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An Efficient Synthesis of 1,3-Cyclohexadienes from Oxabicyclo[2.2.1]heptenes via Tandem Ring Opening-Peterson Elimination Reactions

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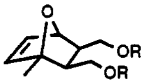
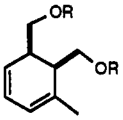
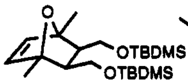
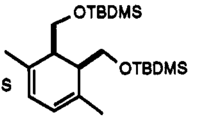
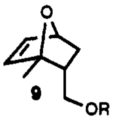
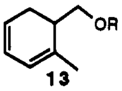
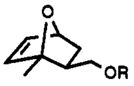
Summary: Oxabicyclo[2.2.1]heptenes react with $PhMe_2SiLi$ or $PhMe_2SiCu{\cdot}LiCN$ to yield 1,3-cyclohexadienes. The reaction pathway is shown to proceed via an addition-elimination-Peterson olefination sequence.

There exist several strategies for the preparation of 1,3-cyclohexadienes. For example, the conversion of an aromatic compound to a cyclohexadiene has been achieved via the Birch reduction,[2] enzymatic cis hydroxylation,[3] or nucleophilic addition to an arene-metal complex.[4] Metal-catalyzed elimination of acetic acid from cyclohexenyl acetates represents an alternative approach which also utilizes a cyclic starting material.[5] Various cyclization strategies have also been employed including the tandem conjugate addition-Wittig reaction of an enolate to a dienyl phosphonium salt[6] or the electrocyclization of a hexatriene.[7] A tandem cycloaddition-extrusion sequence via the intermediacy of a bicyclic intermediate represents yet another entry into these compounds.[8] A pertinent example of the latter strategy relevant to the results described in this work utilizes a Diels-Alder cycloaddition between 2*H*-pyran-2-one (α-pyrone) and a suitable dienophile.[8a,c] Subsequent spontaneous extrusion of CO_2 (via a retro Diels-Alder reaction) at temperatures >110 °C yields the cyclohexadiene directly. However, α-pyrone is prohibitively expensive to make this a generally applicable and widely used strategy.

Herein, we describe an alternative approach which uses a furan in place of α-pyrone. The net process is extrusion of "O" from an oxabicyclic compound.[9-12] Simple routes to the starting materials, moderate reaction temperatures (0 °C to room temperature), and access to substituted cyclohexadienes with complete control of the positioning of the double bonds within the ring are noteworthy features of this methodology.

Table I. Synthesis of Cyclohexadienes from Oxabicyclic Compounds[a]

entry	substrate	product		conditions, time[1]	yield
1	 **7**	 **11**	a R = TIPS	A, O/N	89%[2]
				B, 6h	78%[2]
			b R = Bn	B, 6h	81%
2	 **8**	 **12**		B, 7h	83%[2]
3	 **9**	 **13**	a R = TIPS	A, 4.5h	71%[2]
				B, 5h	58%[2]
			b R = Bn	B, O/N	90%
4	 **10**	**13**	a R = TIPS	A, 5h	79%[2]
				B, 2.5h	70%[2]
			b R = Bn	B, 5h	78%
			c R = H	B, 30 min	79%

[a] Key: (1) conditions: A = 4-8 equiv of $PhMe_2SiLi$ in ether at 0 °C, B = 2-4 equiv of $(PhMe_2Si)Cu{\cdot}LiCN$ in THF, 0 °C to rt; (2) a small amount of a silyl impurity contaminated the product, see ref 16.

The reactions of symmetrical 7-oxabicyclo[2.2.1]heptenes such as **1** serve to illustrate the process. Treatment of **1a** (R = TBDMS) with a solution of $PhMe_2SiLi$ in ether at 0 °C gave diene **2a** as the major product. However, this reaction was capricious, sometimes leading to further reaction of the diene with unreacted silyllithium reagent. The silylcopper species proved to be more chemoselective.[13] Reaction of 1.1 equiv of $PhMe_2SiCu{\cdot}LiCN$ in THF at 0 °C to room temperature for 50 min gave **2a** in 73% yield. The reaction was equally efficient for **1** bearing other protecting groups such as **1b** (R = Me) and **1c** (R = Bn); treatment with $PhMe_2SiCu{\cdot}LiCN$ gave the dienes **2b** and **2c** in 87% and 88% yields respectively.[14-16]

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[1] (a) Alfred P. Sloan Foundation Fellow 1991-1993; NSERC (Canada) University Research Fellow 1987-1992; Bio-Mega Young Investigator 1990-1993. (b) NSERC (Canada) Postgraduate Scholar 1989-92.

