Synthesis of the Tetracyclic Core of Anthracycline Antibiotics through an Intramolecular Dehydro Diels-Alder approach

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Supporting information

Experimental Section: General details

All reactions were carried out under argon atmosphere with magnetic stirring. The solvents were purified and dried using standard procedures. All reagents were purchased and used without further purification. ^1H NMR spectra at 250,13 MHz and ^{13}C NMR spectra at 62,89 MHz were determined on a Bruker WM-250 instrument using CDCl_3 as solvent with tetramethylsilane as internal standard. Mass spectra were measured on a Hewlett-Packard 59970-G/MS spectrometer. Column chromatographies were made on silica gel 230-400 mesh (flash) from Merck.

1-[2-(1-Hydroxy-3-phenyl-propynyl)-phenyl]-3-phenyl-prop-2-yn-1-ol **5**

$n\text{-BuLi}$ (6,85 mL, 1,6 M in hexanes) was slowly added to a solution of phenylacetylene (1,17 g, 11,48 mmol) in dry THF (15 mL) cooled at $-78\text{ }^\circ\text{C}$, and the mixture was stirred for 5 minutes before adding phthaldehyde (0,70 g, 5,22 mmol). After 10 minutes the mixture was allowed to reach room temperature and stirred for 30 minutes. The reaction

was quenched with a saturated aqueous solution of NH_4Cl , diluted with EtOAc and washed with brine (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using hexane/EtOAc 4:1 as eluent to yield **5** (1,77 g, 100%) as a colorless oil.

NMR spectra show a mixture of products (racemate and meso form) corresponding to the different stereochemistry of the propargylic alcohols. ^1H NMR could be assigned by means of experiments with a chiral europium salt, resulting a 1.5:1 mixture of racemate and meso form. For ^{13}C NMR all the observed peaks are given (some of them are duplicated due to the presence of isomers). ^1H NMR (CDCl_3) δ : Racemate: 7,99-7,91 (m, 2H, ArH), 7,55-7,27 (m, 12H, ArH), 6,15 (broad s, 2H, ArCH), 3,58 (broad s, 2H, OH). Meso form: 7,79-7,71 (m, 2H, ArH), 7,55-7,27 (m, 12H, ArH), 6,31 (broad s, 2H, ArCH), 3,97 (broad s, 2H, OH); ^{13}C NMR/DEPT (CDCl_3) δ : 138,3 (C), 137,9 (C), 131,8 (CH), 131,7 (CH), 129,2 (CH), 129,1 (CH), 128,6 (CH), 128,6 (CH), 128,3 (CH), 128,3 (CH), 128,1 (CH), 122,3 (C), 122,2 (C), 88,0 (C), 87,6 (C), 87,3 (C), 63,9 (CH), 62,4 (CH); MS (70 eV) m/z (%): 338 (M^+ , 1), 337 (4), 321 (10), 320 (18), 319 (18), 289 (41), 215 (52), 189 (100), 105 (76), 77 (88).

General procedure for thermal cyclizations

A toluene or toluene/ Et_3N solution of the starting material (concentration from 20 to 65 mM) was placed in a sealed tube and heated overnight at the indicated temperature in a silicon oil bath. After evaporation of the solvent, the crude material was purified by column chromatography on silica gel using hexane/EtOAc mixtures as eluent.

Thermal cyclization of **5**

Conditions A: A solution of **5** (220 mg, 0,65 mmol, 54 mM) in toluene (12 mL) was heated under general conditions at 160 °C. After column chromatography on silica gel using hexane/EtOAc 3:1 as eluent three products were isolated: 17 mg (8%) of 11-phenyl-12H-naphthacen-5-one **8** (R_f 0.66) (yellow prisms); 40 mg (18%) of 12-hydroxy-11-phenyl-12H-naphthacen-5-one **7** (R_f 0.50) (yellow prisms); and 135 mg (61%) of 6-phenyl-5,12-dihydro-naphthacene-5,12-diol **6** (R_f 0.25) (white prisms).

Conditions B: A solution of **5** (80 mg, 0,24 mmol, 21 mM) in toluene (10 mL) and Et₃N (1 mL) was heated under general conditions at 150 °C. After column chromatography on silica gel using hexane/EtOAc 4:1 as eluent two products were isolated: 13 mg (16%) of 6-phenyl-naphthacene-5,12-dione **9** (*R*_f= 0.70) (yellow prisms); and 64 mg (80%) of **6** (*R*_f= 0.20) (white prisms).

