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TETRAHEDRON

Synthesis of (±)-7-(3,4,5-Trimethoxyphenyl)-7-deoxyidarubicinone. A New Family of Anthracycline Analogues

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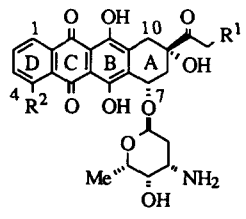
Abstract - The synthesis of the first representative compound of 7-aryl anthracycline analogues, is described. 1-Alkyl-3-trialkylsiloxydienes, prepared from readily available materials, are transformed through a Diels-Alder cycloaddition into a tetracyclic ketone, that is converted into (±)-7-(3,4,5-trimethoxyphenyl)-7-deoxyidarubicinone. The conformations of the target compound and intermediate products are studied.

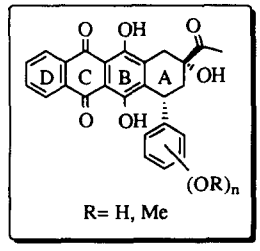
INTRODUCTION

The anthracyclines, a well known family of anticancer agents,[1] are natural or synthetic compounds originally isolated from *Streptomyces* cultures.[2] Among them, Doxorubicin and Daunorubicin,[3] semisynthetic Epirubicin[4] and synthetic Idarubicin[5] are employed in clinic for the chemotherapeutic treatment of different classes of cancer. DNA intercalation and inhibition of topoisomerases have been pointed out as the most important ways by which the anthracyclines act as antineoplastic agents.

Due to this activity, many synthetic approaches have been used for the total synthesis of these compounds,[6] among them the Friedel-Crafts acylation with phtalic anhydride,[7] used in Idarubicin synthesis, or several variations of the Diels-Alder reaction[8] that can be employed in the construction of the tetracyclic anthracycline system. So far, most of this synthetic effort has been directed at the preparation of analogues maintaining the carbocyclic system, by changing the substituents on the sugar moiety, the substitution on the A-ring or on the aromatic B-C-D system.[9]



Daunorubicin: R^1=H, R^2=OMe
Doxorubicin: R^1=OH, R^2=OMe
Idarubicin: R^1=R^2=H



R= H, Me

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In contrast, few studies have addressed the effect of replacing the sugar moiety by other substructures, that could be accommodated in the minor groove of DNA, producing new molecules that might intercalate in the same way as anthracyclines do.[10] The effort to prepare such a class of compounds is mainly guided by the need of obtaining less cardiotoxic[11] anthracycline analogues, which maintain the cytotoxic effect but display higher selectivity against the neoplastic cells.

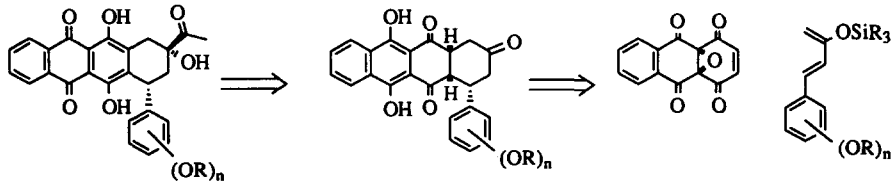
The presence of the polyhydroxy/polyalkoxyphenyl moiety in a wide variety of antineoplastic compounds of natural or synthetic origin, suggested us to start out a new research line aimed at the introduction of these structural residues in different classes of compounds. Natural products such as lignans of the aryltetraline type[12] and lycorane alkaloids,[13] synthetic antifolates trimetrexate[14] and trimethoprym[15] and antimitotic 1069C[16] are examples of known substances carrying these structural moieties. Our synthetic strategy is based on the Diels-Alder reaction of 1-polyhydroxy/polyalkoxyphenyl-3-trialkylsiloxy-1,3-butadienes with selected dienophyles.

Taking all these facts into account, use of the aforecited dienes with tricyclic dienophyles of the anthraquinone type can lead to anthracycline analogues carrying a polysubstituted phenyl moiety replacing the sugar moiety of the anthracyclines. This approach is of synthetic and pharmaceutical interest, due to the great variety of compounds that can be obtained and the modulation of the activity that these structural changes would produce on the activity of anthracyclines. The combination of the planar B,C,D system, the anchoring substituents on the A ring and the trimethoxyphenyl unit offers the possibility of preparing derivatives that could act as intercalating agents and topoisomerase inhibitors, which is the mode of action observed for other drugs such as the lignan derivative etoposide. Some preliminary results in this field have been published, reporting the synthesis through a Diels-Alder methodology and the pharmacological evaluation of rebeccamycin[17] and anthracycline[18] analogues carrying the polysubstituted phenyl group.

In this paper we present the detailed synthesis of the first 7-aryl analogue of anthracyclines, that has been prepared by a straightforward methodology in a good overall yield from available and simple starting materials. This is an example of the synthetic utility of aryldienes for the preparation of different families of compounds.

RESULTS AND DISCUSSION

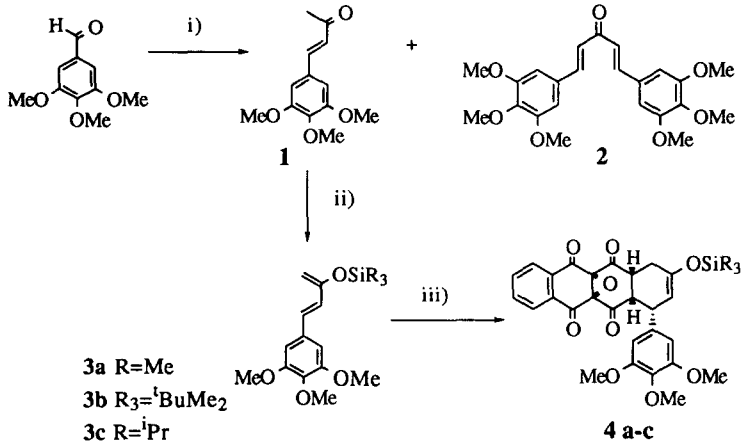
Our synthetic strategy is similar to that used in the synthesis of (+)-4-demethoxydaunomycinone (idarubicinone)[19] in which the key step is an asymmetric Diels-Alder reaction between 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone and a butadiene with a glycosidic chiral auxiliary.



