Plant Bioregulators, 3[+]

Synthetic Disproof of the Structure Proposed for Alectrol, the Germination Stimulant from *Vigna unguiculata*

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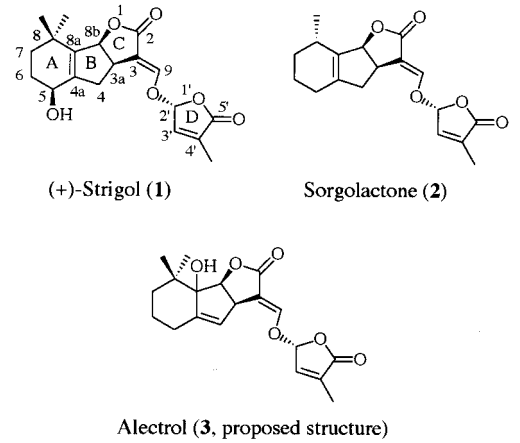
Several compounds [(±)-**3a**, (±)-**3b**, (±)-**10**, (±)-**11**, and (±)-**12**] with structures related to that proposed for alectrol (**3**), the germination stimulant for seeds of parasitic weeds, have been synthesized. Structure (±)-**3a** has been solved by X-ray-crystallographic analysis. Comparison of the ^{1}H-NMR data of the synthetic compounds with those reported for alectrol showed the proposed structure **3** to be incorrect. The synthetic products (±)-**3a** and (±)-**3b** showed significant germination stimulating activity on clover broomrape (*Orobanche minor*) seeds.

The chemical ecology of harmful parasitic weeds of the genera *Alectra*, *Striga* and *Orobanche*, which are known to cause economically important agricultural damage (severe yield losses in grains and legumes in Africa, Asia and the U.S.A.), is an interesting problem in that the seeds of such weeds can recognize their host plants through semiochemical(s) exuded by the host roots.[1] The endeavors of chemists to solve the problem culminated in the isolation and identification of some germination stimulants such as strigol (**1**),[2] sorgolactone (**2**),[3] and alectrol (**3**, proposed structure)[4] (Scheme 1), which were given the general name strigolactones.[5] The former two compounds, **1** and **2**, have been the targets of extensive synthetic studies, as summarized in two recent papers.[6][7]

Following our synthesis of (±)- and (+)-sorgolactone (**2**),[8][9] we initiated a project to synthesize (±)-alectrol (**3**). This compound is of particular interest since its stereochemistry at C-8a has remained unknown.[4] Alectrol is a germination stimulant for the seeds of the root parasites *Alectra vogelii* and *Striga gesnerioides*, and some 300 μg of this compound was isolated from the root exudates collected from 300,000 *Vigna unguiculata*, the genuine host plant.[4] Alectrol was proposed to possess the structure **3** on the basis of a comparison of its spectroscopic properties (UV, IR, ^{1}H NMR, MS and CD) with those reported for (+)-strigol, the structure of which has been rigorously determined by X-ray analysis.[2][10] We recently reported the synthetic disproof of the proposed structure **3** as a preliminary communication.[11] This paper gives full details of the synthesis, ^{1}H-NMR analysis, and biological evaluation of synthetic compounds with the structure **3**.



Scheme 1. Structures of strigolactones, the germination stimulants

Our synthetic route to (±)-**3a** and (±)-**3b** is shown in Scheme 2. Citral (**4**) was converted to the known hydroxylactone (±)-**5** according to Sih et al.[12] and Brooks et al.[13] A sufficient amount of the key intermediate (±)-**6** was then prepared from (±)-**5** as reported by Welzel and coworkers.[14] Epoxidation of (±)-**6** with *m*-chloroperbenzoic acid (*m*CPBA) gave a mixture of two epoxides, (±)-**7** and (±)-**8** (ca. 1:1.5), which could be separated by silica-gel column chromatography. The structures of these epoxides were assigned on the basis of an X-ray analysis of (±)-**3a**, which was obtained from (±)-**7**. Treatment of (±)-**7** with aluminum isopropoxide in toluene under reflux for 5 h followed by acidification with 2 N HCl furnished the oily dihydroxy ester (±)-**9**. This was stirred at room temperature for 10 d in chloroform in the presence of a small amount of acetic acid to give the lactone (±)-**10**, m.p. 169−170°C. Under these mild conditions, the lactonization proceeded in good yield [89% based on (±)-**7**] without decomposition or other

