Studies Toward the Synthesis of Menogaril: Synthesis of A-Ring Precursors and Their Conversion to the Tetracyclic Core via the Benzannulation Reaction

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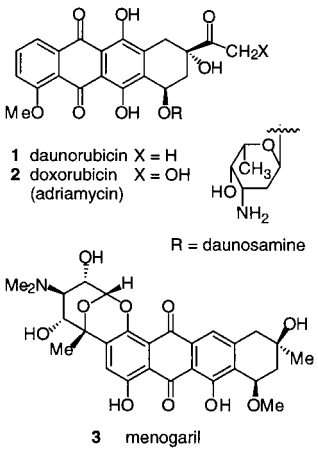
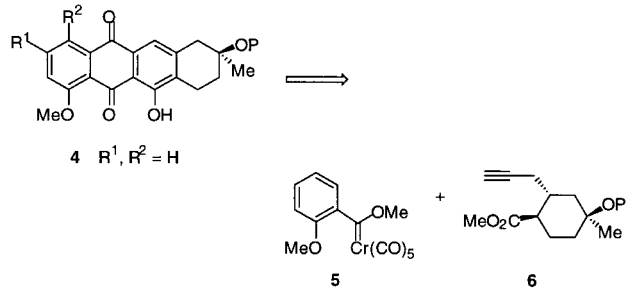
Abstract: A model study for the synthesis of menogaril is reported which involves the benzannulation reaction of a Fischer carbene complex with an alkyne that contains the A-ring of the tetracyclic core of menogaril. The synthesis of methoxy and benzyloxy derivatives of this alkyne are reported as well as the reaction of the methoxy derivative with an *o*-methoxyphenyl carbene complex to generate a tricyclic naphthol containing three of the four rings of menogaril core. Completion of the model study and the synthesis of the tetracyclic anthracyclinone core of menogaril was accomplished by an intramolecular Friedel–Crafts cyclization.

Key words: benzannulation reaction, Fischer carbene complex, Friedel–Crafts cyclization, anthracyclinones, menogaril

Daunorubicin **(1)** and adriamycin **(2)** belong to the anthracycline family of antitumor antibiotics and are isolated from *Streptomyces* species. Ever since the recognition of their pharmacological activities in the 1960s,[1,2] daunorubicin **(1)** and adriamycin **(2)** have emerged as among the most widely used compounds in the treatment of cancers such as acute leukemia, breast cancer, Hodgkin's disease, non-Hodgkin's lymphomas and sarcomas.[3–4] Menogaril **(3)** is a semi-synthetic derivative of the natural product nogalamycin and its activity is somewhat superior to that of adriamycin **(2)** and in addition it is several fold less cardiotoxic.[5] Recent studies have shown that menogaril **(3)** is unique among anthracyclines in that it binds to the major rather than the minor groove of DNA[6] and that it is active after oral administration, thus extravasion is not a side effect.[7] As an orally active drug, menogaril **(3)** is a candidate for the development of out-patient chemotherapy of lymphoma and myeloma.[7a]



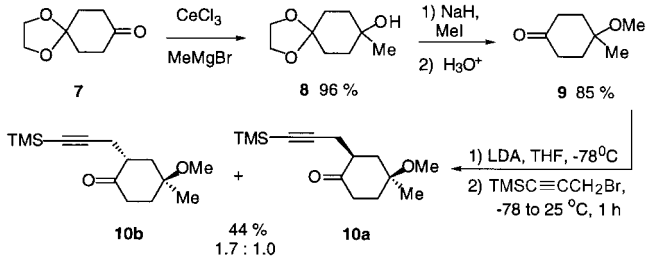
Our interest in the synthesis of anthracyclines[8] lies in the development of a general approach to anthracyclines utilizing the benzannulation reaction of Fischer carbene complexes.[9] These efforts, as well as those of others, have resulted in the synthesis of several anthracyclinones utilizing Fischer carbene complexes.[9] Herein we describe our initial results directed to the development of a strategy for the synthesis of menogaril **(3)**. The syntheses of the methoxy and benzyloxy derivatives of alkyne **6** are reported along with the synthesis of the tetracyclic intermediate **4** via the reaction of these alkynes with the carbene complex **5** in a model study of the strategy for the construction of the fully functionalized tetracyclic core of menogaril **(3)**. The retrosynthetic strategy is shown in Scheme 1.



Scheme 1

Commercially available ketone **7** was treated with methyllithium or methylmagnesium bromide to give the tertiary alcohol **8** in 75% yield with a 25% recovery of the starting material. The reaction could not be driven to completion under more forcing conditions. However, pretreatment of the Grignard reagent with $CeCl_3$ significantly improved the yield to 96%.[10] Exposure of the alcohol to sodium hydride and iodomethane followed by deprotection of the ketal gave the desired ketone **9** in 85% yield. The propargylation of ketones is often problematic and ketone **9** proved no exception. Allenic by products are often observed[11] and it has been reported that the propargylation reaction could be effected in fair to good yields and with little allene formation if the C-terminus is substituted with a trimethylsilyl group.[12] However, reaction of ketone **9** with LDA and then 3-bromo-1-(trimethylsilyl)prop-1-yne in the presence of two equivalents of HMPA afforded the propargylated product **10** in only 30–35% yield. The

starting material was recovered in 10–20% yield and at least two side products were observed which were tentatively assigned as dialkylated products. On some occasions, the desilylated product was isolated in 5% yield. This was disappointing since the use of HMPA has been reported to increase the amount of monoalkylation of carbonyls.[13] Other methods that have been reported to suppress polyalkylation failed to give improved results including triethanolamine borate (TEAB),[14] dimethyl zinc[15] and the dicobalt hexacarbonyl complexation.[16] The best conditions that were found gave **10** in 44% yield as a 1.7:1 mixture of diastereomers. This reaction was conducted by generating the enolate of **9** by LDA at –78 °C in THF and then treatment with 3-bromo-1-(trimethylsilyl)prop-1-yne for one hour (Scheme 2).



Scheme 2

The relative stereochemistry of **10b** was initially assigned as *trans* and this was subsequently confirmed by an X-ray structure on a compound derived from **10b**.[17] Interestingly, the *cis* and *trans* isomers have quite distinct ^{1}H NMR spectra. As indicated in the Figure, there is a 0.30 ppm difference between the axial methine proton of the two diastereomers with the more downfield shifted methine proton in the axial position in the *trans* isomer.[18] The more downfield shifted methyl group is observed for the *cis* isomer where the methyl is in an axial position.

