Selective Transformations of Substituted Aryl Compounds to Fluorenes and Phosphoramidates: Synthetic and Spectroscopic Studies

Thesis presented in fulfilment of
the thesis requirement for the degree of
Doctor of Philosophy in Natural Sciences (Dr. rer. nat.)

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presented by

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Die vorliegende Arbeit wurde unter der Leitung von Herrn Prof. Dr. Uwe Beifuss am Institut für Chemie der Universität Hohenheim in der Zeit von August 2006 bis Oktober 2009 durchgeführt.

I wish to express my cordial endless thanks and sincere gratitude to *Prof. Dr. Uwe Beifuss* for his supervision, valuable support and constructive encouragement that were the solid pillars for the achievement of this research. Without his advice and endless interest, this study could not have been carried out and completed.

TO MY PARENTS

MY WIFE & MY CHILDREN

MY BROTHER & MY SISTERS!

PRELMINARY REMARKS

The work presented in this thesis was carried out under the supervision of Prof. Dr. Uwe Beifuss at the Institute of Chemistry, University of Hohenheim, from August 2006 to October 2009. Parts of the results have already been published in an international peer reviewed journal:

1 REDA HAGGAM, JÜRGEN CONRAD and UWE BEIFUSS
"Pactical and reliable synthesis of dialkyl *N*-arylphosphoramidates with nitroarenes as substrates"
Tetrahedron Lett. **2009**, *50*, 6627–6630.

Concerning the co-authors:

Prof. Dr. Uwe Beifuss was the supervisor of this work. He was always available for scientific discussions and valuable suggestions. He was involved in preparing the manuscript throughout the whole process of publication and was responsible for all aspects of publication. He is also the corresponding author of the publication.

Dr. Jürgen Conrad advised on all analytical processes and assisted in the interpretation of NMR data. He was always available for scientific discussions. Also, he measured all of the NMR samples on the 500 MHz Varian ^{Unity}Inova spectrometer.

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1 INTRODUCTION

The synthesis of fluorenones is of great interest because they play an important role in pharmaceutical applications,[1-3] as photo-sensitizors,[4] and as key intermediates in organic synthesis.[5]

A number of biologically active fluoren-9-ones has been isolated from plants. As an example, 1,4,5-trihydroxy-7-methoxyfluoren-9-one (**1**), dendroflorin (**2**) and denchrysan A (**3**) have been obtained from *Dendrobium chrysotoxum* which is used as a health-food.[6] The three compounds were evaluated in vitro for their inhibitory effects against the growth of the human leukaemia cell lines K562 and HL-60, the human lung adenocarcinoma A549 and the human stomach cancer SGC-7901. All three fluorenones displayed selective cytotoxicity against BEL-7402 (Figure 1).

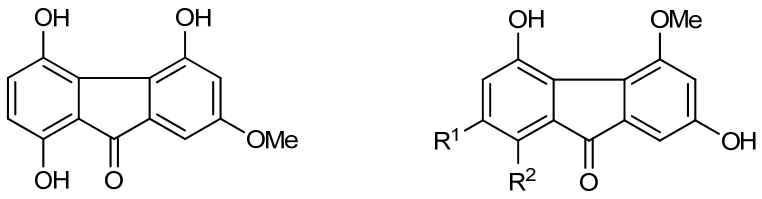


Figure 1: The structures of 1,4,5-trihydroxy-7-methoxyfluoren-9-one (**1**), dendroflorin (**2**) and denchrysan A (**3**) isolated from *Dendrobium chrysotoxum.*[6]

Recently, hipposudoric acid (**4**) and norhipposudoric acid (**5**), two natural dyes with a fluorene skeleton, have been isolated from the red sweat of *Hippopotamus amphibius* by Hashimoto, Nakata et al.[1b-d] So far, the biological function of these two dyes is not known. The isolation, the properties as well as the synthesis of **4** and **5** will be discussed in greater detail in chapter 1.

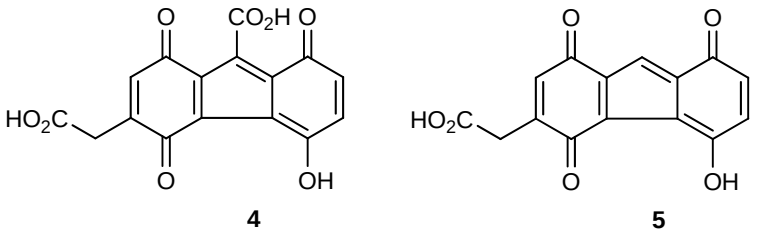
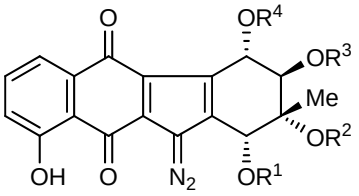


Figure 2: The structures of hipposudoric acid (**4**) and norhipposudoric acid (**5**).[1b-d]

Apart from natural products with a fluorene skeleton a number of naturally occuring benzo[*b*]fluorenes has been isolated over the last decades. The benzo[*b*]fluorene family comprises two major groups: the kinamycin antibiotics kinamycin A-F (**6-11**) (Figure 3)[7a-c,8] and their aromatic congeners prekinamycin (**12**), isoprekinamycin (**13**)[7,9,10], the stealthins A-C (**14-16**),[5,11,12], kinafluorenone (**17**),[13] kinobscurinone (**18**),[5b,12,14,15,] seongomycin (**19**),[15a] cysfluoretin (**20**),[7b,12,16] and the glycosylated dimeric lomaivicitins A and B (**21**, **22**)[7a] (Figure 4).



Nr	Kinamycin		R^1	R^2	R^3	R^4
6	"	A	H	Ac	Ac	Ac
7	"	B	H	Ac	H	H
8	"	C	Ac	H	Ac	Ac
9	"	D	Ac	H	Ac	H
10	"	E	Ac	H	H	H
11	"	F	H	H	H	H

Figure 3: The structures of the kinamycins A-F.[7a-c,8]

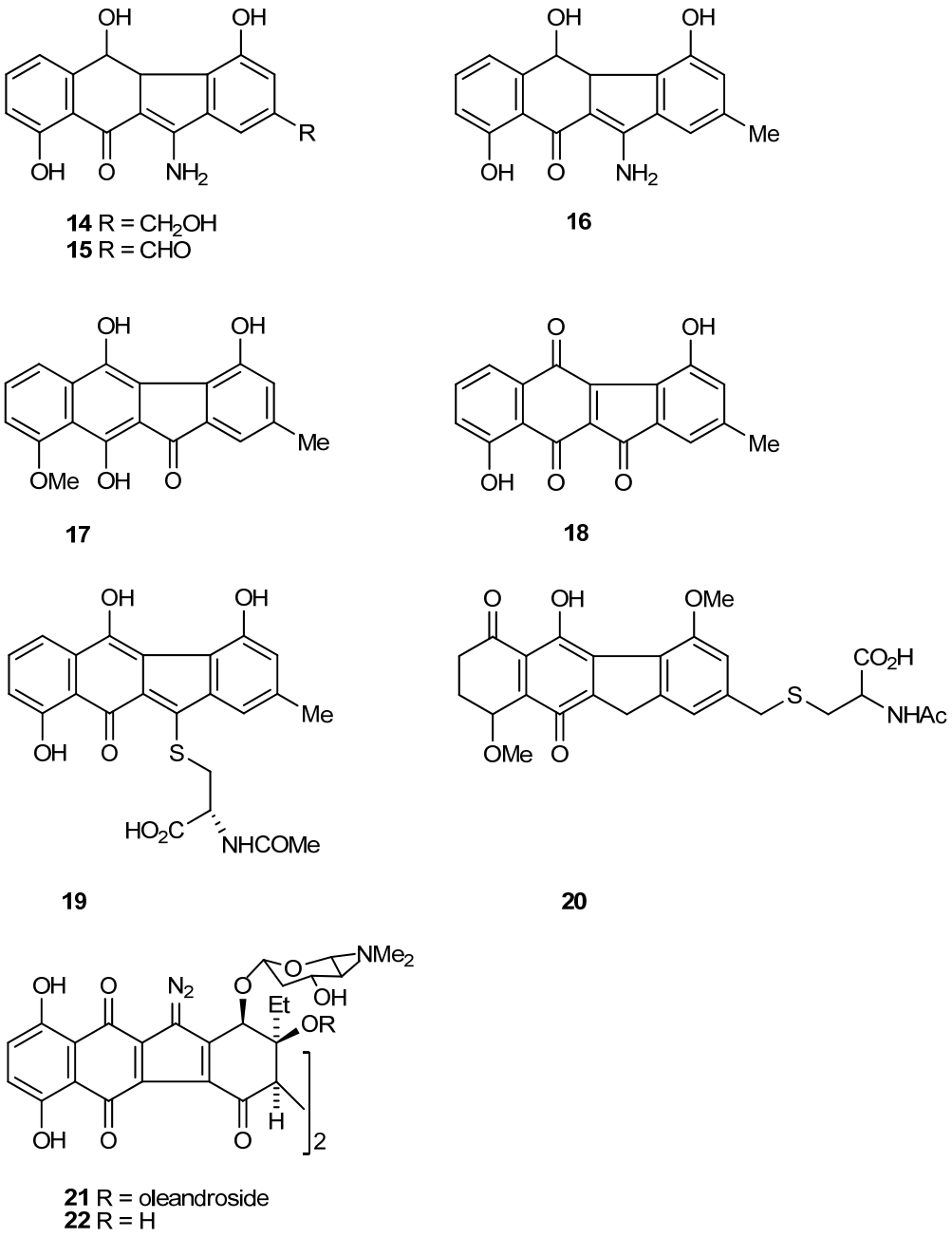
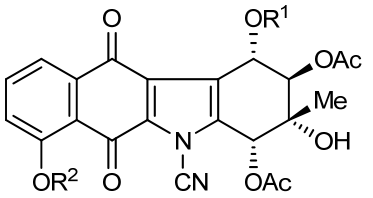


Figure 4: The structures of some naturally occuring compounds with a benzo[*b*]fluorene skeleton.

The kinamycins A-D (**6-9**) were isolated in 1970 from the culture broth of *Streptomyces Murayamaensis* sp. nov. by Omura et al.[17] They are strongly active against Gram-positive bacteria.[7c] Kinamycin C (**8**) also exhibits antitumor activity.[7b,c,18]

The structural assignment of the kinamycins has been the subject of revision.[7b,c,8,18-23] Kinamycin C (**8**) was originally reported as a *N*-cyanobenzo[*b*]carbazole **23** (Figure 5).[7b,c,8]



23 **a** $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = p$-BrPhCO

Figure 5: The structure of *N*-cyanobenzo[*b*]carbazole **23**.

In 1994, the structure of kinamycin C (**8**) was revised to contain a dibenzofluorene moiety by Gould [22] and Dmitrienko[23] based on X-ray and NMR experiments as well as synthetic studies.

The novel and challenging chemical structures of the kinamycins combined with their marked biological activities have prompted numerous synthetic studies. In the meantime, the total syntheses of prekinamycin (**12**),[7a] stealthin C (**16**),[5,7c,11] kinafluorenone (**17**),[13] kinobscurinone (**18**),[5b,12,14,15] $O^{4,9}$-dimethyl stealthins A and C,[5a,11] and tri-*O*-methylkinafluorenone,[7c,24] have been reported. Only recently, the total syntheses of the more challenging structures of (-)-kinamycin C (**8**),[25] kinamycins C and F (**8**, **11**),[26] kinamycin F (**11**)[27] and (±)-*o*-methyl-kinamycin C[28] have been achieved as well.

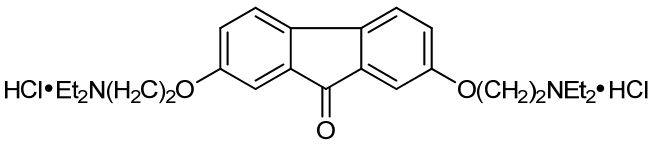


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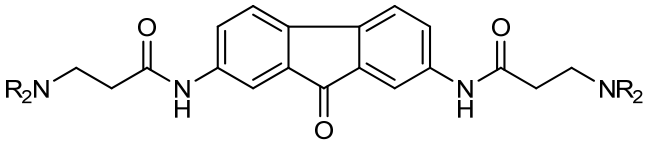
Figure 6: Structure of tilorone hydrochloride (**24**).

Tilorone hydrochloride (**24**) is the first synthetic compound of low molecular weight that has been recognized to be an orally active interferon stimulating agent.[29] It has been shown that it actively supresses the reproduction of a number of viral families. Therefore, it is in use an antiviral drug for the treatment of a number of viral diseases, including influenza, hepatitis, diarihea and herpes.[30]

The telomerase enzyme is an essential factor in tumorigenesis.[31] Therefore, there is agreat interest in the inhibition of telomerase as a new anticancer strategy.[32] Recently, a number of

2,7-disubstituted amidofluoren-9-one derivatives **25** have been identified as efficient inhibitors of the human telomerase.[3d] (Figure 7).



25

Figure 7: Structure of 2,7-disubstituted amidofluoren-9-one derivatives **25**.

In summary, fluorenes and related compounds exhibit a broad spectrum of biological activities. This is why the development of methods for the synthesis of this class of compounds is of great interest in organic synthesis.

2 HIPPOSUDORIC ACID (4) AND NORHIPPOSUDORIC ACID (5)

A couple of years ago Saikawa et al. have been able to isolate hipposudoric acid (**4**) and norhipposudoric acid (**5**) from the red sweat of *Hippopotamus amphibius*.[1b-d]

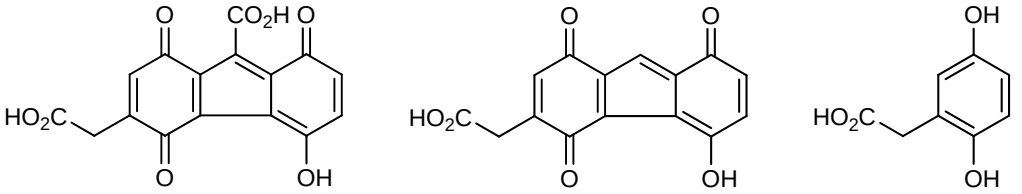
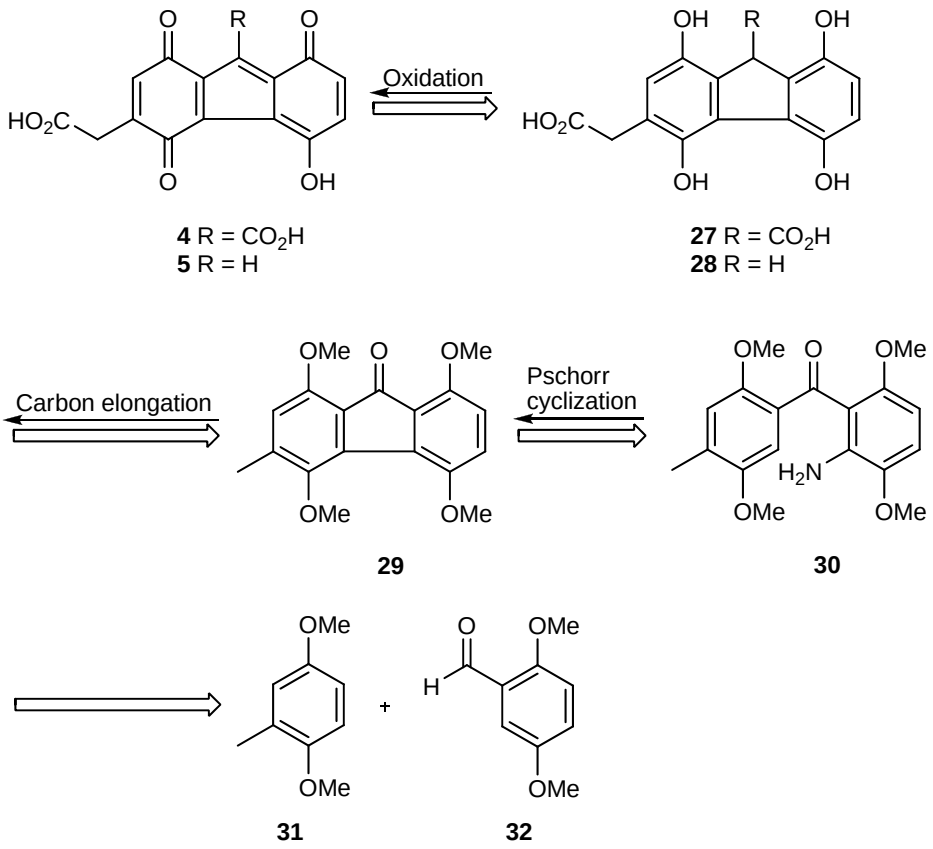


Figure 8: The structures of hipposudoric acid (**4**), norhipposudoric acid (**5**) and homogentisic acid (**26**).

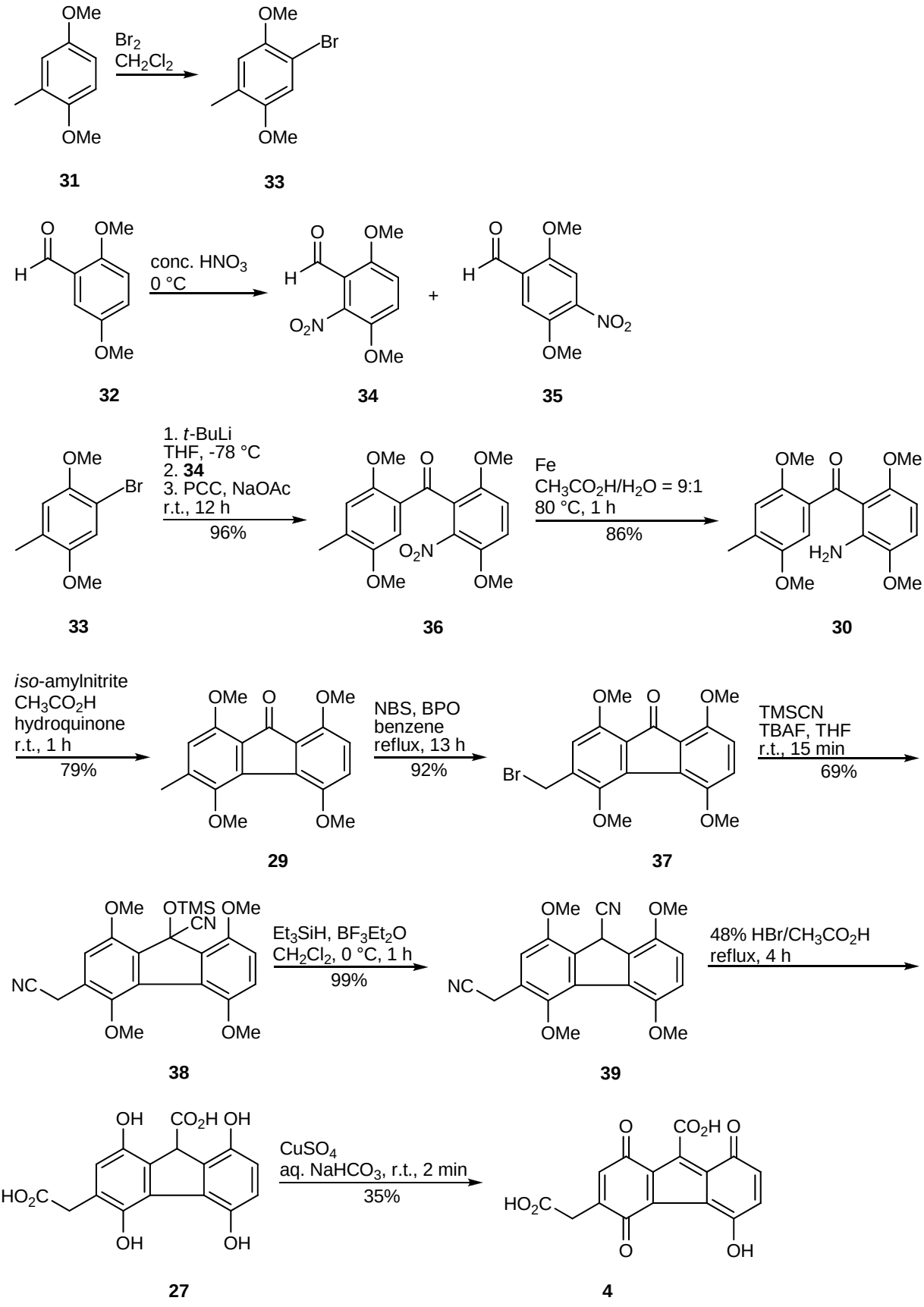
Hippopotamuses secrete a viscous alkaline liquid over their face and back. The colorless sweat turns red within a few minutes and then brown. The Japanese researchers have collected the highly alkaline red secretion by wiping the face and the back of a hippopotamus with gauze. Extraction and subsequent purification yielded solutions of a red and an orange dye. From the results of the spectroscopic characterization (^{1}H NMR, UV and MS) the structures of the two highly unstable pigments could be determined. The red compound was named hipposudoric acid (**4**) and the orange compound norhipposudoric acid (**5**). It has been postulated that **4** and **5** are derived from oxidative dimerization of homogentisic acid (**26**).
The function of **4** and **5** and the resulting brown polymer, as far as the hippopotamus is concerned, remains unclear. However, it has been shown that **4** and **5** may act as sunscreens.[1b,d] In addition, it has been demonstrated that **4** exhibits antibiotic activity. For further investigations of the chemical and biological properties of the scarcely available compounds it was necessary to obtain larger amounts of **4** and **5**. Therefore, Hashimoto and Nakata have performed the synthesis of hipposudoric acid (**4**) and norhipposudoric acid (**5**).

Their retrosynthetic analysis is presented in Scheme 1. The targets **4** and **5** would be obtained by oxidation of the corresponding hydroquinones **27** and **28** followed by enolization. **28** would be available by a single one-carbon elongation of **29** and **27** would be available by a double one-carbon elongation of **29**. The key intermediate **29** would be synthesized by Pschorr cyclization of **30**. The precursors of **30** would be **31** and **32**.



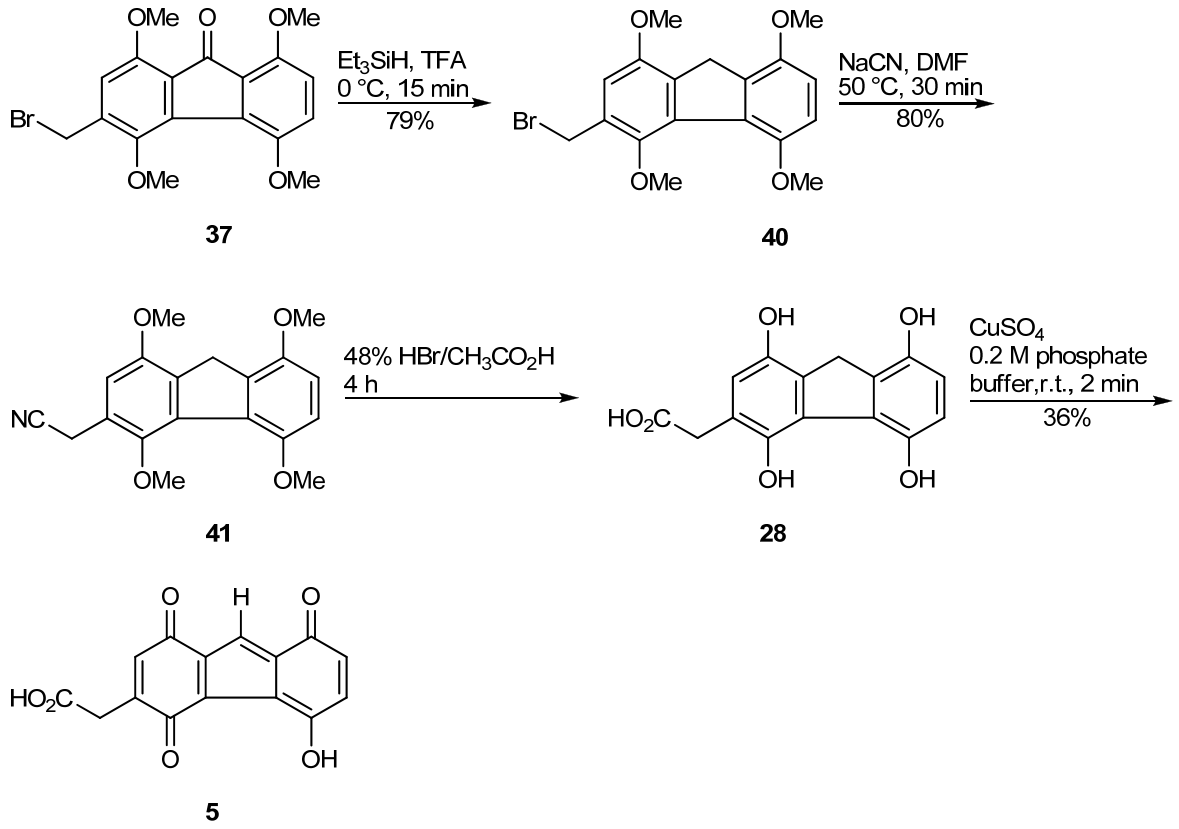
Scheme 1: Retrosynthesis of hipposudoric acid (**4**) and norhipposudoric acid (**5**).

Hashimoto and Nakata started with the bromination of 2,5-dimethoxytoluene (**31**) to give the desired bromo compound **33** (Scheme 2). The commercially available 2,5-dimethoxybenzaldehyde (**32**) was nitrated to afford the two isomers **34** and **35** in a 3:1 ratio. Lithiation of **33**, followed by reaction with the aldehyde **34** yielded an alcohol which was oxidized with pyridinium chlorochromate (PCC) to deliver the ketone **36**. The nitro group of **36** was reduced with iron to produce the amine **30** which was subjected to the Pschorr cyclization. For this purpose, **30** was oxidized with isoamylnitrite and the resulting diazonium salt was treated with hydroquinone leading to the desired fluorenone **29** in one pot.[33] The methyl group in **29** was then brominated with *N*-bromosuccinimide to give **37** which is the key intermediate for the synthesis of both pigments. Hipposudoric acid (**4**) was synthesized as follows: Reaction of **37** with TMSCN in the presence of TBAF yielded **38**, the product of a double one-carbon elongation. The resulting cyanohydrin **38** was deoxygenated with $Et_3SiH/BF_3{\cdot}Et_2O$ to yield the nitrile **39**. The hydrolysis of both nitrile groups and the cleavage of the four methyl ether groups could be achieved by treatment with aqueous HBr/CH_3CO_2H to deliver the highly unstable hydroquinone **27**. Oxidation of **27** with $CuSO_4$ under basic conditions yielded hipposudoric acid (**4**).



Scheme 2: Synthesis of hipposudoric acid (**4**) according to Hashimoto and Nakata.[1b-d]

The conversion of the key intermediate **37** into norhipposudoric acid (**5**) was achieved following a similar strategy (Scheme 3).

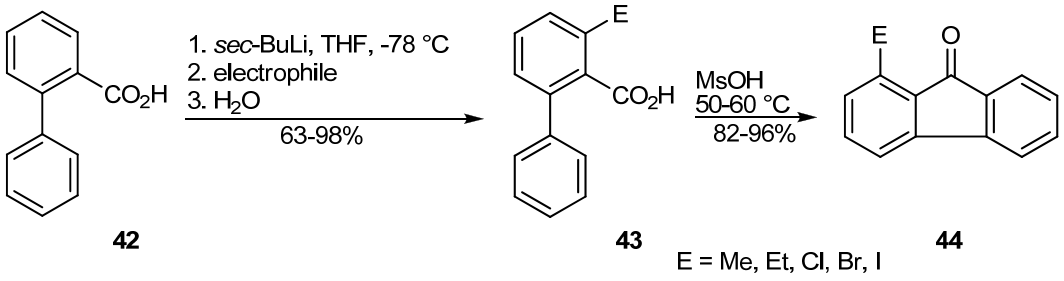


Scheme 3: Synthesis of norhipposudoric acid (**5**) according to Hashimoto and Nakata.[1b-d]

3 SYNTHESIS OF FLUORENES

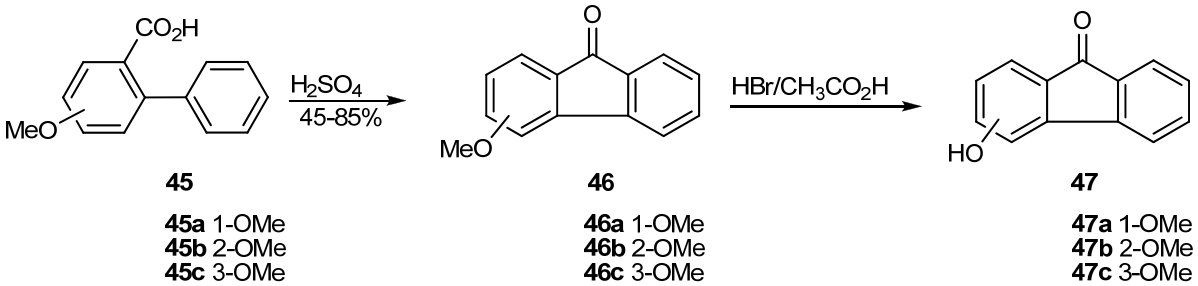
3.1 Electrophilic aromatic cyclizations

Mortier et al. have demonstrated that the combination of a directed *o*-metalation with an intramolecular Friedel-Crafts reaction provides an efficient route to the regioselective synthesis of 1-substituted fluoren-9-ones.[34] They have found that the reaction of 2-biphenyl carboxylic acid (**42**) with *sec*-butyllithium at –78 °C followed by quenching with electrophiles leads to 3-substituted 2-biphenyl carboxylic acids **43**. Treatment of **43** with methanesulfonic acid produced the fluoren-9-ones **44** with yields ranging from 82-96 % (Scheme 4).



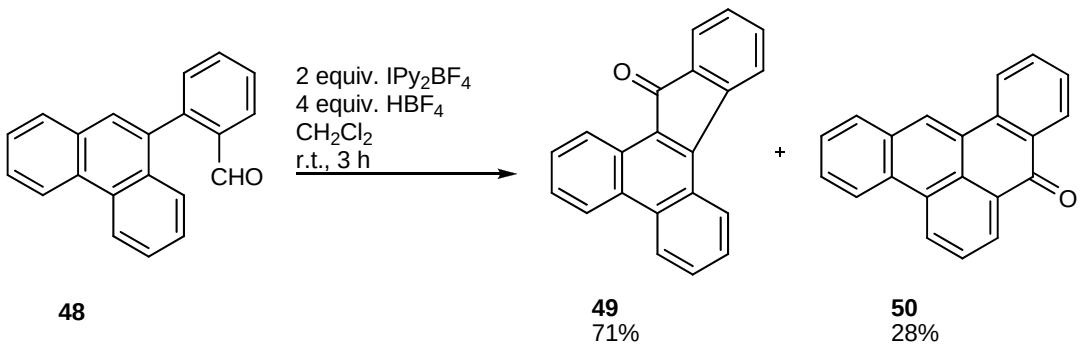
Scheme 4: Synthesis of 1-substituted fluoren-9-ones **44**.[34]

A similar cyclization has been reported by Coelho et al.[35] Cyclization of of 2-phenyl benzoic acids **45a-c** with sulphuric acid afforded the methoxyfluoren-9-ones **46a-c** with yields ranging from 45 to 85 %. Treatment of the protected fluoren-9-ones with a hydrobromic acid and acetic acid gave the hydroxyfluoren-9-ones **47a-c** with quantitative yields (Scheme 5).



Scheme 5: Synthesis of the fluorenones **47a-c** by cyclization of the phenyl benzoic acids **45a-c**, followed by deprotection of the methoxyfluoren-9-ones **46a-c**.[35]

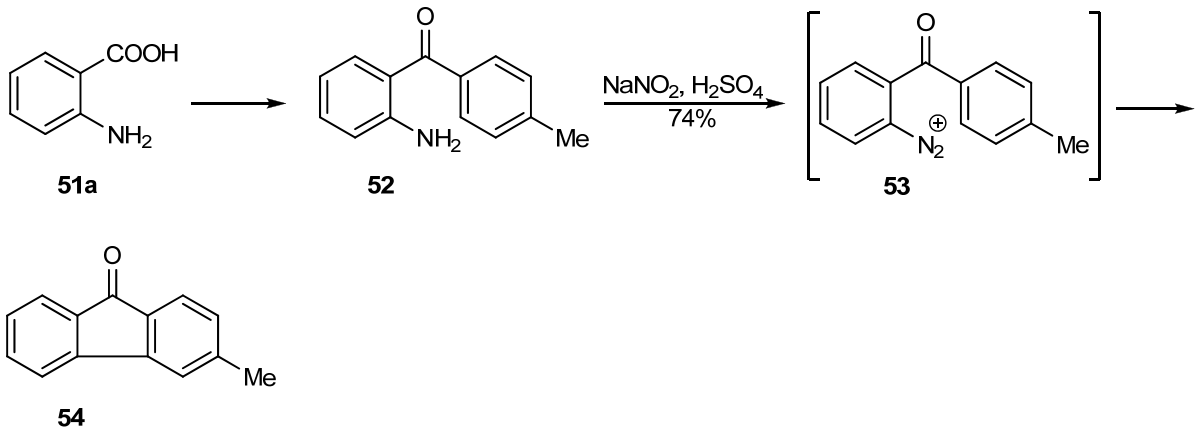
It is also possible to use aldehydes as acylating agents for the intramolecular Friedel-Crafts arylation of arenes as has been demonstrated by Barluenga et al.[36] Their method is straightforward and allows the synthesis of polycyclic aromatic ketones. As an example, reaction of 2-(9-phenanthrenyl)benzenecarboxaldehyde (**48**) with IPy_2BF_4/HBF_4 afforded a mixture of the two polycyclic aromatic ketones **49** and **50** (Scheme 6).



Scheme 6: The synthesis of polycyclic aromatic ketones by intramolecular Friedel-Crafts acylation of **48**.[36]

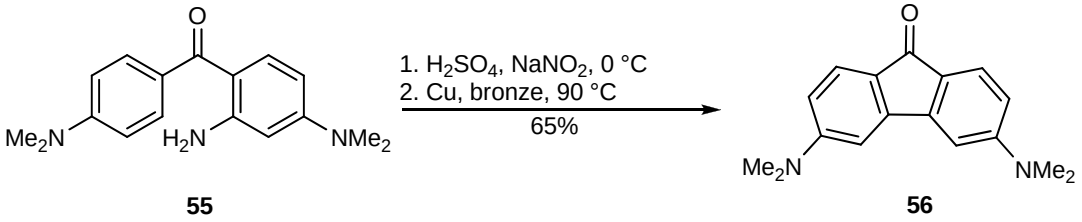
3.2 Radical cyclizations

Radical cyclizations are among the most important methods for the synthesis of the fluorene skeleton.[37] The required aryl radicals can be obtained from the corresponding anilines or haloarenes.[33a] Starting from anthranilic acid (**51a**), the aminobenzophenone **52** was obtained. Reaction of **52** with sodium nitrite and sulphuric acid afforded 3-methylfluoren-9-one (**54**) with 74 % yield. Probably, the reaction proceeds via formation and decomposition of the diazonium salt **53**. The resulting aryl radical undergoes an intramolecular radical arylation (Scheme 7).[3b]



Scheme 7: Synthesis of 3-methylfluoren-9-one (**54**).[3b]

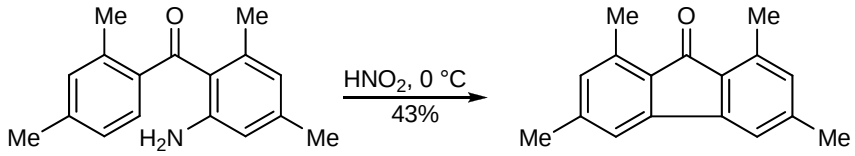
In a similar way 3,6-bis(dimethylamino)fluoren-9-one (**56**) was synthesized from 2-amino-4,4'- bis(dimethylamino)benzophenone (**55**) via diazotization and intramolecular coupling of the derived radical with 65 % yield (Scheme 8).[37d]



55 **56**

Scheme 8: Synthesis of 3,6-bis(dimethylamino)fluoren-9-one (**56**).[37d]

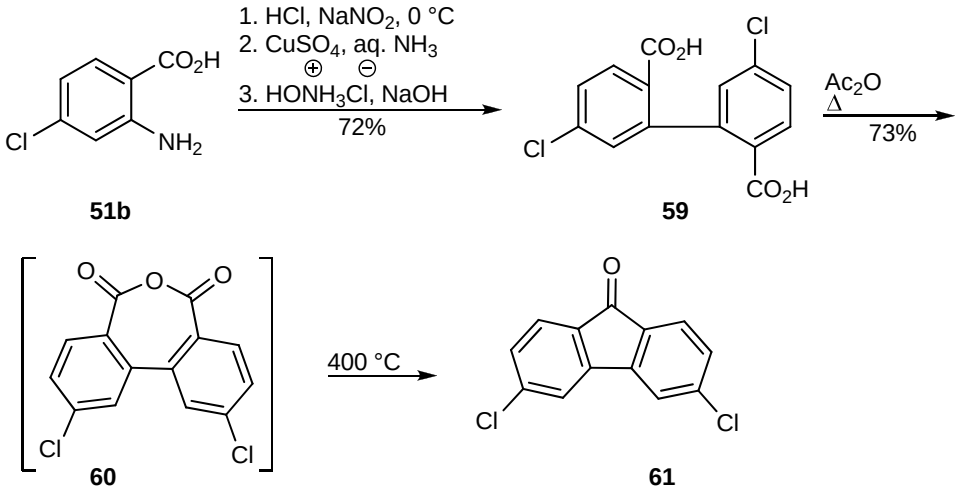
A third example for the Pschorr ring closure is the treatment of aminobenzophenone **57** with HNO_2 which provided the fluoren-9-one **58** (Scheme 9).[38]



57 **58**

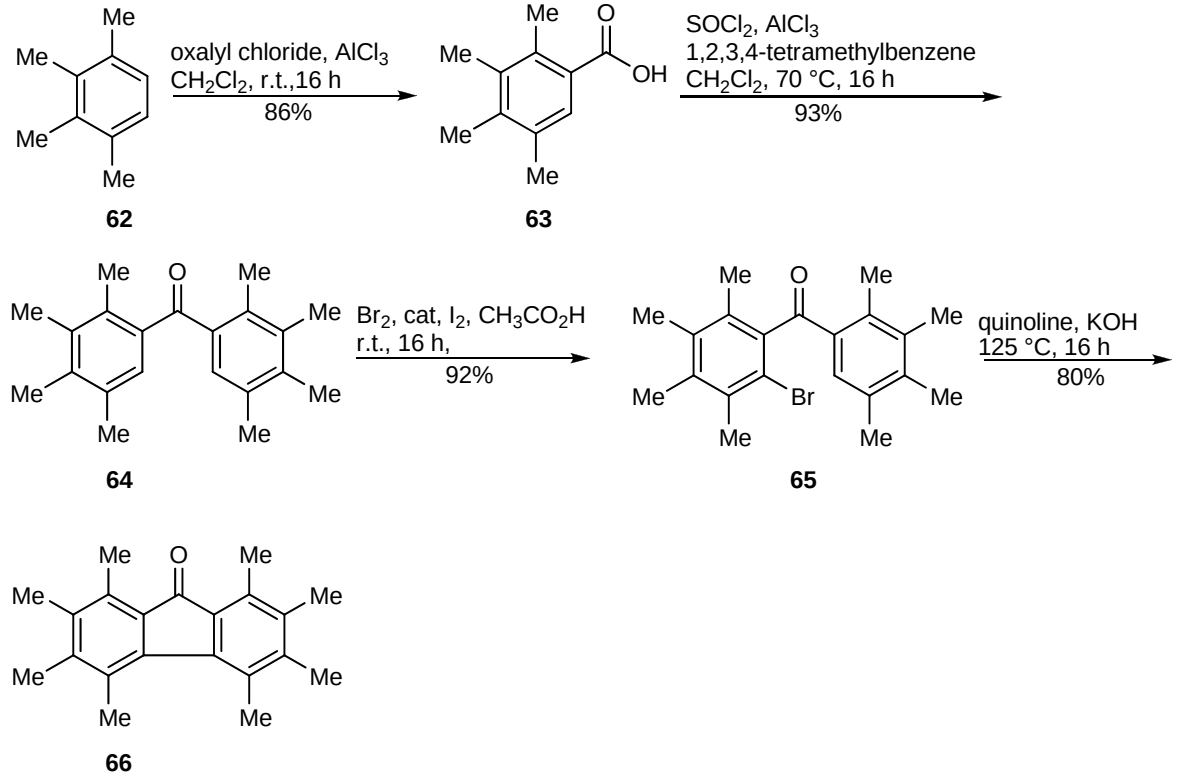
Scheme 9: Synthesis of 1,3,6,8-tetramethylfluoren-9-one (**58**).[38]

A remarkable example is the oxidative dimerization of two molecules of **51b**. It can be assumed that 4-chloroanthranilic acid (**51b**) after diazotization underwent self-coupling in the presence of aq. copper(II) sulphate and ammonia to give 5,5'-dichlorobiphenyl-2,2'-dicarboxylic acid (**59**). Transformation into the anhydride **60** was performed using acetic anhydride. The intermediate **60** was then transformed by *in situ* pyrolysis into 3,6-dichlorofluoren-9-one (**61**) with 53 % yield (Scheme 10).[37d]



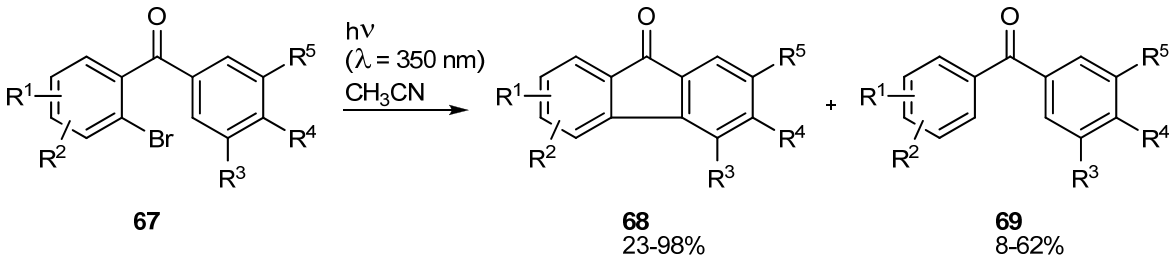
Scheme 10: Synthesis of 3,6-dichlorofluoren-9-one (**61**).[37d]

The 2-aroylaryl radicals required for the intramolecular ring closure reaction can also be generated from 2-bromobenzophenones. Heating of 6-bromo-2,2,3,3',4,4',5,5'-octamethylbenzophenone (**65**) which can be obtained from **62** by the sequence illustrated in Scheme 11 in the presence of quinoline at 125 °C for 16 h delivered 1,2,3,4,5,6,7,8-octamethylfluoren-9-one (**66**) with high yield (Scheme 11).[39]



Scheme 11: Synthesis of 1,2,3,4,5,6,7,8-octamethylfluoren-9-one (**66**).[39]

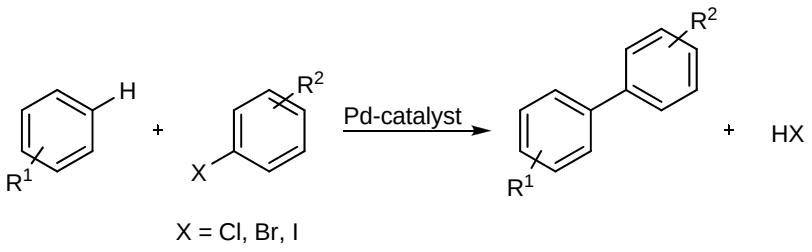
2-Aroylaryl radicals can also be generated by photoinduced homolysis of 2-bromoarylketones. Irradiation of **67** afforded the fluoren-9-ones **68** in moderate to excellent yields and the benzophenone derivatives **69** as byproducts (Scheme 12).[40] The results from the photochemical reactions established that the substituents of the two phenyl rings of the 2-bromobenzophenone exert a dramatic influence on the reactivity of the derived 2-aroylaryl radicals.



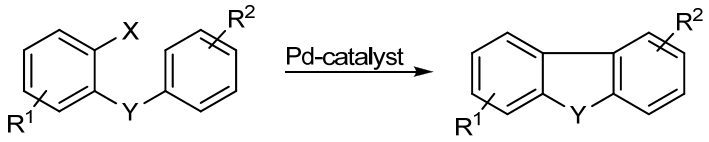
Scheme 12: Photoinduced homolysis of 2-bromoarylketones **67**.[40]

3.3 Palladium-mediated cyclizations for the synthesis of fluorenes and related skeletons

Over the last decades, the use of palladium reagents has become very popular in organic synthesis. It has been found that direct arylation of aryl C-H bonds can be performed using Pd reagents as catalysts. As outlined in Schemes 13 and 14 the direct arylation of aryl C-H bonds can be performed intermolecularly as well as intramolecularly.

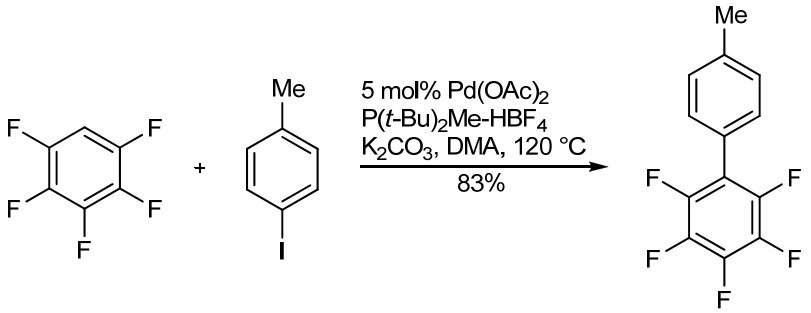


Scheme 13: The palladium-catalyzed intermolecular direct arylation for the synthesis of biaryls.



Scheme 14: The palladium-catalyzed intramolecular direct arylation.

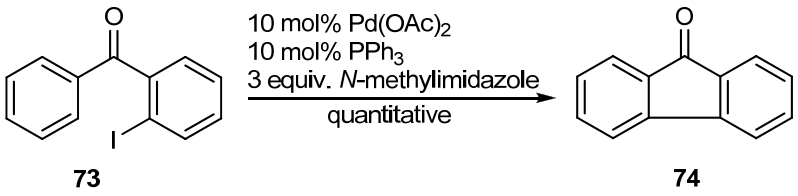
An example for the intermolecular direct arylation is presented in Scheme 15. 4-Iodotoluene (**71**) was reacted with pentafluorobenzene (**70**) in the presence of potassium carbonate as a base in *N*,*N*-dimethylacetamide at 120 °C with a catalyst generated *in situ* from $Pd(OAc)_2$ and the HBF_4 salt of di-*tert*-butylmethylphosphine to give the cross-coupled arylation product **72** with 83 % yield (Scheme 15).[41]



Scheme 15: The intermolecular direct arylation of pentafluorobenzene (**70**) according to Fagnou et al.[41]

Intramolecular direct arylations have been extensively utilized as a route to a multitude of polycyclic ring systems including fluorenes and related skeletons.

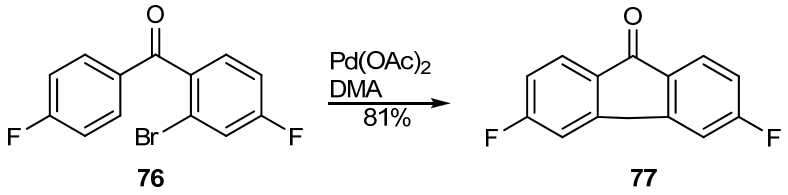
Ames and Opalko have investigated the palladium-catalyzed cyclization of 2-iodobenzophenone (**73**) to fluoren-9-one (**74**) under a variety of reaction conditions.[42] When 2-iodobenzophenone (**73**) was treated with 10 mol % palladium acetate and 10 mol % triphenyl phophine in 3 equivalents *N*-methylimidazole at 190 °C fluoren-9-one (**74**) was obtained quantitatively (Scheme 16).[42a]



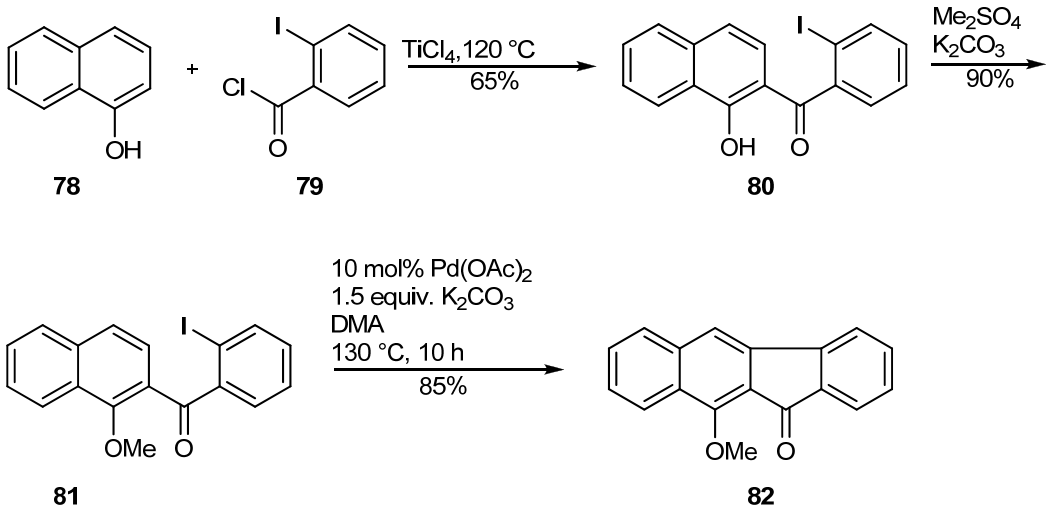
Scheme 16: Synthesis of fluoren-9-one (**74**) according to Ames and Opalko.[42a]

Similar results were observed when they used 2-bromobenzophenone (**75**) as a precursor.[42a]

The reaction has also been employed for the preparation of substituted fluoren-9-ones.[43] Balasubramanian and coworkers reported that the $Pd(OAc)_2$-catalyzed intramolecular arylation of 2-bromo-4,4'-difluorobenzophenone (**76**) in *N*,*N*-dimethylacetamide gave 3,6-difluorofluoren-9-one (**77**) with 81% yield (Scheme 17).

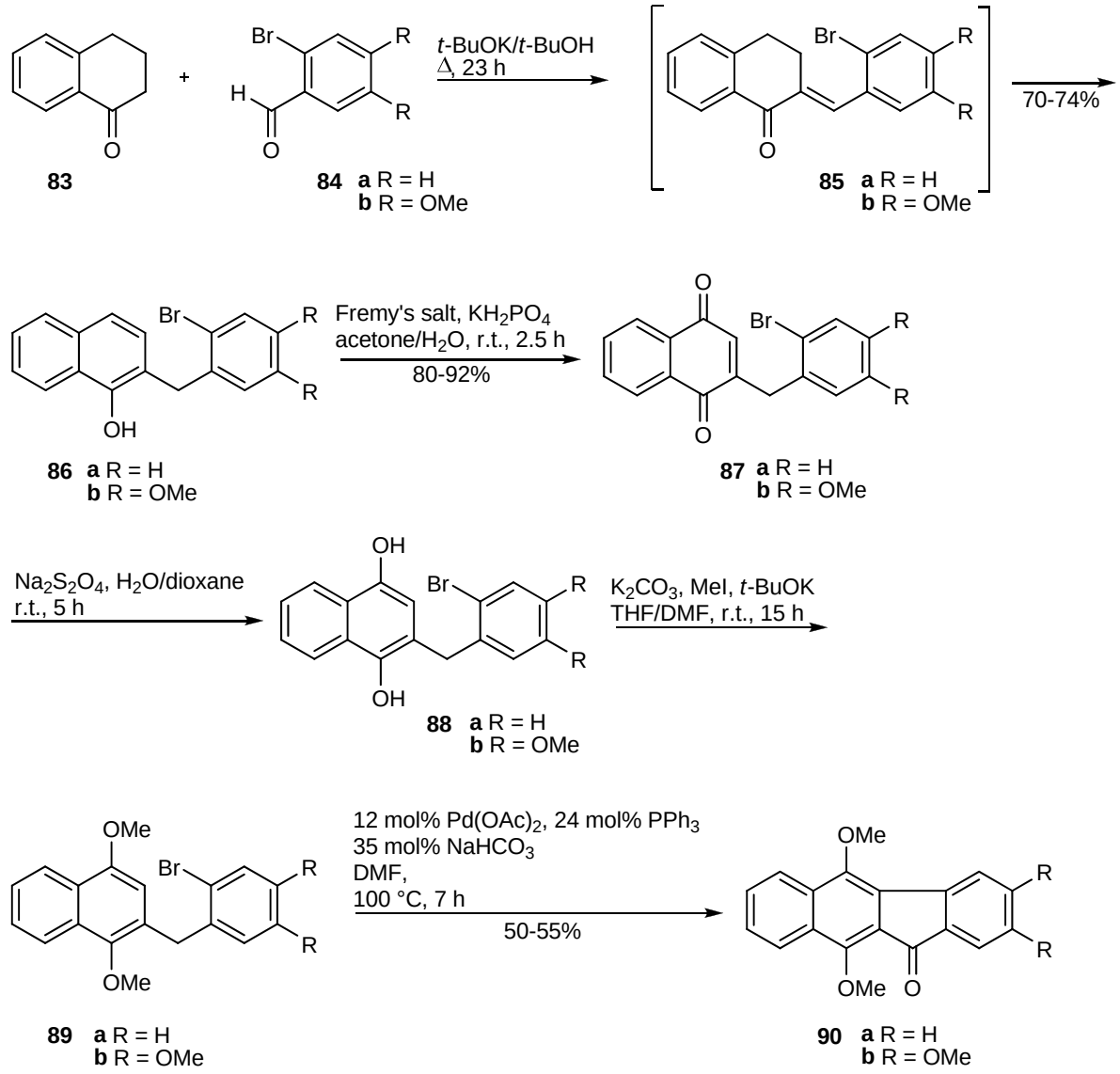


Scheme 17: Synthesis of 3,6-difluorofluoren-9-one (**77**) according to Balasubramanian et al.[43]



Scheme 18: Synthesis of 10-methoxy-11*H*-benzo[b]fluoren-11-one (**82**) according to Qabaja and Jones.[24]

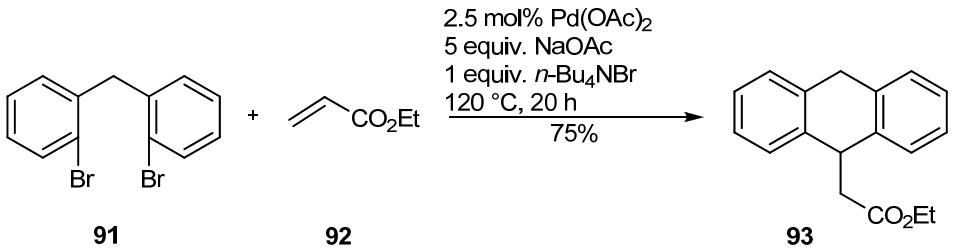
The intramolecular direct arylation can not only be used for the preparation of fluoren-9-ones but has also been employed for the synthesis of benzo[*b*]fluorenones. As an example, Qabaja and Jones described the synthesis of 10-methoxy-11*H*-benzo[*b*]fluoren-11-one (**82**) (Scheme 18).[24] Reaction of α-naphthol (**78**) with 2-iodobenzoyl chloride (**79**) in the presence of titanium tetrachloride gave **80** as a key intermediate. Methylation of **80** with dimethylsulfate under basic conditions afforded the methyl ether **81**. The palladium-mediated intramolecular direct arylation was conducted using a variety of methods with limited success. Best results were observed when the ring closure of **81** was performed with 10 mol % $Pd(OAc)_2$ in DMA at 130 °C for 10 h. Under these conditions 10-methoxy-11*H*-benzo[*b*]fluoren-11-one (**82**) could be isolated with 85 % yield.



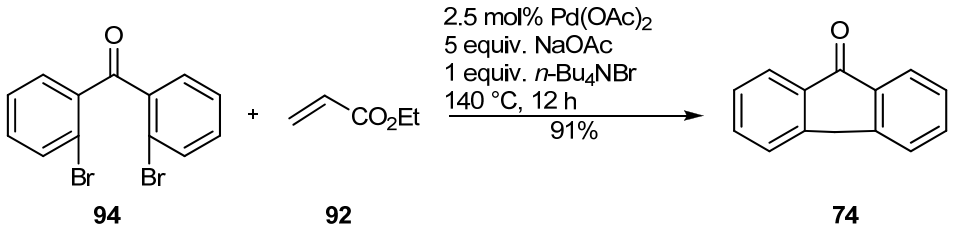
Scheme 19: A novel approach for the synthesis of benzo[*b*]fluoren-11-ones **90a,b**.

A similar approach has been used by Estevez et al. to synthesize two other substituted benzo[*b*]fluoren-11-ones.[9] Aldol condensation of 1-tetralone (**83**) with *o*-bromobenzaldehydes **84** resulted in the fromation of 2-benzylidene-1-tetralone (**85**) which underwent an isomerization under reaction conditions to give the 2-benzyl-1-naphthols **86**. Oxidation of **86** with Fremy's salt yielded the corresponding 2-benzyl-1,4-naphthoquinones **87** that were reduced with sodium dithionite to afford the dinaphthols **88**. The dinaphthols **88** were then converted into the dimethoxynaphthalenes **89** by treatment with MeI under basic conditions. When **89a** was heated with a mixture of $Pd(OAc)_2$, $P(Ph)_3$ and Na_2CO_3 in DMF at 100 °C for 7 h cyclization occured and **90a** could be isolated with 55 % yield. The cyclization of **89b** was achieved under similar conditions.

Unfortunately, the experimental details provided by the authors do not allow to judge whether their approach is of great value for the synthesis of substituted benzo[*b*]fluoren-11-ones (Scheme 19).



Scheme 20: Double Heck reaction between **91** and **92**.[44]

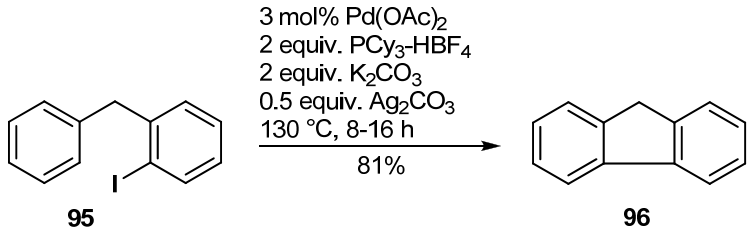


Scheme 21: Conversion of *o,o'*-dibromobenzophenone (**94**) into fluoren-9-one (**74**).[44]

Prashad et al. have reported some interesting observations.[44] When *o,o'*-dibromobiaryls like **91** were reacted with ethyl acrylate (**92**) in the presence of 2.5 mol% $Pd(OAc)_2$ a double Heck reaction took place to afford the substituted anthracene **93** with 75 % yield (Scheme 20). However, when this reaction was performed with *o,o'*-dibromobenzophenone (**94**) as substrate fluoren-9-one (**74**) was formed with 91 % yield (Scheme 21).

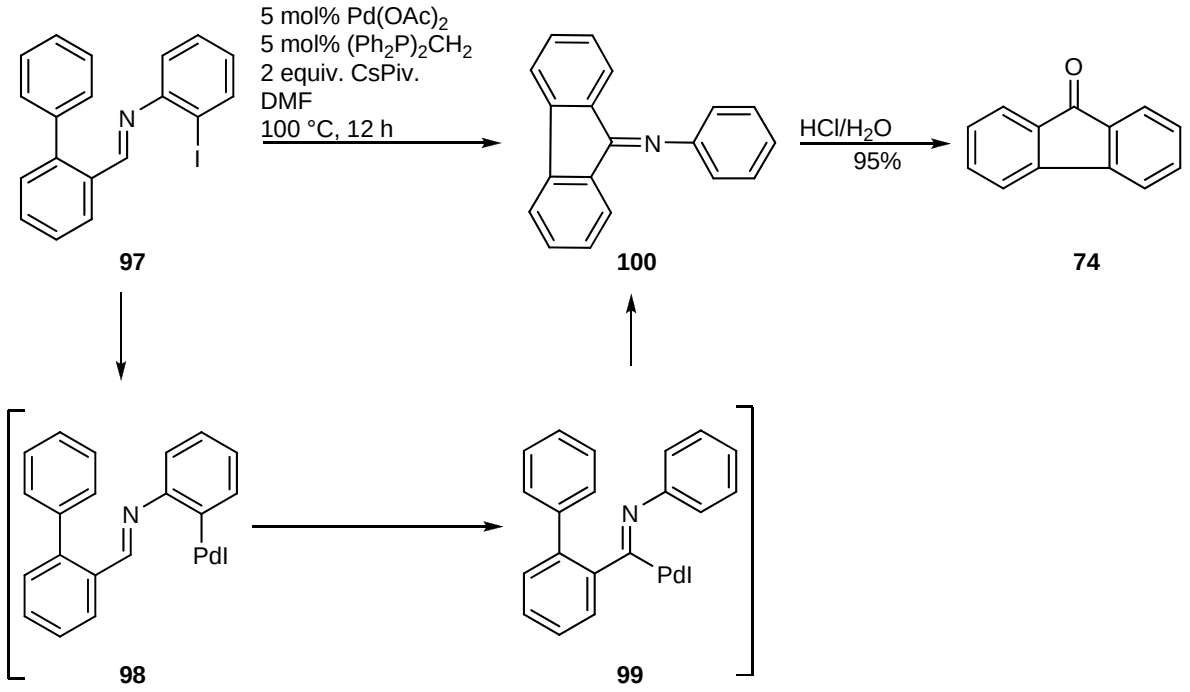
Fagnou et al. have demonstrated that the synthesis of fluorene derivatives by intramolecular direct arylation is not restricted to *o*-halobenzophenones as substrates but can also be performed with *o*-iodobiphenyl methane as starting material.[45] They have developed the intramolecular direct arylation of a broad range of simple and heterocyclic arenes with aryl iodides, bromides and chlorides. These reactions occur in excellent yield and are highly selective. Studies with aryl iodides as substrates revealed that catalyst poisoning occurs due to the accumulation of iodide in the reaction media. This can be overcome by the addition of silver salts that also permit these reactions to occur at lower temperature. Five-membered ring biaryls can be formed to give the carbazole and fluorene products. As an example, *o*-iodobiphenyl methane (**95**) has been transformed with 3 mol % palladium acetate, 2

equivalents potassium carbonate, 0.5 equivalents silver carbonate and 2 equivalents PCy_3-HBF_4 in *N*,*N*-dimethylacetamide at 130 °C into fluorene (**96**) with 81 % yield (Scheme 22).



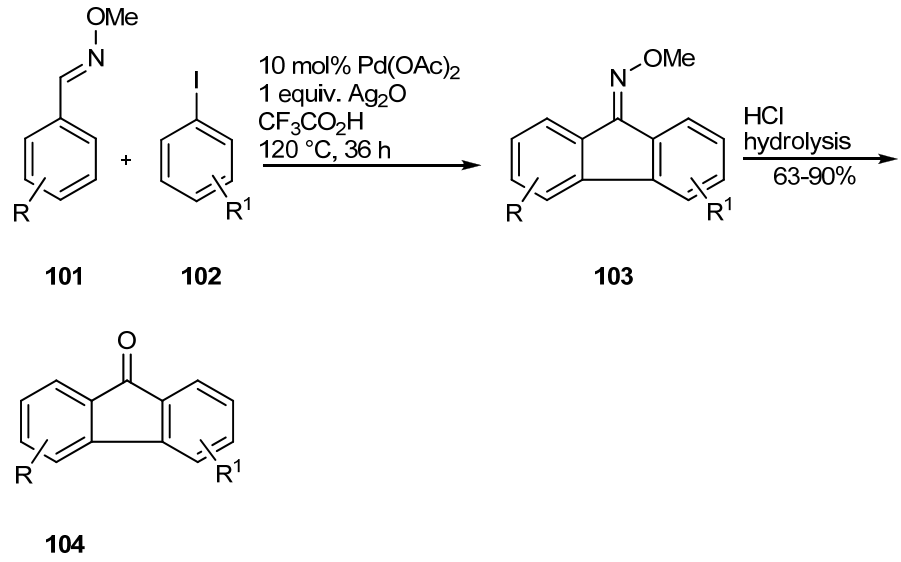
Scheme 22: Synthesis of fluorene (**96**) according to Fagnou et al.[45]

A different palladium-based approach for the synthesis of fluoren-9-one has been reported by Larock et al.[46] They have been able to synthesize a number of fluoren-9-ones by a novel aryl to imidoyl palladium migration, which is followed by intramolecular arylation. Larock has proposed that the reactions involve both a palladium migration mechanism and a C-H activation process proceeding through an unprecedented organopalladium (IV) hydride intermediate. For example, the imine **97** was treated with 5 mol % palladium acetate, 5 mol % bis(diphenylphosphino) methane (dppm) and 2 equivalents CsO_2CCMe_3 (cesium pivalate) in DMF at 100 °C to afford the imine **100**. After hydrolysis with aq. hydrochloric acid in acetone fluoren-9-one (**74**) was isolated with 95 % yield (Scheme 23).[46]



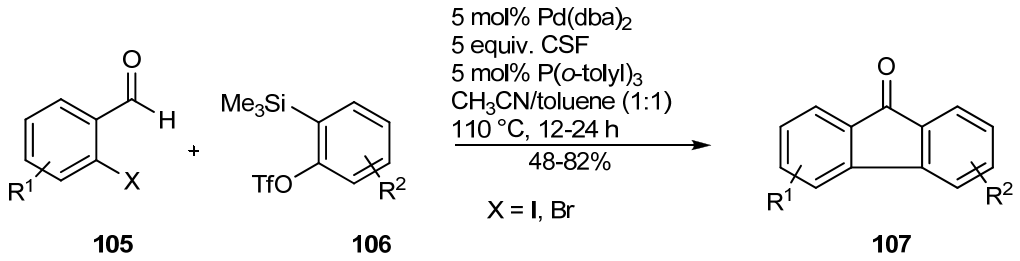
Scheme 23: Synthesis of fluoren-9-one (**74**) according to Larock et al.[46]

A further development of this approach came from the laboratory of Cheng et al.[47] They have successfully reported a new and efficient Pd-catalyzed synthesis of fluoren-9-ones from substituted aromatic oxime ethers and aryl halides. The conversion involves an unprecedented one-pot dual C-H activation and an oxidative Heck cyclization. Upon treatment of an aromatic oxime ether **101** and an aryl iodide **102** with 10 mol % palladium acetate and 1 equivalent of silver oxide in trifluoroacetic acid for 36 h at 120 °C a mixture of the fluoren-9-one oxime ether **103** and the fluoren-9-one **104** was isolated. The mixture was hydrolyzed to afford the fluoren-9-one **104** with yields ranging from 63 to 90 % (Scheme 24).



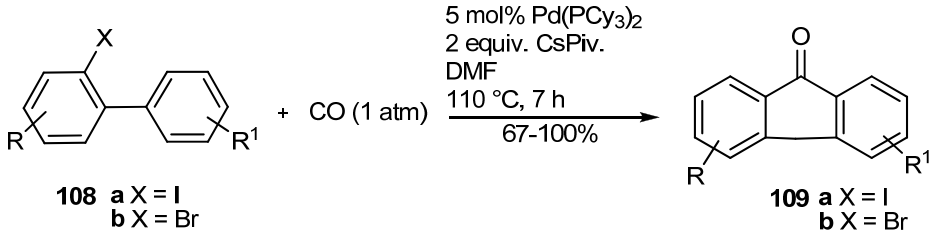
Scheme 24: Synthesis of fluoren-9-one derivatives **104** according to Cheng et al.[47]

Arynes generated *in situ* from 2-(trimethylsilyl)aryl triflates and CsF undergo annulation with *o*-haloarenecarboxaldehydes in the presence of a palladium catalyst to furnish a useful method for the synthesis of fluoren-9-ones with good yields.[48] So, reaction of 2-halobenzaldehyde **105** with silylphenyl triflate **106** and 5 mol % $Pd(dba)_2$, 5 equivalents CsF and 5 mol % P(*o*-tolyl)$_2$ as a catalyst in acetonitrile/toluene (1:1) led to the fluoren-9-ones **107** with yields ranging from 48 to 82 % (Scheme 25).



