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Heterogeneous acid-catalyzed (2,5) oxonium-ene reaction for eight-membered ring formation

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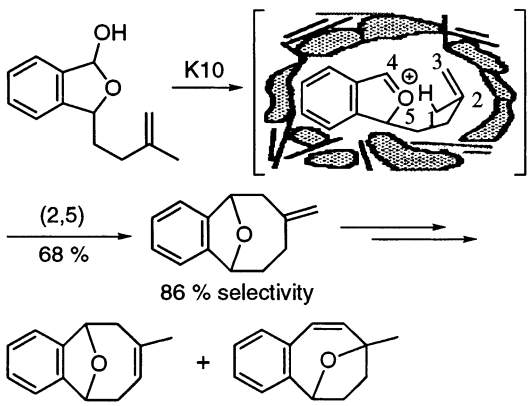
Abstract—The (2,5) ene cyclization of cyclic allylic lactol ether **1** as a substrate gave aldehyde **3** presumably via the intermediate **2**. Furthermore, ring cleavage at the C–O bond of the oxolane moiety in the aldehyde **3** under reductive conditions afforded the eight-membered ring regioselectively. © 2001 Published by Elsevier Science Ltd.

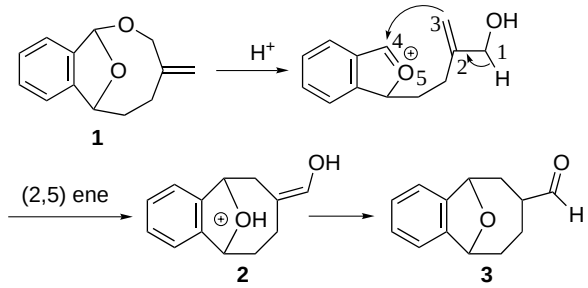
Among the six different types of intramolecular ene reaction,[1,2] only the (2,5) ene cyclization remains unexplored. Recently, we have reported the first example of a (2,5) ene cyclization,[3] involving an oxonium ion[4,5] as the enophile component, employing mesoporous solid acids[6–8] as shown in Scheme 1. However, the isomerization of the (2,5) ene product to other regioisomers is problematic. We now disclose a new type of (2,5) ene cyclization to overcome the isomerization problem and illustrate the synthetic usefulness of this reaction for the construction of functionalized eight-membered ring compounds.[9,10]

It was planned to design the reaction in order to trap the ene product as an enol, so that the ene product would be transformed to the corresponding aldehyde, and, consequently, regioisomerization would be suppressed. Therefore, a cyclic allylic lactol ether **1** was selected as a substrate (Scheme 2).[4] The results obtained in the reactions of the cyclic allylic lactol ether **1** with several acids are summarized in Table 1.

Analogously to the method employed in our earlier report on the intermolecular oxonium-ene reaction of cyclic allylic lactol ethers,[4] a homogeneous Lewis acid, TMSOTf, was first used. However, substrate **1** was decomposed in the presence of this Lewis acid (Table 1, run 1). Therefore, mesoporous solid acids were investigated. The reaction using montmorillonite K10[11] gave the desired aldehyde **3**,[12,13] though in low yield even after long reaction times (run 2), whereas the reaction with Amberlyst® 15E gave the aldehyde in better yield in a shorter reaction time (run 3). The yield was better when the reaction was performed using CH_2Cl_2 rather than THF or toluene as solvent (runs 3, 4 and 5). Increased dilution also improved the yield of the reaction (runs 3, 6 and 7). The time required for the reaction to proceed to completion was critically depen-



Scheme 1.



Scheme 2.