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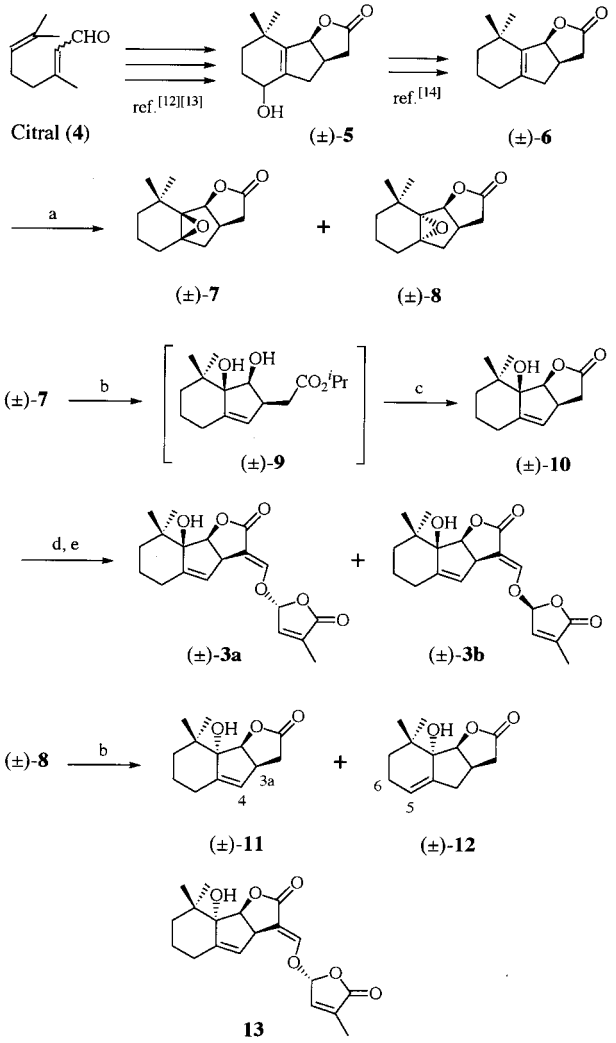
side reactions. The two remaining steps, formylation and alkylation with (±)-4-bromo-2-methyl-2-buten-4-olide,[15] were carried out according to conventional procedures as reported previously,[8,9,12,13] to afford a mixture of (±)-**3a** and (±)-**3b** [ca. 1.2:1, as determined by HPLC (silica gel)] in 78% yield. The two isomers were separated by medium-pressure liquid chromatography (MPLC, silica gel, hexane/ethyl acetate, 4:1) to give crystalline (±)-**3a** and (±)-**3b**. The structure (±)-**3a** could be assigned to the faster-moving isomer with m.p. 200−202°C on the basis of its X-ray analysis. The slower moving isomer with m.p. 132−134°C was thus (±)-**3b**. The spectroscopic properties (^{1}H NMR, ^{13}C NMR, IR and MS) of (±)-**3a** and (±)-**3b** were almost identical. A perspective view of (±)-**3a** is shown in Figure 1.



Scheme 2. Synthesis of (±)-**3a** and (±)-**3b**; reagents: (a) *m*CPBA, CH_2Cl_2 [39% of (±)-**7** and 60% of (±)-**8**]; (b) $Al(OiPr)_3$, toluene [4% of (±)-**11** and 67% of (±)-**12**]; (c) AcOH, $CHCl_3$ [89% from (±)-**7**]; (d) NaH, HCO_2Et, Et_2O/THF; (e) 1. K_2CO_3, (±)-4-bromo-2-methyl-2-buten-4-olide, *N*-methylpyrrolidone [78%, (±)-**3a**/(±)-**3b** ≈ 1.2:1]; 2. MPLC separation

Prof. T. Yokota (Teikyo University) kindly sent us a copy of the ^{1}H-NMR spectrum (600 MHz, $CDCl_3$) of alectrol isolated from the root exudates of red clover, *Trifolium pratense*.[16] The spectrum was in complete accord with that reported for alectrol by Müller et al.[4] Despite the presence of some contaminants, the low-field region of the spectrum was of excellent quality and did not match that of our synthetic product (±)-**3a**. It was thus apparent that the structure of alectrol was somewhat different from that of **3a**. The remaining possible structure for alectrol was considered to be **13**, with an α-OH group at C-8a.

