STATE RESEARCH INSTITUTE CENTER FOR PHYSICAL SCIENCES AND TECHNOLOGY

VILNIUS UNIVERSITY

ROMUALDAS STRIELA

# SYNTHESIS AND PROPERTIES OF POLYFUNCTIONAL PYRIDINES

Summary of doctoral dissertation
Physical sciences, chemistry (03P)

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The work was carried out in a period 2012 – 2016 at State Research Institute Center for Physical Sciences and Technology.

**Scientific supervisor:**

Dr. Linas Labanauskas (State Research Institute Center for Physical Sciences and Technology, Physical sciences, chemistry (03P).

**Dissertation is defended at the Council of Chemistry sciences meeting:**

Chairman – prof. habil. dr. Albertas Malinauskas (State Research Institute Center For Physical Sciences And Technology, Physical sciences, chemistry (03P).

Members:

prof. habil. dr. Margus Lopp (Tallinn University of Technology), Physical Sciences, Chemistry – 03P).

prof. dr. Vytas Martynaitis (Kaunas University of Technology, Physical Sciences, Chemistry – 03P);

prof. habil. dr. Algirdas Šačkus (Kaunas University of Technology, Physical Sciences, Chemistry – 03P);

prof. habil. dr. Sigitas Tumkevičius (Vilnius University, Physical Sciences, Chemistry – 03P);

The thesis defense will take place at 12 p.m. on September 22nd, 2017, at Auditorium of D401 at State Research Institute Center for Physical Sciences and Technology.

Address: Saulėtekio av. 3, LT-10257, Vilnius, Lithuania.

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VALSTYBINIS MOKSLINIŲ TYRIMŲ INSTITUTAS FIZINIŲ IR TECHNOLOGIJOS MOKSLŲ CENTRAS

VILNIAUS UNIVERSITETAS

ROMUALDAS STRIELA

# DAUGIAFUNKCINIŲ PIRIDINO DARINIŲ SINTEZĖ IR SAVYBIŲ TYRIMAS

Daktaro disertacijos santrauka

Fiziniai mokslai, Chemija (03P)

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**Mokslinis vadovas:**

Vyriausiasis mokslo darbuotojas dr. Linas Labanauskas (Valstybinis mokslinių tyrimų institutas fizinių ir technologijos mokslų centras, fiziniai mokslai, chemija – 03P).

**Disertacija ginama viešame gynimo tarybos posėdyje:**

Pirmininkas – prof. habil. dr. Albertas Malinauskas (Fizinių ir technologijos mokslų centras, fiziniai mokslai, chemija – 03P).

Nariai:

prof. habil. dr. Margus Lopp (Talino technologijos universitetas, fiziniai mokslai, chemija – 03P);

prof. dr. Vytas Martynaitis (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P);

prof. habil. dr. Algirdas Šačkus (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P);

prof. habil. dr. Sigitas Tumkevičius (Vilniaus universitetas, fiziniai mokslai, chemija – 03P).

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# INTRODUCTION

Pyridine ring bearing compounds are found in many natural products, active pharmaceuticals and functional materials. According “MDL Drug Data Report” pyridine fragment is the most abundant heterocyclic fragment found in the drug molecules and is present in more than 7000 existing drugs [1]. Bipyridine and terpyridine carcasses are well known for their chelating ability [2-5], which is exploited in many fields including enantioselective catalysis [6] and chemotherapy [7; 8]. 1,4-Dihydropyridine can be used as core fragment for fluorescent sensors [9]. Pyridine ring is also used as electron acceptor for electron transfer in organic light emitting diodes [10; 11].

It is not surprising that more than a century of synthetic history yields many diverse methods for synthesis of pyridine derivatives. The most powerful and versatile approach allowing synthesize even pentafunctionalized pyridines is the ring formation. This approach can be fulfilled by many methods and pyridine ring can be assembled in many combinations (characterized by the number of atoms participating in the cyclization): [2+2+1+1], [2+2+2], [3+2+1], [3+3], [4+2] and [5+1]. Thus correct and perceptive selection of starting compounds is a key to successful synthesis of pyridine derivatives.

Nevertheless, the functionalization of existing pyridine ring is still crucially important. While pyridine ring is quite resistant for modification, there are many methods developed for direct or indirect (via N-oxides) functionalization. Still, there are many functional groups that are sensitive for usually harsh conditions of transformation in pyridine ring, thus milder, more selective and innovative methods are constantly on the demand.

Our attention was drawn to four problematic fields. First, the demand of 5-hydroxyomeprazole and lack of data on chemical synthesis of this compound encouraged us to develop total synthesis of this valuable primary metabolite of widely used drug omeprazole. While there is an efficient synthetic route for the drug molecule, the main challenge was to develop synthetic method for different pyridine ring bearing precursor of metabolite. Second, the necessity to synthesize pyridine derivatives bearing bromo and cyclopropyl moieties led to development of non-aqueous Sandmeyer reaction capable to produce such compounds. Third, the increasing interest in orelanine, natural toxin from fungus *Cortinarius orellanus*, as a drug substance encouraged development of more efficient and transition metal catalysis free synthesis of this compound. Finally, terpyridine carcass bearing compounds possess very interesting electronic properties, highly applicable in fluorometry. A building block with this carcass ready for functionalization both on 4' and 6,6" positions would be very valuable starting point for synthesis of library of these compounds.

### Aim of the work

Development of synthetic methods for 5-hydroxyomeprazole, bromocyclopropylpyridines, orelanine and terpyridine building blocks.

**Tasks of the work**

1. Development of synthetic route for (4-methoxy-5,6-dimethyllpyridin-3-yl)methanol.
2. Synthesis of (4-methoxy-6-(((5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)sulfinyl)methyl)-5-methlpyridin-3-yl)methanol (5-hydroxyomeprazole).
3. Synthesis of a series of aminocyclopropylpyridines for and development of non-aqueous Sandmeyer reaction of aminocyclopropylpyridines.
4. Development of safe and scalable synthetic route for 3,4-dimethoxypyridine.
5. Development of transition metal catalysis free homocoupling of 3,4-dimethoxypyridine and synthesis of 3,3',4,4''-tetrahydroxy-2,2'-bipyridine (orelanine).
6. Development of synthetic route for 6,6''-bis(bromomethyl)-4'-(4-nitrophenyl)-2,2':6',2''-terpyridine.
7. Development of synthetic route for 4'-bromo-6,6''-bis(bromomethyl)-2,2':6',2''-terpyridine.

**Scientific novelty and practical significance of the dissertation**

1. Developed synthetic method for (4-methoxy-5,6-dimethylpyridin-3-yl)methanol and applied in multigram scale synthesis
2. Developed novel synthetic route for (4-methoxy-6-(((5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)sulfinyl)methyl)-5-methlpyridin-3-yl)methanol (5-hydroxyomeprazole)
3. Developed novel synthetic route for bromo(chloro)cyclopropylpyridines. Synthesized novel 2-bromo- and 4-bromo-3-cyclopropylpyridines.
4. Developed novel synthetic route for 3,4-dimethoxypyridine. Our method has the same efficiency as previously reported, but benefits by milder reaction conditions and safer reagents.
5. Developed transitiom metal catalysis free homocoupling of 3,4-dimethoxypyridine.
6. Improved overall yield of total synthesis of 3,3',4,4'-tetrahydroxy-2,2'-bipyridine (orelanine) from 3.7% (9 steps) up to 16 % (6 steps).
7. Developed synthetic route for 6,6''-bis(bromomethyl)-4'-(4-nitrophenyl)-2,2':6',2''-terpyridine.

**Main statements of the dissertation**

1. (4-methoxy-6-(((5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)sulfinyl)methyl)-5-ethlpyridin-3-yl)methanol (5-hydroxyomeprazole) can be synthesised in the simmilar manner as omeprazole from different precursor.
2. The reaction of aminopyridines with copper(II) bromide and alkylnitrites goes both in cathionic and radical pathways.

3. Homocoupling of 3,4-dimethoxypyridine can be carried out without transition metal catalysis.
4. The most efficient synthetic route for 6,6''-bis(bromomethyl)-4'-(4-nitrophenyl)-2,2':6',2''-terpyridine is Kröhnke pyridine synthesis.

**Scientific approbation and publication of presented work**

The results of this study have been published in 8 publications: 2 articles are published in journals included in the Thompson Reuters ISI database and 6 poster presentations at international conferences.