[2] (a) Birch, A. J.; Jenkins, I. D. *Transition Metals in Organic Synthesis*; Alper, H., Ed.; Academic Press: New York, 1976; pp 1-82. (b) Pearson, A. J. *Acc. Chem. Res.* 1980, *13*, 463. Subsequent isomerization of the 1,4-diene to the conjugated 1,3-diene is required.

[3] Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* 1970, *9*, 1626. For examples of the utility of this reaction in organic synthesis, see: (a) Ley, S. V.; Redgrave, A. J. *Synlett.* 1990, 393. (b) Hudlicky, T.; Price, J. D.; Luna, H.; Andersen, C. M. *Synlett.* 1990, 309 and references cited therein.

[4] Kundig, E. P.; Simmons, D. P. *J. Chem. Soc.*, Chem. *Commun.* 1983, 1320.

[5] For a recent example, see: Trost, B. M.; Tometzki, G. B. *Synthesis* 1991, 1235 and references cited therein.

[6] Fuchs, P. L. *Tetrahedron Lett.* 1974, 4055.

[7] For a recent review of cyclohexadiene-forming reactions including electrocyclic processes, see: Okamura, W.; De Lara, A. R. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 699.

[8] (a) Stark, B. P.; Duke, A. J. *Extrusion Reactions*; Pergamon Press: New York, 1967 and references therein. (b) Extrusion of SO_2 has also been observed, for example: Jung, F.; Molin, M.; Van Den Elzen, R.; Durst, T. *J. Am. Chem. Soc.* 1974, *96*, 935. (c) This strategy has been used in a synthesis of copaenes and ylangenes, see: Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* 1973, *95*, 2303. (d) For a review of α-pyrones, see: Staunton, J. *Comprehensive Organic Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1979; Vol. 4, p 629.

[9] For the ring opening of [3.2.1] systems with organocuprates and organolithium reagents, see: (a) Lautens, M.; DiFelice, C.; Huboux, A. *Tetrahedron Lett.*, 1989, *30*, 6817. (b) Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* 1990, *55*, 5305.

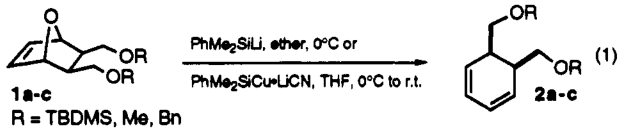
[10] For the ring opening of [2.2.1] systems, see: (a) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* 1989, *30*, 6437. (b) Lautens, M.; Smith, A. C.; Abd-El-Aziz, A. S.; Huboux, A. H. *Tetrahedron Lett.* 1990, *31*, 3253.

[11] Silylcuprates undergo addition but not elimination in oxabicyclo[3.2.1]octenes; see: Lautens, M.; Belter, R. K.; Lough, A. *J. Org. Chem.* 1992, *57*, 422. The increase in strain in [2.2.1] systems may be responsible for the ring opening described in the current work.

[12] Utilization of oxabicyclo[2.2.1] systems for the preparation of "naked sugars" has been elegantly demonstraed by Vogel, see: Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett.* 1990, *1*, 173.

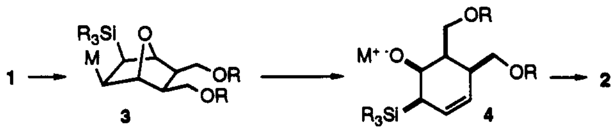
[13] Fleming, I.; Landais, Y.; Raithby, P. R. *J. Chem. Soc.*, Perkin *Trans. 1* 1991, 715 and references cited therein.

0022-3263/92/1957-4065$03.00/0



1a-c
R = TBDMS, Me, Bn
2a-c

Scheme I



The proposed mechanism for conversion of the starting material to the diene invokes a silacupration or silalithiation of the highly strained olefin from the exo face to give **3** which undergoes subsequent ring opening to the alkoxysilane **4**, Scheme I.[10,11] Finally, Peterson elimination provides the diene **2**.[17] This mechanism is supported by the isolation of all of the proposed intermediates in the sequence.[18]

An examination of the scope of this reaction was undertaken. Table I lists the range of substrates studied. A comparison was made between PhMe$_2$SiLi and PhMe$_2$SiCu·LiCN (conditions A and B in Table I). In contrast to **1**, oxabicyclic compounds **7–10** bearing substituents at the bridgehead position react smoothly with either the silyllithium or silylcopper reagent. Yields of the dienes ranged from 58–90%. Usually, 1.5–4 equiv of PhMe$_2$SiCu·LiCN is necessary to ensure complete consumption of the starting material, whereas 6–8 equiv of PhMe$_2$SiLi are routinely required. When following the reaction progress by TLC, rapid formation of a more polar product (presumably either **5** or **6**) is observed.[18] Upon increasing the temperature, the diene is isolated. Efficiency, regioselectivity, and mildly basic conditions are characteristics of this methodology; no further isomerization of the olefins has been observed. The reaction is equally useful for small to medium scale and the yields improve with increasing scale. The rates of consumption of the oxabicyclic compounds are nearly identical regardless of the presence or absence of substituents at the bridgehead. However, the subsequent ring opening or Peterson elimination occur at different rates as a function of the substrate. Thus, while **1a** requires 50 min for conversion to the diene, **8** and **9** require 5–7 h.

