SYNTHESIS AND CHIROPTICAL PROPORTIES OF 2,3-DIHYDROBENZO[B]FURAN-TYPE COMPOUNDS

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1. Introduction

Herbs have been used to cure several diseases for centuries, however the structures of biological active molecules have not been known exactly in several cases. In our days according to the strict rules of dispensatory, study of structure and structure-activity relationship of naturally occurring compounds is one of the most important field of organic and pharmacutical chemistry.

Neolignans possessing the 2,3-dihydrobenzo[*b*]furan skeleton are a class of naturally occurring heterocyclic compounds with hepatoprotective, hormone blocking, antibacterial, antifungal, plant growth regulator and antioxidant activity.

The biosynthesis of these compounds is carried out in several steps starting from tyrosin or phenylalanine, which are converted into the corresponding *p*-propenyl-phenols by tyrosin or phenylalanine ammonia-lyase. These phenols are transformed into the basic ring system of 2,3-dihdrobenzo[b]furan-types neolignans – *via* their resonance stabilized radicals – by peroxidase enzyme.

Until now the practical synthetic routes to this structure were based on this biomimetic process by chemical oxidants [Ag(I)-, Tl(III)-, Pb(IV)-, Fe(III)-salts] or electrochemical methodes.

In continuation of our investigations on the synthesis and structure elucidation of naturally occurring O-heterocycles, at Organic Chemistry Department of University of Debrecen, our aim was to develop a new and environmentally friendly synthesis of 2,3-dihydrobenzo[b]furan-types neolignans using hypervalent iodine compounds. Beside the study of the enantioselective synthesis and the enzyme catalised kinetic resolution of 2-aryl-3-hydroxymetyl-2,3-dihydrobenzo[b]furans our goal was to investigate the chiroptical proporties of these compounds.

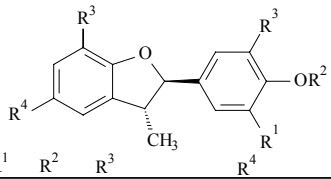
2. Experimental

In our work we used micro- semimicro and macro methods of modern organic chemistry. Progress of reactions and purity of starting materials were checked by TLC, and reaction mixtures were purified by classical or *flash* columnchromatograpy, or preparative TLC. Products were identified by classical (elemental analysis, melting piont, optical rotation) and modern analitical methodes (HPLC, CD-HPLC, MS, ^{1}H-,^{13}C-NMR)

3.Results

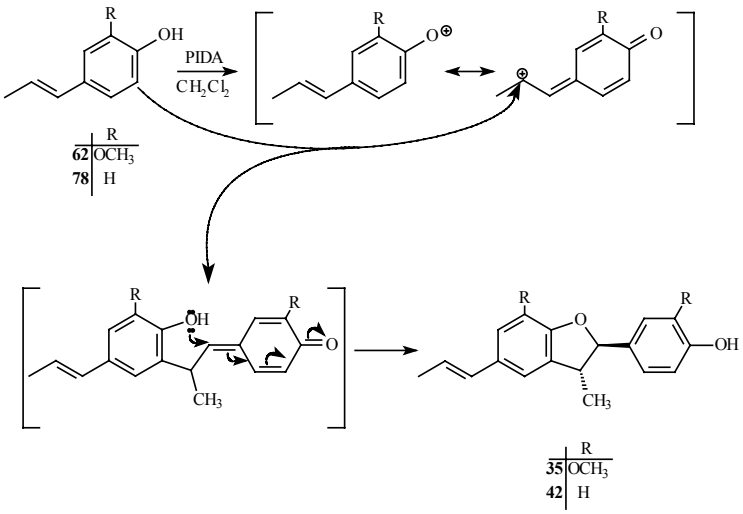
3.1. Synthesis of 2-aryl-2,3-dihydrobenzo[b]furan-type neolignans with biological activity using hipervalent iodine compounds

Hattori and co-workers isolated four 2,3-dihydrobenzo[b]furan-type neolignans [dehydrodiisoeugenol (**35**), fragnasol-A (**37**), –B (**38**), and –C (**39**)] from *Myristica fragrans* having biological activity against S*treptococcus mutans*. Licarin-D (**41**) – isolated from *Magnolia kachirachirai* by Ito *et al.* – were found to be a good inhibitor of rat liver acyl transferase. Drust and co-workers isolated conocarpan (**42**), and decurrenal (**43**) from P*iper decurrens*, which showed a moderate biological activity against mosquito's and European corn borer's larvas.