**Contents of the dissertation**

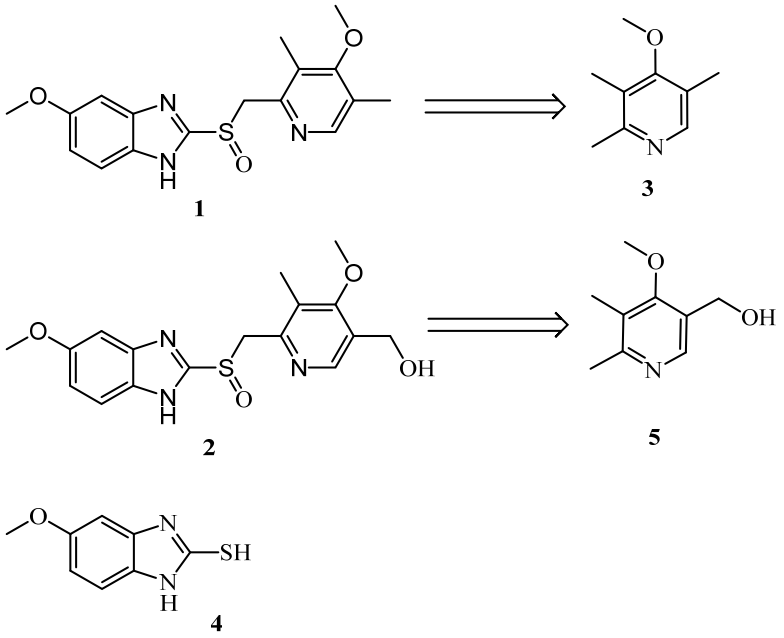
The dissertation is written in Lithuanian on 125 pages and includes 3 tables, 48 schemes and 197 references.

## RESULTS AND DISCUSSION

### 1. Synthesis of 5-hydroxyomeprazole

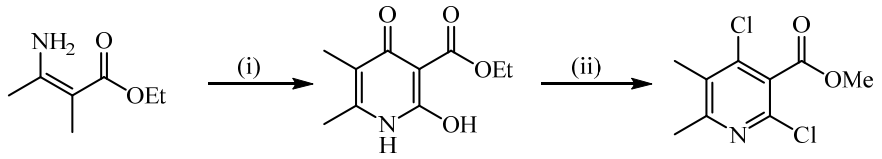
Omeprazole (**1**) and its analogues, so-called proton pump inhibitors that inhibits gastric acid secretion by interacting with the ($H^+/K^+$)-ATPase, is a class of compounds widely used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal and laryngopharyngeal reflux. The investigation of omeprazole has disclosed many another useful properties. It was applied for the treatment of gastric ulcer caused by infection with *Helicobacter pylori*. It is known that in liver it is metabolized by several cytochrome P-450 (CYP) isoenzymes to products of oxidation - omeprazole sulphone and 5-hydroxyomeprazole (**2**) [12; 13]. Omeprazole and its metabolites are widely used in search for new applications of these compounds, in routine blood analysis, studies of specific cases of metabolism [14] or pharmacokinetics [15], investigation of reactions with enzymatic catalysis [16; 17].

Although synthesis of omeprazole (**1**) and its analogues is well known [18; 19], to the best of our knowledge no data on the chemical synthesis of its primary metabolite 5-hydroxyomeprazole (**2**) is published. Present work introduces one of possible routes for a total synthesis of compound **2**. Since the structures of 5-hydroxyomeprazole (**2**) and omeprazole (**1**) differs only by substituent at 5$^{th}$ position of pyridine ring, we have decided to use the same synthetic strategy, i.e. conversion of 2-methyl group to 2-chloromethyl group in pyridines **3** and **5** and coupling of obtained intermediates with 5-methoxy-1*H*-benzimidazolethiol (**5**) (Scheme 1.1). While 5-methoxy-1*H*-benzimidazolethiol (**4**) is commercially available, to the best of our knowledge no literature data on the synthesis of pyridine **5** is published.




**Scheme 1.1.** Synthetic strategy of omeprazole (**1**) and 5-hydroxyomeprazole (**2**).

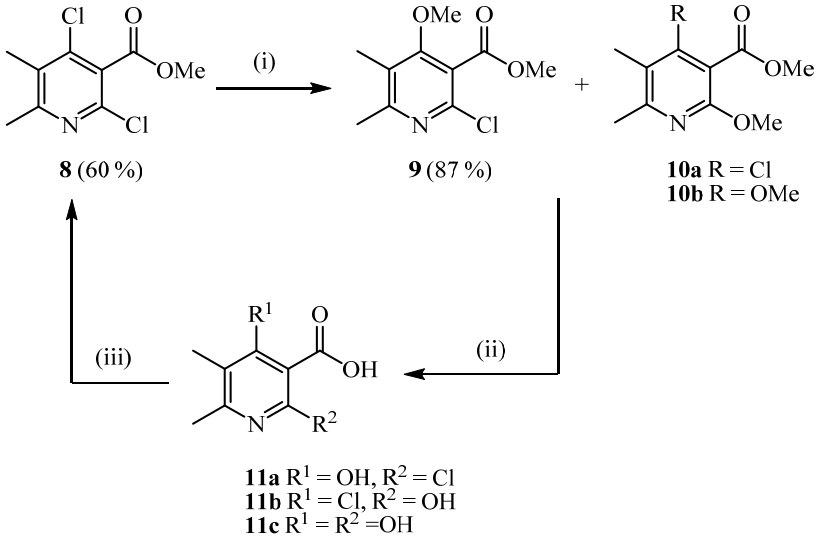
The analysis of the available literature data have suggested that the pyridone **7**, which can be easily obtained by reaction of β-aminocrotonates **6** with diethylmalonate (Scheme 1.2), could be used as a synthetic precursor en route to pyridine **5**.




**6** **7** (36 %) **8** (80 %)

**Scheme 1.2.** (i): NaO*i*-Pr, 1,3-diethyl propanedioate, toluene, 2-propanol, Ar, Δ. (ii): 1. $POCl_3$, 60 °C; 2. MeOH, 0 °C.

Methyl 2,4-dichloro-5,6-dimethylnicotinate (**8**) was synthesized following the modified procedure reported by Seeman [20]. Conversion of pyridones to chloropyridines is typically performed by reaction with phosphorus oxychloride and often requires the use of a sealed tube, which both limits the scale of a reaction and causes risk of explosion. In our hands deoxygenative chlorination of ethyl dioxonicotinate **7** could be performed at atmospheric pressure under mild conditions. The substitution of chlorine at 4$^{th}$ position to methoxy group using 2 equiv. of sodium methoxide in dry methanol at 30 °C yielded methoxypyridine **9** in good yield (87%). Only small amount of isomer **10a** (10%) and dimethoxyderivative **10b** (3%) has formed (Scheme 1.3). By performing the same reaction without cooling (up to 65 °C), the content of compounds **9**, **10a** and **10b** has changed to 28%, 5.5% and 65%, respectively.