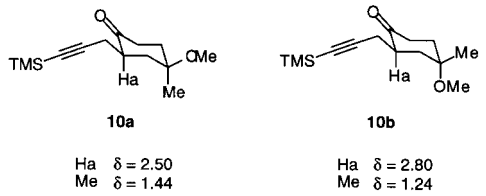
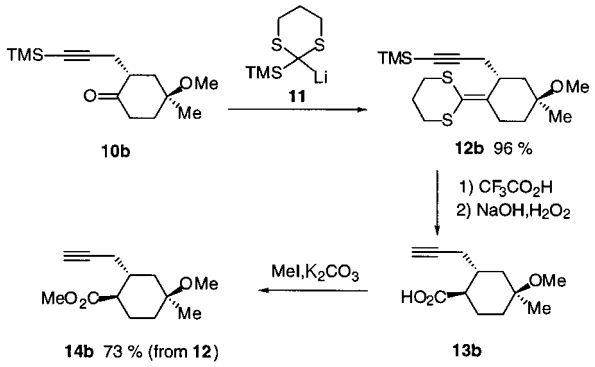


Figure. ^{1}H NMR Data of Ha and CH_3 Protons of Conformers **10a** and **10b**

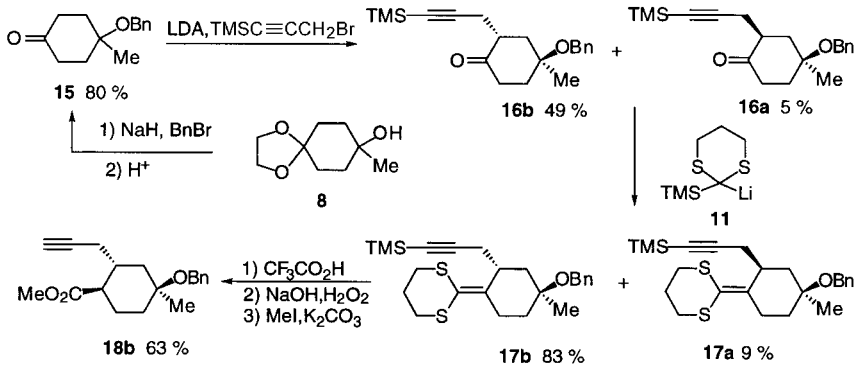
Although the propargylation of ketone **9** produced a mixture of diastereomers, this did not limit the synthetic viability of this intermediate since the new chiral center would be destroyed eventually when the B-ring is aromatized. The synthesis of alkyne **14** was carried out with the purified major isomer **10b** for the convenience of characterization of intermediates, however, it was shown that the minor isomer **10a** could be converted to the diastereomeric alkyne **14**. The Peterson olefination of **10b** indicated in Scheme 3 worked well to afford the ketene thioacetal **12b** in 96% yield.[19] Most commonly, the conversion of ketene thioacetals to acids is accomplished by the use of mercuric oxide.[20] However, these reaction conditions would not be compatible with **12b** which has an alkynyl group. Instead, a two-step procedure was developed which involved acid hydrolysis of the ketene thioacetal[21] followed by basic hydrolysis of the crude reaction mixture containing the *S*-thioester[22] which was found to be facilitated by oxidation with hydrogen peroxide. The trimethylsilyl group was lost during this base hydrolysis producing the acid **13b**. Esterification gave the alkyne **14b** in 73% yield for the three steps from **12b**.



Scheme 3

The synthesis of the alkyne **18b** follows from the strategy developed for **14b** discussed above. It was anticipated that the benzyl protecting group would be stable to strongly acidic and basic conditions that will be required for the synthesis of the tetracyclic carbon core intermediate of menogaril **(3)**. The synthesis of alkyne **18b** begins from the same ketone **7** that was used in the synthesis of alkyne **14b**. The alcohol **8** was then isolated and subsequently treated with sodium hydride and benzyl bromide. Deprotection of the ketal afforded the desired ketone **15** in 80% yield. It was pleasing to find that propargylation of **15** gave both a higher yield and a better stereoselectivity than the corresponding propargylation of ketone **9** (Scheme 4). The monoalkylation product **16** was isolated as a 10:1 mixture of diastereomers in 54% yield, favoring the *trans* isomer **16b**. Also observed was a 14% yield of a dialkylated product and a 26% recovery of the starting material **15**. The relative stereochemistry of **16b** was assigned as *trans* by a correlation of the chemical shifts of the methine proton and the methyl group with those of the **10a** and **10b**. Compound **16a** was not separated from **16b** and the mixture of **16** was converted to the ketene acetal **17** which was also produced as approximately a 10:1 mixture of diastereomers. The major isomer **17b** was purified and subjected to acidic hydrolysis, oxidative basic hydrolysis and esterification to give the desired ester **18b** in 63% yield.

The benzannulation of carbene complex **5** with alkyne **14b** was carried out under a few different conditions (Scheme 5) and the results are summarized in the Table. Polar and nonpolar solvents can have very different effects on the benzannulation reaction but in this particular case changing the solvent from acetonitrile to benzene has

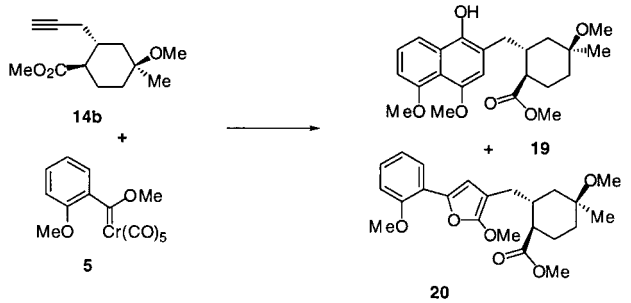


Scheme 4

very little effect on the yield of the phenol product **19.**[23] The furan product **20** was isolated as a minor product in two cases. In the optimal case, the naphthol **19** was obtained in 60% yield and the furan in 10% yield from the reaction in benzene. An account of the remainder of the mass balance in this reaction was not made. The furan could be readily separated by silica gel chromatography to provide naphthol **19** in pure form.

