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DISSERTATION

Titel der Dissertation

„The total synthesis of idarubicin; an API technology approach towards the total synthesis of established and new anthracycline antibiotics. “

Verfasser

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1 KURZFASSUNG

Seit der Entdeckung der Anthrazykline wie Doxorubicin oder Idarubicin in den fünfziger Jahren gehört diese Substanzklasse immer noch zu den besten Wirkstoffen in der Krebstherapie.

Obwohl großer Aufwand für die Totalsynthese dieser Anthrazykline betrieben wurde, speziell für unser Zielmolekül Idarubicin, ist bis heute noch immer die Kombination aus fermentativer und partieller Synthese für die industrielle Produktion die angewandte Methode.

In dieser Arbeit wird eine neue Synthese für Idarubicinon **12** vorgestellt. Diese Synthese benutzt Anthrachinon **83** und L-Äpfelsäure **96** als leicht zugängliche Ausgangprodukte. Dabei wird **83** in fünf Stufen in das Bromderivat **88** mit einer Gesamtausbeute von 49% übergeführt. Der zweite Synthesebaustein **165** wird ausgehend von L-Äpfelsäure in drei Stufen mit einer Ausbeute von 75% über diese drei Stufen hergestellt.

Die Verknüpfung zu **166** erfolgte durch Alkylierung des Bromderivat **88** mit **165** in 89% Ausbeute und einer hervorragenden Diastereoselektivität von über 99%. Nach einigen erfolglosen Versuchen zur Zyklisierung zum Anthrazyklinon Grundgerüst gelang ein Ringschluß zum gewünschten tetrazyklischen Produkt mit Hilfe einer *Marshalk* Reaktion von **196** zum Deoxyanthrazyklinon **211** bei Raumtemperatur in 67% Ausbeute. Die Herstellung des Ausgangsprodukts **196** für diesen Ringschluß gelang ausgehend von **166** über sieben Stufen mit einer Gesamtausbeute von 62%. Die restlische Synthese zum Aglycon von Idarubicin **12** erfolgte ausgehend von **211** durch Oxidation der Hydroxylgruppe in Position C-13 und Hydroxylierung in Position C-7 in einer Gesamausbeute von 11% beginnend von **88** im Labormaßstab.

Idarubicin Hydrochlorid 6-HCl wurde durch Glykosylierung von **12** und anschließender schrittweiser Entzschützung der beiden Schutzgruppen der Zuckerhälfte mit 30% Gesamtausbeute erhalten.

Neben der Laborsynthese wurden erste Versuche zur Herstellung größerer Mengen hinsichtlich einer industriellen Produktion unternommen. So konnte jeder Schritt bis zum Aldehyd **199a+b** in einen Maßstab von mindestens 10 g durchgeführt werden. Zwar sank die Gesamausbeute dabei etwas von 23% auf 18% dafür konnten einige chromatographische Schritte durch Kristallisation ersetzt werden.

Die hier beschriebene Syntheseroute eignet sich zur Herstellung auch Anthrazykline-Analoga.

2 ABSTRACT

Anthracyclines represent one of the most important antitumor drugs especially for the treatment of human solid tumors and leukaemias. Since their discovery in the 1950s, considerable efforts were accomplished towards the understanding of their mode of action and towards the synthesis of anthracyclines approved to be used in cancer therapy such as doxorubicin or idarubicin and new analogs.

Despite of the extensive efforts accomplished in the total synthesis of anthracyclines, especially of our target Idarubicin, industrial production is still done in a semi-synthetic manner. Therefore, elaboration of new total synthesis of Idarubicin able to be translated in an industrial process is very interesting.

In the presented work, a new total synthesis of idarubicinone **12** / idarubicin **6** is reported starting from the anthraquinone **83** and L-malic acid **96**. In this synthesis the anthraquinone **83** was converted in 5 steps into the bromo derivative **88** in 49 % overall yields without the need of chromatography and L-malic acid **96** was converted to the compound **165** in 3 steps in 75 % overall yield.

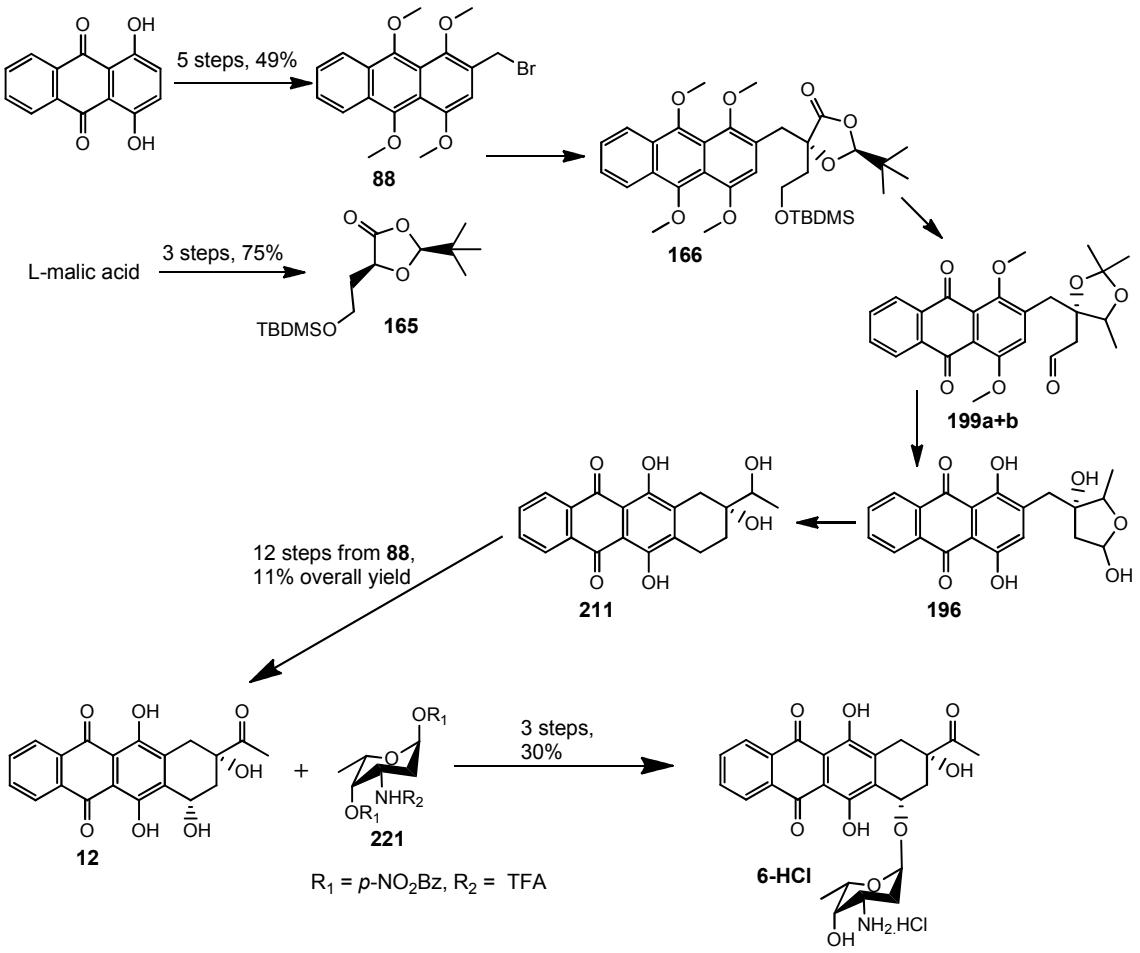
The alkylation of the bromo derivative **88** with **165** led to **166** in 89% yield and excellent *de* (>99%). After several attempts to obtain the tetracyclic structure of the targeted anthracycline, the compound **166** was converted to the lactol **196** in 7 steps in 62 % overall yield from **166**. Intramolecular cyclization of lactol **196** under Marschalk conditions at room temperature afforded the 7-deoxyanthracyclinone **211** in 67 % yield which was subjected to subsequent oxidation of the hydroxyl group at the position C-13 and hydroxylation at C-7, followed by epimerisation of the undesired epimer, to afford the aglycone of idarubicin **12** in 11% overall yield from **88** on a labor scale.

Glycosidation of **12** followed by subsequent cleavage of the protecting group present in the sugar moiety afforded idarubicin hydrochloride **6-HCl** in 30% overall yield from **12**.

Up-scaling of the sequence was also explored. Every step to the aldehyde **199a**+**b** was carried out on a 10 g scale at least. Overall yield was slightly decreased from 23% to 18% but some chromatography steps were substituted by recrystalisation or trituration.

The described synthesis pathway may be suitable for the preparation of further known or new anthracycline derivatives.

3 GRAPHICAL ABSTRACT



4 INTRODUCTION

4.1 API (Active Pharmaceutical Ingredients) Technology, from Laboratory Procedures to Processes

Without any doubt, technology plays an important role also in the “pharmaceutical science”. However, when speaking about “pharmaceutical technology”, there is a common understanding that this part of sciences covers only formulation and not the technology of the active compound (API) itself. Nevertheless, the manufacturing of the API is a central part of the drug registration process. This process is under strict control of the regulatory agencies. The “drug master file”, describing the API, its manufacturing and its quality is an important part of the full documentation.

The requirement for a drug master file also derives the requirement for the development of a suited manufacturing process according to which the API will be manufactured. This process is; as a rule; nor identical with the first synthesis of the material, but is the result of intense RD activity to prepare a material that is both compliant with quality standards and with production under economic condition.

In organic synthesis, the effectiveness and complexity of a synthetic pathway is commonly defined by the number of steps and the overall yield. For a manufacturing technology, these requirements are still important but other crucial conditions have to be taken into consideration in addition.

- First of all, the number of steps is not defined by the number of chemical transformations of a molecule. The number of reactions taking place in a vessel is more or less insignificant, when compared to the number of isolation steps and the tediousness of work up to arrive at the final product.

- Furthermore, the overall yield influences only partially the feasability of a process. A high yielding process can be uneconomical if expensive reagents or complicated purification or works up steps are required. On the other hand,

a simple synthetic route with low overall yield can be profitable depending on the cost of the chemicals.

- Moreover, all simple manipulations in the laboratory have to be studied in detail to be translated in a process. For example, drying over sodium sulfate seems to be trivial to any lab chemist, but this procedure is more tedious on a large scale. Instead of a few minutes needed in the laboratory scale, this procedure can take hours in an industrial process.

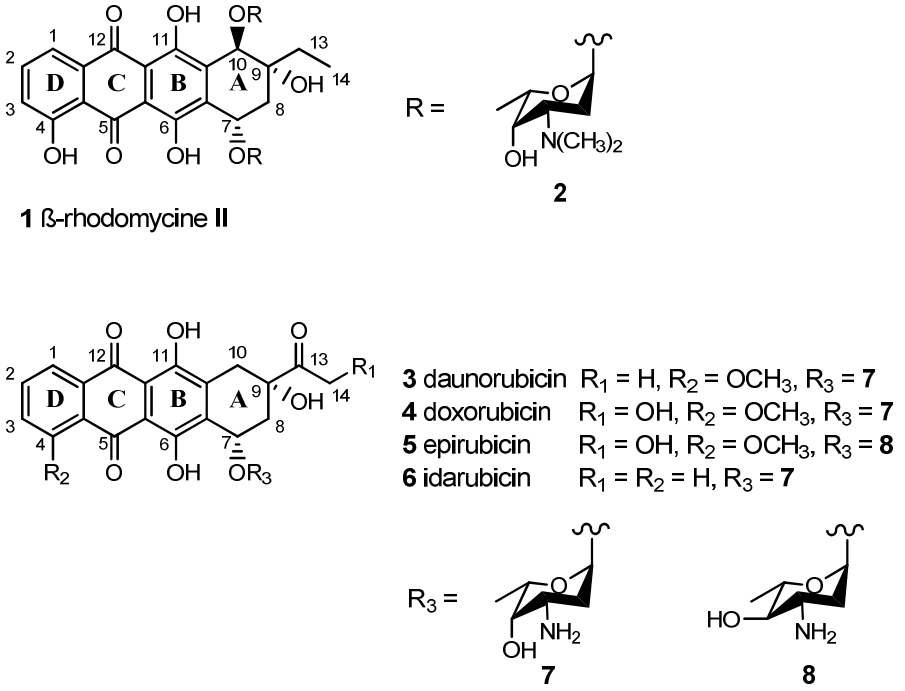
- Every parameter, such as time of filtration, amount of sodium sulphate or solvent, has to be taken into consideration and optimised to reduce the costs for chemicals, labour and disposal.

- It has to be considered that centrifugation is the most effective industrial separation method and that oily products are much more difficult to handle than pure crystallie material.

- To resume, the price of the final product is the most important measure to define the effictiveness of an industrial process.

4.2 Anthracyclines, General Introduction

The anthracyclines constitute a major class of antitumor antibiotics. Anthracyclines are red aromatic polyketides and their basic structure shares an aglyconic (called anthracyclinone) and a sugar moiety. The aglycone consists of a tetracyclic ring (ABCD) with adjacent quinone-hydroquinone groups in ring C-B and at least two stereocenters in ring A with a small side chain at C-9. The first discovered anthracycline, β-rhodomycine II **1** (Scheme 1), was isolated by Brockman and Bauer in 1950 from the actinomycete *Streptomyces purpurascens*[1]. Despite of its high antibacterial activity, no further development into a clinically useful chemotherapeutic agent were investigated owing to its toxicity.



Scheme 1

In the 1960's, further anthracyclines were isolated in other laboratories[2-3], which led to the discovery of two key anthracyclines, daunorubicin **3** (also called daunomycin) and doxorubicin **4** (also called adriamycin). Since 1974, doxorubicin is in clinical use and is still one of the most widely used antibiotics with the broadest spectrum to antitumor activity especially for treatment of human solid tumors and leukaemias[4]. Because of their high therapeutic value in cancer chemotherapie[5-8], anthracycline derivatives have been one of the best studied natural products over the past 50 years. The major side effect of this type of drugs is the dose-related cardiotoxicity which restrict their applicability. As a consequence, much effort was invested in the synthesis of analogs of doxorubicin, especially in the 1980's and the 1990's, in order to improve the toxicological profile and to reduce the cardiotoxicity. Therefore, epirubicin **5** which is characterised by an inversed hydroxyl group at position 4 of the amino sugar, showed an improvement in the activity and a reduced cardiotoxicity. Another successful example was idarubicin **6** which lacks a methoxy group on ring D of the aglycone. Idarubicin showed superior therapeutic efficacy and reduced cardiotoxicity relative to daunorubicin. In addition, oral absorption of this drug is

possible due to its enhanced lipophilicity, which provides an additional advantage in comparison to daunorubicin which is completly inactive when administrated orally. However, idarubicin did not possess the broad spectrum of activity of doxorubicin and its use is limited to the treatment of leukemia.

4.3 Mechanism of Action

Since the 1970's, extensive investigation in order to understand the mechanism of action of the anthracyclines were accomplished. With regard to the well documented reviews, the mechanism of action is still not completely even clarified. It is commonly accepted that several parallel cytotoxic mechanisms are involved in the antitumor activity of anthracycline derivatives. The following mechanisms appear to contribute predominantly to the antitumor activity:

- Drug-DNA intercalation complex.
- Irreversible topoisomerase II-mediated double-strand break.
- Free radical formation.
- Interaction with the cell membrane

The first mechanism elucidated was the intercalation of the anthracycline moiety between bases pair of DNA[9-10]. By this mechanism the planar tetracyclic chromophore inserts between DNA bases and electrostastic interactions stabilize the complex which induces local structural changes to the DNA strand. This modification can lead to functional changes, inducing inhibition of transcription and replication. However, the cytotoxic activity depends not only on the ability of the drug to bind to DNA. Additional mechanisms for inhibition of DNA function, as mentioned above, are responsible for the remarquably high activity of anthracyclines. Among these mechanisms topoisomerase II inhibition and free radical formation are best characterized.

Topoisomerases are enzymes that unwind and wind DNA, in order to control the synthesis of proteins, and to facilitate DNA functions. In order to help overcome problems caused by the double helix, topoisomerases bind to either single-stranded

or double-stranded DNA and cut the phosphate backbone of the DNA. This intermediate break allows the DNA to be untangled or unwound, and, at the end of these processes, the DNA is reconnected again[11]. Thus, anthracyclines inhibit this enzyme mechanism as they build a drug-stabilized cleavable complex. Afterwards, the backbone of the DNA is cut as described above but in an irreversible way, preventing replication.

Moreover, free radical formation contributes also to the cytotoxic effects[12-13]. Anthracyclines can undergo reduction to the corresponding intermediate semiquinone free radicals which can, in turn, reduce oxygen to superoxide ($\cdot O_2^-$) and other reactive oxygen species such as hydrogen peroxide and hydroxyl radicals[14]. These potent reactive species can lead to DNA damage but their involvement in the antitumor activity of anthracyclines is very complex and still not completely understood. It has to be expected radical formation is also a source of side effects in particular at high drug concentrations.

Experiments towards the study of effects of an anthracycline linked to a polymer[15-16] in cellular test lead to the conclusion that this type of drugs can be also active without entering in the cell. Interaction of the anthracycline with the cell membrane induced cascades of mechanisms that finally lead to DNA damage.

In conclusion, even if considerable efforts have been expended over the last 50 years to identify mechanisms of action of anthracyclines, it appears that they are still only partially understood and that several mechanisms are involved, which all seem to all contribute to the cytotoxicity of the drug.

4.4 Side Effects of Anthracycline

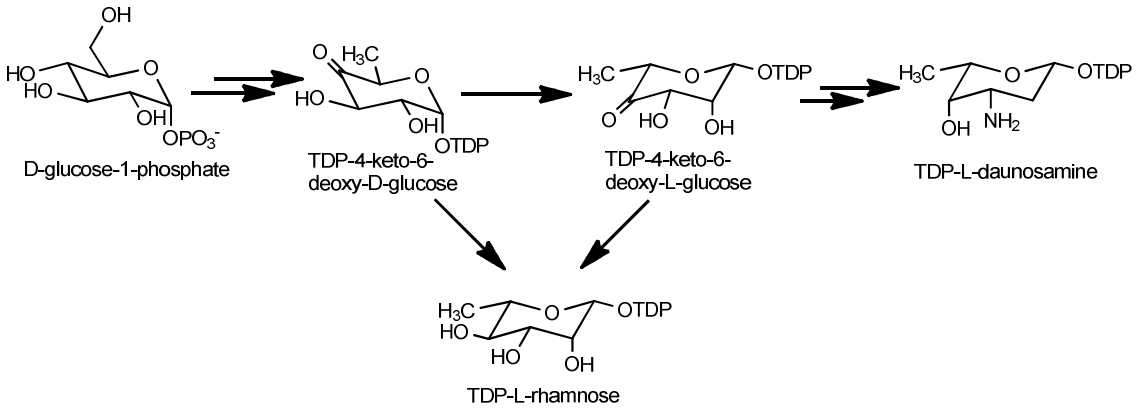
Like any other chemotherapeutic agents, anthracycline drugs induce some side effects. Most commonly, they are manifested by fatigue, nausea and vomiting. However, the major toxicities of anthracyclines include cardiotoxicity which is developed after prolonged treatment with lower doses or after treatment with high doses[17-18]. Cardiotoxicity induced by anthracycline is irreversible and is the major

limitation of their clinical use. More details about the cardiotoxicities of anthracyclines may be found in a very well documented review published by Krohn in 2008 with contributions by several distinguished scientist. This review covers a large area from synthesis of anthracycline to clinical applications[19-26].

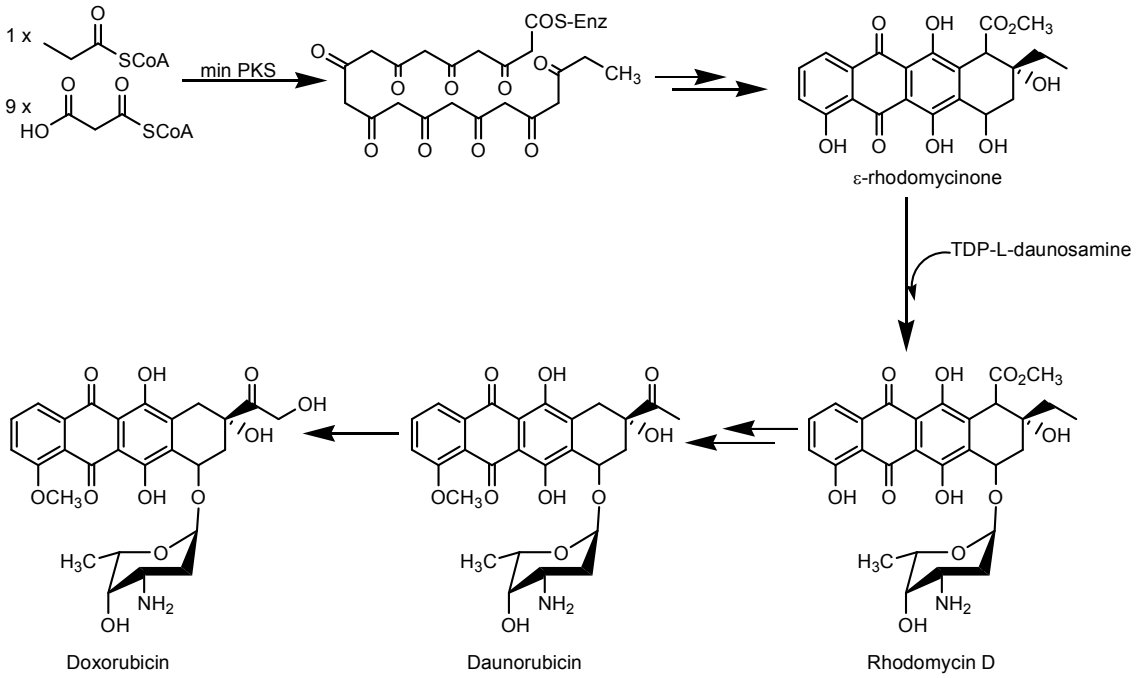
4.5 Synthesis of Anthracycline

4.5.1 Biosynthetic and Semi-Synthetic Approaches

Natural anthracyclines such as mentioned above are usually produced by strains of *Streptomyces* and related bacteria. More than 2000 derivatives have been produced by biosynthesis and the industrial production of doxorubicin (one of the most widely used antitumor drug) is done by this fermentative pathway. In this chapter we will first focus our attention on the production of daunorubicin / doxorubicin from *Streptomyces,* describing briefly the biosynthetic pathway and the limitation of this production. In the second part of this chapter the semi-syntesis of idarubicinone (aglycone of idarubicin) will be described.



Scheme 2



Scheme 3

The biosynthesis of doxorubicin / daunorubicin is completed in three steps (Scheme 2 and Scheme 3):

- Formation of the aglycone part called ε-rhodomycinone starting from one propionyl-coenzyme A and nine malonyl coenzyme A precursor units.

- Formation of the sugar moiety, TDP-L-daunosamine starting from D-glucose-1-phosphate (Scheme 2).

- Glycosylation and other modifications such as decarboxylation or hydroxylation.

The anthracyclinone core is assembled by a type II polyketide synthase (PKS) in *Streptomyces* starting from one proprionyl coenzyme A and nine malonyl coenzyme A[27-29]. Thus, the unstable polyketide formed is subjected to the action of aromatase, cyclase and other tailoring enzymes, which produce the tetracyclic skeleton named ε-rhodomycinone[30].

At the same time, the biosynthhesis of TDP-L-daunosamine take place in the culture, starting from D-glucose-1-phosphate; it is obtained after action of at least six enzymes[31].

Finally, the ε-rhodomycinone is glycosylated with TDP-L-daunosamine at the position C-7 in the presence of glycosyltransferase to afford rhodomycin-D. Daunorubicin and doxorubicin are then formed after methylation, hydroxylation, oxidation and an additional hydroxylation step in the case of doxorubicin[32-33].

Although remarkable improvement[34-35] has been achieved since the first biosynthesis of doxorubicin, its production, especially in industrial scale, is still limited by several factors[36].

First, the low availibity of TDP-L-daunoamine[37] affects the doxorubicin biosynthesis. In addition of that, competitive synthesis of TDP-L-rhamnose consummed the intermediate TDP-4-keto-6-deoxy-D-glucose, which reduced the yield of the TDP-L-daunosamine.

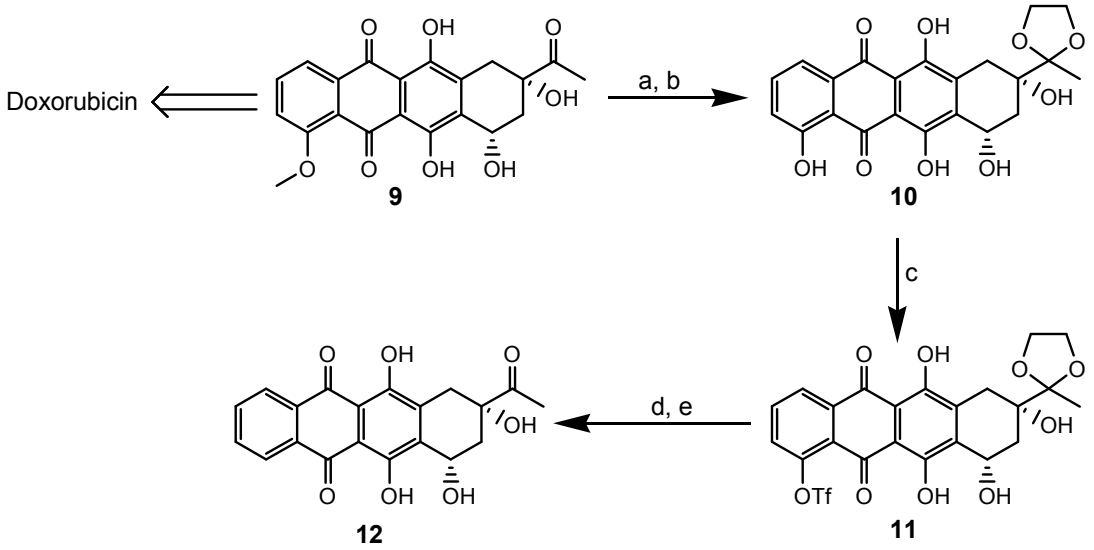
Further, ε-rhodomycinone is glycosilated with TDP-L-daunosamine via action of enzymes called dnrS and dnrQ to produce the intermediate rhodomycin D[38-39]. However, due to the folding effects, dnrS is not soluble when expressed in heterologous systems inducing the low glycosylation efficiency of dnrS which causes the limited production of rhodomycin D.

Moreover, the enzyme doxA, which catalyzed three oxidation steps at the end of the process[32] lacks of efficacy to convert daunorubicin into doxorubicin[33]. As a consequence, in industrial production of doxorubicin, the last oxidation steps can also be performed by chemical manner[40]. Furthermore, accumulation of doxorubicin in the fermentative process inhibits the activity of doxA, thereby limiting the production.

Finally, the inherent cytotoxicity of doxorubicin against the producing strains hinder its own production by inducing intercalation in DNA whith the result of DNA dammage and cell death[41]. The production of doxorubicin needs a long time of incubation (initiated after 36 hrs and maximal around 60hrs). Unfortunatly, doxorubicin and

daunorubicin are converted into acid sensitive baumycin-like higher glycoside[29,42] during this time, which gradually decrease the amount of doxorubicin and daunorubicin.

Unnatural anthracyclines such as Idarubicin, which is one of the most valuable anthracycline, are not available directly by biosynthesis and some additional synthetic steps are necessary. Starting from the natural daunorubicin, produced by biosynthesis as described above, the aglycone of idarubicin **12** (also called idarubicinone) can be synthesised in 6 steps[43-45] (Scheme 4).



Reagents and conditions : a) $AlCl_3$, DCM, 88% ; b) $(CH_2OH)_2$, *p*-TsOH, benzene, 90%; c) Tf_2O, iPr_2EtN, 4-Me_2-N-py, 67%; d) $Pd(OAc)_2$, DPPF 0.5 mol%, HCO_2H, Et_3N, DMF, 82%; e) TFA, 90%.

Scheme 4

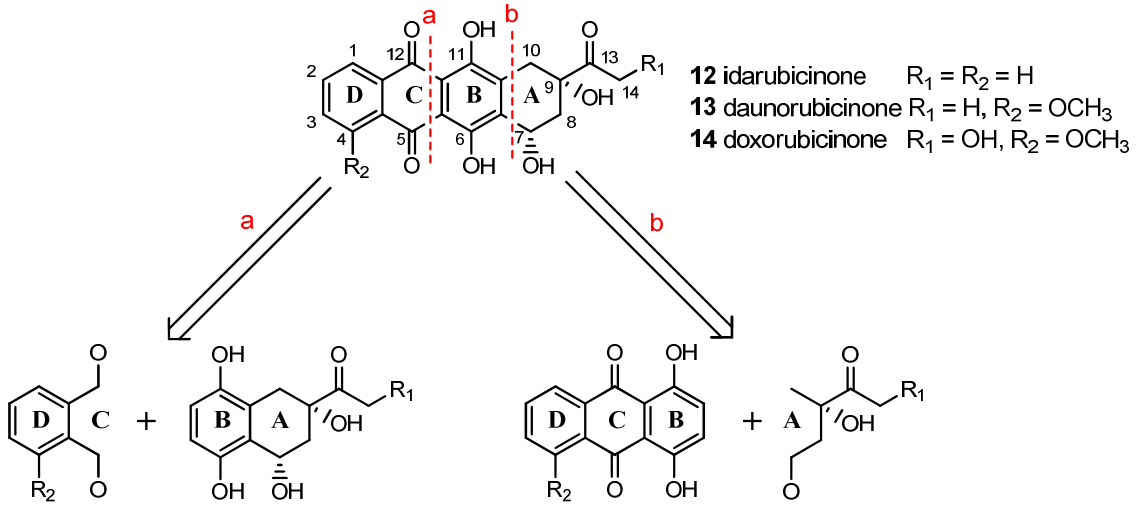
In the first step, the cleavage of the glycosidic bond can be carried out under acidic condition[46-47] to deliver the daunorubin aglycone. Kelly et al.[44] reported in 1990 the synthesis of idarubicinone starting from daunorubicinone. They first treated **9** with $AlCl_3$ to demethylate the methyl ether, followed by ketalisation of the keto group to reach the phenol **10**. Selective formation of the 4-trifluoromethanesulfonate **11** from the corresponding phenol followed by palladium catalyzed reduction, and cleavage of the ketal led to the desired idarubicinone **12** in 39% overall yield from daunorubicinone. A recent patent[45] of an italian group, reported a easier way to

obtain idarubicinone **12** avoiding the ketalisation of the C-13 keto group and involving an easy purification of the end products.

In summary, despite of the limitations of anthracycline biosynthesis (low availability of TDP-L-dauosamine, low efficiency of glycosylation, low activity of doxA in doxorubicin formation and formation of baumycin-like higher glycosides), production of this type of drugs is still carried out by a fermentative process. Nevertheless, the productivity of these processes is still unsatisfactory. For example *Streptomyces peucetius* produces ca. 40 mg/L of ε-rhodomycinone, while only ca. 1.8 mg/L of doxorubicin can be isolated under normal laboratories conditions[35]. Extensive efforts are still performed to enhance the production of doxorubicin. In addition to that, several anthracyclines such as idarubicin or epirubicin, are not directly available through biosynthesis and are obtained by semi-synthetisis. Therefore, total synthesis of anthracyclines is still a remarkable challenge in order to synthesize analogs and to compete with the biosynthesis production of these drugs. The next chapter will summarize the different methodologies developed in the last 30 years to synthesise natural and unnatural anthracyclines.

4.5.2 Synthetic Approaches.

Due to their importance as chemotherapeutic agents, the anthracyclines and their derivatives have been a very popular synthetic target by several research groups. In the meantime, the synthesis and coupling of the sugar moiety are well developed[48-49], the synthetic challenge remains in the efficient formation of the aglycone (also called anthracyclinone), consisting on the tetracyclic ABCD ring system. The biological activity of anthracyclines depends almost exclusively on the accurate absolute configuration of the ring A at C-7 and C-9 especially[50-51] (Scheme 5). Therefore, the synthesis of enantiomerically pure aglycones with the desired absolute configuration became the principal focus in anthracycline chemistry. In fact, there are two major issues in the anthracycline synthesis: the insertion of the stereocenters in the appropriate absolute configuration and, in the case of anthracycines bearing a nonsymmetrical D ring in relation to the A ring stereocenters, regiochemical control of the formation of the tetracyclic chromophore.



Scheme 5

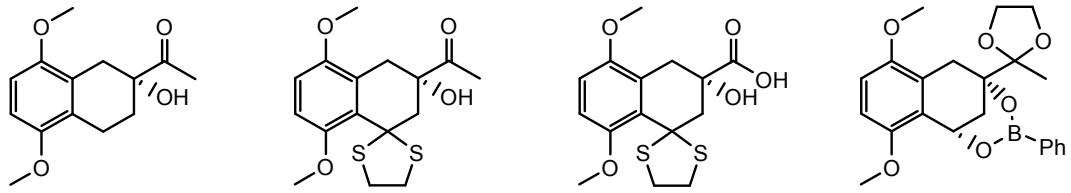
With these tasks in mind, several methodologies have been developed towards the synthesis of the aglycone leading to three main type of approaches[52-54] : the Friedel-Crafts based syntheses; the Diels-Alder strategies with the ability to disconnect the A,B and C rings in several ways; and the anthraquinone based syntheses such as the Marschalk reaction with ucleophilic key steps. These general strategies will be described by examining several selected syntheses divided in two major categories as shown in Scheme 5 : first the AB + CD approaches (a disconnection) in which the AB building blocks is the synthetic challenge; and second the A+BCD approaches (b disconnection).

4.5.2.1 AB+CD Approaches

With regard to the literature published since the 1980's towards anthracyclinone syntheses, it appeared that the favoured used strategy is the AB+CD approach. This convergent methodology is focus on the synthesis of the AB ring with the desired absolute configuration and the appropriate substituted CD rings moiety.

The synthesis of the AB building blocks is very well developed and has been successfully performed in several ways by different groups. Achmatowicz reported in

2008[30], several AB building blocks[55-65] (Scheme 6) and the efforts of many research groups since the last 20 years are summarized in this review.

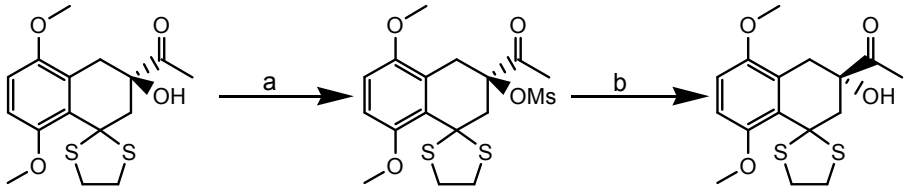


15 **16** **17** **18**

Scheme 6

The most complicated issue to synthesise the AB building block is to find an efficient route to enantiopure AB synthons. Several methodologies were developed.

First, the resolution of racemic intermediates or end products as key step in some synthetic approaches at the begining of the investigations towards the anthracyclinone synthesis was investigated. One recently developed method [66] uses the recrystallization of the diastereoisomeric imines obtained from *rac*-**16** and (-)-S)-phenylethylamine from THF. A method to convert the C-9 in ketone (R)-**16** uses the reaction of (R)-**16** with methanesulfonyl chloride in the presence of N,N,N',N'-tetramethylhexane-1,6-diamine to afford the methanesulfonate (R)-**19** followed by treatment with NaOH in H_2O-DCM in the presence of tetrabuylammonium hydrogensulfate to give (S)-**16** in 40% yield and 99.5 % ee (Scheme 7). Even if this method improved the resolution of *rac*-**16**, it is not an efficient way to reach enantiopure AB synthons.



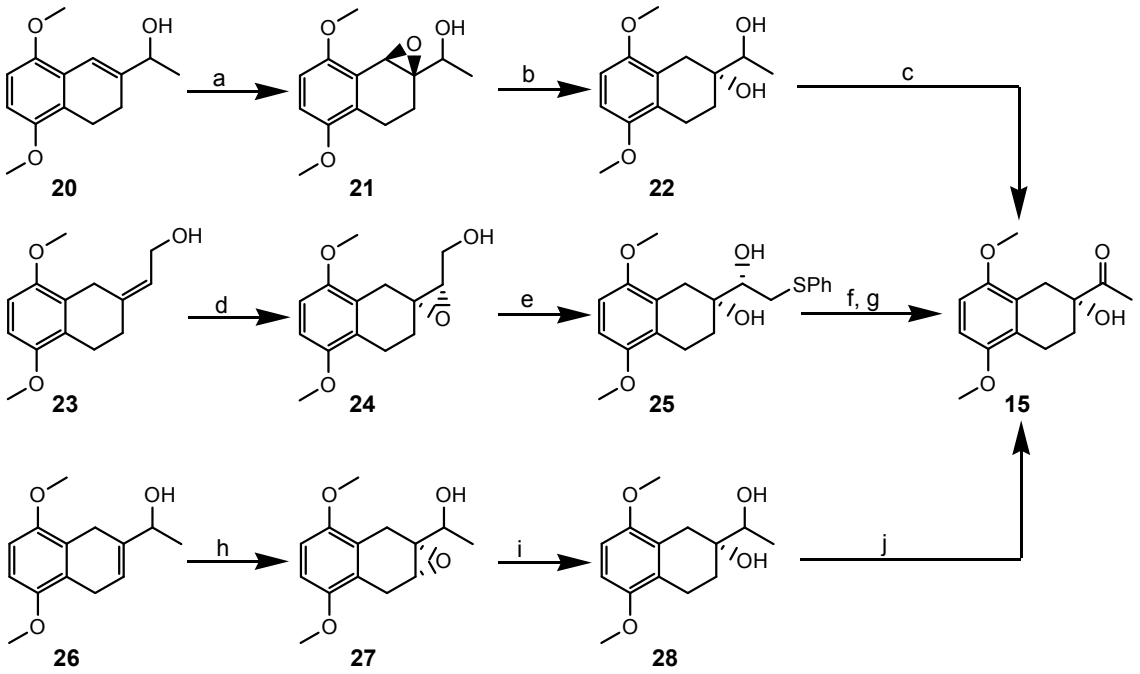
(R)-**16** (R)-**19** (S)-**16**

Reagents and conditions: a) MsCl, N,N,N', N'-tetramethylhexane-1,6-diamine, DCM; b) 20% $NaOH_{aq}$, Bu_4NHSO_4, DCM, 40% over two steps, 99.5% *ee.*

Scheme 7

A second approach uses the stereoselective oxidation as an efficient way to produce enantiopure building blocks. Various reaction types are used such as Sharpless epoxidation[67] or catalytic dihydroxylation. Additionally to the reduction of carbonyl groups with LAH modified by chiral additives can be applied.

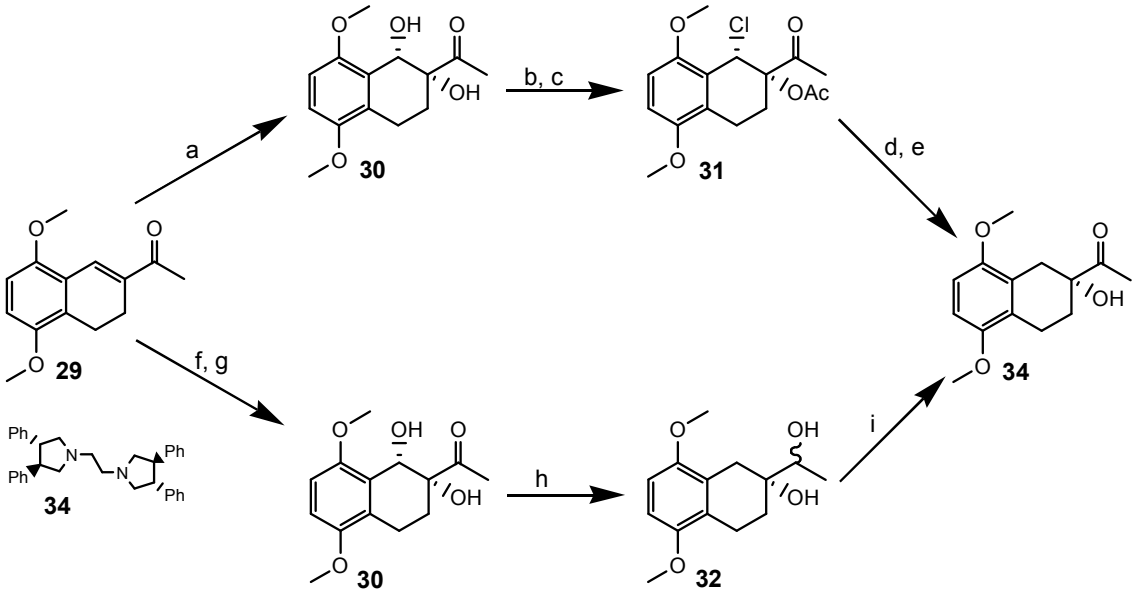
The enantioselective Sharpless epoxidation was extensively investigated with several substrates[68-71] (Scheme 8). The corresponding oxirane is usually opened in a reductive way and the remaining secondary alcohol is oxidized to give one of the AB building block mentioned above.



Reagents and conditions : a) (+)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, *t*-BuOOH, DCM; b) LAH, THF, 42% over two steps; c) Ag_2CO_3 on celite, PhH, 78%; d) (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, *t*-BuOOH, DCM, 97%, 93.2% *ee*; e) PhSH, 0.5 M NaOH, *t*-BuOH, 76%; f) Raney-Ni (W-2), EtOH, 90%; g) SO_3-py, DMSO, NEt_3, 84% ; h) (-)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, *t*-BuOOH, DCM ; i) LAH, THF, 43% over two steps ; j) Ag_2CO_3, PhH, 80%.

Scheme 8

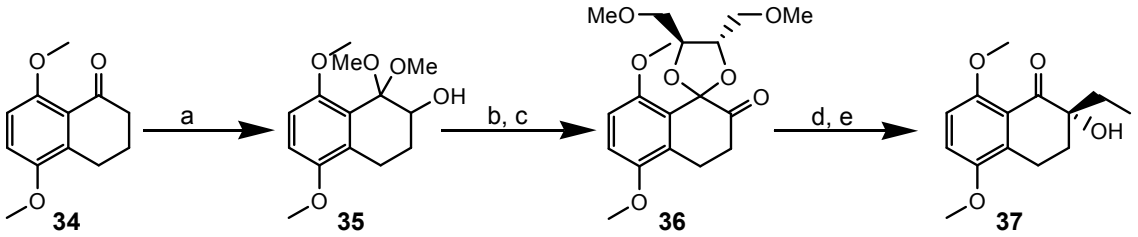
The dihydroxylation with similar substrates was also investigated by different groups (Scheme 9). The Sharpless dihydroxylation[72] or the dihydroxylation with OsO_4 complexed with a chiral diamine **34**[73-74] led to good enantiomeric excess. Reduction of the benzylic alcohol followed by some straightforward steps leads to the AB synthon (R)-**15**.



Reagents and conditions : a) AD-mix-α, 1% $K_2OsO_2(OH)_4$, H_2O-*t*BuOH, $MeSO_2NH_2$, 71%, 98% *ee*; b) $MeC(OMe)_3$, PPTS, DCM; c) TBDMSCl, DCM, 99%; d) Bu_3SnH, AIBN, PhH; e) Amberlyst IRA-400(OH), MeOH, 73%; f) **34**, OsO_4, THF ; g) $NaHSO_3$, H_2O, 96% ; h) $HSiEt_3$, TFA, 78% ; i)SO_3-py, NEt_3, DMSO, 87%.

Scheme 9

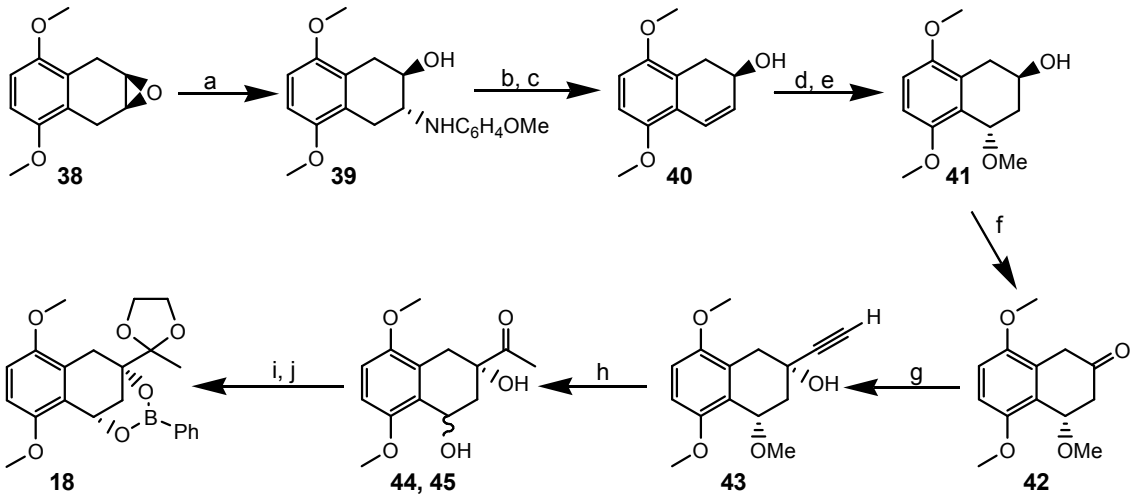
Alternatively to the dihydroxylation, chiral auxiliaries are also known to achieve diastereoselctive transformations such as alkylations or Diels Alder reactions. These methods to reach enantiopure AB synthons were very well investigated by Krohn and Ekkundi and later by Achmatowycz[57]. A representative example of this methodology was worked out by Moriarty et al.[75-76]. The tetralone **34** was converted to the hydroxyketone **37** by treatment with phenyliodine (III) diacetate and potassium hydroxide in methanol followed by trans-ketalization with (2S, 3S)-1,4-dimethoxynutane-2,3-diol to afford the compound **36**. Subsequent treatment of **36** with ethylmagnesium chloride and cleveage of the ketal under acidic conditions yielded stereoselectively the hydroxyketone **37** with the desired configuration at C-9 (Scheme 10).



Reagents and conditions : a) $PhI(OAc)_2$, KOH, MeOH; b) (2S, 3S)-1,4-dimethoxynutane-2,3-diol, *p*-TsOH, DCM, 72%; c) PDC, Ac_2O, DCM, 90%; d) EtMgCl, THF, 93%, 100% *ee*; e) conc. HCl-THF (1 : 3), 92%.

Scheme 10

Another recent approach was used by Shibasaki et al.[77] involving an enantioselective catalysed key step in the synthesis of the enantiopure AB segment **18**. He reported a catalytic asymmetric formal synthesis of idarubicin using an enantioselective opening of the oxirane ring of the *meso*-epoxide **38** with *p*-anisidine and catalytic amouts of BINOL, followed methylation of the amin and Hoffmann elimination (Scheme 11). After optimisation, the *trans*-aminoalcohol **39** was obtained in 40 % yield and 95% *ee* after recrystallisation. After regio- and diastereoselective oxymercuration of **40** followed by reduction and oxidation of the alcohol, diastereoselective insertion of the ethenyl group yielded the compound **43** in a *de* of 10:1 which was converted to the keton by treatment with $HgSO_4$ and cat. H_2SO_4 in acetone. Then, the methylether was cleaved to the keto alcohol **44, 45** and was ketalized. Finally, the benzylic alcohol was coverted with phenylboronic acid to the corresponding diester under acidic coditions. This diester **18** is the only formed product with both hydroxyl groups cis to each other.

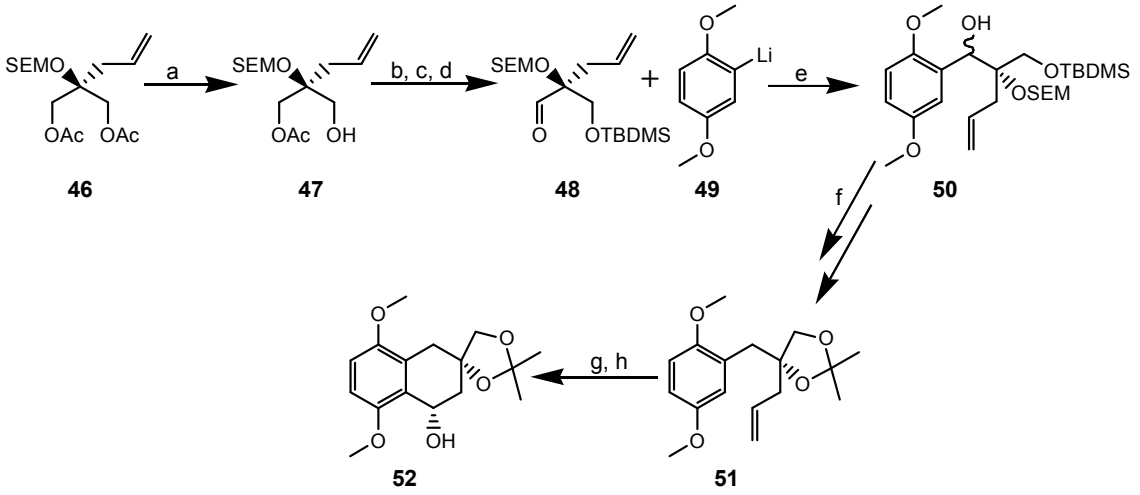


Reagents and conditions : a) (R)-BINOL, $Pr(O\text{-}i\text{-}Pr)_3$, $Ph_3P=O$, *p*-anisidine, toluene, 40%, 95% *ee*; b) MeI, K_2CO_3, MeOH; c) BuLi, THF, 52% over two steps, 90% *ee*; d) $Hg(OAc)_2$, MeOH; e) $NaBH_4$, NaOH, H_2O, 74% over two steps ; f) DMP, DCM, 95%, 90% *ee* ; g) ethynylmagnesium bromide, $CeCl_3$, THF, 76% ; h) $HgSO_4$ (20 mol%), 2% H_2SO_4, acetone ; i) $(CH_2OH)_2$, $MgSO_4$, *p*-TsOH, ; j) $PhB(OH)_2$, *p*-TsOH, toluene, 70% over three steps.

Scheme 11

Finally, insertion of a chiral pool, obtained either from natural or non-natural sources, into adequate substrates is a very useful methodology in the syntheses of enantiomerically pure compounds, especially in the synthesis of complex natural products[78]. This methodology will be introduced by examinig two selected syntheses, one with a substrate derived from a non-natural chiral pool and a recent synthesis with a natural chiral pool (for others see *tetrahedron* **1984***, 40,* issue 22 and *topics in current chemistry,* **2008***, volume 282*).

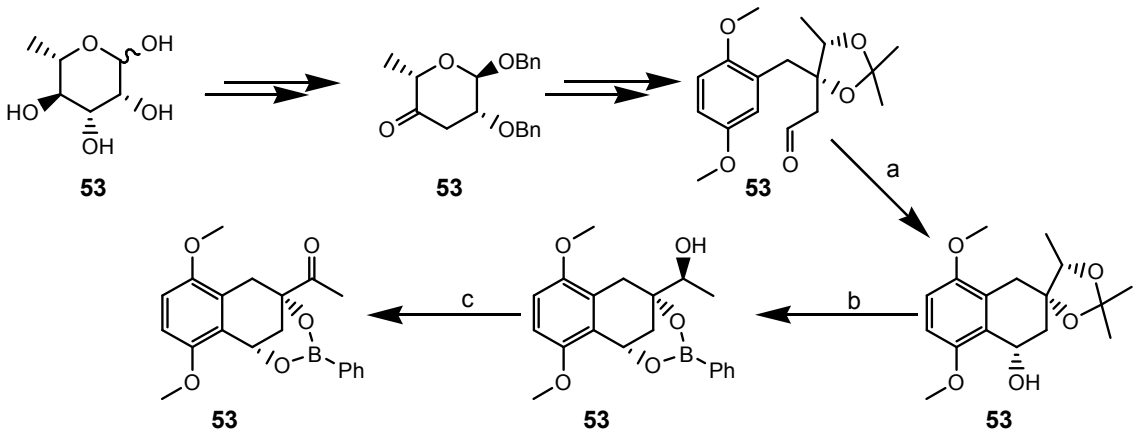
The first example was developed by Watanabe et al.[79] (Scheme 12). He reported a synthesis of **52** from 2,5-dimethoxyphenyl and the aldehyde **48** obtained by enantioselective enzymatic hydrolysis of the diacetate **46** using lipase LP (87% *ee*)[80] followed by subsequent protection of the free hydroxyl group with TBDMS, deacetylation and oxidation of the corresponding alcohol with PDC. Reaction of this aldehyde with the lithium derivative **49** led to the alcohol **50** which can be converted to **51** in a few steps. Following the known procedure developed by Monneret et al.[81], **51** was converted into **52** in 25% overall yield from **47** and 87% *ee*.



Reagents and conditions : a) Lipase LT, O.O6 M buffer-DMF (1 : 1), 87% *ee*; b) TBDMSCl, imidazole, DMF; c) K_2CO_3, MeOH; d) PDC, DCM, 88% over three steps; f) 53% over four steps; g) OsO_4-$NaIO_4$, dioxane-H_2O (1 : 1) ; h) $SnCl_4$, DCM, 55% over two steps, 87% *ee*.

Scheme 12

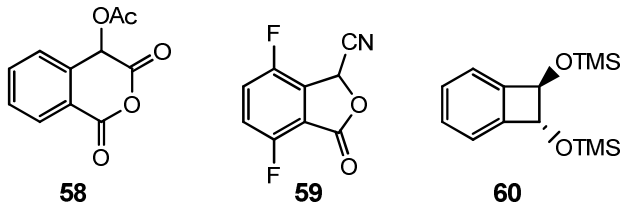
A more recent synthesis of AB synthon was published by Achmatowicz et al. starting from the natural substrate L-rhamnose **53**. He reported an efficient synthesis of the tetralinol **56** which was obtained in 13 steps from L-rhamnose in 17% overall yield[82] (Scheme 13). Recently, he extended his methodology to the synthesis of the phenylboronic acid ester **18**[83] which is also a very useful AB building block in the synthesis of anthracyclinone.



Reagents and conditions : a) SnCl4, DCM, 17% overall yield from L-rhamnose; b) PhB(OH)2, *p*-TsOH, toluene; c) PCC, DCM, 70% over two steps.

Scheme 13

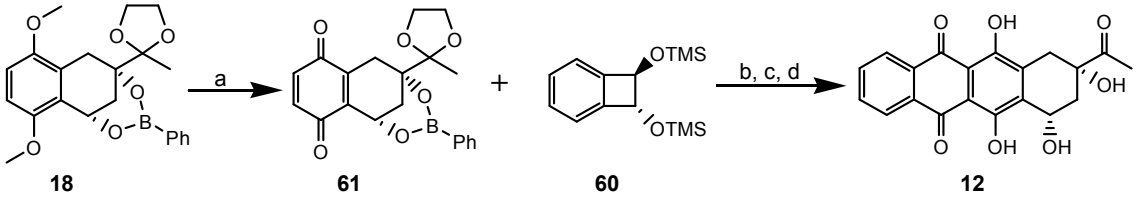
With these different AB building blocks, several coupling methodologies were developed to reach the tetracyclic structure. They involved distinct approaches such as Diels-Alder reaction, base-induced cycloaddition reaction of homophtalic anhydride or the annelation of hemiketal with the anion of 3-cyano-1(3*H*)-isobenzofuranone derivatives. Three corresponding CD precursors are as follows: homophtalic anhydride derivatives of type **58**, 3-cyano-1(3*H*)-isobenzofuranone derivatives of type **59** and precursors of *o*-quinone dimethide of type **60** which are shown in scheme 14. For details about their syntheses see the following references[62,81,84-86].



58 **59** **60**

Scheme 14

For the Diels-Alder reaction with the homophtalic anhydride, the AB synthon had to be oxidized with CAN to the corresponding quinone **61**[63] (scheme 15) which reacts as the dienophil in the cycloaddition of **60** and **61.** Subsequent removal of protected groups gave idarubicinone **12**[86] in 65% overall yield.



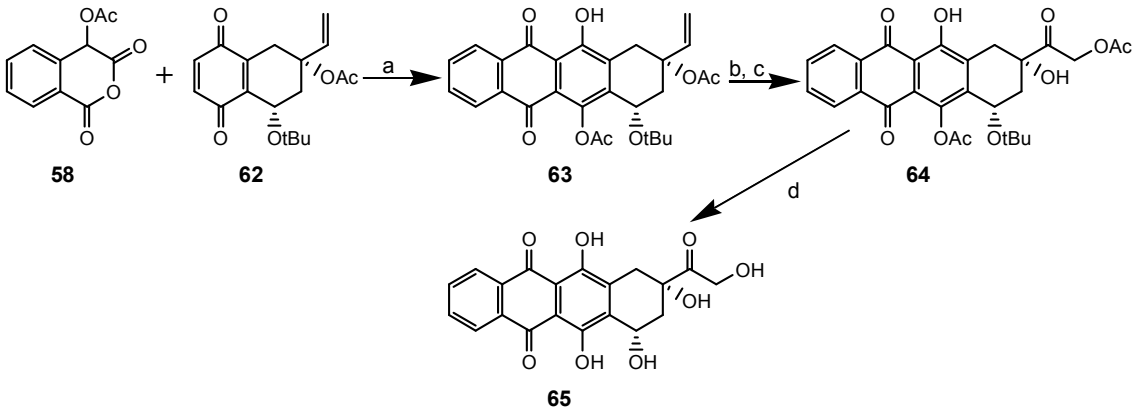
18 **61** **60** **12**

reagents and condition : a) CAN, MeCN, H_2O, 85%; b) 50°C, then DDQ ; c) H_2O_2, NaOH, THF; d) *p*-TsOH, acetone, 65% over three steps.

Scheme 15

Alternatively, the tetracyclic moiety of the aglycone can also be obtained by base-induced (in this case NaH) cycloaddition[87-88] of **58** and **62** in 70% yield followed by

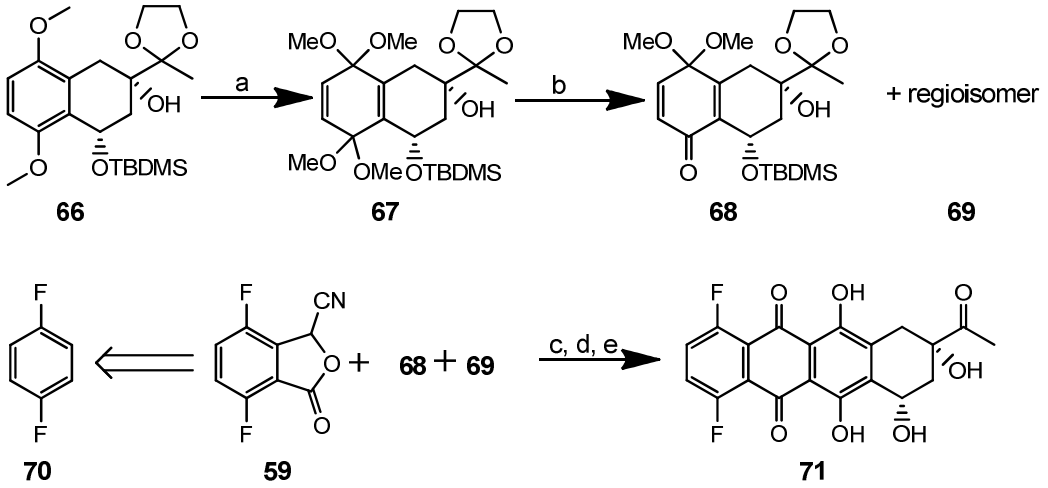
some functionnalisation and deprotection steps to give the aglycone **65**[89] (Scheme 16).



Reagents and conditions : a) NaH, THF, 70% ; b) $PdCl_2$(MeCN) cat., toluene, 99%; c) $RuCl_3$ cat., AcOH, MeCN, DCM, H_2O, 60%, d) 1.2 M HCl, *i*-PrOH, 50%.

Scheme 16

In the case of 3-cyano-1(3*H*)-isobenzofuranone derivatives of type **59**, the AB synthon have to be converted into its corresponding hemiketal by known procedures which gave a mixture of two regioisomers[65,90]. This method can be applied to the synthesis of idarubicinone analogs, which lacks the methoxy group in the D ring, but will be avoided to the synthesis of anthracyclinone which own a substituted D ring. Swenton et al.[91] reported the annelation of the mixture of regioisomers of type **68** and **69** with the anion of fluorinated 3-cyano-1(3*H*)-isobenzofuranone derivatives **59** followed by deprotection of the protecting groups (scheme 17) to give the analog of idarubicinone **71**.



Reagents and conditions : a) aniodic oxidation, KOH, MeOH, Pt, 1.3V ; b) AcOH, H_2O, acetone, 64% yield from 87 ; c) DMSO, THF, MeLi ; d) THF, HCl ; e) BCl_3, DCM, 52% overallyield from monoketal + regio

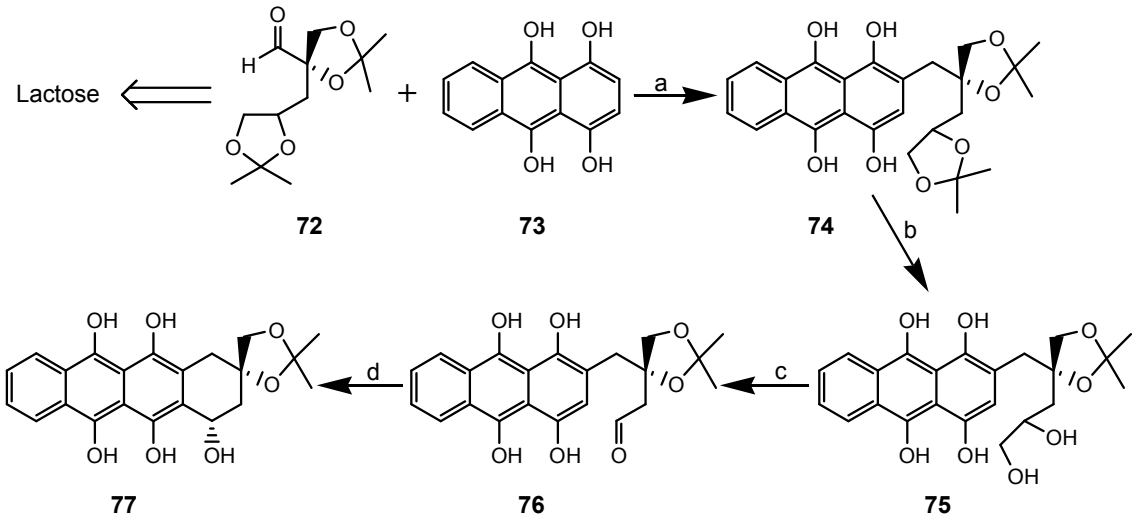
Scheme 17

4.5.2.2 A+BCD Approaches.

As anthraquinones are cheap, readily available compounds, and already contain three of the four rings of the aglycone, intensive efforts were accomplished to begin the synthesis with various anthraquinones as staring materials. Once again, the strategies mentioned above are used in the enantioselective synthesis of the aglycone such as resolution of racemic mixture or use of chiral pool. To illustrate these methodologies, three selected syntheses will be described.

A french group[92], developed a synthesis of optically active 4-demethoxy anthracyclinones using the aldehyde **72** as chiral moiety (scheme 18), which was obtained from lactose. Condensation of the aldehyde **72** with leucoquinizarine **73** (reflux in presence of piperidinium acetate) led to the di-acetonide subtrate **74** which was selectively hydrolysed to afford the diol **75**. The diol **75** was then treated with sodium periodate to produce the aldehyde **76** which was subjected to intramolecular cyclization under Marschalk conditions to give exclusively the derivative **77**. This example illustrates that anthraquinones are valuable starting materials for anthracyclinones syntheses, eve if several of the syntheses are hampered by low yields and the need to separate regio- and stereoisomers. Additional examples of

Marschalk reactions, keto-ester cyclizations and nucleophilic additions towards various natural and synthetic anthracyclines are also known[52-53].

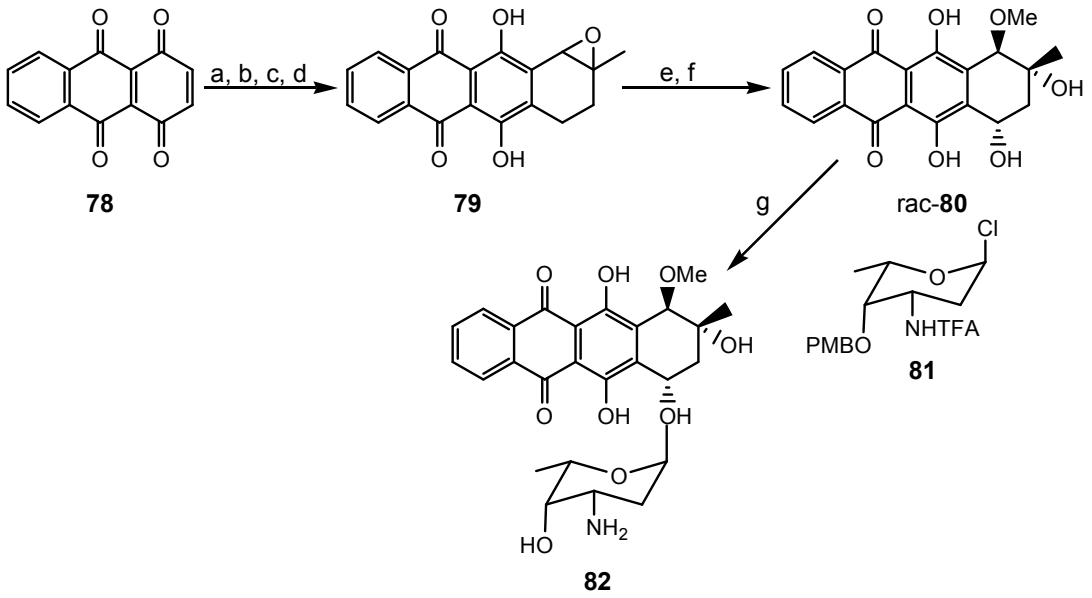


Reagents and conditions : a) piperidine acetate, iPrOH, reflux, 75% ; b) AcOH, H_2O, RT, 88% ; c) $NaIO_4$, MeOH, THF, H_20, AcOH, RT, 99%; d) $Na_2S_2O_4$, NaOH, THF, MeOH, H_2O, then air, 75%.

Scheme 18

Enantiopure anthracyclines can also be obtained by glycosidation of racemic aglycone and separation of the resulting diastereoisomers. Two different syntheses starting from anthraquinone will be described here involving different strategies to reach a racemic aglycone which was glycosilated to give a mixture of diastereoisomeres separable by chromatography.

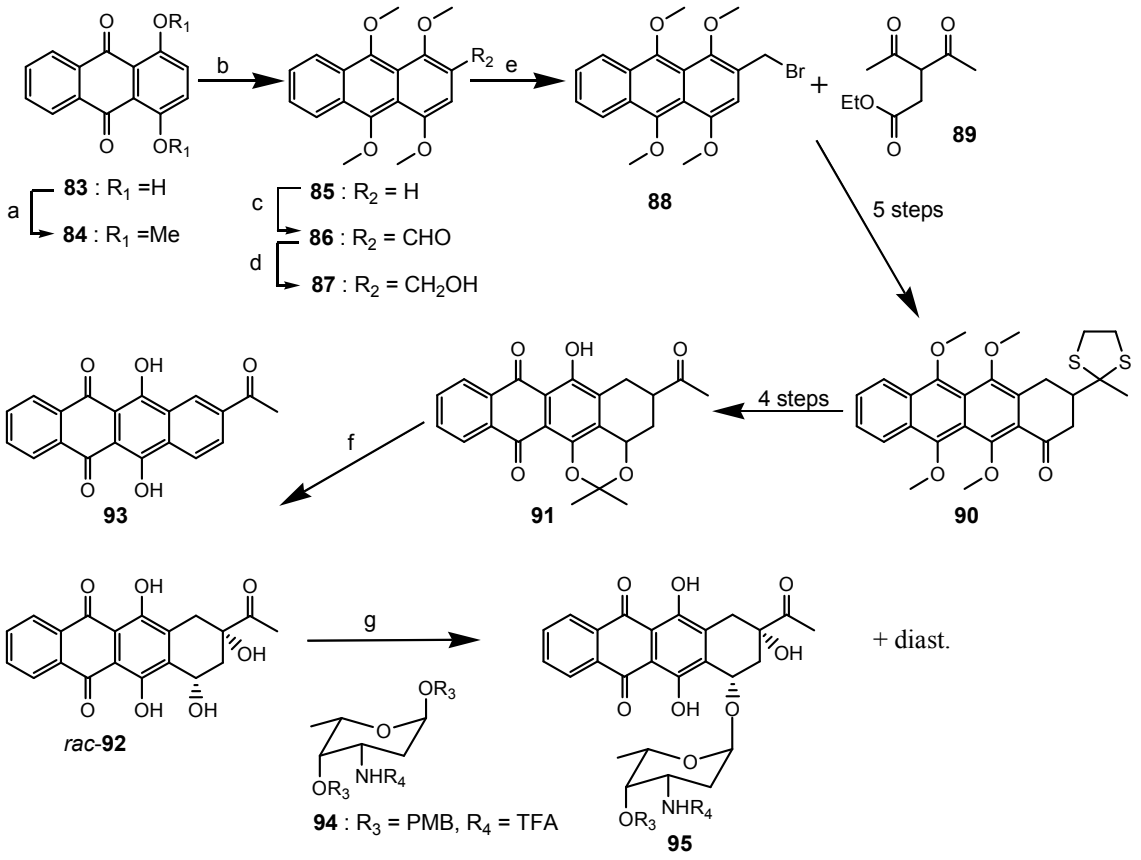
First, Confalone et al.[93] reported the synthesis of a serie of racemic aglycones obtained as shown in scheme 19. Diels-Alder addition of isoprene to the dienophil **78** gave a tetracyclic subtrate. The epoxide **79** was obtained after tautomerisation, migration of the double bond and epoxidation. Opening of the oxirane ring was caried out with various nucleophiles (SEt, OAc, SOEt, SO_2Et, OCH_3) in a stereospecific fashion followed by stereoselective introduction of the hydroxyl group at position C-7 by oxidation with NBS in aqueous CCl_4 in the presence of AIBN. Therefore, glycosidation of rac-**80** with the L-daunopyranosyl chlorides **81** afforded a mixture of diastereoisomeres which were separated by chromatography to give **82** and its isomers.



