Synthesis of oxygen containing macrocyclic compounds

PhD theses

János Gerencsér

Supervisors:

Dr. Mihály Nógrádi

Dr. Péter Huszthy

Budapest University of Technology and Economics

Department of Organic Chemistry

2004.

First Part

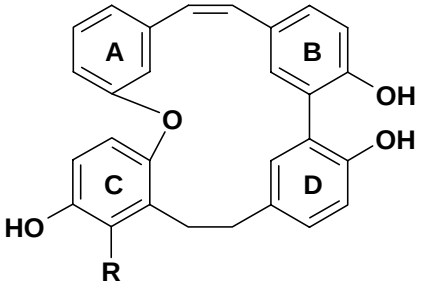
Synthesis of Isoplagiochin A[1]

The numbering of the compounds is identical to that used in the dissertation.

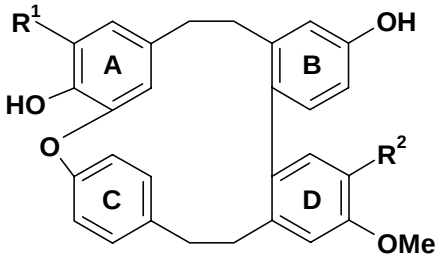
1. Introduction and aims

The extracts of low-order plant species are widely used in the far-east folk therapy, contrary to the conventional European therapy. Natural products of liverwort species show antiallergic, bactericide and diuretic effects. Bis(bibenzyls) are plant metabolites occurring exclusively in liverwort species. Their isolation and structural elucidation can be mainly attributed to Asakawa and his co-workers, while their synthesis has been almost exclusively realized by Professor Nógrádi and his co-workers.

Recently from another *Plagiochila* species (*P. fruticosa*) new bis(bibenzyls) called isoplagiochins A and B were isolated (*Scheme 1.*).



	R
Isoplagiochin A	H
B	OH



	R^1	R^2
Plagiochin A	OH	OH
B	OH	H
C	H	OH
D	H	H

Scheme 1.

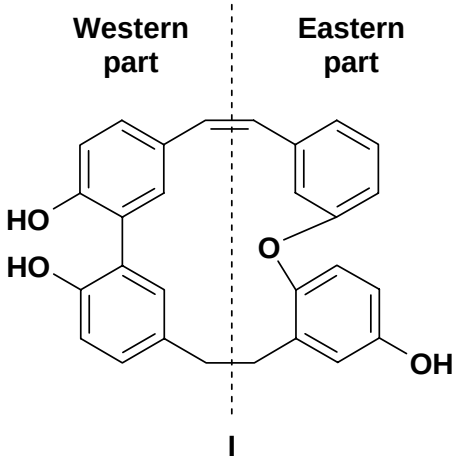
At the Department of Organic Chemistry of TUB Professor Nógrádi and his research group have been working on the synthesis of macrocyclic bis(bibenzyls). Several

marchantines and plagiochins A, B, C and D were successfully synthesized during their activity.

In my thesis I report the synthesis of isoplagiochin A (**I**).

2. Summary of novel scientific results

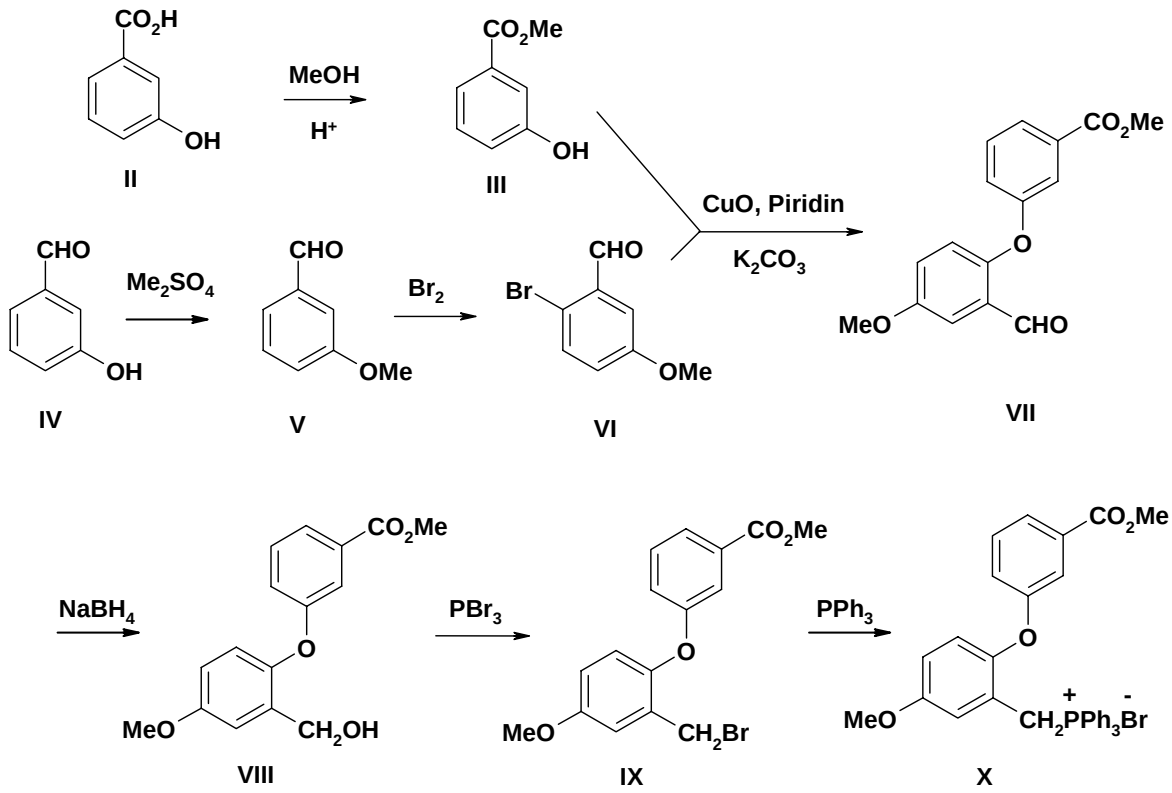
The targeted compound can be divided into two parts called „Eastern" and „Western" part (Scheme 2.).