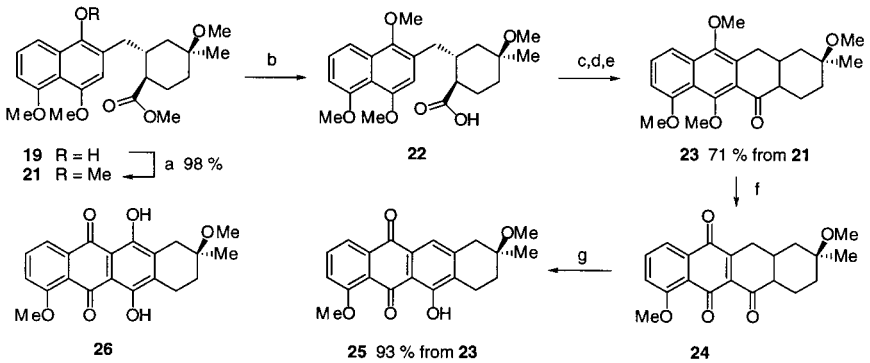
Table. Benzannulation of Complex **5** with Alkyne **14**

Mole Ratio of **5**:**14b**	Solvent	Yield (%)	
		Major Product **19**	Minor Product **20**
1.00:0.85	MeCN	53	not detected
1.00:0.85	hexane	34	not detected
1.00:0.85	benzene	54	9
1.00:1.20	benzene	60	10



Scheme 5

The phenol function in **19** was protected as its methyl ether in preparation for the Friedel–Crafts ring closure. This was accomplished in 98% yield with methyl iodide and potassium carbonate in refluxing acetone. Hydrolysis of the methyl ester with sodium hydroxide provided the acid **22**. The Friedel–Crafts closure of **22** with strong acid such as trifluoroacetic acid can give varying amounts of elimination of methanol from the tertiary ether. In order to minimize the amount of acid present and the elimination of methanol, the acid **22** was treated with one equivalent of aqueous sodium hydroxide and then lyophilized under reduced pressure to give the dry sodium carboxylate. This salt was converted to the acid chloride by addition of pyridine and oxalyl chloride. Addition of tin tetrachloride induced the closure of the B-ring to form the tetracyclic intermediate **23** in 71% overall yield from **21** (Scheme 6). The oxidation of the C-ring to a quinone was unsuccessful with cerium (IV) ammonium nitrate and with iodine. Both reactions gave a complicated mixture of products. Oxidation with lead(IV) tetraacetate resulted in a mixture of two compounds one of which was found to be the desired quinone **24**. The successful oxidation of **23** was finally achieved cleanly with excess silver oxide. The quinone **24** could be obtained by treatment with AgO in acetone for a few minutes. Nitric acid is necessary for the reaction to go to completion. The oxidative aromatization of **24** by molecular oxygen in DMF was quite efficient giving the target anthracyclinone **25** in 93% yield. Occasionally this reaction will produce the over oxidation product **26** in small amounts along with two other unidentified compounds (Scheme 5). It was not possible to isolate **26** in pure form away from the product **25** since they coelute on



Reagent and conditions: a) MeI/K_2CO_3; b) 2 N NaOH c) NaOH (1 equiv); d) $(COCl)_2$/pyridine; e) $SnCl_4$; f) AgO/HNO_3; g) O_2/DMF

Scheme 6

silica gel with a number of different solvent systems. In a control experiment, it was shown that a pure sample of **25** could not be oxidized to **26** under the reaction conditions. Since **25** could not be separated from **26**, it was desirable to find reliable conditions for the efficient oxidation of **24**. Finally, it was found that compound **25** could be reproducibly obtained in 85–92% yield from **23** if the quinone **24** was coated on the inside of a flask and heated at 100 °C in the presence of air in the absence of solvent. This reaction is very clean and in no case could the byproduct **26** be detected.

In summary, a synthesis of the alkyne **6** has been developed which is to serve as the A-ring precursor in the synthesis of menogaril **(3)** via the benzannulation of this alkyne with an aryl Fischer carbene complex. The methyl and benzyl derivatives **14b** and **18b** were prepared in eight steps from the commercially available ketone **7** in 25% and 24% overall yields, respectively. In a model study for the synthesis of **3**, alkyne **14b** was reacted with carbene complex **5** to give the naphthol **19** in 60% yield. The success of this model study followed from subsequent Friedel–Crafts ring closure of the B-ring in 71% yield and the oxidation of the C and B-rings in 93% yield. The target tetracyclic intermediate **25** was thus achieved in 38% overall yield from alkyne **14b**. The viability of the use of the benzannulation reaction in the synthesis of menogaril **(3)** is established and further studies directed to this goal will be reported in due course.

Unless otherwise stated, all chemicals were obtained from commercial suppliers and were used without further purification. THF, benzene and Et_2O were distilled from sodium benzophenone ketyl immediately prior to use. CH_2Cl_2, diisopropylamine and HMPA were distilled from CaH_2. Elemental analyses were carried out by Galbraith Labs., Inc. Routine proton NMR spectra were recorded on either a DS-1000 500MHz spectrometer or a GE-300 MHz instrument in $CDCl_3$. The ^{13}C NMR data were obtained on the QE-300 or W-500 spectrometer. IR spectra were taken on a Nicolet 20SX FTIR spectrometer. Low resolution mass spectra were recorded on a Finnigan 1015 mass spectrometer. High resolution mass spectra were recorded on a VG 70–250 instrument or obtained from the Midwest Center for Mass Spectrometry in Lincoln, Nebraska. Elemental analysis were done by Galbraith Laboratories in Knoxville, Tennessee.

4-Methoxy-4-methylcyclohexanone (9)

A sample of $CeCl_3 \cdot 7\ H_2O$ (17.91 g, 48.06 mmol, 1.25 equiv) was heated under vacuum (0.5 Torr) in a 500 mL flask at 130 °C for 2 h. This flask was cooled to 0 °C, filled with argon and then THF (100 mL) and MeMgBr (16 mL, 3.0 M, 48.06 mmol, 1.25 equiv) were added and stirred for 1 h. A solution of ketone **7** (5.0 g, 32.05 mmol, 1 equiv) in THF (30 mL) was transferred to the above solution. The mixture was stirred at 0 °C for 2.5 h and then quenched with a pH 7 buffer (30 mL). Extraction with excess Et_2O (8×50 mL), drying ($MgSO_4$), filtration through Celite and removal of the solvent gave 6.4 g white solid **8** in 96% yield.

A dispersion of NaH in mineral oil (60% by weight, 3.48 g, 87.00 mmol, 2 equiv) was washed with hexane three times before use. The hexane was removed by a pipette and the flask was flushed with N_2 and THF (20 mL) was added. A solution of the tertiary alcohol **8** (7.49 g, 43.54 mmol, 1 equiv) in THF (80 mL) was added by cannula at r.t. The mixture was stirred under N_2 for 30 min and then MeI (11 mL, 174.16 mmol, 4 equiv) and Me_4NBr (1.65 g, 10.88 mmol, 0.25 equiv) were quickly added and the solution was stirred under N_2 overnight. The reaction was quenched by the addition of a pH 7 buffer (50 mL). The solvent was removed in vacuo and the residue was extracted with Et_2O. The organic layer was washed with brine and stripped of the solvent to give a yellow oil which was treated with conc. HCl (8.4 mL), acetone (48 mL) and H_2O (70 mL). After the mixture was stirred at r. t. for 2 h, it was neutralized with solid K_2CO_3. The volume was reduced to one half followed by extraction with a large excess of Et_2O. The organic layer was washed with brine and dried ($MgSO_4$) and filtered through Celite. Removal of the solvent gave 5.24 g of the ketone **9** as yellow oil in 85% yield; R_f 0.37 (Et_2O/CH_2Cl_2/hexane, 1:1:1).

