

## Asymmetric Approach to Pauson-Khand Bicyclization. Enantioselective Formal Synthesis of Hirsutene†

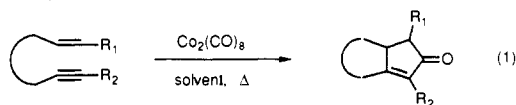
J. Castro,† H. Sørensen,§ A. Riera,† C. Morin,§ A. Moyano,\*‡ M. A. Pericàs,\*‡ and A. E. Greene\*‡§

Departament de Química Orgànica, Universitat de Barcelona  
Martí i Franquès, 1-11, 08028-Barcelona, Spain  
LEDSS, Universitè J. Fourier, BP 53X  
38041 Grenoble, France

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Largely overlooked during the decade following its discovery, the Pauson-Khand reaction<sup>1</sup> is now regarded as one of the most potent methods for cyclopentenone construction.<sup>2</sup> This operationally simple and often quite efficient method unites an olefin, an acetylene, and carbon monoxide to form a five-membered ring,<sup>3</sup> while tolerating a wide range of functional groups and substitution patterns.

The intramolecular mode of the Pauson-Khand reaction,<sup>1</sup> which permits the rapid assembly of a variety of polycyclic molecules with the attendant benefit of favorable entropic effects, has provided some of the most impressive results to date (eq 1). The key skeletal constructions in racemic approaches<sup>4</sup> to several polyquinane natural products offer elegant illustrations of Pauson-Khand bicyclization.



An efficient asymmetric version of this powerful reaction would obviously be of great value. Efforts devoted to this objective, however, have so far been only marginally successful.<sup>5,6</sup> Bicyclization of acetylenic enol ethers derived from chiral alcohols ( $R_1 = OR^*$ , eq 1) appeared to us to be of potential interest in that the newly created asymmetric center would be immediately adjacent to the carbon bearing the chiral auxiliary. High levels of diastereoselection had, in fact, already been attained with *O*-alkyl enol ethers in intermolecular 2 + 2, 2 + 3, and 2 + 4 cycloadditions.<sup>7</sup>

† This paper is dedicated to Professor Fèlix Serratosa on the occasion of his 65th birthday.

‡ Universitat de Barcelona.

§ Universitè J. Fourier.

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(3) For excellent reviews of methods for the construction of 5-membered carbocycles, see: (a) Ramaiah, M. *Synthesis* **1984**, 529-570. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1-163. (c) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry. Synthesis and Reactions*; Springer: Berlin, 1987. For more recent methods, see: (d) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691-6707 and references cited therein.

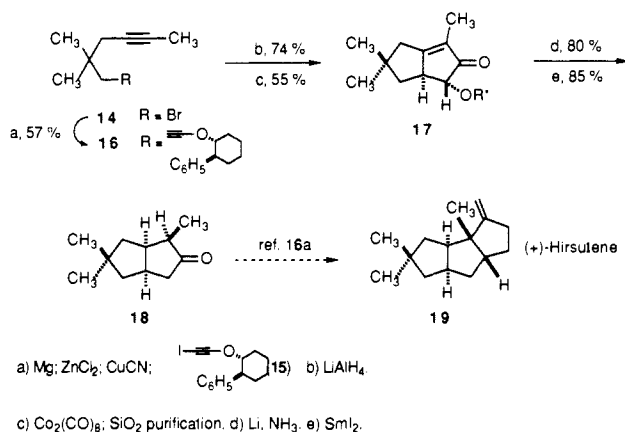
(4) (a) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861-5869. (b) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1986**, *51*, 1483-1486. (c) Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224-5225. (d) Magnus, P.; Slater, M. J.; Principe, L. M. *J. Org. Chem.* **1989**, *54*, 5148-5153.

