Pergamon

Tetrahedron Letters, Vol. 37, No. 37, pp. 6635-6638, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01494-3

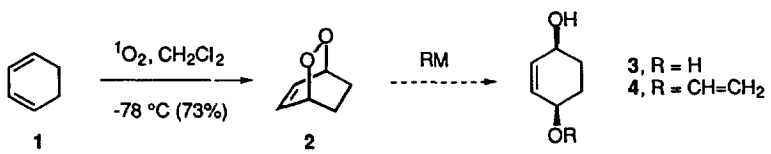
ORGANOMETALLIC NUCLEOPHILIC RING-OPENING OF ENDO PEROXIDES

Michael K. Schwaebe and R. Daniel Little*

Department of Chemistry
University of California, Santa Barbara
Santa Barbara, CA 93106

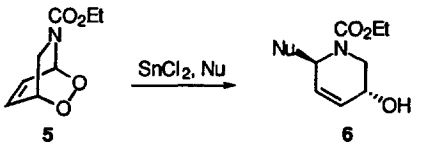
Abstract: The reaction of symmetrical and unsymmetrical endo peroxides with organometallic reagents affords hydroxy ethers. Primary, secondary, vinyl and aryl groups can be transferred with alkyllithium and Grignard reagents providing the best yields, organozincates, moderate. This demonstrates a new reactivity pattern for endoperoxides and provides a novel method for the formation of a variety of useful building blocks.

Bicyclic endo peroxides serve as a convenient source of cis-1,4-diols.[1] For example, treatment of 1,3-cyclohexadiene with singlet oxygen followed by reductive cleavage of the peroxide bond affords the diol **3**. Selective mono-functionalization at one of the hydroxyl groups is, of course, complicated by the symmetrical nature of this material. Our approach to desymmetrization focused on the possible direct addition of an organometallic, RM, across the peroxide bridge. We are pleased to report that this is an effective strategy, one that provides an exceptionally direct route to a variety of useful materials.



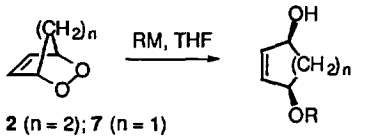
1 2

While the reaction of organometallics with acyclic alkyl peroxides is well known, similar chemistry with bicyclic systems is not nearly as well developed.[2] That which has been reported suggests that the transformation illustrated above will not occur. For example, treatment of ascaridole with methylmagnesium iodide affords a mixture of products, none of which included the hydroxy methyl ether.[3,4] Furthermore, the peroxides of 9,10-diphenyl, 9,10-di-*p*-tolyl, and 9,10-di-*m*-tolyl anthracenes react with phenylmagnesium bromide to afford in quantitative yield, the 1,4-diol and biphenyl.[5] On the other hand, the endoperoxides of 1,2-dihydropyridines do undergo reductive cleavage of the peroxide linkage when treated with an enol ether or enamine in the presence of stannous chloride.[6] The product results from nucleophilic attack at carbon of an intermediate allylic cation to afford products of the type illustrated below.



5 6

Our initial efforts were directed toward the assembly of vinyl ether **4** (R = $CH{=}CH_2$), the latter to be used in a subsequent Claisen rearrangement. While traditional etherification methods are known to provide **4**,[7] we explored the direct addition of vinylmagnesium bromide or vinyllithium, initially in the presence of 1.25 equiv of BF_3. The results were encouraging, **4** being obtained in yields ranging from 69-84%, after only 0.5 h at -78 °C. Eventually, we discovered that the reaction occurred with greater reducibility and in higher yields in the absence of the Lewis acid. In this case, 1.25 equiv of vinyllithium was added to a solution of the peroxide **2** at -78 °C in THF. When the addition was complete, the cooling bath was removed and the solution allowed to warm to 0 °C, at which time workup was initiated. As shown in the Table, the generality of the process was explored and its scope expanded by demonstrating that straight chain and cyclic alkyl, as well as



2 (n = 2); **7** (n = 1)

4, R = $CH_2{=}CH$-, n = 2
8, R = *n*-Bu-, n = 2
9, R = Ph-, n = 2
10, R = cyclohexyl, n = 2
11, R = $CH_2{=}CH$-, n = 1

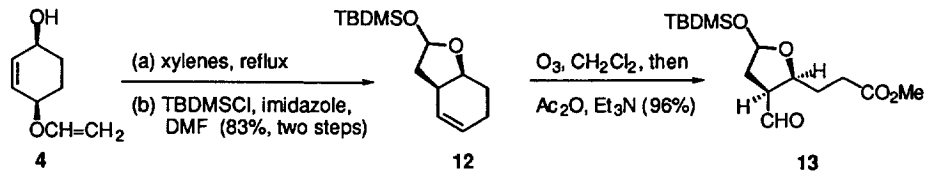
entry	RM	n	product	yield (%)
1	$CH_2{=}CHMgBr$	2	**4**	93
2	$CH_2{=}CHLi$	2	**4**	94
3	$(CH_2{=}CH)_3Zn$	2	**4**	45
4	*n*-BuLi	2	**8**	96
5	$(n\text{-Bu})_3Zn$	2	**8**	50
6	PhMgBr	2	**9**	98
7	$C_6H_{11}MgBr$	2	**10**	69
8	$CH_2{=}CHLi$	1	**11**	83

aryl groups can also be added. Grignard and organolithium reagents are most effective, organozinc-ates work, but in modest yield, while alanates failed to add cleanly.

