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Asymmetric Synthesis of Bicyclo[4.3.0]nonan-8-ones by Intramolecular Pauson-Khand Reaction

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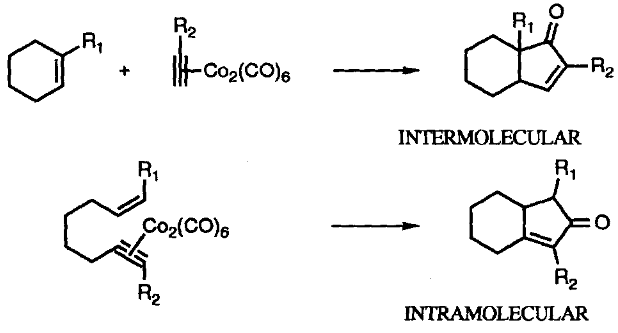
Abstract: *The intramolecular Pauson-Khand reaction of (E)-1-alkoxy-1-octen-7-ynes derived from (1S,2R)-2-phenylcyclohexanol is described. 7-Alkoxybicyclo[4.3.0]non-1(9)-en-8-ones are obtained in yields up to 65% and with diastereoselectivities higher than 10:1. The absolute configuration of the major diastereomer obtained has been ascertained and can be rationalized on the basis of the preferential conformation of the precursor.*

Since its discovery 20 years ago,[1] the cobalt-induced Pauson-Khand reaction has become one of the most powerful methods for cyclopentenone synthesis,[2] and has been widely used for the preparation of both natural and non-natural products containing five-membered carbocycles. The construction of the bicyclo[4.3.0]nonane ring system by means of the Pauson-Khand reaction can be achieved in principle either in an intermolecular way (by reaction of a cyclohexene derivative with an alkyne dicobalt hexacarbonyl complex) or intramolecularly, through the bicyclization of the corresponding complex derived from an 1-octen-7-yne (Scheme 1).

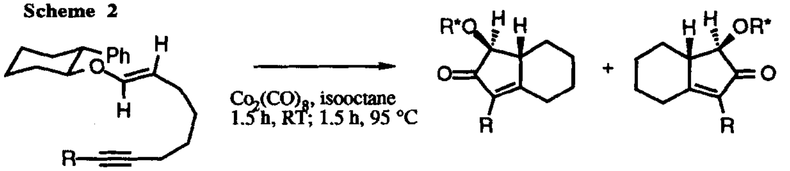
Scheme 1



Notwithstanding, and in accordance to the known reluctance of cyclohexenes to participate in cycloaddition processes, the intermolecular Pauson-Khand approach to the synthesis of bicyclo[4.3.0]nonenones has been shown to be very inefficient.[3] On the other hand, it is very surprising that while the intramolecular Pauson-Khand reaction has been extensively used for the synthesis of diquinanes[2,4] and of triquinanes,[2,5] the analogous construction of bicyclo[4.3.0]non-1(9)-en-8-ones has been almost completely disregarded. In fact, after the initial report by Schore that heating during 4 days of an isooctane solution of the dicobalt hexacarbonyl complex of 1-octen-7-yne affords bicyclo[4.3.0]non-1(9)-en-8-one in 35% yield,[6] the only related example appearing in the literature is the N-oxide promoted bicyclization of the complex derived from 5-(*tert*-butyldimethylsiloxy)-4,4-dimethyl-1-octen-7-yne.[7,8]

In the past few years, we have been involved in the development of efficient, reliable asymmetric approaches to both the intermolecular[9] and the intramolecular[10] versions of the Pauson-Khand reaction. As a result of these studies, we have demonstrated that 4-alkoxybicyclo[3.3.0]oct-1(2)-en-3-ones can be obtained in diastereomerically pure form through Pauson-Khand bicyclization of 1-alkoxy-1-hepten-6-ynes derived from chiral alcohols, thus providing a convenient route to the enantioselective preparation of bicyclo[3.3.0]octan-3-ones.[10a] In this communication, we wish to disclose the first efficient asymmetric approach to the bicyclo[4.3.0]nonan-8-one system, based on the chiral auxiliary-stereodirected intramolecular Pauson-Khand reaction of *(E)*-1-alkoxy-1-octen-7-ynes.

Scheme 2



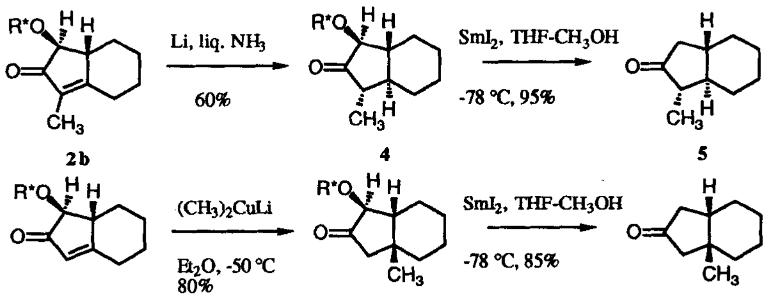
1 a (R=H)
1 b ($R=CH_3$)

2 a + **3a** (45%, 10:1 d.r.)
2 b + **3 b** (65%, ≥11:1 d.r.)

