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The First Total Synthesis Of The Naturally Occurring Germination Stimulant Sorgolactone

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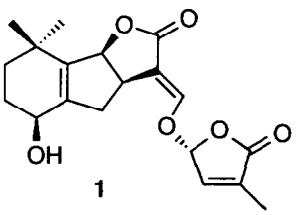
Abstract: The first total synthesis of sorgolactone is reported, which confirms the proposed structure of the naturally occurring germination stimulant. © 1997 Elsevier Science Ltd.

Strigol **1**, sorgolactone **2** and alectrol **3** belong to the class of strigolactones, which are highly potent germination stimulants for the seeds of the parasitic weeds *Striga* and *Orobanche*, that cause severe damage to food crops in tropical and semi-tropical areas of the eastern hemi-sphere. Thus far, several total syntheses of strigol have been reported[1] and its absolute structure has been firmly established by X-ray crystallography[2]. Sorgolactone has been isolated in 1990 from root exudates of the genuine host plant *Sorghum bicolor* by Hauck *et al.* [3,4]. Its structure has been tentatively assigned as depicted. Based on spectroscopic evidence the gross structure was elucidated. The absolute configuration of the stereogenic centers C3a, C8b and C2' was deduced from the similar circular dichroic (CD) data by comparison with those of (+)-strigol.



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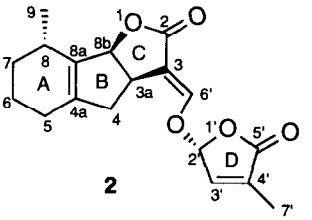

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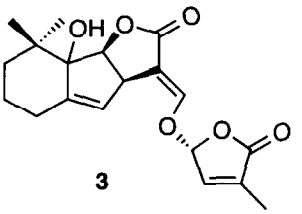
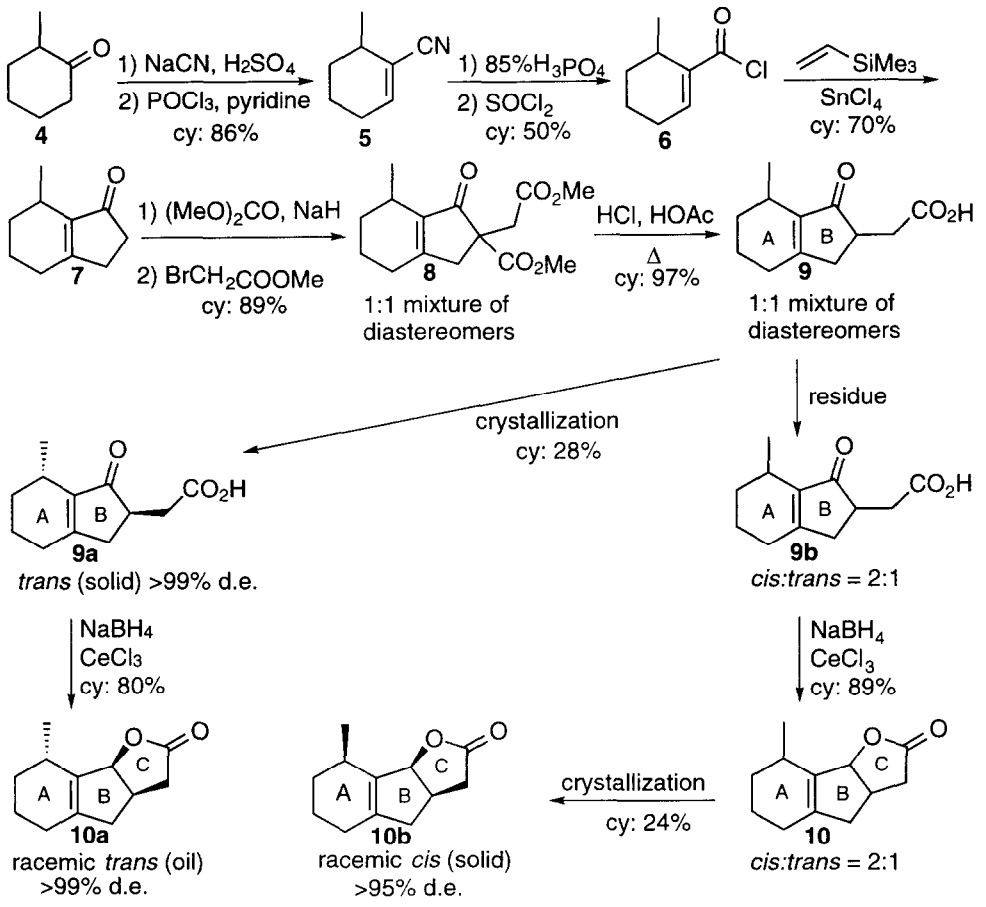


