Study on the Synthesis of Phytuberin from Elemol

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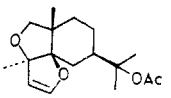
Phytuberin lactone (**14a**) has been synthesized starting from elemol (**2**). The known indenone **5**, which was prepared from **2** by a modified procedure, was autoxidized to give α-hydroxy ketone **6a**. Reaction of **6a** with the lithium dianion of acetic acid followed by acetylation provided tricyclic lactone **7b**. OsO_4 oxidation of **7b** and successive treatment of the oxidation product **10** with base yielded butenolide **11**, from which hydroxyphytuberin lactone (**12a**) was derived by oxidative cleavage with $Pb(OAc)_4$ followed by reduction with $NaBH_4$. The product obtained by treatment of the *p*-toluenesulfonate **12b** with $NaBH_3CN$ in HMPT was cyclopropane derivative **13**, which was then converted to phytuberin lactone (**14a**), the known progenitor of phytuberin (**1**), with lithium in liquid NH_3.

The relative stereochemistry of phytuberin (**1**), a stress metabolite isolated from fungal-infected potato tubers, was determined by spectroscopic methods[1] and by X-ray crystal analysis of its dihydro derivative.[2] These results revealed this antifungal compound to be an *A*-secoeudesmane sesquiterpene. Its unique hydrofurofuran structure has attracted much attention as an interesting synthetic target. The first synthesis of **1** from (+)-α-cyperone, reported by Masamune et al., also established the absolute configuration of **1**.[3] Two alternative and high-overall-yield syntheses were described by Caine and Smith[4] and Findlay et al.,[5] who started with (−)-2-carone and (−)-carvone, respectively.

This paper describes the details of our synthesis starting with elemol (**2**),[6] starting material chosen on the basis of a convenient assemblage of functional groups relevant to construction of the molecule of **1** and its availability.



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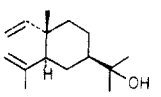
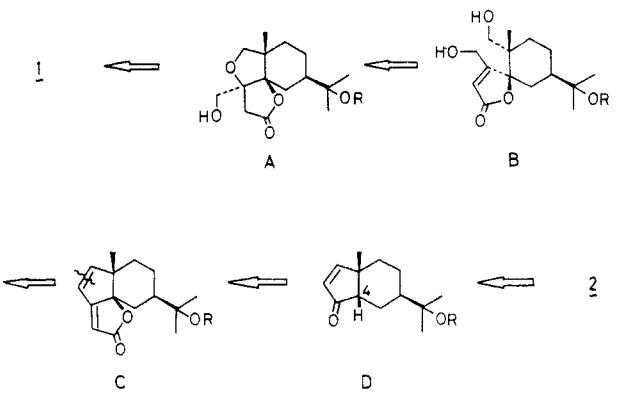


2

The retrosynthetic scheme is shown in Scheme I. We presumed that in butenolide C which seemed to be derivable from the known compound D (R = H) previously prepared from **2**,[7] its γ,δ-double bond would suffer selective oxidation to give B and that as reported by Masamune et al.[3] and other workers[4,5] ready intramolecular conjugate addition of the hydroxyl to the butenolide double bond can be expected to produce the hydrofurofuran system A.

Although ozonolysis of **2** at 0° C and consecutive aldol cyclization of the resulting minor product, keto aldehyde **4a**, to indenone **5** have been reported,[7] the vinyl group in **2** was indeed resistant to ozonolysis, and the predominant product, even with excess ozone, was ketone **3a** (Scheme II). In order to improve overall yield of **5**, we explored stepwise oxidation of two double bonds of **2**. Ozone was passed at −78 °C until unreacted **2** disappeared in TLC monitoring. Under these conditions, it was observed that almost selective ozonolysis took place on the methylene

Scheme I



double bond of **2**. While hydroxy ketone **3a** itself, obtained by treatment of the ozonide with Me_2S, gave **4a** on the Lemieux–Johnson oxidation only in a low yield, its acetate **3b** underwent smooth oxidation with the same reagent to afford acetate **4b** in good yield. According to the literature,[7] the indenone **5** was obtained from **4b** with methanolic NaOH in 36% overall yield from **2**. We were thus able to secure **5** from elemol (**2**) on a multigram scale.