^1H NMR ($CDCl_3$): δ = 1.23 (s, 3 H), 1.69 (dt, 2 H, *J* = 4.6, 13.5 Hz), 2.10–2.22 (m, 4 H), 2.58 (dt, 2H, *J* = 6.1, 14.3 Hz), 3.28 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 22.97, 35.02, 36.44, 48.71, 71.46, 211.22.

IR (neat): ν = 2967 s, 2940 s, 2827 m, 1715 s, 1467 m, 1374 m, 1312 m, 1137 s, 1122 m, 1078 s, 862 m cm^{-1}.

MS: *m/z* (% rel. intensity) = 142 (M^+, 25), 127 (10), 116 (4), 110 (7), 99 (5), 97 (7), 95 (17).

Anal calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.71; H, 10.22.

4-Methoxy-4-methyl-2-(3-trimethylsilylprop-2-yn-1-yl)cyclohexanone (10)

Lithium diisopropylamide was freshly prepared by treatment of distilled $(i\text{-Pr})_2NH$ (4.34 mL, 30.99 mmol, 1.1 equiv) with BuLi (19.37 mL, 1.6 M, 30.99 mmol, 1.1 equiv) in THF (32 mL) at –78 °C under N_2 for 15 min. The ketone **9** (4.0 g, 28.17 mmol) was transferred neat by dropwise addition via cannula to the LDA solution at –78 °C. After 10 min the dry ice/acetone bath was replaced by an ice bath and the mixture was stirred for 30 min before it was recooled to –78 °C. After dropwise addition of neat 3-bromo-1-(trimethylsilyl)prop-1-yne (5.92 g, 30.99 mmol, 1.1 equiv) via syringe to the enolate solution at –78 °C, the solution was stirred for 30 min and then warmed up to 0 °C and stirred for 1 h. The solution was warmed to r.t. and stirred for 20 min before it was quenched with H_2O (20 mL). The solvent was removed and the residue extracted with Et_2O. The organic layer was washed with aq sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and filtered through Celite. After removal of the solvent the residue was chromatographed over silica gel (Et_2O/CH_2Cl_2/hexane, 1:1:4) to give 1.97 g of **10b** and 1.15 g of **10a** as yellow oils in a total of 44% yield.

10a: R_f 0.20 (Et_2O/CH_2Cl_2/hexane, 1:1:4).

^1H NMR ($CDCl_3$): δ = 0.17 (s, 9 H), 1.44 (s, 3 H), 1.75 (t, 1 H, *J* = 12.6 Hz), 1.95–1.97 (m, 2 H), 2.25–2.34 (m, 3 H), 2.44–2.55 (m, 2 H), 2.70 (dd, 1 H, *J* = 4.4, 17.2 Hz), 3.27 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 0.68, 21.12, 22.20, 35.97, 37.49, 41.31, 46.03, 49.75, 73.88, 86.80, 105.38, 210.71.

IR (neat): ν = 2945 vs, 2905 vs, 2838 s, 2175 vs, 1717 vs, 1425 s, 1377 s, 1249 vs, 1138 vs, 1071 vs, 844 vs cm^{-1}.

MS: *m/z* (% rel. intensity) = 252 (M^+, 1), 237 (4), 220 (31), 205 (44), 192 (6), 165 (12), 141 (8), 131 (14), 85 (44), 73 (100).

10b: R_f 0.28 (Et_2O/CH_2Cl_2/hexane, 1:1:4).

^1H NMR ($CDCl_3$): δ = 0.14 (s, 9 H), 1.23 (s, 3 H), 1.42 (t, 1 H, *J* = 13.5 Hz), 1.71 (dt, 1 H, *J* = 4.5, 13.8 Hz), 2.13–2.26 (m, 3 H), 2.52–2.60 (m, 1 H), 2.63–2.71 (m, 2 H), 2.76–2.83 (m, 1 H), 3.32(s, 3 H).

^{13}C NMR ($CDCl_3$): δ = –0.01, 19.37, 23.34, 36.78, 36.98, 40.68, 43.85, 48.87, 72.48, 85.74, 105.06, 210.82.

IR (neat): ν = 2963–2901brs, 2827 m, 2176 s, 1715 s, 1467 m, 1374 m, 1250 s, 1142 m, 1098 m, 1072 m, 1044 m, 843 m cm^{-1}.

MS-CI: m/z (% rel. intensity) = 253 $(M+1)^+$ (50), 221 (100), 220 (20), 210 (33), 205 (18).

Anal calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.32; H, 9.75.

2-[4-Methoxy-4-methyl-2-(3-trimethylsilylprop-2-yn-1-yl)]cyclohexylidene-1,3-dithiane (12b)

Freshly distilled 2-trimethylsilyl-1,3-dithiane (3.17 g, 16.47 mmol, 1.4 equiv) was dissolved in THF (12 mL) and treated with BuLi (10.3 mL, 1.6 M, 16.48 mmol, 1.4 equiv) under N_2 at 0 °C for 40 min. A solution of **10b** (2.97 g, 11.78 mmol) in THF (10 mL) was transferred dropwise to the above solution and the resulting mixture was stirred for 3 h at 0 °C before it was quenched with H_2O (20 mL). The solvent was removed in vacuo and the residue was extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered through Celite and stripped of the solvent. Purification of the product by chromatography on silica gel (Et_2O/CH_2Cl_2/hexane, 1:1:10) gave 4.00 g of **12b** as a colorless oil in 96% yield; R_f 0.20 (Et_2O/CH_2Cl_2/hexane, 1:1:10).

^{1}H NMR ($CDCl_3$): δ = 0.18 (s, 9 H), 1.30 (s, 3 H), 1.60 (dt, 1 H, *J* = 5.3, 12.8 Hz), 1.64–1.73 (m, 1 H), 1.79 (dd, 1 H, *J* = 6.9, 13.9 Hz), 2.02–2.10 (m, 2 H), 2.11–2.18 (m, 2 H), 2.34 (dd, 1 H, *J* = 9.7, 14.0 Hz), 2.38 (dd, 1 H, *J* = 6.2, 14.0 Hz), 2.78–3.18 (m, 5 H), 3.20 (s, 3 H), 3.38–3.41 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 0.04, 23.47, 24.35, 25.01, 25.16, 30.29, 35.82, 36.46, 37.50, 48.60, 73.45, 86.48, 105.29, 119.87, 143.14.

