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Synthesis of 4-oxepanones by the Lewis acid-promoted ring-expansion reaction of cyclopropapyranones

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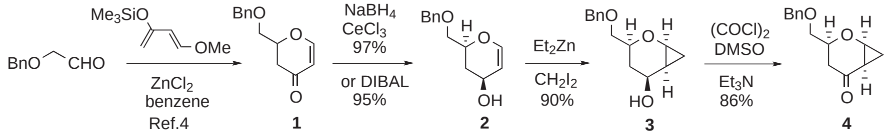
Abstract—In the presence of a Lewis acid, cyclopropapyranones easily reacted with silyl enolates to give the 4-oxepanones in good yields. In this reaction, the *trans*-isomer was mainly obtained. © 2001 Elsevier Science Ltd. All rights reserved.

Seven-membered oxacycles containing natural products have attracted the attention of synthetic organic chemists due to their unique molecular structures and potent biological activities.[1] Various methods for the construction of the seven-membered oxacycles have been reported.[2]

We postulated that the treatment of cyclopropapyranones with a Lewis acid readily generates a cyclic 1,3-zwitterion, which can react with nucleophiles to produce the oxepanes. Cyclopropanes with donor and acceptor substituents at the vicinal positions on the cyclopropane ring are the equivalent of the ring-opened 1,3-zwitterion, which is expected to react with both nucleophiles and electrophiles.[3] Because cyclopropapyranones have an alkoxy group as a donor and a carbonyl group as an acceptor in the pyran ring, formation of a cyclic 1,3-zwitterionic intermediate would be expected. We now report the stereoselective synthesis of 4-oxepanones by the reaction of cyclopropapyranones as the synthetic equivalent of the cyclic 1,3-zwitterion.

3-Benzyloxymethylcyclopropapyran-5-one (**4**) was chosen as the substrate. This was easily synthesized in three steps starting from the known dihydropyranone (**1**).[4] Thus, the reduction of **1** with $NaBH_4$ in the presence of cerium chloride[5] or DIBAL afforded the dihydropyranol (**2**) in good yield.[6] Cyclopropanation of the pyranol double bond was achieved by the Simmons–Smith reaction to give the cyclopropapyranol (**3**) in 90% yield as the single isomer.[7] The stereochemistry of **3** was assigned based on NOE experiments.[8] Finally, the oxidation of **3** gave the desired cyclopropapyranone (**4**) in 86% yield (Scheme 1).

The reaction of **4** with silyl enol ether (**5a**) was chosen as the model, and several reaction conditions were examined. As expected, under the Lewis acid-promoted conditions, cyclopropapyranone (**4**) reacted with **5a** to afford the oxepanone (**6**). These results are summarized in Table 1. In the presence of a catalytic amount of TMSOTf in MeCN, **4** was reacted with **5a** to give the oxepanone in 37% yield (entry 1). From this reaction,



Scheme 1.

Keywords: cyclopropanes; oxepanes; zwitterions.

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the *trans*-isomer was mainly obtained (*trans*:*cis* = 92:8, entry 1). However, when using dichloromethane as the solvent, both the yield and diastereoselectivity slightly decreased (entry 2). Furthermore, the use of a stoichiometric amount of TMSOTf led to a complex reaction mixture (entry 3). In order to improve the yield of this reaction, we examined the use of various Lewis acids such as $\mathrm{La(OTf)_3}$, $\mathrm{In(OTf)_3}$, $\mathrm{SnCl_4}$, and $\mathrm{BF_3{\cdot}OEt_2}$, etc. Among the various Lewis acids tested, the $\mathrm{BF_3{\cdot}OEt_2}$-promoted reaction gave the best result. It was found that the use of a stoichiometric amount of $\mathrm{BF_3{\cdot}OEt_2}$ in $\mathrm{CH_2Cl_2}$ resulted in an enhancement of the chemical yield (entry 8). On the other hand, a decrease in the *trans*/*cis* ratio was observed when toluene was used as the solvent (entry 9).

