NOVEL METHOD FOR THE SYNTHESIS OF CHIRAL 4-ARYL-γ-BUTYROLACTONES *VIA* CASCADE ASYMMETRIC EPOXIDATION—RING EXPANSION—BAEYER-VILLIGER REACTION OF CYCLOPROPYLIDENE DERIVATIVES

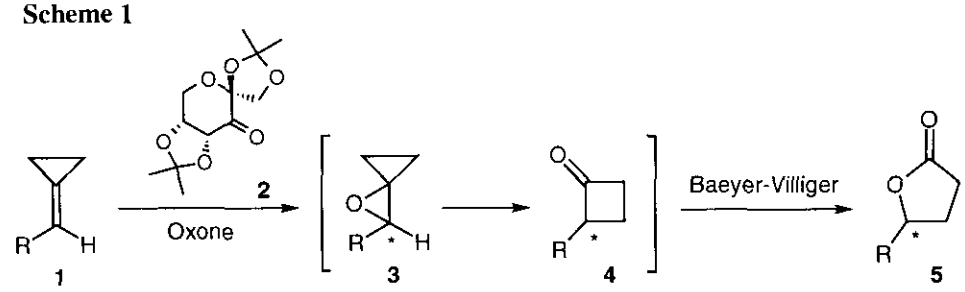
Masahiro Yoshida, Mohamed Abdel-Hamid Ismail, Hideo Nemoto, and Masataka Ihara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Abstract- Asymmetric epoxidation–ring expansion–Baeyer-Villiger reaction of cyclopropylidene derivatives using Oxone and fructose-derived ketone afforded chiral 4-aryl-γ-butyrolactones in one-pot process.

Since γ-butyrolactones are important synthetic unit in organic synthesis[1] and are the key structural elements in many naturally occurring compounds,[2] there are numerous methods for the synthesis of γ-butyrolactone.[3] In this communication, we describe a novel methods for the synthesis of chiral 4-aryl-γ-butyrolactones *via* cascade reaction of cyclopropylidene derivative utilizing Shi's asymmetric epoxidation method.[4]

Scheme 1

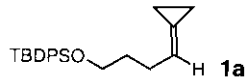
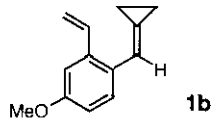
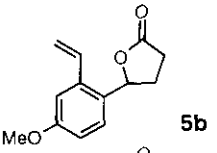
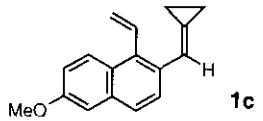
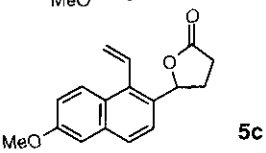


As outlined in Scheme 1, our preliminary goal in this paper involved the asymmetric epoxidation of the cyclopropylidene derivative (**1**) using Oxone and fructose-derived ketone (**2**)[4] to form the oxaspiropentane

(**3**), whose enantiospecific rearrangement, followed by Baeyer-Villiger oxidation of the cyclobutanone (**4**) to yield the chiral γ-butyrolactone (**5**).

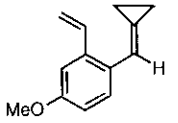
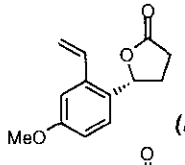
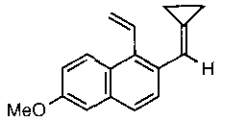
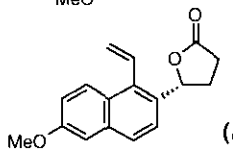
When cyclopropylidene derivatives were treated with excess trifluoroacetone and Oxone,[5] a formation of γ-butyrolactones was observed. Reactions were carried out with substrate (1 equiv.), trifluoroacetone (2 equiv.), Oxone (2 equiv.), and K_2CO_3 (6 equiv.) in CH_3CN-0.05M $Na_2B_4O_7 \cdot 10H_2O$ of aqueous Na_2(EDTA) (4×10^{-4}M) solution (adjusted to pH 10.5)[6] (1:1 *v/v*) at 0 °C for 45 min. Although the corresponding lactone was not obtained in the case of the alkyl substituted cyclopropylidene derivatives (**1a**) (Table 1, entry 1), the substrates (**1b**) and (**1c**) having aromatic ring, which were more electron rich substrates than **1a**, could be converted into lactones (**5b**) and (**5c**) in 32% and 36% yields (entries 2 and 3).

Table 1. Racemic γ-butyrolactone synthesis using trifluoroacetone and Oxone

entry	substrate	product	yield (%)
1	 **1a**	not obtained	—
2	 **1b**	 **5b**	32
3	 **1c**	 **5c**	36

Since the lactone formation was carried out as the racemic form, asymmetric reaction conditions were then examined (Table 2). When **1b** was treated with chiral ketone (**2**)[4] (2 equiv.), Oxone (2 equiv.) and K_2CO_3 (6 equiv.) in CH_3CN-0.05M $Na_2B_4O_7 \cdot 10H_2O$ of aqueous Na_2(EDTA) (4×10^{-4}M) solution (adjusted to pH 10.5) (1:1 *v/v*) at 0 °C for 45 min, the reaction was successfully proceeded to give the chiral lactone ((***R***)-**5b**) in 56% yield with 37% ee (entry 1). Furthermore, the reaction of **1c** possessing naphthalene ring gave (***R***)-**5c** in 60% yield with 72% ee (entry 2). It is interesting that yields of the chiral lactones were increased comparing with the case of racemate.

Table 2. Asymmetric γ-butyrolactone synthesis using chiral ketone (**2**) and Oxone.

entry	substrate	product[a]	yield (%)	ee (%)[b]
1	 **1b**	 ***(R)*-5b**	56	37
2	 **1c**	 ***(R)*-5c**	60	72

[a] Absolute configuration was tentatively assigned on the basis of the authentic sample of (***R*)-5c**, which was prepared from corresponding chiral cyclobutanone.[7] [b] Enantiomeric excess was determined by chiral HPLC (Chiralcel OA or OJ).

In conclusion, we have developed a novel method for the synthesis of chiral γ-butyrolactones using Oxone and fructose-derived ketone (**2**). The scope and limitation of the above cascade reaction are the subject of our current study.

ACKNOWLEDGMENTS

This work was partly supported by Grant-in Aid for Scientific Research on Priority Areas (10132205) from the Ministry of Education, Science, Culture and Sports, Japan. M. Y. acknowleges support from the Research Fellowships of the Japan Society for the Promotion of Scienece for Young Scientists.

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6. Desired lactones were produced more effectively at a higher pH >10 than at a lower pH 7-8.
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Received, 3rd September, 1998