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Tandem Intramolecular Nicholas and Pauson–Khand Reactions for the Synthesis of Tricyclic Oxygen-Containing Heterocycles

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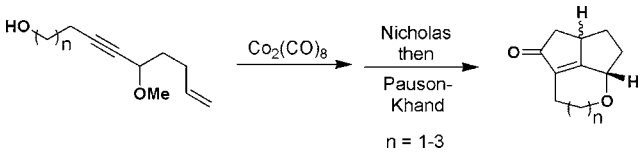
ABSTRACT



Simple acyclic enynes can be easily converted into tricyclic ethers upon treatment with $Co_2(CO)_8$ followed by Nicholas and Pauson–Khand reactions. Tricyclic [5,8,5]- and [5,7,5]-systems can be prepared in high overall yields in only seven synthetic steps.

The Nicholas and Pauson−Khand reactions are among the most important transformations that incorporate cobalt-complexed alkynes.[1] The Nicholas reaction enables nucleophilic substitution of propargyl alcohols, ethers, and esters, usually with carbon nucleophiles.[2] The Pauson−Khand reaction furnishes cyclopentenones upon combination of alkenes and cobalt-complexed alkynes either inter- or intramolecularly.[3]

Although both transformations incorporate dicobalt hexacarbonyl complexed alkynes, surprisingly little is known about sequential combinations of these two reactions. Several groups have studied intermolecular Nicholas reactions followed by intramolecular Pauson−Khand reactions to yield bicyclic products;[4] however, only Schreiber has investigated a transformation that involves both intramolecular Nicholas and Pauson−Khand reactions to furnish a tricyclic ring system.[5] This was the first report of a successful endocyclic intramolecular Nicholas cyclization to yield a cobalt-complexed cyclic alkyne.[6] Using knowledge gained from this pioneering model study, Schreiber then applied the strategy in a total synthesis of epoxydictymene.[7] It is important to note that the Nicholas reactions in these studies involved use of allylsilane nucleophiles to furnish carbocyclic rings.

The goal of our research is to expand the scope of the tandem intramolecular Nicholas/Pauson−Khand strategy to include the synthesis of a variety of tricyclic heterocycles. We plan to study the use of heteroatom nucleophiles in the endocyclic Nicholas reaction, and we envision producing several differently sized tricyclic ring systems. Our current investigation demonstrates that this strategy is a powerful method for quickly accessing complex [5,8,5]- and [5,7,5]-tricyclic ethers that are otherwise not easily available.

(1) For a review of cobalt mediated cyclizations, see: Fletcher, A. J.; Christie, D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657.

(2) For reviews, see: (a) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Kidlington, 1995; Vol. 12, p 685.

(3) For reviews, see: (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (b) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Kidlington, 1995; Vol. 12, p 703.

(4) (a) Jeong, N.; Yoo, S.; Lee, S. J.; Lee, S. H.; Chung, Y. K. *Tetrahedron Lett.* **1991**, *32*, 2137. (b) Smit, W. A.; Buhanjuk, S. M.; Simonyan, S. O.; Shashkov, A. S.; Struchkov, Y. T.; Yanovsky, A. I.; Caple, R.; Gybin, A. S.; Anderson, L. G.; Whiteford, J. A. *Tetrahedron Lett.* **1991**, *32*, 2105.

(5) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

(6) For a review of recent syntheses of cyclic cobalt-complexed alkynes, see: Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809.

(7) (a) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353. (b) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5505.

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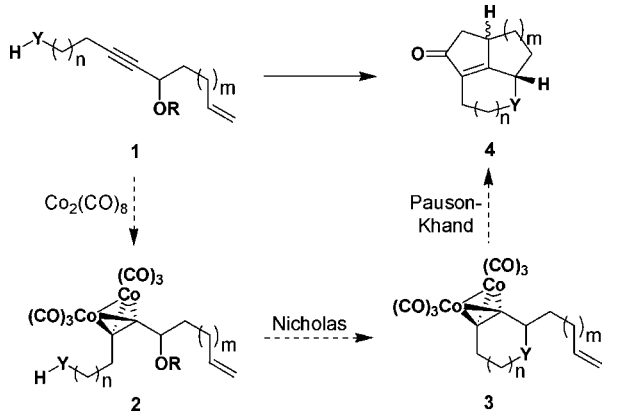
Our general synthetic outline for this study is presented in Scheme 1. We plan to convert enyne **1** into tricyclic heterocycle **4** by way of a three-step sequence involving a cobalt complexation (to provide **2**), a Nicholas reaction (to furnish **3**), and a Pauson−Khand reaction. This route should enable the conversion of a relatively simple starting material (**1**) into a complex tricyclic heterocycle containing two stereogenic centers (**4**). One key advantage of this strategy is that it should provide Pauson−Khand products such as **4** without the formation of a true cyclic alkyne. Most standard syntheses of **4** via the Pauson−Khand reaction would require a cyclic alkyne synthetic intermediate that would be challenging or impossible to synthesize. Cobalt-complexed cyclic alkynes such as **3** are much easier to prepare[8] and should perform well in the key Pauson−Khand step.

