# Synthesis of the Naphthoquinone Nucleus of Awamycin

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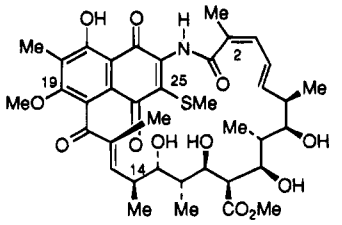
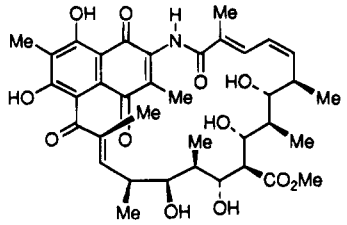
A synthesis of ketone **4**, corresponding to the fully elaborated naphthoquinone nucleus of awamycin, is described. The synthesis involves the Diels–Alder reaction between diene **8** and quinone **9** to construct naphthoquinone **10**, the coupling of bromide **15** and an ansa chain surrogate **17** via an aryllithium intermediate, and a late stage 1,4-addition of NaSMe to naphthoquinone **23** to afford the ketone **4**.

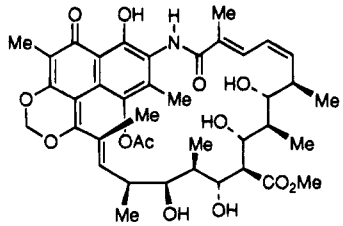
Awamycin (**1**) is a structurally complex ansamycin antibiotic isolated from several *Streptomyces* species.[1,2] Awamycin is active against Gram-positive bacteria, protozoa, and murine tumors *in vivo* and is cytotoxic to HeLa cells *in vitro*.[1,2] The stereostructure of awamycin, proposed initially on the basis of spectroscopic correlations to other well-known ansamycin antibiotics,[2–4] was subsequently confirmed by a single crystal X-ray analysis, which also established the absolute configuration.[5]




awamycin (**1**)




damavaricin D (**2**, DmD)




streptovaricin D (**3**, SvD)

Awamycin is structurally similar to damavaricin D (**2**, DmD),[6] a degradation product and a biosynthetic precursor of the even more complex ansamycin antibiotic streptovaricin D (**3**).[4,7] The stereochemistry of the C(5)–C(14) segment of awamycin is identical to that proposed for DmD. The structures of DmD and awamycin differ in that the diene system in DmD is 2(*E*),4(*Z*), whereas the diene system in awamycin is 2(*Z*),4(*E*), as in the rifamycins.[4] Also, the C(19) phenol in DmD is replaced by a methyl ether in awamycin, while C(25) in awamycin is substituted with a thiomethyl group *versus* a methyl group in DmD.

The ansamycins have been the target of many synthetic endeavors over the past two decades.[8] We are currently pursuing the total synthesis of streptovaricin D by a route that proceeds via damavaricin D.[9] We have reported on syntheses of the fully elaborated C(1)–C(15) ansa chain segment,[9a] suitably protected naphthoate precursors, and the methodology for their coupling.[9b] As yet unpublished are our successful macrocyclization experiments in this series.[9c] Several other synthetic approaches to the streptovaricin ansa chains also have been published.[10]

We report herein on a synthesis of ketone **4** representing the fully elaborated aromatic nucleus of **1**. The synthesis involves a Diels–Alder reaction between diene **8**[11] and quinone **9**,[12] paralleling the strategy used in our synthesis of the naphthalenic nucleus of DmD.[9b,13] Sub-

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1995.

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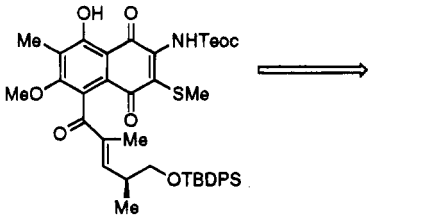
sequent elaboration of the Diels–Alder adduct **10** to the targeted awamycin naphthoquinone model **4** includes the coupling of the derived bromide **15** and aldehyde **17** *via* the aryllithium intermediate prepared from **15**. The final stages of the synthesis involve generation of naphthoquinone **23** and introduction of the thiomethyl substituent *via* a 1,4-addition reaction, a process patterned after previous work with the thiazorifamycins.[14] This synthesis not only enabled us to develop conditions for introduction of the C(25) thiomethyl substituent but also allowed us to explore conditions for the late stage generation of the quinone functionality, which should prove useful in the completion of syntheses of both awamycin and DmD.

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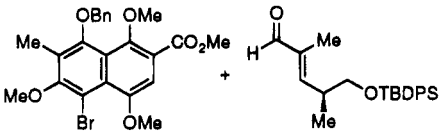
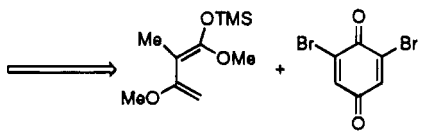



15 17

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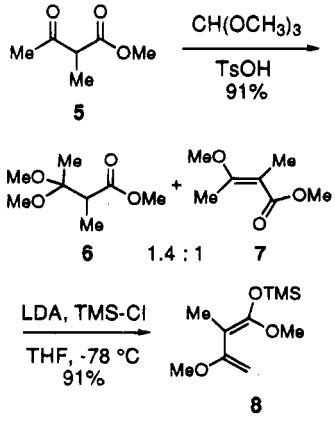
## Results and Discussion

Diene **8** was synthesized starting from methyl 2-methylacetoacetate **5**, which when treated with trimethyl orthoformate and catalytic TsOH for 24 h at ambient temperature afforded a 1.4:1 mixture of dimethyl ketal **6** and the known methyl enol ether **7**[15] in 91% yield. Because we were unable to develop conditions that effected complete conversion of ketal **6** to methyl enol ether **7** in good yield, the mixture of **6** and **7** was used directly in the subsequent step. Thus, treatment of a 1.4:1 mixture of **6** and **7** with 1.8 equiv of LDA and excess TMSCl at −78 °C afforded crude diene **8** in 91% yield. Diene **8** is thermally unstable[11] and was used directly in the cycloaddition step without purification.




