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FACILE SYNTHESIS OF [5.n.1.0^{1,5}] TRICYCLES MEDIATED BY INTRAMOLECULAR PAUSON-KHAND REACTION OF 3-ALKYNYL-1-ALKYLIDENECYCLIC COMPOUNDS

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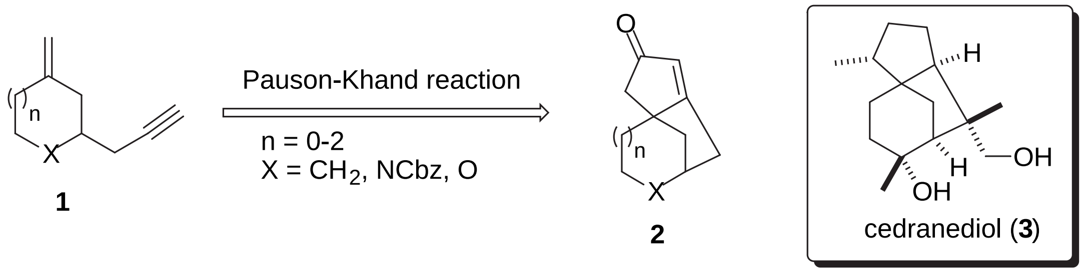
Abstract – Intramolecular Pauson-Khand reaction of various 3-alkynyl-1-alkylidenecyclic compounds gave corresponding [5.n.1.0^{1,5}] tricyclic compounds (n = 2-4). Facile construction of core structure for total synthesis of cedrene-type terpenoid, cedranediol, was also investigated.

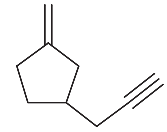
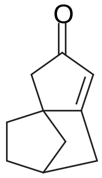
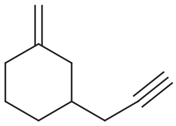
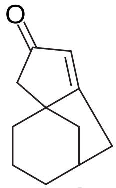
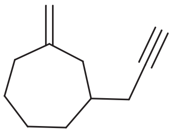
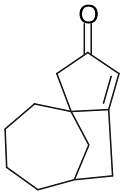
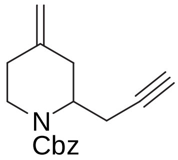
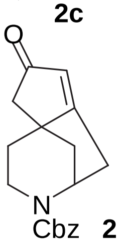
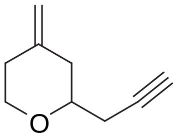
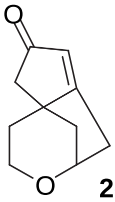
In this decade, Pauson-Khand reaction[1] has much attention for construction of cyclopentenone structures including natural product synthesis.[2] In our continuing studies on Pauson-Khand reaction of *exo*-cyclic enynes,[3] we wish to report facile synthesis of [5.n.1.0^{1,5}] tricyclic compounds (n = 2-4) by intramolecular Pauson-Khand reaction of various 3-alkynyl-1-alkylidenecyclic compounds (Scheme 1) and its application to construct functionalized core structure of oxygenated cedrane derivative, cedranediol (**3**).[4,5]



Scheme 1

At first, various 3-alkynyl-*exo*-1-cycloalkenes (**1a-e**)[6,7] were synthesized and examined intramolecular Pauson-Khand reaction by standard methods (refluxing in toluene or oxidative treatment with *N*-methylmorpholine *N*-oxide[8] at room temperature). The results are shown in Table 1. The reaction of methylenecyclo-hexane (**1b**) and –heptane (**1c**) gave corresponding tricyclic compounds (**2b**,**c**) in moderate to good yield. However, with methylenecylopentane (**1a**), although starting material was consumed, isolated yield of **2a** was quite low. The result would be due to highly strained tricyclic system