The required aryldienes are readily obtained from commercially available aromatic aldehydes. Condensation between acetone and 3,4,5-trimethoxybenzaldehyde in basic media produced the expected unsaturated ketone **1** and the product of double condensation **2** (Scheme 1).

After optimization of the reaction conditions, the use of acetone/aldehyde/NaOH (molar ratio of 5:1:3) in EtOH/H_2O as solvent, gave **1** in 72% yield. Only minor amounts of **2** were produced (16%) and directly removed by insolubilization from the reaction mixtures. 1-Aryl-3-trialkylsiloxy-1,3-butadienes of increasing stability **3a-c** were obtained by treatment of ketone **1** with silylating reagents. The stability of dienes **3** is an important fact to take into account, as they must be stable during the Diels-Alder reaction and produce silyl enol ethers easy to hydrolyze in subsequent steps of the synthesis.

The Diels-Alder reaction between dienes **3a-c** and 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone[20] yielded the tetracyclic compounds **4** in all cases. Trimethylsiloxy diene **3a** and the reaction product **4a** have lower stability and they are hydrolyzed during the reaction, thus producing mixtures and a decrease of the yield. As the change of solvent, temperature or the use of Lewis acid catalyst did not produce any improvement of the reaction, dienes **3b** and **3c** were used as starting materials in the synthesis. In both cases medium yields of pure crystallized products **4b** and **4c** were obtained. These are stable and useful products for new reactions, isolated as simple non hydrolyzed compounds.



Scheme 1. i) acetone, NaOH 10%, EtOH/H_2O, 45 min., r.t., 78%; ii) Et_3N, R_3SiOTf, 1h., r.t., 95% (**3a**), 97% (**3b**), 99% (**3c**), iii) 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone; acetone, 43% (**4b**), benzene/CH_2Cl_2, 32% (**4c**).

The Diels-Alder reaction of these dienes is stereospecific, producing single stereoisomers as a consequence of the facial selectivity towards the non oxiranic face of the dienophile -*anti* attack- and the *endo* preferred transition state for the cycloaddition (Figure 1). Both circumstances are necessary for a full stereoselection, that has also been observed in the reaction of Danishefsky and related dienes with the same dienophile.[21] Molecular modelling of the transition state to compound **4b** also agree with these results, a higher stability being observed for the *anti-endo* approach between both reagents.

This stereochemical result was supported by several experimental facts such as: the shielding of the C4'-OMe, the cyclization produced during the hydrolysis (see below) and the stereochemistry deduced for products obtained in further steps of the synthesis.

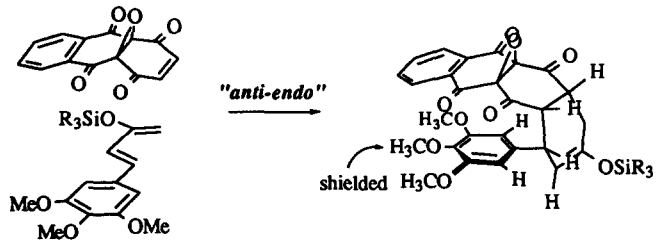
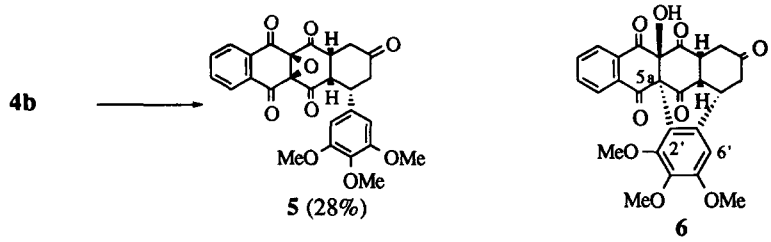


Figure 1. Conformation for the *"anti-endo"* approach in the Diels-Alder reaction.

We first planned to continue the synthesis *via* hydrolysis of the siloxyderivatives, to produce the 5a,11a-oxirane-9-ketone **5** (Scheme 2), but the desired reaction products were not obtained or were isolated in low yields (28% from **4b**). In one of these attempts it was possible to isolate a more complex molecule, lacking the symmetry of the trimethoxyphenyl moiety. Its spectroscopic properties allowed us to propose structure **6** for this compound, whose formation can be explained in terms of an intramolecular alkylation of the activated phenyl group by the protonated oxirane.



Scheme 2. Hydrolysis of the cycloadducts

This fact requires a close proximity between C-5a and C-2', that is observed for the lower energy conformation of compounds **4** and **5** obtained by molecular modelling (Figure 2).[22] In this conformation, the trimethoxyphenyl moiety (ring E) lies under the planar C,D-rings system, thus explaining the observed shielding of the C4'-OMe. This preferred conformation can be the result of π-stacking of C, D and E rings, which can only be produced if the relative stereochemistry is that depicted for **4** as consequence of the *"anti-endo"* Diels-Alder reaction (Figure 1).

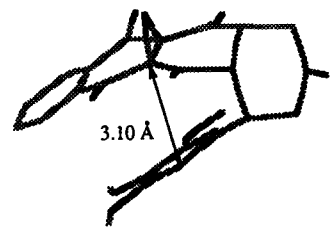
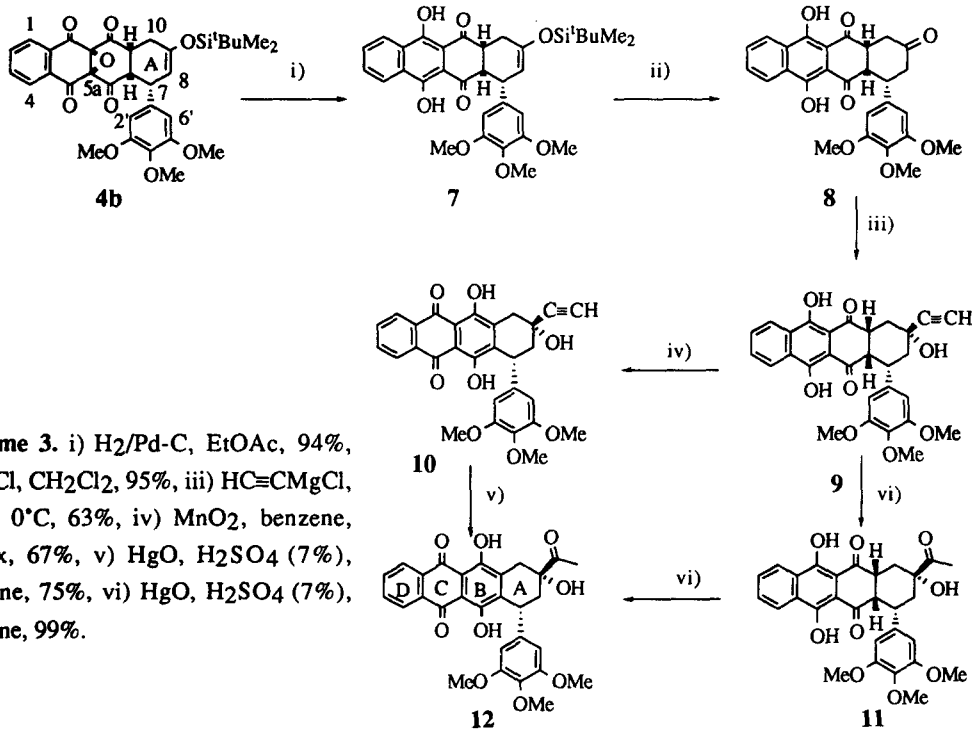