Introduction of a hydroxyl group into the C(4) position of **5** was effectively achieved by autoxidation according to Gardner et al.,[8] i.e., the sodium enolate of **5** in a mixture of THF, DMF, and *t*-BuOH was oxidized with oxygen in the presence of triethyl phosphite to give hydroxy ketone **6a** stereoselectively in good yield. The stereochemistry of the newly introduced hydroxyl group was, on this stage, tentatively assigned as cis in relation to the angular methyl on the analogy of cis stereoselectivity in a similar system.[9] This assignment was ultimately confirmed by the synthesis of phytuberin lactone (**14a**).

A two-carbon unit was introduced into the ketone carbonyl of **6a** with the lithium dianion of acetic acid. While the reaction in THF provided the desired hydroxy ketone **7a** in low yield, replacement of the solvent with a diglyme–HMPT mixture considerably improved the yield. The crude product obtained was acetylated without purification to give acetate **7b**.

Treatment of **7b** with Et_3N afforded the desired unsaturated lactone **8** in quantitative yield. Contrary to our expectations, regioselective cleavage of the α,β-double bond of **8** could not be achieved with ozone or OsO_4 oxidation. Ozonolysis of **8** under controlled conditions[10] yielded, after

(1) Coxon, D. T.; Price, K. R.; Haward, B.; Curtis, R. F. *J. Chem. Soc., Perkin Trans. 1* **1977**, 53.
(2) Hughes, D. L.; Coxon, D. T. *J. Chem. Soc., Chem. Commun.* **1974**, 822. Hughes, D. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1338.
(3) Murai, A.; Ono, M.; Abiko, A.; Masamune, T. *J. Am. Chem. Soc.* **1978**, *100*, 7751. Murai, A.; Ono, M.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1202.
(4) Caine, D.; Smith, T. L., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7568.
(5) Findlay, J. A.; Desai, D. N.; Lonergan, G. C.; White, P. S. *Can. J. Chem.* **1980**, *58*, 2827.
(6) (Preliminary communication) Kido, F.; Kitahara, H.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1236.
(7) Thomas, A. F.; Vial, C.; Ozainne, M.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 2270.
(8) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294.
(9) For example, a high stereoselective β-epoxidation of a 14-androstene has been reported. Sondeheimer, F.; Burstein, S.; Mechoulam, R. *J. Am. Chem. Soc.* **1960**, *82*, 3209.
(10) Majetich, G.; Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2327.

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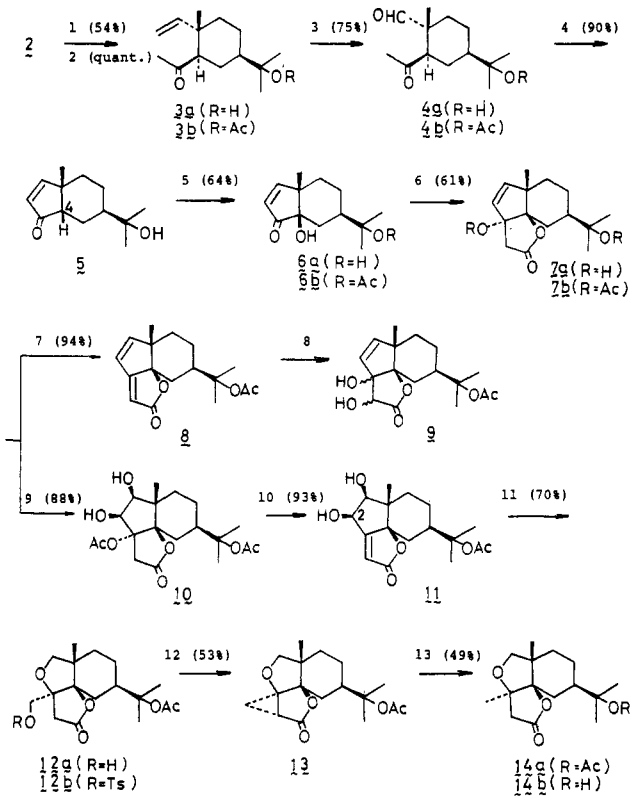
Scheme II[a]



