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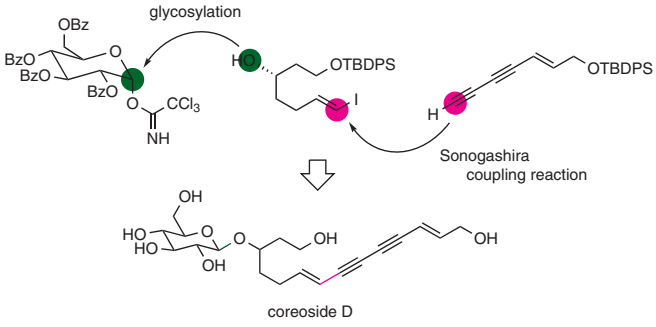
Stereoselective Synthesis of Coreoside D and Determination of Its Absolute Configuration

Narihito Ogawa*
Ryoya Imaizumi

Department of Applied Chemistry, Meiji University, 1-1-1, Higashimita, Tama-ku, Kawasaki, Kanagawa 214-8571, Japan
narihito@meiji.ac.jp



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Abstract We report the stereoselective synthesis of (3*S*)- and (3*R*)-coreoside D. The conjugated diyne in the C1–C14 moiety was synthesized through two types of palladium-catalyzed cross-coupling reaction. The introduction of the glucopyranose was achieved by a glycosylation reaction using an imidate derivative in the presence of a Lewis acid. The asymmetric center at the C3-position was constructed by the chiral-pool method using D-malic acid. The stereochemistry at the C3-position of the natural product was determined to be *R* by comparing the $[\alpha]_D$ values of the synthetic stereoisomers with that reported for the natural product.

Key words asymmetric synthesis, coreoside D, polyacetylene glycoside, palladium catalysis, coupling reaction, glycosylation

Plains coreopsis (*Coreopsis tinctoria*) is an annual plant of the asteraceae family, and contains such chemical components as polyacetylene glycosides, flavonoids, and phenolic compounds.[1] In China, it is consumed as 'snow tea' or 'snow chrysanthemum' as a medicinal drink for treating hypertension and hyperlipidemia.[1a] In addition, it has been reported that a polyacetylene glycoside component of *C. tinctoria*, exhibits various physiological activities, such as antiallergic, antiinflammatory, and anti-HIV activities.[1e,2] Consequently, polyacetylene glycosides are attracting attention as pharmaceuticals and health foods. However, although there have been many reports on the biological activity of *C. tinctoria*, the absolute stereostructure of its bioactive compounds remained unclear.

In 2013, Zhang et al. isolated coreosides A–D (**1**–**4**, respectively) from the capitula of plains coreopsis (Figure 1).[1a] Coreosides E (**5**) and F (**6**) were subsequently isolated from the plains coreopsis by Guo et al. in 2017.[1b] These coreosides are polyacetylene glycosides that combine an aglycone containing a diyne skeleton with glucopyranose. The coreosides have been reported to exhibit potent cyclooxygenase-2 (COX-2) inhibitory activity. Zhang et al. reported that only trace amounts of these compounds can be obtained from their natural sources, and that the stereochemistry of the C3-position was yet to be determined. Here, we report the first stereoselective syntheses of (3*S*)- and (3*R*)-coreoside D in an attempt to determine the absolute conformations of natural coreosides.

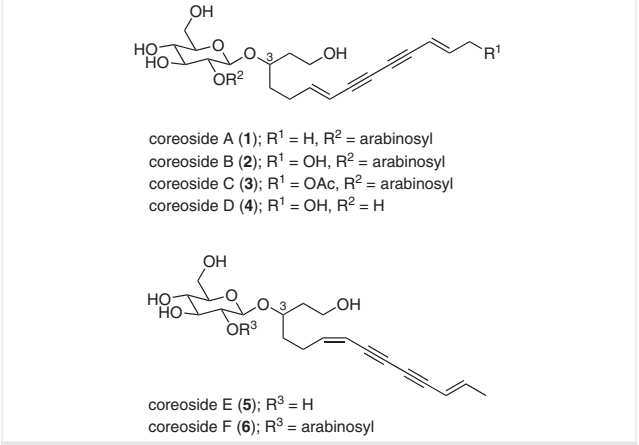

Figure 1 The structures of coreosides A–F

Scheme 1 outlines our proposed synthesis of (3*S*)-coreoside D (**4a**). We surmised that (3*S*)-coreoside D (**4a**) might be obtainable by glycosylation by imidate **7** of the C1–C14 aglycone **8**, synthesized by a Sonogashira coupling reaction between iodoolefin **9** and acetylene **10**. Iodoolefin **9**, in turn, might be synthesized from D-malic acid by a Takai reaction to give the *trans*-iodoalkene moiety. On the other hand, diyne **10** might be prepared from propargyl alcohol by two types of palladium-catalyzed coupling reaction.

