Titel der Dissertation

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

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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.


Idarubicin Hydrochlorid 6-HCl wurde durch Glykosylierung von 12 und anschließender schrittweiser Entschützung der beiden Schutzgruppen der Zuckerhälfe 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-Analoge.
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

[Diagram of chemical reactions and structures]

- 5 steps, 49%
- 3 steps, 75%
- 12 steps from 88, 11% overall yield

L-malic acid to TBDMSO

12 steps from 88, 11% overall yield

R₁ = p-NO₂Bz, R₂ = TFA

- 3 steps, 30%
- 6-HCl
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 feasibility 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 crystalline material.

- To resume, the price of the final product is the most important measure to define the effectiveness 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-rhodomycin II 1 (Scheme 1), was isolated by Brockman and Bauer in 1950 from the actinomycete Streptomyces purpurascens1. Despite of its high antibacterial activity, no further development into a clinically useful chemotherapeutic agent were investigated owing to its toxicity.
In the 1960’s, further anthracyclines were isolated in other laboratories\textsuperscript{2-3}, which led to the discovery of two key anthracyclines, daunorubicin \textit{3} (also called daunomycin) and doxorubicin \textit{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\textsuperscript{4}. Because of their high therapeutic value in cancer chemotherapy\textsuperscript{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 \textit{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 \textit{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 completely 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. 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 remarkably 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\textsuperscript{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\textsuperscript{12-13}. Anthracyclines can undergo reduction to the corresponding intermediate semiquinone free radicals which can, in turn, reduce oxygen to superoxide (\(\cdot \text{O}_2^\cdot\)) and other reactive oxygen species such as hydrogen peroxide and hydroxyl radicals\textsuperscript{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\textsuperscript{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.

\subsection*{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\textsuperscript{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 scientists. This review covers a large area from synthesis of anthracycline to clinical applications\textsuperscript{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 \textit{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 \textit{Streptomyces}, describing briefly the biosynthetic pathway and the limitation of this production. In the second part of this chapter the semi-synthesis of idarubicinone (aglycone of idarubicin) will be described.

\begin{center}
\textbf{Scheme 2}
\end{center}
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 propionyl coenzyme A and nine malonyl coenzyme A units. 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.
At the same time, the biosynthesis 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\textsuperscript{31}.

Finally, the ε1rhodomycinone 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\textsuperscript{32-33}.

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

First, the low availability of TDP-L-daunoamine\textsuperscript{37} affects the doxorubicin biosynthesis. In addition of that, competitive synthesis of TDP-L-rhamnose consumed the intermediate TDP-4-keto-6-deoxy-D-glucose, which reduced the yield of the TDP-L-daunosamine.

Further, ε1rhodomycinone is glycosilated with TDP-L-daunosamine via action of enzymes called dnrS and dnrQ to produce the intermediate rhodomycin D\textsuperscript{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\textsuperscript{32} lacks of efficacy to convert daunorubicin into doxorubicin\textsuperscript{33}. As a consequence, in industrial production of doxorubicin, the last oxidation steps can also be performed by chemical manner\textsuperscript{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 with the result of DNA damage and cell death\textsuperscript{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\textsuperscript{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\textsuperscript{43-45} (Scheme 4).

![Scheme 4](image_url)

Reagents and conditions: a) AlCl\textsubscript{3}, DCM, 88%; b) \((\text{CH}_2\text{OH})_2\), p-TsOH, benzene, 90%; c) TF\textsubscript{2}O, iPr\textsubscript{2}EtN, 4-Me\textsubscript{2}N-py, 67%; d) Pd(OAc)\textsubscript{2}, DPPF 0.5 mol%, HCO\textsubscript{2}H, Et\textsubscript{3}N, DMF, 82%; e) TFA, 90%.

In the first step, the cleavage of the glycosidic bond can be carried out under acidic condition\textsuperscript{46-47} to deliver the daunorubin aglycone. Kelly et al.\textsuperscript{44} reported in 1990 the synthesis of idarubicinone starting from daunorubicinone. They first treated 9 with AlCl\textsubscript{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\textsuperscript{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-daunosamine, 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 ε1rhodomycinone, 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-synthesis. 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 anthracyclines bearing a nonsymmetrical D ring in relation to the A ring stereocenters, regiochemical control of the formation of the tetracyclic chromophore.
With these tasks in mind, several methodologies have been developed towards the
synthesis of the aglycone leading to three main type of approaches\textsuperscript{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, several AB building blocks (Scheme 6) and the efforts of many research groups since the last 20 years are summarized in this review.

![Chemical structures](image)

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 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 H₂O-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.
Reagents and conditions: a) MsCl, N,N,N', N'-tetramethylhexane-1,6-diamine, DCM; b) 20% NaOH\textsubscript{aq}, Bu\textsubscript{4}NHSO\textsubscript{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\textsuperscript{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\textsuperscript{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-i-Pr)$_4$, t-BuOOH, DCM; b) LAH, THF, 42% over two steps; c) Ag$_2$CO$_3$ on celite, PhH, 78%; d) (+)-DET, Ti(O-i-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-i-Pr)$_4$, t-BuOOH, DCM; i) LAH, THF, 43% over two steps; j) Ag$_2$CO$_3$, 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$_2$OsO$_4$(OH)$_4$, H$_2$O-τBuOH, MeSO$_2$NH$_2$, 71%, 98% ee; b) MeC(OMe)$_3$, PPTS, DCM; c) TBDMSCl, DCM, 99%; d) Bu$_3$SnH, AIBN, PhH; e) Amberlyst IRA-400(OH), MeOH, 73%; f) 34, OsO$_4$, THF; g) NaHSO$_3$, H$_2$O, 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 diastereoselective 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-dimethoxyxynutane-2,3-diol to afford the compound 36. Subsequent treatment of 36 with ethylmagnesium chloride and cleavage of the ketal under acidic conditions yielded stereoselectively the hydroxyketone 37 with the desired configuration at C-9 (Scheme 10).
Another recent approach was used by Shibasaki et al.\textsuperscript{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 \textit{meso}-epoxide 38 with \textit{p}-anisidine and catalytic amounts of BINOL, followed methylation of the amine and Hoffman elimination (Scheme 11). After optimisation, the \textit{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 \textit{de} of 10:1 which was converted to the keton by treatment with HgSO\textsubscript{4} and cat. H\textsubscript{2}SO\textsubscript{4} in acetone. Then, the methylether was cleaved to the keto alcohol 44, 45 and was ketalized. Finally, the benzylic alcohol was converted with phenylboronic acid to the corresponding diester under acidic conditions. This diester 18 is the only formed product with both hydroxyl groups cis to each other.
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. This methodology will be introduced by examining 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. (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) 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., 51 was converted into 52 in 25% overall yield from 47 and 87% ee.

**Scheme 11**

Reagents and conditions: a) (R)-BINOL, Pr(O-i-Pr)₃, Ph₃P=O, p-anisidine, toluene, 40%, 95% ee; b) MeI, K₂CO₃, MeOH; c) BuLi, THF, 52% over two steps, 90% ee; d) Hg(OAc)₂, MeOH; e) NaBH₄, NaOH, H₂O, 74% over two steps; f) DMP, DCM, 95%, 90% ee; g) ethynylmagnesium bromide, CeCl₃, THF, 76%; h) HgSO₄ (20 mol%), 2% H₂SO₄, acetone; i) (CH₃OH)₂, MgSO₄, p-TsOH, ; j) PhB(OH)₂, p-TsOH, toluene, 70% over three steps.

![Scheme 11](image-url)
Reagents and conditions: a) Lipase LT, O.O6 M buffer-DMF (1 : 1), 87% ee; b) TBDMS, imidazole, DMF; c) K$_2$CO$_3$, MeOH; d) PDC, DCM, 88% over three steps; f) 53% over four steps; g) OsO$_4$-NaIO$_4$, dioxane-H$_2$O (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) SnCl$_4$, 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 homophthallic anhydride or the annelation of hemiketal with the anion of 3-cyano-1(3H)-isobenzofuranone derivatives. Three corresponding CD precursors are as follows: homophthallic anhydride derivatives of type 58, 3-cyano-1(3H)-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\textsuperscript{62,81,84-86}.

![Scheme 14](image)

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

![Scheme 15](image)

reagents and condition: a) CAN, MeCN, H\textsubscript{2}O, 85%; b) 50°C, then DDQ; c) H\textsubscript{2}O\textsubscript{2}, NaOH, THF; d) p-TsOH, acetone, 65% over three steps.

Alternatively, the tetracyclic moiety of the aglycone can also be obtained by base-induced (in this case NaH) cycloaddition\textsuperscript{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$_2$O, 60%; d) 1.2 M HCl, i-PrOH, 50%.

Scheme 16

In the case of 3-cyano-1(3H)-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(3H)-isobenzofuranone derivatives 59 followed by deprotection of the protecting groups (scheme 17) to give the analog of idarubicinone 71.
Reagents and conditions: a) anodic oxidation, KOH, MeOH, Pt, 1.3V; b) AcOH, H₂O, acetone, 64% yield from 87; c) DMSO, THF, MeLi; d) THF, HCl; e) BCl₃, DCM, 52% overall yield 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 group⁹², 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
Marschall reactions, keto-ester cyclizations and nucleophilic additions towards various natural and synthetic anthracyclines are also known\textsuperscript{52-53}.

![Diagram of lactose and anthracyclines]

Reagents and conditions: a) piperidine acetate, iPrOH, reflux, 75%; b) AcOH, H\textsubscript{2}O, RT, 88%; c) NaIO\textsubscript{4}, MeOH, THF, H\textsubscript{2}O, AcOH, RT, 99%; d) Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4}, NaOH, THF, MeOH, H\textsubscript{2}O, 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 diastereoisomers separable by chromatography.

First, Confalone et al.\textsuperscript{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 subrate. 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, SO\textsubscript{2}Et, SO\textsubscript{2}Et, OCH\textsubscript{3}) in a stereospecific fashion followed by stereoselective introduction of the hydroxyl group at position C-17 by oxidation with NBS in aqueous CCl\textsubscript{4} in the presence of AIBN. Therefore, glycosidation of rac-80 with the L-daunopyranosyl chlorides 81 afforded a mixture of diastereoisomers 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$_2$SO$_4$, 0°C, 81%; d) MCPBA, NaHCO$_3$, DCM, RT, 99%; e) MeOH, p-TsOH, reflux, 60%; f) NBS, CCl$_4$, H$_2$O, 60°C, 51%; g) (i) CF$_3$CO$_2$Ag, DMF / DCM, RT 75%; (ii) Et$_3$N, H$_2$O, 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 yields 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 oxidation reaction with potassium t-butoxide and oxygen and triethylphosphite in t-butoanol 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 cleavage of the protecting groups.
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 anthracyclines 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 feasibility 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\textsuperscript{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.
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., 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)” 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) SOCl₂, SnCl₄, DCM, 0°C, 82%; c) Zn(BH₄)₂, benzene, 10°C, 78%; d) sodium methylsulfinyl carbanion, DMSO/THF, 0°C then aluminium-amalgam, THF/H₂O, 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 procedure¹⁰² followed by deprotection of the different protected groups should afford the desired idarubicinone 12.
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\textsuperscript{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 varied between 93/7 and 20/80. It appeared to us that H$_2$SO$_4$ could overrule the kinetic control of the acetalisation to the detriment of the thermodynamically 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$_2$SO$_4$. By applying p-TsOH alone as catalyst, even with a long reaction time (~5 days instead of 48 hrs with H$_2$SO$_4$) the desired cis-isomer 97a was obtained in good yield (86%), excellent diastereoselectivity (> 97% de) and perfect reproducibility (Scheme 24).
Reagents and conditions: (a) pTsOH, pivalaldehyde, pentane, 86% in 97a, >97% de; (b) pTsOH, H₂SO₄, 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 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. 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 slightly 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, and X-Ray analysis of 99a (Figure 1).
By substituting LiHMDS by KHMDS we were able to increase the yield to 53%. Furthermore 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.
Table 1: Formation of 99a from alkyltion of 98 and 97a

<table>
<thead>
<tr>
<th>98</th>
<th>97a</th>
<th>Base</th>
<th>temperature after addition of 98</th>
<th>Yield in 99a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 eq.</td>
<td>1 eq.</td>
<td>LiHMDS, 3 eq.</td>
<td>-76 °C</td>
<td>35%, &gt;92% de</td>
</tr>
<tr>
<td>1.5 eq.</td>
<td>1 eq.</td>
<td>KHMDS, 3 eq.</td>
<td>-76 °C</td>
<td>53%, &gt;92% de</td>
</tr>
<tr>
<td>1.5 eq.</td>
<td>1 eq.</td>
<td>KHMDS, 3 eq.</td>
<td>-40 °C</td>
<td>59%, &gt;92% de</td>
</tr>
</tbody>
</table>

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).

![Scheme 26](image-url)
Table 2: Formation of 108 from alkylation of 97a and 106 or 107

<table>
<thead>
<tr>
<th>Substrate (1 eq.)</th>
<th>KHMDS</th>
<th>temperature after addition of 106 or 107</th>
<th>Yield(^a) in 108 a+b (calculated from NMR of crude product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>97a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 eq.</td>
<td>106</td>
<td>3.5 eq.</td>
<td>50% product / 50% 106</td>
</tr>
<tr>
<td>1.5 eq.</td>
<td>106</td>
<td>3.5 eq.</td>
<td>87% product / 10% 106</td>
</tr>
<tr>
<td>4 eq.</td>
<td>106</td>
<td>8.5 eq.</td>
<td>57% product / 43% 106</td>
</tr>
<tr>
<td>1.5 eq.</td>
<td>107</td>
<td>3.5 eq.</td>
<td>58% product / 42% 107</td>
</tr>
</tbody>
</table>

\(^a\) 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.

![Scheme 27](image)

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 substrates 114a->d leading to a complex mixture of 8 diastereoisomerers and starting materials. In order to simplify the purification by column chromatography, the lactonisation was completed using cat. CDI and DMAP. The desired two diastereoisomerers 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).
1.) -75 bis -65 °C
THF
2.) 1N HCl / EtOAc

1) CDI / cat. DMAP in EtOAc / r.t.
2) acidic (1N HCl) workup
3) NaHCO₃ (to remove remaining malic acid deriv.)