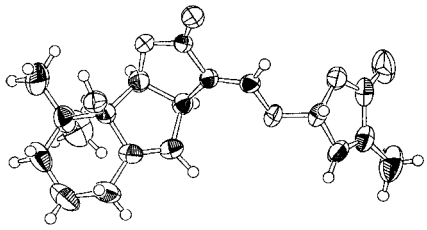
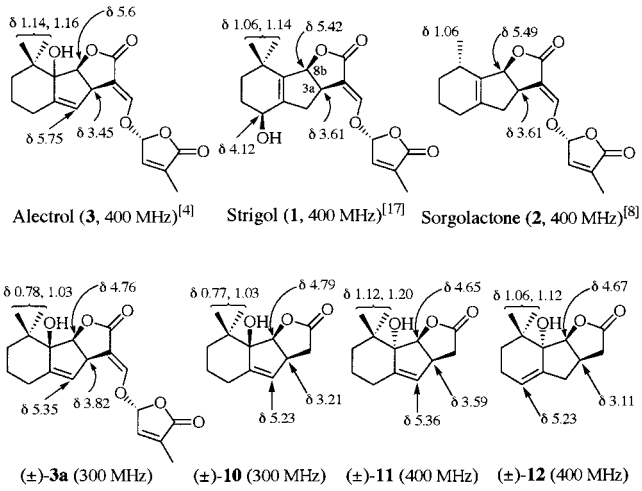


Figure 1. Perspective view of (±)-**3a**

The isomeric epoxide (±)-**8** was also treated with aluminum isopropoxide in toluene under reflux for 85 h. The cooled mixture was then acidified with 2 N HCl and the products were purified by silica-gel column chromatography to give (±)-**11** (4% yield), m.p. 155−157°C, and (±)-**12** (67% yield), m.p. 129−130°C. The structures of (±)-**11** and (±)-**12** were assigned on the basis of their ^{1}H-NMR spectra (COSY). The spectrum of the lactone (±)-**11** showed coupling between the signal due to the olefinic proton at C-4 (δ = 5.36) and the signal due to the proton at C-3a (δ = 3.59), whereas that of (±)-**12** featured a doublet at δ = 5.68 due to the olefinic proton at C-5, which showed coupling to the signal due to the proton at C-6 (δ = 1.98−2.18).

Scheme 3 summarizes some of the characteristic ^{1}H-NMR data of alectrol, together with those of strigol (**1**),[17] sorgolactone (**2**),[8][9] and the synthetic products (±)-**3a**, (±)-**10**, (±)-**11**, and (±)-**12** (measured in $CDCl_3$). The signals due to the proton at C-8b in (±)-**3a**, (±)-**10**, and (±)-**11** were observed in the range δ = 4.65−4.79, while the same proton in alectrol was reported to give rise to a signal at δ = 5.6, in the same region as found for strigol (δ = 5.42) and sorgolactone (δ = 5.49). Although we could not attach the D-ring to (±)-**11** due to the very limited amount of material available, the δ value of the proton at C-8b in **13** was thought to be similar to that in (±)-**11** [cf. δ = 4.76 in (±)-**3a**; δ = 4.79 in (±)-**10**].[8,17,18] It should be added that the δ value for the proton at C-3a in alectrol (δ = 3.45) differs considerably from that in (±)-**3a** (δ = 3.82) and is even further upfield than that in (±)-**11** (δ = 3.59), the precursor of (±)-**13** in which the proton at C-3a is sandwiched between the two double bonds. This fact leads us to believe that alectrol does not have the structure **13** either.

Finally, the bioactivities of (±)-**3a** and (±)-**3b** as germination stimulants were evaluated (Table 1). Seeds of clover broomrape (*Orobanche minor*) were used as the test parasitic weed seed.[19] Both lactones proved effective in stimulating the germination of the seeds at concentrations of 10^{-4} to 10^{-6} M. This result supports the view that the bioactivity of these systems as germination stimulants stems from the C/D ring part of the molecules.[20]



Scheme 3. Selected ^{1}H-NMR data of alectrol and its related compounds (measured in $CDCl_3$)

In conclusion, we have carried out syntheses of several compounds [(±)-**3a**, (±)-**3b**, (±)-**10**, (±)-**11**, and (±)-**12**] with structures related to **3**, which has been proposed as the structure of alectrol. Detailed comparison of the ^{1}H-NMR data of the synthetic compounds with those reported for alectrol has shown the proposed structure **3** to be incorrect. The results in this paper highlight the importance of organic synthesis in the structure elucidation of a scarce natural product.

Table 1. Biological activities of (±)-**3a** and (±)-**3b** as germination stimulants

Concentration [M]	Relative germination of *Orobanche minor* seeds[a] (%)		
	(±)-**3a**	(±)-**3b**	(±)-strigol
10^{-4}	90.9 ± 2.5	92.5 ± 2.0	–
10^{-6}	83.7 ± 2.4	88.3 ± 1.7	–
10^{-8}	1.2 ± 0.7	15.9 ± 2.8	94.4 ± 1.4
10^{-10}	0	0	89.0 ± 1.6

[a] Control, 0%.