[a] (1) O_3, MeOH, then Me_2S; (2) AcCl, $C_6H_5NEt_2$, $CHCl_3$; (3) OsO_4, $NaIO_4$, aqueous dioxane; (4) aqueous NaOH; (5) NaH, $(EtO)_3P$, *t*-BuOH, DMF, then O_2; (6) $LiCH_2CO_2Li$, HMPT, diglyme, then AcCl, $C_6H_5NEt_2$, $CHCl_3$; (7) Et_3N, $CHCl_3$; (8) OsO_4, *N*-methylmorpholine *N*-oxide, *t*-BuOH, Me_2CO; (9) OsO_4, pyridine; (10) DBU, PhH; (11) $Pb(OAc)_4$, PhH; (12) TsCl, pyridine, then $NaBH_3CN$, HMPT; (13) Li, liquid NH_3, *t*-BuOH.

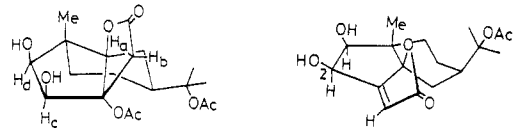


Figure 1. Perspective views of diol **10** (left) and butenolide **11** (right).

treatment of the ozonide with $NaBH_4$, acetate **6b** as the sole isolable product. On the other hand, a diol was obtained from **8** by OsO_4 oxidation according to Kelly et al.,[11] but spectroscopic evidence indicated that this compound has been oxidized at the site of the butenolide double bond again, i.e., to be **9**. These demonstrated that the γ,δ-double bond of **8** was inert to oxidation presumably due to steric blocking of both faces of this moiety.

In a modification of our route, the diacetate **7b** was submitted to OsO_4 oxidation. The stereochemistry of diol **10** obtained in excellent yield was shown as depicted by decoupling experiments in ^1H NMR; i.e., two doublets of doublets were observed at δ 2.49 (H_b) and 4.40 (H_c) and irradiation on the respective signal revealed the presence of a small coupling (1 Hz) between both protons (W coupling, Figure 1). Other coupling was also consistent with the stereochemistry shown (see Experimental Section for detailed data).

Elimination of acetic acid from **10** was performed with DBU to yield butenolide **11** quantitatively. In the ^1H NMR spectrum of **11** an allylic coupling (2 Hz) observed between the C(2) proton and the olefinic proton also supported the proposed structure **11** (see also Figure 1) in light of the angle dependency of allylic couplings. $Pb(OAc)_4$ oxidation of the product followed by $NaBH_4$ reduction provided hydroxyphytuberin lactone (**12a**) as expected. The difficult step in this synthesis proved to be the reductive removal of the hydroxyl group from **12a**. Owing to its neopentylic structure, many attempts were unsuccessful in substituting the hydroxyl of **12a** with hydrogen or other functional groups, mostly resulting in recovery of the substrate.[12] Fortunately, **12a** smoothly underwent sulfonylation with *p*-toluenesulfonyl (or methanesulfonyl) chloride to give sulfonate in quantitative yield. Attempted reductive removal of the sulfonate group from *p*-toluenesulfonate **12b** with $NaBH_3CN$ in HMPT at ca. 100 °C unexpectedly produced cyclopropane derivative **13** in 53% yield (77% yield based on consumed **12b**). The cyclopropane structure was implied by a cyclopropane methylene absorption at 3060 cm^{-1} in the IR spectrum.[13] While the molecular ion of this cyclopropane could not be observed in electron impact mass spectrometry under standard conditions, the M + 1 ion was observed at m/z 309 by employing field-desorption techniques. Meanwhile, we were unable to detect cyclopropane protons in the ^1H NMR spectrum of **13**.

