A Convenient Synthesis of (±)-4-Prenylpterocarpin

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Received 19 November 1991; revised 12 February 1992

Coupling of 7-methoxy-8-(3-methyl-2-butenyl)-2*H*-1-benzopyran (**4a**) with 2-chloromercurio-4,5-methylenedioxyphenol (**5**) yields (±)-6a,12a-*cis*-dihydro-3-methoxy-4-(3-methyl-2-butenyl)-6*H*-[1,3]dioxolo[5,6]benzofuro[3,2-*c*][1]benzopyran (**6**; ±-4-prenylpterocarpin) in an efficient manner. An improved procedure for the preparation of chromenes is reported.

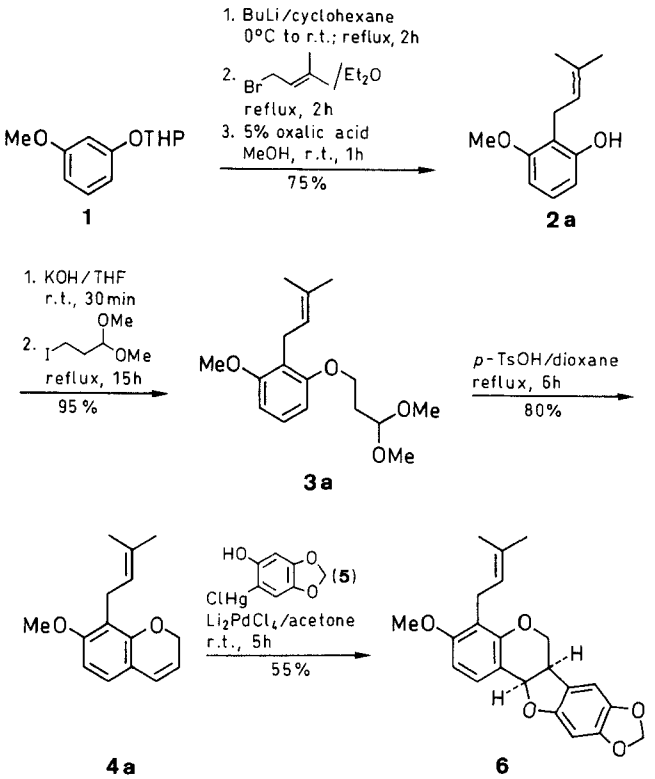
Pterocarpans are an important group of naturally occurring products.[1] Many of these compounds act as phytoalexins. For example, phaseollidin[2] and erybraedins A, B and C[3] possess relevant antibiotic activities. Further, Nakanishi and co-workers demonstrated that cabenegrins A-I and A-II are the active components of a brazilian folk medicine used against snake venoms. These compounds are active in dogs against the venom of *Bothrops atrox*.[4] More recently researchers at this center demonstrated that wedelolactone, a closely related isoflavonoid, is the main active component of *Eclipta prostata*, a plant also used in Brazil as venom neutralizer.[5]

A common structural feature of many relevant pterocarpans is the presence of a prenyl substituent which seems essential for their biological activity.

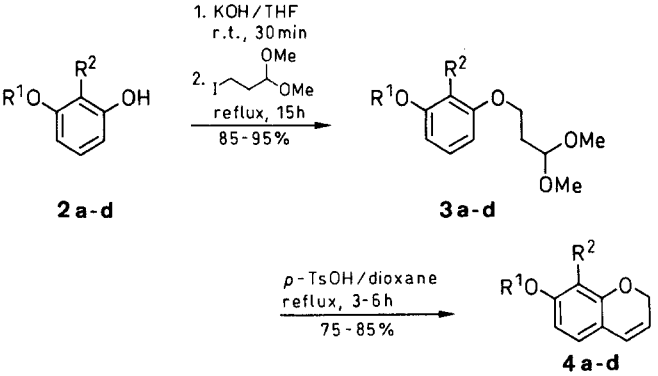
The most efficient approaches for the synthesis of pterocarpans have used chromenes as the key intermediates.[6] However, the obtention of pterocarpans with prenyl groups in the A-ring, remains problematic,[7] as the necessary prenylated chromenes have not been reported.

