

Master projects Spring 2008

Prof. Lise-Lotte Gundersen, Department of Chemistry.

In this document, current possible master projects in the Gundersen-group are presented. We are members of the Section for Life sciences; research group “Synthesis and Structures” at the Department of Chemistry, University of Oslo. We are also members of the program “Structure guided organic synthesis targeted for applications in life sciences” recently appointed a strategic research area within the Faculty of Mathematics and Natural Sciences.

The Gundersen-group focuses on synthetic organic chemistry, natural product synthesis, and medicinal chemistry; development of potential drugs against infectious diseases (especially tuberculosis and other tropical diseases), cancer and Parkinsons disease. For more information about the group and projects, please consult our web page (<http://folk.uio.no/llotte/>) and contact Lise-Lotte Gundersen. room ø217 (Chemistry building), phone (+47) 228 57019, e-mail: l.l.gundersen@kjemi.uio.no.

You may also find some links describing our research activities here (Norwegian text):

- <http://www.forskning.no/Artikler/2007/april/1177566360.24>
- http://www.apollon.uio.no/vis/art/2004/3/tuberkulose_kjemi
- <http://www.kjemi.uio.no/publikum/index.php?dok=popart&id=13>

The available master projects (listed alphabetically) are:*

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* These projects are 60 study point master projects; 30 study point project may be designed in some of these fields.

Are agelasines acting as antimicrobials by interaction with cell membranes?

NMR studies of agelasine – phospholipid bilayer interactions

This project is suitable for one master student

Both Lise-Lotte Gundersen (organic synthesis) and Frode Rise (NMR; <http://folk.uio.no/froderi/>) will act as supervisors

Background

More than >25% of all deaths pr. year worldwide are a direct result of an infectious disease.¹ Many of these occur in developing countries and access to current drugs, vaccines and even clean drinking water may indeed reduce the number of unnecessary deaths, but in case of many tropical diseases there is an immediate need for new drugs. “Reduction of child mortality” and “Combat HIV/AIDS, malaria and other diseases” are two of the eight UN Millennium Development Goals.² WHO calls for “A globally coordinated effort to bring the resources of modern science to bear on the control of ten major tropical diseases.”³

Nature is a rich source of bioactive compounds and potential drugs. The so-called secondary metabolites are structures involved in interaction between organisms, for instance chemical defense. Studies of such metabolites have led to the discovery of many life-saving drugs, including antibiotics, but also immunosuppressant and antineoplastic agents.⁴ The last 50 years, there has been an increasing interest for marine natural products as potential drugs and molecular tools, since an enormous chemical and biological diversity are found among metabolites from marine species.⁵ However, most bioactive marine products can only be isolated in very minute amounts, and bioprospecting must be combined with state-of-the-art organic synthesis in order to explore the true potential of these chemically complex structures.

Agelasines are 7,9-dialkylpurinium salts isolated from marine sponges (*Agelas* sp., Fig. 1). At the present a total of 11 9-methyladeninium salts, Agelasine A-I, epiagelasine C and agelin B, are known.⁶⁻¹² All compounds carry a diterpenoid side chain in the adenine 7-position (Structure of agelasine D, see Fig. 2). The Gundersen-group has recently completed the syntheses of agelasine E and *ent*-agelasine E¹³ from *ent*-trixagol and trixagol,¹⁴ and agelasine D¹⁵ from manool. These agelasines as well as several agelasine analogs display a broad spectrum of antimicrobial activities as well as high activity against several cancer cell lines.^{13,15b,16} The mechanism of action for agelasines and analogs as antimicrobial or anticancer compound is not known. Our current hypothesis is that these compounds, which has a hydrophilic “head” (the purine ring) and a long lipophilic “tail”, may interact with cell membranes, and disrupt normal functions. A cartoon of a potential interaction between agelasine D and the phospholipid bilayer of a cell membrane, is shown in Fig. 3.



