Pergamon

Tetrahedron, Vol. 53, No. 27, pp. 9159-9168, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00616-9

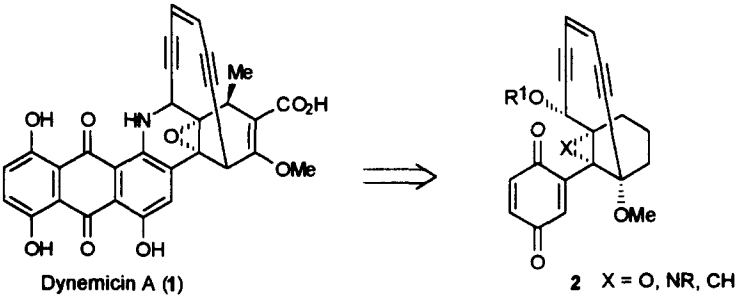
Cross-coupling Approach towards Dynemicin Analogs without the Nitrogen

Folkert Boße, Ashok Rao Tunoori and Martin E. Maier*

Martin-Luther-Universität Halle-Wittenberg, Fachbereich Chemie, Institut für Organische Chemie
Kurt-Mothes-Strasse 2, D-06120 Halle (Saale), Germany

Abstract: Utilizing a cross-coupling reaction between the arylstannane **5** and the iodoenone **7**, the arylcyclohexenone **8** was prepared. This compound was then transformed into the enediyne aldehydes **16a,b**. Treatment of **16a** with cat. amounts of TBAF gave rise to the macrocyclic dynemicin analog **17a**. This was converted to the phenolic enediyne **18**. © 1997 Elsevier Science Ltd.

Dynemicin A[1,2] is a member of the family of enediyne antitumor antibiotics.[3] Among these compounds it is unique in that it represents a hybrid between an anthraquinone and a bicyclic enediyne. The antitumor activity is caused by the enediyne structure which can undergo a cycloaromatization to a cytotoxic diradical. However, to prevent a premature diradical formation, dynemicin A has been equipped with a blocking group that stabilizes the enediyne structure. This kinetic stabilization of the enediyne is due to the *trans*-anellated epoxide which causes a highly strained transition state of the Bergman cyclization.[4] The activation, that is opening of the epoxide is initiated by a two-electron reduction of the quinone.[3b] In designing structurally simple analogs,[2,5] several issues come to mind: Which functional groups on the aryl system or ring E are essential for binding to DNA? What is the role of the nitrogen atom? To answer some of these questions we designed compounds that lack the nitrogen heterocycle. In principle, these analogs of type **2** should undergo activation upon reduction of the quinone. Instead of the epoxide, one also could use other small rings as blocking device.

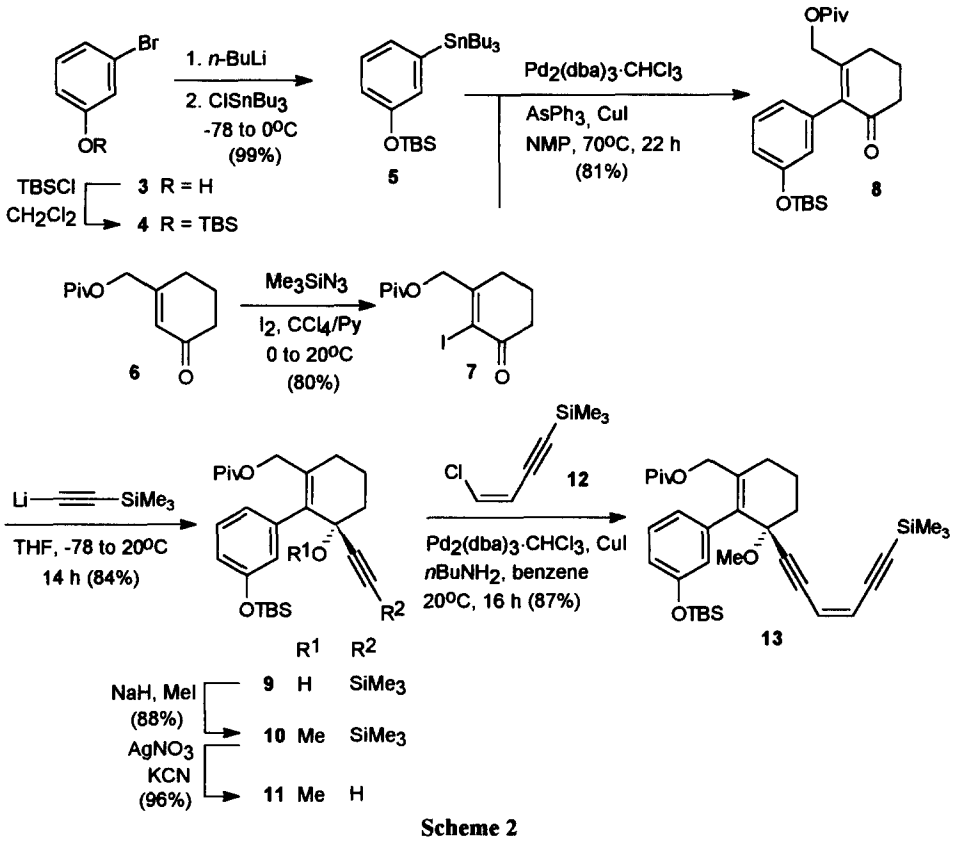


Scheme 1

In a forward direction, the quinone will be generated from an electron-rich aryl system through an oxidation reaction. Because the aryl ring should not be too electron-rich to prevent an unwanted epoxide opening during the synthesis and at the same time will have to be easy to oxidize in the final step, the choice of the aryl ring is crucial. Therefore, we selected a 3-*tert*-butyldimethylsilyloxyphenyl group as a quinone precursor. In a recent paper we showed that arylmetal compounds can be coupled to functionalized cyclohexenes with a leaving group (iodide or triflate) at the vinylic position.[6] Now we describe on the basis of this strategy the construction of an advanced dynemicin analog **18**.

The synthesis commenced with 3-bromophenol (**3**) which was first silylated to yield **4**[7] and then converted to the arylstannane **5** (1.05 equiv *n*-BuLi, -78°C, then 1.05 equiv $ClSnBu_3$). The other coupling partner **7** was prepared from the enone **6**. To introduce a iodine in the 2-position, **6**[8] was treated with trimethylsilyl azide in tetrachloromethane followed by the addition of iodine to provide **7** in good yield.[9] Other methods for

