Pergamon

Tetrahedron Letters 39 (1998) 6023–6026

TETRAHEDRON LETTERS

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

Kenji Mori[a*], Junichi Matsui[a†], Masahiko Bando[b], Masaru Kido[b] and Yasutomo Takeuchi[c]

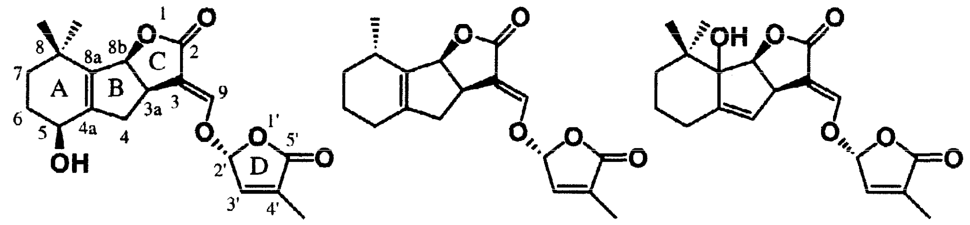
[a]Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162-8601, Japan
[b]Otsuka Pharmaceutical Co., Ltd., Kawauchi, Tokushima 771-0130, Japan
[c]Weed Science Center, Utsunomiya University, Mine-machi, Utsunomiya, Tochigi 321-0943, Japan

Received 22 May 1998; revised 11 June 1998; accepted 12 June 1998

Abstract: Several compounds [(±)-**3a**, (±)-**3b**, (±)-**10**, (±)-**11** and (±)-**12**] with the structures related to that (**3**) proposed for alectrol, the germination stimulant, were synthesized. The structure (±)-**3a** was solved by X-ray crystallographic analysis. Comparison of the ^{1}H NMR data of the synthetic compounds with those reported for alectrol disproved the correctness of the proposed structure **3**.

Keywords: Biologically active compound; Lactones; NMR; X-Ray crystal structure

Chemical ecology of parasitic weeds of the *Alectra*, *Striga* and *Orobanche* is an interesting problem, because the seeds of such weeds can recognize their correct host plants through semiochemical(s) exuded by the host roots.[1] Chemists' endeavor to solve the problem culminated in the isolation and identification of some germination stimulants (Figure 1) such as strigol (**1**),[2] sorgolactone (**2**),[3] and alectrol (**3**, proposed structure).[4] Synthesis of the former two compounds **1** and **2** has been pursued extensively as summarized in the recent two papers.[5,6]



