Application of an *ortho*-Formylation Reaction in One-pot Procedures and Natural Product Syntheses

Dissertation for the degree of Ph.D.

Hany Fakhry Anwar

Department of Pharmaceutical Chemistry

School of Pharmacy

Faculty of Mathematics and Natural Sciences

University of Oslo

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Lastly, I would like to thank my wife, Sylvia Antoun, for her love, encouragement and patience over these years.

Hany F. Anwar

Oslo, May 2009

Table of Contents

Abstract

This thesis has focused on the Casnati-Skattebøl *ortho*-formylation method by which phenols are converted to salicylaldehydes using a combination of paraformaldehyde and $MgCl_2$-Et_3N in THF, and the development of one-pot methods *via* salicylaldehydes for the synthesis of useful starting materials: *i.e. ortho*-hydroxycinnamate esters, salicylamines, and salicylnitriles. The same method was applied for the synthesis of dihydro-2*H*-1,3-benzoxazines in a one-pot procedure.

In order to broaden the scope of the $MgCl_2$-Et_3N base system in organic synthesis, phenols were converted to their magnesium salts with the $MgCl_2$-Et_3N base system and subsequently reacted with Eschenmoser's salt (*N*,*N*-dimethylmethylene iminium iodide), affording *N*,*N*-dimethyl substituted benzylamines in 66-98% yields.

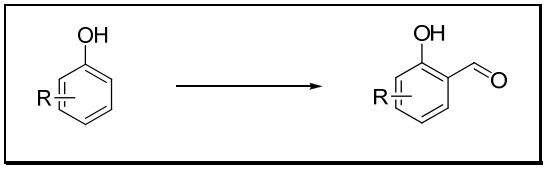
The first total synthesis of (±)-powelline was reported in 10% overall yield over eight steps. The key reactions were an *ortho*-formylation reaction of 2,3-(methylenedioxy)-phenol and an intramolecular oxidative phenolic coupling reaction.

Finally, the first total synthesis of the marine natural product *all*-(*Z*)-5,7-dihydroxy-2-(4,7,10,13,16-nonadecapentaenyl)chromone has been achieved in six steps and in 14% overall yield, starting from the ethyl ester of eicosapentaenoic acid.

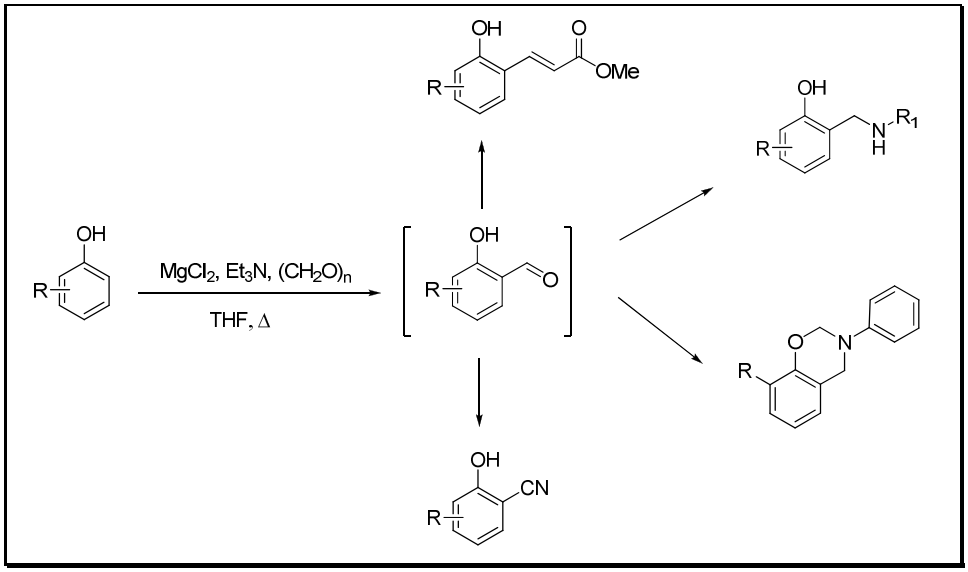
Additional experimental work, not presented in any of the Papers (**I**-**V**), is included as an Appendix.

Graphical Abstract

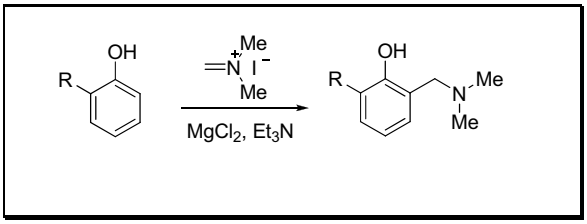
Introduction: Synthesis of Salicylaldehydes



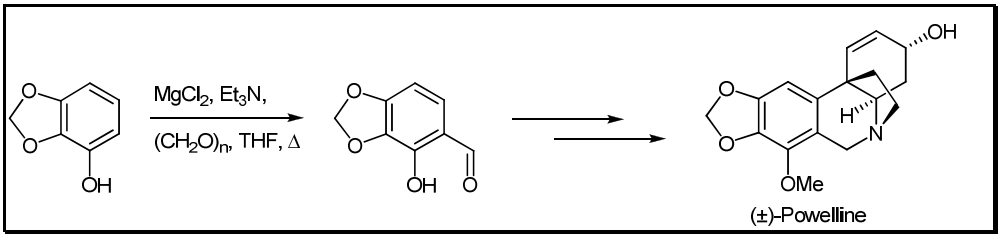
One-pot Synthesis of Substituted *Ortho*-hydroxycinnamate Esters, Salicylamines, Dihydro-2*H*-1,3-benzoxazines, and Salicylnitriles



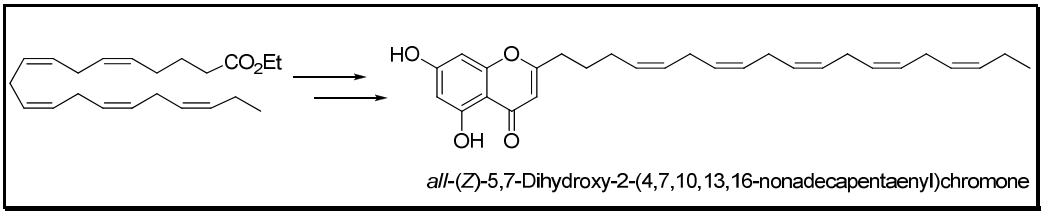
Synthesis of Substituted Salicylamines by the Mannich Reaction



First Total Synthesis of (±)-Powelline



First Total Synthesis of a Polyunsaturated Chromone Metabolite Isolated from the Brown Algae *Zonaria tournefortii*



Abbreviations

aq.	aqueous
Boc	*tert*-butoxycarbonyl
decomp.	decomposition
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMP	Dess-Martin periodinane (1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one)
dr	diastereomeric ratio
equiv.	equivalent(s)
HMPA	hexamethylphosphoric acid triamide
HMT	hexamethylenetetramine
IBX	2-iodoxybenzoic acid
SIBX	Stabilized IBX: 2-Iodoxybenzoic acid contains 45 wt. % benzoic acid and isophthalic acid as stabilizer.
LDA	lithium diisopropylamide
MOM	methoxymethyl
MVK	methyl vinyl ketone
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PIFA	[*bis*(trifluoroacetoxy)iodo]-benzene
ppm	parts per million
temp.	temperature
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMEDA	*N*,*N*,*N*`,*N*`-tetramethyl-1,2-ethylenediamine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Δ	reflux/heat

List of Publications

This thesis is based on the following papers:

Paper I

One-pot Synthesis of *ortho*-Hydroxycinnamate Esters. Anwar, H. F.; Skattebøl, L.; Skramstad, J.; Hansen, T. V. *Tetrahedron Lett.* **2005**, *46,* 5285-5287.

Paper II

Synthesis of Substituted Salicylamines and Dihydro-2*H*-1,3-benzoxazines. Anwar, H. F.; Skattebøl, L.; Hansen, T. V. *Tetrahedron* **2007**, *63,* 9997-10002.

Paper III

A One-pot Synthesis of Substituted Salicylnitriles. Anwar, H. F.; Hansen, T. V. *Tetrahedron Lett.* **2008**, *49,* 4443-4445.

Paper IV

First Total Synthesis of (±)-Powelline. Anwar, H. F.; Hansen, T. V. *Synlett* **2008**, 2681-2683.

Paper V

First Total Synthesis of a Polyunsaturated Chromone Metabolite Isolated from fhe Brown Algae *Zonaria tournefortii.* Anwar, H. F.; Hansen, T. V. *Org. Lett.* **2009**, *11,* 587-588.

1. INTRODUCTION

1.1 Synthesis of Salicylaldehydes

Salicylaldehydes are excellent precursors for the preparation of important classes of organic compounds such as oxygen-containing heterocyclic compounds,[1,2] cinnamic acid derivatives,[3] salen derivatives,[4] and useful industrial metal extractants.[5]

Formylation of aromatic compounds for the synthesis of salicylaldehydes is an important classical reaction in organic chemistry, and numerous methods are available.[6,7] Salicylaldehydes are accessible from the corresponding phenols by several of these classical formylation reactions (Figure 1.1). However, for many of these reactions, the yields of salicylaldehydes are often only moderate and the lack of regioselectivity is problematic.[8] Moreover, the reaction conditions are quite harsh, involve safety problems at a large scale, and employ environmentally harmful reagents.

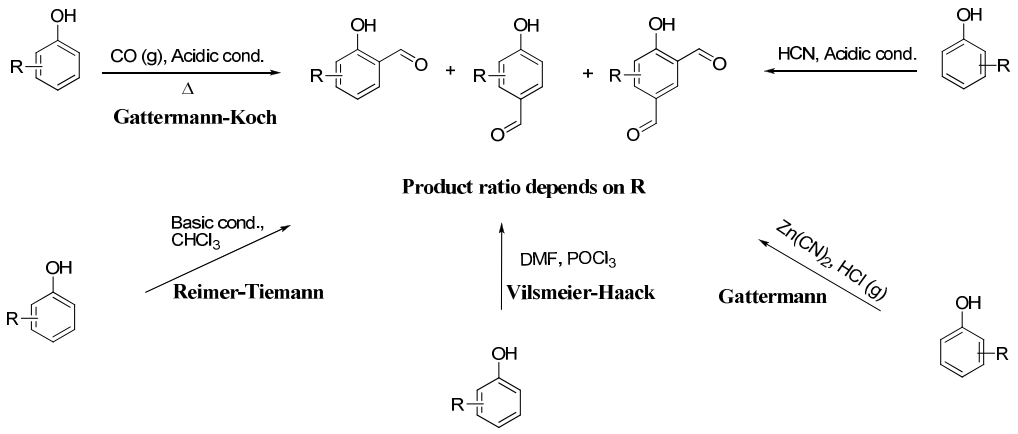
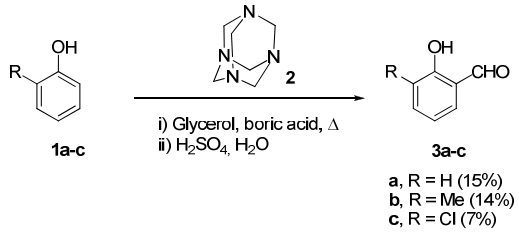


Figure 1.1 Classical formylation reactions methods

Over the years, many of the formylation methods depicted in Figure 1.1 have been improved. For instance, the Gattermann-Koch reaction has been improved by using $CO/HF/BF_3$ to give *para*-selectivity.[9,10] The Reimer-Tiemann reaction has also been

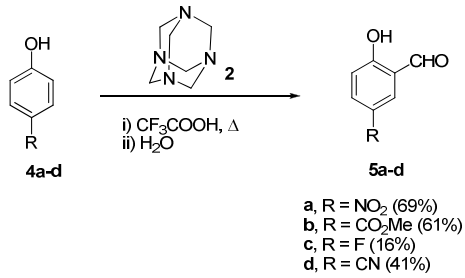
modified to give *ortho*-selective formylations of phenols by using H_2O:EtOH (9:1) as a solvent.[11] Highly selective *para*-hydroxybenzaldehydes were obtained with the same reaction by using *β*-cyclodextrin derivatives.[12] In the Reimer-Tiemann reaction, trichloroacetaldehyde (chloral)[13] and trichloroacetic acid[14] have replaced chloroform.