Figure 2. Molecular modelling of ketone **5**, showing distance C_{5a}-$C_{2'}$.

As attempts to reduce compound **5** were unsuccessful, it was decided to change the synthetic strategy, by inversion of the sequence, in order to overcome these problems (Scheme 3). Using compound **4b** we obtained a clean reduction to **7** by catalytic hydrogenation. Hydrolysis of the silylenolether in acidic medium produced triketone **8**, thus completing a high-yield two-step process from **4b** to **8** which by transformation of its carbonyl group at C-9 and oxidation of the B,C ring system would lead to the desired 7-aryl-7-deoxyanthracyclinones.

The addition of a two carbon fragment to the carbonyl group at C-9 is required for the introduction of the acetyl and hydroxyl groups. This is usually achieved in the synthesis of anthracyclines by reaction with ethynyl organometallic reagents followed by mercury catalyzed hydration.[19] We applied this sequence with the oxidation step either before of after the hydration reaction. Ethynylation of ketone **8** with ethynylmagnesium chloride afforded compound **9**, that was isolated from the reaction crude by insolubilization with ether and converted into the anthracyclinone **10** by manganese dioxide oxidation or in the triketoderivative **11** by hydration. In the same way, final product **12** was obtained by hydration of **10** under the same conditions.

The synthesis of target compound **12** was achieved in a good 29% overall yield from the Diels-Alder reaction product **4b**.

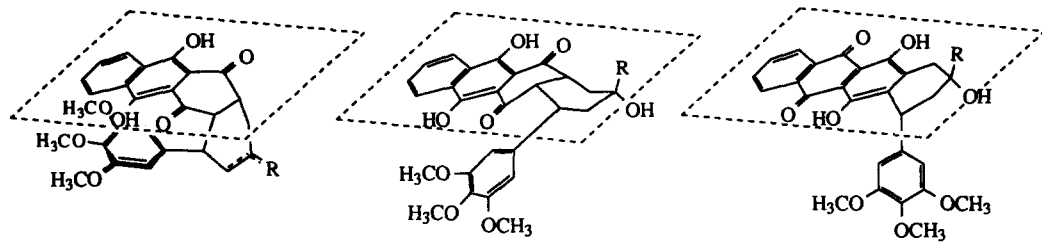


Scheme 3. i) H_2/Pd-C, EtOAc, 94%, ii) HCl, CH_2Cl_2, 95%, iii) HC≡CMgCl, THF, 0°C, 63%, iv) MnO_2, benzene, reflux, 67%, v) HgO, H_2SO_4 (7%), acetone, 75%, vi) HgO, H_2SO_4 (7%), acetone, 99%.

CONFORMATIONAL ANALYSIS

The appearance of the cyclization product **6** and the observation of the shielding on different atoms in the ^{1}H-NMR spectra of some of these compounds, prompted us to study the preferred conformation of A, B rings and the spatial disposition of the 7-aryl moiety. This is also of interest for the interpretation of the cytotoxicity studies related to their potential antitumoral activity.[18] Molecular modelling of Diels-Alder cycloadducts, final product and intermediate compounds, showed different preferences for the disposition of the aryl moiety (ring E) with respect to the A, B, C, D-rings system depending on the A, B-rings junction and the C-9 hybridization.

Three types of conformations (Figure 3) are observed: 1) "folded" conformation, with the aryl moiety under and parallel to the plane defined by C, D ring system; 2) "planar" conformation, with the aryl moiety (C7-C1'-C4' axis) in the plane defined by C, D ring system; and 3) "orthogonal" conformation, with the C7-C1' bond orthogonal to the plane defined by the polycyclic system. The latter conformation is adopted by molecules lacking hydrogen atoms at C-6a and C-10a, such as **10** and **12**, the planar B-ring forcing ring A to maintain C7-aryl moiety in a pseudoaxial disposition. Molecules having hydrogen atoms at these positions, can adopt two close minimal energy conformations: "folded" and "planar" conformations.



"folded" *"planar"* *"orthogonal"*

Figure 3. Preferred conformations for compounds **4-12**, deduced from MM studies and ^{1}H-NMR data

These conformational changes, in agreement with molecular modelling results, account for the differences in the ^{1}H-NMR spectra (table 1). Compounds with an sp^3 hybridization at C-9 have non shielded H-2',6' (>6.60 ppm), while those with an sp^2 hybridization at this carbon atom have shielded H-2',6' (<6.25 ppm) and C4'-OMe (<3.35-2.85 ppm). These data agree with a "planar" conformation for C-9 sp^3 hybridized compounds **9** and **11** and a "folded" conformation for C-9 sp^2 hybridized compounds **4b**, **4c**, **5**, **7** and **8**. It is also possible to distinguish between "more folded" compounds **4b**, **4c** and **7**, with a very high shielding of the C4' methoxyl group due to a closer proximity to the C,D, rings system, and "less folded" compounds **5** and **8**, with weaker shielding due to a higher distance to the C,D-rings system. "More folded" derivatives are those having a C8-C9 double bond and "less folded" molecules are those carrying a C-9 ketone.

Table 1. ^{1}H-NMR shifts of representative protons, which define the conformational preference of the synthesized compounds.

