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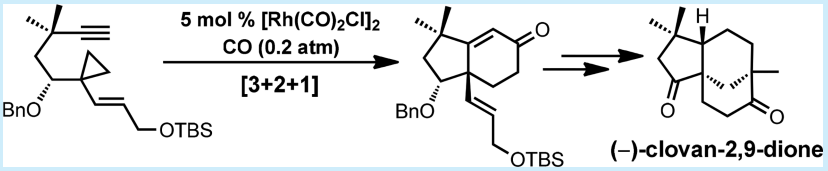
Asymmetric Total Synthesis of (−)-Clovan-2,9-dione Using Rh(I)-Catalyzed [3 + 2 + 1] Cycloaddition of 1-Yne-vinylcyclopropane and CO

Jun Yang, Wenbo Xu, Qi Cui, Xing Fan, Lu-Ning Wang, and Zhi-Xiang Yu*

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

Supporting Information



ABSTRACT: The asymmetric total synthesis of clovan-2,9-dione with a [6.3.1.0^{1,5}]dodecane skeleton has been achieved. The synthesis features a Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of 1-yne-vinylcyclopropane (1-yne-VCP) with CO and an intramolecular aldol reaction to obtain the skeleton of the target molecule.

Clovan-2,9-dione and rumphellclovanes A−E (Figure 1) belong to a novel class of clovane-type sesquiterpenes,

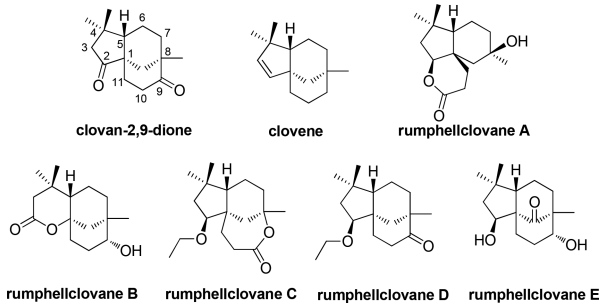


Figure 1. Representative clovane-type sesquiterpenes.

isolated from the gorgonian coral *Rumphella antipathies* collected at the southern coast of Taiwan by Sung et al.[1] These molecules with an intriguing tricyclic bridged-ring skeleton not only further enriched structural diversity and biological activities of marine sesquiterpenes[2] but also attracted the attention of chemists for further study. In 2012, Siegel reported that clovanemagnolol displayed the ability to promote the growth of embryonic hippocampal and cortical neurons.[3] Sung and co-workers found that clovan-2,9-dione had apparent effects in inhibiting production of superoxide anion and elastase released by human neutrophils.[1c]

Clovan-2,9-dione and other clovane-type natural products contain a tricycle [6.3.1.0^{1,5}]dodecane skeleton with three quaternary carbon centers at C1, C4, and C8. The differences of these molecules are manifested in the oxidation states of C2 and C9. Before isolation from *Rumphella antipathies* in 2013, clovan-2,9-dione and related derivatives were biosynthesized from *β*-caryophyllene.[4] Barton made pioneering contributions to the synthesis of derivatives of *β*-caryophyllene and determined their structures.[4a] However, examples of total syntheses of molecules with clovane skeleton are rare. In 1965, (±)-clovene (Figure 1), one of the transformation products obtained from *β*-caryophyllene, was synthesized via Robinson annulation and Dieckmann condensation.[5a] In 1988, Funk reported an elegant synthesis of (±)-clovene using ketene [2 + 2]/ring-expansion strategy.[5b] Kundu and co-workers realized the total synthesis of (±)-clovan-9-one and (±)-clovane.[6] In 2003, Mukherjee reported the total synthesis of (±)-clovan-3-one, (±)-*epi*-clovan-3-one, and (±)-pseudoclovene A.[7] However, to the best of our knowledge, asymmetric total synthesis of clovane-type natural products starting from simple chemical materials has not been reported. Herein, we report an asymmetric total synthesis of (−)-clovan-2,9-dione (a racemic version was also accomplished; see the Supporting Information).