The Duff reaction[15] is a formylation method for electron-rich phenols using hexamethylenetetramine (HMT, **2**) as the formylating agent in the presence of glycerol and boric acid. The reaction is followed by an aqueous workup to give salicylaldehydes usually in low yields (Scheme 1.1).[16]



Scheme 1.1

Suzuki and Takahashi modified the Duff reaction by using strong acids, such as methanesulfonic-, trifluoroacetic-, or polyphosphoric acid as solvent. This modification has successfully formylated many electron-deficient phenols which were unreactive under the classical Duff conditions (Scheme 1.2).[17]



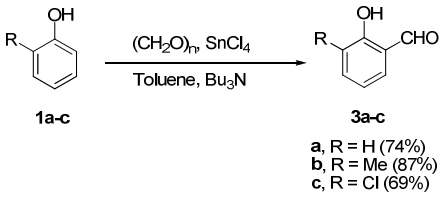
Scheme 1.2

Another adaptation of the Duff reaction has been applied for the preparation of 3,5-difluorosalicylaldehyde and 5-bromo-3-fluorosalicylaldehyde under mild conditions when using trifluoroacetic acid as solvent. The phenols were converted to imine products by HMT and trifluoroacetic acid. Then the imine products were hydrolyzed to aldehydes in 79% and

78% yields,[18] respectively. This reaction was also applied in the preparation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde from 2,6-di-*tert*-butylphenol in 60% yield.[19]

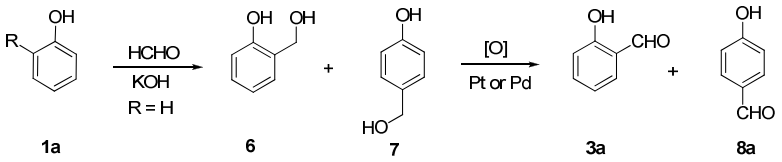
Phenol can be *ortho*-formylated by formaldehyde in the presence of one of several metal salt catalysts (*e.g.* Ti, Zr, Al, Cr, and Fe), but these reactions require high pressure and are unattractive for industrial processes.[20]

Another method that employs paraformaldehyde as the formylating reagent is the combination of tin tetrachloride and tributylamine which produce salicylaldehydes with high selectivity.[21] This reaction has also been carried out in the presence of 2,6-dimethylpyridine instead of tributylamine (Scheme 1.3).[22]



Scheme 1.3

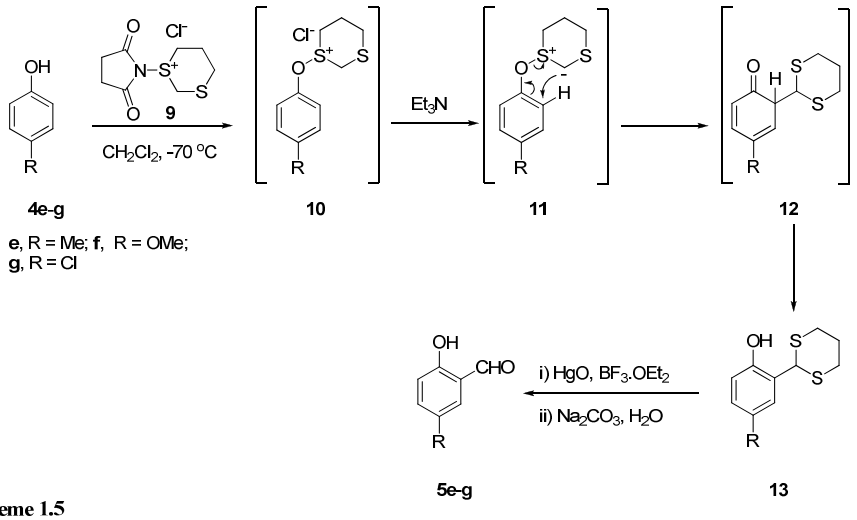
A widely used industrial process for the production of salicylaldehydes was the base-catalyzed reaction of formaldehyde with phenol (**1a**) affording a mixture of the hydroxybenzyl alcohols **6** and **7**. The alcohols were subsequently oxidized by an oxidizing agent, in the presence of metal catalyst, *e.g.* palladium, silver, or platinum, to produce the hydroxybenzaldehydes **3a** and **8a** (Scheme 1.4).[23]



Scheme 1.4

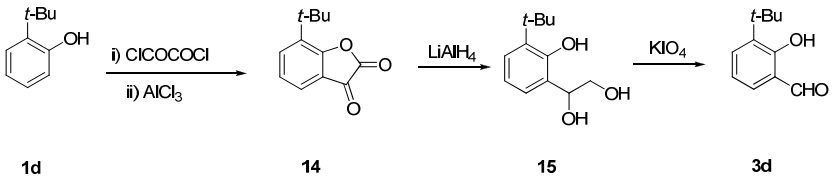
Selective *ortho*-formylation of *para*-substituted phenols **4** has been achieved with the sulfonium salt **9**, which was formed by the reaction of *N*-chlorosuccinimide and dithiane. In

the presence of triethylamine at -70 °C, dithiane **13** was obtained. After hydrolysis, salicylaldehydes **5** were obtained in 20-35% yield over the two steps (Scheme 1.5).[24]



Scheme 1.5

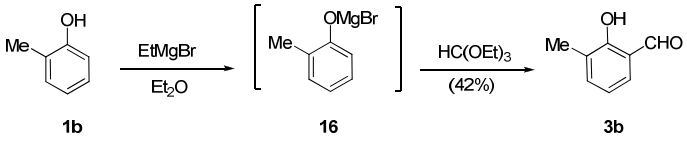
Reaction of phenol **1d** with oxalyl chloride and 4-(*N*,*N*-dimethylamino)-pyridine as a catalyst gave the phenoxyoxalyl chloride, which by ring closure with aluminium chloride afforded 2,3-dioxo-benzofurans **14**. Reduction with lithium aluminium hydride yielded 2-(1`,2`-dihydroxyethyl)-phenol **15**, that was finally oxidized with potassium metaperiodate to afford the *ortho*-hydroxybenzaldehyde derivative **3d**. The overall yield of the three step synthesis was 54% (Scheme 1.6).[25]



Scheme 1.6

Unfortunately, all these reactions are hampered by one or more of the following disadvantages: the use of large amounts of Lewis acids, hazardous reagents, difficult separations of isomers, and multistage synthesis. Today, there is a general need for more environmentally friendly synthetic methods.[26]

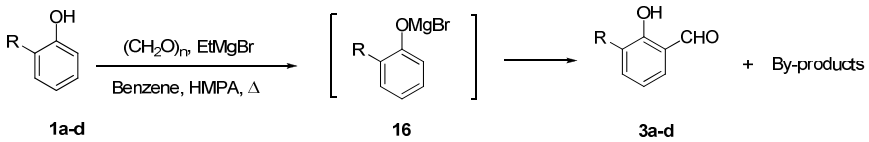
In 1965 Casnati *et al.* used phenoxymagnesium bromide **16** and excess triethyl orthoformate as a formylation agent to obtain the corresponding salicylaldehyde **3b** without any detection of the *para*-isomer (Scheme 1.7).[27]



1b **16** **3b**

Scheme 1.7

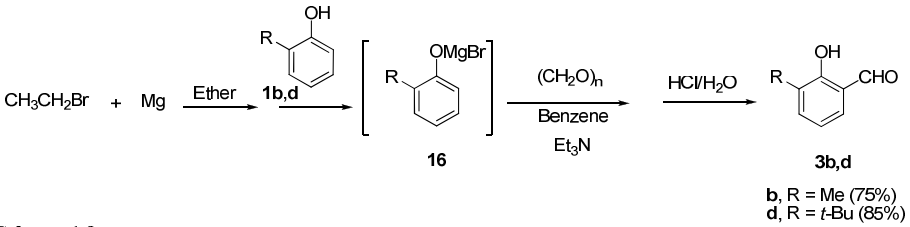
Some years later, Casnati and co-workers reported that the reaction of paraformaldehyde and magnesium phenoxides **16**, formed from the respective phenol and ethyl magnesium bromide solvated in benzene and in the presence of stoichiometric amounts of hexamethylphosphoric acid triamide (HMPA), resulted in monoformylation exclusively at the *ortho* position in 23-90% yields. However, by-products such as methylenediphenol and 2,6-bis(*o*-hydroxybenzyl)phenol were formed in most of the reactions (Scheme 1.8).[28,29] No formylation was observed by the Casnati method using phenols substituted with electron withdrawing groups like NO_2, COMe, and CO_2Me.[27,28]



1a-d **16** **3a-d**

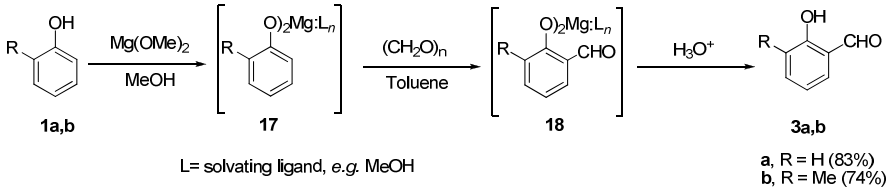
Scheme 1.8

A modification of the original Casnati *ortho*-formylation method was reported in 1994 when triethylamine was used instead of the carcinogenic metal complexing agent HMPA. Salicylaldehydes **3** were obtained in good yields (Scheme 1.9).[30]



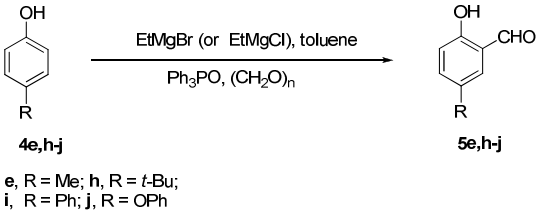
Scheme 1.9

Aldred *et al.* reported in 1994 a modification of the Casnati method.[31] First, they reacted phenol with magnesium dimethoxide to obtain bis(phenoxide) intermediates **17** using methanol as a cosolvent instead of HMPA. The free methanol was removed by distillation with the addition of toluene. The *ortho*-formylation proceeded by the addition of paraformaldehyde which afforded salicylaldehyde magnesium salts **18**. The salicylaldehydes **3** were obtained from their magnesium salts by acidic work-up (Scheme 1.10).



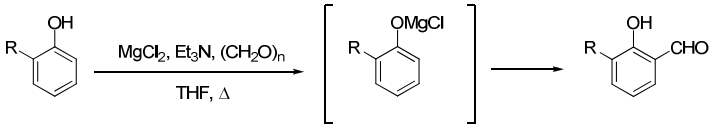
Scheme 1.10

Salicylaldehydes **5** were prepared with high selectivity by the reaction of phenols **4** with Grignard reagent EtMgX (X = Cl, Br) and paraformaldehyde in the presence of triphenylphosphine oxide with yields ranging from 51-78% (Scheme 1.11).[32] Triphenylphosphine oxide was also replaced with either DMSO or *N*-methylpiperidine.[33]



Scheme 1.11

In 1999 Hofsløkken and Skattebøl used a combination of $MgCl_2$-Et_3N as a base and acetonitrile or tetrahydrofuran (THF) as a solvent in order to improve Casnati's method. This base system gives higher yields, fewer by-products, and the use of HMPA becomes superfluous.[34] This reaction was later optimized by Hansen and Skattebøl by reducing the number of equivalents of magnesium dichloride, triethylamine, and paraformaldehyde to 2, 2, and 3, respectively. Salicylaldehydes **3** are easily obtained in good to excellent yields (70-99%, Scheme 1.12). This method also works well with methyl-4-hydroxybenzoate (88% yield), but unfortunately only poor yields were obtained using phenols substituted with electron withdrawing groups (CN and NO_2).[35]



1b,c,e **19** **3b,c,e**

b, R = Me; **c**, R = Cl; **e**, R = F

Scheme 1.12

A plausible mechanism for the *ortho*-formylation of phenols **1**, *via* phenoxymagnesium chloride **19**, obtained from the reaction of the phenol with magnesium dichloride and triethylamine is proposed below (Figure 1.2). The intermediate **A** reacts with paraformaldehyde through the cyclohexadienone structure **B** to give the magnesium salt of salicyl alcohol **C**. This intermediate subsequently reacts with another equivalent of formaldehyde, forming salicylaldehydes **3** and methanol.[34]

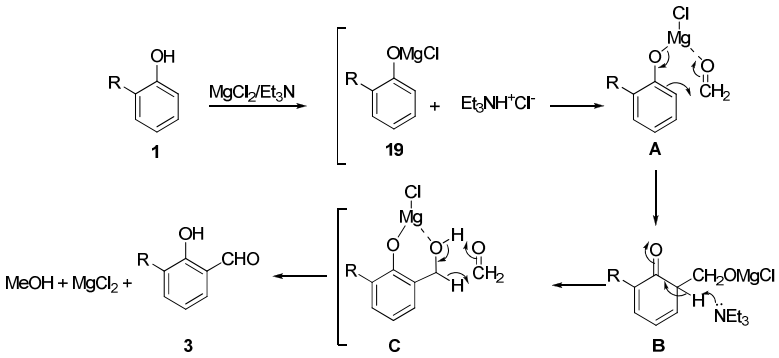
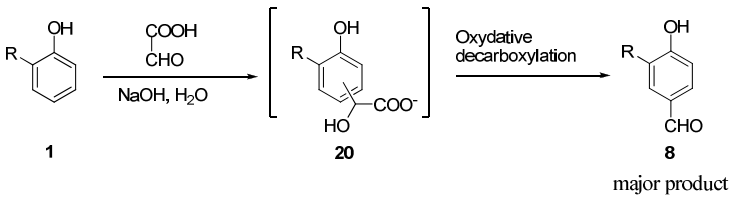


Figure 1.2 A plausible mechanism for the *ortho*-formylation of phenols using $MgCl_2$ and Et_3N

1.2 Alternative Formylation Methods of Phenols

Condensation of phenol **1** (R = OMe) with glyoxylic acid in basic media gave substituted mandelic acid **20**, which on oxidative decarboxylation yielded the corresponding *para*-hydroxyaldehyde **8** (vanillin) as major product together with *ortho*-hydroxy and di-hydroxyaldehyde as by-products.[36] This method was applied to prepare ethyl vanillin (R = OEt) in 100% yield by using NaOH and $CuSO_4$ followed by hydrolysis H_2SO_4-H_2O (Scheme 1.13).[37]

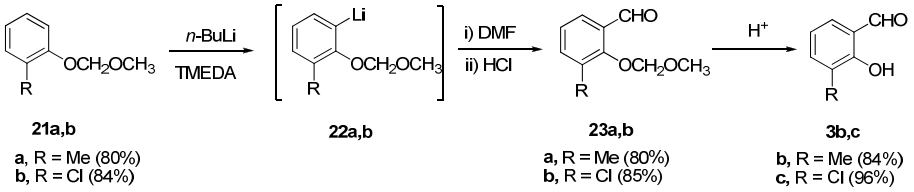


Scheme 1.13

Methyl formate can be used as the formylating agent of phenols in the presence of a mixture of hydrogen fluoride and boron trifluoride to convert the phenols to the corresponding aldehydes.[38] However, this method mostly leads to product mixtures and requires a large excess of boron trifluoride.