Scheme 2.

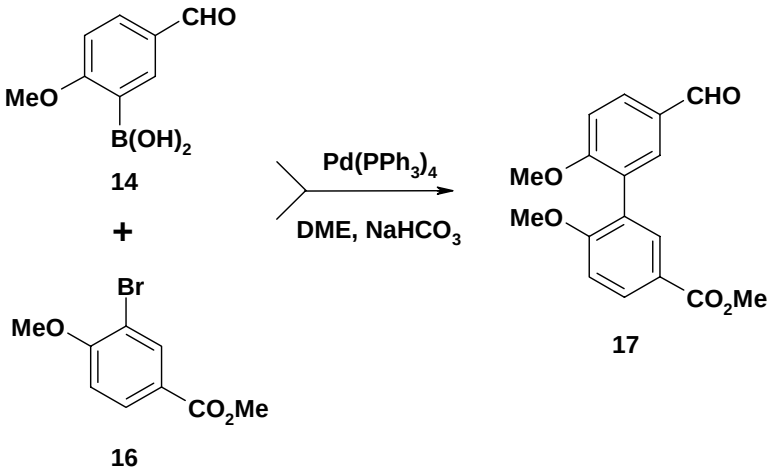
The "Eastern" and "Western" parts were prepared separately.

For the preparation of the „Eastern" half methyl 3-hydroxybenzoate (**III**) and 2-bromo-5-methoxybenzaldheyde (**VI**) were coupled by the Ulmann-reaction. The so obtained diarylether **VII** was then transformed in three steps into key intermediate **X** (**VII→VIII→IX→X**) (*Scheme 3.*).



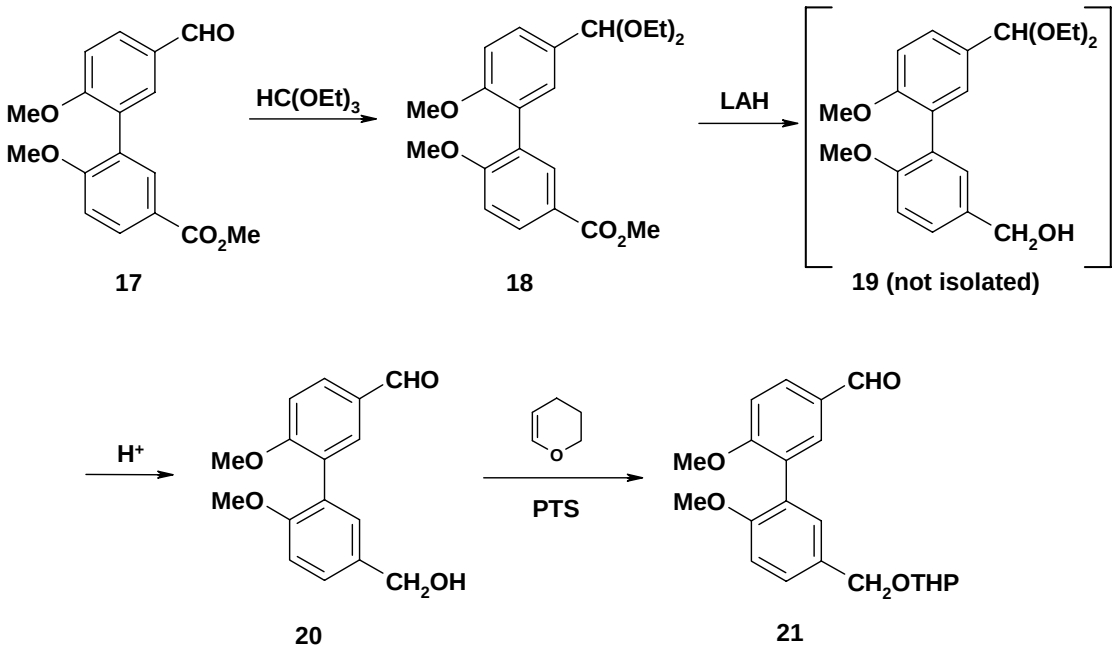
Scheme 3.

The "Western" half of the tetracyclic structure was constructed by a Suzuki reaction, coupling 3-borono-4-methoxybenzaldehyde (**XIV**) – prepared from 3-bromo-4-methoxy-benzaldehyde – with methyl 3-bromo-4-methoxybenzoate (**XVI**) to give the biphenyl **XVII** (*Scheme 4.*).



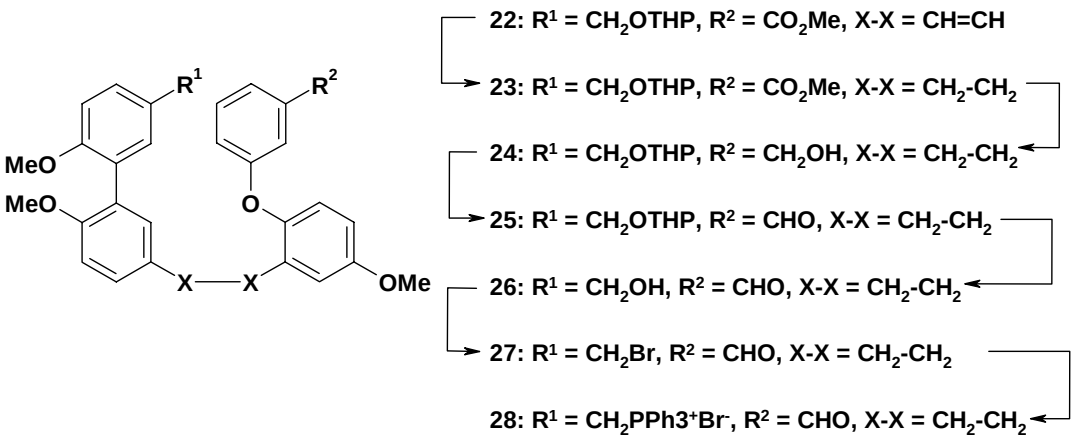
Scheme 4.