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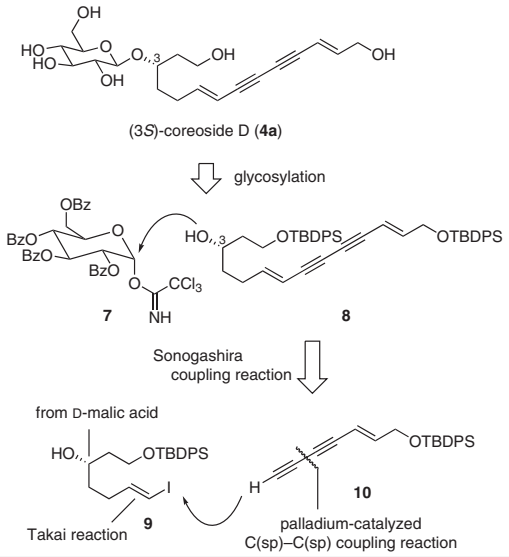
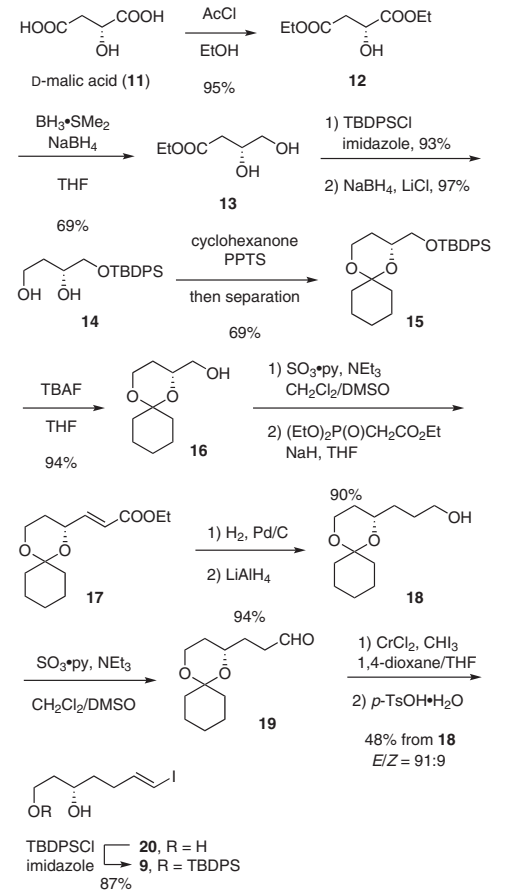


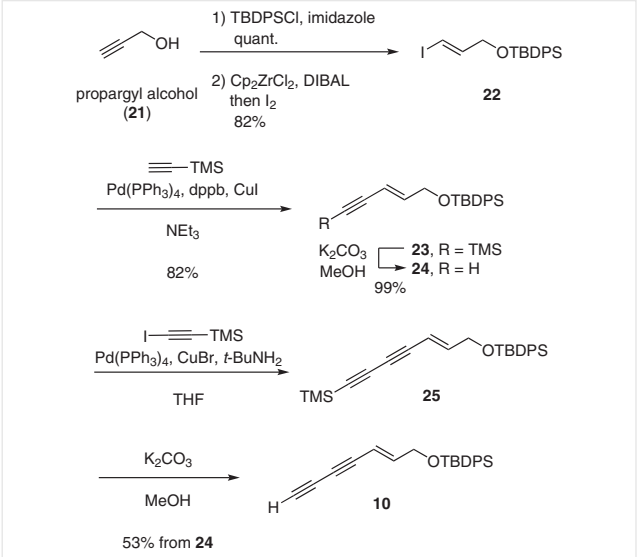
Scheme 1 Proposed synthesis of (3*S*)-coreoside D (**4a**)



Scheme 2 Synthesis of iodoolefin **9**

Diethyl ester **12** was prepared from D-malic acid (**11**) by esterification with AcCl/EtOH (Scheme 2). Reduction of **12** with $BH_3{\cdot}SMe_2/NaBH_4$ gave diol **13** as the major product in a 93:7 mixture, as observed by ^1H NMR spectroscopy; the minor product was formed by reduction of the other ester moiety (the structure of the minor product is not shown).[3] After protection of alcohol **13** using TBDPSCl, reduction of the ester group afforded **14**.[4] Diol **14** was protected by treatment with cyclohexanone in the presence of PPTS to give acetal **15**. At this stage, the desired acetal **15** was cleanly isolated as the sole isomer by silica gel column chromatography. Subsequently, deprotection of acetal **15** with TBAF afforded alcohol **16** in a good yield. Parikh–Doering oxidation of **16** followed by a Horner–Wadsworth–Emmons reaction gave the α,β-unsaturated ester **17** in 90% yield. Ester **17** was converted into alcohol **18** upon reduction of the C=C double bond and ester moiety. Parikh–Doering oxidation of **18** gave aldehyde **19**, which was subjected to a Takai reaction in 1,4-dioxane–THF by a modified version of the reported procedure.[5] The resulting iodoolefin was treated with $TsOH{\cdot}H_2O$ to afford diol **20** (*E*/*Z* = 91:9). The *E*- and *Z*-olefins could not be separated by purification, and were used as a mixture in the next reaction. Finally, the hydroxy group in **20** was protected by using TBDPSCl to give iodoalkene **9** in 87% yield.

