Synthesis of a dynemicin A analog without the nitrogen†

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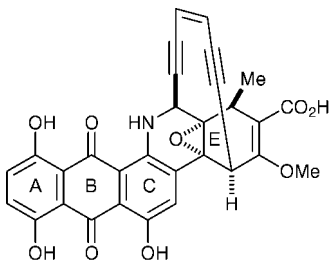
By combining the arylstannane **5** and the cyclohexenyl triflate **6** in a palladium-catalyzed cross-coupling reaction the ring system **7** was established. After attachment of an enediyne group and macrocyclization by a fluoride-induced reaction of **17a** the dynemicin A analog **19** was obtained. The X-ray analysis of **19** revealed that the aryl ring is rotated with regard to the aryl system in dynemicin A. One can thus conclude that in dynemicin A the nitrogen heterocycle serves to fix the conformation of the anthraquinone part with respect to the enediyne.

Due to their structural and functional complexity cells are susceptible to cytotoxic agents at many locations and pathways. The central role of DNA in the cell makes it an obvious target for chemical interference. For example, antitumor activity can result from alkylating and intercalating agents as well as from topoisomerase inhibitors. Cleavage of DNA is another way of inducing a cytotoxic effect.[1] In this context the family of the enediyne antitumor antibiotics is of particular interest.[2] A common feature of these compounds is that after an activation step the unsaturated, conjugated system undergoes a cyclization reaction to an aromatic diradical.[3] This in turn induces cleavage of DNA by hydrogen abstraction. Because diradicals are produced, a highly damaging double strand cleavage is possible. Since in the natural enediynes the cycloaromatization occurs after removal of a blocking device they represent natural prodrugs. For this reason they are ideal lead compounds for the development of more selective and effective antitumor compounds.[4] Among the natural enediynes dynemicin A (**1**) is unique in that it combines an anthraquinone substructure with a ten-membered enediyne.[5,6,7]



dynemicin A (**1**)

The activation of dynemicin A is initiated by two-electron reduction to provide an intermediate anthraquinol. This electron-rich intermediate rearranges to a quinone methide with simultaneous opening of the epoxide. Basically, the epoxide serves as a blocking device because the Bergman cycloaromatization in dynemicin A is retarded due to the *trans*-annelation of the epoxide and the ten-membered ring. Just as with the anthracyclines,[8] the aromatic sector provides room for ample modifications. Moreover, the blocking group, the functional groups in the E ring, and the nitrogen heterocycle present themselves for changes.

The nitrogen atom could have a three-fold function. It could be engaged in an intra- or intermolecular hydrogen bond. In addition, it might contribute to the epoxide opening by donating electron density to the benzylic position. Indeed, some designed analogs rely on the electron-donating effect of an unprotected nitrogen to induce epoxide opening.[2b,6c,9] Finally, the function of the nitrogen heterocycle might be to fix the arrangement of the anthraquinone part with regard to the subunit that contains the enediyne. Possibly, all three aspects are of importance. To learn more about the role of the nitrogen we designed compounds that lack the nitrogen heterocycle. In dynemicin A activation of the epoxide ring occurs upon reduction of the quinone. In our model compound it was planned to replace the anthraquinone part of dynemicin A with a substituted phenyl ring. We chose an electron-rich aryl ring with the hope that it might induce opening of the epoxide under acidic or basic conditions as a reduced quinone does. Alternatively, oxidation of the aromatic ring might produce a quinone precursor of the required hydroxyquinone. As it turned out however, the oxidation of a similar enediyne with a 3-methoxy- or a 3-hydroxyphenyl group proved to be difficult.[10] Moreover, the synthesis of analogs with a 2,5-disubstituted aryl ring was not possible since the macrocyclization did not work. Electrochemical and chemical studies on an analog with a 3-hydroxyphenyl group led us to suspect that the oxidation might produce biaryls.[11] Therefore, to block the *ortho*-position next to the hydroxy group, a dimethyl substituted phenol residue was used instead.

Results and discussion

Starting from the 1,3-diketone **2**,[12] the protected 5-bromo-2,3-dimethylphenol **4** was prepared.[13] Subsequent metallation with *n*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediamine (TMEDA) and addition of tributylin chlo-

† Supplementary material available: table and plot of calculated energies *versus* dihedral angle for **19**. For direct electronic acess see http://www.rsc.org/suppdata/nj/1999/749/, otherwise available from BLDSC (No. SUP 57553, 3 pp.) or the RSC Library. See Instructions for Authors, 1999, Issue 1 (http://www.rsc.org/njc).
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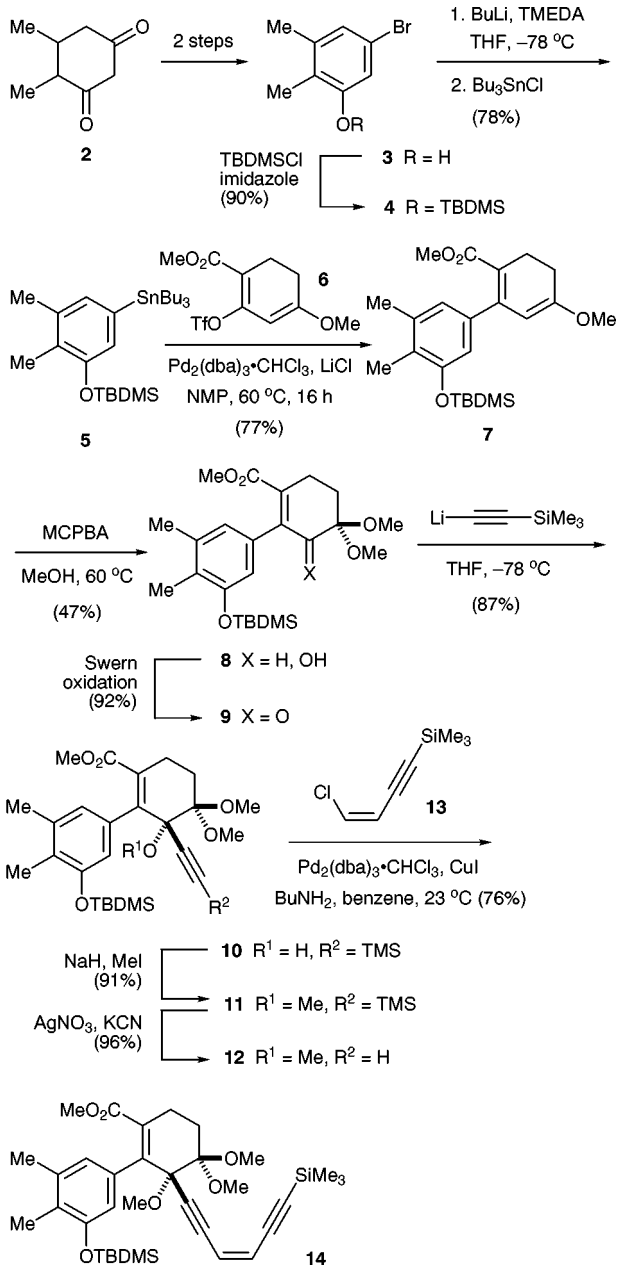
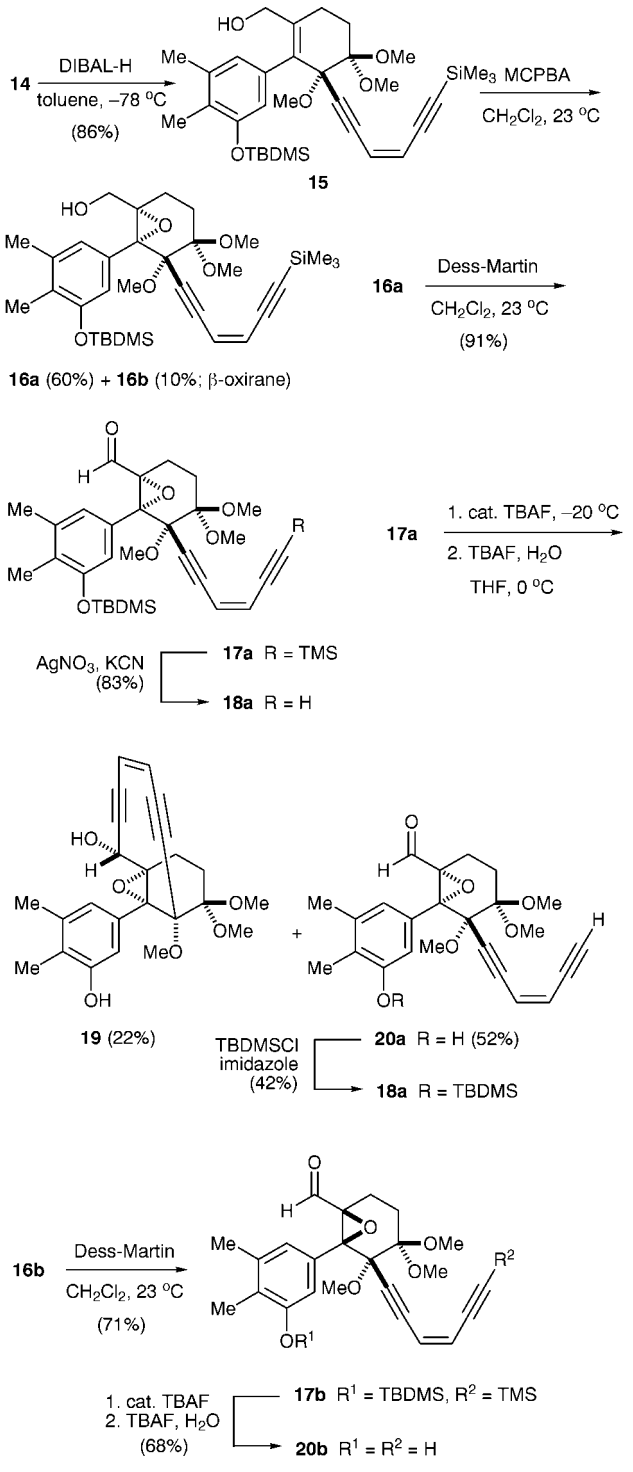
ride gave the arylstannane **5** (Scheme 1). This compound could be used without further purification in the cross-coupling reaction. For the coupling the cyclohexadienyl triflate **6**[14] was used, a compound that also is prepared from a cyclic 1,3-diketone. As will be seen the enol ether function of **6** serves as a latent α-acetal ketone.[15] This conversion was reached by epoxidation of the coupling product **7** in methanol, which led directly to the alcohol **8**. A subsequent Swern oxidation[16] provided the ketone **9** in high yield. The next task involved the installment of an enediyne subunit across the ester and the ketone carbon atoms. This started with the reaction between lithium trimethylsilylacetylide and the cyclohexenone **9** furnishing the tertiary alcohol **10**. In the subsequent step, the alcohol function was transformed to the corresponding methyl ether using sodium hydride and methyl iodide. According to a well-established method, the trimethylsilyl group of **11** was removed from the acetylene without endangering the phenolic protecting group using the combination of silver nitrate and potassium cyanide.[17] The resulting alkyne **12** was now subjected to a modified Stephens–Castro coupling[18] with the vinyl chloride[19] **13**. It was essential to carefully exclude oxygen from the reaction to prevent formation of a butadiyne resulting from oxidative dimerization of **12**. The yield for the desired enediyne **14** amounted to 76%.



