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A Practical and Efficient Multigram Approach to Daunomycinone and Derivatives

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Abstract: (+/-)-Daunomycinone and (+/-)-4-demethoxydaunomycinone have been synthesized via two successive Diels-Alder reactions from naphthazarin. Key steps for the construction of the A-ring of the anthracyclinone are the Diels-Alder reaction of the BCD fragments with 1-*tert*-butoxy-3-trimethylsilyloxybuta-1,3-diene and further functionalisation of the hydrolysed product with trimethylsilylethynyl lithium. these steps allow multigram synthesis of the anthracyclinone with a very high cis-selectivity for the 7,9-hydroxy groups of the A-ring

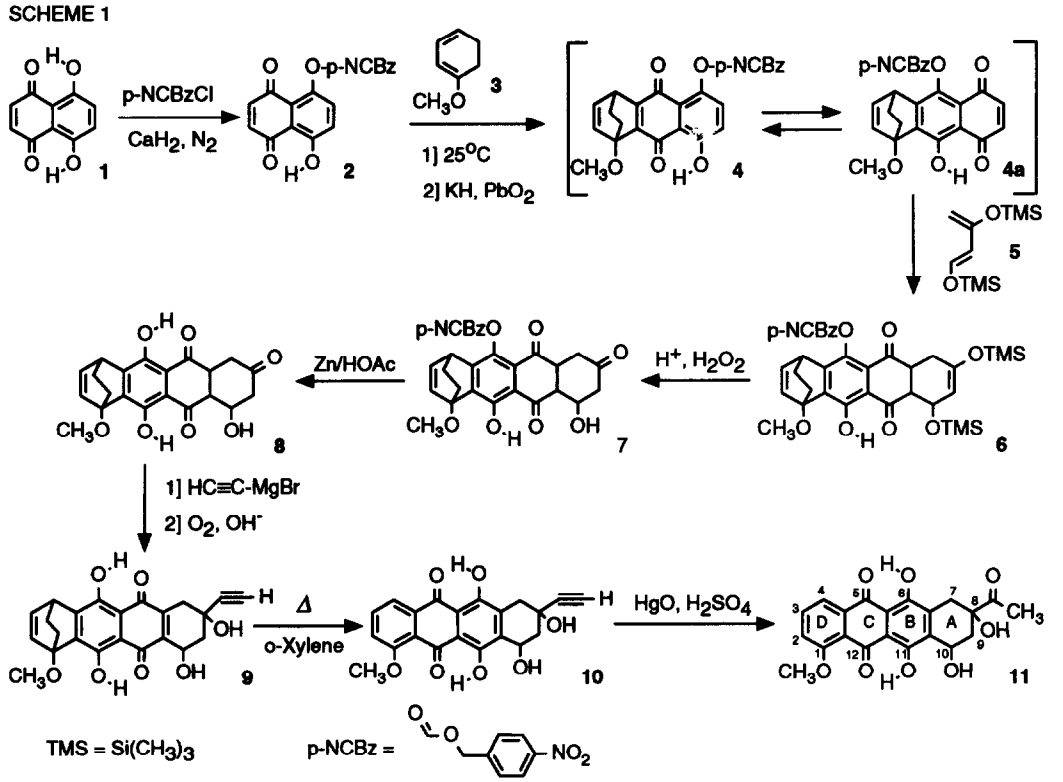
Anthracyclinones are today still the most commonly used drugs in combination anticancer chemotherapy[1,2]. Over the years the synthesis of the anthracyclinone part has been extensively investigated as part of the ongoing search to derivatives with a higher therapeutic index[3,4]. The daunomycinone derivatives can be generally and straightforwardly synthesized via two successive Diels-Alder additions to naphthazarin[4-7]. A key step in this synthesis is the construction of the A-ring via a cycloaddition with 1-oxy substituted 3-trimethylsilyloxybuta-1,3-dienes.

In this paper we present our results based on fundamental improvements of the approach which was originally used by Kelly *et al*[6] for the synthesis of (+/-)-daunomycinone (**11**, Scheme 1). An important aim was to develop a route which allowed synthesis of the aglycones on a multigram scale or more.

In a proceeding paper[7] we demonstrated the advantages of 1-*tert*-butoxy-1,3-trimethylsilyloxybuta-1,3-diene (**13**) over bis 1,3-trimethylsilyloxybuta-1,3-diene (**5**). Cycloadducts are also formed in high endo diastereoselectivity and they are more stable. Furthermore the *tert*-butoxy group can be effectively used for stereocontrol in following reactions and it can be easily transformed into a hydroxy group. We rationalized that the use of **13** in stead of **5** in Scheme 1 could lead to a higher cis stereoselectivity in the formation of compound **9**.

In following the sequence of Kelly's work we encountered two serious problems which appeared to be major drawbacks for the synthesis of daunomycinone analogs on a larger scale.

SCHEME 1



- The oxidation of the cycloadduct of **2** and **3** into **4** could not be reproduced and did not lead to acceptable yields. Cleavage of the protective group had become a major side reaction. The presence of the protective group is essential for the necessary regioselectivity in the next step (conversion of **4** into **6**). Also Kelly[8] and his group reported to have problems with the use of KH/PbO_2. The particle size of commercial KH seemed to be very important. Also when the amount of KH was reduced to 0.05 equivalents as suggested by Kelly *et al*[8], it was not possible to obtain **4** in acceptable amounts. In addition we tried a variety of oxidation methods without any success.