Fig. 1. An example of a Agelas sponge;
Agelas conifera

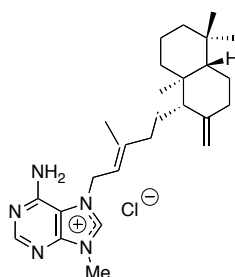


Fig 2. Structure of
agelasine D.

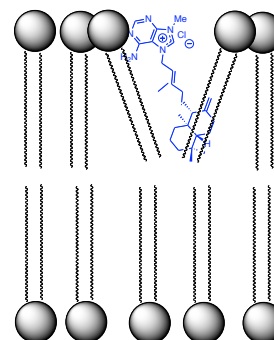


Fig. 3. Hypothetical Agelasine D (blue) –
phospholipid bilayer interaction

Goals

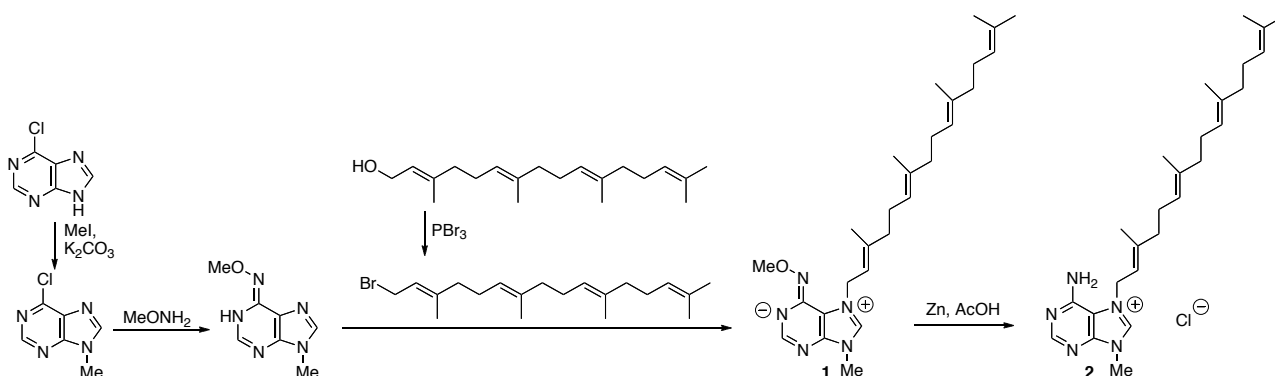
We want to test our hypothesis that agelasines and close analogs act as antimicrobial- and anticancer compounds by an interaction with cell membranes. Knowledge of the mechanism of action will, in the long run, facilitate synthesis of agelasine analogs with improved biological activities and eventually also lead to antimicrobial and / or anticancer drugs.

Methods

This project include some organic synthesis, but the major part of the project will be NMR studies of interactions between agelasine analogs and micelles, which act as models for cell membranes.

Synthesis

The first part of the project will be synthesis of the agelasine analogs required for the NMR studies. Compounds **1** and **2** will be used as agelasine model substances and they will be resynthesized according to our published procedure¹³ as shown in Scheme 1. Depending on the NMR results (see below) agelasine analogs with some structural variations in the terpenoid side chain may be included at a later stage.



Scheme 1

NMR studies

The initial NMR studies will focus on measuring ^1H T_1 relaxation time constants for the different positions in the agelasine molecules in heavy water (D_2O) and embedded in fully deuterated micelles dissolved in D_2O .¹⁷ Then the same measurements will be performed with a paramagnetic species is added. The paramagnetic species will shorten the T_1 values. The idea here is that the

deeper the lipophilic side chain is embedded in the micelle membrane the less the T_1 values will be changed by the paramagnetic relaxation agent.¹⁸ These studies may later be extended to studies of lipophilic bilayer membranes oriented perpendicular to the magnetic field generated by the NMR magnetic field if specific positions of the agelasine molecules can be labeled with ^{13}C atoms. Attempts at studying the diffusion rates of water (H_2O) and other small polar substances across membranes can also be envisaged.¹⁹ If the agelasines indeed do make real holes in the membranes the diffusion rates of small polar molecules or ions will increase. Measurements of these processes will involve the so called DOSY experiments as well as regular diffusion measurements.

