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Stereoselective Ring Expansion via Bicyclooxonium Ion. A Novel Approach to Oxocanes

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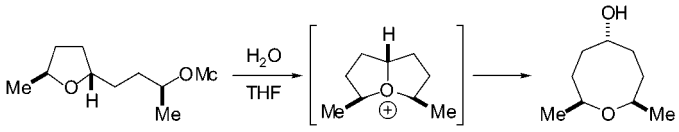
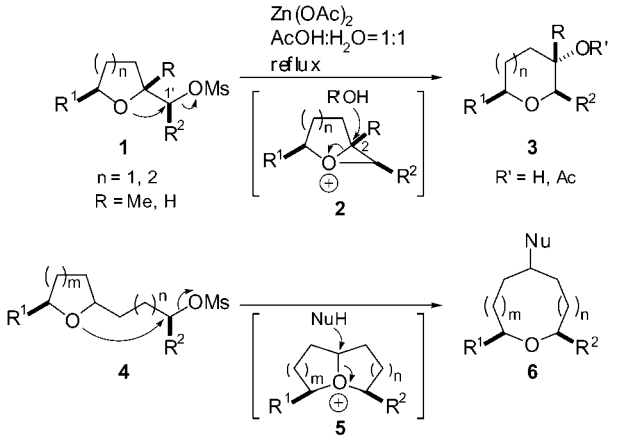
ABSTRACT



The stereoselective 1,4-rearrangement–ring expansion of tetrahydrofurans via bicyclo[3.3.0]oxonium ions was developed to synthesize oxocanes. On the basis of this rearrangement, the stereoselective synthesis of 2,8-*syn*-2,8-dimethyloxocane was accomplished.

Medium-sized cyclic ethers are found as a part of the structure of many natural products, such as brevetoxins[1] and lauroxanes,[2] isolated mainly from marine organisms. In the synthesis of these compounds, most of which have alkyl substituents next to the oxygen atom on the cycle, the stereoselective construction of the cyclic units is essential. We already developed an efficient method for the stereoselective synthesis of tetrahydropyrans **3** (n = 1) and oxepanes **3** (n = 2) based on a $Zn(OAc)_2$-mediated 1,2-rearrangement−ring expansion of tetrahydrofurans **1** (n = 1) and tetrahydropyrans **1** (n = 2) having a C1′-mesylate, respectively (Scheme 1).[3] Recently, the present method was further improved by using a monochlate (OSO_2CH_2Cl = OMc),[4] instead of the mesylate, as an efficient leaving group and was successfully applied to the synthesis of the CD-ring of hemibrevetoxin B[5] and the E-ring of brevetoxin B.[6] These ring expansions would proceed through (1) stereo-

Scheme 1. Rearrangement−Ring Expansion Reactions



(1) For reviews, see: (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(2) For reviews, see: (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, pp 43−121. (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol V, pp 131−257. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1. See also his previous reviews in *Nat. Prod. Rep*.

(3) (a) Nakata, T.; Nomura, S.; Matsukura, H. *Tetrahedron Lett.* **1996**, *37*, 213. (b) Nakata, T.; Nomura, S.; Matsukura, H.; Morimoto, M. *Tetrahedron Lett.* **1996**, *37*, 217. (c) Nakata, T.; Nomura, S.; Matsukura, H. *Chem. Pharm. Bull.* **1996**, *44*, 627. (d) Nagasawa, K.; Hori, N.; Shiba, R.; Nakata, T. *Heterocycles* **1997**, *44*, 105. (e) Nagasawa, K.; Hori, N.; Koshino, H.; Nakata, T. *Heterocycles* **1999**, *50*, 919.

(4) (a) Hori, N.; Nagasawa, K.; Shimizu, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2145. (b) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145. (c) Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. *Synthesis* **1999**, 1373.

(5) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365.

(6) Matsuo, G.; Hori, N.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 7677.