11-phenyl-12*H*-naphthacen-5-one **8**. ¹H NMR (CDCl₃) δ: 9,04 (s, 1H, Ar*H*), 8,40 (d, *J*= 7,9 Hz, 1H, Ar*H*), 8,11 (d, *J*= 8,5 Hz, 1H, Ar*H*), 7,64-7,40 (m, 8H, Ar*H*), 7,36-7,30 (m, 3H, Ar*H*), 4,12 (s, 2H, ArCH₂); ¹³C NMR/DEPT (CDCl₃) δ: 185,0 (CO), 141,0 (C), 138,5 (C), 138,4 (C), 134,7 (C), 133,0 (CH), 132,8 (C), 131,7 (C), 131,6 (C), 129,9 (CH), 129,8 (2 x CH), 129,7 (C), 129,0 (2 x CH), 128,9 (CH), 128,7 (CH), 128,4 (CH), 127,7 (CH), 127,6 (CH), 126,9 (CH), 126,0 (2 x CH), 31,8 (CH₂); MS (70 eV) *m/z* (%): 320 (M⁺, 100), 289 (30), 243 (18), 215 (22).

12-hydroxy-11-phenyl-12*H*-naphthacen-5-one **7**. ¹H NMR (CDCl₃) δ: 8,88 (s, 1H, Ar*H*), 8,27 (d, *J*= 7,0 Hz, 1H, Ar*H*), 8,06 (d, *J*= 8,3 Hz, 1H, Ar*H*), 7,67-7,47 (m, 9H, Ar*H*), 7,44-7,35 (m, 2H, Ar*H*), 5,74 (s, 1H, ArCH), 2,38 (broad s, 1H, OH); ¹³C NMR/DEPT (CDCl₃) δ: 184,8 (CO), 142,2 (C), 140,3 (C), 137,4 (C), 135,4 (C), 134,7 (C), 133,8 (CH), 132,6 (C), 131,7 (C), 131,0 (CH), 130,1 (CH), 129,8 (CH), 129,6 (CH), 129,6 (CH), 128,9 (CH), 128,9 (CH), 128,7 (2 x CH), 128,7 (C), 128,2 (CH), 127,6 (CH), 126,9 (CH), 126,7 (CH), 65,1 (CH); MS (70 eV) *m/z* (%): 336 (M⁺, 100), 335 (17), 319 (22), 259 (77), 202 (39), 77 (43).

6-phenyl-5,12-dihydro-naphthacene-5,12-diol **6**. (Only the peaks of the mayor isomer are given) ¹H NMR (CDCl₃) δ: 7,84 (s, 1H, Ar*H*), 7,75 (d, *J*= 7,8 Hz, 1H Ar*H*), 7,51-7,03 (m, 12H, Ar*H*), 5,55 (d, *J*= 6,3 Hz, 1H, ArCH), 5,32 (d, *J*= 6,3 Hz, 1H, ArCH), 3,94 (d, *J*= 6,3 Hz, 1H, OH), 3,54 (d, *J*= 6,3 Hz, 1H, OH); ¹³C NMR/DEPT (CDCl₃) δ: 140,3 (C), 140,2 (C), 139,7 (C), 137,7 (C), 137,2 (C), 134,7 (C), 132,9 (C), 132,8 (C), 130,8 (CH), 130,4 (CH), 129,0 (CH), 128,5 (CH), 128,4 (CH), 128,2 (CH), 128,1 (CH), 128,0 (CH), 127,9 (CH), 127,7 (CH), 127,6 (CH), 127,1 (CH), 126,5 (CH), 126,4 (CH), 73,2 (CH), 69,4 (CH); MS (70 eV) *m/z* (%): 338 (M⁺, 100), 321 (63), 320 (88), 303 (42), 302 (49), 261 (25), 215 (48), 105 (23), 77 (22).

6-phenyl-naphthacene-5,12-dione **9**. ¹H NMR (CDCl₃) δ: 9,01 (s, 1H, Ar*H*), 8,39-8,34 (m, 1H, Ar*H*), 8,20-8,11 (m, 2H, Ar*H*), 7,81-7,64 (m, 3H, Ar*H*), 7,61-7,50 (m, 6H, Ar*H*), 7,29-7,27 (m, 1H, Ar*H*); ¹³C NMR/DEPT (CDCl₃) δ: 183,4 (CO), 183,3 (CO), 144,2 (C), 139,7 (C), 136,2 (C), 135,7 (C), 134,5 (C), 134,2 (CH), 133,6 (CH + C), 130,3 (C), 130,2 (CH), 130,1 (CH), 129,3 (CH), 129,1 (CH), 128,9 (CH), 128,5 (2 x CH), 128,4 (2 x CH), 127,7 (CH), 127,2 (CH), 126,9 (CH), 125,1 (C); MS (70 eV) *m/z* (%): 334 (M⁺, 56), 333 (100), 276 (22).

