Pergamon

Tetrahedron Letters, Vol. 35, No. 8, pp. 1153-1156, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0404-8

First Example of Reversal of Normal Stereoselectivity in the Intramolecular Pauson-Khand Reaction

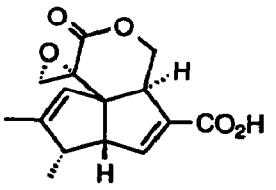
Joseph A. Casalnuovo[1], Robert W. Scott, Eric A. Harwood, and Neil E. Schore*

Department of Chemistry, University of California, Davis, California 95616, U. S. A.

Abstract: Stereoselectivity favoring *exo* substituent orientation in the intramolecular Pauson-Khand reaction of 3-methyl-4-hydroxy-1,6-heptenynes to form bicyclo[3.3.0]octenones is affected by the relative stereochemistry at C3 and C4. Cycloaddition of one stereoisomer of 3,5-dimethyl-4-propargyl-1,6-heptadiene gives predominantly the bicyclo[3.3.0]octenone isomer containing both substituents in more hindered *endo* orientations. An explanation based upon the effect of conformational preferences prior to metallacycle formation is proposed.

The factors that contribute to stereoselectivity in the intramolecular Pauson-Khand cyclization of heptenynes to bicyclo[3.3.0]octenones have generally been well-explained in the literature.[2,3,4] A preference for substituents at the allylic and propargylic positions of the heptenyne substrate to end up on the *exo* face of the bicyclic product is observed, with steric interactions between the *endo* allylic and propargylic positions and the substituent at the alkyne terminus being responsible. The use of bulky substituents at these positions has been shown to provide good to excellent *exo* selectivity. This result has been exploited in numerous syntheses of *exo* substituted bicyclic precursors to natural products.[2,5,6,7,8]

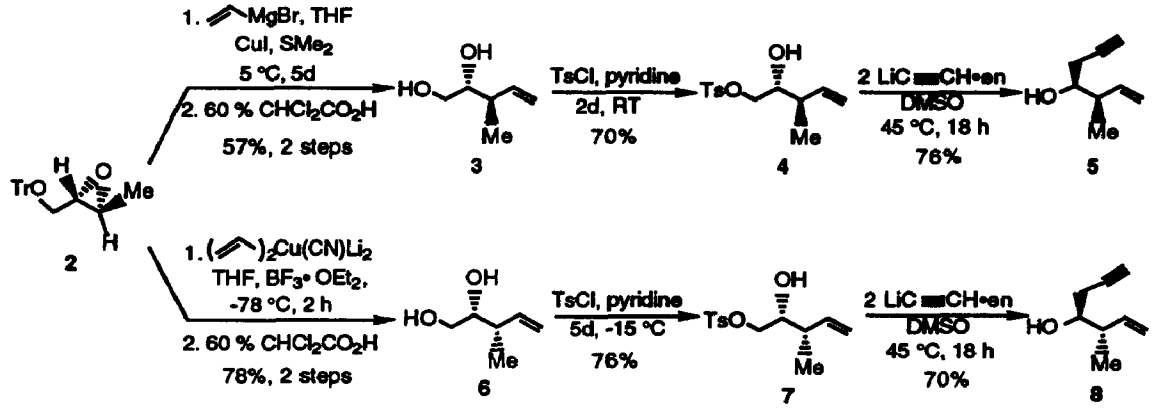
We are currently investigating the design of Pauson-Khand substrates with allylic substituents that may cyclize to afford predominantly *endo*-substituted bicyclic products. Such capability would significantly extend the scope and utility of the Pauson-Khand reaction in natural product synthesis. For instance, such methodology would be applicable in the synthesis of pentalenolactone **1**, one of a varied group of antibiotics among which the parent possesses an *endo* methyl substituent.[9]