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Development of geranylgeraniol derivatives as potential antituberculosis drugs

This project is suitable for one master student.

Background

More than >25% of all deaths per year worldwide are a direct result of an infectious disease.¹ Many of these occur in developing countries and access to current drugs, vaccines and even clean drinking water may indeed reduce the number of unnecessary deaths, but in case of many tropical diseases there is an immediate need for new drugs. “Reduction of child mortality” and “Combat HIV/AIDS, malaria and other diseases” are two of the eight UN Millennium Development Goals.² WHO calls for “A globally coordinated effort to bring the resources of modern science to bear on the control of ten major tropical diseases.”³

Globally, tuberculosis (TB) takes a life every 15 sec., and it is estimated that ca. one-third of the world's population is infected with *Mycobacterium tuberculosis*. In sub-Saharan Africa, two thirds of all HIV infected are co-infected with TB, and TB is the actual cause of death for 30% of the AIDS patients worldwide. Today, the standard drug combinations used to treat tuberculosis, must be taken for six to nine months. There has been no major breakthrough in TB drug development for 30 years and at the same time multi-drug resistant TB (MDR-TB) is a growing problem.⁴



Fig. 1. “Sick child” by Edward Munch pictures his sister died from TB.

Our group has recently discovered that *trans,trans*-geranylgeranol (Fig. 2) exhibits high activity against *Mycobacterium tuberculosis in vitro*.⁵ Geranylgeraniol appears to be selective against *M. tuberculosis* and the compound exhibits low toxicity towards mammalian cells.

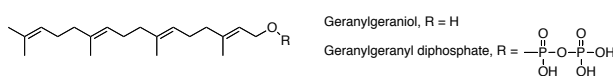


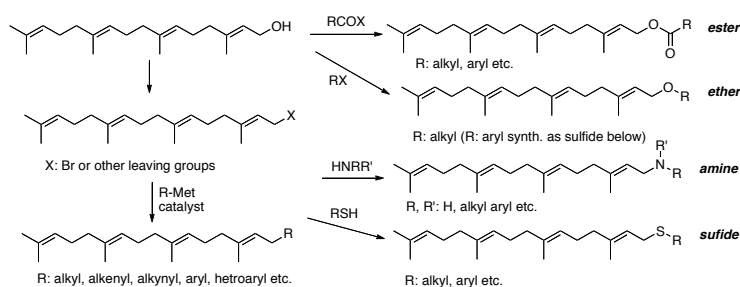
Fig. 2. *trans,trans*-Geranylgeraniol is abundant in nature. Geranylgeranyl diphosphate is the biosynthetic precursor of all diterpenes and a wide variety of other natural products incl. vitamins E and K and the anticancer compound paclitaxel (Taxol®).

Goals

We want to synthesize derivatives of geranylgeraniol and examine their antimycobacterial activity.

Methods

The target compounds will be synthesized from geranylgeraniol as depicted in Scheme 1. The database SciFinder will be used for synthesis planning.



Scheme 1

The product will be purified by chromatographic techniques and the structures determined by spectroscopic methods, mainly various NMR techniques and MS. Other spectroscopic techniques (i.e. IR, UV) may be applied if necessary. The same is true for X-ray crystallography.

The compounds will be examined as antimycobacterials at Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) in USA (<http://www.taacf.org/>). Toxicity towards mammalian cells is also determined by TAACF. Other antimicrobial activities may be determined in collaboration with Assoc. Prof. C. Charnock (Oslo University College). SAR (structure-activity relationships) analysis will be performed on the biological activity data.

References

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Development of heterocyclic potential antituberculosis drugs

This master project is a part of a larger on-going NFR-supported project and master projects for more than one student can be designed.

