Tetrahedron Letters,Vol.29,No.48,pp 6219-6222,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

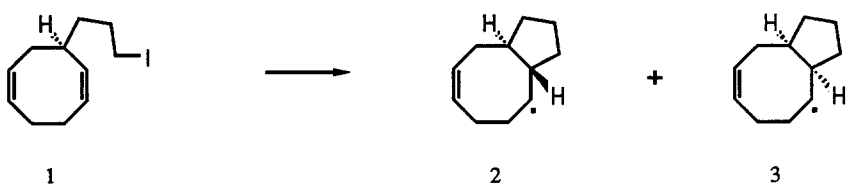
EIGHT-MEMBERED RING TEMPLATES FOR STEREOSELECTIVE RADICAL CYCLIZATIONS+

Jeffrey D. Winkler*[1], V. Sridar[2]
Searle Chemical Laboratories, Department of Chemistry, The University of Chicago, Chicago, Illinois 60637

ABSTRACT. *The radical cyclization of suitably disubstituted cyclooctadienes and cyclooctenes leads to the formation of trans-bicyclo[6.3.0]undecane ring systems with exceedingly high levels of stereochemical control.*

The conformational biases of medium rings can lead to valuable templates for stereoselective carbon-carbon bond formation.[3] We have shown that the cyclization of the radical derived from mono-substituted cyclooctadiene **1** leads to the formation of a mixture of products, reflecting a ca. 3:1 partitioning between trans- and cis-bicyclo[6.3.0]undecenyl radicals **2** and **3**, respectively (Scheme I).[4] In an attempt to magnify the conformational biases of this system so that synthetically useful selectivities could be obtained, we have now examined the effect of a second cyclooctadiene substituent on the stereochemical outcome of the cyclization. We report herein that the intramolecular radical cyclization of suitably disubstituted cyclooctadienes leads to the formation of trans-bicyclo[6.3.0]undecane ring systems, corresponding to **2**, with exceedingly high levels of stereochemical control.

SCHEME I



1 2 3

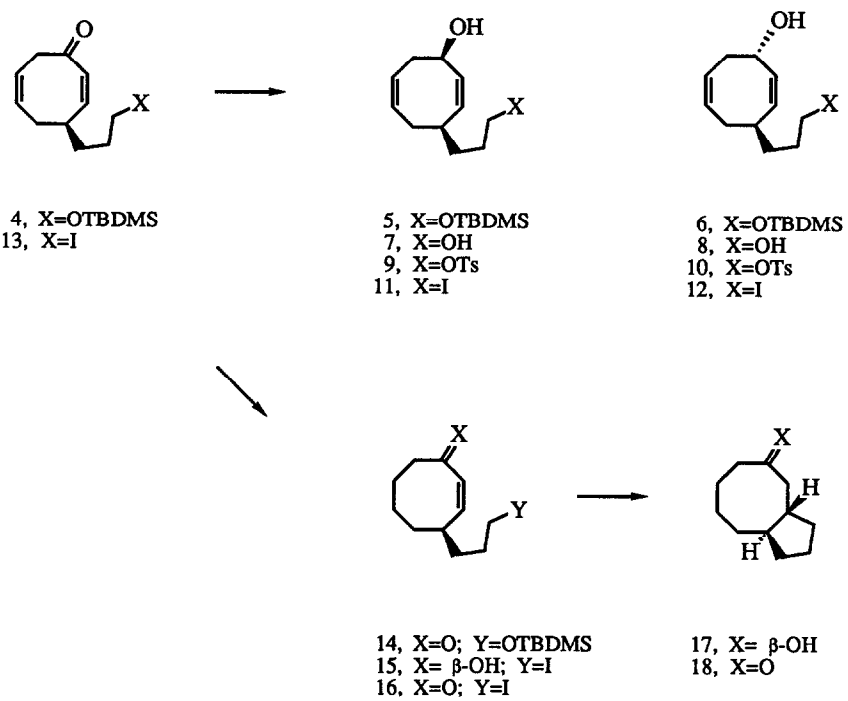
A B

The conformational analysis that was used to explain the stereochemical outcome of the cyclization of **1** (Scheme I; A: X=Y=H)[4] leads to very different predictions for the reaction of cis- and trans-disubstituted cyclooctadienes, respectively. A cis substituent at the 4-position of the cyclooctadiene (X=R; Y=H) should avoid the unfavorable transannular interaction shown in conformation B (X=R; Y=H), reinforcing the

+ Dedicated to Professors Gerhard Closs and N. C. Yang on the occasion of their sixtieth birthdays.

preference for the exo-orientation of the propyl chain (conformation A). However, a trans substituent (X=H; Y=R) should decrease the preference for the exo-orientation of the propyl substituent, since both conformations A and B would suffer transannular repulsive interactions. Based on this analysis, the trans/cis selectivity in the cyclization of a cis-disubstituted cyclooctadiene should be greater than that observed with monosubstituted-**1** (ca. 70:30), while the trans/cis selectivity for the trans-disubstituted substrate should be less than that observed with **1**.