1

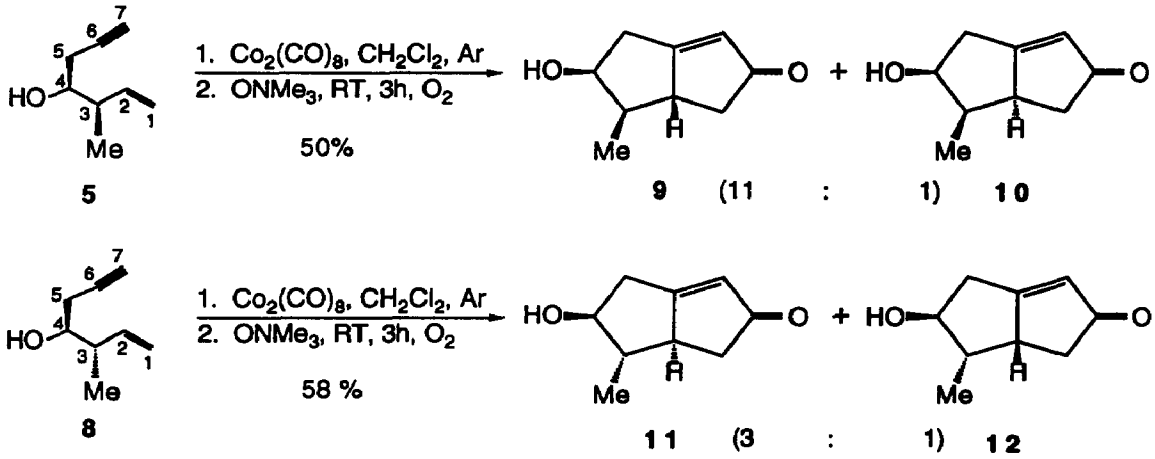
To this end we have synthesized a pair of stereoisomeric homoallylic alcohols, **5** and **8**, in high enantiomeric purity starting from optically pure epoxide **2**.[10] Treatment of **2** with excess 1M vinylmagnesium bromide in THF, followed by deprotection, leads to diol **3**. Conversely, reaction of **2** with a higher order vinyl cuprate in the presence of BF_3·OEt_2 at low temperature, followed by deprotection, gives diol **6**. Diols **3** and **6** react similarly to form tosylates, which in the presence of two equivalents of lithium acetylide-ethylene diamine complex in DMSO at 45°C in a sealed tube give homoallylic alcohols **5** and **8**, respectively.[11]

Cyclization of **5** was carried out by a modification of the Pauson-Khand reaction [$Co_2(CO)_8$, CH_2Cl_2, Me_3NO, O_2, 25°C[12]], to afford **9** and **10** as an 11:1 mixture of stereoisomers. The ^1H NMR spectrum of the mixture contained methyl resonances belonging to the major (δ 1.16) and minor isomers (δ 0.71) The high field resonance in **10** suggested that it had the *endo* methyl stereochemistry as has been seen in similar polycyclic



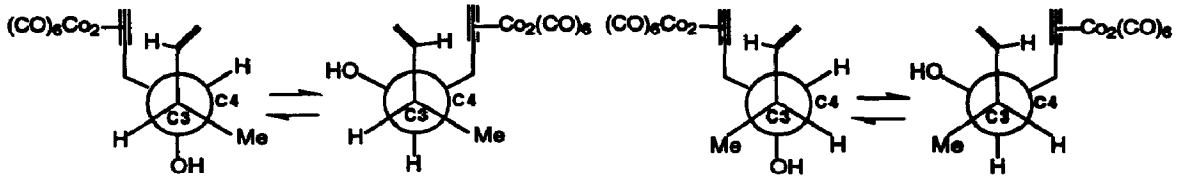
systems.[13] Single crystal X-ray diffraction analysis of **9**[14] confirmed our assignment of the major isomer as containing the *exo* methyl stereochemistry.

