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Total Synthesis of (±)-5-Deoxystrigol via Reductive Carbon−Carbon Bond Formation

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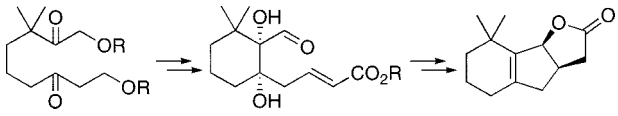
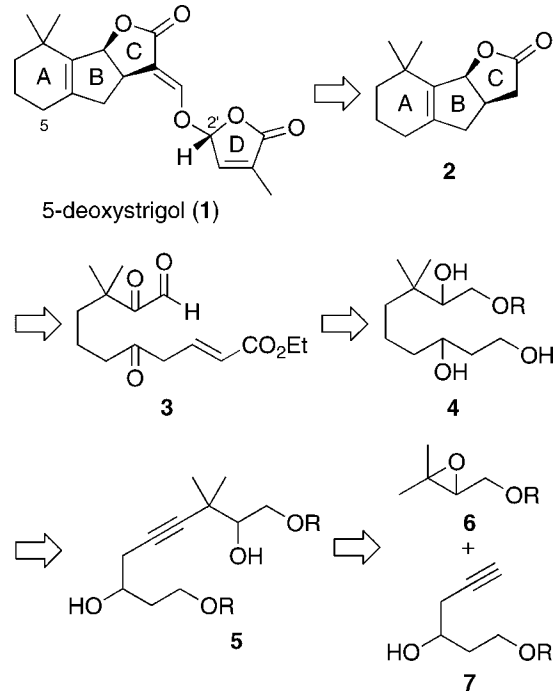


The total synthesis of 5-deoxystrigol was successfully carried out via the regioselective coupling reaction between the aluminum ate complex of an alkyne and an epoxide and the two reductive carbon−carbon bond formations in the presence of transition metals as key steps.

Although it is well-known that more than 80% of terrestrial plants utilize symbiotic associations with fungi[1] in which plants provide glucose to fungi and in return fungi provide phosphates to plants, the concise mechanisms of such mutualism has yet to be defined. In 2005, Akiyama and co-workers reported that the roots of *Lotus japonicus* secrete 5-deoxystrigol (**1**), a signaling molecule that induces hyphal branching in arbuscular mycorrhizal fungi.[2] Moreover, **1** was also very recently reported as a new phytohormone inhibiting shoot branching.[3] Thus, the biological significance of **1** dramatically increases in many fields such as chemical ecology, chemical biology, and plant biology. To date, seven naturally occurring strigolactones including **1** have been isolated.[4] Unfortunately, because of its low prevalence in plant materials and the instability of the molecule, very limited amounts of **1** are available from nature. Thus, the synthetic supply of **1** and preparation of its derivatives that could act as molecular probes are strongly desired for further biological research.

SCHEME 1



The synthesis of **1** has been carried out by Welzel and co-workers (as a synthetic derivative of strigol)[5] and by Akiyama and co-workers to confirm the structure of the natural product.[2] In most cases of the synthesis of strigolactones,[5,6] the preparations of the tricyclic strigolactone framework involved stepwise construction. In contrast, we envisioned a one-step polycyclization strategy that was inspired by terpene biosynthesis.[7] As shown in Scheme 1, the retrosynthetic analysis of **1** is described as follows: (i) the side chain of **1** can be introduced into lactone **2** following reported procedures,[5,6] (ii) the tricyclic skeleton of **2** can be formed in one step via transition metal-mediated reductive carbon−carbon bond formation from acyclic compound **3**, (iii) diketoaldehyde **3**, which possesses every requisite