3

Because of lack of spectroscopic detail due to the small amount of sorgolactone obtained (5 μg from 300.000 sorghum plants) and the extremely laborious isolation procedure, the proposed structure has not been ascertained. Therefore, the total synthesis of sorgolactone was undertaken to verify this tentative structure and to unambiguously establish the absolute stereochemical configuration.

Retrosynthesis of the target compound involves coupling of the D-ring to the ABC-part of the molecule. For a successful application of our strategy it is essential that the *trans*- and *cis*-form of the ABC-fragment can be obtained diastereomerically pure. The synthesis of the sorgolactone AB-part was accomplished by a Nazarov cyclisation of the *in situ* formed cyclopentadienyl cation of intermediate **6**[5] (scheme 1). Bicyclic enone **7** was then converted *via* standard procedures[6] into keto acid **9** as a 1:1 mixture of diastereomers of which the *trans*-isomer **9a** crystallized and could thus be obtained with >99% d.e.. The residue, enriched with the *cis*-diastereomer, was subjected to a Luche reduction yielding the sorgolactone ABC-fragment **10**. The *cis*-tricyclic lactone **10b**[7] was crystalline and obtained in >95% % d.e..

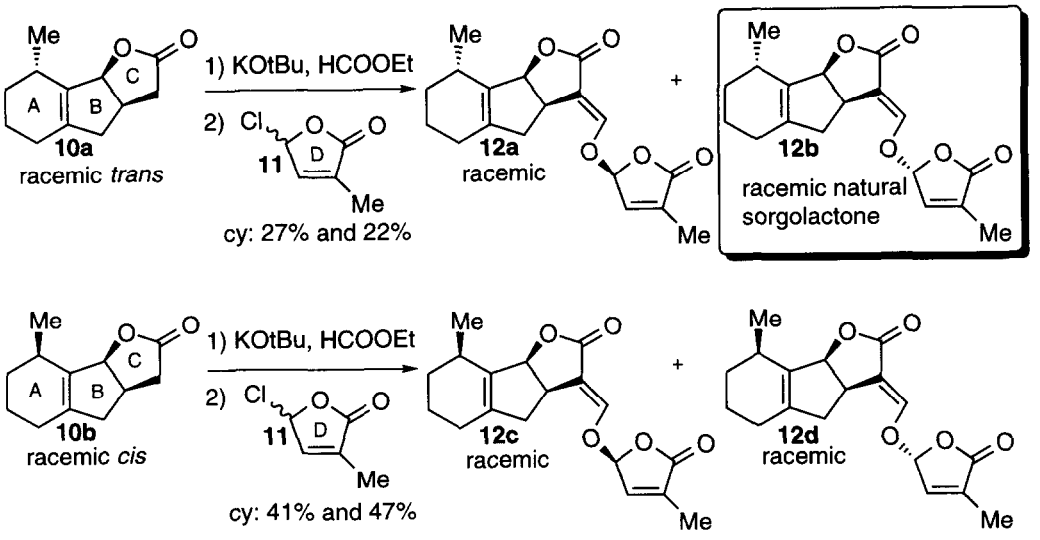


Scheme 1

Luche reduction of the diastereomerically pure *trans*-AB-intermediate **9a** proceeds with complete retention of stereochemistry, leading to the diastereomerically pure *trans*-sorgolactone ABC-part **10a**[7]. The relative configurations of **10a** and **10b** were assigned on the basis of 2D-NOESY experiments. We conclude that H8b of diastereomer **10a** shows its characteristic doublet at 5.5 ppm, whereas the corresponding proton of **10b** resonates at 5.3 ppm.