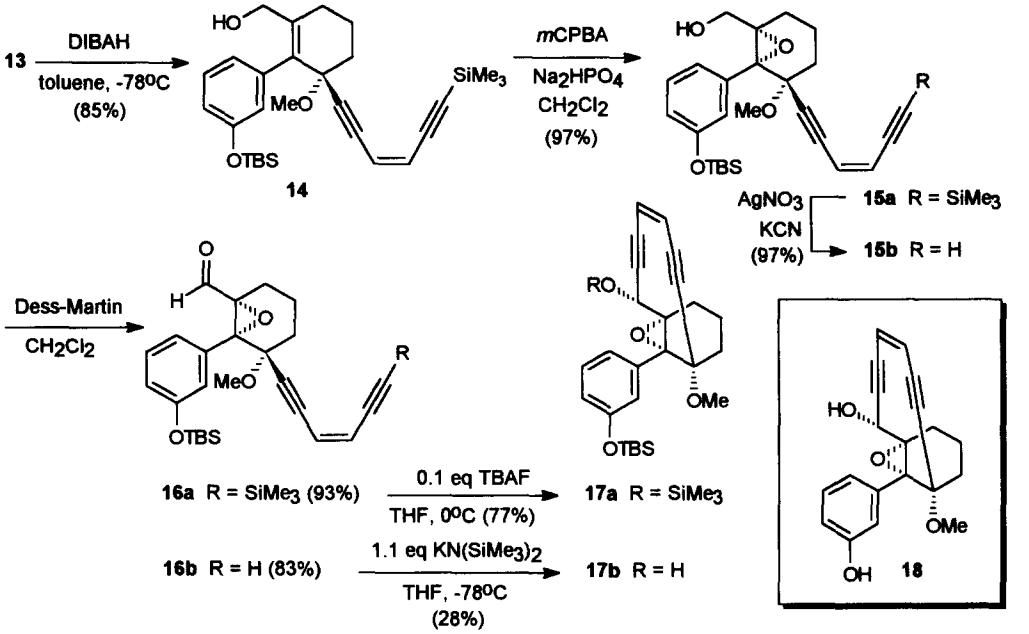
the iodination were less efficient.[10] The palladium-catalyzed cross-coupling reaction of **5** (1.1 equiv) with the iodoenone **7**[6] in *N*-methyl-2-pyrrolidinone (NMP) provided the 2-arylcyclohexenone **8** in excellent yield on a 10 g scale.[11] The construction of the enediyne started with the addition of lithium trimethylsilylacetylide to the enone **8**, providing the alcohol **9**. Then the hydroxyl group of **9** was protected as methyl ether under carefully controlled conditions (1.5 equiv NaH, 3.0 equiv 1,3-dimethyl-2-imidazolidinone, 4.0 equiv MeI, THF, 0 → 20°C, 3 h). Some starting material (9%) was recovered from this reaction.



Scheme 2

Selective cleavage of the C-$SiMe_3$ bond to give **11** was possible with silver nitrate and potassium cyanide[5b]. Coupling of the alkyne **11** with the vinyl chloride **12**[12] in the presence of copper(I) iodide and a Pd(0) catalyst completed the synthesis of the enediyne **13**.[13] Reductive removal of the pivaloyl protecting group (DIBAH) gave the allyl alcohol **14** which was converted to the epoxide **15a** (single diastereomer) with buffered *m*-chloroperbenzoic acid (*m*CPBA). From **15a** two cyclization substrates **16a** and **16b** were prepared. Thus, oxidation of the alcohol **15a** with the Dess-Martin reagent[14] gave rise to the cyclization substrate **16a**. On the other hand, removal of the acetylenic $SiMe_3$ group as above furnished the enediyne **15b** whose oxidation provided **16b**. The crucial cyclization was examined first with compound **16b**. While the reactions appear very clean on TLC, the isolated yields so far are moderate. The best result was obtained with 1.1 equiv of $LiN(SiMe_3)_2$ as base (0.01 M in THF, -78°C, 2 h) which provided the macrocycle **17b** in 28% yield (+28% recovered starting material). A much better result was realized from the cyclization of **16a**. Although **16a** contains two silyl groups, treatment of **16a** with catalytic amounts of anhydrous TBAF[15] delivered the macrocycle **17a** in 77% isolated yield. Only one diastereomer at the new stereogenic center was formed. On the basis of our previous work,[16] the stereochemistry was assigned as shown. Due to steric hindrance around the aryl-cyclohexyl C-C-bond, **17a** exists as a mixture of two rotamers (≈ 54:46 ratio in C_6D_6). Treatment of **17a**

with potassium carbonate in methanol provided **17b**. Removal of the TBS group to give the enediyne **18** was accomplished with TBAF. Alternatively, the macrocycle **18** is accessible directly from **16a** by reaction with catalytic amounts of anhydrous TBAF followed by the addition of water-containing TBAF in 78% yield. The mass spectrum of **18** showed the M^+-peak at m/z = 322, supporting the cyclization reaction. In addition, there is a characteristic fragment at m/z = 121 which corresponds to $HOC_6H_4CO^+$.



Scheme 3

In summary, we developed an efficient route to dynemicin A analogs that lack the nitrogen heterocycle. The synthetic scheme is compatible with a silylprotected phenol ring. This should allow for a mild oxidation to the quinone.[17] In addition, the secondary hydroxyl group might be replaced in a S_N2 reaction with a nitrogen nucleophile, thus opening a route to quinone imines.[5c,18] Studies along these lines are currently underway in our laboratory.

EXPERIMENTAL

General

^1H NMR: Varian Unity 500 (500 MHz). - ^{13}C NMR: Varian Unity 500 (125 MHz); all spectra were recorded in $CDCl_3$ or C_6D_6 as solvent. - The signal multiplicities were determined by means of the DEPT and APT technique; + for CH or CH_3, - for CH_2, × for C. - IR: Carl Zeiss Jena SPECORD IR 75. - 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: $Pd_2(dba)_3 \cdot CHCl_3$,[19] trimethylsilylacetylene,[20] Dess-Martin periodinane,[14] enone **6**,[8] vinyl chloride **12**.[12]

1-Bromo-3-(tert-butyldimethylsilyloxy)benzene (**4**):[7] To a solution of 3-bromophenol (25.0 g, 0.145 mol) in CH_2Cl_2 (150 ml) was added imidazole (25.0 g, 0.361 mol) at 0°C. After 10 min *tert*-butyldimethylsilyl chloride (24.0 g, 0.159 mol) was added and the mixture was stirred for 14 h at room temp. The mixture was

diluted with ether (350 ml) and filtered. The filtrate was washed with satd. NH_4Cl solution (4 × 50 ml), satd. $NaHCO_3$ solution (50 ml) and brine (50 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **4** as a colorless oil (40.8 g, 98%) which was used without further purification. - TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.82. - IR (film): $\tilde{\nu}_{max}$ = 3067 cm^{-1}, 2956, 2932. - ^1H NMR (500 MHz, $CDCl_3$): δ = 0.19 [s, 6 H, $Si(CH_3)_2$], 0.97 [s, 9 H, $C(CH_3)_3$], 6.73-6.76 (m, 1 H, aryl-H), 6.99-7.00 (m, 1 H, aryl-H), 7.06-7.07 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = -4.48 [+, $Si(CH_3)_2$], 18.16 (×, CMe_3), 25.59 [+, $C(CH_3)_3$], 118.80 (+, aryl-C), 122.44 (×, aryl-CBr), 123.50, 124.45, 130.39 (+, aryl-C), 156.51 (×, aryl-COTBS). - MS (EI), *m/z* (%): 288 (17) [M^+, ^{81}Br], 231 (100) [M^+ - CMe_3], 201 (3) [M^+ - CMe_3 - 2 Me].