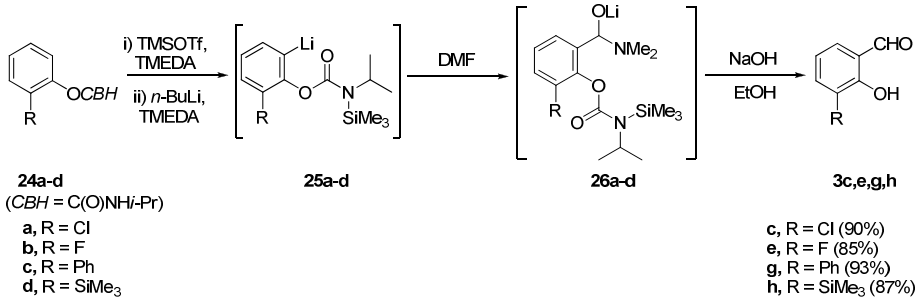
The formylation of phenols with 1,1-dichloromethoxymethane ($MeOCHCl_2$) and aluminum trichloride or titanium tetrachloride proceeded with poor yields of aldehydes and also with low selectivity.[39]

Salicylaldehydes **3** were prepared *via* the *ortho*-lithio derivatives of methoxymethyl-protected phenols **21** in a three-step protocol. First by the preparation of the phenyl ether **21**, second by a combined *ortho*-lithiation and formylation step, and finally by the cleavage of the ether linkage of compounds **23**. Overall yields ranged from 53-68% (Scheme 1.14).[40]



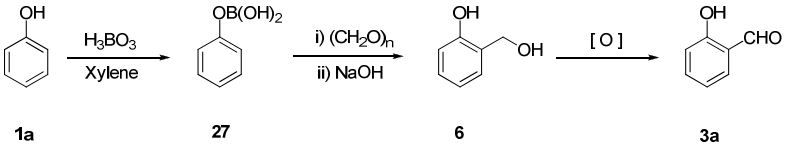
Scheme 1.14

Alternatively, a two-step protocol for the *ortho*-specific formylation of phenols exists *via* directed *ortho*-lithiation of *ortho*-aryl *N*-isopropylcarbamates **24**, which are obtained from the corresponding phenols and isopropyl isocyanate. After a DMF quench of the intermediate aryllithium **25** and basic work-up, the corresponding salicylaldehydes **3** were obtained in 85-93% yields. However, no yields were reported for the protection step (Scheme 1.15).[41]



Scheme 1.15

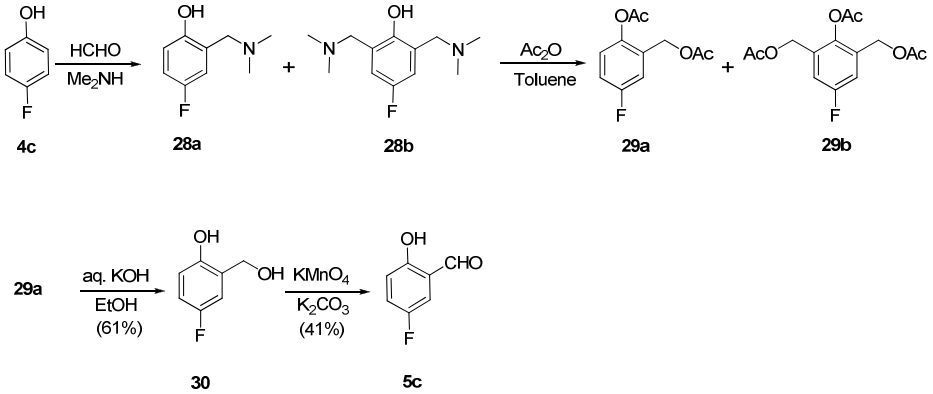
Hydroxymethylation of the borate ester **27** with paraformaldehyde followed by hydrolysis with NaOH yielded 2-hydroxybenzyl alcohol (**6**). Oxidization by oxygen with 10% platinum on carbon catalyst (or palladium) in aqueous NaOH yielded 60.5% of salicylaldehyde **3a** (Scheme 1.16).[42,43]



1a **27** **6** **3a**

Scheme 1.16

5-Fluorosalicylaldehyde (**5c**) has been prepared from 4-fluorophenol (**4c**) in four steps in order to make 5-fluorosalicylic acid, an important derivative that has anti-inflammatory and other biological activity.[44] The procedure started with reductive amination of **4c** using HCHO-Me_2NH to give the amino derivative **28a** and bis-diamino derivative **28b** as a 6:1 mixture, which was converted with excess Ac_2O to the corresponding acetates **29a** and **29b** as by-product. The major component was isolated and deacetylated with aqueous KOH in ethanol, followed by $KMnO_4$ oxidation of the resulting hydroxybenzyl alcohol **30**, to give the salicylaldehyde **5c** (Scheme 1.17).[45]



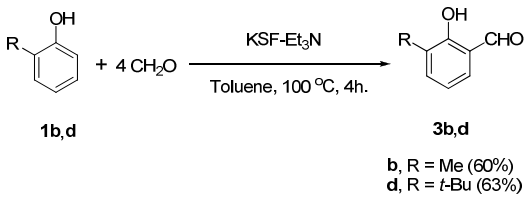
4c **28a** **28b** **29a** **29b**

30 **5c**

Scheme 1.17

Recently, Sartori and co-workers[46] synthesised substituted salicylaldehydes in good yields (60-63%) and excellent selectivity (89-92%) from alkyl substituted phenols and formaldehyde using montmorillonite KSF-Et_3N as a heterogeneous catalyst (Scheme 1.18). Unfortunately, recycling of the montmorillonite was problematic, as one additional cycle

yielded only 36% of the product. Moreover, four equivalents of formaldehyde were employed.



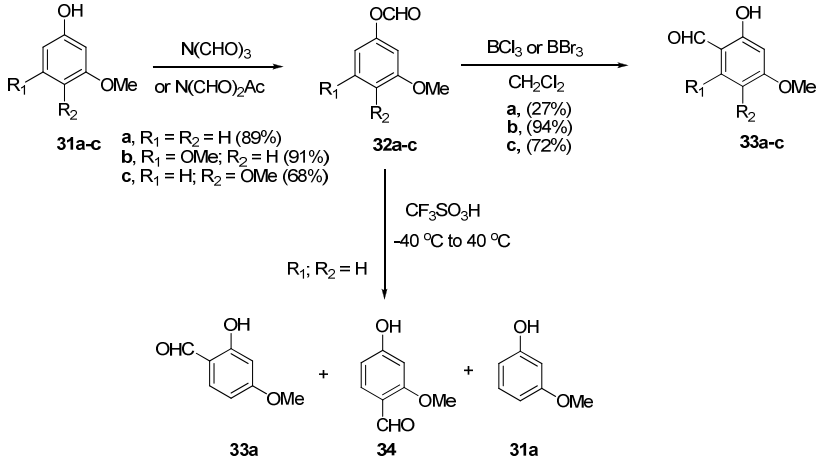
1b,d **3b,d**

b, R = Me (60%)
d, R = *t*-Bu (63%)

Scheme 1.18

Salicylaldehydes **33a-c** can be obtained by the Fries reaction, in which aryl formates **32a-c** are rearranged in the presence of a Lewis acid to give hydroxyaromatic aldehydes.[47] The yields in this reaction depend on the reaction conditions, *e.g.* temperature, solvent, the Lewis acid catalyst used, and the position of the substituent. Aryl formates **32a-c** were prepared by the formylation of hydroxyarenes **31a-c** with *N*,*N*-diformylacetamide or *N*,*N*-diformylformamide in good yields (Scheme 1.19).

Fries rearrangement of the formyl group can also be induced by trifluoromethanesulfonic acid, but in this case a mixture of regioisomeric aldehydes **33a**, **34** and the deformylated product **31a** was formed in a 1: 1: 2 ratio, respectively (Scheme 1.19).[48]



31a-c **a**, $R_1 = R_2 = H$ (89%)
b, $R_1 = OMe$; $R_2 = H$ (91%)
c, $R_1 = H$; $R_2 = OMe$ (68%)

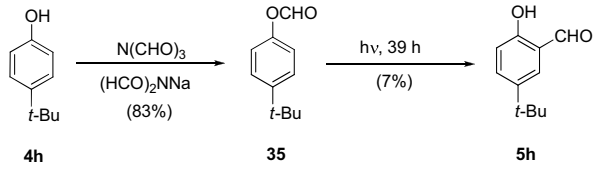
32a-c **33a-c**

33a **34** **31a**

Scheme 1.19

The Fries reaction can also be performed photochemically and the rearrangement of a formyl group under such conditions has been observed. When 4-*tert*-butylphenyl formate

(**35**) was irradiated for 39 hours in benzene, 5-*tert* butyl-2-hydroxybenzaldehyde (**5h**) could be isolated in 7% yield (Scheme 1.20).[49]

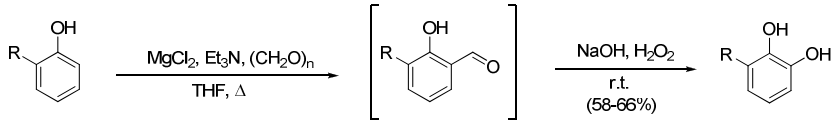


4h **35** **5h**

Scheme 1.20

1.3 Applications of the $MgCl_2$-Et_3N *ortho*-Formylation Method

Phenols **1** have been converted to salicylaldehydes **3** by *ortho*-formylation using $MgCl_2$-Et_3N and $(CH_2O)_n$ in THF and subsequently treated with aqueous $NaOH/H_2O_2$ (Dakin oxidation), affording the corresponding catechols **36** in a one-pot procedure (Scheme 1.21).[50]

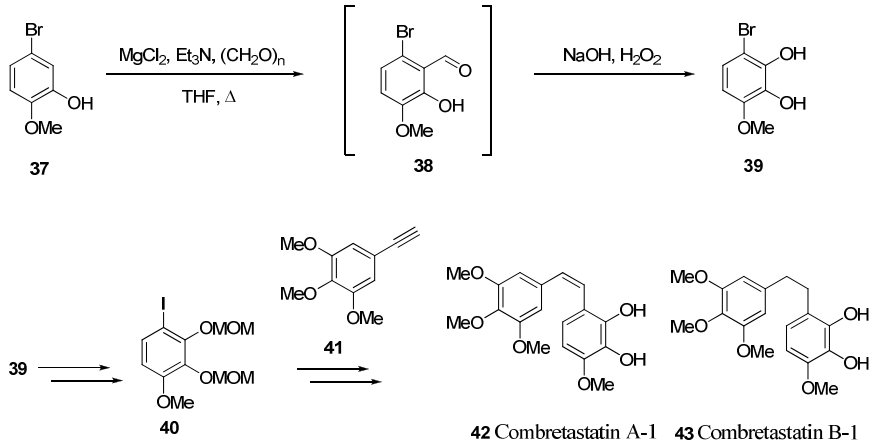


1b,c,e **3b,c,e** **36a-c**

a, R = Me (66%)
b, R = Cl (58%)
c, R = F (66%)

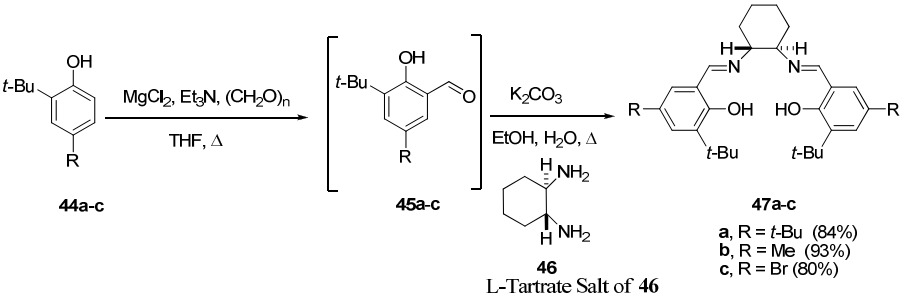
Scheme 1.21

This method was used to develop a facile synthesis of combretastatins A-1 (**42**) and B-1 (**43**). The natural products were obtained by coupling MOM-protected iodomethoxycatechol **40** with 3,4,5-trimethoxyphenylacetylene (**41**) in a Sonogashira reaction followed by reduction (Scheme 1.22).[51]



Scheme 1.22

Another application of the *ortho*-formylation method was accomplished by converting the phenols **44** to salicylaldehydes **45**, which subsequently were treated with (+)-(*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **46** affording the corresponding salen ligands **47** in high yields. The reactions were conveniently carried out as a one-pot procedure (Scheme 1.23).[52] This method afforded the salen ligands in more than twice the yields previously reported by Jacobsen and co-workers.[16b]

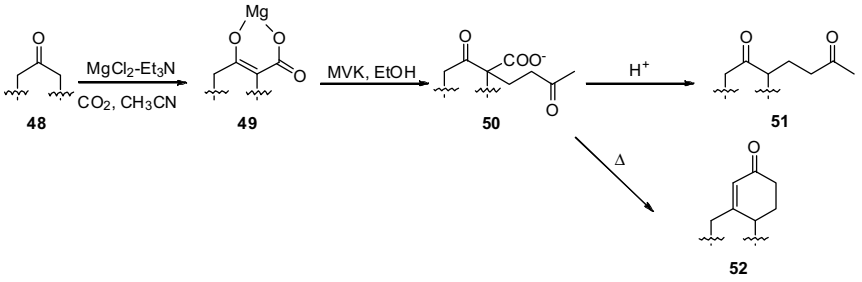


Scheme 1.23

1.4 Other Applications of the $MgCl_2$-Et_3N Base System

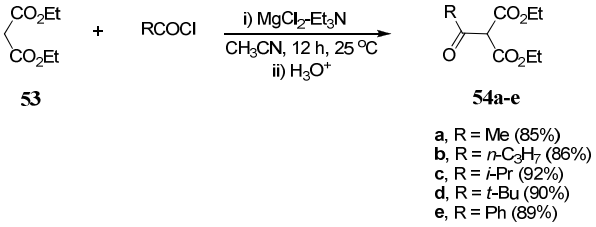
The combination of $MgCl_2$ and Et_3N is a useful base system in organic synthesis. This combination is a considerably stronger base than Et_3N alone and has been used in different base induced reactions.[53]

α-Carboxylation of ketones **48** with carbon dioxide in the presence of $MgCl_2$-Et_3N, followed by reaction with methyl vinyl ketone (MVK), gives the Michael adducts **51** in 42-75% yields or the Robinson adducts **52** in 56-75% yields. This method reduced the polymerization of MVK under strongly basic conditions (Scheme 1.24).[54]



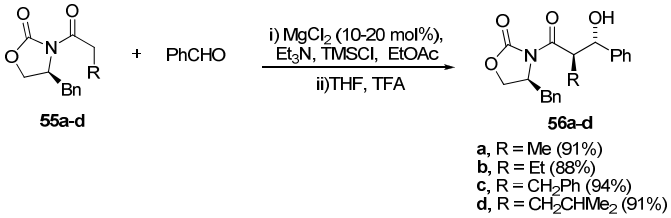
Scheme 1.24

Acylation of diethyl malonate **53** with an acid chloride using $MgCl_2$-Et_3N as base system gives adducts **54** in excellent yields (Scheme 1.25).[55] This method was also used for preparation of *β*-oxo esters from ethyl malonate mono potassium salt and acid chlorides in 92-99% yields.[56]



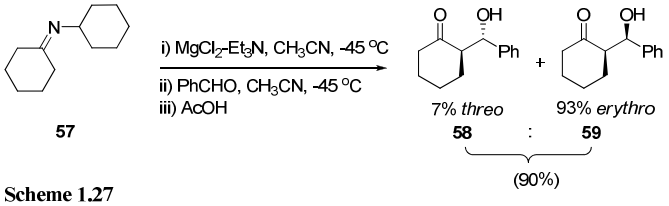
Scheme 1.25

In 2002 Evans *et al.*[57] used $MgCl_2$-Et_3N in *anti*-aldol reactions of chiral *N*-acyloxazolidinones **55a-d** in the presence of chlorotrimethylsilane. The adducts **56a-d** were formed with high diastereoselectivity (up to 32:1 dr) (Scheme 1.26).