	R^1	R^2	R^3	R^4
35	H	H	OCH_3	(*E*) -CH=CH-CH_3
37	H	H	OCH_3	*eritro*-CH(OCH_3)CH(OH)-CH_3
38	H	H	OCH_3	-CH_2-CH_2-OH
39	H	CH_3	OCH_3	(*E*)-CH=CH-CH_2OH
41	H	CH_3	OCH_3	(*E*)-CH=CH-CH_3
42	H	H	H	(*E*)-CH=CH-CH_3
43	H	H	H	CHO

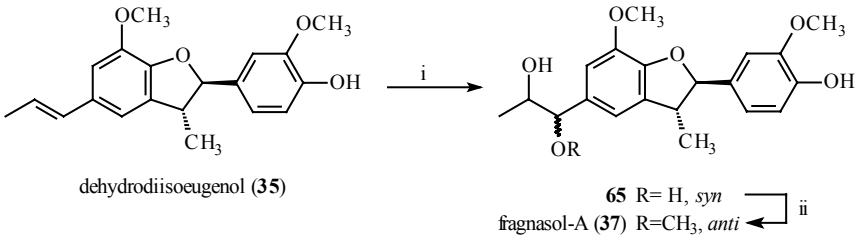
The total synthesis of these natural products was carried out from commercially available *p*-propenyl phenols (**62**, **78**) using hypervalent iodine reagent. The phenoxenium ion – generated from **62** and **78** with IDA in dry dichloromethane – presumably reacts smoothly with **62** and **78** - to form dehydrodiisogenol (**35**) and conocarpan (**42**).



	R
62	OCH_3
78	H

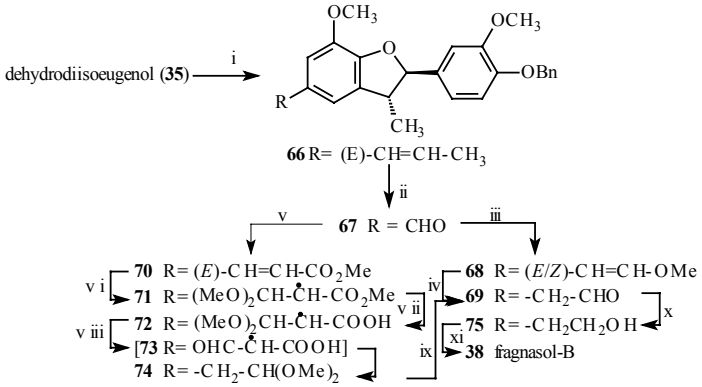
	R
35	OCH_3
42	H

The synthesis of fragnasol-A (**37**) could be achieved in two steps by stereospecific modification of unsaturated side chain of dehydrodiisoeugenol (**35**).



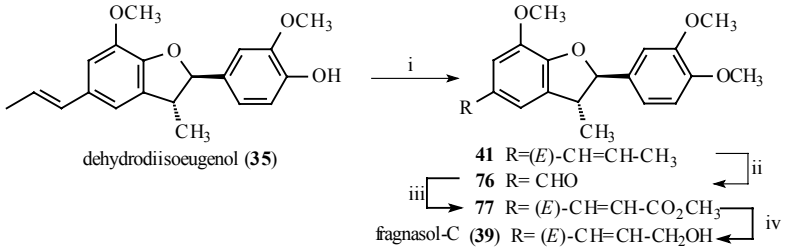
i) OsO_4, dry. dioxane, 25°C; ii) $BF_3 \bullet OEt_2$, dry. methanol, 25°C.