5

6 1.4 : 1 7

8

Cyclocondensation of diene **8** with quinone **9** afforded the corresponding naphthoquinone **10** in 85% yield. Benzylation of the crude naphthoquinone **10** with benzyl bromide and $Ag_2O$ in $CHCl_3$ afforded benzyl ether **11** in 81% yield. Attempted reductive methylation of **11** using Luche conditions ($NaBH_4$ and $CeCl_3$, followed by $Me_2SO_4$ and NaOH),[16] as employed in our earlier synthesis of the naphthalenic nucleus of DmD,[9b] was unsuccessful. We then turned to a reductive methylation procedure described by Kraus,[17] which involved reduction of benzyl ether **11** with aqueous $Na_2S_2O_4$ in THF in the presence of *n*-$Bu_4NBr$ as a phase transfer catalyst followed by methylation *in situ* (50% KOH, $Me_2SO_4$), which gave dimethyl ether **12** in 78% yield. Following the precedent established in the synthesis of the naphthalenic unit of DmD,[9b] we decided to delay the introduction of the aniline functionality until after coupling with the surrogate ansa chain. Thus, treatment of dimethyl ether **12** with *t*-BuLi in THF at −78 °C and subsequent addition of $CO_2$ gas afforded acid **13** in 85% yield. Esterification of **13** with DBU and MeI in $CH_3CN$ then provided methyl ester **14** in 97% yield. Attempts at producing methyl ester **14** directly from **12** by treatment with *n*-BuLi and subsequent addition of methyl chloroformate produced significant amounts (15–30%) of ketone **16** along with other unidentified products (Scheme 1).

Bromination of methyl ester **14** was necessary to facilitate the coupling with the α,β-unsaturated aldehyde **17**. However, subjection of **14** to a variety of standard bromination conditions (NBS in refluxing $CHCl_3$, $Br_2$ in HOAc, and NBS in DMF) provided relatively low yields (10–25%) of bromide **15**. After much experimentation, we found that the reaction of methyl ester **14** with NBS and catalytic $H_2SO_4$ in THF[18] gave the desired bromide **15** in 94% yield.

Treatment of a solution of **15** in THF at −100 °C with *n*-BuLi followed by addition of the model ansa chain aldehyde **17**[19] gave alcohol **18** as a *ca.* 1:1 mixture of diastereomers in 70% yield. Oxidation of the mixture of alcohols **18** with the Dess–Martin periodinane[20] and pyridine in $CH_2Cl_2$ gave enone **19** as an inseparable 1:1 mixture of atropisomers in 85% yield.[21] Hydrolysis of **19** by treatment with $LiOH·H_2O$ in 2:2:1 THF/MeOH/$H_2O$ provided acid **20** in 92% yield, again as an inseparable 1:1 mixture of atropisomers. Acid **20** was then subjected to standard Curtius rearrangement conditions in the

(13) Syntheses of the naphthalenic ring systems of several other ansamycin antibiotics have utilized analogous cycloaddition strategies: (a) Kozikowski, A. P.; Sugiyama, K.; Springer, J. P. *Tetrahedron Lett.* **1980**, *21*, 3257. (b) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899. (c) Parker, K. A.; Petraitis, J. J. *Tetrahedron Lett.* **1981**, *22*, 397. (d) Nakata, M.; Wada, S.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1801. (e) Trost, B. M.; Pearson, W. H. *Tetrahedron Lett.* **1983**, *24*, 269. (f) Kelly, T. R.; Behforouz, M.; Echavarren, A.; Vaya, J. *Tetrahedron Lett.* **1983**, *24*, 2331.

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(16) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

