Tutor/s

Dr. Pier Giorgio Cozzi
Departament de Química Orgànica
Università di Bologna

Dr. Fèlix Urpí
Departament de Química Orgànica i Inorgànica

Grau de Química

Treball Final de Grau

Towards the Total Synthesis of the Baulamycin A
Aproximació a la Síntesi Total de la Baulamicina A

Anna Yin Zheng

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Luck is what happens when preparation meets opportunity

Seneca

Gràcies. Gràcies a tots els professors que m'han ajudat i m'han ensenyat que el coneixement es guanya per a un mateix. Gràcies a tots aquells nous amics que he fet durant la meva estada a Bologna que m'han fet sentir com a casa. Gràcies a la meva família perquè sense ells no hagués pogut gaudir d'aquesta experiència tan enriquidora. Gràcies a cadascun dels meus companys del laboratori per fer que el dia a dia fos divertit i entretingut. Gràcies JM per ajudar-me a la recta final quan més ho necessitava. De veritat, gràcies a tots i espero que tant com m'heu donat vosaltres a mi, us hagi pogut donar una mica jo també.

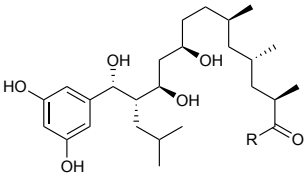
Per a tots vosaltres

REPORT

CONTENTS

1. SUMMARY

Baulamycin A and B are a new structural class of antibiotics. They come from marine microbial-derived natural product extracts collected in Costa Rica, Panama and Papua New Guinea.

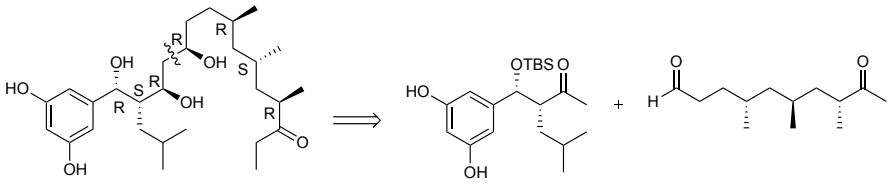


Baulamycin A R=Et
Baulamycin B R=Me

From the two types of Baulamycin, Baulamycin A is the one that we are going to synthesize because it is able to inhibit microorganisms resistant to *Staphylococcus aureus* (MRSA), the main cause of serious hospital infections. Furthermore, it has been found that Baulamycin is also able to inhibit the dangerous and deadly bacterium Anthrax, a bio-terrorist potential agent that is cured with extreme difficulty by common antibiotics.

Unfortunately, Baulamycin A was isolated in a very small quantity and its potential antibiotic capacity has not been studied nor has done activity studies. Its structure has been proposed only by the analysis of its spectroscopy data. However, the main problem to synthesize this molecule is that it owns 7 stereocenters. In order to confirm the structure and test its effectiveness in a comprehensive manner as possible drug, the total synthesis is essential.

My research team in Bologna embarked on the total synthesis of this antibiotic and they have identified two possible precursors for the total synthesis. Synthon B can be prepared through the execution of three consecutive organocatalytic reactions developed in our laboratories.



1 Baulamycin A

2 Synthon A

3 Synthon B

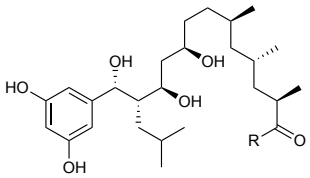
Figure 1: Baulamycin structure and precursors

My research in this project is to scale up the reactions to synthon B, try to synthesize synthon A and control the relative configuration of the newly formed stereogenic centers. Also, we will try to increase the yield obtained in each step in order to get more product.

However, very recently a research group of the Department of Organic Chemistry of the Indian Association for the Cultivation of Science of Jadavpur in Kolkata (India) have published in *the Journal of Organic Chemistry* an article on the *Total Synthesis of Reported Structure of Baulamycin A and its Congeners*. This paper disclosed that the reported structure of Baulamycin A needs to be revised, as the spectroscopic data described for the synthetic compound are not identical with the real Baulamycin A.

Keywords: Baulamycin A, total synthesis, stereocenters, synthon.

2. RESUM



Baulamycin A R=Et
Baulamycin B R=Me

La Baulamicina A i B pertanyen a una nova classe estructural d'antibiòtics. Es vàrem aïllar en extractes marins microbians de Costa Rica, Panamà i Papua Nova Guinea.

Tot i que hi ha dues Baulamicines, la que pretenem sintetitzar és la Baulamicina A, ja que és capaç d'eliminar els microorganismes resistents a l'*Staphylococcus aureus* (MRSA) de manera efectiva, bacteris són la primer causa d'infeccions hospitalàries. A més a més, s'ha trobat que la Baulamicina pot eliminar l'àntrax, malaltia produïda per un bacteri perillós i mortal, que avui en dia és molt difícil de curar amb els antibiòtics que tenim.

Malauradament, la Baulamicina A va ser aïllada en petites quantitats i el seu potencial com a antibiòtic encara no s'ha pogut avaluar amb precisió ni se'n ha obtingut en prou quantitats per fer estudis sobre la seva activitat. Ara per ara, només s'ha pogut arribar a proposar la seva estructura mitjançant l'anàlisi de les seves dades espectroscòpiques. Per tal de poder confirmar la seva estructura i provar-ne l'eficàcia per ser utilitzat com un nou medicament és essencial realitzar la seva síntesi total. Ara bé, la síntesi és complicada degut als 7 estereocentres que té la seva possible estructura.

El meu grup de recerca de la Universitat de Bologna està desenvolupant un projecte per sintetitzar-la via els dos precursors indicats a la Figura 1. El sintó B pot ser preparat mitjançant tres reaccions organocatalítiques consecutives.

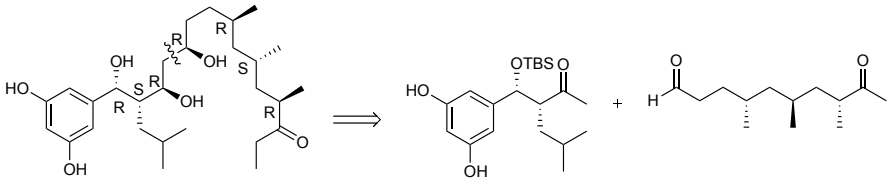


Figura 2: Estructura de la Baulamicina A i els precursors

L'objectiu del meu projecte en aquesta línia d'investigació és intentar augmentar l'escala de les reaccions assajades fins ara i intentar controlar la configuració relativa dels nous centres estereogènics formats. També procurarem augmentar el rendiment obtingut a cada pas per tal de poder obtenir més producte final.

Molt recentment un grup de recerca del Departament de Química Orgànica de la Indian Association for the Cultivation of Science de Jadavpur a Kolkata (India) ha publicat al Journal of Organic Chemistry un article anomenat *Total Synthesis of Reported Structure of Baulamycin A and its Congeners*. Aquest article demostra que cal revisar l'estructura de la Baulamicina A ja que les dades espectroscòpiques descrites pel compost sintetitzat no coincideix del tot amb les de la Baulamicina A descrita en el seu aïllament.

Paraules clau: Baulamicina A, síntesi total, sintó, estereocentres.

3. INTRODUCTION

Nowadays multidrug-resistant pathogens are a serious threat to human health because of its ability to develop resistance to antibiotics, this is endangering the management of a multitude of serious infections.

Siderophores are high-affinity iron chelators produced by microorganisms and frequently contribute to the virulence of human pathogens. The inhibition of the biosynthesis of siderophores is believed to be a potential approach to fight against pathogens. This siderophores have developed immunity against antibiotics and this is the reason why the discovery of new chemical inhibitors of siderophore biosynthesis is crucial for the development of anti-infective agents.

In order to identify a new structural class of antibiotics, we have selected a marine microbial-derived natural product extract which is Baulamycin A because it is an underexplored source of novel chemical structures.

3.1. BACTERIA

Bacteria are the most numerous and adaptable living organism that inhabit on Earth. They take part in the 60% of the Earth biomass and are microscopic single-celled organisms. Their dimensions can vary from 0,2 μm to 30 μm and can assume different forms.

For this class of microorganisms, we can classify them in different shape and appearance. The three basic shape of bacteria are spherical, rod shaped and spiral. Not all bacteria are capable of causing disease, but each morphology based group has at least some disease-causing representatives. From its morphology, they can be distinguished as Coccus, Bacillus, Vibrio, Spirillum and Spirochete.

Since bacterial organisms are so minute, it is impossible to view the organisms without a compound microscope, so in order to visualize the cellular components and to differentiate bacteria from other microbial agents, staining techniques to categorize different bacteria are used by scientist.

Gram staining is a special method that involves dying the outer covering of the bacterial cell wall that prevents it from physical and environmental trauma. This method was named thus for Hans Christian Gram, who developed the technique in 1884. Based on gram staining, bacteria are widely classified as gram positive, which are the bacteria with the cell wall, and the gram negative, which are the bacteria without cell-wall. Cultures of several bacterial pathogens containing Baulamycins A and B revealed that these natural products can inhibit the growth of both Gram-positive and Gram-negative bacteria.