IR (CH_2Cl_2): ν = 2956–2933 brs, 2172 s, 1422 m, 1249 s, 1104 m, 1075 s, 1039 m, 910 s, 843 vs, 759 s cm^{-1}.

MS: m/z (% rel. intensity) = 354 (M^+ , 2), 322 (5), 243 (88), 211 (30), 171 (100), 97 (15), 73 (15).

Anal calcd for $C_{18}H_{30}OSi$: C, 60.96; H, 8.53. Found: C, 60.46; H, 9.17.

Methyl 4-Methoxy-4-methyl-2-(prop-2-yn-1-yl)-1-cyclohexane carboxylate (14b)

Compound **12b** (4.0 g, 11.30 mmol) was treated with CF_3CO_2H (12.3 mL, 14.14 equiv) in MeCN (123, mL) and H_2O (37 mL). The mixture was stirred at r.t. for 20 h. The solvent (and CF_3CO_2H) was completely removed in vacuo at 70 °C. The crude mixture was extracted with Et_2O/pentane (1:1, 150 mL). After separation, the organic layer was washed with H_2O (3 × 10 mL) until the odor of CF_3CO_2H was no longer present in the organic layer. After removal of the solvent, the yellow oil was treated with a mixture of THF (74 mL), EtOH (31 mL) and 2 N NaOH (30.8 mL, 5.4 equiv) and then 30% H_2O_2 (9.85 mL, 8.5 equiv) was added. The mixture was stirred at r.t. for 3 h and/or until TLC showed only one spot (R_f 0, Et_2O/CH_2Cl_2/hexane, 1:1:4). If more than one spot was present, then 1 equiv of NaOH was added and stirred for another hour and repeated until they were gone. After neutralization with conc. HCl, the solvent was removed and the residue was extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and filtered through Celite. The solvent was removed and resulting yellow oil was dissolved in acetone (128 mL) and treated with MeI (14 mL, large excess) and K_2CO_3 (15.63 g). The mixture was refluxed under N_2 at 70 °C for 5 h before it was cooled down to r.t. Filtration through Celite removed the excess solid K_2CO_3. The solvent was removed to give essentially pure **14b** (1.85 g, 73%) as judged by ^{1}H NMR; colorless oil; R_f 0.37 (Et_2O/CH_2Cl_2/hexane, 1:1:4).

^{1}H NMR ($CDCl_3$): δ = 1.12 (s, 3 H), 1.14–1.28 (m, 2 H), 1.70–1.74 (m, 1 H), 1.75–1.83 (m, 1 H), 1.86–1.92 (m, 1 H), 1.97–2.03 (m, 2 H), 2.12–2.23 (m, 4 H), 3.15 (s, 3 H), 3.68 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 23.73, 25.09, 25.53, 33.18, 34.84, 40.24, 47.60, 48.96, 52.00, 70.71, 73.00, 82.09, 176.23.

IR (neat): ν = 3292 s, 2967 s, 2938 s, 2826 s, 1732 s, 1464 m, 1435 s, 1374 m, 1332 s, 1263 s, 1242 s, 1193 s, 1169 s, 1138 m, 1080 s, 1029 m cm^{-1}.

MS: *m/z* (% rel. intensity) = 224 (M^+, 1), 209 (48), 185 (100), 169 (13), 149 (18), 123 (70), 93 (42), 85 (81), 72 (73).

Anal calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.61; H, 9.13.

4-Benzyloxy-4-methylcyclohexanone (15)

NaH (60% in dispersion, 2.46 g, 61.6 mmol, 2 equiv) was washed three times with hexane and then a solution of alcohol **8** (5.3 g, 30.8 mmol, 1 equiv) in THF (120 mL) was slowly added under N_2 at 0 °C. After stirring for 1 h at r.t. benzyl bromide (7.5 mL, 2 eq) and Bu_4NBr (2.48 g, 0.25 eq) were added. The mixture was refluxed at 80 °C under N_2 overnight and carefully quenched by H_2O. After removal of solvent, H_2O (10 mL) was added and the mixture was extracted with Et_2O (2 × 60 mL). The solvent was removed and the residue was treated with conc. HCl (6.7 mL), H_2O (60 mL) and acetone (40 mL). After stirring for 2 h the volume of the solution was reduced to half. Extraction with Et_2O (4 × 60 mL) followed by removal of the solvent gave a yellow residue. The product was purified by chromatography (Et_2O/CH_2Cl_2/hexane, 1:1:6) on a silica gel column (4 × 20 cm) to give the ketone **15** (5.4 g) in 80% yield; yellow liquid; R_f 0.25 (Et_2O/CH_2Cl_2/hexane, 1:1:6).

^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 3 H), 1.79 (dt, 2 H, *J* = 5.9, 13.5 Hz), 2.22–2.32 (m, 4 H), 2.70 (dt, 2 H, *J* = 5.7, 13.5 Hz), 4.54 (s, 2 H), 7.20–7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 24.46, 36.09, 37.18, 63.82, 72.67, 127.57, 127.30, 128.59, 139.17, 211.00.

IR (neat): ν = 2984 s, 1713 s, 1497 m, 1452 s, 1383 s, 1313 s, 1263 s, 1126 s, 1028 s, 887 s, 723 s cm–^{1}.

MS: *m/z* (% rel intensity) = 218 M^+, 7), 160 (5), 112 (77), 104 (61), 99 (28), 91 (100), 77 (20), 71 (54), 65 (39).

Anal calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.56, H 8.41.

4-Benzyloxy-4-methyl-2-(3-trimethylsilylprop-2-yn-1-yl)cyclohexanone (16)

To a solution of $(i\text{-Pr})_2NH$ (3.78 mL, 26.99 mmol, 1.1 equiv) in THF (36 mL) cooled to 0 °C was added dropwise BuLi (10.8 mL, 2.5 M, 26.99 mmol, 1.1 equiv). The mixture was stirred for 15 min and then cooled to –78 °C and treated with a solution of the ketone **15** (5.35 g, 24.54 mmol, 1 equiv) in THF (89 mL) which was slowly transferred via cannula. After 10 min the mixture was warmed to 0 °C for 30 min before it was recooled to –78 °C. 3-Bromo-1-(trimethylsilyl)prop-1-yne (4.79 g, 24.54 mmol, 1 equiv) in THF (18 mL) was added slowly and after 30 min the mixture was warmed to 0 °C for 48 h. The reaction was quenched by addition of brine (10 mL). The solvent was removed and the residue was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered through Celite. Removal of the solvent gave a mixture of three compounds which were separated by column chromatography on silica gel (Et_2O/CH_2Cl_2/hexane, 1:1:6) to give 4.35g of the desired product **16** in 54% yield (diastereomeric ratio, 10:1) along with a 26% recovery of the ketone **15** and a 14% yield of the dialkylated product.