SCHEME II



4, X=OTBDMS
13, X=I

5, X=OTBDMS
7, X=OH
9, X=OTs
11, X=I

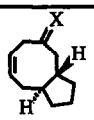
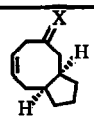
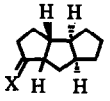
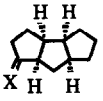
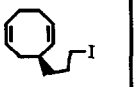
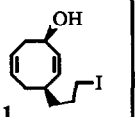
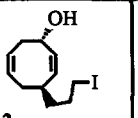
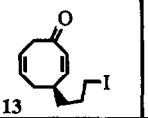
6, X=OTBDMS
8, X=OH
10, X=OTs
12, X=I

14, X=O; Y=OTBDMS
15, X= β-OH; Y=I
16, X=O; Y=I

17, X= β-OH
18, X=O

The cyclization substrates required to test these predictions were prepared as outlined in Scheme II. Reaction of cyclooctatetraene oxide with 2 equiv of 3-t-butyldimethylsilyloxy-propyllithium in tetrahydrofuran (THF) [10°C→reflux (1h), 85% yield] produced dienone **4**.[6,7] Reduction of **4** with L-Selectride (2 equiv in THF, -10°C, 74% yield) furnished a single alcohol, **5**, to which the cis-stereochemistry was assigned by careful analysis of the COSY-^{1}HNMR spectrum.[8] Reduction of **4** with $NaBH_4$ ($CeCl_3$, aq. MeOH, 25°C, 99% yield)[9] led to a mixture of two epimeric alcohols, **5** and **6** in a 3:1 ratio. The major $NaBH_4$ reduction product was identical with the L-Selectride product, so the minor product, **6**, was therefore assigned the trans stereochemistry. Conversion of silyl ethers **5** and **6** to the iodide cyclization substrates cis-**11** and trans-**12** proceeded via desilylation (n-Bu_4NF, THF, 90% yield), tosylate formation (1.5 equiv p-toluenesulfonyl chloride, 1.5 equiv triethylamine, 4-dimethylaminopyridine (cat.), dichloromethane, 65% yield), and conversion to the iodide (3 equiv sodium iodide, acetone, 98% yield). Dienone iodide **13** was prepared by oxidation of **9** (pyridinium dichromate, dichloromethane, 50% yield), followed by displacement of the tosylate with iodide (2 equiv sodium iodide, acetone, 90% yield).

TABLE

				
 1	73	11	11	5
 11	>99	<1	--	--
 12	50	10	20	20
 13	95	5	--	--

The results of the cyclizations of **11**, **12**, and **13** (1.1 equiv tributyltin hydride, AIBN (cat.), benzene, 150W sunlamp irradiation, in 65%, 70% and 65% yield, respectively), along with the earlier result obtained with **1** (see Table), are in good agreement with the predictions outlined above. The cyclization of **11** is indeed more selective for the formation of trans-bicyclo[6.3.0]undecane products than that of **1**, which, in turn, is more selective than the analogous reaction of **12**. The results obtained with the cyclization of the diene substrate **13** deserve special comment. Molecular mechanics calculations reveal that the conformation (Scheme I; B: X=Y=O) of **13** with the endo-oriented propyl chain is ca. 2.5 kcal/mol more stable than the conformation (A) with the exo-oriented propyl substituent.[10] However, the cyclization of **13** leads to the predominant (95:5) formation of the trans-fused bicyclic product (see Table). These results are consistent with a conformational change in B (Scheme I; X=Y=O) prior to cyclization (i.e., planarization of the enone) which leads to the exclusive formation of the trans-fused bicyclic product.

Finally, we note than equally high levels of stereochemical control are possible using eight-membered rings containing a single olefin, suggesting that local conformation biases are also important in these systems.[3b] Reduction of **4** (PtO_2, 1 atm. H_2, ethyl acetate, 100% yield) provided **14**, which, when submitted to the same steps outlined above, led to the formation of cyclization substrates **15** and **16**. Treatment of **15** and **16** with tributyltin hydride (1.1 equiv, azoisobutyronitrile (cat.), benzene, 150W sunlamp irradiation) led to the exclusive formation of **17** (70% yield) and **18** (79% yield), respectively. These results demonstrate that suitably substituted medium rings serve as very effective templates for highly stereoselective carbon-carbon bond formation. The extension of this methodology to other ring systems is currently in progress in our laboratory and will be reported in due course.