Background

More than >25% of all deaths pr. year worldwide are a direct result of an infectious disease.¹ Many of these occur in developing countries and access to current drugs, vaccines and even clean drinking water may indeed reduce the number of unnecessary deaths, but in case of many tropical diseases there is an immediate need for new drugs. “Reduction of child mortality” and “Combat HIV/AIDS, malaria and other diseases” are two of the eight UN Millennium Development Goals.² WHO calls for “A globally coordinated effort to bring the resources of modern science to bear on the control of ten major tropical diseases.”³

Globally, tuberculosis (TB) takes a life every 15 sec., and it is estimated that ca. one-third of the world's population is infected with *Mycobacterium tuberculosis*. In sub-Saharan Africa, two thirds of all HIV infected are co-infected with TB, and TB is the actual cause of death for 30% of the AIDS patients worldwide. Today, the standard drug combinations used to treat tuberculosis, must be taken for six to nine months. There has been no major breakthrough in TB drug development for 30 years and at the same time multi-drug resistant TB (MDR-TB) is a growing problem.⁴

Our group has identified certain 6-arylpurines (Fig. 2) as potent antimycobacterials with high activity against drug resistant strains, low toxicity towards mammalian cells, and narrow spectrum of antibacterial activity, pointing towards a novel antimycobacterial mechanism of action.⁵



Fig. 1. “Sick child” by Edward Munch pictures his sister died from TB.

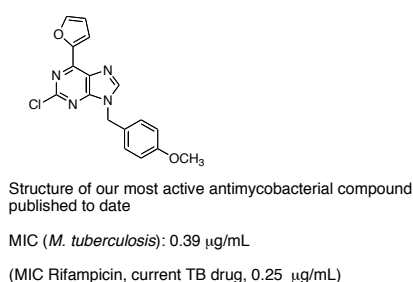


Fig. 2. Lead compound.

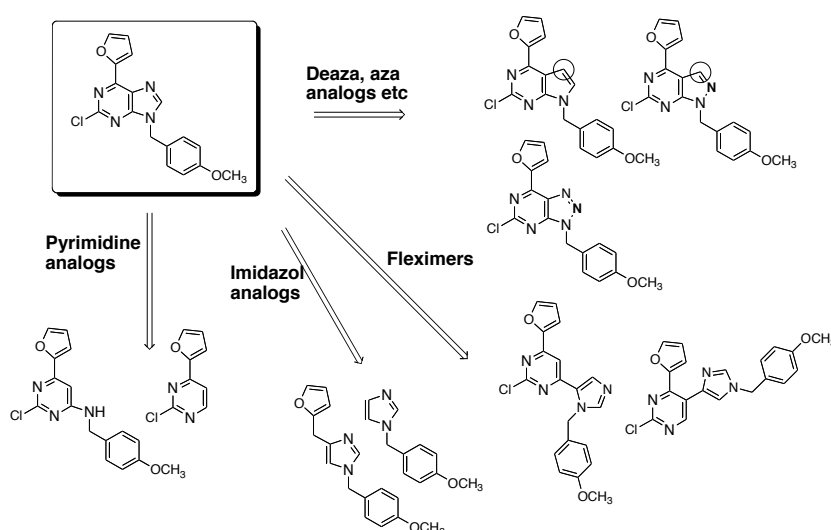


Fig. 3. Possible new synthetic targets

Goals

We want to synthesize compounds with structural resemblance to the active antimycobacterials identified so far. At this stage, we will focus on non-purine compounds (Fig. 3). The goal is to understand more about structure-activity relationships (SAR) for these potential antituberculosis drugs and ideally prepare compounds with better biological activities than the currently known structures.

Methods

The target compounds will be identified based on the current knowledge of SAR when the project starts and the compounds will be synthesized using known organic reactions applied on relevant starting materials. The database SciFinder will be used for synthesis planning.

The product will be purified by chromatographic techniques and the structures determined by spectroscopic methods, mainly various NMR techniques and MS. Other spectroscopic techniques (i.e. IR, UV) may be applied if necessary. The same is true for X-ray crystallography.

The compounds will be examined as antimycobacterials at Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) in USA (<http://www.taacf.org/>). Toxicity towards mammalian cells is also determined by TAACF. Other antimicrobial activities may be determined in collaboration with Assoc. Prof. C. Charnock (Oslo University College). SAR analysis will be performed on the biological activity data.

