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Synthesis of (3aR,8S,8bS,2'*R*)-(+)-Sorgolactone and Its Stereoisomers, the Germination Stimulant from *Sorghum bicolor*

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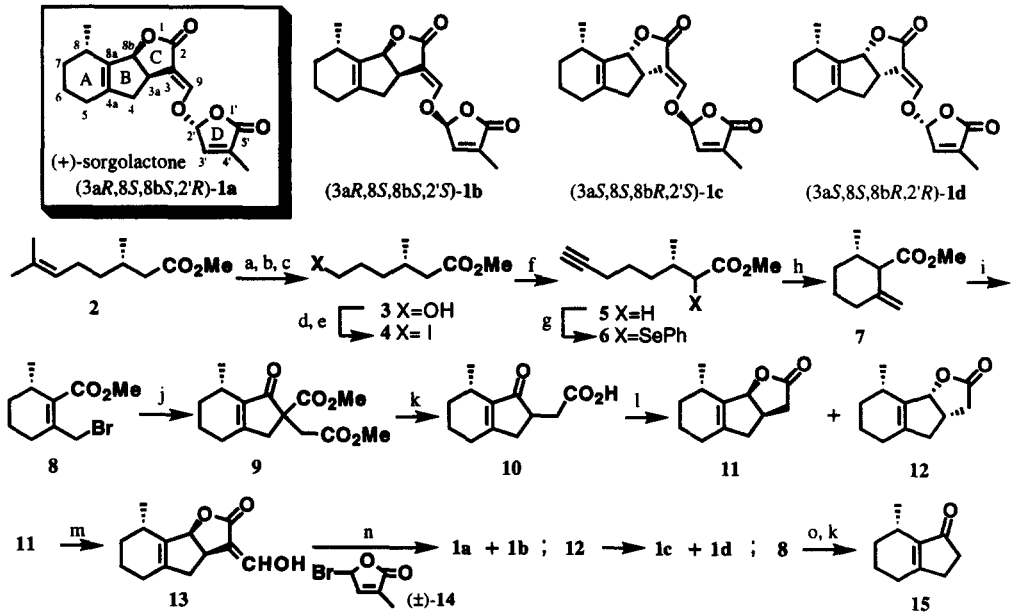
Abstract: Methyl (*S*)-citronellate (**2**) was converted to (3a*R*,8*S*,8b*S*,2'*R*)-(+)-sorgolactone (**1a**) by employing the radical cyclization of **6** to **7** as the key-step. Three other stereoisomers (**1b**, **1c** and **1d**) of sorgolactone were also prepared. The CD spectrum of **1a** was in accord with that reported for the natural product. © 1997 Elsevier Science Ltd.

Sorgolactone was isolated from *Sorghum bicolor* as the germination stimulant for parasitic weeds by Hauck *et al.* in 1992[1]. They proposed **1a** as its structure based on its ^{1}H NMR and CD studies[1]. The scarcity of the material (5 μg) at the time of isolation coupled with the fact that the natural sample is no more available prompted chemists to achieve the synthesis of sorgolactone. We recently reported a synthesis of **1a-1d** as racemates[2], while Zwanenburg and his co-workers synthesized (+)-**1a** and *ent*-(-)-**1b** together with the four racemates[3]. Zwanenburg's strategy for the synthesis of (+)-**1a** was the resolution of the A-B-C tricyclic



Reagents: (a) MCPBA, CH_2Cl_2.- (b) $HIO_4{\cdot}2H_2O$, THF / Et_2O.- (c) $NaBH_4$, MeOH (91%, 3 steps).- (d) TsCl, C_5H_5N.- (e) NaI, acetone (82%, 2 steps).- (f) LiC≡CH·EDA, THF / DMSO (37%).- (g) 1) LDA (2 eq.), THF; 2) PhSeBr; 3) dil. HCl (69%).- (h) *n*-Bu_3SnH, AIBN, C_6H_6 (55%).- (i) 1) $C_5H_5N{\cdot}HBr{\cdot}Br_2$, $CHCl_3$; 2) C_5H_5N (52%).- (j) 1) NaH, $CH_2(CO_2Me)_2$, THF; 2) $BrCH_2CO_2Me$ (81%).- (k) 6N-HC AcOH (96% for **10**; 72% for **15**).- (l) 1) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, then dil. HCl; 2) MPLC separation (21% of **11** and 30% of **12**).- (m) NaH, HCO_2Et, Et_2O (quant.)- (n) K_2CO_3, (±)-**14**, *N*-methylpyrrolidone; 2) SiO_2 chromatog. (42% of **1a** and 41% of **1b**).- (o) 1) NaOMe, $CH_2(CO_2Me)_2$, MeOH; 2) AcOH (70%).

precursor (±)-**13** with an optically active ring-D precursor corresponding to **14**. Welzel and his co-workers also devised a similar strategy applicable to the synthesis of **1a**[4]. Our own plan for the synthesis of (3a*R*, 8*S*,8b*S*,2'*R*)-**1a** is to convert methyl (*S*)-citronellate (**2**) to the optically active **13**, the A-B-C tricyclic precursor, which is to be coupled with (±)-**14** to give a separable mixture of **1a** and **1b**. As the key-step, we envisaged a radical cyclization[5] of **6** to **7** to give an optically active ring-A building block.

