Total Synthesis of Pterocarpan: (±)-Neorautenane

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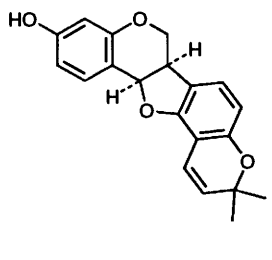
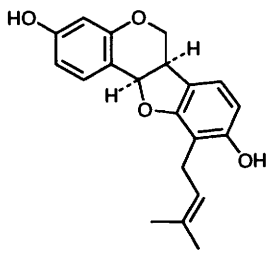
A new approach to the total synthesis of (±)-neorautenane **14** is described, using the chemoselective coupling of benzodipyran **12** and *o*-chloromercuriophenol **13** as the key step. Compound **12** is synthesized in four steps from chromanone **7**.

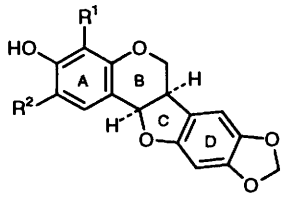
The number of naturally occurring biologically active pterocarpans identified is ever increasing. This group of compounds is of great interest because of their reputed pathological activity as phytoalexins (*e.g.* phaseollin **1**, phaseollidin **2**).[1] In 1982, Nakagawa *et al.* isolated two prenylated pterocarpans, cabenegrine A-I **3** and A-II **4** from materials used for Brazilian folk medicine, which were active, *in vivo*, against the venom of *Bothrops atrox*.[2] These bioactive pterocarpans have phenyl moieties in the A and D rings.

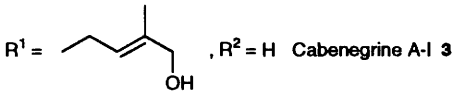


Phaseollin **1**

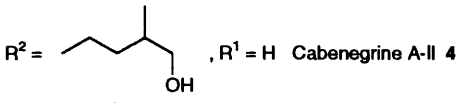


Phaseollidin **2**

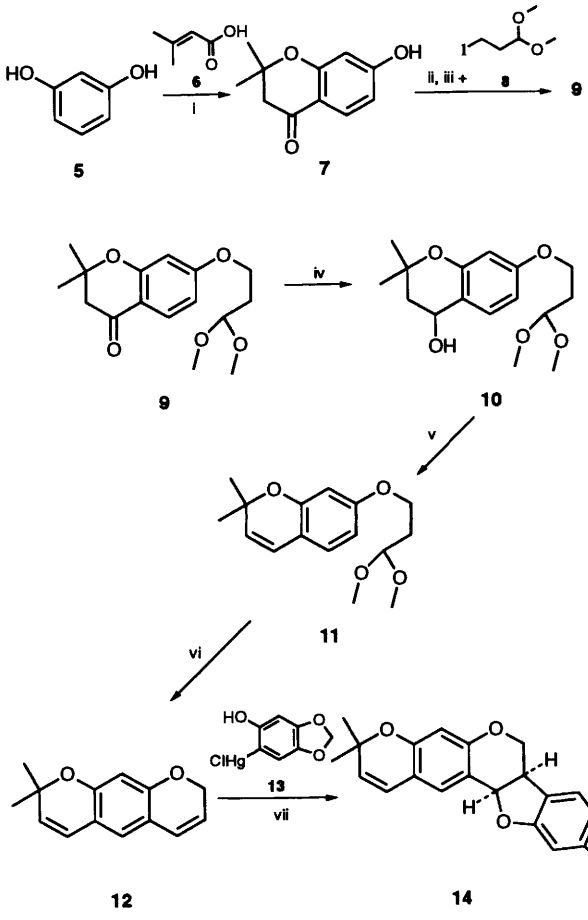




Cabenegrine A-I **3**



Cabenegrine A-II **4**



Scheme 1 *Reagents and conditions:* i, $MeSO_3H$, P_2O_5, 70 °C, 30 h; ii, NaH, DMF, 0 °C, 5 h; iii, toluene, 48 h; iv, $NaBH_4$, EtOH, room temp., 24 h; v, *p*-TsOH, THF, reflux, 1.5 h; vi, *p*-TsOH, dioxane, reflux, 3 h; vii, Li_2PdCl_4, acetone, room temp., 24 h

Herein, we describe a total synthesis of (±)-neorautenane **14**, which has a 2,2-dimethyl-2*H*-pyrano moiety as part of its structure.[3] Our strategy employed the chemoselective coupling[4] of benzodipyran **12** and *o*-chloromercuriophenol **13** as the key step.

Results and Discussion

We initiated our work with the condensation of 3-methylbut-2-enoic acid **6**[5] and resorcinol **5** in the presence of methanesulfonic acid and phosphorus pentoxide. Under these conditions the hydroxychromanone **7** was obtained in good yield (see Scheme 1).[6] Alkylation of the free phenolic group of **7** using 3-iodopropanal dimethyl acetal **8**[7] in the presence of NaH as base and dimethylformamide (DMF)–toluene under reflux led to the desired ether **9** in excellent yield. Compound **9** was reduced with sodium tetrahydroboranuide to give the alkoxy alcohol **10** in 84.5% yield.

