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Rapid syntheses of (±)-pterocarpans and isoflavones via the gold-catalyzed annulation of aldehydes and alkynes

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Abstract—(±)-Pterocarpan and analogues (**4a–c**) have been synthesized efficiently via the annulation of salicylaldehydes (**1a**, **1b** and **1c**) and *o*-methoxymethoxylphenylacetylene (**2a**), followed by a one-pot reduction and acidic cyclization of the ketones (**3a–c**). In addition, isoflavone derivatives (**5a–c**) have been synthesized rapidly, in two steps, via the annulation of salicylaldehyde (**1a**) and arylacetylenes (**2b**, **2c** and **2d**), followed by IBX/DMSO oxidation of the isoflavanones (**3d**, **3e** and **3f**).

Pterocarpans are the second largest group of natural isoflavanoids[1] (Fig. 1). They are potent phytoalexins[2] which are used for their antitoxin,[3] antifungal,[4] antiviral[3] and antibacterial[5] properties. The classical methods for synthesizing (±)-pterocarpans are (i) the reduction and cyclization of the corresponding 2′-hydroxyisoflavanones;[6] (ii) 1,3-Michael–Claisen annulation;[7a,b] (iii) cycloaddition reaction of 2H-chromenes with 2-alkoxy-1,4-benzo-quinones;[8a,b] and (iv) Heck arylation of 2H-chromenes with *o*-chloromercuriphenol using lithium chloropalladite as a catalyst.[9a–c]

Isoflavones such as daidzein[10a] (Fig. 1) are phytoestrogens with weak oestrogenic activity.[10b,c] They are present in the human diet in soy beans and soy derived products.[10d] The major synthetic methods of isoflavones are as follows: (i) cyclization of deoxybenzoin with a free 2′-hydroxy group;[11] (ii) oxidative rearrangement of chalcone by thallium(III) reagent;[12] (iii) rearrangement via an epoxyketone produced by the action of hydrogen peroxide;[13] (iv) the Suzuki coupling reaction of 3-bromochromone with an aryl boronic acid using palladium(0);[14] and (v) the treatment of 2′-benzoyloxychalcones with hypervalent iodine(III) reagent.[15]

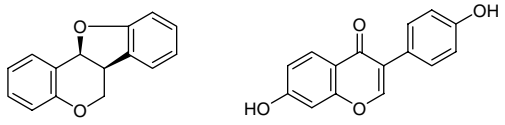

Figure 1. Natural products containing (±)-pterocarpan[1b] and isoflavone (daidzein).[10b]

It is noteworthy that the previous methods for synthesizing the natural products, (±)-pterocarpans and isoflavones, required several steps and some needed the use of expensive starting materials and toxic reagents. Recently, we reported a novel and highly atom economical[16] direct annulation of simple salicylaldehyde with phenylacetylene or 2-tosylaminobenzenaldehyde catalyzed by gold(I) to give isoflavanone[17a] and aza-isoflavanone[17b]-type structures efficiently. Herein, we wish to report the application of this annulation in rapid syntheses of the two classes of natural products: (±)-pterocarpans and isoflavones.

Our approach towards (±)-pterocarpans and isoflavones as well as their derivatives based on the annulation is described in Scheme 1. Both types of natural products can be formed from the common isoflavanone intermediates. Thus, to synthesize (±)-pterocarpan **4a**, salicylaldehyde **1a** and 2-(methoxymethoxy)-alkynebenzene **2a**, which can be obtained readily by the Sonogashira coupling[18] from 2-iodophenol, catalyzed by gold(I) provided the desired isoflavanone **3a**[19] in 73% isolated yield. The treatment of isoflavanone **3a** with $NaBH_4$ in a mixture of THF/MeOH at room temperature for 2 h followed by the addition of an excess amount of