Experimental Section

General: Boiling points and melting points (Yanaco MP-S3): Uncorrected values. – IR: Shimadzu FT-IR 8100 or Jasco IRA-102. – ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-EX 270L (270 MHz), Bruker DPX 300 (300 MHz), or Jeol JNM-LA 400 (400 MHz) (TMS at δ_H = 0.00, $CHCl_3$ at δ_H = 7.26 as internal standards). – ^{13}C NMR: Jeol JNM-EX 270L (67.8 MHz), Bruker DPX 300 (75.5 MHz), or Jeol JNM-LA 400 (100.4 MHz) ($CDCl_3$ at δ_C = 77.0 as internal standard). – MS: Jeol JMX-DX 303 (70 eV). – CC: Merck Kieselgel 60 Art 1.07734. – TLC: 0.25 mm Merck silica gel plates (60F-254).

(±)-(3a*R,8b*S**)-8,8-Dimethyl-3,3a,4,5,6,7,8,8b-octahydroindeno-[1,2-*b*]furan-2-one [(±)-6]:** According to the procedure of Welzel et al.,[14] 8,8-dimethyl-5-hydroxy-3,3a,4,5,6,7,8,8b-octahydroindeno-[1,2-*b*]furan-2-one (**5**), prepared from citral (**4**) in 8 steps,[8][9] was transformed to the deoxylactone (±)-**6** in 2 steps (64%); m.p. 40–41°C (hexane) [ref.[14] 43–45°C]. – IR (KBr): $\tilde{\nu}$ = 1760 cm^{-1} (s, C=O), 1170 (m, C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, 8-Me), 1.10 (s, 3 H, 8-Me), 1.32–1.54 (m, 2 H, 7-CH_2), 1.67 (m, 2 H, 6-CH_2), 1.97 (m, 2 H, 5-CH_2), 2.15 (dd, 1 H, J = 16.6, J' = 1.6 Hz, 4-H), 2.32 (dd, 1 H, J = 18.1, J' = 4.9 Hz, 3-H), 2.61 (dd, 1 H, J = 16.6, J' = 8.5 Hz, 4-H′), 2.79 (dd, 1 H, J = 18.1, J' = 10.3 Hz, 3-H′), 3.00 (m, 1 H, 3a-H), 5.47 (d, 1 H, J = 7.3 Hz, 8b-H).

(±)-(3a*R,4a*R**,8a*S**,8b*S**)- and (±)-(3a*R**,4a*S**,8a*R**,8b*S**)-8,8-Dimethyl-4a,8a-epoxy-3,3a,4,4a,5,6,7,8,8a,8b-decahydroindeno[1,2-*b*]-furan-2-one [(±)-7 and (±)-8]:** To an ice-cooled solution of the unsaturated lactone **6** (175 mg, 0.85 mol) in CH_2Cl_2 (12 mL), *m*-chloroperbenzoic acid (*m*CPBA) (ca. 70%, 272 mg, 1.11 mmol) was carefully added in several portions. The resulting mixture was stirred for 5 h at room temperature, quenched by the addition of satd. $Na_2S_2O_3$ solution and satd. $NaHCO_3$ solution, and then extracted with CH_2Cl_2. The combined organic layers were successively washed with satd. $NaHCO_3$ solution, water and brine, and dried with $MgSO_4$. Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (hexane/ethyl acetate, 10:1 → 4:1) to afford first 113 mg (60%) of (±)-**8** (R_f = 0.65, hexane/ethyl acetate, 1:1) as colorless crystals, and then 73 mg (39%) of (±)-**7** (R_f = 0.50, hexane/ethyl acetate, 1:1) as colorless needles. The structures of (±)-**7** and (±)-**8** were deduced following transformation of (±)-**7** to (±)-**3a**, which was analyzed by X-ray crystallography. – **(±)-7:** M.p. 110–111°C (hexane/diethyl ether). – IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1} (m, C–H), 1770 (s, C=O), 1180 (m, C–O), 1040 (m, C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (m, 1 H, 7-H), 1.12 (s, 3 H, 8-Me), 1.17 (s, 3 H, 8-Me), 1.31–1.52 (m, 3 H, 6-CH_2 and 7-H′), 1.89–2.03 (m, 1 H, 5-H′), 1.91 (m, 1 H, 5-H), 1.98 (dd, 1 H, J = 14.6, J' = 8.2 Hz, 4-H), 2.09 (dd, 1 H, J = 14.6, J' = 1.2 Hz, 4-H′), 2.40 (dd, 1 H, J = 17.9, J' = 8.8 Hz, 3-H), 2.56 (dd, 1 H, J = 17.9, J' = 11.2 Hz, 3-H′), 2.85 (m, 1 H, 3a-H), 5.13 (d, 1 H, J = 8.6 Hz, 8b-H). – $C_{13}H_{18}O_3$ (222.3): calcd. C 70.24, H 8.16; found C 70.16, H 8.29. – **(±)-8:** M.p. 61–62°C (diethyl ether). – IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1} (m, C–H), 1780 (s, C=O), 1175 (m, C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (m, 1 H, 7-H), 1.13 (s, 3 H, 8-Me), 1.21 (s, 3 H, 8-Me), 1.36–1.53 (m, 3 H, 6-CH_2 and 7-H′), 1.47 (dd, 1 H, J = 13.9, J' = 7.8 Hz, 4-H), 1.76–1.98 (m, 2 H, 5-CH_2), 2.31 (d, 1 H, J = 17.0 Hz, 3-H), 2.40 (dd, 1 H, J = 13.9, J' = 8.3 Hz, 4-H′), 2.59 (m, 1 H, 3a-H), 2.67 (dd, 1 H, J = 17.1, J' = 8.3 Hz, 3-H′), 4.88 (d, 1 H, J = 5.4 Hz, 1-H). – $C_{13}H_{18}O_3$ (222.3): calcd. C 70.24, H 8.16; found C 69.76, H 8.09.