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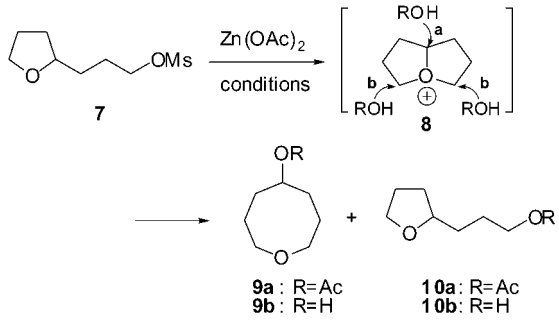
selective formation of bicyclo[3.1.0] and [4.1.0]oxonium ions **2** (n = 1, 2) as a reaction intermediate and (2) regio- and stereoselective nucleophilic attack of H_2O or AcOH at the C2-position of **2**. These results led us to investigate 1,n+3-rearrangement−ring expansion via bicyclo[m+2.n+2.0]-oxonium ion **5**.[7] We report here a stereoselective synthesis of oxocanes by 1,4-rearrangement−ring expansion of tetrahydrofurans[8] via bicyclo[3.3.0]oxonium ion **5** (m = n = 1), which is known as a reaction intermediate for solvolysis[9] and ring contraction.[10]

First, the ring expansion of the simple substrate **7** having a mesylate[11] was examined (Table 1). Treatment of **7** under

Table 1. Reaction of Mesylate **7** with $Zn(OAc)_2$[a]



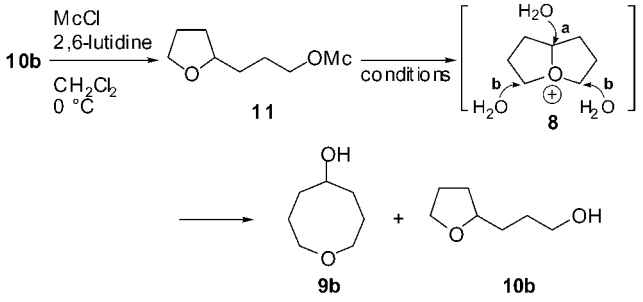
entry	solvent	temp (°C)	time (h)	yield[b] (%)	**9a**:**9b**:**10a**:**10b**[c]
1	AcOH−H_2O, 1:1	50	1.5	83	6.3:5.0:2.0:1
2	THF−H_2O, 1:1	50	5	91	6.0:5.0:2.0:1
3	THF−H_2O, 1:1	rt	48	93	11.7:8.6:2.8:1

[a] All reactions were carried out with 4 equiv of $Zn(OAc)_2$. [b] Combined yield of **9a**, **9b**, **10a**, and **10b**. [c] Determined by ^1H NMR spectroscopy.

the standard conditions, $Zn(OAc)_2$ in AcOH−H_2O at 50 °C, for our 1,2-rearrangement, effected ring expansion to afford 5-acetoxy- and 5-hydroxyoxocanes (**9a** and **9b**) along with **10a** and **10b** in 6.3:5:2:1 ratio (entry 1). The nucleophilic attack of AcOH and H_2O to the bicyclooxonium ion **8** by the path **a** could afford the expanded products **9a** and **9b**, respectively. This result showed that the attack of H_2O has a slightly higher selectivity (**9b**:**10b** = 5:1) than that of AcOH (**9a**:**10a** = 3.15:1). However, use of the THF−H_2O solvent system instead of AcOH−H_2O resulted in almost the same ratio (entry 2). The results also suggest that $Zn(OAc)_2$ is a source of the OAc group as a nucleophile in this reaction. The lower reaction temperature increased the selectivity of ring expansion (entry 3, **9**:**10** = 20.3:3.8 at room temperature; entry 2, **9**:**10** = 11:3 at 50 °C), although the reaction required rather longer time for completion (entry 3).