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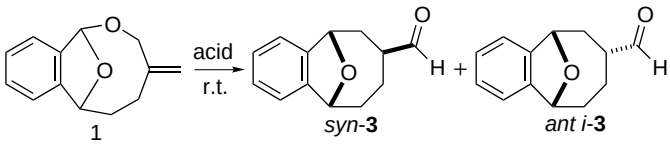
Table 1. Solid acid catalyzed cyclization

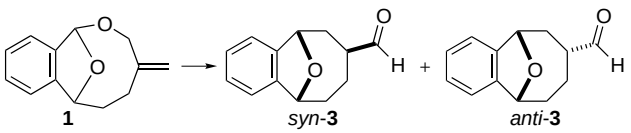


Run	Acid (g/mol)	Solvent (M)	Time (h)	Yield[a] (%)	*syn*:*anti*[b]
1[c]	TMSOTf (0.1 equiv.)	CH_2Cl_2 (0.1)	3	Trace	–
2	K10 (0.8)		96	21	58:42
3	Amberlyst® 15E (0.5)		8	46	54:46
4		THF	78	43	55:45
5		Toluene	11	39	56:44
6		CH_2Cl_2 (0.3)	4	32	54:46
7		(0.01)	16	65	55:45
8	Amberlyst® 15E (0.1)	(0.1)	84	41	55:45
9	Amberlyst® 15E (0.1)		1.5	44	54:46
10		(0.01)	5	72	54:46

[a] Combined yield of *syn*- and *anti*-**3**.
[b] Determined by capillary GC.
[c] –78°C→rt.

dent on the amount of Amberlyst® 15E employed (runs 8 and 9). Finally, under optimized conditions, in a dilute (0.01 M) solution with 1 g of Amberlyst® 15E (run 10), a combined yield of 72% was achieved.

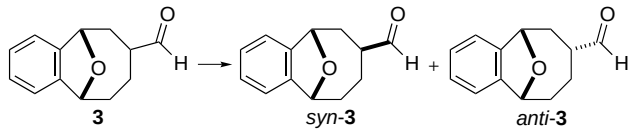
Table 2. Isomer ratio during the reaction[a]



Time	*syn*:*anti*[b]
5 min	54:46
30 min	54:46
1 h	55:45
6 h	54:46

[a] Amberlyst® 15E (0.5 g/mmol), CH_2Cl_2, 0.1 M.
[b] Determined by capillary GC.

Table 3. Slow isomerization under the reaction condition[a]

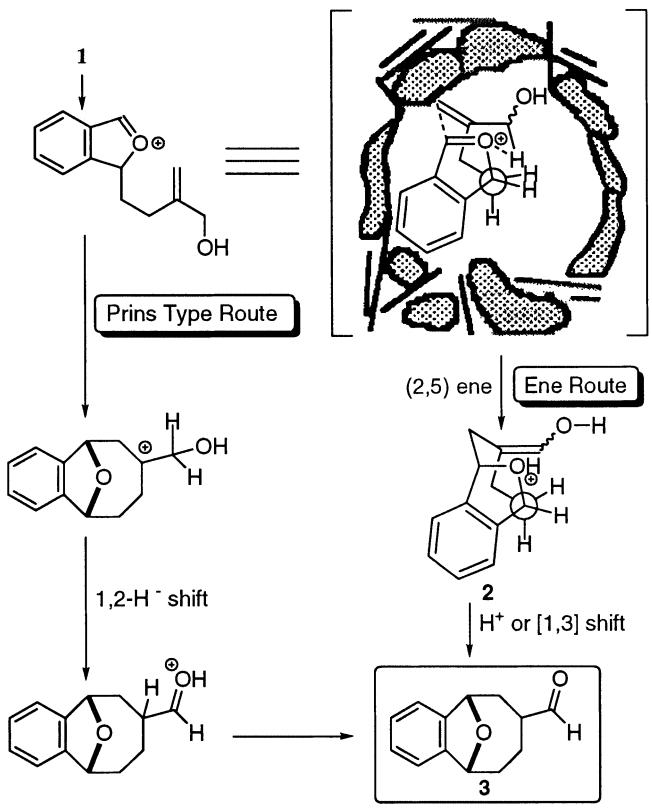


Time	*syn*:*anti*[b]	*syn*:*anti*[b]
Start	92:8	18:82
5 min	85:15	23:77
15 min	73:27	35:65
30 min	64:36	44:56
1 h	56:44	52:48
8 h	56:44	54:46

