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Pd-Catalyzed Stereocontrolled Synthesis of γ-Alkylidenebutenolide, Freelingyne[1]

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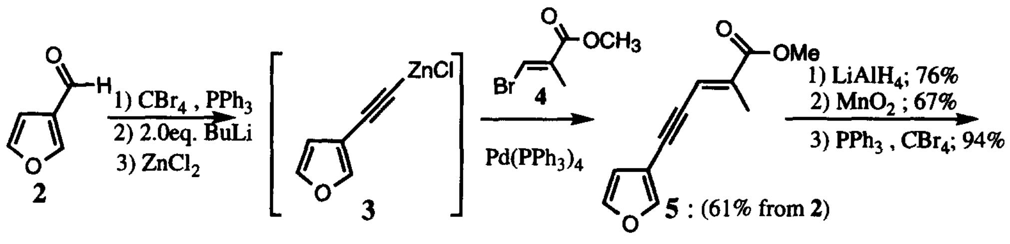
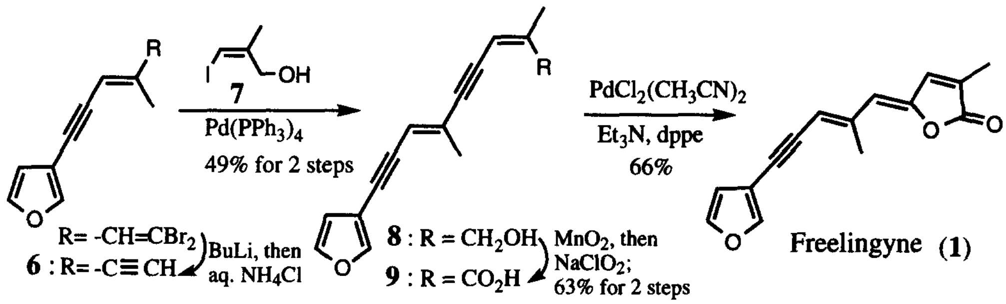
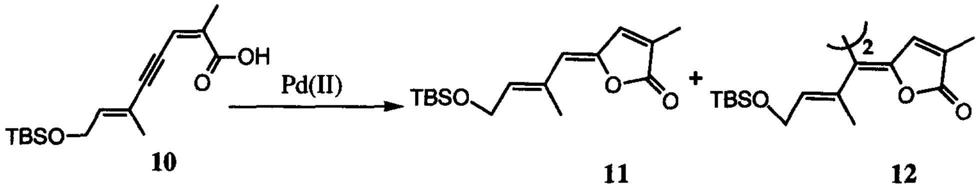
Abstract: A stereocontrolled synthesis of freelingyne was established by Pd (0)-catalyzed coupling of vinyl halides with acetylene derivatives, followed by Pd(II)-catalyzed intramolecular stereoselective γ-(Z)-alkylidenebutenolide formation. © 1997 Elsevier Science Ltd.

Freelingyne (**1**) is a furano-sesquiterpenoid which possesses a conjugated γ-(Z)-alkylidenebutenolide and an acetylene group conjugated with furan. This novel terpenoid was isolated from *Eremophila freelingii* as the first acetylenic terpenoid[2] and was synthesized by two groups.[3] Both syntheses, however, are non-stereoselective in the construction of the alkylidenbutenolide moiety, and include some unsatisfactory steps of poor yield. We now describe the stereocontrolled synthesis of freelingyne **1** by Pd(0)-catalyzed coupling of vinyl halides with acetylene derivatives, followed by Pd(II)-catalyzed intramolecular stereoselective formation of γ-(Z)-alkylidenebutenolide.