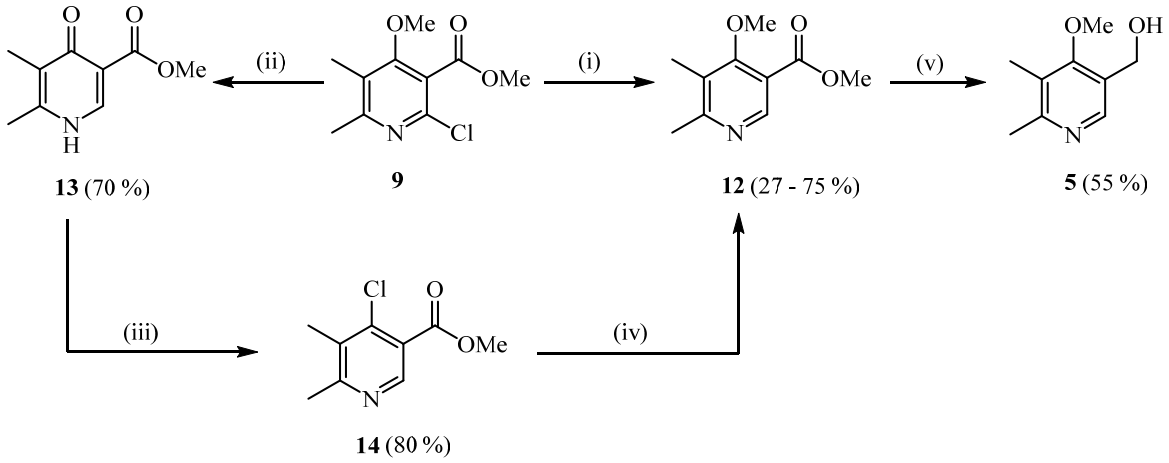

**8** (60 %) **9** (87 %) **10a** R = Cl, **10b** R = OMe

**11a** $R^1$ = OH, $R^2$ = Cl
**11b** $R^1$ = Cl, $R^2$ = OH
**11c** $R^1$ = $R^2$ =OH

**Scheme 1. 3.** (i): NaOMe, MeOH, 20 – 30 °C. (ii): conc. HBr, Δ. (iii): 1. $POCl_3$, 60 °C; 2. MeOH, 0 – 20 °C.

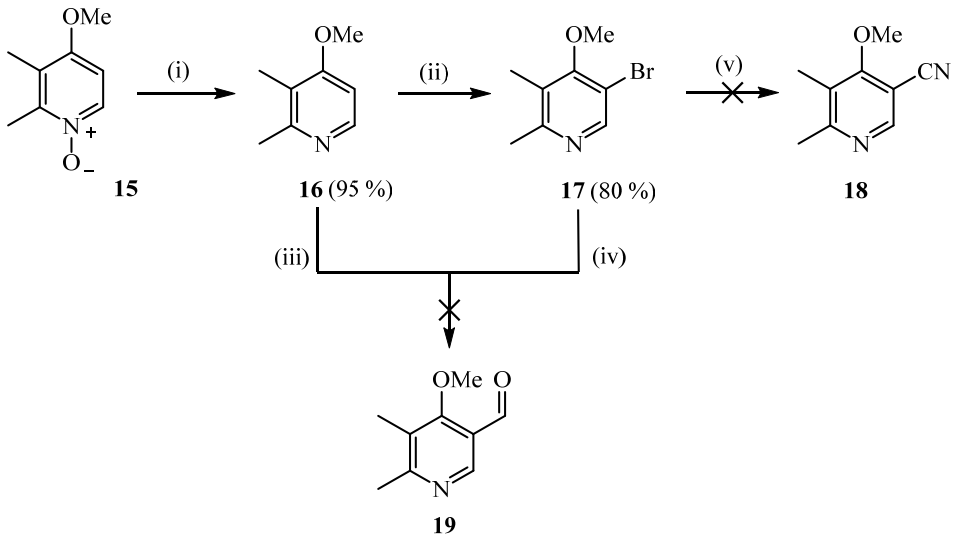
Synthesis under controlled reaction conditions was reproducible on large scale (500-1000 g) and afforded pyridine **9** in 80% yield. The mixture of compounds **9**, **10a** and **10b**, recovered from filtrates after recrystallization of compound **9**, could be recycled to compound **8** in two steps. The mixture was first hydrolyzed by refluxing in

concentrated hydrobromic acid to yield pyridines **11a-c**, which were treated with $POCl_3$ and then with methanol to form dichloropyridine **8** in good overall yield (60% of total weight of the mixture of compounds **9**, **10a** and **10b**) (Scheme 1.3). The hydrogenative dehalogenation of compound **9** with Zn in acetic acid [21] was unsuccessful, whereas hydrogenative dehalogenation using 10% Pd/C – $H_2$ at atmospheric pressure yielded pyridine **12** (Scheme 1.4) in low yield (27%). Reduction of **9** at increased pressure (80 atm) has led to the formation of compound **13**, apparently as a result of hydrolysis of methoxy group at 4$^{th}$ position of pyridine ring by HCl, released during hydrogenative dehalogenation. Nevertheless, target methoxyderivative **12** could be synthesized in good overall yield (60%) by heating pyridine **13** with $POCl_3$ and subsequent treatment of obtained chloroderivative **14** with sodium methoxide (Scheme 1.4). Reduction of pyridine **12** with $LiAlH_4$ under standard conditions [22] led to inseparable mixture of products. Gratifyingly, the reduction of pyridine **12** was successful by using $NaBH_4$ – MeOH system in THF to afford the crucial intermediate, hydroxymethyl derivative **3** in 55% yield.



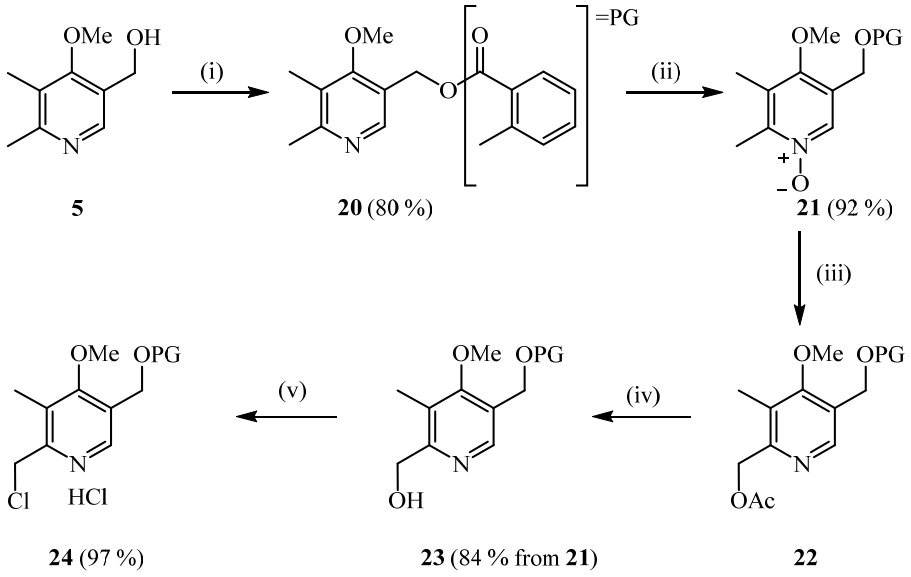

**Scheme 1.4.** (i): Pd/C, $H_2$, MeOH, 1 atm, 20 °C. (ii): Pd/C, $H_2$, MeOH, 80 atm, 20 °C. (iii): 1. $POCl_3$, 60 °C; 2. MeOH, 0 – 20 °C. (iv): NaOMe, MeOH, 20 °C to reflux. (v): $NaBH_4$–MeOH, THF, Δ.

Low overall yield (3.2%) and long synthetic route (8 steps) prompted us to investigate other synthetic routes to compound **5**. An alternative synthetic strategy involved the use of 2,3-dimethyl-4-methoxypyridine *N*-oxide (**15**) (Scheme 1.5) as a starting material which in turn was obtained from 2,3-dimethylpyridine N-oxide in 2 steps following procedure reported by Kühler [19]. Pyridine *N*-oxide was treated with $PCl_3$ to form pyridine **16**. Since the substitution of hydrogen in 5$^{th}$ position using LDA or LTMP did not proceed, we synthesized 2,3-dimethyl-4-methoxy-5-bromopyridine (**17**) (Scheme 1.5). Surprisingly, however, substitution of bromine to cyano group using CuCN has failed and only unreacted compound **17** could be recovered. The efforts of formylation of bromide **17** using Grignard reaction under various conditions led to the reduction of bromine via Grignard reagent and formation of compound **16** (Scheme 1.5).




**Scheme 1.5.** (i): $PCl_3$, DCM, Δ. (ii): NBS, $H_2SO_4$, 60 °C. (iii): 1. LDA or LTMP, -78 °C; 2. DMF, -78 to 20 °C. (iv): 1. *i*-PrMgBr, 0 °C; 2. DMF. (v): CuCN, DMF, Δ.

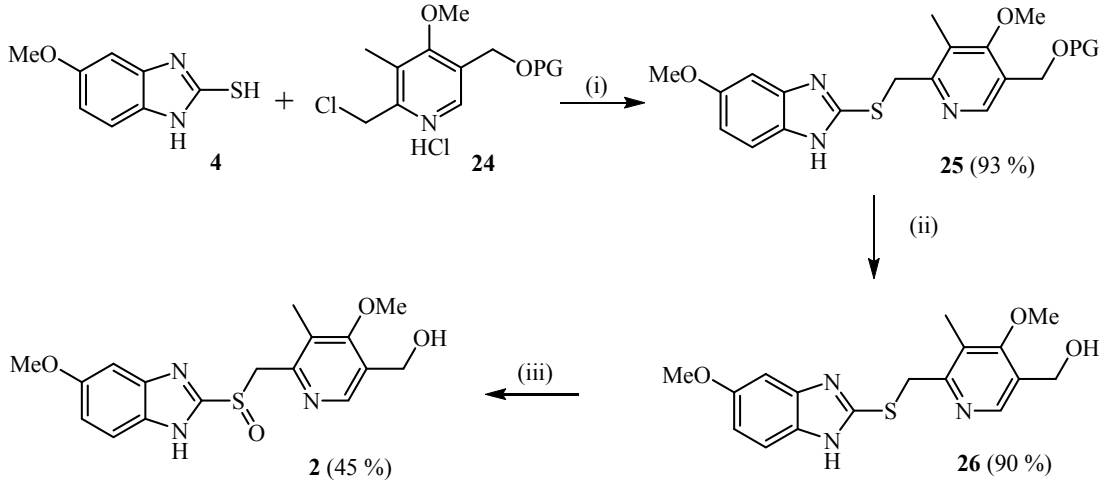
With derivative **5** in hand, we focused on the synthesis of 5-hydroxyomeprazole (**2**). Thus, hydroxy group of pyridine **5** was protected using 2-methylbenzoyl chloride (Scheme 1.6). Obtained ester **20** was oxidized to *N*-oxide **21**, which was treated with acetic anhydride to furnish Boekelheide rearrangement product **22**. Hydrolysis of the latter with aqueous NaOH yielded hydroxymethylpyridine **23**, which was then chlorinated with $SOCl_2$ to yield chloromethyl pyridine **24** in excellent yield. Overall yield of five step synthesis was 55% (Scheme 1.6).




