PROGRESS IN ORGANIC SYNTHESIS

POSTĘPY SYNTEZY ORGANICZNEJ

Gdańsk, 23–25 June 2016
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Abstract Book

Scientific conference organized
to mark the 70th birthday of
prof. Janusz Rachoń

Konferencja naukowa zorganizowana
z okazji 70. urodzin
prof. Janusza Rachonia

Gdańsk 2016

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Oral presentations / Prezentacje ustne

Poster presentations / Prezentacje posterowe

Organizing Committee / Komitet Organizacyjny

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Progress in Organic Synthesis – Conference Schedule / Postępy syntezy organicznej – program konferencji

Thursday 23.06.2016	
Localization	The Lecture Hall (room 300, the main building of the Gdańsk University of Technology)
09:00–20:00	**Registration** – the Conference Office in the main building of the Gdańsk University of Technology
9:30–10:00	**Opening Ceremony**
10:00–10:30 10:30–11:00	The speeches of invited guests **Wojciech Kuźmierkiewicz** *Polpharma – Polish innovative pharmaceutical company*
11:00–11:30	Coffee break
Lectures of Invited Speakers	
Chair	**Dariusz Witt**
11:30–12:15	**Lucedio Greci** *Some Aspects on the Synthesis, Reactivity and Applications of Aromatic Nitroxides*
12:15–13:00	**Mieczysław Mąkosza** *How Does Nucleophilic Aromatic Substitution Really Proceed*
13:00–14:30	**Lunch** – the Hevelius Courtyard in the main building of the Gdańsk University of Technology
14:45–17:00	**Poster session and Get together Party** – the main building (second floor) of the Gdańsk University of Technology
18:00–21:00	**Excursion to European Solidarity Centre** (optional)
Friday 24.06.2016	
Localization	The Lecture Hall (room 300) in the main building of the Gdańsk University of Technology
Lectures of Invited Speakers	
Chair	**Krystyna Dzierzbicka**
9:30–10:15	**Eric Fillion** *Exploring and Exploiting New Reactivity of Alkyl-Tricarbastannatranes in Lewis Acid and Transition Metal Catalysis*

10:15–11:00	**Marek Chmielewski** *Asymmetric Kinugasa Reaction as an Entry to Important β-lactam Compounds*
11:00–11:30	**Coffee break**
Lectures of Invited Speakers	
Chair	**Sławomir Makowiec**
11:30–12:00	**Janusz Jurczak** *C_3-Symmetrical Triptycene-Based Anion Receptor Highly Selective for Dihydrogen Phosphate*
12:00–12:30	**Michał Pietrusiewicz** *A New Entry to P-Stereogenic Six-Membered Phosphorus Heterocycles*
12:30–13:00	**Marek Stankevič** *Phenyl Group at Phosphorus – the Beginning of the Story*
13:00–14:30	**Lunch (**the Hevelius Courtyard in the main building of the Gdańsk University of Technology)
Oral Presentations – Forum of Young Scientists	
Chair	**Sebastian Demkowicz**
14:45–15:00	**Jacek Nycz** *Synthesis of 5-azo-8-hydroxy-2-methylquinoline dyes and relevant spectroscopic studies*
15:00–15:15	**Damian Kulawik** *Friendly Batteries For Environment Based On The Functionalized Carbon Nanotube By Salts Containing Sulfur And Phosphorus Heteroatoms*
15:15–15:30	**Artur Mucha** *Synthesis and Structural Modifications of Phosphinic Dipeptide Analogues*
15:30–15:45	**Piotr Drelich** *Organocatalytic approach to optically active α-hydroxy-β-amino aldehydes bearing a quaternary stereogenic centre*
15:45–16:15	**Coffee break**
16:15–16:30	**Małgorzata Petryk** *Kinetyczne, chiralne [4+6] organiczne klatki molekularne*
16:30–16:45	**Patrycja Mrowiec** *Reakcje nukleofilowego fluorowania pochodnych kwasów α-hydroksy-fosfonowych*
16:45–17:00	**Aneta Kosińska** *Badania degradacji kompleksów typu CpM(CO)$_x$(η^1-N-imidato) przy zastosowaniu spektroskopii FT-IR i LC-MS*

Saturday 25.06.2016	
Localization	The Lecture Hall (room 300, the main building of the Gdańsk University of Technology)
Lectures of Invited Speakers	
Chair	**Witold Przychodzeń**
9:30–10:00	**Józef Drabowicz** *Selected Heteroorganic Compounds with a Stereogenic Heteroatom: Synthetic, Structural and Application Aspects*
10:00–10:30	**Paweł Kafarski** *Three component reaction as a mean to prepare aminomethylenebis-phosphonates: the example how one reaction could be fascinating*
10:30–11:00	**Marcin Kwit, Jacek Gawroński** *Synteza kierowana symetrią – funkcjonalne, chiralne makrocykle i klatki molekularne*
11:00–11:30	**Coffee break**
Chair	**Magdalena Śliwka-Kaszyńska**
Oral Presentations – Forum of Young Scientists	
11:30–11:45	**Joanna Wolska** *Synteza α,α-(difluorometylo)styrenu i badania jego reaktywności w reakcjach polimeryzacji rodnikowej*
11:45–12:00	**Daria Lizińska** *Wykorzystanie kompleksów metalokarbonylowych do znakowania białek*
12:00–12:15	**Sławomir Makowiec** *Meldrum's acid Derivatives as a Versatile Starting Point for the Preparation of Biologicaly Active Compounds*
12:15–12:30	**Sebastian Demkowicz** *Recent Developments in Steroid Sulfatase Inhibitors as Anti-CancerAgents*
12:30–12:45	**Dariusz Witt** *The Reactivity of Disulfanyl Derivatives of Phosphorodithioic Acid*
13:00–14:30	**Lunch (**the Hevelius Courtyard in the main building of the Gdańsk University of Technology)
17:00–19:00	**Closing Ceremony** **The best poster award** **Concert** The Main Hall (Aula PG) in the main building of the Gdańsk University of Technology
19:00–21:00	**Conference Banquet** (the Fahrenheit Courtyard in the main building of the Gdańsk University of Technology)

Professor Janusz Rachoń, Head of the Organic Chemistry Department at the Gdańsk University of Technology, member of the Upper Chamber of the Polish Parliament (2007–2011); Senator (deputy chairman of the European Union Affairs Committee and member of the Foreign Affairs Committee) . He was born 11.08.1946 in Nowy Sącz, graduated from the Faculty of Chemistry at Gdańsk University of Technology (1969). During his studies, he was elected President of the University Parliament of the Polish Students' Association at Gdańsk University of Technology. In 1978–1980 he was a fellow of the Alexander von Humboldt Foundation at the University of Goettingen (Germany); and in 1985–1990 he worked as a visiting professor at the Department of Chemistry at The Florida State University; Tallahassee; USA. In 2002 he was elected Rector of Gdańsk University of Technology and held this position until 2008. In 2005 he was elected President of the Polish Higher Education-Business Forum. Polish Higher Education-Business Forum is an association of leaders of Polish businesses and universities. The aims of the Forum are to increase communication among the sectors, analyze issues of mutual concern, and to consider the course of action that will effect change on these topics. To carry out its agenda, the Forum holds semi annual meetings, convenes occasional roundtable discussions and seminars, and publishes reports.

In 2006 prof. Rachoń was nominated Chairman of the Council of the National Centre for Research and Development; Poland.

Professor Janusz Rachoń carries out his research in organic synthesis and reaction mechanisms. His scientific output comprises around 150 scientific articles, papers, reviews and 14 patents. Of outmost importance are the technologies for the synthesis of novel hydroxybisphosphonates used to treat osteoporosis as well as Paget's disease developed by Prof. Rachoń's group which were implemented and scaled-up by the Polish Pharmaceutical Company POLPHARMA SA. More specifically, the methods have allowed the production of the precursors ibandronic acid, risendronic acid, zolenronic acid, and sodium alendronate, and the drug Ostemax 70 comfort; this is a great example of cooperation between a Polish public University and the Polish pharmaceutical industry. Ostemax 70 comfort is a new Polpharma's drug used in the treatment of osteoporosis. The drug allows for an effective and convenient treatment of the patients. Consequently, the Polish company POLPHARMA is the world biggest producer of sodium alendronate, which is produced according to Prof. Rachoń's technology. The hydroxybisphosphonates synthesis protocol, as described by Prof. Rachoń, has been employed by the Polish pharmaceutical industry,

and other independent manufacturers of medicines against osteoporosis in the country and abroad. The synthetic methodologies developed and used for the large-scale preparation of new generation of hydroxybisphosphonates namly: ibandronic acid, risendronic acid, zolenronic acid, and sodium alendronate have been patented, and are protected by European and international patents.

For his achievements he was awarded The Economic Award of the President of the Republic of Poland in 2005, and in 2006 the Prize of The Prime Minister of the Republic of Poland. In 2011 he was awarded the Jan Hevelius' Science Prize and in 2015 the Ignacy Mościcki Medal of the Polish Chemical Society .

Prof. Janusz Rachoń participates in many international, local and regional initiatives. He is member of many national and international organizational committees for scientific conferences. As member of Gdańsk Scientific Association Management Board, he has been organizing annual meetings "Politics-Science-Business". Moreover, he promotes the growth of regional R&D laboratories and it was his idea to set up Central Library of Natural and Technical Sciences in Poland. Prof. Janusz Rachoń was chosen "the Man of the Year 2007" in the poll organized by the daily newspaper "Dziennik Bałtycki".

Prof. Janusz Rachoń believes that politics consists in the art of foreseeing and good social relations are the basis for appropriate and precise legislation. He believes that one has to be pragmatic and consistent in life. He has got a good sense of humor and considers its lack a peculiar spiritual disability.

Prof. Rachoń is married and has two sons. Hobby: so called on-border culture, jazz, gospel and spiritual music, Salvador Dali's works.

Polpharma – Polish innovative pharmaceutical company

Jolanta Pawłowska, Bogdan Maślanek and Wojciech Kuźmierkiewicz

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Polpharma is an European producer of Active Pharmaceutical Ingredients (API) delivering products to pharmaceutical companies worldwide. We are present in 6 continents, in more than 60 countries, and our market share is constantly growing. Our well-balanced and expanding portfolio consisting of 43 API's, along with our scientific know-how and experience, allow us to offer attractive solutions for drug developers.

We provide a one-stop shop solution of vertically integrated services from API development to FDF formulation and manufacturing, scale-up capabilities based on in-house or external custom developed technologies, to regulatory support.

Our products are manufactured in accordance with the most stringent requirements of our customers and health authorities: US FDA, EMA, EDQM, SKFDA, PMDA, ANVISA, Polish Main Pharmaceutical Inspectorate. Regular FDA audits enabled us to register and sell a number of APIs in the US market and confirm our reliability and credibility towards our business partners around the world.

Development and commercialization of new, attractive APIs is the priority of Polpharma's API R&D Department which possess state-of-the-art equipment and consists of 57 highly qualified professionals, including 14 with doctoral degrees.

The R&D Department includes process development laboratory, analytical development laboratory, process maintenance and continuous improvement laboratories, and regulatory department.

The key to our success is the combination of experience and expertise of our own research team as well as effective co-operation with scientific institutions.

The result of such cooperation with scientists from Faculty of Chemistry of Gdańsk University of Technology is the new method for preparing four bisphosphonates – substances used for the treatment of osteoporosis. Development and implementation of innovative, patent protected technologies has enabled Polpharma to increase the efficiency of the manufacturing process, improve the competitiveness of manufactured substances and minimize the impact of production on the environment. This has led to achieve by Polpharma the market share for Alendronate sodium (one of the four bisphosphonates) at a level above 40%.

Another dimension of Polpharma's activities is established in 2001 Polish Scientific Foundation. Its mission is supporting the development of pharmaceutical and medicinal sciences through the financing of scientific research in those fields.

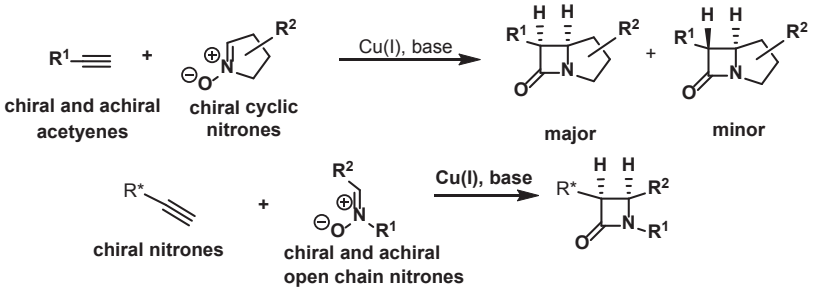
Lectures of Invited Speakers / Wykłady zaproszone

Asymmetric Kinugasa Reaction as an Entry to Important β-lactam Compounds

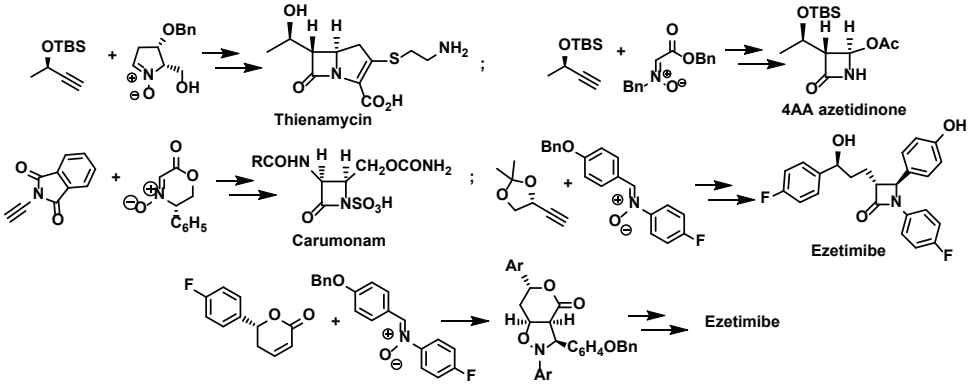
Marek Chmielewski

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

The copper(I) mediated reaction of nitrones and terminal acetylenes, which is known as Kinugasa reaction, represents an attractive method of direct formation of the β-lactam ring. [1] The reaction can be performed in many ways. The most attractive are diastereo-versions including cyclic chiral nitrones, or chiral acetylenes with open-chain nitrones. [2]



Herein, we present our studies on application of Kinugasa reaction in synthesis of carbapenems (Thienamycin [3] and 4AA azetidinone [4]), monobactams (Carumonam) [5] and Ezetimibe, [6] a powerful cholesterol absorption inhibitor. The latter compound was also successfully synthesized by us using the other strategy. [7]



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C_3-Symmetrical Triptycene-Based Anion Receptor Highly Selective for Dihydrogen Phosphate

Janusz Jurczak, Jakub Grabowski and Jarosław M. Granda

Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Interest in anion recognition has long been motivated by applications in anion sensors, responsive gels, extraction and separation of anions, transmembrane transport, anion-driven supramolecular architectonics, and catalysis. Among the biologically active anions, phosphates are particularly important, forming part of various genetic information and energy carrying molecules. In this spirit, designing receptors able to selectively bind phosphates poses a particular challenge for synthetic and supramolecular chemists.

In this presentation a new anion binding motif based on triptycene core is proposed. It has been successfully synthesized from 2,7,14-trinitrotriptycene (Fig. 1). Its well-defined binding pocket allowed for the selective recognition and sensing of dihydrogen phosphate in DMSO-d_6 + 0.5% H_2O.

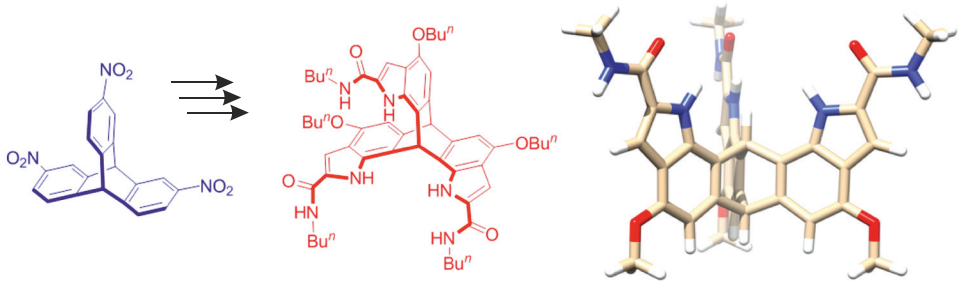


Fig. 1. Triptycene-based receptor studied in this work

References

J.M. Granda, J. Grabowski, J. Jurczak, *Org. Lett.*, **2015**, 17, 5882–5885.

