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Total Synthesis of Clovan-2,9-dione via [3 + 2 + 1] Cycloaddition and Hydroformylation/Aldol Reaction

Yi Zhou, Jun-Long Qin, Wenbo Xu, and Zhi-Xiang Yu*

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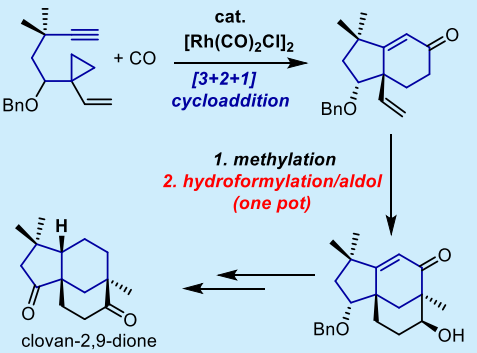
ABSTRACT: Here we report the total synthesis of clovan-2,9-dione via Rh-catalyzed [3 + 2 + 1] cycloaddition/hydroformylation/aldol reaction. The [3 + 2 + 1] reaction of 1-yne-vinylcyclopropane and CO was used for the generation of a 5/6 bicyclic skeleton with a bridgehead vinyl group. The hydroformylation reaction converted the congested olefin of the [3 + 2 + 1] cycloadduct to a one-carbon elongated aldehyde, which underwent in situ aldol reaction, with the carbonyl group in the [3 + 2 + 1] cycloadduct, to generate the tricyclic bridged-ring skeleton of the target molecule.



Clovane-type sesquiterpenes, including clovan-2,9-dione (**1**), clovene, and rumphellcolvanes B, D, E, have an intriguing tricyclic bridged-ring skeleton with three quaternary carbon centers (Figure 1). These natural products were mainly

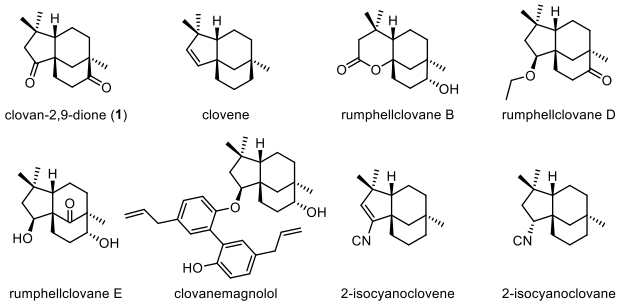


Figure 1. Selected clovane-type sesquiterpenes.

isolated from the gorgonian coral *Rumphella antipathies*.[1] Recently, two clovane-type sesquiterpenes, 2-isocyanoclovene and 2-isocyanoclovane (Figure 1), have been isolated from the Nudibranch *Phyllidia ocellata*.[2] These molecules have been the synthetic targets of chemists since the 1960s.[3] One reason for this is attributed to the diverse structures of these molecules that require chemists to design either creative strategies or reactions to conquer them. The other reason is that many of these molecules have attractive biological activities. For example, clovan-2,9-dione shows inhibitory effects on the human neutrophils,[1c] and clovanemagnolol significantly enhances the neurite outgrowth for embryonic cortical neurons at 0.01 μM,[4] while 2-isocyanoclovene and 2-isocyanoclovane are promising antimalarial lead compounds, with great bioactivities against *Plasmodium falciparum* (IC_{50} 0.26−0.30 μM).[2]

The reported strategies to construct the skeletons of clovane-type natural products can be divided into several catalogs according to the sequence of building the three rings in the molecules, as shown in Scheme 1.[3,5] As early as the last century, three different strategies, including A-AB-ABC, B-BC-ABC, C-BC-ABC, have been used to synthesize clovene, with Dieckmann condensation or aldol condensation as the key reactions.[3] Recently, Liu's group reported another strategy (B-AB-ABC) in the asymmetric synthesis of rumphelllcolvane E, using reductive aldol condensation as the key reaction.[5] For the total synthesis of clovan-2,9-dione, two different strategies have been reported. The first asymmetric total synthesis from our group[6] was achieved by using the Rh-catalyzed [3 + 2 + 1] reaction[7] to build the AB ring, followed by aldol reaction to finish the ABC skeleton. This strategy requires 17 steps to complete the asymmetric synthesis of the target molecule, while the racemic synthesis requires 15 steps when using a racemic alcohol. We once tried to shorten our synthesis by applying a Dieckmann condensation in the expected [3 + 2 + 1] product from substrate **I** with an ester in the vinyl position (Scheme 1e). Unfortunately, this substrate gave both [3 + 2] (major) and [3 + 2 + 1] (minor) products, preventing us from

