SYNTHESIS OF DEUTERIUM LABELED PTEROCARPANS

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Abstract: A simple synthesis of the deuterium labeled pterocarpans **3b-h** has been achieved by the stereocontrolled transformation of 2'-hydroxyisoflavone (**1**).

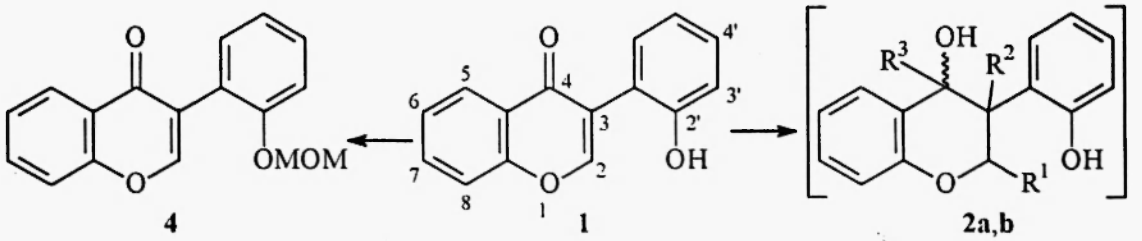
Introduction

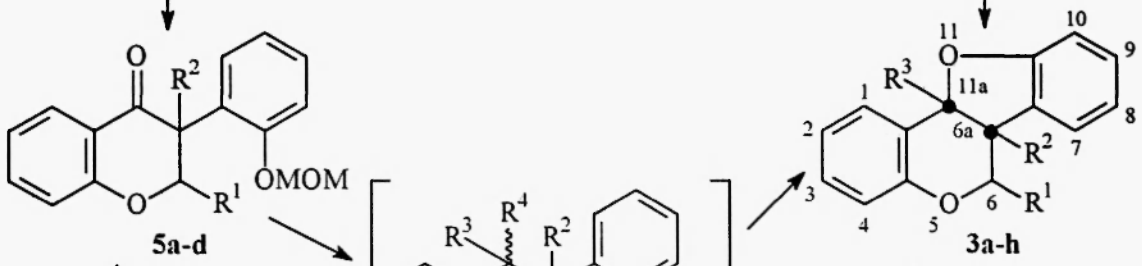
The *cis*-6a,11a-dihydro-6*H*-benzofuro[3,2-c][1] benzopyran ring system (**3a**) is the basic skeleton of the naturally occurring pterocarpans possessing antifungal (1), antibacterial (2) and anti snake-venom activity (3). Although the chemical and spectroscopic behaviour of this second largest group of the natural isoflavonoids has been investigated in detail (4,5), surprisingly only a few data have appeared about their mass spectrometric properties (6-9). In order to provide suitable products for a detailed study of fragmentation behaviour a series of deuterium labeled pterocarpans (**3b-h**) has been synthesized.

Results and Discussion

The synthetic approach to **3a** was based on the well-documented transformation of 2'-hydroxyisoflavone (**1**) into the stereoisomeric mixture of 2'-hydroxyisoflavan-4-ol (**2a**) by either sodium borohydride (10) or lithium aluminum hydride (11) followed by ring closure (**2a** → **3a**) upon treatment with boron trifluoride diethyl etherate (12) as depicted in Scheme 1. According to this procedure, **1** was transformed to **2b** by reduction with sodium borodeuteride in a mixture of tetrahydrofuran and deuteromethanol (CD_3OD) at room temperature, followed by cyclization furnishing **3b** in moderate yield (29%). The synthesis of further deuterated pterocarpans (**3c-h**) was achieved from 2'-methoxymethoxyisoflavone (**4**) prepared by a simple alkylation of **1** with methoxymethyl chloride in the presence of potassium carbonate in acetone. Previously, one of us reported (13) that isoflavones could be reduced very smoothly to the corresponding isoflavanones by DIBAH at low temperature (-60°C), and therefore it seemed to be obvious to attempt this

Scheme 1.





