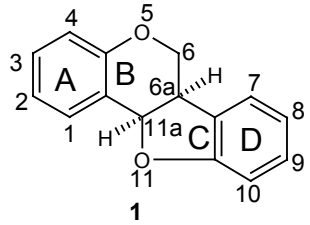
1. Introduction and the aim of the dissertation

Pterocarpans possessing a 6a,11a-dihydro-6*H*-benzofuro[3,2-*c*][1]benzopyran skeleton, constitute the second largest group of natural isoflavonoids. Many of them are phytoalexins produced in plants during infection by fungi, bacteria or viruses. Some pterocarpans also possess significant oestrogenic activity and several of them have been reported to inhibit HIV-1 in cell cultures. Furthermore, Nakanishi and co-workers have demonstrated that two representatives of these natural products are active against snake and spider venoms. Due to this wide variety of biological effects these natural products recently are of great interest. Although pterocarpans contain two chiral centers, only the configurations of 6a*R*,11a*R* and 6a*S*,11a*S* are sterically possible. Dextrorotatory and racemic pterocarpans are known in nature, and most of the chiral compounds have 6a*R*,11a*R* absolute configuration. Computational studies agree in that the *trans*-fused *B/C*-ring system (6a*R*,11a*S* and 6a*S*,11a*R*) is much less favorable than the *cis*-fused one, observed in all natural pterocarpans.



1

My research program was directed toward the synthesis of the basic pterocarpan skeleton and natural pterocarpans as well. Among the variety of synthetic routes to pterocarpans, only few methods permitted enantioselective access to this class of compounds so far. The aim of my work was to develop synthetic methods, permitting efficient synthesis of pterocarpans in racemic and enantiomeric pure form as well.

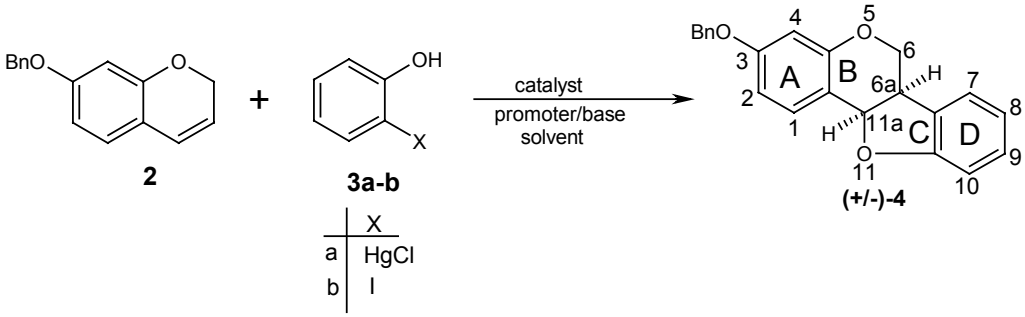
2. Applied methods

In the course of our work, macro, semi-micro and micro preparative organic methods have been used. The reactions were monitored by thin-layer chromatography. The isolation and purification of the products were carried out by crystallization or by column chromatography. The prepared products were identified and characterized by H-NMR, C-NMR, MS, HPLC, CD, X-ray and elemental analysis.

3. New results of the dissertation

3.1. Synthesis of pterocarpans by Heck-oxyarylation reaction

In 1976, Horino and Inoue obtained racemic pterocarpans (**1**) by the Heck-oxyarylation of 2*H*-chromenes using 2-chloromercuryphenols (**3a**), in the presence of lithium-chloride and palladium(II)-chloride. Although this method is a very efficient and widely used one-step procedure for the synthesis of naturally occurring pterocarpans, it still suffers from limitations, such as the preparation of toxic 2-chloromercuryphenol derivatives upon mercuration of the corresponding phenols and the need of a stoichiometric quantity of the expensive palladium(II)-chloride. While studying the literature of Heck-reaction we have set our sights on the extension of this method for the more available 2-iodophenols. We expected from this method that catalytic amount of the palladium(II) salt would be enough in this reaction. We also expected that by using the palladium compound in combination with optically active ligands, an asymmetric version of this reaction can be developed.