3-tert-Butyldimethylsilyloxy-(tributylstannyl)benzene (**5**): To a cooled (-78°C) solution of bromide **4** (40.8 g, 0.142 mol) in THF (200 ml) was added *n*-BuLi (1.6 M in hexane, 93 ml, 0.149 mol). After stirring for 10 min *n*-Bu_3SnCl (48.5 g, 0.149 mol) was added dropwise and the solution was stirred for 5 h during which time it was allowed to warm to 0°C. The mixture was diluted with petroleum ether (500 ml), washed with water (100 ml) and brine (100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give stannane **5** (69.9 g, 99%) as a colorless oil which was used without further purification. - TLC (petroleum ether): R_f = 0.85. - IR (film): $\tilde{\nu}_{max}$ = 3019 cm^{-1}, 2957, 2928, 1577. - ^1H NMR (500 MHz, $CDCl_3$): δ = 0.19 [s, 6 H, $Si(CH_3)_2$], 0.86-1.04 (m, 6 H, $SnCH_2$), 0.88 (t, ^3J = 7.3 Hz, 9 H, CH_2CH_3), 0.98 [s, 9 H, $C(CH_3)_3$], 1.27-1.36 (m, 6 H, CH_2), 1.44-1.56 (m, 6 H, CH_2), 6.74-6.76 (m, 1 H, aryl-H), 6.93-6.94 (m, 1 H, aryl-H), 7.00-7.01 (m, 1 H, aryl-H), 7.16-7.19 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = -4.35 [+, $Si(CH_3)_2$], 9.65 (-, $SnCH_2$), 13.66 (+, CH_2CH_3), 18.27 (×, CMe_3), 25.76 [+, $C(CH_3)_3$], 27.37, 29.12 (-, CH_2), 119.77, 127.82, 128.77, 129.28 (+, aryl-C), 143.14, 155.11 (×, aryl-C). - MS (EI), *m/z* (%): 498 (0.5) [M^+, ^{120}Sn], 441 (100) [M^+ - Bu].

2-Iodo-3-oxo-1-cyclohexenylmethyl pivalate (**7**): To a solution of enone **6** (20.2 g, 96.1 mmol) in CCl_4 was added trimethylsilyl azide (22.1 g, 192 mmol) at 0°C. After 3 h a solution of iodine (97.5 g, 384 mmol) in CCl_4/pyridine (200 ml, 1:1) was added. After being stirred for 22 h at room temp., the mixture was diluted with ether (1 l), washed with water (2 × 150 ml), 20% aqueous $Na_2S_2O_3$ (3 × 100 ml) and brine (100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in heptane, concentrated under reduced pressure to remove the pyridine and then purified by flash chromatography (petroleum ether/ethyl acetate, 6:1 to petroleum ether/ethyl acetate, 4:1) to give the iodoenone **7** (25.9 g, 80%) as a pale yellow solid of m.p. 46-47°C. For spectroscopic data, see ref[6].

2-[3-(tert-Butyldimethylsilyloxy)phenyl]-3-oxo-1-cyclohexenylmethyl pivalate (**8**): A suspension of iodoenone **7** (8.10 g, 24.0 mmol), CuI (3.44 g, 18.1 mmol), $AsPh_3$ (1.48 g, 4.82 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (0.623 g, 0.602 mmol) in NMP (150 ml) was degassed and stirred for 15 min. The flask was lowered into an oil-bath (70°C) and stannane **5** (13.2 g, 26.5 mmol) was added. The solution was stirred for 22 h at 70°C. After being cooled to room temp. the mixture was diluted with ether (1 l), washed with water (4 × 100 ml) and brine (100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether to petroleum ether/ethyl acetate, 4:1) to give the enone **8** (8.12 g, 81%) as a pale yellow oil. - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.59. - IR (film): $\tilde{\nu}_{max}$ = 3063 cm^{-1}, 2957, 2859, 1732, 1682. - ^1H NMR (500 MHz, C_6D_6): δ = 0.16 (s, 6 H, $Si(CH_3)_2$], 0.99 (s, 9 H, $C(CH_3)_3$], 1.47-1.52 (m, 2 H, CH_2), 2.01-2.03 (m, 2 H, CH_2), 2.17-2.19 (m, 2 H, CH_2), 4.57 (s, 2 H, CH_2OPiv), 6.76-6.81 (m, 1 H, aryl-H), 6.82-6.83 (m, 1 H, aryl-H), 6.89-6.90 (m, 1 H, aryl-H), 7.08-7.11 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.36 [+, $Si(CH_3)_2$], 18.35 (×, $SiCMe_3$), 22.15 (-, CH_2), 25.86 [+, $SiC(CH_3)_3$], 27.19 (-, CH_2), 27.22 [+, $C(O)C(CH_3)_3$], 38.20 (-, CH_2), 39.80 [×, $C(O)CMe_3$], 64.94 (-, CH_2OPiv), 119.72, 122.35, 123.43, 129.26 (+, aryl-C), 136.43, 139.04, 151.92, 155.81 (×, aryl-C, vinyl-C), 177.09 [×, C(O)*t*Bu], 195.72 (×, CO). - MS (EI), *m/z* (%): 416 (5) [M^+], 359 (21) [M^+ - CMe_3], 315 (12) [M^+ - CO_2tBu], 159 (100). - $C_{24}H_{36}O_4Si$ (416.6): calcd. C 69.19, H 8.71; found C 68.98, H 8.93.

2-[3-(tert-Butyldimethylsilyloxy)phenyl]-3-hydroxy-3-(2-trimethylsilyl-1-ethynyl)-1-cyclohexenylmethyl pivalate (**9**): To a solution of trimethylsilylacetylene (6.39 g, 65.1 mmol) in THF (140 ml) was

added *n*-BuLi (1.6 M in hexane, 39 ml, 62.4 mmol) at -50°C. The mixture was stirred for 1 h, cooled to -78°C and then a solution of the enone **8** (22.6 g, 54.2 mmol) in THF (50 ml) was added dropwise. After stirring for 2 h the mixture was treated with satd. $NaHCO_3$ solution (50 ml) and allowed to warm to room temp. The mixture was diluted with ether (1 l), the phases were separated and the organic phase was washed with brine (100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1 to petroleum ether/ethyl acetate, 3:1) to give the alcohol **9** (23.4 g, 84%) as a colorless oil. - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.65. - IR (film): $\tilde{\nu}_{max}$ = 3478 cm^{-1}, 2958, 2933, 2162, 1731. - ^1H NMR (500 MHz, C_6D_6): δ = 0.14 [s, 9 H, $Si(CH_3)_3$], 0.15, 0.16 [2 s, 3 H each, $Si(CH_3)_2$], 1.00 [s, 9 H, $SiC(CH_3)_3$], 1.09 [s, 9 H, $C(O)C(CH_3)_3$], 1.70-1.75 (m, 1 H, CH_2), 1.86-1.91 (m, 1 H, CH_2), 2.02-2.07 (m, 3 H, CH_2), 2.25-2.29 (m, 1 H, CH_2), 4.45 (s, 2 H, CH_2OPiv), 6.80-6.82 (m, 1 H, aryl-H), 7.07-7.09 (m, 3 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.36 [+, $Si(CH_3)_2$], -0.01 [+, $Si(CH_3)_3$], 18.36 (×, $SiCMe_3$), 19.49 (-, CH_2), 25.87 [+, $SiC(CH_3)_3$], 26.96 (-, CH_2), 27.27 [+, $C(O)C(CH_3)_3$], 38.33 (-, CH_2), 38.78 [×, $C(O)CMe_3$], 65.59 (-, CH_2OPiv), 68.65 (×, COH), 89.78, 109.94 (×, alkyne-C), 119.58, 122.91, 124.08, 129.20 (+, aryl-C), 132.52, 138.70, 139.88, 155.75 (×, aryl-C, vinyl-C), 177.20 [×, C(O)*t*Bu]. - MS (EI), *m/z* (%): 514 (1) [M^+], 557 (18) [M^+ - CMe_3], 439 (17) [M^+ - CMe_3 - H_2O], 159 (100). - $C_{29}H_{46}O_4Si_2$ (514.8): calcd. C 67.65, H 9.01; found C 67.63, H 8.88.