3.2. ANTIBIOTICS

The human being is considered a natural habitat for bacteria, whom will be colonized and used for their own benefits in order to guarantee their survival. This is the reason why until the discovery of the first antibiotic, many diseases often caused death. Modern research began when accidentally penicillin was discovered by Alexander Fleming in 1928. After so, it began a period of discoveries and isolation of antibiotics from natural sources, bio-fermentation, and chemical synthesis.

Antibiotics are typically used to treat bacterial infections. However, in recent years, the improper or unnecessary use of antibiotics has promoted the expansion of several strains of antibiotic-resistant bacteria.

One of the most notorious antibiotic resistant bacterial strains is methicillin-resistant *Staphylococcus aureus* (MRSA), which resists methicillin and other antibiotics through skin contact. MRSA infections occurs in health care where it can lead to pneumonia or bloodstream infections. An important facet of combating antibiotic resistance is to be careful about their use.

Although it is obvious that antibiotics have evolved effectiveness during these years, natural selection pressure is imposed thus forcing the growth of the phenomenon of resistance. This is the reason why now the medication effectiveness is decreasing and the infection persists and increases the risks of contagious and death. A method by which it was possible to discover and develop new antibacterial therapies was the semi-synthesis or chemical synthesis from natural substances with the aim of improving their effectiveness. But, due to the marked antibacterial resistance, this approach is becoming increasingly difficult.

3.3. INHIBITION OF THE SIDEROPHORE

Siderophores are small molecules that exhibit high binding affinity to iron. These are secreted by bacteria in order to acquire iron from their surroundings.

For over 60 yeas, investigations into the bioinorganic chemistry of these molecules, including fundamental coordination chemistry studies, have provided insight into the crucial role that siderophores play in bacterial iron homeostasis.

An important aspect in the research and development of new antibiotics, is the study of new metabolic pathways that can be used to inhibit the development of pathogenic bacteria. Among them, a system that is producing discrete results is what interferes with the iron absorption systems by the pathogens agents. Most living organisms, in fact, need iron as an essential element for a wide range of metabolic pathways and biosynthetic cells.

The importance of understanding the fundamental chemistry underlying bacterial life has been highlighted evermore in recent years because of the emergence of antibiotic-resistant bacteria and the need to prevent the global rise of these superbugs.

The acquisition of iron is very difficult for many microorganisms, including many important human and animal pathogens. Increasing reports of siderophores functioning in capacities other than iron transport have appeared recently, but reports of 'non-classical' siderophore functions have long paralleled those of iron transport. One particular non-classical function of these iron chelators is called antibiotic activity.

An example of siderophore is Enterobaction, which is found mainly in gram-negative bacteria such as *Escherichia Coli* and *Salmonella*. *Typhimurium* and Ferrocrom complex consist of a cyclic hexapeptide produced by mushrooms of *Aspergillus*, *Ustilago* and *Penicillium* kind. In pathogenic organisms are also frequently employed directly to find iron from the body host. In this case, the siderophores of the pathogenic bacteria can directly extract the iron protein in order to contribute to its proliferation in the vertebrates.

The research group of Professor Sherman has managed to isolate directly from the Marine organisms *Streptomyces Tempisquenis* harvested in Playa Grande in Costa Rica the Baulamycin A. This molecule has shown very promising effects on the inhibition of siderophores like, for example, in the *Staphyloferrin B* of Staphylococcus aureus, which has been attributed to more than 20.000 deaths in one year in the United States, and also *Bacillus Anthacis Petrolaction* the agent that causes Anthrax.

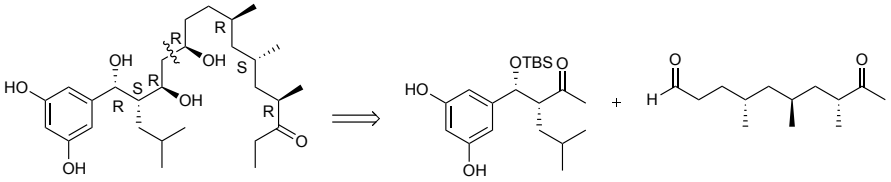
In particular, Baulamycin A is able to interfere in the first step of the biosynthesis of the siderophore, that is the condensation of the citric acid with both spermidine, which is a polyamine compound found in ribosomes and living tissues and 2,3-amino propionic acid, with the use of AsbA enzymes and SbnE. Even so, the precise inhibition mechanism is still under investigation by Sherman's research team.

3.4. RETROSYNTHESIS OF THE BAULAMYCIN

Unfortunately, the extraction of Baulamycin from the marine microorganisms requires large amounts of biological material to get a few milligrams of compound after a long process of purification.

In the light of the promising results of biological activity, the research group of Professor Cozzi has decided to undertake the total synthesis of this molecule, both to confirm the stereochemistry and to undertake a deep study of its inhibition capacity on bacteria resistant to antibiotics.

Such studies are possible thanks to the collaboration with the research group of Professor Vittorio Sambri and Doctor Antonella Marangoni who work in the Policlinic San d'Orsola of Bologna. The Baulamycin retrosynthesis was designed by the research group and it is briefly illustrated below in Scheme 1. The first disconnection of the Baulamycin leads to the synthon A (**2**) and B (**3**)**.**



1
Baulamycin A

2
Synthon A

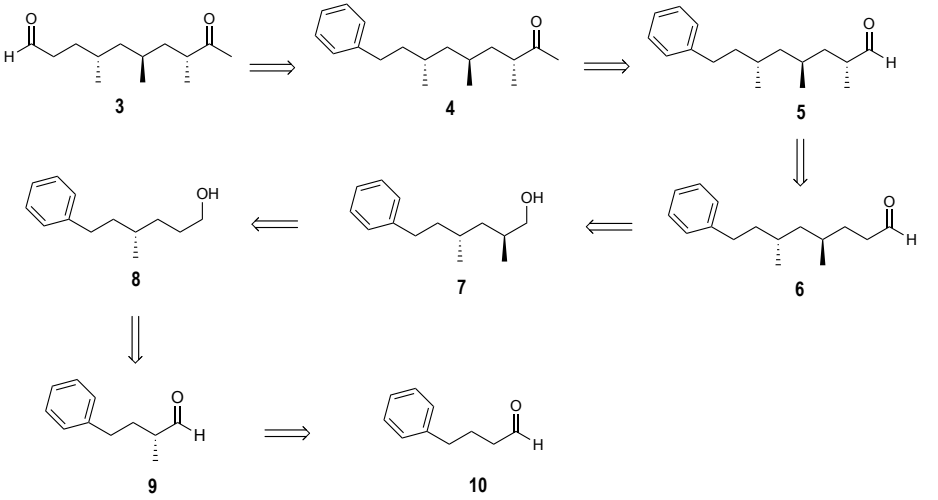
3
Synthon B

Scheme 1**:** Baulamycin Retrosynthesis with synthons **2** and **3**

The synthesis of the synthon A (**2**) has already been studied in detail by the research group whereas the synthesis of the synthon B (**3**) is not since it is much more demanding, due to the presence of three stereogenic centers bearing a methyl substituent in relative anti-configuration.

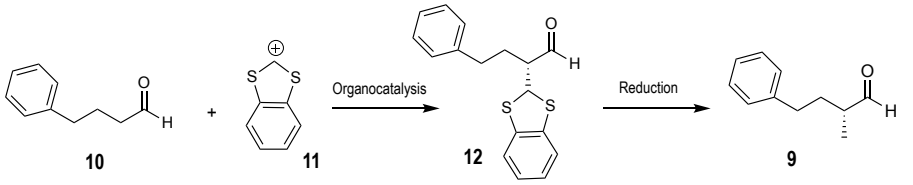
In scheme 2 we can see that the enantioselective synthesis of such a fragment requires the construction of a stereogenic center at a time.

My contribution to the research group of Dr. Cozzi was synthesizing synthon B up to the first methylation (intermediate **8**). The same methodology can be used for the next two methylations keeping the stereoselectivity by following the homologation process on which the α-methylation procedure can be repeated twice in an iterative manner. These reactions have not been experimentally tested but there is an approximated idea of how it can be proceed.



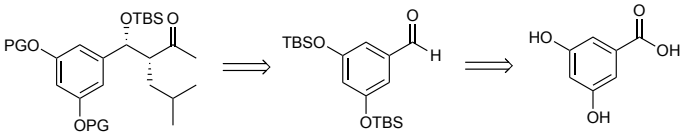
Scheme 2: Retrosynthesis of Synthon B

In scheme 3, it has been summarized the synthetic approach to obtain synthon B (**3**) through an organocatalytic reaction developed by Professor Cozzi research team. This approach allows to carry out an enantioselective α-methylation of aldehydes thanks to the alkylation with the 1,3-benzodithiolylium tetrafluoroborate (**11)** via enamine catalysis.



Scheme 3: Organocatalytic synthesis

On the other hand, the aim of the synthesis of synthon A is to find a protecting group for the hydroxyls of the aromatic ring. In a previous study, benzyl protecting group was tried but finally that approach did not succeed due to the low yield of the reaction. This is the reason why we protected the hydroxyl groups with *tert*-butyldimethylsilyl ether in the aldehyde (**25**) (see Scheme 4). The starting material is commercially available and, with a matter of 4 steps, we can get to the aldehyde (**25**) which will be the precursor of methyl ketone (**20**).



