IV) sulfate in diluted sulfuric acid and/or iodine. The optical rotations, UV and NMR (100 MHz) spectra were measured in chloroform, ethanol, and chloroform-*d* respectively, unless otherwise stated.

1β-Hydroxy-β-rotunol (3). To a solution of diisopropylamine (0.24 ml, 1.3 mmol) in dry THF (3 ml) cooled at −78 °C was added dropwise butyllithium in hexane (0.94 ml, 1.3 mmol) under nitrogen, and the solution was stirred at 0 °C for 15 min. To the solution cooled at −78 °C was added a solution of β-rotunol (**2**) (138 mg, 0.52 mmol) in dry THF (3 ml). To the reaction mixture, stirred at −78 °C for 1 h, was added rapidly molybdenum peroxide (MoOPH) (738 mg, 1.3 mmol). The whole mixture was stirred continuously for 1 h at −78 °C and then at room temperature for 30 min. After being treated with water, the reaction mixture was concentrated *in vacuo* to leave oily residue, which was extracted with ethyl acetate, repeatedly. The acetate solution was washed with 2 M† hydrochloric acid, saturated sodium hydrogencarbonate, and water, dried, and evaporated to leave an oil (141 mg), which was separated by chromatography over preparative TLC over silica gel with ethyl acetate–hexane (1 : 2). Fractions (70 mg) with higher R_f value, showing a single spot on TLC, afforded **3** with low mp; $[\alpha]_D$ +27.6°; MS, *m/e* 250 (M^+), 232, and 111; IR (neat), 3400 (br), 3100, 1680, 1630, and 890 cm^{-1}; NMR, δ 1.28 (3H, s, 15-H), 1.80 and 2.04 (each 3H, each s, 13- and 14-H), 3.60 (1H, br s, 1α-H), 4.76 (2H, br s), and 5.88 (1H, s, 3-H). Found: C, 71.77; H, 8.45%. Calcd for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80%. Fractions (24 mg) with lower R_f value, showing a single spot on TLC, afforded the unreacted starting material (**2**). Acetate of **3**, oil; MS, *m/e* 292 (M^+), 274, 234, 214; IR (neat), 1745 cm^{-1}; NMR, δ 2.19 (3H, s, $OCOCH_3$), and 4.96 (1H, s). Acetonide (**4**) of **3**, mp 125—129 °C; IR (Nujol), 1696, 1663, 1645, 1405, 1200, 1155, and 1100 cm^{-1}; NMR, δ 0.79 (3H, s, 15-H), 1.30 and 1.41 [each 3H, s, $(CH_3)_2$], 1.94 (9H, s, 12-, 13-, and 14-H), 3.51 (1H, s, 1α-H), and 5.92 (1H, br s, W_H= 5 Hz, 3-H).

1β-Hydroxy-11,12-epoxy-β-rotunol (5). Compounds **3** (55 mg, 0.22 mmol) was stirred with *m*-chloroperbenzoic acid (45.6 mg) in a heterogeneous mixture of dichloromethane (5 ml) and 5% aqueous sodium hydrogencarbonate (5 ml) at −15 °C for 4 h. The reaction mixture was washed with 5% aqueous sodium thiosulfate and water, dried, and evaporated to leave amorphous residue (**5**)(58 mg), showing a single spot on TLC: MS *m/e* 266 (M^+), and 248; IR (neat), 3380, 1680, 1625, 1020, and 910 cm^{-1}; NMR, δ 1.24, 1.32, and 2.00 (each 3H, 15-, 13-, and 14-H), 2.62 (2H, br s, W_H=9 Hz, 12-H), 3.50 (1H, br s, 1α-H), and 5.84 (1H, s, 3-H). This was used for the next reaction without purification because sample of unstability.

Eudesm-3-ene-1β,2ξ,5β,11-tetrol (6). To a stirred solution of **5** (83 mg) in dry DME (5 ml) at −78 °C was added dropwise a suspension (3 ml) of LAH (100 mg) in dry THF (5 ml) during 15 min. The mixture was stirred at room temperature for 2 h, mixed with water (0.5 ml) and 5% aqueous sodium hydroxide (0.5 ml), and was filtered. The filtrate was dried and evaporated to leave amorphous residue (85 mg), which was purified by column chromatography (3 g) over silica gel with ethyl acetate–hexane (4 :1) to give **6** (77 mg), gum; MS, *m/e* 270 (M^+), 252, and 234; IR (neat), 3580, 3500, and 1620 cm^{-1}; NMR, δ 1.12 (6H, s, 12- and 13-H), 1.20 and 1.22 (total 3H, each s, 14-H), 3.56 (1H, br s, W_H=5 Hz, 1α-H), 4.14 (1H, br, W_H= 10 Hz, 2-H), 5.35 and 5.56 [total 1H (1 : 3), each br, W_H=5 and 9 Hz, 3-H]. Found: C, 66.88; H, 9.55%. Calcd for $C_{15}H_{26}O_4$: C, 66.67; H, 9.63%.