After protection of the aldehyde function (**18**) the ester group was transformed into a protected primary alcohol group in two steps (**18→20→21**) to provide the building block (**21**) for the Wittig reaction (*Scheme 5.*).



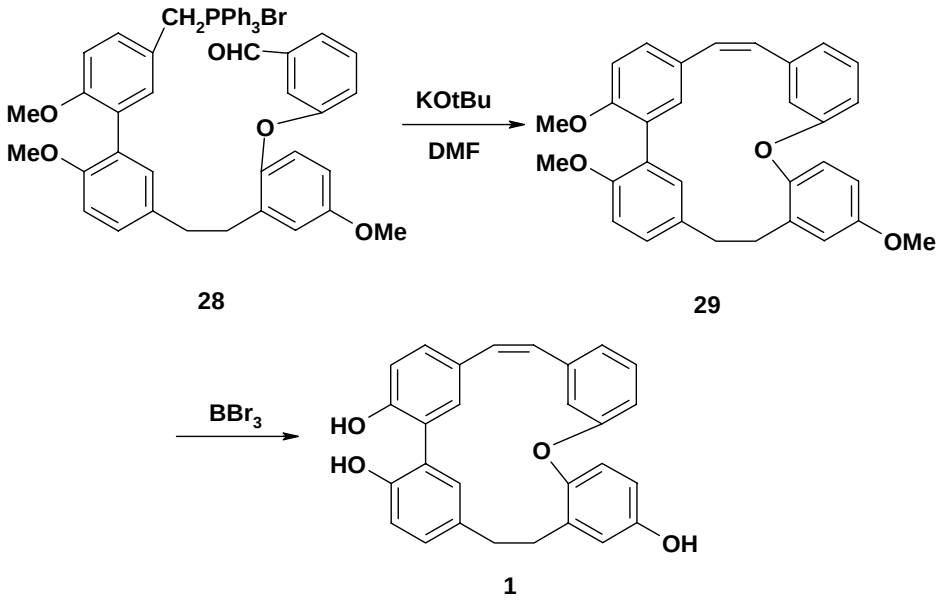
Scheme 5.

Joining "East" (**10**) and "West" (**21**) by a Wittig-reaction using sodium methylate as a base provided olefin **13** as an *E*/*Z* mixture containing all the four aryl rings. Further functional group transformations (**22→23→24→25→26→27→28**) led to **19** open chain key intermediate (*Scheme 6.*).



Scheme 6.

The cyclization of the macroring was performed by an intramolecular Wittig reaction using potassium *tert.*-butoxide as a base in DMF providing **29** trimethyl ether. Demethylation with boron tribromide in dichloromethane yielded, along with unidentifiable byproducts, the trihydroxy compound **1** (*Scheme 7.*).



Scheme 7.

At this point a comparison with the few available NMR data reported for **1** became possible. The spectrum of our product showed significant deviations with the available NMR data for isoplagiochin A. Thus, we utilized more sophisticated NMR techniques (COSY, TOCSY, HMQC, HMBC, NOESY) and molecular mechanic calculations to clarify the structures of our synthetic products. These investigations also confirmed the postulated structures of our macrocycles **29** and **1**. Finally, on our second request Professor Asakawa kindly sent us the original NMR spectra and a 10-mg sample of isoplagiochin A. Recording the spectra revealed that the spectra of the natural product and **1** were identical.

Based on the above results the structure of isoplagiochin A was unambiguously verified and we also showed that some NMR data in the original publication were incorrect.

Second Part

Synthesis of new lipophilic, optically active pyridino/pyridono- and bis-pyridino/bis-pyridono-18-crown-6 ligands containing four chiral centers

The numbering of the compounds is identical to that used in the dissertation.

1. Introduction and aims

Dr. Péter Huszthy after spending several years in the mid 80's at the Brigham Young University (Provo, U.S.A.) continued his research on the synthesis of proton-ionizable and enantiomerically pure 18-crown-6 type ligands containing nitrogen consisting heterocycles for their studies on enantioselective complexation and their use for resolvation of racemates.

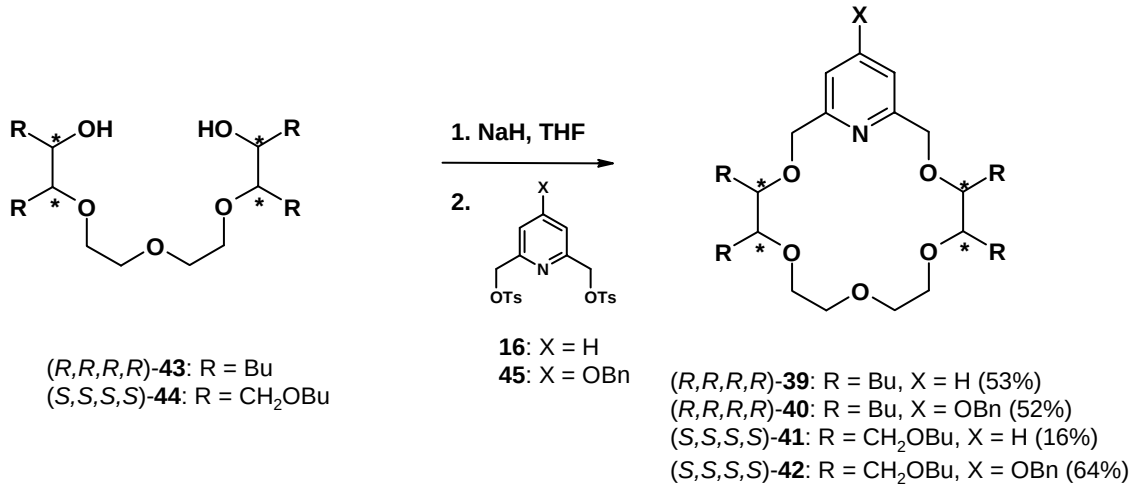
The aim of my Ph.D. research was to synthesize lipophilic pyridino/pyridono- and bis-ryridino/bis-pyridono-18-crown-6 type ligands, which contain four chiral centers and that would show high enantioselectivity in the complexation of chiral organic ammonium salts and/or that would be enable the study of the selective transport of metal ions in an aqueous source phase/lipophilic organic membrane/aqueous receiving phase system.

