Tetrahedron Letters, Vol. 34, No. 22, pp. 3547-3550, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

The Synthesis of Plicatin B via the Heck Reaction

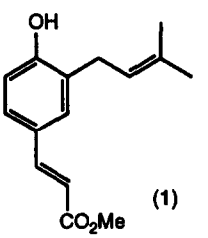
Roderick W Bates* and Christine J Gabel

Department of Chemistry, University of North Texas, PO Box 5068, Denton, TX 76203

Abstract: The anti-microbial natural product Plicatin B has been synthesized in 53% overall yield using a Heck reaction as the key step. The optimum conditions for this reaction have been determined. Halophenols proved much less reactive than their corresponding acetates.

Plants produce a variety of phenolic natural products which have unsaturated side-chains. We became interested in using palladium catalyzed reactions for their synthesis,[1] however the electron donating nature of the hydroxyl substituent makes this strategy difficult, presumably because alkene insertion is slowed by the electron rich ring. In addition a number of side reactions can occur.[2]

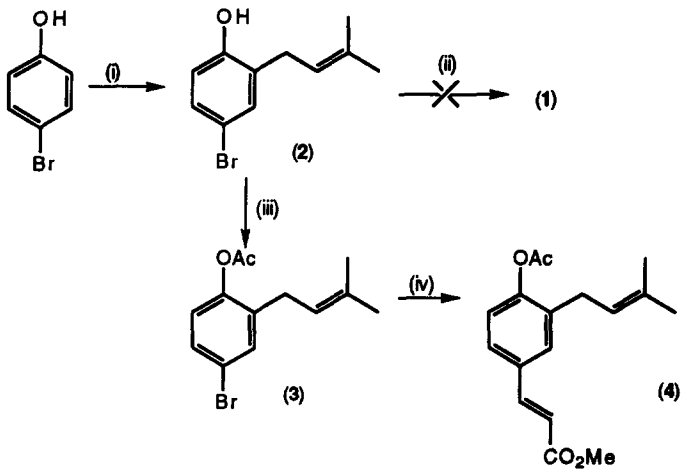
To study the optimum conditions for this strategy, we selected the natural product Plicatin B (**1**), the anti-microbial principle of *psoralea juncea* and other species.[3]



(1)

Accordingly, *para*-bromophenol was C-prenylated using the method of Fatope.[4,5] It was hoped that Heck reaction of the phenol (**2**) with methyl acrylate would give Plicatin B directly (scheme 1). Under a variety of normal Heck conditions (e.g. 5 mole% $(Ph_3P)_2PdCl_2$, 1.2eq Et_3N, toluene, 100°C) no reaction was observed.[6] Heck and Ziegler have showed that bromophenols are moderately reactive at best.[2] Surprisingly, the additional alkyl group of (**2**) seems to be sufficiently electron donating to block the arylation pathway totally.

We therefore converted the phenol (**2**) to its acetate (**3**) to reduce its electron rich nature. The reaction with methyl acrylate under Heck conditions now proceeded to give Plicatin B acetate (**4**) (scheme 1) in 60% yield under optimum conditions (5 mole% $Pd(OAc)_2$, 10 mole% tri-*o*-tolylphosphine, triethylamine, toluene, 100°C, 24 hours). The use of triphenylphosphine or a larger amount of tri-*o*-tolylphosphine led to reduced yields. In all cases, only the *E*-isomer of the product could be detected.

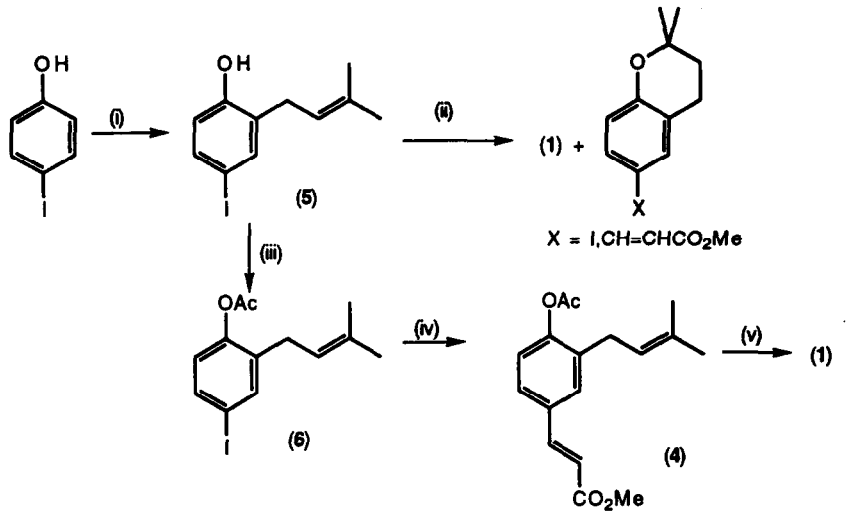


Scheme 1

(i) NaH, toluene, prenyl bromide, (57%); (ii) methyl acrylate, $(Ph_3P)_2PdCl_2$, Et_3N, CH_3CN or toluene, 100°C, 14 hrs; (iii) AcCl, Et_3N, DMAP, CH_2Cl_2, (78%); (iv) methyl acrylate,$Pd(OAc)_2$, $(o\text{-tol})_3P$, Et_3N.