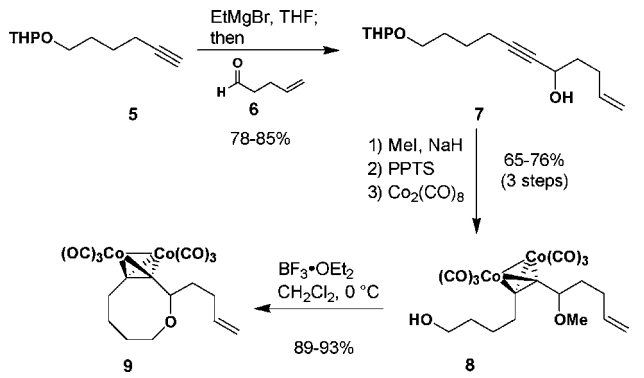
Scheme 1



To begin our investigation, we decided to focus on the synthesis of cyclic ethers (Y = O in Scheme 1), keeping the distance between the alkyne and alkene constant ($m = 1$) and varying the length of the connecting chain between the nucleophile and the alkyne ($n = 1-3$). Use of alcohol nucleophiles in intramolecular endocyclic Nicholas reactions is well-precedented from Isobe's studies toward the synthesis of ciguatoxin.[9] Furthermore, intramolecular Pauson−Khand reactions proceed most efficiently when synthesizing bicyclic 5,5-systems.[3]

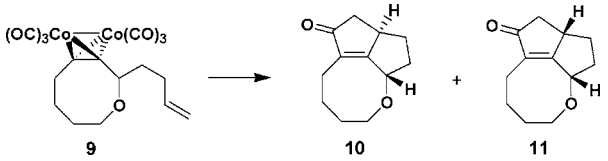
For our initial target, we focused on the synthesis of the [5,8,5]-tricyclic ether (**4**, Y = O, $m = 1$, $n = 3$). Synthesis of the key cobalt-complexed cyclic alkyne **9** proceeded uneventfully as outlined in Scheme 2. The requisite alkyne starting material **5**[10] was deprotonated with ethylmagnesium bromide and then combined with 4-pentenal (**6**) to furnish the desired addition product **7**. This alcohol was subsequently converted into a methyl ether using methyl iodide and sodium hydride, the THP protecting group was removed upon exposure to pyridinium *p*-toluenesulfonate,[11] and the alkyne reacted with dicobalt octacarbonyl to afford the Nicholas reaction precursor **8**. Treatment of this cobalt-complexed alkyne with boron trifluoride diethyl etherate induced ionization of the methyl ether[12] to yield a cobalt-stabilized cation that reacted with the internal alcohol nucleophile to furnish cyclic ether **9** in 89−93% yield.

Scheme 2



Pauson−Khand reactions on cobalt−alkyne complex **9** successfully yielded the desired tricyclic ethers (**10** and **11**); the results for these reactions are summarized in Table 1.

Table 1. Pauson−Khand Reactions To Form [5,8,5]-Tricycles



entry	conditions	yield of **10** + **11** (%)	ratio of **10**:**11**
1	CH_3CN, Δ	86	55:45
2	NMO	60	88:12
3	$CyNH_2$, Δ	55	74:26
4	*i*PrSMe, Δ	50	86:14
5	PhSMe, Δ	25	89:11

Compounds **10** and **11** are available in good to excellent yields under a variety of conditions. Refluxing acetonitrile in air[7] provided the target molecules in 86% yield but with little selectivity. Treatment of **9** with *N*-methylmorpholine-*N*-oxide (NMO) in dichloromethane[13] proved selective (88:12 ratio of **10**:**11**) and furnished the products in good overall

(8) For a review of cyclic alkynes, see: Gleiter, R.; Merger, R. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: New York, 1995; p 285.