2. Summary of novel scientific results

2.1 Synthesis of novel crown compounds

2.1.1 Preparation of pyridino-18-crown-6 type ligands[2]

Four new, optically active pyridino-18-crown-6 type macrocycles containing four chiral centers [(*R,R,R,R*)-**39**-(*S,S,S,S*)-**42**] were successfully prepared in a so-called „one-to-one" type sodium ion template assisted cyclization, condensing the appropriate 2,6-bis(tosyloxymethyl)-pyridine derivatives (**16** and **45**) with the corresponding optically active tetraethylene glycol derivatives [(*R,R,R,R*)-**43** and (*S,S,S,S*)-**44**] (Scheme 8.).



(*R*,*R*,*R*,*R*)-**43**: R = Bu
(*S*,*S*,*S*,*S*)-**44**: R = CH_2OBu

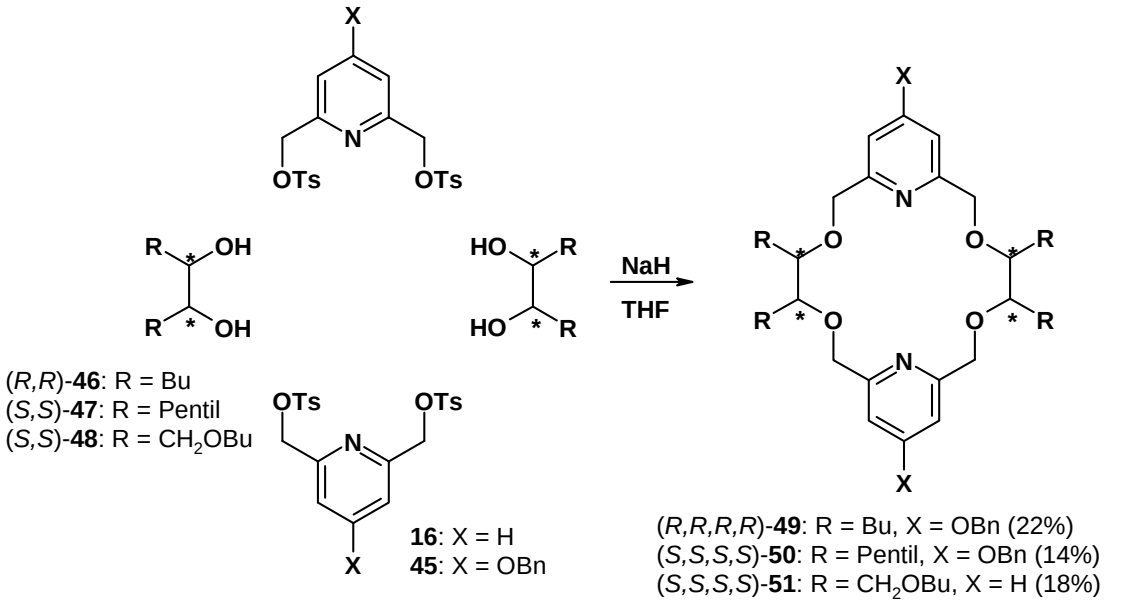
16: X = H
45: X = OBn

(*R*,*R*,*R*,*R*)-**39**: R = Bu, X = H (53%)
(*R*,*R*,*R*,*R*)-**40**: R = Bu, X = OBn (52%)
(*S*,*S*,*S*,*S*)-**41**: R = CH_2OBu, X = H (16%)
(*S*,*S*,*S*,*S*)-**42**: R = CH_2OBu, X = OBn (64%)

Scheme 8.

2.1.2 Preparation of bis-pyridino-18-crown-6 type ligands[3]

Four new, optically active bis-pyridino-18-crown-6 type macrocycles containing four chiral centers [(*R*,*R*,*R*,*R*)-**49**-(*S*,*S*,*S*,*S*)-**52**] were successfully prepared in a so-called „two-to-two" type sodium ion template assisted cyclization, condensing the appropriate 2,6-bis(tosyloxymethyl)-pyridine derivatives (**16** and **45**) with the corresponding optically active diethylene glycol derivatives [(*R*,*R*)-**46**-(*S*,*S*)-**48**], similarly as for the pyridino species (Scheme 9.).