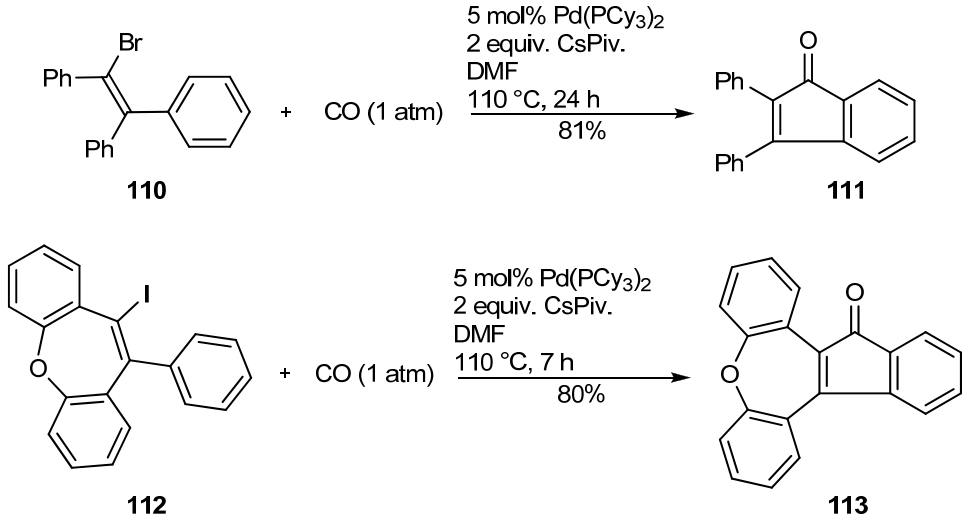
Scheme 25: Synthesis of fluoren-9-ones **107** from 2-halobenzaldehydes **105** and silylphenyl triflates **106**.[48]

Larock and Campo have also reported another method for the synthesis of fluoren-9-ones which is based on a novel palladium-catalyzed cyclocarbonylation of *o*-halobiaryls.[49] It has been demonstrated that this method can be utilized for the preparation of a variety of fluorenones and related skeletons in high yields and with good regioselectivity from *o*-halobiaryls and CO. This method provides a highly efficient and direct route to the fluoren-9-one skeleton as well as other related cyclic aromatic ketones. So, the palladium-catalyzed cyclocarbonylation has been carried out by reaction of **108** and CO in the presence of 5 mol % of a Pd catalyst, 5 or 10 mol % of an appropriate ligand, 2 equivalents of a base like sodium acetate, cesium carbonate or cesium pivalate at 110 °C for 7 h. Under these conditions the fluoren-9-ones **109** have been obtained with high yields (Scheme 26).



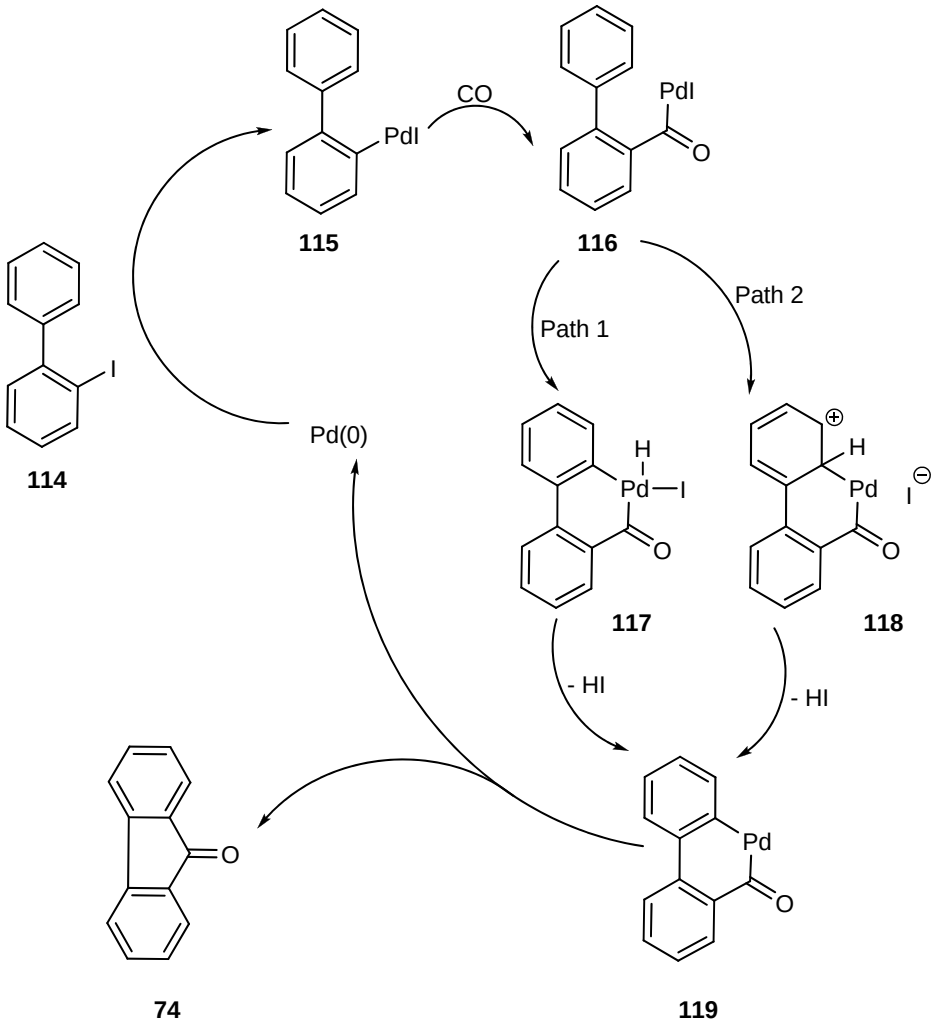
Scheme 26: Palladium-catalyzed cyclocarbonylation of *o*-halobiaryls **108** according to Larock and Campo.[49]

The palladium-catalyzed cyclocarbonylation can also be applied to vinylic halides.[49] For instance, the cyclocarbonylation of 1,2,2-triphenyl-1-bromoethene (**110**) resulted in 2,3-diphenyl-1-indenone (**111**) with 81% yield (Scheme 27). Furthermore, 5-iodo-6-phenyldibenz[*b,f*]oxepine (**112**) produced indeno[5,6]dibenz-[*b,f*]oxepin-14-one (**113**) with 80 % yield as also shown in Scheme 27.



Scheme 27: Palladium-catalyzed cyclocarbonylation of vinylic halides.[49]

The reaction mechanism that has been proposed by Larock and Campo for this palladium-catalyzed synthesis of fluoren-9-ones involves the following steps: 1) Oxidative addition of an aryl halide like 2-iodobiphenyl **114** to Pd(0), 2) insertion of CO to generate the acylpalladium intermediate **116**, 3) either oxidative addition of the neighboring aryl C-H to the acylpalladium **116** to generate a Pd(IV) intermediate (Path 1) or electrophilic palladation (Path 2) and subsequent elimination of HI to generate intermediate **119**, 4) reductive elimination of the ketone with simultaneous regeneration of the Pd(0) catalyst (Scheme 28).[49]



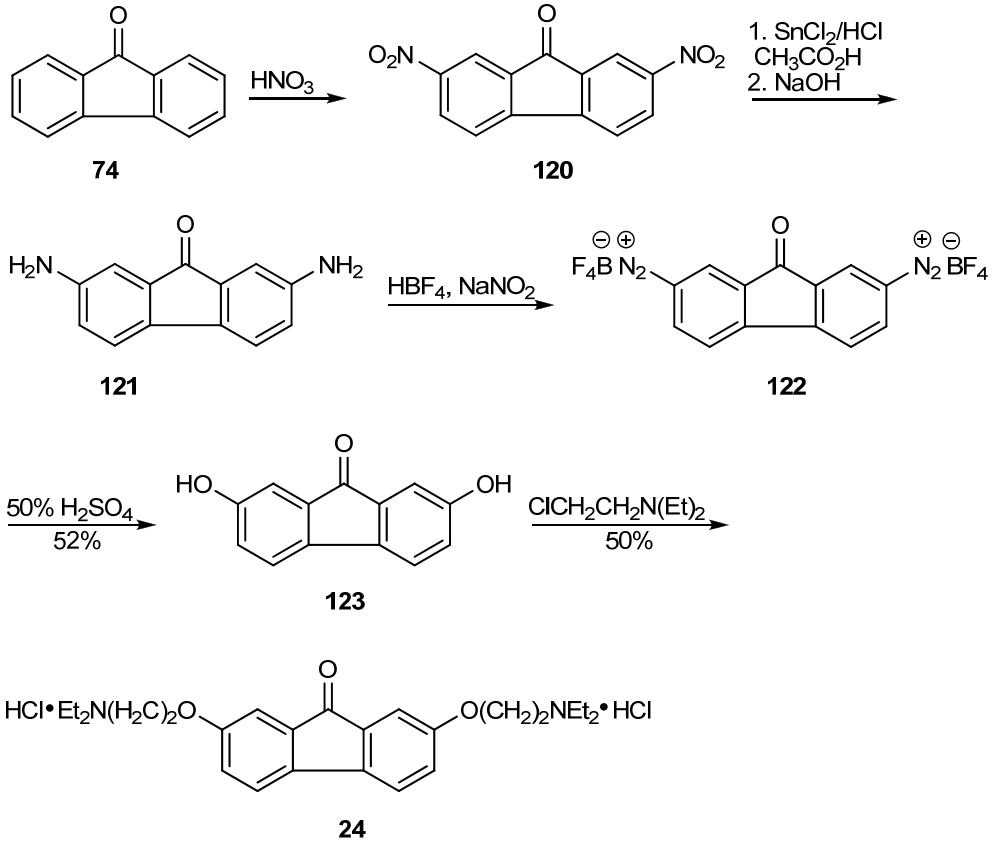
Scheme 28: Possible reaction mechanism of the palladium-catalyzed synthesis of fluoren-9-one (**74**) according to Larock and Campo.[49]

In summary, a number of Pd-based approaches to the synthesis of the fluorene and related ring systems has been developed. However, in many cases only the synthesis of simple model compounds like fluoren-9-one(**74**) has been reported. So far, little is known on scope and limitations of these synthetic methods.

3.4 Modification of the fluorene skeleton

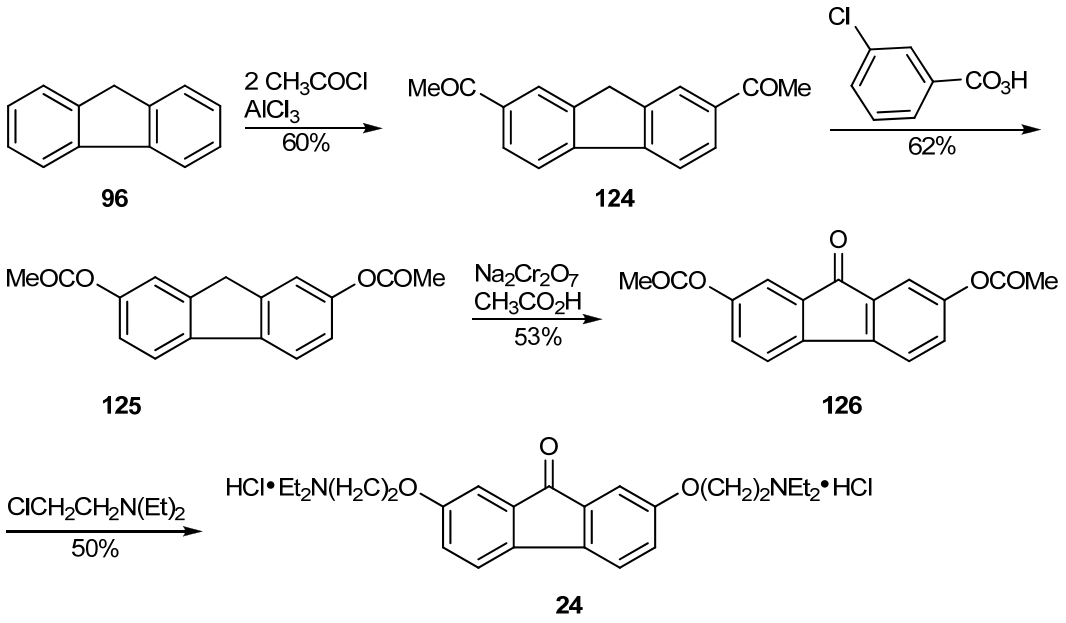
In addition to methods for the synthesis of the fluorene skeleton many approaches have been developed that are based on the modification of simple fluorenes. Good examples are two syntheses of tilorone hydrochloride (**24**) – a compound of great biological interest – starting from fluoren-9-one and fluorene, respectively. Both syntheses have been reported by Burke and Jollie.[29]

The first route starts with the nitration of fluoren-9-one (**74**) with nitric acid.[29] The resulting 2,7-dinitrofluorenone (**120**) was reduced with stannous chloride/hydrochloric acid to afford 2,7-diaminofluorenone (**121**) that was converted into the yellow tetrazonium salt **122** quantitatively. Compound **122** is decomposed slowly when it was added in small portions to boiling 50 % sulphuric acid a vigorous nitrogen evolution was noted. After cooling the reddish-brown 2,7-dihydroxyfluoren-9-one **123** was obtained with 52 % yield. Alkylation of **123** with *N*-chloroethyl *N,N*-diethylamine led to tilorone hydrochloride (**24**) with 50 % yield (Scheme 29).



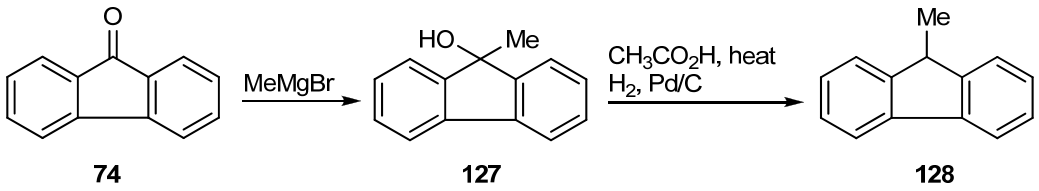
Scheme 29: Synthesis of tilorone hydrochloride (**24**) starting from fluoren-9-one (**74**).[29]

The second route for the synthesis of tilorone hydrochloride (**24**) starts with the acetylation of fluorene (**96**) to afford 2,7-diacetylfluorene (**124**).[6] Baeyer-Villiger rearrangement of **124** with *m*-chloroperbenzoic acid gave the diacetate **125** with 62 % yield which was oxidized with sodium dichromate in acetic acid to 2,7-fluoren-9-onediol diacetate (**126**). Alkylation with diethylaminoethyl chloride hydrochloride produced tilorone hydrochloride (**24**) (Scheme 30).



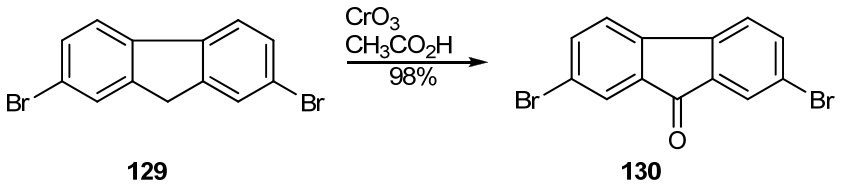
Scheme 30: Synthesis of tilorone hydrochloride (**24**) starting from fluorene (**96**).[29]

The introduction of alkyl groups at C-9 is illustrated by the synthesis of the indicator 9-methylfluorene (**128**) which could be obtained starting from fluoren-9-one (**74**) as a substrate.[50] The ketone was reacted with methyl magnesium bromide to yield **127** which was heated in acetic acid followed by reduction to afford the target molecule **128** (Scheme 31).



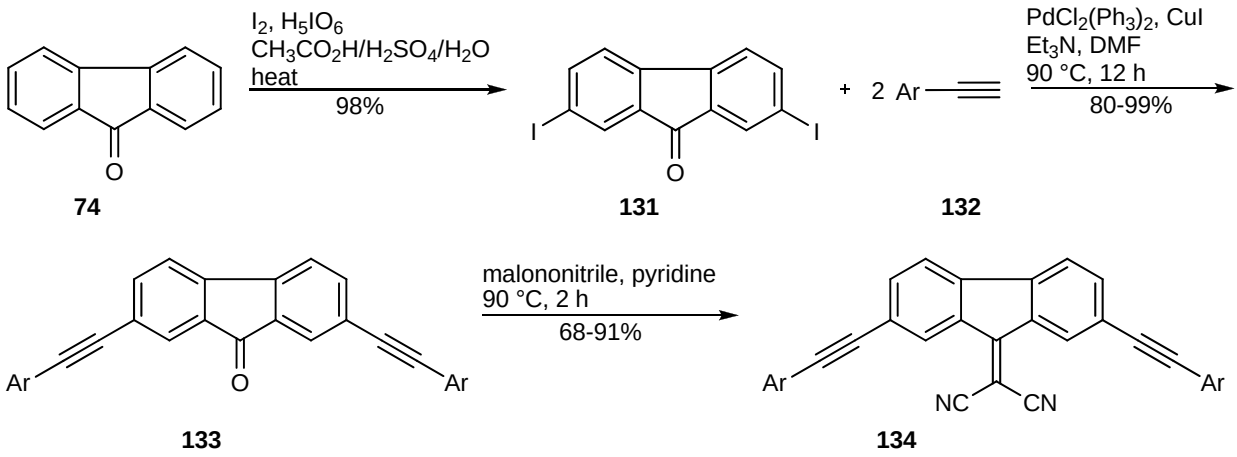
Scheme 31: Synthesis of 9-methylfluorene (**128**).[50]

The transformation of fluorenes into fluoren-9-ones is demonstrated by the treatment of 2,7-dibromofluorene (**129**) with chromium oxide in anhydrous acetic acid to give 2,7-dibromofluoren-9-one (**130**) in very high yield (Scheme 32).[51]



Scheme 32: Oxidation of 2,7-dibromofluorene (**129**).[51]

Finally, the transformation of fluoren-9-one (**74**) into several fluoren-9-ylidene malononitrile derivatives **134** should be mentioned.[52] Iodination of **74** afforded 2,7-diiodofluoren-9-one (**131**) which was reacted with two equivalents of an arylacetylene **132** in a Pd-catalyzed reaction to give **133**. Treatment of **133** with malononitrile resulted in the 2,7-disubstituted fluoren-9-ylidene malononitriles **134** with yields ranging from 68 to 91 % (Scheme 33).



Scheme 33: Synthesis of fluoren-9-ylidene malononitrile derivatives **134**.[52]

4 NATURAL PRODUCTS WITH A BENZO[*b*]FLUORENE SKELETON

4.1 Isolation

Prior to 1993 naturally occurring benzo[*b*]fluorenes were unknown. Once again, work on the biosynthesis of kinamycins resulted in the discovery of these compounds. The first three natural products of this class were discovered within a couple of months.[7b] Shin-Ya et al. reported the isolation of stealthin A (**14**) and B (**15**) (Figure 9), two free radical scavengers produced by *S. viridochromogenes*.[12] Cone et al. isolated kinafluorenone (**17**) which is the major colored metabolite from *S. murayamaensis* (mutant strain MC2).[13] Until the kinamycins were recognized to be diazobenzo[*b*]fluorenes, kinafluorenone was believed to be a shunt metabolite derived from an intermediate before nitrogen insertion.[7b,16] After the report on the isolation of **14**, **15** and **17** it was found that cysfluoretin **20** was produced by an unidentified *Streptomyces* species. It was established that **20** acts as an inhibitor of glutathione *S*-transferase.[7b,12,16]

Figure 9 shows the structures of the naturally occurring benzo[*b*]fluorenes stealthin A (**14**),[5,12] stealthin B (**15**),[12] stealthin C (**16**),[5] kinafluorenone (**17**),[13] kinobscurinone (**18**),[12,15] seongomycin (**19**),[15a] and cysfluoretin (**20**).[12] All these metabolites have been found in the extract of *S. murayamaensis*.[7b,c]

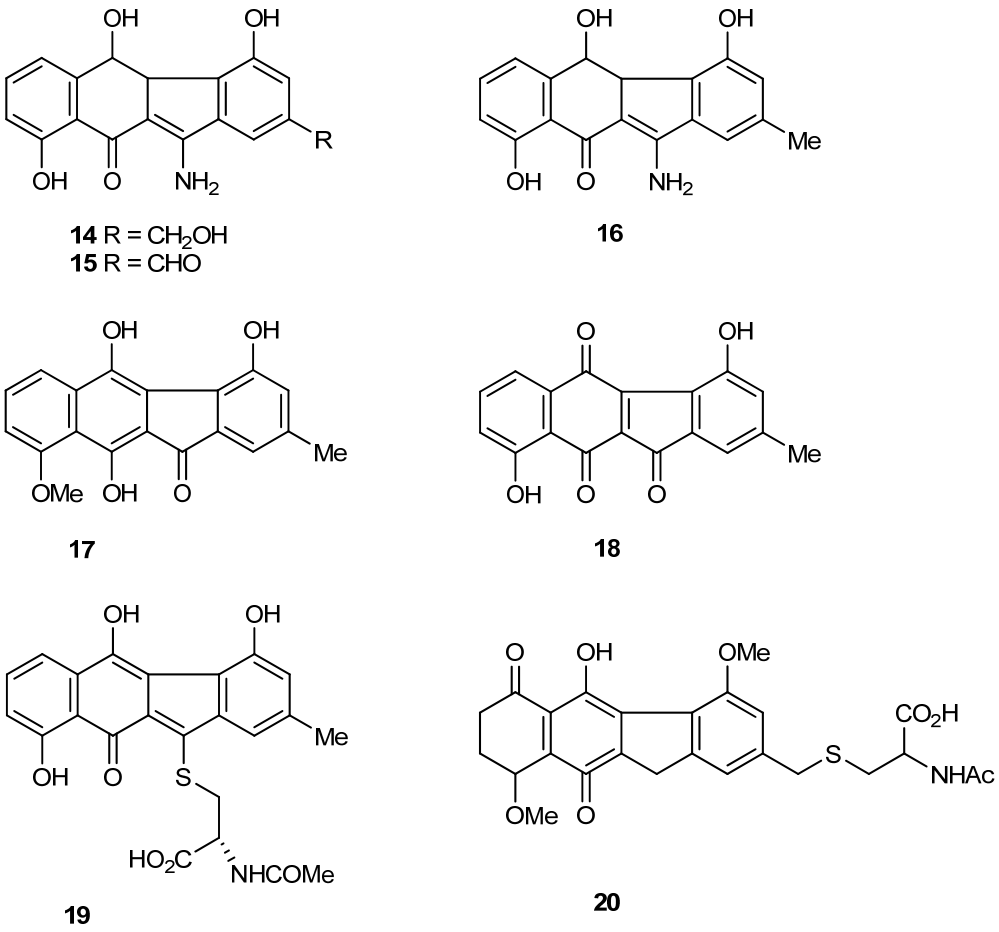
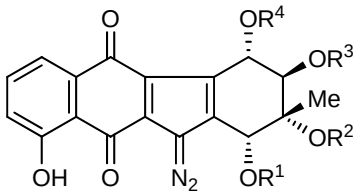


Figure 9: Structures of naturally occuring benzo[*b*]fluorenes **14**-**20**.

The kinamycin antibiotics A-F **6-11** were isolated from the culture broth of *Streptomyces Murayamaensis* sp. by Omura and co-workers.[17] (Figure 3).

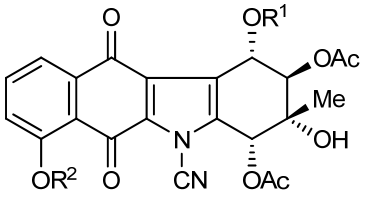


Nr	Kinamycin		R^1	R^2	R^3	R^4
6	"	A	H	Ac	Ac	Ac
7	"	B	H	Ac	H	H
8	"	C	Ac	H	Ac	Ac
9	"	D	Ac	H	Ac	H
10	"	E	Ac	H	H	H
11	"	F	H	H	H	H

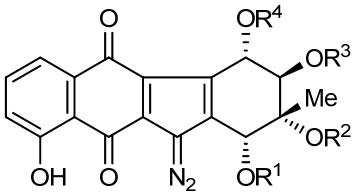
Figure 3: The structural assignment of the kinamycins A-F.[7a-c,8]

4.2 Structure elucidation of the kinamycins

The kinamycin antibiotics are naturally occuring diazo compounds[53] with a benzo[*b*]fluorene framework.[12,15,16] (Figure 10). Although the kinamycins have been known in the literature since 1970[17,18-22] an incorrect structural assignment of their basic skeleton formed the basis of all work until the correct structure of the skeleton was determined in 1994.[22,23] For more than 20 years the kinamycins were believed to be *N*-cyanobenzo[*b*]carbazoles[7b,c,8] [e.g, **23a** for kinamycin D (**9**)], but in fact they are diazo-substituted benzo[*b*]fluorenes (Figure 10).



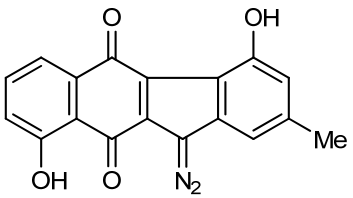
23a $R^1 = R^2 = H$



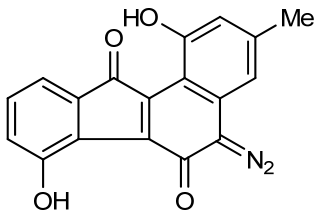
Nr	Kinamycin		R^1	R^2	R^3	R^4
6	"	A	H	Ac	Ac	Ac
7	"	B	H	Ac	H	H
8	"	C	Ac	H	Ac	Ac
9	"	D	Ac	H	Ac	H
10	"	E	Ac	H	H	H
11	"	F	H	H	H	H

Figure 10: Incorrect and correct structural assignment of kinamycins.[7b,c,8]

Gould and Dmitrienko have recently established the structure of prekinamycin (**12**) (Figure 11) based on an X-ray crystal structure analysis and detailed NMR analysis as well as synthetic studies.[7c,23] Also, they have determined the structure of compound **13** which has been renamed isoprekinamycin and its structure corresponds to a diazobenzo[*a*]fluorene rather than a diazobenzo[*b*]fluorene (Figure 11).[7c,10]



12



13

Figure 11: The correct structures of prekinamycin (**12**) and isoprekinamycin (**13**).[7c,10]

4.3 Biological activity

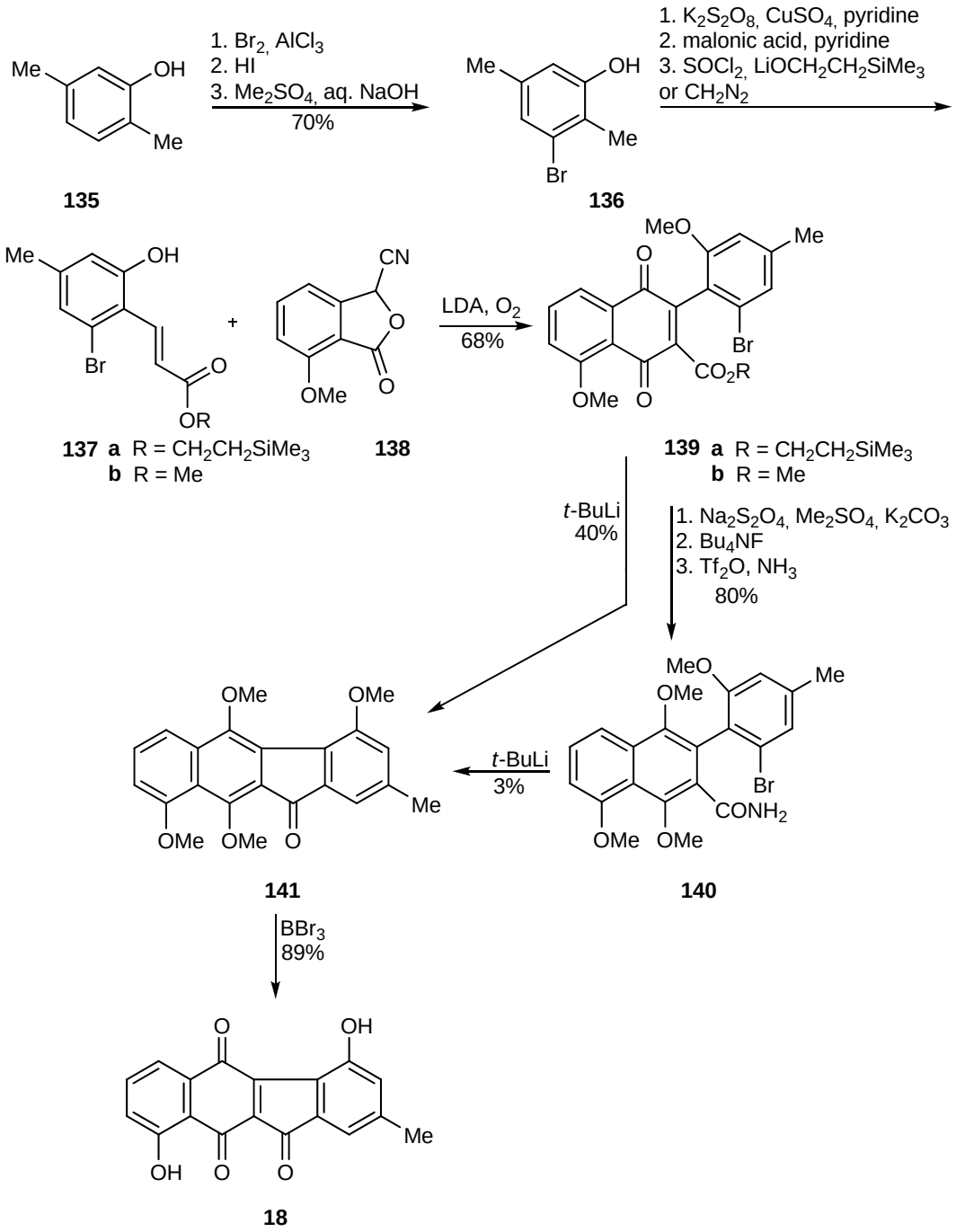
Kinamycins exhibit strong activity against Gram-positive and to a lesser extent against Gram-negative bacteria.[7c] In addition, kinamycin C shows antitumor activity.[7b,c,18] Benzo[*b*]fluorenes such as prekinamycin (**12**),[7,9] stealthin C (**16**),[5b] kinafluorenone (**17**),[13] and kinobscurinone (**18**)[12,15] exhibit antibacterial and antitumoral activity.[7c] Stealthin A (**14**) and stealthin B (**15**) exhibit a potent *in vitro* free radical scavenging activity. They also inhibit the hemolysis of the rat erythrocytes.[12]

4.4 Synthesis of natural products with a benzo[*b*]fluorene skeleton

A number of naturally occurring benzo[*b*]fluorenes have been made available by total synthesis. The first synthesis of kinobscurinone (**18**) has been reported by Gould and Snieckus,[15a,14] other total syntheses of this compound have been published by Snieckus et al.[14] and Gould et al.[5b, 15b] In addition, the total synthesis of the unnatural derivatives $O^{4,9}$-dimethyl stealthin A (**14**) and C (**16**) has been published by Kamikawa and Koyama.[5a,11] In 2007, Birman et al. have reported the total synthesis of prekinamycin (**12**).[7a] Of greater interest from a synthetic point of view is the synthesis of members of the kinamycin and lomaiviticin families.[7a] The first stereoselective total synthesis of (-)-kinamycin C (**8**) has been developed by Porco et al.[25] Soon after, Nicolaou et al. reported on the stereoselective total synthesis of the kinamycins C (**8**), F (**11**) and J.[26] In 2010, Herzon et al. have published the second stereoselective synthesis of kinamycin F (**11**).[27] An interesting approach to the synthesis of (±)-*o*-methyl-kinamycin C (**8**) stems from Ishikawa.[28] The synthesis of the benzo[*b*]fluorene core of the kinamycin has been reported by Echavarren et al.[54] Here, the synthesis of kinobscurinone (**18**), tri-*O*-methylkinafluorenone (**141**) and stealthin C (**16**) is presented.

In the total syntheses of kinobscurinone (**18**) that have been carried out by the group of Gould[15a] and Snieckus[14] the final step was the demethylation of tri-*O*-methylkinafluorenone (**141**) using boron tribromide as a reagent.[15a,14] Gould prepared compound **141** for the first time and with very poor yield starting from 2,5-dimethylphenol (**135**).[14,55] The quinone moiety in the intermediate **139a** was obtained by reaction of the substituted cinnamate **137a** with cyanophthalide **138**.[56] Unfortunately, the intramolecular acylation of amide **140**

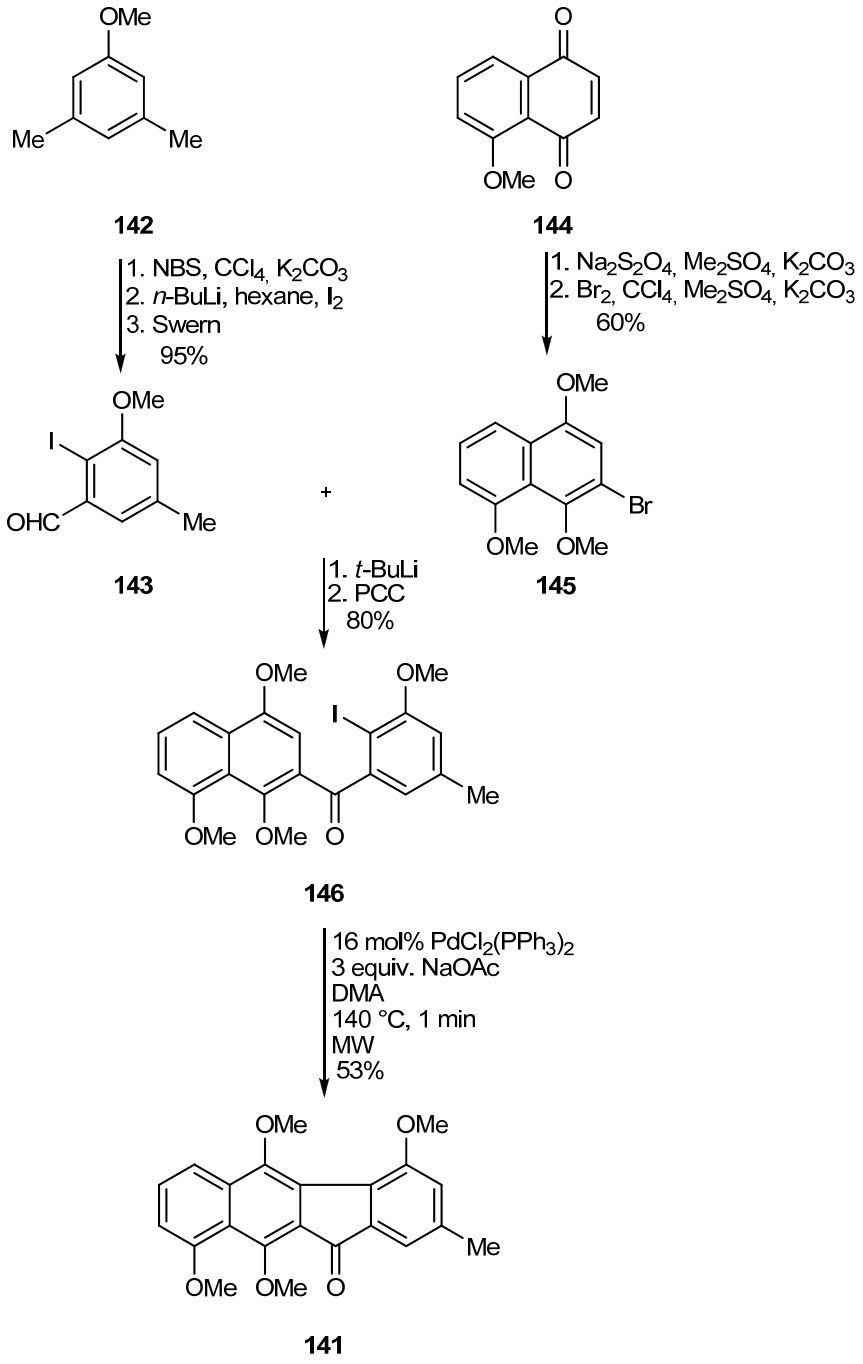
afforded **141** in only 3 % yield. However, the yield could be increased to 40 % by reaction of bromoester **139b** with *t*-BuLi[5b] (Scheme 34).



Scheme 34: The first total synthesis of kinobscurinone (**18**) according to Gould et al.[7c,14,15a]

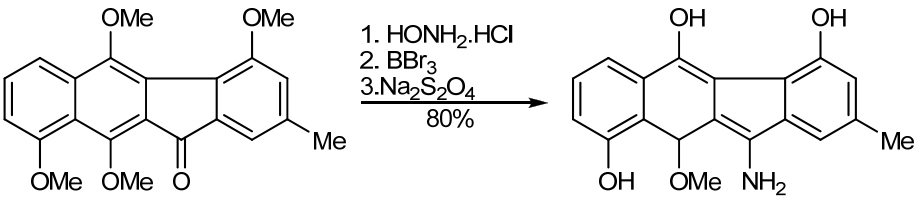
More recently, Qabaja and Jones described the synthesis of tri-*O*-methylkinafluorenone (**141**) following a different strategy.[24] In their approach the central step was the intramolecular ring closure of the highly functionalized iodobenzophenone **146** by means of a palladium-

catalyzed reaction. Starting with dimethylanisole **142** the iodoaldehyde **143** was obtained after a series of standard reactions as illustrated in Scheme 35. The partner for the coupling reaction – compound **145** – could easily be prepared from methoxyjuglone (**144**). Treatment of **144** with *t*-BuLi afforded a carbanion which was reacted with aldehyde **143**. Oxidation of the crude product with pyridinium chlorochromate (PCC) delivered the key intermediate **146**. The palladium-mediated ring closing reaction of **146** was achieved by treatment with $PdCl_2(PPh_3)_2$ under microwave conditions. Using this protocol **141** could be isolated with 53 % yield.



Scheme 35: Synthesis of tri-*O*-methylkinafluorenone (**141**) according to Jones.[7c,24]

Gould[5b,7c] and co-workers have also demonstrated that tri-*O*-methylkinafluorenone (**141**) can be transformed into stealthin C (**16**). In the first step **141** was reacted with hydroxyl amine to give the corresponding oxime (99 % yield) which in turn was treated with boron tribromide and sodium dithionite to afford the target molecule **16** (Scheme 36).



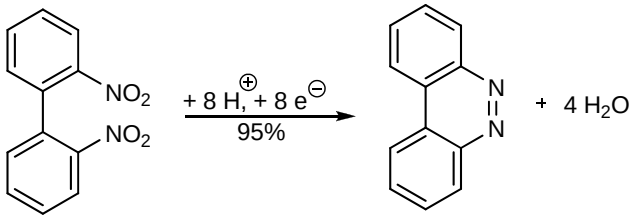
141 **16**

Scheme 36: Synthesis of stealthin C (**16**) according to Gould.[5b,7c]

5 DEOXYGENATION OF NITROAROMATICS

5.1 Early stage intramolecular cyclizations of nitroaromatics

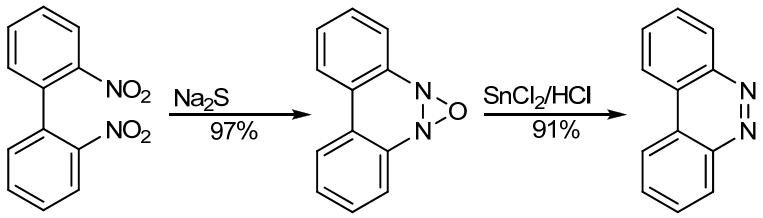
Störmer and Brockerhof reported one of the earliest methods for the transformation of ω-nitroketones into *N*-heterocycles under reductive conditions. Inorganic compounds like Sn or $SnCl_2$/HCl were used as reducing agents.[57] The electrochemical reduction of 2,2'-dinitrodiphenyl (**147**) to give 3,4-benzocinnoline (**148**) in one step has been reported by Wohlfart (Scheme 37).[58]



147 **148**

Scheme 37: Formation of 3,4-benzocinnoline (**148**) by electrochemical reduction of 2,2'-dinitrodiphenyl (**147**).[58]

The synthesis of 3,4-benzocinnoline (**148**) by reduction of 2,2'-dinitrodiphenyl (**147**) in two steps has been shown by Wohlfart,[58] Ullmann[59] and King.[60] It starts with the reduction of 2,2'-dinitrodiphenyl (**147**) to give the 3,4-benzocinnoline *N*-oxide (**149**). The intermediate **149** was then reduced with $SnCl_2$ under acidic conditions (or by electrochemical reduction) to lead to the final product **148** (Scheme 38).

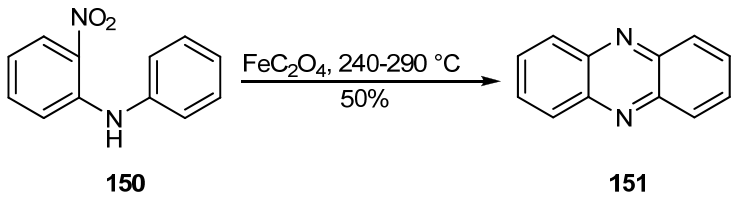


147 **149** **148**

Scheme 38: The transformation of 2,2'-dinitrodiphenyl (**147**) into **148** in two steps.[58-60]

Waterman and Vivian described the deoxygenation of nitroaromatics using reducing agents like metallic iron or ferrous(II) oxalate (FeC_2O_4).[61] This procedure was one of the most

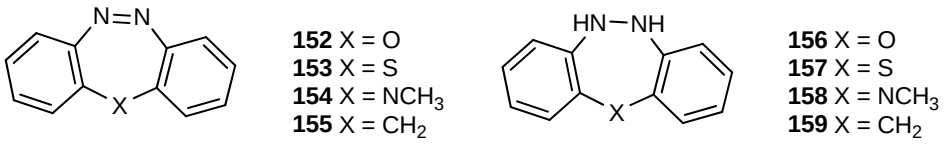
widely used methods for the synthesis of phenazines. A typical example is the reductive cyclization of 2-nitrodiphenylamine (**150**) with Fe or ferrous(II) oxalate (FeC_2O_4) to give phenazine (**151**) with 50 % yield (Scheme 39).



150 **151**

Scheme 39: Cyclization of 2-nitrodiphenylamine (**150**) to phenazine (**151**).[61]

The reductive of intramolecular cyclization of nitroaromatics using reducing agents like $LiAlH_4$, Raney-Ni/N_2H_4, Na_2S or Zn/NH_3 has been extended to the synthesis of numerous heteroaromatic systems[62-64] including **152-159** (Figure 12).



152 X = O
153 X = S
154 X = NCH_3
155 X = CH_2

156 X = O
157 X = S
158 X = NCH_3
159 X = CH_2

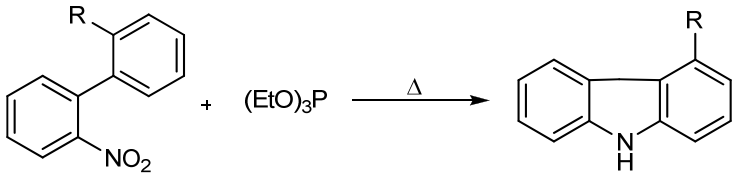
Figure 12: The structures of *N*-heterocycles **152-159** synthesized by reductive cyclization of dinitroaromatics.[62-64]

The reductive cyclization of nitroaromatics has been achieved by a number of research groups using several reducing agents, different reaction conditions and different nitroaromatic substrates.[57-64] Therefore a large number of *N*-heterocycles has been synthesized.[62-64] FeC_2O_4 has been shown to be one of the most efficient reagents for the synthesis of phenazine derivatives.[61]

5.2 Cyclizations of nitroaromatics with tervalent phosphorous reagents

Cadogan et al. discovered that nitroaromatics can be reacted with tervalent phosphorous compounds like trialkyl phosphites, trialkyl- and triarylphophines to prepare heterocyclic nitrogen ring systems owing to the deoxygenation of the nitro group.[65,66] The corresponding phosphates are also formed as byproducts. The major driving force of these reactions is the great strength of the formed phosphorous oxygen bond (P=O).[66] The products derived from

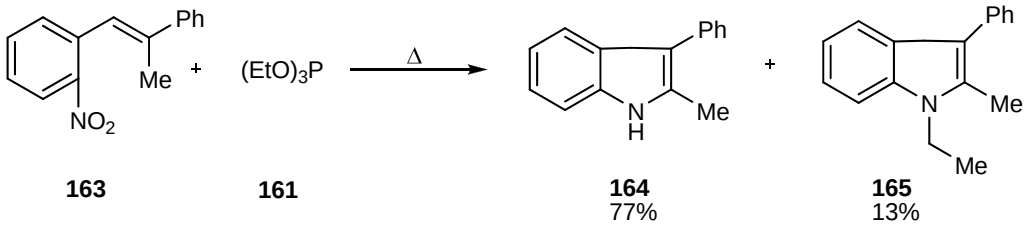
the reactions of nitroaromatics with tervalent phosphorous reagents are similar to the products obtained from thermal and photochemical reactions of azides and azirines.[67] Triethyl phosphate is the most commonly used deoxygenating reagent while triphenyl phosphine, phosphorous trihalides and diethoxy methylphosphine have been employed less frequently.[68] Depending on the structure of the substrate and reaction conditions the deoxygenated fragments have also been isolated in the form of azoxy compounds,[69-71] derivatives of phosphorimidic acid[69,72] and as tars.[65b,72] The deoxygenation of aromatic nitro compounds by trivalent phosphorous compounds has been extensively developed not only by Cadogan but also by Sundberg.[73] Sundberg demonstrated the close similarity between the azide decomposition and the deoxygenation of nitroaromatics with tervalent phosphorous reagents. He concluded that a reactive electron deficient nitrogen atom is formed during the deoxygenation of nitroaromatics. For the deoxygenation of nitroaromatics a number of intermediates has been suggested. Generally, the resulting product is almost identical to the product formed from the azide decomposition. Since the discovery of the reaction in 1962 the reduction of nitro compounds using triethyl phosphite and related reagents has been recognized as a general route to a wide variety of nitrogen containing heterocycles including carbazoles[65,74a] and benz[*a*]carbazoles.[74b,c] The deoxgenation of 2-nitrobiphenyl (**160a**) or 2'-bromo-2-nitrobiphenyl (**160b**) under reflux conditions with triethy phosphite (**161**) yielded carbazoles **162a** and **162b** (Scheme 40).[65] Several functional groups including alkyl, methoxy, halide and ester groups are tolerated by the conditions of the reaction and the corresponding carbazoles have been prepared in good yields.[75]



Scheme 40: $(EtO)_3P$-mediated cyclizations of **160a,b** under thermal conditions.

Sundberg reported that the deoxygenation of β,β-disubstituted *o*-nitrostyrenes with triethyl phosphite results in the formation of indole derivatives and is accompanied by a rearrangement.[76a] A study of the migratory aptitude was carried out by Sundberg and Kotchmar.[76b] An example is the synthesis of 2-methyl-3-phenylindole (**164**) from α-methyl-2'-nitrostilbene (**163**) that underwent deoxygenation followed by rearrangement (Scheme

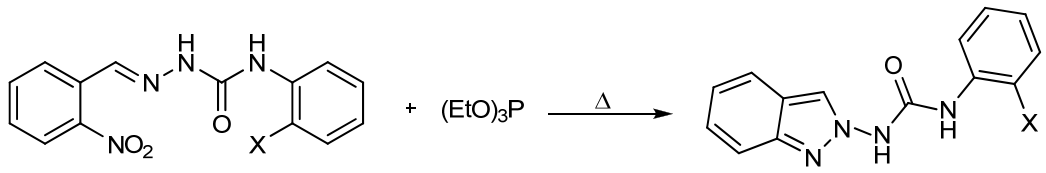
41).[76a] It has been assumed that the 1-ethyl derivative **165** has been formed from **164** by alkylation with triethyl phosphate which in turn is the oxidation product of triethyl phosphite.[65b,72,76a,77] The migration of a phenyl over a methyl group depends on the stereochemical configuration of the aromatic nitro compounds.[76b,c]



163 **161** **164** 77% **165** 13%

Scheme 41: Synthesis of 2-methyl-3-phenylindole (**164**) and *N*-ethyl-2-methyl-3-phenylindole (**165**).

Some carbazoles such as indolocarbazoles[78a] and indolo[2,3-*a*]carbazoles[78b,c] have been prepared via thermal deoxygenation of nitrocarbazole derivatives or terphenyl compounds with triphenyl phosphine or triethyl phosphite, respectively. The selective formation of 1-isoindol-2-yl-3-phenylurea **167a,b** from phenyl semicarbazone **166a,b** has been achieved by an exces of triethyl phosphite (Scheme 42). A nitrene has been postulated as the intermediate. The selectivity of the transformation is remarkable as the nitrene could not only cyclize to give the five-membered isoindole system but could also cyclize to give the six-membered 1,2,3-benzotriazine.[79]

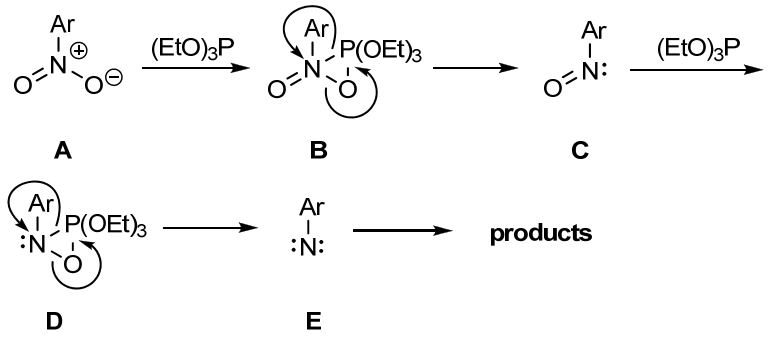


166a X = H
166b X = Br
161 60% 40%
167a X = H
167b X = Br

Scheme 42: The synthesis of 1-isoindol-2-yl-3-phenylurea **167a,b**.[79]

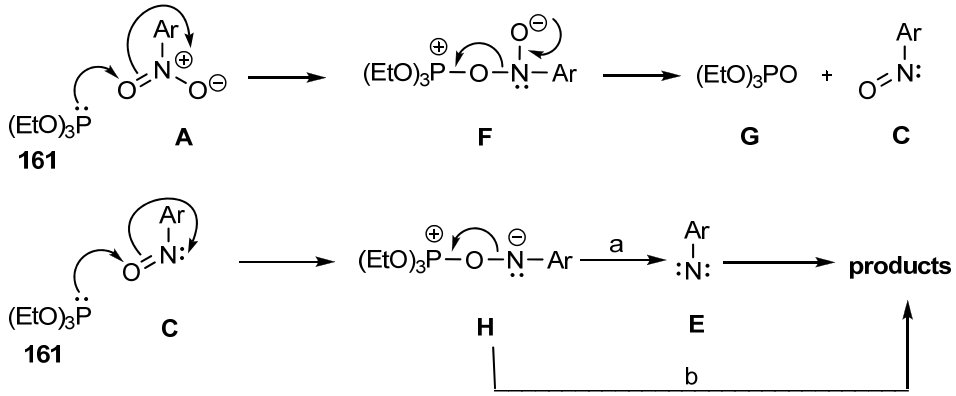
The irradiation of nitroaromatics such as a solution of nitrobenzene in triethyl phosphite has been described by Sundberg et al.[80a] This leads to oxygen transfer reactions at room temperature and results in the formation of a mixture of products including pyridines, anilines and phosphates as well as phosphorimidates. In another publication Sundberg showed that the presence of acetic acid in the reaction of triethyl phosphite with nitroaromatics under photochemical conditions exhibits a marked influence on the nature of the reaction

products.[80b] He deduced that the products of the deoxygenation of nitroaromatics can usually be rationalized in terms of arylnitrene intermediates. Moreover, he found that the presence of acetic acid resulted in the formation of products which appeared to arise from nucleophilic aromatic substitution process.[80c] Regarding the mechanism of the cyclization of nitroaromatics with triethyl phosphite it is believed that the reduction of the nitro compounds takes place in two steps.[81,82] The first step is the reduction of the nitro group to a nitroso compound **C** via electrophilic attack of the phosphorous atom at the nucleophilic oxygen atom in a concerted mechanism via **B**. The second step is the deoxygenation of **C** to give the nitrene **E** via **D** (Scheme 43).



Scheme 43: Proposed mechanism for the deoxygenation of nitroaromatics **A** to nitrenes **E**.[81,82]

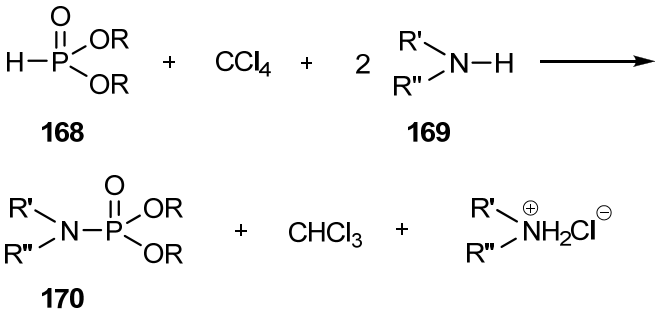
The proposal that the deoxygenation of nitroaromatics with tervalent phosphorous reagents proceeds via arylnitrenes as intermediates is based on the similarity of the products found in the photolysis of arylazides.[82] It has also been suggested that the intramolecular cyclization of nitroaromatics or nitrosoaromatics with triethyl phosphite generally proceeds via a non concerted mechanism.[65a,69,83] The nucleophilic attack of the phosphorous atom takes place on both the nitro and the nitroso oxygen. It is supposed that the nitro group of **A** is deoxygenated to the nitroso compound **C** via **F**. The nitroso compound **C** reacts with a second molecule of triethyl phosphite to give the corresponding intermediate **H** which can form the products a) via nitrene **E** or b) directly via a non-nitrene route (Scheme 44).



Scheme 44: Proposed non concerted mechanism for the deoxygenation of nitro- and nitrosoaromatics a) via a nitrene route b) via a non-nitrene route.[65b,69,83]

5.3 Synthetic approaches to phosphoramidates

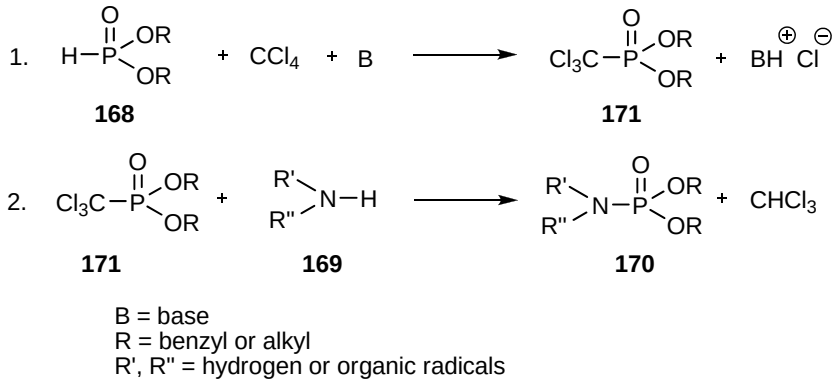
The standard method for the synthesis of phosphoramidates **170** dates back to Todd and Atherton who published the reaction of ammonia, primary and secondary amines with a dialkyl or dibenzyl phosphite in the presence of a halogen source such as carbon tetrachloride (Scheme 45).[84,85] No reaction takes place with weak bases like aniline unless a strong base like a tertiary amine is added. By using pentachloroethane or hexachloroethane instead of carbon tetrachloride, dialkyl phosphites undergo a similar reaction. Although the reaction occurs more readily with dialkyl or dibenzyl phosphites it does not occur at any rate under the same conditions with triethyl phosphite.[84]



Scheme 45: Synthesis of phosphoramidates **170** according to Todd and Atherton.[84,85]

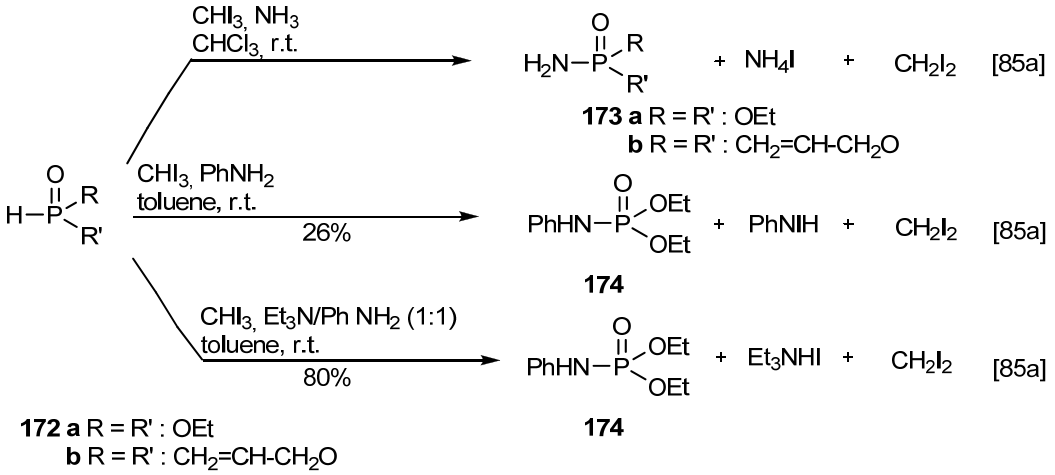
The mechanism of the phosphorylation of amines by reaction of dialkyl or dibenzyl phosphite with carbon tetrachloride in the presence of strong bases can be explained as follows.[84,85] It has been suggested that the reaction proceeds in two steps with the intermediate formation of

a trichloromethylphosphonate **171**.[84] In the first step carbon tetrachloride reacts with the phosphite **168** in the presence of a base to afford **171**. In the second step the trichloromethylphosphonate **171** reacts with a molecule of a primary or a secondary amine to yield phosphoramidate **170** and chloroform (Scheme 46).[84,85]



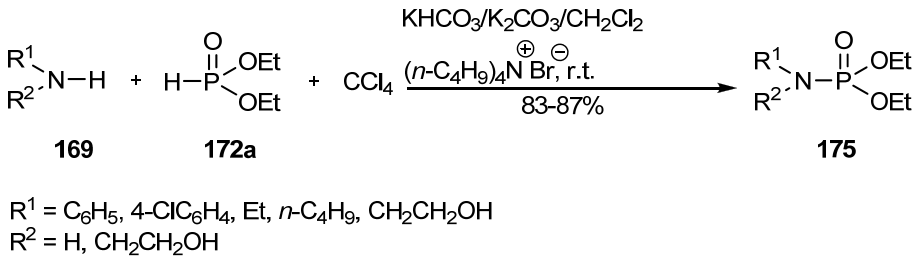
Scheme 46: Proposed mechanism for synthesis of phosphoramidates **170** according to Todd and Atherton.[84,85]

A number of convenient and valuable modifications of the original method have been introduced. Some of the modifications are based on the use of alternative halogen sources such as iodoform.[85] Treatment of diethyl phosphites **172a,b** with a solution of iodoform and liquid or gaseous ammonia in toluene or chloroform afforded diethyl phosphoramidates **173a,b** with high yields within a few minutes.[85a] However, when the reaction of diethyl phosphite **172a** was performed with iodoform and dry aniline in a toluene solution at room temperature diethyl *N*-phenylphosphoramidate (**174**) was isolated with low yield (26 %).[85a] When the reaction was performed in the presence of an equimolar mixture of aniline and triethylamine diethyl *N*-phenylphosphoramidate (**174**) could be obtained with 80 % yield (Scheme 47).[85a]



Scheme 47: Synthesis of diethyl phosphoramidates **173a,b** and diethyl *N*-phenylphosphoramidate **174**.[85a]

Another modification of the original method for the synthesis of phosphoramidates[84,85] has been published by Zwierzak.[86] He found that the phosphorylation of amines can be achieved in aqueous systems if it is run in the presence of catalytic amounts (ca. 5 mol %) of triethylbenzylammonium chloride or tetrabutylammonium bromide as solid phase transfer catalysts. A mixture of potassium hydrogen carbonate and solid potassium carbonate has been used as the base. In many cases the phase transfer method is more efficient and versatile in comparison to the original method. As an example, the diethyl *N*-alkyl-(aryl)-phosphoramidates **175** can be prepared by reaction of amines **169** and diethyl phosphite (**172a**) in quantitative yields (Scheme 48).

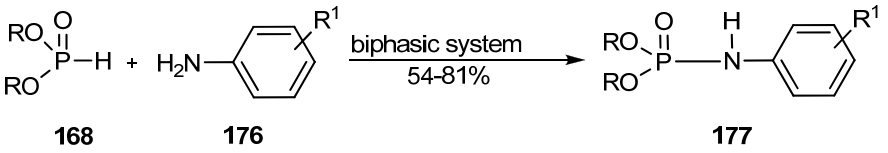


Scheme 48: Synthesis of diethyl *N*-alkyl-(aryl)-phosphoramidates **175** using a phase transfer catalyst according to the method of Zwierzak.[86]

The original method developed by Todd[84] and Atherton[85] is useful for the phosphorylation of ammonia but has a number of drawbacks when amines are phosphorylated:

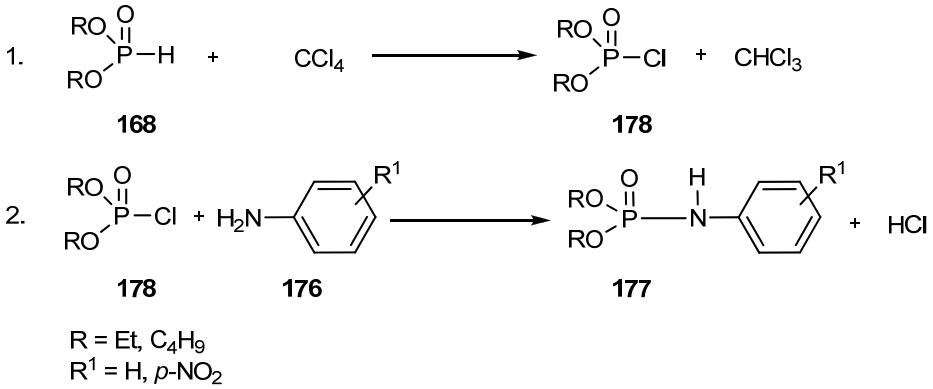
1) From the two equivalents of amine used, one equivalent is lost as the corresponding chlorohydrate; 2) the isolation of the amine salt is laborious and sometimes ineffective; 3) when dibenzylphosphite is used partial monodebenzylation takes place.

Ilia et al. have reported that anilines can be phosphorylated successful in biphasic systems such as liquid-liquid and liquid-solid systems.[87] Best results have been obtained when a solution of equimolar amounts of a dialkyl phosphite **168** and an aniline derivative **176** was added to a stirred two-phase system consisting of dichloromethane, potassium carbonate and a phase transfer catalyst (Scheme 49).



Scheme 49: The synthesis of dialkyl *N*-arylphosphoramidates **177** using a biphasic system.[87]

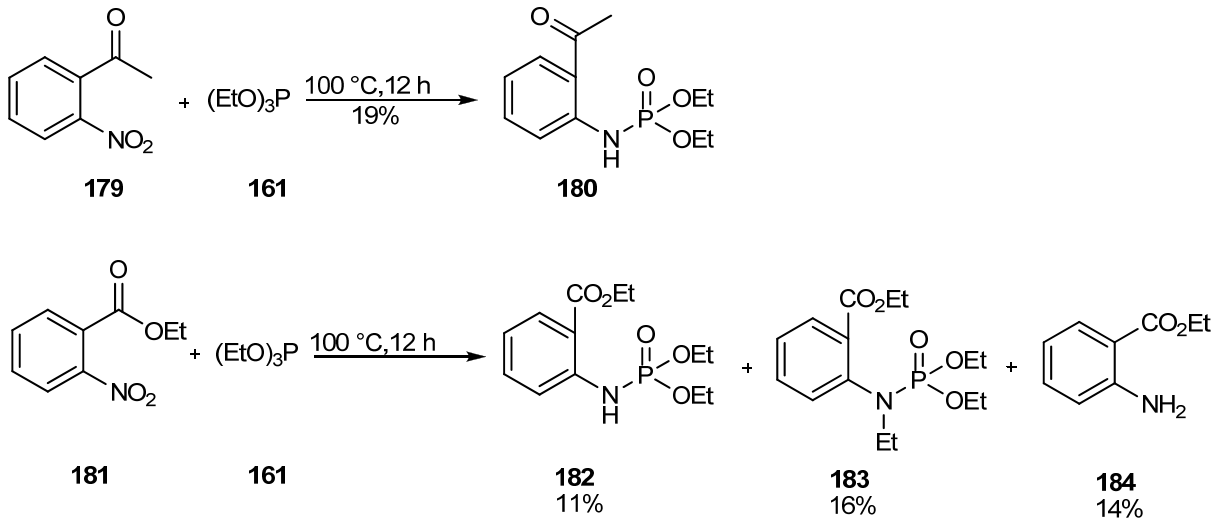
It has been proposed that the reactions start with the oxidation of **168** with tetrachloromethane to give the corresponding chlorophosphate **178** which in turn reacts with the aniline **176** by nucleophilic substitution to deliver the corresponding dialkyl *N*-arylphosphoramidate derivatives **177** and hydrochloric acid. The hydrochloric acid is neutralized by base (Scheme 50).[87]



Scheme 50: Proposed mechanism for the formation of dialkyl *N*-arylphosphoramidates **177** by reaction of **168** with **176**.[87]

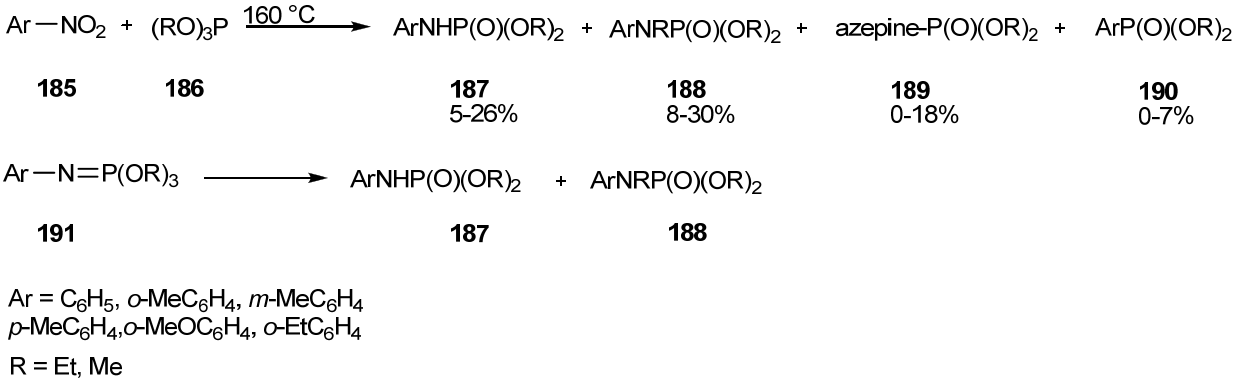
When aromatic nitro compounds are treated with tervalent phosphorous reagents *N*-arylphosphoramidates are also formed but in low yields. Cadogan et al. reported that the treatment of *o*-nitroacetophenone (**179**) with triethyl phosphite (**161**) under nitrogen for 12 h

at 100 °C afforded diethyl *N*-(2-acetylphenyl)phosphoramidate (**180**) with 19 % yield as the only identified product.[88] Another example is the reduction of ethyl-2-nitrobenzoate (**181**) with triethyl phosphite in the absence of any solvent. Under these conditions the only products that could be isolated were diethyl *N*-(2-ethoxycarbonylphenyl)phosphoramidate (**182**) with 11 % yield, diethyl *N*-(2-ethoxycarbonylphenyl)-*N*-ethylphosphoramidate (**183**) with 16 % yield and ethyl anthranilate (**184**) with 14 % yield (Scheme 51).[88]



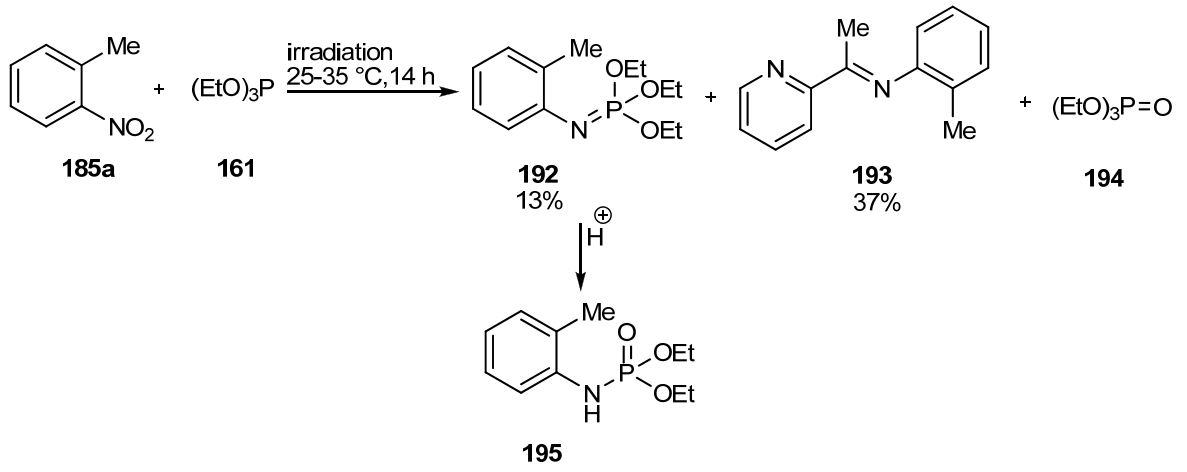
Scheme 51: Synthesis of diethyl *N*-alkylphosphoramidates **180** and **182** according to the method of Cadogan et al.[88]

Cadogan et al. have found that reaction of substituted nitroarenes **185** with an excess of trialkyl phosphite $(RO)_3P$ **186** at 160 °C for 14-17 h gives mixtures of the corresponding dialkyl *N*-arylphosphoramidates $[(RO)_2P(=O)NHAr]$ **187** (5-26%), dialkyl *N*-alkyl-*N*-arylphosphoramidates $[(RO)_2P(=O)NRAr]$ **188** (8-30%), dialkyl *N*-alkyl-3*H*-azepin-7-ylphosphonates $[(RO)_2P(=O)azepine]$ **189** (0-18%) and dialkyl arylphosphonates $[(RO)_2P(=O)Ar]$ **190** (0-7%). In some cases the corresponding trialkyl *N*-arylphosphorimidates $[(RO)_3P=NAr]$ **191** could also be isolated. Probably, the trialkyl *N*-arylphosphorimidates $[(RO)_3P=NAr]$ **191** are intermediates in the reaction of nitrobenzene, *o*-ethylnitrobenzene and *o*-nitrotoluene with trialkyl phosphite to the dialkyl *N*-arylphosphoramidates $[(RO)_2P(=O)NHAr]$ **187** (Scheme 52).[89]



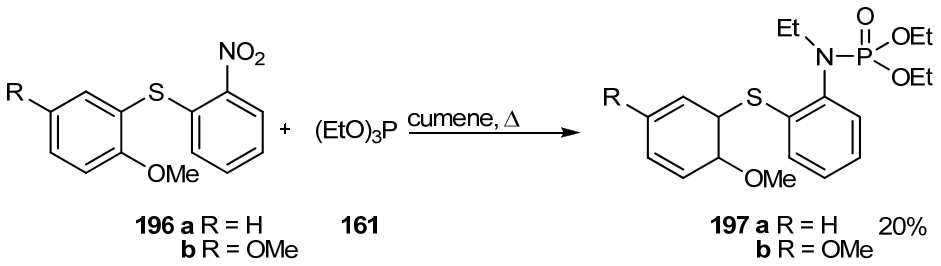
Scheme 52: Product spectrum from the reaction of substituted nitroarenes **185** with trialkyl phosphite **186**.[89]

Nitrobenzene and substituted nitrobenzenes also underwent deoxygenation when they were irradiated in the presence of triethyl phosphite (**161**).[80a,90] Triethyl phosphite (**161**) was oxidized to triethyl phosphate (**194**) and the aromatic nitro compound was converted into the corresponding triethyl *N*-arylphosphorimidates **192** as well as aniline derivatives **193**. As an example, irradiation of *o*-nitrotoluene (**185a**) in the presence of triethyl phosphite (**161**) resulted in the formation of a mixture of triethyl *N*-2-methylphenylphosphorimidate (**193**), *N*-(*o*-tolyl)-2-acetimidylpyridine (**193**) and triethyl phosphate (**194**). During chromatography on silica gel triethyl *N*-2-methylphenylphosphorimidate (**192**) was converted into diethyl *N*-2-methylphenylphosphoramidate (**195**) with low yield (5 %) (Scheme 53).[72,80a,82,90]



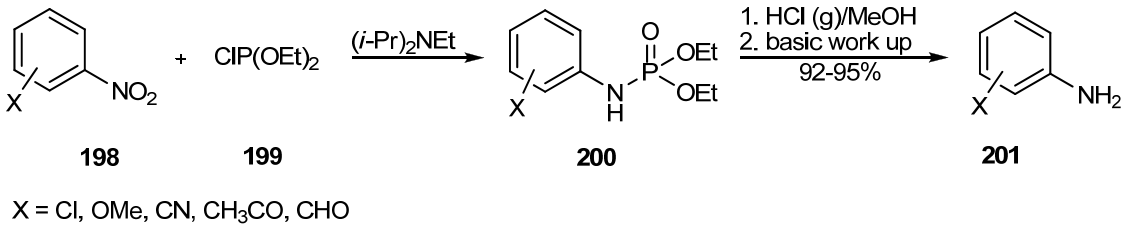
Scheme 53: The photochemical deoxygenation of *o*-nitrotoluene (**185a**).[90]

The thermal deoxygenation of 2'-methoxy-2-nitrodiphenyl sulphide (**196a**) with triethyl phosphite (**161**) in cumene as a solvent yielded diethyl *N*-ethyl-*N*-[*o*-(2-methoxyphenylthio)phenyl]-phosphoramidate (**197a**) with 20 % yield. Similar results were observed when 2',5'-dimethoxy-2-nitrodiphenyl sulphide (**196b**) was reacted (Scheme 54).[91]



Scheme 54: The synthesis of diethyl *N*-alkylphosphoramidate **197a,b**.