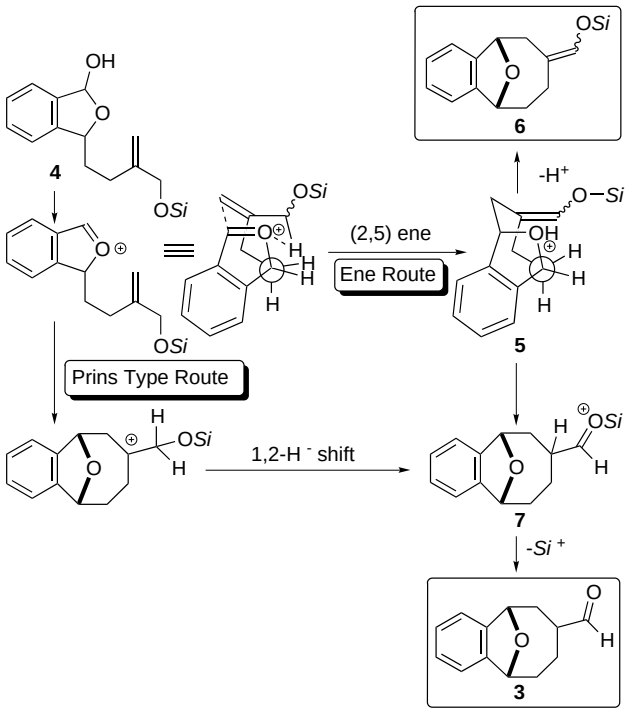
[a] Amberlyst® 15E (0.5 g/mmol), CH_2Cl_2, 0.1 M.
[b] Determined by capillary GC.

The ratio of *syn*- and *anti*-isomers of the aldehyde **3** did not vary throughout the reaction (5 min–6 h) (Table 2), although under these conditions the aldehyde could slowly isomerize to the epimer after several hours (Table 3).

Two possible mechanisms can be envisaged for these reactions. One involves a (2,5) ene cyclization and the other a Prins type reaction (Scheme 3). In the (2,5) ene



Scheme 3.



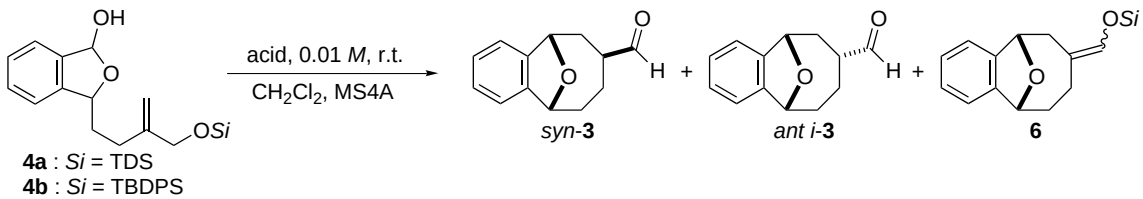
Scheme 4.

cyclization route, the aldehyde **3** would be obtained via the intermediate **2** in the mesopore of the solid acid. In the Prins type route, by contrast, a cationic cyclization followed by 1,2-hydride shift would give the aldehyde **3**. To elucidate whether a (2,5) ene reaction was involved in this cyclization, the reaction of lactol **4** bearing an allylic silyl ether moiety was investigated (Scheme 4). When lactol **4** is subjected to acid treatment, the aldehyde **3** will be obtained in either ene or Prins type route. However, in the case of a (2,5) ene cyclization, there is the possibility[14] of obtaining silyl enol ether **6** through chair or boat transition states.