Scheme 1. The synthesis of 3-benzyloxypterocarpan by Heck oxyarylation reaction

The Heck-reaction of 7-benzyloxy-2*H*-chromene (**2**) with 2-iodophenol (**3b**), resulting in racemic 3-benzyloxypterocarpan, has been systematically studied in the presence of various catalyst systems formed by palladium chloride or acetate (with or without tertiary phosphine) in combination with an inorganic base and different solvents. In order to compare the efficiency of our results with those of the traditional Heck-oxyarylation process, racemic **4** was also prepared from **2** and **3a** under the conditions described by Horino and Inoue (entry 1, table 1.). During our experiments, we have found that the mercuric compound could be replaced by the most available 2-iodophenols prepared by simple iodination of the corresponding phenols. Interestingly, no transformation of **3b** could be detected under the Horino's conditions (entry 2). If silver carbonate as a base was also present, the reaction resulted in racemic **4** in the same yield (entry 3) as found under the conditions given in entry 1. Although the decrease of the amount of the palladium salt to 10 mol % has a significant influence on the reaction rate, its

turnover number (TON) has valuably increased (entry 4). Comparison of entries 4 and 5 clearly reveals the influence of the phosphine ligand. In order to study the role of the phosphine compound, the oxyarylation was performed with different biphosphine derivatives as well (entries 6 - 9).

Table 1.

Entry	X	Catalyst (mol % Pd)	Promoter[a] (mol %)	Base (mol %)	Solvent[b]	Reac. time (h)	%	TON[c]
1	HgCl	$PdCl_2$ (100)	LiCl (200)	–	A	14	36	0.36
2	I	$PdCl_2$ (100)	LiCl (200)	–	A	24	–	–
3	I	$PdCl_2$ (100)	LiCl (200)	Ag_2CO_3 (300)	A	8	34	0.33
4	I	$Pd(OAc)_2$ (10)	LiCl (20)	Ag_2CO_3 (300)	A	36	27	2.7
5	I	$Pd(OAc)_2$ (10)	Ph_3P (20)	Ag_2CO_3 (300)	A	14	42	4.18
6	I	$Pd(OAc)_2$ (10)	dppe (10)	Ag_2CO_3 (300)	A	22	49	4.87
7	I	$Pd(OAc)_2$ (10)	dppp (10)	Ag_2CO_3 (300)	A	20	44	4.38
8	I	$Pd(OAc)_2$ (10)	dppb (10)	Ag_2CO_3 (300)	A	24	16	1.59
9	I	$Pd(OAc)_2$ (10)	dppb (10)	Ag_2CO_3 (300)	B	24	24	2.39
10	I	$Pd(Ph_3P)_2Cl_2$ (10)	–	Ag_2CO_3 (300) $CaCO_3$ (600)	A	26	33	3.28

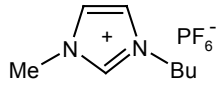
a) 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenyphosphino)propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb); b) acetone (A), THF (B); c) mmolproduct/mmol Pd

The coupling of **3b** in the presence of bis(diphenylphosphino)ethane (dppe) resulted racemic **4** in the highest yield (entry 6). Elongation of the carbon chain with two methylene groups resulted in a drastic decrease of the TON (entry 8). This effect could be somewhat moderated by the exchange of the solvent (entry 9). Finally **3b** was also subjected to Heck-oxyarylation with **2** using dichlorobis-(triphenylphosphine)palladium(II) as a highly stable form of palladium(II) but racemic **4** could be obtained only in a moderate yield (entry 10).

Although we have developed a more efficient procedure for the synthesis of pterocarpans than that presented earlier by Horino and Inoue, unfortunately, we were not able to obtain better than 50% yields in these transformations. We suppose that the active palladium catalyst looses its ligands during the catalytic cycle forming the inactive black palladium. It is interesting to note that among the wide variety of solvents used in the Heck-reactions, acetone and to a certain extent tetrahydrofurane proved to be suitable for this type of reaction in our case. Since

the solvent had an essential effect in the oxyarylation reaction, the determination of its role required a more intense study.

Several recent publications describe the Heck coupling of aryl halides with alkenes in room temperature ionic liquids, showing exellent yields. These recyclable "green" solvents not only allow relatively easy product isolation and catalyst recovery but often improve the yields of synthetic reactions through their interaction with the metal complex catalyst. It seemed reasonable to examine the above mentioned Heck-oxyarylation of 2*H*-chromene (**2**) with 2-iodophenol (**3b**) in this type of solvents as well.

