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SYNTHESIS OF THE HEMIACETAL PHEROMONE OF THE SPINED CITRUS BUG *BIPRORULUS BIBAX* UTILIZING AN IRIIDIUM CATALYZED OXIDATIVE LACTONIZATION

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Abstract – *cis*-3,4-bis[(*E*)-1-butenyl]tetrahydro-2-furanol, the pheromone of the *Biprorulus bibax*, was synthesized by the iridium catalyzed oxidative lactonization.

INTRODUCTION

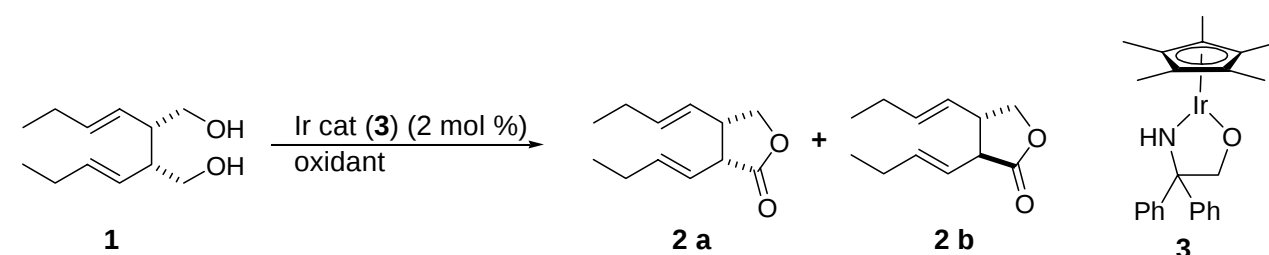
The oxidative lactonization of diol is one of the powerful methods to synthesize lactones.¹ We have previously reported the amino alcohol-based iridium bifunctional complex as a versatile catalyst for oxidative lactonization,^{2a-b} Oppenauer oxidation,^{2c} oxidative dimerization,^{2d} and Tishchenko reaction.^{2e-f} In this paper, as an effective utilization of our iridium complex, a convenient preparation of the pheromone of the *Biprorulus bibax* is described.

The spined citrus bug, *Biprorulus bibax*, is an Austrian citrus pest. The structure of the male-produced pheromone of the pest was determined by Oliver and James.³ Mori et al. determined the absolute configuration of the natural pheromone as 3*R*, 4*S* by asymmetric synthesis.⁴ However, female spined citrus bug did not discriminate both enantiomers, thus unnatural enantiomer was also bioactive.⁵ They reported the improved synthesis of the racemate by employing Ireland's ester enolate Claisen rearrangement as the key step.⁶ Also, for the construction of the lactone moiety, Fetizon reagent⁷ (Ag₂CO₃, 20eq) was used, which is a typical reagent for the oxidative lactonization. However this method needs large excess of the expensive silver salts. Recently we have developed a catalytic method for the mild oxidative lactonization. Herein we present the application of this methodology for the synthesis of the pheromone of the *Biprorulus bibax*.

RESULTS AND DISCUSSION

The requisite diol (**1**) was prepared according to the procedure developed by Mori from tetrahydropyranyl (THP) ether of propargyl alcohol.⁶ The catalytic oxidative lactonization of the diol (**1**) was examined under the conditions as shown in Table 1. Using 13.6 mol equivalents of acetone at 30 °C in the presence of 2 mol % of Ir catalyst (**3**),^{2a} the reaction was slow and gave diastereomixture of lactone (**2**) in 74% yield (Entry 1). Although we have not observed any epimerization in the oxidative lactonization of *cis*- or *trans*- 1,2-bis(hydroxymethyl)cyclohexane, the epimerization product was accompanied in the typical condition. When the reaction was carried out under dilution condition (136 mol equiv. of acetone), the yield and selectivity was improved and 85% yield of the lactones were obtained in 78:22 ratio of **2a** and **2b** (Entry 2). The reflux condition in 2-butanone afforded the quantitative yield after 24 h, however the ratio of the undesired epimer was also increased (Entry 3). We were pleased to find that the reaction proceeded in 90% yield without any epimerization by using 5 mol equiv. of *p*-benzoquinone in toluene (Entry 4). DIBALH reduction of the lactone (**2a**) to **4** was accomplished in 95% yield according to the Mori's procedure (Scheme 1).

Table 1. Oxidative lactonization of **1** catalyzed by Ir complex (**3**)

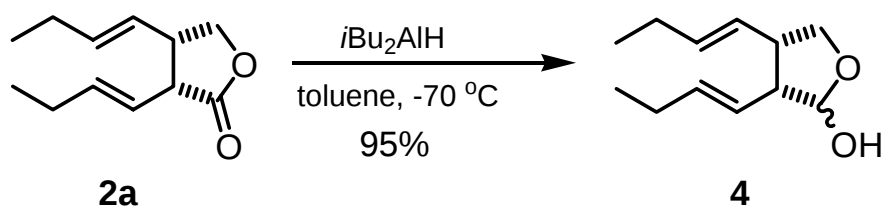


Entry	Oxidant (mol eq)	Temp. (°C)	Time (h)	Yield of 2 (%) ^c	Ratio of 2a : 2b ^d	recovery of 1 (%) ^c
1 ^a	acetone (13.6)	30	60	74	59 : 41	23
2 ^a	acetone (136)	30	36	85	78 : 22	15
3 ^a	2-butanone (44.8)	reflux	24	100	40 : 60	0
4 ^b	<i>p</i> -benzoquinone (5)	30	36	90	100 : 0	10

a) The reaction was carried out using 0.25 mmol of **1** in acetone or 2-butanone in the presence of 2 mol % of **3**.

b) The reaction was carried out using 5 mol eq of *p*-benzoquinone in toluene (0.25 M).

c) Isolated yield. d) Determined by ¹H-NMR.



