Opening of Oxabicyclo[3.2.1]octenes with Organolithium Reagents. A Route to Cyclic and Acyclic Compounds with High Stereocontrol

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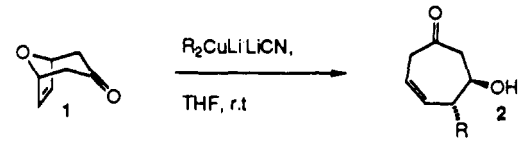
Summary: A range of oxabicyclo[3.2.1]octenes has been found to undergo opening when treated with organolithium reagents. Up to five stereocenters are created in two steps. Oxidative cleavage leads to a stereocontrolled synthesis of polysubstituted cycloheptanediols.

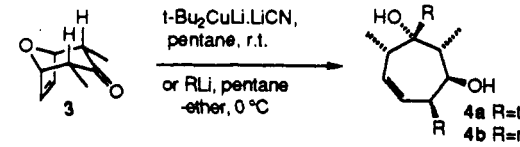
The oxidative cleavage of seven-membered rings bearing multiple stereocenters has proven to be an extremely attractive approach to the synthesis of polysubstituted acyclic compounds.[2] The obstacle associated with this strategy is clearly the efficient preparation of highly substituted cycloheptenes. It remains a challenge to devise methods that control the relative stereochemistry in this particular ring due to its conformational flexibility. One solution that has been reported by Pearson and co-workers involves the reaction of cycloheptadiene–metal complexes with nucleophiles where the metal template acts as a control element.[3] As an alternative approach, we envisage direct cleavage of the bridging C–O bond in an oxabicyclic compound for the synthesis of substituted cycloheptenes.[4] Because simple methods to achieve this end are not in hand, the merits of this strategy have not been explored.[5] Since oxabicyclic compounds are readily available compounds,[6] we have become interested in effecting cleavage of this bond as an entry into the stereocontrolled synthesis of cycloheptenes and subsequently acyclic compounds. In this paper we report that addition of organolithium reagents to oxabicyclooctenes provides an extremely efficient route to seven-membered rings where three to five contiguous stereocenters are created in two operations.

We have recently reported that 8-oxabicyclo[3.2.1]oct-5-en-3-one (1) reacts with organocuprates, giving hydroxycycloheptenones **2** where the major product arises from S_N2' attack to furnish the trans isomer, eq 1.[7] During our



(1)

studies of the reaction of t-$Bu_2CuCNLi_2$ with the more highly substituted oxabicyclic compound **3**,[8] we noted that changing the solvent from THF to pentane led to a new major product, **4a**, where 2 equiv of the organolithium had been incorporated. We suspected that addition of the alkyl group to the carbonyl had preceded the opening.[9] Since organocuprates were previously shown to be unreactive toward oxabicyclic compounds lacking the carbonyl group,[7] we concluded that the free organolithium, not the cuprate, was the reactive component in the ring opening. When the experiment was repeated with t-BuLi in ether–pentane mixtures at 0 °C, we obtained **4a** in 73% yield as a white crystalline solid, eq 2.[10] n-Butyllithium reacted in an



(2)

analogous fashion to provide **4b** in 78% yield. The stereochemistry of these additions could not be unambiguously assigned by using ^1H NMR spectroscopy but X-ray crystallographic analysis confirmed that the structure is as represented by **4a**. That is, attack on the carbonyl had occurred to furnish the axial alcohol, which was subsequently attacked from the exo face creating a cis-1,2 relationship of the hydroxyl and *tert*-butyl groups.[11] *Stereochemically complementary hydroxycycloheptenes are now available by simply changing from a cuprate to an organolithium reagent.*

We are aware of no previous reports of reaction with oxabicyclo[3.2.1] compounds with organolithium reagents although benzoxabicyclic compounds are known to undergo the addition followed by an elimination reaction, yielding hydroxyl-1,4-dihydronaphthalenes.[12] These results parallel those of earlier workers who have shown that organolithium compounds add to other strained olefins such as norbornene. More recently, Fernandez de la Pradilla and Arjona have reported that organolithium species react with 7-oxabicyclo[2.2.1]hept-5-en-2-one to

(1) (a) NSERC(Canada) University Research Fellow 1987–1992, Bio-Mega Young Investigator 1990–1992. (b) NSERC(Canada) Postdoctoral Fellow 1990. (c) Author to whom inquiries regarding the crystal structure should be addressed.

