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Camphor-derived alcohols as chiral auxiliaries for asymmetric Pauson–Khand bicyclizations. Enantioselective synthesis of α-methoxyenones *

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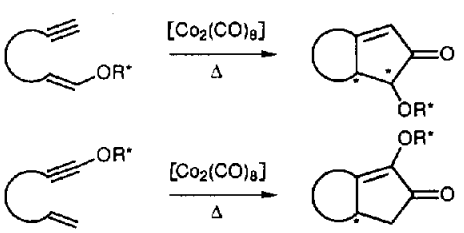
Abstract

The intramolecular Pauson–Khand reaction of enol and ynol ethers of Oppolzer's camphor-derived neopentyloxy alcohols is described. Bicyclic products are obtained in yields of up to 65% and with diastereoselectivities as high as 94:6 under very mild reaction conditions. The absolute configurations of the major stereoisomers obtained when (1*R*, 2*S*, 3*R*, 4*S*)-3-neopentyloxy-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol is used as a chiral auxiliary are rationalized on the basis of the theoretically predicted preferential conformations of model precursors. A simple procedure for obtaining auxiliary-free, enantiopure bicyclic α-methoxyenones is also presented.

The development of a reliable efficient asymmetric approach to the intramolecular Pauson–Khand reaction [1], a highly powerful method for the rapid assembly of complex, cyclopentenone-containing polycyclic structures [2], is a worthy objective. We have recently demonstrated that both alkynyl-substituted enol ethers (approach I) [3] and alkenyl-substituted ynol ethers (approach II) [4] can produce the corresponding alkoxybicycloalkenones diastereoselectively [5].



(1)

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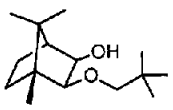
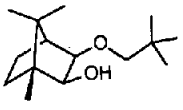
* Dedicated to Professor Peter L. Pauson.

In an effort to improve the yield and the diastereoselectivity of these two processes, a systematic study of easily available chiral inductors has been undertaken. Now we wish to report particularly promising results obtained with Oppolzer's readily available [6*] camphor-derived neopentyl ethers **1a** and **1b** [7], as well as a synthetically useful transformation of the Pauson–Khand products that arise from approach II.



1a

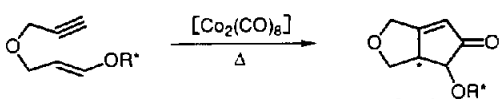


1b

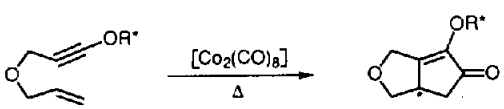
In that allyl propargyl ethers are readily prepared and known to efficiently undergo Pauson-Khand bicyclization [3,8], enol ethers **4a**, **4b** and ynol ethers **5a**, **5b** were chosen as substrates for our study. Their preparation from **1a**, **1b** is shown in Scheme 1.

Alcohols **1a**, **1b** were converted to the propargyl derivatives **2a**, **2b** by a high-yield, one-pot procedure previously developed in our laboratories [3,9]. Lithium aluminum hydride reduction of **2a**, **2b** led exclusively to the *E* allylic alcohols **3a**, **3b**, which in turn were subjected to propargylation to afford the alkynyl-substituted enol ethers **4a**, **4b** in high yield. Alternatively, allylation of **2a**, **2b** gave the alkenylsubstituted ynol ethers **5a**, **5b** also in excellent yield.

The transformation, under various Pauson–Khand conditions, of the enynes **4a**, **4b** and **5a**, **5b** to the 7-oxabicyclo[3.3.0]oct-1-en-3-ones **6a**, **6b** and **7a**, **7b**, respectively, was next examined (Table 1).



4a, b 6a, b (3)

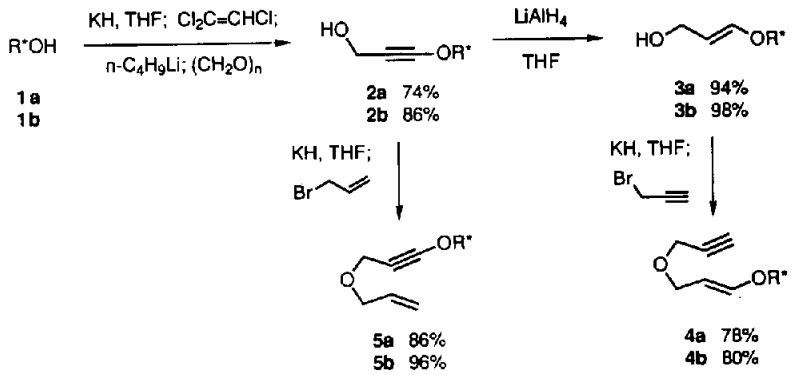


5a, b 7a, b (4)

While the results obtained with enol ether **4a** (approach I) were modest, exposure of enol ether **4b** to dicobalt octacarbonyl at temperatures considerably lower than those usually employed for Pauson–Khand reactions (entry 3) produced the expected bicyclooctenone **6b** as a readily separable (simple column chromatography) 90 : 10 mixture of diastereomers in 53% yield. The effect of the temperature on the yield and the diastereoselectivity of this transformation is particularly noteworthy (compare entries 2 and 3) and may be quite general. The analogous enyne derived from *trans*-2-phenylcyclohexanol gave an 82 : 18 mixture of diastereomers in 41% yield at 100°C [3].

