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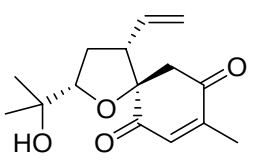
STEREOSELECTIVE SYNTHESIS OF 5-SUBSTITUTED 2-ALLYL-3-OXOTETRAHYDROFURAN-2-CARBOXYLATES USING RHODIUM(II)-CATALYZED OXONIUM YLIDE FORMATION–[2,3] SHIFT

Takayuki Yakura,[1]* Katsuaki Matsui,[1,2] Kazumasa Matsuzaka,[1] and Masayuki Yamashita[2]

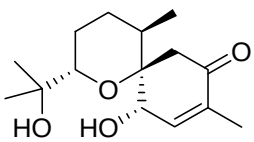
[1]Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan [2]Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan
E-mail: yakura@pha.u-toyama.ac.jp

Abstract – Reaction of 5-allyloxy-2-diazo-3-ketoesters **1** with catalytic amount of dirhodium(II) tetraacetate in dichloromethane proceeded in high yields with excellent stereoselectivities to give methyl 5-substituted 2-allyl-3-oxotetrahydrofuran-2-carboxylates **2**, which are suitable intermediates for synthesis of heliespirones and their derivatives.

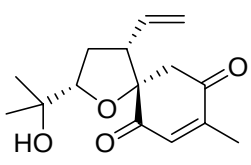
Heliespirones A,[1,2] B,[2,3] and C[2] were isolated from leaves of *Helianthus annuus* L. in 1998 and 2006 as members of a new family of bioactive sesquiterpenes, potential allelopathic agents. These compounds display unusual previously unknown spirosesquiterpene skeletons. Heliespirones A and C have a 2,2,3,5-tetrasubstituted tetrahydrofuran framework; heliespirone B has a 2,2,3,6-tetrasubstituted tetrahydropyran framework. Stereoselective construction of substituted tetrahydrofurans and pyrans is an important subject for synthesis of these attractive sesquiterpenes and their analogues. Herein, we describe the synthesis of 5-substituted 2-allyl-3-oxotetrahydrofuran-2-carboxylates **2**, which might become suitable intermediates for the synthesis of heliespirones, in high yields with excellent stereoselectivities by rhodium(II)-catalyzed oxonium ylide formation-[2,3] shift of α-diazo-β-ketoesters **1**.



heliespirone A

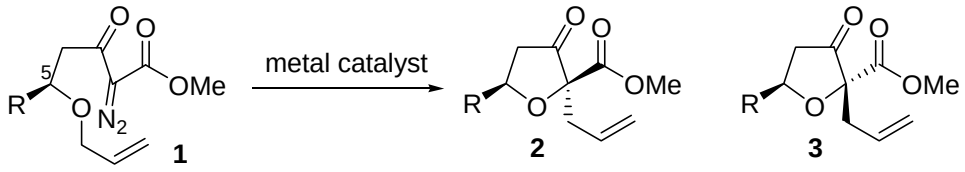


heliespirone B



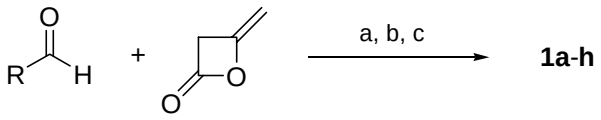
heliespirone C

Metal-catalyzed carbenoid reactions[4] have become a powerful tool for synthesis of functionalized cyclic compounds including oxacycles. However, it is sometimes difficult to control their chemoselectivity because of the high reactivity of the metal carbenoid intermediates, which can react with heteroatoms, inactivated C–H bonds, C–C multiple bonds, *etc*. Moreover, the bulkiness of metal carbenoid influences its chemoselectivity.[5,6] Formation of cyclic allylic oxonium ylide by intramolecular reaction of diazocarbonyl compound containing suitably positioned allylic ethereal oxygen atom and its subsequent [2,3] shift offer an effective approach to the stereoselective construction of substituted cyclic ethers. In contrast to the metal-catalyzed oxonium ylide formation-rearrangement reactions of diazoketones,[7,8] those of α-diazo-β-ketoester have been little investigated.[9] Although the Pirrung group[9a] and West group[9e] reported, respectively, oxonium ylide formation-[2,3] shift of simple α-diazo-β-ketoester, methyl 5-allyloxy-2-diazo-3-ketopentanoate, using dirhodium(II) tetraacetate and copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$] to give 2-allyl-3-oxotetrahydrofuran-2-carboxylate in high yield (R=H, Scheme 1), no information related to chemoselectivity and diastereoselectivity of similar reactions of substituted α-diazo-β-ketoesters is available. Therefore we envisioned investigation of metal-catalyzed reactions of substituted α-diazo-β-ketoesters (**1**, R≠H) to 2,2,5-trisubstituted 3-oxotetrahydrofurans (**2** or **3**, R≠H), which are expected to provide a feasible method for synthesis of the 2,2,3,5-tetrasubstituted tetrahydrofuran framework of heliespirones A and C, as outlined in Scheme 1.