Scheme 1

The synthetic plan called now for the reduction of the ester group and a stereoselective introduction of the epoxide. The reduction of the ester **14** to the allyl alcohol **15** proceeded uneventfully with DIBAL-H in toluene (Scheme 2). While in related studies[10,14,20,21] the oxirane formation occurred in a stereospecific manner, treatment of **15** with *m*-chloroperbenzoic acid (MCPBA) gave rise to two diastereomeric epoxides **16a** and **16b** in a ratio of 87 : 13. At this point it was not possible to definitely assign the relative configuration. This however, would be later shown indirectly by the macrocyclization reaction, since only with the *anti*-orientation of enediyne and epoxide is the ring closure possible. Oxidation of the major isomer **16a** with the Dess–Martin periodinane provided the cyclization substrate **17a**. We intended to study



Scheme 2

the macrocylization under various conditions that in a formal sense would add an acetylide anion to the aldehyde function (Scheme 2). Thus, removal of the trimethylsilyl group from the enediyne was affected as described above and produced the enediyne aldehyde **18a** from **17a** in good yield. Alternatively, **18a** could be prepared from the phenol **20a** by silylation. The phenol **20a** turned out to be a by-product in the fluoride-induced ring closure as shown below. In a similar manner the minor oxirane **16b** was converted to the enediyne aldehyde **17b**.

The cyclization was first studied with compound **18a**. It was planned to induce macrocyclization by deprotonation of the acetylene followed by trapping of the secondary alcohol with an electrophile.[22] However, the desired macrocyclic enediyne could not be isolated. The conditions we tried were the following: 0.01 M of **18a** in the THF, −78 °C, 1.05 equiv. of $LiN(TMS)_2$, 10 equiv. of MeI; 0.01 M of **18a** in THF, −78 °C, 1.05 equiv. of $KN(TMS)_2$, 2.2 equiv. of $CeCl_3$, 10 equiv. of MeI. Finally, success could be realized by a fluoride-induced cyclization[23] on substrate **17a**. This reaction was performed by adding catalytic amounts of anhydrous TBAF (5 mol%) to a 0.01 M solution of **17a** in THF. This induces a group transfer reaction to yield an intermediate silyl ether. Without isolation, all silyl ether functions were cleaved with additional TBAF. Besides a relatively large amount of **20a**, the macrocyclic enediyne **19** could be isolated in 22% yield. The same reaction conditions were also applied to the isomer **17b**. As expected, only the desilylated enediyne aldehyde **20b** could be isolated.

As evidenced from the ^1H NMR spectrum, the enediyne **19** exists in solution as a 3:1 mixture of stereoisomers. For example, the methine proton of the secondary hydroxyl group is seen as two singlets at $\delta = 4.24$ and 4.42. These stereoisomers are rotamers rather than configurational isomers. This can be concluded from the X-ray structure analysis of **19** (Fig. 1) and the fact that a solution of the X-rayed crystals showed again a 3:1 mixture of stereoisomers in the ^1H NMR spectrum. In addition, the X-ray structure analysis of **19** reveals the stereochemistry of the oxirane **16a**. The secondary hydroxy group points away from the aryl ring. Similar results have been observed before.[10,21] This orientation also allows one to infer the reactive conformation of the precursor aldehyde. In comparison to dynemicin A (cd = 354 pm) the corresponding distance in **19** (cd = 362 pm) is enlarged. However, the most striking feature is the twisting of the aryl ring in **19** with regard to the situation in dynemicin A. It is obvious that in this conformation the aryl ring is not able to assist in the epoxide opening for stereoelectronic reasons.

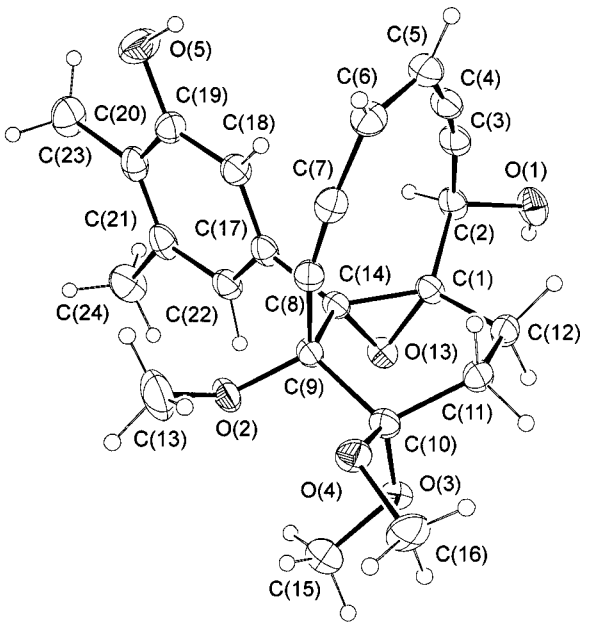


Fig. 1 X-ray structure of **19**.