(±)-(3a*R,8a*S**,8b*S**)-8,8-Dimethyl-8a-hydroxy-3,3a,5,6,7,8,8a,8b-octahydroindeno[1,2-*b*]furan-2-one [(±)-10]:** A mixture of the epoxide (±)-**7** (222 mg, 1.0 mmol) and aluminum isopropoxide (1.02 g, 5.0 mmol) in toluene (15 mL) was refluxed for 5 h under argon. The cooled reaction mixture was then treated with 2 N HCl and extracted with ethyl acetate. The combined organic layers were washed with water and brine, and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude diol (±)-**9**, isopropyl 1,7a-dihydroxy-7,7-dimethyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-ylacetate, as a yellowish oil, which was sufficiently pure for use in the subsequent step without further purification. – n_D^{24} = 1.4989. – IR (film): $\tilde{\nu}$ = 3560–3300 cm^{-1} (s, O–H), 2950 (s, C–H), 1730 (s, C=O), 1370 (s, O–H), 1300 (s, O–H), 1175 (s, C–O), 1110 (s, C–O). – ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.75 (s, 3 H, 7-Me), 0.93 (s, 3 H, 7-Me), 1.08 (m, 1 H, 6-H), 1.16 [d, 3 H, J = 6.3 Hz, –CH(CH_3)$_2$], 1.17 [d, 3 H, J = 6.3 Hz, –CH(CH_3)$_2$], 1.28–1.63 (m, 2 H, 5-CH_2), 1.83 (td, 1 H, J = 13.4, J' = 4.3 Hz, 6-H′), 2.04–2.23 (m, 2 H, 4-CH_2), 2.33 (dd, 1 H, J = 15.8, J' = 5.3 Hz, –CH_aH$_b$CO$_2$–), 2.44 (dd, 1 H, J = 15.8, J' = 8.3 Hz, –CH$_a$$H_bCO_2$–), 2.78–2.92 (m, 1 H, 2-H), 2.88 (s, 1 H, 7a-OH),

3.24 (d, 1 H, J = 5.6 Hz, 1-OH), 4.23 (dd, 1 H, J = 7.6, J' = 5.6 Hz, 1-H), 4.93 [quint, 1 H, J = 6.3 Hz, $-CH(CH_3)_2$], 5.20 (s, 1 H, 3-H). − ^{13}C NMR (22.4 MHz, $CDCl_3$): δ = 21.7, 21.7, 22.6, 23.8, 25.2, 34.8, 36.1, 37.5, 43.9, 67.8, 70.1, 84.3, 124.4, 144.2, 174.0. − To a solution of the above diol (±)-**9** in $CHCl_3$ (10 mL) were added a few drops of acetic acid. The mixture was stirred for 10 d at room temperature and then concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate, 9:1) to afford 197 mg (89%) of (±)-**10** as colorless plates, m.p. 169−170°C (diethyl ether). − IR (KBr): $\tilde{\nu}$ = 3475 cm^{-1} (s, O−H), 2985 (s, C−H), 1770 (s, C=O), 1380 (m, O−H), 1195 (s, C−O), 1125 (m, C−O), 1005 (m, C−O). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 8-Me), 1.03 (s, 3 H, 8-Me), 1.14 (dt, 1 H, J = 13.4, J' = 3.1 Hz, 7-H), 1.44 (m, 1 H, 6-H), 1.63 (m, 1 H, 6-H′), 1.94 (td, 1 H, J = 13.6, J' = 4.3 Hz, 7′-H), 2.21 (m, 2 H, 4-CH_2), 2.39 (dd, 1 H, J = 18.1, J' = 2.7 Hz, 3-H), 2.39 (s, 1 H, OH), 2.73 (dd, 1 H, J = 18.1, J' = 9.9 Hz, 3-H′), 3.21 (m, 1 H, 3a-H), 4.79 (d, 1 H, J = 6.4 Hz, 8b-H), 5.23 (s, 1 H, s, 4-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.1, 22.7, 23.8, 24.7, 34.5, 35.5, 38.1, 42.5, 82.2, 85.5, 121.3, 147.0, 176.3. − $C_{13}H_{18}O_3$ (222.3): calcd. C 70.24, H 8.16; found C 70.28, H 8.24.