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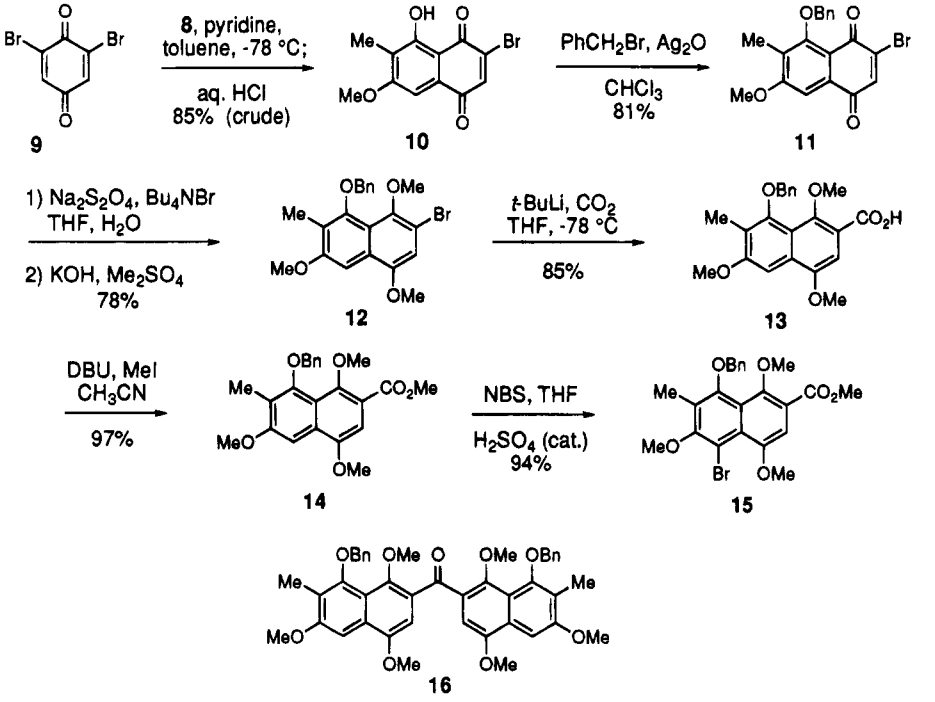
(19) Aldeyde **17** was prepared by standard transformations starting from commercially available (*R*)-methyl β-hydroxyisobutyrate: (a) Patterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182. (b) Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menendez, J. C.; Organ, H. M.; White, A. D.; Banks, B. J. *Tetrahedron* **1992**, *48*, 7899. (c) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, *52*, 316.

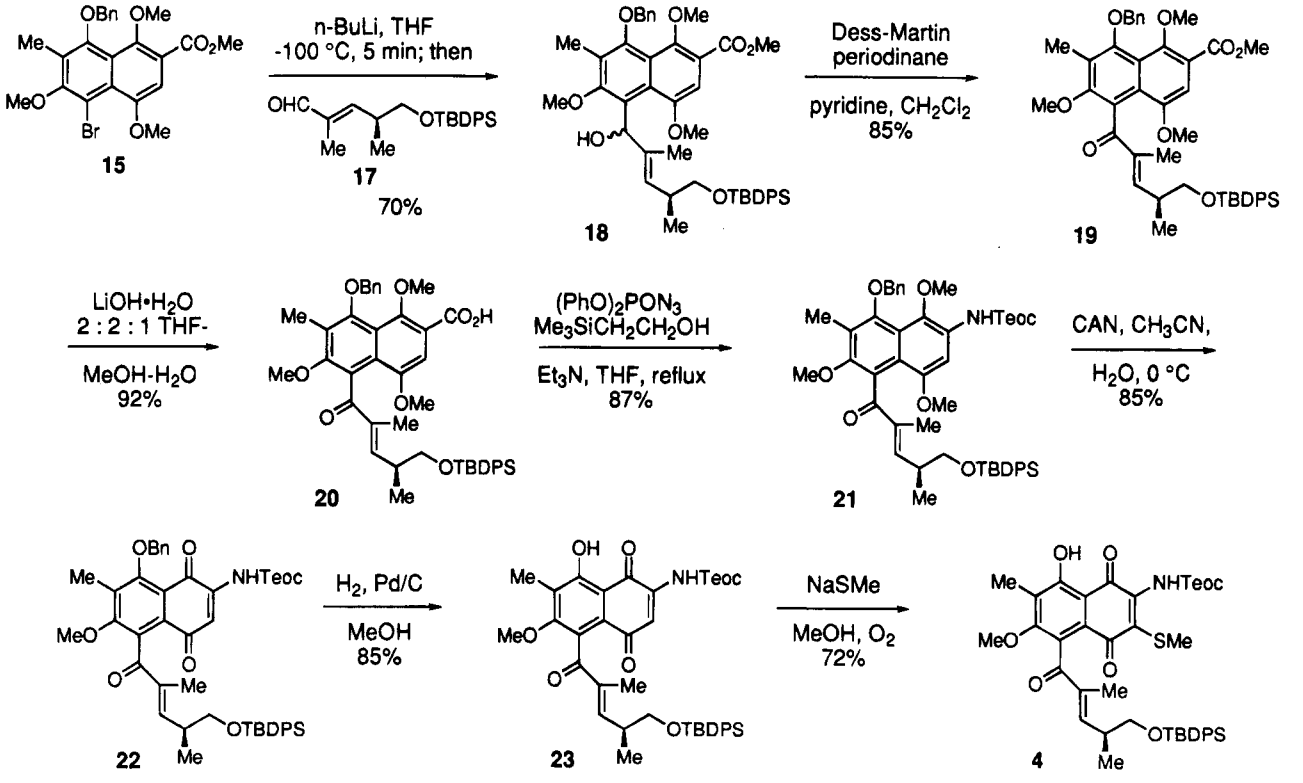
(20) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(21) Variable-temperature $^1H$ NMR studies revealed the coalescence temperature of **19** to be ca. 140 °C. For a general review of atropisomerism, see: (a) Oki, M. *Top. in Stereochem.* **1983**, *14*, 1. (b) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219.