The twisting of the aryl ring is probably caused by the avoidance of *syn*-pentane interactions. It was therefore of interest to calculate the change of energy upon the rotation of the bond that connects the aryl ring with the remainder of the molecule. For these calculations the MM2 force field of Chem3D was used. The dihedral angle C(22)–C(17)–C(14)–C(9) was increased in 10° steps and at each point the steric energy calculated. By this procedure two minima and two maxima could be localized. The minima are at angles of 80° and 260°. They are of almost equal energy with the conformer resembling the X-ray structure (dihedral angle of 260°) being favoured by 0.058 kcal mol^{-1}. The corresponding angle in the X-ray structure is 253.6°. The calculated maxima at 160° (21.45 kcal mol^{-1}) and 340° (21.21 kcal mol^{-1}) are also very close in energy. (The complete results of the calculations are available as supplementary material.) It should be mentioned that the forcefield calculations do not reproduce the observed ratio (3:1) of the atropisomers. One might thus conclude that the nitrogen heterocycle in dynemicin A serves to fix the conformation of the anthraquinone part with respect to the enediyne. This allows optimal intercalation of the anthraquinone and at the same time positions the enediyne into the minor grove of DNA.[24] Currently we are studying the oxidation of the enediyne **19** to the corresponding quinone.

Experimental

^1H [$CHCl_3$ (7.24 ppm) as internal standard in $CDCl_3$ or C_6HD_5 (7.16 ppm) as internal standard in C_6D_6] and ^{13}C [$CDCl_3$ (77.00 ppm) as internal standard in $CDCl_3$ or C_6D_6 (128.00 ppm) as internal standard in C_6D_6] NMR spectra were acquired on Varian Unity 500, Varian Gemini 2000 and Bruker AM 400 spectrometers. *J* values are given in Hz. The signal multiplicities were determined by means of the DEPT and APT techniques; + for CH or CH_3, − for CH_2, × for C. IR spectra: Perkin–Elmer Spectrum 1000 spectrometer. Melting points: Dr. Tottoli melting point apparatus. EI-MS: AMD Intectra GmbH AMD 402. Flash chromatography: J. T. Baker silica gel 30–60 μm. TLC: Merck Si 60 F_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 35–65 °C was used; THF was distilled from sodium diphenyl ketyl immediately before use. All reactions were carried out under an atmosphere of argon. The pH 7 buffer solution used in the workup procedures was prepared by dissolving potassium dihydrogen phosphate (85.0 g) and sodium hydroxide (14.5 g) in water (1 l). The following reagents and compounds were prepared according to literature procedures: $Pd_2(dba)_3 \cdot CHCl_3$,[25] Dess–Martin periodinane,[26] trimethylsilylacetylene,[27] triflate **6**,[14] vinyl chloride **13**.[19]

Syntheses

5-Bromo-2,3-dimethyl-1-*tert*-butyldimethylsilyloxyphenol (4). A solution of phenol **3**[13] (5.23 g, 26.0 mmol) and imidazole (3.72 g, 54.6 mmol) in CH_2Cl_2 (180 ml) was stirred at 0 °C for 5 min followed by the addition of *tert*-butyldimethylsilyl chloride (4.12 g, 27.3 mmol). The resulting mixture was then stirred for 16 h at rt. Subsequently it was diluted with ether (150 ml), washed with pH 7 buffer (150 ml), satd. NH_4Cl (3 × 100 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether) to give compound **4** (7.4 g, 90%) as a colorless oil; TLC (petroleum ether): $R_f = 0.50$; δ_H(400 MHz; $CDCl_3$) 0.19 [6 H, s, $Si(CH_3)_2$], 0.99 [9 H, s, $SiC(CH_3)_3$], 2.04 (3 H, s, aryl-CH_3), 2.20 (3 H, s, aryl-CH_3), 6.76 (1 H, d, *J* 1.5, aryl-H) and 6.90 (1 H, d, *J* 1.5, aryl-H).