The key step of the synthesis of fragnasol-B was the conversion of (*E*)-propenyl side-chain of **35** into a β-hydroxyethyl chain. This transformation could be achieved on two different routes (**67→68→69→75**; **67→70→71→72→74→75**) after the protection of the hydroxy group of **35** and oxidative cleavage of its side-chain (**35→66→67**).



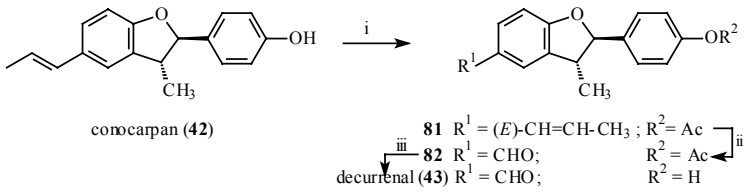
i) BnCl, K_2CO_3, DMF, 100°C; ii) OsO_4, $NaIO_4$, dioxane-H_2O; iii) $MOMPPh_3Cl$, KOtBu, THF, 0°C; iv) 10% HCl, CH_2Cl_2 25°C; v) $MeOOCCH=PPh_3$, benzene, reflux; vi) TTN, MeOH, reflux; vii) KOH, MeOH, 60°C; viii) 10% HCl, MeOH, 60°C; ix) 10% HCl, CH_2Cl_2 25°C; x) $NaBH_4$, MeOH, 25°C; xi) H_2, Pd, MeOH.

Fragnasol-C (**39**) was prepared from dehidrodiisoeugenol (**35**) *via* licarin-D (**41**) in three steps procedure (**41→76→77→39**).



i) $(CH_3)_2SO_4$, K_2CO_3, acetone, 60°C; ii) OsO_4, $NaIO_4$, dioxane-H_2O; iii) $MeOOCCH=PPh_3$, benzene, reflux; vi) $LiAlH_4$, THF, 25°C.

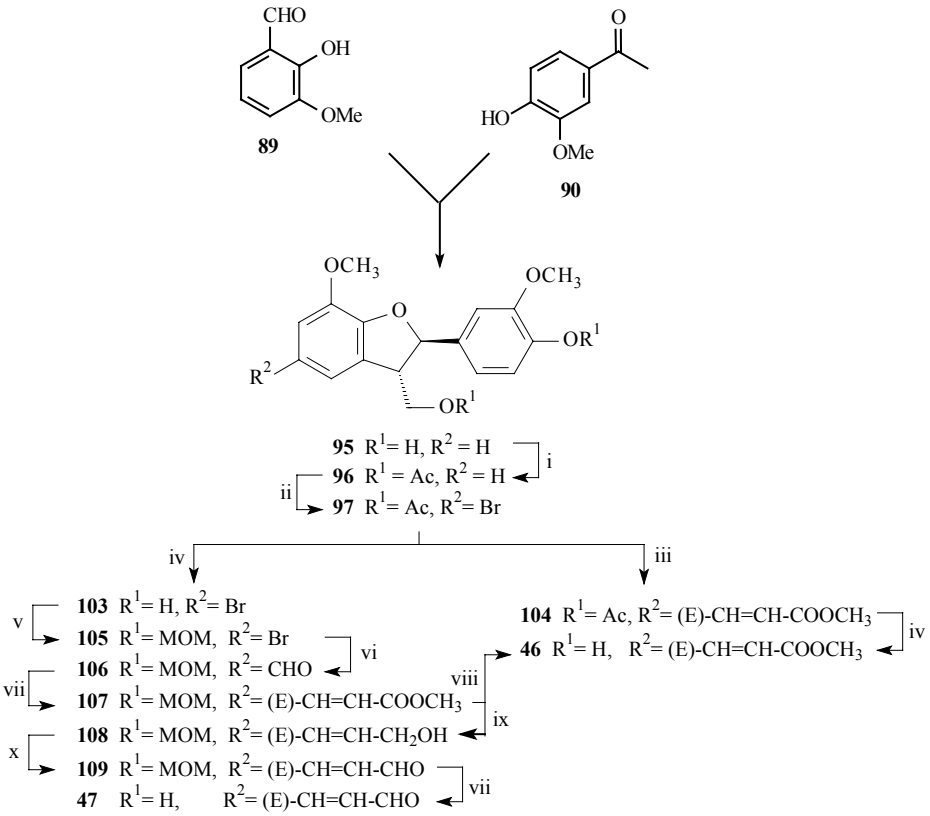
Total synthesis of decurrenal (**43**) was carried out from conocarpan (**42**) by oxidative cleavage ($OsO_4/NaIO_4$) of its propenyl side-chain after acetylation of the phenolic hydroxyl group (**42** → **81** → **82** → **43**).