**Scheme 1**




**Scheme 2**




presence of $Me_3SiCH_2CH_2OH$ ($(PhO)_2PON_3$, $Et_3N$, THF, reflux)[22] which provided carbamate **21** as a 1:1 mixture of atropisomers in 87% yield. Treatment of **21** with ceric ammonium nitrate (CAN) in aqueous $CH_3CN$ at 0 °C generated naphthoquinone **22** as a 1:1 mixture of atropisomers in 85% yield. The benzyl group of **22** was removed by hydrogenolysis ($H_2$, 10% Pd/C, MeOH, 85% yield). Partial reduction of the naphthoquinone was observed under these conditions, but the dihydronaphthoquinone was easily reoxidized by bubbling air through the solution once the hydrogenolysis was complete. Reversal of the two preceding steps (*i.e.*, removal of the benzyl group followed by CAN oxidation) resulted in much lower yields of naphthoquinone **23** (50–65%). Thus, the former sequence was preferred (Scheme 2).

With **23** in hand, we were ready to attempt the introduction of the thiomethyl group. We assumed that MeSH would undergo 1,4-addition to the quinone to form the hydroquinone and that subsequent air oxidation

(22) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

would provide the desired product, **4**. However, initial attempts at introducing the thiomethyl group were only marginally successful. For example, treatment of **23** with NaSMe[23] (2.0 equiv) in MeOH for 30 min gave **4** but in only 25–30% yield, along with recovered **23** (20–30%) and several other unidentified products. Interestingly, however, products resulting from 1,4-addition to the side chain enone were not observed. Longer reaction times led to the production of greater amounts of products believed to derive from hydrolysis of the carbamate group, and shorter reaction times (5–10 min) resulted in the isolation of unreacted **23** and only small amounts of **4**. Further experimentation showed that the yield of **4** was improved by using a larger number of equivalents of NaSMe and a more concentrated solution of naphthoquinone **23**. Longer reaction times (*ca.* 30 min), however, again resulted in the formation of what appeared to be carbamate hydrolysis products. After extensive experimentation, we also determined that the yields of **4** were improved if the reactions were performed under an $O_2$ atmosphere. In the final analysis, the optimal conditions involved treating a solution of naphthoquinone **23** (0.2 M in MeOH) with a large excess of NaSMe (15 equiv) under an $O_2$ atmosphere for 10 min, which gave **4** as a 1:1 mixture of atropisomers in 72% yield. Here again, products of 1,4-addition to the side chain enone were not observed.

In summary, an efficient synthesis of the aromatic nucleus of awamycin has been accomplished. We anticipate that the conditions we have developed for introduction of the thiomethyl substituent should be useful in the final stage of an awamycin synthesis.

## Experimental Section

**General.** All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under dry argon or nitrogen. All solvents were purified before use. Ether, THF, and toluene were distilled from sodium benzophenone ketyl. $CH_2Cl_2$ and $CH_3CN$ were distilled from $CaH_2$. $CH_3OH$ was distilled from magnesium turnings. Low-temperature reactions were maintained by using a Neslab Cryocool CC-100 II cooling apparatus.

NMR and IR spectra were measured on commercially available instruments. High-resolution mass spectra were measured at 70 eV. Analytical and semipreparative HPLC separations were performed by using a HPLC system composed of two Rainin HXPL pumps (gradient), a Rheodyne 7125 injector, a Dynamax UV-C detector, and a Shimadzu CR601 integrator. Analytical thin-layer chromatography (TLC) was performed by using plates coated with a 0.25 mm layer of silica gel (Kieselgel). Compounds were visualized by staining (and charring) of the TLC plates with vanillin or ceric ammonium molybdate solutions. Preparative thin-layer chromatography was performed by using 20 cm × 20 cm plates coated with a 0.25 or 0.5 mm thick layer of silica gel (Kieselgel). Flash chromatography was performed as described by Still using Kieselgel 60 (230–400 mesh) silica gel.[24] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by $^1H$ analysis) for use in subsequent reactions.

**Methyl 3,3-Dimethoxy-2-methylbutanoate (6) and Methyl 3-Methoxy-2-methyl-2-butenoate (7).** A solution of methyl 2-methylacetoacetate (20.0 g, 150 mmol), trimethyl orthoformate (24.5 g, 230 mmol), and *p*-toluenesulfonic acid monohydrate (1.5 g, 7.7 mmol) was stirred for 24 h at 23 °C. Excess trimethyl orthoformate was removed by distillation, and the crude product was then purified by vacuum distillation (63–69 °C at 6 mmHg) to give a 1.4:1 mixture of ketal **6** and the known[15] methyl enol ether **7** (22.8 g, 91% yield) as a clear liquid. Data for ketal **6**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.69 (s, 3 H), 3.22 (s, 3 H), 3.17 (s, 3 H), 2.97 (q, $J$ = 7.2 Hz, 1 H), 1.35 (s, 3 H), 1.15 (d, $J$ = 7.2 Hz, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.2, 102.2, 51.8, 48.5, 47.8, 44.6, 17.4, 13.0; IR ($CHCl_3$) 2998, 2953, 1732 $cm^{-1}$; HRMS calcd for $C_7H_{13}O_4$ ($M^+ - CH_3$) 161.0814, found 161.0813. $^1H$ NMR data for methyl enol ether **7**:[15] $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.72 (s, 3 H), 3.69 (s, 3 H), 2.38 (q, $J$ = 1.2 Hz, 3 H), 1.79 (q, $J$ = 1.2 Hz, 3 H).