	4b*	4c*	5*	7*	8*	9‡	10$	11‡	12$
H-2',6'	6.25	6.25	6.23	6.13	6.01	6.64	6.34	6.68	6.41
C3',5'-OMe	3.86	3.86	3.84	3.65	3.60	3.90	3.77	3.83	3.76
C4'-OMe	2.95	2.95	3.31	2.85	3.18	3.85	3.81	3.69	3.83

Shaded: shielded signals. Underlined: deshielded signals

Preferred conformations: *Folded. ‡Planar. $Orthogonal

This generalization has been observed for all of the synthesized products and allows an easy determination of the preferred conformation from the spectroscopic data. As it has been previously discussed[18] the active compounds are those with folded conformation, while those with orthogonal disposition of the phenyl moiety, closer to model anthracyclines, do not have any toxicity against tumoral cell lines, thus suggesting a different mechanism for the cytotoxicity of active compounds.

In conclusion, a methodology for the synthesis of new 7-aryl anthracycline analogues has been developed. Synthetic and conformational issues related to this methodology have been studied and will be applied in further studies on this new class of cytotoxic agents.

EXPERIMENTAL SECTION

(E)-4-(3,4,5-Trimethoxyphenyl)-3-buten-2-one **(1)**

To 3,4,5-trimethoxybenzaldehyde (2.0 g, 10.2 mmol) dissolved in aqueous ethanol (136 mL, 50% v/v), acetone (3.6 mL, 51.0 mmol) and a 10% solution of NaOH (12.0 mL, 30.0 mmol) were slowly added from a dropping funnel. After 45 min, a yellow precipitate (340 mg, 16%) was filtered from the solution corresponding to the double condensation product **2**; m.p. 128°C; IR (KBr): 1650, 1620, 1580 and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.90 (6H, s, 4'-OCH_3), 3.91 (12H, s, 3'- and 5'-OCH_3), 6.85 (4H, s, 2'- and 6'-H), 6.99 (2H, d, *J* 15.8 Hz, 2- and 4-H) and 7.67 (1H, d, *J* 15.8 Hz, 1- and 5-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.2 (3'- and 5'-OCH_3), 60.9 (4'-OCH_3), 105.9 (C-2'and C-6'), 124.8 (C-2 and C-4), 130.3 (C-1'), 140.5 (C-4'), 143.2 (C-1 and C-5), 153.5 (C-3' and -5') and 188.4 (C-3); MS(FAB) *m/z*(%): 461 (M^++2Na, 10), 437 (M^++Na, 3), 415 (M^++1, 12), 277 (10), 207 (5), 185 (100), 147 (3) and 115 (8). The filtrate was neutralized with HCl 2N and extracted with CH_2Cl_2. The organic layer was washed with a brine, dried (Na_2SO_4) and evaporated under vacuum. Crystallization from CH_2Cl_2 / hexane gave the title compound **1** as white crystals (1.9 g, 78%); m.p. 84°C; IR (KBr): 1670, 1625, 1580 and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.36 (3H, s, 1-H), 3.88 (9H, s, 3'-, 4'- and 5'-OCH_3), 6.62 (1H, d, *J* 16.2 Hz, 3-H), 6.78 (2H, s, 2'- and 6'-H) and 7.43 (1H, d, *J* 16.2 Hz, 4-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.2 (C-1), 56.0 (3'- and 5'-OCH_3), 60.7 (4'-OCH_3), 105.7 (C-2'and C-6'), 126.4 (C-3), 129.8 (C-1'), 140.5 (C-4'), 143.1 (C-4), 153.8 (C-3' and -5') and 197.7 (C-2); MS(FAB) *m/z*(%): 236 (M^+, 100), 221 (70), 205 (52), 190 (18), 147 (14), 43 (32); Anal. Calc. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.29; H, 6.95%.

(E)-3-Trimethylsiloxy-1-(3,4,5-trimethoxyphenyl)-1,3-butadiene **(3a)**

A solution of **1** (500 mg, 2.12 mmol) in CH_2Cl_2 (12 mL) was stirred at room temperature under argon. Triethylamine (0.6 mL, 4.31 mmol) and trimethylsilyltriflate (0.82 mL, 4.24 mmol) were added dropwise to the solution. The reaction mixture was allowed to react for an hour, washed with aqueous saturated $NaHCO_3$

and brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the diene **3a** (620 mg, 95%) as a yellow oil; IR (NaCl): 1605, 1595 and 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.29 (9H, s, $OSiMe_3$), 3.84 (3H, s, 4'-OCH_3), 3.88 (6H, s, 3' and 5'-OCH_3), 4.42 (1H, s, 4-H), 4.48 (1H, s, 4-H), 6.51 (1H, d, *J* 15.5 Hz, 2-H), 6.65 (2H, s, 2'- and 6'-H) and 6.73 (1H, d, *J* 15.5 Hz, 1-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -0.02 ($OSiMe_3$), 56.1 (3'- and 5'-OCH_3), 60.1 (4'-OCH_3), 96.4 (C-4), 104.3 (C-2' and C-6'), 125.9 (C-2), 129.1 (C-1), 132.4 (C-1'), 138.8 (C-4'), 153.4 (C-3' and -5') and 155.0 (C-3).

(E)-3-Tert-butyldimethylsiloxy-1-(3,4,5-trimethoxyphenyl)-1,3-butadiene **(3b)**
Compound **1** (3.0 g, 12.7 mmol) in CH_2Cl_2 (300 mL) was treated with triethylamine (8 mL, 58 mmol) and *tert*-butyldimethylsilyltriflate (5.5 mL, 25.4 mmol) as described in the previous experiment. The diene **3b** was obtained (4.0 g, 97%) as a white crystalline solid; m.p. 218°C (CH_2Cl_2/hexane); IR (KBr): 1605 and 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.15 (6H, s, $OSiMe_2$), 0.94 (9H, s, OSi^tBu), 3.77 (3H, s, 4'-OCH_3), 3.81 (6H, s, 3' and 5'-OCH_3), 4.33 (1H, s, 4-H), 4.37 (1H, s, 4-H), 6.41 (1H, d, *J* 15.5 Hz, 2-H), 6.54 (2H, s, 2'- and 6'-H) and 6.68 (1H, d, *J* 15.5 Hz, 1-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.5 ($OSiMe_2$), 18.4 ($OSiC(CH_3)_3$), 25.9 ($OSiC(CH_3)_3$), 56.2 (3'- and 5'-OCH_3), 60.8 (4'-OCH_3), 96.4 (C-4), 104.4 (C-2' and C-6'), 126.2 (C-2), 129.2 (C-1), 132.6 (C-1'), 138.6 (C-4'), 153.5 (C-3' and -5') and 155.3 (C-3); Anal. Calc. for $C_{19}H_{30}O_4Si$: C, 65.11; H, 8.63. Found: C, 64.95; H, 8.57%.

