Total Syntheses of Proposed Structures of 4,10-Dihydroxy 8,12-Guaianolides

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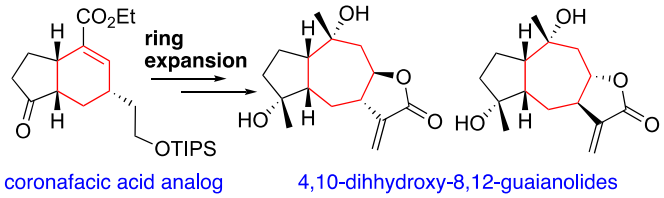


ABSTRACT: The first total syntheses of two 4,10-dihydroxy 8,12-guaianolides that were reported to be natural products, were achieved. Toward the syntheses of a collection of related guaianolides, the typical 5,7-fused system of 8,12-guaianolides was constructed by a ring expansion reaction of a hydroxylated coronafacic acid analog that can be practically synthesized and optically resolved. The total syntheses of these compounds revealed that the previously reported structures of both natural products were incorrect.

Guaianolide sesquiterpene lactones (GSLs) have received a great deal of attention as pharmaceutical lead compounds due to their potent antitumor and anti-inflammatory activities,[1] and certain GSL analogs have advanced to human clinical trials.[2] GSLs are comprised of a tricyclic fused ring system of cyclopentane (or cyclopentene), cycloheptane (or cycloheptene), and γ-lactone, and are divided into two subclasses, known as 6,12-guaianolides and 8,12-guaianolides, with different positions of lactones that bind to the central seven-membered ring.

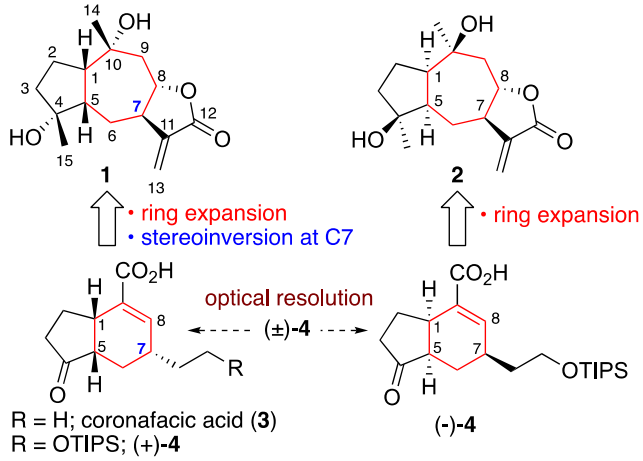


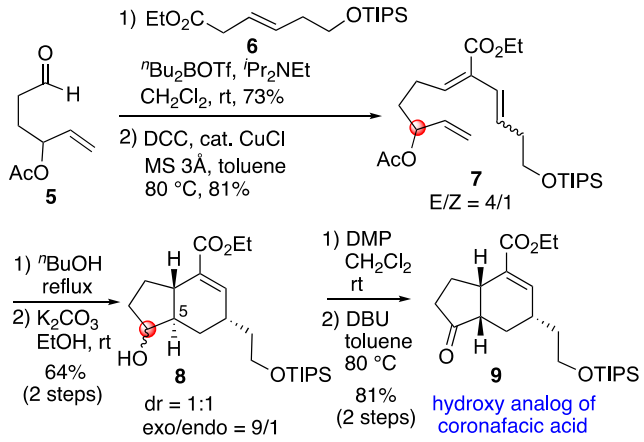
Figure 1. Structure of natural products **1** and **2** as types of 4,10-dihydroxy-8,12-guaianolide, and their synthetic plan from hydroxylated coronafacic acid analog **4**.

Numerous synthetic and mechanistic studies have been conducted on 6,12-guaianolides, but relatively few studies have investigated 8,12-guaianolides.[3] To find additional promising pharmaceutical lead compounds derived from GSLs, we decided to synthesize various 8,12-guaianolide analogs and evaluate their detailed biological activities. As the first step in this process, we herein attempted to synthesize dihydroxy analogs **1** and **2** from 4,10-dihydroxy-8,12-guaianolides (Figure 1).