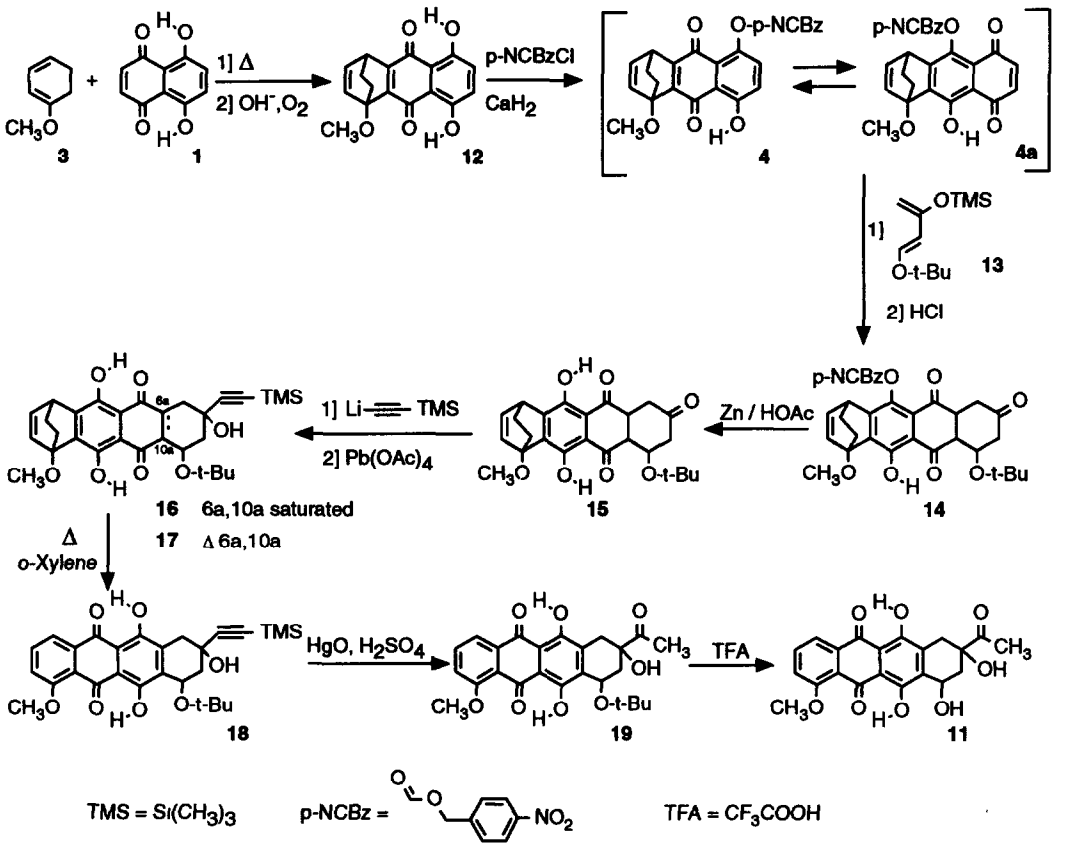
- Another problem in this synthesis of daunomycinone was the reaction with the Grignard reagent (conversion of **8** into **9**) in order to convert the ketone into α-hydroxy,ethynyl functionality. The use of 30 equivalents of ethynyl magnesiumbromide is very inefficient and in addition we encountered serious problems with the upscaling of this reaction in this and similar examples. The yields were reasonable at 100 mg scale but strongly dropped when doing the reaction at gram scale[9].

Synthesis of (+/-)-daunomycinone.

We have developed a gram scale synthesis of (+/-)-daunomycinone through the Diels-Alder approach of Kelly *et al* but circumventing the disadvantages of this method as given in Scheme 2.

First we tried more stable protecting groups for **1** having the possibility of "acylwanderung"[10]. The

SCHEME 2

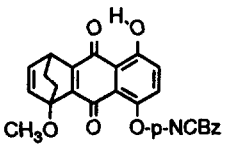


ability to be transferred intramolecular from OH to carbonyl appeared to be only successful with Kelly's *p*-nitrobenzyloxycarbonyl group. Other ester or carbamate groups could be attached to naphthazarin (**1**) but either oxidation or intramolecular shift could not be achieved.

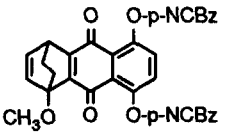
Finally we decided to protect the oxidized cycloadduct (**12**). From the protective groups we tried such as acetyl, benzoyl, benzyloxycarbonyl and mandeloyl only the *p*-nitrobenzyloxycarbonyl was successful. Three possible products can be formed. So we had to find a way to make this reaction as selective as possible. We tried several bases such as NaH, KO-*t*-Bu, Na_2CO_3 DABCO and CaH_2. In addition we made numerous attempts in variation of the equivalents of base and *p*-nitrobenzyl chloroformate. It appeared to be quite successful when 1 equivalent of the protective group and 1.6 equivalent of calcium hydride was used. Only minor amounts of the wrong mono-protected (**20**) and diprotected cycloadduct (**21**) were formed (Figure 1). Unreacted naphthazarin could be recovered after column chromatography.

Initially the reaction was very slow (6 days room temperature, conversion 30-40%) but acceleration could be accomplished by the use of an Direct Immersion Sonic Horn[11] (Cell disruptor) and a glass rosette cell

FIGURE 1



20



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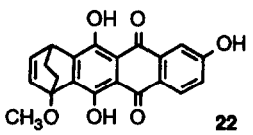
or/and the use of an ultrasonic cleaning bath. The reaction time decreased to 30 h and the conversion raised to 75-80%. The isolated yield after column chromatography was 50%. All the formed side products are easily reconverted into naphthazarin and can be used again.