As part of our program in the synthesis of isoflavonoids,[8] we now wish to report the synthesis of 4-prenylpterocarpin **6** where a prenylated chromene, **4a**, is the key intermediate. This latter compound was obtained from the resorcinol derivative **1**, as shown in Scheme 1. Thus, compound **1** was regioselectively lithiated with butyllithium in refluxing cyclohexane,[9] followed by trapping the formed intermediate by the addition of prenyl bromide in diethyl ether under reflux. The tetrahydropyranyl group (THP) was removed in situ by addition of 5% aqueous oxalic acid giving, after chromatography on silica gel, the prenylated resorcinol **2a** in 75% yield. The high regioselectivity of this process was confirmed by the complete absence of signals in the ^1H NMR and ^{13}C NMR spectra that could be attributed to isomers.

The transformation of **2a** into the chromene **4a** is based in the two-step sequence described by Schuda and Phillips.[10] Even though for simple chromenes the yields reported are acceptable, if the brevity of the procedure is considered, we felt that for the prenylated intermediates the procedure should be further developed. Thus, we have found that the use of 3-iodopropionaldehyde dimethyl acetal as the alkylation agent (instead of 2-[2-chloroethyl]-1,3-dioxolane) leads to the desired ethers in excellent yields and the time of the reaction is shortened from 3–4 days to only 15 hours. Further, the use of dioxane in the cyclization step (instead of benzene), results in the



Scheme 1



2–4	R^1	R^2	Yield (%)	
			3[a]	4[a]
a	Me	$CH_2CHC(CH_3)_2$	95	80
b	Me	CH_2CHCH_2	92	75
c	Bn	H	90	85[b]
d	Me	H	85	75[b,c]

[a] Yields after purification.

[b] Chromenes **4c** and **4d** were reported by Schuda[10] in 50 and 44% yield, respectively. The use of dioxane does not change the high degree of regioselectivity demonstrated in the cyclization step.

[c] Attempt to cyclize the ethyleneglycol acetal analog of **3d** in dioxane led to chromene **4d** in only 40% yield.

Scheme 2

formation of chromenes in much higher yields and shorter reaction times are observed. A summary of our results is shown in Scheme 2.

Chemoselective coupling of **4a** with *o*-(chloromercurio)phenol **5** under the conditions described by Horino and Inoue[11] led to (±)-4-prenylpterocarpin **6** almost exclusively. While this work was under way, Iyer and co-workers,[12] demonstrated that bischromenes having two conjugated double bonds undergo chemoselective Heck arylation in the less sterically hindered olefin. However, the reported yields are much lower than in our case where the second olefn is not conjugated. Work is now in progress in our laboratory to evaluate the scope of this procedure.

Dioxane, Et_2O and cyclohexane were distilled from Na/benzophenone. Prenyl bromide was distilled from CaH_2 prior to use. Acetone was dried (K_2CO_3), distilled and stored over 4 Å molecular sieves. *p*-TsOH was dried for 4 h, in vacuo ~ 1 Torr) prior to use. 2-Chloromercurio-4,5-methylenedioxyphenol **(5)**,[6a] 1-methoxy-3-(2-tetrahydropyranyloxy)benzene **(1)**,[13] 3-benzyloxyphenol **(2c)**[14] and 3-iodopropionaldehyde dimethyl acetal[15] were prepared according to literature procedures.

^{1}H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) instrument using TMS as standard and $CDCl_3$ as solvent. ^{13}C NMR spectra were obtained at 50 MHz. The coupling constants (*J*) are in hertz (Hz). Mass spectra were recorded on a Micromass MM 12 F and a VG Autospec spectrometer.

3-Methoxy-2-(3-methyl-2-butenyl)phenol (2a); Typical Procedure:
To a cooled (0 °C) solution of 1-methoxy-3-(2-tetrahydropyranyloxy)benzene (**1**; 300 mg, 1.48 mmol), in cyclohexane (1.0 mL), BuLi (1.35 mL, 2.16 mmol, 1.6 M) was added under N_2 atmosphere. The mixture was warmed to r.t., refluxed for 2 h, and cooled (r.t.). After this time a solution of prenyl bromide (0.48 mL, 3.92 mmol) was added and the resulting mixture refluxed for 2 h. The reaction was quenched by addition of sat. aq NH_4Cl (20 mL), and extracted with Et_2O (3 × 30 mL). The organic layer was washed with 10% solution of NaOH (3 × 30 mL), brine, H_2O, dried (Na_2SO_4), filtered and concentrated. The crude product was immediately treated with 5% aq. oxalic acid solution (1.0 mL) in MeOH (10 mL) over 1 h (r.t.). Solid $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting product was purified by column chromatography on silica gel giving **2a** as a yellow oil (208 mg, 75%).

