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Stereochemistry, Total Synthesis, and Biological Evaluation of the New Plant Hormone Solanacol

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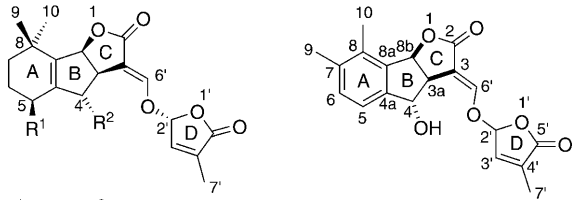
Dedicated to Professor Jean-Yves Lallemand on the occasion of his retirement

Strigolactones—a new group of hormones present in all plants[1]—have been studied in pea, *Arabidopsis*, petunia, and rice. These hormones are formed mainly in the lower parts of the stem and roots and transported to the aerial parts of the plant where they suppress shoot branching[2] and are possibly involved in nodule formation[3] and root growth.[4] The production would be inversely correlated to the concentration of phosphate available for the plants.[5] Strigolactones belong to a class of compounds that was first identified in 1966 as stimulants of the seed germination of the parasitic weeds *Orobanche* and *Striga*[6] and are produced in trace amounts with partial excretion in the rhizosphere. These molecules were recently identified as stimulants for spore germination and hyphal proliferation of arbuscular mycorrhizal fungi (AMF).[7] In the plant–AMF symbioses, plants receive water and mineral nutrients from their fungal partners, hence promoting optimal plant growth conditions. Strigolactones are suggested to have additional biological functions in rhizosphere communications and in development; properties that will certainly be rapidly established. The structural core of strigolactones is a tricyclic lactone (ABC rings) connected through an enol ether linkage to an α,β-unsaturated furanone moiety (D ring) (Scheme 1). Strigolactones are thought to be derived from the carotenoid pathway, as cleavage products of β-carotene.[8] Strigol (**1**) and orobanchol (**2**) are two major strigolactones found in nature. Solanacol (**3**)—the first natural strigolactone containing a phenyl ring—was recently isolated from tobacco and tomato root exudates.[9,10]



Scheme 1. Structures of natural strigolactones.

The great importance of strigolactones in many areas of plant chemical biology and their extremely low bioavailability prompted us to develop a new strategy for the synthesis of this class of compounds and to unambiguously confirm the structure of **3** by means of MS/MS, ^{1}H NMR and circular dichroism (CD) data.[9–11] The covalent structure was recently reported by correcting the positions of the methyl groups on aromatic ring A, but the relative stereochemistry at C2′ on ring D was left unresolved as well as the absolute configuration of the molecule.[11] Herein, we report the first total

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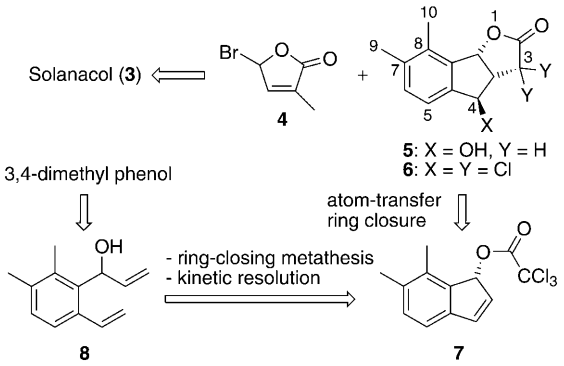
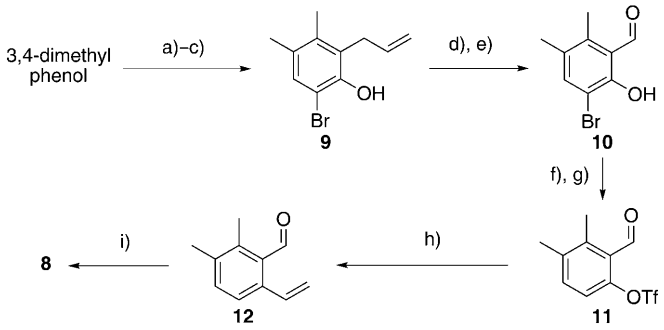
synthesis of **3** and preliminary biological activities. Our retrosynthetic analysis is outlined in Scheme 2.



