Synthesis of 3-Hydroxy-5-oxonene *via* 2,3-Epoxy-5-oxonene

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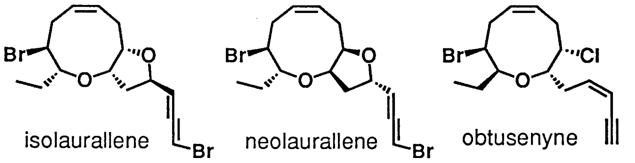
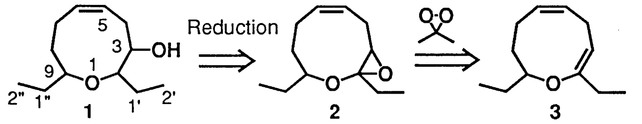
Synthesis of 2r, 3t, 9t- and 2r, 3t, 9c-2, 9-diethyl-3-hydroxy-5-oxonenes was achieved by the reduction of 2, 9-diethyl-2, 3-epoxy-5-oxonene which was prepared from 2, 9-diethyl-2, 5-oxonadiene and dimethyldioxirane. Stereoselective conversion of these 3-hydroxy-5-oxonenes was also described.

Development of the general method for synthesis of 5-oxonene structure, which is often seen in marine natural products, such as isolaurallene,[1] neolaurallene,[2] and obtusenynes,[3] is now one of the important subjects for synthetic chemists.[4] As part of our studies on the total synthesis of the above natural products,[4j] we describe here the facile synthesis of monocyclic 3-hydroxy-5-oxonene and its stereoselective conversion.



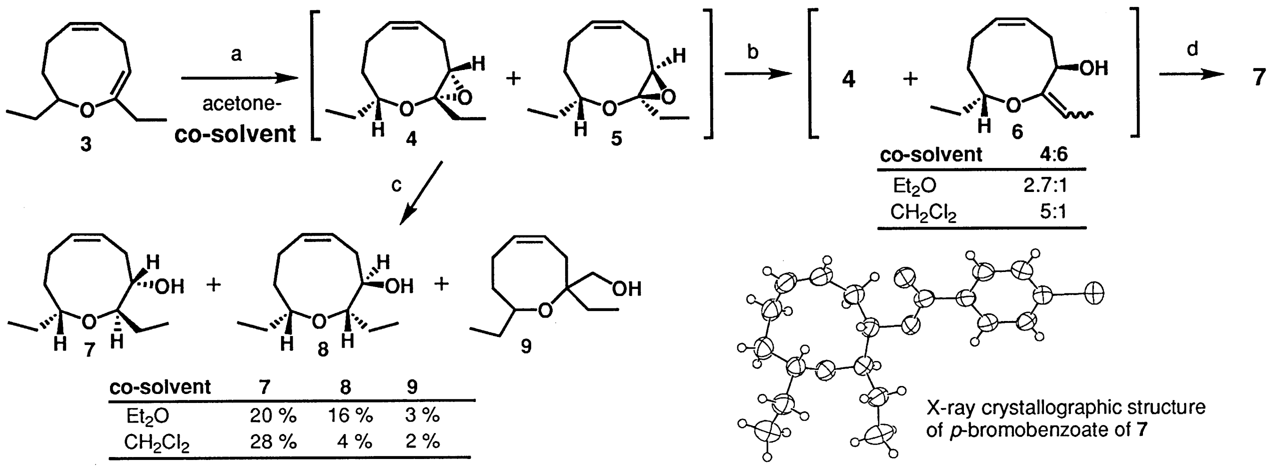


Scheme 1.

Our plan for 2-step construction of 3-hydroxy-5-oxonene structure **1** from 2, 5-oxonadiene **3** is shown in Scheme 1:[5] alcohol **1** would be given by the reduction of 2, 3-epoxy-5-oxonene **2** which could be produced by the epoxidation of dienol ether **3** with dimethyldioxirane[6] under neutral conditions. Here, some questions existed: 1) does epoxidation occur at the 2-position of monocyclic **3** selectively? ;[5] 2) is epoxide **2** stable enough to handle? ; 3) how is the stereoselection in epoxidation step and reduction step? We intended to answer these questions.

The epoxidation of dienol ether **3**[7] with dimethyldioxirane was performed in the following way (Scheme 2). Anhydrous dimethyldioxirane solution in acetone[6c] (1.5 eq.) was added dropwise to a solution of **3** in co-solvent (CH_2Cl_2 or Et_2O) (acetone/co-solvent=1 : 1) at -70 °C. After 10 min, the temperature was raised at -40 °C and maintained for 10 min. Then, 2-methyl-2-butene[8] was added to the reaction mixture to quench unreacted dimethyldioxirane. After solvent removal at 0 °C in vacuo (20 Torr), a crude mixture of 2, 3-epoxy-5-oxonenes **4**[9] and **5**[9] was given as an almost pure form. Under the conditions, epoxidation occurred at the 2-position selectively.[4c] Although both epoxides were unstable to silica gel and could not be detected by TLC, they could be observed by ^{1}H NMR.[9] Major epoxide **4** was stable in neutral solution at 20 °C for several hours. On the other hand, minor **5** was converted to enol ether **6** spontaneously and cleanly in CH_2Cl_2, $CDCl_3$ and benzene-d_6 at 20 °C, and the conversion was completed in all cases within 30 min. Accordingly, the mixture of epoxides required quick handling at low temperature (below 0 °C). The stereoselectivity in epoxidation varied with co-solvent. The ratio of **4** to **5** which could be estimated accurately by ^{1}H NMR after complete conversion of **5** to **6** in CH_2Cl_2 at 20 °C was higher in CH_2Cl_2 (5 : 1) than in Et_2O (2.7 : 1). The stereochemistry of **4** and **5** was unknown at this stage.