Since **13** seemed to be a promising progenitor of phytuberin lactone (**14a**), we further examined, in expectation of higher yields, the reaction of **12b** with bases. Treatment with LDA culminated, however, in recovery of unchanged **12b**, while reaction with ethyldiisopropylamine gave a complex mixture. Although we have not further investigated this reaction, the formation of the cyclopropane derivative **13** with $NaBH_3CN$ would be rationalized by thermal enolization of the lactone **12b** in HMPT and by coordination of its toluenesulfonyl group with a borane, formed by decomposition of $NaBH_3CN$, which assists leaving of the sulfonyl group.

The remaining task was the reductive cleavage of the cyclopropane ring of **13**, and this was accomplished by using lithium in liquid NH_3 in the presence of a proton donor. The product of this reduction was a mixture of phytuberin lactone (**14a**) and deacetyl phytuberin lactone (**14b**), and the latter product was converted to the former by reacetylation. Identification of phytuberin lactone obtained was made by comparison with an authentic sample (IR, ^1H NMR, $[\alpha]_D$, and TLC). Further transformation of **14a** to phytuberin (**1**), i.e., $LiAlH_4$ reduction[1] and acetylation of the reduction product followed by thermolysis,[5] is the known procedure.

Experimental Section

All melting points were determined with a Yamato melting point apparatus, Model MP-21, and are uncorrected. IR spectra were recorded on a Hitachi EPI-S2 or a Jasco A-3 spectrophotometer and ^1H NMR spectra on JEOL C-60HL (60 MHz) or JEOL PS-100 (100 MHz) spectrometer, except where noted, in $CDCl_3$. Chemical shifts are expressed in δ values relative to Me_4Si as internal standard. Coupling constants (J) are given in hertz.

(3a*S*,6*R*,7a*S*)-3a,4,5,6,7,7a-Hexahydro-3a-methyl-6-(1-methyl-1-hydroxyethyl)-1*H*-inden-1-one (5). Ozone was passed through a methanolic solution (200 mL) of elemol (**2**; 5.83 g, 26.3 mmol) at −78 °C, while monitoring unreacted **2** by TLC. When **2** disappeared in the reaction mixture, Me_2S (22.7 mL, 0.31 mol) was added with stirring. The mixture was then allowed to warm to room temperature and stirring was continued overnight. After

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(12) For details, see: Kitahara, H. Ph.D. Dissertation, Tohoku University, Sendai, Japan, 1981.

(13) Cole, A. R. H. *J. Chem. Soc.* **1954**, 3807.

removal of the solvent, the residue was diluted with ether and washed with water. An oil obtained by evaporation was chromatographed on silica gel with CH_2Cl_2–ether (1:1) to give ketone **3a** (3.21 g, 54% yield), whose spectral data were identical with reported values.[7]

Acetyl chloride (24.5 mL, 0.34 mol) was added dropwise to a stirred solution of **3a** (25.6 g, 115 mmol) and *N,N*-diethylaniline (33.7 mL, 0.21 mol) in $CHCl_3$ (60 mL) at 0 °C under N_2, and the mixture was stirred at room temperature overnight. The mixture was poured onto ice–water and extracted with ether. The extract was washed with aqueous $NaHCO_3$ and then with water and, after drying, evaporated to give almost pure acetate **3b**: IR (liquid) 1725, 1705, 912 cm^{-1}; ^1H NMR δ 1.01 (s, 3 H), 1.60 (s, 6 H), 1.94, and 2.08 (s, 3 H respectively), 4.97 (dd, 1 H, J = 2 and 17), 4.99 (dd, 1 H, J = 2 and 8), 5.87 (dd, 1 H, J = 8 and 17).