1-[2-(3-Cyclohex-1-enyl-1-hydroxyprop-2-ynyl)phenyl]-3-ethoxyprop-2-yn-1-ol 13

n-BuLi (1,45 mL, 1,6 M in hexanes) was slowly added to a solution of ethynylcyclohexene (0,25 g, 2,35 mmol) in dry THF (6 mL) cooled at -78 °C, and the mixture was stirred for 5 minutes before adding to a cooled solution of phthalaldehyde **4** (0,30 g, 2,24 mmol) in THF (10 mL). After 10 minutes a solution of lithium ethoxyethynyl acetylide [prepared by reacting *n*-BuLi (2,10 mL, 1,6 M in hexanes) with ethylethynyl ether (0,60 g, 40% wt in hexanes, 3,35 mmol)] was added via canula and the reaction mixture was allowed to reach room temperature and stirred for 90 minutes. The reaction was quenched with a saturated aqueous solution of NH₄Cl, diluted with EtOAc and washed with brine (2 x 50 mL). The organic layer was dried over anhydrous Na₂SO₄ and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using hexane/EtOAc 5:2 as eluent to yield **13** (0,43 g, 62%) as a slightly yellow oil. . NMR spectra show a mixture of isomers; only the signals of the mayor isomer are given. ¹H NMR (CDCl₃) δ: 7,87-7,77 (m, 2H, ArH), 7,43-7,31 (m, 2H, ArH), 6,24-5,92 (m, 3H, 2 x ArCH + C=CH), 4,19 (c, *J* = 7,0 Hz, 2H, OCH₂), 3,19 (broad s, 1H, OH), 3,01 (broad s, 1H, OH), 2,22-2,05 (m, 4H, CH₂), 1,70-1,53 (m, 4H, CH₂), 1,41 (t, *J* = 7,0 Hz, 3H, CH₃); ¹³C NMR/DEPT (CDCl₃) δ: 138,7 (C), 137,7 (C), 135,3 (CH), 128,4 (CH), 128,3 (CH), 127,5 (CH), 127,4 (CH), 119,8 (C), 95,7 (C), 88,9 (C), 85,0 (C), 74,6 (CH₂), 61,6 (CH), 61,2 (CH), 37,4 (C), 28,8 (CH₂), 25,3 (CH₂), 22,0 (CH₂), 21,2 (CH₂), 14,2 (CH₃); MS (70 eV) *m/z* (%): 310 (M⁺, 15), 292 (35), 265 (68), 264 (75), 247 (47), 236 (47), 235 (82), 219 (62), 191 (73), 165 (100), ..., 29 (73).

1-[2-(3-Cyclohex-1-enyl-1-hydroxyprop-2-ynyl)-phenyl]-3-trimethylsilylprop-2-yn-1-ol 14

n-BuLi (4,62 mL, 1,6 M in hexanes) was slowly added to a solution of trimethylsilylacetylene (0,76 g, 7,75 mmol) in dry THF (10 mL) cooled at -78 °C, and the mixture was stirred for 5 minutes before adding to a cooled solution of phthalaldehyde **4** (0,95 g, 7,05 mmol) in THF (10 mL). After 10 minutes a solution of the lithium acetylide of ethynylcyclohexene [prepared by reacting *n*-BuLi (4,84 mL, 1,6 M in hexanes) with ethynylcyclohexene (0,90 g, 8,45 mmol)] was added via canula and the reaction mixture was allowed to reach room temperature and stirred for 60 minutes. The reaction was quenched with a saturated aqueous solution of NH₄Cl, diluted with EtOAc and washed with brine (3 x 25 mL). The organic layer was dried over anhydrous Na₂SO₄ and evaporated to dryness. The crude residue was purified by column

