Total Synthesis of (+)-Coriamyrtin via a Desymmetric Strategy of a 1,3-Cyclopentanedione Moiety

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The memory of Prof. Hidetoshi Yamada deceased on November 23, 2019, and Prof. Toshiyuki Kan deceased on July 24, 2021.

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Abstract: This paper describes the total synthesis of (+)-coriamyrtin, a picrotoxane-type sesquiterpene. The natural product is widely known as a neurotoxin of the Coriariaceae family and bears a highly functionalized *cis*-hydrindane skeleton. Despite being biologically and synthetically attractive molecule, only two examples of the total synthesis are reported to date. Our synthetic strategy involves the highly stereoselective construction of the *cis*-hydrindane skeleton via the desymmetric strategy of a 1,3-cyclopentanedione moiety using an intramolecular aldol reaction and elaborate functionalization of the cyclopentane ring in the bicyclic structure for the formation of the 1,3-diepoxide moiety of coriamyrtin. Our method could be applied to synthesize various natural products with similar bicyclic skeletons and to expand neurobiological studies using synthesized products.

Picrotoxane-type sesquiterpenes are widely distributed in plants, such as Coriariaceae, Orchidaceae, and Menispermaceae.[1] As picrotoxin, which is a poisonous compound composed of a 1:1 mixture of picrotoxinin (**1**) and picrotin, was found in *Menispermum cocculus* in 1818, more than 130 picrotoxane-type natural products have been isolated to date (Figure 1).[2] Because **1** is a strong antagonist of the γ–aminobutyric acid (GABA) receptor, resulting in excitatory effects in the central nervous system,[3] **1** is frequently used as a chemical tool for investigations in neurobiology.[4] Picrotoxane-type sesquiterpenes bear a *cis*-hydrindane skeleton as a common structure, and its bicyclic core is highly oxy-functionalized by hydroxy groups, lactones, and epoxides. Owing to the intriguing biological and structural features of **1**, Corey *et al*.,[5] Yamada *et al*.,[6] Yoshikoshi *et al*.,[7] Trost *et al*.,[8] Shenvi *et al*.,[9] and Nakazaki *et al*.[10] reported the total synthesis of **1**.

Coriamyrtin (**2**) is mainly found in the Coriariaceae family and shows strong neurotoxicity, similar to **1**.[11] The major difference between **1** and **2** is the oxidation stage of the cyclopentane ring in the *cis*-hydrindane skeleton. The presence of two epoxides in the five-membered ring makes the total synthesis of **2** difficult. Pioneering total synthesis has been achieved by the groups of Tanaka and Inubushi[12] as well as Yamada;[6] however, both methods have critical drawbacks. Tanaka and Inubushi group constructed a 1,3-diepoxide moiety through a very low-yield step (3%). Although Yamada *et al*. formed the 1,3-diepoxide moiety in moderate yields, the total synthesis of **2** required more than 40 steps from a commercially available compound. The diepoxide moiety is observed in novel picrotoxane-type sesquiterpenes, some of which are further derivatized through epoxide opening (Figure 1).[13] Thus, the establishment of an efficient synthetic route of **2** can contribute to the development of the synthesis of such natural products. Herein, we describe the asymmetric total synthesis of **2** in 20 steps.

