Synthesis of 4,11-Dideoxydaunomycinone by a Claisen/Diels–Alder Sequence

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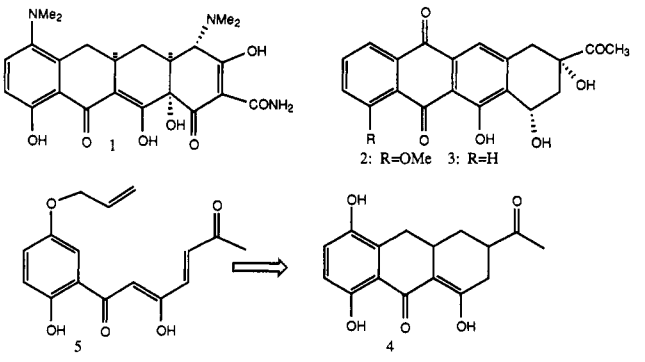
The synthesis of **3** from ketone **6** by a Claisen/Diels–Alder sequence uncovered some fascinating differences between the benzene and naphthalene series. The most direct pathway to **3** is **6–20–21–16–17–18**.

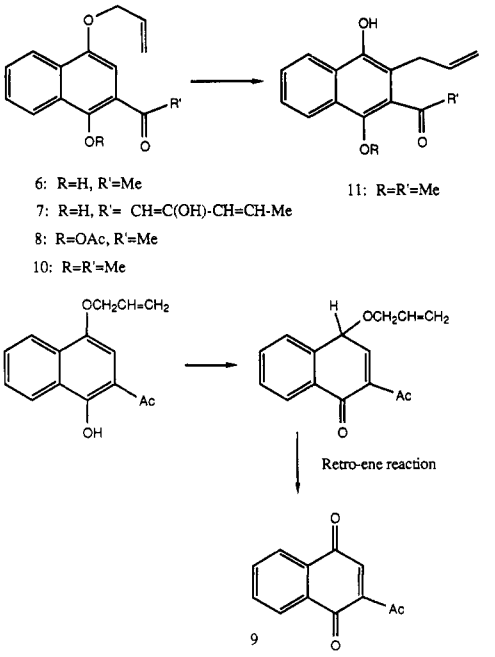
The tetracyclines and the anthracyclines are two medicinally significant classes of compounds. Minocycline (**1**)[1] is a broad spectrum tetracycline antibiotic whose duration of activity is longer than that of tetracycline itself. This is in part due to the absence of the 6-hydroxyl group which can cause the fragmentation of the tetracycline skeleton. Compound **2** is 11-deoxydaunomycinone, an anthracycline anticancer agent.[2] We recently developed a tandem Claisen/Diels–Alder reaction sequence for the preparation of a common intermediate to both classes of compounds[3] (Scheme I). This sequence was highly regioselective and led to the synthesis of **2** and its 4-demethoxy analogue **3**.[4] Elaboration of the tricyclic intermediate **4** for the synthesis of a useful tetracycline has not yet been achieved. An attractive alternative would be to begin with a substituted naphthalene and simply append the remaining two rings by the tandem Claisen/Diels–Alder sequence. The recent discovery by Scott and Wasserman that tetracyclines could be regenerated from certain naphthalenes by singlet oxygen protocol[5] should make the route applicable to either anthracyclines or tetracyclines.

The readily available ketone **6** was converted into diketone **7** by acyl transfer chemistry.[6] Diketone **7** was heated at 230 °C in degassed benzene in a pressure tube to initiate the tandem Claisen/Diels–Alder reaction. Unfortunately, a tarry mixture of several products resulted. In order to better understand this unexpected result, the ketone **6** was also heated at 230 °C in benzene. Again, a mixture of products resulted. The major identifiable product was the naphthoquinone **9**. After several experiments it became clear that the Claisen reaction did not proceed cleanly unless the phenol was blocked by either an acyl group or a methoxyl group. Our best rationale for this unexpected behavior is depicted in Scheme II. Compound **6** could tautomerize to **12**, which may lose propene by an intramolecular retro-ene reaction. Some retro-ene reactions do take place around 220 °C.[7] This provides a plausible route to naphthoquinone **9**. This proposed mechanism is consistent with the observation that acetylated or methylated phenols afford the normal Claisen rearrangement products.

