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Synthetic disproof of the structure proposed for solanacol, the germination stimulant for seeds of root parasitic weeds

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ABSTRACT

The structure proposed for solanacol, the germination stimulant for seeds of root parasitic weeds isolated from tobacco (*Nicotiana tabacum* L.), was synthesized. Comparison of the ^{1}H NMR data of the synthetic compounds with those reported for solanacol showed the previously proposed structure to be incorrect.

Witchweeds (*Striga* spp.) and broomrapes (*Orobanche* and *Phelipanche* spp.) are the two most devastating parasitic plants; they cause enormous losses of agricultural production in tropical and subtropical areas. Seeds of these parasites germinate only when stimulated by a chemical exuded from the roots of the host as well as some non-host plants.[1] These chemicals include strigol,[2] sorgolactone,[3] orobanchol,[4] and alectrol,[5] which are collectively named strigolactones.[6] Strigolactones appear to be widely distributed in the plant kingdom and are used as host recognition signals for arbuscular mycorrhizal (AM) fungi.[7] Quite recently, strigolactones have been proposed as a new plant hormone class that inhibits shoot branching.[8]

In 2007, Xie et al. reported the isolation and structural elucidation of solanacol, a novel strigolactone, from tobacco (*Nicotiana tabacum* L.).[9] Tobacco is a host for *Phelipanche ramosa* L. The structure proposed for solanacol (**1**) is unique: its A-ring is a substituted benzene, making it the first natural strigolactone that contains a benzene ring (Fig. 1). Inspired by the interesting biological profiles of strigolactones and the unique structure of solanacol, we initiated the synthesis of solanacol as a continuation of our synthetic studies on strigolactones and their derivatives.[10] Comparison of the ^{1}H NMR data of our synthetic compounds with those reported for solanacol disproved the correctness of the proposed structure **1**.

Scheme 1 shows the synthesis of **1**. The known key substrate **2** was prepared, based on the literature procedure, from 2,5-dimethylfuran and maleic anhydride.[11] Installation of an acetate unit into **2** was somewhat troublesome, because alkylation under the reported conditions[12] ($BrCH_2CO_2Et$, K_2CO_3, $CHCl_3$, reflux, 24 h) afforded the desired product **3** only in low yield. Thus, we tried to find appropriate reaction conditions by changing the solvent ($CHCl_3$, acetone, THF, 1,4-dioxane, or toluene), the base (K_2CO_3, *t*-BuOK, Cs_2CO_3, or NaH), and the temperature (room temperature or reflux). It should be noted that a considerable amount of the undesired **4** was obtained under all the conditions used, even with only 1 equiv of $BrCH_2CO_2Et$. This finding meant that the reaction

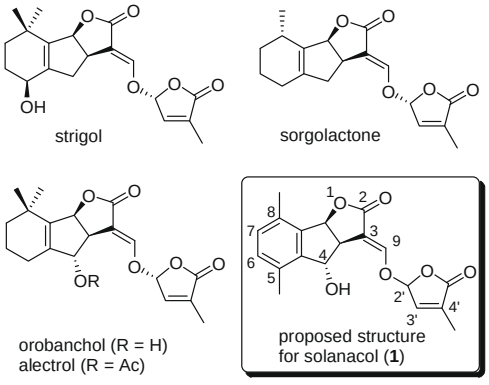

Figure 1. Structures of strigolactones.