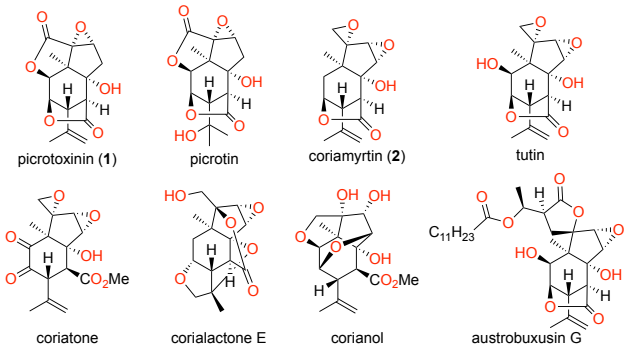
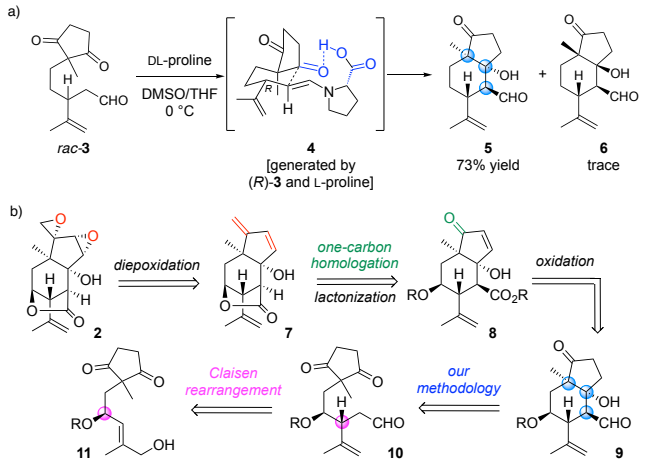


Figure 1. Representative Structures of picrotoxane-type sesquiterpenoids.

We recently reported a method for the desymmetrization of a 1,3-cyclopentadione moiety via the intramolecular aldol reaction of *rac*-aldehyde **3** with DL-proline (Scheme 1a).[14] This reaction involves an intramolecular hydrogen bond formation between a carbonyl group in the 1,3-cyclopentanedione and the carboxylic group of enamine intermediate **4**, derived from (*R*)-**3** and L-proline, or (*S*)-**3** and D-proline (not be shown in Scheme 1a), to afford the bicyclic compound **5** in 73% yield along with a trace amount of its diastereomer **6**. The two contiguous centers of the angular

positions of **5** correspond to those in **2**, which inspired us to develop this methodology for the total synthesis of **2**.

The retrosynthesis of coriamyrtin (**2**) is shown in Scheme 1b. The formation of the 1,3-diepoxide moiety was designed at the later stage of the synthesis owing to its instability. Thus, we planned to form the moiety via the diepoxidation of 1,3-diene **7**, which would be prepared via one-carbon homologation of ketone **8**, followed by lactonization. The synthesis of **8** could be prepared from bicyclic aldehyde **9** through the oxidation of its cyclopentane ring, and that of **9** would be achieved via our established methodology; thus, the desymmetrization of the 1,3-cyclopentane ring of aldehyde **10**. We speculated that the relative configuration between the oxy-functional group and the isopropenyl group of **10** could be constructed via stereoselective Claisen rearrangement controlled by the stereogenic center in allylic alcohol **11**. The enantioselective synthesis of **11** was carried out following the literature for the preparation of a similar compound as **11** reported by Nagorny *et al*. [15]

