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Direct Synthesis of 3-Arylphthalides Promoted by Eaton's reagent

Enzo Eddebbarh,[a, b] Léa Moutardier,[b] Jérôme Thibonnet,[a] Emilie Camiade,[b] and Julien Petrignet*[a]

A rapid method has been developed for the synthesis of 3-arylphthalides from readily available starting materials. We describe herein a direct approach based on a simple Friedel-Crafts condensation between an aromatic ester and an aldehyde promoted by a mixture of phosphorus pentoxide and methanesulfonic acid (Eaton's reagent) under metal and solvent-free conditions. Due to their similarity to cytosporone E (a natural antibacterial phthalide), some of the synthesized compounds were tested as antibacterial agents against methicillin-resistant strain of *Staphylococcus aureus*.

Introduction

Phthalides are structures found in various biotopes, including plants, fungi or marine organisms. The literature describes numerous natural and synthetic phthalides with a wide range of anti-infectious activities, such as antibacterial, antiviral, and antifungal properties, depending on the nature of the substituent on the five functionalisable positions.[1] The natural compounds shown in Figure 1 are representative examples of this range of biological effects. The synthesis of phthalides has been extensively researched, and recent reviews offer a comprehensive overview of the various methods developed.[1b,2] Among these approaches, one of the routes for the synthesis of 3-arylphthalides consists to form the fused γ-lactone ring by condensation of aromatic esters or acids onto aldehydes through a metal insertion into a C–X bond,[3] by *ortho*-metalation,[4] or by a catalytic C–H bond activation.[5] *Ortho*-metalation and C–H activation are interesting strategies from an atom economy perspective. However, they require sensitive organometallic reagents or expensive catalysts (Figure 2).

We investigated the possibility of a metal-free version of direct condensation of the ester onto the aldehyde, assuming the ester has a directing group. To the best of our knowledge, only two examples of such direct Friedel-Crafts condensation have been reported in the literature. Xu et al showed that it was possible to condense electron-rich aromatic acids onto glyoxylic acid in an AcOH/H_2SO_4 mixture.[6] Earlier, in 1999, Mori and coworkers also reported a single example of the condensa-

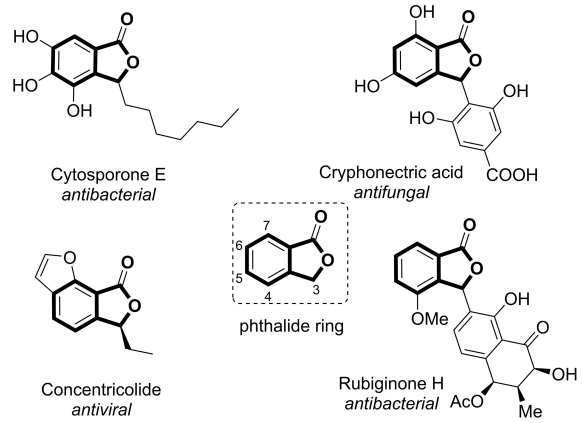

Figure 1. Representative natural 3-substituted phthalides.

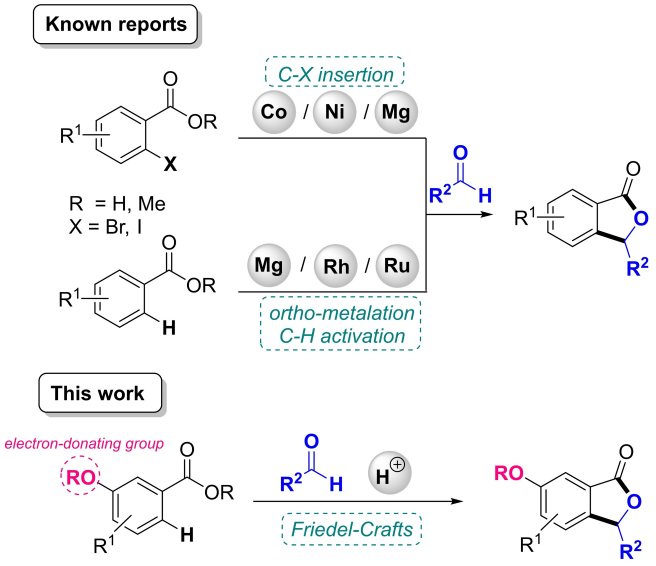

Figure 2. Strategies for the synthesis of phthalides from aromatic esters/acids and aldehydes