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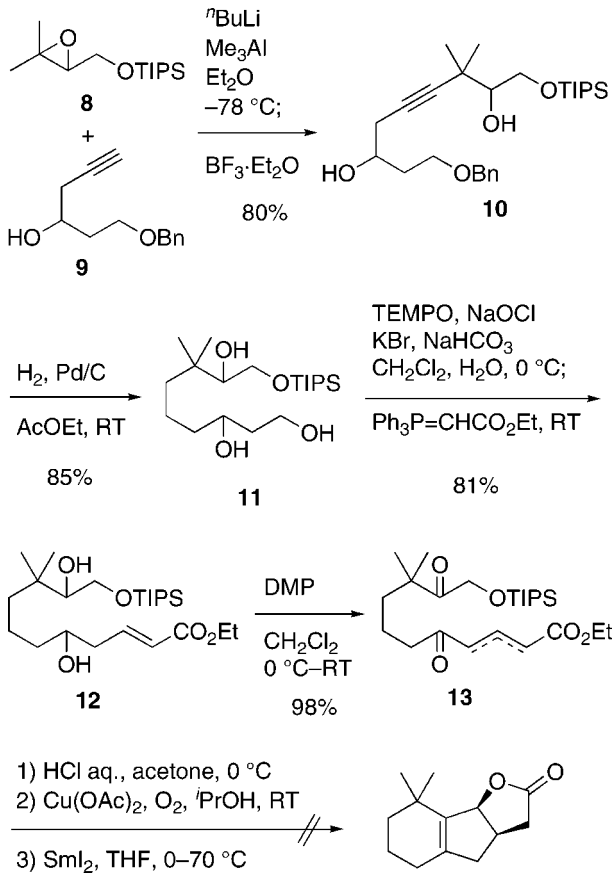
SCHEME 2



functional group, can be afforded via regioselective oxidation and the Wittig reaction of **4**, and (iv) triol **4** can be furnished via regioselective carbon−carbon bond formation of epoxide **6** and alkyne **7**, followed by reduction of the resulting alkyne **5**.

As shown in Scheme 2, a coupling component, epoxide **8**, was prepared from prenyl alcohol via TIPS protection and epoxidation. The other coupling component, alcohol **9**, was prepared from 1,3-propanediol via monobenzylation, SO_3−pyridine oxidation,[8] and propargylation. Regioselective carbon−carbon bond formation was accomplished via the coupling reaction between the epoxide **8** and the aluminum ate complex of alkyne **9** to give **10**.[9] Diol **10** was reacted as a mixture of two diastereomers because the latter oxidation provided diketone without stereocenters (vide infra). For this coupling reaction, the hydroxy group of **9** was not protected because, otherwise, elimination would proceed to give the enyne derivative of **9**.

Next, triol **11** was afforded via hydrogenation of the triple bond and cleavage of the benzyl ether of **10**. Regioselective TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) oxidation[10] of the primary hydroxy group of **11** followed by a Wittig reaction provided diol **12**, which possesses the carbon skeleton of the tricyclic core of **1**. Because the direct oxidation of the desilylated triol derived from **12** was deemed too difficult, diol **12** was oxidized using Dess−Martin periodinane[11] to the corresponding diketone, which was obtained as a 1:1 equilibrium mixture of α,β- and β,γ-unsaturated esters **13** (as determined by ^{1}H NMR). Attempts to prepare the desired diketoaldehyde **3**, that is, removal of the TIPS group of **13** followed by $Cu(OAc)_2/O_2$ oxidation,[12] were hard to attain because of its instability. Disappointingly, immediate treatment of the crude product after the oxidation with an excess amount of samarium(II) iodide did not give the desired tricyclic compound **2**. Because the low reactivity of the cyclization can be attributed to the flexibility of the acyclic chain structure of the diketoaldehyde, we switched to the alternative strategy of first constructing the A ring of **1** to fix the conformation before constructing the B and C rings.

As shown in Scheme 3, oxidation of diol **10** followed by hydrogenation gave diketone **14**. Since the pinacol coupling reaction[13,14] of hydroxy-free diketone **14** and corresponding benzyl or *p*-methoxybenzyl ether resulted in low yield, the primary alcohol was protected as pivalate to provide **15**. The intramolecular pinacol coupling reaction under the conditions of Mukaiyama et al.[14c] furnished the desired cyclohexanediol **16** in good yield. Removal of the pivaloyl group of **16** followed by TEMPO oxidation and subsequent Horner−Wadsworth−Emmons olefination afforded (*E*)-α,β-unsaturated ester **17**, selectively.