Scheme 28
The four diastereoisomers 114a-d were separated and analysed by NMR. Relevant NOE-effect of three from the four diastereoisomers permitted us to assign the relative configuration of each product (Scheme 29).

![Diagram of compounds 114a, 114b, 114c, and 114d with NOE effects indicated]

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 absolute configuration of the four spiro compounds was assessed. This assignment was approved by X-Ray analysis of the two diastereoisomers 114a and 114c (Figures 2 and 3).
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.

Reagents and conditions : a) H₂, 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 reversibility 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. Unfortunately 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%).

Reagents and conditions : a) SOCl₂, SnCl₄, 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\textsuperscript{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.

![Scheme 32](image)

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

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\textsuperscript{94} and is straightforward. In the present work, we only slightly modified the sequence (Scheme 33).
The bromo derivative 88 was obtained in 5 steps from available quinizarin 83. Quinizarin was first methylated with dimethylsulfate and K₂CO₃ in acetone¹⁰⁸ to yield after recrystallisation 84 (91%). 84 was subjected to a reductive methylation using a known procedure¹⁰⁹ 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.
5.3.1.1 Alkylation

As we could more or less reproduce the results from Krohn et. Al.\textsuperscript{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 described 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%). Fortunately, we were able to obtain a 46% yield by increasing the temperature to -40 °C before addition of the substrate. 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 quantitatively the compound 118.
Table 3: Formation of 117a from alkylation of 88 and 97a

<table>
<thead>
<tr>
<th>97a</th>
<th>88</th>
<th>KHMDS</th>
<th>temperature</th>
<th>Isolated yield in 117a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 eq.</td>
<td>1 eq.</td>
<td>3 eq.</td>
<td>-76 °C a,b</td>
<td>23%</td>
</tr>
<tr>
<td>1.3 eq.</td>
<td>1 eq.</td>
<td>3 eq.</td>
<td>-76°C a then -40 °C b</td>
<td>27%</td>
</tr>
<tr>
<td>1.5 eq.</td>
<td>1 eq.</td>
<td>3.5 eq.</td>
<td>-40 °C b</td>
<td>46%</td>
</tr>
</tbody>
</table>

* temperature before addition of 88. ** 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 and subsequent methylation of phenolic alcohols as described earlier (dimethylsulfate, K₂CO₃, acetone) led to the anthraquinone 122 which was brominated with NBS under radical conditions 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.

Scheme 37

Reagents and conditions: (a) TFAA, cat. TFA, RT, 25% yield in 125, 46% of 117a recovered
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 occurred 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-7 present 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\textsuperscript{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.\textsuperscript{81-82}. Substrates 130 as well as 131 were readily cyclised with high stereoselectivity by
treatment with SnCl₄ 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 occurred 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](image)

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 completely 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 interesting to notice that no epimerisation of the acetal chiral center was observed. Two plausible explanations were envisaged: epimerisation is a slow process, and the short reaction time did not allow it to occur; low temperature seem to inhibit the epimerisation.
Reagents and conditions: (a) SnCl₄, 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 occurred 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 able 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 separated 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).
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 disappointing 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 CDCl₃ (filtered through Alox) led to complete decomposition of 139.
In order to prepare the tetracyclic product 141, various lewis acids such as SnCl₄, BF₃·Et₂O, mixture of TFA and TFAA, TFA in THF or TFA in DCM, MgCl₂ were investigated. Nevertheless, no clean reaction was observed. Most of the experiments led to complex mixtures of products which were difficult to separate 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 BF₃·Et₂O in DCM respectively. In both cases, a complex mixture of products was obtained and undesired demethylation occurred.

Even if the useful tetracyclic product 142 was detected and isolated, it appeared obvious to us that the aldehyde 139 was not an appropriate substrate 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 substrates 144 and 145. Actually, substrates 144 and 145 were resistant to these reaction conditions and could be recovered almost quantitatively.
Mono or complete demethylation of 144 and 145 was achieved by treatment with 1.2 equivalent or 4.8 equivalent BCl₃ respectively, in good to excellent yield (78% to 95%) with epimerisation of the acetal stereocenter (Scheme 45). The mono demethylation was regioselective and occurred 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 Krohn⁵³,¹¹¹,¹¹⁴ and were attributed to the apparent strong electron-withdrawing property of the anthraquinone system.
Reagents and conditions: (a) 1.5 eq. BCl$_3$, DCM, $-45^\circ$C, 82% of 148a+b, 80% of 149a+b; (b) 4.5 eq. BCl$_3$, DCM, $-45^\circ$C, 95% of 150a+b, 90% of 151a+b; (c) NaOH, Na$_2$S$_2$O$_4$, THF / MeOH, H$_2$O, 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. Unfortunately, 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 substrate 150a+b did not react in an 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 obtain 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 anthracene 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) BH₃·THF, THF, 2°C to RT, 50%; (d) DMSO, oxalylchlorid, DCM, Et₃N, -70°C, 85%; (e) CAN, CH₃CN / H₂O, 2°C to RT, 74% (144), 93% (145); (f) TFAA, TFA DCM, -70°C, 9%; (g) 1.5 eq. BCl₃, DCM, -45°C, 82% of 148a+b, 80% of 149a+b or 4.5 eq. BCl₃, 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.
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 analagous 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 diastereoselectivity (>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. Unfortunately, lactonisation occurred 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.
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\textsuperscript{116-117} to afford the desired compound in good yield (77%).
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 completely consumed 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, singlet 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).

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\textsuperscript{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.

\[
\begin{align*}
\text{Scheme 54}
\end{align*}
\]

Alternatively, the compound 171 was subjected to an oxidative demethylation by treatment with CAN in H\textsubscript{2}O/CH\textsubscript{3}CN. As described earlier, the silyl group was also partially cleaved to give the lactol 180. Using EtOAc instead of CH\textsubscript{3}CN 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 planned the ketalisation of the carbonyl group in 171 or in 176 (Scheme 55). Various reagents and conditions were investigated. Unfortunately, we failed to obtain the desired ketal 181 or thioketal 182. Surprisingly, we were never able to detect or isolate these compounds.

Treatment of the ketone 171 under usual ketalisation conditions\textsuperscript{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\textsubscript{4} as catalyst and ethandithiol in DCM\textsuperscript{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.

![Chemical结构](image)