i) Ac_2O/dry pyridine, rt.; ii) OsO_4, $NaIO_4$/dry dioxane; iii) NaOMe/dry MeOH.

*3.2. New synthesis of neolignan component of Zizyphus jujuba (**46**) and balanophonin* (**47**).

In the synthesis of neolignan component of *Zizyphus jujuba* (**46**) and balanophonin (**47**) we developed a new approach to the synthesis of 2,3-dihydrobenzo[b]furan-type neolignans differing in the side-chain (R^2) at C-5. The strategy of our methode was based on the well-documented synthetic availability of racemic **95** from the commercially available starting materials *o*-vanillin (**89**) and acetovanillone (**90**). Bromination of the acethyl derivative of **95** (**96**) furnished **97** in good yield, whose structure was independently proved by an eight-step synthesis, and the regioselectivity of bromination (**96→97**) was demonstrated by quantum chemical calculations.



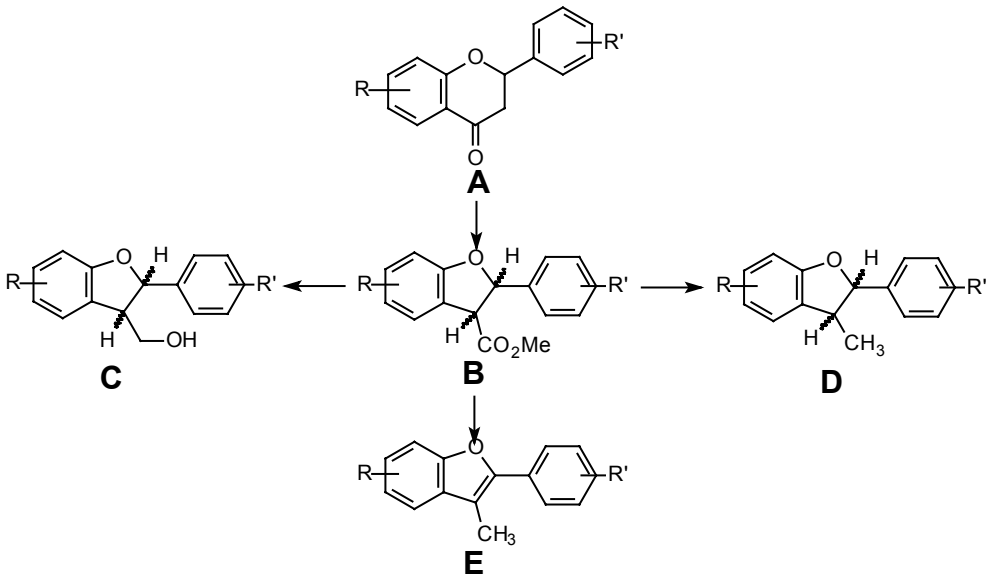
i) Ac_2O. dry. pyridine; ii) Br_2, AcOH; iii) CH_2=$CHCOOCH_3$, $Pd(OAc)_2$, PPh_3, Et_3N, 100 °C; iv) NaOMe, MeOH; v) MOMCl, iPr_2EtN, CH_2Cl_2; vi) DMF, BuLi, THF, -78 °C; vii) Ph_3P=$CHCOOCH_3$, benzene; viii) 5% HCl, MeOH; ix) $LiAlH_4$, Et_2O; x) MnO_2, CH_2Cl_2;

The brominated derivatives (**97**) could be converted into the neolignan component of *Zizyphus jujuba* (**46**) in two ways. First, **97** was allowed to react with methyl acrylate under the conditions of Heck reaction (**97→104→46**), in the other route the unsaturated side chain was introduced by Wittig reaction (**106→107→46**) after the Br → CHO exchange

(**97→103→105→106**). Balanophonin (**47**) was prepared from **107** in a three-step procedure (**107→108→109→47**).

