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SYNTHESIS OF LACTONE-FUSED CYCLOPROPANES BY RING CONTRACTIVE α-KETOL REARRANGEMENT OF KETAL-FUSED CYCLOBUTANONES

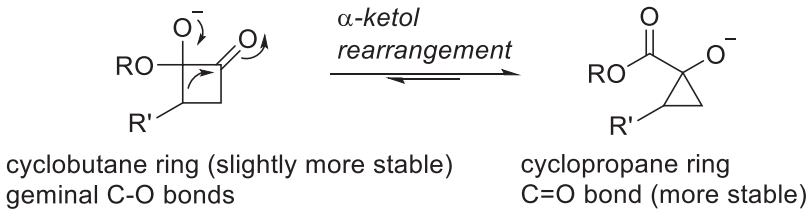
Kiyosei Takasu,* Koichi Shigenaga, Kazuma Shimoda, Hiroshi Takikawa, and Yousuke Yamaoka

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
E-mail: kay-t@pharm.kyoto-u.ac.jp

Abstract – Ring contraction of cyclic silyl ketal-fused cyclobutanones into lactone-fused cyclopropanes under desilylative conditions is described. The reaction affords 1-hydroxy- and 1-amino-1-cyclopropanecarboxylic acid derivatives from cyclobutanone substrates and their imine congeners, respectively.

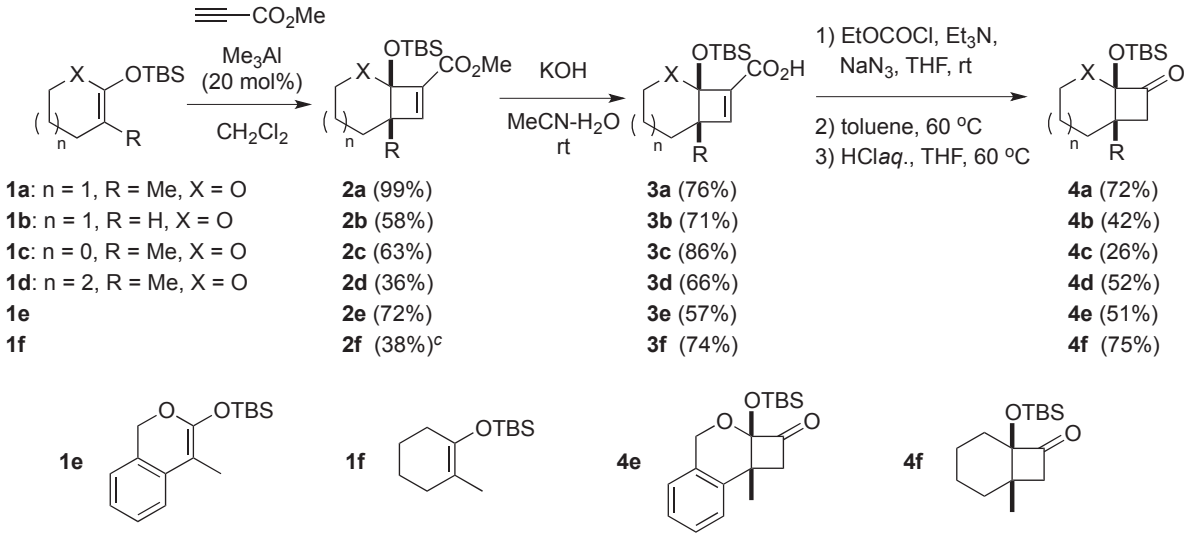
Cyclopropanes, one of strained carbocycles, provide important scaffolds in the design of drug candidates[1] and are advantageous substances in molecular transformations[2] due to their unique structure, bond properties and reactivity. The cyclopropane subunit is also found in nature as secondary metabolites.[3] Many powerful syntheses of cyclopropane compounds have been extensively explored.[4] One of the most investigated approaches to cyclopropanes is the [2+1] annulation of vinylic compounds with amphiphilic C1 units, such as Simmons-Smith reaction and Johnson-Corey-Chaykovsky reaction. Alternatively, the cyclization of linear substances is utilized for the formation of the cyclopropane ring. Although the ring contraction of cyclobutane compounds into cyclopropanes is possible way, the reported examples are still rare.[5] The strain energy of the cyclopropane ring (115.1 kJ/mol) is slightly higher than that of the cyclobutane ring (110.0 kJ/mol).[6] Therefore, selective conversion into the cyclopropane compounds would be possible by installing an additional destabilizing factor to the cyclobutane substrates. We envisaged that the conversion of geminal C–O bonds into a C=O double bond would drive the ring contraction by a 1,2–rearrangement, such as α-ketol-type rearrangement[7-10] (Scheme 1). The ring expansive α-ketol rearrangement of cyclopropanes into cyclobutanes was well investigated,[9] whereas the studies of its retro reaction are limited.[10] In this paper, we describe the ring-contractive synthesis of lactone-fused hydroxycyclopropanes from cyclic ketal fused-cyclobutanones by an α-ketol-type rearrangement.

