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A highly efficient and selective synthesis of lissoclinolide featuring hydrogen transfer hydrozirconation, *trans*-selective Pd-catalyzed cross coupling of alkenylzirconiums with 1,1-dibromoalkenes and Ag-catalyzed lactonization providing (*Z*)-γ-alkylidenebutenolides

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Abstract:

An antibiotic lissoclinolide has been synthesized from propargyl alcohol in 9 steps and in 32% overall yield *via* (i) hydrogen transfer hydrozirconation of TBS-protected propargyl alcohol with *i*-$BuZrCp_2Cl$, (ii) Pd-catalyzed *trans*-selective cross coupling of the hydrozirconation product with a key 1,1-dibromoalkene intermediate **5** and (iii) Ag-catalyzed lactonization of a trienynoic acid precursor **2**.

We have recently [1] reported that the Pd-catalyzed cross coupling-lactonization tandem process [2] based on Sonogashira coupling [3] can be optimized to give (*Z*)-γ-alkylidenebutenolides in high yields, one of the key findings being the desirability of the use of a Pd-PPh_3 mixture, in which the PPh_3/Pd ratio is ≥4 [4]. This tandem process has been successfully applied to the syntheses of natural products, such as rubrolides [1a], (+)-goniobutenolide [1b], and freelingyne [1c], which provided, for the first time, examples of natural products syntheses *via* Pd-catalyzed lactonization of ynoic acids [1d]. We have also reported [1a] that, despite the lack of opportunity for exploiting the highly efficient cross coupling-lactonization tandem process, lactonization of (*Z*)-2-en-4-ynoic acids catalyzed by Ag salts [5] can provide (*Z*)-γ-alkylidenebutenolides in excellent yields under dilute conditions.

We now report that the Ag-catalyzed lactonization is significantly superior to the Pd-catalyzed procedure in the synthesis of lissoclinolide (**1**) [6] from its precursor **2**. Coupled with hydrogen transfer hydrozirconation [7] of TBS-protected propargyl alcohol, where TBS is *t*-$BuMe_2Si$, to give **3** and Pd-catalyzed *trans*-selective cross coupling [8] of **3** with 1,1-dibromoalkene **5**, lissoclinolide has been synthesized in 9 steps and in 32% overall yield from propargyl alcohol with nearly complete (>98%) regio- and stereo-control (Scheme 1).