Next, we examined the conversion of epoxides **4** and **5** to 3-hydroxy-oxonenes. Among the several attempts to reduce the epoxides, only DIBAH gave the desired products. The immediate reaction of the mixture of **4** and **5** prepared in Et_2O-acetone with DIBAH in CH_2Cl_2 at 0 °C gave oxonenes **7** and **8** in 20% and



co-solvent	4:6
Et_2O	2.7:1
CH_2Cl_2	5:1

co-solvent	7	8	9
Et_2O	20 %	16 %	3 %
CH_2Cl_2	28 %	4 %	2 %

X-ray crystallographic structure of *p*-bromobenzoate of **7**

Scheme 2. Reagents and conditions: a) dimethyldioxirane (1.5 eq), acetone-co-solvent (1:1), -70 °C, 10 min, then -40 °C, 10 min, then 2-methyl-2-butene (1.5 eq), 5 min, then solvent removal at 0 °C in vacuo (20 Torr); b) CH_2Cl_2, 20 °C, 1 h; c) DIBAH (4 eq), hexane-CH_2Cl_2 (1:1.6), -75 °C, 10 min, then 0 °C, 6.5 h; d) DIBAH (4 eq), hexane-CH_2Cl_2 (1:1.6), -75 °C, 10 min, then 0 °C, 21 h, 18% (from **3**), (a 5:1 mixture of **4** and **6** was used.).

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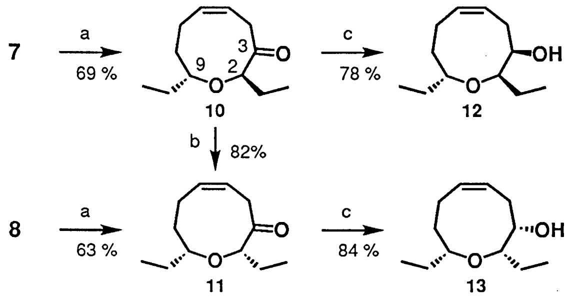
16% yields from **3**, respectively, together with a small amount of oxocene **9**.[10,11] On the other hand, the epoxides prepared in CH_2Cl_2-acetone produced **7** and **8** in 28% and 2% yields, respectively, under the same conditions.[10] The product ratio of **7** and **8** seemed to correspond to the ratio of starting **4** and **5**, respectively. Indeed, when the mixture of epoxides was treated with DIBAH after complete conversion of **5** to unreactive **6**, **7** was given as only oxonene product from **4**.[10]

The stereochemistry of **7** and **8**[4j] was determined by ^1H NMR. Furthermore, the structure of **7** was confirmed by X-ray crystallographic analysis after conversion to the crystalline *p*-bromobenzoate. The preference of β-attack in the epoxidation step was clarified at this time. Interestingly, the hydride substitution at C-2 of both **4** and **5** occurred in the same side to the oxygen of epoxide in the reduction step.



Scheme 3. Reagents and conditions: a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 20 min, then Et_3N; b) DBU (5 eq), benzene, reflux, 96 h; c) L-Selectride (3 eq), THF, -78 °C, 20 min, then 20 °C, 45 min.

Then, stereochemical conversion of **7** and **8** was examined (Scheme 3). Swern oxidation of **7** and **8** gave ketones **10** and **11**, respectively. The treatment of **10** with DBU in refluxing benzene induced complete epimerization at the 2-position (>99 : 1) to give thermodynamically stable **11** in 82% yield without olefin migration.[12] Reduction of ketones **10** and **11** with L-Selectride produced only 2, 3-*cis*-3-hydroxy oxonenes **12** and **13** in good yield, respectively.[13] Thus, all four diastereomers of 2, 9-diethyl-3-hydroxy-5-oxonene were prepared from dienol ether **3**.

In conclusion, facile 2-step synthesis of 3-hydroxy-5-oxonenes **7** and **8** from dienol ether **3** *via* 2, 3-epoxy-5-oxonenes **4** and **5** was accomplished. The usage of CH_2Cl_2 as co-solvent in epoxidation step heightened the ratio of **4** to **5**. The stereoselective conversion of **7** and **8** to **12** and **13** was also achieved.