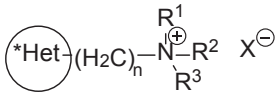
Selected Heteroorganic Compounds with a Stereogenic Heteroatom: Synthetic, Structural and Application Aspects

Dorota Krasowska[1], Bogdan Dudziński[2], Stanislaw Miroshnichenko[2], Patrycja Pokora-Sobczak[1], Wojciech Ciesielski[2] and Józef Drabowicz[1,2]

[1] Department of Heteroorganic Chemistry, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Lodz, Poland, e-mail draj@cbmm.lodz.pl
[2] Insitute of Chemistry, Environmental Protection and Biotechnology, Jan Dlugosz University in Czestochowa, Czestochowa, Poland

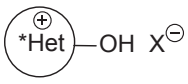
In more than century-old studies devoted to stereochemical aspects in the chemistry of organic sulfur [1, 2] or phosphorus [3] derivatives one can easily recognize two streams. The first one, which dominated until the end of the sixties of the twentieth century, was associated with methodological studies, which were focused on the synthesis of optically active compounds with a stereogenic heteroatom having various valency and/or coordination number, determination of their optical and chemical stability and reactivity, stereochemistry of the basic functional group interconversions and basic structural parameters including their chiroptical properties. The second stream, which dominates currently, is focused on research aimed at the use of such optically active derivatives as chiral auxiliaries or catalysts in asymmetric synthesis [4, 5] and chiral substrates useful in the synthesis of new materials and new biologically active derivatives. [6] The lecture will discuss our current research devoted to a few topics from both streams which are aimed among others at:

a) synthesis of new ionic liquids containing chiral phosphinyl or sulfinyl moiety and having the general structure 1, 2 or 3 [7, 8]



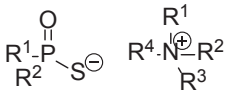
Het*=R'R''P(O); ArS(O)

1



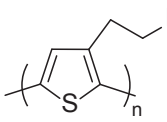
Het*=t-BuPhP(O); ArSR

2



3

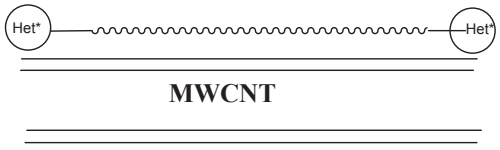
b) chirality of thiophenes (mono, oligo and poly), induced by heteroatom-containing substituents, including the isolation of (*S*)-*t*-butylphenyl-2-(3'-thienylethylphosphine oxide **4a**, [9] its X-ray analysis and polymerization.



4

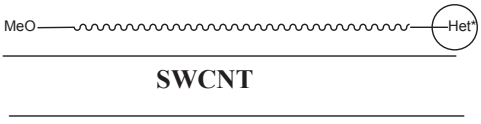
Het = (O)PPhBu-*t;* S(O)PPhBu-*t;* Se(O)PPhBu-*t,*
S(O)R (R = *p*-Tol, $C_{16}H_{33}$); S(O)(NH)R (R = *p*-Tol, $C_{16}H_{33}$)
n=1, or n>1,

c) the isolation and characterization of chiral „supramolecular" complexes between MWCNTs or SWCNTs and heteroorganic derivatives, which bear simultaneously a stereogenic heteroatom and a substituent with extended n electron systems having the general structures **5** or **6**. [10,11]



= polyethyleneglycol chain
Het = S or P

5



= polyethyleneglycol chain
Het = S or P

6

Acknowledgements

The authors thank for the support from the fund of the National Science Center awarded on the basis of the decisions UMO-2011/03/B/ST5/03233, UMO-2011/01/B/ST5/06304, UMO-2011/01/B/ST5/06664 and N N204 518539.

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Exploring And Exploiting New Reactivity of Alkyl-Tricarbastannatranes in Lewis Acid and Transition Metal Catalysis

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My research group has recently characterized the structure and determined the Lewis acidity of tricarbastannatranes $[N(CH_2CH_2CH_2)_3Sn]^+(X)^-$ (X = BF_4, SbF_6, $B[(3,5–(CF_3)_2(C_6H_3)]_4$). The tin complexes were prepared by the reaction of $N(CH_2CH_2CH_2)_3SnCl$ with $AgBF_4$, $AgSbF_6$, and $AgB[(3,5–(CF_3)_2(C_6H_3)]_4$, respectively (Fig. 1). In parallel, the reactivity of hypervalent alkyl-tricarbastannatranes with $B(C_6F_5)_3$ was investigated; the apical alkyl ligand is transferred from the tin center to the boron center, with the exception of isopropyl, for which hydride transfer was observed. Furthermore, it has been demonstrated that $[N(CH_2CH_2CH_2)_3Sn]^+[MeB(C_6F_5)_3]^-$ promotes the conjugate addition of alkyl-tricarbastannatranes (alkyl and hydride) to electron-deficient alkenes such as benzylidene Meldrum's acids; detailed mechanistic studies will be presented. [1] In addition, it has been shown that pentacoordinated alkyl-tricarbastannatranes efficiently transmetalate with cationic Pd(II) centers, [2] and cationic Rh(I) catalysts (Fig. 1).

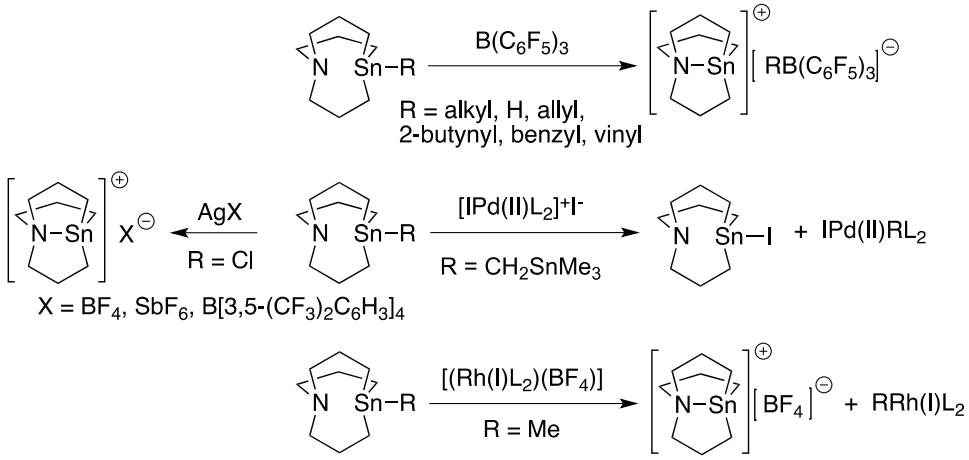

Fig. 1. Reactivity of alkyl-tricarbastannatranes

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Synteza kierowana symetrią – funkcjonalne, chiralne makrocykle i klatki molekularne

Marcin Kwit[1,2] i Jacek Gawroński[1]

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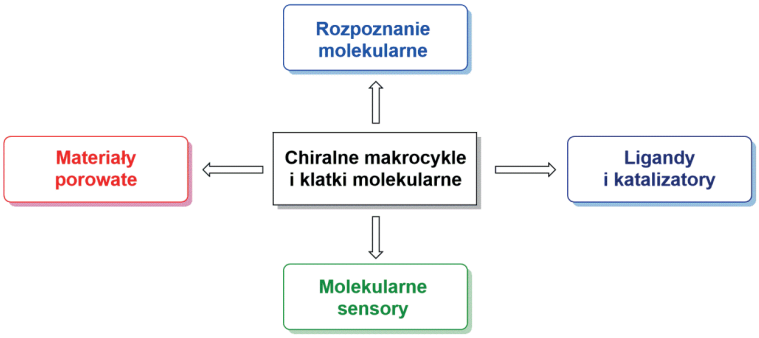
Agregacja i samoorganizacja małych cząsteczek w duże układy jest jednym z fundamentalnych procesów przebiegających w układach biologicznych. [1] Bazująca na koncepcji dynamicznej chemii wiązań kowalencyjnych, predyspozycji strukturalnej i preorganizacji substratów reakcja iminowania dipodalnych amin – di- lub tripodalnymi aldehydami umożliwia efektywną syntezę nowych połączeń o strukturze cyklicznej bądź klatkowej. [2] Spośród możliwych produktów, z reguły dominującym lub wyłącznie powstającym jest produkt o najwyższej możliwej dla danego układu symetrii, pod warunkiem, że proces kontrolowany będzie termodynamicznie.

Odpowiednia funkcjonalizacja fragmentu donorowego lub akceptorowego pozwala na racjonalne modyfikowanie struktury, ale przede wszystkim właściwości tego typu związków. Modyfikowane makrocykle i klatki molekularne są nie tylko układami zdolnymi do tworzenia złożonych architektur strukturalnych zarówno w krysztale jak i w roztworze, ale mogą również pełnić określone funkcje – ligandów, katalizatorów, materiałów porowatych, sensorów i żelatorów.



Rys. 1. Przykłady zastosowań chiralnych makrocykli i klatek molekularnych

W trakcie wykładu zostaną omówione wybrane problemy syntezy, dynamiki i architektury strukturalnej oraz przykładowe zastosowania chiralnych makrocykli i klatek molekularnych.

Podziękowania

Badania finansowane z grantu NCN 2012/06/A/ST5/00230.

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Some Aspects on the Synthesis, Reactivity and Applications of Aromatic Nitroxides

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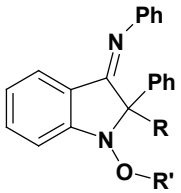
Nitroxide radicals are in general stable compounds, which over time have had many applications in different fields. They can be either aliphatic or aromatic, the present communication only deal with nitroxides having an aromatic structure.

Aromatic nitroxides have the ability to give coupling reaction at conjugated position of the nitroxide function with oxygen-centred radicals, and at the oxygen of the nitroxide group with nitrogen, sulphur and carbon centred radicals. For this, their properties have been used as antioxidants, proving to be efficient towards all biological systems: lipids, proteins and DNA. [1]

An unusual synthesis of nitroxides aromatic radicals through the intermediate formation of diazo-compounds never observed before, was carried out in one-step by reacting nitric oxide with nitroso derivatives,: the mechanism of the reaction, which can be extended to the synthesis of azo compounds, will be discussed in the present communication. [2]

In the last twenty years, much work has been devoted to the use of nitroxides in the controlled radical polymerization. [3] Actually compounds used in Nitroxide Mediated Polymerization (NMP) are the alkoxyamines, which generally are prepared by nitroxides and work through a mechanism, which has been called *persistent radical effect*. [4] In this communication will be discussed a synthesis of alkoxyamines having the following structure. [5]



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Three Component Reaction as a Mean to Prepare Aminomethylenebisphosphonates: the Example how One Reaction Could Be Fascinating

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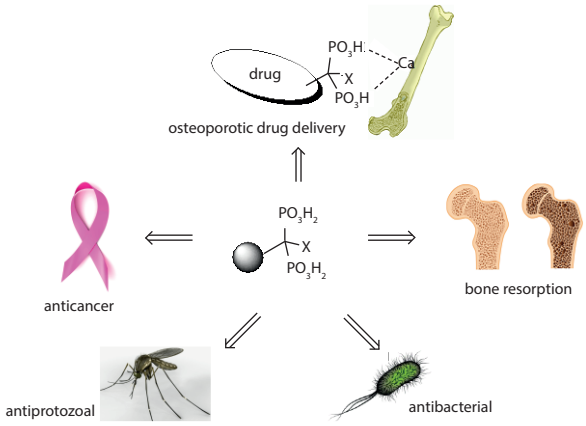
Bisphosphonates are one of the oldest classes of organophosphorus compounds. They are drugs used to slow or prevent bone damage and thus, are commonly used for the prevention and treatment of osteopenia and osteoporosis. Despite this important medicinal use, they display a variety of physiologic activities, which make them promising anti-cancer, anti-protozoal, antibacterial and antiviral agents. [1]



Three component reaction between amines, triethyl orthoformate and diethyl phosphite (Scheme 1) is perhaps the simplest and most commonly used for the preparation of *N*-subtituted aminomethylenebisphosphonic acids.

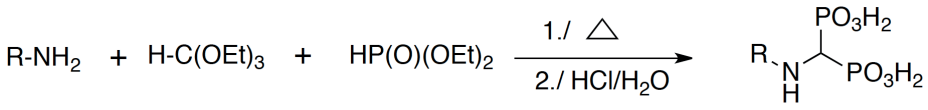


Fig. 1. Three-component reaction leading to aminomethylenebisphosphonates

Usually it yields a complex mixture of products the composition of which depends on structure of starting amine and reaction conditions. This reaction will be discussed in some detail.

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How Does Nucleophilic Aromatic Substitution Really Proceeds

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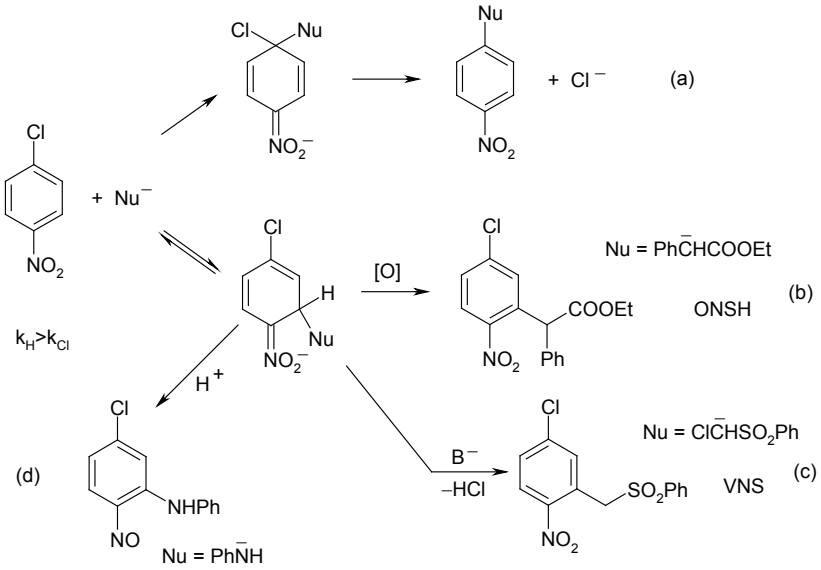
Nucleophilic aromatic substitution in halonitroarenes, S_NAr, is a fundamental process of organic chemistry widely applied in laboratory and industrial synthesis. According to the generally accepted mechanism the reaction proceeds via addition of nucleophiles to the nitroaromatic rings at positions occupied by halogen (or other nucleofugal groups X), to form σ^X adducts, followed by fast departure of X^- anions. In recent years we have shown that reversible addition of nucleophiles proceeds faster at positions occupied by hydrogen, however hydride anions, H^- are unable to depart from the σ^H adducts formed, so these adducts usually dissociate and slower addition at positions occupied by X and S_NAr is possible. σ^H– Adducts of some nucleophiles under properly selected conditions can undergo fast further conversion into products of nucleophilic substitution of hydrogen S_NArH on a few ways e.g.: b, c, d. Exemplification is shown in scheme.



Nucleophilic substitution of hydrogen, S_NArH, proceeds via fast addition to form σ^H adducts followed by fast conversion hence proceeds faster than S_NAr of halogens. Thus S_NAr is a secondary process and its generally accepted mechanism should be corrected.

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A New Entry to P-Stereogenic Six-Membered Phosphorus Heterocycles

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Chiral cyclic phosphines constitute an important group of organophosphorus compounds which are sought for their advantageous performance as chiral ligands in various transition metals catalyzed asymmetric transformations. Although numerous chiral five-membered phospholane ligands [1a] and four-membered phosphetane ligands [1b] were developed to meet the demand, the corresponding six-membered phosphorinane systems have remained practically undeveloped. [1] Apparently, this has been due to limited versatility of methods available for synthesis of the phosphorinane ring system. Especially rare are resolved P-stereogenic phosphorinanes as well as those bearing additional functional groups which could enable their further predesignated structural elaborations.

Our efforts to fill this gap have started with conversion of easily available 1-phenylphosphorinan-4-one oxide (**1**) [3] to a P-stereogenic phosphorin-2-en-4-one oxide **2** designed as a versatile, suitably functionalized precursor to other mono and polycyclic ring systems possessing stereogenic phosphorus incorporated in the six-membered ring. The presentation will highlight recent developments from our group on the enantioselective synthesis as well as resolution of phosphorinenone **2**. Some of the studied straightforward transformations of the resolved **2** leading to phosphadecalones and benzophosphorinenones are signaled in Scheme 1. An efficient protocol for a direct *one-pot eight-step* conversion of saturated **1** to dibenzophosphorinanones **3** has also been developed.

Scope, stereochemical aspects and the development of a catalytic oxidation protocol will be discussed in details.

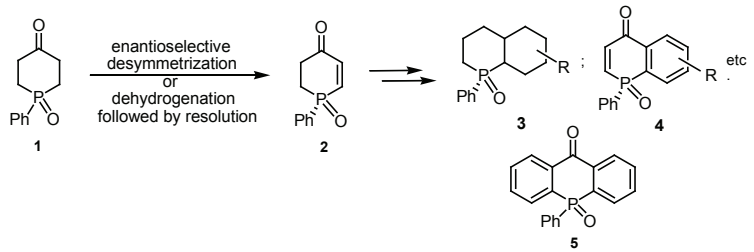

Fig. 1. Desymmetrization and selected transformations of phosphorinanones

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Phenyl Group at Phosphorus – the Beginning of the Story

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Organophosphorus compounds with phenyl group at phosphorus are very common molecules which could be easily prepared either from phenylphosphonous dichloride ($PhPCl_2$) or from chlorodiphenylphosphine (Ph_2PCl). But, placement of this substituent at phosphorus usually means blocking any further modifications of the molecule. In case where the analogous compound with phenyl group replaced with aryl/alkyl group is needed, the synthesis must be repeated from the beginning. The possible solution of this problem might be modification/replacement of phenyl group but, up to now, this approach has never been considered as a method of synthesis of organophosphorus compounds. It would be therefore highly desirable to develop some new methods for modification of phenyl group in organophosphorus compounds.

