A Convenient Synthesis of Polycyclic γ-Lactams *via* Pauson-Khand Reaction

Seok Won Kang, Yong Hoon Kim, Hea Jeong Kim, Joo Hee Lee, and Sung Hoon Kim*

Department of Chemistry, Konkuk University, Seoul 143-701, Korea *E-mail: shkim@konkuk.ac.kr*
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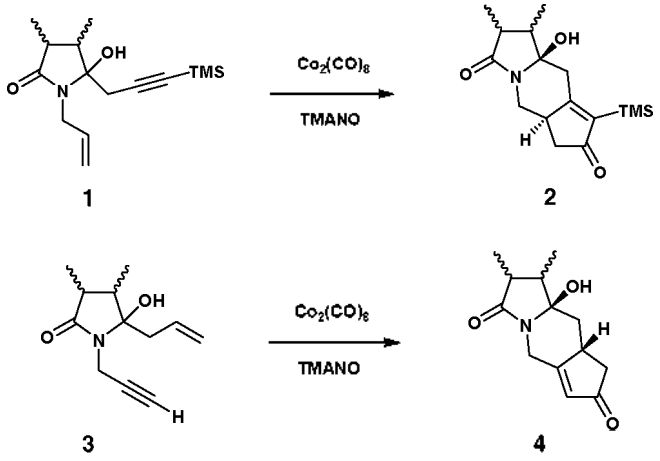
Pauson-Khand reaction of hydroxyenynes with $Co_2(CO)_8$ in the presence of *N*-methylmorpholine *N*-oxide or trimethylamine *N*-oxide as a promoter produced polycyclic γ-lactams as single stereoisomers in moderate to excellent yield. These are the first examples of an intramolecular Pauson-Khand reaction on a hydroxyenyne system tethered to a three- and four-membered ring as new skeletons with 5,6,5 fused ring systems.

Key Words: Polycyclic γ-lactams, Pauson-Khand reaction, 5,6,5 Fused ring systems, $Co_2(CO)_8$

Introduction

The nitrogen-containing heterocycles undoubtedly are fundamental to organic chemistry, especially common substructures found widely in biologically active materials.[1] They are of broad interest in the areas of pharmaceutical and natural product synthesis.[2] Accordingly, a variety of synthetic methodologies involving these heterocycles have been developed in recent years.[3-9] There still exists, however, a need for more efficient procedures for the synthesis of complex aza-polycyclic ring systems. Transition metal chemistry facilitates the combination of unsaturated functional groups in ways that are difficult or impossible to accomplish using conventional synthetic methods. The Pauson-Khand reaction (PKR), the intramolecular cyclization of enynes mediated by $Co_2(CO)_8$, ranks among the best methods to increase molecular complexity in a single synthetic step.[10] PKR involving [2+2+1] cycloaddition of an alkene, alkyne and CO to generate cyclopentenones is of significant synthetic utility.[11] With this in mind, we report here the Pauson-Khand cyclization of hydroxyenynes **1** and **3** to yield tricyclic γ-lactams **2** and **4** as single stereoisomers (Scheme 1). Tricyclic and tetracyclic lactam derivatives have been known to possess many interesting biological activities.[12] We previously reported the cyclization of *N*-allyl 5-allyl-5-hydroxylactams, using RCM to construct tetrahydroindolizinone derivatives.[13] In the present paper, we give an account of our efforts dealing with this unique skeleton.

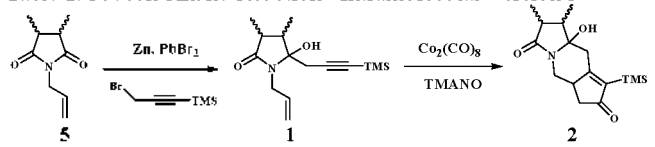


Scheme 1.