Scheme 1. Synthesis of the pheromone (**4**)

Next we turned our attention to the mechanistic investigation of the epimer formation. The pure lactone (**2a**) or (**2b**) were treated with 2 mol% of the catalyst (**3**), in acetone or 2-butanone under the conditions shown in Table 2. The epimerization of **2a** took place easily in both acetone and butanone. The epimerization product was obtained in 57 % after 22 h in refluxing 2-butanone (Entry 2). On the other hand the epimerization of **2b** afforded less than 4 % yield of **2a** even after 22 h in refluxing butanone (Entry 4). These results clearly suggest **2b** is thermodynamically more stable than **2a**. The present reaction conditions did not use any hydrogen donor in reaction system, even though the epimerization took place. This suggests that the epimerization proceeded not through the addition-elimination mechanism of the metal hydride to olefin but by the slight basic character of the metal amide (**3**).⁸

Table 2. Epimerization of **2** under reaction condition^a

2 a or 2 b $\xrightarrow{\text{Ir cat (3) (2 mol \%)}}$					
Entry	Substrate	Solvent	Temp (°C)	Recovery of lactone (%)	Ratio of (2 a : 2 b) ^b
1	2 a	acetone	30	100	81 : 19
2	2 a	2-butanone	reflux	100	43 : 57
3	2 b	acetone	30	100	4 : 96
4	2 b	2-butanone	reflux	100	4 : 96

a) The reaction was carried out using 0.07 M solution of **2** (0.07 mmol) in the presence of 2 mol % of **3** for 22 h. b) Determined by ¹H-NMR.

In conclusion an efficient synthesis of the pheromone of the *Biprorulus bibax* has been achieved utilizing the iridium catalyzed oxidative lactonization as a key step. Further studies are in progress.

EXPERIMENTAL

Iridium-catalyzed oxidative lactonization of diol (**1**)

A mixture of Ir complex (**3**)^{2a} (2.7 mg, 0.005 mmol), *meso*-diol (**1**)⁶ (0.25 mmol) and *p*-benzoquinone (135.1 mg, 1.25 mmol) in toluene (1.0 mL) was stirred at 30 °C under Ar. After 36 h the resulting mixture was passed through a short silica gel column and evaporated, the residue was purified by column chromatography (SiO₂, hexane/Et₂O, 4:1) to give lactone (**2a**) (43.8 mg, 90%).

cis-3,4-Di[(*E*)-1-butenyl]dihydro-2(3*H*)furanone **2a**)

^1H NMR (270 MHz, C_6D_6): δ 0.79 (t, $J = 7.4$ Hz, 3H), 0.85 (t, $J = 7.5$ Hz, 3H), 1.71-1.93 (m, 4H), 2.43 (m, 1H), 2.80 (t, $J = 7.8$ Hz, 1H), 3.59 (dd, $J = 5.4, 8.7$ Hz, 1H), 3.67 (dd, $J = 6.3, 8.7$ Hz, 1H), 5.05 (m, 1H), 5.15-5.30 (m, 2H), 5.59 (m, 1H).

trans-3,4-Di[(*E*)-1-butenyl]dihydro-2(3*H*)furanone (**2b**)

^1H NMR (270 MHz, C_6D_6): δ 0.79 (t, $J = 7.5$ Hz, 3H), 0.87 (t, $J = 7.4$ Hz, 3H), 1.73-1.80 (m, 2H), 1.88-1.93 (m, 2H), 2.34-2.42 (m, 2H), 3.23 (m, 1H), 3.74 (dd, $J = 7.4, 8.6$ Hz, 1H), 4.76 (m, 1H), 5.19 (m, 1H), 5.34 (m, 1H), 5.54 (m, 1H).

cis-3,4-Bis[(*E*)-1-butenyl]tetrahydro-2-furanol (**4** major anomer)

To a solution of the lactone (**2a**) (43.9 mg, 0.226 mmol) in toluene (1.9 mL) was added DIBAL (1.0 M toluene solution, 0.226 mL, 0.226 mmol) at -78°C . After 10 min the reaction mixture was diluted with ether and quenched by addition of saturated ammonium chloride and extracted with Et_2O , the combined organic extracts were washed with saturated NaHCO_3 and brine, and dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane/ Et_2O , 3:1) to give lactol (**4**) (42.2 mg, 95%)

^1H NMR (270 MHz, C_6D_6): δ 0.87 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 7.5$ Hz, 3H), 1.83-2.01 (m, 4H), 2.35 (brs, 1H), 2.78 (m, 1H), 3.25 (m, 1H), 3.69 (t, $J = 8.3$ Hz, 1H), 4.13 (t, $J = 8.0$ Hz, 1H), 5.05-5.59 (m, 5H).

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