We envisioned that the 5/6/6 ring system with a quaternary carbon center at C1 of (−)-clovan-2,9-dione could be efficiently accessed using the Rh-catalyzed [3 + 2 + 1] cycloaddition of 1-ene/yne-vinylcyclopropane (VCP) and CO,[8a−d] developed in our group (Scheme 1). The ring C of **1** could be built up through intramolecular aldol reaction. The key intermediate of 5/6 bicyclic cyclohexenone **3** could be produced from a linear precursor **4** through a Rh(I)-catalyzed [3 + 2 + 1] cycloaddition with CO. Substrate **4** of the key reaction could be synthesized from simple known compounds **5** and **6**. In this synthetic strategy, there are a couple of significant challenges to be addressed. First, a substrate containing a terminal substituent of the vinyl group for the Rh(I)-catalyzed [3 + 2 + 1]

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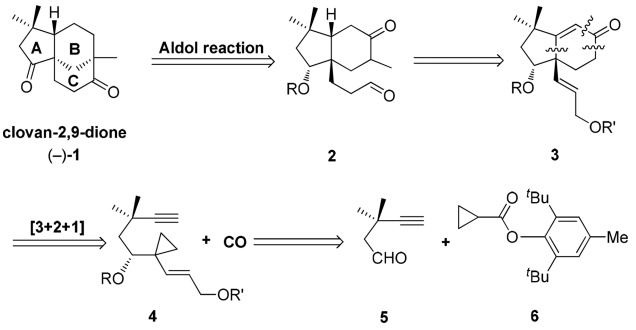
Scheme 1. Retrosynthetic Analysis of Clovan-2,9-dione

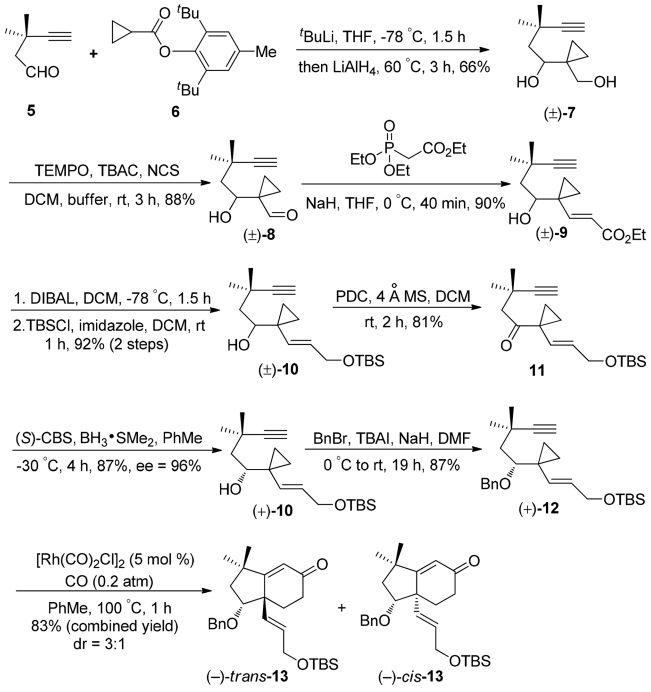


cycloaddition is unprecedented. Second, a chiral substrate-induced asymmetric [3 + 2 + 1] cycloaddition in this system has not been investigated yet.

We embarked on the synthesis from known compounds aldehyde **5**[9] and ester **6**[10] (Scheme 2). The intermolecular aldol reaction and subsequent LAH reduction were operated in one pot, leading to the diol compound (±)-**7** in 66% yield. Next, the primary hydroxyl group in diol (±)-**7** was selectively oxidized to give the aldehyde (±)-**8** in the presence of TEMPO, NCS, and TBAC.[11] Then Horner−Wadsworth−Emmons olefination produced absolute *E*-vinyl cyclopropane (±)-**9** in 90% yield. Treating compound (±)-**9** with DIBAL at −78 °C afforded an alcohol, of which the primary hydroxyl was then protected by TBS to give compound (±)-**10** in 92% yield over two steps. In order to obtain a chiral substrate, the alcohol (±)-**10** was oxidized to ketone **11** with PDC in 81% yield. Corey−Bakshi−Shibata reduction of **11** afforded chiral alcohol (+)-**10** in 87% yield and 96% ee. The configuration of (+)-**10** was proposed as *R* by using Corey's analysis model[12] and also confirmed by synthesis of the target natural product, which had an optical rotation value consistent with literature reports.[1c,4h] The secondary hydroxyl functionality of (+)-**10** was protected by the Bn group to generate the desired [3 + 2 + 1] substrate (+)-**12**. To our delight, the key Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of (+)-**12** and CO occurred smoothly with 5 mol % rhodium dimer catalyst under 0.2 atm CO atmosphere at 100 °C. The reaction afforded the desired product (−)-*trans*-**13** and (−)-*cis*-**13** in 83% combined yield with a diastereomeric ratio of about 3:1. Fortunately, these two diastereomers could be separated by column chromatography. We were happy to find that the [3 + 2 + 1] reaction can be carried out on a gram scale with a yield of 80% for the racemic substrate (see our racemic synthesis of the present natural product in the Supporting Information). We point out that the side product Bn_2O obtained from the protection step could not be separated from (+)-**12**,[13] but this ether could be removed after the [3 + 2 + 1] reaction by column chromatography.

