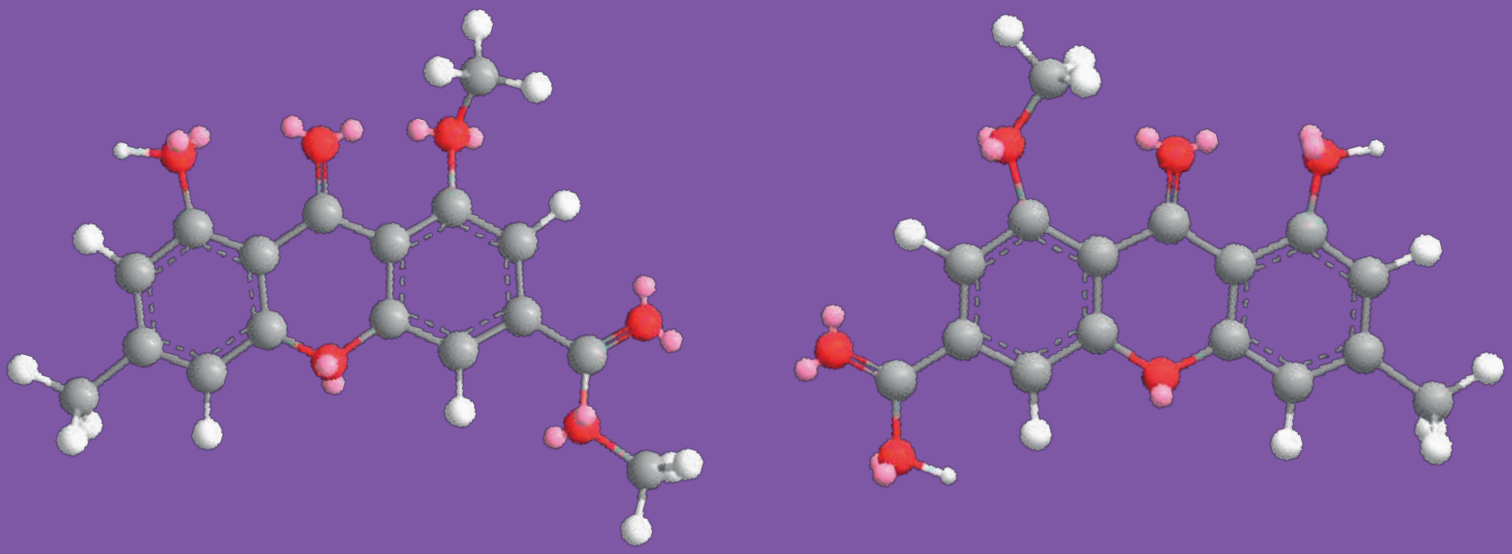

Daniela Raquel Pontes Loureiro

SYNTHESIS OF MARINE XANTHONES: TRACKING YICATHINS B AND C

Dissertação de Mestrado em Química Farmacêutica Industrial, orientada pelo Professor Doutor Jorge Salvador e pelo Professor Doutor Carlos Manuel Magalhães Afonso e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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Universidade de Coimbra

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Synthesis of marine xanthones: tracking yicathins B and C

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AUTHOR'S DECLARATION:

Under the terms of the Decree-Law nº 216/92, of October 13th, is hereby declared that the author afforded a major contribution to the conceptual design and technical execution of the work and interpretation of the results included in this dissertation. Under the terms of the referred Decree-Law, is hereby declared that the following articles/communications were prepared in the scope of this dissertation.

The results presented in this thesis are part of the following scientific communications:

Poster Communications in Conferences

D. Loureiro, J. Soares, S. Cravo, J. Salvador, C. Azevedo, C. Afonso, M. Pinto; "**Preparation of two building blocks for the synthesis yicathins B and C**"; 5th Portuguese Young Chemists Meeting (5th PYCheM) and 1st European Young Chemists Meeting (1st EYCheM), Guimarães, Portugal, 26-29 April, 2016.

D. Loureiro, J. Soares, S. Cravo, J. Salvador, C. Azevedo, C. Afonso, M. Pinto; "**Designing the total synthesis of two marine xanthones: yicathins B and C**"; 9º Encontro de Jovens Investigadores da Universidade do Porto (IJUP16), Porto, Portugal, 17-19 February, 2016.

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ABSTRACT

Nature still is a great source of new potential hits and leads of new drugs. In the last years, an increase interest for marine environment lead to discovering marine natural products with a broad panel of biological activities, namely, antimicrobial activity. The need for new antimicrobials is a very important issue, since the increasing emergence of resistant bacteria and fungus makes the available antimicrobials to lose their effectiveness, whereas new drugs rarely reach the market.

Xanthones, privileged structures frequently occurring in marine environment, are a class of *O*-heterocyclic compounds which hold great promise for the development of new antimicrobials. A bibliographic review (from 1993 - until 2016) of marine derived xanthones with antimicrobial, in particular, antibacterial and antifungal activity and a brief overview of xanthones chemistry and xanthones synthesis are also given.

Recently, two new marine xanthones, Yicathins B and C, were isolated from *Aspergillus wentii*, a fungus present in the inner tissue of the marine red alga *Gymnogongrus flabelliformis*. Yicathins B and C have shown a promising antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Colletotrichum lagenarium*. However, the direct use of these yicathins is hampered by the challenging access to marine environment and the very low quantities obtained from direct extraction.

In this work, a retrosynthetic analysis was performed for the total synthesis of yicathins B and C and analogues. Accordingly, a synthetic pathway was proposed and followed for the synthesis of several building blocks and key intermediates. All the synthesized compounds were purified and structurally elucidated by the usual spectroscopic methods (FTIR, ^{1}H NMR, ^{13}C NMR, EI-MS, HSQC and HMBC).

Keywords: Marine xanthones; Xanthones synthesis; Yicathins; Antimicrobial xanthones.

RESUMO

A natureza continua a ser uma grande fonte de potenciais "hits" e "leads" de novos fármacos. Nos últimos anos, um aumento do interesse pelo ambiente marinho levou à descoberta de produtos naturais com um amplo painel de atividades biológicas, nomeadamente, a atividade antimicrobiana. A necessidade de novos agentes antimicrobianos é uma urgência, uma vez que o aumento da resistência de bactérias e fungos aos antimicrobianos disponíveis faz com que estes percam a sua eficácia, enquanto que, novos medicamentos raramente chegam ao mercado.

As xantonas, estruturas privilegiadas que ocorrem frequentemente em ambiente marinho, são uma classe de compostos *O*-heterocíclicos que são uma grande promessa para o desenvolvimento de novos agentes antimicrobianos. Uma revisão bibliográfica (a partir de 1993 - até 2016), várias xantonas de origem marinha com atividade antimicrobiana, nomeadamente, com atividade antibacteriana e antifúngica, foram encontradas.

Recentemente, duas novas xantonas marinhas, hicatinas B e C, foram isolados a partir de *Aspergillus wentii*, um fungo presente no tecido interno da alga marinha vermelha *Gymnogongrus flabelliformis*. As hicatinas B e C demonstraram uma atividade antibacteriana promissora contra *Escherichia coli* e *Staphylococcus aureus* e atividade antifúngica contra *Colletotrichum lagenarium*. No entanto, o uso direto destas hicatinas é difícil porque o acesso ao meio marinho é um desafio e a quantidade obtida a partir de extração direta é muito pequena.

Neste trabalho apresentamos a análise retrossintética da síntese total de hicatinas B e C e análogos. Deste modo, uma via sintética foi proposta e seguida e, vários blocos de construção e intermediários chave foram sintetizados. Todos os compostos sintetizados foram purificados e estruturalmente elucidados pelos métodos espectroscópicos habituais (IV, EM, ^{1}H RMN, ^{13}C RMN, CHSQ e CHML).

Palavras-Chave: Xantonas marinhas; Síntese xantonas; Hicatinas; Xantonas antimicrobianas.

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LIST OF ABBREVIATIONS AND SYMBOLS

ν	wavenumber
δ_C	carbon chemical shifts
δ_H	proton chemical shifts
^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
AMR	Antimicrobial Resistance
BnBr	Benzyl Bromide
d	doublet
DCM	Dichloromethane
dd	double doublet
DMF	Dimethylformamide
DMG	Directed Metalation Group
DMP	Dess–Martin periodinane
DMSO	Dimethylsulfoxide
DoM	Directed *ortho* metalation
EI-MS	Electron-Impact Mass Spectrometry
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid

IR	Infrared Spectroscopy
J	Coupling Constant
m	Multiplet
MeCN	Acetonitrile
MEM	2-Methoxyethoxymethyl
MEMCl	2-Methoxyethoxymethyl chloride
MeOH	Methanol
MOM	Methoxymethyl
MOMCl	Methoxymethyl chloride
m.p.	Melting Point
MW	Molecular Weight
Na_2SO_4	Sodium sullfate
NMR	Nuclear Magnetic Resonance
$POCl_3$	Phosphorous oxychloride
r.t.	room temperature
s	singlet
SAR	Structure-Activity Relationship
S_EAr	Electrophilic Aromatic Substitution
S_NAr	Nucleophilic Aromatic Substitution
TBDMS	*tert*-Butyldimethylsilyl

TBDMSCl	*tert*-butyldimethylsilyl chloride
THF	Tetrahydrofuran
THF:BH_3	Borane tetrahydrofuran complex solution
TLC	Thin Layer Chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine

OUTLINE OF THE THESIS

The present dissertation consists of six chapters:

1. INTRODUCTION

In this chapter, the relevance of Nature, especially the marine environment, as an important source for discovery and development of new drugs is explained. The biological activities found in marine products, emphasizing antimicrobial activity, are discussed and some examples are stated. In order to highlight the role of marine xanthones as promising antimicrobial activity, a bibliographic overview is presented. Finally, a brief overview of xanthones chemistry and xanthones synthesis is given.

2. AIMS

This chapter summarizes the main objectives of the present work.

3. RESULTS AND DISCUSSION

This section is divided in four parts: i. retrosynthetic plan of yicathins B and C and their analogues, ii. synthesis and structural elucidation of building block A, iii. synthesis and structural elucidation of building blocks B and C and, finally, iv. synthesis and structural elucidation of benzophenone intermediate for the synthesis of yicathins.

4. EXPERIMENTAL PART

In this chapter, the reagents, materials and experimental procedures for the synthesis, purification and structure elucidation of the synthesized compounds are detailed.

5. CONCLUSIONS

This chapter sum up the general conclusions of the developed work and point out the next steps for future development.

6. REFERENCES

1. INTRODUCTION

1. INTRODUCTION

1.1. Importance of the marine environment in the discovery and development of new drugs

Currently, drug discovery is based on three key sources: natural products, semi-synthetic derivatives of natural products and synthetic compounds, many of them derived from combinatorial chemistry (1). The attention to natural sources as source of new potential bioactive molecules has been enormous over the last years (**Figure 1**) (2).

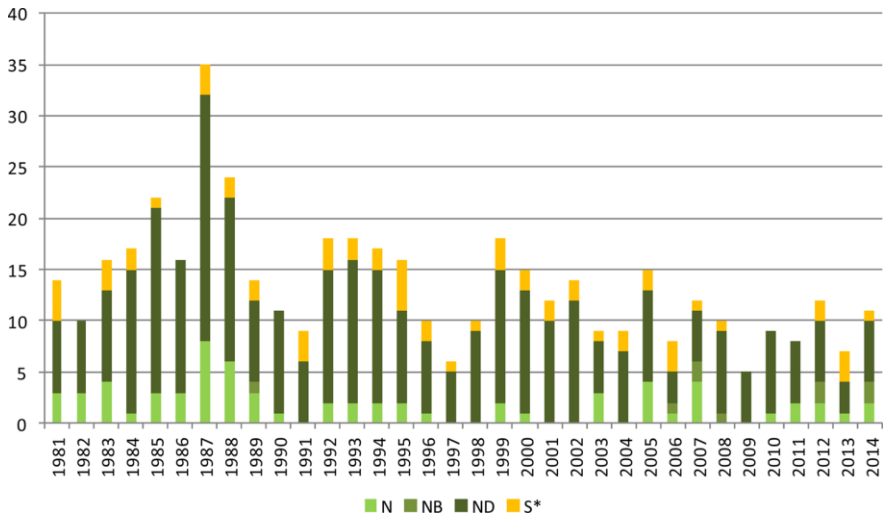


Figure 1 - The percentage of natural product-based compounds and their derivatives approval from 1981 until 2014. (N- Unaltered natural products, NB- Botanical drugs, ND- natural products derivative and S*- Synthetic drugs (but the pharmacophore is/was from a natural product (From (3)).

Although the number of drugs in the market that are either natural products or inspired by them has decreased in recent years, Nature is still a greater source of drugs. The analysis of all small-molecules approved between 1981 and 2014 revealed that only thirty five percent are totally synthetic, being all the other approved compounds either Natural Products or inspired by them (**Figure 2**) (3).

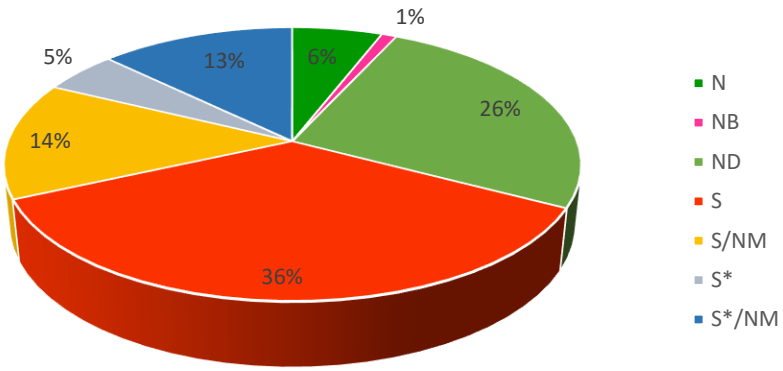


Figure 2 - Sources of small molecules approved from 1981 to 2014. (N- Unaltered natural products, NB- Botanical drugs, ND- natural products derivative, S- Totally synthetic drugs, S*- made by total synthesis but the pharmacophore is/was from a natural product, NM- natural product mimic) (Adapted from (3)).

In the area of anti-infective drugs (antibacterial, fungal, parasitic, and viral), in the last thirty years, approximately forty percent of drugs are from natural origin or derived from them proving the influence of natural products and their structures (3). In fact, natural products possess enormous structural and chemical diversity that is unsurpassed by any synthetic libraries and hold with them a variety of biological actions (4, 5).

Among the different natural sources, marine environment is an important source of novel bioactive natural products (6-8) and is still underexplored (8-10). From mid-1980s until 2012, there has been an outstanding increase in discovered marine natural products (11). In fact, more than 22 000 compounds have been isolated from marine organisms and many of them are bioactive (**Figure 3**) (11).

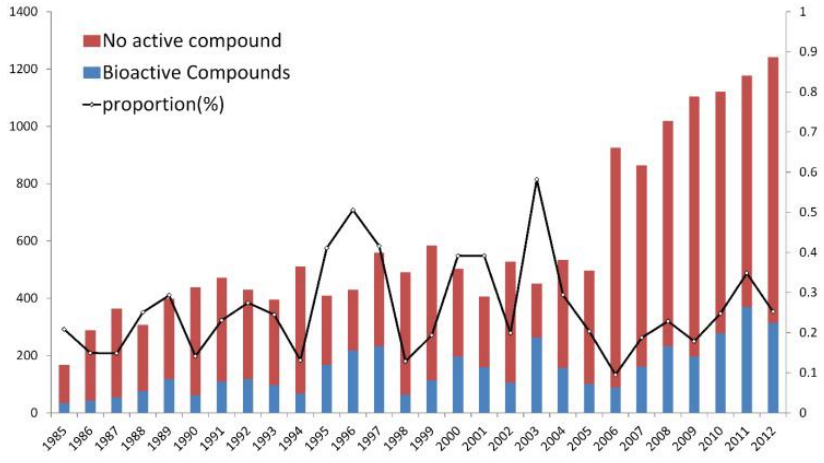


Figure 3 - The number of discovery marine natural products from 1985 to 2012. (From (11))

Most marine natural products are secondary metabolites (6, 7, 12) which are not generated by common biological or metabolic pathways, with no primary function associated with development, growth, or propagation of a species (7).

Recently, it was understood that many compounds previously isolated from marine organisms, such as sponges and algae, for example, are in fact, metabolic products of associated microorganisms (9). This opens and enlarges the potential for the discovery of new bioactive molecules derived from marine environment.

Marine natural products exhibit a broad panel of biological activities such as antitumor, antidiabetic, anticoagulant, anti-inflammatory, antimicrobial, anti-infective, making them a valuable potential source of new drugs (7, 9, 13). In addition, they also have important applications in cosmetics, as nutraceuticals and for agrochemical industries (7, 14, 15). At the moment, eight marine-derived drugs were approved by Food and Drug Administration (FDA) and/or European Medicines Agency (EMEA) and several other compounds are in different phases of the drug pipeline (**Figure 4**) (7, 16). Three of them (Prialt®, Yondelis® and Carragelose®) became drugs without any modification of the original natural molecule, while the remaining suffered lead optimization, in different phases of their development (7).

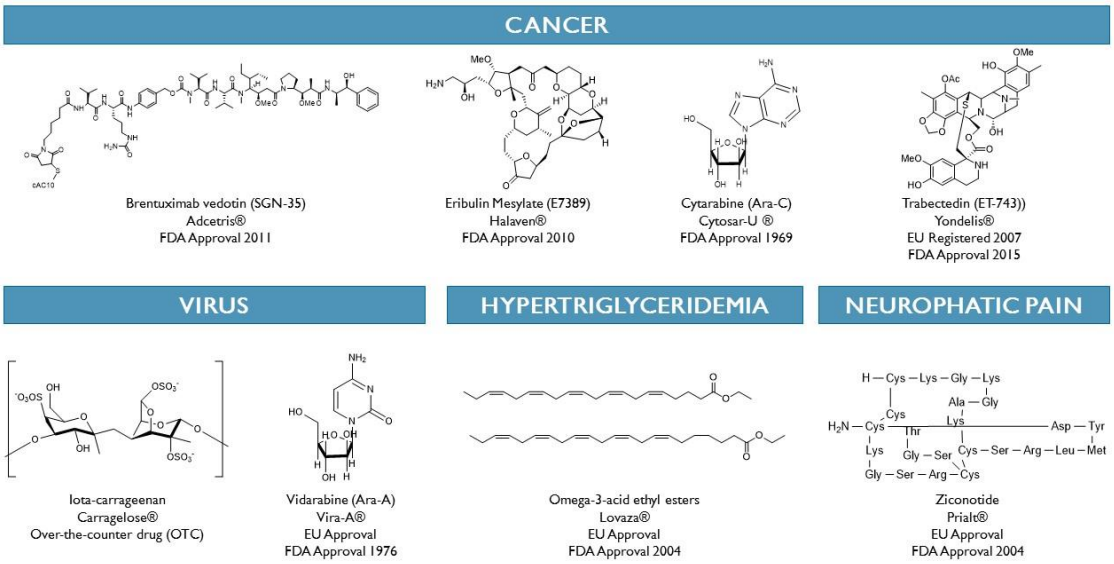


Figure 4 - Chemical structures of approved marine-derived drugs.

The research of marine natural products has some challenges: the access to the marine biodiversity is difficult and the limited quantities of the isolated substances. Therefore, their

direct use almost impossible and the chemical and biological characterization is daunting (7, 8, 17).

On one hand, new technologies, such as advancements in sampling techniques, genome sequencing, structure determination strategies, target identification methods and computation-assisted structural elucidation led to a boost in the chemical and biological characterization of marine chemical space (8, 17).

On the other hand, total or partial synthesis, microbial fermentation and molecular biology became important tools to overcome the supply problem (8).

Additionally, efficient collaborations between academic and industrial research proved to be essential to ensure the future success of marine natural products as new and novel therapeutic entities for the treatment of human diseases (17).

1.2. Antimicrobial Activity

The world changed after the discovery of penicillin in 1928 by Sir Alexander Fleming. However, nowadays infectious diseases still have a great prevalence and still is an important cause of death among children under five (**Figure 5**). Considering children and adults, about sixteen percent of all deaths each year are from infectious diseases (18, 19).

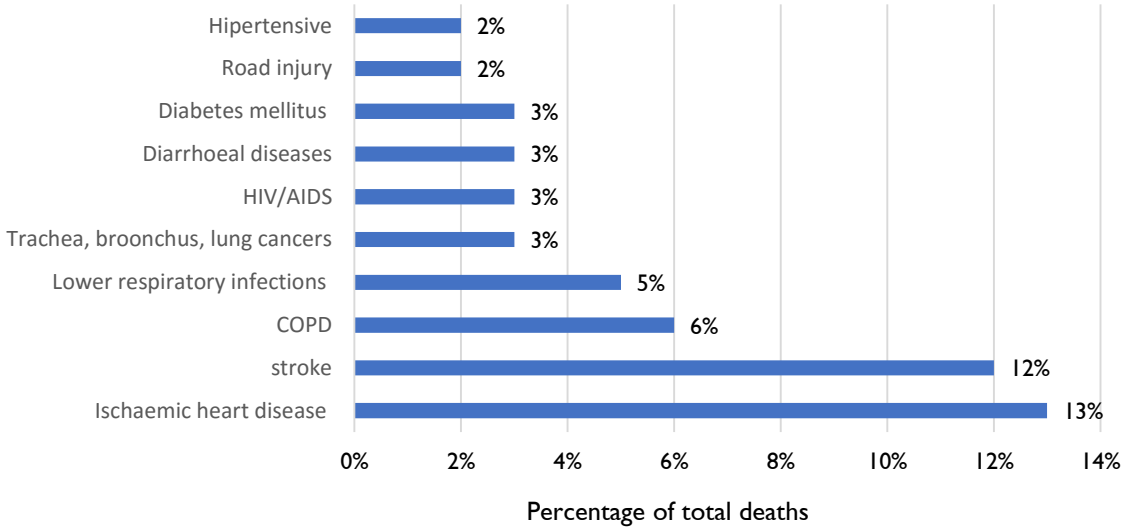


Figure 5 – Main causes of deaths in the World (2012) distributed by causes and gender (Adapted from (20)).

Antimicrobial Resistance (AMR) is one of the major challenges facing public health in the 21st Century, resulting from a combination of the use abusive of antimicrobials leading to the emergence of resistance (21). AMR is mainly caused by the misuse of antimicrobials, threatens the treatment of infectious diseases due to the loss effectiveness of the current antimicrobials. In addition, new drugs rarely reach the market as the interest of big pharmaceutical industries in this therapeutic is scarce. The emergence of new multidrug resistant microorganism deepens this public health problem, increasing the need for new, effective and safe antimicrobials agents (22, 23).

On way to address this challenge to public health could be found in Nature. In fact, marine biodiversity has proven to be an important source of new "hits" and "leads" in drug discovery (7, 13). Several studies have reported novel bioactive marine secondary metabolites isolated from algae, sponges, worm and marine microorganisms, such as cyanobacteria and fungi (**Figure 6**) (13, 24). In fact, as previously reported, many compounds isolated from marine

macroorganisms are associated with microorganisms in a symbiotic relationship or as food (9, 10).

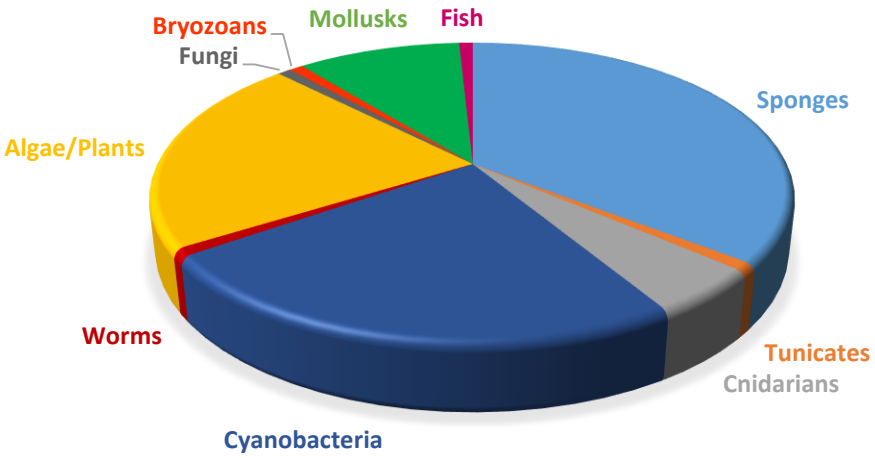
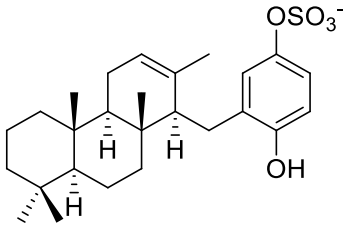
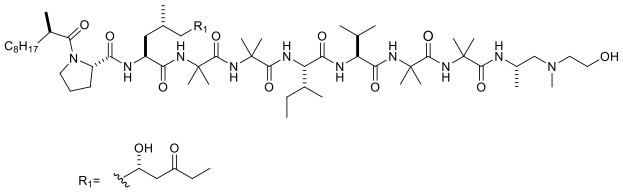
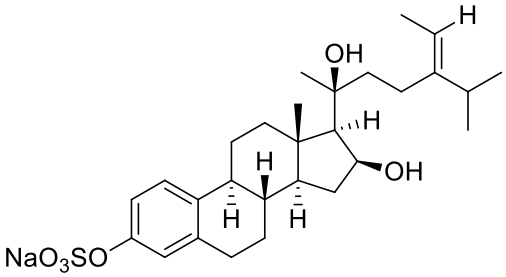
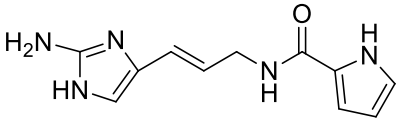
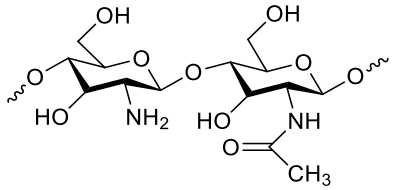
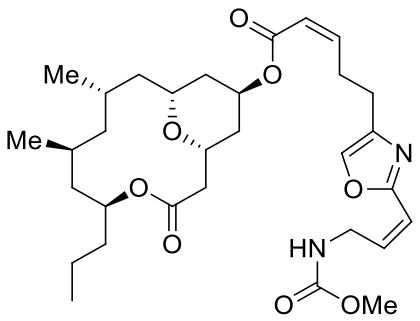
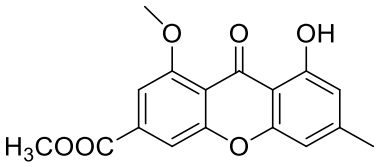


Figure 6 - Sources of bioactive marine natural products (Adapted from (25)).

Concerning antimicrobial activity, it is believed that marine environment is able to provide novel hits/leads against pathogenic agents that are evolving and developing resistance to the existing therapy (13). The most relevant chemical classes of secondary metabolites isolated from the marine biodiversity with antimicrobial activity are: terpenoids, peptides, steroids, alkaloids, polyketides and polysaccharides (**Table 1**) (10, 24). In addition, an interesting class of secondary metabolites which have been isolated from marine sources are xanthone derivatives (10).