Removal of the TIPS group of **17** followed by TEMPO oxidation of the resulting alcohol **18** produced cyclization precursor aldehyde **19**. The reductive carbon−carbon bond formation of aldehyde **19** was carried out in the presence of samarium(II) iodide[15] and subsequent acidic workup to furnish *trans*-fused bicyclic ester **20** and *cis*-fused tricyclic lactone **21** in good yield. For both **20** and **21**, the stereochemistry of the newly formed secondary hydroxy group was *syn* to the adjacent tertiary hydroxy group (NOE correlations are illustrated in Schemes 3 and 4), which can be attributed to the chelation of the samarium(III) cation to the neighboring hydroxy group.[16]

As shown in Scheme 4, inversion of the stereochemistry of the secondary hydroxy group of *trans*-isomer **20** was accomplished via an oxidation−reduction sequence to provide tricyclic lactone **23**. Although oxidation of **20** did not proceed using TEMPO/NaClO, the use of a catalytic amount of AZADO (2-azaadamantane-*N*-oxyl)[17] proved to be effective for the oxidation to afford ketone **22**. Diastereoselective reduction of **22** with $NaBH_4$ followed by acidic workup furnished lactone **23**.

The remaining transformation involves the reductive olefination of 1,2-diol **23**. After some experimentation, diol **23** was successfully converted to the desired alkene **2** via treatment with trimethyl orthoformate and benzoic acid followed by heating of the resulting cyclic ortho esters to afford tetra-substituted

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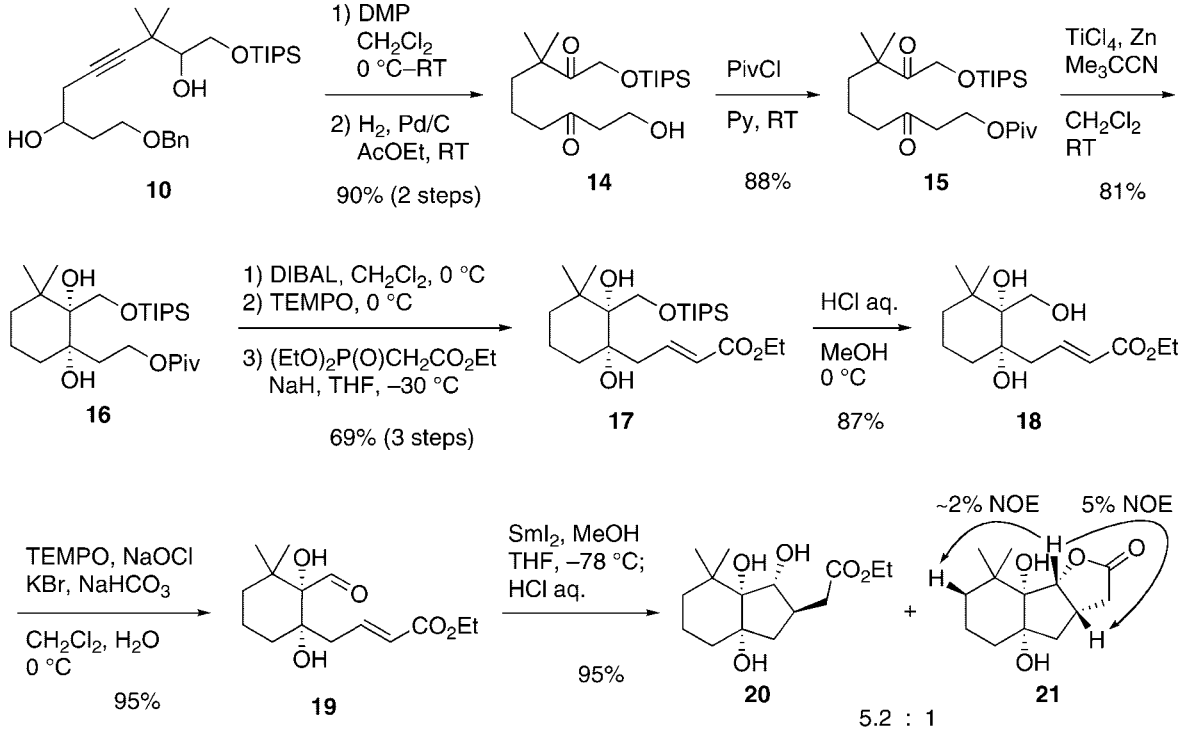
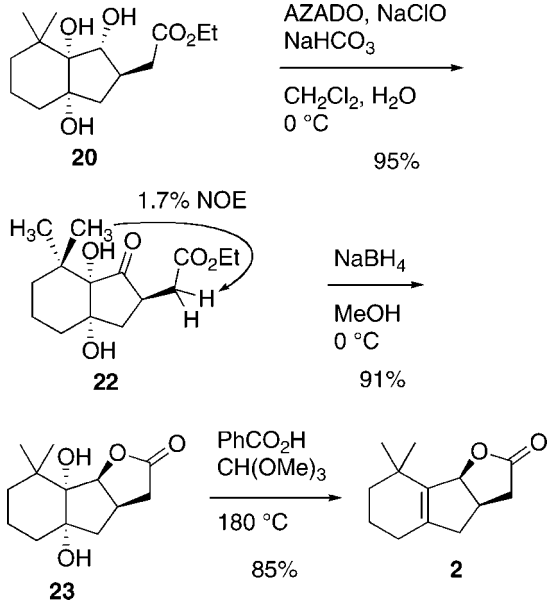
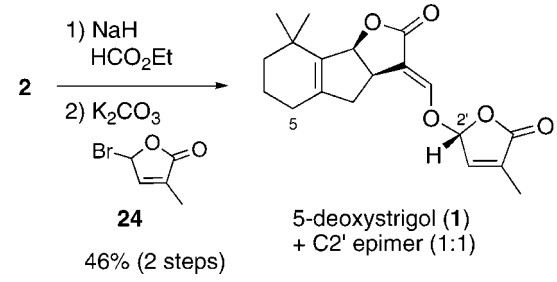
SCHEME 3