5	R^1	R^2
a	H	H
b	D	H
c	H	D
d	D	D

6	R^1	R^2	R^3	R^4
a	H	H	D	OH
b	D	H	D	OD
c	D	H	H	OH
d	H	D	H	OH
e	D	D	H	OH
f	H	D	D	OD

2,3	R^1	R^2	R^3
a	H	H	H
b	D	D	D
c	H	H	D
d	D	H	D
e	D	H	H
f	H	D	H
g	D	D	H
h	H	D	D

transformation using lithium aluminum hydride as well. As expected, reduction of **4** with lithium aluminum hydride in tetrahydrofuran at -60°C resulted in **5a** in 60% yield. Under the same conditions **5b** could also be obtained from **4** with lithium aluminum deuteride. To introduce a D-atom to C-3 of **5a** and **5b** (**5a** → **5c**, **5b** → **5d**) **5a** and **5b** were treated with sodium deutero methoxyde in deuteromethanol, followed by careful neutralization of the reaction mixture with deutero sulfuric acid at room temperature. Reduction of isoflavanones **5a** and **5b** with sodium borodeuteride in deuteromethanol gave a mixture of *cis/trans* **6a** and **6b** which, on treatment – without isolation – with $BF_3 \cdot OEt_2$, gave **3c** and **3d**. Thus, the corresponding benzylic carbocation intermediate could be generated from **6a** and **6b** with $BF_3 \cdot OEt_2$, with simultaneous cleavage of the methoxymethyl group at C-2' to result in a phenolic hydroxyl group, itself required for the ring

closure (**6a** → **3c**, **6b** → **3d**). Compounds **5b**, **5c**, and **5d** were similarly converted (*via* **6c**, **6d**, and **6e**) into **3e**, **3f**, and **3g**, respectively, by sodium borohydride treatment. Finally, reduction of **5c** with sodium borodeuteride in deuteromethanol resulted in a stereoisomeric mixture of **6f**, whose cyclization afforded **3h**. As shown in Table 1, the high-resolution mass spectral measurements unequivocally confirmed the correct elemental compositions of the molecular ions ($M^{+\bullet}$) of pterocarpans **3a-h**, whose structures were also supported by the ^{1}H NMR data. The mass spectrometric characteristics and fragmantation pathways of these compounds with the aid of metastable decomposition (CAD-MIKES) and high resolution measurements are published in a separate paper (14).

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The 360 MHz and the 200 MHz ^{1}H NMR spectra (marked with asterisk*) were recorded on a Bruker AM-360 and WP 200 SY spectrometers, respectively, using TMS as internal standard. The high resolution (R=15000) MS spectra were obtained with a VG-7035 spectrometer (70 eV, emission current 200 μA, 150°C, accelerating voltage 4 kV) using perfluorokerosene (PFK) as a reference compound by peak matching technique. Pre-coated silica gel plates (Kieselgel 60 F_{254}, 0.25 mm, Merck) were used for analytical and preparative TLC. Lithium aluminum deuteride (deuteration degree >99%), sodium borodeuteride (deuteration degree >99%) and deuteromethanol (deuteration degree >99%) were purchased from Sigma-Aldrich. 2'-Hydroxyisoflavone (**4**) was prepared according to a known method (11). For workup the solutions were dried ($MgSO_4$) and concentrated in *vacuo*. Deuteriation degree of the compounds **3d-h** and **5b-d** has been found to be higher than 97% based on the corresponding ^{1}H NMR-data.

2'-Methoxymethoxyisoflavone (4)

A mixture of **1** (750 mg, 3.15 mmol), methoxymethyl chloride (0.9 ml, 11 mmol), and anhydrous potassium carbonate (3 g) was stirred in dry acetone (70 ml) at 65°C for 4h. The reaction mixture was poured into water (150 ml), extracted with ethyl acetate (3x50 ml) and the extract was dried. Evaporation gave a semisolid product, which was purified by column chromatography (toluene/ethyl acetate, 20:3) on silica gel to afford **4** (460 mg, 52%) as a thick oil which solidified on standing at 5°C (m.p. 42°C). R_f=0.45 (toluene/ethyl acetate, 30:2). ^{1}H NMR ($CDCl_3$) *: δ=ppm: 3.43 (s, 3H, OMe), 5.95 (s, 2H, OCH_2OMe), 7.05-7.79 (m, 7H, Ar-H), 7.99 (s, 1H, 2-H), 7.99 (dd,

J=1.64 and 4.48 Hz, 1H, 5-H), MS (70 eV), m/z (%): 282 (52), 237 (14), 221 (84), 152 (18), 131 (20), 45 (100). HRMS: for $C_{17}H_{14}O_4$; calc. 282.0822, found 282.0897.