(*R*,*R*)-**46**: R = Bu
(*S*,*S*)-**47**: R = Pentil
(*S*,*S*)-**48**: R = CH_2OBu

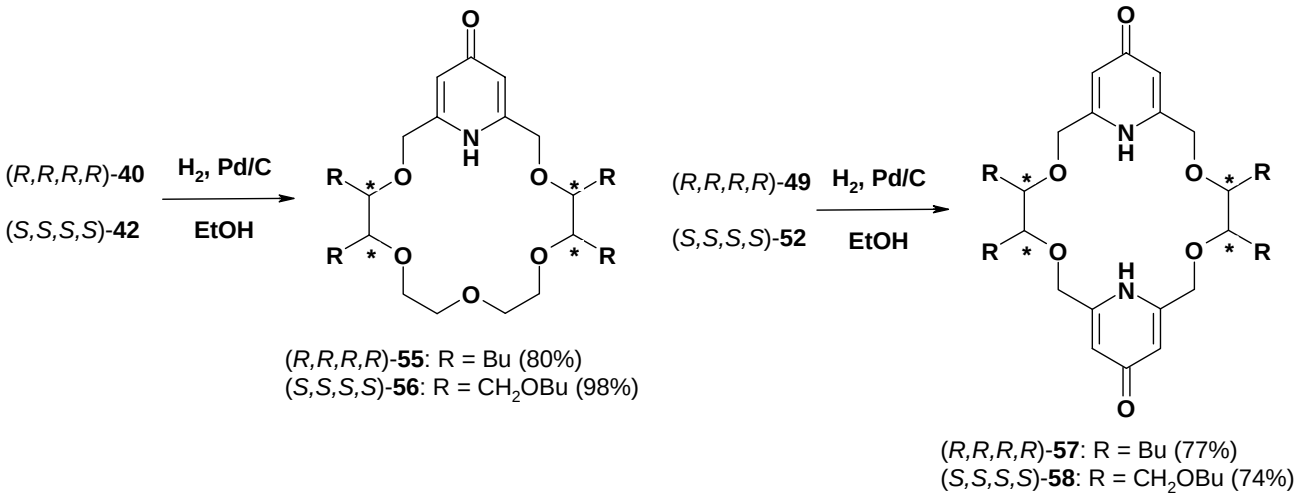
16: X = H
45: X = OBn

(*R*,*R*,*R*,*R*)-**49**: R = Bu, X = OBn (22%)
(*S*,*S*,*S*,*S*)-**50**: R = Pentil, X = OBn (14%)
(*S*,*S*,*S*,*S*)-**51**: R = CH_2OBu, X = H (18%)
(*S*,*S*,*S*,*S*)-**52**: R = CH_2OBu, X = OBn (18%)

Scheme 9.

2.1.3 Preparation of pyridono- and bis-pyridono-18-crown-6 type ligands[2,3]

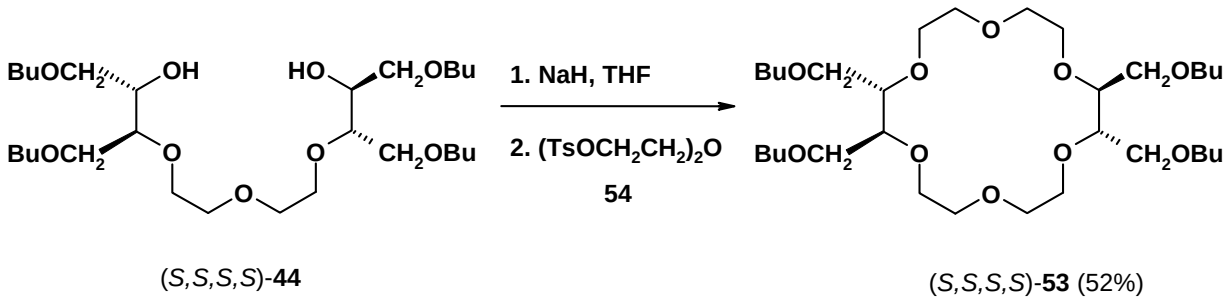
The pyridono- and bis-pyridono-18-crown-6 type ligands [(*R,R,R,R*)-**55**-(*S,S,S,S*)-**58**] were prepared from the appropriate benzyloxy derivatives (*R,R,R,R*)-**40**, (*S,S,S,S*)-**42**, (*R,R,R,R*)-**49** and (*S,S,S,S*)-**52**, respectively, by catalytic debenzylation (*Scheme 10.*).



Scheme 10.

2.1.4 Preparation of the tetra(butoxymethyl)-substituted 18-crown-6 ether ligand[3]

Beside the macrocycles detailed above the synthesis of the new tetrabutoxymethyl-substituted-18-crown-6 ether (*S,S,S,S*)-**53** was also prepared in a "one-to-one" cyclization for comparative studies of its properties to those ligands, which contain pyridine, *p*-benzyloxypyridine and pyridone subcyclic units (*Scheme 11.*).

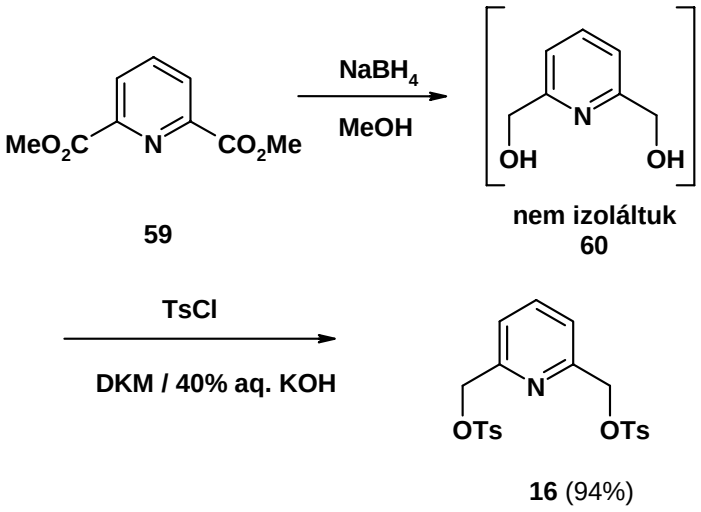


Scheme 11.