Fischer and Sheihet reported on the utility of diethyl chlorophosphite (**199**) as a reagent for the reduction of nitro compounds **198** to the corresponding anilines in two steps.[92] They have established that the reaction of nitroarenes **198** with an excess of diethyl chlorophosphite (**199**) in the presence of a tertiary amine like diisopropylethylamine results in the formation of the diethyl *N*-arylphosphoramidates **200** which yield the corresponding anilines **201** after treatment with gaseous hydrochloric acid and basic work up (Scheme 55).



Scheme 55: The reduction nitroarenes **198** to anilines **201** according to Fischer and Sheihet.[92]

To summarize, it is possible to convert nitroaromatics **179**, **181**, **185**, **192**, **196** and **198** into the corresponding dialkyl *N*-arylphosphoramidates **180**, **182**, **187**, **195** and **197a**,**b** by a number of reactions.[88-91] However, in most cases complex product mixtures are formed and the yields of the dialkyl *N*-arylphosphoramidates **180**, **182**, **187**, **195** and **197a**,**b** are low. The only exception is the reaction of nitroarenes **198** with diethyl chlorophosphite (**199**) in the presence of a tertiary amine.[92] However, the scope of the method is limited and the reagent is very expensive.

6 AIM OF THE WORK

Due to their biological activities and their potential use for the development of new drugs the efficient synthesis of fluorenes and related compounds such as benzo[*b*]fluorenes is of great interest. The most interesting compounds with a benzo[*b*]fluorene skeleton include the naturally occurring kinamycins.[7,9,12,13,15] Recently, hipposudoric acid (**4**) and norhipposudoric acid (**5**) have been isolated from the sweat of hippopotamus (*Hippopotamus amphibius*) (Figure 13).[1] So far, the biological function of the highly unstable dyes remains unknown.

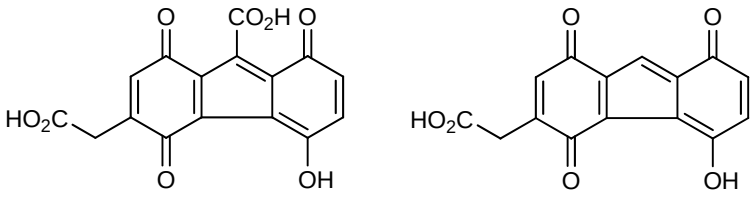
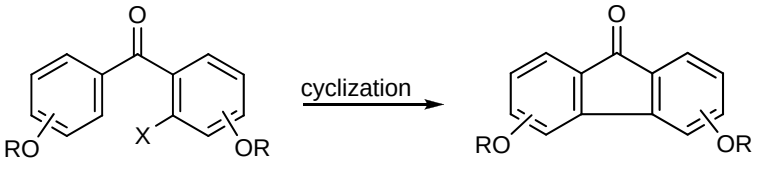


Figure 13: The structures of hipposudoric acid (**4**) and norhipposudoric acid (**5**)

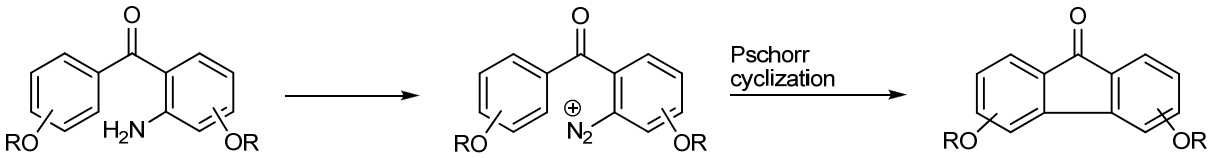
The goal of this study was the development and comparison of efficient synthetic methods for the selective formation of fluoren-9-ones **203** carrying several alkoxy or hydroxyl groups by cyclization of 2-functionalized benzophenones **202**.



202 a X = NH_2
b X = Hal
c X = NO_2

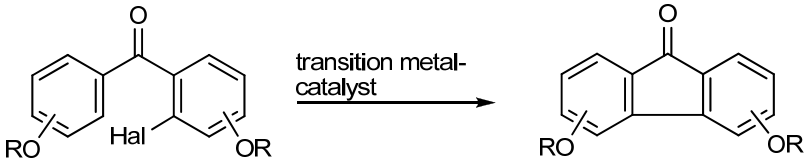
203 R = alkyl

Therefore, it was planned to prepare 2-functionalized benzophenones **202** carrying several alkoxy groups and to study their cyclization under different conditions.



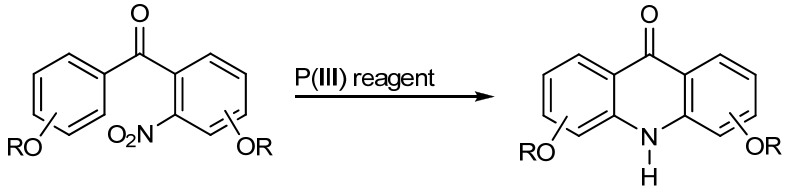
202a **204** **203**

It was envisaged to start with the synthesis of **203** by Pschorr cyclizations. In order to study this type of cyclization it was necessary to generate the diazonium salts **204** which can be obtained from the the corresponding aromatic amines **202a**.



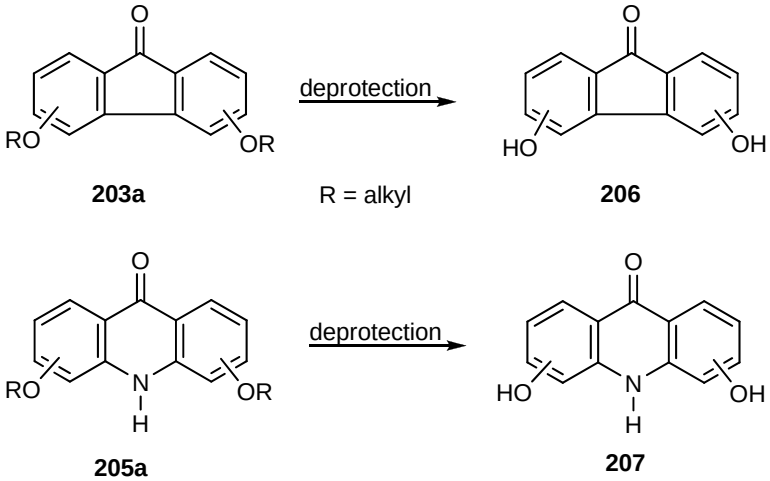
202b **203**

An alternative pathway to fluoren-9-ones **203** is the transition metal-catalyzed cyclization of benzophenones **202b** bearing a halogen atom at C-2.



202c **205**

Finally, it was planned to study the conversion of 2-nitrobenzophenones **202c** into acridinones **205** by reaction with tervalent phosphorous reagents like $P(OR)_3$.

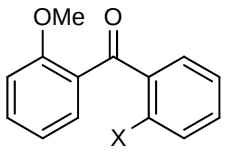


203a **206**

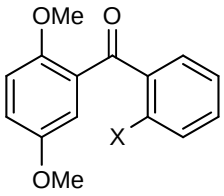
205a **207**

Scheme 56: Deprotection of **203a** and **205a**.

After the successful cyclization it is necessary to transform the alkoxy groups into the corresponding hydroxyl functions (Scheme 56).



208



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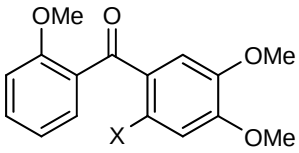

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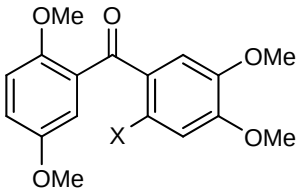

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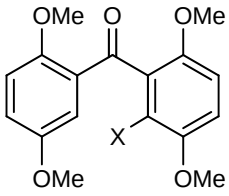
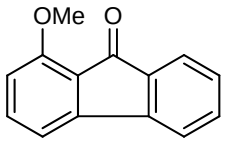


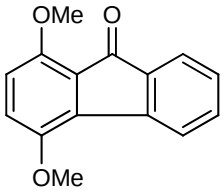
212

X = NH_2, NO_2, Hal

Typical examples for the 2-functionalized benzophenones to be synthesized include compounds **208**-**212**.



213



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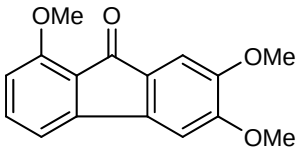

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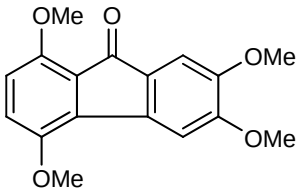

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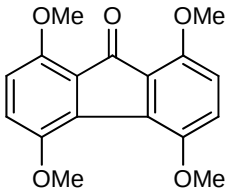
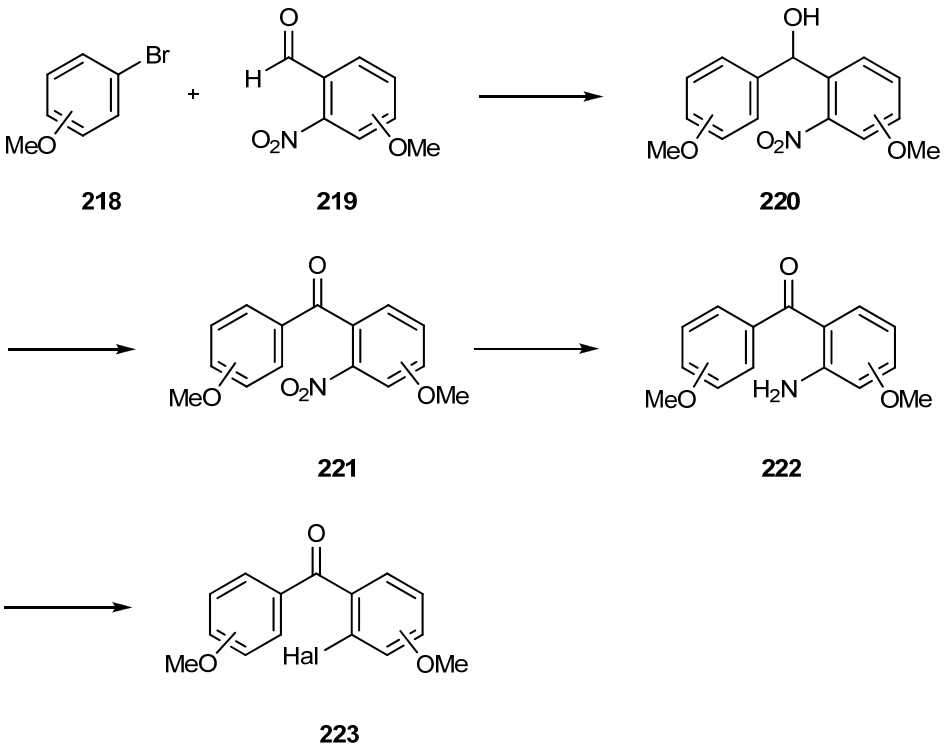


217

With these precursors in hand it should be possible to gain access to the fluoren-9-ones **213**-**217** as well as the corresponding acridinones.



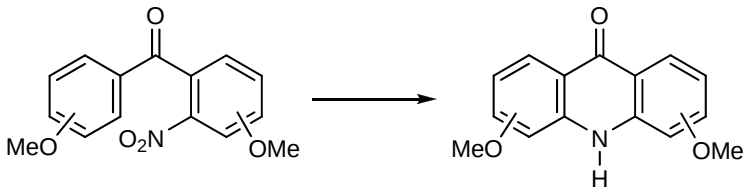
218 **219** **220**

221 **222**

223

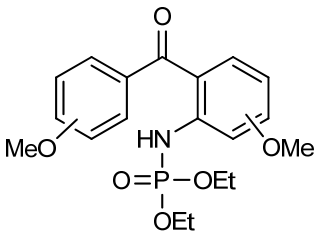
Scheme 57: Synthesis of the cyclization precursors.

Scheme 57 summarizes the projected synthetic approach for the synthesis of the cyclization precursors. It was planned to react an aryllithium compound which can be generated by lithiation of the corresponding arylbromide **218** with a 2-nitrobenzaldehyde **219** to yield the corresponding diarylmethanol **220**. Oxidation of the alcohol function should deliver the substituted 2-nitrodiarylketone **221**.



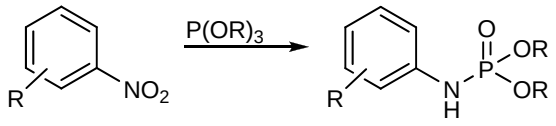
221 **205a**

The nitroaromatic compounds **221** prepared by this route were supposed to be reacted with tervalent phosphorous reagents to yield the acridinones **205a** as cyclization products.



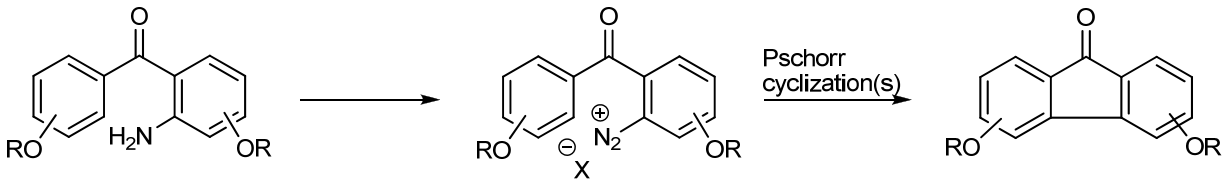
224

However, during the course of this study it was found that these reactions surprisingly result in the formation of phosphoramidates **224** instead of the expected acridinones **205a**. Therefore, it was decided to develop this new reaction into a highly efficient method for the transformation of nitroaromatic compounds **225** into phosphoramidates **226** in one step.



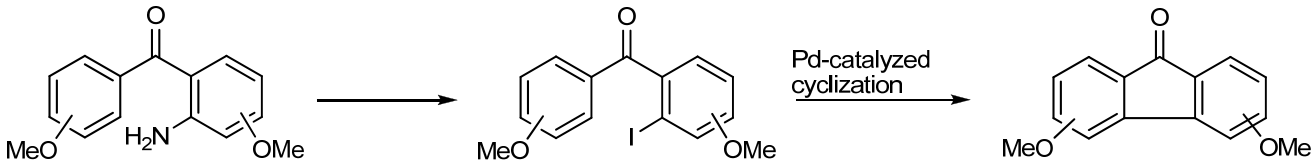
225 **226**

The development of new methods for the synthesis of phosphoramidates is of great interest in synthetic organic chemistry since many compounds with this structural moiety display high biological activities. It was planned to study scope and limitations of the new method as well as the influence of reagents and reaction conditions on the outcome of model transformations.



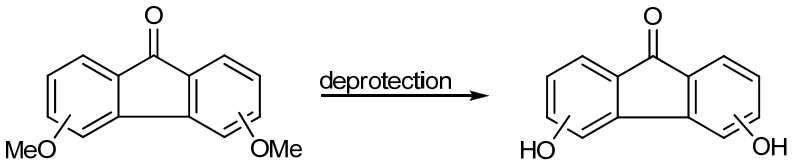
202a **204** **203**

It was expected that the 2-aminodiarylketones **202a** which are required as substrates for the Pschorr cyclizations can be synthesized by simple reduction of the nitro compounds **202c**. Conversion of the resulting amino compounds **202a** into the corresponding diazonium salts **204** affords the precursors that can undergo the Pschorr cyclizations. Again, it was planned to execute formation and cyclization of **204** under a number of different conditions.



222 **227** **203a**

The transition metal-mediated cyclization of 2-halodiarylketones **227** was expected to be an attractive alternative to the Pschorr cyclization of **204**. The iodo compounds **227** were considered to be the most promising substrates for Pd-mediated transformations. Therefore, it was planned to prepare the required 2-iodobenzophenones **227** from the 2-aminobenzophenones **222** and to subject them to Pd- mediated cyclizations.



203a **206**

And finally, it was planned to deprotect the methoxy-substituted cyclization products **203a** in order to obtain the fluoren-9-ones **206** with the free hydroxyl groups for studies of their biological activity.

7 RESULTS AND DISCUSSION

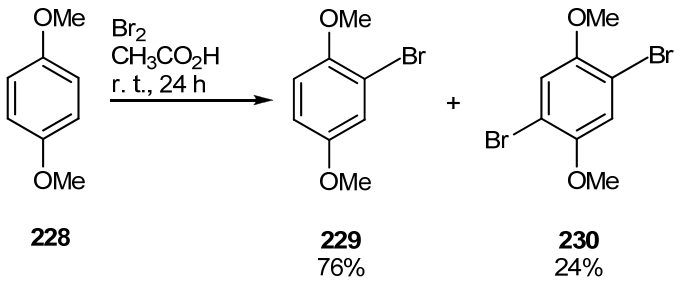
Fluorenes and related compounds are of a remarkable interest due to their important biomedical applications.[1,2] According to the discussion in the preceeding chapters this part of the thesis is divided into five parts. In chapter 7.1 the focaus is on the synthesis of fluoren-9-ones by Pschorr cyclizations of 2-aminobenzophenones. Chapter 7.2 concentrates on the transformation of methoxy-substituted fluoren-9-ones into the corresponding hydroxy-substituted compounds. This is followed by chapter 7.3 dealing with the preparation of fluoren-9-ones by means of palladium-mediated cyclizations of substituted 2-iodobenzophenones. In chapter 7.4 the unexpected transformation of 2-nitrobenzophenones into the corresponding *N*-arylphosphoramidates is presented. And finally, the development of an efficient method for the transformation of a broad range of nitroarenes into *N*-arylphosphoramidates is described in chapter 7.5.

7.1 Synthesis of fluoren-9-ones by Pschorr cyclization

In this chapter the synthesis of hydroxy-substituted fluoren-9-one derivatives **206** through Pschorr cyclization of 2-aminobenzophenone derivatives **202a** is reported.

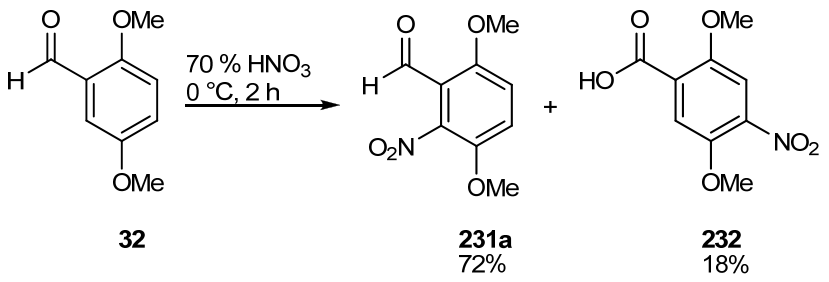
7.1.1 Synthesis of starting materials

First, some starting materials were prepared. 2-Bromo-1,4-dimethoxybenzene (**229**) was synthesized from commercially available 1,4-dimethoxybenzene (**228**) by bromination with bromine in glacial acetic acid.[93] After workup and vacumm distillation **229** was obtained with 76 % yield as a colourless oil. In addition, 24 % of 2,5-dibromo-1,4-dimethoxybenzene (**230**) were isolated as byproduct (Scheme 58).



Scheme 58: Synthesis of 2-bromo-1,4-dimethoxybenzene (**229**).

For the preparation of **231a** commercially available 2,5-dimethoxybenzaldehyde (**32**) was nitrated with 70 % nitric acid at 0 °C according to the procedure of Marblanco[94] (Scheme 59). The crude product obtained by filtration was recrystallized (petroleum ether/chloroform = 1:5) to afford **231** with 72 % yield as yellow crystals. By concentration of the mother liquors the side product 2,5-dimethoxy-4-nitrobenzoic acid (**232**) was isolated with 18 % yield as a pale yellow powder (Scheme 59).



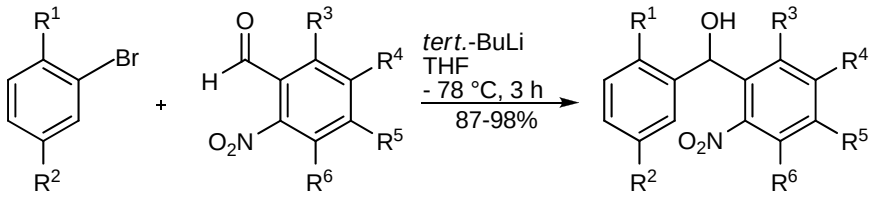
Scheme 59: Synthesis of 3,6-dimethoxy-2-nitrobenzaldehyde (**231**).[94]

7.1.2 Synthesis of the (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanols 233a-e

The substituted diarylmethanols **233a-e** were obtained by reaction of the lithiated bromobenzenes **229a,b** with the nitrobenzaldehydes **231a-c** according to the procedure of Qabaja and Jones.[24b] The reactions of the 2-bromobenzenes **229**, *t*-butyllithium and the nitrobenzaldehydes **231** were performed at –78 °C. After quenching the crude products were purified by recrystallization to afford the (2-nitrophenyl)(phenyl)methanols **233a-e** with yields ranging between 87 and 98 % (Table 1, Figure 14). The high yields of the addition products are in good agreement with the results published by Qabaja and Jones[24b] and Saikawa et al.[1c]

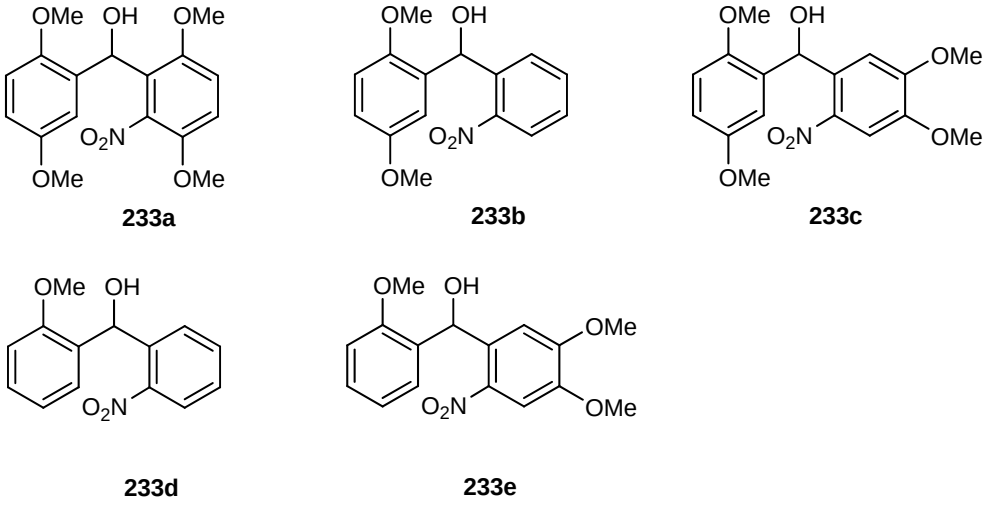
The ^{1}H NMR spectra of **233a-e** exhibited a characteristic peak in the range of δ = 6.28-6.97 ppm for the methine proton of the C*H*OH group. The ^{13}C NMR spectra of **233a-e** displayed a signal in the range of δ = 64.36-67.05 for the carbon atom of the *C*HOH group. The structures of all substituted-(2-nitrophenyl)(phenyl)methanols **233a-e** synthesized have been elucidated unambiguously by analytical and spectroscopic methods including UV, IR, and NMR spectroscopy as well as mass spectrometry.

Table 1: Synthesis of substituted-(2-nitrophenyl)(phenyl)methanols **233a-e**



229 **231** **233**

Entry	**229**	R^1	R^2	**231**	R^3	R^4	R^5	R^6	Product	Yield of **233** [%]
1	**a**	OMe	OMe	**a**	OMe	H	H	OMe	**233a**	88
2	**a**	OMe	OMe	**b**	H	H	H	H	**233b**	98
3	**a**	OMe	OMe	**c**	H	OMe	OMe	H	**233c**	87
4	**b**	OMe	H	**b**	H	H	H	H	**233d**	90
5	**b**	OMe	H	**c**	H	OMe	OMe	H	**233e**	92

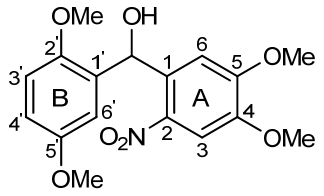


233a **233b** **233c**

233d **233e**

Figure 14: Structures of compounds **233a-e**.

7.1.2.1 Discussion of the spectral data of the (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanols 233a-e



233c

As an example, the discussion of the spectral data of (4,5-dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanol (**233c**) is presented. The structural assignment of **233c** rests mainly on its ^{1}H NMR (Figure 15), ^{13}C NMR (Figure 16), HMBC (Figure 17), ^{1}H,^{1}H-COSY (Figure 18) and HSQC spectra (Figure 19).

The ^{1}H NMR spectrum of **233c** (Figure 15) exhibited two singlets corresponding to the aromatic protons 3-H and 6-H at δ = 7.19 ppm and δ = 7.60 ppm, respectively. The HSQC spectrum (Figure 19) revealed the carbon atoms C-3 at δ = 107.99 ppm and C-6 at δ = 110.72 ppm. Throughout, the HMBC experiment was optimized for 8 Hz to enable the detection of especially the $^{3}J_{CH}$-correlations in the aromatic ring systems. In the HMBC spectrum (Figure 17) the proton 3-H showed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-1 at δ = 133.09 ppm as well as C-5 at δ = 153.51 ppm. The proton 6-H displayed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-2 at δ = 140.81 ppm and C-4 at δ = 148.09 ppm thus establishing the substitution pattern of aromatic ring A. Furthermore, from the ^{1}H NMR and ^{1}H,^{1}H-COSY spectra (Figures 15 and 18) a 1,2,5-trisubstituted aromatic ring B could be deduced that was represented by three aromatic protons. The signal for the proton 6'-H appears as a dublet at δ = 6.62 ppm with $^{4}J_{HH}$ = 2.8 Hz, the signal for the proton 4'-H as a dublet of doublet at δ = 6.77 ppm with $^{3}J_{HH}$ = 8.9 Hz and $^{4}J_{HH}$ = 2.9 Hz and lastly the signal for the proton 3'-H as a doublet at δ = 6.82 ppm with $^{3}J_{HH}$ = 8.8 Hz. Their corresponding carbons C-6' at δ = 133.88 ppm, C-4' at δ = 112.84 ppm and C-3' at δ = 111.73 ppm were identified by HSQC (Figure 19).

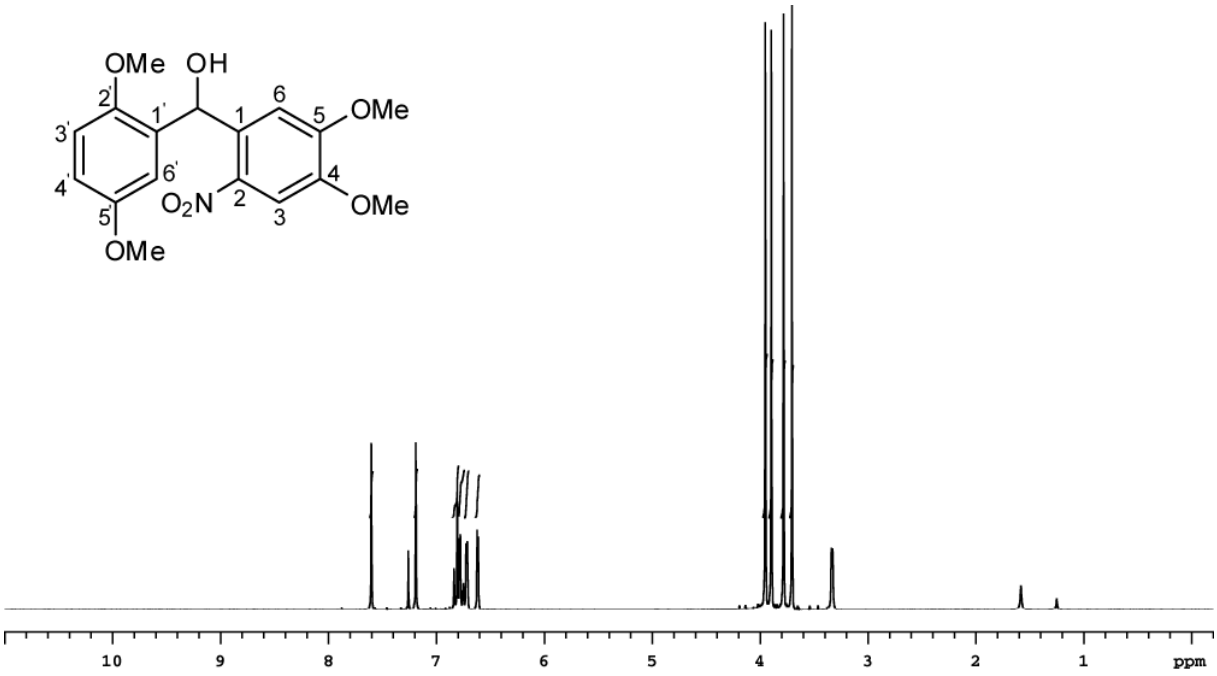


Figure 15: ^{1}H NMR spectrum of **233c** (300 MHz, $CDCl_3$).

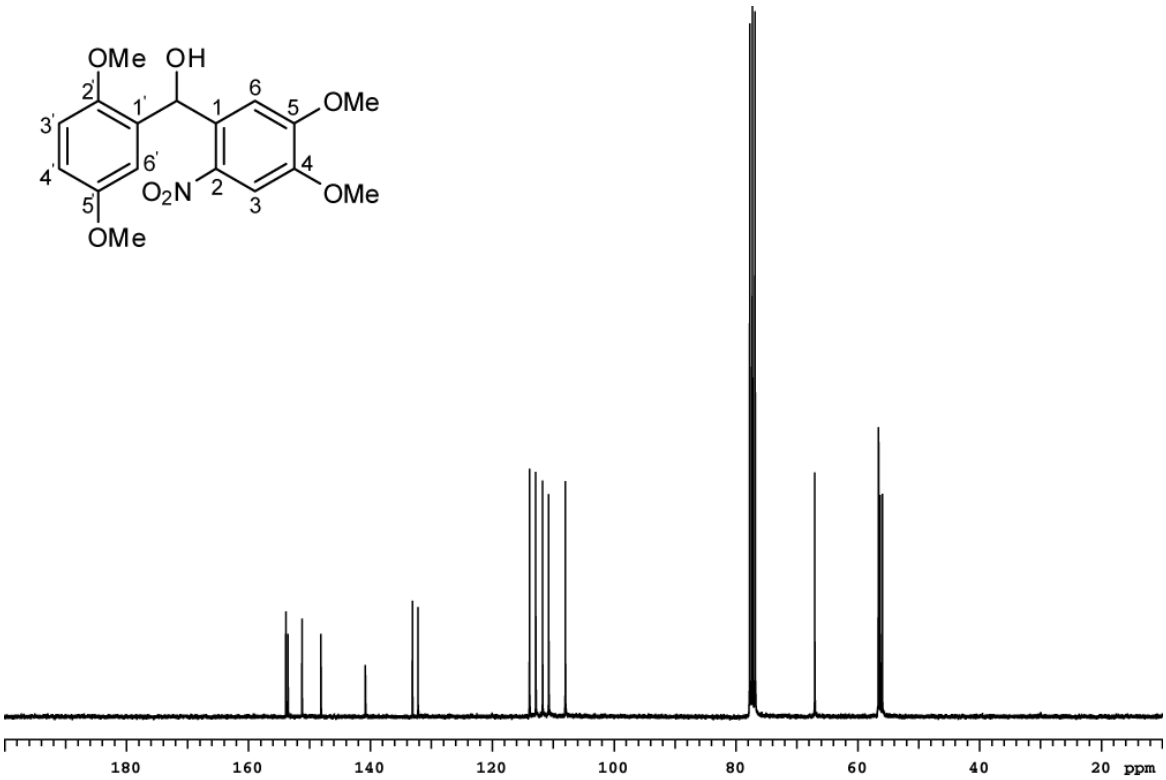
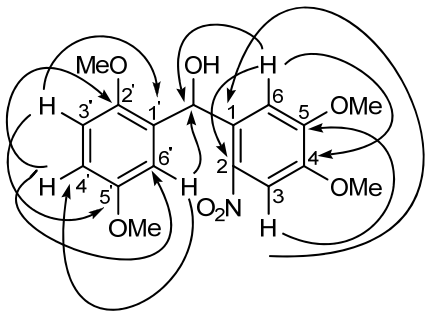


Figure 16: ^{13}C NMR spectrum of **233c** (75 MHz, $CDCl_3$).

In the HMBC spectrum (Figure 17) the proton 4'-H is correlated with the quaternary carbons C-2' at δ = 151.21 ppm and C-6' at δ = 113.88 ppm while the proton 3'-H indicated $^{3}J_{CH}$-

correlations with the quaternary carbons C-1' at δ = 132.18 ppm and C-5' at δ = 153.86 ppm. The proton 6'-H displayed $^{3}J_{CH}$-correlations with the two aromatic carbons C-2' at δ = 151.21 ppm and C-4' at δ = 112.84 ppm and additionally a $^{3}J_{CH}$-correlation with a methine carbon at δ = 67.05 ppm. The corresponding methine proton was identified as doublet at δ = 6.72 ppm ($^{3}J_{HH}$ = 3.1 Hz) by HSQC and the hydroxyl proton appeared as a dublet at δ = 3.33 ppm with a coupling constant of J = 3.4 Hz. In the HMBC spectrum (Figure 17) the methine proton is correlated with both the aromatic carbons C-2' at δ = 151.21 ppm and C-6 at δ = 110.72 ppm which unambiguously establishes that both the aromatic rings A and B are connected by the methine group.

Finally, the ^{1}H NMR spectrum (Figure 15) displayed four sharp singlets at δ = 3.95, 3.90, 3.78 and 3.71 ppm which were assigned to the methoxy groups, their corresponding carbons at δ = 56.60, 56.59, 56.29 and 55.97 ppm were identified by HSQC. Analysis of the HMBC spectrum (Figure 17) revealed that the four methoxy groups were located at the carbons C-4, C-5, C-2' and C-5'.



233c

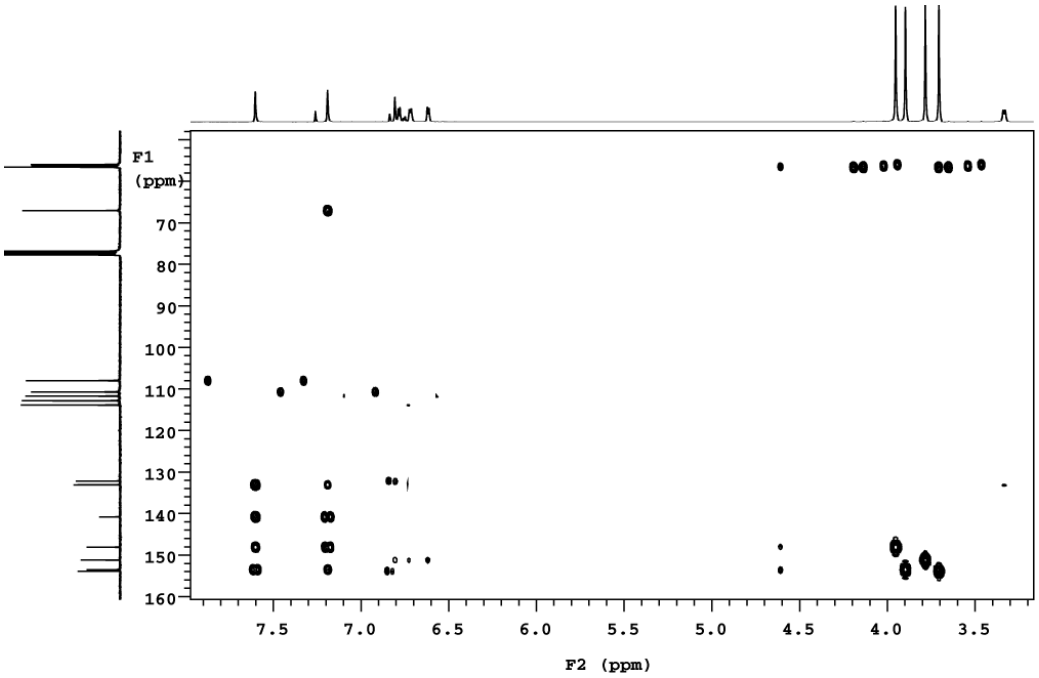


Figure 17: The HMBC spectrum of **233c**.

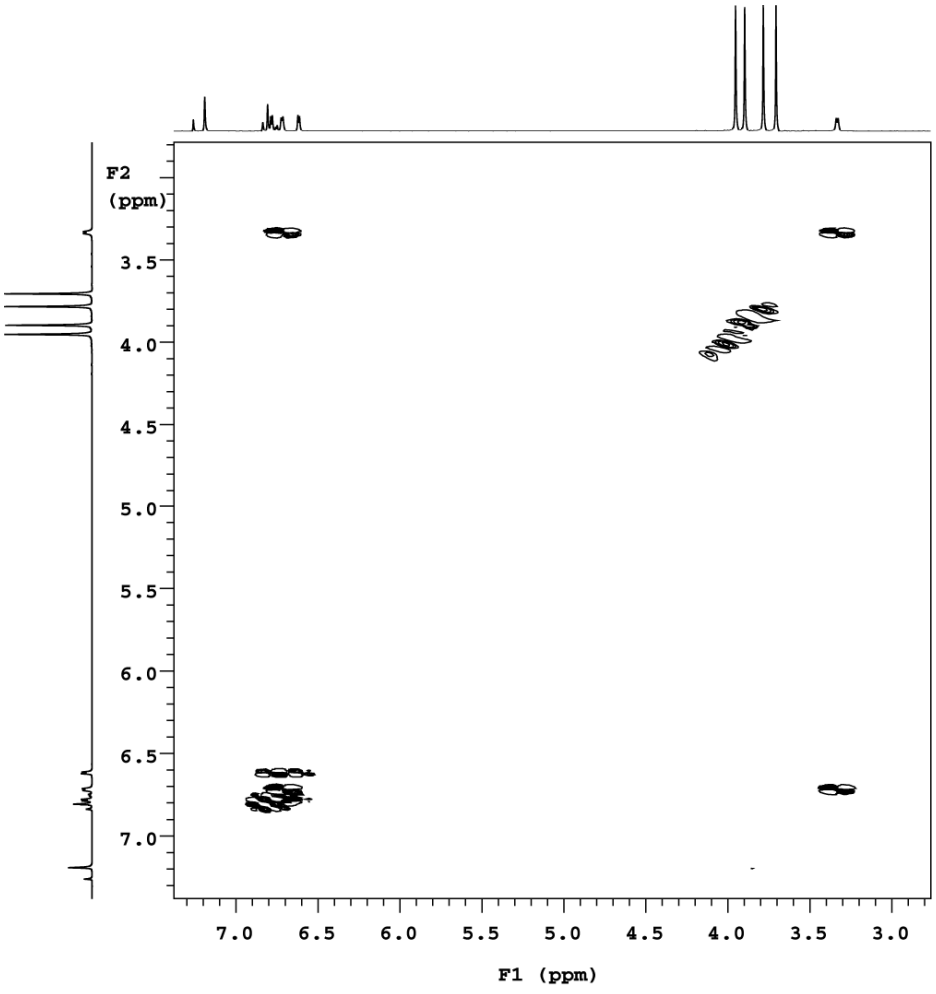


Figure 18: The ^{1}H,^{1}H-COSY spectrum of **233c**.

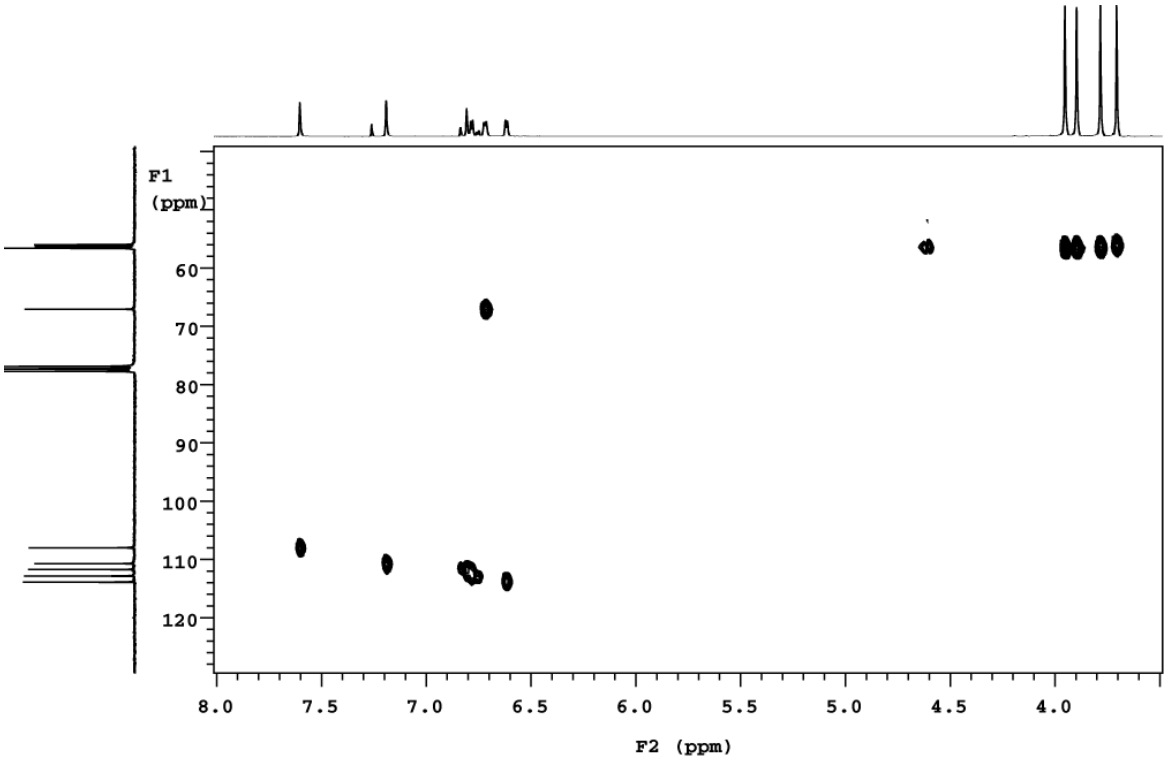


Figure 19: The HSQC spectrum of **233c**.

The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 349. The base peak appeared at *m/z* = 272.

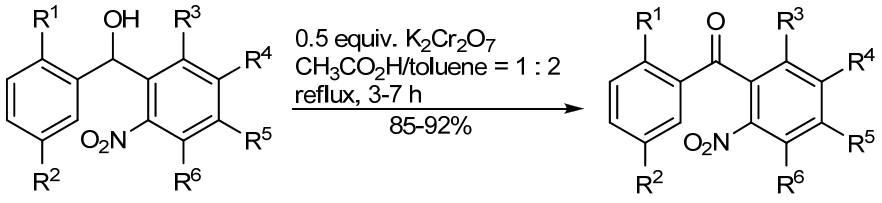
The IR spectrum of **233c** showed a sharp band for the OH stretching vibration at $\tilde{\nu}$ = 3520 cm^{-1}. The bands at $\tilde{\nu}$ = 2960 and 2810 cm^{-1} suggest that aliphatic C-H stretching vibrations are also present. The band at $\tilde{\nu}$ = 1590 cm^{-1} indicates the asymmetric stretching vibration for the O-N-O group. The bands in the range of $\tilde{\nu}$ = 1511-1480 cm^{-1} are in agreement with an aromatic ring due to vibrations of the carbon skeleton. The strong band at $\tilde{\nu}$ = 1265 cm^{-1} confirms the presence of a C-O-C asymmetric stretching vibration.

7.1.3 Synthesis of the (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanones 234a-e

In the next step the oxidation of the secondary alcohols **233a-e** to the corresponding ketones **234a-e** had to be performed. We started using 2 equivalents of pyridinium chlorochromate (PCC) as an oxidant. Treatment of **233a** with 2 equivalents PCC in dichloromethane

according to the procedure of Qabaja and Jones[24] did not yield a trace of the expected benzophenone **234a**. Instead, the starting material could be reisolated. Treatment of **233a** with 2 equivalents of PCC in dichloromethane and in the presence of molecular sieves (3 Å) according to the procedure of Bennett et al.[95] delivered the same disappointing results. Subsequently, it was tried to oxidize **233a** with MnO_2 as an oxidant according to the procedure of Attenburrow et al.[96] Unfortunately, no oxidation of **233a** could be observed. Finally, $K_2Cr_2O_7$ was tried for the oxidation of **233a** to **234a**. According to the procedure described by Fieser and Williamson[97] a mixture of **233a** and 0.5 equivalents of $K_2Cr_2O_7$ was heated in a mixture of acetic acid and toluene at 90 °C for 3-7 h. After work up and recrystallization the substituted-2-nitrobenzophenone **234a** could be isolated with 85 % yield (Table 2, entry 1, Figure 20). By using this procedure it was possible to transform all the secondary alcohols **233a-e** into the corresponding benzophenones **234a-e** with yields ranging from 85-92 % (Table 2, Figure 20). The structures of all benzophenones **234a-e** have been elucidated unambiguously by analytical and spectroscopic methods including UV/VIS-, IR- and NMR spectroscopy as well as mass spectrometry.

Table 2: Synthesis of substituted-2-nitrobenzophenones **234a-e**



233 **234**

Entry	**233**	R^1	R^2	R^3	R^4	R^5	R^6	*t* [h]	Product	Yield of **234** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	4	**234a**	85
2	**b**	OMe	OMe	H	H	H	H	4	**234b**	89
3	**c**	OMe	OMe	H	OMe	OMe	H	7	**234c**	92
4	**d**	OMe	H	H	H	H	H	3	**234d**	88
5	**e**	OMe	H	H	OMe	OMe	H	3	**234e**	87

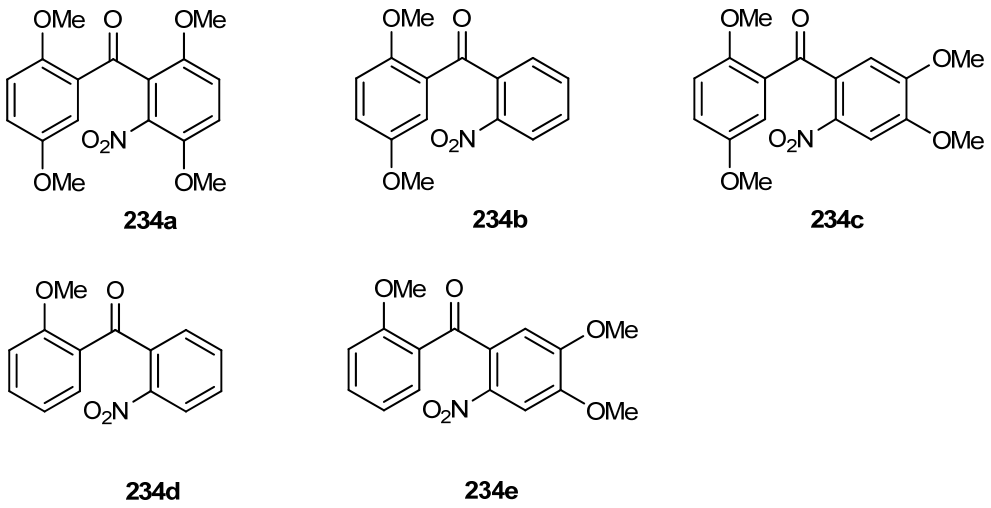
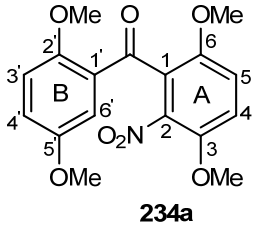


Figure 20: Structures of compounds **234a-e**.

7.1.3.1 Discussion of the spectral data of (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanones 234a-e



As an example, the discussion of the spectral data of (3,6-dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanone (**234a**) is given. The structural assignment of **234a** rests mainly on its ^{1}H NMR (Figure 21), ^{13}C NMR (Figure 22), HMBC (Figure 23), ^{1}H,^{1}H-COSY (Figure 24) and HSQC spectra (Figure 25).

The ^{1}H NMR spectrum of **234a** (Figure 21) showed a singlet at δ = 7.04 ppm integrating for the two aromatic protons 4-H and 5-H. In the multiplicity-edited HSQC spectrum (Figure 25), this singlet exhibited correlations to two methine- and not methylene-carbons at δ = 114.06 and 114.20 ppm. This observation indicated that in $CDCl_3$ the ^{1}H resonances of the aromatic protons 4-H and 5-H are coincided. Neverthless, a small shift difference $\Delta\delta$ = 10 ppb of the signals for the protons 4-H and 5-H could be observed in the HMBC spectrum (Figure 23) which allowed the complete assignment of ring A. The proton 5-H showed $^{3}J_{CH}$-correlations

with the quaternary aromatic carbons C-1 at δ = 128.9 ppm and C-3 at δ = 145.9 ppm. The proton 4-H displayed $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-2 at δ = 138.42 ppm and C-6 at δ = 150.5 ppm. A $^{4}J_{CH}$-correlation of 5-H to a carbonyl group at δ = 189.40 ppm indicated a trisubstituted benzoyl moiety for the aromatic ring A.

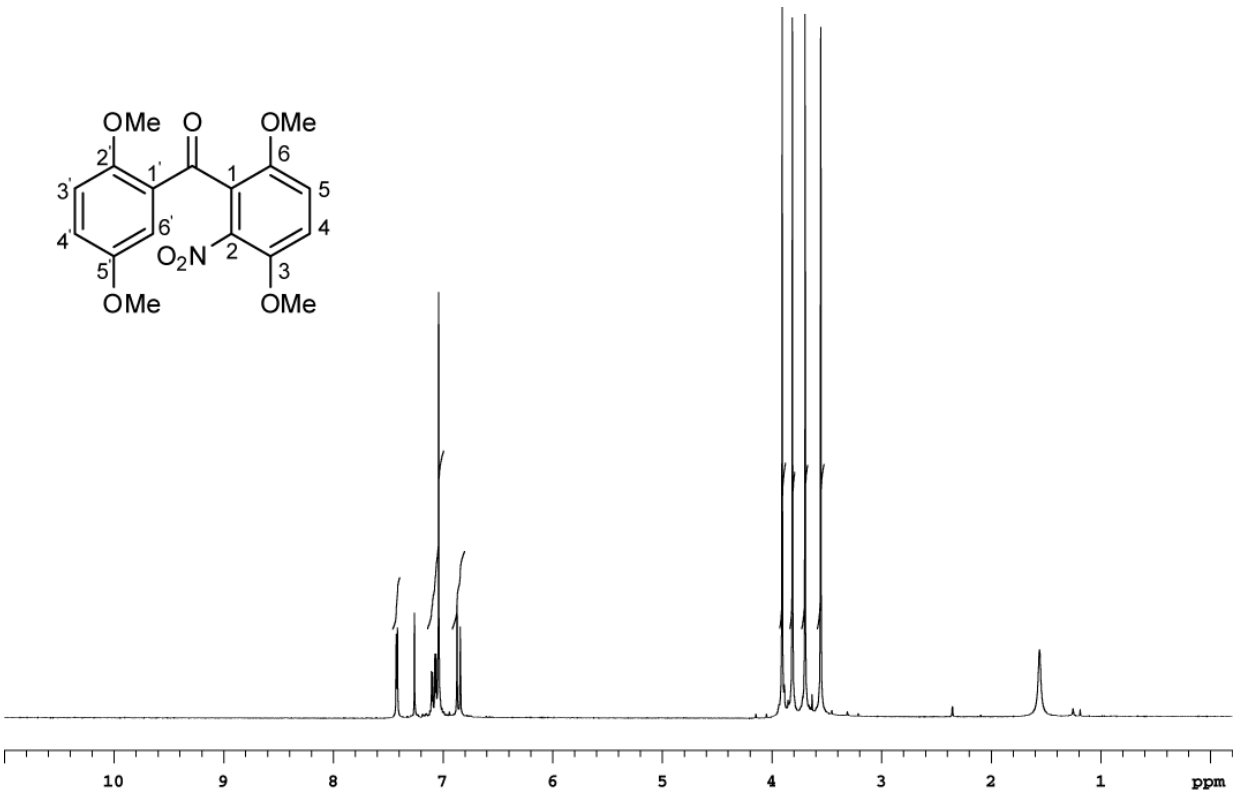


Figure 21: ^{1}H NMR spectrum of **234a** (300 MHz, $CDCl_3$).

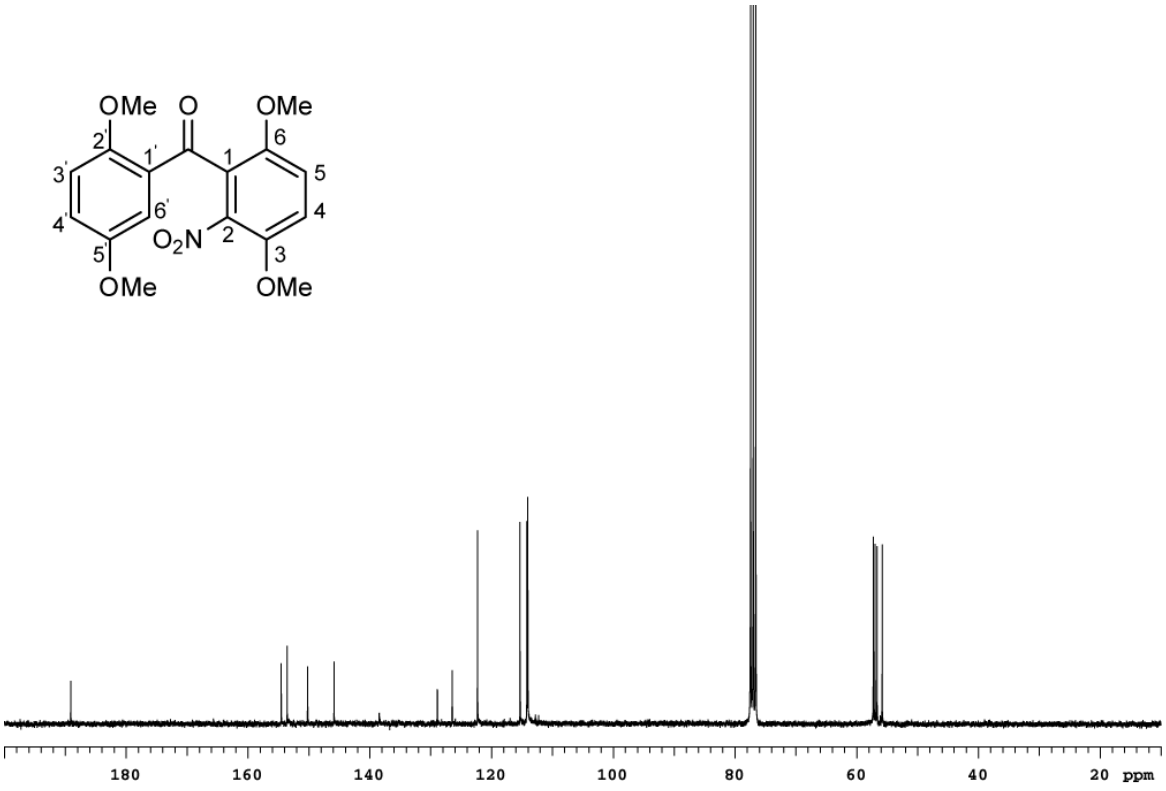
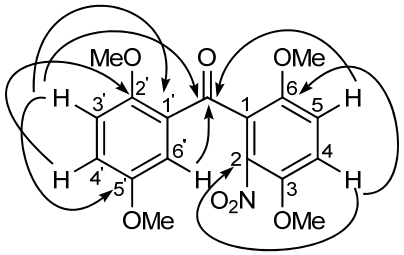


Figure 22: ^{13}C NMR spectrum of **234a** (75 MHz, $CDCl_3$).

As for compound **233c** a 1,2,5-trisubstituted aromatic ring B could be deduced from the signals of the three protons 6'-H at δ = 7.5 ppm (doublet, $^4J_{HH}$ = 3.2 Hz), 3'-H at δ = 6.86 ppm (doublet, $^3J_{HH}$ = 8.9 Hz) and 4'-H at δ = 7.08 ppm (doublet of doublet, $^3J_{HH}$ = 8.9 Hz and $^4J_{HH}$ = 3.2 Hz) (Figures 21 and 24). The HSQC spectrum (Figure 25) revealed their carbons C-6' at δ = 114.03 ppm, C-3' at δ = 114.21 ppm, C-4' at δ = 122.58 ppm, respectively. In the HMBC and ^{13}C NMR spectrum (Figures 23 and 22) the proton 4'-H is correlated with the quaternary carbon C-2' at δ = 154.83 ppm. The proton 3'-H displayed $^3J_{CH}$-correlations with the quaternary carbons C-1' at δ = 126.5 ppm and C-5' at δ = 153.85 ppm as well as a long range $^4J_{CH}$-correlation with a carbonyl group at δ = 189.40 ppm. In addition, the proton 6'-H showed a $^3J_{CH}$-correlation with a carbonyl group at δ = 189.40 ppm. From the $^4J_{CH}$-correlation of the carbonyl group with 5-H and 3'-H it can be deduced that the carbonyl group is the linkage between the two aromatic rings. Further analysis of the 1D and 2D NMR spectra of **234a** revealed the methoxy groups (at δ = 3.94, 3.73, 3.85, and 3.59 ppm) at the positions C-3, C-6, C-5' and C-2'.



234a

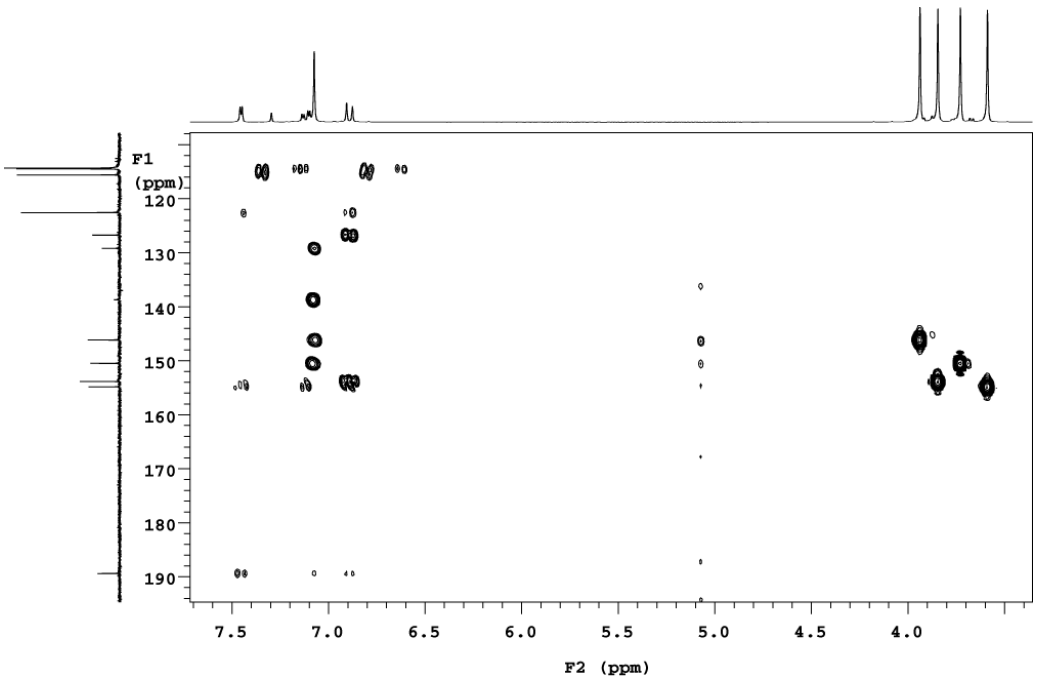


Figure 23: The HMBC spectrum of **234a**.

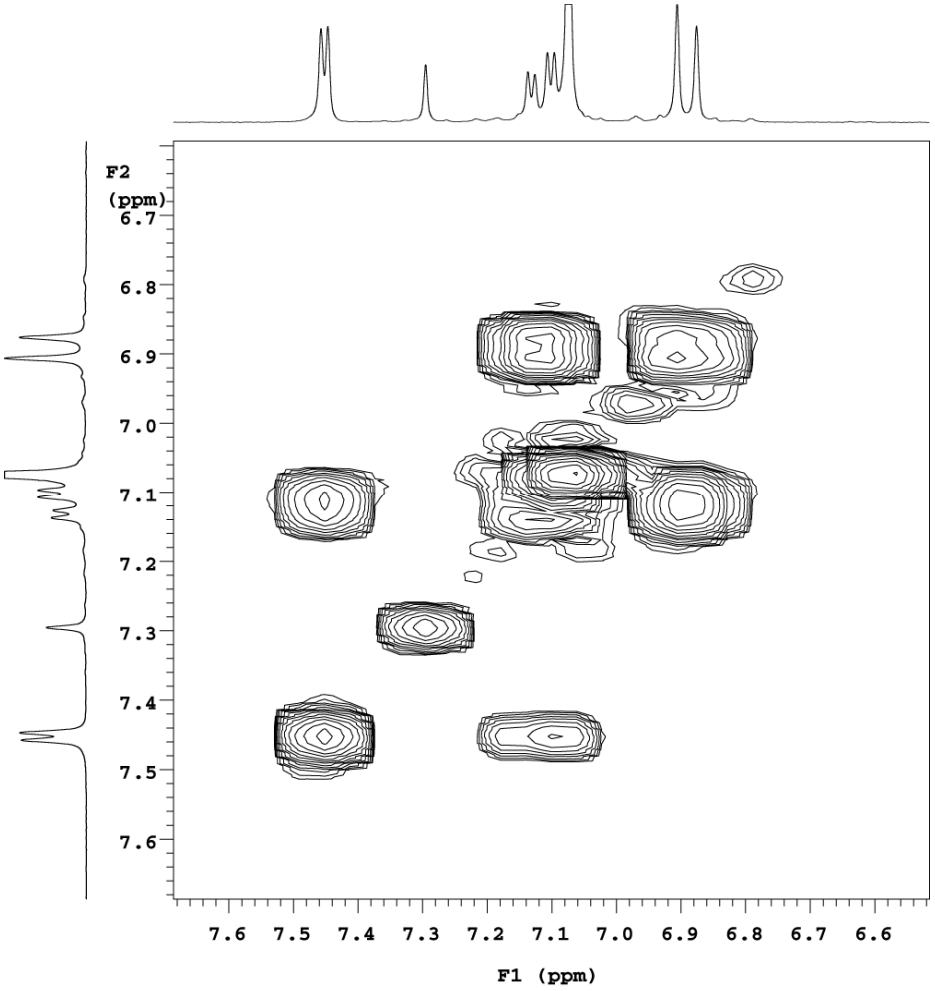


Figure 24: Section of the ^{1}H,^{1}H-COSY spectrum of **234a**.