Preliminary experiments for obtaining benzodipyran **12** from alkoxy alcohol **10** led to mixtures of desired and side products, whose structures were not determined. This observation indicated that water formed during the dehydration step was compromising the process of cyclization. Some procedures for removal of water (*e.g.* using Dean–Stark, orthoformate) were employed, but the results obtained were not satisfactory. Consequently, to avoid this problem, the dehydration step was

carried out using toluene-*p*-sulfonic acid (*p*-TsOH) in tetrahydrofuran (THF) under reflux giving the alkylated chromene **11** in 76% yield. As expected, further cyclization using catalytic amounts of *p*-TsOH in dioxane under reflux resulted in the highly regioselective formation of desired benzodipyran **12**.

Benzodipyran **12** was allowed to react with *o*-chloromercuriophenol **13** in the presence of lithium tetrachloropalladate(II) and acetone, leading to the natural product **14** in 49% yield. This Heck arylation was observed to occur with a high degree of chemoselectivity at the less sterically hindered olefinic bond of **12**. It was confirmed by the complete absence of signals in the ^1H and ^{13}C NMR spectra that could be attributed to other isomer.

Work is now in progress in our laboratory to evaluate the possibility of further developing the described methodology towards the synthesis of other pterocarpans.

Experimental

Dioxane, THF and toluene were distilled from Na–benzophenone. DMF was distilled from CaH_2 and stored over 4 Å molecular sieves. Ethanol was distilled from Mg–I_2 and stored over 4 Å molecular sieves, *p*-TsOH was dried for 4 h, under reduced pressure (~ 1 mmHg) prior to use.

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

7-(3,3-*Dimethoxypropoxy*)-2,2-*dimethyl*-3,4-*dihydro*-2H-1-*benzopyran*-4-*one* **9**.—A mixture of NaH (624 mg, 13 mmol) and 2,2-dimethyl-7-hydroxychroman-4-one **7** (1 g, 5.2 mmol) in DMF (20 cm^3) was stirred for 5 min at 0 °C. 3-Iodopropanal dimethyl acetal **8** (2.4 g, 10.4 mmol) in toluene (20 cm^3) was added slowly to the mixture which was then refluxed for 48 h. The reaction mixture was cooled and then washed with aq. 10% NaOH (3 × 20 cm^3), brine and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated. The crude product was purified by distillation in a bulb-to-bulb apparatus, yielding the title compound **9** as a light yellow oil (1.4 g, 95%), δ_H 1.48 (s, 6 H), 2.21 (m, 2 H), 2.68 (s, 2 H), 3.38 (s, 6 H), 4.09 (t, 2 H), 4.61 (t, 1 H), 6.3 (d, 1 H, J_o 9), 6.58 (dd, 1 H, J_m 3, J_o 9) and 7.8 (d, 1 H, J_o 9); δ_C 26.54 (2 × q), 32.34 (t), 48.40 (t), 53.17 (2 × q), 64.18 (t), 79.38 (s), 101.53 (d), 101.68 (d), 109.39 (d), 113.95 (d), 128.06 (s), 161.78 (s), 165.32 (s) and 109.92 (s); *m/e* 294 (M^+, 100%), 279 (36), 102 (46) and 75 (74).

7-(3,3-*Dimethoxypropoxy*)-2,2-*dimethyl*-3,4-*dihydro*-2H-1-*benzopyran*-4-*ol* **10**.—A solution of alkylated chromanone **9** (100 mg, 0.4 mmol) in THF (14 cm^3) was added to $NaBH_4$ (128 mg, 3.4 mmol) in ethanol (14 cm^3) and this mixture was stirred for 24 h. The solvent was removed and the residue dissolved in saturated aq. NH_4Cl (7 cm^3) and extracted with EtOAc. The extract was washed with saturated aq. $NaHCO_3$, brine and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated. The crude product was purified by flash column chromatography, yielding the title compound **10** as a light yellow oil (85.1 mg, 84.5%), δ_H 1.3 (s, 3 H), 1.45 (s, 3 H), 1.7 (s, 1 H), 1.79 and 2.2 (m, 4 H), 3.35 (s, 6 H), 4.0 (s, 2 H), 4.6 (s, 1 H), 4.7 (t, 1 H), 6.34 (d, 1 H, J_m 3), 6.52 (dd, 1 H, J_m 3, J_o 9.2) and 7.35 (d, 1 H, J_o 9.2); δ_C 25.69 (q), 28.60 (q), 32.58 (t), 42.69 (t), 53.16 (2 × q), 63.26 (t), 63.79 (d), 77.53 (s), 101.96 (d), 101.97 (d), 107.87 (d), 116.74 (d), 128.42 (s), 154.09 (s) and 159.09 (s); *m/e* 278 (M^+ − 18, 36%), 263 (100), 161 (58) and 75 (22).

