Regioselective Synthesis of Prenylisoflavones. Syntheses of Lupiwighteone, Lupiwighteone Hydrate and Related Compounds

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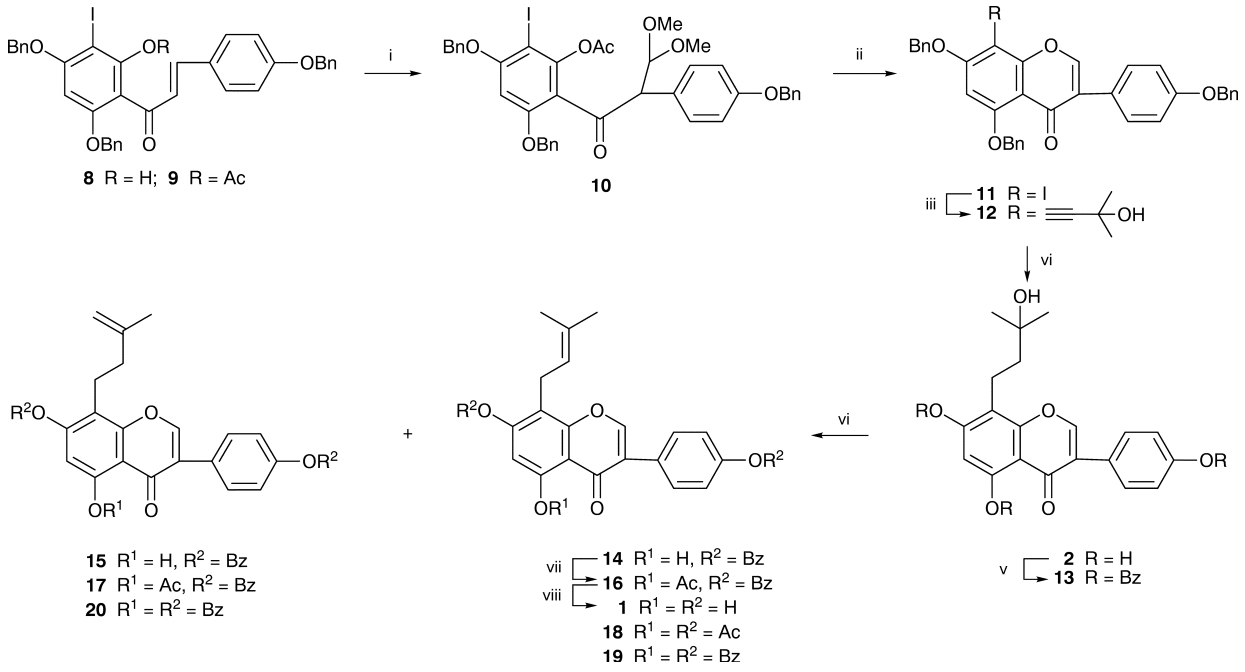
Catalytic hydrogenation and the subsequent dehydration of 8-(3-hydroxy-3-methylbutynyl)isoflavone **12**, which was synthesized by the palladium-catalyzed coupling reaction of 4′,5,7-tris(benzyloxy)-8-iodoisoflavone **11** with 2-methyl-3-butyn-2-ol, gave a mixture of 8-prenylisoflavone **16** and the isomer [5-acetoxy-8-(3-methyl-3-butenyl)isoflavone] **17**, and after the separation of **16** was accomplished by treatment of the mixture with $Hg(NO_3)_2$, hydrolysis of **16** afforded 4′,5,7-trihydroxy-8-prenylisoflavone (lupiwighteone) **1**.

Prenylisoflavones and (3-hydroxy-3-methylbutyl)isoflavones are widely distributed in nature and have strong antifungal activity.[1] Some of them are known as a phytoalexine such as luteone.[1] Prenylisoflavones are useful as precursors of pyranoisoflavones and furanoisoflavones.[2] Although tetraoxygenated prenylisoflavones have been synthesized from suitable isoflavones by acid- and base-catalyzed alkylation, such procedures have resulted in relatively low yields and are not useful for the syntheses of polyhydroxyisoflavones, because *O*- and di-alkylation, deprotection, and lack of regioselectivity are common problems.[3] The reaction of aryl halides with terminal alkynes in the presence of a palladium(0) catalyst is efficient for formation of C—C bonds and alkylation.[4] During the course of our synthetic studies of prenylphenol derivatives, we have recently found that these compounds have been regioselectively synthesized by the palladium-catalyzed method.[5] Therefore, this methodology seems to be easily applicable to the regioselective synthesis of polyoxygenated prenylisoflavones *via* the coupling reaction of the corresponding iodoisoflavones with propargyl alcohol.

The new isoflavones, lupiwighteone [4′,5,7-trihydroxy-8-(3-methyl-2-butenyl)isoflavone] **1** and lupiwighteone hydrate [4′,5,7-trihydroxy-8-(3-hydroxy-3-methylbutyl)isoflavone] **2**, were isolated from the roots of yellow lupin, *Lupinus luteus* L., cv. Barpine (Leguminosae).[6] We wish to report here on the first syntheses of **1**, **2** and angular 4′,5-dihydroxy-2″,2″-dimethylpyrano[6″,5″-*h*]isoflavone (derrone)[7] **5** by using the palladium-catalyzed coupling reaction, and extend the method to the syntheses of 2′-hydroxy-6-(3-methyl-2-butenyl)-7-methoxy-4′,5′-methylenedioxyisoflavone **3**, 2′-hydroxy-6-(3-hydroxy-3-methylbutyl)-7-methoxy-4′,5′-methylenedioxyisoflavone **4** and 2′-acetoxy-6-(3-methyl-2-butenyl)-7-methoxy-4′,5′-methylenedioxyisoflavanone **6**.