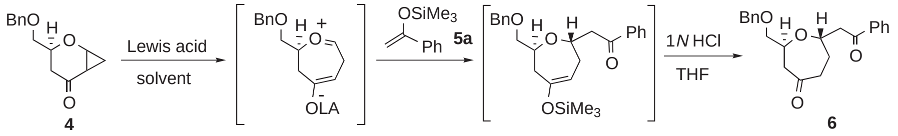
Several examples of the ring-expansion reactions of **4** were examined and the results are summarized in Table 2 (entries 1–4). As for the nucleophiles, the silyl enol ethers (**5a**–**c**) smoothly reacted with **4** in the presence of $\mathrm{BF_3{\cdot}OEt_2}$ in $\mathrm{CH_2Cl_2}$ (Method A) to give the corresponding oxepanones (**6**–**8**) in good yields, albeit a slight decrease in selectivity was observed compared with using TMSOTf in MeCN (Method B, entries 1–3). Next, the reaction of **4** with ketene silyl acetal (**5d**) was investigated. In this case, the use of $\mathrm{SnCl_4}$ as a Lewis acid in $\mathrm{CH_2Cl_2}$ (Method C) gave the best result and the corresponding oxepane (**9**) was obtained in 62% yield as a *trans*:*cis* mixture of 81:19 (entry 4).

To extend the scope of this methodology, we next examined the reactions of several cyclopropapyranones with silyl enolates (entries 5–11). In the cases of the reaction of **10**[4,9] with the silyl enolates, a similar tendency was observed. Namely, while the adduct (**11**) was produced in good yield in the presence of $\mathrm{BF_3{\cdot}OEt_2}$ (Method A), a decrease in the yield and enhancement of the selectivity were observed when the reaction was carried out using TMSOTf in MeCN (entry 5). The reaction of **10** with **5d** also gave the corresponding oxepanone (**13**) in 71% yield when $\mathrm{SnCl_4}$ was used as the Lewis acid (entry 7). Under similar conditions, the chiral cyclopropanes (**14**,[9,10] **17**[9,11]) also reacted with the silyl enolates to give the corresponding oxepanones in good yields with moderate diastereoselectivity (entries 8–11). The stereochemical assignment of the products (**6**, **11**, **13**, and **18**) was mainly established by analysis of their NOE experiments[8] and other products were assigned after a comparative analysis of the ^{1}H NMR spectra.

The mechanism of this ring-expansion reaction is not clear. However, we believe that the stereoselectivity is probably due to the anomeric effect from the ring oxygen atom in a zwitterionic intermediate.[12]

In summary, we have demonstrated that the Lewis acid-promoted ring-opening addition reactions of cyclopropapyranones with silyl enolates proceeded smoothly to afford the corresponding 4-oxepanones in good yields with moderate *trans*-selectivity. The mechanistic aspects and further application of this reaction are now under investigation in our laboratory.

Table 1. Effects of Lewis acids and solvents[a]



Entry	Lewis acid (equiv.)	Solvent	Temp./°C	Time/h	Yield[b]/%	*Trans*:*cis*[c]
1	TMSOTf (0.1)	MeCN	–40	0.5	37[d]	92:8
2	TMSOTf (0.1)	$\mathrm{CH_2Cl_2}$	–78	0.5	34[d]	88:12
3	TMSOTf (1.0)	MeCN	–40	0.5	Mix[d]	–
4	$\mathrm{La(OTf)_3}$ (0.3)	MeCN	rt	4	36	89:11
5	$\mathrm{In(OTf)_3}$ (0.1)	$\mathrm{CH_2Cl_2}$	0	0.5	41	89:11
6	$\mathrm{SnCl_4}$ (0.5)	$\mathrm{CH_2Cl_2}$	–78	0.5	45[d]	90:10
7	$\mathrm{BF_3{\cdot}OEt_2}$ (0.3)	$\mathrm{CH_2Cl_2}$	–78	0.5	62	88:12
8	$\mathrm{BF_3{\cdot}OEt_2}$ (1.0)	$\mathrm{CH_2Cl_2}$	–78	0.5	85	88:12
9	$\mathrm{BF_3{\cdot}OEt_2}$ (1.0)	Toluene	–78	0.5	55	75:25
10	$\mathrm{BF_3{\cdot}OEt_2}$ (1.0)	MeCN	–40	0.5	Mix	–