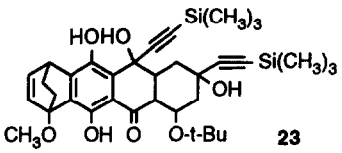
The mono protected ethanoanthracene derivative (**4/4a**) underwent Diels-Alder reaction with 1-*tert*-butoxy-3-trimethylsilyloxybuta-1,3-diene (**13**) to give the adduct **14** in a yield of 80%. Diene (**13**) can be synthesized in 50 gram amount or more, according to the method of Potman *et al*[7] or Danishefsky *et al*[12].

Introduction of the ethynyl functionality in compound **15** via the Grignard reaction trans to the *tert*-butoxy group occurs already with a higher stereoselectivity than in compound **8** trans to the hydroxy group[13]. However partial aromatization to compound **22** can not be avoided and purification of the reaction mixtures is almost impossible (as is also the case in the synthesis of Kelly)

FIGURE 2



22



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A major break through was the use of 2-trimethylsilylethynyl lithium[14]. No more than 6 equivalents were necessary and formation of **22** is strongly suppressed. Clearly the trimethylsilyl acetylide behaves more as a nucleophile and less as a base compared to the non silylated acetylides. We also found that no better results were obtained with cerium acetylides as is described for related reactions[14]. When using the 2-trimethylsilylethynyl lithium only the cis-isomer can be detected by ^{1}H-NMR spectroscopy. This is due to the quasi axial position[7] of the *tert*-butoxy and the bulkiness of the 2-trimethylsilylethynyl group. Separation of the (+/-)-daunomycinone and its (+/-)-10-epimer is now no longer necessary. The reaction was performed at 5 gram scale and the yields were comparable with the reaction at 100 mg scale, so that further upscaling should be possible.

The isolation of pure product **16** was very difficult because of the formation of some bis-adduct (probably **23**) and the spontaneous air oxidation to the product **17**. After oxidation with $Pb(OAc)_4$ and retro Diels-Alder reaction in *o*-xylene the product **18** could however be obtained pure by crystallisation in diethylether (yield 74%).

The transformation of the 2-trimetylsilylethynyl functionality to the acetyl functionality has been done by simple treatment with mercury (II) oxide in dilute sulphuric acid in tetrahydrofuran. Because of the higher

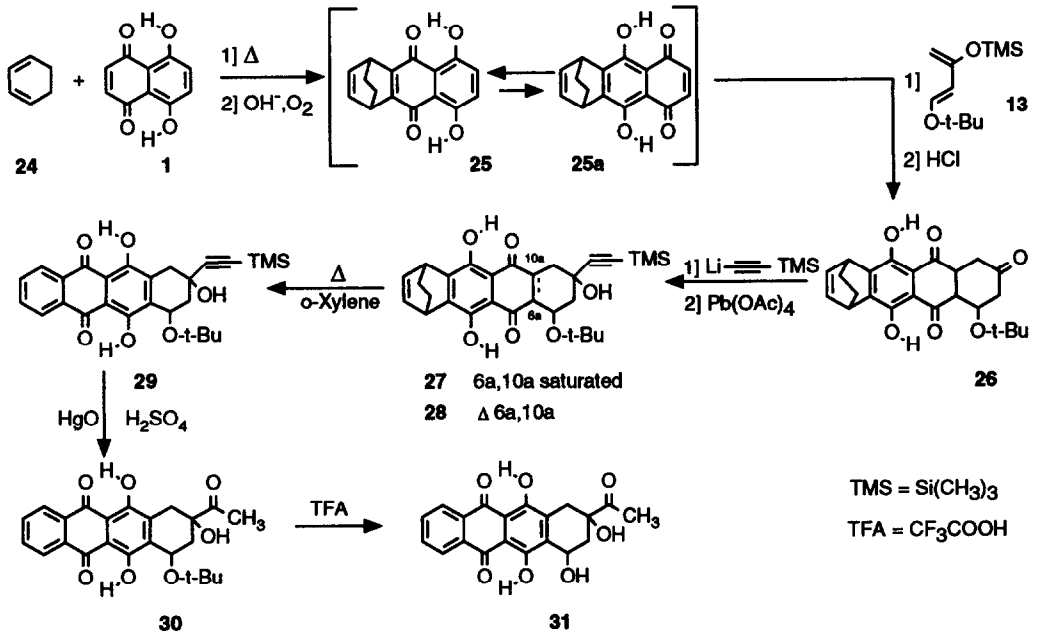
reactivity of the 2-trimethylsilylethynyl functionality and better solubility of compound **18**, compared with the unsubstituted ethynyl compound (**10**), the reaction is much faster (3 hr vs. 1 night) and gives better yields (91% vs. 75%).

Product **19** gives after treatment with trifluoroacetic acid at room temperature (+/-)-daunomycinone (**11**) in an overall yield of 21%. The obtained (+/-)-daunomycinone after recrystallisation from chloroform exhibits spectral and physical properties identical with those previously reported.

Synthesis of (+/-)-4-demethoxydaunomycinone.

The advantages of 1-*tert*-butoxy-3-trimethylsilyloxybuta-1,3-diene (**13**) and lithium trimethylsilylacetylide are generally suitable for the synthesis of anthracyclinones of the daunomycinone-type. This is further illustrated in the synthesis of 4-demethoxydaunomycinone (Scheme 3).

SCHEME 3



24 1 25 25a 29 27 6a,10a saturated 28 Δ 6a,10a 26 30 31

The Diels-Alder reaction of naphthazarin **1** with cyclohexa-1,3-diene **24** was as expected much slower than in the earlier case of 1-methoxycyclohexa-1,3-diene **3**. Compounds **24** and **1** had to be refluxed for 5 days in THF to yield 75% of **25**.