Major isomer **16b**: Yellow oil; R_f 0.40 (Et_2O/CH_2Cl_2/hexane, 1:1:6).

^{1}H NMR ($CDCl_3$): δ = 0.14 (s, 9 H), 1.35 (s, 3 H), 1.48 (t, 1 H, *J* = 13.5 Hz), 1.73 (dt, 1 H, *J* = 4.4, 14.1 Hz), 2.15–2.26 (m, 3 H), 2.62–2.75 (m, 3 H), 2.83–2.88 (m, 1 H), 4.50 (s, 2 H), 7.21–7.34 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 0.32, 19.67, 24.54, 37.22, 37.83, 41.38, 44.29, 63.77, 73.31, 86.14, 105.46, 127.48, 127.61, 128.58, 139.10, 210.97.

IR (neat): ν = 2962 s, 2175 s, 1715 vs, 1249 s, 1144 s, 1097 s, 1060 s, 842 s, 732 s cm^{-1}.

MS: *m*/*z* (% rel intensity) = 328 (M^+, 2), 237 (24), 220 (95), 205 (85), 181 (8), 165 (20), 151 (16), 99 (41), 91 (100), 73 (83), 65 (38).

Anal calcd for $C_{20}H_{28}O_2Si$: C, 73.12; H, 8.59. Found: C, 72.63; H, 8.95.

2-[4-Benzyloxy-4-methyl-2-(3-trimethylsilylprop-2-ynyl)]cyclohexylidene-1,3-dithiane (17)

Freshly distilled 2-(trimethylsilyl)-1,3-dithiane (5.73 mL, 29.88 mmol, 1.4 eq) was dissolved in THF (32 mL) and cooled to 0 °C. BuLi (1.87 mL, 1.6 M, 29.88 mmol, 1.4 equiv) was added and the mixture was stirred under N_2 for 40 min. A solution of the ketone **16** (7.0 g, 21.34 mmol, diastereomeric ratio 10:1) in THF (96 mL) was transferred to the above solution and the ice bath removed. The mixture was stirred for 3 h before it was quenched with aq satd NH_4Cl solution (10 mL). The solvent was removed and the residue extracted with Et_2O. After removal of the solvent, the crude product was loaded onto a silica gel column (4 × 20 cm) and eluted with a 1:1:25 mixture of Et_2O/CH_2Cl_2/hexane to give the unreacted 2-(trimethylsilyl)-1,3-dithiane and then with a 1:1:20 mixture to give 8.40 g (92%, diastereomeric ratio, 10:1) of **17** as a yellow oil. Major isomer R_f 0.35 (Et_2O/CH_2Cl_2/hexane, 1:1:16).

17b

^1H NMR ($CDCl_3$): δ = 0.18 (s, 9 H), 1.38 (s, 3 H), 1.73–1.80 (m, 1 H), 1.81–1.84 (m, 1 H), 2.01 (d, 2 H, *J* = 6.1 Hz), 2.06–2.16 (m, 3 H), 2.32–2.42 (m, 2 H), 2.72–2.78 (m, 1 H), 2.80–2.90 (m, 3 H), 2.99–3.05 (m, 1 H), 3.39–3.45 (m, 1 H), 4.42 (s, 2 H), 7.21–7.31 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 0.34, 24.86, 25.11, 25.28, 25.46, 30.33, 30.45, 35.78, 36.44, 38.52, 63.49, 74.37, 86.60, 105.62, 119.76, 127.22, 127.43, 128.36, 139.88, 143.57.

IR (neat): ν = 2931 s, 2172 s, 1452 m, 1429 m, 1380 m, 1248 s, 1103 s, 843 s, 734 s cm^{-1}.

MS: *m*/*z* (% rel intensity) = 430 (M^+, 8), 319 (21), 261 (23), 213 (100), 171 (22), 91 (95), 73 (45), 65 (13).

Anal calcd for $C_{24}H_{34}OS_2Si$: C,66.92; H, 7.96. Found: C, 65.91; H, 8.21.

Methyl 4-Benzyloxy-4-methyl-2-(prop-2-ynyl)cyclohexanecarboxylate (18b)

Compound **17b** (2.96 g, 6.89 mmol) was dissolved in MeCN (75 mL) and treated with H_2O (23 mL) and CF_3CO_2H (7.5 mL, 14.14 equiv). The mixture was stirred in the air at r.t. for 20 h. The solvent was completely removed in vacuo. The residue was taken up in pentane (60 mL) and Et_2O (60 mL) and the solution was washed with H_2O (3 × 5 mL). The solvent and CF_3CO_2H were removed in vacuo at 70 °C. The crude residue was cooled to 0 °C and treated with THF (55 mL), EtOH (23 mL), NaOH (23.7 mL, 2 N, 6.9 equiv) and H_2O_2 (7.38 mL, 30%, 10.5 equiv). The mixture was stirred at r.t. for several hours and with addition of extra 2 N NaOH as necessary until the TLC indicated that all compounds had been converted to the desired acid at R_f 0.10 (Et_2O/CH_2Cl_2/hexane, 1:1:6). The mixture was carefully neutralized with conc. HCl and the solvent removed. Et_2O (100 mL) was added and the aqueous layer was extracted twice more with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered through Celite. After the solvent was removed, the crude residue was treated with acetone (100 mL), MeI (10 mL) and K_2CO_3 (11.84 g) and refluxed under N_2 at 70 °C for 5 h. The solvent was removed and Et_2O (100 mL) was added. After filtration through Celite and washing the solid residue with several portions of Et_2O, the solvent was removed and the product purified by chromatography on silica gel to give 1.292 g of **18b** as a yellow oil in 63% yield; R_f 0.36 (Et_2O/CH_2Cl_2/hexane, 1:1:6).

^1H NMR ($CDCl_3$): δ = 1.29 (s, 3 H), 1.30–1.34 (m, 2 H), 1.77–1.80 (m, 1 H), 1.94–2.05 (m, 4 H), 2.11–2.27 (m, 1 H), 2.30–2.45 (m, 3 H), 3.69 (s, 3 H), 4.40 (s, 2 H), 7.22–7.37 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 23.50, 25.49, 25.69, 32.94, 35.08, 40.03, 47.24, 51.74, 63.15, 70.56, 73.31, 81.85, 127.33, 127.39, 128.49, 139.62, 175.94.

IR (neat): ν = 3304 s, 2933 s, 2100 w, 1729 s, 1451 s, 1435 s, 1382 m, 1331 s, 1265 s, 1169 s, 697 s cm^{-1}.

MS: *m*/*z* (% rel intensity) = 300 (M^+, 2), 285 (2), 269 (4), 261 (6), 194 (100), 177 (7), 153 (28), 133 (25), 105 (22), 91 (100), 77 (22), 65 (31).