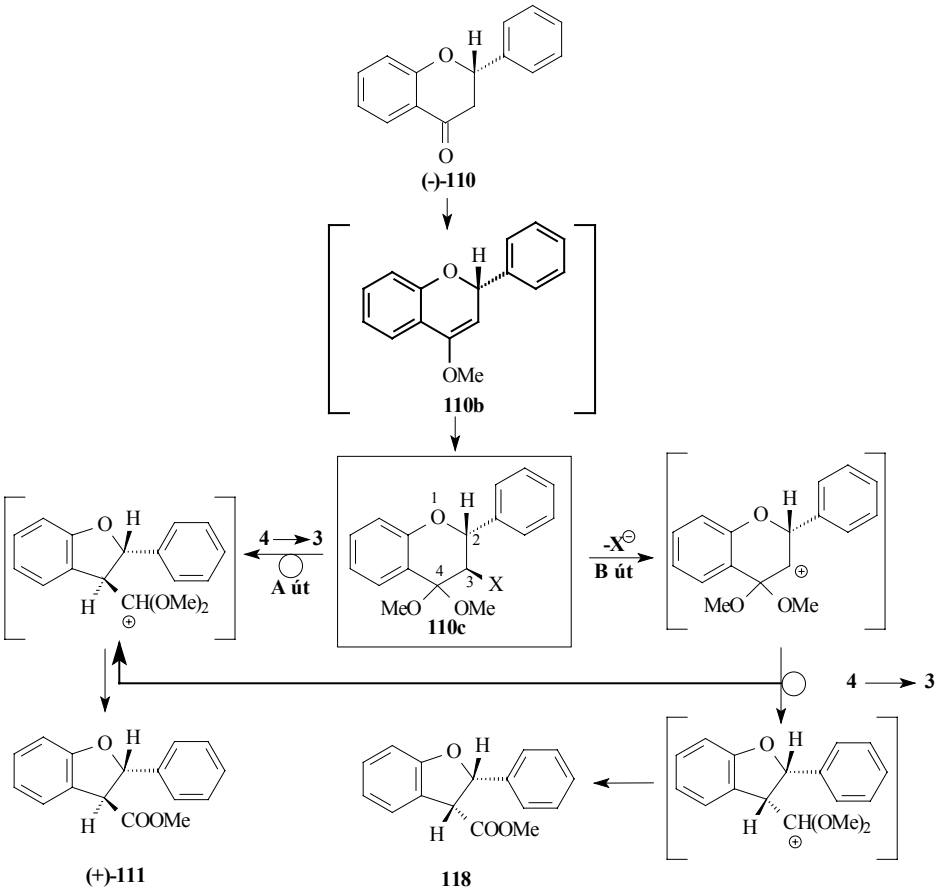
3.3. Transformation of flavanon into the 2,3-dihydrobenzo[b]furan derivatives

We supposed, on the basis of the literature, to be a chemical correlation between the flavanons (A) and the 2-aryl-benzo[b]furan-type derivatives (B – E).