Scheme 1.26

Stereoselective imine aldol reactions of *N*-cyclohexylimine **57** with aromatic aldehydes in the presence of $MgCl_2$-Et_3N at -45 ^oC were examined recently by Hayashi *et al.*;[58] high yields of products were obtained consisting essentially of the *erythro* isomer (Scheme 1.27).



Scheme 1.27

1.5 Aim of the Study

The overall aim of this study was to employ the *ortho*-formylation method reported by Skattebøl and co-workers[34,35] for synthesis of natural products and compounds of medicinal interest.

Also, the environmentally benign conditions in the Casnati-Skattebøl[27,28,34,35] *ortho*-formylation reaction inspired us to develop one-pot methods for the synthesis of useful starting materials like *ortho*-hydroxycinnamate esters, salicylamines, and salicylnitriles.

Natural products have played an eminent role in the discovery and development of new drugs. Over half of the nearly 1000 small-molecule drugs introduced on the market over the past two-three decades are either natural products or in some way related to natural products.[59] Hence, it is still of great interest to synthesize natural products and submit them to biological testing.

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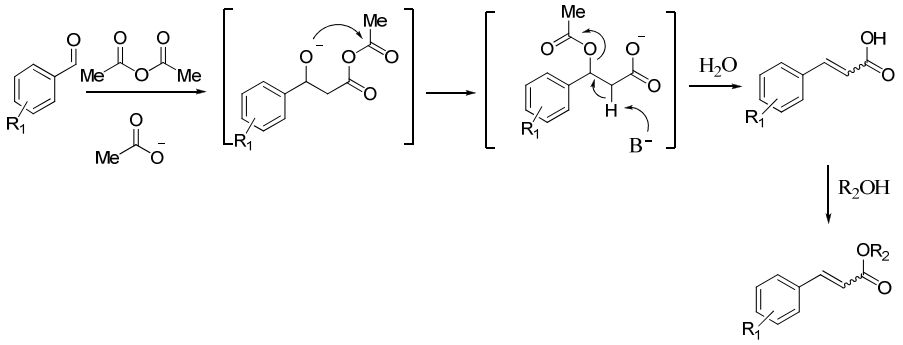
2. RESULTS AND DISCUSSION

2.1 Application of the *ortho*-Formylation Method

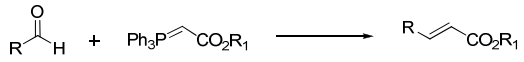
2.1.1 Synthesis of *ortho*-Hydroxycinnamate Esters

The aim of this study was to develop a simple and efficient procedure for the synthesis of cinnamic esters. Cinnamic esters and their derivatives are useful intermediates for the synthesis of heterocyclic compounds[1] and they are also used as antioxidants.[2] One of the most common procedures for the preparation of cinnamic esters is the Perkin reaction. In this reaction, the respective aldehyde reacts with acetic anhydride and anhydrous sodium- or potassium acetate, yielding an α,β-unsaturated acid. Esterification with an alcohol affords the corresponding cinnamate ester (Scheme 2.1).[3] However, the Perkin reaction is often hampered by low yields,[4] especially for the preparation of *ortho*-hydroxycinnamate esters from salicylaldehydes.[5]



Scheme 2.1 Synthesis of α,β-unsaturated esters by Perkin reaction

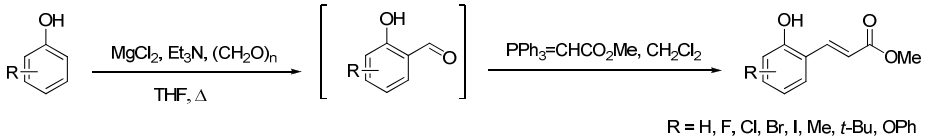
α,β-Unsaturated esters are readily available using the Wittig reaction between an aldehyde and an ylide (Scheme 2.2).[6]



Scheme 2.2 Synthesis of α,β-unsaturated esters using the Wittig reaction

The *ortho*-formylation of phenols (as mentioned in the introduction) to salicylaldehydes was described by Skattebøl *et al.*[7a,b] by heating a mixture of the phenol, anhydrous $MgCl_2$, triethylamine, and paraformaldehyde in refluxing THF. Different alkyl- and halogen-substituted phenols afford excellent yields of the corresponding salicylaldehydes.

Since phenols are inexpensive and readily available, we wanted to use the Casnati-Skattebøl[7] *ortho*-formylation method to prepare *ortho*-hydroxycinnamate esters. Hansen and Skattebøl tried the Perkin reaction by a one-pot procedure but this protocol failed.[8] However, the Wittig reaction was successful. After the phenols were converted to salicylaldehydes, a solution of methyl (triphenylphosphoranylidene)acetate in dichloromethane was added dropwise. After stirring 4–8 hours at ambient temperature conversion was completed (Scheme 2.3).



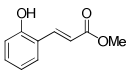
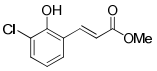
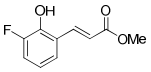
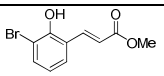
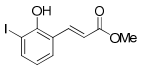
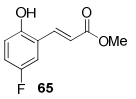
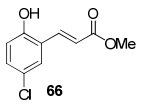
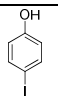
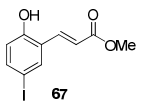
Scheme 2.3 General outline for one-pot synthesis of *ortho*-hydroxycinnamate esters

This reaction was carried out with both 2- and 4-halogen-substituted phenols as starting materials and the corresponding cinnamates were obtained in 60-78% yields (Table 2.1).

Moreover, this one-pot process, with two or more transformations, offers a number of advantages. In particular, the direct transformation of intermediates to the desired products reduces the time normally spent on isolation and purification.

New compounds were characterized on the basis of spectral data. The (*E*)-configuration which is normally observed for this type of Wittig reactions was established by ^{1}H NMR spectroscopy displaying *trans*-coupling constants in the range J = 15.8-16.2 Hz (Paper I).

Table 2.1. One-pot synthesis of *ortho*-hydroxycinnamate esters.

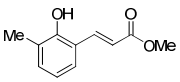
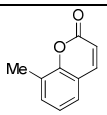
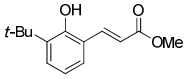
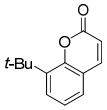
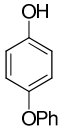
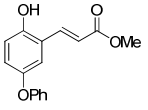
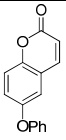
Phenol	Product	Overall yield %
 **1a**	 **60**	74
 **1c**	 **61**	73
 **1e**	 **62**	61
 **1f**	 **63**	63
 **1g**	 **64**	78
 **4c**	 **65**	66
 **4g**	 **66**	65
 **4k**	 **67**	60

Compounds **60** and **66** are known; for references see the Appendix.

In the case of alkyl (R = Me, *t*-Bu) and phenoxy-substituted phenols, the reactions did not go to completion even after stirring at room temperature for 21 hours. However, after heating for 2–10 hours at gentle reflux, complete conversion was observed. The methyl *ortho*-hydroxycinnamates **68**, **69**, and **70** were accompanied by minor amounts of the

corresponding coumarins **71**, **72**, and **73**, respectively (Table 2.2). We anticipate that the *ortho*-hydroxycinnamate esters, upon heating isomerize to the (*Z*)-isomers which cyclize to the coumarins.

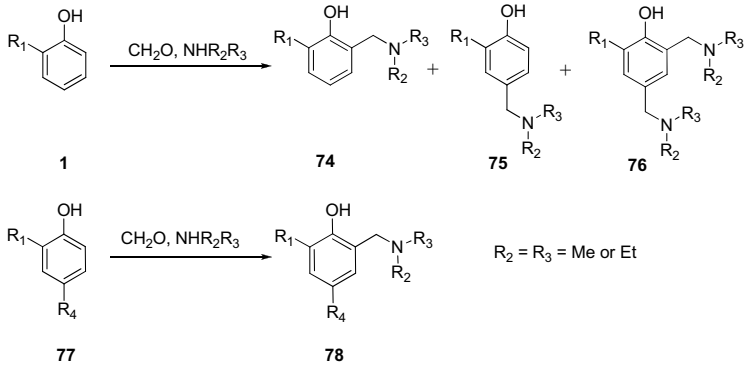
Table 2.2 One-pot synthesis of *ortho*-hydroxycinnamate esters.

Phenol	Product (Overall yield %)	
 **1b**	 **68** (51%)	 **71** (20%)
 **1d**	 **69** (54%)	 **72** (17%)
 **4j**	 **70** (59%)	 **73** (24%)

Compounds **68**, **69**, and **71** are known; for references see the Appendix.

2.1.2 Synthesis of Substituted Salicylamines

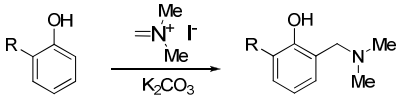
Salicylamines and their derivatives are useful intermediates for the synthesis of heterocyclic compounds, such as benzoxazines,[9] benz[1,2,3]oxathiazine 2-oxides,[10] and benz[1,3]oxazin-2-ones.[11] Some salicylamines were tested as potential metal complexing agents including metal ions extractants.[12] They were also tested as catalyst components in organic synthesis.[13] Some salicylamines possess antimalarial and antimicrobial activity.[14] Aminomethylation of phenols is traditionally achieved with formaldehyde and amines under acidic conditions using the Mannich reaction,[15,16] which occurs readily in *ortho*- and *para*-positions affording polysubstituted phenols.[17] The position and nature of the substituents as well as the reaction conditions play an important role on the orientation of the Mannich reaction (Scheme 2.4).[18]



Scheme 2.4 Synthesis of substituted salicylamines employing the Mannich reaction

When 2-chlorophenol (**1c**) was treated with 37% aqueous formaldehyde and 2-bromoaniline at room temperature, <10% yield of the Mannich product was obtained together with polymeric material.[19]

Pochini *et al*. reported that phenols **1a-d** reacted with Eschenmoser's salt (*N*,*N*-dimethylmethylene iminium iodide) in the presence of potassium carbonate affording exclusively *ortho*-substituted products **79-82** in yields ranging from 75-98% (Scheme 2.5).[20]

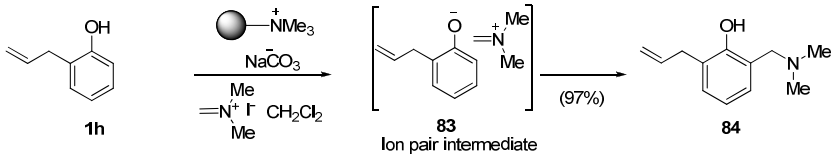


a, R = H; **b**, R = Me
c, R = Cl; **d**, R = *t*-Bu

79, R = H; **80**, R = Me;
81, R = Cl; **82**, R = *t*-Bu

Scheme 2.5

Recently, Ley and co-workers reported one example of a carbonate exchange resin catalyzed reaction between 2-allylphenol (**1h**) and Eschenmoser's salt giving 2-allyl-6-((dimethylamino)-methyl)phenol (**84**) in excellent yield. This method avoids distillation or recrystallization (Scheme 2.6).[21]

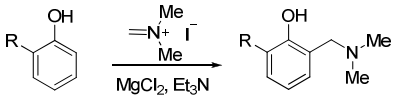


Scheme 2.6

Eschenmoser's salt is commercially available, but can be prepared from *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine with CH_2ClI or CH_2I_2 in DMSO at ambient temperature.[22]

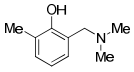
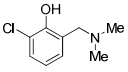
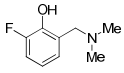
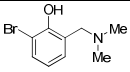
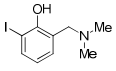
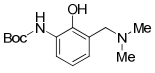
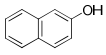
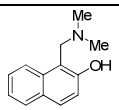
We decided to use the combination of $MgCl_2$-Et_3N as the base system in the Mannich reaction. Eschenmoser's salt was added to a mixture of $MgCl_2$-Et_3N and 2-methylphenol (**1b**) in dichloromethane. After stirring for 3 hours at ambient temperature, complete conversion of the phenol was observed, and only one regioisomer of the Mannich base **80** was isolated in 82% yield (Scheme 2.7 and Table 2.3). Several other 2-substituted phenols were subjected to the same conditions and the corresponding Mannich bases **81-88** were obtained in 66-83% yields. An almost quantitative yield of the product **90** was obtained when *β*-naphthol (**89**) was subjected to these reaction conditions. According to the ^{1}H NMR spectra of the crude reaction mixtures, complete regioselectivity was observed in all cases. The products were identified by physical and spectral data (Paper II).