In the course of our research topic devoted to the development of new synthetic procedures in organophosphorus chemistry we were interested in the development of new pathways for modification of aryl substituent in arylphosphorus compounds. Two possibilities attracted our attention: Birch reduction (Fig. 1) [1] and intramolecular electrophilic substitution reaction (Fig. 2). [2] Results associated with these topics will be summarized in this communication.

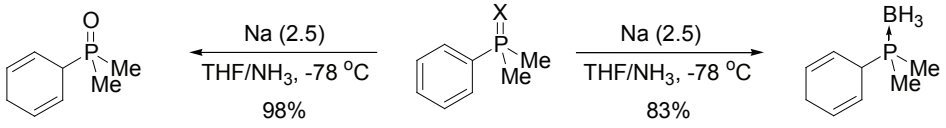

Fig. 1 Birch reduction of organophosphorus compounds

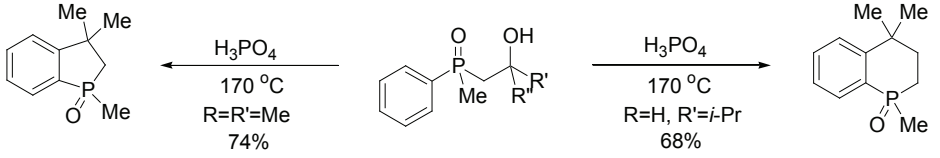

Fig. 2. Cyclization of β-hydroxyalkylphosphine oxides

Acknowledgements

Financial support from Ministry of Science and Higher Education (grant no. N N204 2328 34 and N N204 3539 40) and National Science Centre (SONATA-BIS funding scheme, grant no. 2012/07/E/ST5/00544) is kindly acknowledged.

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Oral presentations / Prezentacje ustne

Recent Developments in Steroid Sulfatase Inhibitors as Anti-Cancer Agents

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Steroid sulfatase (STS) is a target enzyme of growing therapeutic importance. STS is responsible for the hydrolysis of steroid sulfates to their active forms (e.g., estrone sulfate to estrone); therefore, the inhibition of this enzyme decreases the biosynthesis of the active hormones responsible for breast, endometrial or prostate cancer. [1]

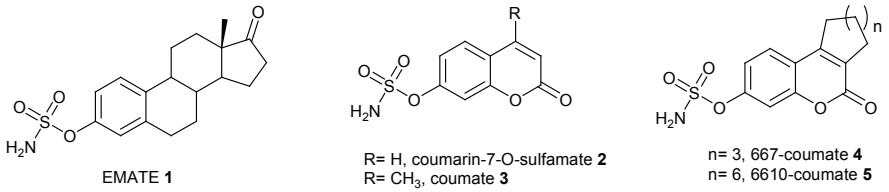

Fig. 1. Chemical structures of STS inhibitors

Approaches for the development of effective and potent STS inhibitors include three different categories of compounds: alternative substrates (including competitive reversible inhibitors), reversible inhibitors, and irreversible inhibitors. EMATE **1**, one of the first irreversible inhibitors, exhibited a very potent activity in MCF-7 cells with an IC_{50} value of 65 pM. [2] Despite the exceptional potency of EMATE **1**, clinical trials for this compound have been discontinued due to its estrogenic properties. [3] The attempts to synthesize nonsteroidal agents (devoid of undesirable adverse endocrine effects *in vivo*) have promoted the generation of coumarin sulfamates. The first potent inhibitors based on the coumarin scaffold were coumarin-7-*O*-sulfamate **2** and 4-methylcoumarin-7-O-sulfamate (coumate) **3**. [4] Further modifications of their structures led to a wide range of tricyclic coumarin derivatives, which showed more potent inhibitory activities. For example, 667-coumate **4** (entered into clinical trials for patients with hormonedependent breast cancer) and 6610-coumate **5** have demonstrated a potent activity toward STS with IC_{50} values of 8 nM and 1 nM, respectively. [5]

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Friendly Batteries for Environment Based on the Functionalized Carbon Nanotube by Salts Containing Sulfur and Phosphorus Heteroatoms

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Functionalization of the multi-walled carbon nanotubes (MWCNT) makes it possible to change their properties and structure. Such modifications contribute to the use of the functionalized MWCNT in many industries. The proposed procedures allow for predicting the most optimal systems prepared by functionalization of the nanotubes to their practical use. System was obtained resulting from the modification of carbon nanotubes substituted covalent atoms of bromine, which is beginning of substituted by many various chemical systems.

The system was subjected to extensive physico-chemical analysis: thermal analysis using DSC/TG, X-RAY measurements and electron microscopy SEM with EDS measurements.

In order to analyse the efficiency of functionalization multi-walled carbon nanotubes was constructed the cell battery with these systems and tested electrochemical were carried out (processes of charging/discharging and cyclic voltammetry).

The achievement of positive results of these studies should increase the availability of suitable derivatives which are the subject of growing interest, due to their interesting properties.

Acknowledgements

This project was financially supported by the National Science Center fund awarded based on the decision 2014/15/B/ST8/00101.

Organocatalytic Approach to Optically Active α-Hydroxy-β-Amino Aldehydes Bearing a Quaternary Stereogenic Centre

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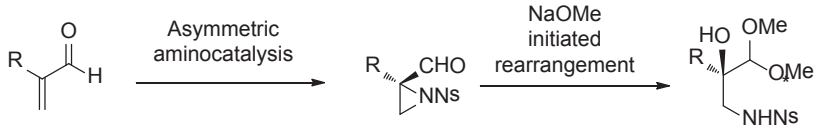
The synthesis of optically active compounds incorporating a quaternary stereogenic centre is one of the most exciting challenges of the contemporary organic synthesis. [1] Especially, the methods for the introduction of 1,2-aminoalcohol moiety, present in many natural products, has witnessed increasing interest. Heretofore, only a few reliable methods are known in the literature for the stereoselective introduction of 1,2-aminoalcohol moiety, most of which are based on the Sharpless' asymmetric aminohydroxylation. [2] Their applicability has been proven in many total syntheses. However, regioselectivity of the reaction and the toxicity of osmium are significant constraints. Therefore, the search for alternative methods, employing simple organocatalysts is of major importance.

Herein, a simple and effective approach for the synthesis of glycerine aldehyde analogues **3** containing 1,2-aminoalcohol moiety and a quaternary stereogenic centre has been disclosed. This method employs α-substituted acroleins as starting materials, which are converted into aziridines **2** with a novel aziridinating agent. Subsequent rearrangement of intermediates **2** initiated by sodium methoxide yields protected α-hydroxy-β-amino aldehydes. Under optimized reaction conditions, target products are obtained with very good yields (up to 90%) and enantioselectivities (up to 95% ee). Furthermore, this one-pot reaction cascade shows a broad substrate scope and benefits from the operational simplicity.



1 **2** **3**

Acknowledgements

This work was realized within the Homing Plus programme of Foundation for Polish Science, co-financed from European Union, Regional Development Fund grant number HOMING-PLUS/2012-6/1.

INNOWACYJNA GOSPODARKA
NARODOWA STRATEGIA SPÓJNOŚCI

UNIA EUROPEJSKA
EUROPEJSKI FUNDUSZ
ROZWOJU REGIONALNEGO

FNP
Fundacja na rzecz Nauki Polskiej

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Badania degradacji kompleksów typu $CpM(CO)_x(\eta^1$-*N*-imidato) przy zastosowaniu spektroskopii FT-IR I LC-MS

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Chemia metaloorganiczna zajmuje się badaniem związków zawierających wiązanie metal-węgiel. Termin „chemia biometaloorganiczna" został wprowadzony w 1985 roku przez G. Jaouena [1–2], obecnie związki biometaloorganiczne znajdują zastosowanie w farmacji, testach biologicznych oraz bioobrazowaniu.

Przykładem związków metaloorganicznych stosowanych w biochemii są kompleksy karbonylowe metali przejściowych. W ostatnich latach w Katedrze Chemii Organicznej Uniwersytetu Łódzkiego prowadzone są badania nad reaktywnością i zastosowaniem kompleksów typu $CpM(CO)_x(\eta^1$-*N*-maleimidato) (M=Fe, Ru x=2; M=Mo, W, x=3). Związki te wykazują silne pasma absorpcji w spektroskopii IR w zakresie 1800–2150 cm^{-1} pochodzące od grup CO, co umożliwia ich zastosowanie jako znaczniki biomolekuł [3–5].

W ramach ostatnio przeprowadzonych badań stwierdzono również, że związki te w odpowiednich warunkach mogą uwalniać tlenek węgla w ilościach terapeutycznych, dzięki czemu mogą znaleźć zastosowanie jako CO-RMs (*Carbon Monoxide-Releasing Molecules*). Tlenek węgla uwalnia się z tych kompleksów w wyniku ich fotodegradacji.

Przedmiotem badań prezentowanych w niniejszej pracy był rozpad kompleksów typu $CpM(CO)_2(\eta^1$-*N*-imidato) (M=Fe, Ru x=2; M=Mo, W, x=3) pod wpływem naświetlania światłem widzialnym oraz UV. Postęp degradacji monitorowano przy użyciu spektroskopii FT-IR oraz LC-MS. W przypadku kompleksów zawierających ligand maleimidato stwierdzono, że jednym z produktów degradacji jest produkt reakcji Dielsa-Aldera kompleksu metalokarbonylowego zawierającego fragment maleimidowy oraz cyklopentadienu uwolnionego z innej cząsteczki badanego kompleksu. [6]

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Wykorzystanie kompleksów metalokarbonylowych do znakowania białek

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Kompleksy metalokarbonylowe mogą być atrakcyjnymi strukturami dla bio-obrazowania, wykazują bowiem silne pasma absorpcji drgań walencyjnych *ν*CO w widmach w podczerwieni w zakresie 1850–2150 cm^{-1}, co umożliwia ich łatwą detekcję w spektroskopii IR. [1]

Od wielu lat w Katedrze Chemii Organicznej Uniwersytetu Łódzkiego prowadzone są badania nad zastosowaniem kompleksów metalokarbonylowych typu $CpM(CO)_x(\eta^1$-*N*-maleimidato) (M= Fe, Mo; x=2, 3) jako znaczników biomolekuł. Wiązanie etylenowe występujące w ligandzie maleimidowym łatwo ulega reakcji z nukleofilami takimi jak tiole, aminy czy imidazole, co umożliwia wprowadzanie znaczników metalokarbonylowych do biocząsteczek. [2]

Precyzyjne znakowanie białek wymaga jednak użycia selektywnych metod wprowadzania znaczników. W tym celu wykorzystuje się reakcje typu „click". [3] Najczęściej stosowaną reakcją jest 1,3-dipolarna cykloaddycja Huisgena (CuAAC). Jednakże toksyczność katalizatora miedziowego uniemożliwia zastosowanie tej metody w badaniach *in vitro* lub *in vivo*. Obecnie poszukuje się alternatywnych metod, które nie wymagają użycia katalizatora metalicznego, jak na przykład reakcja cykloaddycji [3+2] SPAAC. [4] W tej reakcji wykorzystuje się pochodne cyklooktynu, które posiadają mniejszą energię aktywacji w porównaniu do terminalnych alkinów. [5]

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Meldrum's Acid Derivatives as a Versatile Starting Point for the Preparation of Biologically Active Compounds

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Over the one hundred years since the first synthesis of Meldrum's acid, compound consisting of 1,3-dioksa-4,6-dione moiety are still in spot light of organic chemistry. Particularly in last two decades significant growth of interest is observed, mostly due to biological and pharmaceutical applications of compounds prepared using 1,3-dioksa-4,6-diones as keys intermediates. [1, 2, 3]

In our laboratory we have exploited synthetic potential of acyl or alkylidene 1,3-dioxa-4,6-diones on four ways. The first branch of research based on preparation of azetidones through [2+2] cycloaddition of thermally generated ketenes form acyl Meldrum's to aldimines. [4, 5] In this way we prepared representative groups of 3-carbamoyl azetidones as well as 3-acyl azetidones. Moreover, thiocarbamoyl 1,3-dioxa-4,6-diones allowed to obtain 3-thiocarbamoyl azetidones through *N*-alkenyl malonoamides. The second research task concerning modification of bicyclic 2-pirydones prepared from the same ketenes and Δ^2-thiazolines. These bicyclic 2-pirydones are well known agent against uropathogenic *Escherichia coli*. [6] On the other hand, we developed method for preparation of modified peptides based on application of 5-carbamoyl 1,3-dioxa-4,6-diones. Our last research trend aims to preparation series of serotonin transporter inhibitors using a 5-arylidene 1,3-dioxa-4,6-diones as a starting material.

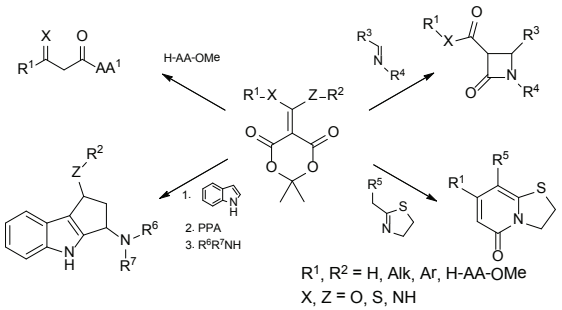

Fig. 1. Synthetic application of Meldrum's acid derivatives

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Reakcje nukleofilowego fluorowania pochodnych kwasów α-hydroksyfosfonowych

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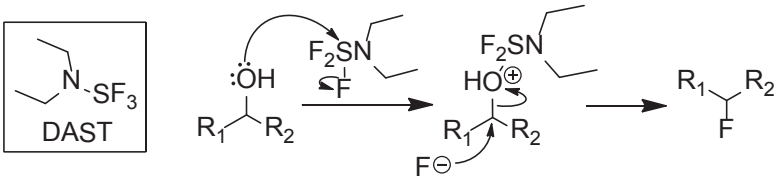
Fluorowane pochodne kwasów fosfonowych wykazują wiele udokumentowanych przykładów aktywności biologicznej. Zawdzięczają to obecności w strukturze ich cząsteczek odpornego na hydrolizę przez fosfatazy wiązania P-C, jak również możliwości specyficznego koordynowania metali znajdujących się w centrach aktywnych enzymów. Obecność atomu(ów) fluoru w pozycji α do grupy fosfonianowej zwiększa podobieństwo fosfonianów do naturalnie występujących w organizmach fosforanów.



Rys. 1. Struktura odczynnika DAST oraz mechanizm nukleofilowego fluorowania

Jedną z możliwości wprowadzenia atomu fluoru do cząsteczki jest podstawienie grupy hydroksylowej α-hydroksyfosfonianu na drodze reakcji nukleofilowego fluorowania. Odczynnikiem wykorzystywanym do tych reakcji jest między innymi trifluorek dietyloaminosiarki (DAST – rys. 1). W reakcji alkoholu R_1R_2CH-OH z odczynnikiem fluorującym kluczowym etapem jest utworzenie związku zawierającego dobrą grupę opuszczającą R_1R_2CH-OSF_2NEt_2, która w kolejnym etapie ulega podstawieniu wytworzonym anionem fluorkowym (rys. 1). Co ciekawe, w reakcjach otrzymywania związków fluoroorganicznych tą metodą istnieje możliwość wystąpienia reakcji dehydratacji bądź przegrupowania związku, prowadząc do syntezy nowych interesujących związków o potencjalnej aktywności biologicznej.

W trakcie wystąpienia zaprezentowane zostaną wyniki przeprowadzonych reakcji nukleofilowego fluorowania wybranych pochodnych węglowodanów oraz aminokwasów zawierających ugrupowanie α-hydroksyfosfonianowe, prowadzące w niektórych przypadkach do otrzymania zaskakujących produktów.