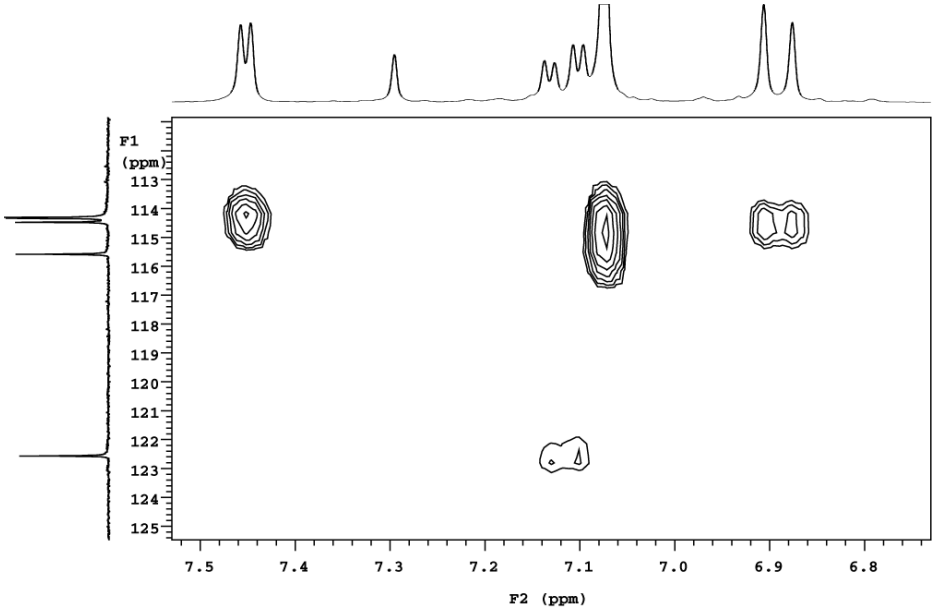


Figure 25: Section of the HSQC spectrum of **234a**.

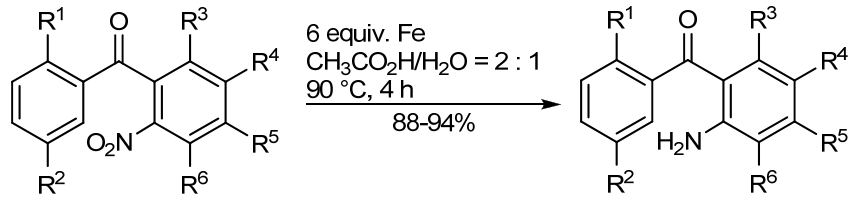
The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 347. This peak represents also the base peak of the spectrum.

The IR spectrum of **234a** shows a characteristic band for the C=O group. The most relevant feature in the IR of this ketone is the C=O stretching vibration at $\tilde{\nu}$ = 1642 cm^{-1}. Other bands present in the spectrum at $\tilde{\nu}$ = 2961 and 2837 cm^{-1} are those of aliphatic C-H stretching vibrations. The band at $\tilde{\nu}$ = 1528 cm^{-1} confirms the presence of asymmetric stretching vibration for the O-N-O group. The bands in the range of $\tilde{\nu}$ = 1496-1460 cm^{-1} suggest the presence of an aromatic ring. The strong band at $\tilde{\nu}$ = 1046 cm^{-1} indicates the presence of an asymmetric stretching vibration of a C-O-C group.

7.1.4 Synthesis of (2-amino-3,4,5,6-tetraalkoxyphenyl)(2',5'-dialkoxyphenyl)methanones 235a-e

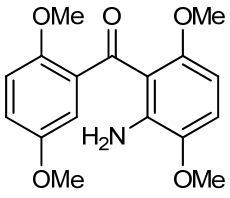
Reduction of the nitro group of the substituted 2-nitrobenzophenones **234a-e** was carried out successfully using iron powder according to the procedure of Stephenson et al.[99] A mixture of the corresponding 2-nitrobenzophenone **234** and 6 equivalents of iron powder in glacial acetic acid was refluxed for 4 h at 90 °C. The crude product was purified by flash chromatography to give the substituted 2-aminobenzophenones **235a-e** with very good yields ranging from 88-94 % (Table 3, Figure 26). The structures of all 2-aminobenzophenones **235a-e** have been elucidated unambiguously by means of analytical and spectroscopic methods including UV/VIS-, IR- and NMR spectroscopic methods as well as mass spectrometry.

Table 3: Synthesis of substituted-2-aminobenzophenones **235a-e**

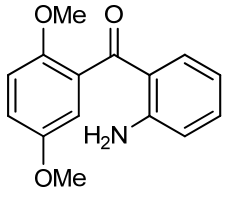


234 **235**

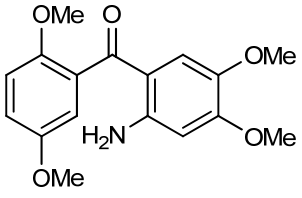
Entry	**234**	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield of **235** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**235a**	91
2	**b**	OMe	OMe	H	H	H	H	**235b**	88
3	**c**	OMe	OMe	H	OMe	OMe	H	**235c**	88
4	**d**	OMe	H	H	H	H	H	**235d**	92
5	**e**	OMe	H	H	OMe	OMe	H	**235e**	94



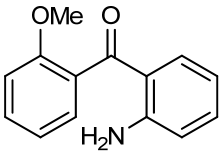
235a



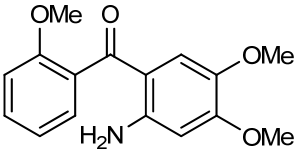
235b



235c



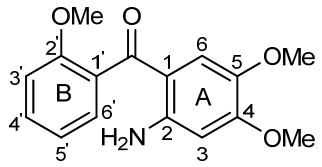
235d



235e

Figure 26: Structures of compounds **235a-e**.

7.1.4.1 Discussion of the spectral data of the (2-amino-3,4,5,6-tetraalkoxyphenyl)(2',5'-dialkoxyphenyl)methanones 235a-e



235e

As an example, the discussion of the spectral data of (2-amino-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (**235e**) is presented. The structural assignment of **235e** rests mainly on its ^{1}H NMR (Figure 27), ^{13}C NMR (Figure 28), HMBC (Figure 29), ^{1}H,^{1}H-COSY (Figure 30) and HSQC spectra (Figure 31).

The ^{1}H NMR spectrum of **235e** (Figure 27) exhibited two singlets corresponding to the aromatic protons 3-H and 6-H at δ = 6.18 ppm and δ = 6.73 ppm, respectively. The HSQC spectrum (Figure 31) revealed their carbons C-3 at δ = 99.07 ppm and C-6 at δ = 117.01 ppm. In the HMBC spectrum (Figure 29) the proton 3-H showed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-1 at δ = 111.14 ppm and C-5 at δ = 148.84 ppm. Moreover, the proton 6-H displayed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-2 at δ = 140.10 ppm and C-4 at δ = 156.06 ppm as well as with a carbonyl group at δ = 196.66 ppm. The ^{1}H NMR spectrum (Figure 27) showed a broad singlet at δ =6.44 ppm for the proton of the amino group, the corresponding carbon C-2 at δ = 140.10 ppm was identified by HMBC. This clearly indicates a trisubstituted aromatic ring attached to a carbonyl group (aromatic ring A). From the ^{1}H NMR spectrum (Figure 27) and the ^{1}H,^{1}H-COSY spectrum (Figure 30) a disubstituted aromatic ring B can be deduced. It was represented by four aromatic protons, namely 3'-H at δ = 7.01 ppm (a broad doublet, $^{3}J_{HH}$ = 8.3 Hz), 4'-H at δ = 7.43 ppm (doublet of doublet of doublet, $^{3}J_{HH}$ = 8.7 Hz, $^{3}J_{HH}$ = 7.5 Hz and $^{4}J_{HH}$ = 1.8 Hz), 5'-H at δ = 7.06 ppm (doublet of doublet of doublet, $^{3}J_{HH}$ = 7.4 Hz, $^{3}J_{HH}$ = 7.4 Hz and $^{4}J_{HH}$ = 0.8 Hz) and 6'-H at δ = 7.28 ppm (doublet of doublet, $^{3}J_{HH}$ = 7.3 Hz and $^{4}J_{HH}$ = 1.5 Hz). Their corresponding carbons C-3' at δ = 111.50 ppm, C-4' at δ = 130.84 ppm, C-5' at δ = 120.70 ppm and C-6' at δ = 128.79 ppm were assigned using the HSQC spectrum of the compound (Figure 31).

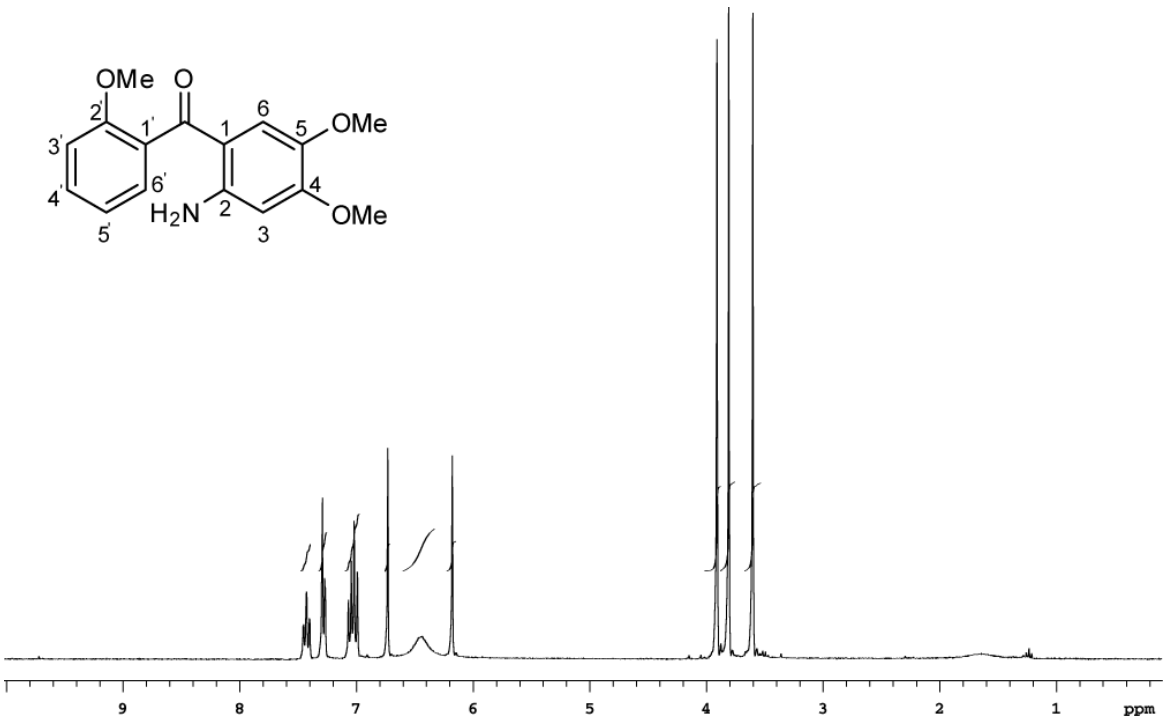


Figure 27: ^{1}H NMR spectrum of **235e** (300 MHz, $CDCl_3$).

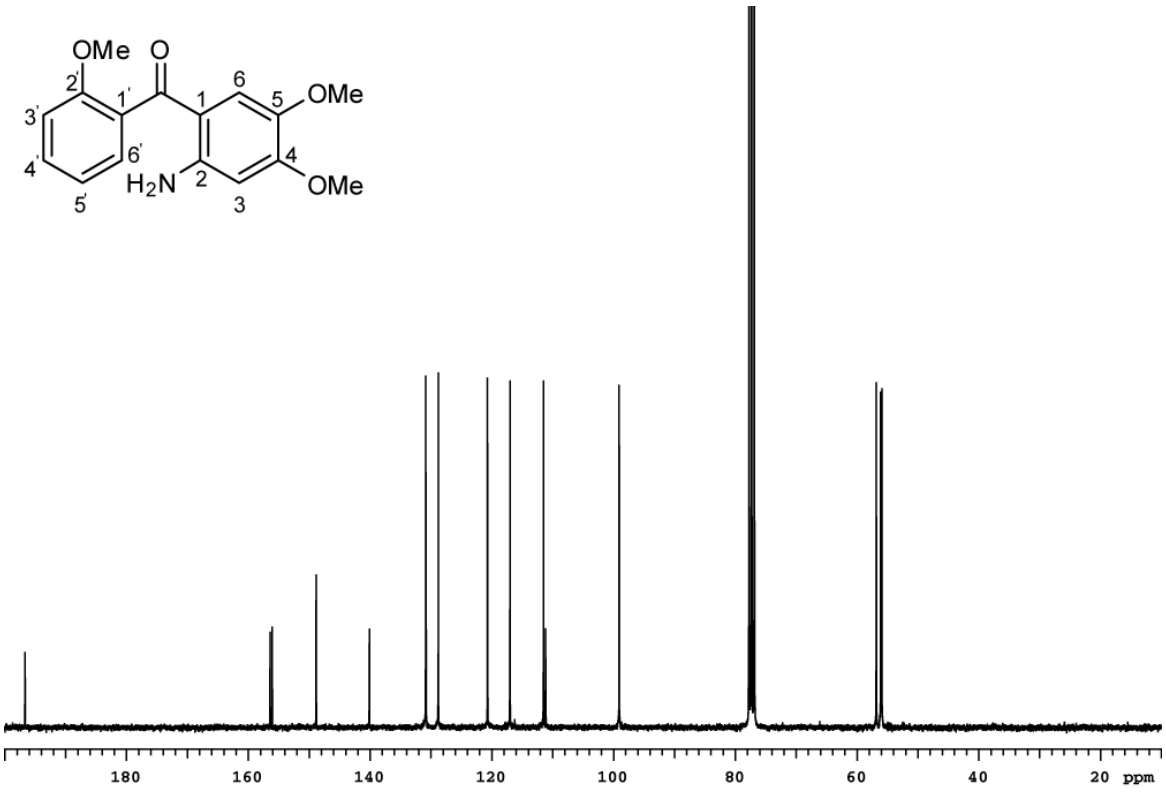
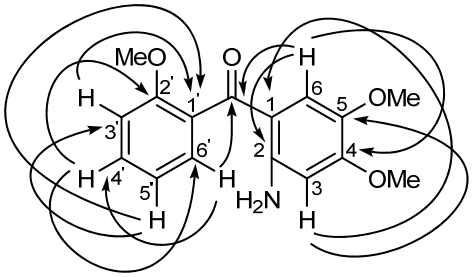


Figure 28: ^{13}C NMR spectrum of **235e** (300 MHz, $CDCl_3$).

In the HMBC and ^{13}C NMR spectrum (Figures 29 and 28) the proton 3'-H is correlated with the quaternary carbon C-1' at δ = 130.8 ppm. The proton 4'-H displayed $^{3}J_{CH}$-correlations with the quaternary carbons C-2' at δ = 156.4 ppm and C-6' at δ = 128.8 ppm. The proton 5'-H exhibited $^{3}J_{CH}$-correlations with the carbons C-1' at δ = 130.8 ppm and C-3' at δ = 111.5 ppm. The proton 6'-H showed $^{3}J_{CH}$-correlations with the quaternary carbon C-2' at δ = 156.4 ppm as well as the carbonyl group at δ = 196.7 ppm. These observations establish that the two aromatic rings are linked by the carbonyl group. Further analysis of the 1D and 2D spectra of **235e** revealed three methoxy groups (at δ = 3.91, 3.81 and 3.60 ppm). The methoxy groups were determined to be attached to the carbons C-4, C-5 and C-2' employing the HMBC spectrum (Figure 29).



235e

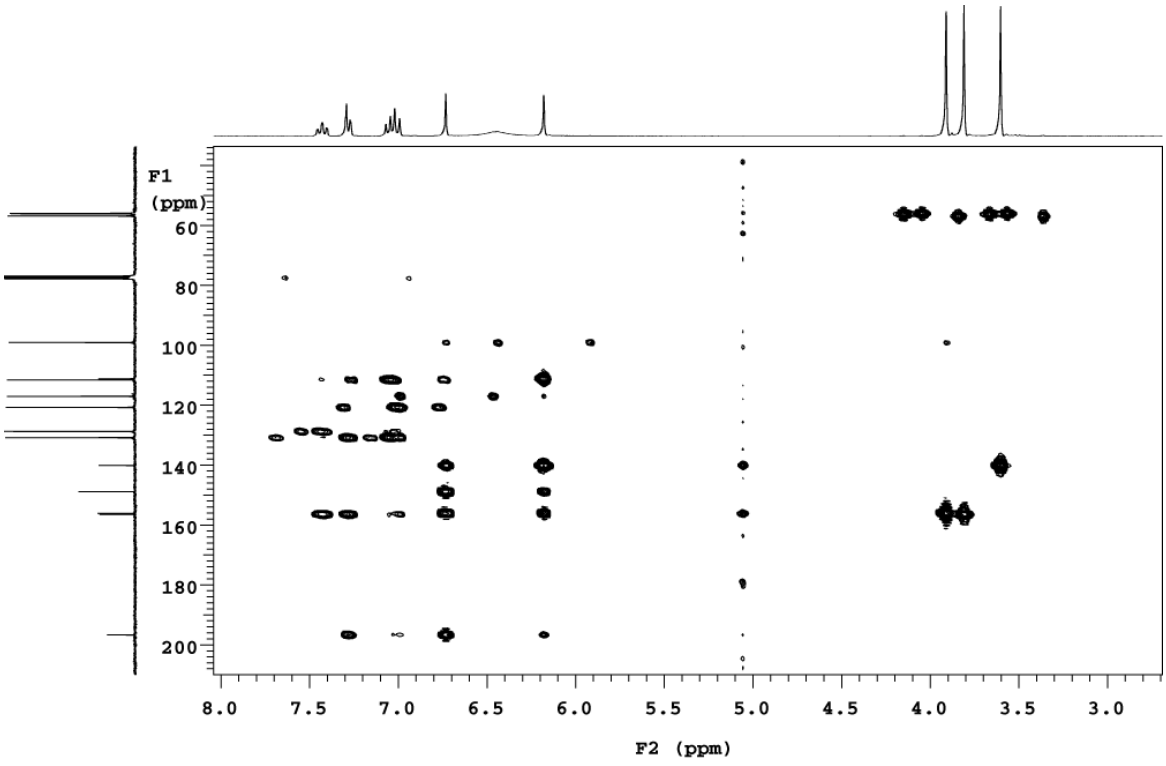


Figure 29: The HMBC spectrum of **235e**.

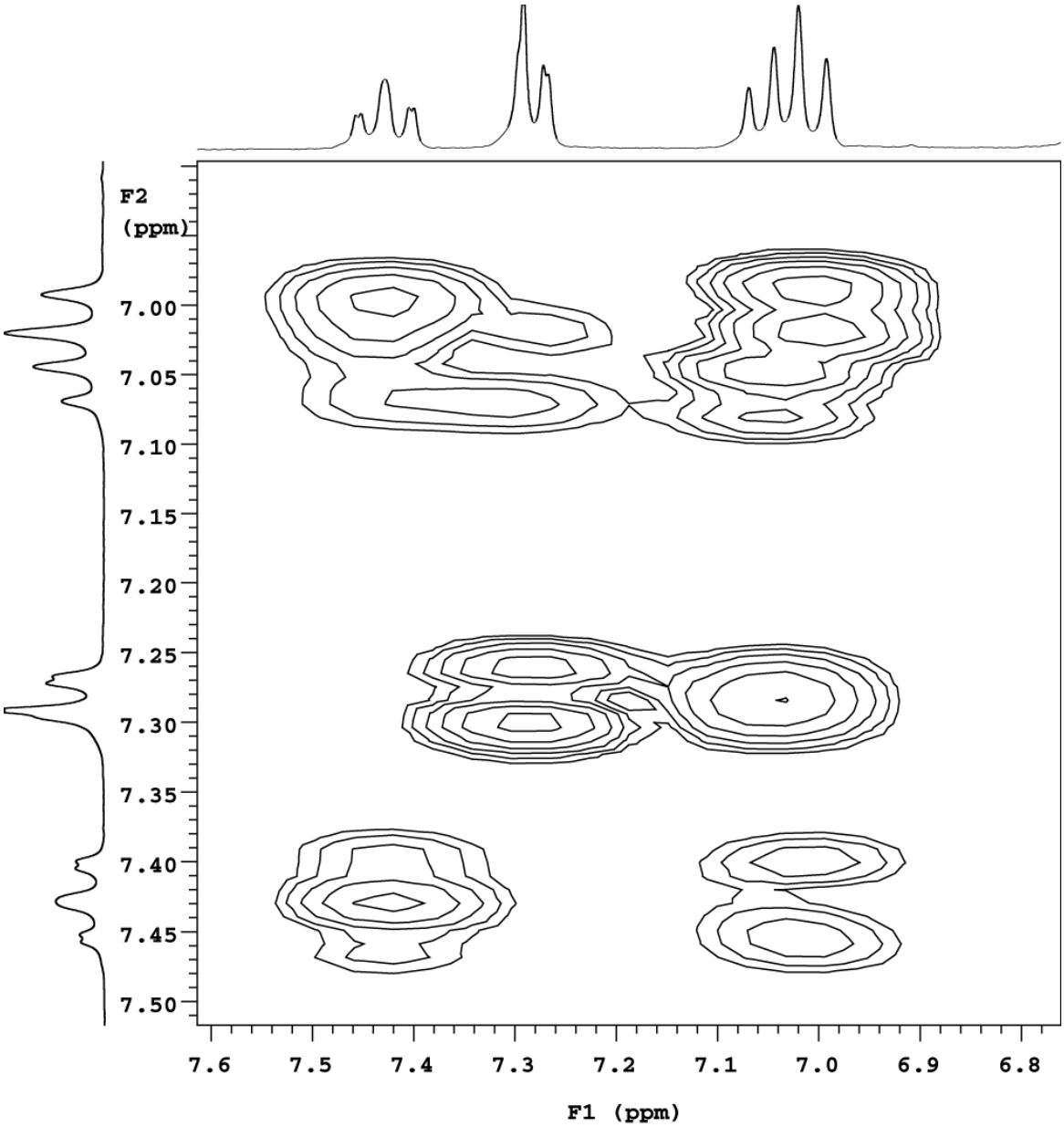


Figure 30: Section of the ^{1}H,^{1}H-COSY spectrum of **235e**.

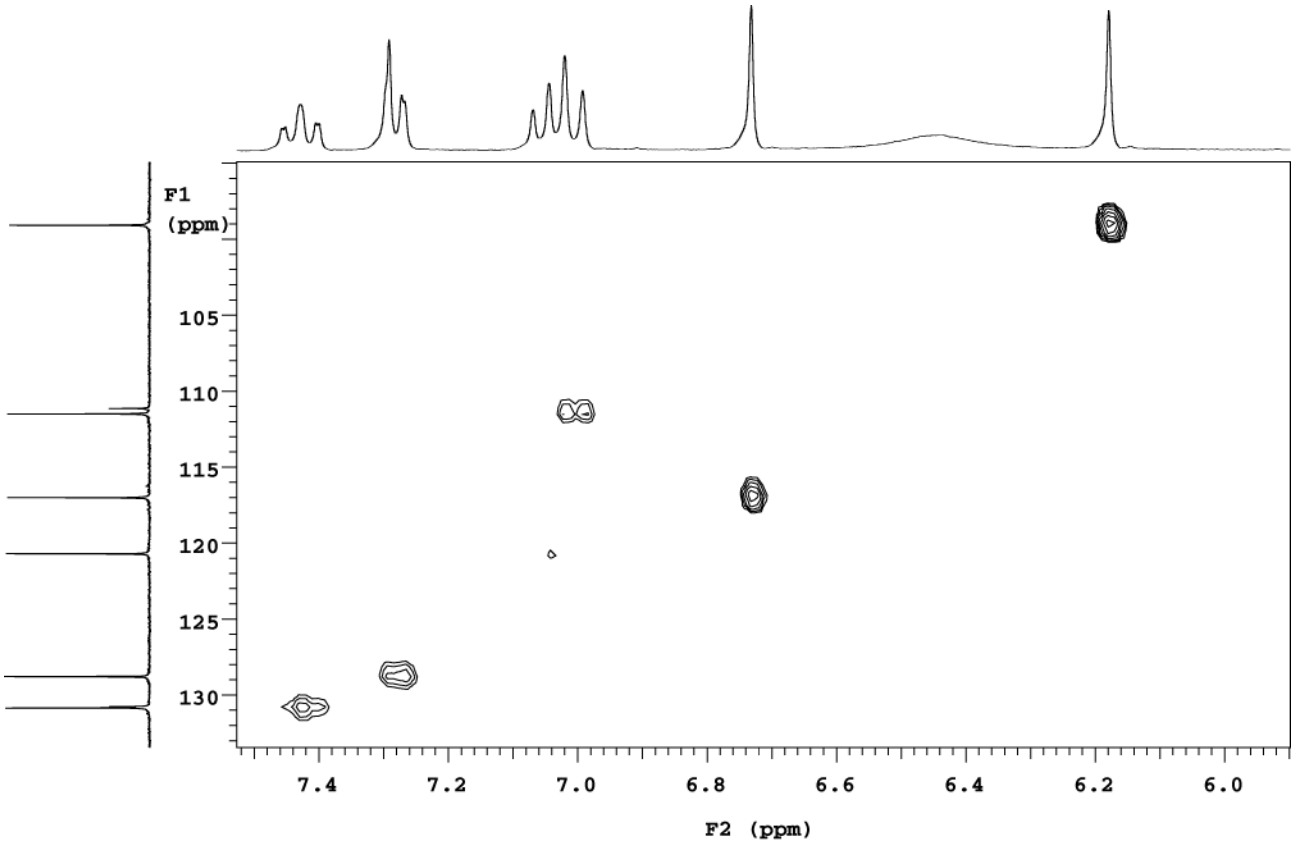


Figure 31: Section of the HSQC spectrum of **235e**.

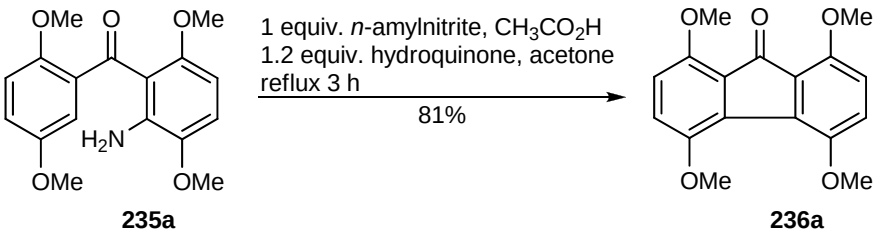
The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 287. This represents the base peak as well.

The IR spectrum of **235e** shows two characteristic sharp bands at $\tilde{\nu}$ = 3478 and 3342 cm^{-1} for the NH_2 group due to N-H stretching. A characteristic band at $\tilde{\nu}$ = 1611 cm^{-1} suggests that the C=O stretching vibration is also present. The bands in the range of $\tilde{\nu}$ = 1600-1531 cm^{-1} are in agreement with an aromatic nucleus. The strong band at $\tilde{\nu}$ = 1244 cm^{-1} confirms the presence of a C-O-C group due to the asymmetric stretching vibration.

7.1.5 Synthesis of the methoxy-substituted fluoren-9-ones 236a-e by Pschorr cyclization

The Gomberg-Bachmann reaction[37a-c] is the intermolecular base-promoted radical C,C-coupling reaction between an aryl diazonium salt and an aromatic compound to form a diaryl compound. The intramolecular version of the Gomberg-Bachmann reaction is known as the Pschorr cyclization.[33a] An efficient way to carry out the Pschorr reaction is to diazotize the

corresponding aniline substrate with isopropyl nitrite in the presence of sodium iodide. This method allows the formation of the cyclization product in one step and has been reported first by Chauncy and Gellert[99] and later by Rapoport et al.[33b,c] Therefore, we tried to cyclize the substituted 2-aminobenzophenone **235a** using sodium iodide and *n*-amylnitrite in acetone at 0 °C according to the procedure of Rapoport et al.[33b,c] Unfortunately, no product was formed under this conditions.



235a **236a**

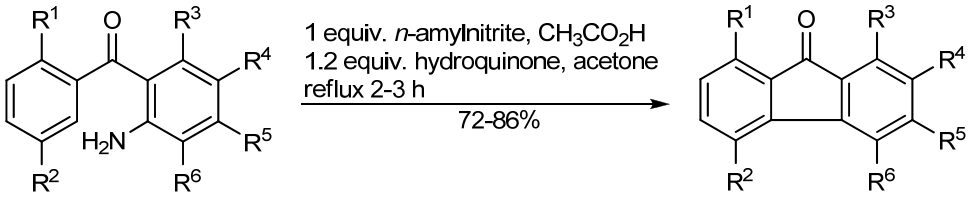
Scheme 60: Pschorr cyclization of **235a** using the method of Hashimoto, Nakata et al.[1c]

As an alternative, it was tried to achieve the Pschorr cyclization of **235a** using the experimental conditions that had been reported by Hashimoto, Nakata et al.[1c] For this purpose, a solution of the substituted 2-aminobenzophenone **235a** in glacial acetic acid was heated with 1 equivalent *n*-amylnitrite at 0 °C. After 1 h stirring at room temperature the reaction mixture was heated with a solution of 1.2 equivalents hydroquinone in acetone. After work up the cyclization product **236a** could be isolated with 81 % yield. Subsequently, the remaining substituted 2-aminobenzophenones **235b-e** were transformed into the corresponding fluore-9-ones **236b-e** with yields ranging from 74 to 86 % (Table 4, entries 2-5, Figure 32). Compound **236c** was obtained with 83 % yield (Table 4, entry 3) and **236e** was prepared with 86 % yield (Table 4, entrie 5). The compounds **236b** and **236d** could be isolated with 74 and 72 % yield, respectively (Table 4, entries 2 and 4).

It should be highlighted that the modified protocol for the Pschorr cyclizations allows the efficient conversion of highly substituted 2-aminobenzophenones **235** into fluoren-9-ones **236** in one synthetic operation and with high yields.

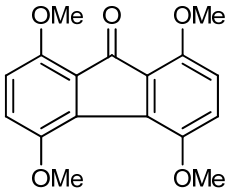
The structures of all fluoren-9-ones **236a-e** have been elucidated unambiguously by means of analytical and spectroscopic methods including UV/VIS-, IR- and NMR spectroscopy as well as mass spectrometry. A characteristic feature in the ^{1}H NMR spectra of all fluoren-9-ones **236a-e** was the lack of the broad singlets for the NH_2 groups of **235a-e** in the range of δ = 6.35-6.44 ppm. This could be taken as a reliable indicator for successful Pschorr cyclizations.

Table 4: Synthesis of methoxy-substituted fluoren-9-ones **236a-e**

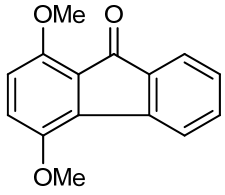


235 **236**

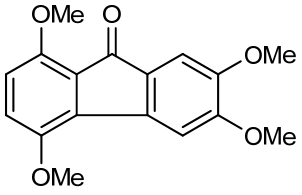
Entry	**235**	R^1	R^2	R^3	R^4	R^5	R^6	*t* [h]	Product	Yield of **236** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	3	**236a**	81
2	**b**	OMe	OMe	H	H	H	H	3	**236b**	74
3	**c**	OMe	OMe	H	OMe	OMe	H	2	**236c**	83
4	**d**	OMe	H	H	H	H	H	3	**236d**	72
5	**e**	OMe	H	H	OMe	OMe	H	2	**236e**	86



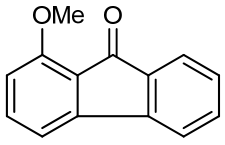
236a



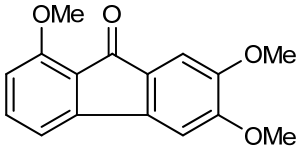
236b



236c



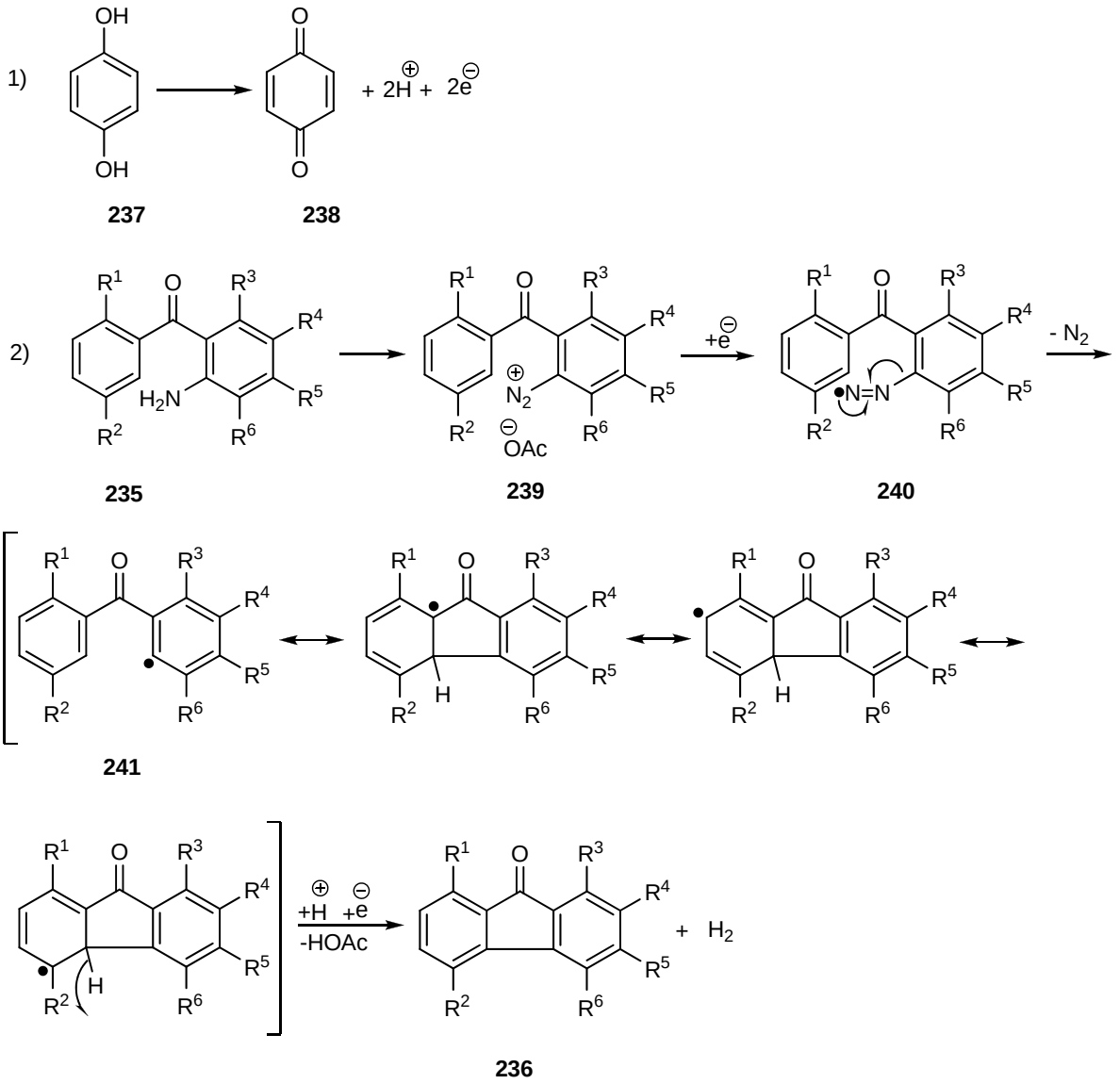
236d



236e

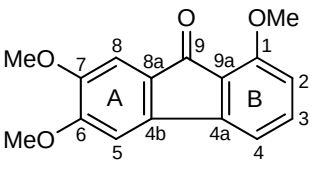
Figure 32: Structures of compounds **236a-e**.

In accordance with the general mechanisms of the Gomberg-Bachmann reaction[37a-c] and the Pschorr cyclization[33] the mechanism of the hydroquinone-mediated Pschorr cyclization was proposed as given in Scheme 60. The oxidation of hydroquinone (**237**) to to *p*-benzoquinone (**238**) delivers the reduction equivalent which is necessary for the reduction of the diazonium salt **239** to the diazo radical **240**. Loss of N_2 results in the formation of an aryl radical **241** which undergoes intramolecular cyclization.



Scheme 61: Proposal for the mechanism of the hydroquinone-mediated Pschorr cyclization of **235**.[33,37a-c]

7.1.5.1 Discussion of the spectral data of the methoxy-substituted fluoren-9-ones 236a-e



236e

As an example, the discussion of the spectral data of 1,6,7-trimethoxyfluoren-9-one (**138e**) is presented in detail. The structural assignment of **236e** rests mainly on its ^{1}H NMR (Figure 33), ^{13}C NMR (Figure 34), HMBC (Figure 35), ^{1}H,^{1}H-COSY (Figure 36) and HSQC spectra (Figure 37).

The ^{1}H NMR spectrum of **236e** (Figure 33) showed two singlets corresponding to the aromatic protons 5-H and 8-H at δ = 6.96 ppm and δ = 7.16 ppm, respectively. Their carbons C-5 at δ = 103.67 ppm and C-8 at δ = 107.11 ppm were assigned using the HSQC spectrum (Figure 37). In the HMBC spectrum (Figure 35) the proton 5-H showed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-7 at δ = 150.16 ppm, C-8a at δ = 127.52 ppm and C-4a at δ = 146.43 ppm. The proton 8-H exhibited strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-6 at δ = 154.19 ppm and C-4b at δ = 138.13 ppm as well as with a carbonyl group at δ = 191.69 ppm. These observations clearly proved that ring A is a tetrasubstituted aromatic nucleus. From the ^{1}H NMR spectrum (Figure 31) and the ^{1}H,^{1}H-COSY spectrum (Figure 36) a trisubstituted aromatic ring B could be deduced by three aromatic protons 2-H at δ = 6.75 ppm (doublet, $^{3}J_{HH}$ = 8.5 Hz), 3-H at δ = 7.35 ppm (doublet of doublet, $^{3}J_{HH}$ = 7.6 Hz) and 4-H at δ = 6.95 ppm (doublet, $^{3}J_{HH}$ = 6.9 Hz). Their corresponding carbons C-2 at δ = 112.85 ppm, C-3 at δ = 136.62 ppm and C-4 at δ = 112.29 ppm were revealed with the help of the HSQC spectrum (Figure 37).

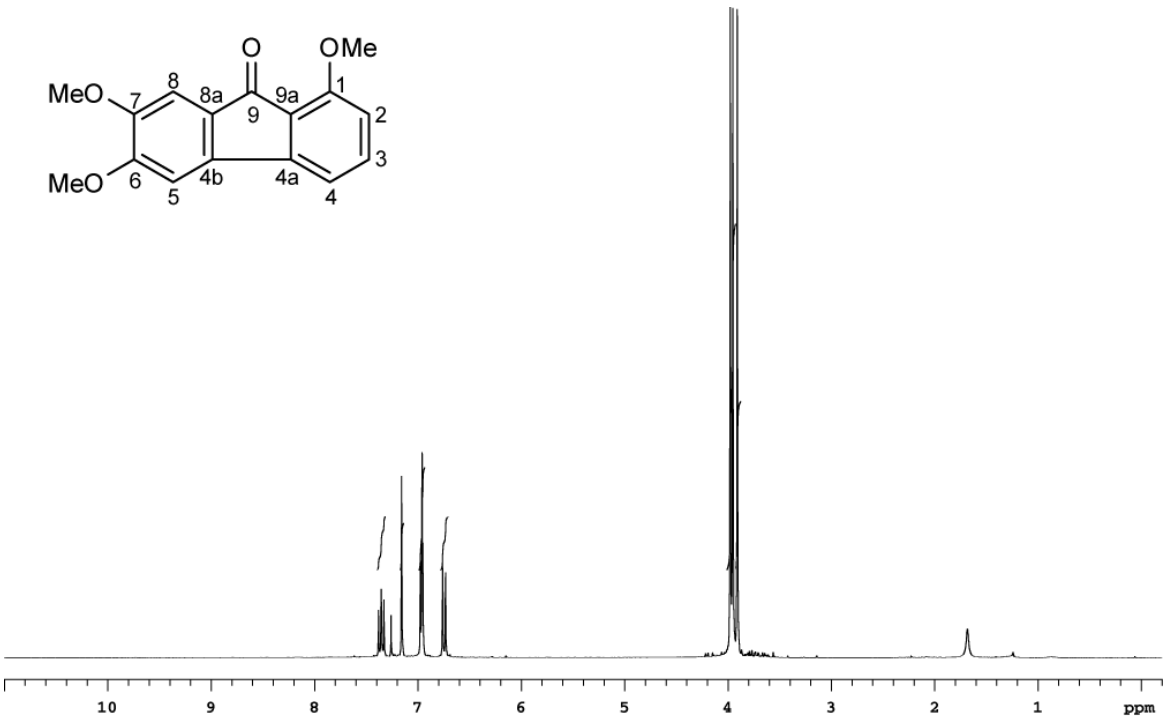


Figure 33: ^{1}H NMR spectrum of **236e** (300 MHz, $CDCl_3$).

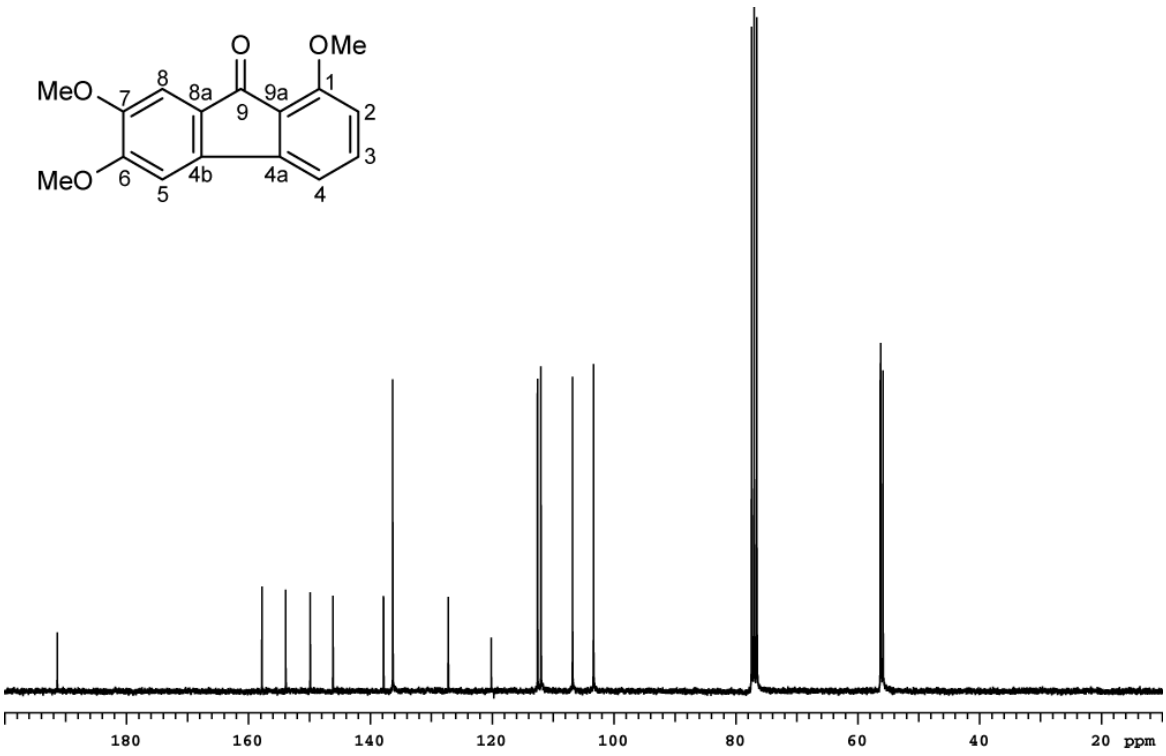
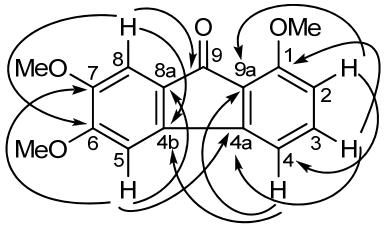


Figure 34: ^{13}C NMR spectrum of **236e** (300 MHz, $CDCl_3$).

Inspection of the HMBC and the ^{13}C NMR spectrum (Figures 35 and 34) revealed $^{3}J_{CH}$-correlations of the proton 2-H with the quaternary carbons C-9a at δ = 120.44 ppm and C-4 at δ = 112.29 ppm. The proton 3-H displayed $^{3}J_{CH}$-correlations with the quaternary carbons C-1 at δ = 158.11 ppm and C-4a at δ = 146.43 ppm while the proton 4-H showed $^{3}J_{CH}$-correlations with the carbons 9a at δ = 120.44 ppm and C-4b at δ = 138.13 ppm. The above mentioned observations and the $^{3}J_{CH}$-correlations between 5-H and C-4a as well as 8-H and the carbon of the carbonyl group indicated that the two aromatic rings A and B are linked by the carbonyl group and a bond between (the two carbons) C-4a and C-4b. Furthermore, the analysis of the 1D and 2D spectra of **236e** revealed three methoxy groups with resonances at δ = 3.91, 3.98 and 3.95 ppm. The methoxy groups were determined to be attached to carbons C-1, C-6 and C-7 by HMBC (Figure 35).



236e

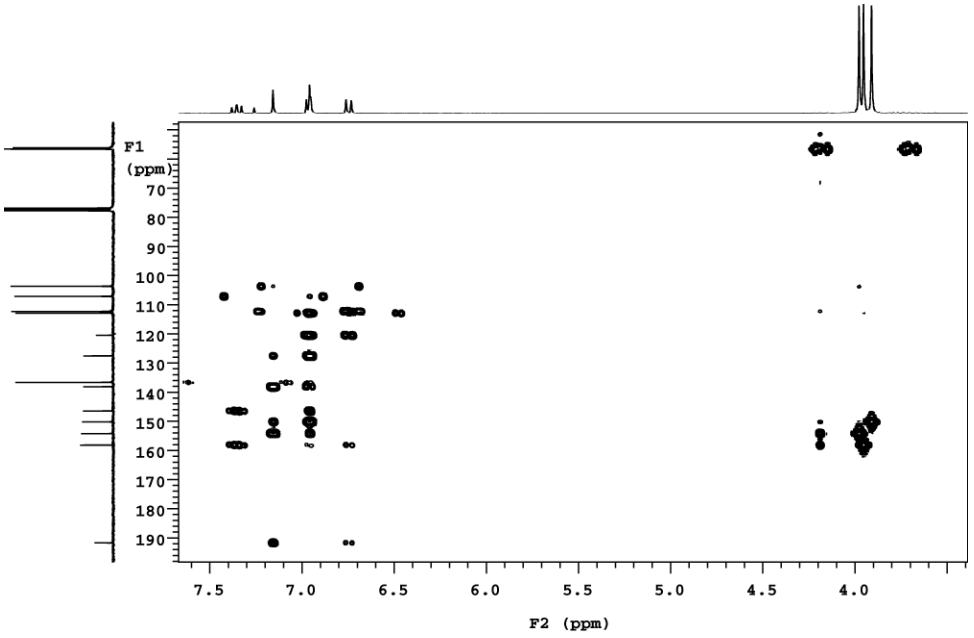


Figure 35: The HMBC spectrum of **236e**.

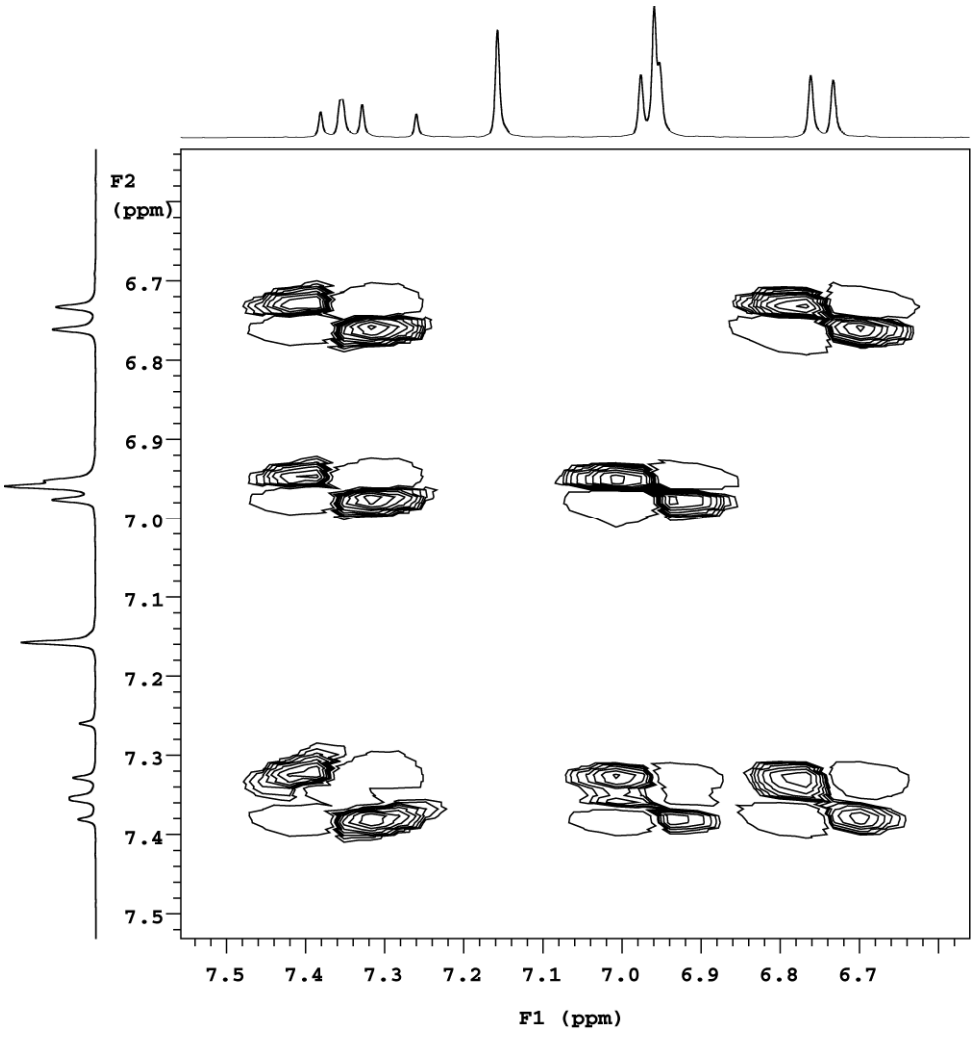


Figure 36: Section of the ^{1}H,^{1}H-COSY spectrum of **236e**.

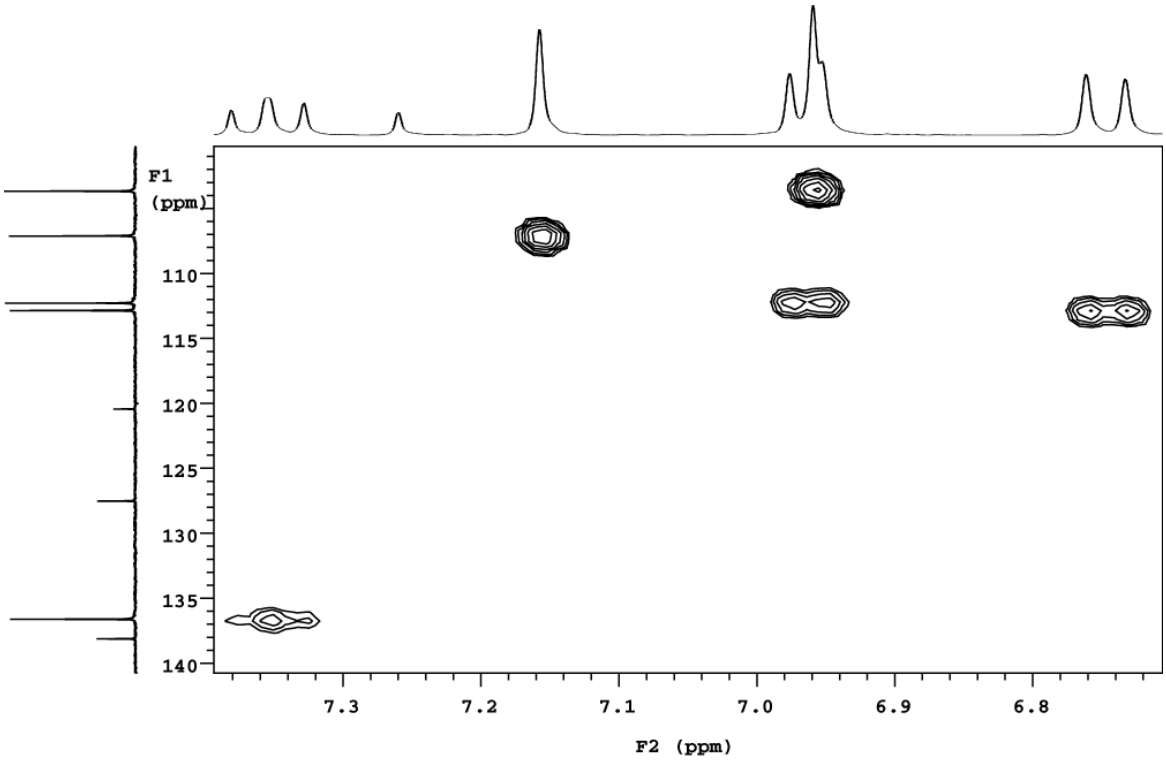


Figure 37: Section of the HSQC spectrum of **236e**.

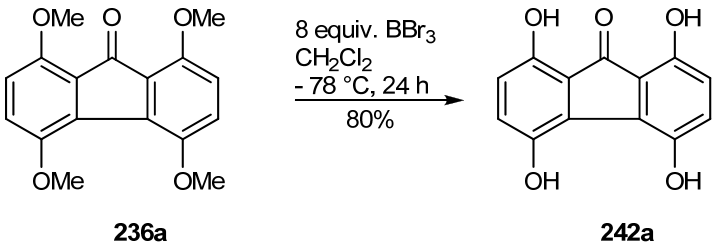
The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 270. This peak is the base peak of the spectrum as well. The ion peak at *m/z* = 239 indicates the loss of a methoxy group [M^+-OMe].

The IR spectrum of **236e** gives rise to a characteristic band at $\tilde{\nu}$ = 1694 cm^{-1} suggesting that the C=O stretching vibration is present. The bands in the range of $\tilde{\nu}$ = 1589-1406 cm^{-1} indicate the presence of an aromatic ring. The strong band at $\tilde{\nu}$ = 1264 cm^{-1} indicates the presence of the asymmetric stretching vibration of a C-O-C group.

7.2 Synthesis of the hydroxy-sustituted fluoren-9-ones 242a-e

After the successful Pschorr cyclization of the 2-aminobenzophenones **235** the methoxy groups in the cyclization products **236** had to be transformed into the corresponding hydroxyl groups. A standard method for the cleavage of methoxy groups is the reaction with 48 % HBr. Therefore, we started with the ether cleavage of the methoxy-sustituted fluoren-9-one **236a** using a mixture of acetic acid and 48 % hydrogen bromide under reflux according to the

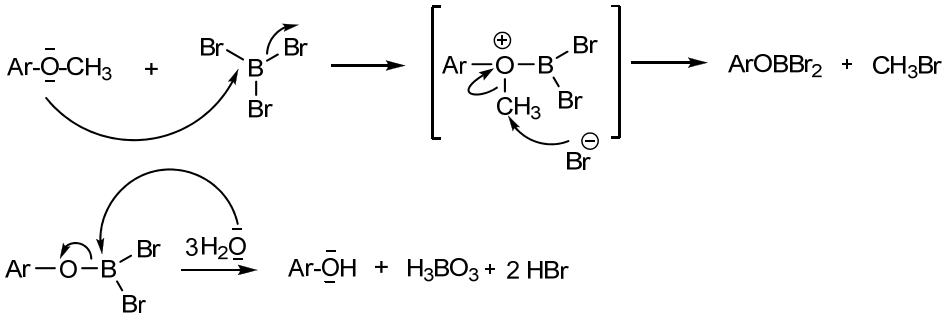
method of Ciske and Jones.[100] After work up and purification of the resulting crude product by flash chromatography on silica gel the hydroxy-sustituted fluoren-9-one **242a** was obtained with 63 % yield.



Scheme 62: Ether cleavage of **236a** using BBr_3 as a reagent.

In order to improve the yield the demethylation of **236a** was also performed using boron tribromide at – 78 °C as a reagent according to the protocol of Bergeron and Bharti.[101] After work up and purification by flash chromatography the hydroxy-substituted fluoren-9-one **242a** was isolated with 80 % yield (Scheme 62). The higher yield for the model reaction **236a** ⟶ **242a** was the reason why the demethylation of the remaining methoxy-substituted fluoren-9-ones **236b-e** was performed with boron tribromide in dichloromethane at – 78 °C. Using this method the hydroxy-substituted fluoren-9-ones **242a-e** were prepared with yields ranging from 60 to 84 % (Table 5, entries 1-5, Figure 38). Both **242a** and **242c** were obtained with 80 % and 83 %, respectively, (Table 5, entries 1 and 3) while compound **242e** was obtained with 84 % yield (Table 5, entry 5).

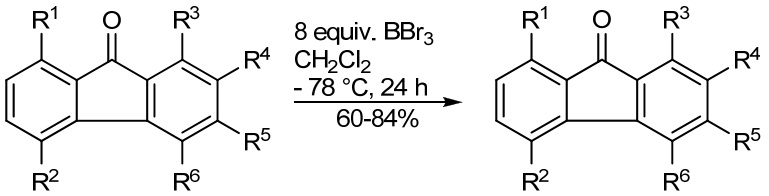
A proposal for the mechanism of the cleavage of aryl methyl ethers using BBr_3 as a reagent is presented in Scheme 63.[102]



Scheme 63: Mechanism for the demethylation of aryl methyl ethers according to West et al.[102]

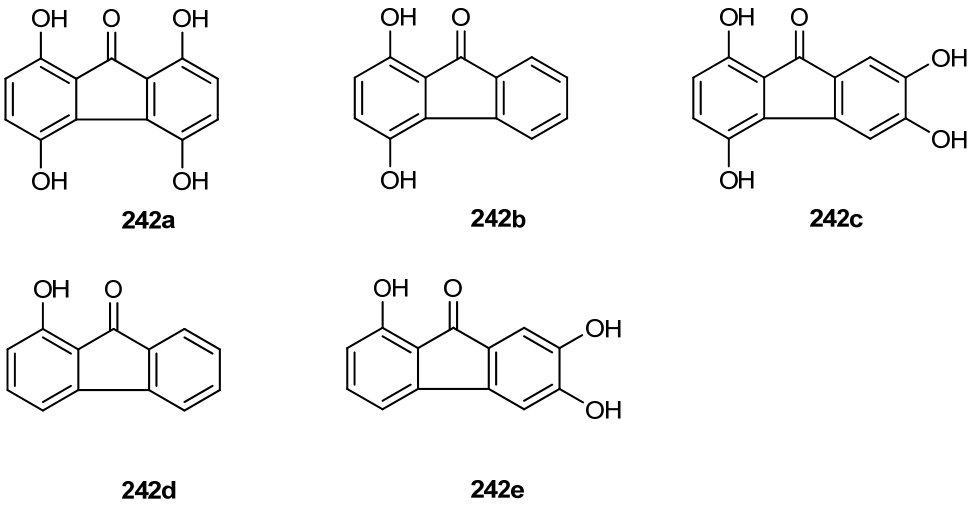
The structures of all hydroxy-sustituted fluoren-9-ones **242a-e** have been established by means of analytical and spectroscopic methods including UV/VIS-, IR- and NMR spectroscopy as well as mass spectrometry. A characteristic feature in the ^{1}H NMR spectra of all fluoren-9-ones **242a-e** was the appearance of broad singlets for the hydroxyl groups in the range of δ = 8.44-10.69 ppm. Combined with the lack of signals for the methoxy groups this was taken as an indicator for the successful demethylation of **236a-e**.

Table 5: Synthesis of hydroxy-substituted fluoren-9-ones **242a-e**



236a-e **242a-e**

Entry	**236**	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield of **242** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**242a**	80
2	**b**	OMe	OMe	H	H	H	H	**242b**	68
3	**c**	OMe	OMe	H	OMe	OMe	H	**242c**	83
4	**d**	OMe	H	H	H	H	H	**242d**	60
5	**e**	OMe	H	H	OMe	OMe	H	**242e**	84

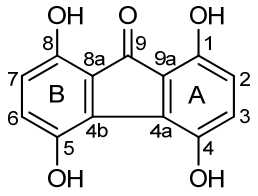


242a **242b** **242c**

242d **242e**

Figure 38: Structures of compounds **242a-e**.

7.2.1 Discussion of the spectral data of the hydroxy-substituted fluoren-9-ones 242a-e



242a

As an example, the spectroscopic data of 1,4,5,8-tetrahydroxyfluoren-9-one (**242a**) are presented. The structural assignment of **242a** rests mainly on its ^{1}H NMR (Figure 39), ^{1}H NMR H/D exchange (Figure 40), ^{13}C NMR (Figure 41), HMBC (Figure 42), ^{1}H,^{1}H-COSY (Figure 43) and HSQC spectra (Figure 44).

The ^{1}H NMR spectrum of **242a** (Figure 39) displayed only half of the expected numbers of signals indicating a symmetrical compound. This is in agreement with the observed molecular mass. The two aromatic protons 2-H and 7-H appear as a doublet at δ = 6.68 ppm with $^{3}J_{HH}$ = 8.9 Hz and the signals for the protons 3-H and 6-H could be found as a doublet at δ = 6.89 ppm with $^{3}J_{HH}$ = 8.9 Hz. The HSQC spectrum (Figure 44) revealed their carbons C-2 and C-7 at δ = 120.56 ppm as well as C-3 and C-6 at δ = 126.28 ppm, respectively. The ^{1}H,^{1}H-COSY spectrum (Figure 43) showed that the two protons 2-H and 3-H are located on adjacent carbons. Thus, two tetrasubstituted aromatic rings A and B could be deduced.

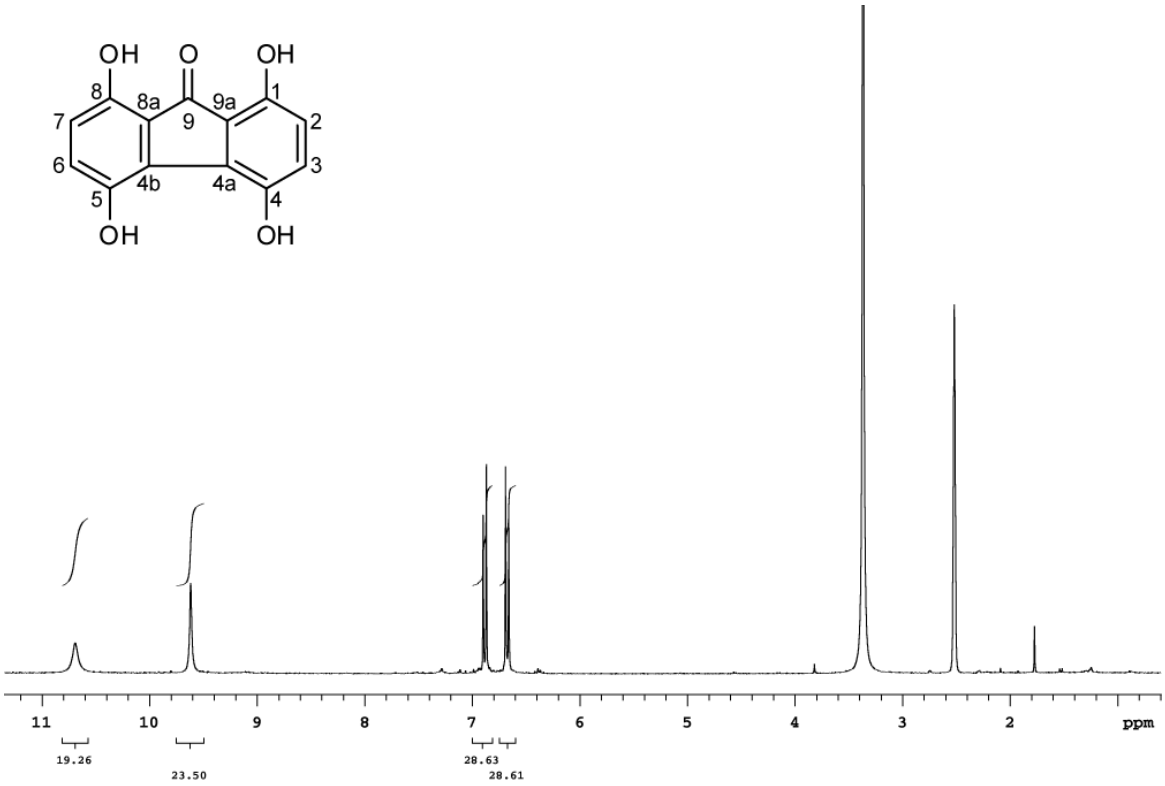


Figure 39: ^{1}H NMR spectrum of **242a** (300 MHz, DMSO-d_6).

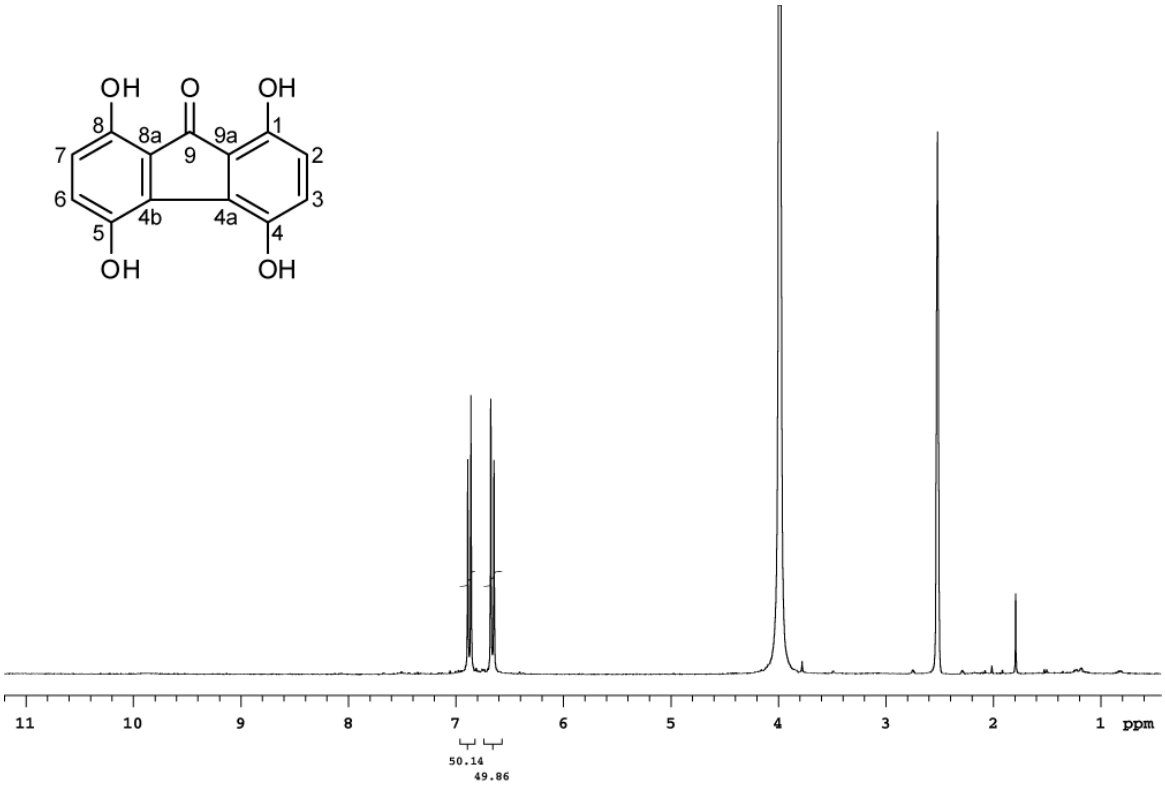


Figure 40: ^{1}H NMR spectrum of **242a** after H/D exchange (300 MHz, DMSO-d_6).