[bmim][PF_6]= 

5

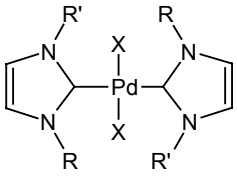
The ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) (**5**) proved to be a suitable alternative solvent for the transformation of **2** at 100°C (table 2.). Not only could be the reaction time drastically shortened, but also the amount of palladium catalyst could be decreased to 1 mol % resulting in a significant increase of the TON of the catalyst (entry 2). It was remarkably that not only the presence of the silver carbonate as base was indispensable, but its amount had an important effect in the transformation (entry 3). It was also found that the anion of the ionic liquid has a great influence in the oxyarylation reaction.

Table 2.

Entry	Catalyst (mol%Pd)	PPh_3 (mol%)	Base (mol%)	Solvent	Temp. (C°)	Reac. time (h)	%	TON[a]
1	$Pd(OAc)_2$ (10)	20	$AgCO_3$ (300)	[bmim][PF_6]	100	3	33	3.3
2	$Pd(OAc)_2$ (1)	2	Ag_2CO_3 (300)	[bmim][PF_6]	100	2	32	32
3	$Pd(OAc)_2$ (10)	20	Ag_2CO_3 (125)	[bmim][PF_6]	100	14	-	-
4	$Pd(OAc)_2$ (10)	20	Ag_2CO_3 (300)	[bmim][Cl]	100	24	-	-
5	$Pd(C_6H_5CN)_2Cl_2$ (10)	20	Ag_2CO_3 (300)	[bmim][PF_6]	100	3	69	6.9
6	$Pd(C_6H_5CN)_2Cl_2$ (1)	2	Ag_2CO_3 (300)	[bmim][PF_6]	100	4	45	45
7	$Pd(OAc)_2$ (10)	20	Ag_2CO_3 (300)	[bmim][PF_6]	100	3	13	1.3
8	$Pd(OAc)_2$ (10)	-	Ag_2CO_3 (300)	[bmim][PF_6]	100	4	31	3.1
9	$PdCl_2$ (10)	-	Ag_2CO_3 (300)	[bmim][PF_6]	100	18	28	2.8

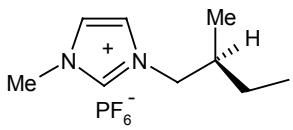
a) mmol product/mmol Pd

When 1-butyl-3-methylimidazolium chloride was used instead ofhexafluorophosphate, no transformation could be observed (entry 4). We suppose that the halogen anion of the ionic liquid reacts with the silver carbonate and this way the base looses its effect during the reaction. It was interesting to observe that the use of the halogen containing catalyst bis(benzonitrile)-dichloro-palladium provided the highest catalytic activity (entries 5 and 6). It was also notable that the ionic liquid after work-up of the reaction could be recycled in a new transformation resulting in a modest yield of the racemic pterocarpan (entry 7). In accordance with recently published data, the Heck-oxyarylation could be performed without the addition of phosphine ligands. On the bases of these results it seemed reasonable to suppose that the imidazolium ion can react with the palladium salt to form an N-heterocyclic carbene complex (**6**) *via* deprotonation at C-2 of the imidazolium skeleton.



6

X=Cl, Br, I, OAc

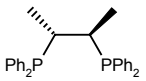


11

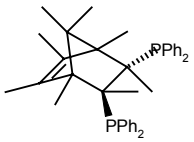
The generated carbene complex was also found to be active in the transformation of **2** giving the racemic **4 (**entry 8). We have found that the palladium chloride could be used without promoters in catalytic amount in the ionic liquid [bmim][PF_6] giving moderate yield of racemic **4** (entry 9). This observation was another proof for the formation of the above mentioned carbene complex.