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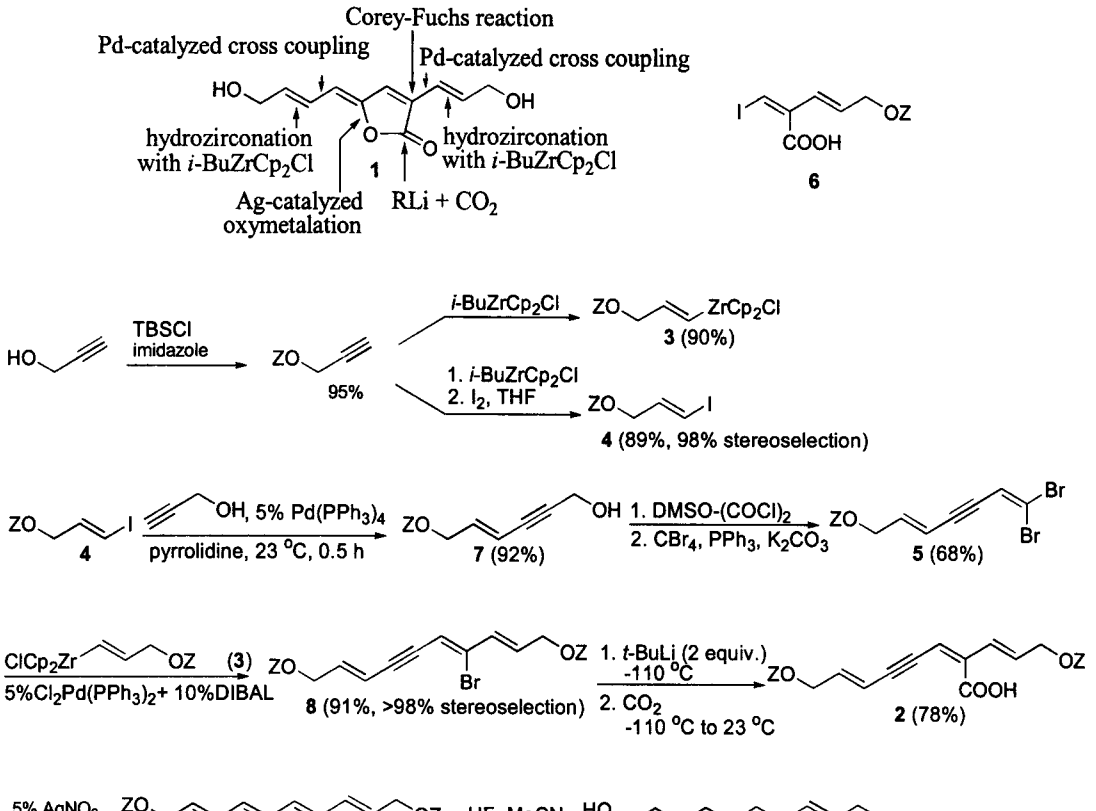
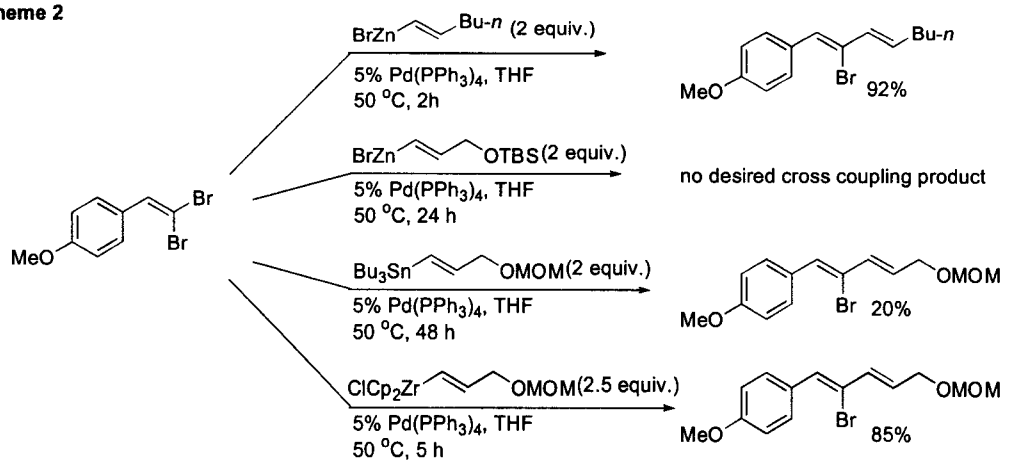
Scheme 1



Scheme 2



Lissoclinolide (**1**) [6], isolated from *Lissoclinum patella*, has been shown to be active against Gram negative bacteria. Interestingly, its (5*E*)-isomer, tetrenolin, is known to be active against Gram positive bacteria [9]. Despite their structural simplicity, their synthesis has not been reported.

We initially envisioned the synthesis of **1** *via* Pd-catalyzed cross coupling-lactonization tandem process [1,2] but encountered difficulties in the synthesis of the requisite (*Z*)-β-iodo acid (**6**). We therefore opted for the synthesis of **2** as a precursor to **1**. This option gave us the flexibility of using either Pd-catalyzed or Ag-catalyzed lactonization, which eventually proved to be crucial in the synthesis of **1**. Hydrogen transfer hydrozirconation of TBS-protected propargyl alcohol at 50 °C in benzene [7] provided **3** (>98% *E*) in 90% yield, while its iodinolysis gave **4** in 89% yield. Since *i*-BuZrCp$_2$Cl is readily generated *in situ* by treatment of commercially available and relatively stable Cp$_2$ZrCl$_2$ with one equiv of *t*-BuMgCl, this represents a convenient alternative to conventional hydrozirconation [10] and its modifications using various metal hydrides [11]. The reaction of **4** with propargyl alcohol in the presence of pyrrolidine and 5 mol% of Pd(PPh$_3$)$_4$ afforded **7** in 92% yield, which was oxidized with (COCl)$_2$ and DMSO [12] and then treated with CBr$_4$ (3 equiv) and PPh$_3$ (6 equiv) [13] to give **5** in 68% yield from **7**. Conversion of **5** into **8** *via* Pd-catalyzed cross coupling was initially attempted with the alkenylzinc derivative generated from **4** *via* lithiation with *t*-BuLi (2 equiv) and zincation with ZnBr$_2$. To our surprise, **8** was not at all formed. The results were puzzling, since a model experiment led to very satisfactory *trans*-selective cross coupling, as shown in Scheme 2. Moreover, the use of a γ-benzyloxyzinc derivative in a similar Pd-catalyzed reaction with a 1,1-dibromoalkene was recently reported [14]. Although not clear, inactivation of the alkenylzinc derivative *via* *E*-to-*Z* isomerization-chelation may be suspected. Fortunately, direct use of **3** was found to be highly satisfactory (>98% *trans*-selective) for the Pd-catalyzed cross coupling. The use of organozirconiums in the Pd-catalyzed *trans*-selective cross coupling of 1,1-dihaloalkenes appears to be unprecedented.