Dedicated to Prof. Dr. Yasuyuki Kita on the occasion of his 77th Birthday



Scheme 1. Ring-contractive α-ketol rearrangement

Cyclobutanone substrates **4a-e** and **4f** were prepared from cyclic ketene silyl acetals **1a-e** and silyl enol ether **1f**, respectively, in 5 steps (Scheme 2). Me_3Al-catalyzed [2+2] cycloaddition[11] of **1a** with methyl propiolate afforded ketal-fused cyclobutenecarboxylate **2a**, which was converted into the corresponding carboxylic acid **3a** in good yield. The Curtius rearrangement of **3a** and subsequent hydrolysis[12] produced bicyclic cyclobutanone **4a** in 72% yield (3 steps). Carbocyclic congener **4f** was prepared from silyl enol ether **1f** in 5 steps.[13]

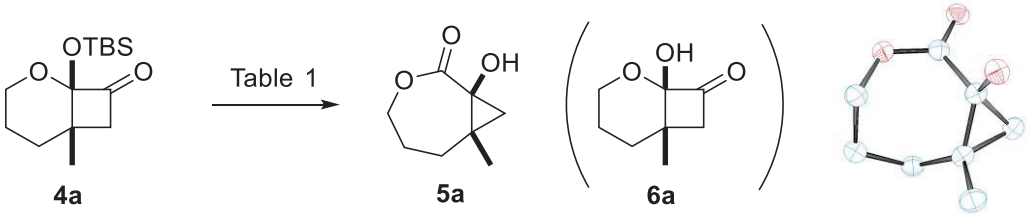


Scheme 2. Preparation of cyclobutanone substrates **4a-4f**[a,b]

[a]Isolated yields were shown in all transformation. [b]Yield optimization for **4b-4f** was not carried out.
[cd]1 Mol% of Tf_2NH was used instead of Me_3Al.

With the series of cyclobutanones in hand, we screened the optimal conditions for ring contraction of **4a** with a desilylative agent (Scheme 3). Treating **4a** with tetrabutylammonium fluoride (TBAF) in THF at rt for 60 min fully consumed **4a** and formed desired ε-lactone-fused cyclopropane **5a** in 44% yield (Table 1, entry 1). X-Ray crystallography confirmed that **5a** had the expected structure.[14] Hemiketal **6a** was not obtained in the above reaction. Although a retro rearrangement of **5a** into **6a** did not proceed under the

same reaction conditions, **5a** gradually decomposed. When the reaction was quenched within 1 min, **5a** was obtained in 71% and 73% yield at room temperature and 0 °C, respectively (entries 2 and 3). The reaction was promoted above –20 °C to give **5a** in 78% yield (entry 4), whereas substrate **4a** was completely recovered at –78 °C even after 60 min (entry 5). The reaction did not proceed using a hydrogen fluoride pyridine complex in THF or hydrogen fluoride instead of TBAF at room temperature. These reagents required a higher temperature (80 °C) for desilylation of **4a** and successive rearrangement. Consequently, the yield of **5a** was low (entries 5 and 6).



Scheme 3. Ring contraction of **4a** and X-ray crystallographic structure of **5a**

Table 1. Optimization of reaction conditions for **4a**[a]

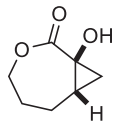
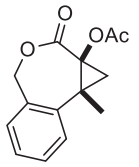
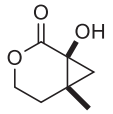
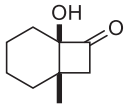
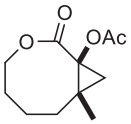
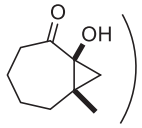
entry	reagent (equiv)	temp. (°C)	time (min)	yield (%) of **5a**[b]	recovery (%) of **4a**[b]
1	TBAF (1.5)	rt	60	44	0
2	TBAF (1.0)	rt	1	71	0
3	TBAF (1.0)	0	1	73	10
4	TBAF (1.0)	–20	10	78	<1
5	TBAF (1.0)	–78	60	0	>95
6	HF•pyridine (3.0)	80	60	15	9
7[c]	HF (3.0)	rt	60	0	>95

[a]**4a** (0.21 mol), desilylating reagent, in THF [b]Isolated yield [c]In MeCN

Having established the optimal conditions for the ring contraction reaction, the scope of the reaction was explored (Table 2). The reaction of **4b**, desmethyl analog of **4a**, furnished cyclopropane **5b** in 46% yield although the reaction must be performed at –20 °C owing to instability of **5b** under the reaction conditions (entry 1). γ-Lactone-fused hydoroxycyclopropane **5c** was obtained in good yield from oxabicyclo[3.2.0]heptanone **4c** (entry 2), but the conversion of **4d** into the ζ-lactone congener **5d** was poor (entry 3). Tricyclic cyclobutanone **4e** also afforded the corresponding cyclopropane **5e**, which was isolated as its acetate in 70% yield (2 steps from **4e**) after treatment with Ac_2O, DMAP and NEt_3 (entry 4).[15] On the other hand, no cyclopropane **5f** was observed in the reaction of carbocyclic substrate **4f**, but formation of hydroxycyclobutanone **6f** was resulted (entry 5). The result clearly indicated that formation