Results and Discussion

For the synthesis of hydroxyenyne **1**, *N*-allyl cyclic imides **5**, which were readily obtained from succinimide, phthalimide, maleic anhydride, and tartaric anhydride as starting

Table 1. Pauson-Khand Reaction : Intramolecular Version I



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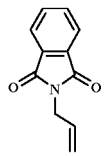
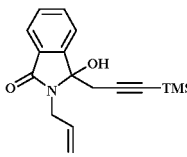
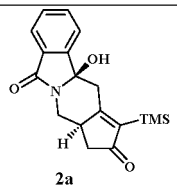
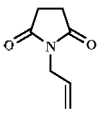
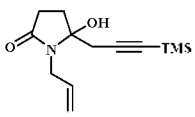
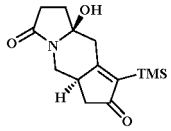
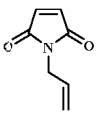
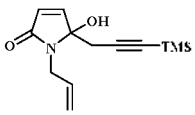
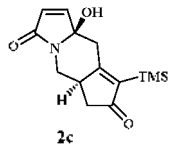
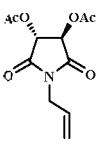
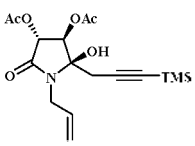
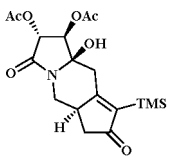
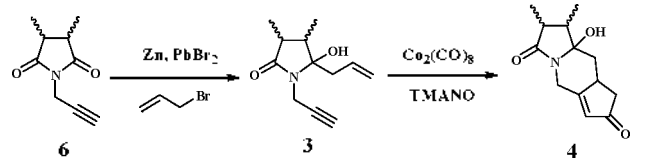
1	 5a	 1a	90	 2a	98
2	 5b	 1b	91	 2b	94
3	 5c	 1c	74	 2c	90
4	 5d	 1d	45	 2d	95

Table 2. Pauson-Khand Reaction : Intramolecular Version II



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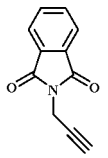
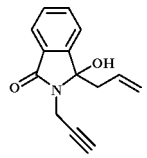
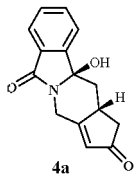
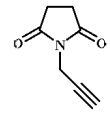
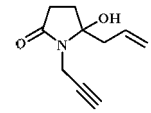
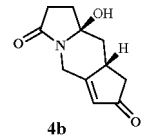
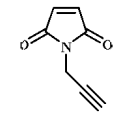
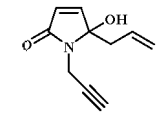
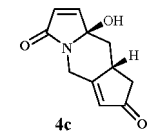
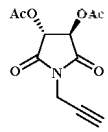
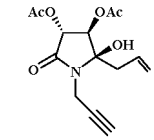
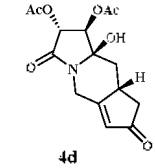
1	 6a	 3a	98	 4a	98
2	 6b	 3b	87	 4b	92
3	 6c	 3c	80	 4c	74
4	 6d	 3d	52	 4d	71

materials.[13] We reported previously that the zinc-mediated Barbier-type propargylation of cyclic imides in the presence of a catalytic amount of $PbBr_2$ proceeded very efficiently.[14] In the reactions of trimethylsilylpropargyl bromide with *N*-allyl cyclic imides **5**, homopropargylic alcohols **1** were obtained as single products without allenic products.

The reactions of propargyl bromide with *N*-allyl cyclic imides **5** were not clean, as expected. About 20 ~ 23% of allenic products were observed from the ^{1}H NMR of the crude products.[15]

The resulting hydroxyenynes **1** were transformed into the corresponding fused polycyclic systems **2** in excellent yields, using the intramolecular version of PKR. Cyclization products, **2a-c**, were obtained in almost quantitative yield as racemates. Product **2d**, which was synthesized from the *R*-configuration of **1d**, was obtained as optically pure product. $[\alpha]_D^{25}$ = - 46 (c = 1.5, CH_2Cl_2). The results are summarized in Table 1.

Similar to the synthesis of hydroxyenyne **1** and *N*-allyl cyclic imides **5**, the hydroxyenyne **3** and *N*-propargyl cyclic imides **6** were readily obtained from succinimide, phthalimide, maleic anhydride, and tartaric anhydride.[16] Also, we reported that the zinc-mediated Barbier-type allylation of cyclic imides in the presence of a catalytic amount of $PbBr_2$ proceeds very efficiently.[17] The results are summarized in Table 2.