Scheme 2. Retrosynthetic analysis for **3**.

We envisaged tricyclic lactone **5**, with the correct relative stereochemistry, as a key precursor that would lead to **3** by coupling to the D-ring precursor, bromofuranone **4**,[12] using well-reported procedures.[12d] The C4-hydroxyl group[13] could be derived from trichloride **6** by stereoselective substitution, with retention of configuration at the benzylic position. Compound **6** could be synthesized from the enantiopure ester **7** by an atom-transfer radical cyclization (ATRC),[14] which, in turn, would originate from a ring-closing metathesis (RCM)/kinetic resolution sequence on diene **8**. This precursor would be formed from the cheap and commercially available 3,4-dimethylphenol.

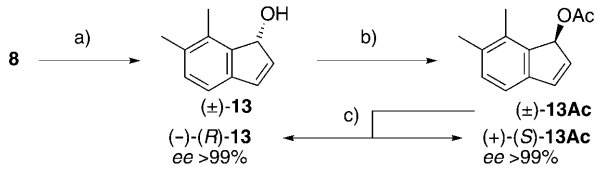
Selective bromination at position 6 of 3,4-dimethylphenol, which serves as a temporary protecting group at this position as well as an attractive solution to deuterium labeling of ring A for future biological studies,[15] was the basis for the sequence to diene **8**. Thus, bromination and alkylation of the phenol with allylbromide and Lewis acid catalyzed Claisen rearrangement were completely regioselective, providing bromide **9** in a 90% overall yield (see Scheme 3). Isomerization of the terminal C=C double bond and ozonolysis



Scheme 3. Formation of the B-ring precursor **8**. Reagents and conditions: a) Br_2, CH_2Cl_2, 0°C, 1 h, 90%; b) allylbromide, K_2CO_3, acetone, reflux, 3 h, quant.; c) cat. Et_2AlCl, hexane, RT, 6 h, quant.; d) *t*BuOK, THF, RT, 48 h, 90%; e) 1) O_3, CH_2Cl_2, −78°C; 2) Me_2S, −78°C to RT, 12 h, 79%; f) Pd/C, H_2, NEt_3, MeOH, RT, 2 h, quant.; g) pyridine (pyr), Tf_2O, CH_2Cl_2, 0°C to RT, 1 h, 74%; h) CH_2=$CHBF_3K$, $PdCl_2$, Cs_2CO_3, PPh_3, THF/H_2O (9/1), 85°C, 12 h, 98%; i) CH_2=CHMgBr, THF, RT, 3 h, 91%.

of **9** gave aldehyde **10**, which was easily debrominated by catalytic hydrogenolysis using hydrogen and Pd/C in the presence of an excess of triethylamine. Triflation under standard conditions gave triflate **11**, which was cross-coupled with vinyltrifluoroborate[17] under Suzuki–Miyaura conditions to give aldehyde **12**, which was easily alkylated with a vinylic Grignard reagent to give diene **8** in an 89% overall yield.

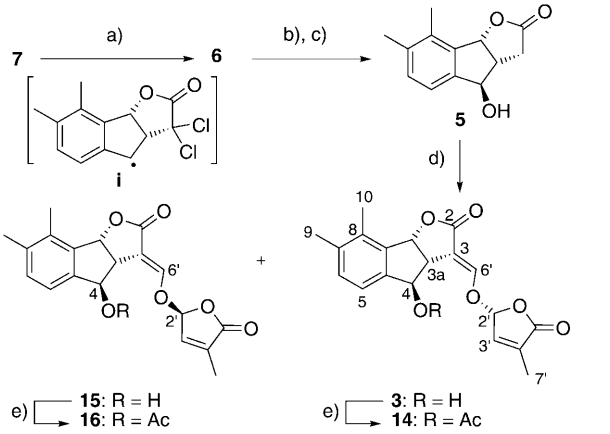
Elaboration of the B ring was performed by using a ruthenium-catalyzed RCM reaction of diene **8** to give the racemic indenol (±)-**13**, which was acetylated to ester (±)-**13Ac** (Scheme 4). Kinetic resolution of ester (±)-**13Ac** with immobilized *Candida antarctica* lipase[18] was remarkably efficient in producing the enantiomerically pure alcohol (*R*)-**13** (>99% enantiomeric excess (*ee*)), as well as the enantiomeric ester (*S*)-**13Ac** (>99% *ee*).[18,19]