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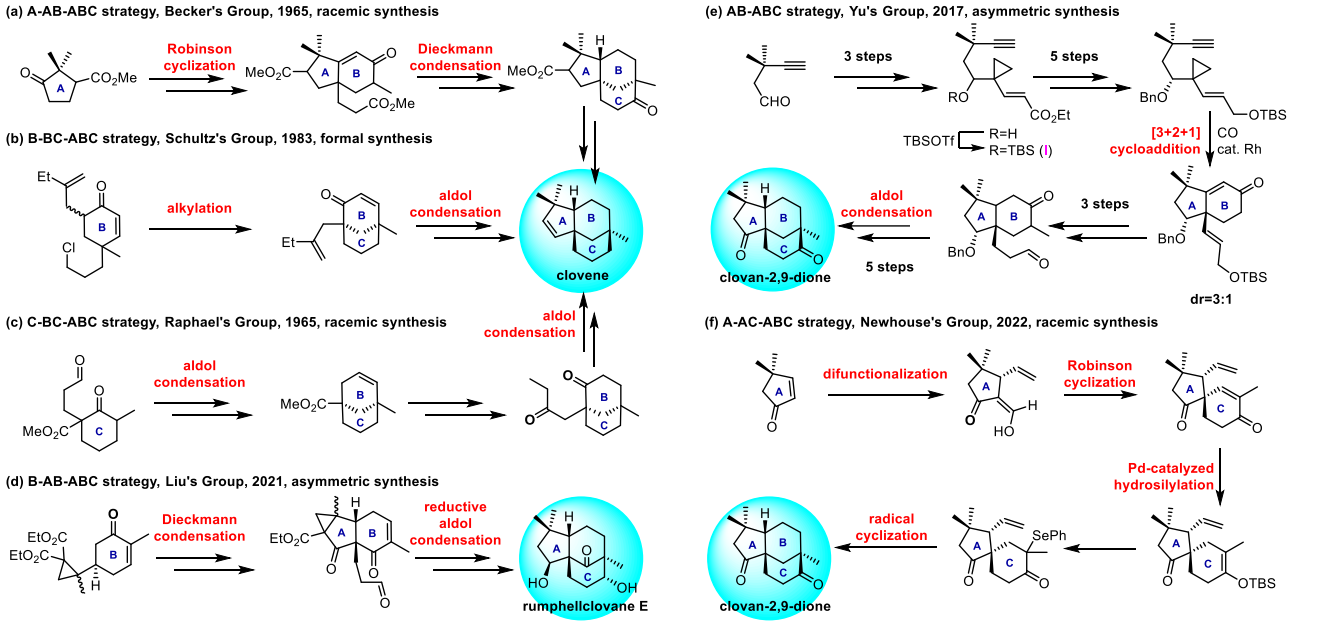
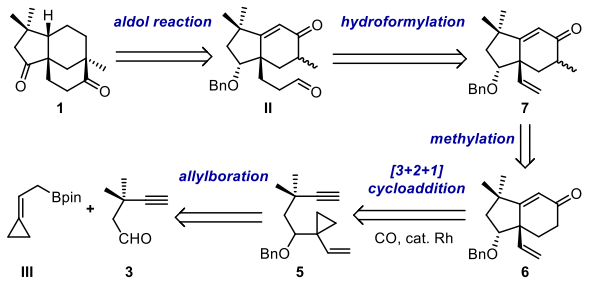
Scheme 1. Different Strategies in the Synthesis of Clovane-Type Natural Products



further executing this idea (Scheme 1e).[6] The second total synthesis was recently reported by Newhouse,[8] who started from the synthesis of the AC ring and then elegantly used radical cyclization to build the B ring (Scheme 1f). This route only requires 5 steps to achieve the racemic total synthesis of clovan-2,9-dione. To further advance the synthesis of clovane-type molecules, new strategies are in high demand. Here we report our second generation of the total synthesis of clovan-2,9-dione using a [3 + 2 + 1] cycloaddition/hydroformylation/aldol strategy (in 9 steps for racemic synthesis and 11 steps for its asymmetric version).

Scheme 2 describes the retrosynthetic analysis of clovan-2,9-dione via a [3 + 2 + 1]/hydroformylation/aldol strategy. This

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



was our initial design of accessing this molecule when we began our adventure in this field. In this design, the key reaction is hydroformylation,[9] converting the vinyl group in our [3 + 2 + 1] product to a one-carbon elongated aldehyde **II**, which then undergoes an intramolecular aldol reaction to give the key skeleton. This hydroformylation step had been tried by us under Rh catalysis, giving no desired product. This failure could be understood because the vinyl group in the [3 + 2 + 1] cycloadduct is linked to a bridgehead quaternary carbon center and is sterically hindered. On the other hand, the Rh-catalyzed hydroformylations using syngas are usually carried out under high pressure,[9] which further brought the inconvenience of testing this reaction in this strategy.