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\textsuperscript{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 diastereoisomers 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\textsuperscript{127-129}. In our case, additional steps such as oxidative demethylation followed by the cleavage of the methoxy groups should lead 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.
successively demethylated by oxidative demethylation followed by deprotection with BCl$_3$. The mixture of the two isomers 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 isomers 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 oxidation of the primary alcohol should complete the sequence to reach the aldehyde 159a+b.
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 polluted 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, CH₃CN / H₂O, 2°C to RT, 15% of 193 and 27% of 190a+b.
Alternatively, compound 187a+b was subjected to oxidative demethylation to give the protected derivative 194a+b with the tri-alcohol 190a+b in 14% and 55% yield respectively (Scheme 61).

```
Reagents and conditions : (a) CAN, CH₃CN / H₂O, 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 BCl₃ 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 occurred 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 approaches 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 substrate. 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 oxidation of the primary alcohol and oxidative demethylation 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, oxalyl chloride, Et3N, DCM, -70°C, 96%; (c) CAN, CH3CN / H2O, 2°C to RT, 98% for 199a and 96% for 199b; (d) BCl3, 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 until 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 CH₃CN/H₂O leading to 199a and 199b in 90 and 98% yield respectively.

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

![Scheme 63](image)

Reagents and conditions : (a) BCl₃, DCM, 2°C, 94%

The simultaneous cleavage of both methoxy groups and the ketal was a tricky step. With regard to the results obtained in previous work BCl₃ seemed to be the adequate reagent to undergo the deprotection. The first experiment was carried out with BCl₃ in DCM at 0 °C and was worked up in an usual way (quenched with sat.NaHCO₃, extracted and concentrated under reduced pressure at 40 °C (bath temperature)). Unfortunately, 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

<table>
<thead>
<tr>
<th>conditions</th>
<th>Products and yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlCl₃, DCM</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>BF₃·Et₂O, DCM</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>TMSI, DCM</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>TMSCl, DCM</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>p-thiocresol, nBuLi, HMPA, toluene</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>Py.HCl, pyridine</td>
<td><strong>200</strong> (78%)</td>
</tr>
<tr>
<td>CeCl₃·7H₂O, NaI, CH₃CN</td>
<td><strong>201</strong> (70%)</td>
</tr>
<tr>
<td>BCl₃, DCM</td>
<td><strong>196a</strong> (94%)</td>
</tr>
</tbody>
</table>

Reactions using reagents such as AlCl₃, TMSCl, TMSI or p-thiocresol with nBuLi and HMPA¹³⁰⁻¹³⁶ 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 CH₃CN in presence of CeCl₃·7H₂O and NaI. Since no reaction was observed at room temperature for each reaction, heating under reflux was necessary but seemed to promote aromatisation of the lactol.

**Reagents and conditions:** (a) py·HCl, py., 195°C, 78%; (b) CeCl₃·7H₂O, NaI, CH₃CN, 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 disappearance 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.
Treatment of \(188a+b\) with CAN in CH\(_3\)CN/H\(_2\)O 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 or at a later stage of the synthesis. As described in Scheme 66, an alkyl group is introduced to the anthraquinone core of hydroxyanthraquinones exclusively ortho to the hydroxyl group in the Marschalk reaction. According to the investigation by Marschalk, the most important feature that affected the reaction course is the necessity to reduce the electron deficient anthraquinone to its electron rich hydroquinone analogue. Therefore, anthraquinone was reduced and deprotonated to the hydroquinone which adds to the aldehyde to give the intermediate. As reported by Shaw and Krohn, 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](image-url)
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\textsuperscript{139-140}.

5.8.2 Marschalk Reaction with Lactol 196a

Lactol anthraquinone derivatives such as 196a and their Marschalk reactions are rarely published\textsuperscript{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\textsubscript{2}S\textsubscript{2}O\textsubscript{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 occurred 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.
Actually, such hydroxylations have been reported several times in sequence is bromination with NBS or Br₂ and AIBN or under irradiation in refluxing CCl₄ (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.

**Scheme 67**

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

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Temperature</th>
<th>Products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>196a</td>
<td>-30°C&lt;T°C&lt;-15°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>196a</td>
<td>-10°C</td>
<td>210a/210b (25% to 52%); 211 (19% to 35%)</td>
</tr>
<tr>
<td>196a</td>
<td>Room temperature</td>
<td>211 (67%)</td>
</tr>
</tbody>
</table>

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 Marschall conditions gave satisfactory yield and good reproducibility, 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 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, CCl₄, H₂O, reflux, 27% of 212, 12% of 12 and 35% of 215; (c) i) TFA, RT, ii) acetone, sat. NaHCO₃, 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 CCl₄ and subsequent hydrolysis with silica gel in wet THF at 0 °C gave the 7,9-cis-diol
stereospecifically in good yield\textsuperscript{143} while treatment under the same condition in refluxing CCl\textsubscript{4}/H\textsubscript{2}O followed by usual work up gave a 2:1 mixture of the two C-7 epimeres in favour of the desired isomer\textsuperscript{145}.

- Epimerisation of the \textit{trans}-dial \textbf{215} is also a well known procedure. There are two possibilities. The conversion of a mixture of \textit{cis}- and \textit{trans}-dial to the corresponding \textit{cis}-boronate which could easily be cleaved under mild conditions in quantitative yield is the most used method\textsuperscript{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\textsuperscript{154-156}.

Product \textbf{211} was oxidised to the ketone \textbf{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 \textbf{212} in order to avoid the protection/deprotection steps. Thus, \textbf{212} was treated with NBS and AIBN in refluxing CCl\textsubscript{4}/H\textsubscript{2}O and quenched with THF/10% aq. K\textsubscript{2}CO\textsubscript{3} to afford the recovery of starting material \textbf{212} (27%) and a mixture of \textbf{12} and \textbf{215} (12% and 35% yield respectively) separated by chromatography.

The 7-epiidarubicinone \textbf{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 \textbf{12} in 73%. Thus, idarubicinone was obtained in 38% from \textbf{212} which was not completely consumed (27% recovered) or in 52% from the consumed starting material.

\textit{5.9.2 From 210a+b}

Since no chemoselective oxidation of \textbf{210a+b} at C-13 is possible as far as we know, two strategies were taken into consideration to reach the aglycone \textbf{12} (Scheme 69).
• Reaction of 210a+b with phenylboronic acid in TFA/toluene should lead to the simultaneous epimerisation at C-7 and formation of the cyclic cis-boronate 216\textsuperscript{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\textsuperscript{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-borane 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 dropped 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) NaBH₄, 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, oxalychloride, Et₃N, DCM, -70 °C, 1 h, 96%; (g) CAN, CH₃CN/H₂O, 0 °C → room temp., 30 min., 90% to 98%; (h) BCl₃, DCM, 0 °C, 40 min., 94%; (i) Na₂S₂O₄, NaOH, THF/MeOH/H₂O, room temp., 1 h 30, 67%; (j) Dess-Martin periodinane (97%), room temp., 5 h, 75%; (k) NBS, AIBN, CCl₄/H₂O, reflux, 4 h, 212 (27%), 12 (12%), 215 (35%); (l) 1)TFA, room temp., 2 h 2) acetone, sat. NaHCO₃, 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 recrystallisation 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 developed.

<table>
<thead>
<tr>
<th>Products</th>
<th>Small scale</th>
<th>Up scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantity (g, mmol)</td>
<td>yield</td>
</tr>
<tr>
<td>84</td>
<td>48 g, 200 mmol</td>
<td>95 %</td>
</tr>
<tr>
<td>85</td>
<td>49 g, 180 mmol</td>
<td>99 %</td>
</tr>
<tr>
<td>86</td>
<td>46 g, 160 mmol</td>
<td>94 %</td>
</tr>
<tr>
<td>87</td>
<td>20 g, 60 mmol</td>
<td>99 %</td>
</tr>
<tr>
<td>88</td>
<td>22 g, 67 mmol</td>
<td>86 %</td>
</tr>
<tr>
<td>166</td>
<td>6 g, 15.3 mmol</td>
<td>81 %</td>
</tr>
</tbody>
</table>

-92-
<table>
<thead>
<tr>
<th>171</th>
<th>4 g, 6.5 mmol</th>
<th>97 %</th>
<th>Column chromatography with Tol / EE 10 : 1</th>
<th>62 g, 0.1 mol</th>
<th>99 %</th>
<th>Flash chromatography with Tol / EE 10 : 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>187a+b</td>
<td>3 g, 5.7 mmol</td>
<td>88 %</td>
<td>Flash chromatography with Tol / EE 5 : 1</td>
<td>56 g, 0.1 mol</td>
<td>89 %</td>
<td>No purification</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flash chromatography with Tol / EE 40 : 1</td>
<td>30.17 g, 0.06 mol</td>
<td>70 %</td>
<td>Flash chromatography with Tol / EE 40 : 1</td>
</tr>
<tr>
<td>188a+b</td>
<td>1.1 g, 2.1 mmol</td>
<td>75 %</td>
<td>Flash chromatography with Tol / EE 3 : 1</td>
<td>38 g, 0.07 mol</td>
<td>91 %</td>
<td>Column chromatography a with Tol / EE 40 : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No purification</td>
<td>16 g, 0.03 mol</td>
<td>99 %</td>
<td>No purification</td>
</tr>
<tr>
<td>197a+b</td>
<td>0.9 g, 1.6 mmol</td>
<td>97 %</td>
<td>Flash chromatography with Tol / EE 6 : 1</td>
<td>14 g, 0.03 mol</td>
<td>90 %</td>
<td>Flash chromatography with Tol / EE 4 : 1</td>
</tr>
<tr>
<td>198a+b</td>
<td>2.2 g, 4.7 mmol</td>
<td>96 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>199a+b</td>
<td>2.1 g, 4.4 mmol</td>
<td>63 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 will not be discussed in more details in this thesis.
Reagents and conditions (a) i) H$_2$SO$_4$, MeOH; ii) 2,2-dimethoxypropane, acetone; iii) NaBH$_4$, MeOH; iv) NaOH, BzCl; v) oxalyl chloride, DMSO, Et$_3$N, DCM; (b) Mg, THF; (c) i) NaOMc, MeOH; ii) p-TsCl, Et$_3$N, DCM; iii) NaBH$_4$, CH$_3$CN; iv) oxalyl chloride, DMSO, Et$_3$N, DCM; v) NH$_3$OH.HCl, py.; vi) LiAlH$_4$, THF; vii) TFA, DMAP, py., DCM; (d) TFA, THF, H$_2$O; (e) p-NO$_2$BzCl, 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 developed 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<sub>2</sub>O, -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. 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 selectivity of the reaction.
The monoglycoside 223 was then converted to idarubicin hydrochloride 6-HCl in two steps. Selective cleavage of the pNO₂Bz 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.
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.

![Chemical structure](image)

Reagents and conditions: (a) i)K₂CO₃, Me₂SO₄, acetone, reflux, 91%; ii) TBABr, Na₂S₂O₄, KOH, Me₂SO₄, THF/H₂O, RT, 99%; iii) POCl₃, DMF, 87°C, 71%; iv) NaBH₄, EtOH, RT, 81%; v) Aq. HBr, toluene, 2°C to RT, 94%; (b) pTsOH, pivalaldehyde, pentane, 86 % in 97a, >97% de; (c) i) BH₃·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. Fortunately, 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).
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. Unfortunately, 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).
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 successfully 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 CCl4 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) NaBH₄, 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, oxalychloride, Et₃N, DCM, -70°C, 1 h, 96%; v) CAN, CH₃CN/H₂O, 0 °C → room temp., 30 min., 90% to 98%; vi) BCl₃, DCM, 0 °C, 40 min., 94%; (c) Na₂S₂O₇, NaOH, THF/MeOH/H₂O, -10°C, 1 h 30, 25 to 50%; (d) Na₂S₂O₇, NaOH, THF/MeOH/H₂O, room temp., 1 h 30, 67%; (e) Dess-Martin periodinane (97%), room temp., 5 h, 75%; ii) NBS, AIBN, CCl₄/H₂O, reflux, 4 h, 212 (27%), 12 (12%), 215 (35%); (f) TFA, room temp., 2 h 2) acetone, sat. NaHCO₃, 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<sub>2</sub>O, -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 recrystallisation or trituration.

There is still an option to improve further the effectives 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.<sup>161</sup>. 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 recorded 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:

\[
\text{CDCl}_3 \quad ^1\text{H} \ 7.26 \text{ ppm} \quad ^{13}\text{C} \ 77.00 \text{ ppm} \\
\text{d}_6\text{-DMSO} \quad ^1\text{H} \ 2.50 \text{ ppm} \quad ^{13}\text{C} \ 39.50 \text{ ppm}
\]

The numbering systems used for anthracycline derivatives and anthraquinone derivatives are illustrated 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 substances were purchased from Sigma Aldrich, Acros Organics, Lancaster and Fluka.
7.2 Synthesis

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

K₂CO₃ (288 g, 2.081 mol) was added to a suspension of 83 (100 g, 0.416 mol) in acetone (2000 mL). Me₂SO₄ (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

¹H NMR (200 MHz, CDCl₃) : δ = 8.15 (m, 2H, 5̈ and 8̈-H), 7.70 (m, 2H, 6- and 7-H), 7.33 (s, 2H, 2̈ and 3̈-H), 3.99 (s, 6H, OCH₃).