Guaianolide **2** was initially isolated by Topcu *et al.* from *Inula* species in 1995,[4] and in 2002 Son and Moon isolated **1** along with **2** from *Carpesium macrocephalum*.[5] However, the biological activities and total syntheses of **1** and **2** have not been reported. Interestingly, the stereocenters of **1** and **2** have an enantiomeric relationship except for the lactone moiety at the C-7 and C-8 positions. As a first step in the complete synthesis of **1** and **2**, we attempted to establish a robust synthetic route for 8,12-guaianolides. For this purpose, we focused on coronafacic acid (**3**).[6] There has been strong interest in **3** due to its various biological activities, which are similar to those of the plant hormone jasmonic acid, and thus many syntheses of **3** have been reported.[7] In particular, Watson established a practical and scalable synthesis of racemic **3** based on the synthesis reported by Charette.[7b,8] We therefore considered that coronafacic acid analogs could be used for the synthesis of 8,12-guaianolides as follows: the bicyclo [3.5.0] decane frameworks of **1** and **2** would be constructed by the ring expansion reaction of hydrox-

ylated coronafacic acids **4**. Because, as stated above, the stereocenters of **1** and **2** have an enantiomeric relationship expect for the lactone moiety, both enantiomers of **4** would be available for the synthesis of **1** and **2**, respectively, although the side chain of the enantiomer corresponding to **1** would require stereoinversion. Both enantiomers of **4** would be obtained by optical resolution of racemic (±)-**4** (Figure 1).We expected that the hydroxylated analog (±)-**4** would be obtained in large quantities in a manner similar to the practical synthesis of **3**.[7b]

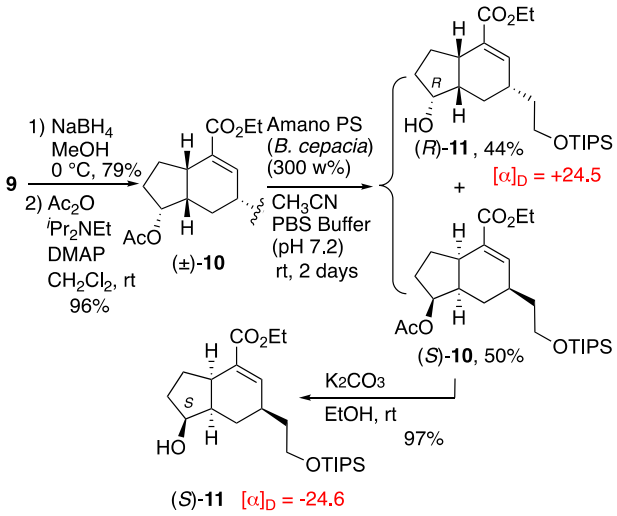
Scheme 1. Synthesis of hydroxylated coronafacic acid analog **9**.



To obtain a hydroxylated analog of coronafacic acid, the ester **6** possessing a silyloxy group[9] was applied to the practical synthesis of **3**. With reference to the modified conditions reported by Kato and Ueda,[7c] the conditions for the aldol reaction of the known aldehyde **5**[7b,c] with the ester **6** were optimized. Mixing **6** and dibutylboryl triflate at room temperature for 1 min/g and then immediately adding the aldehyde **5** afforded the *syn*-adduct (less than 5% of *anti*-adduct) with good reproducibility, and subsequent dehydration according to Charette's conditions[8] afforded **7** in good yield. The *E* configuration of **6** was partially isomerized to the *Z*-form at the aldol reaction. A similar reaction using the *Z*-form of **6** prepared as an alternative also afforded a 4:1 mixture of **7** in favor of the *E* isomer. The IMDA reaction of the *E*-isomer in butanol under reflux conditions proceeded smoothly, and subsequent removal of the acetyl group resulted in bicyclic product **8** as a 1:1 diastereomeric mixture and a 9:1 exo/endo mixture. Since the IMDA reaction of the *Z*-isomer required microwave conditions to proceed, the *Z*-isomer was unreacted under these reaction conditions.[10] Also, although various protecting and directing groups other than the acetyl group were used to investigate the possibility of the chiral transfer from the secondary alcohol, the 1:1 diastereomeric mixture was given in each case, and the chiral transfer was found to be difficult. The diastereomeric and exo/endo mixture **8** converged to a single isomer **9** by oxidation of the secondary alcohol followed by epimerization using DBU at the C_5 position. Thus, the hydroxylated coronafacic acid analog **9** was obtained in multigram scale, as we expected (Scheme 1).