Here, we propose two transition states to rationalize the relative stereochemistry of the [3 + 2 + 1] reaction (Figure 2).

Scheme 2. Synthesis of the Key Bicyclic Intermediate 13



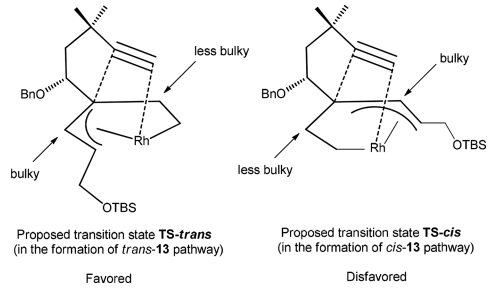
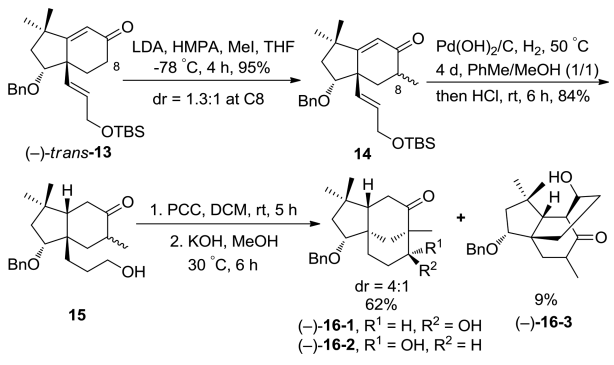


Figure 2. Proposed transition states of alkyne insertions and rationale for relative stereochemistry of the [3 + 2 + 1] reaction.

In the two competing alkyne insertion transition states to the six-membered rhodacycle, the OBn group in the tether experiences steric repulsion from either the allylic moiety or the CH_2CH_2 moiety. We hypothesize that the allylic moiety is bulkier than the CH_2CH_2 moiety, and **TS-*cis*** becomes disfavored slightly than **TS-*trans***; consequently (−)-*trans*-**13** was the major diastereomer of the reaction.

Methylation of enone (−)-*trans*-**13** under LDA/MeI/HMPA conditions gave diastereomers **14** in a combined 95% yield[14] (Scheme 3). Nevertheless, lower diastereoselectivity (diastereomeric ratio was about 1.3:1) had no extra effect on subsequent synthesis. Two carbon−carbon double bonds in **14** were reduced by using $Pd(OH)_2/C$ and H_2 in toluene/methanol, which was followed by deprotection of the TBS group, yielding alcohol **15** in 84% yield. Treatment of **15** with

Scheme 3. Aldol Reaction To Construct the Clovane Skeleton



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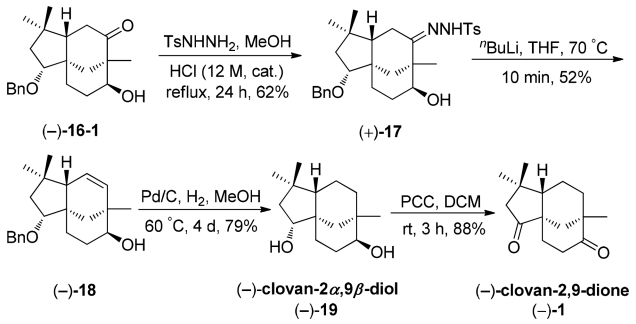
PCC converted this alcohol to an aldehyde, which was subjected to an aldol reaction to afford the desired cyclization product (−)-**16-1** and (−)-**16-2** with a diastereomeric ratio of about 4:1 (Scheme 3). The relative configurations of these two compounds were assigned on the basis of the X-ray structure of (±)-**20**, a derivative of (±)-**16-2** (see the Supporting Information). We also observed a side product (−)-**16-3** in 9% yield from the aldol reaction.

The carbonyl group in **16-1** could be converted to methylene by reduction of tosylhydrazone (Scheme 4).[15] Refluxing

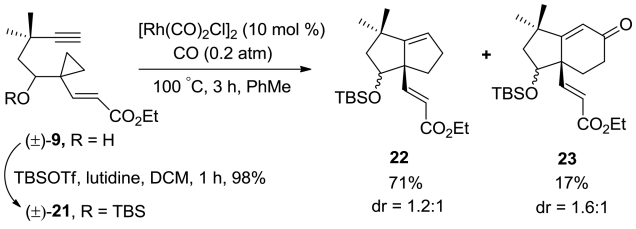
Scheme 4. Total Synthesis of (−)-Clovan-2,9-dione