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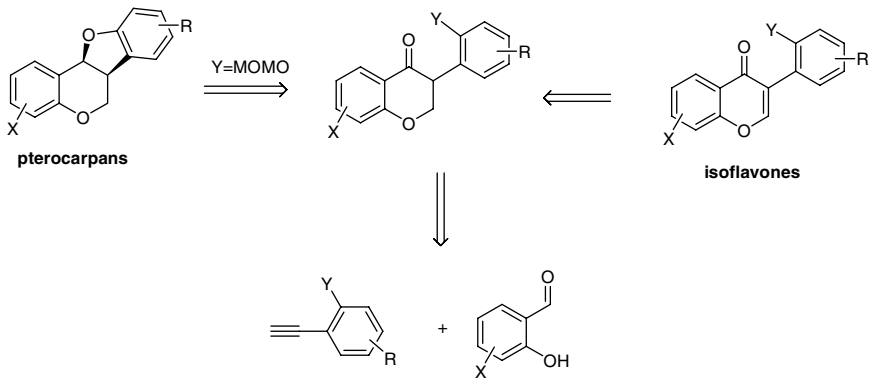
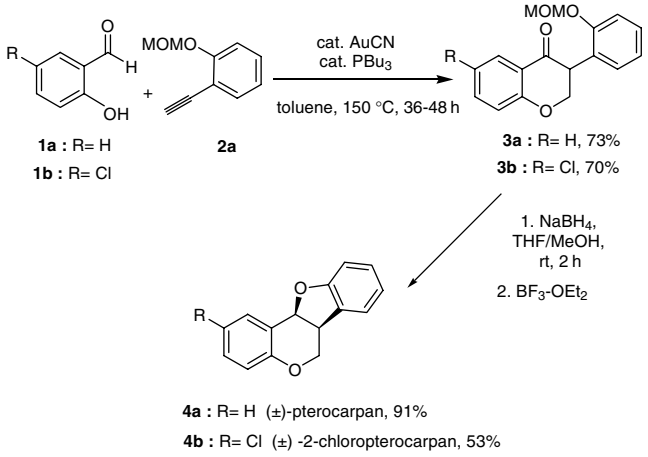


Scheme 1. Retro-synthetic analysis for the synthesis of (±) pterocarpans and isoflavones.

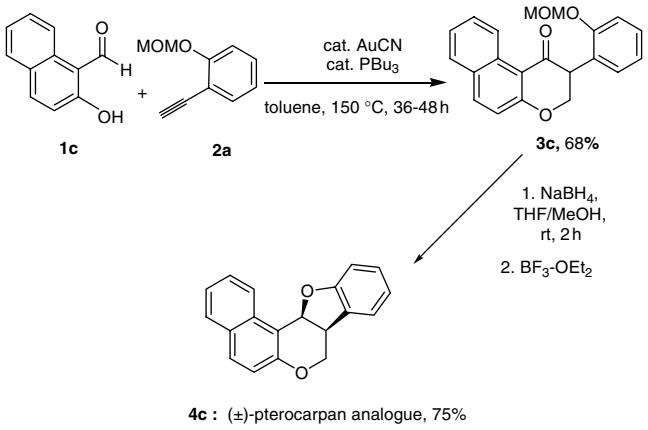


Scheme 2. Synthesis of (±)-pterocarpan **4a** and analogue **4b**.

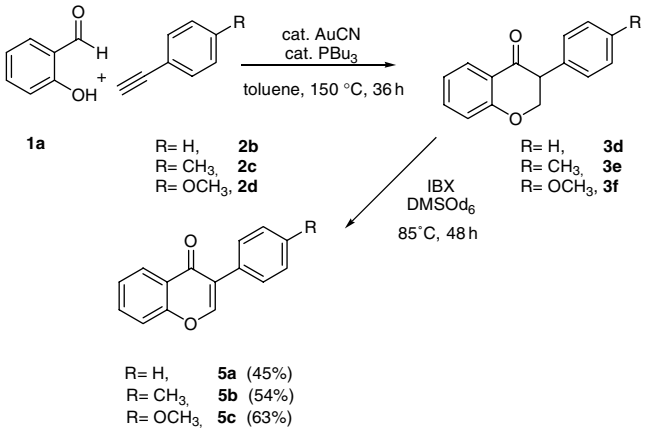
BF_3–OEt_2 afforded (±)-pterocarpan **4a**[19] in 91% (Scheme 2).