[a] E. Eddebbarh, Prof. J. Thibonnet, Dr. J. Petrignet
Laboratoire Synthèse et Isolement de Molécules BioActive (SIMBA) EA 7502
Université de Tours, Faculté de Pharmacie
31, Avenue Monge 37200 Tours (France)
E-mail: julien.petrignet@univ-tours.fr

[b] E. Eddebbarh, L. Moutardier, Dr. E. Camiade
ISP, Bactéries et Risque Materno-Foetal, Université de Tours, INRAE, 37032 Tours, France

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tion of 3,4,5-trimethoxybenzoic acid onto 3,4-dimethoxybenzaldehyde in the presence of polyphosphoric acid (PPA) by refluxing in chlorobenzene.[7]

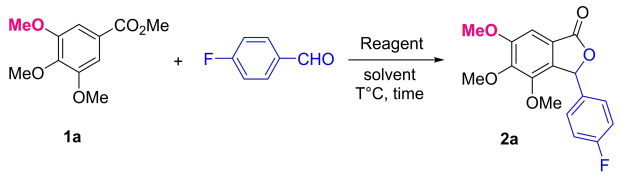
This work presents the optimisation and generalisation of the Friedel-Crafts approach for synthesising 3-arylphthalides from aromatic esters and aldehydes in a single step. Our group's previous work identified some of these 3-arylphthalides as relevant analogues of cytosporone E,[8] an antibacterial phthalide.[9] Consequently, we evaluated the antibiotic activities of selected analogues against a methicillin-resistant strain of *Staphylococcus aureus*.

Results and Discussion

Optimisation, scope and limitation

As a prelude to this work, we first attempted to reproduce the conditions described by Mori using methyl 3,4,5-trimethoxybenzoate **1a** and 4-fluorobenzaldehyde as model substrates. The reaction was carried out in toluene by heating at 90 °C for 3 h and afforded the corresponding phthalide **2a** in 52% yield (Table 1, entry 1). No reaction was observed when PPA was replaced by phosphoric acid (entry 2), and the same observation was made when toluene was replaced by a polar solvent such as DMF (entry 3). Further tests were carried out with toluene as solvent using various Brønsted (entries 4–6) and Lewis (entries 7–8) acids, all of which resulted in the recovery of the starting materials. We also tried to carry out the reaction with the conditions reported by Xu,[6] *i.e.* acetic acid and and sulfuric acid at 90 °C (entry 9), but the formation of **2a** was not observed. At this stage, we considered whether the transformation's key is due to a synergistic effect between acidity and the presence of phosphorus species in the medium. Eaton's reagent, a convenient alternative to PPA, could be prepared by solubilising 10% w/w of phosphorus pentoxide onto methanesulfonic acid.[10] Using this reagent, we were delighted to obtain phthalide **2a** in an excellent yield of 86% after heating for 1 hour at 45 °C (entry 10). The significance of the phosphorus species was confirmed, as no conversion was observed in MsOH alone after heating at 90 °C for 3 hours (entry 11). It should be noted that replacing the ester **1a** with the corresponding carboxylic acid also leads to the formation of **2a**, but in a lower yield (entry 12). Finally, we used supported P_2O_5 on SiO_2 which is reported to be a smoother alternative to the Eaton's reagent.[11] Several attempts were made using different systems, including neat and microwave heating. However, the best conditions (entry 13) only yielded 35%, which could not be improved. Ultimately, it was found that Eaton's medium heated to 45 °C was the most effective condition for promoting this transformation.