(2) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513. Stork, G.; Nair, V. *J. Am. Chem. Soc.* **1979**, *101*, 1315. Pearson, A. J.; Bansal, H. S. *Tetrahedron Lett.* **1986**, *27*, 283. Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735. Pearson, A. J.; Lai, Y.-S.; Lu, W.; Pinkerton, A. A. *J. Org. Chem.* **1989**, *54*, 3882.

(3) Pearson, A. J. *SynLett.* **1990**, *1*, 10 and references therein.

(4) Cleavage of the three-carbon bridge or two-carbon bridge in the bicyclic starting material are far more common strategies, see: (a) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (b) Cowling, A. P.; Mann, J.; Usmani, A. A. *J. Chem. Soc., Perkin Trans.* **1981**, 2116. (c) Rama Rao, A. V.; Yadav, J. S.; Vidyasagar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 55.

(5) White has reported that 1-acetyl-8-oxabicyclo[3.2.1]oct-6-en-3-one can be transformed into a cycloheptene and subsequently into the Prelog–Djerassi lactone by using a Baeyer–Villiger approach where eventual cleavage of the one-carbon bridge has taken place. However, this strategy is viable for this substitution pattern only. White, J. D.; Fukuyama, Y. *J. Am. Chem. Soc.* **1979**, *101*, 226. For the cleavage of a bridging C–O bond in other oxabicyclic systems, see: (a) Rigby, J. H.; Zbur Wilson, J. A. *J. Org. Chem.* **1987**, *52*, 33. (b) Ohtsuka, T.; Shirama, H.; Matsumoto, T. *Chem. Lett.* **1984**, 1923.

(6) See ref 4a and (a) Ashcroft, M. R.; Hoffmann, H. M. R. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 512. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Foehlisch, B.; Gottstein, W.; Herter, R.; Wanner, I. *J. Chem. Res. (S)* **1981**, 246.

(7) Lautens, M.; DiFelice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817. The relative stereochemistry of the R group and hydroxyl group from the cuprate opening was recently proven by X-ray crystallography. Details will be published in our full account of this work.

(8) Unpublished results of A. C. Smith and A. S. Abd-El-Aziz.

(9) A small amount of carbonyl addition product was also isolated from this reaction.

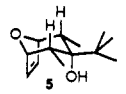
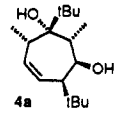
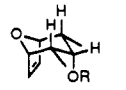
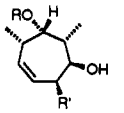
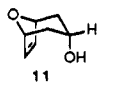
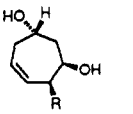
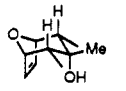
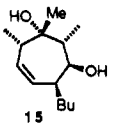
(10) Satisfactory ^1H and ^{13}C NMR, IR, and mass spectral data and/or C,H analyses were obtained for all new compounds.

(11) For full details of the X-ray structure, see the supplementary material.

(12) (a) Caple, R.; Chen, G. M.-S., Nelson, J. D. *J. Org. Chem.* **1971**, *36*, 2874. (b) Mulvaney, J. E.; Garlund, Z. G. *J. Org. Chem.* **1965**, *30*, 917. (c) Wittig, G.; Otten, J. *Tetrahedron Lett.* **1963**, 601. (d) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437.

0022-3263/90/1955-5305$02.50/0

Table I. Organolithium Opening of Oxabicyclo[3.2.1]octenes

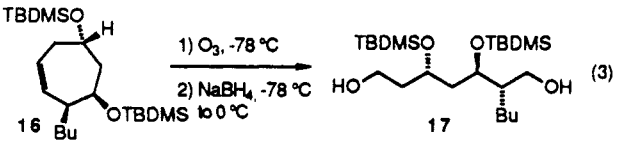
entry	oxabicyclo[3.2.1]-octenes	product	yield,[a] %
1			85
			