Scheme 4: Retrosynthesis of Synthon B

3.5. NEW DISCOVERIES

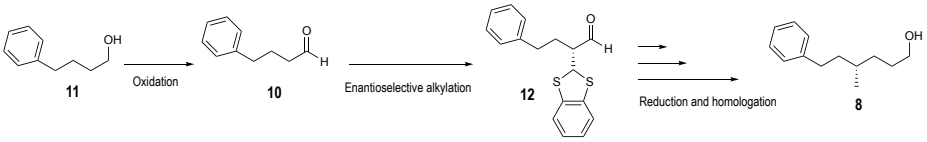
In February 2017, a research group in Kolkata (India) had published in the *Journal of Organic Chemistry* an article on the *Total Synthesis of Reported Structure of Baulamycin A and its Congeners.* The problem was that the spectroscopic data described for the synthetic compound were not identical regarding its natural structure.

This article guided our research group to think that maybe the real structure of the Baulamycin A that we have supposed, was not completely right. We contacted an NMR technician that helped us calculate the exact spectroscopic data and show us the real stereocenters of the molecule.

4. OBJECTIVES

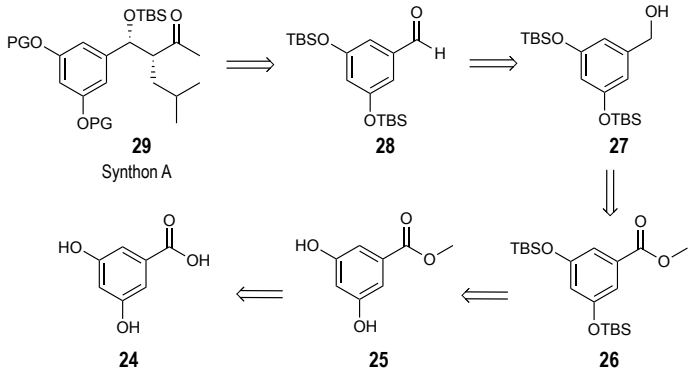
The main objective of this project is the synthesis of Baulamycin A. The synthetic approach can be divided into minor objectives, as shown below:

- Synthesis of an advanced intermediate of synthon A (**2**).
- Synthesis of an advanced intermediate of synthon B (**3**).
- Focus on the synthesis of the key step to deal with a stereoselective reaction using an organocatalytic method in order to obtain the aldehyde (**12**) on a gram scale and proceed towards the total synthesis of synthon B (**3**).
- Scaling up each reaction in order to get more quantity of each advanced intermediate.
- Study the spectroscopic characterization of the synthesized products.



Scheme 5**:** Initial reactant, important intermediate compound and final product

5. TOWARDS THE TOTAL SYNTHESIS OF BAULAMYCIN A. SYNTHON A

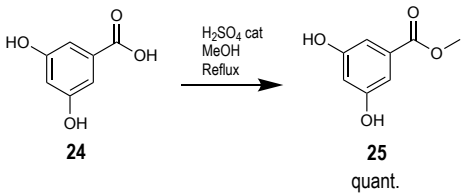


Scheme 6: Retrosynthetic analysis of Baulamycin A. Synthon A

The proposed retrosynthetic analysis in order to obtain synthon A of the Baulamycin A is represented in Scheme 6. These reactions were previously studied in my research group. Firstly, a Fischer esterification occurs in order to transform the carboxylic acid (**24**) into the methyl ester (**25**). Afterwards, the protection of the hydroxyl groups of the ester (**25**) was performed resulting in the methyl ester (**26**) which will be reduced to the benzyl alcohol (**27**) and eventually oxidized to the aldehyde (**28**). In my project, I will synthesize the aldehyde (**28**), which will be our precursor of synthon A (**2**) and I will try to repeat all the steps proposed from my research group and optimize the described reactions.

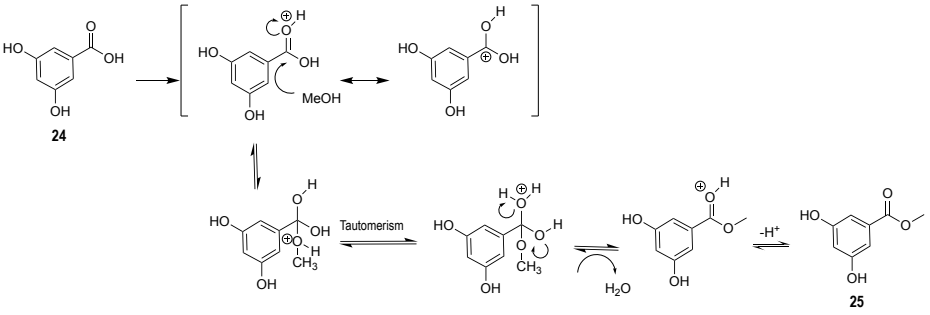
5.1. FISCHER ESTERIFICATION

Fischer Esterification is an organic reaction used to convert a carboxylic acid (**24**) and an alcohol into a methyl ester (**25**) using an acid catalyst. As an alcohol, we used MeOH and as an acid catalyst sulphuric acid. This reaction consists in a nucleophilic acyl substitution based on the electrophilicity of the carbonyl carbon and the nucleophilicity of an alcohol. The reaction was performed at a large scale of 5 grams, giving a quantitative yield as a result.



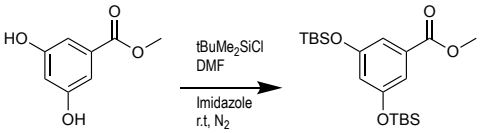
Scheme 7**:** Fischer esterification

The mechanism begins with a protonation of the carbonyl group of the carboxylic acid, which is the attacked by the alcohol. Proton transfer and the subsequent release of water result in an oxonium ion intermediate. A final deprotonation step provides the ester product.



Scheme 8**:** Mechanism of the Fischer esterification

5.2. PROTECTION OF THE ALCOHOL

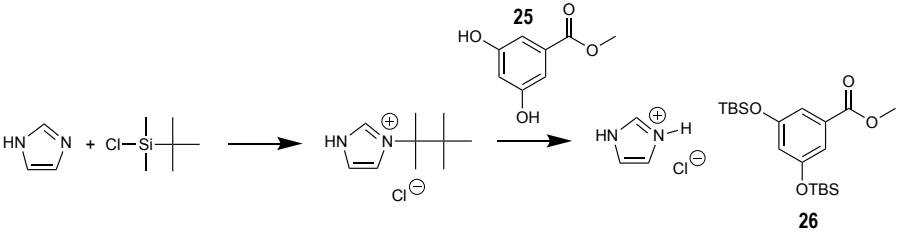


25 **26**

quant.

Scheme 9**:** Protection of the alcohol

A protecting group was introduced into the methyl 3,5-dihydroxybenzoate (**25**) in order to obtain chemoselectivity in the subsequent chemical reaction. The protection of the alcohol is strictly necessary because in the next step, a reduction of an ester is performed in presence of an alcohol and, therefore, the attack of the hydride to the alcohol must be prevented. The reaction was performed using 3.02 g (17.92 mmol) giving a quantitative yield of (**26**).

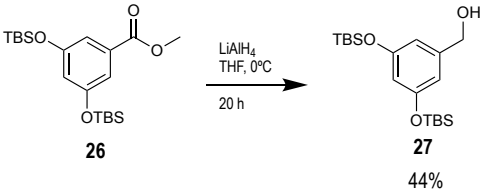


Scheme 10**:** Mechanism of the protection of the hydroxyl groups

In our case we chose TBSCl because later on it will be easier to eliminate the protecting group using TBAF and also because the use of metals will not be necessary.

5.3. REDUCTION OF THE ESTER

Once the hydroxyl groups were protected, we made the reduction of the methyl ester using $LiAlH_4$ in THF at 0 ºC for 20 hours, obtaining (3,5-bis ((*tert*-butyl-dimethylsilyl)oxy)phenyl)-methanol (**27**) in a 44% yield. The ester was first converted to aldehyde which will be right after reduced to primary alcohol.



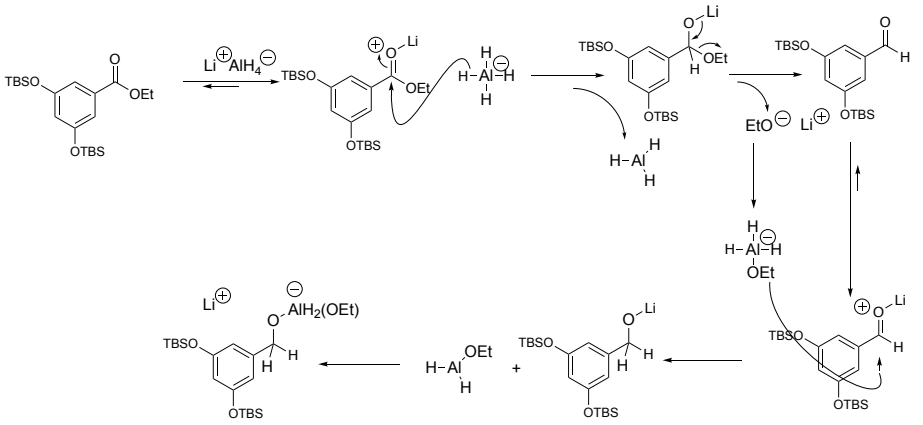
26 **27**

44%

Scheme 11: Reduction of the ester

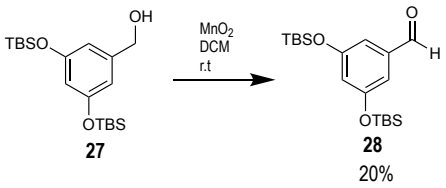
The nucleophilic proton from the hydride reagent assembles with the polar electrophilic carbon from the carbonyl group of the ester and creates a tetrahedral intermediate. This intermediate collapses and the ethoxyde is expelled as a leaving group giving an aldehyde as an intermediate. Later on the reduction of the aldehyde occurs and the nucleophilic H from the hydride complex adds to the electrophilic carbon from the carbonyl group of the aldehyde. Then it occurs the same procedure as mentioned before and finally we obtain the intermediate metal alkoxide complex as shown in scheme 12.

