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Studies of ring-closing mode of 4-hydroxy-2-vinylidenebutanoates: 5-*exo*-trig versus 5-*endo*-dig

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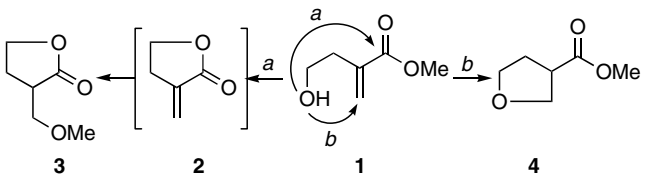
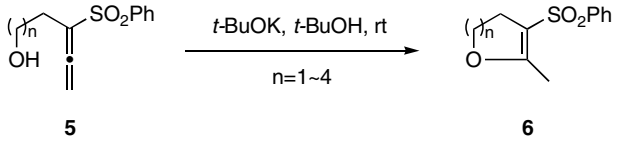
Abstract—The ring-closing mode of benzyl 4-hydroxy-2-vinylidenebutanoates (5-*exo*-trig vs 5-*endo*-dig) could precisely be controlled in a highly selective manner by the proper choice of conditions (solvent and base).

The ring-closing mode, *exo*- versus *endo*-manner, sometimes becomes the central issue in the synthesis of target cyclic compounds. The ring-closing mode might be properly predicted on the basis of Baldwin's rule[1a] that is widely recognized as a reliable empirical rule. As a typical example (Scheme 1), the exclusive formation of α-methoxymethyl-γ-lactone **3**, via the reaction of the intermediate of **2** with the liberated methoxide anion, was observed when the α,β-unsaturated ester **1** was exposed to basic conditions.[1b] This result could be regarded as the so-called '5-*exo*-trig' mode (route *a*), which is a favored pathway based on Baldwin's rule.[1a] An alternative '5-*endo*-trig' mode (a disfavored pathway) leading to compound **4** could not be detected (route *b*).[1b]

During our studies[2] on the ring-closing reaction of phenylsulfonylallenes, we found that 1-(ω-hydroxyalkyl)-1-(phenylsulfonyl)allene derivatives **5** easily underwent the *endo*-dig mode[2a–e] ring-closing reaction[3,4] to produce



Scheme 1. 5-*exo*-Trig versus 5-*endo*-trig.



Scheme 2. Ring-closing reaction of phenylsulfonylallenes **5**.

the five- to eight-membered oxacycles **6** (Scheme 2). In this Letter, we have investigated the ring-closing reaction of 1-(2-hydroxyalkyl)-1-(benzyloxycarbonyl)allene derivatives under basic conditions to determine if the terminal alkoxide species, generated in situ in the reaction vessel, would preferentially attack the carbonyl functionality through the 5-*exo*-trig mode or the central carbon atom of the allene moiety through the 5-*endo*-dig mode,[5] both of which are the favored processes according to Baldwin's rule.[1]

For the initial evaluation, the optimized conditions[2] for the *endo*-dig mode ring-closing reaction of phenylsulfonylallenes **5** was examined for that of benzyl 4-hydroxy-2-vinylidenebutanoate **7**.[6] However, treatment of **7** with *t*-BuOK (1 equiv)[†] in *t*-BuOH (0.1 M solution)[‡] at room temperature for 5 min predominantly produced the *exo*-trig mode product **8**[§] in a 65% yield along with a small amount of the *endo*-dig mode product

Keywords: Allenes; Ring-closing mode; Solvent effect; Baldwin's rule.
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† It took a prolonged time to completely consume the starting material upon exposure to a catalytic amount of *t*-BuOK.
‡ When the reaction ran in THF in the presence of *t*-BuOK, **8** was obtained in a 33% yield as the only isolatable product.
§ The stereochemistry was determined to be (*E*) by an NOE analysis.