Because of the equilibrium between the isomers **25** and **25a** the second Diels-Alder reaction of **25a** with the 1-*tert*-butoxy-3-trimethylsilyloxybuta-1,3-diene (**13**) leads already to the daunomycinone skeleton in two steps in a yield of 75%.

The ABCD-fragment was functionalized with 2-trimethylsilylethynyl lithium to give product **27** with high cis-stereoselctivity. Further oxidation of the crude product with $Pb(OAc)_4$ and purification by column

chromatography yielded **28** (76% from **26**). Retro Diels-Alder reaction in refluxing *o*-xylene afforded compound **29** in 91%. This compound could be easily converted into (+/-)-4-demethoxydaunomycinone (**31**) by hydration with mercury (II) oxide in dilute sulphuric acid/tetrahydrofuran (91%) and subsequent treatment with trifluoroacetic acid (85%). The overall yield is 30%.

Both synthesis of (+/-)-daunomycinone and (+/-)-4-demethoxydaunomycinone have been accomplished on gram scale. It may be concluded that this method allows highly stereoselective synthesis of as well symmetric as asymmetric D-ring derivatives of daunomycinone. The scope depends on the availability of the cyclohexadiene derivatives necessary in the first step.

Experimental section.

General remarks: ^{1}H-NMR-spectra were measured on a Bruker WH-90 spectrometer with $(CH_3)_4Si$ as an internal standard. $CDCl_3$ was used as a solvent. Melting points were taken with a Reichert Thermpan microscope and are uncorrected. IR-spectra were obtained with a Perkin Elmer 298 infrared spectrometer. Mass spectra were taken with a double focusing VG 7070 E mass spectrometer. For column chromatography either Merck Silicagel 60 or Merck silicagel Art. 9385 (flash chromatography) were used.

1,4,9,10-Tetrahydro-5,8-dihydroxy-1-methoxy-9,10-dioxo-1,4-ethanoanthracen (12).

To a solution of 20.9 g (0.11 mol) of 5,8-dihydroxy-1,4-naphthoquinone (1) in 330 ml CH_2Cl_2 was added 28.4 g of 1-methoxycyclohexa-1,3-diene (3) (technical grade 65%, 0.177 mol). The mixture was refluxed 6 h., whereas the temperature of the oil-bad did not exceed 50°C. The solvent was evaporated and the residue stirred with 330 ml of pentane for 5 minutes. The solution was cooled to 0°C and the yellow/brown solid (30.0 g, 91%) was collected by filtration, rinsed with petroleum ether and directly used in the next reaction.

The crude product was dissolved in a solution of 22.0 g (0.55 mol) of sodiumhydroxide in 825 ml of water. Air was passed through the solution and the colour of the mixture changed from green to blue. Samples were taken and after 30 min, when TLC (EtOAc/n-hexane, 2 : 5) showed the reaction to be complete, 46.2 ml of concentrated HCl (37%) was added. The product precipitated as a red solid and it was filtered and dried *in vacuo* over P_2O_5 to give 27.0 g of 12 (83% overall from 1). A sample of the crude product 14 was purified by crystallization in EtOAc/n-hexane to give pure 12; m.p. 169-171°C (dec., Lit.[5] 170°C, lit.[15] 167-169°C). MS., m/e (EI) 298, 283, 270, 252, 240, 224; ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.39-1.92 ppm (4H, m, CH_2-CH_2), δ = 3.69 ppm (3H, s, OCH_3), δ = 4.47-4.61 ppm (1H, m, H_4), δ = 6.40 ppm (1H, dd, J=5.6 Hz and J=8 Hz), δ = 6.64 ppm (1H, dd, J=8 Hz and J=1.5 Hz), δ = 7.12 ppm (2H, s, ArH), δ = 12.60 ppm (1H, s, ArOH), δ = 13.06 ppm (1H, s, ArOH). Anal. calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.01; H, 4.77.

(4-Nitrophenyl)methyl-1,4,9,10-tetrahydro-8-hydroxy-1-methoxy-9,10-dioxo-1,4-ethanoanthracen-5-yl-carbonate (4).

To 12.0 g (0,04 mol) of 14, dissolved in 300 ml of dry THF (distilled from sodium benzophenone ketyl) were added 12.6 g (0,062 mol) of *p*-nitrobenzyl chloroformate and 1.7 g (0,04 mol) of powdered calcium hydride. The suspension was sonicated with a Direct Immersion Sonic Horn[11] (Cell disruptor) in a glass rosette cell[11] at 0°C for 6 hours. After that the mixture was poured in a 500 ml round bottom flask and sonicated for 24 h. in a ultrasonic cleaning bath. The colour of the solution changed from red to yellow and progress was monitored by TLC (EtOAc/n-hexane, 2 : 5). After the reaction had nearly completed, the reaction mixture was quenched by addition of 500 ml 5% NaH_2PO_4 aqueous solution and the mixture was extracted twice with 500 ml of chloroform. The chloroform extract was washed with brine, dried (anhydrous sodium sulfate) and evaporated *in vacuo*. The crude product was purified by flash column chromatography (silicagel, EtOAc/toluene/n-hexane, 1 : 5 : 5). After concentration *in vacuo* the solid residue was stirred overnight in 200 ml of diethylether. Filtration gave 9.6 g (50%) of pure 4. m.p. 136-137°C (Lit[6] 115-116°C); MS, m/e (CI^+) 478, 450, 405, 299, 271; ^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 1.33-1.89 ppm (4H, m, CH_2-CH_2), δ = 3.66 ppm (3H, s, OCH_3), δ = 4.30-4.47 ppm (1H, m, H_4), δ = 5.44 ppm (2H, s, CH_2), δ = 6.34 ppm (1H, dd, J=5.6 Hz and J=8 Hz, H_3), δ = 6.61 ppm (1H, dd, J=8 Hz and J=1.5 Hz, H_2), δ = 7.28 ppm (2H, s, ArH), δ = 7.54 ppm (2H, AB, J=8.5 Hz, ArH), δ = 8.26 ppm (2H, AB, J=8.5 Hz, ArH), δ = 12.72 ppm (1H, s, ArOH). Anal. calcd for $C_{25}H_{19}NO_9$: C, 62.89; H, 4.01; N, 2.93. Found: C, 62.41; H, 3.92; N, 2.95. IR (KBr): 1765

cm^{-1}.