The reaction of 4′,6′-bis(benzyloxy)-2′-hydroxyacetophenone with iodine in the presence of silver trifluoroacetate[9] gave 4′,6′-bis(benzyloxy)-2′-hydroxy-3′-iodoacetophenone[5a] in good yield, which was converted into 4′,6′-bis-



Scheme 1 *Reagents and conditions*: i, TTN, MeOH, $CHCl_3$, 40 °C, 7 h, 10% HCl; ii, THF, EtOH, 10% NaOH, room temperature (79%); iii, $PdCl_2$ (3 mol%), PPh_3 (6 mol%), CuI (3 mol%), NEt_3, DMF, 80 °C, 2.5 h (82%); iv, Raney Ni, MeOH, THF, 18 °C (82%); v, PhCOCl, K_2CO_3, acetone, reflux (80%); vi, $BF_3 \cdot OEt_2$, CH_2Cl_2, room temperature, 4 h; vii, Ac_2O, pyridine, 105 °C (83%); viii, THF, MeOH, 10% NaOH, 50 °C, 50 min (93%)

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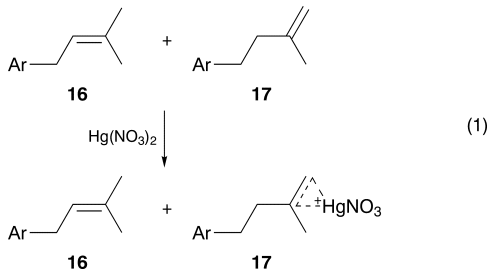
(benzyloxy)-3′-iodo-2′-methoxymethoxyacetophenone **7** with chloromethyl methyl ether in the presence of *N*,*N*-diisopropylethylamine. The condensation of **7** with 4-benzyloxybenzaldehyde gave the corresponding chalcone, and then the methoxymethyl group in the chalcone was cleaved by treatment with hydrochloric acid to afford the 2′-hydroxychalcone **8**. The oxidative rearrangement of the acetate **9**, derived from **8**, with thallium(III) nitrate trihydrate (TTN) gave the acetal derivative **10**, which was converted into the corresponding 8-iodoisoflavone **11**. The coupling reaction of **11** with 2-methyl-3-butyn-2-ol in the presence of Pd^0 gave the desired 8-(3-hydroxy-3-methylbutynyl)isoflavone **12**. Catalytic hydrogenation of **12** over Raney nickel gave 4′,5,7-trihydroxy-8-(3-hydroxy-3-methylbutyl)isoflavone **2**. The ^{1}H NMR and UV spectral data for **2** were identical with those of natural lupiwighteone hydrate. On the basis of these results, the structure of natural lupiwighteone hydrate was unequivocally established to be 4′,5,7-trihydroxy-8-(3-hydroxy-3-methylbutyl)isoflavone **2**.

The 8-alkyltrihydroxyisoflavone **2** was converted into the tribenzoate derivative **13**. The tribenzoate derivate **13** was dehydrated to give a mixture of the 5-hydroxy-8-(3-methyl-2-butenyl)isoflavone **14** and the isomer 5-hydroxy-8-(3-methyl-3-butenyl)isoflavone **15**, which was converted into a mixture of 5-acetoxy-8-prenylisoflavone **16** and the isomer 5-acetoxy-8-(3-methyl-3-butenyl)isoflavone **17**. The ^{1}H NMR spectrum of the mixture of the 5-acetate derivatives (**16** and **17**) showed the ratio of **16** to **17** to be 88:12 [peaks due to $CH_2CH{=}C(CH_3)_2$ at δ 3.55 (2 H, d) and $CH_2CH_2C(CH_3){=}CH_2$ at δ 4.72 and 4.77 (each 1 H, s)]. The complete separation of **16** from the mixture (**16** and **17**) was significantly difficult either by chromatography or recrystallization. A solution to the problem was provided by treatment of the mixture with aqueous mercury(II) nitrate (1.5 equiv. to the isomer **17**) in tetrahydrofuran at room temperature to give the terminal alkylmercurinium ion **17′** as shown by eqn. (1),[5,10] and then the unchanged acetate **16** was quantitatively separated from the mixture by silica gel column chromatography. Hydrolysis of **16** was effected to give the desired 4′,5,7-trihydroxy-8-(3-methyl-2-butenyl)-isoflavone **1**, which was converted into 4′,5,7-triacetoxy-8-prenylisoflavone **18** and the angular 4′,5-dihydroxypyrano-isoflavone **5**.



(1)

The ^{1}H NMR spectra of **1** and the triacetate **18** were identical with those of natural 8-prenylisoflavone (lupiwighteone) and the triacetate. On the basis of these results, the structure of natural lupiwighteone was unequivocally established to be 4′,5,7-trihydroxy-8-(3-methyl-2-butenyl)isoflavone **1**.

In a similar manner, the 6-prenylisoflavone **3**, the 6-(3-hydroxy-3-methylbutyl)isoflavone **4** and the 6-prenylisoflavanone **6** were prepared from the corresponding 6-iodoisoflavone **23**.

The present palladium-catalyzed coupling reactions of iodoisoflavones with 2-methyl-3-butyn-2-ol have been shown to be an efficient and useful procedure for regioselective syntheses of polyhydroxyprenylisoflavones. The excellent chemoselectivity of mercury(II) nitrate or benzonitrile oxide to internal and terminal alkenes have been shown to be remarkably useful for the recognition and separation of terminal alkenes.

Techniques used: ^{1}H NMR, UV spectroscopy, elemental analysis, chromatography

Table 1: ^{1}H NMR data for **1**, **18** and **2**

Schemes: 2

References: 13

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