(*S*)-(-)-Citronellal (96%e.e., Takasago) was converted to methyl (*S*)-citronellate (**2**), which furnished the hydroxy ester **3** after epoxidation, periodate cleavage and reduction. The hydroxy ester **3** afforded the corresponding iodo ester **4** after 2 steps. Ethynylation of **4** gave the acetylenic ester **5** in a moderate yield, which furnished the phenylselenylated ester **6**. The pivotal cyclization reaction was executed by treatment of **6** with tri-*n*-butyltin hydride and AIBN in benzene at 80 °C to generate the desired **7** as a diastereomeric mixture (1:1.2~1.8). Bromination of **7** and subsequent dehydrobromination gave **8**. Alkylation of dimethyl malonate with **8** was followed by Dieckmann-type cyclization, demethoxycarbonylation and alkylation of the resulting sodio enolate of the β-keto ester with methyl bromoacetate to give **9**. Acid hydrolysis of **9** with concomitant decarboxylation gave **10** as a diastereomeric mixture. The keto acid **10** was reduced under the Luche conditions[6], and the resulting hydroxy acid was lactonized. As in the case of the racemates[2], the mixture of **11** and **12** could be separated by MPLC [Lobar LiChroprep® Si 60 (40-63 μm)] to give pure **11** (oil, $[\alpha]_D^{24.6}$ = +3.0 (c 0.60, $CHCl_3$)) and **12** (mp 45-47 °C, $[\alpha]_D^{26.0}$ = -68.4 (c 0.40, $CHCl_3$)), whose ^1H NMR spectra were identical with those reported for (±)-**11** and (±)-**12**[7].

Formylation of **11** gave **13**, which was condensed with (±)-**14**. The resulting mixture of **1a** and **1b** were separated by silica gel chromatography to give crystalline (3a*R*,8*S*,8b*S*,2'*R*)-(+)-sorgolactone (**1a**) and amorphous (+)-**1b**, whose NMR spectra were identical with those of the racemates[7,8]. (+)-Sorgolactone (**1a**) showed a positive Cotton effect at 232 nm (Δε = 21) in accord with those reported for the natural (236 nm)[1] and the synthetic (230 nm)[3] materials. Similarly, **12** yielded (-)-**1c** and (-)-**1d**. The bioactivity of these stereoisomers of sorgolactone to stimulate the germination of clover broomrape (*Orobanche minor*) seeds was **1d** > **1a** > **1b** ≈ **1c**. It should be added that we made several fruitless attempts to construct the C-ring enantioselectively by asymmetric alkylation of **15** or its derivatives. Separation at the stage of **10** was also unsuccessful.

Details of the synthesis and bioassay as well as the rigorous identification of our synthetic (+)-**1a** with the natural sorgolactone (Its reisolation is under way by Prof. T. Yokota at Teikyo University.) will be reported in due course.

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References and Notes

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7. Because the structures of (±)-**12** and (±)-**1** were solved by X-ray analyses[2], the NMR coincidence was sufficient to establish the stereostructures of **11**, **12**, **1a** and **1b**.
8. Properties of **1a**: e.e. = ~100% [determined by HPLC (Chiralcel-OD®)]; m.p. 127-129 °C; R_f 0.42 (hexane-EtOAc 1:1); $[\alpha]_D^{24.8}$ = +285 (c 0.26, $CHCl_3$); IR (KBr) 2930, 2865, 1780, 1765, 1740, 1680, 1180, 1100, 1020 and 940 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.06 (3H, d, *J* = 6.9 Hz, 8-Me), 1.23 (1H, m, 7-H), 1.58 (1H, m, 7-H'), 1.65-1.84 (2H, m, 6-H x 2), 1.93 (2H, m, 5-H x 2), 2.03 (3H, t, *J* = 1.3 Hz, 4'-Me), 2.28-2.43 (2H, m, 4H and 8H), 2.75 (1H, dd, *J* = 14.9 and 8.9 Hz, 4-H'), 3.61 (1H, m, 3a-H), 5.49 (1H, d, *J* = 7.8 Hz, 8b-H), 6.15 (1H, s, 2'-H), 6.92 (1H, t, *J* = 1.5 Hz, 3'-H), 7.41 (1H, d, *J* = 2.6 Hz, 9-H); Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.09; H, 6.18., Properties of **1b**: foam; R_f 0.34 (hexane-EtOAc 1:1); $[\alpha]_D^{23.4}$ = +110 (c 0.10, $CHCl_3$)., Properties of **1c**: m.p. 178-179 °C; R_f 0.42 (hexane-EtOAc 1:1); $[\alpha]_D^{24.6}$ = -355 (c 0.20, $CHCl_3$)., Properties of **1d**: m.p. 136-137 °C; R_f 0.33 (hexane-EtOAc 1:1); $[\alpha]_D^{23.4}$ = -185 (c 0.20, $CHCl_3$).

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