Anal calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.50, H, 8.27.

Annulation of the Carbene Complex 5 with Acetylene 14b

A solution of the complex **5** (0.166 g, 0.48 mmol) and the acetylene **14b** (0.135 g, 0.60 mmol) in benzene (6 mL) was deoxygenated by the freeze-thaw method (3 cycles) and then stirred at 50 °C for 48 h. The mixture was stirred in air for 1 h and then concentrated and loaded onto a silica gel column and eluted with a 1:1:1 mixture of Et_2O/CH_2Cl_2/hexane to give the naphthol **19** as foamy solid in 60% yield (0.116 g, 0.29 mmol, R_f 0.36) along with the furan product **20** as a viscous oil in 10% yield (0.020 g, 0.05 mmol, R_f 0.52).

19

^1H NMR ($CDCl_3$): δ = 0.95–1.05 (m, 1 H), 1.05 (s, 3 H), 1.22–1.32 (m, 1 H), 1.70–1.80 (m, 3 H), 2.00–2.25 (m, 4 H), 2.82 (s, 3 H), 2.90–2.96 (m, 1 H), 3.78 (s, 3 H), 3.89 (s, 3 H), 3.96 (s, 3 H), 6.56 (s, 1 H), 6.81 (d, 1 H, *J* = 8.0 Hz), 7.30 (s, 1 H), 7.33 (t, 1 H, *J* = 8.0 Hz), 7.89 (d, 1 H, *J* = 8.0 Hz).

IR (neat): ν = 3407s, 2935s, 2829w, 1732s, 1706s, 1601s, 1464s, 1388s, 1378s, 1337m, 1292s, 1270s, 1211m, 1129s, 1075s, 1027m, 981m, 754m, 731m cm^{-1}.

MS: *m*/*z* (% rel. intensity) = 402 (M^+, 55), 370 (60), 338 (32), 310 (6), 244 (5), 218 (22), 217 (100), 216 (15), 203 (8), 189 (8), 175(5), 155 (6), 121 (24), 93 (11), 85 (10).

HRMS: *m*/*z* calcd for $C_{23}H_{30}O_6$ 402.2042, found 402.2082.

20

^1H NMR ($CDCl_3$): δ = 1.05–1.28 (m, 2 H), 1.07 (s, 3 H), 1.65–1.94 (m, 4 H), 2.05–2.22 (m, 3 H), 2.30–2.36 (m, 1 H), 3.09 (s, 3 H), 3.67 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 6.71 (s, 1 H), 6.89 (d, 1 H, *J* = 7.8 Hz), 6.95 (t, 1 H, *J* = 7.7 Hz), 7.13 (t, 1 H, *J* = 7.6 Hz), 7.65 (d, 1 H, *J* = 7.7 Hz).

IR (neat): ν = 2937s, 2843–2825br m, 1733s, 1642m, 1498m, 1492m, 1434m, 1282m, 1263m, 1244s, 1191m, 1166s, 1137m, 1080s, 1027m, 752m cm^{-1}.

MS: *m*/*z* (% rel. intensity) = 402 (M^+, 68), 376 (5), 342 (6), 323 (7), 295 (5), 246 (7), 229 (11), 218 (10), 209 (57), 193 (30), 190 (47), 185 (100), 169 (12), 153 (57), 135 (28), 133 (36), 123 (69), 115 (19), 105 (16), 93 (55), 85 (90), 72 (66).

HRMS: *m*/*z* calcd for $C_{23}H_{30}O_6$, found 402.2036.

The annulation reaction of **5** with 0.85 equivalent of acetylene **14b** was carried out in the same way as above. Workup and purification of the reaction mixture provided **19** in 54% yield along with the furan **20** in 9% yield. The reactions of **5** and **14b** in MeCN and hexane were carried out according to the procedure described above. A similar workup and purification procedure afforded a 53% yield of the annulated product **19** in MeCN and a 34% yield of **19** in hexane. The furan product **20** was also seen by ^1H NMR in the crude reaction mixture from MeCN, but it was not isolated.

2-[(2-Methoxycarbonyl-5-methoxy-5-methyl)methylcylohex-1-yl]-1,4,5-trimethoxynaphthalene (21)

A solution of compound **19** (1.362 g, 3.39 mmol) in acetone (70 mL) was refluxed with MeI (4.2 mL, 9.58 g, 67.4 mmol) and K_2CO_3 (4.69 g, 33.9 mmol). The product was purified by flash chromatography on silica gel with a 1:1:2 mixture of Et_2O/CH_2Cl_2/hexane to give **21** in 98% yield as a viscous oil (1.382 g, 3.32 mmol, R_f 0.19).

^{1}H NMR ($CDCl_3$): δ = 0.82–0.88 (m, 1 H), 0.98 (m, 3 H), 1.18–1.24 (m, 1 H), 1.70–1.76 (m, 2 H), 1.78–1.83 (m, 1 H), 1.88–1.93 (m, 1 H), 2.14–2.20 (m, 1 H), 2.32–2.41 (m, 1 H), 2.58–2.64 (m, 1 H), 2.70–2.76 (m 1 H), 2.93 (s, 3 H), 3.68 (s, 3 H), 3.79 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 6.66 (s, 1 H), 6.82 (d, 1 H, *J* = 7.7 Hz), 7.37 (t, 1 H, *J* = 8.1 Hz), 7.63 (d, 1 H, *J* = 8.3 Hz).

IR (neat): ν = 2934s, 2840m, 1732s, 1600s, 1584s, 1463s, 1448s, 1435m, 1383s, 1269s, 1239s, 1191s, 1166s, 1150m, 1130s, 1075s, 1028m, 1008m, 840m, 756m, 736m cm^{-1}.

MS: *m*/*z* (% rel. intensity) = 416 M^+ (100), 402 (10), 370 (11), 338 (6), 309 (11), 277 (4), 231 (10), 217 (31), 203 (17), 185 (5), 165 (5), 153 (4), 121 (7), 93 (8), 85 (13).

HRMS: *m*/*z* calcd for $C_{24}H_{32}O_6$ 416.2199, found 416.2232.