2-[3-(tert-Butyldimethylsilyloxy)phenyl]-3-methoxy-3-(2-trimethylsilyl-1-ethynyl-1-cyclohexenylmethyl pivalate (**10**): To a solution of the alcohol **9** (13.7 g, 26.6 mmol) in THF (175 ml) was added NaH (0.828 g, 34.5 mmol) at 0°C. After 5 min 1,3-dimethyl-2-imidazolidinone (9.09 g, 79.7 mmol) and methyl iodide (15.1 g, 106 mmol) were added, and the mixture was stirred for 1 h at room temp. It was cooled again to 0°C, neutralized with pH-7 buffer solution (100 ml) and diluted with ether (1 l). The organic phase was washed with water (2 × 100 ml) and brine (100 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1 to petroleum ether/ethyl acetate, 8:1) to give the ether **10** (12.3 g, 88%) as a colorless solid of m.p. 51°C, and starting material **9** (1.2 g, 9%). - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.76. - IR (KBr): $\tilde{\nu}_{max}$ = 2958 cm^{-1}, 2931, 2825, 2164, 1728. - ^1H NMR (500 MHz, C_6D_6): δ = 0.10 [s, 9 H, $Si(CH_3)_3$], 0.17, 0.18 [2 s, 3 H each, $Si(CH_3)_2$], 1.01 [s, 9 H, $SiC(CH_3)_3$], 1.10 [s, 9 H, $C(O)C(CH_3)_3$], 1.64-1.70 (m, 1 H, CH_2), 1.72-1.80 (m, 1 H, CH_2), 1.92-1.97 (m, 1 H, CH_2), 2.01-2.10 (m, 3 H, CH_2), 3.25 (s, 3 H, OCH_3), 4.52 (d, ^2J = 12.3 Hz, 1 H, CH_2OPiv), 4.57 (d, ^2J = 12.3 Hz, 1 H, CH_2OPiv), 6.79-6.81 (m, 1 H, aryl-H), 7.09-7.12 (m, 1 H, aryl-H), 7.13-7.14 (m, 1 H, aryl-H), 7.20-7.21 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.30/-4.25 [+, $Si(CH_3)_2$], -0.07 [+, $Si(CH_3)_3$], 18.40 (×, $SiCMe_3$), 18.45 (-, CH_2), 25.93 [+, $SiC(CH_3)_3$], 27.00 (-, CH_2), 27.30 [+, $C(O)C(CH_3)_3$], 33.89 (-, CH_2), 38.79 [×, $C(O)CMe_3$], 51.33 (+, OCH_3), 65.74 (-, CH_2OPiv), 74.64 (×, COMe), 92.63, 106.52 (×, alkyne-C), 119.05, 122.81, 124.26, 128.52 (+, aryl-C), 133.24, 139.14, 140.26, 155.28 (×, aryl-C, vinyl-C), 177.24 [×, C(O)*t*Bu]. - MS (EI), *m/z* (%): 528 (3) [M^+], 513 (4) [M^+ - Me], 439 (18) [M^+ - CMe_3 - MeOH], 413 (13) [M^+ - $Me_3CCO_2CH_2$], 159 (100). - $C_{30}H_{48}O_4Si_2$ (528.9): calcd. C 68.13, H 9.15; found C 67.91, H 9.17.

2-[3-(tert-Butyldimethylsilyloxy)phenyl]-3-(1-ethynyl)-3-methoxy-1-cyclohexenylmethyl pivalate (**11**): To a solution of the acetylene **10** (12.3 g, 23.3 mmol) in THF/ethanol/water (240 ml, 4:1:1) was added silver nitrate (15.8 g, 93.2 mmol) at 0°C. After 25 min KCN (10.6 g, 163 mmol) was added and the solution was stirred for 1 h at room temp. The mixture was diluted with ether (1.2 l) and washed with water (2 × 100 ml) and brine (2 × 100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to give the acetylene **11** as a colorless solid (10.2 g, 96%) of m.p. 74°C. - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.56. - IR (KBr): $\tilde{\nu}_{max}$ = 3272 cm^{-1}, 2938, 2863, 2102, 1732. - ^1H NMR (500 MHz, C_6D_6): δ = 0.16 [s, 6 H, $Si(CH_3)_2$], 1.00 [s, 9 H, $SiC(CH_3)_3$], 1.11 [s, 9 H, $C(O)C(CH_3)_3$], 1.67-1.69 (m, 2 H, CH_2), 1.92-1.96 (m, 2 H, CH_2), 2.00-2.11 (m, 3 H, CH_2, alkyne-H), 3.16 (s, 3 H, OCH_3), 4.50 (d, ^2J = 12.2 Hz, 1 H, CH_2OPiv), 4.54 (d, ^2J = 12.2 Hz, 1 H, CH_2OPiv), 6.79-6.81 (m, 1 H, aryl-H), 7.08-7.13 (m, 2 H, aryl-H), 7.15-7.17 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.33/-4.30 [+, $Si(CH_3)_2$], 18.41 (×, $SiCMe_3$), 18.52 (-, CH_2), 25.90 [+, $SiC(CH_3)_3$], 26.93 (-, CH_2), 27.29 [+, $C(O)C(CH_3)_3$], 34.25 (-, CH_2), 38.78 [×, $C(O)CMe_3$], 51.29

(+, OCH_3), 65.65 (-, CH_2OPiv), 74.16 (×, COMe), 76.15 (+, alkyne-C), 83.98 (×, alkyne-C), 119.31, 122.69, 124.15, 128.29 (+, aryl-C), 133.41, 138.92, 139.85, 155.30 (×, aryl-C, vinyl-C), 177.25 [×, C(O)*t*Bu]. - MS (EI), *m/z* (%): 456 (0.7) [M^+], 425 (1) [M^+ + H - MeOH], 409 (0.3) [M^+ - CH_3 - MeOH], 467 (6) [M^+ - MeOH - CMe_3], 354 (62) [M^+ - Me_3CCO_2H], 159 (100). - $C_{27}H_{40}O_4Si$ (456.7): calcd. C 71.01, H 8.83; found C 71.04, H 8.71.