Osmium tetraoxide (1.16 g, 4.6 mmol) and water (115 mL) were successively added to a stirred solution of the above acetate (31 g) in dioxane (737 mL) at room temperature. After stirring for 30 min, $NaIO_4$ (73.6 g, 0.34 mol) in water (500 mL) was added over 2 h. After being stirred for an additional 1 h, the mixture was filtered, and the filtrate was diluted with ether. The ethereal solution was washed with 5% aqueous Na_2S and then with water. After drying, an oil obtained by evaporation was chromatographed on silica gel with ether–petroleum ether (1:1) to afford keto aldehyde **4b** (22.9 g, 75% yield from **3a**): IR ($CHCl_3$) 2700, 1720, 1710 cm^{-1}; ^1H NMR δ 1.14, 1.48, 2.00, and 2.13 (s, 3 H respectively), 9.50 (s, 1 H).

A mixture of a solution of **4b** (1.44 g, 5.38 mmol) in MeOH (20 mL) and 10% aqueous NaOH (4 mL) was stirred at 60–84 °C for 3 h under N_2 and then neutralized with 6 M HCl. The product was extracted with CH_2Cl_2 and the extract was washed with brine. After drying, an oil obtained by evaporation was chromatographed on silica gel, and ether–petroleum ether (2:1) eluted indenone **5a** (1.0 g, 90% yield), which was identified by comparison of its spectral data with reported ones.[7]

(3a*S*,6*R*,7a*R*)-3a,4,5,6,7,7a-Hexahydro-7a-hydroxy-3a-methyl-6-(1-methyl-1-hydroxyethyl)-1*H*-inden-1-one (6a). The indenone **5** (224 mg, 1.1 mmol) in THF (3.5 mL) was added dropwise to a solution of NaH (52.8 mg, 2.2 mmol) and triethyl phosphite (0.2 mL, 1.1 mmol) in a mixture of *t*-BuOH (0.94 mL) and DMF (1.5 mL), prepared according to the literature,[8] at −25 °C. O_2 was passed through the above solution for 3 h at the same temperature, and then NaOH (172 mg) in MeOH–water (2:1, 4.5 mL) was added. After 1 h, the mixture was acidified with HOAc and extracted with ether. The extract was washed with water and dried. Evaporation left an oil, which was purified by preparative silica gel TLC (EtOAc–ether (1:5)) to give crystals. Recrystallization from EtOAc gave pure **6a**: mp 147 °C (153.4 mg, 64% yield); IR (KBr) 3350, 1690, 1583 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.00 (s, 6 H), 1.05 (s, 3 H), 6.10 and 7.63 (AB quartet, 2 H, J = 6). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.54; H, 9.25.

(3a*R*,5a*S*,8*R*,9a*R*)-2,3,3a,5a,6,7,8,9-Octahydro-3a-acetoxy-5a-methyl-8-(1-methyl-1-acetoxyethyl)-1*H*-indeno[7a,1-*b*]tetrahydrofuran-2-one (7b). Dry AcOH (1.14 mL, 20 mmol) in diglyme (1.0 mL) was added to an LDA solution, prepared from diisopropylamine (5.62 mL, 40 mmol) and BuLi (40 mmol) in diglyme (25 mL), at −15 °C under N_2, and then the solution was warmed up to 43 °C. To this mixture were added a solution of **6a** (224 mg, 1 mmol) in diglyme (3 mL) and then HMPT (1.7 mL, 10 mmol) dropwise with stirring. After being stirred for an additional 30 min, the reaction mixture was acidified with 6 M HCl and the product was extracted with EtOAc. The extract was successively washed with water, aqueous $NaHCO_3$, and water, and, after drying, the solvent was evaporated. The HMPT in the residue was removed in vacuo (6 mmHg at 50 °C). The crude lactone **7a** dissolved in $CHCl_3$ (5 mL) was acetylated by adding *N,N*-diethylaniline (3.21 mL, 20 mmol) and AcCl (2.85 mL, 40 mmol) in that order at 0 °C under N_2, followed by warming up to 43 °C. After being stirred at this temperature overnight, the mixture was diluted with water and extracted with CH_2Cl_2. The extract was successively washed with water, aqueous $NaHCO_3$, and water and dried. An oil obtained by evaporation was purified by preparative TLC (ether–CH_2Cl_2–petroleum ether (1:1:1)) to give **7b** (212.7 mg, 61% yield from **6a**): IR ($CHCl_3$) 1775, 1740, 1724 cm^{-1}; ^1H NMR[14] δ 1.20 (s, 3 H), 1.44 (s, 6 H), 2.00 (s, 3 H), 2.13 (s, 3 H), 2.85 and 3.38 (AB quartet, 2 H, J = 18), 5.98 (s, 2 H). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.75; H, 7.61.