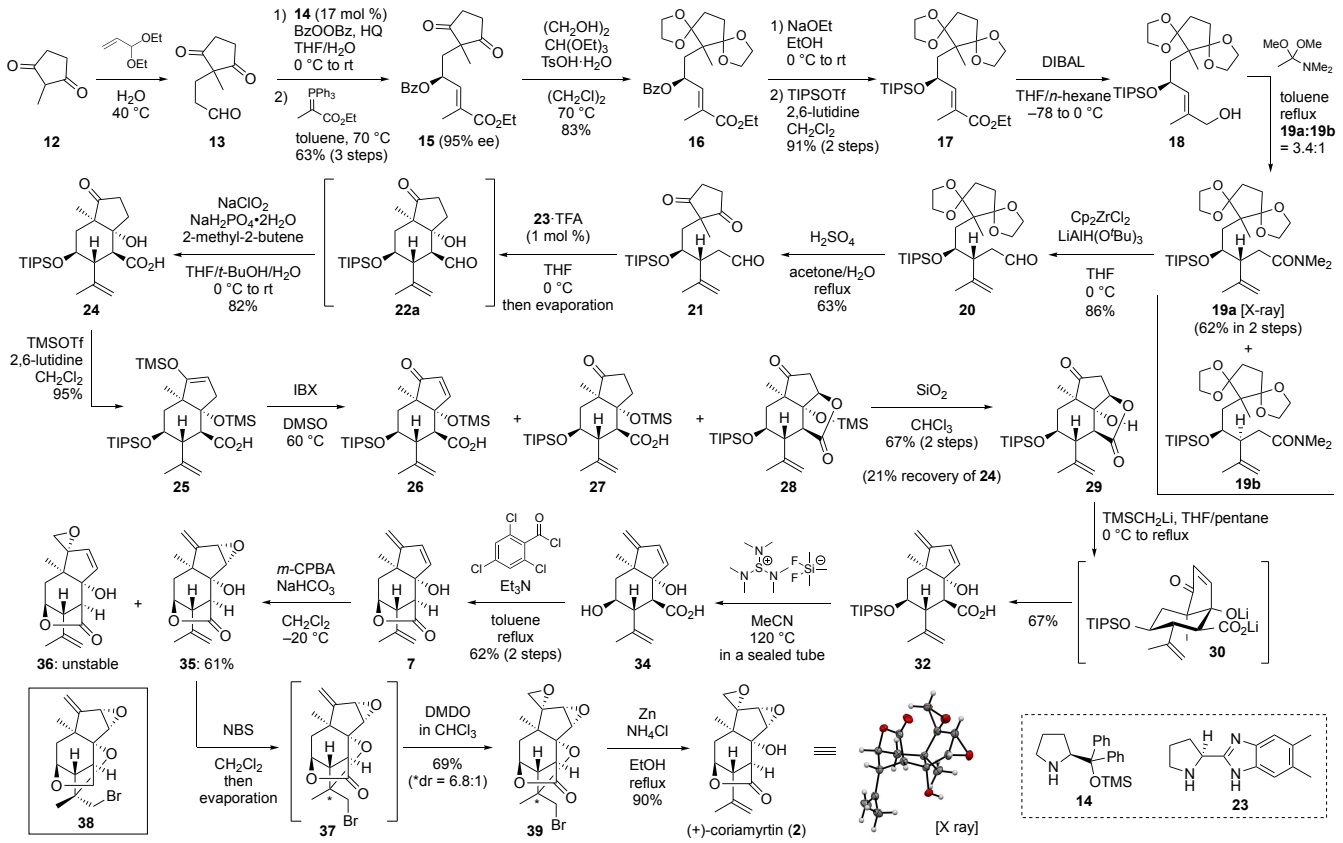


Scheme 1. (a) Our reported method for the stereoselective synthesis of bicyclic compound **5**; (b) Retrosynthetic analysis of coriamyrtin (**2**).

First, we synthesized a precursor for the intramolecular aldol reaction (Scheme 2). Treatment of 2-methyl-1,3-cyclopentanedione (**12**) with acrolein diethyl acetal in water at 40 °C induced the generation of acrolein *in situ*, followed by the Michael addition of **12** to acrolein to afford aldehyde **13**. This reaction does not require an acid catalyst because **12** acts as a Brønsted acid.[16] Enantioselective α-benzoyloxylation of **13** was conducted using the Hayashi-Jørgensen catalyst (**14**)[17] under the conditions reported by Nagorny.[15] The obtained aldehyde was quickly reacted with ethyl 2-(triphenylphosphoranylidene)propionate to afford trisubstituted (*E*)-ester **15** in 63 % yield over three steps in 95% ee. After the bis-acetalization of the diketone moiety in **15** using ethylene glycol and TsOH·H_2O in the presence of triethyl orthoformate, the Bz group of **16** was replaced with a TIPS group via a typical two step procedure. DIBAL reduction of the obtained ester **17** afforded allylic alcohol **18**. Conversion of **18** into a γ,δ-unsaturated carbonyl compound proceeded smoothly under the Eschenmoser–Claisen rearrangement conditions,[18] which afforded amide **19a** with the desired relative configuration in 62% isolated yield over two steps, along with its diastereomer **19b** (**19a**:**19b** = 3.4:1). The X-ray structure of **19a** confirmed its absolute configuration.[19] The stereoselectivity in this reaction was attributed to the presence of the TIPS group and bis-acetal moiety (see Supporting Information (SI)-1 for details). Amide **19a** was reduced to aldehyde **20** via the Schwartz reagent generated by Cp_2ZrCl_2 and LiAlH(O*t*-Bu)$_3$ *in situ*,[20] and the bis-acetal moiety in **20** was hydrolyzed under acidic conditions to give aldol precursor **21**.