**1,3-Dimethoxy-2-methyl-1-(trimethylsiloxy)-1,3-butadiene (8).**[11] To a −78 °C solution of diisopropylamine (39.1 mL, 280 mmol) in THF (217 mL) was added *n*-BuLi (102 mL, 2.5 M, 250 mmol). The solution was stirred for 30 min, and then a 1.4:1 mixture of ketal **6** and methyl enol ether **7** (22.8 g, 140 mmol) was added *via* cannula over a period of 15 min. The solution was stirred for 30 min at −78 °C, and then chlorotrimethylsilane (40.7 mL, 320 mmol) was added. The solution was stirred for 30 min at −78 °C and then allowed to warm to 23 °C over a period of 2 h. The solution was concentrated *via* a vacuum pump and filtered under an Ar atmosphere through a sintered glass funnel. The filtrate was concentrated *via* a vacuum pump to give crude diene **8**[11] (27.4 g, 91% yield) as a yellow oil that was used without further purification: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.10 (d, $J$ = 0.2 Hz, 1 H), 4.05 (d, $J$ = 0.2 Hz, 1 H), 3.55 (s, 3 H), 3.53 (s, 3 H), 1.69 (s, 3 H), 0.20 (s, 9 H).

**3-Bromo-5-hydroxy-7-methoxy-6-methyl-1,4-naphthoquinone (10).** A solution of diene **8** (21.4 g, 99 mmol) in toluene (65 mL) was added to a −78 °C solution of benzoquinone **9**[12] (17.5 g, 66 mmol) and pyridine (12.1 mL, 149 mmol) in toluene (100 mL) over a period of 15 min. The resulting green solution was stirred at −78 °C for 3 h, and then the mixture was poured into 1 N HCl (500 mL). The solution was extracted with EtOAc (3 × 350 mL) and $CH_2Cl_2$ (2 × 350 mL). The combined organic extracts were dried over $MgSO_4$ for 2 h. The orange solution was filtered and concentrated *in vacuo* to afford an orange solid, which was triturated using ice cold hexanes (2 × 250 mL). This gave crude naphthoquinone **10** (16.7 g, 85% yield) which was used directly in the next step without further purification. A small sample was recrystallized from hexanes/EtOAc for characterization purposes: mp 167–168 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 12.04 (s, 1 H), 7.39 (s, 1 H), 7.19 (s, 1 H), 3.99 (s, 3 H), 2.17 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 181.8, 181.3, 163.7, 161.7, 140.2, 139.9, 130.5, 120.7, 108.6, 103.2, 56.3, 8.3; IR ($CHCl_3$) 3200–2900 (br), 1660, 1630, 1585 $cm^{-1}$; HRMS calcd for $C_{12}H_9BrO_4$ ($M^+$) 295.9684, found 295.9689.

**5-(Benzyloxy)-3-bromo-7-methoxy-6-methyl-1,4-naphthoquinone (11).** A solution of crude naphthoquinone **10** (10.0 g, 33.4 mmol) in $CHCl_3$ (100 mL) was added *via* cannula to a solution of benzyl bromide (16.1 mL, 135 mmol) and silver (I) oxide (39.1 g, 169 mmol) in $CHCl_3$ (325 mL) over a period of 30 min. The solution was stirred for 6 h, filtered, and concentrated *in vacuo* to afford a brown oil. Purification of the crude product by flash chromatography with 80% hexanes/15% $Et_2O$/5% $CH_2Cl_2$ afforded benzyl ether **11** (10.5 g, 81% yield) as a yellow solid: mp 161–162 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.59–7.35 (m, 7 H), 4.98 (s, 2 H), 3.97 (s, 3 H), 2.14 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 182.4, 175.5, 163.0, 158.9, 142.5, 138.2, 136.7, 132.7, 129.0, 128.7, 128.5, 128.3, 117.4, 104.8, 75.6, 56.3, 9.7; IR ($CHCl_3$) 3030, 3005, 1665, 1595, 1575 $cm^{-1}$; HRMS calcd for $C_{19}H_{15}BrO_4$ ($M^+$) 388.0134, found 388.0126. Anal. Calcd for $C_{19}H_{15}BrO_4$: C, 58.93; H, 3.90. Found: C, 58.68; H, 4.04.

**5-(Benzyloxy)-3-bromo-1,4,7-trimethoxy-6-methylnaphthalene (12).** Aqueous sodium dithionite (10.8 g, 61.8 mmol, in 30 mL of $H_2O$) was added to a bright yellow solution of benzyl ether **11** (4.0 g, 10.3 mmol) and tetrabutylammonium bromide (0.017 g, 0.052 mmol) in THF (52 mL) and $H_2O$ (21 mL). The solution was stirred for 30 min, at which point the bright yellow color had disappeared, and KOH (15 mL, 50% solution) was added. The resulting dark red solution was stirred for 5 min, then $Me_2SO_4$ (19.5 mL, 206 mmol) was added, and the solution was stirred vigorously for 10 h. The solution was poured into $H_2O$ (200 mL) and extracted with $CH_2Cl_2$ (2

(23) NaSMe was purchased from Fluka.
(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

× 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a brown solid. Purification of the crude product by flash chromatography with 5% $Et_2O$/hexanes afforded dimethyl ether **12** (3.35 g, 78% yield) as a white solid: mp 137–139 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.60–7.35 (m, 6 H), 6.91 (s, 1 H), 4.91 (s, 2 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 3.77 (s, 3 H), 2.32 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.1, 151.9, 151.1, 145.7, 137.8, 128.5, 128.4, 127.9, 126.5, 123.0, 119.1, 111.7, 108.3, 96.7, 76.5, 62.1, 55.9, 55.6, 9.7; IR ($CHCl_3$) 3005, 2978, 2965, 1615, 1588 $cm^{-1}$; HRMS calcd for $C_{21}H_{21}BrO_4$ ($M^+$) 416.0623, found 416.0622. Anal. Calcd for $C_{21}H_{21}BrO_4$: C, 60.44; H, 5.07. Found: C, 60.42; H, 5.10.