Since the phosphine compound of the palladium(II) salt generates the palladium(0) catalyst, we supposed that by using chiral, optically active phosphine ligands with the palladium(II) catalyst, the palladium(0) compound generated in situ could lead to optically active pterocarpans through the oxyaryalation reaction. Several optically active chiral phosphine ligands, such as 2*R*,3*R*(+)diphenylphosphinobutane (CHIRAPHOS) (**7**), NORPHOS (*trans*-2*S*,3*S*-bis(diphenylphosphino)bicyclo[2.2.1]-hept-5-ene) (**8**), TRIPHOS (*R*-1-[2'-diphenylphosphino]phenyl-methoxyethane (**9**), and *R*(+)BINAP (bis-diphenyl-fosphinobinaphtyl) (**10**) were used, and unfortunately, small selectivities have been obtained in these transformations. In the case of (+)*R*-BINAP (**10**) the preferred enantiomer was the 6a*R*,11a*R*(-)-3-benzyloxypterocarpan [(-)-**4**] (entry 1, table 3), while in the presence of ligands **7**, **8**, **9**, the 6a*S*,11a*S*(+)-3-benzyloxypterocarpan [(+)-**4**] have been formed (entries 3, 4 and 5).

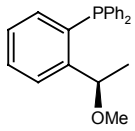
Surprisingly, the optically active palladium(II) salt (+)*R*-bis(diphenylphosphino)palladium-dichloride induced no selectivity in the transformation of **2 (**entry 2). Since the oxyarylation



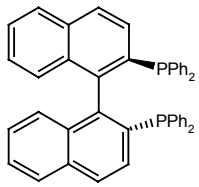
(+)-7



(+)-8



(+)-9



(+)-10

reaction could be effected in ionic liquid in the absence of a phosphine ligand *via* the palladium-carbene complex, we supposed that using a chiral, optically active ionic liquid optically active **4** could be obtained. The optically active ionic liquid **11** have been prepared starting from N-methylimidazol and *S*(+)-1-bromo-2-methylpropane.

Table 3.

Entry	Catalyst	Ligand	Solvent[a]	Reac. time (h)	Temp. (°C)	ee%	Conf. 6a,11a
1	$Pd(OAc)_2$	R(+)BINAP	A	28	60	6	*R,R*
2	$Pd[R(+)BINAP]Cl_2$	-	A	46	60	-	-
3	$Pd(C_6H_5CN)_2Cl_2$	2R,3R(+)dppb	B	23	100	8	*S,S*
4	$Pd(OAc)_2$	NORPHOS	B	3	100	10	*S,S*
5	$Pd(OAc)_2$	TRIPHOS	B	3	100	5	*S,S*
6	$Pd(OAc)_2$	-	C	4	100	4	*R,R*
7	$Pd(C_6H_5CN)_2Cl_2$	(+)α-pinén	A	2	100	-	-

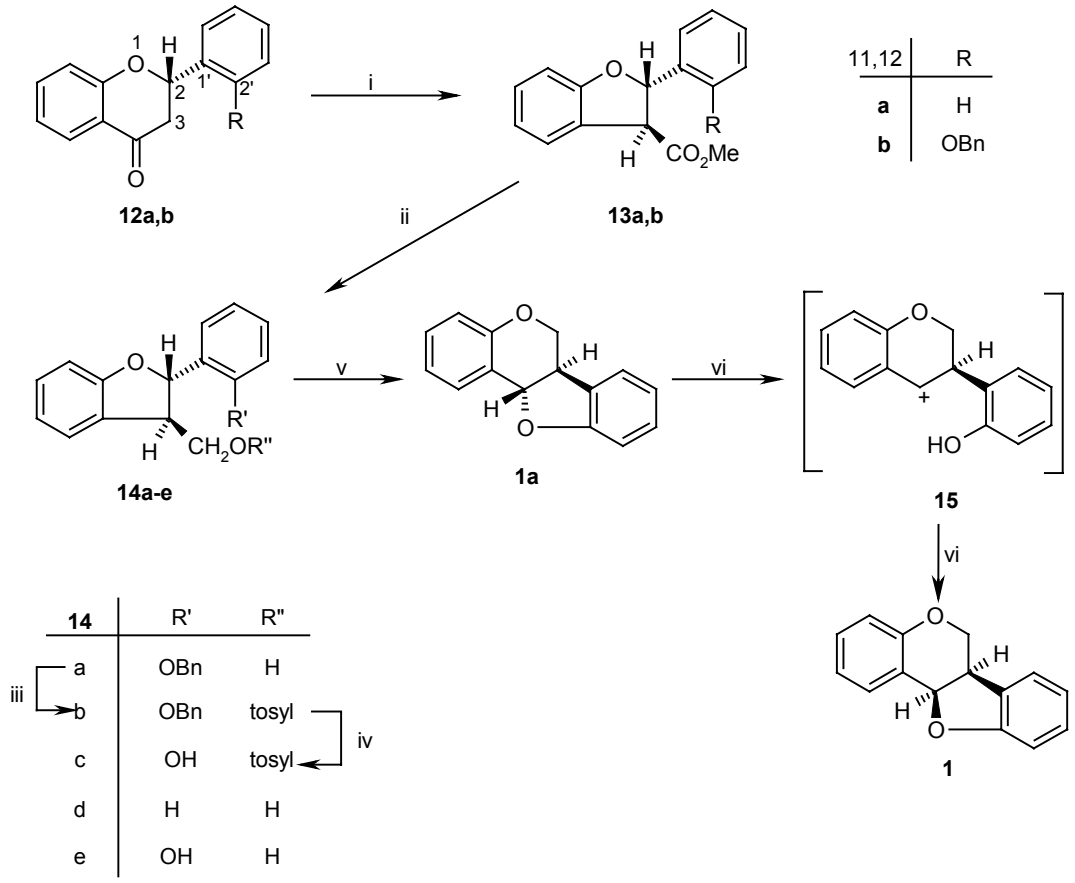
A=THF, B=[bmim][PF_6]; C=[bmim*][PF_6]