¹³C NMR (200 MHz, CDCl₃) : 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 (CH₃).

HRMS (ESI) : calcd. For C₁₆H₁₂O₄Na 291.0633; found 291.0628.
m.p. 173-174 °C
To a mixture of 84 (94 g, 0.350 mol), TBABr (6.8 g, 0.021 mol), Na₂S₂O₄ (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 Me₂SO₄ (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

¹H NMR (200 MHz, CDCl₃) : δ = 8.36 (m, 2H, 51 and 81H), 7.51 (m, 2H, 61 and 71H), 6.68 (s, 2H, 21 and 31H), 4.01 (s, 6H, OCH₃), 3.99 (s, 6H, OCH₃).

HRMS (ESI) : calcd. For C₁₈H₁₈O₄ 298.1205; found 298.1207.
m.p. 145-146 °C
1,4,9,10-tetramethoxyanthracene-2-carbaldehyde 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 bath 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$_2$SO$_4$), 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

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta = 10.62$ (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$_6$Na 381.1314 ; found 381.1318. (M+MeOH+Na)
m.p. 145-147°C
(1,4,9,10-tetramethoxy-2-anthryl)methanol 87

86 (72 g, 0.221 mol) was suspended in EtOH 96% (800 mL) at RT under argon atmosphere and NaBH₄ (8.4 g, 0.221 mol) was added portionwise over a period of 45 min. The temperature was controlled during addition of NaBH₄ and did not raise 26 °C. After addition of 1/3 of NaBH₄ the solid was dissolved. After complete addition of NaBH₄, 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 (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was recrystallised from CHCl₃ (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, CDCl₃) : δ = 8.35 (m, 2H, 51 and 81H), 7.53 (m, 2H, 61 and 71H), 6.77 (s, 1H, 31H), 4.92 (s, 2H, CH₂OH), 4.06 (s, 3H, OCH₃), 3.99 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 2.39 (br s, 1H, OH, D₂O exchangeable).

HRMS (ESI) : calcd. For C₁₉H₂₀O₅ 328.1311; found 328.1310.
m.p. 95-96 °C
2-(bromomethyl)-1,4,9,10-tetramethoxy-anthracene 88

87 (50.5 g, 0.154 mol) was dissolved in toluene (500 mL) and cooled to 2 °C. Aqueous HBr 48% (87 g, 1.077 mol) was slowly added to the solution over a period of 10 min (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. NaHCO₃ (400 mL), and brine (400 mL). The combined organic layers were dried (Na₂SO₄), 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, CDCl₃) : 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, CH₂Br), 4.07 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃).

HRMS (ESI) : calcd. For C₁₉H₁₉O₄Br 390.0467; found 390.0463.
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 apparatus. 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$_2$SO$_4$), filtered and concentrated under reduced pressure to give 129.7 g of 97a (0.642 mol, 86%, >97% de) as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 5.19 (s, 1H, H15); 4.65 (ddd, 1H, J = 0.6 Hz, 3.5 Hz, 7.3 Hz, H13); 3.01 (dd, 1H, J = 3.5 Hz, 17.0 Hz, H12/1); 2.83 (dd, 1H, J = 7.3 Hz, 17.4 Hz, H12/2); 0.97 (s, 9H, H-tBuCH$_3$).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 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$_2$SO$_4$. The reaction mixture was refluxed with a dean and stark apparatus. 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$_2$SO$_4$), 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 recrystallised from Et$_2$O / 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 NaBH₄ (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 EtO₂ (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), 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

¹H NMR (200 MHz, CDCl₃): δ = 6.84 (m, 3H, H-3, H-5 and H-6). 4.54 (s, 2H, H-CH₂); 3.85 (s, 3H, OCH₃); 3.77 (s, 3H, OCH₃); 2.38 (s, 1H, OH).

¹³C NMR (200 MHz, CDCl₃): 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 (CH₂, C-CH₂OH); 55.72 (CH₃, OCH₃).
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$_2$SO$_4$), 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.

$\text{2-(bromomethyl)-1,4-dimethoxy-benzene 98}$

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ = 6.85 (m, 3H, H-13, H-15 and H-16). 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$_3$) : $\delta$ = 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$_2$Br);.
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

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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 6.79 (m, 2H, H-15 and H-16); 6.70 (s, 1H, H-13); 5.09 (s, 1H, H-acetal); 3.76 (s, 3H, OCH₃-11); 3.75 (s, 3H, OCH₃-14); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-1);
55.66 (CH₃, OCH₃-4); 38.72 (CH₂, C-3’); 34.18 (Cq, C-tBu); 32.22 (CH₂, C-1’); 23.64 (CH₃, C-tBuCH₃).

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

¹H NMR (500 MHz, CDCl₃) : δ = 6.89 (d, 1H, J = 2.5 Hz, H13); 6.80 (m, 2H, H15 and H16); 5.31 (s, 1H, H-acetal); 3.78 (s, 3H, OCH₃₁₁); 3.75 (s, 3H, OCH₃₁₄); 3.42 (d, 1H, J = 14.2 Hz, H11´/1); 3.03 (d, 1H, J = 18.0 Hz, H-3´/1); 2.80 (d, 1H, J = 14.2 Hz, H₁´/2); 2.68 (d, 1H, J = 18.0 Hz, H-3´/2); 1.00 (s, 9H, H-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-1); 55.58 (CH₃, OCH₃-4); 39.03 (CH₂, C-3´); 36.81 (CH₂, C-1´); 34.70 (Cq, C-tBu); 23.67 (CH₃, C-tBuCH₃).
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$_2$SO$_4$), 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$_3$) : $\delta$ = 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$_3$-15); 3.83 (s, 3H, OCH$_3$-18); 3.41 (d, 1H, J = 17.7 Hz, H-11/1); 3.12 (d, 1H, J = 15.8 Hz, H-13/1); 3.09 (d, 1H, J = 17.7 Hz, H-12/1); 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$_3$) : $\delta$ = 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$_3$,
(2R,5S)-2-tert-butyl-5',8'-dimethoxy-spiro[1,3-dioxolane-5,3'-tetralin]-1',4-dione\textsuperscript{101}

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{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\textsubscript{3}-15); 3.83 (s, 3H, OCH\textsubscript{3}-18); 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\textsubscript{3}).

\textsuperscript{13}C NMR (500 MHz, CDCl\textsubscript{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\textsubscript{3}, OCH\textsubscript{3}-5); 55.99 (CH\textsubscript{3}, OCH\textsubscript{3}-8); 43.71 (CH\textsubscript{2}, C-3); 34.25 (Cq, C-tBuCH\textsubscript{3}); 31.24 (CH\textsubscript{2}, C-1); 23.25 (CH\textsubscript{3}, C-tBuCH\textsubscript{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


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 NH₄Cl (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 (Na₂SO₄), 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 (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was poured in EtOAc (150 mL) / sat. NaHCO₃ (150 mL). The layers were separated and the organic layer was washed with sat. NaHCO₃ (3 x 100 mL). The combined organic layers were dried (Na₂SO₄), 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 diastereoisomers 114a with 114b (4.65 mmol, 19%) and 1.54 g of a mixture of the 2 diastereoisomers 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 diastereoisomers.

(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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 172.90 (Cq, C5’); 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


$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 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$_3$) : $\delta$ = 172.08 (Cq, C-5’); 167.91 (Cq, C-4’); 155.25 (Cq, C-2); 130.20 (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); 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$_3$) : $\delta = 7.38$ (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$_3$) : $\delta = 172.57$ (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, C-tBu); 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$_3$) : $\delta = 7.44$ (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, OCH$_3$); 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$_3$) : $\delta = 171.70$ (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, C-tBu); 22.98 (CH$_3$, C-tBuCH$_3$).

m.p. 42-44 °C
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 H₂. 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

1H NMR (500 MHz, CDCl₃) : 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, OCH₃); 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-tBuCH₃).
2-((2S,4S)-4-(2-(allyloxy)-5-methoxybenzyl)-2-(tert-butyl)-5-oxo-1,3-dioxolan-4-yl)acetic acid 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 (Na₂SO₄), 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

1H NMR (500 MHz, CDCl₃) : δ = 6.78 (m, 2H, H-15 and H-16); 6.71 (s, 1H, H-13); 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-CH₂allyl/1); 5.28 (d, 1H, J = 10.8 Hz, H-CH₂allyl/2); 5.10 (s, 1H, H-acetal); 4.47 (d, 2H, J = 5.1 Hz, H-CH₂allyl); 3.75 (s, 3H, OCH₃); 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-tBuCH₃).

13C NMR (500 MHz, CDCl₃) : 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 (CH₂, C-CH₂allyl); 113.49 (CH, C-5); 112.82 (CH, C-6); 107.87 (CH, C-...
acetal); 80.44 (Cq, C-2'); 69.60 (CH₂, C-CH₂allyl); 55.63 (CH₃, OCH₃); 38.86 (CH₂, C-3'); 34.21 (Cq, C-tBuCH₃); 32.28 (CH₂, C-1'); 23.61 (CH₃, C-tBuCH₃).

8-(allyloxy)-4-hydroxy-5-methoxy-2-naphthoic acid 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 1 hr 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, CDCl₃) : $\delta$ = 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-CHaallyl); 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, CDCl₃) : $\delta$ = 168.48 (Cq, C-COOH); 154.32 (Cq, C-4); 149.86 (Cq, C-8); 149.67 (Cq, C-5); 133.08 (CH, C-CHaallyl); 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

KHMD (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 rise –72°C) and the mixture was allowed to warm 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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 8.35 (m, 2H, H-15 and H-18); 7.53 (m, 2H, H-16 and H-17); 6.55 (s, 1H, H-13); 5.10 (s, 1H, H-acetal); 4.01 (s, 3H, OCH₃-14); 4.00 (s, 3H, OCH₃-11); 3.95 (s, 3H, OCH₃-9); 3.78 (s, 3H, OCH₃-1); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-9 and OCH₃-10); 62.23 (CH₃, OCH₃-1); 56.30 (CH₃, OCH₃-4); 39.24 (CH₂, C-3’); 34.29 (Cq, C-tBu); 32.96 (CH₂, C-1’); 23.63 (CH₃, C-tBuCH₃).

HRMS (ESI) : calcd. For C₂₈H₃₃O₉ 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
¹H NMR (200 MHz, CDCl₃) : 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, OCH₃-4); 3.99 (s, 3H, OCH₃-10); 3.96 (s, 3H, OCH₃-9); 3.78 (s, 3H, OCH₃-1); 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-tBuCH₃).
(E)-1,2-bis(1,4,9,10-tetramethoxyanthracen-2-yl)ethane 118

\[
\begin{align*}
\text{88} & \quad \text{Br} & \quad \text{118}
\end{align*}
\]

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$_2$SO$_4$), 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$_3$) : $\delta = 8.37$ (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$14); 4.05 (s, 6H, OCH$_3$110); 4.04 (s, 6H, OCH$_3$19); 3.94 (s, 6H, OCH$_3$11)

$^{13}$C NMR (200 MHz, CDCl$_3$) : $\delta = 152.96$ (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).
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$_3$) : $\delta =$ 13.18 (s, 1H, OH11); 12.76 (s, 1H, OH14); 8.24 (m, 2H, H15 and H18); 7.96 (m, 2H, H16 and H17); 7.33 (s, 1H, H13); 2.29 (s, 3H, CH$_3$).

13C NMR (500 MHz, CDCl$_3$) : $\delta =$ 186.86 Cq, C19); 186.00 (Cq, C110); 156.67 (Cq, C14); 156.14 (Cq, C1); 140.47 (Cq, C2); 135.06 (CH, C6); 134.91 (CH, C7); 133.00 (Cq, C8a); 132.00 (Cq, C10a); 128.74 (CH, C3); 126.68 (CH, C5); 126.55 (CH, C8); 111.60 (Cq, C9a); 110.78 (Cq, C4a); 16.00 (CH$_3$).

m.p. 185-187 °C
1,4-dimethoxy-2-methyl-anthracene-9,10-dione 122

To a suspension of 121 (32.3 g, 0.127 mol) in dry acetone (750 mL) K$_2$CO$_3$ (175.4 g, 1.269 mol) was added and stirred for 15 min. Me$_2$SO$_4$ (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$_2$CO$_3$ 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 was hed with water (600 mL) until pH=7. The organic layer were dried (Na$_2$SO$_4$), 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) : $\delta$ = 8.03 (m, 2H, H15 and H18); 7.83 (m, 2H, H16 and H17); 7.51 (s, 1H, H13); 3.90 (s, 3H, OCH$_3$14); 3.77 (s, 3H, OCH$_3$11); 2.38 (s, 3H, CH$_3$).
m.p. 126-128 °C
To a suspension of 122 (20.0 g, 0.071 mol) in CCl₄ (400 mL) was added NBS (15.2 g, 0.085 mol) followed by Bz₂O₂ (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 CCl₄, 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**

**¹H NMR (500 MHz, CDCl₃) :** δ = 8.17 (m, 2H, H15 and H18); 7.74 (m, 2H, H16 and H17); 7.40 (s, 1H, H13); 4.62 (s, 2H, CH₂Br); 4.04 (s, 3H, OCH₃14); 4.02 (s, 3H, OCH₃11).

**¹³C NMR (500 MHz, CDCl₃) :** δ = 182.98 (Cq, C19); 182.73 (Cq, C110); 156.33 (Cq, C14); 152.29 (Cq, C1); 140.80 (Cq, C2); 134.24 (Cq, C8a); 133.78 (CH, C6); 133.69 (Cq, C10a); 133.43 (CH, C7); 127.58 (Cq, C9a); 126.62 (CH, C5); 126.46 (CH, C8); 123.11 (Cq, C4a); 120.64 (CH, C3); 62.80 (CH₃, OCH₃-4); 56.87 (CH₃, OCH₃-1); 26.52 (CH₂, C-CH₂Br).

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

KHMD S (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 (Na₂SO₄), 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

1H NMR (500 MHz, CDCl₃) : δ = 8.19 (m, 4H, H15 and H18); 7.75 (m, 4H, H16 and H17); 7.70 (s, 2H, =CH); 7.60 (s, 2H, H13); 4.12 (s, 6H, OCH₃14); 3.96 (s, 6H, OCH₃11).

13C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-1); 56.91 (CH₃, OCH₃-4).
(2S,5S)-2-tert-butyl-5',6',11',12'-tetramethoxy-spiro[1,3-dioxolane-5,3'-2,4-
dihydrotetracene]-1',4-dione 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. NaHCO₃ (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : 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, OCH₃₁₁); 4.01 (s, 3H, OCH₃₁₁); 4.00 (s, 3H, OCH₃₁₂); 3.84 (s, 3H, OCH₃₁₁); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : δ = 192.08 (Cq, C-3); 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 (CH₃, OCH₃-5); 63.71 (CH₃, OCH₃-12); 63.35 (CH₃, OCH₃-6); 61.62 (CH₃, OCH₃-11); 47.51 (CH₂, C-8); 34.47 (Cq, C-tBu); 28.61 (CH₂, C-10); 23.27 (CH₃, C-tBuCH₃).
