Type-II Pauson-Khand reaction of 1,8-enyne in the attempt of building 7/5 ring of (-)-caribenol A and DFT understanding

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ABSTRACT

An attempt to access the fused 7/5 ring of the highly biologically active terpenoid caribenol A by employing intramolecular Pauson-Khand reaction of 1,8-enyne gave bridged 8-5 ring, the type-II Pauson-Khand reaction product. DFT study has been carried out to elucidate this unexpected regioselectivity.

Keywords:
Terpenoids
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Synthetic study
Computational study

Caribenol A (1), a novel C₁₉ rearranged terpene, was isolated from the West Indian gorgonian octocoral Pseudopterogorgia elisabethae by Rodríguez and co-workers in 2007 [1]. Structurally, caribenol A has an unprecedented tetracyclic ring system carrying six stereocenters (two of which are quaternary carbon centers), and three all-cis methyl groups at the C1, C4 and C8 positions. In addition, it was found to have strong inhibitory activity against Mycobacterium tuberculosis (H₃₇Rv). Infection by this pathogenic bacterium usually causes tuberculosis, a disease that results in over three million deaths worldwide each year [2].

The prominent biological activities and intricate molecular architecture of 1 make it an attractive target for total synthesis [3–6]. To date, three total syntheses of 1 have been reported. In 2010, the group of Yang achieved the first total synthesis of caribenol A by using intramolecular Diels-Alder reaction and biomimetic oxidation as key steps [4]. In 2016, Luo and co-workers reported the total synthesis of caribenol A by employing a stereoselective Cope rearrangement promoted by gold catalysis [5]. In 2017, the group of Trauner also achieved the total synthesis of caribenol A through a late-stage oxidation of furan ring [6].

As part of our ongoing studies towards the concise and efficient synthesis of complex natural products, we were attracted by the intricate molecular architecture of caribenol A. Our retrosynthetic analysis is depicted in Scheme 1. We envisioned that caribenol A could be generated from tetracycle I through late-stage functional transformation. The key 7–5 ring system of 1 could be assembled by an intramolecular Pauson-Khand reaction of enyne II. The Pauson-Khand reaction is widely used in the synthesis of nature product due to its high efficiency on chemical bond formation, atom economy and good regioselectivity [7,8]. The enyne II could be obtained via substitution reaction of allyl chloride III, which could be prepared by Aldol condensation of the known ketone 2 with methacrolein. In turn, the known ketone 2 could be readily prepared from commercially available monoterpene R(-)-carvone through selective allylic chlorination [9].

Scheme 1. Initial retrosynthetic analysis of (-)-caribenol A (1).
As shown in Scheme 2, our synthesis commenced with the known compound 2. Owing to the steric hindrance of the iso-propenyl group [3b], the aldol condensation of 2 with methacrolein furnished alcohol 3 in 90% yield with single configuration at C6 and a pair of separable diastereomers at C5 in a satisfied stereoselectivity (7:1 d.r.). The alcohol 3 was then protected by using TBSCl and 2,6-lutidine to provide the hydroxy masked compound 4 in 98% yield. The Cul-catalyzed substitution reaction of TMS acetylene with allyl chloride 4 afforded the desired enyne 5 in 87% yield [10].

Considering that enyne 5 could serve as a potential cyclization precursor, Pauson-Khand reaction of 5 was firstly investigated (Scheme 2). Unfortunately, although subjecting 5 to Co2(CO)8 in toluene would generate the corresponding Co2(CO)8 complex, which would go back to 5 after heating or treated with excess N-methylmorpholine oxide (NMO). The TMS-deprotected compound 6 was then prepared by treatment 5 with K2CO3. However, Pauson-Khand reaction of enyne 6 gave the same result, which might be due to the far distance between alkene and alkyne impeded the insertion of alkene to cobalt alkyne complex. Other metal catalysts and reaction conditions were also examined, however, all of them failed to give the desired product. We speculated that the distance between alkene and alkyne might become closer after the formation of lactone owing to the conformational restriction. Thus, the construction of lactone was then pursued.