**Scheme 1.6.** (i): 2-methylbenzoyl chloride, TEA, DCM, -5 – 20 °C. (ii): *m*-CPBA, $CHCl_3$, 5 – 25 °C. (iii): $Ac_2O$, 20 – 100 °C. (iv): NaOH, $H_2O$, THF, 20 °C. (v): $SOCl_2$, DCM, 0 to 2 °C.

Sulfide **25** has been synthesized using optimized reaction conditions developed for synthesis of Omeprazole by Kühler [19]. Alkylation of 5-methoxy-1*H*-benzimidazolethiol (**4**) with **24** in the presence of 2 equivalents of NaOH, however,

preceeded with concomitant hydrolysis of 2-methylbenzoyl ester to furnish mixture of **25** and deprotected **26**. It was found that one equivalent of NaOH is sufficient to affect alkylation without the cleavage of protecting group. Subsequent hydrolysis of **25** with NaOH in aqueous methanol overnight furnished **26** in excellent yield (90%). Since Omeprazole (**1**) and it's analogues are sensitive to acidic conditions, oxidation of sulfide **26** with *m*-chloroperbenzoic acid was performed in DCM and aqueous $NaHCO_3$ solution under argon following the procedure reported by Kühler [19]. The 5-hydroxyomeprazole (**2**) was isolated in 45% yield (Scheme 1.7).

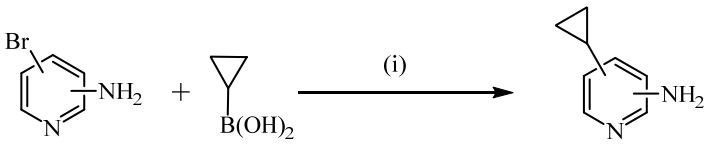



**Scheme 1.7**. (i): NaOH, MeOH/$H_2O$, 20 °C. (ii): NaOH, MeOH/$H_2O$, 20 °C. (iii): *m*-CPBA, $NaHCO_3$, MeOH, DCM, $H_2O$, 2 – 3 °C.

## 2. Synthesis of bromocyclopropylpyridines

The synthesis of 2-halogeno-5-cyclopropylpyridines employing Suzuki coupling reaction seems to be limited to 2-fluoro and 2-chloroderivatives [23; 24], whereas the Negishi coupling reaction of 2,5-dibromopyridine affords the isomeric 5-bromo-2-cyclopropylpyridine. This encouraged us to investigate the possibility to synthesize bromocyclopropylpyridines from aminobromopyridines using an alternative route, *e.g.* Suzuki coupling, followed by the Sandmeyer reaction. The latter reaction is a widely used method for the preparation of aryl halides from aryl amines. Aryl diazonium halides, obtained from aryl amines by diazotization using sodium nitrite/hydrohalic acid in water [25] or alkyl nitrites [26], react with copper halides to form the corresponding halides in average to good yields. However, in the case of substituted 2-aminopyridines, especially those carrying acid sensitive groups, the Sandmeyer reaction gives only average yields or even no reaction under standard conditions [27]. Doyle and co-workers [26] has reported a rapid conversion of aryl amines into aryl chlorides and aryl bromides using alkyl nitrites and anhydrous copper(II) halides in acetonitrile.

Aminocyclopropylpyridines **28a**, **28c** and **28e** were synthesized from the corresponding aminobromopyridines **27a**, **27c**, **27e** and cyclopropylboronic acid using standard Suzuki coupling conditions ($Pd(OAc)_2$, tricyclohexylphosphine, $K_3PO_4$, toluene/water) (Scheme 2.1).



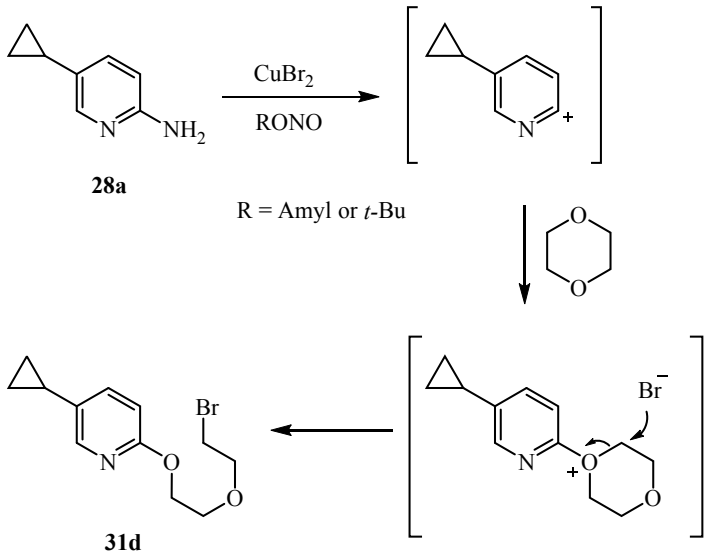

**27a** = 2-$NH_2$, 5-Br
**27c** = 2-$NH_2$; 3-Br
**27e** = 4-$NH_2$; 3-Br

**28a** = 2-NH2; 5-Cyp. 85 %
**28c** = 2-NH2; 3-Cyp. 90 %
**28e** = 4-NH2; 3-Cyp. 62 %

**Scheme 2.1**. (i): $Pd(OAc)_2$, tricyclohexylphosphine, $K_3PO_4$, Ar, toluene, $H_2O$, Δ.

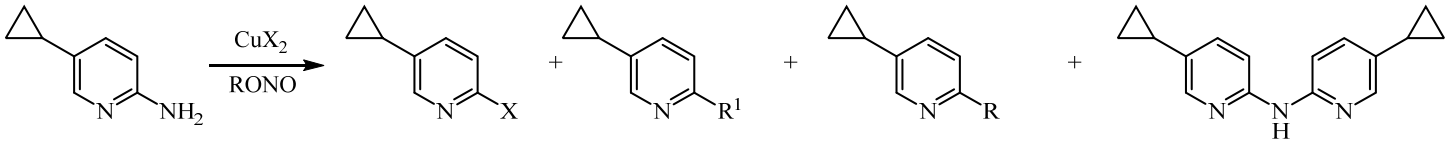
Initial attempts to prepare 2-bromo-5-cyclopropylpyridine **29a** from 2-amino-5-cyclopropylpyridine **28a** using copper(II) bromide and amyl nitrite in acetonitrile at 65 °C produced (pyridin-2-yl)acetamide **31a** as the major product (Table 2.1, entry 1). Decreasing the reaction temperature to 25 °C did not significantly affect the chemoselectivity or ratio of products (Entry 2). Other solvents, such as methanol, THF and dioxane (Entries 3-6), also gave substantial amounts of the corresponding by-products **31b-d**.

None of these solvents reacted with **28a** in the absence of copper(II) bromide; control experiments in the presence of $CuBr_2$ but without amyl nitrite in acetonitrile did not produce **31a** from **28a** either. It is generally accepted that the Sandmeyer reaction is catalyzed by copper(I) halides and proceeds by a radical mechanism, where the diazonium salt is reduced to a diazonium radical *via* single electron-transfer, which quickly loses dinitrogen to afford an aryl radical. Final ligand transfer from the copper(II) salt completes the catalytic cycle and regenerates the copper(I) species. Nevertheless, the 2-pyridinediazonium ion derived from **28a** is apparently unstable in rather polar solvents (Entries 1-6) and undergoes heterolytic cleavage [28]. The so produced highly reactive cation reacts with any available nucleophile. In the case of cyclic ethers (Entries 5, 6), the reaction most likely proceeds *via* a transient oxonium species, which undergo subsequent ring opening reaction to furnish ethers **31c-d** (Scheme 2.2).




**Scheme 2.2.** Plausible mechanism for the formation of **31d**.

**Table 2.1.** Sandmeyer reaction of 2-amino-5-cyclopropylpyridine (**28a**): optimization of the reaction conditions[a]




**28a**

**29a** X = Br
**30a** X = Cl

**31a** $R^1$=NHCOCH$_3$
**31b** $R^1$=OCH$_3$
**31c** $R^1$=O(CH$_2$)$_4$Br
**31d** $R^1$=(OCH$_2$CH$_2$)$_2$Br
**31e** $R^1$=C$_6$H$_4$Cl