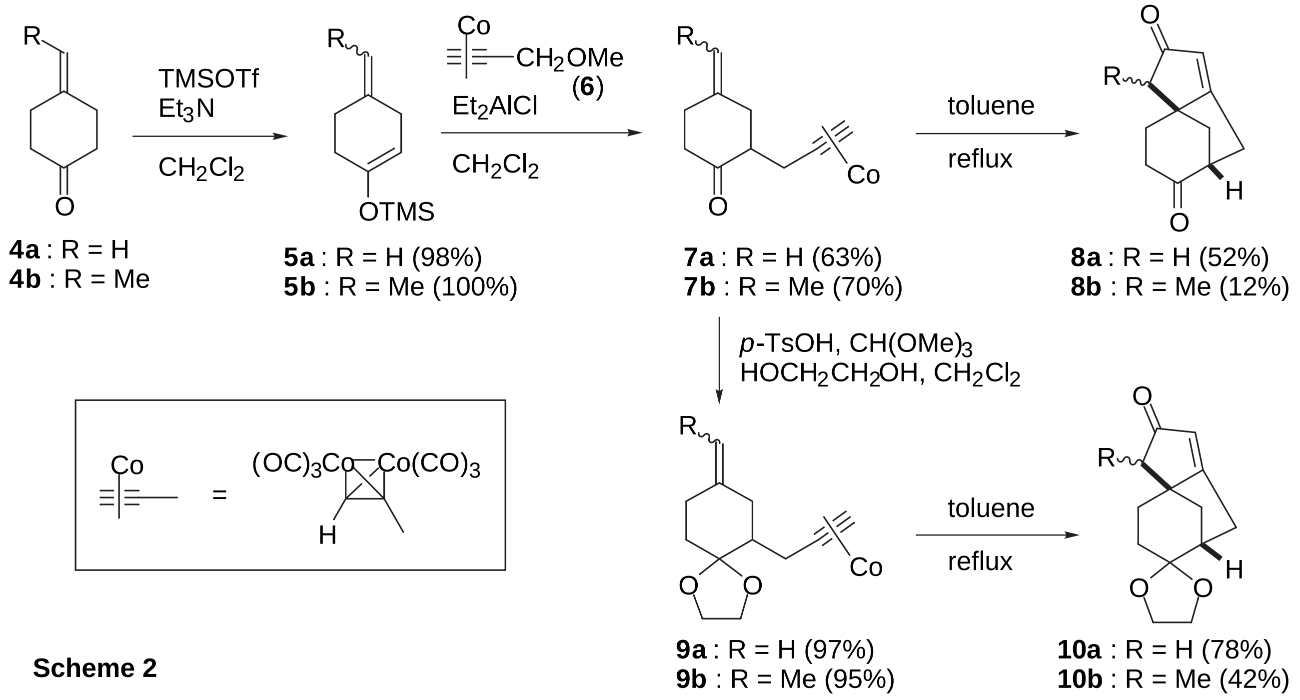
Table 1. Intramolecular Pauson-Khand reaction of various *exo*-cyclic enynes (**2a**-**e**).[a]

Entry	Substrate	Additive[b]	Solvent	Temp.	Time (h)	Product	Yield (%)
1	 **1a**	-	toluene	reflux	4	 **2a**	4
2		NMO	CH_2Cl_2	rt	2		13
3	 **1b**	-	toluene	reflux	10	 **2b**	73
4		NMO	CH_2Cl_2	rt	2		57
5	 **1c**	-	toluene	reflux	3	 **2c**	55
6		NMO	CH_2Cl_2	rt	2		21
7	 **1d**	-	toluene	reflux	5	 **2d**	54
8		NMO	CH_2Cl_2	rt	2		47
9	 **1e**	-	toluene	reflux	5	 **2e**	14
10		NMO	CH_2Cl_2	rt	2		10

a) The reaction was carried out using **1** (0.3-0.5 mmol) with 1.1 equivalent of $Co_2(CO)_8$.
b) Nine (for **1a-c**) or twelve (for **1d,e**) equivalents of NMO was used.

in **2a**. The reaction of aza derivative (**1d**) afforded tricyclic compound (**2d**) in moderate yield. Contrary to other 6-membered enynes (**1b**,**d**), similar reaction of enyne (**1e**) attached to pyran ring resulted in formation of intractable mixtures, so that **1e** gave **2e** in low yield. It was found that generally the reaction in boiling toluene except for **1a** was superior to oxidative condition using NMO.