Acknowledgements. We thank Professor David Lynn for his assistance in obtaining and interpreting the COSY NMR data. Support from the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (CA40250), the Alfred P. Sloan Foundation, an American Cancer Society Institutional Grant, and Merck, Sharp and Dohme is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

References

1. Fellow of the Alfred P. Sloan Foundation (1987-1989). Recipient of a National Institutes of Health Career Development Award (1988-1993) and a Merck Grant for Faculty Development (1985-1986).

2. Current address: Department of Chemistry, Columbia University, New York, NY 10027.

3. a)Still, W. C.; MacPherson, L. J.; Callahan, J. F. Tetrahedron 1984, **40**, 2275; b) Still, W. C.; Galynker, I. Tetrahedron 1981, **37**, 3981; Still W. C.; Galynker, I. J. Am. Chem. Soc. 1982, **104**, 1774; d) Still, W. C.; Novak, V. J. Am. Chem. Soc. 1984, 106, 1148; e) Cameron, A.; Knight, D. J. Chem. Soc., Perkin I 1986, 161; f) Schreiber, S. L.; Hawley, R. C. Tetrahedron Lett. 1987, 35; h) Funk, R. L.; Abelman, M. M.; Munger, J. D. Tetrahedron 1980, **42**, 2831; j) Schreiber S. L.; Hulin, B.; Liew, W. Tetrahedron 1986, **42**, 2831; k) Mehta, G.; Rao, K. J. Am. Chem. Soc. 1986, **108**, 8015; k) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, Y. J. Am. Chem. Soc. 1983, **105**, 625; l) Schreiber, S. L.; Santini, C. J. Am. Chem. Soc. 1984, **106**, 4038; m) Vedejs, E.; Gapinski, D. J. Am. Chem. Soc. 1983, **105**, 5058; n) Corey, E. J.; Nicolaou, K. C.; Melvin, L. J. Am. Chem. Soc. 1975, **97**, 654; o) Doskotch, R.; Kelley, S.; Bufford, C. J. Chem. Soc., Chem. Comm. 1972, 1137. p) Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. J. Org. Chem. 1986, **51**, 3393, 4317; q) Maryanoff, B.; Almond, H. J. Org. Chem. 1986, **51**, 3295; r) Marshall, J. A.; Henson, T.; Dehoff, B. J. Org. Chem. 1986, **51** 5319; s) Raucher, S.; Chi, K.; Hwang, K.; Burks, J. J. Org. Chem. 1986, **51**, 5505; t) Paquette, L.; Lin, H.; Belmont, D.; Springer, J. J. Org. Chem. 1986, 51, 4807; u) Coates, R. M.; Muskopf, J. W.; Senter, P. J. Org. Chem. 1985, **50**, 3541; v) Quinkert, G.; Neim, M.; Glenneberg, J.; Billhardt, V.; Autze, V.; Bats, J.; Dunner, G. Angew. Chem. 1987, **26**, 362; w) Vedejs, E.; Dent, W.; Gapinski, D.; McClure, C. J. Am Chem. Soc. 1987, **109**, 5437.

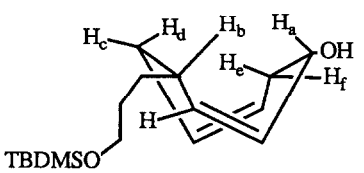
4. Winkler, J.; Sridar, V. J. Am. Chem. Soc. 1986, **108**, 1708.

5. a) Allinger, N.; Sprague, J. Tetrahedron 1975, **31**, 21; b) Anet, F.; Kozerski, L. J. Am. Chem. Soc. 1973, **95**, 3407; c) Ermer, O. J. Am. Chem. Soc. 1976, **98**, 3964.

6. a) Ogawa, M.; Sugishita, M.; Takagi, M.; Matsuda, T. Tetrahedron 1975, **31**, 299; b) Miller, M. J.; Lyttle, M. H.; Streitweiser, Jr., A. J. Org. Chem. 1981, **45** 1977.

7. All new compounds were characterized by full spectroscopic (NMR, IR, MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

8. The COSY-^{1}HNMR spectrum permitted the assignment of the cyclooctadiene ring protons as indicated below. The assignment of the cis stereochemistry was then made based on the coupling constants (J_{ae}=6 Hz; J_{af}= 3Hz; J_{bc}=4 Hz; J_{bd}=12 Hz) and the 1 Hz W-coupling observed between H_c and H_f.



9. Luche, J. L.; Rodriquez-Hahn, L.; Crabbe, P. J. Chem. Soc., Chem. Comm. 1978, 601.

10. Calculated using the Gajewski/Gilbert modification of the Allinger MM2 program (#395, Quantum Chemistry Program Exchange, Indiana University), which is commercially available through Serena Software, Bloomington, IN.

(Received in USA 1 September 1988)