**32a** R=(CH$_2$)$_2$CH(CH$_3$)$_2$
**32b** R=C(CH$_3$)$_3$

**33**

| Entry | $CuX_2$ (eq.) | RONO (eq.) | Solvent | Time (h) | Product distribution (%)[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **28a** | **29a, 30a** | **31a–31e** | **32a–32b** | **33** |
| 1[c] | $CuBr_2$ (1.2) | AmylONO (1.2) | MeCN | 72 | 3 | **29a**, 21 | **31a**, 58 | **32a**, 1 | 0 |
| 2 | $CuBr_2$ (1.2) | AmylONO (1.2) | MeCN | 72 | 9 | **29a**, 26 | **31a**, 57 (52)[d] | **32a**, 1 | 0 |
| 3 | $CuBr_2$ (1.2) | AmylONO (1.2) | MeOH | 16 | 1 | **29a**, 17 | **31b**, 80 | 0 | 0 |
| 4[e] | $CuBr_2$ (1.2) | AmylONO (1.2) | MeOH | 24 | 1 | **29a**, 14 | **31b**, 84 | 0 | 0 |
| 5 | $CuBr_2$ (1.2) | AmylONO (1.2) | THF | 3 | 2 | **29a**, 45 | **31c**, 49 | **32a**, 1 | 2 |
| 6 | $CuBr_2$ (1.2) | AmylONO (1.2) | Dioxane | 16 | 1 | **29a**, 42 | **31d**, 55 (21)[d] | **32a**, 1 | 1 |
| 7 | $CuBr_2$ (1.2) | AmylONO (1.2) | $C_6H_5Cl$ | 72 | 1 | **29a**, 75 | **31e**, 17 | **32a**, 2 | 2 |
| 8 | $CuBr_2$ (1.2) | AmylONO (1.2) | $CH_2Cl_2$ | 6 | 0 | **29a**, 60; **30a**, 36 | 0 | **32a**, 1 | 1 |
| 9 | $CuBr_2$ (1.2) | AmylONO (1.2) | $C_2H_5Br$ | 72 | 1 | **29a**, 80 | 0 | **32a**, 15 | 4 |
| 10 | $CuBr_2$ (1.2) | AmylONO (1.2) | 1,2-$C_2H_4Br_2$ | 72 | 1 | **29a**, 86 | 0 | **32a**, 8 | 5 |
| 11 | $CuBr_2$ (1.2) | *t*-BuONO (1.2) | 1,2-$C_2H_4Br_2$ | 72 | 1 | **29a**, 95 | 0 | **32b**, 2 | 2 |
| 12 | $CuBr_2$ (1.2) | AmylONO (1.2) | $CH_2Br_2$ | 16 | 0 | **29a**, 94 | 0 | **32a**, 3 | 3 |

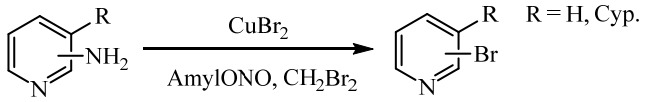
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 13 | $CuBr_2$ (0.5) | AmylONO (1.1) | $CH_2Br_2$ | 24 | 0 | **29a**, 93 (76)[d] | 0 | **32a**, 4 | 3 |
| 14[c] | $CuBr_2$ (0.5) | AmylONO (1.1) | $CH_2Br_2$ | 1 | 0 | **29a**, 80 | 0 | **32a**, 7 | 9 |
| 15 | $CuBr_2$ (0.5) | *t*-BuONO (1.1) | $CH_2Br_2$ | 24 | 0 | **29a**, 90 | 0 | **32b**, 5 | 4 |
| 16 | $CuBr_2$ (0.1) | AmylONO (1.1) | $CH_2Br_2$ | 120 | 2 | **29a**, 81 (51)[d] | 0 | **32a**, 8 | 2 |
| 17 | $CuBr_2$ (0.05) | AmylONO (1.1) | $CH_2Br_2$ | 170 | 8 | **29a**, 79 | 0 | **32a**, 10 | 1 |
| 18 | $CuCl_2$ (0.5) | AmylONO (1.1) | $CH_2Cl_2$ | 24 | 0 | **30a**, 95 (74)[d] | 0 | **32a**, 3 | 1 |

[a] Reaction carried out on a 1 mmol scale in the corresponding solvent (6 mL) at 25 °C, unless stated otherwise.
[b] GC-MS data.
[c] Reaction carried out at 65 °C.
[d] Isolated yield.
[e] Reaction carried out with additional 1 eq. of $(n\text{-Bu})_3NBr$.

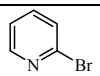
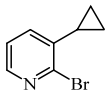
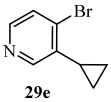
The radical pathway, however, cannot be completely rejected, as the Sandmeyer reaction of **28a** in chlorobenzene (Table 2.1, entry 7) produced a non-negligible amount of arylated pyridine **31e** as a mixture of two isomers. Moreover, a substantial amount of chloropyridine **30a** was produced in dichloromethane (Entry 8), suggesting the intermediacy of radical rather than cationic species. The latter result prompted us to investigate the Sandmeyer reaction of **28a** in bromoalkanes, which could serve both as a non-nucleophilic reaction media and a source of bromine. Thus, clean conversions were attained in bromoethane and 1,2-dibromoethane using amyl- or *tert*-butyl nitrite (Entries 9-11), but the reaction proved to be rather sluggish. The best results were obtained in dibromomethane (Entry 12). Under optimal reaction conditions using 0.5 equiv. of $CuBr_2$ and 1.1 equiv. of amyl nitrite at 25 °C, bromopyridine **29a** was produced in 76% isolated yield (Entry 13). Lower temperatures were beneficial, as the reaction at 65 °C produced more impurities (Entry 14), whereas the use of *tert*-butyl nitrite as the diazotization reagent (Entry 15) offered no advantages. The $CuBr_2$ loading could be further reduced to 10 or even 5 mol% (Entries 16-17), albeit at the expense of the reaction rate. The combination of dichloromethane and $CuCl_2$ (0.5 equiv.) was equally effective and furnished the desired chloropyridine **30a** in 74% yield (Entry 18).

With the optimal reaction conditions in hand, the substitutive deamination reaction of several aminocyclopropylpyridines and aminopyridines **28b-e** was explored (Table 2.2).

**Table 2.2.** Synthesis of bromopyridines **29b-e**[a]




**28b - e** **29b - e**

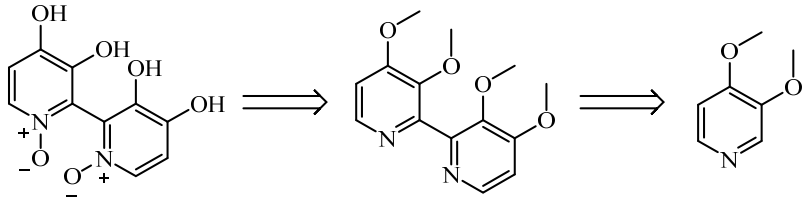
| Entry | Product | Time (h) | GC-MS (isolated) (%) |
|---|---|---|---|
| 1 |  **29b** | 16 | 83 (41) |
| 2 |  **29c** | 24 | 96 (51) |
| 3 |  **29d** | 24 | 0 |
| 4[b] |  **29d** | 1 | 95 (55) |
| 5[b] |  **29e** | 4 | 94 (57) |

[a] Reaction carried out on a 1 mmol scale in dibromomethane (6 mL) in the presence of $CuBr_2$ (0.5 mmol) and amyl nitrite (1.1 mmol) at 25 °C, unless stated otherwise. [b] Reaction carried out at 65 °C.

In comparison with 2-aminopyridine congeners **28a-c**, 4-aminopyridines **28d-e** exhibited notably lower reactivity and required elevated temperatures (Table 2.2, entries 3-5). The corresponding bromopyridines **29b-e** were obtained in good yields. The Sandmeyer reaction of **28d-e** produced practically no ether by-products analogous to **32a** (Table 2.1); pyridine and 3-cyclopropylpyridine, respectively, were the major by-products (up to 5%). Interestingly, these products of reductive deamination were absent in the crude mixtures from the Sandmeyer reaction of 2-aminopyridines **28a-c**.

### 3. Total synthesis of orellanine

The idea of transition metal free synthesis of bipyridines was inspired by few unique papers of Uchida and co-workers [29-31]. Authors have noticed that many tertiary heteroaryl phosphines, tertiary heteroarylphosphine oxides and heteroaryl sulfoxides give ligand coupling products by treatment with organolithium reagents and examined reactions of an excess of heteroaryllithiums with $PCl_3$, $POCl_3$, $SOCl_2$ and another sulfenyl chlorides. Heteroaryllithiums including pyridyllithiums were prepared from corresponding bromides. This method for preparation of heterocyclic biaryls including 2,2′-bipyridyls has never been developed or even employed by another authors. Treacourt and co-workers have showed that 3,4-dimethoxypyridine can be efficiently lithiated using butyl lithium [32]. We decided to investigate the possibility of employing these two combined methods in synthesis of orellanine (**34**). The strategy for the synthesis of this compound was based on synthesis of key intermediate 3,4-dimethoxypyridine (**36**), followed by its homocoupling and oxidation of obtained tetramethylorelline (**35**) followed by hydrolysis of methoxy groups (Scheme 3.1).

