Ph. D. Thesis

New rearrangements of aromatic hydroxycompounds

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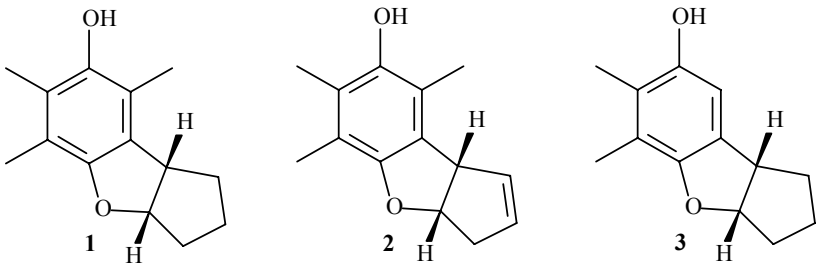
Introduction and aims

The enzyme 5- lipoxygenase directs the biotransformation of polyunsaturated fatty acids leading to leukotrienes. Since leukotrienes are important mediators in several diseases including asthma, arthritis, and psoriasis, inhibition of this enzyme would represent therapeutic intervention in these deseases. We elaborated new methods for the preparation of novel lipoxygenase inhibitors and evaluated the struture-activity relationship. In connection with this research we discovered novel sigmatropic rearrangements of in situ generated aryl-alkenyl ethers.

Many research group of the world produced new selective 5-lipoxygenase enzyme inhibitors in the last years. One of them operate in the Budapest University of Technology and Economics Institute for Organic Chemistry led by Prof. Lajos Novák. This group had prepared a series of 5-lipoxygenase inhibitors (Scheme 1). The most important step in the formation of these compounds was [1,3]- or [3,3]-sigmatropic rearrangement. In my Ph. D. work, I wanted to explore the scope and generality of these new sigmatropic rearrangements, and prepare novel inhibitors of 5-lipoxygenase enzyme.



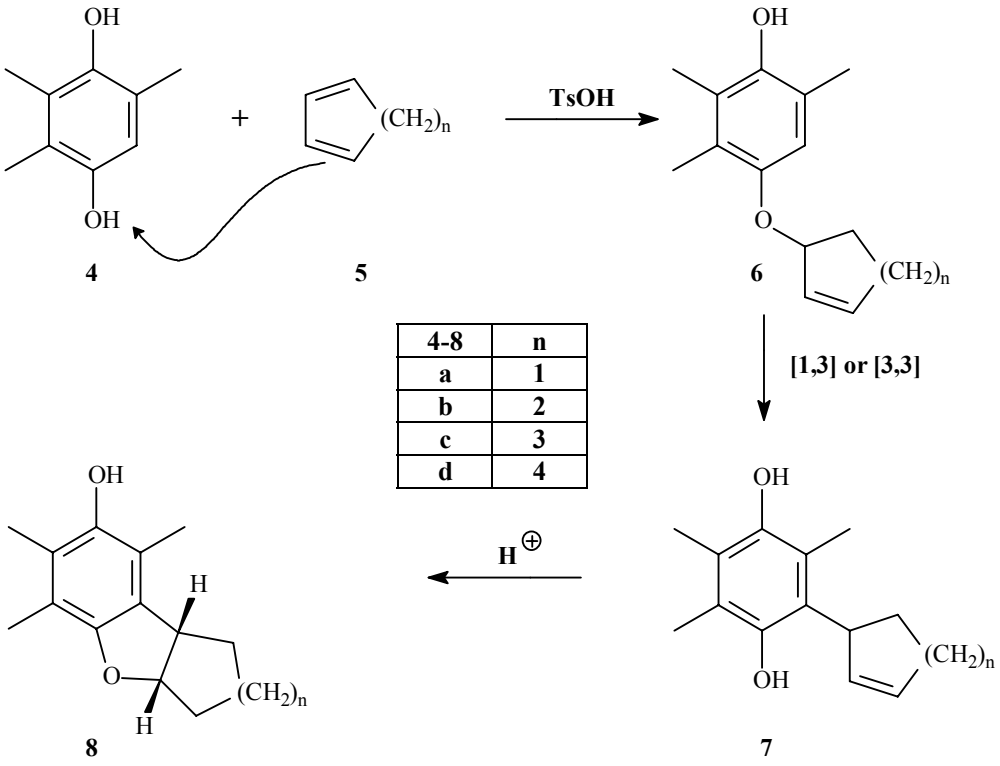
Scheme 1

Contribution to knowledge

I studied acid-catalysed reaction of hydroquinone derivatives with cikloalka-1,3-dienes together with cikloalka-1,2-diols. I also studied *p*-toluenesulfonic acid-catalysed reaction of naphtols and cikloalkane-1,3-dienes. We prepared new tricyclic compounds and proposed mechanism for these new reactions.