SCHEME 4



SCHEME 5



alkene **2** in a good yield.[18,19] In contrast, transformation of **23** to the corresponding 4-trifluoromethyl benzoate and cyclic sulfate[20] followed by reduction with samarium(II) iodide[21] resulted in complex mixture of products.

Finally, conventional introduction of the side chain was performed as shown in Scheme 5. Formylation of lactone **2** followed by a coupling reaction with γ-butenolide **24** in the presence of potassium carbonate afforded a 1:1 mixture of **1** and its C2′-epimer,[6a] and this mixture can be easily separated using preparative TLC. [22] All spectra of synthetic **1** including ^{1}H and ^{13}C NMR, IR, and HRMS were identical to the reported data.[2,5]

In summary, the total synthesis of 5-deoxystrigol (**1**) was successfully carried out. An acyclic precursor that possessed every requisite functional group of the tricyclic core of **1** was prepared via the regioselective coupling reaction of epoxide **8** and the aluminum ate complex of alkyne **9**. The key steps for the synthesis of **1** were (1) the transition metal-mediated reductive carbon−carbon bond formation of six- and five-membered rings and (2) the introduction of tetra-substituted carbon−carbon double bond at the ring junction via an ortho ester.

Experimental Section

Pinacol Coupling Reaction of Diketone 15 to Pinacol 16. To the solution of zinc (1.20 g, 18.4 mmol), $TiCl_4$ (1.00 mL, 9.12 mmol), and trimethylacetonitrile (3.00 mL, 27.1 mmol) in CH_2Cl_2

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(19) Olefination of diol **21** under the same reaction condition also provided **2**.
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(22) Separation condition: AcOEt/hexane = 1/1. The R_f value is 0.50 for **1** and 0.45 for its C2′-epimer.