Table 1 – Examples of most relevant classes of bioactive marine natural products.

Chemical Class	Structure and Compound name	Reference
Terpenoid	 **Fascioquinol A**	(26)
Peptide	 **Trichoderins A**	(27)
Steroid	 **Geodisterol-3-*O*-sulphite**	(28)
Alkaloid	 **Clathrodin**	(29)
Polysaccharide	 **Chitosan**	(30, 31)

Polyketide	 **(+)-neopeltolide**	(32)
Xanthone	 **Yicathin B**	(33)

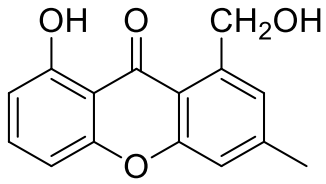
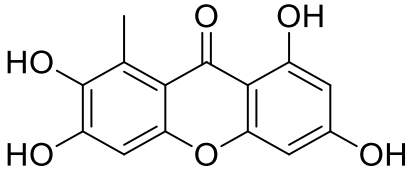
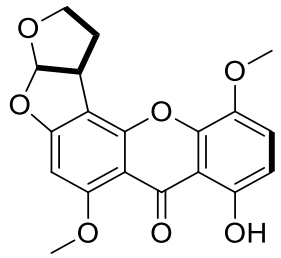
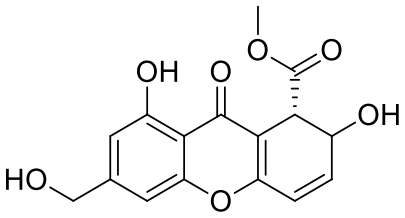
1.3. Antimicrobial xanthones

Xanthones are secondary metabolites that can be found in higher plants, fungi and lichens, and have been also isolated from marine sources, mainly from sponges and algae-associated fungi and from marine bacteria (10). Xanthones can show various biological activities, such as antitumor, anti-inflammatory and antimicrobial activities.

Regarding their antimicrobial activity, several xanthone derivatives found in distinctive sources have shown promising activity (34-39). These analogues can be used to solve the problem associated with microorganism resistance to current therapies. Among all the sources of drugs, marine environment raised in last years as a potential source of new therapeutic agents (7).

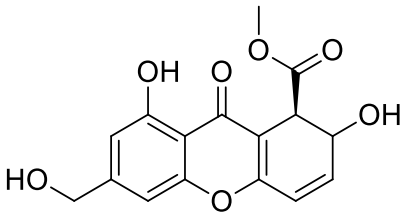
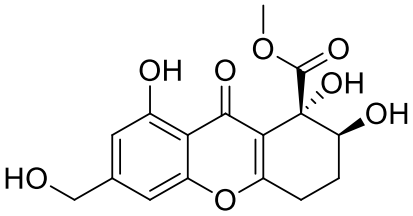
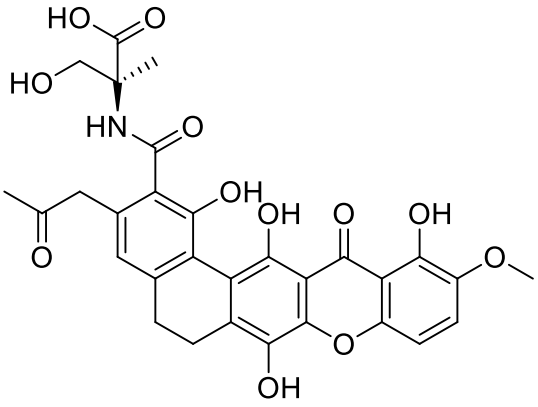
Table 2 and **Table 3** summarize the marine derived xanthones reported in last the years (1993-2016) with antibacterial and antifungal activity, respectively. This bibliographic research was elaborated using Scopus, Web of Science, Pubmed and Academic Google databases. The keywords used for this research were: marine xanthones, marine derived xanthones, xanthones with antimicrobial activity and marine xanthones with antimicrobial activity. The search was made between 25th of April and 10th of June of 2016.

Table 2 - Marine derived xanthones with antibacterial activity.

Structure	Antibacterial Activity	Source	Ref.
1-hydroxy-6-methyl-8-(hydroxymethyl) xanthone 	*Eurotium repens* (inhibition zone 2 mm) Method: **(b)**	*Ulocladium botrytis* (strain no. 193A4), isolated from the marine sponge *Callyspongia vaginalis*, collected from Dominica, Caribbean.	(40)
2,3,6,8-tetrahydroxy-1-methyl-xanthone 	*Microbotryum violaceum* (inhibition zone 1 mm) Method: **(b)**	*Wardomyces anomalus* isolated from the green alga *Enteromorpha sp. (*Ulvaceae*)* collected in the Baltic Sea.	(41)
5-methoxydihydrosterigmatocystin 	*Staphyloccocus aureus* (ATCC 6538)(MIC, 12.5 μg/mL) *Bacillus subtilis* (ATCC 6633) (MIC, 3.125 μg/mL) Method: **(c)**	*Aspergillus versicolor* MF359 isolated from a marine sponge sample of *Hymeniacidon perleve* collected from the Bohai Sea.	(42)
AGI-B4 	*Escherichia coli* (MIC, 64 μg/mL) *Bacillus subtilis* (MIC, 64 μg/mL) Method: **(b)**	*Engyodontium album* DFFSCS021 from a marine sediment sample collected in the South China Sea	(43)

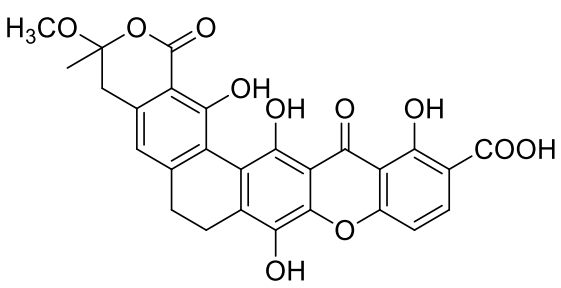
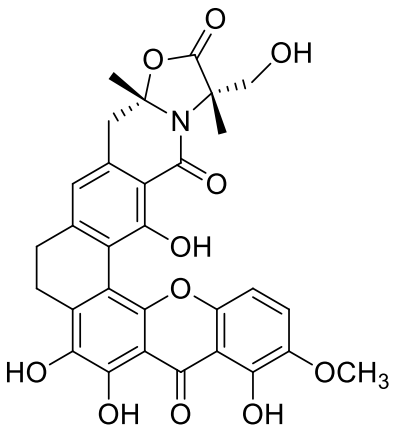
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.*

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Engyodontiumone H 	*Escherichia coli* (MIC, 64 μg/mL) *Bacillus subtilis* (MIC, 32 μg/mL) Method: **(b)**	*Engyodontium album* DFFSCS021 from a marine sediment sample collected in the South China Sea	(43)
Aspergillusone B 	*Escherichia coli* (MIC, 64 μg/mL) *Bacillus subtilis* (MIC, 64 μg/mL) Method: **(b)**	*Engyodontium album* DFFSCS021 from a marine sediment sample collected in the South China Sea	(43)
Buanmycin 	*Staphylococcus aureus* (MIC 10.5 μM) *Bacillus subtilis* (MIC 0.7 μM) *Kocuria rhizophila* (MIC 10.5 μM) *Salmonella entérica* (MIC 0.7 μM) *Proteus hauseri* (MIC 21.1 μM) Inhibited *Staphylococcus aureus* sortase A (IC_{50}: 43.2 μM) Method: **(b)**	*Streptomyces strain* from a tidal mudflat in Buan, Republic of Korea.	(44)

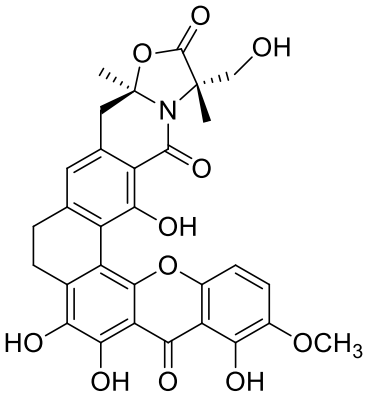
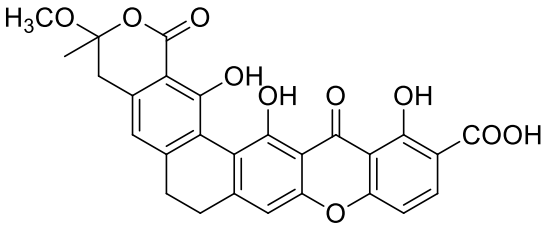
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.*

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Citreaglycon A 	*Staphylococcus haemolyticus* (MIC 8.0 μg/mL) *Staphylococcus aureus* UST950701-005 (MIC 16 μg/mL) *Bacillus subtillis* 769 (MIC 8.0 μg/mL) *Staphylococcus aureus* ATCC43300 (MIC 8.0 μg/mL) Method: **(d)**	*Streptomyces caelestis* from Red Sea	(43, 45)
Citreamicin θ A 	*Staphylococcus haemolyticus* (MIC 0.5 μg/mL) *Staphylococcus aureus* UST950701-005 (MIC 1.0 μg/mL) *Bacillus subtillis* 769 (MIC 0.25 μg/mL) *Staphylococcus aureus* ATCC43300 (MIC 0.25 μg/mL) Method: **(d)**	*Streptomyces caelestis* from Red Sea	(45)

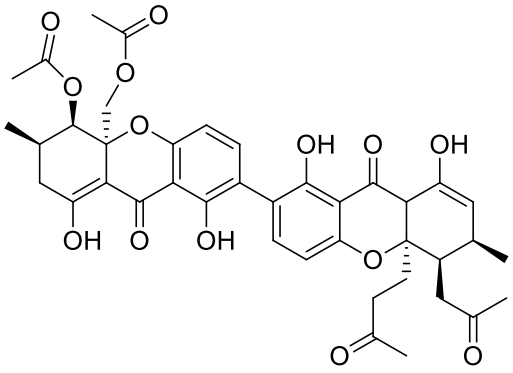
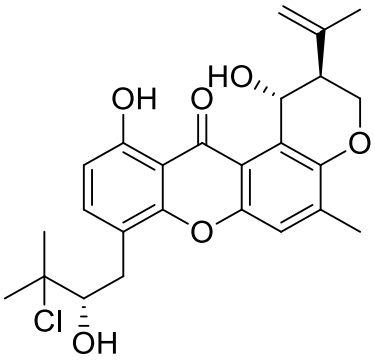
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.*

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Citreamicin θ B 	*Staphylococcus haemolyticus* (MIC 0.5 μg/mL) *Staphylococcus aureus* UST950701-005 (MIC1.0 μg/mL) *Bacillus subtillis* 769 (MIC 0.25 μg/mL) *Staphylococcus aureus* ATCC43300 (MIC 0.25 μg/mL) Method: **(d)**	*Streptomyces caelestis* from Red Sea	(45)
Dehydrocitreaglycon A 	*Staphylococcus haemolyticus* (MIC 8.0 μg/mL) *Staphylococcus aureus* UST950701-005 (MIC 16 μg/mL) *Bacillus subtillis* 769 (MIC 8.0 μg/mL) Method: **(d)**	*Streptomyces caelestis* from Red Sea	(45)

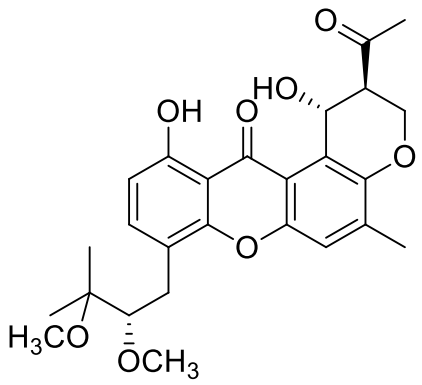
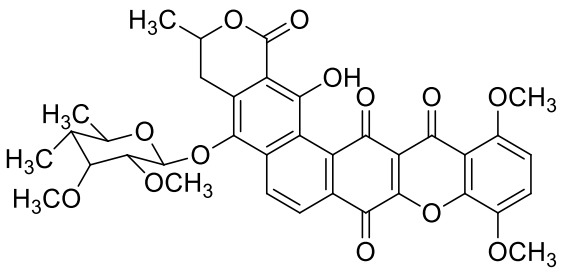
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.*

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Dicerandrol C 	*Staphylococcus aureus* (ATCC 6538) (MIC 1µg/mL) *Staphylococcus saprophyticus* (ATCC 15305) (MIC 2 µg/mL) Method: **(d)**	Endophytic fungus *Phomopsis longicolla* isolated from the tropical red seaweed *Bostrychia radicans* from Brazil	(43, 46)
Emerixanthone A 	*Escherichia coli* (ATCC 29922), *Klebsiella pneumonia* (ATCC 13883), *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Acineto bacterbaumannii* (ATCC 19606), *Aeromonas hydrophila* (ATCC 7966) (Diameters of inhibition zones were all 4–6 mm) Method: **(b)**	*Emericella sp.* SCSIO 05240 from South China Sea	(47)

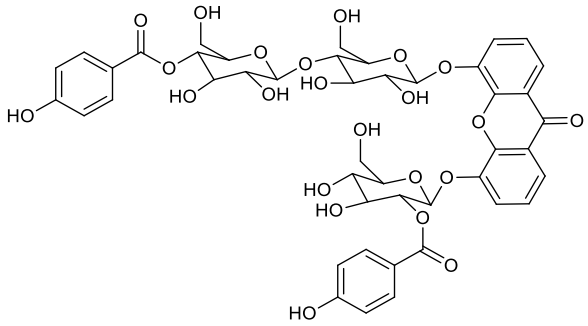
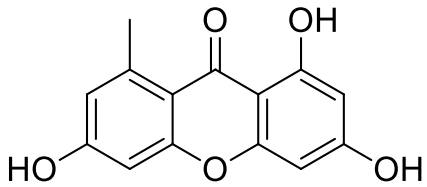
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.*

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Emerixanthone C 	*Escherichia coli* (ATCC 29922), *Klebsiella pneumonia* (ATCC 13883), *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Acineto bacterbaumannii* (ATCC 19606), *Aeromonas hydrophila* (ATCC 7966) (Diameters of Inhibition zones were all 4–6 mm) Method: **(b)**	*Emericella sp.* SCSIO 05240 from South China Sea	(43, 46, 47)(44)
IB-00208 	*Bacillus subtilis* (ATCC 6051) (MIC 1.4 nM) *Staphylococcus aureus* (ATCC 6538P) (MIC=1.4 nM) *Micrococcus luteus* (ATCC 9341) (MIC 0.09 nM) Method: **(e)**	*Actinomadura sp.* collected from northern coast of Spain	(48)

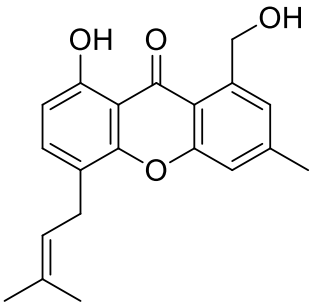
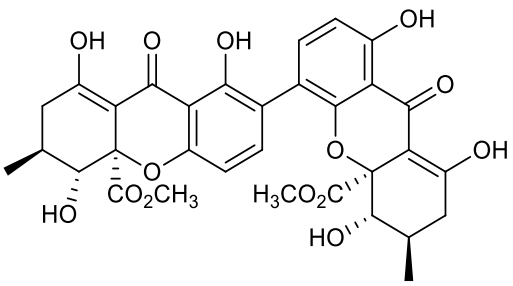
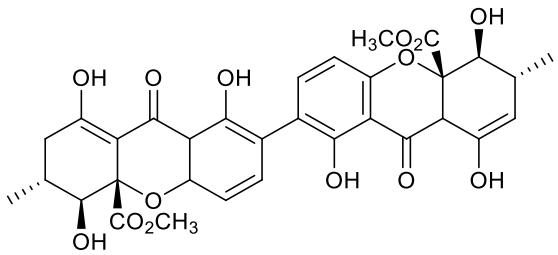
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.*

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Microluside A (new glycosylated xanthone) 	*Enterococcus faecalis* JH212 (MIC 10 μM) *Staphylococcus aureus* NCTC 8325 (MIC 13 μM)	*Micrococcus sp.* EG45 was cultivated from the Red Sea sponge Spheciospongia vagabunda	(49)
Norlichexanthone (3,6,8-trihydroxy-1-methylxanthone) 	*Staphylococcus aureus* (ATCC 27154) (MIC, 12.5 μg/mL) *Sarcina ventriculi* (ATCC 29068) (MIC, 25.0 μg/mL) Pseudomonas aeruginosa (ATCC 25668) (MIC, 25.0 μg/mL) *Bacillus agisterium* (1 mm) Method: **(f)** and **(g)**	*P. raistrikii* obtained from the sponge *Axinella cf.* corrugate or the mangrove endophytic fungus *Talaromyces sp.* ZH-154 and *Wardomyces anomalus* (marine fungus)	(41, 50, 51)

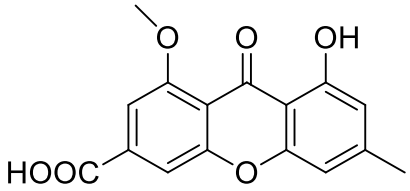
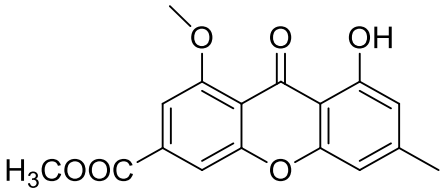
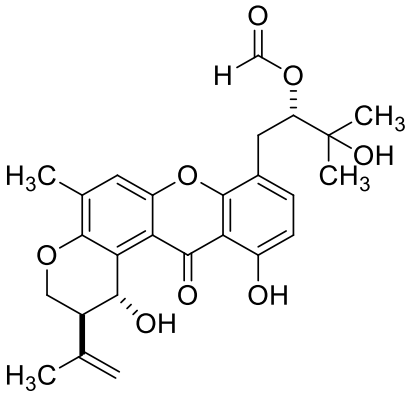
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Paeciloxanthone 	*Escherichia Coli* (inhibitory zones of 12 mm) Method: **(b)**	*Paecilomyces sp.* was isolated from an estuarine mangrove from the Taiwan Strait	(52)
Penicillixanthone A 	*Bacillus subtilis* (MIC 24.4 µg/mL) *Escherichia Coli* JVC1228 (MIC 24.4 µg/mL) *Micrococcus luteus* UST950701- 006 (MIC 24.4 µg/mL) *Pseudoalteromonas nigrifaciens* UST010620-005 (MIC 97.5 µg/mL) Method: **(b)**	*Penicillium sp.* SCSGAF 0023 isolated from South China Sea gorgonian coral *Dichotella gemmacea*	(53)
Secalonic acid A 	*Staphylococcus aureus* (ATCC 27154) (MIC 12.5 µg/mL) *Escherichia coli* (ATCC 25922) (MIC 25 µg/mL) *Sarcina ventriculi* (ATCC 29068) (MIC 12.5 µg/mL) *Pseudomonas aeruginosa* (ATCC 25668) (MIC, 12.5 µg/mL)	*Talaromyces sp.* ZH-154 from the South-China Sea.	(51)

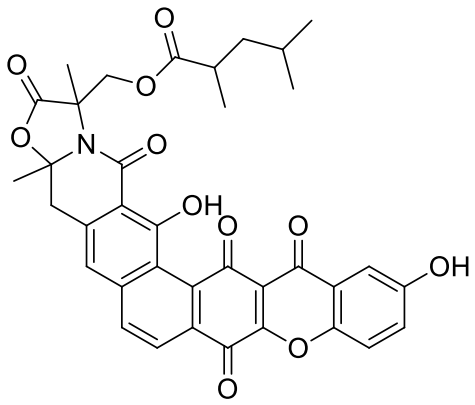
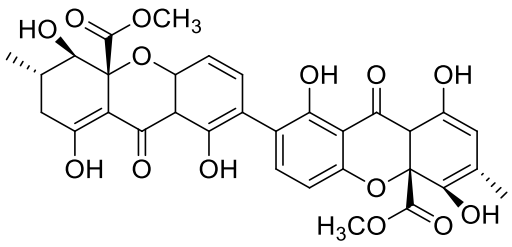
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Yicathin C 	*Escherichia coli* (12.0mm) *Staphylococcus aureus* (7.5mm) Method: **(b)** standard agar diffusion	Aspergillus wentii (red alga *Gymnogongrus flabelliformis*) collected from the coast of Pingtan Island, China	(33)
Yicathin B 	*Escherichia coli* (inhibition diameter 9mm) Method: **(b)**	*Aspergillus wentii* (red alga *Gymnogongrus flabelliformis*) colleted from the coast of Pingtan Island, China	(33)
Varixanthone 	*Escherichia coli* (MIC 12.5 µg/mL) *Proteus sp.* (MIC 12.5 µg/mL) *Bacillus subtilis* (MIC 12.5 µg/mL) *Staphylococcus aureus* (MIC 12.5 µg/mL) *Enterococcus faecalis* (MIC 50 µg/mL) Method: **(g)**	*Emericella variecolor* was isolated from a sponge (*Porifera*) collected in the Caribbean Sea.	(54)

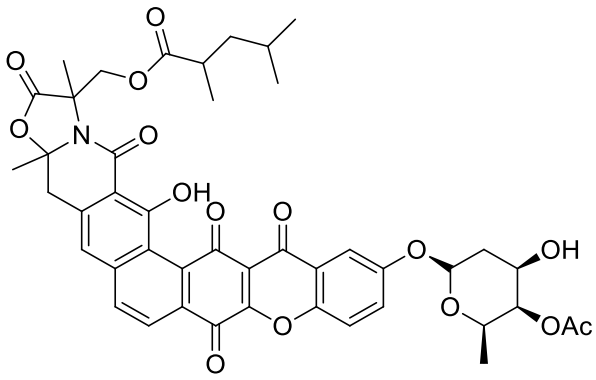
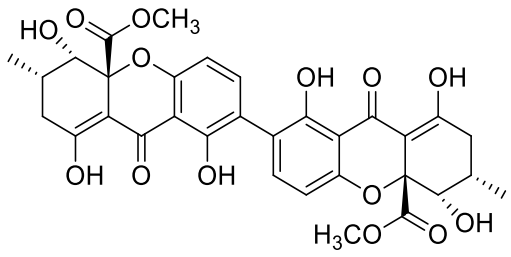
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Neocitreamicins I 	*Bacillus subtilis 1A1* (MIC 0.06 μg/mL) *Staphylococcus aureus* (MRSA NRS1) (MIC 0.50 μg/mL) *Staphylococcus aureus* (MRSA NRS2) (MIC 0.12 μg/mL) *Staphylococcus aureus* (MRSA NRS71) (MIC 0.12 μg/mL) *Enterococcus faecalis* (VRE 51299) (MIC 0.06 μg/mL) *Enterococcus faecalis* (VRE 51575) (MIC 0.12 μg/mL) *Escherichia coli* K-12 (MIC >8.0 μg/mL) Method: **(e)**	*Nocardia strain (G0655)* isolated from a sandy soil sample collected in Falmouth, Massachusetts (USA)	(49, 56)
Secalonic acid D 	*B. subtilis* (MIC 24.4 μg/mL), *E. coli* JVC1228 (MIC 24.4 μg/mL), *M. luteus* UST950701-006 (MIC 24.4 μg/mL), *P. nigrifaciens* UST010620-005 (MIC 97.5 μg/mL), Method: **(b)**	*Penicillium sp.* SCSGAF 0023 isolated from South China Sea gorgonian coral *Dichotella gemmacea*	(53)

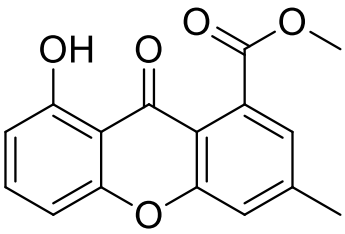
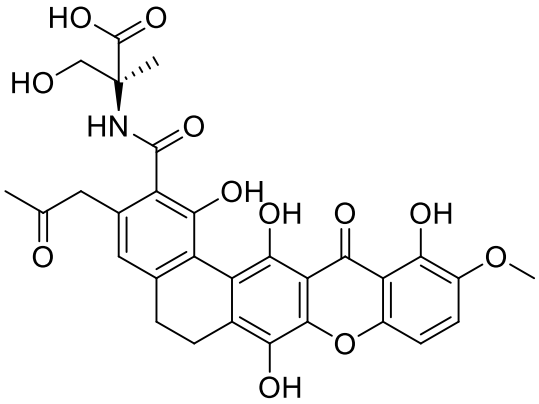
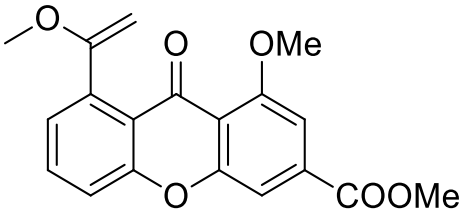
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

Table 2 (continuation)

Structure	Antibacterial Activity	Source	Ref.
Neocitreamicins II 	*Bacillus subtilis* 1A1 (MIC 0.12 μg/mL) *Staphylococcus aureus* (MRSA NRS1) (MIC 1.0 μg/mL) *Staphylococcus aureus* (MRSA NRS2) (MIC 0.50 μg/mL) *Staphylococcus aureus* (MRSA NRS71) (MIC 0.50 μg/mL) *Enterococcus faecalis* (VRE 51299) (MIC 0.06 μg/mL) *Enterococcus faecalis* (VRE 51575) (MIC 0.25 μg/mL) *Escherichia coli* K-12 (MIC >8.0 μg/mL) Method: **(e)**	*Nocardia strain (G0655)* isolated from a sandy soil sample collected in Falmouth, Massachusetts (USA)	(49, 56)
Secalonic acid B 	*Bacillus megaterium* (15mm) Method: **(b)**	*Blennoria s*p. and *Penicillium sp.* SCSGAF 0023 isolated from South China Sea gorgonian coral *Dichotella gemmacea*	(49, 53, 57)

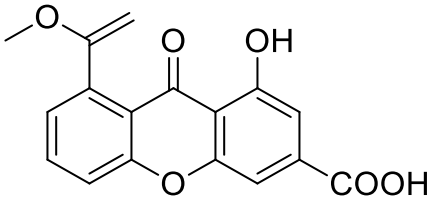
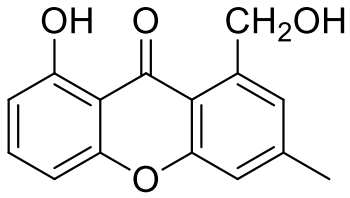
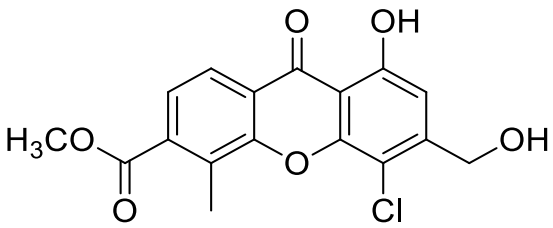
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

Table 3 - Marine derived xanthones with antifungal activity.