7-(3,3-*Dimethoxypropoxy*)-2,2-*dimethyl*-2H-*benzopyran* **11**.—To a solution of *p*-TsOH (catalytic amount) in THF (5 cm^3) was added alkoxy alcohol **10** (185 mg, 0.62 mmol) in THF (5 cm^3). The mixture was refluxed for 1.5 h under N_2. After this time 10% aq. NaOH (10 cm^3) was added and the mixture was extracted with CH_2Cl_2, the organic extract washed with 10% aq. NaOH (3 × 10 cm^3), brine and water and then dried (Na_2SO_4). After concentration and filtration over neutral alumina, the title compound **11** was obtained as a light yellow oil (131.8 mg, 76%), δ_H 1.4 (s, 6 H), 2.1 (m, 2 H), 3.38 (s, 6 H), 4.0 (t, 2 H), 4.62 (t, 1 H), 5.48 (d, 1 H), 6.28 (d, 1 H), 6.30 (d, 1 H), 6.50 (dd, 1 H) and 6.9 (d, 1 H); *m/e* 278 (M^+, 16%), 263 (57), 161 (100) and 75 (59).

2,2-*Dimethyl*-2H,8H-*benzo*[1,2-b:5,4-b′]*dipyran* **12**.—To a solution of *p*-TsOH (catalytic amount) in dioxane (5 cm^3) was added alkylated chromene **11** (47.5 mg, 0.17 mmol) in dioxane (5 cm^3). The mixture was refluxed for 3 h under N_2. After this time 10% aq. NaOH (10 cm^3) was added and the mixture was extracted with CH_2Cl_2, the organic extract washed with 10% aq. NaOH (3 × 10 cm^3), brine and water and then dried (Na_2SO_4). After concentration and filtration over neutral alumina, the title compound **12** was obtained as a light yellow oil (28.5 mg, 77.4%); δ_H 1.40 (s, 6 H), 4.78 (m, 2 H), 5.48 (d, 1 H), 5.62 (m, 1 H), 6.24 (d, 1 H), 6.26 (s, 1 H), 6.34 (1 H) and 6.60 (s, 1 H); *m/e* M^+ 214 (19%) and 199 (100).

9,9-*Dimethyl*-4b,12b-*dihydro*-2H,5H-[1,3]*dioxolo*[5,6]*benzofuro*[3,2-c]*pyrano*[3,2-g][1]*benzopyran* **14**.—To a mixture of $PdCl_2$ (30 mg, 0.17 mmol) and LiCl (14.3 mg, 0.34 mmol) in acetone (5 cm^3) was added benzodipyran **12** (35.6 mg, 0.17 mmol) in acetone (5 cm^3). This mixture was stirred for 15 min and then 2-chloromercurio-4,5-methylenedioxyphenol **13** (64 mg, 0.17 mmol) in acetone (15 cm^3) was added to it. The suspension thus obtained was stirred for 24 h at 25 °C. After this time, brine (20 cm^3) was added to it and the mixture was extracted with CH_2Cl_2, the organic extract dried (Na_2SO_4), filtered and then concentrated. The product was purified by preparative chromatography to give the title compound **14** as a colourless solid (28.7 mg, 49%), mp 166–167 °C (lit.,[14] mp 166 °C) (Found: M^+, 350.115813. $C_{21}H_{18}O_5$ requires M^+, 350.115 424), δ_H 1.40 (s, 3 H), 1.43 (s, 3 H), 3.44 (m, 1 H, *J* 6.6, 10.8, 4.7), 3.60 (t, 1 H, *J* 10.8), 4.20 (dd, 1 H, *J* 10.8, 4.7), 5.42 (d, 1 H, *J*, 6.6), 5.54 (d, 1 H, *J* 9.8), 5.9 (2 × d, 2 H, *J* 5.6, 1.3), 6.30 (d, 1 H, *J* 9.8), 6.38 (s, 1 H), 6.42 (s, 1 H), 6.7 (s, 1 H) and 7.1 (s, 1 H); δ_C 27.8 (q), 28.1 (q), 40.2 (d), 66.4 (t), 77.5 (s), 78.5 (d), 93.7 (d), 101.2 (t), 104.6 (d), 105.0 (s), 112.2 (s), 116.3 (s), 117.9 (d), 121.5 (d), 128.1 (d), 129.0 (d), 141.6 (s), 148.0 (s), 154.1 (s), 154.5 (s) and 156.2 (s); *m/e* M^+ 350 (40.5%) and 335 (100).

Acknowledgements

We thank the CNPq, FINEP, CEPG and FUJB for financial support. The authors are grateful to the Analytic Center at NPPN for the ^1H NMR, ^{13}C NMR and mass spectra.

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Paper 4/06069E
Received 4*th October* 1994
Accepted 18*th October* 1994