Table 1. Optimisation of the reaction conditions.[a]



Entry[a]	Reagent	Solvent	T°C, time	Yield (%)[b]
1	PPA	Toluene	90 °C, 3 h	52
2	H_3PO_4	Toluene	90 °C, 3 h	0
3	H_3PO_4	DMF	90 °C, 3 h	0
4	PTSA	Toluene	90 °C, 3 h	0
5	MsOH	Toluene	90 °C, 3 h	0
6	TfOH	Toluene	90 °C, 3 h	0
7	$AlCl_3$	Toluene	90 °C, 3 h	0
8	AgOTf	Toluene	90 °C, 3 h	0
9	H_2SO_4	AcOH	90 °C, 3 h	0
10[c]	**P_2O_5/MsOH**	–	**45 °C, 1 h**	**86**
11	MsOH	–	90 °C, 3 h	0
12[d]	P_2O_5/MsOH	–	45 °C, 1 h	56
13[e]	P_2O_5/SiO_2	DCE	150 °C, 20 min	35

[a] Reaction conditions: **1a** (0.66 mmol), 4-fluorobenzaldehyde (0.99 mmol), reagent (1.5 equiv.). [b] Isolated yield after column chromatography. [c] P_2O_5 (2.08 mmol) was dissolved in MsOH (2 mL) during 30 min. at 45 °C then aldehyde and ester were successively added [d] **1a** was replaced by 3,4,5-trimethoxybenzoic acid. [e] P_2O_5/SiO_2 (1:1, 600 mg), microwave heating.

Using these optimised conditions, we explored scope of aldehydes (Scheme 1). The reaction was generally efficient with most aromatic aldehydes, regardless of whether they carried electron-withdrawing groups (**2b-g**), no substituent (**2h**) or electron-donating groups (**2i-j**), whether they were monosubstituted in position 2, 3 or 4 (**2a** vs. **2b**,**c**), or di-substituted (**2k-n**). In each case, the corresponding phthalide is obtained in moderate to very good yield ranging from 64 to 97%, a slight decrease in yield being observed in the case of 4-methoxybenzaldehyde (**2i**, 51%). In addition, the presence of a CF_3 group in the ortho position (product **2g**) gave a recrystallizable phthalide whose structure was confirmed by X-ray diffraction and has been deposited at the CCDC.[12] Finally, we were pleased to observe that pyridine-2-carboxaldehyde and 2-formylchromone were suitable substrates and gave compounds **2o-p** in acceptable yields. The lower yield with 2-formylchromone can be explained by a reduction in the reaction rate, since a conversion of 50% was obtained after 24 hours. Finally, it was discovered that insaturated or electron-rich heteroaromatic aldehydes such as *trans*-cinnamaldehyde, indole, furan, and thiophene-carboxaldehyde are incompatible with these conditions, as they produce degradation products. Additionally, it was observed that phthalide formation did not occur with aliphatic aldehydes, as the self-aldolization-crotononization product formed quantitatively.

In the second step, we investigated the ester's scope by using 4-fluoro and 4-trifluoromethylbenzaldehyde as model aldehydes (Scheme 2). We were pleased to find that the reaction worked with a free OH group, as in the case of methyl syringate **1b**, resulting in good yields of phthalides **3a** and **3b**. Phthalides **4** and **5** were obtained in comparable yields (43-82%) by using esters with two methoxy groups, such as methyl