Scheme I



Scheme II



With compound **11** in hand, the next task was the intermolecular acylation. In order to intersect with an intermediate in our previous synthesis, we reacted the lithium enolate of **11** with either acid chloride **13**[4] or the corresponding acyl imidazolide. Several experimental variations provided only traces of the desired diketone. Since the intramolecular acyl transfer reaction had worked well, ketone **11** was first silylated with TBSCl and imidazole to afford **14**. The methyl ether was then cleaved with boron trichloride in methylene chloride to generate **15** in 55% yield from **11**. Acyl transfer using lithium diiso-

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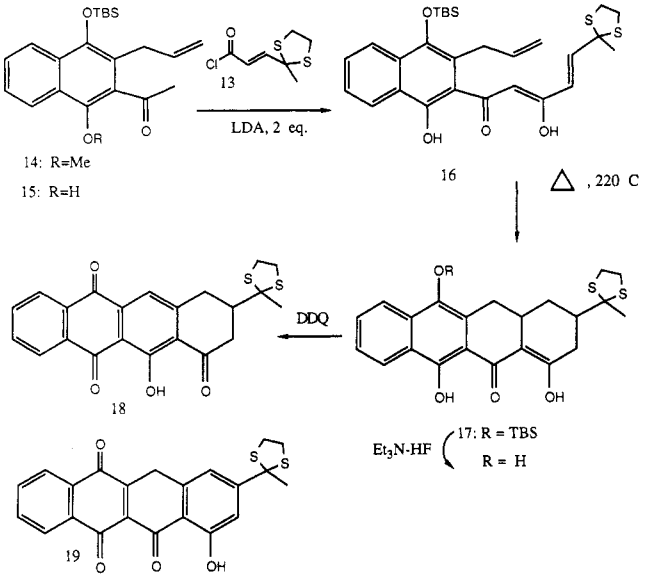
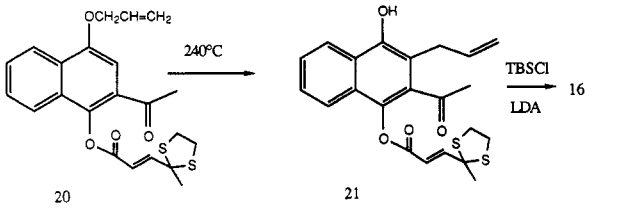
(2) Arcamone, F. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Chapter 1.
(3) Kraus, G. A.; Fulton, B. S. *J. Org. Chem.* **1985**, *50*, 1782.
(4) Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1987**, *52*, 4841.
(5) Wasserman, H. H.; Lu, T. J.; Scott, A. I. *J. Am. Chem. Soc.* **1986**, *108*, 4237.
(6) Kraus, G. A.; Fulton, B. S. *J. Org. Chem.* **1984**, *49*, 3212.
(7) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.

0022-3263/89/1954-3137$01.50/0

Scheme III



Scheme IV



propylamide (LDA) instead of potassium *tert*-butoxide provided diketone **16** in 74% yield. When diketone **16** was heated in degassed benzene at 210 °C for 3 h, a 75% yield of tetracyclic diketone **17** was obtained (Scheme III).

Removal of the TBS group with tetrabutylammonium fluoride afforded a compound whose NMR spectrum exhibited an AB quartet centered around δ 6.5 and no cyclohexanone protons. Fortunately, treatment of **17** with triethylamine–HF provided the naphthydroquinone in 76% yield. It is important to monitor the desilylation reaction carefully, since long reaction times afforded significant amounts of the compound produced in the tetrabutylammonium fluoride reaction. Oxidation of the freshly prepared naphthydroquinone with DDQ in benzene rapidly afforded anthraquinone **18** in 72.3% yield. Compound **18** was partially converted into the unknown compound described above by slow passage through silica gel. Based on proton NMR, mass spectroscopy, and IR spectroscopy, we tentatively postulate the structure of the unknown compound to be anthrone **19**. Anthraquinone **18** was identical with an authentic sample from our previous route by 300-MHz NMR, IR, and TLC comparison.

This route is reasonably direct, despite the modest yields encountered in the removal of the methyl and TBS groups. One way by which the efficiency could be improved is illustrated in Scheme IV. Ketone **20** was readily prepared from phenol **6** and acid chloride **13**. This compound was heated in degassed benzene at 240 °C for 15 h to generate allyl ketone **21** in almost quantitative yield. However, the acyl-transfer reaction with 2 equiv of LDA failed. Other variants involving tBuOK or potassium hexamethyldisilazane also failed. Protection of the phenol with TBSCl and imidazole proceeded in quantitative yield. This protection permitted us to intersect with the route described in Scheme III.