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 atmosphere 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$_2$SO$_4$), 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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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$_8$Na 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$_3$) : $\delta$ = 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

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$_4$Cl (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$_2$SO$_4$), 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, H15 and H16); 6.73 (s, 1H, H13); 4.93 (s, 1H, H-acetal); 3.77 (m, 2H, H14´); 3.76 (s, 3H, OCH$_3$11); 3.75 (s, 3H, OCH$_3$14); 3.12 (d, 1H, J = 13.9 Hz, H11´/1); 3.07 (d, 1H, J = 13.9 Hz, H11´/2); 2.10 (m, 2H, H13´); 0.94 (s, 9H, H-tBuCH$_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$_3$) : $\delta = 6.84$ (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$_3$) : $\delta = 178.41$ (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

27 (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$_2$SO$_4$), 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$_3$) : $\delta$ = 9.63 (s, 1H, H-14´); 6.80 (m, 2H, H-15 and H-16); 6.71 (s, 1H, H-13); 5.11 (s, 1H, H-acetal); 3.76 (s, 3H, OCH$_3$11); 3.75 (s, 3H, OCH$_3$14); 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$_3$) : $\delta$ = 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

To a solution of 129 (200 mg, 0.595 mmol) in DCM (10 mL) cooled to –70 °C under argon atmosphere was slowly added SnCl₄ (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 (Na₂SO₄), 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 diastereoisomers 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 diastereoisomer.

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

¹H NMR (500 MHz, CDCl₃) : 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, OCH₃₁₅); 3.79 (s, 3H, OCH₃₁₈); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-5); 55.59
(CH₃, OCH₃-8); 35.84 (CH₂, C-3); 34.48 (Cq, C-tBuCH₃); 28.77 (CH₂, C-1); 23.43 (CH₃, C-tBuCH₃).

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

¹H NMR (500 MHz, CDCl₃) : δ = 6.77 (d, 1H, J = 8.9 Hz, H-16); 6.73 (d, 1H, J = 8.9 Hz, H-17); 5.26 (s, 1H, H-acetal); 5.22 (m, 1H, H-4); 4.47 (d, 1H, J = 3.5 Hz, OH-14); 3.88 (s, 3H, OCH₃-15); 3.78 (s, 3H, OCH₃-18); 3.04 (d, 1H, J = 17.7 Hz, H-1/1); 3.95 (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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-5); 55.64 (CH₃, OCH₃-8); 36.57 (CH₂, C-3); 34.45 (Cq, C-tBuCH₃); 28.81 (CH₂, C-1); 23.36 (CH₃, C-tBuCH₃).
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$_2$SO$_4$), 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

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta = 6.86$ (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$18); 3.77 (s, 3H, OCH$_3$15); 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$_3$) : $\delta = 171.54$ (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, 1.17 mmol). The reaction mixture was allowed to warmed up to RT, stirred for 1 hr at RT and quenched with sat. NH$_4$Cl (40 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried (Na$_2$SO$_4$), 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 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$_3$) : $\delta$ = 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$_3$).
\textsuperscript{13}C NMR (500 MHz, CDCl\textsubscript{3}) : \(\delta = 197.44\) (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\textsubscript{3}, OCH\textsubscript{3}9 and OCH\textsubscript{3}10); 62.24 (CH\textsubscript{3}, OCH\textsubscript{3}1); 56.29 (CH\textsubscript{3}, OCH\textsubscript{3}11); 48.03 (CH\textsubscript{2}, C-3'); 34.55 (Cq, C-tBuCH\textsubscript{3}); 33.49 (CH\textsubscript{2}, C-1'); 23.51 (CH\textsubscript{3}, C-tBuCH\textsubscript{3}).

HRMS (ESI) : calcd. For C\textsubscript{28}H\textsubscript{36}O\textsubscript{8}Na 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

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) : \(\delta = 8.35\) (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\textsubscript{3}4); 4.00 (s, 3H, OCH\textsubscript{3}10); 3.95 (s, 3H, OCH\textsubscript{3}9); 3.87 (m, 2H, H-4'); 3.79 (s, 3H, OCH\textsubscript{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\textsubscript{3}).

\textsuperscript{13}C NMR (500 MHz, CDCl\textsubscript{3}) : \(\delta = 175.65\) (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\textsubscript{3}, OCH\textsubscript{3}9 and OCH\textsubscript{3}10); 62.22 (CH\textsubscript{3}, OCH\textsubscript{3}1); 58.32 (CH\textsubscript{2}, C-4'); 56.31 (CH\textsubscript{3}, OCH\textsubscript{3}4); 38.19 (CH\textsubscript{2}, C-3'); 34.36 (Cq, C-tBuCH\textsubscript{3}); 33.87 (CH\textsubscript{2}, C-1'); 23.51 (CH\textsubscript{3}, C-tBuCH\textsubscript{3}).

HRMS (ESI) : calcd. For C\textsubscript{28}H\textsubscript{34}O\textsubscript{8}Na 521.2151; found 521.2163.

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

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) : \(\delta = 8.35\) (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\textsubscript{3}4); 4.00 (s, 3H, OCH\textsubscript{3}10); 3.94 (s, 3H, OCH\textsubscript{3}9); 3.85 (s, 1H, OCH\textsubscript{3}1); 3.49 (d, 1H, J
\[ \text{J} = 13.9 \text{Hz, H-1'}/1 \]; 2.99 (d, 1H, J = 13.9Hz, H-1’/2); 2.48 (m, 1H, H-3’/1); 2.26 (m, 1H, H-3’/2).

\[ ^{13}\text{C NMR (500 MHz, CDCl}_3\] : \( \delta = 178.55 \text{ (Cq, C-5'); 152.99 \text{ (Cq, C-4); 149.51 \text{ (Cq, C-10); 147.29 \text{ (Cq, C-9); 146.75 \text{ (Cq, C-1); 127.11 \text{ (Cq, C-8a); 126.66 \text{ (Cq, C-10a); 126.47 \text{ (CH, C-6); 125.95 \text{ (CH, C-7); 123.01 \text{ (CH, C-5); 122.69 \text{ (Cq, C-2); 122.52 \text{ (CH, C-8); 120.37 \text{ (Cq, C-9a); 119.43 \text{ (Cq, C-4a); 106.33 \text{ (CH, C-3); 75.86 \text{ (Cq, C-2'); 65.41 \text{ (CH}_2, \text{ C-4'); 63.56 \text{ (CH}_3, \text{ OCH}_3-10); 63.42 \text{ (CH}_3, \text{ OCH}_3-9); 62.04 \text{ (CH}_3, \text{ OCH}_3-1); 56.47 \text{ (CH}_3, \text{ OCH}_3-4); 37.29 \text{ (CH}_2, \text{ C-1'); 34.64 \text{ (CH}_2, \text{ C-3').}
\]

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

\[ ^{1}\text{H NMR (500 MHz, CDCl}_3\] : \( \delta = 8.34 \text{ (m, 2H, H-5 and H-8); 7.53 \text{ (m, 2H, H-6 and H-7); 6.52 \text{ (s, 1H, H-3); 5.14 \text{ (s, 1H, H-5'); 4.10 \text{ (m, 2H, H-4'); 4.04 \text{ (s, 3H, OCH}_3-4); 4.00 \text{ (s, 3H, OCH}_3-10); 3.95 \text{ (s, 3H, OCH}_3-9); 3.88 \text{ (s, 3H, OCH}_3-1); 3.25 \text{ (d, 1H, J = 13.5 Hz, H-1'}/1); 3.00 \text{ (d, 1H, J = 13.5 Hz, H-1’}/2); 2.10 \text{ (m, 1H, H-3’}/1); 1.97 \text{ (m, 1H, H-3’}/2).}
\]

\[ ^{13}\text{C NMR (500 MHz, CDCl}_3\] : \( \delta = 153.23 \text{ (Cq, C-4); 149.57 \text{ (Cq, C-9); 147.07 \text{ (Cq, C-10); 145.76 \text{ (Cq, C-1); 127.14 \text{ (Cq, C-8a); 126.58 \text{ (Cq, C-10a); 126.51 \text{ (CH, C-6); 125.93 \text{ (CH, C-7); 124.64 \text{ (Cq, C-2); 123.05 \text{ (CH, C-5); 122.47 \text{ (CH, C-8); 120.30 \text{ (Cq, C-9a); 119.32 \text{ (Cq, C-4a); 106.82 \text{ (CH, C-3); 100.51 \text{ (CH, C-5'); 81.03 \text{ (Cq, C-2'); 65.43 \text{ (CH}_2, \text{ C-4'); 63.57 \text{ (CH}_3, \text{ OCH}_3-10); 63.42 \text{ (CH}_3, \text{ OCH}_3-9); 61.93 \text{ (CH}_3, \text{ OCH}_3-1); 56.47 \text{ (CH}_3, \text{ OCH}_3-4); 39.03 \text{ (CH}_2, \text{ C-1'); 37.56 \text{ (CH}_2, \text{ 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

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. Et₃N (0.7 mL, 5.015 mmol) was then added at that temperature and stirring was continue for 1 hr 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. NH₄Cl (40 mL), sat. NaHCO₃ (40 mL) and brine (40 mL). The organic layer was dried (Na₂SO₄), 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, CDCl₃) : 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, OCH₃); 3.92 (s, 3H, OCH₃); 3.79 (s, 3H, OCH₃); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-9 and OCH₃-10); 62.24 (CH₃, OCH₃-1); 56.29 (CH₃, OCH₃-4); 48.03 (CH₂, C-3’); 34.55 (Cq, C-tBuCH₃); 33.49 (CH₂, C-1’); 23.51 (CH₃, C-tBuCH₃).

HRMS (ESI) : calcd. For C₂₈H₃₆O₈Na 551.2257; found 551.2257.
2-[[2R,4S]-2-tert-butyl-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 \( ^{140} \)

To a solution of \( ^{139} \) (80 mg, 0.16 mmol) in DCM (4 mL) cooled at \(-40^\circ C\) under argon atmosphere was added TFA (0.12 mL, 0.19 mmol). The reaction mixture was stirred for 2 hr at \(-40^\circ C\) 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\(_2\)SO\(_4\)), 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.

\( ^1\)H NMR (500 MHz, CDCl\(_3\)) : \( \delta \) = 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-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\(_3\)) : \( \delta \) = 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
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 NaHCO₃ (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na₂SO₄), 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

1H NMR (500 MHz, CDCl₃) : δ = 8.34 (m, 2H, H-11 and H-14); 7.54 (m, 2H, H-12 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, OCH₃-15); 3.99 (s, 3H, OCH₃-11); 3.90 (s, 3H, OCH₃-16); 3.82 (s, 3H, OCH₃-12); 3.90 (s, 3H, OCH₃-6); 3.82 (s, 3H, OCH₃-11); 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-tBuCH₃).
$^{13}$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-dihydtetracene-2,5’-1,3-dioxolane]-4’,5-dione 143

To a solution of 139 (50 mg, 0.10 mmol) in DCM (3 mL) cooled at -40 °C under argon atmosphere was added BF₃·Et₂O (3 mg, 0.02 mmol). The reaction mixture was stirred overnight at -25 °C and poured in sat. NaHCO₃ (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 (Na₂SO₄), 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-dihydtetracene-2,5’-1,3-dioxolane]-4’,5-dione 143

¹H NMR (500 MHz, CDCl₃) : 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, OCH₃); 3.90 (s, 3H, OCH₃); 3.71 (s, 3H, OCH₃); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : δ = 174.28 (Cq, C16 and C113); 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 (CH₃, OCH₃); 62.68 (CH₃, OCH₃); 60.43 (CH₃, OCH₃); 34.35 (CH₂, C-8); 34.32 (Cq, C-tBu); 26.77 (CH₂, C-10); 23.32 (CH₃, C-tBuCH₃).
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 (0.32 g, 0.642 mmol) was dissolved in CH$_3$CN (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$_2$SO$_4$), 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$_3$) : $\delta$ = 9.64 (dd, 1H, J = 0.7 Hz, 2.5 Hz, H-14´); 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$14); 3.91 (s, 3H, OCH$_3$11); 3.39 (d, 1H, J = 13.9 Hz, H-1´/1); 3.31 (d, 1H, J = 13.9 Hz, H-1´/2); 2.97 (dd, 1H, J = 0.7 Hz, 17.4 Hz, H-3´/1); 2.85 (dd, 1H, J = 2.5 Hz, 17.4 Hz, H-3´/2); 0.96 (s, 9H, H-tBuCH$_3$).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 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_{8}Na 521.1788; found 521.1794.

From 228

![chemical_structure](image)

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_{3}N (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_{4}Cl (20 mL), sat. NaHCO_{3} (20 mL) and brine (20 mL). The organic layer was dried (Na_{2}SO_{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

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$_4$Cl (40 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried (Na$_2$SO$_4$), 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$_3$) : $\delta$ = 8.18 (m, 2H, H-15 and H-18); 7.74 (m, 2H, H-16 and H-17); 7.26 (s, 1H, H-13); 5.02 (s, 1H, H-acetal); 3.99 (s, 3H, OCH$_3$14); 3.91 (s, 3H, OCH$_3$10); 3.81 (m, 2H, H-14´); 3.42 (d, 1H, J = 13.9 Hz, H-11´/1); 3.11 (d, 1H, J = 13.9 Hz, H-11´/2); 2.13 (m, 2H, H-3´); 0.97 (s, 9H, H-tBuCH$_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 CH₃CN (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : 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, OCH₃₁₁); 3.90 (s, 3H, OCH₃₁₄); 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-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃⁻¹); 56.72 (CH₃, OCH₃⁻⁴); 38.93 (CH₂, C-3’); 34.39 (Cq, C-tBuCH₃); 32.35 (CH₂, C-1’); 23.59 (CH₃, C-tBuCH₃).

HRMS (ESI) : calcd. For C₂₆H₂₆O₈Na 505.1475; found 505.1475.
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$_2$SO$_4$), 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$_3$) : $\delta$ = 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-15 and H-18); 7.86 (m, 2H, H-16 and H-17); 7.21 (s, 1H, H-13); 5.40 (s, 1H, H-acetal); 3.27 (s, 2H, H-11'); 2.94 (m, 2H, H-3'); 0.98 (s, 9H, H-tBuCH$_3$).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 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-
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$_3$) : $\delta = 13.49$ (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$_3$) : $\delta = 197.80$ (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$_{26}$H$_{26}$O$_9$Na 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$_2$SO$_4$), 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 (0.018 mmol, 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); 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$_3$); 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 (CH₃, OCH₃-1); 38.63 (CH₂, C-3'); 34.34 (Cq, C-tBuCH₃); 32.01 (CH₂, C-1'); 23.63 (CH₃, C-tBuCH₃).

HRMS (ESI): calcd. For C₂₅H₂₄O₉ 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

¹H NMR (500 MHz, CDCl₃): δ = 13.47 (s, 1H, OH11); 12.83 (s, 1H, OH14); 8.37 (m, 2H, H1 and H18); 7.86 (m, 2H, H6 and H7); 7.39 (s, 1H, H13); 5.37 (s, 1H, H1acetal); 3.62 (d, 1H, J = 13.9 Hz, H11'/1); 3.15 (d, 1H, J = 17.5 Hz, H13'/1); 2.93 (d, 1H, J = 13.9 Hz, H11'/2); 2.78 (d, 1H, J = 17.5 Hz, H13'/2); 1.01 (s, 9H, H1tBuCH₃).

¹³C NMR (500 MHz, CDCl₃): 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 (CH₂, C-3'); 36.22 (CH₂, C-1'); 34.68 (Cq, C-tBuC); 23.69 (CH₃, C-tBuCH₃).

HRMS (ESI): calcd. For C₂₄H₂₂O₉Na 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

¹H NMR (500 MHz, CDCl₃): δ = 13.04 (s, 1H, OH14); 8.28 (m, 2H, H5 and H8); 7.81 (m, 2H, H6 and H7); 7.40 (s, 1H, H3); 5.37 (s, 1H, H-acetal); 3.87 (s, 3H, OCH₃-1); 3.57 (d, 1H, J = 13.9 Hz, H11'/1); 3.04 (d, 1H, J = 17.5 Hz, H13'/1); 2.92 (d, 1H, J = 13.9 Hz, H11'/2); 2.67 (d, 1H, J = 16.4 Hz, H13'/2); 0.98 (s, 9H, H-tBuCH₃).