Treatment of **8** with 2 equiv of *t*-BuLi at -110 °C followed by quenching with CO$_2$ produced **2** in 78% yield. It is essential to maintain the reaction temperature at -110 °C. Our attempts to achieve Pd-catalyzed carboxylation of **8** with CO and H$_2$O, which, in principle, could be accompanied by Pd-catalyzed lactonization, have been unsuccessful. With **2** in hand, we had an opportunity to further compare the Pd-catalyzed and Ag-catalyzed lactonization procedures [1]. In the conversion of **2** to **9**, the maximum yield observed with the Pd-catalyzed lactonization was 35%, and the reaction was complicated by some side reactions which were not investigated. On the other hand, the Ag-catalyzed reaction at the concentration of 0.01 mol/L cleanly produced **9** in essentially quantitative yield. The crude product isolated by mere extractive workup and evaporation was ≥98% pure by ^{1}H and ^{13}C NMR spectroscopy, which showed no extraneous signals for byproducts.

The following two procedures describe the two critical steps of the synthesis. **Ag-Catalyzed Lactonization: Conversion of 2 to 9.** To a solution of **2** (109 mg, 0.25 mmol) in MeOH (25 mL)

was added $AgNO_3$ (2 mg, 0.012 mmol). After stirring the mixture at 23 °C for 1 h, analysis by TLC indicated completion of the reaction. After concentration at room temperature and reduced pressure, yellow crystals thus obtained were dissolved in $CDCl_3$, and filtered through a short-path silica gel column to remove $AgNO_3$. Analysis by ^1H NMR spectroscopy using methylene bromide as a standard indicated the formation of **9** in quantitative yield. Evaporation of the solvents provided **9** in 100% yield. **Pd-Catalyzed Cross Coupling of 3 with 5.** To Cp_2ZrCl_2 (2.32 g, 7.95 mmol) in 16 mL of benzene was added at 0 °C 2 M *t*-BuMgCl in Et_2O (4.0 mL, 8.0 mmol), and the reaction mixture was heated to 50 °C for 1 h. The formation of *i*-$BuZrCp_2Cl$ in 94% yield was observed by ^1H NMR spectroscopy. To the solution containing *i*-$BuZrCp_2Cl$ was added TBS-protected propargyl alcohol (1.35 g, 7.95 mmol), and the reaction mixture was stirred at 50 °C for 5 h. Analysis by ^1H NMR spectroscopy indicated the formation of **3** in 90% yield. After evaporation of the solvents under reduced pressure, THF (20 mL), **5** (1.21 g, 3.18 mol) dissolved in 5 mL of THF, $Cl_2Pd(PPh_3)_2$ (0.11 g, 0.16 mmol), and DIBAL-H (0.32 mL of 1 M solution in THF, 0.32 mmol) were sequentially added. The reaction mixture was heated to 50 °C for 5 h. After the usual extractive workup, concentration and chromatography using 3% Et_2O in hexane provided 1.36 g (91%) of **8**.

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References and Notes

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Note added in proof: After submission of this manuscript a paper reporting a different but related synthesis of lissoclinolide was brought to our attention [Rossi R, Bellina F, Biagetti M, Mannina L. Tetrahedron Lett. 1998; 39: 7799].