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Regioselective Synthesis of Prenylisoflavones. Syntheses of 2,3-Dehydrokievitone and Related Compounds

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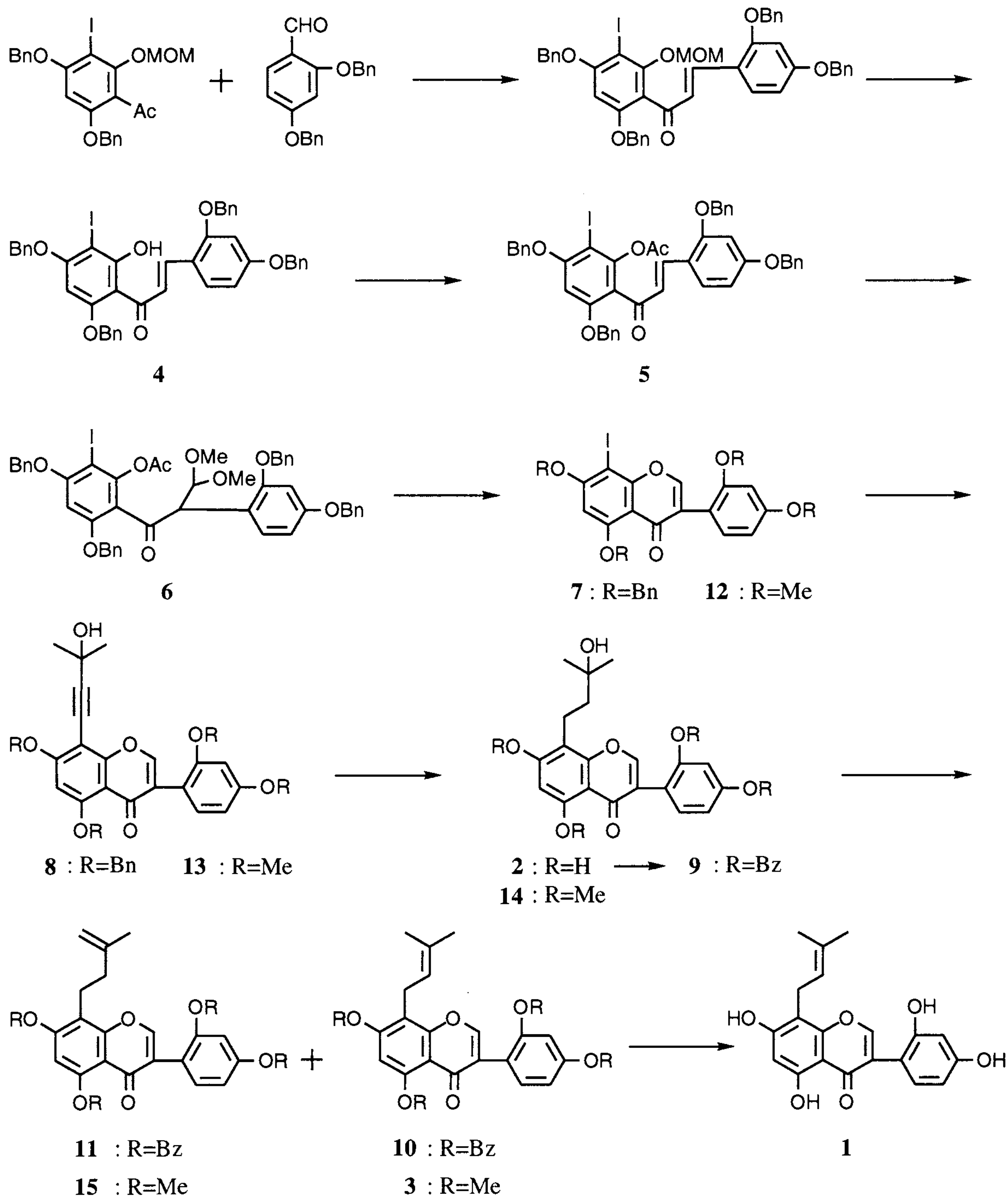
The palladium-catalyzed coupling reaction of 2',4',5,7-tetrakis(benzyloxy)-8-iodoisoflavone with 2-methyl-3-butyn-2-ol gave the corresponding 8-(3-hydroxy-3-methylbutynyl)isoflavone **8**. Dehydration of the benzoate obtained from **8** in two steps gave a mixture of 8-prenylisoflavone **10** and its regioisomer [8-(3-methyl-3-butenyl)isoflavone]. Treatment of the mixture with aq. $Hg(NO_3)_2$ allowed the isolation of **10**, which was hydrolyzed to give 2,3-dehydrokievitone. Similarly, 2,3-dehydrokievitone tetramethyl ether was also synthesized from 8-iodo-2',4',5,7-tetramethoxyisoflavone.