Structure	Antifungal Activity	Source	Ref.
8-Hydroxy-3-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid methylether 	*Gloeosporium musae* (Rate of inhibition 53%) *Peronophthora cichoralearum* (Rate of inhibition 48%) Method: **(b)**	Co-culture broth of two mangrove fungi (strain No. K38 and E33) collected in South China Sea coast.	(58-60)
Buanmycin 	*Candida albicans* (MIC 21.1 μM), *Aspergillus fumigatus* (MIC 84.3 μM) Method: **(b)**	*Streptomyces* strain from a tidal mudflat in Buan, Republic of Korea.	(44)
Dimethyl 8-methoxy-9-oxo-9*H*-xanthene-1, 6-dicarboxylate 	*Fusarium oxysporum f.* sp. *cubense* (MIC 12.5 μg/ml)	*Penicillium* sp. (ZZF 32#) isolated from the South China Sea.	(60, 61)

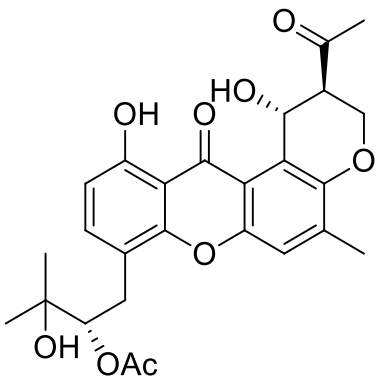
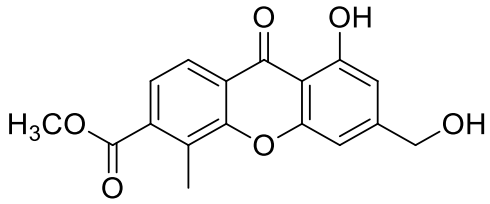
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

Table 3 (continuation)

Structure	Antifungal Activity	Source	Ref.
8-(methoxycarbonyl)-1-hydroxy-9-oxo-9*H*-xanthene-3-carboxylic acid 	*Fusarium oxysporum f.* sp. *cubense* (MIC 39.8 μM)	*Penicillium* sp. (ZZF 32#) isolated from the South China Sea.	(60, 61)
1-hydroxy-6-methyl-8-(hydroxymethyl) xanthone 	*Ustilago violacea* (inhibition zone 2 mm) Method: **(b)**	*Ulocladium botrytis* (strain no. 193A4) was isolated from the marine sponge *Callyspongia vaginalis* collected from Dominica, Caribbean.	(40)
4-chloro-1,5-dihydroxy-3-hydroxymethyl-6-methoxycarbonyl-xanthen-9-one 	*Fusarium graminearum* (MIC107 μM) *Calletotrichum musae* (MIC 214 μM) Method: **(a)**	The culture of the mangrove endophytic fungus *Alternaria sp.* R6 collected from the mangrove in Leizhou peninsula, Guangdong Province, China.	(62)

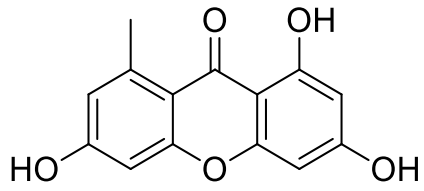
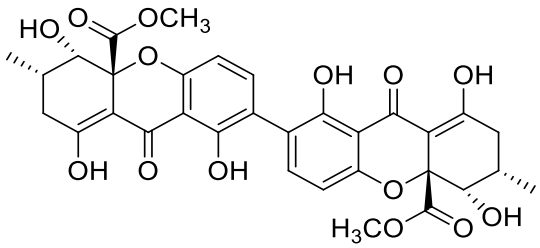
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

Table 3 (continuation)

Structure	Antifungal Activity	Source	Ref.
Emerixanthones D 	*Fusarium sp.*, *Penicillium sp.*, *Aspergillus niger*, *Rhizoctonia solani*, *Fusariumoxy sporium f. sp.* niveum, F*usariumoxy sporium f. sp.* cucumeris, (Diameters of inhibition zones of which were both 3–4 mm) Method: **(b)**	*Emericella sp.* SCSIO 05240 from South China Sea	(47)
Fischexanthone 	*Fusarium graminearum* (MIC 474.68 μM) *Calletotrichum musae* (MIC 474.68 μM) Method: **(a)**	The culture of the mangrove endophytic fungus *Alternaria sp.* R6 collected from the mangrove in Leizhou peninsula, Guangdong Province, China.	(62)

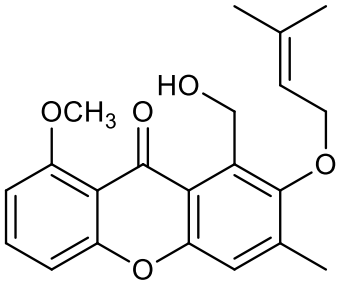
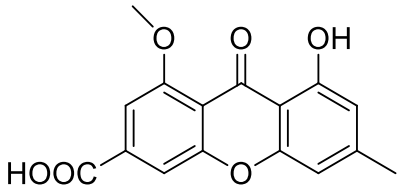
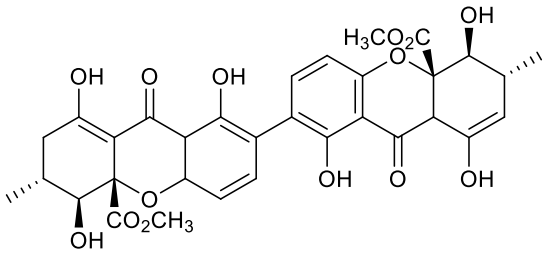
Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

Table 3 (continuation)

Structure	Antifungal Activity	Source	Ref.
Norlichexanthone (3,6,8-trihydroxy-1-methylxanthone) 	*Candida albicans* (ATCC 10231) (MIC 6.25 μg/mL) *Aspergillus niger* (ATCC 13496) (MIC 25.0 μg/mL) *Fusarium oxysporum* f. sp. *cubense* (MIC 50.0 μg/mL) *Eurotium ripens* (1 mm) Method: **(f)** and **(g)**	*P. raistrikii* (obtained from the sponge *Axinella* cf. *corrugate*) or *Talaromyces sp.* ZH-154 from the South-China Sea.and *Wardomyces anomalus*	(41, 50, 51)
Secalonic acid B 	*Microbotryum violaceum* (13 mm) Method: **(b)**	*Blennoria sp.* and *Penicillium sp.* SCSGAF 0023 isolated from South China Sea gorgonian coral *Dichotella gemmacea*	(53, 57)

Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009 (55)

Table 3 (continuation)

Structure	Antifungal Activity	Source	Ref.
Versicone A 	*Colletotrichum cutatum* (MIC 32 μg/mL) *Fusarium Oxysporum* (MIC 128 μg/mL) Method: **(d)**	*Aspergillus versicolor* SCSIO 05879 collected from the Indian Ocean	(63)
Yicathin C 	*C. lagenarium* (11.0mm) Method: **(b)**	*Aspergillus wentii (*red alga *Gymnogongrus flabelliformis*) collected from the coast of Pingtan Island, China	(33)
Secalonic acid A 	*Candida albicans* (ATCC 10231) (MIC 6.25μg/mL), *Aspergillus niger* (ATCC 13496) (MIC 6.25 μg/mL), *Fusarium oxysporum* f. sp. cubense (MIC12.5 μg/mL)	*Talaromyces sp.* ZH-154 from the South-China Sea.	(51)

Methods: **a**) tube dilution, **b**) Agar diffusion assays, **c**) Antimicrobial susceptibility testing standards, **d**) Microdilution method, **e**) Elution techiniques cell grow, **f**) Filter disk, **g**) Kossuga *et al.* 2009(55)

As highlighted in **Table 2** and **Table 3**, some xanthones derivatives have both antibacterial and antifungal activities, being the predominant the antibacterial. Several xanthones derivatives have shown activity against more than one bacteria or fungus species. Most of them show antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and antifungal activity against *Candida albicans* and *Fusarium oxysporum*. Several were isolated from marine microorganisms in a biosynthetic relationship with a macroorganism (sponge or algae).

From the all marine xanthones described in **Table 2** and **Table 3**, two of them, yicathins B and C (**Figure 7**), hold a promising antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Colletotrichum lagenarium* (33). These natural xanthones were isolated from *Aspergillus wentii*, a fungus present in the inner tissue of the marine red alga *Gymnogongrus flabelliformis* (33).

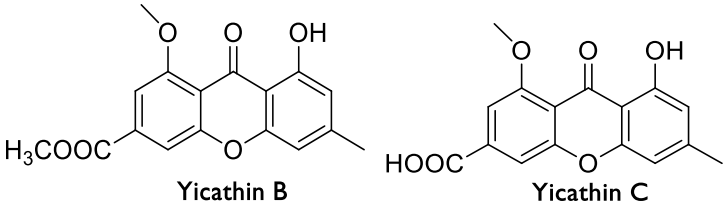


Figure 7 – Yicathins B and C, respectively.

Taking into account their interesting biological activity, yicathins B and C are being studied under the projects PTDC/MAR-BIO/4694/2014 and NORTE-01-0145-FEDER-000035, Research Line NOVELMAR, which devoted particular attention to their total synthesis, to the synthesis of their analogues and to the comprehension and exploration of their biological activity.

1.4. Xanthones

1.4.1. Xanthones: an overview

Xanthones are secondary metabolites commonly present in higher plants, fungi and lichens (39, 64-67). Chemically, xanthones or xanthen-9-ones are *O*-heterocyclic compounds with the dibenzo-γ-pyrone scaffold (**Figure 8**) (64, 65, 67, 68).

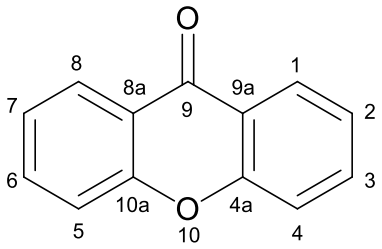


Figure 8 – Xanthone scaffold.

The xanthone scaffold allows a variety of substitution patterns that lead to the diversity of biological/pharmacological activities (68, 69) attributed to this class of secondary metabolites which can be considered as "privileged structures" in Medicinal Chemistry (39).

Depending on the source, xanthones are derived from both shikimate and acetate pathways (66). The biosynthetic pathways of xanthones have been widely discussed by different authors and have been reported in several reviews (39, 65-67). In general, it is proposed that xanthones from fungi and lichens are acetate-derived while xanthones from higher plants are derived from a mixed acetate-shikimate pathways (39, 67, 70).

Xanthones isolated from natural sources can be classified into six groups: simple xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, bisxanthones, and miscellaneous xanthones (66).

The natural biosynthetic pathways do not allow exploring all the possible substitutions on the xanthone scaffold, since it only allows the presence of certain groups in specific positions. This assumes particular relevance in drug discovery, since the imagination and chemical rationality could allow the synthesis of endless structures and to attain a great structural diversity of xanthone scaffold. In fact, the variety of xanthone derivatives that can

be obtained synthetically is huge and several substituents that cannot be found in xanthones of natural origin (epoxide, azole, methylidenebutyrolactone, aminoalcohol, sulfamoyl, methylthiocarboxylic acid, and dihydropyridine, etc) can be considered (65).

1.4.2. Synthesis of xanthones

The biosynthetic pathways can be considered as limiting factor for structural variations in natural xanthones, since it only allows the presence of certain groups in specific positions (64, 68). The use of synthetic methods allows the access to novel xanthonic structures that otherwise could not be reached. Additionally, the use of total synthesis is a way to obtain more quantities of natural xanthones, since these can be extracted from nature only in very limited quantities (64).

Michael and Kostanecki (1883 and 1891) introduced one of the first methods for the synthesis of xanthones, which involved the heating and distillation of a mixture of a phenol, a *o*-hydroxybenzoic acid, and acetic anhydride (**Figure 10**) (68).

Over the years, several methods of the synthesis of xanthones were developed, which can be grouped into three main approaches: i) synthesis of xanthones in one step; ii) synthesis of xanthones via benzophenone; and iii) synthesis of xanthones through a diaryl ether (**Figure 9**). Another important approach that can furnish xanthones with more complex scaffolds is iv) *via* chromen-4-ones (**Figure 9**) (64, 68).

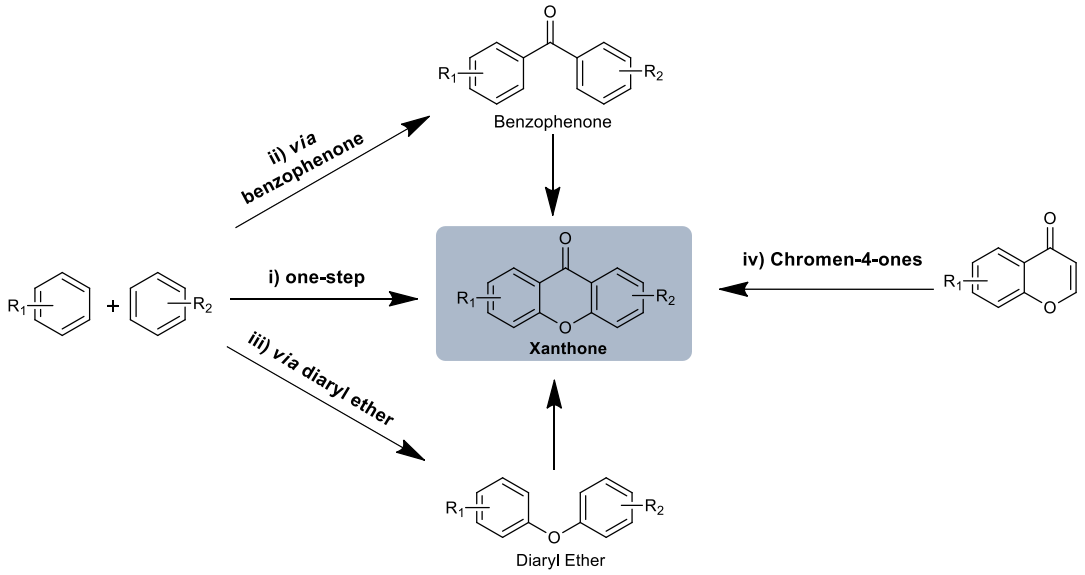
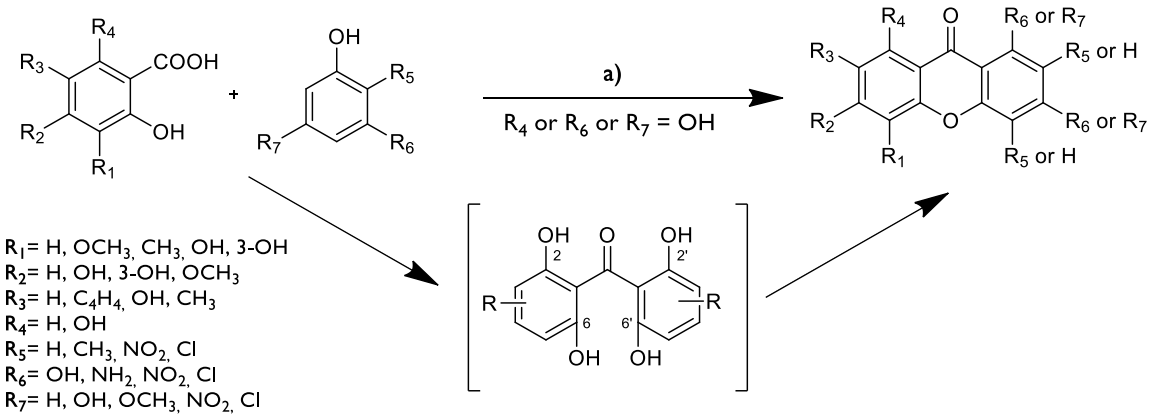


Figure 9 - Schematic representation of three classical methodologies and chromen-4-ones to synthetize the xanthonic scaffold (Adapted from (64)).

The Grover, Shah and Shah (GSS) reaction is the well-known route which leads to the xanthone scaffold in a single step. In this approach, the xanthone is obtained by the reaction of salicylic acids or salicylic esters with polyphenolic compounds, catalyzed by zinc chloride/phosphoryl chloride (64, 68, 71). However, using the same starting materials, other acids catalysts can be used, such as zinc chloride (Nencki reaction), polyphosphoric acid (PPA), and phosphorous pentoxide/methanesulfonic acid (Eaton's reagent) (**Figure 10**) (64). In addition, a recent work described the synthesis of polyoxygenated xanthones in one step catalyzed by other Lewis acids, namely, $AlCl_3$, $TiCl_4$, and $SnCl_2$, under microwave (MW) heating (64, 72). More recently, Genovese et *al.* in 2015 proposed a new method using $Yb(OTf)_3$ hydrate, and also substituted 2-hydroxybenzoic acids and phenols under MW irradiation (**Figure 10**) (73).

Other methods for the one step synthesis of xanthones were also developed and some improvements to these specific methods have also been reported (74-77).



a) acetic anhydride (Michael/Kostanecki), or $ZnCl_2/POCl_3$ (Grover, Shah and Shah), or $ZnCl_2$ (Nencki), or polyphosphoric acid (PPA), or P_2O_5/CH_3SO_3H (Eaton's reagent), or $AlCl_3$, or $TiCl_4$, or $SnCl_2$, or $Yb(OTf)_3$.

Figure 10 - Synthesis of xanthones by the reaction of a salicylic acid derivative with an suitable polyphenolic compound in different conditions (Adapted from (64)).

The development of efficient and selective copper-based catalyst in organic chemistry has been studied as an alternative to other transition metals (78). In fact, the use of copper catalysts has economic and environmental advantages, which is essential in the perspective of green chemistry (78, 79).

A representative example was developed by Hu *et al.*, in 2012. In this new one-step strategy, $CuCl_2$ is used as a catalyst, and phenols and aryl aldehydes react in the presence of

triphenylphosphine by an intermolecular *ortho*-acylation reaction, leading to the desired xanthones (**Figure 11**) (79).

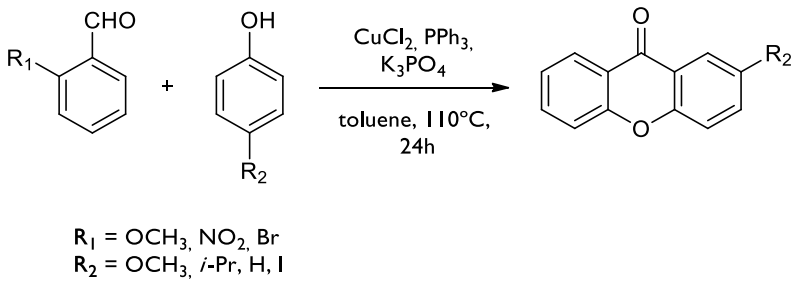


Figure 11 - Synthesis of xanthones by *ortho*-acylation of phenols with different aryl aldehydes (Adapted from (79)).

Menendez *et al.* improved the previous methodology by catalyzing the reaction between *ortho*-substituted benzaldehydes and a wide range of phenol with magnetic nanocatalysts, made of copper nanoparticles (CuNPs) on silica coated maghemite (**Figure 12**) (78). The improvements of this procedure were based on the reduction of reaction times (from 24 to 2h), tolerance to higher functional groups, and absence of a phosphine ligand.

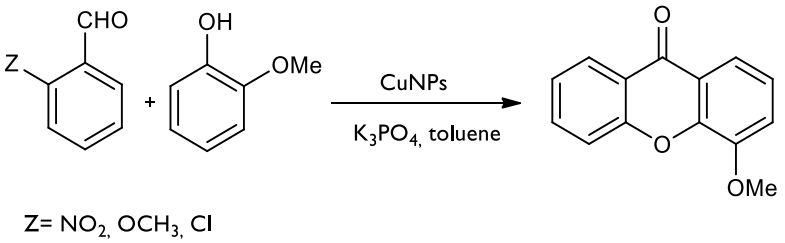


Figure 12 - Synthesis of xanthones by one step reaction between *ortho*-substituted benzaldehydes and phenols, catalyzed by copper nanocatalysts (CuNPs) (Adapted from (78)).

In order to overcome some limitations of the one-step methodologies and to improve the yields, multi-step approaches can be used (64, 68). Among the several strategies, the synthesis *via* benzophenones and *via* diarylethers are the most popular (**Figure 9**). However, the synthesis *via* benzophenone is undeniably the most used due to the high yields generally obtained. This route takes place in two steps, the synthesis of a benzophenone followed by its cyclization to xanthone (**Figure 13**) (64). In **Figure 13** are summarize the principal strategies to synthesize xanthones *via* benzophenones.

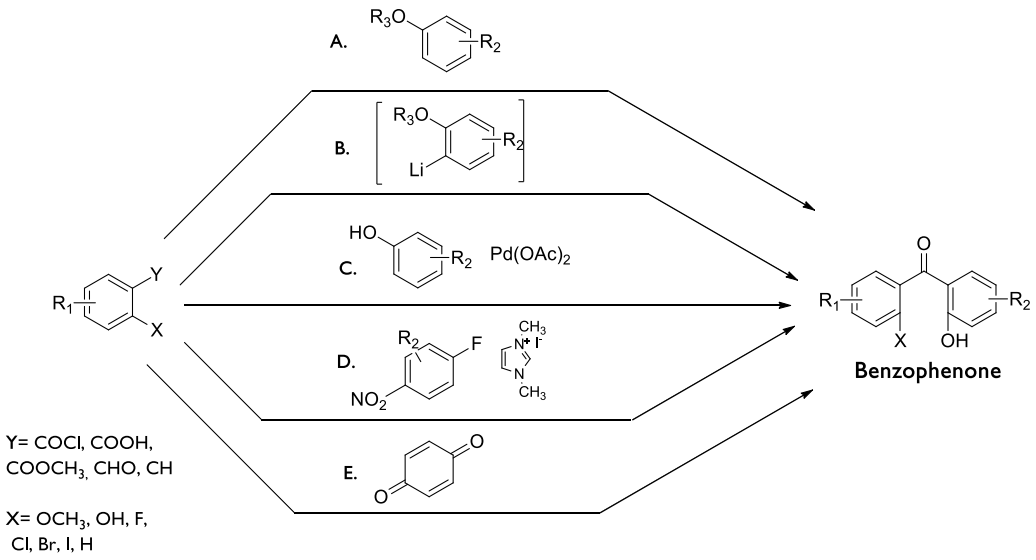


Figure 13 - Synthesis of xanthones through benzophenone route. **A.** Friedel-Crafts acylation; **B.** Addition of an aryllithium intermediate to a benzaldehyde or benzoic acid derivative; **C.** Addition of an arene C-H to nitrile, catalyzed by palladium; **D.** Nucleophilic aroylation catalyzed by imidazolidenyl carbene between benzaldehydes and fluoronitrobenzene derivatives; **E.** photoacylation reaction between a benzaldehyde and a *p*-quinone (Adapted from (64)).

For the synthesis of benzophenones, the most common methodology employed is the Friedel-Crafts acylation of a phenol or a protected phenol-derivative in the presence of an acyl chloride, catalyzed by aluminum chloride (**Figure 14**) (80).

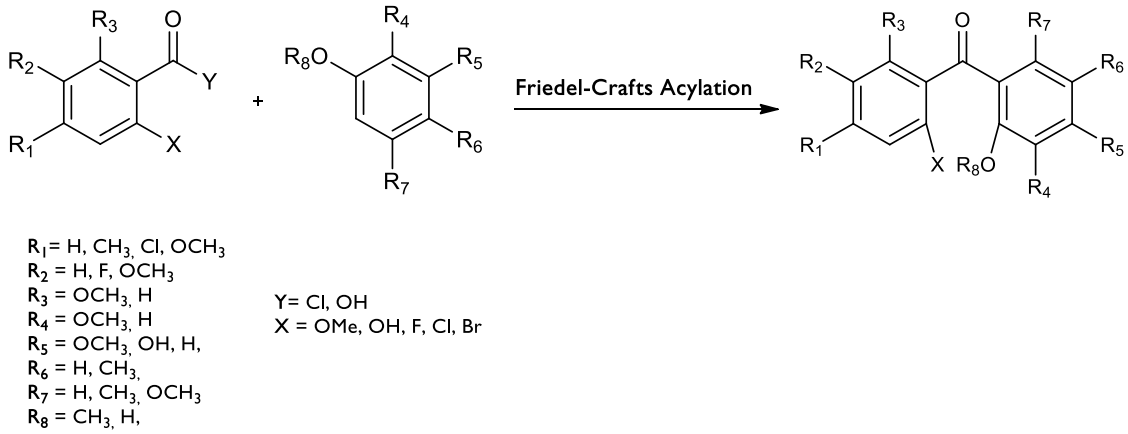


Figure 14 - Synthesis of the benzophenone through a Friedel-Crafts acylation (Adapted from (64)).

Another important strategy to synthetize benzophenones concerns 1,2-nucleophilic addition of an aryllithium intermediate to a carbonyl group. This route always starts with the formation of a strong aryllithium nucleophile, either by a directed *ortho* metalation (D*o*M) or halogen/lithium exchange (64). Then, the aryllithium intermediate nucleophile directly attacks

an ester or acylchloride to give the benzophenone (**Figure 15** (**A**)), or a benzaldehyde, which will give the benzophenone after an extra oxidation step (**Figure 15** (**B**)) (64).

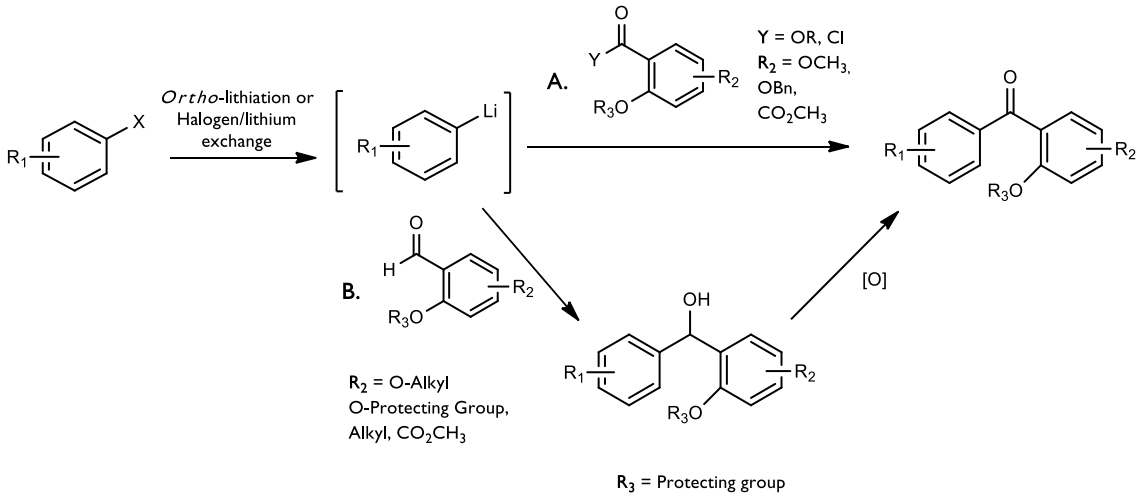


Figure 15 - Synthesis of benzophenones by 1,2-nucleophilic addition of an aryllithium intermediate to a carbonyl group in one (**A**) or two steps (**B**) (Adapted from (64)).

After synthetizing the benzophenone, an ether linkage needs to be formed to give the xanthone nucleus. There are four main alternative reactions: nucleophilic aromatic substitution (S_NAr) (**Figure 16** (**1**)), oxidative coupling (**Figure 16** (**2**)), copper-catalyzed intramolecular *O*-arylation (**Figure 16** (**3**)) and conjugate addition after oxidation of hydroquinone-benzophenones derivatives to quinones (**Figure 16** (**4**)) (64).