Scheme 1

Starting 5-allyloxy-2-diazo-3-ketoesters **1** were prepared from the corresponding aldehyde in three steps: reaction with diketene in the presence of titanium tetrachloride then treatment with methanol,[5,10] followed by allylation, subsequent diazotransfer reaction with *p*-toluenesulfonyl azide (Scheme 2).

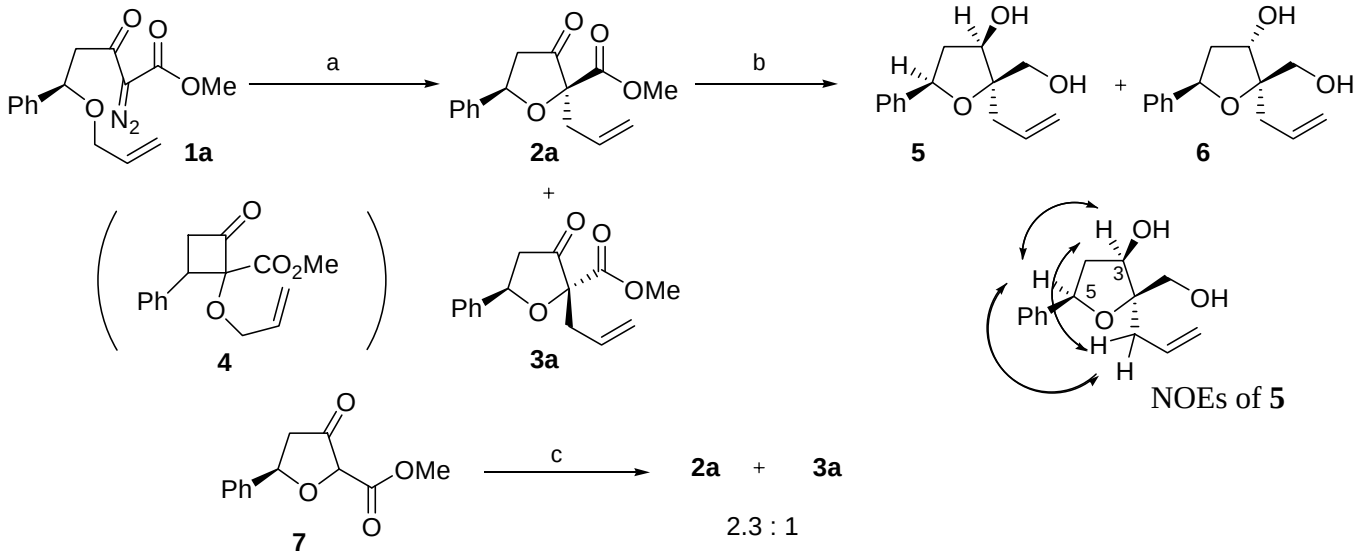


a: R = Ph
b: R = *p*-Tol
c: R = Me
d: R = Et
e: R = CH_2CH_2Ph
f: R = CH_2CHMe_2
g: R = *i*-Pr
h: R = *t*-Bu

Scheme 2. *Reagents and conditions*: a) $TiCl_4$, CH_2Cl_2, -78 °C, then MeOH, -20 °C to rt; b) $Cl_3CC(=NH)OCH_2CH=CH_2$, TfOH, CH_2Cl_2, rt; c) TsN_3, Et_3N, MeCN, rt

First we tested the reaction of phenyl substituted α-diazo-β-ketoester **1a** lacking C–H bonds at the C-6 position that can react with generated metal carbenoid (Scheme 3). Reaction of **1a** with 3 mol% of $Rh_2(OAc)_4$ in dichloromethane[9e] at rt for 30 min proceeded stereoselectively to give separable

tetrahydrofurans **2a** and **3a** in 94% yield and with a high level of diastereocontrol (**2a**:**3a**=91:9) (Table 1, entry 1). Another possible product **4** *via* Stevens [1,2] shift was not detected. A similar reaction of **1a** with $Cu(hfacac)_2$ in CH_2Cl_2[9e] required higher temperature (reflux) and longer time (4 days) to afford a mixture of **2a** and **3a** in 94% yield with a slightly lower diastereoselectivity (79:21) (Table 1, entry 2). The *trans* relation between the phenyl group at C-5 position and migrated allyl group at C-2 position of **2a** was determined after the reduction with diisobutylaluminum hydride (DIBAL-H) to diols **5** and **6**.[11] In the NOESY spectrum of **5**, positive NOEs were observed among H-3 proton and H-5 proton, and allylic methylene protons at C-2 position. As an alternative stereoselective synthesis of **2a**, we attempted allylation of 5-phenyl-3-oxotetrahydrofuran-2-carboxylate **7**.[12] The unstable **7** was treated with allyl bromide in the presence of potassium carbonate as a base in acetonitrile[12a] to give **2a** as a major product. This procedure, however, was unsuitable for synthesis of **2a** because of low yield (39% for a mixture of **2a** and **3a**) and low stereoselectivity (2.3:1).