2-[3-(tert-Butyldimethylsilyloxy)phenyl]-3-methoxy-3-[(Z)-6-trimethylsilyl-3-hexene-1,5-diynyl]-1-cyclohexenylmethyl pivalate (**13**): To a solution of the acetylene **11** (9.72 g, 21.3 mmol) in dry degassed benzene (200 ml) were added CuI (0.608 g, 3.19 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.551 g, 1.06 mmol), *n*-butylamine (7.79 g, 106 mmol) and (4-chloro-3-buten-1-ynyl)-trimethylsilane **12**[12] at 0°C. After 1 h the cooling bath was removed and the solution was stirred for 20 h at room temp. The mixture was diluted with ether (1 l), washed with water (4 × 200 ml) and brine (100 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 40:1) to give the enediyne **13** as a yellow oil (9.54 g, 77%). - TLC (petroleum ether/ethyl acetate, 20:1): R_f = 0.69. - IR (film): $\tilde{\nu}_{max}$ = 3027 cm^{-1}, 2957, 2899, 2824, 2148, 1731. - ^1H NMR (500 MHz, C_6D_6): δ = 0.16 [s, 9 H, $Si(CH_3)_3$], 0.17 [s, 6 H, $Si(CH_3)_2$], 1.01 [s, 9 H, $SiC(CH_3)_3$], 1.13 [s, 9 H, $C(O)C(CH_3)_3$], 1.79-1.83 (m, 2 H, CH_2), 2.08-2.10 (m, 1 H, CH_2), 2.12-2.16 (m, 3 H, CH_2), 3.31 (s, 3 H, OCH_3), 4.57 (d, ^2J = 12.3 Hz, 1 H, CH_2OPiv), 4.59 (d, ^2J = 12.3 Hz, 1 H, CH_2OPiv), 5.46 (s, 2 H, vinyl-H), 6.79-6.81 (m, 1 H, aryl-H), 7.09-7.12 (m, 1 H, aryl-H), 7.17-7.20 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.28 [+, $Si(CH_3)_2$], -0.14 [+, $Si(CH_3)_3$], 18.41 (×, $SiCMe_3$), 18.98 (-, CH_2), 25.93 [+, $SiC(CH_3)_3$], 27.10 (-, CH_2), 27.32 [+, $C(O)C(CH_3)_3$], 34.83 (-, CH_2), 38.81 [×, $C(O)CMe_3$], 51.77 (+, OCH_3), 65.69 (-, CH_2OPiv), 75.09 (×, COMe), 85.92, 98.26, 102.64, 102.95 (×, alkyne-C), 119.31, 119.70, 120.40, 122.71, 124.19, 128.76 (+, aryl-C, vinyl-C), 133.31, 139.23, 139.93, 155.36 (×, aryl-C, vinyl-C), 177.28 [×, C(O)*t*Bu]. - MS (EI), *m/z* (%): 578 (3) [M^+], 546 (33) [M^+ - MeOH], 476 (28) [M^+ - Me_3CCO_2H], 463 (25) [M^+ - $Me_3CCO_2CH_2$], 444 (30) [M^+ - MeOH - Me_3CCO_2H], 73 (100). - $C_{34}H_{50}O_4Si_2$ (578.9): calcd. C 70.54, H 8.71; found C 70.51, H 8.73.

2-[3-(tert-Butyldimethylsilyloxy)phenyl]-3-methoxy-3-[(Z)-6-trimethylsilyl-3-hexene-1,5-diynyl]-1-cyclohexenylmethanol (**14**): To a solution of the ester **13** (8.39 g, 14.5 mmol) in toluene (300 ml) was added DIBAH (1.0 M in CH_2Cl_2, 32 ml, 32 mmol) at -78°C. After 1 h ethyl acetate (10 ml) was added and the mixture was warmed to room temp. before it was diluted with ether (700 ml) and washed with satd. sodium potassium tartrate solution (2 × 100 ml). The aqueous phase was extracted with ether (150 ml) and the combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give the alcohol **14** as a colorless oil (6.09 g, 85%). - TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.18. - IR (film): $\tilde{\nu}_{max}$ = 3387 cm^{-1}, 3026, 2956, 2897, 2824, 2148. - ^1H NMR (500 MHz, C_6D_6): δ = 0.16 [s, 9 H, $Si(CH_3)_3$], 0.17 [s, 6 H, $Si(CH_3)_2$], 1.01 [s, 9 H, $SiC(CH_3)_3$], 1.77-1.87 (m, 2 H, CH_2), 2.04-2.08 (m, 1 H, CH_2), 2.13-2.18 (m, 1 H, CH_2), 2.21-2.23 (m, 2 H, CH_2), 3.32 (s, 3 H, OCH_3), 3.79 (s, br., 2 H, CH_2OH), 5.48 (s, 2 H, vinyl-H), 6.81-6.84 (m, 1 H, aryl-H), 7.10-7.14 (m, 2 H, aryl-H), 7.16-7.17 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.28 [+, $Si(CH_3)_2$], -0.14 [+, $Si(CH_3)_3$], 18.41 (×, $SiCMe_3$), 19.10 (-, CH_2), 25.92 [+, $SiC(CH_3)_3$], 26.98 (-, CH_2), 34.95 (-, CH_2), 51.74 (+, OCH_3), 64.06 (-, CH_2OH), 75.23 (×, COMe), 85.71, 98.69, 102.60, 102.98 (×, alkyne-C), 119.02, 119.57, 120.49, 122.84, 124.32, 128.66 (+, aryl-C, vinyl-C), 136.85, 137.58, 140.54, 155.31 (×, aryl-C, vinyl-C). - MS (EI), *m/z* (%): 494 (3) [M^+], 476 (3) [M^+ - H_2O], 462 (73) [M^+ - MeOH], 405 (11) [M^+ - MeOH - CMe_3], 73 (100). - $C_{29}H_{42}O_3Si_2$ (494.8): calcd. C 70.54, H 8.71; found C 70.51, H 8.73.

5a-[3-(tert-Butyldimethylsilyloxy)phenyl]-5-methoxy-5-[(Z)-6-trimethylsilyl-3-hexene-1,5-diynyl]perhydrobenzo[b]oxiren-1-ylmethanol (**15a**): To a solution of the allyl alcohol **14** (5.07 g, 10.2 mmol) in CH_2Cl_2 (200 ml) were added Na_2HPO_4 (22.0 g, 61.5 mmol) and *m*CPBA (2.65 g, 15.4 mmol) at 0°C. The mixture was stirred for 18 h during which time the temp. was allowed to reach room temp. Ether (600 ml) was added and the mixture was washed with 20% Na_2SO_3 solution (2 × 100 ml), 10% Na_2CO_3 solution (100 ml) and brine (100 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was puri-

fied by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give the epoxide **15a** as a colorless oil (5.03 g, 97%). - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.44. - IR (film): $\tilde{\nu}_{max}$ = 3475 cm^{-1}, 3031, 2956, 2897, 2828, 2147. - ^1H NMR (500 MHz, C_6D_6): δ = 0.14 [s, 9 H, $Si(CH_3)_3$], 0.16 [s, 6 H, $Si(CH_3)_2$], 0.99 [s, 9 H, $SiC(CH_3)_3$], 1.52-1.55 (m, 1 H, CH_2), 1.86-2.16 (m, 5 H, CH_2), 3.12 (d, ^2J = 11.5 Hz, 1 H, CH_2OH), 3.21 (d, ^2J = 11.5 Hz, 1 H, CH_2OH), 3.27 (s, 3 H, OCH_3), 5.43-5.54 (m, 2 H, vinyl-H), 6.79-6.82 (m, 1 H, aryl-H), 7.08-7.11 (m, 1 H, aryl-H), 7.45 (s, br., 2 H, aryl-CH). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.28 [+, $Si(CH_3)_2$], -0.20 [+, $Si(CH_3)_3$], 18.36 (×, $SiCMe_3$), 19.34, 23.60 (-, CH_2), 25.89 [+, $SiC(CH_3)_3$], 31.27 (-, CH_2), 52.04 (+, OCH_3), 65.93 (-, CH_2OH), 67.97, 70.72, 78.38 (×, oxirane-C, COMe), 87.20, 96.73, 102.67, 103.17 (×, alkyne-C), 119.75, 120.18, 127.18, 127.37, 127.57, 128.10 (+, aryl-C, vinyl-C), 138.23 (×, aryl-C). - MS (EI), *m/z* (%): 510 (10) [M^+], 495 (13) [M^+ - CH_3], 480 (100) [M^+ - 2 CH_3], 463 (11) [M^+ - MeOH - CH_3], 449 (88), 235 (41) [$TBSOC_6H_4CO^+$]. - HRMS for $C_{29}H_{42}O_4Si_2$ (M^+) calcd. 510.2621, found 510.2606. - $C_{29}H_{42}O_4Si_2$ (510.8): calcd. C 68.19, H 8.29; found C 68.03, H 8.49.