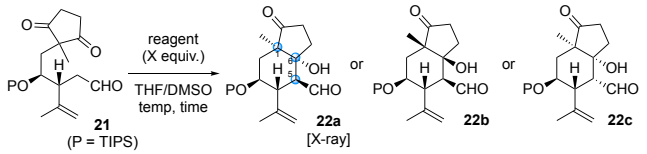
Next, we examined the desymmetric intramolecular aldol reaction of **21** using our reaction conditions, as shown in Scheme 1a (Table 1). The reaction of **21** with 10 equivalents of L-proline in THF/DMSO at 0 °C provided **22a**, where the three stereocenters at the C1, C5, and C6 positions correspond to those of **2**, in high yield and stereoselectivity (entry 1). When the reaction temperature was lowered to –40 °C and then gradually warmed to 0 °C, **22a** was obtained as almost a single isomer (entry 2). The replacement of L-proline with pyrrolidine generated diastereomer **22b** as the major product (entry 3), indicating that the L-proline-mediated reaction proceeded through an enamine intermediate similar to **4**. Interestingly, the use of D-proline selectively provided **22c**, the C5-epimer of **22a**, along with the generation of **22a** and **22b** as minor products (**22a**:**22b**:**22c** = 1:1.1:4.5) (entry 4). Surprisingly, the reaction with the catalytic amount of L-proline decreased the stereoselectivity to afford a 3.2:1 mixture of **22a** and **22b** in 91% yield (entry 5). This result indicated that the non-proline-mediated intramolecular aldol reaction competed under catalytic conditions, which prompted us to change L-proline. The catalytic use of (*S*)-benzimidazole–pyrrolidine **23**[21] afforded **22a** in moderate yield with high stereoselectivity (entry 6). Furthermore, the TFA salt of **23** accelerated the reaction using only 5 mol % to produce **22a** in 96% yield as a single isomer (entry 7). The structure of **22a** was confirmed by the X-ray diffraction analysis.[19] The Pinnick oxidation of **22a** in the presence of 2-methyl-2-butene provided carboxylic acid **24** in 89% yield. We also succeeded in decreasing the amount of **23**·TFA to 1 mol % in the intramolecular aldol reaction of **21** and performed the one-pot synthesis of **24** from **21** in 82% yield (Scheme 2).

Next, the elaborate oxidation of the cyclopentane ring in **24** was performed. We first attempted at the conversion of the ketone moiety in the allyl ester derived from **24** into silyl enol ether; however, no reaction occurred because of steric hindrance around the ketone moiety. In contrast, treatment of **24** with TMSOTf and 2,6-lutidine induced the desired transformation to obtain silyl enol ether **25** in 95% yield. This reaction probably involved the TMS-protection of the carboxyl group, formation of silicate mediated by the angular hydroxy group, reaction of the resulting ketone moiety with the two reagents, and release of the carboxylic group from the silicate. Silicate formation might arise from the conformational change of the bicyclic structure, allowing the reaction of the ketone moiety. The conversion of **25** into cyclopentenone **26** proceeded via the use of IBX in DMSO at 60 °C;[22] however, the hydrolysis of silyl enol ether was competed to produce an inseparable mixture of **26** and ketone **27**.[23] In addition, transformation of enone **26** into lactone **28** via the intramolecular oxa-Michael addition was partially observed. Thus, we exposed the crude product obtained by the IBX oxidation of **25** to silica gel in $CHCl_3$, which simultaneously induced the lactone formation and removal of the angular TMS group, affording lactone **29** in 67% yield and recovering **24** in 21% yield over two steps.