1-tert-Butoxy-3-trimethylsilyloxybuta-1,3-diene (13).

Was prepared as described in literature[9] from 101 g of 1-*tert*-butoxy-1-buten-3-one. Yield 107.5 g (71%), b.p. 57-60°C/0.75 Torr (Lit[9] 50-53°C/0.25 Torr).

1,4,6,6a,7,8,9,10,10a,11-Decahydro-10-(1,1-dimethylethoxy)-12-hydroxy-1-methoxy-6,8,11-(7H)-trioxo-1,4-ethanonaphthacen-5-yl-(4-nitrophenyl)-methyl ester (14).

To a solution of 7.5 g (15.7 mmol) of 4 in 175 ml of dry (distilled from sodium benzophenone ketyl) THF under argon atmosphere, 6.75 g (31.5 mmol) of 1-*tert*-butoxy-3-trimethylsilyloxybuta-1,3-diene (13) was added and the reaction mixture was stirred at room temperature for 2 days. The colour of the solution changed from yellow/orange to yellow/green. The reaction was monitored with (EtOAc/n-hexane, 2 : 5). Without isolation, the cycloadduct was hydrolysed by cooling the reaction mixture to 0°C and the addition of 7.5 ml of 1N HCl. After 15 minutes 175 ml of water was added and the mixture was extracted twice with 125 ml of CH_2Cl_2. The collective organic layers were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the crude product which was stirred overnight with 300 ml of diethylether. Filtration gave 7.8 g (80%) of the product 14. m.p. 147-150°C; MS, m/e (CI) no mol mass peak found 440; ^{1}H-NMR (90 MHz, $CDCl_3$, mixture of isomers, ratio 7 : 3): δ = 0.74 ppm (9H, s, $C(CH_3)_3$), δ = 1.43-1.93 ppm (4H, m, CH_2-CH_2), δ = 2.08-2.62 ppm (3H, m, H_7(ax), H_9(ax) and H_9(eq)), δ = 3.23-3.70 ppm (3H, m, H_{6a}, H_7(eq) and H_{10a}), δ = 3.72 and 3.75 ppm (3H, 2 x s, OCH_3), δ = 4.11-4.26 ppm (1H, m, H_{10}), δ = 4.43-4.56 ppm (1H, brs, H_4), δ = 5.42 ppm (2H, brs, CH_2), δ = 6.26-6.80 ppm (2H, m, H-C=C-H), δ = 7.56-8.33 ppm (4H, 2 x AB, ArH), δ = 13.19 and 13.23 ppm (1H, 2 x s, ArOH). Anal. calcd for $C_{33}H_{33}NO_{11}$: C, 63.97; H, 5.37; N, 2.26. Found: C, 63.33; H, 5.27; N, 2.26. IR (KBr): 1770 (carbonyl carbonate), 1720 (A-ring carbonyl) and 1630 (quinone carbonyl).

1,4,6,6a,7,8,9,10,10a,11-Decahydro-5,12-dihydroxy-10-(1,1-dimethylethoxy)-1-methoxy-1,4-ethanonaphthacene-6,8,11-(7H)-trione (15).

To a stirred solution of 5.0 g (0.008 mol) of 14 in 20 ml of THF, glacial acetic acid (20 ml) and 5.2 g (0.08 mol) of zinc were added. The zinc was first activated by the procedure described by Perrin *et al*[16]. After 15 min another 5.2 g of zinc were added to the reaction mixture until TLC (EtOAc/n-hexane, 3 : 5) revealed that the reaction was complete (30 min). The mixture was diluted with 250 ml of CH_2Cl_2 and the acetic acid was neutralized (to pH 6) with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with 150 ml of CH_2Cl_2. The collective organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was stirred overnight with 500 ml of dry diethylether. After cooling the solution to 0°C, the solid 15 was filtered off (3.45 g, 97%). Analytically pure material was obtained as an off white solid, m.p. 134-136°C by recrystallization from diisopropylether; MS, m/e (EI) 440, 412, 356, 336, 320; ^{1}H-NMR (90 MHz, $CDCl_3$, mixture of isomers, ratio 7 : 3): δ = 0.71 ppm (9H, s, $C(CH_3)_3$), δ = 1.38-1.89 ppm (4H, m, CH_2-CH_2), δ = 2.22-2.64 ppm (3H, m, H_7(ax), H_9(ax) and H_9(eq)), δ = 3.33-3.75 ppm (3H, m, H_{6a}, H_7(eq) and H_{10a}), δ = 3.71 and 3.75 ppm (3H, 2 x s, OCH_3), δ = 4.34-4.62 ppm (2H, m, H_4 and H_{10}), δ = 6.44 ppm (1H, dd, J=8 Hz and J=6.5 Hz, H-C=C), δ = 6.70 ppm (1H, dd, J=8 Hz and J=1.5 Hz, H-C=C), δ = 11.87 and 11.93 ppm (1H, 2 x s, ArOH), δ = 12.94 and 13.00 ppm (1H, 2 x s, ArOH). Anal. calcd for $C_{25}H_{28}O_7$: C, 68.17; H, 6.41. Found: C, 67.91; H, 6.21. IR (KBr): 1720 (A-ring carbonyl) and 1650 and 1620 (quinone carbonyl).