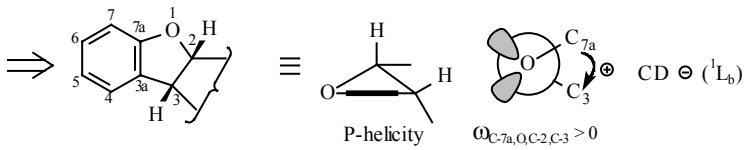
Although a plausible mechanism of this transformation was proposed in the literature, but neither the stereochemistry of the 1,2-aryl migration (**A** → **B**) nor the relative configuration of the stereogenic centers of dihidrobenzo[b]furans (*cis* or *trans*) is clarified in the literature. In order to establish these important details of the above transformation, we decided to investigate the oxidation of racemic and leavorotatory flavanones [(*rac*-**110**, (–)-2*S*-**110**] with PIDA – H_2SO_4 in TMOF. We proved on the basis of NMR evidence (^{1}H-, ^{13}C-NMR and NOE), and by chemical correlation that this reaction – in contrast to the idea of Khanna and co-workers – furnished *trans* ester (B=**111**; R = R' = H; 2H, 3H *trans*), which could be converted into the C – D type dihydrobenzo[b]furan derivatives by simple reactions.

Stereoselectivity of addition of electrophilic iodine(III) reagent at C–3 of the enol ether (**110b**) followed by its rearrangement into **111** could be proved by the transformation of (–)-2*S*-flavanone [(–)-2*S*-**110**]. The optical purity of these compounds [(–)-**110**, (+)-**111**, (+)-**113**, (–)-**115**] were determined by HPLC. These results clearly showed that both the addition of IDA to the enol ether (**110b** →**110c**) and the aryl migration occurred in a stereoselective manner controlled by the configuration of C-2, therefore the mechanism of the ring contraction is best interpreted by **route A** instead of **route B.**



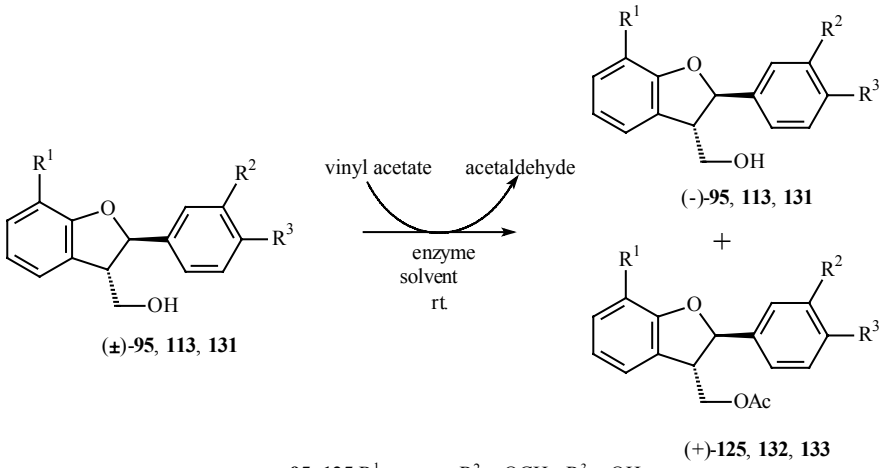
3.4. Lipase Catalised Kinetic Resolution and Absolute Configuration of trans-2-aryl-3-hydroxymethyl-2,3-dihydrobenzo[b]furans

Chiroptical proporties of 2,3-dihydrobenzo[b]furan derivatives have been studied in our researchgroup for years. On the basis of these investigations a helicity rule – *P/M helicity* of the heterocyclic ring leads to a *negative/positive CD* within the ^1L_b band – could be defined, but this rule can only be used for the conformational assignment of 2,3-dihydrobenzo[b]furan-type compounds having no substituents at the fused benzene ring.



In our work we investigated the validity of the former helicity rule among the neolignans possessing the flexible 2-aryl-3-hydroxymetyl-2,3-dyhydrobenzo[b]furan skeleton [(–)-**95**, **113**, **131**] .