The procedure used to prepare vinyl ether **4** is typical, it having been run on a scale up to 80 mmol. Thus, to a tared flask was added 3.5 mL of a 2.23 M solution of endoperoxide **2** in THF. The solvent was removed *in vacuo* and the flask reweighed. The endoperoxide (865 mg, 7.72 mmol) was diluted with 20 mL of THF and chilled to -78 °C under argon. Vinyllithium (5.3 mL, [2.2 M], 11.6 mmol) was added dropwise and the reaction mixture was allowed to warm to 0 °C over 30 min. The resulting solution was poured into a separatory funnel containing 100 mL of Et_2O and 50 mL of saturated ammonium chloride. The aqueous layer was extracted with 25 mL of CH_2Cl_2 followed by 25 mL of Et_2O and the combined organic layers were

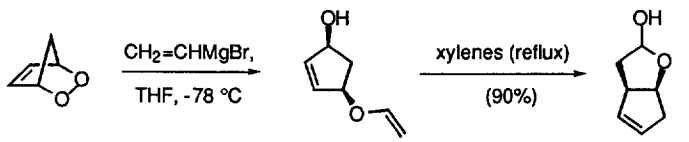
chromatographed on neutral alumina (30% Et_2O/pentane) to afford **4** as a clear, colorless oil (1.156 g, 8.26 mmol, 94%).[8]

We believe the utility of the process is highlighted by the conversion of vinyl ether **4** to the silylated lactol **12**, *via* a Claisen rearrangement and protection of the lactol formed *in situ*. Overall, the process adds a lactol to one of the two π-bonds of 1,3-cyclohexadiene, in a stereochemically defined manner, and leaves the other available for additional functionalization. To meet our needs, the alkene was oxidatively cleaved to afford the simple, yet relatively highly functionalized building block **13**.



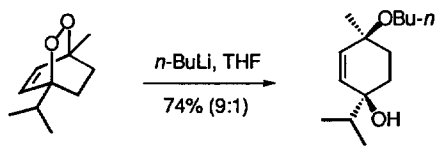
4 **12** **13**

A similar sequence applied to cyclopentadiene (CpH) proved more demanding, given the increased lability of the [2.2.1] endo peroxide **7**. Thus, following the addition of singlet oxygen, the solvent and excess cyclopentadiene were removed *in vacuo*, being exceptionally careful to assure that the temperature did not exceed 0 °C. [CAUTION: at temperatures exceeding 0 °C, this peroxide undergoes a thermal rearrangement.] Prechilled THF (-50 °C) was added, the resulting mixture cooled to -78 °C, and vinylmagnesium bromide (1.2 equiv based on the crude weight of the endoperoxide) was added. Once the addition was complete, workup was initiated, leading to an 83% yield of vinyl ether **11** on a 55 mmol scale.[9] Subsequent Claisen rearrangement proceeded efficiently to afford the useful lactol **14** in a 90% yield.



7 **11** **14**

Finally, we are pleased to report that the methodology is also effective when applied to ascaridole. That is, in contrast to the observation cited in the introduction to this paper,[6,7] treatment of it with *n*-butyllithium afforded a 74% yield of a 9:1 mixture of regioisomeric hydroxy ethers, with **15** corresponding to the major product.



ascaridole **15**

In conclusion, we believe that the methodology described herein provides a useful, direct, and efficient route to materials that can serve as building blocks in a variety of contexts, those illustrated being but a small sample.

Acknowledgements. We are pleased to thank the Natioanl Science Foundation and the National Institutes of Health for their support of our research.

References

1. Balci, M. *Chem. Rev.* **1981,** *81*, 91-108.
2. Razuvaev, G. A.; Shushunov, V. A.; Dodonov, V. A.; Brilkina, T. G. Reactions of Organometallic Compounds with Organic Peroxides. In *Organic Peroxides;* Swern, D. Ed.; John Wiley & Sons: New York, 1972; Vol. 3; pp. 141-270.
3. Treibs, W. *Ber.* **1942,** *75*, 1164.
4. Treibs, W. *Ber.* **1951,** *84*, 438.
5. Mustafa, A. *J. Chem. Soc.* **1949**, 1662.
6. Natsume, M.; Sekine, Y.; Ogawa, M.; Soyagimi, H.; Kitagawa, Y. *Tetrahedron Lett.* **1979,** *36*, 3473-3476.
7. Kondo, K.; Matsumoto, M.; Mori, F. *Angew. Chem. Internat. Edit.* **1975,** *14*, 103.
8. NMR Data for Compound **4**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.340 (dd, J = 5.2, 11.6 Hz, 1H), 5.936 (dd, J = 2.5, 8 Hz, 1H), 5.860 (dd, J = 2.5, 10 Hz, 1H), 4.297 (dd, J = 1.6, 11.6 Hz, 1H), 4.259 (br m, 1H), 4.133 (br m, 1H), 4.042 (dd, J = 1.6, 5.2 Hz, 1H), 1.995 (br s, 1H), 1.725-1.923 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) 150.22, 133.98, 128.51, 88.66, 71.65, 65.20, 28.03, 24.63.
9. NMR Data for Compound **11**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.365 (ddd, J = 0.8, 6.8, 14.4 Hz, 1H), 6.054 (ddd, J = 1.2, 2, 6 Hz, 1H), 5.985 (ddd, J = 1.2, 1.6, 5.6 Hz, 1H), 4.738 (br ap q, J = 1.6, 5.2 Hz, 1H), 4.634 (br m, 1H), 4.236 (dd, J = 1.6, 14 Hz, 1H), 4.032 (ddd, J = 0.8, 2, 6.8 Hz, 1H), 2.803 (br s, 1H), 2.710 (ap quintet, J = 7.6, 14.8 Hz, 1H), 1.627 (ap dt, J = 4, 14.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) 150.02, 138.14, 132.45, 88.30, 80.44, 74.58, 40.49.

(*Received in USA* 2 *July* 1996; *accepted* 23 *July* 1996)