Tributyl(3-*tert*-butyldimethylsilyloxyphenyl-4,5-dimethyl)-stannane (5). To a cooled solution (0 °C) of Bu^nLi (1.6 M in hexane, 16.1 ml, 25.8 mmol) in THF (40 ml) was added *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediamine (3.00 g, 3.90 ml, 25.8 mmol). After 30 min the solution was cooled to −78 °C and bromide **4** (7.40 g, 23.5 mmol) in THF (25 ml) was added dropwise. After stirring for 10 min $Bu^n{}_3SnCl$ (7.3 ml, 27 mmol) was added dropwise and the solution was stirred for 14 h during which time it was allowed to warm to 0 °C. The mixture was diluted with ethyl acetate (100 ml), washed with water (30 ml) and brine (30 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give stannane **5** (13.4 g crude material, yield 78%; determined by ^{1}H-NMR) as a colorless oil, which was used without further purification; TLC (petroleum ether): R_f = 0.80; δ_H(400 MHz; $CDCl_3$) 0.19 [6 H, s, $Si(CH_3)_2$], 0.86 (9 H, t, *J* 7.3, CH_3), 0.90 (6 H, t, *J* 7.3, CH_2), 1.00 [9 H, s, $SiC(CH_3)_3$], 1.26–1.62 (12 H, m, CH_2), 2.10 (3 H, s, aryl-CH_3), 2.22 (3 H, s, aryl-CH_3), 6.73 (1 H, s, aryl-H) and 6.80 (1 H, s, aryl-H).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-4-methoxy-1,3-cyclohexadiene-1-carboxylate (7). A suspension of triflate **6**[14] (5.40 g, 17.2 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.44 g, 0.43 mmol, 2.5 mol%) and LiCl (2.18 g, 51.5 mmol) in NMP (70 ml) was degassed and stirred for 20 min. Stannane **5** (9.92 g, 18.9 mmol) was added and the flask was lowered into an oil bath. The solution was stirred for 16 h at 60 °C. After being cooled to rt, the mixture was filtered over a pad of Celite, and the filtrate washed with water (2 × 100 ml) and brine (50 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether to petroleum ether–ethyl acetate, 20 : 1) to give the ester **7** as a pale yellow oil [Found: C, 68.69; H, 8.57; $C_{23}H_{34}O_4Si$ (402.6) requires C, 68.62; H 8.51]; TLC (petroleum ether–ethyl acetate, 20 : 1): R_f = 0.20; ν_{max}(film)/cm^{-1} 2953, 2858, 1697 (C=O) and 1566 (C=C); δ_H(400 MHz; $CDCl_3$) 0.18 [6 H, s, $Si(CH_3)_2$], 0.99 [9 H, s, $SiC(CH_3)_3$], 2.10, (3 H, s, aryl-CH_3), 2.22 (3 H, s, aryl-CH_3), 2.33–2.38 (2 H, m, CH_2), 2.66–2.70 (2 H, m, CH_2), 3.47 (3 H, s, OCH_3), 3.61 (3 H, s, CO_2CH_3), 5.03 (1 H, s, vinyl-H), 6.44 (1 H, d, *J* 1.5, aryl-H) and 6.57 (1 H, d, *J* 1.5, aryl-H); δ_C(125 MHz; C_6D_6) −4.08 [+, $Si(CH_3)_2$], 12.64 (+, aryl-CH_3), 18.48 (×, $SiCMe_3$), 20.36 (+, aryl-CH_3), 26.04 [+, $SiC(CH_3)_3$], 26.25, 27.64 (−, CH_2), 50.62, 54.64 (+, OCH_3, CO_2CH_3), 99.30 (+, C=CH), 115.86 (×, aryl-C), 116.45, 122.33 (+, aryl-C), 126.28 (×, *C*-aryl), 137.81 (×, aryl-C), 140.98 (×, C–C=O), 146.75 (×, aryl-C), 153.58 (×, COTBS), 163.56 (×, $COCH_3$) and 168.62 (×, C=O); *m*/*z* (EI) 402 (M^+, 98%), 387 (5), 371 (8) and 313 (100).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-3-hydroxy-4,4-dimethoxy-1-cyclohexene-1-carboxylate (8). To a solution of **7** (5.52 g, 13.7 mmol) in anhydrous methanol (100 ml) was added MCPBA (2.60 g, 15.1 mmol). The mixture was stirred for 1 h at 60 °C. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (500 ml), washed with 10% Na_2SO_3 solution (100 ml), 10% Na_2CO_3 solution (100 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 7 : 2) to give the alcohol **8** (2.89 g, 47%) as an oil [Found: C, 63.70; H, 8.44; $C_{24}H_{38}O_6Si$ (450.6) requires C, 63.97; H, 8.50]; TLC (petroleum ether–ethyl acetate, 3:1): R_f = 0.25; ν_{max}(film)/cm^{-1} 3486 (OH), 1716 (C=O) and 1568 (C=C); δ_H(400 MHz; $CDCl_3$) 0.17, 0.18 [3 H each, 2 s, $Si(CH_3)_2$], 0.99 [9 H, s, $SiC(CH_3)_3$], 1.85–2.05 (2 H, m, CH_2), 2.08 (3 H, s, aryl-CH_3), 2.21 (3 H, s, aryl-CH_3), 2.32–2.40 (1 H, m, CH_2), 2.51–2.58 (1 H, m, CH_2), 3.29 (3H, s, OCH_3), 3.30 (3 H, s, OCH_3), 3.46 (3 H, s, CO_2CH_3), 4.16 (1 H, s, C*H*OH), 6.54 (1 H, d, *J* 1.2, aryl-H) and 6.64 (1 H, br s, aryl-H); δ_C(100 MHz; $CDCl_3$) −4.38, −4.32 [+, $Si(CH_3)_2$], 12.33 (+, aryl-CH_3), 18.5 (×, $SiCMe_3$), 20.24 (+, aryl-CH_3), 23.52 (−, CH_2) 25.30 (−, CH_2), 25.72 [+, $SiC(CH_3)_3$], 48.11, 48.89, 51.46 (+, OCH_3, CO_2CH_3), 69.99 (+, CHOH), 100.23 (×, ketal-C), 115.92, 121.79 (+, aryl-CH), 126.95 (×, aryl-C), 130.08 (×, *C*–C=O), 137.82, 138.05, 141.99 (×, aryl-C, *C*-aryl), 153.44 (×, COTBS) and 170.02 (×, C=O); *m*/*z* (EI) 450 (M^+, 10%), 389 (22) and 330 (100).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-4,4-dimethoxy-3-oxo-1-cyclohexene-1-carboxylate (9). To a cooled solution (−78 °C) of oxalyl dichloride (0.94 g, 7.4 mmol, 0.63 ml) in CH_2Cl_2 (7.5 ml) was added dropwise a solution of dimethyl sulfoxide (1.25 g, 16.0 mmol, 1.13 ml) in CH_2Cl_2 (1.5 ml). After stirring for 30 min a solution of **8** (2.77 g, 6.15 mmol) in CH_2Cl_2 (10 ml) was added. After a further 30 min triethylamine (3.11 g, 30.7 mmol, 4.27 ml) was added and the solution was stirred for 2 h during which time it was allowed to warm to rt. Water (10 mol) was added and the solution stirred for 10 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether–ethyl acetate, 4.5 : 1) gave 2.54 g (92%) of the enone **9** [Found: C, 64.18; H, 8.16; $C_{24}H_{36}O_6Si$ (448.6) requires C, 64.25; H, 8.03]; TLC (petroleum ether–ethyl acetate, 3 : 1): R_f = 0.41. ν_{max}(film)/cm^{-1} 2955 (CH_2), 1727 (C=O), 1706 (C=O) and 1571 (C=C); δ_H(400 MHz; $CDCl_3$) 0.20 [6 H, s, $Si(CH_3)_2$], 1.00 [9 H, s, $Si(CH_3)_3$], 2.11 (3 H, s, aryl-CH_3), 2.21 (3 H, s, aryl-CH_3), 2.32 (2 H, t, *J* 5.9, CH_2), 2.78 (2 H, t, *J* 5.9, CH_2), 3.30 (6 H, s, OCH_3), 3.53 (3 H, s, CO_2CH_3), 6.45 (1 H, d, *J* 1.5, aryl-H) and 6.50 (1 H, br s, aryl-H); δ_C(100 MHz; $CDCl_3$) −3.33 [+, $Si(CH_3)_2$], 13.40 (+, aryl-CH_3), 19.18 (×, $SiCMe_3$), 21.20 (+, aryl-CH_3), 26.34 (−, CH_2), 26.79 [+, $SiC(CH_3)_3$], 30.90 (−, CH_2), 50.80, 53.02 (+, OCH_3, CO_2CH_3), 97.48 (×, ketal-C), 118.43, 124.28 (+, aryl-CH), 128.69 (×, aryl-C), 132.39 (×, aryl-C), 138.38 (×, aryl-C), 138.75 (×, *C*-aryl), 147.07 (×, *C*–C=O), 154.22 (×, COTBS), 169.98 (×, C=O, ester) and 193.47 (C=O, ketone); *m*/*z* (EI) 448 (M^+, 23%), 389 (28) and 360 (100).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-4,4-dimethoxy-3-hydroxy-3-(2-trimethylsilyl-1-ethynyl)-1-cyclohexene-1-carboxylate (10). To a solution of trimethylsilylacetylene (0.69 g, 7.1 mmol) in THF (18 ml) was added Bu^nLi (1.6 M in hexane, 4.2 ml, 6.8 mmol) at −78 °C. The mixture was stirred for 45 min and a solution of **9** (2.54 g, 5.66 mmol) in THF (10 ml) was added dropwise. After stirring for 2 h the mixture was treated with satd. $NaHCO_3$ solution (10 ml) and allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 6 : 1) to give the product **10** (2.68 g, 87%) as a viscous yellow oil [Found: C, 63.54; H 8.56; $C_{29}H_{46}O_6Si$ (546.8) requires C, 63.70; H, 8.48]; TLC (petroleum ether–ethyl acetate, 3 : 1): R_f = 0.53; ν_{max}(film)/cm^{-1} 3514 (OH), 2958 (CH_2), 2171 (acetylene) and 1719 (C=O); δ_H(400 MHz; $CDCl_3$) 0.13 [9 H, s, $Si(CH_3)_3$], 0.15, 0.16 [3 H each, 2 s, $Si(CH_3)_2$], 0.98 [9 H, s, $SiC(CH_3)_3$], 2.07 (3 H, s, aryl-CH_3), 2.09–2.16 (2 H, m, CH_2), 2.19 (3 H, s, aryl-CH_3), 2.38–2.42 (2 H, m, CH_2), 2.84 (1 H, s, OH), 3.38 (3 H, s, OCH_3), 3.39 (3 H, s, OCH_3), 3.47 (3 H, s, CO_2CH_3), 6.54 (1 H, d, *J* 1.2, aryl-H)