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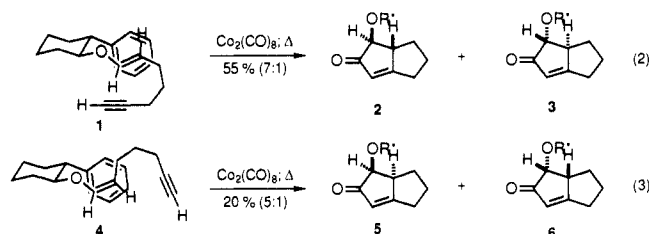
(7) For examples, see: (a) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458-5461. (b) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667-670. (c) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752-4753.

### Scheme 1



In this communication we wish to disclose the first efficient asymmetric approach to the intramolecular Pauson-Khand reaction, based on chiral auxiliary-directed  $\pi$ -face discrimination in acetylenic *O*-alkyl enol ether-dicobalt hexacarbonyl complexes, and its initial application in natural product synthesis.

The prototypical *E* and *Z* enol ethers **1** and **4** (eqs 2 and 3), each efficiently generated from (1*S*,2*R*)-(+)-2-(phenylcyclohexyloxy)ethyne<sup>8</sup> by alkylation with 5-iodo-1-pentyne ( $CH_3Li/DMSO$ ), followed by regio- and stereoselective triple bond reduction (Red-Al or Red-Al-ROH,<sup>9</sup> respectively), were stirred in isooctane with 1.1 equiv of  $Co_2(CO)_8$  at 20 °C for 1.5 h, and the resultant dicobalt hexacarbonyl complexes, without isolation, were then heated at 95 °C for 1.5 h. Most pleasingly, both isomers underwent diastereoselective bicyclization. The *E* isomer proved much more effective in this reaction than the *Z*<sup>10</sup> and produced the easily separable (simple column chromatography) bicyclo[3.3.0]octenones **2** and **3** in remarkably good yield and with an induction level of at least 7:1.<sup>11</sup>



The stereochemical identity of the major diastereomer **2** was determined both by X-ray analysis<sup>12</sup> and through chemical correlation. From **2**, optically pure (1*R*,5*S*)-1-methylbicyclo[3.3.0]octan-3-one ((-)-**7**)<sup>13</sup> was readily secured, as indicated

(8) Prepared from optically pure (1*S*,2*R*)-(+)-phenylcyclohexanol by the procedure described in: (a) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919-2922. Both enantiomers of this alcohol are readily secured: (b) Whitesell, J. K.; Chen, H. H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663-4664. (c) Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318-321. (d) Laumen, K.; Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1990**, 49-51.

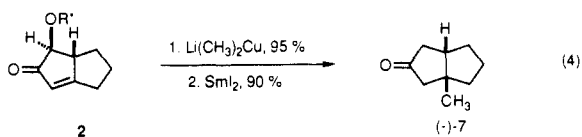
(9) The generality of this novel method for selectively transforming alkoxyacetylenes to *Z* enol ethers is currently being investigated. Red-Al is a trademark of Aldrich Chemical Company.

(10) This can be attributed to the fact that bicyclization of the *Z* isomer requires that the bulky  $OR^*$  group be accommodated in the more sterically confining endo position.

(11) For comparison, 1-hepten-6-yne affords bicyclo[3.3.0]oct-1-en-3-one in 31% yield and 1-octen-7-yne gives bicyclo[4.3.0]non-1(9)-en-8-one in 35-40% yield (95 °C, 4 days). See: Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436-5438. Neither 4-(ethenyloxy)-1-butyne nor 5-(ethenyloxy)-1-pentyne affords any isolable ketonic products on attempted cyclization. See: Croudace, M. C.; Schore, N. E. *J. Org. Chem.* **1981**, *46*, 5357-5363. The diastereoselectivities of the cyclizations of **1**, **4**, **8**, **10**, **12**, and reduced **16** have been determined by NMR and/or from the yields of the purified diastereomers.