2.2 Synthesis of the precursors

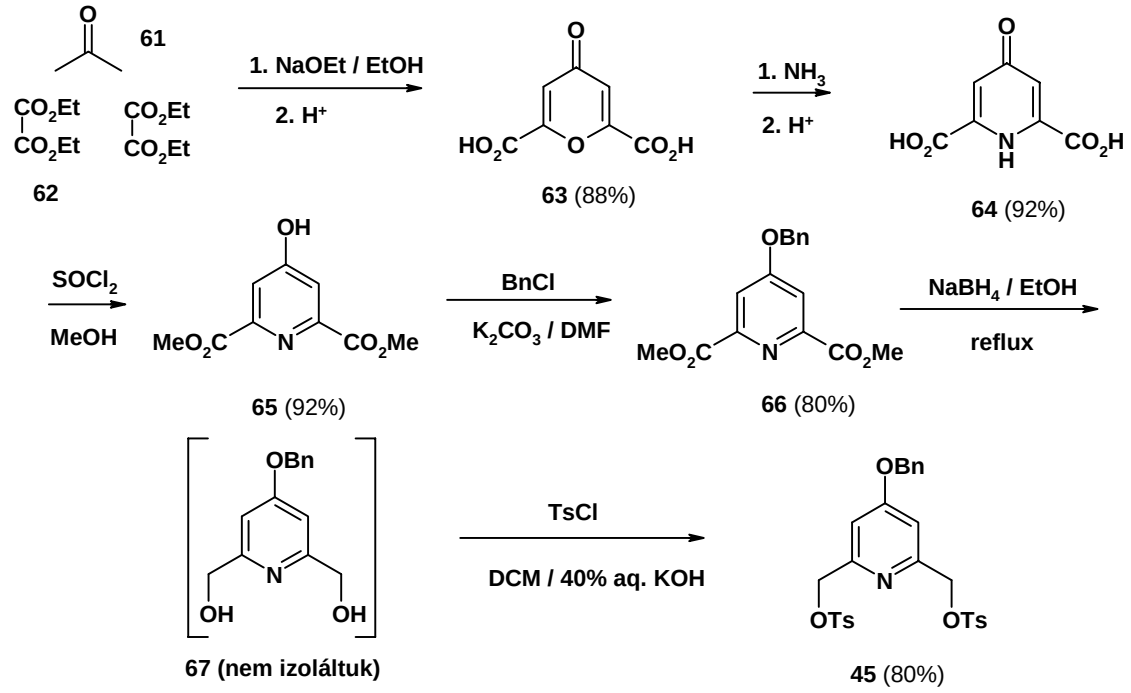
2.2.1 Synthesis of the pyridine precursors

Bis(tosyloxymethyl)-pyridine (**16**) was prepared starting from the commercially available dimethyl pyridine-2,6-dicarboxylate (**59**) (*Scheme 12.*).



Scheme 12.

Ditosylate **45** was prepared in six steps starting from acetone (**61**) and diethyl oxalate (**62**) (*Scheme 13.*).

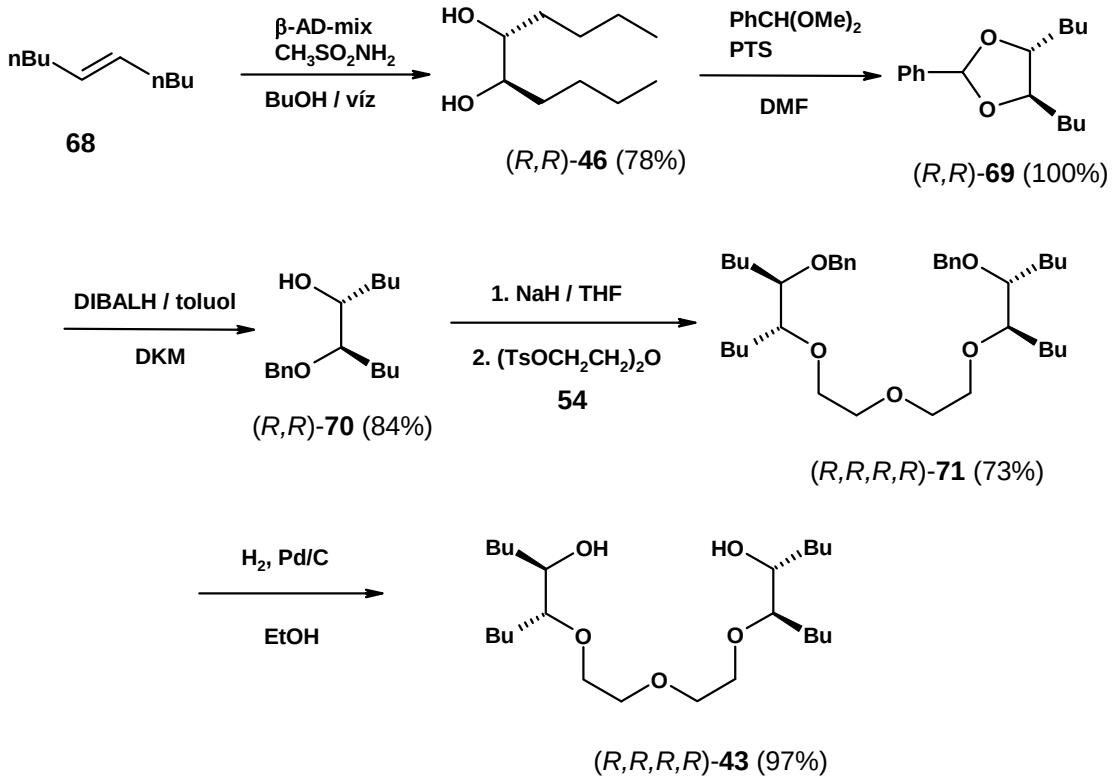


Scheme 13.