Reaction of trimethylhydroquinone with cycloalkane-1,3-dienes

The reaction between trimethylhydroquinone (**4**) and cikloalkane-1,3-dienes (**5**) in the presence of catalytic amounts of *p*-toluenesulfonic acid afforded (Scheme 2) cycloalkanobenzofuran derivatives (**8**). Initial acid-catalysed formation of ethers (**6**), followed by [1,3]- or [3,3]-rearrangements, afforded hydroquinones (**7**), which then underwent acid-catalysed cyclization to yield cycloalkanobenzofurans (**8**). These compounds were prepared by one-pot reaction in good yields.

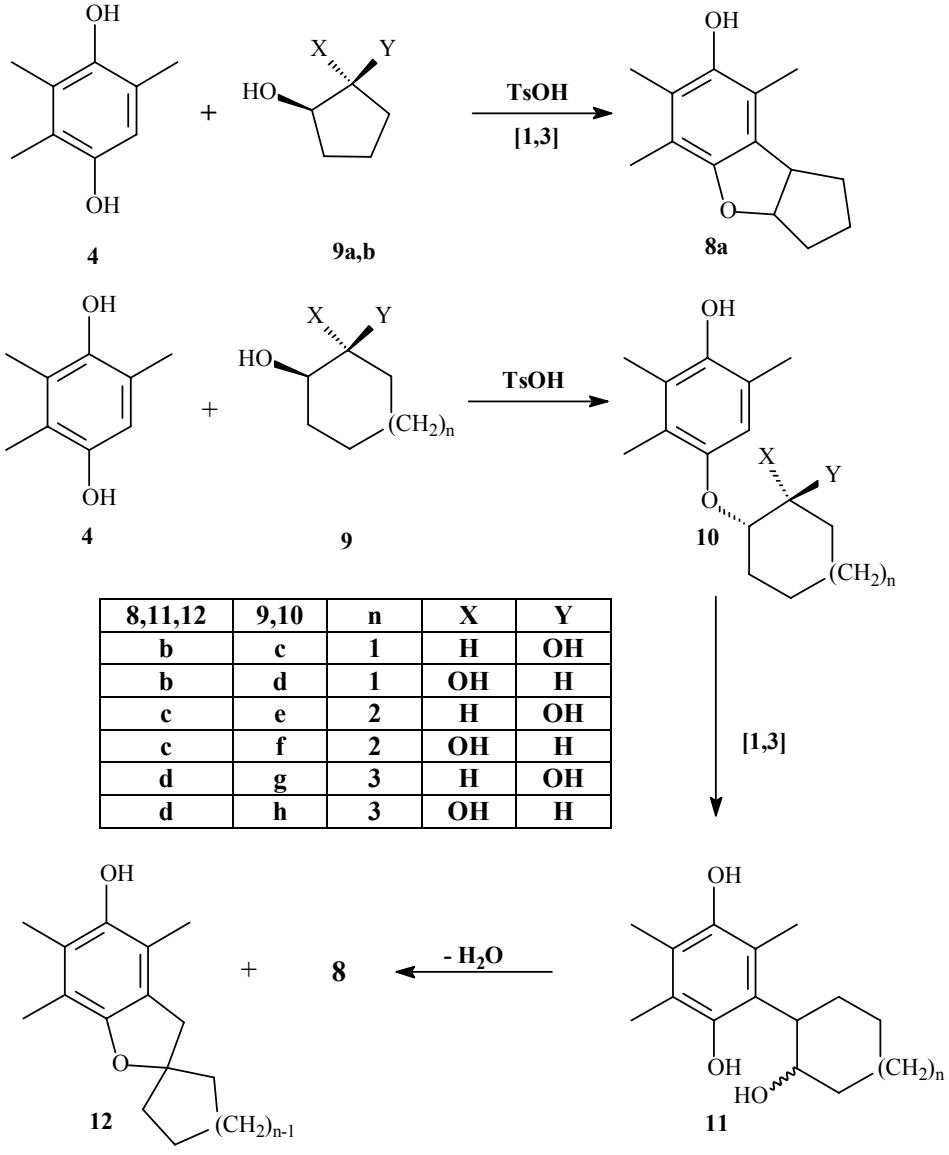


4-8	n
a	1
b	2
c	3
d	4

Scheme 2

Reaction of trimethylhydroquinone with cycloalkane-1,2-diols

Acid-catalysed reaction of trimethylhydroquinone (**4**) with cycloalka-1,3-dienes (**5**) afforded (Scheme 3.) cycloalkanobenzofurans (**8**). Under more forceful condition, the reaction between **4** and cyclopentane-1,2-diols (**9a,b**) also furnished the corresponding cyclopentanobenzofuran (**8a**). However, reaction of **4** with cycloalkane-1,2-diols (**9**) having more than five carbons in the ring led to the formation of two compounds. Besides the expected cycloalkanobenzofurans (**8**), *spiro*-compounds (**12**) were isolated as major products.