Reagents and conditions : a) Isoprene, 50°C, benzene ; b) NaOAc, reflux, 34% over two steps ; c) conc. H_2SO_4, 0°C, 81%; d) MCPBA, $NaHCO_3$, DCM, RT, 99%; e) MeOH, *p*-TsOH, reflux, 60%; f) NBS, CCl_4, H_2O, 60°C, 51%; g) (i) CF_3CO_2Ag, DMF / DCM, RT 75%; (ii) Et_3N, H_2O, MeOH, RT, 80%; (iii) 0.1 M NaOH, THF, 0°C, 66%.

Scheme 19

As last example mentioned here, the work of an Indian group[94] will be described. They started their synthesis with the cheap readily available quinizarin (Scheme 20). After subsequent methylation of the phenolic alcohol, reductive methylation of the keto groups, Vilsmeier-Haack formylation[95], reduction of the aldehyde and treatment of the corresponding alcohol with phosphorous tribromide in pyridine yielde the bromo derivative **88** in 67% overall yield from quinizarin. Condensation of the bromo derivative with ethyl-3-acetyllevulinate **89** followed by deprotections/protection sequence and acid catalyzed cyclization gave the intermediate compound **90**. Four additional steps led to the acetonide derivative **91** which could be converted to racemic **92** by oxigenation reaction with potassium *t*-butoxide and oxigen and triethylphosphite in *t*-butanol in low yield (25%). However, the major product of this oxidation was identified as the aromatized product **93** obtained in 45%. Subsequent glycosidation of the racemic mixture under terashima's condition[48] gave a mixture of two diastereoisomers that could be separated, leading to the pure idarubicin after cleveage of the protecting groups.



Reagents and conditions : a) $(CH_3)_2SO_4$, K_2CO_3, acetone, 93% ; b) $(CH_3)_2SO_4$, $Na_2S_2O_4$, KOH, THF/H_2O, TBABr, 99%; c) DMF, $POCl_3$, 83%; d) $NaBH_4$, ethanol, 96%; e) PBr3, pyridine, 92%; f) $(EtO)_3P$, t-BuOH, t-BuOK, O_2, 25% ; g) TMSOTf, mole. sieves 4 Å, DCM, -40°C, ethanol, aq. $NaHCO_3$, 40%.

Scheme 20

As described above, several pathways were established to synthesized anthracyclinones. Nevertheless, all the described synthesis mentioned above are limited by several factors which make their industrial production impracticable including:

- Low reaction yield,
- High number of steps,
- The formation of regio- and diastereoisomers mixtures,
- Need of chromatography purification,

4.6 Aim

Nowadays, most of the anthracyclies used as drugs are produced biosynthetically or semi-synthetically. The present market for anthracyclines is about 40 kg per year for epirubicin and 2 kg per year for idarubicin, while the costs are about 120.000 euros per kg and 1 to 2.5 millions euros per kg respectively. The difference between these prices can be explained by the need of additional synthetic steps for the production of idarubicin. Although idarubicin showed better activity and lower toxicity as epirubicin, its use in cancer therapy has been limited because of its high cost. Thus, a total synthetic pathway should be economically interesting for an industrial manufacturing of idarubicin.

The aim of this PhD thesis is to exploit the potential of a total synthetic pathway for the industrial manufacture of idarubicin. The work has been divided in two parts covering the investigation towards a new total synthesis of idarubicinone / idarubicin, the feasibilty of up-scaling the sequence to a multigramm scale.

With these scope of work in mind, the project had to be first focused on the elaboration of an efficient and stereoselective total synthesis of idarubicinone / idarubicin which should overcome the following issues :

- To select a convergent strategy to reduce the number of consecutive steps.
- To select reagents and reactions applicable in industrial practice.
- To make use of as few steps as possible.
- To search for stereoselective transformations to obtain the right configuration at C-7 and C-9,
- To reach satisfactory yields (at least 65%),
- To avoid chromatographic purifications as much as possible.

Secondly, the synthetic pathway developed had to be up-scaled to a multigramm scale (at least 10 g batches) to approve the developed synthesis and to make the first step into a process translation.

Finally, the synthesis developed had to be adjustable to the synthesis of various anthracyclinone / anthracycline analogs.

5 MAIN PART RESULT AND DISCUSSION

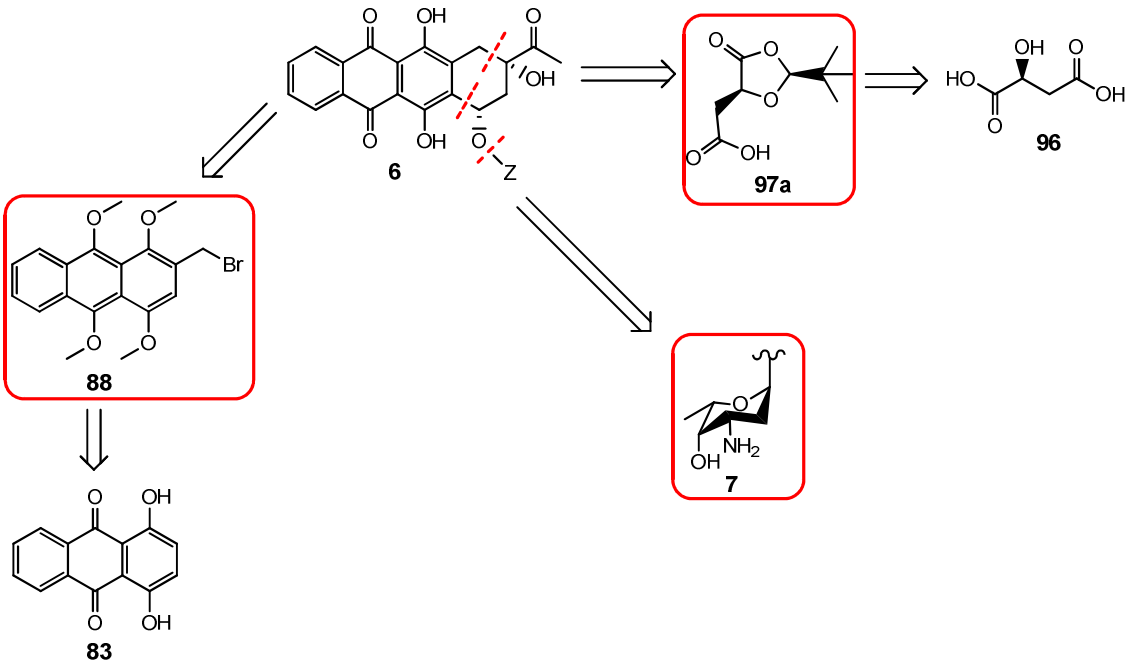
5.1 Retrosynthetic Analysis

This work aimed towards the total synthesis of Idarubicin. As described before, several strategies were already developed. They all share the glycosidation of the final aglycone with the protected sugar followed by deprotection.

The synthesis of the protected sugar has been achieved by several approaches[49,96-99] and was also achieved in our group. A summary of this synthesis will be given later.

Our investigation on the total synthesis of the aglycone of Idarubicin used a fusion of the anthraquinone moiety with an appropriate protected malic acid derivative. This approach is called the A + BCD ring fusion synthesis.

Our retrosynthetic analysis of Idarubicin (Scheme 21) leads to three disconnections, namely two in the A ring and one for the glycosidation of the sugar. This analysis yields three building blocks. First the anthraquinone moiety (BCD ring), second a protected malic acid for the construction of the A ring and finally the sugar moiety were identified.



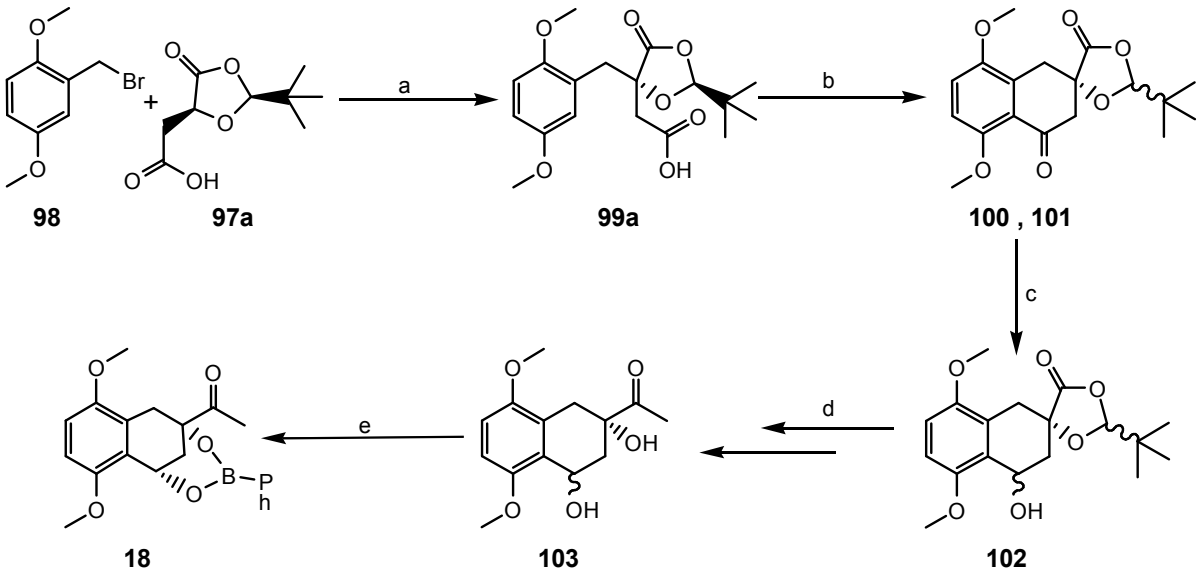
Scheme 21 : Retrosynthetic analysis

The anthraquinone moiety **88** should be suitable to react in an alkylation reaction as electrophile with the nucleophilic dianon of the acetal **97a** of the malic acid **96**. The anthraquinone building block was accessible by several steps, as it will be described later, from the easily available 1,4-dihydroxyanthracene-9,10-dione **83**.

5.2 Preliminary Experiments with Model Substrates (AB Rings Formation)

Based on the work of Krohn et. Al.[100], our first intention was to expend his strategy to the anthraquinone derivative **88**. He reported a synthesis of the AB building block **18** via stereoselective α-alkylation of protected (L)-malic acid with **98** or its iodide analog (Scheme 22). This approach utilised Seebach´s "self-regeneration of stereocenter (SRS)"[101] synthetic principle to build the desired stereocenter at C-9. Friedel Crafts intramolecular cyclisation, reduction of the benzylic ketone group followed by

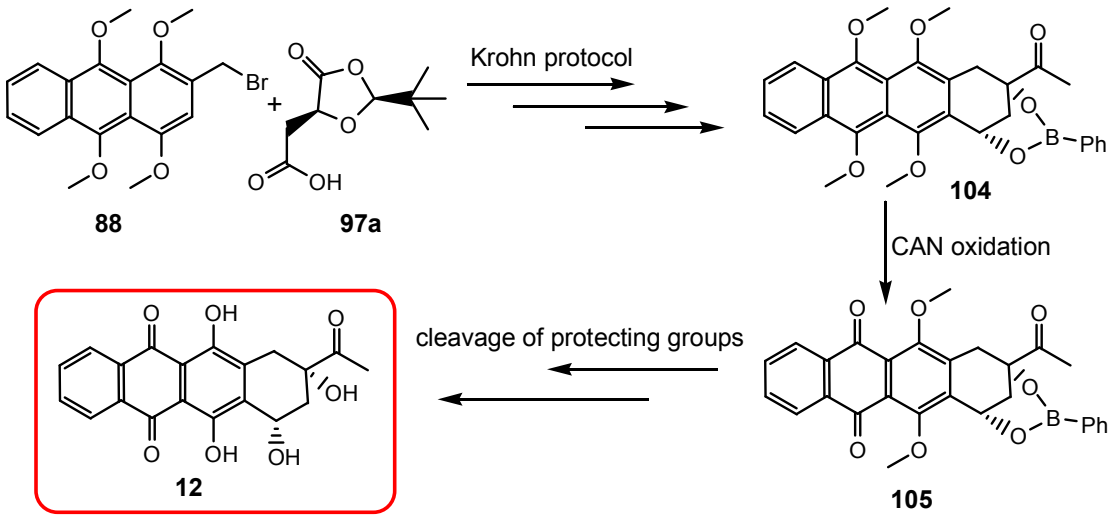
introduction of the methyl group on C-13 and epimerisation at C-7 with a boronester provided the fully functionalised AB building block **18**.



Reagents and conditions : a) LiHMDS, THF, -78°C, 40%; b) $SOCl_2$, $SnCl_4$, DCM, 0°C, 82%; c) $Zn(BH_4)_2$, benzene, 10°C, 78%; d) sodium methylsulfinyl carbanion, DMSO/THF, 0°C then, aluminium-amalgam, THF/H_2O, RT, 90% over two steps; e) Phenylboronic acid, pTsOH, toluene, molecular sieves, RT, 83%.

Scheme 22

We planned to use this methodology to the full anthraquinone derivative **88** (BCD ring) (Scheme 23) for the synthesis of the intermediate **104**. Oxidative demethylation of **104** to the anthraquinone by known procedure[102] followed by deprotection of the different protected groups should afford the desired idarubicinone **12**.

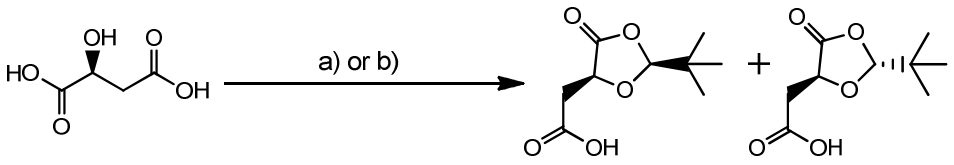


Scheme 23 : first planned synthesis

5.2.1 Synthesis of the A Ring Building Block 97a

Acid-catalysed acetalisation of enantiopure L-malic acid with pivalaldehyde is a well known procedure. We first attempted to reproduce the results published by Seebach[103]. Unfortunately we were not able to obtain the good stereoselectivity of the desired *cis-isomer* **97a**. In fact, we obtained divergent results (even by using the same reaction conditions) in which the ratio *cis-/trans-isomer* variated between 93/7 and 20/80. It appeared to us that H_2SO_4 could overrule the kinetic control of the acetalisation to the detriment of the thermodically more stable *cis-isomer*. In addition, impurities from the sulfuric acid such as metal sulphate, which can operate as a lewis acid, could catalyse epimerisation of the acetal.

Due to these discouraging results we decided to use milder conditions avoiding the catalytic amount of H_2SO_4. By applying p-TsOH alone as catalyst, even with a long reaction time (~5 days instead of 48 hrs with H_2SO_4) the desired *cis-isomer* **97a** was obtained in good yield (86%), excellent diastereoselectivity (> 97% *de*) and perfect reproducibility (Scheme 24).



96 **97a** **97b**

Reagents and conditions : (a) pTsOH, pivalaldehyde, pentane, 86 % in **97a**, >97% *de*; (b) pTsOH, H_2SO_4, pivalaldehyde, pentane, 60 to 90%, ratio **97a**/**97b** between 97/3 to 20/80.

Scheme 24

We did not spend more time to optimise the reaction but Hoye protocol[104] could be an interesting alternative method to avoid the long reaction time.

5.2.2 Reproductibility of Krohn et al. Experiments.

5.2.2.1 Alkylation

Before starting our synthesis we decided to reinvestigate the results published by Krohn et. Al.[100] to optimise the sequence.

We first investigated the alkylation reaction with compounds **98**, **106** and **107** (Scheme 25 and 26, Table 1 and 2).

Therefore we used a slighty modified protocol. The temperature inside the flask was maintained constant and the reaction time was limited to 2 hrs as we did not observe any reaction progress after 1hr by tlc monitoring. Thus, we obtained the same unsatisfactory yield (35%) using LiHMDS as base, even with excellent diastereoselectivities (>92% de). The absolute stereochemistry of **99a** and **99b** was confirmed by comparison with data published by Krohn[100], and X-Ray analysis of **99a** (Figure 1).

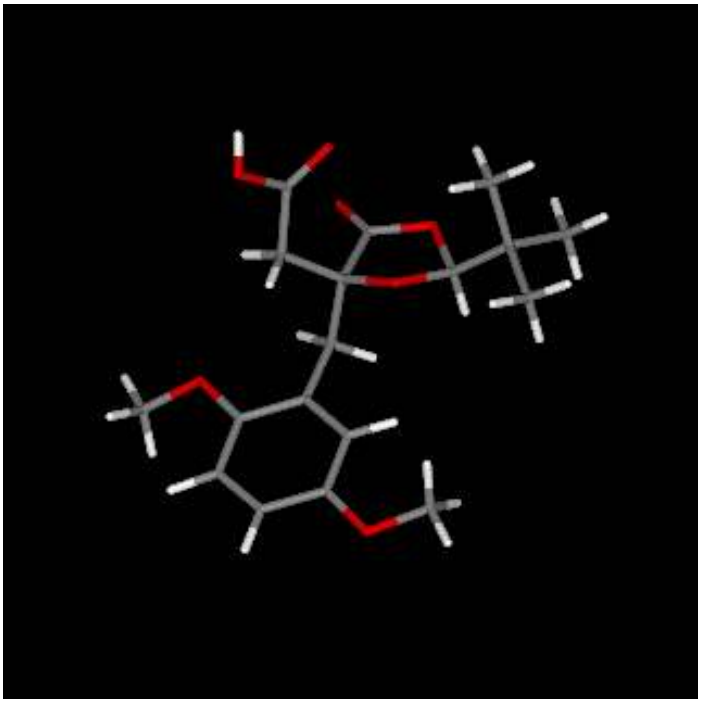
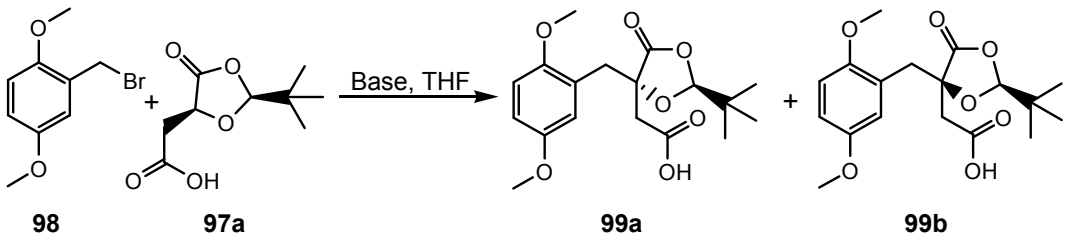


Figure 1 : 3D picture of **99a**

By substituting LiHMDS by KHMDS we were able to increase the yield to 53%. Furthemore we noticed a 59% yield by increasing the temperature to -40 °C after addition of **98**. We also found that deprotonation of the dioxolanone to the dienolat of **97a** gave better results when the dioxolanone was added to the precooled base at -76 °C in dry THF.



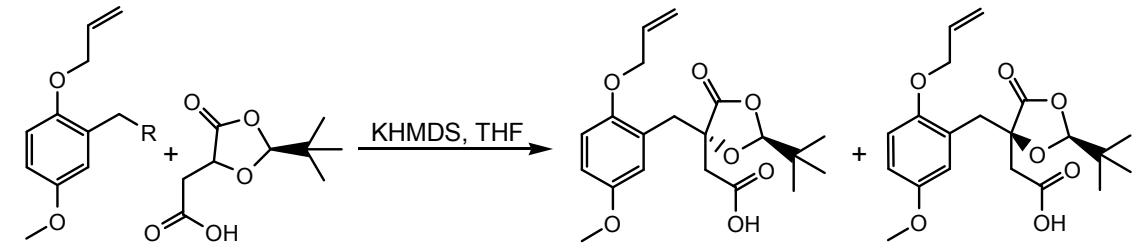
98 **97a** **99a** **99b**

Scheme 25

Table 1 : Formation of **99a** from alkyltion of **98** and **97a**

98	**97a**	Base	temperature after addition of **98**	Yield in **99a**
1.5 eq.	1 eq.	LiHMDS, 3 eq.	-76 °C	35%, >92% de
1.5 eq.	1 eq.	KHMDS, 3 eq.	-76 °C	53%, >92% de
1.5 eq.	1 eq.	KHMDS, 3 eq.	-40 °C	59%,>92% de

A next set of experiments were carried out with the substrates **106** and **107** (Scheme 26). The influence of temperature and excess of dioxolanone were studied. The reaction time was limited to 1 hr as we did not observe any evolution after this time by tlc monitoring. The results are summarized in the table 2 and revealed some interesting findings. The yield of the reaction can be increased in different ways. On the one hand by using a large excess of **97a** (4eq) or by using the iodide **107** derivative instead of the bromo counter part **106**, the yield of the reaction was improved (by 7% and 8% respectively). On the other hand, raising the temperature from -76 °C to -40 °C after addition of the dioxolanone **97a** to the base led to a nearly quantitative yield (87%). The diastereoselectivities were in all cases excellent (>95% de).



106 : R = Br
107 : R = I

97a **108a** **108b**

Scheme 26

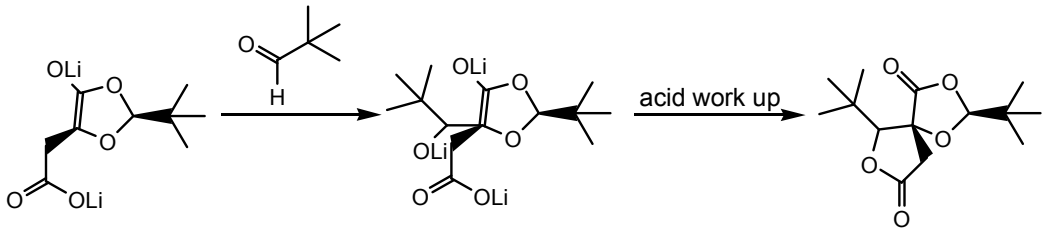
Table 2 : Formation of **108** from alkylation of **97a** and **106** or **107**

97a	Substrate (1 eq.)	KHMDS	temperature after addition of **106** or **107**	Yield[a] in **108 a+b** (calculated from NMR of crude product)
1.5 eq.	**106**	3.5 eq.	-76 °C	50% product / 50% **106**
1.5 eq.	**106**	3.5 eq.	-40 °C	87% product / 10% **106**
4 eq.	**106**	8.5 eq.	-76 °C	57% product / 43% **106**
1.5 eq.	**107**	3.5 eq.	-76 °C	58% product / 42% **107**

[a] calculated from NMR of crude product

5.2.2.2 Aldolisation

Considering the result published by Seebach[103] , it appeared that the dienolate **109** reacted also with pivalaldehyde with lower but still satisfactory diastereoselectivities as shown in scheme 27.



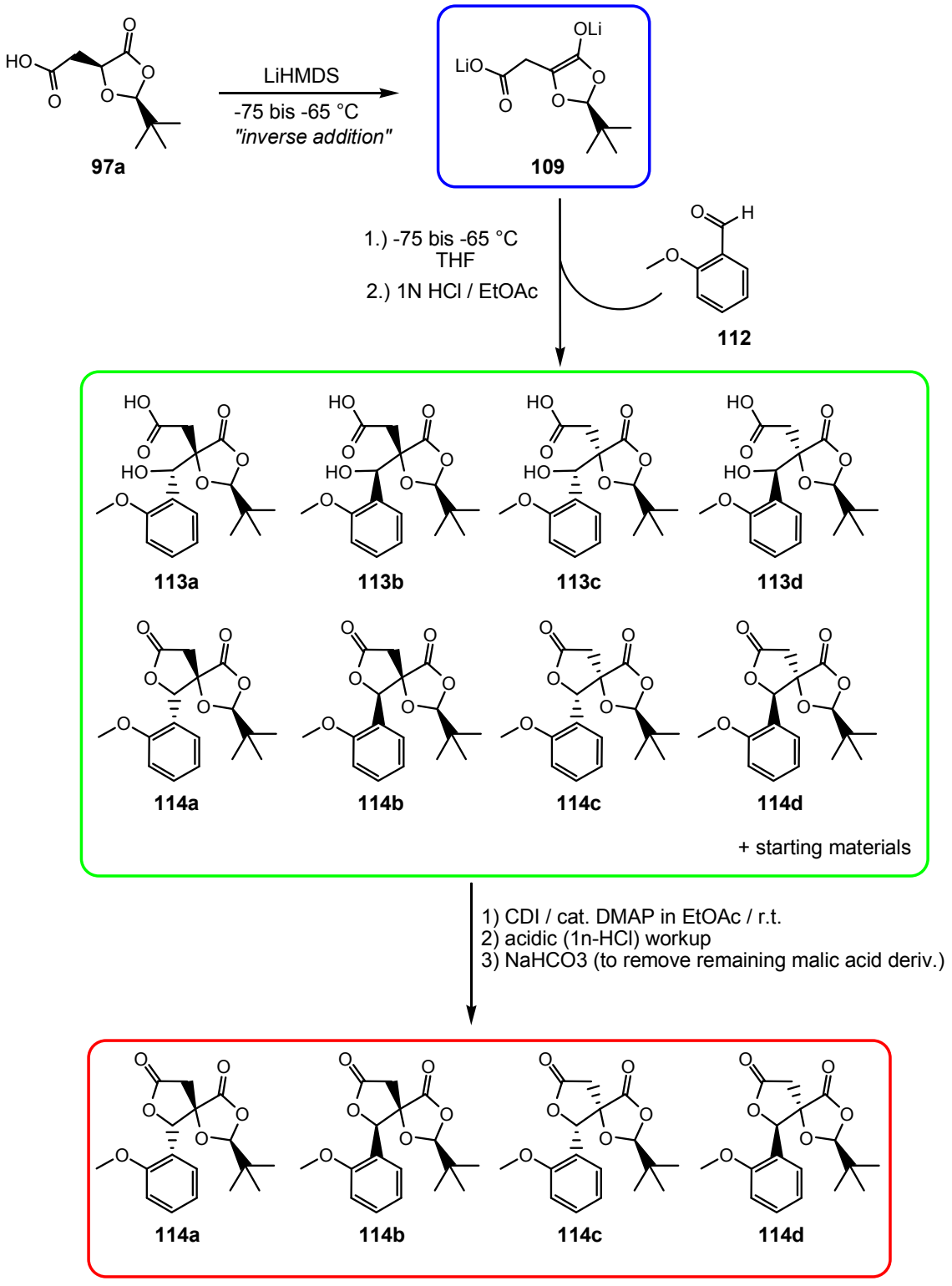
109 **110** **111**

Scheme 27

The aldol product **110** formed was spontaneously converted to the spiro derivative **111** during the acidic work up furnishing product with three asymmetric C atoms. As we planned to use a benzyl aldehyde, we presumed that the benzylic C-O bond

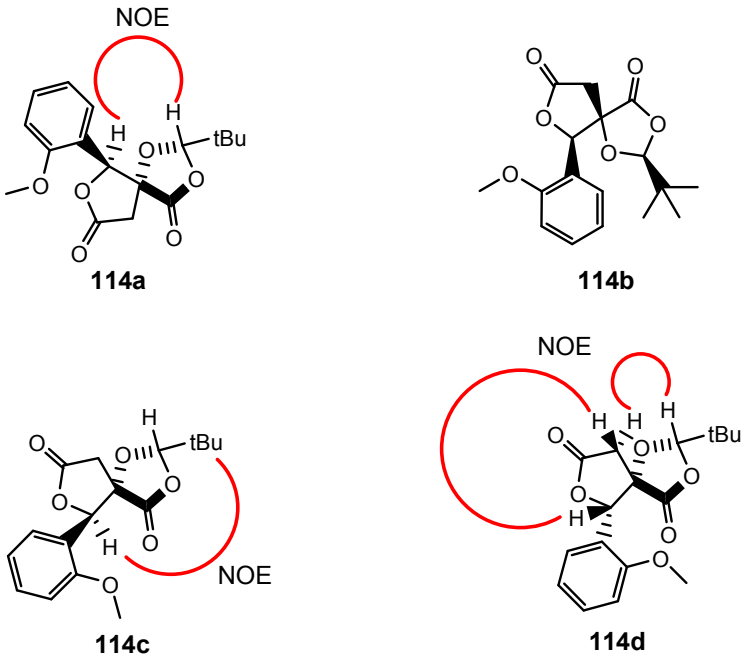
formed could be cleaved by catalytic hydrogenolysis to afford the desired acid substrate.

Thus, we performed the aldolisation with the available aldehyde **112** (Scheme 28). The dienolat was formed as described earlier (dioxolanone added to KHMDS in THF at -76 °C), followed by the addition of the aldehyde. Tlc monitoring of the reaction revealed no reaction progress after 1hr even if the temperature was raised to -40 °C. After acidic work up, starting materials and the presumably four acid intermediates **113a->d** were detected on tlc. After work up and removal of the solvent, these acids were partially converted to their corresponding spiro subtrates **114a->d** leading to a complex mixture of 8 diastereoisomeres and starting materials. In order to simplify the purification by column chromatography, the lactonisation was completed using cat. CDI and DMAP. The desired two diastereoisomeres **114 a + b** were obtained in 30% yield (calculated from NMR of the crude product) and the ratio of **114a+b / 114c+d** was still good (7/3 estimated from NMR of crude product).


LiHMDS
-75 bis -65 °C
"inverse addition"
97a
109
1.) -75 bis -65 °C
THF
2.) 1N HCl / EtOAc
112
113a
113b
113c
113d
114a
114b
114c
114d
+ starting materials
1) CDI / cat. DMAP in EtOAc / r.t.
2) acidic (1n-HCl) workup
3) NaHCO3 (to remove remaining malic acid deriv.)
114a
114b
114c
114d

Scheme 28

The four diastereoisomeres **114a->d** were separated and analysed by NMR. Relevant NOE-effect of three from the four diastereoisomeres permitted us to assign the relative configuration of each product (Scheme 29).



Scheme 29 : Noe effect in **114a→d**

The relative configuration of the missing isomere was deduced from these results. If the acetal chiral center was not affected by the reaction, as well as by the work up and the separation by chromatography, which is a plausible hypothesis, the absolut configuration of the four spiro compounds was assessed. This assignment was approved by X-Ray analysis of the two diastereoisomeres **114a** and **114c** (Figures 2 and 3).

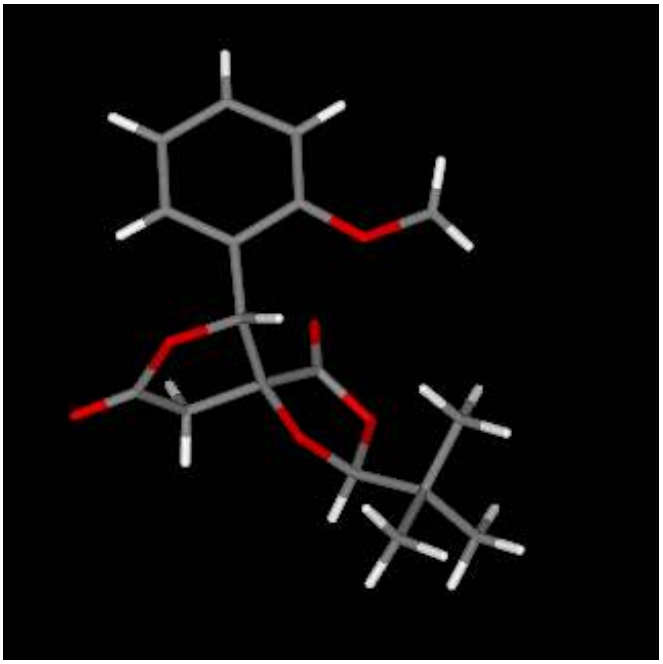


Figure 2 : 3D picture of **114a**

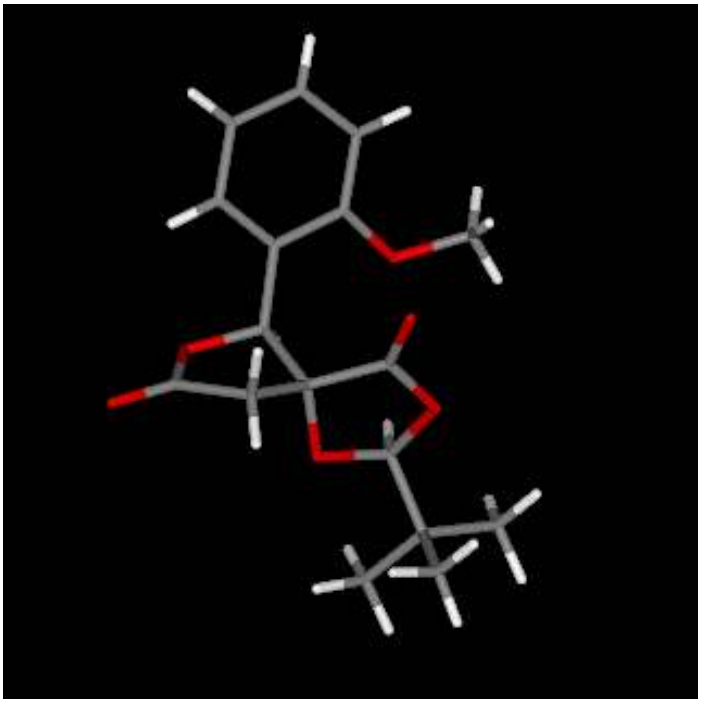
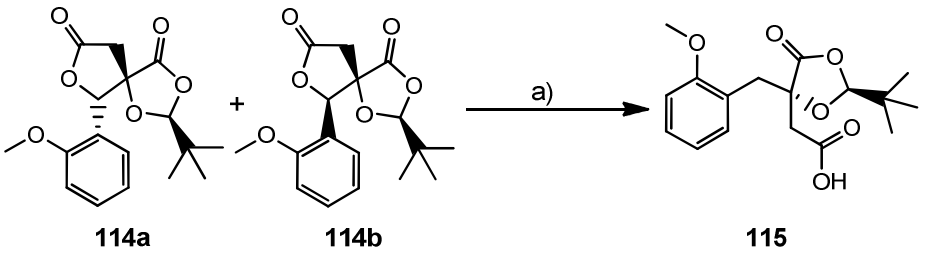


Figure 3: 3D picture of **114c**

Moreover, chemical correlation was in agreement with the NMR and X-ray analysis. Catalytic hydrogenolyse of compounds **114a** and **114b** (Scheme 30) afforded the

same product **115**. Thus, **114a** and **114b** was differentiated only by the chirality on the benzylic chiral center.



114a **114b** **115**

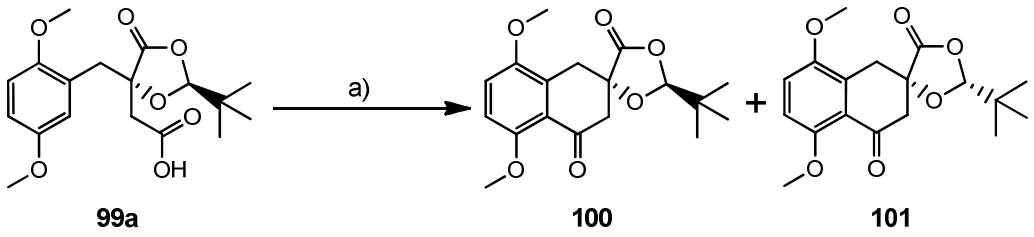
Reagents and conditions : a) H_2, Pd-C, EtOH/EtOAc, 84%.

Scheme 30

Taking this experiment into consideration, it was obvious that the alkylation pathway would be more effective. In fact, the aldolisation pathway afforded disappointing yield presumably due to the revesibility of the reaction and lower diastereoselectivities than the alkylation.

5.2.2.3 Ring Closure

The second part of our preliminary work was focused on the intramolecular ring closure reaction. Krohn et Al.[100] described a Friedel-Crafts intramolecular ring closure (Scheme 31) which yielded (>80%) the desired tetralone **100** and **101** with epimerisation on the acetal chiral center. Unfortunatly we were not able to reproduce this experiment in our laboratory. We also observed epimerisation of acetal chiral center as we obtained poor yield (<20%).

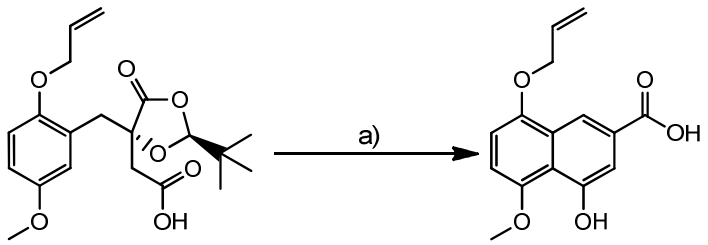


99a **100** **101**

Reagents and conditions : a) $SOCl_2$, $SnCl_4$, DCM, 23%.

Scheme 31

An attempt to improve the yield and/or to avoid the epimerisation was not efficient. Several other acid catalysed intramolecular ring closures were considered like PPA, conc. Sulphuric acid or TFA/TFAA[105-107]. However, we could not improve this reaction. even we observed the intramolecular ring closure by these conditions, undesired side products were detected, for example the aromatisation of the tetralone as shown in (Scheme 32) in the case of **108a**



Reagents and conditions : a) TFAA, cat. TFA, 52%.

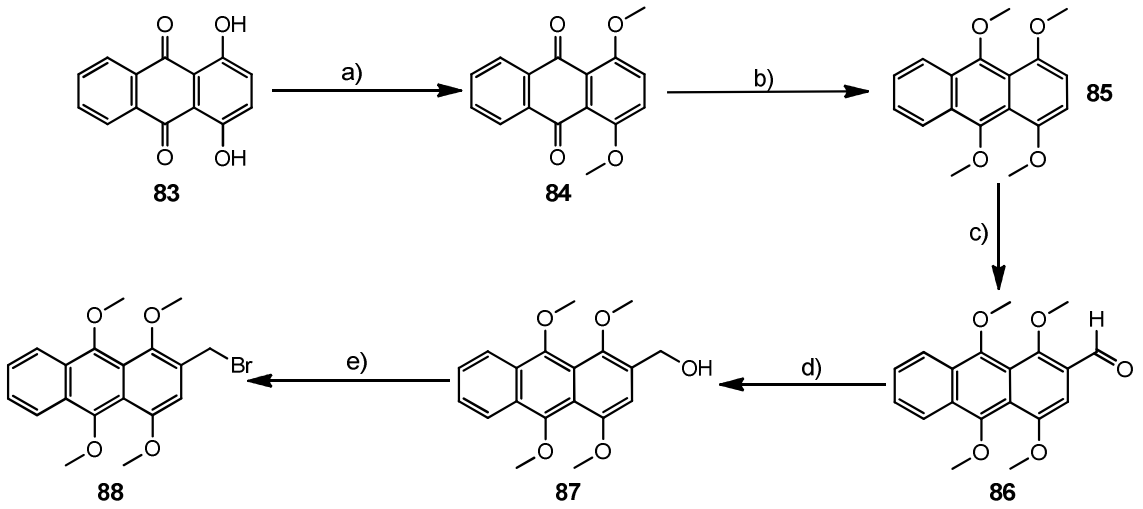
Scheme 32

In spite of these frustrating results we decided to apply the method to our selected substrate.

5.3 Preliminary Experiments with Anthraquinone Derivative 88.

5.3.1 Synthesis of 88

Synthesis of compound **88** was reported only once in literature[94] and is straightforward. In the present work, we only slightly modified the sequence (Scheme 33).



Reagents and conditions : (a) K_2CO_3, Me_2SO_4, acetone, reflux, 91%; (b) TBABr, $Na_2S_2O_4$, KOH, Me_2SO_4, THF/H_2O, RT, 99%; (c) $POCl_3$, DMF, 87°C, 71%; (d) $NaBH_4$, EtOH, RT, 81%; (e) Aq. HBr, toluene, 2°C to RT, 94%.

Scheme 33

The bromo derivative **88** was obtained in 5 steps from available quinizarin **83**. Quinizarin was first methylated with dimethylsulfate and K_2CO_3 in acetone[108] to yield after recrystallisation **84** (91%). **84** was subjected to a reductive methylation using a known procedure[109] followed by Vilsmeier-Haack formylation yielded the corresponding aldehyde **86** in 70% overall yield from **84**. The aldehyde was reduced with sodium borohydride to the corresponding alcohol **87** in 81% yield after recrystallisation which was treated with aqueous HBr in toluene to afford the desired bromo derivative **88** in 94% yield. The synthesis of **88** was achieved in 5 steps in a 49% overall yield from quinizarin **83**. Upscaling the synthesis to 100 g was successfully achieved without need of chromatography purification, or significant change of the overall yield.

It is important to point out that the bromo derivative **88** seemed to be relatively unstable. As shown in Figure 4 and 5, 2D tlc of the corresponding compound revealed his instability, at least through chromatography purification. Nevertheless NMR analysis indicated pure product (>98%). The compound was stored as brown/orange solid in a fridgidaire under argon for months and used without further purification in the next step.

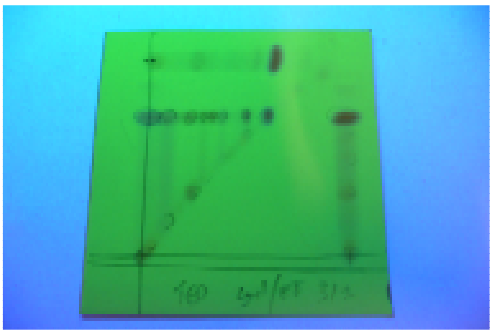


Figure 4

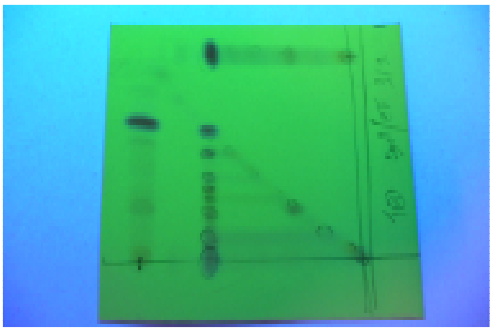
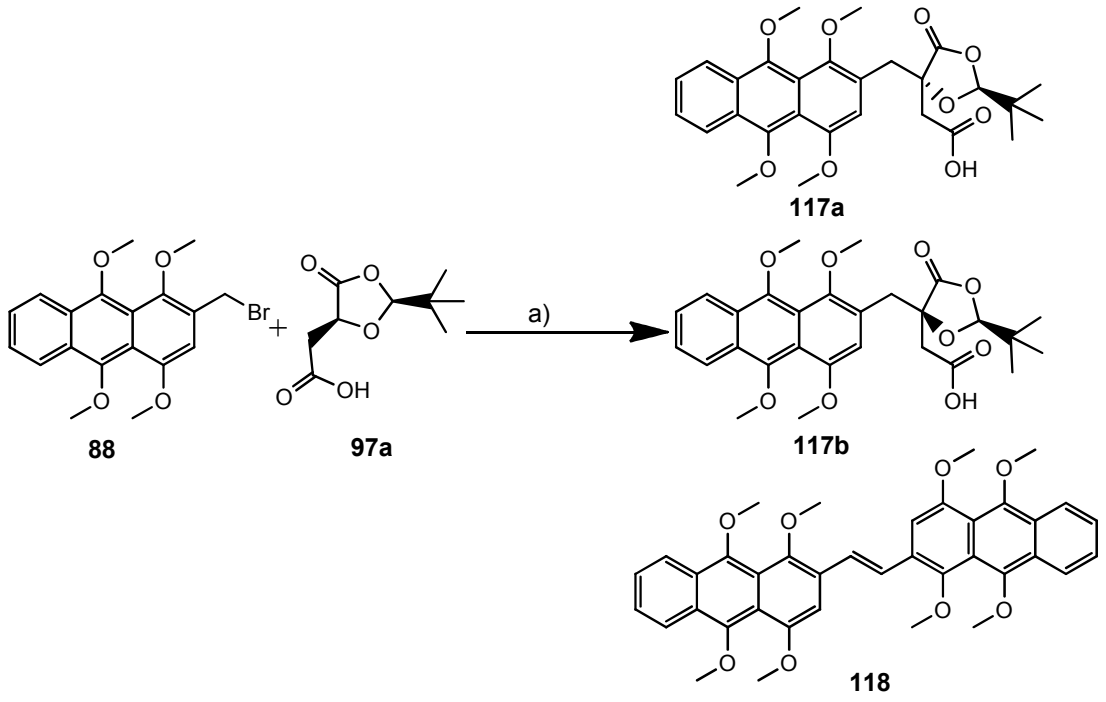


Figure 5

5.3.1.1 Alkylation

As we could more or less reproduce the results from Krohn et. Al.[100], we investigated the sequence with **88** (Scheme 34).



Reagents and conditions : (a) KHMDS, THF, 78°C, up to 46% in **117a**.

Scheme 34

Formation of the dienolate of **97a** was completed as decribed earlier (KHMDS, -76 °C). The reaction was first carried out at -76 °C. This first experiment was performed with poor yield (23%) of the desired product **117a** even if the diastereoselectivity (>99% *de*) was excellent. The main by-product **118** resulted from the dimerisation of the bromo derivative **88** as some starting material (<20%) was recovered.

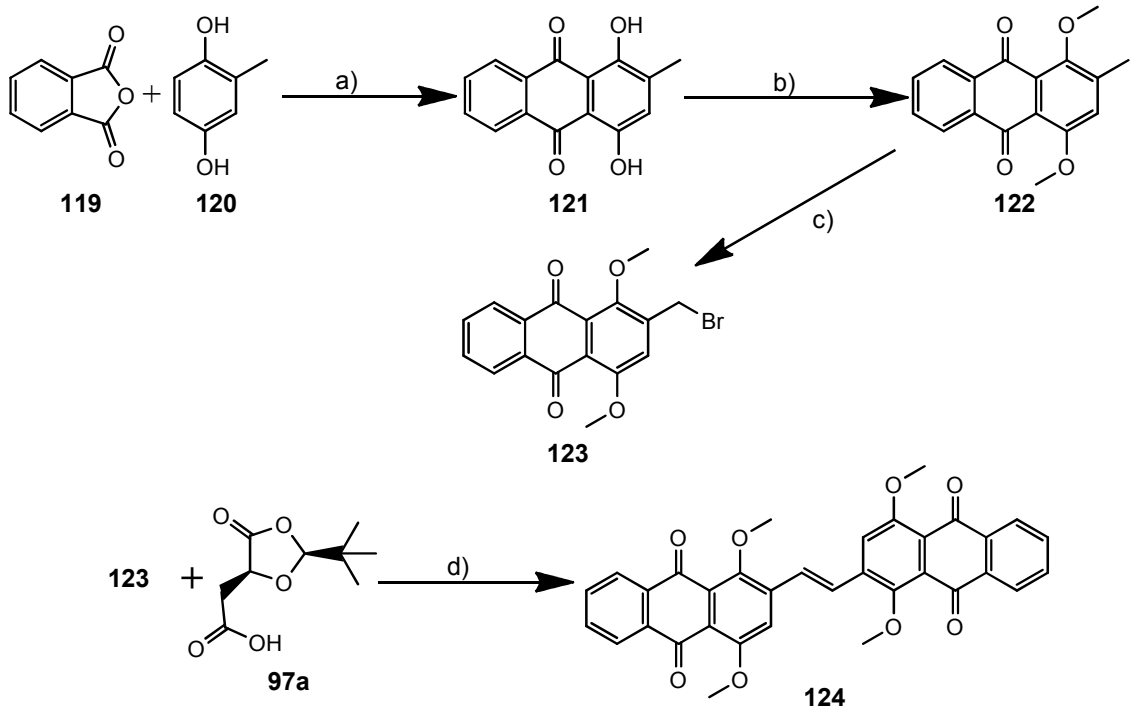
Increasing the temperature to -40 °C after addition of the bromo derivative **88** did not improve the yield (27%). Fortunatly, we were able to obtain a 46% yield by increasing the temperature to -40 °C before addition of the subtrate. These results are summarised in table 3. The poor yields are probably due, to the bad solubilities of both substrates in THF and to the modest basicity but bad nucleophilic properties of the dienolate. In fact, an additional experiment was investigated to approve this last hypothesis. Treatment of the bromo derivative **88** with KHMDS at -76 °C under argon atmosphere afforded almost quantitativly the compound **118**.

Table 3 : Formation of **117a** from alkylation of **88** and **97a**

97a	**88**	KHMDS	temperature	Isolated yield in **117a**
1.3 eq.	1 eq.	3 eq.	-76 °C [a,b]	23%
1.3 eq.	1 eq.	3 eq.	- 76°C [a] then - 40 °C [b]	27%
1.5 eq.	1 eq.	3.5 eq	-40 °C [b]	46%

[a] temperature before addition of **88**. [b] temperature after addition of **88**

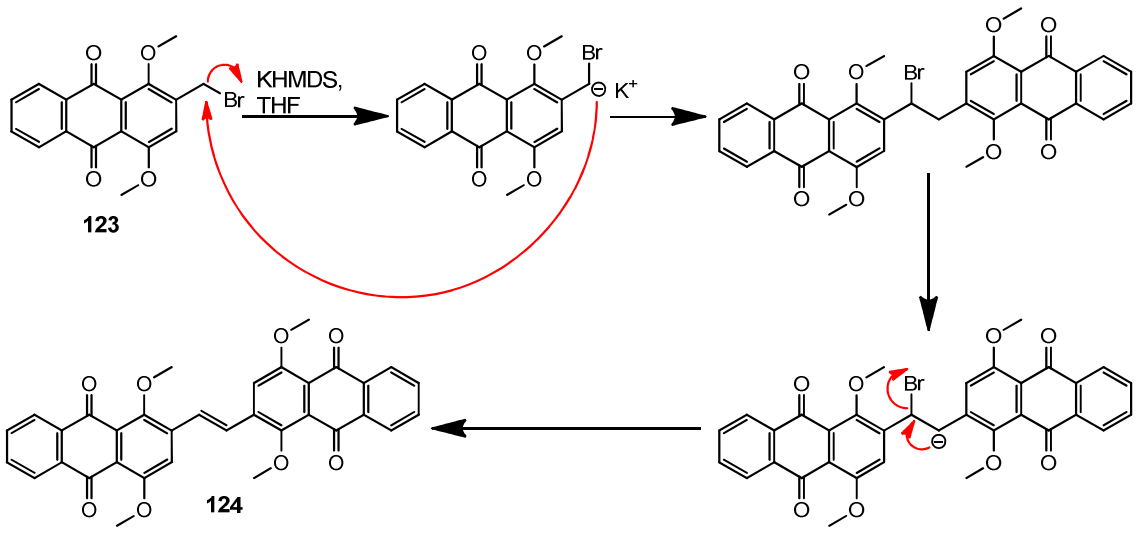
Condensation of **123** with the dioxolanone **97a** under our alkylation conditions (-76 °C) was also investigated. Synthesis of **123** was achieved in three steps from readily available benzoic anhydride **119** and methylhydrochinon **120** (Scheme 35). Friedel Crafts alkylation of these two substrates[110-111] and subsequent methylation of phenolic alcohols as described earlier (dimethylsulfate, K_2CO_3, acetone) led to the anthraquinone **122** which was brominated with NBS under radical conditions[111] to afford the desired bromo derivative **123** in 39% overall yield.



Reagents and conditions : (a) AlCl3, NaCl, 170°C, 77%; (b) K2CO3, Me2SO4, acetone, reflux, 83%; (c) NBS, Bz2O2, CCl4, reflux, 61%; (d) KHMDS, THF, -78°C, 65%.

Scheme 35

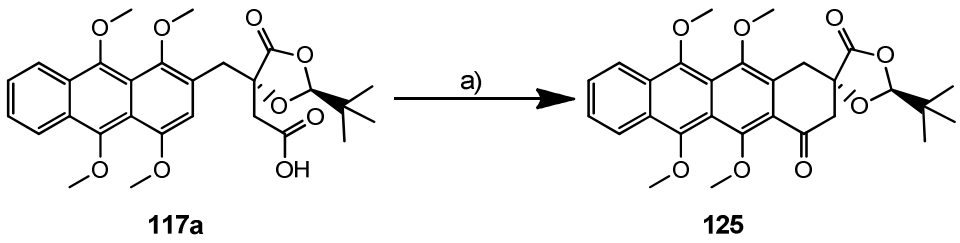
Condensation of **123** with the **97a** under usual reaction conditions (-76 °C) afforded a complex mixture of products. The bromo derivative was consumed quickly (less than 10 min) to give the dimere **124**, resulting from the condensation of the bromo derivative with himself, as main product (Scheme 36).



Scheme 36 : formation of **124**

*5.3.1.2 Ring Closure of **117a***

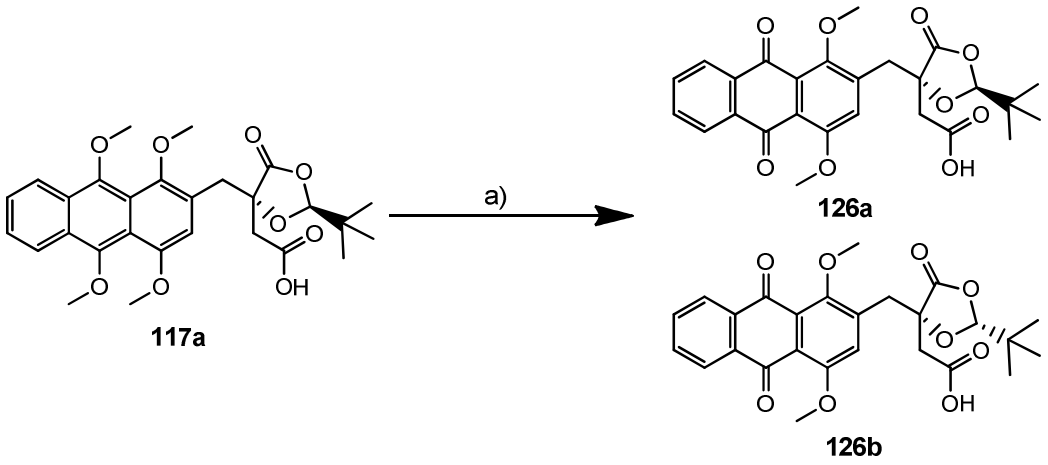
With compound **117a** in hand we tried to prepare the tetracyclic product **125** by intramolecular cyclisation (Scheme 37). Therefore we used methods described earlier.



Reagents and conditions : (a) TFAA, cat. TFA, RT, 25% yield in **125**, 46% of **117a** recovered

Scheme 37

Friedel-Crafts cyclisation did not deliver the desired product **125** (Scheme 38). In fact, the use of Lewis acids ($SnCl_4$ or $AlCl_3$) led to an oxidative demethylation of **117a** to the anthraquinone derivatives **126a** and **126b** with epimerisation of the acetal stereocenter as observed earlier.



Reagents and conditions : (a) $SOCl_2$, $SnCl_4$, DCM, RT, 43% of **126a** / **126b** : 1 /1

Scheme 38

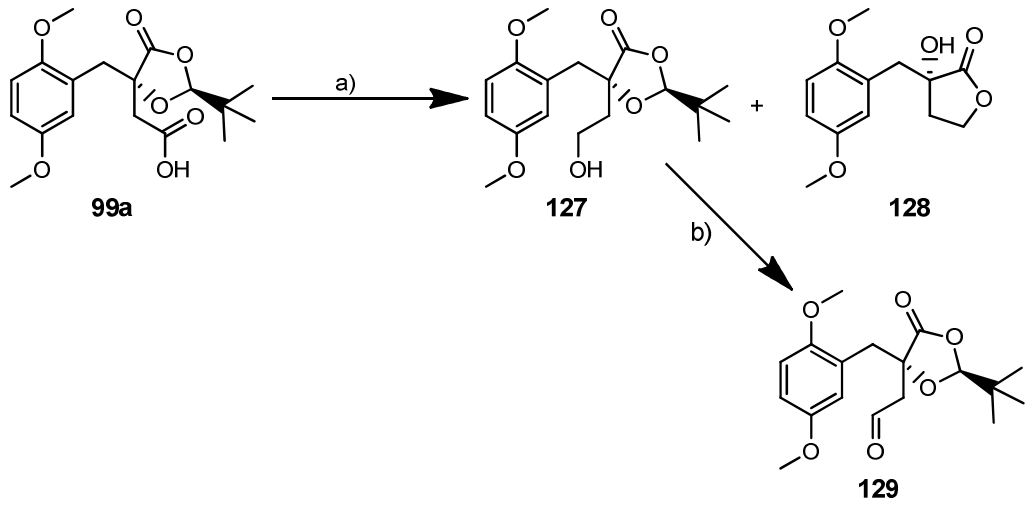
The attempt to use other reagents such as PPA or Eaton reagent[112] (7.7 wt% phosphorous pentoxide solution in methanesulfonic acid) also failed to give the desired product **125**. Finally, unsatisfactory cyclisation of **117a** occured with a mixture of trifluoroacetic acid and trifluoroacetic anhydride yielding the key intermediate **125** in the best case in 25% yield, and 46% recovery of starting material. Surprisingly, no aromatisation of ring A was observed.

Since the intramolecular ring closure did not give acceptable results by Friedel Crafts cyclisation, our attention was diverted to explore an alternative approach to obtain a tetracyclic derivative.

5.3.2 Investigation towards Other Ring Closures

*5.3.2.1 With **99a***

Difficulties encountered during the attempts to cyclise the acid derivative led us to turn our attention toward the corresponding aldehyde (Scheme 39) which should be more reactive in the ring closure reaction. In addition to the higher reactivity of the aldehyde instead of the acid in the intramolecular cyclisation, it should lead directly to the desired hydroxyl group at position C-7present in the target molecule.



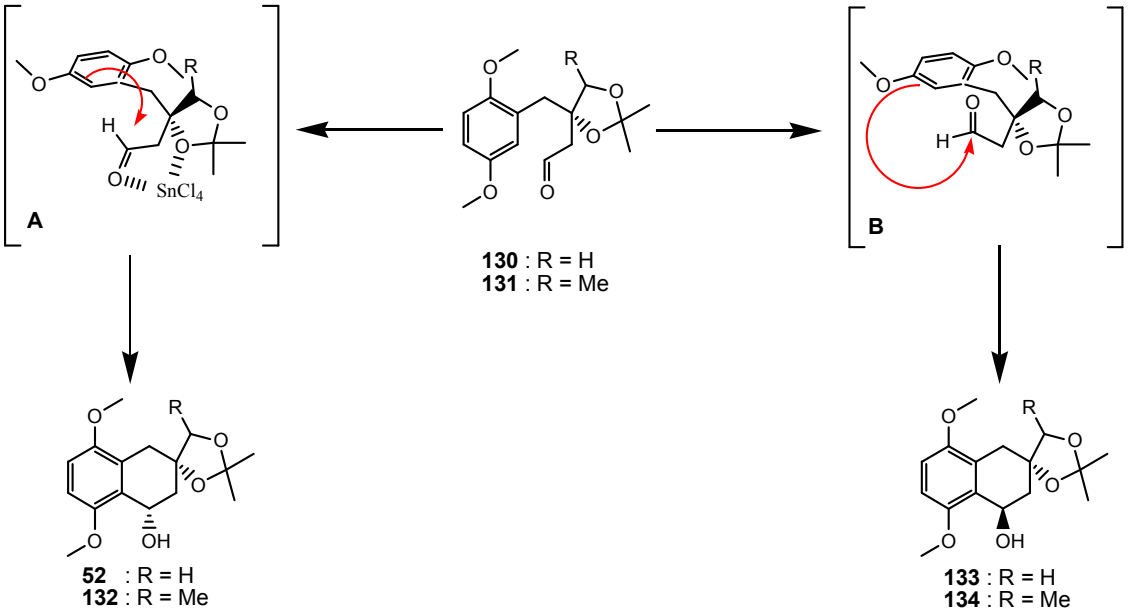
Reagents and conditions : (a) BH3.THF, THF, 3°C to RT, 75%; (b) Dess-Martin periodinane (97%), DCM, RT, 69%.

Scheme 39

The acid was reduced chemoselectively with borane complex in THF[113] to the alcohol **127** that was treated with Dess-Martin periodinane in DCM yielding the aldehyde **129** in 52% overall yield. This yield was increased from 52% to 68% by avoiding chromatography purification of the alcohol which promoted the lactonisation of **127** into **128**.

With the aldehyde **129** in hand, acid-catalyst promoted ring closures were investigated. Ring closures of similar substrates were reported by Monneret et al.[81-82]. Substrates **130** as well as **131** were readily cyclised with high stereoselectivity by

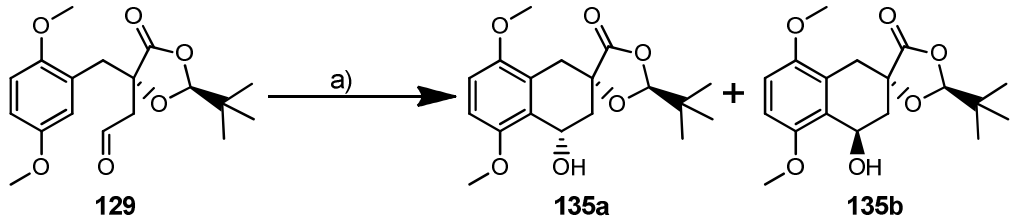
treatment with $SnCl_4$ at -70 °C. The predominant (S) configuration of the new stereogenic center in **52** and **132** was explained by the favoured transition state **A** in which chelation can occured between the aldehyde and the oxygen of the tertiary alcoxy group compared to the transition state **B**, giving the trans tetralone **133** and **134** (Scheme 40).



Scheme 40

Therefore our first experiment was carried out with these reaction conditions (Scheme 41). As expected, aldehyde **129** was more reactive than our previous acid substrate **99a** and was completly consumed after 30 min. A mixture of two tetralones **135a** and **135b** was obtained after purification in 65% yield with the desired isomere **135a** as the major product (**135a** / **135b** : 61% / 39%, estimated by NMR analysis). The lower stereoselectivities observed compared to those described above are presumably due to the carboxyl group which could be implicated in other chelation form.

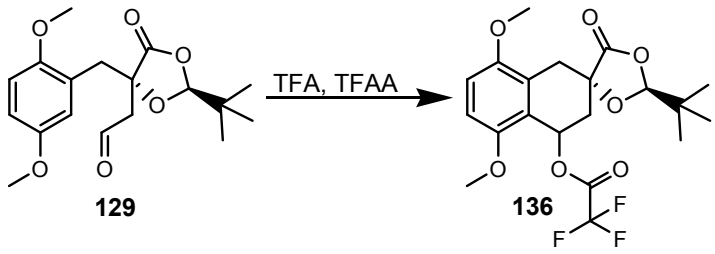
It is also interessant to notice that no epimerisation of the acetal chiral center was observed. Two plausible explications were envisaged: epimerisation is a slow process, and the short reaction time did not allow it to occure; low temperature seem to inhibit the epimerisation.



Reagents and conditions : (a) $SnCl_4$, DCM, -70°C, 65% of **135a** / **135b** : 1 /0.65

Scheme 41

In an additional attempt to the ring closure we investigated a mixture of trifluoroacetic anhydride and trifluoroacetic acid at room temperature (Scheme 42). The cyclisation occured fast under these conditions (less than 10 min) and yielded after work up the compound **136** as single diastereoisomere.



Scheme 42

By NMR analysis we were enable to get enough informations to assign the configuration at C-7. Attempts to recrystallise the product failed. However, comparing the ^1H NMR with **135a** led us to postulate that the desired configuration was obtained. The two benzylic protons (H-1/1 and H-1/2) in **136** are seprated by 0.58 ppm as the desired isomere **135a** showed a shift difference of the corresponding protons by 0.45 ppm, while this shift difference by the undesired tetralone **135b** was only 0.09 ppm (Figure 6).

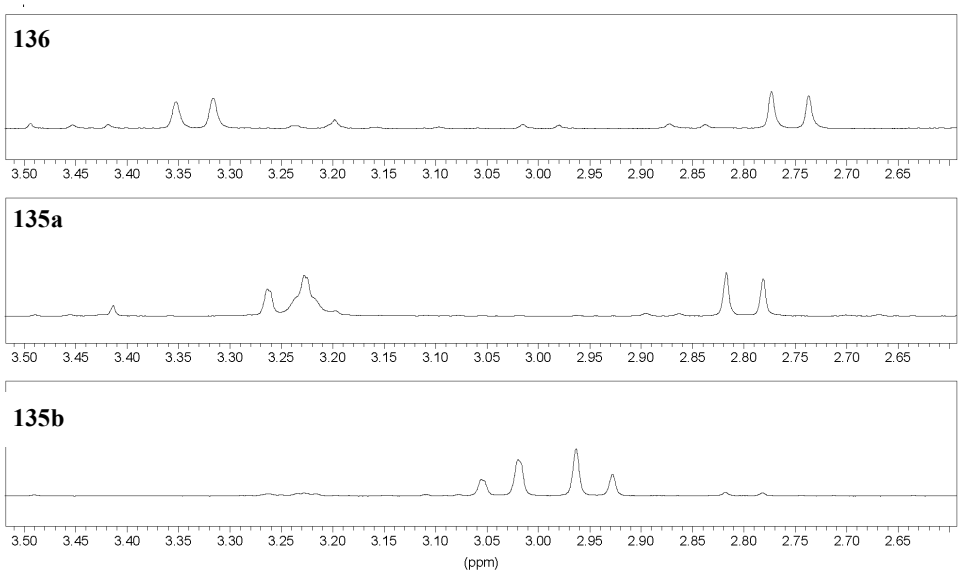
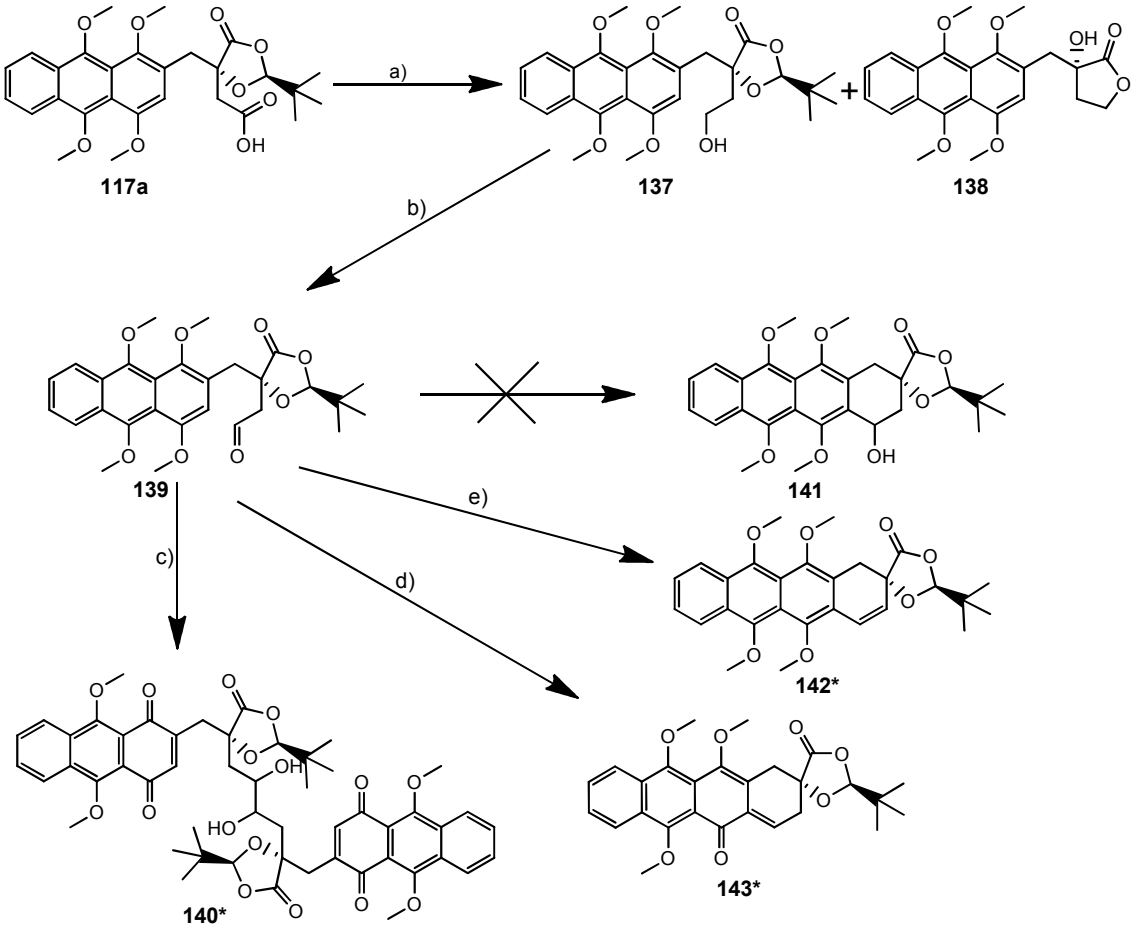


Figure 6 : Benzylic proton shifts of 136, **135a** and **135b**

5.3.2.2 With Different Anthraquinone Derivatives

Considering these promising results we converted the acid **117a** into the corresponding aldehyde **139** (Scheme 43) as described above. Reduction with borane complex in THF afforded the wanted aldehyde **139** in the dissapointing yield of 4% and the alcohol **137** that undergo lactonisation in small amount through the purification process. Oxidation under mild conditions (Swern oxidation) led to the reactive aldehyde **139** in 55% overall yield. We also observed by NMR and tlc analysis its instability in solution. One night in $CDCl_3$ (filtered throug Alox) led to complete decomposition of **139**.