**5-(Benzyloxy)-1,4,7-dimethoxy-6-methyl-3-naphthoic Acid (13).** To a −78 °C solution of dimethyl ether **12** (1.78 g, 4.3 mmol) in THF (21 mL) was added *t*-BuLi (1.7 M, 5.8 mL, 9.8 mmol) over a period of 10 min. The resulting red solution was stirred for 15 min, and then dry $CO_2$ was bubbled through the solution for 30 min. The solution was stirred for an additional 30 min at −78 °C and then allowed to warm to rt. The solution was partitioned between 1 M $NaHSO_4$ (50 mL) and EtOAc (75 mL). The aqueous phase was extracted with EtOAc (75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a brown oil. Purification of the crude product by flash chromatography (65% hexanes/30% EtOAc/5% HOAc) afforded acid **13** (1.4 g, 85% yield) as a white solid: mp 169–171 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.50–7.39 (m, 7 H), 4.85 (s, 2 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 2.33 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.4, 159.5, 152.8, 151.4, 150.4, 137.1, 130.6, 128.6, 128.3, 128.2, 123.7, 116.4, 115.66, 103.8, 97.1, 76.7, 65.2, 56.0, 55.8, 9.6; IR ($CHCl_3$) 3300–2900 (br), 1730, 1615 $cm^{-1}$; HRMS calcd for $C_{22}H_{22}O_6$ ($M^+$) 382.1417, found 382.1418.

**Methyl 5-(Benzyloxy)-1,4,7-trimethoxy-6-methylnaphth-3-oate (14).** 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.90 mL, 6.0 mmol) and $CH_3I$ (0.47 mL, 7.5 mmol) were added to a solution of acid **13** (1.2 g, 3.0 mmol) in $CH_3CN$ (5 mL). The solution was stirred for 2 h and then was diluted with $H_2O$ (30 mL) and EtOAc (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a light brown solid. Purification of the crude product by flash chromatography (10% $Et_2O$/hexanes) afforded the methyl ester **14** (1.2 g, 97% yield) as a white solid: mp 113–115 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58–7.35 (m, 6 H), 7.11 (s, 1 H), 4.92 (s, 2 H), 4.02 (s, 3 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 2.30 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 158.7, 153.8, 151.3, 150.3, 137.7, 129.6, 128.5, 128.4, 127.8, 122.8, 118.7, 118.4, 104.0, 96.5, 76.6, 63.9, 55.9, 55.7, 52.2, 9.7; IR ($CHCl_3$) 3000, 2960, 1730, 1605, 1575 $cm^{-1}$; HRMS calcd for $C_{23}H_{24}O_6$ ($M^+$) 396.1573, found 396.1592. Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.69; H, 6.10. Found: C, 69.36; H, 6.26.

**Methyl 5-(Benzyloxy)-8-bromo-1,4,7-trimethoxy-6-methylnaphth-3-oate (15).** To a 23 °C solution of ester **14** (0.74 g, 1.5 mmol) in THF (19 mL) were added *N*-bromosuccinimide (NBS) (0.35 g, 2.0 mmol) and $H_2SO_4$ (50 $\mu$L). The solution was stirred for 6 h, and then $NaHCO_3$ (75 mg) was added, followed by 10% aqueous $NaHSO_3$ (20 mL). The resulting mixture was stirred for 10 min and then poured into EtOAc (75 mL). The phases were separated, and the organic phase was washed with $H_2O$ (2 × 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a brown oil. Purification of the crude product by flash chromatography (15% $Et_2O$/hexanes) afforded the bromide **15** (0.81 g, 94% yield) as a light yellow oil: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.50–7.35 (m, 5 H), 7.19 (s, 1 H), 4.87 (s, 2 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.36 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.0, 157.3, 153.8, 151.9, 150.4, 137.3, 128.5, 128.4, 128.0, 127.4, 126.8, 123.1, 121.3, 107.5, 107.1, 76.7, 64.0, 60.1, 56.1, 52.4, 11.0; IR ($CHCl_3$) 3020, 3000, 2930, 1725, 1600, 1575 $cm^{-1}$; HRMS calcd for $C_{23}H_{23}BrO_6$ ($M^+$) 476.0658, found 476.0678. Anal. Calcd for $C_{23}H_{23}BrO_6$: C, 58.12; H, 4.88. Found: C, 58.31; H, 4.98.