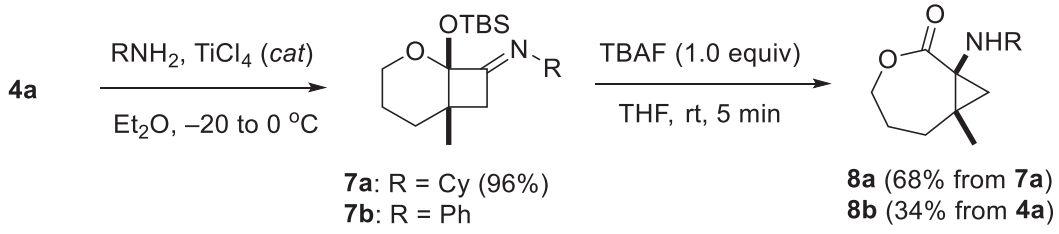
of the hemiketal moiety after desilylation would be a driving force for the ring contractive α-ketol rearrangement.

Table 2. Scope of the ring contraction reaction of **4**[a]

entry	substrates	products	%yield[b]	entry	substrates	products	%yield[b]
1	**4b**	**5b** 	46	4	**4e**	**5e'** 	70[d]
2	**4c**	**5c** 	62	5[c]	**4f**	**6f** 	79
3	**4d**	**5d'** 	33[d]			**5f** 	0

[a]**4** (1 equiv), TBAF (1 equiv), in THF, at –20 °C, 5–40 min [b]Isolated yield [c]At rt, 5 h [d]The products **5d** and **5e** were isolated after transfomation into the corresponding acetates **5d'** and **5e'**, respectively, by treatment with Ac_2O, DMAP and NEt_3. Two-steps yields were shown.

The ring contraction reaction can be extended to synthesize 1-aminocyclopropanecarboxylic acid (ACC)[16] derivatives, which are useful modules for clinical drugs, starting from the imine analogs of **4** as a substrate (Scheme 4). Cyclobutaneimines **7a** and **7b** were prepared by titanium(IV) chloride catalyzed imination of **4a** with cyclohexylamine and aniline, respectively.[17] Treatment of **7a**, which was obtained in 96% yield from **4a** as a pure form, with TBAF at room temperature gave desired aminocyclopropane **8a** in 68% yield. In contrast, **8b** was synthesized from **4a** in 2 steps (34% yield) without chromatographic purification of **7b** due to its instability against silica gel.



Scheme 4. Synthesis of lactone-fused aminocyclopropanes

In summary, a ring contractive α-ketol rearrangement giving lactone-fused hydroxycyclopropanes from cyclic silyl ketal-fused cyclobutanones is described. It is noteworthy that the aminocyclopropane congeners are accessible from imine derivatives.

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SUPPORTING INFORMATION

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at URL: https://wwwheterocycles.jp.

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14. Data of **5a**: Colorless plates. Mp 104−106 °C (recrystallization from hexane/Et_2O). TLC R_f = 0.38 (hexane/AcOEt 1:1, *p*-anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (ddd, *J* = 12.5, 12.5, 4.0 Hz, 1H), 4.26 (ddd, *J* = 12.5, 6.0, 0.5 Hz, 1H), 4.05 (br, 1H), 2.06 (ddd, *J* = 15.0, 6.0, 1.0 Hz, 1H), 1.91 (ddddd, *J* = 15.0, 12.5, 7.0, 6.0, 1.0 Hz, 1H), 1.77 (ddddd, *J* = 14.5, 12.5, 6.0, 4.0, 0.5 Hz, 1H), 1.20 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 1H), 0.83 (ddd, *J* = 15.0, 12.5, 7.0 Hz, 1H), 0.80 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 65.5, 60.4, 30.6, 25.2, 23.5, 21.5, 14.4. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_8H_{13}O_3^+$, 157.0859, found 157.0858. IR ($CHCl_3$): ν 3360, 2932, 1724, 1258, 1192, 910, 737 cm^{-1}. X-ray: *triclinic*, P–1; *a* = 6.3587(3), *b* = 7.4781(4), *c* = 8.4653(3); *α* = 90.605(4), *β* = 97.016(3), *γ* = 99.753(4); *V* = 393.54 (3), *Z* = 2, D_{calc} = 1.318, *R* = 0.0512, R_w = 0.1545, GOF = 1.145. CCDC 1989254 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
15. The isolation of **5d** and **5e** from the by-products by silica gel chromatography was difficult.
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