Reagents and conditions : (a) BH_3.THF, THF, 2°C to RT, 50% of **137**, 16% of **138**; (b) DMSO, oxalylchlorid, DCM, Et_3N, -70°C, 85%; (c) TFA, DCM, -40°C, 15%; (d) $BF_3.Et_2O$, DCM, -40°C, 19%; (e) TFAA, TFA DCM, -70°C, 9%.

Scheme 43

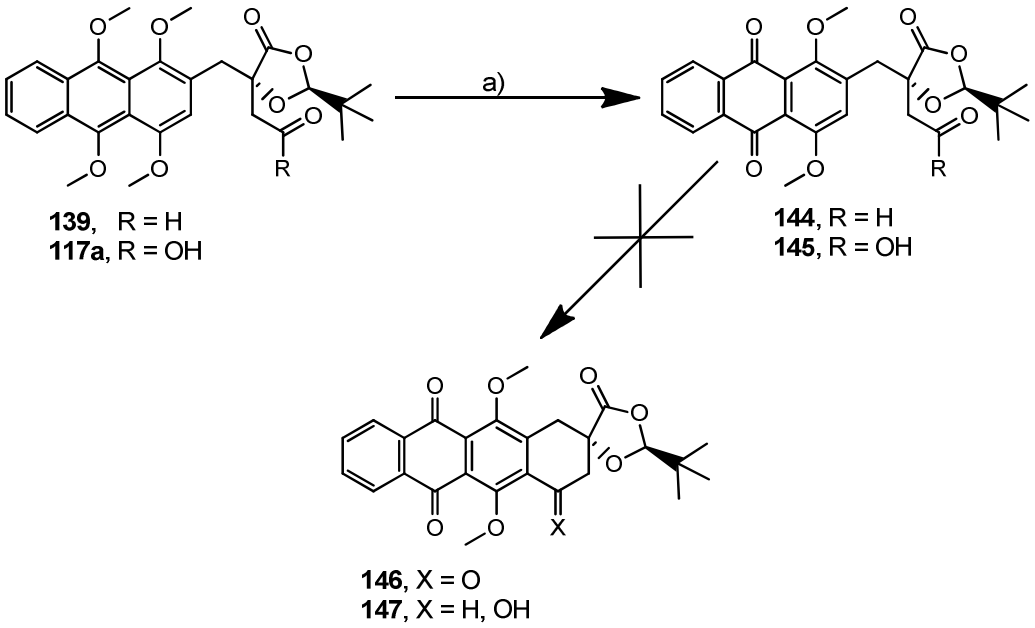
In order to prepare the tetracyclic product **141**, various lewis acids such as $SnCl_4$, $BF_3.Et_2O$, mixture of TFA and TFAA, TFA in THF or TFA in DCM, $MgCl_2$ were investigated. Nevertheless, no clean reaction was observed. Most of the experiments led to complex mixtures of products which were difficult to seperate by chromatography on silica gel. In most of the cases we were able to isolate the tetracyclic compound **142** in poor yield (<10%) resulting from the ring closure of **139** followed by fast elimination of the benzylic hydroxyl group. However, we did not succeed to isolate the key intermediate **141** (with C-7 hydroxyl group). We assumed that the C-7 hydroxyl group undergoes spontaneous elimination during the reaction

due to the electron rich anthracene structure which tended to stabilise the molecule with an additional conjugation.

After consecutive purifications, additional tetracyclic products such as **140** and **143** were isolated from the reaction using TFA in DCM and $BF_3.Et_2O$ in DCM respectivly. In both cases, a complex mixture of products was obtained and undesired demethylation occured.

Even if the usefull tetracyclic product **142** was detected and isolated, it appeared obvious to us that the aldehyde **139** was not an appropriate subtrate to obtain the intermediate **141**.

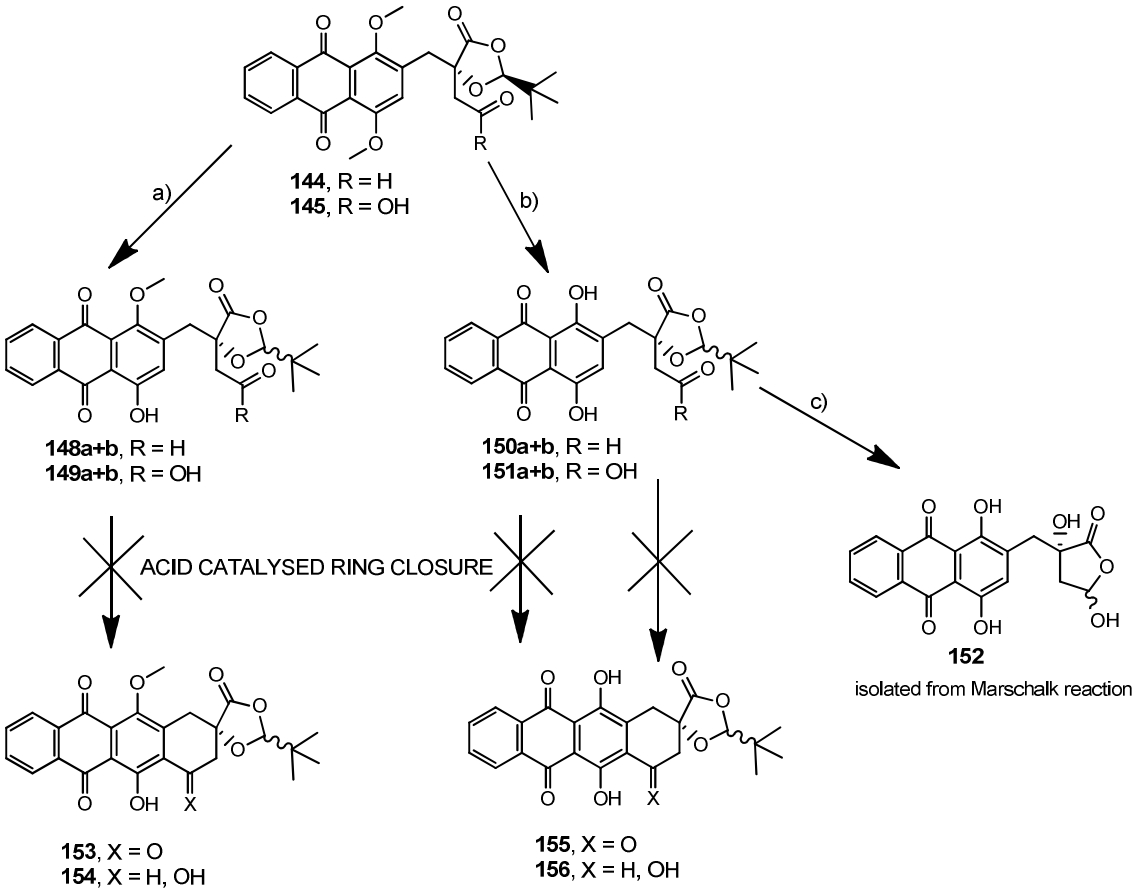
Therefore, we modified our synthetic strategy and explored the possibility of a ring closure at a later stage. Considering the instability of aldehyde **139**, we decided to convert it to the more stable anthraquinone analogue **144** by oxidative demethylation with CAN in 74% yield (Scheme 44). A similar approach was carried out with the acid derivative **117a** that was converted to **145** in 93% yield in a parallel work. Ring closure using a variety of acidic reagents failed to give any tetracyclic products with both subtrates **144** and **145**. Actually, subtrates **144** and **145** were resistant to these reaction conditions and could be recovered almost quantitatively.



Reagents and conditions : (a) CAN, CH_3CN / H_2O, 2°C to RT, 74% of **144**, 93% of **145**.

Scheme 44

Mono or complete demethylation of **144** and **145** was achieved by treatment with 1.2 equivalent or 4.8 equivalent BCl_3 respectively, in good to excellent yield (78% to 95%) with epimerisation of the acetal stereocenter (Scheme 45). The mono demethylation was regioselective and occured at the methoxy group at the position C-4. Another set of experiments was carried out with various acidic reagents such as cited above, but failed to give any cyclisation products. Resistance of anthraquinone derivatives to acid catalysed ring closure was already observed by Krohn[53,111,114] and were attributed to the apparent strong electron-withdrawing property of the anthraquinone system.



Reagents and conditions : (a) 1.5 eq. BCl_3, DCM, -45°C, 82% of **148a+b**, 80% of **149a+b**; (b) 4.5 eq. BCl_3, DCM, -45°C, 95% of **150a+b**, 90% of **151a+b**; (c) NaOH, $Na_2S_2O_4$, THF / MeOH, H_2O, RT, 47%.

Scheme 45

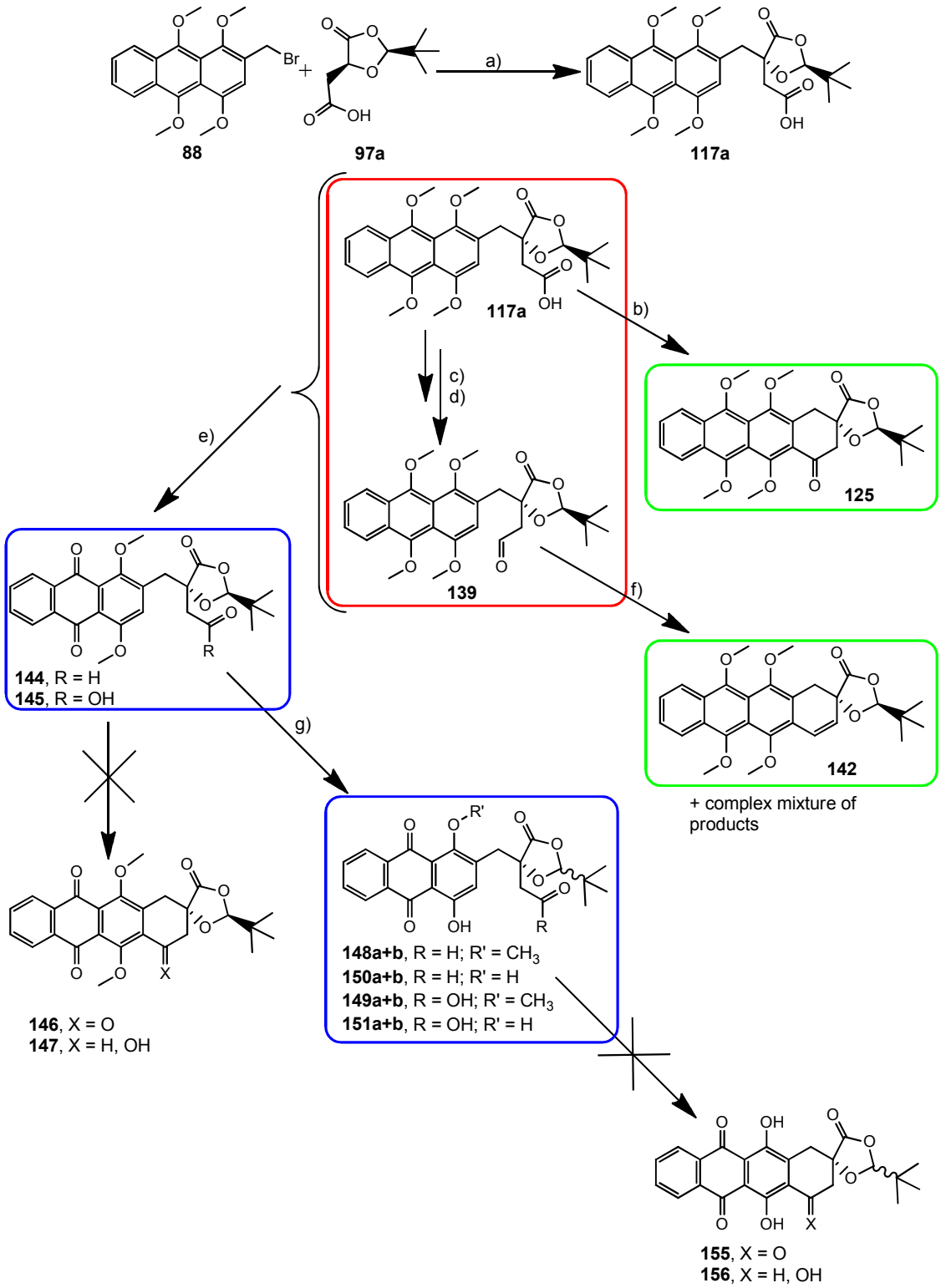
To overcome this obstacle, it appeared necessary to convert the electron poor anthraquinone into an electron-rich system. This could be achieved by the known Marschalk reaction[53,115] which will be discussed in a later chapter in detail. Unfortunatly, no cyclisation was observed. The reaction with the aldehyde **150a+b** under Marschalk condition led to unreacted starting material, isolated lactol **152** and complex mixture of undefined products. We assumed that the subtrate **150a+b** did not react in a intramolecular ring closure due to the carbonyl group at C-13 which reduces or inhibits the reactivity of the aldehyde.

5.4 Summary of the Preliminary Work:

In spite of intensive investigations to obtai a tetracyclic derivative in an early stage of the synthesis, the results obtained were unsatisfactory and are summarized in scheme 46.

On the one hand, despite the constantly high diastereoselectivities, alkylation of **88** with **97a** led to poor yield (46%) even after optimisation of the reaction's conditions. It appeared to us that the dienolate was not nucleophilic enough to afford acceptable yield.

On the other hand, cyclisation to the ring A gave no promising results. Several ring closures were observed for either the tetramethoxy antrhacene **117a** or **139**. Regardless of the reaction conditions we used, we only obtained a complex mixture of products that were difficult to separate by usual purification methods. In addition to these discouraging results, anthraquinone derivatives such as **144**, **145**, **148→149a+b** seemed to be resistant to ring closure under several conditions mentioned above. Even the Marschalk reaction, which is one of the most effective reaction in anthraquinone chemistry to introduce an alkyl side chain failed to give a tetracyclic derivative. One plausible reason of this failure is the presence of the carboxyl group, protected as acetal, at C-13 which underwent cleavage under Marshalk reaction conditions and led to a complex mixture of products including the stable lactol **152**.

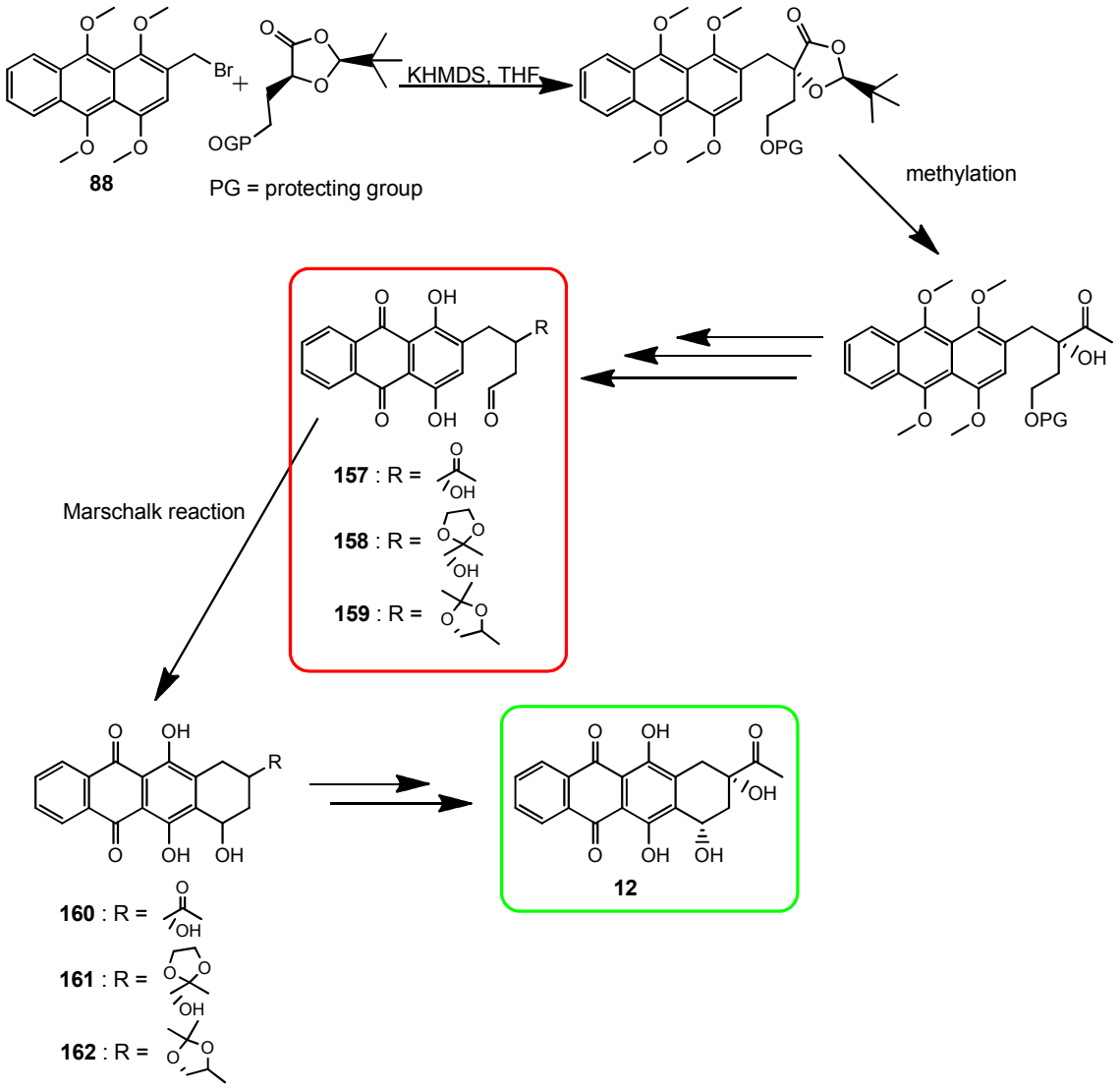


Reagents and conditions : (a) KHMDS, THF, -70°C, 46%, >99% de; (b) TFAA, cat. TFA, RT, <30%; (c) BH_3.THF, THF, 2°C to RT, 50%; (d) DMSO, oxalylchlorid, DCM, Et_3N, -70°C, 85%; (e) CAN, CH_3CN / H_2O, , 2°C to RT, 74% (**144**), 93% (**145**); (f) TFAA, TFA DCM, -70°C, 9%; (g) 1.5 eq. BCl_3, DCM, -45°C, 82% of **148a+b**, 80% of **149a+b** or 4.5 eq. BCl_3, DCM, -45°C, 95% of **150a+b**, 90% of **151a+b**.

Scheme 46

5.5 New Synthetic Approaches

Due to the modest results described above, we decided to review our synthetic sequence. The first decision considered was to convert the malic acid derivative **97a** into a higher nucleophilic precursor (Scheme 47). With this goal in mind, the carboxylic function should be modified to a corresponding analogue suitable to afford a simple enolate. Thus, the acid derivative could be reduced to the corresponding alcohol which would be protected with an adequate protecting group.

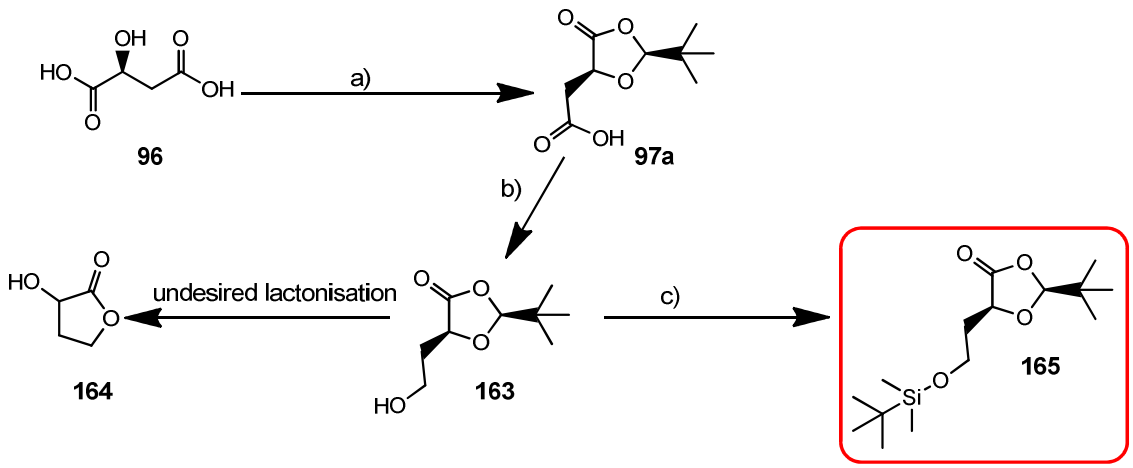


Scheme 47

Considering the poor yield of the ring closure under the investigated acid-catalysed cyclisation conditions, we focussed our attention to the Marschalk reaction which could be attempted at a late stage. As mentioned previously, the acetal group disturbed the performance of this reaction. Therefore, it should be converted by methylation to a ketone derivative introducing the methyl group needed for the target molecule. After further simple transformations, several aldehyde substrates suitable to react under Marschalk reaction should be obtained such as **157** which could lead to a competitive ring closure. Aldehydes **158** and **159** in which the carbonyl group is protected as ketal or acetal analogue (outline in red) should be also appropriate for the ring closure reaction. The consecutive cyclisation and recovery of the ketone group if needed followed by a possible additional epimeristion step of the benzylic alcohol at C-7 should afford the aglycone of Idarubicin (outline in green).

5.5.1 Modification of the Malic Acid Derivatives

Starting from the L-malic acid as previously reported, the acid substrate **97a** was reduced by treatment with BH_3.THF complex in THF to the corresponding alcohol **163** which was protected as the silyl derivative **165** with pyridine and TBDMSCl in DCM in 87% overall yield from **97a** (Scheme 48).



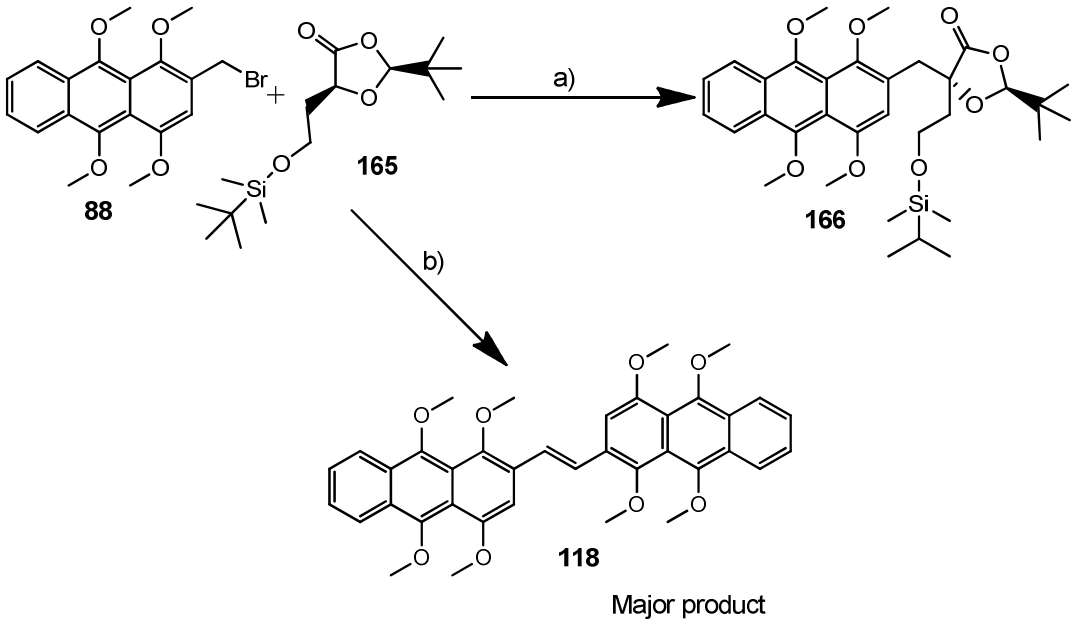
Reagents and conditions : (a) pTsOH, pivalaldehyde, pentane, 86 %, >97% *de*; (b) BH_3.THF, THF, 2°C to RT; (c) TBDMSCl, py., DCM, RT, 87% overall yield from **97a**.

Scheme 48

In order to avoid the undesired lactonisation of **163** into the corresponding lactone **164** the reaction must be performed carefully. Such problems were already encountered with analaguous molecules **127** and **137** but in the case of the derivative **97a** avoiding this side reaction was more tedious. Thus temperature of the reaction, addition of reagent and purification had to be controlled cautiously. It was first notice that the reaction is very exothermic and led almost quantitatively to the undesired lactone when the reagent was added to fast even if the reaction mixture was cooled to 0 °C. As a consequence the reagent had to be added very slowly and the temperature maintained below 10 °C until complete addition. Afterwards, the temperature was raised to room temperature without promoting the lactonisation. After unproblematic work up the product **163** was used without purification (almost pure according to the NMR analysis) since a column chromatography on silica gel converted the desired alcohol **163** to the corresponding lactone **164**.

5.5.2 Alkylation with the Silyl Derivatives 165

With the compound **165** in hand, the alkylation was investigated with the bromo derivative **88** (Scheme 49). The enolate of **165** was formed, as mentioned in earlier chapter, by inverse addition of the silyl derivative to the precooled base in THF (-76 °C). The first attempt was carried out with KHMDS as base, the temperature was maintained at -76 °C during the procedure and the reaction time was limited to 1 hr as no more evolution was detected by tlc monitoring. Thus the desired compound **166** was obtained after purification in 89 % yield with excellent diastereoselctivity (>99% de). The other isomere could not be detected either on NMR analysis of crude product or on tlc. This result confirmed the hypothesis proposed earlier that the acid derivative **97a** was not nucleophilic enough to react efficiently with the bromo derivative **88**.

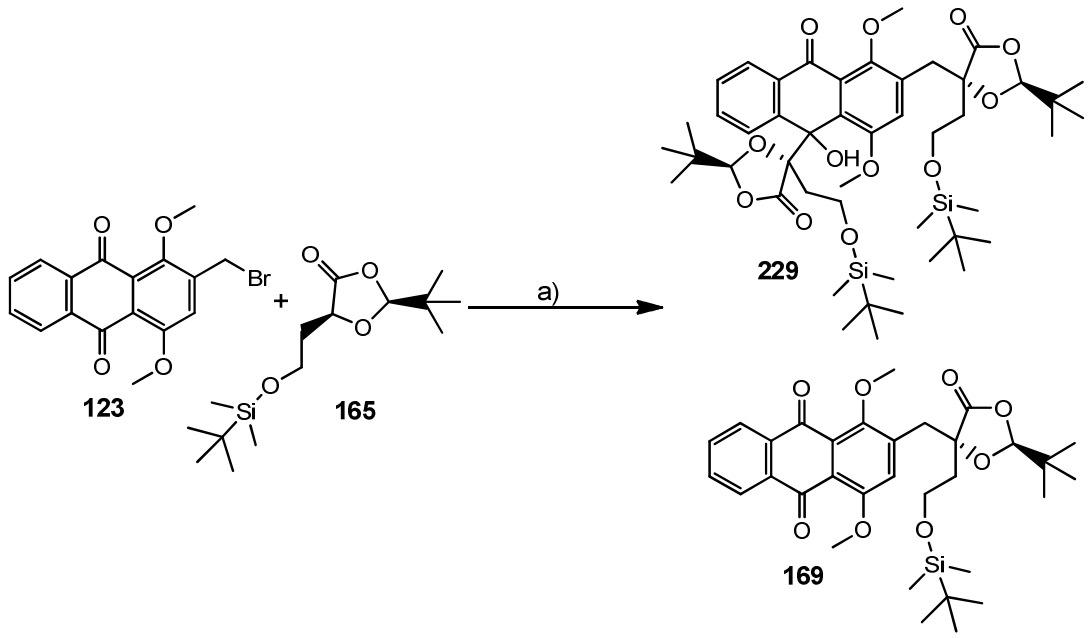


Reagents and conditions : (a) KHMDS, THF, -76 °C, 89%, >99% de; (b) LDA, THF, -76 °C, 75%.

Scheme 49

Other bases such as LDA (prepared in situ with n-BuLi and diisopropylamine) or LiHMDS gave no improvement. In the case of LDA, under the same conditions as for KHMDS, the dimerisation product **118** of the bromo derivative **88** was obtained as main product with only traces of the desired alkylated compound **166**.

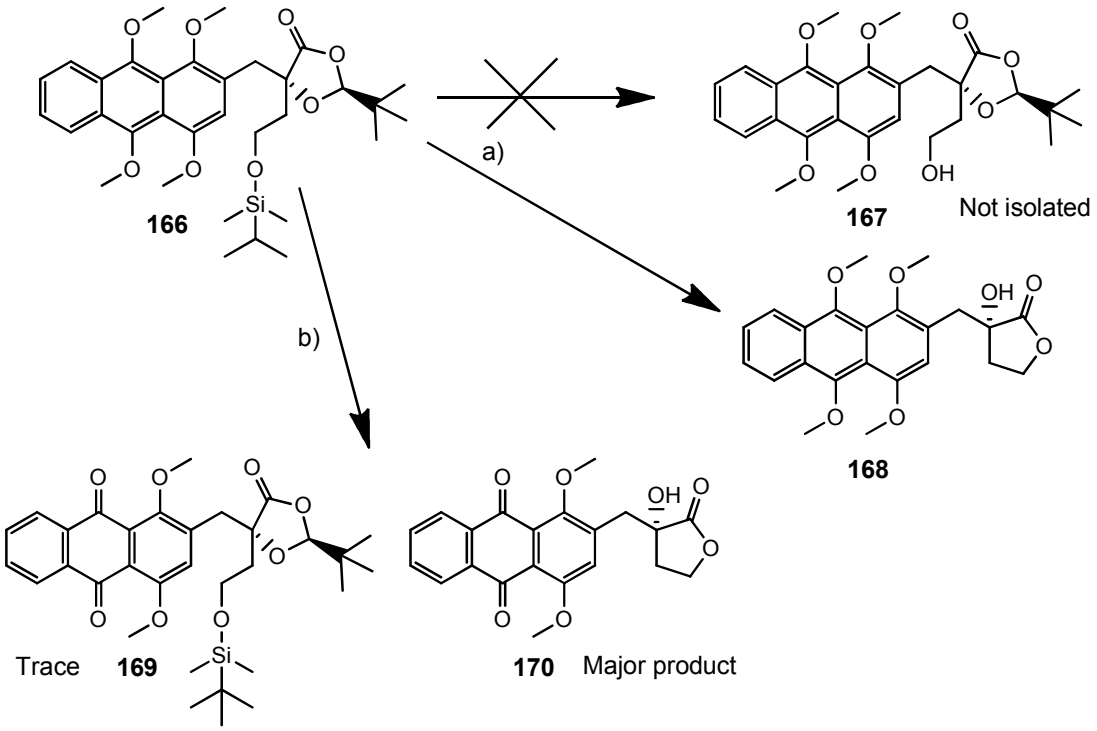
Condensation of **123** and **165** was investigated under the alkylation conditions described above to give the expected alkylated product **169** in poor yield (<30%), recovery of starting material (25%) and the di-alkylated derivative **229** in 52% yield. This result confirmed our choice to work with the reduced form of **123** which avoided undesired side product such as **229**.



Reagents and conditions : (a) KHMDS, THF, -76 °C, 52% of **229**, <10% of **169**.

Scheme 50

The cleavage of the silyl protecting group of **166** with TBAF should lead to the corresponding alcohol **167**. Unfortunatly, lactonisation occured spontaneously and no desired alcohol could be isolated (Scheme 51). The oxidative demethylation of the anthracene derivative to the more stable anthraquinone analogue was also investigated by treatment of **166** with CAN in a mixture of water and acetonitrile. This reaction sequence led to a mixture of products containing some traces of the desired anthraquinone derivative **169** but again the lactone **170** as main product from the subsequent cleavage of the silyl group. As a consequence, introduction of the methyl group on position C-13 appeared to be the logical next step.

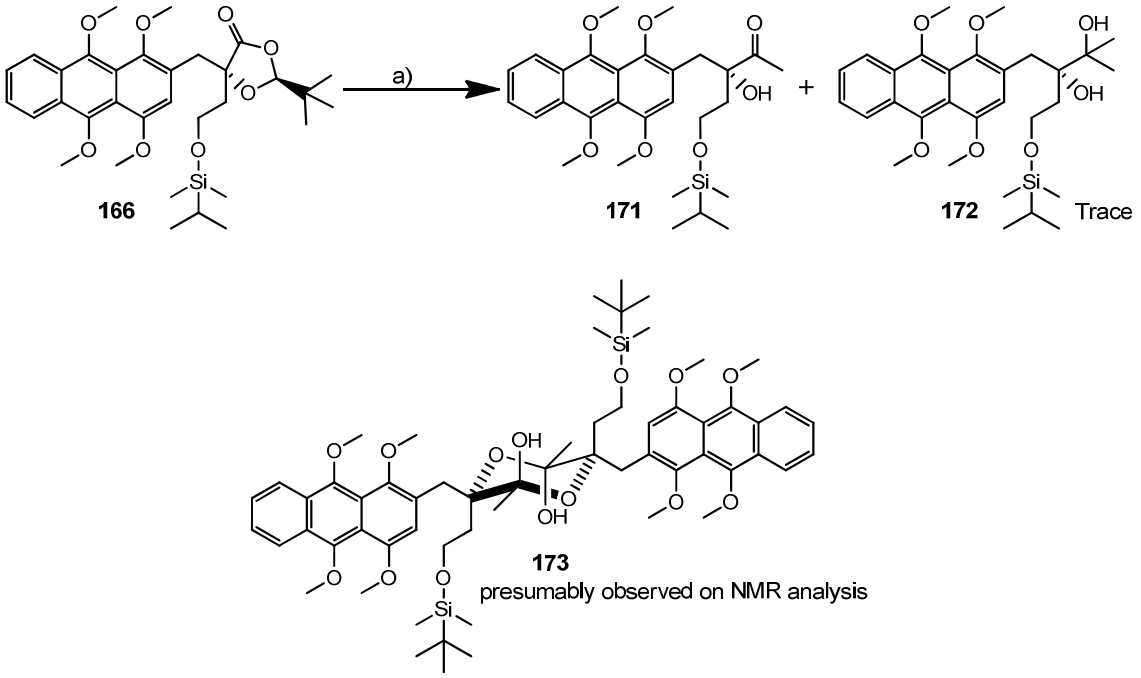


Reagents and conditions : (a) TBAF, THF, RT, 43%; (b) CAN, CH_3CN / H_2O, 2°C to RT, 81%.

Scheme 51

5.5.3 Introduction of the Methyl Group on C-13

Methylation of the Seebach lactone was published by several groups. A two steps sequence was reported by Krohn (Liebigs annal Chem. 515-520, 1987) in which the lactone was first treated with the dimethylsulfoxide sodium salt to give the corresponding sulfoxide intermediate which was reduced with aluminium amalgam to the desired ketone derivative. More recently, treatment of the lactone with methyl lithium in THF was reported[116-117] to afford the desired compound in good yield (77%).



Reagents and conditions : (a) MeLi, THF, -76 °C, 99%.

Scheme 52

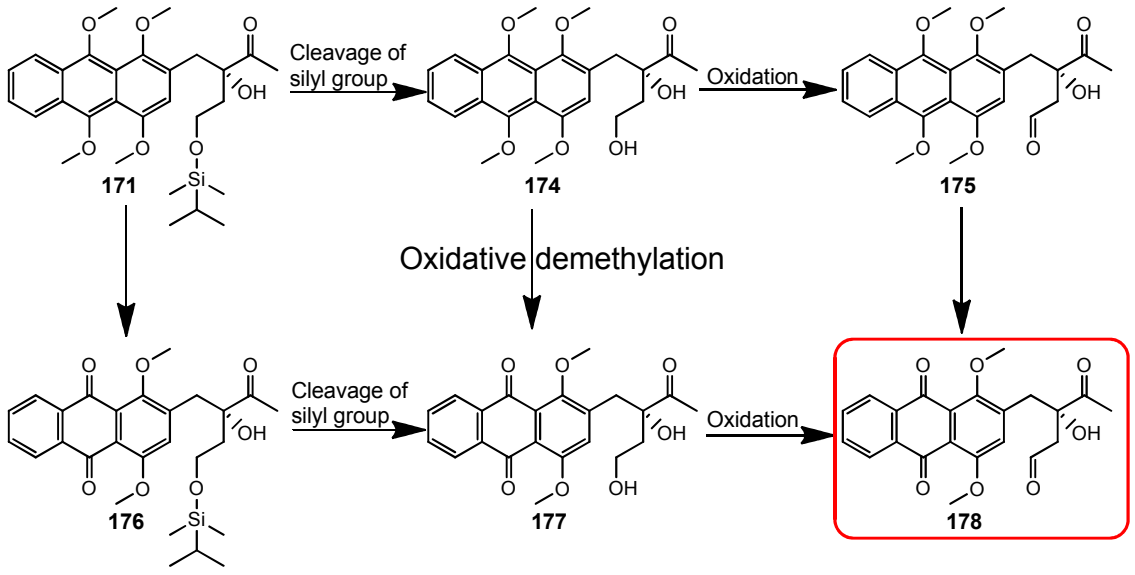
Methylation of **166** was investigated by treatment with methyl lithium (Scheme 52). A solution of **166** in THF cooled to -76 °C under argon atmosphere was first treated with 1.2 equivalent of MeLi. After 1h30 stirring, starting material was not completly consummed and no evolution was detected by tlc monitoring. Thus another 1.2 equivalent of reagent was added and the reaction was completed after 30 min. In further experiments, the reaction was carried out directly with 2.2 equivalent of MeLi to give the desired product **170** in almost quantitative yield (99%) with some trace of the compound **172**.

Even if excellent yields were achieved, we encountered some problems to identified the product by NMR. Actually, NMR analysis of the pure product did not point out a single product but two different substrates. The desired ketone structure was ascertained by its typical singulet by 2.33 ppm, which corresponds to the methyl group of the ketone and by detailed study of the 2D NMR. The other product was more tedious to identify. We postulate that it could be the double hemiacetal **173** (scheme 52) resulting from the self condensation of **171**. Indeed, singulet at arround 1 ppm, corresponding to the methyl group, is in accordance with this hypothesis.

5.6 Experiments Towards the Synthesis of Intramolecular Marschalk Reaction Precursors

5.6.1 Attempt to Reach 157

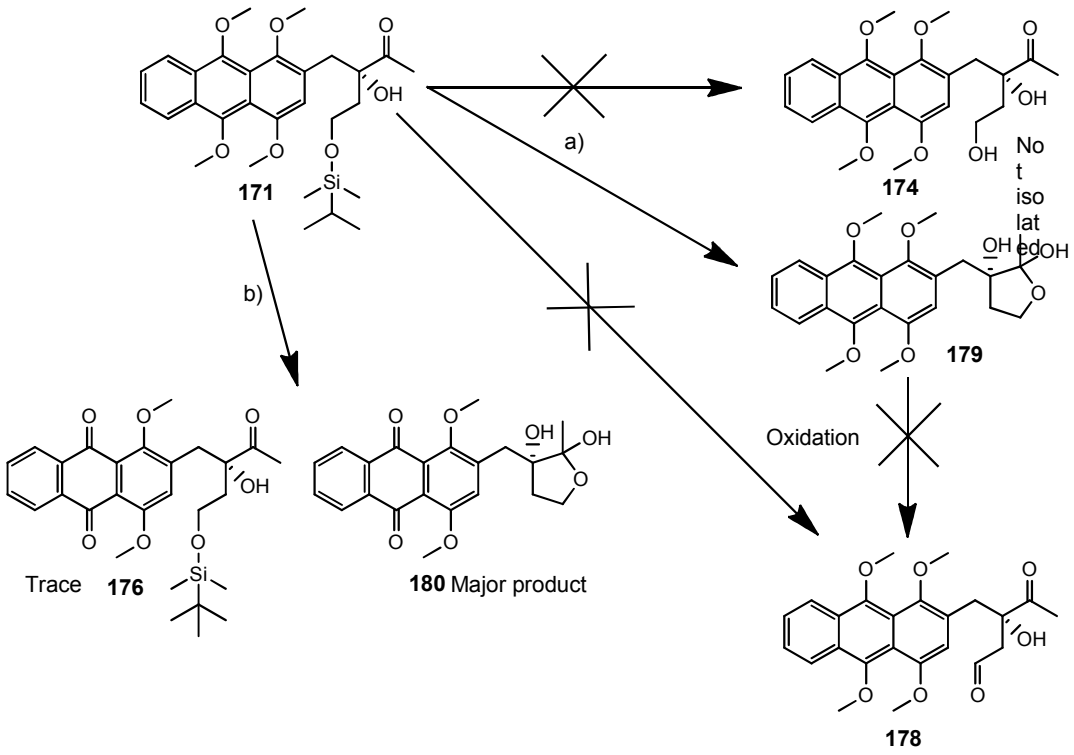
The first candidate to a cyclisation under Marschak conditions was the aldehyde **157**. Therefore, we first planned the cleavage of the silyl group in compound 171 under standard conditions[118] (TBAF in THF), followed by subsequent Swern oxidation to the aldehyde **175** and oxidative demethylation to the desired substrate **178** which could be converted to the dihydroxy-anthraquinone **157** by cleavage of the methoxy group. Alternatively, the oxidative demethylation step could also be carried out at every stage depending on the yield of each reaction (Scheme 53).



Scheme 53

Unfortunatly we failed to obtain the desired substrate **175** at all the projected ways (Scheme 54). Indeed, these synthetic approaches were dismissed at early step. Even if the silyl group was cleaved almost quantitatively, lactolisation occured spontaneously during the reaction to give the lactol **179**. Attempts to oxidise the lactol **179** to the aldehyde analogue **178** were not successfull. Chromium reagents[119] led to an oxidative demethylation of **179** to **180** and no reaction to the wanted aldehyde **178** were detected with other oxidation reagents such as Dess-Martin periodinane or

Swern oxidation conditions. In the same manner, oxidation of the primary silyl ether was also investigated. Previous work[120-121] reported deprotective oxidation of primary silyl ether under Swern conditions or by treatment with quinolinium fluorochromate. However, the substrate **171** was resistant under Swern conditions and gave the anthraquinone derivative **176** in poor yield by treatment with the chromate reagent.



Reagents and conditions : (a) TBAF, THF, RT, 80%; (b) CAN, CH_3CN / H_2O, 2°C to RT, 54%.

Scheme 54

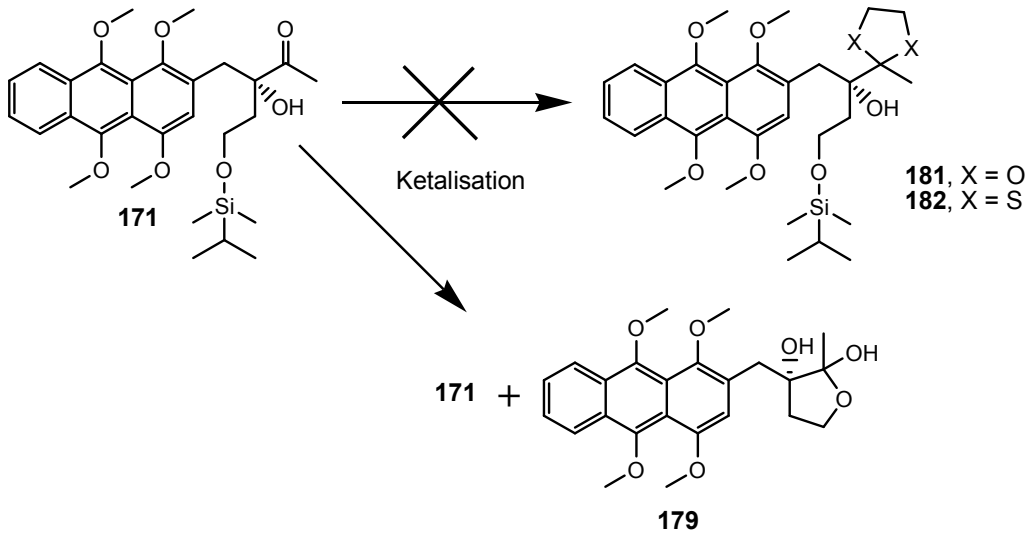
Alternatively, the compound **171** was subjected to an oxidative demethylation by treatment with CAN in H_2O/CH_3CN. As described earlier, the silyl group was also partially cleaved to give the lactol **180**. Using EtOAc instead of CH_3CN limited the deprotection of the silyl group to give **176** in moderate yield. Optimisations to reach the lactol **180** in good yields were also unsuccessful. However, cleavage of the silyl group with TBAF gave the lactol **180** which was resistant to oxidation as its analogue **179**.

In spite of these frustrating results discussed above, this set of experiments led to the following observation: the carbonyl group had to be modified, by protection as ketal

or by reduction and subsequent acetalisation, in order to avoid the formation of the unreactive lactol **179** or **180**.

5.6.2 Attempt to Reach 158

In respect to the results reported in the above chapter, we first planed the ketalisation of the carbonyl group in **171** or in **176** (Scheme 55). Various reagents and conditions were investigated. Unfortunatly, we failed to obtain the desired ketal **181** or thioketal **182**. Surpringly, we were never able to detect or isolate these compounds.

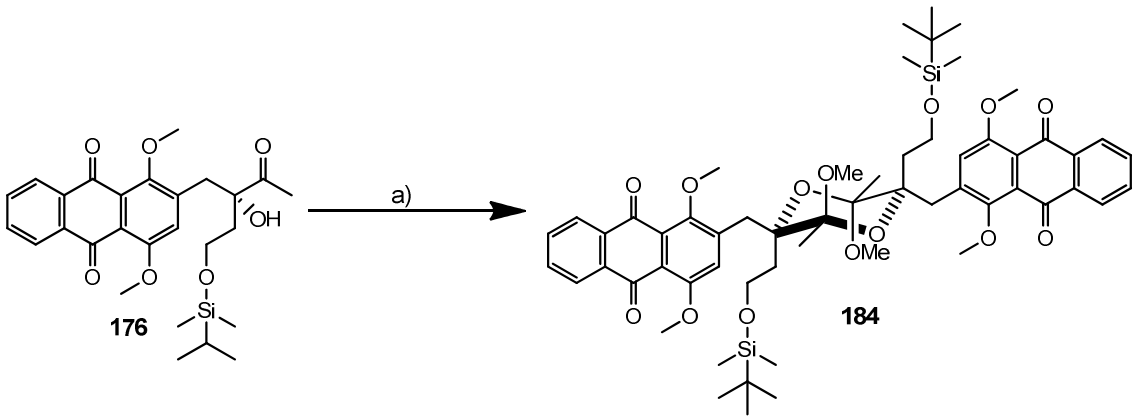


Scheme 55

Treatment of the ketone **171** under usual ketalisation conditions[122-124] gave in general no desired reaction. In fact the starting material was recovered most of the time with some lactol **179** resulting from the deprotection of the silyl group. Conversion of the carbonyl group to his thioketal analogue using $TiCl_4$ as catalyst and ethandithiol in DCM[125] also failed but gave a complex mixture of products which was not further examined.

Interestingly, the product **184** was isolated in 10% yield from the reaction of **176** with ethylene glycol, trimethyl formate and pTsOH in toluene (Scheme 56). We already met such structure during the analysis of compound **171** by NMR and isolation of the

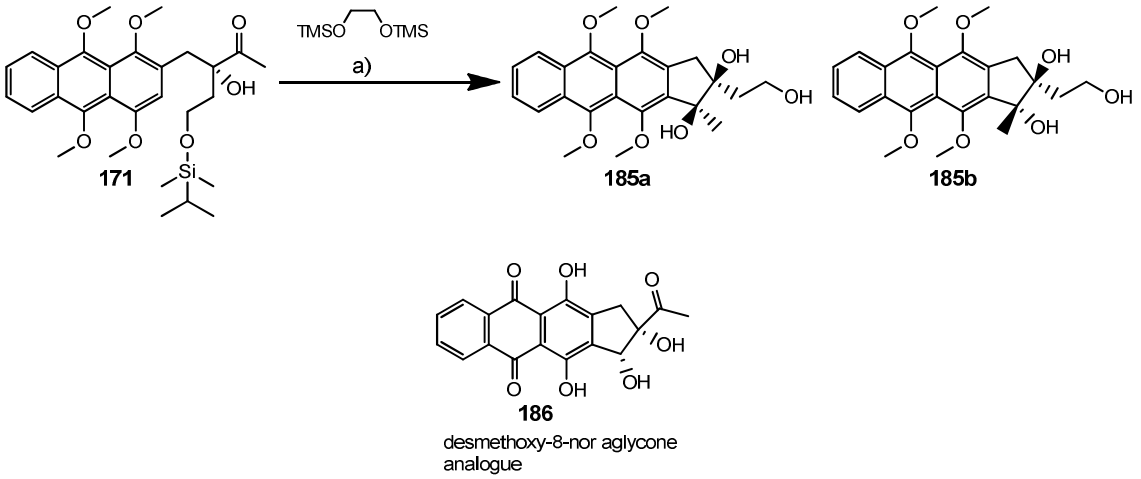
protected hemiacetal **184** confirmed our hypothesis. Under these conditions, product **176** reacted with itself to give the protected acetal **184**. Nevertheless, further attempts to improve the yield in **184** were unsuccessful. As a consequence, the use of this derivative as intermediate in the synthesis of Marschalk cyclisation precursor was not further investigated.



Reagents and conditions : (a) ethylene glycol, trimethylformate, pTsOH, toluene, RT, 10% of **184** and 27% of **180**

Scheme 56

Finally, attempts to ketalise **171** were carried out under more drastic conditions using trimethylsilyl triflate and ethylene glycol protected with trimethylsilyl protecting group[126]. Although no ketalisation was observed, this reaction led to interesting results. We observed an intramolecular cyclisation followed by cleavage of the silyl group which gave the two diastereoisomeres **185a** and **185b** in 67% yield with a diastereoisomeric excess of 40/60 respectively (Scheme 57). Configurations of both isomers were assigned by NOE NMR analysis of each isolated isomer. These results showed the possibility of an almost clear intramolecular ring closure at an early stage of the synthesis with the restriction that no elimination of the benzylic alcohol can occur.



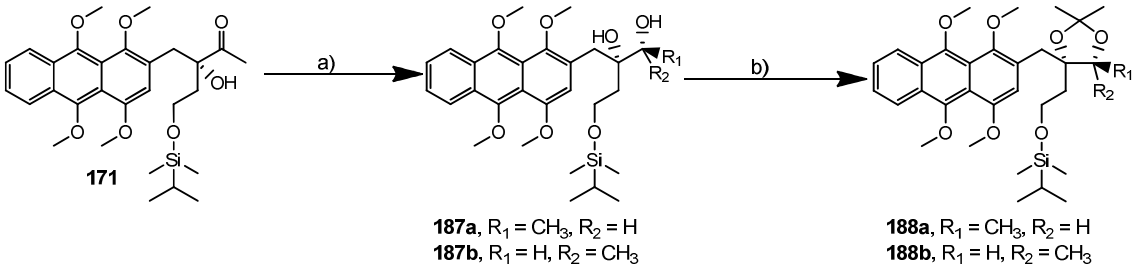
Reagents and conditions : (a) trimethylsilyl trifluoromethane sulfonate 3 mol%, DCM, -60°C to 0°C, 27% of **185a** and 40% of **185b**.

Scheme 57

Aglycones containing a five membered ring as ring A are known as for example desmethoxy-8-nor aglycone analogue. Their structures and synthesis are already reported[127-129]. In our case, additional steps such as oxidative demethylation followed by the cleavage of the methoxy groups should led to a new aglycone analogue. However, since no advantages over other anthracycline derivatives, such as doxorubicin, were observed in experimental tumor system with 8-nor aglycone such as **186**, we decided to focus on our first target molecule.

5.6.3 Attempt to Reach 159

Accepting the failure to obtain the aldehyde **157** and **158**, a synthesis of the next planned intermediate **159** was investigated. With that goal in mind, the ketone group had to be reduced to its alcohol derivative **187a+b** which would be ketalised to the product **188a+b** (Scheme 58). By reduction of the carbonyl group, a second stereogenic center should be formed but no effort to achieve diastereoselectivity is required since the alcohol will be reoxidised in a later stage.

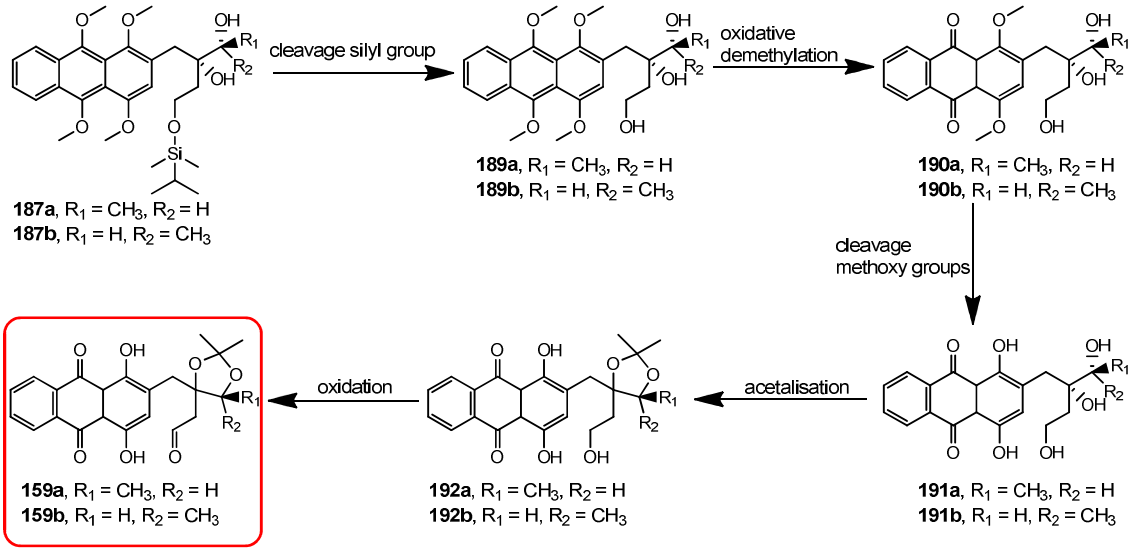


Reagents and conditions : (a) $NaBH_4$, EtOH, RT, 90% of **187a** / **187b** : 2 /1; (b) dimethoxypropane, pTsOH, acetone, RT, 83%.

Scheme 58

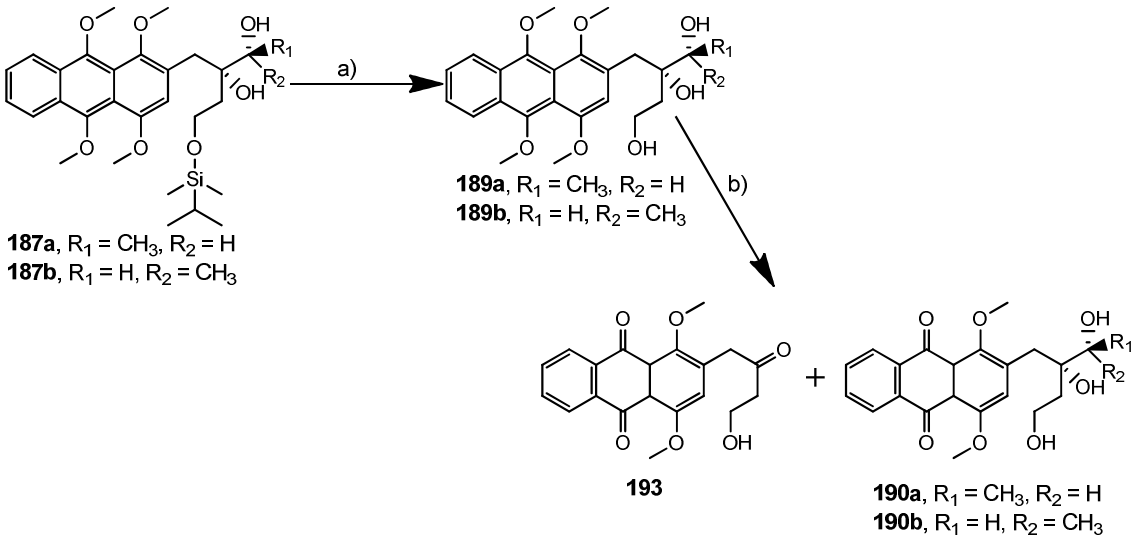
Reduction of the carbonyl group was performed by treatment of **171** with $NaBH_4$ in EtOH to the diastereoisomers **187a** and **187b** in excellent yield (90%). Separation of the two isomeres was not possible but the distribution was evaluated by NMR as we found a ratio of about 2 : 1 of **187a** / **187b**. The mixture of the two isomeres was subjected to ketalisation with dimethoxypropane and pTsOH in acetone to give the corresponding acetals **188a** and **188b** in 83 % yield. Once again, separation of the two isomeres at this stage was almost impossible and was therefore put back to a later stage of the projected synthesis.

Since the ketal protecting group should be unstable to the deprotection of the phenolic methoxy group, the first selected strategy was to perform the ketalisation step in a later stage of the synthesis. Thus, compounds **187a** and **187b** should be successively demethylated by oxidative demethylation followed by deprotection with BCl_3 to afford the tri-alcohol **191a** and **191b** (Scheme 59). Ketalisation of **191a** and **191b** followed by oxydation of the primary alcohol should complete the sequence to reach the aldehyde **159a+b**.



Scheme 59 : synthetic approach to reach **159**

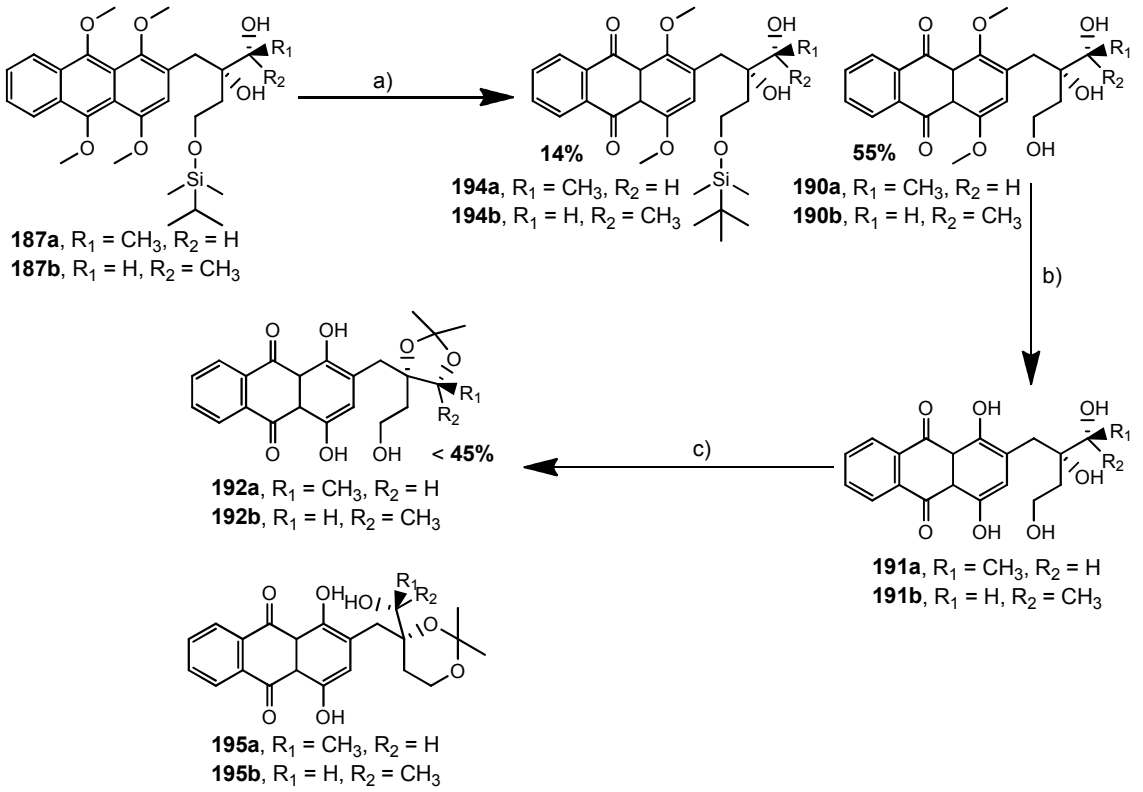
By applying the planned synthesis, compound **189a+b** was obtained in 89% yield by treatment of **187a+b** with TBAF in THF. Nevertheless, oxidative demethylation led to poor yield (27%) in the corresponding anthraquinone derivative **190a+b** polluated by **193** isolated in 15% yield resulting from the oxidative elimination of the side chain (Scheme 60).



Reagents and conditions : (a) TBAF, THF, RT, 89%; (b) CAN, CH_3CN / H_2O, 2°C to RT, 15% of **193** and 27% of **190a+b**.

Scheme 60

Alternatively, compound **187a+b** was subjected to oxidative demethylation to give the protected derivative **194a+b** with the tri-alohol **190a+b** in 14% and 55% yield respectively (Scheme 61).



Reagents and conditions : (a) CAN, CH_3CN / H_2O, 2°C to RT, 14% of **194a+b** and 55% of **190a+b**; (b) BCl3, DCM, -45°C, 54%; (c) dimethoxypropane, pTsOH, acetone, RT, <45%.

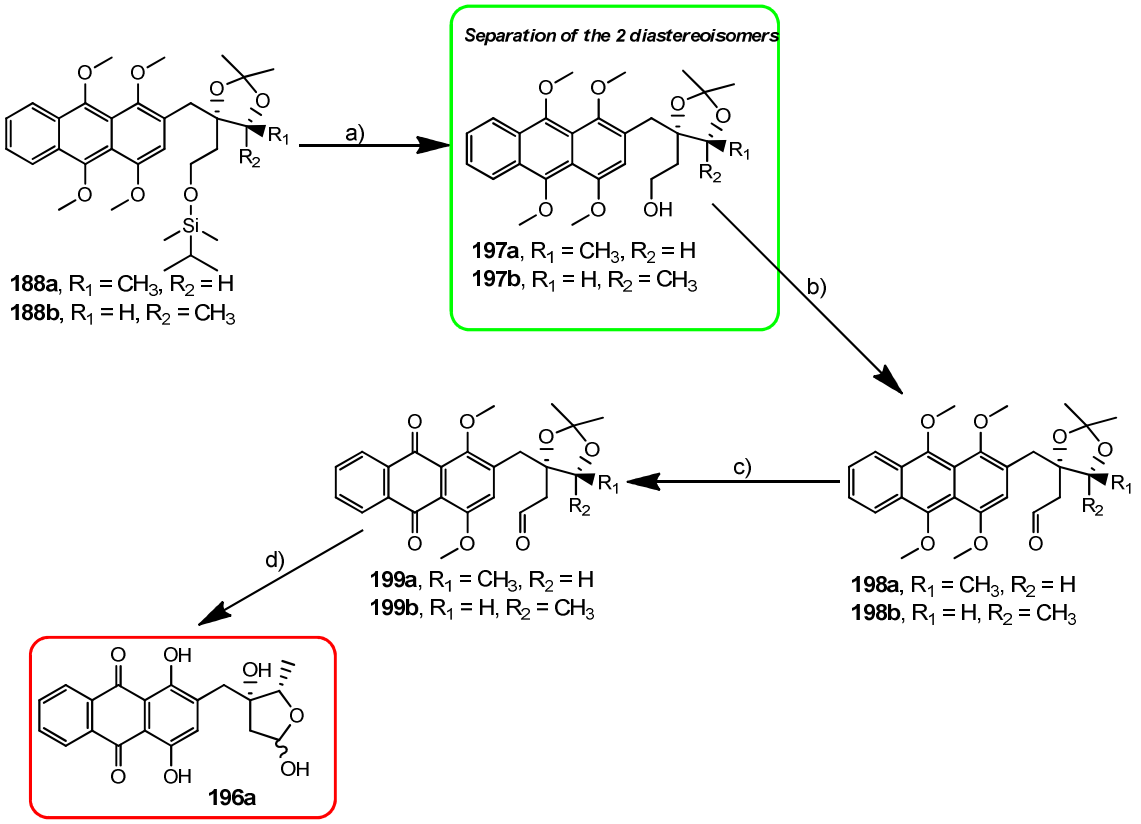
Scheme 61

Deprotection of the remaining methoxy groups with BCl_3 afforded the dihydroxy-anthraquinone **191a+b** in unsatisfactory yield (54%). Despite of the low yield of the last two steps, ketalisation of **191a+b** was still studied. Same conditions as described above were used but unsatisfactory results were obtained. On the one hand, the yield of the desired ketal **192a+b** was poor (44%). On the other hand, when the desired ketal **192a+b** was the major product, ketalisation occured also between the primary alcohol and the tertiary alcohol to give the 6 ring ketal **195a+b** as by-product which could not be separated from its analogue **192a+b**.

Due to the lack of an efficient synthesis of compound **159a+b**, alternative aproaches were taken into consideration involving synthesis of the lactol **196**.

5.7 Alternative approach: Synthesis of Lactol 196

With regard to the good yield obtained by acetalisation of **187a+b** to **188a+b**, we decided to carry on the synthesis from this subtrate. In order to reach the desired lactol **196a** (Scheme 62), the silyl group from **188a+b** should be cleaved to yield the corresponding alcohol **197a+b** which by subsequent oxydation of the primary alcohol and oxidative demethylaion would give the aldehyde **199a+b**. Simultaneous cleavage of the methoxy group and the acetal would afford the lactol **196** which should react under Marschalk reaction as well as other aldehyde analogues.

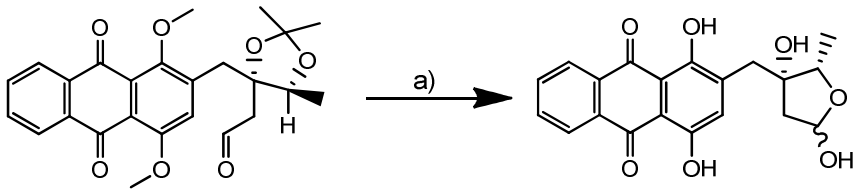


Reagents and conditions : (a) TBAF, THF, RT, 98%; (b) DMSO, oxalylchloride, Et_3N, DCM, -70°C, 96%; (c) CAN, CH_3CN / H_2O, 2°C to RT, 98% for **199a** and 96% for **199b**; (d) BCl_3, DCM, 2°C, 94% (reaction carried out only with the diastereoisomer **199a**).

Scheme 62

As expected, the few steps to the aldehyde **198a+b** and **199a+b** were straightforward. Cleavage of the silyl group with TBAF in THF afforded the alcohols **197a** and **199b** in 98% yield which were able to be separated by chromatography. The next steps were carried out separately with each diastereoisomere untill the aldehydes **199a** and **199b**. Oxidation of the primary alcohol was achieved with Swern oxidation to give **198a** and **198b** in 96% which were treated with CAN in CH_3CN/H_2O leading to **199a** and **199b** in 90 and 98% yield respectively.

5.7.1 Conversion of Aldehyde 199a to the Lactol 196a (Scheme 63)



199a **196a**

Reagents and conditions : (a) BCl_3, DCM, 2°C, 94%

Scheme 63

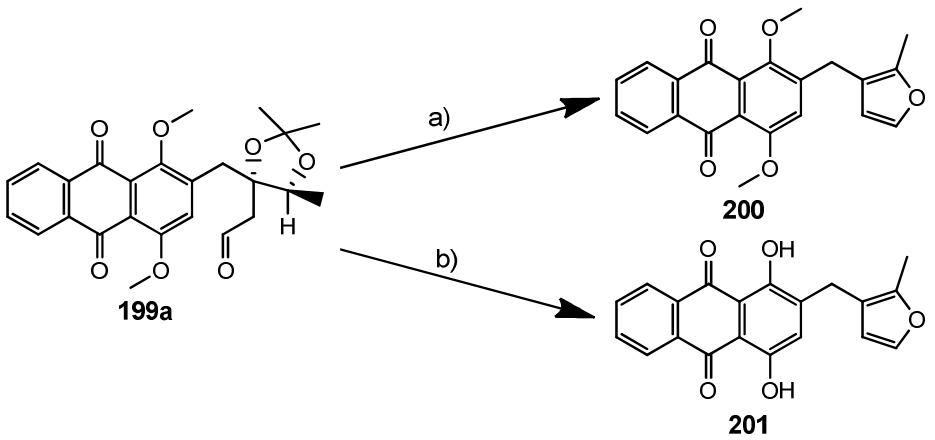
The simultaneous cleavage of both methoxy groups and the ketal was a tricky step. With regard to the results obtained in previous work BCl_3 seemed to be the adequate reagent to undergo the deprotection. The first experiment was carried out with BCl_3 in DCM at 0 °C and was worked up in an usual way (quenched with sat.$NaHCO_3$, extracted and concentrated under reduced pressure at **40 °C** (bath temperature)). Unfortunatly, only poor yield of the desired aldehyde **196a** (30%) which exists in its hemiacetal form (as shown by NMR spectra), was isolated after purification. Although the tlc monitoring of the reaction indicated a clear conversion (almost spot to spot reaction!!!!!!!), a very complex mixture of products was obtained after removal of the solvent from the worked up reaction.

Before spending time and energy to optimise this reaction which will be discussed in more detail below, various reagents (Table 4) were investigated. Unfortunately, no efficient methods were found. Indeed, either a complex mixture of products or side reactions were observed (Scheme 64 and table 4).