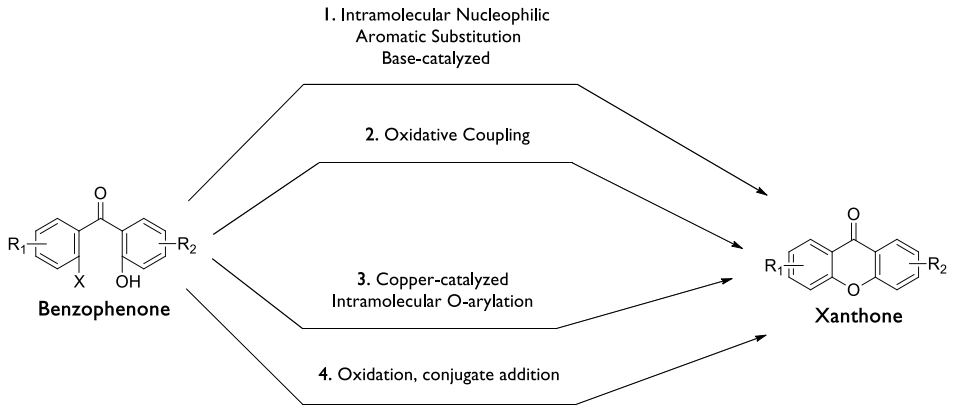


Figure 16 - The main reactions to form an ether linkage needs to give the xanthone nucleus. (Adapted from (64)).

The third classical route to xanthones derivatives uses a diaryl ether as a key intermediate (64, 68). In this case, the ether linkage between the two aromatic rings is the

first synthetic step followed cyclization, to give the desired xanthone scaffold (64). The methodologies to synthetize xanthones *via* diaryl ether and subsequently its cyclization, are summarized in **Figure 17**.

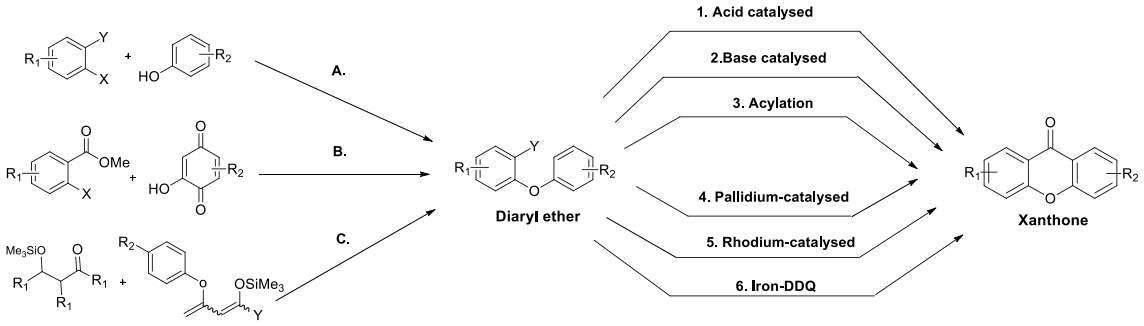


Figure 17 - Synthesis of xanthones *via* diaryl ether. **A.** Ullmann-ether synthesis; **B.** Conjugate substitution between a phenol and a 1,4-halobenzoquinone; **C.** Formal [3+3] cyclocondensation (Adapted from (64)).

The most important approach for the synthesis of diaryl ethers uses an aryl halide and phenol derivatives as building blocks. Often, a copper catalyzed Ullmann-ether synthesis is used for the formation of the ether bond (**Figure 17** (**A**)) (81).

After synthetizing the ether linkage, a carbonyl bridge between the two aryl rings must be formed to obtain the xanthone. The most common methodology to obtain the carbonyl linkage is the acid catalyzed pathway (**Figure 17** (**1**)). However, another five strategies can be applied: base catalyzed (**Figure 17** (**2**)), acylation (**Figure 17** (**3**)), palladium-catalyzed (**Figure 17** (**4**)), rhodium-catalyzed (**Figure 17** (**5**)) and iron-DDQ (**Figure 17** (**6**)) (64).

The three classical strategies to synthetize xanthones that were described use two aryl derivatives as building blocks, and the xanthonic scaffold is then obtained through the formation of either the ether or the ketone linkage (64). However, it possible to synthetize the xanthonic moiety using chromen-4-ones as building blocks, which allows the synthesis of xanthones with more complex substitution patterns. Depending on the substituents at positions 2 and 3 of the chromen-4-ones, different reactions can be used to obtain xanthones (**Figure 18**) (64).

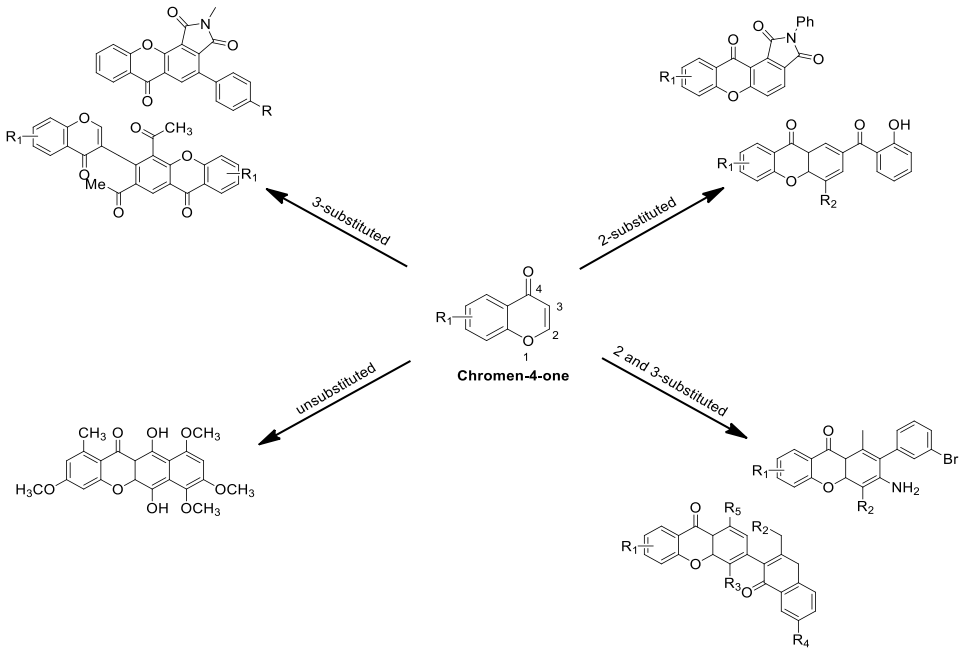


Figure 18 - Some examples of synthesis of xanthones from chromen-4-one as key intermediate (Adapted from (64)).

There are other less common methodologies which should be referred since they could be useful alternatives to classical approaches. More details on the synthesis of xanthones can be found in Azevedo *et al.* (64) and Sousa *et al.* (68).

2. AIMS

2. AIMS

The main goal of this thesis is to contribute towards the total synthesis of the marine derived xanthones yicathins B and C and their analogues. Yicathins B and C were never synthesized. Therefore, our goal is to open a way to their total synthesis, using retrosynthetic analysis and synthesizing important building blocks that could lead to these yicathins.

Different synthetic methodologies were applied, considering the use of convergent reactions and a limited number of steps. All synthetized substances were purified by chromatographic procedures and their structures were elucidated by the usual spectrometric methods.

Based on this, the specific aims of this thesis were:

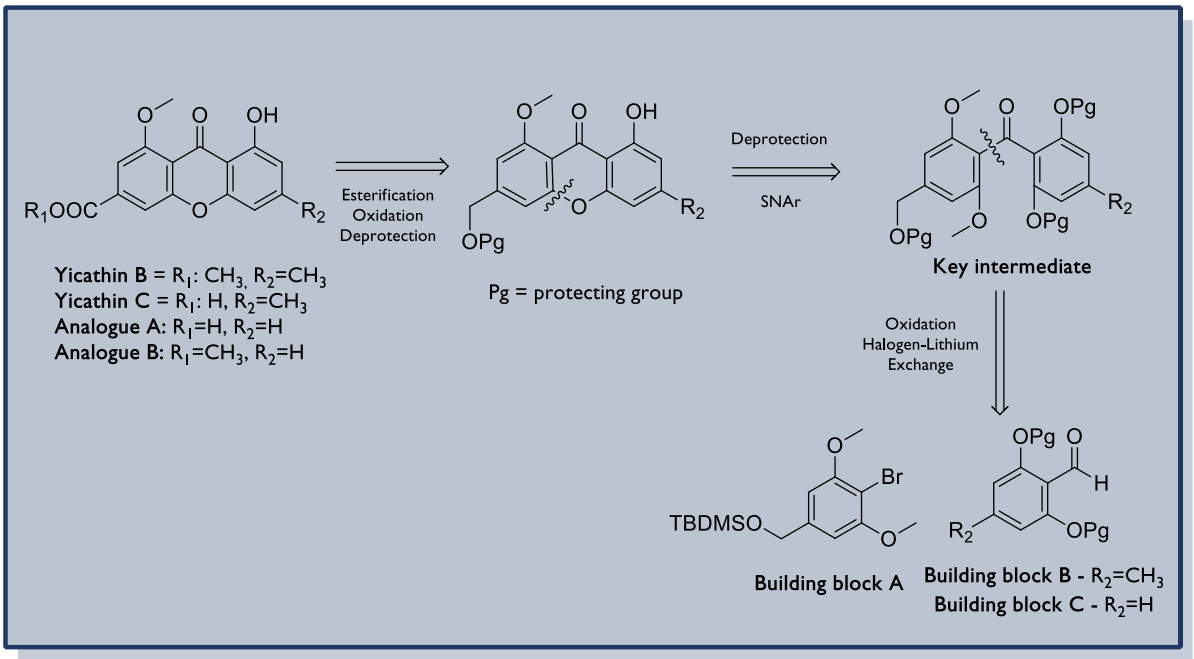
1. To present the retrosynthetic analysis in order to "plan" the total synthesis of yicathins B and C (**Scheme 1**, page 38);
2. To synthesize the building blocks A, B and C (**Scheme 2,** page 40);
3. To synthetize key intermediates for the synthesis of yicathins A and B and analogues A and B, from building blocks A, B and C (**Scheme 1**, page 38 and **Scheme 2**, page 40);
4. To apply different methodologies to the synthesis of xanthones derivatives – "classical" and "non-classical" – in order to achieve, shorter reactions times, more selectivity, lower costs and less environmental damage;
5. To purify and elucidate the structures of the new compounds using chromatographic and spectrometric techniques (FTIR, GC-MS and NMR (^{1}H, ^{13}C, HSQC and HMBC)).

3. RESULTS AND DISCUSSION

3. RESULTS AND DISCUSSION

3.1. Retrosynthesis of Yicathins B and C

The retrosynthetic analysis of yicathins B and C provided a synthetic pathway based on benzophenone key intermediates, which converge from two building blocks: A and B (**Scheme 1**).

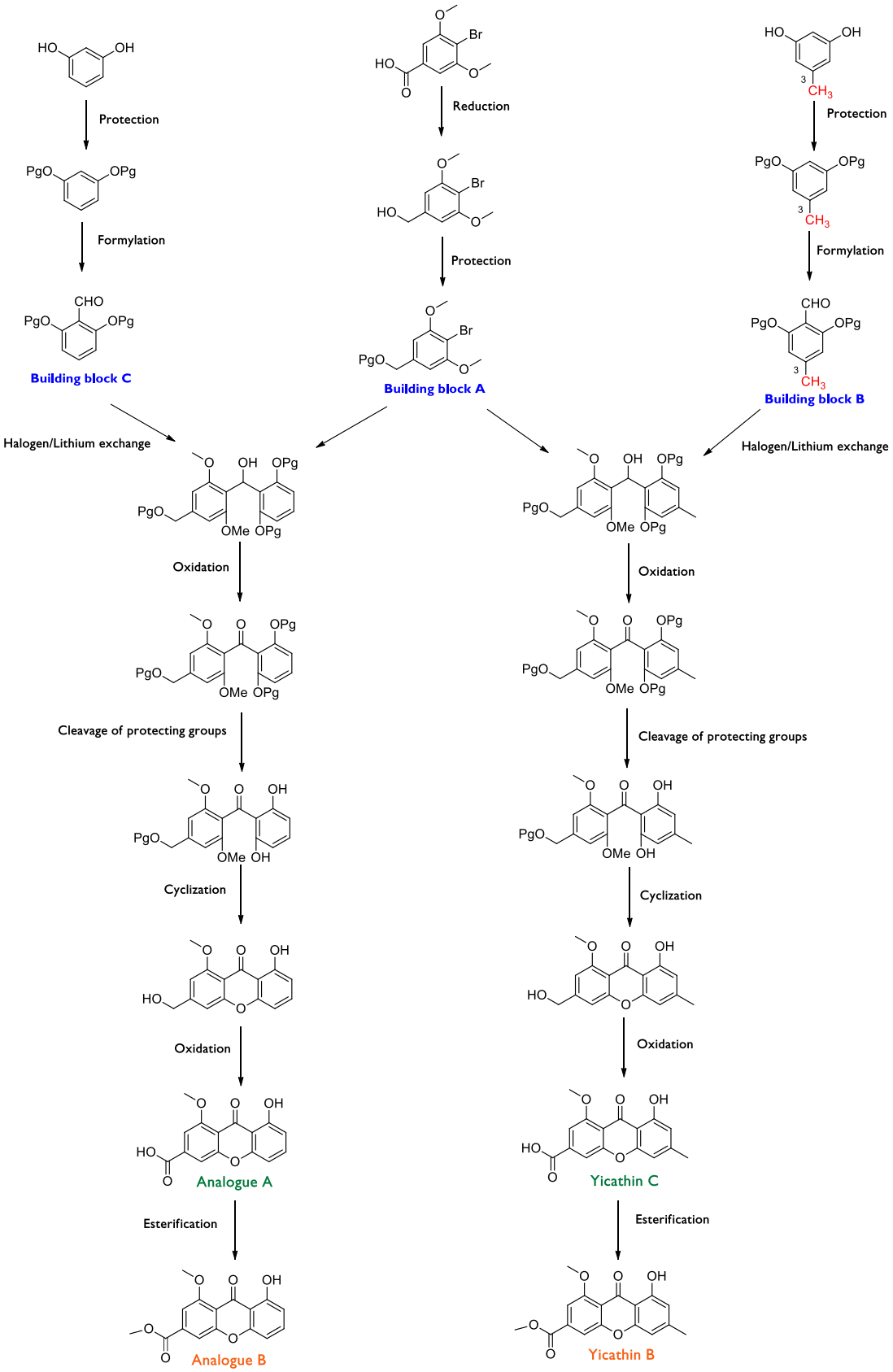


Scheme 1 – Retrosynthetic plan for yicathins B and C and for analogues A and B.

According to the retrosynthetic plan, yicathin C could be obtained in six steps and yicathin B on seven steps (**Scheme 1**). The desired compounds could be synthetized through the benzophenone intermediate using the building blocks A and B. For that propose, the benzophenone could be obtained joining the building blocks by halogen-lithium exchange, followed by an oxidation step. After this, a deprotection and an intramolecular nucleophilic aromatic substitution is needed to obtain the xanthonic nucleus. Yicathin C could be obtained by removing the protecting group and oxidation of the benzylic alcohol. Finally, yicathin B could be synthetized by an esterification of yicathin C (**Scheme 2**).

Analogues A and B differ from yicathins C and B, respectively, because they do not have the C3 methyl group (**Scheme 2**). The synthesis of these analogues can also be proposed by the same retrosynthetic plan (**Scheme 1**). However, in this case, building blocks A and C are required to form the benzophenone key intermediate (**Scheme 2**).

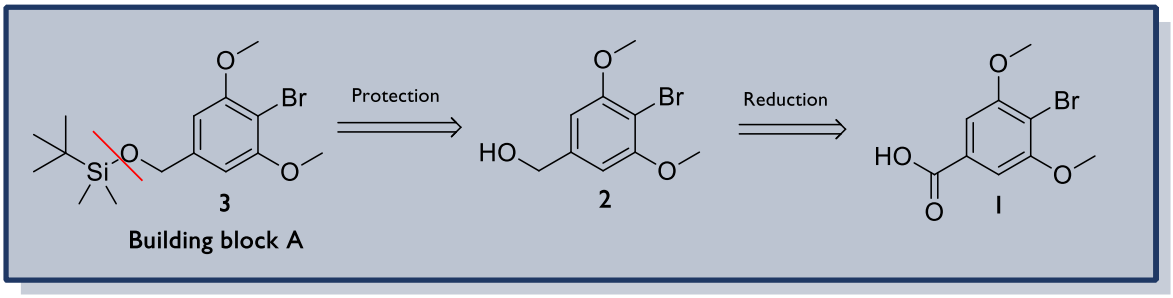
In this chapter, the synthetic strategies used for the synthesis of yicathins B and C, and analogues A and B are described. For better understanding, this chapter will be divided in three sections. The first section includes the synthesis of building block A, the second one include the synthesis of building blocks B and C, and finally, the third section embraces the series of followed steps that lead to the benzophenone key intermediates for the synthesis of yicathins B and C and analogues A and B. The reasons that led to the choice of each specific synthetic route and the experimental data that allowed the structural unequivocal identification of each compound are justified and explained.



Scheme 2 – General synthetic plan for the synthesis of Yicathin B and C as well analogues A and B.

3.2. Synthesis of building block A

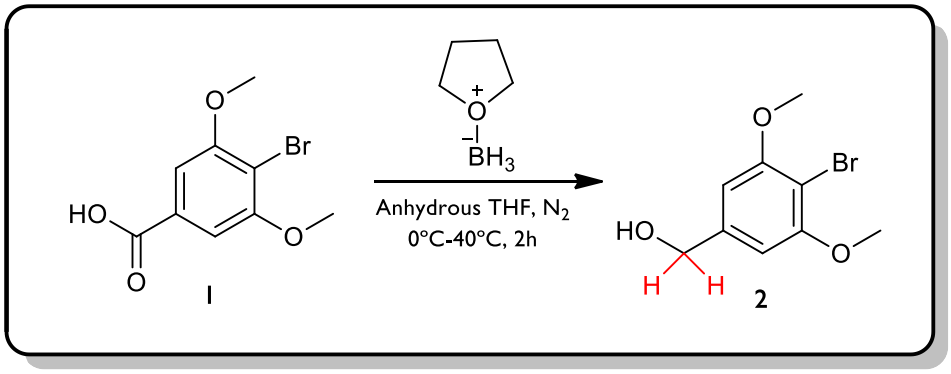
Scheme 3 shows the retrosynthetic plan used to obtain **building block A**. It was proposed that it could be obtained by protecting the hydroxyl group of (4-bromo-3,5-dimethoxyphenyl)methanol (**2**), which could be obtained by reduction of 4-bromo-3,5-dimethoxybenzoic acid (**1**). The *O*-protecting group of compound **2** was necessary to avoid the interference of the hydroxyl group in the group in the followings steps.



Scheme 3 – Retrosynthetic plan for building block A ((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl)dimethylsilane); (**1**) - 4-bromo-3,5-dimethoxybenzoic acid; (**2**) - (4-bromo-3,5-dimethoxyphenyl)methanol.

3.2.1. Synthesis of (4-bromo-3,5-dimethoxyphenyl)methanol (**2**)

Scheme 4 shows the synthesis of (4-bromo-3,5-dimethoxyphenyl)methanol (**2**).



Scheme 4 – Reduction of 4-bromo-3,5-dimethoxybenzoic acid with BH_3:THF.

The first step was the reduction of 4-bromo-3,5-dimethoxybenzoic acid (**1**) to (4-bromo-3,5-dimethoxyphenyl)methanol (**2**).

The reduction of carboxylic acids to the corresponding alcohols can been performed with a variety of metal hydrides and complex metal hydrides, such as $LiAlH_4$, boranes, and combinations of borane-Lewis acids (82).

In particular, borane (BH_3) is an electrophilic reducing agent and its unique properties and high selectivity, make it widely used in reduction of several functional groups (83, 84). Being a pyrophoric gas, borane is normally used as borane-Lewis base complexes, as they are safer and more convenient to handle. Borane-tetrahydrofuran complex (BH_3:THF) is one of the most used in organic synthesis (83, 84).

So, 4-bromo-3,5-dimethoxybenzoic acid was reduced with BH_3:THF in anhydrous THF and nitrogen atmosphere at 40 °C, giving the desired 4(4-bromo-3,5-dimethoxyphenyl) methanol (**2**) in quantitative yield (85, 86).

Compound **2** was identified on the basis of IR, EIMS, ^{1}H NMR, ^{13}C NMR and by HMBC and HSQC and all spectra were in the accordance with the literature (85). The ^{1}H NMR spectrum showed the signals of two methoxyl groups δ_H 3.91 (s, 6H), two methylene protons δ_H 4.64 (s, 2H), two aromatic protons δ_H 6.60 (s, 2H) and the proton corresponding to the hydroxyl group δ_H 3.65 (s, 1H). The ^{13}C NMR spectrum revealed the presence of the two methoxyl carbons δ_C 56.5, six aromatic carbons and one methylene carbon δ_C 65.2. Assignments of these resonances are given in the Experimental Part. The IR spectrum of compound **2** show a large stretching attributed to O-H (3242 cm^{-1}) and the absence of any C=O stretching bands. The EIMS show the typical isotope ratio (approximately 1:1) referent to the bromine atom m/z 248 ($[M+2]^{+\cdot}$) and m/z 246 ($[M]^{+\cdot}$).

The position of the substituents in the compound **2** skeleton was determined on the basis of HSQC and HMBC spectral analysis. In HMBC spectrum of compound **2** the hydrogen bonded to C(1') correlated with carbons C(2) and C(6) (**Figure 19**).

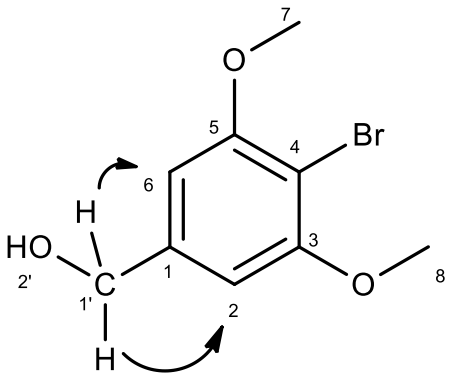
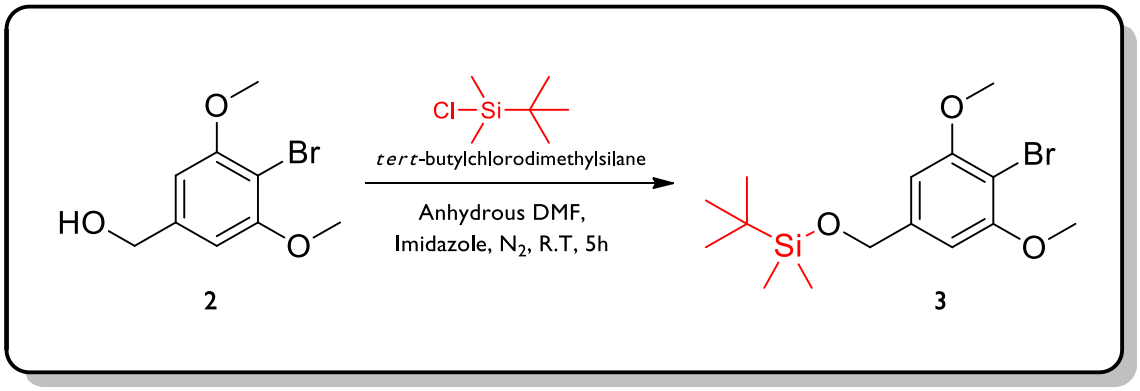


Figure 19 – Main connectivities found in the HMBC spectrum for compound **2**.

3.2.2. Synthesis of ((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl) dimethylsilane (**3**)

Scheme 5 shows the synthesis of ((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl)dimethylsilane (**3**, **building block A**).



Scheme 5 – Protection of hydroxyl group with *tert*-butylchlorodimethylsilane (TBDMSCl).

According to the retrosynthetic plan, an *O*-protecting group must be introduced. This group should be resistant to the basic conditions used in halogen-lithium exchange that will be done further ahead (section **3.4.1**). Among the different protecting strategies applied to protecting primary and secondary alcohols, silylation is one of the most important protecting-group strategies, namely by using *tert*-butylchlorodimethylsilane

(TBDMSCl) (87-89). Venkateswarlu and Corey in 1972 (Corey method) developed a protocol which uses TBDMSCl in DMF and imidazole as base and catalyst (88).

So, 4(4-bromo-3,5-dimethoxyphenyl)methanol (**2**) was treated with TBDMSCl, imidazole in anhydrous DMF for 5 hours at room temperature obtaining the **building block A** with 88 % yield, after purification (90).

Compound **3** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR, HMBC and HSQC data and all spectra were in agreement with the expected (85). The ^{1}H NMR spectrum showed similar profile relatively to the compound **2** for signals of the methoxyl group, the two methylene protons and the two aromatic protons. The introduction of TBDMS was evidenced in ^{1}H NMR by the presence of a *tert*-butyl group δ_H 0.11 (s, 9H) and two geminal methyl groups δ_H 0.95 (s, 6 H). The ^{13}C NMR spectrum showed 15 distinct resonance signals, in agreement with the structure of compound **3**. Assignments of these resonances are given in the Experimental Part.

Relatively to IR spectrum, it was noteworthy the absence of an O-H stretching band and an increase in the number of C-H aliphatic stretching bands (2953 cm^{-1}, 2928 cm^{-1} and 2855 cm^{-1}) when compared with compound **2**. The EIMS of compound **3** show the typical isotope ratio of the bromine in the structure, 362 ([M+2]$^{+\cdot}$) and 360 ([M]$^{+\cdot}$).

The position of the protecting group on compound **3** was determined on the basis of HSQC and HMBC spectral analysis (**Figure 20**). In HMBC spectrum of compound **3** the carbon C(4') correlated with the three methyl groups C(5'), C(6') and C(7'). And the hydrogen bonded to carbon C(1') correlated with carbon C(2) and with carbon C(6).