(5a*S*,8*R*,9a*R*)-2,5a,6,7,8,9-Hexahydro-5a-methyl-8-(1-methyl-1-acetoxyethyl)-1*H*-indeno[7a,1-*b*]-2,5-dihydrofuran-2-one (8). A solution of **7b** (79.5 mg, 0.23 mmol) and Et_3N (0.2 mL) in $CHCl_3$ (2 mL) was kept at 74 °C under N_2 overnight and then neutralized with 3 M HCl. The product was extracted with ether and the extract was washed with 3 M HCl, water, and then brine. After drying, the solvent was evaporated to give an oil, which was purified by preparative TLC (ether–petroleum ether (9:5)) to give **8** (62.2 mg, 94% yield): ^1H NMR[14] δ 0.94 (s, 3 H), 1.38 (s, 6 H), 1.94 (s, 3 H), 5.71 (s, 1 H), 6.44 and 6.63 (AB quartet, 2 H, J = 7).

Ozonolysis of 8. Methylene chloride (4.5 mL) saturated with ozone[10] (ca. 0.18 mmol) at −78 °C was mixed with a solution of **8** (35 mg, 0.12 mmol) in MeOH (5 mL), and the mixture was stirred at the same temperature for 30 min. After warming up to room temperature, 25% of the amount of $NaBH_4$ (6.8 mg, 0.18 mmol) was added to the mixture at intervals of 15 min with stirring, and the mixture was then acidified with HOAc at −15 °C. The solvent was removed and the residue was diluted with EtOAc. The solution was washed with water and dried. An oil obtained by evaporation was purified by TLC (ether–petroleum ether (3:1)) to afford the acetate **6b** (9 mg), which was identical with an authentic sample prepared as follows: To a solution of hydroxy ketone **6a** (33.6 mg, 0.15 mmol) and *N,N*-diethylaniline (0.2 mL) in $CHCl_3$ (0.2 mL) was added AcCl (0.013 mL, 0.18 mmol) 0 °C with stirring. Then the mixture was warmed up to 45 °C, and stirring was further continued overnight. Cold diluted HCl was added to the mixture, and the product was extracted with ether. After successive washing with water, aqueous $NaHCO_3$, and water, the organic layer was dried and evaporated to give an oil, which was purified by preparative TLC (ether–petroleum ether (5:2)) to give **6b** (8.3 mg): ^1H NMR δ 1.18 (s, 3 H), 1.40 (s, 6 H), 1.93 (s, 3 H), 6.20 and 7.05 (AB quartet, 2 H, J = 6).

Osmium Tetraoxide Oxidation of 8. According to Kelly et al.,[11] a solution of **8** (38.0 mg, 0.13 mmol) in acetone (2.0 mL) was added to a solution of OsO_4 (1.5 mg) and *N*-methylmorpholine *N*-oxide (24.5 mg, 0.16 mmol) in a mixture of *t*-BuOH (0.6 mL) and acetone (0.5 mL), and the mixture was stirred at room temperature overnight.

To this mixture were added $NaHSO_3$ (1.3 mg), $MgSiO_3$ (15.6 mg), and water (0.5 mL) with stirring. After filtration, the filtrate was acidified with H_2SO_4 (0.5 M) and evaporated in vacuum for removal of the organic solvent. Brine was added to the residue, and the product was extracted with EtOAc. The extract was washed with brine, dried, and concentrated. An oil obtained was purified by preparative TLC (ether–petroleum ether (5:1)) to give **9** (20.0 mg): IR ($CHCl_3$) 3500, 3350, 1765, 1722, 920 cm^{-1}; ^1H NMR δ 1.17, 1.36, 1.48, and 1.97 (s, 3 H respectively), 4.11 (s, 1 H), 5.51 and 6.00 (AB quartet, 2 H, J = 6).