(E)-3-Triisopropylsiloxy-1-(3,4,5-trimethoxyphenyl)-1,3-butadiene **(3c)**
Compound **1** (1.5 g, 6.35 mmol) in CH_2Cl_2 (15 mL) was treated with triethylamine (4 mL, 12.6 mmol) and *tri*isopropylsilyltriflate (1.9 mL, 6.66 mmol) as described. The diene **3c** was obtained (2.5 g, 99%) as a yellow oil; IR (NaCl): 1590 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.17 (18H, d, *J* 6.0 Hz,, $CHMe_2$), 1.27 (3H, c, *J* 6.0 Hz, OSiCH), 3.88 (3H, s, 4'-OCH_3), 3.90 (6H, s, 3' and 5'-OCH_3), 4.43 (2H, s, 4-H_2), 6.51 (1H, d, *J* 15.5 Hz, 2-H), 6.65 (2H, s, 2'- and 6'-H) and 6.87 (1H, d, *J* 15.5 Hz, 1-H).

(±)(5aS,6aS,7S,10aR,11aR)-9-Tert-butyldimethylsiloxy-5a,11a-epoxy-7-(3,4,5-trimethoxyphenyl)-5a,6a,7,10,10a,11a-hexahydronaphthacene-5,6,11,12-tetraone **(4b)**
4a,9a-Epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone (1.1g, 3.99 mmol) and **3b** (1.4 g, 4.32 mmol) were dissolved in acetone (55 mL). The reaction mixture was allowed to react at room temperature in the dark for 15 h. The solvent was concentrated in vacuo and the residue left to crystallize at -10°C overnight. Filtration of the precipitate gave **4b** (1.12 g, 43%) as a white crystalline solid in a pure state; m.p. 224°C; IR (KBr): 1730, 1605, 1595 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.26 (3H, s, OSiMe), 0.32 (3H, s, OSiMe), 0.99 (9H, s, OSi^tBu), 2.23 (1H, dd, *J* 17,5 and 6,0 Hz, 10β-H), 2.91 (1H, d, *J* 17.5 Hz, 10α-H), 2.95 (3H, s, 4'-OCH_3), 3.38-3.50 (2H, m, 6a- and 10a-H), 3.86 (6H, s, 3' and 5'-OCH_3), 4.05 (1H, dd, *J* 5.6 and 4.8 Hz 7-H), 4.91 (1H, d, *J* 4.8 Hz, 8-H), 6.25 (2H, s, 2'- and 6'-H), 7.70 (2H, m, 1- and 4-H) and 7.88 (2H, m, 2- and 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.1 ($OSiMe_2$), 18.1 ($OSiC(CH_3)_3$), 25.7 ($OSiC(CH_3)_3$ and C-10), 40.0 (C-10a), 42.4 (C-7), 53.3 (C-6a), 55.7 (3'- and 5'-OCH_3), 59.6 (4'-OCH_3), 103.7 (C-8), 106.9 (C-2' and C-6'), 127.2 (C-1 and C-4), 131.0 (C-1'), 131.4 (C-4a), 132.6 (C-12a), 134.8 (C-2 and C-3), 137.7 (C-4'), 150.8 (C-9), 153.3 (C-3' and -5') and 196.2 (C-5 and C-12); MS *m/z*(%): 604 (M^+, 6), 588 (M^+-O, 13), 558 (M^+-OMe_2, 15), 397 (34), 375 (28), 287 (36), 256 (100), 173 (54), 105 (31) and 82 (79); Anal. Calc. for $C_{33}H_{36}O_9Si$: C, 65.54; H, 6.00. Found: C, 65.18; H, 6.01%.

(±)(5aS,6aS,7S,10aR,11aR)-5a,11a-Epoxy-9-triisopropylsiloxy-7-(3,4,5-trimethoxyphenyl)-5a,6a,7,10,10a,11a-hexahydronaphthacene-5,6,11,12-tetraone **(4c)**
4a,9a-Epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone (70 mg, 0.23 mmol) and **3c** (100 mg, 0.25 mmol) were dissolved in benzene (7 mL) and 10 drops of CH_2Cl_2 were added. The reaction mixture was allowed to react at room temperature in the dark for 24h. The solvent was removed in vacuo yielding **4c** (48 mg, 32%) as a white crystalline solid; m.p. 164°C; IR (CH_2Cl_2): 1730, 1600 and 1520 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.12-1.16 (21H, m, OSi^iPr_3), 2.24 (1H, ddd, *J* 18.1, 6.0 and 1.5 Hz, 10β-H), 2.95 (3H, s, 4'-OCH_3), 3.02 (1H, d, *J* 18.1 Hz, 10α-H), 3.39-3.50 (2H, m, 6a- and 10a-H), 3.86 (6H, s, 3' and 5'-OCH_3), 4.06 (1H, dd, *J* 5.5 and 5.1 Hz 7-H), 4.87 (1H, d, *J* 5.1 Hz, 8-H), 6.25 (2H, s, 2'- and 6'-H), 7.68-7.72 (2H, m, 1-

and 4-H) and 7.85-7.92 (2H, m, 2- and 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.7 (OSiCH), 18.1 ($OSiCH(CH_3)_2$), 25.6 (C-10), 39.8 (C-10a), 42.4 (C-7), 53.2 (C-6a), 55.8 (3'- and 5'-OCH_3), 59.5 (4'-OCH_3), 101.6 (C-8), 106.4 (C-2' and C-6'), 127.1 (C-1 and C-4), 130.8 (C-1'), 131.2 (C-4a), 132.9 (C-12a), 134.9 (C-2 and C-3), 136.4 (C-4'), 150.8 (C-9), 153.2 (C-3' and -5'), 183.8 and 184.4 (C-6 and C-11) and 195.5 and 196.2 (C-5 and C-12); Anal. Calc. for $C_{36}H_{42}O_9Si$: C, 66.85; H, 6.55. Found: C, 66.39; H, 6.23%.