(±)-(3a*R,8a*S**,8b*S**,2′*R**)- and (±)-(3a*R**,8a*S**,8b*S**,2′*S**)-3-[(*E*)-2′,5′-Dihydro-4′-methyl-5′-oxo-2′-furanyloxymethylene]-8,8-dimethyl-8a-hydroxy-3,3a,5,6,7,8,8a,8b-octahydroindeno[1,2-*b*]furan-2-one [(±)-3a and (±)-3b]:** To a stirred suspension of NaH (ca. 60% suspension in oil, 51 mg, ca. 1.29 mmol), washed repeatedly with dry diethyl ether, in dry diethyl ether (2.0 mL) at room temperature under argon, was added a solution of the hydroxylactone (±)-**10** (95 mg, 0.43 mmol) in dry diethyl ether (1.5 mL) and dry THF (1.5 mL), followed by ethyl formate (0.60 mL, ca. 3 mmol). After stirring for 20 h at room temperature, the mixture was acidified with 1 N HCl and then extracted with ethyl acetate. The combined organic layers were washed with water and brine, and dried with $MgSO_4$. Evaporation of the solvent left a pale-orange solid, which was washed with ice-cooled diethyl ether to give 110 mg (quant.) of the hydroxymethylene lactone. This was used directly for the subsequent transformation without further purification. To a stirred mixture of the above hydroxymethylene lactone (110 mg, 0.43 mmol) and K_2CO_3 (119 mg, 0.86 mmol) in anhydrous *N*-methylpyrrolidone (2.0 mL) at room temperature under argon, was added a solution of (±)-4-bromo-2-methyl-2-buten-4-olide[15] (152 mg, 0.86 mmol) in anhydrous *N*-methylpyrrolidone (1.0 mL). After stirring for 18 h at room temperature, the reaction mixture was poured into 1 N HCl (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with water (twice) and brine, and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave 116 mg (78%) of a diastereomeric mixture of the products (ca. 1.2:1, as determined by HPLC analysis) as a yellowish oil. This mixture was separated by medium-pressure liquid chromatography (MPLC, silica gel, hexane/ethyl acetate, 4:1) to afford first (±)-**3a** as colorless rods (R_f = 0.42, hexane/ethyl acetate, 1:1), and then its 2′-epimer (±)-**3b** as colorless plates (R_f = 0.42, hexane/ethyl acetate, 1:1). The stereostructures of (±)-**3a** and (±)-**3b** were established following an X-ray analysis of (±)-**3a**. − **(±)-3a:** M.p. 200−202°C (diethyl ether). − IR (KBr): $\tilde{\nu}$ = 3460 cm^{-1} (m, O−H), 2940 (m, C−H), 1785 (s, C=O), 1750 (s, C=O), 1685 (s, C=C), 1350 (m, O−H), 1335 (m, O−H), 1180 (s, C−O), 1090 (s, C−O), 1015 (s, C−O), 955 (m), 870 (m), 750 (m). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (s, 3 H, 8-Me), 1.03 (s, 3 H, 8-Me), 1.16 (dt, 1 H, J = 13.4, J' = 3.2 Hz, 7-H), 1.44 (m, 1 H, 6-H), 1.62 (m, 1 H, 6-H′), 1.95 (td, 1 H, J = 13.6, J' = 4.3 Hz, 7-H′), 2.01 (t, 3 H, J = 1.2 Hz, 4′-Me), 2.22 (m, 2 H, 5-CH_2), 2.38 (s, 1 H, OH), 3.82 (dd, 1 H, J = 6.8, J' = 1.3 Hz, 3a-H), 4.76 (d, 1 H, J = 6.8 Hz, 8b-H), 5.35 (br. s, 1 H, 4-H), 6.16 (t, 1 H, J = 1.2 Hz, 2′-H), 6.94 (t, 1 H, J = 1.5 Hz, 3′-H), 7.40 (d, 1 H, J = 2.1 Hz, 9-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.7, 21.2, 22.4, 23.7, 24.8, 35.5, 38.1, 45.4, 79.7, 85.2, 100.5, 111.6, 118.8, 135.9, 140.8, 146.6, 150.2, 170.2, 170.5. − HRMS: calcd. for $C_{19}H_{22}O_6$ 346.1415; found 346.1414. − MS (EI, 70 eV): *m/z* = 346 [M$^+$], 328, 290, 249, 231, 203, 181, 163, 137, 97, 69, 41. − $C_{19}H_{22}O_6$ (346.4): calcd. C 65.88, H 6.40; found C 65.69, H 6.39. − **(±)-3b:** M.p. 132−134°C (diethyl ether). − IR (KBr): $\tilde{\nu}$ = 3600−3300 cm^{-1} (m, O−H), 2940 (m, C−H), 1775 (s, C=O), 1750 (s, C=O), 1685 (s, C=C), 1355 (m, O−H), 1190 (s, C−O), 1095 (s, C−O), 1020 (s, C−O), 960 (s). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (s, 3 H, 8-Me), 1.04 (s, 3 H, 8-Me), 1.16 (dt, 1 H, J = 13.3, J' = 3.1 Hz, 7-H), 1.44 (m, 1 H, 6-H), 1.62 (m, 1 H, 6-H′), 1.93 (td, 1 H, J = 13.6, J' = 4.3 Hz, 7-H′), 2.02 (t, 3 H, J = 1.5 Hz, 4′-Me), 2.21 (m, 2 H, 5-CH_2), 2.35 (s, 1 H, OH), 3.82 (d, 1 H, J = 6.5 Hz, 3a-H), 4.76 (d, 1 H, J = 6.8 Hz, 8b-H), 5.31 (s, 1 H, 4-H), 6.16 (s, 1 H, 2′-H), 6.93 (t, 1 H, J = 1.5 Hz, 3′-H), 7.38 (d, 1 H, J = 2.1 Hz, 9-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.7, 21.1, 22.5, 23.7, 24.8, 35.5, 38.1, 45.4, 79.7, 85.3, 100.4, 111.7, 118.8, 136.0, 140.9, 146.5, 149.8, 170.1, 170.5. − HRMS: calcd. for $C_{19}H_{22}O_6$ 346.1415; found 346.1403. − MS (EI, 70 eV): *m/z* = 346 [M$^+$], 290, 249, 231, 203, 181, 163, 137, 97, 69, 41. − $C_{19}H_{22}O_6$ (346.4): calcd. C 65.88, H 6.40; found C 65.64, H 6.49.