Cis-(+/-)-8-(2-trimethylsilylethynyl)-7,8,9,10-tetrahydro-10-(1,1-dimethylethoxy)-1-methoxy-6,8,11-trihydroxy-1-methoxy-naphthacene-5,12-dione (18).

5.7 g (0.058 mol) of 2-trimethylsilylacetylene (96%) was dissolved in 750 ml of dry (distilled from sodium benzophenone ketyl) THF under argon atmosphere. The reaction mixture was cooled to -78°C and 37.9 ml of BuLi (1.5 M) was added dropwise over 10 min. The reaction mixture was stirred for 30 min at -78°C and 5.0 g (0.0114 mol) of 15 was added. Progress of the reaction was monitored with TLC (and the colour of the solution changed from green to yellow/green). After 2 h. the reaction mixture was slowly heated to R.T. and 250 ml of a 10% aqueous solution of NH_4Cl was added. The mixture was stirred for 15 min, quenched with 500 ml of water, and extracted twice with 500 ml of $CHCl_3$. The combined organic layer was washed with brine, dried (anhydrous sodium sulfate) and concentrated *in vacuo*.

The residue was dissolved in 100 ml of glacial acetic acid and 5.5 g (0.012 mol) of lead tetraacetate was

added. The mixture was stirred overnight at room temperature which made the colour of the mixture change from yellow/red to red. The reaction mixture was poured on to 400 ml of water, the red solid which precipitated was filtered off and dissolved in chloroform. The organic layer was extracted twice with a solution of saturated sodiumhydrogen carbonate, washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. After column filtration (silicagel 60, 1:4, EtOAc/n-hexane) and evaporation of the solvent *in vacuo*, the solid residue was dissolved in 50 ml of *o*-xylene and refluxed for 3 h. (temperature of the oilbath 150°C). After evaporation of the solvent, the product was recrystallized in dry diethylether to give 4.2 g (74%) of orange crystals (18). m.p. 247-250°C; MS, m/e (EI) 508, 493, 452, 434, 416; ^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 0,23 ppm (9H, s, $Si(CH_3)_3$), δ = 1.39 ppm (9H, s, $C(CH_3)_3$), δ = 1.99 ppm (1H, dd, J=15 Hz and J=3 Hz, H_9(ax)), δ = 2.72 ppm (1H, d, J=15 Hz, H_9(eq)), δ = 2.98 ppm (1H, d, J=20 Hz, H_7(ax)), δ = 3.64 ppm (1H, d, J=20 Hz, H_7(eq)), δ = 4.05 ppm (3H, s, OCH_3), δ = 5.30-5.40 ppm (1H, m, H_{10}), δ = 5.92 ppm (1H, s, OH), δ = 7.35 ppm (1H, dd, J=8.25 Hz and J=1.0 Hz, H_2), δ = 7.74 ppm (1H, t, J =8 Hz and J=8.25 Hz, H_4), δ = 8.00 ppm (1H, dd, J=8 Hz and J=1 Hz, H_3), δ = 13.30 ppm (1H, s, ArOH), δ = 14.10 ppm (1H, s, ArOH). The compound was not obtained completely pure due to some splitting off of the TMS group.

Cis-(+/-)-8-acetyl-7,8,9,10-tetrahydro-10-(1,1-dimethylethoxy)-1-methoxy-6,8,11-trihydroxy-5,12-naphthacenedione (19).

2.5 g of (18) was dissolved in 120 ml of THF and 1.05 g of HgO and 60 ml of 3M H_2SO_4 were added. The mixture was stirred for 3 h. at room temperature, poured into 250 ml of 1N HCl and extracted three times with 250 ml of chloroform. After drying on anhydrous sodium sulfate and evaporation *in vacuo* the solid was recrystallized from $CHCl_3$/n-hexane to give 2.05 g (91%) of (19). Without further purification the compound could be used in the next step. An analytical pure sample was prepared by column filtration (silicagel 60, 2% methanol/chloroform), dissolving the obtained solid in dichloromethane followed by filtration (hyflo) and precipitation with hexane. Finally the amorphous solid is treated with diisopropyl ether, filtered and dried in vacuo. m.p. 251-253 °C (dec); Anal. calcd. for $C_{25}H_{26}O_8$: C 66.07, H 5.77. Found : C 66.22, H 5.77. ^{1}H-NMR (100 MHz, $CDCl_3$): δ = 1.39 ppm (9H, s, $C(CH_3)_3$), δ = 1.91 ppm (1H, dd, J=14.5 Hz and J=3 Hz, H_9(ax)), δ = 2.37 ppm (1H, brd, J=14.5 Hz, H_9(eq)), δ = 2.42 ppm (3H, s, CH_3), δ = 2.99 ppm (1H, d, J=19.2 Hz, H_7(ax)), δ = 3.26 ppm (1H, d, J=19.2 Hz, H_7(eq)), δ = 4.08 (3H, s, OCH_3), δ = 5.40-5.49 ppm (1H, m, H_{10}), δ =5.99 ppm (1H, s, 9-OH), δ = 7.36 ppm (1H, dd, J=7.5 Hz and J=1.0 Hz, H_2), δ = 7.75 ppm (1H, t, J =7.7 Hz and J=7.5 Hz, H_4), δ = 8.00 ppm (1H, dd, J=7.7 Hz and J=1 Hz, H_3), δ = 13.32 ppm (1H, s, ArOH), δ = 14.09 ppm (1H, s, ArOH).

(+/-)-Daunomycinone (11).