Our most effective pathway to **3** proceeds in six steps in 26% overall yield from phenol **6**. While it is not as direct as the tandem Claisen/Diels–Alder strategy that we originally projected, it will be useful for the synthesis of certain analogues. Additionally, with the requisite diene segment, the route described herein could become an attractive one for the synthesis of tetracyclines.

Experimental Section

The purity of all title compounds was judged to be ≥90% by ^{1}H NMR spectral determinations.

1-(1-Methoxy-4-(2-propenyloxy)-2-naphthyl)ethan-1-one (10). To a solution of hydroxy ketone **6** (1.51 g, 6.24 mmol) in 25 mL of acetone was added potassium carbonate (1.72 g, 12.48 mmol) followed by methyl iodide (2.65 g, 18.7 mmol). The mixture was heated to reflux for 12 h. The reaction was cooled, diluted with water, and acidified to pH 6 with 2 N HCl. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography with 7:1 hexanes–ethyl acetate to afford 1.57 g of ketone **10** (98% yield). NMR ($CDCl_3$): δ 2.80 (s, 3 H), 3.90 (s, 3 H), 4.6–4.8 (m, 2 H), 5.2–5.6 (m, 2 H), 6.1–6.4 (m, 1 H), 7.1 (s, 1 H), 7.5–7.9 (m, 2 H), 8.1–8.2 (m, 1 H), 8.25–8.4 (m, 1 H). IR (CH_2Cl_2): 1670, 1590, 910 cm^{-1}. MS: *m/e* 115, 165, 181, 198, 226, 241, 256. HMRS: *m/e* calcd 256.10995, measured 256.11036. TLC (10:1 H:EA): R_f 0.16. Yellow oil.

1-(4-Hydroxy-1-methoxy-3-(2-propenyl)-2-naphthyl)ethan-1-one (11). A solution of ketone **10** (1.56 g, 6.1 mmol) in 14 mL of benzene was deoxygenated and sealed in a glass tube. The tube was heated at 240 °C for 16 h. The tube was cooled, the reaction mixture was concentrated, and the residue was purified by flash chromatography with 6:1 hexanes–ethyl acetate to afford 1.31 g of ketone **11** (84% yield). NMR ($CDCl_3$): δ 2.60 (s, 3 H), 3.4–3.48 (m, 2 H), 3.88 (s, 3 H), 5.1–5.32 (m, 2 H), 5.05 (s, 1 H), 5.95–6.15 (m, 1 H), 7.5–7.6 (m, 2 H), 8.0–8.1 (m, 1 H), 8.19–8.28 (m, 1 H). IR ($CDCl_3$): 1690, 1590, 1420, 890 cm^{-1}. MS: *m/e* 115, 128, 165, 198, 226, 241, 256. HRMS: calcd 256.10995, measured 256.11036. TLC (7:1 H:EA): R_f = 0.31. Yellow oil.

1-[4-[(*tert*-Butyldimethylsilyl)oxy]-1-methoxy-3-(2-propenyl)-2-naphthyl]ethan-1-one (14). To a solution of ketone **11** (1.02 g, 3.98mmol) in 7 mL of DMF at 0 °C was added imidazole (0.81 g, 11.94 mmol) and TBSCl (1.20 g, 7.96 mmol). The reaction was allowed to warm to ambient temperature and stir for 8 h. The solution was diluted with ether, washed with brine, dried, and concentrated. The crude product was purified by flash chromatography with 7:1 hexanes–ethyl acetate to afford 1.43 g of ketone **14** (97% yield). NMR ($CDCl_3$): δ 0.40 (s, 6 H), 1.10 (s, 9 H), 2.60 (s, 3 H), 3.41–3.64 (m, 2 H), 3.80 (s, 3 H), 4.81–5.14 (m, 2 H), 5.67–5.97 (m, 1 H), 7.41–7.63 (m, 2 H), 7.97–8.18 (m, 2 H). IR ($CDCl_3$): 1680, 1570, 1350, 870 cm^{-1}. MS: *m/e* 73, 165, 223, 270, 298, 313, 340, 355, 370. HRMS: calcd 370.19643, measured 370.19636. ^{13}C NMR ($CDCl_3$): δ -2.97, -2.70, 18.70, 26.14, 26.3, 31.0, 33.1, 63.5, 116.6, 121.12, 121.9, 123.7, 127.2, 129.0, 133.3, 136.3, 145.5, 147.2, 205.7. TLC (7:1 H:EA): R_f = 0.45. White solid, mp 70–71 °C (EtOAc). Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.37; H, 8.17. Found: C, 71.58; H, 8.27.