Reactions run with aluminium based reagents like $LiAlH_4$ form aluminium hydroxide upon aqueous quenching, which can create emulsions. In order to quench these and get rid of the aluminium salts we use the Fieser method which consists on adding water, 15% aqueous sodium hydroxide and anhydrous magnesium sulfate then filter over Celite. The protonation of the alkoxide oxygen creates the primary alcohol product from the intermediate complex.



Scheme 12: Mechanism of the reduction of the ester

5.4. OXIDATION OF THE ALCOHOL



Scheme 13: Oxidation of the alcohol

In order to oxidize the alcohol group to the aldehyde we used manganese dioxide which is a mild reagent and very selective in benzylic alcohols.

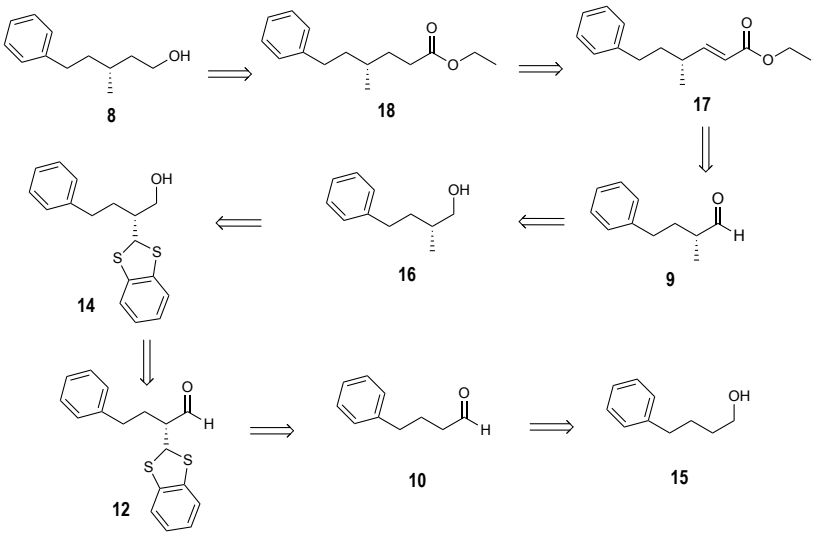
This reaction was carried out in two different scales, a smaller scale and a bigger scale. The oxidation reaction took place inside an open air balloon for 48 hours. Checking the reaction by TLC we could not see any spot. Consequently, we increased the equivalence of MnO_2 from four to six in order to promote the reaction.

The product was purified by performing a column chromatography obtaining 0.036 g (0.09 mmol) in the reaction carried out in the smaller scale and 1 g (0.271 mmol) in the bigger scale.

Neither of the two reactions were as successful as expected. In the smaller scale there was no product and in the large scale we achieved 20% yield. The fact that the reaction did not work better could be that the quantity of equivalents of MnO_2 were not enough so the MnO_2 could not be activated or the quality of the reactant was not good.

We could not remake the reaction again under other conditions. Luckily, we succeeded in our attempt to synthesize in higher amounts of the alcohol (**27**), which will be my precursor for synthon A (**2**).

6. TOWARDS THE TOTAL SYNTHESIS OF BAULAMYCIN A. SYNTHON B



Scheme 14: Retrosynthetic analysis of baulamycin A. Synthon B

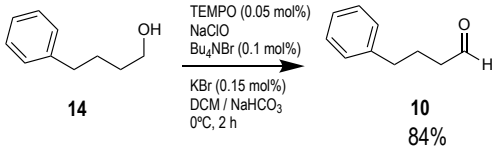
The proposed retrosynthetic analysis to obtain Baulamycin A is represented in Scheme 14.

It was planned to use the primary alcohol (**15**) as a starting material, after its oxidation to the aldehyde (**10**) using TEMPO. The key step of the sequence involves the organocatalysis with (*R*)-MacMillan catalyst that was also synthesized. The configuration of the new stereocenter was completely controlled due to the imidazolidinone, which provided the single enantiomer (**12**).

After the catalytic reaction, removal of the imidazolidinone was possible using Raney Nickel giving the chiral alcohol (**16**), which then it should be oxidised to give the aldehyde (**9**)**.** In order to add more carbon atoms to the chain the homologation process should be taken place with a Wittig reaction to afford the unsaturated ester (**17**) and after the reduction of ester (**18**). The final reaction will be the reduction of the ester into the alcohol (**8**).

6.1. OXIDATION OF THE ALCOHOL (14) USING TEMPO

The first step of the synthesis is the oxidation of the alcohol into the aldehyde by using the catalyst TEMPO as shown in scheme 15.



14 **10** 84%

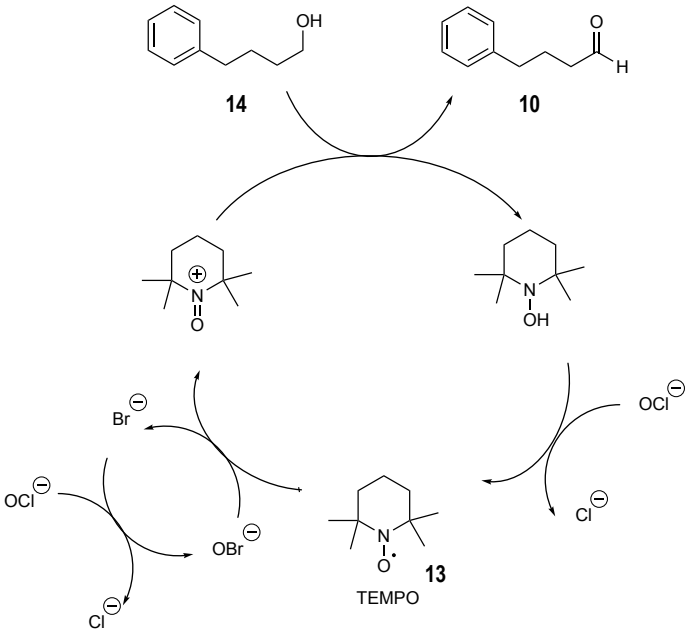
Scheme 15**:** Oxidation of the alcohol using TEMPO

TEMPO is a stable free radical and its stability is attributed to the resonance provided by non-binding electrons on the nitrogen atom. In addition, the four methyl substituents adjacent to the nitrogen atom group give a good steric protection preventing the dimerization. TEMPO is particularly used in the oxidation of primary and secondary alcohols to their respective aldehydes. The addition of KBr produces a substantial acceleration of the oxidation rate because of the generation of HOBr. This reagent is formed from HOCl and KBr, and it is apparently a better oxidant for the regeneration of oxoammonium salts than HOCl.

The reaction is much quicker at pH 8.6, therefore, a buffer solution of $NaHCO_3$ was added. However, at a very basic pH the concentration of HOBr, which is the oxidant regenerating the oxoammonium salt, becomes very low in comparison with the concentration of the hypobromide anion (BrO^-).

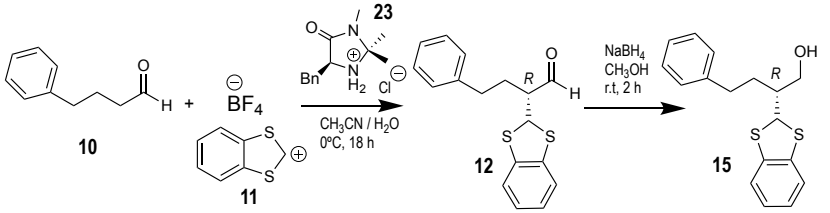
The alcohol (**14**) is oxidized by sodium hypoclorite, stoichiometric oxidizer which generated nitrosonium cation, the actual oxidizing agent of the beginning. During the oxidation of the alcohol, the cation is reduced to hydroxylamine which then is oxidized and returned to nitrosonium ion, completing the catalytic cycle represented in scheme 16.

Hypochlorite is used as primary oxidant together with bromide as a co-catalyst. Tetrabutyl ammonium bromide is used as a phase transfer catalyst to carry hypoclorite through the organic phase and make the reaction to take place.