**Methyl 5-(Benzyloxy)-8-[(4′*S*,2′*E*)-5′-(*tert*-butyldiphenylsiloxy)-1′-hydroxy-2′,4′-dimethylpent-2′-en-1′-yl]-1,4,7-trimethoxy-6-methylnaphth-3-oate (18).** To a −100 °C ($Et_2O$/liquid $N_2$) solution of bromide **15** (1.2 g, 2.6 mmol) in THF (9.0 mL) were added dropwise *n*-BuLi (0.90 mL, 2.5 M, 2.3 mmol) over a period of 10 min. The resulting solution was stirred for 5 min, and then a solution of aldehyde **17** (0.64 g, 1.7 mmol) in THF (4.0 mL) was added *via* cannula over a period of 15 min. This mixture was stirred at −100 °C for 30 min and subsequently allowed to warm to 23 °C over 1 h. The solution was then partitioned between brine (100 mL) and $Et_2O$ (100 mL). The organic phase was washed with brine (2 × 100 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification of the crude product by flash chromatography (25% $Et_2O$/hexanes) afforded the alcohol **18** (0.94 g, 1.2 mmol, 70% yield based on **17**) as a 1:1 mixture of diastereomers. Also recovered were **14** (0.20 g, 0.50 mmol, 19%) and **15** (0.31 g, 0.65 mmol, 25%). Small samples of the two diastereomers were separated by HPLC (22% EtOAc/hexane, 15 mL/min) for characterization purposes.

**Data for diastereomer A**: $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 7.78–7.73 (m, 4 H), 7.45 (s, 1 H), 7.43 (s, 1 H), 7.26–7.10 (m, 10 H), 6.51 (d, $J$ = 11.2 Hz, 1 H), 5.22 (broad s, 1 H), 4.74 and 4.72 (AB quartet, $J_{AB}$ = 10.6 Hz, 2 H), 4.34 (d, $J$ = 11.6 Hz, 1 H), 3.85 (s, 3 H), 3.62 (s, 3 H), 3.59 (s, 3 H), 3.57 (m, 1 H), 3.38 (B of ABX, $J_{AB}$ = 8.8 Hz, $J_{BX}$ = 8.8 Hz, 1 H), 3.08 (s, 3 H), 2.69 (m, 1 H), 2.31 (s, 3 H), 1.63 (s, 3 H), 1.15 (s, 9 H), 1.01 (d, $J$ = 6.4 Hz, 3 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) $\delta$ 167.1, 159.5, 154.4, 151.7, 140.2, 138.2, 136.0, 136.0, 134.4, 134.3, 130.0, 129.9, 128.58, 128.6, 126.5, 121.4, 106.6, 76.5, 68.9, 64.0, 61.7, 54.9, 51.9, 35.7, 27.1, 19.5, 17.9, 14.8, 10.7; IR ($CHCl_3$) 3500, 3020, 3005, 2950, 2925, 1720, 1605, 1580 $cm^{-1}$.

**Data for diastereomer B**: $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 7.70–7.67 (m, 4 H), 7.45 (s, 1 H), 7.43 (s, 1 H), 7.21–7.13 (m, 10 H), 6.51 (d, $J$ = 12.0 Hz, 1 H), 5.09 (d, $J$ = 7.2 Hz, 1 H), 4.74 and 4.71 (AB quartet, $J_{AB}$ = 10.6 Hz, 2 H), 4.39 (d, $J$ = 12.4 Hz, 1 H), 3.86 (s, 3 H), 3.62 (s, 3 H), 3.57 (s, 3 H), 3.46 and 3.36 (AB of ABX, $J_{AB}$ = 9.7 Hz, $J_{AX}$ = 5.2 Hz, $J_{BX}$ = 7.4 Hz, 2 H), 3.10 (s, 3 H), 2.66 (m, 1 H), 2.33 (s, 3 H), 1.78 (s, 3 H), 1.10 (s, 9 H), 0.95 (d, $J$ = 6.8 Hz, 3 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) $\delta$ 167.1, 159.4, 154.4, 151.7, 140.2, 138.2, 136.0, 134.3, 134.2, 129.9, 128.7, 128.6, 128.5, 126.4, 124.8, 123.1, 121.4, 106.7, 76.5, 68.9, 64.0, 61.7, 55.0, 51.9, 35.8, 27.0, 19.4, 14.8, 10.7; IR ($CHCl_3$) 3500, 1725, 1605, 1580 $cm^{-1}$; HRMS calcd for $C_{42}H_{45}O_8Si$ ($M^+ - C_4H_9$) 705.2884, found 705.2892.