Table 4 : Investigation towards cleavage of both methoxy groups and ketal group

conditions	Products and yields
$AlCl_3$, DCM	Complex mixture of products
$BF_3.Et_2O$, DCM	Complex mixture of products
TMSI, DCM	Complex mixture of products
TMSCl, DCM	Complex mixture of products
p-thiocresol, nBuLi, HMPA, toluene	Complex mixture of products
Py.HCl, pyridine	**200** (78%)
$CeCl_3.7H_2O$, NaI, CH_3CN	**201** (70%)
BCl_3, DCM	**196a** (94%)

Reactions using reagents such as $AlCl_3$, TMSCl, TMSI or p-thiocresol with nBuLi and HMPA[130-136] led to complex mixtures and were discarded. The treatment with Py.HCl in pyridine under reflux afforded the furane derivative **200** (Scheme 64), resulting from the subsequent cleavage of the acetal, lactolisation and aromatisation of the lactol to furane, in 78%. It appeared that Py.HCl was not strong enough to deprotect the methoxy group. Similarly, the furane analogue **201** was obtained in 70% yield when aldehyde **199A** was heated under reflux in CH_3CN in presence of $CeCl_3.7H_2O$ and NaI. Since no reaction was observed at room temperature for each reaction, heating under reflux was neccessary but seemed to promote aromatisation of the lactol.



Reagents and conditions : (a) py.HCl, py., 195°C, 78%; (b) $CeCl_3.7H_2O$, NaI, CH_3CN, reflux, 70%.

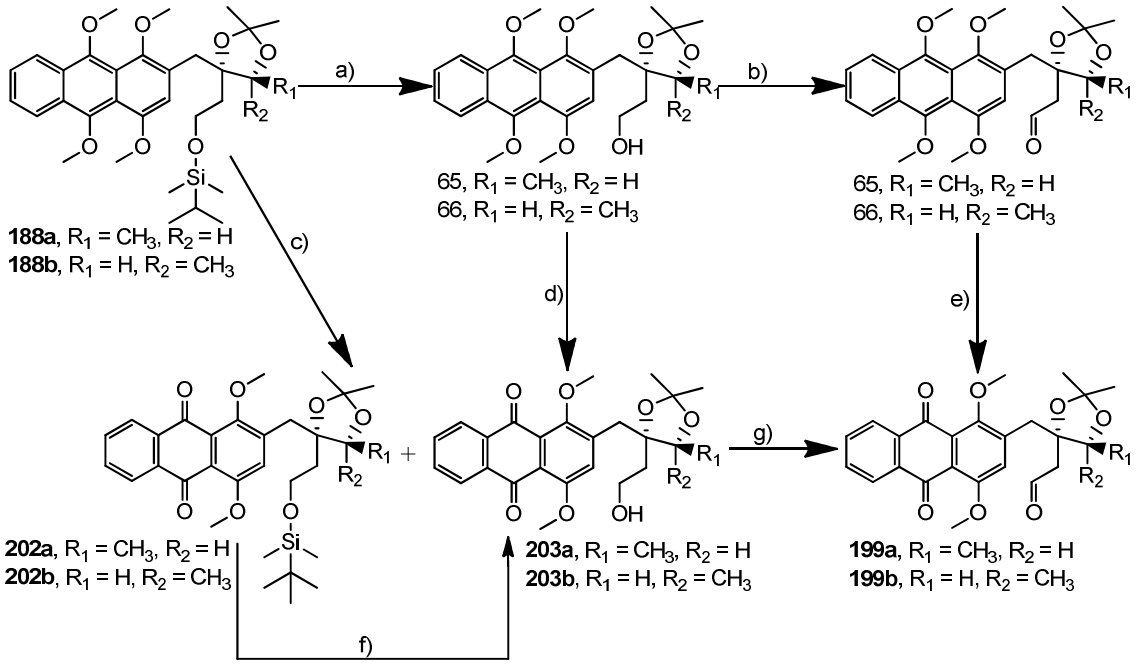
Scheme 64

Compared to the first experiment with BCl_3 which gave a clear conversion according to the tlc monitoring, the other reagents mentioned above were not appropriate. As a consequence more effort were undertaken to optimise the yield in lactol **196a** by treatment with BCl_3.

Since degradation of the product occured during the work up, we focussed our attention to optimise this step. First we attempted to quench the reaction with MeOH as it is usually doe according to literature, but in our case it led quickly to the disappearrance of the lactol in favour of a mixture of undefined products. After that, we repeated the conditions of our first experiment but with removal of the solvent at **15 °C** (bath temperature) under reduced pressure. By this modification, the yield of the reaction could be raised up to 49% after purificaton. Next, we substituted sat. $NaHCO_3$ by 1N NaOH which dissolved the lactol **196a**. The aqueous layer was washed with DCM acidified with 1N HCl at 0 °C and extracted with DCM. The organic layer was then concentrated under reduced pressure at **15 °C** to give the lactol **196a** as a red solid in 94% yield. No purification was needed according to the NMR analysis of the crude product which indicated a purity up to 98%.

5.7.2 When Should the Oxidative Demethylation Step Be Done?

Substrates with the tetramethoxy anthracene structure are, after the alkylation step, all a solid foam or oily while their anthraquinone derivatives are solid and more stable by long time storage. As a consequence, oxidative demethylation at each step mentioned above was investigated and results obtained are summarised in Scheme 65.



Reagents and conditions : (a) TBAF, THF, RT, 98%; (b) DMSO, oxalylchloride, -70°C, 96%; (c) CAN, CH_3CN / H_2O, 2°C to RT, 12% of **202** and 59% of **203**; (d) CAN, CH_3CN / H_2O, 2°C to RT, 99%; (e) CAN, CH_3CN / H_2O, 2°C to RT, 90% for **199a** and 98% for **199b**; (f) TBAF, THF, RT, 90%; (g) DMSO, oxalylchloride, -70°C, 76%.

Scheme 65

Treatment of **188a+b** with CAN in CH_3CN/H_2O led to the expected mixture of 4 products, namely two silyl derivatives **202a+b** in 12% yield and the 2 alcohols **203a+b** in 59% yield which were separable by chromatography. Cleavage of the silyl group in **202a+b** afforded the corresponding alcohol **203a+b** in excellent yield (90%). Alternatively, alcohol **197a+b** were converted to their anthraquinone derivatives **203a+b** under the same conditions in 99% yield.

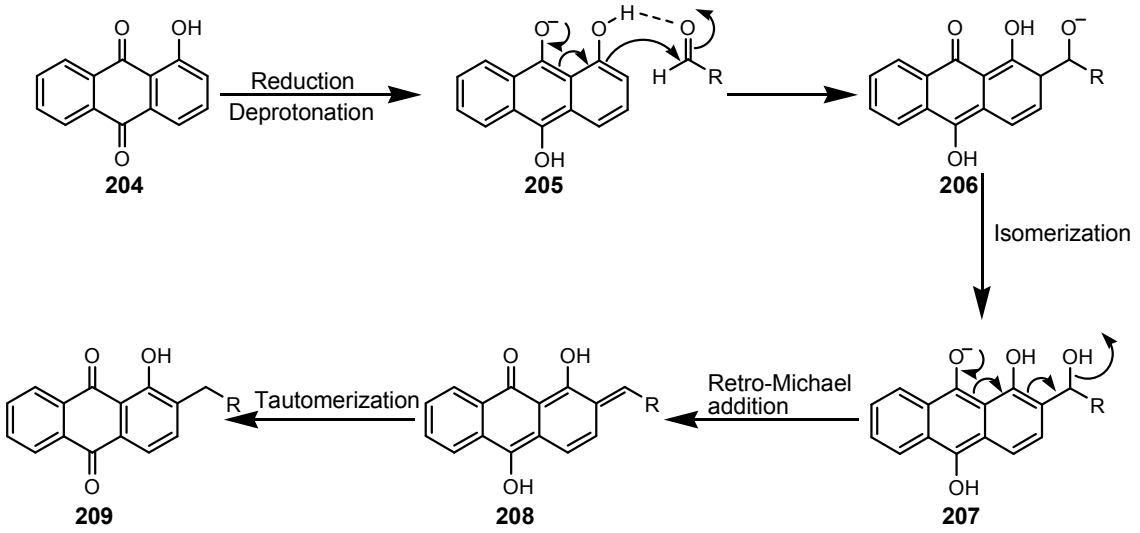
Oxidation to the corresponding adehyde was achieved under Swern conditions giving the substrate **199a+b** in 76% yield.

In summary, based on the yield obtained at each step, the oxidative demethylation step should be carried out with the aldehyde **198a+b** to give the key intermediate **199a+b** in 92% overall yield from **188a+b**. Nevertheless, earlier oxidative demethylation gave also decent yield but brought down the overall yield in **199a+b** to 74% in the best case.

5.8 Intramolecular Ring Closure: the "Marschalk Reaction"

5.8.1 Marschalk Reaction Mechanism

Two ways are known to arrive at the anthraquinone core structure, either an electrophilic or a nucleophilic addition. In this thesis, only electrophilic additions were taken into consideration. We already pointed out that Friedel-Crafts conditions failed to afford intramolecular ring closure in satisfactory yields. With regards to electrophilic additions, the Marschalk reaction is one of the most important reactions in anthracyclines syntheses involving anthraquinone derivatives either at the beginning[53,115] or at a later stage of the synthesis[92,137]. As described in Scheme 66, an alkyl group is introduced to the anthraquinone core of hydroxyanhraquinones **204** exclusively *ortho* to the hydroxyl group in the Marschalk reaction. According to the investigation by Marschalk, the most important feature that affected the reation course is the necessity to reduce the electron deficient anthraquinone to its electron rich hydroquinone analogue. Therfore, anthraquinone **204** was reduced and deprotonated to the hydroquinone **205** which adds to the aldehyde to give the intermediate **206**. As reported by Shaw and Krohn[92,138], the *ortho*-selectivity is probably due to the hydrogen bonding of the aldehyde to the phenolic group.



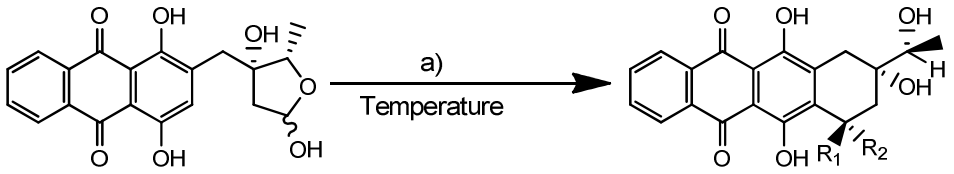
Scheme 66 : proposed pathway of the Marschalk reaction

After isomerization and subsequent retro-Michael reaction involving lose of water, *ortho*-quinone methide such as **208** are obtained which are well characterized intermediates in the metabolism of anthracyclines. Further tautomerization leads to the *ortho*-substituted anthraquinone **209**. Since the aldehyde addition proceeds faster than the retro-Michael reaction, reoxidation of intermediates such as **207**, which will allow the introduction of hydroxyl group present in anthracycline derivatives, is possible but requires most of the time low temperatures[139-140].

5.8.2 Marschalk Reaction with Lactol 196a

Lactol anthraquinone derivatives such as **196a** and their Marschalk reactions are rarely published[92,141]. As reported, three products can be obtained depending on the temperature of the reaction, the 7-deoxyanthracyclinone **211** and the two diastereoisomeres **210a** and **210b**. The intramolecular Marschalk reaction carried out at room temperature afforded only the 7-deoxy derivatives **211** while cooling the reaction to -10 °C led to a mixture of the 7-deoxy derivatives **211** and the two 7-hydroxy isomeres **210a** and **210b**.

Since the hydroxyl group at C-7 is required in the aimed aglycone, first attempts were carried out at low temperature (Scheme 67 and Table 5). Under usual Marschalk conditions (aqueous 5 eq. NaOH, 1.5 eq. $Na_2S_2O_4$ in a mixture of THF / MeOH 1/1 and then rapid reoxidation with air bubbling), the influence of the temperature was studied. It appeared that no reaction occured at temperature lower than -15 °C. From -15 °C to 0 °C, the three mentioned products were detected by tlc examination but yields of the desired two 7-hydroxy derivatives **210a** and **210b** reached, in the best case (-10 °C), 52% with the 7-deoxy analogue **211** in 19% yield as by-product. The two diastereoisomeres were not separable but their ratio was estimated by NMR analysis and found to be about 77/23 in the favour of the wrong isomer **210a**. In addition to that, the reaction was almost not repeatable affording yields of the two 7-hydroxy compounds between 25% and 52% after purification.



196a

210a, R_1 = OH, R_2 = H
210b, R_1 = H, R_2 = OH
211, R_1 = H, R_2 = H

Reagents and conditions : (a) NaOH, $Na_2S_2O_4$, THF/MeOH : 1/1, H_2O, then air oxidation.

Scheme 67

Table 5 : temperature and products obtained by the Marschalk intramolecular ring closure of **196a**.

Starting material	Temperature	Products (yield)
196a	-30°C<T°C<-15°C	No reaction
196a	-10°C	**210a/210b** (25% to 52%); **211** (19% to 35%)
196a	Room temperature	**211** (67%)

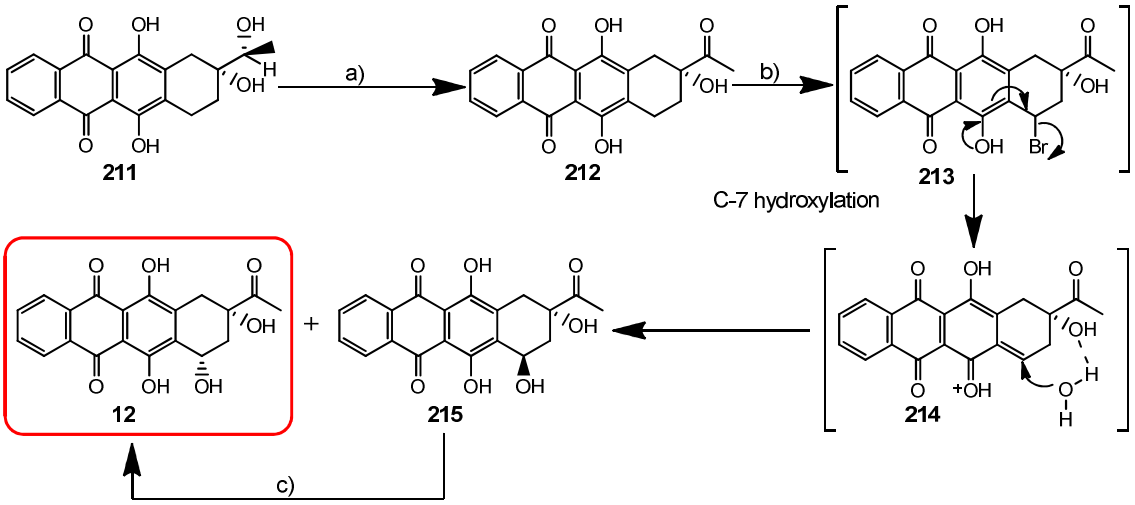
The investigation at room temperature gave exclusively the 7-deoxy derivatives **211** in 67% after trituration in toluene / EtOAc (1/1). The reaction was, in this case, reproducible and no 7-hydroxy derivatives were detected either by NMR or by tlc of the crude product.

5.9 Strategy to Reach Idarubicinone 12 from 211 and from 210a+b

5.9.1 From 211, Hydroxylation at C-7

Since ring closure at room temperature under Marschalk conditions gave satisfactory yield and good repoducibility, compound **211** was chosen to continue the synthesis of idarubicinone. Oxidation of the alcohol at C-13 followed by hydroxylation at C-7 should afford the targeted aglycone (Scheme 68). The key reaction is the hydroxylation at C-7 with the need of stereospecificity to yield the 7,9-*cis*-diol **12**. Actually, such hydroxylations have been reported several times[87,142-148]. The used sequence is bromination with NBS or Br_2 and AIBN or under irradiation in refluxing CCl_4 (in presence of water in some cases) following by subsequent solvolysis of the bromine **213**. High stereoselectivities were reported in some case while yield varied

between 35% and 81% with different substrates. The high stereoselectivity is commonly explained in the following way: the C-7 brominated product **213** readily provided the cation intermediate **214**, to which water approaches stereospecifically from the same side as the C-9 hydroxyl group assisted by hydrogen bonding.



Reagents and conditions : (a) Dess-Martin periodinane (97%), DCM, RT, 75%; (b) NBS, AIB, CCl_4, H_2O, reflux, 27% of **212**, 12% of **12** and 35% of **215**; (c) i)TFA, RT, ii) acetone, sat. $NaHCO_3$, 73%.

Scheme 68

With regard to the well documented methods, several features have to be pointed out:

- According to the work on anthracycline by Broadhurst *et al.*[146,149], conversion of di-hydroxy substrates such as **211** gave poor yield. Applying similar hydroxylation to protected substrate improved the yield up to 60%. In contrast to this observation, hydroxylation of di-hydroxy derivatives were also reported to give acceptable yield of the 7,9-*cis*-diol (up to 58%)[150].

- C-13 acetalisation should prevent the bromination at the C-10 and C-14 positions and favoured the formation of the desired *cis* product.

- Solvolysis conditions seemed to affect the ratio of the *cis*- and *trans*-diols. For example, bromination with NBS and AIBN in anhydrous CCl_4 and subsequent hydrolysis with silica gel in wet THF at 0 °C gave the 7,9-*cis*-diol

stereospecifically in good yield[143] while treatment under the same condition in refluxing CCl_4/H_2O followed by usual work up gave a 2:1 mixture of the two C-7 epimeres in favour of the desired isomer[145].

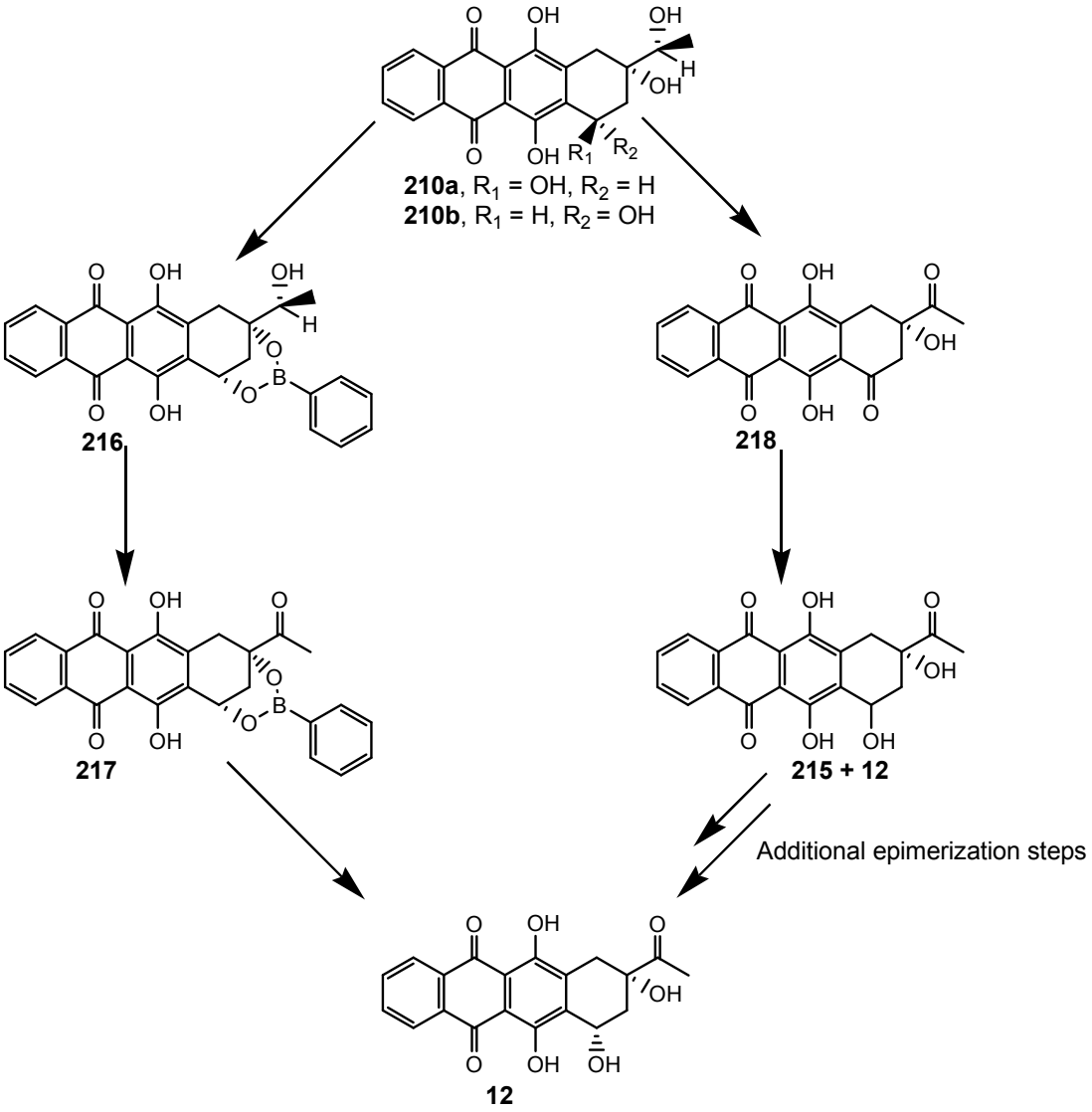
- Epimerisation of the *trans*-diol **215** is also a well known procedure. There are two possibilities. The conversion of a mixture of *cis*- and *trans*-diol to the corresponding *cis*-boronate which could easily be cleaved under mild conditions in quantitative yield is the most used method[151-153] but need two steps to lead to the desired epimer. On the other hand, it is well known that anthracyclinone having a C-7β-equatorial hydroxyl group can be epimerised directly with a strong acid such as TFA[154-156].

Product **211** was oxidised to the ketone **212** with Dess-Martin periodinane in 75% yield. Even if it was pointed out in the above paragraph that acetalisation of ketone group should provide better results, hydroxylation was carried out with the compound **212** in order to avoid the protection/deprotection steps. Thus, **212** was treated with NBS and AIBN in refluxing CCl_4/H_2O and quenched with THF/10% aq. K_2CO_3 to afford the recovery of starting material **212** (27%) and a mixture of **12** and **215** (12% and 35% yield respectively) separated by chromatography.

The 7-epiidarubicinone **215** was epimerised by dissolving in TFA and stirring for 2hr at room temperature, aqueous work up and silica gel chromatography to give the desired epimer **12** in 73%. Thus, idarubicinone was obtained in 38% from **212** which was not completely consummed (27% recovered) or in 52% from the consummed starting material.

5.9.2 From 210a+b

Since no chemoselective oxidation of **210a+b** at C-13 is possible as far as we know, two strategies were taken into consideration to reach the aglycone **12** (Scheme 69).



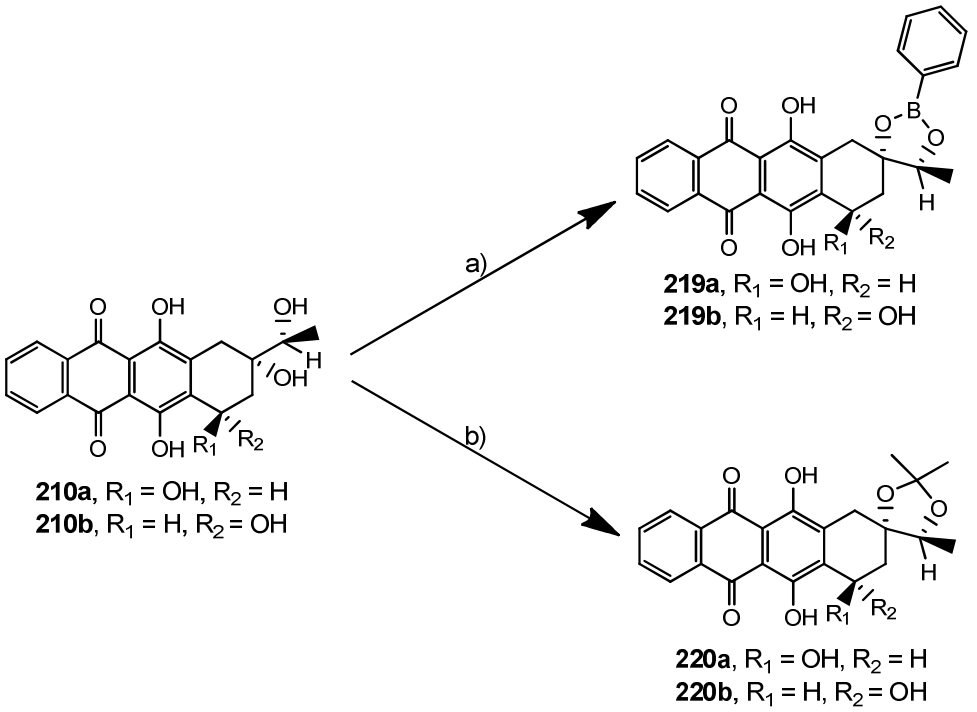
Scheme 69 : strategies to reach **12** from **210**

- Reaction of **210a+b** with phenylboronic acid in TFA/toluene should led to the simultaneous epimerisation at C-7 and formation of the cyclic *cis*-boronate **216**[152] at the same time which after subsequent oxidation at C-13 and cleavage of the boronate should afford the idarubicinone **12** in a three steps sequence.

- Alternatively, oxidation of both alcohols at C-7 and C-13 should give the diketone **218** which should be chemoselectively reduced at the C-7[157-159]. Since epimerisation at C-7 was already reported, no stereo control is needed

for the reduction. Once again, the aglycone **12** should be obtained in this way in a two or four steps (if epimerisation is necessary) synthesis.

The more attractive strategy, involving formation of the cyclic *cis*-boronate **216** at the first step, was first investigated. Nevertheless, unwanted cyclic boronate **219a+b** (Scheme 70) was formed in 58% yield by treatment of **210a+b** with phenylboronic acid in TFA/toluene and no desired **216** was detected. In the same manner, acetalisation of **210a+b** with pTsOH in 2,2-dimethoxypropane afforded selectively the two acetals **220a** and **220b** in 78% yield. Aglycone **12** should also be obtained from this acetal by protection of the alcohol at C-7, cleavage of the acetal, oxidation at C-13, deprotection at C-7 and the finally epimerisation process. However, this way was droped due to the high number of additional steps.



Reagents and conditions : (a) phenylboronic acid, TFA, toluene, 0°C to RT, 58%; (b) 2,2-dimethoxypropane, pTsOH, RT, 78%.

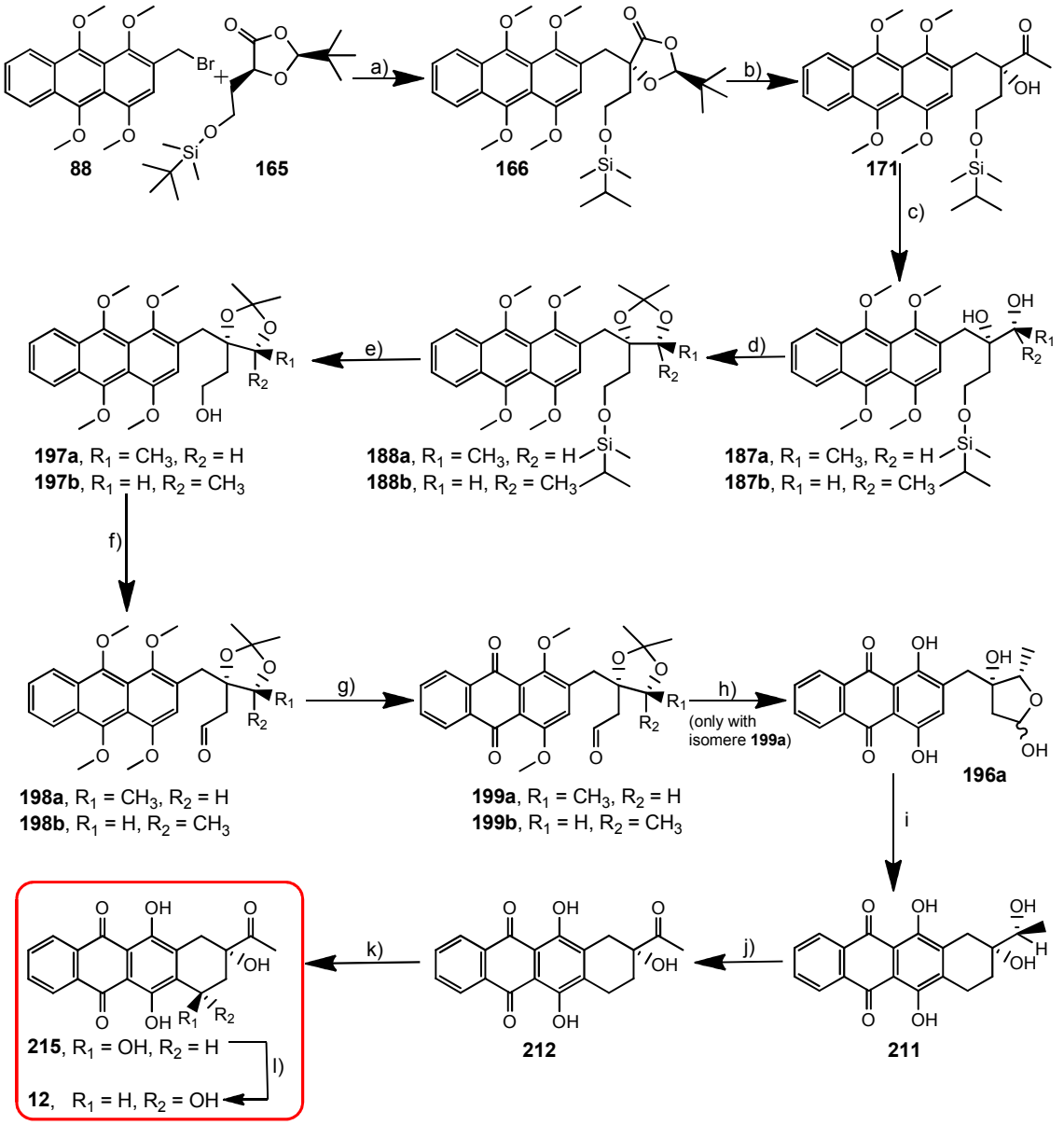
Scheme 70

Direct oxidation of the triol **210a+b** to the diketone **218** was also attempted with various reagents such as Swern oxidation, Moffat oxidation, Dess Martin periodinane or Jones reagent. In most cases, oxidation failed probably due to the very bad

solubility of **210a+b** in organic solvents. Only treatment with Jones reagent gave the diketone **218** in poor yield (45%) after purification. Because of the low yield obtained by the Marschalk reaction and the oxidation, no up-scaling was performed to investigate the reduction step.

5.10 Overview of the Total Synthesis of Idarubicinone

After several preliminary experiments mentioned in the above chapters, the best way to reach Idarubicinone **12** elaborated in our lab is described below in Scheme 71 starting from the bromo derivative **88** and the substrate **165** in a 12 steps sequence in 11% overall yield from **88**. Syntheses of **88** and **165** were described earlier.



Reagents and conditions (a) KHMDS, THF, -76 °C, 1 h, 89%, (>99% de); (b) MeLi, THF, -76 °C, 1h30, 99%; (c) $NaBH_4$, EtOH, room temp., 1 h, 90%; (d) pTsOH, 2,2-dimethoxypropane, acetone, room temp., 1 h 30, 83%; (e) TBAF, THF, room temp., 1 h, 98%; (f) DMSO, oxalylchloride, Et_3N, DCM, -70 °C, 1 h, 96%; (g) CAN, CH_3CN/H_2O, 0 °C → room temp., 30 min., 90% to 98%; (h) BCl_3, DCM, 0 °C, 40 min., 94%; (i) $Na_2S_2O_4$, NaOH, THF/MeOH/H_2O, room temp., 1 h 30, 67%; (j) Dess-Martin periodinane (97%), room temp., 5 h, 75%; (k) NBS, AIBN, CCl_4/H_2O, reflux, 4 h, **212** (27%), **12** (12%),**215** (35%); (l) 1)TFA, room temp., 2 h 2) acetone, sat. $NaHCO_3$, room temp. 30 min, 73%.

Scheme 71

5.11 Up-scaling of the Synthesis

Since the present work was achieved in order to investigate an eventual industrial process, the up-scaling of the sequence was also studied. Every step until the aldehyde **199a** and **199b** were carried out at least in a 10 g scale. Overall yield from quinizarin was slightly decreased from 23 % to 18 % over 12 steps. However, purification of every intermediate was studied and up scaling allowed to substitute some chromatography separations by recrystalisation or trituration process. The results obtained are summarised in the following Table 6. Each reaction was carried out under the same conditions either in small scale or by up scaling.

Table 6 : Up-scaling of the synthetic route developped.

Products	Small scale			Up scaling		
	Quantity (g, mmol)	yield	purification	Quantity (g, mol)	yield	purification
84	48 g, 200 mmol	95 %	Crystallisation in H_2O	300 g, 1.25 mol	85 %	Recrystalisation from toluene
85	49 g, 180 mmol	99 %	Crystallisation in H_2O	143 g, 0.53 mol	99 %	Crystallisation in H_2O
86	46 g, 160 mmol	94 %	Trituration in MTBE	424 g, 1.42 mol	85 %	Trituration in MTBE / PE 1:1
87	20 g, 60 mmol	99 %	No purification	179 g, 0.55 mol	70 %	Recrystalisation from $CHCl_3$ / PE 1 : 4
88	22 g, 67 mmol	86 %	No purification	140 g, 0.43 mol	90 %	No purification
166	6 g, 15.3 mmol	81 %	Column chromatography with Tol / EE 40 : 1	22 g, 0.06 mol	82 %	Trituration with MTBE / PE 1 : 6

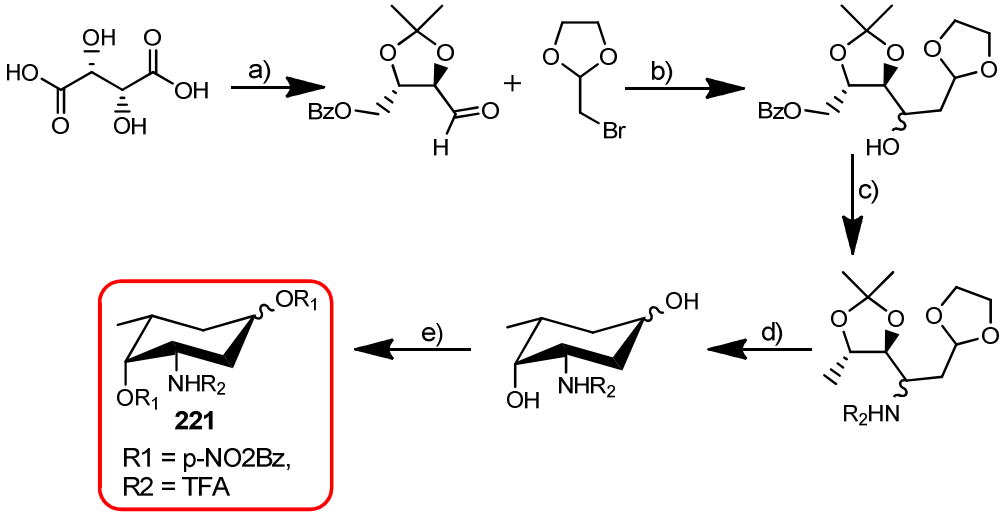
171	4 g, 6.5 mmol	97 %	Column chromatography with Tol / EE 10 : 1	62 g, 0.1 mol	99 %	Flash chromatography with Tol / EE 10 : 1
187a+b	3 g, 5.7 mmol	88 %	Flash chromatography with Tol / EE 5 : 1	56 g, 0.1 mol	89 %	No purification
188a+b	1.1 g, 2.1 mmol	75 %	Flash chromatography with Tol / EE 40 : 1	30.17 g, 0.06 mol	70 %	Flash chromatography with Tol / EE 40 : 1
197a+b	0.9 g, 1.6 mmol	97 %	Flash chromatography with Tol / EE 3 : 1	38 g, 0.07 mol	91 %	Column chromatography [a] with Tol / EE 40 : 1
198a+b	2.2 g, 4.7 mmol	96 %	No purification	16 g, 0.03 mol	99 %	No purification
199a+b	2.1 g, 4.4 mmol	63 %	Flash chromatography with Tol / EE 6 : 1	14 g, 0.03 mol	90 %	Flash chromatography with Tol / EE 4 : 1

[a] the two diastereoisomers can be separated at this step.

5.12 Glycosidation

5.12.1 Synthesis of Protected L-Daunosamine

Synthesis of the sugar moiety was performed in our lab by Dipl. Ing. Michael Sonntagbauer. The synthesis is resumed in Scheme 72 and started from tartaric acid to afford after 15 steps the protected L-daunosamine **221**. Discussion and experiments related to this synthesis are documented in the diploma thesis of Dipl. Ing. Michael Sonntagbauer and wil not be discussed in more details in this thesis.

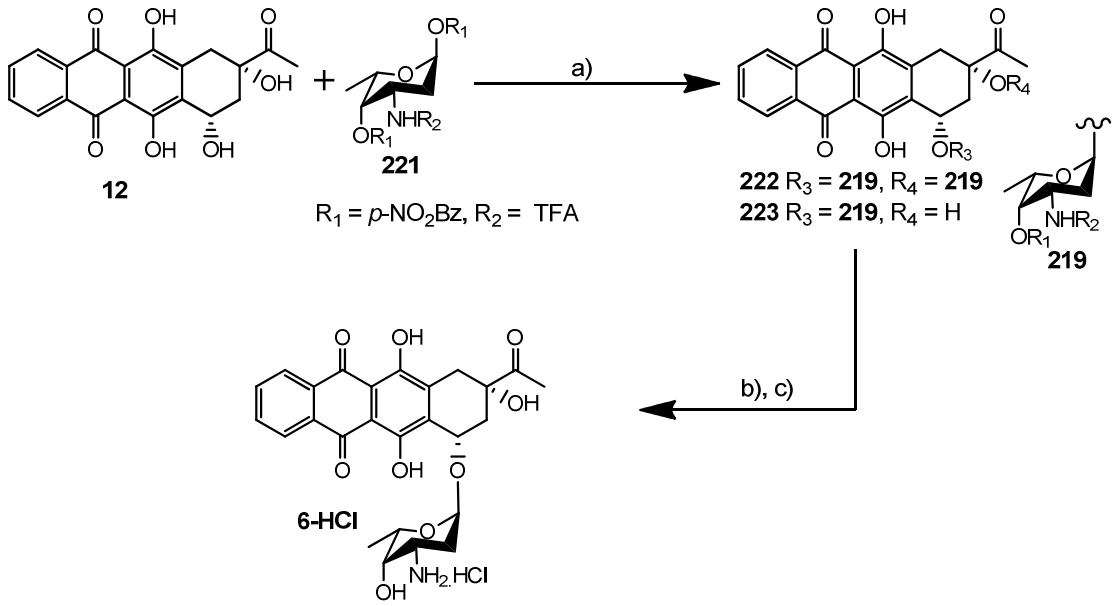


Reagents and conditions (a) i) H_2SO_4, MeOH ; ii) 2,2-dimethoxypropane, acetone ; iii) $NaBH_4$, MeOH ; iv) NaOH, BzCl ; v) oxalyl chloride, DMSO, Et_3N, DCM ; (b) Mg, THF ; (c) i) NaOMe, MeOH ; ii) p-TsCl, Et_3N, DCM ; iii) $NaBH_4$, CH_3CN ; iv) oxalyl chloride, DMSO, Et_3N, DCM ; v) $NH_2OH.HCl$, py. ; vi) $LiAlH_4$, THF ; vii) TFA, DMAP, py., DCM ; (d) TFA, THF, H_2O ; (e) p-NO_2BzCl, py.

Scheme 72

5.12.2 Glycosidation

Glycosidation of the anthracycline was the focus of numerous synthetic efforts in the 1980s and 1990s. The most common and famous methods are the Koenigs-Knorr methodology which consist on the condensation of the aglycone with a 1-halo sugar by Hg(II) salt or Ag(I) salt [64], and the method develloped by Terashima *et al.* involving the coupling of the protected sugar moiety mentioned previously with the aglycone in the presence of molecular sieve and trimethylsilyl triflate (TMSOTf)[48,160]. While Koenigs-Knorr methodologies are reported to give mixture of α- and β-glycosides, Terashima *et al.* method provides only the α-anomer in excellent yield. As a consequence, this coupling reaction was our first choice in the current study.



Reagents and conditions : (a) TMSOTf, molecular sieves, DCM/Et_2O, -40°C to -15°C, 64% of **223** and 9% of **222**; (b) 1) NaOH, DCM/MeOH, 0°C, 72%, 2) NaOH, then MeOH.HCl, RT, 65% (46% from **223**).

Scheme 73

Therefore, condensation of idarubicinone **12** with the protected sugar moiety under standard conditions described by Terashima *et al.* already afforded the desired mono glycoside (α-anomer) **223** in 64% yield (Scheme 73). Even if no β-anomer was detected the diglycoside product **222** (having an additional sugar molecule **224** coupled to position 9) was also formed in 9% yield and separation of the mono- and diglycoside products was very troublesome. After chromatography on silica gel followed by preparative tlc, the two products were isolated and characterised by NMR (in accordance with published data). The formation of the diglycoside **222** under Terashima conditions was also reported by Irvine *et al.*[152]. To overcome this issue, they found that lowering the reaction temperature and increasing the ratio of sugar to aglycone resulted in a slightly increase in the yield of the desired monoglycoside. Further experiments should be carried out after this thesis to improve the yield and the selectivty of the reaction.

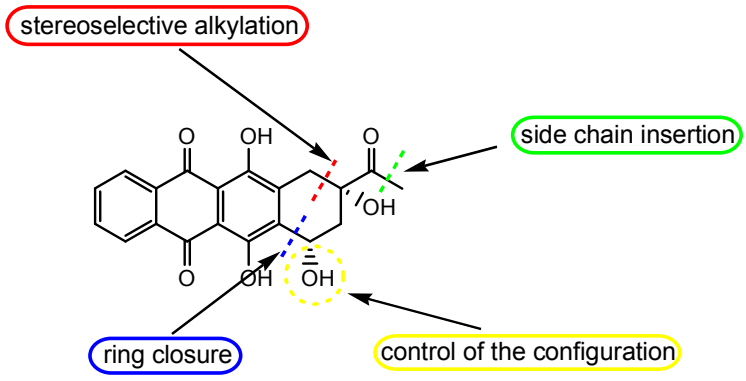
The monoglycoside **223** was then converted to idarubicin hydrochloride **6-HCl** in two steps. Selective cleavage of the pNO_2Bz protecting group was carried out by treatment with 0.1 NaOH in a mixture of DCM and MeOH. Further treatment with 0.1 NaOH followed by salt formation with hydrogen chloride afforded idarubicin hydrochloride **6-HCl** in 46% from **223**.

6 SUMMARY

Anthracyclines represent one of the most important class of antitumor drugs especially for the treatment of human solid tumors and leukaemias. Since their discovery in the 1950s, considerable efforts were accomplished towards the understanding of their mode of action and towards the synthesis of anthracyclines approved to be used in cancer therapy such as doxorubicin or idarubicin and new analogs. Investigation towards these syntheses led to different possibilities involving biosynthesis of anthracyclines produced by different strains of *Streptomyces* and synthesis of anthracyclines either in a semi-synthetic manner or a total synthetic manner.

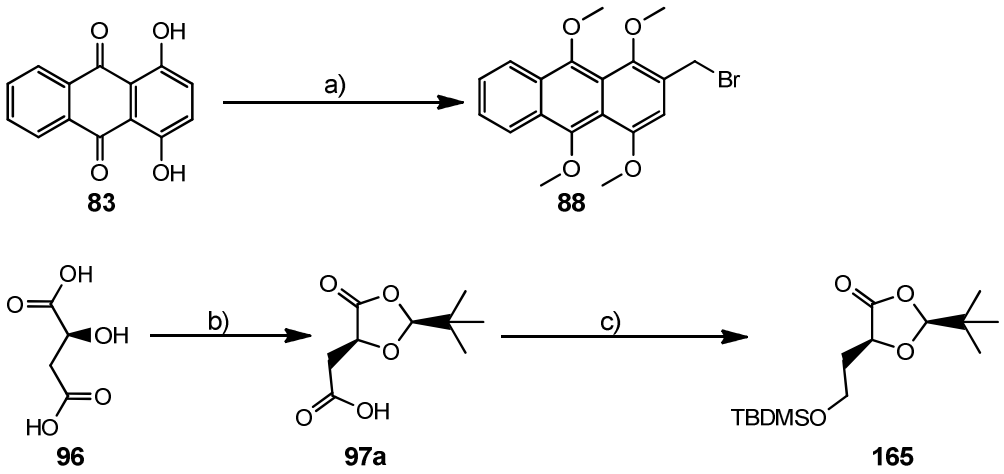
Despite of the extensive efforts accomplished in the total synthesis of anthracyclines, especially of our target idarubicin, industrial production is still done in a semi-synthetic manner. Therefore, the elaboration of new total synthesis of idarubicin suited to be translated in an industrial process is very interesting.

Our synthetic strategy involved four key reactions (Scheme 79) : quantitative and stereoselective alkylation of the starting materials, ring closure leading to the tetracyclic core structure of anthracycline, insertion of the side chain at C-13 and introduction of the correct configuration at C-7.



Scheme 74

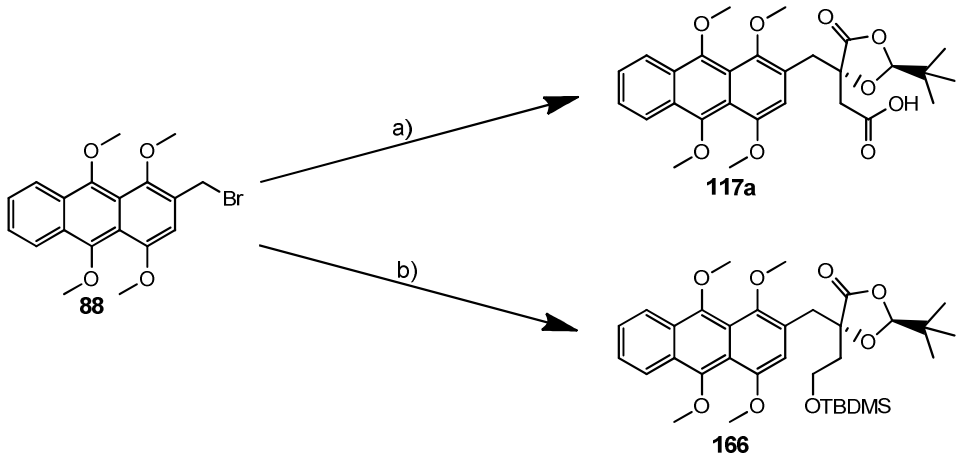
In the presented work, a new total synthesis of idarubicinone **12** / idarubicin **6** is reported starting from the anthraquinone **83** and L-malic acid **96** (Scheme 80). In this synthesis, the anthraquinone **83** was converted in 5 steps into the bromo derivative **88** in 49 % overall yield without the need of chromatography. The L-malic acid **96** was either used as its acetal form **97a** obtained in 86 % yield or as the compound **165** obtained after 3 steps in 75 % overall yield from L-malic acid **96**.



Reagents and conditions : (a) i)K_2CO_3, Me_2SO_4, acetone, reflux, 91%; ii) TBABr, $Na_2S_2O_4$, KOH, Me_2SO_4, THF/H_2O, RT, 99%; iii) $POCl_3$, DMF, 87°C, 71%; iv) $NaBH_4$, EtOH, RT, 81%; v) Aq. HBr, toluene, 2°C to RT, 94%; (b) pTsOH, pivalaldehyde, pentane, 86 % in **97a**, >97% *de*; (c) i) BH_3.THF, THF, 2°C to RT; ii) TBDMSCl, py., DCM, RT, 75% overall yield from L-malic acid.

Scheme 75

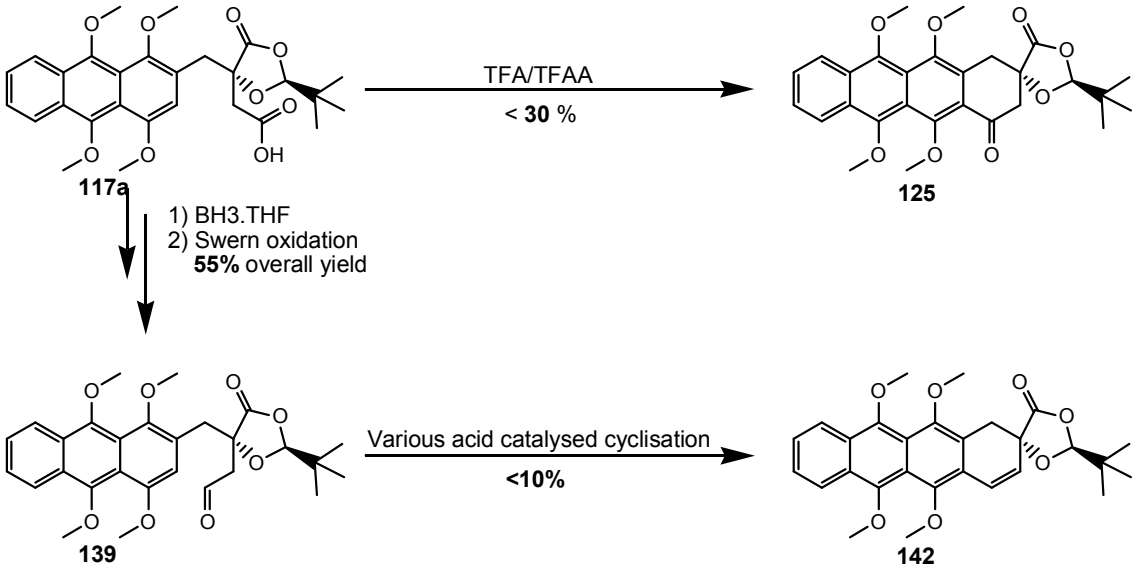
The alkylation reaction was first performed with the bromo derivative **88** and the compound **97a** leading to almost only the desired diastereoisomer **117a** (>99 % *de*) with the desired configuration at C-9. About 46 % yield was obtained after optimisation of the reaction conditions. Fortunatly, using the modified starting material **165** instead of **97a** allowed us to improve the yield in **166** up to 89 % with an excellent de (>99 %) (Scheme 81).



Reagents and conditions : (a) KHMDS, **97a**, THF, -78°C, 46%, >99% *de*; (b) KHMDS, **165**, THF, -78°C, 89%, >99% *de*.

Scheme 76

Conversion of the products of type **117a** and **166** to a tetracyclic structure was proven as the key step of this synthesis. The first approach was to perform the ring closure in an early step of the synthesis. Various ring closures conditions with different substrates such as the acid **117a** and the aldehyde **139** lead to various tetracyclic compounds shown in Scheme 82. Unfortunatly, cyclisation reaction led often to a complex mixture of several products and the yields obtained were very low (< 30 % for **125** and < 10 % for **142**).

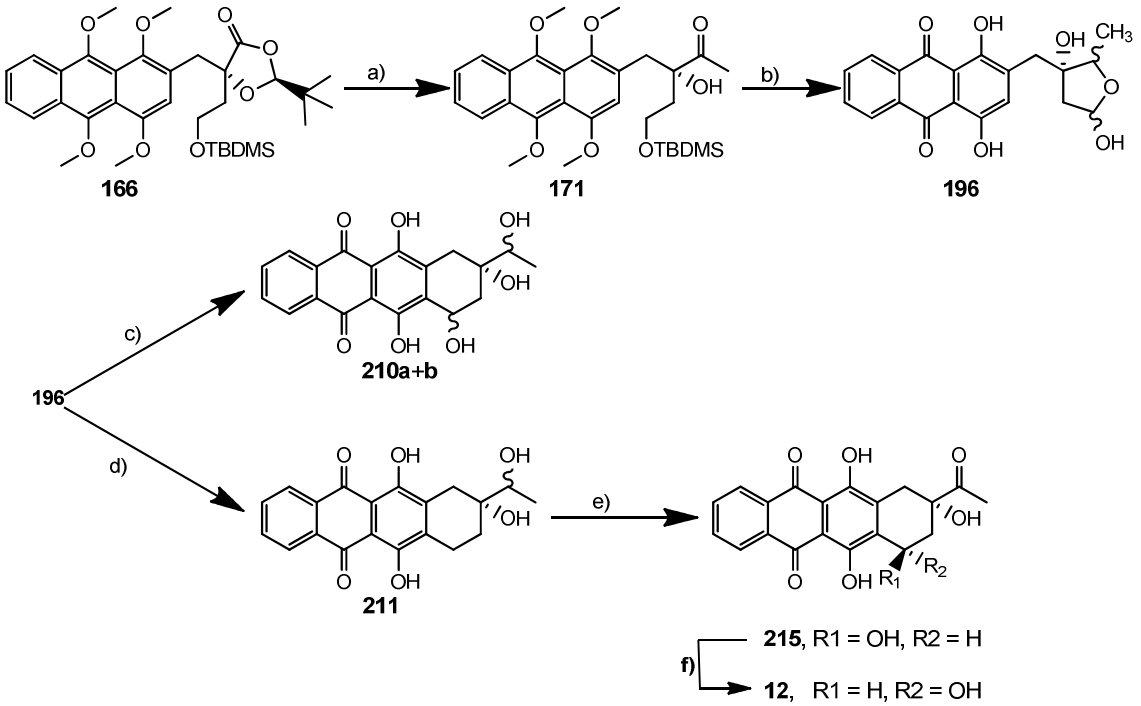


Scheme 77

Since the ring closure at an early stage of the synthesis gave unsatisfactory results our strategy was changed to explore an alternative approach that uses the ring closure at a later stage.

Therefore, the alkylated product **166** was converted to the lactol **196** in 7 steps in 62 % overall yield from **166** (Scheme 83). The methyl group at C-13 from the side chain was introduced succesfully at the first step by treatment of the lactone **166** with methyllithium in THF. Further protection / deprotection steps led to the lactol which is an appropriate substrate for a Marschalk intramolecular ring closure. By controlling the temperature of the Marschalk reaction we were able to isolate the compounds **210a** and **210b** bearing a hydroxyl group at the position C-7 in poor yield (25 % to 50 %) but these reaction conditions were difficult to be reproduced. However, intramolecular cyclization of lactol **196** under Marschalk conditions at room temperature afforded the 7-deoxyanthracyclinone **211** in 67% yield. Subsequent oxidation of the hydroxy group at the position C-13 and hydroxylation at C-7 by treatment with NBS and AIBN in aqueous CCl_4 afforded a mixture of the aglycone of idarubicin **12** and its epimer at C-7 **215** which can be epimerised by treatment with TFA.

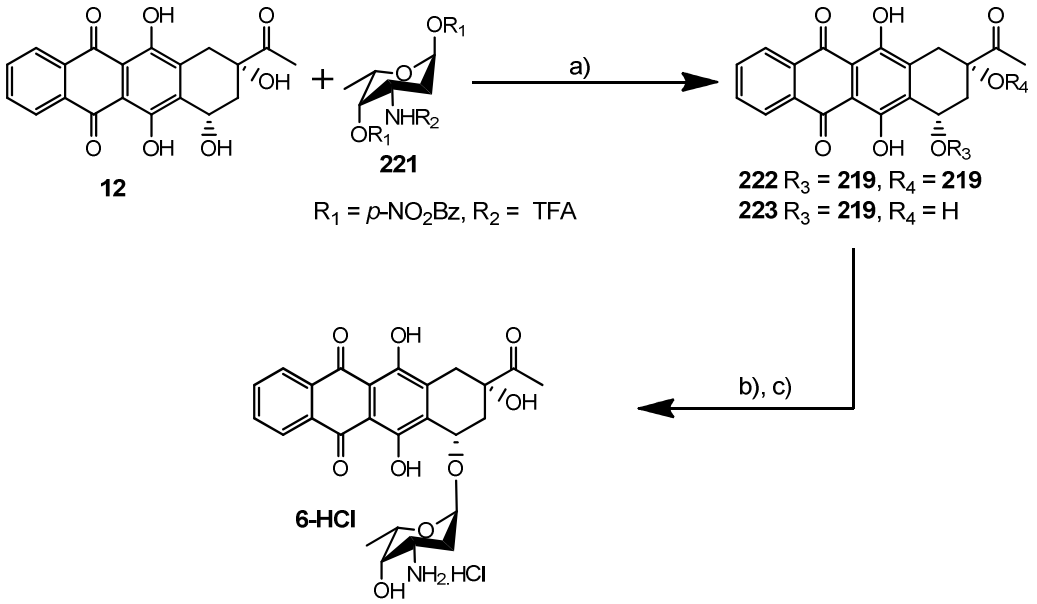
In summary the synthesis of idarubicinone **12** was achieved in 12 steps starting from the bromo derivative **88** and the modified L-malic acid **165** in 11% overall yield in a laboratory scale.



Reagents and conditions (a) MeLi, THF, -76 °C, 1h30, 99%; (b) i) $NaBH_4$, EtOH, room temp., 1 h, 90%; ii) pTsOH, 2,2-dimethoxypropane, acetone, room temp., 1 h 30, 83%; iii) TBAF, THF, room temp., 1 h, 98%; iv) DMSO, oxalylchloride, Et_3N, DCM, -70°C, 1 h, 96%; v) CAN, CH_3CN/H_2O, 0 °C → room temp., 30 min., 90% to 98%; vi) BCl_3, DCM, 0 °C, 40 min., 94%; (c) $Na_2S_2O_4$, NaOH, THF/MeOH/H_2O, -10°C., 1 h 30, 25 to 50%; (d) $Na_2S_2O_4$, NaOH, THF/MeOH/H_2O, room temp., 1 h 30, 67%; (e) i)Dess-Martin periodinane (97%), room temp., 5 h, 75%; ii) NBS, AIBN, CCl_4/H_2O, reflux, 4 h, **212** (27%), **12** (12%),**215** (35%); (f) TFA, room temp., 2 h 2) acetone, sat. $NaHCO_3$, room temp. 30 min, 73%.

Scheme 78

Glycosidation of **12** was also investigated (Scheme 79) using the methodology developed by Terashima et al. to give the desired α-glycoside **223** in 64% yield. Subsequent deprotection of the protecting groups from the sugar afforded idarubicin hydrochloride **6-HCl** in 46% yield from **223**



Reagents and conditions : (a) TMSOTf, molecular sieves, DCM/Et_2O, -40°C to -15°C, 64% of **223** and 9% of **222**; (b) 1) NaOH, DCM/MeOH, 0°C, 72%, 2) NaOH, then MeOH.HCl, RT, 65%, 46% from **223**.

Scheme 79

The presented work was done with the goal in mind to make it upscaleable to an industrial process. Thus, every step to the aldehyde **199a**+**b** was carried out on a 10 g scale at least until now. The overall yield was slightly decreased from 23% to 18%. However, purification of every intermediate was studied and up scaling allowed to substitute some chromatography steps by recrystalisation or trituration.

There is still an option to improve further the effectivess of the synthesis. For example, the compound **85** can be prepared in one step from quinizarin **83** using the reductive methylation method reported by Kraus et al.[161]. Such further optimisation can be carried out during the scale up process.

Synthesis of analogs are also planned in order to decrease the toxicity of idarubicin either by the addition of different side chains at C-13 using other lithium salt derivatives than the methyl lithium or by glycosidation with new sugar moieties.

7 EXPERIMENTAL PART

7.1 Material and Methods

7.1.1 Melting Points

The melting points were determined with the melting temperature microscope Leica Galen III (Ser. No. 1413 WT) and are uncorrected.

7.1.2 Nuclear Magnetic Resonance Spectroscopy (NMR)

The nuclear magnetic resonance spectroscopy were recorded on a Bruker Spectrospin for 200 MHz 1H-NMR and 50 MHz 13C-NMR. Complicated and demanding samples were recoreded with 500 MHz 1H-NMR and 125 MHz 13C-NMR spectra on a Varian Unity spectrometer. The chemical shifts (δ) are given in ppm, the coupling constants are in Hertz (Hz). All spectra were measured at room temperature.

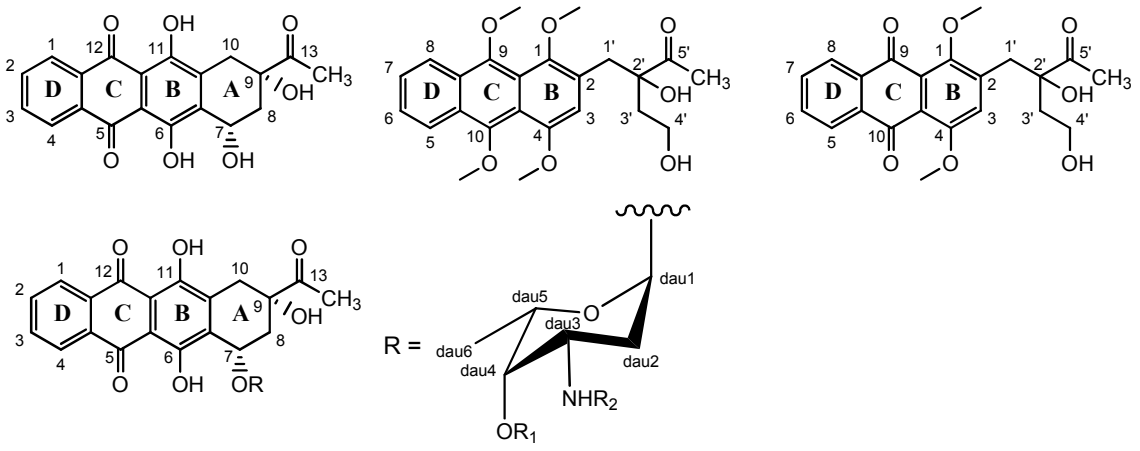
Proton signal are mentioned as following:

s	singlet
brs	broad singlet
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
t	triplet
dt	doublet of triplet
m	multiplet
q	quartet

The spectra were calibrated to the solvent peaks as listed :

$CDCl_3$	^1H 7.26 ppm	^{13}C 77.00 ppm
d_6-DMSO	^1H 2.50 ppm	^{13}C 39.50 ppm

The numbering systems used for anthracycline derivatives and anthraquinone derivatives are illusrated below. Other numbering systems used are illustrated in the experimental part. It has also become customary to label the individual rings as shown.



7.1.3 High Resolution Mass Spectrometry

The HRMS were performed by Herr Peter Unteregger. The used equipment was a MAT 900S from Finniga MAT. The results are given +/- 5ppm.

7.1.4 Elemental Analysis

The elemental analyses were performed by the microanalytical laboratory of the institute of physical chemistry (Mag. Johannes Theiner), university of Vienna. The used equipment was a “2400 CHN-Elemental Analyser” Perkin Elmer.

7.1.5 Thin Layer Chromatography (TLC)

Precoated TLC plates silica gel 60 F_{254} from Merck were used. The detection of substances was done either by ultraviolet light (254 nm) or by spraying with Seebach reagent.

7.1.6 Column Chromatography / Flash Chromatography

Column chromatography was carried out with silica gel 60A (particle size 0.035-0.070 mm). For separation of 1 g of crude product 100g of silica gel was used.
Flash chromatography was carried out with the same silica gel as for column chromatography. For separation of 1 g of crude product 30 g of silica gel was used.

7.1.7 Formation of Anhydrous Solvents

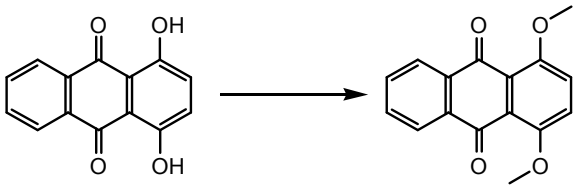
The solvent were distilled over an adequate desiccant under argon atmosphere and directly used for the reaction.

Dichloromethane	refluxing over phosphor pentoxide and distillation
Dimethylsulfoxide	storage over molecular sieve 4 Å under argon atmosphere (at least 1 day)
Pyridine	refluxing over potassium hydroxyde and distillation
Tetrahydrofuran	refluxing over sodium and benzophenone and distillation
Toluene	refluxing over sodium and benzophenone and distillation
Diethylether	refluxing over sodium and benzophenone and distillation

Other chemicals and solvents were used in common quality as offered by commercial chemical suppliers. All substannces were purchased from Sigma Aldrich, Acros Organics, Lancaster and Fluka.

7.2 Synthesis

1,4-dimethoxyanthracene-9,10-dione **84**



83 **84**

K_2CO_3 (288 g, 2.081 mol) was added to a suspension of **83** (100 g, 0.416 mol) in acetone (2000 mL). Me_2SO_4 (262 g, 2,081 mol) was added at RT and the reaction mixture was heated under reflux for 24 hrs. The reaction mixture was cooled to RT and acetone was removed under reduced pressure. The resulting residue was poured in water (5000 mL) and stirred overnight. The solid obtained was filtered. This crude product was poured in toluene (500 mL), heated at 60 °C and stirred at that temperature for 30 min. The resulting solid was filtered and washed with petrol ether to give 101.6 g of **84** (0.379 mol, 91%) as a yellow solid.

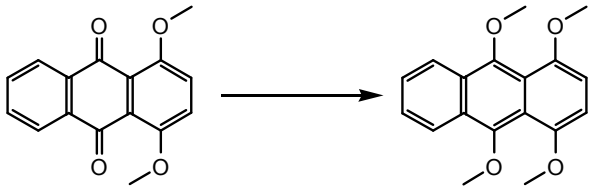
*1,4-dimethoxyanthracene-9,10-dione **84***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 8.15 (m, 2H, 5- and 8-H), 7.70 (m, 2H, 6- and 7-H), 7.33 (s, 2H, 2- and 3-H), 3.99 (s, 6H, OCH_3).

^{13}C NMR (200 MHz, $CDCl_3$) : 183.22 (Cq, C-9 and C-10); 154.12 (Cq, C-1 and C-4); 134.20 (Cq, C-8a and C-10a); 133.29 (CH, C-6 and C-7); 126.41 (CH, C-5 and C-8); 123.02 (Cq, C-4a and C-9a); 120.19 (CH, C-2 and C-3); 57.00 (CH_3).

HRMS (ESI) : calcd. For $C_{16}H_{12}O_4Na$ 291.0633; found 291.0628.
m.p. 173-174 °C

1,4,9,10-tetramethoxyanthracene **85**



84 **85**

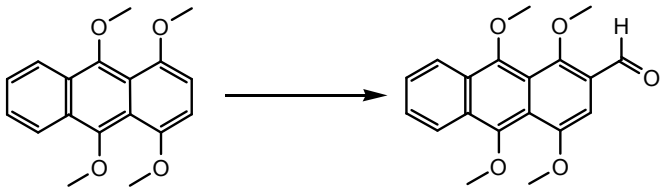
To a mixture of **84** (94 g, 0.350 mol), TBABr (6.8 g, 0.021 mol), $Na_2S_2O_4$ (384 g, 2.205 mol) in THF (740 mL) and water (740 mL) stirred 20 min under argon atmosphere at 25°C, was added KOH in water (500 mL) under stirring during 20 min (the temperature inside did not raise 30°C).The reaction mixture was then cooled to 10 °C and Me_2SO_4 (667 g, 5.284 mol) was slowly added over a period of 1 hr. The reaction mixture was then stirred 1 hr at RT. The reaction mixture was poured in water (4000 mL) and stirred 1 hr. The resulting solid was filtered, washed with water until neutral pH and dried under high vacuum at 60 °C overnight to give 103 g of **85** (0.345 mol, 99%) as a yellow solid.

*1,4,9,10-tetramethoxyanthracene **85***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 8.36 (m, 2H, 5- and 8-H), 7.51 (m, 2H, 6- and 7-H), 6.68 (s, 2H, 2- and 3-H), 4.01 (s, 6H, OCH_3), 3.99 (s, 6H, OCH_3).

HRMS (ESI) : calcd. For $C_{18}H_{18}O_4$ 298.1205; found 298.1207.
m.p. 145-146 °C

1,4,9,10-tetramethoxyanthracene-2-carbaldehyde **86**



85 **86**

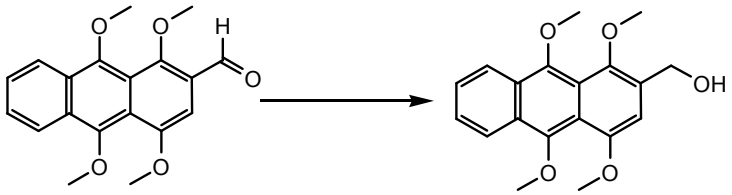
$POCl_3$ (498 g, 3.249 mol) was added dropwise to DMF (315 g, 4.309 mol) cooled to 5 °C with ice bath over a period of 1 h 20 under argon atmosphere (the temperature inside did not raise 19°C). The mixture was then stirred for 30 min and allowed to warm up to RT. **85** (102 g, 0.342 mol) was added in one portion to the reaction mixture at RT. The reaction mixture was then heated to 87 °C (oil bad 95°C) and stirred at that temperature for 30 min.The dark red solution was slowly added under well stirring to ice / water (5000 mL) containing 400 g of sodium acetate. The aqueous layer was extracted with EtOAc (3 x 1000 mL). The combined organic layers were washed with water until pH 5 was obtained, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown solid was stirred overnight in PE (300 mL) / MTBE (300 mL). The solid was filtered, washed with PE and dried under high vacuum at 50 °C for 2 hrs to give 79.24 g of **86** (0.243 mol, 71%) as a orange / brown solid.

*1,4,9,10-tetramethoxyanthracene-2-carbaldehyde **86***

^1H NMR (200 MHz, $CDCl_3$) : δ = 10.62 (s, 1H, -CHO), 8.39 (m, 2H, 5- and 8-H), 7.61 (m, 2H, 6- and 7-H), 7.03 (s, 1H, 3-H), 4.09 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3).