2.2.2 Preparation of the optically active ethylene glycol and tetraethylene glycol precursors[2,3]

2.2.2.1 Synthesis of the (5*R*,6*R*)-decan-5,6-diol [(*R*,*R*)-46] and the tetrabutyl substituted tetraethylene glycol derivative [(*R*,*R*,*R*,*R*)-43]

Diol (*R,R*)-**46** was prepared from *trans*-dec-5-ene (**68**) in the presence of *β*-AD-mix chiral catalyst according to Sharpless' dihydroxylation method (*Scheme 14.*). The so obtained (*R,R*)-**46** diol was used for the preparation of (*R,R,R,R*)-**49** macrocycle (see *Scheme 9.*). Tetraethylene glycol (*R,R,R,R*)-**43** was prepared from (*R,R*)-**46** in four steps (*Scheme 14.*).

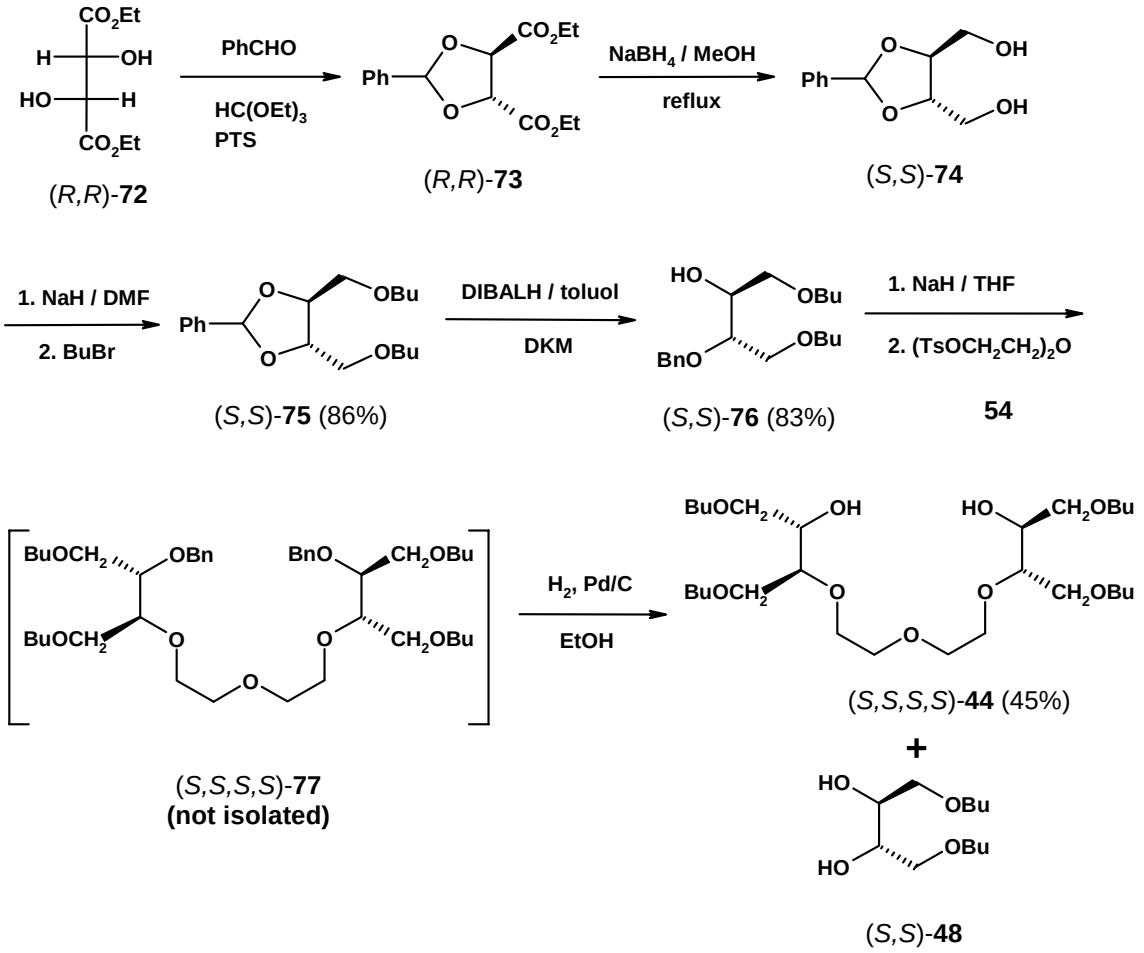


Scheme 14.

3.2.2.2 Synthesis of the butoximethyl substituted optically active (*S,S*)-48 ethylene glycol and (*S,S,S,S*)-44 tetraethylene glycol

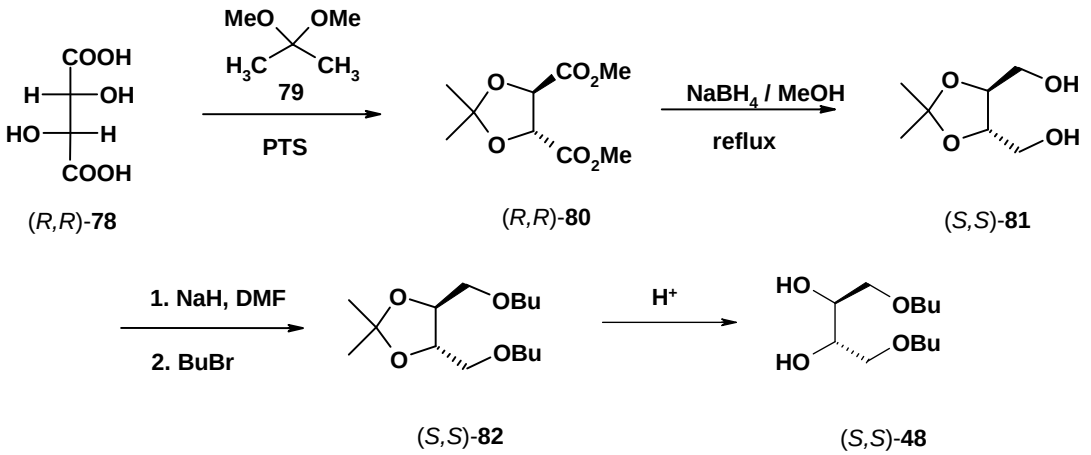
The syntheses of the optically active (*S,S*)-**48** and (*S,S,S,S*)-**44** were realized in two different paths starting from tartaric acid or from diethyl tartrate (*Scheme 15. and 16.*).