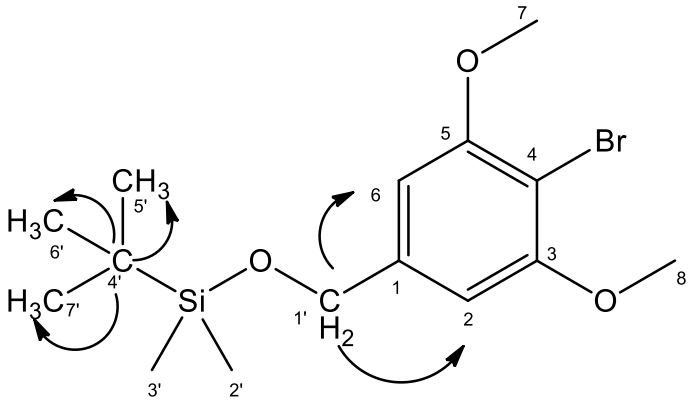
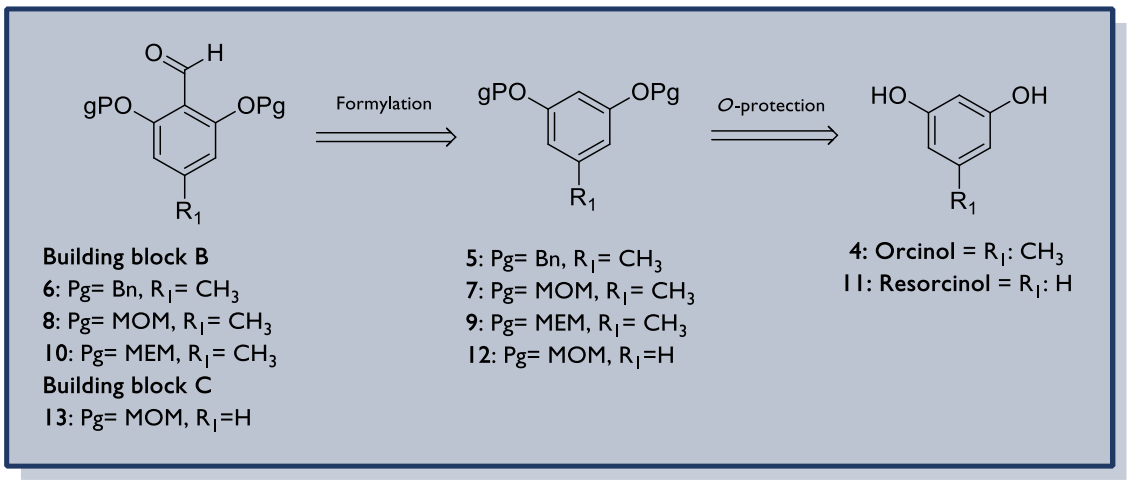


Figure 20 – Main connectivities found in the HMBC spectrum for compound **3**.

3.3. Synthesis of building blocks B and C

Scheme 6 shows the retrosynthetic plan used to obtain **building block B** and **building block C** (an analogue of building block B). Building block B is crucial to obtain yicathins B and C and orcinol was used as starting material to synthesize it. Building block C was designed for synthesis of analogues and resorcinol was used as starting material to synthesize it.

According to the retrosynthetic plan, the building blocks B and C could be obtained by introducing *O*-protecting groups in orcinol and resorcinol, respectively, followed by formylation (**Scheme 6**).



Scheme 6 – Retrosynthetic plan for building block B and building block C.

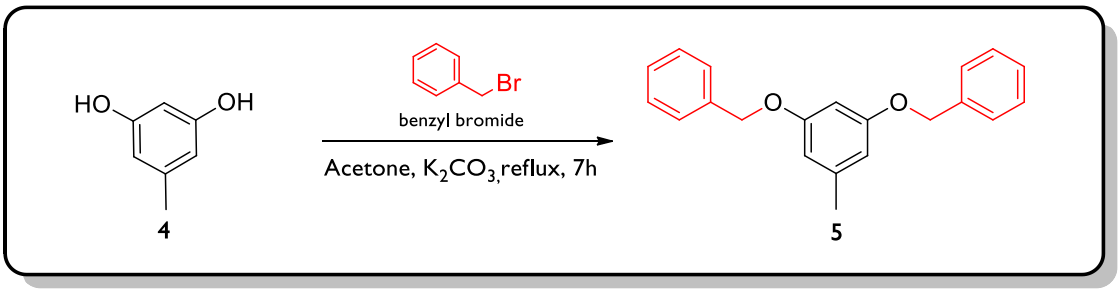
3.3.1. Synthesis of building block B: protection and formylation

3.3.1.1. Synthesis of 2,6-bis(benzyloxy)-4-methylbenzaldehyde (**6**)

According to the proposed retrosynthetic plan, the introduction of an *O*-protecting group in 5-methylbenzene-1,3-diol (orcinol) is crucial to avoid the interference of the hydroxyls groups in formylation (section **3.3.1** and **3.3.2**) and halogen/lithium exchange (section **3.4.1**). For that reason, the protecting group chosen must be resistant to the basic conditions used in both processes.

Several protecting groups of phenols could be used namely, benzyl bromide, methoxymethyl (MOM) and 2-methoxyethoxymethyl (MEM) (87). Since they are resistant under basic conditions and can be easily removed in mild conditions (87).

The protecting reagent firstly chosen was benzyl bromide (**Scheme 7**) (87).



Scheme 7 – Synthesis of (((5-methyl-1,3-phenylene)bis(oxy))bis(methylene)) dibenzene (**5**).

So, orcinol was treated with benzyl bromide in anhydrous acetone in the presence of K_2CO_3, giving the desired ((5-methyl-1,3-phenylene)bis (oxy))bis(methylene))dibenzene (**5**), which was isolated in 82% yield, after purification (**Scheme 7**) (87).

Compound **5** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The introduction of the benzyl group was evidenced in ^{1}H NMR by the presence of two methylene groups δ_H 5.01 (s, 4H) and ten aromatic protons δ_H 7.43-7.25 (m, 10H) in the spectrum and in IR by the absence of any typical broad O-H stretching band spectrum. The ^{13}C NMR spectrum showed 22 distinct resonance signals,

in agreement with the structure. Assignments of these resonances are given in the Experimental Part. Relatively to the EIMS, the compound **5** show, among others, a peak corresponding to the molecular ion of 304 *m/z.*

The relative position of the benzyl protecting groups in compound **5** was confirmed by the correlations found in HMBC spectral analysis. In the HMBC spectrum of compound **5** the hydrogen bonded to C(1') and the hydrogen bonded to C(1") correlated with carbon of C(2) and C(6), respectively (**Figure 21**).

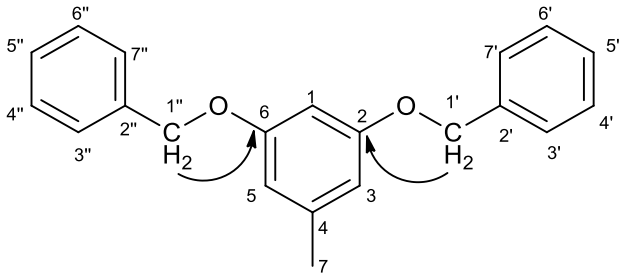
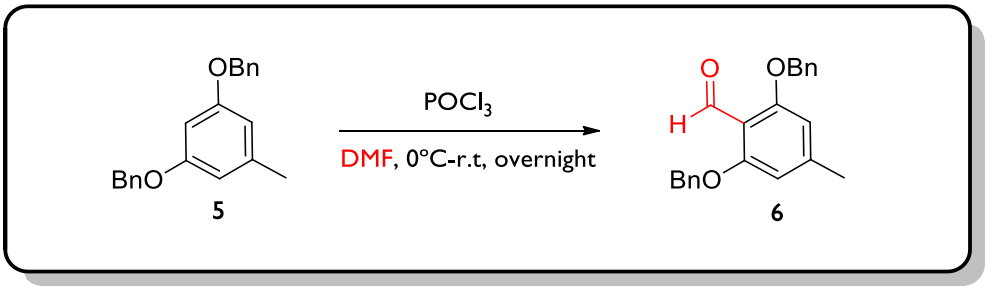


Figure 21 – Main connectivities found in the HMBC spectrum of compound **5**.

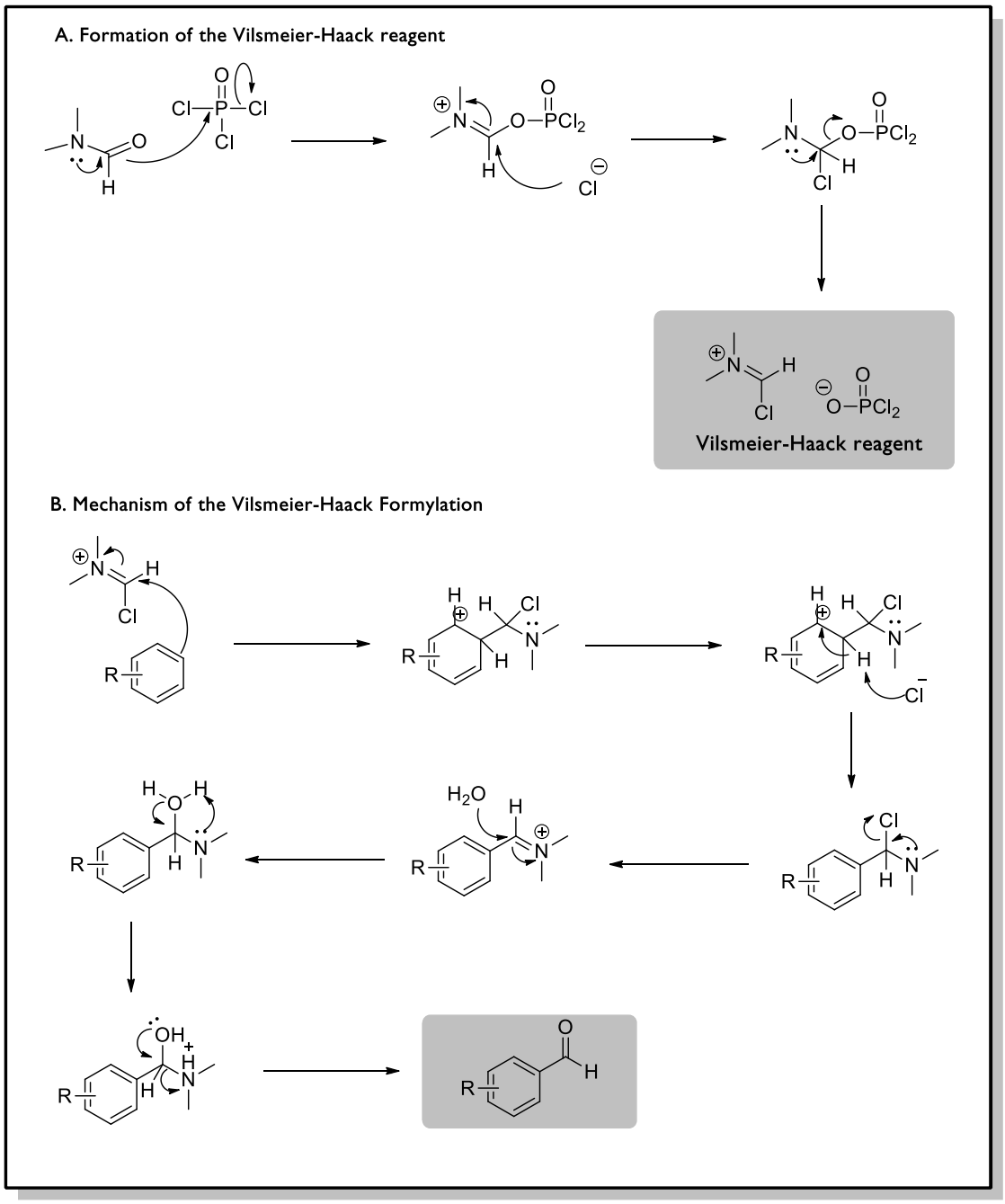
The next step was a Vilsmeier-Haack formylation of compound **5** to give **building block B**: 2,6-bis(benzyloxy)-4-methylbenzaldehyde (**6**) (**Scheme 8**).



Scheme 8 – Synthesis of 2,6-bis(benzyloxy)-4-methylbenzaldehyde (**6**) by a Vilsmeier-Haack reaction.

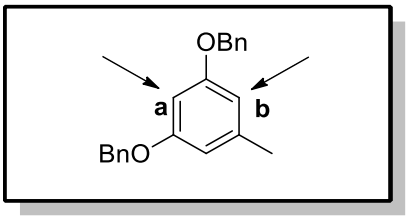
The Vilsmeier-Haack reaction has found many applications in the preparation of several aromatic aldehydes (91, 92). In general, the formylating agent, also known as the Vilsmeyer-Haack reagent, is formed *in situ* when a disubstituted formamide or amide, typically *N,N*-dimethylformamide (DMF) is treated with phosphorous oxychloride

($POCl_3$). Vilsmeyer-Haack reagent reacts with electron rich arene to form an aldehyde after hydrolysis of the α-chloroamine (**Scheme 9**) (92).



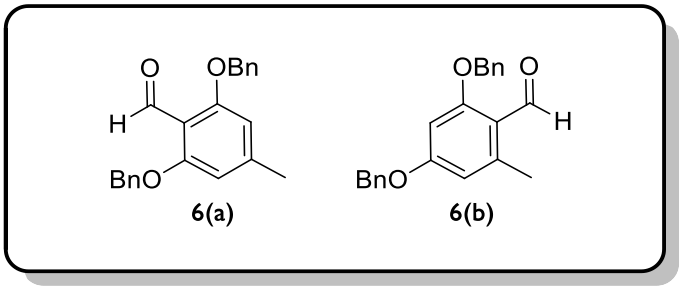
Scheme 9 – Mechanism of the formation of the Vilsmeier–Haack reagent (**A**) and mechanism of the Vilsmeier-Haack formylation (**B**) (Adapted from (93)).

Compound **5** have two possible sites for the formylation (**Scheme 10**). Our aim was to introduce the carbonyl group in the *ortho* position to the two benzyl groups in compound **5** (position **a**). Accordingly to literature, when the alkoxy groups are two methoxyl groups, the major product corresponds to the desired product (position **a**) (94).



Scheme 10 – The two possibilities to introduce the carbonyl group in compound (**5**).

Two products were obtained by the treatment of ((5-methyl-1,3-phenylene)bis(oxy))bis(methylene)) (**5**) with the Vilsmeier–Haack (**Scheme 11**): 22,6-bis(benzyloxy)-4-methylbenzaldehyde (**6**(**a**)) and 2,4-bis(benzyloxy)-6-methyl benzaldehyde (**6**(**b**)).



Scheme 11 – The two formylation products obtained from Vilsmeier–Haack reaction: 2,6-bis(benzyloxy)-4-methylbenzaldehyde (**6**(**a**)) and 2,4-bis(benzyloxy)-6-methylbenzaldehyde (**6**(**b**)).

However, the obtained major product was the unwanted compound **6**(**b**) (92%). The obtained yield for the wanted aldehyde was only 8. And we hypothesize that the huge difference in yields was due to steric hindrance promoted by the benzyl groups.

The compound **6**(**a**) was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The introduction of the carbonyl group could be evidenced in the ^{1}H NMR spectrum by the presence of the aldehyde proton δ_H 10.6 (s, 1H) and also in the ^{13}C

NMR by the presence of the typical aldehyde carbonyl carbon absorption δ_C 188.7. Assignments of these resonances are given in the Experimental Part. In the IR spectra it was present a strong C=O stretching band at 1687 cm^{-1}. Relatively to the EIMS, the compound **6**(**a**) show a peak corresponding to the molecular ion of 332 *m/z.*

The relative position of the carbonyl group in compound **6**(**a**) was confirmed by the correlations found in HMBC spectral analysis The hydrogen bonded to C(8) correlated with carbons C(2) and C(6) (**Figure 22**).

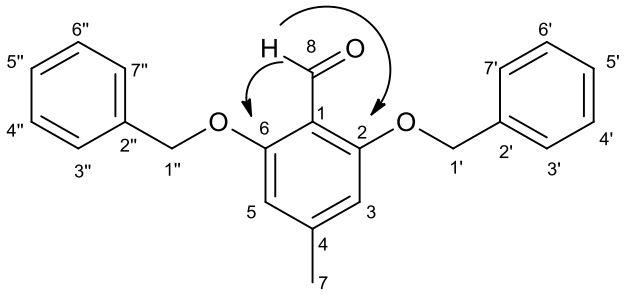


Figure 22 – Main connectivities found in the HMBC spectrum of compound **6**(**a**).

The compound 6(**b**) was characterized by IR, EIMS, ^1H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The introduction of the carbonyl group could be also evidenced in the ^1H NMR by the presence of the aldehyde proton δ_H 10.6 (s, 1H) and also in the ^{13}C NMR by the presence of the one carbonyl carbon δ_C 190.6. Assignments of these resonances are given in the Experimental Part. In IR spectra it was also present a strong C=O stretching band at 1680 cm^{-1}. Like to the compound **6**(**a**), the EIMS of compound **6**(**b**) show, among others, a peak corresponding to molecular ion of 332 *m/z.*

The position of the carbonyl group in compound **6**(**b**) was confirmed by the correlations found in HMBC spectral analysis. In HMBC spectrum of compound **6**(**b**) the hydrogen bonded to C(8) correlated with carbon C(4) (**Figure 23**).

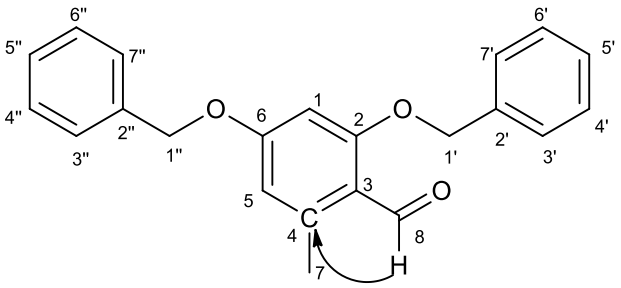
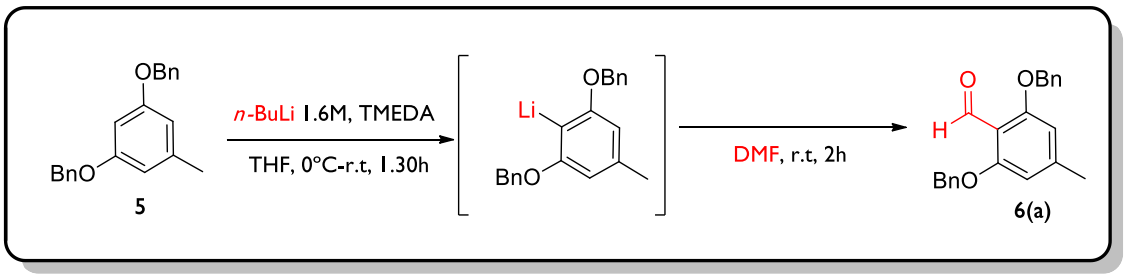


Figure 23 – Main connectivities found in the HMBC spectrum of compound **6(b)**.

Since the previously described Vilsmeier–Haack formylation did not furnish the expected results, an alternative route was explored: the directed *ortho*-metalation (D*o*M) to synthetize the desired 2,6-bis(benzyloxy)-4-methylbenzaldehyde **6(a)** (**Scheme 12**).



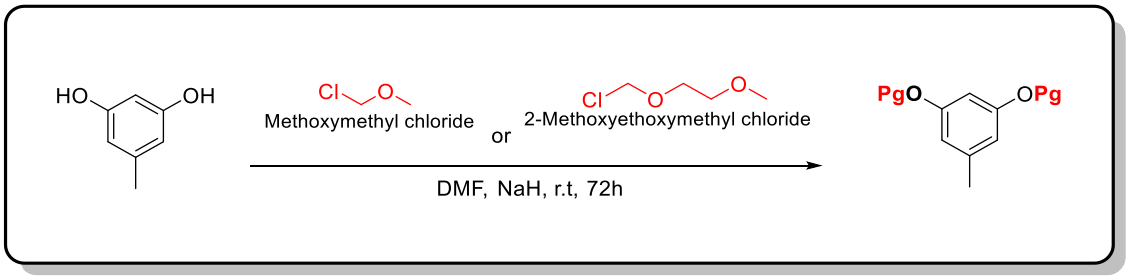
Scheme 12 – Synthesis of 2,6-bis(benzyloxy)-4-methylbenzaldehyde (**6(a)**) by directed *ortho*-metalation.

However, the desired benzaldehyde was not obtained. This could be rationalized by the high acidity of the benzyl hydrogens, which can be competitively deprotonated by *n*-BuLi, causing the formation of unexpected by-products and low quantities of the desired compound (95).

Since the quantity obtained by the Vilsmeier–Haack reaction was very low and D*o*M was not possible, another strategy was followed using different protecting groups: MOMCl and MEMCl. MOM and MEM are common protecting group for phenols (87). In addition, MOM is also known to be a good directed metalating group in D*o*M reactions (96-98).

3.3.1.2. Synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene (**8**) and 2,6-bis((2-methoxyethoxy)methoxy)-4-methylbenzaldehyde (**10**)

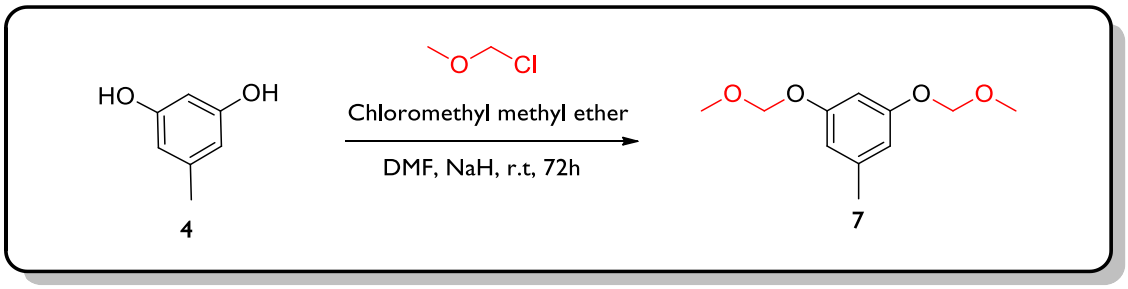
Scheme 13 shows the use of the two different protecting reagents: MEMCl and MOMCl, both using the same approach. The MEM and MOM ethers are similar in their stability, namely in the basic conditions needed in the D*o*M reaction (87).



Scheme 13 – Two different groups to protected hydroxyls group of orcinol.

Method A: MOMCl

The **Scheme 14** shows the synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**) using the MOMCl as protecting group.



Scheme 14 – Synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**).

Orcinol was treated with MOM in anhydrous DMF, in the presence of NaH, giving the desired 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**), which was isolated in 91% yield after purification (**Scheme 14**) (99).

Compound **7** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR, HMBC and HSQC and data were in the accordance with the expected (99). HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The introduction of the MOM group was elucidated by the presence of two methoxyl groups δ_H 3.47 (s, 6H) and two methylene groups δ_H 5.01 (s, 4H) in the ^{1}H NMR spectrum and by the absence of any broad O-H stretching band in the IR spectrum. The ^{13}C NMR spectrum showed the two carbons of methoxyl groups δ_C 55.9 and the two carbons of methylene groups δ_C 94.4 referent to the methoxymethyl ether. Assignments of these resonances are given in the Experimental Part. The EIMS spectrum of compound **7** show, among others, a peak corresponding to molecular ion of 212 *m/z*.

The position of the methoxymethyl ether in compound **7** was confirmed by the correlations found in HMBC spectral analysis (**Figure 24**). In HMBC spectrum of compound **7** the hydrogen bonded to C(1') and C(1") correlated with carbon C(2) and C(6), respectively.

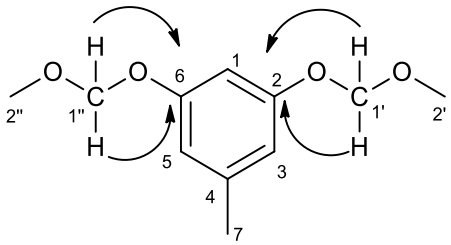
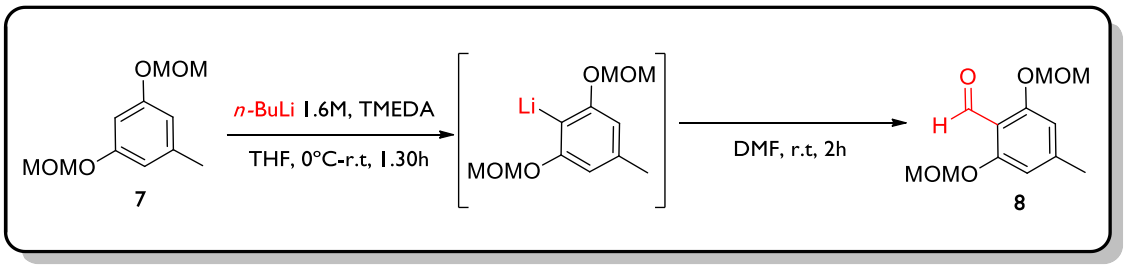


Figure 24 – Main connectivities found in the HMBC spectrum of compound **7**.

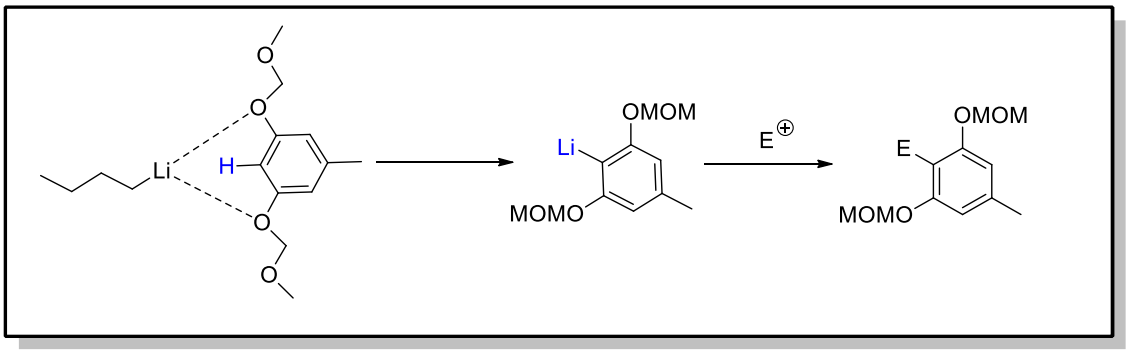
The following step was the directed *ortho* metalation (D*o*M) in order to synthesize the 2,6-bis(methoxymethoxy)-4-methylbenzaldehyde (**8**) (**Scheme 15**).



Scheme 15 – Synthesis of 2,6-bis(methoxymethoxy)-4-methylbenzaldehyde (**8**) by D*o*M.

The D*o*M reaction comprises the deprotonation of a site *ortho* to a heteroatom-containing a directed metalation group (DMG) by a strong base, usually an alkylithium reagent. The DMG enables the coordination of its heteroatom with the lithium, leading to an *ortho*-lihiated-species intermediate, which reacts with an electrophile producing selectively the corresponding *ortho*-substituted product (**Scheme 16**) (96, 100).

The reaction requires a good DMG, which is important to be able to coordinate to the lithium (100). MOM ether is a DMG which promotes the D*o*M with substantial selectivity (98). Compound **7** have two MOM groups, in *meta* positions to each other, so the lithiated intermediate should be formed easily and regioselectively (**Scheme 16**).



Scheme 16 – The Directed *ortho*-lithiation reaction.

The most common alkyllithium base is *n*-BuLi (101). This alkyl lithium exists as various aggregates in solution depending of the solvent used. In case of THF, *n*-BuLi exists in a mixture of dimeric and tetrameric structures (96, 101, 102). The use of amine additives, in particular TMEDA, allows the breakup of these aggregates, improving *n*-BuLi reactivity (96, 102).

Given that the lithiated intermediate is extremely reactive, the lithiation was performed at low temperatures and in inert atmosphere (96). So, into a flask containing 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**) in anhydrous THF and anhydrous TMEDA, *n*-BuLi was added dropwise (99). Once the lithiaded intermediate was formed, anhydrous DMF was added to the solution. The target benzaldehyde (**8**) was obtained in 79% yield, after purification.