HRMS (ESI) : calcd. For $C_{20}H_{22}O_6Na$ 381.1314 ; found 381.1318. (M+MeOH+Na)
m.p. 145-147°C

(1,4,9,10-tetramethoxy-2-anthryl)methanol **87**



86 **87**

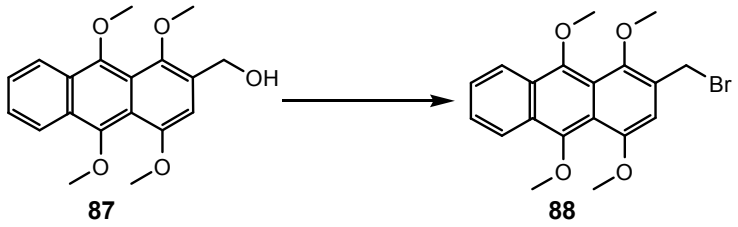
86 (72 g, 0.221 mol) was suspended in EtOH 96% (800 mL) at RT under argon atmosphere and $NaBH_4$ (8.4 g, 0.221 mol) was added portionwise over a period of 45 min. The temperature was controlled during addition of $NaBH_4$ and did not raise 26 °C. After addition of 1/3 of $NaBH_4$ the solid was dissolved. After complete addition of $NaBH_4$, the reaction mixture was stirred at RT for 1 hr. EtOH (~550 mL) was removed under reduced pressure and the remaining solution was poured in water (1600 mL) under stirring. The brownish sticky substance was extracted with EtOAc (4 x 500 mL).The combined organic layers were washed with brine (3 x 300 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was recrystallised from $CHCl_3$ (200 mL) / PE (800 mL) to give 58.8 g of **87** (0.179 mol, 81%) as a yellow solid.

*(1,4,9,10-tetramethoxy-2-anthryl)methanol **87***

^1H NMR (200 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, 5- and 8-H), 7.53 (m, 2H, 6- and 7-H), 6.77 (s, 1H, 3-H), 4.92 (s, 2H, CH_2OH), 4.06 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 2.39 (br s, 1H, OH, D_2O exchangeable).

HRMS (ESI) : calcd. For $C_{19}H_{20}O_5$ 328.1311; found 328.1310.
m.p. 95-96 °C

2-(bromomethyl)-1,4,9,10-tetramethoxy-anthracene **88**



87 **88**

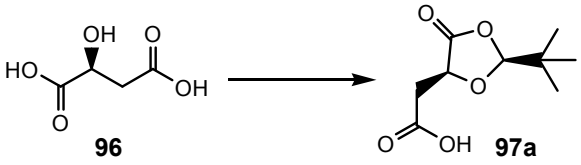
87 (50.5 g, 0.154 mol) was dissolved in toluene (500 mL) and cooled to 2 °C. Aqueous HBr 48% (87 g, 1.077mol) was slowly added to the solution over a period of 10min (the temperature did not raise 7 °C). The reaction mixture was then allowed to warmed up to RT and stirred vigorously for 24 hrs. The layers were separated. The organic layer was washed with sat. $NaHCO_3$ (400 mL), and brine (400 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 56.6 g of **88** (0.145 mol, 94%) as a brownish yellow solid.

*2-(bromomethyl)-1,4,9,10-tetramethoxy-anthracene **88***

^1H NMR (200 MHz, $CDCl_3$) : δ = 8.36 (m, 2H, 5- and 8-H), 7.55 (m, 2H, 6- and 7-H), 6.66 (s, 1H, 3-H), 4.82 (s, 2H, CH_2Br), 4.07 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3).

HRMS (ESI) : calcd. For $C_{19}H_{19}O_4Br$ 390.0467; found 390.0463.

2-[(2S,4S)-2-tert-butyl-5-oxo-1,3-dioxolan-4-yl]acetic acid ***97a***



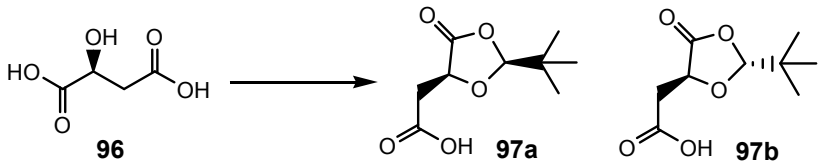
To a suspension of L(-)-malic acid (100 g, 0.746 mol) in pentane (1200 mL) were added pivalaldehyde (99.6 g, 1.156 mol) and pTsOH (9.9 g, 0.052 mol). The reaction mixture was refluxed with a dean and stark apparatur. The reaction was monitored by ^{1}H NMR analysis (a sample of the suspension was filtered and the solid was analysed by ^{1}H NMR). The reaction mixture was refluxed for 5.5 days. The reaction mixture was cooled to RT. The suspension was filtered and the filter cake was dissolved in DCM (700 mL). The organic layer was washed twice with 8% aqueous phosphoric acid (400 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 129.7 g of **97a** (0.642 mol, 86%, >97% de) as a white solid.

2-[(2S,4S)-2-tert-butyl-5-oxo-1,3-dioxolan-4-yl]acetic acid

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 5.19 (s, 1H, H-5); 4.65 (ddd, 1H, J = 0.6 Hz, 3.5 Hz, 7.3 Hz, H-3); 3.01 (dd, 1H, J = 3.5 Hz, 17.0 Hz, H-2/1); 2.83 (dd, 1H, J = 7.3 Hz, 17.4 Hz, H-2/2); 0.97 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 175.06 (Cq, C-1); 172.07 (Cq, C-4); 109.88 (CH, C-5); 71.39 (CH, C-3); 35.35 (CH_2, C-2); 34.23 (Cq, C-tBu); 23.39 (CH_3, C-tBuCH_3).

*2-[(2S,4S)-2-tert-butyl-5-oxo-1,3-dioxolan-4-yl]acetic acid **97a** and 2-[(2R,4S)-2-tert-butyl-5-oxo-1,3-dioxolan-4-yl]acetic acid **97b***



To a suspension of L(-)-malic acid (49.1 g, 366.2 mmol) in pentane (600 mL) were added pivalaldehyde (48.9 g, 567.6 mmol), pTsOH (4.9 g, 25.6 mmol) and 8 drops of conc. H_2SO_4. The reaction mixture was refluxed with a dean and stark apparatur. The reaction was monitored by ^{1}H NMR analysis (a sample of the suspension was filtered and the solid was analysed by ^{1}H NMR). The reaction mixture was refluxed for 48 hrs. The reaction mixture was cooled to RT. The suspension was filtered and the filter cake was dissolved in DCM (400 mL). The organic layer was washed twice with 8% aqueous phosphoric acid (100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 52 g of **97a** and **97b** (257.2 mmol, 70%, S,S / R,S: 2 / 8). The crude product was recristallised from Et_2O / pentane to give 36.5 g of **97b** (180.5 mmol, 49%, >97% de) as a white solid.

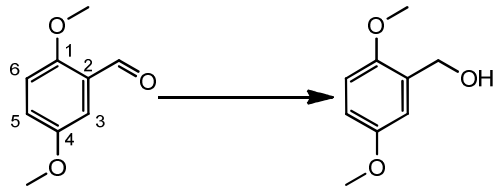
*2-[(2R,4S)-2-tert-butyl-5-oxo-1,3-dioxolan-4-yl]acetic acid **97b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 5.34 (d, 1H, J = 1.6 Hz, H-5); 4.61 (dt, 1H, J = 1.6 Hz, 4.7 Hz, H-3); 3.96 (d, 1H, J = 5.7 Hz, H-2/1); 2.95 (d, 1H, J = 6.3 Hz, H-2/2); 0.95 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 175.49 (Cq, C-1); 172.37 (Cq, C-4); 111.34 (CH, C-5); 70.69 (CH, C-3); 35.89 (Cq, C-tBu); 35.79 (CH_2, C-2); 23.15 (CH_3, C-tBuCH_3).

Synthese of 98

(2,5-dimethoxyphenyl)methanol



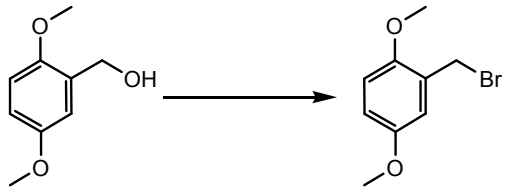
To a solution of 2,5-dimethoxybenzaldehyde (69.1 g, 0.415 mol) in MeOH (250 mL) cooled to 0 °C under argon atmosphere was added portionwise $NaBH_4$ (7.9 g, 0.208 mol). The reaction mixture was then allowed to warmed up to RT, stirred for 3 hrs and quenched with water (20 mL). The solvent was removed under reduced pressure and the aqueous layer was extracted with EtO_2 (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 65.8 g of the desired product (0.391 mol, 94%) as a light yellow oil.

(2,5-dimethoxyphenyl)methanol

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 6.84 (m, 3H, H-3, H-5 and H-6). 4.54 (s, 2H, H-CH_2); 3.85 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 2.38 (s, 1H, OH).

^{13}C NMR (200 MHz, $CDCl_3$) : δ = 153.56 (Cq, C-1); 151.50 (Cq, C-4); 130.02 (Cq, C-1); 114.78 (CH, C-6); 112.96 (CH, C-5); 111.08 (CH, C-3); 62.09 (CH_2, C-CH_2OH); 55.72 (CH_3, OCH_3).

2-(bromomethyl)-1,4-dimethoxy-benzene ***98***



98

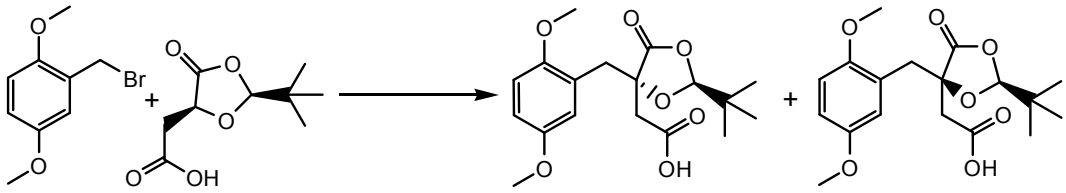
To a solution of (2,5-dimethoxyphenyl)methanol (51.95 g, 0.309 mol) in toluene (600 mL) cooled to 0 °C was slowly added HBr (48%) (120 mL, 2.200 mol). The reaction mixture was allowed to warmed up to RT and stirred for 4 hrs. The reaction mixture was then washed with sat. $NaHCO_3$ (200 mL), water (200 mL) and brine (200 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was recrystallised from PE to give after drying under reduced pressure 61.15 g of the desired product (0.265 mol, 86%) as a white crystal.

2-(bromomethyl)-1,4-dimethoxy-benzene ***98***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 6.85 (m, 3H, H-3, H-5 and H-6). 4.54 (s, 2H, H-CH_2); 3.85 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3).

^{13}C NMR (200 MHz, $CDCl_3$) : δ = 153.36 (Cq, C-1); 151.63 (Cq, C-4); 126.87 (Cq, C-1); 116.33 (CH, C-6); 114.99 (CH, C-5); 112.14 (CH, C-3); 56.16 (CH_3, OCH_3); 55.72 (CH_3, OCH_3); 28.91 (CH_2, C-CH_2Br);.

2-[(2S,4S)-2-tert-butyl-4-[(2,5-dimethoxyphenyl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **99a** and 2-[(2S,4R)-2-tert-butyl-4-[(2,5-dimethoxyphenyl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **99b**



98 **97a** **99a** **99b**

KHMDS (5.18 g, 25.95 mmol) was dissolved in dry THF (60 mL) under argon and cooled to –76°C. **97a** (1.75 g, 8.65 mmol) in THF (6 mL) was added dropwise (the temperature did not raise –72°C and the reaction mixture was stirred for 45 min. **98** (3 g, 12.98 mmol) in THF (6 mL) was added dropwise at –76 °C and the reaction mixture was stirred at –76 °C for 2 hr and then at –50 °C for 30 min. The reaction mixture was poured in 1N HCl (150 mL) / EtOAc (250 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with DCM / isopropanol (10/1) to give in order of elution 1.81 g of the desired product **99a** (5.14 mmol, 59%) as white solid and 0.14 g of **99b** (0.39 mmol, 4.5%) as white solid.

*2-[(2S,4S)-2-tert-butyl-4-[(2,5-dimethoxyphenyl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **99a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 6.79 (m, 2H, H-5 and H-6); 6.70 (s, 1H, H-3); 5.09 (s, 1H, H-acetal); 3.76 (s, 3H, OCH_3-1); 3.75 (s, 3H, OCH_3-4); 3.12 (d, 1H, J = 13.9 Hz, H-1´/1); 3.06 (d, 1H, J = 13.9 Hz, H-1´/2); 3.94 (d, 1H, J = 16.4 Hz, H-3´/1); 2.72 (d, 1H, J = 16.4 Hz, H-3´/2); 0.92 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 173.93 (Cq, C-5´); 173.82 (Cq, C-4´); 153.22 (Cq, C-4); 152.20 (Cq, C-1); 123.00 (Cq, C-2); 118.01 (CH, C-3); 113.41 (CH, C-5); 111.35 (CH, C-6); 107.93 (CH, C-acetal); 80.47 (Cq, C-2´); 55.74 (CH_3, OCH_3-1);

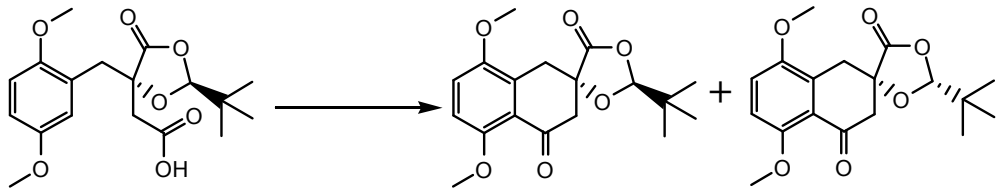
55.66 (CH_3, OCH_3-4); 38.72 (CH_2, C-3´); 34.18 (Cq, C-tBu); 32.22 (CH_2, C-1´); 23.64 (CH_3, C-tBuCH_3).

2-[(2S,4R)-2-tert-butyl-4-[(2,5-dimethoxyphenyl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid ***99b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 6.89 (d, 1H, J = 2.5 Hz, H-3); 6.80 (m, 2H, H-5 and H-6); 5.31 (s, 1H, H-acetal); 3.78 (s, 3H, OCH_3-1); 3.75 (s, 3H, OCH_3-4); 3.42 (d, 1H, J = 14.2 Hz, H-1´/1); 3.03 (d, 1H, J = 18.0 Hz, H-3´/1); 2.80 (d, 1H, J = 14.2 Hz, H-1´/2); 2.68 (d, 1H, J = 18.0 Hz, H-3´/2); 1.00 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 175.51 (Cq, C-4´); 174.50 (Cq, C-5´); 153.22 (Cq, C-4); 152.04 (Cq, C-1); 123.52 (Cq, C-2); 117.53 (CH, C-3); 113.34 (CH, C-5); 111.53 (CH, C-6); 110.54 (CH, C-acetal); 79.54 (Cq, C-2´); 55.82 (CH_3, OCH_3-1); 55.58 (CH_3, OCH_3-4); 39.03 (CH_2, C-3´); 36.81 (CH_2, C-1´); 34.70 (Cq, C-tBu); 23.67 (CH_3, C-tBuCH_3).

(2S,5S)-2-tert-butyl-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-1',4-dione **100** and (2R,5S)-2-tert-butyl-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-1',4-dione **101**



99a **100** **101**

To a suspension of **99a** (0.85 g, 2.41 mmol) in DCM (100 mL) under argon atmosphere was added $SOCl_2$ (0.84 mL, 11.45 mmol) and the suspension was stirred for 18hrs. The suspension was cooled to 3°C and $SnCl_4$ 99% anhydrous (2.7 mL, 22.90 mmol) was slowly added to the reaction mixture over a period of 2min. The mixture was allowed to warmed up to RT and stirred for 1h30 at RT. The reaction mixture was quenched with ice / water (200 mL). The resulting mixture was stirred for 50 min. The layers were separated. The aqueous layer was extracted with DCM (2 x 100ml). The combined organic layers were washed with sat. $NaHCO_3$ (2 x 150ml) and brine (150 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with DCM / EtOAC (10/0,4) to give in order of elution 108 mg of **100** (0.323 mmol, 13%), 40 mg of a mixture of **100** and **101** (0.120 mmol, 5%), and 39 mg of **101** (0.117 mmol, 5%).

*(2S,5S)-2-tert-butyl-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-1',4-dione **100***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.05 (d, 1H, J = 9.2 Hz, H-7); 6.87 (d, 1H, J = 9.2 Hz, H-6); 5.26 (s, 1H, H-acetal); 3.88 (s, 3H, OCH_3-5); 3.83 (s, 3H, OCH_3-8); 3.41 (d, 1H, J = 17.7 Hz, H-1/1); 3.12 (d, 1H, J = 15.8 Hz, H-3/1); 3.09 (d, 1H, J = 17.7 Hz, H-1/2); 2.83 (dd, 1H, J = 1.9 Hz, 15.8 Hz, H-3/2); 0.92 (s, 9H, H-tBuCH_3).

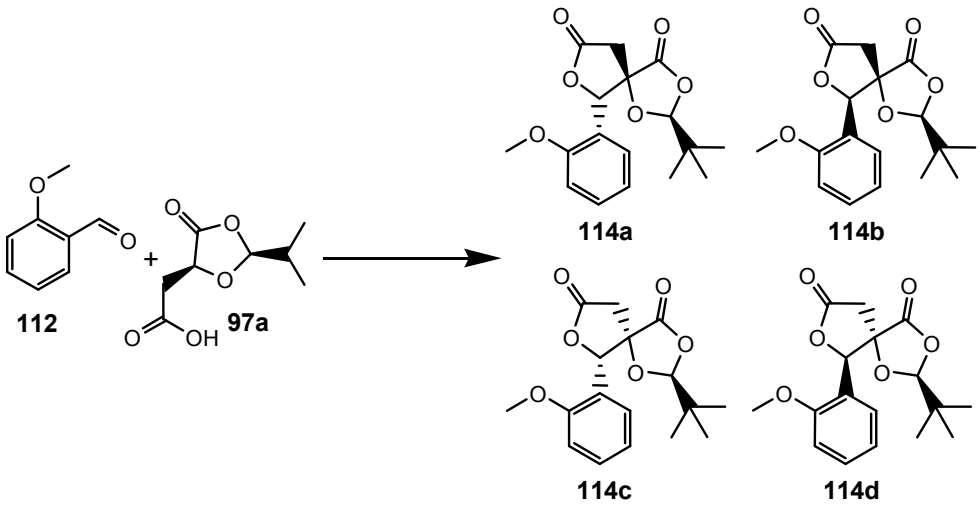
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 191.97 (Cq, C-4); 172.87 (Cq, C-9); 153,98 (Cq, C-5); 150.46 (Cq, C-8); 128.45 (Cq, C-8a); 121.48 (Cq, C-4a); 116.34 (CH, C-7); 110.85 (CH, C-6); 108.51 (CH, C-acetal); 79.10 (Cq, C-2); 56.30 (CH_3, OCH_3-5); 55.97 (CH_3,

OCH_3-8); 46.78 (CH_2, C-3); 34.42 (Cq, C-tBuCH_3); 28.66 (CH_2, C-1); 23.23 (CH_3, C-tBuCH_3).
m.p. 112-113°C

(2R,5S)-2-tert-butyl-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-1',4-dione ***101***
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.05 (d, 1H, J = 9.2 Hz, H-7); 6.86 (d, 1H, J = 9.2 Hz, H-6); 5.27 (s, 1H, H-acetal); 3.88 (s, 3H, OCH_3-5); 3.83 (s, 3H, OCH_3-8); 3.33 (d, 1H, J = 18.3 Hz, H-1/1); 3.27 (d, 1H, J = 18.3 Hz, H-1/2); 2.96 (s, 2H, H-3); 0.92 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 191.83 (Cq, C-4); 172.68 (Cq, C-9); 153,78 (Cq, C-5); 150.44 (Cq, C-8); 129.21 (Cq, C-8a); 121.33 (Cq, C-4a); 116.38 (CH, C-7); 110.57 (CH, C-6); 108.07 (CH, C-acetal); 79.35 (Cq, C-2); 56.29 (CH_3, OCH_3-5); 55.99 (CH_3, OCH_3-8); 43.71 (CH_2, C-3); 34.25 (Cq, C-tBuCH_3); 31.24 (CH_2, C-1); 23.25 (CH_3, C-tBuCH_3).
m.p. 71-73°C

(4S,5S,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione **114a**, (4R,5S,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione**114b**, (4S,5R,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione **114c**, (4R,5R,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione **114d**



LiHMDS (1.82 g, 10.89 mmol) was dissolved in dry THF (31 mL) under argon and cooled to –76°C. **97a** (1.00 g, 4.95 mmol) in THF (11 mL) was added dropwise (the temperature did not raise –72°C and the reaction mixture was stirred for 15 min. **112** (0.81 g, 5.94 mmol) in THF (6 mL) was added dropwise at –76 °C and the reaction mixture was stirred at –76 °C for 1 hr and then at –50 °C for 30 min. The reaction mixture was poured in NH_4Cl (100 mL) / EtOAc (200 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 0.76 g of crude product as a yellow oil. To a solution of this crude product in DCM (150 mL) was added DCI (0.73 g, 4.5 mmol) and DMAP (cat. Amount). The reaction mixture was stirred at RT for 45 min. 1N HCl (300 mL) was added and the resulting mixture was stirred for 10 min. The layer were separated. The aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was poured in EtOAc (150 mL) / sat. $NaHCO_3$ (150 mL). The layers were separated and the organic layer was washed with sat. $NaHCO_3$ (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered

and concentrated under reduced pressure. The crude product was first purified by column chromatography on silica gel with toluene / acetonitrile (50/1) to give in order of elution 2.45 g of a mixture of **112** and **114a** with **114b** (73 / 27), 1.49 g of a mixture of the 2 diastereoisomeres **114a** with **114b** (4.65 mmol, 19%) and 1.54 g of a mixture of the 2 diastereoisomeres **114c** with **114d** (4.81 mmol, 19%). The 2nd and 3rd fractions were separately purified by column chromatography on silica gel with DCM to afford pure sample of each diastereoisomeres.

(4S,5S,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione **114a**

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.37 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-4); 7.22 (d, 1H, J = 7.6 Hz, H-6); 7.04 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-5); 6.88 (d, 1H, J = 8.2 Hz, H-3); 5.97 (s, 1H, H-1´); 5.44 (s, 1H, H-acetal); 3.80 (s, 3H, OCH_3); 3.09 (d, 1H, J = 18.3 Hz, H-3´/1); 2.70 (d, 1H, J = 18.3 Hz, H-3´/2); 1.02 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 172.90 (Cq, C-5´); 168.98 (Cq, C-4´); 155.25 (Cq, C-2); 130.45 (CH, C-4); 124.77 (CH, C-6); 121.45 (Cq, C-1); 121.26 (CH, C-5); 110.18 (CH, C-3); 108.61 (CH, C-acetal); 84.18 (Cq, C-2´); 82.71 (CH, C-1´); 54.62 (CH_3, OCH_3); 37.11 (CH_2, C-3´); 34.12 (Cq, CtBu); 23.28 (CH_3, C-tBuCH_3).
m.p. 137-139 °C

(4R,5S,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione**114b**

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.49 (d, 1H, J = 7.6 Hz, H-6); 7.37 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-4); 7.03 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-5); 6.88 (d, 1H, J = 8.2 Hz, H-3); 6.04 (s, 1H, H-1´); 4.12 (s, 1H, H-acetal); 3.81 (s, 3H, OCH_3); 3.36 (d, 1H, J = 18.0 Hz, H-3´/1); 2.85 (d, 1H, J = 18.0 Hz, H-3´/2); 0.74 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 172.08 (Cq, C-5´); 170.71 (Cq, C-4´); 155.68 (Cq, C-2); 130.20 (CH, C-4); 127.56 (CH, C-6); 120.88 (CH, C-5); 120.77 (Cq, C-1); 110.26 (CH, C-acetal); 109.52 (CH, C-3); 83.13 (Cq, C-2´); 80.64 (CH, C-1´); 54.82 (CH_3, OCH_3); 40.67 (CH_2, C-3´); 34.29 (Cq, CtBu); 22.88 (CH_3, C-tBuCH_3).
m.p. 101-103 °C

(4S,5R,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione

114c

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.38 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-4); 7.20 (d, 1H, J = 7.6 Hz, H-6); 7.03 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-5); 6.88 (d, 1H, J = 8.2 Hz, H-3); 5.98 (s, 1H, H-1´); 5.15 (s, 1H, H-acetal); 3.77 (s, 3H, OCH_3); 2.92 (d, 1H, J = 17.7 Hz, H-3´/1); 2.79 (d, 1H, J = 17.7 Hz, H-3´/2); 1.07 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 172.57 (Cq, C-5´); 168.77 (Cq, C-4´); 156.33 (Cq, C-2); 130.42 (CH, C-4); 124.99 (CH, C-6); 121.27 (Cq, C-1); 120.80 (CH, C-5); 110.19 (CH, C-3); 108.39 (CH, C-acetal); 84.41 (Cq, C-1´); 82.43 (CH, C-2´); 54.83 (CH_3, OCH_3); 36.09 (CH_2, C-3´); 34.39 (Cq, CtBu); 23.38 (CH_3, C-tBuCH_3).
m.p. 199-201 °C

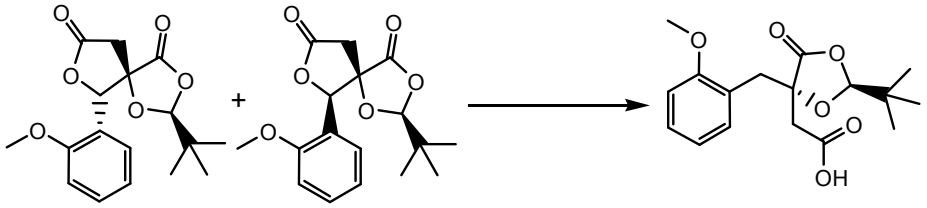
(4R,5R,8S)-8-tert-butyl-4-(2-methoxyphenyl)-3,7,9-trioxaspiro[4.4]nonane-2,6-dione

114d

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.44 (d, 1H, J = 7.6 Hz, H-6); 7.32 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-4); 7.01 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-5); 6.80 (d, 1H, J = 8.2 Hz, H-3); 6.13 (s, 1H, H-1´); 4.98 (s, 1H, H-acetal); 3.74 (s, 3H, OCH3); 3.12 (d, 1H, J = 18.0 Hz, H-3´/1); 2.94 (d, 1H, J = 18.0 Hz, H-3´/2); 0.59 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 171.70 (Cq, C-5´); 170.99 (Cq, C-4´); 155.81 (Cq, C-2); 129.86 (CH, C-4); 127.20 (CH, C-6); 120.71 (Cq, C-1); 120.48 (CH, C-5); 109.60 (CH, C-3); 108.72 (CH, C- acetal); 82.06 (Cq, C-2´); 81.11 (CH, C-1´); 54.53 (CH_3, OCH_3); 37.85 (CH_2, C-3´); 33.87 (Cq, CtBu); 22.98 (CH_3, C-tBuCH_3).
m.p. 42-44 °C

2-((2S,4S)-2-(tert-butyl)-4-(2-methoxybenzyl)-5-oxo-1,3-dioxolan-4-yl)acetic acid **115**

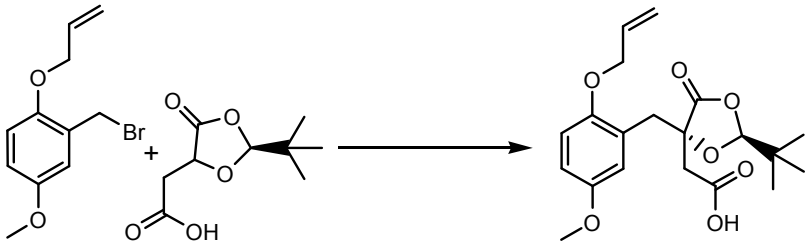


114a **114b** **115**

To a solution of **114a+b** (250 mg, 0.780 mmol) in EtOH / EtOAc 1 / 1 (15 mL) was added Pd/C 10 wt% on activated carbon (100 mg). The flask was purged with argon, and then with H_2. The reaction mixture was stirred for 24 hrs, purged with argon and filtered. The mother liquor was concentrated under reduced pressure to give 210 mg of **115** (0.651 mmol, 84%) as a white solid.

*2-((2S,4S)-2-(tert-butyl)-4-(2-methoxybenzyl)-5-oxo-1,3-dioxolan-4-yl)acetic acid **115***
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.28 (m, 1H, H-6); 7.12 (dd, 1H, J = 7.6 Hz, 8.2 Hz, H-4); 6.90 (m, 2H, H-3 and H-5); 5.05 (s, 1H, H-acetal); 3.81 (s, 3H, OCH_3); 3.14 (s, 2H, H-1´); 2.96 (d, 1H, J = 16.3 Hz, H-3´/1); 2.74 (d, 1H, J = 16.3 Hz, H-3´/2); 0.92 (s, 9H, H-tBuCH_3).

2-((2S,4S)-4-(2-(allyloxy)-5-methoxybenzyl)-2-(tert-butyl)-5-oxo-1,3-dioxolan-4-yl)acetic acid **108a**



106 **97a** **108a**

KHMDS (8.15 g, 40.85 mmol) was dissolved in dry THF (45 mL) under argon and cooled to –76°C. **97a** (3.54 g, 17.51 mmol) in THF (4 mL) was added dropwise (the temperature did not raise –72°C and the reaction mixture was stirred for 45 min. **106** (3.00 g, 11.67 mmol) in THF (2 mL) was added dropwise at –76 °C and the reaction mixture was stirred at –40 °C for 1 hr. The reaction mixture was poured in 1N HCl (150 mL) / EtOAc (300 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / isopropanol (20/1) to give 3.09 g of **108a** (8.17 mmol, 70%) as white solid.

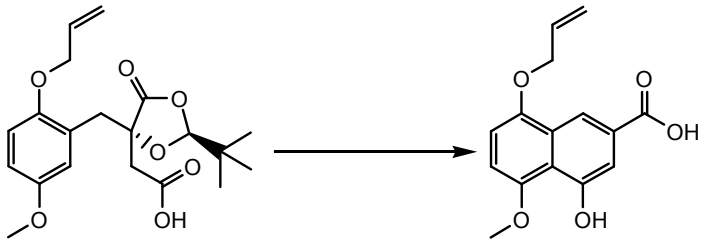
*2-((2S,4S)-4-(2-(allyloxy)-5-methoxybenzyl)-2-(tert-butyl)-5-oxo-1,3-dioxolan-4-yl)acetic acid **108a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 6.78 (m, 2H, H-5 and H-6); 6.71 (s, 1H, H-3); 6.04 (ddt, 1H, J = 5.1 Hz, 10.8 Hz and 17.0 Hz, H-CHallyl); 5.39 (d, 1H, J = 17 Hz, H-CH_2allyl/1); 5.28 (d, 1H, J = 10.8 Hz, H-CH_2allyl/2); 5.10 (s, 1H, H-acetal); 4.47 (d, 2H, J = 5.1 Hz, H-CH_2allyl); 3.75 (s, 3H, OCH_3); 3.20 (d, 1H, J = 14.2 Hz, H-1'/1); 3.05 (d, 1H, J = 13.9 Hz, H-1'/2); 2.96 (d, 1H, J = 16.4 Hz, H-3'/1); 2.74 (d, 1H, J = 16.4 Hz, H-3'/2); 0.92 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 174.19 (Cq, C-5'); 173.66 (Cq, C-4'); 153.37 (Cq, C-4); 151.23 (Cq, C-1); 133.34 (CH, C-CHallyl); 123.35 (Cq, C-2); 117.89 (CH, C-3); 117.59 (CH_2, C-CH_2allyl); 113.49 (CH, C-5); 112.82 (CH, C-6); 107.87 (CH, C-

acetal); 80.44 (Cq, C-2'); 69.60 (CH_2, C-CH_2allyl); 55.63 (CH_3, OCH_3); 38.86 (CH_2, C-3'); 34.21 (Cq, C- tBuCH_3); 32.28 (CH_2, C-1'); 23.61 (CH_3, C-tBuCH_3).

8-(allyloxy)-4-hydroxy-5-methoxy-2-naphthoic acid **116**



108a **116**

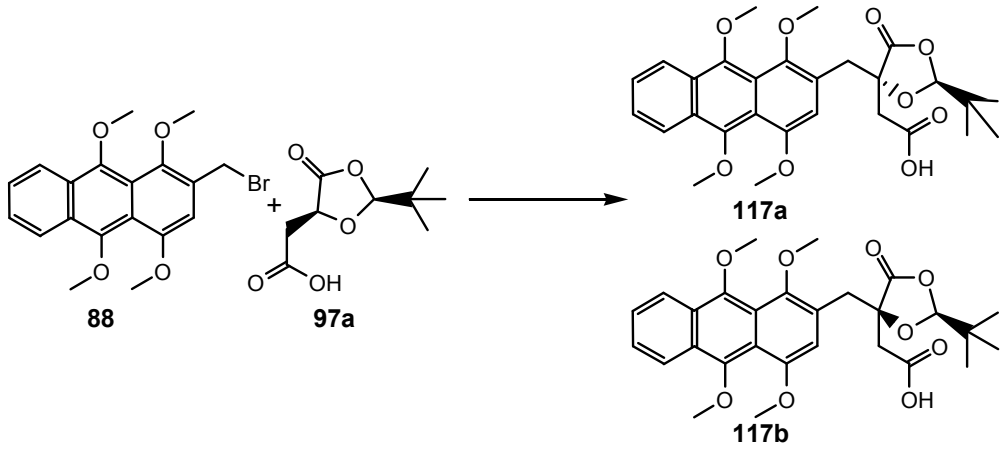
To a suspension of **108a** (100 mg, 0.264 mmol) in TFAA (1.5 mL) cooled to 0 °C was added TFA (0.02 mL). The reaction mixture was stirred for 1hr at 0 °C and then for 6 hrs at RT. The resulting solid was filtered, washed with PE and dried under high vacuum to give 38 mg of **116** (0.137 mmol, 52%) as a white solid.

*8-(allyloxy)-4-hydroxy-5-methoxy-2-naphthoic acid **116***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.42 (brs, 1H, H-OH); 8.49 (s, 1H, H-1); 7.44 (s, 1H, H-3); 6.73 (d, 1H, J = 8.6 Hz, H-6); 6.66 (d, 1H, J = 8.6 Hz, H-7); 6.09 (m, 1H, H-CHallyl); 5.43 (d, 1H, J = 17.4 Hz, H-CH2allyl); 5.27 (d, 1H, J = 10.4 Hz, H-CH2allyl); 4.62 (d, 1H, J = 5.1 Hz, H-CH2allyl); 3.98 (s, 3H, H-OCH3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 168.48 (Cq, C-COOH); 154.32 (Cq, C-4); 149.86 (Cq, C-8); 149.67 (Cq, C-5); 133.08 (CH, C-CHallyl); 129.30 (Cq, C-4a); 127.74 (Cq, C-8a); 117.62 (Cq, C-2); 117.49 (CH2, C-CH2allyl); 116.13 (CH, C-1); 110.75 (CH, C-3); 105.58 (CH, C-6); 105.03 (CH, C-7); 69.28 (CH2, C-CH2allyl); 56.32 (CH3, OCH3.

2-[(2S,4S)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetic acid **117a** and 2-[(2S,4R)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetic acid **117b**



KHMDS (24.93 g, 124.99 mmol) was dissolved in dry THF (320 mL) under argon and cooled to –76°C. **97a** (10.83 g, 53.57 mmol) in THF (15 mL) was added dropwise (the temperature did not raise –72°C) and the mixture was allowed to warmed up to –40 °C and stirred for 50. **88** (13.97 g, 35.71 mmol) in THF (25 mL) was added dropwise at –40 °C and the reaction mixture was stirred at –40 °C for 1 hr. The reaction mixture was poured in 1N HCl (500 mL) / EtOAc (800 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by trituration in toluene to give 5,12 g of **117a** (9.989 mmol, 28%) as a yellow solid. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel with toluene / isopropanol (20/1) to give 3.30 g of **117a** (6.438 mmol, 18%) as yellow solid and 0.03 g of **117b** (0.06 mmol, 0.05%) as a yellow solid. The main by product **118** was also isolated for analysis.

*2-[(2S,4S)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetic acid **117a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.55 (s, 1H, H-3); 5.10 (s, 1H, H-acetal); 4.01 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.95 (s, 3H, OCH_3-9); 3.78 (s, 3H, OCH_3-1); 3.41 (d, 1H, J = 13.9 Hz, H-1´/1);

3.21 (d, 1H, J = 13.9 Hz, H-1´/2); 3.09 (d, 1H, J = 16.4 Hz, H-3´/1); 2.89 (d, 1H, J = 16.4 Hz, H-3´/2); 0.92 (s, 9H, H-tBuCH_3).

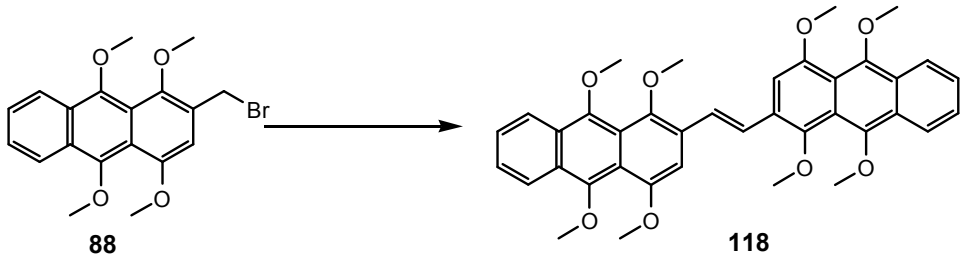
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 174.03 (Cq, C-5´); 173.34 (Cq, C-4´); 152.42 (Cq, C-4); 149.42 (Cq, C-10); 147.67 (Cq, C-1); 147.62 (Cq, C-9); 127.10 (Cq, C-8a); 126.72 (Cq, C-10a); 126.39 (CH, C-6); 125.98 (CH, C-7); 122.98 (CH, C-5); 122.63 (CH, C-8); 121.56 (Cq, C-2); 120.50 (Cq, C-9a); 119.45 (Cq, C-4a); 108.31 (CH C-acetal); 105.85 (CH, C-3); 80.90 (Cq, C-2´); 63.54 (CH_3, OCH_3-9 and OCH_3-10); 62.23 (CH_3, OCH_3-1); 56.30 (CH_3, OCH_3-4); 39.24 (CH_2, C-3´); 34.29 (Cq, C-tBu); 32.96 (CH_2, C-1´); 23.63 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{28}H_{33}O_9$ 513.2125; found 513.2125.
m.p. 210-212 °C

2-[(2S,4R)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetic acid ***117b***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.75 (s, 1H, H-3); 5.38 (s, 1H, H-acetal); 4.02 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.96 (s, 3H, OCH_3-9); 3.78 (s, 3H, OCH_3-1); 3.47 (d, 1H, J = 13.9 Hz, H-1´/1); 3.18 (d, 1H, J = 17.7 Hz, H-3´/1); 2.99 (d, 1H, J = 13.9 Hz, H-1´/2); 2.86 (d, 1H, J = 17.7 Hz, H-3´/2); 1.00 (s, 9H, H-tBuCH_3).

(E)-1,2-bis(1,4,9,10-tetramethoxyanthracen-2-yl)ethane **118**



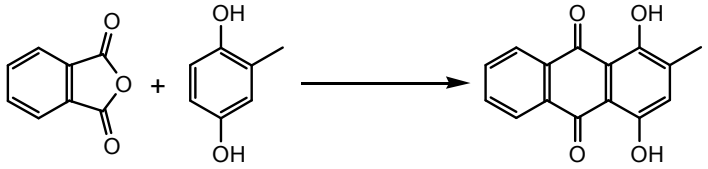
To a solution of **88** (2.2 g, 5.6 mmol) in dry THF (60 mL) cooled to – 76 °C under argon atmosphere was slowly added a solution of KHMDS (1.8 g, 9 mmol) in THF (10 mL). After few second the starting material was consumed and the reaction mixture was poured in 1N HCl (200 mL) / EtOAc (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluen / EtOAc (3/1 → 1/1) to give 1.3 g of **118** (2.1 mmol, 75%) as yellow solid foam.

*(E)-1,2-bis(1,4,9,10-tetramethoxyanthracen-2-yl)ethane **118***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 8.37 (m, 4H, H-5 and H-8); 7.86 (s, 2H, =CH); 7.55 (m, 4H, H-6 and H-7); 7.17 (s, 2H, H-3); 4.19 (s, 6H, OCH_3-4); 4.05 (s, 6H, OCH_3-10); 4.04 (s, 6H, OCH_3-9); 3.94 (s, 6H, OCH_3-1)

^{13}C NMR (200 MHz, $CDCl_3$) : δ = 152.96 (Cq, C-4); 149.35 (Cq, C-10); 147.52 (Cq, C-1); 147.31 (Cq, C-9); 127.15 (Cq, C-8a); 126.85 (Cq, C-10a); 126.40 (CH, C-6); 125.95 (CH, C-7); 125.85 (Cq, C-2); 123.74 (CH, =CH); 123.11 (CH, C-5); 122.64 (CH, C-8); 121.05 (Cq, C-9a); 119.76 (Cq, C-4a); 100.63 (CH, C-3); 63.64 (CH_3, OCH_3-9); 63.53 (CH_3, OCH_3-10); 62.93 (CH_3, OCH_3-1); 56.64 (CH_3, OCH_3-4).

1,4-dihydroxy-2-methyl-anthracene-9,10-dione **121**



119 **120** **121**

A mixture of anhydrous $AlCl_3$ (125.0 g, 0.937 mol) and NaCl (27.5 g, 0.469 mol), was heated at 130 °C in an oil bath till melted (about 30 min).The appearance of the melting was milky. A homogeneous mixture of **119** (27.5 g, 0.187 mol) and **120** (23.2 g, 0.187 mol) was added. The temperature was increased and maintained at 170 °C for 3 hr 30. The colour of the melting turned to dark red and the melting was still miscible during the heating time. After 1 hr 30 of stirring the mixture was less viscous. After 3 hr 30 stirring the reaction mixture was cooled to RT, 20% HCl (1 L) was added and the mixture was refluxed at 130 °C for 1hr. After cooling down with an ice bath the suspension was filtered and washed with deionised water till the filtrate was neutral. Then the precipitate was dried at 70°C in high vacuum over night to give 36.5 g of **121** (0.144 mol, 77%) as a red solid.

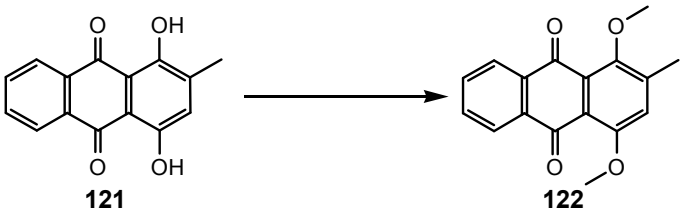
*1,4-dihydroxy-2-methyl-anthracene-9,10-dione **121***

^1H NMR (500 MHz, $CDCl_3$) : δ = 13.18 (s, 1H, OH-1); 12.76 (s, 1H, OH-4); 8.24 (m, 2H, H-5 and H-8); 7.96 (m, 2H, H-6 and H-7); 7.33 (s, 1H, H-3); 2.29 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 186.86 Cq, C-9); 186.00 (Cq, C-10); 156.67 (Cq, C-4); 156.14 (Cq, C-1); 140.47 (Cq, C-2); 135.06 (CH, C-6); 134.91 (CH, C-7); 133.00 (Cq, C-8a); 132.00 (Cq, C-10a); 128.74 (CH, C-3); 126.68 (CH, C-5); 126.55 (CH, C-8); 111.60 (Cq, C-9a); 110.78 (Cq, C-4a); 16.00 (CH_3).

m.p. 185-187 °C

1,4-dimethoxy-2-methyl-anthracene-9,10-dione **122**



121 **122**

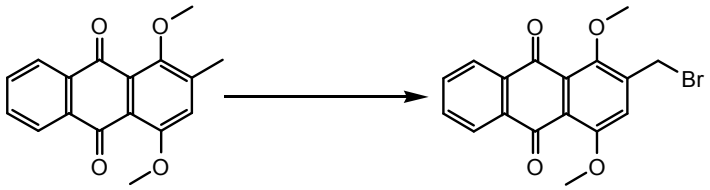
To a suspension of **121** (32.3 g, 0.127 mol) in dry acetone (750 mL) K_2CO_3 (175.4 g, 1.269 mol) was added and stirred for 15 min. Me_2SO_4 (108 mL, 1.142 mol) was then added and the reaction mixture was stirred under reflux for 20 hrs. The reaction mixture was cooled to RT. K_2CO_3 was filtered, washed with acetone (3 x 150 mL) and the filtrate was concentrated under reduced pressure. The crude product was dissolved with EtOAc (500 mL) under warming and washed with water (600mL) until pH=7. The organic layer were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was stirred in MTBE (300 mL), filtered and washed with MTBE (3 x 50 mL). The yellow solid was dried at 40°C under high vacuum to give 29,8 g of **122** (0.106 mol, 83%) as a yellow solid.

*1,4-dimethoxy-2-methyl-anthracene-9,10-dione **122***

^{1}H NMR (200 MHz, d6-DMSO) : δ = 8.03 (m, 2H, H-5 and H-8); 7.83 (m, 2H, H-6 and H-7); 7.51 (s, 1H, H-3); 3.90 (s, 3H, OCH_3-4); 3.77 (s, 3H, OCH_3-1); 2.38 (s, 3H, CH_3).

m.p. 126-128 °C

2-(bromomethyl)-1,4-dimethoxy-anthracene-9,10-dione **123**



122 **123**

To a suspension of **122** (20.0 g, 0.071 mol) in CCl_4 (400 mL) was added NBS (15.2 g, 0.085 mol) followed by Bz_2O_2 (5.2 g, 0.021 mol) under argon at RT. The reaction was then stirred under reflux for 3 hrs and cooled to 10 °C. The resulting precipitate was filtered, washed with CCl_4, dried under high vacuum and recrystallised from AcOH to give 11.94 g of **123** (0.033 mol, 47%) as orange needles. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel with toluene / EtOAc (30/1) to give additional 3.6 g of **123** (0.010 mol, 14 %) as yellow solid.

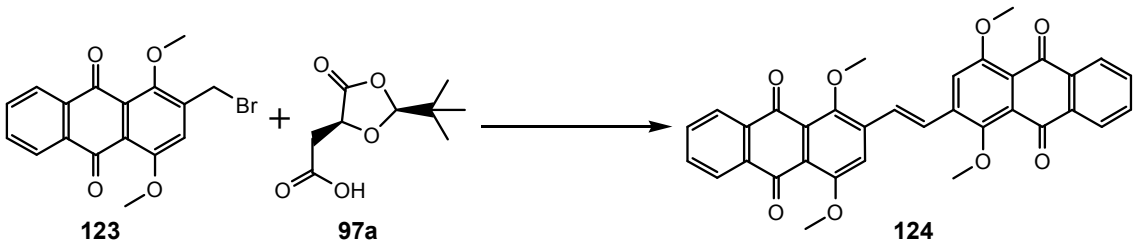
*2-(bromomethyl)-1,4-dimethoxy-anthracene-9,10-dione **123***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.74 (m, 2H, H-6 and H-7); 7.40 (s, 1H, H-3); 4.62 (s, 2H, CH_2Br); 4.04 (s, 3H, OCH_3-4); 4.02 (s, 3H, OCH_3-1).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 182.98 (Cq, C-9); 182.73 (Cq, C-10); 156.33 (Cq, C-4); 152.29 (Cq, C-1); 140.80 (Cq, C-2); 134.24 (Cq, C-8a); 133.78 (CH, C-6); 133.69 (Cq, C-10a); 133.43 (CH, C-7); 127.58 (Cq, C-9a); 126.62 (CH, C-5); 126.46 (CH, C-8); 123.11 (Cq, C-4a); 120.64 (CH, C-3); 62.80 (CH_3, OCH_3-4); 56.87 (CH_3, OCH_3-1); 26.52 (CH_2, C-CH_2Br).

m.p. 181-183 °C

2-[(E)-2-(1,4-dimethoxy-9,10-dioxo-2-anthryl)vinyl]-1,4-dimethoxy-anthracene-9,10-dione **124**



123 **97a** **124**

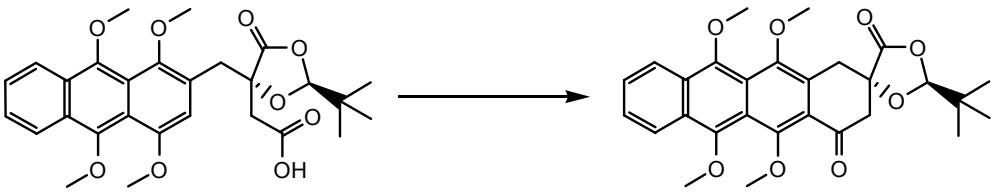
KHMDS (1.16 g, 5.82 mmol) was dissolved in dry THF (100 mL) under argon and cooled to –76°C. **97a** (1.76 g, 8.73 mmol) in THF (10 mL) was added dropwise (the temperature did not raise –72°C) and the mixture was allowed to warmed up to –40 °C and stirred for 50. **123** (2 g, 5.54 mmol) in THF (10 mL) was added dropwise at –40 °C and the reaction mixture was stirred at –40 °C. After few second the starting material was consumed and the reaction mixture was poured in 1N HCl (200 mL) / EtOAc (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluen / EtOAc (3/1 → 1/1) to give 1.0 g of **124** (1.8 mmol, 65%) as yellow solid foam.

*2-[(E)-2-(1,4-dimethoxy-9,10-dioxo-2-anthryl)vinyl]-1,4-dimethoxy-anthracene-9,10-dione **124***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.19 (m, 4H, H-5 and H-8); 7.75 (m, 4H, H-6 and H-7); 7.70 (s, 2H, =CH); 7.60 (s, 2H, H-3); 4.12 (s, 6H, OCH_3-4); 3.96 (s, 6H, OCH_3-1).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.31 (Cq, C-9); 182.56 (Cq, C-10); 156.64 (Cq, C-4); 152.30 (Cq, C-1); 139.17 (Cq, C-2); 134.36 (Cq, C-8a); 133.82 (Cq, C-10a); 133.78 (CH, C-6); 133.38 (CH, C-7); 128.05 (Cq, C-9a); 126.77(CH, =CH); 126.64 (CH, C-5); 126.43 (CH, C-8); 122.69 (Cq, C-4a); 115.83 (CH, C-3); 62.81 (CH_3, OCH_3-1); 56.91 (CH_3, OCH_3-4).

(2S,5S)-2-tert-butyl-5',6',11',12'-tetramethoxy-spiro[1,3-dioxolane-5,3'-2,4-dihydrotetracene]-1',4-dione **125**



117a **125**

To a suspension of **117a** (300 mg, 0.585 mmol) in TFAA (1.5 mL) cooled to 0 °C was added TFA (0.02 mL). The reaction mixture was stirred for 30 min at 0 °C and then for 20 hrs at RT. The reaction mixture was poured in sat. $NaHCO_3$ (15 mL) / EtOAc (10 mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene → toluene / EtOAc (20/1) to give 72 mg of **125** (0.146 mmol, 25%) as a yellow foam and 138 mg of starting material (0.269 mmol, 46%).

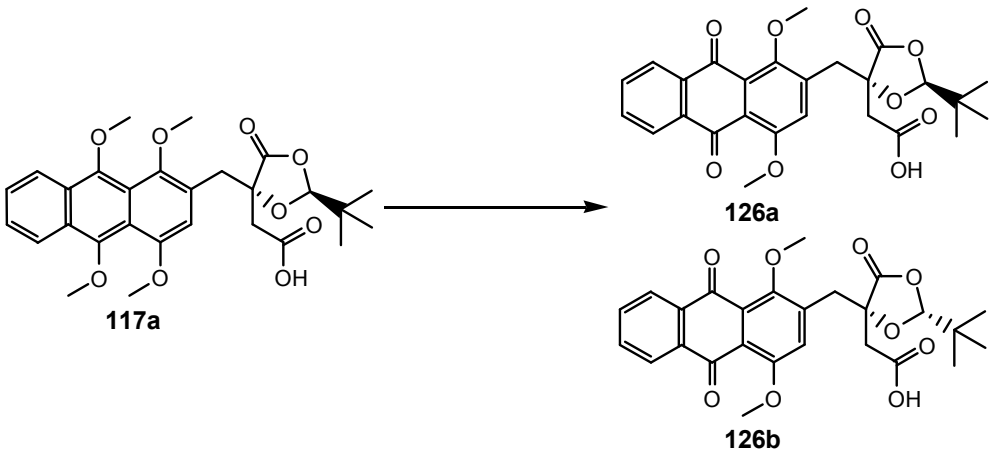
*(2S,5S)-2-tert-butyl-5',6',11',12'-tetramethoxy-spiro[1,3-dioxolane-5,3'-2,4-dihydrotetracene]-1',4-dione **125***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.39 (d, 1H, J = 8.5 Hz, H-4); 8.36 (d, 1H, J = 8.5 Hz, H-1); 7.59 (m, 2H, H-2 and H-3); 5.35 (s, 1H, H-acetal); 4.04 (s, 3H, OCH_3-5); 4.01 (s, 3H, OCH_3-6); 4.00 (s, 3H, OCH_3-12); 3.84 (s, 3H, OCH_3-11); 3.74 (dd, 1H, J = 2.6 Hz, 16.8 Hz, H-10/1); 3.31 (d, 1H, J = 16.8 Hz, H-10/2); 3.23 (d, 1H, J = 16.7 Hz, H-8/1); 2.95 (dd, 1H, J = 2.6 Hz, 16.7 Hz, H-8/2); 0.95 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 192.08 (Cq, C-7); 173.03 (Cq, C-13); 156.41 (Cq, C-6); 152.23 (Cq, C-5); 148.91 (Cq, C-11); 147.46 (Cq, C-12); 128.84 (Cq, C-12a); 127.68 (Ch, C-2); 127.20 (Cq, C-4a); 126.50 (CH, C-3); 123.30 (CH, C-4); 122.70 (Cq, C-6a); 122.69 (CH, C-1); 122.11 (Cq, C-5a); 120.80 (Cq, C-11a); 120.63 (Cq, C-10a); 108.53 (CH, C-acetal); 78.69 (Cq, C-9); 64.17 (CH_3, OCH_3-5); 63.71 (CH_3, OCH_3-12); 63.35 (CH_3, OCH_3-6); 61.62 (CH_3, OCH_3-11); 47.51 (CH_2, C-8); 34.47 (Cq, C-tBu); 28.61 (CH_2, C-10); 23.27 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{28}H_{30}O_8$ 495.2019; found 495.2016 (MH+).
m.p. 70-72 °C

2-[(2S,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **126a** and 2-[(2R,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **126b**



To a solution of **117a** (200 mg, 0.390 mmol) in DCM (10 mL) under argon atmosphere was added $SOCl_2$ (0.14 mL, 1.95 mmol) and the reaction mixture was stirred for 3hrs. The solvent was removed under reduced pressure and the crude product was dissolved in DCM (10 mL) under argon atmosphre and cooled to 2 °C. $SnCl_4$ 99% anhydrous (0.11 mL, 0.975 mmol) was slowly added to the reaction mixture over a period of 3 min. The mixture was allowed to warmed up to RT and stirred for 1hr. The reaction mixture was quenched with ice / water (40 mL). The resulting mixture was stirred for 10 min. The layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by preparative tlc on silica gel with toluene / isopropanol (15/1) to give in order of elution 40 mg of **126a** (0.083 mmol, 21%) as a yellow solid and 42 mg of **126b** (0.087 mmol, 22%) as a yellow solid.

2-[(2S,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid ***126a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.74 (m, 2H, H-6 and H-7); 7.24 (s, 1H, H-3); 5.09 (s, 1H, H-acetal); 3.98 (s, 3H, OCH_3-4); 3.90 (s, 3H, OCH_3-1); 3.42 (d, 1H, J = 13.9 Hz, H-1´/1); 3.13 (d, 1H, J = 13.9 Hz, H-1´/2); 2.98 (d, 1H, J = 16.4 Hz, H-3´/1); 2.72 (d, 1H, J = 16.4 Hz, H-3´/2); 0.94 (s, 9H, H-tBuCH_3).

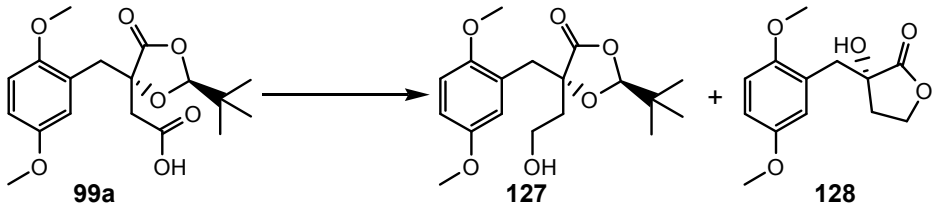
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.14 (Cq, C-9); 182.87 (Cq, C-10); 173.20 (Cq, C-5´); 171.98 (Cq, C-4´); 155.88 (Cq, C-4); 153.04 (Cq, C-1); 137.21 (Cq, C-2); 134.22 (Cq, C-8a); 133.76 (Cq, C-10a and CH, C-6); 133.45 (CH, C-7); 127.30 (Cq, C9a); 126.58 (CH, C-5); 126.51 (CH, C-8); 122.59 (Cq, C-4a); 121.75 (CH, C-3); 108.22 (CH, C-acetal); 80.33 (Cq, C-2´); 62.65 (CH_3, OCH_3-1); 56.72 (CH_3, OCH_3-4); 38.93 (CH_2, C-3´); 34.39 (Cq, C-tBuCH_3); 32.35 (CH_2, C-1´); 23.59 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{26}H_{26}O_8Na$ 505.1475; found 505.1485

*2-[(2R,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid****126b***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 8.18 (m, 2H, H-5 and H-8); 7.74 (m, 2H, H-6 and H-7); 7.45 (s, 1H, H-3); 5.39 (s, 1H, H- acetal); 4.00 (s, 3H, OCH_3-4); 3.89 (s, 3H, OCH_3-1); 3.61 (d, 1H, J = 13.8 Hz, H-1´/1); 3.06 (d, 1H, J = 17.4 Hz, H-3´/1); 2.96 (d, 1H, J = 13.8 Hz, H-1´/2); 2.70 (d, 1H, J = 17.4 Hz, H-3´/2); 0.97 (s, 9H, H-tBuCH_3).

(2S,5S)-2-tert-butyl-5-[(2,5-dimethoxyphenyl)methyl]-5-(2-hydroxyethyl)-1,3-dioxolan-4-one **127** and (3S)-3-[(2,5-dimethoxyphenyl)methyl]-3-hydroxy-tetrahydrofuran-2-one **128**



99a **127** **128**

To a stirred solution of **99a** (1 g, 2.838 mmol) in dry THF (5 mL) cooled to 3°C was slowly added BH_3.THF complex 1 M in THF (3.41 mL, 3.406 mmol). The reaction mixture was allowed to warmed up to RT and stirred for 3hrs. The mixture was quenched with sat. NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. $NaHCO_3$ (3 x 20mL), dried (Na_2SO_4), filtered and concentrated under reduced. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (2/1) to give 720 mg of **127** (2.128 mmol, 75%) as a colourless oil and some trace of lactone **128**.
NB : NMR analysis showed decomposition of the product after few weeks storage at RT.

*(2S,5S)-2-tert-butyl-5-[(2,5-dimethoxyphenyl)methyl]-5-(2-hydroxyethyl)-1,3-dioxolan-4-one **127***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 6.79 (s, 2H, H-5 and H-6); 6.73 (s, 1H, H-3); 4.93 (s, 1H, H-acetal); 3.77 (m, 2H, H-4´); 3.76 (s, 3H, OCH_3-1); 3.75 (s, 3H, OCH_3-4); 3.12 (d, 1H, J = 13.9 Hz, H-1´/1); 3.07 (d, 1H, J = 13.9 Hz, H-1´/2); 2.10 (m, 2H, H-3´); 0.94 (s, 9H, H-tBuCH_3).

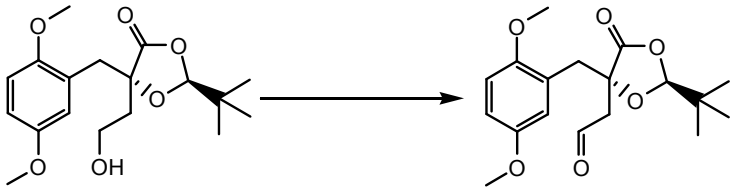
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 175.22 (Cq, C-5´); 153.20 (Cq, C-4); 152.34 (Cq, C-1); 123.73 (Cq, C-2); 117.96 (CH, C-3); 113.23 (CH, C-5); 111.30 (CH, C-6); 108.11 (Ch, C-acetal); 82.36 (Cq, C-2´); 58.33 (CH_2, C-4´); 55.74 (CH_3, OCH_3-4); 55.67 (CH_3, OCH_3-1); 37.55 (CH_2, C-3´); 34.25 (Cq, C-tBuCH_3); 34.25 (CH_2, C-1´); 23.53 (CH_3, C-tBuCH_3).

(3S)-3-[(2,5-dimethoxyphenyl)methyl]-3-hydroxy-tetrahydrofuran-2-one ***128***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 6.84 (d, 1H, J = 8.5 Hz, H-6); 6.79 (dd, 1H, J = 2.6 Hz, 8.5 Hz, H-5); 6.75 (d, 1H, J = 2.6 Hz, H-3); 4.34 (dt, 1H, J = 4.1 Hz, 8.5 Hz, H-4´/1); 4.12 (dd, 1H, J = 8.5 Hz, 15.5 Hz, H-4´/2); 3.80 (s, 3H, OCH_3-1); 3.76 (s, 3H, OCH_3-4); 3.32 (d, 1H, J = 13.9 Hz, H-1´/1); 2.82 (d, 1H, J = 13.9 Hz, H-1´/2); 2.35 (m, 1H, H-3´/1); 2.22 (m, 1H, H-3´/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 178.41 (C-5´); 153.66 (Cq, C-4); 151.70 (Cq, C-1); 124.26 (Cq, C-2); 118.22 (CH, C-3); 112.78 (CH, C-5); 111.62 (CH, C-6); 75.38 (Cq, C-2´); 65.12 (CH_2, C-4´); 55.97 (CH_3, OCH_3-1); 55.67 (CH_3, OCH_3-4); 36.89 (CH_2, C-1´); 34.47 (CH_2, C-3´).

2-[(2S,4S)-2-tert-butyl-4-[(2,5-dimethoxyphenyl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **129**



127 **129**

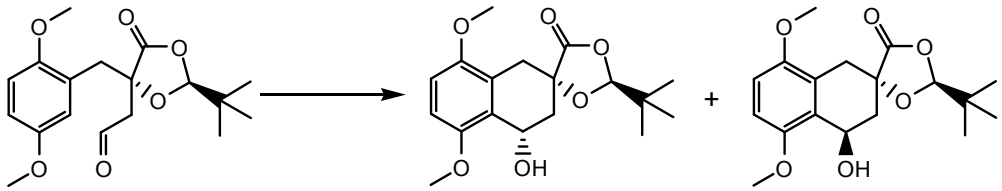
127 (0.55 g, 1.625 mmol) in DCM (20 mL) was added to a suspension of Dess Martin periodinane 97% (1.72 g, 4.063 mmol) in DCM (20 mL) under argon atmosphere at RT and the reaction mixture was stirred at RT for 3hrs. The reaction mixture was then poured in sat. $NaHCO_3$ (150 mL) / EtOAc (100 mL). The layers were separated and the organic layer was washed with sat. $NaHCO_3$ (2 x 50mL). The organic layer were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (8/1) to give 377 mg of **129** (1.121 mmol, 69%) as a colourless oil.

*2-[(2S,4S)-2-tert-butyl-4-[(2,5-dimethoxyphenyl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **129***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.63 (s, 1H, H-4´); 6.80 (m, 2H, H-5 and H-6); 6.71 (s, 1H, H-3); 5.11 (s, 1H, H-acetal); 3.76 (s, 3H, OCH_3-1); 3.75 (s, 3H, OCH_3-4); 3.17 (d, 1H, J = 13.9 Hz, H-1´/1); 3.09 (d, 1H, J = 13.9 Hz, H-1´/2); 2.82 (m, 2H, H-3´); 0.94 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 197.61 (CH, C-4´); 173.87 (Cq, C-5´); 153.26 (Cq, C-4); 152.12 (Cq, C-1); 122.84 (Cq, C-2); 118.00 (CH, C-3); 113.50 (CH, C-5); 111.35 (CH, C-6); 108.39 (CH, C-acetal); 79.83 (Cq, C-2´); 55.66 (CH_3, OCH_3-1 and OCH_3-4); 47.56 (CH_2, C-3´); 34.25 (Cq, C-tBuCH_3); 32.89 (CH_2, C-1´); 23.51 (CH_3, C-tBuCH_3).

(1'S,2S,5S)-2-tert-butyl-1'-hydroxy-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-4-one **135a** and (1'R,2S,5S)-2-tert-butyl-1'-hydroxy-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-4-one **135b**



129 **135a** **135b**

To a solution of **129** (200 mg, 0.595 mmol) in DCM (10 mL) cooled to –70 °C under argon atmosphere was slowly added $SnCl_4$ (153 mg, 0.595 mmol). The reaction mixture was then stirred at –70°C for 30 min. The reaction mixture was poured into 2N NaOH (50 mL) and energetically stirred for 20 min under ice cooling. The layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure at 25 °C. The crude was purified by column chromatography on silica gel with DCM / EtOAc (8 / 1) to give : 130 mg of a mixture of the 2 diastereoisomeres **135a** and **135b** (0.384 mmol, 65%, S;S;S / R;S;S : 1 / 0.65) as a light yellow solid. The mixture was partially purified by preparative tlc on silica gel with DCM / EtOAc (200/1) to give a pure sample of each diastereoisomeres.

*(1'S,2S,5S)-2-tert-butyl-1'-hydroxy-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-4-one **135a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.78 (d, 1H, J = 9.5 Hz, H-7); 7.76 (d, 1H, J = 9.5 Hz, H-6); 5.30 (s, 1H, H-acetal); 5.20 (m, 1H, H-4); 3.87 (s, 3H, OCH_3-5); 3.79 (s, 3H, OCH_3-8); 3.25 (d, 1H, J = 18.0 Hz, H-1/1); 3.23 (brs, 1H, OH-4); 2.80 (d, 1H, J = 18.0 Hz, H-1/2); 2.38 (dt, 1H, J = 3.2 Hz, 14.6 Hz, H-3/1); 2.29 (dd, 1H, J = 5.1 Hz, 14.6 Hz, H-3/2); 0.97 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 174.72 (Cq, C-9); 151.81 (Cq, C-5); 151.05 (Cq, C-8); 126.54 (Cq, C-4a); 120.66 (Cq, C-8a); 109.33 (CH, C-6); 108.73 (CH, C-7); 108.50 (CH, C-acetal); 77.86 (Cq, C-2); 61.69 (CH, C-4); 55.99 (CH_3, OCH_3-5); 55.59

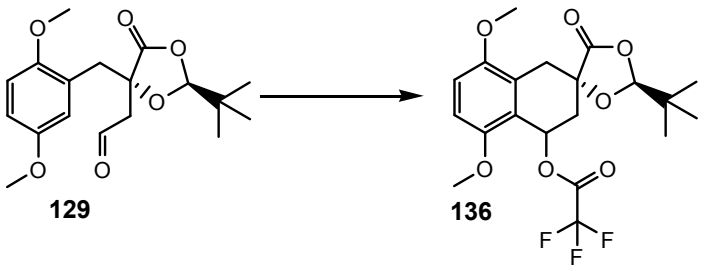
(CH_3, OCH_3-8); 35.84 (CH_2, C-3); 34.48 (Cq, C-tBuCH_3); 28.77 (CH_2, C-1); 23.43 (CH_3, C-tBuCH_3).

(1'R,2S,5S)-2-tert-butyl-1'-hydroxy-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-4-one ***135b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 6.77 (d, 1H, J = 8.9 Hz, H-6); 6.73 (d, 1H, J = 8.9 Hz, H-7); 5.26 (s, 1H, H-acetal); 5.22 (m, 1H, H-4); 4.47 (d, 1H, J = 3.5 Hz, OH-4); 3.88 (s, 3H, OCH_3-5); 3.78 (s, 3H, OCH_3-8); 3.04 (d, 1H, J = 17.7 Hz, H-1/1); 2.95 (d, 1H, J = 17.7 Hz, H-1/2); 2.37 (ddd, 1H, J = 1.9 Hz, 6.3 Hz, 13.6 Hz, H-3/1); 2.21 (dd, 1H, J = 9.2 Hz, 13.6 Hz, H-3/2); 0.95 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 174.89 (Cq, C-9); 151.66 (Cq, C-5); 151.36 (Cq, C-8); 127.35 (Cq, C-4a); 121.88 (Cq, C-8a); 108.99 (CH, C-7); 108.57 (CH, C-6); 108.42 (CH, C-acetal); 78.20 (Cq, C-2); 64.14 (CH, C-4); 55.78 (CH_3, OCH_3-5); 55.64 (CH_3, OCH_3-8); 36.57 (CH_2, C-3); 34.45 (Cq, C-tBuCH_3); 28.81 (CH_2, C-1); 23.36 (CH_3, C-tBuCH_3).