(±)(5aS,6aR,7S,10aR,11aR)-5a-11a-Epoxy-7-(3,4,5-trimethoxyphenyl)-5a,6a,7,8,9,10,10a,11a-octahydronaphthacene-5,6,9,11,12-pentaone **(5)**

Cycloadduct **4b** (87 mg, 0.13 mmol) dissolved in CH_2Cl_2 (2.0 mL) was treated with HCl 2N (1.5 mL). After 5 h, the reaction mixture was washed with saturated $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was crystallized in CH_2Cl_2 / hexane, yielding ketone **5** (18 mg, 28%) as a brown solid; m.p. 105-110°C; IR (CH_2Cl_2): 1715, 1625 and 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.53 (1H, dd, *J* 15.5 and 6.6 Hz, 10α-H), 2.79 (1H, dd, *J* 16.1 and 6.6 Hz, 8α-H), 3.04 (1H, ddd, *J* 16.1, 5.1 and 1.4 Hz, 8β-H), 3.19 (1H, ddd, *J* 15.5, 4.4 and 1.4 Hz, 10β-H), 3.31 (3H, s, 4'-OCH_3), 3.66-3.90 (3H, m, 6a-, 7 and 10a-H), 3.84 (6H, s, 3'- and 5'-OCH_3), 6.23 (2H, s, 2'- and 6'-H), 7.72-7.79 (2H, m, 1- and 4-H) and 7.85-7.98 (2H, m, 2- and 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.5 (C-10), 41.3 (C-8), 44.0 (C-10a), 44.5 (C-7), 51.4 (C-6a), 56.3 (OCH_3-3' and -5'), 60.1 (OCH_3-4'), 105.7 (C-2' and C-6'), 127.3 (C-1 and C-4), 130.1 (C-4a), 130.8 (C-12a), 133.2 (C-1'), 135.1 and 135.2 (C-2 and C-3), 136.8 (C-4'), 153.4 (C-3' and -5'), 155.0 and 155.9 (C-5a and C-11a), 186.8 and 187.1 (C-6 and C-11), 193.9 and 195.1 (C-5 and C-12) and 205.9 (C-9).

(±)(5aR,6aR,7S,10aR,11aR)-11a-Hydroxy-5a,7-(3,4,5-trimethoxy-o-phenylen)-5a,6a,7,8,9,10,10a,11a-octahydronaphthacene-5,6,9,11,12-pentaone **(6)**

Cycloadduct **4b** (850 mg, 1.40 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with 1.5 mL of concentrated HCl. The solution was left at room temperature for one hour, neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography (hexane/ AcOEt) gave **6** (120 mg, 17%) as a red amorphous compound; IR (CH_2Cl_2): 3500, 1725, 1600 and 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.39 (1H, dd, *J* 15.0 and 3.8 Hz, 8α-H), 2.40 (1H, dd, *J* 18.0 and 6.7 Hz, 10β-H), 2.80 (1H, dd, *J* 15.0 and 3.9 Hz, 8β-H), 3.20 (1H, dd, *J* 18.0 and 1.0 Hz, 10β-H), 3.26-3.35 (2H, m, 7- and 10a-H), 3.52 (1H, apparent t, *J* 1.8 Hz, 6a-H), 3.75 (3H, s, 3'-OCH_3), 3.77 (3H, s, 5'-OCH_3), 3.97 (3H, s, 4'-OCH_3), 6.28 (1H, s, 2'-H), 6.94 (1H, s, OH) and 7.72-8.10 (4H, m, 1-, 2-, 3- and 4-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.2 (C-10a), 38.6 (C-10), 41.9 (C-7), 50.3 (C-6a), 51.7 (C-8), 55.9 (OCH_3-5'), 60.8 (OCH_3-4'), 62.1 (OCH_3-3'), 75.0 (C-5a), 105.3 (C-11a), 106.5 (C-2'), 107.9 (C-6'), 127.0 and 127.4 (C-1 and C-4), 132.0 (C-4a), 132.2 (C-12a), 134.6 and 134.9 (C-2 and C-3), 135.5 (C-1'), 137.5 (C-4'), 154.0 (C-5'), 155.0 (C-3'), 185.8 (C-5), 187.7 (C-12), 197.1 (C-11) and 206.6 (C-6 and C-9); Anal. Calc. for $C_{27}H_{22}O_9$: C, 66.11; H, 4.52. Found: C, 65.48; H, 4.19%.

(±)(6aS,7S,10aR)-9-Tert-butyldimethylsiloxy-5,12-dihydroxy-7-(3,4,5-trimethoxyphenyl)-6a,7,10,10a-tetrahydronaphthacene-6,11-dione **(7)**

The cycloaduct **4b** (1.0 g, 1.73 mmol) was dissolved in EtOAc (300 mL), Pd / C (5%) (200 mg) was added and the reaction was allowed to react in a H_2 atmosphere for 90 min. The Pd/C was filtered out and the solvent removed by distillation in vacuo, giving the title compound **7** (0.96 g, 95%) as a yellow solid; m.p. 130°C; IR (NaCl): 3440, 1780 and 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.27 (3H, s, OSiMe), 0.32 (3H, s, OSiMe), 1.01 (9H, s, OSi^tBu), 2.35 (1H, dd, *J* 17.4 and 7.6 Hz, 10β-H), 2.82 (1H, d, *J* 17.4 Hz, 10α-H), 2.85 (3H, s, 4'-OCH_3), 3.5 (2H, m, 6a- and 10a-H), 3.65 (6H, s, 3' and 5'-OCH_3), 3.98 (1H, ta, *J* 5.6 Hz 7-H), 5.05 (1H, d, *J* 5.6 Hz, 8-H), 6.13 (2H, s, 2'- and 6'-H), 7.64 (2H, m, 1- and 4-H), 8.28 (2H, m, 2- and 3-H) and 13.17 and 13.70 (5- and 12-OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -4.1 ($OSiMe_2$), 18.1 ($OSiC(CH_3)_3$), 25.2 (C-10), 25.7 ($OSiC(CH_3)_3$), 42.7 (C-10a), 43.2 (C-7), 50.3 (C-6a), 55.6 (3'- and 5'-OCH_3), 59.5 (4'-OCH_3), 104.6 (C-8), 106.0 (C-2' and C-6'), 109.2 (C-5a and C-11a), 124.4 (C-1 and C-4), 128.4 and 129.0 (C-4a and C-12a), 130.0 and 130.3 (C-2 and C-3), 134.4 (C-1'), 136.5 (C-4'), 150.8 (C-9), 152.0 (C-3' and -5'), 153.0 (C-5), 154.7 (C-12), 201.3 (C-11) and 204.0 (C-6).

