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) 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 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 protocol6 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. This proposed mechanism is consistent with the observation that acetylated or methylated phenols afford the normal Claisen rearrangement products.

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 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 TBSCI 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-
propylamid (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 triethylamine-HF provided the naphthydroquinone in 78% yield. The 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 TBSCI 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/Dieck-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 1H NMR spectral determinations.

1-(1-Methoxy-4-(2-propenylxoy)-2-naphthyl)acetyl-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 acidic 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 6:l hexanes-ethyl acetate to afford 1.57 g of ketone 10 (98% yield). NMR (CDCl3): 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 (CH2Cl2): 1670, 1650, 910 cm-1. MS: m/e 115, 165, 191, 226, 241, 256. HRMS: m/e calcd 256.10995, measured 256.11036. TLC (10:1 H2O:EA): Rf = 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:l hexanes-ethyl acetate to afford 1.31 g of ketone 11 (84% yield). NMR (CDCl3): 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 (CDCl3): 1690, 1590, 820 cm-1. MS: m/e 115, 128, 165, 196, 226, 241, 256. HRMS: m/e calcd 256.10995, measured 256.11036. TLC (7:1 H2O:EA): Rf = 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, 3.88 mmol) in 7 mL of DMF at 0 °C was added imidazole (0.81 g, 11.94 mmol) and TBSCI (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 6:l hexanes-ethyl acetate to afford 0.86 g of ketone 14 (71% yield). NMR (CDCl3): 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), 4.85-5.14 (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 (CDCl3): 1680, 1570, 870 cm-1. MS: m/e 73, 165, 223, 270, 293, 313, 340, 355, 370. HRMS: m/e calcd 570.19643, measured 570.19636. 13C NMR (CDCl3): δ 7.1-9.4. 1H NMR (CDCl3): δ 26.14, 26.3, 31.0, 33.1, 63.5, 112.6, 121.12, 121.8, 123.7, 127.2, 129.0, 133.2, 134.3, 145.5, 147.2, 205.7. TLC (7:1 H2O:EA): Rf = 0.45. White solid, mp 70-71 °C (EtOAc). Anal. Calcd for C27H31O3Si: 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 (1.15 g, 12.6 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:l hexanes-ethyl acetate to afford 0.55 g of ketone 15 (55% yield). NMR (CDCl3): 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, 1 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 (CDCl3): 1620, 1570, 1370, 890 cm-1. MS: m/e 187, 207, 224, 256, 281, 299, 323, 338, 356. HRMS: m/e calcd 356.18073, measured 356.18137. 13C NMR (CDCl3): 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 H2O:EA): Rf = 0.41. Yellow oil. Anal. Calcd for C27H31O3Si:
Acyclic Naphthol Diketone 16. To a suspension of hexane-washed NaH (0.46 g, 2.2 mmol) in THF was added triethylamine-HF (0.08 g, 0.58 mmol) in 4 mL of THF at 0 °C. The solution was stirred for 20 min. The solution was cooled at 0 °C and added dropwise, and the solution was stirred for 15 min. The solution was then filtered and concentrated. The crude product was purified by chromatography with 3:1 hexanes-ethyl acetate to afford 0.23 g (99% yield). NMR (CDCl3): 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), 7.50-7.66 (m, 1 H), 8.10-8.19 (m, 1 H). IR (CDCl3): 1730, 1640, 1420, 890 cm⁻¹. MS: m/e 105, 173, 198, 240, 314. HRMS: calc 414.0956, measured 414.0958. TLC (5:1 H:EA): Rf = 0.30. Yellow solid, mp 154-156 °C (EtOAc-hexanes).

1-[(4-Ethenedithio-2-pentenyl)oxy]-4-[(2-propenyl)oxy]-3-(2-propenyl)-2-naphthyllethan-1-one (21). To 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 (99% yield). NMR (CDCl3): δ 2.50 (s, 3 H), 2.99 (s, 3 H), 2.91-3.13 (m, 6 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), 8.52-8.54 (m, 1 H). IR (CDCl3): 1730, 1580, 1360, 910 cm⁻¹. MS: m/e 75, 102, 155, 173, 210, 242, 414. HRMS: calc 414.0956, measured 414.0958. 13C NMR (CDCl3): 6 δ 27.9, 29.7, 31.3, 32.3, 40.3, 63.3, 114.2, 114.7, 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, 203.4. TLC (5:1 H:EA): Rf = 0.20. Yellow solid, mp 154-156 °C (EtOAc-hexanes).