In summary, we have shown that ring opening of [2.2.1]oxabicyclic compounds occurs with silyllithium or silylcopper reagents to form cyclohexadienes. Efforts to utilize this reaction sequence in the preparation of biologically active compounds are in progress and will be reported in due course.

Acknowledgment. This research was supported by the Alfred P. Sloan Foundation, the Natural Sciences and Engineering Research Council (NSERC) of Canada, Bio-Mega Inc., and the Merck Frosst Centre for Therapeutic Research.

Supplementary Material Available: Experimental procedures and spectral data for all new compounds including ^{1}H and ^{13}C NMR spectra (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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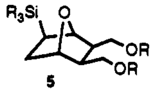
[14] Satisfactory ^{1}H and ^{13}C NMR, IR, and mass spectral data were obtained for all new compounds.

[15] A typical experimental procedure is as follows: Phenyldimethylsilyllithium is prepared by stirring phenyldimethylchlorosilane (1 mL) and lithium in tetrahydrofuran (14 mL) at 0 °C for 24 h to make an approximately 0.4 M solution. **General Conditions A.** A solution of phenyldimethylsilyllithium (4–8 equiv) was added to a flame-dried flask fitted with a vacuum adapter, and the THF was removed under vacuum. The resulting red-black concentrate was dissolved in diethyl ether at 0 °C (concentration was approximately 0.8 M). The oxabicyclic compound was dissolved in an equal volume of diethyl ether and transferred via cannula to the flask. After 8 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. Flash chromatography gave the diene. **General Conditions B.** Copper cyanide was added to a flask and dried overnight in vacuo (0.1 mmHg). The flask was cooled in an ice bath, and a solution of phenyldimethylsilyllithium (1:1 ratio of Si–Cu, 2–4 equiv based on oxabicyclic compound) was added. After 30 min at 0 °C, the oxabicyclic compound was added as a solution in THF. After 30 min, the mixture was allowed to warm to room temperature and stirred for 4 h or until TLC indicated that all the starting material was consumed. Workup and purification were carried out as described above.

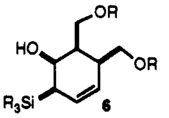
[16] When the substrate has a silyl protecting group, the dienes produced are contaminated with approximately 5% of a phenyldimethylsilyl-containing compound. Cleavage of the PhMe$_2$Si group (5 equiv of Bu_4NF, THF, rt) gave the more polar diols which were readily purified.

[17] For a review of the Peterson elimination, see: Ager, D. J. *Org. React.* **1990**, *38*, 1.

[18] Reaction of 1 with PhMe$_2$SiCu·LiCN at −40 °C rather than 0 °C, followed by workup (NH_4Cl), leads to the isolation of **5** (89% yield). Treatment of **1a** with (PhMe$_2$Si)$_2$CuCNLi$_2$ in THF at 0 °C gave a 36% yield of **5** accompanied by 41% of the ring-opened product **6**. These results are in contrast to those obtained from reaction of oxabicyclo[3.2.1] substrates, see ref 11.



5



6

Ni(0)-Catalyzed Cross Coupling of Aryl *O*-Carbamates and Aryl Triflates with Grignard Reagents. Directed Ortho Metalation-Aligned Synthetic Methods for Polysubstituted Aromatics via a 1,2-Dipole Equivalent[†]

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Summary: The first Ni(0)-catalyzed cross-coupling reactions of aryl *O*-carbamates and aryl triflates with Grignard reagents (Scheme I) to give diversely polysubstituted aromatics **2d** and **2e** (Table I) which feature regiospecificity based on directed ortho metalation (carbamate), minimal β-hydride elimination (triflate), and dependence on steric and electronic effects are described.

We report on the first Ni(0)-catalyzed aryl *O*-carbamate and aryl triflate cross-coupling reactions with Grignard

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[†] Dedicated to Professor Virgil Boekelheide on the occasion of the first VB Reunion, University of Oregon, Aug 1991.

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