***(±)(6aS,7S,10aR)-5,12-Dihydroxy-7-(3,4,5-trimethoxyphenyl)-6a,7,8,9,10,10a-hexahydronaphthacene-6,9,11-trione* (8)**

To a solution of the silyl derivative **7** (1.11 g, 1.88 mmol) in CH_2Cl_2 (26 mL), concentrated HCl (1.8 mL) was added and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated in vacuo giving the title compound **8** (850 mg, 95%) in a slightly impure state. Crystallization from CH_2Cl_2 / hexane gave **8** as brown crystals; m.p. 205°C; IR (KBr): 3390, 1760, 1590 and 1505 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.59 (1H, dd, *J* 17.0 and 6.5 Hz, 10β-H), 2.94 (2H, d, *J* 6.2 Hz, 8-H), 3.18 (3H, s, 4'-OCH_3), 3.73 (1H, d, *J* 17.0 Hz, 10α-H), 3.65-3.97 (3H, m, 6a-, 7- and 10a-H), 3.60 (6H, s, 3'- and 5'-OCH_3), 6.01 (2H, s, 2'- and 6'-H), 8.25-8.30 (2H, m, 1- and 4-H), 8.40-8.47 (2H, m, 2- and 3-H) and 13.10 and 13.76 (5- and 12-OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.1 (C-10), 44.5 (C-10a), 45.2 (C-7), 45.2 (C-8), 51.7 (C-6a), 55.7 (3'- and 5'-OCH_3), 59.9 (4'-OCH_3), 105.3 (C-2' and C-6'), 109.2 (C-5a and C-11a), 124.4 (C-1 and C-4), 128.6 and 129.2 (C-4a and C-12a), 130.5 and 130.8 (C-2 and C-3), 133.4 (C-1'), 136.9 (C-4'), 152.2 (C-3' and -5'), 154.2 (C-5), 155.2 (C-12), 199.5 (C-11), 202.3 (C-6) and 207.5 (C-9); LRMS m/z (I, %): 476 (M^+, 100), 458 (20), 415 (10), 254 (35), 240 (40), 223 (20), 194 (58), 181 (66) and 151 (15); HRMS Calc. for $C_{27}H_{24}O_8$: 476,1471. Found: 476,1483; Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 67.74; H, 4.88%.

***(±)(6aS,7S,9S,10aR)-9-Ethynyl-5,9,12-trihydroxy-7-(3,4,5-trimethoxyphenyl)-6a,7,8,9,10,10a-hexahydronaphthacene-6,11-dione* (9)**

Ethynylmagnesium chloride (0,5 M in THF) (12.5 mL, 6.30 mmol) was added dropwise to a solution of ketone **8** (200 mg, 0.420 mmol) in freshly dried THF (30 mL) at 0°C in an Ar atmosphere. The reaction was stirred at this temperature for 30 min, poured over ice/cold aqueous amonium choride and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was precipitated by addition of Et_2O, then dried to give the ethynyl derivative **9** (132 mg; 63%) as a brown solid; m.p. 238°C; IR (KBr): 3420, 3280, 1640, 1615, 1590 and 1505 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.83 (1H, dd, *J* 13.4 and 12.7 Hz, 10α-H), 2.35 (1H, dd, *J* 12.7 and 3.4 Hz, 10β-H), 2.44 (1H, s, 9-OH), 2.49 (2H, d, *J* 8.6 Hz, 8-H), 2.67 (1H, s, C≡CH), 3.26 (1H, dt, *J* 8.6, 8.6 and 4.4 Hz, 7-H), 3.46 (1H, ddd, *J* 13.4, 4.6 and 3.4 Hz, 10a-H), 3.76 (1H, dd, *J* 4.6 and 4.4 Hz, 6a-H), 3.85 (3H, s, 4'-OCH_3), 3.90 (6H, s, 3' and 5'-OCH_3), 6.64 (2H, s, 2'- and 6'-H), 7.75-7.85 (2H, m, 1- and 4-H), 8.30-8.55 (2H, m, 2- and 3-H) and 13.16 and 13.57 (5- and 12-OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.1 (C-10), 40.7 (C-7), 41.1 (C-8), 49.5 (C-10a), 50.3 (C-6a), 56.0 (3'- and 5'-OCH_3), 60.7 (4'-OCH_3), 68.3 (C≡CH), 73.8 (C-9), 86.1 (C≡CH), 104.8 (C-2' and C-6'), 106.0 and 107.3 (C-5a and C-11a), 124.5* (C-1 and C-4), 126.9* (C-4a), 129.5* (C-12a), 130.2* (C-2), 130.6* (C-3), 134.5 (C-1'), 138.2 (C-4'), 152.6 (C-3' and -5'), 154.5 (C-5), 155.8 (C-12), 201.1 (C-11) and 202.5 (C-6); LRMS m/z(I, %): 502 (M^+, 100), 484 (40), 368 (15), 254 (30), 240 (34), 213 (22), 181 (45), 179 (25), and 44 (17); HRMS Calc. for $C_{29}H_{26}O_8$: 502,1628. Found: 502,1639.