2.05 g of (19) was dissolved in 40 ml of trifluoroacetic acid and stirred for 10 min at room temperature. The reaction mixture was diluted with 100 ml of dichloromethane and extracted twice with 75 ml of water, dried (anhydrous sodium sulfate) and concentrated *in vacuo* to give 1.75 g (95%) of (+/-)-daunomycinone (11), m.p. 212-214°C (lit 212-213°C); Spectral data (^{1}H-NMR, MS) were in full agreement with the literature data[6].

1,4,9,10-Tetrahydro-5,8-dihydroxy-9,10-dioxo-1,4-ethanoanthracene (25).

19.0 g (0.1 mol) of 5,8-dihydroxy-1,4-naphthoquinone (1) and 12.5 g (0.16 mol) of cyclohexa-1,3-diene (24) were refluxed for 5 days in 190 ml of THF. The reaction progress was monitored by TLC (EtOAc/n-hexane, 2 : 5) and the colour of the reaction mixture changed from red to yellow/brown. After the solvent had been removed *in vacuo* the residue was stirred in 200 ml petroleum ether (40/65) for 1 h. The solid was collected by filtration, rinsed with petroleum ether and used directly in the next reaction.

The yellow solid was added to a solution of 20.0 g of NaOH in 750 ml of water. The reaction mixture was stirred while air was bubbled through the solution. The reaction was monitored by TLC (EtOAc/n-hexane, 2 : 5). After 1 h. 35 ml conc. HCl (37%) was added, the red solid which precipitated was filtered off and dissolved in chloroform. The organic layer was washed with saturated $NaHCO_3$, water, brine, dried (anhydrous sodium sulfate) and evaporated to give 20.1 g (75%) of a red solid residue (25). m.p 203-204°C; MS, m/e (EI) 268, 240, 212, 183; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.16-1.58 ppm (4H, m, CH_2-CH_2), δ = 4.47-4.65 ppm (2H, m, H_1 and H_4), δ = 6.35 ppm (2H, dd, J=7.5 Hz and J=2.5 Hz, H-C=C-H), δ = 7.03 ppm (2H, s, ArH), δ = 12.48 ppm (2H, s, ArOH). Anal. calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.15; H, 4.47.

1,4,6,6a,7,8,9,10,10a,11-Decahydro-5,12-dihydroxy-7-(1,1-dimethylethoxy)-1,4-ethanonaphthacene-6,9,11-(10H)-trione (26).

To a solution of 19.4 g (0.072 mol) of (25/25a) in 300 ml of dry toluene was added 23.2 g (0.108 mol) of 1-*tert*-butoxy-3-trimethylsilyloxybuta-1,3-diene (13) at room temperature and the reaction was stirred under argon atmosphere for 5 days. The reaction could be monitored with TLC (EtOAc/n-hexane, 2 : 5). The solvent was concentrated *in vacuo* and the residue was dissolved in 190 ml of cold THF (0°C). 9.7 ml of 1N HCl was added and the reaction mixture was stirred at 0°C for 15 min until TLC (EtOAc/n-hexane, 2 : 5) showed the reaction to be complete. 500 ml of water were added and the mixture was extracted twice with 500 ml of dichloromethane. The CH_2Cl_2 layers were combined, washed with brine, dried (anhydrous sodium sulfate) and evaporated *in vacuo*. The residue was stirred overnight in dry diethylether (200 ml) and the yellow solid was filtered off. The filtrate was evaporated and the residue was purified by flash chromatography (EtOAc/n-hexane, 2 : 5) to give a total of 22.2 g (75%) of (26). m.p. 154-158°C; MS, m/e (EI) 410, 382, 354, 326; ^{1}H-NMR (90 MHz, $CDCl_3$, mixture of isomers, ratio 1 : 1): δ = 0.68 and 0.71 ppm (9H, 2 x s, $C(CH_3)_3$), δ = 1.38-1.72 ppm (4H, m, CH_2-CH_2), δ = 2.23-2.62 ppm (3H, m, H_{10}(ax) + H_8(eq) + H_8(ax)), δ = 3.30-3.66 ppm (3H, m, H_{10a} + H_{6a} + H_{10}(eq)), δ = 4.38-4.50 ppm (1H, m, H_7), δ = 4.53-4.69 ppm (2H, m, H_1 + H_4), δ = 6.48 ppm (1H, d, J=3.5 Hz, H-C=C), δ = 6.51 ppm (1H, d, J=3.5 Hz, H-C=C), δ = 11.89 and 11.94 ppm (1H, 2 x s, ArOH), δ = 12.34 and 12.35 ppm (1H, 2 x s, ArOH). Anal. calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.45; H, 6.48.

Cis-(+/-)-9-(2-trimethylsilylethynyl)-1,4,6,7,8,9,10,11-octahydro-7-(1,1-dimethylethoxy)-5,9,12-trihydroxy-1, 4-ethanonaphthacene-6,11-dione (28).

