A Simple Conversion of 2′-Benzyloxyflavanone to Pterocarpan

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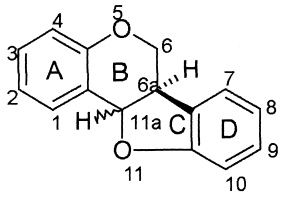
Pterocarpan, Thallium(III) Nitrate, Ring Contraction

A new synthesis of *cis*-6a*H*,11a*H*-pterocarpan (**1a**) was achieved *via* its *trans*-isomer **1b** starting from the readily available 2′-benzyloxyflavanone (**2b**).

Pterocarpans possessing a 6a,11a-dihydro-6*H*-benzofuro[3,2-*c*][1]benzopyran skeleton (**1a**) of *cis* B/C-ring junction constitute the second largest group of natural isoflavonoids [1], (Scheme 1). Many of them are phytoalexins which are produced in plants during infection by fungi, bacteria or viruses and subsequently act as protective agents for plants [2]. While some pterocarpans have antifungal [3], antitubercular and oestrogenic activity [4], others have been reported to inhibit HIV-1 in cell cultures [5, 6]. Furthermore, Nakanishi and co-workers have demonstrated that two representatives of these natural products are antagonists against some snake venoms [7]. Among the wide variety of synthetic routes to pterocarpans [8–15], the most common approach involves the reduction and cyclization of the corresponding 2′-hydroxyisoflavones [14, 15].



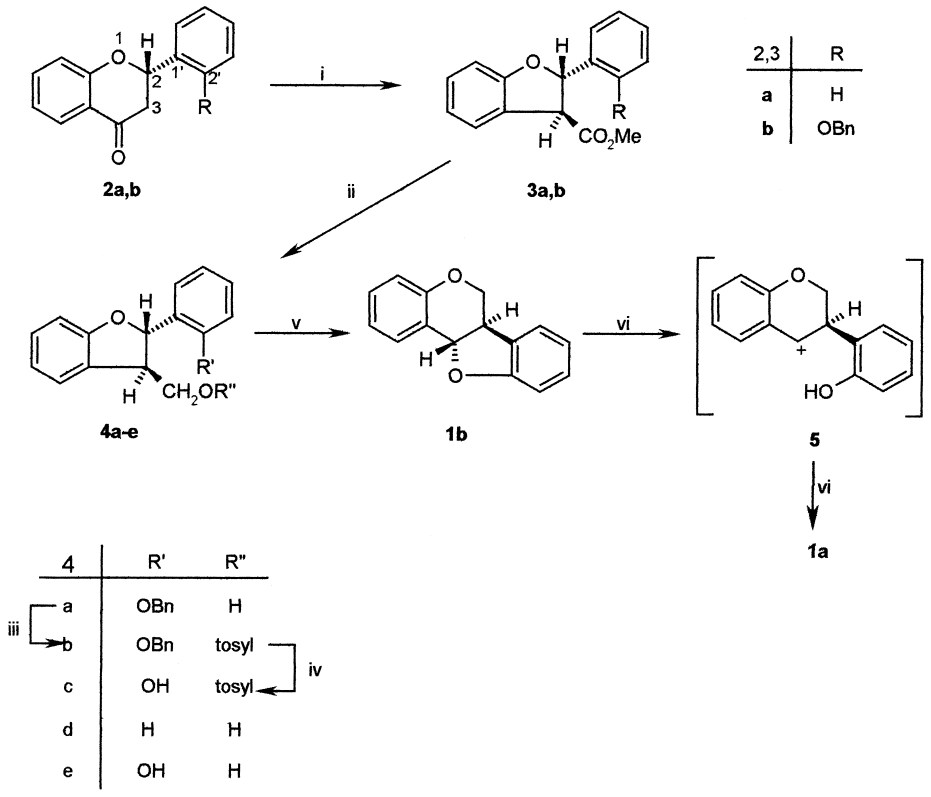
1a,b

	11a-H
a	α
b	β

Scheme 1.