Two major milestones in the Pauson-Khand reaction are the carbon monoxide free protocol, using stoichiometric $Co_2(CO)_8$, and cleavage of the resulting $Co_2(CO)_6$-alkyne complex, using a promoter such as *N*-methylmorpholine *N*-oxide (NMO) or trimethylamine *N*-oxide (TMANO). Treatment with TMANO gave effectively the desired tricyclic compounds, **2a-d** and **4a-d**. Compounds **2a-d** and **4a-b** were obtained in almost quantitative yield by filtration of the metal residue through Celite.[18] Better yields of tricyclic **2** and **4** were obtained when TMANO was used instead of NMO. The hydroxylactams **2** and **4** could also serve as a potentially valuable synthetic intermediate for the synthesis of certain natural products containing an azapolycyclic system to access new compounds with 5,6,5 fused ring systems. To the best of our knowledge, PKR has not been used for the synthesis of 5,6,5 tricyclic compounds **2** and **4**, using hydroxyenyne **1** as starting material.

A single diastereomer of the final product was produced in all cases. The structures of tricyclic compounds **2** and **4** were assigned from one- and two-dimensional correlation spectroscopy. The stereochemical assignments of **2d** and **4d** were carried out using nuclear Overhauser effect spectroscopy or NOESY as illustrated in Figure 1.

In the **2d** case, irradiation of the hydroxyl hydrogen led to a 9.68% increment in the H2 signal and no increment in the H1 signal. And irradiation of the H_α at C4 led to a 9.84% increment in the H4*a* signal, indicating that **2d** possesses *R*-configuration at 4*a* position.

In the **4d** case, irradiation of the hydroxyl hydrogen led to a 12.29% increment in the H2 signal and no increment in the H1 signal. And irradiation of H7*a* led to a 2.48% increment in H2 signal, 4.77% increment in H8 β and 5.09% increment in H7β indicating that **4d** possesses *R*-configuration at 7*a* position.

The doublet signal of **2d** at 4.234 ppm (^4J = 1.6 Hz) indicates the presence of a known W coupling between OH hydrogen and $H8_\alpha$. We carried out a homodecoupling experiment, which eliminates coupling selectively. On the irradiation of $H8_\alpha$, the OH doublet is transformed to a singlet. A similar result was observed for cyclization products **4d** (4.234 ppm, ^4J = 2.0 Hz) which indicates that W coupling between OH hydrogen and $H8_\alpha$.

These results could be characteristic of the geometric arrange

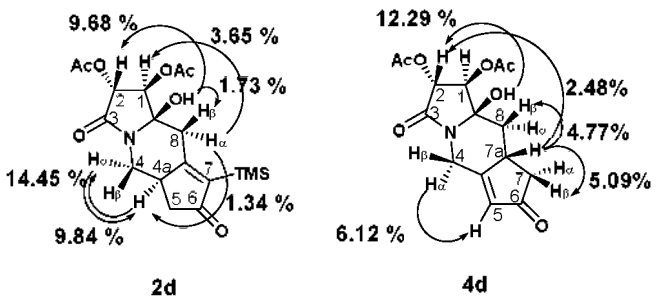


Figure 1. Nuclear Overhauser effect of **2d** and **4d**.

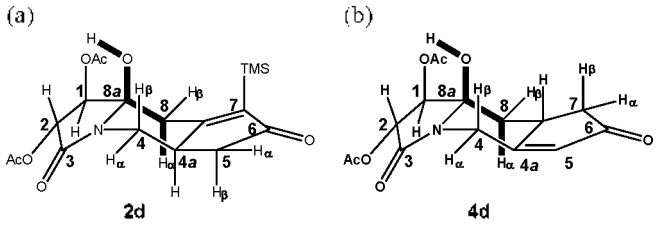


Figure 2. Suggested geometrical arrangement for **2d** and **4d**.

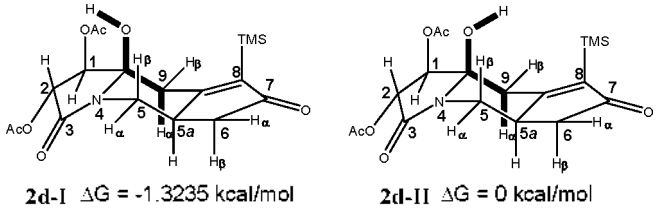


Figure 3. Suggested geometrical arrangement for **2d** and **4d**.

ments in which H-O-C8*a*-C8-H8$_\alpha$ present a well-known W conformation (Figure 2).

Conformation study of these compounds was carried out to confirm the results. The initial global energy minima for possible conformations (I, II) were obtained using CAChe program[19] using PM3. Each minimized structure was optimized with the hybrid density functional B3LYP with 6-311 + G(2d, p) basis set, which is available in the Gaussian 03 program.[20] According to the results of free energy calculations, structure **2d-I** with W conformation is 1.3235 kcal/mol more stable than **2d-II**. The equilibrium constant K*eq* at 298 K was calculated to be 9.3 for the preference of conformer **2d-I** to **2d-II** (Figure 3).

