Tetrahedron Letters 60 (2019) 151001

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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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ARTICLE INFO

Article history:
Received 30 March 2019
Revised 25 July 2019
Accepted 31 July 2019
Available online 2 August 2019

Keywords:
Terpenoids
Type-II Pauson-Khand reaction
Synthetic study
Computational study

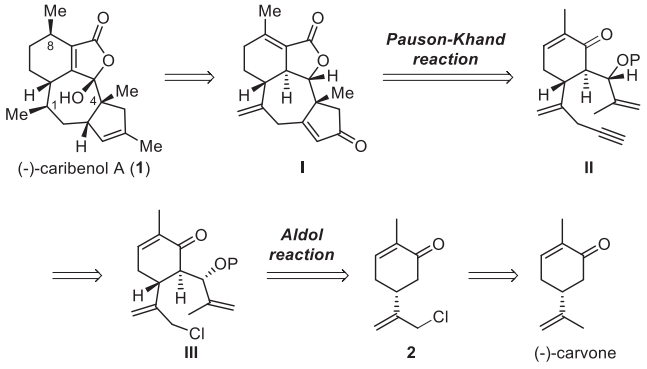
ABSTRACT

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.

Caribenol A (**1**), a novel C_{19} 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 ($H_{37}Rv$). 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 choride **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**).

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https://doi.org/10.1016/j.tetlet.2019.151001
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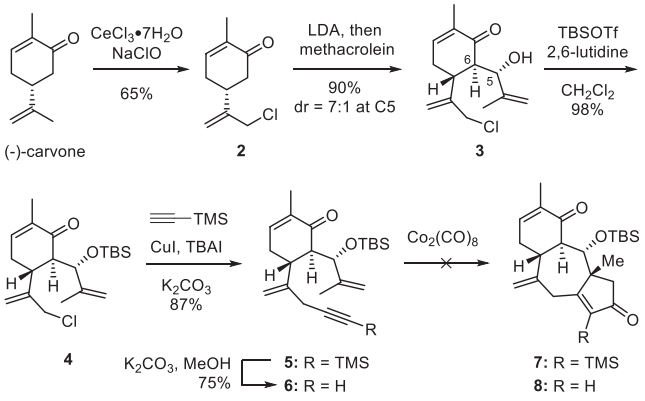
As shown in Scheme 2, our synthesis commenced with the known compound **2**. Owing to the steric hindrance of the isopropenyl group [3b], the aldol condensation of **2** with methacrolein furnished alcohol **3** in 90% yield with single configuration at C6 and a pair of separable diastereomers at C5 in a satisfied stereselectivity (7:1 d.r). The alcohol **3** was then protected by using TBSOTf and 2,6-lutidine to provide the hydroxy masked compound **4** in 98% yield. The CuI-catalyzed substitution reaction of TMS acetylene with allyl chloride **4** afforded the desired enyne **5** in 87% yield [10].

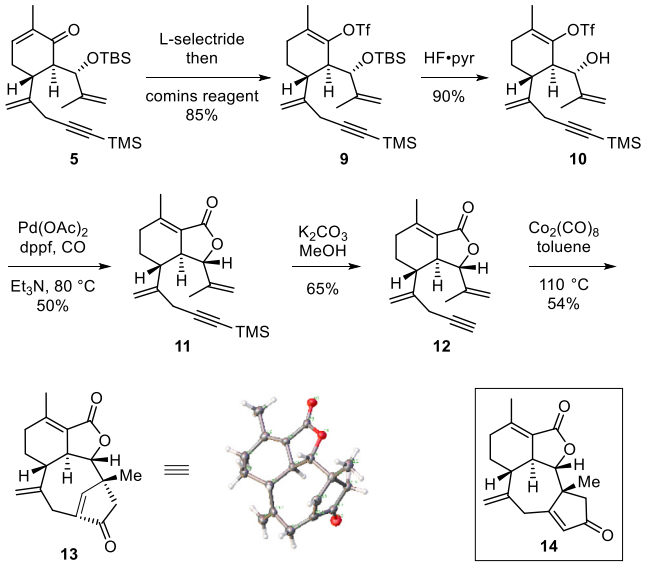
Considering that enyne **5** could serve as a potential cyclization precursor, Pauson-Khand reaction of **5** was firstly investigated (Scheme 2). Unfortunately, although subjecting **5** to $Co_2(CO)_8$ in toluene would generate the corresponding $Co_2(CO)_6$ complex, which would go back to **5** after heating or treated with excess *N*-methylmorpholine oxide (NMO). The TMS-deprotected compound **6** was then prepared by treatment **5** with K_2CO_3. 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 carbonylation-lactone formation smoothly took place in the presence of $Pd(OAc)_2$ and dppf to furnish the bicyclic lactone **11** in 50% yield [11]. Desilylation of **11** with K_2CO_3 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 ($Co_2(CO)_8$, 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 ($\delta = 7.06$ 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



Scheme 2. Synthesis of compounds **5** and **6**.