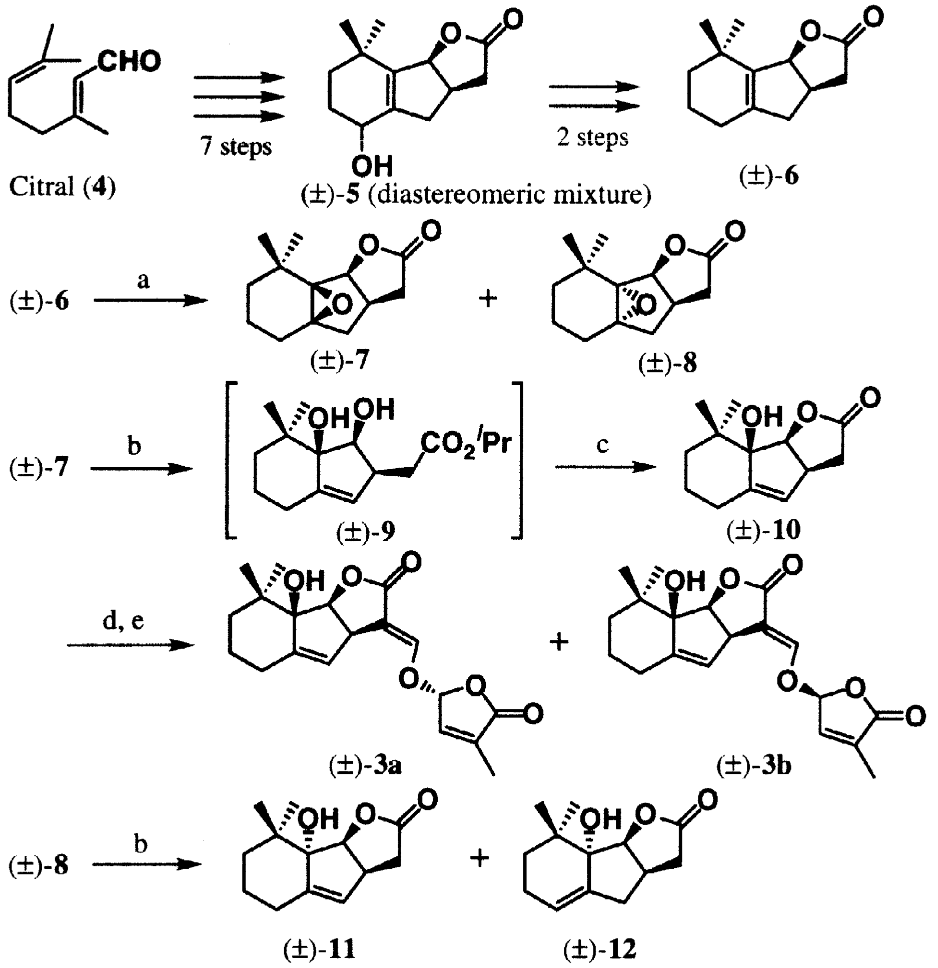
(+)-Strigol (**1**) Sorgolactone (**2**) Alectrol (**3**, proposed structure)

Figure 1. Structures of the germination stimulants

In continuation of our synthesis of (±)- and (+)-sorgolactone (**2**),[7,8] we initiated a project to synthesize (±)-alectrol (**3**), especially because its stereochemistry at C-8a remained unknown.[4] Alectrol is a germination stimulant for the seeds of the root parasites *Alectra vogelii* and *Striga gesnerioides*, and 300 μg of it 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 its spectroscopic studies (UV, IR, ^{1}H NMR, MS and CD).[4] Comparison of the ^{1}H NMR spectra of our synthetic products (±)-**3a**, (±)-**3b**, (±)-**10**, (±)-**11** and (±)-**12** (Figure 2) with those reported for alectrol[4] disproved the correctness of the proposed structure **3**.

Our synthetic route to (±)-**3a** and (±)-**3b** is shown in Figure 2. Citral (**4**) was converted to the known hydroxy lactone (±)-**5** according to Sih,[9] Brooks,[10] and their respective coworkers. A sufficient amount of the key intermediate (±)-**6** was prepared from (±)-**5** as reported by Welzel and his co-workers.[11] Epoxidation of

0040-4039/98/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)01238-6



Reagents: (a) MCPBA, CH_2Cl_2 [39% for (±)-**7** and 60% for (±)-**8**].- (b) $Al(O\textit{i}\text{-}Pr)_3$, toluene [4% for (±)-**11** and 60% for (±)-**12**].- (c) AcOH, $CHCl_3$ [89% from (±)-**7**].- (d) NaH, HCO_2Et, Et_2O.- (e) 1) K_2CO_3, 4-bromo-2-methyl-2-buten-4-olide, *N*-methylpyrrolidone [78%, (±)-**3a**:(±)-**3b** = ~1.2:1]; 2) MPLC separation.