To a solution of 4.2 g (0.043 mol) of trimethylsilylacetylene in 450 ml of dry (distilled from sodium benzophenone ketyl) THF at -78°C under argon atmosphere was added 26.2 ml of 1.6 M n-BuLi (0.042 mol). After stirring the reaction mixture at -78°C for 30 min 3.1 g (0.0076 mol) of (26) was added. The reaction was monitored with TLC (EtOAc/n-hexane, 2 : 5). After 3 h. the reaction mixture was allowed to come to room temp and 150 ml of a 10% aqueous solution of NH_4Cl was added. The mixture was stirred at room temp for 15 min and 300 ml of water was added. The mixture was extracted twice with 300 ml of $CHCl_3$ and the organic layers were combined, washed with brine and concentrated *in vacuo*. The residue was dissolved in 60 ml of glacial acetic acid and 3.4 g (0.0077 mol) of lead tetraacetate was added to the solution. After stirring the reaction mixture overnight, 200 ml of water was added and the red solid which precipitated was dissolved in 300 ml of chloroform. The organic layer was washed respectively with a saturated solution of $NaHCO_3$, water and brine and dried (anhydrous sodium sulfate). The solution was evaporated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane, 1 : 4) to give 2.9 g (76%) of red solid (28). m.p. 116-118°C; ^{1}H-NMR (90 MHz, $CDCl_3$, mixture of isomers): δ = 0.27 ppm (9H, s, $Si(CH_3)_3$), δ = 1.40 ppm (9H, s, $C(CH_3)_3$), δ = 1.20-1.80 ppm (4H, m, CH_2-CH_2), δ = 1.94 ppm (1H, dd, J=14.5 Hz and J=3 Hz, H_8(ax)), δ = 2.67 ppm (1H, d, J=14.5 Hz, H_8(eq)), δ = 3.04 ppm (1H, d, J=17.5 Hz, H_{10}(ax)), δ = 3.55 ppm (1H, d, J=17.5 Hz, H_{10}(eq)), δ = 4.63 ppm (2H, m, H_1 + H_4), δ = 5.27 ppm (1H, m, H_7), δ = 5.72 ppm (1H, s, OH), δ = 6.48 ppm (2H, m, H-C=C-H), δ = 12.95 ppm (1H, s, ArOH), δ = 13.12 ppm (1H, s, ArOH). The compound was not obtained completely pure due to some splitting off of the TMS group and used without further purification in the following step.

Cis-(+/-)-9-(2-trimethylsilylethynyl)-7,8,9,10-tetrahydro-7-(1,1-dimethylethoxy)-6,9,11-trihydroxy-5,12-naphthacenedione (29).

A solution of 2.9 g (5.7 mmol) of 28 in 30 ml of *o*-xylene was refluxed for 5 h. (temp. of the oilbath 150°C). The solution was evaporated *in vacuo* and the solid residue was recrystallized in dry diethylether to give 2.5 g (91%) of 29. m.p. 214-216°C; MS, m/e (EI) 478, 463, 422, 404, 389; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 0.18 ppm (9H, s, $Si(CH_3)_3$), δ = 1.40 ppm (9H, s, $C(CH_3)_3$), δ = 1.99 ppm (1H, dd, J=14.5 Hz and J=3 Hz, H_8(ax)), δ = 2.76 ppm (1H, d, J=14.5 Hz with long-range coupling, H_8(eq)), δ = 3.02 ppm (1H, d, J=19.5 Hz, H_{10}(ax)), δ = 3.67 ppm (1H, dd, J=19.5 Hz and J=1.5 Hz, H_{10}(eq)), δ = 5.31-5.39 ppm (1H, m, H_7), δ = 5.87 ppm (1H, s, OH), δ = 7.72-7.87 ppm (2H, m, ArH), δ = 8.25-8.39 ppm (2H, m, ArH), δ = 13.33 ppm (1H, s, ArOH), δ = 13.67 ppm (1H, s, ArOH). Anal. calcd for $C_{27}H_{30}O_6Si$: C, 67.76; H, 6.32. Found: C, 67.53; H, 6.28.

Cis-(+/-)-9-acetyl-7,8,9,10-tetrahydro-7-(1,1-dimethylethoxy)-6,9,11-trihydroxy-5,12-naphthacenedione (30).

To a solution of 2.5 g (5.2 mmol) of 29 in 110 ml of THF were added 1.2 g (5.2 mmol) of HgO and 55 ml of 3M H_2SO_4. The reaction mixture was stirred for 24 h. at room temperature, poured into 270 ml of 1N HCl and extracted tree times with 200 ml of chloroform. After drying on anhydrous sodium sulfate and removal of the solvent *in vacuo* the solid was purified by column chromatography (EtOAc/n-hexane, 2 : 5) to give 1.6 g (91%) of (30). m.p. 217-220°C; MS, m/e (EI) 424, 368, 350, 332, 307; ^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 1.39

ppm (9H, s, $C(CH_3)_3$), δ = 1.88 ppm (1H, dd, J=14.5 Hz and J=3 Hz, H_8(ax)), δ = 2.37 ppm (1H, d, J=14.,5 Hz, H_8(eq)), δ = 2.42 ppm (3H, s, CH_3), δ = 3.04 ppm (1H, d, J_{gem}=19 Hz, H_{10}(ax)), δ = 3.25 ppm (1H, d, J_{gem}=19 Hz, H_{10}(eq)), δ = 5.35-5.44 ppm (1H, m, H_7), δ = 5.94 ppm (1H, s, OH), δ = 7.71-7.84 ppm (2H, m, ArH), δ = 8.21-8.33 ppm (2H, m, ArH), δ = 13.26 ppm (1H, s, ArOH), δ = 13.61 ppm (1H, s, ArOH). Anal. calcd for $C_{24}H_{24}O_7$: C, 67.92; H, 5.70. Found: C, 68.19; H, 5.65.

(+/-)-4-Demethoxydaunomycinone (31).

1.6 g (3.8 mmol) of 30 was dissolved in 20 ml of trifluoroacetic acid. After 10 min 50 ml of water was added and the water layer was extracted twice with 75 ml of dichloromethane. The combined organic layers were washed with water and brine, dried and evaporated *in vacuo*. The crude 31 was recrystallized from $CHCl_3$/diethylether to give 1.2 g (85%) of pure 4-demethoxydaunomycinone. m.p. 183-184°C (Lit.[17] 182.5-183°C). MS and ^{1}H-NMR data are in full agreement with those described in the literature.

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