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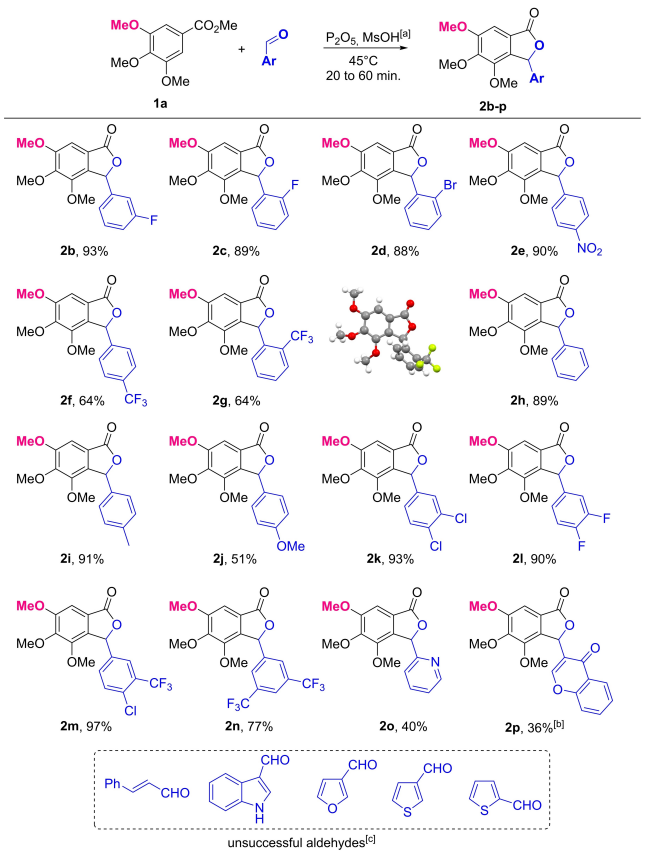
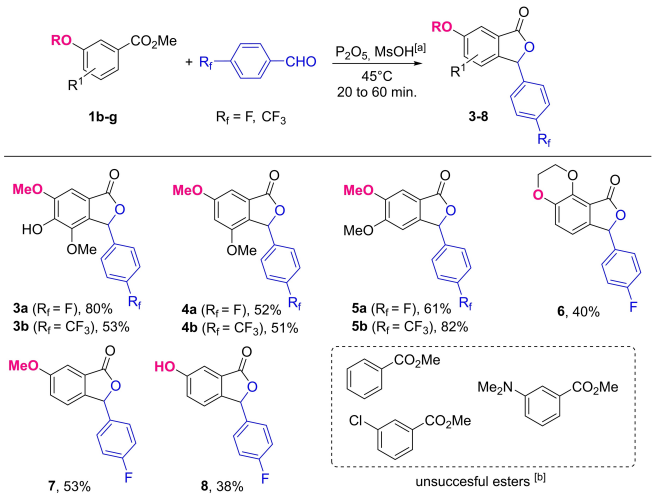


[a] **1a** (150 mg, 0.66 mmol), aldehyde (1 mmol), P_2O_5 (296 mg, 1.04 mmol), MsOH (2 mL). [b] A conversion of 50% was obtained after heated at 55°C during 24h. [c] Degradation products were obtained

Scheme 1. Aldehyde scope of phthalides **2a-p**.



[a] **1b-f** (150 mg, 0.66 mmol), 4-fluorobenzaldehyde or 4-trifluoromethylbenzaldehyde (1 mmol), P_2O_5 (296 mg, 1.04 mmol), MsOH (2 mL). [b] Starting materials were recovered

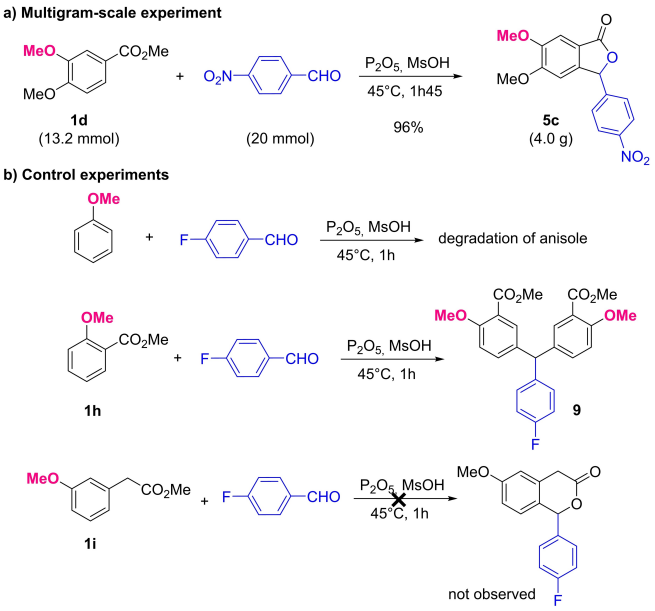
Scheme 2. Ester scope of phthalides **3–8**.