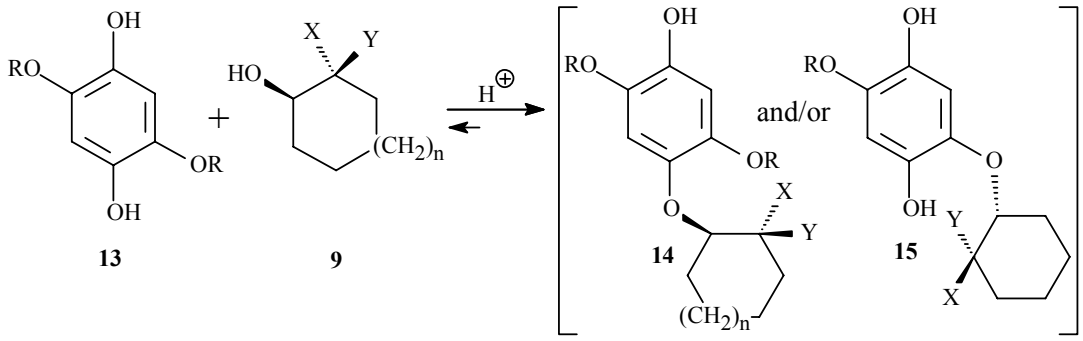


8,11,12	9,10	n	X	Y
b	c	1	H	OH
b	d	1	OH	H
c	e	2	H	OH
c	f	2	OH	H
d	g	3	H	OH
d	h	3	OH	H

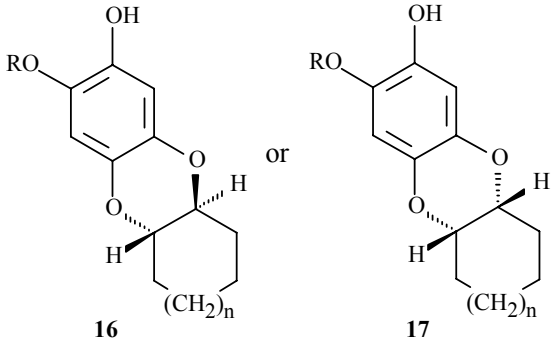
Scheme 3

Reaction of 2,5-dialkoxyhydroquinone with cycloalkane-1,2-diols

Benzo[1,4]dioxine derivatives (**16** and **17**) were prepared in one operation from 2,5-dialkoxyhydroquinone (**13**) and cycloalkane-1,2-diol (**9**). The new method is efficient in terms of ready availability of the starting material and high stereospecificity. Besides the new synthesis we could extend our recently discovered reactions - hydroquinone derivatives and diol (**9**) affording cycloalkanobenzofurans and *spiro*-compound - to 2,5-dialkoxyhydroquinone (**13**), by continuous separation of water formed in the reaction. The new compounds are of potential biological interest.