Mannich bases are versatile intermediates for the synthesis of a wide range of biologically active compounds, and our protocol compares favorably with others when considering yields, regioselectivity, and simplicity.[23]



Scheme 2.7 General outline for syntheses of substituted *N*,*N*-dimethylsalicylamines employing the Mannich reaction

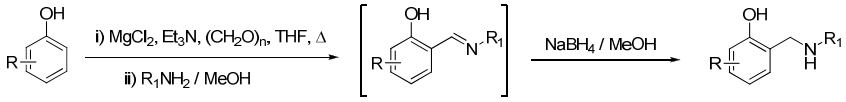
Table 2.3 Synthesis of substituted *N*,*N*-dimethylsalicylamines by Mannich reaction

Phenol	Product	Overall yield %	Time (h) /solvent
 **1b**	 **80**	82	5/toluene
 **1c**	 **81**	77	3/CH_2Cl_2
 **1e**	 **85**	82	8/CH_2Cl_2
 **1f**	 **86**	83	3/CH_2Cl_2
 **1g**	 **87**	79	2/CH_2Cl_2
 **1i**	 **88**	66	12/CH_2Cl_2
 **89**	 **90**	98	0.5/CH_2Cl_2

Compounds **80**, **81**, and **90** are known; for references see the Appendix.

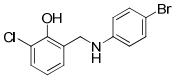
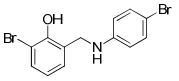
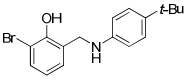
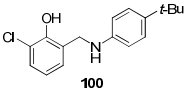
Then we tried another iminium salt[24] under the same reaction conditions, but this was unsuccessful. Since few other methods for the synthesis of salicylamines have been reported,[25] facile and efficient procedures for the synthesis of mono *N*-substituted salicylamines are still desirable. We turned our attention to the synthesis of *N*-substituted salicylamines by a simple and regioselective method (Scheme 2.8).[26]

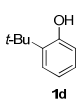
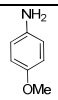
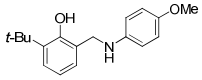
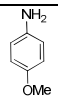
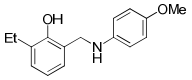
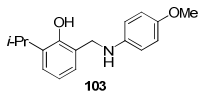
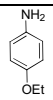
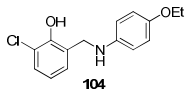
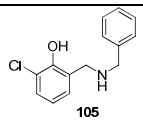
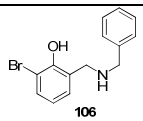
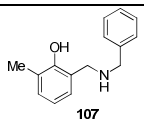
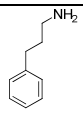
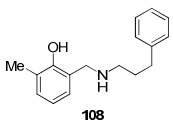
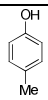
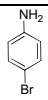
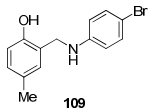
As previously described, the salicylaldehydes were prepared from phenols **1** and **4** by our *ortho*-formylation method.[7a] A solution of an amine followed by addition of $NaBH_4$ was then added in a one-pot procedure. After heating to reflux for 30 minutes and further stirring the reaction mixture for another 2–10 hours at room temperature, the reaction mixture was worked up in the usual manner. When necessary, the products **97-112** were purified by column chromatography and characterized by physical and spectral data. This one-pot procedure combining formylation and reductive amination was carried out with both alkyl and halogen substituted phenols as starting materials, and the overall yields ranged from 51-74% (Scheme 2.8 and Table 2.4).

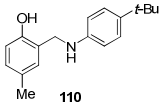
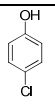
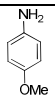
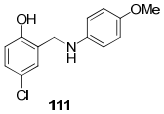
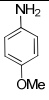
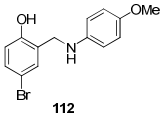


Scheme 2.8 General outline for syntheses of mono *N*-substituted salicylamines

Table 2.4 Syntheses of mono *N*-substituted salicylamines

Phenol	Amine	Product	Overall yield %
 **1c**	 **91**	 **97**	51
 **1f**	 **91**	 **98**	56
 **1f**	 **92**	 **99**	57
 **1c**	 **92**	 **100**	58

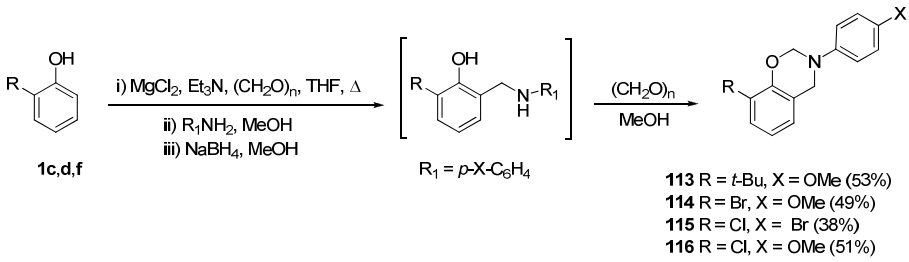
 **1d**	 **93**	 **101**	68
 **1j**	 **93**	 **102**	61
 **1k**	 **93**	 **103**	55
 **1c**	 **94**	 **104**	56
 **1c**	 **95**	 **105**	61
 **1f**	 **95**	 **106**	51
 **1b**	 **95**	 **107**	64
 **1b**	 **96**	 **108**	63
 **4e**	 **91**	 **109**	74

 **4e**	 **92**	 **110**	73
 **4g**	 **93**	 **111**	66
 **4l**	 **93**	 **112**	69

Compounds **109** and **111** are known; for references see the Appendix.

2.1.3 One-pot Synthesis of Substituted Dihydro-2*H*-1,3-benzoxazines

The aforementioned protocol for the preparation of dihydro-2*H*-1,3-benzoxazines was investigated further. The solution of mono *N*-substituted benzylamine was treated with two equivalents of paraformaldehyde which gave, after purification, substituted dihydro-2*H*-1,3-benzoxazines **113-116** in 38-53% isolated yields in a one-pot sequence (Scheme 2.9). Benzoxazines have previously been reported to exhibit a wide range of interesting biological activities.[27] The operational simplicity of this method makes it attractive for preparative use as well as for the synthesis of screening libraries for drug discovery.

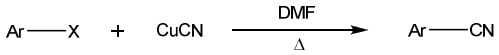


Scheme 2.9 One-pot syntheses of *N*-substituted dihydro-2*H*-1,3-benzoxazines

2.1.4 Synthesis of Substituted Salicylnitriles

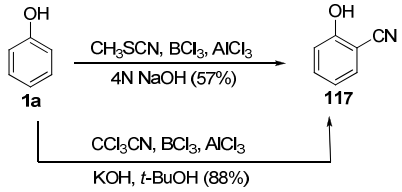
The aim of this study was to convert phenols to substituted salicylnitriles by a mild and reliable method.

Aromatic nitriles can be prepared by the Rosenmund-von Braun reaction[28,29] using metal-mediated displacement of aromatic halides by cyanide ion (Scheme 2.10). These compounds are versatile starting materials for amides, amines, esters, carboxylic acids, etc., as well as for the synthesis of heterocyclic and biologically active compounds.[30] The disadvantage of this method is the use of toxic cyanide salts and high temperatures (>150-160 ºC), which are not suitable for industrial applications. Hence, it is not surprising that only few examples of the preparation of substituted salicylnitriles have been reported using the Rosenmund-von Braun reaction.[31]



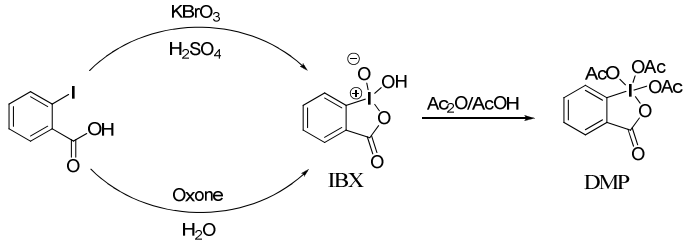
Scheme 2.10 Synthesis of aromatic nitriles by Rosemund-von Braun reaction

There are few other methods to convert phenol (**1a**) to salicylnitrile (**117**, 2-hydroxybenzonitrile) (Scheme 2.11);[32] however, several methods are known for the transformation of salicylaldehyde to salicylnitrile *via* dehydration of aldoximes[33] or by using reagents such as sodium bis(trimethylsilyl)amide,[34] aqueous ammonia/sodium dichloroiodate,[35] and 1,1-dimethylhydrazine/dimethyl sulphate in the presence of K_2CO_3.[36]



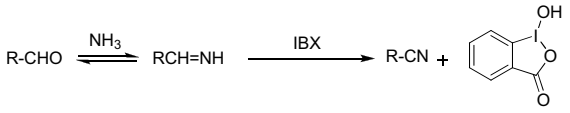
Scheme 2.11

Recently, hypervalent iodine reagents such as 2-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP) have attracted interest as oxidation agents.[37] These reagents are commercially available or can be prepared from 2-iodobenzoic acid (Scheme 2.12).[38]



Scheme 2.12 Syntheses of IBX and DMP

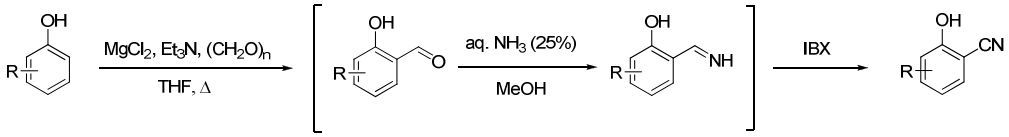
The oxidation of imines to nitriles using IBX in aqueous ammonia was recently reported by Akamanchi and co-workers (Scheme 2.13).[39]



Scheme 2.13

We decided to adapt this method for the synthesis of substituted salicylnitriles from phenols. A complete regioselective introduction of the nitrile group, *via* oxidation of imine intermediates from salicylaldehydes, was expected to give the desired salicylnitriles. Furthermore, few substituted salicylnitriles are commercially available.

Salicylaldehydes were formed by the *ortho*-formylation of the corresponding phenols as previously discussed, and subsequent treatment with aqueous ammonia afforded the corresponding salicylimines. The imines were then oxidized with 1.2 equivalents of IBX (SIBX) to salicylnitriles in a one-pot operation (Scheme 2.14).

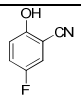
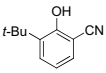
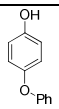
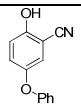
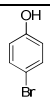
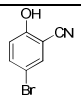
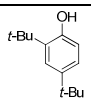
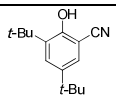
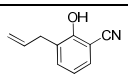
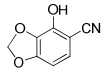


Scheme 2.14 General outline for one-pot synthesis of substituted salicylnitriles

2-Alkyl and 2-halogen substituted phenols **1b-f, h** were subjected to this protocol, affording the corresponding salicylnitriles **119-124** in 48-71% isolated yields over three steps. As expected, the reaction of 4-substituted phenols **4c, h, j, l** furnished the 5-substituted

salicylnitriles **125-128** in comparable yields. Similarly, 2,4-di-substituted phenol **44a** gave **129** in 56% yield. (Table 2.5).

Table 2.5. One-pot synthesis of substituted salicylnitriles.

Phenol	Product	Overall yield %	Phenol	Product	Overall yield %
 **1b**	 **119**	62	 **4c**	 **125**	67
 **1c**	 **120**	70	 **4h**	 **126**	67
 **1d**	 **121**	71	 **4j**	 **127**	54
 **1e**	 **122**	48	 **4l**	 **128**	70
 **1f**	 **123**	55	 **44a**	 **129**	56
 **1h**	 **124**	53	 **118**	 **130**	58

Compounds **119**, **120**, **123**, **124**, **128**, and **129** are known; for references see the Appendix.

Compound **124** was useful for the synthesis of a benzofuran derivative as described by Sekizaki *et al.*[40] Moreover, 2,3-(methylenedioxy)-phenol (**118**) was converted in 58% yield to the corresponding salicylnitrile **130**, which may be of interest as a starting material for

the syntheses of some highly oxygenated natural products such as powelline, narciclasine and pancratistatin (Figure 2.1).[41,42]

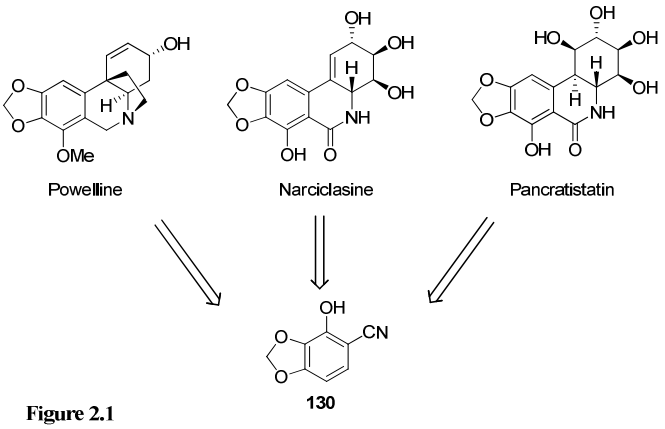
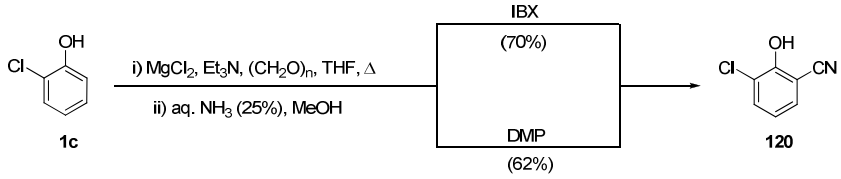


Figure 2.1

As expected complete regioselectivity was observed in all cases. All products were identified and characterized by physical and spectral data.

Starting from 2-chlorophenol (**1c**) we also tried to use DMP as the oxidant but the yield was lower than with IBX under same reaction conditions (Scheme 2.15).



Scheme 2.15

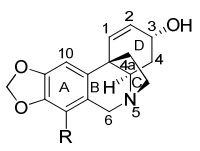
These results have been summarized in Paper **I**, **II**, and **III**.

2.2 Applications of the *ortho*-Formylation Method in Natural Product Synthesis

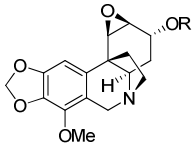
2.2.1 First Total Synthesis of (±)-Powelline

The aim of this study was to achieve an efficient total synthesis of (±)-powelline **132**, a natural product not previously synthesized.