Fortunately, a Pd-catalyzed hydroformylation using $HCOOH/Ac_2O$ as the syngas surrogate (without using high pressure) was recently reported by Shi and co-workers.[10] We perceived that this reaction may help us realize our initial design, considering that multisubstituted and sterically congested alkenes are compatible for Shi's hydroformylation reaction. This reaction was also applied by Xu in the total synthesis of caldaphnidine J,[11] giving us more confidence to continue our previous journey of total synthesis. To further improve the efficiency of this second-generation synthesis, we replaced the previous route to the 1-yne-vinylcyclopropane substrate of the [3 + 2 + 1] reaction, by using the allylboration reaction (Scheme 2).[12]

Accordingly, we started our second-generation synthesis of clovan-2,9-dione (Scheme 3) from the common building block **2**[13] and the known compound **3**.[14] The allylboration of aldehyde **3** using allylboronate **III** generated in situ under Pd-catalyzed conditions gave alcohol (±)-**4** in 62% yield. This one-pot synthesis for the substrate of the [3 + 2 + 1] reaction is shorter than the previous 3-step route (Scheme 1e). Then, BnBr was used to protect the hydroxyl group as well as to increase the bulkiness of this substituent for stereochemistry induction in the [3 + 2 + 1] reaction. This step prepared the [3 + 2 + 1] substrate **5** in 86% yield. To our delight, the key Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of **5** and CO (with 5 mol % rhodium catalyst under 0.2 atm CO atmosphere at 100 °C) afforded *trans*-isomer *trans*-**6** and *cis*-isomer *cis*-**6** in 73% combined yield with a diastereomeric ratio of about 3.5:1, which is consistent with the stereochemistry model proposed previously.[6] Methylation of the major isomer *trans*-**6** under LDA/MeI/HMPA conditions gave diastereomers **7** in a combined 79% yield.

We then tested Shi's hydroformylation/aldol reaction. First, we applied their original reaction conditions (3.9 equiv HCOOH, 3.0 equiv Ac_2O, 20 mol % dppp with 10 mol % $Pd(OAc)_2$), finding that the desired product could be observed, but the substrate conversion was very low. To our delight, increasing the catalyst loading (20 mol %), the equivalents of HCOOH (6.5 equiv) and Ac_2O (5.0 equiv),[11]

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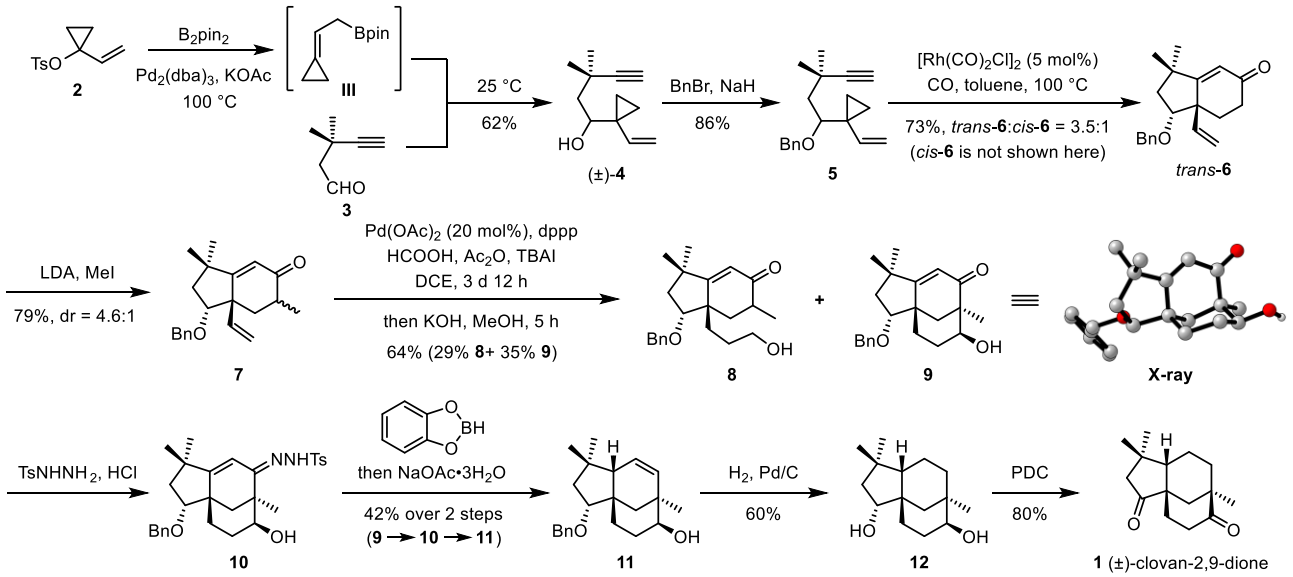
Scheme 3. Total Synthesis of Clovan-2,9-dione in a Racemic Version