¹³C NMR (500 MHz, CDCl₃): 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 (CH₃, OCH₃-1); 36.65 (CH₂, C-3’); 34.62 (CH₂, C-1’); 31.91 (Cq, C-tBuCH₃); 23.65 (CH₃, C-tBuCH₃).

HRMS (ESI) : calcd. For C_{25}H_{24}O₉ 469.1499; found 468.1503

NB : using 4.5 eq of BCl₃ 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$_2$S$_2$O$_4$ (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$_2$SO$_4$), 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$_3$) : $\delta$ = 13.71 (s, 1H, OH11); 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, H14´); 3.28 (d, 1H, J = 13.9 Hz, H1´/1); 3.11 (d, 1H, J = 13.9 Hz, H1´/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$_3$) : $\delta$ = 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 (CH₂, C-3'); 36.05 (CH₂, C-1').

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

¹H NMR (500 MHz, CDCl₃): δ = 13.56 (s, 1H, OH-1); 12.82 (s, 1H, OH-4); 8.35 (m, 2H, H-15 and H-18); 7.85 (m, 2H, H-16 and H-17); 7.27 (s, 1H, H-13); 5.46 (dd, 1H, J = 2.3 Hz, 4.8 Hz, H-14'); 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').

¹³C NMR (500 MHz, CDCl₃): 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 (CH₂, C-3'); 38.20 (CH₂, 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. BH₃·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. NH₄Cl (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 NaHCO₃ (2 x 300 mL), brine (300 mL) and then dried (Na₂SO₄), 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

1H NMR (500 MHz, d₆-DMSO) : δ = 5.40 (s, 1H, H-15); 4.66 (t, 1H, J = 5.4 Hz, OH-11); 4.55 (dd, 1H, J = 4.1 Hz, 8.2 Hz, H-13); 3.53 (m, 2H, H-11); 1.92 (m, 1H, H-12/1); 1.72 (m, 1H, H-12/2); 0.91 (s, 9H, H-tBuCH₃).

13C NMR (500 MHz, d₆-DMSO) : δ = 173.74 (Cq, C-14); 108.27 (CH, C-15); 71.54 (CH, C-13); 56.32 (CH₂, C-1); 33.69 (Cq, C-tBu); 33.62 (CH₂, C-2); 23.16 (CH₃, C-tBuCH₃).

TBDMSCI (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 NaHCO₃ (200 mL), dried (Na₂SO₄), 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**

**1H NMR** (500 MHz, CDCl$_3$) : $\delta = 5.15$ (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$_3$).

**13C NMR** (500 MHz, CDCl$_3$) : $\delta =$173.95 (Cq, C-4); 109.43 (CH, C-5); 71.74 (CH, C-3); 58.40 (CH$_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$_4$SiNa 325.1811; found 325.1810.
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 (Na₂SO₄), 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.

**1H NMR** (500 MHz, CDCl₃) : δ = 8.35 (m, 2H, H₁₅ and H₁₈); 7.52 (m, 2H, H₁₆ and H₁₇); 6.64 (s, 1H, H₁₃); 4.84 (s, 1H, H-acetal); 4.02 (s, 3H, OCH₃₁₄); 4.00 (s, 3H, OCH₃₁₀); 3.95 (s, 3H, OCH₃₁₁); 3.83 (m, 2H, H₁₄’); 3.75 (s, 3H, OCH₃₁₁); 3.44 (d, 1H, J = 13.9 Hz, H₁₁’/₁); 3.18 (d, 1H, J = 13.9 Hz, H₁₁’/₂); 2.17 (m, 2H, H₁₃’); 0.89 (s, 9H, H-tBuCH₃); 0.88 (s, 9H, H-SitBuCH₃); 0.05 (s, 3H, H-SiCH₃); 0.04 (s, 3H, H-SiCH₃).

**13C NMR** (500 MHz, CDCl₃) : δ = 175.23 (Cq, C₁₅’); 152.17 (Cq, C-4); 149.32 (Cq, C-10); 147.59 (Cq, C⁻�); 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-SiBuCH$_3$); 23.55 (CH$_3$, C-tBuCH$_3$); -5.43 (CH$_3$, C-SiCH$_3$).

HRMS (ESI) : calcd. For C$_{34}$H$_{48}$O$_8$SiNa 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$_2$SO$_4$), 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$_3$) : $\delta =$ 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$_3$): $\delta = 178.55$ (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)silyloxyethyl]-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-dimethoxyanthracene-9,10-dione 169

KHMDS (0.83 g, 4.15 mmol) was dissolved in dry THF (30 mL) under argon and cooled to $-76^\circ$C. 165 (1.2 g, 3.97 mmol) in THF (2 mL) was added dropwise (the temperature did not raise $-72^\circ$C) and the mixture was stirred for 50 min at $-76^\circ$C. 123 (0.6 g, 1.66 mmol) in THF (4 mL) was added dropwise at $-75^\circ$C and the reaction mixture was stirred at $-75^\circ$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$_2$SO$_4$), 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(dimethyl)silyloxyethyl]-5-oxo-1,3-dioxolan-4-yl]-10-hydroxy-1,4-dimethoxy-9-oxo-2-anthryl[methyl]-5-[2-tert-butyl(dimethyl)silyloxyethyl]-1,3-dioxolan-4-one 229

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta = 7.99$ (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$_3$-1); 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$_3$) : $\delta = 183.98$ (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-SiBuCH$_3$); 23.63 (CH$_3$, C-tBuCH$_3$); 23.51 (CH$_3$, C-tBuCH$_3$); 18.23 (Cq, C-SiBu and C-SiBu´); -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$_2$Na 907.4460; found 907.4475.
2-[(2S,4S)-2-tert-butyl-4-[2-tert-butyl(dimethyl)silyloxyethyl]-5-oxo-1,3-dioxolan-4-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione 169

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 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$_3$-14); 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-SitBuCH$_3$); 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$_3$) : $\delta$ = 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 Et₂O (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. NH₄Cl (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 16.67 (m, 2H, H₁₅ and H₁₈); 7.51 (m, 2H, H₁₆ and H₁₇); 6.70 (s, 1H, H₁₃); 4.01 (s, 3H, OCH₃₁₄); 3.98 (s, 3H, OCH₃₁₁₀); 3.92 (s, 3H, OCH₃₁₉); 3.82 (td, 1H, J = 4.1 Hz, 9.2 Hz, H₁₄´/₁); 3.77 (s, 3H, OCH₃₁₁); 3.70 (dt, 1H, J = 5.1 Hz, 10.4 Hz, H₁₄´/₂); 3.27 (d, 1H, J = 12.9 Hz, H₁₁´/₁); 3.12 (d, 1H, J = 12.9 Hz, H₁₃´/₂); 2.39 (m, 1H, H₁₃´/₁); 2.33 (s, 3H, CH₃); 1.96 (dt, 1H, J = 4.4 Hz, 14.2 Hz, H₁₁´/₂); 0.86 (s, 9H, H-SiBuCH₃); 0.02 (s, 3H, H-SiCH₃); 0.01 (s, 3H, H-SiCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃₁₀); 63.25 (CH₃, OCH₃₉); 61.78 (CH₃, OCH₃₁); 58.84 (CH₂, C-
(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$_3$) : $\delta$ = 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-SiBuCH$_3$); -0.02 (s, 3H, H-SiCH$_3$); -0.05 (s, 3H, H-SiCH$_3$).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ =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-SiBuCH$_3$); 24.88 (CH$_3$); 24.72 (CH$_3$); 18.05 (Cq, C-SiBu); -5.61 (CH$_3$, C-SiCH$_3$); -5.69 (CH$_3$, C-SiCH$_3$).
HRMS (ESI): calcd. For C$_3$H$_{46}$O$_7$SiNa 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$_2$SO$_4$), 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$_3$): $\delta$ = 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$_3$): $\delta$ = 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-[[3(S)-2,3-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dimethoxy-anthracene-9,10-dione **180**

![Chemical Structures](image)

**171** (0.46 g, 0.848 mmol) was dissolved in CH$_3$CN (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$_2$SO$_4$), 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 yellow 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$_3$-14); 3.88 (s, 3H, OCH$_3$-11); 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-SiBuCH$_3$); 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
(CH₂, C1’); 25.79 (CH₃, C-SiBuCH₃); 25.46 (CH₃); 18.21 (Cq, C-SiBu); -5.85 (CH₃, SiCH₃).

HRMS (ESI) : calcd. For C₂₈H₃₆O₇SiNa 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

¹H NMR (500 MHz, CDCl₃) : 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, OCH₃-4); 3.94 (m, 1H, H-4’/1); 3.89 (s, 3H, OCH₃-1); 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, CH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₂, C-4’); 62.29 (CH₃, OCH₃-1); 56.47 (CH₃, OCH₃-4); 37.46 (CH₂, C-3’); 30.94 (CH₂, C-1’); 20.71 (CH₃).
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$_2$SO$_4$), 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 yellow 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

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$_2$SO$_4$), 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 yellow 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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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-[[3(3S)-2,3-dihydroxy-2-methyl-tetrahydrofuran-3-yl]methyl]-1,4-dimethoxyanthracene-9,10-dione 180

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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

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. Et₃N (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 Et₂O 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 cyclohexane / EtOAc (4/1) to give 8.2 g (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, CDCl₃) : δ = 3.64 (s, 4H, H-CH₂); 0.12 (s, 18H, H-SiCH₃).

¹³C NMR (500 MHz, CDCl₃) : δ = 63.88 (CH₂); -0.45 (CH₃, C-SiCH₃).
(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

![Chemical Structure](image)

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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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
(CH₂, C-13); 63.95 (CH₃, OCH₃-6); 63.63 (CH₃, OCH₃-5); 63.57 (CH₃, OCH₃-10); 61.62 (CH₃, OCH₃-11); 41.08 (CH₂, C-12); 39.29 (CH₂, C-9); 19.65 (CH₃).

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

¹H NMR (500 MHz, CDCl₃) : δ = 8.34 (m, 2H, H11 and H14); 7.52 (m, 2H, H-2 and H-3); 4.11 (m, 1H, H-13/1); 4.00 (s, 3H, OCH₃-11); 3.99 (s, 3H, OCH₃-5); 3.97 (s, 3H, OCH₃-6); 3.89 (s, 3H, OCH₃-10); 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, CH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₂, C-13); 63.62 (CH₃, OCH₃-5 and OCH₃-11); 63.40 (CH₃, OCH₃-6); 61.57 (CH₃, OCH₃-10); 41.59 (CH₂, C-12); 39.50 (CH₂, C-9); 19.26 (CH₃).

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. NaBH₄ (2.36 g, 0.062 mol) was added and the reaction mixture was stirred at RT for 1 hr. 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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 8.34 (m, 2H, H-15 and H-18); 7.51 (m, 2H, H-16 and H-17); 6.75 (s, 1H, H-13); 4.02 (s, 3H, OCH₃-14); 3.99 (s, 3H, OCH₃-110); 3.96 (m, 2H, H-14´); 3.94 (s, 3H, OCH₃-19); 3.83 (s, 3H, OCH₃-11); 3.63 (q, 1H, J = 6.3 Hz, H-15´); 3.26 (d, 1H, J = 13.6 Hz, H-11´/1); 2.96 (d, 1H, J = 13.6 Hz, H-11´/2); 1.91 (m, 2H, H-3´); 1.22 (d, 3H, J = 6.3 Hz, CH₃); 0.95 (s, 9H, H-SitBuCH₃); 0.13 (s, 6H, H-SiCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-10); 63.36 (CH₃, OCH₃-9); 62.12 (CH₃, OCH₃-1); 60.37 (CH₂, C-
(2R,3S)-5-(tert-butyl(dimethyl)silyl)oxy-3-[(1,4,9,10-tetramethoxy-2-anthryl)methyl]pentane-2,3-diol 187b

1H NMR (500 MHz, CDCl3) : δ = 8.34 (m, 2H, H15 and H18); 7.51 (m, 2H, H-6 and H-7); 6.75 (s, 1H, H-3); 4.03 (s, 3H, OCH3-4); 4.00 (s, 3H, OCH3-10); 3.96 (m, 2H, H-4'); 3.93 (s, 3H, OCH3-9); 3.81 (s, 3H, OCH3-1); 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, CH3); 0.91 (s, 9H, H-SitBuCH3); 0.09 (s, 6H, H-SiCH3).

13C NMR (500 MHz, CDCl3) : 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 (CH3, OCH3-10); 63.36 (CH3, OCH3-9); 61.73 (CH3, OCH3-1); 60.37 (CH2, C-4'); 56.32 (CH3, OCH3-4); 37.22 (CH2, C-3'); 36.91 (CH2, C-1'); 25.81 (CH3, C-SitBuCH3); 18.10 (Cq, C-SitBu); 16.63 (CH3), -5.58 (CH3, C-SiCH3).
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]silane 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$_2$SO$_4$), 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$_3$) : $\delta$ = 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$_3^{14}$); 3.98 (s, 3H, OCH$_3^{11}$); 3.92 (s, 3H, OCH$_3^{19}$); 3.73 (s, 3H, OCH$_3^{11}$); 3.69 (m, 2H, H-14'); 3.19 (d, 1H, J = 13.6 Hz, H-11'/1); 2.75 (d, 1H, J = 13.6 Hz, H-11'/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-Si$tBu$CH$_3$); 0.01 (s, 6H, H-Si$CH_3$).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 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-acetone); 84.64 (Cq, C-2'); 76.93 (CH, C-5'); 63.42 (CH₃, OCH₃-10); 63.26 (CH₃, OCH₃-9); 61.70 (CH₃, OCH₃-1); 58.81 (CH₂, C-4'); 56.02 (CH₃, OCH₃-4); 37.79 (CH₂, C-3'); 32.49 (CH₂, C-1'); 28.72 (CH₃, C-acetone); 26.71 (CH₃, C-acetone); 25.83 (CH₃, C-SitBuCH₃); 18.07 (Cq, C-SitBu); 14.16 (CH₃); -5.19 (CH₃, C-SiCH₃).

HRMS (ESI) : calcd. For C₃₃H₄₈O₇Si 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

¹H NMR (500 MHz, CDCl₃) : δ = 8.35 (m, 2H, H₁₅ and H₁₈); 7.50 (m, 2H, H₁₇); 6.75 (s, 1H, H₁₃); 4.08 (m, 2H, H₁₄'); 4.04 (s, 3H, OCH₃₁₄); 3.99 (s, 3H, OCH₃₁₁₀); 3.95 (s, 3H, OCH₃₁₉); 3.92 (q, 1H, J = 6.3 Hz, H₅'); 3.76 (s, 3H, OCH₃₁'); 3.13 (s, 2H, H₁₁'); 1.91 (m, 1H, H₃-1'/1); 1.77 (m, 1H, H₃-2'/2); 1.41 (s, 3H, H-acetone); 1.22 (d, 3H, J = 6.3 Hz, CH₃); 1.00 (s, 3H, H-acetone); 0.94 (s, 9H, H-SitBuCH₃); 0.13 (s, 6H, H-SiCH₃).

¹³C NMR (500 MHz, CDCl₃) : 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-acetone); 83.88 (Cq, C-2'); 76.01 (CH, C-5'); 63.47 (CH₃, OCH₃-10); 63.42 (CH₃, OCH₃-9); 61.77 (CH₃, OCH₃-1); 59.51 (CH₂, C-4'); 56.42 (CH₃, OCH₃-4); 37.38 (CH₂, C-3'); 34.68 (CH₂, C-1'); 28.44 (CH₃, C-acetone); 26.75 (CH₃, C-acetone); 26.01 (CH₃, C-SitBuCH₃); 18.35 (Cq, C-SitBu); 13.62 (CH₃); -5.44 (CH₃, C-SiCH₃).

HRMS (ESI) : calcd. For C₃₃H₄₈O₇Si 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. NaHCO₃ (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : 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; OCH₃-4); 4.00 (s, 3H, OCH₃-10); 3.94 (s, 3H, 
OCH₃-9); 3.90 (m, 2H, H-4´); 3.87 (s, 3H, OCH₃-1); 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, CH₃).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-10); 63.47 (CH₃, OCH₃-9); 62.11 (CH₃, OCH₃-1); 59.31 (CH₂, C- 
4´); 56.45 (CH₃, OCH₃-4); 37.11 (CH₂, C-3´); 36.32 (CH₂, C-1´); 16.49 (CH₃).
(3S,4R)-3-[(1,9-dihydroxy-4,10-dimethoxy-2-anthryl)methyl]pentane-1,3,4-triol 189b

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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$_3$).
From 189a

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