Compound **8** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR, HMBC and HSQC and data were in the accordance with the expected (99). HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The ^{1}H NMR spectrum showed similar profile relatively to its precursor, compound **7**, revealing the signals corresponding to the methoxymethyl ether groups and the two aromatic protons. The introduction of the carbonyl was also evidenced in the ^{1}H NMR spectrum by the presence of the typical aldehyde proton signal δ_H 10.5 (s, 1H) and in the ^{13}C NMR spectrum by the presence of the carbonyl carbon signal δ_C 188.8. Assignments of these resonances are given in the Experimental Part.

The IR spectrum shows a strong C=O stretching band at 1681cm^{-1} supporting the presence of the aldehyde carbonyl group. The EIMS spectrum of compound **8** shows a peak corresponding to the molecular ion 240 *m/z*.

The position of the carbonyl group in compound **8** was confirmed by the correlations found in HMBC spectral analysis (**Figure 25**). In HMBC spectrum of compound **8**, the hydrogen bonded to carbon C(8) correlated with carbon C(2) and with carbon C(6).

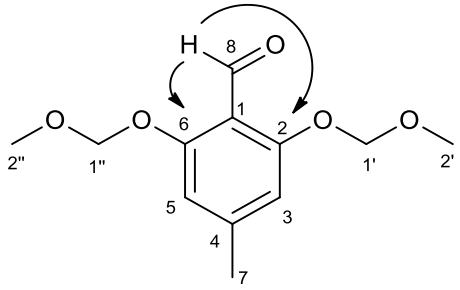
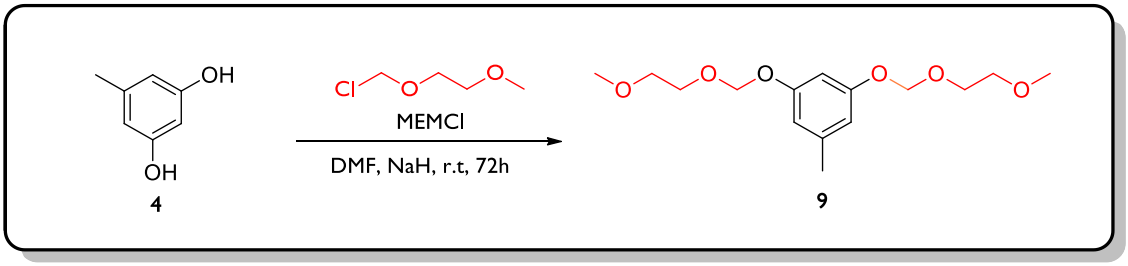


Figure 25 – Main connectivities found in the HMBC spectrum of compound **8**.

Method B: MEMCl

Scheme 17 shows the synthesis of 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**) using MEM as protecting group.



Scheme 17 – Synthesis of 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**).

The 2-methoxyethylmethyl (MEM) group can be introduced by the same way of that methoxymethyl group (MOM) was introduced (87, 103). In this case, orcinol was treated with MEMCl in anhydrous DMF, in the presence of NaH, giving the desired 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**), which was isolated in 93% yield after purification (87).

Compound **9** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The introduction of MEM was evidenced in ^{1}H NMR and ^{13}C NMR by the presence of two methoxyl groups (δ_H 3.37 s and δ_C 58.9) and six methylene groups (δ_H 3.57-3.54 m and δ_C 71.6; δ_H 3.82-3.79 m and δ_C 67.6; δ_H 5.22 s and δ_C 93.4) (**Figure 26**). Assignments of these resonances are given in the Experimental Part.

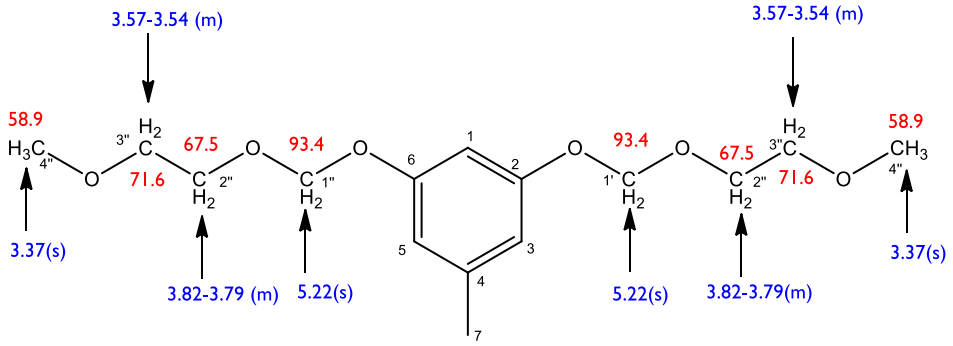


Figure 26 – Assignments of ^{1}H NMR (blue) and ^{13}C NMR (red) of MEM groups.

The IR spectrum shows the absence of any broad O-H stretching band, present in the precursor. The EIMS of compound **9** show a peak corresponding to the molecular ion 300 *m/z*.

The position of the protecting group in compound **9** was confirmed by the correlations found in HMBC spectral analysis (**Figure 27**). In HMBC spectrum of compound **9** hydrogens bonded to carbon C(1') and C(1") correlated with carbon C(2) and with carbon C(6).

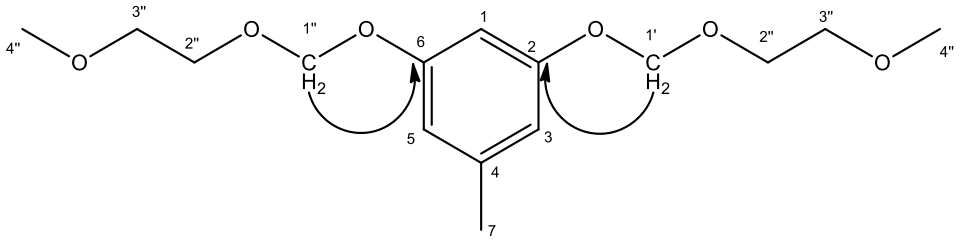
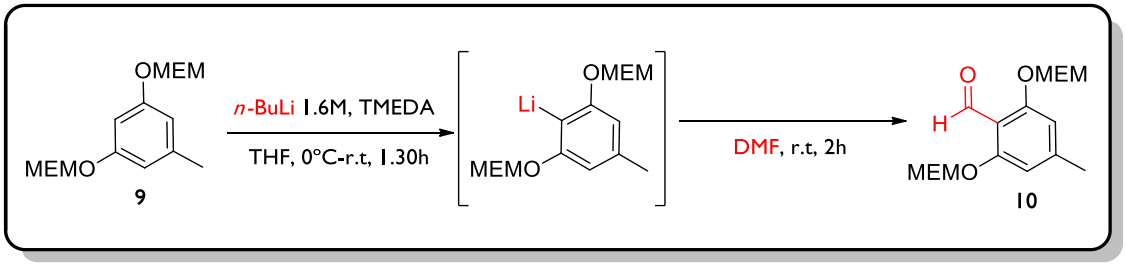


Figure 27 – Main connectivities found in the HMBC spectrum of compound **9**.

Scheme 18 shows the synthesis of 2,6-bis((2-methoxyethoxy)methoxy)-4-methylbenzaldehyde (**10**) using a D*o*M, as it was done for the synthesis of compound **8**. However, since it shares a great structural similarity with the MOM group, it is excepted that MEM group could allow the coordination with lithium promoting the D*o*M of 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**), yielding 2,6-bis(methoxymethoxy)-4-methylbenzaldehyde (**10**).



Scheme 18 – Synthesis of 2,6-bis((2-methoxyethoxy)methoxy)-4-methylbenzaldehyde (**10**) by D*o*M.

The procedures used in this step were the same as with MOM. Into a flask containing 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**) in anhydrous THF and anhydrous TMEDA, *n*-BuLi was added dropwise (99). Once the lithiaded

intermediate was formed, anhydrous DMF was added to the solution. The desired benzaldehyde (**10**) was obtained in 45% yield, after purification.

Compound **10** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The ^{1}H NMR spectrum showed a similar profile relatively to the compound **9** for signals of the common protecting group MEM and the aromatic protons. The introduction of a carbonyl group was evidenced by the presence of the aldehyde proton δ_H 10.4 (s, 1H) in ^{1}H NMR spectrum and by one carbonyl carbon δ_C 188.6 in the ^{13}C NMR spectrum. Assignments of these resonances are given in the Experimental Part.

Relatively to IR spectrum, it showed a strong C=O stretching band at 1680 cm^{-1}, also denoting the presence of the carbonyl. The EIMS spectrum of compound **10** shows a peak corresponding to the molecular ion 328 *m/z*.

The position of the carbonyl group in compound **10** was confirmed by the correlations found in HMBC spectral analysis (**Figure 28**). In HMBC spectrum of compound **10** the hydrogen at C(8) correlated with carbon C(2) and with carbon C(6).

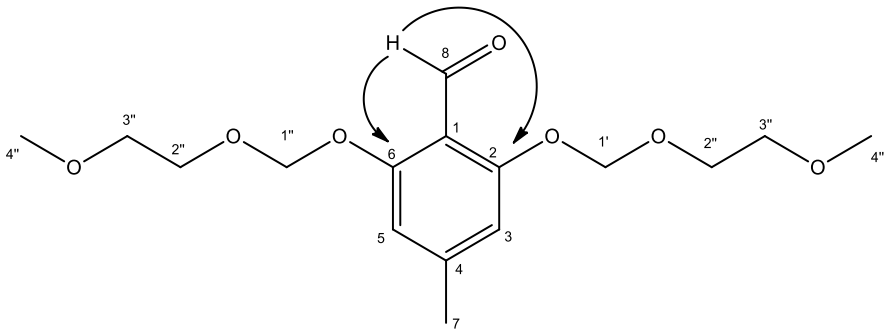


Figure 28 - Main connectivities found in the HMBC spectrum of compound **10**.

Benzaldehydes **8** and **10** only differ in the protecting groups. Benzaldehyde **8** was prepared using MOM protection, while benzaldehyde **10** was prepared using MEM protection. In the case of MOM, the major product is the target benzaldehyde (**8**), while with MEM, two products were obtained: the target benzaldehyde (**10**) and the benzaldehyde formylated between OMEM and the methyl groups, almost in the same proportion (55% vs 45%). This might be explained by the larger molecular size of MEM. In fact, the steric hindrance promoted by the presence of two MEM group could difficult

the formation of the lithium intermediate at the position surrounded by two MEM groups (**Figure 29**).

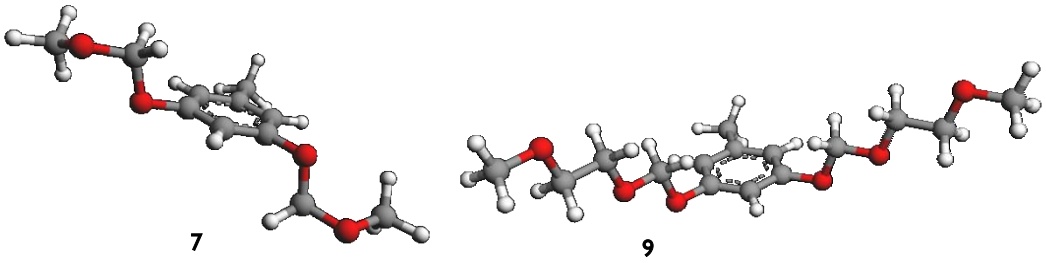


Figure 29 - 3D structure representation of 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**) and 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**).

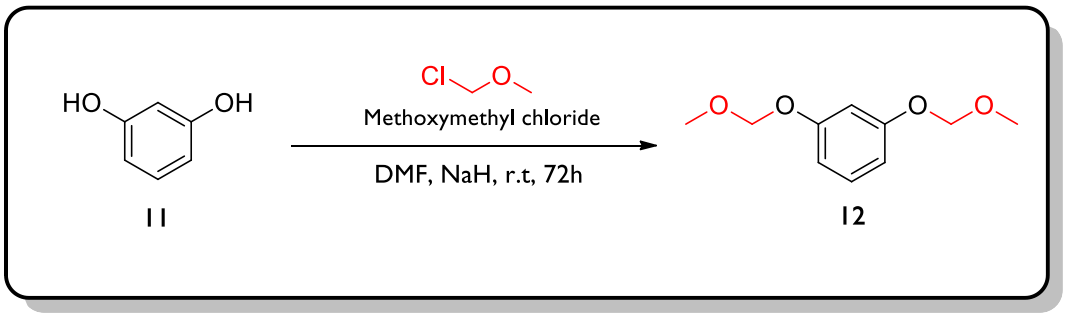
3.3.2. Synthesis of building block C

Resorcinol was chosen as starting material to synthetize the **building block C**, which will lead to analogues A and B. The same synthetic plan as with orcinol was applied in this case (**Scheme 6**).

3.3.2.1. Synthesis 2,6-bis(methoxymethoxy)benzaldehyde (**13**)

The first step is the *O*-protection of resorcinol (section **3.4.1**). Taking into account the results previously discussed, only MOM was used as resorcinol protecting group.

Scheme 19 shows the synthesis of 1,3-bis(methoxymethoxy)benzene (**12**).



Scheme 19 - Synthesis of 1,3-bis(methoxymethoxy)benzene (**12**).

Resorcinol (**11**) was treated with MOM in anhydrous DMF, in the presence of NaH, giving the desired 1,3-bis(methoxymethoxy)benzene (**12**), which was isolated in 95% yield, after purification (99).

Compound **12** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The introduction of the methoxymethyl group was established by the presence of two methoxyl groups (δ_H 3.48 (s, 6H) and δ_C 56.0) and two methylene groups (δ_H 5.16 (s ,4H) and δ_C 94.5) in the ^{1}H NMR and ^{13}C NMR spectra. Assignments of these resonances are given in the Experimental Part. In the IR spectrum, the introduction of MOM was confirmed by the absence of any broad O-H stretching band.

Relatively to the EIMS spectrum, compound **12** shows a peak corresponding to the molecular ion 198 *m/z*.

The position of the methoxymethyl ether in compound **12** was confirmed by the correlations found in HMBC spectral analysis (**Figure 30**). In HMBC spectrum of compound **12** the hydrogens bonded to C(1') and C(1'') correlated with carbon C(2) and C(6), respectively.

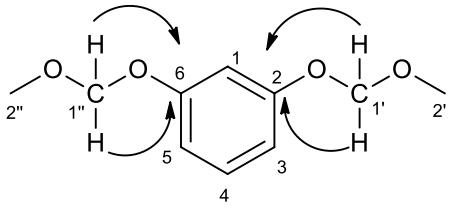
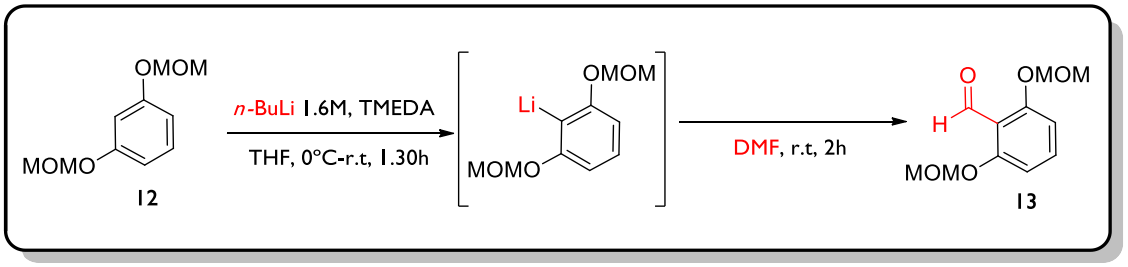


Figure 30 - Main connectivities found in the HMBC for compound **12**.

Scheme 20 shows the synthesis of 2,6-bis(methoxymethoxy)benzaldehyde (**13**).



Scheme 20- Synthesis of 2,6-bis(methoxymethoxy)benzaldehyde (**13**).

This step consists in the synthesis of benzaldehyde (**13**) by directed *ortho* metalation (D*o*M) of compound **12**. Into a flask containing 1,3-bis(methoxymethoxy)benzene (**12**) in anhydrous THF and anhydrous TMEDA, *n*-BuLi was added dropwise (99). Once the lithiaded intermediate was formed, anhydrous DMF was added to solution. The desired benzaldehyde (**13**) was obtained in 85% yield, after purification.

Compound **13** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The ^{1}H NMR spectrum showed a similar profile relatively to compound **12** for signals corresponding to the common parts, such as the methoxymethyl ether groups and the aromatic protons. The introduction of the carbonyl was established in ^{1}H NMR

by the presence of the aldehyde proton signal δ_H 10.54 (s, 1H). In the ^{13}C NMR spectrum, the carbonyl could be demonstrated by the presence of one carbonyl carbon signal δ_C 189.3. Assignments of these resonances are given in the Experimental Part. Also in the IR spectrum it could be evidenced the presence of a strong C=O stretching band at 1680 cm^{-1} confirming the presence of the carbonyl group. The EIMS of compound **13** shows a peak corresponding to the molecular ion 226 *m/z*.

The position of the carbonyl group in compound **13** was confirmed by the correlations found in HMBC spectral analysis (**Figure 31**). In HMBC spectrum of compound **13**, hydrogen at C(8) correlated with carbon C(2) and with carbon C(6).

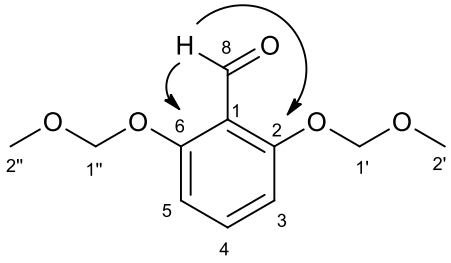
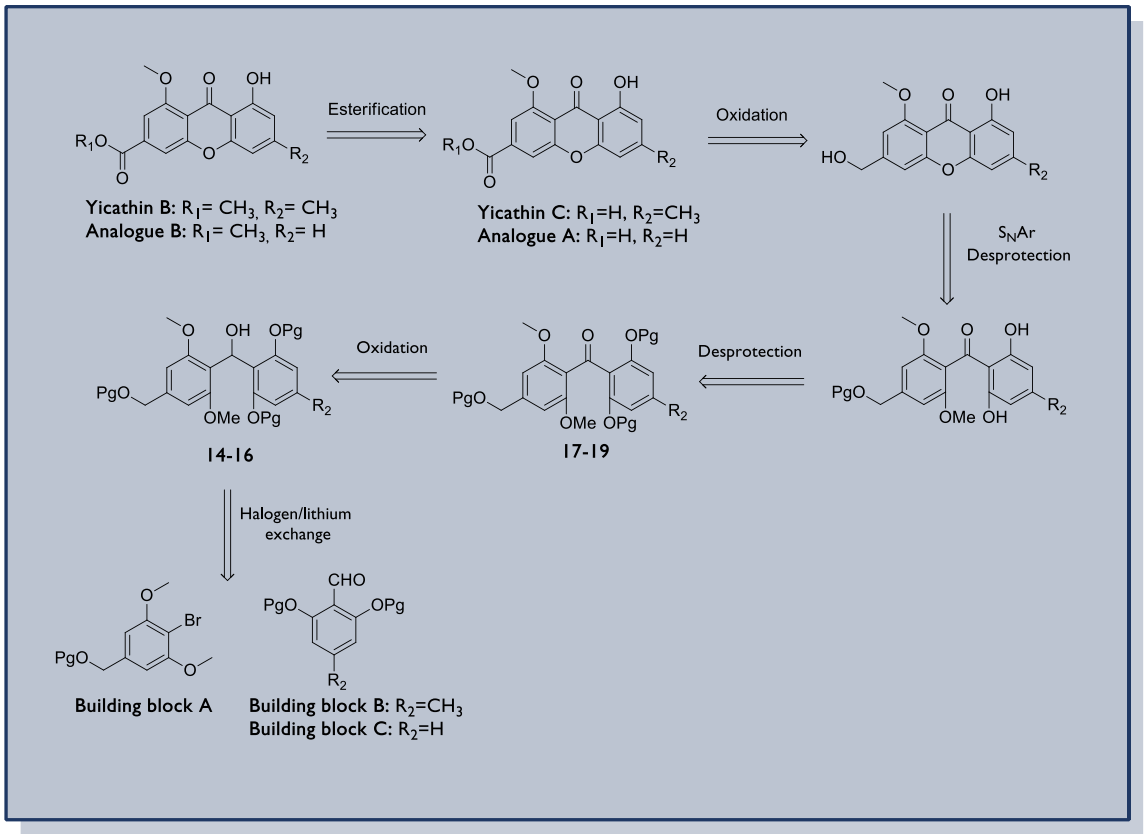


Figure 31 - Main connectivities found in the HMBC spectrum of compound **13.**

3.4. Synthesis of Yicathin B and C and analogues

Scheme 21 shows the retrosynthetic plan to obtain the marine xanthones – yicathin B and C - and their analogues.

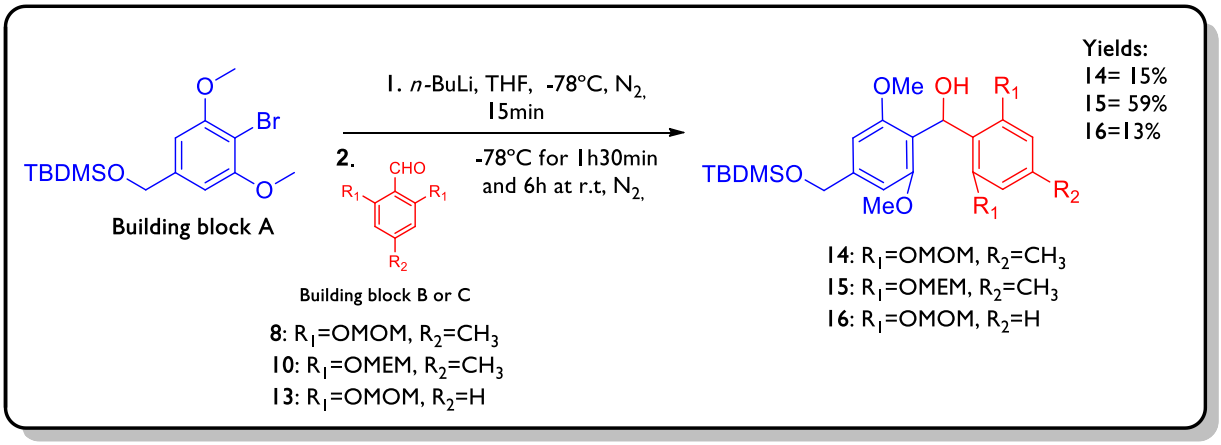


Scheme 21- Retrosynthetic plan for yicathin B and C and analogues A and B.

The first step of these synthetic pathway is the synthesis of a diarylmethanol intermediate. This intermediate is obtained by the halogen-lithium exchange of the **building block A**, which will then behave as a nucleophile and add to the carbonyl of a protected benzaldehyde (**building block B** or **C**). The secondary alcohol obtained from this step is oxidized to ketone yielding a benzophenone key intermediate. Once it was *O*-deprotected, this key intermediate is cyclized to give the xanthone moiety. Yicathin C and analogue A can be obtained by oxidation of the benzylic alcohol. Finally, yicathin B and analogue B can be synthetized by an esterification of yicathin C and analogue A, respectively.

3.4.1. Synthesis of diarylmethanols

Scheme 22 shows the general synthesis of the diarylmethanol (compounds **14-16**).

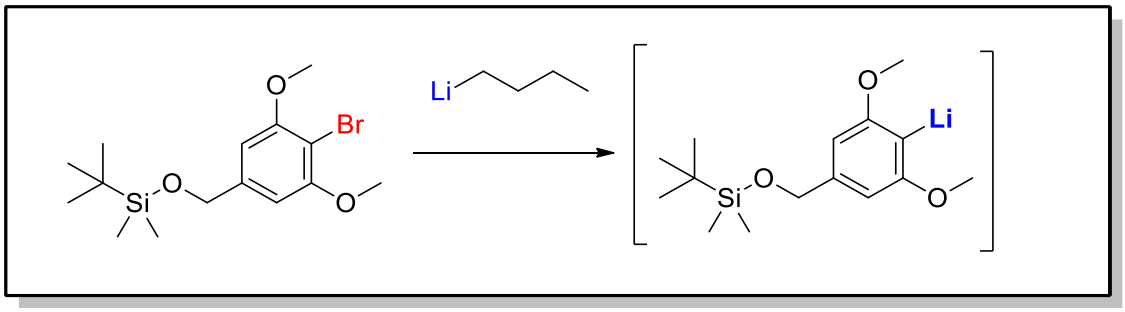


Scheme 22 – Synthesis of the diarylmethanols (**14-16**).

Benzophenones are the most common intermediates to obtain xanthones (**Figure 15**) (64). They can be obtained by a nucleophilic acyl, if an ester or acyl chloride were used. On the other hand, if the carbonyl group is a benzaldehyde, it leads to a secondary alcohol which needs an extra step, an oxidation to achieve the benzophenone (**Figure 15 (B)**) (64). Therefore, diarylmethanols are considered precursors of the benzophenone key intermediate.

A well-known strategy to synthetize diarylmethanols is the 1,2-nucleophilic addition of an aryllithium intermediate, obtained by a directed *ortho* metalation or halogen/lithium exchange, to a benzaldehyde (64). The use of halogen/lithium exchange to form the lithiated intermediate had already been used with success for the synthesis of highly hindered diarylmethanols (104-107).

In this specific case, the bromine of building block A can be exchanged with lithium in order to obtain an aryllithium intermediate (**Scheme 23**).



Scheme 23 – The halogen/lithium exchange of building block A to obtain the lithiated intermediate.

The mechanism of halogen-lithium exchange is still under debate, but it is believed that the reaction proceeds through radical intermediates (**Figure 32 - A**) or through nucleophilic substitution at the halogen (**Figure 32 - B**) (107).

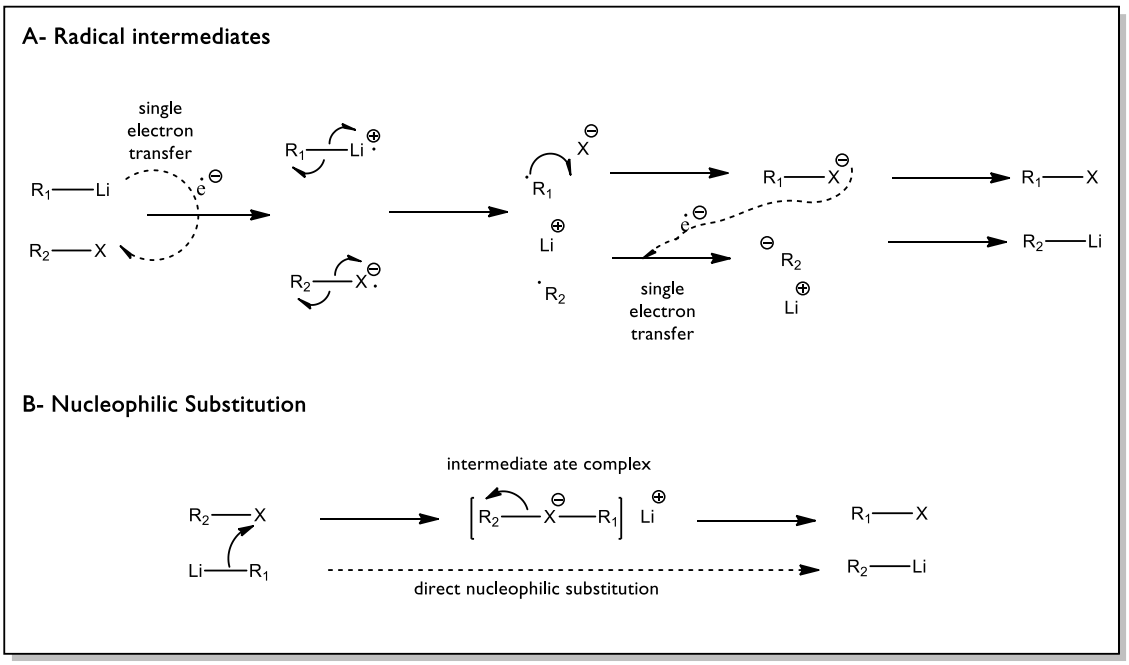


Figure 32 - Two mechanism hypothesis for the halogen-lithium exchange: **A** - Radical intermediates and **B** - Nucleophilic substitution (Adapted from (107)).

