A Simple Conversion of 2′-Benzylxyflavanone to Pterocarpan

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

Pterocarpans possessing a 6a,11a-dihydro-6H-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, Nakani- shi 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].

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′-benzylxyflavanone (2b) was prepared from the readily available 2-hydroxyacetophenone and salicylaldehyde via 2-benzylxy-2′-hydroxychalcone as described [18]. Transformation of 2b to the trans-2,3-dihydrobenzo[b]-furan derivative 3b could be performed by Tl(NO3)3 in the presence of 70% perchloric acid in trimethyl orthoformate in 48% yield. Subsequent reduction of 3b by LiAlH4 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 SN2-type reaction. TLC monitoring of this reaction indicated transformation into a single product which was identified as 6aH,11aH-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 Hax and Has in cis-pterocarpan with respect to trans-pterocarpan...
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 occurring 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 pterocarpans 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 F254 (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 (MgSO₄) and concentrated in vacuo. ¹H NMR and ¹³C NMR spectra were recorded on Bruker WP-200 and Bruker Avance DRX 500 spectrometers in CDCl₃ 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*·3R*·2-(2-Benzoyloxyphenyl)·3-carboxymethoxy-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 aqueous saturated NaHCO₃ solution, and the product was extracted. 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, –CH₂OH), 4.95 (d, 2H, 2-H, J = 6 Hz), 7.35 (m, 13H, Ar–H). – HRMS: m/z = 360.1364 (calcd. for C₂₃H₂₀O₄: 360.1362).

25*·3R*·2-(2-Benzoyloxyphenyl)·3-hydroxymethyl-2,3-dihydrobenzo[b]furan (rac-4a)

To a stirred solution of LiAlH₄ (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 NH₄Cl solution and the product was extracted with ethyl acetate. The organic layer was dried and concentrated. The crude product was purified on a silica gel column (hexane–dichloromethane, 7:3) yielding rac-4a 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, –CH₂OH), 4.95 (d, 2H, –CH₂Ar), 5.75 (d, 1H, 2-H, J = 5 Hz), 6.65–7.35 (m, 13H, Ar–H). – HRMS: m/z = 332.1410 (calcd. for C₂₅H₂₀O₃: 332.1412).

25*·3S*·2-(2-Benzoyloxyphenyl)·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 ofaq. HCl (10%) was added dropwise to this mixture until neutral pH was reached. The product was extracted with ethyl acetate, washed with saturated NaHCO₃ 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, –CH₃), 3.6 (d, 1H, 3-H, J = 4.8 Hz), 4.0–4.27 (m, 2H, –CH₂O–), 4.98 (d, 2H, –CH₂Ar), 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 C₂₉H₂₆SO₄: 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, 6ax-H), 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), 6.7–7.05 (m, 4H, Ar–H), 7.06–7.22 (m, 3H, Ar–H), 7.37 (d, 1H, Ar–H). – ¹³C 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), 122.97 (C-8), 124.23 (C-6b), 127.1 (C-11b), 128.49 (C-1), 128.75 (C-7), 153.52 (C-11a), 161.21 (C-10a). – Analysis C₁₅H₁₂O₃ (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 NaHCO₃ 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). – ¹³C 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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