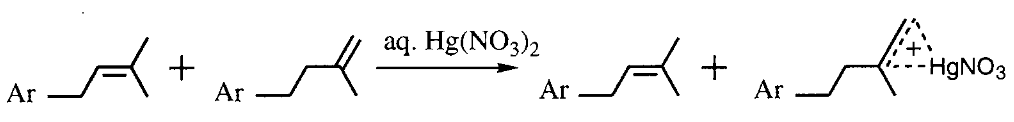
Among prenylisoflavones, widely distributed in nature, 2',4',5,7-tetraoxygenated prenylisoflavones have strong antifungal activity.[1] Prenylisoflavones are useful as precursors of pyranoisoflavones and furanoisoflavones.[2] Although tetraoxygenated prenylisoflavones have been synthesized from the suitable isoflavones by acid- and base-catalyzed alkylation, such protocols are not useful for the synthesis of tetrahydroxyprenylisoflavones, since *O*- and di-alkylation, deprotection, and lack of the regioselectivity are common problems.[3] The reaction of aryl halides with terminal alkynes in the presence of a Pd catalyst is very useful for alkylation,[4] and seems to be applicable to synthesis of tetraoxygenated prenylisoflavones *via* the coupling reaction of the corresponding 8-iodoisoflavones with propargyl alcohol.

The new isoflavones, 2,3-dehydrokievitone and 2,3-dehydrokievitone hydrate, were isolated from the roots of yellow lupin, *L. luteus* L., cv. Barpine, and the former was assigned as 2',4',5,7-tetrahydroxy-8-(3-methyl-3-butenyl)isoflavone (**1**), and the latter was identified as 2',4',5,7-tetrahydroxy-8-(3-methyl-3-hydroxybutyl)isoflavone (**2**) by spectroscopic and chemical studies.[5] We wish to report here on the first syntheses of **1**, **2**, and 2',4',5,7-tetramethoxy-8-(3-methyl-3-butenyl)isoflavone (**3**) by the Pd-catalyzed approach.

The condensation of 4',6'-bis(benzyloxy)-3'-iodo-2'-methoxymethoxyacetophenone, synthesized from 4',6'-bis(benzyloxy)-2'-hydroxy-3'-iodoacetophenone,[6] with 2,4-bis(benzyloxy)benzaldehyde in the presence of KOH in ethanol under reflux for 4 h gave the corresponding chalcone, and then the methoxymethyl group in the chalcone was cleaved by treatment with HCl in a mixture of MeOH and $CHCl_3$ at room temperature for 3.5 h to give 2'-hydroxychalcone **4** (78% yield). The oxidative rearrangement of acetate **5**, derived from **4**, with thallium(III) nitrate (TTN) in a mixture of MeOH and $CHCl_3$ at 40 °C for 2 h gave acetal **6** (80% yield), which was converted into the 8-iodoisoflavone **7**[7] (80% yield) by treatment with 10% sodium hydroxide in a mixture of 1,4-dioxane and MeOH at 50 °C for 50 min. The coupling reaction of **7** (1 mmol) with 2-methyl-3-butyn-2-ol (3 mmol) in the presence of $PdCl_2$ (0.03 mmol), CuI (0.03 mmol), PPh_3 (0.06 mmol) in



Scheme 1.