Scheme 16: Catalytic cycle of TEMPO

6.2. ORGANOCATALYSIS USING (*R*)-MACMILLAN IMIDAZOLIDINONE



Scheme 17**:** Reaction with the aldehyde **10** and the carbocation **11,** with the (*R*)-MacMillan catalyst **23**

Organocatalysts which display secondary amine functionality can be described as performing enamine catalysis by forming catalytic quantities of an active enamine nucleophile. This mechanism is typical for covalent organocatalysis. Covalent binding of substrate normally requires high catalyst loading, typically 20 mol%.

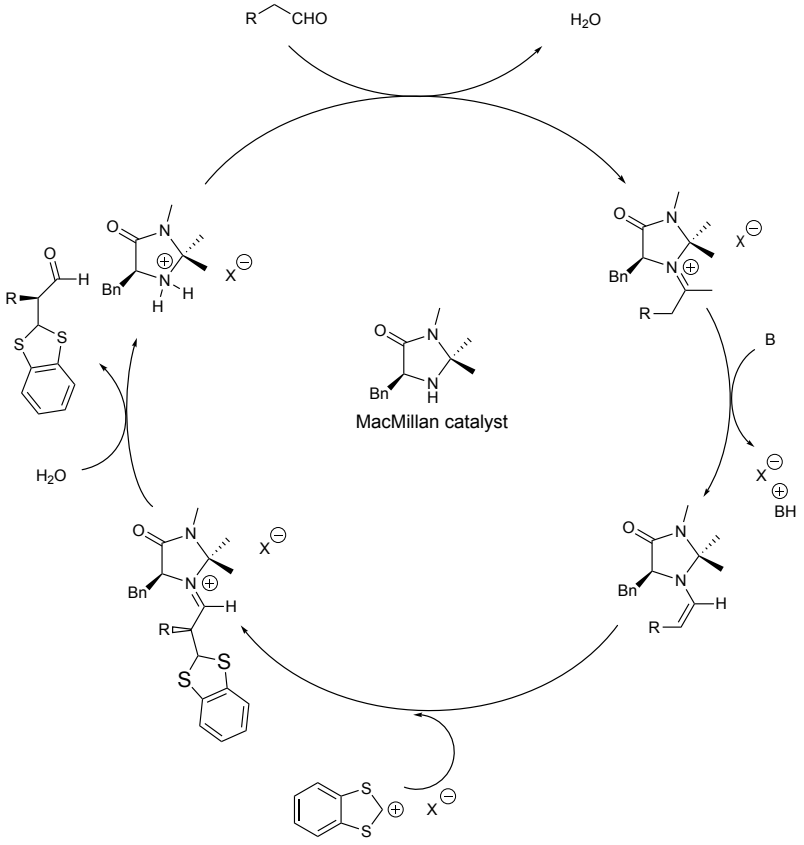
Imidazolidinone compounds, which are also called MacMillan organocatalysts, are suitable catalysts for many asymmetric reactions such as Diels-Alder reactions.

The enantioselective alkylation was the key reaction of synthon B, the aldehyde (**10**) reacted with 1,3-benzodithiolylium tetrafluoroborate (**11**) and with (*R*)-MacMillan catalyst to obtain compound (**12**)**,** which was reduced with $NaBH_4$ in CH_3OH at room temperature for 2 hours.

We repeated this experiment 16 times in order to get enough product to keep on with the synthesis. Each time we used 222 mg of starting aldehyde and the obtained yields were comprised between 52% and 68%. The total product (**15**) weight was 2.383 g and the average enantiomeric excess was 95%, this enantiomeric excess was done by HPLC and the conditions are shown in section 7.1.

In scheme 18 below, it is illustrated the mechanism of organocatalysis via enamine employing the catalyst (*R*)-MacMillan and the 1,3-benzodithiolylium tetrafluoroborate (**11**) as carbocation. Benzodithiolylium (**11**) is commercially available and it can be handled without any problem or particular precaution.

The (*R*)-MacMillan imidazolidinone catalyst was present in catalytic quantities (20 mol%) and it was chosen because the yield obtained was the highest achieved so far and it provided a good enantioselectivity. Moreover, as the catalyst is a secondary amine, it was able to react with the aldehyde by releasing water and forming the corresponding enamine as shown in the below scheme 18.



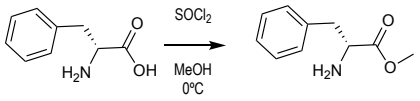
Scheme 18: Catalytic cycle of (R)-MacMillan

6.2.1. SYNTHESIS OF THE (*R*)-MACMILLAN CATALYST

The MacMillan organocatalyst was derived from the biomolecule phenylalanine in two chemical steps. The first one consisted in an amidation with methylamine followed by a condensation reaction with acetone that kept the chirality unchanged.

6.2.1.1. FROM THE ACID 19 TO THE METHYL ESTER 20

The first step in the synthesis of the (*R*)-MacMillan catalyst, thionyl chloride converts carboxylic acids into acid chlorides and then the transformation into an ester occurs. *D*-phenylalanine (**19**) is introduced in a solution of MeOH and $SOCl_2$ is added dropwise. This reaction was worked under 0ºC and we obtained (**20**) with a 76% yield (1.985 g).



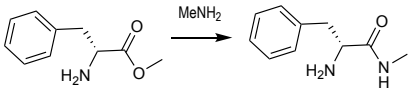
19 **20**

76%

Scheme 19: Catalytic cycle of TEMPO

6.2.1.2. AMIDATION WITH METHYLAMINE

This is the second step for the formation of the oxazolidinone catalyst. In this reaction we worked with a methylamine solution in absolute ethanol. The reaction type is a nucleophilic acyl substitution to prepare an amide in which we obtained the desired *N*-methyl amide (**21**) in a quantitative yield.



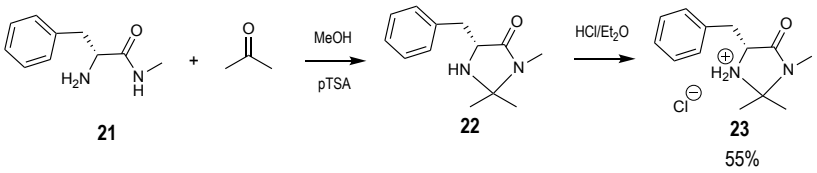
20 **21**

quant.

Scheme 20: Catalytic cycle of TEMPO

6.2.1.3. CONDENSATION REACTION WITH ACETONE

The last step of this synthesis consisted in the condensation of the acetone with the amide (**21**) using *p*-toluenesulfonic acid (PTSA) as catalyst and anhydrous MeOH as solvent. This reaction produced the imine that reacted with HCl in Et_2O 1.0 M giving room to the precipitated (*R*)-MacMillan imidazolidinone catalyst (1.572 g, 55%).



Scheme 21: Formation of the oxazolidinone catalyst

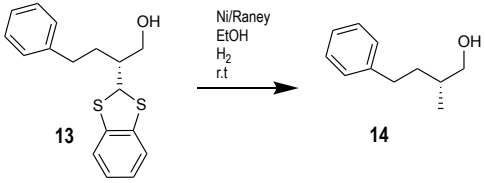
6.3. REDUCTION WITH RANEY NICKEL

Subsequently, a reduction is made in order to preserve the integrity of the stereogenic center of alcohol (**13**) using the Raney nickel reagent. This reagent is solid catalyst consisting of a nickel alloy (about 85%) and Aluminium (to give porosity) in very fine grains and it is very used in many processes in industrial chemistry.

At a macroscopic level, Raney Nickel reagent looks like a fine grey powder stored and it is stored in aqueous solution because of its high propensity for self-expression when it is exposed to atmospheric oxygen. However, microscopically, each granule represents a sort of sieve 3D with irregular shape and pores.

Prior to reacting directly to the substrate, a number of washings must be performed with water and ethanol. These washings are very important to avoid mild racemization of the stereogenic center during the reaction. Probably this helps to eliminate any basic aluminated that might be responsible for this partial racemization.

This reaction was performed under a nitrogen atmosphere at room temperature. Once all the reactants were added inside the balloon, a rubber balloon filled with hydrogen was attached as reservoir, the reaction was stirred for 48 hours and checked by TLC to see if it was completed. This reaction took place in two different balloons in which we obtained 0.467 g (72% yield) and 0.569 g (88% yield). Below in scheme 22 the reduction reaction is shown.

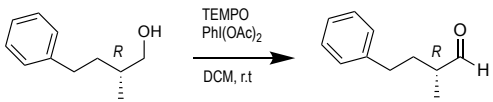


Scheme 22: Reduction with Raney nickel

6.4. OXIDATION OF THE ALCOHOL

The next step, shown in scheme 23, involves the oxidation of the alcohol (**16**) to the aldehyde (**9**). The mechanism in this case is also regulated by the oxidant used in the first reaction named (i.e. TEMPO). However, in this case, we changed the stoichiometric oxidant for diacetate phenyl iodine and the reaction solvent is now dichloromethane.

The reaction was ran at room temperature and quenched with sodium thiosulphite and it allows getting the aldehyde **9** in 99 % yield. The procedure was chosen because it avoided the racemization of the stereocenter in alpha of the aldehyde.