(±)-(3a*R,8a*R**,8b*S**)-8,8-Dimethyl-8a-hydroxy-3,3a,5,6,7,8,8a,8b-octahydroindeno[1,2-*b*]furan-2-one and (±)-(3a*R**,8a*R**,8b*S**)-8,8-Dimethyl-8a-hydroxy-3,3a,4,6,7,8,8a,8b-octahydroindeno[1,2-*b*]-furan-2-one [(±)-11 and (±)-12]:** A mixture of the epoxide (±)-**8** (111 mg, 0.50 mmol) and aluminum isopropoxide (2.04 g, 10 mmol) in toluene (10 mL) was refluxed for 85 h under argon. The cooled reaction mixture was then treated with 2 N HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The yellowish residue thus obtained was chromatographed on silica gel (hexane/ethyl acetate, 3:1) to afford 4 mg [4% based on consumed (±)-**8**] of (±)-**11** (R_f = 0.26, hexane/ethyl acetate, 1:1) as colorless crystals, 67 mg [67% based on consumed (±)-**8**] of (±)-**12** (R_f = 0.27, hexane/ethyl acetate, 1:1) as colorless needles, and 13 mg (11%) of the starting material (±)-**8**. − **(±)-11:** M.p. 155−157°C (hexane/ethyl acetate). − IR (KBr): $\tilde{\nu}$ = 3460−3400 cm^{-1} (m, O−H), 1750 (s, C=O), 1195 (m, C−O), 1165 (m, C−O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 8-Me), 1.20 (s, 3 H, 8-Me), 1.43 (s, 1 H, OH), 1.48 (m, 1 H, 7-H), 1.52−1.64 (m, 2 H, 6-CH_2), 1.80 (dd, 1 H, J = 14.1, J' = 3.7 Hz, 5-H), 1.87 (m, 1 H, 7-H′), 1.95 (dt, 1 H, J = 13.3, J' = 3.3 Hz, 5-H′), 2.40 (dd, 1 H, J = 18.0, J' = 1.7 Hz, 3-H), 2.74 (dd, 1 H, J = 18.0, J' = 9.5 Hz, 3-H′), 3.59 (dddd, 1 H, J = 9.5, J' = 5.2, J'' = 1.7, J'''' = 1.5 Hz, 3a-H), 4.65 (dd, 1 H, J = 5.2, J' = 0.8 Hz, 8b-H), 5.36 (br s, 1 H, 4-H). − ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 17.4, 28.4, 29.9, 32.8, 33.4, 33.6, 39.7, 41.2, 84.1, 90.0, 125.3, 153.4, 176.2. − HRMS: calcd. for $C_{13}H_{18}O_3$ 222.1256; found 222.1270. − MS (EI, 70 eV): *m/z* = 222 [M$^+$], 207, 189, 180, 163, 154, 147, 138, 123, 109, 95, 69, 55. − $C_{13}H_{18}O_3$ (222.3): calcd. C 70.24, H 8.16; found C 70.14, H 8.24. − **(±)-12:** M.p. 129−130°C (hexane/ethyl acetate). − IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1} (m, O−H), 1760 (s, C=O), 1210 (m, C−O), 1175 (m, C−O), 1005 (m, C−O). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, 8-Me), 1.12 (s, 3 H, 8-Me), 1.14 (ddd, 1 H, J = 13.5, J' = 5.6, J'' = 3.2 Hz, 7-H), 1.46 (s, 1 H, OH), 1.64 (ddd, 1 H, J = 13.5, J' = 9.8, J'' = 5.9 Hz, 7-H′), 1.98−2.18 (m, 3 H, 4-H and 6-CH_2), 2.28 (dd, 1 H, J = 17.8, J' = 1.7 Hz, 3-H), 2.72 (dd, 1 H, J = 17.8, J' = 8.5 Hz, 3-H′), 2.97 (m, 1 H, 4-H′), 3.11 (m, 1 H, 3a-H), 4.67 (d, 1 H, J = 5.2 Hz, 8b-H), 5.68 (d, 1 H, J = 2.7 Hz, 5-H). − ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 22.9, 22.9,