When this ionic liquid (**11**) was used as solvent, small selectivity has also been achieved (entry 6). Interestingly, when the optically active α(+)-pinene was used in the reaction the racemic **4** has been obtained in the highest yield (71%), (entry 7). The small asymmetric induction found in the oxyarylation of **2** with **3b** allow us to suppose that its mechanism is not the same as described for the classical Heck reaction. The determination of the exact mechanism for this transformation needs more experimental work which is now in progress in our laboratory.

3.2. Synthesis of pterocarpans by ring-contraction reaction of 2'-benzyloxyflavanone

Recently we have published that the ring-contraction of (-)-2*S*-flavanone (**12a**) 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 (+)-2*S*,3*S* *trans*-2-phenyl-3-carbomethoxy-2,3-dihydrobenzo[*b*]furan **13a** as shown in Scheme 2. This compound can also be transformed into (+)-2*S*,3*S*-*trans*-2-phenyl-3-hydroxymethyl-2,3-dihydrobenzo[*b*]furan **14d** in high yield. Therefore, we supposed that in the presence of an oxygen function at C-2' of **12a,** a simple three steps sequence *via* **14c** would allow the construction of the pterocarpan skeleton with *trans* B/C-ring junction (**1a**). Isomerisation of **1a** might then lead to the *cis* isomer **(1**) as a result of its higher thermodynamic stability as predicted by computational studies.