Even more significant improvements, however, were found in the bicyclization of acetylenic ethers **5a**, **5b** (approach II). When **5a** was subjected to Pauson–Khand

* Reference number with asterisk indicates a note in the list of references.



Scheme 1.

conditions at 50°C, **7a** was obtained as an 88:12 mixture of diastereomers in 65% yield. Remarkably, with **5b**, the bicyclization took place at room temperature under dinitrogen to give **7b** in 54% yield and with a diastereoselectivity of 94:6! Once again, the diastereomers could be readily separated by simple column chromatography. The use of a more polar solvent (THF), photochemical promotion (257 nm irradiation) or chemical activation (trialkylamine-*N*-oxide [10]), in efforts to increase the reaction rate, had a deleterious effect on reaction yields. Prior to these results, the best diastereoselectivity realized in approach II (in a related system) was only 76:24 (38% yield) [4].

The absolute configuration of the major stereoisomers of **6a** and **6b** was determined by chemical correlation with (1*R*, 5*S*)-(−)-*cis*-1-methyl-7-oxabicyclo[3.3.0]octan-3-one through a reported procedure [3]. For **7b**, a single crystal of the minor stereoisomer was used to establish [11*] the absolute configuration at C-5 by X-ray diffraction, and this was found to be *S* (see Fig. 1); therefore, that at C-5 of the major diastereomer of **7b** is *R*.

With the goal of obtaining auxiliary-free substances, compounds **7a** and **7b** were subjected to a variety of copper-mediated conjugate addition processes [4], but without success. Most pleasingly, however, we discovered that treatment of these enones simply with a catalytic amount of hydrochloric acid in methanol led, with

Table 1

Pauson–Khand bicyclization of **4** and **5** [a]

Entry	Enyne	Reaction conditions [b]	Bicyclooctenone [c,d]		Yield	Diastereoselectivity [e]
1	**4a**	Iso; 20°C (2 h)+75°C (3 h); CO	**6a**	(5*S*)	38%	67:33
2	**4b**	Iso; 20°C (2 h)+70°C (1 h); CO	**6b**	(5*S*)	20%	80:20
3	**4b**	Iso; 20°C (2 h)+50°C (12 h); CO	**6b**	(5*S*)	53%	90:10
4	**5a**	Iso; 20°C (3 h)+90°C (2 h); CO	**7a**	(5*S*)	59%	85:15
5	**5a**	Iso; 20°C (2 h)+50°C (17 h); CO	**7a**	(5*S*)	65%	88:12
6	**5b**	Hex; 22°C (18 h); CO	**7b**	(5*R*)	53%	91:9
7	**5b**	Hex; 18°C (2 h)+25° (2 h); N_2	**7b**	(5*R*)	54%	94:6

[a] **4a** and **5a** are derived from alcohol **1a**; **4b** and **5b**, from **1b**. [b] Iso: isooctane; Hex: hexanes. [c] Alkoxyl group in **6a**, **b** is *exo*. [d] C-5 configuration given is for the major diastereomer (see text). [e] By NMR and/or weight of isolated diastereomers.

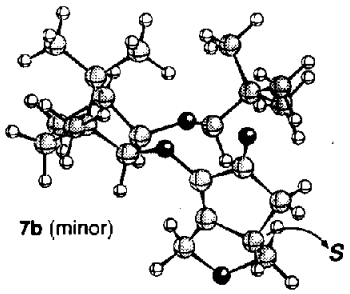
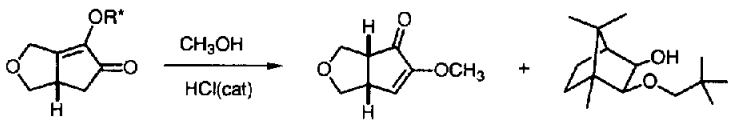
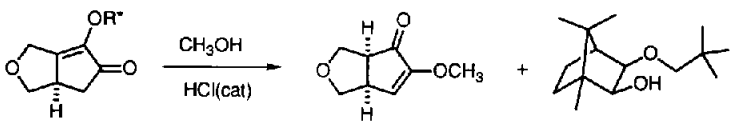


Fig. 1.

complete regioselectivity and in excellent yield, to α-methoxyenones **8**, with nearly quantitative recovery of the inductors. While potentially offering general access to versatile, auxiliary-free enantiopure compounds [12], this method, in the present instance, allowed an unambiguous assignment to be made of the absolute configuration (5*S*) of the major diastereomer of **7a**.