Next, the optical resolutions of the coronafacic acid analogs were examined. Although Kato and Ueda reported the useful optical resolution of coronafacic acid by the condensation of carboxylic acid with chiral oxazolidinone for conversion into a diastereomeric mixture,[7c] we tried to develop enzymatic resolution as a simple and scalable method. The ketone group of **9** was converted into an acetoxy group as a reaction site of the enzyme to give **10**. Among various enzymes, lipase PS Amano SD was found to completely recognize and hydrolyze (*R*)-**10** to give (*R*)-**11** in excellent yield. The absolute configuration of the secondary alcohol was determined by its conversion into Mosher's ester,[11] and the diastereomer derived from the (*S*)-isomer was not detected by ^{1}H NMR. Treatment of the remaining (*S*)-**10** with K_2CO_3 in ethanol afforded (*S*)-**11** in quantitative yield, and the absolute value of the specific optical rotation of (*S*)-**11** showed complete agreement with that of (*R*)-**11**. Thus, a method of synthesizing optically pure hydroxylated analogs of coronafacic acid was established (Scheme 2).

Scheme 2. Optical resolution of hydroxylated coronafacic acid analog.



With the hydroxylated coronafacic analog **11** in hand, we next tried to expand the cyclohexane ring. Prior to the use of optically pure **11**, we first studied the racemic total syntheses of **1** and **2**. The addition of methyllithium to **9** occurred on the convex face, and subsequent DIBAL reduction afforded allyl alcohol **12** in acceptable yield. The Mitsunobu reaction of **12** with *tert*-butoxycarbonylnosylamide (NsNHBoc) followed by deprotection of the nosyl group resulted in **13** in good yield.[12] Dihydroxylation using osmium tetroxide proceeded on the convex face to give the ring expansion reaction precursor **14**. Next, an application of the Tiffeneau–Demjanov rearrangement for ring expansion was examined.[13] Deprotection of the Boc group by TFA followed by treatment of the resulting amine salt with sodium nitrite and acetic acid afforded undesired epoxide as a major product,[14] which was formed by the intramolecular substitution reaction of tertiary alcohol with the diazo group generated from the primary amine. Thus, the Boc group was removed by Ohfune's method[15] using TMSOTf and ^{i}Pr$_2$NEt in order to simultaneously protect alcohols with TMS groups, and the subsequent direct addition of nitrite ester and acetic acid afforded the desired seven-membered ring **15** in acceptable yield without the formation of epoxide (Scheme 3).[16] As the formation of epoxide is often a problem in a Tiffeneau–Demjanov rearrangement, this method may also be useful for a variety of other ring expansion reactions.

Scheme 3. Ring expansion of the coronafacic acid analog

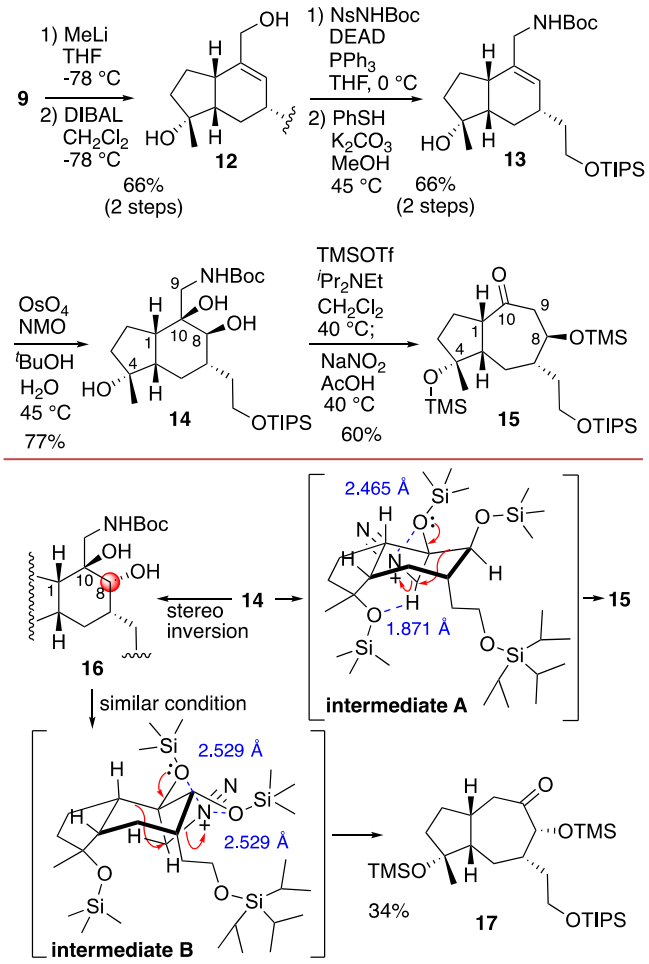
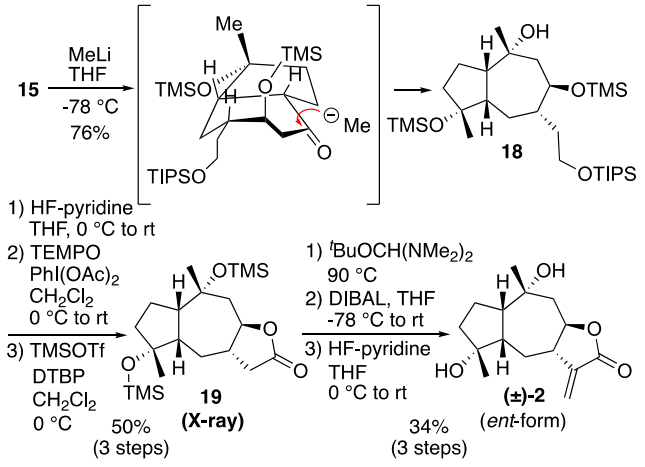