16 **9**

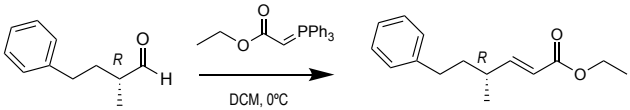
99%

Scheme 23**:** Oxidation of the alcohol

6.5. WITTIG REACTION

The Wittig reaction consists in reacting an aldehyde woith a triphenyl phosphonium ylide to give an alkene and triphenylphosphine oxide. The Wittig reaction is known experimentally as a [2+2] cycloaddition reaction, in which there is an attack by the nucleophilic carbon to the electrophilic carbon of the aldehyde group. The next elimination of the phosphine leads to the formation of the alkene.

The reaction is conducted under an inert atmosphere at 0 ºC in dichloromethane and the reagents are taken with the double needle technique. The yield obtained was 58% and after the reaction was carried out, a ^{1}H NMR test was performed in order to verify the formation of the desired product and then was isolated by doing a chromatography column.



9 **18**

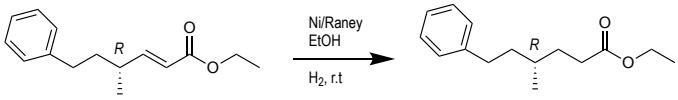
58%

Scheme 24**:** Wittig's reaction

6.6. REDUCTION OF THE UNSATURATED ESTER (18) WITH RANEY NICKEL

The resultant unsaturated ester (**18**) is reduced again with Nickel Raney reagent because in Palladium on Carbon (Pd/C) can occur catalyst poisoning. This fenomena involves partial or total deactivation of the catalyst brought about by its exposure to a range of chemical compounds such as amines, sulphides, thiols, lead and certain metal oxides.

Moreover, and unlike Pd/C, a catalytic amount of Raney nickel is enough to make the reaction. Also, one have to consider the importance of pre-washing the Raney nickel with water and ethanol under a hydrogen atmosphere and run the reaction overnight. When the conversion is completed, then it can be washed with EtOH and DCM to separate the product from the solid catalyst. The ester (**19**) yield was 77 % and is shown in the following scheme 25.



18 **19**

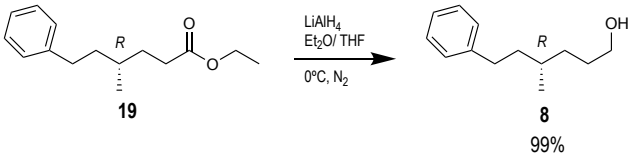
77%

Scheme 25: Reduction with Ni/Raney of the double bond in the ester **18** to give the intermediate **19**

6.7. REDUCTION OF THE ESTER (19)

The last assessed reaction was the reduction of the ester (**19**) with $LiAlH_4$. This reductant is used because ester and carboxylic acids are less reactive to nucleophiles than aldehydes or ketones. As a consequence, they can only be reduced using $LiAlH_4$. The reaction normally ran in Et_2O and followed by the Fieser method to work up the reaction, this process is explained in section 5.3.

The reaction was conducted at 0ºC under an inert atmosphere. The yield of this last step was 99%. This alcohol (**8**) shown in the scheme 26 is our advanced precursor of interest.



19 **8**

99%

Scheme 26: Reduction with $LiAlH_4$

7. EXPERIMENTAL SECTION

7.1. MATERIALS AND METHODS

Some reactions were conducted under a heat-dried or flame dried glassware under inert atmosphere of dry nitrogen with anhydrous solvents. Catalysis and reductions with sodium borohydride, were conducted to the air, all of the others have been conducted under anhydrous conditions and inert atmosphere. All solvents were anhydride which were supplied by Aldrich in Sureseal® bottles and used without purification.

Analytical thin-layer chromatography (TLC) were carried out on Merck silica gel 60 F254 plates and analysed by UV (254 nm) and stained with potassium permanganate ($KMnO_4$) or cerium ammonium molybdate (CAM), with the specifically eluent needed in each case.

Column chromatographies were performed under low-pressure (flash) conditions and performed on silica gel 240-400 mesh.

^{1}H NMR and 13C NMR spectra were obtained using the Varian Mercury 400 spectrometer MHz. Chemical shifts (δ) are reported in ppm as compared to tetramethylsilane standard (TMS), using solvent resonance as an internal standard (Deuterated chloroform: δ 7.27 ppm). Data is reported with the following order: Chemical shifts, multiplicity (s=singlet, d= doublet, t=triplet, q=quartet, m=multiplet, dd= doublet of doublets, ddd= doublet of doublet of doublets and their corresponding combinations). Coupling constants, *J*, were reported in Hertz.

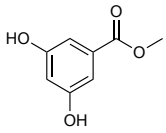
Specific rotations ($[\alpha]_D$) were determined at 25 ºC on a Perkin-Elmer 241 MC polarimeter. They were measured on $CHCl_3$ and the wavelength used was the D line of sodium (589 nm).

Enantiomeric exces was determined by high liquid chromatography performance with Agilent Technologies 1200 equipped with UV detector a variable wavelength (deuterium lamp: 190-600 nm), using Daicel Chiralpak columns (0.46 cm x 25 cm) using as solvent for elution a mixture of isopropanol and n-hexane (15:85) with degree of purity for HPLC at 30ºC and a flow of 0.7 mL/min.

7.2. TOWARDS THE TOTAL SYNTHESIS OF BAULAMYCIN A. SYNTHON A

7.2.1. Synthesis of methyl 3,5-dihydroxybenzoate (25)

In a balloon 3,5-dihydroxybenzoic acid (5 g, 32.467 mmol) is mixed with MeOH (20 mL) and half a Pasteur of sulphuric acid. This reaction is left under heat in a reflux system for 72 h and the resultant solution is quenched using H_2O and extracted with EtOAc (3x20 mL). The solvent is removed by vacuum and the resulting product is a beige solid (6.327 g, 99%).

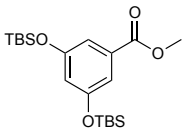


25

Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (s,2H), 6.94 (d, J = 2.3 Hz, 2H), 6.51 (t, J = 2.3 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.9, 159.8, 128.6, 109.6, 107.9, 51.5.

7.2.2. Synthesis of methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)benzoate (26)

The reaction is worked under nitrogen using a two-neck balloon. The ester (**25**) is first added (0.200 g, 1.19 mmol), imidazole (0.324 g, 4.76 mmol), DMF (2 mL) and TBSCl (0.833 g, 5.528 mmol). The reaction is left for 48 h and quenched with H_2O (10 mL). It is extracted with EtOAc (3x20 mL), the solvent is removed by vacuum and the desired ester (**26**) is isolated as colourless oil in quantitative yield pure by ^{1}H NMR (0.472 g).

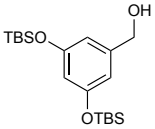


26

Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (d, J = 2.2 Hz, 2H), 6.50 (t, J = 2.2 Hz, 1H), 3.88 (d, J = 9.1 Hz 3H), 0.96 n(s, 18H), 0.24 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.9, 157.2, 127.5, 116.7, 112.8, 30.3, 25.9, -4.43.

7.2.3. Synthesis of (3,5-bis ((tert-butyldimethylsilyl)oxy)phenyl)methanol (27)

This reaction was carried under nitrogen, previously the system was worked under vacuum and heated to dry all the material. The ester (**26**) (7101.4 mg, 17.922 mmol, 1 equiv) is introduced inside a balloon with anhydrous THF (20 mL) after solid $LiAlH_4$ (1630.3 mg, 35.84 mmol, 2 equiv) was added. The reaction was stirred at 0 ºC for 72 h under nitrogen. To work up the reaction, first the mixture was diluted with diethyl ether at 0 ºC and it was added carefully 1.3 mL of H_2O, then 1.3 mL of 15% aqueous sodium hydroxide and again 3.9 mL of H_2O. The reaction is warmed to room temperature and stirred for 15 min. Then $MgSO_4$ anhydrous was added and stirred for 15 min and the reaction mixture was filtered to remove the salts. The solvent was eliminated at vacuum and the product obtained is a white solid. The compound is purified using a column chromatography, and it is obtained pure alcohol (**27**) (1 g, 45%).

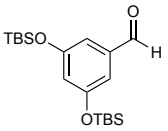


27

Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.38 (s, 2H), 6.24 (s, 1H), 4.61 (s, 2H), 0.98 (s, 18H), 0.21 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.7, 143.0, 111.7, 111.1, 65.1, 25.6, - 4.43.

7.2.4. Synthesis of 3,5-bis((*tert*-butyldimethylsilyl)oxy)benzaldehyde (28)

The benzylic alcohol (**27**) is introduced in an open air balloon (100 mg, 0.27 mmol, 1 equiv) in DCM (3 mL) and MnO_2 (0.141 g, 1.62 mmol, 4 equiv). The mixture was stirred at room temperature for 16 hours, washed with DCM (3x10 mL) and then filtered through celite. The filtrate was concentrated *in vacuo* to provide the product as a colourless oil, the product was purified by column chromatography and obtained 1g and 20% yield.



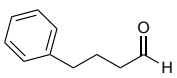
28

Colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.84 (s, 1H), 6.94 (d, *J* = 2.2 Hz, 2H), 6.54 (t, *J* = 2.3 Hz,1H), 4.61 (s, 2H), 0.98 (s, 18H), 0.21 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 191.8, 157.2, 138.3, 118.4, 114.3, 31.4, 25.6, -4.43.