[(2S,4S)-2-tert-butyl-5',8'-dimethoxy-5-oxo-spiro[1,3-dioxolane-4,3'-tetralin]-1'-yl] 2,2,2-trifluoroacetate **136**



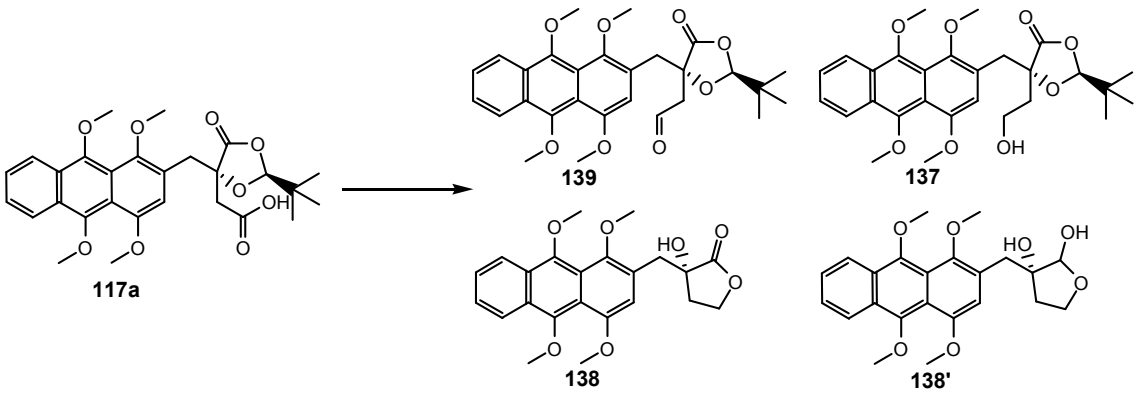
In the NMR assay from **129** was first added one drop of TFAA. NMR was measured and showed no reaction. An additional drop of TFA was then added. NMR was measured and showed complete consumption of the aldehyde. The $CDCl_3$ layer was diluted with DCM (5 mL) and poured in sat. $NaHCO_3$ (10 mL). The layers were separated and the organic layer was washed with $NaHCO_3$ (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was then analysed by NMR (500 MHz) and identified as a single diastereoisomere of **136**.

*[(2S,4S)-2-tert-butyl-5',8'-dimethoxy-5-oxo-spiro[1,3-dioxolane-4,3'-tetralin]-1'-yl] 2,2,2-trifluoroacetate **136***

^1H NMR (500 MHz, $CDCl_3$) : δ = 6.86 (d, 1H, J = 9.2 Hz, H-6); 6.76 (d, 1H, J = 9.2 Hz, H-7); 6.50 (m, 1H, H-4); 5.27 (s, 1H, H-acetal); 3.81 (s, 3H, OCH_3-8); 3.77 (s, 3H, OCH_3-5); 3.33 (d, 1H, J = 18.0 Hz, H-1/1); 2.75 (d, 1H, J = 18.0 Hz, H-1/2); 2.40 (m, 2H, H-3); 0.92 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 171.54 (Cq, C-9); 150.98 (Cq, C-8); 149.86 (Cq, C-5); 122.86 (Cq, C-4a); 119.48 (Cq, C-8a); 111.15 (CH, C-6); 108.74 (CH, C-acetal); 108.44 (CH, C-7); 75.85 (Cq, C-2); 67.04 (CH, C-4); 55.69 (CH_3, OCH_3-8); 55.65 (CH_3, OCH_3-5); 34.37 (Cq, C-tBuCH_3); 33.79 (CH_2, C-3); 27.87 (CH_2, C-1); 23.13 (CH_3, C-tBuCH_3).

2-[(2S,4S)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde **139**, (2S,5S)-2-tert-butyl-5-(2-hydroxyethyl)-5-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-one **137**, (3S)-3-hydroxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2-one **138** and (3S)-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2,3-diol **138'**



To a stirred solution of **117a** (500 mg, 0.975 mmol) in dry THF (5 mL) cooled to 2 °C under argon atmosphere, was added dropwise BH_3.THF complex 1M in THF (1.2 mL, 1.17mmol). the reaction mixture was allowed to warmed up to RT, stirred for 1 hr at RT and quenched with sat. NH_4Cl (40 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (3/1) to give in order of elution 20 mg of the aldehyde **139** (0.040 mmol, 4%) as a yellow solid foam, 242 mg of **137** (0.485 mmol, 50%) as a yellow solid foam, 72 mg of a mixture (1/1) of **137** and the l**138**, 66 mg of **138** (0.160 mmol, 16%) as a yellow solid foam and some trace of **138'**.

*2-[(2S,4S)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde **139***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.72 (s, 1H, H-4´); 8.36 (m, 2H, H-5 and H-8); 7.54 (m, 2H, H-6 and H-7); 6.55 (s, 1H, H-3); 5.13 (s, 1H, H-acetal); 4. 02 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.92 (s, 3H, OCH_3-9); 3.79 (s, 3H, OCH_3-1); 3.43 (d, 1H, J = 13.9 Hz, H-1´/1); 3.25 (d, 1H, J = 13.9 Hz, H-1´/2); 2.96 (m, 2H, H-3´); 0.94 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 197.44 (CH, C-4´); 174.17 (Cq, C-5´); 152.48 (Cq, C-4); 149.45 (Cq, C-10); 147.64 (Cq, C-1 and C-9); 127.13 (Cq, C-8a); 126.75 (Cq, C-10a); 126.43 (CH, C-6); 126.01 (CH, C-7); 122.97 (CH, C-5); 122.62 (CH, C-8); 121.39 (Cq, C-2); 120.45 (Cq, C-9a); 119.44 (Cq, C-4a); 108.76 (CH, C-acetal); 105.70 (CH, C-3); 80.27 (Cq, C-2´); 63.58 (CH_3, OCH_3-9 and OCH_3-10); 62.24 (CH_3, OCH_3-1); 56.29 (CH_3, OCH_3-4); 48.03 (CH_2, C-3´); 34.55 (Cq, C-tBuCH_3); 33.49 (CH_2, C-1´); 23.51 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{28}H_{36}O_8Na$ 551.2257; found 551.2241.

(2S,5S)-2-tert-butyl-5-(2-hydroxyethyl)-5-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-one ***137***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.60 (s, 1H, H-3); 4.94 (s, 1H, H-acetal); 4.02 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.95 (s, 3H, OCH_3-9); 3.87 (m, 2H, H-4´); 3.79 (s, 3H, OCH_3-1); 3.43 (d, 1H, J = 13.9 Hz, H-1´/1); 3.21 (d, 1H, J = 13.9 Hz, H-1´/2); 2.22 (m, 2H, H-3´); 0.92 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 175.65 (Cq, C-5´); 152.33 (Cq, C-4); 149.40 (Cq, C-10); 147.62 (Cq, C-1); 147.58 (Cq, C-9); 127.07 (Cq, C-8a); 126.64 (Cq, C-10a); 126.36 (CH, C-6); 125.91 (CH, C-7); 122.97 (CH, C-5); 122.60 (CH, C-8); 122.20 (Cq, C-2); 120.51 (Cq, C-9a); 119.39 (Cq, C-4a); 108.51 (CH, C-acetal); 105.88 (CH, C-3); 82.67 (Cq, C-2´); 63.53 (CH_3, OCH_3-9 and OCH_3-10); 62.22 (CH_3, OCH_3-1); 58.32 (CH_2, C-4´); 56.31 (CH_3, OCH_3-4); 38.19 (CH_2, C-3´); 34.36 (Cq, C-tBuCH_3); 33.87 (CH_2, C-1´); 23.51 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{28}H_{34}O_8Na$ 521.2151; found 521.2163.

(3S)-3-hydroxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2-one ***138***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.54 (s, 1H, H-3); 4.40 (m, 1H, H-4´/1); 4.23 (m, 1H, H-4´/2); 4.03 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.94 (s, 3H, OCH_3-9); 3.85 (s, 1H, OCH_3-1); 3.49 (d, 1H, J

= 13.9 Hz, H-1′/1); 2.99 (d, 1H, J = 13.9Hz, H-1′/2); 2.48 (m, 1H, H-3′/1); 2.26 (m, 1H, H-3′/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 178.55 (Cq, C-5′); 152.99 (Cq, C-4); 149.51 (Cq, C-10); 147.29 (Cq, C-9); 146.75 (Cq, C-1); 127.11 (Cq, C-8a); 126.66 (Cq, C-10a); 126.47 (CH, C-6); 125.95 (CH, C-7); 123.01 (CH, C-5); 122.69 (Cq, C-2); 122.52 (CH, C-8); 120.37 (Cq, C-9a); 119.43 (Cq, C-4a); 106.33 (CH, C-3); 75.86 (Cq, C-2′); 65.41 (CH_2, C-4′); 63.56 (CH_3, OCH_3-10); 63.42 (CH_3, OCH_3-9); 62.04 (CH_3, OCH_3-1); 56.47 (CH_3, OCH_3-4); 37.29 (CH_2, C-1′); 34.64 (CH_2, C-3′).

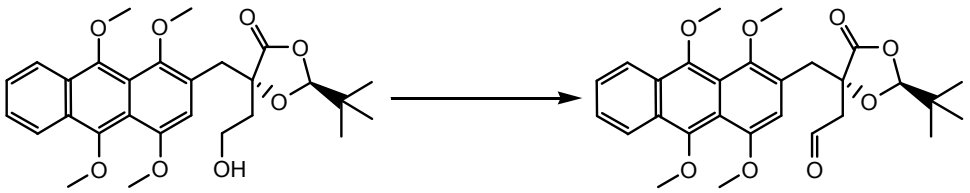
(3S)-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2,3-diol ***138'***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 652 (s, 1H, H-3); 5.14 (s, 1H, H-5′); 4.10 (m, 2H, H-4′); 4.04 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.95 (s, 3H, OCH_3-9); 3.88 (s, 3H, OCH_3-1); 3.25 (d, 1H, J = 13.5 Hz, H-1′/1); 3.00 (d, 1H, J = 13.5 Hz, H-1′/2); 2.10 (m, 1H, H-3′/1); 1.97 (m, 1H, H-3′/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 153.23 (Cq, C-4); 149.57 (Cq, C-9); 147.07 (Cq, C-10); 145.76 (Cq, C-1); 127.14 (Cq, C-8a); 126.58 (Cq, C-10a); 126.51 (CH, C-6); 125.93 (CH, C-7); 124.64 (Cq, C-2); 123.05 (CH, C-5); 122.47 (CH, C-8); 120.30 (Cq, C-9a); 119.32 (Cq, C-4a); 106.82 (CH, C-3); 100.51 (CH, C-5′); 81.03 (Cq, C-2′); 65.43 (CH_2, C-4′); 63.57 (CH_3, OCH_3-10); 63.42 (CH3, OCH_3-9); 61.93 (CH_3, OCH_3-1); 56.47 (CH_3, OCH_3-4); 39.03 (CH_2, C-1′); 37.56 (CH_2, C-3′).

HRMS (ESI) : calcd. For $C_{23}H_{26}O_7Na$ 437.1576; found 437.1572.

2-[(2S,4S)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde **139**



137 **139**

To a solution of DMSO (0.16 mL, 2.207 mmol) in DCM (13 mL) cooled to –70 °C under argon atmosphere was added dropwise oxalylchloride (0.10 mL, 1.103 mmol) and the reaction mixture was stirred for 1 hr at –70°C. **137** (0.5 g, 1.003 mmol) in DCM (2 mL) was slowly added at –70°C and the reaction mixture was stirred for 1 hr. Et_3N (0.7 mL, 5.015 mmol) was then added at that temperature and stirring was continue for 1hr allowing the temperature to warmed up slowly to 0°C. The reaction mixture was then poured in brine (40 mL) / DCM (30 mL). The layers were separated and the organic layer was successively washed with sat. NH_4Cl (40 mL), sat. $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (6/1) to give 0.42 g of **139** (0.851 mmol, 85%) as a yellow solid foam.

*2-[(2S,4S)-2-tert-butyl-5-oxo-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde **139***

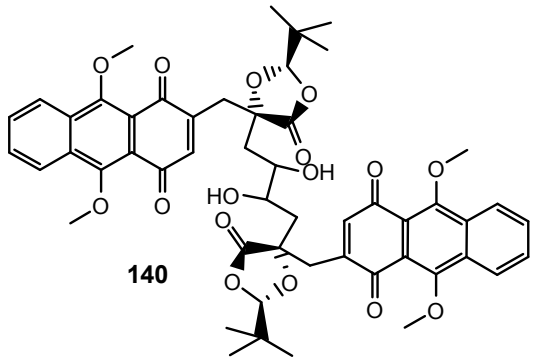
^1H NMR (500 MHz, $CDCl_3$) : δ = 9.72 (s, 1H, H-4´); 8.36 (m, 2H, H-5 and H-8); 7.54 (m, 2H, H-6 and H-7); 6.55 (s, 1H, H-3); 5.13 (s, 1H, H-acetal); (4. 02 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.92 (s, 3H, OCH_3-9); 3.79 (s, 3H, OCH_3-1); 3.43 (d, 1H, J = 13.9 Hz, H-1´/1); 3.25 (d, 1H, J = 13.9 Hz, H-1´/2); 2.96 (m, 2H, H-3´); 0.94 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 197.44 (CH, C-4´); 174.17 (Cq, C-5´); 152.48 (Cq, C-4); 149.45 (Cq, C-10); 147.64 (Cq, C-1 and C-9); 127.13 (Cq, C-8a); 126.75 (Cq, C-10a); 126.43 (CH, C-6); 126.01 (CH, C-7); 122.97 (CH, C-5); 122.62 (CH, C-8); 121.39 (Cq, C-2); 120.45 (Cq, C-9a); 119.44 (Cq, C-4a); 108.76 (CH, C-acetal);

105.70 (CH, C-3); 80.27 (Cq, C-2´); 63.58 (CH_3, OCH_3-9 and OCH_3-10); 62.24 (CH_3, OCH_3-1); 56.29 (CH_3, OCH_3-4); 48.03 (CH_2, C-3´); 34.55 (Cq, C-tBuCH_3); 33.49 (CH_2, C-1´); 23.51 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{28}H_{36}O_8Na$ 551.2257; found 551.2257.

2-[[(2R,4S)-2-tert-butyl-4-[4-[(2R,4S)-2-tert-butyl-4-[(9,10-dimethoxy-1,4-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]-2,3-dihydroxy-butyl]-5-oxo-1,3-dioxolan-4-yl]methyl]-9,10-dimethoxy-anthracene-1,4-dione **140**



140

To a solution of **139** (80 mg, 0.16 mmol) in DCM (4 mL) cooled at -40 °C under argon atmosphere was added TFA (0.12 mL, 0.19 mmol). The reaction mixture was stirred for 2 hr at -40 °C and poured in sat. $NaHCO_3$ (20 mL) / DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (6/1) to give 22 g of **140** (0.024 mmol, 15%) as a yellow solid foam.

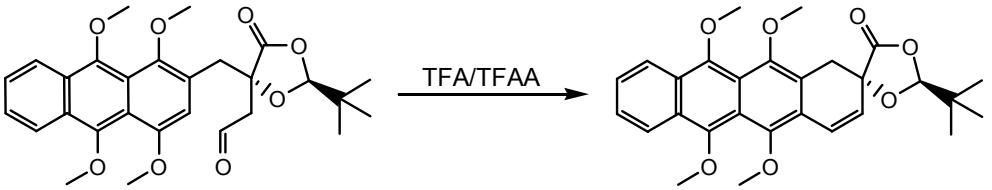
*2-[[(2R,4S)-2-tert-butyl-4-[4-[(2R,4S)-2-tert-butyl-4-[(9,10-dimethoxy-1,4-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]-2,3-dihydroxy-butyl]-5-oxo-1,3-dioxolan-4-yl]methyl]-9,10-dimethoxy-anthracene-1,4-dione **140***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.36 (d, 2H, J = 7.9 Hz, H-5); 8.12 (d, 2H, J = 8.5 Hz, H-8); 7.66 (m, 2H, H-6); 7.60 (m, 2H, H-7); 6.55 (s, 2H, H-3); 5.47 (s, 2H, H-acetal); 5.33 (m, 2H, H-4´); 4.50 (d, 2H, J = 11.7 Hz, OH-4´); 4.03 (s, 6H, OCH_3); 4.02 (s, 6H, OCH_3); 2.99 (m, 2H, H-1´/1); 2.82 (m, 4H, H-1´/2 and H-3´/1); 2.20 (m, 2H, H-3´/2); 1.00 (s, 18H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.52 (Cq, C-4); 176.07 (Cq, C-1); 151.16 (Cq, C-9); 149.64 (Cq, C-10); 135.33 (Ch, C-3); 131.55 (Cq, C-8a); 130.34 (Cq, C-10a); 128.93 (CH, C-6); 127.92 8Cq, C-9a); 127.58 (Cq, C-4a); 127.14 (Ch, C-7); 124.68

(CH, C-5); 123.05 (CH, C-8); 121.71 (Cq, C-2); 109.78 (CH, C-acetal); 80.73 (Cq, C-2´); 71.14 (CH, C-4´); 62.91 (CH_3, OCH_3); 62.71 (CH_3, OCH_3); 37.44 (CH_2, C-1´); 34.61 (CH_2, C-3´); 34.56 (Cq, C-tBu); 23.18 (CH_3, C-tBuCH_3).

(2S,5S)-2-tert-butyl-5',6',11',12'-tetramethoxy-spiro[1,3-dioxolane-5,2'-1H-tetracene]-4-one **142**



139 **142** Isolated product from complex mixture

To a solution of **139** (20 mg, 0.040 mmol) in DCM (4 mL) cooled to –70 °C under argon atmosphere was added TFAA (0.2 mL) and TFA (0.2 mL). The reaction mixture was allowed to warmed up to 0 °C and stirred for 2 hrs. The reaction mixture was poured in sat $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a complex mixture of product. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (50/1) and only 1 product was isolated in 9% yield.

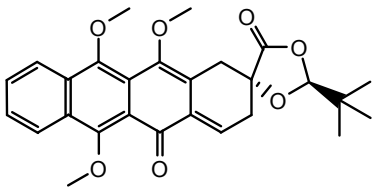
*(2S,5S)-2-tert-butyl-5',6',11',12'-tetramethoxy-spiro[1,3-dioxolane-5,2'-1H-tetracene]-4-one **142***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-1 and H-4); 7.54 (m, 2H, H-2 and H-3); 7.42 (d, 1H, J = 9.8 Hz, H-7); 5.95 (d, 1H, J = 9.8 Hz, H-8); 5.43 (s, 1H, H-acetal); 4.00 (s, 3H, OCH_3-5); 3.99 (s, 3H, OCH_3-12); 3.90 (s, 3H, OCH_3-6); 3.82 (s, 3H, OCH_3-11); 3.57 (d, 1H, J = 16.4 Hz, H-10/1); 3.41 (d, 1H, J = 16.4 Hz, H-10/2); 1.01 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 173.96 (Cq, C-13); 149.02 (Cq, C-5); 148.76 (Cq, C-6 and C-11); 147.93 (Cq, C-12); 127.72 (CH, C-7); 127.21 (Cq, C-4a); 126.81 (Cq, C-12a); 126,39 (CH, C-3); 126.16 (CH, C-2); 124.41 (CH, C-8); 122.79 (CH, C-4); 122.75 (CH, C-1); 121.24 (Cq, C-6a); 120.85 (Cq, C-5a); 120.47 (Cq, C-11a); 119.41 (Cq, C-10a); 108.24 (CH, C-acetal); 77.48 (Cq, C-9); 63.74 (CH_3, OCH_3-5); 63.64 (CH_3, OCH_3-12); 63.19 (CH_3, OCH_3-6); 61.66 (CH_3, OCH_3-11); 34.57 (Cq, C-tBuCH_3); 28.45 (CH_2, C-10); 23.38 (CH_3, C-tBuCH_3).

Products isolated from attempts to cyclize **139** with various lewis acid :

(2R,2'S)-2'-tert-butyl-6,11,12-trimethoxy-spiro[1,3-dihydrotetracene-2,5'-1,3-dioxolane]-4',5-dione **143**



143

To a solution of **139** (50 mg, 0.10 mmol) in DCM (3 mL) cooled at -40 °C under argon atmosphere was added $BF_3.Et_2O$ (3 mg, 0.02 mmol). The reaction mixture was stirred overnight at -25 °C and poured in sat. $NaHCO_3$ (20 mL) / DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with PE / MTBE (6/1) to give 9 mg of **143** (0.019 mmol, 19%) as a yellow solid foam.

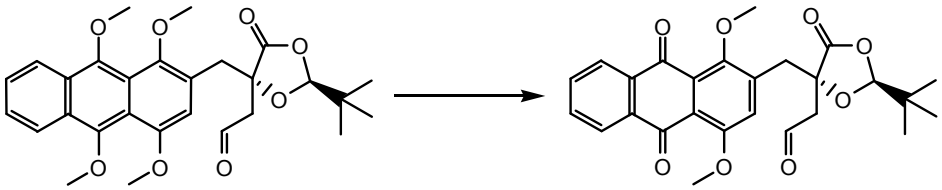
*(2R,2'S)-2'-tert-butyl-6,11,12-trimethoxy-spiro[1,3-dihydrotetracene-2,5'-1,3-dioxolane]-4',5-dione **143***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.32 (d, 1H, J = 8.2 Hz, H-4); 8.20 (d, 1H, J = 8.5 Hz, H-1); 7.62 (m, 2H, H-2 and H-3); 7.12 (dd, 1H, J = 3.8 Hz, 5.5 Hz, H-7); 5.34 (s, 1H, H-acetal); 4.04 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 3.24 (d, 1H, J = 16.1 Hz, H-10/1); 2.99 (dd, 1H, J = 3.8 Hz, 20.2 Hz, H-8/1); 2.75 (d, 1H, J = 16.1 Hz, H-10/2); 2.71 (dd, 1H, J = 5.5 Hz, 20.1 Hz, H-8/2); 0.96 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 174.28 (Cq, C-6 and C-13); 159.69 (Cq, C-5); 159.34 (Cq, C-12); 159.19 (Cq, C-11); 133.14 (CH, C-7); 129.70 (CH, C-3); 127.41 (CH, C-2); 124.76 (CH, C-4); 122.98 (CH, C-1); 108.13 (CH, C-acetal); 63.33 (CH_3, OCH_3); 62.68 (CH_3, OCH_3); 60.43 (CH_3, OCH_3); 34.35 (CH_2, C-8); 34.32 (Cq, C-tBu); 26.77 (CH_2, C-10); 23.32 (CH_3, C-tBuCH_3).

2-[(2S,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **144**

From **139**



139 **144**

139 (0.32 g, 0.642 mmol) was dissolved in CH_3CN (5 mL) and cooled to 2 °C. CAN (1.06 g, 2.543 mmol) in water (13 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 20 min and then at RT for 1 hr. The reaction mixture was diluted with water (30 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene/ EtOAc (3/1) to give 0.22 g of **144** (0.476 mmol, 74%) as a yellow solid foam.

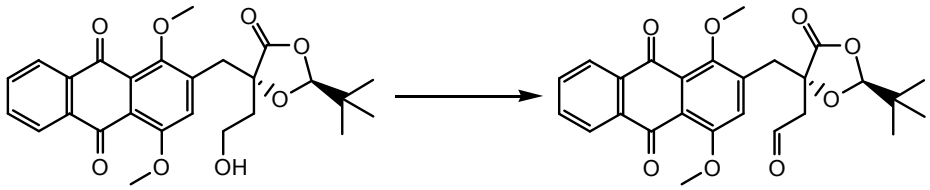
*2-[(2S,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **144***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.64 (dd, 1H, J = 0.7 Hz, 2.5 Hz, H-4´); 8.18 (m, 2H, H-5 and H-8); 7.75 (m, 2H, H-6 and H-7); 7.22 (s, 1H, H-3); 5.14 (s, 1H, H-acetal); 3.99 (s, 3H, OCH_3-4); 3.91 (s, 3H, OCH_3-1); 3.39 (d, 1H, J = 13.9 Hz, H-1´/1); 3.31 (d, 1H, J = 13.9 Hz, H-1´/2); 2.97 (dd, 1H, J = 0.7 Hz, 17.4 Hz, H-3´/1); 2.85 (dd, 1H, J = 2.5 Hz, 17.4 Hz, H-3´/2); 0.96 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 196.36 (CH, C-4´); 183.11 (Cq, C-9); 182.82 (Cq, C-10); 173.32 (Cq, C-5´); 155.88 (Cq, C-4); 152.95 (Cq, C-1); 137.03 (Cq, C-2); 134.20 (Cq, C-8a); 133.81 (CH, C-6); 133.72 (Cq, C-10a); 133.48 (CH, C-7); 127.31 (Cq, C-9a); 126.59 (CH, C-5); 126.51 (CH, C-8); 122.64 (Cq, C-4a); 121.71 (CH, C-3); 108.58 (CH, C-acetal); 79.55 (Cq, C-2´); 62.66 (CH_3, OCH_3-1); 56.72 (CH_3, OCH_3-4); 47.49 (CH_2, C-3´); 34.45 (Cq, C-tBu); 32.80 (CH_2, C-1´); 23.56 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{27}H_{30}O_8Na$ 521.1788; found 521.1794.

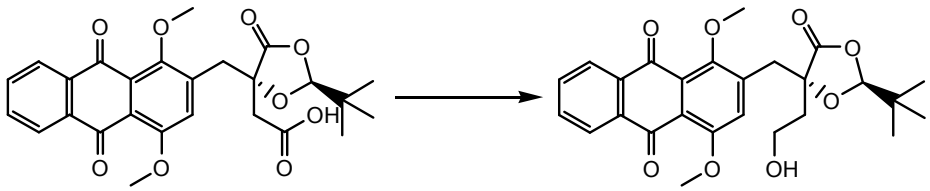
From **228**



228 **144**

To a solution of DMSO (0.04 mL, 0.512 mmol) in DCM (5 mL) cooled to –70 °C under argon was added dropwise oxalylchloride (0.03 mL, 0.282 mmol) and the reaction mixture was stirred for 1 hr at –70°C. **228** (120 mg, 0.256 mmol) in DCM (2 mL) was slowly added at –70°C and the reaction mixture was stirred for 1 hr. Et_3N (0.18 mL, 1.28 mmol) was then added at that temperature and stirring was continue for 1hr allowing the temperature to warmed up slowly to 0°C. The reaction mixture was then poured in brine (20 mL) / DCM (20 mL). The layers were separated and the organic layer was successively washed with sat. NH_4Cl (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 82 mg of **144** (0.176 mmol, 69%). The aldehyde was pure enough to be used in the next step.

2-(((2S,4S)-2-(tert-butyl)-4-(2-hydroxyethyl)-5-oxo-1,3-dioxolan-4-yl)methyl)-1,4-dimethoxyanthracene-9,10-dione **228**



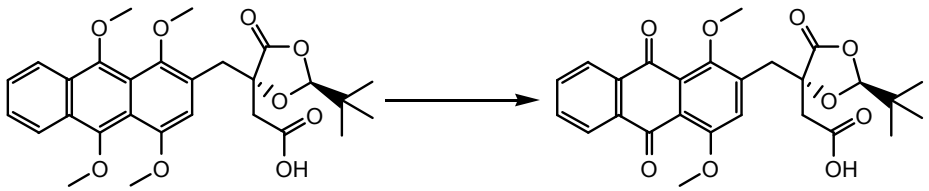
145 **228**

To a stirred solution of **145** (450 mg, 0.933 mmol) in dry THF (5 mL) cooled to 2 °C under argon atmosphere, was added dropwise BH_3.THF complex 1M in THF (1.1 mL, 1.120 mmol). the reaction mixture was allowed to warmed up to RT, stirred for 1 hr at RT and quenched with sat. NH_4Cl (40 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (1/1) to give 230 mg of the **228** (0.49 mmol, 53%) as a yellow solid foam.

*2-(((2S,4S)-2-(tert-butyl)-4-(2-hydroxyethyl)-5-oxo-1,3-dioxolan-4-yl)methyl)-1,4-dimethoxyanthracene-9,10-dione **228***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 8.18 (m, 2H, H-5 and H-8); 7.74 (m, 2H, H-6 and H-7); 7.26 (s, 1H, H-3); 5.02 (s, 1H, H-acetal); 3.99 (s, 3H, OCH_3-4); 3.91 (s, 3H, OCH_3-10); 3.81 (m, 2H, H-4´); 3.42 (d, 1H, J = 13.9 Hz, H-1´/1); 3.11 (d, 1H, J = 13.9 Hz, H-1´/2); 2.13 (m, 2H, H-3´); 0.97 (s, 9H, H-tBuCH_3).

2-[(2S,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **145**



117a (0.99 g, 1.93 mmol) was dissolved in CH_3CN (16 mL) and cooled to 2 °C. CAN (3.17 g, 5.79 mmol) in water (40 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 20 min and then at RT for 1 hr. The reaction mixture was diluted with water (60 mL) and the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 0.87 g of **145** (1.803 mmol, 93%) as a yellow solid. The product was pure enough for the next step.

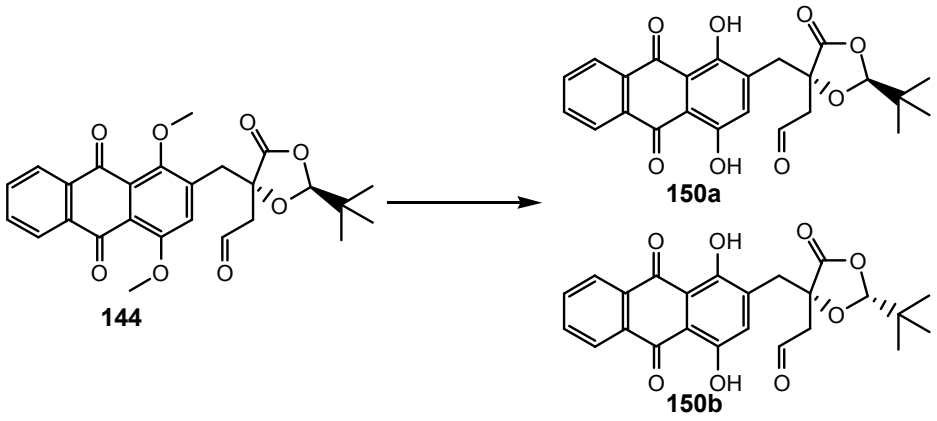
*2-[(2S,4S)-2-tert-butyl-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **145***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.74 (m, 2H, H-6 and H-7); 7.24 (s, 1H, H-3); 5.09 (s, 1H, H-acetal); 3.98 (s, 3H, OCH_3-4); 3.90 (s, 3H, OCH_3-1); 3.42 (d, 1H, J = 13.9 Hz, H-1´/1); 3.13 (d, 1H, J = 13.9 Hz, H-1´/2); 2.98 (d, 1H, J = 16.4 Hz, H-3´/1); 2.72 (d, 1H, J = 16.4 Hz, H-3´/2); 0.94 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.14 (Cq, C-9); 182.87 (Cq, C-10); 173.20 (Cq, C-5´); 171.98 (Cq, C-4´); 155.88 (Cq, C-4); 153.04 (Cq, C-1); 137.21 (Cq, C-2); 134.22 (Cq, C-8a); 133.76 (Cq, C-10a and CH, C-6); 133.45 (CH, C-7); 127.30 (Cq, C9a); 126.58 (CH, C-5); 126.51 (CH, C-8); 122.59 (Cq, C-4a); 121.75 (CH, C-3); 108.22 (CH, C-acetal); 80.33 (Cq, C-2´); 62.65 (CH_3, OCH_3-1); 56.72 (CH_3, OCH_3-4); 38.93 (CH_2, C-3´); 34.39 (Cq, C-tBuCH_3); 32.35 (CH_2, C-1´); 23.59 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{26}H_{26}O_8Na$ 505.1475; found 505.1475.

2-[(2S,4S)-2-tert-butyl-4-[(1,4-dihydroxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **150a** and 2-[(2R,4S)-2-tert-butyl-4-[(1,4-dihydroxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **150b**



To a solution of **144** (180 mg, 0.386 mmol) in DCM (15 mL) cooled to –45 °C under argon atmosphere was slowly added BCl_3 1M in DCM (1.85 mL, 1.853 mmol). The reaction mixture was stirred at –45 °C for 1 h 30 and quenched with water (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 160 mg of a mixture of **150a** and **150b** (1/1) (0.365 mmol, 95%) as a red solid. The product is not stable on tlc and was pure enough to be used in next step.

*2-[(2S,4S)-2-tert-butyl-4-[(1,4-dihydroxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde **150a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.45 (s, 1H, OH-1); 12.81 (s, 1H, OH-4); 9.67 (d, 1H, J = 2.8 Hz, H-4´); 8.36 (m, 2H, H-5 and H-8); 7.86 (m, 2H, H-6 and H-7); 7.21 (s, 1H, H-3); 5.40 (s, 1H, H-acetal); 3.27 (s, 2H, H-1´); 2.94 (m, 2H, H-3´); 0.98 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 196.52 (CH, C-4´); 187.28 (Cq, C-9); 186.67 (Cq, C-10); 173.06 (Cq, C-5´); 156.74 (Cq, C-4); 156.70 (Cq, C-1); 135.18 (Cq, C-2); 134.74 (CH, C-6); 134.71 (CH, C-7); 133.41 (Cq, C-8a); 133.24 (Cq, C-10a); 130.94 (CH, C-3); 127.18 (CH, C-5); 127,07 (CH, C-8); 112.67 (Cq, C-4a); 112.62 (Cq, C-

9a); 108.46 (CH, C-acetal); 79.22 (Cq, C-2´); 47.11 (CH_2, C-3´); 34.31 (Cq, C-tBuCH_3); 31.85 (CH_2, C-1´); 23.58 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{25}H_{26}O_9Na$ 493.1475; found 493.1471. (M+MeOH+Na)

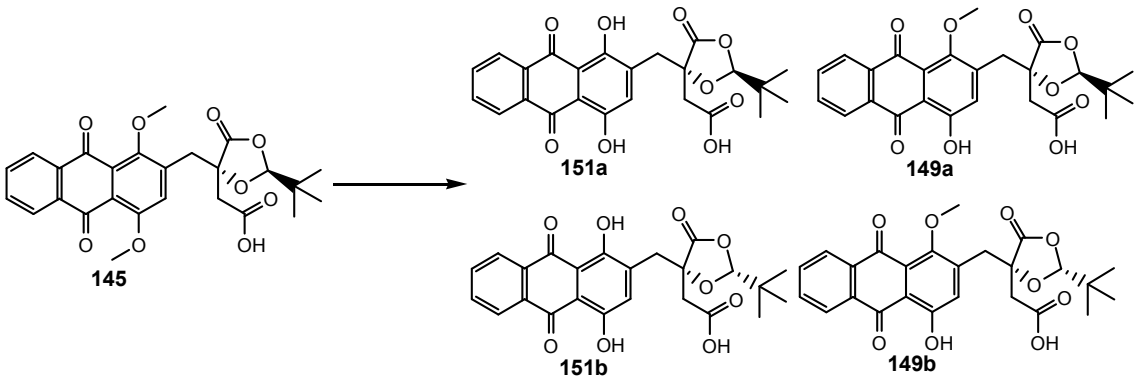
2-[(2R,4S)-2-tert-butyl-4-[(1,4-dihydroxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetaldehyde ***150b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.49 (s, 1H, OH-1); 12.81 (s, 1H, OH-4); 9.68 (s, 1H, H-4´); 8.36 (m, 2H, H-5 and H-8); 7.86 (m, 2H, H-6 and H-7); 7.37 (s, 1H, H-3); 5.37 (s, 1H, H-acetal); 3.61 (d, 1H, J = 14.2 Hz, H-1´/1); 3.19 (d, 1H, J = 18.6 Hz, H-3´/1); 2.98 (d, 1H, J = 18.6 Hz, H-3´/2); 2.93 (d, 1H, J = 14.2 Hz, H-1´/2); 1.00 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 197.80 (CH, C-4´); 187.28 (Cq, C-9); 186.67 (Cq, C-10); 173.52 (Cq, C-5´); 156.88 (Cq, C-1); 156.64 (Cq, C-4); 136.00 (Cq, C-2); 134.74 (CH, C-6); 134.71 (CH, C-7); 133.41 (Cq, C-8a); 133.24 (Cq, C-10a); 131.02 (CH, C-3); 127.18 (CH, C-5); 127,07 (CH, C-8); 112.67 (Cq, C-4a); 112.62 (Cq, C-9a); 110.24 (CH, C-acetal); 77.98 (Cq, C-2´); 48.38 (CH_2, C-3´); 36.08 (CH_2, C-1´); 34.58 (Cq, C-tBuCH_3); 23.65 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{25}H_{26}O_9Na$ 493.1475; found 493.1471. (M+MeOH+Na)

2-[(2S,4S)-2-tert-butyl-4-[(4-hydroxy-1-methoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **149a**, 2-[(2R,4S)-2-tert-butyl-4-[(1,4-dihydroxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **151a**, 2-[(2R,4S)-2-tert-butyl-4-[(4-hydroxy-1-methoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **149b**



To a solution of **145** (100 mg, 0.207 mmol) in DCM (5 mL) cooled to 0 °C under argon atmosphere was slowly added BCl_3 1M in DCM (0.31 mL, 0.311 mmol). The reaction mixture was stirred at 0 °C for 2 h 30 and quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give in order of elution 8 mg of **151a** (0.018mmol, 9%), 47 mg of **149a** (0.100 mmol, 48%), 5 mg of **151b** (0.011 mmol, 5%) and 29 mg of **149b**(0.062 mmol, 30%).

*2-[(2S,4S)-2-tert-butyl-4-[(4-hydroxy-1-methoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid **149a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.05 (s, 1H, OH-4); 8.28 (m, 2H, H-5 and H-8); 7.81 (m, 2H, H-6 and H-7); 7.20 (s, 1H, H-3); 5.21 (s, 1H, H-acetal); 3.88 (s, 3H, OCH_3-1); 3.31 (d, 1H, J = 13.9 Hz, H-1´/1); 3.13 (d, 1H, J = 13.9 Hz, H-1´/2); 3.00 (d, 1H, J = 16.4 Hz, H-3´/1); 2.71 (d, 1H, J = 16.4 Hz, H-3´/2); 0.96 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 188.43 (Cq, C-10); 181.65 (Cq, C-9); 173.08 (Cq, C-5´); 172.46 (Cq, C-4´); 158.97 (Cq, C-4); 153.38 (Cq, C-1); 140.31 (Cq, C-2); 134.90 (CH, C-6); 134.62 (Cq, C-8a); 133.78 (CH, C-7); 132.31 (Cq, C-10a); 128.14

(CH, C-3); 127.43 (CH, C-5); 126.49 (CH, C-8); 123.79 (Cq, C-9a); 115.78 (Cq, C-4a); 108.11(CH, C-acetal); 80.04 (Cq, C-2´); 62.21 (CH_3, OCH_3-1); 38.63 (CH_2, C-3´); 34.34 (Cq, C-tBuCH_3); 32.01 (CH_2, C-1´); 23.63 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{25}H_{24}O_9$ 469.1499; found 469.1503 (MH+) .

2-[(2R,4S)-2-tert-butyl-4-[(1,4-dihydroxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid ***151b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.47 (s, 1H, OH-1); 12.83 (s, 1H, OH-4); 8.37 (m, 2H, H- and H-8); 7.86 (m, 2H, H-6 and H-7); 7.39 (s, 1H, H-3); 5.37 (s, 1H, H-acetal); 3.62 (d, 1H, J = 13.9 Hz, H-1´/1); 3.15 (d, 1H, J = 17.5 Hz, H-3´/1); 2.93 (d, 1H, J = 13.9 Hz, H-1´/2); 2.78 (d, 1H, J = 17.5 Hz, H-3´/2); 1.01 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 187.24 (Cq, C-9); 186.68 (Cq, C-10); 173.52 (Cq, C-5´); 172.47 (Cq, C-4´); 156.88 (Cq, C-4); 156.74 (Cq, C-1); 135.99 (Cq, C-2); 134.68 (CH, C-6); 134.59 (CH, C-7); 133.45 (Cq, C-8a); 133.32 (Cq, C-10a); 127.19 (CH, C-5); 127.04 (CH, C-8); 112.60 (Cq, C-4a); 112.44 (Cq, C-9a); 110.68 (CH, C-acetal); 79.21 (Cq, C-2´); 38.97 (CH_2, C-3´); 36.22 (CH_2, C-1´); 34.68 (Cq, C-tBuC); 23.69 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{24}H_{22}O_9Na$ 477.1162; found 477.1167.

2-[(2R,4S)-2-tert-butyl-4-[(4-hydroxy-1-methoxy-9,10-dioxo-2-anthryl)methyl]-5-oxo-1,3-dioxolan-4-yl]acetic acid ***149b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.04 (s, 1H, OH-4); 8.28 (m, 2H, H-5 and H-8); 7.81 (m, 2H, H-6 and H-7); 7.40 (s, 1H, H-3); 5.37 (s, 1H, H-acetal); 3.87 (s, 3H, OCH_3-1); 3.57 (d, 1H, J = 13.9 Hz, H-1´/1); 3.04 (d, 1H, J = 17.5 Hz, H-3´/1); 2.92 (d, 1H, J = 13.9 Hz, H-1´/2); 2.67 (d, 1H, J = 16.4 Hz, H-3´/2); 0.98 (s, 9H, H-tBuCH_3).

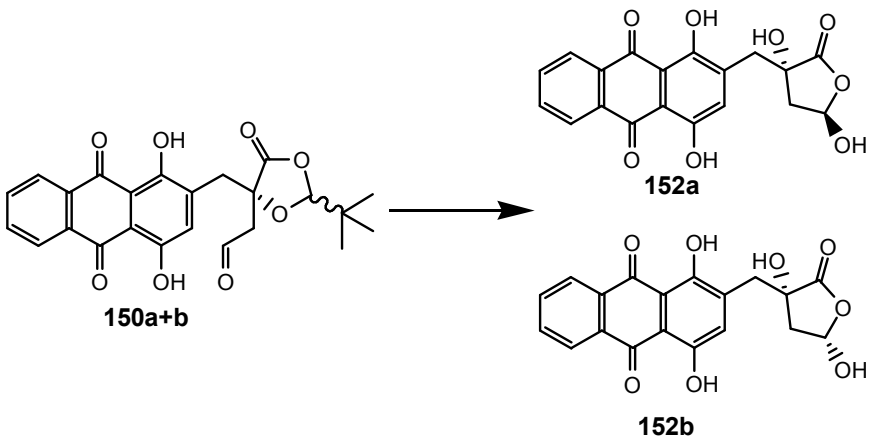
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 188.38 (Cq, C-10); 181.74 (Cq, C-9); 174.09 (Cq, C-5´); 173.15 (Cq, C-4´); 159.10 (Cq, C-4); 153.28 (Cq, C-1); 141.27 (Cq, C-2); 134.85 (CH, C-6); 134.62 (Cq, C-8a); 133.76 (CH, C-7); 132.32 (Cq, C-10a); 127.89 (CH, C-3); 127.45 (CH, C-5); 126.47 (CH, C-8); 123.85 (Cq, C-9a); 115.61 (Cq, C-

4a); 110.56 (CH, C-acetal); 79.57 (Cq, C-2´); 62.08 (CH_3, OCH_3-1); 36.65 (CH_2, C-3´); 34.62 (CH_2, C-1´); 31.91 (Cq, C-tBuCH_3); 23.65 (CH_3, C-tBuCH_3).

HRMS (ESI) : calcd. For $C_{25}H_{24}O_9$ 469.1499; found 468.1503

NB : using 4.5 eq of BCl_3 instead of 1.5 under the same condition led after purification to **151a** and **151b** in 90% yield.

2-[[(3S,5R)-3,5-dihydroxy-2-oxo-tetrahydrofuran-3-yl]methyl]-1,4-dihydroxy-anthracene-9,10-dione **152a**, 2-[[(3S,5S)-3,5-dihydroxy-2-oxo-tetrahydrofuran-3-yl]methyl]-1,4-dihydroxy-anthracene-9,10-dione **152b**



A solution of $Na_2S_2O_4$ (0.12 g, 0.684 mmol) in water (3 mL) was added dropwise at -10 °C to a solution of **150a+b** (0.10 g, 0.228 mmol) in THF (5 mL) / MeOH (5 mL) under an argon atmosphere. Sat. $NaHCO_3$ (3 mL) was then added at -10 °C and the reaction mixture was stirred for 1 hr 30. The reaction mixture was quenched at -10 °C by bubbling air through it for 30 min. The reaction mixture was then poured in 0.05 N HCl (15 mL) / EtOAc (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / isopropanol (15 / 1) to give 40 mg of **150a+b** (0.108 mmol, 47 %) as a red solid.

*2-[[(3S,5R)-3,5-dihydroxy-2-oxo-tetrahydrofuran-3-yl]methyl]-1,4-dihydroxy-anthracene-9,10-dione **152a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.71 (s, 1H, OH-1); 12.85 (s, 1H, OH-4); 8.48 (m, 2H, H-5 and H-8); 7.79 (m, 2H, H-6 and H-7); 7.35 (s, 1H, H-3); 5.42 (dd, 1H, J = 3.8 Hz, 5.4 Hz, H-4´); 3.28 (d, 1H, J = 13.9 Hz, H-1´/1); 3.11 (d, 1H, J = 13.9 Hz, H-1´/2); 2.64 (dd, 1H, J = 5.4 Hz, 14.2 Hz, H-3´/1); 2.14 (dd, 1H, J = 3.8 Hz, H-3´/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 192.54 (Cq, C-9 and C-10); 186.59 (Cq, C-5´); 157.67 (Cq, C-4); 156.43 (Cq, C-1); 137.05 (Cq, C-2); 133.51 (Cq, C-8a and C-10a);

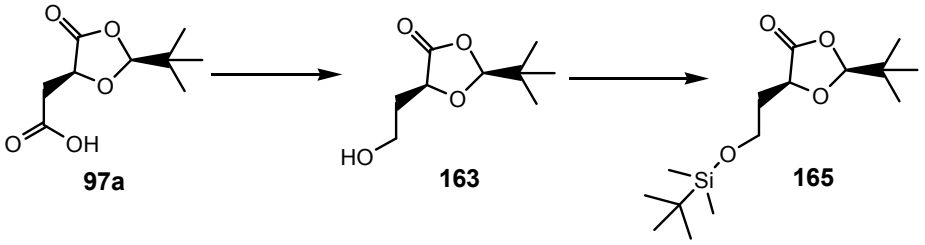
131.77 (CH, C-6); 131.13 (CH, C-3); 130.89 (CH, C-7); 124.97 (CH, C-5 and C-8); 113.56 (Cq, C-4a); 112.64 (Cq, C-9a); 103.01 (CH, C-4´); 40.81 (CH_2, C-3´); 36.05 (CH_2, C-1´).

2-[[(3S,5S)-3,5-dihydroxy-2-oxo-tetrahydrofuran-3-yl]methyl]-1,4-dihydroxy-anthracene-9,10-dione ***152b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.56 (s, 1H, OH-1); 12.82 (s, 1H, OH-4); 8.35 (m, 2H, H-5 and H-8); 7.85 (m, 2H, H-6 and H-7); 7.27 (s, 1H, H-3); 5.46 (dd, 1H, J = 2.3 Hz, 4.8 Hz, H-4´); 3.64 (d, 1H, J = 13.9 Hz, H-1´/1); 3.09 (d, 1H, J = 13.9 Hz, H-1´/2); 2.43 (m, 2H, H-3´).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 192.54 (Cq, C-9 and C-10); 186.59 (Cq, C-5´); 157.67 (Cq, C-4); 156.43 (Cq, C-1); 137.70 (Cq, C-2); 134.79 (CH, C-6); 134.60 (CH, C-7); 133.51 (Cq, C-8a and C-10a);131.13 (CH, C-3); 127.08 (CH, C-5 and C-8); 113.56 (Cq, C-4a); 112.64 (Cq, C-9a); 102.38 (CH, C-4´); 40.37 (CH_2, C-3´); 38.20 (CH_2, C-1´).

(2S,5S)-2-tert-butyl-5-[2-(tert-butyl(dimethyl)silyl)oxyethyl]-1,3-dioxolan-4-one **165**



97a (40 g, 0.198 mol) was dissolved in THF (300 mL) under argon atmosphere and cooled to 0°C. BH_3.THF complex 1M in THF (238 mL, 0.238 mol) was slowly added during 1 hr (the temperature did not raise 5 °C). After complete addition of the reagent, the reaction mixture was stirred 20 min at 0 °C and then allowed to warm to RT and stirred for 3 h 30. The reaction mixture was poured in sat. NH_4Cl (600 mL) / EtOAc (600 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 x 300 mL), brine (300 mL) and then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **163** (32 g) which was directly used without further purification in the next step.

*(2S,5S)-2-tert-butyl-5-(2-hydroxyethyl)-1,3-dioxolan-4-one **163***

^{1}H NMR (500 MHz, d6-DMSO) : δ = 5.40 (s, 1H, H-5); 4.66 (t, 1H, J = 5.4 Hz, OH-1); 4.55 (dd, 1H, J = 4.1 Hz, 8.2 Hz, H-3); 3.53 (m, 2H, H-1); 1.92 (m, 1H, H-2/1); 1.72 (m, 1H, H-2/2); 0.91 (s, 9H, H-tBuCH_3).

^{13}C NMR (500 MHz, d6-DMSO) : δ = 173.74 (Cq, C-4); 108.27 (CH, C-5); 71.54 (CH, C-3); 56.32 (CH_2, C-1); 33.69 (Cq, C-tBu); 33.62 (CH_2, C-2); 23.16 (CH_3, C-tBuCH_3).

TBDMSCl (43 g, 0.285 mol) was dissolved in DCM (500 mL) and pyridine (45.1 g, 0.57 mol) was added. The solution was stirred for 10 min and **163** in DCM (100 mL) was added. The reaction mixture was stirred at RT for 16 hrs and then poured in water (500 mL). The layers were separated and the organic layer was washed with 5% aqueous $NaHCO_3$ (200 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica

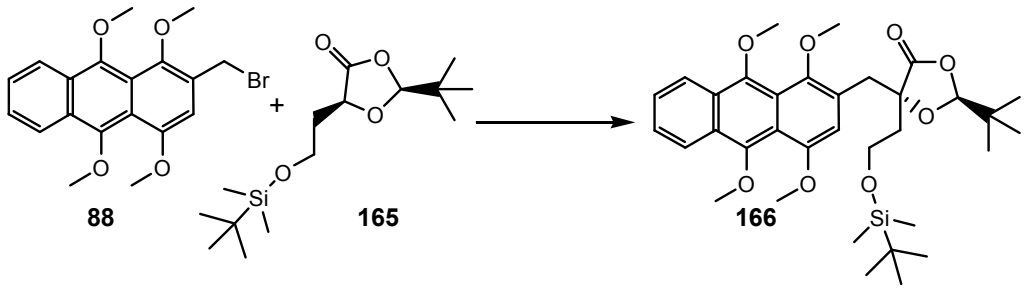
gel with toluene to give 52.3 g of **165** (0.173 mol, 87% overall yield) as a colourless oil.

*(2S,5S)-2-tert-butyl-5-[2-(tert-butyl(dimethyl)silyl)oxyethyl]-1,3-dioxolan-4-one **165***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 5.15 (s, 1H, H-5); 4.43 (dd, 1H, 3.8 Hz, 8.5 Hz, H-3); 3.80 (m, 2H, H-1); 2.12 (m, 1H, H-2/1); 1.86 (m, 1H, H-2/2); 0.97 (s, 9H, H-tBuCH_3); 0.89 (s, 9H, H-SitBuCH_3); 0.06 (s, 6H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ =173.95 (Cq, C-4); 109.43 (CH, C-5); 71.74 (CH, C-3); 58.40 (CH_2, C-1); 34.21 (Cq, C-tBu); 33.97 (CH_2, C-2); 25.86 (CH_3, C-SitBuCH_3); 23.40 (CH_3, C-tBuCH_3); 18.29 (Cq, C-SitBu); -5.41 (CH_3, C-SiCH_3); -5.51 (CH_3, C-SiCH_3).
HRMS (ESI) : calcd. For $C_{15}H_{30}O_4SiNa$ 325.1811; found 325.1810.

(2S,5S)-2-tert-butyl-5-[2-(tert-butyl(dimethyl)silyl)oxyethyl]-5-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-one **166**



KHMDS (18.0 g, 0.09 mol) was dissolved in dry THF (680 mL) under argon and cooled to –76°C. **165** (25.6 g, 0.085 mol) in THF (30 mL) was added dropwise (the temperature did not raise –72°C) and the mixture was stirred for 50 min at –76°C. **88** (22 g, 0.056 mol) in THF (40 mL) was added dropwise at –75°C and the reaction mixture was stirred at –75°C for 20 min. The reaction mixture was poured in 1N HCl (800 mL) / EtOAc (1400 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 400 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was triturated with MTBE (50 mL) / PE (200 mL), filtered and washed with PE to give the **166** (23.4 g, 0.038 mol, 68%) as a yellow solid. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel with toluene / EtOAc (30/1) to give 7.4 g of **166** (0.012 mol, 21%) as a yellow solid.

*(2S,5S)-2-tert-butyl-5-[2-(tert-butyl(dimethyl)silyl)oxyethyl]-5-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-one **166***

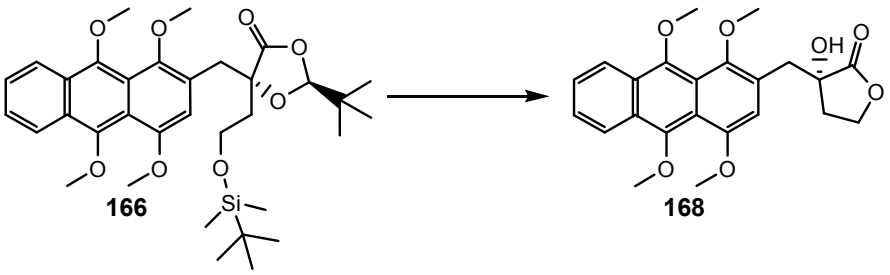
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.52 (m, 2H, H-6 and H-7); 6.64 (s, 1H, H-3); 4.84 (s, 1H, H-acetal); 4.02 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.95 (s, 3H, OCH_3-9); 3.83 (m, 2H, H-4´); 3.75 (s, 3H, OCH_3-1); 3.44 (d, 1H, J = 13.9 Hz, H-1´/1); 3.18 (d, 1H, J = 13.9 Hz, H-1´/2); 2.17 (m, 2H, H-3´); 0.89 (s, 9H, H-tBuCH_3); 0.88 (s, 9H, H-SitBuCH_3); 0.05 (s, 3H, H-SiCH_3); 0.04 (s, 3H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 175.23 (Cq, C-5´); 152.17 (Cq, C-4); 149.32 (Cq, C-10); 147.59 (Cq, C-1); 147.57 (Cq, C-9); 126.99 (Cq, C-8a); 126.53 (Cq, C-10a); 126.24 (CH, C-6); 125.80 (CH, C-7); 122.95 (CH, C-5); 122.75 (Cq, C-2); 122.60

(CH, C-8); 120.57 (Cq, C-9a); 119.36 (Cq, C-4a); 108.27 (CH, C-acetal); 106.08 (CH, C-3); 81.74 (Cq, C-2´); 63.51 (CH_3, OCH_3-9 and OCH_3-10); 62.19 (CH_3, OCH_3-1); 58.25 (CH_2, C-4´); 56.28 (CH_3, OCH_3-4); 38.81 (CH_2, C-3´); 34.37 (Cq, C-tBu); 34.28 (CH_2, C-1´); 25.84 (CH_3, C-SitBuCH_3); 23.55 (CH_3, C-tBuCH_3); -5.43 (CH_3, C-SiCH_3).

HRMS (ESI) : calcd. For $C_{34}H_{48}O_8SiNa$ 635.3016; found 635.3021.
m.p. 160-162 °C

(3S)-3-hydroxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2-one **168**

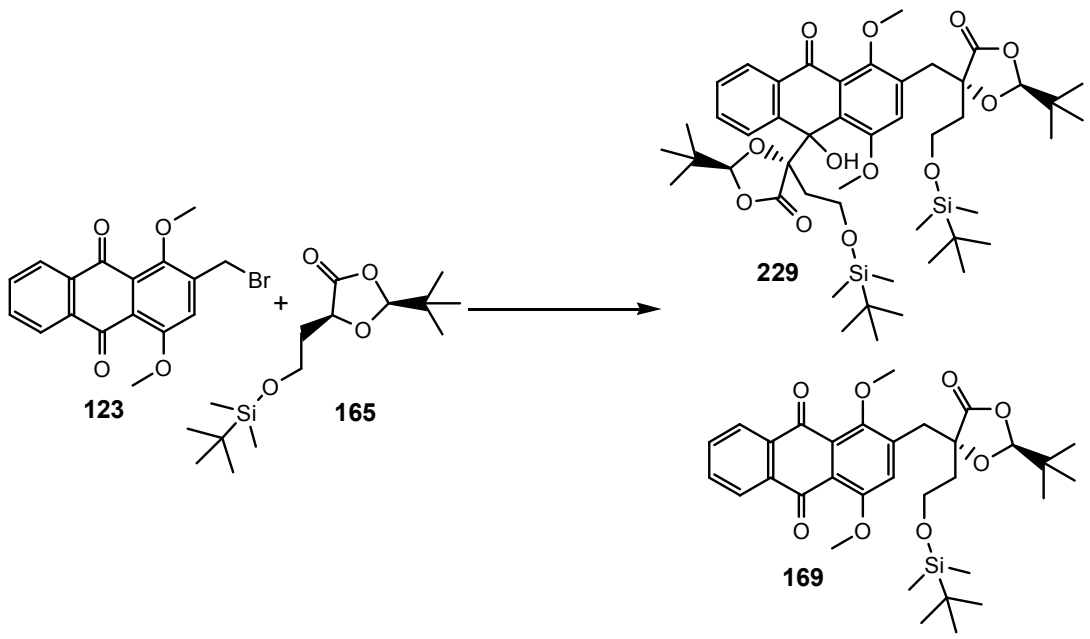


To a solution of **166** (0.21 g, 0.338 mmol) in dry THF (5 mL) under argon was added TBAF 1M in THF (1.36 mL, 1.36 mmol) at RT. The reaction mixture was stirred for 1 hr at RT and then poured in 5% $NaHCO_3$ (15 mL) / EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene/ EtOAc (4/1) to give 60 mg of **168** (0.145 mmol, 43%) as a yellow solid foam.

*(3S)-3-hydroxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2-one **168***
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.54 (s, 1H, H-3); 4.40 (m, 1H, H-4´/1); 4.23 (m, 1H, H-4´/2); 4.03 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.94 (s, 3H, OCH_3-9); 3.85 (s, 1H, OCH_3-1); 3.49 (d, 1H, J = 13.9 Hz, H-1´/1); 2.99 (d, 1H, J = 13.9Hz, H-1´/2); 2.48 (m, 1H, H-3´/1); 2.26 (m, 1H, H-3´/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 178.55 (Cq, C-5´); 152.99 (Cq, C-4); 149.51 (Cq, C-10); 147.29 (Cq, C-9); 146.75 (Cq, C-1); 127.11 (Cq, C-8a); 126.66 (Cq, C-10a); 126.47 (CH, C-6); 125.95 (CH, C-7); 123.01 (CH, C-5); 122.69 (Cq, C-2); 122.52 (CH, C-8); 120.37 (Cq, C-9a); 119.43 (Cq, C-4a); 106.33 (CH, C-3); 75.86 (Cq, C-2´); 65.41 (CH_2, C-4´); 63.56 (CH_3, OCH_3-10); 63.42 (CH_3, OCH_3-9); 62.04 (CH_3, OCH_3-1); 56.47 (CH_3, OCH_3-4); 37.29 (CH_2, C-1´); 34.64 (CH_2, C-3´).

(2S,5S)-2-tert-butyl-5-[[10-[(2S,4S)-2-tert-butyl-4-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-oxo-1,3-dioxolan-4-yl]-10-hydroxy-1,4-dimethoxy-9-oxo-2-anthryl]methyl]-5-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-1,3-dioxolan-4-one **229** and 2-[[(2S,4S)-2-tert-butyl-4-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-oxo-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **169**



KHMDS (0.83 g, 4.15 mmol) was dissolved in dry THF (30 mL) under argon and cooled to –76°C. **165** (1.2 g, 3.97 mmol) in THF (2 mL) was added dropwise (the temperature did not raise –72°C) and the mixture was stirred for 50 min at –76°C. **123** (0.6 g, 1.66 mmol) in THF (4 mL) was added dropwise at –75°C and the reaction mixture was stirred at –75°C for 30 min. The reaction mixture was poured in 1N HCl (50 mL) / EtOAc (80 mL) and the layers were separated. The aqueous layer was

extracted with EtOAc (2 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (30/1 → 8/1) to give in order of elution 758 mg of **229** (0.858 mmol, 52%) and 164 mg of a mixture **169** and **123** (1/1).

(2S,5S)-2-tert-butyl-5-[[10-[(2S,4S)-2-tert-butyl-4-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-oxo-1,3-dioxolan-4-yl]-10-hydroxy-1,4-dimethoxy-9-oxo-2-anthryl]methyl]-5-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-1,3-dioxolan-4-one ***229***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.99 (m, 2H, H-5 and H-8); 7.62 (m, 1H, H-6); 7.51 (m, 1H, H-7); 7.07 (s, 1H, H-3); 6.52 (s, 1H, OH-10); 5.31 (s, 1H, H-acetal´); 5.06 (s, 1H, H-acetal); 3.90 (s, 3H, OCH_3-4); 3.85 (s, 3H, OCH_3-1); 3.65 (m, 2H, H-4´); 3.38 (m, 2H, H-8´); 3.27 (d, 1H, J = 14.2 Hz, H-1´/1); 3.02 (d, 1H, J = 14.2 Hz, H-1´/2); 2.27 (m, 1H, H-7´/1); 2.05 (m, 1H, H-3´/1); 1.75 (m, 1H, H-3´/2); 1.54 (m, 1H, H-7´/2); 0.95 (s, 9H, H-tBuCH_3); 0.83 (s, 9H, H-SitBuCH_3´); 0.80 (s, 9H, H-SitBuCH_3); 0.73 (s, 9H, H-tBuCH_3´); -0.05 (s, 12H, H-SiCH_3 and H-SiCH_3´).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.98 (Cq, C-9); 174.39 (Cq, C9´); 127.23 (Cq, C-5´); 153.45 (Cq, C-1); 152.72 (Cq, C-4); 139.95 (Cq, C-10a); 133.93 (Cq, C-8a); 131.97 (Cq, C-2); 131.42 (CH, C-6); 129.16 (Cq, C-9a); 128.57 (CH, C-7); 128.03 (Cq, C-4a); 126.88 (CH, C-5); 125.74 (CH, C-8); 119.32 (CH, C-3); 109.75 (CH, C-acetal´); 107.58 (CH, C-acetal); 85.54 (Cq, C-6´); 80.93 (Cq, C-2´); 77.39 (Cq, C-10); 63.06 (CH_3, OCH_3-1); 58.38 (CH_2, C-8´); 57.72 (CH_2, C-4´); 56.67 (CH_3, OCH_3-4); 37.24 (CH_2, C-7´); 36.60 (CH_2, C-3´); 34.43 (Cq, C-tBu´); 34.31 (Cq, C-tBu); 32.00 (CH_2, C-1´); 25.83 (CH_3, C-SitBuCH_3); 23.63 (CH_3, C-tBuCH_3´); 23.51 (CH_3, C-tBuCH_3); 18.23 (Cq, C-SitBu and C-SitBu´); -5.40 (CH_3, C-SiCH_3); -5.56 (CH_3, C-SiCH_3).

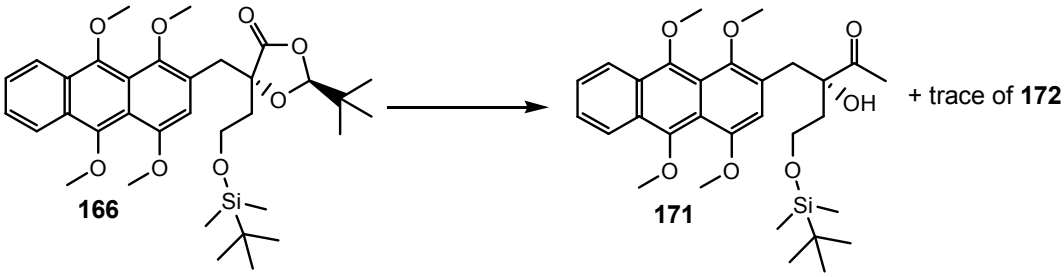
HRMS (ESI) : calcd. For $C_{47}H_{72}O_{12}Si_2Na$ 907.4460; found 907.4475.

2-[[(2S,4S)-2-tert-butyl-4-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-oxo-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione ***169***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.73 (m, 2H, H-6 and H-7); 7.29 (s, 1H, H-3); 4.91 (s, 1H, H-acetal); 3.99 (s, 3H, OCH_3-4); 3.90 (s, 3H, OCH_3-1); 3.77 (m, 2H, H-4´); 3.45 (d, 1H, J = 13.9 Hz, H-1´/1); 3.07 (d, 1H, J = 13.9 Hz, H-1´/2); 2.12 (m, 1H, H-3´/1); 1.96 (m, 1H, H-3´/2); 0.94 (s, 9H, H-tBuCH_3); 0.86 (s, 9H, H-SitBuCH_3); 0.03 (s, 3H, H-SiCH_3); 0.02 (s, 3H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.21 (Cq, C-9); 182.94 (Cq, C-10); 174.39 (Cq, C-5´); 155.76 (Cq, C-4); 153.29 (Cq, C-1); 138.64 (Cq, C-2); 134.24 (Cq, C-8a); 133.82 (Cq, C-10a); 133.76 (CH, C-6); 133.41 (CH, C-7); 127.05 (Cq, C-9a); 126.61 (CH, C-5); 126.45 (CH, C-8); 122.15 (Cq, C-4a); 121.56 (CH C-3); 108.07 (CH, C-acetal); 81.17 (Cq, C-2´); 62.61 (CH_3, OCH_3-1); 57.84 (CH_2, C-4´); 56.67 (CH_3, OCH_3-4); 38.20 (CH_2, C-3´); 34.50 (Cq, C-tBu); 33.37 (CH_2, C-1´); 25.83 (CH_3, C-SitBuCH_3); 23.55 (CH_3, C-tBuCH_3); 18.23 (Cq, C-SitBu); -5.51 (CH_3, C-SiCH_3).

(3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-hydroxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentan-2-one **171**



166 (62 g, 0.101 mol) was dissolved in dry THF (700 mL) under argon and cooled to -78°C. MeLi 1.6 M in Et_2O (164 mL, 0.263 mol) was added dropwise (the temperature did not raise –71 °C). The reaction mixture was stirred at -75°C for 1 hr 30 and poured in sat. NH_4Cl (1200 mL) / EtOAc (1600 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2 x 400 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (10/1) to give 54.2 g of **171** (0.100 mol, 99%) as a yellow foam and some trace of **172** as a yellow foam.

*(3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-hydroxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentan-2-one **171***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 16.67 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.70 (s, 1H, H-3); 4.01 (s, 3H, OCH_3-4); 3.98 (s, 3H, OCH_3-10); 3.92 (s, 3H, OCH_3-9); 3.82 (td, 1H, J = 4.1 Hz, 9.2 Hz, H-4´/1); 3.77 (s, 3H, OCH_3-1); 3.70 (dt, 1H, J = 5.1 Hz, 10.4 Hz, H-4´/2); 3.27 (d, 1H, J = 12.9 Hz, H-1´/1); 3.12 (d, 1H, J = 12.9 Hz, H-1´/2); 2.39 (m, 1H, H-3´/1); 2.33 (s, 3H, CH_3); 1.96 (dt, 1H, J = 4.4 Hz, 14.2 Hz, H-3´/2); 0.86 (s, 9H, H-SitBuCH_3); 0.02 (s, 3H, H-SiCH_3); 0.01 (s, 3H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 212.70 (Cq, C5´); 151.99 (Cq, C-4); 149.27 (Cq, C-10); 147.20 (Cq, C-9); 146.23 (Cq, C-1); 126.80 (Cq, C-8a); 126.36 (Cq, C-10a); 126.11 (CH, C-6); 125.61 (CH, C-7); 124.11 (Cq, C-2); 122.96 (CH, C-5); 122.47 (CH, C-8); 120.36 (Cq, C-9a); 119.34 (Cq, C-4a); 107.33 (CH, C-3); 81.31 (Cq, C-2´); 63.46 (CH_3, OCH_3-10); 63.25 (CH_3, OCH_3-9); 61.78 (CH_3, OCH_3-1); 58.84 (CH_2, C-

4´); 56.30 (CH_3, OCH_3-4); 40.89 (CH_2, C-3´); 39.45 (CH_2, C-3´); 25.87 (CH_3, C-SitBuCH_3); 25.68 (CH_3); 18.29 (Cq, C-tBu); -5.75 (CH_3, C-SiCH_3); -5.78 (CH_3, C-SiCH_3).

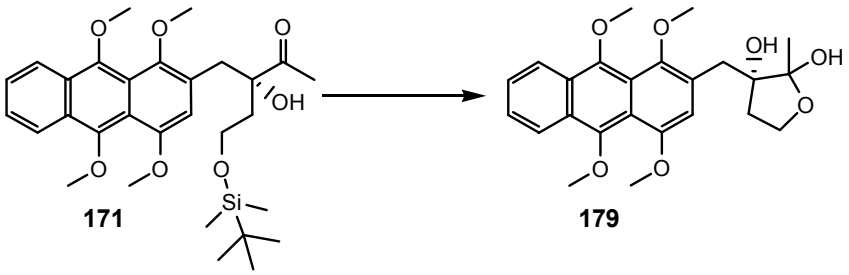
(3S)-5-(tert-butyl(dimethyl)silyl)oxy-2-methyl-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-2,3-diol ***172***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-5 and H-8); 7.52 (m, 2H, H-6 and H-7); 6.79 (s, 1H, H-3); 4.03 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.93 (s, 3H, OCH_3-9); 3.80 (s, 3H, OCH_3-1); 3.68 (m, 2H, H-4´); 3.13 (d, 1H, J = 13.9 Hz, H-1´/1); 3.06 (d, 1H, J = 13.9 Hz, H-1´/2); 1.98 (m, 1H, H-3´/1); 1.77 (m, 1H, H-3´/2); 1.39 (s, 6H, H-CH_3); 0.83 (s, 9H, H- SitBuCH_3); -0.02 (s, 3H, H-SiCH_3); -0.05 (s, 3H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ =152.12 (Cq, C-4); 149.32 (Cq, C-10); 147.06 (Cq, C-9); 146.20 (Cq, C-1); 127.10 (Cq, C-2); 126.82 (Cq, C-8a); 126.26 (Cq, C-10a); 126.16 (CH, C-6); 125.57 (CH, C-7); 123.00 (CH, C-5); 122.49 (CH, C-8); 120.56 (Cq, C-9a); 119.25 (Cq, C-4a); 107.97 (CH, C-3); 79.28 (Cq, C-2´); 75.36 (Cq, C-5´); 63.48 (CH_3, OCH_3-10); 63.41 (CH_3, OCH_3-9); 61.74 (CH_3, OCH_3-1); 60.33 (CH_2, C-4´); 56.34 (CH_3, OCH_3-4); 36.52 (CH_2, C-3´); 36.26 (CH_2, C-1´); 25.76 (CH_3, C-SitBuCH_3); 24.88 (CH_3); 24.72 (CH_3); 18.05 (Cq, C-SitBu); -5.61 (CH3, C-SiCH_3); -5.69 (CH3, C-SiCH_3).