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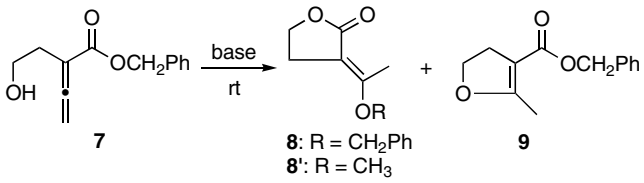
Table 1. Ring-closing reaction of primary alcohol

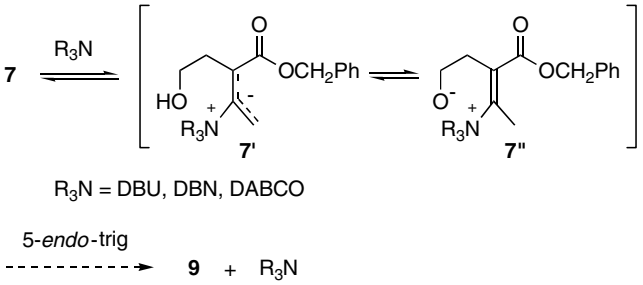


Entry	Base (equiv)	Solvent	Time	Yield of **8** (%)	Yield of **9** (%)
1	*t*-BuOK (1.0)	*t*-BuOH	5 min	65	6
2	*t*-BuONa (1.0)	*t*-BuOH	5 min	47	8
3	*t*-BuOLi (1.0)	*t*-BuOH	12 h	55	—[a]
4	MeOK (2.0)	MeOH	2 h	45[b]	—
5	MeOLi (2.0)	MeOH	6 h	34[b]	—
6	Cs_2CO_3 (1.0)	THF	24 h	49	—[a]
7	Cs_2CO_3 (1.0)	CH_2Cl_2	24 h	55	—[a]
8	Cs_2CO_3 (1.0)	DMF	4 h	12	41
9	K_2CO_3 (1.0)	DMF	8 h	6	45
10	Cs_2CO_3 (1.0)	MeCN	4 h	10	45
11	Cs_2CO_3 (1.0)	DMSO	2 h	6	54
12	DBU (1.5)	THF	2 h	—[c]	53
13	DBU (1.5)	DMF	30 min	—[c]	64
14	DBU (1.5)	DMSO	30 min	—[c]	72
15	DBN (1.5)	DMSO	1 h	—[c]	70
16	DABCO (3.0)	DMSO	24 h	—[c]	49
17	TBAF (1.5)	DMSO	5 min	—[c]	65

[a] A trace amount of **9** was detected by TLC.
[b] (*E*)-2-(1-Methoxyethylidene)-γ-lactone (**8′**) was obtained instead of **8**.
[c] A trace amount of **8** was detected by TLC.