In the **4d** case, a similar result was obtained. Conformer with W conformation is 2.147 kcal/mol more stable than the other less stable conformer. The equilibrium constant K*eq* at 298 K was calculated to be 36.9.

Conclusion

We have synthesised polycyclic γ-lactams, using an intramolecular Pauson-Khand reaction on hydroxyenyne. The stereochemical assignment of cyclization products was carried out using nuclear Overhauser effect spectroscopy and homodecoupling experiments. We have confirmed the conformation of cyclization products, using Gaussian 03 program. This synthetic approach is a short and highly efficient method to construct new skeletons with 5.6.5 fused ring systems. The methodology described here is potentially applicability to the synthesis of complex natural and non-natural compounds because of the presence of the double bond, carbonyl group and hydroxyl group, which are available for further functionalization. We anticipate that this unexplored class of compounds will possess interesting biological properties.

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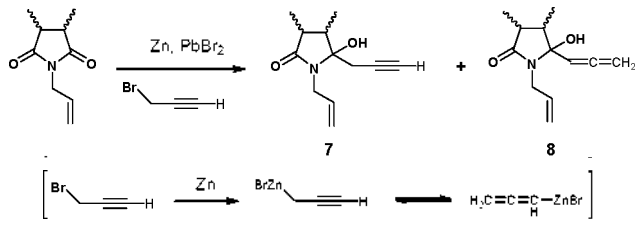
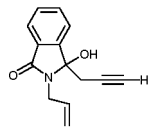
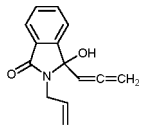
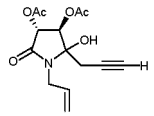
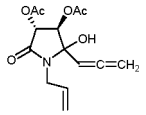
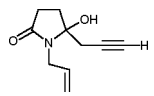
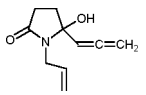
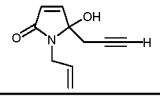
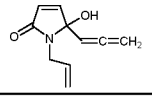
15. Reaction of propargylic zinc reagent.



entry	hydroxyenyne	allene **8**	allene(%)	yield(%)
a			37	72
b			29.4	42
c			28.5	54
d			23.2	85