Scheme 3. *Reagents and conditions*: a) see Table 1; b) DIBAL-H, CH_2Cl_2, -80-0 °C, 2 h (50% for **5**, 39% for **6**); c) K_2CO_3, allyl bromide, MeCN, rt, 4 h (39%)

Because $Rh_2(OAc)_4$ showed better results than copper catalyst did, we next investigated reactions using other solvents (Table 1, entries 3 and 4) and other rhodium(II) catalysts (Table 1, entries 5–9). Unfortunately, better results than that of entry 1 were not obtained. Interestingly, rhodium catalysts having bulky ligands such as pivaloate and triphenylacetate decreased the stereoselectivities (entries 8 and 9).

Reactions of several α-diazo-β-ketoesters **1b**–**1h** with 3 mol% of $Rh_2(OAc)_4$ in CH_2Cl_2 were investigated as standard conditions.[13] Table 2 presents the results. All reactions were completed within 30 min. Reaction of **1b** (R = *p*-Tol) produced almost identical results as that of **1a** (Entry 1). Alkyl substituted derivatives **1c**–**1g**, which have reactive C–H bonds at the C-6 position, reacted chemoselectively at the ether oxygen to give the corresponding tetrahydrofurans in high yields with excellent

diastereoselectivities (Entries 2–6). Reaction of **1h** having bulky *tert*-butyl group at the C-5 position decreased the chemical yield because of steric hindrance around the ethereal oxygen atom (Entry 7). The yield was increased when **1h** reacted with $Rh_2(OCOC_7H_{15})_4$ in stead of $Rh_2(OAc)_4$ (Entry 8).

Table 1. Metal-catalyzed reaction of **1a**

Entry	Catalyst (mol%)	Solvent	Temperature	Time	Yield (%)	**2a**:**3a** [a]
1	$Rh_2(OAc)_4$ (3)	CH_2Cl_2	rt	30 min	94	91: 9
2	$Cu(hfacac)_2$ (10)	CH_2Cl_2	reflux	4 d	94	79:21
3	$Rh_2(OAc)_4$ (3)	benzene	rt	4 h	94	90:10
4	$Rh_2(OAc)_4$ (3)	THF	rt	4 h	no reaction	
5	$Rh_2(OCOCF_3)_4$ (3)	CH_2Cl_2	rt	30 min	94	86:14
6	$Rh_2(OCOC_7H_{15})_4$ (3)	CH_2Cl_2	rt	5 min	97	89:11
7	$Rh_2(OCOC_7H_{15})_4$ (3)	CH_2Cl_2	0 °C	90 min	94	89:11
8	$Rh_2(OCOCMe_3)_4$ (3)	CH_2Cl_2	rt	5 min	94	83:17
9	$Rh_2(OCOCPh_3)_4$ (3)	CH_2Cl_2	rt	5 min	92	54:46

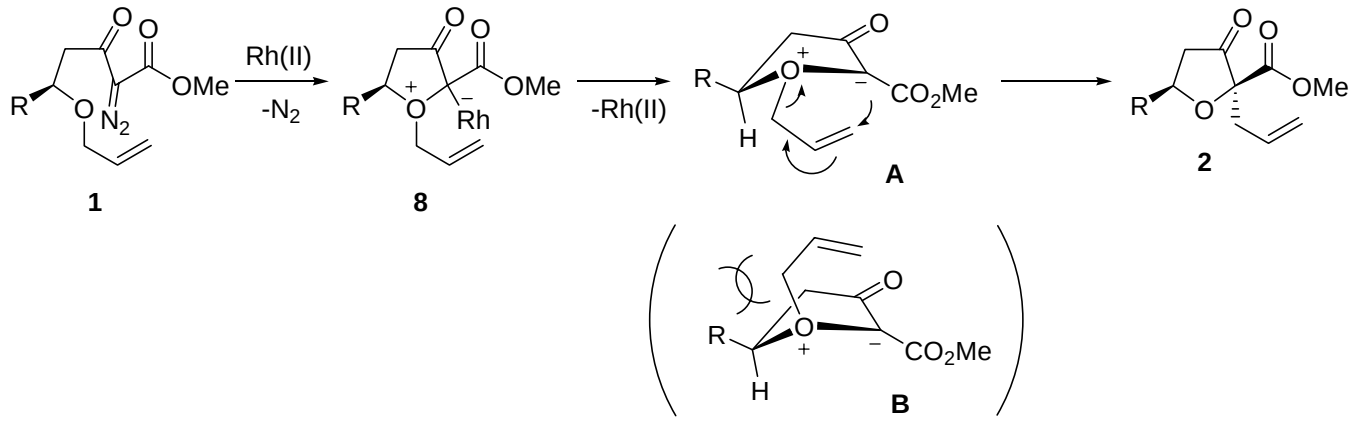
a) Determined by ^{1}H-NMR.