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Synthesis and Structural Modifications of Phosphinic Dipeptide Analogues

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Phosphinic dipeptides are intensively explored organophosphorus compounds, mainly as transition state analogue inhibitors of metalloproteases. The synthetic challenge of their preparation is construction of the pseudopeptidic backbone bearing appropriate side-chain substituents. Typically, this involves a multistep preparation of two individual building blocks, which are combined in the final step in a phospha-Michael or amidoalkylation reaction. [1] Accordingly, development of a series of novel compounds that incorporate P1 and P1' side-chain residues of a rationally optimized and complex structure, together with their biological activity, is presented. [2]

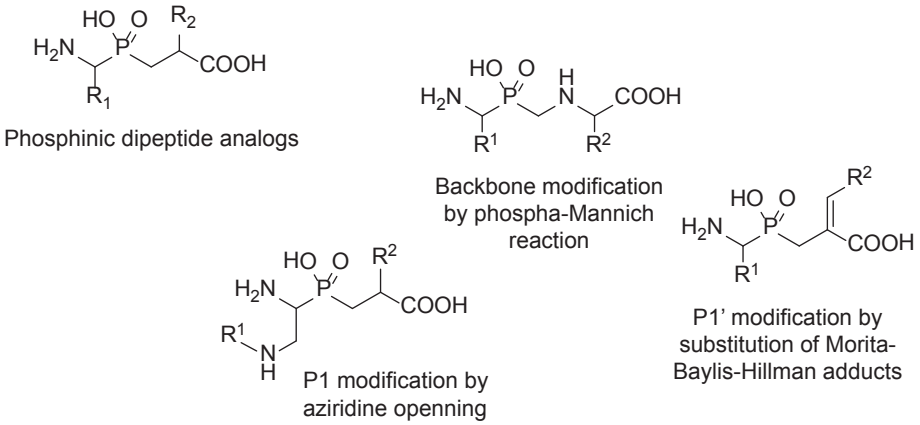

Fig. 1. Fundamental phosphinic dipeptide structure and its specific modifications

The two general methodologies mentioned above hardly allow variation of the substituents, thus, many efforts have been dedicated to the development of alternative approaches. We also describe our recent results on elaboration of individual and parallel synthetic pathways leading to specific derivatives, in principal, designed as inhibitors of selected aminopeptidases (Fig. 1). [3, 4]

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Synthesis of 5-Azo-8-hydroxy-2-methylquinoline Dyes and Relevant Spectroscopic Studies

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We are going to present the synthetic, spectroscopy and mechanistic studies of sixteen derivatives of 5-azo-8-hydroxy-2-methylquinoline dyes with fifteen novel structures which have been synthesized in an efficient one-pot synthesis protocol. For all cases we isolated only one regioisomer with newly formed N–$C_{quinoline}$ bond in C5 position (**3**). For the first time we were able to detect a second possible regioisomer with newly formed N–$C_{quinoline}$ bond in C7 position (**4**). Mostly the chemistry was based on cheap commercially available **1a** (R=H) and two others, **1b** (R=Me) and **1c** (R=Cl), and readily accessible aminopyridine and aniline analogues **2** possess methyl, methoxyl, halogen (Cl and Br), hydroxyl and NO_2 groups in their constitution. Two of the novel dyes have been synthesized as hydrochloride salts and structurally characterized by X-ray crystallography. The measured visible absorption spectra of the dyes were discussed regarding the effects of substituent, varying pH and solvent upon their absorption ability. The different substituents were chosen in order to represent different electronic features. The solvents effects on the absorption spectra of the studied dyes indicated the existence of azo hydrazone tautomerism. The obtained dyes were successfully incorporated into polyester fabrics and their light fastness properties were evaluated. Among the designed dye candidates, –NO_2 substituted compounds are promising materials in respect to their dyeing and light fastness properties.

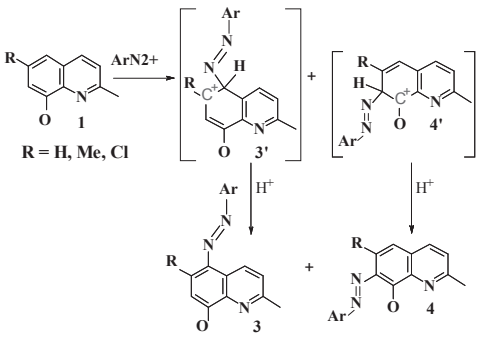

Fig. 1. Synthesis of dyes **3**; *Reagents and conditions*: (i); $ArNH_2$ (ii); $NaNO_2$, *aq*. HCl, <5°C

Despite their potential value, there are only limited examples of azoquinolines often without NMR characteristics, especially without ^{13}C NMR, to the best of our knowledge according to literature data. Some characterizations contained mistakes e.g. Kaliyappan *et al*. who announced azoquinoline structure with newly formed N–$C_{quinoline}$ bond in 4 position (pyridine ring), instead of 5 (prefer activated position on phenol ring).

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Kinetyczne, chiralne [4+6] organiczne klatki molekularne

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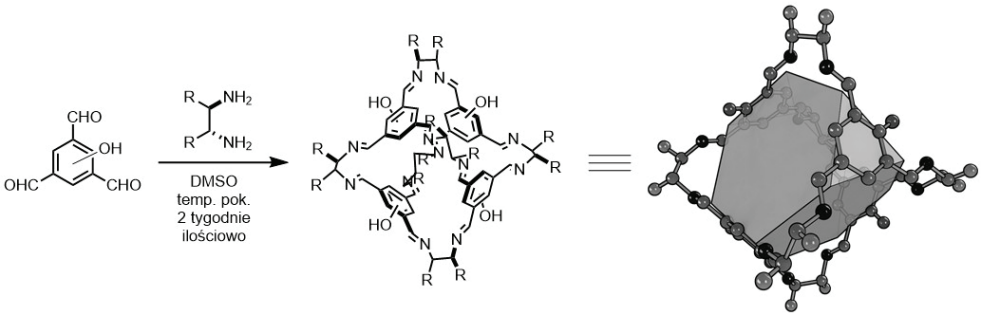
W ostatnich latach, synteza nowych organicznych makrocykli i klatek molekularnych stanowi dynamicznie rozwijającą się dziedzinę chemii organicznej. Tylko niewielka ilość struktur tego typu otrzymywana jest przez kowalencyjne reakcje pozwalające na odwracalne tworzenie wiązań kowalencyjnych [1]. Reakcja iminowania, bazująca na koncepcji dynamicznej chemii wiązań kowalencyjnych (ang. *Dynamic Covalent Chemistry*), pozwala na otrzymywanie różnorodnych dużych pierścieni i klatek molekularnych z strukturalnie predysponowanych substratów.

W naszym Zespole, po raz pierwszy opracowana została metoda syntezy klatek molekularnych o nietypowej symetrii *T* [2]. Związki tego typu mogą być zdolne do selektywnej *enkapsulacji*, czyli wiązania wewnątrz klatki jonów lub cząsteczek obojętnych strukturalnie dopasowanych do wewnętrznej luki klatki [3].

Nowa metoda syntezy klatek molekularnych, zaprezentowana tutaj, opiera się na kondensacji 2,4,6-triformylofenolu z różnymi wicynalnymi diaminami i pozwala na efektywne otrzymywanie nowej klasy związków typu COF (ang. *covalent organic frame)* (rys. 1).



Rys. 1. Otrzymywanie chiralnych klatek salenowych

Obecność grupy hydroksylowej powoduje obniżenie symetrii aldehydu, a tworzące się klatki molekularne są produktami kinetycznymi, a nie termodynamicznymi.

Modyfikacja warunków syntezy pozwala w prosty sposób modelować niektóre właściwości produktu, np. porowatość.

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The Reactivity of Disulfanyl Derivatives of Phosphorodithioic Acid

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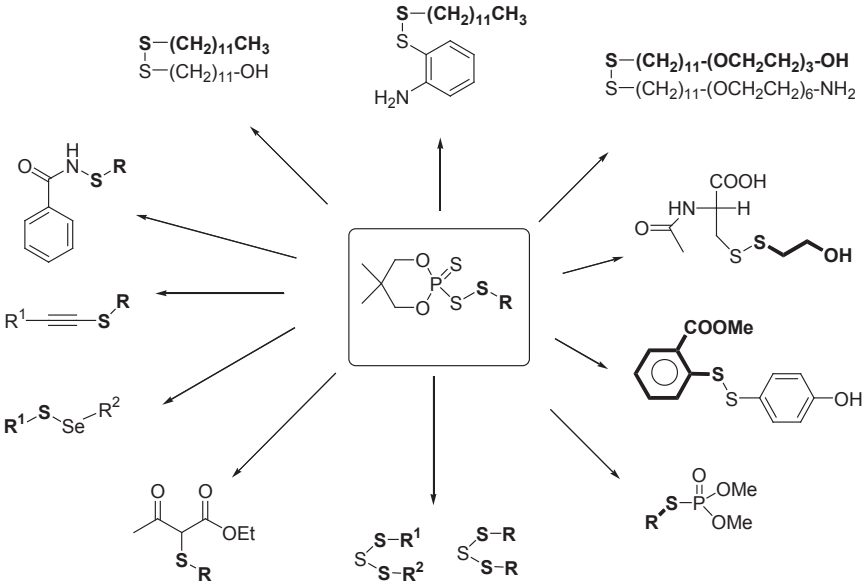
Phosphorodithioic acids are readily available by the reaction of P_4S_{10} with alcohols and diols. The increased polarizability of sulfur (2.90) versus oxygen (0.802) makes phosphorodithioic acids more acidic (pK_a 2) and nucleophilic than their oxygenated analogues. The corresponding sulfenyl bromides, readily available from phosphorodithioic acid or its disulfane made possible to gain the access to activated and functionalized thiols in the form of *S*-phosphorylated disulfanes with yield varying from 91 to 100%.



Disulfanyl derivatives of phosphorodithioic acid are prone to nucleophilic attack by sulfur, carbon, nitrogen, and trivalent phosphorus nucleophiles leading to disulfanes, trisulfanes, sulfenamides, and phosphorothioates respectively. The efficient preparation of functionalized unsymmetrical molecules can be achieved by that approach. The chemoselectivity of disulfanyl derivatives is crucial and responsible for their successful use in the synthesis of these compounds in the presence of other unprotected functional groups. The developed protocol is very convenient. Starting materials are easily accessible, reaction times are short, yields and purities are very high. The scope and limitation of developed method will be presented and discussed.

Synteza *α*-difluorometylostyrenu i badania jego reaktywności w reakcjach polimeryzacji rodnikowej

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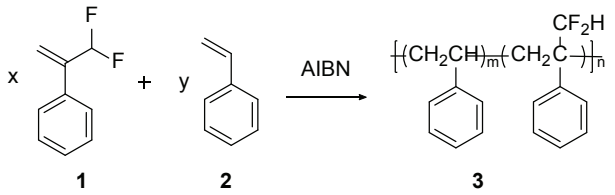
Od kilkudziesięciu lat obserwowany jest gwałtowny rozwój chemii polimerów. Opracowywanie nowych materiałów jest związane z postępem technologicznym, ponieważ trudno sobie wyobrazić rozwój przemysłu bez syntezy nowatorskich makrocząsteczek. Dzięki zastosowaniu nowych metod syntezy czy modyfikacji można uzyskać tworzywa o pożądanej strukturze i coraz lepszych właściwościach funkcjonalnych [1].

Do grupy polimerów, łączących unikalne cechy należą polimery fluoroorganiczne. Ze względu na wysoką wartość energii wiązania węgiel-fluor (485 kJ/mol), polimery te są stabilne termicznie i odporne chemicznie. Ponadto, niska polaryzowalność wiązania C-F ujawnia się w znikomej absorpcyjności wody materiałów przez nie tworzonych. Atomy fluoru sprawiają, że fluoropolimery charakteryzują się niską energią powierzchniową, przez co są odporne na ścieranie [2].

Jedną z interesujących grup fluoropolimerów są fluorowane polimery aromatyczne (FPA). Zastosowanie monomerów zawierających w strukturze pierścień aromatyczny przyczynia się do zwiększenia wytrzymałości mechanicznej, natomiast wbudowanie fluorowanego fragmentu w aromatyczny łańcuch polimerowy może powodować poprawę właściwości termicznych otrzymywanych materiałów.

Celem badań była synteza fluorowanego monomeru aromatycznego – *α*-difluorometylostyrenu (DFMST) **1** oraz sprawdzenie jego reaktywności w reakcjach polimeryzacji rodnikowej ze styrenem (ST) **2** [3]. Otrzymano nowy związek z grupy FPA – *poli*(DFMST-*co*-ST) **3**, który scharakteryzowano wykonując analizę jądrowego rezonansu magnetycznego, chromatografię żelową, analizę termograwimetryczną oraz skaningową kalorymetrię różnicową. Prezentowane wyniki potwierdzają unikalne właściwości otrzymanego fluoropolimeru i sprawiają, że może on mieć potencjalne zastosowanie w chemii materiałowej.



Rys. 1 Reakcja kopolimeryzacji difluorowanego *α*-metylostyrenu **1** ze styrenem **2**.

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Poster presentations / Prezentacje posterowe

Modyfikowane, mostkowane makrocykle trianglaminowe jako nowe prekursory materiałów porowatych, chiralnych selektorów i ligandów

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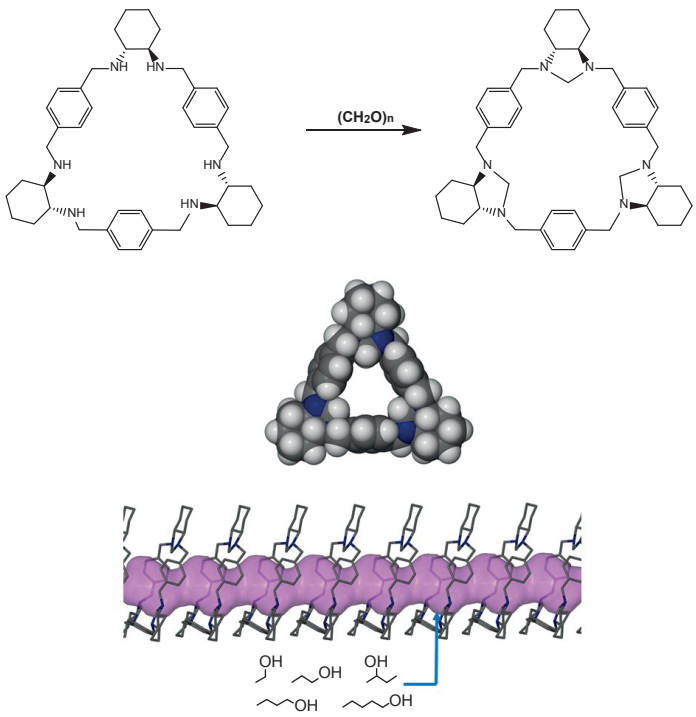
Modyfikacja trianglaminy poprzez podstawienie protonów związanych z atomem azotu skutkuje przeważnie zwiększeniem mobilności konformacyjnej makrocykla, a tym samym trudnościami w interpretacji widm NMR i krystalizacji. Mostkowanie trianglaminy za pomocą paraformaldehydu prowadzi do otrzymania makrocykla z trzema mostkami metylenowymi, co częściowo usztywnia strukturę, przez co w ciele stałym obserwuje się tworzenie kanałów, do których może wnikać rozpuszczalnik. Powstaje trwały materiał porowaty, w którym po usunięciu rozpuszczalnika kanały zostają zachowane, a struktura nie zapada się. W zależności od rozpuszczalnika użytego do krystalizacji otrzymuje się kryształy o zróżnicowanych parametrach i stechiometrii gość–gospodarz.



Rys. 1. Synteza mostkowanej trianglaminy oraz struktura kanałów w krysztale

Poprzez wprowadzenie do pierścienia aromatycznego makrocykla podstawników o zróżnicowanych rozmiarach i właściwościach chemicznych (m.in. Br, CN, NO_2, Ar), można sterować powinowactwem wnęki makrocyklicznej i jednocześnie kontrolować wielkość tworzących się w ciele stałym kanałów. Dodatkowo, użycie niesymetrycznego dialdehydu do syntezy trianglamin może zmieniać stereoselektywność reakcji makrocyklizacji – produkt cyklokondensacji może charakteryzować się symetrią C_3 lub C_1, podczas gdy symetrycznych dialdehydów maksymalna symetria to D_2. Celem projektu jest synteza biblioteki związków makrocyklicznych na bazie trianglaminy, modyfikowanych w części aldehydowej, mostkowanie ich oraz poddanie badaniom strukturalnym.

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Dephosphorylation of Phosphonic and Phosphinic Derivatives of Heterocyclic Compounds in Acidic Conditions

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Phosphorus (P) is an essential element for life. In biological systems, P is typically present in the form of inorganic phosphate or its derivatives, such as organophosphate esters and anhydrides. In recent years, it was discovered, that some P compounds such as phosphonates and phosphinates (which contain stable C–P bonds in place of the labile O–P bonds in the organophosphates), also play prominent roles in agriculture and medicine. [1] Importantly, many phosphonates are metabolized as a source of inorganic phosphate by microorganisms living in phosphate poor environments.

In light of the agricultural and medical importance of organophosphonic and phosphinic acids, the study of dephosphorylation of heterocyclic phosphonate and phosphinate derivatives, (which is caused in fact, by C-P bond cleavage in these compounds [2–4]), is important in understanding of the mechanism of biological C-P bond scission and conversions, accompanied with those transformations.

Herein we report on our recent findings on dephosphorylation of some heterocyclic phosphonic and phosphinic derivatives in acidic conditions. We observed that the scission of C-P occurs not only in the presence of a proton as electrophile but also in the presence of other electrophiles *e.g.* Br_2 [5, 6] and NO_2BF_2 [7] and in aprotic solvent such as $CHCl_3$ (Fig. 1). These results are very important in light of explanation and clarification of the possible mechanisms of C-P bond cleavage in heterocyclic phosphonates and phosphinates.