So, into a flask containing ((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl) dimethylsilane (**3, building block A**) in anhydrous THF, *n*-BuLi was added dropwise. Once the lithiated intermediate was formed, a solution of the suitable benzaldehyde in anhydrous THF was added dropwise (108). Given that the exchange reaction is extremely fast and the lithiated intermediate is extremely reactive (96, 107) two variations of the same procedure were explored.

In our first attempt, anhydrous THF obtained by simple storage over 3Å molecular sieves (109) and a nitrogen atmosphere were used. However, with this experimental conditions the major compound was the building block A without the bromine atom (**Figure 33**).

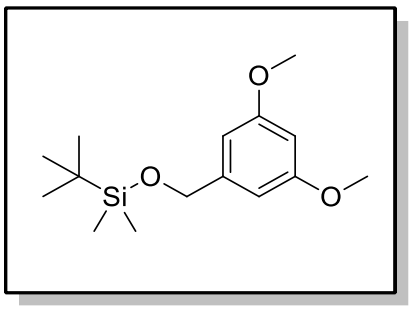


Figure 33 – Major product obtained by halogen/lithium exchange of building block A.

We hypothesized that this unexpected result derives from the high susceptibility of the aryllithium intermediate to the presence of air and water in the reaction media. For that reason, a variation of the procedure was used employing anhydrous THF obtained by distilled under sodium (110) and kept in 3Å molecular sieves (109) and employing a nitrogen flowing instead of a nitrogen atmosphere (**Figure 34**). The desired diarylmethanols (**14-16**) were isolated in lower to moderate yields (14-59%), after purification.

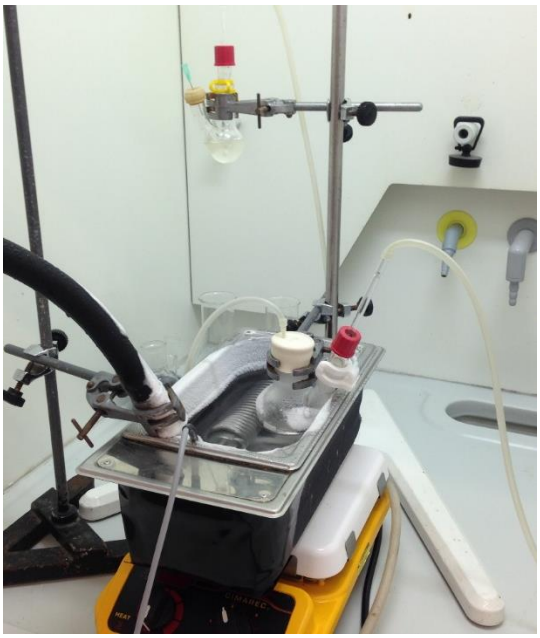


Figure 34 – Apparatus assembled for the synthesis of diarylmethanol using nitrogen flowing.

Diarylmethanol **15** obtained from the reaction between benzaldehyde **10** and compound **3** (**building block A**) was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The ^{1}H NMR spectrum showed similar profile relatively to that of compound **3** for signals corresponding to the protecting group (δ_H 0.09 s and δ_H 0.94 s), the methylene group (δ_H 4.66 s), the aromatic protons (δ_H 6.49 s) and the two methoxyl groups (δ_H 3.74 s). Also, for **building block B** (**10**) moiety the ^{1}H NMR spectrum showed the signals originated by the protecting group used (MEM) (δ_H 5.18 s, δ_H 3.64 m, δ_H 3.48 m and δ_H 3.36 s), the aromatic protons (δ_H 6.63 s) and the methyl group (δ_H 2.25 s). The structure of the diarylmethanol **15** was also confirmed by the presence of the hydroxyl (δ_H 5.56, broad s) corresponding to the alcohol moiety. The ^{13}C NMR spectrum showed 27 distinct resonance signals, in agreement with the structure. Assignments of these resonances are given in the Experimental Part. Compounds **14** and **16** were characterized based only on IR and EIMS spectra.

The presence of the hydroxyl group was also evidenced by the IR by the presence of a broad band of the O-H stretching (3564 cm^{-1} for compound **14**; 3542 cm^{-1} for compound **15**; 3545 cm^{-1} for compound **16**). Relatively to the EIMS, the mass spectra of compounds **14, 15** and **16** showed, among other, the peaks corresponding to the molecular ions 522 *m/z*, 610 *m/z*, and 508 *m/z*, respectively.

The position of the substituents in diarylmethanol **15** as confirmed by the correlations found in HMBC spectral analysis (**Figure 35**). In HMBC spectrum of compound **15** the hydrogen-bonded C(10b) correlated with carbon C(10a) and hydrogen-bonded C(8a) correlated with carbon C(8). The hydrogen at C(4b) correlated with carbon C(4a) and hydrogen at C(1a) correlated with carbon C(1).

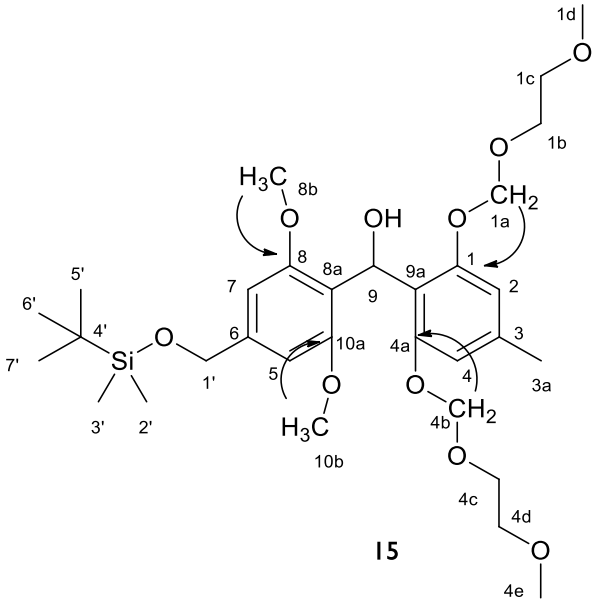
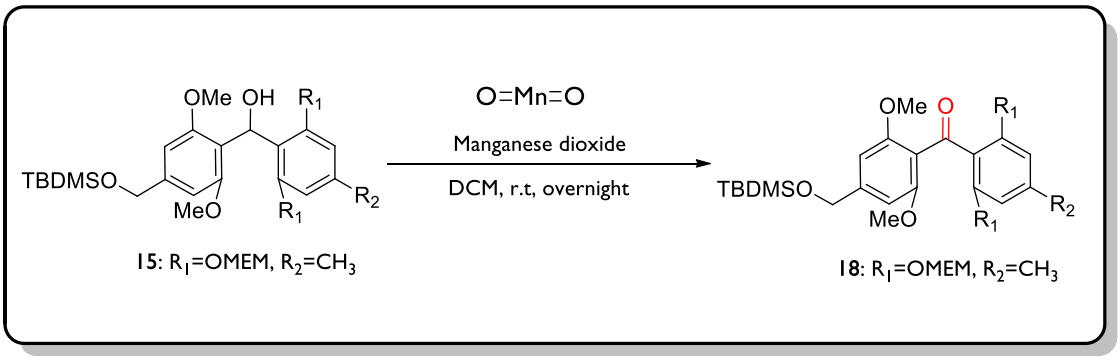


Figure 35 - Main connectivities found in the HMBC spectrum of compound **15**.

3.4.2. Synthesis of benzophenones

The oxidation of diarylmethanols (secondary alcohols) to ketones can be accomplished using different oxidizing reagents (105, 111-113). Manganese dioxide (MnO_2) is a useful selective and relatively mild oxidizing reagent, often used for the oxidation of benzylic and allylic alcohols and it was chosen for carrying out this transformation (114, 115).

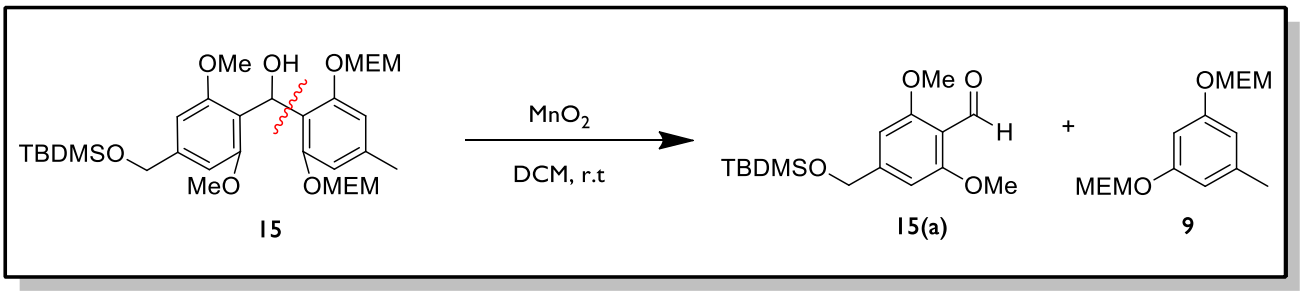
Scheme 24 shows the synthesis of benzophenone intermediates **18** using manganese dioxide as oxidizing agent of diarylmethanol **15**.



Scheme 24 - Proposed synthesis of benzophenone **18** using manganese dioxide (MnO_2).

Diarylmethanol **15** was dissolved in dichloromethane and then, the MnO_2 was added to the solution at room temperature (113, 116-118). However, the desired benzophenone was not obtained, being the main products of this reaction: 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde **15(a)** and 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene **9** (synthetized in section **3.3.1.2**) (**Scheme 25**).

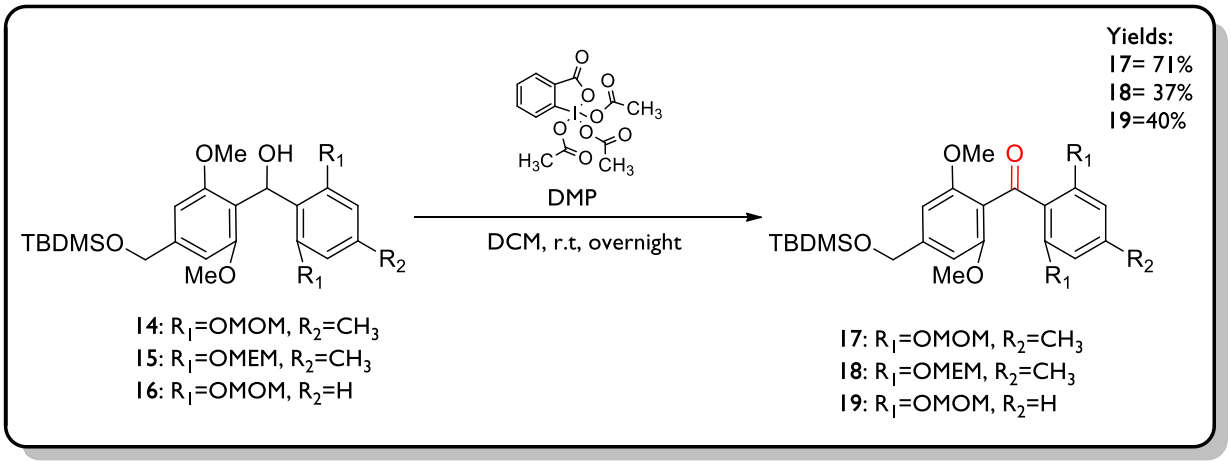
These compounds could result from the cleavage of diarylmethanol **15** as shown in **Scheme 25** and their structures is confirmed by NMR (^{1}H and ^{13}C) and GC-MS analysis (assignments of these resonances and GC-MS analysis are given in the Experimental Part).



Scheme 25 - Major products obtained from oxidation of compound **15** by MnO_2.

Bearing in mind the results obtained with MnO_2, other oxidizing agent was explored. Hypervalent iodine reagents are important oxidizing agents, because of their selective, mild, and environmentally friendly properties as oxidizing agents in organic synthesis (119). IBX (2-iodoxibenzoic acid) and DMP (Dess-Martin periodinane = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) are two examples of these oxidants. Therefore, DMP was chosen and used, since an inert atmosphere is not needed and the reaction could be carried out at room temperature (119, 120).

Scheme 26 shows the synthesis of benzophenones (compound **17-19**) using DMP as oxidizing reagent.



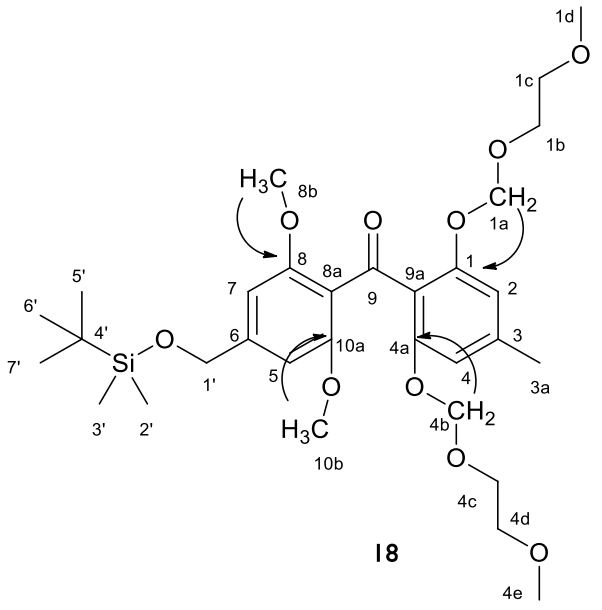
Scheme 26 – Synthesis of benzophenones (**17-19**).

So, diarylmethanol **14-16** were dissolved in dichloromethane and then, DMP was added to the solution at room temperature (111, 121). The benzophenones were obtained in lower to moderate yields (37-71%) (**Scheme 26**).

Only the structure of benzophenone **18** was characterized by IR, EIMS, ^{1}H NMR, ^{13}C NMR. HSQC and HBMC spectra completed the assignment of the protons and carbons present in the structure. The ^{1}H NMR spectrum showed similar profile relatively to the compound **15**, except the absence of the hydroxyl signal. Instead, by ^{13}C NMR the disappearance of the alcohol carbon signal was observed and the presence of the carbonyl carbon was evidenced δ_C 192.9. Assignments of these resonances are given in the Experimental Part.

In the IR spectrum of compound **18** the presence of the carbonyl group was also confirmed by the strong C=O stretching band (1704 cm^{-1} for compound **17**; 1678 cm^{-1} for compound **18**; 1729 cm^{-1} for compound **19**) as well as no O-H stretching band were present. Relatively to the EIMS, the compounds **17**, **18** and **19** showed peaks corresponding to the molecular ions 608 *m/z,* 520 *m/z* and 506 *m/z,* respectively.

The position of the substituents and the carbonyl group in compound **18** was confirmed by the correlations found in HMBC spectral analysis (**Figure 36**). In HMBC spectrum of compound **18** the hydrogen-bonded C(10b) correlated with carbon C(10a) and hydrogen-bonded C(8a) correlated with carbon C(8). The hydrogen at C(4b) correlated with carbon C(4a) and hydrogen at C(1a) correlated with carbon C(1).



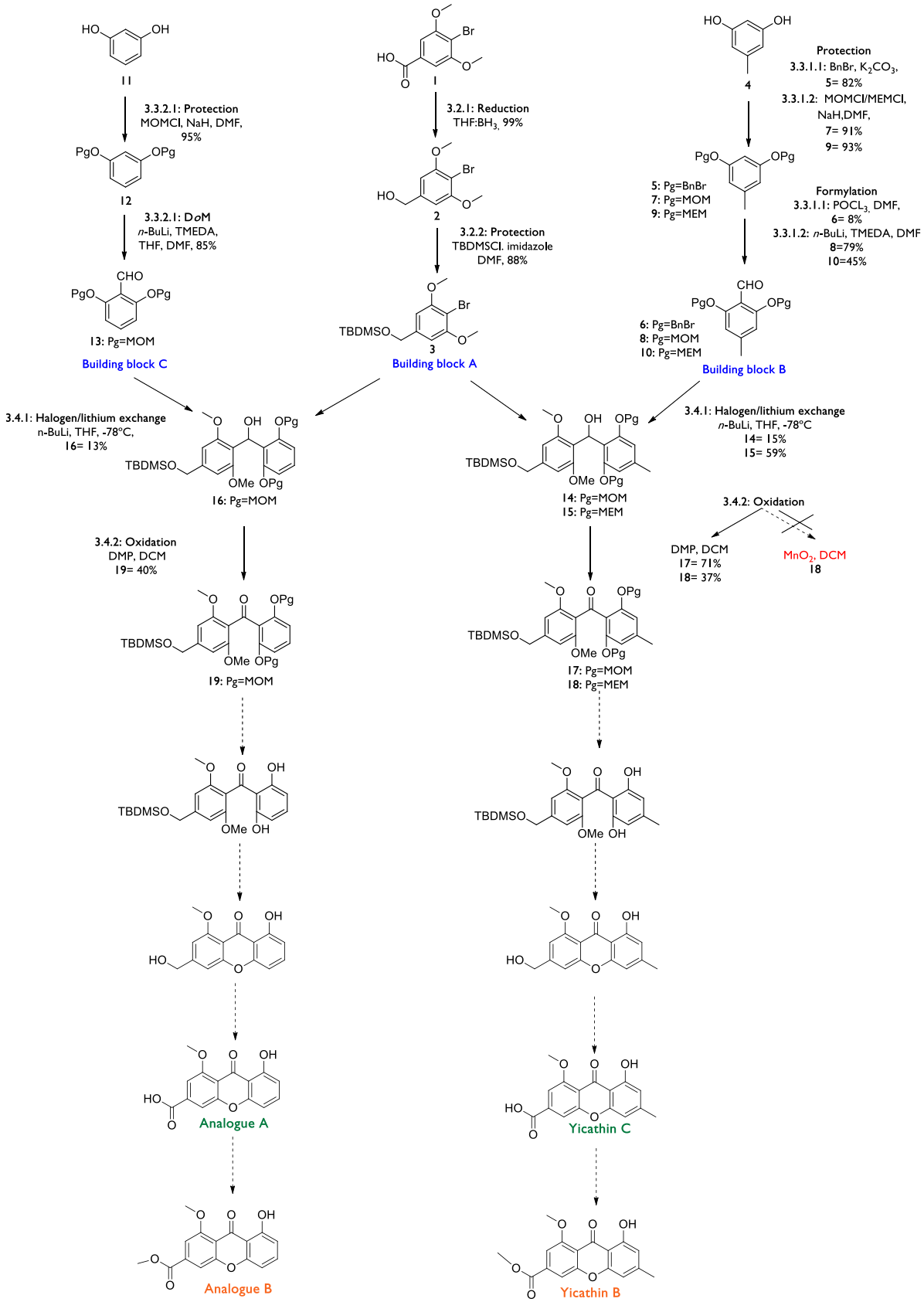
18

Figure 36- Main connectivities found in the HMBC spectrum of compound **18.**

Based on the retrosynthetic plan (**Scheme 1**, page 38), a synthetic pathway to the total synthesis of yicathins B and C and analogues A and B (**Scheme 2,** page 40) was designed.

Following this plan and tracking yicathins B and C and analogues, 15 compounds were synthesized, using different reactions (*O*-protection/deprotection with four different protecting groups, lithiations by halogen-lithium exchange and directed *ortho* metalation, reduction with borane complex and DMP oxidation).

Scheme 27 (page 73) shows the performed synthesis (full arrows) and the reactions (dashed arrows) that will complete the synthesis of yicathins B and C.



Scheme 27 – Reactions performed for the synthesis of Yicathin B and C and their analogues (A and B). (Full arrows: reaction accomplished; Dashed arrows: proposed reactions to achieve yicathins B and C and analogues A and B).

4. EXPERIMENTAL PART

4. EXPERIMENTAL PART

General Methods

Purifications of compounds were performed by flash column chromatography by using Merck silica gel 60 (0.040-0.063 mm).

Reactions were monitored by TLC and/or GC-MS. The visualization of the chromatograms was made under UV light at 254 and 365 nm. Gas chromatography analyses (GC) were carried out on Trace GC 2000 Series (DB5 –capilar column, RTX® - 5MS (crossbond 5% diphenyl 95% dimethylpolysiloxane)) with electron-impact mass spectra recorded on GCQ plus and referred to m/e (fragments %).

MW reactions were performed using glassware setup for atmospheric-pressure reactions and also 12 mL closed glass reactors (internal reaction temperature measurement with a fiber-optic probe sensor) and were carried out using an Ethos MicroSYNTH 1600 Microwave Labstation from Milestone.

Melting points were obtained in a Köfler microscope and are uncorrected.

IR spectra were measured on a KBr microplate (cm^{-1}) in a FTIR spectrometer Nicolet iS10 from Thermo Scientific with Smart OMNI-Transmisson accessory (Software OMNIC 8.3).

^{1}H and ^{13}C NMR spectra were performed in the Departamento de Química, Universidade de Aveiro, and were taken in $CDCl_3$ (Deutero GmbH) at room temperature, on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) or Bruker DRX-500 (500.13 and/or 300.13 MHz for ^{1}H and 125.77 and/or 75.47 MHz for ^{13}C) spectrometers. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference and assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd). ^{13}C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 and 1 Hz) or by comparison with the assignments of similar molecules.

All the reagents were purchased from Sigma Aldrich, Acros or TCI and all the solvents were PA used without further purification. Solvents were evaporated using rotary evaporator under reduced pressure (Buchi Waterchath B-480). Anhydrous

solvents were either purchased from Sigma-Aldrich or dried according to the published procedures (110).

Compounds were identified according IUPAC nomenclature but the numbering used in NMR assignments was used for convenience.

4.1. Synthesis of building block A

4.1.1. Synthesis of (4-Bromo-3,5-dimethoxyphenyl) methanol (**2**)

In a two necked round-bottom flask of 500 mL was added 4-bromo-3,5-dimethoxybenzoic acid (5.00 g, 19.15 mmol) and 110 mL dry tetrahydrofuran, under nitrogen. The reaction mixture was cooled in an ice-water bath, and then THF:BH_3 (1 M solution in THF, 42.2 mL, 42.2 mmol) was added dropwise. The reaction mixture was warmed to room temperature and then heated at 40 °C for two hours. The excess boranes were quenched by dropwise addition of an aqueous saturated potassium carbonate. The reaction mixture was acidified with 1 M HCl and washed three times with 50 mL water. The ether solution was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. Compound **2** was obtained as a fine white powder (4.69 g, 99%).

(4-Bromo-3,5-dimethoxyphenyl) methanol (2)

m.p.: 100-102°C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.60 (s, H-C(6) and H-C(2)), 4.68 (s, H-C(1')), 3.90 (s, 6H, OCH_3), 3.65 (s, OH).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 157.1 (C(5) and C(3)), 141.7 (C(1)), 102.9 (C(2) and C(6)), 99.6 (C(4)), 65.2 (C(1')), 56.5 (OCH_3).

IR ν_{max} (cm^{-1}) (KBr): 3242, 2837,1592,1454, 1416, 1324, 1242, 1074, 1054, 997, 910, 812, 685, 591.

EIMS m/z (%): 249 (1, $[M+2]^{+\cdot}$), 248 (10, $[M+1]^{+\cdot}$), 247 (100,$[M]^{+\cdot}$), 218 (34), 216 (48), 214 (26), 167 (24), 139 (100), 124 (100), 108 (40), 77 (24).

4.1.2 Synthesis of ((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl)dimethylsilane (**3**)

In a two necked round-bottom flask of 100 mL was added compound (4-bromo-3,5-dimetoxiphenil)methanol (**2**) (400 mg, 1.62 mmol), imidazole (275.5 mg, 4.05 mmol), and TBDMSCl (293 mg, 1.94 mmol). The mixture was placed under nitrogen atmosphere and 10 mL of DMF anhydrous was added. The solution was kept under stirring at room temperature for 4h. The reaction mixture was then poured into water (10 mL) and extracted with 3 x 15 mL of ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was purified by silica gel flash chromatography (n-hexane/ethyl acetate 9:1) and compound **3** was isolated as white solid (515 mg, 88%).

((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl)dimethylsilane (3)

MP: 80-81°C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.57 (s, H-C(2) and H-C(6)), 4.71 (s, H-C(1')), 3.89 (s, 6H, OCH_3), 0.95 (s, 9H, H-C(5'), H-C(6') and C(7')), 0.11 (s, 6H, H-C(2') and H-C(3')).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 156.9 (C(5) and C(3)), 102.08 (C(6) and C(2)), 98.68 (C(4), 64.7 (C(1')), 56.4 (C(7) and C(8)), 30.6 (C(4')), 25.9 (C(5'), C(6') and C(7')), 18.4 (C(4')), -5.23 (C(2') and C(3')).

IR ν_{max} (cm^{-1}) (KBr): 3422, 3106, 3018, 2928, 2892, 2855, 2360, 2341, 1414, 1386, 1330, 1263, 1248, 1231, 1163, 1040, 1004, 970, 938, 914, 858, 677, 630, 599.

EIMS m/z (%): 362 (1, $[M+2]^{+\cdot}$), 361 (1, $[M+1]^{+\cdot}$), 360 (2,$[M]^{+\cdot}$), 323 (25), 305 (100), 273 (100), 232 (23), 231 (100), 229 (84), 224 (66), 209 (18), 120 (18), 92 (23), 91 (32), 77 (34).

4.2. Synthesis of building block B

4.2.1. Synthesis of (((5-methyl-1,3-phenylene)bis(oxy))bis(methylene)) dibenzene (**5**)

In a two round-bottom flask of 250 mL, orcinol (**4**) (1.40 g, 11.26 mmol) and K_2CO_3 (3.11 g, 22.52 mmol) were placed, under nitrogen atmosphere. Anhydrous acetone (77 mL) was added and after about 45 minutes, benzyl bromide (3.85 g, 2.68 mL, 22.52 mmol) was added. The reaction mixture was heated at reflux for 8 hours. The mixture was allowed to cool to room temperature and filtered. The extract was purified by silica gel flash chromatography (*n*-hexane). Compound **5** was obtained as white crystals (2.83g, 82.3%).

(((5-methyl-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (5)

m.p.: 28-31°C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.43-7.25 (m, 10H), 6.44 (s, 3H), 5.01 (s, 4H, H-C(1'/1")), 2.29 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 159.9 (C(6) and C(2)), 140.3 (C(4)), 137.0 (C(2'/2")), 128.6-127.5 (C(3'-7'/3"-7")), 108.3 (C(3/5)), 99.2 (C(1)), 69.9 (C(1') and C(1")), 21.9 (C(7)).