Therefore, the use of monochlate as an efficient leaving group was next investigated for this expansion. The reaction of monochlate **11**, prepared from alcohol **10b**[12] with chloromethanesulfonyl chloride (McCl) and 2,6-lutidine in CH_2Cl_2, was examined in several aqueous solvent systems (Table 2). To our surprise, even in the absence of a Lewis acid, the

Table 2. Reaction of Monochlate **11** without Lewis Acid

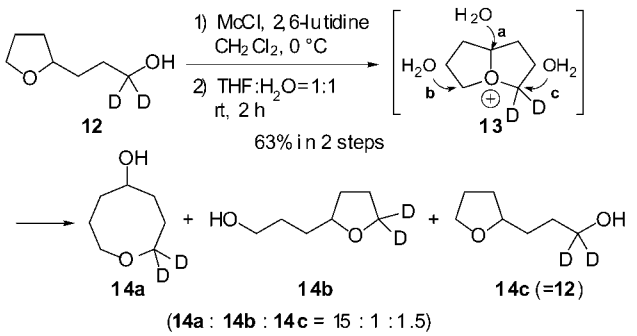


entry	solvent	temp	time (h)	yield[a] (%)	**9b**:**10b**[b]
1	THF−H_2O, 1:1	rt	2	82	8.0:1
2	THF−H_2O, 4:1	rt	5	56	6.7:1
3	MeCN−H_2O, 1:1	rt	2	60	8.0:1
4	MeCN−H_2O, 4:1	rt	2	55	6.2:1
5	acetone−H_2O, 1:1	rt	2	30	6.0:1

[a] Combined yield of **9b** and **10b** in 2 steps from the starting **10b**. [b] Determined by ^1H NMR spectroscopy.

rearrangement of monochlate **11** in aqueous solvent took place very smoothly. The best result was obtained in THF−H_2O (1:1) at room temperature within 2 h to give the ring-expanded **9b** in good yield and high selectivity (entry 1).

Scheme 2



(7) 1,4- and 1,5-Rearrangement−ring expansion of oxiranes via bicyclo-[3.1.0] and [4.1.0]oxonium ions, respectively, were reported. (a) Hayashi, N.; Fujiwara, K.; Murai, A. *Chem. Lett.* **1996**, 341. (b) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 6173. (c) Hayashi, N.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 793. (d) Fujiwara, K.; Murai, A. *Tetrahedron* **1997**, *53*, 12425. (e) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561. (f) Hayashi, N.; Noguchi, H.; Tsuboi, S. *Tetrahedron* **2000**, *56*, 7123.

(8) (a) Kamada, T.; Ge-Qing; Abe, M.; Oku, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 413. (b) Mukai, C.; Yamashita, H.; Ichiryu, T.; Hanaoka, M. *Tetrahedron* **2000**, *56*, 2203.

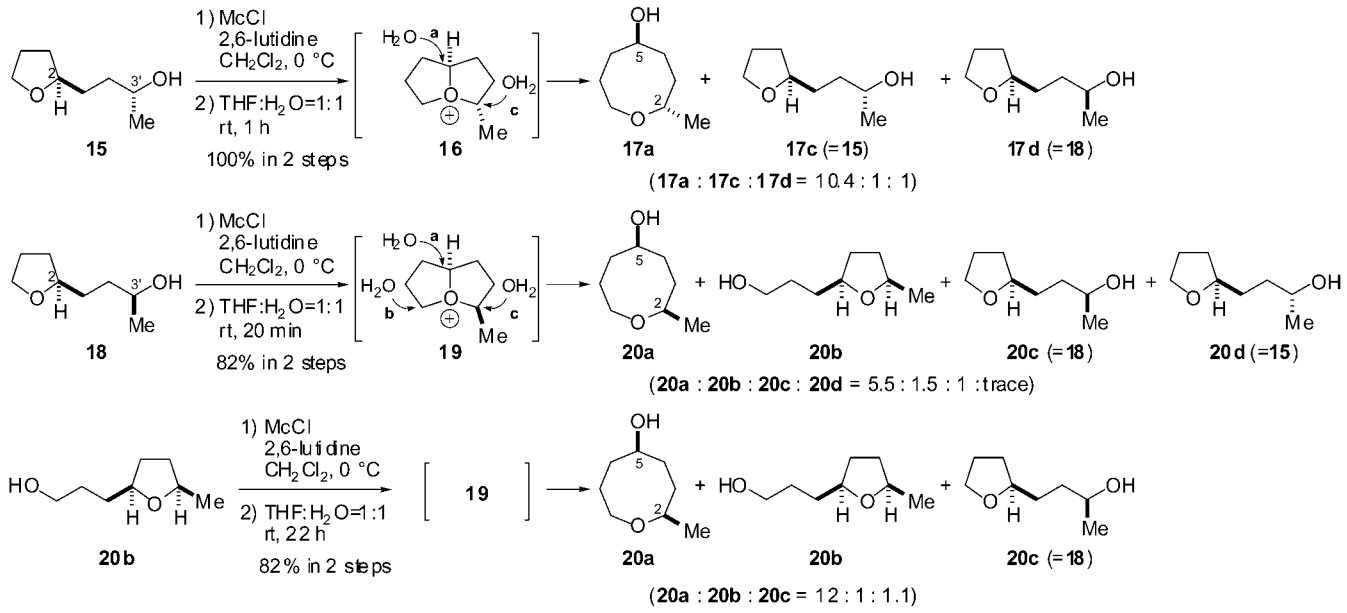
(9) Kwiatkowski, G. T.; Kavarnos, S. J.; Closson, W. D. *J. Heterocycl. Chem.* **1965**, *2*, 11.