HRMS (ESI) : calcd. For $C_{31}H_{46}O_7SiNa$ 581.2911; found 581.2915.

(3S)-2-methyl-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2,3-diol **179**



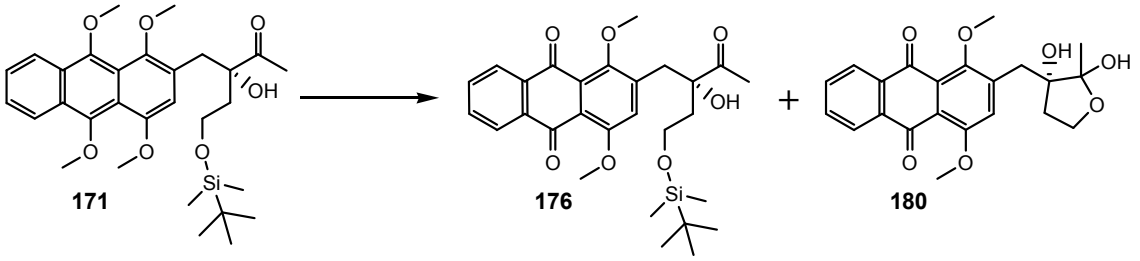
171 (50 mg, 0.092 mmol) was dissolved in dry THF (4 mL) under argon. TBAF 1M in THF (0.14 mL, 0.138 mmol) was added at RT and the reaction mixture was stirred at RT for 1 hr. The reaction mixture was poured in sat. $NaHCO_3$ (15 mL) / EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (15/1) to give 32 mg of **179** (0.074 mmol, 80%) as a yellow foam.

*(3S)-2-methyl-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]tetrahydrofuran-2,3-diol **179***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.80 (s, 1H, H-3); 4.01 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.94 (s, 3H, OCH_3-9); 3.91 (m, 2H, H-4´); 3.77 (s, 3H, OCH_3-1); 3.21 (d, 1H, J = 13.6 Hz, H-1´/1); 2.99 (d, 1H, J = 13.6 Hz, H-1´/2); 2.06 (m, 1H, H-3´/1); 1.84 (dd, 1H, J = 4.4 Hz, 12.9 Hz, H-3´/2); 1.67 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 151.87 (Cq, C-4); 149.25 (Cq, C-10); 147.28 (Cq, C-9); 146.52 (Cq, C-1); 126.81 (Cq, C-8a); 126.29 (Cq, C-10a); 126.09 (CH, C-6); 125.62 (Cq, C-2); 125.57 (CH, C-7); 122.95 (CH, C-5); 122.52 (CH, C-8); 120.64 (Cq, C-9a); 119.28 (Cq, C-4a); 113.78 (Cq, C-5´); 106.82 (CH, C-3); 91.74 (Cq, C-2´); 65.45 (CH_2, C-4´); 63.47 (CH_3, OCH_3-10); 63.35 (CH_3, OCH_3-9); 62.00 (CH_3, OCH_3-1); 56.07 (CH_3, OCH_3-4); 37.52 (CH_2, C-3´); 30.71 (CH_2, C-1´); 20.92 (CH_3).

2-[(2S)-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-2-hydroxy-3-oxo-butyl]-1,4-dimethoxy-anthracene-9,10-dione **176** and 2-[[(3S)-2,3-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **180**



171 (0.46 g, 0.848 mmol) was dissolved in CH_3CN (8 mL) and cooled to 2 °C. CAN (1.39 g, 2.543 mmol) in water (16 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 20 min and then at RT for 1 hr. The reaction mixture was diluted with water (40 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene/ EtOAc (4/1) to give 170 mg of **180** (0.459 mmol, 54%) as a yelow foam and some trace of **176**.

*2-[(2S)-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-2-hydroxy-3-oxo-butyl]-1,4-dimethoxy-anthracene-9,10-dione **176***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.16 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.43 (s, 1H, H-3); 4.56 (s, 1H, OH-2´); 3.99 (s, 3H, OCH_3-4); 3.88 (s, 3H, OCH_3-1); 3.74 (m,1H, H-4´); 3.74 (m, 1H, H-4´/1); 3.65 (m, 1H, H-4´/2); 3.13 (d, 1H, J = 13.9 Hz, H-1´/1); 3.09 (d, 1H, J = 13.9 Hz, H-1´/2); 2.32 (m, 1H, H-3´/1); 2.30 (s, 3H, CH_3); 1.80 (m, 1H, H-3´/2); 0.84 (s, 9H, H-SitBuCH_3); 0.00 (s, 3H, H-SiCH_3); -.0 02 (s, 3H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 212.17 (Cq, C-5´); 183.39 (Cq C-9); 182.99 (Cq, C-10); 155.79 (Cq, C-4); 152.40 (Cq, C-1); 139.59 (Cq, C-2); 134.30 (Cq, C-8a); 133.83 (Cq, C-10a); 133.59 (CH, C-6); 133.24 (CH, C-7); 126.97 (Cq, C-9a); 126.45 (CH, C-5); 126.36 (CH, C-8); 122.48 (CH, C-3); 121.69 (Cq, C-4a); 80.80 (Cq, C-2´); 62.26 (CH_3, OCH_3-1); 58.92 (CH_2, C-4´); 56.68 (CH_3, OCH_3-4); 40.02 (CH_2, C-3´); 38.22

(CH_2, C1´); 25.79 (CH_3, C-SitBuCH_3); 25.46 (CH_3); 18.21 (Cq, C-SitBu); -5.85 (CH_3, $SiCH_3$).

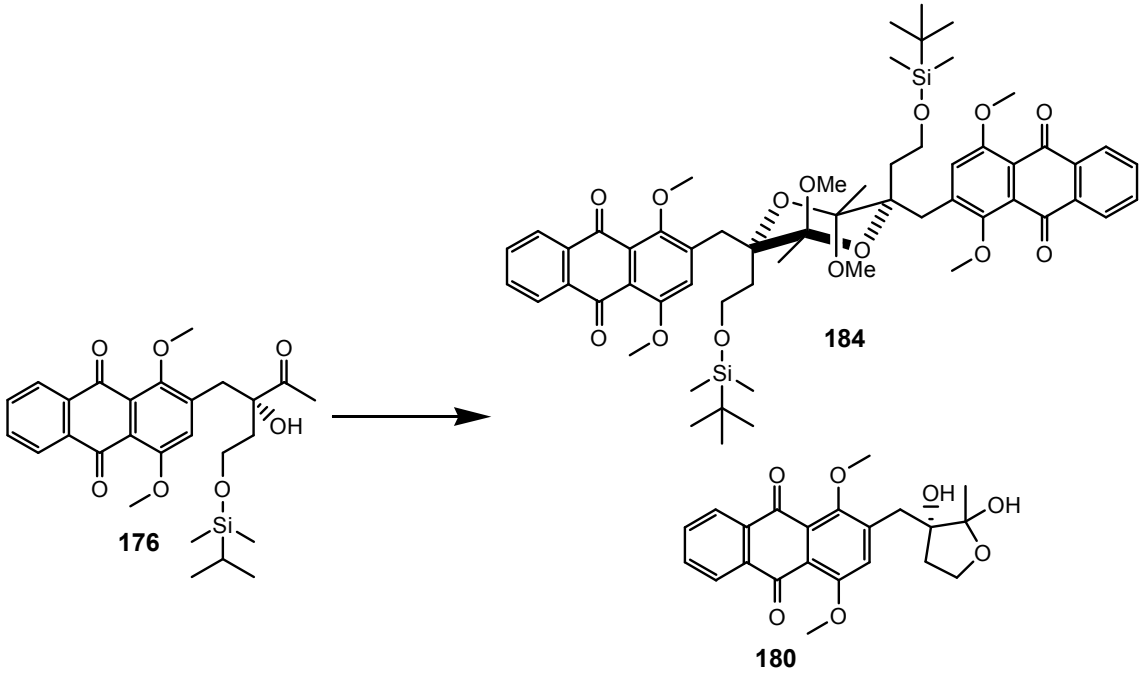
HRMS (ESI) : calcd. For $C_{28}H_{36}O_7SiNa$ 535.2128; found 535.2120.
m.p. 76-78 °C

2-[[(3S)-2,3-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione ***180***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.45 (s, 1H, H-3); 3.98 (s, 3H, OCH_3-4); 3.94 (m, 1H, H-4´/1); 3.89 (s, 3H, OCH_3-1); 3.81 (m, 1H, H-4´/2); 3.16 (d, 1H, J = 13.6 Hz, H-1´/1); 2.90 (d, 1H, J = 13.6 Hz, H-1´/2); 1.93 (dt, 1H, J = 7.9 Hz, 12.6 Hz, H-3´/1); 1.70 (dd, 1H, J = 4.4 Hz, 12.6 Hz, H-3´/2); 1.62 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.43 (Cq, C-9); 183.03 Cq, C-10); 155.83 (Cq, C-4); 152.52 (Cq, C-1); 141.21 (Cq, C-2); 134.33 (Cq, C-8a); 133.86 (Cq, C-10a); 133.61 (CH, C-6); 133.27 (CH, C-7); 126.96 (Cq, C-9a); 126.50 (CH, C-5); 126.44 (CH, C-8); 113.80 (Cq, C-5´); 90.81 (Cq, C-2´); 65.44 (CH_2, C-4´); 62.29 (CH_3, OCH_3-1); 56.47 (CH_3, OCH_3-4); 37.46 (CH_2, C-3´); 30.94 (CH_2, C-1´); 20.71 (CH_3).

2-[[(2S,5S)-2,5-bis[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-3,6-dimethoxy-3,6-dimethyl-1,4-dioxan-2-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **184** and 2-[[(3S)-2,3-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **180**



To a solution of **176** (110 mg, 0.215 mmol) in toluene (10 mL), was added ethylene glycol (140 mg, 2.258 mmol), trimethyl formate (159 mg, 1.075 mmol) and pTsOH (2 mg, 0.009 mmol) at RT and the reaction mixture was stirred for 1 hr. The reaction mixture was quenched with sat. $NaHCO_3$ (15 mL), the aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene/ EtOAc (10/1) to give 23 mg of **184** (0.022 mmol, 10%) as a yelow foam and 23 mg of **180** (0.056 mmol, 27%).

*2-[[(2S,5S)-2,5-bis[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-3,6-dimethoxy-3,6-dimethyl-1,4-dioxan-2-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **184***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 4H, H-5 and H-8); 7.76 (s, 2H, H-3); 7.71 (m, 4H, H-6 and H-7); 3.98 (s, 6H, OCH_3-1); 3.86 (s, 6H, OCH_3-4); 3.68 (m, 4H, H-

4´); 3.23 (s, 6H, OCH_3); 3.21 (d, 2H, J = 14.8 Hz, H-1´/1); 3.16 (d, 2H, J = 14.8 Hz, H-1´/2); 1.77 (m, 2H, H-3´/1); 1.67 (m, 2H, H-3´/2); 1.38 (s, 6H, CH_3); 0.77 (s, 18H, H-SitBuCH_3); -0.07 (s, 6H, H-SiCH_3); -0.08 (s, 6H, H-SiCH_3).

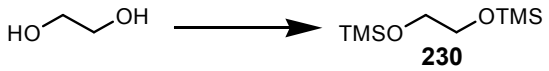
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.47 (Cq, C-9); 183.16 (Cq, C-10); 155.55 (Cq, C-4); 152.95 (Cq, C-1); 143.62 (Cq, C-2); 134.40 (Cq, C-8a); 134.09 (Cq, C-10a); 133.37 (CH, C-6); 133.11 (CH, C-7); 126.62 (Cq, C-9a); 126.42 (CH, C-5); 126.33 (CH, C-8); 121.91 (CH, C-3); 120.74 (Cq, Cq-4a); 107.21 (Cq, C-5´); 86.95 (Cq, C-2´); 62.18 (CH_3, OCH_3-1); 59.20 (CH_2, C-4´); 56.40 (CH_3, OCH_3-4); 47.90 (CH_3, OCH_3); 40.18 (CH_2, C-3´); 30.60 (CH_2, C-1´); 25.88 (CH_3, C-SitBuCH_3); 18.24 (Cq, C-tBu); 16.25 (CH_3); -5.39 (CH_3, C-SiCH_3); -5.41 (CH_3, C-SiCH_3).

2-[[(3S)-2,3-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione ***180***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.45 (s, 1H, H-3); 3.98 (s, 3H, OCH_3-4); 3.94 (m, 1H, H-4´/1); 3.89 (s, 3H, OCH_3-1); 3.81 (m, 1H, H-4´/2); 3.16 (d, 1H, J = 13.6 Hz, H-1´/1); 2.90 (d, 1H, J = 13.6 Hz, H-1´/2); 1.93 (dt, 1H, J = 7.9 Hz, 12.6 Hz, H-3´/1); 1.70 (dd, 1H, J = 4.4 Hz, 12.6 Hz, H-3´/2); 1.62 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.43 (Cq, C-9); 183.03 Cq, C-10); 155.83 (Cq, C-4); 152.52 (Cq, C-1); 141.21 (Cq, C-2); 134.33 (Cq, C-8a); 133.86 (Cq, C-10a); 133.61 (CH, C-6); 133.27 (CH, C-7); 126.96 (Cq, C-9a); 126.50 (CH, C-5); 126.44 (CH, C-8); 113.80 (Cq, C-5´); 90.81 (Cq, C-2´); 65.44 (CH_2, C-4´); 62.29 (CH_3, OCH_3-1); 56.47 (CH_3, OCH_3-4); 37.46 (CH_2, C-3´); 30.94 (CH_2, C-1´); 20.71 (CH_3).

2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane **230**



230

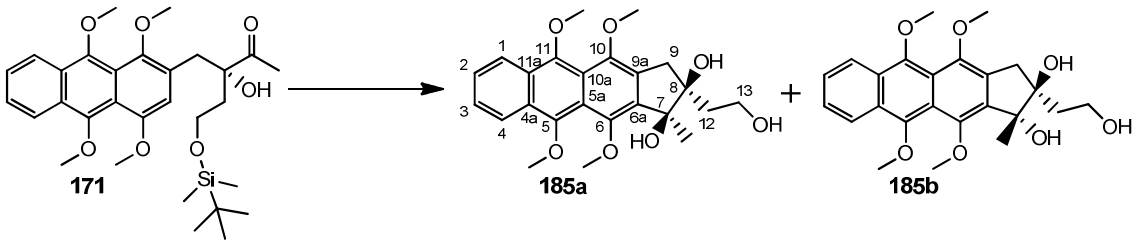
A flask purged with argon was charged with ethylene glycol (3.1 g, 0.05 mol) and DCM (250 mL) under argon and cooled to 5°C in an ice-water bath. Et_3N (20.85 mL, 0.15 mol) was added followed by dropwise addition of TMSCl (15.98 mL, 0.13 mol). The reaction mixture was then allowed to warmed up to RT and stirred at RT for 3h30. During the reaction the suspension changed colour gradually from white to pink. The mixture was filtered and the precipitate was washed with Et_2O several time. The operation was repeated several times until no more precipitate was formed in the flask. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with cylohexane / EtOAc (4/1) to give 8,2g (0.04 mol, 79%) of **230** as a colourless liquid.

*2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane **230***

^1H NMR (500 MHz, $CDCl_3$) : δ = 3.64 (s, 4H, H-CH_2); 0.12 (s, 18H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 63.88 (CH_2); -0.45 (CH_3, C-SiCH_3).

(2S,3S)-2-(2-hydroxyethyl)-4,5,10,11-tetramethoxy-3-methyl-1H-cyclopenta[b]anthracene-2,3-diol **185a** and (2S,3R)-2-(2-hydroxyethyl)-4,5,10,11-tetramethoxy-3-methyl-1H-cyclopenta[b]anthracene-2,3-diol **185b**



To a dry flask under argon atmosphere cooled at – 60 °C were added DCM (5 mL), trimethylsilyl trifluoromethane sulfonate 3 mol% and a solution of **230** (170 mg, 0.830 mmol) in DCM (1 mL). The mixture was stirred for 10 min and a solution of **171**(300 mg, 0.553 mmol) in DCM (1 mL) was added dropwise. The reaction mixture was allowed to warmed up to 0 °C and stirred at that temperature for 2h 30. The reaction was then quenched with pyridine (0.27 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (20/1 → 2/1) to give in order of elution 64 mg of **185a** (0.149 mmol, 27%) as a yellow foam and 95 mg of **185b** (0.221 mmol, 40%) as a yellow foam.

*(2S,3S)-2-(2-hydroxyethyl)-4,5,10,11-tetramethoxy-3-methyl-1H-cyclopenta[b]anthracene-2,3-diol **185a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-1 and H-4); 7.51 (m, 2H, H-2 and H-3); 4.12 (m, 1H, H-13/1); 4.01 (s, 3H, OCH_3-11); 3.99 (s, 3H, OCH_3-5); 3.97 (s, 3H, OCH_3-6); 3,91 (s, 3H, OCH_3-10); 3.79 (m, 1H, H-13/2); 3.56 (d, 1H, J = 16.1 Hz, H-9/1); 3.09 (d, 1H, J = 16.1 Hz, H-9/2); 2.26 (m, 1H, H-12/1); 2.09 (m, 1H, H-12/2); 1.66 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 149.30 (Cq, C-11); 148.56 (Cq, C-5); 147.55 (Cq, C-6); 146.66 (Cq, C-10); 134.82 (Cq, C-6a); 128.21 (Cq, C-9a); 126.26 (Cq, C-11a); 125.99 (Cq, C-4a); 125.90 (CH, C-3); 125.64 (CH, C-2); 122.79 (CH, C-4); 122.48 (CH, C-1); 122.02 (Cq, C-5a and C-10a); 94.43 (Cq, C-8); 89.15 (Cq, C-7); 66.24

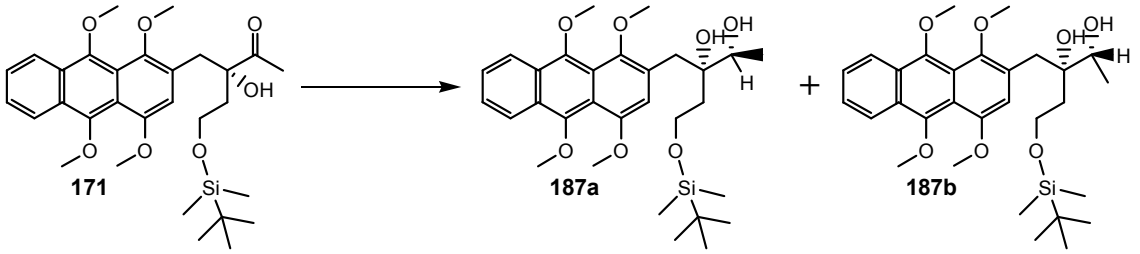
(CH_2, C-13); 63.95 (CH_3, OCH_3-6); 63.63 (CH_3, OCH_3-5); 63.57 (CH_3, OCH_3-10); 61.62 (CH_3, OCH_3-11); 41.08 (CH_2, C-12); 39.29 (CH_2, C-9); 19.65 (CH_3).

(2S,3R)-2-(2-hydroxyethyl)-4,5,10,11-tetramethoxy-3-methyl-1H-cyclopenta[b]anthracene-2,3-diol ***185b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-1 and H-4); 7.52 (m, 2H, H-2 and H-3); 4.11 (m, 1H, H-13/1); 4.00 (s, 3H, OCH_3-11); 3.99 (s, 3H, OCH_3-5); 3.97 (s, 3H, OCH_3-6); 3,89 (s, 3H, OCH_3-10); 3.72 (m, 1H, H-13/2); 3.63 (d, 1H, J = 16.8 Hz, H-9/1); 3.09 (d, 1H, J = 16.8 Hz, H-9/2); 2.25 (m, 2H, H-12); 1.74 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 149.45 (Cq, C-6); 148.61 (Cq, C-11); 147.66 (Cq, C-5); 146.87 (Cq, C-10); 134.06 (Cq, C-6a); 128.22 (Cq, C-9a); 126.37 (Cq, C-11a); 126.05 (Cq, C-4a); 126.01 (CH, C-3); 125.74 (CH, C-2); 122.78 (CH, C-4); 122.51 (CH, C-1); 122.19 (Cq, C-10a); 121.92(Cq, C-5a); 93.02 (Cq, C-8); 87.87 (Cq, C-7); 65.77 (CH_2, C-13); 63.62 (CH_3, OCH_3-5 and OCH_3-11); 63.40 (CH_3, OCH_3-6); 61.57 (CH_3, OCH_3-10); 41.59 (CH_2, C-12); 39.50 (CH_2, C-9); 19.26 (CH_3).
m.p. 70-72 °C

(2S,3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-2,3-diol **187a** and (2R,3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-2,3-diol **187b**



171 (33.82 g, 0.062 mol) was dissolved in EtOH (340 mL) under argon. $NaBH_4$ (2.36 g, 0.062 mol) was added and the reaction mixture was stirred at RT for 1hr. The reaction mixture was quenched with brine (500 mL) / EtOAc (600 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (5/1) to give 30.70 g of a mixture of **187a** and **187b** (2 / 1)(0.056 mol, 90%) as a yellow foam.

*(2S,3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-2,3-diol **187a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.75 (s, 1H, H-3); 4.02 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.96 (m, 2H, H-4´); 3.94 (s, 3H, OCH_3-9); 3.83 (s, 3H, OCH_3-1); 3.63 (q, 1H, J = 6.3 Hz, H-5´); 3.26 (d, 1H, J = 13.6 Hz, H-1´/1); 2.96 (d, 1H, J = 13.6 Hz, H-1´/2); 1.91 (m, 2H, H-3´); 1.22 (d, 3H, J = 6.3 Hz, CH_3); 0.95 (s, 9H, H-SitBuCH_3); 0.13 (s, 6H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 152.19 (Cq, C-4); 149.35 (Cq, C-10); 146.88 (Cq, C-9); 145.89 (Cq, C-1); 126.86 (Cq, C-8a); 126.27 (Cq, C-10a); 126.16 (CH, C-6); 125.95 (Cq, C-2); 125.57 (CH, C-7); 122.97 (CH, C-5); 122.45 (CH, C-8); 120.17 (Cq, C-9a); 119.21 (Cq, C-4a); 108.02 (CH, C-3); 77.72 (Cq, C-2´); 70.77 (CH, C-5´); 63.44 (CH_3, OCH_3-10); 63.36 (CH_3, OCH_3-9); 62.12 (CH_3, OCH_3-1); 60.37 (CH_2, C-

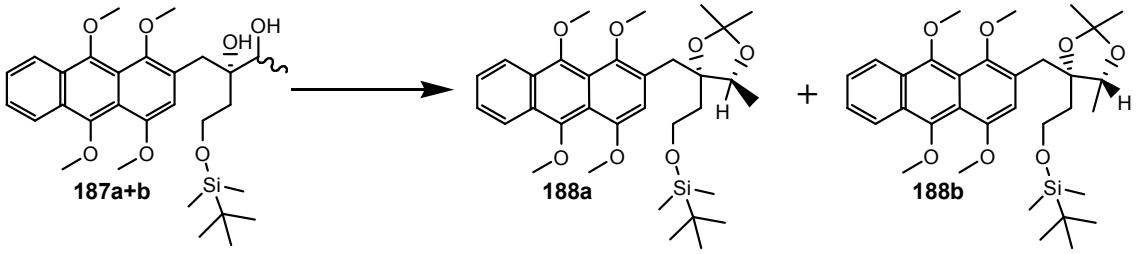
4´); 56.12 (CH_3, OCH_3-4); 35.51 (CH_2, C-1´); 35.37 (CH_2, C-3´); 25.81 (CH_3, C-SitBuCH_3); 18.04 (Cq, C-SitBu); 16.08 (CH_3), -5.62 (CH_3, C-SiCH_3).

(2R,3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-2,3-diol ***187b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.75 (s, 1H, H-3); 4.03 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.96 (m, 2H, H-4´); 3.93 (s, 3H, OCH_3-9); 3.81 (s, 3H, OCH_3-1); 3.75 (q, 1H, J = 6.3 Hz, H-5´); 3.12 (d, 1H, J = 13.6 Hz, H-1´/1); 3.00 (d, 1H, J = 13.6 Hz, H-1´/2); 2.00 (m, 1H, H-3´/1); 1.59 (m, 1H, H-3´/2); 1.33 (d, 3H, J = 6.3 Hz, CH_3); 0.91 (s, 9H, H-SitBuCH_3); 0.09 (s, 6H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 152.19 (Cq, C-4); 149.31 (Cq, C-10); 147.01 (Cq, C-9); 145.96 (Cq, C-1); 126.86 (Cq, C-8a); 126.27 (Cq, C-10a); 126.16 (CH, C-6); 125.95 (Cq, C-2); 125.57 (CH, C-7); 122.97 (CH, C-5); 122.45 (CH, C-8); 120.44 (Cq, C-9a); 119.21 (Cq, C-4a); 107.89 (CH, C-3); 77.40 (Cq, C-2´); 71.50 (CH, C-5´); 63.44 (CH_3, OCH_3-10); 63.36 (CH_3, OCH_3-9); 61.73 (CH_3, OCH_3-1); 60.37 (CH_2, C-4´); 56.32 (CH_3, OCH_3-4); 37.22 (CH_2, C-3´); 36.91 (CH_2, C-1´); 25.81 (CH_3, C-SitBuCH_3); 18.10 (Cq, C-SitBu); 16.63 (CH_3), -5.58 (CH3, C-SiCH_3).

tert-butyl-dimethyl-[2-[(4S,5S)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethoxy]silan **188a** and tert-butyl-dimethyl-[2-[(4S,5R)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethoxy]silane **188b**



187a+b (5.26 g, 9.655 mmol) was dissolved in acetone (dried over molecular sieves, 100 mL) under argon atmosphere. Dimethoxypropane (3.6 mL, 28.966 mmol) was added followed by pTsOH (0.09 g, 0.483 mmol). The reaction mixture was stirred at RT for 1 hr 30 and poured in sat. $NaHCO_3$ (200 mL) / EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 70 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (40/1) to give 4.66 g of a mixture of **188a** and **188b** (7.968 mmol, 83%) as a yellow foam.

*tert-butyl-dimethyl-[2-[(4S,5S)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethoxy]silan **188a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.50 (m, 2H, H-6 and H-7); 6.97 (s, 1H, H-3); 4.54 (q, 1H, J = 6.3 Hz, H-5´); 4.02 (s, 3H, OCH_3-4); 3.98 (s, 3H, OCH_3-10); 3.92 (s, 3H, OCH_3-9); 3.73 (s, 3H, OCH_3-1); 3.69 (m, 2H, H-4´); 3.19 (d, 1H, J = 13.6 Hz, H-1´/1); 2.75 (d, 1H, J = 13.6 Hz, H-1´/2); 1.91 (m, 1H, H-3´/1); 1.77 (m, 1H, H-3´/2); 1.74 (s, 3H, H-acetonide); 1.45 (d, 3H, J = 6.3 Hz, CH_3); 1.44 (s, 3H, H-acetonide); 0.86 (s, 9H, H-SitBuCH_3); 0.01 (s, 6H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 151.46 (Cq, C-4); 149.18 (Cq, C-10); 147.08 (Cq, C-9); 146.93 (Cq, C-1); 126.66 (Cq, C-8a); 126.12 (Cq, C-10a); 125.96 (Cq, C-2); 125.93 (CH, C-6); 125.39 (CH, C-7); 122.95 (CH-5); 122.52 (CH, C-8); 120.61 (Cq,

C-9a); 119.26 (Cq, C-4a); 107.86 (CH, C-3); 106.61 (Cq, C-acetonide); 84.64 (Cq, C-2´); 76.93 (CH, C-5´); 63.42 (CH_3, OCH_3-10); 63.26 (CH_3, OCH_3-9); 61.70 (CH_3, OCH_3-1); 58.81 (CH_2, C-4´); 56.02 (CH_3, OCH_3-4); 37.79 (CH_2, C-3´); 32.49 (CH_2, C-1´); 28.72 (CH_3, C-acetonide); 26.71 (CH_3, C-acetonide); 25.83 (CH_3, C-SitBuCH_3); 18.07 (Cq, C-SitBu); 14.16 (CH_3); -5.19 (CH_3, C-SiCH_3).

HRMS (ESI) : calcd. For $C_{33}H_{48}O_7Si$ 585.3247; found 585.3238 (MH+).

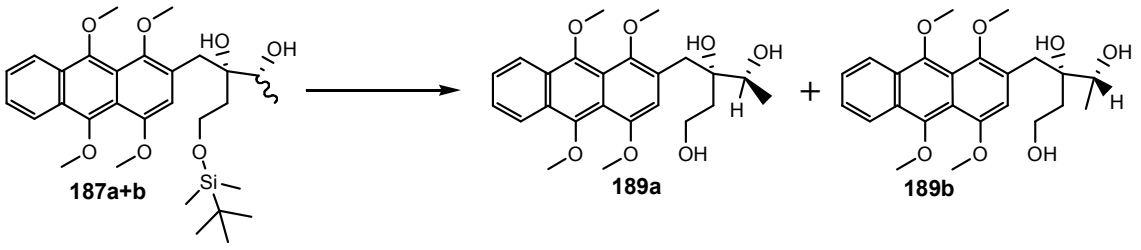
tert-butyl-dimethyl-[2-[(4S,5R)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethoxy]silane ***188b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.50 (m, 2H, H-6 and H-7); 6.75 (s, 1H, H-3); 4.08 (m, 2H, H-4´); 4.04 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.95 (s, 3H, OCH_3-9); 3.92 (q, 1H, J = 6.3 Hz, H-5´); 3.76 (s, 3H, OCH_3-1); 3.13 (s, 2H, H-1´); 1.91 (m, 1H, H-3´/1); 1.77 (m, 1H, H-3´/2); 1.41 (s, 3H, H-acetonide); 1.22 (d, 3H, J = 6.3 Hz, CH_3); 1.00 (s. 3H, H-acetonide); 0.94 (s, 9H, H-SitBuCH_3); 0.13 (s, 6H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 151.42 (Cq, C-4); 149.18 (Cq, C-10); 147.26 (Cq, C-9); 146.75 (Cq, C-1); 126.76 (Cq, C-8a); 126.24 (Cq, C-10a); 126.05 (CH, C-6); 125.53 (CH, C-7); 125.38 (Cq, C-2); 122.91 (CH-5); 122.52 (CH, C-8); 120.53 (Cq, C-9a); 119.24 (Cq, C-4a); 108.55 (CH, C-3); 106.44 (Cq, C-acetonide); 83.88 (Cq, C-2´); 76.01 (CH, C-5´); 63.47 (CH_3, OCH_3-10); 63.42 (CH_3, OCH_3-9); 61.77 (CH_3, OCH_3-1); 59.51 (CH_2, C-4´); 56.42 (CH_3, OCH_3-4); 37.38 (CH_2, C-3´); 34.68 (CH_2, C-1´); 28.44 (CH_3, C-acetonide); 26.75 (CH_3, C-acetonide); 26.01 (CH_3, C-SitBuCH_3); 18.35 (Cq, C-SitBu); 13.62 (CH_3); -5.44 (CH_3, C-SiCH_3).

HRMS (ESI) : calcd. For $C_{33}H_{48}O_7Si$ 585.3247; found 585.3238 (MH+).

(3S,4S)-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-1,3,4-triol **189a** and (3S,4R)-3-[(1,9-dihydroxy-4,10-dimethoxy-2-anthryl)methyl]pentane-1,3,4-triol **189b**



187a+b (200 mg, 0.367 mmol) was dissolved in dry THF (7 mL) under argon. TBAF 1M in THF (0.92 mL, 0.918 mmol) was added at RT and the reaction mixture was stirred at RT for 1 hr. The reaction mixture was poured in sat. $NaHCO_3$ (20 mL) / EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (1/2) to give 140 mg of a mixture of **189a** and **189b** (0.325 mmol, 89%) as a yellow foam.

*(3S,4S)-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-1,3,4-triol **189a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.60 (s, 1H, H-3); 4.04 (s, 3H; OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.94 (s, 3H, OCH_3-9); 3.90 (m, 2H, H-4´); 3.87 (s, 3H, OCH_3-1); 3.76 (q, 1H, J = 6.3 Hz, H-5´); 3.42 (d, 1H, J = 13.6 Hz, H-1´/1); 2.79 (d, 1H, J = 13.6 Hz, H-1´/2); 1.98 (dt, 1H, J = 4.1 Hz, 14.6 Hz, H-3´/1); 1.84 (ddd, 1H, J = 3.5 Hz, 6.9 Hz, 14.6 Hz, H-3´/2); 1.26 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 152.88 (Cq, C-4); 149.53 (Cq, C-10); 146.98 (Cq, C-9); 145.85 (Cq, C-1); 127.10 (Cq, C-8a); 126.51 (Cq, C-10a); 126.45 (CH, C-6); 125.85 (CH, C-7); 125.06 (Cq, C-2); 123.03 (CH, C-5); 122.48 (CH, C-8); 120.18 (Cq, C-9a); 119.26 (Cq, C-4a); 107.62 (CH, C-3); 78.58 (Cq, C-2´); 71.33 (CH, C-5´); 63.56 (CH_3, OCH_3-10); 63.47 (CH_3, OCH_3-9); 62.11 (CH_3, OCH_3-1); 59.31 (CH_2, C-4´); 56.45 (CH_3, OCH_3-4); 37.11 (CH_2, C-3´); 36.32 (CH_2, C-1´); 16.49 (CH_3).

(3S,4R)-3-[(1,9-dihydroxy-4,10-dimethoxy-2-anthryl)methyl]pentane-1,3,4-triol ***189b***

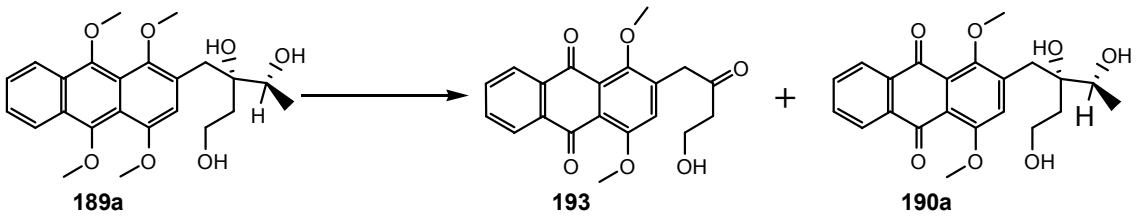
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.34 (m, 2H, H-5 and H-8); 7.53 (m, 2H, H-6 and H-7); 6.52 (s, 1H, H-3); 4.03 (s, 3H; OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.94 (s, 3H, OCH_3-9); 3.90 (m, 2H, H-4´); 3.86 (s, 3H, OCH_3-1); 3.76 (q, 1H, J = 6.3 Hz, H-5´); 3.06 (m, 2H, H-1´); 2.05 (m, 1H, H-3´/1); 1.64 (ddd, 1H, J = 2.5 Hz, 5.7 Hz, 14.8 Hz, H-3´/2); 1.32 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 152.88 (Cq, C-4); 149.53 (Cq, C-10); 147.04 (Cq, C-9); 145.85 (Cq, C-1); 127.10 (Cq, C-8a); 126.51 (Cq, C-10a); 126.45 (CH, C-6); 125.85 (CH, C-7); 124.84 (Cq, C-2); 123.03 (CH, C-5); 122.48 (CH, C-8); 120.24 (Cq, C-9a); 119.26 (Cq, C-4a); 107.35 (CH, C-3); 78.20 (Cq, C-2´); 72.01 (CH, C-5´); 63.56 (CH_3, OCH_3-10); 63.43 (CH_3, OCH_3-9); 61.85 (CH_3, OCH_3-1); 58.86 (CH_2, C-4´); 56.45 (CH_3, OCH_3-4); 38.74 (CH_2, C-1´); 36.48 (CH_2, C-3´); 16.59 (CH_3).

2-[(2S)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione **190**

From **189a**

2-(4-hydroxy-2-oxo-butyl)-1,4-dimethoxy-anthracene-9,10-dione **193** and 2-[(2S,3S)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione **190a**



189a **193** **190a**

189a (0.10 g, 0.232 mmol) was dissolved in CH_3CN (3 mL) and cooled to 2 °C. CAN (0.38 g, 0.697 mmol) in water (6 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 30 min. The reaction mixture was diluted with water (20mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with EtOAc / MeOH (30/1) to give in order of elution 12 mg of **193** (0.034 mmol, 15%) as a yelow solid and 25 mg of **190a** (0.062 mmol, 27%) as a yellow solid.

*2-(4-hydroxy-2-oxo-butyl)-1,4-dimethoxy-anthracene-9,10-dione **193***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.16 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.18 (s, 1H, H-3); 4.00 (s, 3H, OCH_3-4); 3.89 ((m, 4H, H-1´and H-4´); 3.83 (s, 3H, OCH_3-1); 2.84 (t, 2H, J = 5.4 Hz, H-3´).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 207.28 (Cq, C-2´); 183.27 (Cq, C-9); 182.73 (Cq, C-10); 156.30 (Cq, C-4); 152.31 (Cq, C-1); 137.90 (Cq, C-2); 134.28 (Cq, C-8a); 133.73 (CH, C-6); 133.68 (Cq, C-10a); 133.32 (CH, C-7); 127.05 (Cq, C-9a); 126.59 (CH, C-5); 126.40 (CH, C-8); 122.08 (Cq, C-4a); 121.37 (CH, C-3); 62.08 (CH_3, OCH_3-1); 57.79 (CH_2, C-4´); 56.81 (CH_3, OCH_3-4); 45.20 (CH_2, C-1´); 44.62(CH_2, C-3´).

HRMS (ESI) : calcd. For $C_{20}H_{18}O_6$ 355.1182; found 355.1175.

*2-[(2S,3S)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione **190a***

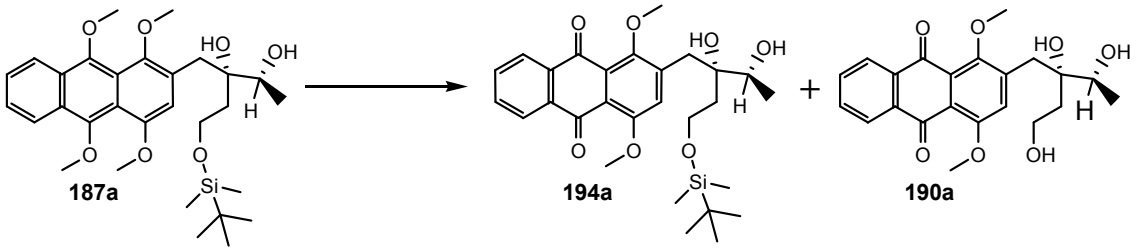
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.16 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.38 (s, 1H, H-3); 4.01 (s, 3H, OCH_3-4); 3.94 (s, 3H, OCH_3-1); 3.87 (m, 2H, H-4´); 3.79 (q, 1H, J = 6.3 Hz, H-5´); 3.19 (d, 1H, J = 13.6 Hz, H-1´/1); 2.88 (d, 1H, J = 13.6 Hz, H-1´/2); 1.79 (m, 2H, H-3´); 1.25 (d, 3H, J,= 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.37 (Cq, C-9); 182.87 (Cq, C-10); 156.21 (Cq, C-4); 152.07 (Cq, C-1); 141.27 (Cq, C-2); 134.30 (Cq, C-8a); 133.71 (Cq, C-10a and CH, C-6); 133.30 (CH, C-7); 127.00 (Cq, C-9a); 126.54 (CH, C-5); 126.43 (CH, C-8); 123.24 (CH, C-3); 121.66 (Cq, C-4a); 77.75 (Cq, C-2´); 71.40 (CH, C-5´); 62.28 (CH_3, OCH_3-1); 59.17 (CH_2, C-4´); 56.80 (CH_3, OCH_3-4); 36.63 (CH_2, C-3´); 35.49 (CH_2, C-1´); 16.72 (CH_3).

HRMS (ESI) : calcd. For $C_{22}H_{24}O_7Na$ 423.1420; found 423.1417.

From **187a**

2-[(2S,3S)-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-2,3-dihydroxy-butyl]-1,4-dimethoxy-anthracene-9,10-dione **194a** and 2-[(2S,3S)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione **190a**



187a (40 mg, 0.073 mmol) was dissolved in CH_3CN (2mL) and cooled to 2 °C. CAN (120 mg, 0.219 mmol) in water (5 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 10 min and then at RT for 20 min. The reaction mixture was diluted with water (15 mL) and the aqueous layer was extracted with EtOAc (3 x

20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with EtOAc / MeOH (1/0→30/1) to give in order of elution 5 mg of **194a** (0.010 mmol, 14%) as a yelow solid and 15 mg of **190a** (0.037 mmol, 55%) as a yellow solid.

2-[(2S,3S)-2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-2,3-dihydroxy-butyl]-1,4-dimethoxy-anthracene-9,10-dione ***194a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.49 (s, 1H, H-3); 4.00 (s, 3H, OCH_3-4); 3.91 (s, 3H, OCH_3-1); 3.86 (m, 1H, H-4´/1); 3.80 (m, 1H, H-4´/2); 3.72 (q, 1H, J = 6.3 Hz, H-5´); 3.02 (d, 1H, J = 13.3 Hz, H-1´/1); 2.98 (d, 1H, J = 13.3 Hz, H-1´/2); 1.78 (m, 1H, H-3´/1); 1.70 (m, 1H, H-3´/2); 1.22 (d, 3H, J = 6.3 Hz, CH_3); 0.87 (s, 9H, H-SitBuCH_3); 0.06 (s, 3H, H-SiCH_3); 0.03 (s, 3H, H-SiCH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.55 (Cq, C-9); 183.04 (Cq, C-10); 155.92 (Cq, C-4); 152.46 (Cq, C-1); 141.93 (Cq, C-2); 134.38 (Cq, C-8a); 133.87 (Cq, C-10a); 133.59 (CH, C-6); 133.19 (CH, C-7); 126.74 (Cq, C-9a); 126.50 (CH, C-5); 126.39 (CH, C-8); 123.41 (CH, C-3); 121.54 (Cq, C-4a); 77.40 (Cq, C-2´); 71.20 (CH, C-5´); 62.28 (CH_3, OCH_3-1); 60.15 (CH_2, C-4´); 56.63 (CH_3, OCH_3-4); 35.48 (CH_2, C-3´); 34.10 (CH_2, C-1´); 25.72 (CH_3, C-SitBuCH_3); 17.96 (Cq, C-SitBu); 16.32 (CH_3); -5.65 (CH_3, C-SiCH_3); -5.70 (CH_3, C-SiCH_3).

2-[(2S,3S)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione ***190a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.16 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.38 (s, 1H, H-3); 4.01 (s, 3H, OCH_3-4); 3.94 (s, 3H, OCH_3-1); 3.87 (m, 2H, H-4´); 3.79 (q, 1H, J = 6.3 Hz, H-5´); 3.19 (d, 1H, J = 13.6 Hz, H-1´/1); 2.88 (d, 1H, J = 13.6 Hz, H-1´/2); 1.79 (m, 2H, H-3´); 1.25 (d, 3H, J = 6.3 Hz, CH_3).

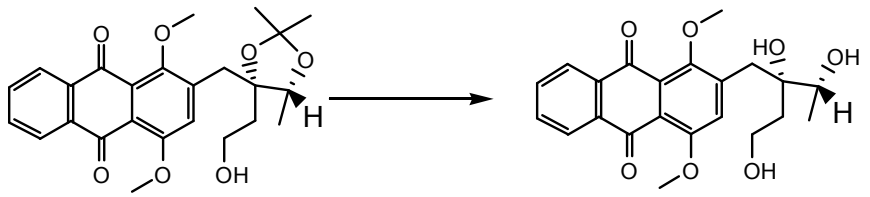
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.37 (Cq, C-9); 182.87 (Cq, C-10); 156.21 (Cq, C-4); 152.07 (Cq, C-1); 141.27 (Cq, C-2); 134.30 (Cq, C-8a); 133.71 (Cq, C-10a and CH, C-6); 133.30 (CH, C-7); 127.00 (Cq, C-9a); 126.54 (CH, C-5); 126.43 (CH, C-8);

123.24 (CH, C-3); 121.66 (Cq, C-4a); 77.75 (Cq, C-2´); 71.40 (CH, C-5´); 62.28 (CH_3, OCH_3-1); 59.17 (CH_2, C-4´); 56.80 (CH_3, OCH_3-4); 36.63 (CH_2, C-3´); 35.49 (CH_2, C-1´); 16.72 (CH_3).

HRMS (ESI) : calcd. For $C_{22}H_{24}O_7Na$ 423.1420; found 423.1417.

From **203b**

2-[(2S,3R)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione **190b**



203b **190b**

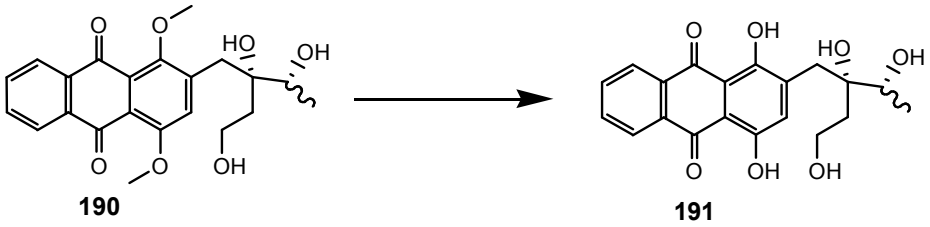
To a solution of **203b** (50 mg, 0.114 mmol) in CH_3CN (5 mL) was added $CeCl_3.7H_2O$ (127 mg, 0.342 mmol) and NaI (51 mg, 0.342 mmol). The reaction mixture was stirred under reflux for 24 hr and then diluted with water (20 mL) and acidified with 1N HCl. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 44 mg of **190b** (0.110 mmol, 96%) as a red solid.

*2-[(2S,3R)-2,3-dihydroxy-2-(2-hydroxyethyl)butyl]-1,4-dimethoxy-anthracene-9,10-dione **190b***

^{1}H NMR (500 MHz, d6-DMSO) : δ = 13.48 (s, 1H, OH-1); 12.78 (s, 1H, OH-4); 8.28 (m, 2H, H-5 and H-8); 7.98 (m, 2H, H-6 and H-7); 7.49 (s, 1H; H-3); 4.73 (d, 1H, J= 5.1 Hz, OH-5´); 4.50 (dd, 1H, J = 4.7 Hz, 5.1 Hz, OH-4´); 4.41 (s, 1H, OH-2´); 3.54 (m, 3H, H-4´and H-5´); 3.07 (d, 1H, J = 13.6 Hz, H-1´/1); 2.68 (d, 1H, J = 13.6 Hz, H-1´/2); 1.79 (m, 1H, H-3´/1); 1.31 (m, 1H, H-3´/2); 1.15 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, d6-DMSO) : δ = 187.05 (Cq, C-9); 186.13 (Cq, C-10); 156.90 (Cq, C-1); 156.01 (Cq, C-4); 141.52 (Cq, C-2); 135.07 (CH, C-6); 134.96 (CH, C-7); 133.05 (Cq, C-8a); 1323.93 (Cq, C-10a); 131.18 (CH, C-3); 126.76 (CH, C-5); 126.58 (CH, C-8); 111.61 (Cq, C-9a); 111.00 (Cq, C-4a); 76.11 (Cq. C-2´); 70.16 (CH, C-5´); 56.74 (CH_2, C-4´); 37.22 (CH_2, C-3´); 33.07 (CH_2, C-1´); 17.35 (CH_3).

2-((2S)-2,4-dihydroxy-2-(1-hydroxyethyl)butyl)-1,4-dihydroxyanthracene-9,10-dione **191**



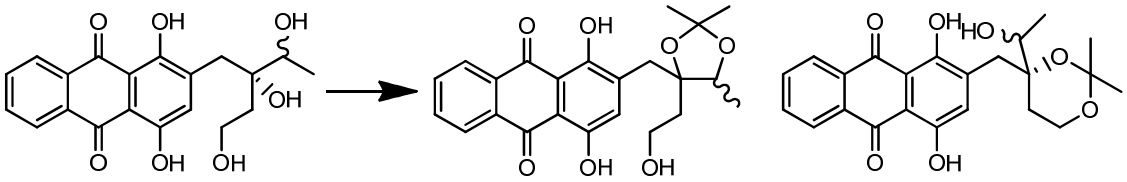
190 **191**

To a solution of **190a+b** (40 mg, 0.099 mmol) in DCM (5 mL) cooled to –45 °C under argon atmosphere was slowly added BCl_3 1M in DCM (0.21 mL, 0.210 mmol). The reaction mixture was stirred at –45 °C for 1 h 30 and quenched with water (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel wiith EtOac to give 20 mg of a mixture of **191a** and **191b** (0.054 mmol, 54%) as a red solid.

2-((2S)-2,4-dihydroxy-2-(1-hydroxyethyl)butyl)-1,4-dihydroxyanthracene-9,10-dione ***191***

^1H NMR (200 MHz, $CDCl_3$) : δ = 13.84 (s, 1H, OH-1); 12.75 (s, 1H, OH-4); 8.31 (m, 2H, H-5 and H-8); 7.83 (m, 2H, H-6 and H-7); 7.32 (s, 1H, H-3); 3.87 (m, 2H, H-4´); 3.46 (q, 1H, J = 6.3 Hz, H-5´); 3.23 (d, 1H, J = 13.6 Hz, H-1´/1); 2.86 (d, 1H, J = 13.6 Hz, H-1´/2); 1.77 (m, 2H, H-3´); 1.25 (d, 3H, J = 6.3 Hz, CH_3).

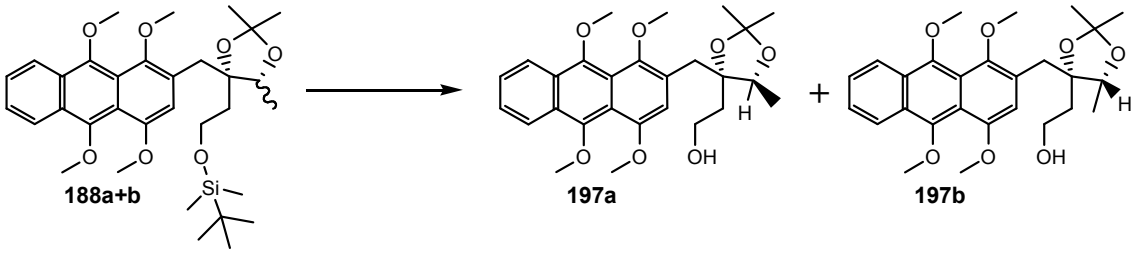
1,4-dihydroxy-2-((4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)anthracene-9,10-dione **191** and 1,4-dihydroxy-2-(((4S)-4-(1-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)anthracene-9,10-dione **192**



191 **192** **195**

To a solution of **187a+b** (65 mg, 0.175 mmol) in acetone (5 mL) was added molecular sieves 4A, 2,2-dimethoxypropane (55 mg, 0.525 mmol) and pTsOH (2 mg, 0.009 mmol) under an argon atmosphere. The reaction mixture was stirred at RT for 24 hrs and poured in sat. $NaHCO_3$ (15 mL) / EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (10/1) to give 32 mg of a mixture of **192** and **195** (0.078 mmol, 44%) which was not separable by chromatography.

2-[(4S,5S)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethanol **197a** and 2-[(4S,5R)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethanol **197b**



188a+b (4.57 g, 7.814 mmol) was dissolved in dry THF (90 mL) under argon atmosphere. TBAF 1M in THF (19.5 mL, 19.535 mmol) was added at RT and the reaction mixture was stirred at RT for 1 hr. The reaction mixture was poured in sat. $NaHCO_3$ (150 mL) / EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 70 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (2/1) to give in order of elution 2.203 g of **197a** (4.682 mmol, 60%) as a yellow foam, 0.18 g of a mixture **197a** and **197b** (0.378 mmol, 5%) as a yellow foam and 1.22 g of **197b** (2.593 mmol, 33%) as a yellow foam.

*2-[(4S,5S)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethanol **197a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.93 (s, 1H, H-3); 4.37 (q, 1H, J = 6.3Hz, H-5´); 4.02 (s, 3H, OCH_3-4); 4.00 (s, 3H, OCH_3-10); 3.93 (s, 3H, OCH_3-9); 3.81 (m, 1H, H-4´/1); 3.78 (s, 3H, OCH_3-1); 3.66 (m, 1H, H-4´/2); 3.22 (d, 1H, J = 13.6 Hz, H-1´/1); 2.81 (brs, 1H, OH-4´); 2.75 (d, 1H, J = 13.6 Hz, H-1´/2); 1.88 (m, 2H, H-3´); 1.75 (s, 3H, H-acetonide); 1.48 (d, 3H, J = 6.3 Hz, CH_3); 1.47 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 151.74 (Cq, C-4); 149.29 (Cq, C-10); 147.04 (Cq, C-9); 146.64 (Cq, C-1); 126.77 (Cq, C-8a); 126.27 (Cq, C-10a); 126.07 (CH, C-6); 125.58 (Cq, C-2); 125.53 (CH, C-7); 122.97 (CH, C-5); 122.51 (CH, C-8); 120.45 (Cq,

C-9a); 119.30 (Cq, C-4a); 107.75 (CH, C-3); 107.33 (Cq, C-acetonide); 85.02 (Cq, C-2´); 77.05 (CH, C-5´); 63.46 (CH_3, OCH_3-10); 63.31 (CH_3, OCH_3-9); 61.84 (CH_3, OCH_3-1); 58.92 (CH_2, C-4´); 56.08 (CH_3, OCH_3-4); 36.82 (CH_2, C-3´); 33.00 (CH_2, C-1´); 28.76 (CH_3, C-acetonide); 26.68 (CH_3, C-acetonide); 14.20 (CH_3).

HRMS (ESI) : calcd. For $C_{27}H_{34}O_7Na$ 493.2202; found 493.2210.

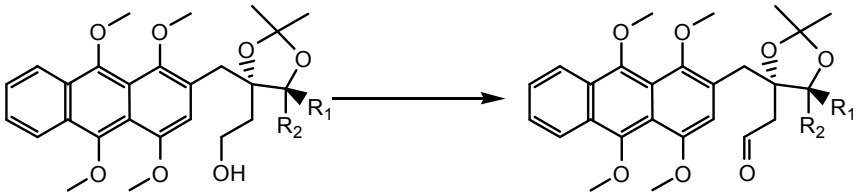
2-[(4S,5R)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]ethanol ***197b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.35 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.68 (s, 1H, H-3); 4.24 (m, 1H, H-4´/1); 4.09 (q, 1H, J = 6.3Hz, H-5´); 4.03 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.97 (m, 1H, H-4´/2); 3.94 (s, 3H, OCH_3-9); 3.76 (s, 3H, OCH_3-1); 3.18 (d, 1H, J = 13.6 Hz, H-1´/1); 3.14 (d, 1H, J = 13.6 Hz, H-1´/2); 2.11 (ddd, 1H, J = 5.1 Hz, 9.8Hz, 14.5 Hz, H-3´/1); 1.62 (dt, 1H, J = 4.1 Hz, 14.5 Hz, H-3´/2); 1.48 (s, 3H, H-acetonide); 1.22 (d, 3H, J = 6.3 Hz, CH_3); 0.98 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 151.61 (Cq, C-4); 149.26 (Cq, C-10); 147.29 (Cq, C-9); 146.87 (Cq, C-1); 126.83 (Cq, C-8a); 126.36 (Cq, C-10a); 126.17 (CH, C-6); 125.67 (CH, C-7); 124.71 (Cq, C-2); 122.92 (CH, C-5); 122.51 (CH, C-8); 120.45 (Cq, C-9a); 119.27 (Cq, C-4a); 108.34 (CH, C-3); 106.97 (Cq, C-acetonide); 85.57 (Cq, C-2´); 76.06 (CH, C-5´); 63.51 (CH_3, OCH_3-10); 63.42 (CH_3, OCH_3-9); 61.79 (CH_3, OCH_3-1); 59.63 (CH_2, C-4´); 56.45 (CH_3, OCH_3-4); 35.26 (CH_2, C-3´); 34.31 (CH_2, C-1´); 28.16 (CH_3, C-acetonide); 26.47 (CH_3, C-acetonide); 13.69 (CH_3).

HRMS (ESI) : calcd. For $C_{27}H_{34}O_7$ 471.2383; found 471.2392. (MH+)

2-[(4S,5S)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde **198a**



197a :R_1 = CH_3, R_2 = H
197b :R_1 = H, R_2 = CH_3

198a :R_1 = CH_3, R_2 = H
198b :R_1 = H, R_2 = CH_3

To a solution of DMSO (0.99 mL, 13.95 mmol) in DCM (55 mL) cooled to –70 °C under argon was added dropwise oxalylchloride (0.61 mL, 6.98 mmol) and the reaction mixture was stirred for 1 hr at –70°C. **197a** (2.19 g, 4.65 mmol) in DCM (4 mL) was slowly added at –70°C and the reaction mixture was stirred for 1 hr. Et_3N (4.27 mL, 30.69 mmol) was then added at that temperature and stirring was continue for 1hr allowing the temperature to warmed up slowly to 0°C. The reaction mixture was then poured in brine (60 mL) / EtOAc (100 mL). The layers were separated and the organic layer was successively washed with sat. NH_4Cl (60 mL), sat. $NaHCO_3$ (60 mL) and brine (60 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 2.1 g of **198a** (4.48 mmol, 96%) as a yellow foam.

*2-[(4S,5S)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde **198a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.65 (dd, 1H, J = 1.3 Hz, 2.2 Hz, H-4´); 8.34 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.81 (s, 1H, H-3); 4.28 (q, 1H, J = 6.3 Hz, H-5´); 4.03 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.91 (s, 3H, OCH_3-9); 3.70 (s, 3H, OCH_3-1); 3.23 (d, 1H, J = 13.6 Hz, H-1´/1); 2.77 (dd, 1H, J = 2.2 Hz, 16.4 Hz, H-3´/1); 2.73 (d, 1H, J = 13.6 Hz, H-1´/2); 2.62 (dd, 1H, J = 1.3 Hz, 16.34 Hz, H-3´/2); 1.74 (s, 3H, H-acetonide); 1.55 (d, 3H, J = 6.3 Hz, CH_3); 1.40 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 200.98 (CH, C-4´); 151.85 (Cq, C-4); 149.32 (Cq, C-10); 147.24 (Cq, C-9); 146.90 (Cq, C-1); 126.87 (Cq, C-8a); 126.39 (Cq, C-10a); 126.13 ((CH, C-6); 125.63 (CH, C-7); 124.86 (Cq, C-2); 122.96 (CH, C-5); 122.53

(CH, C-8); 120.58 (Cq, C-9a); 119.42 (Cq, C-4a); 107.92 (CH, C-3); 107.64 (Cq, C-acetonide); 82.93 (Cq, C-2´); 78.74 (CH, C-5´); 63.48 (CH_3, OCH_3-10); 63.46 (CH_3, OCH_3-9); 61.57 (CH_3, OCH_3-1); 56.07 (CH_3, OCH_3-4); 49.71 (CH_2, C-3´); 33.69 (CH_2, C-1´); 28.67 (CH_3, C-acetonide); 26.44 (CH_3, C-acetonide); 14.24 (CH_3).

HRMS (ESI) : calcd. For $C_{27}H_{32}O_7$ 469.2226; found 469.2221 (MH+) .

NB : the same procedure as for **198a** was used from **197b** to give **198b** in 96% yield.

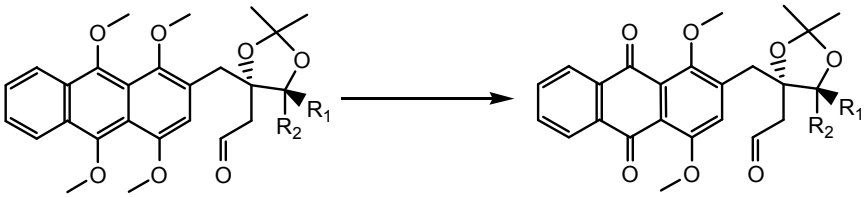
2-[(4S,5R)-2,2,5-trimethyl-4-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]-1,3-dioxolan-4-yl]acetaldehyde ***198b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.95 (dd, 1H, J = 1.9 Hz, 3.5 Hz, H-4´); 8.34 (m, 2H, H-5 and H-8); 7.51 (m, 2H, H-6 and H-7); 6.70 (s, 1H, H-3); 4.18 (q, 1H, J = 6.3 Hz, H-5´); 4.04 (s, 3H, OCH_3-4); 3.99 (s, 3H, OCH_3-10); 3.94 (s, 3H, OCH_3-9); 3.76 (s, 3H, OCH_3-1); 3.21 (d, 1H, J = 13.6 Hz, H-1´/1); 3.14 (d, 1H, J = 13.6 Hz, H-1´/2); 2.70 (dd, 1H, J = 1.9 Hz, 15.2 Hz, H-3´/1); 2.46 (dd, 1H, J = 3.5 Hz, 15.2 Hz, H-3´/2); 1.47 (s, 3H, H-acetonide); 1.19 (d, 3H, J = 6.3 Hz, CH_3); 1.18 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 203.29 (CH, C-4´); 151.90 (Cq, C-4); 149.31 (Cq, C-10); 147.44 (Cq, C-9); 146.82 (Cq, C-1); 126.93 (Cq, C-8a); 126.49 (Cq, C-10a); 126.22 (CH, C-6); 125.74 (CH, C-7); 123.89 (Cq, C-2); 122.94 (CH, C-5); 122.53 (CH, C-8); 120.47 (Cq, C-9a); 119.36 (Cq, C-4a); 107.81 (CH, C-3); 107.62 (Cq, C-acetonide); 83.59 (Cq, C-2´); 76.96 (CH, C-5´); 63.54 (CH_3, OCH_3-9 and OCH_3-10); 61.83 (CH_3, OCH_3-1); 56.42 (CH_3, OCH_3-4); 47.66 (CH_2, C-3´); 36.68 (CH_2, C-1´); 28.29 (CH_3, C-acetonide); 26.58 (CH_3, C-acetonide); 13.84 (CH_3).

HRMS (ESI) : calcd. For $C_{27}H_{32}O_7$ 469.2226; found 469.2217 (MH+).

2-[(4S,5S)-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetaldehyde **199a**



198a :R_1 = CH_3, R_2 = H
198b :R_1 = H, R_2 = CH_3

199a :R_1 = CH_3, R_2 = H
199b :R_1 = H, R_2 = CH_3

198a (2.08 g, 4.44 mmol) was dissolved in CH_3CN (60 mL) and cooled to 2 °C. CAN (7.3 g, 13.32 mmol) in water (130 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 30 min. The reaction mixture was diluted with water (80 mL) and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (6/1) to give 1.91 g of **199a** (4.35 mmol, 98%) as a yellow solid.

*2-[(4S,5S)-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetaldehyde **199a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.62 (dd, 1H, J = 1.6 Hz, 2.5 Hz, H-4´); 8.16 (m, 2H, H-5 and H-8); 7.71 (m, 2H, H-6 and H-7); 7.45 (s, 1H, H-3); 4.25 (q, 1H, J = 6.3 Hz, H-5´); 4.00 (s, 3H, OCH_3-4); 3.81 (s, 3H, OCH_3-1); 3.18 (d, 1H, J = 12.9 Hz, H-1´/1); 2.66 (d, 1H, J = 12.9 Hz, H-1´/2); 2.65 (dd, 1H, J = 2.5 Hz and 16.4 Hz, H-3´/1); 2.48 (dd, 1H, J = 1.6 Hz, 16.4 Hz, H-3´/2); 1.64 (s, 3H, H-acetonide); 1.50 (d, 3H, J = 6.3 Hz, CH_3); 1.34 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 200.27 (CH, C-4´); 183.37 (Cq, C-9); 182.92 (Cq, C-10); 155.60 (Cq, C-4); 152.78 (Cq, C-1); 140.54 (Cq, C-2); 134.27 (Cq, C-8a); 133.78 (Cq, C-10a); 133.59 (CH, C-6); 133.24 (CH, C-7); 127.03 (Cq, C-9a); 126.47 (CH, C-5); 126.39 (CH, C-8); 123.35 (CH, C-3); 121.76 (Cq, C-4a); 107.69 (Cq, C-acetonide); 82.09 (Cq, C-2´); 78.52 (CH, C-5´); 61.90 (CH_3, OCH_3-1); 56.47 (CH_3,

OCH_3-4); 49.25 (CH_2, C-3´); 33.76 (CH_2, C-1´); 28.58 (CH_3, C-acetonide); 26.19 (CH_3, C-acetonide); 14.14 (CH_3).

HRMS (ESI) : calcd. For $C_{25}H_{26}O_7$ 438.1679; found 438.1676.

NB : the same procedure as for **199a** was used from **198b** to give **199b** in 96% yield.

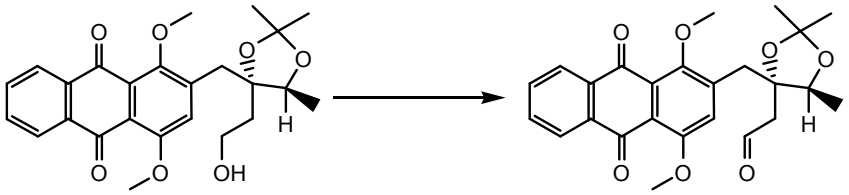
2-[(4S,5R)-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetaldehyde **199b**

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.96 (dd, 1H, J = 1.9 Hz, 3.8 Hz, H-4´); 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.37 (s, 1H, H-3); 4.02 (s, 3H, OCH_3-4); 3.88 (s, 3H, OCH_3-1); 3.85 (q, 1H, J = 6.3 Hz, H-5´); 3.14 (d, 1H, J = 13.9 Hz, H-1´/1); 3.07 (d, 1H, J = 12.9 Hz, H-1´/2); 2.81 (dd, 1H, J = 1.9 Hz and 14.5 Hz, H-3´/1); 2.37 (dd, 1H, J = 3.8 Hz, 14.5 Hz, H-3´/2); 1.46 (s, 3H, H-acetonide); 1.18 (d, 3H, J = 6.3 Hz, CH_3); 0.99 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 202.67 (CH, C-4´); 183.31 (Cq, C-9); 182.89 (Cq, C-10); 155.61 (Cq, C-4); 152.73 (Cq, C-1); 139.38 (Cq, C-2); 134.26 (Cq, C-8a); 133.77 (Cq, C-10a); 133.65 (CH, C-6); 133.30 (CH, C-7); 126.91 (Cq, C-9a); 126.53 (CH, C-5); 126.43 (CH, C-8); 123.60 (CH, C-3); 121.89 (Cq, C-4a); 107.79 (Cq, C-acetonide); 83.08 (Cq, C-2´); 75.92 (CH, C-5´); 62.15 (CH_3, OCH_3-4); 56.78 (CH_3, OCH_3-1); 48.09 (CH_2, C-3´); 35.23 (CH_2, C-1´); 28.22 (CH_3, C-acetonide); 26.60 (CH_3, C-acetonide); 13.70 (CH_3).

HRMS (ESI) : calcd. For $C_{25}H_{26}O_7$ 438.1679; found 438.1682.

2-[(4S,5S)-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetaldehyde ***199a***



203a **199a**

To a solution of DMSO (0.03 mL, 0.425 mmol) in DCM (4 mL) cooled to –70 °C under argon was added dropwise oxalylchloride (0.02 mL, 0.212 mmol) and the reaction mixture was stirred for 1 hr at –70°C. **203a** (85 mg, 0.193 mmol) in DCM (2 mL) was slowly added at –70°C and the reaction mixture was stirred for 1 hr. Et_3N (0.13 mL, 0.965 mmol) was then added at that temperature and stirring was continue for 1hr allowing the temperature to warmed up slowly to 0°C. The reaction mixture was then poured in brine (15 mL) / EtOAc (10 mL). The layers were separated and the organic layer was successively washed with sat. NH_4Cl (15 mL), sat. $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 64 mg of **198a** (0.147 mmol, 76%) as a yellow foam.