IR ν_{max} (cm^{-1}) (KBr): 3062, 3025, 2915, 2860, 2260, 1955, 1876, 1292, 1256, 1028, 979, 633, 562, 526, 477, 465.

EIMS m/z (%): 304 (8, $[M]^{+\cdot}$), 213 (61), 181 (95), 180 (100), 179 (24), 91 (88), 92 (20), 65 (56).

4.2.2. Synthesis of 2,6-bis(benzyloxy)-4-methylbenzaldehyde (**6(a)**) and 2,4-bis(benzyloxy) -6-methylbenzaldehyde (**6(b)**)

Phosphorus oxychloride ($POCl_3$) (1 mL) was added dropwise into 5 mL of DMF at 0 °C with rapid stirring over 30 minutes. A solution of (((5-methyl-1,3-phenylene)bis(oxy)) bis(methylene))dibenzene (**5**) (1.00 g, 3.29 mmol) in 5 mL of DMF was added slowly keeping the temperature at 0 °C. The mixture was warmed to room temperature and stirred for 22h. Ice and 10% aq. NaOH were then added successively until the pH was 9-10 and solid appeared. The mixture was heated to boiling for 10/20 min, then the pH was adjusted to 3 with 10% aq. HCl after cooling to room temperature. The mixture was extracted with ethyl acetate (3x10mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate (9:1)). Compound **6(a)** was obtained as colorless oil (18 mg, 8%) and compound **6(b)** was obtained as white solid (1g, 92%).

2,6-bis(benzyloxy)-4-methylbenzaldehyde (6(a))

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.59 (s, CHO), 7.41-7.25 (m, 10H), 6.46 (s, H-C(5) and H-C(3)), 5.17 (s, 4H, H-C(1') and H-C(1")), 2.34 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 188.7 (CHO), 161.2 ((C(6) and (C(2))), 147.2 (C(4)), 136.4 ((C(2') and C(2"))), 128.6-126.9 ((C(2'-7') and (C(2"-7"))), 106.5 ((C(5) and C(3))), 70.5 ((C(1') and C(1"))), 22.9 (C(7)).

IR ν_{max} (cm^{-1}) (KBr): 3402, 3019, 3005, 2921, 1679, 1590, 1449, 1439, 1297, 1216, 819, 798.

EIMS m/z (%): 303(18, $[M]^{+\bullet}$), 241 (20), 213 (18), 91 (100), 65 (18).

2,4-bis(benzyloxy)-6-methylbenzaldehyde (6(b))

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.58 (s, CHO), 7.41-7.25 (m, 10H), 6.46 (s, H-C(5) and H-C(6)), 5.17 (s, 4H, H-C(1') and H-C(1")), 2.34 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm):190.6 (CHO), 164.3 (C(6)), 163.5(C(2), 144.7 (C(4)), 136.1 (C(2") and C(2')), 128.7-127.3 ((C(2"-7")) and (C(2'-7'))), 117.8 (C(3)), 110.0 (C(5)), 97.9 (C(1)), 70.6 (C(1") and (C1')), 22.4 (C(7)).

IR ν_{max} (cm^{-1}) (KBr): 3424, 3031, 3003, 2921, 1687, 1595, 1453, 1443, 1297, 1216, 819, 798.

EIMS m/z (%): 303(18, $[M]^{+\bullet}$), 241 (20), 213 (18), 91 (100), 65 (18).

4.2.3. Synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**)

In a two-necked round-bottom flask of 250 mL, orcinol (2,00 g, 16.11 mmol) in dry DMF (70 mL), maintained under nitrogen atmosphere at 0 °C, was treated with NaH (580 mg of a 60% suspension in mineral oil, 14.5 mmol). The ensuing mixture was stirred magnetically at this temperature until no further evolution of H_2 gas was observed. At this point the mixture was treated, dropwise with MOM-Cl (2.45 mL, 32.22 mmol) and then allowed to warm to room temperature. Stirring was continued at this temperature for 3 days. After which time the reaction mixture was poured into water (50 mL) and extracted with diethyl ether (3 x 60 mL). The combined ethereal extracts were washed with brine (1 x 40 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was purified by silica gel flash chromatography (*n*-hexane/Ethyl acetate 8:2). After concentrated the appropriate fractions compound **7** was obtained as colorless oil (3.10 g, 91%).

1,3-bis(methoxymethoxy)-5-methylbenzene (7)

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.55-6.52 (m, 3H), 5.13 (s, 4H, H-C(1') and H-C(/1")), 3.46 (s, 6H, OCH_3), 2.29 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 158.2 (C(2/6)), 140.4 (C(4)), 110.4 (C(4/5)), 102.1 (C(1)), 94.4 (C(1'/1")), 55.9 (C(2'/2")), 21.7 (C(7)).

IR ν_{max} (cm^{-1}) (KBr): 3526, 2960, 2825, 2789, 2359, 241, 2071, 2000, 1689, 1595, 1471, 1397, 1290, 1259, 1213, 1141, 1083, 922, 823, 800, 687, 668, 576, 511.

EIMS m/z (%):213 (30, $[M+1]^+$), 212 (100, $[M]^{+\cdot}$), 152 (35), 138 (50), 123 (71), 108 (82), 79 (75), 91 (58).

4.2.4. Synthesis of 2,6-bis(methoxymethoxy)-4-methylbenzaldehyde (**8**)

A solution of *n*-BuLi in *n*-hexane (1.6 M, 5.51 mL) was added dropwise to a solution of 1,3-bis(methoxymethoxy)-5-methylbenzene (**7**) (850 mg, 4 mmol), in anhydrous THF (15 mL) and anhydrous TMEDA (1.32, 8.81 mmol) in a 250 mL two-necked flask, at 0 °C under nitrogen. The mixture was stirred for 1.5h at room temperature. Then, DMF (1.02 mL, 13.22 mmol) was added dropwise and the reactions was kept under stirring for more 30 minutes. The reaction was quenched with NH_4Cl. The mixture was extracted with ethyl acetate (3x20mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel flash chromatography (n-hexane/ethyl acetate (8:2)). Compound **8** was obtained as pale-yellow solid (764 mg, 79 %).

2,6-bis(methoxymethoxy)-4-methylbenzaldehyde (8)

m.p.: 38-40°C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.48 (s, CHO), 6.67 (s, H-C(5) and H-C(3)), 5.25 (s, 4H, H-C(1') and H-C(1")), 3.50 (s, 6H, OCH_3), 2.35 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 188.8 (CHO), 159.5 (C(2) and C(6)), 147.3 (C(4)), 113.8 (C(1)), 109.4 (C(3) and C(5)), 94.7 (C(1') and C(1")), 56.5 (C(2') and C(2")), 22.7 (C(7)).

IR ν_{max} (cm^{-1}) (KBr): 3098, 2911, 2828, 2776, 1642, 1567, 1416, 1398, 1251, 1205, 820, 730, 527, 442.

EIMS m/z (%): 240 (2, $[M]^{+\bullet}$), 181 (12), 165 (20), 164 (100), 149 (20).

4.2.5. Synthesis of 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**)

In a two-necked round-bottom flask of 250 mL, orcinol (2.00 g, 16.11 mmol) in dry DMF (75 mL), maintained under nitrogen atmosphere at 0 °C, was treated with NaH (1.42 mg of a 60% suspension in mineral oil, 35.44 mmol). The ensuing mixture stirred magnetically at this temperature until no further evolution of H_2 gas was observed. At this point the mixture was treated, dropwise with MEM-Cl (4.04 mL, 35.44 mmol) and then allowed to warm to room temperature. Stirring was continued at this temperature for 3 days. The reaction mixture was then poured into water (50 mL) and extracted with diethyl ether (3 x 60 mL). The combined ethereal extracts were washed with brine (1 x 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was purified by silica gel flash chromatography (*n*-hexane/Ethyl acetate 8:2). The appropriate fractions were concentrate to give compound **9** as colorless oil (3.82g, 93%).

1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (9)

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.53 (m, 3H), 5.22 (s, 4H, H-C(1') and H-C(1")), 3.82-3.79 (m, 4H, H-C(2') and H-C(2")), 3.57-3.37 (m, 4H, H-C(3') and H-C(3")), 3.37 (s, 6H, OCH_3), 2.28 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 158.1(C(2) and C(6)), 140.3 (C(4)), 110.4 (C(5/3)), 102.1 (C(1)), 93.4 (C(1') and C(1")), 71.6 (C(3') and C(3")), 67.6 (C(2') and C(2")), 58.9 (C(4') and C(4")), 21.7 (C(7)).

IR ν_{max} (cm^{-1}) (KBr): 3503, 2921, 2818, 1597, 1471, 1403, 1366, 1332, 1242, 1199, 1103, 1042, 994, 845, 688, 509.

EIMS m/z (%): 300 (2, $[M]^{+\cdot}$), 193 (4), 165 (27), 151 (20), 89 (100), 59 (96).

4.2.6. Synthesis of 2,6-bis((2-methoxyethoxy)methoxy)-4-methyl benzaldehyde (**10**)

A solution of *n*-BuLi in *n*-hexane (1.6 M, 5.86 mL) was added dropwise to a solution of 1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (**9**) (1.28 mg, 4.26 mmol), anhydrous THF (50 mL) and anhydrous TMEDA (1.41, 9.38 mmol) in a 250 mL two-necked flask, under nitrogen atmosphere at 0 °C. The mixture was stirred for 1.5h at room temperature. Then, DMF (990 µL, 12.79 mmol) was added dropwise and the reactions was kept under stirring for more 30 minutes. The reaction was quenched with NH_4Cl. The mixture was extracted with ethyl acetate (3x25mL). The combined ethereal extracts dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate (8:2 to 7:3)). Compound **10** was obtained as pale-yellow oil (850 mg, 45 %).

2,6-bis((2-methoxyethoxy)methoxy)-4-methyl benzaldehyde (10)

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.4 (CHO), 6.63 (s, 2H, H-C(5) and H-C(3)), 5.27 (s, 4H, H-C(1') and H-C(1")), 3.80-3.76 (m, 4H, H-C(2') and H-C(2")), 3.50-3.47 (m, 4H, H-C(3') and H-C(3")), 3.3 (s, 6H, OCH_3), 2.34 (s, 3H, H-C(7)).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 188.8 (CHO), 159.4 (C(6) and C(3)), 147.4 (C(4)), 113.7 (C(1)), 109.4 (C(3) and C(5)), 93.7 (C(1') and C(1")), 71.5 (C(3') and C(3")), 68.1 (C(2') and C(2")), 58.9 (C(4') and C(4")), 22.5(C(7)).

IR ν_{max} (cm^{-1}) (KBr): 2980, 2876, 2815,1681, 1608, 1571, 1462, 1399, 1302, 1285, 1241, 1159, 1130, 1117, 1091, 1064, 1014, 962, 912, 839, 641, 576.

EIMS m/z (%): 328 (1, $[M]^{+\bullet}$), 166 (6), 151 (12), 122 (12), 89 (70), 77 (20), 59 (100).

4.3. Synthesis of building block C

4.3.1. Synthesis of 1,3-bis(methoxymethoxy)benzene (**12**)

In a two-necked round-bottom flask of 250 mL, resorcinol (2.00 g, 18.16 mmol) in dry DMF (60 mL), maintained under nitrogen atmosphere at 0 °C, was treated with NaH (1.74 g of a 60% suspension in mineral oil, 72.65 mmol). The ensuing mixture stirred magnetically at this temperature until no further evolution of H_2 gas was observed. At this point the mixture was treated, dropwise with MOM-Cl (5.52 mL, 72.65mmol) and then allowed to warm to room temperature. Stirring was continued at this temperature for 3 days. The reaction mixture was then poured into water (50 mL) and extracted with diethyl ether (3 x 60 mL). The combined ethereal extracts were washed with brine (1 x 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The extract was purified by silica gel flash chromatography (n-hexane/ethyl acetate (9:1)). Compound **12** was obtained as colorless oil (3.52g, 95%).

1,3-bis(methoxymethoxy)benzene (12)

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 7.18 (t, J=8.34, 7.95, H-C(1)), 6.75-6.73 (t, J=2.37, 2.01, H-C(4)), 6.72-6.71 (d, J=2.31, H-C(5)), 6.69-6.68 (d, J=2.31, H-C(3)), 5.17 (s, 4H), 3.48 (s, 6H, OCH_3).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 158.4 (C(2) and C(6)), 109.6 (C(3) and C(5)), 105.0 (C(1)), 94.9 (C(1') and C(1")), 55.6 (C(2') and C(2")).

IR ν_{max} (cm^{-1}) (KBr): 2931, 2829, 1597, 1460, 1404, 1313, 1291, 1242, 1101, 1019, 926.

EIMS m/z (%): 198(100, $[M]^{+\bullet}$), 167 (24), 138 (12), 124 (16), 63 (14).

4.3.2. Synthesis of 2,6-bis((2-methoxyethoxy)methoxy)benzaldehyde (**13**)

A solution of *n*-BuLi in *n*-hexane (1.6 M, 378 µL) was added dropwise to a solution of 1,3-bis(benzyloxy)benzene (**12**) (600 mg, 505 µmol), anhydrous THF (7 mL) and anhydrous TMEDA (91 µL, 605 µmol) in a 100 mL two-necked flask, under nitrogen atmosphere at 0 °C. The mixture was stirred for 1.5h at room temperature. Then, DMF was added dropwise and the reactions was kept under stirring for more 30 minutes. The reaction was quenched with NH_4Cl. The mixture was extracted with ethyl acetate (3x10mL). The combined ethereal extracts were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate (8:2)). Compound **13** was obtained as pale-yellow solid (515 mg, 85 %).

2,6-bis(methoxymethoxy)benzaldehyde (13)

m.p.: 37-39°C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.5 (CHO), 7.43-7.37 (t, J=8.49, 8.43, H-C(4)), 6.86-6.83 (d, J= 8.46, H-C(5) and H-C(3)), 5.27 (s, 4H, H-C(1') and H-C(1")), 3.52 (s, 6H, OCH_3).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 189.3 (CHO), 159.4 (C(2) and C(6)), 135.5 (C(4), 108.6 (C(5) and C(3), 94.8 (C(1') and C(1")), 56.5 (C(2') and C(2").

IR ν_{max} (cm^{-1}) (KBr): 3098, 2911, 2828, 2776, 1680, 1596, 1442, 1416, 1398, 1251, 1205, 820, 730, 527, 442.

EIMS m/z (%): 226 (2, $[M]^{+\cdot}$), 181 (12), 165 (20), 164 (100), 149 (20).

4.4. Synthesis of yicathin B and C and analogues

4.3.1. Synthesis of diarylmethanols (**14**-**16**)

In a typical experiment: in a two necked round-bottom flask of 250 mL was added compound ((4-bromo-3,5-dimethoxybenzyl)oxy)(*tert*-butyl) dimethylsilane (**3**) (1 g, 2.77 mmol) and anhydrous THF (30 mL). The mixture was allowed at -78 °C and a solution of *n*-BuLi in hexanes (1.6 M, 2.59 mL, 4.15 mmol) was added dropwise. Then, after about 5 minutes of 2,6-bis((2-methoxyethoxy)methoxy)-4-methylbenzaldehyde (**10**) (1.09 g, 3.32 mmol) was added. The solution was slowly warm to room temperature (about 6 hours). After this time, the reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with 3 x 40 mL of ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2) and compound **15** was obtained as colorless oil (1.00 g, 59%).

(2,6-bis(methoxymethoxy)-4-methylphenyl)(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanol (14) as a colorless oil in lower yield (256 mg, 15%).

IR ν_{max} (cm^{-1}) (KBr): 3564, 2956, 2859, 2826, 1613, 1586, 1455, 1396, 1293, 1223, 1154, 1111, 1042, 964, 923, 825, 725, 683, 590.

EIMS m/z (%): 522 (0.1, $[M]^{+\cdot}$), 474 (0.1), 417 (0.1), 369 (1), 334 (1), 282 (2), 281 (29), 241 (17), 181 (27), 165 (100), 152 (36), 137 (44), 121 (90), 91 (14), 77 (13).

(2,6-bis((2-methoxyethoxy)methoxy)-4-methylphenyl)(4-(((tert-butyldimethylsilyl)oxy) methyl)-2,6-dimethoxyphenyl)methanol (15) as a colorless oil in moderate yield (1.00g, 59%).

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.63 (s, 2H, H-C(4) and H-C(2)), 6.49 (s, 2H, H-C(7) and H-C(5), 5.56 (s, OH), 5.28 (d, J=1.6, 1H, H-C(9)), 5.18 (m, 4H, H-C(1a) and H-C(4b)), 4.66 (s, 2H, H-C(1')), 3.75 (s, 6H, OCH_3), 3.64 (m, 4H, H-C(1b) and H-C(4c)),

3.48 (m, 4H, H-C(1c) and H-C(4d)), 3.36 (s, 6H, OCH_3), 2.25 (s, 3H, H-C(3a)), 0.94 (s, 9H, H-C(5'), H-C(6') and H-C(7')), 0.09 (s, 6H, H-C(2') and H-C(3')).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 158.1 (C(8) and C(10a)), 155.6 (C(1) and C(4a)), 141.5 (C(6)), 138.2 (C(3)), 119.2 (C(9a)), 118.6 (C(8a)), 109.3 (C(4) and C(2)), 102.0 (C(7) and C(5)), 93.6 (C(1a) and C(4b)), 71.6 (C(1c) and C(4d)), 67.9 (C(9)), 67.4 (C(1b) and C(4c)), 60.4 (C(1')), 58.9 (C(4e) and C(1d)), 56.9 (C(8b) and C(10b)), 25.9 (C(5'), C(6') and C(7')), 21.8 (C(3')), 18.4 (C(4')), -5.24 (C(2') and C(3')).

IR ν_{max} (cm^{-1}) (KBr): 3542, 2928, 1609, 1585, 1455, 1417, 1367, 1308, 1200, 1046, 913, 838, 778, 681, 591.

EIMS m/z (%): 610 (1, $[M]^{+\cdot}$), 495 (1), 437 (1), 368 (1), 292 (2), 249 (2), 218 (4), 217 (8), 216 (24), 203 (100), 175 (15), 161 (13), 121 (9), 105 (14), 91 (7), 89 (8), 59 (45).

(2,6-bis(methoxymethoxy)phenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanol (16) as a colorless oil in lower yield (146 mg,13%).

IR ν_{max} (cm^{-1}) (KBr): 3445, 2927, 2859, 2853, 1620, 1461, 1335, 1396, 1239, 1200, 1046, 947, 789.

EIMS m/z (%): 508 (0.1, $[M]^{+\cdot}$), 480 (1), 417 (0.1), 438 (1), 401 (2), 346 (4), 317 (1), 245 (2), 213 (5), 184 (7), 183 (71), 151 (100), 137 (29), 123 (10), 81 (12), 65 (18), 63 (41).

4.3.2. Synthesis of benzophenone (**17-19**)

Manganese Dioxide (MnO_2):

In a round-bottom flask was placed compound **15** (100 mg, 164 µmol) and 10 mL of dichloromethane, Then, manganese dioxide (1 g, 12 mmol) was added at room temperature and mixture was stirred overnight. The solid materials were filtered through Celite, and the filtrate was concentrated under reduced pressure to dryness. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2). Compound **15(a)** was obtained as colorless oil (18 mg, 8%) and compound **9** was obtained as colorless oil (1g, 92%).

4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde (15(a))

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 10.47 (s, CHO), 6.57 (s, H-C(2) and H-C(6)), 4.74 (s, H-C(1')), 3.89 (s, 6H, OCH_3), 0.96 (s, 9H, H-C(5'), H-C(6') and C(7')), 0.11 (s, 6H, H-C(2') and H-C(3')).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 189.1 (C(9), 162.4 (C(5) and C(3)), 150.9 (C(1)), 112.0 (C(4), 100.7 (C(6) and C(2)), 64.7 (C(1')), 55.8 (C(7) and C(8)), 30.6 (C(4')), 25.8 (C(5'), C(6') and C(7')), 18.4 (C(4')), -5.30 (C(2') and C(3')).

EIMS m/z (%): 311 (10, $[M]^{+\cdot}$), 271 (28), 253 (94), 223 (54), 179 (82), 151 (100), 121 (24), 91 (56), 77 (46), 75 (28).

1,3-bis((2-methoxyethoxy)methoxy)-5-methylbenzene (9) (section **4.2.5**, page 87)

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.66 (m, 3H), 5.21 (s, 4H, H-C(1') and H-C(1")), 3.79-3.76 (m, 4H, H-C(2') and H-C(2")), 3.56-3.53 (m, 4H, H-C(3') and H-C(3")), 3.37 (s, 6H, OCH_3), 2.31 (s, 3H, H-C(7)).

EIMS m/z (%): 300 (2, $[M]^{+\cdot}$), 193 (4), 165 (27), 151 (20), 89 (100), 59 (96).

Dess-Martin periodinane (DMP):

In a typical experiment: in a round-bottom flask was placed compound **14** (250 mg, 478 µmol) and 10 mL of dichloromethane. Then it was added Dess-Martin periodinane (DMP) (1.49 mL, 717 µmol). The reaction mixture instantly turned bright orange. After 12 hours the reaction was quenched with the addition of a 10% solution of NaOH and distilled water. The aqueous phase was then extracted with 3 x 15 mL of DCM. The organic phase was dried over sodium sulfate anhydrous, filtered and the organic solvent evaporated. The crude product was purified by silica gel flash chromatography (n-hexane/ethyl acetate 8:2) and compound **17** was isolated as colorless oil (176 mg, 71 %).

(2,6-bis(methoxymethoxy)-4-methylphenyl)(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanone (17) as a colorless oil in good yield (176 mg, 71%).

IR ν_{max} (cm^{-1}) (KBr): 2956, 2827, 1704, 1608, 1584, 1557, 1463, 1455, 1392, 1238, 1153, 1085, 1046, 966, 823, 681, 566, 407.

EIMS m/z (%): 520 (0.1, $[M]^{+\cdot}$), 475 (1), 444 (2), 413 (4), 359 (4), 299 (4), 297 (20), 297 (100), 265 (26), 239 (47), 234 (56), 219 (53), 179 (60), 151 (43), 136 (33), 121 (21), 91 (25), 75 (19).

(2,6-bis((2-methoxyethoxy)methoxy)-4-methylphenyl)(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanone (18) as white solid in lower yield (360 mg, 37%).

m.p.: 55-57 °C

^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 6.62 (s, 2H, H-C(4) and H-C(2)), 6.50 (s, 2H, H-C(7) and H-C(5), 5.09 (m, 4H, H-C(1a) and H-C(4b)), 4.69 (s, 2H, H-C(1')), 3.67 (s, 6H, OCH_3), 3.63-3.61 (m, 4H, H-C(1b) and H-C(4c)), 3.48-3.46 (m, 4H, H-C(1c) and H-C(4d)), 3.35 (s, 6H, OCH_3), 2.29 (s, 3H, H-C(3a)), 0.94 (s, 9H, H-C(5'), H-C(6') and H-C(7')), 0.09 (s, 6H, H-C(2') and H-C(3')).

^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm): 192.9 (C(9)), 158.5 (C(8) and C(10a)), 155.5 (C(1) and C(4a)), 145.3 (C(6)), 141.5 (C(3)), 121.3 (C(9a)), 120.4 (C(8a)), 109.6 (C(4)

and C(2)), 101.7 (C(7) and C(5)), 93.5 (C(1a) and C(4b)), 71.5 (C(1c) and C(4d)), 67.4 (C(1b) and C(4c)), 64.7 (C(1')), 59.0 (C(4e) and C(1d)), 56.1 (C(8b) and C(10b)), 25.9 (C(5'), C(6') and C(7')), 22.1 (C(3')), 18.4 (C(4')), -5.25 (C(2') and C(3')).

IR ν_{max} (cm^{-1}) (KBr): 2928, 2737, 1678, 1607, 1462, 1416, 1366, 1321, 1227, 1200, 1126, 970, 905, 840, 840, 777, 718, 675, 602, 573.

EIMS m/z (%): 608 (0.1, $[M]^{+\cdot}$), 578 (1), 526 (1), 488 (1), 447 (2), 413 (14), 387 (4), 342 (5), 297 (8), 295 (16), 269 (17), 225 (17), 209 (24), 179 (10), 165 (50), 133 (38), 105 (16), 91 (32), 89 (50), 73 (100), 59 (64).

(2,6-bis(methoxymethoxy)phenyl)(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanone (19) as a colorless oil (76mg, 40%).

IR ν_{max} (cm^{-1}) (KBr): 2923, 2851, 1729, 1644, 1596, 1463, 1288, 1254, 1204, 1156, 1078, 1044, 1014, 925, 838, 742.

EIMS m/z (%): 506 (2, $[M]^{+\cdot}$), 488(1), 426 (0.5), 395 (4), 359 (1), 350 (0.1), 306 (0.1), 284 (3), 283 (23), 243 (2), 241 (100), 226 (59), 211 (10), 166 (30), 123 (18), 75 (5).

5. CONCLUSIONS

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Nature has been an important and indispensable source of hits and leads of new drugs. Over 50% of the today marketed drugs are either extracted from natural sources or produced by synthesis using natural products as templates or starting materials. In the last decades, marine environment has ignited the interest of research community since its macro and microbiome can be a source of new and innovative drugs.

Xanthone nucleus is regarded as a privileged structure in Medicinal Chemistry. In fact, several biological activities have been found for xanthone derivatives, either isolated as natural secondary metabolites or obtained by laboratorial synthesis.

In this work, a bibliographic review (from 1993 - until 2016) of marine derived xanthones with antibacterial and antifungal activities was presented (**Table 2,** page 10 and **Table 3**, page 21) and a brief overview of xanthones chemistry and xanthones synthesis was exposed (**section 1.4**, page 28).

However, the main focus of this work relies on two recently discovered marine xanthones, which have shown promising antibacterial and antifungal activities – yicathins B and C. We presented the retrosynthetic analysis of yicathins B and C (**Scheme 1**, page 38). Based on the retrosynthetic plan, it was possible to define a synthetic pathway to the total synthesis of yicathins B and C and analogues A and B (**Scheme 2,** page 40).

The synthetic pathway was followed and lead to the synthesis of building blocks A, B and C. These building blocks allowed the synthesis of the three key intermediates benzophenones which are relevant for the synthesis of yicathins B and C and analogues A and B (**Scheme 2,** page 40). **Scheme 27** (page 73) shows the fifteen compounds that were synthesized in this work and the next steps needed to achieve the desired yicathins and analogues.

To obtain the synthesized compounds, different reactions were performed, which include *O*-protection/deprotection with four different protecting groups, lithiations by halogen-lithium exchange and directed *ortho* metalation, reduction with borane complex and DMP oxidation.

The structure of all the synthesized compounds was established by spectroscopic methods, namely, IR, EIMS, ^{1}H NMR and ^{13}C NMR, and two-dimensional NMR (HSQC and HMBC).

The synthetic pathways used in this work will be applied not only for the total synthesis of two relevant marine products (yicathins B and C), but also for the synthesis of analogues that will help to understand and to modulate the pharmacodynamics and pharmacokinetics of this bioactive xanthones.

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