Scheme 4. Elaboration of B ring and enzymatic kinetic resolution of (±)-**13**. Reagents and conditions: a) Grubbs I catalyst (5 mol%), CH_2Cl_2, RT, 12 h; b) Ac_2O, pyr, THF, 0°C, 15 min, 81% for two steps; c) immobilized *Candida antarctica* lipase, CH_3CN, H_2O, 24 h, (*R*)-**13** 50%, (*S*)-**13Ac** 50%.

At this stage, the synthesis was pursued with (±)-**7**, as well as the enantiopure compounds, obtained by trichloroacetylation of **13** ($(Cl_3CCO)_2O$, pyr, THF, 0°C, 15 min, 98%). Stereoselective lactonization to the ABC tricyclic system **6** was obtained in 83% yield, through an ATRC catalyzed by copper(I) coordinated to 4,4′-di-*n*-heptylbipyridine (dHbipy; Scheme 5).[20,21] Sterically controlled halogen transfer to benzylic radical **i** from the Cu^{II} complex generated in the catalytic process proceeded stereoselectively *anti* to ring C. The stereochemistry was unambiguously established by X-ray analysis of trichloride **6** (see the Supporting Information). Subsequent substitution with retention of configuration of the benzylic chlorine atom in **6** by a hydroxyl group was achieved with good stereocontrol (9:1 *anti*/*syn* to ring C) under S_N1 conditions, by heating a solution of **6** in water/hexafluoroisopropanol.[22] Dechlorination of the *gem*-dichloro motif with zinc dust afforded tricyclic lactone **5** in a 91% overall yield from **6**. Careful formylation of **5**, followed by coupling in the same pot with D-ring precursor **4** by controlling the temperature, completed the synthesis to provide compound **3**, identified as (−)-solanacol (see below) and (−)-2′-epi-solanacol (**15**) in a 76% combined yield. The two compounds were separated by chromatography on silica gel.

The stereochemistry at C2′ relative to the other asymmetric centers was unambiguously assessed by X-ray analysis of compounds **3** (Figure 1) and **15**, showing an *R* configuration at C2′ in **3** and an *S* configuration at this center in **15**. Furthermore, comparison of the ^{1}H NMR spectra of **3** and **15**



Scheme 5. Final steps in the synthesis of (−)-solanacol **3** and (−)-2′-epi-solanacol **15**. Reagents and conditions: a) ATRC, CuCl (5 mol%), dHbipy (5 mol%), $ClCH_2CH_2Cl$, 90°C, 6 h, 83%; b) H_2O, hexafluoroisopropanol (HFIP), 90°C, 30 min; c) Zn dust, NH_4Cl, MeOH, 0°C to reflux, 2 h, 91% for two steps; d) 1) *t*BuOK, ethyl formate, THF, −78 to −40°C, 6 h; 2) **4**, −60°C to RT, 12 h, **3** 38%; **15** 38%; e) Ac_2O, pyr, RT, 12 h, 92%.