Recently we have published that the ring-contraction of flavanone (**2a**) took place smoothly in the presence of iodobenzene diacetate or thallium(III) nitrate and a small amount of sulfuric or perchloric acid in trimethyl orthoformate to result stereoselectively in *trans*-3-carbomethoxy-2-phenyl-2,3-dihydrobenzo[*b*]furan (**3a**) as shown in Scheme 2 [16]. This compound can also be transformed into *trans*-3-hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]furan (**4d**) in high yield (87%). Therefore, in the presence of an oxygen function at C-2′ of **2a,** a simple three steps sequence *via* **4c** would allow the construction of the pterocarpan skeleton with *trans* B/C-ring junction (**1b**). Isomerisation of **1b** might then lead to the *cis* isomer **(1a**) as a result of its higher thermodynamic stability as predicted by computational studies [17].

The starting racemic 2′-benzyloxyflavanone (**2b**) was prepared from the readily available 2-hydroxyacetophenone and salicylaldehyde *via* 2-benzyloxy-2′-hydroxychalcone as described [18]. Transformation of **2b** to the *trans*-2,3-dihydrobenzo[*b*]-furan derivative **3b** could be performed by $Tl(NO_3)_3$ in the presence of 70% perchloric acid in trimethyl orthoformate in 48% yield. Subsequent reduction of **3b** by $LiAlH_4$ gave the primary alcohol **4a** in high yield (97%) which was then converted smoothly to the tosylate **4b** (79%). Debenzylation of **4b** by catalytic hydrogenation afforded the phenolic derivative **4c** which was treated with 1 N sodium methoxide in methanol to promote cyclization *via* an S_N2-type reaction. TLC monitoring of this reaction indicated transformation into a single product which was identified as 6a*H*,11a*H*-*trans*-pterocarpan (**1b**) by comparison of its NMR data with those of the *cis*-isomer (**1a**) described by us recently [19]. The remarkably large coupling constant *J* (6a-H,11a-H) (13.4 Hz) is an unequivocal proof for the *trans* relationship of the bridge protons. The large upfield shifts of H_{ax} and H_{eq} in *cis*-pterocarpan with respect to *trans*-pterocarpan



Scheme 2. i) $PhI(OAc)_2$ or $Tl(NO_3)_3/HC(OMe)_3$, H^+, rt; ii) $LiAlH_4$/dry ether, rt; iii) *p*TsCl/pyridine, rt; iv) Pd(C)/H_2, MeOH; v) NaOMe/MeOH, rt; vi) *p*TosOH/benzene, Δ.

are due to ring currents as a result of different spatial relationship of ring D in the two epimers **1a** and **1b**. Surprisingly, the melting point of our product (131–132 °C) was quite different from that published (89 °C) [20]. Ferreira *et al.* performed the synthesis of **1b** through Mitsunobu cyclization of **4e** itself prepared in three steps from the aldol condensation product between MOM-protected methyl 2-hydroxyphenylacetate and salicylaldehyde. Quantum chemical calculations indicated that the *trans*-fused B/C-ring of the pterocarpan skeleton is much preferred to the observed *cis*-isomer ($\Delta\Delta H$ = −10.02 kcal/mol) [17]. Therefore, we assumed that **1b** might be isomerized into **1a** by proton catalyzed ring-opening reaction *via* a carbocation intermediate **5**. Accordingly, treatment of **1b** in the presence of *p*-toluenesulfonic acid in benzene at 80 °C led to *cis*-pterocarpan (**1a**) in good yield (74%). In fact this transformation resulted in a mixture of **1a**:**1b** (*ca.* 8.5:1 respectively, detected by HPLC). Crystallization of the crude product from methanol gave pure **1a**.