Similarly, the reaction of 5-chloro salicylaldehyde **1b** with acetylene **2a** under the same reaction conditions for 48 h afforded isoflavanone **3b**[19] in 70% yield. Further treatment of **3b** with $NaBH_4$ and BF_3–OEt_2 gave (±)-pterocarpan **4b**[19] in 53% yield (Scheme 2). By a similar procedure, 2-hydroxy-1-naphthaldehyde **1c** was reacted with acetylene **2a** under the gold(I)-catalyzed annulation conditions to isoflavanone **3c**[19] in 68% yield. Subsequent reduction by $NaBH_4$ followed by the BF_3-catalyzed cyclization in situ afforded (±)-pterocarpan analogue **4c**[19] in 75% yield (Scheme 3).

In order to obtain the isoflavone derivatives **5a**–**c** (Scheme 4), we need to find a dehydrogenation method of the isoflavanone derivatives **3d**, **3e** and **3f** which were obtained via the annulation between salicylaldehyde (**1a**) and phenylacetylenes (**2b**, **2c** and **2d**).[17a] It was found that common dehydrogenation reagents such as DDQ and Dess–Martin were less effective as oxidant reagents for the desired transformation. Only trace amounts of the isoflavone products were observed and most isoflavanones were recovered under these conditions. On the other hand, Nicolaou et al. reported that *o*-iodoxybenzoic acid (IBX) is a highly effective dehydrogenation reagent for the synthesis of α,β-unsaturated carbonyl compounds.[20] Following this procedure, isoflavanones **3d**, **3e** and **3f** were mixed with IBX and heated at 85 °C in DMSO-d_6. The reactions were followed by ^{1}H NMR until the starting materials were consumed completely. The desired isoflavone products **5a**–**c** were obtained successfully in modest to good yields. A slight increase in the yield of the isoflavones **5a**–**c**[21] was observed when an electro-donating group was attached on the isoflavanones **3d**, **3e** and **3f** (Scheme 4).



Scheme 3. Synthesis of (±)-pterocarpan analogue **4c**.



Scheme 4. Synthesis of isoflavone derivatives **5a**–**c**.

In conclusion, the rapid syntheses of (±)-pterocarpan, isoflavone and their analogues were succeeded by applying the gold-catalyzed annulation of hydroxyarylaldehydes and alkynes. The method provides both natural and unnatural (±)-pterocarpan and isoflavone derivatives readily. Further studies regarding the biological activities of such derivatives are in progress.