5a-[3-(tert-Butyldimethylsilyloxy)phenyl]-5-[(Z)-3-hexene-1,5-diynyl]-5-methoxyperhydrobenzo[b]-oxiren-1-ylmethanol (**15b**): To a solution of the enediyne **15a** (355 mg, 0.695 mmol) in THF/ethanol/water (15 ml, 4:1:1) was added silver nitrate (472 mg, 2.78 mmol) at 0°C. After 20 min KCN (317 mg, 4.86 mmol) was added and the solution was stirred for 0.5 h at 0°C and for 0.5 h at room temp., diluted with ether (200 ml), washed with water (2 × 20 ml) and brine (20 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give the enediyne **15b** as a colorless oil (296 mg, 97%). - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.38. - IR (film): $\tilde{\nu}_{max}$ = 3456 cm^{-1}, 3286, 3035, 2933, 2828, 2093. - ^1H NMR (500 MHz, C_6D_6): δ = 0.15 [s, 6 H, $Si(CH_3)_2$], 0.99 [s, 9 H, $SiC(CH_3)_3$], 1.48-1.52 (m, 1 H, CH_2), 1.85-2.14 (m, 5 H, CH_2), 3.04 (d, ^3J = 2.4 Hz, 1 H, alkyne-H), 3.13-3.22 (m, 5 H, CH_2OH, OCH_3), 5.40-5.52 (m, 2 H, vinyl-H), 6.77-6.79 (m, 1 H, aryl-H), 7.07-7.08 (m, 1 H, aryl-H), 7.44-7.48 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.36/-4.30 [+, $Si(CH_3)_2$], 18.37 (×, $SiCMe_3$), 19.06, 23.39 (-, CH_2), 25.89 [+, $SiC(CH_3)_3$], 31.06 (-, CH_2), 52.04 (+, OCH_3), 65.91 (-, CH_2OH), 67.99, 70.88, 78.38 (×, oxirane-C, COMe), 81.12 (+, alkyne-C), 85.58, 87.00, 96.72 (×, alkyne-C), 119.41, 119.73, 121.11, 128.92 (+, aryl-C, vinyl-C). - MS (EI), *m/z* (%): 438 (1) [M^+], 423 (1) [M^+ - CH_3], 407 (90) [M^+ - H - 2 CH_3], 376 (12) [M^+ - MeOH - CH_3], 293 (67), 235 (58) [$TBSOC_6H_4CO^+$], 73 (100). - $C_{26}H_{34}O_4Si$ (438.6): calcd. C 71.19, H 7.81; found C 70.88, H 7.83.

5a-[3-(tert-Butyldimethylsilyloxy)phenyl]-5-methoxy-5-[(Z)-6-trimethylsilyl-3-hexene-1,5-diynyl]perhydrobenzo[b]oxiren-1a-carbaldehyde (**16a**): To a solution of Dess-Martin periodinane (3.92 g, 9.23 mmol) in CH_2Cl_2 (90 ml) was added a solution of the alcohol **15a** (3.93 g, 7.69 mmol) in CH_2Cl_2 (30 ml) at 0°C. After being stirred for 3 h at room temp. satd. $NaHCO_3$ solution (30 ml) and 20% $Na_2S_2O_3$ solution (30 ml) were added and the mixture was stirred for 15 min. Ether (500 ml) was added and the organic phase was washed with 20% $Na_2S_2O_3$ solution (2 × 75 ml), 10% Na_2CO_3 solution (100 ml) and brine (75 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1 to petroleum ether/ethyl acetate, 10:1) to give the aldehyde **16a** as a colorless oil (3.65 g, 93%). - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.74. - IR (film): $\tilde{\nu}_{max}$ = 3048 cm^{-1}, 2955, 2898, 2859, 2147, 1728. - ^1H NMR (500 MHz, C_6D_6): δ = 0.12/0.13 [s, 6 H, $Si(CH_3)_2$], 0.17 [s, 9 H, $Si(CH_3)_3$], 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.38-1.52 (m, 2 H, CH_2), 1.85-1.96 (m, 3 H, CH_2), 2.70-2.75 (m, 1 H, CH_2), 3.24 (s, 3 H, OCH_3), 5.39-5.54 (d, ^3J = 11.1 Hz, 1 H, vinyl-H), 5.50 (d, ^3J = 11.1 Hz, 1 H, vinyl-H), 6.73-6.76 (m, 1 H, aryl-H), 6.97-7.04 (m, 1 H, aryl-H), 7.35-7.41 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.41/-4.32 [+, $Si(CH_3)_2$], -0.19 [+, $Si(CH_3)_3$], 18.34 (×, $SiCMe_3$), 18.79, 19.17 (-, CH_2), 25.84 [+, $SiC(CH_3)_3$], 31.15 (-, CH_2), 52.23 (+, OCH_3), 68.87, 70.93, 78.41 (×, oxirane-C, COMe), 87.88, 95.19, 102.45, 103.58 (×, alkyne-C), 119.23, 120.45, 120.57, 121.99, 123.34, 128.87 (+, aryl-C, vinyl-C), 135.78, 155.42 (×, aryl-C), 198.64 (+, C=O). - MS (EI), *m/z* (%): 508 (3) [M^+], 493 (6) [M^+ - CH_3], 479 (37) [M^+ - H - CO], 476 (35) [M^+ - MeOH], 447 (23) [M^+ - MeOH - H - CO], 419 (4) [M^+ - MeOH - CMe_3], 235 (13) [$TBSOC_6H_4CO^+$], 73 (100). - $C_{29}H_{40}O_4Si_2$ (508.8): calcd. C 68.46, H 7.92; found C 68.42, H 7.71.