General procedure for the preparation of isoflavanones ***5a*** *and* ***5b***

To a stirred solution of **4** (1 mmol) in dry tetrahydrofuran at -55-60°C lithium aluminum hydride [deuteride] (10 mmol) was added in four portions. After transformation of **4**, monitored by TLC (toluene/ethyl acetate, 10:1), the mixture was carefully quenched with 2.5% aqueous hydrochloric acid and allowed to warm to room temperature. The product was extracted with dichloromethane, dried and after evaporation purified by preparative TLC (toluene/ethyl acetate, 10:1) to give **5a** [**5b**] as a thick colourless oil. R_f=0.50, **5a** [169 mg (60%)]. ^{1}H NMR (C_6D_6): δ=ppm: 4.17 (dd, $J_{2eq,3ax}$=5.4 Hz, $J_{2ax,3ax}$=11.8 Hz, 1H, H-3ax), 4.22 (dd, $J_{2ax,2eq}$=10.8 Hz, $J_{2eq,3ax}$=5.4 Hz, 1H, H-2eq), 4.49 (dd, $J_{2ax,3ax}$=11.8 Hz, $J_{2ax,2eq}$=10.8 Hz, 1H, H-2ax), 4.70 (dd, J=6.8 Hz, 2H, OCH_2O). MS (70 eV), m/z (%): 284 (45), 239 (32), 164 (95), 120 (32), 45 (100). **5b** [188 mg (66%)]. ^{1}H NMR (C_6D_6): 4.17 (dd, $J_{2eq,3ax}$=5.4 Hz, $J_{2ax,3ax}$=11.8 Hz, 1H, H-3ax), 4.22 (d, $J_{2eq,3ax}$=5.4 Hz, 0.5H, H-2eq), 4.49 (d, $J_{2ax,3ax}$=11.8 Hz, 0.5H, H-2ax), 4.70 (dd, J=6.8 Hz, 2H, OCH_2O). MS (70 eV), m/z (%): 285 (49), 240 (30), 165 (90), 120 (35), 45 (100).

General procedure for the preparation of isoflavanones ***5c*** *and* ***5d***

To a solution of **5a** or **5b** (0.1 mmol) in deuteromethanol (1 ml) 1N sodium deutero methoxide (0.15 mmol) was added at room temperature. After 15 min the reaction mixture was carefully quenched with diluted deutero sulfuric acid until neutral and then poured into water. The usual workup afforded **5c** (25 mg, 89%) and **5d** (22 mg, 78%) respectively. **5c**: 4.21 (d, J=10.9 Hz, 0.5H, H-2eq), 4.49 (d, J=10.9 Hz, 0.5H, H-2ax), 4.70 (dd, J=6.8 Hz, 2H, OCH_2O). MS (70 eV), m/z (%): 285 (64), 240 (39), 165 (95), 121 (30), 45 (100). **5d**: 4.19 (s, 0.5H, H-2eq), 4.47 (s, 0.5H, H-2ax), 4.70 (dd, J=6.8 Hz, 2H, OCH_2O). MS (70 eV), m/z (%): 286 (44), 241 (14), 165 (70), 121 (98), 45 (100).

General procedure for the preparation of pterocarpans ***3a-b***

A. To a stirred solution of **1** (0.52 mmol) in a 1:1 mixture of dry tetrahydrofuran (3 ml) and methanol [deuteromethanol] (4 ml) sodium borohydride [borodeuteride] (120 mg, 3.6 mmol) was added in 1h at room temperature. After 2h the residue was dissolved in water (10 ml) and carefully neutralized with diluted hydrochloric acid. The product (**2a** or **2b**) was extracted with dichloromethane and dried, and then it was treated with boron trifluoride diethyl etherate (0.1

ml) at room temperature. After 1.5h the reaction mixture was washed with 10% aqueous sodium carbonate (4x5 ml), then with water until neutral and dried. Evaporation gave a solid residue whose crystallization from methanol resulted in **3a** [51 mg (44%), m.p. 123-125°C, Lit. (11) 126-127°C] and **3b** [34 mg (29%), m.p. 131-132°C], respectively.