In summary we have accomplished a new synthesis of the basic skeleton of naturally occuring pterocarpans (**1a**) *via* its *trans*-isomer **1b** which in turn could be prepared from 2′-benzyloxyflavanone (**2b**) in stereocontrolled manner. Our method offers also a new approach for the enantioselective synthesis of peterocarpans starting from the corresponding optically pure 2′-benzyloxyflavanone derivative. Work on this project is now in progress in our laboratory.

Experimental Section

General experimental procedures

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Analytical and preparative TLC was performed on Kieselgel 60 F_{254} (Fa. Merck) plates. The reagents were purchased from Sigma-Aldrich. *Rac*-**2b** was pre-

pared as described in the literature [18]. For workup the solutions were dried ($MgSO_4$) and concentrated *in vacuo*. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker WP-200 and Bruker Avance DRX 500 spectrometers in $CDCl_3$ with TMS as internal standard. The chemical shifts (δ) are given in ppm. Elemental analyses were carried out with a Carlo Erba 1106 analyser. HRMS were recorded on a VG 7035 spectrometer (70eV, emission current 200 μA, 150 °C, accelerating voltage 4 kV) using perfluorokerogene (PKF) as a reference compound by peak matching technique.

2S,3S*-2-(2′-Benzyloxyphenyl)-3-carbomethoxy-2,3-dihydrobenzo[b]furan* (*rac*-**3b**)

To the stirred solution of *rac*-**2b** (2 g, 6 mmol) and thallium(III) nitrate (4 g, 9 mmol) in trimethyl orthoformate (20 ml) 70% perchloric acid (1.7 ml) was added dropwise and stirring was continued for 2 h at 20 °C. Subsequently it was diluted with ethyl acetate, washed with aquous saturated $NaHCO_3$ solution. The organic layer was dried and concentrated. The crude product was purified on a silica gel column (hexane–toluene, 3:7) yielding *rac*-**3b** as a colourless oil. – ^1H NMR (200.13 MHz): δ = 3.41 (s, 1H, $-CH_3$), 4.15 (d, 1H, 3-H, J = 6 Hz), 4.98 (s, 2H, $-CH_2Ar$), 6.32 (d, 1H, 2-H, J = 6 Hz), 6.71–7.5 (m, 13H, Ar–H). – HRMS: m/z = 360.1364 (calcd. for $C_{23}H_{20}O_4$: 360.1362).

2S,3R*-2-(2′-Benzyloxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzo[b]furan* (*rac*-**4a)**

To a stirred solution of $LiAlH_4$ (300 mg, 7.9 mmol) in dry ether (5 ml) a solution of *rac*-**3b** (600 mg, 1.67 mmol) was added dropwise at 0 °C and the stirring was continued at 20 °C for 1 h. The excess of the reagent was decomposed with saturated NH_4Cl solution and the product was extracted with ethyl acetate. The organic layer was dried and evaporated to give *rac*-**4a** (520 mg, 97%) as a colourless oil. – ^1H NMR (200.13 MHz): δ = 3.35 (d, 1H, 3-H, J = 5 Hz), 3.55–3.70 (m, 2H, $-CH_2OH$), 4.95 (d, 2H, $-CH_2Ar$), 5.75 (d, 1H, 2-H, J = 5 Hz), 6.65–7.35 (m, 13H, Ar–H). – HRMS: m/z = 332.1410 (calcd. for $C_{22}H_{20}O_3$: 332.1412).

2S,3R*-2-(2′-Benzyloxyphenyl)-3-tosyloxymethyl-2,3-dihydrobenzo[b]furan* (*rac*-**4b**)

The compound *rac*-**4a** (500 mg, 1.55 mmol) and tosyl chloride (888 mg, 4.65 mmol) were stirred in anhydrous pyridine (8 ml) 20 °C for 13 h. Then a solution of aq. HCl (10%) was added dropwise to this mixture until neutral pH was reached. The product was extracted with ethyl acetate, washed with saturated $NaHCO_3$ solution and dried. Evaporation resulted in *rac*-**4b** as a yellowish coloured oil (582 mg, 79%). – ^1H NMR (200.13 MHz): δ = 2.3 (s, 3H, $-CH_3$), 3.6 (d, 1H, 3-H, J = 4.8 Hz), 4.0–4.27 (m, 2H, $-CH_2O-$), 4.98 (d, 2H, $-CH_2Ar$), 5.12 (d, 1H, 2-H, J = 4.8 Hz), 6.7–7.55 (m, 17H, Ar–H). – HRMS: m/z = 486.1502 (calcd. for $C_{29}H_{26}SO_4$: 486.1501).