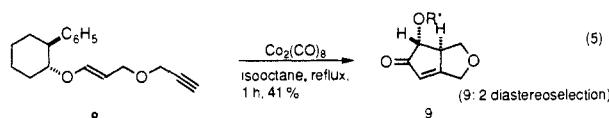
(12) The X-ray analysis will be published separately. We thank Dr. X. Solans for this determination.

below, in 86% yield. Significantly, the chiral auxiliary could be recovered in 92% yield.<sup>14</sup>

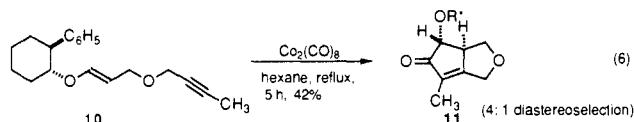


The Pauson-Khand products **2** and **5** presumably arise from the dicobalt hexacarbonyl complexes of the enol ethers **1** and **4** through the indicated *s-trans* conformation (eqs 2 and 3). This exposes the C<sub>α</sub>-re face of the double bonds to intramolecular attack by the C<sub>2</sub>Co<sub>2</sub> group, while positioning the C<sub>α</sub>-si face so as to be shielded by the phenyl group.

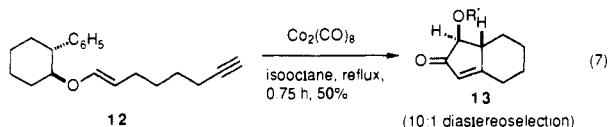
This asymmetric version of the Pauson-Khand reaction appears to be notably broad in scope. An oxygen atom can be accommodated in the chain (eq 5).<sup>15</sup>



Furthermore, a terminal alkyl substituent is also tolerated (eq 6).<sup>15</sup>



Preliminary results indicate that diastereoselection may be even greater in the formation of bicyclo[4.3.0]nonenones; bicyclic enone **13**, for example, is obtained from enyne **12** with 10:1 diastereoselectivity (eq 7).<sup>11</sup>



The considerable potential of this approach is illustrated by an enantioselective formal total synthesis of hirsutene (**19**), the proposed biogenetic precursor of the hirsutanes (Scheme I).<sup>16</sup>

Homochiral diyne **16** was conveniently prepared through a novel copper-mediated coupling procedure<sup>17</sup> that involved the zinc reagent derived from bromide **14** and the iodoacetylene **15**. Conversion of **16** to the corresponding *E* enol ether could be selectively accomplished with LiAlH<sub>4</sub> in THF. The key bi-

cyclization occurred smoothly under unusually mild conditions (exposure to 1.1 equiv of Co<sub>2</sub>(CO)<sub>8</sub> in hexane, followed by warming at 42 °C for 12 h)<sup>11,18</sup> to produce diastereoselectively (5-6:1) enone **17**, mp 96-97 °C, easily purified by simple chromatography.<sup>19</sup> Birch reduction or, less efficiently, catalytic hydrogenation<sup>20</sup> delivered the dihydro derivative, mp 44-46 °C, from which the auxiliary could readily be cleaved<sup>21</sup> (91% recovery) to give **18**, [α]<sub>D</sub><sup>24</sup> -68° (c 1.5, CH<sub>2</sub>Cl<sub>2</sub>). In that the bicyclic ketone **18**, in racemic form, has previously been converted to hirsutene, the present work constitutes an enantioselective approach to this substance.<sup>16</sup>

The results described in this paper establish both the feasibility and the practicality of chiral auxiliary-directed asymmetric Pauson-Khand bicyclization. Further investigation is warranted and is actively being pursued in our laboratories.

**Acknowledgment.** We thank Prof. J. Lhomme and Dr. J. L. Luche for their interest in our work, Prof. G. Magnusson for the spectra of racemic **18**, and the DGICYT (Grant PB86-0510) and the CNRS (UA 332) for financial support. Fellowships from Ministerio de Educación y Ciencia (to J.C.) and the Swedish National Board for Technical Development (to H.S.) are gratefully acknowledged.

**Registry No.** **1**, 130121-38-9; **2**, 130121-39-0; **3**, 130194-15-9; **4**, 130194-16-0; **5**, 130121-40-3; **6**, 130194-17-1; (-)-**7**, 102849-89-8; **8**, 130121-41-4; **9**, 130121-42-5; **9** (diastereomer), 130194-19-3; **10**, 130121-43-6; **11**, 130121-44-7; **11** (diastereomer), 130121-45-8; **12**, 130195-29-8; **13**, 130121-46-9; **13** (diastereomer), 130195-30-1; **14**, 130121-47-0; **15**, 130121-48-1; **16**, 130121-49-2; **16** ((*E*)-enol ether), 130121-51-6; **17**, 130121-50-5; **17** (diastereomer), 130194-20-6; **17** (dihydro derivative), 130121-52-7; **18**, 130194-18-2; **19**, 59372-72-4.