References

1. Morens, D. M.; Folkers, G. K.; Fauci, A. S. The challenge of emerging and re-emerging infectious diseases. *Nature* **2004**, *430*, 242-249.
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Development of potential intercalating anti-cancer drugs

This project is suitable for one master student.

Background

Cancer is one of the principal causes of death in developed countries. It may affect people at all ages, but risk tends to increase with age. Cancer is caused by damage to the DNA, often due to exposure to environmental factors. Once diagnosed, cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy. For some cancers, there are already specific drugs on the market, but not all types of cancer cells respond well to existing chemotherapy. Several pyrido[1,2-*e*]purines are reported to exhibit inhibitory activity against certain cancer cell lines (incl. activity against multi-drug resistant cell lines) comparable to or better than the anti-cancer drug doxorubicin.¹ The structure of these compounds are shown in Fig. 1. These drug candidates intercalate in DNA and thereby inhibit normal replication of the cancer cells (Fig. 2.). The current syntheses of the pyrido[1,2-*e*]purines are rather tedious.

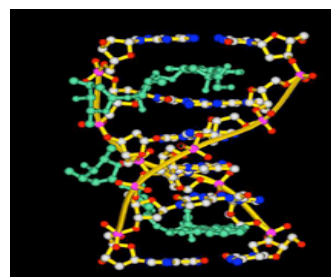
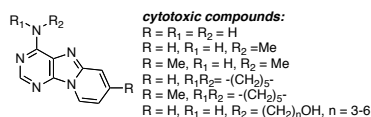


Fig. 1. Structure of known anti-cancer pyrido[1,2-*e*]purines.

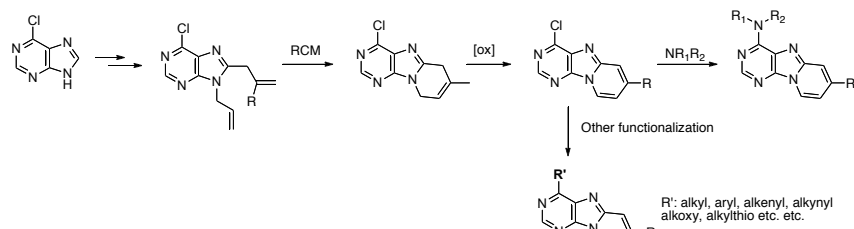
Fig. 2. The anticancer drugs anthracyclines (in green) also intercalates between the base-pairs in DNA

Goals

We want to develop an efficient synthetic route to known anti-cancer pyrido[1,2-*e*]purines. Furthermore, we want to synthesize analogs of the known compounds and examine their ability to inhibit growth of cancer cells. The goal is to understand more about structure-activity relationships (SAR) for these potential drugs and ideally prepare compounds with better biological profile than the currently known structures.

Methods

The compounds will be synthesized with the ring-closing metathesis reaction (RCM)² as a key-step as depicted in Scheme 1. The database SciFinder will be used for synthesis planning. The chemistry described in Scheme 1 may also be used for the synthesis of analogs of sildenafil (Viagra[®]),³ see Fig. 2, as well as to create a number of novel heterocyclic structures (Schemes 2-3).



Scheme 1.

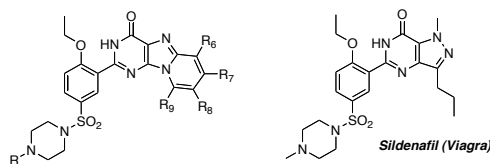
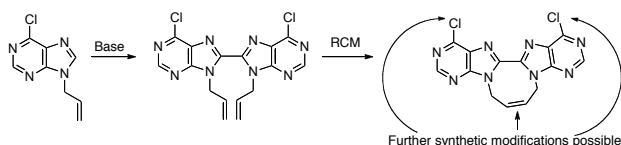
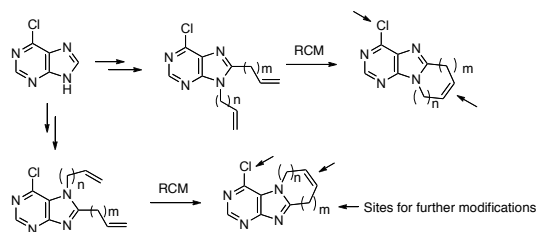


Fig. 2. Structure of a potential targets (sildenafil analogs).