The 2,3,4,4*a*-tetrahydro-1*H*,6*H*-5,10*b*-ethanophenanthridine (*cis*-3a-aryloctahydroindole nucleus) skeleton characterizes the crinine sub-class of *Amaryllidaceae* alkaloids such as crinine (**131**), powelline (**132**), crinamidine (**133**), and undulatine (**134**) (Figure 2.2).[43] (+)-Powelline **132** has been isolated from several *Amaryllidaceae* species like *Crinum bulbispermum*[44] and *Crinum moorei.*[45]



131 (Crinine R = H)
132 (Powelline R = OMe)



133 (Crinamidine R = H)
134 (Undulatine R = Me)

Crinum bulbispermum is one of many species of Amaryllidaceae native to South Africa

Figure 2.2

Several members in this class of alkaloids display interesting biological properties such as acetylcholinesterase inhibition,[46] cytotoxicity,[47] and antimalarial[48] effects. Due to their interesting structures, limited supply, and their bioactivities, these natural products constitute obvious targets for total synthesis.[49]

Our strategy was dependent on an intramolecular phenolic coupling reaction and an intramolecular Michael addition as key steps (Figure 2.3).

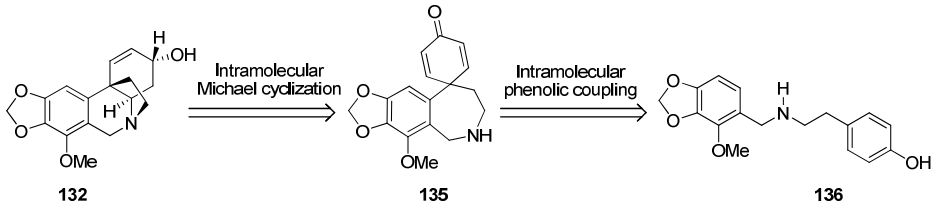
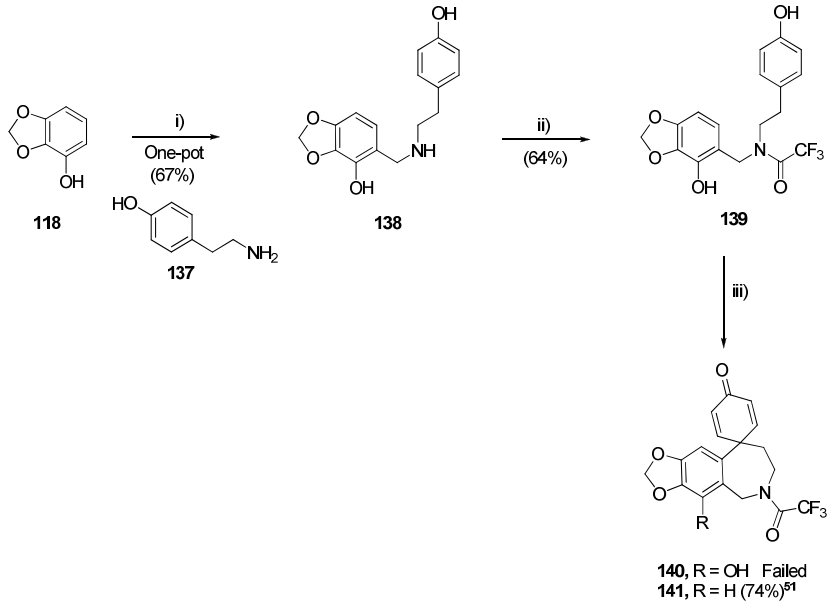


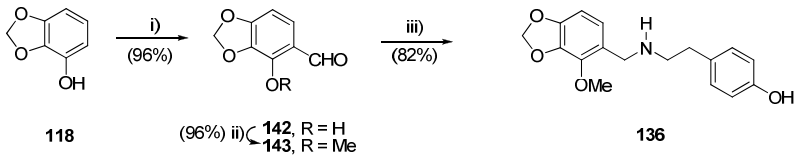
Figure 2.3 Retrosynthetic analysis of powelline

We started our synthesis of this alkaloid with *ortho*-formylation of 2,3-methylenedioxyphenol (**118**). The salicylaldehyde was, without isolation, treated with tyramine (**137**) and $NaBH_4$ in a one-pot reaction as previously described[50] to yield the secondary amine **138**. Monoprotection of the amine group with TFA-anhydride and DMAP as a base afforded **139**. The attempted intramolecular phenolic coupling of **139** using the hypervalent iodine reagent [*bis*(trifluoroacetoxy)iodo]-benzene (PIFA) in trifluoroethanol failed to give compound **140**. However, compound **141** has previously successfully synthesized by Kodama *et al*. in 74% yield under the same reaction conditions.[51] Hence, we decided to protect the methylenedioxyphenol hydroxyl group before performing the intramolecular phenolic coupling reaction (Scheme 2.16).



Scheme 2.16. i) a) $MgCl_2$, Et_3N, $(CH_2O)_n$, THF, 70 °C, b) tyramine (**137**), MeOH, r.t., c) $NaBH_4$, MeOH, r.t.; ii) $(CF_3CO)_2O$, DMAP, CH_2Cl_2, 0 °C to r.t.; iii) $PhI(O_2CCF_3)_2$, CF_3CH_2OH, 0 °C.

Our new approach started with the preparation of salicylaldehyde **142** in 96% yield. Protection of the hydroxyl group with MeI and K_2CO_3 afforded **143** in 96% yield, followed by reductive amination with tyramine (**137**) to the amine **136** in 82% yield (Scheme 2.17).



Scheme 2.17. i) a) $MgCl_2$, Et_3N, $(CH_2O)_n$, THF, 70 °C; ii) MeI, K_2CO_3, DMF, r.t.; iii) a) tyramine (**137**), MeOH, r.t., b) $NaBH_4$, MeOH, r.t.

Although we no longer have our one-pot procedure we prepared 2-methoxy-3,4-methylenedioxybenzaldehyde (**143**, croweacin aldehyde), which has been used as a key intermediate for the syntheses of a variety of natural products (Figure 2.4).[52] It was first obtained as an oxidative degradation product of 1-allyl-2-methoxy-3,4-methylenedioxybenzene (**144**, croweacin), which occurs in the essential oil separated from the leaves and terminal branchlets of *Eriostemon crowei.* At the same time, **143** was synthesized from 7,8-dihydroxycoumarin (**146**, daphnetin).[53] Since then, croweacin aldehyde (**143**) has been obtained by several routes. Apparently, the Vilsmeier formylation of **148** is the best method reported in the literature, although the product was contaminated by its regioisomer **149** (10-35%) (Scheme 2.18).[52c,54] We have developed a mild and reliable method to synthesize **143** with excellent yield (92%) over two steps from **118**, and with complete regioselectivity using the Casnati-Skattebøl *ortho*-formylation method.[7]

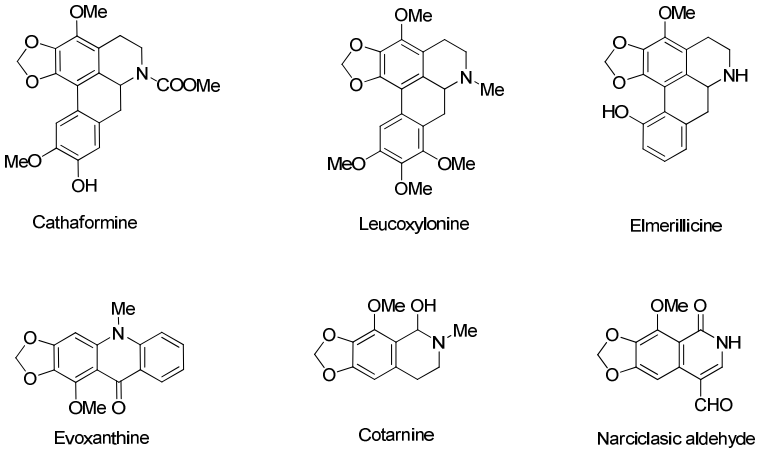
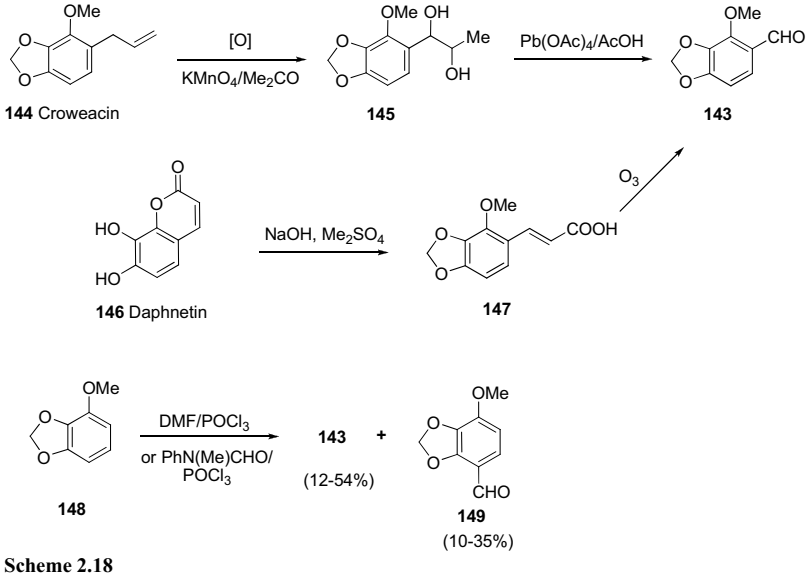
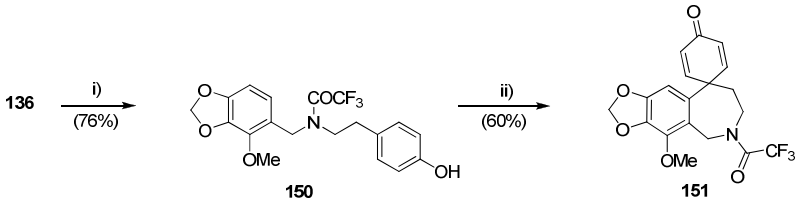


Figure 2.4



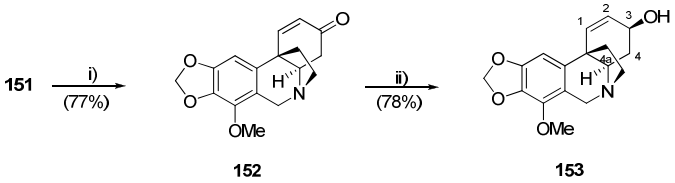
Scheme 2.18

The next step was monoprotection of the amine function in **136** with TFA-anhydride using DMAP as a base in dichloromethane to afford **150**. Reaction of the protected amine with the hypervalent iodine reagent [*bis*(trifluoroacetoxy)iodo]-benzene (PIFA) in trifluoroethanol gave compound **151** in 46% yield over the two steps (Scheme 2.19).



Scheme 2.19. i) $(CF_3CO)_2O$, DMAP, CH_2Cl_2, 0 ºC to r.t.; ii) PIFA, CF_3CH_2OH, 0 ºC.

The intramolecular Michael cyclization reaction of compound **151** was achieved with aqueous potassium hydroxide affording racemic oxopowelline **152**. Subsequent Luche reduction[55,56] using $NaBH_4$ and $CeCl_3$ gave alcohol **153** in 60% yield over the two steps (Scheme 2.20). A NOE effect was observed between protons H-4a (3.02 ppm) and H-3 (4.16 ppm), confirming the relative stereochemistry depicted for compound **153** (Figure 2.5 and 2.6).



Scheme 2.20. i) KOH (10% aq.) MeOH, r.t.; ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, r.t.

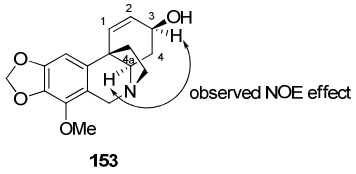


Figure 2.5

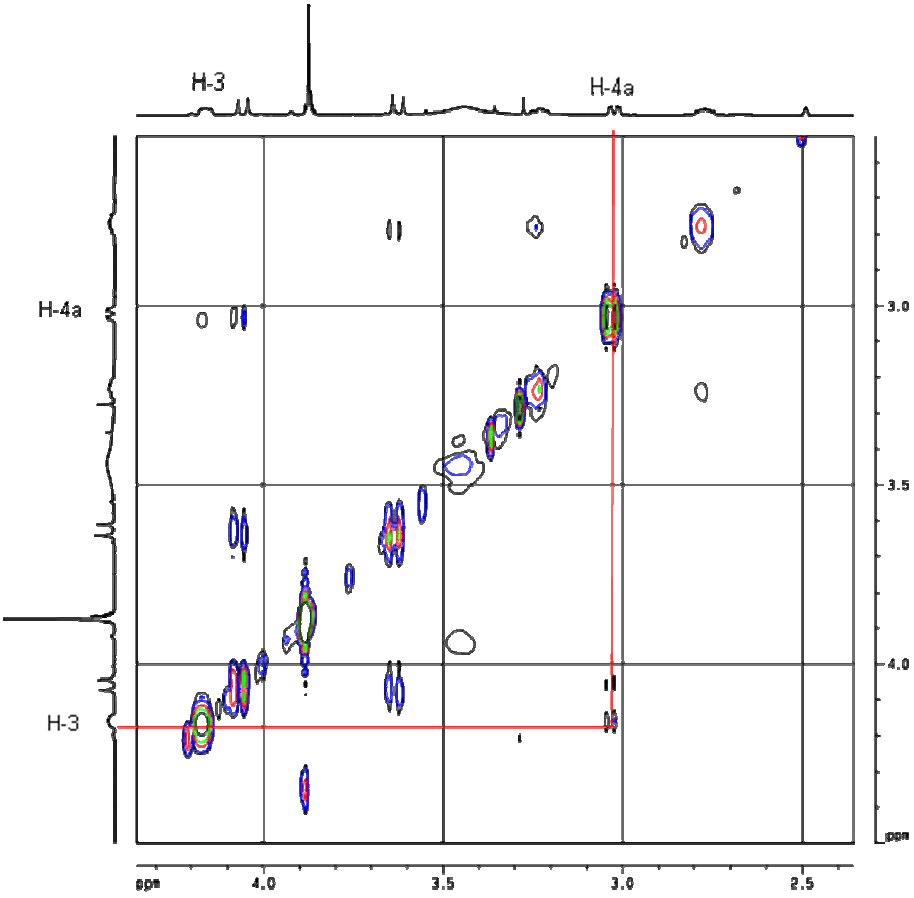
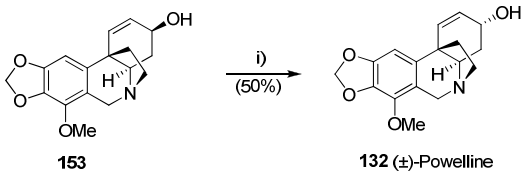


Figure 2.6. NOESY experiment of compound **153**. The spectrum was recorded on a Bruker Avance DPX- 600 MHz

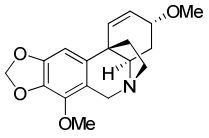
Finally, Mitsunobu inversion[57] of the C-3 hydroxyl group yielded racemic powelline **132** in 50% yield with spectral data in accord with those previously reported [58,44] (Scheme 2.21).