(9) Takai, S.; Sawada, N.; Isobe, M. *J. Org. Chem.* **2003**, *68*, 3225 and references therein.

(10) Synthesized in one step from the commercially available alcohol according to Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6291.

(11) Lee, Y. B.; Folk, J. E. *Bioorg. Med. Chem.* **1998**, *6*, 253.

(12) An alcohol and a benzyl ether were also investigated for use as the ionizable propargyl groups; however, the methyl ether was the easiest to handle and could be made most efficiently.

(13) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

yield. Use of promoters such as cyclohexylamine in refluxing dimethoxyethane[14] and isopropyl methyl sulfide or thioanisole in refluxing dichloroethylene[15] afforded the target tricycles in varying yields and selectivities.

The major isomer of the Pauson−Khand reaction was unambiguously identified as trans isomer **10** by difference NOE experiments (see Figure 1). Although we were unable to chromatographically separate diastereomers **10** and **11**, the product mixture from the NMO reaction was sufficiently enriched in the major isomer that NMR analysis proved straightforward.

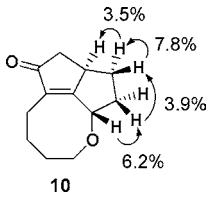
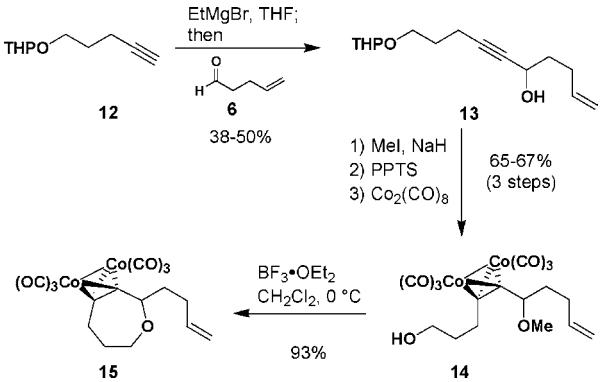


Figure 1. Difference NOE results for tricycle **10** (only most relevant enhancements shown for clarity).

Our initial case proved the validity of our synthetic strategy. We prepared complex oxygen-containing tricycles in seven steps from commercially available starting materials in 39−46% overall yield. Our next goal was to investigate the synthesis of a differently sized ring system, and we chose to pursue the synthesis of the [5,7,5]-tricyclic ether target.

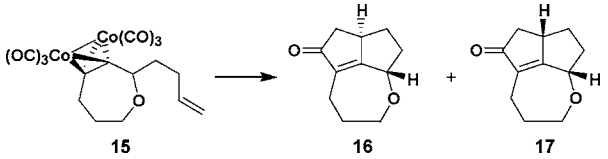
The synthesis is analogous to the [5,8,5]-tricycle and is outlined in Scheme 3. Using the same steps already described in Scheme 2 we were able to prepare cyclic ether **15** in five steps from alkyne **12** in 22−31% overall yield.

Scheme 3



Pauson−Khand reactions of **15** provided easy access to the target [5,7,5]-tricycles **16** and **17** as outlined in Table 2. In this case, promotion of the reaction with cyclohexylamine provided the best yield (91%) of the desired products. Use of NMO again afforded the best ratio of trans:cis products; however, it was much less selective than in the [5,8,5]-system. Interestingly, in entries 1 and 2 the cis diastereomer was the major product. Similarly to Figure 1, we were able to use difference NOE experiments to determine the structures of the two isomers formed in this reaction.