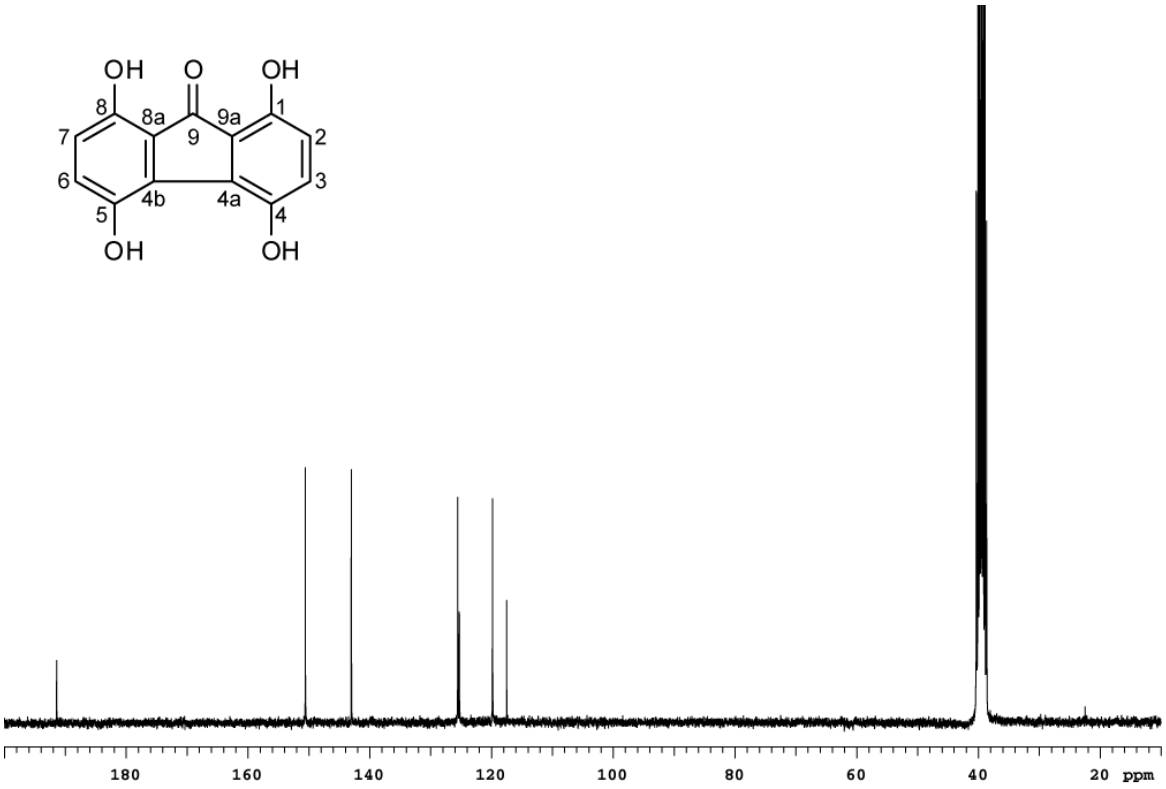
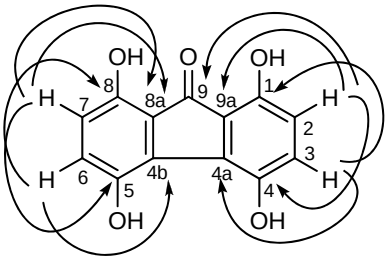


Figure 41: ^{13}C NMR spectrum of **242a** (300 MHz, DMSO-d_6).

In the HMBC spectrum (Figure 42) the protons 3-H and 6-H showed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-1 and C-8 at δ = 151.31 ppm and C-4a and C-4b at δ = 126.01 ppm. The protons 2-H and 7-H displayed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-4 and C-5 at δ = 143.75 ppm and C-9a and C-8a at δ = 118.23 ppm as well as a long range $^{4}J_{CH}$-correlation with the carbonyl group at δ =192.16 ppm. The $^{4}J_{CH}$-correlations between both 5-H and 7-H and the carbon of the carbonyl group indicate that the two aromatic rings A and B are connected by the carbonyl group.

Finally, the ^{1}H NMR spectrum (Figure 39) displayed two singlets representing four hydroxyl protons at δ = 9.62 ppm (4-OH and 5-OH) and at δ = 10.69 ppm (1-OH and 8-OH). HMBC correlations of the sharp singlet at δ = 9.56 ppm with the carbons C-1, C-2 and C-9a revealed that the hydroxyl group is attached to C-1. After H/D exchange (Figure 40) we observed the disappearance of the signals at δ = 10.69 and at δ = 9.62 ppm in the ^{1}H NMR spectrum. This observation supports the presence of hydroxyl groups in **242a**.



242a

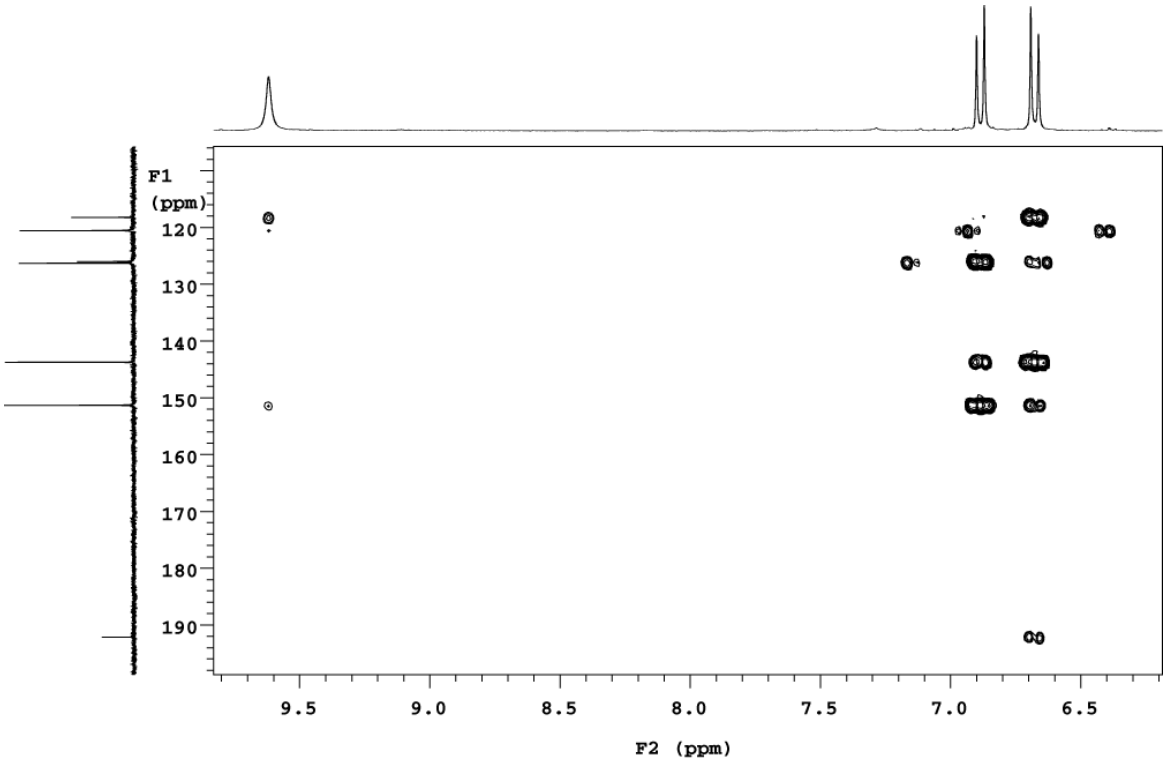


Figure 42: The HMBC spectrum of **242a**.

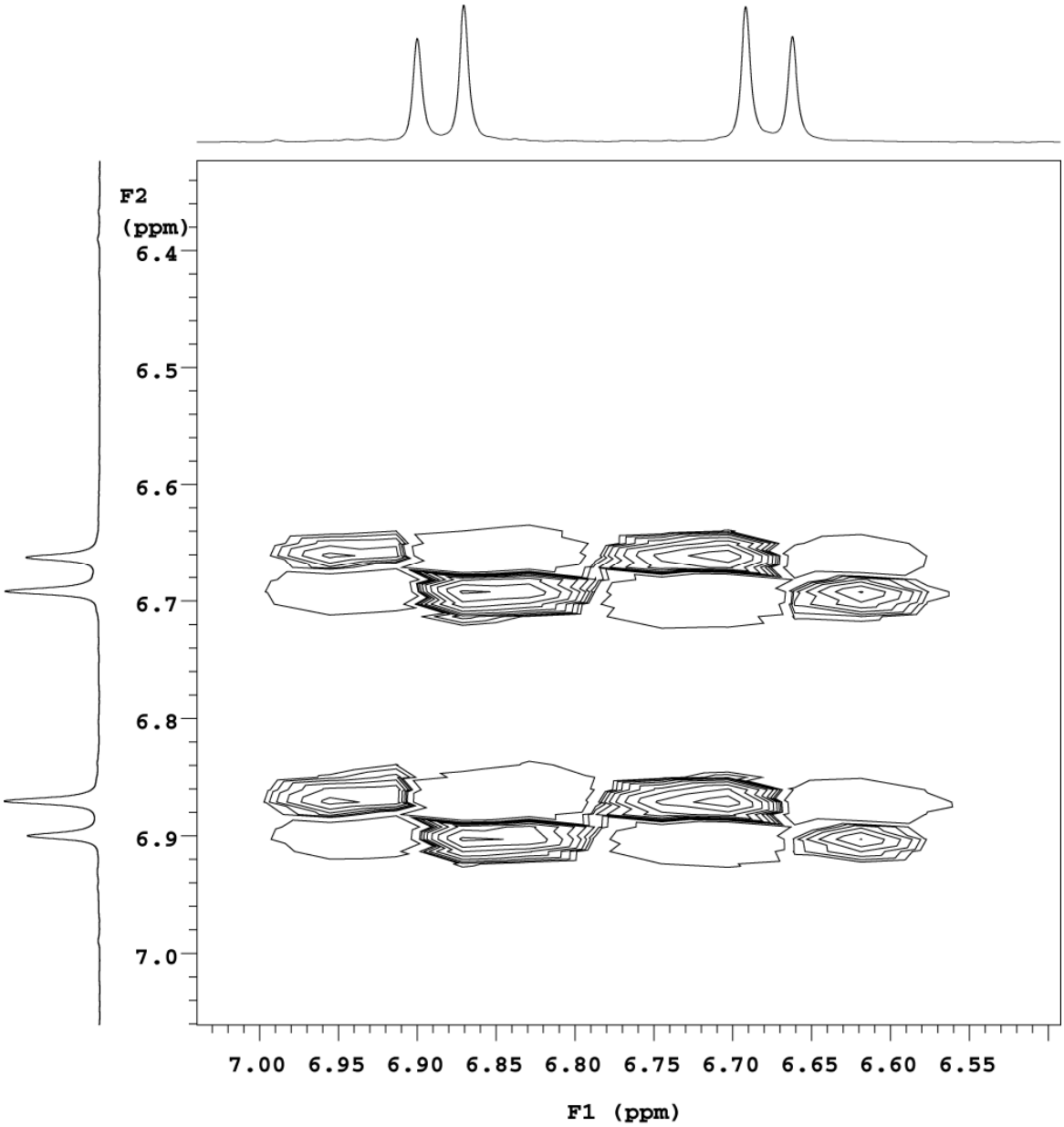


Figure 43: Section of the ^{1}H,^{1}H-COSY spectrum of **242a**.

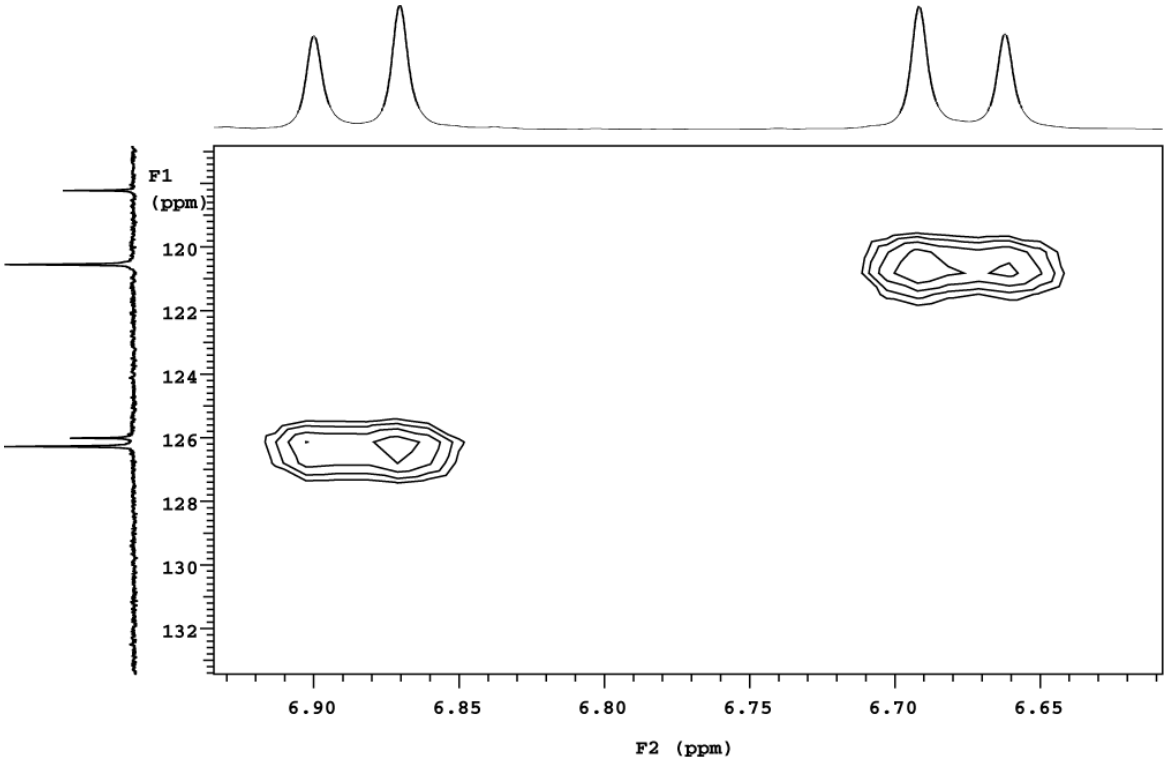


Figure 44: Section of the HSQC spectrum of **242a**.

The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 244.

The IR spectrum of **242a** shows a broad band in the range of $\tilde{\nu}$ = 3300-2980 cm^{-1} suggesting the presence of a stretching vibration of associated OH groups. The strong band at $\tilde{\nu}$ = 1259 cm^{-1} confirms the presence of a stretching vibration of a C-O group. A characteristic band at $\tilde{\nu}$ = 1659 cm^{-1} indicates that the C=O stretching vibration is present. The bands in the range of $\tilde{\nu}$ = 1601-1449 cm^{-1} indicate the presence of an aromatic ring.

7.3 Synthesis of methoxy-substituted fluoren-9-ones by intramolecular palladium-mediated arylation

Nowadays, Pd-catalyzed reactions play a central role in the transition metal-catalyzed formation of C,C-bonds.[103] Oxidative addition of Pd(0) species into unsaturated halides or triflates provides a popular method for the formation of the σ-bond organopalladium (II) species. These intermediates can undergo electrophilic palladation to give organopalladium (II) intermediates. Subsequently, the organopalladium (II) intermediates undergo elimination

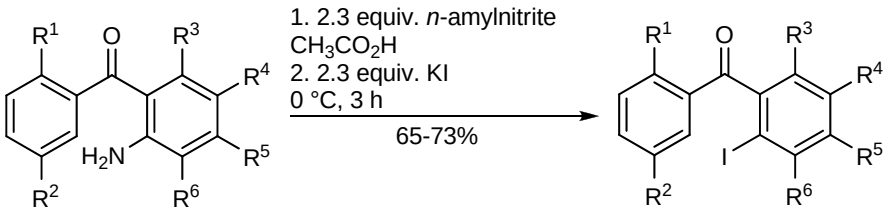
of hydrogen halide to generate new organopalladium (II) intermediates which undergo reductive elimination with simultaneous regeneration of the Pd(0) catalyst.

In the following chapter the synthesis of methoxy-substituted fluoren-9-ones by palladium-mediated intramolecular dehydrohalogenation of 2-halobenzophenones is presented. For this purpose the corresponding 2-halobenzophenones **202b** had to be prepared in an efficient manner. It turned out that the 2-iodobenzophenones **243a-e** could be obtained in one synthetic step from the corresponding 2-aminobenzophenones **235a-e**. The corresponding 2-bromobenzophenones could not be synthesized by this approach.

7.3.1 Synthesis of the (2,5-dialkoxyphenyl)(2'-iodo-3',4',5',6'-tetraalkoxyphenyl)methanones 243a-e

It was found that the amino group of the sustituted-2-aminobenzophenones **235a-e** could be replaced with an iodine atom by reaction of **235a-e** with *n*-amylnitrite and potassium iodide in acetic acid at 0 °C according to the procedure of Coffen et al.[104] The crude products were purified by flash chromatography and afforded the sustituted 2-iodobenzophenones **243a-e** with yields ranging from 65-73 % (Table 6).

Table 6: Synthesis of substituted 2-iodobenzophenones **243a-e**



235 **243**

Entry	**235**	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield of **243** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**243a**	66
2	**b**	H	H	H	H	H	H	**243b**	73
3	**c**	OMe	OMe	H	OMe	OMe	H	**243c**	65
4	**d**	OMe	H	H	H	H	H	**243d**	69
5	**e**	OMe	H	H	OMe	OMe	H	**243e**	72

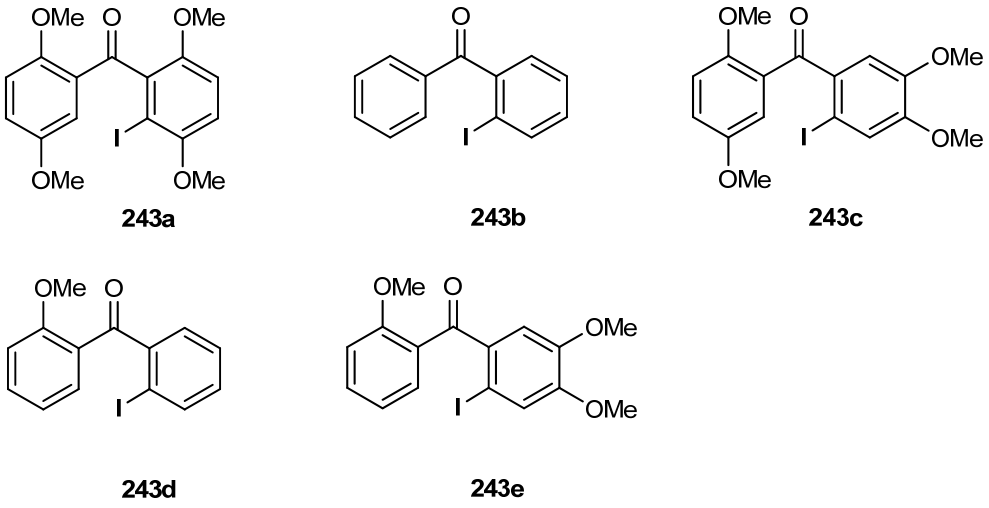
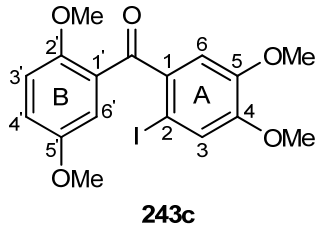


Figure 45: Structures of compounds **243a-e**.

7.3.1.1 Discussion of the spectral data of the (2,5-dialkoxyphenyl)(2'-iodo-3',4'-5',6'-tetraalkoxyphenyl)methanones 243a-e



243c

The discussion of the spectroscopic data of (2',5'-dimethoxyphenyl)(2-iodo-4,5-dimethoxyphenyl)methanone (**243c**) is taken as an example. The structural assignment of **243c** rests mainly on its ^{1}H NMR (Figure 46), ^{13}C NMR (Figure 47), HMBC (Figure 48), ^{1}H, ^{1}H-COSY (Figure 49) and HSQC spectra (Figure 50).

The ^{1}H NMR spectrum of **243c** (Figure 46) displayed two singlets corresponding to the aromatic protons 3-H and 6-H at δ = 7.30 ppm and δ = 6.94 ppm, respectively. The HSQC spectrum (Figure 50) revealed the carbons C-3 at δ = 122.79 ppm and C-6 at δ = 113.46 ppm. In the HMBC spectrum (Figure 48) the proton 3-H showed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-1 at δ = 137.36 ppm and C-5 at δ = 151.16 ppm as well. The proton 6-H displayed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-2 at δ = 82.52 ppm and C-4 at δ = 149.00 ppm as well as with the carbonyl group at δ = 195.82 ppm.

On the basis of these results, a tetrasubstituted aromatic ring A linked to the carbonyl group could be deduced. As for compound **234a** a 1,2,5-trisubstituted aromatic ring B could be deduced from the occurrence of three aromatic protons [6'-H at δ = 7.12 ppm (doublet, $^{4}J_{HH}$ = 3.1 Hz), 3'-H at δ = 6.88 ppm (doublet, $^{3}J_{HH}$ = 8.9 Hz), 4'-H at δ = 7.06 ppm (doublet of doublet, $^{3}J_{HH}$ = 8.9 Hz and $^{4}J_{HH}$ = 3.1 Hz) and the corresponding carbons C-6' at δ = 115.84 ppm, C-3' at δ = 113.93 ppm and C-4' at δ = 120.75 ppm]. We observed that the two protons 3'-H and 4'-H are adjacent to each other.

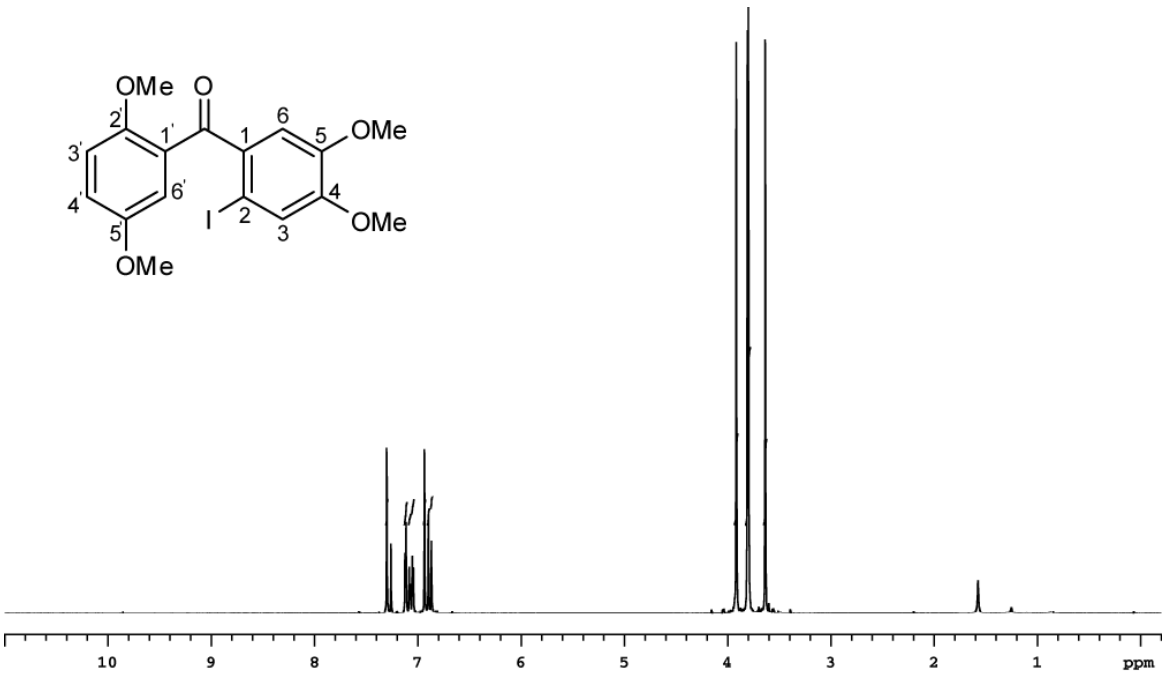


Figure 46: ^{1}H NMR spectrum of **243c** (300 MHz, $CDCl_3$).

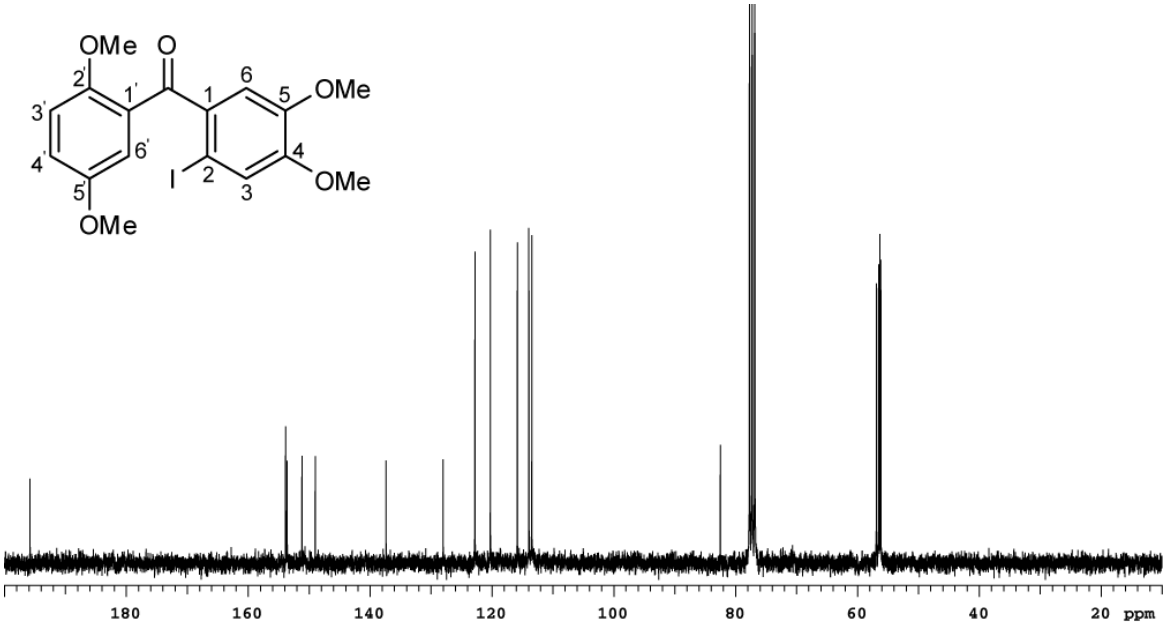
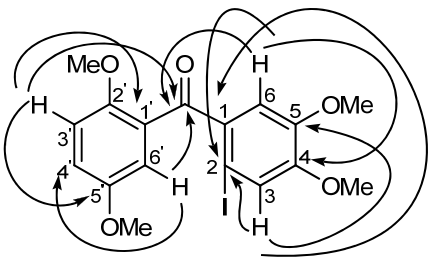


Figure 47: ^{13}C NMR spectrum of **243c** (300 MHz, $CDCl_3$).

In the HMBC spectrum (Figure 48) the proton 3'-H showed $^3J_{CH}$-correlations with the quaternary carbons C-1' at δ = 128.01 ppm and C-5' at δ = 153.86 ppm as well as a long range $^4J_{CH}$-correlation with the carbonyl group at δ = 195.82 ppm. In addition, the proton 6'-H displayed $^3J_{CH}$-correlations with the two aromatic carbons C-2' at δ = 153.62 ppm and C-4' at δ = 120.75 ppm as well as the carbonyl group at δ = 195.82 ppm. From the $^3J_{CH}$-correlations of both 6-H and 6'-H with the carbon of the carbonyl group we can deduce that the carbonyl group is the linkage between the two aromatic rings A and B. Further analysis of the 1D and 2D NMR spectra of **243c** revealed four methoxy groups resonating at δ = 3.92, 3.81, 3.80 and 3.64 ppm, respectively. The methoxy groups were shown to be attached to carbons C-4, C-5, C-2' and C-5', respectively, with the help of the HMBC spectrum (Figure 48).



243c

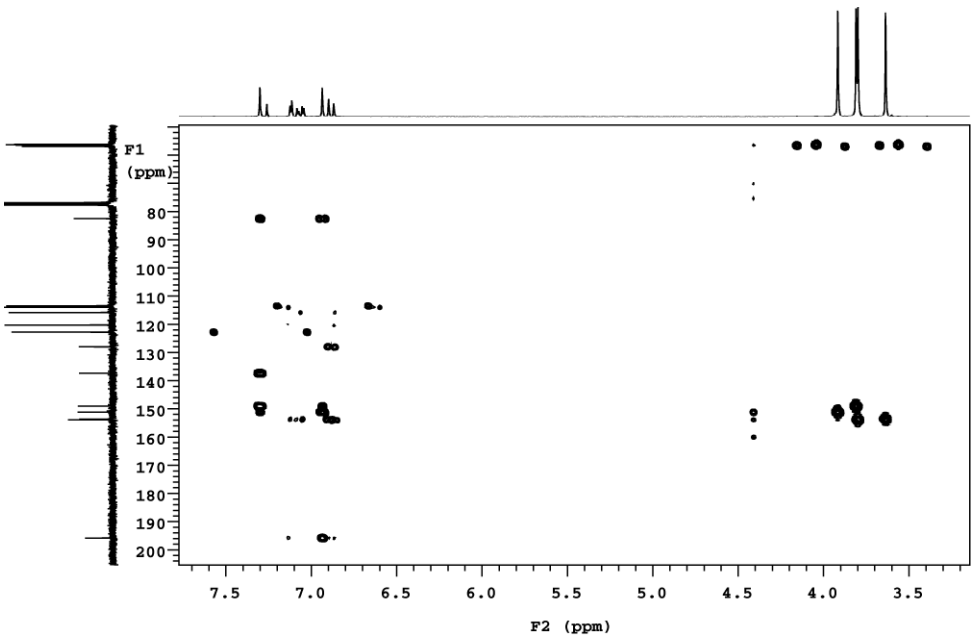


Figure 48: The HMBC spectrum of **243c**.

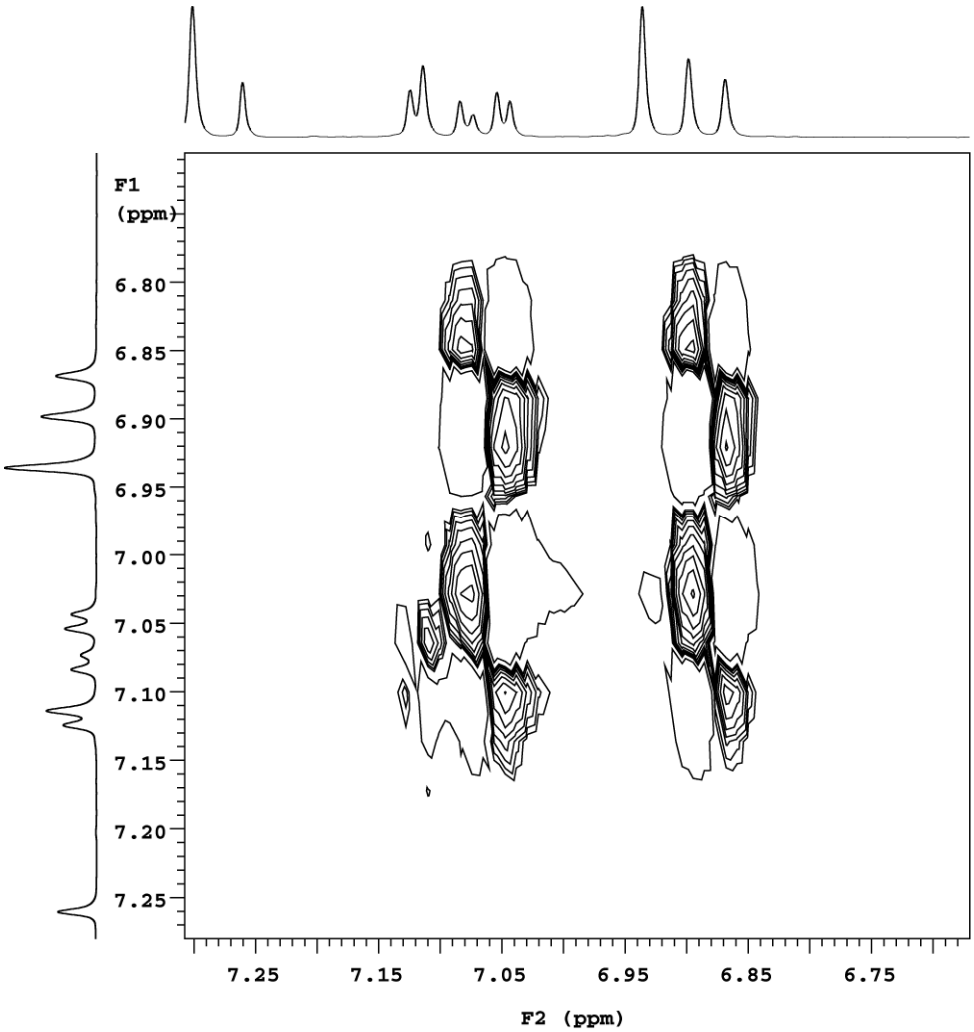


Figure 49: Section of the ^{1}H,^{1}H-COSY spectrum of **243c**.

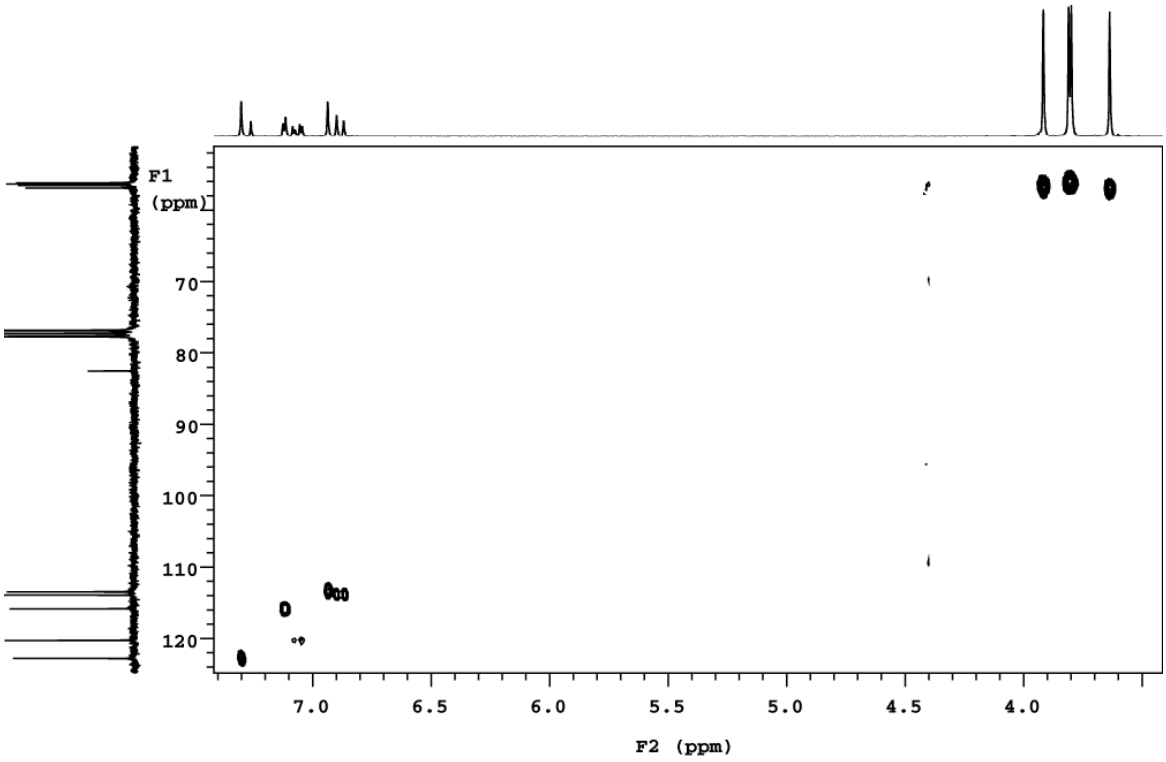


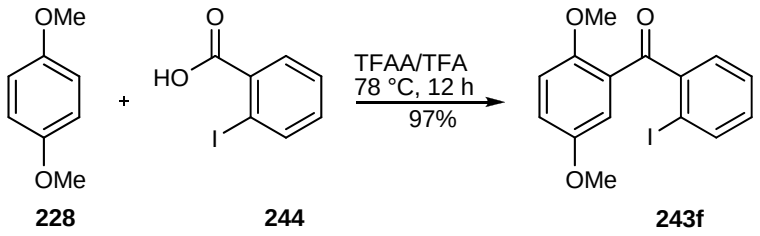
Figure 50: Section of the HSQC spectrum of **243c**.

The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 428. This peak represents also the base peak of the spectrum.

The IR spectrum of **243c** shows a characteristic band at $\tilde{\nu}$ = 1661 cm^{-1} suggesting a C=O stretching vibration. The other bands in the range of $\tilde{\nu}$ = 1585-1461 cm^{-1} are in agreement with an aromatic ring. The strong band at $\tilde{\nu}$ = 1261 cm^{-1} suggests the presence of an asymmetric stretching vibration of a C-O-C group.

7.3.2 Synthesis of the (2,5-dimethoxyphenyl)(2'-iodophenyl)methanone (243f)

(2,5-Dimethoxyphenyl)(2'-iodophenyl)methanone (**243f**) was synthesized according to the procedure described by Qabaja and Jones by Friedel-Crafts acylation of **228** with **244**.[24] The crude product was purified by recrystallization to yield **243f** with 97 % yield (Scheme 64).



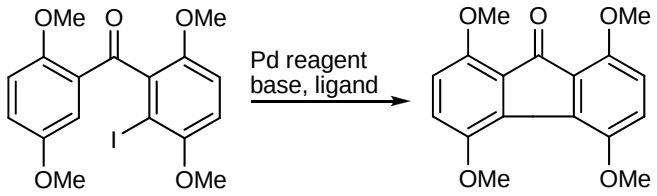
228 **244** **243f**

Scheme 64: Synthesis of (2,5-dimethoxyphenyl)(2'-iodophenyl)methanone (**243f**).

7.3.3 Palladium-mediated arylations of the 2-iodobenzophenones 243a-f

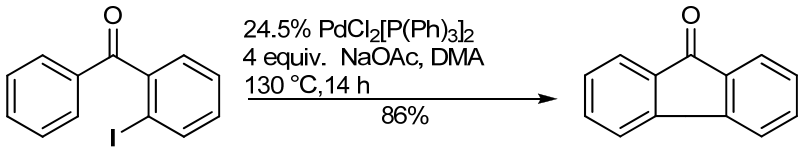
With the substituted 2-iodobenzophenones **243a-f** in hand we were ready to investigate their palladium-mediated cyclizations to the corresponding methoxy-substituted fluoren-9-ones **236a-e**. We started with the cyclization of **243a** which was reacted using different amounts of $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ respectively, in the presence of different bases, in the presence and absence of a ligand and in different solvents under a variety of reaction conditions (Table 7). The best yield of **236a** was observed when **243a** was treated with 40 mol % $PdCl_2(PPh_3)_2$, 4 equivalents of NaOAc and with DMA as the solvent for 32 h at 130 °C (Table 7, entry 12). The yield of **236a**, however, amounted to only 31 % (Table 7).

Table 7: Palladium-mediated cyclization of **243a** under different reaction conditions.



243a **236a**

Entry	Pd reagent	mol%	Base (equiv.)	Ligand (mol%)	Solvent	*T*[°C]	*t* [h]	Yield of **236a** [%]
1	$Pd(OAc)_2$	8.8	TEA (2)	-	CH_3CN	85	51	-
2	$Pd(OAc)_2$	9	K_2CO_3 (2)	-	DMA	200	1	-
3	$Pd(OAc)_2$	40	NaOAc (3.3)	-	DMA	130	28	-
4	$Pd(OAc)_2$	9	K_2CO_3 (2)	-	DMA	170	26	10
5	$Pd(OAc)_2$	3	K_2CO_3 (2)	$P(Ph)_3$ (6)	DMA	130	32	7
6	$Pd(OAc)_2$	1.2	Na_2CO_3 (2)	$P(Ph)_3$ (5)	DMF	100	43	9
7	$Pd(OAc)_2$	2	NaO^tBu (1.5)	$P(Ph)_3$ (4)	toluene	80	40	-
8	$PdCl_2[P(Ph)_3]_2$	15.6	TEA (3)	-	THF/CH_3CN	80	40	-
9	$PdCl_2[P(Ph)_3]_2$	15	NaOAc (3)	-	DMA	140	2.5	-
10	$PdCl_2[P(Ph)_3]_2$	15	NaOAc (3)	-	DMA	160	25	6
11	$PdCl_2[P(Ph)_3]_2$	21	NaOAc (4)	-	DMA	130	19	30
12	$PdCl_2[P(Ph)_3]_2$	40	NaOAc (4)	-	DMA	130	32	31



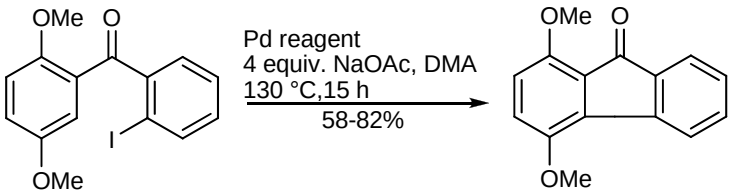
243b **74**

Scheme 65: Palladium-mediated cyclization of **243b**.

Next, the Pd-mediated cyclization of the the unsubstituted 2-iodobenzophenone (**243b**) was studied. To our delight fluoren-9-one (**74**) was isolated with 86 % yield (Scheme 65) when the reaction was run using 24.5 mol % $PdCl_2(PPh_3)_2$ as a Pd reagent, 4 equivalents NaOAc as a base and DMA as a solvent at 130 °C for 14 h. This result is in good agreement with the results of Ames and Opalko who obtained **74** by cyclization of **243b** using 10 mol %

$Pd(OAc)_2$, 10 mol % triphenylphosphine and 3 equivalents *N*-methylimidazole as a base with 100 % yield.[42b] Fluoren-9-one (**74**) has also been synthesized from **243b** by Larock et al. using 5 mol % $Pd(OAc)_2$ and 5 equivalents cesium floride with 75 % yield.[48]

Table 8 Palladium-mediated arylation of **243f**

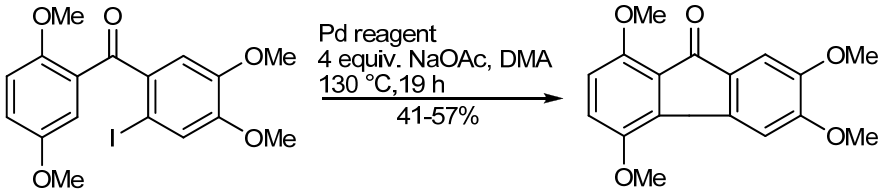


243f **236b**

Entry	Pd reagent	mol%	Yield of **236b** [%]
1	$PdCl_2[P(Ph)_3]_2$	5	58
2	$PdCl_2[P(Ph)_3]_2$	10	75
3	$PdCl_2[P(Ph)_3]_2$	15	82
4	$PdCl_2[P(Ph)_3]_2$	24.5	82
5	$Pd(OAc)_2$	23.5	81

It could be established that the cyclization of **243f** to **236b** could be achieved using $Pd(OAc)_2$ or $PdCl_2(PPh_3)_2$ as Pd reagents. With 23.5 mol % $Pd(OAc)_2$ and 4 equivalents NaOAc 1,4-dimethoxyfluoren-9-one **236b** was obtained with 81 % (Table 8, entry 5). A similar result was observed when 24.5 mol % $PdCl_2(PPh_3)_2$ were used as the reagent (Table 8, entry 4). The latter result is in good agreement with the work of Qabaja and Jones who obtained **236b** with 92 % yield when **243f** was treated with 24.5 mol % $PdCl_2(PPh_3)_2$ and 4 equivalents NaOAc.[24] This reaction was used to study the influence of the amount of the Pd reagent on the yield of the cyclization. It was found that the amount of $PdCl_2(PPh_3)_2$ could be reduced to 15 mol % without affecting the yield (Table 8, entry 3). A further decrease of the amount of the Pd complex to 10 and 5 mol % led to a decrease of the yield to 75 and 58 %, respectively (Table 8, entries 1 and 2).

Table 9: Palladium-mediated arylation of **243c**

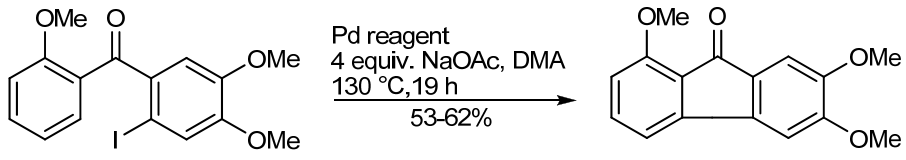


243c **236c**

Entry	Pd reagent	mol%	Yield of **236c** [%]
1	$PdCl_2[P(Ph)_3]_2$	40	41
2	$PdCl_2[P(Ph)_3]_2$	60	57
3	$Pd(OAc)_2[P(Ph)_3]_2$	40	47
4	$Pd(OAc)_2[P(Ph)_3]_2$	60	52

In order to achieve the cyclization of the substituted 2-iodobenzophenone **243c** using the conditions developed for the cyclization of **243f** the amount of $PdCl_2(PPh_3)_2$ had to be increased. With 40 mol % of the reagent the yield of **236c** amounted to 41 % and with 60 mol % $PdCl_2(PPh_3)_2$ the cyclization product could be isolated with 57 % yield (Table 9, entries 1 and 2). Similar results were observed when $PdCl_2(PPh_3)_2$ was replaced by $Pd(OAc)_2(PPh_3)_2$ (Table 9, entries 3 and 4).

Table 10: Palladium-mediated arylation of **243e**



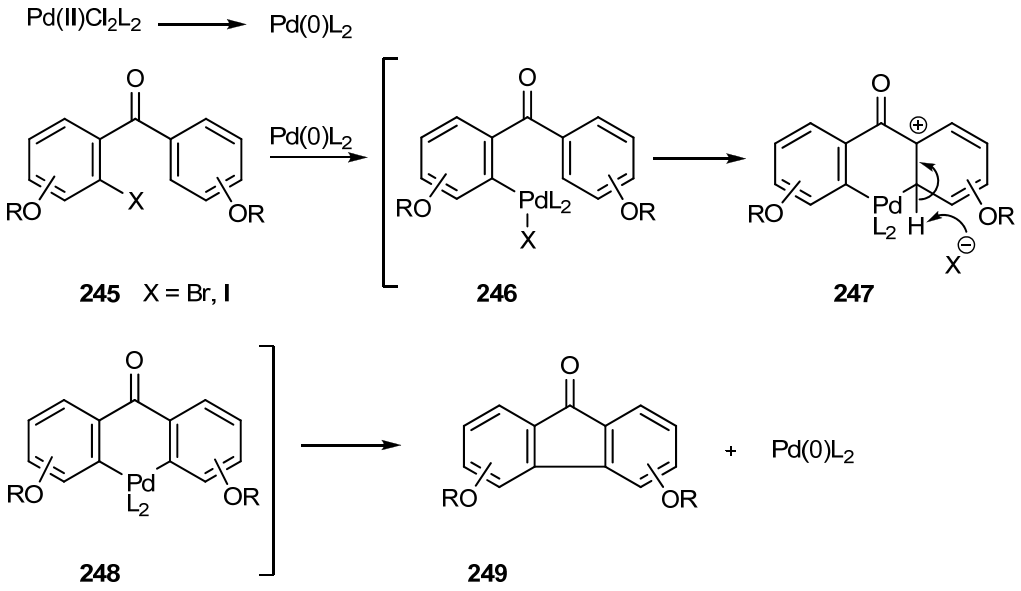
243e **236e**

Entry	Pd reagent	mol%	Yield of **236e** [%]
1	$PdCl_2[P(Ph)_3]_2$	60	62
2	$Pd(OAc)_2[P(Ph)_3]_2$	60	53

Finally, the cyclization of the substituted 2-iodobenzophenone **243e** was investigated. Again, large amounts of the Pd complexes were necessary to achieve acceptable yields of the

cyclization product **236e**. With 60 mol % of $PdCl_2(PPh_3)_2$ the fluoren-9-one **236e** was isolated with 62 % yield and with 60 mol % of $Pd(OAc)_2(PPh_3)_2$ the yield amounted to 53 % (Table 10, entries 1 and 2).

A proposal for the reaction mechanism of the intramolecular palladium-catalyzed cyclization of *o*-halobenzophenones **245** to fluorenones **249** is shown in Scheme 66.[42,105] It is assumed that the reaction starts with the formation of a coordinatively unsaturated Pd(0) species. The second step of the sequence is the oxidative addition of the palladium complex into the C-Hal bond of **245** generating the intermediate **246** which undergoes electrophilic palladation to afford the Pd(II) intermediate **247**. Subsequently, elimination of HX forms **248**. Reductive elimination of the intermediate **248** gives fluorenones **249** with simultaneous regeneration of the Pd(0) catalyst.



Scheme 66: Proposal for the reaction mechanism of the intramolecular palladium-mediated cyclization of *o*-halobenzophenones **245** to fluorenones **249**.[42,105]

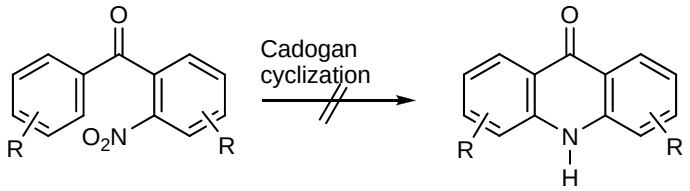
In conclusion, it has been demonstrated that the Pd-mediated cyclization of methoxy-substituted 2-iodobenzophenones **243a-e** to the corresponding methoxy-substituted fluoren-9-ones **236a-e** can be achieved. Unfortunately, the required Pd reagents have to be used in large amounts to obtain acceptable yields of the cyclization products. Another disadvantage is that the yields of the Pd-mediated arylations of the 2-iodobenzophenones **243a-e** depend on the substitution pattern of the precursors.

In summary, it has to be stated that the intramolecular Pschorr cyclizations of 2-aminofluoren-9-ones **235a-e** are superior to the intramolecular Pd-mediated cyclizations of 2-

iodobenzophenones **243a-e** with respect to the number of steps required (from the nitrobenzaldehydes and bromobenzenes as common precursors), the yields and the efficiency.

7.4 Cyclization studies of 2-nitrobenzophenones with triethyl phosphite

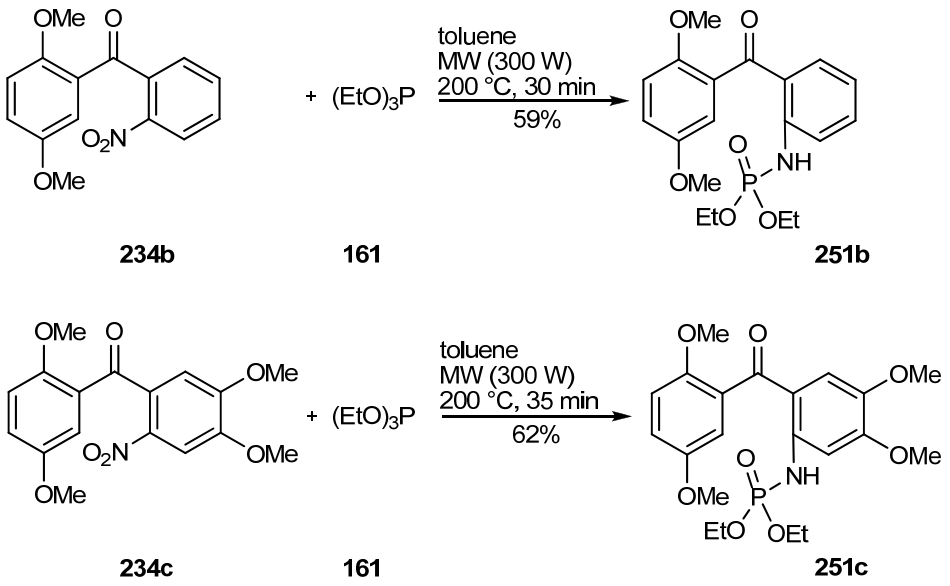
Finally, the Cadogan cyclization of the 2-nitrobenzophenones **234b,c** to the corresponding acridin-9-ones **250b,c** was tried to achieve.[66a] For this purpose **234b,c** were treated with triethyl phosphite (**161**) under microwave conditions (300 W) at 200 °C in toluene as a solvent. However, the formation of the acridin-9-ones **250b,c** could not be achieved (Scheme 67).



234b,c **250b,c**

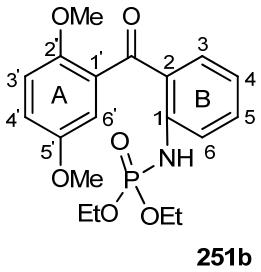
Scheme 67: Attempted Cadogan cyclization of **234b,c**.

Instead, the exclusive formation of the corresponding diethyl *N*-arylphosphoramidates **234b,c** was observed. It was found that the best yields of **251b,c** were obtained when **234b,c** were reacted with 6 equivalents triethyl phosphite (**161**) for 30-35 min (Scheme 68). With shorter reaction times the transformations were not complete. The work up of the reaction mixtures was very easy.



Scheme 68: Synthesis of diethyl *N*-arylphosphoramidates **251b,c**.

7.4.1 Discussion of the spectral data of the diethyl *N*-2-(2',5'-dialkylbenzoyl)-3,4,5,6-tetraalkylphenylphosphoramidates 251b,c



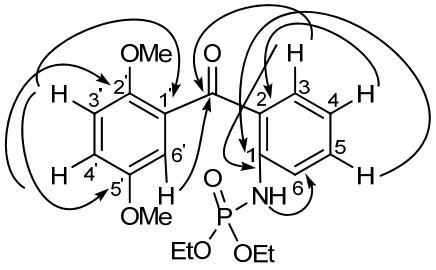
251b

As an example, the spectral data of diethyl *N*-2-(2',5'-dimethoxybenzoyl)phenylphosphoramidate (**251b**) are presented.

As in compounds **233c** and **234a** a trisubstituted aromatic ring A could be deduced from the three aromatic protons 3'-H at δ = 6.90 ppm (doublet, $^{3}J_{HH}$ = 9.0 Hz), 6'-H at δ = 6.80 ppm (doublet, $^{4}J_{HH}$ = 2.1 Hz) and 4'-H at δ = 6.98 ppm (doublet of doublet, $^{3}J_{HH}$ = 9.0 Hz and $^{4}J_{HH}$ = 2.1 Hz). The HSQC spectrum showed the corresponding carbons C-3' at δ = 110.59 ppm, C-6' at δ = 111.57 ppm and C-4' at δ = 114.47 ppm, respectively. In the HMBC spectrum the proton 3'-H showed strong $^{3}J_{CH}$-correlations with the quaternary aromatic carbons C-1' at δ = 127.57 ppm and C-5' at δ = 151.10 ppm while the proton 4'-H is correlated with the aromatic carbon C-2' at δ = 148.31 ppm. The proton 6'-H displayed $^{3}J_{CH}$-correlations with the

quaternary carbon C-2' at δ = 148.31 ppm as well as with the carbonyl group at δ = 197.42 ppm. The ^{1}H,^{1}H-COSY spectrum revealed that the protons 3'-H and 4'-H are adjacent. In summary, these observations established a trisubstituted aromatic ring A attached to the carbonyl group. From the ^{1}H NMR and the ^{1}H,^{1}H-COSY spectrum a disubstituted aromatic ring B could be established by the four aromatic protons 3-H at δ = 7.45 ppm (doublet of doublet, $^{3}J_{HH}$ = 7.0 Hz and $^{4}J_{HH}$ = 1.1 Hz), 4-H at δ = 6.84 ppm (doublet of doublet of doublet, $^{3}J_{HH}$ = 7.1, $^{3}J_{HH}$ = 7.1 Hz and $^{4}J_{HH}$ = 1.1 Hz), 5-H at δ = 7.38-7.43 ppm (multiplet) and 6-H at δ = 7.52 ppm (doublet of doublet, $^{3}J_{HH}$ = 7.1 Hz, $^{4}J_{HH}$ = 1.1 Hz). Their corresponding carbons C-3 at δ = 132.75 ppm, C-4 at δ = 117.46 ppm, C-5 at δ = 132.71 ppm and C-6 at δ = 115.84 ppm (doublet, $^{3}J_{P\text{-}C}$ = 2.9 H) were identified with the help of the HSQC spectrum.

In the HMBC spectrum the proton 4-H showed a strong $^{3}J_{CH}$-correlation with the quaternary aromatic carbon C-2 at δ = 119.07 ppm (dublet, $^{3}J_{P\text{-}C}$ = 8.8 Hz) and 5-H is correlated with the aromatic carbon C-1 at δ = 141.87 ppm (dublet, $^{2}J_{P\text{-}C}$ = 2.2 Hz). The proton 3-H displayed strong $^{3}J_{CH}$-correlations with the quaternary carbon C-1 at δ = 141.87 ppm (doublet, $^{2}J_{P\text{-}C}$ = 2.2 Hz) as well as with the carbonyl group at δ = 197.42 ppm. The $^{3}J_{CH}$-correlations of both 3-H and 6'-H with the carbon of the carbonyl group establishes that the carbonyl group is the linkage between the two aromatic rings A and B. The ^{1}H NMR and the ^{1}H,^{1}H-COSY spectrum showed a doublet at δ = 9.97 ppm (doublet, $^{2}J_{P\text{-}H}$ = 11.0 Hz) for the NH proton that displayed $^{3}J_{CH}$-correlations with the quaternary carbon C-6 at δ = 115.84 ppm (doublet, $^{3}J_{P\text{-}C}$ = 2.9 Hz), 2 × OCH_2 at δ = 4.13-4.27 ppm (multiplet) and 2 × CH_3 at δ = 1.36 ppm (triplet, $^{3}J_{HH}$ = 7.2 Hz). Their corresponding carbons at δ = 60.96 ppm (doublet, $^{2}J_{P\text{-}C}$ = 5.2 Hz) and at δ = 13.87 ppm (doublet, $^{3}J_{P\text{-}C}$ = 6.5 Hz) were revealed by the HSQC and the ^{13}C NMR spectrum. Further analysis of the 1D and 2D NMR spectra of **251b** revealed two methoxy groups at δ = 3.77 and at δ = 3.68 ppm. The methoxy groups were demonstrated to be attached to carbons C-2' and C-5', respectively, by means of the HMBC spectrum.



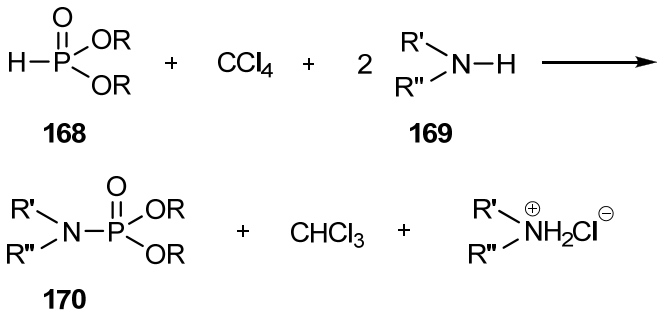
251b

The EI-MS spectrum showed that the molecular ion peak [M^+] at *m/z* = 393. This peak represents the base peak as well.

The IR spectrum of **251b** shows a characteristic band at $\tilde{\nu}$ = 3190 cm^{-1} for a N-H stretching vibration. Another characteristic band at $\tilde{\nu}$ = 1631 cm^{-1} suggests a C=O stretching vibration. The bands in the spectrum in the range of $\tilde{\nu}$ = 1605-1578 cm^{-1} indicate that there is an aromatic ring. The strong band at $\tilde{\nu}$ = 1258 cm^{-1} suggests that a C-O-C group is present owing to asymmetric stretching vibration. The band at $\tilde{\nu}$ = 1215 cm^{-1} is in agreement with the P=O group.

7.5 Synthesis of dialkyl *N*-arylphosphoramidates using nitroarenes as starting materials

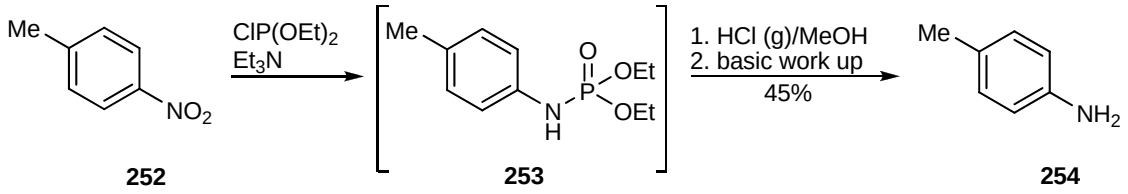
During the last years microwave heating has become a convenient and broadly used tool in organic synthesis. Under microwave irradiation, chemical reactions usually proceed faster, in higher yields and with fewer byproducts.[106] Phosporamidate oligonucleotides are among the most interesting synthetic derivatives that have been considered for diagnostic and therapeutic applications in the antisense field.[107,108] The development of new methods for the synthesis of phosphoramidate-substituted nucleosides is also of remarkable interest due to their anticancer, spermicidal and antiviral (anti-HIV) activities.[109] Moreover, phosphoramidates play a significant role in the organic synthesis. One of the most prominent fields for the use of dialkyl, dibenzyl- and diphenyl phosphoramidates is the protection of the amino group.[110] There are many synthetic applications of *N*-arylphosphoramidates concerned with the properties of their stabilized anions. For example, *N*-arylphosphoramidates have been utilized for the construction of imines by aza-Wittig reactions.[111] The alkylation of diethyl phosphoramidates is a simple method for the synthesis of secondary amines.[112] In addition, other applications come from the area of heterocycles and involve the synthesis of 2,4-(*1H,3H*)-quinazolinediones.[113] Recently, *N*-arylphosphoramidates have been exploited for the preparation of functionalized aziridines by means of nucleophile-induced cyclizations.[114] It was found that *N*-arylphosphoramidates could be reacted with Baylis-Hillman adducts to give 1,2-disubstituted azetidines in a highly diastereoselective manner.[115] In a one-pot procedure 1,2,4-trisubstituted azetidines could be synthesized by treatment of aza-Michael adducts with *N*-arylphosphoramidates.[116]



Scheme 69: Synthesis of phosphoramidates **170** according to Todd and Atherton.[84, 85]

In contrast to the marked interest in phosphoramidates the number of published synthetic approaches is quite limited. The standard method dates back to Todd and Atherton who reported the reaction of ammonia, primary and secondary amines with a dialkyl or dibenzyl phosphite and a halogen source like CCl_4 (Scheme 69).[84,85] Other methods rely on the nucleophilic substitution of phosphate diesters by alkylamines[117] and the oxidation of phosphite triesters with iodine in the presence of alkylamines.[118] All methods for the synthesis of phosphoramidates discussed so far have in common that amines are used as starting materials and that they are subjected to phosphorylation. With the results of the conversion of the substituted 2-nitrobenzophenones **234** into substituted diethyl *N*-arylphosphoramidates **251** in mind, it was decided to try to develop a new and general method for the one pot transformation of nitroarenes into dialkyl *N*-arylphosphoramidates. Much to our astonishment we found that the number of synthetic methods for this kind of transformation is rather limited and that the reports in the literature are inconsistent. Cadogan et al. reported that they obtained mixtures of the corresponding dialkyl *N*-arylphosphoramidates $(RO)_2P(=O)NHAr$ (5-26 %), dialkyl *N*-alkyl-3*H*-azepin-7-ylphosphonates (0-18 %), dialkyl *N*-alkyl-*N*-arylphosphoramidates $(RO)_2P(=O)NRAr$ (8-30 %), and dialkyl arylphosphonates $(RO)_2P(=O)Ar$ (0-7 %) when substituted nitroarenes were refluxed with an excess of a trialkyl phosphite $(RO)_3P$.[89,90] In contrast to these findings, Sundberg isolated triethyl *N*-arylphosphorimidates $(EtO)_3P{=}NAr$ instead of diethyl *N*-arylphosphoramidates $(EtO)_2P(=O)NHAr$ as the main products when *o*-alkylnitrobenzenes were boiled with an excess of $(EtO)_3P$.[72,82] An alternative is the two-step transformation of nitroarenes to anilines with diethyl chlorophosphite as a reagent since the corresponding phosphoramidates had been identified as intermediates.[92] Although the scope of this method is quite limited and the reagent is very expensive some of the reactions reported by Fischer and Sheihet were repeated. However, we were unable to reproduce their yields. With *p*-

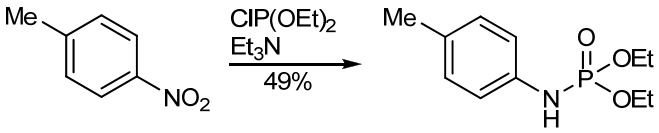
nitrotoluene as the substrate the corresponding aniline was isolated with only 45 % instead of > 95 % (Scheme 70).



252 **253** **254**

Scheme 70: Transformation of *p*-nitrotoluene (**252**) into the corresponding aniline (**254**) according to the procedure of Fischer and Sheihet.[92]

Without performing the second step, i.e. the hydrolysis, it was possible to isolate the corresponding *N*-arylphosphoramidate **253**; the yield, however, amounted to only 49 % (Scheme 71). With these results in mind it was clear that the method of Fischer and Sheihet can not be used as a practical and reliable method for the transformation of nitroarenes into *N*-arylphosphoramidates $(RO)_2P(=O)NHAr$.



252 **253**

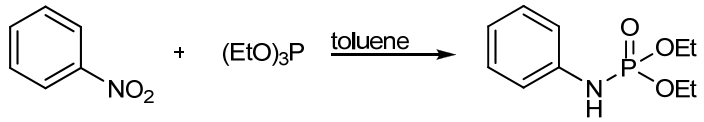
Scheme 71: Transformation of *p*-nitrotoluene (**252**) into the corresponding *N*-arylphosphoramidate **253** according to the procedure of Fischer and Sheihet.[92]

In this part it will be demonstrated that the reaction of nitroarenes with tervalent phosphorous reagents can be used for the efficient synthesis of dialkyl *N*-arylphosphoramidates in a single step if carried out under suitable reaction conditions.[119]

First, nitrobenzene (**255a**) was reacted with triethyl phosphite (**161**) under different reaction conditions (Table 11). Under microwave conditions at 200 °C (300 W) in toluene the formation of **256a** was observed only if an excess of **161** was employed. With 2.5 or 3.0 equivalents of **161** the starting material was consumed only partially (Table 11, entries 1,2). Thus, mixtures of the substrate **255a** and diethyl *N*-phenylphosphoramidate (**256a**) were isolated after column chromatography. With an excess of 6 equivalents **161** the reaction could be forced to completion and the product **256a** was exclusively formed in 78 % yield (Table

11, entry 3). These findings are consistent with the results of the cyclization experiments of **234b,c**. Comparable results were observed when the transformations were performed in a sealed tube under thermal conditions (Table 11, entries 4-6). Since the microwave transformations resulted in slightly higher yields than the sealed tube reactions all further transformations were run in a microwave oven.

Table 11: The influence of the amount of $(EtO)_3P$ (**161**) on the transformation of **255a** into **256a**

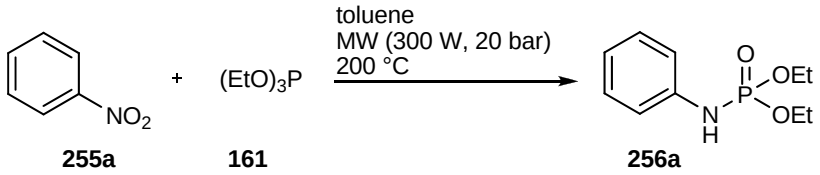


255a **161** **256a**

Entry	Equiv. $(EtO)_3P$	Reaction Conditions; *T* [°C]/*t* [min]	Yield of **256a** [%]
1	2.5	MW[a]; 200/15	38
2	3.0	MW[a]; 200/15	43
3	6.0	MW[a]; 200/15	78
4	2.0	Sealed tube; 200/15	34
5	4.0	Sealed tube; 200/15	51
6	6.0	Sealed tube; 200/15	71

Subsequently, the reaction time of the transformation **255a** → **256a** was optimized (Table 12). The highest yields (78 %) were obtained when the microwave assisted reactions were run for 15-20 min (Table 12, entries 4,5). It is remarkable that with shorter reaction times (3 to 10 min) no product **256a** was formed (Table 12, entries 1-3). With longer reaction times the yields dropped slightly to 76 and 75 %, respectively (Table 12, entries 6,7).

Table 12: The influence of the reaction time on the transformation of **255a** into **256a**

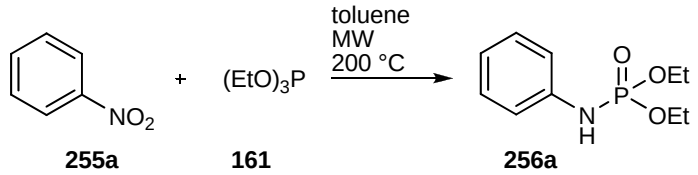


255a **161** **256a**

Entry	Equiv. $(EtO)_3P$	*t* [min]	Yield of **256a** [%]
1	6.0	3	-
2	6.0	5	-
3	6.0	10	-
4	6.0	15	78
5	6.0	20	78
6	6.0	30	76
7	6.0	40	75

Further experiments revealed that the power of the microwave irradiation affected the outcome of the transformation (Table 13). With microwave irradiation of up to 200 Watt no product formation was observed after 15 min (Table 13, entries 1-3). With 250 W a mixture of 35 % *N*-arylphosphoramidate **256a** and starting material **255a** was isolated (Table 13, entry 4). It was found that it takes 300 W to ensure complete conversion of **255a** within 15 min and a high yield of *N*-arylphosphoramidate **256a** (Table 13, entry 5).