Scheme 2



Scheme 3

The product will be purified by chromatographic techniques and the structures determined by spectroscopic methods, mainly various NMR techniques and MS. Other spectroscopic techniques (i.e. IR, UV) may be applied if necessary. The same is true for X-ray crystallography.

The novel compounds will be examined for activity against cancer cell lines by our collaborators at the University of Uppsala. Screening of antimicrobial activities may also be carried out in collaboration with Assoc. Prof. C. Charnock (Oslo University College). SAR analysis will be performed on the biological activity data.

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Development of selective adenosine A_{2A} antagonists –

Potential anti-Parkinson drugs

This project is suitable for one master student.

Background

Parkinson's disease (PD) is a chronic disease. The four primary symptoms of PD are tremor, or trembling in hands, arms, legs, jaw, and face; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. There is currently no cure for PD, but some drugs provide relief from the symptoms in many PD patients. In the UK, one in 500 people, around 120,000 individuals have Parkinson's, most of them are over 50 years old. In PD, there is a loss of nerve cells in the brain that produces the neurotransmitter / signal substance dopamine.

Adenosine (Fig. 1) plays an important role in regulation of a number of physiological functions, and act via four major receptor subtypes (A₁, A_{2A}, A_{2B} and A₃). A_{2A} receptors are present in the central nervous system and contribute to the control of motorical behavior. The A_{2A}-receptors are involved in control of the release of several neurotransmitters and inhibition of A_{2A}-receptors may counteract effects from lack of dopamine. Selective A_{2A} antagonists (blockers of adenosine binding to A_{2A}-receptors) are known to have antiparkinsonian activity in monkeys.¹ One example of a known A_{2A}-antagonist is compound **1** (Fig. 1).^{1c} This compound is structurally related to antimycobacterial compounds **2** (Fig. 1) developed in our group.²

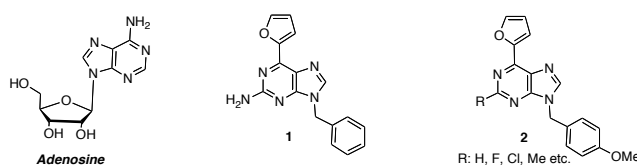


Fig. 1. Adenosine, adenosine A_{2A} antagonist **1** and related antimycobacterial compound **2**.

Goals

We want to develop efficient synthetic routes to selective and potent adenosine A_{2A} antagonists structurally related to compounds **1** and **2**. The goal is to understand more about structure-activity relationships (SAR) for these potential antiparkinson-drugs and ideally prepare compounds with better biological profile than the currently known structures.

Methods

The compounds with the general structure shown in Fig. 2 will be synthesized. Many synthetic routes will be closely related to those employed in the project directed towards antimycobacterial compounds.² The database SciFinder will also be used for synthesis planning. Compounds from the antimycobacterial project are currently under testing as A_{2A} antagonists, and the results from this

screening will determine the detailed structures of the synthetic targets in the planned project. The product will be purified by chromatographic techniques and the structures determined by spectroscopic methods, mainly various NMR techniques and MS. Other spectroscopic techniques (i.e. IR, UV) may be applied if necessary. The same is true for X-ray crystallography.

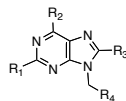


Fig. 2. General structure target compounds.

The novel compounds will be examined for activity as adenosine A_{2A} antagonists by Prof. Christa Müller and co-workers at the University of Bonn (Germany). SAR analysis will be performed on the biological activity data.

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Synthesis directed towards asmarines and analogs; potential anti-infectious- and anti-cancer drugs

This master project is a part of a larger on-going project and master projects for more than one student can be designed.