13	R
a	Me
b	Et



9	n	X	Y
c	1	H	OH
d	1	OH	H
e	2	H	OH
f	2	OH	H

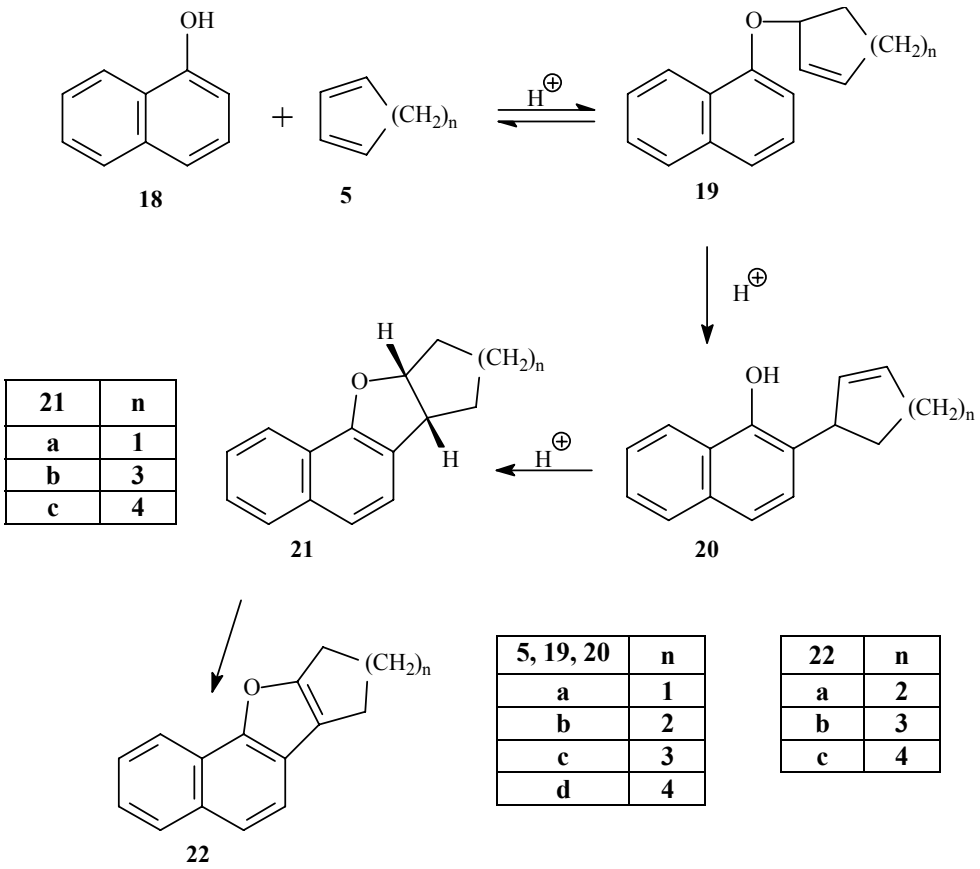
14,15	n	R	X	Y
a	1	Me	H	OH
b	1	Me	OH	H
c	1	Et	H	OH
d	1	Et	OH	H
e	2	Me	H	OH
f	2	Me	OH	H

16,17	n	R
a	1	Me
b	1	H
c	1	Et
d	2	Me
e	2	H

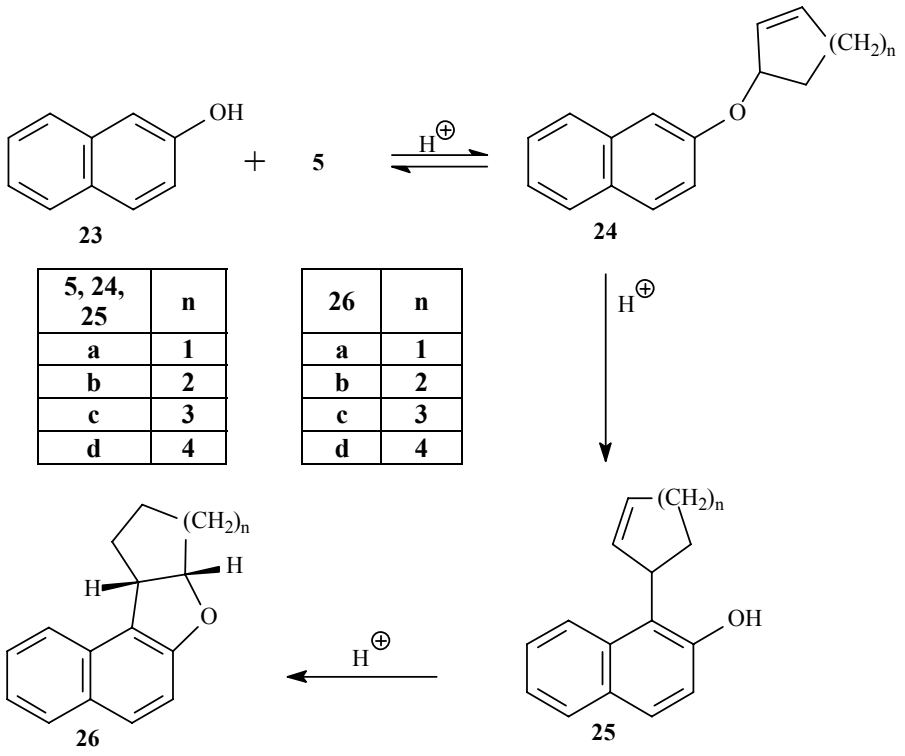
Scheme 4

Reaction of naphtols with cycloalkadienes

We have found that naphtols (**18** and **23**) react with cycloalka-1,3-dienes (**5**) to afford naphtofuran derivatives (Scheme 5 and 6; **21, 22** and **26**), in one operation. This new acid-catalysed method is an extension of our recently discovered reaction of hydroquinone and cycloalkadienes yielding cycloalkanobenzofuran derivatives. The new compounds are of potential biological interest.