Figure 2. Synthesis of (±)-**3a** and (±)-**3b**

(±)-**6** with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of two epoxides (±)-**7** and (±)-**8** (1:1.5), which could be separated by SiO_2 chromatography. The structures of these epoxides were assigned on the basis of the X-ray analysis of (±)-**3a** derived from (±)-**7**. Treatment of (±)-**7** with aluminum isopropoxide in toluene under reflux for 5 h was followed by acidification with 2N HCl to furnish the oily dihydroxy ester (±)-**9**. This was stirred for 10 days in chloroform in the presence of a small amount of acetic acid to give the lactone (±)-**10**, mp 169-170 °C, in 89% yield based on (±)-**7**. The remaining two steps followed the conventional route reported previously[7-10] to afford a mixture of (±)-**3a** and (±)-**3b** (1.2:1) in 78% yield. The two isomers were separated by medium pressure liquid chromatography (MPLC) to give crystalline (±)-**3a**[12] and (±)-**3b**.[13] The structure (±)-**3a** could be assigned to the isomer with mp 200-202 °C on the basis of its X-ray analysis.[14] The perspective view of (±)-**3a** is shown in Figure 3.

The isomeric epoxide (±)-**8** was also treated with aluminum isopropoxide in toluene under reflux for 85 h. The mixture was acidified with 2N HCl, and the products were purified by SiO_2 chromatography to give (±)-**11** (4% yield), mp 155-157 °C, and (±)-**12** (60% yield), mp 129-130 °C.[15]

Figure 4 summarizes some of the ^{1}H NMR data of alectrol together with those of strigol (**1**), sorgolactone (**2**), and the synthetic products (±)-**3a**, (±)-**10**, (±)-**11** and (±)-**12**. The signals due to the proton at C-8b of (±)-**3a**, (±)-**10** and (±)-**11** were observed at δ = 4.65-4.79, while the same proton of alectrol was reported to exhibit a signal at δ = 5.6. Although we could not attach the D-ring to (±)-**11** due to the scarcity of the material, the δ-value of the proton at C-8b of the expected diastereomer of (±)-**3a** at C-8b was thought to be similar to that of (±)-**11** [cf. δ = 4.76 in (±)-**3a** and δ = 4.79 in (±)-**10**]. Considering also the signals due to other protons, we conclude that the structure **3** proposed for alectrol must be in error.[16-18]

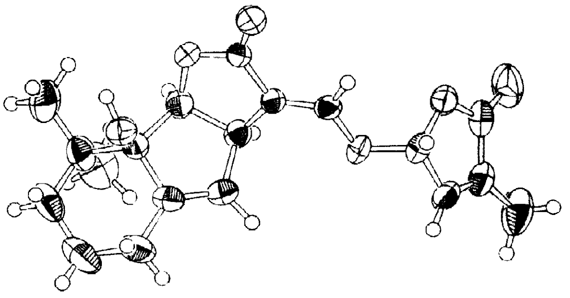
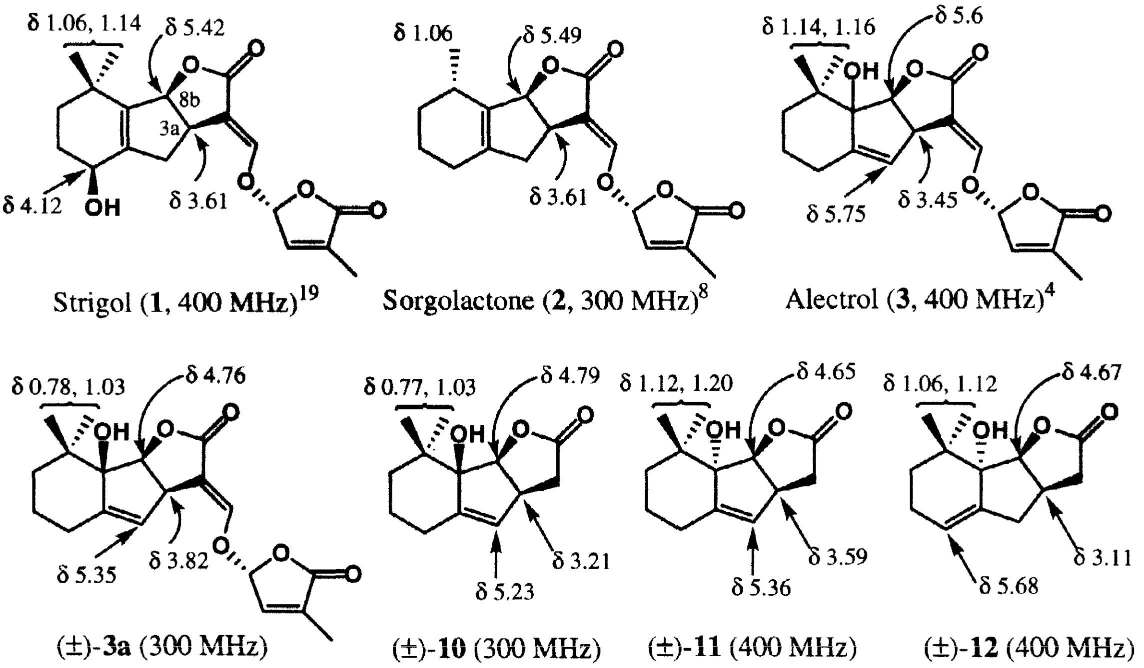


