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CHELATION-CONTROLLED REGIOSELECTIVE EPOXIDE-CARBONYL REARRANGEMENT OF 1-OXASPIROHEXANE DERIVATIVES

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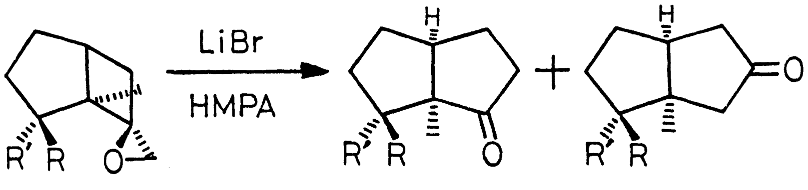
Lithium bromide-catalyzed epoxide-carbonyl rearrangement of 7,8-epoxy-7-methylenebicyclo[3.2.0]heptane derivatives gave 2,8-difunctionalized bicyclo[3.3.0]octanes in high selectivity.

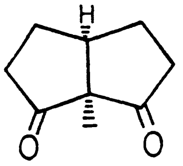
Much attention has been focused on the development of new efficient five-membered-ring annelation methods because of increasing current interest in polyquinane chemistry.[1)] Lithium halide-catalyzed epoxide-carbonyl rearrangement of 1-oxaspirohexane derivatives is one of the most useful methods for such transformation.[2)] The regioselectivity of the rearrangement is dominated by electronic factor; the most highly substituted carbon migrates preferentially, though the selectivity is not satisfactory in some cases.[2c,e)] We disclose herein highly regioselective epoxide-carbonyl rearrangement of 1-oxaspirohexane derivatives (1a-d) giving 2,8-difunctionalized bicyclo[3.3.0]octanes (2a-d) through migration of the less substituted carbon, whose selectivity is controlled by chelation of intramolecular oxygen bearing group to the lithium cation.[3)]



1a-d 2a-d 3b-d

	R	R'
a	OH	H
b	OMe	H
c	OCH_2OMe	H
d	OCH_2CH_2O	

The syn-epoxides **1a**-**d** were prepared from 2-methylcyclopentenone in regio- and stereoselective manner.4,5) When the alcohol **1a** was treated with 1 equiv. of lithium bromide and hexamethylphosphoramide in boiling benzene,6) the hydroxy ketone **2a** was obtained as a sole product in 86% yield. The structure of **2a** was confirmed by PCC oxidation to give the symmetrical diketone **4** (58% yield) which showed six signals in ^{13}C NMR spectrum.5) Similarly, the ethers **1b** and **1c** and the ethylene acetal **1d** gave the corresponding 2,8-disubstituted diquinanes **2b**-**d** in high selectivity in 75% (**2b**:**3b**=99:1), 88% (**2c**:**3c**=98:2), and 94% (**2d**:**3d**=96:4) yields, respectively.7) In a marked contrast, the anti-epoxy acetal **5** did not afford **2d** but gave **3d** as the only ring expanded product (24%) together with the enol ether **6**5) (54%) derived by cleavage of the C(1)-C(7) bond and the acetal linkage.



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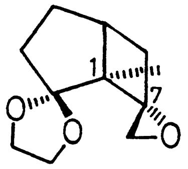

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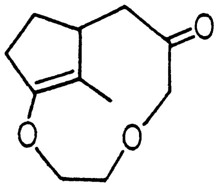

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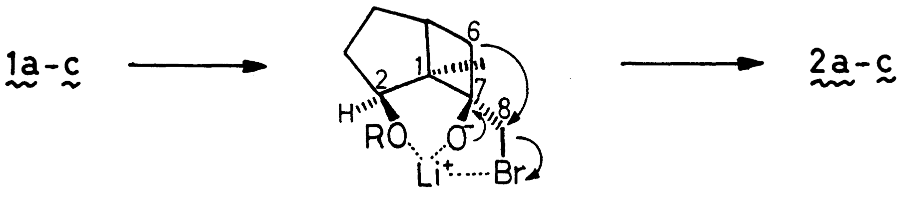
The remarkable selectivity in the rearrangement of **1a**-**d**, in which the less substituted carbon C(6) migrates predominantly, should be contrasted with other ring enlargements of this type. 2,8) The above selectivity is envisaged as resulting from chelation of the endo oxygen atom at C(2) to the lithium cation in a transition state **7**. 6) Namely, the rotation around the C(7)-C(8) bond is hindered by the chelation locking the conformation as that of **7** in which the