Table 13: The influence of the microwave power on the transformation of **255a** into **256a**

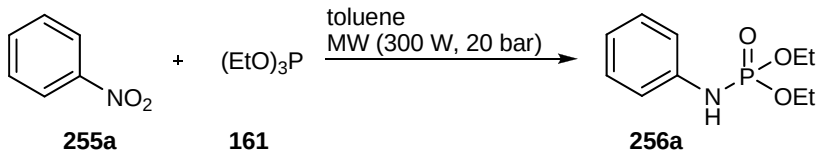


255a **161** **256a**

Entry	Equiv. $(EtO)_3P$	*t* [min]	Power [W]	Yield of **256a** [%]
1	6.0	15	50	-
2	6.0	15	150	-
3	6.0	15	200	-
4	6.0	15	250	35
5	6.0	15	300	78

At the end the influence of the reaction temperature on the formation of **256a** was studied. It was observed that no reaction between **255a** and **161** could be observed until 200 °C (Table 14, entries 1-4).

Table 14: The influence of the temperature on the transformation of **255a** into **256a**

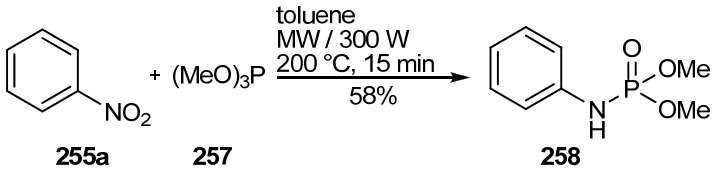


255a **161** **256a**

Entry	Equiv. $(EtO)_3P$	*t* [min]	*T* [°C]	Yield of **256a** [%]
1	6.0	15	50	-
2	6.0	15	100	-
3	6.0	15	150	-
4	6.0	15	200	78

Optimizing the reaction of **255a** and **161** led to a practical and efficient procedure for the synthesis of **256a** with high yield. The work up was very easy. First the volatiles were removed by distillation in vacuo and then the dichloromethane soluble residue was washed with water and purified by flash chromatography on silica gel.

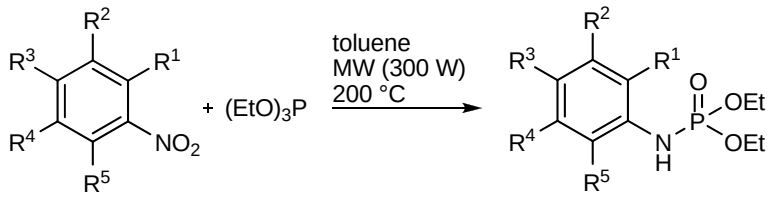
In addition, triethyl phosphite (**161**) could be replaced by other trialkyl phosphites such as trimethyl phosphite (**257**). Under the optimized reaction conditions discussed above the transformation of nitrobenzene (**255a**) with trimethyl phosphite (**257**) delivered the dimethyl *N*-phenylphosphoramidate (**258**), which was isolated with 58 % after column chromatography (Scheme 72).



Scheme 72: Reaction of nitrobenzene (**255a**) with $(MeO)_3P$ (**257**) in toluene under microwave conditions.

In order to evaluate the scope of the transformation of nitroarenes into phosphoramidates we studied the effects of substitution on the aromatic ring. A number of substituents at different positions of the aromatic ring were tested. To this end the transformation was performed with a number of mono-, di- and trisubstituted nitroarenes using the optimized protocol (Table 15). It could be established that a number of nitroarenes carrying one or two methyl groups can be successfully transformed into the corresponding *N*-arylphosphoramidates **256b-g**. However, the method is not restricted to methyl-substituted nitroarenes. It is also possible to successfully convert substrates with methoxy-, halide-, methoxycarbonyl- and cyano substituents (**255h-o**) into the corresponding *N*-arylphosphoramidates **256h-o**. Yields were in the range between 52 and 79 %; side product formation was negligible.

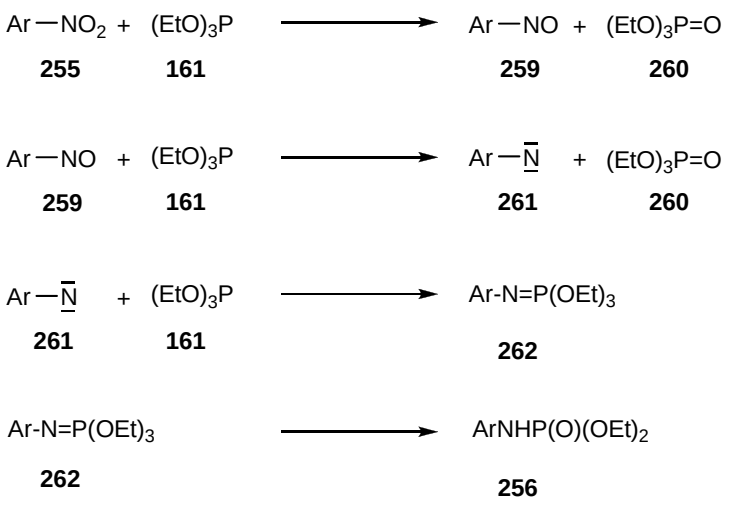
Table 15: Synthesis of diethyl *N*-arylphosphoramidates **256a-o** under microwave conditions.



255 **161** **256**

Entry	**255**	R^1	R^2	R^3	R^4	R^5	*t* [min]	**256**	Yield of **256** [%]
1	**a**	H	H	H	H	H	15	**a**	78
2	**b**	Me	H	H	H	H	15	**b**	68
3	**c**	H	Me	H	H	H	15	**c**	73
4	**d**	H	H	Me	H	H	15	**d**	66
5	**e**	Me	H	H	Me	H	15	**e**	75
6	**f**	H	Me	H	Me	H	15	**f**	79
7	**g**	Me	H	Me	H	H	15	**g**	77
8	**h**	H	H	OMe	H	H	15	**h**	71
9	**i**	H	H	Cl	H	H	10	**i**	52
10	**j**	Br	H	H	H	H	10	**j**	68
11	**k**	I	H	H	H	H	10	**k**	56
12	**l**	H	H	CO_2Me	H	H	10	**l**	62
13	**m**	H	H	CN	H	H	10	**m**	63
14	**n**	Br	H	H	OMe	H	10	**n**	73
15	**o**	Cl	Me	Cl	H	H	10	**o**	57

With respect to the reaction mechanism of this transformations it is assumed that in the first step of the reaction cascade the nitroarene **255** is reduced with triethyl phosphite (**161**) to the corresponding nitrosoarene **259** and triethyl phosphate (**260**) (Scheme 73).[66] Further reduction of **259** with triethyl phosphite (**161**) gives the arylnitrene **261** which reacts with **161** to yield the *N*-arylphosphorimidate **262** as an intermediate. The latter undergoes hydrolysis under the conditions of work up and purification by chromatography to afford the *N*-arylphosphoramidate **256**. In accordance with this proposal the *N*- arylphosphoramidates **256** could not be obtained when aniline (**263**) was treated with an excess of either triethyl phosphite (**161**) or triethyl phosphate (**260**) under different reaction conditions.

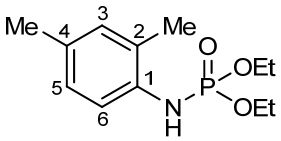


Scheme 73: Proposal for the reaction mechanism of the transformation of nitroarenes **250** into dialkyl *N*-arylphosphoramidates **256** according to Cadogan.[66]

The results obtained clearly indicate that the reaction of nitroarenes with trialkyl phosphites is a practical and efficient method for the selective preparation of dialkyl *N*-arylphosphoramidates if carried out under proper reaction conditions.

The structures of diethyl *N*-arylphosphoramidates **256a-o** described here have been elucidated unambiguously by NMR spectroscopic methods including HMBC, HSQC as well as ^{1}H,^{1}H-COSY experiments.

7.5.1 Discussion of the spectral data for the diethyl *N*-arylphosphoramidates 256a-o



256g

As an example, the spectroscopic data of (**256g**) are discussed in detail. The structural assignment of **256g** rests mainly on its ^{1}H NMR (Figure 51), ^{13}C NMR (Figure 52), HMBC (Figure 53), ^{1}H,^{1}H-COSY (Figure 54) and HSQC spectra (Figure 55).

The ^{1}H NMR spectrum of **256g** (Figure 51) showed the two protons 3-H and 5-H to appear as a broad signal at δ = 6.94 ppm. The proton 6-H showed a dublet at δ = 7.10 ppm with $^{3}J_{HH}$ =

8.7 Hz. The HSQC spectrum (Figure 53) revealed their corresponding carbons C-3 at δ = 127.79 ppm, C-5 at δ = 131.54 ppm and C-6 at δ = 117.46 ppm (doublet, $^{3}J_{P\text{-}C}$ = 1.5 Hz), respectively. In the HMBC spectrum (Figure 53) the proton 3-H showed a $^{3}J_{CH}$-correlation with the aromatic carbon C-5 at δ = 131.54 ppm while the proton 5-H showed a strong $^{3}J_{CH}$-correlation with the aromatic carbon C-3 at δ = 127.79 ppm. Lastly the proton 6-H is correlated with the quaternary aromatic carbon C-2 at δ = 125.44 ppm (dublet, $^{3}J_{P\text{-}C}$ = 10.8 Hz).

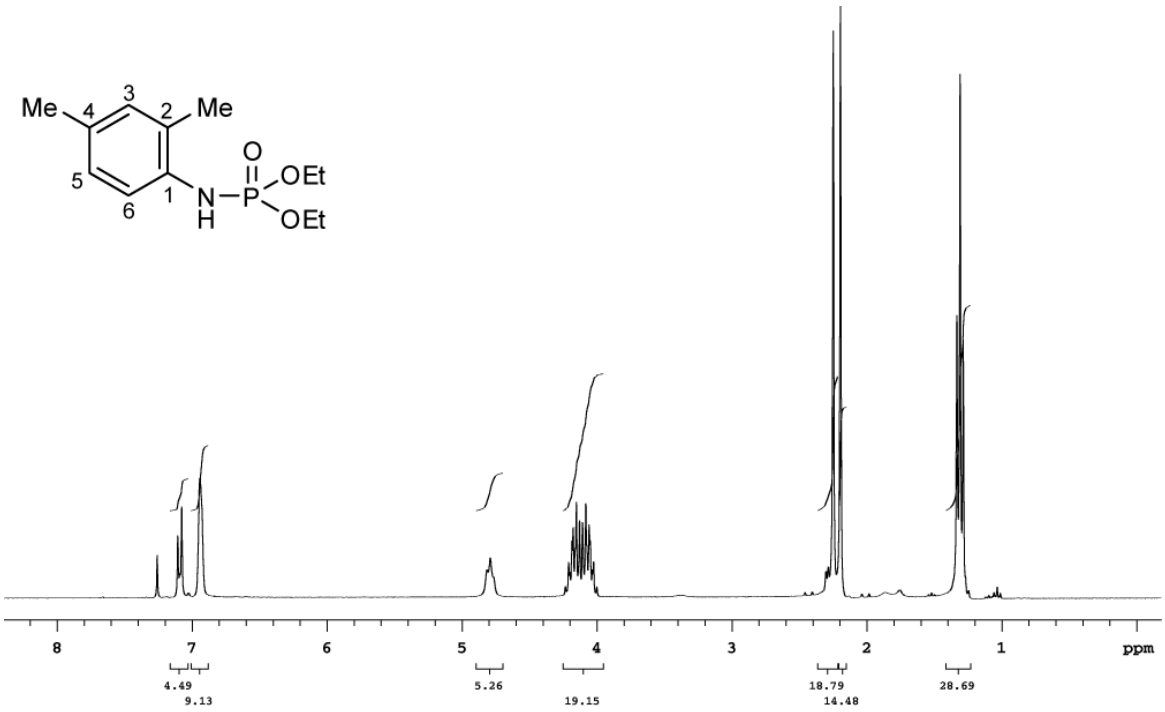


Figure 51: ^{1}H NMR spectrum of **256g** (300 MHz, $CDCl_3$).

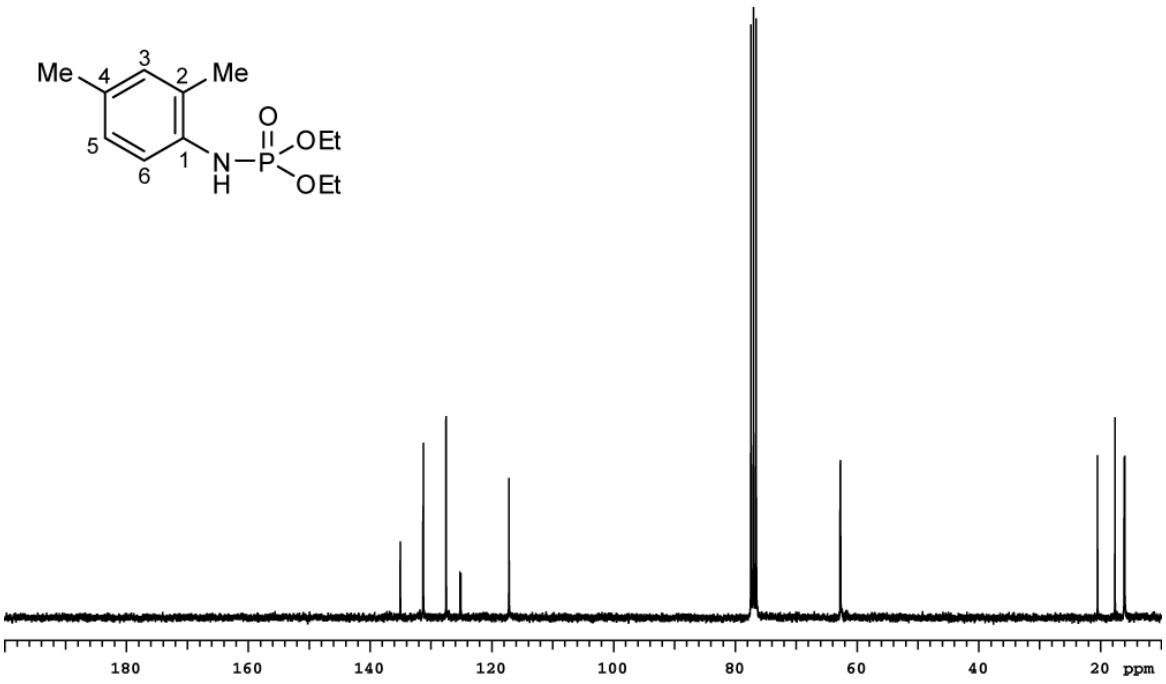
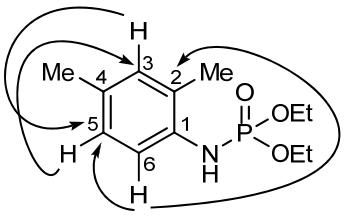


Figure 52: ^{13}C NMR spectrum of **256g** (300 MHz, $CDCl_3$).

Further analysis of the 1D and 2D NMR spectra of **256g** revealed the signals for a NH proton at δ = 4.80 ppm (doublet, $^2J_{P\text{-}H}$ = 7.2 Hz) and two methyl groups at δ = 2.20 ppm (s) and at δ = 2.25 ppm (s). It was demonstrated that the methyl groups were attached to the carbon atoms C-2 and C-4, respectively (HMBC spectrum). The ^{1}H NMR resonances of the ethyl groups were identified at δ = 4.03-4.21 ppm (m, 4H, 2 × CH_2) and at δ = 1.31 ppm (t, $^3J_{HH}$ = 7.0 Hz, 6H, 2 × CH_3).



256g

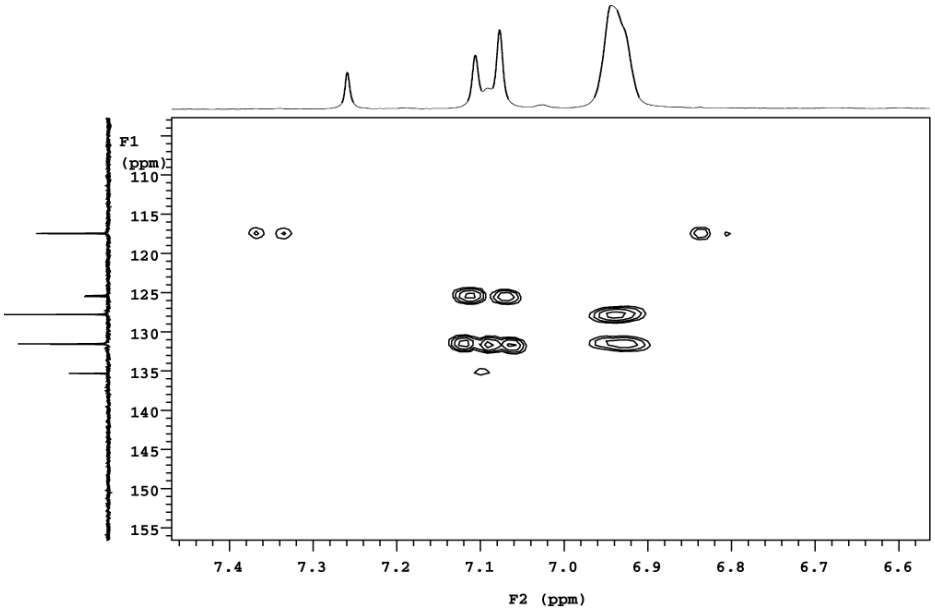


Figure 53: Section of the HMBC spectrum of **256g**.

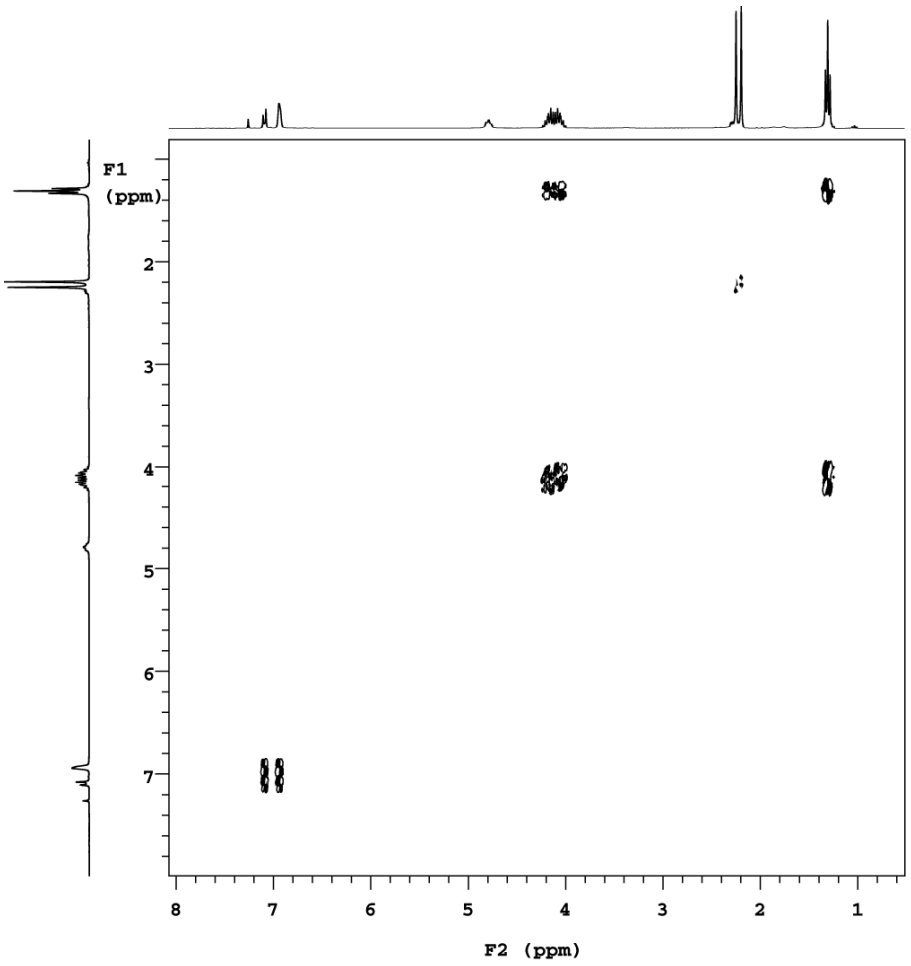


Figure 54: The ^{1}H,^{1}H-COSY spectrum of **256g**.

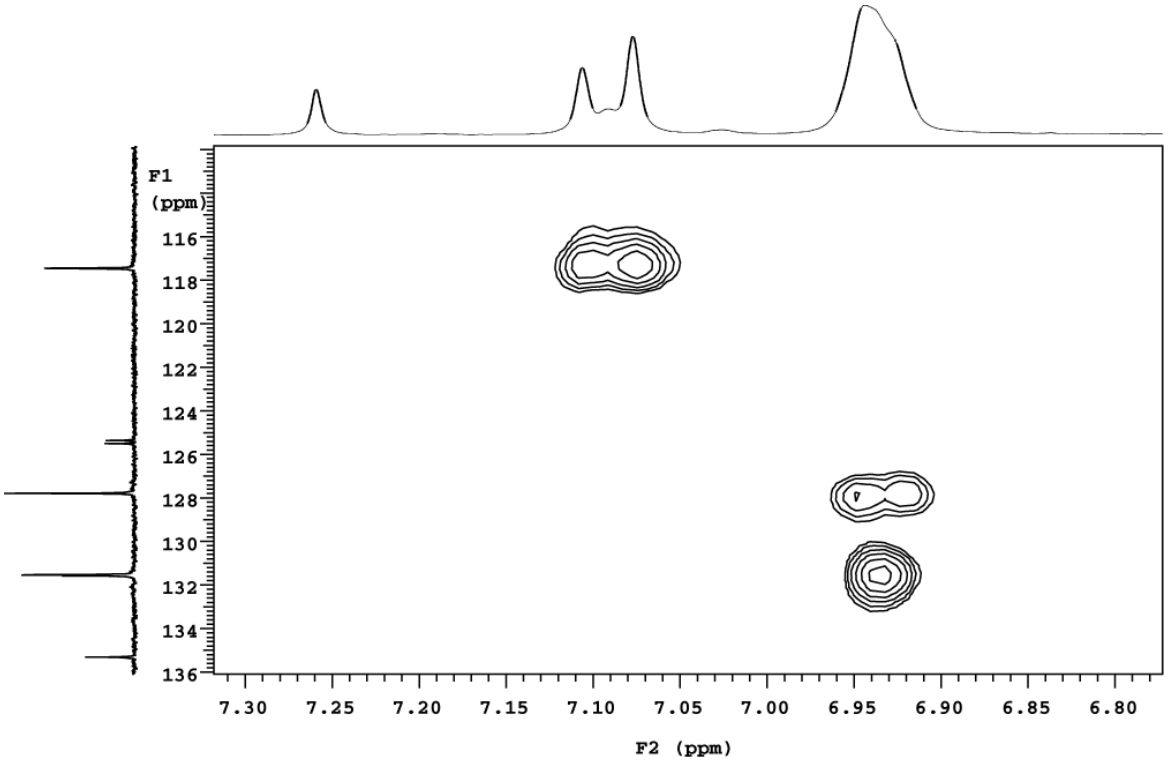


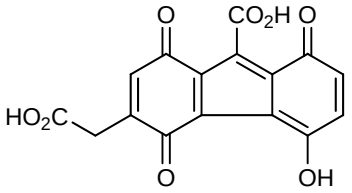
Figure 55: Section of the HSQC spectrum of **256g**.

The EI-MS spectrum showed the molecular ion peak [M^+] at *m/z* = 257. This peak represents also the base peak of the spectrum.

The IR spectrum of **256g** shows a characteristic band at $\tilde{\nu}$ = 3201 cm^{-1} due to the N-H stretching vibration. The bands at $\tilde{\nu}$ = 2984 and 2902 cm^{-1} suggest that aliphatic C-H stretching vibrations are also present. The two bands at $\tilde{\nu}$ = 1419 and 1384 cm^{-1} can be assigned to C-H bending vibrations of the CH_2 and CH_3 groups. The band at $\tilde{\nu}$ = 1287 cm^{-1} confirms the presence of a C-O group owing to asymmetric stretching vibration. The band at $\tilde{\nu}$ = 1240 cm^{-1} is in agreement with the P=O group.

8 SUMMARY

Because of their diverse biological properties and their high potential for the development of new drugs the synthesis of fluorenes and related systems such as benzo[*b*]fluorenes is of great interest in the fields of organic and medicinal chemistry. The most relevant benzo[*b*]fluorenes include the naturally occurring kinamycins. Recently, two fluorene derivatives have been isolated from the sweat of hippopotamus (*Hippopotamus amphibius*). The biological function of the two dyes named hipposudoric acid (**4**) and norhipposudoric acid (**5**) is still unknown.



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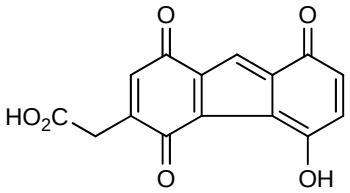

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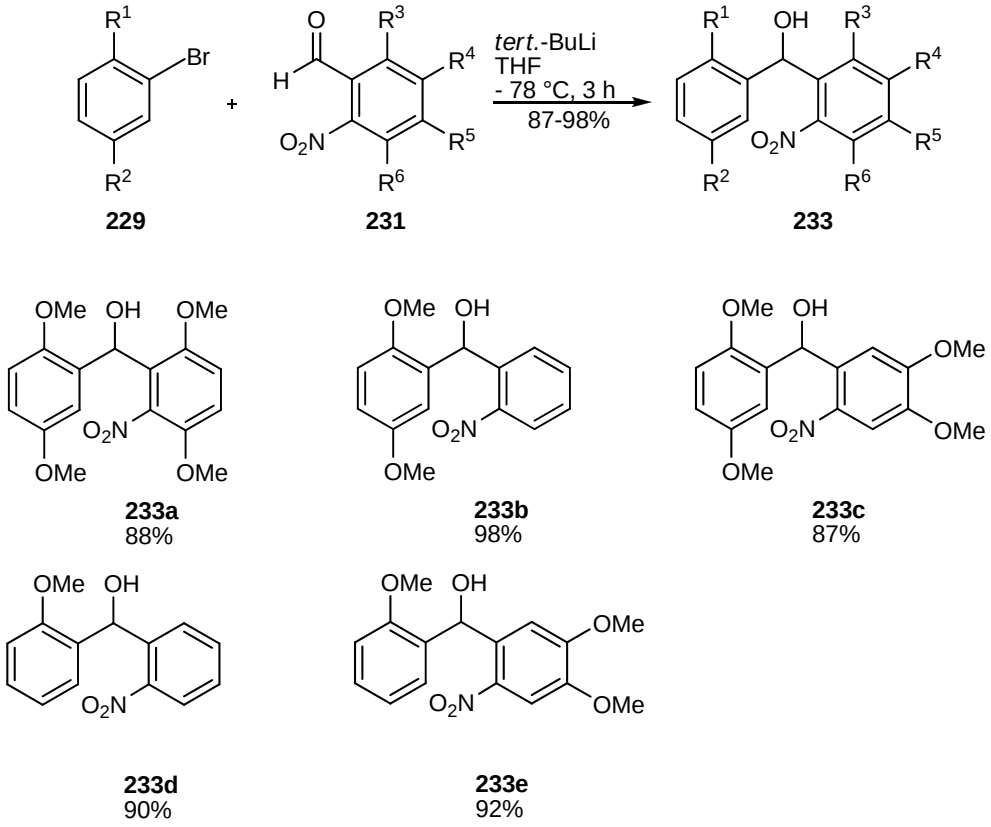
For the synthesis of fluorenes a number of synthetic approaches have been developed. Among the most important methods there are the intramolecular electrophilic substitution, the Pschorr cyclization and palladium-mediated intramolecular cyclizations. The first part of the present study focusses on the construction of fluorenes carrying several methoxy groups by employing the Pschorr cyclization and the palladium-mediated intramolecular cyclization of suitable substrates. A comparison of the two methods is also presented. In addition, the cleavage of the methyl ethers **203** into the corresponding hydroxy-substituted fluoren-9-ones **206** is also included in the first part.

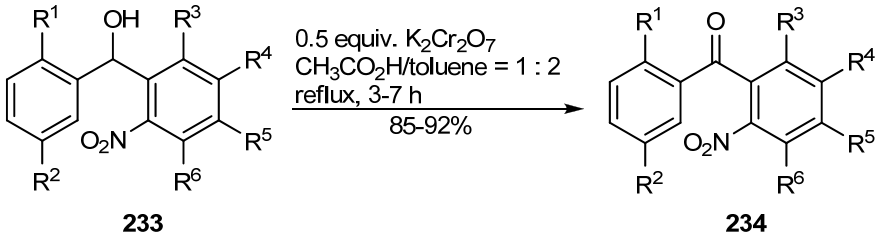
To begin with, the synthesis of hydroxy- and alkoxy-substituted fluoren-9-ones through Pschorr cyclizations was studied. For the preparation of the substrates **233** the bromides **229** were first lithiated with *t*-butyllithium and then reacted with the aldehydes **231**. Using this method it was possible to prepare the secondary alcohols **233a-e** with excellent yields ranging from 87 to 98 % (Scheme 74).



Scheme 74: Synthesis of the substituted secondary alcohols **233a-e**.

Treatment of the secondary alcohols **233a-e** using $K_2Cr_2O_7$ as an oxidant gave the corresponding ketones **234a-e** with very good yields (85 to 92 %; Table 16).

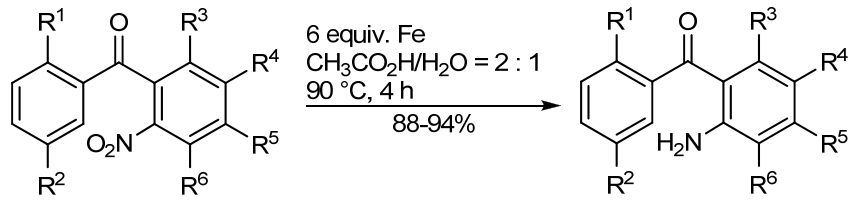
Table 16: Synthesis of the substituted diarylketones **234a-e**.



Entry	**233**	R^1	R^2	R^3	R^4	R^5	R^6	*t* [h]	Product	Yield of **234** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	4	**234a**	85
2	**b**	OMe	OMe	H	H	H	H	4	**234b**	89
3	**c**	OMe	OMe	H	OMe	OMe	H	7	**234c**	92
4	**d**	OMe	H	H	H	H	H	3	**234d**	88
5	**e**	OMe	H	H	OMe	OMe	H	3	**234e**	87

Reduction of the nitro group of the substituted ketones **234a-e** using iron powder resulted in the formation of substituted 2-aminobenzophenones **235a-e** with very good results (Table 17).

Table 17: Synthesis of the substituted 2-aminobenzophenones **235a-e**.

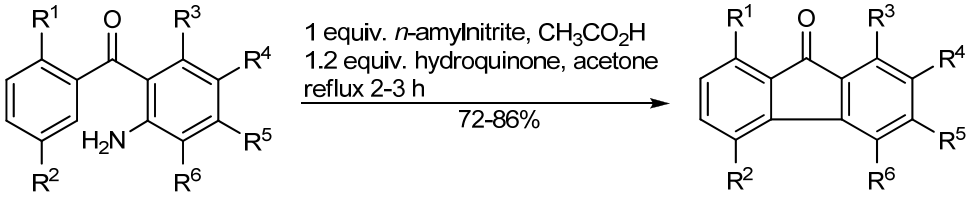


234 **235**

Entry	**234**	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield of **235** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**235a**	91
2	**b**	OMe	OMe	H	H	H	H	**235b**	88
3	**c**	OMe	OMe	H	OMe	OMe	H	**235c**	88
4	**d**	OMe	H	H	H	H	H	**235d**	92
5	**e**	OMe	H	H	OMe	OMe	H	**235e**	94

The compounds **235a-e** were cyclized to furnish the methoxy-substituted fluoren-9-ones by Pschorr cyclizations. For this purpose the substituted 2-aminobenzophenones **235a-e** were oxidized to the corresponding diazonium salts with *n*-amylnitrite in glacial acetic acid at 0 °C which underwent cyclization to give the methoxy-substituted fluoren-9-ones **236a-e** with yields ranging from 72 to 86 % (Table 18).

Table 18: Synthesis of the methoxy-substituted fluoren-9-ones **236a-e** by Pschorr cyclizations.

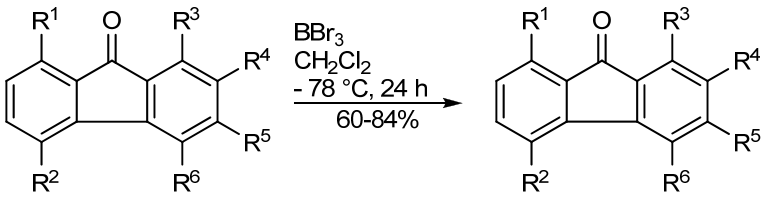


235 **236**

Entry	**235**	R^1	R^2	R^3	R^4	R^5	R^6	*t* [h]	Product	Yield of **236** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	3	**236a**	81
2	**b**	OMe	OMe	H	H	H	H	3	**236b**	74
3	**c**	OMe	OMe	H	OMe	OMe	H	2	**236c**	83
4	**d**	OMe	H	H	H	H	H	3	**236d**	72
5	**e**	OMe	H	H	OMe	OMe	H	2	**236e**	86

Ether cleavage of the methoxy-substituted fluoren-9-ones **236a-e** performed using boron tribromide resulted in the formation of the hydroxy-substituted fluoren-9-ones **242a-e** with yields between 60 and 84 % (Table 19).

Table 19: Deprotection of the methoxy-substituted fluoren-9-ones **236a-e**



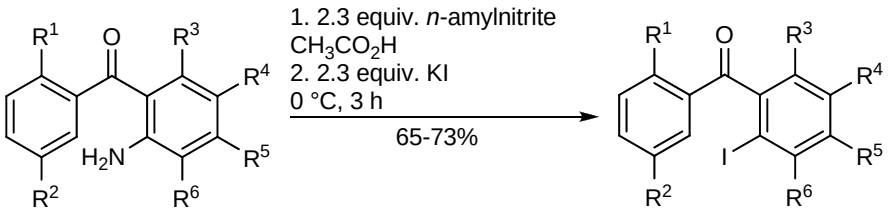
236a-e **242a-e**

Entry	**236**	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield of **242** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**242a**	80
2	**b**	OMe	OMe	H	H	H	H	**242b**	68
3	**c**	OMe	OMe	H	OMe	OMe	H	**242c**	83
4	**d**	OMe	H	H	H	H	H	**242d**	60
5	**e**	OMe	H	H	OMe	OMe	H	**242e**	84

These results show that the Pschorr cyclization allows for the preparation of substituted fluoren-9-ones in four steps from readily available starting materials.

Palladium-mediated reactions play a very important role in current organic synthesis. Therefore, it was studied whether the palladium-mediated cyclizations of 2-iodo-substituted benzophenones **243** can be employed for the efficient synthesis of fluoren-9-ones. It was of great interest to learn whether this method is superior to the Pschorr cyclization approach. For this purpose, the 2-iodobenzophenone derivatives **243a-f** were synthesized. They were obtained by reaction of the 2-amino-substituted benzophenones **235** with *n*-amylnitrite followed by treatment with KI. Following this procedure, the iodides **243a-e** could be obtained with yields between 65 and 73 % (Table 20).

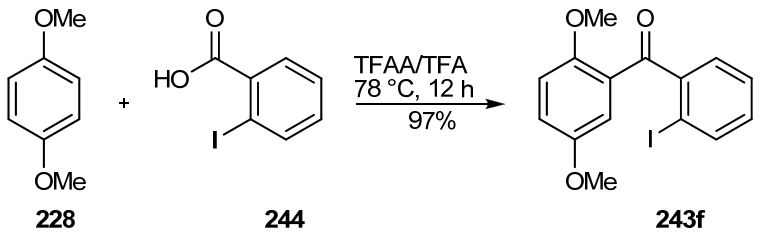
Table 20: Synthesis of the substituted 2-iodobenzophenones **243a-e**



235 **243**

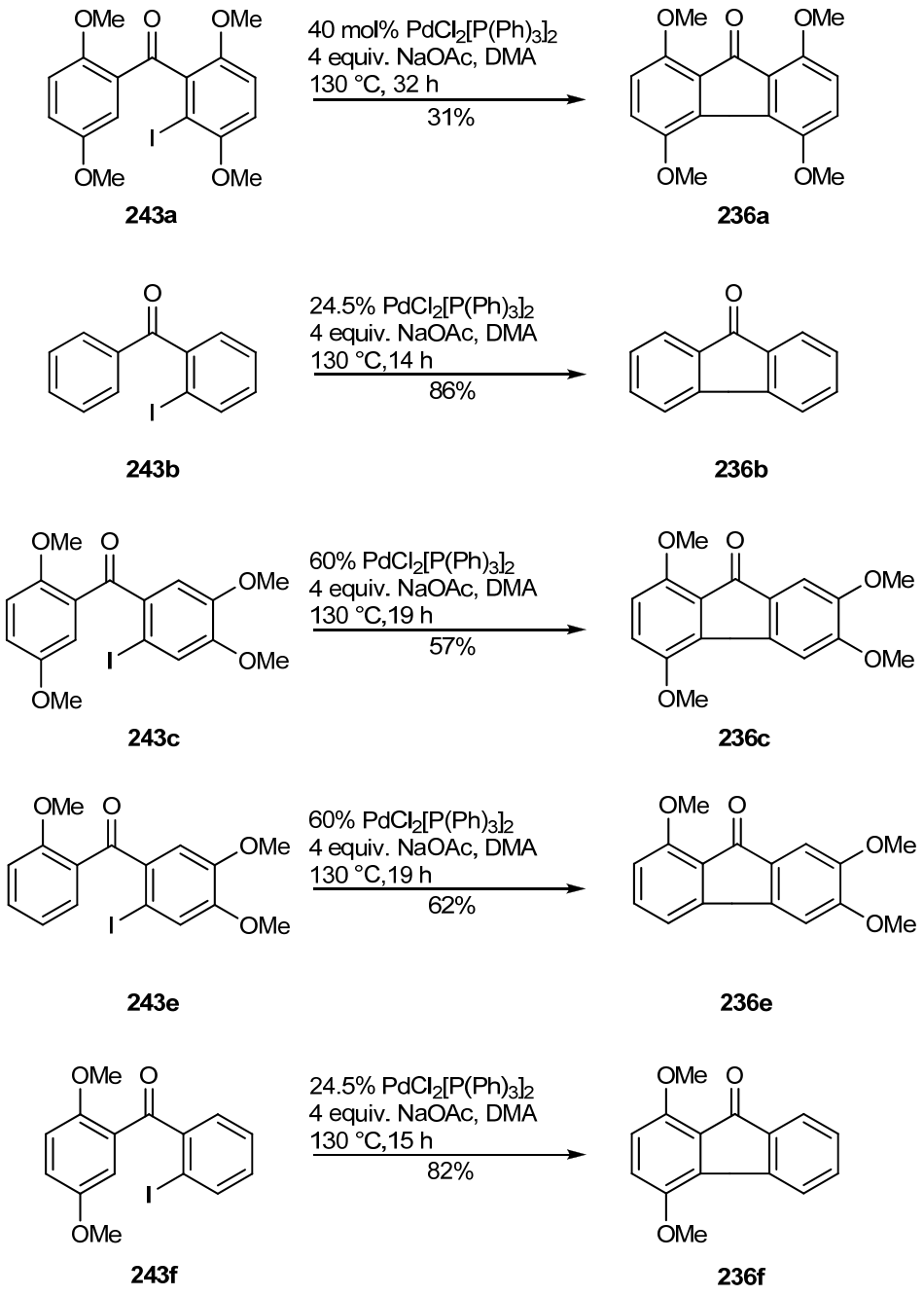
Entry	**235**	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield of **243** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**243a**	66
2	**b**	H	H	H	H	H	H	**243b**	73
3	**c**	OMe	OMe	H	OMe	OMe	H	**243c**	65
4	**d**	OMe	H	H	H	H	H	**243d**	69
5	**e**	OMe	H	H	OMe	OMe	H	**243e**	72

Compound **243f** was synthesized by intermolecular Friedel-Crafts acylation of **228** with **244** in 97 % yield (Scheme 75).



Scheme 75: Synthesis of the iodo compound **243f**.

It turned out that the best results for the palladium-mediated cyclization of the iodides **243a-c,e,f** could be achieved when $PdCl_2(PPh_3)_2$ was used as a palladium reagent in the presence of NaOAc as a base and DMA as a solvent. Heating at 130 °C afforded the fluoren-9-ones **236a-c,e,f** with yields in the range between 31 and 86 % (Scheme 76).

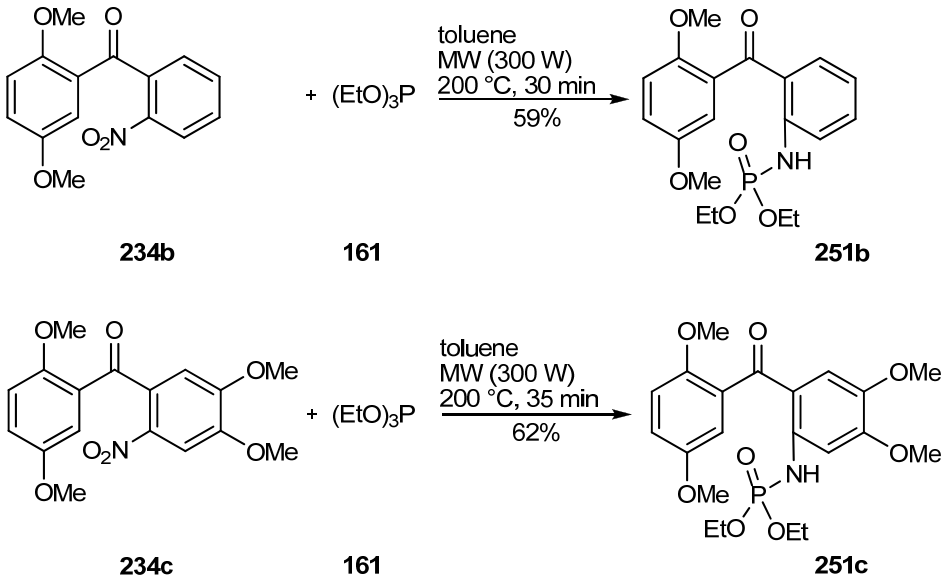


Scheme 76: Palladium-mediated cyclization of the iodo compounds **243a-c,e,f**.

On the whole, it can be concluded that the palladium-catalyzed intramolecular arylations of **243** suffer from high palladium-loadings, high reaction temperatures and long reaction times. In addition, in a few cases the yields for the palladium-mediated cyclizations are not sufficient. Compared to the results of the Pschorr cyclizations the palladium-mediated cyclizations need an extra step; i.e. the transformation of the 2-aminobenzophenones **235** into

the corresponding 2-iodobenzophenones **243**. This is why the Pschorr cyclization is more efficient for the synthesis of fluoren-9-ones **236** than the palladium-mediated cyclization.

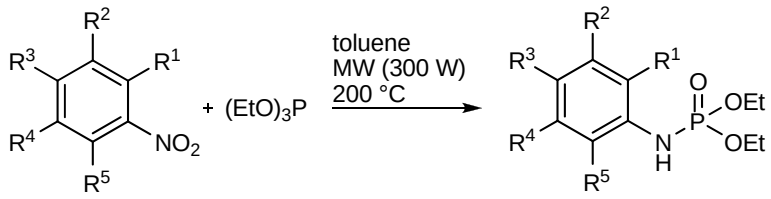
In addition, attempts were undertaken to cyclize the substituted 2-nitrobenzophenones **234b,c** to the corresponding acridinones **205**. When the benzophenones were treated with triethyl phosphite (**161**) the unexpected formation of diethyl *N*-arylphosphoramidates **251b** (59 % yield) and **251c** (62 % yield) was observed.



Scheme 77: Unexpected formation of diethyl *N*-arylphosphoramidates **251b,c**.

With these unexpected results in hand it was decided to develop a new synthetic protocol for the efficient conversion of nitroarenes into the corresponding phosporamidates. Phosporamidate oligonucleotides play an important role in medicinal chemistry because they have been considered for diagnostic as well as therapeutic applications within the antisense field. The preparation of phosphoramidate substituted nucleoside analogues is also of great interest as many of them exhibit anticancer, antiviral (anti-HIV) and spermicidal activities. Therefore, the second goal of this thesis was to develop a practical and efficient method for the synthesis of dialkyl N-arylphosphoramidates by reaction of readily available nitroarenes with tervalent phosphorous reagents such as triethyl phosphite or trimethyl phosphite under both thermal and microwave conditions. In order to evaluate the scope of this conversion it was necessary to study the effects of substitution on the aromatic ring at different positions. It was found that nitroarenes **255a-o** can easily be transformed into the corresponding diethyl N-arylphosphoramidates **256a-o** by treatment with an excess of triethyl phosphite (**161**) or trimethyl phosphite (**257**). Yields were in the range of 52 to 79 % (Table 21).

Table 21: Synthesis of diethyl *N*-arylphosphoramidates **256a-o** under microwave conditions.



255 **161** **256**

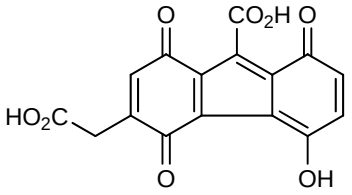
Entry	**255**	R^1	R^2	R^3	R^4	R^5	*t* [min]	**256**	Yield of **256** [%]
1	**a**	H	H	H	H	H	15	**a**	78
2	**b**	Me	H	H	H	H	15	**b**	68
3	**c**	H	Me	H	H	H	15	**c**	73
4	**d**	H	H	Me	H	H	15	**d**	66
5	**e**	Me	H	H	Me	H	15	**e**	75
6	**f**	H	Me	H	Me	H	15	**f**	79
7	**g**	Me	H	Me	H	H	15	**g**	77
8	**h**	H	H	OMe	H	H	15	**h**	71
9	**i**	H	H	Cl	H	H	10	**i**	52
10	**j**	Br	H	H	H	H	10	**j**	68
11	**k**	I	H	H	H	H	10	**k**	56
12	**l**	H	H	CO_2Me	H	H	10	**l**	62
13	**m**	H	H	CN	H	H	10	**m**	63
14	**n**	Br	H	H	OMe	H	10	**n**	73
15	**o**	Cl	Me	Cl	H	H	10	**o**	57

The results obtained clearly indicate that – in contrast to previous reports – the reaction of nitroarenes with trialkyl phosphites is a practical and efficient method for the selective preparation of dialkyl *N*-arylphosphoramidates in one synthetic operation.

The structures of all compounds prepared during this study have been elucidated unambiguously by analytical and spectroscopic methods including NMR spectroscopy, mass spectrometry, UV spectroscopy, IR spectroscopy and elemental analysis.

9 ZUSAMMENFASSUNG

Aufgrund ihrer vielfältigen biologischen Eigenschaften und ihres großen Potentials für die Entwicklung neuer Medikamente ist die effiziente Synthese von Fluorenen und verwandten Systemen wie den Benzo[*b*]fluorenen von großem Interesse in der Organischen und Medizinischen Chemie. Zu den interessantesten Benzo[*b*]fluorenen zählen die natürlich vorkommenden Kinamycine. Kürzlich wurden zwei Fluorenderivate aus dem Schweiß des Nilpferdes (*Hippopotamus amphibius*) isoliert, die als Hipposudorinsäure (**4**) und Norhipposudorinsäure (**5**) bezeichnet wurden. Über die biologische Funktion dieser zwei Farbstoffe ist bislang nur wenig bekannt.



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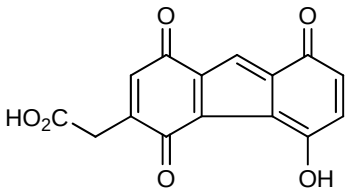

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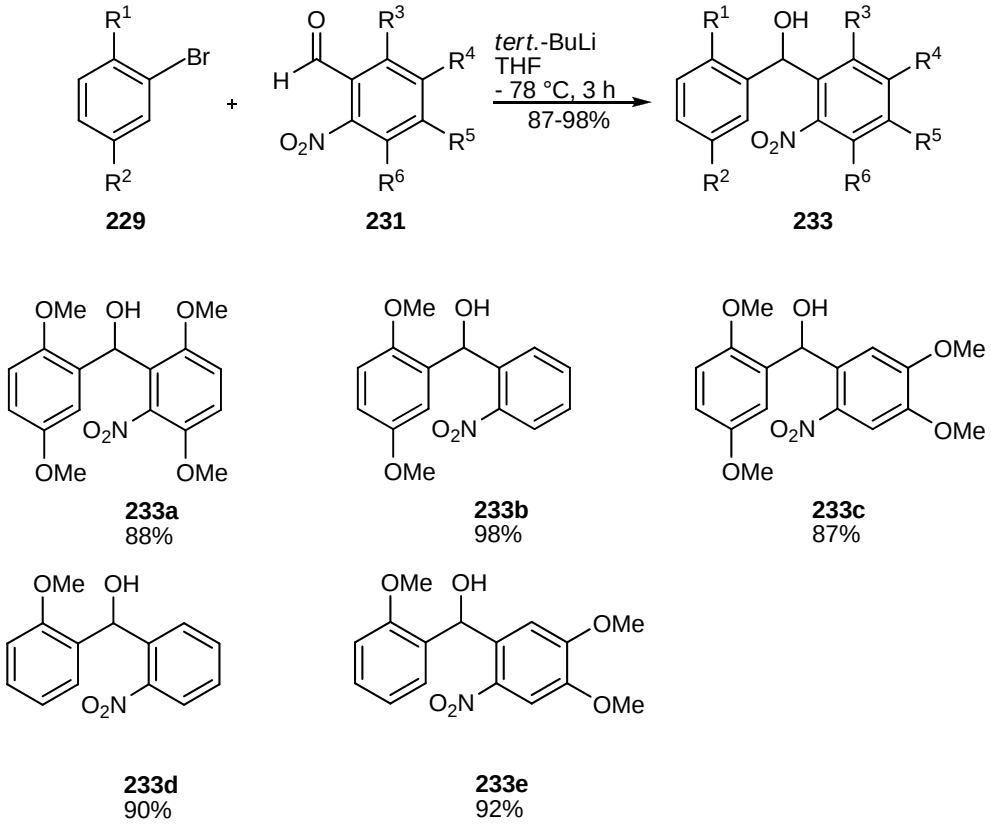
Für die Synthese von Fluorenen setzt man vor allem intramolekulare elektrophile aromatische Substitutionen, Pschorr-Cyclisierungen und Palladium-vermittelte intramolekulare Cyclisierungen ein.
Im ersten Teil der vorliegenden Arbeit wird der Aufbau mehrfach Methoxy-substituierter Fluorenone durch Pschorr-Cyclisierungen und Palladium-vermittelte intramolekulare Cyclisierungen geeigneter Substrate beschrieben und miteinander verglichen. Darüberhinaus wird die Spaltung der Methylether in die entsprechenden Hydroxy-substituierten Fluorenone vorgestellt.

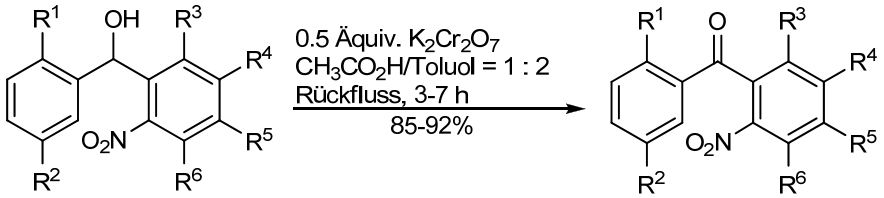
Zunächst wurde die Synthese von Hydroxy- und Alkoxy-substituierten Fluoren-9-onen durch Pschorr-Cyclisierung untersucht. Für die Darstellung der Substrate **233** wurden die Bromide **229** mit *t*-Butyllithium lithiiert und dann mit den Aldehyden **231** umgesetzt. Unter Verwendung dieser Methode war es möglich, die sekundären Alkohole **233a-e** mit ausgezeichneten Ausbeuten zwischen 87 und 98 % herzustellen (Schema 74).



Schema 74: Synthese der substituierten sekundären Alkohole **233a-e**.

Die anschließende Behandlung der sekundären Alkohole **233a-e** mit $K_2Cr_2O_7$ als Oxidationsmittel ergab die entsprechenden Ketone **234a-e** mit sehr guten Ausbeuten zwischen 85 und 92 % (Tabelle 16).

Tabelle 16: Synthese der substituierten Diarylketone **234a-e**.

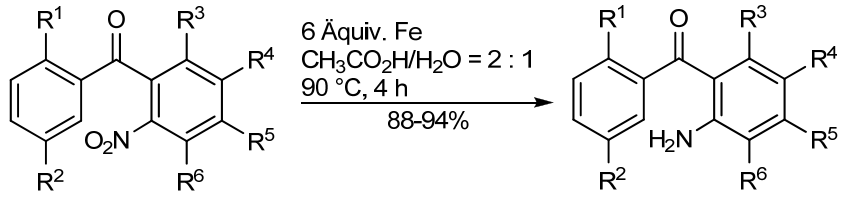


233 **234**

Nr.	**233**	R^1	R^2	R^3	R^4	R^5	R^6	*t* [h]	Produkt	Ausbeute **234** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	4	**234a**	85
2	**b**	OMe	OMe	H	H	H	H	4	**234b**	89
3	**c**	OMe	OMe	H	OMe	OMe	H	7	**234c**	92
4	**d**	OMe	H	H	H	H	H	3	**234d**	88
5	**e**	OMe	H	H	OMe	OMe	H	3	**234e**	87

Die Reduktion der Nitrogruppe der substituierten Ketone **234a-e** mit Eisenpulver führte mit sehr guten Ausbeuten zur Bildung der substituierten 2-Aminobenzophenone **235a-e** (Tabelle 17).

Tabelle 17: Synthese der substituierten 2-Aminobenzophenone **235a-e**.



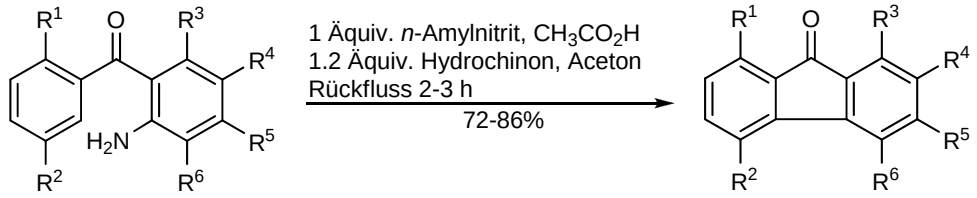
234 **235**

Nr.	**234**	R^1	R^2	R^3	R^4	R^5	R^6	Produkt	Ausbeute **235** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**235a**	91
2	**b**	OMe	OMe	H	H	H	H	**235b**	88
3	**c**	OMe	OMe	H	OMe	OMe	H	**235c**	88
4	**d**	OMe	H	H	H	H	H	**235d**	92
5	**e**	OMe	H	H	OMe	OMe	H	**235e**	94

Es gelang dann, die Verbindungen **235a-e** durch Pschorr-Cyclisierung in die Methoxy-substituierten Fluoren-9-one umzuwandeln. Dazu wurden die substituierten 2-

Aminobenzophenone **235a-e** unter Verwendung von *n*-Amylnitrit in Essigsäure bei 0 °C zu den entsprechenden Diazoniumsalzen oxidiert. Die so gebildeten Diazoniumsalze cyclisierten dann mit Ausbeuten zwischen 72 und 86 % zu den Methoxy-substituierten Fluoren-9-onen **236a-e** (Tabelle 18).

Tabelle 18: Synthese der Methoxy-substituierten Fluoren-9-one **236a-e** durch Pschorr-Cyclisierung.

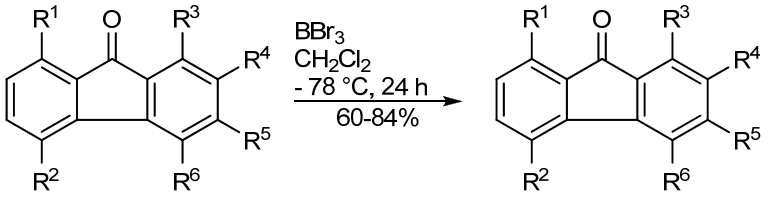


235 **236**

Nr.	**235**	R^1	R^2	R^3	R^4	R^5	R^6	*t* [h]	Produkt	Ausbeute **236** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	3	**236a**	81
2	**b**	OMe	OMe	H	H	H	H	3	**236b**	74
3	**c**	OMe	OMe	H	OMe	OMe	H	2	**236c**	83
4	**d**	OMe	H	H	H	H	H	3	**236d**	72
5	**e**	OMe	H	H	OMe	OMe	H	2	**236e**	86

Die Etherspaltung der Methoxy-substituierten Fluoren-9-one **236a-e** gelang mit Bortribromid und lieferte die entsprechenden Hydroxy-substituierten Fluoren-9-one **242a-e** mit 60 bis 84 % Ausbeute (Tabelle 19).

Tabelle 19: Entschützung der Methoxy-substituierten Fluoren-9-one **236a-e**



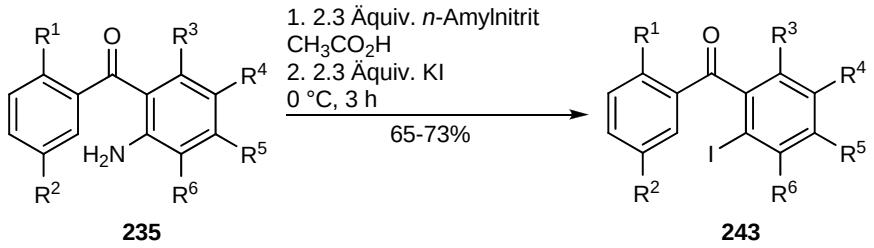
236a-e **242a-e**

Nr.	**236**	R^1	R^2	R^3	R^4	R^5	R^6	Produkt	Ausbeute **242** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**242a**	80
2	**b**	OMe	OMe	H	H	H	H	**242b**	68
3	**c**	OMe	OMe	H	OMe	OMe	H	**242c**	83
4	**d**	OMe	H	H	H	H	H	**242d**	60
5	**e**	OMe	H	H	OMe	OMe	H	**242e**	84

Diese Ergebnisse zeigen, dass man substituierte Fluoren-9-one mit Hilfe der Pschorr-Cyclisierung aus leicht zugänglichen Substraten in insgesamt vier Stufen darstellen kann.

Palladium-vermittelte Reaktionen spielen in der modernen organischen Synthese eine sehr wichtige Rolle. Daher wurde untersucht, ob man Palladium-vermittelte Cyclisierungen substituierter 2-Iodobenzophenone **243** für die effiziente Synthese von Fluoren-9-onen einsetzen kann. Von großem Interesse war in diesem Zusammenhang vor allem die Frage ob diese Methode der klassischen Pschorr-Cyclisierung überlegen ist. Dazu wurden zunächst die 2-Iodobenzophenone **243a-e** synthetisiert. Sie ließen sich durch Reaktion der substituierten 2-Aminobenzophenone **235a-e** mit *n*-Amylnitrit und anschließender Behandlung mit KI zugänglich machen. Nach diesem Verfahren erhielt man die Iodide **243a-e** mit Ausbeuten zwischen 65 und 73 % (Tabelle 20).

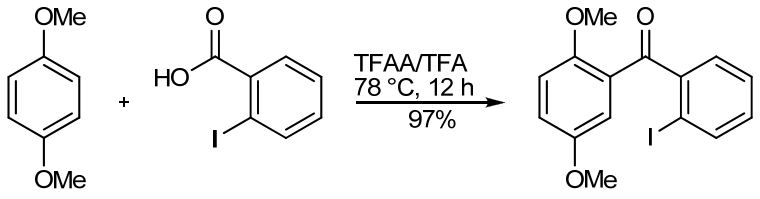
Tabelle 20: Synthese der substituierten 2-Iodobenzophenone **243a-e**



235 **243**

Nr.	**235**	R^1	R^2	R^3	R^4	R^5	R^6	Produkt	Ausbeute **243** [%]
1	**a**	OMe	OMe	OMe	H	H	OMe	**243a**	66
2	**b**	OMe	OMe	H	H	H	H	**243b**	73
3	**c**	OMe	OMe	H	OMe	OMe	H	**243c**	65
4	**d**	OMe	H	H	H	H	H	**243d**	69
5	**e**	OMe	H	H	OMe	OMe	H	**243e**	72

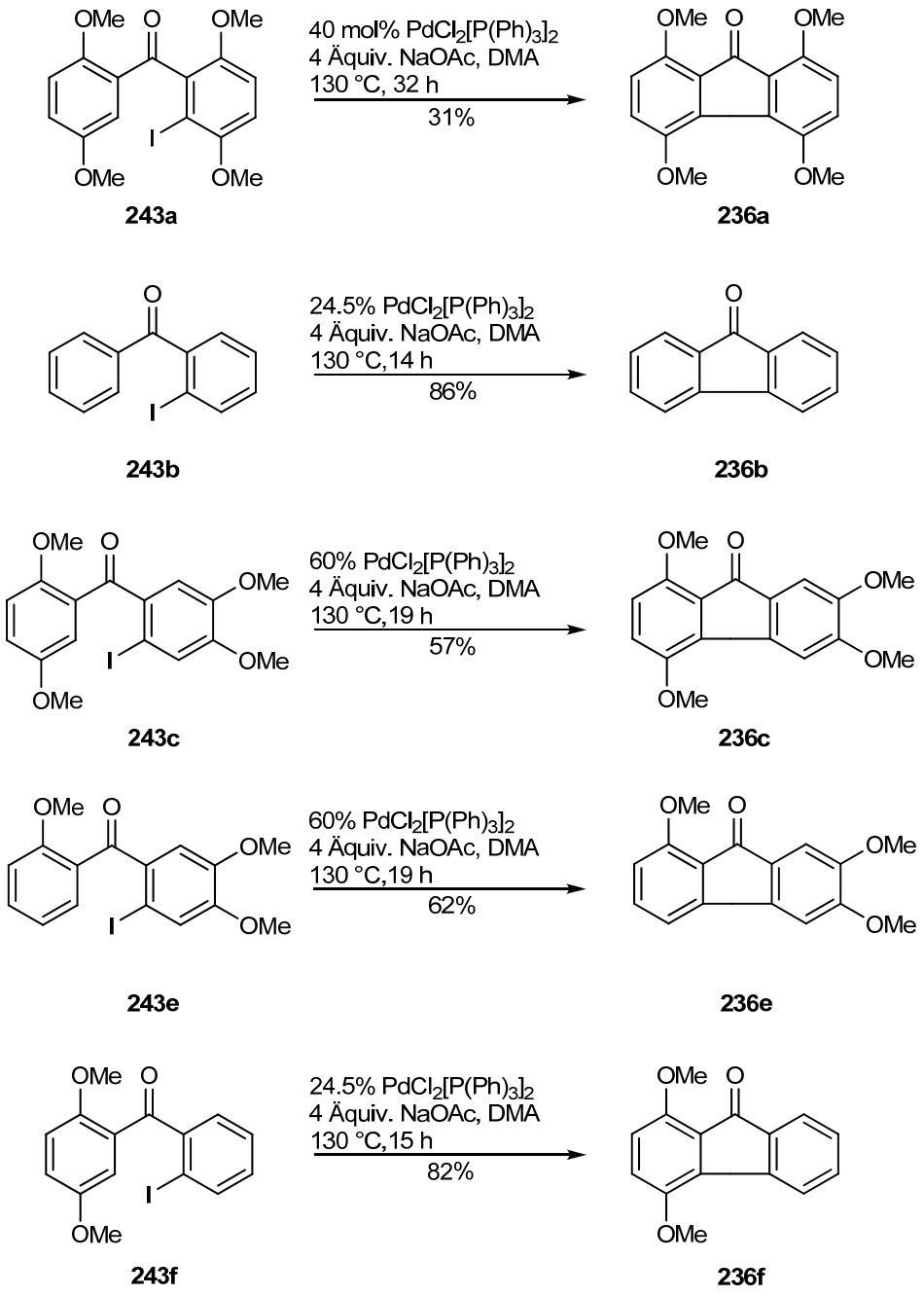
Die Verbindung **243f** wurde durch eine intermolekulare Friedel-Crafts Acylierung von **228** mit **244** in einer Ausbeute von 97 % synthetisiert (Schema 75).



228 **244** **243f**

Schema 75: Synthese der Iodverbindung **243f**.

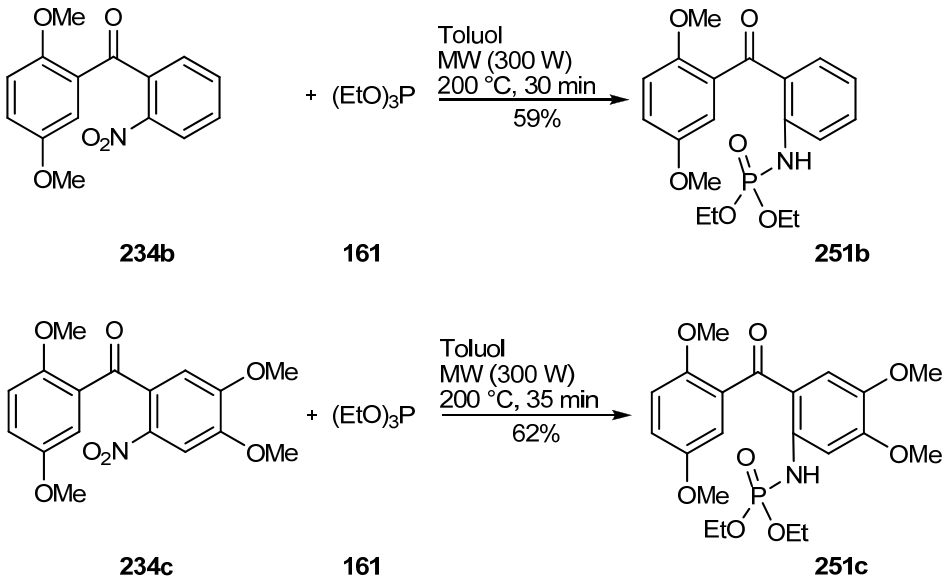
Im weiteren Verlauf der Arbeit zeigte sich, dass man die besten Ergebnisse für die Palladium-vermittelten Cyclisierungen der Iodide **243** erhielt, wenn man $PdCl_2(PPh_3)_2$ als Palladium-Reagenz in Gegenwart von NaOAc als Base und DMA als Lösungsmittel einsetzte. Erhitzen der Reaktionsmischung auf 130 °C führte zur Bildung der Fluoren-9-one **236a-c,e,f** mit Ausbeuten zwischen 31 und 86 % (Schema 76).



Schema 76: Palladium-vermittelte Cyclisierungen der Iodverbindungen **243a-c,e,f**.

Alles in Allem bleibt festzuhalten, dass die Palladium-vermittelten intramolekularen Arylierungen von **243** verschiedene Nachteile, wie die große Menge an benötigten Palladium-Reagenzien, die hohen Reaktionstemperaturen sowie die langen Reaktionszeiten, aufweisen. Dazu kommt, dass in einigen wenigen Fällen die Ausbeuten nicht ausreichend sind. Im direkten Vergleich mit den Pschorr-Cyclisierungen zeigt sich auch, dass man zur Durchführung der Palladium-vermittelten Cyclisierungen einen zusätzlichen Reaktionsschritt, und zwar die Umwandlung der 2-Aminobenzophenone **235** in die entsprechenden 2-

Iodbenzophenone **243**, benötigt. Aus diesen Gründen ist die Pschorr-Cyclisierung für den effizienten Aufbau der Fluoren-9-one **236** besser geeignet als die Palladium-vermittelte Cyclisierung.



Schema 77: Unerwartete Bildung der Diethyl *N*-arylphosphoramidate **251b,c**.

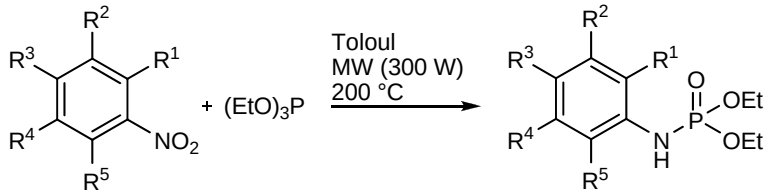
Im Weiteren versuchte man die Cyclisierung der substituierten 2-Nitrobenzophenone **234b,c** zu den entsprechenden Acridinonen **205.** Wenn die Benzophenone mit Triethylphosphit (**161**) zur Reaktion gebracht wurden, beobachtete man die unerwartete Bildung der Diethyl-*N*-arylphosphoramidate **251b** (59 % Ausbeute) und **251c** (62 % Ausbeute) (Schema 77).