(Eq. 1)

10 11 10 11'

Et_3N-DMF under N_2 at 80-85 °C for 6 h afforded the desired 8-(3-hydroxy-3-methylbutynyl)isoflavone **8**[8] in 83% yield. Catalytic hydrogenation of **8** in the presence of Pd/C in MeOH at 20 °C gave 2',4',5,7-tetrahydroxy-8-(3-hydroxy-3-methylbutyl)isoflavone (**2**),[9] which was identical with a natural sample of 2,3-dehydrokievitone hydrate.[5] Compound **2** was converted into tetrabenzoate **9**, which was dehydrated by treatment with $TsOH \cdot H_2O$ in toluene at 110 °C for 1.5 h to give a mixture of the desired prenylisoflavone **10** and the regioisomer **11** in 85% yield. ^1H NMR showed the ratio of **10** and **11** to be 85:15 [peaks due to $C\underline{H}_2CH=C(CH_3)_2$ at δ 3.31 (2H, d) and $CH_2CH_2C(CH_3)=C\underline{H}_2$ at δ 4.75 (2H, s)]. Separation of **10** from the mixture was difficult either by chromatography or recrystallization. A solution to the problem was provided by treatment of the mixture with aq. $Hg(NO_3)_2$ (1.5 equiv. to **11**) in THF at room temperature for 40 min to give the terminal alkylmercurinium ion **11'** by Eq. 1,[10] and then unchanged **10**[11] was separated in 78% yield based on **9** by silica-gel column chromatography [$CHCl_3$:$(CH_3)_2CO$=50:1 as the solvent]. This is the first successful attempt to separate a desired prenylisoflavone from a mixture of internal and terminal alkenes. Hydrolysis of **10** was effected by treatment with dil. aqueous sodium hydroxide in a mixture of 1,4-dioxane and MeOH under N_2 at 50 °C to give the desired tetrahydroxy-8-prenylisoflavone **1**.[12] The ^1H NMR spectral data of the synthetic 8-prenylisoflavone **1** and the corresponding natural 2,3-dehydrokievitone are given in Table 1.

Table 1. ^1H NMR (400 MHz, CD_3COCD_3) data for the prenylisoflavones **1** and **3**[a]

Compd	2-H	6-H	3'-H	5'-H	6'-H	Me x 2	CH_2	CH=C	OH or OMe
1	8.27s	6.40s	6.49d (J=2.4)	6.45dd (J=8.3, 2.4)	7.15d (J=8.3)	1.66s 1.81s	3.46d (J=7.3)	5.25t (J=7.3)	8.39s, 8.52s 9.80b 12.72s
Natural[5] product (**1**)	8.26s	6.39s	6.49d	6.44dd (J=8.6, 1.7)	7.18d (J=8.6)	1.66s 1.81s	3.46d (J=7.1)	5.26t (J=7.1)	12.70s
3	7.90s	6.68s	6.60d (J=2.4)	6.54dd (J=8.3, 2.4)	7.16d (J=8.3)	1.65s 1.80s	3.45d (J=7.3)	5.20t (J=7.3)	3.75s, 3.83s 3.89s, 4.01s

a) s: singlet; d: doublet; dd: double doublet; t: triplet; b: broad. J = Hz.

The ^1H NMR spectrum of **1** was identical with that of natural prenylisoflavone. The melting point of synthetic **1** did not depress by admixture with a natural sample. On the basis of these results, the structure of natural 2,3-dehydrokievitone was unequivocally established to be 2',4',5,7-tetrahydroxy-8-(3-methyl-3-butenyl)isoflavone (**1**).

In a similar manner, 8-iodotetramethoxyisoflavone **12** was synthesized by the oxidative rearrangement of the corresponding chalcone with TTN in MeOH. The coupling reaction of **12** with 2-methyl-3-butyn-2-ol in the presence of Pd for 3 h gave 8-(3-hydroxy-3-methylbutynyl)isoflavone **13** in 80% yield. Catalytic hydrogenation of **13** in the presence of Pd/C gave 8-(3-hydroxy-3-methylbutyl)isoflavone **14**, which was dehydrated with $TsOH \cdot H_2O$ to give a mixture of prenylisoflavone **3** and its isomer **15** in 84% total yield. The mixture was similarly treated with aq. $Hg(NO_3)_2$ to give 2',4',5,7-tetramethoxy-8-(3-methyl-3-butenyl)isoflavone (**3**)[13]

(65% yield based on **14**), which was identical with 2,3-dehydrokievitone tetramethyl ether[5] derived from natural 2,3-dehydrokievitone.

The approach described above is a useful method for the synthesis of polyhydroxyprenylisoflavones.