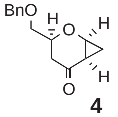
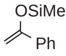
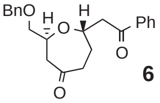
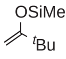
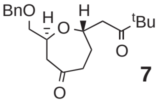
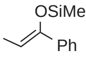
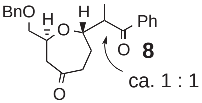
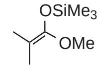
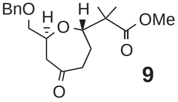
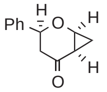
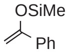
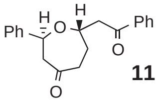
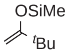
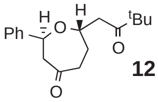
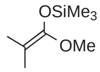
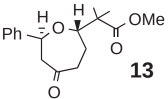
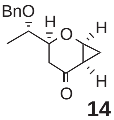
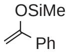
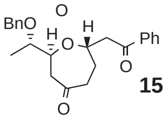
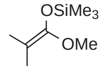
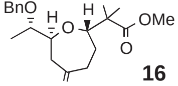
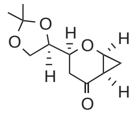
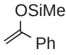
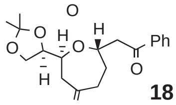
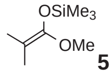
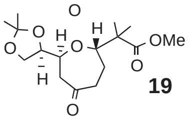
[a] To a solution of **5a** (2 equiv.) and the Lewis acid was added a solution of **4**.

[b] Isolated yield.

[c] The ratio of the stereoisomers was determined by ^{1}H NMR.

[d] To a solution of **4** and **5a** was added the Lewis acid.

Table 2. Ring-expansion reactions of cyclopropapyranones with silyl enolates[a]

Entry		Nucleophile	Method[b]	Product	Yield[c]/%	*trans* : *cis*[d]
1	 **4**	 **5a**	A B	 **6**	85 (62)[e] 37[f]	88 : 12 (88 : 12)[e] 92 : 8
2	**4**	 **5b**	A B	 **7**	64 24[f]	85 : 15 95 : 5
3	**4**	 **5c**	A B	 **8**	79 36[f]	>95 : 5 >95 : 5
4	**4**	 **5d**	A C	 **9**	42 62[f]	74 : 26 81 : 19
5	 **10**	 **5a**	A B	 **11**	84 (86)[e] 46	84 : 16 (84 : 16)[e] 96 : 4
6	**10**	 **5b**	A	 **12**	52 (47)[e]	92 : 8 (92 : 8)[e]
7	**10**	 **5d**	C	 **13**	71	70 : 30
8	 **14**	 **5a**	A	 **15**	78	89 : 11
9	**14**	 **5d**	C	 **16**	88	80 : 20
10	 **17**	 **5a**	A	 **18**	75	90 : 10
11	**17**	 **5d**	C	 **19**	48	68 : 32

[a] To a solution of the silyl enolate and the Lewis acid was dropwise added a solution of cyclopropapyranone. [b] Method A: silyl enolate (2 eq.), BF$_3$·OEt$_2$ (1 eq.), CH$_2$Cl$_2$, -78 °C; Method B: silyl enolate (2 eq.), TMSOTf (0.1 eq.), MeCN, -40 °C; Method C: silyl enolate (2 eq.), SnCl$_4$ (0.3 eq.), CH$_2$Cl$_2$, -78 °C. [c] Isolated yield. [d] The ratio of the stereoisomers was determined by 500 Mz ^{1}H NMR. [e] 0.3 eq. of BF$_3$·OEt$_2$ was used. [f] To a solution of cyclopropapyranone and silyl enolate was added the Lewis acid.

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8. The stereochemical assignment of the compounds (**3**, **6**, **11**, **13**, and **18**) was mainly established by analysis of their NOE experiments (see figure below).
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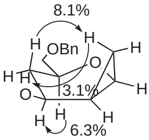

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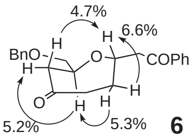

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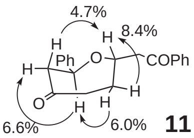

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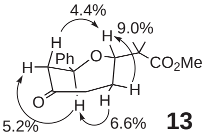

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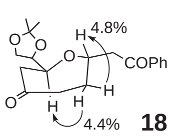

18