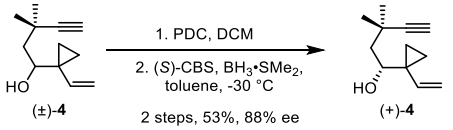
and the reaction time (see Supporting Information for the detailed conditions) can improve the reaction yield. In this case, four products, alcohol product **8**, aldol product **9**, in situ generated aldehyde **8′**, and esterification product **8″**, could be observed.[15] Therefore, we added KOH to the reaction system to help further the aldol reaction (converting aldehyde **8′** to **9**) and to hydrolyze ester **8″** to **8**. This two-step procedure (hydroformylation and adding base) gave two products: alcohol product **8** (in 29% isolated yield) and aldol product **9** (in 35% isolated yield). The desired 5/6/6 tricyclic aldol product **9** as a single diastereomer was confirmed by X-ray diffraction analysis. The alcohol product **8** from the reaction was proposed to be generated by the reduction of in situ generated aldehyde **8′** by $HCOOH/Pd(OAc)_2$ for a long reaction time.[16] This alcohol product **8** was also utilized for the synthesis of the target natural product through oxidation/aldol reaction, and in this case, cyclization product **9** and its diastereomer **9′** in 43% yield over 2 steps with a diastereomeric ratio of about 1:1.3 was realized (see Supporting Information for the experiments).

To complete the total synthesis, we carried out the following reactions. First, refluxing **9** with $TsNHNH_2$ in the presence of concentrated HCl generated tosylhydrazone **10**. Subsequent 1,2-reduction of the unsaturated hydrazone with catecholborane afforded **11** in 42% yield over 2 steps.[17] Then, reduction of the double bond and deprotection of the benzyl group in **11**, using $Pd/C/H_2$, provided diol **12**, which can be oxidized by PDC to deliver the natural product of clovan-2,9-dione **1**.

The second-generation total synthesis of clovan-2,9-dione can be changed to its asymmetric version if the enantiomerically enriched substrate was used, considering that the diastereoselectivity of this [3 + 2 + 1] cycloaddition was 3.5:1.[6] Therefore, we performed oxidation of (±)-**4** using PDC to obtain ketone, and then the (*S*)-CBS (Corey−Bakshi−Shibata) reduction gave the enantiomerically enriched substrate (+)-**4** in 88% ee (Scheme 4).[18]

In conclusion, the second-generation total synthesis of clovan-2,9-dione via the [3 + 2 + 1]/hydroformylation/aldol sequence was achieved in 9 steps in a racemic fashion. The asymmetric version can be also anticipated, with an additional two steps by converting the racemic substrate of the [3 + 2 + 1] reaction to an enantiomerically enriched substrate through oxidation and (*S*)-CBS reduction. The success of this synthesis is partially due to the concise synthesis of the [3 + 2 + 1] substrate using an allylboration reaction. The present strategy of the Rh-catalyzed [3 + 2 + 1] cycloaddition/hydroformylation/aldol reaction is very concise in building the key skeleton of the target natural product. Shi's hydroformylation of a congested olefin is also critical to the success of the present synthesis. We are continuing and encouraging more leading chemists to apply the [3 + 2 + 1] reaction for the synthesis of more cyclic natural products with bridgehead quaternary carbon centers. Synthesis of 2-isocyanoclovene and 2-isocyanoclovane[2] is our next goal in this direction.

Scheme 4. Preparing Enantiomerically Enriched [3 + 2 + 1] Substrate (+)-4



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02111.

Experimental procedures, characterization data, and crystallographic data for all new compounds (PDF)

Accession Codes

CCDC 2180760 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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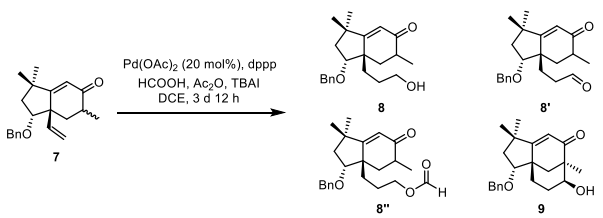
(15) The hydroformylation gave four products shown here. Detailed discussion can be found in the Supporting Information.



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(18) Other asymmetric conditions such as the Roush asymmetric allylation were also tested but gave no desired product or poor enantioselectivity. See Supporting Information for the detailed reaction conditions.

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