(3a*R*,4*S*,5*S*,5a*S*,8*R*,9a*R*)-Perhydro-3a-acetoxy-4,5-dihydroxy-5a-methyl-8-(1-methyl-1-acetoxyethyl)indeno-[7a,1-*b*]tetrahydrofuran-2-one (10). A solution of **7b** (61.4 mg, 0.18 mmol) in pyridine (1 mL) was slowly added to a pyridine solution (0.5 mL) of OsO_4 (50.8 mg, 0.2 mmol), and the mixture was left in the dark for 2 days. An aqueous solution of $NaHSO_3$ (94 mg, 0.9 mmol) was added and the mixture was stirred for 5 h. The product was extracted with EtOAc, and the extract was washed with water and dried. Removal of the solvent left an oil, which was purified by preparative TLC (ether–petroleum ether–EtOAc (20:1:1)) to yield **10** (59.2 mg, 88%): mp 169 °C (recrystallized from benzene); IR 3530, 1775, 1720 cm^{-1}; ^1H NMR δ 1.23, 1.39, 1.46, 1.97, and 2.21 (s, 3 H respectively), 2.48 (dd, 1 H, J = 1 and 19, H_b[15]), 3.68 (d, 1 H, J = 19, H_a[15]), 3.73 (d, 1 H, J = 4, H_d[15]), 4.40 (m, 1 H, collapsed to dd, J = 1 and 4 on addition of D_2O, H_c[15]). Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.46. Found: C, 59.66; H, 7.46.

(4*R*,5*S*,5a*S*,8*R*,9a*R*)-2,4,5,5a,6,7,8,9-Octahydro-4,5-dihydroxy-5a-methyl-8-(1-methyl-1-acetoxyethyl)-1*H*-indeno[7a,1-*b*]-2,5-dihydrofuran-2-one (11). A solution of **10** (59.2 mg, 0.15 mmol) and DBU (0.06 mL) in dry benzene (2.5 mL)

(14) Data at 100 MHz.
(15) For the denotation of proton, see Figure 1.

was kept for 1 h under N_2 and then acidified with dilute HCl in an ice bath. The product was extracted with EtOAc, and the extract was successively washed with dilute HCl, water, aqueous $NaHCO_3$, and water. After drying, the extract was evaporated to leave an oil, which was purified by preparative TLC (EtOAc) to provide **11** (46.6 mg, 93% yield): IR ($CHCl_3$) 3400, 1745, 1722, 1662 cm^{-1}; ^1H NMR δ 0.80, 1.42, 1.48, and 1.97 (s, 3 H respectively), 4.25 (d, 1 H, J = 8), 4.91 (dd, 1 H, J = 2 and 8), 6.00 (d, 1 H, J = 2). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.58; H, 7.58.

(3a*S*,5a*S*,8*R*,9a*R*)-Perhydro-3a-(hydroxymethyl)-5a-methyl-8-(1-methyl-1-acetoxyethyl)benzo[*g*]furo[3,2-*b*]-furan-2-one (12a). Lead tetraacetate (66.5 mg, 0.15 mmol) was dissolved in a solution of **11** (44.3 mg, 0.14 mmol) in dry benzene (2 mL) at 7 °C under N_2, and the solution was kept at 7–10 °C for 1 h. After dilution with ether, the solution was filtered through a pad of Celite–$MgSO_4$ and then the filtrate was concentrated in vacuum to leave an oil. $NaBH_4$ (8.0 mg, 0.21 mmol) dissolved in EtOH (0.7 mL) was added dropwise to a stirred solution of the above product in EtOH (2 mL) in an ice bath. After being stirred for an additional 30 min, dilute HCl was added at the same temperature, and the product was extracted with EtOAc. The extract was successively washed with water, aqueous $NaHCO_3$ and water and dried. Removal of the solvent left an oil, which was purified by preparative TLC (ether–petroleum ether (10:1)) to give **12a** (31.3 mg, 70% yield from **11**): IR ($CHCl_3$) 3500, 1763, 1720 cm^{-1}; ^1H NMR[14] δ 1.10, 1.36, 1.49, and 1.99 (s, 3 H respectively), 2.61 (d, 1 H, J = 19), 3.18 (d, 1 H, J = 19), 3.60 and 3.66 (AB quartet, 2 H, J = 9), 3.73 and 3.95 (AB quartet, 2 H, J = 11). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.58; H, 8.24.