4,6β-Dimethyl-6α-formyl-9β-(2-hydroxy-2-methyl)ethyl-1-oxaspiro-[4.5]dec-3-en-2-one (7). To a stirred solution of **6** (40 mg) in dry pyridine (3 ml) was added lead(IV) acetate (recrystallized freshly from acetic acid, 295 mg) at room temperature. The reaction mixture was stirred for 30 min and, after addition of oxalic acid (950 mg) and water (2 drops) to decompose excess of the reagent, was submitted to filtration. The filtrate was diluted with water and extracted with ethyl acetate, repeatedly. The acetate solution was washed with 2 M hydrochloric acid, saturated sodium hydrogencarbonate, and water, dried, and evaporated to leave an oil (42 mg), showing a single spot on TLC, which was purified by preparative TLC over silica gel with ethyl acetate–hexane (2 : 1) to yield **7** (32 mg), oil; MS, *m/e* 266 (M^+) and 248; IR (neat), 3480, 2710, 1755, 1720, 1630, and 1380 cm^{-1}; NMR,[10] δ 1.19 (6H, s, 12- and 13-H), 1.35 and 2.16 (each 3H, each s, 15- and 14-H), 5.66 (1H, s, 3-H), and 9.36 (1H, s, 1-H). Found: C, 68.00; H, 8.55%. Calcd for $C_{15}H_{22}O_4$: C, 67.67; H, 8.27%.

Phytuberol (1a). To a stirred solution of **7** (17 mg, 0.064 mmol) in dry DME (5 ml) was added DIBAH in hexane (0.13 ml, 0.224 mmol) at −78 °C under nitrogen. The whole reaction mixture was stirred at −78 °C for 30 min,

† 1 M=1 mol dm^{-3}.

at −20 °C for 30 min, and then at 0 °C for 30 min. The reaction was quenched by addition of water (10 drops), and the mixture was diluted with 2 M hydrochloric acid and extracted with ether, repeatedly. The ether solution was washed with saturated sodium hydrogencarbonate and water, dried, and evaporated to leave colorless oil (21 mg), showing a single spot on TLC [ethyl acetate–hexane (1 : 1)], which was purified by preparative TLC over silica gel with ethyl acetate–hexane (1 : 1) to yield **1a** (13 mg), oil; $[\alpha]_D$ −40.6°; MS, *m/e* 252 (M^+) and 234; IR (neat), 3490, 3090, 1625, 1153, 1088, 1040, 1027, and 735 cm^{-1}; NMR, δ 1.00 and 1.55 each 3H, s, 15- and 14-H), 1.20 (6H, s, 12- and 13-H), 3.24 and 3.39 (each 1H, ABq, J=8 Hz, 1-H), 4.66 and 6.42 (each 1H, d, J=2.8 Hz, 3- and 2-H). Natural sample,[5] oil, $[\alpha]_D$ −36.9°; MS, *m/e* 252.1710; IR (neat), 3440, 3080, 1624, 1153, 1088, 1040, 1027, and 735 cm^{-1}; NMR, δ 0.99 and 1.53 (each 3H, s), 1.18 (6H, s), 3.23 and 3.37 (each 1H, ABq, J=8.5 Hz), 4.64 and 6.41 (each 1H, d, J=2.8 Hz).

Phytuberin (1). A mixture of **1a** (12 mg), acetic anhydride (0.5 ml), and 4-(dimethylamino)pyridine (2 mg) in dry triethylamine (2 ml) was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with ether. The ether solution was worked up as usual to leave colorless oil (14 mg), showing a single spot on TLC, which was purified by preparative TLC over silica gel with ethyl acetate–hexane (1 : 4) to yield **1** (9.8 mg), oil; $[\alpha]_D$ −38.8°; MS, *m/e* 294 (M^+), 249, 234, 219, 205, 189, and 107; IR (neat) 3085, 1730, 1625, 1262, 1154, 1080, and 732 cm^{-1}; NMR, δ 1.02, 1.45, 1.48, and 1.57 (each 3H, s, 15-, 12-, 13-, and 14-H), 1.99 (3H, s, $OCOCH_3$), 3.28 and 3.42 (each 1H, ABq, J=8 Hz, 1-H), 4.68 and 6.44 (each 1H, d, J=3 Hz, 3- and 2-H). Natural sample,[5] oil; $[\alpha]_D$ −35.9°; MS, *m/e* 294.1849; 294, 249, 234, 219, 205, 191, 189, 149, and 107; IR (neat), 3080, 1728, 1620, 1260, 1088, and 735 cm^{-1}; NMR, δ 1.02, 1.44, 1.47, and 1.56 (each 3H, s), 1.99 (3H, s), 3.28 and 3.41 (each 1H, ABq, J=8.5 Hz), 4.68 and 6.44 (each 1H, d, J=2.8 Hz).

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10) The numbering of the carbon atoms (the figures in the parentheses of formula **7**) refer to that of the original eudesmane (**6**).