9 (6%) (Table 1, entry 1). *t*-BuONa and *t*-BuOLi gave similar results, but with lower yields (entries 2 and 3). Changing the alkoxide/alcohol system from *t*-BuOK/*t*-BuOH to MeOK/MeOH or MeOLi/MeOH resulted in the exclusive formation of (*E*)-2-(1-methoxyethylidene)-γ-lactone (**8′**)[¶] in rather low yields (45% and 34% yield, respectively) (entries 4 and 5). Cs_2CO_3 in THF or CH_2Cl_2 again exclusively afforded the *exo*-trig mode product **8** (entries 6 and 7). In contrast to these results, the *endo*-dig mode product **9** unexpectedly became the major product (41%) when **7** was exposed to Cs_2CO_3 (1 equiv) in DMF at room temperature for 4 h (entry 8). K_2CO_3 was found to use instead of Cs_2CO_3 for the preferential formation of the *endo*-dig mode product **9** (entry 9). Both MeCN and DMSO could also be used as a suitable solvent for the selective production of **9** (entries 10 and 11). Furthermore, tertiary amines, such as DBU, DBN (1,5-diazabicyclo[4.3.0]non-5-ene), and DABCO, were shown to be suitable bases for the highly selective formation of the *endo*-dig mode product **9** (entries 12–16). In particular, the best result (72%) was obtained when **7** was treated with DBU (1.5 equiv)[‖] in DMSO at room temperature for 30 min (entry 14). TBAF behaved like the tertiary amines, but with a much faster consumption of the starting material (entry 17).[7] There are several points that deserve to be mentioned. An alkoxide/alcohol system consistently produced the 5-*exo*-trig mode product **8** in a highly selective manner (entries 1–5), whereas the almost exclusive formation of the 5-*endo*-dig mode product **9** was achieved when treated with tertiary amine bases (entries 12–16). If the tertiary amines, such as DBU, DBN, and DABCO, attack first at the sp-hybridized carbon center of compound **7**, the corresponding benzyl 3-trialkylammonium-2-(2-hydroxyethyl)-2-butenoate species **7′** must be formed in situ (Scheme 3).[8] The transformation of thus formed α,β-unsaturated ester intermediates into compound **9** should involve the 5-*endo*-trig mode ring-closing process of **7″**, which is, however, believed to be the disfavored pathway on the basis of Baldwin's rule. Thus, it might be reasonable to describe that the ring-closing reaction of compound **7** leading to **9** would proceed via the 5-*endo*-dig mode by the direct attack of the terminal alkoxide group at the sp-hybridized carbon center. In addition, the complementary production of compounds **8** and **9** could be realized by simply changing the solvent upon exposure of **7** to Cs_2CO_3. The order of solvent possessing a higher dielectric constant is as follows: DMSO (46.45) > DMF (36.71) > MeCN (35.94) > CH_2Cl_2 (8.93) > THF (7.58).[9] On the basis of the dielectric constant, these five solvents can be clearly divided into two groups; one consists of DMSO, DMF, and MeCN, and the other, CH_2Cl_2 and THF. The former group predominantly afforded the 5-*endo*-dig product **9**, whereas the latter group exclusively produced the 5-*exo*-trig product **8**. Although a full mechanistic discussion for the ring-closing reaction of compound **7** is premature at this point, the dielectric constant of the solvent might govern the preferred conformation[10] of compound **7** and/or the transition state of the ring-closing process as long as Cs_2CO_3 was used as a base.

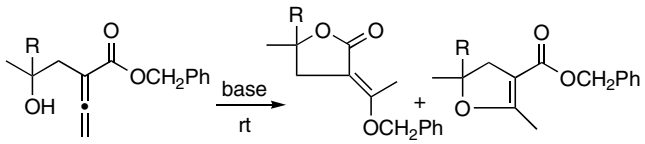
Secondary and tertiary alcohols **10**, **11** were used for the ring-closing reaction under the typical four conditions (entries 1, 6, 11, and 14 in Table 1). These results are summarized in Table 2. All reactions proceeded in a highly selective manner to afford the 5-*exo*-trig mode products **12**, **14** or the 5-*endo*-dig mode products **13**, **15** depending on the reaction conditions, although the chemical yields of dimethyl derivatives **14**, **15** are consistently lower than those of products **8**, **9** derived from the primary alcohol **7**. Thus, it became obvious that the ring-closing mode (5-*exo*-trig vs 5-*endo*-dig) could be controlled in a highly selective manner by the proper choice of the reaction conditions,[11] regardless of the bulkiness of the nucleophilic alcohol moiety of the starting allenes.



Scheme 3.

[¶] Compound **8** could not be detected in the reaction mixture.
[‖] 1 equiv of DBU could mediate the ring-closing reaction, but it took a prolonged time to completely consume the starting material.