1-[4-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-3-(2-propenyl)-2-naphthyl]ethan-1-one (15). To a solution of ketone **14** (1.04 g, 2.8 mmol) in 6 mL of methylene chloride at -78 °C was added a solution of boron trichloride (1.65 g, 14 mmol) in 7 mL of methylene chloride. The solution initially turned orange and then to red after the addition. The solution was stirred at -78 °C for 10 min and then at ambient temperature for 10 min. The solution was diluted with water, a saturated solution of NaOAc was added, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography with 6:1 hexanes–ethyl acetate to afford 0.55 g of ketone **15** (55% yield). NMR ($CDCl_3$): δ 0.13 (s, 6 H), 1.12 (s, 9 H), 2.67 (s, 3 H), 3.78–3.89 (m, 2 H), 4.85–5.1 (m, 2 H), 5.75–5.95 (m, 1 H), 7.41–7.65 (m, 2 H), 7.98 (d, J = 8.4 Hz, 1 H), 8.40 (d, J = 8.4 Hz, 1 H), 13.05 (s, 1 H). IR ($CDCl_3$): 1620, 1570, 1370, 890 cm^{-1}. MS: *m/e* 167, 207, 224, 256, 281, 299, 323, 338, 356. HRMS: calcd 356.18078, measured 356.18137. ^{13}C NMR ($CDCl_3$): δ -3.1, -2.9, 18.6, 26.1, 26.3, 31.8, 32.7, 116.1, 116.4, 120.8, 123.0, 124.4, 125.3, 127.8, 129.0, 131.4, 137.0, 141.6, 156.0, 206.1. TLC (8:1 H:EA): R_f = 0.41. Yellow oil. Anal. Calcd for $C_{21}H_{28}O_3Si$:

C, 70.80; H, 7.92. Found: C, 70.37; H, 7.91.

Acyclic Naphthol Diketone 16. To a suspension of hexane-washed NaH (0.04 g, 1.64 mmol) in 2 mL of THF was added a solution of ketone **15** (0.53 g, 1.49 mmol) in THF. The resulting solution was stirred at 0 °C for 15 min. A solution of acid chloride **13** (0.34 g, 1.64 mmol) in THF was added dropwise, and the solution was stirred at 0 °C for 30 min. The solution was then cooled to −78 °C, and LDA (3.28 mmol) in THF was added dropwise. The solution was then stirred for 15 min. It was diluted with water and acidified to pH 6 with 6 N HCl. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography with 7:1 hexanes–ethyl acetate to afford 0.58 g of ketone **16** (74% yield). NMR ($CDCl_3$): δ 0.17 (s, 6 H), 1.10 (s, 9 H), 1.96 (s, 3 H), 3.40–3.75 (m, 6 H), 4.9–5.1 (m, 2 H), 5.90–5.97 (m, 1 H), 6.02 (d, J = 16 Hz, 1 H), 7.00 (d, J = 16 Hz, 1 H), 7.5–7.6 (m, 2 H), 7.97 (d, J = 8.4 Hz, 1 H), 8.34 (d, J = 8.4 Hz, 1 H), 11.03 (s, 1 H), 14.98 (s, 1 H). IR ($CDCl_3$): 1640, 1570, 1360, 910 cm^{-1}. MS: m/e 73, 173, 257, 299, 314, 356, 409, 439, 453, 471, 495, 510, 528. HRMS: calcd 528.18244, measured 528.18244. ^{13}C NMR ($CDCl_3$): δ −2.9, −2.5, 18.7, 26.1, 28.6, 33.4, 40.4, 64.1, 103.5, 116.1, 116.7, 120.3, 121.1, 123.0, 123.9, 124.7, 125.5, 128.2, 130.6, 136.3, 142.4, 146.6, 152.5, 174.1, 196.5. TLC (7:1 H:EA): R_f = 0.30. Orange solid, mp 180 °C dec. Anal. Calcd for $C_{28}H_{36}O_4S_2Si$: C, 63.66; H, 6.87. Found: C, 63.38; H, 6.94.