and 6.74 (1 H, br s, aryl-H); δ_C(100 MHz; $CDCl_3$) −4.33, −4.28 [+, $Si(CH_3)_2$], −0.42 [+, $Si(CH_3)_3$], 12.34 (+, aryl-CH_3), 18.13 (×, $SiCMe_3$), 20.28 (+, aryl-CH_3), 24.80 (−, CH_2), 25.76 [+, $SiC(CH_3)_3$], 26.63 (−, CH_2), 49.51, 51.41 (+, OCH_3, CO_2CH_3), 73.85 (×, COH), 92.75 (×, CSi), 99.09 (×, ketal-C), 104.09 (×, *C*–C–OH), 118.11, 124.13 (+, aryl-CH), 126.71 (×, aryl-C), 129.10 (×, *C*–C=O), 134.39 (×, aryl-C), 136.92 (×, aryl-C), 144.41 (×, *C*-aryl), 152.71 (×, COTBS) and 169.61 (×, C=O); *m/z* (EI) 546 (M^+, 12%), 458 (46) and 73 (100).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-3,4,4-trimethoxy-3-(2-trimethylsilyl-1-ethynyl)-1-cyclohexene-1-carboxylate (11). To a solution of the alcohol **10** (2.68 g, 4.90 mmol) in THF (30 ml) was added NaH (153 mg, 6.38 mmol) at 0 °C. After 5 min 1,3-dimethyl-2-imidazolidinone (1.68 g, 1.61 ml, 14.7 mmol) and methyl iodide (2.78 g, 1.22 ml, 19.6 mmol) were added, and the mixture was stirred for 1 h at rt. It was cooled again to 0 °C, neutralized with pH 7 buffer solution (20 ml) and diluted with ethyl acetate (30 ml). The organic layer was washed with water (2 × 20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 7 : 1) to give the product **11** (2.5 g, 91%) as a yellow oil [Found: C, 63.85; H, 8.69; $C_{30}H_{48}O_6Si_2$ (560.9) requires C, 64.24; H, 8.63]; TLC (petroleum ether–ethyl acetate, 3 : 1): $R_f = 0.67$; ν_{max}(film)/cm^{-1} 2958 (CH_2), 2167 (acetylene) and 1720 (C=O); δ_H(400 MHz; $CDCl_3$) 0.09 [9 H, s, $SiC(CH_3)_3$], 0.17, 0.18 [6 H, 2 s, $Si(CH_3)_2$], 1.01 [9 H, s, $Si(CH_3)_3$], 2.09 (3 H, s, aryl-CH_3), 2.11–2.16 (2 H, m, CH_2), 2.19 (3 H, s, aryl-CH_3), 2.41–2.45 (2 H, m, CH_2), 3.20, 3.38, 3.39, 3.44 (3 H each, 4 s, OCH_3, CO_2CH_3), 6.59 (1 H, d, *J* 1.1, aryl-H) and 6.67 (1 H, br s, aryl-H); δ_C(100 MHz; $CDCl_3$) −3.32, −3.23 [+, $Si(CH_3)_2$], 0.50 [+, $Si(CH_3)_3$], 13.38 (+, aryl-CH_3), 19.17 (×, $SiCMe_3$), 21.13 (+, aryl-CH_3), 26.02 (−, CH_2), 26.82 [+, $SiC(CH_3)_3$], 27.12 (−, CH_2), 51.15, 51.22, 52.32, 55.60 (+, OCH_3, CO_2CH_3) 80.56 (×, $COCH_3$), 98.84 (×, CSi), 101.90 (×, ketal-C), 102.45 (×, acetylene-C), 118.91, 125.56 (+, aryl-CH), 127.20 (×, aryl-C), 130.42 (×, *C*–C=O), 136.44 (×, aryl-C), 137.57 (×, aryl-C), 144.86 (×, *C*-aryl), 153.52 (×, COTBS) and 170.76 (×, C=O); *m/z* (EI) 560 (M^+, 10%), 472 (50) and 73 (100).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-3-(1-ethynyl)-3,4,4-trimethoxy-1-cyclohexene-1-carboxylate (12). To a solution of the acetylene **11** (2.50 g, 4.46 mmol) in THF–water–ethanol (45 ml, 4 : 1 : 1) was added silver nitrate (3.03 g, 17.8 mmol) at 0 °C. After 25 min KCN (2.03 g, 31.2 mmol) was added and the solution was stirred for 1 h at rt. The mixture was diluted with ethyl acetate (200 ml) and washed with water (50 ml) and brine (50 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 6 : 1) to give the acetylene **12** (2.1 g, 96%) as a slightly yellow oil [Found: C, 66.07; H 8.28; $C_{27}H_{40}O_6Si$ (488.7) requires C, 66.36; H, 8.25]; TLC (petroleum ether–ethyl acetate, 3 : 1): $R_f = 0.52$; ν_{max}(film)/cm^{-1} 2951 (CH_2), 2244 (acetylene) and 1721 (C=O); δ_H(400 MHz; $CDCl_3$) 0.16, 0.18 [3 H each, 2 s, $Si(CH_3)_2$], 0.99 [9 H, s, $SiC(CH_3)_3$], 2.08 (3 H, s, aryl-CH_3), 2.15–2.16 (2 H, m, CH_2), 2.17 (3 H, s, aryl-CH_3), 2.41–2.45 (2 H, m, CH_2), 2.70 (1 H, s, acetylene-H), 3.16, 3.37, 3.41, 3.43 (3 H each, 4 s, OCH_3, CO_2CH_3), 6.65 (1 H, s, aryl-H) and 6.68 (1 H, s, aryl-H); δ_C(100 MHz; $CDCl_3$) −4.39, −4.35 [+, $Si(CH_3)_2$], 12.36 (+, aryl-CH_3), 18.18 (×, $SiCMe_3$), 20.05 (+, aryl-CH_3), 24.97 (−, CH_2), 25.79 [+, $SiC(CH_3)_3$], 26.19 (−, CH_2), 50.26, 50.30, 51.34, 54.88 (+, OCH_3, CO_2CH_3), 79.50, 80.05, 80.20 (×, $COCH_3$, acetylene-C), 100.79 (×, ketal-C), 117.72, 124.43 (+, aryl-CH), 126.37 (×, aryl-C), 129.77 (×, *C*–C=O), 134.90 (×, aryl-C), 136.93 (×, aryl-C), 143.46 (×, *C*-aryl), 152.55 (×, COTBS) and 169.59 (×, C=O); *m/z* (EI) 488 (M^+, 13%), 400 (55) and 73 (100).