Thus, the reaction of lactol **4** with K10 and Amberlyst® 15E was investigated (Table 4). First, the reaction of lactol **4a** possessing thexyldimethylsilyl ether group was studied. The reaction with Amberlyst® 15E gave aldehyde **3** exclusively (run 1). On the other hand, the reaction with K10 gave silyl enol ether **6a** (run 2). The yield of silyl enol ether **6a** remained unchanged when the amount of the acid was decreased (run 3). Then, lactol **4b** possessing a *tert*-butyldiphenylsilyl ether group, which is more acid-stable, was investigated. The silyl enol ether **6b** was obtained in 8 and 16% yields using Amberlyst® 15E (run 4) and K10 (run 5), respectively. Therefore, it can be concluded that at least a part of aldehyde **3** was formed via a (2,5) ene cyclization in the solid acid-catalyzed reaction of these lactols **4** and, hence, of the cyclic allylic lactol ether **1**.

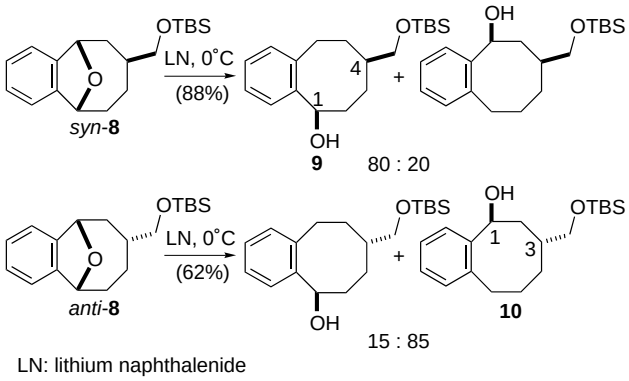
To demonstrate the synthetic utility of this new type of ene cyclization, we have studied its application to the synthesis of eight-membered rings. Accordingly, the ring opening of the oxolane moiety in the aldehyde **3** was examined under reductive conditions to provide a new approach to the highly functionalized eight-membered ring formation (Scheme 5).[15] The two stereoisomers of aldehyde **3** were separated by column chromatography and were each converted to the corresponding silyl ethers **8** after reduction to the

Table 4. The reaction of **4a** and **4b** using solid acids



Run	Sub.	Acid (g/mmol)	Time	Yield (%)	*syn*:*anti*[b]	Yield (%)
				3[a]		**6**[c]
1	**4a**	Amberlyst® 15E (1)	1.5 h	64	52:48	0
2		K10 (0.8)	10 min	65	58:42	9
3		K10 (0.2)	1.5 h	37	58:42	9
4	**4b**	Amberlyst® 15E (1)	3 h	73	53:47	8
5		K10 (0.8)	10 min	60	67:33	16

[a] Combined yield of *syn*- and *anti*-isomers of **3**.
[b] Determined by capillary GC.
[c] Combined yield of *Z*/*E* mixture of **6**.



Scheme 5.

corresponding alcohols. Then silyl ethers **8** were subjected to reductive conditions using lithium naphthalenide (LN).[16] The ring-opened products were obtained regioselectively. That is, the *syn*- and *anti*-isomers of the silyl ethers **8** gave 1,4-*syn*-regioisomer **9**[17] and 1,3-*anti*-regioisomer **10**[18] as the major products, respectively.[19]

We have thus reported a new type of (2,5) ene cyclization, and its application to the synthesis of eight-membered rings, by regioselective cleavage of the C–O bond of the oxolane ring. Using allylic lactol ether **1** or lactol **4** as substrates, the aldehyde **3** was obtained presumably via the intermediate **2**. Subsequent reductive ring opening of the oxolane moiety in the aldehyde **3** gave eight-membered ring products regioselectively. This provides a novel approach to oxygenated eight-membered ring compounds.