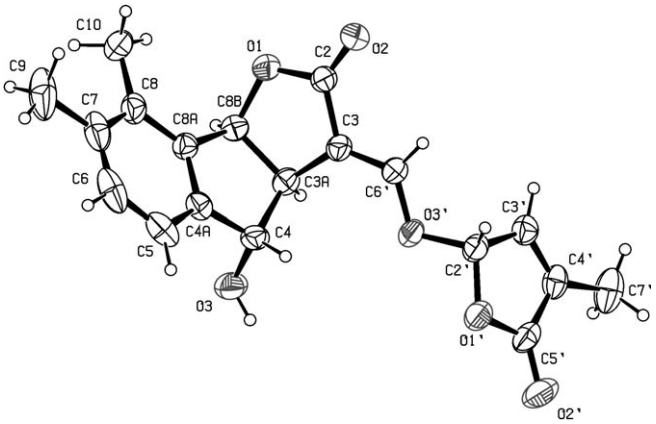


Figure 1. X-ray structure of solanacol (±)-**3**.

with that of a natural sample of **3**[9,10b] clearly showed that the natural product corresponded to the more polar, synthetic diastereomer **3** with diagnostic chemical shifts for H2′, H4, and H6′ (see the Supporting Information). Comparison of the CD spectrum of (−)-**3** with that of the natural product[9] conclusively defined the stereostructure of solanacol as (−)-**3**.[23] This first total synthesis of solanacol **3** and **15** involved 15 linear steps with a 21% overall yield.

The bud-outgrowth inhibition exerted by **3**, **15**, and acetate derivatives **14** and **16** was evaluated in pea plants and compared to the active synthetic strigolactone analogue (±)-GR24.[2a] The solution to be tested (10 μL per plant) was applied directly onto the axillary bud at node four of ten-day-old *rms1/ccd8* plants,[2a] (see the Supporting Information). The results are summarized in Figure 2.

At a concentration of 1 μM, a significant [ANOVA test with $P<0.05$ and $n=24$ (P=probability for the F test, n=

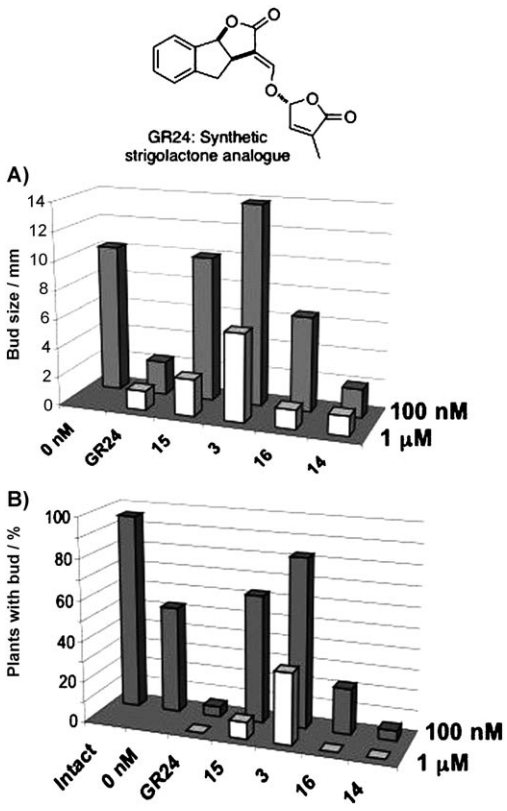


Figure 2. Bud-outgrowth inhibition of the solanacol series. A) Size of bud 10 days after treatment [mm]; B) % of plants with a bud >5 mm.

number of plants per treatment)] repression in bud outgrowth was observed for the four new compounds and GR24.[2a] Compound **3** was the least active compound in comparison with 2′-epimer **15**, acetates **14** and **16**, and GR24. At a concentration of 100 nM, a significant effect (ANOVA test with $P<0.05$ and $n=24$) was only observed for GR24 and acetate **14**. Generally, acetates **14** and **16** were more active than their corresponding alcohols **3** and **15**, with dose-dependent activity similar to that of GR24 for compound **14**. This may be attributed to instability in an aqueous solution or lower lipophilicity of **3** than the corresponding acetate **14** (see the Supporting Information), making it difficult for **3** to reach its receptor. The higher activity of **14** was confirmed by a higher expression than **3** in the axillary bud at node 4 of the transcription factor *PsBRC1*— the homologue from pea of the *Arabidopsis BRANCHED1* (*BRC1)* and the *TEOSINTE BRANCHED1 (TB1)* from maize—6 h after application of **14** (or GR24).[24] Interestingly, and in sharp contrast, the acetylation of **1** or **2** resulted in significant reduction of both the germination-stimulating activity of the parasitic weeds and the hyphal branching activity of the AMF.[25,26]