Background

More than >25% of all deaths pr. year worldwide are a direct result of an infectious disease.¹ Many of these occur in developing countries and access to current drugs, vaccines and even clean drinking water may indeed reduce the number of unnecessary deaths, but in case of many tropical diseases there is an immediate need for new drugs. “Reduction of child mortality” and “Combat HIV/AIDS, malaria and other diseases” are two of the eight UN Millennium Development Goals.² WHO calls for “A globally coordinated effort to bring the resources of modern science to bear on the control of ten major tropical diseases.”³

Nature is a rich source of bioactive compounds and potential drugs. The so-called secondary metabolites are structures involved in interaction between organisms, for instance chemical defense. Studies of such metabolites have led to the discovery of many life-saving drugs, including antibiotics, but also immunosuppressant and antineoplastic agents.⁴ The last 50 years, there has been an increasing interest for marine natural products as potential drugs and molecular tools, since an enormous chemical and biological diversity are found among metabolites from marine species.⁵ However, most bioactive marine products can only be isolated in very minute amounts, and bioprospecting must be combined with state-of-the-art organic synthesis in order to explore the true potential of these chemically complex structures.

Asmarines have been isolated from marine sponges (*Raspailia* sp, See Fig. 1). Currently 11 asmarines (asmarine A – K, Figure 2) are known.⁶ Little is known regarding bioactivities of asmarines, but we have previously found profound activity against a broad spectrum of pathogenic microorganisms for the structurally related natural products agelasines⁷ (Fig. 3).



Fig. 1. An example of a Raspailia sponge; the organe finger sponge *Raspailia topsenti*.

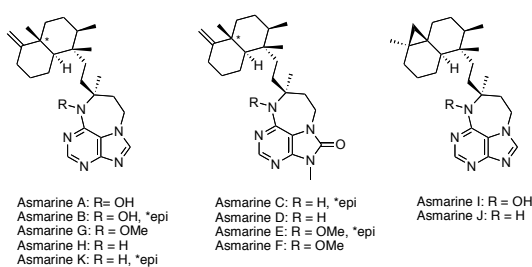


Fig 1. Structures of known asmarines.

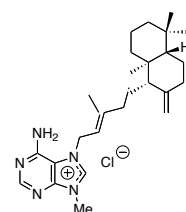
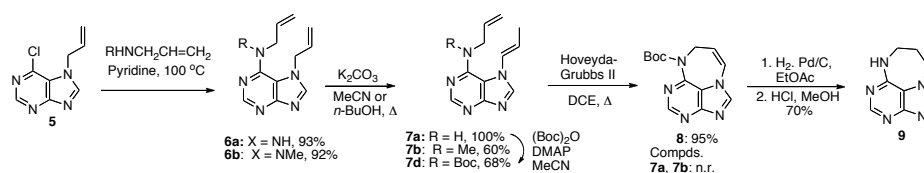


Fig. 3. Structure of agelasine D.

We have recently synthesized the heterocyclic part of asmarines employing ring-closing metathesis (RCM) as a key-reaction (Scheme 1).⁸



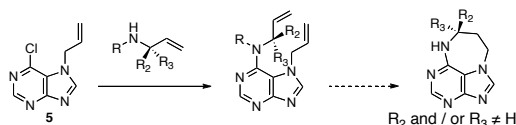
Scheme 1

Goals

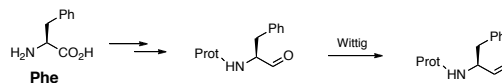
We want to continue synthetic studies directed towards asmarines and close analogs. Our ultimate goal is to complete the first total syntheses of asmarines, and to explore bioactivities (activities against pathogenic microorganisms as well as cancer cell lines) of asmarines and analogs. Specific synthetic goals will be to develop good methods for the synthesis of the terpenoid parts of the agelasines and for the oxidation of the N-atom in the 7-membered ring of the asmarines and model substances.

Methods

A continuance of our previous work (Scheme 1) will be to synthesize asmarine analogs as depicted in Scheme 2. The methods that will be evaluated for the synthesis of the amines required for the introduction of model side chains are briefly discussed below.