Scheme 5



5, 24, 25	n
a	1
b	2
c	3
d	4

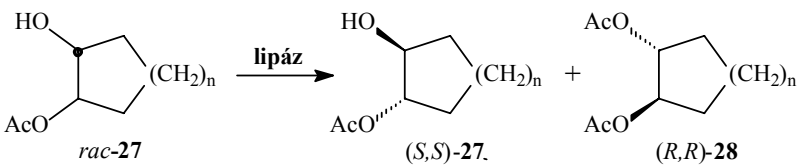
26	n
a	1
b	2
c	3
d	4

Scheme 6

Kinetic resolution of trans-2-acetoxycycloalkane-1-ols by lipase-catalysed enantiomer selective acylation

For simple kinetic resolution of the monoacetates of *trans*-cycloalkane-1,2-diols a number of enantiomer selective enzymes were found. These enzymes enable the preparation of highly enantiopure diacetates [(*R,R*)-**28**] and monoacetates [(*S,S*)-**27**] in good yields. Our screen showed that most of the enzymes are significantly less selective towards the monoacetate of *trans*-cyclooctane-1,2-diol (*rac*-**27h**). We found an efficient extraction system for the separation of products without chromathography.

27,28	n
b	1
d	2
f	3
h	4



Scheme 7

Publications

1. Lajos Novák, Péter Kovács, Pál Kolonits, Olivér Orovecz, Jenő Fekete, Csaba Szántay: „Rearrangement of Allyl Aryl Ethers IV. Reaction of Trimethylhydroquinone with Cycloalkanediols"; *Synthesis*, **2000**, 809.

2. Olivér Orovecz, Péter Kovács, Pál Kolonits, László Párkányi, Éva Szabó, Lajos Novák: „Rearrangement of Allyl Aryl Ethers V: Reaction of 2,5-Dialkoxyhydroquinone with Cycloalkanediols"; *Synthesis*, **2002**, 2711.

3. Olivér Orovecz, Péter Kovács, Pál Kolonits, Zoltán Kaleta, László Párkányi, Éva Szabó, Lajos Novák: „Rearrangement of Allyl Aryl Ethers VI: Reaction of Naphtols with Cycloalkadienes"; *Synthesis*, **2003**, in press.

4. Viktória Bódai, Olivér Orovecz, György Szakács, Lajos Novák, László Poppe, „Kinetic resolution of trans-2-acetoxycycloalkane-1-ols by lipase-catalysed enatiomer selective acylation"; *J. Chem. Soc. Chem. Comm.*, **2003**, accepted for publication.

Presentations

1. Olivér Orovecz, Péter Kovács, Lajos Novák: *Reaction of hydroquinone derivatives with cycloalknea-1,2-diols*, The 2002 Younger European Chemists' Conference; **Heidelberg (Germany), 2002**.

2. Lajos Novák, Péter Kovács, Olivér Orovecz, Pál Kolonits, Csaba Szántay: *Sigmatropic rearrangement of hidroquinone derivatives;* Conference of Chemical Research, Central Research Institute of Chemistry; **Budapest, 2002**.

3. Lajos Novák, Péter Kovács, Olivér Orovecz, Pál Kolonits, Csaba Szántay: *New rearrangement of hidroquinone derivatives,* Conference of Hungarian Chemical Society; **Hajdúszoboszló, 2001**.

4. Pál Kolonits, Péter Kovács, Olivér Orovecz, Lajos Novák, Csaba Szántay: *Unusual rearrangement of alkoxyhidroquinones*; Committee for Phlavonoid Research, Hungarian Academy of Sciences; Central Research Institute of Chemistry; **Budapest, 2001**.

5. Orovecz Olivér, Péter Kovács, Pál Kolonits, Lajos Novák: *New sigmatropic rearrangements*, Committee for Terpenoid Research Hungarian Academy of Sciences, University of Technology and Economics; **Budapest, 2001**.

6. Olivér Orovecz, Péter Kovács, Pál Kolonits, Lajos Novák: *Sigmatropic rearrangemenst*, Committee for Terpenoid Research Hungarian Academy of Sciences, University of Technology and Economics; **Budapest, 2000**.

7. Olivér Orovecz, Péter Kovács, Pál Kolonits, Lajos Novák, Csaba Szántay: *Sigmatropic rearrangement of aryl-cycloalkyl ethers*, XXII. Joint Conference of the Hungarian Chemical Society and Pharmaceutical Society; **Szeged, 1999**.