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 (0.10 g, 0.232 mmol) was dissolved in CH₃CN (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 (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na₂SO₄), 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 yellow 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, CDCl₃) : δ = 8.16 (m, 2H, H-15 and H-18); 7.72 (m, 2H, H-16 and H-17); 7.18 (s, 1H, H-13); 4.00 (s, 3H, OCH₃14); 3.89 (m, 4H, H-11´and H-14´); 3.83 (s, 3H, OCH₃11); 2.84 (t, 2H, J = 5.4 Hz, H-13´).

$^{13}$C NMR (500 MHz, CDCl₃) : δ = 207.28 (Cq, C12´); 183.27 (Cq, C19); 182.73 (Cq, C110); 156.30 (Cq, C14); 152.31 (Cq, C-11); 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 (CH₃, OCH₃-1); 57.79 (CH₂, C-4´); 56.81 (CH₃, OCH₃-4); 45.20 (CH₂, C-1´); 44.62(CH₂, C-3´).

HRMS (ESI) : calcd. For C₂₀H₁₈O₆ 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$_3$) : $\delta = 8.16$ (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$_3$) : $\delta = 183.37$ (C, C-9); 182.87 (C, C-10); 156.21 (C, C-4); 152.07 (C, C-1); 141.27 (C, C-2); 134.30 (C, C-8a); 133.71 (C, C-10a and CH, C-6); 133.30 (CH, C-7); 127.00 (C, C-9a); 126.54 (CH, C-5); 126.43 (CH, C-8); 123.24 (CH, C-3); 121.66 (C, C-4a); 77.75 (C, 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$_7$Na 423.1420; found 423.1417.

From 187a

2-[(2S,3S)-2-[tert-butyldimethylsilyl]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$_3$CN (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 (Na₂SO₄), 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 yellow 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-buty]l-1,4-dimethoxy-anthracene-9,10-dione 194a

1H NMR (500 MHz, CDCl₃) : δ = 8.17 (m, 2H, H15 and H18); 7.72 (m, 2H, H-5 and H-8); 7.49 (s, 1H, H-3); 4.00 (s, 3H, OCH₃-4); 3.91 (s, 3H, OCH₃-1); 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, CH₃); 0.87 (s, 9H, H-SiBuCH₃); 0.06 (s, 3H, H-SiCH₃); 0.03 (s, 3H, H-SiCH₃).

13C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-1); 60.15 (CH₂, C-4´); 56.63 (CH₃, OCH₃-4); 35.48 (CH₂, C-3´); 34.10 (CH₂, C-1´); 25.72 (CH₃, C-SiBuCH₃); 17.96 (Cq, C-SiBu); 16.32 (CH₃); -5.65 (CH₃, C-SiCH₃); -5.70 (CH₃, C-SiCH₃).

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

1H NMR (500 MHz, CDCl₃) : δ = 8.16 (m, 2H, H-5 and H-8); 7.72 (m, 2H, H-5 and H-7); 7.38 (s, 1H, H-3); 4.01 (s, 3H, OCH₃-4); 3.94 (s, 3H, OCH₃-1); 3.87 (m, 1H, 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, CH₃).

13C NMR (500 MHz, CDCl₃) : 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 (CH3, OCH3-1); 59.17 (CH2, C-4´); 56.80 (CH3, OCH3-4); 36.63 (CH2, C-3´); 35.49 (CH2, C-1´); 16.72 (CH3).

HRMS (ESI) : calcd. For C22H24O7Na 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

To a solution of 203b (50 mg, 0.114 mmol) in CH3CN (5 mL) was added CeCl3.7H2O (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 (Na2SO4), 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

1H NMR (500 MHz, d6-DMSO) : δ = 13.48 (s, 1H, OH-11); 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-13); 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 (m, 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, CH3).
$^{13}$C NMR (500 MHz, d6-DMSO) : $\delta$ = 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 (CH2, C-4’); 37.22 (CH2, C-3’); 33.07 (CH2, C-1’); 17.35 (CH3).

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

![Chemical Structure](image)

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 BCl3 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 ($\text{Na}_2\text{SO}_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with 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

$^1$H NMR (200 MHz, CDCl3) : $\delta$ = 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, CH3).
1,4-dihydroxy-2-((4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methyl)anthracene-9,10-dione \textit{191} and 1,4-dihydroxy-2-(((4S)-4-(1-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)anthracene-9,10-dione \textit{192}.

To a solution of \textit{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\textsubscript{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\textsubscript{2}SO\textsubscript{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 \textit{192} and \textit{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. NaHCO₃ (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : 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-5ʻ); 4.02 (s, 3H, OCH₃-4); 4.00 (s, 3H, OCH₃-10); 3.93 (s, 3H, OCH₃-9); 3.81 (m, 1H, H-4ʼ/1); 3.78 (s, 3H, OCH₃-1); 3.66 (m, 1H, H-4ʼ/2); 3.22 (d, 1H, J = 13.6 Hz, H-1ʼ/1); 2.81 (brs, 1H, OH-4ʼ); 2.75 (d, 1H, J = 13.6 Hz, H-1ʼ/2); 1.88 (m, 2H, H-3ʼ); 1.75 (s, 3H, H-acetonide); 1.48 (d, 3H, J = 6.3 Hz, CH₃); 1.47 (s, 3H, H-acetonide).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-10); 63.31 (CH₃, OCH₃-9); 61.84 (CH₃, OCH₃-11); 58.92 (CH₂, C-4’); 56.08 (CH₃, OCH₃-4); 36.82 (CH₂, C-3’); 33.00 (CH₂, C-1’); 28.76 (CH₃, C-acetonide); 26.68 (CH₃, C-acetonide); 14.20 (CH₃).

HRMS (ESI) : calcd. For C_{27}H_{34}O_{7}Na 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

³¹H NMR (500 MHz, CDCl₃) : 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, OCH₃-4); 3.99 (s, 3H, OCH₃-10); 3.97 (m, 1H, H-4’/2); 3.94 (s, 3H, OCH₃-9); 3.76 (s, 3H, OCH₃-1); 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, CH₃); 0.98 (s, 3H, H-acetonide).

³¹C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-10); 63.42 (CH₃, OCH₃-9); 61.79 (CH₃, OCH₃-1); 59.63 (CH₂, C-4’); 56.45 (CH₃, OCH₃-4); 35.26 (CH₂, C-3’); 34.31 (CH₂, C-1’); 28.16 (CH₃, C-acetonide); 26.47 (CH₃, C-acetonide); 13.69 (CH₃).

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

To a solution of DMSO (0.99 mL, 13.95 mmol) in DCM (55 mL) cooled to –70 °C under argon was added dropwise oxalyl chloride (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. Et₃N (4.27 mL, 30.69 mmol) was then added at that temperature and stirring was continue for 1 hr 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. NH₄Cl (60 mL), sat. NaHCO₃ (60 mL) and brine (60 mL). The organic layer was dried (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 9.65 (dd, 1H, J = 1.3 Hz, 2.2 Hz, H-14´); 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, OCH₃14); 3.99 (s, 3H, OCH₃110); 3.91 (s, 3H, OCH₃19); 3.70 (s, 3H, OCH₃11); 3.23 (d, 1H, J = 13.6 Hz, H11´/1); 2.77 (dd, 1H, J = 2.2 Hz, 16.4 Hz, H13´/2); 1.74 (s, 3H, H-acetonide); 1.55 (d, 3H, J = 6.3 Hz, CH₃); 1.40 (s, 3H, H-acetonide).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-10); 63.46 (CH₃, OCH₃-9); 61.57 (CH₃, OCH₃-1); 56.07 (CH₃, OCH₃-4); 49.71 (CH₂, C-3’); 33.69 (CH₂, C-1’); 28.67 (CH₃, C-acetonide); 26.44 (CH₃, C-acetonide); 14.24 (CH₃).

HRMS (ESI) : calcd. For C₂₇H₃₂O₇ 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

¹H NMR (500 MHz, CDCl₃) : 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, OCH₃-4); 3.99 (s, 3H, OCH₃-10); 3.94 (s, 3H, OCH₃-9); 3.76 (s, 3H, OCH₃-1); 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, CH₃); 1.18 (s, 3H, H-acetonide).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-9 and OCH₃-10); 61.83 (CH₃, OCH₃-1); 56.42 (CH₃, OCH₃-4); 47.66 (CH₂, C-3’); 36.68 (CH₂, C-1’); 28.29 (CH₃, C-acetonide); 26.58 (CH₃, C-acetonide); 13.84 (CH₃).

HRMS (ESI) : calcd. For C₂₇H₃₂O₇ 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 (2.08 g, 4.44 mmol) was dissolved in CH₃CN (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 9.62 (dd, 1H, J = 1.6 Hz, 2.5 Hz, H-14´); 8.16 (m, 2H, H-5 and H-8); 7.71 (m, 2H, H-6 and H-7); 7.45 (s, 1H, H-13); 4.25 (q, 1H, J = 6.3 Hz, H-15´); 4.00 (s, 3H, OCH₃₁₄); 3.81 (s, 3H, OCH₃₁₁); 3.18 (d, 1H, J = 12.9 Hz, H₁₁´/₁); 2.66 (d, 1H, J = 12.9 Hz, H₁₁´/₂); 2.65 (dd, 1H, J = 2.5 Hz and 16.4 Hz, H₁₁´/₁); 2.48 (dd, 1H, J = 1.6 Hz, 16.4 Hz, H₃´/₂); 1.64 (s, 3H, H-acetonide); 1.50 (d, 3H, J = 6.3 Hz, CH₃); 1.34 (s, 3H, H-acetonide).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃₁₁); 56.47 (CH₃,
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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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.
To a solution of DMSO (0.03 mL, 0.425 mmol) in DCM (4 mL) cooled to –70 °C under argon was added dropwise oxalyl chloride (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. Et₃N (0.13 mL, 0.965 mmol) was then added at that temperature and stirring was continue for 1 hr 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. NH₄Cl (15 mL), sat. NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried (Na₂SO₄), 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

1H NMR (500 MHz, CDCl₃) : δ = 9.62 (dd, 1H, J = 1.6 Hz, 2.5 Hz, H-14´); 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-15´); 4.00 (s, 3H, OCH₃₁₄); 3.81 (s, 3H, OCH₃₁₁); 3.18 (d, 1H, J = 12.9 Hz, H-11´/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, CH₃); 1.34 (s, 3H, H-acetonide).

13C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃₁-1); 56.47 (CH₃,
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

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$_2$SO$_4$), 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$_3$) : \( \delta = 13.66 \) (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$_3$) : \( \delta = 187.46 \) (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 (CH₂, C-3’); 36.16 (CH₂, C-1’); 14.96 (CH₃).

HRMS (ESI) : calcd. For C₂₀H₁₈O₇Na 393.0950; found 393.0948.

1,4-dimethoxy-2-[(2-methyl-3-furyl)methyl]anthracene-9,10-dione 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. NH₄Cl (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. NaHCO₃ (20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give 11 mg of 200 (0.030 mmol, 78%) as an yellow foam.

1H NMR (500 MHz, CDCl₃) : δ = 8.17 (m, 2H, H15 and H18); 7.71 (m, 2H, H16 and H17); 7.26 (d, 1H, J = 1.6 Hz, H14’); 7.10 (s, 1H, H13); 6.15 (d, 1H, J = 1.6 Hz, H13’); 3.92 (s, 3H, OCH₃14); 3.87 (s, 3H, OCH₃11); 3.85 (s, 2H, H11’); 2.29 (s, 3H, CH₃).

13C NMR (500 MHz, CDCl₃) : 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);
To a solution of 199a (60 mg, 0.137 mmol) in CH₃CN (5 mL) was added CeCl₃.7H₂O (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 (Na₂SO₄), 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-furylmethyl]anthracene-9,10-dione 201

\[
\begin{align*}
\text{199a} & \quad \rightarrow \quad \text{201}
\end{align*}
\]

\(\text{1H NMR (500 MHz, CDCl}_3\text{) : } \delta = 13.43 \text{ (s, 1H, OH-1)}; 12.93 \text{ (s, 1H, OH-4)}; 8.32 \text{ (m, 2H, H-5 and H-8)}; 7.81 \text{ (m, 2H, H-6 and H-7)}; 7.28 \text{ (d, 1H, } J = 1.6 \text{ Hz, H-Fu5)}; 7.04 \text{ (s, 1H, H-3)}; 6.23 \text{ (d, 1H, } J = 1.6 \text{ Hz, H-Fu4)}; 3.79 \text{ (s, 2H, H-CH2)}; 2.29 \text{ (s, 3H, CH}_3\text{).}
\]

\(\text{13C NMR (500 MHz, CDCl}_3\text{) : } \delta = 187.13 \text{ (Cq, C-9)}; 186.31 \text{ (Cq, C-10)}; 157.80 \text{ (Cq, C-4)}; 156.71 \text{ (Cq, C-1)}; 148.89 \text{ (Cq, C-Fu2)}; 143.26 \text{ (Cq, C-2)}; 140.44 \text{ (CH, C-Fu5)}; 134.40 \text{ (CH, C-6)}; 134.26 \text{ (CH, C-7)}; 133.59 \text{ (Cq, C-8a)}; 133.43 \text{ (Cq, C-10a)}; 127.89 \text{ (CH, C-3)}; 126.98 \text{ (CH, C-5)}; 126.89 \text{ (CH, C-8)}; 114.63 \text{ (Cq, C-Fu3)}; 112.06 \text{ (Cq, C-9a)}; 112.00 \text{ (CH, C-Fu4)}; 111.30 \text{ (Cq, C-4a)}; 25.26 \text{ (CH}_2\text{)}; 11.54 \text{ (CH}_3\text{).}
\]
2-[[4S]-4-[2-[tert-butyl(dimethyl)silyloxyethyl]-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\textsubscript{3}CN (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\textsubscript{2}SO\textsubscript{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 yellow 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\textsubscript{31}H\textsubscript{42}O\textsubscript{7}SiNa 577.2598; found 577.2585.

1H NMR (500 MHz, CDCl\textsubscript{3}) : 8 = 8.17 (m, 2H, H-15 and H-18); 7.72 (m, 2H, H-16 and H-17); 7.60 (s, 1H, H-13); 4.36 (q, 1H, J = 6.3 Hz, H-15´); 3.99 (s, 3H, OCH\textsubscript{3}14); 3.86 (s, 3H, OCH\textsubscript{3}14); 3.78 (s, 3H, OCH\textsubscript{3}14).
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-acetoni); 1.45
(s, 3H, H-acetoni); 1.41 (d, 3H, J = 6.3 Hz, CH$_3$).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 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-acetoni); 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-acetoni); 26.57 (CH$_3$, C-
acetoni); 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

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 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-acetoni); 1.22 (d,
3H, J = 6.3 Hz, CH$_3$); 0.88 (s, 3H, H-acetoni);

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 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-acetoni); 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-acetoni); 26.70 (CH$_3$, C-
acetoni); 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 (0.30 g, 0.638 mmol) was dissolved in CH3CN (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 (30 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na2SO4), 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 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

1H NMR (500 MHz, CDCl3) : δ = 8.17 (m, 2H, H15 and H18); 7.72 (m, 2H, H16 and H17); 7.60 (s, 1H, H13); 4.36 (q, 1H, J = 6.3 Hz, H15´); 3.99 (s, 3H, OCH314); 3.86 (s, 3H, OCH311); 3.74 (m, 1H, H14´/1); 3.57 (m, 1H, H14´/2); 3.13 (d, 1H, J = 13.6 Hz, H11´/1); 2.70 (d, 1H, J = 13.6 Hz, H11´/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, CH3).

13C NMR (500 MHz, CDCl3) : 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 (CH3, OCH3-1); 58.67 (CH2, C-4´); 56.51 (CH3, OCH3-4); 36.09 (CH2, C-3´); 32.72 (CH2, C-1´); 28.69 (CH3, C-acetonid); 26.57 (CH3, C-acetonid); 13.86 (CH3).
From 202a

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. NaHCO₃ (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 (Na₂SO₄), 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

1H NMR (500 MHz, CDCl₃) : δ = 8.17 (m, 2H, H15 and H18); 7.72 (m, 2H, H16 and H17); 7.60 (s, 1H, H13); 4.36 (q, 1H, J = 6.3 Hz, H15´); 3.99 (s, 3H, OCH₃14); 3.86 (s, 3H, OCH₃11); 3.74 (m, 1H, H14´/1); 3.57 (m, 1H, H14´/2); 3.13 (d, 1H, J = 13.6 Hz, H11´/1); 2.70 (d, 1H, J = 13.6 Hz, H11´/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, CH₃).