2	(a) **6**, R = H (b) **6**; R = H (c) **9**; R = TBDMS	**7**, R = H, R′ = Bu **8**; R = H, R′ = Me **10**; R = TBDMS, R′ = Bu	92 72[b] 79
			
3	(a) (b)	**12**; R = *t*-Bu **13**; R = *n*-Bu	82 88
4			74

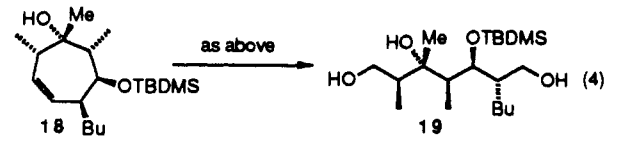
[a] Isolated yields of analytically pure material. [b] 1:1 ether/TMEDA were required as solvent before reaction occurred.

give ring-opened products.[12d]

Several examples are shown in Table I that demonstrate the utility of this reaction. Tertiary and primary lithium reagents react with equal facility with several of the substrates, implying that there is little or no steric effect associated with the opening. Methyllithium failed to react with several of the substrates under similar conditions. However, upon adding TMEDA, ring opening occurred smoothly. The basicity or electron-transfer ability of the starting lithium reagent vs the product derived from addition of RLi across the olefin may be very important in explaining the lack of reactivity of the less basic methyllithium in the absence of TMEDA. Carbonyl addition does precede ring opening as shown by treating the ketone at low temperature (−78 to 0 °C) with 1 equiv of *t*-BuLi to give the tertiary alcohol **5**. Treatment of **5** under the standard conditions (3 equiv of RLi, 1:1 ether/pentane, 0 °C) provided **4a** in very good yield. Reduction of the carbonyl group in compounds **3** and **1** was effected by using L-Selectride,[13] which gave the axial alcohols **6** and **11** to avoid the double addition process. Each of these compounds underwent facile opening with an organolithium to provide **7**, **8**, **12**, and **13**. Protection of the alcohol in **6** as its silyl ether followed by opening gave **10** in which the two secondary alcohols have been differentiated. We also took advantage of the higher reactivity of the carbonyl group vs the bicyclic opening for the addition of two different "R" groups. Methyllithium reacted with ketone **3** to provide tertiary alcohol **14**. When **14** was treated with 3 equiv of *n*-BuLi at 0 °C in ether we isolated diol **15**. Compounds **12** and **13** contain a 1,2,4 stereochemical array while **4a,b**, **7**, **8**, **10**, and **15** contain five contiguous stereocenters. *Thus, in two (or three) steps, furan is converted into a cycloheptene with control at three to five stereocenters.*

We have subjected two of the protected cycloheptenes to ozonolysis and reduction to show the utility of this methodology for the synthesis of acyclic chains bearing multiple stereocenters.[2] Treatment of **16** and **18**[14] with ozone followed by treatment of the ozonide with sodium borohydride furnished diols **17** and **19** in 92 and 78% yields, respectively, eqs 3 and 4. The use of the oxabicyclic framework to control the stereochemistry of the tertiary alcohol in the eventual acyclic chain is noteworthy.





These results demonstrate the viability of a strategy based on the double ring opening of oxabicyclic compounds for rapid entry into polysubstituted 1,7-hexanediol fragments. Studies are in progress on the application of this sequence to the synthesis of natural products.

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, the Bickell Foundation, and BioMega Inc.

Supplementary Material Available: Preparation and spectral data for all new compounds including X-ray parameters for compound **4a** (20 pages); observed and calculated structure factors for **4a** (6 pages). Ordering information is given on any current masthead page.

(13) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(14) Compounds **15** and **16** were prepared by silylation of the secondary alcohols using TBDMSCl, imidazole, DMF; see: Corey, E. J.; Venkateswarlu, Y. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Zr(O-*t*-Bu)$_4$, an Efficient and Convenient Basic Reagent in Organic Synthesis. Utilization in Cross and Intramolecular Aldol Reactions

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Summary: Zr(O-*t*-Bu)$_4$ has been found to be a mild basic reagent that can be utilized in cross aldol reactions and intramolecular aldol reactions, in which the use of usual metal enolates such as Li enolate and Cp_2ZrCl enolate give unsatisfactory results (2-cyclopentenone → **5**, **7** → **8**, and **13** → **14**).