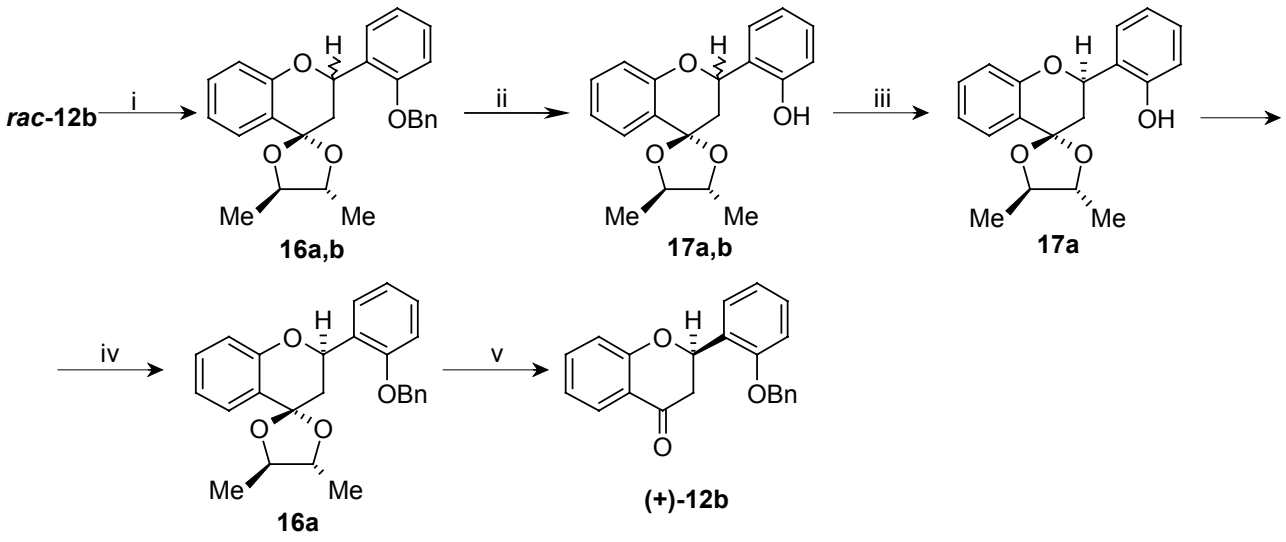


Scheme 2. i) $PhI(OAc)_2$ or $Tl(NO_3)_3/HC(OMe)_3$, H^+, 20°C; ii) $LiAlH_4$/anh.. ether, 20°C; iii) pTsCl/pyridine, 20°C; iv) Pd(C)/H_2, MeOH; v) NaOMe/MeOH, 20°C; vi) pTosOH/benzene, Δ

The starting racemic 2'-benzyloxyflavanone (**12b**) was prepared from the readily available 2-hydroxyacetophenone and salicylaldehyde *via* 2-benzyloxy-2'-hydroxychalcone. Transformation of **12b** to the *trans*-2,3-dihydrobenzo[*b*]furan derivative **13b** could be performed by $Tl(NO_3)_3$ in the presence of 70% perchloric acid in trimethyl orthoformate. Subsequent reduction of **13b** by $LiAlH_4$ gave the primary alcohol **14a** in high yield which was then converted smoothly to the tosylate **14b**. Debenzylation of **14b** by catalytic hydrogenation

afforded the phenolic derivative **14c** which was treated with 1N 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 6aH,11aH-*trans*-pterocarpan **1a** by comparison of its NMR data with those of the *cis*-isomer. The remarkably large coupling constant *J* (6a-H,11a-H) (13.4 Hz) was 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 are due to ring currents as a result of different spatial relationship of ring D in the two epimers **1** and **1a**. Quantum chemical calculations indicated that the *trans*-fused B/C-ring of the pterocarpan skeleton is much preferred to the observed *cis*-isomer. Therefore, we assumed that **1a** might be isomerized into **1** by proton catalyzed ring-opening reaction *via* a carbocation intermediate **15**. Accordingly, treatment of **1a** in the presence of p-toluenesulfonic acid in benzene at 80 °C led to *cis*-pterocarpan (**1**) in good yield (Scheme 2). In fact this transformation resulted in a mixture of 1:1a (ca. 8.5:1 respectively, detected by HPLC). Crystallization of the crude product from methanol gave pure **1**.

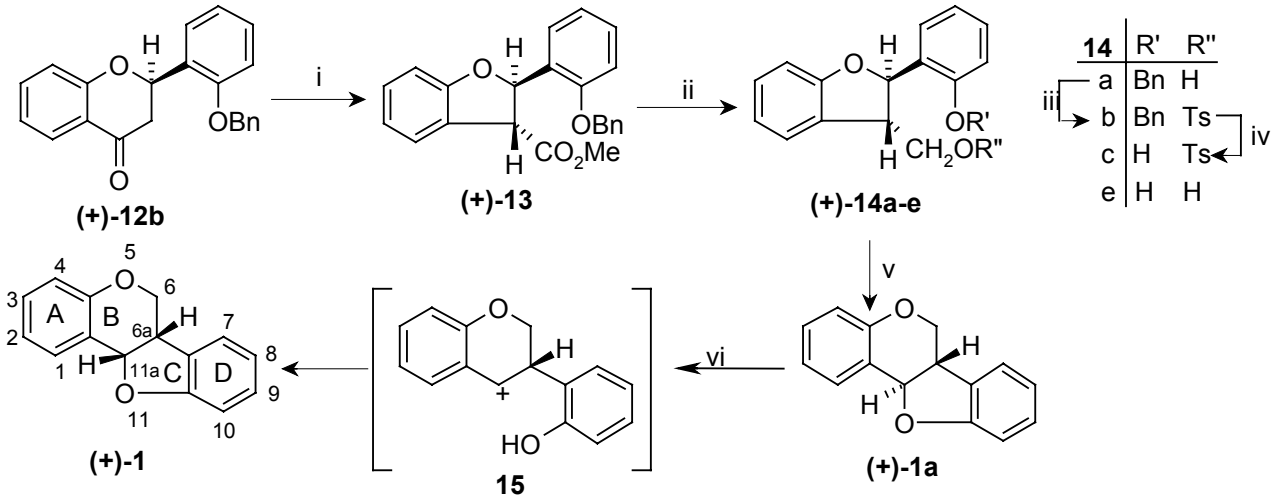
Our method presented above offers a new approach toward the enantioselective synthesis of peterocarpans, starting from the corresponding optically pure 2'-benzyloxyflavanone derivative, *via* **14d**. In order to achieve the synthesis of **1** in optically pure form, the starting material of the synthesis, the 2'-benzyloxyflavanone (*rac*-**12b**), had to be resolved. For this purpose, the readily available chiral resolving agent, (2*R*,3*R*)-butanediol has been utilized.