7.3. TOWARDS THE TOTAL SYNTHESIS OF BAULAMYCIN A. SYNTHON B

7.3.1 Synthesis of 4-phenylbutanal (10)

To an ice-cold solution of alcohol (**14**) (1.35 g, 9 mmol, 1 equiv) in DCM (12 mL), a solution of KBr (0.147 g, 0.45 mmol, 0.1 equiv), Bu_4NBr (0.107 g, 0.9 mmol, 0.05 equiv) in H_2O (3 mL) and another solution of TEMPO (0.021 g, 0.1 mmol, 0.01 equiv) in DCM (3.3 mL) were introduced also with a $NaHCO_3$ saturated aq. solution (11.4 mL) inside the balloon. NaOCl (21 mL) and a $NaHCO_3$ aq. saturated solution (21 mL) were added dropwise over 30 min. The reaction mixture was stirred for 2 h, and quenched with a solution of $Na_2S_2O_3$. The resultant mixture was extracted with Et_2O (3 x 20 mL), washed with water and brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by flash column chromatography (5% EtOAc in cyclohexane as eluent) to afford aldehyde (**10**) (1.246 g, 94%) as a yellowish oil.

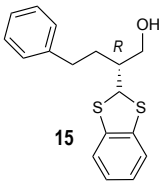


10

Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.64 (s, 1H), 7.58-6.82 (m, 5H), 2.66 (t, *J* = 8.0 Hz, 2H), 2.53-2.36 (t, *J* = 6.0 Hz, 2H), 2.09-1.84 (m, 2H).

7.3.2 Synthesis of (*R*)-2-(benzo[*d*][1,3]dithiol-2-yl)-4-phenylbutan-1-ol (15)

To a solution of aldehyde (**10**) (222 mg, 1.5 mmol, 2 equiv) in 1,3-benzodithiolylium tetrafluoroborate (0.18 g, 0.75 mmol, 1 equiv) was added (*R*)-MacMillan catalyst imidazolidinone (0.038 g, 0.015 mmol, 0.02 equiv) in solution with CH_3CN (2.9 mL) and H_2O (2.9 mL). The mixture was stirred overnight at 0 ºC and extracted with Et_2O (3x10 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The crude oil was worked-up by adding 4 mL of CH_3OH and $NaBH_4$ (0.250 g, 3 mmol, 2 equiv) at 0 ºC. After checking the reaction by TLC, H_2O was added in order to quench the reaction. The crude reaction mixture was concentrated in vacuum again to remove the CH_3OH and extracted with EtOAc (3x10 mL), after was purified by flash column chromatography (10% EtOAc in cyclohexane as eluent) to give the corresponding alcohol **15** (308.8 mg, 68%) as a yellow oil with an enantiomeric exces of 92%- 96%.

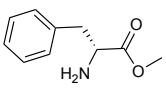


15

Yellowish oil. $[\alpha]_D^{25}$ -21.2 (*c* 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.14 (m, 7H), 7.02-6.97 (m, 2H), 5.20 (d, *J* = 6.1 Hz, 1H), 3.86 (dd, J_1= 11.1 Hz, J_2= 4.2 Hz, 1H), 3.76 (dd, J_1 = 11.1 Hz, J_2 =4.2 Hz, 1H), 2.77-2.58 (m, 2H), 1.97-1.88 (m, 2 H), 1.83-1.74 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.5, 137.5, 128.3, 128.2, 125.9, 125.4, 122.0, 62.1, 47.0, 33.3, 29.7.

7.3.2.1. Synthesis of methyl *D*-phenylalaninate (20)

A 500 mL, two-necked, round-bottom flask, attached to an over-head stirrer, nitrogen inlet, reflux condenser bearing a drying tube, and a rubber septum, was purged with nitrogen and charged with *D*-phenylalanine (**19)** (2.404 g, 14.55 mmol, 1 equiv), followed by the addition of MeOH (10 mL). Thionyl chloride (2.6 g, 21.82 mmol, 1.5 equiv), was added cautiously by a dropping funnel over 25 min. to the rapidly stirring solution at 0 ºC. The nitrogen inlet was removed after the addition was complete and the nitrogen inlet was replaced with a rubber septum. The MeOH was removed under reduced pressure by rotary evaporation to provide the product (**20**) as a white solid (1.985 g, 76%).

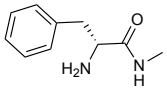


20

White solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.32 (m, 5H), 3.75 (s, 3H), 3.72 (dd, J_1=7.9, J_2=8.2 Hz, 1H), 3.09 (dd, J_1= 13.5, J_2= 5.2 Hz, 1H), 2.85 (dd, J_1= 13.5, J_2= 7.9 Hz,1H).

7.3.2.2. Synthesis of (*R*)-2-amino-N-methyl-3-phenylpropanamide (21)

In a schlenk flask, *D*-phenylalaninate (**20)** (1.985 g, 11.084 mmol) was added dropwise to a $MeNH_2$/EtOH (33% m/m) (4.13 mL) solution. The resulting mixture was refluxed at 80 ºC in an oil bath under nitrogen and stirred overnight. The resulting residue was poured onto DCM (3 x 10 mL) and the combined organic extracts were dried with Na_2SO_4 and concentrated to provide the amide (**21**) as a white solid (1.999 g, quantitative).

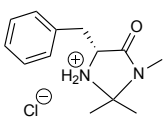


21

White solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.20 (m, 5H), 4.16 - 4.12 (m, 1H), 3.63 (dd, *J* = 9.1, 4.1 Hz, 1H), 3.27 (dd, *J* 1= 13.7, J2= 4.1 Hz, 1H), 2.79 (d, *J* = 4.6 Hz, 3H), 2.69 (dd, J_1= 13.7, J_2 = 9.1, 1H).

7.3.2.3. Synthesis of the (*R*)-MacMillan catalyst (23)

In a two neck balloon under nitrogen, anhydrous MeOH (0.5 mL) was added to clean the balloon and then another 21.5 mL of MeOH were added for the reaction with a solution of amide (**21**) (1.999 g, 11.22 mmol, 1 equiv), purified acetone (4.08 mL, 55 mmol, 5 equiv) and pTSA (0.0193 g, 172 mmol, 0.01 equiv) at the reaction mixture was heated to reflux for 12 h. MeOH was removed in vacuum from the balloon and the resulting residue was precipitated with a solution of Et_2O and HCl 1.0 M (15 mL) at 0ºC for overnight and then filtered through a gutch with one finger of silide in order to eliminate the possible residues. Then the liquid face is separated and it is evaporated to afford pure compound (**23**) (1.572 g, 55%).

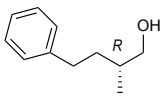


23

White solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29- 7.16 (m, 5H), 3.12 (dd, J_1 = 14.2, J_2=6.8 Hz, 1H), 2.98 (dd, J_1= 14.2, J_2= 4.5 Hz, 1H), 2.68 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H).

7.3.3 Synthesis of (*R*)-2-methyl-4-phenylbutan-1-ol (16)

A mixture of alcohol (**15**) (2.383 g, 7.89 mmol, 1 equiv) and Raney nickel (18 mL), which had been previously washed four times with 10 mL of water and three times with 10 mL of EtOH under hydrogen, were stirred and left 48 hours at room temperature. After the resulting mixture was washed with EtOH (6x10 mL) and DCM (6x10 mL) and AcOEt (5x10 mL) and then it was filtered through a silica gel pad with one finder of silica and then concentrated in vacuum to obtain the corresponding alcohol (**16**) (0.569 g, 88%), which was used in the following step without purification, we obtained 90% of enantiomeric excess.

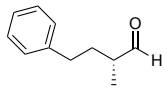


16

Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.14 (m, 3H), 7.19-7.14 (m, 2H), 4.21-3.95 (m, 1H), 3.53 (ddd, J_1 = 28.2, J_2 = 10.5 Hz, J_3 = 6.0 Hz 1H), 2.73-2.54 (m, 2H), 1.80-1.62 (m, 2H), 1.48-1.39 (m, 1H), 0.98 (d, J= 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.5, 129.1, 128.3, 128.2, 125.8, 125.6, 67.9, 35.2, 34.8, 33.2, 17.0.

7.3.4 Synthesis of (*R*)-2-methyl-4-phenylbutanal (17)

To a water bath solution of alcohol (**16**) (937 mg, 5.7 mmol, 1 equiv) in DCM (5.7 mL) was added TEMPO (89.1 mg, 0.57 mmol, 0.1 equiv) and $PhI(OAc)_2$ (2207 mg, 6.8 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h at room temperature and subsequently quenched with $Na_2S_2O_3$ (5 mL). The resultant mixture was extracted with DCM (3x10 mL) and washed with brine (20 mL), dried over Na_2SO_4 and filtered. The solvent is removed in vacuum to obtain aldehyde (**17**) (0.926 g, 99%) that is used in the following step without purification.



17

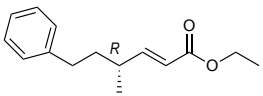
Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97-6.94 (m, 5H), 1.99 (d, J= 4.9, 1H), 1.95 (dt, J_1 = 4.9, J_2 = 2.5 Hz, 2H), 1.32 (t, J = 7.1 Hz, 2H), 1.18 (dt, J_1 = 14.7, J_2 = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 204.1, 142.6, 128.5, 128.1, 125.9, 46.0, 34.2, 30.1, 14.0.