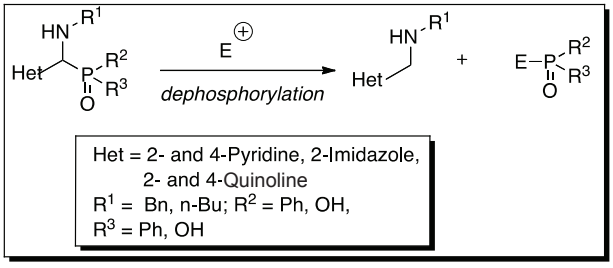

Fig. 1. Dephosphorylation of phosphorus-containing derivatives of heterocyclic compounds

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Various routes to 1*H*-Indol-2-ylphosphonate Afford New Procedures for the Synthesis of its Analogues and Homologues

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In recent years organophosphorus heteroaromatic compounds received intensive interest because of their useful biological and practical applications. Heteroaromatic phosphonic acids are not easy to prepare and therefore have been scarcely studied.

Basing on the results described by Olive [1] we had expected the formation of desired bisphosphonates in a reaction of structurally variable benzolactams with trialkyl phosphite and phosphoryl chloride. In contrast to aliphatic lactams, which gave cyclic aminomethylene-*gem*-bisphosphonates the corresponding benzoannulated lactams usually provide monophosphonates of variable structures, which depend on the size of the substrate aliphatic ring. Among them 1*H*-indol-2-ylphosphonate was obtained. It is not surprising if taking into account that the formed product is an aromatic one and thus aromatization is a driving force for its production. [2]

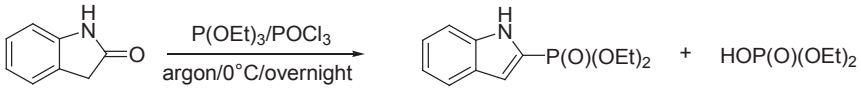

Fig. 1. Reaction of oxoindoles with triethyl phosphite and phosphoryl chloride

All the obtained phosphonate esters appeared to be unstable upon acid hydrolysis and upon storage. Mechanism of acid catalyzed degradation of these compounds has been proposed.

Also one-pot lithiation-phosphonylation procedure has been proposed as a mean to prepare 1*H*-indol-2-ylphosphonate. It relays on direct lithiation of indole followed by phosphonylation with diethyl chlorophosphite followed by oxidation with hydrogen peroxide. This protocol applied to other heteroaromatics provides the general procedure for the preparation of respective phosphonates with satisfactory yields.

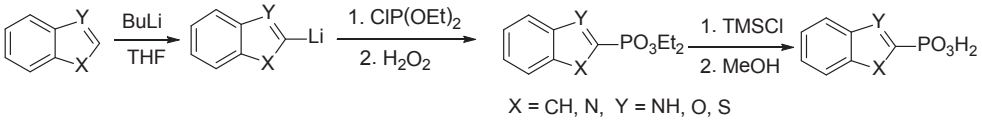

Fig. 2. Phosphonylation of benzothiophene, benzothiazole and benzoxazole

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A Novel and Efficient Synthesis of Functionalized *S*-Alkynyl Sulfanes

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The synthesis of *S*-Alkynyl sulfanes plays a significant role as an important transformation in organic synthesis and medicinal chemistry. *S*-Alkynyl sulfanes have also been used in organic materials, like dyes as well as in biomolecule and polymers. [1–2] These compounds are used in numerous transformation, such as cycloaddition and cross-coupling reaction. [3–4]

On the basis of previous research results, we developed a new, efficient and convenient method synthesis of *S*-Alkynyl sulfanes. This method is based on the reaction between lithium acetylide A and unsymmetrical phosphorodithioic acid disulfanyl derivatives B (Fig.1).

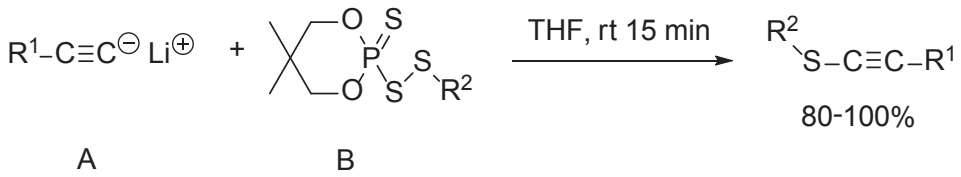

Fig. 1. Synthesis of functionalized *S*-Alkynyl sulfanes, where R^1: –Ph, $–CH_2OCH_2Ph$, $–CH_2NHBoc$; R^2: – $(CH_2)_{11}CH_3$, – $(CH_2)_{11}OH$, – $(CH_2)_{10}COOH$, $–PhCH_3$

Optimal reaction conditions as well as the scope and versatility of developed method will be presented. Further applications reactions with this compounds will be also discussed. The mechanism of the reactions will be proposed.

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Halogenated Carbon Nanotubes Functionalized by Salts Containing Stereogenic Heteroatoms as Electrodes in their Battery Cells

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Lithiated transition metal oxides are of great interest for fundamental studies and practical applications such as positive electrode materials for rechargeable lithium-ion batteries. The process of Li insertion into chromium oxides by both chemical and electrochemical methods was first presented by Koksbang and Norby. Chromium oxides, especially LiCr3O8, are attractive as constituents for cathode materials because they have high capacity at low discharge rates. The developments in the energy market of natural resources In the industrialized world the development of energy resources (e.g., oil, natural gas) has become essential for agriculture, transportation, waste collection, information technology, communications that have become prerequisites of a developed society. The forecasts for energy needs make it necessary to look for new alternative sources of energy for environmentally friendly batteries. Currently, a very promising solution is to store energy using cells composed of ternary systems such as alloys and composites. This storage of energy has the greatest potential of the many methods proposed so far. We have developed lightweight alloys and intermetallic compounds. Lithium Li-Me-O can be used as electrodes in batteries. This study concentrates on electrochemical properties of groups of multi-walled (MWCNT) carbon nanotubes functionalized with substituents containing a stereogenic heteroatom bonded covalently to the surface of the carbon nanotube. This system was tested in Swagelok-type cells. The cells consisted of a system (CNT or CNT-Br or functionalized CNT with salts containing S and P atoms) with a working electrode, microfiber separators soaked with electrolyte solution and a lithium foil counter/reference (commercial LiCoO2) electrode., Galvanostatic cycling was performed on the cells at room temperature with a CH Instruments Model 600E potentiostat/galvanostat electrochemical measurements using standard techniques (chronoamperometry/chronopotentiometry).

Our method of bromination leads to covalently brominated MWCNTs. The brominated derivatives of MWCNTs react with anions containing a stereogenic phosphorus atom. The process of charge/discharge (lithuation/delithuation) of electrode is very fast and shows the possibility of using phosphorous containing MWCNT derivatives as “efficient” model electrodes in batteries.

Acknowledgements

The studies presented here were in part financially supported (as grants for J.D.) by National Science Center award 2014/15/B/ST8/00101.

Synthesis and Steroid Sulfatase Inhibitory Activity of *N*-Phosphorylated 3-(4-aminophenyl)-coumarin-7-*O*-Sulfamates

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The aim of the our research is design, synthesis and biological evaluation of the new steroid sulfatase (STS) inhibitors based on *N*-phosphorylated 3-(4-aminophenyl)-coumarin-7-*O*-sulfamates as potential drugs used in treatment of hormone-dependent breast cancer. Breast cancer is a major cause of mortality of postmenopausal women in developed countries, therefore it is of great priority to find a new and effective treatment methods. According to the *National Cancer Institute* (NCI) approximately 1 in 9 women are affected by breast cancer during their lifetime. Recent research clearly indicate the influence of endocrine precursors, such as estrogens, on stimulating of the cancer cell proliferation. Considering the STS action mechanism that includes the estrogen sulfates hydrolysis leading to obtain their biologically active forms, it seems that STS may have a very important role in breast cancer cell proliferation. [1] One of the most promising anticancer strategy is obtaining of the biologically active compounds that precise inhibit STS enzyme. The hypothesis of our research assumes that proposed structures of new sulfamated inhibitors containing additionally various organophosphorus moieties demonstrate great binding ability to the active site of STS (confirmed by the preliminary molecular modeling studies). The presence of organophosphorus groups in structures of the new STS inhibitors may result in the formation of numerous electrostatic interactions with amino acid residues, that play crucial role in the binding of potential ligand in the catalytic region of STS. This additional interactions, e.g., hydrogen bonds, may also stabilize the enzyme-inhibitor complex and increase the activity of tested compounds.

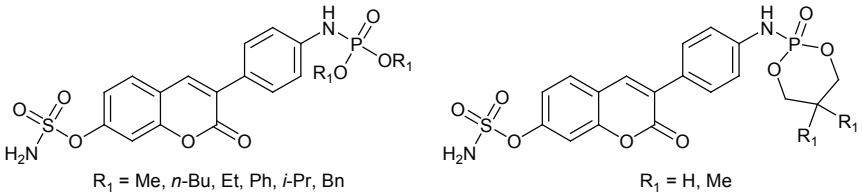

Fig. 1. Chemical structures of the STS inhibitors

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Complexes of a Ternary Systems (Carbohydrate, Lipid, Protein) with Carbon Structures (Nanotubes and Fullerenes)

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Carbon structures like nanotubes and fullerens submits to modifications in order to improve their physicochemical properties. Carbon nanotubes and starch (mainly amylose fraction) have the ability to form inclusion complexes.

The aim of study was create of a ternary type systems: potato starch/stearic acid/albumin from egg, potato starch/albumin from egg/stearic acid and stearic acid/albumin from egg/potato starch at 7% concentration of systems with oxidized multiwalled carbon nanotubes (MWCNT) and oxidized fullerenes.

The reactions with potato starch were proceeded in aqua environment. The starch was gelatinized in the ternary system and was added oxidized carbon nanotubes in 1:1 weight ratio. The same systems were reacted with oxidized fullerenes in 1:1 weight ratio.

Thermal analysis (TG/DSC) of a ternary systems, ternary systems with oxidized MWCNT and fullerenes were made. The thermal behavior of investigated systems indicates an increase the stability of the following systems: ternary system/MWCNT and ternary system/oxidized fullerenes. Also scanning electron microscope (SEM) with EDS detector and FTIR studies were carried out. These analyzes show possibility of creation of new structures/complexes.

The conducted analysis confirm the interesting physicochemical properties of tested systems, which will allow for their potential use as environmentally friendly "green cells".

Synteza oligopeptydowych analogów akrydyny/akrydonu

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Bardzo często standardowe drogi podawania leków w pełni nie wykorzystują terapeutycznych możliwości stosowanych medykamentów. Jednym ze skutecznych sposobów dostarczania leków do miejsca docelowego w organizmie jest zastosowanie koniugatów lek-nośnik, w których składnik aktywny jest związany kowalencyjnie z nośnikiem, np. peptydem [1].

Otrzymano nowe oligopeptydowe analogi akrydyny/akrydonu jako potencjalne leki przeciwnowotworowe. W pierwszym etapie prac syntetycznych uzyskano kwas *N*-fenyloantranilowy w reakcji kondensacji Ullmana pomiędzy kwasem *o*-halogeno-benzoesowym, a pochodną aniliny. Następnie cyklizacja w obecności $POCl_3$ dała 9-chloroakrydyny, które w dalszych etapach przekształcono w stabilniejsze 9-fenoksypochodne. Z kolei cyklizacja w stężonym kwasie siarkowym prowadziła do otrzymania 1-chloropochodnych akrydonu. Syntezę zaplanowanych fragmentów peptydowych przeprowadzono stosując metodę mieszanych bezwodników z chloromrówczanem izobutylu i NMM w bezwodnym DMF. W ostatnim etapie, w reakcji aromatycznej substytucji nukleofilowej (S_NAr) uzyskanych pochodnych akrydyny/akrydonu z odpowiednim peptydem, otrzymano zaplanowane związki. Końcowe produkty oczyszczano stosując chromatografię kolumnową na żelu krzemionkowym oraz preparatywną TLC, a następnie scharakteryzowano za pomocą widm MS i NMR.

Podziękowania

Praca finansowana przez Narodowe Centrum Nauki (NCN) grant nr 2014/13/B/NZ7/02234.

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CD Oxoanions as a Tool for Synthesis of Cyclodextrin Polymers

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[1] Institute of Chemistry, Environmental Protection and Biotechnology, Jan Dlugosz University in Częstochowa, Częstochowa, Poland
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Water soluble b-cyclodextrin-based polymers were synthesized by reaction between cyclodextrin oxoanion and pyromellitic anhydride. The synthesis method utilizes possibility of activation the secondary hydroxyl groups in the anhydrous DMF solution with the use of NaH. In these conditions, like in the case of the cyclodextrin reactions in the highly alkaline media, there is a nucleophilic substitution of difunctional compounds, which results in development of a polymer network with various cyclodextrin substitution. However, as opposed to the reaction in concentrated water solution of NaOH, where the reaction of deprotonation occurs nonspecifically, the direction of preferred deprotonation in the anhydrous DMF is in position "2". [1] Another route for the synthesis of similar systems i.e. cyclodextrin-based nanosponges, is a direct reaction between β-CD and pyromellitic dianhydride in DMSO and Et_3N as a weak base. [2, 3]

b-CD was dissolved in DMF, and then solid NaH was added into the solution with vigorous stirring over 2 hours at room temperature. After that time the solution become solid. Then solid pyromelitic anhydride was added. The flask was strongly shaken and the reaction mixture become a solution again. Reaction mixture was continuously stirred for the next 24 h. Samples were prepared with different molar ratio between β-CD, NaH and pyromellitic anhydride. The polymer samples was purified by extraction by aceton in Soxhlet apparatus.

The ultrafiltration process at Millipore UF Stirred Cell 76 mm with Ultrafiltration Membrane, Regenerated Cellulose PLCC 5000 Da was carried out. The solubility test in wide range of pH and metal ion complexation process was also investigated. DSC, FT-IR, NMR, LC-MS, MALDI-TOF were conducted to characterized the polymers.

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C_3-Symmetric Anion Receptor Based on a Triptycene Scaffold

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Triptycene was first synthesised by Bartlett [1] in order to study its radical activity. Over the years, however, triptycene has found numerous applications in various fields of chemistry, including catalysis, [2] polymer chemistry, [3] and supramolecular chemistry. [4, 5]

Due to the unique structural properties of triptycene, such as rigid structure and C_3 symmetry, we have decided to synthesise an anion receptor **1** (Fig. 1), in which pyrrole rings are fused to the triptycene skeleton. Using molecular modelling, we have determined that this receptor would have a well-defined binding pocket, which would allow it to bind anions effectively, even in highly demanding solvents.

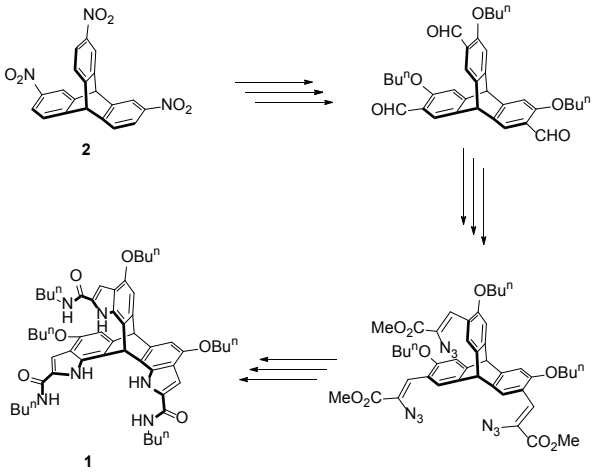

Fig. 1. Triptycene based receptor 1 and the substrate 2 used for its synthesis

Starting from 2,7,14-trinitrotriptycene **2** we have synthesised receptor **1** in eight steps, with the key reaction being the formation of pyrrole rings using the Hemetsberger reaction. Then we proceeded to study the anion binding properties of compound **1** using fluorescence titration, which has shown a very high selectivity of receptor **1** towards dihydrogen phosphate in a DMSO + 0.5% H_2O mixture.

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Trwałe selenylosulfidy – synteza, struktura i reaktywność

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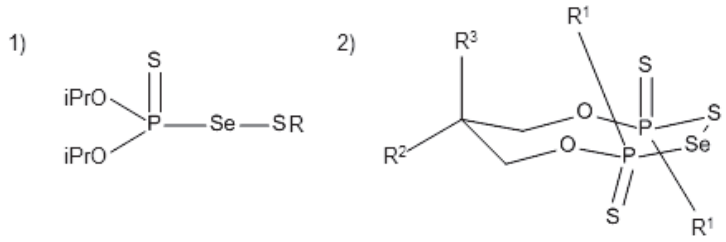
Otrzymano trwałe, nie ulegające dysproporcjonowaniu mieszane selenylosulfidy $(iPrO)_2P(S)SeSR$ **1** oraz symetryczny cykliczny selenylosulfid bistiofosforylowy **2** (R^1 = anizyl, R^2,R^3= $-CH_3$).

Struktury związków potwierdziła analiza widm ^{1}H NMR, ^{13}C NMR i ^{31}P NMR, a także analiza rentgenograficzna (**2**).

Synteza selenylosulfidów **1** polegała na reakcji bromku *O*,*O*-diizopropylofosforotioselenylu z odpowiednimi tiolanami (wyd. 35–90%) lub reakcji DDQ z odpowiednim diselenidem i tiolem. Produkt **2** otrzymano z odpowiedniego cyklicznego disulfidu w 3-etapowym procesie (desulfuryzacja, podstawienie na atomie fosforu selenkiem sodu, utlenienie jodem) z wydajnością 95%.