The requisite *(E)*-enol ethers **1a** and **1b** (see Scheme 2) were generated from (1*S*,2*R*)-(+)-2-(phenylcyclohexyloxy)ethyne[11] through one-pot preparation of the corresponding diynes (**1a**: CH_3Li, THF; 5-hexynal; TsCl, DMAP; LAH, 30%; **1b**: *n*-butyllithium, THF; 7-iodo-2-heptyne, HMPA, 61%) and subsequent regio- and stereoselective triple bond reduction[12] (**1a**: 3 eq. Red-Al®, refl. THF, 2 h, 68%;**1b**: 4 eq. LAH, refl. THF, 4 h, 65%). Enol ethers **1a** and **1b** were subsequently stirred in isooctane in the presence of 1.1 eq. of dicobalt octacarbonyl at room temperature for 1.5 h, and the resulting dicobalt hexacarbonyl complexes were heated in the same flask at 95 °C for 1.5 h, to produce in both instances an easily separable (simple column chromatography) mixture of the 7-alkoxybicyclo[4.3.0]octenones **2** and **3**, in moderate to good yield *and with an induction level of at least 10:1*, which is far superior to the highest obtained (7:1) by the cyclization of the homologous alkoxyenynes with one methylene less in the chain.[10a]

The configurational identity of the major diastereomer **2b**, *isolated in 60% yield from 1b*, was determined as follows (Scheme 3):

Scheme 3



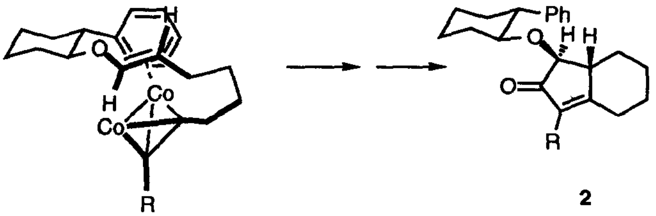
2b **4** **5**

2a **6**

Birch reduction of **2b** cleanly produced,[13] probably as a result of thermodynamic control,[14] the dihydro derivative **4**, in which the *trans* relationship of the vicinal hydrogen pairs both at C1-C9 and at C6-C7 was clearly apparent from the magnitude of the coupling constants ($J_{H1\text{-}H9} = J_{H6\text{-}H7} = 11.5$ Hz). Subsequent reductive cleavage with samarium diiodide[10a,10b,15] afforded the *trans*-7-methylbicyclo[4.3.0]nonan-8-one **5** in an excellent 95% yield, along with a 98% recovery of the chiral auxiliary. The relative stereochemistry of the bicyclic ketone **5** was deduced from extensive ^{1}H and ^{13}C RMN studies (selective decoupling, NOE and HETCOR experiments), as well as by independent synthesis of the stereoisomeric *cis*-7-methylbicyclo[4.3.0]nonan-8-one (mixture of epimers at C7) starting from cyclohexene (CCl_3COCl, Zn-Cu, $POCl_3$, Et_2O; CH_2N_2, CH_3OH, Et_2O; Zn, AcOH; LDA, THF, CH_3I).[16] In that the ketone **5** showed a positive Cotton effect for the n-π^* transition in the circular dichroism spectrum ($[\theta]_{300} = +8444$, c = 1.18×10^{-2} M, pentane, 20 °C), it follows that its absolute configuration is that depicted in Scheme 3 (1*S*,6*R*,7*S*). The absolute configuration of the two stereogenic centers created in the Pauson-Khand bicyclization is therefore (6*R*,7*S*) in the major diastereomer **2b**. The preponderant diastereomer (**2a**) resulting from the cyclization of **1a** was converted in turn to the *cis*-1-methylbicyclo[4.3.0]nonan-8-one **6** by an efficient two-step process (2 eq. $(CH_3)_2CuLi$, Et_2O, -50 °C, 80%; SmI_2, THF, CH_3OH, -78 °C, 85% and 95% recovery of the chiral auxiliary).[10a]

Finally, it should be noted that the absolute configurations of the major diastereomers **2a**, **2b** can be predicted simply by assuming an extended *s-trans* conformation of the enol ether moiety of the alkoxyenyne complex (Scheme 4).[10a,10c] As can be readily seen, the (C-α)-*si*, (C-β)-*re* face of the double bond is appreciably shielded by the phenyl group of the chiral auxiliary; accordingly, the attack by the dicobalt cluster will occur preferentially in the opposite (C-α)-*re*, (C-β)-*si* face, ultimately leading to a (6*R*,7*S*) configuration in **2**, in full agreement with what is experimentally observed.

Scheme 4



2

Acknowledgements

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