4,6-Dihydroxy-11-[(*tert*-butyldimethylsilyl)oxy]-2-(2-methyl-1,3-dithiolan-2-yl)tetrahydronaphthacen-5-one (17). A solution of ketone **16** (0.86 g, 1.64 mmol) in 8 mL of benzene was degassed and sealed in a glass tube. The solution was heated to 220 °C for 3 h. The reaction mixture was cooled and concentrated. The crude product was purified by chromatography with 3:1 hexanes–ethyl acetate to afford 0.63 g of compound **17** (73% yield). NMR ($CDCl_3$): δ 0.11 (s, 3 H), 0.13 (s, 3 H), 1.12 (s, 9 H), 1.80 (s, 3 H), 2.1–3.66 (m, 11 H), 7.45–7.62 (m, 2 H), 7.96 (d, J = 8.4 Hz, 1 H), 8.37 (d, J = 8.4 Hz, 1 H), 13.2 (s, 1 H), 14.17 (s, 1 H). IR ($CDCl_3$): 1610, 1570, 1420, 905 cm^{-1}. MS: m/e 73, 91, 111, 173, 356, 409, 436, 528. HRMS: calcd 528.18244, measured 528.18340. ^{13}C NMR ($CDCl_3$): δ −3.05, −3.056, 18.73, 26.20, 29.77, 30.77, 31.80, 32.30, 33.97, 39.36, 40.42, 40.67, 70.34, 107.71, 110.38, 122.85, 124.12, 124.68, 125.21, 129.09, 132.27, 138.67, 157.1, 176.52, 193.05. TLC (10:1 H:EA): R_f = 0.19. Orange solid, mp 164–166 °C (EtOAc). Anal. Calcd for $C_{28}H_{36}O_4S_2Si$: C, 63.66; H, 6.87. Found: C, 64.35; H, 6.89.

4,6,11-Trihydroxy-2-(2-methyl-1,3-dithiolan-2-yl)tetrahydronaphthacen-5-one. To a solution of ketone **17** (0.24 g, 0.46 mmol) in 4 mL of THF was added triethylamine–HF (0.08 g, 0.69 mmol). The solution was stirred at ambient temperature until TLC indicated that the starting material was gone (ca. 1 h). The solution was concentrated, and the crude product was purified by chromatography with 3:1 hexanes–ethyl acetate to afford 0.14 g (76% yield) of pure product that was normally taken onto the next step immediately. NMR ($CDCl_3$): δ 1.89 (s, 3 H), 2.25–3.58 (m, 11 H), 4.65 (s, 1 H), 7.4–7.75 (m, 2 H), 8.01 (d, J = 8.4 Hz, 1 H), 8.38 (d, J = 8.4 Hz, 1 H), 13.21 (s, 1 H), 14.01 (s, 1 H). IR ($CDCl_3$): 1730, 1420, 890 cm^{-1}. MS: m/e 83, 173, 239, 265, 318, 414. HRMS: calcd 414.09596, measured 414.09587. TLC (3:1 H:EA): R_f = 0.26. Orange solid, mp 225 °C dec.

5-Hydroxy-2-(2-methyl-1,3-dithiolan-2-yl)dihydronaphthacene-4,6,11-trione (18). To a solution of the ketone from the desilylation reaction (0.14 g, 0.34 mmol) in 4 mL of benzene at 5 °C was added DDQ (0.16 g, 0.71 mmol). The solution was allowed to warm to ambient temperature over 1 h. The suspension was filtered and concentrated. The crude product was purified on silica gel with 2:1 hexanes–ethyl acetate to afford 0.10 g (72.3% yield) of quinone **18**. TLC (1:1 H:EA): R_f = 0.23. The spectral data are identical with those described in ref 4.

1-[4-(2-Propenyloxy)-1-[[4,4-(ethylenedithio)-2-pentenoyl]oxy]-2-naphthyl]ethan-1-one (20). To a suspension of hexane-washed NaH (.05 g, 2.2 mmol) in 2 mL of THF at 0 °C was added a solution of hydroxy ketone **6** (0.48 g, 1.98 mmol) in THF. The resulting solution was stirred at 0 °C for 15 min. Acid chloride **13** (0.46 g, 2.2 mmol) was added dropwise, and the solution was allowed to warm to ambient temperature over 1 h. The solution was diluted with water. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude product was purified by chromatography with 5:1 hexanes–ethyl acetate to afford 0.71 g of ester **20** (87% yield). NMR ($CDCl_3$): δ 2.02 (s, 3 H), 2.61 (s, 3 H), 3.33–3.53 (m, 4 H), 4.74–4.80 (m, 2 H), 5.36–5.66 (m, 2 H), 6.15–6.28 (m, 1 H), 6.93 (d, J = 15 Hz, 1 H), 7.18 (s, 1 H), 7.41 (d, J = 15 Hz, 1 H), 7.54–7.60 (m, 2 H), 7.62–7.84 (m, 1 H), 8.32–8.34 (m, 1 H). IR ($CDCl_3$): 1730, 1680, 1590, 1410, 890 cm^{-1}. MS: m/e 85, 102, 127, 155, 173, 210, 242, 414. HRMS: calcd 414.09596, measured 414.09582. ^{13}C NMR ($CDCl_3$): δ 27.84, 27.90, 30.40, 40.3, 63.3, 69.1, 103.1, 115.2, 117.7, 122.4, 122.6, 126.9, 127.6, 127.7, 127.8, 128.4, 132.6, 140.3, 152.0, 154.5, 165.1, 197.1. TLC (5:1 H:EA): R_f = 0.31. Yellow solid, mp 85–87 °C (EtOAc–hexanes).