3,5 and 3,4-dimethoxybenzoate (**1c** and **1d**). It is important to mention that using a 2,3-substituted ester with a dioxin unit instead of methoxy groups (**1e**) resulted in the production of phthalide **6** with a yield of 40%. The reaction was also successful with methyl 3-methoxybenzoate **1f** and methyl 3-hydroxybenzoate **1g**, yielding phthalides **7** and **8** at 53% and 38%, respectively.

It was found that esters lacking an activating group in the 3-position, such as methyl benzoate or methyl 3-chlorobenzoate, did not undergo any reaction. Similarly, no conversion was observed with methyl 3-dimethylaminobenzoate, presumably due to the aniline being fully protonated in methanesulfonic acid.

To evaluate the efficiency of this reaction, we prepared the phthalide **5c** on a multigram scale using **1d** and 4-nitrobenzaldehyde as substrates. After purification, we obtained 4.0 g of **5c** in a yield of 98% (Scheme 3a).

In order to understand the reaction mechanism, several control experiments were carried out (Scheme 3b). Firstly, the P_2O_5/MsOH mixture was used to condense the anisole onto 4-fluorobenzaldehyde, resulting in the degradation of the anisole. This suggests that the ester function plays a crucial directing role in this reaction. Secondly, methyl 2-methoxybenzoate **1h** was used, confirming the importance of the synergy between the ester function and the activating group in the reaction. As anticipated, the formation of the corresponding phthalide was not observed. However, triarylmethane **9** was formed, [13] the formation of the latter can be explained by the position of the OMe group, which directed the addition of the aldehyde to its *para* position. Since lactonisation was not possible, we assume that an intermediate benzylic carbocation was formed and underwent a Friedel-Crafts addition of a second equivalent of **1g**. We investigated whether this reaction would lead to the formation of the isochromanone resulting from the condensation of **1i** with 4-fluorobenzaldehyde. However, we only observed the degradation of the ester, indicating that this transformation is highly specific to the formation of the γ-lactone core.



Scheme 3. Gram-scale synthesis of phthalide **5c** and mechanistic studies.

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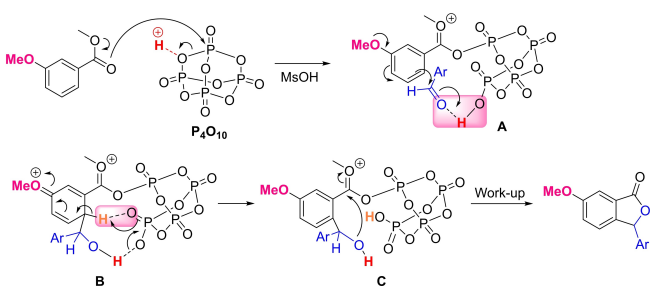
Scheme 4 proposes a plausible mechanism that highlights the synergistic role of the ester and the *para*-directing group. The first step involves the condensation of the ester function onto a phosphorus atom of P_4O_{10} driven by the P-O bond force and promoted by the acidic medium. The resulting phosphoric acid function activates the carbonyl of the aldehyde function, which is then attacked by the activated position of the aromatic ester (intermediate **A**). The stabilized Wheland intermediate resulting from this attack could then easily re-aromatize through the intramolecular transfer of the proton on the polyphosphoric unit (intermediate **B**). Subsequently, lactonization can occur by attacking the alcohol function on the activated ester (intermediate **C**). It was assumed that the lactone ring was formed through an A_{AC2} mechanism rather than an A_{AL1} mechanism. Indeed, the alcohol produced by the attack of the benzoate on the aldehyde would rapidly attack the ester function activated by the phosphorus species, rather than forming the corresponding carbocation. Moreover, in acidic conditions, the ester is likely to be protonated and therefore a poor nucleophile. Finally, Eaton's reagent enables double activation of the aldehyde and the ester (or carboxylic acid if the latter is used) in this transformation. At the end, the hydrolysis step yields the phthalide product.