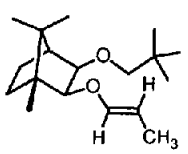
7a (+)-**8** 94% **1a** 96% (5)

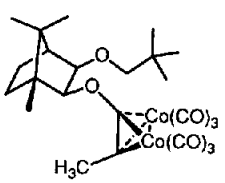


7b (-)-**8** 83% **1b** 94% (6)

In order to rationalize the absolute configurations of the major bicyclo[3.3.0]-octanone diastereomers obtained with the chiral auxiliary **1b**, theoretical calculations were performed on the model compounds **9** and **10**.

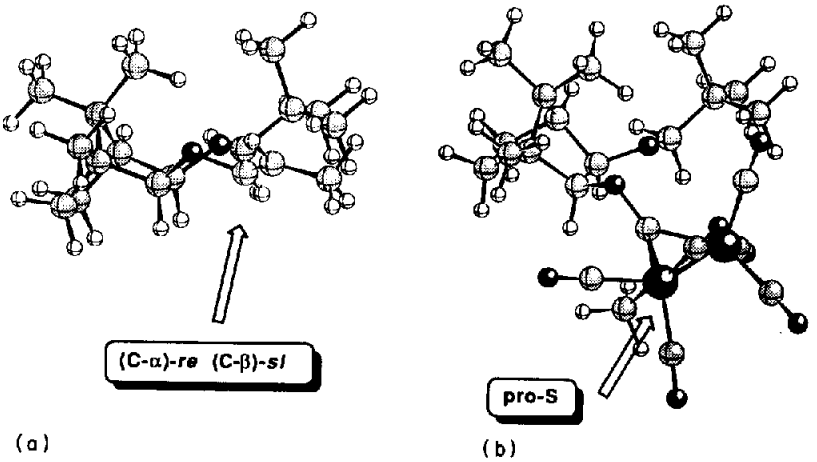
(9)





(10)

Compound **9** constitutes an adequate, yet simplified, model for the dicobalt hexacarbonyl complex of **4b**. In fact, the only factor determining the absolute configuration of the newly created (C-5) chiral centre in **6b** is the diastereofacial selectivity (*re* or *si*) in the interaction between the enol ether moiety and the dicobalt cluster, and this depends, ultimately, on the conformational preferences of the enol ether. The molecular geometry of **9** was optimized using the semi-empirical SCF-MO method AM1 [13] (Fig. 2a). As can be readily seen, the (C-α)-*si* (C-β)-*re* face of the enol ether is completely shielded by the neopentyloxy group. Accordingly, it is predicted that the attack by the dicobalt cluster will occur on the



(a) (b)

Fig. 2.

(C-α)-*re* (C-β)-*si* face, ultimately leading to a *S* configuration at C-5 in **6b** in full agreement with what is experimentally observed.

On the other hand, **10** represents a model of the dicobalt hexacarbonyl complex of **5b**. In this case, assuming the formation of a *cis*-cobaltabicyclo-intermediate [2a], the factor that ultimately controls the absolute stereochemistry at C-5 in **7b** is the cobalt tricarbonyl group (*pro-R* or *pro-S*) in the prochiral dicobalt cluster which intervenes in the formation of the cobaltabicyclo-intermediate. The molecular geometry of **10** was optimized by molecular mechanics techniques with the MMX force field [14*] (Fig. 2b). As readily observed, the *pro-R* cobalt tricarbonyl group is shielded by the neopentyloxy substituent of the chiral auxiliary. It is thus predicted that in the real molecule, (**5b**)$Co_2(CO)_6$, the vinyl group will preferentially interact with the *pro-S* cobalt tricarbonyl group, leading ultimately to a 5*R* configuration in **7b**, in full accord with our experimental observations.

In summary, both diastereoselective Pauson–Khand approaches (I and II) developed in our laboratories appear to be substantially improved through the use of the camphor-derived inductors **1a** and **1b**, especially at moderate temperatures. The yields and diastereoselectivities that have been obtained are significantly better than those previously reported [3,4], particularly in the case of approach II. Finally, it should be noted that the absolute configurations of the 7-oxabicyclo[3.3.0]oct-1-en-3-ones obtained with **1b**, the more useful of the two chiral controllers in terms of efficiency and ease of purification of the major diastereomers (for enantiopure compounds), can be predicted through the analysis of the conformational preferences of the corresponding open-chain precursors. Extensions and applications of these asymmetric approaches to the Pauson–Khand reaction are in progress in our laboratories and will be reported in due course.

Acknowledgments

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