Scheme 2.21. i) a) DEAD, PPh_3, HCO_2H, THF, r.t., (53%); b) NaOH, THF, r.t., (94%).

Next, we tried reducing oxopowelline **152** to powelline **132** by an asymmetric reduction of the carbonyl group. However, using both CBS catalysts ((*R*)-2-methyl-CBS-oxazaborolidine and (*S*)-2-methyl-CBS-oxazaborolidine) and 2-(3-nitrophenyl)-1,3,2-dioxaborolane-4*S*,5*S*-dicarboxylic acid failed to give the correct configuration of powelline, instead complex diastereomeric mixtures of epipowelline and powelline were obtained.

Future work in our group includes total syntheses of crinamidine (**133**), undulatine (**134**), and buphanidrine (**154**) from the common intermediate **152**, as well as developing asymmetric syntheses of the alkaloids **132**, **133**, **134**, and **154** (Figure 2.7).



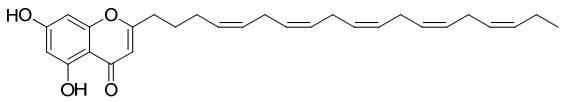
154 Buphanidrine

Figure 2.7

These results have been summarized in Paper **IV** and the experimental procedures, physical data, and spectroscopic data have been presented in the Appendix.

2.2.2 First Total Synthesis of a Polyunsaturated Chromone

The aim of this study was to develop an efficient total synthesis of *all*-(*Z*)-5,7-dihydroxy-2-(4,7,10,13,16-nonadecapentaenyl)chromone (**155**). To the best of our knowledge, no total synthesis has previously been reported for this natural product (Figure 2.8).

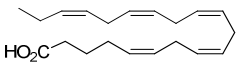


155 (*all*-(*Z*)-5,7-Dihydroxy-2-(4,7,10,13,16-nonadecapentaenyl)chromone)

Figure 2.8

Marine organisms have proven to be a rich source of biologically interesting secondary metabolites.[59,60] The isolation and structural elucidation of dihydroxychromone **155** from the pacific brown algae *Zonaria tournefortii* was reported in 1982 by Plattelli and Tringali[61] Later, this natural product was also isolated from two other *Zonaria* species.[62]

Compound **155** contains the same number of methylene interrupted *cis* double bonds as those present in eicosapentaenoic acid (**156**, EPA), which is a polyunsaturated fatty acid of the ω-3 family found in fish oil (Figure 2.9).



156 (EPA)

Figure 2.9

Our retrosynthetic analysis lead to EPA and a protected phloroglucinol aldehyde as starting materials (Figure 2.10).

A substantial amount of pharmacological and clinical data accumulated in the last 15-20 years indicates a wide spectrum of biological effects of EPA;[63] the chromone **155** may be regarded as an analogue. Hence, it would be of interest to develop a total synthesis of **155** to obtain sufficient material for biological testing.

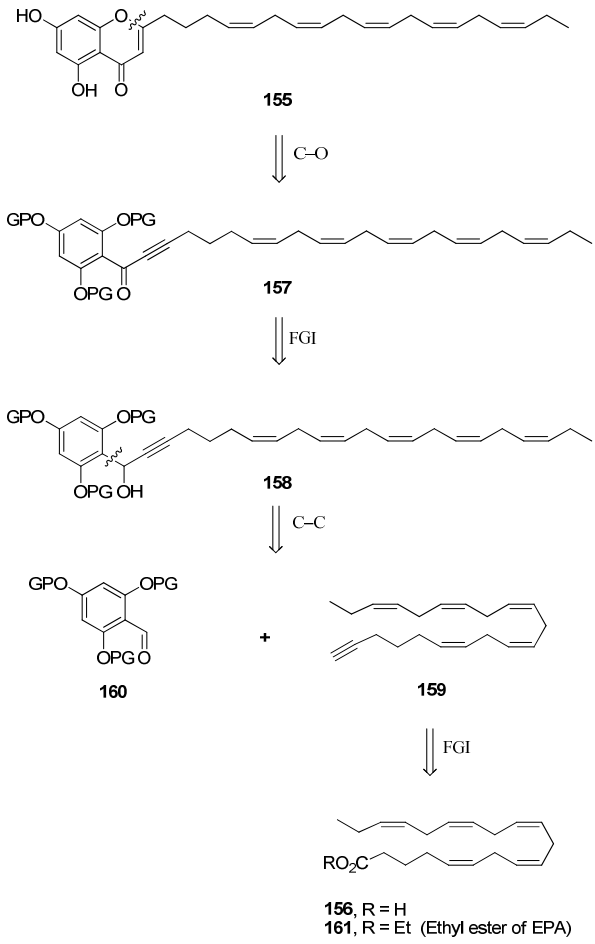
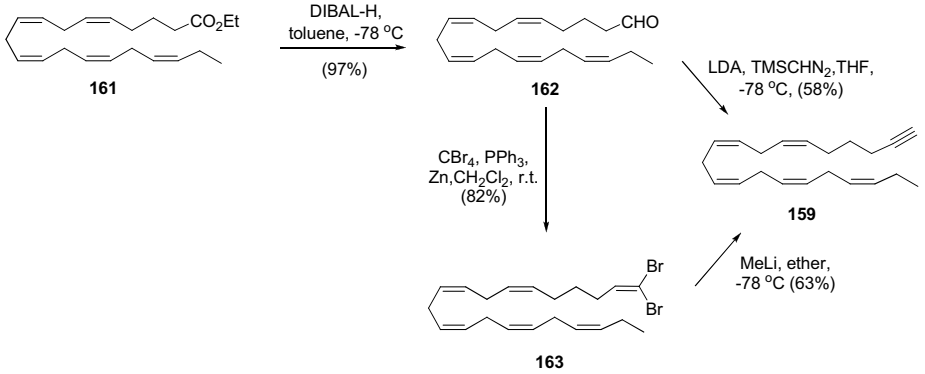


Figure 2.10 Retrosynthetic analysis of polyunsaturated chromone **155**

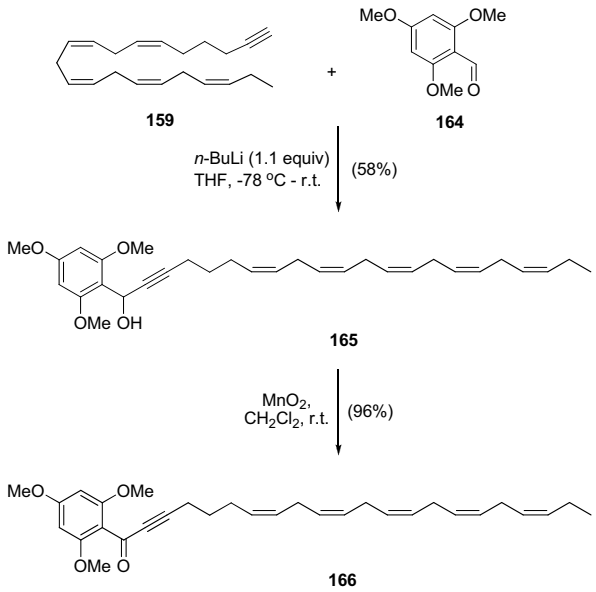
Our synthesis of **155** started with the preparation of aldehyde **162** in 97% yield as previously described.[64] The aldehyde was transformed to the terminal alkyne **159** by either a Colvin rearrangement[65] (58% yield) or by the Corey-Fuchs reaction[66] (52% yield) (Scheme 2.22).



161 **162** **159** **163**

Scheme 2.22

The reaction of the lithium carbanion of **159** at -78 °C with a THF solution of 2,4,6-trimethoxybenzaldehyde (**164**) yielded the acetylene **165**. Oxidation of **165** with MnO_2 afforded ketone **166** (Scheme 2.23).



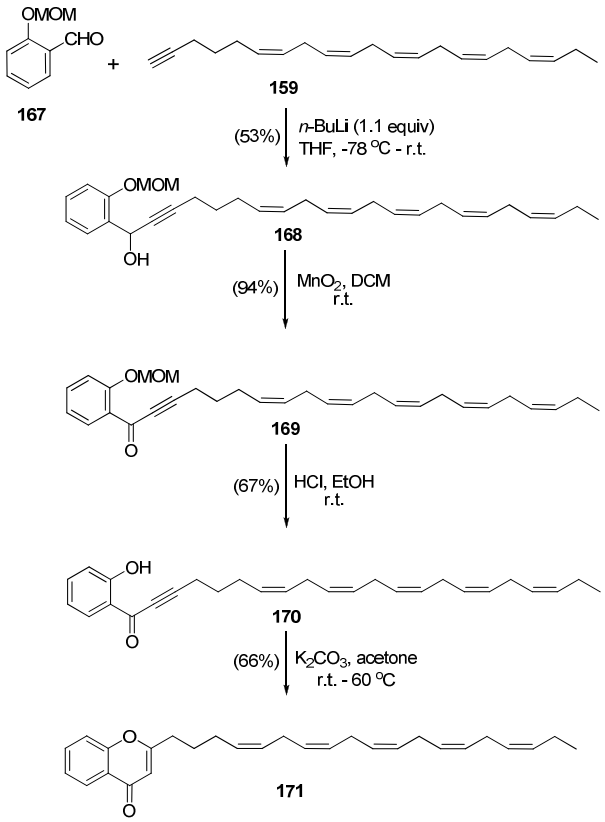
159 **164** **165** **166**

Scheme 2.23

We expected that deprotection of **166**, followed by an intramolecular Michael addition, would yield the natural product **155**. However, decomposition of the starting material was

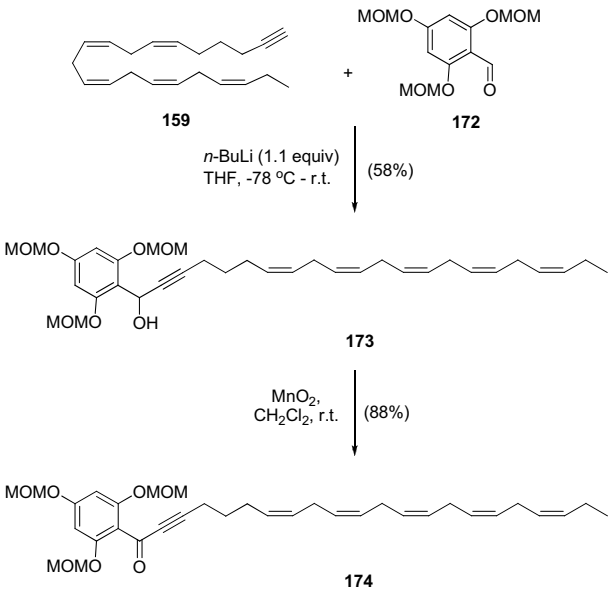
observed with most common deprotection methods, such as $AlCl_3/CH_3CN$, BBr_3/CH_2Cl_2, and MeSNa/DMF.[67]

Then, we decided to perform some model studies. Reaction of MOM-protected salicylaldehyde **167** with the carbanion of **159** at -78 °C gave the secondary alcohol **168** in 53% yield. Oxidization with MnO_2 produced the ketone **169** in 94% yield. Mild deprotection of **169** with HCl in EtOH at ambient temperature afforded **170** in 67% yield. An intramolecular Michael addition under mild basic conditions (K_2CO_3, acetone), afforded the didehydroxy natural product **171** in 66% yield (Scheme 2.24).



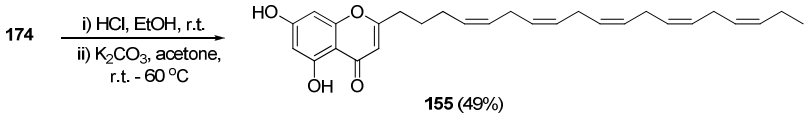
Scheme 2.24

We then prepared the known 2,4,6-tris(methoxymethoxy)benzaldehyde **172** according to a literature procedure.[68] Addition of the aldehyde **172** in THF to the carbanion of **159** at -78 °C yielded the secondary alcohol **173** in 60% yield. Oxidiation of **173** with MnO_2 yielded the MOM-protected ketone **174** in 88% yield (Scheme 2.25).



Scheme 2.25

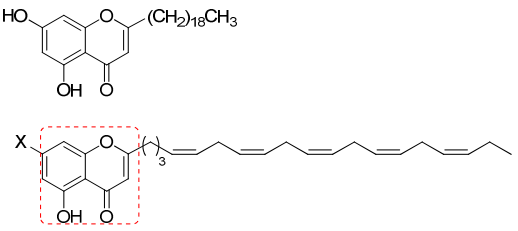
Mild deprotection of **174** with HCl in EtOH at ambient temperature, followed by the intramolecular Michael addition under basic conditions (K_2CO_3, acetone), afforded the natural product **155** in 49% yield for the last two steps (Scheme 2.26). All spectral data (^1H, ^{13}C, Dept-NMR, IR, MS, HRMS, and LC-MS) were in agreement with those previously reported for the natural product.[61,62]



Scheme 2.26

These results have been described in Paper **V** and the experimental procedures, physical data, and spectroscopic data have been compiled in the Appendix.