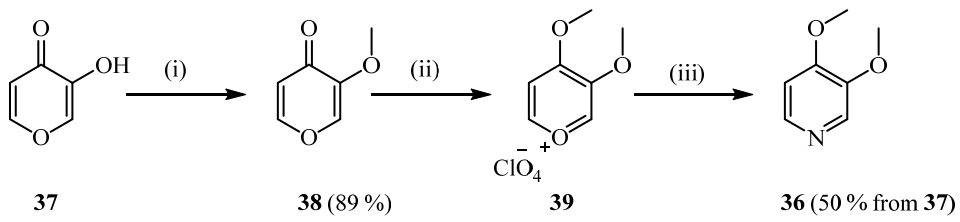


**34** **35** **36**

**Scheme 3.1.** Strategy of Orellanine (**34**) synthesis.

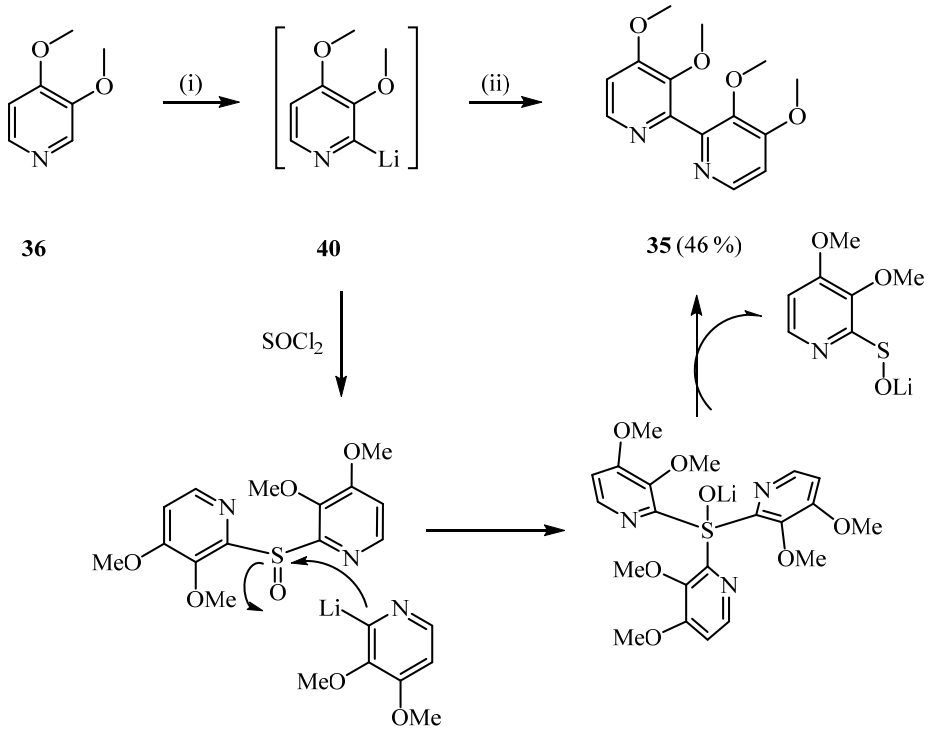
There are several examples of starting 3,4-dimethoxypyridine (**36**) synthesis [32-36]. Most efficient method [32] is based on lithiation of 4-methoxypyridine, leading to 3-hydroxy-4-methoxypyridine and subsequent *O*-methylation with diazomethane, which is unacceptable in larger scale.

3,4-Dimethoxypyridine (**36**) was synthesized from commercially available 3-hydroxypyran-4-one (**37**) in three simple steps with 45% overall yield (Scheme 3.2). Compound **37** was *O*-methylated with dimethylsulphate in basic media to give 3-methoxypyran-4-one (**38**) in excellent yield (89%). Target compound **36** was synthesized via perchlorate **39** using reaction conditions described by Campbell [37].




**Scheme 3.2**. (i): $Me_2SO_4$, NaOH, MeOH, $H_2O$, 25 °C. (ii): 1. $Me_2SO_4$, 50 °C; 2. 20 % $HClO_4$, 0 °C. (iii): 10 % $(NH_4)_2CO_3$, 0 °C.

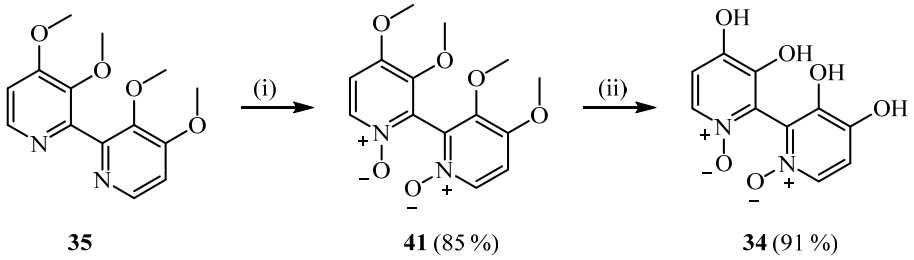
With the 3,4-dimethoxypyridine (**36**) in hand, we turned our attention to the synthesis of tetramethylorelline (**35**). Compound (**36**) was successfully lithiated using 2.2 eq. of *n*-butyllithium at -70 – 78 °C[9] and treated with $SOCl_2$. It was found that reaction with $SOCl_2$ should be performed at -40 °C. Quenched reaction mixture contains only target product (**35**) and starting pyridine (**36**) which can be re-used after simply recovery procedure. At lower temperatures this reaction didn't occur and only starting pyridine **36** was recovered. At higher temperature (-20 °C) reaction with $SOCl_2$ takes another path. After quenching reaction mixture only 50 % of pure pyridine **36** was recovered. Possibly side-products were greatly soluble in water and couldn't be isolated. No traces of target product **35** were observed. Possible reaction mechanism, which is similar to the ones described by Furukawa [38; 39], Ushida and Uae [31] is presented in scheme 3.3.




**Scheme 3.3.** (i): *n*-BuLi, THF, -70 °C. (ii): $SOCl_2$, THF, -40 °C.

Obtained tetramethylorelline (**35**) was oxidized to corresponding *N,N*′′-dioxide **41** using *m*-chloroperbenzoic acid under standard conditions. Orellanine (**34**) was obtained

by refluxing *N,N′*-dioxide **41** in 48% HBr for 5 hours in 91% yield (Scheme 3.4).

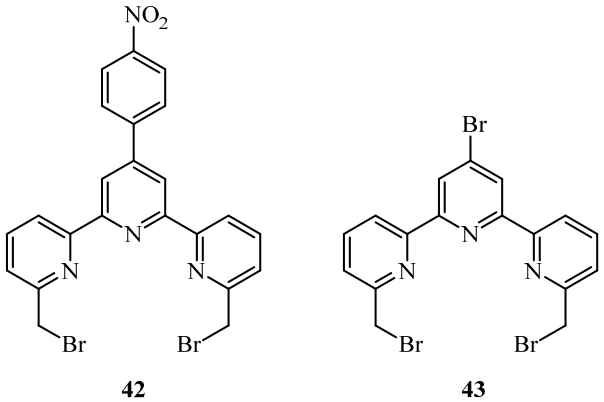



**Scheme 3.4.** (i): *m*-CPBA, DCM, 25 °C. (ii): conc. HBr, Δ.

This novel 6 step total synthesis of orellanine (**34**) starting from 3-hydroxypyran-4-one (**37**) furnishes target product in overall 16% yield and far more efficient than strategies reported previously by Dehmolow and Schulz (7-9 steps, 0.4 - 1.4% yield) [33; 35], or Tiecco (9 steps, 3.7% yield) [34]. Moreover this is transition metal catalysis free synthesis what makes it more attractive for the production of the compound for the medicinal uses.

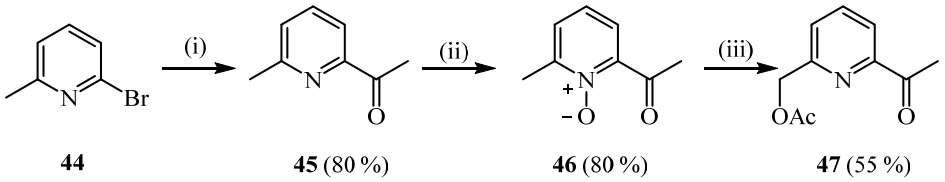
## 4. Synthesis of terpyridines

Terpyridine carcass bearing compounds possess very interesting electronic properties, which are highly applicable in fluorometry [40]. A building block with this carcass ready for functionalization both on 4' and 6,6" positions would be very valuable precursor for synthesis of library of terpyridnes. With this approach two target compounds **42** and **43** were selected (scheme 4.1). Both of compounds possess bromomethyl substituents at 6- and 6"-position. Terpyridine **42** at 4'-position has *p*-nitrophenyl moiety, which can be easily reduced to corresponding aniline and further functionalized. Terpyridine **43** at 4'-position has bromine atom ready for cross-coupling reactions.