Our strategy for the synthesis of freelingyne includes a novel application of Pd(II)-catalyzed intramolecular lactonization to conjugated ene-yne carboxylic acid **9**,[4] which can be synthesized from 3-furaldehyde (**2**), (E)-vinyl bromide **4**, and (Z)-vinyl iodide **7** via Pd(0)-catalyzed coupling retaining their respective stereochemistry. Thus, reaction of **2** with carbon tetrabromide and triphenylphosphine gave a vinyl bromide[5] which was treated with butyl lithium and then zinc chloride to afford zinc acetylide **3** *in situ*. The compound **3** was successively reacted with (E)-vinyl bromide **4**[6] in the presence of palladium(0) to yield ene-yne ester **5** [$Pd(PPh_3)_4$; 3 mol%, THF, room temp., 24hr; 61% from **2**]. The ester **5** was transformed to an acetylene derivative **6** by reduction (LAH; 76%), oxidation (MnO_2; 67%), and then the acetylene formation (CBr_4/ PPh_3; 94%, 2eq.BuLi, then aq.NH_4Cl). Coupling of **6** with **7**[7] was successfully catalyzed again by the same palladium complex in piperidine[8] to afford allyl alcohol **8** (40 °C, 7hr; 49% yield for two steps) which was transformed to the acid **9** by oxidation (MnO_2, $NaClO_2$; 63% yield for 2 steps). Thus, fully-conjugated carboxylic acid was stereospecifically prepared. Prior to construction of the α-methyl-γ-alkylidenebutenolide moiety in **1**, the Pd (II)-catalyzed intramolecular lactonization was investigated by use of **10**. Treatment of **10** under the similar conditions reported by Lu [$PdCl_2(PPh_3)_2$, 1 eq. Et_3N, CH_3CN] gave dimer **12** as a major product,[9] and use of an acetonitrile complex of palladium chloride afforded the desired lactone **11** and the dimer **12** each in 28% yield. The successful intramolecular lactonization of **10** was realized by Pd(II)-catalyzed reaction in the presence of dppe in benzene (60% yield), and these reaction conditions were applied to **9**.[10] Thus, treatment of **9** with the palladium chloride acetonitrile complex (5mol%) in the presence of dppe (10 mol%) and triethylamine (0.1 equivalent) in benzene (40 °C, 2hr) afforded the desired lactone **1**, mp 159-161.5 °C[3a] in 66% yield without any stereoisomer at the alkylidenebutenolide double bond. The spectral data of the synthesized compound were in good agreement with those reported for natural freelingyne.







REFERENCES AND NOTES

1. This work was reported at the 72th Annual Meeting of Chemical Society of Japan, March 27, 1997(Tokyo).
2. Massey-Westropp, R. A.; Reynolds, G. D.; Spotswood, T. K. *Tetrahedron*, **1966**, *18*, 1939.
3. a) Pattenden, G. ; Knight, D. W. *J. Chem. Soc., Perkin Trans. I*, **1975**, 641. b) Ingram, C. F.; Massey-Westropp, R. A.; Reynolds, G. D. *Aust. J. Chem.*, **1974**, *27*, 1477.
4. Most recently, Negishi et al. reported the stereoselective construction of a non-conjugated and unsubstituted (Z)-alkylidenebutenolide by similar lactonization using $PdCl_2(PPh_3)_2$, PPh_3, CuI, and Et_3N in CH_3CN, which lactonization was originally reported by Lu et al.; a) Kotora, M.; Negishi. E. *Tetrahedron Lett.*,**1996**, *37*, 9041. b) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.*, **1993**, *34*, 5963.
5. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.*, **1972**, 3769.
6. Bieber, P. *Ann. Chem.*, **1954**, *9*, 674.
7. Duboudin, J. G.; Jousseaume, B. J. *Organomet. Chem.*, **1979**, *168*, 227.
8. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.*, **1993**, *34*, 6403.
9. Lu et al. originally reported the one-pot construction of γ-alkylidenbutenolide from 3-(Z)-halo-unsaturated carboxylic acids and terminal acetylene compounds. In our case, the preparation of the corresponding carboxylic acid of **7** was not easy and we did not try the one-pot procedure.
10. Quite recently, Negishi et al. have reported their further study of the intramolecular lactonization including the one-pot construction of β-phenyl-substituted γ-alkylidenebutenolides; Kotora, M.; Negishi. E. *Synthesis*, **1997**, 121.

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