IR (neat): ν = 3546, 2924; 1220; 787 cm^{-1}.

^{1}H NMR: δ = 7.1 (t, 1 H, J = 8); 6.5 (d, 2 H, J = 8); 5.4 (br, 1 H); 5.3 (m, 1 H); 3.8 (s, 3 H); 3.4 (d, 2 H, J = 7); 1.8 (s, 3 H); 1.7 (s, 3 H).

^{13}C NMR: δ = 17.6 (q); 22.1 (t); 25.6 (q), 55.6 (q); 103.1 (d); 108.7 (d); 115.3 (s); 122.0 (d); 126.9 (d); 133.7 (s); 155.1 (s); 157.9 (s).

MS (70 eV): *m/z* (%) = 192 (M$^+$, 58); 175 (30); 137 (100); 77 (30).

HRMS (70 eV): *m/z*, $C_{12}H_{16}O_2$, calc.: 192.1150; found: 192.1184.

2-Allyl-3-methoxyphenol **(2b)**:

This compound was obtained in similar manner to **2a** in 80% yield.

IR (neat): ν = 3597; 2985; 1587; 1449 cm^{-1}.

^{1}H NMR: δ = 7.0 (t, 1 H, J = 8); 6.5 (d, 2 H, J = 8); 5.9 (m, 1 H); 5.1 (m, 2 H); 3.8 (s, 3 H); 3.4 (d, 2 H, J = 7).

MS (70 eV): *m/z* (%) = 164 (M$^+$, 100); 149 (30); 135 (30); 107 (30).

3-[3-Methoxy-2-(3-methyl-2-butenyl)phenoxy]propionaldehyde Dimethyl Acetal (3a); Typical Procedure:
A mixture of KOH (112.2 mg, 2.0 mmol) and 3-methoxy-2-(3-methyl-2-butenyl)phenol (**2a**; 325 mg, 1.71 mmol) in THF (20 mL), was stirred for 30 min at r.t. Then 3-iodopropionaldehyde dimethyl acetal (470 mg, 2.0 mmol) in THF (20 mL) was added slowly and the resulting mixture refluxed for 15 h. The reaction was cooled, washed with aq. 10% NaOH (3 × 20 mL), brine and H_2O. The organic layer was dried (Na_2SO_4), filtered and concentrated. This crude product was purified by distillation in a bulb-to-bulb apparatus, yielding **3a** as a light yellow oil (473 mg, 95%).

IR (neat): ν = 2920; 1590; 925; 725 cm^{-1}.

^{1}H NMR: δ = 7.1 (t, 1 H, J = 8); 6.5 (d, 2 H, J = 8); 5.2 (m, 1 H); 4.7 (t, 1 H, J = 6); 4.0 (t, 2 H, J = 6); 3.8 (s, 3 H); 3.4 (br, 8 H); 2.1 (q, 2 H, J = 6); 1.8 (s, 3 H); 1.7 (s, 3 H).

^{13}C NMR: δ = 17.6 (q); 22.1 (t); 25.6 (q); 32.0 (t); 53.1 (q); 55.5 (q); 64.0 (t); 102.0 (d); 103.6 (d); 104.4 (d); 118.2 (s); 123.0 (d); 126.5 (d); 130.4 (s); 157.1 (s); 158.0 (s).

MS (70 eV): *m/z* (%) = 294 (M$^+$, 1.6); 262 (60); 230 (75); 215 (60); 163 (60); 75 (70); 71 (100).

HRMS (70 eV): *m/z*, $C_{17}H_{26}O_4$, calc.: 294.1831; found: 294.1833.