16. (a) Marson, C. M.; Khan, A.; Porter, R. A. *J. Org. Chem.* **2001**, *66*, 4771. (b) Butler, D. N.; Shang, M.; Warrener, R. N. *Tetrahedron Lett.* **2000**, *41*, 5985.
17. Kang, S. W.; Heo, E. Y.; Jun, J. G.; Kim, S. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1924.
18. A representative procedure for the preparation of polycyclic γ-lactams **2** and **4** from hydroxyenynes **1** and **3**. (a) Compound **2a** : Solid $Co_2(CO)_8$ (0.82 g, 1.2 eq.) was added to a solution of hydroxyenynes **1a** (0.60 g, 2 mmol) in anhydrous CH_2Cl_2 (25 mL) under argon. The dark solution thus obtained was stirred at room temperature until complete complex formation by TLC (ca. 4 h). The resulting solution of $Co_2(CO)_6$-alkyne complex was cooled to 5 °C, then anhydrous TMANO (0.30g, 2.0 eq.) was added. The reaction flask was open to the air and warmed to room temperature by immediate removal of the ice bath. After 30 min, the reaction mixture was cooled to 5 °C, another portion of TMANO (0.30g, 2.0 eq.) was added, and the solution was warmed again to room temperature by immediate removal of the ice bath. This sequence was repeated until a total of 6.0 eq. (0.90 g) of anhydrous TMANO was added. The reaction mixture was stirred for 2 h at room temperature, and then the crude mixture was filtered through a short path of Celite. The solvent was removed and the residue was purified *via* silica gel chromatography eluting with 70% EtOAc / hexanes to afford 0.64g of polycyclic γ-lactams **2a** in 98% yield as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 0.31 (s, 9H), 2.00 ~ 2.06 (dd, *J* = 18.6 Hz and 2.5 Hz, 1H), 2.24 ~ 2.27 (dd, *J* = 13.6 Hz and 2.3 Hz, 1H), 2.45 ~ 2.51 (dd, *J* = 18.6 Hz and 7 Hz, 1H), 2.54 ~ 2.68 (m, 1H), 2.74 ~ 2.80 (t, *J* = 11.5 Hz, 1H), 3.70 ~ 3.73 (d, *J* = 13.6 Hz, 1H), 3.82 ~ 3.83 (d, *J* = 2.3 Hz, 1H, -OH), 4.30 ~ 4.33 (dd, *J* = 11.6 Hz and 6.5 Hz, 1H), 7.38 ~ 7.61 (m, 4H), ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 211.8, 181.9, 165.4, 147.6, 142.6, 133.0, 130.4, 130.1, 123.9, 121.8, 88.0, 41.9, 41.8, 41.3, 39.5, 0.0. (b) Compound **2d** : $[\alpha]^{25}_D$ = -46 (c = 1.5, CH_2Cl_2), ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 0.23 (s, 9H), 2.02 ~ 2.07 (dd, *J* = 18.6 Hz and 2.5 Hz, 1H), 2.18 ~ 2.23 (d, *J* = 13.6 Hz, 6H), 2.46 ~ 2.49 (dd, *J* = 13.6 Hz and 1.6 Hz, 1H), 2.46 ~ 2.54 (dd, *J* = 18.6 Hz and 7 Hz, 1H), 2.70 ~ 2.80 (m, 1H), 2.85 ~ 2.81 (t, *J* = 11.5 Hz, 1H), 3.13 ~ 3.16 (d, *J* = 13.6 Hz, 1H), 3.92 (d, *J* = 1.6 Hz, 1H, -OH), 4.33 ~ 4.38 (dd, *J* = 12.5 Hz and 6.5 Hz, 1H), 5.09 ~ 5.10 (d, *J* = 4.5 Hz, 1H), 5.29 ~ 5.30 (d, *J* = 4.5 Hz, 1H), ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 210.9, 180.7, 171.3, 171.1, 165.0, 143.4, 88.1, 80.6, 75.6, 43.2, 41.2, 39.2, 37.5, 21.0, 20.9, -0.16. (c) Compound **4a** : ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 1.21 ~ 1.28 (td, *J* = 13.1 Hz and 2.7 Hz, 1H), 1.92 ~ 1.98 (dd, *J* = 18.6 Hz and 3 Hz, 1H), 2.65 ~ 2.72 (dd, *J* = 18.6 Hz and 6.5 Hz, 1H), 2.79 ~ 2.83 (dd, *J* = 13.1 Hz and 5.5 Hz, 1H), 3.52 ~ 3.60 (m, 1H), 3.85 ~ 3.89 (d, *J* = 15.6 Hz, 1H), 4.39 ~ 4.40 (d, *J* = 2.7 Hz, 1H, -OH), 4.86 ~ 4.90 (d, *J* = 15.6 Hz, 1H), 5.97 (s, 1H), 7.37 ~ 7.66 (m, 4H) ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 207.7, 173.1, 165.7, 147.4, 133.1, 130.3, 130.2, 128.8, 123.8, 122.0, 87.1, 42.1, 41.5, 38.7, 36.0. (d) Compound **4d** : ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 1.45 ~ 1.52 (td, *J* = 13.1 Hz and 2 Hz, 1H), 2.03 ~ 2.09 (dd, *J* = 18.6 Hz and 3 Hz, 1H), 2.18 (s, 3H), 2.20 (s, 3H), 2.23 ~ 2.27 (dd, *J* = 13.1 Hz and 5 Hz, 1H), 2.67 ~ 2.74 (dd, *J* = 18.6 Hz and 6.5 Hz, 1H), 3.49 ~ 3.52 (m, 1H), 4.03 ~ 4.07 (d, *J* = 15.6 Hz, 1H), 4.34 ~ 4.35 (d, *J* = 2 Hz, 1H, -OH), 4.86 ~ 4.87 (d, *J* = 3.5 Hz, 1H), 4.89 ~ 4.93 (d, *J* = 15.6 Hz, 1H), 5.34 ~ 5.36 (d, *J* = 4.5 Hz, 1H), 6.05 (s, 1H), ^{13}C-NMR (100 MHz, $CDCl_3$) : δ 207.1, 171.8, 171.4, 170.8, 165.6, 129.5, 87.5, 80.1, 76.5, 41.5, 39.9, 38.3, 35.7, 21.1, 21.0.
19. *CAChe*, Work System Pro Version 5.02; Fujitsu Ltd., Oxford Molecular Group Inc.: 2000-2002.
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