7.3.5 Synthesis of ethyl (*R*,*E*)-4-methyl-6-phenylhex-2-enoate (18)

To a solution of the unpurified aldehyde (**17**) (98 mg, 0.609 mmol, 1 equiv) in anhydrous DCM (1 mL) is added the Wittig reagent (ethoxycarbonylmethylene)triphenylphosphorane (233 mg, 0.669 mmol, 1.1 equiv) under nitrogen and the resulting mixture is stirred at 0ºC overnight.

The solvent was removed in vacuum, AcOEt and 2 spoons of silica were added inside the balloon in order to prepare the solid for the column chromatography. The crude was purified by flash column chromatography on silica gel first with 100% cyclohexane and after removing

the PPh_3, the polarity was increased to 95:5 (Cyclohexane/Et_2O) and the ester unsaturated (**18**) is obtained (81 mg, 62%).

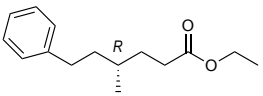


18

Yellowish oil. $[\alpha]_D^{25}$ –24.4 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.62 (m, 2H), 7.57-7.42 (m, 3H), 6.90 (dd, J_1= 15.7, J_2= 8.0 Hz, 1H), 5.80 (d, *J* = 15.7, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.64-2.54 (m, 2H), 2.37-2.29 (m, 1H), 1.73-1.64 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H).^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.6, 154.0, 141.9, 128.3, 125.8, 60.2, 37.6, 36.0, 33.4, 19.4, 14.3.

7.3.5 Synthesis of ethyl (*R*)-4-methyl-6-phenylhexanoate (19)

A mixture of α,β-unsaturated ester (**18**) (697.2 mg, 3.19 mmol, 1 equiv) and Raney nickel (2 mL), which had been previously washed with EtOH (3x10 mL) and DCM (3x10 mL) under hydrogen, were stirred 12 hours at room temperature. After the resulting mixture was washed with EtOH (6x10 mL) and DCM (6x10 mL). These solvents were concentrated under reduced pressure. The suspension was filtered through a silica pad and washed with AcOEt (5x10 mL) and then concentrated in vacuum to obtain the desired ester (**16**) (545 mg, 77%), which was used in the following step without purification.



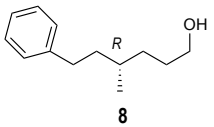
19

Yellowish oil. $[\alpha]_D^{25}$ +3.04 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.10 (q, *J* = 7.1 Hz, 2H), 2.68-2.52 (m, 2H), 2.38-2.20 (m, 2H), 1.75-1.58 (m,2H), 1.54-1.39 (m, 1H), 1.53-1.39 (m, 2H), 1.25-1.22 (m, 3H), 0.93 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 173.9, 142.6, 129.1, 128.3, 128.2, 125.6, 60.2, 38.6, 33.3, 32.1, 32.0, 31.8, 19.2, 14.2.

7.3.7 Synthesis of (*R*)-3-methyl-5-phenylpentan-1-ol (8)

A 50 mL, three-necked, round-bottom flask, equipped with a magnetic stir-bar, was purged with nitrogen and charged with ester (**19**) (545 mg, 2.32 mmol, 1 equiv) followed by anhydrous Et_2O (8 mL). The solution was then cooled to 0 ºC using an ice bath. Lithium aluminium hydride in THF (1M, 2.78 mL, 2.78 mmol, 1.2 equiv) was added cautiously by a dropping funnel over 10 min. After the addition was complete the resulting solution was stirred at room temperature for 3 h, whereupon the solution was once again cooled to 0 ºC and H_2O (0.1 mL), 15% NaOH (0.10 mL), H_2O (0.3 mL) were added sequentially. Upon warming the reaction mixture to room

temperature, anhydrous $MgSO_4$ (200 mg) were added and the resulting white suspension was filtered through Celite (5 g) and the Celite pad was washed with Et_2O (40 mL). The filtrate was concentrated under reduced pressure by rotary evaporation to afford a yellow oil (443 mg, 99%) of alcohol (**8**).



8

Yellowish oil. $[\alpha]_D^{25}$ +6.42 (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.23 (m, 2H), 7.20-7.12 (m, 3H), 3.61 (t, *J* = 6.7, 2H), 2.70-2.52 (m, 2H), 1.70-1.51 (m, 3H), 1.50-1.36 (m, 3H), 1.26-1.14 (m, 1H), 0.94 (m, *J* = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 142.9, 128.3, 128.2, 123.8, 63.1, 38.8, 36.3, 33.4, 32.8, 32.3, 21.0.

8. CONCLUSIONS

The study of the Baulamycin A has shown that in the synthesis of the synthon A compounds **25** and **26** were obtained in excellent yields. However, the yields obtained from compounds **27** and **28** did not meet the foreseen expectations. Therefore, further studies regarding the oxidation of the alcohol using MnO_2 must be reviewed.

Synthon B compounds **10**, **16**, **17**, **19** and **8** have also been obtained in high yields. The organocatalysis using (*R*)- MacMillan imidazolidinone allowed for achieving the product **15** needed in order to be able to proceed with the synthesis. The enantiomeric excess was also high giving 92-96% of pure optical compound **15**.

The synthesis of (*R*)- MacMillan catalyst has afforded product **23** in an overall yield of 55%, this yield is not what should be expected because probably the solution of Et_2O in HCl 1.0M did not make the precipitation of the compound completed.

In conclusion, 4 steps were required to synthesize the synthon A and 6 steps for the synthon B.

We succeeded in our attempt to get the aimed intermediates and, from now on, further reactions of the addition of the stereocenters in synthon B and formation of other groups in synthon A have to be performed.

9. REFERENCES AND NOTES

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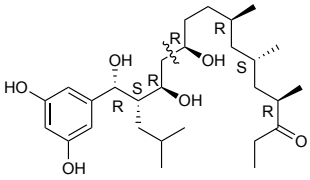
10. ACRONYMS

MRSA	Methicillin-resistant Staphylococcus aureus
AsbA	Anthracis siderophore biosynthesis protein A
SbnE	Synthetase E of Staphyloferrin B
NMR	Nuclear magnetic resonance
PG	Protecting group
r.t.	Room temperature
TBDMSCl	*tert*-butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
EtOH	Ethanol
MeOH	Methanol
DMF	Dimethylformamide
UV	Ultraviolet
EtOAc	Ethyl Acetate
PTSA	p-Toluenesulfonic acid
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
DCM	Dicloromethane
S_N2	Bimolecular nucleophilic substitution
Et_2O	Diethyl ether
Ni/Raney	Raney Nickel

H_2	Hidrogen
N_2	Nitrogen
Pd/C	Palladium on carbon
HPLC	High performance liquid chromatography
$CDCl_3$	Deuterated chloroform

APPENDICES

APPENDIX : COMPOUND NUMERATION



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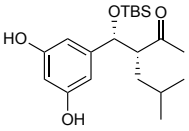
Baulamycin A



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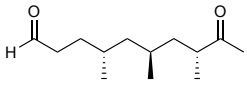
Synthon A



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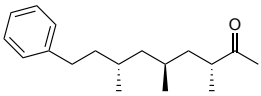
Synthon B



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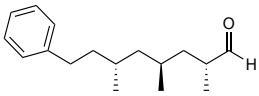

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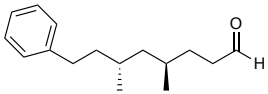

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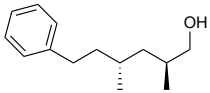

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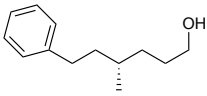

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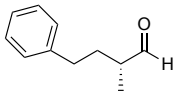

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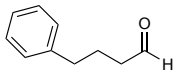

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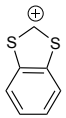

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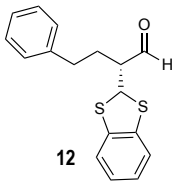

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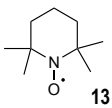

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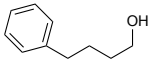

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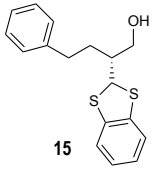

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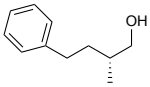

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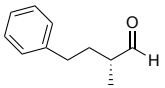

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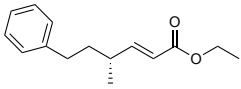

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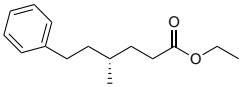

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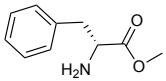

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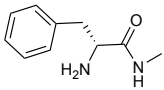

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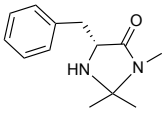

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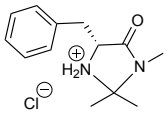

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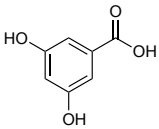
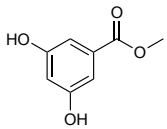


24



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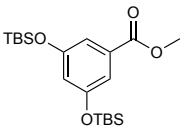
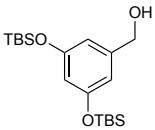
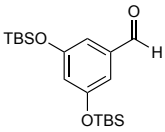


26



27



28