Table 2. Rh(II)-catalyzed reactions of 5-allyloxy-2-diazo-3-ketoesters **1** [a]

Entry	**1**	Yield (%)	**2**:**3** [b]
1	**b**	94	88:12
2	**c**	80	96: 4
3	**d**	86	>99: 1
4	**e**	93	>99: 1
5	**f**	86	>99: 1
6	**g**	89	>99: 1
7	**h**	58	>99: 1
8 [c]	**h**	65	>99: 1

a) Reactions were carried out with 3 mol% of $Rh_2(OAc)_4$ in CH_2Cl_2 at rt for 30 min.
b) Determined by ^{1}H-NMR.
c) $Rh_2(OCOC_7H_{15})_4$ (3 mol%) was used.

A possible rationalization of the observed stereoselectivity in rhodium(II)-catalyzed reaction of **1** is based on the consideration of the conformations of oxonium ylides **A** and **B**,[7k,7m,8] generated through rhodium-bound ylide **8**[7e] (Scheme 4).[14] In conformer **A**, both the allyl group and the substituent at C-5 position can be accommodated in pseudoequatorial positions. In contrast, in conformer **B**, severe steric repulsion between these two groups becomes evident. We assumed, therefore, that the oxonium ylide formation-[2,3] shift would proceed *via* the sterically favored conformer **A** to form tetrahydrofuran **2**.



Scheme 4

In conclusion, rhodium(II)-catalyzed reaction of 5-allyloxy-2-diazo-3-ketoesters **1** gave methyl 5-substituted 2-allyl-3-oxotetrahydrofuran-2-carboxylates **2** in high yields with excellent stereoselectivities. Synthetic studies on the heliespirones using this methodology are now in progress.

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5. Treatment of methyl 5-*tert*-butyldimethylsilyloxy-2-diazo-3-oxoheptanoate with Rh(II) catalyst selectively afforded the C–H insertion product. See, T. Yakura, S. Yamada, A. Ueki, and M. Ikeda, *Synlett*, 1997, 185; T. Yakura, S. Yamada, Y. Kunimune, A. Ueki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3643.
6. Chemoselectivity (C–H insertion reaction *vs*. oxonium ylide formation) in Rh(II)-catalyzed reaction of 5,6-dioxygenated 2-diazo-3-oxohexanoates was controlled by their *O*-protecting groups. See, T. Yakura, A. Ueki, Y. Morioka, T. Kurata, K. Tanaka, and M. Ikeda, *Chem. Pharm. Bull.*, 1997, **46**, 1182; T. Yakura, A. Ueki, T. Kitamura, K. Tanaka, M. Nameki, and M. Ikeda, *Tetrahedron*, 1999, **55**, 7461.
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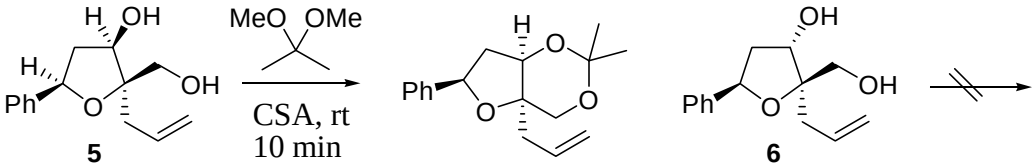
11. Treatment of **5** with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA) gave the corresponding acetonide within 10 min, although a similar reaction of **6** did not proceed after 24 h.



5 **6**

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13. Typical reaction procedure: A solution of **1** (0.2 mmol) and $Rh_2(OAc)_4$ (0.006 mmol) in CH_2Cl_2 (20 mL) was stirred at rt. After **1** was consumed completely, as indicated by TLC, the mixture was concentrated and purified using column chromatography on silica gel to give pure **2**. All new compounds gave satisfactory spectroscopic data.
14. Alternatively, the reaction may proceed through stepwise allyl-transfer to rhodium metal followed by reductive elimination, in analogy to that proposed in the case of [1,2] shift of benzyl group by Dhavale group[15].
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