Methyl 2-(3-*tert*-butyldimethylsilyloxy-4,5-dimethylphenyl)-3,4,4-trimethoxy-3-[(*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl]-1-cyclohexene-1-carboxylate (14). To a solution of acetylene **12** (2.1 g, 4.3 mmol) in dry degassed benzene (50 ml) were added CuI (123 mg, 0.64 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (111 mg, 0.11 mmol), *n*-butylamine (1.57 g, 2.10 ml, 21.5 mmol) and vinyl chloride **13** (0.82 g, 5.2 mmol) at 0 °C. After 1 h the cooling bath was removed and the mixture was stirred for 20 h at room temperature under an atmosphere of argon. The mixture was diluted with ether (200 ml), washed with water (2 × 30 ml) and brine (20 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 8 : 1) to give the enediyne **14** (2.0 g, 76%) as a slightly yellow oil [Found: C, 66.30; H, 8.32; $C_{27}H_{40}O_6Si$ (610.9) requires C, 66.84; H, 8.25]; TLC (petroleum ether–ethyl acetate, 6 : 1): $R_f = 0.44$; ν_{max}(film)/cm^{-1} 2953 (CH_2), 2143 (acetylene) and 1721 (C=O); δ_H(400 MHz; C_6D_6) 0.13 [9 H, s, $Si(CH_3)_3$], 0.25 [6 H, s, $Si(CH_3)_2$], 1.05 [9 H, s, $SiC(CH_3)_3$], 2.10 (3 H, s, aryl-CH_3), 2.14 (3 H, s, aryl-CH_3), 2.16–2.22 (2 H, m, CH_2), 2.52–2.58 (2 H, m, CH_2), 3.17, 3.23, 3.45, 3.62 (3 H each, 4 s, OCH_3, CO_2CH_3), 5.42 (1 H, d, *J* 11.1, vinyl-H), 5.46 (1 H, d, *J* 11.1, vinyl-H), 7.06 (1 H, s, aryl-H) and 7.07 (1 H, s, aryl-H); δ_C(125 MHz; $CDCl_3$) −4.39, −4.35 [+, $Si(CH_3)_2$], −0.39 [+, $Si(CH_3)_3$], 12.43 (+, aryl-CH_3), 18.18 (×, $SiMe_3$), 20.08 (+, aryl-CH_3), 25.08 (−, CH_2), 25.88 (+, $SiC(CH_3)_3$, 26.70 (−, CH_2), 50.23, 50.35, 51.27, 55.11 (+, OCH_3, CO_2CH_3), 80.07, 89.32, 93.37, 100.88, 102.00, 102.67 (×, $COCH_3$, acetylene-C, ketal-C), 117.62, 119.34, 119.65, 124.48 (+, aryl-CH, vinyl-C), 126.08 (×, aryl-C), 129.23 (×, *C*–C=O), 134.82, 136.65 (×, aryl-C), 143.86 (×, *C*-aryl), 152.38 (×, COTBS) and 169.33 (×, C=O); *m/z* (EI) 610 (M^+, 8%), 579 (8), 522 (12) and 73 (100).

2-(3-*tert*-Butyldimethylsilyloxy-4,5-dimethylphenyl)-3,4,4-trimethoxy-3-[(*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl]-1-cyclohexenylmethanol (15). To a solution of the ester **14** (1.26 g, 2.06 mmol) in toluene (45 ml) was added DIBAL-H (1.0 M in CH_2Cl_2, 4.55 ml, 4.55 mmol) at −78 °C. After 1 h ethyl acetate (2 ml) was added and the mixture was warmed to rt before it was diluted with ether (100 ml) and washed with satd. sodium potassium tartrate solution (2 × 20 ml). The aqueous phase was extracted with ether (2 × 20 ml) and the combined organic layers were washed with brine (20 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 3 : 1) to give the alcohol **15** (1.04 g, 86%) as a colorless oil [Found: C, 67.76; H, 8.99; $C_{33}H_{50}O_5Si_2$ (582.9) requires C, 68.00; H, 8.65]; TLC (petroleum ether–ethyl acetate, 3 : 1): $R_f = 0.22$; ν_{max}(film)/cm^{-1} 3444 (OH), 2958 (CH_2), 2146 (acetylene) and 1569 (C=C); δ_H(400 MHz; C_6D_6) 0.13 [9 H, s, $Si(CH_3)_3$], 0.23 [6 H, s, $Si(CH_3)_2$], 1.05 [9 H, s, $SiC(CH_3)_3$], 2.13 (3 H, s, aryl-CH_3), 2.17 (3 H, s, aryl-CH_3), 2.26–2.34 (2 H, m, CH_2), 2.37–2.43 (2 H, m, CH_2), 3.30 (3 H, s, OCH_3), 3.51 (3 H, s, OCH_3), 3.63 (3 H, s, OCH_3), 3.90 (2 H, s, CH_2OH), 5.44 (1 H, d, *J* 11.0, vinyl-H), 5.51 (1 H, d, *J* 11.0, vinyl-H) and 6.97 (2 H, s, aryl-H); δ_C(100 MHz; C_6D_6) −4.24 [+, $Si(CH_3)_2$], −0.48 [+, $Si(CH_3)_3$], 12.38 (+, aryl-CH_3), 18.28 (×, $SiCMe_3$), 20.12 (+, aryl-CH_3), 25.21 (−, CH_2), 25.88 [+, $SiC(CH_3)_3$], 26.75 (−, CH_2), 49.65, 50.43, 55.15 (+, OCH_3), 63.85 (−, CH_2OH), 80.43, 89.80, 96.18, 102.22, 103.01 (×, $COCH_3$, acetylene-C, ketal-C), 119.00, 119.06, 120.28, 125.92 (+, aryl-CH, vinyl-CH), 135.78, 136.36,

137.05, 137.18 and 153.32 (×, aryl-C, *C*-CH_2OH, *C*-aryl, COTBS); *m/z* (EI) 550 ($M^+ - CH_3OH$, 12%), 463 (20), 73 (100) and 57 (83).

5a-(3-*tert*-Butyldimethylsilyl-4,5-dimethylphenyl)-4,4,5-trimethoxy-5-[(*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl]perhydrobenzo[*b*]oxiren-1-ylmethanol (16a and 16b). To a solution of the allyl alcohol **15** (0.50 g, 0.86 mmol) in CH_2Cl_2 (18 ml) were added Na_2HPO_4 (1.85 g, 5.16 mmol) and MCPBA (0.22 g, 1.3 mmol) at 0 °C. The mixture was stirred for 18 h during which time the temperature was allowed to reach rt. Ether was added (20 ml) and the mixture was washed with 20% Na_2SO_3 solution (2 × 10 ml), 10% Na_2CO_3 solution (10 ml) and brine (10 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 6 : 1) to give the two epoxides **16a** (0.31 g, 60%) and **16b** (0.05 g, 10%) as colorless oils.

Compound **16a**. Found: C, 65.97; H, 8.67; $C_{33}H_{50}O_6Si_2$ (598.9) requires C, 66.18; H, 8.41; TLC (petroleum ether–ethyl acetate, 3 : 1): $R_f = 0.30$; ν_{max}(film)/cm^{-1} 3441 (OH), 2957 (CH_2), 2146 (acetylene) and 1463 (C=C); δ_H(500 MHz; DMSO-d_6, 70 °C) 0.14 [9 H, s, $Si(CH_3)_3$], 0.17 [6 H, s, $Si(CH_3)_2$], 0.99 [9 H, s, $SiC(CH_3)_3$], 1.64–1.70 (1 H, m, CH_2), 1.82–1.88 (1 H, m, CH_2), 1.91–1.98 (1 H, m, CH_2), 2.04 (3 H, s, aryl-CH_3), 2.05–2.10 (1 H, m, CH_2), 2.19 (3 H, s, aryl-CH_3), 3.08 (2 H, s, CH_2OH), 3.29 (3 H, s, OCH_3), 3.38 (3 H, s, OCH_3), 3.44 (3 H, s, OCH_3), 5.66–5.70 (1 H, m, vinyl-H), 5.81 (1 H, d, *J* 11, vinyl-H), 6.63 (1 H, br s, aryl-H) and 6.72 (1 H, br s, aryl-H); δ_C(125 MHz; DMSO-d_6) −4.64/−4.44 [$Si(CH_3)_2$], −0.45 [$Si(CH_3)_3$], 12.00, 17.85, 19.81, 21.24, 22.24 (aryl-CH_3, CH_2, $SiCMe_3$), 25.61 [$SiC(CH_3)_3$], 48.31/48.48, 50.56/50.89, 53.20 (OCH_3), 64.08/64.70, 65.02/65.95 (oxirane-C), 68.68 (CH_2OH), 79.17, 79.49 ($COCH_3$, acetylene-C), 90.00, 91.13, 95.31, 100.04, 102.38 (acetylene-C, aryl-CH, ketal-C), 118.63, 120.17 (vinyl-CH, aryl-CH), 124.40, 125.03 (vinyl-CH, aryl-C), 125.03, 135.40/135.65 (aryl-C, *C*-aryl) and 151.15/151.88 (COTBS); *m/z* (EI) 598 (M^+, 1%) and 567 (14).