Scheme 3. (i) 2*R*,3*R*-butanediol, pTosOH, toluene, reflux; (ii) H_2 / Pd, MeOH, (iii) recrystallization from hexane:benzene 15:1 (iv) BnCl, K_2CO_3, acetone, reflux; (v) 10% HCl, acetone.

The diastereomeric ketals (**16a,b**) were prepared with acid catalysis but they could not be separated by either chromatography or crystallization (Scheme 3). Thus, the benzyl protective

groups of the diastereomers were removed and crystallization from hexane/benzene 15:1 gave the diastereomer **17a** whose 2*R* absolute configuration was determined by X-ray analysis. The benzylation of **17a** and removal of the chiral auxiliary afforded the optically active flavanone (+)-**12b** (ee=77%) whose enantiomeric purity was determined by HPLC on a Chiralcel-OD column using a mixture of hexane/isopropanol 9:1 as eluent. Starting from (+)-**12b**, the first enantioselective synthesis of the *trans*-6a*S*,*11*a*R*-pterocarpan (**1**) could be performed by the above presented synthetic method (Scheme 2). The ring contraction [(+)-**12b**→(+)-**13**] retained the *R* absolute configuration at C-2 and it also defined the *R* configuration of the new stereogenic center at C-3 in the *trans*-dihydrobenzo[b]furan skeleton.



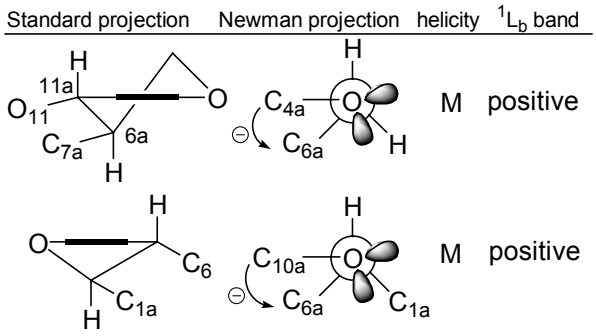
Scheme 4. (i) TTN/TMOF, H^+, 20°C; (ii) $LiAlH_4$ / anh. ether, 20°C; (iii) p-TosCl / pyridine, 20°C; (iv) Pd(C) / H_2, MeOH; (v) NaOMe / MeOH, 20°C; (vi) p-TsOH / benzene, reflux.

The reduction (**13**→**14a**), introduction of the tosyl leaving group (**14a**→**14b**), deprotection (**14b**→**14c**) and ring closure (**14c**→**1b**) did not influence the stereogenic centers and hence the obtained *trans*-pterocarpan had 6a*S*,11a*R* configuration. The *trans*-pterocarpan (**1a**) being thermodinamically less stable than the *cis*-pterocarpan (**1**) could be converted to **1** (Scheme 4). After crystallization of the crude product from methanol, the obtained crystals have a specific rotation of +151.3 (c=1.5, $CHCl_3$, ee=77%, determined by HPLC).

In summary the extension of this new method would permit the enantioselective synthesis of other natural pterocarpans starting from the corresponding optically active 2'-benzyloxyflavanones.