Selenylosulfidy **1** z II-rzędowym atomie węgla na atomie siarki okazały się ulegać znacznie szybciej dysproporcjonowaniu w środowisku kwaśnym, a także o wiele bardziej reaktywne, niż odpowiednie pochodne III-rzędowych tioli. Zbadano reaktywność otrzymanych selenylosulfidów z odczynnikami nukleofilowymi m.in. z PPh_3 – reakcja ta okazała się być chemoselektywna, produktami reakcji są głównie produkty odselenylowania, czyli sulfidy fosforylu i bisfosforylu.



Rys. 1. Schemat selenylosulfidów 1) R = *tert*-butyl, trytyl, adamantyl, cykloheksyl, (+)–neomentyl 2) R^1 = anizyl, R^2,R^3= $-CH_3$.

Asymmetric Organocatalysis in the Synthesis of Organosulfur Compounds

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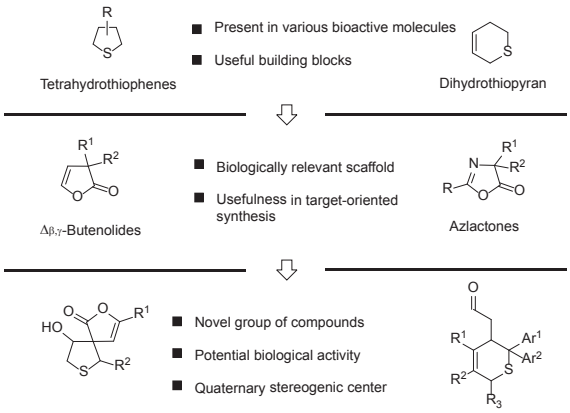
The chemistry of organosulfur compounds occupies a very important place in the contemporary organic chemistry. Among the organosulfur derivatives tetrahydrothiophenes and dihydrothiopyrans, deserves a special attention. Tetrahydrothiophenes constitute an interesting group of biologically relevant molecules with a broad applicability in organic chemistry. This structural motif is also present in various natural products. [1] Dihydrotiopyrans have interesting pharmacological properties and are widely employed in medicine. [2]

This study demonstrates the stereoselective synthesis of spirocyclic tetrahydrothiophenes containing a butenolide or azlactone structural motif [3] and dihydrothiopyran derivatives. [4] The developed synthetic strategy benefits from high efficiency and broad scope.



Acknowledgements

This project was realized within Lider programme from the National Center for Research and Development (NCBR, grant number LIDER/01/87/L-3/11/NCBR/2012) and supported by the Young Scientists' Fund at the Faculty of Chemistry, Lodz University of Technology (grant W-3/FMN/21G/2015). Thanks are expressed to prof. G. Mlostoń and dr M. Jasiński for the preparation of thioketones.

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Synthesis of P,N-Ligand Precursors Using Deprotonation-Phosphinylation Methodology

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Chelating P,N-type ligands possessing both phosphorus and nitrogen atoms in their structure appear as very efficient ligands in many transition metal-catalyzed enantioselective transformations. [1] Nevertheless, the development of new ligands of this type is still a hot topic in organic chemistry due to a steady need in the preparation of more efficient and selective ligands. One of the possible approaches leading to the title compounds relies on the use of simple and non-chiral organic compounds with incorporated nitrogen atom as substrates for enantioselective deprotonation of prochiral CH_2 or CH groups followed by a treatment with phosphorus electrophile.

In this communication, deprotonation-phosphinylation of protected amines or amides and nitrogen group-substituted ferrocenes will be presented.

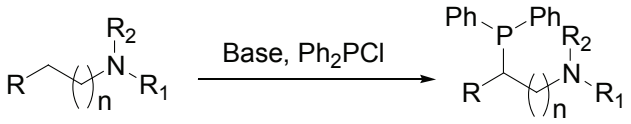

Fig. 1. Deprotonation-phosphinylation of organic compounds

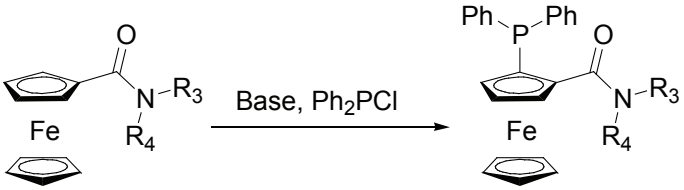

Fig. 2. Deprotonation-phosphinylation of substituted ferrocenes

Acknowledgements

Financial support from National Science Centre (SONATA-BIS funding scheme, grant no. 2012/07/E/ST5/00544) is kindly acknowledged.

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Convenient synthesis of (1,1-dietoxyethyl)-*N*-Boc-1-aminoalkylphosphinates

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The synthesis of phosphonic acid derivatives has attracted considerable attention [1] due to their biological activities and application as enzyme inhibitors. [2, 3]. In this communication we report a new approach to the synthesis of structurally diverse (1,1-dietoxyethyl)-*N*-Boc-1-aminoalkylphosphinates **3** (Fig. 1).

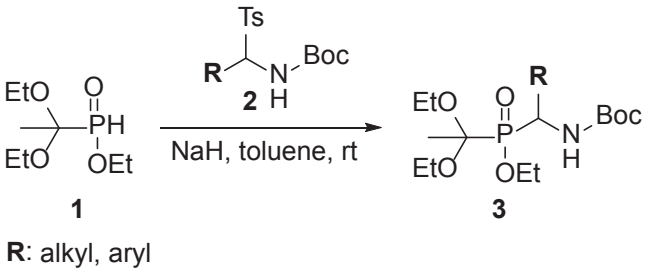

Fig. 1

The title compounds were obtained in the reaction of ethyl (1,1-diethoxyethyl) phosphinate (**1**) with amidosulfones **2** in toluene, in the presence of sodium hydride as a base. A series of aminoalkylophosphinates **3** with aromatic and aliphatic substituent was obtained in moderate yields and with low diastereoselectivity.

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Synthesis of Cyclic Phosphine Derivatives

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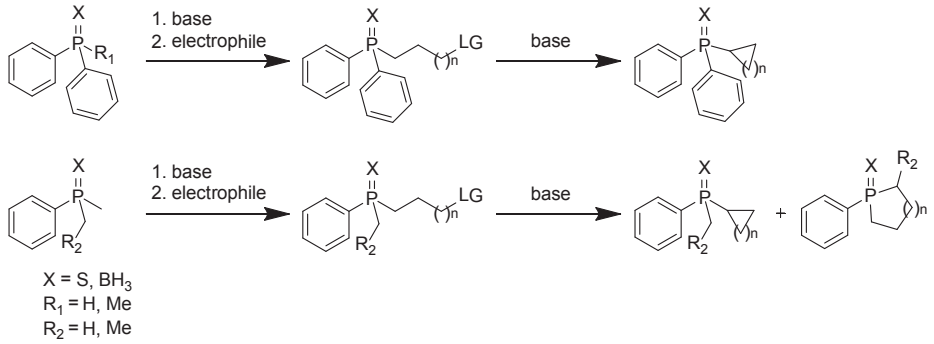
Complexes of organophosphorus compounds with transition metals play an important role in asymmetric catalysis. Among these compounds a very useful class of ligands are phosphines, especially diphosphines possessing a chiral center at phosphorus atom or at carbon atom. [1, 2] Currently, the number of known *C*-chiral phosphine ligands is bigger than the number of *P*-chiral ligands. Despite this, new methods of synthesis of highly selective and efficient ligands with an asymmetric center at the phosphorus atom are still developed. Desymmetrization of CH_2 group attached to the phosphorus atom followed by cyclization seems to be a simple route to cyclic achiral and *P*-chiral phosphine ligand precursors. [3]

Herein, attempted synthesis of cyclic phosphine derivatives will be presented.



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Phosphate and Thiophosphate Flavone Analogs as Steroid Sulfatase Inhibitors

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There has been an increased interest in scientific researches toward designing and obtaining new steroid sulfatase (STS) inhibitors – compounds that enhance the efficacy of anticancer therapy. [1] Only few inhibitors based on phosphate and thiophosphate derivatives have been synthesized so far, thus its potential in breast cancer therapy has not been thoroughly utilized. [2]

A series of phosphate and thiophosphate flavone derivatives were synthesized and biologically evaluated *in vitro* for inhibition of STS activity. The described synthesis includes the straightforward preparation of 7-hydroxy-2-phenyl-4*H*-chromen-4-one, 2-(4-fluorophenyl)-7-hydroxy-4*H*-chromen-4-one, 7-hydroxy-2-(4-(trifluoromethyl)phenyl)-4*H*-chromen-4-one and 7-hydroxy-2-(*p*-tolyl)-4*H*-chromen-4-one modified with different phosphate or thiophosphate moieties (Fig. 1).

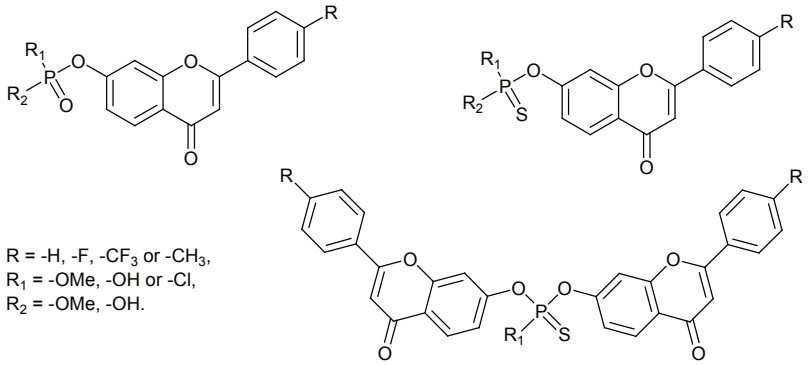

Fig. 1. Novel steroid sulfatase inhibitors phosphate and thiophosphate based on flavone derivatives

The inhibitory properties of the synthesized compounds were tested against human placenta STS. Some of the novel inhibitors had good activities against STS. In particular, the bis-(4-oxo-2-(*p*-tolyl)-4*H*-chromen-7-yl) hydrogenthiophosphate had the most potent inhibitory effect with an IC_{50} value of 8.50 μM for the 2-(4-trifluoromethylphenyl)-chrome n-4-one-7-*O*-sulfamate used as a reference.

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Synthesis of 3,4-Dihydrocoumarin Derivatives Bearing a Pyrrolidine Scaffold

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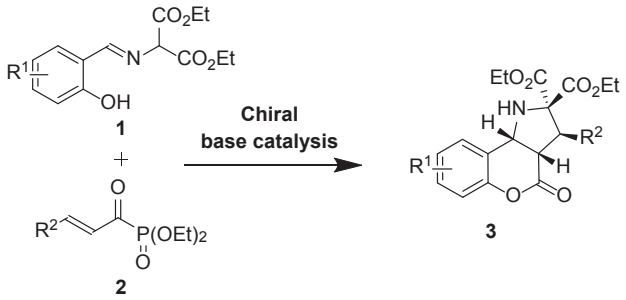
Pyrrolidine [1] and 3,4-dihydrocoumarin derivatives [2] occupy a prominent position among biologically active molecules and constitute a privileged scaffold of various natural products.

Herein, we raport a novel organocatalytic approach to 3,4-dihydrocoumarins **3** bearing a pyrrolidine ring. [3] It is based on a cascade reactivity of β,γ-unsaturated-α-ketophosphonates **2** and imines **1** (derived from various salicylaldehydes and diethyl aminomalonate) as starting materials. The metodology can be described as a doubly annulative strategy where both the pyrrolidine moiety and the δ-lactone ring of the 3,4-dihydrocoumarin framework are constructed starting from the acyclic precursors. This approach is promoted by readily available and cheap dihydroquinine and ensures high efficiency and stereoselectivity of the cascade as well as a very broad substrate scope. Target products bearing two new heterocyclic moieties and three adjacent stereogenic centers are obtained in excellent yields in a highly stereoselective manner.



Acknowledgements

This work was made possible by a financial support from the Young Scientists' Fund at the Faculty of Chemistry, Lodz University of Technology (grant W-3/FMN/18G/2015).

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Synthesis of Cathepsin C Inhibitors Based on Dehydrodipeptide Motif

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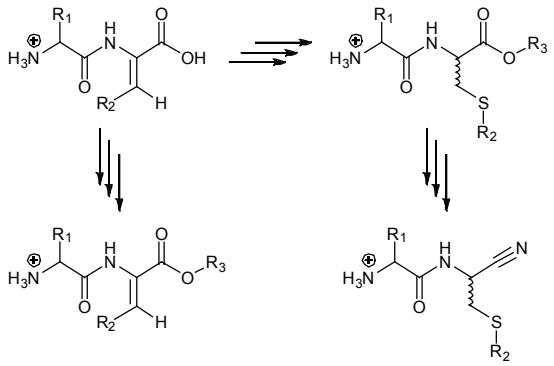
Cathepsins C is cysteine protease which belongs to papain family. A search of its inhibitors seems to be interesting from therapeutical point of view because of its capability to proenzyme activation of neutrophil serine proteases since the active form of these proteases are release during inflammation and support elimination of pathogen. Their uncontrolled activity cause degradation of tissue and favour the spread of chronic inflammation associated with some autoimmune disorders such as chronic obstructive pulmonary disorders, rheumatoid arthritis, cystic fibrosis and multiple sclerosis. [1, 2]

In order to synthesise cathepsin C inhibitors we used a dehydrodipeptide motif as a starting point. The presence in the structure conjugated α,β-unsaturated double bond makes it prone to nucleophilic addition of various nucleophiles including thiol moiety. [3] Therefore, the dehydrodipeptides might act as inhibitors of this thiol enzyme and can be used as substrates for synthesis of more complex structures. In this study we synthesized a series dipeptide esters containing in the P1 position dehydoamino acid residues or *S*-substituted cysteine obtained by 1,4-nucleophilic addition of variable thiols to the double bond of dehydropeptides. Finally, the hydrolyzable ester moiety was converted to electropihlic nitrile therefore shows the potential of synthesized compounds as a lead substances for further inhibitor design.



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Synteza oraz badania strukturalne benzhydrylowych pochodnych kwasu winowego

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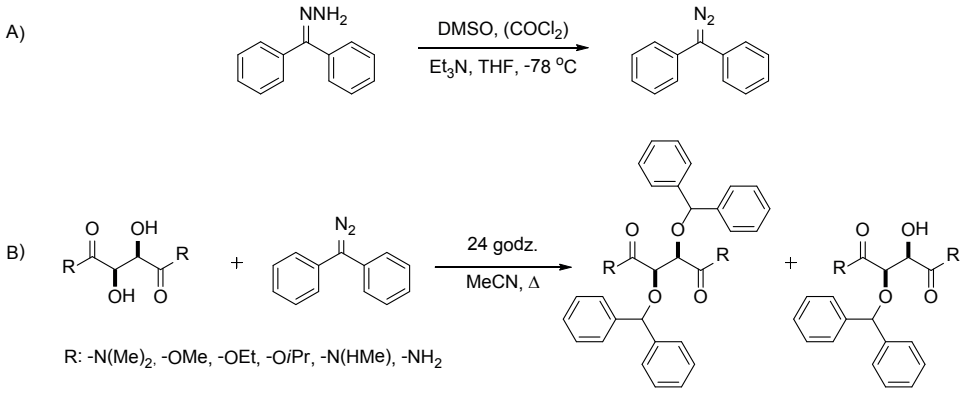
Najskuteczniejsza metoda syntezy pochodnych kwasu winowego zawierających grupę benzhydrylową w pozycjach eterowych opiera się na zastosowaniu diazodifenylometanu. Otrzymuje się w łatwy sposób i z dobrą wydajnością z handlowo dostępnego hydrazonu benzofenonu [1]. Alkilowaniu ulegają diamidowe oraz diestrowe pochodne kwasu winowego prowadząc do otrzymania związków mono- i dipodstawionych na grupach hydroksylowych.



Rys. 1. Metoda syntezy diazodifenylometanu (A) oraz benzhydrylowych pochodnych kwasu winowego

Hydrofobowy charakter grupy benzhydrylowej powoduje zwiększenie lipofilowości, natomiast jej duża objętość wprowadza dodatkowe zawady steryczne, a tym samym ma znaczny wpływ na zmianę struktury otrzymanych produktów [2]. Badania ułożenia przestrzennego przeprowadzono z użyciem modelowania molekularnego i spektroskopii dichroizmu kołowego. Poznanie dokładnej struktury otrzymanych pochodnych kwasu winowego jest bardzo istotne, ponieważ stanowi wstęp do zastosowania tych związków przy rozdziale mieszanin racemicznych oraz jako chiralnych bloków budulcowych do syntezy bardziej złożonych układów.

Podziękowania

Pracę wykonano w ramach projektu badawczego CHIKADI PBS2/A1/14/2014.

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Novel and Efficient Synthesis of 2-alkylsulfanyl-*O*-thio-Phosphorylated Enoles and New Method of Synthesis Alkynyl Sulfides

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We have investigated the reactivity and applications of 5,5-dimethyl-2-thiolo-2-thioxo-1,3,2-dioxaphosphoriane and it`s derivatives for several years. [1] Exceptional reactivity of sulfur and it`s importance in biology, medicine, and materials science, [2] targeted a series of thiol-based transformations including thiol alkylations as well as the thiol-ene and thiol-yne reaction among others. [3] Unlike the well established S-Csp^3 bond forming processes, existing methods to construct S-Csp bonds are rare in number and often lack generality or require harsh conditions.