B. To a stirred solution of **5a-d** (0.1 mmol) in methanol [deuteromethanol] (2 ml) sodium borohydride [borodeuteride] (0.15 mmol) was added at room temperature. After transformation of the starting material, monitored by TLC (n-hexane/ethyl acetate, 5:1), the reaction mixture was treated with boron trifluoride diethyl etherate (1.5 ml) and then it was set aside overnight. The workup described above resulted in **3c** [19 mg (71%), m.p. 127-128°C], **3d** [14 mg (51%), m.p. 128-129°C], **3e** [12 mg (46%), m.p. 127-128°C], **3f** [14 mg (54%), m.p. 127-128°C], **3g** [20 mg (74%), m.p. 128-130°C] and **3h** [8 mg (32%), m.p. 129-130°C], respectively.

Table 1. Selected physical data of compounds

Comp.	Mol. Formula	Mol. Wt. Calculated Found	Characteristic ^{1}H NMR data in C_6D_6
3a	$C_{15}H_{12}O_2$	224,0837 224,0842	5.11 (d, $J_{11a,6a}$=7.3 Hz, 1H, H-11a), 3.85 (dd, $J_{6a,6eq}$=4.7 Hz, $J_{6eq,6ax}$=11.0 Hz, 1H, H-6eq), 3.38 (t, $J_{6a,6ax}$=$J_{6eq,6ax}$=11.0 Hz, 1H, H-6ax), 3.00 (m, 1H, H-6a)
3b	$C_{15}H_9D_3O_2$	227,1026 227,1035	3.80 (s, 0.5H, H-6eq); 3.38 (s, 0.5H, H-6ax)
3c	$C_{15}H_{11}DO_2$	225,0900 225,0904	3.85 (dd, $J_{6a,6eq}$=4.7 Hz, $J_{6a,6ax}$=11.0 Hz, 1H, H-6eq), 3.38 (t, $J_{6a,6ax}$=$J_{6eq,6ax}$=11.0 Hz, H-6ax), 3.01 (dd, $J_{6a,6eq}$=11.0 Hz, $J_{6a,6eq}$=4.7 Hz, 1H, H-6a)
3d	$C_{15}H_{11}DO_2$	225,0900 225,0905	3.85 (d, $J_{6a,6eq}$=4.7 Hz, 0.5H, H-6eq), 3.38 (d, $J_{6a,6ax}$=11.0 Hz, 0.5H, H-6ax), 3.01 (dd, $J_{6a,6ax}$=11.0 Hz, $J_{6a,6eq}$=4.7 Hz, 1H, H-6a)
3e	$C_{15}H_{10}D_2O_2$	226,0963 226,0970	5.11 (d, $J_{11a,6a}$=7.3 Hz, 1H, H-11a), 3.85 (d, $J_{6a,6eq}$=4.7 Hz, 0.5H, H-6eq), 3.38 (d, $J_{6a,6ax}$=11.0 Hz, 0.5H, H-6ax), 3.01 (dd, $J_{6a,6ax}$=11.0 Hz, $J_{6a,6eq}$=4.7 Hz, 1H, H-6a)
3f	$C_{15}H_{11}DO_2$	225,0900 225,0808	5.11 (s, 1H, H-11a), 3.85 (d, $J_{6a,6eq}$=11.0 Hz, 1H, H-6eq), 3.38 (d, $J_{6a,6eq}$=11.0 Hz, 1H, H-6eq)
3g	$C_{15}H_{10}D_2O_2$	226,0963 226,0967	3.85 (d, $J_{6ax,6eq}$=11.0 Hz, 1H, H-6eq), 3.38 (d, $J_{6ax,6eq}$=11 Hz, 1H, H-6eq)
3h	$C_{15}H_{10}D_2O_2$	226,0963 226,0966	5.11 (s, 1H, H-11a), 3.85 (s, 0.5H, H-6eq), 3.38 (s, 0.5H, H-6ax)

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