In summary, we have exploited an efficient RCM/enzymatic kinetic resolution/ATRC sequence of key transformations to construct the key ABC ring system in the first synthesis of the aromatic strigolactone **3**. This firmly established the complete structure. The aromatic chemistry developed

will also be useful for isotope labeling in future work in an effort to search for and localize the strigolactone binding proteins and quantify natural strigolactones. This approach can also be applied to other natural strigolactones and analogues. We have further demonstrated that **14** showed the best hormonal activity in inhibiting bud outgrowth in the pea model. More detailed structure–activity studies are being developed in our laboratories.

Experimental Section

Detailed experimental procedures are provided in the Supporting Information.

Preparation of 6: Commercial CuCl (5.0 mg, 0.05 mmol, 0.05 equiv) and dHbipy[27] (19.0 mg, 0.05 mmol, 0.05 equiv) were dissolved in degassed dichloroethane (2 mL) and stirred at room temperature under argon. The solution turned dark brown after 10 min and a solution of trichloroester **7** (328.0 mg, 1.07 mmol, 1 equiv) in degassed dichloroethane (4 mL) was added. The mixture was heated at 90 °C for 6 h, cooled to RT, and the solvent was evaporated under reduced pressure. The crude product was directly separated by column chromatography (heptane/ethyl acetate 95:5). Product **6** was obtained as a white solid (271 mg, 0.89 mmol, 83 %). Mp: 135–137 °C; $[\alpha]_D^{26} = -130.5$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J_{6,5} = 7.9$ Hz, 1H; H6), 7.20 (d, $J_{5,6} = 7.9$ Hz, 1H; H5), 6.03 (d, $J_{8b,3a} = 5.8$ Hz, 1H; H8b), 5.40 (d, $J_{4,3a} = 5.8$ Hz, 1H; H4), 3.98 (t, $J_{3a,4} = 5.8$, $J_{3a,8b} = 5.8$ Hz, 1H; H3a), 2.34 (s, 3H; H10), 2.31 ppm (s, 3H; H9); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.1$ (C2), 140.3 (C4a), 139.1 (C7), 135.2 (C8), 133.9 (C8a), 133.8 (C6), 122.7 (C5), 82.3 (C8b), 78.9 (C3), 66.0 (C3a), 60.6 (C4), 19.6 (C9), 15.4 ppm (C10); IR (film): $\tilde{\nu} = 1794$, 1481, 1161, 955, 825 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{11}Cl_3O$: C 51.10, H 3.63, O 10.47; found: C 51.05, H 3.56, O 10.32.

Preparation of 3 and 15: Potassium *tert*-butoxide (67.9 mg, 0.61 mmol, 2.2 equiv) was added to a mixture of lactone **5** (60.0 mg, 0.28 mmol, 1 equiv) and ethyl formate (0.23 mL, 2.80 mmol, 10 equiv) in THF (1 mL) at −78 °C under argon. It was then warmed to −40 °C and stirred for 6 h at this temperature. The mixture was cooled to −60 °C and (±)-4-bromo-2-methyl-2-buten-4-olide (99.8 mg, 0.56 mmol, 2.05 equiv) was gradually added. The mixture was warmed to room temperature. The reaction was quenched with AcOH (1 mL) after 12 h at this temperature. The solvent was evaporated and the crude product was purified by preparative TLC (heptane/ethyl acetate 50:50) to afford the two diastereomers as two pure fractions (fraction 1 = **15**: 36.0 mg, 0.11 mmol, 38 %; fraction 2 = **3**: 36.0 mg, 0.11 mmol, 38 %).