Compound **16b**. TLC (petroleum ether–ethyl acetate, 3 : 1): $R_f = 0.26$; δ_H(400 MHz; C_6D_6) 0.10 [9 H, s, $Si(CH_3)_3$], 0.26 [6 H, s, $Si(CH_3)_2$], 1.06 [9 H, s, $SiC(CH_3)_3$], 1.81–1.88 (2 H, m, CH_2), 2.07/2.08 (3 H, s, aryl-CH_3), 2.12–2.24 (2 H, m, CH_2), 2.14/2.15 (3 H, s, aryl-CH_3), 3.08/3.13 (3 H, s, OCH_3), 3.19 (2 H, s, CH_2OH), 3.22/3.24 (3 H, s, OCH_3), 3.44/3.47 (3 H, s, OCH_3), 5.47 (1 H, d, *J* 11, vinyl-H), 5.64 (1 H, d, *J* 11, vinyl-H), 7.09 (1 H, s, aryl-H) and 7.26 (1 H, s, aryl-H); δ_C(100 MHz; C_6D_6) −4.53/−4.33 [+, $Si(CH_3)_2$], −0.53/0.50 [+, $Si(CH_3)_3$], 12.00 (+, aryl-CH_3), 18.26 (×, $SiCMe_3$), 19.99/20.10 (+, aryl-CH_3), 23.31/23.39 (−, CH_2), 24.20/24.42 (−, CH_2), 25.87 [+, $SiC(CH_3)_3$], 48.64/49.02, 50.67/50.85, 53.71/53.80 (+, OCH_3), 65.58/65.84, 67.19/68.03, 70.26/70.37 (oxirane-C, CH_2OH), 81.79/82.18, 87.07/87.23, 92.93/93.21, 100.73/100.89, 102.48/102.56, 102.90/102.97 (×, $COCH_3$, acetylene-C, ketal-C), 117.45/118.14, 119.82, 120.29/120.45, 122.93/124.22 (+, aryl-CH, vinyl-CH), 126.86, 133.89, 137.35/137.51 (×, aryl-C, *C*-aryl) and 152.99/153.66 (COTBS); *m/z* (EI) 598 (M^+, 2%), 567 (46), 105 (100) and 73 (54).

5a-(3-*tert*-Butyldimethylsilyloxy-4,5-dimethylphenyl)-4,4,5-trimethoxy-5-[(*Z*)-6-trimethylsilyl-3-hexen-1,5-diynyl]perhydrobenzo[*b*]oxiren-1a-carbaldehyde (17a). To a solution of Dess–Martin periodinane (0.26 g, 0.62 mmol) in CH_2Cl_2 (5 ml) was added a solution of the alcohol **16a** (0.31 g, 0.52 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After being stirred for 3 h at rt, satd. $NaHCO_3$ solution (5 ml) and 20% $Na_2S_2O_3$ solution (5 ml) were added and the mixture was stirred for 15 min. Ether (150 ml) was added and the organic layer was washed with 20% $Na_2S_2O_3$ solution (2 × 20 ml), 10% Na_2CO_3 solution (20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 10 : 1) to give the aldehyde **17a** (0.28 g, 91%) as a colorless oil; TLC (petroleum ether–ethyl acetate, 6 : 1): $R_f = 0.54$; ν_{max}(film)/cm^{-1} 2924 (CH_2), 2143 (acetylene), 1725 (C=O) and 1465 (C=C); δ_H(400 MHz; C_6D_6) 0.12 [9 H, s, $Si(CH_3)_3$], 0.22/0.23 [6 H, s, $Si(CH_3)_2$], 1.03 [9 H, s, $SiC(CH_3)_3$], 1.66 (1 H, dd, *J* 16.2 and 6.1, CH_2), 1.70–1.76 (1 H, m, CH_2), 2.04 (3 H, s, aryl-CH_3), 2.08 (3 H, s, aryl-CH_3), 2.22–2.30 (1 H, m, CH_2), 2.50–2.59 (1 H, m, CH_2), 3.13 (3 H, s, OCH_3), 3.61 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.23 (1 H, d, *J* 11.1, vinyl-H), 5.27 (1 H, d, *J* 11.1, vinyl-H), 7.09 (2 H, br s, aryl-H) and 8.83 (1 H, s, HC=O); δ_C(100 MHz; C_6D_6) −4.47 [+, $Si(CH_3)_2$], −0.43 [+, $Si(CH_3)_3$], 12.23 (+, aryl-CH_3), 18.48 (×, $SiCMe_3$), 19.34 (−, CH_2), 20.26 (+, aryl-CH_3), 21.70 (−, CH_2), 26.22 [+, $SiC(CH_3)_3$], 49.02, 51.88, 54.47 (+, OCH_3), 66.73, 70.47 (oxirane-C), 80.89, 92.14, 95.10, 101.04, 102.36, 102.71 (×$COCH_3$, acetylene-C, ketal-C), 119.08, 119.55, 120.34, 127.09 (+, aryl-CH, vinyl-CH), 131.98, 134.56, 137.62 (×, aryl-C, *C*-aryl), 153.28 (COTBS) and 199.05 (+, C=O); *m/z* (EI) 596 (M^+, 3%), 567 (28), 536 (18), 105 (100) and 73 (94); HRMS for $C_{32}H_{47}O_5Si_2$ (M^+ − CHO) calcd. 567.2965, found 567.2961.

The diastereomer **17b** was obtained by a similar procedure in 71% yield; TLC (petroleum ether–ethyl acetate, 6 : 1): $R_f = 0.52$; δ_H(400 MHz; C_6D_6) 0.10 [9 H, s, $Si(CH_3)_3$], 0.25 [6 H, s, $Si(CH_3)_2$], 1.03 [9 H, s, $SiC(CH_3)_3$], 1.70–1.86 (2 H, m, CH_2), 2.02–2.08 (1 H, m, CH_2), 2.09 (3 H, s, aryl-CH_3), 2.10 (3 H, s, aryl-CH_3), 2.56–2.64 (1 H, m, CH_2), 3.15 (3 H, s, OCH_3), 3.20 (3 H, s, OCH_3), 3.36 (3 H, s, OCH_3), 5.50 (1 H, d, *J* 11.1, vinyl-H), 5.58 (1 H, d, *J* 11.1 vinyl-H), 7.05 (1 H, br s, aryl-H), 7.34 (1 H, br s, aryl-H) and 8.87 (1 H, s, HC=O); δ_C(100 MHz; C_6D_6) −4.33 [+, $Si(CH_3)_2$], −0.54 [+, $Si(CH_3)_3$], 12.34 (+, aryl-CH_3), 18.25 (×, $SiCMe_3$), 19.36 (−, CH_2), 19.96 (+, aryl-CH_3), 23.67 (−, CH_2), 25.82 [+, $SiC(CH_3)_3$], 49.06, 50.63, 54.10 (+, OCH_3), 71.12 (×, oxirane-C), 87.68, 92.41, 100.82, 102.75, 102.96 (×, $COCH_3$, acetylene-C, ketal-C), 119.86, 120.36, 128.31 (+, aryl-CH, vinyl-CH), 128.35, 131.99, 137.86 (×, aryl-C, *C*-aryl), 154.31 (COTBS) and 199.54 (+, C=O); *m/z* (EI) 596 (M^+, 1%), 567 (16), 536 (10), 105 (100) and 73 (76).