Next, we turned our attention to Pauson-Khand reaction of methylenecyclohexanones, because facile access to functionalized core structure of cedranediol (**3**), which is one of naturally occurring oxygenated cedrene-type terpenoids, could be expected. To synthesize Pauson-Khand precursor bearing carbonyl group, we adopted Nicholas reaction[9] reported by Schreiber,[10] in which direct synthesis of Pauson-Khand furnishes alkyne-cobalt complex (**7a**,**b**)[6,12] in moderate yields. The reaction of **7a** in boiling toluene afforded expected [5.3.1.0^{1,5}] tricyclic compound (**8a**)[6] in 52% yield, whereas similar reaction of **7b** afforded **8b**[6]



Scheme 2

(76 : 24 diastereomeric mixture)[13] in only 12% yield. This findings suggested to be attributable to the carbonyl group in **7a**,**b**, because Pauson *et al.* have reported that similar reaction of acetal substrate gave the tricycle in high yield.[5] Therefore, conversion of the carbonyl group in **7a,b** to acetal group[14] might proceed in a transition state through favored conformation by reactive rotamer effect[15] (Figure 1) to increase the yield of tricyclic products. As expected, the reaction of enyne (**9a**)[6] gave **10a** in 78% yield. Also, yield of **10b**[6] (74 : 26 diastereomeric mixture)[13] from **9b**[6] was improved to 42%.

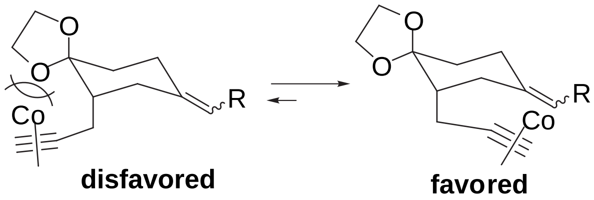


Figure 1

In conclusion, we have investigated intramolecular Pauson-Khand reaction of various 3-alkynyl-1-alkylidenecyclic derivatives to give corresponding $[5.n.1.0^{1,5}]$ tricyclic compounds (n = 2-4). Straightforward synthesis of alkyne-cobalt complex using Schreiber's method and subsequent Pauson-Khand reaction offered facile access to functionalized core structure of cedranediol.

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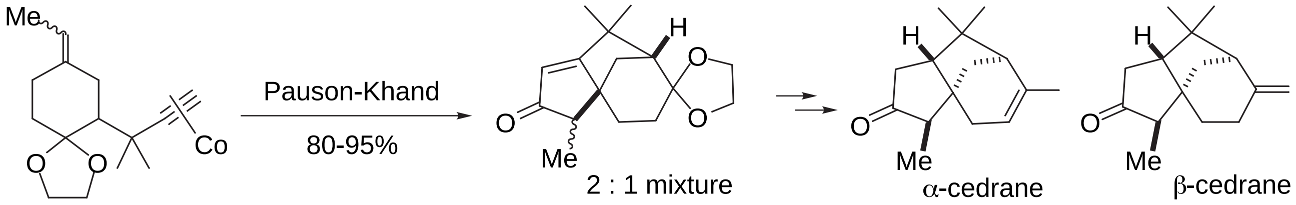
5. During development of this work, formal total synthesis of α- and β-cedrenes by Pauson-Khand reaction of *exo*-cyclic enyne was reported; W. J. Kerr, M. McLaughlin, A. J. Morrison, and P. L. Pauson, *Org. Lett.*, 2001, **3**, 2945.



6. All new compounds gave satisfactory ^{1}H-NMR, IR, and MS spectral data.

7. Enynes (**1a-e**) were obtained by Wittig olefination of the corresponding ketones.[16]

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11. The silyl enol ether (**5b**) was obtained a mixture of regioisomers (68 : 32).

12. The alkyne-cobalt complex (**7b**,**8b**) were obtained as a mixture of regioisomers. Ratio of each complex was estimated by ^{1}H-NMR spectral analysis after decomplexation with $Ce(NH_4)_2(NO_3)_6$ (57 : 43 for **7b** and 58 : 42 for **8b**).

13. The ratio was determined by ^{1}H-NMR spectral analysis. Stereochemistry of each product could not be established at this stage and will be reported in due course.

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