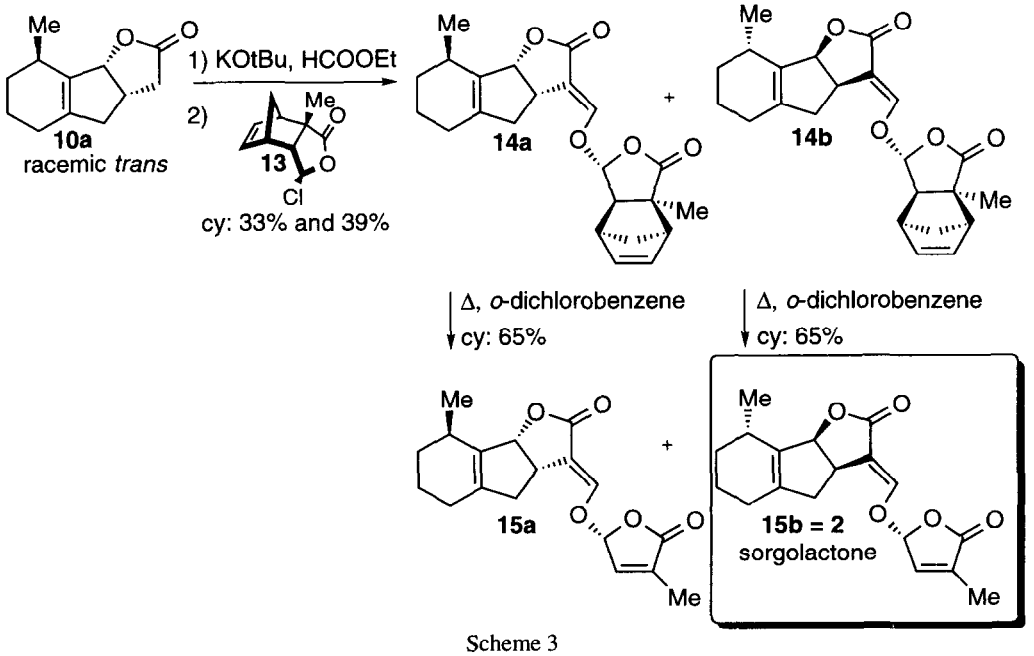
Both racemic ABC-diastereomers **10a** and **10b** were then coupled to racemic chlorobutenolide **11** to give sorgolactone diastereomers **12a**, **12b**, and **12c**, **12d**, respectively[8] (scheme 2). The mixtures thus obtained were readily separated by flash chromatography. The chemical shifts (H8b) of diastereomers **12a-d** were compared with the corresponding value reported by Hauck[3]. We conclude that the original tentative assignment of a *trans* relationship between the A-ring methyl moiety and the C-ring is correct.

In order to establish the absolute stereochemistry of the naturally occurring sorgolactone isomer a stereoselective coupling of diastereomerically pure *trans*-ABC **10a** with enantiopure D-ring synthon **13** was undertaken[9] (scheme 3). The chirality of **13** was chosen such that the proposed natural configuration will be



Scheme 2

obtained in the coupling product. Separation of the thus obtained diastereomers **14a** and **14b** and their subsequent deprotection (thermal retro Diels Alder reaction) afforded two single stereoisomers of sorgolactone, **15a**[10] and **15b**[10]. The CD-spectrum of isomer **15b** was identical with that of the natural compound[3], which implies that the chiral centers in the vicinity of the chromophores must have the same configuration, *i.e.* 3a(R), 8b(S), 2'(R). The CD-spectra of all isomers of desmethyl sorgolactone support this conclusion.[11]



Scheme 3

We have presented the first asymmetric synthesis of sorgolactone **2**. Combination of the relative *trans*-configuration of the natural sorgolactone ABC-part (determined by NMR) with the absolute stereochemistry between the C-ring stereogenic centers C8b/C3a and C2' of naturally occurring sorgolactone (determined by CD-spectrometry) leads to the conclusion that the proposed absolute structure of natural sorgolactone is correct. The synthesis of all 8 stereoisomers of sorgolactone, following the strategy shown in scheme 3 is under active investigation and will be reported in due time along with the bioactivities of all isomers.