References and Notes

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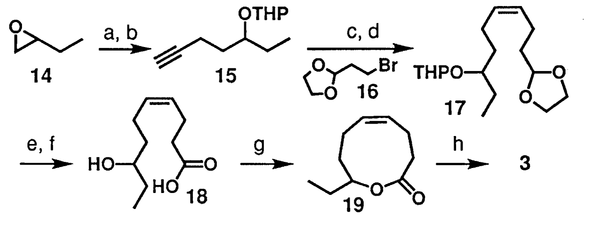
5 Similar plan for the synthesis of oxepane-fused 3-hydeoxy-5-oxonene was reported by Nicolaou's group, but selective epoxidation of enol ether with dimethyldioxirane was not succeeded.[4c]

6 a) R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985); b) W. Adam, Y.-Y. Chan, D. Cremer, J. Gauss, D. Scheutzow, and M. Schindler, *J. Org. Chem.*, **52**, 2800 (1987); c) Dimethyldioxirane-acetone solution prepared according to Adam's method was dried with molecular sieves 4 Å before use.

7 Dienol ether **3** was prepared from 1, 2-epoxybutane in 8 steps as follows:



Reagents and conditions: a) HC≡CCH_2Br, Mg, $HgCl_2$ (cat.), Et_2O, reflux, then **14**, 97%; b) DHP, PTS•H_2O (cat.), CH_2Cl_2, 20 °C, 1.5 h, 97%; c) BuLi (1 eq), THF, -20 °C, 10 min, then **16** (0.5 eq), THF-HMPA (5:1), -20 °C, 2 h, then 20 °C, 2 h, 73% (from **16**), 45% recovery of **15**; d) Lindlar cat., H_2, quinoline-EtOH (1:250), 20 °C, 1 h, 98%; e) 2M HCl-THF (1:1), 20 °C, 5 h; f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (3.5:1), 0 °C, 1 h, 87% (2 steps); g) EDCI•HCl, DMAP, DMAP•HCl, $CHCl_3$, reflux, 2 days, 72%; h) KHMDS, HMPA, THF, -78 °C, 1 h, then $PhNTf_2$, -78 °C, 1 h, then $Et_2CuMgBr$, Me_2S, -78°C, 10 min, then -40°C, 16 h, 82%.

8 The reactivity of 2-methyl-2-butene with dimethyldioxirane was comparable as that of the enol ether part of **3** at -40 °C.

9 Selected ^1H NMR data (400MHz, $CDCl_3$, 23 °C) for epoxides **4** and **5**. Epoxide **4**: δ 0.91 (3H, t, J=7 Hz, H2" or 2'), 1.01 (3H, t, J=7 Hz, H2" or 2'), 2.50 (1H, td, J=5, 13 Hz, H4a), 2.57-2.67 (1H, m, H4b), 2.92 (1H, dd, J=5, 9 Hz, H3), 3.56 (1H, tdd, J=4, 7, 10 Hz, H9), 5.60-5.68 (2H, m, H5 and 6); Epoxide **5**: δ 0.86 (3H, t, J=8 Hz, H2' or 2"), 0.93 (3H, t, J=8 Hz, H2" or 2'), 2.35 (1H, brtd. J=7, 13 Hz, H4a), 2.83-2.90 (1H, J=2, 7, 13 Hz, H4b), 3.02 (1H, dd, J=2, 7 Hz, H3), 3.89 (1H, brtdd, J=4, 7, 12 Hz, H9), 5.44-5.54 (2H, m, H5 and 6).

10 There is no other product but a complex mixture of high-polar compounds. Although enol ether **6** was not reacted with DIBAH, **6** was decomposed under work-up conditions. Work-up was done as follows: saturated aqueous potassium sodium tartarate solution was added to the reaction mixture at 0 °C, and the mixture was extracted with Et_2O after stirring for 2 hours at 20 °C.

11 Unexpected production of oxocene **9**, which was a mixture of diastereomers (3:1~2:1), was probably due to Lewis acidity of DIBAH. When the mixture of epoxides treated with $AlMe_3$ as Lewis acid, ring contracting aldehyde **20** was produced in 35% yield (a mixture of diasteromers), which was reduced with $LiAlH_4$ to give **9**. We wish to describe the rearrangement in detail elsewhere. For aluminum reagent catalyzed rearrangement of epoxide, see: K. Maruoka, S. Nagahara, T. Ooi, and H. Yamamoto, *Tetrahedron Lett.*, **30**, 5607 (1989).

12 The same tendency in 2, 8-disubstituted 5-oxocen-3-one system has been reported: T. Masamune and H. Matsue, *Chem. Lett.*, **1975**, 895; Isomerization of 2, 9-disubstituted oxonan-3-one has also been reported.[4g]

13 The same tendency in 2, 8-disubstituted 5-oxocen-3-one system has been reported: K. Tsushima and A. Murai, *Tetrahedron. Lett.*, **33**, 4345 (1992); *Cis*-selective reduction of 2, 9-disubstituted oxonan-3, 8-dione has also been reported.[4m]