In a similar procedure **3b**, **3c** and **3d** were obtained from the corresponding phenols **2**:

3-(2-Allyl-3-methoxyphenoxy)propionaldehyde Dimethyl Acetal **(3b)**:

IR (neat): ν = 3063; 2920; 1645; 1593 cm^{-1}.

^{1}H NMR: δ = 7.2 (t, 1 H, J = 8); 6.5 (d, 2 H, J = 8); 6.0 (m, 1 H); 4.9 (m, 2 H); 4.7 (t, 1 H, J = 6); 4.0 (t, 2 H, J = 6); 3.8 (s, 3 H); 3.4 (dt, 2 H, J = 1.3, 6.2); 3.3 (s, 6 H); 2.1 (q, 2 H, J = 6).

MS (70 eV): *m/z* (%) = 234 (20); 203 (40); 161 (22); 75 (100).

3-(3-Benzyloxyphenoxy)propionaldehyde Dimethyl Acetal **(3c)**:

IR (neat): ν = 3050; 2930; 1610 cm^{-1}.

^{1}H NMR: δ = 7.4 (m, 5 H); 7.2 (t, 1 H, J = 8); 6.6 (m, 3 H); 5.0 (s, 2 H); 4.6 (t, 1 H, J = 5.5); 4.0 (t, 2 H, J = 5.5); 3.4 (s, 3 H); 2.1 (q, 2 H, J = 5.5).

MS (70 eV): *m/z* (%) = 302 (M$^+$, 23); 91 (100); 75 (24); 71 (30).

3-(3-Methoxyphenoxy)propionaldehyde Dimethyl Acetal **(3d)**:

IR (neat): ν = 2930; 2820; 1595 cm^{-1}.

^{1}H NMR: δ = 7.2 (t, 1 H, J = 8); 6.5 (m, 3 H); 4.6 (t, 1 H, J = 6); 4.0 (t, 2 H, J = 6); 3.8 (s, 3 H); 3.4 (s, 6 H); 2.1 (q, 2 H, J = 6).

MS (70 eV): *m/z* = 226 (M$^+$, 20); 161 (92); 75 (100).

7-Methoxy-8-(3-methyl-2-butenyl)-2*H*-1-benzopyran (4a); Typical Procedure:
To a solution of *p*-TsOH (10 mg) in dioxane (10 mL), 3-[3-methoxy-2-(3-methyl-2-butenyl)phenoxy]propionaldehyde dimethyl acetal (**3a**; 200 mg) in dioxane (10 mL) was added. The mixture was refluxed for 6 h under N_2. After this time 10% aq NaOH (10 mL) was added and the mixture was partitioned with Et_2O, washed with NaOH (3 × 10 mL), brine, H_2O and dried (Na_2SO_4). After concentration and distillation in a bulb-to-bulb apparatus compound **4a** was obtained as a light yellow oil (125 mg, 80%).

IR (neat): ν = 2900; 2830; 1635; 1575 cm^{-1}.

^{1}H NMR: δ = 6.8 (d, 1 H, J = 8); 6.4 (d, 1 H, J = 8); 6.4 (dt, 1 H, J = 10 and 2); 5.7 (dt, 1 H, J = 10, and 3.8); 5.2 (m, 1 H), 4.7 (dd, 2 H, J = 3.8, and 2); 3.8 (s, 3 H); 3.3 (d, 2 H, J = 7); 1.8 (s, 3 H); 1.7 (s, 3 H).

^{13}C NMR: δ = 17.6 (q); 22.0 (t); 25.7 (q); 55.5 (q); 65.3 (t); 103.1 (d); 116.0 (s); 117.4 (s); 119.0 (d); 122.5 (d); 124.1 (d); 124.6 (d); 131.1 (s); 152.5 (s); 158.0 (s).

MS (70 eV): *m/z* (%) = 230 (M$^+$, 90); 215 (100); 187 (55); 115 (30).

HRMS (70 eV): *m/z*, $C_{15}H_{18}O_2$, calc.: 230.1307; found: 230.1302.

In a similar procedure **4b**, **4c** and **4d** were obtained from the corresponding ethers **3**:

8-Allyl-7-methoxy-2H-1-benzopyran **(4b)**:

IR (neat): ν = 2858, 1640, 1610, 1590 cm^{-1}.