Homoallylic alcohol **8** was similarly cyclized to give **11** and **12** as a 3:1 mixture. The ^{1}H NMR shifts of the methyl groups in the products again showed the major isomer **11** to possess *exo* methyl stereochemistry [δ 1.20 (major), δ 0.63 (minor)]. Significantly, while substrates (3*R*,4*S*)-**5** and (3*S*,4*S*)-**8** differ only in the relative configurations of the methyl and propargyl groups (*syn* for **5**, *anti* for **8**), the predominance of the *exo* stereoisomer in the cyclization of **8** is substantially reduced compared to the cyclization of **5**. This finding is consistent with other literature examples of analogous Pauson-Khand cyclizations: substrates with the *anti* relationship of propargyl and allylic substituents led to higher proportions of *endo* product compared to the corresponding substrates with the *syn* configuration.[8,15]



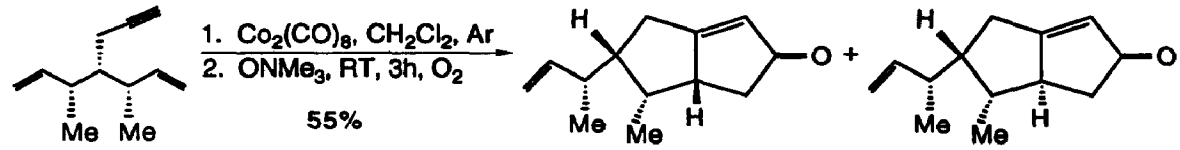
To explain this phenomenon, we propose that "anti" substrate **8** shows a pre-reaction conformational preference at the C3-C4 bond which increases the favorability of forming an *endo* methyl cyclization product. Newman projections of the relevant conformers **13** and **14**, leading to *endo* and *exo* methyl products, respectively, suggest that **13**, which contains two *gauche* interactions, should be favored over **14**, which places four groups mutually *gauche*. Further, **13** places the very bulky $Co_2(CO)_6$•alkyne group *gauche* to only one

other group, while **14** places it *gauche* to two. Application of the same analysis to the cyclization of **5** suggests that conformer **16**, which leads to the *endo* product, should still be favored over **15**, but to a smaller extent. These conformational preferences occur prior to the steric interactions which develop in the transition state upon insertion of the alkene into the cobalt-alkyne metallacycle. The observed product ratios will result from the combined contributions of pre-insertion conformational energies and steric interactions associated with the transition state for insertion itself.[16] That both **5** and **6** give *exo* methyl isomers as major products indicates that the latter interactions still dominate in this system (but to a lesser extent than in the cases of **20** and **21**, in which the alkyne terminus is alkyl-substituted[15]).



13 **14** **15** **16**

In a parallel study, we are investigating the Pauson-Khand cyclizations of the series of three stereoisomeric 3,5-dimethyl-4-(2-propynyl)-1,6-heptadienes. The symmetry characteristics of systems such as these provide excellent probes of conformational effects, e.g. alkene face selectivity.[17] Furthermore, changing the substituent at C4 should affect pre-insertion conformational preferences more than insertion itself.[6] The *syn, syn* isomer **17** has been prepared from the respective dienoic acid[17] in good yield by reduction to the alcohol, tosylation, and nucleophilic displacement with excess lithium acetylide•ethylene diamine complex in DMSO at room temperature. Pauson-Khand cyclization of **17** under the previously described conditions gave a 55% yield of the bicyclooctenones **18** and **19** in a 3:1 ratio, respectively.[18] ***Remarkably, the major product 18 has both alkyl substituents in endo configurations*** [ring methyl: δ 0.55 (major), δ 1.15 (minor)]. *Endo* selectivity for an allylic substituent has never before been observed in an intramolecular Pauson-Khand reaction. This result is in spite the fact that the dienyne has a *syn, syn* configuration. Even greater *endo* selectivity should be expected from the *anti, syn* and *anti, anti* isomers, whose preparation we are currently pursuing and will report on in due course.



17 **18** (3 : 1) **19**

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM 26294) and the Committee on Research of the University of California, Davis. RWS and EAH thank the Teaching Resources Center of the University of California, Davis for President's Undergraduate Fellowships.

REFERENCES AND NOTES

[1]Present address: Chemistry Department, California State Polytechnic University, Pomona, Ca. 91768 U.S.A.
[2]Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477.
[3]Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851.