Figure 2. Mechanistic studies of Tiffeneau-Demjanov rearrangement.

Of the two possible rearrangement sites, i.e., the carbon hydroxylated (C_8) or the carbon on the five-membered ring (C_1), we found that the former was rearranged. Thus, the conformation of the diazo intermediate was investigated by DFT calculation to elucidate the rearrangement tendency. The structure of silyl-protected diazo intermediate **A** was optimized, and the stabilities of the ring-expanded products **15** (C_8) and **15'** (C_1) were also compared (Figures S1 and S2). The most stable structure of intermediate **A** showed an interaction between the nitrogen of the diazo group and the oxygen of the silyloxy group at the C_{10} position (O_{10}-N = 2.465 Å), and a strong interaction between the hydrogen at the C_9 position and the oxygen of the silyloxy group at the C_4 position (O_4-H_9 = 1.871 Å). These electrostatic interactions kept the leaving group opposite the C_8, resulting in the rearrangement at the C_8. In addition, the corresponding product **15** is more stable than **15'** (Figure S2). To confirm the directing effect of the oxygen functional groups, the configuration of the secondary alcohol at the C_8 position was inverted to give **16**, and its rearrangement reaction was also examined. The reaction of **16** proceeded with opposite regioselectivity to give **17** as a major product, and no byproducts rearranged at the C_8 were detected. The DFT study showed that the diazo intermediate **B** from **16** has the two O–N interactions (O_{10}-N = O_8-N = 2.529 Å), which directed the leaving group N_2 opposite the C_1, causing rearrangement at C_1 instead of C_8 (Figure S1). In addition, the corresponding product **17** is more stable than **17'** (Figure S3). Thus, we revealed that the neighboring oxygen functional group serves as a directing group in the Tiffeneau–Demjanov rearrangement (Figure 2).

Having constructed a 5,7-fused system of 8,12-guaianolides, we next tried the total synthesis (Scheme 4). The addition of methyllithium to the ketone of **15** occurred from the desired face to give **18** as a single diastereomer. The DFT calculation suggested that the most stable conformation occurs when the ketone group is directed to the bottom face, as depicted in scheme 4 (see Figure S4). Thus, the methyl anion approached from the convex face. All silyl groups of **18** were removed by HF-pyridine, and subsequent TEMPO oxidation afforded the desired lactone. The two remaining alcohols were protected again by the TMS group to give **19** in 50% yield from **18**. After various examinations, the introduction of exomethylene was accomplished by treatment with Bredereck's reagent[17] followed by DIBAL reduction.[3j,18] Finally, deprotection of the TMS group afforded the racemic **2** in 34% yield from **19**. Thus, we achieved the first total synthesis of the proposed structure of natural product **2**. Unfortunately, however, the ^{1}H and ^{13}C NMR spectra of synthesized **2** did not match the reported data for natural product **2** (Figure S5). To confirm the validity of the synthesis, we attempted to synthesize natural product **1**, which was isolated and structurally determined by a group different from the researchers that originally reported **2**.