Diese unerwarteten Ergebnisse führten zur Entwicklung einer neuen Synthesemethode für die effiziente Transformation von Nitroarenen in die entsprechenden Phosporamidate. Phosporamidat-Oligonucleotide spielen in der Medizinischen Chemie eine wichtige Rolle, da sie im Rahmen von Antisense-Ansätzen sowohl für den Einsatz in der Diagnostik als auch für den Einsatz als Therapeutika in Betracht kommen. Die Herstellung von Phosporamidat-substituierten Nucleosidanaloga ist ebenfalls von großem Interesse, da viele von ihnen Antitumor-Eigenschaften aufweisen bzw. antiviral (anti-HIV) oder spermizid wirksam sind.

Daher war es das Ziel, eine praktische und effiziente Methode für den Aufbau von Dialkyl *N*-arylphosphoramidaten durch Umsatz leicht zugänglicher Nitroarene mit tervalenten Phosphor-Reagenzen wie Triethylphosphit oder Trimethylphosphit sowohl unter thermischen als auch unter Mikrowellenbedingungen zu entwickeln. Um die Anwendungsbreite der Reaktion zu untersuchen, war es nötig, den Einfluss verschiedener Substituenten an unterschiedlichen Ringpositionen des Nitroaromaten zu untersuchen. Es konnte gezeigt

werden, dass sich die Nitroarene **255a-o** leicht und mit Ausbeuten zwischen 52 und 79 % durch Reaktion mit einem Überschuss an Triethylphosphit (**161**) bzw. Trimethylphosphit (**257**) in die entsprechenden Diethyl *N*-arylphosphoramidate **256a-o** umwandeln lassen (Tabelle 21).

Tabelle 21: Synthese der Diethyl *N*-arylphosphoramidate **256a-o** unter Mikrowellenbedingungen.



255 **161** **256**

Nr.	**255**	R^1	R^2	R^3	R^4	R^5	*t* [min]	**256**	Ausbeute **256** [%]
1	**a**	H	H	H	H	H	15	**a**	78
2	**b**	Me	H	H	H	H	15	**b**	68
3	**c**	H	Me	H	H	H	15	**c**	73
4	**d**	H	H	Me	H	H	15	**d**	66
5	**e**	Me	H	H	Me	H	15	**e**	75
6	**f**	H	Me	H	Me	H	15	**f**	79
7	**g**	Me	H	Me	H	H	15	**g**	77
8	**h**	H	H	OMe	H	H	15	**h**	71
9	**i**	H	H	Cl	H	H	10	**i**	52
10	**j**	Br	H	H	H	H	10	**j**	68
11	**k**	I	H	H	H	H	10	**k**	56
12	**l**	H	H	CO_2Me	H	H	10	**l**	62
13	**m**	H	H	CN	H	H	10	**m**	63
14	**n**	Br	H	H	OMe	H	10	**n**	73
15	**o**	Cl	Me	Cl	H	H	10	**o**	57

Die hier vorgestellten Ergebnisse zeigen ganz klar, dass die Reaktion von Nitroarenen mit Triethylphosphit – abweichend von bislang bekannten Ergebnissen – ein praktisches und effizientes Verfahren für die selektive Darstellung von Dialkyl *N*-arylphosphoramidaten in einem Schritt darstellt.

Die Strukturen aller im Rahmen dieser Arbeit synthetisierten Substanzen wurden zweifelsfrei durch analytische und spektroskopische Methoden, wie NMR-Spektroskopie, Massenspektrometrie, UV-Spektroskopie, IR-Spektroskopie und Elementaranalyse aufgeklärt.

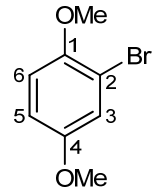
B EXPERIMENTAL PART

1. General Methods

All starting materials were purchased from commercial suppliers (Sigma-Aldrich Chemical Co., Acros Organics Lancaster Organics) and were used without further purification unless otherwise indicated. All reactions with moisture sensitive compounds were carried out under an argon atmosphere in oven-dried glassware and with magnetic stirring. Temperatures are reported as inner temperatures. Microwave assisted reactions were performed with a Discover™ single mode cavity microwave synthesizer (CEM Corp.), producing continuous irradiation at 2450 MHz. The average power of the radiation was approximately 300 W for all reactions performed at 200 °C. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on Alugram SIL G/UV $_{254}$ (Macherey and Nagel). Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in an ethanolic vanillin solution or an ethanolic 2,4-dinitrophenylhydrazine solution followed by heating. Products were purified by recrystallization or by flash chromatography on silica gel 60 M, 230-400 mesh (Macherey & Nagel). Melting points were determined on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. IR spectra were measured on a Perkin-Elmer Spectrum One (FT-IR-spectrometer). UV/VIS spectra were recorded with a Varian Cary 50. ^{1}H (^{13}C) NMR spectra were recorded at 300 (75.4) MHz on a Varian ^{Unity}Inova spectrometer using $CDCl_3$ or DMSO as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26/77.00 ($CDCl_3$) and at $\delta_{H/C}$ 2.49/39.50 (DMSO) relative to TMS as internal standards. HSQC-, HMBC- and COSY-spectra were recorded on a Varian ^{Unity}Inova at 300 MHz. Coupling constants *J* [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Low-resolution electron impact mass spectra (MS) and exact mass electron impact mass spectra (HRMS) were obtained at 70 eV on a Finnigan MAT 90 spectrometer. Elemental analyses were carried out by F. Hambloch, Institut für Organische und Biomolekulare Chemie der Universität Göttingen.

2. Synthesis of starting materials

2.1 2-Bromo-1,4-dimethoxybenzene (229)[93]



229

To a solution of 10 g (72.4 mmol) 1,4-dimethoxybenzene (**228**) in 100 mL glacial acetic acid a solution of 3.72 mL (11.6 g, 72.4 mmol) bromine in 50 mL glacial acetic acid was added dropwise with stirring over 1 h at 0 °C. The reaction mixture was stirred overnight at room temperature. 200 mL Water was added and the reaction mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined organic phases were washed with 50 mL water, 2M sodium hydroxide solution (2 × 50 mL) and 100 mL of a 3 % sodium sulfite solution. After drying over anhydrous sodium sulfate and concentration in vacuo the resulting residue was distilled at 11 mbar / 113 °C to give the title compound **229**.

Yield: 12.0 g (76 %) as colourless oil.

$\mathbf{R}_f$ = 0.73 (SiO_2; CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 2942 and 2834 (CH aliph.), 1575, 1490, 1641 (C=C arom.), 1436 (CH_3), 1270, 1213, 1179 (C-O), 1036, 1016 (C-Br), 862, 796, 730 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 295 nm (3.59).

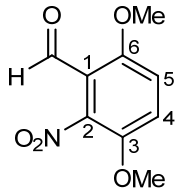
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, ^3J = 2.2 Hz, 1H, 5-H or 6-H), 6.82 (d, ^3J = 2.6 Hz, 1H, 5-H or 6-H), 3.77 (s, 3H, 1-OCH_3), 3.76 ppm (s, 3H, 4-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.30 (C-4), 150.57 (C-1), 119.27 (C-3), 113.94 (C-5), 113.19 (C-6), 112.23 (C-2), 57.12 (1-OCH_3), 56.17 ppm (4-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 215 (100) [M^+], 200 (98) [M^+-CH_3], 174 (12), 172 (18), 122 (6), 107 (10), 79 (5).

2.2 3,6-Dimethoxy-2-nitrobenzaldehyde (231)[94]

A suspension of 15 g (90.3 mmol) 2,5-dimethoxybenzaldehyde (**32**) in 180 mL conc. nitric acid was stirred at 0 °C for 2 h. The reaction mixture was poured into 150 mL water and neutralized with 90 mL 10 % sodium hydroxide solution. The crude product was collected by filtration, washed with water (4 × 25 mL), dried in vacuo and recrystallized from petroleum ether/chloroform = 1:5 to give the title compound **231** as yellow crystals. By concentration of the filtrate and neutralization with 25 mL conc. hydrochloric acid the side product 2,5-dimethoxy-4-nitrobenzoic acid (**232**) was isolated as a pale yellow powder.



231

Yield: 13.7 g (72 %).

M.p. = 168 °C (ref.[94] 176 °C).

$\mathbf{R}_f$ = 0.63 (SiO_2; CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 3099 (CH arom.), 2947 (CH aliph.), 2898, 2846 (CH aldehyde), 1689 (C=O), 1537 (N=O), 1489, 1451, 1443 (C=C arom.), 1433, 1367 (CH_3), 1270, 1186 cm^{-1} (C-O).

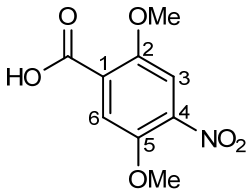
UV/VIS (MeCN): λ_{max} (log ε) = 354 (3.67), 252 (3.74), 220 nm (4.30).

^{1}H NMR (300 MHz, $CDC1_3$): δ = 10.40 (s, 1H, CHO), 7.32 (d, ^3J = 9.2 Hz, 1H, 5-H), 7.14 (d, ^3J = 9.2 Hz, 1H, 4-H), 3.99 (s, 3H, 3-OCH_3), 3.90 ppm (s, 3H, 6-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.31 (CHO), 155.56 (C-3), 144.81 (C-6), 120.27 (C-5), 116.97 (C-2), 116.50 (C-1), 114.39 (C-4), 57.51 (6-OCH_3), 57.03 ppm (3-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 211 (60) [M^+], 194 (10) [M^+-OH], 181 (16) [M^+-N=O], 166 (42), 151 (100) [M^+-$C_2H_4O_2$], 136 (58), 107 (30), 92 (24), 79 (28).

2.3 2,5-Dimethoxy-4-nitrobenzoic acid (232)[120]



232

Yield: 3.69 g (18 %).

M.p. = 192 °C (ref.[120] 192 °C).

$\mathbf{R}_f$ = 0.18 (SiO_2; acetone/EtOAc = 3:1).

IR (ATR): $\tilde{\nu}$ = 3200-3000 (OH broad), 2853 (CH aliph.), 1706 (C=O), 1672, 1622 and 1580 (C=C arom.), 1520 and 1500 (N=O) 1215, 1022 cm^{-1} (C-O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1H, 3-H), 7.52 (s, 1H, 6-H), 3.91 (s, 3H, 5-OCH_3), 3.84 ppm (s, 3H, 2-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.86 (C=O), 151.33 (C-2), 145.73 (C-5), 141.39 (C-1), 127.79 (C-4), 116.35 (C-6), 109.78 (C-3), 57.81 (5-OCH_3), 57.49 ppm (2-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 227 (100) [M^+], 198 (8), 167 (25), 166 (13), 136 (15), 123 (12), 53 (11).

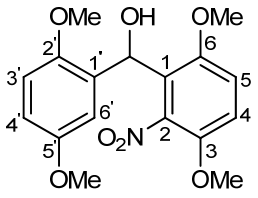
3. Synthesis of (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanols 233a-e

3.1 General procedure for the synthesis of the (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanols 233[1c]

A mixture of 40 mL (60 mmol) *tert*-butyllithium (1.5 *M* in pentane) in 50 mL dry tetrahydrofurane was added dropwise over 30 min to a solution of 40 mmol of a alkoxy-substituted bromobenzene **229** in 50 mL dry tetrahydrofurane at – 78 °C under argon with stirring. After stirring for 30 min a solution of 32 mmol of the alkoxy-substituted nitrobenzaldehyde **231** in 50 mL dry tetrahydrofurane was added and the reaction mixture was left for 10 min at – 78 °C and then allowed to warm up to room temperature with stirring

during 3 h. After quenching with 200 mL water the reaction mixture was extracted with dichloromethane or *tert*-butylmethyl ether (4 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL). The crude product was obtained after drying over anhydrous magnesium sulfate and concentration in vacuo. It was purified by recrystallization.

3.2 (3,6-Dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanol (233a)



233a

According to the general procedure 8.7 mL (8.8 g, 40 mmol) 2-bromo-1,4-dimethoxybenzene (**229a**) were reacted with 6.80 g (32 mmol) 3,6-dimethoxy-2-nitrobenzaldehyde (**231a**). After recrystallization from ethanol the title compound **233a** was isolated as yellow crystals.

Yield: 9.88 g (88 %).

M.p. = 174 °C.

$\mathbf{R}_f$ = 0.37 (SiO_2; PE/CH_2Cl_2 = 1:1).

IR (ATR): $\tilde{\nu}$ = 3530 (OH), 3107 (CH arom.), 2943 and 2840 (CH aliph.), 1532 (N=O), 1496, 1484 and 1456 (C=C arom.), 1430 and 1366 (CH_3), 1274, 1238, 1215, 1033 and 1022 cm^{-1} (C-O).

UV/VIS (MeCN): λ_{max} (log ε) = 294 nm (3.82).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (s, 2H, 4-H, 5-H), 6.82 (br, 1H, 6'-H), 6.76 (br s, 1H, 3'-H), 6.75 (s, 1H, 4'-H), 6.28 (s, 1H, C*H*-OH), 3.85 (s, 3H, 3-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.74 (s, 3H, 5'-OCH_3), 3.73 (s, 3H, 2'-OCH_3), 3.51 ppm (br, 1H, OH).

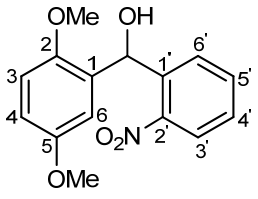
^{13}C NMR (300 MHz, $CDCl_3$): δ = 153.57 (C-5'), 151.22 (C-6), 151.12 (C-2'), 145.42 (C-3), 141.62 (C-2), 130.93 (C-1'), 124.39 (C-1), 114.61 (C-6'), 113.68 (C-5), 113.00 (C-4'), 112.49 (C-5), 111.37 (C-3'), 66.50 (*C*H-OH), 57.23 (3-OCH_3), 56.89 (2'-OCH_3), 56.05 (6-OCH_3), 56.02 ppm (5'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 349 (100) [M^+], 316 (8), 314 (14), 285 (32), 272 (52), 257 (26), 242 (36), 213 (18), 197 (109), 165 (24), 72 (6).

HRMS (EI, M^+): calcd for $C_{17}H_{19}NO_7$: 349.1156; found: 349.1138.

Elemental analysis (%) calcd for $C_{17}H_{19}NO_7$: C 58.43, H 5.48, N 4.01; found: C 58.36, H 5.42, N 3.88.

3.3 (2,5-Dimethoxyphenyl)(2'-nitrophenyl)methanol (233b)



233b

According to the general procedure 8.7 mL (8.8 g, 40 mmol) 2-bromo-1,4-dimethoxybenzene (**229a**) were reacted with 4.84 g (32 mmol) 2-nitrobenzaldehyde (**231b**). After recrystallization from ethanol the title compound **233b** was isolated as yellow crystals.

Yield: 9.06 g (98 %).

M.p. = 100 °C.

$\mathbf{R}_f$ = 0.31 (SiO_2; CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 3451 (OH), 3100 (CH arom.), 2920 (CH aliph.), 1515 (N=O), 1493, 1465 (C=C arom.), 1357 (CH_3), 1211, 1156, 1038 (C-O), 857, 823, 787 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 290 (3.19), 226 nm (3.49).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, ^3J = 8.4 Hz, 1H, 3'-H), 7.59 (d, ^3J = 7.9 Hz, 1H, 6'-H), 7.54 (d, ^3J = 7.9 Hz, 1H, 5'-H), 7.38-7.44 (m, 1H, 4'-H), 6.91 (br s, 1H, 3-H), 6.82 (s, 2H, 4-H and 6-H), 6.60 (s, 1H, C*H*-OH), 3.79 (s, 3H, 5-OCH_3), 3.73 ppm (s, 3H, 2-OCH_3).

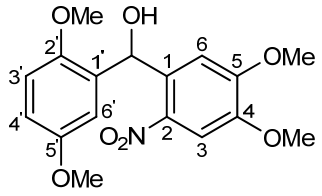
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.97 (C-5), 150.83 (C-2), 149.00 (C-1'), 137.95 (C-2'), 133.27 (C-5'), 131.59 (C-1), 129.62 (C-6'), 128.45 (C-4'), 124.41 (C-3'), 113.61 (C-3), 113.29 (C-4), 111.72 (C-6), 66.91 (*C*H-OH), 56.07 (5-OCH_3), 56.00 ppm (2-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 289 (52) [M^+], 254 (15), 213 (118), 212 (100) [M^+-C_6H_5], 197 (37), 169 (30), 139 (17), 77 (14).

HRMS (EI, M^+): calcd for $C_{15}H_{15}NO_5$: 289.0946; found: 289.0936.

Elemental analysis (%) calcd for $C_{15}H_{15}NO_5$: C 62.26, H 5.23, N 4.84; found: C 62.15, H 4.92, N 5.10.

3.4 (4,5-Dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanol (233c)



233c

According to the general procedure 8.7 mL (8.8 g, 40 mmol) 2-bromo-1,4-dimethoxybenzene (**229a**) were reacted with 6.75 g (32 mmol) 6-nitroveratraldehyde (**231c**). After recrystallization from ethanol the title compound **233c** was isolated as yellow crystals.

Yield: 9.67 g (87 %).

M.p. = 114 °C.

$\mathbf{R_f}$ = 0.45 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3520 (OH), 2960 and 2810 (CH aliph.), 1590 (N=O), 1511, 1495 and 1480 (C=C arom.), 1437 and 1325 (CH_3), 1264, 1221, 1178, 1063 and 1023 (C-O), 795, 715 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 347 (3.29), 294 (3.39), 202 nm (4.20).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (s, 1H, 6-H), 7.19 (s, 1H, 3-H), 6.82 (d, ^3J = 8.8 Hz, 1H, 3'-H), 6.77 (dd, ^3J = 8.9 Hz, ^4J = 2.9 Hz, 1H, 4'-H), 6.72 (d, ^3J = 3.1 Hz, 1H, C*H*-OH), 6.62 (d, ^4J = 2.8 Hz, 1H, 6'-H), 3.95 (s, 3H, 4-OCH_3), 3.90 (s, 3H, 5-OCH_3), 3.78 (s, 3H, 2'-OCH_3), 3.71 (s, 3H, 5'-OCH_3), 3.33 ppm (d, ^3J = 3.4 Hz, 1H, OH).

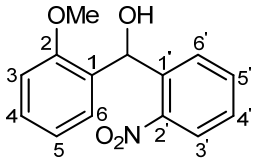
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.86 (C-5'), 153.51 (C-5), 151.21 (C-2'), 148.09 (C-4), 140.81 (C-2), 133.09 (C-1), 132.18 (C-1'), 113.88 (C-6'), 112.84 (C-4'), 111.73 (C-3'), 110.72 (C-6), 107.99 (C-3), 67.05 (*C*H-OH), 56.60 (4-OCH_3), 56.59 (5-OCH_3), 56.29 (2'-OCH_3), 55.97 ppm (5'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 349 (22) [M^+], 300 (11), 273 (18), 272 (100) [M^+-C_6H_5], 257 (23), 206 (23), 165 (11), 136 (8), 77 (5).

HRMS (EI, M^+): calcd for $C_{17}H_{19}NO_7$: 349.1156; found: 349.1154.

Elemental analysis (%) calcd for $C_{17}H_{19}NO_7$: C 58.43, H 5.48, N 4.01; found: C 58.50, H 5.34, N 3.80.

3.5 (2-Methoxyphenyl)(2'-nitrophenyl)methanol (233d)[121]



233d

According to the general procedure 5.0 mL (7.48 g, 40 mmol) 2-bromoanisole (**229b**) were reacted with 4.84 g (32 mmol) 2-nitrobenzaldehyde (**231b**). After recrystallization from cyclohexane the title compound **233d** was isolated as yellow crystals.

Yield: 7.41 g (90 %).

M.p. = 72 °C.

$\mathbf{R}_f$ = 0.40 (SiO_2; cyclohexane/EtOAc = 3:1).

IR (ATR): $\tilde{\nu}$ = 3434 (OH), 2960 and 2840 (CH aliph.), 1600 (N=O), 1519, 1490, 1463 and 1435 (C=C arom.), 1353 (CH_3), 1290, 1245, 1182, 1161 and 1022 (C-O), 784, 753 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 267 nm (3.44).

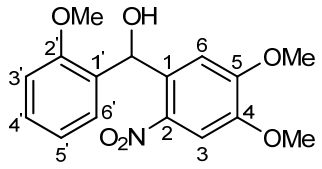
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, ^3J = 8.2 Hz, 1H, 3'-H), 7.61 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, 6'-H), 7.56 (t, ^3J = 7.1 Hz, 1H, 5'-H), 7.41 (dt, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, 4'-H),

7.25-7.31 (m, 2H, 3-H, 5-H), 6.95 (t, ^3J = 7.6 Hz, 1H, 4-H), 6.86 (d, ^3J = 8.1 Hz, 1H, 3-H), 6.64 (s, 1H, C*H*-OH), 3.75 ppm (s, 3H, 1-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.06 (C-1), 146.43 (C-2'), 135.55 (C-1'), 130.65 (C-5'), 127.91 (C-6), 127.06 (C-6'), 126.81 (C-3), 125.81 (C-4), 124.45 (C-5), 121.82 (C-3'), 118.40 (C-4), 108. 19 (C-2), 64.36 (*C*H-OH), 53.02 ppm (1-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 259 (4) [M^+], 224 (22), 212 (31), 196 (36), 183 (40), 182 (100) [M^+-C_6H_5], 168 (85), 154 (82), 152 (33), 135 (30), 77 (62).

3.6 (4,5-Dimethoxy-2-nitrophenyl)(2'-methoxyphenyl)methanol (233e)



233e

According to the general procedure 5 mL (7.48 g, 40 mmol) 2-bromoanisole (**229b**) were reacted with 6.75 g (32 mmol) 6-nitroveratraldehyde (**231c**). After recrystallization from ethanol the title compound **233e** was isolated as yellow crystals.

Yield: 9.30 g (92 %).

M.p. = 112 °C.

R_f = 0.59 (SiO_2; cyclohexane/EtOAc = 1:2).

IR (ATR): $\tilde{\nu}$ = 3548 (OH), 2937 and 2835 (CH aliph.), 1582 (N=O), 1506, 1436 and 1390 (C=C arom.), 1326 (CH_3), 1271, 1186, 1158, 1063 and 1014 (C-O), 985, 792, 770, 740 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 355 (3.62), 287 (3.67), 245 nm (4.04).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (s, 1H, 6-H), 7.28 (t, ^3J = 7.4 Hz, ^3J = 7.4 Hz, ^4J = 1.6 Hz, 1H, 4'-H), 7.23 (s, 1H, 3-H), 7.06 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H, 3'-H), 6.94 (br, 1H, 5'-H), 6.91 (dd, ^3J = 7.4 Hz, ^4J = 1.6 Hz, 1H, 6'-H), 6.79 (br, 1H, C*H*-OH), 3.98 (s, 3H, 4-OCH_3), 3.93 (s, 3H, 5-OCH_3), 3.86 (s, 3H, 2'-OCH_3), 3.34 ppm (br, 1H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.93 (C-2'), 153.45 (C-5), 148.04 (C-4), 140.84 (C-2), 133.33 (C-1), 130.95 (C-1'), 129.37 (C-4'), 126.83 (C-3'), 120.92 (C-6'), 110.82 (C-5'), 110.81 (C-3), 107. 97 (C-6), 66.99 (*C*H-OH), 56.60 (4-OCH_3), 56.56 (5-OCH_3), 55.77 ppm (2'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 319 (4) [M^+], 286 (84), 273 (18), 242 (100) [M^+-C_6H_5], 199 (56), 183 (32), 164 (24), 135 (20).

HRMS (EI, M^+): calcd for $C_{16}H_{17}NO_6$: 319.1015; found: 319.1050.

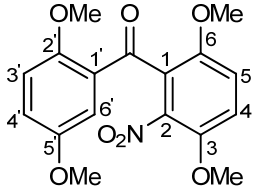
Elemental analysis (%) calcd for $C_{16}H_{17}NO_6$: C 60.17, H 5.37, N 4.39; found: C 60.25, H 5.07, N 4.55.

4. Synthesis of the (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanones 234a-e

4.1 General procedure for the synthesis of (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanones 234[97]

5 g (16.98 mmol) potassium dichromate were dissolved in 60 mL glacial acetic acid. A solution of 25.86 mmol (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanol **233** in 100 mL toluene was added at room temperature. The reaction mixture solidified to a brown-black mass. It was heated for 3-7 h at 90 °C while the colour of the reaction mixture changed to green-brown. After cooling to room temperature the reaction mixture was filtered and extracted with water (3 × 100 mL) to remove the acetic acid and the chromium salts. Then the mixture was extracted with ethyl acetate (4 × 80 mL). The combined organic phases were washed with brine (2 × 50 mL) and 10 % sodium hydroxide solution (2 × 50 mL). After drying over anhydrous magnesium sulfate the solvents were removed in vacuo and the crude product was purified by recrystallization.

4.2 (3,6-Dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanone (234a)



234a

According to the general procedure 8.62 g (25.86 mmol) (3,6-dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanol (**233a**) were reacted with 5 g (16.98 mmol) potassium dichromate. After recrystallization from ethanol the title compound **234a** was isolated as yellow crystals.

Yield: 7.63 g (85 %).

M.p. = 138 °C.

$\mathbf{R_f}$ = 0.34 (SiO_2; CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 2961, 2837 (CH aliph.), 1642 (C=O), 1528 (N=O), 1496, 1486, and 1460 (C=C arom.), 1424, 1365 (CH_3), 1263, 1219 and 1046 cm^{-1} (C-O).

UV/VIS (MeCN): λ_{max} (log ε) = 354 (3.79), 223 nm (3.81).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, ^4J = 3.2 Hz, 1H, 6'-H), 7.08 (dd, ^3J = 8.9 Hz, ^4J = 3.2 Hz, 1H, 4'-H), 7.04 (s, 2H, 4-H, 5-H), 6.88 (d, ^3J = 8.9 Hz, 1H, 3'-H), 3.94 (s, 3H, 3-OCH_3), 3.85 (s, 3H, 5'-OCH_3), 3.73 (s, 3H, 6-OCH_3), 3.59 ppm (s, 3H, 2'-OCH_3).

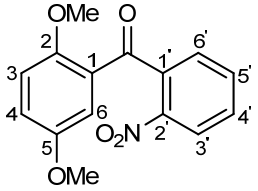
^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.40 (C=O), 154.83 (C-2'), 153.85 (C-5'), 150.50 (C-6), 145.9 (C-3), 138.42 (C-2), 128.90 (C-1), 126.50 (C-1'), 122.58 (C-4'), 114.03 (C-6'), 114.21 (C-3'), 114.06 (C-4), 114.31 (C-5), 57.55 (3-OCH_3), 57.26 (6-OCH_3), 56.93 (2'-OCH_3), 56.19 ppm (5'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 347 (100) [M^+], 165 (44), 107 (4).

HRMS (EI, M^+): calcd for $C_{17}H_{17}NO_7$: 347.1000; found: 347.1006.

Elemental analysis (%) calcd for $C_{17}H_{17}NO_7$: C 58.77, H 4.94, N 4.03; found: C 58.53, H 4.87, N 3.91.

4.3 (2,5-Dimethoxyphenyl)(2'-nitrophenyl)methanone (234b)



234b

According to the general procedure 7.47 g (25.86 mmol) (2,5-dimethoxyphenyl)(2'-nitrophenyl)methanol (**233b**) were reacted with 5 g (16.98 mmol) potassium dichromate. After recrystallization from ethanol the title compound **234b** was isolated as yellow crystals.

Yield: 6.63 g (89 %).

M.p. = 76 °C.

$\mathbf{R}_f$ = 0.74 (SiO_2; CH_2Cl_2/cyclohexane = 2:1).

IR (ATR): $\tilde{\nu}$ = 2941 and 2831 (CH aliph.), 1647 (C=O), 1517, 1493 and 1409 (C=C arom.), 1348 and 1330 (CH_3), 1220, 1146 and 1041 (C-O), 810, 738, 706 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 347 (3.16), 260 (3.64), 226 nm (3.84).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1H, 6'-H), 7.74 (ddd, ^3J = 7.6 Hz, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, 5'-H), 7.61 (ddd, ^3J = 8.9 Hz, ^3J = 6.9 Hz, ^4J = 1.5 Hz, 1H, 4'-H), 7.61 (d, ^4J = 3.2 Hz, 1H, 6-H), 7.42 (dd, ^3J = 9.5 Hz, ^4J = 3.2 Hz, 1H, 3'-H), 7.13 (dd, ^3J = 9.1 Hz, ^4J = 3.2 Hz, 1H, 4-H), 6.85 (d, ^3J = 9.1 Hz, 1H, 3-H), 3.48 (s, 3H, 5-OCH_3), 3.44 ppm (s, 3H, 2-OCH_3).

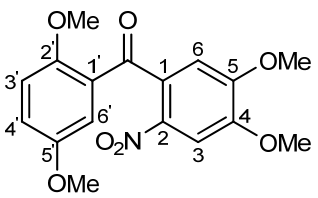
^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.85 (C=O), 154.18 (C-2), 154.02 (C-5), 146.54 (C-2'), 140.25 (C-1'), 134.10 (C-5'), 129.64 (C-4'), 127.98 (C-3'), 125.45 (C-1), 123.75 (C-6'), 122.75 (C-4), 114.25 (C-3), 114.10 (C-6), 56.35 (2-OCH_3), 56.15 ppm (5-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 287 (100) [M^+], 165 (23), 153 (11), 125 (20), 104 (11).

HRMS (EI, M^+): calcd for $C_{15}H_{13}NO_5$: 287.0790; found: 287.0788.

Elemental analysis (%) calcd for $C_{15}H_{13}NO_5$: C 62.70, H 4.56, N 4.88; found: C 62.47, H 4.36, N 5.04.

4.4 (4,5-Dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanone (234c)



234c

According to the general procedure 9.03 g (25.86 mmol) (4,5-dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanol (**233c**) were reacted with 5 g (16.98 mmol) potassium dichromate. After recrystallization from ethanol the title compound **234c** was isolated as yellow crystals.

Yield: 8.23 g (92 %).

M.p. = 147 °C.

$\mathbf{R_f}$ = 0.30 (SiO_2; cyclohexane/CH_2Cl_2 = 3:2).

IR (ATR): $\tilde{\nu}$ = 2835 (CH aliph.), 1650 (C=O), 1600, 1530 and 1495 (C=C arom.), 1430, 1333 (CH_3), 1282, 1216, 1067 and 1042 (C-O), 872, 823, 787, 731 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 348 (3.42), 224 nm (3.85).

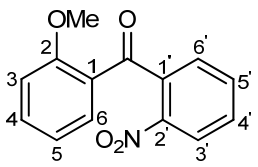
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1H, 3-H), 7.51 (d, ^4J = 3.2 Hz, 1H, 6'-H), 7.07 (dd, ^3J = 9.1 Hz, ^4J = 3.2 Hz, 1H, 4'-H), 6.82 (d, ^3J = 9.1 Hz, 1H, 3'-H), 6.79 (s, 1H, 6-H), 4.00 (s, 3H, 5'-OCH_3), 3.95 (s, 3H, 2'-OCH_3), 3.83 (s, 3H, 5-OCH_3), 3.48 ppm (s, 3H, 4-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.71 (C=O), 154.12 (C-2'), 153.89 (C-5), 153.89 (C-4), 149.14 (C-5'), 139.47 (C-2), 134.50 (C-1), 125.72 (C-1'), 122.25 (C-4'), 114.60 (C-6'), 114.04 (C-3'), 109.55 (C-6), 106.55 (C-3), 56.87 (5'-OCH_3), 56.80 (5-OCH_3), 56.60 (4-OCH_3), 56.14 ppm (2'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 347 (100) [M^+], 286 (14), 271 (10), 194 (23), 165 (31) 153 (27), 125 (26).

HRMS (EI, M^+): calcd for $C_{17}H_{17}NO_7$: 347.1000; found: 347.1018.

4.5 (2-Methoxyphenyl)(2'-nitrophenyl)methanone (234d)[122]



234d

According to the general procedure 6.70 g (25.86 mmol) (2-methoxyphenyl)(2'-nitrophenyl)methanol (**233d**) were reacted with 5 g (16.98 mmol) potassium dichromate. After recrystallization from ethanol the title compound **234d** was isolated as yellow crystals.

Yield: 5.85 g (88 %).

M.p. = 148 °C .

$\mathbf{R}_f$ = 0.69 (SiO_2; cyclohexane/CH_2Cl_2 = 1:3).

IR (ATR): $\tilde{\nu}$ = 1657 (C=O), 1595, 1519, and 1483 (C=C arom.), 1346, 1303 (CH_3), 1252, 1151, 1015 (C-O), 932, 755, 720 cm^{-1}.

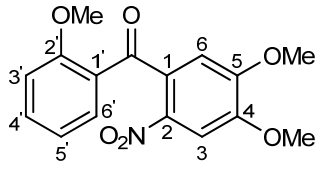
UV/VIS (MeCN): λ_{max} (log ε) = 313 (3.50), 255 (3.98), 214 nm (4.24).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, ^3J = 8.2 Hz, 1H, 3'-H), 7.99 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, 6-H), 7.70 (t, ^3J = 7.4 Hz, 1H, 5'-H), 7.57 (d, ^3J = 7.4 Hz, 1H, 4'-H), 7.52 (dt, ^3J = 7.9 Hz, ^4J = 1.6 Hz, 1H, 4-H), 7.39 (d, ^3J = 6.8 Hz, 1H, 6'-H), 7.07 (t, ^3J = 7.5 Hz, 1H, 5-H), 6.88 (d, ^3J = 8.4 Hz, 1H, 3-H), 3.53 ppm (s, 3H, 1-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.14 (C=O), 159.58 (C-2), 146.60 (C-2'), 140.13 (C-1'), 135.50 (C-4'), 134.08 (C-5'), 131.75 (C-6), 129.74 (C-4), 128.13 (C-6'), 125.29 (C-1), 123.81 (C-3'), 121.17 (C-5), 112.33 (C-3), 55.81 ppm (1-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 257 (54) [M^+], 223 (12), 183 (10), 182 (36), 154 (55), 135 (95), 123 (100) [M^+-$C_8H_6O_2$], 140 (71), 77 (84), 76 (53), 51 (28).

4.6 (4,5-Dimethoxy-2-nitrophenyl)(2'-methoxyphenyl)methanone (234e)



234e

According to the general procedure 8.25 g (25.86 mmol) (4,5-dimethoxy-2-nitrophenyl)(2'-methoxyphenyl)methanol (**233e**) were reacted with 5 g (16.98 mmol) potassium dichromate. After recrystallization from ethanol the title compound **234e** was isolated as yellow crystals.

Yield: 7.13 g (87 %).

M.p. = 114 °C.

$\mathbf{R}_f$ = 0.37 (SiO_2; cyclohexane/CH_2Cl_2 = 2:1).

IR (ATR): $\tilde{\nu}$ = 3003 (CH arom.), 2977 and 2841 (CH aliph.), 1656 (C=O), 1600, 1575 and 1520 (C=C arom.), 1438, 1333 (CH_3), 1295, 1252, 1217, 1067 and 1018 (C-O), 873, 832, 790, 758, 672 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 314 (3.64), 249 (3.95), 215 nm (4.10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (dd, ^3J = 7.9 Hz, ^4J = 1.6 Hz, 1H, 6'-H), 7.68 (s, 1H, 3-H), 7.53 (t, ^3J = 8.5 Hz, 1H, 4'-H), 7.07 (t, ^3J = 7.6 Hz, 1H, 5'-H), 6.92 (d, ^3J = 8.5 Hz, 1H, 3'-H), 6.84 (s, 1H, 6-H), 4.04 (s, 3H, 4-OCH_3), 3.98 (s, 3H, 5-OCH_3); 3.86 ppm (s, 3H, 2'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.99 (C=O), 159.56 (C-2'), 153.86 (C-5), 149.20 (C-4), 139.53 (C-2), 135.23 (C-4'), 134.36 (C-1), 131.77 (C-6'), 125.24 (C-1'), 121.00 (C-5'), 112.32 (C-3'), 109.72 (C-3), 106.61 (C-6), 56.88 (4-OCH_3), 56.80 (5-OCH_3), 56.04 ppm (2'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 317 (84) [M^+], 270 (12), 256 (14), 195 (64), 164 (98), 123 (100) [M^+-$C_{10}H_{10}O_4$], 97 (90).

HRMS (EI, M^+): calcd for $C_{16}H_{15}NO_6$: 317.0895; found: 317.0910.

Elemental analysis (%) calcd for $C_{16}H_{15}NO_6$: C 60.55, H 4.77, N 4.42; found: C 60.79, H 4.54, N 4.23.

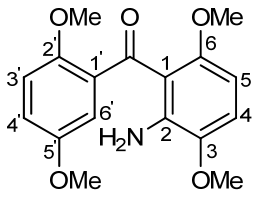
5. Synthesis of (2-amino-3,4,5,6-tetralkoxyphenyl)(2',5'-dialkoxyphenyl)methanones 235a-e

5.1 General procedure for the synthesis of (2-amino-3,4,5,6-tetraalkoxyphenyl)(2',5'-dialkoxyphenyl)methanones 235[98]

A solution of 22.50 mmol (2,5-dialkoxyphenyl)(2',3',4',5'-tetraalkoxy-6'-nitrophenyl)methanone **234** in 100 mL glacial acetic acid and 30 mL water was treated with 7.5 g (135 mmol) iron powder during 30 min at 90 °C with vigorous stirring. After 45 min 20 mL water were added and the reaction mixture was refluxed for 4 h. After cooling to room temperature the reaction mixture was diluted with 150 mL water and 100 mL 2 M sodium

hydroxide solution. The reaction mixture was extracted with ethyl acetate (5 × 50 mL). The combined organic phases were washed with water (2 × 50 mL) and 2 M sodium hydroxide solution (2 × 50 mL) and then dried over anhydrous magnesium sulfate. After removal of the solvent in vacuo the crude product was purified by column chromatography on silica gel.

5.2 (2-Amino-3,6-dimethoxyphenyl)(2',5'-dimethoxyphenyl)methanone (235a)



235a

According to the general procedure 7.81 g (22.50 mmol) (3,6-dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanone (**234a**) were treated with 7.5 g (135 mmol) iron powder. After column chromatography (SiO_2; petroleum ether/EtOAc = 2:1) the title compound **235a** was isolated as yellow crystals.

Yield: 6.49 g (91 %).

M.p. = 105 °C.

$\mathbf{R}_f$ = 0.69 (SiO_2; EtOAc).

IR (ATR): $\tilde{\nu}$ = 3491 and 3346 (NH_2), 3067 (CH arom.), 2961, 2939 and 2837 (CH aliph.), 1604 (C=O), 1536, 1492 and 1458 (C=C arom.), 1419 and 1354 (CH_3), 1276, 1211 and 1179 cm^{-1} (C-O).

UV/VIS (MeCN): λ_{max} (log ε) = 364 (3.57), 294 nm (3.88).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.89 (m, 1H, 4'-H), 6.87 (s, 1H, 6'-H), 6.82 (m, 1H, 3'-H), 6.75 (d, ^3J = 8.7 Hz, 1H, 4-H), 5.99 (d, ^3J = 8.7 Hz, 1H, 5-H), 3.84 (s, 1H, 3-OCH_3), 3.76 (s, 3H, 2'-OCH_3), 3.67 (s, 1H, 5'-OCH_3), 3.36 ppm (s, 3H, 6-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.59 (C=O), 155.30 (C-6), 153.59 (C-2'), 151.54 (C-5'), 141.89 (C-3), 141.53 (C-1), 134.73 (C-1'), 116.50 (C-4'), 113.59 (C-6'), 113.46 (C-4), 113.04

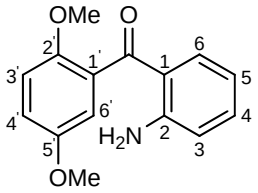
(C-3'), 112.63 (C-2), 97.01 (C-5), 57.00 (5'-OCH_3), 56.39 (3-OCH_3), 56.11 (2'-OCH_3), 55.92 ppm (6-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 317 (100) [M^+], 302 (16) [M^+-CH_3], 286 (42) [M^+- OCH_3], 256 (64), 165 (28), 164 (48), 150 (22), 122 (26), 107 (18).

HRMS (EI, M^+): calcd for $C_{17}H_{19}NO_5$: 317.1258; found: 317.1242.

Elemental analysis (%) calcd for $C_{17}H_{19}NO_5$: C 64.33, H 6.04, N 4.42; found: C 64.16, H 5.76, N 4.19.

5.3 (2-Aminophenyl)(2',5'-dimethoxyphenyl)methanone (235b)[123]



235b

According to the general procedure 6.45 g (22.50 mmol) (2,5-dimethoxyphenyl)(2'-nitrophenyl)methanone (**234b**) were treated with 7.5 g (135 mmol) iron powder. After column chromatography (SiO_2; cyclohexane/CH_2Cl_2 = 1:2) the title compound **235b** was isolated as yellow crystals.

Yield: 5.11 g (88 %).

M.p. = 92 °C (ref.[123] 128 °C).

$\mathbf{R}_f$ = 0.41 (SiO_2; CH_2Cl_2).

IR (ATR): $\tilde{\nu}$ = 3466 and 3349 (NH_2, sharp), 2931 and 2835 (CH aliph.), 1628 (C=O), 1614, 1581 and 1547 (C=C arom.), 1491 (CH_3), 1302, 1274 and 1216 (C-O), 960, 796, 753 cm^{-1}.

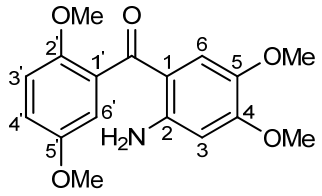
UV/VIS (MeCN): λ_{max} (log ε) = 375 (3.13), 263 (3.22), 230 nm (3.73).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.35 (m, 2H, 4-H, 6-H), 6.99 (dd, ^3J = 9.1 Hz, ^4J = 2.8 Hz, 1H, 4'-H), 6.94 (d, ^3J = 8.9 Hz, 1H, 3'-H), 6.85 (d, ^4J = 2.6 Hz, 1H, 6'-H), 6.77 (d, ^3J = 8.1 Hz, 1H, 3-H), 6.60 (t, ^3J = 7.5 Hz, 1H, 5-H), 3.81 (s, 3H, 2'-OCH_3), 3.75 ppm (s, 3H, 5'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.69 (C=O), 153.65 (C-2$^{'}$), 150.75 (C-2), 150.57 (C-5$^{'}$), 135.26 (C-6), 134.96 (C-4), 131.11 (C-1$^{'}$), 118.96 (C-1), 117.3 (C-3), 116.35 (C-5), 116.30 (C-4$^{'}$), 113.99 (C-6$^{'}$), 113.11 (C-3$^{'}$), 56.68 (5$^{'}$-OCH_3), 56.11 ppm (2$^{'}$-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 257 (100) [M^+], 226 (98) [M^+-OCH_3], 211 (16), 165 (11), 120 (22), 92 (15), 65 (9).

5.4 (2-Amino-4,5-dimethoxyphenyl)(2$^{'}$,5$^{'}$-dimethoxyphenyl)methanone (235c)



235c

According to the general procedure 7.81 g (22.50 mmol) (4,5-dimethoxy-2-nitrophenyl)(2$^{'}$,5$^{'}$-dimethoxyphenyl)methanone (**234c**) were treated with 7.5 g (135 mmol) iron powder. After column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) the title compound **235c** was isolated as yellow crystals.

Yield: 6.28 g (88 %).

M.p. = 124 °C.

R_f = 0.31 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3472, 3340 (NH_2), 2830, 2965 (CH aliph.), 1614 (C=O), 1580, 1536 and 1491 (C=C arom.), 1462, 1417 (CH_3), 1274, 1206, 1097 and 1046 (C-O), 951, 811, 726 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 377 (3.61), 285 (3.62), 250 nm (3.95).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (dd, ^3J = 9.1 Hz, ^4J = 2.8 Hz, 1H, 4$^{'}$-H), 6.90 (d, ^3J = 8.8 Hz, 1H, 3$^{'}$-H), 6.82 (d, ^4J = 2.5 Hz, 1H, 6$^{'}$-H), 6.72 (s, 1H, 6-H), 6.41 (br, 2H, NH_2), 6.14 (s, 1H, 3-H), 3.88 (s, 3H, 5$^{'}$-OCH_3), 3.77 (s, 3H, 2$^{'}$-OCH_3), 3.73 (s, 3H, 4-OCH_3), 3.59 ppm (s, 3H, 5-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.17 (C=O), 156.16 (C-5), 153.70 (C-2$^{'}$), 150.48 (C-5$^{'}$), 148. 87 (C-4), 140.18 (C-1), 131.47 (C-1$^{'}$), 116.95 (C-6), 116.21 (C-4$^{'}$), 113.94 (C-6$^{'}$),

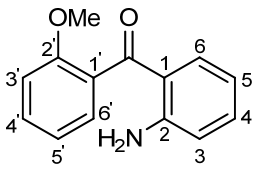
112.99 (C-3'), 110.90 (C-2), 99.04 (C-3), 56.87 (5-OCH_3), 56.65 (4-OCH_3), 56.12 (2'-OCH_3), 56.10 ppm (5' -OCH_3).

MS (EI, 70 eV): *m/z* (%) = 317 (100) [M^+], 286 (47), 271 (16), 242 (9), 164 (10), 136 (4), 28 (5).

HRMS (EI, M^+): calcd for $C_{17}H_{19}NO_5$: 317.1258; found: 317.1254.

Elemental analysis (%) calcd for $C_{17}H_{19}NO_5$: C 64.33, H 6.04, N 4.42; found: C 64.18, H 5.88, N 4.22.

5.5 (2-Aminophenyl)(2'-methoxyphenyl)methanone (235d)[124]



235d

According to the general procedure 5.78 g (22.50 mmol) (2-methoxyphenyl)(2'-nitrophenyl)methanone (**234d**) were treated with 7.5 g (135 mmol) iron powder. After column chromatography (SiO_2; cyclohexane/EtOAc = 4:1) the title compound **235d** was isolated as yellow crystals.

Yield: 4.70 g (92 %).

M.p. = 113 °C (ref.[124] 110 °C).

$\mathbf{R_f}$ = 0.53 (SiO_2; cyclohexane/EtOAc = 2:1).

IR (ATR): $\tilde{\nu}$ = 3468, 3347 (NH_2), 1626 (C=O), 1576, 1546 (C=C arom.), 1479 and 1433 (CH_3), 1301, 1238 (C-O), 923, 747 cm^{-1}.

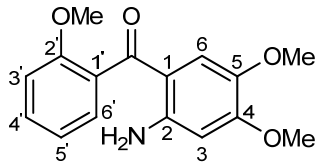
UV/VIS (MeCN) λ_{max} (log ε) = 372 (3.81), 260 nm (3.31).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dt, ^3J = 8.3 Hz, ^4J = 1.6 Hz, 1H, 4'-H), 7.29 (d, ^3J = 7.8 Hz, 1H, 6-H), 7.23-7.27 (m, 2H, 4-H, 6'-H), 7.02 (t, ^3J = 7.5 Hz, 1H, 5'-H), 6.98 (d, ^3J = 8.2 Hz, 1H, 3'-H), 6.76 (d, ^3J = 8.7 Hz, 1H, 3-H), 6.57 (t, ^3J = 7.5 Hz, 1H, 5-H), 6.35 (br s, 2H, NH_2), 3.76 ppm (s, 3H, 2'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.60 (C=O), 154.11 (C-2'), 147.71 (C-2), 132.64 (C-6'), 132.30 (C-6), 128.53 (C-4'), 130.11 (C-1), 118.09 (C-5'), 116.78 (C-1'), 114.98 (C-3), 113.86 (C-5), 108 99 (C-3'), 53.35 ppm (2'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 227 (100) [M^+], 212 (79), 196 (78), 180 (25), 167 (20), 135 (68), 120 (74), 92 (82), 77 (51), 65 (50).

5.6 (2-Amino-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (235e)



235e

According to the general procedure 7.13 g (22.50 mmol) (4,5-dimethoxy-2-nitrophenyl)(2'-methoxyphenyl)methanone (**234e**) were treated with 7.5 g (135 mmol) iron powder. After column chromatography (SiO_2; cyclohexane/EtOAc = 3:2) the title compound **235e** was isolated as yellow crystals.

Yield: 6.07 g (94 %).

M.p. = 110 °C.

$\mathbf{R}_f$ = 0.37 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3478, 3342 (NH_2), 2967 and 2825 (CH aliph.), 1611 (C=O), 1600, 1575 and 1531 (C=C arom.), 1463, 1380 (CH_3), 1277, 1244, 1208, 1125 and 1020 (C-O), 914, 826, 788, 754, 669 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 377 (3.81), 284 (3.88), 249 nm (4.16).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (ddd, ^3J = 7.5 Hz, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 1H, 4'-H), 7.28 (dd, ^3J = 7.3 Hz, ^4J = 1.5 Hz, 1H, 6'-H), 7.06 (ddd, ^3J = 7.4 Hz, ^3J = 7.4 Hz, ^4J = 0.8 Hz, 1H, 5'-H), 7.01 (br d, ^3J = 8.3 Hz, 1H, 3'-H), 6.73 (s, 1H, 6-H), 6.44 (br, 2H, NH_2), 6.18 (s, 1H, 3-H), 3.91 (s, 3H, 4-OCH_3), 3.81 (s, 3H, 5-OCH_3), 3.60 ppm (s, 3H, 2'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.66 (C=O), 156.40 (C-2'), 156.06 (C-4), 148.84 (C-5), 140.10 (C-2), 130.84 (C-4'), 130.8 (C-1'), 128.79 (C-6'), 120.70 (C-5'), 117.01 (C-6), 111.50 (C-3'), 111.14 (C-1), 99.07 (C-3), 56.83 (2'-OCH_3), 56.11 (4-OCH_3), 55.91 ppm (5-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 287 (100) [M^+], 272 (50), 240 (15), 212 (6), 164 (24), 136 (10), 77 (9).

HRMS (EI, M^+): calcd for $C_{16}H_{17}NO_4$: 287.1153; found: 287.1161.

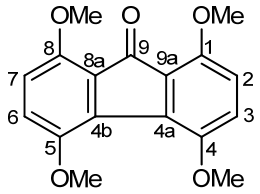
Elemental analysis (%) calcd for $C_{16}H_{17}NO_4$: C 66.88, H 5.97, N 4.88; found: C 67.30, H 5.71, N 5.09.

6. Synthesis of the methoxy-substituted fluoren-9-ones 236a-e

6.1 General procedure for the synthesis of the methoxy-substituted fluoren-9-ones 236[1c]

A solution of 18 mmol (2-amino-3,4,5,6-tetraalkoxyphenyl)(2',5'dialkoxyphenyl)methanone **235** in 30 mL glacial acetic acid was prepared. 5.4 mL (4.62 g, 18 mmol) *n*-amylnitrite were added at 0 °C and the resulting reaction mixture was stirred for 1 h at room temperature. A solution of 2.38 g (21.6 mmol) hydroquinone in 40 mL acetone was added dropwise and the reaction mixture was stirred for 2-3 h at room temperature. Subsequently, the reaction mixture was poured into 400 mL water, neutralized with 80 mL 10 % sodium hydroxide solution and extracted with dichloromethane (4 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) and brine (2 × 50 mL) and dried over anhydrous magnesium sulfate. The volatiles were removed in vacuo and the remaining viscous black crude product was purified by column chromatography.

6.2 1,4,5,8-Tetramethoxyfluoren-9-one (236a)[125]



236a

According to the general procedure 5.71 g (18 mmol) (2-amino-3,6-dimethoxyphenyl)(2',5'-dimethoxyphenyl)methanone (**235a**) were treated with 5.4 mL (4.62 g, 18 mmol) *n*-amylnitrite and 2.38 g (21.6 mmol) hydroquinone. After column chromatography (SiO_2; petroleum ether/EtOAc = 1:1) the title compound **236a** was isolated as yellow orange crystals.

Yield: 4.38 g (81 %).

M.p. = 133 °C (ref.[125] 235 °C).

$\mathbf{R_f}$ = 0.29 (SiO_2; CH_2Cl_2/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 2939, 2836 (CH aliph.), 1692 (C=O), 1587, 1577, 1493 (C=C arom.), 1464, 1438 (CH_3), 1265, 1220, 1175 cm^{-1} (C-O).

UV/VIS (MeCN): λ_{max} (log ε) = 443 (3.83), 360 (3.53), 245 (3.82), 214 nm (3.80).

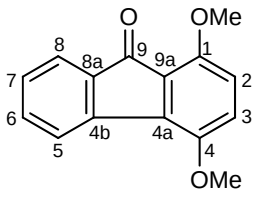
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, ^3J = 8.9 Hz, 2H, 3-H and 6-H), 6.86 (d, ^3J = 8.9 Hz, 2H, 2-H and 7-H), 3.96 (s, 6H, 4-OCH_3 and 5-OCH_3), 3.91 ppm (s, 6H, 1-OCH_3 and 8-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.92 (C=O), 153.66 (C-4 and C-5), 149.34 (C-1 and C-8), 131.77 (C-4a and C-4b), 123.98 (C-3 and C-6'), 121.99 (C-8a and C-9a), 115.34 (C-2 and C-7), 58.82 (4-OCH_3 and 5-OCH_3), 56.75 ppm (1-OCH_3 and 8-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 300 (60) [M^+], 285 (100) [M^+-CH_3], 242 (16), 227 (10), 71 (20).

HRMS (EI, M^+): calcd for $C_{17}H_{16}O_5$: 300.0993; found: 300.0996.

6.3 1,4-Dimethoxyfluoren-9-one (236b)[24]



236b

According to the general procedure 4.63 g (18 mmol) (2-aminophenyl)(2',5'-dimethoxyphenyl)methanone (**235b**) were treated with 5.4 mL (4.62 g, 18 mmol) *n*-

amylnitrite and 2.38 g (21.6 mmol) hydroquinone. After column chromatography (SiO_2; cyclohexane/EtOAc = 3:1) the title compound **236b** was isolated as yellow orange crystals.

Yield: 3.20 g (74 %).

M.p. = 170 °C (ref.[24] 150 °C).

$\mathbf{R}_f$ = 0.26 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3012 (CH arom.), 2930, 2839 (CH aliph.), 1698 (C=O), 1584, 1499, (C=C arom.), 1453, 1437 (CH_3), 1263, 1177 and 1055 (C-O), 950, 801, 748 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 433 (2.95), 373 (2.96), 250 (4.15), 244 nm (4.03).

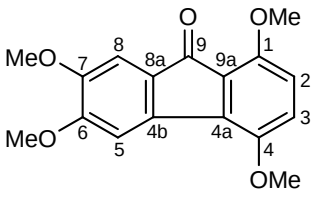
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, ^3J = 7.8 Hz , 1H, 5-H), 7.62 (d, ^3J = 7.2 Hz, 1H, 8-H), 7.42 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1H, 6 -H), 7.21 (dd, ^3J = 7.4 Hz, ^4J = 0.8 Hz , 1H, 7-H), 7.02 (d, ^3J = 9.0 Hz, 1H, 3-H), 6.78 (d, ^3J = 9.0 Hz, 1H, 2-H), 3.96 ppm (s, 6H, 1-OCH_3, 4-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.39 (C=O), 152.76 (C-4), 149.89 (C-1), 142.75 (C-4b), 136.80 (C-4a), 134.37 (C-8a), 134.22 (C-6), 132.62 (C-9a), 128.51 (C-7), 124.55 (C-5), 123.95 (C-8), 120.55 (C-3), 114.38 (C-2), 56.49 (4-OCH_3), 56.31 ppm (1-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 240 (100) [M^+], 211 (85) [M^+-CHO], 197 (37), 169 (30), 139 (17), 77 (14).

HRMS (EI, M^+): calcd for $C_{15}H_{12}O_3$: 240.0783; found: 240.0803.

6.4 1,4,6,7-Tetramethoxyfluoren-9-one (236c)



236c

According to the general procedure 5.71 g (18 mmol) (2-amino-4,5-dimethoxyphenyl)(2',5'-dimethoxyphenyl)methanone (**235c**) were treated with 5.4 mL (4.62 g, 18 mmol) *n*-

amylnitrite and 2.38 g (21.6 mmol) hydroquinone. After column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) the title compound **236c** was isolated as yellow orange crystals.

Yield: 4.48 g (83 %).

M.p. = 135 °C.

$\mathbf{R_f}$ = 0.42 (SiO_2; cyclohexane/EtOAc = 1:2).

IR (ATR): $\tilde{\nu}$ = 2947, 2825 (CH aliph.), 1694 (C=O), 1583, 1488, 1475 (C=C arom.), 1430, 1366 (CH_3), 1255, 1209, 1178, 1112 (C-O), 999, 796, 757, 700 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 487 (2.96), 325 (2.84), 312 (2.89), 279 (3.73), 264 nm (3.80).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 1H, 5-H), 7.16 (s, 1H, 8-H), 6.96 (d, ^3J = 9.1 Hz, 1H, 3-H), 6.71 (d, ^3J = 9.1 Hz, 1H, 2-H), 3.98 (s, 3H, 6-OCH_3), 3.91 ppm (s, 9H, 1-OCH_3, 4-OCH_3, 7-OCH_3).

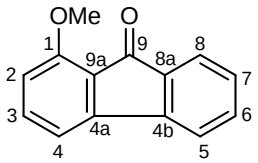
^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.72 (C=O), 153.94 (C-6), 152.43 (C-4), 149.31 (C-1), 149.01 (C-7), 134.66 (C-8a), 131.95 (C-9a), 126.95 (C-4b), 121 59 (C-4a), 120.36 (C-3), 113.98 (C-2), 107 80 (C-5), 107.06 (C-8), 56.50 (6-OCH_3), 56.46 (1-OCH_3, 7-OCH_3), 56.32 ppm (4-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 300 (100) [M^+], 269 (35) [M^+-OCH_3], 242 (14), 150 (7).

HRMS (EI, M^+): calcd for $C_{17}H_{16}O_5$: 300.0993; found: 300.0960.

Elemental analysis (%) calcd for $C_{17}H_{16}O_5$: C 67.98, H 5.37; found: C 67.86, H 5.08.

6.5 1-Methoxyfluoren-9-one (236d)[36]



236d

According to the general procedure 4.09 g (18 mmol) (2-aminophenyl)(2'-methoxyphenyl)methanone (**235d**) were treated with 5.4 mL (4.62 g, 18 mmol) *n*-amylnitrite and 2.38 g (21.6 mmol) hydroquinone. After column chromatography (SiO_2; cyclohexane/CH_2Cl_2 = 1:1) the title compound **236d** was isolated as yellow crystals.

Yield: 2.72 g (72 %).

M.p. = 133 °C (ref.[36] 139 °C).

$\mathbf{R}_f$ = 0.33 (SiO_2; cyclohexane/EtOAc = 8:1).

IR (ATR): $\tilde{\nu}$ = 3058 (CH arom.), 2947, 2838 (CH aliph.), 1660 (C=O), 1597, 1580, 1486 (C=C arom.), 1449, 1435 (CH_3), 1293, 1241, 1021 (C-O), 923, 751, 699 cm^{-1}.

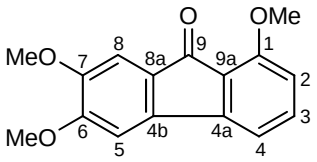
UV/VIS (MeCN) λ_{max} (log ε) = 249 (3.89), 203 nm (4.15).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, ^3J = 7.5 Hz, 1H, 8-H), 7.58 (dd, ^3J = 7.2 Hz, ^3J = 7.3 Hz, 1H, 3-H), 7.44-7.53 (m, 2H, 5-H, 6-H), 7.40 (dd, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, 7-H), 7.09 (t, ^3J = 7.5 Hz, 1H, 4-H), 7.03 (dd, ^3J = 8.5 Hz, ^4J = 1.3 Hz, 1H, 2-H), 3.76 ppm (s, 3H, 1-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.74 (C=O), 157.62 (C-1), 138.09 (C-4a), 133.18 (C-4b), 132.14 (C-3), 130.09 (C-8), 130.08 (C-7), 129.84 (C-8a), 129.13 (C-9a), 128.48 (C-5), 120.76 (C-2), 111.73 (C-4), 55.87 ppm (1-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 212 (87) [M^{+2}], 195 (66), 194 (33), 136 (15), 135 (100) [M^{+2}-C_6H_5], 105 (73), 77 (90), 51 (40).

6.6 1,6,7-Trimethoxyfluoren-9-one (236e)



236e

According to the general procedure 5.17 g (18 mmol) (2-amino-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (**235e**) were treated with 5.4 mL (4.62 g, 18 mmol) *n*-amylnitrite and 2.38 g (21.6 mmol) hydroquinone. After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **236e** was isolated as yellow crystals.

Yield: 4.18 g (86 %).

M.p. = 177 °C.

$\mathbf{R_f}$ = 0.49 (SiO_2; cyclohexane/EtOAc = 2:1).

IR (ATR): $\tilde{\nu}$ = 3003 (CH arom.), 2932, 2825 (CH aliph.), 1694 (C=O), 1589, 1499, 1406 (C=C arom.), 1474, 1372 (CH_3), 1264, 1241, 1212, 1094 and 1025 (C-O), 992, 795, 762, 695 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 365 (3.50), 316 (3.76), 304 (3.77), 281 (4.20), 260 (4.20), 213 nm (4.18).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (dd, ^3J = 7.6 Hz, ^3J = 8.1 Hz, 1H, 3-H), 7.16 (s, 1H, 8-H), 6.96 (s, 1H, 5-H), 6.95 (d, ^3J = 6.9 Hz, 1H, 4-H), 6.75 (d, ^3J = 8.5 Hz, 1H, 2-H), 3.98 (s, 3H, 6-OCH_3), 3.95 (s, 3H, 7-OCH_3), 3.91 ppm (s, 3H, 1-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.69 (C=O), 158.11 (C-1), 154.19 (C-6), 150.16 (C-7), 146.43 (C-4a), 138.13 (C-4b), 136.62 (C-3), 127.52 (C-8a), 120.44 (C-9a), 112.85 (C-2), 112.29 (C-4), 107.11 (C-8), 103.67 (C-5), 56.58 (6-OCH_3), 56.54 (7-OCH_3), 56.15 ppm (1-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 270 (100) [M^+], 255 (16), 239 (36) [M^+-OCH_3], 227 (12), 212 (14), 184 (8), 126 (10).

HRMS (EI, M^+): calcd for $C_{16}H_{14}O_4$: 270.0888; found: 270.2917.

Elemental analysis (%) calcd for $C_{16}H_{14}O_4$: C 71.09, H 5.22; found: C 71.36, H 5.44.

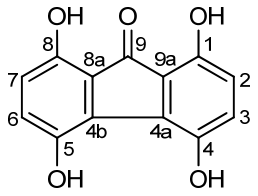
7. Synthesis of the hydroxyl-substituted fluoren-9-ones 242a-e

7.1 General procedure for the deprotection of the methoxy-substituted fluoren-9-ones 236[101]

1.33 mL (1.33 mmol) 1M boron tribromide in dichloromethane was added dropwise to a solution of 0.67 mmol of the methoxy-substituted fluoren-9-one **236** in 15 mL dichloromethane at – 78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. After quenching with 100 mL ice-cold water at 0 °C the precipitate was filtered. The filtrate was extracted with *tert*-butylmethyl ether (4 × 50 mL). The combined etheral extracts were washed with brine (2 × 50 mL) and dried over anhydrous magnesium

sulfate. The volatiles were removed in vacuo and the residue was purified by flash chromatography.

7.2 1,4,5,8-Tetrahydroxyfluoren-9-one (242a)



242a

According to the general procedure 200 mg (0.67 mmol) 1,4,5,8-tetramethoxyfluoren-9-one (**236a**) were treated with 1.33 mL (1.33 mmol) boron tribromide in dichloromethane. After column chromatography (SiO_2; cyclohexane/EtOAc = 1:3) the title compound **242a** was isolated as dark red crystals.

Yield: 135 mg (80 %).

M.p. = 238 °C.

$\mathbf{R_f}$ = 0.62 (SiO_2; TBME/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3300-2980 (OH, broad), 1659 (C=O), 1601, 1492, 1449 (C=C arom.), 1259, 1133, 1015 cm^{-1} (C-O).

UV/VIS (MeCN): λ_{max} (log ε) = 474 (3.22), 364 (2.95), 243 (3.98), 217 nm (3.72).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.69 (s, 2H, 1-OH and 8-OH), 9.62 (s, 2H, 4-OH and 5-OH), 6.89 (d, ^3J = 8.9 Hz, 2H, 3-H and 6-H), 6.68 ppm (d, ^3J = 8.9 Hz, 2H, 2-H and 7-H).

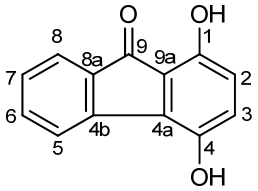
^{1}H NMR (300 MHz, $CDCl_3$, H/D-exchange): δ = 6.89 (d, ^3J = 8.9 Hz, 2H, 3-H and 6-H), 6.68 ppm (d, ^3J = 8.9 Hz, 2H, 2-H and 7-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.16 (C=O), 151.31 (C-1 and C-8), 143.75 (C-4 and C-5), 126.28 (C-3 and C-6), 126.01 (C-4a and C-4b), 120.56 (C-2 and C-7), 118.23 ppm (C-8a and C-9a).

MS (EI, 70 eV): *m/z* (%) = 244 (20) [M^+], 222 (75), 177 (18), 150 (15), 28 (100) [M^+-$C_{12}H_8O_4$].

HRMS (EI, M^+): calcd for $C_{13}H_8O_5$: 244.0369; found: 244.0331.

7.3 1,4-Dihydroxyfluoren-9-one (242b)[100]



242b

According to the general procedure 161 mg (0.67 mmol) 1,4-dimethoxyfluoren-9-one (**236b**) were treated with 1.33 mL (1.33 mmol) boron tribromide in dichloromethane. After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **242b** was isolated as dark red crystals.

Yield: 97 mg (68 %).

M.p. = 268 °C (ref.[100] 264°C).

$\mathbf{R_f}$ = 0.29 (SiO_2; cyclohexane/ EtOAc = 2:1).

IR (ATR): $\tilde{\nu}$ = 3300-3000 (OH, broad), 1673 (C=O), 1595 and 1485 (C=C arom.), 1380, 1282, 1251 and 1177 (C-O), 988, 873, 737 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 442 (2.99), 368 (2.96), 250 nm (3.19).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.83 (s, 1H, 4-OH), 9.79 (s, 1H, 1-OH), 7.82 (d, ^3J = 7.7 Hz, 1H, 5-H), 7.50-7.55 (m, 2H, 7-H, 8-H), 7.28 (dd, ^3J = 7.3 Hz, 1H, 6-H), 6.95 (d, ^3J = 8.8 Hz, 1H, 3-H), 6.68 ppm (d, ^3J = 8.9 Hz,1H, 2-H).

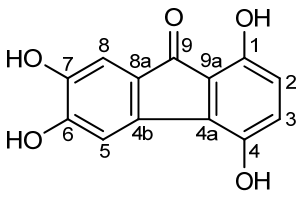
^{1}H NMR (300 MHz, $CDCl_3$, H/D-exchange): δ = 7.82 (d, ^3J = 7.7 Hz, 1H, 5-H), 7.50-7.55 (m, 2H, 7-H, 8-H), 7.28 (dd, ^3J = 7.3 Hz, 1H, 6-H), 6.95 (d, ^3J = 8.8 Hz, 1H, 3-H), 6.68 ppm (d, ^3J = 8.9 Hz, 1H, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.37 (C=O), 150.67 (C-1), 146.95 (C-4), 143.47 (C-8a), 135.03 (C-8), 134.18 (C-4b), 128.36 (C-6), 127.37 (C-4a), 127.24 (C-3), 124.37 (C-5), 123.72 (C-7), 121.08 (C-2), 118.55 ppm (C-9a).

MS (EI, 70 eV): *m/z* (%) = 212 (100) [M^+], 184 (13), 183 (7), 128 (11), 59 (10).

HRMS (EI, M^+): calcd for $C_{13}H_8O_3$: 212.0471; found: 212.0464.

7.4 1,4,6,7-Tetrahydroxyfluoren-9-one (242c)



242c

According to the general procedure 200 mg (0.67 mmol) 1,4,6,7-tetramethoxyfluoren-9-one (**236c**) were treated with 1.33 mL (1.33 mmol) boron tribromide in dichloromethane. After column chromatography (SiO_2; cyclohexane/EtOAc = 2:3) the title compound **242c** was isolated as dark red crystals.

Yield: 140 mg (83 %).

M.p. = 270 °C (dec.).

$\mathbf{R_f}$ = 0.25 (SiO_2; cyclohexane/EtOAc = 2:3).