Scheme 2. Synthetic method for (+)-coriamyrtin (**2**). Bz = benzoyl, HQ = hydroquinone, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl, TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl, DIBAL = diisobutylalminium hydride, Cp = cyclopentadienyl, TFA = trifluoroacetic acid, IBX = 2-idoxybenzoic acid, DMSO = dimethyl sulfoxide, *m*-CPBA = *m*-chloroperbenzoic acid, NBS = *N*-bromosuccinimide, DMDO = dimethyldioxirane.

Table 1. Optimization of the intramolecular aldol reaction of **21**.



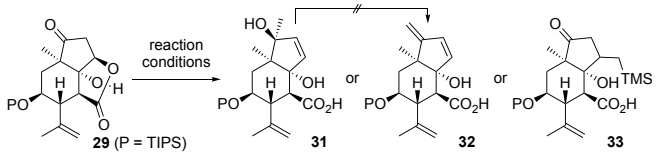
entry	reagent (X)	temp/time	yield, diastereomeric ratio[a]
1	L-proline (10)	0 °C/18 h	94%, **22a**:**22b** = 21:1
2	L-proline (10)	–40 to 0 °C/60 h	95%, **22a**:**22b** = 46:1
3	pyrrolidine (10)	–40 to 0 °C/19 h	97%, **22a**:**22b** = 1:1.7
4	D-proline (10)	–40 to 0 °C/20 h	64% **22a**:**22b**:**22c** = 1:1.1:4.5
5	L-proline (0.2)	–40 to 0 °C/40 h	91%, **22a**:**22b** = 3.2:1
6[b]	**23** (0.1)	0 °C/6 h	44%, **22a**:**22b** = 23:1
7[b]	**23**·TFA (0.05)	0 °C/4 h	96%, **22a** only

[a] Determined from the ^{1}H NMR spectrum of the purified compound. [b] THF was used as the solvent.

Subsequently, the formation of the diene moiety was investigated (Table 2). The reaction of **29** with MeLi proceeded smoothly via the generation of dianion intermediate **30** as shown in Scheme 2, to produce **31** in 82% yield (entry 1). However, the transformation of **31** into diene **32** under dehydration conditions failed. Although the methylenation under the modified Wittig reaction conditions[24] did not produce diene **32** (entry 2), the Peterson olefination using $TMSCH_2Li$ in refluxed THF afforded **32** in 67% yield along with a 1,4-addition product **33** in 17% yield (entry 3). The selection of the solvent was crucial in this reaction; thus, the use of Et_2O or toluene resulted in a decrease in the yield of **32** (entries 4 and 5). The reaction using Bu_3SnCH_2Li [25] did not occur to recover **29** in 60% yield (entry 6). Decomposition of **29** was observed when $TMSCH_2MgCl$ was used (entry 7). Surprisingly, the addition of $LaCl_3$·2LiCl under the conditions for entry 3 resulted in a low conversion of **29** and produced **33** predominately (entry 8). These results indicate that the bulkiness of the reagent inhibited the deprotonation of the α-proton in ketone of **29** and induction of the 1,2-addition to **30**.

Next, γ-lactone and 1,3-diepoxide moieties were prepared for the synthesis of **2** (Scheme 2). The TIPS group in **32** was removed using tris(dimethylamino)sulfonium difluorotrimethylsilicate in MeCN at 120 °C in a sealed tube to afford seco acid **34**. Subsequent lactonization proceeded smoothly via the use of the Yamaguchi reagent[26] and Et_3N, providing lactone **7** in 62% yield over two steps. The chemoselective epoxidation of the diene moiety of **7** proceeded using *m*-CPBA and $NaHCO_3$ at –20 °C to obtain **35** in 61% yield.[27] This reaction also afforded **36** as a minor product, where the terminal olefin of the diene reacted; however, it was very unstable and decomposed during the purification procedure. Because the