***(±)(7R,9R)-9-Ethynyl-6,9,11-trihydroxy-7-(3,4,5-trimethoxyphenyl)-7,8,9,10-tetrahydronaphthacene-5,12-dione* (10)**

Manganese(IV) oxide (1.0 g, 11.8 mmol) was added to a solution of the ethynyl derivative **9** (60 mg, 0.119 mmol) in freshly distilled benzene (25 mL). The reaction mixture refluxed under Ar atmosphere for 13 h., filtered through celite and washed with CH_2Cl_2. The combined filtrates were evaporated and the residue crystallized from CH_2Cl_2 / Et_2O giving compound **10** (40 mg, 67%) as a red crystalline solid; m.p. 216°C; IR (KBr): 3420, 1615 and 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.22 (1H, dd, *J* 13.2 and 8.2 Hz, 8α-H), 2.60 (1H, dd, *J* 13.2 and 7.8 Hz, 8β-H), 2.45 (1H, s, C≡CH), 3.10 (1H, d, *J* 18.0 Hz, 10α-H), 3.51 (1H, d, *J* 18.0 Hz, 10β-H), 3.77 (6H, s, 3' and 5'-OCH_3), 3.81 (3H, s, 4'-OCH_3), 4.50 (1H, dd, *J* 8.2 and 7.8 Hz, 7-H), 6.34 (2H, s, 2'- and 6'-H), 7.78-7.87 (2H, m, 1- and 4-H), 8.30-8.39 (2H, m, 2- and 3-H) and 13.42 and 13.57 (5- and 12-OH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 30.0 (C-10), 38-42 (C-7 and C-8 hidden under DMSO), 55.8 (3'- and 5'-OCH_3), 59.9 (4'-OCH_3), 64.8 (C≡CH), 74.0 (C-9), 86.9 (C≡CH), 104.6 (C-2' and C-6'), 110.1 and 110.3 (C-5a and C-11a), 126.6 (C-1 and C-4), 131.9 (C-1'), 132.9 (C-4'), 132.9

and 133.0 (C-4a and C-12a), 138.7 and 141.2 (C-6a and C-10a), 134.9 (C-2 and C-3), 152.7 (C-3' and -5'), 155.1 (C-6), 156.5 (C-11) and 186.4 (C-5 and C-12).

***(±)(7R,9R)-9-Acetyl-6,9,11-trihydroxy-7-(3,4,5-trimethoxyphenyl)-7,8,9,10-tetrahydronaphthacene-5,12-dione* (12)**

A suspension of the ethynyldione **10** (15 mg, 0.03 mmol) and red mercury(II) oxide (64 mg, 0.03 mmol) in acetone (2 mL) and 7% sulphuric acid (2 mL) was heated under reflux for 4h. The mixture was then cooled, diluted with hydrochloric acid 1M and extracted with EtOAc. Once washed with water and brine, the organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica (hexane / EtOAc 7:3-3:7) giving the anthracycline **12** (11 mg, 75%) as a red solid; m.p. 177°C; IR (KBr): 3500, 1610 and 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.28 (1H, d, *J* 14.6 Hz, 8α-H), 2.31 (3H, s, $COCH_3$), 2.53 (1H, dd, *J* 14.6 and 7.3 Hz, 8β-H), 2.74 (1H, s, 9-OH), 3.17 (2H, s, 10-H), 3.76 (6H, s, 3' and 5'-OCH_3), 3.83 (3H, s, 4'-OCH_3), 4.67 (1H, da, *J* 7.3 Hz, 7-H), 6.41 (2H, s, 2'- and 6'-H), 7.82-7.87 (2H, m, 1- and 4-H), 8.33-8.41 (2H, m, 2- and 3-H) and 13.51 and 13.57 (5- and 12-OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ *inter alia*: 29.7 (C-10), 33.2 (C-8), 37.8 (C-7), 56.3 (3'- and 5'-OCH_3), 60.9 (4'-OCH_3), 77 (C-9 hidden under $CDCl_3$), 104.9 (C-2' and C-6'), 106.0 and 107.3 (C-5a and C-11a), 127.1 (C-1 and C-4), 134.5 (C-2 and C-3), 136.8 (C-4'), 153.4 (C-5) and 156.6 (C-12); MS *m/z*(%): 518 (M^+, 23), 475 (8), 307 (M^+-Ph(OMe)$_3$, 45), 105 (27) and 57 (100).

***(±)(6aS,7S,9S,10aR)-9-Acetyl-5,9,12-trihydroxy-7-(3,4,5-trimethoxyphenyl)-6a,7,8,9,10,10a-hexahydronaphthacene-6,11-dione* (11)**

A suspension of the ethynyldione **9** (30 mg, 0.06 mmol) and mercury(II) oxide (130 mg, 0.697 mmol) in acetone (5 mL) and 7% sulphuric acid (5 mL) was heated under reflux for 2h 30 min. The mixture was then cooled, diluted with hydrochloric acid 1M and extracted with EtOAc. Once washed with water and brine, the organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographied on silica (hexane / EtOAc 7:3-3:7) giving anthracycline **11** (30 mg, 99%) as a brown solid; m.p. 212°C; IR (KBr): 3580, 3520, 1710, 1615, 1590 and 1505 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.85 (1H, dd, *J* 13.7 and 11.7 Hz, 10α-H), 2.35 (3H, s, $COCH_3$), 2.37-2.58 (3H, m, 8α-, 8β- and 10β-H), 3.19 (1H, td, *J* 10.5 and 4.5 Hz, 7-H), 3.55 (1H, dt, *J* 12.7 and 4.5 Hz, 10a-H), 3.69 (3H, s, 4'-OCH_3), 3.67 (1H, t, *J* 4.5 Hz, 6a-H), 3.83 (6H, s, 3' and 5'-OCH_3), 6.68 (2H, s, 2'- and 6'-H), 7.70-7.75 (2H, m, 1- and 4-H), 8.35-8.42 (2H, m, 2- and 3-H) and 13.26 and 13.48 (5- and 12-OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.3 (C-10), 35.7 (C-8), 40.2 (C-7), 47.8 (C-10a), 50.7 (C-6a), 56.2 (3'- and 5'-OCH_3), 60.8 (4'-OCH_3), 105.7 (C-2' and C-6'), 107.8 (C-5a and C-11a), 124.8 (C-1 and C-4), 129.4 and 129.7 (C-4a and C-12a), 130.6 and 130.9 (C-2 and C-3), 137.3 (C-4'), 152.7 (C-3' and C.5'), 154.9 (C-5), 156.0 (C-12), 201.9 (C-11), 202.7 (C-6) and 211.3 ($COCH_3$); LRMS m/z(I, %): 520 (M^+, 75), 502 (15), 459 (30), 283 (37), 241 (86), 194 (25), 181 (48), 57 (20), and 44 (100); HRMS Calc. for $C_{29}H_{28}O_9$: 520,1733. Found: 520,1730.

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