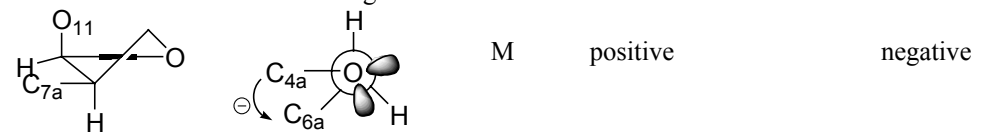
3. 3. Chiroptical properties of pterocarpans

Using HPLC-CD on-line technique, the chiroptical properties of pterocarpans have been studied. We have determined that from CD point of view, the chromophore system of pterocarpans can be considered the sum of a chromane and a 2,3-dihydrobenzo[b]furan chromophore, since exciton coupled interaction between these two chromophores can not be observed in pterocarpans. The relationship between the absolute conformation of the heteroring and the sign of the ^1L_b band is presented in Scheme 5. The CD spectra of *trans*-(+)-6a*S*,11a*R*-pterocarpan [(+)-**1b**] unambiguously proved this relationship.

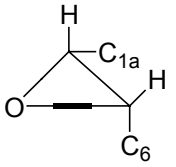
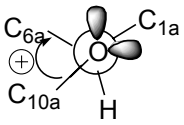


Scheme 5. Standard and Newman projections of *trans*-6aS,*11aR*-pterocarpan **1a** showing the relationship between the helicity of the heterorings and the signs of the ^1L_b band CDs.

In the naturally occurring pterocarpans the heterorings are annulated *cis*, the C-6, C-6a carbon-carbon bond and the C-11a, O-11 carbon-oxygen bond is *pseudoaxially* oriented.



Scheme 6. The chiroptical contribution of the chromane chromophore in the *cisz*-6a*S*,11a*S*-pterocarpan

Standard projction	Newman projection with torsional angles	Helicity	^1L_b-band CD	
			2. chiral sphere contribution	3. chiral sphere
		P	negative	pozitive

Scheme 7. The chiroptical contribution of the 2,3-dihydrobenzo[b]furan chromphor in the *cisz*-6a*S*,11a*S*-pterocarpan

According to the CD spectra of *cis*-(+)-6a*S*,11a*S*-pterocarpan the 3. chiral sphere contribution resulted in the sign inversion of the ^1L_b band (Scheme 6 and 7).

List of publications

1) **L. Kiss**, S. Antus, *A Convenient Synthesis of Pterocarpans*
Heterocyclic Communications, **2000**, *6*, 309-314
2) Sz. Szarvas, Gy. Szókán, M. Hollósi, **L. Kiss**, S. Antus, *Determination of the Absolute Configuration of Synthetic Pterocarpans by Chiral HPLC Using On-Line CD Detection*
Enantiomer, **2001**, *5*, 535-543
3) S. Antus, T. Kurtán, L. Juhász, **L. Kiss**, M. Hollósi, Zs. Májer, *Chiroptical Properties of 2,3-Dihydrobenzo[b]furan and Chromane Chromophores in Naturally O-Heterocycles*
Chirality, **2001**, *8*, 493-506
4) **L. Kiss**, G. Papp, F. Joó, S. Antus, *Efficient Synthesis of Pterocarpans by Heck Oxyarylation in Ionic Liquids*
Heterocyclic Communications, **2001**, *7*, 417-420
5) **L. Kiss**, L. Szilágyi, S. Antus, *A Simple Conversion of 2'-Benzyloxyflavanone to Pterocarpan*
Zeitschrift für Naturforschung B, accepted for publication
6) **L. Kiss**, T. Kurtán, S. Antus, A. Bényei, *The First Enantioselective Synthesis of* (+)-6a*S*,11a*S*-*Pterocarpan*
Tetrahedron Letters, submitted for publication

Lectures and posters

1) **L. Kiss**, G. Papp, F. Joó, S. Antus, *Efficient Synthesis of Pterocarpans by Heck Oxyarylation in Ionic Liquids*
Hungarian COST Chemistry Day, Budapest, 2000, October (P)
2) **L. Kiss**, S. Antus, Syntheis of *Pterokarpans by Heck Oxyarylation Reaction*
Annual Meeting of the Flavonoid Chemistry Committe, Budakalász, 2000, December (E)
3) **L. Kiss**, S. Antus, *Enantioselective Synthesis of Pterocarpans of Potential Biological Activity*
Hungarian, German, Italian, Polish Joint Meeting on Medicinal Chemistry, Budapest, 2001, September (P)
4) **L. Kiss**, S. Antus, *Enantioselective Synthesis of Pterocarpans*
Annual Meeting of the Flavonoid Chemistry Committe, Budapest, 2001, December (E)