(1*S*,4*R*,6*R*,9*R*,11*R*)-11-(1-Methyl-1-acetoxyethyl)-7-oxo-3,8-dioxatetracyclo[7.4.0.^{1,9}0.^{4,6}0.^{4,9}]tridecane (13). *p*-Toluenesulfonyl chloride (57.6 mg, 0.3 mmol) was dissolved in a solution of **12a** (19.7 mg, 0.06 mmol) in pyridine (0.5 mL), and the solution was stirred at room temperature overnight. After dilution with ether, an excess of dilute HCl was added to the reaction mixture at 0 °C and the aqueous layer was extracted with ether. The combined extracts were successively washed with dilute HCl, water, aqueous $NaHCO_3$, and water, and, after drying, the product was obtained by evaporation of the solvent. Preparative TLC of the crude product (ether–petroleum ether (2:1) as solvent) provided *p*-toluenesulfonate **12b** (28.6 mg, 99% yield): IR (liquid) 1780, 1725, 1600, 830 cm^{-1}; ^1H NMR δ 1.07, 1.41, 1.45, 1.98, and 2.43 (s, 3 H respectively), 2.51 and 2.97 (AB quartet, 2 H, J = 19), 3.60 and 4.20 (s, 2 H, respectively), 7.32 and 7.82 (AB quartet, 2 H, J = 9).

Sodium cyanoborohydride (46.1 mg, 0.73 mmol) was added to a solution of the above **12b** (35.2 mg, 0.07 mmol) in HMPT (0.75 mL), and the mixture was heated at ca. 100 °C for 3 days. The reaction mixture was acidified with 2 M HCl, and the product was extracted with ether. After the extract had been washed with water and dried, evaporation of the solvent left an oil, which was purified by preparative TLC (CH_2Cl_2–ether–hexane (10:1:1)) to give **13** (12.0 mg, 53% yield) and recovered **12b** (8.6 mg): IR ($CHCl_3$) 3060, 1763, 1728 cm^{-1}; ^1H NMR[14] δ 1.13, 1.42, 1.45, and 1.97 (s, 3 H respectively), 3.68 and 3.97 (AB quartet, 2 H, J = 9); MS, m/z M + 1^+, 309 (field-desorption method). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.58; H, 8.24.

Phytuberin Lactone (14a). Lithium (1 mg) was dissolved in dry liquid NH_3 (10 mL) at −78 °C, and then **13** (24 mg, 0.08 mmol) dissolved in a mixture of THF (0.5 mL) and *t*-BuOH (10 μL) was added. After being stirred at −70 °C for 10 min, the reaction was quenched by adding NH_4Cl, and the NH_3 was evaporated. The residue was extracted with CH_2Cl_2, and the extract was washed with water and brine. After drying, the solvent was removed to leave an oil, which was separated by preparative TLC (CH_2Cl_2–ether (10:1)) to give **14a** (6 mg, 28% yield), $[\alpha]_D$ + 44.3° (*c* 0.9, EtOH) (lit.[1] $[\alpha]_D$ + 48.0° (*c* 1.0, EtOH)) and deacetylphytuberin lactone (**14b**) (3 mg, 21% yield). The phytuberin lactone obtained was identified by comparison of the IR and ^1H NMR spectra and of mobility in TLC with those of an authentic sample.

The latter product (**14b**) obtained was reacetylated with AcCl and *N*,*N*-diethylaniline in $CHCl_3$ at 46 °C, and gave, by customary workup, **14a** quantitatively.

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