Figure 3. Perspective view of (±)-**3a**



Strigol (**1**, 400 MHz)[19] Sorgolactone (**2**, 300 MHz)[8] Alectrol (**3**, 400 MHz)[4]

(±)-**3a** (300 MHz) (±)-**10** (300 MHz) (±)-**11** (400 MHz) (±)-**12** (400 MHz)

Figure 4. Some of ^{1}H NMR data of alectrol and related compounds (measured in $CDCl_3$)

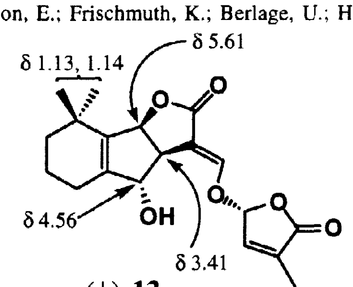
Acknowledgment: We thank Prof. Takao Yokota (Teikyo University, Utsunomiya) for kindly sending us a copy of the ^{1}H NMR spectrum of alectrol. This work was financially supported by Kanebo Co., Ltd.

References and Notes

[†] Research fellow on leave from Kanebo Co., Ltd. (1996-1998). Present address: Cosmetic laboratory, Kanebo Co., Ltd., Kotobuki-cho 5-3-28, Odawara, Kanagawa 250-0002, Japan.

1. Parker, C.; Riches, C. R. *Parasitic Weeds of the World, Biology and Control*, CAB International, Wallingford, U. K., **1993**.
2. Cook, C. E.; Whichard, L. P.; Wall, M. E.; Egley, G. H.; Coggon, P.; Luhan, P. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1972**, *94*, 6198-6199.
3. Hauck, C.; Müller, S.; Schildknecht, H. *J. Plant Physiol.* **1992**, *139*, 474-478.
4. Müller, S.; Hauck, C.; Schildknecht, H. *J. Plant Growth Regul.* **1992**, *11*, 77-84.
5. Sugimoto, Y.; Wigchert, S. C. M.; Thuring, J. W. J. F.; Zwanenburg, B. *J. Org. Chem.* **1998**, *63*, 1259-1267 and refs. therein.
6. Röhrig, S.; Hennig, L.; Findeisen, M.; Welzel, P. *Tetrahedron* **1998**, *54*, 3439-3456 and refs. therein.
7. Mori, K.; Matsui, J.; Bando, M.; Kido, M.; Takeuchi, Y. *Tetrahedron Lett.* **1997**, *38*, 2507-2510.
8. Mori, K.; Matsui, J. *Tetrahedron Lett.* **1997**, *38*, 7891-7892.