(40 mL) was added the solution of diketone **15** (424 mg, 0.929 mmol) in CH_2Cl_2 (6 mL) dropwise at room temperature under argon atmosphere, and the mixture was stirred for 15 min. The reaction mixture was quenched with 0.1 M HCl(aq), and the organic materials were extracted with AcOEt. The organic phase was washed with sat. $NaHCO_3$(aq) and brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 0/1−1/20) to afford **16** (343 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.04 (3H, s), 1.05−1.16 (23H, m), 1.19 (9H, s), 1.36−1.56 (2H, m), 1.60−1.68 (2H, m), 1.76 (1H, td, J = 13.2, 4.0 Hz), 1.86 (1H, dt, J = 14.0, 6.8 Hz), 2.23 (1H, dt, J = 14.0, 7.6 Hz), 3.70 (1H, s), 3.91 (1H, s), 3.91 (1H, d, J = 10.4 Hz), 4.09 (1H, d, J = 10.4 Hz), 4.24−4.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 17.7, 17.86, 17.91, 19.0, 24.8, 27.1, 27.3, 31.8, 34.5, 37.0, 37.5, 61.2, 65.6, 76.7 (2C), 178.5; FT-IR (neat) ν 3452, 2944, 2868, 1729, 1463, 1159, 1061, 882, 685 cm^{-1}. HRMS (DART-TOF) $[M + H]^+$ calcd for $C_{25}H_{51}O_5Si$, 459.3506; found, 459.3512.

Samarium(II) Iodide-Mediated Cyclization of Aldehyde 19 to Triol 20 and Lactone 21. A solution of aldehyde **19** (19.7 mg, 0.0694 mmol), MeOH (8 μL, 0.2 mmol), and HMPA (72 μL, 0.41 mmol) in THF (2 mL) was degassed by freeze and thaw cycles. To the mixture was added SmI_2 solution (0.1 M in THF, 2.1 mL, 0.21 mmol) dropwise at −80 °C under argon atmosphere. After 2 h, the reaction mixture was quenched with 1 M HCl(aq) and stirred for 1 h at room temperature. The organic materials were extracted with AcOEt. The organic phase was washed with sat. $NaHCO_3$(aq) and brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt/hexane = 1/10−1/1) to afford triol **20** (15.7 mg, 79%) as a colorless solid and lactone **21** (2.7 mg, 16%) as a colorless solid. **20**: R_f value 0.47 (AcOEt/hexane = 1/1); mp 119.5−120.0 °C (recryst. from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.12 (3H, s), 1.20−1.46 (5H, m), 1.28 (3H, t, J = 7.2 Hz), 1.72−1.84 (2H, m), 2.24−2.39 (2H, m), 2.47−2.62 (3H, m), 3.21 (1H, s), 3.66 (1H, d, J = 2.8 Hz), 3.96 (1H, dd, J = 5.6, 2.8 Hz), 4.16 (2H, q, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.0, 22.8, 27.3, 36.8, 37.6, 38.1, 38.8, 40.2, 44.9, 61.0, 78.3, 79.1, 81.7, 174.5; FT-IR (neat) ν 3483, 2934, 2871, 1719, 1459, 1377, 1299, 1184, 1097, 1031 cm^{-1}. HRMS (DART-TOF) $[M + H]^+$ calcd for $C_{15}H_{27}O_5$, 287.1859; found, 287.1870. **21**: R_f value 0.30 (AcOEt/hexane = 1/1); mp 166.0−166.7 °C (recryst. from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, s), 1.13 (3H, s), 1.20−1.52 (4H, m), 1.76−1.90 (3H, m), 2.10 (1H, dd J = 12.4, 9.2 Hz), 2.31 (1H, s), 2.35 (1H, d, J = 12.4 Hz), 2.51 (1H, d, J = 2.0 Hz), 2.70−2.84 (2H, m), 4.95 (1H, d, J = 8.4 Hz), 4.09 (1H, d, J = 10.4 Hz), 4.24−4.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 22.0, 26.5, 31.3, 35.1, 35.9, 36.4, 37.8, 47.4, 79.6, 80.8, 83.7, 178.2; FT-IR (neat) ν 3471, 2937, 2871, 1767, 1454, 1369, 1316, 1192, 1048, 1013, 948, 864 cm^{-1}. HRMS (DART-TOF) $[M + H]^+$ calcd for $C_{13}H_{21}O_4$, 241.1440; found, 241.1451.

Supporting Information Available: Detailed experimental procedures for the transformations described herein and the spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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