Scheme 3. Synthesis of compound **13**.

due to formation of bridged 8/5 ring product. The widely used Pauson-Khnad 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 alkyne–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 cobaltacycle **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 intermolecular PK reactions of terminal aliphatic alkynes 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

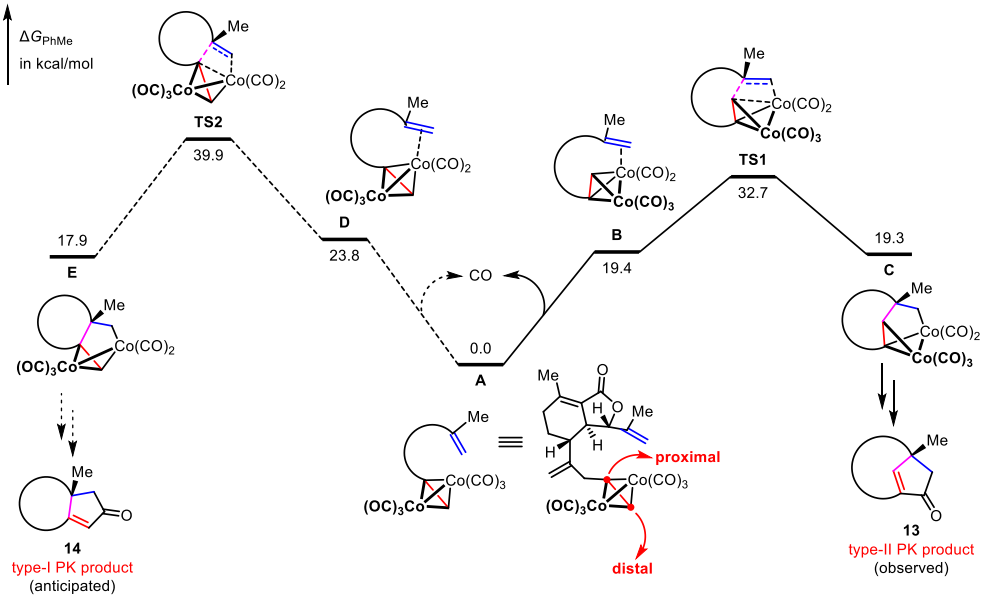


Figure 1. Gibbs energy profile for the regioselective PK reaction. Computed at the B3LYP/6-311+G(d) (SDD for Co)//B3LYP/6-31G(d)(LANL2DZ for Co) level.

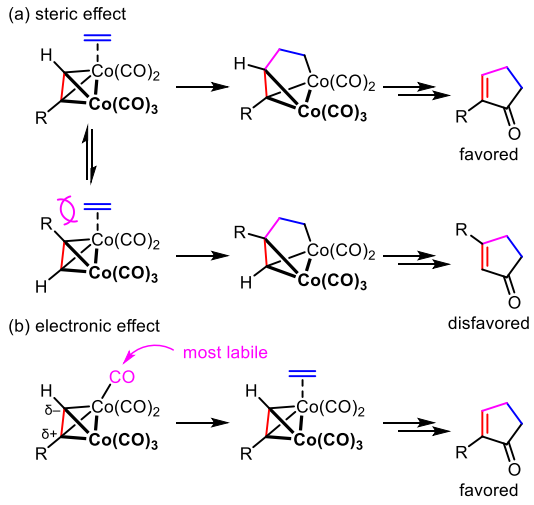


Figure 2. Selectivities for intermolecular PK reaction of terminal aliphatic alkynes.

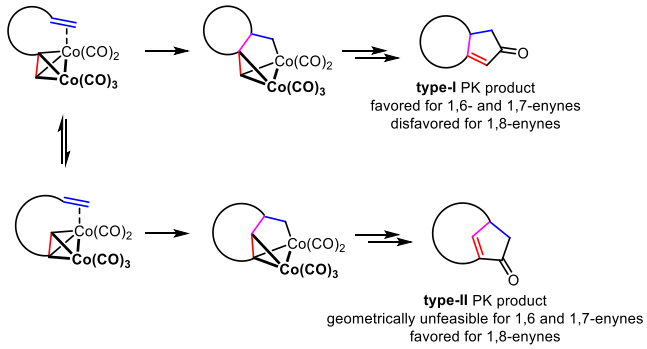


Figure 3. Selectivities for intramolecular PK reaction of terminal enynes.

type-II Pauson-Khand product. DFT study has been carried out to explain the observed regioselectivity. We proposed that for 1,8-eneynes, 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-eneynes, ring stains 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.

Acknowledgments

We are grateful for the generous financial support by the National Natural Science Foundation of China (Nos. 21871013 and 21572008).

Appendix A. Supplementary data

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

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