chromatography on silica gel using hexane/EtOAc 4:1 as eluent to yield **14** (2,25 g, 94%) as a colorless oil. NMR spectra show a mixture of isomers; for ^1H NMR only the signals of the mayor isomer are given; for ^{13}C NMR all the observed peaks are given (some of them are duplicated due to the presence of isomers). ^1H NMR (CDCl_3) δ : 7,87-7,60 (m, 2H, ArH), 7,44-7,33 (m, 2H, ArH), 6,24-5,87 (m, 3H, 2 x ArCH + C=CH), 3,44 (broad s, 1H, OH), 3,10 (broad s, 1H, OH), 2,22-2,03 (m, 4H, CH_2), 1,71-1,52 (m, 4H, CH_2), 0,22 (s, 9H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR/DEPT (CDCl_3) δ : 138,5 (C), 138,0 (C), 138,0 (C), 137,5 (C), 137,5 (C), 135,7 (CH), 135,6 (CH), 129,0 (CH), 128,9 (CH), 128,8 (CH), 128,8 (CH), 127,9 (CH), 119,9 (C), 119,8 (C), 104,4 (C), 104,1 (C), 92,3 (C), 92,2 (C), 89,3 (C), 88,9 (C), 85,1 (C), 84,9 (C), 63,5 (CH), 63,3 (CH), 62,6 (CH), 61,9 (CH), 28,9 (CH_2), 28,8 (CH_2), 25,5 (CH_2), 22,1 (CH_2), 21,3 (CH_2), -0,3 ($\text{Si}(\text{CH}_3)_3$); MS (70 eV) m/z (%): 338 (M^+ , 47), 337 (100), 336 (60), 335 (83), 329 (63), 327 (64) ... 73 (48).

3-Cyclohex-1-enyl-1-[2-(1-hydroxyprop-2-ynyl)-phenyl]-propynol **15**

To a solution of **14** (0,86 g, 2,54 mmol) in THF (5 mL) and MeOH (5 mL), cooled at 0 °C, KOH (aq) (20 mg, 0,36 mmol; in 2 mL of water) was added, resulting in the formation of a dark mixture; after stirring 1 hour, volatiles were removed and the residue was solved in EtOAc and washed with brine (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using hexane/EtOAc 4:1 as eluent to yield **15** (0,68 g, 100%) as a colorless oil. NMR spectra show a mixture of isomers; for ^1H NMR only the signals of the mayor isomer are given; for ^{13}C NMR all the observed peaks are given (some of them are duplicated due to the presence of isomers). ^1H NMR (CDCl_3) δ : 7,90-7,61 (m, 2H, ArH), 7,45-7,33 (m, 2H, ArH), 6,24-5,92 (m, 3H, 2 x ArCH + C=CH), 3,21 (broad s, OH), 2,87 (broad s, OH), 2,72 (d, $J = 2,2$ Hz, $\text{C}\equiv\text{CH}$), 2,22-2,00 (m, 4H, CH_2), 1,71-1,49 (m, 4H, CH_2); ^{13}C NMR/DEPT (CDCl_3) δ : 137,8 (C), 137,4 (C), 136,1 (CH), 129,0 (CH), 127,9 (CH), 119,8 (C), 89,8 (C), 89,4 (C), 85,0 (C), 84,7 (C), 82,8 (C), 82,4 (C), 75,6 (CH), 75,3 (CH), 63,9 (CH), 62,9 (CH), 62,4 (CH), 61,5 (CH), 28,9 (CH_2), 25,6 (CH_2), 22,1 (CH_2), 21,3 (CH_2); MS (70 eV) m/z (%): 266 (M^+ , 0,2), 265 (3), 248 (26), 219 (52), 205 (38), 191 (82), 165 (100), 152 (65), 142 (55), 131 (79), 115 (79), 105 (36), 77 (63).

Thermal cyclization of **15**

A solution of **15** (115 mg, 0,43 mmol, 48 mM) in toluene (8 mL) and Et₃N (1 mL) was heated under general conditions at 150 °C. After column chromatography on silica gel using a gradient of hexane/EtOAc from 9,5:0,5 to 3:1 as eluent two products were isolated: 41 mg (36%) of 5,7,8,9,10,12-hexahydro-naphthacene-5,12-diol **16** (*R*_f = 0,80, hexane/EtOAc 4:1) and 60 mg (52%) of 7,8,9,10-tetrahydro-naphthacene-5,12-dione **17** (*R*_f = 0,13), both as white solids. Compound **16** appears as a mixture of isomers and its structure was confirmed by oxidation to **17** by treatment with activated MnO₂.

7,8,9,10-tetrahydro-naphthacene-5,12-dione **17**: ¹H NMR (CDCl₃) δ: 8,31-8,24 (m, 2H, ArH), 7,96 (s, 2H, ArH), 7,80-7,73 (m, 2H, ArH), 2,92 (broad s, 4H, CH₂), 1,86 (broad s, 4H, CH₂); ¹³C NMR/DEPT (CDCl₃) δ: 183,3 (2 x CO), 144,6 (2 x C), 133,8 (2 x CH), 133,7 (2 x C), 130,9 (2 x C), 127,9 (2 x CH), 127,0 (2 x CH), 29,8 (2 x CH₂), 22,5 (2 x CH₂); MS (70 eV) *m/z* (%): 262 (M⁺, 100), 247 (39), 234 (7).

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