6aR,11aS*-Pterocarpan* (*rac*-**1b**)

Compound *rac*-**4b** (920 mg, 1.93 mmol) was hydrogenated in the presence of Pd/C (700 mg) in methanol (20 ml). The usual work up resulted in *rac*-**4c** (830 mg) which was dissolved in anhydrous methanol (20 ml); then, 1 N NaOMe (3.5 ml) was added. After stirring at room temperature for 3 h the mixture was neutralized with acetic acid and concentrated. The residue was taken up in ethyl acetate, washed with water, dried, concentrated, and purified on a silica gel column (hexane–dichloromethane, 7:3) to give **1b** as colourless crystals (200 mg, 46%), m.p. = 131–132 °C (benzene/hexane). – ^1H NMR (500.14 MHz): δ = 3.45–3.65 (ddd, 1H, 6a-H, J = 14 Hz, J = 5 Hz, J = 14 Hz), 4.38–4.51 (dd, 1H, 6ax-H, J = 14 Hz, J = 10 Hz), 4.8–4.9 (dd, 1H, 6eq-H, J = 10 Hz, J = 5 Hz), 5.07–5.18 (d, 1H, J = 14 Hz), 6.77–7.05 (m, 4H, Ar–H), 7.06–7.22 (m, 3H, Ar–H), 7.37 (d, 1H, Ar–H). – ^{13}C NMR (500.14 MHz): δ = 44.96 (C-6a), 68.58 (C-6), 83.51 (C-11a), 110.91 (C-10), 116.01 (C-4), 120.02 (C-3), 121.3 (C-9), 122.86 (C-2), 122.97 (C-8), 124.23 (C-6b), 127.1 (C-11b), 128.49 (C-1), 128.75 (C-7), 153.52 (C-4a), 161.21 (C-10a). – Analysis $C_{15}H_{12}O_2$ (224.08): calcd. C 80.40, H 5.76; found C 80.15, H 5.59.

6aR,11aR*-Pterocarpan* (*rac*-**1a**):

A solution of *rac*-**1b** (30 mg) in benzene (6 ml) was stirred in the presence of *p*-toluenesulfonic acid (10 mg) for 6 h. The cooled mixture was washed with saturated $NaHCO_3$ solution. The organic layer was dried, concentrated, and purified by thin layer chromatography over silica gel (hexane–dichloromethane, 7:3) yielding *rac*-**1a** (22 mg, 74%), m.p. = 129–130 °C (EtOH) (lit [8]: m.p. 125–127 °C). – ^1H NMR (500.14 MHz): δ = 3.12–3.21 (m, 2H, 6a-H, 6ax-H), 4.28–4.33 (dd, 1H, 6eq-H, J = 5 Hz, J = 10 Hz), 5.55 (d, 1H, 11a-H, J = 6 Hz), 6.75–7.55 (m, 8H, Ar–H). – ^{13}C NMR (500.14 MHz): δ = 40.36 (C-6a), 66.34

(C-6), 77.61 (C-11a), 110.21 (C-10), 117.43 (C-4), 120.02 (C-7a), 120.95 (C-2), 121.74 (C-8), 124.72 (C-7), 127.05 (C-11b), 129.23 (C-9), 130.06 (C-3), 131.11 (C-1), 155.48 (C-4a), 159.3 (C-10a). – Analysis for $C_{15}H_{12}O_2$ (224.08): C 80.40, H 5.76; found C 80.30, H 5.58.

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