Table 2. Ring-closing reaction of secondary and tertiary alcohols



10: R = H
11: R = Me

12: R = H
14: R = Me

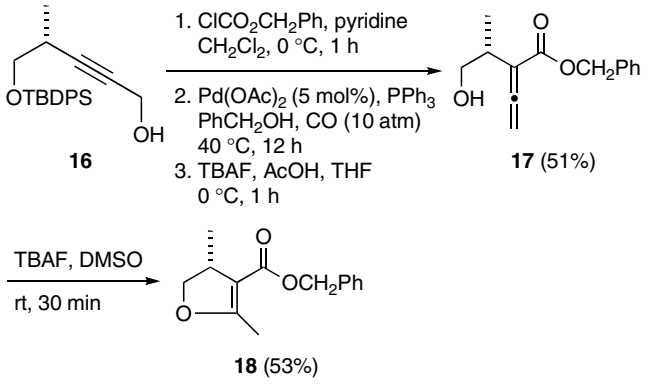
13: R = H
15: R = Me

Entry	Substrate	Base (equiv)	Solvent	Time	*exo*-Prod (%)	*endo*-Prod (%)
1	**10**	*t*-BuOK (1.0)	*t*-BuOH	5 min	**12** (61)	—[a]
2	**10**	Cs_2CO_3 (1.0)	THF	24 h	**12** (44)	—[a]
3	**10**	Cs_2CO_3 (1.0)	DMSO	4 h	—[b]	**13** (52)
4	**10**	DBU (1.5)	DMSO	30 min	—[b]	**13** (70)
5	**11**	*t*-BuOK (1.0)	*t*-BuOH	5 min	**14** (51)	—[c]
6	**11**	Cs_2CO_3 (1.0)	THF	24 h	**14** (38)	—[c]
7	**11**	Cs_2CO_3 (1.0)	DMSO	3 h	—[d]	**15** (46)
8	**11**	DBU (1.5)	DMSO	30 min	—[d]	**15** (65)

[a] A trace amount of **13** was detected by TLC.
[b] A trace amount of **12** was detected by TLC.
[c] A trace amount of **15** was detected by TLC.
[d] A trace amount of **14** was detected by TLC.

Newly developed *endo*-dig mode ring-closing procedure could nicely be applied to the synthesis of chiral dihydrofuran **18** (Scheme 4). The methyl ester congener of **18** has been shown to be a key synthetic intermediate for the first total synthesis of (−)-xyloketal A.[12] The known propargyl alcohol **16**,[13] derived from methyl (*S*)-3-hydroxy-2-methylpropionate, was treated with benzyl chloroformate to give the corresponding carbonate, conversion of which into allene **17** was achieved by the successive $Pd(OAc)_2$-mediated rearrangement[14] under 10 atm CO at 40 °C and conventional deprotection reaction. Treatment of **17** with TBAF in DMSO at room temperature exclusively furnished the 5-*endo*-dig mode product **18** in a 53% yield.

In conclusion, we have described that the ring-closing mode (5-*exo*-trig vs 5-*endo*-dig) of benzyl 4-hydroxy-2-vinylidenebutanoates could precisely be controlled in a highly selective manner by the proper choice of conditions (solvent and base). The *endo*-dig mode ring-closing protocol of allenes was extended to the synthesis of a key intermediate for the synthesis of (−)-xyloketal A. Further studies on the reaction mechanism of this ring-closing reaction, and application of it to the preparation of the larger-membered oxacycles as well as to the synthesis of natural products are currently underway.



Scheme 4. Synthesis of dihydrofuran **18**.

Acknowledgment

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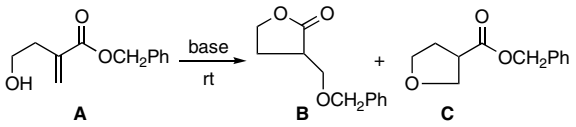
11. The ring-closing reaction of benzyl 2-methylenebutanoate **A** (benzyl ester congener of compound **1** in Scheme 1) was examined under the several aforementioned basic conditions as control experiments. In these cases, the corresponding α-benzyloxymethyl-γ-lactone **B** (benzyloxy congener of **3** in Scheme 1) was consistently obtained as the only isolatable product in the range of 55–78% yield regardless of the conditions.



A **B** **C**

Base	Solvent	Yield	
t-BuOK	*t*-BuOH	78%	0%
Cs_2CO_3	THF	67%	0%
Cs_2CO_3	DMSO	55%	0%
DBU	DMSO	62%	0%

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