Table 2. Pauson−Khand Reactions To Form [5,7,5]-Tricycles



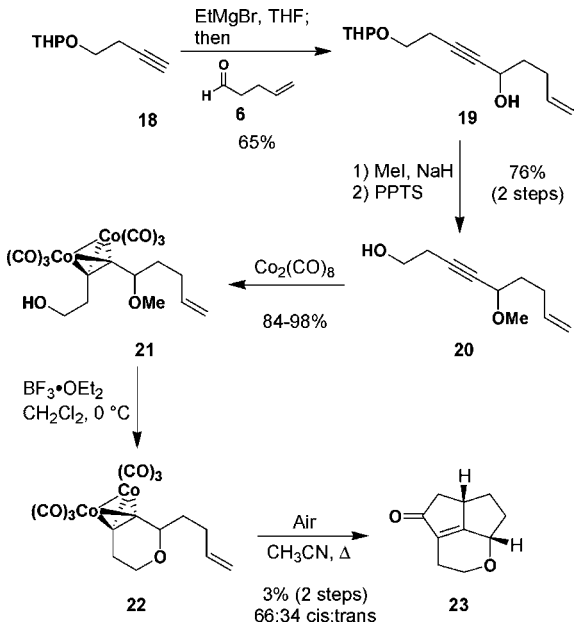
entry	conditions	yield of **16** + **17** (%)	ratio of **16**:**17**
1	$CyNH_2$, Δ	91	42:58
2	CH_3CN, Δ	63	37:63
3	NMO	30	72:28
4	*i*-PrSMe, Δ	29	67:33

The diastereoselectivities of Pauson−Khand reactions often vary with the use of different promoters; however, it is unusual to see a complete reversal in selectivity between the major and minor isomers (e.g., entries 2 and 3 in Table 2).[3] We are intrigued by these results and hope that further study of compound **15** and related systems will help us develop a more sophisticated mechanistic understanding of the role the promoter plays in these intramolecular reactions.

Having proven that we could efficiently produce both the [5,8,5]- and [5,7,5]-tricyclic ethers, we next turned our attention to production of the [5,6,5]-system. Following the general strategy already described, we were able to obtain the target tricyclic cyclopentenone **23**[16] albeit in disappointing overall yield. Production of the key cobalt-complexed alkyne **21** proceeded smoothly; however, both the Nicholas reaction to yield cyclic ether **22** and the Pauson−Khand reaction to furnish tricycle **23** were very inefficient transformations. Intramolecular Nicholas reactions to form cyclic ethers are thermodynamically controlled processes;[17] however, exposure of **21** to temperatures greater than 0 °C caused decomposition of both the starting material and the desired product. Furthermore, an efficient synthesis of cobalt-complexed cyclic alkynes in rings smaller than seven members is an ongoing synthetic challenge.[6] The disappointing yield in the Pauson−Khand step is presumably due to the strain inherent in this tricyclic system.

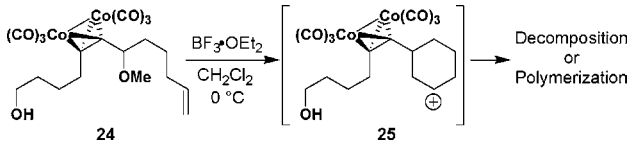
(14) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801.
(15) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771.
(16) Both diastereomers were obtained; cis was the major product in a 64:36 ratio.
(17) (a) Liu, T.-Z.; Li, J.-M.; Isobe, M. *Tetrahedron* **2000**, *56*, 10209. (b) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509.

Scheme 4



We obtained an interesting result when we attempted to prepare an eight-membered ring cyclic ether that would lead to formation of the [6,8,5]-tricyclic system. The starting material synthesis was identical to that described in Scheme 2 except that 5-hexenal[18] was used in place of 4-pentenal (**6**), thus inserting an extra methylene group between the alkene and alkyne. Attempted Nicholas reaction of cobalt−alkyne complex **24** yielded only a trace of the desired eight-membered ring cyclic ether product. Instead, we believe the cobalt-stabilized cation preferentially undergoes an exocyclic Nicholas reaction with the alkene acting as a nucleophile to generate carbocation **25** (or the corresponding 5-exo cyclization product).[19] This unstabilized carbocation leads to a complex mixture of uncharacterizable products either by decomposition or polymerization. We hope to confirm this hypothesis by incorporating a substituent on the alkene that will stabilize the resulting carbocation.

Scheme 5



In summary, we have developed a strategy for the rapid construction of tricyclic oxygen-containing heterocycles using a sequential combination of the Nicholas and Pauson−Khand reactions. Thus, we can transform simple acyclic enynes into complex tricyclic enones in a rapid and efficient manner. Studies are currently underway in our group to extend this method to the production of tricyclic amines and lactones via use of amines and carboxylic acids as nucleophiles in the Nicholas reaction.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Tetrahedron* **1994**, *50*, 11665.

(19) In an unrelated system containing two alcohol nucleophiles, Isobe observed a similar result in which 5-exo is favored over 7-endo cyclization; see: Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37.