13C NMR (500 MHz, CDCl₃) : 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 (CH₃, OCH₃-1); 58.67 (CH₂, C-4´); 56.51 (CH₃, OCH₃-4); 36.09 (CH₂, C-3´); 32.72 (CH₂, C-1´); 28.69 (CH₃, C-acetonid); 26.57 (CH₃, C-acetonid); 13.86 (CH₃).
A solution of NaOH (38 mg, 0.945 mmol) and Na$_2$S$_2$O$_4$ (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$_2$SO$_4$), 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) : $\delta$ = 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) : $\delta =$ 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$_3$) : $\delta =$ 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$_3$) : $\delta =$ 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$_3$) : $\delta =$ 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, $J = 6.3$ 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

\[ 211 \]

A solution of NaOH (0.43 g, 10.665 mmol) and Na\(_2\)S\(_2\)O\(_4\) (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 min 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\(_2\)SO\(_4\)), 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) : \(\delta = 13.36\) (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) : \(\delta = 186.05\) (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

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. NaHCO₃ (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 13.48 (s, 1H, OH₁₁); 13.47 (s, 1H, OH₁₆); 8.35 (m, 2H, H₁₁ and H₁₄); 7.83 (m, 2H, H₁₂ and H₁₃); 3.16 (m, 1H, H₁₇/₁); 3.07 (d, 1H, J = 18 Hz, H₁₀/₁); 2.95 (m, 2H, H₁₀/₂ and H₁₇/₂); 2.39 (s, 3H, CH₃); 2.00 (m, 2H, H-8).

¹³C NMR (500 MHz, CDCl₃) : 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 (CH₂, C-10); 29.03 (CH₂, C-8); 23.85 (CH₃); 19.76 (CH₂, C-7).

HRMS (ESI) : calcd. For C₂₀H₁₆O₆ 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 CCl₄ (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% K₂CO₃ (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 (Na₂SO₄), 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

¹H NMR (500 MHz, CDCl₃) : δ = 13.53 (s, 1H, OH16); 13.25 (s, 1H, OH111); 8.31 (m, 2H, H11 and H14); 7.84 (m, 2H, H12 and H13); 5.29 (brs, 1H, H17); 4.58 (s, 1H, OH19); 3.86 (d, 1H, J = 5.0 Hz, OH17); 3.17 (dd, 1H, J = 2.2 Hz, 18.6 Hz, H110/1); 2.94 (d, 1H, J = 18.6 Hz, H110/2); 2.44 (s, 3H, CH₃); 2.35 (m, 1H, 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, CH₃); 2.35 (m, 1H, H-8/1); 2.17 (dd, 1H, J = 5.1 Hz, 14.5 Hz, H-8/2).

¹³C NMR (500 MHz, CDCl₃) : 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); 145.71 (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 (CH₂, C-8); 33.22 (CH₂, C-10); 24.46 (CH₃).
HRMS (ESI) : calcd. For C$_{20}$H$_{16}$O$_7$Na 391.0784; found 391.0786.

(7R,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione 215

$^1$H NMR (500 MHz, CDCl$_3$) : $\delta = 13.93$ (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 = 6.1 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$_3$) : $\delta = 209.60$ (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$_3$).
(7R,9S)-9-acetyl-6,7,9,11-tetrahydroxy-8,10-dihydro-7H-tetracene-5,12-dione (from 215)

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 and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was dissolved in acetone (1 mL) and sat. NaHCO₃ (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 (Na₂SO₄), 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, CDCl₃) : 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, CH₃); 2.35 (m, 1H, H-8/1); 2.17 (dd, 1H, J = 5.1 Hz, 14.5 Hz, H-8/2).

^1^H NMR (500 MHz, CDCl₃) : 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 (CH₂, C-8); 33.22 (CH₂, C-10); 24.46 (CH₃).

Mp 183-185°C
To a suspension of 210a+b 72 mg, 0.194 mmol) in acetone (14 mL) was added at RT a solution of CrO3 (117 mg, 1.166 mmol) in conc. H2SO4 (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. NaHCO3. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na2SO4), 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

1H NMR (200 MHz, CDCl3) : δ = 14.09 (s, 1H, OH11); 13.16 (s, 1H, OH16); 8.36 (m, 2H, H11 and H14); 7.87 (m, 2H, H12 and H13); 3.40 (d, 1H, J = 18.3 Hz, H110/1); 3.33 (d, 1H, J = 18.3 Hz, H110/2); 3.16 (d, 1H, J = 15.5 Hz, H8/1); 2.80 (d, 1H, J = 15.5 Hz, H8/2); 2.44 (s, 3H, CH3).

13C NMR (200 MHz, CDCl3) : δ = 207.61 (Cq, C113); 192.80 (Cq, C17); 187.60 (Cq, C15); 185.91 (Cq, C112); 157.62 (Cq, C111); 154.20 (Cq, C16); 141.59 (Cq, C16a); 135.27 (CH, C13); 134.63 (CH, C12); 133.73 (Cq, C14a); 132.74 (Cq, C112a); 127.40 (CH, C14); 127.34 (Cq, C10a); 127.16 (CH, C11); 115.70 (Cq, C5a); 112.92 (Cq, C11a); 78.21 (Cq, C9); 47.78 (CH2, C8); 32.99 (CH2, C10); 24.00 (CH3).

HRMS (ESI) : calcd. For C20H14O7Na 389.0637; found 389.0632.
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'S)-6',7',11'-tri hydroxy-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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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$_2$SO$_4$), 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$_3$) : $\delta$ = 13.82 (s, 1H, OH-16); 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-17); 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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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$_3$) : $\delta$ = 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

\[
\begin{align*}
\text{12} & \quad + \quad \text{OR}_1 \\
\text{221} & \quad \rightarrow \quad \text{222} \\
R_1 & = p\text{-NO}_2\text{Bz}, \quad R_2 = \text{TFA}
\end{align*}
\]

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) / EtO (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. NaHCO₃ (20 mL) / EtOAc (20 mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL) the combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), 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

\(^1\text{H NMR (500 MHz, CDCl}_3\):} \delta = 13.70 (s, 1H, OH-6); 13.49 (s, 1H, OH-12); 8.28 (m, 6H, H-1, H-4, H-pNO₂Bz); 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\(^\text{\textdagger}\)); 5.68 (d, 1H, J = 3.5 Hz, H-dau1\(^\text{\textdagger}\)); 5.46 (s, 1H, H-dau4\(^\text{\textdagger}\)); 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\(^\text{\textdagger}\)); 4.71 (m, 1H, H-dau3); 4.60 (m, 1H, H-
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$^\ddagger$); 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$^\ddagger$); 0.61 (d, 3H, J = 6.3 Hz, H-dau6).

$^{13}$C NMR (500 MHz, CDCl$_3$) : $\delta$ = 208.95 (Cq, C-13); 186.83 (Cq, C-5); 186.74 (Cq, C-12); 165.82 (Cq, C-COPNO$_2$Bz); 165.33 (Cq, C-COPNO$_2$Bz$^\ddagger$); 157.24 (Cq, C-6); 157.15 (Cq, C-COTFA); 156.86 (Cq, C-COTFA$^\ddagger$); 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$^\ddagger$); 133.95 (Cq, C-10a); 133.52 (Cq, C-4a); 133.30 (Cq, C-12a); 131.15 (CH, CH-pNO$_2$Bz); 127.18 (CH, C-1); 127.00 (CH, C-4); 123.85 (CH, CH-pNO$_2$Bz); 111.27 (Cq, C-11a); 110.51 (Cq, C-5a); 101.61 (CH, C-dau1$^\ddagger$); 94.39 (CH, C-dau1); 81.65 (Cq, C-9); 73.35 (CH, C-dau4$^\ddagger$); 73.24 (CH, C-dau4); 71.08 (CH, C-7); 67.22 (CH, C-dau5); 66.72 (CH, C-dau5$^\ddagger$); 47.45 (CH, C-dau3$^\ddagger$); 36.70 (CH$_2$, C-8); 30.70 (CH$_2$, C-dau2); 30.53 (CH$_2$, C-dau2$^\ddagger$); 27.08 (CH$_2$, C-10); 24.54 (CH$_3$); 17.10 (CH$_3$, -dau6$^\ddagger$); (CH$_3$, -dau6).

$^{1}$H NMR (500 MHz, CDCl$_3$) : $\delta$ = 13.67 (s, 1H, OH-6); 13.33 (s, 1H, OH-12); 8.28 (m, 6H, H-1, H-4, H-pNO$_2$Bz); 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$_3$) : $\delta$ = 211.66 (Cq, C-13); 186.90 (Cq, C-5); 186.74 (Cq, C-12); 164.56 (Cq, C-COPNO$_2$Bz); 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$_2$Bz); 130.99 (CH, CH-pNO$_2$Bz); 127.07 (CH, C-4); 127.00 (CH, C-1); 123.85 (CH, CH-pNO$_2$Bz); 123.73 (CH, CH-pNO$_2$Bz); 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 (CH₂, C-8); 33.63 (CH₂, C-10); 30.03 (CH₂, C-dau2); 24.83 (CH₃); 16.99 (CH₃, -dau6).

Mp 172-174°C

Idarubicin hydrochloride 6-HCl

\[
\begin{array}{c}
\text{O} & \text{O} & \text{O} \\
\text{OH} & \text{OH} & \text{OH} \\
\text{O} & \text{O} & \text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} & \text{O} & \text{O} \\
\text{OH} & \text{OH} & \text{OH} \\
\text{O} & \text{O} & \text{O}
\end{array}
\]

\[223 \quad R_1 = \text{pNO}_2\text{Bz}, R_2 = \text{TFA}\]

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 argon atmosphere. The reaction mixture was stirred for 20 min 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 (Na₂SO₄), 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 and 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 H₂O (2 x 10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was dissolved in a small amount of CHCl₃ 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) : $\delta = 13.557$ (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
## APPENDIX

### 8.1 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>Aq.</td>
<td>aqueous</td>
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<tr>
<td>AlCl₃</td>
<td>aluminium chloride</td>
</tr>
<tr>
<td>AIBN</td>
<td>azo-bis-(isobutyronitril)</td>
</tr>
<tr>
<td>Bz₂O₂</td>
<td>bezoyl peroxide</td>
</tr>
<tr>
<td>BH₃·THF</td>
<td>boran THF complex</td>
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<td>BF₃·Et₂O</td>
<td>boron trifluoride diethyl etherate</td>
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<tr>
<td>BCl₃</td>
<td>boron trichloride</td>
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<tr>
<td>Br₂</td>
<td>bromine</td>
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<td>CAN</td>
<td>cerium ammonium nitrate</td>
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<td>CDI</td>
<td>N,N-carboymidazole</td>
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<td>CCl₄</td>
<td>carbon tetrachloride</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>CeCl₃·7H₂O</td>
<td>cerium chloride heptahydrate</td>
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<tr>
<td>CHCl₃</td>
<td>chloroform</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<td>EtOAc</td>
<td>ethyl acetate</td>
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<tr>
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<tr>
<td>Et₂O</td>
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<tr>
<td>H₂SO₄</td>
<td>sulfuric acid</td>
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<td>Hr</td>
<td>hour</td>
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<tr>
<td>HCl</td>
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<td>water</td>
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<tr>
<td>HBr</td>
<td>hydrogen bromide</td>
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</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<tr>
<td>KHMDS</td>
<td>potassium bis (trimethylsilyl)amide</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
<td>LiHMDS</td>
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<td>MgCl₂</td>
<td>magnesium chloride</td>
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<td>NaHCO₃</td>
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</tr>
<tr>
<td>Na₂S₂O₄</td>
<td>sodium dithionite</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>sodium borohydride</td>
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<tr>
<td>NaCl</td>
<td>sodium chloride</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimid</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NaI</td>
<td>sodium iodide</td>
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<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
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<tr>
<td>Na₂SO₄</td>
<td>sodium sulfate</td>
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<tr>
<td>PhB(OH)₂</td>
<td>phenylboronic acid</td>
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<td>phosphoryl chloride</td>
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<tr>
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<td>polyphosphoric acid</td>
</tr>
<tr>
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<td>pyridine</td>
</tr>
<tr>
<td>Py.HCl</td>
<td>pyridine hydrochloride</td>
</tr>
<tr>
<td>PE</td>
<td>petrol ether</td>
</tr>
<tr>
<td>SOCl₂</td>
<td>thionyl chloride</td>
</tr>
<tr>
<td>SnCl₄</td>
<td>tin (IV) chloride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
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<td>Abbreviation</td>
<td>Full Name</td>
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<tr>
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<td>-----------</td>
</tr>
<tr>
<td>TBABr</td>
<td>tetra-n-butylammonium bromide</td>
</tr>
<tr>
<td>Tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TBDMSCI</td>
<td>ter-butyl dimethylsilylchloride</td>
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<tr>
<td>TiCl₄</td>
<td>titan (IV)- chloride</td>
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<td>TMSI</td>
<td>trimethylsilyl iodide</td>
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<td>TMSCl</td>
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<tr>
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<td>toluene</td>
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<tr>
<td>TMSOTf</td>
<td>trimethylsilyl triflate</td>
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8.2 References

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8.3 Curriculum Vitae

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AUSBILDUNG


Juni 2001  Matura (Spezialisierung Naturwissenschaften) am Lycée Edmond Rostand in St Ouen l’Aumone.

BERUFSERFAHRUNG

Mai. 2010  Universitätassistent am Dep. für Med./Pharm. Chemie (Wien, Österreich)

Nov. 2009  Produkem Molekulares Design GmbH (Wien, Österreich)

Sept. 2007  PHARMACON GmbH (Wien, Österreich)
Feb. 2007- Juli 2007  AB SCIENCE (Lyon, Frankreich)

Juli 2005- Juni 2006  PRIATON GmbH (München, Deutschland)

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.
- Selbstandige 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


Führerschein B

SOZIALE KOMPETENZEN


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.