14-(3-Hydroxy-4,5-dimethylphenyl)-9,10,10-trimethoxy-13-oxatricyclo[7.3.2.0^{1,14}]-5-tetradecen-5-3,7-diyn-2-ol (19) and 5-[(*Z*)-3-Hexen-1,5-diynyl]-5a-(3-hydroxy-4,5-dimethylphenyl)-4,4,5-trimethoxyperhydrobenzo[*b*]oxirene-1a-carbaldehyde (20a). A solution of the aldehyde **17a** (280 mg, 0.47 mmol) in THF (50 ml) was stirred with molecular sieves (4 Å, 0.23 g) at −20 °C. Subsequently, a solution of tetrabutylammonium fluoride (0.1 M in THF, stirred for 1 h over molecular sieves 4 Å, 230 µl, 23 µmol) was added. After 1 h this was followed by the addition of further tetrabutylammonium fluoride (1.0 M in THF ⩽ 5% H_2O, 0.98 ml, 0.98 mmol) and the mixture was stirred for 2 h at −20 °C. The reaction was quenched with pH 7 buffer solution (10 ml) and diluted with ether (250 ml). The organic phase was washed with water (25 ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether–ethyl acetate, 3.5 : 1 to 1.5 : 1) to give the aldehyde **20a** (100 mg, 52%) and 60 mg of a crude product, which was further purified by preparative HPLC [ethyl acetate–*n*-hexane, 1 : 1, flow rate: 6 ml min^{-1}, amount per run: 20 mg, column: MN LiChrosorb Si 60 (5 µm) Hibar–Merck, pump: LC-10AT Shimadzu] to give the enediyne **19** (42 mg, 22%) as a slightly yellow oil that crystallizes upon cooling.

Enediyne **19**. TLC (petroleum ether–ethyl acetate, 1 : 1): $R_f = 0.23$; δ_H(500 MHz; C_6D_6) 1.86–1.96 (2 H, m, CH_2), 1.90/2.13 (3 H, s, aryl-CH_3), 2.02/2.14 (3 H, s, aryl-CH_3), 2.46–2.58 (1 H, m, CH_2), 2.72–2.82 (1 H, m, CH_2), 3.12/3.15 (3 H, s,

OCH_3), 3.32/3.33 (3 H, s, OCH_3), 3.40/3.43 (3 H, s, OCH_3), 4.24/4.42 (1 H, s, CHOH), 5.36–5.47 (2 H, m, vinyl-H), 5.48 (1 H, s, aryl-OH), 7.35/7.42 (1 H, s, aryl-H), 7.56/7.65 (1 H, s, aryl-H); δ_C(125 MHz; C_6D_6, C-H correlation) 11.02/11.27 (aryl-CH_3), 19.82/20.35 (aryl-CH_3), 48.46/50.89, 53.04/54.55, 56.93/57.15 (OCH_3), 67.00 (CHOH), 113.74/115.54, 122.65, 122.91 and 124.69/125.04 (aryl-CH, vinyl-CH); *m/z* (ESI) 469 ($M^+ - 1 + AcOH$), 409 ($M^+ - 1$); HRMS (FAB with NBA) for $C_{24}H_{26}O_6Na$ (M^+) calcd. 433.1683, found 433.1677.

Compound **20a**. TLC (petroleum ether–ethyl acetate, 1 : 1): $R_f = 0.53$; δ_H(400 MHz; C_6D_6) 1.73–1.79 (1 H, m, CH_2), 2.00 (3 H, s, aryl-CH_3), 2.08 (3 H, s, aryl-CH_3), 2.18–2.26 (1 H, m, CH_2), 2.43–2.48 (1 H, m, CH_2), 2.49–2.57 (1 H, m, CH_2), 2.82–2.88 (1 H, m, acetylene-H), 3.14 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 5.16 (1 H, dd, *J* 10.9 and 2.1, vinyl-H), 5.25 (1 H, dd, *J* 10.9 and 0.8, vinyl-H), 7.00 (2 H, br s, aryl-H) and 8.84 (1 H, s, aldehyde-H); δ_C(100 MHz; C_6D_6) 13.71 (+, aryl-CH_3), 19.21 (−, CH_2), 19.74 (+, aryl-CH_3), 20.39 (−, CH_2), 48.70, 51.50, 54.08 (+, OCH_3), 66.90 (×, oxirane-C), 83.68 (+, acetylene-CH), 80.92, 84.68, 91.63, 100.50, 100.90 (×, $COCH_3$, acetylene-C, ketal-C), 112.71, 115.48, 118.56, 121.44 (+, aryl-CH, vinyl-CH), 127.28, 134.11 (×, aryl-C, *C*-aryl) and 199.45 (+, aldehyde-CH); *m/z* (EI) 381 ($M^+ - CHO$, 14%), 350 (6), 149 (16) and 75 (100). Due to the low amount of compound an elemental analysis was not performed.

Compound **20*b***. The reaction was performed according to the preceding procedure to yield the deprotected phenol aldehyde **20b** (68%); TLC (petroleum ether–ethyl acetate, 1 : 1): $R_f = 0.56$; ν_{max}(film)/cm^{-1} 2920 (CH_2), 2093 (acetylene), 1724 (C=O) and 1455 (C=C); δ_H(500 MHz; C_6D_6) 1.72–1.84 (2 H, m, CH_2), 1.98 (3 H, s, aryl-CH_3), 2.02 (3 H, s, aryl-CH_3), 2.03–2.12 (2 H, m, CH_2), 2.86–2.91 (1 H, m, acetylene-H), 3.02 (3 H, s, OCH_3), 3.16 (3 H, s, OCH_3), 3.39 (3 H, br s, OCH_3), 5.35 (1 H, d, *J* 10.1, vinyl-H), 5.54–5.62 (1 H, m, vinyl-H), 7.36 (1 H, s, aryl-H), 7.40 (1 H, s, aryl-H) and 8.88 (1 H, br s, HC=O); δ_C(100 MHz; C_6D_6) 13.99 (+, aryl-CH_3), 19.34 (−, CH_2), 19.87 (+, aryl-CH_3), 20.76 (−, CH_2), 48.30, 51.76, 53.78 (+, OCH_3), 68.34 (×, oxirane-C), 85.53 (+, acetylene-CH), 81.03, 81.49, 87.31, 100.52 (×, $COCH_3$, acetylene-C, ketal-C), 114.55, 120.02, 121.12, 126.91 (+, aryl-CH, vinyl-CH), 127.52, 131.62, 138.06, 154.69 (×, aryl-C, *C*-aryl) and 199.14 (+, C=O); *m/z* (EI) 381 ($M^+ - CHO$, 38%), 350 ($M^+ - CHO - CH_3O$, 14), 149 (14).

X-Ray structure determination of 19

$C_{24}H_{26}O_6$, *M* 410.45, triclinic, space group $P\bar{1}$ (No. 2), *T* 298(1) K, *a* 7.708(2), *b* 7.999(2), *c* 17.145(5) Å, α 84.41(3), β 82.44(3), γ 76.70(3)°, *U* 1017.3(5) Å^3 [by refinement of 2000 reflections automatically centered with $2.8 \leqslant \theta \leqslant 24.0°$, λ_0 (MoK_α) 0.71073 Å], $Z = 2$, D_x 1.340 g cm^{-3}, size 0.40 × 0.30 × 0.30 mm, μ 0.096 mm^{-1}. Data collection was carried out on a Stoe IPDS diffractometer with area detector, 100 frames each oscillating the crystal 1.5° around the φ axis. 4857 reflections were measured with $2.73 \leqslant \theta \leqslant 24.02°$, 2931 unique reflections (R_{int}: 0.0984), giving 2306 observed reflections with $I \geqslant 2\sigma(I)$ used to refine 315 parameters. No correction for absorption was applied, no decay during the measurement was observed. The structure was solved using direct methods (SHELXS-86)[28] and refined on F^2 (SHELXL-93)[29] with all non-H atoms anisotropic. Hydrogen atoms were located from the difference Fourier map and refined isotropically, except those of the methyl groups whose positions were determined initially by rotation in 15° steps around the C–C axes and then fixed in their optimized positions. Final *R* values: R_1 (obs.) 0.0725, R_1 (all data) 0.0864, wR_2 (obs.) 0.2039, wR_2 (all data) 0.2229, *S* (all data) 1.060. Residual electron density (peak/hole 0.345/−0.267).

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