As the reactivity of the bromoacetate remained borderline at best we turned to the more reactive iodo compounds (scheme 2). The prenylated iodophenol (**5**) was prepared as before.[4] Reaction with methyl acrylate in the presence of 5 mole% palladium and 10 mole% tri-*o*-tolylphosphine and an excess of triethylamine gave a low yield of Plicatin B (33%). In addition a mixture of starting material and other products was isolated. These appeared to be dimethylchromans, indicated by a downfield shift of the methyl groups from 1.7 to 1.3 ppm.[7]

The corresponding acetate (**6**) reacted with methyl acrylate more smoothly. Using palladium acetate (5 mole%) as the catalyst, but without added ligands, a 62% yield of (**4**) was obtained. Although it has been reported that addition of ligands inhibits the Heck reaction of iodides,[2] we were pleased to find that a 96% yield of Plicatin B acetate (**4**) was obtained in the presence of tri-*o*-tolylphosphine (10 mole%).[8,9] This yield enhancement appears to be due to the general low reactivity of the alkyl phenol derivatives. Experiments to clarify the role of additional aryl substituents are in progress.



Scheme 2

(i) NaH, toluene, prenyl bromide, (68%); (ii) methyl acrylate, $(Ph_3P)_2PdCl_2$, Et_3N, CH_3CN or toluene, 100°C,14 hrs; (iii) AcCl, Et_3N, DMAP, CH_2Cl_2, (91%); (iv) methyl acrylate, $Pd(OAc)_2$, $(o\text{-}tol)_3P$, Et_3N, toluene; (v) K_2CO_3, MeOH, (89%)

The synthesis was completed by methanolysis of the acetate (**4**) to give Plicatin B (**1**) in 53% overall yield. The ^1H and ^{13}C NMR spectra of the synthetic and natural compounds were in close agreement.[3] Various melting points are reported for Plicatin B[3]. We observed a melting point of 70-72°C, in close agreement with that reported by Rasool et al[3b].

Palladium mediated reactions are eminently suitable for the synthesis of this class of compounds provided the substituent pattern is carefully chosen and the reaction conditions are optimized. Further studies in this area are in progress.

Acknowledgment: We thank the Robert A Welch Foundation (Grant No. B-1216) and the University of North Texas (Faculty Research Grant) for support of this work

References and Notes

1. For an application to dihydrocoumarins, see Davies, S.G., Pyatt, D.,Thomson, C., *J.Organometallic Chem.*, **1990**, *387*, 381.

2. Ziegler, C.B., Heck, R.F.,*J.Org.Chem.*, **1978**, *43*, 2941.

3a. Schmitt, A., Telikepalli, H., Mitscher, L.A., *Phytochemistry*, **1991**, *30*, 3569; 3b. Rasool, N., Khan, A.Q., Malik, A., *Phytochemistry*, **1990**, *29*, 3979; 3c. Bohlmann, F., Knauf, W., King, R.M., Robinson, H.,*Phytochemistry*, **1979**, *18*, 1011.

4. Fatope, M.O., Okogun, J.I., *JCS Perkin Trans 1*, **1982**, 1601.
5. Attempts to prepare (**2**) by rearrangement of the O-prenyl isomer with Lewis acid catalysis were unsuccessful: Gerrard, W., Lappert, M.F., Silver, H.B., *Proc.Chem.Soc.*, **1957**, 19. Similarly, in our hands, the use of isoprene/ TMSCl/ NaI was ineffective: Sharma, D.N., Barush, P., Pandey, U.C., Sharma, R.P., *Tetrahedron Lett.*, **1984**, *25*, 5581.
6. Heck, R.F., Palladium Reagents in Organic Synthesis, Academic Press, New York, **1985**, 276.
7. *o*-Prenylphenols are readily cyclized: Molyneux, R.J., Jurd, L., *Tetrahedron*, **1970**, *26*, 4743.
8. Typical procedure: a solution of the iodide (**6**) (97 mg, 0.29 mmole), methyl acrylate (131 µl, 1.5 mmole), distilled triethylamine (81 µl, 0.59 mmole), tri-o-tolylphosphine (9 mg, 0.03 mmole), and palladium acetate (3.3 mg, 0.015 mmole) in dry toluene (2 ml) was heated for 20 hours under nitrogen in a sealed tube. At the end of this time, a precipitate of triethylammonium iodide and some palladium metal had formed. The mixture was allowed to cool to room temperature, diluted with ether and filtered through celite. The filtrate was washed with saturated aqueous NH_4Cl. The aqueous layer was re-extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (3 g), eluting with 5:95 ether/ hexane to give Plicatin B acetate (**4**) (76 mg, 96%) as a white solid, m.p.: 45-47°C, found: C,71.04; H 7.19, $C_{17}H_{20}O_4$ requires C, 70.81; H 6.99.
9. All new compounds were satisfactorily characterized.

(Received in USA 10 February 1993; accepted 29 March 1993)