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7. **10a**. 400MHz ^{1}H NMR ($CDCl_3$): δ 1,05 (d, 3H, J=7.0Hz, CH_3); 1.25 (m, 1H, H7); 1.60 (m, 1H, H6); 1.76 (m, 2H, H6+H7); 1.97 (m, 2H, 2xH5); 2.14 (dd, 1H, J=1.9Hz, 16.5Hz, H4); 2.29 (dd, 1H, J= 5.7Hz, 18.4Hz, H3); 2.36 (m, 1H, H8); 2.71 (dd, 1H, J=8.2Hz, 16.6Hz, H4); 2.83 (dd, 1H, J=10.7Hz, 18.3Hz, H3); 3.05 (m, 1H, H3a); 5.47 (d, 1H, J=7.5Hz, H8b). 400MHz 2D-NOESY NMR ($CDCl_3$): δ 5.31 (H8b) cross peak with δ 3.04 (H3a), δ 1.11 (CH_3) not with δ 2.32 (H8). ^{13}C NMR ($CDCl_3$): δ 18.60; 20.67; 26.08; 27.91; 31.16; 34.00; 36.61; 42.58; 89.92; 137.44; 140.95; 177.73. **10b**. mp: 54-57°C, 400MHz ^{1}H NMR ($CDCl_3$): δ 1,11 (d, 3H, J=7.1Hz, CH_3); 1.35 (m, 1H, H7); 1.55 (m, 1H, H6); 1.73 (m, 2H, H6+H7); 1.98 (m, 2H, 2xH5); 2.19 (bd, 1H, J=16.5Hz, H4); 2.32 (m, 1H, H8); 2.35 (dd, 1H, J= 4.4Hz, 18.2Hz, H3); 2.61 (ddd, 1H, J=3.0Hz, 8.8Hz, 16.8Hz, H4); 2.81 (dd, 1H, J=10.4Hz, 18.0Hz, H3); 3.04 (m, 1H, H3a); 5.31 (d, 1H, J=7.3Hz, H8b). 400MHz 2D-NOESY NMR ($CDCl_3$): δ 5.31 (H8b) cross peak with δ 3.04 (H3a), δ 1.11 (CH_3) and δ 2.32 (H8). ^{13}C NMR ($CDCl_3$): δ 19.85; 20.37; 26.24; 30.07; 31.63; 34.72; 36.20; 42.41; 92.60; 136.89; 142.84; 177.76.
8. **12a**. (slow moving isomer): 400MHz ^{1}H NMR ($CDCl_3$): δ 1.06 (d, 3H, J=6.9Hz, 3xH9); 1.25 (m, 1H, H7); 1.55 (m, 1H, H6); 1.70 (m, 1H, H6); 1.77 (m, 1H, H7); 1.93 (m, 2H. 2xH5); 2.03 (s, 3H, 3xH7'); 2.33 (bd, 1H, J=15.9Hz, H4); 2.36 (m, 1H, H8); 2.73 (dd, 1H, J=8.5Hz,15.9Hz, H4); 3.60 (m, 1H, H3a); 5.49 (d, 1H, J=7.7Hz, H8b); 6.14 (s, 1H, H2'); 6.94 (s, 1H, H3'); 7.43 (d, 1H, J=2.6Hz, H6'). **12b**. (fast moving isomer): 400MHz ^{1}H NMR ($CDCl_3$): δ 1.06 (d, 3H, J=6.9Hz, 3xH9); 1.25 (m, 1H, H7); 1.55 (m, 1H, H6); 1.70 (m, 1H, H6); 1.78 (m, 1H, H7); 1.93 (m, 2H. 2xH5); 2.03 (s, 3H, 3xH7'); 2.34 (bd, 1H, J=15.9Hz, H4); 2.36 (m, 1H, H8); 2.75 (dd, 1H, J=8.5Hz,15.9Hz, H4); 3.61 (m, 1H, H3a); 5.49 (d, 1H, J=7.6Hz, H8b); 6.15 (s, 1H, H2'); 6.93 (s, 1H, H3'); 7.43 (d, 1H, J=2.6Hz, H6'). **12c + 12d**. (relative stereochemistry not yet determined) (slow moving isomer): 400MHz ^{1}H NMR ($CDCl_3$): δ 1.12 (d, 3H, J=7.0Hz, 3xH9); 1.36 (m, 1H, H7); 1.54 (m, 