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5) Y. Hashidoko, S. Tahara, and J. Mizutani, *Agric. Biol. Chem.*, **50**, 1797 (1986). Natural 2,3-dehydrokievitone: mp 145-146 °C; UV λ_{max} nm (MeOH) 265; (+$AlCl_3$) 275, 316, 376; (+NaOAc) 279. Natural 2,3-dehydrokievitone hydrate: mp 134-136 °C; ^{1}H NMR (CD_3COCD_3) δ=1.25 (6H, s, CH_3 x 2), 1.73 and 2.87 (each 2H, m, CH_2), 6.37 (1H, s, 6-H), 6.44 (1H, dd, *J*=8.5 and 2.2 Hz, 5'-H), 6.49 (1H, incomplete, 3'-H), 7.15 (1H, d, *J*=8.5 Hz, 6'-H), 8.26 (1H, s, 2-H), 12.68 (1H, s, 5-OH). 2,3-Dehydrokievitone tetramethyl ether: ^{1}H NMR (CD_3COCD_3) δ=1.68 and 1.81 (each 3H, br. s, CH_3), 3.45 (2H, br.s, *J*=7.3 Hz, CH=), 3.57, 3.83, 3.89 and 4.01 (each 3H, s, OCH_3), 5.20 (1H, br.t, *J*=7.1 Hz, CH_2), 6.53 (3H, dd, *J*=8.0 and 2.4 Hz, 5'-H), 6.60 (1H, s, *J*=2.4 Hz, 3'-H), 6.68 (1H, s, 6-H), 7.16 (1H, br.s, *J*=8.0 Hz, 6'-H), 7.89 (1H, s, 2-H). M. D. Woodward, *Phytochemistry*, **18**, 2007 (1979).
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7) Compound **7**: mp 161-163 °C; ^{1}H NMR ($CDCl_3$) δ=5.03 and 5.17 (each 4H, s, PhC$\underline{H}_2$ x 2), 6.46-6.67 3H, m, 3'-H, 4'-H, 6-H), 7.15-7.6 (21H, m, Ar-H x 21), 7.80 (1H, s, 2-H). Found: C, 66.65; H, 4.45%. Calcd for $C_{43}H_{33}O_6I$: C, 66.84; H, 4.30%.
8) Compound **8**: mp 223-224 °C; ^{1}H NMR ($CDCl_3$) δ=1.60 (6H, s, CH_3 x 2), 2.20 (1H, s, OH), 4.82-5.3 (8H, m, PhC$\underline{H}_2$ x 4), 7.2-7.7 (21H, m, Ar-H x 21), 7.78 (1H, s, 2-H). Found: C, 78.81; H, 5.55%. Calcd for $C_{48}H_{40}O_7$: C, 79.10; H, 5.53%.
9) Compound **2**: mp 211-213 °C; ^{1}H NMR (400 MHz, CD_3OD) δ=1.28 (6H, s, CH_3 x 2), 1.67 and 2.81 (each 2H, m, CH_2), 6.29 (1H, s, 6-H), 6.36 (1H, d, *J*=2.5 Hz, 3'-H), 6.39 (1H, dd, *J*=2.51 and 7.8 Hz, 5'-H), 7.05 (1H, d, *J*=7.8 Hz, 6'-H), 8.10 (1H, s, 2-H), OH was not observed. Found: C, 64.40; H, 5.57%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.
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11) Compound **10**: mp 158-160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=1.55 and 1.60 (each 3H, s, CH_3), 3.52 (2H, d, *J*=6.84 Hz, CH_2=), 5.14 (1H, t, *J*=6.84 Hz, CH=), 7.06 (1H, s, 6-H), 7.20-8.20 (23H, m, Ar-H x 23), 7.97 (1H, s, 2-H). Found: C, 74.60; H, 4.49%. Calcd for $C_{48}H_{34}O_{10}$: C, 74.79; H, 4.45%.
12) Compound **1**: mp 141-143 °C; UV λ_{max} nm (MeOH) 266, 335; (+$AlCl_3$) 272, 316 376; (+NaOAc) 268, 282, 335. Found: C, 67.55; H, 5.40%. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.
13) Compound **3**: mp 85-87 °C; Found: C, 70.00; H, 6.10%. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38%.

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