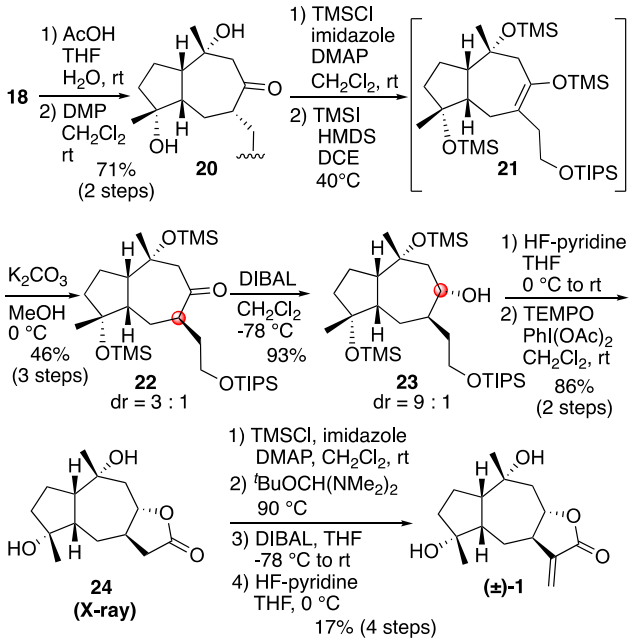
Scheme 4. Total synthesis of the proposed structure of **2**.



The TMS groups of intermediate **18** were removed, and oxidation using Dess–Martin periodinane afforded ketone **20**. As the epimerization of the silyloxyethyl group under basic conditions did not proceed, the ketone group was converted into silyl enol ether **21** by treatment with TMSI after TMS protection of tertiary alcohols. Subsequent treatment of the crude **21** with K_2CO_3 in methanol afforded the desired ketone **22** as a 3:1 diastereomeric mixture, in which the stereochemistry of the siloxyethyl group was inverted. DIBAL reduction of the ketone **22** resulted in the

secondary alcohol **23** with the desired configuration as the major product, while the use of $NaBH_4$ predominantly gave an alcohol with the opposite configuration. As the stereocenters of the lactone moiety (C_7 and C_8) were successfully modified to those of **1**, the alcohol **23** was converted into (±)-**1** in a manner similar to the synthesis of (±)-**2** (Scheme 5). Thus, the first total synthesis of **1** was also accomplished. However, ^1H and ^{13}C NMR spectra of synthesized **1** were also not consistent with the reported data for natural product **1** (Figure S6).

Scheme 5. Total synthesis of the proposed structure of **1**.



Fortunately, synthetic intermediates **19** and **24**, the precursors of the final step introducing exomethylene, were found to be crystals. X-ray analyses demonstrated that the tricyclic systems of **19** and **24** were constructed with the correct stereochemistries (Figures S7 and S8).[19] Therefore, the synthetic products **1** and **2** were certainly consistent with the proposed structures, and the reported structures for natural products **1** and **2** were found to be incorrect. Because of these errors, asymmetric total synthesis using chiral **11** was temporarily stopped, and the identification of the correct structures of the natural products is underway in our laboratory.

In conclusion, we achieved the total syntheses of the proposed structures of 8,12-guaianolides **1** and **2**. The hydroxylated analog of coronafacic acid, which can be used for coronafacic acid-based probes, was synthesized on multigram scales and a practical method for optical resolution was developed. The central seven-membered ring of the guaianolides was constructed by ring expansion reaction, and the regioselective tendency of the Tiffeneau–Demjanov rearrangement was elucidated by DFT calculation analysis. Finally, the construction of the lactone ring directly and after stereoinversion, followed by exomethylene introduction, afforded the proposed structures **2** and **1**, respectively. These total syntheses revealed that the reported structures of natural products **1** and **2** are incorrect. The structures of natural products are often determined based on previous reports of related compounds. Thus, the structures of dihydroxy-8,12-guaianolides, for which many stereoisomers have been reported, require further validation for pharmacological use, because the structures of the two natural products synthesized in this study have both been incorrectly characterized for some time now. Further synthesis of related 8,12-guaianolides is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

DFT analysis; NMR data comparison; ORTEP structures of **19** and **24**; key NOESY correlations of synthesized **1** and **2**; experimental details and characterization data; computational details; ^1H and ^{13}C NMR spectra of new compounds; 2-D NMR spectra of **1** and **2** (PDF)

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Notes

The authors declare no competing financial interest.

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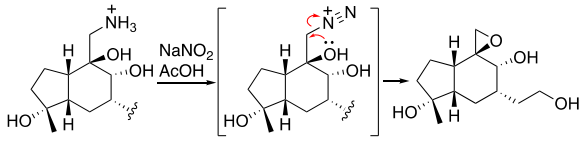

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(19) CCDC 2127714 and 2127722 contain the supplementary crystallographic data for **19** and **24**, respectively. These data are provided free of charge by The Cambridge Crystallographic Data Centre.