5a-[3-(tert-Butyldimethylsilyloxy)phenyl]-5-[(Z)-3-hexene-1,5-diynyl]-5-methoxyperhydrobenzo[b]oxiren-1a-carbaldehyde (**16b**): To a solution of Dess-Martin-periodinane (218 mg, 0.514 mmol) in CH_2Cl_2 (5 ml) was added a solution of the alcohol **15b** (188 mg, 0.429 mmol) in CH_2Cl_2 (5 ml). After being stirred for 90 min at room temp., satd. $NaHCO_3$ solution (5 ml) and 10% $Na_2S_2O_3$ solution (5 ml) were added and the mixture was stirred for 15 min. Ether (200 ml) was added and the organic phase was washed with 10% $Na_2S_2O_3$ solution (2 × 20 ml), 10% Na_2CO_3 solution (20 ml) and brine (20 ml) before it was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1 to petroleum ether/ethyl acetate, 15:1) to give the aldehyde **16b** as a pale yellow oil (156 mg, 83%). - TLC (petroleum ether/ethyl acetate, 10:1): R_f = 0.33. - IR (film): $\tilde{\nu}_{max}$ = 3292 cm^{-1}, 3053, 2955, 2897, 2858, 2095, 1727. - ^1H NMR (500 MHz, C_6D_6): δ = 0.12, 0.13 [2 s, 3 H each, $Si(CH_3)_2$], 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.35-1.37 (m, 1 H, CH_2), 1.44-1.50 (m, 1 H, CH_2), 1.77-1.79 (m, 1 H, CH_2), 1.88-1.92 (m, 2 H, CH_2), 2.65-2.69 (m, 1 H, CH_2), 3.07 (d, ^3J = 1.7 Hz, 1 H, alkyne-H), 3.17 (s, 3 H, OCH_3), 5.34-5.39 (m, 2 H, vinyl-H), 6.73-6.75 (m, 1 H, aryl-H), 6.98-7.01 (m, 1 H, aryl-H), 7.40-7.44 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.45/-4.37 [+, $Si(CH_3)_2$], 18.34 (×, $SiCMe_3$), 18.47, 18.97 (-, CH_2), 25.83 [+, $SiC(CH_3)_3$], 30.86 (-, CH_2), 52.30 (+, OCH_3), 68.88, 70.96, 78.42 (×, oxirane-C, COMe), 80.95 (×, alkyne-C), 85.86 (+, alkyne-C), 87.83, 95.24 (×, alkyne-C), 119.93, 120.45, 120.63, 122.22, 123.49, 128.87, (+, aryl-C, vinyl-C), 135.76, 155.76 (×, aryl-C), 199.00 (+, C=O). - MS (EI), *m/z* (%): 436 (8) [M^+], 407 (58) [M^+ - H - CO], 404 (56) [M^+ - MeOH], 375 (31) [M^+ - H - CO - MeOH], 347 (14) [M^+ - MeOH - CMe_3], 235 (50) [$TBSOC_6H_4CO^+$], 73 (100). - $C_{26}H_{32}O_4Si$ (436.6): calcd. C 71.52, H 7.39; found C 71.27, H 7.46.

14-[3-(tert-Butyldimethylsilyloxy)phenyl]-9-methoxy-2-trimethylsilyloxy-13-oxatricyclo[7.3.2.0^{1,14}]-tetradec-5-ene-3,7-diyne (**17a**): A solution of the aldehyde **16a** (472 mg, 0.928 mmol) in THF (100 ml) was stirred with molecular sieves (4 Å, 0.5 g) at 0°C. Tetrabutylammonium fluoride (0.1 M in THF, stirred for 1 h over molecular sieves, 4 Å, 0.92 ml, 92 µmol) was added and the mixture was stirred for 2 h at 0°C. Ether (300 ml) was added and the mixture was washed with water (50 ml) and brine (50 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 15:1) to give the enediyne **17a** as a colorless oil (367 mg, 77%). - TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.71. - ^1H NMR (500 MHz, C_6D_6): δ = 0.06/0.07 [s, 9 H, $Si(CH_3)_3$], 0.14/0.15/0.18/0.19 [s, 6 H, $Si(CH_3)_2$], 0.98/1.01 [s, 9 H, $SiC(CH_3)_3$], 1.58-1.63 (m, 1 H, CH_2), 1.76-1.94 (m, 2 H, CH_2), 2.21-2.36 (m, 2 H, CH_2), 2.65-2.70 (m, 1 H, CH_2), 3.01/3.02 (s, 3 H, OCH_3), 4.40/4.43 (s, 1 H, CHOTMS), 5.48/5.50 (s, 2 H, vinyl-H), 6.75-6.81 (m, 1 H, aryl-H), 7.01-7.11 (m, 1 H, aryl-H), 7.58-7.60 (m, 1 H, aryl-H), 7.91-8.01 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.31/-4.26 [+, $Si(CH_3)_2$], -0.16/-0.12 [+, $Si(CH_3)_3$], 18.24 (×, $SiCMe_3$), 18.34/18.44, 21.06/21.13 (-, CH_2), 25.87/25.93 [+, $SiC(CH_3)_3$], 29.65/29.72 (-, CH_2), 52.79/52.90 (+, OCH_3), 68.17/68.25 (+, CHOTMS), 72.12, 73.77/73.87, 79.87 (×, oxirane-C, COMe), 87.59, 93.13/93.31, 100.95, 101.12 (×, alkyne-C), 119.69/120.17, 121.42, 122.18/122.30, 122.41/122.44, 123.47/123.57, 128.48/128.86 (+, aryl-C, vinyl-C), 138.08/138.36, 154.76/155.74 (×, aryl-C).

14-[3-(tert-Butyldimethylsilyloxy)phenyl]-9-methoxy-13-oxatricyclo[7.3.2.0^{1,14}]tetradec-5-ene-3,7-diyn-2-ol (**17b**): a) A solution of the aldehyde **16b** (53 mg, 121 µmol) in THF (12 ml) was cooled to -78°C and treated with bis-(trimethylsilyl)potassium amide (0.5 M in toluene, 267 µl, 134 µmol). After 2 h ether (50 ml) was added and the mixture was washed with water (2 × 10 ml) and brine (10 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give the enediyne **17b** as a colorless oil (15 mg, 28%) and starting material **16b** (15 mg).

b) A solution of the enediyne **17a** (305 mg, 0.599 mmol) in methanol/CH_2Cl_2 (20 ml, 1:1) was treated with K_2CO_3 (91 mg, 0.659 mmol) at 0°C. The mixture was stirred for 45 min before pH-7 buffer solution (5 ml) and ether (150 ml) were added. The organic phase was washed with water (30 ml), brine (30 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified as described before to give the enediyne **17b** (230 mg, 88%). - TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.19. - IR (film): $\tilde{\nu}$

ν_{max} = 3452 cm^{-1}, 2927, 2856. - ^1H NMR (500 MHz, C_6D_6): δ = 0.13/0.14/0.19/0.20 [s, 6 H, $Si(CH_3)_2$], 0.97/1.04 [s, 9 H, $SiC(CH_3)_3$], 1.52-1.57 (m, 1 H, CH_2), 1.73-1.87 (m, 2 H, CH_2), 2.14-2.24 (m, 2 H, CH_2), 2.45-2.50 (m, 1 H, CH_2), 3.00/3.02 (s, 3 H, OCH_3), 4.03-4.05 (m, 1 H, C*H*OH), 5.45-5.51 (m, 2 H, vinyl-H), 6.79-6.99 (m, 1 H, aryl-H), 7.08-7.13 (m, 1 H, aryl-H), 7.55-7.61 (m, 1 H, aryl-H), 7.86-7.97 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = -4.37/-4.33/-4.27 [+, $Si(CH_3)_2$], 18.17/18.26 (-, CH_2), 18.35/18.41 (×, $SiCMe_3$), 20.60/20.68 (-, CH_2), 25.85/25.93 [+, $SiC(CH_3)_3$], 29.57/29.65 (-, CH_2), 52.80/52.90 (+, OCH_3), 67.57/67.68 (+, CHOH), 71.77/71.83, 73.50/73.57, 79.43/79.50 (×, oxirane-C, COMe), 87.81, 93.08/93.27, 100.72, 100.89 (×, alkyne-C), 119.51/120.07, 121.42, 122.30/122.45, 122.52/123.30, 123.49/123.64, 128.38/128.87 (+, aryl-C, vinyl-C), 137.99/138.32, 154.71/155.74 (×, aryl-C). - MS (EI), *m/z* (%): 436 (3) [M^+], 419 (11) [M^+ - OH], 404 (15) [M^+ - MeOH], 375 (9) [M^+ - H - CO - MeOH], 347 (13) [M^+ - MeOH - CMe_3], 235 (100) [$TBSOC_6H_4CO^+$]. - HRMS for $C_{26}H_{32}O_4Si$ (M^+) calcd. 436.2069, found 436.2061.