The model compounds (–)-**95**, (–)-**113**, (–)-**131**, (+)-**125**, (+)-**132** and (+)-**133** were prepared by lipase catalysed kinetic resolution using different lipases, and by stereocontrolled ring contraction of (–)-2*S*-flavanone [(–)-2*S*-**110**→(+)-2S,3R-**113**→(–)-2S,3S-**115**]



(±)-**95**, **113**, **131**

(-)-**95**, **113**, **131**

(+)-**125**, **132**, **133**

95, **125** $R^1 = OCH_3$, $R^2 = OCH_3$, $R^3 = OH$
131, **133** $R^1 = H$, $R^2 = OCH_3$, $R^3 = OH$
113, **132** $R^1 = R^2 = R^3$ H

The enantiomer preferences of *Pseudomonas cepacea* was controlled by kinetic resolution of racemic **113** and **131**.

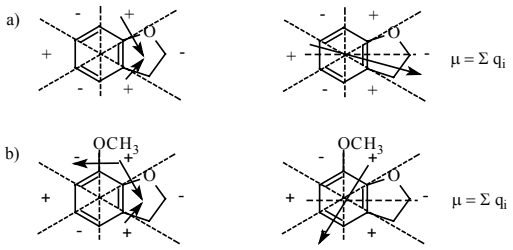
We found that the *Pseudomonas cepacea* lipase always acetylated the dextrarotatory enantiomers of (±)-**95**, (±)-**113**, (±)-**131** possessing 2*S*,3*R* absolute configuration much faster than their levorotatory antipode with 2*R*,3*S*.

The ^1L_b band CD data and the helicity of these flexible compounds are tabulated in the following table:

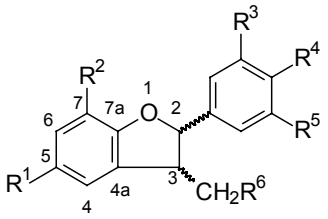
	^1L_b	*Helicity*	*absolute configuration*
(–)-95	–	M	2R,3S
(–)-113	+	M	2R,3S
(–)-131	+	M	2R,3S

As it can be concluded from the former table, the contribution of phenyl group at C-2 to the CD is negligible compared to that of the 2,3-dihidrobenzo[b]furan chromophore, thus the substitution of C-2 phenyl ring does not influence significantly the ^1L_b band CD either [(–)-**113** and (–)-**131**], so the original helicity rule is valid (*M helicity* of the heterocyclic ring leads to a *positive CD* within the ^1L_b band). On the other hand, the substitution of fused aromatic ring at the C-7 position by a methoxy group changes the sign of the ^1L_b band, which could be explained by making "spectroscopic moments" (q_i) for achiral substituents of benzene chromophore which have been investigated by Platt and Petruska. The sum of spectroscopic

moments of the substituents gives the eletric transition moment vector ($\mu \approx Q = \Sigma q_i$), whose rotation leads to a sign inversion.



Application of our above mentioned helicity rule led to the revision of the absolute configuration assignment of several neolignans (**35**, **136**–**138**), and on the basis of our data a general chiroptical rule for the 2,3-dihydrobenzo[b]furan-type neolignans could be established.



	R^1	R^2	R^3	R^4	R^5	R^6
35	(E)-CH=CH–CH_3	OMe	OMe	OH	H	H
136	(E)-CH=CH–CH_3	OMe	H	OH	H	H
137	(E)-CH=CH–CH_3	OMe	OCH_2O		H	H
138	(E)-CH=CH–CH_2OH	OMe	OMe	OMe	OMe	OH

	^1L_b *CD*	*Helicity*	**Published configuration**	**Revised configuration**
35	+	P	2R;3R	2S;3S
136	+	P	2R;3R	2S;3S
137	–	M	2S;3S	2R;3R
138	+	P	2R;3S	2S;3R

Revised configuration of naturally occurring neooignans

C–5	*C–7*	^1L_b*-CD*	*Helicity*
H	H	– / +	P / M
H	OCH_3	+ /–	P / M
saturated side-chain	H	– / +	P / M
α,β-unsaturated side-chain	H	+ /–	P / M
α,β-unsaturated side-chain	OCH_3	+ /–	P / M

Genaral helicity rule for 2,3-dihydrobenzo[b]furan-type compounds

Lectures and posters:

1. **L. Juhász**, S. Antus : Experiments on the synthesis of 2-aryl-2,3-dihydrobenzo[b]furan-type compounds with optical activity. Symposium of Flavanoid committee of Hungarian Academy of Sciences; Budapest (1995), (L) bizottság
2. **L. Juhász**, S. Antus : Experiments on the synthesis of 2-aryl-2,3-dihydrobenzo[b]furan-type compounds with optical activity. Chemist's conference; Siófok (1997), (P)
3. **L. Juhász**, L. Kürti, S. Antus : Simple Synthesis of Benzofuranoid Neolignans from *Myristica fragrans*. 7th Blue Danube Symposium on Heterocyclic Chemistry; Eger (1998), (P)
4. **L. Juhász**, L. Kürti, S. Antus: Simple Synthesis of Benzofuranoid Neolignans from *Myristica fragrans*. Symposium of Flavanoid committee of Hungarian Academy of Sciences; Debrecen (1998), (L)
5. **L. Juhász**, J. Visy, M. Simonyi, K. Krohn, S. Antus: Lipase Catalysed Enantioselective Synthesis of 2,3-Dihydrobenzo[*b*]furan-type Neolignans. 8th Blue Danube Symposium on Heterocyclic Chemistry; Bled / Slovenia (2000), (P)
6. S. Antus, E. Baitz-Gács, Z. Dinya, Á. Gottsegen, **L. Juhász**, M. Simonyi, J. Visy, H. Wagner: Synthesis and Absolute Configuration of Naturally Occurring Dihydrobenzo[b]furan-type Neolignans of Potential Biological Activity. 3rd International Congress on Phytomedicine; München (2000), (P).
7. **L. Juhász**, S. Antus, J. Visy, F. Zsila, M. Simonyi: The study of ring contraction of flavanone. A new route to the synthesis of neolignans possessing 2,3-dihydrobenzo[b]furan skeleton. Symposium of Flavanoid Committee of Hungarian Academy of Sciences; Budakalász, (2000), (L)

Közlemények listája:

1. **L. Juhász**, L. Kürti, S. Antus; Simple Synthesis of Benzofuranoid Neolignans from *Myristica fragrans. J.A.C.S. J. Nat. Prod.*, **63**, 866–870 (2000).
2. **L. Juhász**, Z. Dinya, T. Gunda and S. Antus; A New Approach for the Synthesis of Naturally Occurring Dihydrobenzo[b]furan-type Neolignans of Potential Biological Activity. *Tetrahedron Lett.*, **41,** 2491-2494 (2000).
3. S. Antus, E. Baitz-Gács, Z. Dinya, Á. Gottsegen, **L. Juhász**, M. Simonyi, J. Visy, H. Wagner: Synthesis and Absolute Configuration of Naturally Occuring

Dihydrobenzo[b]furan-type Neolignans of Potential Biological Activity. *Phytomedicine Supp II*., **7**, 90 (2000).

4. **L. Juhász**, Z. Dinya, S. Antus, and T. Gunda; A New Synthesis of Two Naturally Occurring Dihydrobenzo[*b*]furan-Type Neolignans of Potential Biological Activity. *Z. Naturforsch B*, **56b**, *6*, 554-559 (2001).
5. S. Antus, T Kurtán, **L. Juhász**, L. Kiss, M. Hollósi and Zs. Major; Chiroptical Properties of 2,3-Dihydrobenzo[b]furan and Chromane Chromophores in Naturally Occurring O-heterocycles. *Chirality*, **13** (8), 493-506 (2001).
6. **L. Juhász**, J. Visy, M. Simonyi, L. Szilágyi, S. Antus; New Insights into the Mechanism of Hypervalent Iodine Oxidation of Flavanones. *Tetrahedron* (in press.).
7. **L. Juhász**, J. Visy, M. Simonyi, K. Krohn, S. Antus; Lipase–Catalised Kinetic Resolution and Absolute Configuration of *trans*-2-Phenyl-3-Hydroxymethyl-2,3-Dihydro-benzo[b]furans. (in press.).