1-[1-[[4-(Ethylenedithio)-2-pentenoyl]oxy]-4-hydroxy-3-(2-propenyl)-2-naphthyl]ethan-1-one (21). A solution of ester **20** (0.24 g, 0.58 mmol) in 6 mL of benzene was degassed and sealed in a glass tube. The solution was heated to 240 °C for 15 h. The solution was cooled, concentrated and purified by chromatography with 3:1 hexanes–ethyl acetate to afford 0.237 g of ester **21** (99% yield). NMR ($CDCl_3$): δ 2.00 (s, 3 H), 2.51 (s, 3 H), 3.33–3.51 (m, 6 H), 5.20–5.27 (m, 2 H), 5.70 (s, 1 H), 5.55–6.10 (m, 1 H), 6.24 (d, J = 15 Hz, 1 H), 7.34 (d, J = 15 Hz, 1 H), 7.45–7.53 (m, 2 H), 7.60–7.66 (m, 1 H), 8.10–8.19 (m, 1 H). IR ($CDCl_3$): 1730, 1680, 1420, 890 cm^{-1}. MS: m/e 105, 173, 198, 240, 414. HRMS: calcd 414.09596, measured 414.09587. ^{13}C NMR ($CDCl_3$): δ 27.9, 31.2, 32.3, 40.3, 63.3, 114.2, 114.7, 116.7, 120.7, 121.8, 125.5, 125.8, 126.5, 126.9, 132.6, 135.2, 135.6, 148.3, 154.7, 165.4, 203.4. TLC (5:1 H:EA): R_f = 0.30. Yellow solid, mp 154–156 °C (EtOAc–hexanes).

1-[1-[[4-(Ethylenedithio)-2-pentenoyl]oxy]-4-[(*tert*-butyldimethylsilyl)oxy]-3-(2-propenyl)-2-naphthyl]ethan-1-one. To a solution of hydroxy ester **21** (0.08 g, 0.19 mmol) in 2 mL of DMF at 0 °C were added imidazole (0.04 g, 0.60 mmol) and TBSCl (0.04 g, 0.29 mmol). The solution was allowed to warm to ambient temperature and to stir for 8 h. The solution was then diluted with ether, washed with brine, dried, and concentrated. The ester (0.096 g) was isolated in 96% yield. NMR ($CDCl_3$): δ 0.20 (s, 6 H), 1.12 (s, 9 H), 1.99 (s, 3 H), 2.48 (s, 3 H), 3.30–3.60 (m, 6 H), 4.9–5.05 (m, 2 H), 5.78–5.93 (m, 1 H), 6.24 (d, J = 15.3 Hz, 1 H), 7.33 (d, J = 15.3 Hz, 1 H), 7.47–7.50 (m, 2 H), 7.62–7.65 (m, 1 H), 8.06–8.08 (m, 1 H). IR ($CDCl_3$): 1730, 1640, 1420, 890 cm^{-1}. MS: m/e 73, 173, 299, 338, 356, 528. HRMS: calcd 528.18203, measured 528.18244. ^{13}C NMR ($CDCl_3$): δ −3.03, −2.96, 18.73, 25.60, 26.06, 27.95, 31.09, 32.36, 40.40, 63.44, 67.92, 88.52, 115.11, 116.43, 120.84, 121.66, 123.55, 126.33, 126.65, 126.75, 128.64, 133.38, 136.11, 137.19, 147.40, 154.49, 164.84, 203.17. TLC (5:1 H:EA): R_f = 0.45. Yellow oil. Anal. Calcd for $C_{28}H_{30}O_4S_2Si$: C, 63.66; H, 6.87. Found: C, 63.55; H, 6.74.

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