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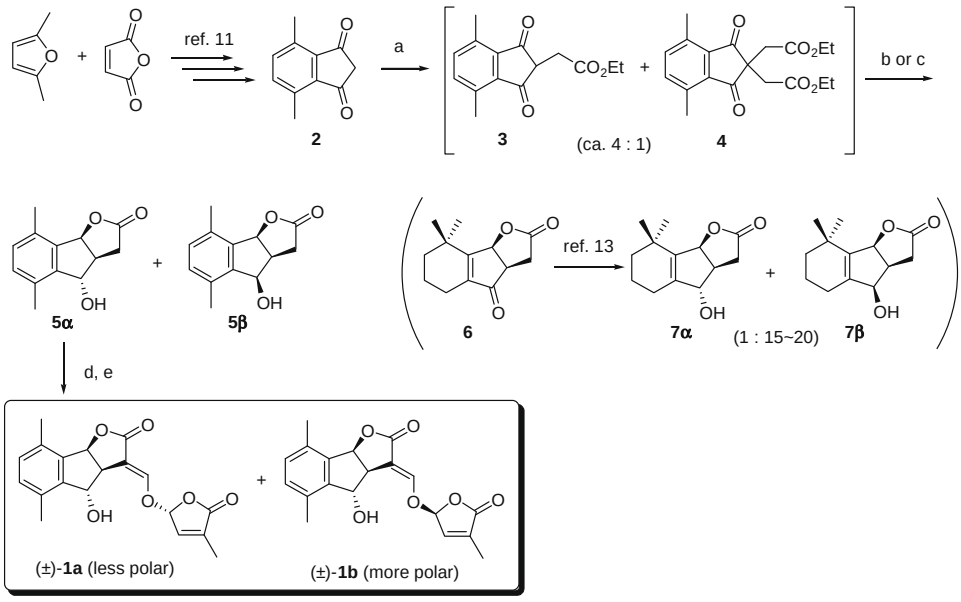
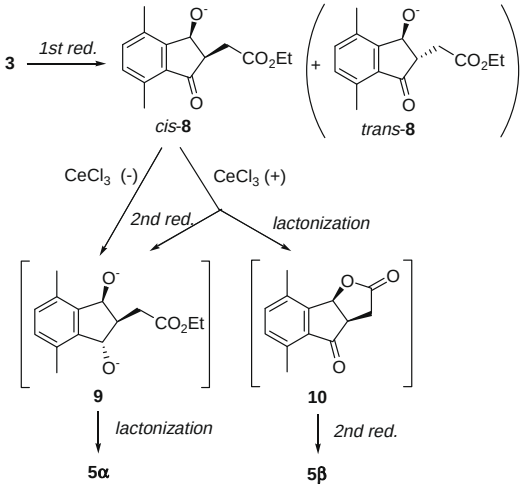


Scheme 1. Synthesis of (±)-**1a** and (±)-**1b**. Reagents and conditions: (a) $BrCH_2CO_2Et$, Cs_2CO_3, $CHCl_3$, room temperature, 4 d; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (17% of **5α** and 26% of **5β** in two steps); (c) $NaBH_4$, MeOH (39% of **5α** in two steps); (d) NaH, HCO_2Et, Et_2O; (e) (±)-4-bromo-2-methylbut-2-en-4-olide, DME (54% in two steps).



Scheme 2. Account for diastereoselectivity in the reduction of **3**.

rate of the second alkylation was not slow enough to allow selective formation of **3**, as compared to that of the first.

As a result, the desired outcome was observed under the following conditions: $BrCH_2CO_2Et$, Cs_2CO_3, $CHCl_3$, room temperature, 4 days. These conditions yielded an inseparable mixture of **3** and **4** (**3**:**4** = *ca.* 4:1, >95% conversion). This mixture was subjected to Luche reduction to yield 17% of **5α** and 26% of **5β** in two steps. The relative stereochemistry of these two diastereomers could be easily clarified by comparing NMR data for **5α**/**β** and **7α**/**β**.[13] This diastereoselectivity was predictable, because a similar preference was reported in the course of orobanchol synthesis (**6**→**7α**/**β**).[13] Along with these two isomers, a complex mixture of unidentified products was obtained. However, we found that $NaBH_4$ reduction of **3** in the absence of $CeCl_3{\cdot}7H_2O$ gave only **5α** (39% in two steps). This dramatic and desirable change in diastereoselectivity is explainable as shown in Scheme 2. The first reduction of **3** gave *cis*-**8** as a major product. If the second reduction proceeded in an intramolecular manner with the assistance of an alkoxide anion, the major product should be **9**, which was then lactonized to give **5α**. In the absence of $CeCl_3$, the above-mentioned pathway was predominant, while in the presence of $CeCl_3$, some part of *cis*-**8** might be lactonized to furnish **10** before the second reduction, because lactonization was accelerated by Lewis acid. Lactone **10** was then diastereoselectively reduced to mainly give **5β** due to the steric effect. Thus, in the presence of $CeCl_3$, a mixture of **5α** and **5β** was obtained. This hypothetical mechanism would account for the change in diastereoselectivity that depends on the presence or absence of $CeCl_3$.

With the advanced intermediate **5α** in hand, we continued our synthesis. The remaining two steps were successfully performed in the conventional manner to give a diastereomeric mixture of **1a** and **1b** in 54% yield. This mixture was then carefully separated by SiO_2 column chromatography (elution with hexane–EtOAc) to give pure (±)-**1a**[14] (less polar) and (±)-**1b**[15] (more polar). Structures of these two diastereomers were tentatively assigned (Scheme 1) based on the similarity in NMR data between (±)-**1a**/**b** and orobanchol/2′-epiorobanchol.[13] We thereby accomplished the synthesis of the structure proposed for solanacol.