*Compound **15***: Colorless oil; $[\alpha]_D^{26} = -176.4$ ($c = 1.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (d, $J_{6',3a} = 2.6$ Hz, 1H; H6′), 7.25 (d, $J_{6,5} = 7.7$ Hz, 1H; H6), 7.17 (d, $J_{5,6} = 7.7$ Hz, 1H; H5), 7.00 (t, $J_{3',2'} = 1.5$, $J_{3',7'} = 1.5$ Hz, 1H; H3′), 6.24 (t, $J_{2',3'} = 1.5$, $J_{2',7'} = 1.5$ Hz, 1H; H2′), 6.15 (d, $J_{8b,3a} = 7.5$ Hz, 1H; H8b), 5.27 (d, $J_{4,3a} = 5.8$ Hz, 1H; H4), 3.81 (ddd, $J_{3a,8b} = 7.5$, $J_{3a,4} = 5.8$ Hz, $J_{3a,6'} = 2.6$ Hz, 1H; H3a), 2.37 (s, 3H; H10), 2.31 (s, 3H; H9), 2.08 (d, 1H; OH), 2.05 ppm (t, $J_{7',2'} = 1.5$, $J_{7',3'} = 1.5$ Hz, 3H; H7′); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.0$ (C2), 170.2 (C5′), 151.5 (C6′), 141.9 (C4a or C8), 141.0 (C3′), 139.0 (C7 or C8a), 138.4 (C7 or C8a), 136.6 (C4′), 135.7 (C4), 132.9 (C6), 122.5 (C5), 110.9 (C3), 100.7 (C2′), 84.2 (C8b), 80.3 (C4), 50.8 (C3a), 19.8 (C9), 15.8 (C10), 11.1 ppm (C7′); IR (film): $\tilde{\nu} = 3437$, 1780, 1740,1677, 1334, 1186, 1092, 1016, 957 cm^{-1}; MS: *m/z* (%): 365 $[M+Na]^+$ (100), 343 $[M+H]^+$ (75); HRMS (ESI): *m/z*: calcd for $C_{19}H_{18}NaO_6$ $[M+Na^+]$: 365.1001; found: 365.1010.

*Compound **3***: Colorless oil; $[\alpha]_D^{26} = -164.2$ ($c = 2.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J_{6',3a} = 2.6$ Hz, 1H; H6′), 7.23 (d, $J_{6,5} = 7.7$ Hz, 1H; H6), 7.16 (d, $J_{5,6} = 7.7$ Hz, 1H; H5), 6.99 (t, $J_{3',2'} = 1.5$, $J_{3',7'} = 1.5$ Hz, 1H; H3′), 6.22 (t, $J_{2',3'} = 1.5$, $J_{2',7'} = 1.5$ Hz, 1H; H2′), 6.15 (d, $J_{8b,3a} = 7.5$ Hz, 1H; H8b), 5.25 (d, $J_{4,3a} = 5.8$ Hz, 1H; H4), 3.81 (ddd, $J_{3a,8b} = 7.5$, $J_{3a,4} = 5.8$ Hz, $J_{3a,6'} = 2.6$ Hz, 1H; H3a), 2.37 (s, 3H; H10), 2.30 (s, 3H; H9), 2.06 (d, 1H; OH), 2.05 ppm (t, $J_{7,2'} = 1.5$ Hz, $J_{7,3'} = 1.5$ Hz, 3H; H7′); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.0$ (C2), 170.3 (C5′), 151.8 (C6′), 141.9 (C4a or C8), 141.1 (C3′), 138.9 (C7 or C8a), 138.3 (C7 or C8a), 136.4 (C4′), 135.6 (C4), 132.9 (C6), 122.6 (C5), 110.8 (C3), 100.9 (C2′), 84.3 (C8b), 80.2 (C4), 50.6 (C3a), 19.8 (C9), 15.8 (C10), 11.0 ppm (C7′). IR (film): $\tilde{\nu} = 3333$, 1781, 1737,1675, 1329, 1183, 953 cm^{-1}; MS: *m/z* (%): 365 $[M+Na]^+$ (100), 343 $[M+H]^+$ (75); HRMS (ESI): *m/z*: calcd for $C_{19}H_{18}NaO_6$: 365.1001 $[M+Na^+]$; ; found: 365.1015.

CCDC-784236 and 784237 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: hormones · kinetic resolution · radical reactions · strigolactones

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