Antibacterial assays

Buiding on our previous work, we have demonstrated that certain 3-arylphthalides possess anti-MRSA properties similar to cytosporone E.[8] This is especially evident in compounds containing an OH group in position 5 and a CF_3 group on the aromatic ring, such as compounds **10a** and **10b**, both of which exhibit MIC values similar to those of cytosporone E (Table 2, entries 1–3). Therefore, we selected phthalide that one or more lipophilic groups on position 3 from the previously synthesized ones to compare their activity against MRSA with that of compounds **10a-b**.

Before carrying out the antibacterial assays, we demethylated the OMe groups. This step was carried out in the presence of an excess of BBr_3 in CH_2Cl_2 to afford compounds **10–11** (Scheme 5, see SI for details).

The antibacterial activities of the selected compound against Gram-positive methicilin-resistant *Staphylococcus aureus* were evaluated using the broth microdilution method in accordance with the guidelines of the Clinical and Laboratory Standards Institute,[14] and the Minimal Inhibitory Concentrations (MIC) values are reported in Table 2.

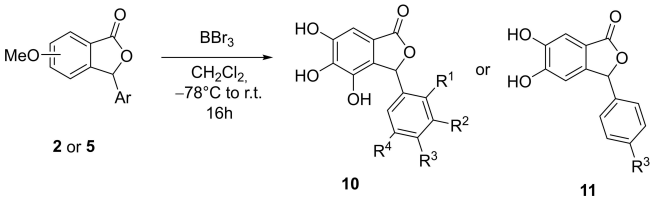


Scheme 4. Proposed mechanism.

Table 2. Minimal inhibitory concentrations (MIC) in μM of selected compounds against methicillin-resistant strain of *Staphylococcus aureus* (MRSA).[a]

Entry	Compound	MIC (μM)
1[b]	Cytosporone E	22.3
2[b]	**10a** ($R^3=CF_3$, $R^1=R^2=R^4=H$)	19.2
3[b]	**10b** ($R^2=CF_3$, $R^1=R^3=R^4=H$)	38.4
4	**10c** ($R^1=CF_3$, $R^2=R^3=R^4=H$)	>400
5	**10d** ($R^3=CH_3$, $R^1=R^2=R^4=H$)	68.9
6	**10e** ($R^3=F$, $R^1=R^2=R^4=H$)	136
7	**10f** ($R^2=F$, $R^1=R^3=R^4=H$)	34
8	**10g** ($R^2=R^4=CF_3$, $R^2=R^3=H$)	47.6
9	**10h** ($R^2=CF_3$, $R^3=Cl$, $R^1=R^4=H$)	13.0
10	**10i** ($R^2=R^3=Cl$, $R^1=R^4=H$)	14.3
11	**10j** ($R^2=R^3=Cl$, $R^1=R^4=H$)	8.0
12	**3b**	>400
13	**11a** ($R^3=CF_3$)	30.2
14	**11b** ($R^3=NO_2$)	261

[a] Assay experiments were performed in triplicates at three independent times. [b] Preparation and antibacterial assays are reported in previous work.



Scheme 5. Synthesis of phthalides **10** and **11**.