Acknowledgements

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19. *Experimental and characterizations of new compounds*: *6-Chloro-2,3-dihydro-3-(2-(methoxymethoxy)phenyl)chromen-4-one* (**3b**). Following the reported procedure, the product was isolated by flash-column chromatography on silica gel (hexane/ethyl acetate = 15:1; $R_f = 0.32$). IR (neat, NaCl): ν_{max} 1698, 1603, 1493, 1477, 1457, 1419, 1277, 1236, 1202, 1186, 1154, 1116, 1080, 999, 923, 825, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.94 (d, $J = 2.8$ Hz, 1H), 7.44 (dd, $J = 8.8$, 2.8 Hz, 1H), 7.28 (dt, $J = 8.4$, 1.6 Hz, 1H), 7.17–7.11 (m, 2H), 7.02–6.97 (m, 2H), 5.14 (s, 2H), 4.68 (dd, $J_{3ax.2ax} = 12.4$ Hz, $J_{3ax.2eq} = 10.8$ Hz, 1H, H-3ax), 4.55 (dd, $J_{2eq.3ax} = 10.8$ Hz, $J_{2eq.2ax} = 5.2$ Hz, 1H, H-2eq), 4.33 (dd, $J_{2ax.3ax} = 12.4$ Hz, $J_{2ax.2eq} = 5.2$ Hz, 1H, H-2ax), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 191.1, 160.3, 155.1, 135.5, 130.5, 129.4, 127.0, 126.9, 123.5, 122.3, 122.1, 119.6, 114.5, 94.5, 70.8, 56.2, 48.8; MS (GC/MS) *m*/*z* (%) 318 (M^+), 287, 273 (100), 256, 199, 164, 155, 132, 119, 103, 91, 77, 63, 51; HRMS calcd for $C_{17}H_{15}ClO_4$: 318.06589; found, 318.06524.
2,3-Dihydro-2-(2-(methoxymethoxy)phenyl)benzo[f]chromen-1-one (**3c**). Following the reported procedure, the product was isolated by flash-column chromatography on silica gel (hexane/ethyl acetate = 15:1; $R_f = 0.13$). IR (neat, NaCl): ν_{max} 1674, 1617, 1597, 1568, 1512, 1493, 1435, 1375, 1344, 1279, 1233, 1207, 1154, 1113, 1079, 992, 921, 825, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 9.48 (d, $J = 8.8$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.62 (dt, $J = 7.2$, 1.6 Hz, 1H), 7.44 (dt, $J = 6.8$, 0.8 Hz, 1H), 7.29 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.19–7.13 (m, 3H), 7.01 (dt, $J = 7.6$, 1.2 Hz, 1H), 5.16 (s, 2H), 4.81 (dd, $J_{3ax.2ax} = 11.6$ Hz, $J_{3ax.2eq} = 10.8$ Hz, 1H, H-3ax), 4.66 (dd, $J_{2eq.3ax} = 10.8$ Hz, $J_{2eq.2ax} = 5.6$ Hz, 1H, H-2eq), 4.47 (dd, $J_{2ax.3ax} = 11.6$ Hz, $J_{2ax.2eq} = 5.6$ Hz, 1H, H-2ax), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 193.4, 163.8, 155.2, 137.3, 131.9, 130.4, 129.6, 129.4, 129.1, 128.4, 126.1, 124.8, 124.7, 122.1, 118.8, 114.5, 113.3, 94.6, 70.6, 56.2,49.5; MS (EI) *m*/*z* (%) 334 (M^+), 302, 289, 271, 215 (100), 185, 164, 132, 91, 69, 45, 51; HRMS calcd for $C_{21}H_{18}O_4$: 334.12051; found, 334.12007.
General procedure for the synthesis of (±)-*pterocarpans* **4a**–**c**. To a stirred solution of **3a**–**c** in a 1:1 mixture of dry THF and methanol, sodium borohydride was added at room temperature. The reaction was monitored by TLC. After 2 h the reaction mixture was treated with boron trifluoride diethyl etherate. After 2 h the residue was washed with 10% aqueous sodium carbonate, then with water until neutral and dried. The solvent was evaporated in vacuo. The residue was purified by flash-column chromatography on silica gel with the appropriate mixture of hexane and EtOAc to give (±)-pterocarpans **4a**–**c**.
(±)-*Pterocarpan* (**4b**). Following the above general procedure with **3b** (48 mg, 0.15 mmol) and sodium borohydride (11.4 mg, 0.30 mmol), the residue was neutralized with dilute aqueous hydrochloric acid, extracted with dichloromethane, passed through a small silica gel column with hexane/ethyl acetate = 5:1 and then it was treated with boron trifluoride diethyl etherate (0.1 ml). The residue was purified by flash-column chromatography on silica gel (hexane/ethyl acetate = 5:1, $R_f = 0.55$). IR (neat, NaCl): ν_{max} 1610, 1598, 1484, 1463, 1424, 1316, 1254, 1231, 1183, 1126, 1083, 1023, 938, 883, 855, 825, 751 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz, ppm) δ 7.43 (d, $J = 2.8$ Hz, 1H), 6.91 (t, $J = 7.6$ Hz, 1H), 6.86 (dd, $J = 8.8$, 2.8 Hz, 1H), 6.75–6.72 (m, 2H), 6.67 (t, $J = 7.6$ Hz, 1H), 6.58 (d, $J = 8.8$ Hz, 1H),