We are currently working on the synthesis of derivatives of this natural product, including one with a saturated alkyl chain. Polyunsaturated fatty acids and their derivatives are expected to show strong binding to peroxisome proliferator-activated receptors (PPARs). Hence, these types of derivatives may be used as a basis for the development of drugs against diabetes and metabolic syndrome.[69] The results from biological testing will be reported in due course (Figure 2.11).



X = H, OMe, F, Cl, ...

Figure 2.11

3. SUMMARY

We have reported the transformation of phenols into *ortho*-hydroxycinnamates, salicylamines, benzoxazines, and salicylnitriles in good overall yields by simple, regioselective, and one-pot procedures using the advantage of the *ortho*-formylation method. Moreover, these one-pot processes offer the advantage of both economic and environmentally benign methods. We also used the $MgCl_2$-Et_3N base system in the Mannich reaction with complete regioselectity.

We have described the first total synthesis of (±)-powelline in 10% overall yield over eight steps.

We have reported the first total synthesis of the naturally occurring *all*-(*Z*)-5,7-dihydroxy-2-(4,7,10,13,16-nonadecapentaenyl)chromone in six steps from the ethyl ester of eicosapentaenoic acid with an overall of 14% yield.

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4. APPENDIX

Experimental

General Information

All reagents and solvents were used as purchased without further purification. Melting points are uncorrected. Analytical TLC was performed using silica gel 60 F_{254} Aluminium sheets (Merck). Flash column chromatography was performed on silica gel 60 (40–60 μm, Fluka). NMR spectra were recorded on a Bruker Avance DPX-300 MHz spectrometer for ^{1}H NMR and 75 MHz for ^{13}C NMR. Coupling constants (*J*) are reported in Hertz, and chemical shifts are reported in parts per million (δ) relative to $CDCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C), DMSO-d_6 (2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C), and CD_3OD (3.31 ppm for ^{1}H and 49.15 ppm for ^{13}C). Mass spectra were recorded at 70 eV with Fission's VG Pro spectrometer. High resolution mass spectra were performed with a VG Prospec mass spectrometer and with a Micromass Q-TOF-2^{TM}. The LC/MS analyses were performed on an Agilent Technologies 1200 Series (Eclipse XDB-C18 5μm 4.6×150mm), coupled with an Agilent 6310 ion trap.

2-(Methoxymethoxy)benzaldehyde (**167**) was prepared according to a literature procedure.[1]

6-((4`-Hydroxyphenethylamino)methyl)-2,3-(methylenedioxy)-phenol (138)

Anhydrous magnesium chloride (0.95 g, 10 mmol), triethylamine (1.01 g, 10 mmol), and paraformaldehyde (0.45 g, 15 mmol) were added to a dry THF solution (30 mL) of phenol **118** (0.69 g, 5 mmol). The reaction mixture was heated to reflux under an argon atmosphere for 4.5 h and the reaction was monitored by TLC (hexane/EtOAc 4:1). After complete consumption of the phenol, a solution of the amine **137** (0.70 g, 5.1 mmol) in MeOH (5 mL) was added dropwise. The reaction mixture was heated to reflux for 30 min and further stirred at room temperature for an additional 2 h while monitored by TLC (hexane/EtOAc 1:4). After complete consumption of the salicylaldehyde, a solution of $NaBH_4$ (0.38 g, 10 mmol) in MeOH (10 mL)

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was added dropwise over 15 min. The reaction mixture was stirred at ambient temperature for 10 h and the reaction monitored by TLC (hexane/EtOAc 1:4). After complete reduction of the imine, the pH was adjusted to 5 by addition of HCl (1 N) and the reaction mixture extracted with CH_2Cl_2 (2×30 mL). The organic layer was washed with brine (20 mL), dried using $MgSO_4$, and the product purified by column chromatography (SiO_2, hexane/EtOAc 1:1) to afford **138** (0.96 g, 67%) as a yellow solid. Mp = 95-97 ^oC.^1H NMR (CD_3OD): δ = 7.04 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 6.56 (d, J = 7.9 Hz, 1H), 6.19 (d, J = 7.9 Hz, 1H), 5.84 (s, 2H), 3.94 (s, 2H), 3.73 (brs, 1H), 2.88-3.00 (m, 2H), 2.74-2.85 (m, 2H); ^{13}C NMR (CD_3OD): δ = 157.32, 150.12, 147.02, 136.72, 130.80, 130.34, 123.51, 119.03, 116.66, 101.90, 98.79, 51.46, 50.09, 34.52; MS: *m/z* 287 (M^+, 100%).

_N_-Trifluoroacetyl-_N_-(2`-hydroxy-3`,4`-methylenedioxyphenylmethyl)-[2-(4-hydroxyphenyl)]ethylamine (139)

A mixture of polymer-supported DMAP (1.0 g, 3 mmol, 3 equiv.) and amine **138** (0.29 g, 1 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 ^oC. Trifluoroacetic acid anhydride (0.25 g, 1.2 mmol, 1.2 equiv.) was added dropwise through a syringe. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was filtered, washed with MeOH (3×15 mL) and concentrated in vacuo. The product was purified by flash chromatography (SiO_2, hexane/EtOAc 1:4) to afford **139** (0.25 g, 64%) as a white solid. Mp = 185-186 ^oC. ^1H NMR (DMSO-d_6): δ = 9.88 (brs, 1H), 9.22 (brs, 1H), 6.92 (m, 2H), 6.64 (m, 3H), 6.45 (m, 1H), 5.98 (d, J = 1.8 Hz, 2H), 4.58 (s, 1H), 4.30 (s, 1H), 3.33 (s, 2H), 2.67-2.83 (m, 1H), 2.55-2.66 (m, 1H).^{13}C NMR (DMSO-d_6): δ = 156.02, 155.94, 155.83, 155.80, 155.48, 155.34, 148.09, 148.02, 139.23, 138.90, 134.58, 134.54, 129.54, 129.50, 128.20, 127.61, 122.77, 121.17, 118.41, 118.32, 118.18, 117.70, 115.34, 115.21, 115.14, 114.58, 114.49, 100.98, 100.90, 100.27, 48.09, 47.97, 45.66, 43.87, 33.41, 31.21; MS: *m/z* 383 (M^+, 100%).

***all-Z*-1,1-Dibromoheneicosa-1,6,9,12,15,18-hexaene (163)**

A mixture of triphenylphosphine (806 mg, 3.1 mmol), zinc (200 mg, 3.1 mmol) and tetrabromomethane (1.02 g, 3.1 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 20 h before a solution of freshly prepared aldehyde **162** (324 mg, 1.13 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 2 h at room temperature. Evaporation of the solvent at reduced pressure and filtration through a plug of SiO_2 with hexane gave the dibromide **163** (410 mg, 82%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ = 6.37 (t, J = 7.2 Hz, 1H), 5.51-5.22 (m, 10H), 2.66-2.96 (m, 8H), 1.96-2.19 (m, 6H), 1.41-1.59 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 138.46 (CH), 132.05 (CH), 129.18 (CH), 128.62 (CH), 128.58 (CH), 128.26 (CH), 128.24 (CH), 128.12 (CH), 128.10 (CH), 127.88 (CH), 127.01 (CH), 88.89 (C), 32.58 (CH_2), 27.70 (CH_2), 26.60 (CH_2), 25.66 (CH_2), 25.55 (CH_2), 20.56 (CH_2), 14.27 (CH_3).

***all-Z*-Heneicosa-6,9,12,15,18-pentaen-1-yne (159)**

A solution of the dibromide **163** (398 mg, 0.9 mmol) in dry ether (15 mL) was cooled to -78 ^{o}C before addition of methyllithium (1.6 M in ether, 1.0 mL, 1.6 mmol). The mixture was stirred overnight at -78 ^{o}C. A saturated aqueous solution of NH_4Cl and hexane (20 mL) were added. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc 99:1) to yield **159** (160 mg, 63%).

***all-Z*-1-(2-(Methoxymethoxy)phenyl)docosa-7,10,13,16,19-pentaen-2-yn-1-ol (168)**

n-BuLi (1.9 mL, 3 mmol, 1.6 M in hexane) was added to a solution of **167** (0.79 g, 2.8 mmol) in THF (25 mL) under argon at -78 °C and stirred at this temperature for 10 min. A solution of **159** (0.46 g, 2.8 mmol) in THF (15 mL) was added dropwise over 15 min. The mixture was stirred at -78 °C for 1 h before the solution was left to reach ambient temperature over 1 h. The

reaction was quenched by the addition of aqueous NH_4Cl until pH = 8, and the mixture was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and the solvent removed in vacuo. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 4:1) to yield **168** (0.66 g, 53%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$): δ = 7.60 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.24-7.80 (m, 1H), 7.00-7.06 (m, 2H), 5.72-5.74 (m, 1H), 5.31-5.40 (m, 10H), 5.27, 5.24 (AB, *J* = 6.9 Hz, 2H), 3.50 (s, 3H), 2.76-2.83 (m, 8H), 2.29 (td, *J* = 7.2, 2.1 Hz, 2H), 2.15-2.21 (m, 2H), 2.07 (p, *J* = 7.5 Hz, 2H), 1.62 (p, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H);^{13}C NMR ($CDCl_3$): δ = 154.45 (C), 135.82 (CH), 132.03 (CH), 130.25 (C), 129.51 (CH), 129.01 (CH), 128.74 (CH), 128.30 (CH), 128.24 (CH), 128.11 (CH), 127.92 (CH), 127.87 (CH), 127.00 (CH), 122.09 (CH), 121.85 (CH), 114.55 (CH), 94.71 (CH_2), 86.66 (C), 79.66 (C), 61.08 (CH), 56.29 (CH_3), 28.53 (CH_2), 26.39 (CH_2), 25.62 (CH_2), 25.53 (CH_2), 20.55 (CH_2), 18.41 (CH_2), 14.26 (CH_3); HRMS calcd. for $C_{30}H_{40}O_3$ (M^+): 448.2977, found: 448.2957.

***all-Z*-1-(2-(Methoxymethoxy)phenyl)docosa-7,10,13,16,19-pentaen-2-yn-1-one (169)**

Manganese dioxide (1.93 g, 22.2 mmol, 20.0 equiv.) was added in small portions over 1.5 h to a solution of alcohol **168** (0.50 g, 1.11 mmol) in CH_2Cl_2 (15 mL). The resulting suspension was stirred for 16 h, then filtered through a pad of celite. The celite was washed with CH_2Cl_2 (4×15 mL), and the combined organics concentrated under reduced pressure to give the ketone **169** as a pale yellow oil. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 4:1) to yield **169** (0.47 g, 94%) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ = 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.44-7.50 (m, 1H), 7.18-7.23 (m, 1H), 7.04-7.11 (m, 1H), 7.31-7.41 (m, 10H), 7.26 (s, 2H), 3.52 (s, 3H), 2.79-2.84 (m, 8H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.23 (q, *J* = 7.5 Hz, 2H), 2.07 (p, *J* = 7.5 Hz, 2H), 1.72 (p, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 177.06 (C), 157.02 (C), 134.37 (CH), 132.40 (CH), 129.30 (CH), 128.57 (CH), 128.46 (CH), 128.37 (CH), 128.28 (CH), 128.08 (CH), 128.04 (CH), 127.93 (C), 127.86 (CH), 127.00 (CH), 125.49 (CH), 121.53 (CH), 116.17 (CH), 94.93 (CH_2), 94.61 (C), 82.00 (C), 56.39 (CH_3), 27.79 (CH_2), 26.41 (CH_2), 25.66 (CH_2), 25.62 (CH_2), 25.53 (CH_2), 20.55 (CH_2), 18.77 (CH_2), 14.27 (CH_3); HRMS calcd. for $C_{30}H_{38}O_3$ (M^+): 446.2821, found: 446.2829.

***all-Z*-2-(Nonadeca-4,7,10,13,16-pentaenyl)-4*H*-chromen-4-one (171)**

To a stirred solution of **169** (0.36 g, 0.89 mmol) in ethanol (10 mL) was added dropwise HCl (2.5 mL, 6 M). The mixture was stirred for 3 h, then diluted with water (10 mL) and extracted with diethyl ether (2×10 mL). The organic layer was washed with brine (15 mL), dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, hexane/EtOAc 9:1) to yield **170** (0.24 g, 67%) as a pale yellow oil. To a solution of **170** (0.23 g, 0.57 mmol) in acetone (10 mL) was added K_2CO_3 (0.24 g, 1.71 mmol, 3 equiv.). The resulting suspension was stirred for 2 h at room temperature, then heated at reflux for 1 h, then cooled down to room temperature, diluted with water (10 mL), and extracted with diethyl ether (2×20 mL). The organic layer was successively washed with brine (15 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc 4:1) to yield **171** (0.15 g, 66%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$): δ = 8.18 (dd, J = 8.0, 1.5 Hz, 1H), 7.61-7.64 (m, 1H), 7.38-7.43 (m, 2H), 6.18 (s, 1H), 5.32-5.44 (m, 10H), 2.78-2.85 (m, 8H), 2.65 (t, J = 7.5 Hz, 2H), 2.17-2.23 (m, 2H), 2.10 (p, J = 7.5 Hz, 2H), 1.83 (p, J = 7.5 Hz, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 178.31 (C), 169.41 (C), 156.51 (C), 133.43 (CH), 132.06 (CH), 129.23 (CH), 128.63 (CH), 128.60 (CH), 128.30 (CH), 128.29 (CH), 128.05 (CH), 128.02 (CH), 127.85 (CH), 127.00 (CH), 125.71 (CH), 124.92 (CH), 123.77 (C), 117.82 (CH), 109.92 (CH), 33.79 (CH_2), 26.71 (CH_2), 26.49 (CH_2), 25.70 (CH_2), 25.64 (CH_2), 25.55 (CH_2), 20.56 (CH_2), 14.27 (CH_3); MS EI *m/z* 402 (M^+, 19%), 173 (100), 160 (28) HRMS calcd. for $C_{28}H_{34}O_2$ (M^+): 402.2559, found: 402.2558.