24.6, 34.0, 35.4, 35.4, 35.8, 35.8, 81.4, 89.0, 124.5, 139.9, 176.9. – $C_{13}H_{18}O_3$ (222.3): calcd. C 70.24, H 8.16; found C 69.90, H 8.29.

X-ray Analysis of (±)-3a: Crystal size 0.3 × 0.5 × 0.5 mm. Crystal and intensity data were obtained on a Rigaku AFC-5S automated four-circle diffractometer using graphite-monochromated Mo-K_α radiation. Final lattice parameters were obtained from a least-squares refinement using 25 reflections. Crystal data: $C_{19}H_{22}O_6$, M_r = 346.38, monoclinic, space group $P2_1/n$, a = 9.955(8), b = 9.70(2), c = 18.88(1) Å, β = 93.61(6)°, V = 1819(4) Å^3, Z = 4, D_X = 1.265 gcm^{-3}, F(000) = 736, μ(Mo-K_α) = 0.938 cm^{-1}. The intensities were measured using ω/2θ scans up to 45°. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors. An absorption correction was applied, but not a decay correction. Of the 3493 independent reflections collected, 1836 reflections with $I > 3.0\ \sigma(I)$ were used for the structure determination. The structure was solved by direct methods using the TEXSAN crystallographic software package.[21] All non-H atoms were located in a Fourier map. All H atoms were calculated at geometrical positions and were not refined. Atomic parameters were refined by full-matrix least-squares methods, using anisotropic temperature factors for all non-H atoms. The final refinement converged with R = 0.060 and R_w = 0.079 for 314 parameters. The minimum and maximum peaks in the final difference Fourier map were −0.23 and 0.24 eÅ^{-3}. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography".[22] Supplementary material available includes lists of atomic coordinates for the non-H atoms, the bond lengths and angles in (±)-**3a**, with their e.s.d.s in parentheses.[23]

Bioassays:[19] Seeds of *Orobanche minor* (clover broomrape) were harvested at the riverside of Watarase river in Tochigi in 1994, dried, and stored in a refrigerator. Compounds to be tested were dissolved in 10^{-4} M gibberelin A_3 solution. For preconditioning, the seeds were spread on a glass fibre filter paper (5 mm diameter), wetted with 10^{-4} M gibberelin A_3 solution, and stored in the dark for 10 d at room temperature. The seeds were then treated with test solutions of (±)-**3a** and (±)-**3b**. After incubation in the dark for 6 d, germination rates were determined under a microscope. In each test series, 10^{-4} M gibberelin A_3 solution was used as a negative control and (±)-strigol as a positive control. Tests were replicated 3 times.

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