Scheme 2



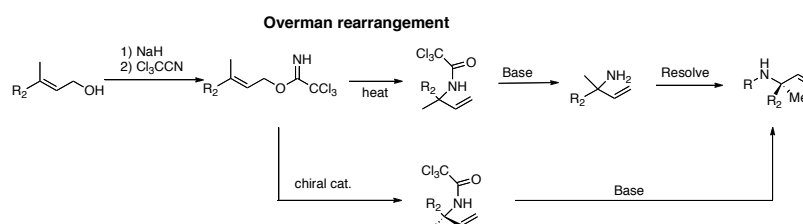
Scheme 3

A. From α -amino acids

α -Amino acid derivatives (*i.e.* derivatives of phenylalanine, Scheme 3) may be attractive starting materials for simple α -monosubstituted allylic amines.

B. From primary allylic alcohols employing the Overman rearrangement

An attractive route to α,α -disubstituted allylic amines is shown in Scheme 4. The starting point is a suitable primary allylic alcohol, which is converted to the corresponding tertiary allylic amine employing the Overman rearrangement. Finally the amine may be resolved, or the recently reported asymmetric version of the Overman rearrangement may be employed.

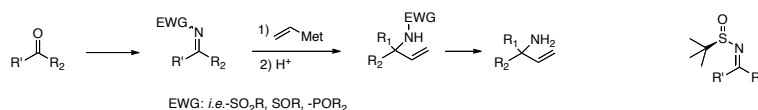


Scheme 4

C. Synthesis from aldehydes or methyl ketones via activated imines

An activated aldimine or ketimine may react with a suitable vinylic organometallic compound to give allylic amines (Scheme 5). The ideal imine should be easily available from the corresponding

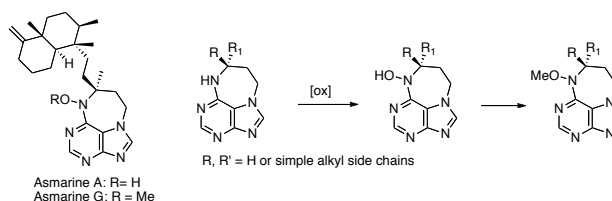
aldehyde or ketone, reasonable stable, but yet reactive towards organometallic nucleophiles in 1,2-addition reactions. Furthermore, the activation group should be easily to remove after the addition, and asymmetric synthesis of the amine should ideally be possible. We find *N*-*tert*-butanesulfinylimines especially attractive (for a general structure, see Scheme 5).



Scheme 5

Oxidation of the 7-membered ring nitrogen - Synthesis directed towards asmarines A and G

Reaction methods previously reported to oxidize secondary amines to the corresponding hydroxylamines, will be screened. The first goal will be to find conditions, which oxidize the secondary amine nitrogen without affecting any of the purine ring nitrogen atoms. We will start with the unsubstituted tricyclic compound 9 (see Scheme 1), and continue with model substances produced according to Schemes 2-5.



Scheme 6

The product will be purified by chromatographic techniques and the structures determined by spectroscopic methods, mainly various NMR techniques and MS. Other spectroscopic techniques (i.e. IR, UV) may be applied if necessary. The same is true for X-ray crystallography.

Novel compounds synthesized in this project will be screened for antimicrobial activities in collaboration with associate professor Collin Charnock at the Oslo University College. Initially, compounds will at least be tested against *Staphylococcus aureus* (gram positive bacterium) and *Escherichia coli* (gram negative bacteria), but a panel of other pathogenic bacteria as well as fungi and protozoa may be included. Compounds prepared in this project, will be screened for activity against *M. tuberculosis* H₃₇Rv at Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) in USA. We will also offer our compounds to the WHO Special Programme for Research and Training in Tropical Diseases (TDR) for screening against parasites causing neglected diseases as for instance malaria, African trypanosomiasis and leishmaniasis. In collaboration with Prof. Lars Bohlin, University of Uppsala, novel compounds can be tested for cytotoxic effects against mammalian cell lines.

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