^{1}H NMR: δ = 6.8 (d, 1 H, J = 8); 6.4 (d, 1 H, J = 8); 6.4 (dt, 1 H, J = 2, and 10); 6.0 (m, 1 H); 5.7 (dt, 1 H, J = 3.8, 10); 5.0 (m, 2 H); 4.7 (dd, 2 H, J = 2.0, 3.8); 3.9 (s, 3 H); 3.4 (dt, 2 H, J = 1.7, 6.2).

MS (70 eV): *m/z* (%) = 202 (M$^+$, 100); 201 (77); 187 (22); 171 (25).

7-Benzyloxy-2H-1-benzopyran **(4c)**:

IR (neat): ν = 3045; 2850; 1645; 1605 cm^{-1}.

^{1}H NMR: δ = 7.4 (m, 5H); 6.9 (d, 1H, J = 9.8); 6.5 (dd, 2H, J = 9.8, 3.0); 6.5 (d, 1H, J = 3), 6.4 (dt, 1H, J = 13, 3.2); 5.6 (dt, 1H, J = 13, 4.9); 5.0 (s, 2H); 4.8 (dd, 2H, J = 4.9, 3.2).

7-Methoxy-2H-1-benzopyran **(4d)**.

IR (neat): ν = 2960; 2840; 1615; 1280 cm^{-1}.

^{1}H NMR: δ = 6.8 (d, 1H, J = 8); 6.4 (m, 3H); 5.6 (dt, 1H, J = 3.5, 9.8); 4.8 (dd, 2H, J = 3.5, 2.0); 3.7 (s, 3H).

MS (70 eV): m/z (%) = 162 (M^+, 60); 161 (100); 147 (30).

(±)-6a,12a-*cis*-Dihydro-3-methoxy-4-(3-methyl-2-butenyl)6*H*-[1,3]-dioxolo[5,6]benzofuro[3,2-*c*][1]benzopyran (4-prenylpterocarpin) (6): To a mixture of $PdCl_2$ (57 mg, 0.32 mmol) and LiCl (28 mg, 0.32 mmol) in acetone (10 mL) was added 7-methoxy-8-(3-methyl-2-butenyl)-2*H*-chromene **4a** (74 mg, 0.32 mmol) in dry acetone (10 mL). This mixture was stirred for 15 min and 2-chloromercurio-4,5-methylenedioxyphenol (**5**; 120 mg, 0.32 mmol) in acetone (10 mL) was added. The suspension thus obtained was stirred for 5 h at r. t. After this time, brine (20 mL) was added and the mixture was extracted with benzene, dried (Na_2SO_4), filtered and concentrated. The product was purified by column chromatography leading to **6** as a colorless solid. (65 mg, 55%). mp = 185–186°C.

IR (KBr): ν = 3050; 1615; 1486; 1250 cm^{-1}.

^{1}H NMR: δ = 7.3 (d, 1H, J = 8); 6.7 (s, 1H); 6.6 (d, 1H, J = 8); 6.4 (s, 1H); 5.9 (2d, 2H); 5.5 (d, 1H, J = 6.7); 5.2 (m, 1H); 4.2 (dd, 1H, J = 11, 4.4); 3.8 (s, 3H); 3.6 (t, 1H, J = 11); 3.5 (m, 1H); 3.3 (d, 2H, J = 7); 1.8 (s, 3H); 1.7 (s, 3H).

^{13}C NMR: δ = 17.6 (q); 22.2 (t); 26.7 (q); 40.1 (d); 55.7 (d); 66.6 (t); 79.1 (d); 93.6 (d); 101.1 (t); 104.6 (d); 112.8 (d); 118.0 (s); 118.1 (s); 122.4 (d); 128.5 (d); 131.3 (s); 141.5 (s); 147.7 (s); 153.8 (s); 154.2 (s); 158.2 (s).

MS (70 eV): m/z (%) = 366 (M^+, 100); 310 (40); 175 (10); 149 (25).

HRMS (70 eV): m/z, $C_{22}H_{22}O_5$, calc.: 366.1467; found: 366.1444.

Financial support was provided by the Secretary of Science and Technology (CNPq, FINEP). We wish to thank Dr. A.J.R. da Silva and E. Miguez for Mass and NMR spectra.

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