[4]Reviews: (a) Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2. (b) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. (c) Pauson, P. L. in *Organometallics in Organic Synthesis. Aspects of a Modern Interdisciplinary Field*; A. de Meijere, H. tom Dieck, Eds.; Springer: Berlin, 1988; p. 233. (d) Schore, N. E. "Pauson-Khand Reaction" in *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: Oxford, 1991. (e) Schore, N. E. *Org. React.* **1991**, *40*, 1.

[5]Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483.

[6]Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861.

[7]Magnus, P.; Slater, M. J.; Principe, L. M. *J. Org. Chem.* **1989**, *54*, 5148.

[8]Mulzer, J.; Graske, K.-D.; Kirste, B. *Liebigs Ann. Chem.* **1988**, 891.

[9](a) Koe, B. K.; Sobin, B. A.; Celmer, W. D. *Antibiot. Annu.* **1956-7**, 672. (b) Takeuchi, S.; Ogawa, Y.; Yonehara, H. *Tetrahedron Lett.* **1969**, 2737. (c) Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. D. *Tetrahedron Lett.* **1970**, 4901. (d) Duchamp, D. J.; Chidester, C. G. *Acta Crystallogr., Sect. B* **1972**, *28*, 173.

[10]Available from Sharpless epoxidation of crotyl alcohol in 92% ee and recrystallized to ≥ 98% optical purity: (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Kobayashi, Y.; Kitano, Y.; Takeda, Y.; Sato, F. *Tetrahedron* **1986**, *42*, 2937.

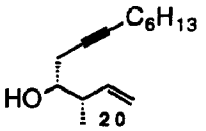
[11]Compounds **3**, **4**, and **5** contained small amounts (< 10%) of the respective diastereomers **6**, **7**, and **8** and were used without further purification.

[12]Typical procedure: Alcohol **5** (24 mg) and $Co_2(CO)_8$ (80 mg) were combined with 2 mL CH_2Cl_2 in a 4 mL microvial with a spin vane and sealed with a septum and screw cap under a light Ar purge. After 8 h at rt the mixture was cooled to 0°C and an O_2 purge initiated for 20 m. A solution of 100 mg Me_3NO in 1.5 mL CH_2Cl_2 was added at rt over 2 h and stirring of the resulting slurry continued for 1 h. The solvent was evaporated and the mixture triturated with ether, open to the air, for 15 m. The slurry was filtered (celite) and washed through ca. 5 cm Florisil with ca. 100 mL ether. Evaporation gave 17 mg of virtually pure **9** and **10**. Cf. Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289 and Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220.

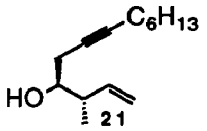
[13](a) Schore, N. E.; Knudsen, M. J. *J. Org. Chem.* **1987**, *52*, 569. (b) Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853.

[14]Separated from **10** by MPLC (20% ether in petroleum ether) and recrystallized by slow diffusion of petroleum ether into an ether solution. We thank R. L. Sturgeon for carrying out the structure determination.

[15]Syntheses and Pauson-Khand reactions of **20** (69% ee) and **21** (88% ee) were recently reported (Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1991**, *32*, 6285). The "syn" substrate **20** gave an *exo* methyl enone product with 23:1 selectivity, wheras selectivity from "anti" substrate **21** dropped to 11:1. Note that our use of "syn" and "anti" refers to the propargyl and methyl groups; with respect to the hydroxy and methyl substituents the designations would be reversed.

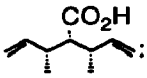


20



21

[16]Krafft, M. E. *Tetrahedron Lett.* **1988**, *29*, 999.

[17]I. e., 

: Kurth, M. E.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844.

[18]All new compounds were fully characterized by high field ^1H and ^{13}C NMR and IR. Satisfactory elemental analyses were obtained for **3**, 3-trityl ether, **4**, **6**, 6-trityl ether, **7**, **9**, **10**, **11**, and **12**.

(*Received in USA* 22 *October* 1993; *revised* 7 *December* 1993; *accepted* 10 *December* 1993)