(18) For a discussion of the Thorpe-Ingold effect, see: Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 197-202.

(19) The absolute configuration of **17** has been assigned on the basis of those established for **2** and **9**.

(20) (a) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438-2443.

(b) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988-3992.

(21) (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135-1138.

(b) Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439-442.

(13) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525-5528. Ketone (-)-**7** displayed at 300 nm the expected negative maximum in its CD spectrum. An optical purity of >99% was established by <sup>13</sup>C NMR. See: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183-2186.

(14) In addition, it was found that diastereomers **2** (Li(CH<sub>3</sub>)<sub>2</sub>Cu) and **6** (Li(CH<sub>3</sub>)<sub>2</sub>Cu; equilibration with *t*-C<sub>4</sub>H<sub>9</sub>OK) gave the same 4-alkoxy-1-methylbicyclo[3.3.0]octan-3-one, as did **3** and **5**. Sml<sub>2</sub> converted that derived from **2** and **6** to (-)-**7** and that from **3** and **5** to (+)-**7**.

(15) Diethers **8** and **10** were prepared in 51-72% yield by sequential treatment of *trans*-2-phenylcyclohexanol with KH, Cl<sub>2</sub>C=CHCl, C<sub>6</sub>H<sub>5</sub>Li, and CH<sub>2</sub>O (one pot), followed by exposure to KH and BrCH<sub>2</sub>C≡CH or MsOCH<sub>2</sub>C≡CCH<sub>3</sub>, and then reduction. The absolute configuration of **9** was assigned on the basis of the positive CD maximum of the derived 1-methyl-7-oxabicyclo[3.3.0]octan-3-one (Li(CH<sub>3</sub>)<sub>2</sub>Cu; Sml<sub>2</sub>) and can also be rationalized by assuming an *s-trans* conformation (analogous to that indicated for **1**) of the dicobalt hexacarbonyl complex of enol ether **8**.

(16) For previous work in this area, see: (a) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195-198. (b) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088-4090. (c) Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507-515 and references cited therein. The absolute configuration of natural (+)-hirsutene has been established by Hua through total synthesis<sup>16b</sup> and corresponds to that depicted in **19**.

(17) (a) Verboom, W.; Westmijze, H.; Bos, H. J. T.; Vermeer, P. *Tetrahedron Lett.* **1978**, 1441-1442. (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799-4802. The scope of this acetylenic ether preparation will be discussed in a future publication.

## The *g* = 4.1 EPR Signal of the S<sub>2</sub> State of the Photosynthetic Oxygen-Evolving Complex Arises from a Multinuclear Mn Cluster

Dennis H. Kim,<sup>†,‡</sup> R. David Britt,<sup>\*§</sup> Melvin P. Klein,<sup>\*†</sup> and Kenneth Sauer<sup>\*†,‡</sup>

Laboratory of Chemical Biodynamics  
Lawrence Berkeley Laboratory and  
Department of Chemistry, University of California  
Berkeley, California 94720  
Department of Chemistry, University of California  
Davis, California 95616

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The process of water oxidation and dioxygen evolution by the photosystem II (PSII) component of plant photosynthesis is cyclic, with intermediate states of the oxygen-evolving complex (OEC) designated S<sub>0</sub> through S<sub>4</sub>.<sup>1</sup> Two electron paramagnetic resonance (EPR) signals have been assigned to the S<sub>2</sub> state of the complex. A "multiline" EPR signal centered at the *g* = 2 region of the spectrum shows 16 or more partially resolved Mn hyperfine

<sup>†</sup> Lawrence Berkeley Laboratory.

<sup>‡</sup> University of California, Berkeley.

<sup>§</sup> University of California, Davis.

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