IR (ATR): $\tilde{\nu}$ = 3350-2900 (OH, broad), 1648 (C=O), 1600, 1579, 1480 (C=C arom.), 1277, 1174, 1148 (C-O), 840, 782 and 694 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 474 (3.22), 364 (2.95), 243 (3.98), 217 nm (3.72).

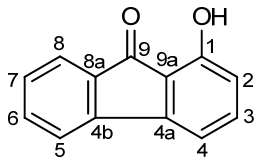
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.88 (s, 1H, 6-OH), 9.53 (s, 1H, 4-OH), 9.33 (s, 1H, 1-OH), 9.28 (s, 1H, 7-OH), 7.23 (s, 1H, 5-H), 6.88 (s, 1H, 8-H), 6.84 (d, ^3J = 8.8 Hz, 1H, 3-H), 6.51 ppm (d, ^3J = 8.9 Hz, 1H, 2-H).

^{1}H NMR (300 MHz, $CDCl_3$): H/D-exchange δ = 7.23 (s, 1H, 5-H), 6.88 (s, 1H, 8-H), 6.84 (d, ^3J = 8.8 Hz, 1H, 3-H), 6.51 ppm (d, ^3J = 8.9 Hz, 1H, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.28 (C=O), 151.78 (C-7), 149.90 (C-1), 145.64 (C-4), 145.47 (C-6), 137.11 (C-4b), 127.49 (C-4a), 126.54 (C-3), 125.91 (C-8a), 119.65 (C-2), 119.18 (C-9a), 112.23 (C-5), 111.44 ppm (C-8).

MS (EI, 70 eV): *m/z* (%) = 244 (100) [M^+], 216 (9), 170 (6), 99 (5).

7.5 1-Hydroxyfluoren-9-one (242d)[36]



242d

According to the general procedure 141 mg (0.67 mmol) 1-methoxyfluoren-9-one (**236d**) was treated with 1.33 mL (1.33 mmol) boron tribromide in dichloromethane. After column chromatography (SiO_2; cyclohexane/CH_2Cl_2 = 4:3) the title compound **242d** was isolated as orange crystals.

Yield: 97 mg (60 %).

M.p. = 110 °C (ref.[36] 115°C).

$\mathbf{R_f}$ = 0.39 (SiO_2; cyclohexane/CH_2Cl_2 = 1:1).

IR (ATR): $\tilde{\nu}$ = 3358 (OH), 1684 (C=O), 1595, 1468, 1437 (C=C arom.), 1283, 1161, 1131, 1037 (C-O), 933, 886 and 755 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 352 (3.04), 250 (4.12), 205 nm (3.81).

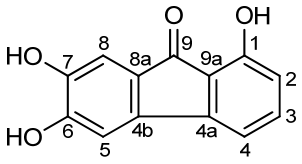
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (br s, 1H, 1-OH), 7.63 (d, ^3J = 7.3 Hz, 1H, 8-H), 7.49 (overlapped, ^3J = 5.9 Hz, 1H, 5-H), 7.48 (overlapped, ^3J = 7.1 Hz, 1H, 6-H), 7.36 (dd, ^3J = 7.9 Hz, 1H, 3-H), 7.30 (dt, ^3J = 7.0 Hz, ^4J = 1.9 Hz, 1H, 7-H), 7.03 (d, ^3J = 7.2 Hz, 1H, 2-H), 6.76 ppm (d, ^3J = 8.5 Hz, 1H, 4-H).

^{1}H NMR (300 MHz, $CDCl_3$, H/D-exchange): δ = 7.63 (d, ^3J = 7.3 Hz, 1H, 8-H), 7.49 (overlapped, ^3J = 5.9 Hz, 1H, 5-H), 7.48 (overlapped, ^3J = 7.1 Hz, 1H, 6-H), 7.36 (t, ^3J = 7.9 Hz, ^3J = 7.9 Hz, 1H, 3-H), 7.30 (dt, ^3J = 7.0 Hz, ^4J = 1.9 Hz, 1H, 7-H), 7.03 (d, ^3J = 7.2 Hz, 1H, 2-H), 6.76 ppm (d, ^3J = 8.5 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.38 (C=O), 157.41 (C-1), 144.18 (C-8a), 143.88 (C-4a), 137.51 (C-3), 134.70 (C-6), 134.27 (C-4b), 129.13 (C-7), 124.10 (C-8), 121.05 (C-5), 118.22 (C-4), 117.45 (C-9a), 112.85 ppm (C-2).

MS (EI, 70 eV): *m/z* (%) = 196 (40) [M^+], 168 (26) [M^+-CO], 139 (17), 44 (10), 32 (24), 28 (100) [M^+-$C_{12}H_8O$].

7.6 1,6,7-Trihydroxyfluoren-9-one (242e)



242e

According to the general procedure 181 mg (0.67 mmol) 1,6,7-trimethoxyfluoren-9-one (**236e**) were reacted with 1.33 mL (1.33 mmol) boron tribromide in dichloromethane. After column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) the title compound **242e** was isolated as dark red crystals.

Yield: 128 mg (84 %).

M.p. = 282 °C.

$\mathbf{R}_f$ = 0.30 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3446, 3251 (OH, broad), 1665 (C=O), 1600, 1595, 1469 (C=C arom.), 1303, 1274, 1140, 1067, 1035 (C-O), 875, 806, 774, 744 and 693 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 364 (2.56), 316 (2.50), 304 (2.48), 271 (2.43), 211 nm (2.32).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.05-9.71 (br, 3H, 1-OH, 6-OH and 7-OH), 7.26 (t, ^3J = 7.8 Hz, 1H, 3-H), 7.03 (s, 1H, 5-H), 6.94 (d, ^3J = 7.1 Hz, 1H, 4-H), 6.90 (s, 1H, 8-H), 6.65 ppm (d, ^3J = 8.6 Hz, 1H, 2-H).

^{1}H NMR (300 MHz, $CDCl_3$, H/D-exchange): δ = 7.26 (t, ^3J = 7.8 Hz, 1H, 3-H), 7.03 (s, 1H, 5-H), 6.94 (d, ^3J = 7.1 Hz, 1H, 4-H), 6.90 (s, 1H, 8-H), 6.65 ppm (d, ^3J = 8.6 Hz, 1H, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.82 (C=O), 156.41 (C-1), 151.99 (C-6), 146.75 (C-7), 145.90 (C-4a), 137.14 (C-4b), 136.81 (C-3), 126.49 (C-8a), 118.65 (C-9a), 118.54 (C-2), 111.67 (C-4), 111.25 (C-8), 109.13 ppm (C-5).

MS (EI, 70 eV): *m/z* (%) = 228 (100) [M^+], 200 (40) [M^+-CO], 171 (8), 154 (7), 126 (9), 100 (11).

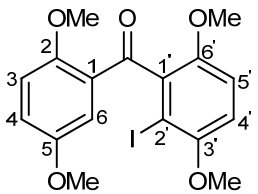
HRMS (EI, M^+): calcd for $C_{13}H_8O_4$: 228.0420; found: 228 .0420.

8. Synthesis of (2,5-dialkoxyphenyl)(2'-iodo-3',4'-5',6'-tetralkoxyphenyl)methanones 243a-e

8.1 General procedure for the synthesis of the (2,5-dialkoxyphenyl)(2'-iodo-3',4'-5',6'-tetraalkoxyphenyl)methanones 243

1.46 mL (1.26 g, 10.73 mmol) *n*-amylnitrite was added dropwise to a solution of 4.73 mmol (2-amino-3,4,5,6-tetraalkoxyphenyl)(2',5'-dialkoxyphenyl)methanone **235** in 50 mL glacial acetic acid and the resulting reaction mixture was stirred for 1 h at 0 °C. A solution of 1.78 g (10.70 mmol) potassium iodide in 10 mL water was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into 300 mL ice-cold water, neutralized with 80 mL 10 % sodium hydroxide solution and extracted with dichloromethane (4 × 80 mL). The combined organic phases were washed with water (2 × 100 mL) and brine (2 × 50 mL) and dried over anhydrous magnesium sulfate. The volatiles were removed in vacuo and the crude product was purified by column chromatography.

8.2 (2,5-Dimethoxyphenyl)(2'-iodo-3',6'-dimethoxyphenyl)methanone (243a)



243a

According to the general procedure 1.50 g (4.73 mmol) (2-amino-3,6-dimethoxyphenyl)(2',5'-dimethoxyphenyl)methanone (**235a**) were treated with 1.46 mL (1.26 g, 10.73 mmol) *n*-amylnitrite and 1.78 g (10.70 mmol) potassium iodide. After column chromatography (SiO_2; cyclohexane/EtOAc = 3:1) the title compound **243a** was isolated as pale yellow crystals.

Yield: 1.34 g (66 %).

M.p. = 195 °C.

$\mathbf{R_f}$ = 0.60 (SiO_2; cyclohexane/ EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 2918, 2800 (CH aliph.), 1649 (C=O), 1496, 1471 and 1416 (C=C arom.), 1283, 1252, 1217 and 1024 (C-O), 993, 832, 799, 717 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 354 (3.09), 260 (3.34), 226 nm (3.77).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, ^4J = 3.2 Hz , 1H, 6-H), 7.09 (dd, ^3J = 8.9 Hz, ^4J = 3.2 Hz, 1H, 4-H), 6.89 (d, ^3J = 8.9 Hz, 1H, 3-H), 6.89 (d, ^3J = 8.9 Hz, 1H, 5'-H), 6.79 (d, ^3J = 8.9 Hz, 1H, 4'-H), 3.86 (s, 3H, 6'-OCH_3), 3.81 (s, 3H, 2-OCH_3), 3.68 (s, 3H, 3'-OCH_3), 3.59 ppm (s, 3H, 5-OCH_3).

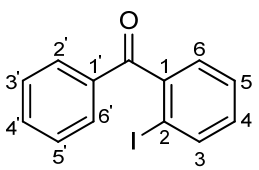
^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.20 (C=O), 155.12 (C-5), 153.78 (C-2), 152.66 (C-6'), 151.13 (C-3'), 139.69 (C-1'), 126.16 (C-1), 122.11 (C-4), 115.57 (C-6), 114.77 (C-5'), 112.21 (C-3), 110.86 (C-4'), 84.67 (C-2'), 57.41 (6'-OCH_3), 57.05 (3'-OCH_3), 57.02 (5-OCH_3), 56.10 ppm (2-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 428 (100) [M^+], 301 (13) [M^+-I], 209 (35), 165 (45), 151 (10).

HRMS (EI, M^+): calcd for $C_{17}H_{17}IO_5$: 428.0071; found: 428.0073.

Elemental analysis (%) calcd for $C_{17}H_{17}IO_5$: C 47.66, H 4.00; found: C 48.09, H 3.90.

8.3 2-Iodobenzophenone (243b)[126]



243b

According to the general procedure 1.50 g (4.73 mmol) 2-aminobenzophenone (**235b**) were treated with 1.46 mL (1.26g, 10.73 mmol) *n*-amylnitrite and 1.78 g (10.70 mmol) potassium iodide. After column chromatography (SiO_2; cyclohexane/EtOAc = 32:1) the title compound **243b** was isolated as a pale yellow liquid.

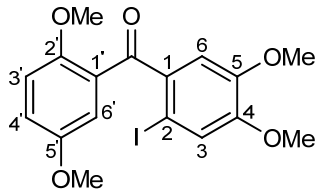
Yield: 1.32 g (73 %).

$\mathbf{R_f}$ = 0.40 (SiO_2; PE/EtOAc = 20:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, ^3J = 8.0 Hz, 1H, 3-H), 7.81 (d, ^3J = 7.5 Hz, 2H, 2'-H, 6'-H), 7.61 (t, ^3J = 7.5 Hz, 1H, 4'-H), 7.48 (d, ^3J = 7.7 Hz, 2H, 3'-H, 5'-H), 7.44 (dd, ^3J = 7.2 Hz, ^4J = 1.9 Hz, 1H, 4-H), 7.30 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, 6-H), 7.19 ppm (dt, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.51 (C=O), 144.63 (C-1'), 139.99 (C-3), 135.88 (C-1), 133.99 (C-5), 131.40 (C-4), 130.76 (C-3' or C-5'), 128.94 (C-2' or C-6'), 128.77 (C-6), 128.07 (C-5'), 92.49 ppm (C-2).

8.4 (2',5'-Dimethoxyphenyl)(2-iodo-4,5-dimethoxyphenyl)methanone (243c)



243c

According to the general procedure 1.50 g (4.73 mmol) (2-amino-4,5-dimethoxyphenyl)(2',5'-dimethoxyphenyl)methanone (**235c**) were treated with 1.46 mL (1.26 g, 10.73 mmol) *n*-amylnitrite and 1.78 g (10.70 mmol) potassium iodide. After column chromatography (SiO_2; cyclohexane/EtOAc = 3:1) the title compound **243c** was isolated as pale yellow crystals.

Yield: 1.32 g (65 %).

M.p. = 107 °C.

$\mathbf{R_f}$ = 0.45 (SiO_2; cyclohexane/EtOAc = 2:1).

IR (ATR): $\tilde{\nu}$ = 2960, 2820 (CH aliph.), 1661 (C=O), 1585, 1493 and 1461 (C=C arom.), 1420, 1336 (CH_3), 1282, 1261, 1171, 1204 and 1019 (C-O), 792, 776, 728 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 327 (3.15), 260 nm (3.34).

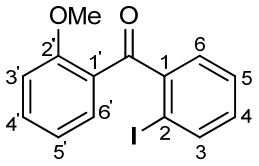
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (s, 1H, 3-H), 7.12 (d, ^4J = 3.1 Hz, 1H, 6'-H), 7.06 (dd, ^3J = 8.9 Hz, ^4J = 3.1 Hz, 1H, 4'-H), 6.94 (s, 1H, 6-H), 6.88 (d, ^3J = 8.9 Hz, 1H, 3'-H), 3.92 (s, 3H, 5-OCH_3), 3.81 (s, 3H, 4-OCH_3), 3.80 (s, 3H, 5'-OCH_3), 3.64 ppm (s, 3H, 2'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.82 (C=O), 153.86 (C-5'), 153.62 (C-2'), 151.16 (C-5), 149. 00 (C-4), 137.36 (C-1), 128.01 (C-1'), 122.79 (C-3), 120.25 (C-4'), 115.84 (C-6'), 113.93 (C-3'), 113.46 (C-6), 82.52 (C-2), 56.89 (2'-OCH_3), 56.52 (5-OCH_3), 56.31 (4-OCH_3), 56.16 ppm (5'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 428 (100) [M^+], 291 (28), 286 (83), 271 (16), 255 (10), 165 (25), 151 (17), 135 (9), 107 (6).

Elemental analysis (%) calcd for $C_{17}H_{17}IO_5$: C 47.66, H 4.00; found: C 47.75, H 3.84.

8.5 (2-Iodophenyl)(2'-methoxyphenyl)methanone (243d)



243d

According to the general procedure 1.07 g (4.73 mmol) (2-aminophenyl)(2'-methoxyphenyl)methanone (**235d**) were treated with 1.46 mL (1.26 g, 10.73 mmol) *n*-amylnitrite and 1.78 g (10.70 mmol) potassium iodide. After column chromatography (SiO_2; cyclohexane/EtOAc = 8:1) the title compound **243d** was isolated as pale yellow crystals.

Yield: 1.10 g (69 %).

M.p. = 120 °C.

R_f = 0.45 (SiO_2; cyclohexane/EtOAc = 4:1).

IR (ATR): $\tilde{\nu}$ = 3058 (CH arom.), 2927, 2830 (CH aliph.), 1664 (C=O), 1638, 1595, 1481 (C=C arom.), 1455 (CH_3), 1301, 1239, 1154, 1015 (C-O), 929, 752 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 333 (3.08), 285 (2.88), 260 (3.43), 237 nm (3.85).

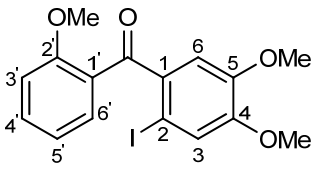
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, ^3J = 7.9 Hz, 1H, 6-H), 7.64 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, 3-H), 7.52 (dt, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, 4-H), 7.37 (t, ^3J = 7.2 Hz, 1H, 5'-H), 7.30 (dd, ^3J = 7.6 Hz, ^4J = 1.8 Hz, 1H, 6'-H), 7.11 (dt, ^3J = 7.6 Hz, ^4J = 1.8 Hz, 1H, 5-H), 7.03 (t, ^3J = 7.5 Hz, 1H, 4'-H), 6.94 (d, ^3J = 8.4 Hz,1H, 3'-H), 3.66 ppm (s, 3H, 2'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.79 (C=O), 159.69 (C-2'), 146.12 (C-1), 140.11 (C-3), 134.65 (C-4), 132.31 (C-6), 131.24 (C-5), 129 18 (C-4'), 127.02 (C-1'), 120.91 (C-6'), 118.27 (C-5'), 112.33 (C-3'), 92.26 (C-2), 56.06 ppm (2'-OMe).

MS (EI, 70 eV): *m/z* (%) = 338 (31) [M^+], 196 (100) [M^+-CH_3I], 32 (18).

HRMS (EI, M^+): calcd for $C_{14}H_{11}IO_2$: 337.9756; found: 337.9830.

8.6 (2-Iodo-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (243e)



243e

According to the general procedure 1.36 g (4.73 mmol) (2-amino-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (**235e**) were treated with 1.46 mL (1.26 g, 10.73 mmol) *n*-amylnitrite and 1.78 g (10.70 mmol) potassium iodide. After column chromatography (SiO_2; cyclohexane/EtOAc = 4:1) the title compound **243e** was isolated as pale yellow crystals.

Yield: 1.35 g (72 %).

M.p. = 81 °C.

R_f = 0.35 (SiO_2; cyclohexane/EtOAc = 3:1).

IR (ATR): $\tilde{\nu}$ = 2967, 2830 (CH aliph.), 1645 (C=O), 1584, 1488 and 1455 (C=C arom.), 1435, 1370 (CH_3), 1296, 1252, 1208, 1180, 1143 and 1021 (C-O), 990, 874, 851, 774 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 317 (3.53), 239 (4.03), 209 nm (4.24).

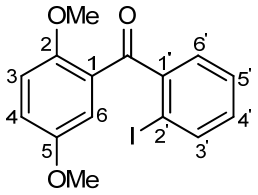
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55-7.47 (m, 2H, 5'-H, 6'-H), 7.30 (s, 1H, 3-H), 7.02 (t, ^3J = 7.5 Hz, 1H, 4'-H), 6.95 (d, ^3J = 7.2 Hz, 1H, 3'-H), 6.94 (s, 1H, 6-H), 3.91 (s, 3H, 4-OCH_3), 3.80 (s, 3H, 5-OCH_3), 3.72 ppm (s, 3H, 2'-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.09 (C=O), 59.27 (C-2'), 151.16 (C-4), 149.00 (C-5), 137.40 (C-1), 134.04 (C-5'), 132.04 (C-6'), 127.54 (C-1'), 122.81 (C-3), 120.87 (C-4'), 113.53 (C-6), 112.13 (C-3'), 82.67 (C-2), 56.52 (4-OCH_3), 56.31 (5-OCH_3), 56.14 ppm (2'-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 398 (100) [M^+], 290 (40), 271 (26), 256 (92), 240 (16), 151 (24), 135 (80), 92 (10), 77 (20).

HRMS (EI, M^+): calcd for $C_{16}H_{15}IO_4$: 397.9966; found: 398.0012.

8.7 (2,5-Dimethoxyphenyl)(2'-iodophenyl)methanone (243f)[24]



243f

890 mg (6.41 mmol) 1,4-dimethoxybenzene (**228**) were treated with 10 mL (14.90 g, 130.67 mmol) trifluoroactic acid, 5 mL (7.55 g, 35.95 mmol) trifluoroacetic anhydride and 1.50 g (6.41 mmol) 2-iodobenzoic acid (**244**) and the reaction mixture was refluxed for 12 h. After cooling to room temperature 100 g crushed ice were added, followed by 100 mL *tert*-butylmethyl ether. After phase separation the organic layer was washed with 25 mL saturated sodium hydrogencarbonate solution. The organic extract was washed with water (2 × 50 mL), brine (1 × 50 mL) and dried over anhydrous magnesium sulfate. After removal of the volatiles under reduced pressure the crude product was purified by recrystallization from cyclohexane to obtain the title compound **243f** as colourless crystals.

Yield: 2.32 g (98 %).

M.p. = 79 °C (ref.[24] 75°C).

$\mathbf{R}_f$ = 0.57 (SiO_2; cyclohexane/EtOAc = 3:1).

IR (ATR): $\tilde{\nu}$ = 2941, 2840 (CH aliph.), 1656 (C=O), 1577, 1491, 1467 (C=C), 1417 (CH_3), 1287, 1216, 1017 (C-O), 880, 803, 750 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 348 (3.17), 229 (4.09), 207 nm (4.16).

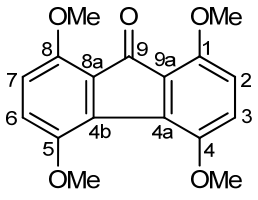
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, ^3J = 7.9 Hz, 1H, 3'-H), 7.37 (dt, ^3J = 7.3 Hz, ^4J = 1.8 Hz, 1H, 4-H), 7.29 (dd, ^3J = 7.6 Hz, ^4J = 1.76 Hz, 1H, 3-H), 7.24 (d, ^4J = 1.8 Hz, 1H, 6-H), 7.07-7.13 (m, 2H, 4'-H, 5'-H), 6.87 (d, ^3J = 9.1 Hz, 1H, 6'-H), 3.81 (s, 3H, 5-OCH_3), 3.56 ppm (s, 3H, 2-OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.53 (C=O), 154.17 (C-2), 153.88 (C-5), 146.25 (C-1'), 140.01 (C-3'), 131.17 (C-4'), 128.98 (C-3), 127.91 (C-4), 127.26 (C-1), 121.25 (C-5'), 115.55 (C-6), 114.21 (C-6'), 92.05 (C-2'), 56.77 (2-OCH_3), 56.16 ppm (5-OCH_3).

MS (EI, 70 eV): *m/z* (%) = 368 (100) [M^+], 230 (41), 226 (12), 165 (42), 151 (11), 76 (7).

9. Palladium-mediated cyclizations of the substituted 2-iodobenzophenones 243a-e

9.1 Synthesis of 1,4,5,8-tetramethoxyfluoren-9-one (236a)[125]



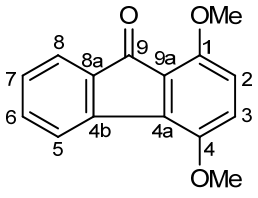
236a

Procedure A: A mixture of 100 mg (0.23 mmol) (2,5-dimethoxyphenyl)(2'-iodo-3',6'-dimethoxyphenyl)methanone (**243a**), 5 mg (0.02 mmol) $Pd(OAc)_2$ and 64 mg (0.47 mmol) anhydrous potassium carbonate was suspended in 10 mL dry *N*,*N*-dimethylacetamide and the reaction mixture was refluxed for 26 h under argon at 170 °C. After cooling to room temperature the mixture was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and 1 M hydrochloric acid (2 × 15 mL).

The organic phase was dried over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2; CH_2Cl_2/EtOAc = 1:1) to give 8 mg (10 %) 1,4,5,8-tetramethoxyfluoren-9-one (**236a**) as yellow crystals (Table 7, entry 4).

Procedure B: A mixture of 117 mg (0.27 mmol) (2,5-dimethoxyphenyl)(2'-iodo-3',6'-dimethoxyphenyl)methanone (**243a**), 77 mg (0.11 mmol) $PdCl_2(PPh_3)_2$ and 100 mg (1.2 mmol) anhydrous sodium acetate was dissolved in 10 mL dry *N*,*N*-dimethylacetamide. The reaction mixture was degassed for 2 h and then refluxed for 32 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/EtOAc = 1:1) to give 25 mg (31 %) 1,4,5,8-tetramethoxyfluoren-9-one (**236a**) as yellow crystals (Table 7, entry 12).

9.2 Synthesis of 1,4-dimethoxyfluoren-9-one (236b)[24]



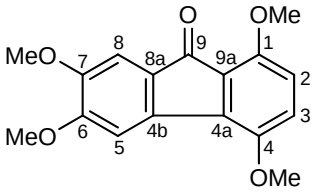
236b

A 111 mg (0.3 mmol) (2,5-dimethoxyphenyl)(2'-iodophenyl)methanone (**243f**) were reacted with 49 mg (0.07 mmol) $PdCl_2(PPh_3)_2$ and 100 mg (1.2 mmol) anhydrous sodium acetate in the presence of 10 mL dry *N*,*N*-dimethylacetamide. The reaction mixture was degassed for 2 h and then refluxed for 15 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with tert-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2;

cyclohexane/EtOAc = 7:3) to give 59 mg (82 %) 1,4-dimethoxyfluoren-9-one (**236b**) as yellow crystals (Table 8, entry 4).

B 111 mg (0.3 mmol) (2,5-dimethoxyphenyl)(2'-iodophenyl)methanone (**243f**) were reacted with 16 mg (0.070 mmol) $Pd(OAc)_2$ and 100 mg (1.2 mmol) anhydrous sodium acetate in the presence of 10 mL dry *N*,*N*-dimethylacetamide. The reaction mixture was degassed for 2 h and then refluxed for 15 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 7:3) to give 58 mg (81 %) 1,4-dimethoxyfluoren-9-one (**236b**) as yellow crystals (Table 8, entry 5).

9.3 Synthesis of 1,4,6,7-tetramethoxyfluoren-9-one (236c)

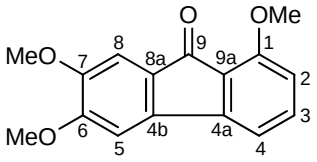


236c

A 117 mg (0.270 mmol) (2',5'-dimethoxyphenyl)(2-iodo-4,5-dimethoxyphenyl)methanone (**243c**) were reacted with 114 mg (0.109 mmol) $PdCl_2(PPh_3)_2$ and 100 mg (1.20 mmol) anhydrous sodium acetate in the presence of 10 mL dry *N,N*-dimethylacetamide. The reaction mixture was degassed for 2 h and then refluxed for 19 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) to give 46 mg (57 %) 1,4,6,7-tetramethoxyfluoren-9-one (**236c**) as yellow orange crystals (Table 9, entry 2).

B 117 mg (0.27 mmol) (2',5'-dimethoxyphenyl)(2-iodo-4,5-dimethoxyphenyl)methanone (**243c**) were reacted with 126 mg (0.11 mmol) $Pd(OAc)_2(PPh_3)_2$ and 100 mg (1.2 mmol) anhydrous sodium acetate in the presence of 10 mL dry *N*,*N*-dimethylacetamide. The reaction mixture was degassed for 2 h and then refluxed for 19 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) to give 42 mg (52 %) 1,4,6,7-tetramethoxyfluoren-9-one (**236c**) as yellow orange crystals (Table 9, entry 4).

9.4 Synthesis of 1,6,7-trimethoxyfluoren-9-one (236e)



236e

A 119 mg (0.3 mmol) (2-iodo-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (**243e**) were reacted with 126 mg (0.18 mmol) $PdCl_2(PPh_3)_2$ and 100 mg (1.2 mmol) anhydrous sodium acetate in the presence of 10 mL dry *N*,*N*-dimethylacetamide. The reaction mixture was degassed for 2 h and then refluxed for 19 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent removed in vacuo and the crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) to give 50 mg (62 %) 1,6,7-trimethoxyfluoren-9-one (**236e**) as yellow orange crystals (Table 10, entry 1).

B 119 mg (0.3 mmol) (2-iodo-4,5-dimethoxyphenyl)(2'-methoxyphenyl)methanone (**243e**) were reacted with 134 mg (0.18 mmol) $Pd(OAc)_2(PPh_3)_2$ and 100 mg (1.2 mmol) anhydrous sodium acetate in the presence of 10 mL dry *N*,*N*-dimethylacetamide. The reaction

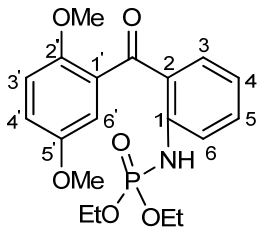
mixture was degassed for 2 h and then refluxed for 19 h under argon at 130 °C. After cooling to room temperature the mixture was extracted with *tert*-butylmethyl ether (3 × 50 mL). The combined etheral extracts were washed with water (2 × 50 mL) and 6 M hydrochloric acid (2 × 25 mL). The organic phase was dried over anhydrous magnesium sulfate, the solvent removed in vacuo and the crude product was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) to give 43 mg (53 %) 1,6,7-trimethoxyfluoren-9-one (**236e)** as yellow orange crystals (Table 10, entry 2).

10. Synthesis of the diethyl *N*-2-(2',5'-dialkoxybenzoyl)-3,4,5,6-tetraalkoxyphenylphosphoramidates 251b,c

10.1 General procedure for the synthesis of the diethyl *N*-2-(2',5'-dialkoxybenzoyl)-3,4,5,6-tetraalkoxyphenylphosphoramidates 251

A mixture of 1 mmol **234**, 6 mmol triethyl phosphite (**161**) and 3 mL dry toluene was sealed in a 10 mL septum reaction vial and irradiated with microwaves (Discover^{TM} by CEM, 2450 MHz, 300 W, 200 °C) for 30-35 min. After removal of triethyl phosphite and triethyl phosphate at reduced pressure (10^{-1} mbar) and temperatures between 41 and 52 °C the residue was diluted with 20 mL CH_2Cl_2 and washed with water (2 × 50 mL) and brine (3 × 20 mL). After drying over anhydrous magnesium sulfate and concentration in vacuo the crude product was purified by column chromatography over silica gel.

10.2 Diethyl *N*-2-(2',5'-dimethoxybenzoyl)phenylphosphoramidate (251b)



251b

According to the general procedure 287 mg (1 mmol) (2,5-dimethoxyphenyl)(2'-nitrophenyl)methanone (**234b**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**).

After column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) the title compound **251b** was isolated.

Yield: 231 mg (59 %).

M.p. = 70 °C.

$\mathbf{R}_f$ = 0.27 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3190 (NH), 2981, 2825 (CH aliph.), 1631 (C=O), 1605, 1578 (C=C), 1496, 1461 (CH_3), 1258 (C-O), 1215, 1021 (P=O), 957, 800 cm^{-1}.

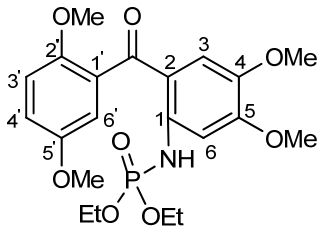
UV/VIS (MeCN): λ_{max} (log ε) = 339 (3.52), 264 (3.76), 225 nm (3.22).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.97 (d, $^2J_{P\text{-}H}$ = 11 Hz, 1H, NH), 7.52 (dd, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1H, 6-H), 7.45 (dd, ^3J = 7.0 Hz, ^4J = 1.1 Hz, 1H, 3-H), 7.38-7.43 (m, 1H, 5-H), 6.98 (dd, ^3J = 9.0 Hz, ^4J = 2.1 Hz, 1H, 4'-H), 6.90 (d, ^3J = 9.0 Hz, 1H, 3'-H), 6.84 (dd, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1H, 4-H), 6.80 (d, ^4J = 2.1 Hz, 1H, 6'-H), 3.77 (s, 3H, 5'-OCH_3), 3.68 (s, 3H, 2'-OCH_3), 4.13-4.27 (m, 4H, 2 × OCH_2), 1.36 ppm (t, ^3J = 7.2 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 197.42 (C=O), 151.10 (C-5'), 148.31 (C-2'), 141.87 (d, $^2J_{P\text{-}C}$ = 2.2 Hz, C-1), 132.75 (C-3), 132.71 (C-5), 127.57 (C-1'), 119.07 (d, $^3J_{P\text{-}C}$ = 8.8 Hz, C-2), 117.46 (C-4), 115.84 (d, $^3J_{P\text{-}C}$ = 2.9 Hz, C-6), 114.47 (C-4'), 111.57 (C-6'), 110.59 (C-3'), 60.96 (d, $^2J_{P\text{-}C}$ = 5.2 Hz, 2 × OCH_2), 54.02 (2'-OCH_3), 53.55 (5'-OCH_3), 13.87 ppm (d, $^3J_{P\text{-}C}$ = 6.5 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 393 (100) [M^+], 375 (74), 362 (73), 334 (55), 306 (37), 256 (30), 240 (41), 239 (76), 226 (71), 225 (26), 210 (23), 165 (34), 120 (33).

10.3 Diethyl-*N*-2-(2',5'-dimethoxybenzoyl)-4,5-dimethoxyphenylphosphoramidate (251c)



251c

According to the general procedure 347 mg (1 mmol) (4,5-dimethoxy-2-nitrophenyl)(2',5'-dimethoxyphenyl)methanone (**234c**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:3) the title compound **251c** was isolated.

Yield: 282 mg (62 %).

$\mathbf{R}_f$ = 0.52 (SiO_2; EtOAc).

IR (ATR): $\tilde{\nu}$ = 2982, 2830 (CH aliph.), 1618 (C=O), 1571 1519, 1494 (C=C), 1402, 1343 (CH_3), 1267 (C-O), 1011 (P=O), 962, 809 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 356 (3.51), 289 (3.55), 244 nm (3.89).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.30 (d, $^2J_{P-H}$ = 10.6 Hz, 1H, NH), 7.22 (s, 1H, 3-H), 7.01 (dd, ^3J = 9.0 Hz, ^4J = 2.9 Hz, 1H, 4'-H), 6.95 (d, ^3J = 8.9 Hz, 1H, 3'-H), 6.87 (br, 1H, 6-H), 6.85 (d, ^4J = 2.8 Hz, 1H, 6'-H), 3.98 (s, 3H, 5-OCH_3), 3.81 (s, 3H, 5'-OCH_3), 3.74 (s, 3H, 2'-OCH_3), 3.65 (s, 3H, 4-OCH_3), 4.18-4.25 (m, 4H, 2 × OCH_2), 1.40 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.87 (C=O), 155.88 (C-5), 153.72 (C-2'), 150.58 (C-5'), 142.46 (C-4), 141.65 (d, $^2J_{P-C}$ = 2.1 Hz, C-2), 130.38 (C-1'), 117.08 (C-6), 116.94 (C-4'), 114.06 (d, $^3J_{P-C}$ = 2.4 Hz, C-1), 113.92 (C-6'), 113.05 (C-3'), 101.26 (d, $^3J_{P-C}$ = 2.4 Hz, C-3), 63.55 ($^2J_{P-C}$ = 5.4 Hz, 2 × OCH_2), 56.60 (4-OCH_3), 6.58 (2'-OCH_3), 56.39 (5-OCH_3), 56.12 (5'-OCH_3), 16.49 ppm (d, $^3J_{P-C}$ = 6.7 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 453 (100) [M^+], 422 (20), 364 (7), 302 (30), 286 (18), 244 (5).

HRMS (EI, M^+): calcd for $C_{21}H_{28}NO_8P$: 453.1557; found: 453.1563.

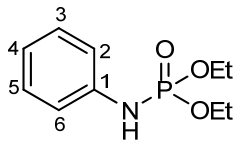
11. Synthesis of the diethyl *N*-arylphosphoramidates 256a-o

11.1 General procedure for the synthesis of the diethyl *N*-arylphosphoramidates 256 under microwave conditions

A mixture of 1 mmol **255**, 6 mmol triethyl phosphite (**161**) and 3 mL dry toluene was sealed in a 10 mL septum reaction vial and irradiated with microwaves (Discover™ by CEM, 2450 MHz, 300 W, 200 °C). After removal of triethyl phosphite (**161**) and triethyl phosphate (**260**)

at reduced pressure (10^{-1} mbar) and temperatures between 40 and 70 °C the residue was diluted with 30 mL CH_2Cl_2 and washed with water (2 × 50 mL) and brine (3 × 20 mL). After drying over anhydrous magnesium sulfate and concentration in vacuo the resulting residue was purified by column chromatography over silica gel.

11.2 Diethyl *N*-phenylphosphoramidate (256a)[127]



256a

According to the general procedure 123 mg (1 mmol) nitrobenzene (**255a**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) the title compound **256a** was isolated.

Yield: 179 mg (78 %).

M.p. = 93 °C (ref.[127] 94°C).

$\mathbf{R_f}$ = 0.36 (SiO_2; cyclohexane/EtOAc = 3:1).

IR (ATR): $\tilde{\nu}$ = 3198 (NH), 2983-2901 (CH aliph.), 1601, 1493 (C=C arom.), 1412 (CH_2), 1393 (CH_3), 1288 (C-O), 1218 (P=O), 755 cm^{-1}.

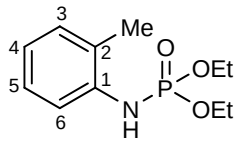
UV/VIS (MeCN): λ_{max} (log ε) = 274 (2.70), 229 nm (3.52).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, ^3J = 7.8 Hz, 2H, 3-H, 5-H), 7.04 (d, ^3J = 7.8 Hz, 2H, 2-H, 6-H), 6.98 (d, ^3J = 7.4 Hz, 1H, 4-H), 6.18 (d, $^2J_{P\text{-}H}$ = 9.1 Hz, 1H, NH), 4.08-4.25 (m, 4H, 2 × OCH_2), 1.35 ppm (t, ^3J = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.01 (C-1), 129.52 (C-3 and C-5), 121.79 (C-4), 117.54 (d, $^3J_{P\text{-}C}$ = 7.2 Hz, C-2 and C-6), 63.00 (d, $^2J_{P\text{-}C}$ = 5.1 Hz, 2 × OCH_2), 16.35 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 229 (75) [M^+], 201(36) [M^+-CH_2=CH_2], 173 (100) [M^+-2 × CH_2=CH_2], 155 (70), 120 (15), 93 (37), 65 (21).

11.3 Diethyl *N*-*o*-tolylphosphoramidate (256b)[89]



256b

According to the general procedure 137 mg (1 mmol) 2-methylnitrobenzene (**255b**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) the title compound **256b** was isolated.

Yield: 165 mg (68 %).

M.p. = 92 °C (ref.[89] 110°C).

$\mathbf{R}_f$ = 0.29 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3184 (NH), 2986-2900 (CH aliph.), 1584, 1500 (C=C arom.), 1420 (CH_2), 1391 (CH_3), 1287 (C-O), 1231 (P=O), 771 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 349 (1.71), 275 nm (3.11).

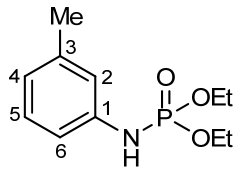
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, ^3J = 7.8 Hz, 1H, 6-H), 7.14 (t, ^3J = 7.6 Hz, 1H, 4-H), 7.12 (d, ^3J = 7.6 Hz, 1H, 3-H), 6.90 (t, ^3J = 7.3 Hz, 1H, 5-H), 4.93 (d, $^2J_{P\text{-}H}$ = 8.2 Hz, 1H, NH), 4.04-4.22 (m, 4H, 2 × OCH_2), 2.23 (s, 3H, Ar-CH_3), 1.31 ppm (t, ^3J = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.99 (C-1), 130.83 (C-3), 127.36 (C-4), 125.31 (d, $^3J_{P\text{-}C}$ = 11.1 Hz, C-2), 122.13 C-5), 117.26 (d, $^3J_{P\text{-}C}$ = 1.8 Hz, C-6), 63.11 (d, $^2J_{P\text{-}C}$ = 5.1 Hz, 2 × OCH_2), 17.97 (Ar-*C*H_3), 16.35 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 243 (66) [M^+], 215 (22) [M^+-CH_2=CH_2], 187 (25), 169 (15), 106 (100) [M^+-$C_4H_{10}O_3P$], 77 (14%).

HRMS (EI, M^+): calcd for $C_{11}H_{18}NO_3P$: 243.1049; found: 243.4495.

11.4 Diethyl *N*-*m*-tolylphosphoramidate (256c)[89]



256c

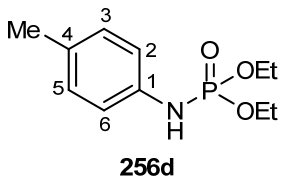
According to the general procedure 137 mg (1 mmol) 3-methylnitrobenzene (**255c**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:1) the title compound **256c** was isolated.

Yield: 177 mg (73 %).
M. P = 98 °C (ref.[89] 98°C).
$\mathbf{R}_f$ = 0.38 (SiO_2; cyclohexane/EtOAc = 1:2).

IR (ATR): $\tilde{\nu}$ = 3170 (NH), 2985-2907 (CH aliph.), 1609, 1594, 1509 (C=C arom.), 1486 (CH_2), 1403 (CH_3), 1294 (C-O), 1225 (P=O), 778 cm^{-1}.
UV/VIS (MeCN): λ_{max} (log ε) = 274 (3.45), 201 nm (3.89).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (t, ^3J = 7.6 Hz, 1H, 5-H), 6.82 (d, ^3J = 7.6 Hz, 1H, 6-H), 6.80 (s, 1H, 2-H), 6.76 (t, ^3J = 7.6 Hz, 1H, 4-H), 5.83 (d, $^2J_{P\text{-}H}$ = 9.1 Hz, 1H, NH), 4.04-4.22 (m, 4H, 2 × OCH_2), 2.30 (s, 3H, Ar-CH_3), 1.31 ppm (t, ^3J = 7.1 Hz, 6H, 2 × CH_3).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.98 (C-1), 139.40 (C-3), 129.33 (C-5), 122.60 (C-4), 118.23 (d, $^3J_{P\text{-}C}$ = 7,8 Hz, C-2), 114.59 (d, $^3J_{P\text{-}C}$ = 6.9 Hz, C-6), 62.93 (d, $^2J_{P\text{-}C}$ = 4.8 Hz, 2 × OCH_2), 21.75 (Ar-CH_3), 16.36 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 243 (90) [M^+], 215 (37) [M^+-CH_2=CH_2], 187 (100) [M^+-2 × CH_2=CH_2], 169 (75), 106 (24), 77 (15).

11.5 Diethyl *N*-*p*-tolylphosphoramidate (256d)[89]



256d

According to the general procedure 137 mg (1 mmol) 4-methylnitrobenzene (**255d**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) the title compound **256d** was isolated.

Yield: 160 mg (66 %).

M.p. = 90 °C (ref.[89] 95°C).

$\mathbf{R}_f$ = 0.32 (SiO_2; cyclohexane/EtOAc = 1:2).

IR (ATR): $\tilde{\nu}$ = 3176 (NH), 2982 (CH aliph.), 1615, 1514 (C=C arom.), 1394 (CH_3), 1283 (C-O), 1218 (P=O), 812 cm^{-1}.

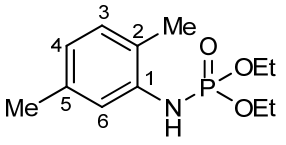
UV/VIS (MeCN): λ_{max} (log ε) = 275 (3.23), 231 nm (3.24).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04 (d, ^3J = 8.3 Hz, 2H, 2-H, 6-H), 6.90 (d, ^3J = 8.3 Hz, 2H, 3-H, 5-H), 5.88 (d, $^2J_{P\text{-}H}$ = 8.9 Hz, 1H, NH), 4.03-4.21 (m, 4H, 2 × OCH_2), 2.27 (s, 3H, Ar-CH_3), 1.30 ppm (t, ^3J = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.36 (C-1), 131.19 (C-4), 130.03 (C-3 and C-5), 117.58 (d, $^3J_{P\text{-}C}$ = 7.2 Hz, C-2 and C-6), 62.91 (d, $^2J_{P\text{-}C}$ = 4.8 Hz, 2 × OCH_2), 20.82 (Ar-$\underline{C}H_3$), 16.36 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 243 (90) [M^+], 215 (48) [M^+-CH_2=CH_2], 187 (100) [M^+-2 × CH_2=CH_2], 169 (75), 106 (49), 77 (18).

11.6 Diethyl *N*-2,5-dimethylphenylphosphoramidate (256e)[90]



256e

According to the general procedure 151 mg (1 mmol) 2-nitro-*p*-xylene (**255e**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 10:1) the title compound **256e** was isolated.

Yield: 192 mg (75 %).

M.p. = 73 °C (ref.[90] 67°C).

R_f = 0.44 (SiO_2; cyclohexane/EtOAc = 1:1).

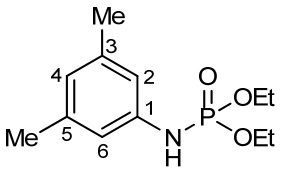
IR (ATR): $\tilde{\nu}$ = 3152 (NH), 2982-2908 (CH aliph.), 1598, 1553, (C=C arom.), 1493 (CH_2), 1366 (CH_3), 1302, 1280 (C-O), 1218 (P=O), 827 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 274 nm (3.38).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (s, 1H, 6-H), 7.03 (d, ^3J = 7.7 Hz, 1H, 3-H), 6.75 (d, ^3J = 7.5 Hz, 1H, 4-H), 4.89 (d, $^2J_{P\text{-}H}$ = 8.1 Hz, 1H, NH), 4.07-4.26 (m, 4H, 2 × OCH_2), 2.32 (s, 3H, 5-CH_3), 2.21 (s, 3H, 2-CH_3), 1.39 ppm (t, ^3J = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.76 (C-1), 137.11 (C-5), 130.61 (C-3), 122.87 (C-4), 122.12 (C-2), 117.93 (d, $^3J_{P\text{-}C}$ = 1.5 Hz, C-6), 63.10 (d, $^2J_{P\text{-}C}$ = 4.8 Hz, 2 × OCH_2), 21.55 (5-*C*H_3), 17.51 (2-*C*H_3), 16.37 ppm (d, $^3J_{P\text{-}C}$ = 6.9 Hz, 2 × CH_3).

11.7 Diethyl *N*-3,5-dimethylphenylphosphoramidate (256f)



256f

According to the general procedure 151 mg (1 mmol) 5-nitro-*m*-xylene (**255f**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **256f** was isolated.

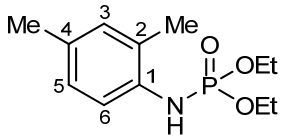
Yield: 203 mg (79 %).
M.p. = 89 °C.
R_f = 0.31 (SiO_2; cyclohexane/EtOAc = 1:3).
IR (ATR): $\tilde{\nu}$ = 3174 (NH), 2982-2901 (CH aliph.), 1598, 1517 (C=C arom.), 1403 (CH_2), 1394 (CH_3), 1227 (P=O), 1195, 1023 (C-O), 806 cm^{-1}.
UV/VIS (MeCN): λ_{max} (log ε) = 274 (3.36), 206 nm (3.56).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (s, 2H, 4-H and 6-H), 5.94 (d, $^2J_{P\text{-}H}$ = 6.7 Hz, 1H, NH), 4.06-4.19 (m, 4H, 2 × OCH_2), 2.26 (s, 6H, 3-CH_3 and 5-CH_3), 1.32 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.81 (C-1), 139.25 (C-3 and C-5), 123.66 (C-4), 115.31 (d, $^3J_{P\text{-}C}$ = 7.2 Hz, C-2 and C-6), 62.93 (d, $^2J_{P\text{-}C}$ = 4.8 Hz, 2 × OCH_2), 21.64 (3-*C*H_3 and 5-*C*H_3), 16.38 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 257 (94) [M^+], 229 (38), 201 (100) [M^+-2 × CH_2=CH_2], 183 (53), 148 (12), 121 (32).

HRMS (EI, M^+): calcd for $C_{12}H_{20}NO_3P$: 257.1178; found: 257.1182.

11.8 Diethyl *N*-2,4-dimethylphenylphosphoramidate (256g)[90]



256g

According to the general procedure 151 mg (1 mmol) 4-nitro-*m*-xylene (**255g**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **256g** was isolated.

Yield: 198 mg (77 %).

M.p. = 84 °C (ref.[90] 88°C).

R_f = 0.33 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3201 (NH), 2984-2902 (CH aliph.), 1509 (C=C arom.), 1419 (CH_2), 1384 (CH_3), 1287 (C-O), 1240, 1215 (P=O), 813 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 277 (3.25), 230 nm (3.15).

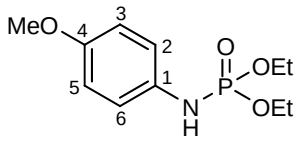
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, ^3J = 8.7 Hz, 1H, 6-H), 6.94 (br s, 2H, 3-H, 5-H), 4.80 (d, $^2J_{P\text{-}H}$ = 7.2 Hz, 1H, NH), 4.03-4.21(m, 4H, 2 × OCH_2), 2.25 (s, 3H, 4-C*H*$_3$), 2.20 (s, 3H, 2-C*H*$_3$), 1.31 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.32 (C-1), 131.56 (d, $^3J_{P\text{-}C}$ = 3.9 Hz, C-4), 131.54 (C-5), 127.79 (C-3), 125.44 (d, $^3J_{P\text{-}C}$ = 10.8 Hz, C-2), 117.46 (d, $^3J_{P\text{-}C}$ = 1.5 Hz, C-6), 63.03 ($^2J_{P\text{-}C}$ = 5.1 Hz, 2 × OCH_2), 20.77 (4-*C*H_3), 17.92 (2-*C*H_3), 16.36 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 257 (100) [M^+], 229 (47), 201 (80), 183 (40), 120 (98), 91 (14).

HRMS (EI, M^+): calcd for $C_{12}H_{20}NO_3P$: 257.1178; found: 257.1181.

11.9 Diethyl *N*-*p*-methoxyphenylphosphoramidate (256h)[89,92]



256h

According to the general procedure 151 mg (1 mmol) 4-nitroanisole (**255h**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **256h** was isolated.

Yield: 198 mg (71 %).

$\mathbf{R}_f$ = 0.33 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3180 (NH), 2983-2920 (CH aliph.), 1511 (C=C arom.), 1393 (CH_3), 1241, 1220 (P=O), 1019 (C-O), 963, 825, 797 cm^{-1}.

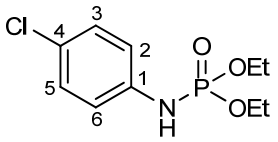
UV/VIS (MeCN): λ_{max} (log ε) = 290 (3.04), 232 (3.92), 202 nm (4.03).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (d, ^3J = 8.9 Hz, 2H, 2-H and 6-H), 6.81 (d, ^3J = 8.9 Hz, 2H, 3-H, 5-H), 5.46 (d, $^2J_{P\text{-}H}$ = 8.8 Hz, 1H, NH), 4.07-4.17 (m, 4H, 2 × OCH_2), 3.75 (s, 3H, 4-OCH_3), 1.31 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.03 (C-4), 133.07 (C-1), 119.28 (d, $^3J_{P\text{-}C}$ = 6.9 Hz, C-2 and C-6), 114.85 (C-3 and C-5), 62.92 (d, $^2J_{P\text{-}C}$ = 5.1 Hz, 2 × OCH_2), 55.78 (4-OCH_3), 16.37 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 287 (100) [M^+], 259 (95), 244 (40), 216 (68).

11.10 Diethyl *N*-*p*-chlorophenylphosphoramidate (256i)[86a,92]



256i

According to the general procedure 157 mg (1 mmol) 4-chloronitrobenzene (**255i**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:5) the title compound **256i** was isolated.

Yield: 135 mg (52 %).

M.p. = 74 °C (ref.[86a] 77°C).

$\mathbf{R}_f$ = 0.25 (SiO_2; cyclohexane/EtOAc = 2:5).

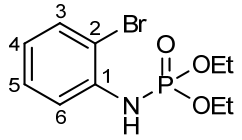
IR (ATR): $\tilde{\nu}$ = 3199 (NH), 1587, 1515 (C=C arom.), 1402 (CH_2), 1285 (C-O), 1238 (P=O), 964 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 270 nm (3.42).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, ^3J = 8.6 Hz, 2H, 3-H and 5-H), 6.94 (d, ^3J = 8.8 Hz, 2H, 2-H, 6-H), 6.27 (d, $^2J_{P\text{-}H}$ = 8.9 Hz, 1H, NH), 4.03-4.21 (m, 4H, 2 × OCH_2), 1.31 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.78 (C-1), 129.46 (C-3 and C-5), 126.84 (C-4), 118.81 (d, $^3J_{P\text{-}C}$ = 7.5 Hz, C-2 and C-6), 63.14 (d, $^2J_{P\text{-}C}$ = 4.8 Hz, 2 × OCH_2), 16.34 ppm (d, $^3J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

11.11 Diethyl *N*-2-bromophenylphosphoramidate (256j)



256j

According to the general procedure 202 mg (1 mmol) 2-bromonitrobenzene (**255j**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **256j** was isolated.

Yield: 208 mg (68 %).

$\mathbf{R}_f$ = 0.29 (SiO_2; cyclohexane/EtOAc = 2:1).

IR (ATR): $\tilde{\nu}$ = 3169 (NH), 2977-2896 (CH aliph.), 1587, 1484 (C=C arom.), 1407 (CH_2), 1390 (CH_3), 1250 (C-O), 1240 (P=O), 764 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 274 (3.39), 202 nm (3.66).

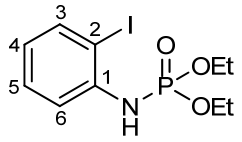
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, ^3J = 8.1 Hz, 1H, 3-H), 7.32 (dd, ^3J = 8.2 Hz, ^4J = 1.3 Hz, 1H, 6-H), 7.22 (ddd, ^3J = 8.3 Hz, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, 5-H), 6.83 (dt, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, 4-H), 5.63 (d, $^2J_{P-H}$ = 8.3 Hz, 1H, NH), 4.06-4.23 (m, 4H, 2 × OCH_2), 1.32 ppm (t, ^3J = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.82 (d, $^2J_{P-C}$ = 3.4 Hz, C-1), 132.86 (C-3), 128.75 (C-5), 122.99 (C-4), 117.92 (d, $^3J_{P-C}$ = 1.5 Hz, C-6), 112.67 (d, $^3J_{P-C}$ = 12.9 Hz, C-2), 63.44 (d, $^2J_{P-C}$ = 5.1 Hz, 2 × OCH_2), 16.33 ppm (d, $^3J_{P-C}$ = 6.9 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 309 (71) [M^{+2}], 307 (70) [M^+], 228 (80), 200 (89), 172 (100) [M^{+2}-$C_4H_{10}O_3P$], 154 (78), 108 (29), 91 (52), 65 (22).

Elemental analysis (%) calcd for $C_{10}H_{15}NPBrO_3$: C 38.96, H 4.91, N 4.55; found: C 39.34, H 4.67, N 4.75.

11.12 Diethyl *N*-2-iodophenylphosphoramidate (256k)



256k

According to the general procedure 249 mg (1 mmol) 2-iodonitrobenzene (**255k**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **256k** was isolated.

Yield: 198 mg (56 %).

$\mathbf{R}_f$ = 0.35 (SiO_2; cyclohexane/EtOAc =1:1).

IR (ATR): $\tilde{\nu}$ = 3468 (NH), 2980-2901 (CH aliph.), 1586, 1470 (C=C arom.), 1391 (CH_2), 1338 (CH_3), 1295, 1249 and 1166 (C-O), 1015 (P=O), 823 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 271 nm (3.39).

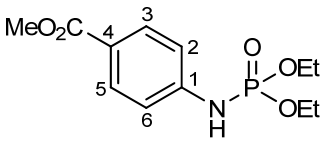
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, ^3J = 7.9 Hz, 1H, 3-H), 7.30 (dd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1H, 6-H), 7.24 (dt, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, 5-H), 6.68 (dt, ^3J = 7.9 Hz, ^4J = 1.6

Hz, 1H, 4-H), 5.46 (d, $^{2}J_{P\text{-}H}$ = 8.1 Hz, 1H, NH), 4.05-4.23 (m, 4H, 2 × OCH_2), 1.31 ppm (t, ^{3}J = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.53 (d, $^{2}J_{P\text{-}C}$ = 3.3 Hz, C-1), 139.44 (C-3), 129.73 (C-5), 123.62 (C-4), 117.36 (d, $^{3}J_{P\text{-}C}$ = 1.5 Hz, C-6), 88.86 (d, $^{3}J_{P\text{-}C}$ = 13.5 Hz, C-2), 63.45 (d, $^{2}J_{P\text{-}C}$ = 5.1 Hz, 2 × OCH_2), 16.35 ppm (d, $^{3}J_{P\text{-}C}$ = 7.2 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 355 (84) [M^+], 228 (56) [M^+-I], 200 (68), 172 (100) [M^+-C_4H_8I], 154 (60), 91 (45).

11.13 Diethyl *N*-*p*-methoxycarbonylphenylphosphoramidate (256l)[92]



256l

According to the general procedure 181 mg (1 mmol) *p*-nitromethylbenzoate (**255l**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) the title compound **256l** was isolated.

Yield: 178 mg (62 %).

$\mathbf{R}_f$ = 0.23 (SiO_2; cyclohexane/EtOAc = 1:2).

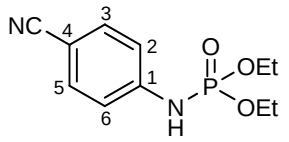
IR (ATR): $\tilde{\nu}$ = 3180 (NH), 2983-2901 (CH aliph.), 1610 (C=O), 1518 (C=C arom.), 1437 (CH_2), 1394 (CH_3), 1259, (P=O), 1166, 1103, 1017 (C-O), 965, 798 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 264 (3.86), 212 nm (3.67).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, ^{3}J = 8.5 Hz, 2H, 3-H, 5-H), 7.01 (d, ^{3}J = 8.7 Hz, 2H, 2-H, 6-H), 6.11 (d, $^{2}J_{P\text{-}H}$ = 8.9 Hz, 1H, NH), 4.06-4.16 (m, 4H, 2 × OCH_2), 3.88 (s, 3H, 4-OCH_3), 1.34 ppm (t, ^{3}J = 7.0 Hz, 6H, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 287 (88) [M^+], 259 (39) [M^+-CO], 231 (51) [M^+-2 × CH_2=CH_2], 200 (100) [M^+-$C_4H_7O_2$], 182 (27), 151 (7), 120 (10), 92 (8).

11.14 Diethyl *N*-*p*-cyanophenylphosphoramidate (256m)[92]



256m

According to the general procedure 148 mg (1 mmol) 4-nitrobenzonitrile (**255m**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) the title compound **256m** was isolated.

Yield: 161 mg (63 %).

$\mathbf{R}_f$ = 0.24 (SiO_2; cyclohexane/EtOAc = 1:2).

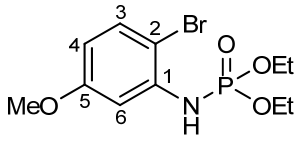
IR (ATR): $\tilde{\nu}$ = 3170 (NH), 2984-2916 (CH aliph.), 2222 (CN), 1609, 1514 (C=C arom.), 1480 (CH_2), 1394 (CH_3), 1258 (P=O), 1166, 1017 (C-O), 964, 797 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 258 (3.82), 200 nm (3.89).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, ^3J = 8.7 Hz, 2H, 3-H, 5-H), 7.07 (d, ^3J = 8.7 Hz, 2H, 2-H, 6-H), 7.01 (d, $^2J_{P\text{-}H}$ = 9.2 Hz, 1H, NH), 4.06-4.21 (m, 4H, 2 × OCH_2), 1.33 ppm (t, ^3J = 6.6 Hz, 6H, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 254 (60) [M^+], 226 (31) [M^+-CH_2=CH_2], 198 (100) [M^+-2 × CH_2=CH_2], 180 (43), 145 (5), 118 (32).

11.15 Diethyl *N*-2-bromo-5-methoxyphenylphosphoramidate (256n)



256n

According to the general procedure 232 mg (1 mmol) 4-bromo-3-nitroanisole (**255n**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 1:2) the title compound **256n** was isolated.

Yield: 247 mg (73 %).

M.p. = 58 °C.

$\mathbf{R}_f$ = 0.41 (SiO_2; cyclohexane/EtOAc = 1:2).

IR (ATR): $\tilde{\nu}$ = 3222 (NH), 2986 (CH aliph.), 1600, 1577 (C=C arom.), 1493 (CH_2), 1398 (CH_3), 1301 (C-O), 1254 (P=O), 1060 (C-Br), 777 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 275 (3.15), 209 nm (3.36).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (dd, ^3J = 8.8 Hz, ^5J = 1.2 Hz, 1H, 3-H), 6.94 (d, ^4J = 2.8 Hz, 1H, 6-H), 6.43 (dd, ^3J = 8.9 Hz, ^4J = 2.8 Hz, 1H, 4-H), 5.60 (d, $^2J_{P\text{-}H}$ = 8.5 Hz, 1H, NH), 4.02-4.24 (m, 4H, 2 × OCH_2), 3.77 (s, 3H, OCH_3), 1.34 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

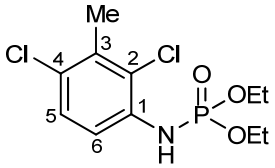
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.11 (C-5), 138.55 (d, $^2J_{P\text{-}C}$ = 2.9 Hz, C-1), 132.99 (C-3), 108.89 (C-4), 104.03 (d, $^3J_{P\text{-}C}$ = 1.5 Hz, C-6), 103.39 (d, $^3J_{P\text{-}C}$ = 12.56 Hz, C-2), 63,46 (d, $^2J_{P\text{-}C}$ = 5.1 Hz, 2 × OCH_2), 55.72 (OCH_3), 16.37 ppm (d, $^3J_{P\text{-}C}$ = 6.9 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 339 (30) [M^+], 337 (32) [M^+-2], 258 (80) [M^+-Br], 230 (61), 202 (100) [M^+-$C_4H_{10}O_3P$], 184 (17), 138 (19).

HRMS (EI, M^+): calcd for $C_{11}H_{17}NPBrO_4$: 337.0076; found: 337.0080.

Elemental analysis (%) calcd for $C_{11}H_{17}NPBrO_4$: C 39.17, H 5.08, N 4.16; found: C 39.13, H 4.94, N 3.91.

11.16 Diethyl *N*-2,4-dichloro-3-methylphenylphosphoramidate (256o)



256o

According to the general procedure 206 mg (1 mmol) 2,6-dichloro-3-nitrotoluene (**255o**) were reacted with 995 mg (6 mmol) triethyl phosphite (**161**). After column chromatography (SiO_2; cyclohexane/EtOAc = 2:1) the title compound **256o** was isolated.

Yield: 177 mg (57 %).

M.p. = 84 °C.

$\mathbf{R}_f$ = 0.45 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3218 (NH), 2986-2906 (CH aliph.), 1583 (C=C arom.), 1460 (CH_2), 1360 (CH_3), 1259 (C-O), 1242, (P=O), 752 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 276 (3.43), 207 nm (3.71).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, ^3J = 8.9 Hz, 1H, 5-H), 7.14 (d, ^3J = 8.9 Hz, 1H, 6-H), 5.67 (d, $^2J_{P-H}$ = 8.5 Hz, 1H, NH), 4.04-4.22 (m, 4H, 2 × OCH_2), 2.45 (s, 3H Ar-CH_3), 1.32 ppm (t, ^3J = 7.0 Hz, 6H, 2 × CH_3).

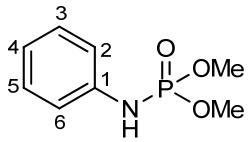
^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.61 (d, $^2J_{P-C}$ = 3.4 Hz, C-1), 134.97 (C-4), 128.01 (C-5), 127.65 (C-3), 123.32 (d, $^3J_{P-C}$ = 11.9 Hz, C-2), 115.62 (d, $^3J_{P-C}$ = 1.5 Hz, C-6), 63.50 (d, $^2J_{P-C}$ = 5.1 Hz, 2 × OCH_2), 18.43 (Ar-CH_3), 16.34 ppm (d, $^3J_{P-C}$ = 6.9 Hz, 2 × CH_3).

MS (EI, 70 eV): *m/z* (%) = 311 (70) [M^+], 278 (20), 276 (72) [M^+-Cl], 248 (62), 221 (47), 220 (100) [M^+-C_4H_8Cl], 201 (20), 77 (10).

HRMS (EI, M^+): calcd for $C_{11}H_{16}NPCl_2O_3$: 311.0244; found: 311.0259.

Elemental analysis (%) calcd for $C_{11}H_{17}NPBrO_4$: C 42.44, H 5.18, N 4.50; found: C 42.75, H 4.88, N 4.33.

11.17 Dimethyl *N*-phenylphosphoramidate (258)[128]



258

A mixture of 123 mg (1 mmol) nitrobenzene (**255a**), 744 mg (6 mmol) trimethyl phosphite (**257**) and 3 mL dry toluene was sealed in a 10 mL septum reaction vial and irradiated with microwaves (Discover^{TM} by CEM, 2450 MHz, 300 W, 200 °C). After removal of trimethyl phosphite (**257**) and trimethyl phosphate at reduced pressure (10^{-1} mbar) and temperatures between 40 and 70 °C the residue was diluted with 30 mL CH_2Cl_2 and washed with water (2 × 50 mL) and brine (3 × 20 mL). After drying over anhydrous magnesium sulfate and concentration in vacuo the resulting residue was purified by column chromatography (SiO_2; cyclohexane/EtOAc = 1:3) to give the title compound **258**.

Yield: 117 mg (58 %).

R_f = 0.29 (SiO_2; cyclohexane/EtOAc = 1:1).

IR (ATR): $\tilde{\nu}$ = 3190 (NH), 2958, 2851 (CH aliph.), 1605 (C=C arom.), 1499 (CH_2), 1419 (CH_3), 1259, 1228, 1185 (C-O), 1019 (P=O), 960, 839, 753, 695 cm^{-1}.

UV/VIS (MeCN): λ_{max} (log ε) = 276 (2.61), 228 nm (3.63).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, ^{3}J = 7.2 Hz, 2H, 3-H, 5-H), 6.98 (d, ^{3}J = 7.2 Hz, 2H, 2-H, 6-H), 6.95 (br, 1H, 4-H), 5.76 (d, $^{2}J_{P\text{-}H}$ = 8.8 Hz, 1H, NH), 3.79 (s, 3H, OCH_3), 3.76 ppm (s, 3H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.28 (C-1), 129.26 (C-3, C-5), 121.76 (C-4), 117.28 (d, $^{3}J_{P\text{-}C}$ = 7.06 Hz, C-2, C-6), 54.27 (OCH_3), 54.20 ppm (OCH_3).

MS (EI, 70 eV): *m/z* (%) = 201 (100) [M^+], 169 (42), 109 (18), 106 (70), 93 (24), 65 (18).

C APPENDIX

1. References

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2. Abbreviations

A	absorbance
Ac	acetyl
Ac_2O	acetic anhydride
aq	aqueous
br	broad (NMR)
br s	broad singlet (NMR)
br d	broad dublet (NMR)
calcd	calculated
concd	concentrated
COSY	correlated spectroscopy
d	doublet (NMR)
dppm	bis(diphenylphosphino) methane
dd	doublet of doublet (NMR)
DMA	*N,N*-dimethylacetamide
δ	chemical shift
Δ	heating
DMF	*N,N*-dimethylformamide
dq	doublet of quartet (NMR)
dt	doublet of triplet (NMR)
EI	electron impact mass spectromerty
ē	electron
ε	absorption coefficient
equiv.	equivalent
Et	ethyl
eV	electron volt (MS)
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple-bond spectroscopy
HMQC	heteronuclear multiple-quantum spectroscopy
HRMS	high Resolution mass-spectroscopy
HSQC	heteronuclear single quantum spectroscopy
Hz	hertz

IR	infrared spectroscopy
J	coupling constant
λ	wavelength (nm)
LRMS	low resolution mass spectrometry
M^+	molecular ion
m	multiplet (NMR)
Me	methyl
min	minute
mL	millilitres
mol	mole (s)
M.p.	melting point
MS	mass spectrometry
MW	microwave
m/z	mass/charge ratio
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
$\tilde{\nu}$	wavenumber
o	*ortho*
PCC	pyridinum chlorochromate
Py	pyridin
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet (NMR)
R_f	ratio of fronts (TLC)
ROESY	rotating-frame nuclear overhauser enhancement spectroscopy
r.t.	room temperature
s	singlet (NMR)
Soln	solution
sec-BuLi	*sec*-butyllithium
t	triplet (NMR)
t-Bu	*tert*-butyl
t-BuLi	*tert*-butyllithium
TBAF	tetrabutylammoniumfluoride

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMSCN	trimethylsilylcyanide
THF	tetrahydrofuran
TLC	thin layer chromatography
TOCSY	total correlated spectroscopy
TMS	tetramethylsilane
UV	ultraviolet spectroscopy
UV/VIS	ultraviolet visible spectroscopy

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5. Erklärung

Hiermit erkläre ich, dass ich, Reda Haggam, die Dissertation selbstständig angefertigt habe, nur die angegebenen Quellen und Hilfsmittel benutzt und wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe.

Hohenheim, im 03.08. 2010

(Reda Haggam)