(10) (a) Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6751. (b) Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6760. (c) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386.

(11) Mesylate **7** was prepared from alcohol **10b** with mesyl chloride and triethylamine in CH_2Cl_2 at 0 °C. See ref 12 for preparation of **10b**.

(12) Alcohol **10b** was prepared by a known procedure; see: Hornberger, C. S., Jr.; Heitmiller, R. F.; Gunsalus, I. C.; Schnakenberg, G. H. F.; Reed, L. J. *J. Am. Chem. Soc.* **1953**, *75*, 1273.

Scheme 3

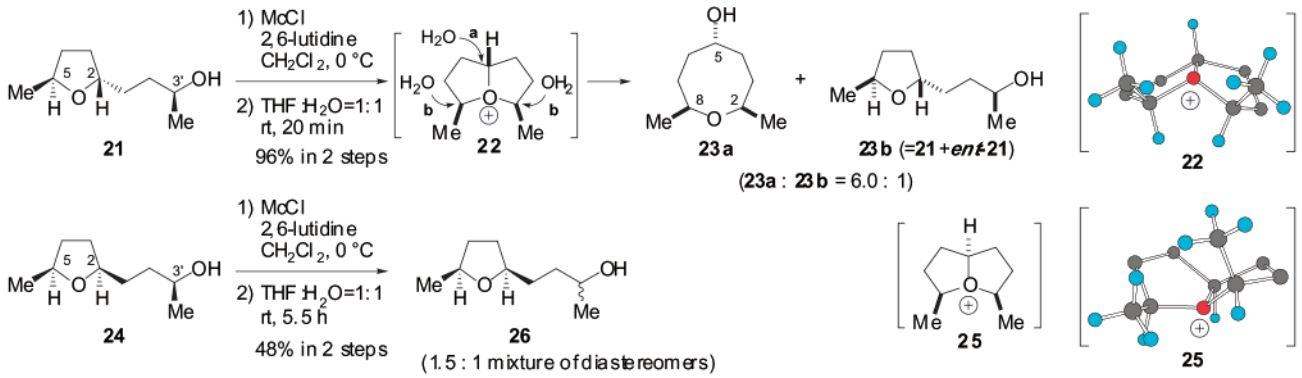


To investigate the present rearrangement in more detail, a deuterated substrate **12** was subjected to this reaction (Scheme 2). The production of **14a** and **14b** confirmed the existence of bicyclooxonium ion **13** as the reaction intermediate. The preferred production of **14c** to **14b** would suggest a contribution of the direct solvolysis of the starting monochlate.