In the first method (*Scheme 15.*) the hydroxy groups of the diethyl tartrate [(*R,R*)-**72**] were masked as a benzylidene acetal [(*R,R*)-**73**]. The ester moieties of (*R,R*)-**73** were then reduced using sodium borohydride, then the resulting (*S,S*)-**74** diol was reacted with butyl bromide to obtain (*S,S*)-**75** dioxolane, which was then cleaved to (*S,S*)-**76** monobenzylether giving (*S,S*)-**48** as a byproduct. Monobenzylether (*S,S*)-**76** was reacted with diethylene glycol ditosylate (**54**) followed by catalytic debenzylation, which led to our key intermediate (*S,S,S,S*)-**44** also giving (*S,S*)-**48** as a byproduct.



Scheme 15.

In the second method natural tartaric acid [(*R,R*)-**78**] was used as starting material, which was transformed to (*R,R*)-**80** in one step using acetone-dimethylacethal (*Scheme 16.*).

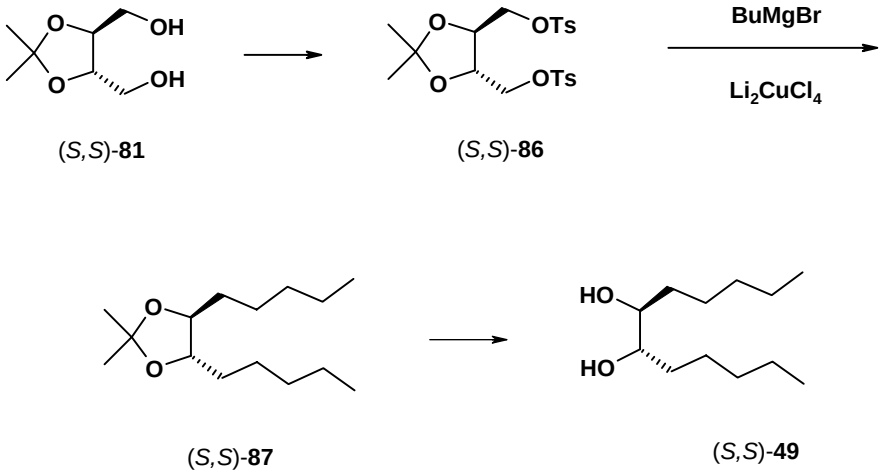


Scheme 16.

The ester groups of (*R,R*)-**80** were reduced using sodium borohydride as a reducing agent and the resulting (*S,S*)-**81** diol was reacted with butyl-bromide to obtain (*S,S*)-**82**, which was cleaved under acidic conditions providing 1,4-O,O'-dibutylthreitol [(*S,S*)-**48**] (*Scheme 16.*). (*S,S*)-**48** was transformed to (*S,S,S,S*)-**44** according to the method described above for (*R,R,R,R*)-**43** tetraethylene glycol.

2.2.2.3 Preparation of (6*S*,7*S*)-dodecan-6,7-diol [(*S,S*)-49]

In the first step of the synthesis diol (*S,S*)-**81** was tosylated yielding ditosylate (*S,S*)-**86**, which was coupled with butyl magnesium-bromide in the presence of lithium tetrachlorocuprate to give acetonide (*S,S*)-**87**. Cleavage of the latter under acidic conditions gave diol (*S,S*)-**49** (*Scheme 17.*).



Scheme 17.

Publications

1. Papers

[1] J. Gerencsér, G.M. Keserű, I. Macsári, M. Nógrádi, M. Kajtár-Peredy, Á. Szöllősy: *J. Org. Chem.*, **1997**, *62*, 3666.

[2] J. Gerencsér, N. Báthori, M. Czugler, P. Huszthy, M. Nógrádi: *Tetrahedron: Asymm.*, **2003**, *14*, 2803.

[3] G. Horváth, C. Rusa, Z. Köntös, J. Gerencsér, P. Huszthy: *Synth. Commun.*, **1999**, *29*, 3719.

[4] J. Gerencsér, P. Huszthy, M. Nógrádi: *Arkivoc*, **2004**, *VII*, 7.

2. Presentations

[5] Gerencsér, J., Macsári, I.: *"Az isoplagiochin A(?) szintézise"*, Országos Tudományos Diákköri Konferencia, Pécs, **1996**.

[6] Gerencsér, J., Huszthy, P., Nógrádi, M.: *"Új, enantiomertiszta, négy aszimmetriacentrumot és piridin- vagy piridonegységet tartalmazó koronaéterek szintézise"*, Heterociklusos Munkabizottsági Ülés, Balatonszemes, May, **2002**.

[7] Gerencsér, J., Huszthy, P., Nógrádi, M.: *"Négy kiralitáscentrummal rendelkező új, lipofil koronaéterek szintézise"*, Terpenoidkémiai Munkabizottsági Ülés, Budapest, September, **2002**.

[8] J. Gerencsér, P. Huszthy, M. Nógrádi: *"Synthesis of new optically active pyridino-, pyridono-, bis-pyridino-, and bis-pyridono-18-crown-6 ligands containing four lipophilic chains"*, XXVII International Symposium on Macrocyclic Chemistry, Park City (Utah, U.S.A.), June, **2002**.

3. Posters

[9] J. Gerencsér, G.M. Keserű, I. Macsári, M. Nógrádi: *"Synthesis of Isoplagiochin A(?)"*, 20th IUPAC Symposium on Natural Products, Chicago, September, **1996**.