(−)-**16-1** with $TsNHNH_2$ in methanol in the presence of HCl (12 M, aq) gave tosylhydrazone (+)-**17** in 62% yield. Shapiro reaction afforded (−)-**18** smoothly by using 6 equiv of *n*-BuLi at 70 °C.[16] Reduction of the double bond as well as deprotection of the Bn group afforded clovan-2*α*,9*β*-diol (−)-**19**. Finally, two hydroxyl groups in (−)-**19** were oxidized by PCC to generate the natural product (−)-clovan-2,9-dione (−)-**1** (Scheme 4). The characterizations of (−)-clovan-2,9-dione including ^1H NMR, ^{13}C NMR, HRMS, and optical rotation were consistent with Collado's and Sung's reports ($[\alpha]_D^{20} = -100.5$, $c = 0.63$ in $CHCl_3$; lit.[4h] $[\alpha]_D^{25} = -97.0$, $c = 0.01$ in $CHCl_3$; lit.[1c] $[\alpha]_D^{25} = -52$, $c = 0.08$ in $CHCl_3$), suggesting that the asymmetric total synthesis of (−)-clovan-2,9-dione was realized.

In our original plan for the total synthesis, TBS-protected compound (±)-**21** with *α*,*β*-unsaturated ester could be used to synthesize (±)-**23**, which could reach the key skeleton of the final product by Dieckmann condensation (Scheme 5). The

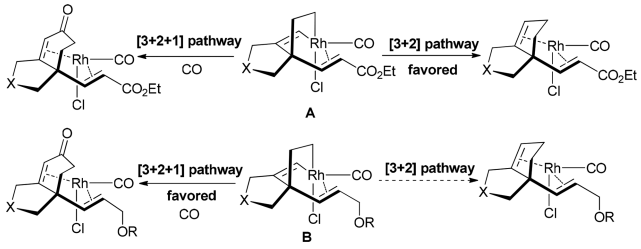
Scheme 5. Preparation of Substrate with Ester Group and Exploration of its [3 + 2 + 1] Reaction



hydroxyl group of (±)-**9** was protected by a TBS group using TBSOTf in the presence of 2,6-lutidine to give ester (±)-**21**. Under the conditions of [3 + 2 + 1] reaction, we found that the major product with the 5/5-fused structure arising from the [3 + 2] cycloaddition reaction[17,18] in 71% yield, and the desired [3 + 2 + 1] product was isolated in 17% yield. These results indicated that the [3 + 2] reaction was favored over the [3 + 2 + 1] reaction when a substrate with an ester-substituted VCP was used. Attempts to improve the yield of desired product were not successful (including changing the temperature, solvent, and pressure of CO). In addition, both [3 + 2] and [3 + 2 + 1] reactions gave lower diastereoselectivities, and their diastereomers could not be separated by column chromatography.

A rationale for 1-yne-VCP with an ester group favoring the [3 + 2] reaction while 1-yne-VCP with an alkyl group in the vinyl group favoring [3 + 2 + 1] reaction is provided in Scheme 6. The electron-withdrawing ester group (intermediate **A**,

Scheme 6. Rationale for the Competition of [3 + 2 + 1] and [3 + 2] Reactions



Scheme 6) makes the vinyl group electron deficient, leading to weak coordination of vinyl group to Rh center. Consequently, direct reductive elimination from **A** to [3 + 2] is favored. However, in intermediate **B** the vinyl group is electronically richer and has a stronger coordination to the Rh center, which disfavors the direct reductive elimination to give the [3 + 2] cycloadduct. Then CO coordination and insertion into intermediate **B** can take place, leading to the favored [3 + 2 + 1] reaction.

In conclusion, the first asymmetric total synthesis of (−)-clovan-2,9-dione has been accomplished starting from 3,3-dimethylpent-4-ynal **5** and 2,6-di-*tert*-butyl-4-methylphenyl cyclopropane carboxylate **6**. Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of 1-yne-VCP and CO and intramolecular aldol reaction were utilized as key steps. The present total synthesis merging [3 + 2 + 1] and aldol reactions provides a new way to synthesize clovane skeleton. Constructing 5/6 and 6/6 bicyclic systems with bridgehead quaternary centers in such a way would have great potential in the synthesis of other natural products and pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02656.

Experimental procedures, spectra for all new compounds, HPLC chromatograms, and X-ray crystallographic data for compound (±)-**20** (PDF)

X-ray data for compound (±)-**20** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yuzx@pku.edu.cn.

ORCID

Zhi-Xiang Yu: 0000-0003-0939-9727

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Paul A. Wender (Stanford University) on the occasion of his 70th birthday.

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