4,5,9,12-Tetramethoxy-9-methyl-6,7,8,9,10,11-hexahydronaphthacen-6-one (23)

The methyl ester **21** (74.6 mg, 0.18 mmol) was first hydrolyzed with NaOH solution (4 mL, 2 N) in MeOH (4 mL) at 75 °C for 4 h. After workup, the corresponding carboxylic acid **22** was obtained as oily residue which was subsequently treated with NaOH solution (0.1 N, 1.8 mL, 0.18 mmol). The mixture was lyophilized to dryness under reduced pressure and then dissolved in benzene (10 mL) and pyridine (0.2 mL). The mixture was cooled to 0 °C before oxalyl chloride (0.20 mL, 0.291 g, 2.29 mmol) was introduced. There was an immediate evolution of gases. The mixture was allowed to warm to r.t. for about 15 min. until no further evolution of gases was observed. $SnCl_4$ (0.10 mL) was slowly added and the resulting mixture was stirred at r.t. for 20 min before addition of H_2O (6 mL) and a 1:1 mixture of Et_2O and CH_2Cl_2 (30 mL). The organic phase was separated, washed with brine and H_2O, and dried ($MgSO_4$). After removal of the volatiles, elution of the residue on silica gel with a 1:1:1 mixture of Et_2O/CH_2Cl_2/hexane gave the product **23** in 72% overall yield (48.6 mg, 0.13 mmol, R_f 0.26) along with 1.5 mg of a yellow compound (R_f 0.44) which was not identified. The reaction was carried out on a gram scale without a change in the yield; mp 184–185 °C.

^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 3 H), 1.25–1.33 (m, 2 H), 1.65–1.74 (m, 1 H), 2.02–2.21 (m, 5 H), 2.49 (dd, 1 H, *J* = 16.5 Hz, 12 Hz), 3.15 (s, 3 H), 3.28 (dd, 1 H, *J* = 16.5 Hz, 3.9 Hz), 3.83 (s, 3 H), 3.90 (s, 3 H), 3.97 (s, 3 H), 6.83 (d, 1 H, *J* = 7.7 Hz), 7.46 (t, 1 H, *J* = 8.1 Hz), 7.62 (d, 1 H, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 21.34, 24.73, 31.15, 33.58, 33.84, 44.19, 48.56, 52.62, 56.41, 60.82, 63.24, 72.24, 72.42, 106.44, 114.25, 120.46, 123.51, 129.01, 130.52, 133.38, 147.97, 155.93, 158.67, 198.85.

IR (neat): ν = 2970s, 2920s, 2842m, 1681s, 1603m, 1557s, 1457m, 1432m, 1377m, 1362s, 1329s, 1273m, 1243m, 1069s, 1042m cm^{-1}.

MS: *m*/*z* (% rel. intensity) = 384 (M^+,1 00), 369 (40), 337 (5), 329 (9), 305 (7), 269 (7), 255 (6), 243 (11), 225 (5), 201 (5), 181 (5), 165 (8), 152 (6), 139 (5), 128 (5), 115 (7), 105 (5), 85 (34), 72 (15).

HRMS: *m*/*z* calcd for $C_{23}H_{28}O_5$ 384.1937, found 384.1958.

Anal calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found C, 71.74; H, 7.48.

6-Hydroxy-4,9-dimethoxy-9-methyl-7,8,9,10-tetrahydronaphthacen-5,12-dione (24)

To a solution of the naphthacenone **23** (42.7 mg, 0.11 mmol) in acetone (6 mL) were added 2 N HNO_3 (2.25 mL, 4.5 mmol) and AgO (279 mg, 2.25 mmol). The resulting mixture was stirred at r.t. and the reaction was monitored by TLC. After the starting material was consumed, a buffer solution (pH = 7.0, 10 mL) and CH_2Cl_2 (30 mL) were added. The organic phase was separated, washed with brine and H_2O, and dried ($MgSO_4$). After removal of the solvents, the crude quinone **24** was obtained as a orange foam.

^{1}H NMR ($CDCl_3$): δ = 1.16 (s, 3 H), 1.20–1.32 (10), 3.13 (s, 3 H), 3.95 (s, 3 H), 7.27 (d, 1 H, *J* = 8.2 Hz), 7.60–7.67 (m, 2 H).

IR (neat): ν = 2937s, 2826m, 1704s, 1663s, 1603m, 1586s, 1472s, 1305m, 1275s, 1241m, 1074m, 729m cm^{-1}.

The quinone **24** was dissolved in DMF (5 mL) and oxygen was gently bubbled through the solution at 100 °C for 2 h. After the DMF was removed by heating under vacuum, the orange solid was purified by flash chromatography on silica gel with a 1:1:1 mixture of Et_2O/CH_2Cl_2/hexane to afford the product **25** in 93% (35.8 mg, 0.10 mmol) overall yield from **23**. This reaction was conducted many times and occasionally it gave rise to a mixture of the products **25** and **26**. They could not be separated by chromatography. The formation of the undesired product **26**, however, could be avoided if the second oxidation was performed without solvent. The crude quinone **24** was coated on the inside of the flask which was heated opened to air at 70 °C for 24 h. Flash chromatography of the residue on silica gel provided the product **25** in a range of 85–92% yield.

Spectral Data for 26 (extracted from a mixture of 25 and 26)

^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 3 H), 1.55–1.65 (m, 1 H), 2.00–2.08 (m, 1 H), 2.48–2.55 (m, 1 H), 2.70–3.01 (m, 3 H), 3.18 (s, 3 H), 4.00 (s, 3 H), 7.27 (d, 1 H, *J* = 7.7 Hz), 7.66 (t, 1 H, *J* = 7.9 Hz), 7.92 (d, 1 H, *J* = 8.1 Hz), 13.40 (s, 1 H), 13.77 (s, 1 H).

MS: *m*/*z* (% rel. intensity) = 368 (M^+, 100), 352 (40), 336 (70), 296 (30), 280 (17).

25: mp 164–166 °C.

^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3 H), 1.70–1.78 (m, 1 H), 2.07–2.13 (m, 1 H), 2.77–2.90 (m, 3 H), 2.98–3.04 (m, 1 H), 3.23 (s, 3 H), 4.06 (s, 3 H), 7.32 (d, 1 H, *J* = 8.5 Hz), 7.49 (s, 1 H), 7.70 (t, 1 H, *J* = 7.8 Hz), 7.93 (d, 1 H, *J* = 7.6 Hz), 13.32 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 20.85, 23.09, 30.89, 41.35, 49.17, 56.64, 72.00, 114.07, 117.95, 119.80, 120.06, 120.92, 129.69, 133.20, 135.47, 135.96, 143.88, 160.66, 160.74, 182.81, 188.83.

IR (neat): ν = 3345br w, 2968m, 2926s, 2849m, 1670m, 1625s, 1586s, 1445m, 1383m, 1298m, 1273s, 1251s, 1240s, 1105m, 739m cm^{-1}.

MS: *m*/*z* (% rel. intensity) = 352 (M^+, 20), 337 (15), 321 (30), 320 (100), 305 (58), 293 (12), 280 (14), 262 (9).

HRMS: *m*/*z* calcd for $C_{21}H_{20}O_5$ 352.1310, found 352.1302.

Anal calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.51; H, 6.01.

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