4.83 (d, $J_{13a.8a} = 7.2$ Hz, 1H, H-13a), 3.71 (dd, $J_{8eq.8ax} = 11.2$ Hz, $J_{8eq.8a} = 5.2$ Hz, 1H, H-8eq), 3.22 (t, $J_{8ax.8eq} = J_{8ax.8a} = 11.2$, 1H, H-8ax), 2.89–2.83 (m, 1H, H-8a); ^{13}C NMR (C_6D_6, 75 MHz, ppm) δ 159.6, 154.4, 131.0, 130.0, 129.4, 126.8, 126.5, 124.7, 122.2, 120.9, 119.0, 110.3, 76.8, 66.2, 40.2; MS (GC/MS) *m*/*z* (%) 258 (M^+) (100), 241, 223, 205, 194, 176, 165, 152, 131, 118, 102, 89, 77, 63, 51; HRMS calcd for $C_{15}H_{11}ClO_2$: 258.04476; found, 258.04406.

(±)-*Pterocarpan* (**4c**). Following the above general procedure with **3c** (43 mg, 0.129 mmol), sodium borohydride (10 mg, 0.258 mmol) and boron trifluoride diethyl etherate (1.5 ml), the residue was purified by flash-column chromatography on silica gel (hexane/ethyl acetate = 15:1, $R_f = 0.33$). IR (neat, NaCl): ν_{max} 1625, 1600, 1514, 1476, 1438, 1248, 1232, 1090, 1025, 966, 909, 880, 845, 827,749 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz, ppm) δ 8.33 (d, $J = 8.8$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.39 (dt, $J = 8.8$, 0.8 Hz, 2H), 7.18 (t, $J = 7.2$, 1H), 7.07 (d, $J = 8.8$ Hz, 1H), 6.94 (t, $J = 7.6$ Hz, 1H), 6.82 (dd, $J = 7.6$, 1.0 MHz, 2H), 6.70 (t, $J = 7.6$, 1H), 5.50 (d, $J_{13a.8a} = 6.4$ Hz, 1H, H-13a), 3.91 (dd, $J_{8eq.8ax} = 10.8$ Hz, $J_{8eq.8a} = 5.6$ Hz, 1H, H-8eq), 3.45 (t, $J_{8ax.8eq} = J_{8ax.8a} = 10.8$, 1H, H-8ax), 3.01–2.93 (m, 1H, H-8a); ^{13}C NMR (C_6D_6, 100 MHz, ppm) δ 159.6, 153.8, 134.2, 130.7, 129.5, 129.1, 128.3, 127.1, 127.0, 124.6, 124.0, 123.9, 120.6, 118.6, 112.2, 110.1, 76.0, 65.9, 39.6; MS (GC/MS) *m*/*z* (%) 258 (M^+), 170 (100), 241, 223, 205, 194, 176, 165, 152, 131, 118, 102, 89, 77, 63, 51; HRMS calcd for $C_{19}H_{14}O_2$: 274.09938; found, 274.09865.

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21. *General procedure for the synthesis of isoflavone derivatives* **5a**–**c**. IBX (3 equiv) was added to a solution of isoflavanones **3d**, **3e** and **3f** (1 equiv) in DMSO-d_6. The reaction mixture was heated at 85 °C until complete consumption of the starting material was observed by ^{1}H NMR. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$ (3×), H_2O (1×) and dried ($MgSO_4$) followed by the removal of the solvent in vacuo. The residue was purified by flash-column chromatography on silica gel with the appropriate mixture of hexane and EtOAc to give the isoflavone derivatives **5a**–**c**.