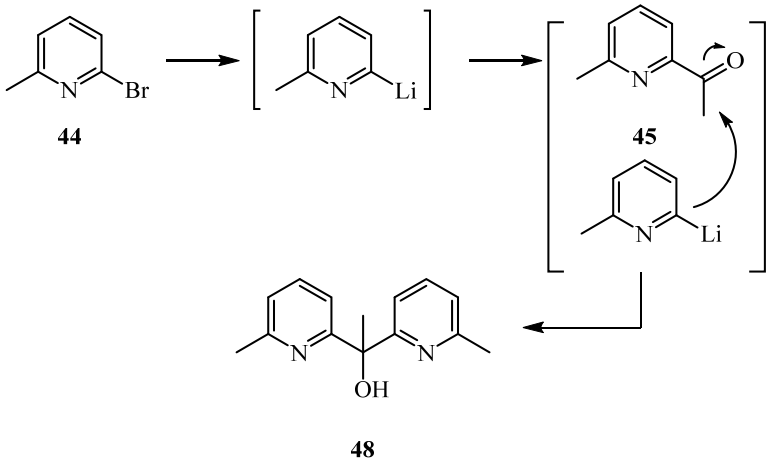

**Scheme 4.1.** Target terpyridines

Acetylpyridine **47** was selected as a precursor for terpyridine **42**. This compound can be modified in two ways to yield intermediates for Kröhnke pyridine synthesis [41].



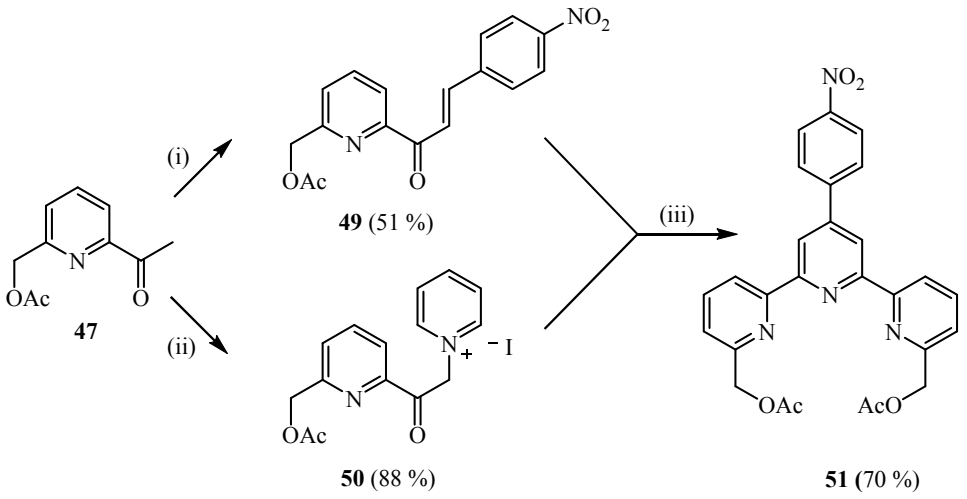

**Scheme 4.2**. (i): 1. *n*-BuLi, THF, Ar, -78 °C; 2. $AcNMe_2$, -78 °C. (ii): *m*-CPBA, DCM, 0 – 20 °C. (iii): $Ac_2O$, 90 – 120 °C.

In order to synthesize 2-acetyl-6-methylpyridine (**45**), 2-bromo-6-methylpyridine (**44**) was converted to corresponding 2-pyridinyllithium and treated with various electrophiles – acetonitrile, acetic anhydride or dimethylacetamide. Only treatment with dimethylacetamide yielded target compound in 80 %. Treatment with acetonitrile yielded unseparable multicomponent mixture of compounds. Treatment o piridinyllithium with acetic anhydride resulted formation of another product **48**, whose structure is not fully determined, but in accordance with GC-MS data this is the product of double nucleophilic addition of pyridine to the acetyl group (Scheme 4.3).



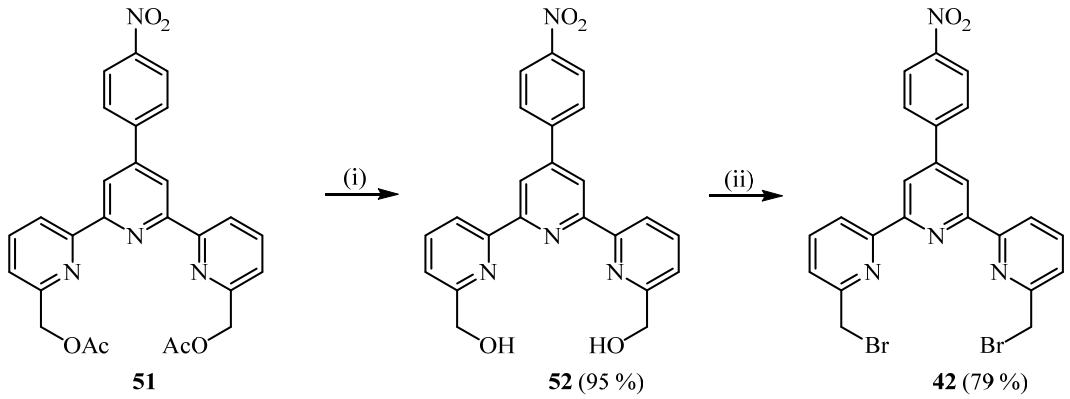

**Schema 4.3.** Possible reaction mechanism of bromopyridine **44** reaction with $Ac_2O$.

2-Acetyl-6-methylpyridine (**45**) was oxidized to corresponding *N*-oxide **46** with *m*-chloroperbenzoic acid under standard conditions. Folowing Boekelheide rearrangement yielded target pyridine **47**, the precursor for two terpyridine **42** intermediates. The first, (*E*)-(6-(3-(4-nitrophenyl)acryloyl)pyridin-2-yl)methyl acetate (**49**), was synthesized upon Claisen-Schmidt condensation [42] of pyridine **47** with 4-nitrobenzaldehyde. The second, 1-(2-(6-(acetoxymethyl)pyridin-2-yl)-2-oxoethyl)pyridin-1-ium iodide (**50**) was synthesized by treatment of pyridine **47** with iodine in pyridine (Scheme 4.4).



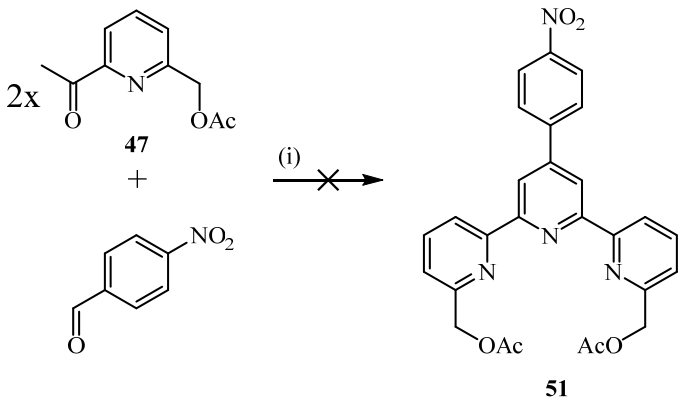

**Schema 4.4.** (i): 4-nitrobenzaldehyde, KOH, MeOH, $H_2O$ 0 – 2 °C. (ii): $I_2$, Pyridine, Δ. (iii): $NH_4OAc$, MeOH, Ar. Δ.

Kröhnke pyridine synthesis conditions were succesfully aplied in condensation and cyclization of intermediates **49** and **50** in the presence of ammonium acetate and terpyridine **51** was synthesized in 70% yield (Scheme 4.4). Hydrolysis with 10% hydrochloric acid performed poorly in case of terpyridine **51**, and target diol **52** was separated only in 36% yield. On the other hand, terpyridine **51** was succesfuly hydrolized with methanolic – aqueous solution of sodium hydroxide almost quantitively (scheme 4.5). Resulting terpyridine diol **52** was treated with $PBr_3$ in DMF and target terpyridine **42** was separated in 79% yield. Total 8 step yield starting from 2-bromo-6-methylpyridine (**44**) is 8.2%.



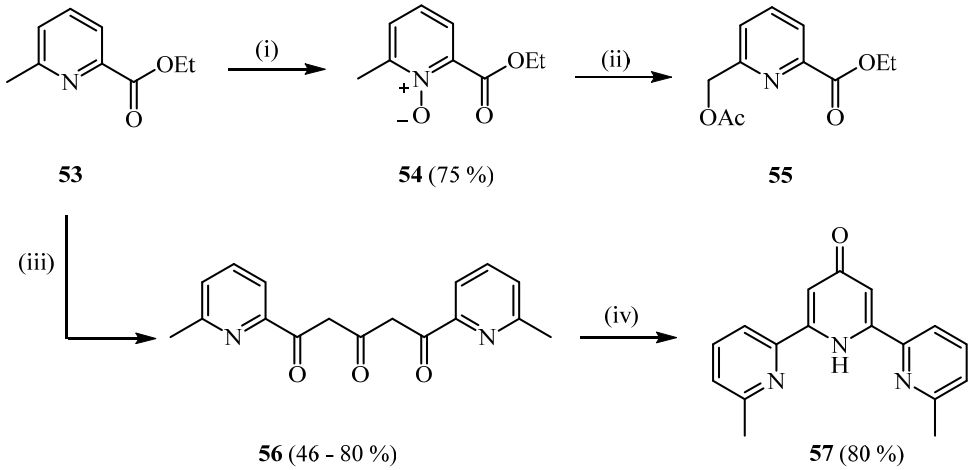

**Schema 4.5.** (i): 1 N NaOH, MeOH, 20 °C. (ii): $PBr_3$, DMF, 20 – 60 °C.

It is known [43], that in some terpyridine synthesis cases formation of pyridine ring can be performed in one pot synthesis without activation of acetylpyridine. Unfortunately, in our case double condensation of 4-nitrophenylbenzaldehyde with (6-acetylpyridin-2-yl)methyl acetate (**47**) in aqueous ammonia solution was not succesful, yet it is unknown was it due to sensitivity of estrer moiety under reaction conditions or the second condensation reaction did not resulted the expected outcome and target terpyridine **51** did not form (Scheme 4.6).