Table 2. Examination of one-carbon homologation of ketone **29**



entry	reaction conditions	yield of products[a]
1	MeLi[b] (4 equiv.), THF, reflux, 1 h	**31**: 82%
2	CH_2=PPh_3 (5 equiv.) DMSO, 80 °C, 20 h	complex mixture
3	$TMSCH_2Li$[c] (4 equiv.) THF, 0 °C to reflux, 4 h	**32**: 67%, **33**: 17%
4	$TMSCH_2Li$[c] (4 equiv.) toluene, 0 to 80 °C, 5 h	**32**: 29%
5	$TMSCH_2Li$[c] (4 equiv.), Et_2O 0 °C to reflux, 4 h	**32**: 16%[f]
6	Bu_3SnCH_2Li (5 equiv.), THF –78 °C to reflux, 4 h	**29**: 60%
7	$TMSCH_2MgCl$[d] (7 equiv.), THF reflux, 4 h	complex mixture
8	$TMSCH_2Li$[c] (4 equiv.) $LaCl_3 \cdot 2LiCl_2$[e] (4 equiv.) THF, reflux, 5 h	**29**: 30%[f], **33**: 31%[f]

[a] Isolated yield. [b] 1.09 M solution in Et_2O. [c] 1 M solution in pentane. [c] 1 M solution in Et_2O. [e] 0.6 M solution in THF. [f] NMR yield.

reactivity of 1,3-dienemonoepoxide in **35** was very low, further epoxidation of **35** occurred at the isopropenyl group. Thus, the isopropenyl group was protected in bromoether form using NBS to give **37**. Although epoxidation of **38**, a compound similar to **37**, mediated by *m*-CPBA was reported,[6] the reaction of **37** barely occurred despite the use of excess amounts of *m*-CPBA under reflux conditions. In contrast, exposure to excess amounts of DMDO in acetone solution detected **39** although its conversion efficiency was low. As the reactivity of DMDO varies according to the solvent,[28] we replaced the solvent with $CHCl_3$.[29] To our delight, this reaction completely transformed **37** to **39**. The bromoetherification of **35** and DMDO-mediated epoxidation of **37** provided a one-pot protocol, which afforded **39** in 69% yield with a 6.8:1 diastereomeric mixture corresponding to the tetra-substituted carbon of the bromoether. Finally, the reaction of **39** with Zn and NH_4Cl in refluxed EtOH reproduced the isopropenyl group to complete the total synthesis of (+)-**2**. The synthetic structure was confirmed by X-ray diffraction analysis.[19]

In summary, we achieved the total synthesis of (+)-coriamyrtin (**2**) via 20 steps from 2-methyl-1,3-cyclopentanedione (**12**). The application of our established desymmetrization strategy for the 1,3-cyclopentanedione moiety and the ingenious transformation of the cyclopentane ring in the *cis*-hydrindane skeleton of **24** leads to the successful formation of **2**. The acquisition of epoxide **35** from dienyl lactone **7** is expected to be developed for the synthesis of various picrotoxane-type sesquiterpenes, where the five-membered ring of the *cis*-hydrindane skeleton is more highly functionalized than that of **2**. In addition, the use of **35** and its analog would expand to neurobiological studies, including structure-relationship activity based on **2**.

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Keywords: coriamyrtin • *cis*-hydrindane skeleton • 1,3-diepoxide • desymmetrization • total synthesis

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[27] We found that when DMDO in acetone solution was used as the oxidant for diene **7**, **36** was generated as the major product. However, owing to its instability, the transformation of **36** was difficult.

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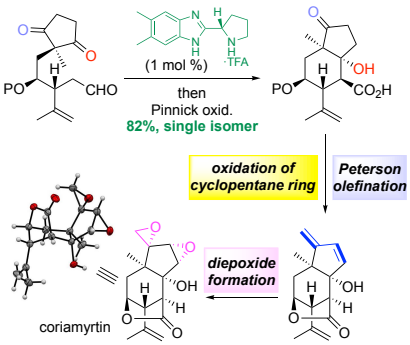

Herein, we describe the total synthesis of (+)-coriamyrtin with a highly functionalized *cis*-fused 5,6-ring skeleton. Our method involves the highly stereoselective construction of the bicyclic skeleton via the desymmetric strategy of a 1,3-cyclopentanedione moiety using an intramolecular aldol reaction and the elaborate functionalization of the cyclopentane ring for the formation of the 1,3-diepoxide of coriamyrtin.