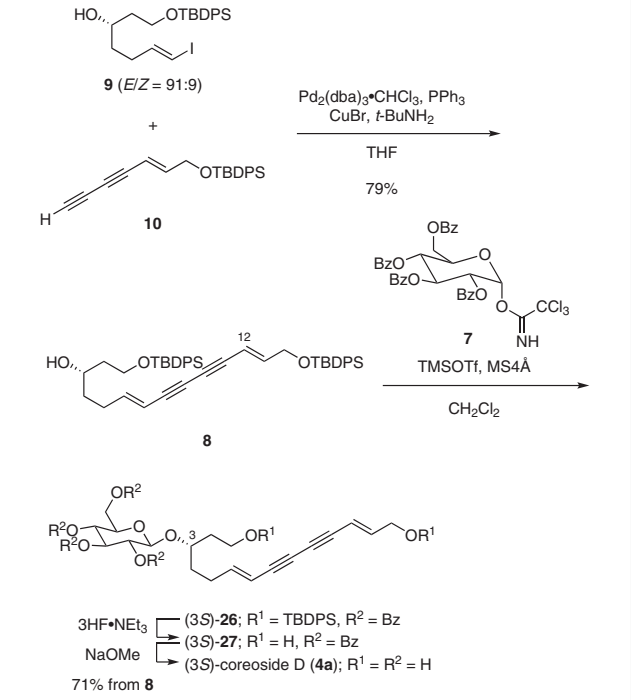
The results of the two types of palladium-catalyzed coupling reaction used to prepare diyne **10** are summarized in Scheme 3. Propargyl alcohol (**21**) was converted into iodoolefin **22** in 82% yield.[6] Sonogashira coupling of iodoolefin **22** with (trimethylsilyl)acetylene afforded enyne **23**, which was then subjected to a deprotection step to remove the trimethylsilyl group to produce **24** in good yield. A palladium-catalyzed C(sp)–C(sp) cross-coupling reaction was



Scheme 3 Synthesis of diyne **10**

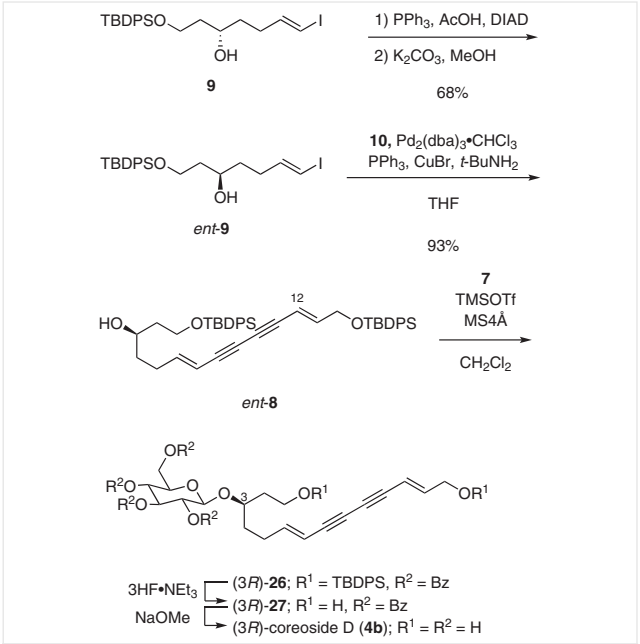
then carried out to afford diyne **25**.[7] Finally, the trimethylsilyl group in **25** was removed by using K_2CO_3/MeOH to give the desired diyne **10**.