Our team developed three unique methods of synthesis alkynyl sulfides. One of them was based on the rearrangement of α-thiophosphorylated ketones under basic conditions followed by subsequent alkylation and elimination. Synthesis of 1-((5,5-dimethyl-2-thioxo-1,3,2-dioxa-phosphorinan-2-yl)sulfanyl) ketones was accomplished with 88 – 90% yield. A rearrangement of α-thiophosphorylated ketones was observed under mild condition. Subsiquent alkylation provided 2-alkylsulfanyl-*O*-thio-phosphorylated enoles **1** with exellent yield.

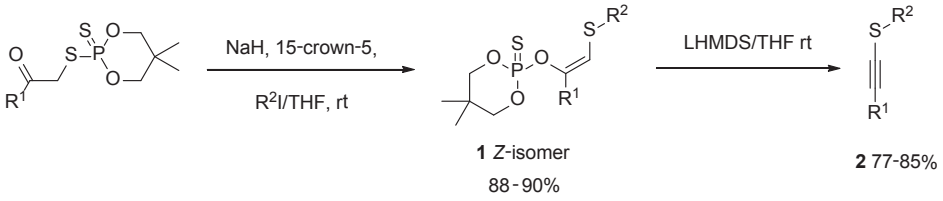

Fig. 1. Preparation of 2-alkylsulfanyl-*O*-thiophophosphorylated enoles and synthesis of alkynyl sulfides

The formation of alkynyl sulfides **2** from compounds **1** in the presence of base will be also presented.

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Thiourea Organocatalysts in Asymmetric Catalysis

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First organocatalytic reaction was discovered in 1859, but so far this field has just flourish. About 60 publications devoted to *organocatalysis* appeared in 2006, but today it is possible to find above 600 articles written only in 2016. Tenfold increasing number of papers proves that organocatalysts` sphere has been staying open.

One of the main group of organocatalysts are thioureas. They have many significant advantages, for instance simple and inexpensive synthesis, non-toxic character, lack of sensitivity to moisture, comfortable storage for even several months at room temperature. What is more, the most often tiny amount of catalyst is sufficient to catalyse a reaction cycle and it can be recovered and used again.

One of the earliest information about taking advantage of chiral thiourea as a catalyst appeared in 1998. It was Strecker reaction. [1] In this case and many others (for example Pudovic reaction, [2] Mannich raction [3]) thiourea allows to stereocontrolled 1,2 addition to double bond. However stereocontrolled 1,4 Michael addition also is possible thanks to thioureas catalysts. [4]

Despite so various applications of chiral thioureas, exact mechanism of the catalysis still is unknown. Presumably hydrogen bonds are responsible for interacting between thiourea and reagents. For this reason thioureas are more effective than ureas. Also trend of hydrogen bonds reinforcement is visible, for instance through replacement sulfur of dicyanomethylene group. [2]

Convenient way to synthesis chiral thioureas is using of natural chiral products, for example aminoacids. We decided to take this path and obtained series of chiral catalysts. They proved to be useful in Friedel Craft`s alkylation of indole. According their universal properties, they can be also applied in stereocontrolled 1,2 addition do double bond.

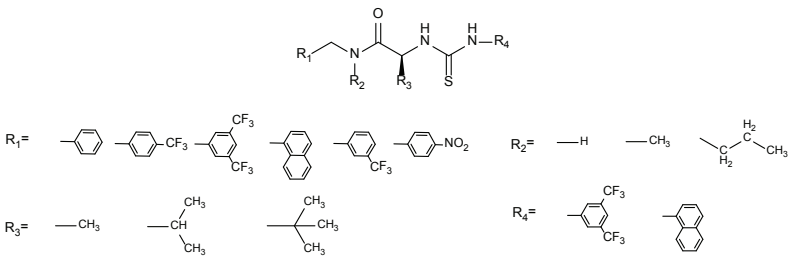

Fig. 1. Obtained chiral thiourea organocatalysts

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An Analytical Protocol for Isolation and Identification of Natural Organic Dyes Present in the Historical Artistic Paints

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Natural organic dyestuffs are components of many objects of cultural heritage. Identification of natural dyes in historical objects is useful for the development of effective and appropriate conservation strategies; to obtain historical information necessary for the purposes of documenting an artwork; as well as to determine origin of an artefact and a work's authenticity. Organic dyestuffs derived from natural sources usually contain several colouring substances that in the first stage should be separated into individual components prior to identification. For this reason, our studies will be conducted using liquid chromatography coupled with UV-Vis diode array detector and mass spectrometry (LC-DAD-MS). Reversed phase liquid chromatography with electrospray mass spectrometric detection seem to be the most efficient tools for the analysis of very small samples of materials of complex matrices. [1] Most of the natural dyestuffs are of the mordant type in a lake form obtained by co-precipitation with an inorganic substrate, in which the dyes are chemically bound by difficult to dissociate chelate bonds. Mixtures of organic solvents and strong acid such as HCl or H_2SO_4 are successful in extracting the dyestuffs from lakes, but hydrolyze many of them into less informative aglycones. Alternative effective method is based on the hydrofluoric acid, which is both a weaker acid and a strong metal-complexing agent for extraction of mordant-type dyestuffs with preservation of glycoside bonds. [2]

The aim of the research project is the identification of organic colouring substances of natural origin, which are components of artists' paints used in the second half of the 19th-century by most famous polish painters (J. Matejko, L. Wyczółkowski, J. Malczewski).

In the present work, an analytical protocol for the identification of natural organic dyes using HPLC-DAD-MS is presented and it was successfully applied to identification of the main components of the historical red and yellow lakes obtained from *Rubia tinctorum L.* (Fig.1.), *Coccus Costa* and *Reseda luteola.*

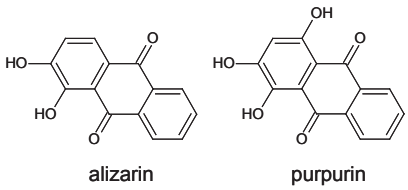

Fig. 1. Structures of organic dyestuffs identified in the red lake labelled *Laque de Garance*

Acknowledgements

The research work has been financially supported by the NCN National Science Centre of Poland via Preludium project No. 2015/17/N/HS2/03310.

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ortho-O,S-Thioacetal-diarylmethanol Derivatives as Substrates for the Friedel-Crafts/Bradsher Type Cyclization

Krzysztof Owsianik[1], Agnieszka Bodzioch[1], Emilia Kowalska[1], Joanna Skalik[1] and Piotr Bałczewski[1,2]

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[2] Jan Długosz University in Częstochowa, Institute of Chemistry, Environmental Protection and Biotechnology, The Faculty of Matematics and Natural Sciences, Częstochowa, Poland

Our interest in organic small molecules, containing pi-extended, aromatic systems, is associated with their potential application in optoelectronic elements as photo- and electroactive materials.

Here, we report a method for synthesis of substituted acenes **3** utilizing *ortho-O,S*-thioacetal-diarylmethanol derivatives **2** as convenient substrates for the Friedel-Crafts/Bradsher type cyclization reaction. This reaction is based on analogous reactions of *O,O*-acetals [1] and *S,S*-dithioacetals, [2] obtained from aromatic *o*-bromoaldehydes **1**. The derivatives **2** containing *O,S*-acetal moiety lead under nonaqueous ($FeCl_3$/KI) or aqueous reaction conditions HCl/MeOH to formation of acenes **3** and other unexpected non-aromatic derivatives in a ratio depending on the nature of the substituent R.

The obtained compounds **3** will subsequently be used for studies of their physicochemical, optoelectronic and electrochemical properties.

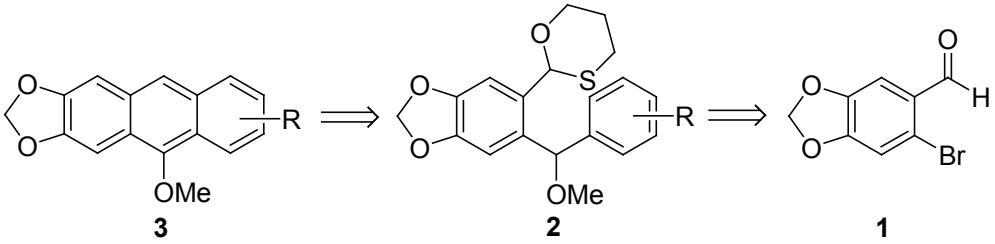

Fig. 1. Rethroanalysis of the Friedel-Crafts/Bradsher type cyclization leading to acenes **3**

Acknowledgements

The research was funded by National Science Centre Poland; Grant OPUS (UMO--2013/11/B/ST5/01610).

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Optically Active *t*-Butyl-4-trifluoromethylphenylphosphinothioic Acid: Synthesis and Application as a Chiral Solvating Agent (CSA)

Patrycja Pokora-Sobczak, Grażyna Mielniczak, Dorota Krasowska, Jacek Chrzanowski, Adrian Zając and Józef Drabowicz

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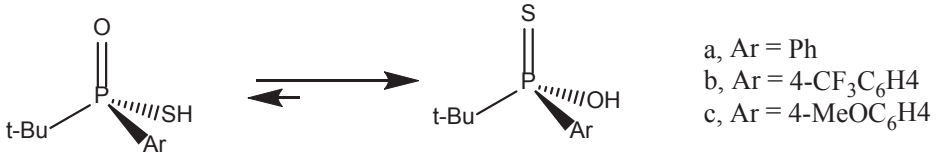
Since the first observation reported as early as 1973 by Harger [1] optically active *t*-butylphenylphosphinothioic **1a** has been often applied as a chiral solvating agent (CSA) for the determination of the enantiomeric excesses of chiral compounds with a stereogenic carbon atom or heteroatom. [2]



1a-c (tautomer A) **1a-c** (tautomer **B)**

The spectral noneqivalence observed for a wide range of organic compounds in the presence of (+)- or (–)–**1a** is due to at least two factors. The first results from a specific structural feature of this thioacid which is a proton donor and simultaneously hydrogen bond acceptor (electrophilic center acceptor). Therefore, it can interact with other compounds utilizing its acidic and basic centers. The second is the presence of the aromatic ring in **1a** and its diamagnetic shielding effect. Taking into consideration both factors it is reasonable to expect that in the family of *t*-butylarylthiophosphinic acids **1a–c** the strength of interaction and diamagnetic shielding effect should be influenced by the presence of both donor and acceptor substituents in the benzene ring. To check this assumption we are preparing now new optically active members of a family of thiophoshinic acids and using them as new CSAs in NMR spectroscopies. This communication will present a part of this studies devoted to the synthesis of optically active *t*-butyl-4-trifluoromethyl-phenylphosphinothioic acid **1b** and its application as a chiral solvating agent.

Acknowledgments

The authors thank for the support from the fund of the National Science Center awarded on the basis of the decisions UMO-2015/17/N/ST5/03908 and UMO-2011/01/B/ST5/06664

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Metody tworzenia wiązania estrowego w syntezie nowych pochodnych adenozyny

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Jedną z efektywnych metod tworzenia wiązania estrowego w syntezie związków biologicznie czynnych jest reakcja Yamaguchi [1]. Pomimo swoich zalet, do których możemy zaliczyć łagodne warunki prowadzenia reakcji, dobrą wydajność oraz prostą i powtarzalną procedurę posiada ona również ograniczenia. Jednym z nich jest brak chemoselektywności reakcji w przypadku obecności więcej niż jednej grupy hydroksylowej. Otrzymaliśmy nowe estrowe pochodne adenozyny w pozycji 5'–OH D-rybozy [2]. Standardowe warunki reakcji Yamaguchi wymagały ochrony grup hydroksylowych w położeniu 2' i 3'. Podjęliśmy próby modyfikacji tej metody poprzez zmianę stosowanych zasad i rozpuszczalników. Zweryfikowaliśmy również inne metody tworzenia estrów adenozyny z Fmoc-chronionymi niebiałkowymi aminokwasami z wykorzystaniem wybranych odczynników kondensujących. Otrzymane końcowe produkty zostały scharakteryzowane za pomocą widm MS i NMR.

Podziękowania

Praca finansowana przez Narodowe Centrum Nauki (NCN), grant nr 2013/11/B/NZ7/04838.

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A Novel Approach for the Aminocatalytic Activation of Furfural Derivatives

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Identification of new activation modes of organic compounds leading to the discovery of new reactions constitutes one of the most significant tasks of the contemporary organic chemistry. In this respect, aminocatalytic trienamine-mediated strategies have recently proved their potential. [1]

Current work describes a novel approach for the aminocatalytic remote functionalization of heteroaromatic aldehydes. [2] Trienamine HOMO-rising strategy disclosed constitutes an enantio- and diastereoselective tool for the ε-functionalization of 5-benzylfurfural derivatives. Cyclic trienamine intermediate is generated *via* the dearomatization of furan ring, resulting in its non-classical geometry and providing a unique reactivity pattern. Developed methodology utilizes an H-bonding aminocatalyst to control the stereochemical outcome of the reaction. Desired alkylation products bearing two adjacent stereocenters are obtained with very high yields and moderate to high stereoselectivity. A plausible stereochemical course of the reaction is proposed and rationalized based on the absolute configuration assignments.

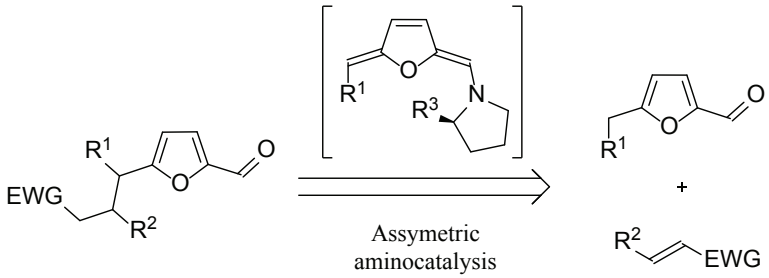

Fig. 1. Retrosynthetic analysis of desired products

Acknowledgements

This work was realized within the Homing Plus programme (HOMINGPLUS/2012-6/1/styp2) of Foundation for Polish Science, co-financed from European Union, Regional Development Fund.

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Wymiana wszystkich ligandów w kompleksach $CpM(CO)_2I$ (M=Fe, Ru) w reakcji z β-diketonami

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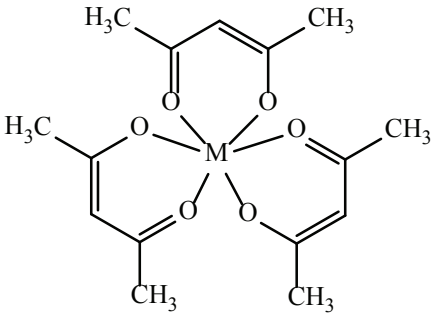
Związki metaloorganiczne posiadają strukturę wykorzystywaną do projektowania skutecznych katalizatorów, stosowanych między innymi w metatezie olefin, jak również do syntezy substancji wykazujących aktywność antynowotworową [1, 2].

Kompleksy typu $CpM(CO)_2I$ (M=Fe, Ru) reagują z wybranymi β-diketonami (np. acetyloaceton), które mają właściwości CH- kwasów. Na podstawie przeprowadzonych badań stwierdzono, iż w wyniku reakcji fotolizy z wybranymi β-diketonami w obecności diizopropyloaminy następuje podstawienie wszystkich ligandów wyjściowych kompleksów $CpM(CO)_2I$ (M= Fe, Ru) przez ligandy organiczne.



Rys. 1. Produkt reakcji $CpM(CO)_2I$ (M= Fe, Ru) z acetyloacetonem

Otrzymane kompleksy (rys. 1) były ocenione pod względem właściwości przeciwnowotworowych w stosunku do komórek raka piersi linii MCF-7. Wykazano, iż związki zmniejszają przeżywalność badanych komórek, ograniczają ich wzrost oraz zwiększają odsetek komórek apoptotycznych.

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Synthesis and Cytotoxic Activity of Amino Acid Derivatives of Mycophenolic Acid

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Mycophenolic acid (MPA) shows antibacterial, antifungal, antiviral, immunosuppressive and anticancer properties. It is a non-competitive and reversible inhibitor of IMPDH. [1] Until now, there are clinically used two derivatives of MPA mycophenolate mofetil (*CellCept*) and mycophenolate sodium (*Myfortic*). However, they cause troublesome side effects. These problems and the process of glucuronidation MPA *in vivo* limits use of these pharmaceuticals. Therefore, one is still looking for more effective analogs that could be less toxic to the organism and thus allow to extend and improve the quality of life of patients. Studies carried out so far, suggested that the presence in the amino acid derivative of MPA, additional polar groups, preferably influences for the observed antiproliferative activity *in vitro.* [2]

We are currently receiving novel analogues of MPA by modifying the side chain of mycophenolic acid molecules, by attaching the chosen amino acids e.g. aminomalonic acid, Thr, Asp. The optimization of an amide bond formation between the carboxyl group in MPA and amine group of corresponding amino acids was proceeded with EDCI/DMAP or T3P/Et_3N. The obtained derivatives of MPA have been characterized by spectra ^{1}H NMR, ^{13}C NMR and MS. In the next phase we are going to conduct studies of biological activity.