Conjugated reduction of α,β-unsaturated ketone 5 with L-selectride in –78 °C generated the corresponding lithium enolate, which was subsequently converted to the enol triflate 9 in 85% yield by addition of Comins reagent (Scheme 3). Selective removal of the O-TBS in 9 was then investigated. After several trials, we found that treatment of 9 with hydrogen fluoride-pyridine in THF successfully gave the desired alcohol 10. The intramolecular carboxylation-lactone formation smoothly took place in the presence of Pd(OAc)2 and dppe to furnish the bicyclic lactone 11 in 50% yield [11]. Deisolation of 11 with K2CO3 in methanol provided the key Pauson-Khand precursor 12 in 65% yield.

With the key cyclization precursor 12 in hand, we proceeded to strategically construct the 7–5 ring system. Under the classic Pauson-Khand reaction condition (Co2(CO)8, toluene, 110 °C) [12], a single product was obtained in 54% yield. To our surprise, although the mass spectrum of the product revealed the same result with our design compound 14, the NMR data of the product looked pretty confused. The 1H NMR spectrum of the product showed a signal of β-enone proton instead of α-enone proton (δ = 7.06 vs 6.30–6.47). Fortunately, this compound provided crystal for analysis by X-ray crystallography. The result obtained from this determination was quite amazing: the Pauson-Khand reaction afforded a [5.2.1] bicyclooctane bridged ring product 13! Here we call this as the type-II intramolecular Pauson-Khand reaction due to formation of bridged 8/5 ring product. The widely used Pauson-Khand reaction to build fused 6/5 or 7/5 ring is named type-I Pauson-Khand reaction.

Then, we performed DFT (B3LYP) calculations to understand the unusual regioselectivity of the PK reaction of enyne 12 (Figure 1). According to the previous computational studies [13], the regioselectivity of the PK reaction was plausibly controlled by the rate-determining alkene insertion step. We computed the two reaction pathways (type-I and type-II Pauson-Khand reactions) leading to the experimentally observed cycloadduct 13 and the anticipated product 14, respectively (see Supporting Information for more details). First, ligand displacement of CO in alkene–dicobalt complex A by the alkene moiety results in the generation of two isomers B and D. After that, intermediate B may undergo alkene insertion into the C(distal)–Co bond via transition state TS1 (the overall Gibbs energy of activation for this pathway is 32.7 kcal/mol). The resulting cobaltalicyclic C then proceeds through CO insertion and reductive elimination to furnish α-substituted cyclopentenone 13 (type-II Pauson-Khand pathway).

Alternatively, intermediate D may undergo a similar reaction pathway to form β-substituted cyclopentenone 14, in which the rate-determining step is the alkene insertion into the C(proximal)–Co bond via TS2 (the overall Gibbs energy of activation is 39.9 kcal/mol). This pathway is expected to give the traditional type-I Pauson-Khand product. Our DFT calculations suggested that formation of cycloadduct 13 is the final product because type-I pathway is disfavored by 7.2 kcal/mol compared to type-II pathway, which is in good accordance with our experimental observations.

Previous DFT calculations from several groups found that, the intramolecular PK reactions of terminal aliphatic alkyynes favored the formation of α-substituted cyclopentenones in view of both steric and electronic effects (Figure 2) [14]. In the intramolecular PK reactions, for 1,6- and 1,7- enynes, the ring strains overrode the steric and electronic effects so that the type-I PK reactions took place in most cases (Figure 3). In contrast, for 1,8- enynes such as 12, the ring strains were not so severe. Therefore, the type-II PK reactions were favored, leading to the generation of α-substituted cyclopentenone 13 [15]. The above calculations confirmed these.

In summary, the work reported herein describes our synthetic studies toward ¬(−)-caribenol A by using intramolecular type-I Pauson-Khand reaction. We got an unexpected cyclization product, the
type-II Pauson-Khand product. DFT study has been carried out to explain the observed regioselectivity. We proposed that for 1,8-enynes, the ring strain is small and the electronic effect and steric effect favor the type-II Pauson-Khand reaction, whereas for 1,6- and 1,7-enynes, ring strains make them prefer type-I Pauson-Khand reaction. Currently, we are adjusting the precursor structure of Pauson-Khand reaction to force the reaction to undergo through exo-exo orientation as we designed. We will report on this and other aspects of this work in due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151001.

References

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Figure 1. Gibbs energy profile for the regioselective PK reaction. Computed at the B3LYP/6-311+G(d) (SDD for Co)/B3LYP/6-31G(d)(LANL2DZ for Co) level.

Figure 2. Selectivities for intermolecular PK reaction of terminal aliphatic alkynes.

Figure 3. Selectivities for intramolecular PK reaction of terminal enynes.