**Schema 4.6.** (i): NaOH, $NH_4OH$, Ar, Δ.

Ethyl 6-(acetoxymethyl)picolinate **55** was selected as a precursor for terpyridine **43** (Scheme 4.7). The precursor was synthesized by oxidation of ethyl 6-methylpicolinate **53** to the corresponding *N*-oxide **54** by treatment of starting compound with *m*-chloroperbenzoic acid under typical conditions (Scheme 4.7). The reaction of *N*-oxide **54** with acetic anhydride undergoes not only Boekelheide rearrangement but also many other side reactions. Atlthoug there is a full conversion of *N*-oxide **54**, only 40% of expected mass was harvested. Moreover, the crude picolinate **55** could not be purified not only due to complexicity of mixture but also there was observed decomposition of product upon purification process.




**Scheme 4.7.** (i): *m*-CPBA, DCM, 20 °C. (ii): $Ac_2O$, 60 – 120 °C. (iii): NaH, THF, Ar, Δ. (iv): $NH_4OAc$, 2-propanol, Ar, Δ.

An alternative strategy for the synthesis of terpyridine **43** was investigated. It is known [44] that oxidation of terpyridines with *m*-chloroperbenzoic acid affects only the first and the third pyridine rings. Furthermore, the Boekelheide rearrangement can be succesfuly carried out in such terpyridine *N,N*"-dioxides [45]. Picolinate **53** serves as starting point in this synthetic pathway aswell. Although condensation of picolinate **53** with acetone yields target trione **56**, the reaction is unambiguous and consistent yield was not achieved and varies from 46% to 80% (scheme 4.7).

The trione **56** was cyclization to terpyridine **57** under typical conditions, namely under reflux in methanol with ammonium acetate was accomplished in poor yield. However subsitution of methanol to 2-propanol as solvent led to increase of yield and target terpyridine **57** was separated in 80% yield. There are still few steps to the final terpyridine **43** remaining.

## CONCLUSIONS

1. It was found, that product distribution of methyl-2,4-dichloro-5,6-dimethylpyridine-3-carboxylate treatment with sodium methoxide depends on reaction temperature. Reaction carried out in 20-30°C results formation of methyl 2-chloro-5,6-dimethyl-4-methoxypyridine-3-carboxylate, and the reaction carried out in 65°C yields 5,6-dimethyl-2,4-dimethoxypyridin-3-carboxylate.
2. It was found that upon hydrogenative dehalogenation of 2-chloro-5,6-dimethyl-4-methoxypyridine-3-carboxylate at 80 atm pressure methoxygroup at 4-position of pyridine ring suffers hydrolysis, probably due to hydrogen chloride released upon the reaction.
3. Total synthesis of (4-methoxy-6-(((5-methoxy-1*H*-benzo[*d*]imidazol-2-yl)sulfinyl)methyl)-5-methylpyridin-3-yl)methanol (5-hydroxyomeprazole) in 14 steps and overall 1.3% yield was developed.
4. It was found that Sandmeyer reaction of aminocyclopyridines with copper(II) halides and alkylnitrites undergoes both in cationic and radical pathways
5. Optimal reaction conditions for synthesis of bromo(chloro)cyclopropylpyridines were developed.
6. Unique synthetic method for ω-halogenealcoxypyridines was observed.
7. Efficient method for 3,4-dimethoxypyridine synthesis in aqueous media and transition metal catalysis free homocoupling of 3,4-dimethoxypyridine was developed.
8. Novel 6 step total synthesis of orelanine with overall 16% yield starting from 3-hydroxypyr-4-one was developed.
9. 8 step synthesis of ,6''-bis(bromomethyl)-4'-(4-nitrophenyl)-2,2':6',2''-terpyridine with 8.2% overall yield was developed.

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## REZIUME

Piridino fragmentą turinčių darinių sintezė apima daugelį tyrimo sričių, o susidarę junginiai pasižymi vertingomis, praktikoje pritaikomomis savybėmis. Remiantis „MDL Drug Data Report“ duomenimis, piridino fragmentas yra labiausiai pasitaikantis heterociklinis fragmentas gydymui naudojamų vaistų struktūroje. Bipiridino ir terpiridino fragmentus turintys junginiai naudojami įvairių chelatų sintezėje. Šie kompleksai sėkmingai pritaikomi asimetrinėje katalizėje ir chemoterapijoje. 1,4-Dihidropiridino pagrindu sintetinamos į dirgiklius reaguojančios fluorescencinės medžiagos. Piridino žiedas naudojamas ir kaip elektronų akceptorius elektronų pernašai aukšto efektyvumo organinėse šviesą spinduliuojančiose medžiagose.

Šio darbo tikslas - sukurti naujus arba patobulinti žinomus 5-hidroksiomeprazolo, bromciklopropilpiridinų, orelanino ir terpiridino darinių sintezės metodus. Kiekvienos iš tiriamų sistemų įprasti sintezės keliai turi trūkumų, o toks junginys, kaip 5-hidroksiomeprazolas chemiškai dar nebuvo susintetintas.

Sukurtas 5-hidroksiomeprazolo cheminės sintezės metodas. Darbo metu nustatyta, kad metil-2,4-dichlor-5,6-dimetilpiridin-3-karboksilatui reaguojant su dviem ekvivalentais natrio metoksido, produktų pasiskirstymas priklauso nuo reakcijos temperatūros, bei sukurta metil-2,4-dichlor-5,6-dimetilpiridin-3-karboksilato reakcijos su dviem ekvivalentais natrio metoksido šalutinių reakcijos produktų perdirbimo į pradinį metil-2,4-dichlor-5,6-dimetilpiridin-3-karboksilatą metodika. Buvo nustatyta, kad atliekant 2-chlor-5,6-dimetil-4-metoksipiridin-3-karboksilato hidrodehalogeninimo reakciją 80 atmosferų slėgyje, reakcijos metu vyksta ir 4-osios padėties metoksigrupės hidrolizė.

Surastos optimalios brom(chlor)ciklopropilpiridinų sintezės sąlygos. Nustatyta, kad aminociklopropilpiridinų Sandmeyer reakcija su vario(II) halogenidais ir alkilnitritais vyksta tiek katijoniniu, tiek radikaliniu reakcijos mechanizmais. Diazonio druska, susidariusi reaguojant su 2-amino-5-ciklopropilpiridinui su vario(II) bromidu ir alkilnitritu, yra nestabili reakcijos sąlygomis ir dalyvauja heterolitiniame skilime susidarant aktyviam katijonui, kuris reaguoja su bet kuriuo esamu nukleofilu, bei pastebėtas naujas ω-halogenalkoksipiridinų susidarymo būdas.

Sukurtas naujas 3,3',4,4'-tetrahidroksi-2,2'-bipiridino *N,N*'-dioksido (Orelanino) sintezės būdas sutrumpinant bendrą sintezės kelią ir kelis kartus pagerinant bendrą išeigą. Sukurtas efektyvus 3,4-dimetoksipiridino sintezės būdas vandeninėje terpėje, naudojant mažiau pavojingus reagentus nei ankščiau aprašytuose metoduose, ir 3,4-dimetoksipiridino C-C homo-jungimo sintezės metodas nenaudojant pereinamųjų metalų katalizatorių.

Surastas 6,6''-bis(brommetil)-4'-(4-nitrofenil)-2,2':6',2''-terpiridino sintezės būdas panaudojant Kröhnke piridinų sintezės metodą.

## CURRICULUM VITAE

Name, surname: Romualdas Striela

Date and place of birth: 26th of October, 1984, Klaipėda, Lithuania

Contact details: Phone: +37067048833

e-mail: romualdas.striela@gmail.lt

**Education:**

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|---|---|
| 2012-2016 | Phd studies in State research institute Center for Physical Sciences and Technology |
| 2010-2012 | MSc studies in Vilnius University, Faculty of Chemistry |
| 2003-2009 | BSc studies in Vilnius University, Faculty of Chemistry |
| 2001-2003 | Klaipėda Smeltės high school |
| 1995-2001 | Klaipėda Gedminų progymnasium |
| 1991-1995 | Klaipėda Vyturio primary school |