Acknowledgements

This work was supported by the Gdańsk University of Technology (Grant DS No. 031431).

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Synthetic and Mechanistic Aspects of Preparation of Selected Quinolylphosphonic and Quinolylphosphinic Acids

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We are going to present the synthetic, spectroscopy and mechanistic studies of selected quinolylphosphonic, quinolylphosphinic, aminophenylphosphonic and aminophenylphosphinic acids. A mechanism explanation was proposed based on the experiment and computation studies. Quinolylphosphonic and quinolylphosphinic acids derivatives with phosphorus (phosphinic or phosphonic) acid group function are of great interest due to their analogy to the precursor of a promising HIV-1 integrase inhibitor, 2-[(*E*)-2-(3,4-dihydroxy-5-methoxyphenyl)ethenyl]-8-hydroxyquinoline-7-carboxylic acid (shortly named FZ-41) which has been demonstrated to block the replication of HIV-1 in cell cultures at nontoxic concentrations. Studies on the structure and reaction mechanism of quinolylphosphonic and quinolylphosphinic acids derivatives will provide valuable information to new drug discovery in the treatment of HIV.

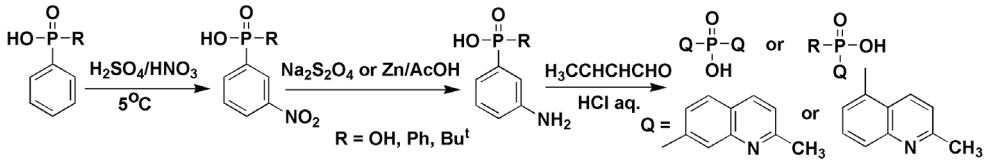

Fig. 1. Synthesis of selected quinolylphosphonic and quinolylphosphinic acids

Our synthesis protocol of selected quinolylphosphonic and quinolylphosphinic acids, adapting from Skraup–Doebner–Miller reaction, has demonstrated the advantages in speed, efficiency and simplicity in general use. It afforded the target products up to 48% yield during 16 h. A drawback of this methodology is the accompaniment of regioisomers. The regioselectivity of the transformation is influenced by both steric and electronic factors of substituents. It is worth to mentioning that our methodologies used easily accessible and commercially available reagents and materials. We elaborated two procedures for the synthesis of aminophenylphosphonic and aminophenylphosphinic acids afforded the target products up to 87% yield during 48 h. Acids were in-depth spectroscopically characterized and rationalized by computational studies.

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Polihydroksylowe chiralne makrocykle i klatki molekularne

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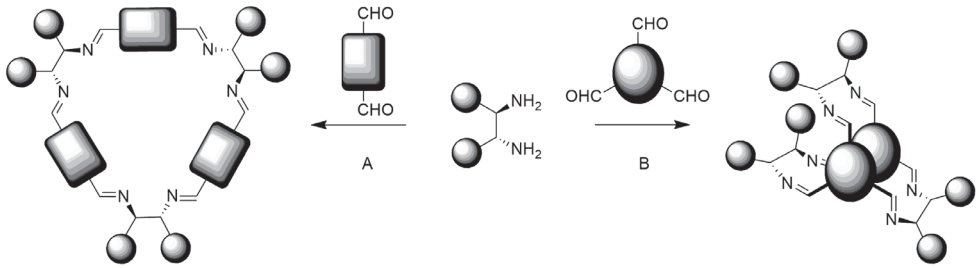
Jednym z wiodących zagadnień współczesnej chemii jest tworzenie układów molekularnych i supramolekularnych o zdefiniowanej strukturze i właściwościach.

Bazująca na koncepcji Dynamicznej Chemii Wiązań Kowalencyjnych reakcja cykloiminowania chiralnych dipodalnych amin przez dipodalne lub tripodalne aldehydy pozwala na otrzymywanie molekularnych makrocykli i makroklatek z praktycznie ilościowymi wydajnościami [1–3].

Zmiana charakteru łącznika aromatycznego i/lub aminy wpływa na właściwości produktu, m. in. na rozpuszczalność, sposób upakowania w krysztale, a co za tym idzie na właściwości sorpcyjne czy też zdolności chelatujące. Wprowadzenie do struktury aldehydu grup hydroksylowych skutkuje nie tylko zwiększeniem stabilności chemicznej otrzymywanych produktów, ale wpływa również na stechiometrię, strukturę, a przede wszystkim na właściwości tworzących się produktów (rys. 1).

Przedmiotem prezentacji będzie synteza oraz badania strukturalne chiralnych polihydroksylowych związków makrocyklicznych i klatek molekularnych.



Rys. 1. Reakcje cykloiminowania chiralnej diaminy dipodalnym (A) i tripodalnym (B) aldehydem

Podziękowania

Badania finansowane z grantu NCN 2012/06/A/ST5/00230.

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Synthesis of Fluorinated Phosphonic Analogues of Phenylglycine

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Aminophosphonic acid derivatives constitute interesting class of compounds with a broad spectrum of biological activity. Due to their pharmacological properties they play an important role in bioorganic and medicinal chemistry. These compounds possess ability to inhibit different class of enzymes. [2] Among them aminophosphonate derivatives bearing phenyl ring have been synthesized and evaluated as inhibitors of certain enzymes with analogues of phenylglycine being lead compounds for phenylalanine ammonia lyase effectors.

Aminophosphonates containing fluorine and other substituents (eg. Cl, CH3, CN) in the aromatic ring have been synthesized by Oleksyszyn-Soroka reaction. [3–5] The structures of these compounds was determined by means of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR and ESI-MS methods.

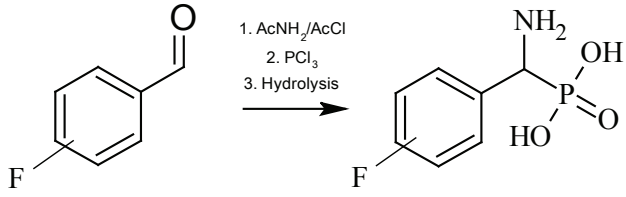

Fig. 1. Preparation of α-aminophosphonic acid analogues of phenylglycine

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Exploring the Chiral Recognition of Carboxylates by Sugar Decorated Artificial Receptors

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Anions are ubiquitous in the natural world and play important roles in biological and chemical features. [1] Among them, chiral anions represent very interesting group of guests in supramolecular systems, because their chemical and biological activity depends on their stereochemistry. Therefore design, synthesis, and studies on binding properties of chiral receptors are supposed to open new possibilities, for example in enantioseparation of racemic compounds and enantioselective catalysis. [2]

Herein, we report synthesis and anion binding studies of two neutral urea-based receptors **1** and **2** (Fig. 1), containing chromenone and indole skeleton, respectively. To estimate potential of receptors **1** and **2** in chiral recognition, we evaluated their binding properties by titration under ^{1}H NMR control in very demanding medium, namely DMSO-d_6+5% H_2O, with structurally differentiated guests derived from mandelic acid and α-amino acids. Both receptors exhibit a high affinity towards chiral carboxylates. However, receptor **1** demonstrates a significantly higher enantiodiscrimination than receptor **2** in all cases investigated, with K_S/K_R ratio up to 2.

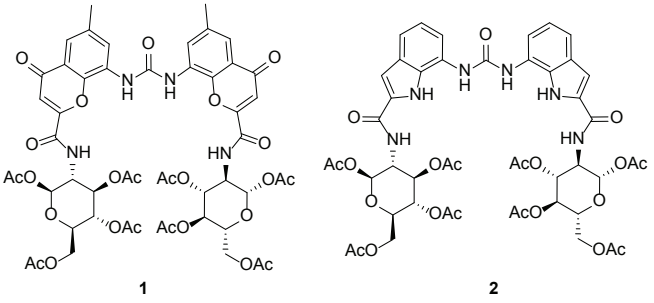

Fig. 1. Receptors **1** and **2**

Our research shows that appropriate conformation and geometry of binding platform plays an important role in enantioselective binding of chiral anions by sugar-containing receptors.

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Desymmetrization – Cyclization of Dimethylphenylphosphine Derivatives – a Novel Route Towards the Synthesis of γ-thioloalkylphosphine Oxides

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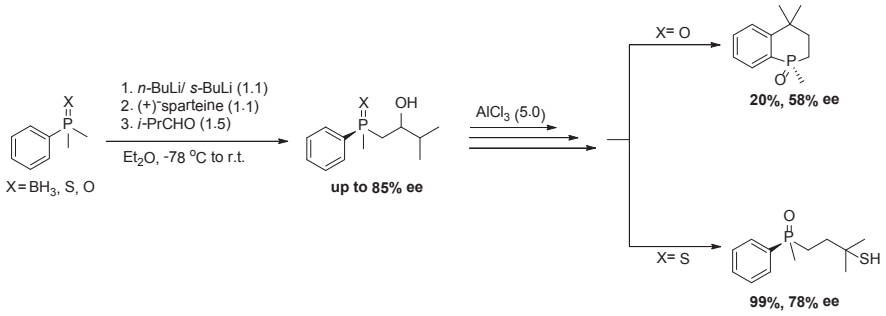
Stereoselective deprotonation with a chiral base is a well-known method for the synthesis of chiral compounds in organophosphorus chemistry. [1] Desymmetrization of symmetrically substituted tertiary phosphines derivatives using a chiral base was used for the synthesis of *P*-chiral organophosphorus compounds, mainly diphosphine ligands. During the course of our current research project concerning the desymmetrization of dimethylphenylphosphine derivatives we were interested in the synthesis of *P*-chiral cyclic organophosphorus compounds possessing phosphaindane skeleton through the action of strong Lewis acid. [2] Interestingly, in case of reaction of sulfide analogues with $AlCl_3$, the substrate undergoes an intramolecular migration of sulfur atom.



Herein, we wish to present some results concerning the attempts to synthesize of *P*-stereogenic cyclic phosphine derivatives in a non-racemic form and novel as well unexpected method of synthesis of γ-thioloalkylphosphine oxide through the intramolecular P=S migration.

Acknowledgements

This work was supported by National Science Centre under Grant No. 2012/07/E/ST5/00544.

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Synthesis and Inhibitory Activity of Cyclic Peptide Against menin-MLL Interaction

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Menin is a specific tumor suppressor protein encoded by the multiple endocrine neoplasia 1 (Men1) gene which controls cell growth in different organs. [1] Menin is a highly specific partner for mixed lineage leukemia (MLL) protein. Chromosomal translocations in MLL gene result in human acute leukemias. Menin functioning as an essential oncogenic cofactor of MLL fusion proteins in leukemia. Menin-MLL interaction is among wild-type MLL and all MLL fusion proteins. [2]

Inhibition of the menin-MLL interaction is a promising strategy to block leukemogenic MLL fusion proteins. On the basis on the crystal structure of menin complexed with MLL_{MBM} (menin-binding motif of MLL), which consist of linear octameric peptide (RWRF-PARP), a series of cyclic peptides was designed. [3] The synthesis of target molecules was carried out on a solid support using Fmoc chemistry with microwaves. The cyclisation was performed using a ring closing metathesis reaction (with second generation Grubbs catalyst) of two allylglycine residues incorporated in the peptides. Cyclic peptides were hydrogenated using Wilinson's catalyst. All synthesized compounds were assayed for their activity of inhibition of menin-MLL interaction. Crystal structures of protein-inhibitor complexes were obtained for the most active peptides.

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Stereoselective Method for the Synthesis of β-lactams with the Use of Meldrum's Acid Derivatives

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The β-lactam skeleton is primarily known as the core structure for both natural and synthetic antibiotics. However, over the last years β-lactams have gathered significant interest among chemists as synthons for many compounds with biological and medicinal properties. Therefore, 2-azetidones are used as important building blocks for alkaloids or toxoids drugs exhibiting ancticancer and cholesterolcontrolling activities. [1, 2] While the optical purity is essential in the synthesis of biologically active compounds, the need to develop new methods for asymmetric synthesis of β-lactames is also obvious.

Since the first reported by Staudinger in 1907 synthesis of β-lactams by ketene-imine cycloadditon, [3] it has still been the most direct and widely used method. The general mechanism involves a two-step process initiated by nucleophilic attack of the imine nitrogen to the electrophilic carbon of ketene, and ended by ring closure to give four-membered product. In most cases ketenes are obtained from acid chlorides and a base.

In 1980, Watanabe proposed an alternative method for the generation of ketenes in the synthesis of 2-azetidones. [4] This approach was based on the thermal decomposition of Meldrum's acid derivatives as a source of ketenes.

Asymmetric synthesis of β-lactams can be realized through the [2+2] cycloaddition of an achiral ketene to a chiral imine. Chiral imines can be prepared from chiral amines and achiral aldehydes or from chiral aldehydes and achiral amines.

We present examples of stereoselective formation of 2-azetidone from 5-carbamoyl Meldrum's acid as a ketene source and chiral imines. As a source of asymmetric induction we have used chiral imines, which are easily formed from commercially available optically pure amines or from chiral aldehyde synthesized according to literature.

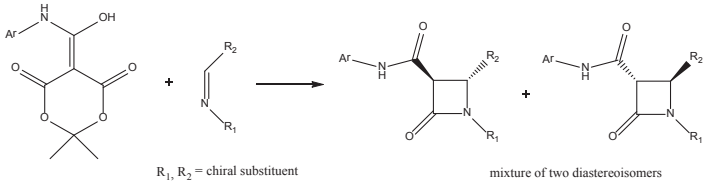

Fig. 1. Obtained β-lactams

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Derivatives of Carbon Nanotubes Synthesized by Selenoorganic Salt

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Native carbon nanotubes are chemically inactive, but the connection of functional groups to CNT improve the properties such as a dispersion in organic solvents or enhancing chemical reactivity. The aim of study was the synthesis of brominated multiwalled carbon nanotubes (MWCNT) [1] with sodium *O,O*-diethyl phosphoroselenoate, $(EtO)_2P(O)Se^- Na^+$. This approach takes advantage of the electrophilic nature of the carbon sphere of halogenated nanotubes in which nucleophilic substitution can be accomplished. [2, 3] The reaction was carried out for 3 days in an argon atmosphere using diethyl ether solvent. The product was purified in two steps by washing with deionized water and methanol. Then samples were shaking on vortex mixer and centrifugation. The purified product was dried for 12 h at 60°C.

After completed the purification the chemical analysis in microareas by energy dispersive X-ray spectroscopy (EDS) with the aim of determining the presence of selenium and phosphorus atoms was carried out. Thermal studies (TG/DSC) of native and synthesized with the selenoorganic salt MWCNT were made. The product of synthesis was also characterized by scanning electron microscopy (SEM) and FTIR spectroscopy. EDS analysis show the presence of selenium and phosphorus atoms. Other studies confirm the significant changes and the possibility to create new structures.

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1-Butyl-3-methylimidazolium Chloride as the Effective Medium for Both the Partial Gelatinisation and Lipase-Catalysed Esterification of Carbohydrate Polymer

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The search for potential candidates to replace the conventional solvents of carbohydrate polymers started among the compounds known as ionic liquids (ILs), mainly due to their biodegradability and low toxicity. In addition to being environmental friendly, ionic liquids have more advantages like low hydrophobicity, low viscosity, electrochemical stability, thermal stability, enhancement of reaction rates with higher selectivities that can achieve higher yields and are non-flammable. [1] A few years ago, researchers discovered the some ionic liquids have the ability to dissolve natural polymer. Because of the unique properties they might be applied as solvents or plasticizers for native starch. This polysaccharide has a semicrystalline, granular structure which affects that it is highly insoluble in most solvents and usually needs physical or chemical modification prior to use. Some kind of ILs has a strong tendency to break inter and intramolecular hydrogen bonds in starch, hence resulting in its dissolution, depolymerisation or gelatinisation. [1, 2] In addition, various chemical modifications of starch, such as esterification, acid-catalysed hydrolysis, enzymatic transformations or graft copolymerisation could be performed in some common ionic liquids based on simple imidazolium salts. It has been very challenging to catalyse the reactions with carbohydrates using insoluble enzymes in organic solvents because polymers of this type are only soluble in a few of them such as pyridine, DMSO or DMF, which are very toxic and induce low enzyme activities. Recent studies have confirmed that some ILs improved the stability of the enzymes, and moreover could be their activators. [2]

In presented studies, the esters of potato starch with higher fatty acid was successfully synthesised by an immobilised lipase-catalysed esterification in only one ionic liquid (1-butyl-3-methylimidazolium chloride), as a reaction medium for both the pregelatinisation and the esterification of the starch. The used chloride did not provide a complete dissolution of the potato starch, but only resulted in its partial gelatinisation and the relaxation of the macrostructure. However, this was enough for the synthesis of new potato starch esters. In order to confirm esterification, the reaction product was subjected to Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopic analyses. The results of X-ray diffraction (XRD) and scanning electron microscopy(SEM) analyses revealed that the crystallinity and morphology of native potato starch were significantly damaged during the formation of starch esters. The application of an unsaturated fatty acid, as an esterifying agent may provide opportunities for the further functionalisation of the resulting ester.

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