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C(6)-C(7) and C(8)-Br bonds have anti periplanar alignment. Thus the present rearrangement constitutes the key step of the regioselective five-membered-ring annelation to cycloalkenones which has been successfully applied to the total synthesis of triquinane natural products.[9)]

References

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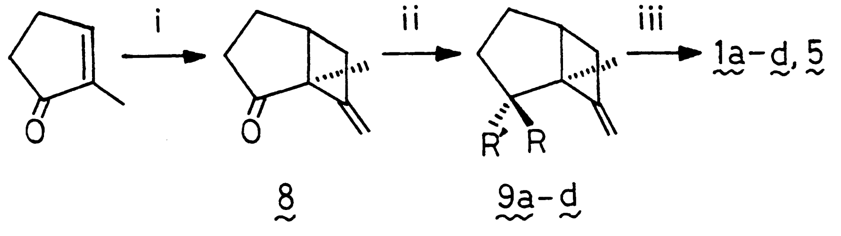
3) Similar but less efficient regiocontrol has been reported recently.[2e)]

4) (i) Photocycloaddition of allene to give 8 (71%; Head to Head:Head to Tail= 92:8). (ii) Lithium aluminum hydride reduction to afford 9a (95%; endo:exo= 96:4) followed by treatment of 9a with sodium hydride and methyl iodide or methoxymethyl chloride to give 9b-c, or acetalization (ethylene glycol, pyridinium tosylate, 90%) to give 9d. (iii) Oxidation with m-chloroperbenzoic acid (Na_2HPO_4, 0 °C, 86-94% yields); selectivity are as follows: 1a (100%), 1b (100%), 1c (90%) and 1d:5=71:29. The syn/anti stereochemistry of 1a-d and 5 was elucidated on the basis of (a) the sharp hydroxyl absorption (3500 cm^{-1}) in IR spectrum of 1a due to intramolecular hydrogen-bonding and (b) the difference in the chemical shift in each epoxy methylene proton: The syn epoxide 1a-d showed $\Delta\delta$ 0.14-0.19 whereas anti isomers of 1c-d $\Delta\delta$ 0.62-0.65 ppm.



	R	R'
a	OH	H
b	OMe	H
c	OCH_2OMe	H
d	OCH_2CH_2O	

5) All new compounds gave satisfactory analytical and spectral data. Selected data for **4** and **6** follow:

4: mp 45 °C; IR (KBr) 1765, 1715 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.22 (s, 3H), 1.6-2.5 (m, 8H), 2.73 (br t, J=6 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 212.7 (s, 2C), 65.0 (s), 46.5 (d), 36.5 (t, 2C), 24.3 (t, 2C), 19.0 (q).

6: mp 75 °C; IR (KBr) 1705, 1685 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.78 (d, J=1 Hz, 3H), 1.8-2.3 (m, 4H), 2.4-2.8 (m, 3H), 3.3-4.0 (m, 6H); ^{13}C NMR (CDCl$_3$) δ 210.1 (s), 152.6 (s), 117.7 (s), 77.1 (t), 76.7 (t), 69.4 (t), 45.9 (t), 44.9 (d), 27.9 (t), 24.8 (t), 11.4 (q).

6) B. Rickborn and R. M. Gerkin, J. Am. Chem. Soc., **93**, 1693 (1971).

7) **2c** and **2d** were related to **2a** and **4**, respectively, by hydrolysis.

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