The stereoselectivity of the present rearrangement was explored with a pair of diastereomers **15** and **18** having a secondary monochlate (Scheme 3). Treatment of 2,3′-*syn*-tetrahydrofuran **15** with McCl followed by treatment of the resultant monochlate in THF−H_2O (1:1) stereoselectively afforded the expanded 2,5-*anti*-oxocane **17a**[13] in high yield within 1 h along with **17c**,**d**. The 2,3′-*anti*-tetrahydrofuran **18** under the same conditions produced 2,5-*syn*-oxocane **20a**[13] stereoselectively along with **20b**−**d**. These results revealed that the present rearrangement−ring expansion takes place stereoselectively and stereospecifically. The byproducts **17c** and **20c** were given by the solvolysis with double inversion via bicyclooxonium ion **16** and **19** in path **c**, respectively, while **17d** and **20d** were provided by the direct solvolysis with inversion and not via the bicyclooxonium ion intermediate. The ring-migrated product **20b** was obtained via bicyclooxonium ion **19** in path **b**. As was expected, the monochlate prepared from **20b** also gave the expanded oxocane **20a** by this rearrangement via the same bicyclooxonium ion **19**, although it took 22 h for completion.

On the basis of this stereoselective ring expansion, the synthesis of *cis*-2,8-dialkyloxocanes, which are the structures found in brevetoxins and lauroxanes, was examined (Scheme 4). Treatment of an optically pure 2,5-*anti*-2,3′-*syn*-tetrahydrofuran **21** with McCl followed by treatment in THF−H_2O (1:1) stereoselectively afforded the desired 2,5-*anti*-2,8-*syn*-2,8-dimethyl-5-hydroxyoxocane (**23a**)[13] along with tetrahydrofuran **23b**[14] in 96% combined yield (**23a**:**23b** = 6:1) within 20 min. On the other hand, 2,5-*syn*-2,3′-*anti*-tetrahydrofuran **24** gave no ring-expanded ether but gave a 1.5:1 mixture of epimeric tetrahydrofurans **26**. These results could

Scheme 4



be explained by the ease of formation of the bicyclooxonium ion. In the reaction of the monochlate derived from **24**, bicyclooxonium ion **25** would be hardly formed as a reaction intermediate because the dimethyl groups directed to the concave face have steric hindrance. Thus, **26** was provided by the direct solvolysis. In contrast, the monochlate derived from **21** can easily form bicyclooxonium ion **22**, because **22** has the dimethyl groups in the convex face without severe steric repulsion.

In summary, we have developed a stereoselective 1,4-rearrangement−ring expansion of tetrahydrofurans via bicyclo[3.3.0]oxonium ions to afford oxocanes. On the basis of this rearrangement, we have accomplished the synthesis of 2,8-*syn*-2,8-dimethyloxocane. Applications of the present rearrangement to natural product synthesis are in progress in this laboratory.

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(13) **^{1}H and ^{13}C NMR Data for Oxocanes 17a**, **20a**, **and 23a. 17a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (tt, J = 7.9, 3.6 Hz, 1H), 3.72 (ddd, J = 12.0, 8.3, 3.6 Hz, 1H), 3.62 (ddq, J = 6.4, 3.0, 6.4(q) Hz, 1H), 3.48 (ddd, J = 12.0, 6.4, 3.4 Hz, 1H), 1.48−1.92 (m, 8H), 1.14 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.2, 70.8, 67.1, 34.2, 33.9, 31.5, 26.0, 21.3. **20a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (tt, J = 5.5, 3.3 Hz, 1H), 3.73 (ddd, J = 12.4, 8.1, 3.9 Hz, 1H), 3.60 (m, 1H), 3.49 (ddd, J = 12.4, 6.4, 3.8 Hz, 1H), 1.56−1.98 (m, 8H), 1.17 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 74.5, 70.4, 67.9, 34.4, 32.3, 31.2, 26.0, 22.1. **23a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (tt, J = 9.0, 3.4 Hz, 1H), 3.60 (ddq, J = 6.4, 3.0, 6.4(q) Hz, 2H), 1.94 (m, 2H), 1.86 (m, 2H), 1.59 (m, 2H), 1.45 (m, 2H), 1.14 (d, J = 6.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 74.3, 71.7, 33.9, 32.7, 22.0.

(14) The tetrahydrofuran **23b** was a 1:1 mixture of **21** and ***ent*-21**. The ratio was determined by ^{1}H NMR spectrum analysis of the diastereomeric mixture of their (*R*)-MTPA ester derivatives. This result indicates that **23b** was produced via *meso*-bicyclooxonium ion intermediate **22**.