14-(3-Hydroxyphenyl)-9-methoxy-13-oxatricyclo[7.3.2.0^{1,14}]tetradec-5-ene-3,7-diyn-2-ol (**18**): a) A solution of the aldehyde **16a** (0.735 g, 1.44 mmol) in THF (150 ml) was stirred with molecular sieves (4 Å, 0.7 g) at -20°C. Tetrabutylammonium fluoride (0.1 M in THF, stirred for 1 h over molecular sieves, 4 Å, 0.72 ml, 72 μmol) was added and after 40 min more tetrabutylammonium fluoride (1.0 M in THF ≤ 5% H_2O, 3.0 ml, 3.0 mmol) was added and the mixture was stirred for 40 min at -20°C. The reaction was quenched with pH-7 buffer solution (30 ml) and diluted with ether (750 ml). The organic phase was washed with water (100 ml) and brine (75 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 2:1) to give the enediyne **18** as a colorless solid (360 mg, 78%) of m.p. 88-89°C.

b) To a solution of the enediyne **17b** (21 mg, 48 μmol) in THF (5 ml) was added tetrabutylammonium fluoride (1.0 M in THF, 48 μl, 48 μmol) at 0°C. After 15 min pH-7 buffer solution (5 ml) and ether (30 ml) were added. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified as described before to give the enediyne **18** (13 mg, 81%). - TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.55. - IR (KBr): $\tilde{\nu}_{max}$ = 3400 cm^{-1}, 2935, 2192. - ^1H NMR (500 MHz, C_6D_6): δ = 1.54-1.58 (m, 1 H, CH_2), 1.66-1.86 (m, 2 H, CH_2), 2.17-2.23 (m, 2 H, CH_2), 2.44-2.51 (m, 1 H, CH_2), 3.00/3.01 (s, 3 H, OCH_3), 4.01 (s, 1 H, C*H*OH), 5.42/5.43 (s, 2 H, vinyl-H), 6.36-6.37/6.56-6.58 (m, 1 H, aryl-H), 6.99-7.06 (m, 1 H, aryl-H), 7.24/7.81 (s, 1 H, aryl-H), 7.48-7.50/7.84-7.86 (m, 1 H, aryl-H). - ^{13}C NMR (125 MHz, C_6D_6): δ = 18.18 (-, CH_2), 20.61/20.97 (-, CH_2), 29.45/29.68 (-, CH_2), 52.77/52.96 (+, OCH_3), 65.88 (×, oxirane-C), 67.52/67.58 (+, CHOH), 73.84, 79.51 (×, oxirane-C, COMe), 87.84, 93.43, 100.57, 100.65 (×, alkyne-C), 114.95/115.03, 116.68/117.48, 121.25, 122.36/122.42, 122.55/123.35, 128.60/128.80 (+, aryl-C, vinyl-C), 138.04/138.21, 155.13/156.23 (×, aryl-C). - MS (EI), *m/z* (%): 322 (1) [M^+], 321 (1) [M^+ - H], 305 (4) [M^+ - OH], 293 (8) [M^+ - H - CO], 261 (85) [M^+ - H - CO - MeOH], 201 (100), 121 (68) [$HOC_6H_4CO^+$]. - $C_{20}H_{18}O_4$ (322.3): calcd. C 68.46, H 7.92; found C 68.42, H 7.71.

Acknowledgments: Financial support by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged. A. R. Tunoori thanks the Humboldt foundation for an AvH fellowship.

REFERENCES AND NOTES

Dedicated to Professor Dr. *Peter Welzel* on the occasion of his 60th birthday.

1. (a) Ichikawa, A.; Kuboya, T.; Aoyama, T.; Sugiura, Y. *Biochemistry* **1992**, *31*, 6784-6787. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715-3716.
2. (a) Myers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, D. J. *Chem. Biol.* **1995**, *2*, 33-43. (b) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509-9525.

3. (a) Nicolaou, K. C.; Dai, W. M. *Angew. Chem.* **1991**, *103*, 1453-1481; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387-1416. (b) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 5881-5888. (c) Skrydstrup, T.; Ulibarri, G.; Audrain, H.; Grierson, D. S. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Gabor Lukacs, Eds.; Vol. 2; Springer-Verlag: Berlin Heidelberg, 1993; pp. 213-292. (d) Maier, M. E. *Synlett* **1995**, 13-26.
4. (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25-31. (b) Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630-7632. c.Nicolaou, K. C.; Sorensen, E. J.; Discordia, R.; Hwang, C. K.; Minto, R. E.; Bharucha, K. N.; Bergman, R. G. *Angew. Chem.* **1992**, *104*, 1094-1096; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1044-1046. (d) Banfi, L.; Guanti, G. *Angew. Chem.* **1995**, *107*, 2613-2615; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2393-2395.
5. (a) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393-395. (b) Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendeborn, S. V.; Dai, W. M.; Chadha, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8890-8907. (c) Myers, A. G.; Fraley, M. E.; Tom, N. J. *J. Am. Chem. Soc.* **1994**, *116*, 11556-11557. (d) Elbaum, D.; Porco Jr., J. A.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 211-225. (e) Wender, P.; Beckham, S.; O'Leary, J. G. *Synthesis* **1994**, 1278-1282. (f) Magnus, P. *Tetrahedron* **1994**, *50*, 1397-1418. (g) Myers, A. G.; Cohen, S. B.; Tom, N. J.; Madar, D. J.; Fraley, M. E. *J. Am. Chem. Soc.* **1995**, *117*, 7574-7575. (h) Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fukazawa, Y. *Angew. Chem.* **1995**, *107*, 1443-1446; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1345-1348. (i) Nishikawa, T.; Ino, A.; Isobe, M. *Tetrahedron* **1994**, *50*, 1449-1468.
6. Boße, F.; Tunoori, A. R.; Niestroj, A. J.; Gronwald, O.; Maier, M. E. *Tetrahedron* **1996**, *52*, 9485-9498.
7. (a) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102-2106. (b) Martinelli, M. J.; Peterson, B. C.; Hutchison, D. R. *Heterocycles* **1993**, *36*, 2087-2098.
8. Knochel, P.; Chou, T.-S.; Jubert, C.; Rajagopal, D. *J. Org. Chem.* **1993**, *58*, 588-599.
9. Sha, C.-K.; Huang, S.-J. *Tetrahedron Lett.* **1995**, *36*, 6927-6928.
10. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917-918.
11. Nishikawa, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 5621-5632.
12. (a) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217-4220. (b) Kadow, J. F.; Cook, D. J.; Doyle, T. W.; Langley, D. R.; Pham, K. M.; Vyas, D. M.; Wittman, M. D. *Tetrahedron* **1994**, *50*, 1519-1538.
13. (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313-3315. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.
14. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549-7552.
15. Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975-982.
16. Maier, M. E.; Abel, U. *Synlett* **1995**, 38-40.
17. Preliminary experiments to oxidize **18** to the corresponding 4,4-dimethoxy-2,5-cyclohexadien-1-one show that this is indeed possible with $PhI(O_2CCF_3)_2$ in methanol (32% yield).
18. Shair, M. D.; Yoon, T.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem.* **1994**, *106*, 2578-2580; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2477-2479.
19. Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253-266.
20. Holmes, A. B.; Sporikou, C. N. *Org. Synth.* **1987**, *65*, 61-67.

(*Received in Germany* 28 *April* 1997; *accepted* 23 *May* 1997)