Table 1 shows the ^{1}H NMR data for synthetic (±)-**1a/b** and natural solanacol. It is apparent that neither of the synthesized compounds were identical to the natural product. Because the noticeable disagreements were observed in the A-ring portion

Table 1
^{1}H NMR data (in $CDCl_3$) for synthetic (±)-**1a/b** and natural solanacol

Position	(±)-**1a**[a] δ, mult., *J* (Hz)	(±)-**1b**[a] δ, mult., *J* (Hz)	Solanacol[b] δ, mult., *J* (Hz)
3a	3.81, ddd, 7.5, 2.7, 1.5	3.82, ddd, 7.5, 2.7, 1.5	3.81 ddd, 7.3, 3.4, 1.5
4	5.35, s	5.31, s	5.25, s
5-Me	2.38, s	2.36, s	2.37, s
6	7.12, s	7.11, s	7.16 and 7.23, AB quartet,
7	7.12, s	7.11, s	7.8
8-Me	2.42, s	2.41, s	2.30, s
8b	6.16, d, 7.5	6.15, d, 7.5	6.15, d, 7.3
9	7.53, d, 2.7	7.55, d, 2.7	7.55, d, 2.4
2′	6.25, t, 1.5	6.22, t, 1.5	6.22, t, 1.5
3′	7.01, t, 1.5	6.99, t, 1.5	6.99, t, 1.5
4′-Me	2.05, t, 1.5	2.05, t, 1.5	2.05, t, 1.5

[a] Recorded at 300 MHz.
[b] Recorded at 400 MHz.

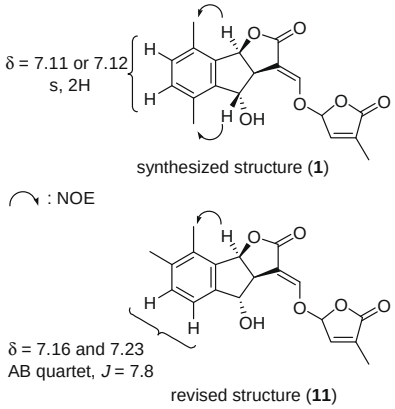


Figure 2. Structural revision of solanacol.

data, the A-ring structure became the next focus of our work. While the peaks due to 6-H and 7-H were observed as an AB quartet in natural solanacol, those of synthetic (±)-**1a/b** were observed as a coincident singlet. However, the correctness of the position of two benzylic methyl groups in synthetic **1** was confirmed by NOE measurements (Fig. 2). Inconsistency between synthetic samples and natural solanacol was also confirmed by GC–MS analyses.[16] We therefore conclude that the structure proposed for solanacol (**1**) is incorrect, and the correct structure of natural solanacol must be **11** as illustrated in Figure 2. This structure does not conflict with all the reported NMR data, and is more reasonable than **1**, taking into consideration the postulated biosynthetic pathway.[17]

In summary, we have accomplished the synthesis of the structure proposed for solanacol [(±)-**1a**/**b**], which enabled us to disprove the previously reported structure (**1**). The correct structure of natural solanacol must be **11**. Thus, for the unambiguous clarification of the structure of solanacol, synthesis of the revised structure (**11**) is now under way in our group.

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14. Properties of (±)-**1a**: white crystalline powder, mp 201–203 °C. ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 10.81, 17.85, 18.09, 29.68, 50.22, 79.21, 84.11, 100.41, 110.35, 131.36, 132.09, 133.13, 134.23, 136.42, 138.10, 140.81, 141.77, 151.42, 170.02, 170.74. HRESIMS *m/z* $[M+Na]^+$: calcd for $C_{19}H_{18}O_6Na$, 365.1001; found, 365.0996.
15. Properties of (±)-**1b**: white crystalline powder, mp 94–96 °C. ^{13}C NMR δ_C ($CDCl_3$, 75 MHz): 10.79, 17.85, 18.07, 29.67, 50.12, 79.09, 84.17, 100.72, 110.29, 131.30, 132.08, 133.22, 134.10, 136.16, 138.01, 140.92, 141.82, 151.89, 170.13, 170.84. HRESIMS *m/z* $[M+Na]^+$: calcd for $C_{19}H_{18}O_6Na$, 365.1001; found, 365.1007.
16. EI-GC–MS [Instrument: JEOL JMS-Q1000GC; column: J&M DB-5, 5 m × 0.25 mm i.d.; carrier gas: He; flow rate 3 ml/min; temperature: 130–270 °C (+10 °C/min)]: t_R = 11.30 min [(±)-**1b**], 11.49 min [(±)-**1a**], 12.07 min (natural solanacol). MS profiles of (±)-**1a/b** were closely similar to that of the natural solanacol and almost indistinguishable from each other.
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