The activities of compounds **10** with OH groups in positions 4, 5 and 6 were examined. Compounds **10a** and **10b** with a trifluoromethyl group in the *para* and *meta* positions of the aryl group exhibited similar activities. However, there was a complete loss of activity when the CF_3 group was in the *ortho* position (**10c**, entry 3). As expected, replacing the CF_3 group on the *para* position with a less lipophilic CH_3 resulted in a decrease in antibacterial activity (**10d**, entry 5). Similar observations were made when replacing CF_3 with a single fluorine atom (**10e**, entry 5). However, antibacterial activity was restored to levels similar to cytosporone E when the fluorine atom was in the *meta* position (**10f**, entry 7). Using these trends, we then selected molecules with lipophilic groups in both para/meta positions. The molecule **10g** which carries CF_3 groups in both meta positions exhibited an antibacterial activity of 47.6 μM (entry 8). Compounds **10h-j**, which carry lipohilic groups (Cl or CF_3) at the *para* and *meta* positions, were even more active with MIC values of 8.0 to 14.3 μM (entries 9–11).

The pharmacomodulations on the aromatic ring of the phthalide were then explored. It was discovered that com-

pounds **3 b**, for which the OH group in positions 4 and 6 were replaced by OMe, exhibited a complete loss of activity (entry 12).

Finally, it was demonstrated that the presence of OH in position 4 of the phthalide appears to be less significant for antibacterial activity, as compound **11 a** has a MIC very similar to that of compound **10 a** (entry 13). Additionally, it was observed in this series that substituting the CF_3 group with a nitro resulted in a significant reduction in antibacterial activity (**11 b**, entry 14).

Conclusions

In summary, a convenient approach for the synthesis of 3-arylphthalides promoted by phosphorus pentoxide in methanesulfonic acid has been developed. The protocol employs readily available aromatic esters and aldehydes, mild heating, low-cost and bench-stable reagent. The reaction, which can be scaled up to multi-gram quantities, has been extended to many substrates, resulting in good yields of phthalides. Several synthesized phthalides underwent antibacterial testing against methicillin-resistant *Staphylococcus aureus*. This allowed for a refinement of the structure-activity relationship study for these analogues of cytosporone E.

Experimental section

Only general procedures are presented here. The synthesis and characterization of all compounds are provided in the supporting information.

General procedure for the synthesis of phthalides 2–8: In a flask maintained at 45 °C containing the prepared solution of Eaton's Reagent (296 mg of P_2O_5 / 2 mL of MsOH), the ester (0.66 mmol) and the corresponding aldehyde (1 mmol) were added and the reaction mixture was stirred at 45°C. The product formation was followed by TLC, once the starting material was completely consumed the mixture was allowed to cool to room temperature then treated. The reaction mixture was alkalinized with a saturated solution of Na_2CO_3 (20 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

General procedure for the demethylation of phthalides : A dry flask equipped with a magnetic stirrer and a septum was charged with a solution of phthalide (1 equiv.) in dry CH_2Cl_2 (5 mL) and was cooled at -78°C. A solution of boron tribromide (1 M in CH_2Cl_2, 5-7 equiv.) was added dropwise and the reaction mixture was left to stir overnight, returning gently to room temperature. The reaction mixture was carefully hydrolysed with methanol (2 mL) and concentrated under reduced pressure. Then the mixture was subjected to a liquid-liquid extraction with brine (10 mL) and with EtOAc (3×15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Antibacterial assays: Methicillin resistant *Staphylococcus aureus* NCTC 12493 has been used to test the antibacterial activity. Tested compounds were dissolve in ethanol to get a mother solution of 3 mg/mL and then further dilutions were made in Mueller Hinton (MH) to get a range of tested concentration (200, 100, 50, 25, 12.5, 6.25, 3.125, 1.563 $\mu g.mL^{-1}$). Broth microdilution method was used for the determination of minimal inhibitory concentrations and is detailed in Supporting Information.

Supporting Information

Additional references cited within the Supporting Information.[15-16]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Friedel-Crafts · Eaton's reagent · phthalides · anti-MRSA

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