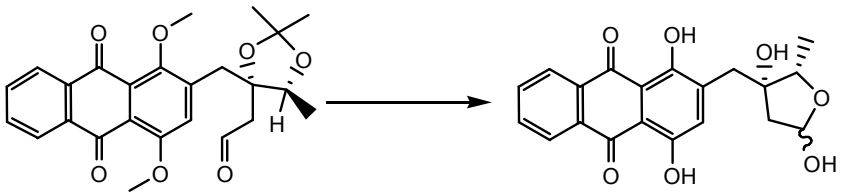
2-[(4S,5S)-4-[(1,4-dimethoxy-9,10-dioxo-2-anthryl)methyl]-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetaldehyde ***199a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 9.62 (dd, 1H, J = 1.6 Hz, 2.5 Hz, H-4´); 8.16 (m, 2H, H-5 and H-8); 7.71 (m, 2H, H-6 and H-7); 7.45 (s, 1H, H-3); 4.25 (q, 1H, J = 6.3 Hz, H-5´); 4.00 (s, 3H, OCH_3-4); 3.81 (s, 3H, OCH_3-1); 3.18 (d, 1H, J = 12.9 Hz, H-1´/1); 2.66 (d, 1H, J = 12.9 Hz, H-1´/2); 2.65 (dd, 1H, J = 2.5 Hz and 16.4 Hz, H-3´/1); 2.48 (dd, 1H, J = 1.6 Hz, 16.4 Hz, H-3´/2); 1.64 (s, 3H, H-acetonide); 1.50 (d, 3H, J = 6.3 Hz, CH_3); 1.34 (s, 3H, H-acetonide).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 200.27 (CH, C-4´); 183.37 (Cq, C-9); 182.92 (Cq, C-10); 155.60 (Cq, C-4); 152.78 (Cq, C-1); 140.54 (Cq, C-2); 134.27 (Cq, C-8a); 133.78 (Cq, C-10a); 133.59 (CH, C-6); 133.24 (CH, C-7); 127.03 (Cq, C-9a); 126.47 (CH, C-5); 126.39 (CH, C-8); 123.35 (CH, C-3); 121.76 (Cq, C-4a); 107.69 (Cq, C-acetonide); 82.09 (Cq, C-2´); 78.52 (CH, C-5´); 61.90 (CH_3, OCH_3-1); 56.47 (CH_3,

OCH_3-4); 49.25 (CH_2, C-3´); 33.76 (CH_2, C-1´); 28.58 (CH_3, C-acetonide); 26.19 (CH_3, C-acetonide); 14.14 (CH_3).

2-[[(2S,3S)-3,5-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dihydroxy-anthracene-9,10-dione **196a**



199a **196a**

To a solution of **199a** (1 g, 2.281 mmol) in DCM (55 mL) cooled to 2 °C was slowly added BCl_3 1M in DCM (13.7 mL, 13.68 mmol) under an argon atmosphere. The reaction mixture was stirred for 40 min at 2°C and then poured in 0.5 N NaOH (100 mL) / DCM (50 mL). The organic layer was washed with 0.5 N NaOH (2 x 50 mL). The combined aqueous layers were acidified to pH = 6 with 1N HCl under ice cooling and extracted with DCM (3 x 70 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure at **15 °C** to give 0.79 g of **196a** (2.133 mmol, 94%) as a red solid.

*2-[[(2S,3S)-3,5-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dihydroxy-anthracene-9,10-dione **196a***

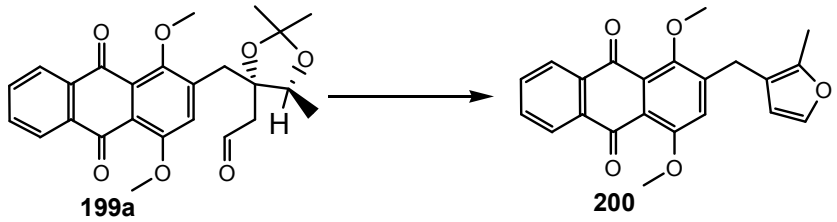
^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.66 (s, 1H, OH-1); 12.87 (s, 1H, OH-4); 8.36 (m, 2H, H-5 and H-8); 7.85 (m, 2H, H-6 and H-7); 7.29 (s, 1H, H-3); 5.38 (m, 1H, H-4´); 4.01 (q, 1H, J = 6.3 Hz, H-6´); 3.52 (d, 1H, J= 7.3 Hz, OH-4´); 3.39 (s, 1H, OH-2´); 3.07 (d, 1H, J = 13.6 Hz, H-1´/1); 2.90 (d, 1H, J = 13.6 Hz, H-1´/2);; 2.21 (dd, 1H, J = 5.1, 13.3 Hz, H-3´/1); 1.99 (d, 1H, J = 13.3 Hz, H-3´/2); 1.34 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 187.46 (Cq, C-9); 186.50 (Cq, C-10); 157.30 (Cq, C-4); 156.44 (Cq, C-1); 139.15 (Cq, C-2); 134.73 (CH, C-6); 134.51 (CH, C-7); 133.54 (Cq, C-8a); 133.27 (Cq, C-10a); 130.71 (CH, C-3); 127.15 (CH, C-5); 127.07

(CH, C-8); 112.59 (Cq, C-9a); 112.00 (Cq, C-4a); 97.71 (CH, C-4´); 83.13 (CH, C-6´); 80.00 (Cq, C-2´); 45.42 (CH_2, C-3´); 36.16 (CH_2, C-1´); 14.96 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{18}O_7Na$ 393.0950; found 393.0948.

1,4-dimethoxy-2-[(2-methyl-3-furyl)methyl]anthracene-9,10-dione **200**



199a **200**

Py.HCl (34 mg, 0.291 mmol) was added to a solution of **199a** (17 mg, 0.039 mmol) in pyridine (1.5 mL). The reaction mixture was heated at 195 °C and stirred for 4 hrs. The mixture was cooled to RT and concentrated under reduced pressure. The crude product was partitioned between sat. NH_4Cl (10 mL) and EtOAc (15 mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 11 mg of **200** (0.030 mmol, 78%) as an yellow foam.

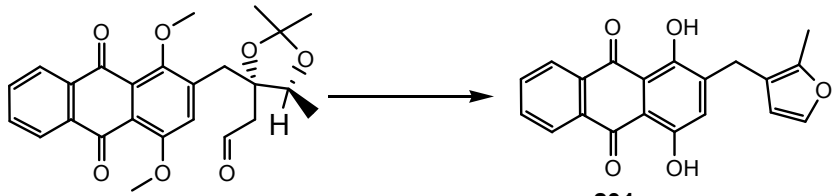
*1,4-dimethoxy-2-[(2-methyl-3-furyl)methyl]anthracene-9,10-dione **200***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.71 (m, 2H, H-6 and H-7); 7.26 (d, 1H, J = 1.6 Hz, H-4´); 7.10 (s, 1H, H-3); 6.15 (d, 1H, J = 1.6 Hz, H-3´); 3.92 (s, 3H, OCH_3-4); 3.87 (s, 3H, OCH_3-1); 3.85 s, 2H, H-1´); 2.29 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.53 (Cq, C-9); 182.89 (Cq, C-10); 156.50 (Cq, C-4); 152.37 (Cq, C-1); 148.54 (Cq, C-5´); 144.71 (Cq, C-2); 140.52 (CH, C-4´); 134.36 (Cq, C-8a); 133.88 (Cq, C-10a); 133.57 (CH, C-6); 133.21 (CH, C-7); 127.07 (Cq, C-9a); 126.51 (Cq, C-5); 126.38 (Cq, C-8); 121.10 (Cq, C-4a); 119.88 (CH, C-3);

115.63 (Cq, C-2´); 111.76 (CH, C-3´); 61.88 (CH_3, OCH_3-1); 56.66 (CH_3, OCH_3-4); 25.79 (CH_2, C-1´); 11.59 (CH_3).

1,4-dihydroxy-2-[(2-methyl-3-furyl)methyl]anthracene-9,10-dione **201**



199a **201**

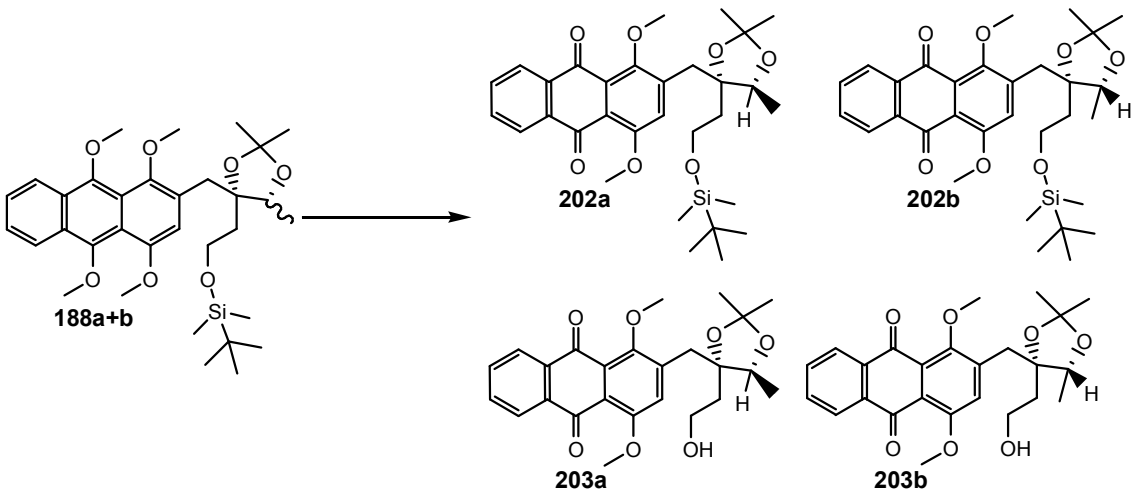
To a solution of **199a** (60 mg, 0.137 mmol) in CH_3CN (5 mL) was added $CeCl_3.7H_2O$ (306 mg, 0.822 mmol) and NaI (124 mg, 0.822 mmol). The reaction mixture was stirred under reflux for 24 hr and then diluted with water (20 mL) and acidified with 1N HCl. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 32 mg of **201** (0.096 mmol, 70%) as a red solid.

*1,4-dihydroxy-2-[(2-methyl-3-furyl)methyl]anthracene-9,10-dione **201***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.43 (s, 1H, OH-1); 12.93 (s, 1H, OH-4); 8.32 (m, 2H, H-5 and H-8); 7.81 (m, 2H, H-6 and H-7); 7.28 (d, 1H, J = 1.6 Hz, H-Fu5); 7.04 (s, 1H, H-3); 6.23 (d, 1H, J = 1.6 Hz, H-Fu4); 3.79 (s, 2H, H-CH2); 2.29 (s, 3H, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 187.13 (Cq, C-9); 186.31 (Cq, C-10); 157.80 (Cq, C-4); 156.71 (Cq, C-1); 148.89 (Cq, C-Fu2); 143.26 (Cq, C-2); 140.44 (CH, C-Fu5); 134.40 (CH, C-6); 134.26 (CH, C-7); 133.59 (Cq, C-8a); 133.43 (Cq, C-10a); 127.89 (CH, C-3); 126.98 (CH, C-5); 126.89 (CH, C-8); 114.63 (Cq, C-Fu3); 112.06 (Cq, C-9a); 112.00 (CH, C-Fu4); 111.30 (Cq, C-4a); 25.26 (CH_2); 11.54 (CH_3).

2-[[(4S)-4-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **202**, 2-[[(4S,5S)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **203b** and 2-[[(4S,5R)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **203b**



188a+b(153 mg, 0.27 mmol) was dissolved in CH_3CN (3 mL) and cooled to 2 °C. CAN (444 mg, 0.81 mmol) in water (6 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 30 min. The reaction mixture was diluted with water (15 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (1/1) to give in order of elution 18 mg of a mixture of **202a** and **202b** (0.032 mmol, 12%) as a yelow solid, 36 mg of **203a** (0.082 mmol, 30%) as a yellow solid and 35 mg of **203b** (0.079 mmol, 29%) as a yellow solid.

202a+b

HRMS (ESI) : calcd. For $C_{31}H_{42}O_7SiNa$ 577.2598; found 577.2585.

2-[[(4S,5S)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione ***203a***

^1H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.60 (s, 1H, H-3); 4.36 (q, 1H, J = 6.3 Hz, H-5´); 3.99 (s, 3H, OCH_3-4); 3.86 (s, 3H,

OCH_3-1); 3.74 (m, 1H, H-4´/1); 3.57 (m, 1H, H-4´/2); 3.13 (d, 1H, J = 13.6 Hz, H-1´/1); 2.70 (d, 1H, J = 13.6 Hz, H-1´/2); 1.72 (m, 2H, H-3´); 1.67 (s, 3H, H-acetonid); 1.45 (s, 3H, H-acetonid); 1.41 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.55 (Cq, C-9); 182.97 (Cq, C-10); 155.66 (Cq, C-4); 152.91 (Cq, C-1); 141.27 (Cq, C-2); 134.32 (Cq, C-8a); 133.86 (Cq, C-10a); 133.57 (CH, C-6); 133.21 (CH, C-7); 126.78 (Cq, C-9a); 126.49 (CH, C-5); 126.38 (CH, C-8); 122.64 (CH, C-3); 121.42 (Cq, C-4a); 107.54 (Cq, C-acetonid); 84.50 (Cq, C-2´); 76.74 (CH, C-5´); 62.18 (CH_3, OCH_3-1); 58.67 (CH_2, C-4´); 56.51 (CH_3, OCH_3-4); 36.09 (CH_2, C-3´); 32.72 (CH_2, C-1´); 28.69 (CH_3, C-acetonid); 26.57 (CH_3, C-acetonid); 13.86 (CH_3).

HRMS (ESI) : calcd. For $C_{25}H_{28}O_7$ 441.1913; found 441.1909 (MH+).

2-[[(4S,5R)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione ***203b***

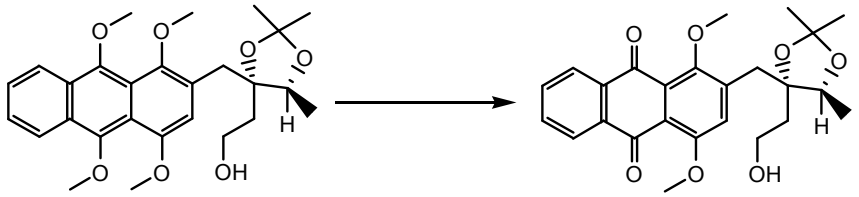
^1H NMR (500 MHz, $CDCl_3$) : δ = 8.18 (m, 2H, H-5 and H-8); 7.73 (m, 2H, H-6 and H-7); 7.36 (s, 1H, H-3); 4.13 (m, 1H, H-4´/1); 4.02 (s, 3H, OCH_3-4); 3.94 (m, 1H, H-4´/2); 3.88 (s, 3H, OCH_3-1); 3.74 (q, 1H, J = 6.3 Hz, H-5´); 3.17 (d, 1H, J = 13.9 Hz, H-1´/1); 3.16 (d, 1H, J = 13.9 Hz, H-1´/2); 2.11 (ddd, 1H, J = 5.7 Hz, 9.5 Hz, 14.5 Hz, H-3´/1); 1.57 (dt, 1H, J = 4.8 Hz, 14.5 Hz, H-3´/2); 1.45 (s, 3H, H-acetonid); 1.22 (d, 3H, J = 6.3 Hz, CH_3); 0.88 (s, 3H, H-acetonid);

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.43 (Cq, C-9); 182.98 (Cq, C-10); 155.54 (Cq, C-4); 152.94 (Cq, C-1); 140.41 (Cq, C-2); 134.30 (Cq, C-8a); 133.83 (Cq, C-10a); 133.64 (CH, C-6); 133.29 (CH, C-7); 126.81 (Cq, C-9a); 126.54 (CH, C-5); 126.44 (CH, C-8); 123.72 (CH, C-3); 121.67 (Cq, C-4a); 107.21 (Cq, C-acetonid); 84.83 (Cq, C-2´); 75.53 (CH, C-5´); 62.10 (CH_3, OCH_3-1); 59.34 (CH_2, C-4´); 56.78 (CH_3, OCH_3-4); 35.46 (CH_2, C-3´); 33.50 (CH_2, C-1´); 28.09 (CH_3, C-acetonid); 26.70 (CH_3, C-acetonid); 13.58 (CH_3).

HRMS (ESI) : calcd. For $C_{25}H_{28}O_7$ 441.1913; found 441.1913 (MH+).

2-[[(4S,5S)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **203a**

From **197a**



197a **203a**

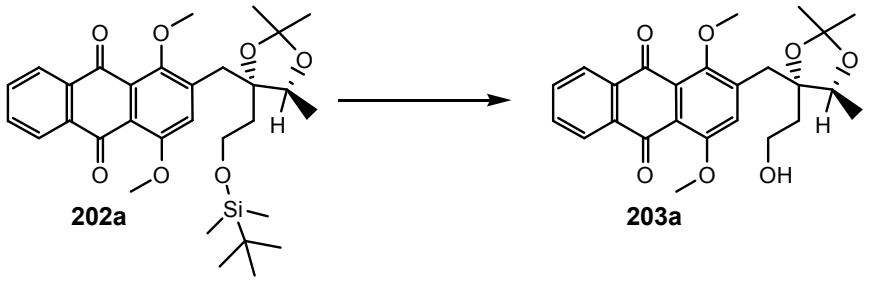
197a(0.30 g, 0.638 mmol) was dissolved in CH_3CN (9 mL) and cooled to 2 °C. CAN (1.05 g, 0.81 mmol) in water (20 mL) was added to the solution and the reaction mixture was stirred at 2 °C for 30 min. The reaction mixture was diluted with water (30mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / EtOAc (1/1) to give 280 mg of **203a** (0.636 mmol, 99%) as a yelow solid.

*2-[[(4S,5S)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **203a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.60 (s, 1H, H-3); 4.36 (q, 1H, J = 6.3 Hz, H-5´); 3.99 (s, 3H, OCH_3-4); 3.86 (s, 3H, OCH_3-1); 3.74 (m, 1H, H-4´/1); 3.57 (m, 1H, H-4´/2); 3.13 (d, 1H, J = 13.6 Hz, H-1´/1); 2.70 (d, 1H, J = 13.6 Hz, H-1´/2); 1.72 (m, 2H, H-3´); 1.67 (s, 3H, H-acetonid); 1.45 (s, 3H, H-acetonid); 1.41 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.55 (Cq, C-9); 182.97 (Cq, C-10); 155.66 (Cq, C-4); 152.91 (Cq, C-1); 141.27 (Cq, C-2); 134.32 (Cq, C-8a); 133.86 (Cq, C-10a); 133.57 (CH, C-6); 133.21 (CH, C-7); 126.78 (Cq, C-9a); 126.49 (CH, C-5); 126.38 (CH, C-8); 122.64 (CH, C-3); 121.42 (Cq, C-4a); 107.54 (Cq, C-acetonid); 84.50 (Cq, C-2´); 76.74 (CH, C-5´); 62.18 (CH_3, OCH_3-1); 58.67 (CH_2, C-4´); 56.51 (CH_3, OCH_3-4); 36.09 (CH_2, C-3´); 32.72 (CH_2, C-1´); 28.69 (CH_3, C-acetonid); 26.57 (CH_3, C-acetonid); 13.86 (CH_3).

From **202a**



202a **203a**

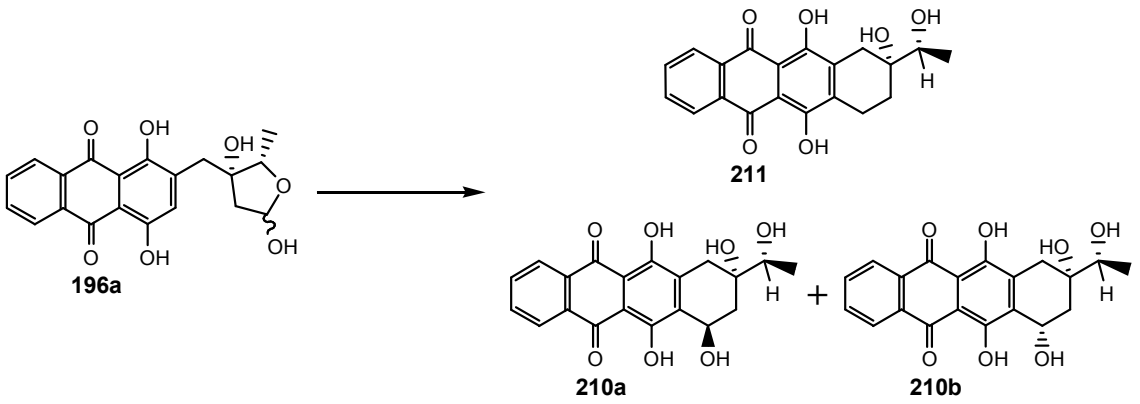
202a (3 g, 5.415 mmol) was dissolved in dry THF (70 mL) under argon atmosphere. TBAF 1M in THF (13.5 mL, 13.538 mmol) was added at RT and the reaction mixture was stirred at RT for 1 hr. The reaction mixture was poured in sat. $NaHCO_3$ (100 mL) / EtOAc (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (1/1) to give 2.14 g of **197b** (4.874 mmol, 90%) as a yellow solid.

2-[[(4S,5S)-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione ***203a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 8.17 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-6 and H-7); 7.60 (s, 1H, H-3); 4.36 (q, 1H, J = 6.3 Hz, H-5´); 3.99 (s, 3H, OCH_3-4); 3.86 (s, 3H, OCH_3-1); 3.74 (m, 1H, H-4´/1); 3.57 (m, 1H, H-4´/2); 3.13 (d, 1H, J = 13.6 Hz, H-1´/1); 2.70 (d, 1H, J = 13.6 Hz, H-1´/2); 1.72 (m, 2H, H-3´); 1.67 (s, 3H, H-acetonid); 1.45 (s, 3H, H-acetonid); 1.41 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 183.55 (Cq, C-9); 182.97 (Cq, C-10); 155.66 (Cq, C-4); 152.91 (Cq, C-1); 141.27 (Cq, C-2); 134.32 (Cq, C-8a); 133.86 (Cq, C-10a); 133.57 (CH, C-6); 133.21 (CH, C-7); 126.78 (Cq, C-9a); 126.49 (CH, C-5); 126.38 (CH, C-8); 122.64 (CH, C-3); 121.42 (Cq, C-4a); 107.54 (Cq, C-acetonid); 84.50 (Cq, C-2´); 76.74 (CH, C-5´); 62.18 (CH_3, OCH_3-1); 58.67 (CH_2, C-4´); 56.51 (CH_3, OCH_3-4); 36.09 (CH_2, C-3´); 32.72 (CH_2, C-1´); 28.69 (CH_3, C-acetonid); 26.57 (CH_3, C-acetonid); 13.86 (CH_3).

(7R,9S)-6,7,9,11-tetrahydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione **210a** and (7S,9S)-6,7,9,11-tetrahydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione **210b**



A solution of NaOH (38 mg, 0.945 mmol) and $Na_2S_2O_4$ (49 mg, 0.284 mmol) in water (1.2 mL) was added dropwise at –10 °C to a solution of **196a** (70 mg, 0.189 mmol) in THF (5 mL) / MeOH (5 mL) under argon atmosphere. After stirring for 2 hrs the reaction mixture was quenched at –10 °C by bubbling air through it for 30 min. The reaction mixture was then poured in 0.05 N HCl (30 mL) / EtOAc (45 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / isopropanol (30/1) to give in order of elution 13 mg of **211** (0.037 mmol, 19 %) as a red solid and 37 mg of a mixture of **210a** and **210b** (77 / 23) (0.099 mmol, 52%) as a red solid.

(9R)-6,9,11-trihydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione ***211***

^{1}H NMR (500 MHz, d_6-DMSO) : δ = 13.36 (s, 1H, OH-11); 13.35 (s, 1H, OH-6); 8.21 (m, 2H, H-1 and H-4); 7.94 (m, 2H, H-2 and H-3); 4.69 (d, 1H, J = 6.3 Hz, OH-13); 4.28 (s, 1H, OH-9); 3.56 (m, 1H, H-13); 2.82 (d, 1H, J = 18.3 Hz, H-7/1); 2.66 (m, 3H, H-7/2 and H-10); 1.88 (m, 1H, H-8/1); 1.51 (m, 1H, H-8/2);1.14 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, d_6-DMSO) : δ = 186.05 (Cq, C-5); 186.01 (Cq, C-12); 156.47 (Cq, C-6); 155.70 (Cq, C-11); 138.42 (Cq, C-6a); 137.73 (Cq, C-10a); 134.80 (CH, C-2 and C-3); 132.92 (Cq, C-4a and C-12a); 126.48 (CH, C-1 and C-4); 109.02 (Cq, C-5a); 108.88 (Cq, C-11a); 72.14 (CH, C-13); 70.19 (Cq, C-9); 32.16 (CH_2, C-10); 25.79 (CH_2, C-8); 20.05 (CH_2, C-7); 17.08 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{18}O_6$ 354.1103; found 354.1104.

(7R,9S)-6,7,9,11-tetrahydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione ***210a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.60 (s, 1H, OH-6); 13.33 (s, 1H, OH-11); 8.23 (m, 2H, H-1 and H-4); 7.95 (m, 2H, H-2 and H-3); 5.17 (d, 1H, *J* = 5.7 Hz, OH-7); 5.05 (m, 1H, H-7); 4.85 (d, 1H, *J* = 5.7 Hz, OH-13); 4.45 (s, 1H, OH-9); 3.54 (q, 1H, J = 6.3 Hz, H-13); 2.85 (d, 1H, J = 18.3 Hz, H-10/1); 2.68 (d, 1H, J = 18.3 Hz, H-10/2); 2.14 (m, 1H, H-8/1); 1.75 (m, 1H, H-8/2); 1.14 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 186.33 (Cq, C-5); 186.22 (Cq, C-12); 156.70 (Cq, C-6); 155.80 (Cq, C-11); 139.18 (Cq, C-6a); 138.41 (Cq, C-10a); 134.96 (CH, C-3); 134.88 (CH, C-2); 133.03 (Cq, C-4a); 132.87 (Cq, C-12a); 126.59 (CH, C-4); 126.55 (CH, C-1); 110.25 (Cq, C-11a); 109.71 (Cq, C-5a); 72.37 (CH, C-13); 72.10 (Cq, C-9); 62.64 (CH, C-7); 36.46 (CH_2, C-8); 33.36 (CH_2, C-10); 17.11 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{18}O_7$ 370.1053; found 370.1050.

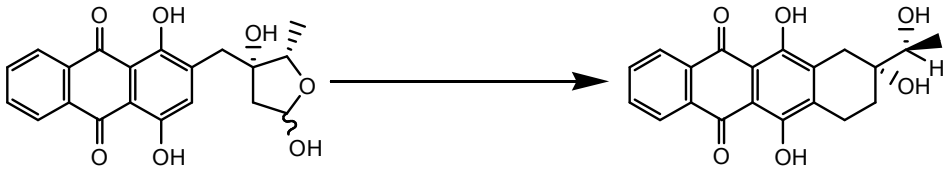
(7S,9S)-6,7,9,11-tetrahydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione ***210b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.42 (s, 1H, OH-6); 13.30 (s, 1H, OH-11); 8.23 (m, 2H, H-1 and H-4); 7.95 (m, 2H, H-2 and H-3); 5.30 (d, 1H, J = 7.9 Hz, OH-7); 5.14 (s, 1H, OH-9); 5.00 (m, 1H, H-7); 4.81 (d, 1H, J = 5.7 Hz, OH-13); 3.54 (q, 1H, 6.3 Hz, H-13); 2.88 (d, 1H, J = 18.3 Hz, H-10/1); 2.75 (d, 1H, J = 18.3 Hz, H-10/2); 2.14 (m, 1H, H-8/1); 1.75 (m, 1H, H-8/2); 1.16 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 186.38 (Cq, C-5); 186.05 (Cq, C-12); 156.50 (Cq, C-6); 155.96 (Cq, C-11); 137.81 (Cq, C-6a); 136.96 (Cq, C-10a); 134.96 (CH, C-3); 134.88, (CH, C-2); 133.03 (Cq, C-4a); 132.87 (Cq, C-12a); 126.59 (CH, C-4); 126.55 (CH, C-1); 110.43 (Cq, C-11a); 109.81 (Cq, C-5a); 72.30 (Cq, C-9); 71.67 (CH, C-13); 60.84 (CH, C-7); 33.07 (CH_2, C-8); 32.92 (CH_2, C-10); 16.94 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{18}O_7$ 370.1053; found 370.1050.

(9R)-6,9,11-trihydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione **211**



196a **211**

A solution of NaOH (0.43 g, 10.665 mmol) and $Na_2S_2O_4$ (0.56 g, 3.199 mmol) in water (5.3 mL) was added dropwise at RT to a solution of **196a** (0.79 g, 2.133 mmol) in THF (31 mL) / MeOH (31 mL) under an argon atmosphere. After stirring for 1 hr 30 the reaction mixture was quenched at RT by bubbling air through it for 30 min. The reaction mixture was then poured in 0.05 N HCl (60 mL) / EtOAc (80 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was triturated with toluene / EtOAc (1/1, 6 mL) to give 0.51 g of **211** (1.431 mmol, 67 %) as a red solid.

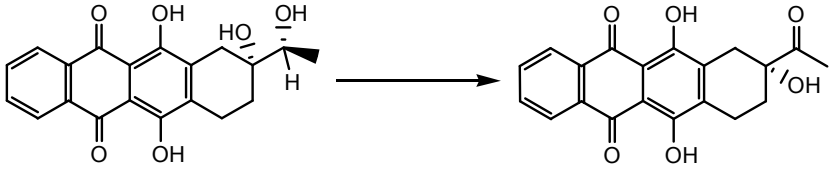
(9R)-6,9,11-trihydroxy-9-[(1S)-1-hydroxyethyl]-8,10-dihydro-7H-tetracene-5,12-dione ***211***

^{1}H NMR (500 MHz, d_6-DMSO) : δ = 13.36 (s, 1H, OH-11); 13.35 (s, 1H, OH-6); 8.21 (m, 2H, H-1 and H-4); 7.94 (m, 2H, H-2 and H-3); 4.69 (d, 1H, J = 6.3 Hz, OH-13); 4.28 (s, 1H, OH-9); 3.56 (m, 1H, H-13); 2.82 (d, 1H, J = 18.3 Hz, H-7/1); 2.66 (m, 3H, H-7/2 and H-10); 1.88 (m, 1H, H-8/1); 1.51 (m, 1H, H-8/2);1.14 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, d_6-DMSO) : δ = 186.05 (Cq, C-5); 186.01 (Cq, C-12); 156.47 (Cq, C-6); 155.70 (Cq, C-11); 138.42 (Cq, C-6a); 137.73 (Cq, C-10a); 134.80 (CH, C-2 and C-3); 132.92 (Cq, C-4a and C-12a); 126.48 (CH, C-1 and C-4); 109.02 (Cq, C-5a); 108.88 (Cq, C-11a); 72.14 (CH, C-13); 70.19 (Cq, C-9); 32.16 (CH_2, C-10); 25.79 (CH_2, C-8); 20.05 (CH_2, C-7); 17.08 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{18}O_6$ 354.1103; found 354.1104.

(9R)-9-acetyl-6,9,11-trihydroxy-8,10-dihydro-7H-tetracene-5,12-dione **212**



211 **212**

To a solution of **211** (0.80 g, 2.258 mmol) in DCM (45 mL), under a argon atmosphere, was added at RT the Dess-Martin periodinane (97%) (1.58 g, 3.725 mmol). The reaction mixture was stirred for 5 hrs at RT. The reaction mixture was poured in sat. $NaHCO_3$ (75 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (80 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with DCM / EtOAc (7/1) to give 0.60 g of **212** (1.694 mmol, 75%) as a red solid.

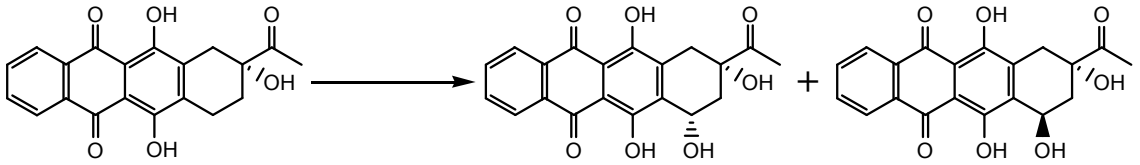
*(9R)-9-acetyl-6,9,11-trihydroxy-8,10-dihydro-7H-tetracene-5,12-dione **212***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.48 (s, 1H, OH-11); 13.47 (s, 1H, OH-6); 8.35 (m, 2H, H-1 and H-4); 7.83 (m, 2H, H-2 and H-3); 3.16 (m, 1H, H-7/1); 3.07 (d, 1H, J = 18 Hz, H-10/1); 2.95 (m, 2H, H-10/2 and H-7/2); 2.39 (s, 3H, CH_3); 2.00 (m, 2H, H-8).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 211.04 (Cq, C-13); 186.68 (Cq, C-5); 186.59 (Cq, C-12); 156.79 (Cq, C-11); 156.39 (Cq, C-6); 137.63 (Cq, C-6a); 134.43 (Cq, C-10a; 134.27 (CH, C-2 and C-3); 133.62 (Cq, C-4a); 133.57 (Cq, C-12a); 126.93 (CH, C-4); 126.91 (CH, C-1); 109.88 (Cq, C-5a and C-11a); 75.71 (Cq, C-9); 32.52 (CH_2, C-10); 29.03 (CH_2, C-8); 23.85 (CH_3); 19.76 (CH_2, C-7).

HRMS (ESI) : calcd. For $C_{20}H_{16}O_6$ 352.0947; found 352.0947.

(7R,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione **12** and (7S,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione **215**



To a suspension of **212** (130 mg, 0.369 mmol) in CCl_4 (35 mL) were added sequentially water (1 mL), NBS (74 mg, 0.413 mmol) and AIBN (18 mg, 0.111 mmol). The reaction mixture was then heated under reflux for 1 hr 30. An additional 33 mg of NBS was added and the reaction mixture was stirred under reflux for 2 hrs. The mixture was cooled to 20 °C in an ice bath and diluted with 10% K_2CO_3 (15 mL) and THF (20 mL). After 10 min stirring, the aqueous layer (brought to pH = 1 with 1 N HCl) was extracted with DCM (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (10/1) to give in order of elution 35 mg of **212** (0.099 mmol, 27%), 16 mg of **12** (0.044 mmol, 12 %) as a red solid and 48 mg of **215** (0.129 mmol, 35 %) as a red solid.

*(7S,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione **12***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.53 (s, 1H, OH-6); 13.25 (s, 1H, OH-11); 8.31 (m, 2H, H-1 and H-4); 7.84 (m, 2H, H-2 and H-3); 5.29 (brs, 1H, H-7); 4.58 (s, 1H, OH-9); 3.86 (d, 1H, J = 5.0 Hz, OH-7); 3.17 (dd, 1H, J = 2.2 Hz, 18.6 Hz, H-10/1); 2.94 (d, 1H, J = 18.6 Hz, H-10/2); 2.44 (s, 3H, CH_3); 2.35 (m, 1H, H-8/1); 2.17 (dd, 1H, J = 5.1 Hz, 14.5 Hz, H-8/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 211.56 (Cq, C-13); 187.78 (Cq, C-5); 186.64 (Cq, C-12); 156.39 (Cq, C-11); 156.16 (Cq, C-6); 135.71 (Cq, C-6a); 134.82 (Cq, C-10a); 134.57 (CH, C2 and C-3); 133.37 (Cq, C-4a); 133.32 (Cq, C-12a); 127.08 (CH, C-4); 127.02 (CH, C-1); 111.27 (Cq, C-11a); 110.81 (Cq, C-5a); 77.00 (Cq, C-9); 61.68 (CH, C-7); 35.38 (CH_2, C-8); 33.22 (CH_2, C-10); 24.46 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{16}O_7Na$ 391.0784; found 391.0786.

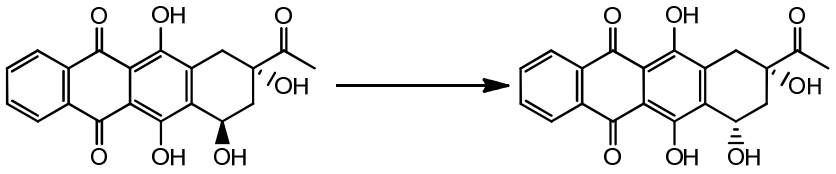
(7R,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione ***215***

^1H NMR (500 MHz, $CDCl_3$) : δ = 13.93 (s, 1H, OH-6); 13.30 (s, 1H, OH-11); 8.35 (m, 2H, H-1 and H-4); 7.85 (m, 1H, H-2 and H-3); 5.40 (dd, 1H, J = 7.9 Hz, 8.6 Hz, H-7); 4.28 (d, 1H, J = 1.6 Hz, OH-7); 3.90 (s, 1H, OH-9); 3.10 (d, 1H, J = 18.0 Hz, H-10/1); 2.94 (d, 1H, J = 18.0 Hz, H-10/2); 2.41 (s, 3H, CH_3); 2.35 (m , 1H, H-8/1); 2.18 (dd, 1H, J = 9.8 Hz, 13.0 Hz, H-8/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 209.60 (Cq, C-13); 187.15 (Cq, C-5); 186.75 (Cq, C-12); 156.30 (Cq, C-6 and C-11); 137.77 (Cq, C-6a); 135.08 (Cq, C-10a); 134.66 (CH, C-3); 134.58 (CH, C-2); 133.41 (Cq, C-4a); 133.34 (Cq, C-12a); 127.11 (CH, C-4); 127.07 (CH, C-1); 11.07 (Cq, C-11a); 110.94 (Cq, C-5a); 77.00 (Cq, C-9); 64.47 (CH, C-7) 37.23 (CH_2, C-8); 32.80 (CH_2, C-10); 23.76 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{16}O_7Na$ 391.0784; found 391.0789.

(7R,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione **12**
(from **215**)



215 **12**

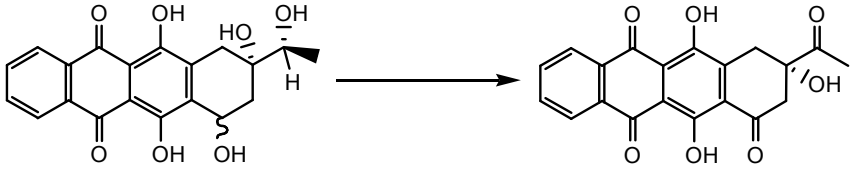
215 (26 mg, 0.071 mmol) was dissolved in TFA (1.3 mL) and stirred at RT for 2 hrs. Water (15 mL) was added ad the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was dissolved in acetone (1 mL) and sat. $NaHCO_3$ (20 mL) was added. The mixture was stirred at RT for 10 min and extracted with DCM (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (10/1) to give 15 mg of **12** (0.041 mmol, 73 %) as a red solid

*(7S,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione **12***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.53 (s, 1H, OH-6); 13.25 (s, 1H, OH-11); 8.31 (m, 2H, H-1 and H-4); 7.84 (m, 2H, H-2 and H-3); 5.29 (brs, 1H, H-7); 4.58 (s, 1H, OH-9); 3.86 (d, 1H, J = 5.0 Hz, OH-7); 3.17 (dd, 1H, J = 2.2 Hz, 18.6 Hz, H-10/1); 2.94 (d, 1H, J = 18.6 Hz, H-10/2); 2.44 (s, 3H, CH_3); 2.35 (m, 1H, H-8/1); 2.17 (dd, 1H, J = 5.1 Hz, 14.5 Hz, H-8/2).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 211.56 (Cq, C-13); 187.78 (Cq, C-5); 186.64 (Cq, C-12); 156.39 (Cq, C-11); 156.16 (Cq, C-6); 135.71 (Cq, C-6a); 134.82 (Cq, C-10a); 134.57 (CH, C2 and C-3); 133.37 (Cq, C-4a); 133.32 (Cq, C-12a); 127.08 (CH, C-4); 127.02 (CH, C-1); 111.27 (Cq, C-11a); 110.81 (Cq, C-5a); 77.00 (Cq, C-9); 61.68 (CH, C-7); 35.38 (CH_2, C-8); 33.22 (CH_2, C-10); 24.46 (CH_3).
Mp 183-185°C

(3S)-3-acetyl-3,5,12-trihydroxy-2,4-dihydrotetracene-1,6,11-trione **218**



210a+b **218**

To a suspension of **210a+b**72 mg, 0.194 mmol) in acetone (14 mL) was added at RT a solution of CrO_3 (117 mg, 1.166 mmol) in conc. H_2SO_4 (0.11 mL) and water (0.76 mL). The reaction mixture was stirred for 1 hr at RT and quenched with isopropanol (1 mL) to destroy the rest of reagent. Water (20 mL) was added and the mixture was neutralised with sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with toluene / isopropanol (30/1) to give 32 mg of **218** (0.087 mmol, 45%) as a red solid.

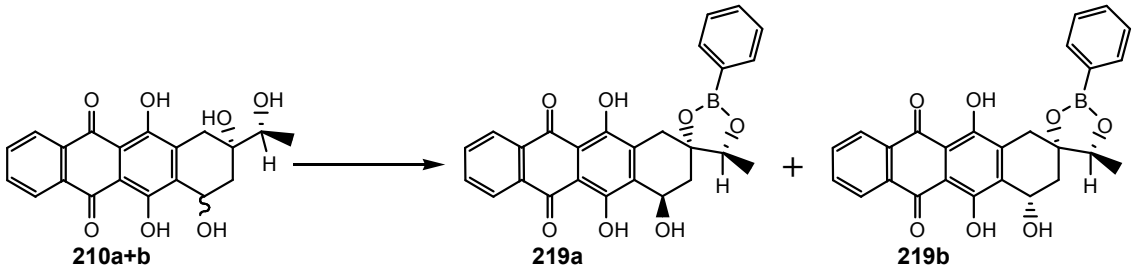
*(3S)-3-acetyl-3,5,12-trihydroxy-2,4-dihydrotetracene-1,6,11-trione **218***

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 14.09 (s, 1H, OH-11); 13.16 (s, 1H, OH-6); 8.36 (m, 2H, H-1 and H-4); 7.87 (m, 2H, H-2 and H-3); 3.40 (d, 1H, J = 18.3 Hz, H-10/1); 3.33 (d, 1H, J = 18.3 Hz, H-10/2); 3.16 (d, 1H, J = 15.5 Hz, H-8/1); 2.80 (d, 1H, J = 15.5 Hz, H-8/2); 2.44 (s, 3H, CH_3).

^{13}C NMR (200 MHz, $CDCl_3$) : δ = 207.61 (Cq, C-13); 192.80 (Cq, C-7); 187.60 (Cq, C-5); 185.91 (Cq, C-12); 157.62 (Cq; C-11); 154.20 (Cq, C-6); 141.59 (Cq, C-6a); 135.27 (CH, C-3); 134.63 (CH, C-2); 133.73 (Cq, C-4a); 132.74 (Cq, C-12a); 127.40 (CH, C-4); 127.34 (Cq, C-10a); 127.16 (CH, C-1); 115.70 (Cq, C-5a); 112.92 (Cq, C-11a); 78.21 (Cq, C-9); 47.78 (CH_2, C-8); 32.99 (CH_2, C-10); 24.00 (CH_3).

HRMS (ESI) : calcd. For $C_{20}H_{14}O_7Na$ 389.0637; found 389.0632.

(4S,5S,7'S)-6',7',11'-trihydroxy-5-methyl-2-phenyl-spiro[1,3,2-dioxaborolane-4,9'-8,10-dihydro-7H-tetracene]-5',12'-dione **219a** and (4S,5S,7'R)-6',7',11'-trihydroxy-5-methyl-2-phenyl-spiro[1,3,2-dioxaborolane-4,9'-8,10-dihydro-7H-tetracene]-5',12' **219b**



To a suspension of **210a+b** (25 mg, 0.068 mmol) in toluene (1.2 mL) cooled to 0 °C was added under argon atmosphere phenylboronic acid (25 mg, 0.203 mmol) and TFA (1.2 mL). The reaction mixture was stirred for 3 hrs at 0°C and then 16 hrs at RT. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel with toluene / isopropanol (30/1) to give 18 mg of a mixture **219a** and **219b** (0.039, 58%).

(4S,5S,7'R)-6',7',11'-trihydroxy-5-methyl-2-phenyl-spiro[1,3,2-dioxaborolane-4,9'-8,10-dihydro-7H-tetracene]-5',12' ***219a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.51 (s, 1H, OH-6); 13.26 (s, 1H, OH-11); 8.34 (m, 2H, H-1 and H-4); 8.21 (d, 2H, J = 7.3 Hz, H-Ph2 and H-Ph6); 7.84 (m, 2H, H-2 and H-3); 7.58 (m, 1H, H-Ph4); 7.51 (m, 2H, H-Ph3 and H-Ph5); 5.80 (m, 1H, H-7); 3.94 (q, 1H, J = 6.3 Hz, H-13); 3.30 (d, 1H, J = 19.3 Hz, H-10/1); 2.93 (d, 1H, J = 19.3 Hz, H-10/2); 2.52 (d, 1H, J = 13.6 Hz, H-8/1); 1.97 (d, 1H, J = 13.6 Hz, H-8/2); 1.46 (d, 3H, J = 6.3 Hz, CH_3).

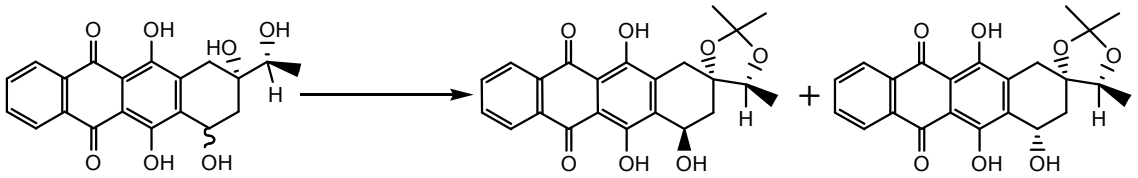
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 186.90 (Cq, C-5); 186.48 (Cq, C-12); 156.54 (Cq, C-11); 155.93 (Cq, C-6); 136.42 (Cq, C6a); 135.80 (Cq, C-10a); 135.44 (CH, C-Ph2 and C-Ph6); 134.60 (CH, C-1); 134.51 (CH, C-4); 133.43 (Cq, C-4a); 133.33 (Cq, C-12a); 132.37 (CH, C-Ph4); 127.91 (CH, C-Ph3 and C-Ph5); 127.08 (CH, C-2); 126.99 (CH, C-3); 111.57 (Cq, C-11a); 111.05 (Cq, C-5a); 73.56 (Cq, C-9); 73.29 (CH, C-13); 60.41 (CH, C-7); 30.98 (CH_2, C-10); 32.03 (CH_2, C-8); 16.86 (CH_3).

(4S,5S,7'S)-6',7',11'-trihydroxy-5-methyl-2-phenyl-spiro[1,3,2-dioxaborolane-4,9'-8,10-dihydro-7H-tetracene]-5',12'-dione ***219b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.80 (s, 1H, OH-6); 13.34 (s, 1H, OH-11); 8.34 (m, 2H, H-1 and H-4); 7.84 (m, 2H, H-2 and H-3); 7.77 (d, 2H, J = 7.9 Hz, H-Ph2 and H-Ph6); 7.45 (m, 1H, H-Ph4); 7.34 (m, 2H, H-Ph3 and H-Ph5); 5.48 (dd, 1H, J = 7.0 Hz, 14.5 Hz, H-7); 4.63 (q, 1H, J = 6.3 Hz, H-13); 4.05 (s, 1H, OH-7); 3.11 (d, 1H, J = 18.3 Hz, H-10/1); 2.97 (d, 1H, J = 18.3 Hz, H-10/2); 2.55 (dd, 1H, J = 6.7 Hz, 13.6 Hz, H-8/1); 2.09 (dd, 1H, J = 7.9 Hz, 13.6 Hz, H-8/2); 1.43 (d, 3H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 187.03(Cq, C-5); 186.69 (Cq, C-12); 156.41 (Cq, C-6); 156.31 (Cq, C-11); 137.83 (Cq, C6a); 136.16 (Cq, C-10a); 134.84 (CH, C-Ph2 and C-Ph6); 134.60 (CH, C-1); 134.51 (CH, C-4); 133.43 (Cq, C-4a); 133.33 (Cq, C-12a); 131.50 (CH, C-Ph4); 127.74 (CH, C-Ph3 and C-Ph5); 127.08 (CH, C-2); 126.99 (CH, C-3); 111.05 (Cq, C-11a); 110.85 (Cq, C-5a); 81.69 (Cq, C-9); 81.25 (CH, C-13); 64.88 (CH, C-7); 40.98 (CH_2, C-8); 31.02 (CH_2, C-10); 17.44 (CH_3).

(4S,5S,7'R)-6',7',11'-trihydroxy-2,2,5-trimethyl-spiro[1,3-dioxolane-4,9'-8,10-dihydro-7H-tetracene]-5',12'-dione **220a** and (4S,5S,7'S)-6',7',11'-trihydroxy-2,2,5-trimethyl-spiro[1,3-dioxolane-4,9'-8,10-dihydro-7H-tetracene]-5',12'-dione **220b**



210a+b (30 mg, 0.081 mmol) were dissolved under argon in dimethoxypropane (5 mL) and pTsOH (1 mg, 0.004 mmol) was added. The reaction mixture was stirred at RT for 2 hr 30 and then diluted with water (15 mL). The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 26 mg of the pure enough mixture of **220a** and **220b** (0.063 mmol, 78%) as a red solid.

*(4S,5S,7'R)-6',7',11'-trihydroxy-2,2,5-trimethyl-spiro[1,3-dioxolane-4,9'-8,10-dihydro-7H-tetracene]-5',12'-dione **220a***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.82 (s, 1H, OH-6); 13.33 (s, 1H, OH-11); 8.32 (m, 2H, H-1 and H-4); 7.82 (m, 2H, H-2 and H-3); 5.38 (dd, 1H, J = 6.9 Hz, 7.3 Hz, H-7); 4.15 (q, 1H, J = 6.3 Hz, H-13); 3.88 (brs, 1H, OH-7); 2.95 (d, 1H, J = 18.0 Hz, H-10/1); 2.80 (d, 1H, J = 18.0 Hz, H-10/2); 2.32 (ddd, 1H, J = 1.6 Hz, 7.0 Hz, 13.6 Hz, H-8/1); 1.96 (dd, 1H, J = 7.6 Hz, 13.6 Hz, H-8/2); 1.41 (s, 3H, H-acetonid); 1.39 (s, 3H, H-acetonid); 1.31 (d, 1H, J = 6.3 Hz, CH_3).

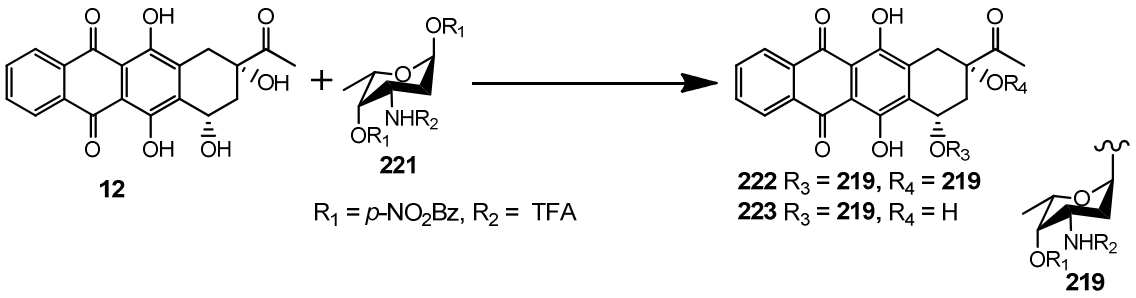
^{13}C NMR (500 MHz, $CDCl_3$) : δ = 186.92 (Cq, C-5); 186.68 (Cq, C-12); 156.53 (Cq, C-11); 156.31 (Cq, C-6); 137.84 (Cq, C-6a); 137.12 (Cq, C-11a); 134.52 (CH, C-2); 134.42 (CH, C-3); 133.46 (Cq, C-4a); 133.34 (Cq, C-12a); 127.03 (CH, C-1); 126.93 (CH, C-4); 110.97 (Cq, C-11a); 110.66 (Cq, C-5a); 107.22 (Cq, C-acetonid); 80.36 (Cq, C-9); 78.92 (CH, C-13); 65.14 (CH, C-4); 38.88 (CH_2, C-8); 30.26 (CH_2, C-10); 28.50 (CH_3, C-acetonid); 26.85 (CH_3, C-acetonid); 14.80 (CH_3).

(4S,5S,7'S)-6',7',11'-trihydroxy-2,2,5-trimethyl-spiro[1,3-dioxolane-4,9'-8,10-dihydro-7H-tetracene]-5',12'-dione ***220b***

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.61 (s, 1H, OH-6); 13.39 (s, 1H, OH-11); 8.32 (m, 2H, H-1 and H-4); 7.82 (m, 2H, H-2 and H-3); 5.18 (m, 1H, H-7); 4.20 (d, 1H, J = 9.8 Hz, OH-7); 4.15 (q, 1H, J = 6.3 Hz, H-13); 3.21 (d, 1H, J = 18.3 Hz, H-10/1); 2.52 (d, 1H, J = 18.3 Hz, H-10/2); 2.22 (m, 1H, H-8/1); 2.02 (dd, 1H, J = 5.4 Hz, 14.2 Hz, H-8/2); 1.43 (s, 3H, H-acetonid); 1.42 (s, 3H, H-acetonid); 1.37 (d, 1H, J = 6.3 Hz, CH_3).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 186.81 (Cq, C-5); 186.42 (Cq, C-12); 157.01 (Cq, C-6); 156.53 (Cq, C-11); 137.59 (Cq, C-6a); 135.61 (Cq, C-11a); 134.52 (CH, C-2); 134.42 (CH, C-3); 133.56 (Cq, C-4a); 133.39 (Cq, C-12a); 127.03 (CH, C-1); 126.93 (CH, C-4); 111.11 (Cq, C-11a); 110.66 (Cq, C-5a); 108.04 (Cq, C-acetonid); 80.28 (Cq, C-9); 79.23 (CH, C-13); 62.51 (CH, C-4); 37.66 (CH_2, C-8); 30.07 (CH_2, C-10); 28.42 (CH_3, C-acetonid); 26.81 (CH_3, C-acetonid); 14.80 (CH_3).

[(2S,3S,4S,6R)-6-[[(1S,3S)-3-acetyl-3,5,12-trihydroxy-6,11-dioxo-2,4-dihydro-1H-tetracen-1-yl]oxy]-2-methyl-4-[(2,2,2-trifluoroacetyl)amino]tetrahydropyran-3-yl]4-nitrobenzoate **223** and [(2S,3S,4S)-6-[[(2S,4S)-2-acetyl-5,12-dihydroxy-4-[(2R,4S,5S,6S)-6-methyl-5-(4-nitrobenzoyl)oxy-4-[(2,2,2-trifluoroacetyl)amino]tetrahydropyran-2-yl]oxy-6,11-dioxo-3,4-dihydro-1H-tetracen-2-yl]oxy]-2-methyl-4-[(2,2,2-trifluoroacetyl)amino]tetrahydropyran-3-yl] 4-nitrobenzoate **222**



TMSOTf (0.06 mL, 0.311 mmol) was added to a stirred suspension of **221** (56 mg, 0.103 mmol) and molecular sieves 4A in DCM (4 mL) / Et_2O (3.3 mL) at -40°C under an argon atmosphere. The reaction mixture was stirred at 0°C for 1h and then cooled to -15°C. A solution of **12** (27 mg, 0,073 mmol) in DCM (8 mL) was added and the reaction mixture was stirred at -15°C for 2h and poured in sat. $NaHCO_3$ (20 mL) / EtOAc (20 mL). The layers were separated. The aqeous layer was extracted with EtOAc (2 x 15 mL). the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with toluene / EtOAc (4/1) and then by preparative tlc with the same eluent to give 35 mg of **223** (0,047 mmol, 64%) as an orange/red solid and 7 mg of **222** (0.007 mmol, 9%) as an orange solid.

223

^1H NMR (500 MHz, $CDCl_3$) : δ = 13.70 (s, 1H, OH-6); 13.49 (s, 1H, OH-12); 8.28 (m, 6H, H-1, H-4, H-pNO_2Bz); 7.85 (m, 2H, H-2 and H-3); 7.41 (d, 1H, J = 5.7 Hz, NH); 6.96 (d, 1H, J = 7.6 Hz, NH"); 5.68 (d, 1H, J = 3.5 Hz, H-dau1"); 5.46 (s, 1H, H-dau4"); 5.29 (s, 1H, H- dau4); 5.14 (d, 1H, J = 3.2 Hz, H-dau1); 5.07 (d, 1H, J = 5.4 Hz, H-7); 4.75 (q, 1H, J = 6.3 Hz, h-dau5"); 4.71 (m, 1H, H-dau3); 4.60 (m, 1H, H-

dau3"); 3.98 (q, 1H, J = 6.7 Hz, H-dau5); 3.80 (d, 1H, J = 19.3 Hz, H-10/1); 3.03 (d, 1H, J = 19.3 Hz, H-10/2); 2.63 (d, 1H, J = 14.8 Hz, H-8/1); 2.39 (s, 3H, H-CH_3); 2.31-2.07 (m, 4H, H-dau2 and H-dau2"); 1.99 (dd, 1H, J = 6.3 Hz and 15.4 Hz, H-8/2); 1.37 (d, 3H, J = 6.6 Hz, H-dau6"); 0.61 (d, 3H, J = 6.3 Hz, H-dau6).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 208.95 (Cq, C-13); 186.83 (Cq, C-5); 186.74 (Cq, C-12); 165.82 (Cq, C-COpNO_2Bz); 165.33 (Cq, C-COpNO_2Bz"); 157.24 (Cq, C-6); 157.15 (Cq, C-COTFA); 156.86 (Cq, C-COTFA"); 156.09 (Cq, C-11); 150.95 (Cq, C-CNO_2); 136.12 (Cq, C-6a); 134.70 (Cq, C-3); 134.60 (Cq, C-2): 134.44 (Cq, C-COO); 134.19 (Cq, C-COO"); 133.95 (Cq, C-10a); 133.52 (Cq, C-4a); 133.30 (Cq, C-12a); 131.15 (CH, CH-pNO_2Bz); 127.18 (CH, C-1); 127.00 (CH, C-4); 123.85 (CH, CH-pNO_2Bz); 111.27 (Cq, C-11a); 110.51 (Cq, C-5a); 101.61 (CH, C-dau1"); 94.39 (CH, C-dau1); 81.65 (Cq, C-9); 73.35 (CH, C-dau4"); 73.24 (CH, C-dau4); 71.08 (CH, C-7); 67.22 (CH, C-dau5); 66.72 (CH, C-dau5"); 47.45 (CH, C-dau3); 46.49 (CH, C-dau3"); 36.70 (CH_2, C-8); 30.70 (CH_2, C-dau2); 30.53 (CH_2, C-dau2"); 27.08 ((CH_2, C-10); 24.54 (CH_3); 17.10 (CH_3, -dau6"); (CH_3, -dau6).

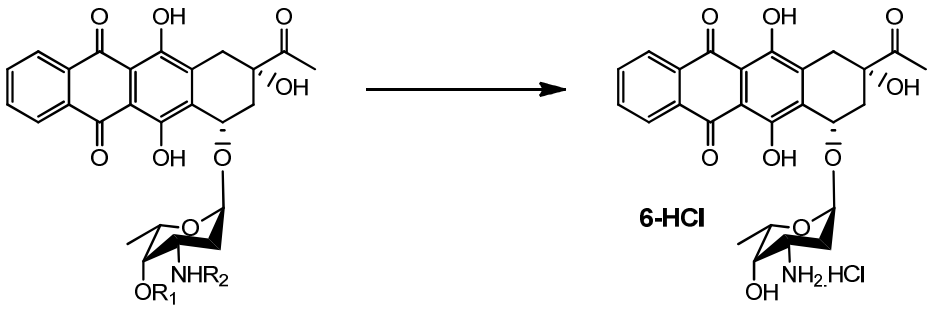
223

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 13.67 (s, 1H, OH-6); 13.33 (s, 1H, OH-12); 8.28 (m, 6H, H-1, H-4, H-pNO_2Bz); 7.85 (m, 2H, H-2 and H-3); 6.34 (d, 1H, J = 6.9 Hz, NH); 5.70 (s, 1H, H-dau1); 5.50 (s, 1H, H- dau4); 5.33 (brs, 1H, H-7); 4.47 (m, 2H, H-dau3 and H-dau5); 3.30 (d, 1H, J = 18.6 Hz, H-10/1); 2.99 (d, 1H, J = 18.6 Hz, H-10/2); 2.45 (s, 3H, H-CH_3); 2.52 (m, 1H, H-8/1); 2.19 (m, 1H, H-8/2); 2.09 (m, 2H, H-dau2); 1.27 (d, 3H, J = 6.5 Hz, H-dau6).

^{13}C NMR (500 MHz, $CDCl_3$) : δ = 211.66 (Cq, C-13); 186.90 (Cq, C-5); 186.74 (Cq, C-12); 164.56 (Cq, C-COpNO_2Bz); 157.49 (Cq, C-COTFA); 156.52 (Cq, C-6); 156.31 (Cq, C-11); 150.95 (Cq, C-CNO_2); 135.88 (Cq, C-6a); 134.64 (Cq, C-3); 134.60 (Cq, C-2): 134.27 (Cq, C-COO); 133.41 (Cq, C-4a); 133.35 (Cq, C-12a); 133.13 (Cq, C-10a); 131.02 (CH, CH-pNO_2Bz); 130.99 (CH, CH-pNO_2Bz); 127.07 (CH, C-4); 127.00 (CH, C-1); 123.85 (CH, CH-pNO_2Bz); 123.73 (CH, CH-pNO_2Bz); 111.62 (Cq, C-11a); 110.94 (Cq, C-5a); 99.96 (CH, C-dau1); 76.51 (Cq, C-9); 71.53 (CH, C-dau4); 70.05

(CH, C-7); 66.12 (CH, C-dau5); 45.61 (CH, C-dau3); 35.16 (CH_2, C-8); 33.63 (CH_2, C-10); 30.03 (CH_2, C-dau2); 24.83 (CH_3); 16.99 (CH_3, -dau6).
Mp 172-174°C

Idarubicin hydrochloride **6-HCl**



223 R_1= pNO_2Bz, R_2 = TFA

0.1 NaOH (0.0054 mL, 0.054 mmol) was added to an ice cooled solution of **223** (40 mg, 0.054 mmol) in DCM (0.33 mL) and MeOH (21 mL) under an argo atmosphere. The reaction mixture was stirred for 20 mi at 0°C and a drop of glacial AcOH was added. EtOAc (30 mL) and brine (30 mL) were successively added to the mixture. The separated organic layer was washed with brine (2 x 20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with DCM / acetone (9/0.5) to give 23 mg (0.039 mmol, 72%) of an orange solid (mp 150--152°C).
This product was dissolved in 0.1 N NaOH (5.2 mL) under an argon atmosphere ad stirred for 30 min at RT. The solution was neutralised with 1N HCl to pH = 8 and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was dissolved I a small amout of $CHCl_3$ ad MeOH (9/1) and 0.25 M hydrogen chloride in MeOH was added. Et2O was added to the solution to give 13 mg of **6-HCl** (0.025 mmol, 65%, 46% from **223**) as an orange solid.

Idarubicin hydrochloride ***6-HCl***

^{1}H NMR (200 MHz, DMSO) : δ = 13.557 (s, 1H, OH-6); 13.34 (s, 1H, OH-12); 8.31 (m, 2H, H-1, H-4); 7.00 (m, 2H, H-2 and H-3); 7.69 (brs, 3H, NH_3); 5.55 (s, 1H, H-OH-9); 5.58 (m, 1H, H- dau4); 5.32 (brs, 1H, H-dau1); 4.97 (brs, 1H, H-7); 4.22 (q, 1H, J = 6.3 Hz, H-dau5); 3.53 (m, 1H, H-dau4); 3.00 (brs, 2H, H-10); 2.28 (s, 3H, H- CH_3); 2.18-1.70 (m, 4H, H-dau2 and H-8); 1.17 (d, 3H, J = 6.3 Hz, H-dau6).

MS (ESI) *m/ z*: 498 (MH+)

Mp 182-184°C

8 APPENDIX

8.1 Abbreviations

API	active pharmaceutical ingredient
Aq.	aqueous
$AlCl_3$	aluminium chloride
AIBN	azo-bis-(isobutyronitril)
Bz_2O_2	bezoyl peroxide
BH_3.THF	boran THF complex
$BF_3.Et_2O$	boron trifluoride diethyl etherate
BCl_3	boron trichloride
Br_2	bromine
CAN	cerium ammonium nitrate
CDI	N,N-carboyldiimidazole
CCl_4	carbon tetrachloride
CH_3CN	acetonitrile
$CeCl_3.7H_2O$	cerium chloride heptahydrate
$CHCl_3$	chloroform
DNA	deoxyribonucleic acid
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
Et_2O	diethyl ether
H_2SO_4	sulfuric acid
Hr	hour
HCl	hydrochloric acid
H_2O	water
HBr	hydrogen bromide

HMPA	hexamethylphosphoramide
KHMDS	potassium bis (trimethylsilyl)amide
K_2CO_3	potassium carbonate
KOH	potassium hydroxide
LDA	lithium diisopropylamide
LiHMDS	lithium bis (trimethylsilyl)amide
Me_2SO_4	dimethyl sulfate
$MgCl_2$	magnesium chloride
MeLi	methyl lithium
MeOH	methanol
MTBE	methyl tert-butyl ether
Me_3SiCHN_2	trimethylsilyldiazomethane
$NaHCO_3$	sodium bicarbonate
$Na_2S_2O_4$	sodium dithionite
$NaBH_4$	sodium borohydride
NaCl	sodium chloride
NBS	N-bromosuccinimid
NMR	nuclear magnetic resonance
n-BuLi	n-butyllithium
NaI	sodium iodide
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
$PhB(OH)_2$	phenylboronic acid
pTsOH	p-toluene sulfonic acid
$POCl_3$	phosphoryl chloride
PPA	polyphopshoric acid
Py	pyridine
Py.HCl	pyridine hydrochloride
PE	petrol ether
$SOCl_2$	thionyl chloride
SnCl4	tin (IV) chloride
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

TBABr	tetra-n-butylammonium bromide
Tlc	thin layer chromatography
TBDMSCl	ter-butyl dimethylsilylchloride
$TiCl_4$	titan (IV)- chloride
TMSI	trimethylsilyl iodide
TMSCl	trimethylsilyl chloride
Tol	toluene
TMSOTf	trimethylsilyl triflate

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8.3 Curriculum Vitae

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AUSBILDUNG

2007-dato Dissertation an der Universität Wien in organischer Chemie unter Betreuung von Prof. Noe. Totalsynthese eines Cytostatikums basierend auf Anthracycline.

2001-2007 Studium der „Chemie/Verfahrenstechnik“ an der Ecole Superieure CPE Lyon. Ein Semester Spezialisierung auf „Lebenswissenschaften“. Abschluß als Diplomingenieur.

Juni 2001 Matura (Spezialisierung Naturwissenschaften) am Lycée Edmond Rostand in St Ouen l’Aumone.

BERUFSERFAHRUNG

Mai. 2010 -dato **Universitätassistent am Dep. für Med./Pharm. Chemie (Wien, Österreich)**
Dissertation an der Universität Wien in organischer Chemie unter Betreuung von Prof. Noe. Totalsynthese eines Cytostatikums basierend auf Anthracycline sowie Optimierung und Scale-Up für industrielle Produktion. Testen verschiedener Synthesewege.

Nov. 2009 -Apr. 2010 **Produkem Molekulares Design GmbH (Wien, Österreich)**
Dissertation an der Universität Wien in organischer Chemie unter Betreuung von Prof. Noe. Totalsynthese eines Cytostatikums basierend auf Anthracycline sowie Optimierung und Scale-Up für industrielle Produktion. Testen verschiedener Synthesewege

Sept. 2007 -Okt. 2009 **PHARMACON GmbH (Wien, Österreich)**
Dissertation an der Universität Wien in organischer Chemie unter Betreuung von Prof. Noe. Totalsynthese eines Cytostatikums basierend auf Anthracycline sowie Optimierung und Scale-Up für industrielle Produktion. Testen verschiedener Synthesewege

Feb. 2007- Juli 2007 **AB SCIENCE (Lyon, Frankreich)**
6 Monate Praktikum in einem organischen Syntheselabor: Verfassen der Diplomarbeit. Synthese von potentiellen Inhibitoren einer Tyrosinkinase.

Juli 2005- Juni 2006 **PRIATON GmbH (München, Deutschland)**
12 Monate Praktikum in einem organischen Syntheselabor: Synthese von Isocyaniden, Synthese von bioaktiven Molekülen für die pharmazeutische Industrie, Erstellung einer chemischen Bibliothek von 300 Molekülen mit Hilfe einer MCR (Multi Component Reaction), gefolgt von Palladium-Kupplungsreaktionen.

Juli 2004 **CIBA (Saint Fons, Frankreich)**
Arbeitspraktikum. Fließbandarbeit: Packaging.

BESONDERE KENNTNISSE UND FÄHIGKEITEN

Fähigkeiten am Arbeitsplatz

- Durchführung von Literaturrecherchen über organisch chemische Synthesemöglichkeiten, Auswahl und Anwendung der geeigneten Reaktionen.
- Selbstständige Durchführung von chemischen Reaktionen.
- Entwicklung und Optimierung von Aufarbeitungsprozessen nach organisch chemischen Reaktionen.
- Auswahl, Anwendung und Optimierung von geeigneten Methoden zur Reinigung organisch chemischer Verbindungen (Chromatographie, Kristallisation, Destillation).
- Up-Scaling chemischer Reaktionen.
- Anwendung und Auswertung reaktionsbegleitender Analysenverfahren wie DC, NMR, MS.
- Organisation eines Chemielabors.

Sprachen

Französisch	Muttersprache
Englisch	Fliessend. : *Niveau First Certificate – Cambridge (FCE)*
Deutsch	Gut

EDV-Kenntnisse Microsoft Office, Win-NMR, IsisDraw, Sci Finder, ChemDraw.

Führerschein B

SOZIALE KOMPETENZEN

Vereine Mitglied des « bureau des élèves » (Studentenvertretung) von 2002 bis 2003.

Projekte Mitwirkung an der Erstellung eines nachhaltigen Entwicklungprojektes für die Ausbildung in Indien (Lyon Solidaire).

Sport Handball (Meisterschaften), Rugby, Klettern, Alpinismus, Ski.

Reisen USA, Indien, Argentinien, Chile, Großbritannien, Deutschland.