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

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Supporting Information

ABSTRACT: The asymmetric total synthesis of clovan-2,9-dione with a [6.3.1.01,5]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 rumphelclovanes A–E (Figure 1) belong to a novel class of clovane-type sesquiterpenes, isolated from the gorgonian coral Rumphella antipathies collected at the southern coast of Taiwan by Sung et al. These molecules with an intriguing tricyclic bridged-ring skeleton not only further enriched structural diversity and biological activities of marine sesquiterpenes 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. 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.

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-vinylcyclopropane (VCP) with CO. Substrate of the key reaction could be synthesized from simple known compounds.

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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 and ester 6 (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. 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 and also confirmed by synthesis of the target natural product, which had an optical rotation value consistent with literature reports. 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).

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

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 CH₂CH₂ moiety. We hypothesize that the allylic moiety is bulkier than the CH₂CH₂ 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 (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 H₂ in toluene/methanol, which was followed by deprotection of the TBS group, yielding alcohol 15 in 84% yield. Treatment of 15 with

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

Scheme 2. Synthesis of the Key Bicyclic Intermediate 13

Scheme 3. Aldol Reaction To Construct the Clovane Skeleton
PCC converted this alcohol to an aldehyde, which was subjected to an aldol reaction to afford the desired cyclization product \((-\text{16-1})\) and \((-\text{16-2})\) 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 \((-\text{20})\), a derivative of \((\pm)\text{-16-2}\) (see the Supporting Information). We also observed a side product \((-\text{16-3})\) in 9% yield from the aldol reaction.

The carbonyl group in \text{16-1} could be converted to methylene by reduction of tosylhydrazone (Scheme 4).15 Refluxing \text{(-16-1)} with \text{TaNHNH}_2 in methanol in the presence of HCl (12 M, aq) gave tosylhydrazone \((\pm)\text{-17}) in 62% yield. Shapiro reaction afforded \((-\text{18})\) smoothly by using 6 equiv of \text{n-BuLi} at 70 °C.16 Reduction of the double bond as well as deprotection of the \text{Bn} group afforded clovan-2,9-diol \((-\text{19})\). Finally, two hydroxyl groups in \((-\text{19})\) were oxidized by PCC to generate the natural product \((-\text{clovan-2,9-dione})\) (Scheme 4). The characterizations of \((-\text{clovan-2,9-dione})\) including \(^1H\) NMR, \(^{13}C\) NMR, HRMS, and optical rotation were consistent with Collado’s and Sung’s reports \([(\alpha)_D]^{20} = -100.5, c = 0.63 \text{in CHCl}_3\); lit.4b \((\alpha)_D^{25} = -97.0, c = 0.01 \text{in CHCl}_3\); lit.1c \((\alpha)_D^{25} = -52, c = 0.08 \text{in CHCl}_3\) and thus suggested the assumption that the asymmetric total synthesis of \((-\text{clovan-2,9-dione})\) was realized.

In our original plan for the total synthesis, TBS-protected compound \((-\text{21})\) with \(\alpha,\beta\)-unsaturated ester could be used to synthesize \((\pm)\text{-23})\), which could reach the key skeleton of the final product by Dieckmann condensation (Scheme 5). The hydroxyl group of \((\pm)\text{-9})\) was protected by a TBS group using TBSCl in the presence of 2,6-lutidine to give ester \((\pm)\text{-21})\). 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 reaction17,18 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) 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 \((-\text{clovan-2,9-dione})\) has been accomplished starting from 3,3-dimethylpent-4-ynal 5 and 2,6-di-tert-butyl-4-methylphenyl cyclopropane carboxylate 6. Rh(1)-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.or-glett.7b02656.

Experimental procedures, spectra for all new compounds, HPLC chromatograms, and X-ray crystallographic data for compound \((\pm)\text{-20}\) (PDF)

X-ray data for compound \((\pm)\text{-20}\) (CIF)

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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.

REFERENCES