1H, H6); 1.72 (m, 2H, H6+H7); 1.95 (m, 2H. 2xH5); 2.03 (s, 3H, 3xH7'); 2.31 (m, 1H, H8); 2.33 (bd, 1H, J=16.9Hz, H4); 2.69 (ddd, 1H, J=2.9Hz, 12.1Hz, 16.9Hz, H4); 3.61 (m, 1H, H3a); 5.35 (d, 1H, J=7.7Hz, H8b); 6.13 (s, 1H, H2'); 6.93 (s, 1H, H3'); 7.42 (d, 1H, J=2.5Hz, H6'). (fast moving isomer): 400MHz ^{1}H NMR ($CDCl_3$): δ 1.13 (d, 3H, J=7.0Hz, 3xH9); 1.34 (m, 1H, H7); 1.54 (m, 1H, H6); 1.72 (m, 2H, H6+H7); 1.98 (m, 2H. 2xH5); 2.03 (s, 3H, 3xH7'); 2.31 (m, 1H, H8); 2.33 (bd, 1H, J=16.9Hz, H4); 2.71 (ddd, 1H, J=3.1Hz, 9.2Hz, 16.8Hz, H4); 3.62 (m, 1H, H3a); 5.35 (d, 1H, J=7.6Hz, H8b); 6.15 (s, 1H, H2'); 6.92 (s, 1H, H3'); 7.42 (d, 1H, J=2.5Hz, H6').
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10. **15a**. $[\alpha]_D$=-133,3° (c=0.2, $CDCl_3$); purity 92%, e.e.=98.7% (determined by HPLC); 400MHz ^{1}H NMR ($CDCl_3$): δ 0.99 (d, 3H, J=6.9Hz, 3xH9); 1.17 (m, 1H, H7); 1.49 (m, 1H, H6); 1.63 (m, 1H, H6); 1.70 (m, 1H, H7); 1.87 (m, 2H. 2xH5); 1.96 (s, 3H, 3xH7'); 2.26 (bd, 1H, J=15.9Hz, H4); 2.29 (m, 1H, H8); 2.66 (dd, 1H, J=8.6Hz,15.9Hz, H4); 3.53 (m, 1H, H3a); 5.43 (d, 1H, J=7.7Hz, H8b); 6.07 (s, 1H, H2'); 6.87 (s, 1H, H3'); 7.36 (d, 1H, J=2.6Hz, H6'). ^{13}C NMR ($CDCl_3$): δ 10.47; 18.60; 20.66; 26.02; 27.81; 31.60; 36.46; 41.41; 88.03; 100.60; 114.56; 135.84; 137.16; 140.99; 141.52; 150.28; 170.28; 171.82. CD (CH_3CN, c=29.1μM): λ_{max}=240nm, Δε=-3. **15b**. mp: 139-142°C; $[\alpha]_D$=+271.2° (c=0.25, $CDCl_3$); purity 99,7%, e.e.=100% (determined by HPLC); Anal. calcd. for $C_{18}H_{20}O_5$: C 68.34, H 6.37 found: C 68.15, H 6.32. 400MHz ^{1}H NMR ($CDCl_3$): δ 1.06 (d, 3H, J=6.9Hz, 3xH9); 1.26 (m, 1H, H7); 1.55 (m, 1H, H6); 1.70 (m, 1H, H6); 1.77 (m, 1H, H7); 1.94 (m, 2H. 2xH5); 2.03 (s, 3H, 3xH7'); 2.33 (bd, 1H, J=15.4Hz, H4); 2.36 (m, 1H, H8); 2.75 (dd, 1H, J=9.0Hz,15.4Hz, H4); 3.61 (m, 1H, H3a); 5.49 (d, 1H, J=7.4Hz, H8b); 6.15 (s, 1H, H2'); 6.92 (s, 1H, H3'); 7.41 (d, 1H, J=2.6Hz, H6'). ^{13}C NMR ($CDCl_3$): δ 10.76; 18.60; 20.68; 26.06; 27.84; 31.16; 36.50; 41.35; 88.01; 100.41; 114.54; 136.04; 137.34; 140.90; 141.32; 149.96; 170.20; 171.80. CD (CH_3CN, c=35,9μM): λ_{max}=230nm, Δε=20.
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