In the last stage, we completed the synthesis and characterization of (3*S*)-coreoside D (**4a**), as shown in Scheme 4. Construction of the C1–C14 moiety of (3*S*)-coreoside D (**4a**) was achieved by Sonogashira coupling of **9** (*E*/*Z* = 91:9) and **10** to give alcohol **8**.[8] In this coupling reaction, up to 5% of the the *E*-olefin at the C12–C13 position isomerized to the *Z*-isomer upon conducting the reaction for more than two hours. In addition, (*Z*)-**9** did not react in the coupling reaction. Subsequently, the glycosylation reaction with imidate **7**[9] in the presence of TMSOTf and 4Å MS proceeded smoothly to afford acetal **26**.[10] Finally, deprotection and hydrolysis of **26** afforded (3*S*)-coreoside D (**4a**) in 71% yield from **8**. The ^{1}H NMR, ^{13}C NMR, and UV spectral data for the synthetic (3*S*)-coreoside D (**4a**) were in good agreement with those reported for the natural product. However, the optical rotation of the synthetic compound was inconsistent with the literature data: $[\alpha]_D^{21}$ –31 (*c* 0.06, MeOH); Lit.[1] $[\alpha]_D^{21}$ –13 (*c* 0.04, MeOH). This result suggested that the stereochemistry at the C3-position was incorrect, and prompted us to synthesize the corresponding (3*R*)-isomer **4b**.



Scheme 4 Synthesis of (3*S*)-coreoside D (**4a**)

The synthesis of the (3*R*)-isomer (**4b**) is summarized in Scheme 5. Iodoolefin **9** was converted into *ent*-**9** in 68% yield by a Mitsunobu reaction. Thereafter, (3*R*)-coreoside D (**4b**) was synthesized in the same manner as shown in Scheme 4. The ^{1}H NMR, ^{13}C NMR, and UV spectral data obtained for (3*R*)-coreoside D (**4b**) were in good agreement with those reported for the natural product. The optical rotation was also in agreement with the literature data: $[\alpha]_D^{22}$ –13 (*c* 0.05, MeOH); Lit.[1] $[\alpha]_D^{22}$ –13 (*c* 0.04, MeOH).



Scheme 5 Synthesis of (3*R*)-coreoside D (**4b**)

In conclusion, we have accomplished stereoselective syntheses of (3*S*)-coreoside D (**4a**) and its (3*R*)-isomer **4b**. The key intermediate, iodoolefin **9** was synthesized by Horner–Wadsworth–Emmons and Takai reactions from D-malic acid (**11**) as a starting material. On the other hand, diyne **10** was derived from propargyl alcohol (**21**) by two types of palladium-catalyzed coupling reaction. The C1–C14 carbon chain was constructed by a Sonogashira coupling reaction of iodoolefin **9** and diyne **10**, after which the glucose moiety was introduced to synthesize (3*S*)-coreoside (**4a**) over 18 steps in a total yield of 7.6% from D-malic acid (**11**). The chiral carbon in alcohol **9** was inverted through a Mitsunobu reaction to afford *ent*-**9**, which was transformed into (3*R*)-coreoside D (**4b**) in the same manner. A comparison of the $[\alpha]_D$ values of **4a** and **4b** with that reported for natural coreoside D was decisive in determining the *R* configuration of the C3 stereocenter in coreoside D and thus, the reported chirality was revised.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690876.

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(11) **(3*S*)-Coreoside** (**4a**)

A 1.02 M solution of NaOMe in MeOH (0.25 mL, 0.255 mmol) was added to a solution of diol (3*S*)-**27** (0.126 mmol) in 1:1 MeOH–THF (4 mL), and the mixture was stirred at r.t. for 1 h, then neutralized with Amberlite IR-120 (hydrogen form). The resulting mixture was filtered through paper and concentrated. The residue was purified by chromatography [silica gel, CH_2Cl_2–MeOH (4:1)] to give a white solid; yield: 35.6 mg [71% from alcohol (*S*)-**8**]; mp 40 °C; R_f = 0.25 (CH_2Cl_2–MeOH, 4:1); $[\alpha]^{21}_D$ –31 (*c* 0.06, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 1.56–1.83 (m, 4 H), 2.30 (q, *J* = 7.1 Hz, 2 H), 3.16 (t, *J* = 8.3 Hz, 1 H), 3.21–3.40 (m, 3 H), 3.62–3.72 (m, 2 H), 3.72–3.81 (m, 1 H), 3.81–3.92 (m, 2 H), 4.14 (dd, *J* = 4.7, 2.0 Hz, 2 H), 4.34 (d, *J* = 8.3 Hz, 1 H), 5.66 (d, *J* = 16.0 Hz, 1 H), 5.83 (d, *J* = 15.6 Hz, 1 H), 6.35 (dt, *J* = 15.6, 7.1 Hz, 1 H), 6.37 (dt, *J* = 16.0, 4.7 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 30.1, 35.4, 38.2, 59.5, 62.68, 62.75, 71.6, 73.1, 74.9, 75.3, 77.8, 77.9, 78.2, 79.7, 81.2, 103.9, 109.0, 109.7, 147.4, 150.0. HRMS (FD): *m/z* [M]$^+$ calcd for $C_{20}H_{28}O_8$: 396.17842; found: 396.17676. UV (MeOH): λ_{max} 262, 276, 293, 313 nm.