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12. *anti*-**3**: ^{1}H NMR (300 MHz, C_6D_6) δ 0.51 (dddd, $J=3.0$, 10.5, 12.3, 14.1 Hz, 1H), 1.35–1.44 (m, 2H), 1.49–1.56 (m, 1H), 1.68 (dddd, $J=3.3$, 4.2, 11.7, 13.8 Hz, 1H), 2.27 (dddd, $J=1.2$, 5.7, 8.4, 13.8 Hz, 1H), 2.35–2.45 (m, 1H), 5.22 (d, $J=8.4$ Hz, 1H), 5.27 (d, $J=4.2$ Hz, 1H), 6.68–6.78 (m, 2H), 6.96–7.02 (m, 2H), 9.10 (s, 1H); EI-MS $m/z=202$ ($M^{+\bullet}$), HRMS (EI) calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0998 ($M^{+\bullet}$); capillary GC (OV-1701, 170°C, INJ/DET, 200°C). $t_R=21.1$ min.
13. *syn*-**3**: ^{1}H NMR (300 MHz, C_6D_6) δ 1.20 (dddd, $J=0.9$, 5.1, 9.6, 14.1 Hz, 1H), 1.38–1.51 (m, 2H), 1.59 (dt, $J=5.1$, 9.9 Hz, 1H), 1.62–1.69 (m, 1H), 1.97 (ddd, $J=5.7$, 9.6, 14.1 Hz, 1H), 2.10 (ddt, $J=5.1$, 7.5, 14.1 Hz, 1H), 5.19 (d, $J=7.8$ Hz, 1H), 5.29 (d, $J=4.5$ Hz, 1H), 6.68–6.78 (m, 2H), 6.96–7.04 (m, 2H), 9.14 (s, 1H); EI-MS $m/z=202$ ($M^{+\bullet}$), HRMS (EI) calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0989 ($M^{+\bullet}$); capillary GC (OV-1701, 170°C, INJ/DET, 200°C). $t_R=21.8$ min.
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17. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.52 (ddt, J=4.2, 6.6, 13.8 Hz, 1H), 0.87 (s, 9H), 0.96–1.09 (m, 1H), 1.36 (ddd, J=3.6, 4.5, 14.4 Hz, 1H), 1.51–1.61 (m, 2H), 2.04–2.17 (m, 2H), 2.79 (dt, J=2.4, 14.1 Hz, 1H), 2.87 (ddd, J=3.3, 6.0, 14.1 Hz, 1H), 3.25 (dd, J=7.8, 9.9 Hz, 1H), 3.30 (dd, J=6.6, 9.9 Hz, 1H), 5.20 (dd, J=5.4, 10.8 Hz, 1H), 7.11 (dd, J=1.5, 7.5 Hz, 1H), 7.20 (dt, J=1.8, 7.5 Hz, 1H), 7.27 (dt, J=1.5, 7.2 Hz, 1H), 7.51 (dd, J=1.2, 7.5 Hz, 1H); FAB-MS m/z=359 ([M+K]$^+$), HRMS (FAB$^+$) calcd for $C_{19}H_{32}O_2SiK$ 359.1810, found 359.1826 ([M+K]$^+$).
18. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.04 (s, 6H), 0.84 (s, 9H), 0.87–0.93 (m, 1H), 1.26–1.40 (m, 2H), 1.60–1.72 (m, 2H), 1.83 (dt, J=5.7, 12.3 Hz, 1H), 2.02–2.11 (m, 1H), 2.76–2.79 (m, 1H), 3.24 (dd, J=6.6, 9.6 Hz, 1H), 3.29 (dd, J=6.3, 9.6 Hz, 2H), 5.25 (dd, J=5.4, 10.8 Hz, 1H), 7.09 (dd, J=1.5, 7.5 Hz, 1H), 7.18 (dt, J=1.5, 7.5 Hz, 1H), 7.26 (dt, J=1.5, 7.5 Hz, 1H), 7.52 (dd, J=1.5, 7.5 Hz, 1H); FAB-MS m/z=359 ([M+K]$^+$), HRMS (FAB$^+$) calcd for $C_{19}H_{32}O_2SiK$ 359.1810, found 359.1807 ([M+K]$^+$).
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