9. Heather, J. B.; Mittal, R. S. D.; Sih, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 3661-3669.
10. Brooks, D. W.; Bevinakatti, H. S.; Kennedy, E.; Hathaway, J. *J. Org. Chem.* **1985**, *50*, 628-632.
11. Frischmuth, K.; Samson, E.; Kranz, A.; Welzel, P.; Meuer, H.; Sheldrick, W. S. *Tetrahedron* **1991**, *47*, 9793-9806.
12. Properties of (±)-**3a**: colorless rods (diethyl ether), mp 200-202 °C; R_f 0.42 (hexane/ethyl acetate 1:1); IR (KBr) 3460, 1785, 1750, 1685, 1350, 1335, 1225, 1210, 1180, 1090, 1015, 955, 870, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (3H, s, 8-Me), 1.03 (3H, s, 8-Me), 1.16 (1H, dt, *J* = 13.4, 3.2 Hz, 7-H), 1.44 (1H, m, 6-H), 1.62 (1H, m, 6-H'), 1.95 (1H, td, *J* = 13.6, 4.3 Hz, 7-H'), 2.01 (3H, t, *J* = 1.2 Hz, 4'-Me), 2.22 (2H, m, 5-CH_2), 2.38 (1H, s, OH), 3.82 (1H, dd, *J* = 6.8, 1.3 Hz, 3a-H), 4.76 (1H, d, *J* = 6.8 Hz, 8b-H), 5.35 (1H, br s, 4-H), 6.16 (1H, t, *J* = 1.2 Hz, 2'-H), 6.94 (1H, t, *J* = 1.5 Hz, 3'-H), 7.40 (1H, d, *J* = 2.1 Hz, 9-H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): 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): m/z 346(M^+), 290, 249, 231, 203, 181, 163, 137, 97, 69, 41; Anal. calcd. for $C_{19}H_{22}O_6$: C 65.88, H 6.40; found C 65.69, H 6.39.
13. Properties of (±)-**3b**: colorless plates (diethyl ether), mp 132-134 °C; R_f 0.42 (hexane/ethyl acetate 1:1); IR (KBr) 3495, 2940, 1775, 1750, 1685, 1355, 1190, 1095, 1020, 960 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$): δ = 0.78 (3H, s, 8-Me), 1.04 (3H, s, 8-Me), 1.16 (1H, dt, *J* = 13.3, 3.1 Hz, 7-H), 1.44 (1H, m, 6-H), 1.62 (1H, m, 6-H'), 1.93 (1H, td, *J* = 13.6, 4.3 Hz, 7-H'), 2.02 (3H, t, *J* = 1.5 Hz, 4'-Me), 2.21 (2H, m, 5-CH_2), 2.35 (1H, s, OH), 3.82 (1H, d, *J* = 6.5 Hz, 3a-H), 4.76 (1H, d, *J* = 6.8 Hz, 8b-H), 5.31 (1H, s, 4-H), 6.16 (1H, s, 2'-H), 6.93 (1H, t, *J* = 1.5 Hz, 3'-H), 7.38 (1H, d, *J* = 2.1 Hz, 9-H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): 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, 135.0, 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): m/z 346(M^+), 290, 249, 231, 203, 181, 163, 137, 97, 69, 41; Anal. calcd. for $C_{19}H_{22}O_6$: C 65.88, H 6.40; found C 65.64, H 6.49.
14. X-Ray analysis of (±)-**3a**: Crystal size, 0.3 x 0.5 x 0.5 mm. The crystal data and intensity data were obtained on Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Crystal data: $C_{19}H_{22}O_6$, $Mr = 346.38$, monoclinic, space group $P2_1/n$, $a = 9.955(8)$ Å, $b = 9.70(2)$ Å, $c = 18.88(1)$ Å, $\beta = 93.61(6)°$, $V = 1819(4)$ $Å^3$, $Z = 4$, $Dx = 1.265$ gcm^{-3}, $F(000) = 736$ and $\mu(\text{Mo } K\alpha) = 0.938$ cm^{-1}. Of the 3493 independent reflections collected, 1836 reflections with $I > 3.0\sigma(I)$ were used for the structure determination. The final refinement converged with $R = 0.060$ and $Rw = 0.079$ for 314 parameters. Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.
15. The structures of (±)-**11** and (±)-**12** were assigned based on their ^1H NMR spectra. The lactone with mp 155-157 °C showed signals at δ = 1.12 (3H, s, 8-Me), 1.20 (3H, s, 8-Me), 1.43 (1H, br s, OH), 1.48 (1H, m, 7-H), 1.52-1.64 (2H, m, 6-CH_2), 1.80 (1H, dd, *J* = 14.1, 3.9 Hz, 5-H), 1.87 (1H, m, 7-H'), 1.95 (1H, dt, *J* = 13.3, 3.3 Hz, 5-H'), 2.40 (1H, dd, *J* = 18.0, 1.7 Hz, 3-H), 2.74 (1H, dd, *J* = 18.0, 9.5 Hz, 3-H'), 3.59 (1H, ddt, *J* = 9.5, 5.2, 1.7 Hz, 3a-H), 4.65 (1H, dd, *J* = 5.2, 0.8 Hz, 8b-H), 5.36 (1H, br s, 4-H), and therefore it must be (±)-**11**, while that with mp 129-130 °C was thought to be (±)-**12** with signals at δ = 1.06 (3H, s, 8-Me), 1.12 (3H, s, 8-Me), 1.30 (1H, ddd, *J* = 13.5, 5.6, 3.2 Hz, 7-H), 1.46 (1H, s, OH), 1.64 (1H, ddd, *J* = 13.5, 9.8, 5.9 Hz, 7-H'), 1.98-2.18 (3H, m, 4-H and 6-CH_2), 2.28 (1H, dd, *J* = 17.8, 1.7 Hz, 3-H), 2.72 (1H, dd, *J* = 17.8, 8.5 Hz, 3-H'), 2.97 (1H, m, 4-H'), 3.11 (1H, m, 3a-H), 4.67 (1H, d, *J* = 5.2 Hz, 8b-H), 5.68 (1H, d, *J* = 2.7 Hz, 5-H).
16. Prof. T. Yokota kindly sent us a copy of the ^1H NMR spectrum (600 MHz, $CDCl_3$) of alectrol isolated from the root exudates of red clover, *Trifolium pratense* (Yokota, T; personal communication to K. M. dated February 19, 1997). Even in the presence of some contaminants, the low field portion of his spectrum was of excellent quality, and different from that of our synthetic products. Prof. Yokota's spectrum was in complete accord with that reported by Müller et al.[4]
17. We also synthesized (±)-**13** (Matsui, J.; unpublished results). Its ^1H NMR spectrum was also different from that of alectrol, because (±)-**13** showed a signal at δ = 4.56.
18. Both the lactones (±)-**3a** and (±)-**3b** were bioactive (see Table 1) as the germination stimulant when the seeds of clover broomrape (*Orobanche minor*) was used as the test parasitic weed.[20] This fact supports the view that the bioactivity as the germination stimulant resides on the C/D ring parts of the molecule.[21]
19. Samson, E.; Frischmuth, K.; Berlage, U.; Heinz, U.; Hobert, K.; Welzel, P. *Tetrahedron* **1991**, *47*, 1411-1416.



(±)-**13**

Concentration	Relative Germination of *Orobanche minor* (%)		
	(±)-**3a**	(±)-**3b**	
10^{-6} M	90.9 ± 2.5	92.5 ± 2.0	
10^{-7} M	83.7 ± 2.4	88.3 ± 1.7	*cf.* (±)-strigol
10^{-8} M	1.2 ± 0.7	15.9 ± 2.8	94.4 ± 1.4
10^{-9} M	0	0	89.0 ± 1.6

(Control 0%)

Table 1. Bioactivity of (±)-**3a** and (±)-**3b** as the germination stimulant

20. Takeuchi, Y.; Omigawa, Y.; Ogasawara, M.; Yoneyama, K.; Konnai, M.; Worsham, A. D. *Plant Growth Regul.* **1995**, *16*, 153-160.
21. Zwanenburg, B.; Thuring, J. W. J. F. *Pure Appl. Chem.* **1997**, *69*, 651-654.