**Methyl 5-(Benzyloxy)-8-[(4′*S*,2′*E*)-5′-(*tert*-butyldiphenylsiloxy)-2′,4′-dimethyl-1′-oxopent-2′-en-1′-yl]-1,4,7-trimethoxy-6-methylnaphth-3-oate (19).** To a 0 °C solution of Dess–Martin periodinane[22] (0.30 g, 0.71 mmol) and pyridine (0.057 mL, 0.71 mmol) in $CH_2Cl_2$ (1.0 mL) was added dropwise a solution alcohol **18** (0.36 g, 0.47 mmol, 1:1 mixture of diastereomers) in $CH_2Cl_2$ (1.4 mL). The resulting solution was allowed to warm to 23 °C and stir for 1 h. The solution was then diluted with saturated aqueous $NaHCO_3$ (25 mL) and 1 M $Na_2S_2O_3$ (25 mL). The biphasic solution was stirred for 30 min and then extracted with $Et_2O$ (100 mL). The organic phase was washed with brine (2 × 25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of the crude product by flash chromatography (40% $Et_2O$-hexanes) afforded ketone **19** (0.31 g, 85% yield) as an approximate 1:1 mixture of atropisomers (white foam): $[\alpha]^{25}_D$ −28.6 (*c* 0.8, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58–7.49 (m, 12 H), 7.43–7.28 (18 H), 7.04 (s, 1 H), 6.98 (s, 1 H), 5.98 (dd, $J$ = 9.6 Hz, $J$ = 1.2 Hz, 2 H), 4.92 and 4.90 (AB quartet, $J_{AB}$ = 10.0 Hz, 4 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.58 (s, 3 H), 3.48 and 3.44 (AB of ABX, $J_{AB}$ = 9.7 Hz, $J_{AX}$ = 5.2 Hz, $J_{BX}$ = 5.8 Hz, 2 H), 3.41 and 3.35 (A′B′ of A′B′X′, $J_{AB}$ = 9.7 Hz, $J_{AX}$ = 5.6 Hz, $J_{BX}$ = 5.8 Hz, 2 H), 2.80 (m, 2 H), 2.32 (s, 3 H), 2.31 (s, 3 H), 2.03 (d, $J$ = 1.6 Hz, 3 H), 1.98 (d, $J$ = 1.2 Hz, 3 H), 1.02 (d, $J$ = 6.8 Hz, 6 H), 0.92 (s, 9 H), 0.90 (s, 9 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 198.2, 198.1, 167.1, 167.0, 156.3, 156.2, 154.7, 151.0, 150.7, 146.7, 146.3, 138.53, 137.5, 135.5, 135.4, 133.5, 129.6, 128.4, 127.9, 127.6, 127.0, 126.3, 126.2, 125.3, 125.1, 121.3, 120.8, 105.9, 105.5, 67.3, 67.3, 64.0, 62.1, 56.0, 52.3, 36.3, 36.2, 26.6, 26.6, 19.1, 16.6, 16.3, 11.6, 10.3; IR ($CHCl_3$) 1730, 1700, 1605, 1575 $cm^{-1}$; HRMS calcd

for $C_{42}H_{43}O_8Si$ ($M^+ - C_4H_9$) 703.2728, found 703.2739. Anal. Calcd for $C_{46}H_{52}O_8Si$: C, 72.60; H, 6.89. Found: C, 72.39; H, 6.94.

**5-(Benzyloxy)-8-[(4′*S*,2′*E*)-5′-(*tert*-butyldiphenylsiloxy)-2′,4′-dimethyl-1′-oxopent-2′-en-1′-yl]-1,4,7-trimethoxy-6-methyl-3-naphthoic Acid (20).** $LiOH·H_2O$ (0.10 g, 2.4 mmol) was added to a solution of ester **19** (0.12 g, 0.16 mmol) in 2:2:1 THF/MeOH/$H_2O$ (20 mL). The resulting solution was stirred at 23 °C for 18 h and then was partitioned between 1 N $NaHSO_4$ (50 mL) and $Et_2O$ (50 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification of the crude product by flash chromatography (50% $Et_2O$/45% hexanes/5% HOAc) afforded acid **20** (0.11 g, 92% yield) as an approximate 1:1 mixture of atropisomers (white foam): $[\alpha]^{25}_D$ −26.5° (*c* 0.9, $CHCl_3$); $^1H$ NMR (400 MHz, $C_6D_6$) δ 7.67−7.49 (m, 10 H), 7.30−7.13 (m, 22 H), 6.25 (dd, *J* = 9.2 Hz, *J* = 1.2 Hz, 1 H), 6.18 (dd, *J* = 8.8 Hz, *J* = 1.6 Hz, 1 H), 4.56−4.48 (m, two overlapping AB quartets, 4 H), 3.62 (s, 3 H), 3.59 (s, 3 H), 3.44 (A of ABX, $J_{AB}$ = 9.6 Hz, $J_{AX}$ = 5.2 Hz, 1 H), 3.37−3.32 (m, overlap of AB of ABX and A′B′X′, 2 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 3.28 (B′ of A′B′X′, $J_{AB}$ = 9.8 Hz, $J_{BX}$ = 5.4 Hz, 1 H), 3.14 (s, 3 H), 3.09 (s, 3 H), 2.64 (m, 2 H), 2.22 (s, 3 H), 2.19 (s, 3 H), 2.14 (d, *J* = 1.6 Hz, 3 H), 2.12 (d, *J* = 1.2 Hz, 3 H), 1.05 (s, 9 H), 0.95 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.67 (d, *J* = 6.8 Hz, 3 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) δ 196.5, 166.6, 157.5, 157.4, 154.3, 152.2, 150.7, 145.6, 145.2, 139.3, 139.1, 137.6, 135.9, 135.8, 135.8, 133.9, 133.6, 129.9, 128.7, 128.4, 127.2, 127.1, 127.0, 120.3, 120.3, 119.6, 106.5, 106.2, 76.7, 67.6, 64.6, 62.4, 55.9, 55.8, 36.5, 36.4, 26.9, 26.9, 19.4, 19.3, 16.6, 16.3, 12.0, 11.9, 10.3; IR ($CHCl_3$) 3300 (br), 1730, 1705, 1605, 1575 $cm^{-1}$; HRMS calcd for $C_{45}H_{51}O_8Si$ ($M^+$ + 1) 747.3354, found 747.3330.

**5-(Benzyloxy)-8-[(4′*S*,2′*E*)-5′-(*tert*-butyldiphenylsiloxy)-2′,4′-dimethyl-1′-oxopent-2′-en-1′-yl]-1,4,7-trimethoxy-6-methyl-3-[*N*-[[2″-(trimethylsilyl)ethoxy]carbonyl]amino]-naphthalene (21).** A solution of acid **20** (0.090 g, 0.12 mmol), diphenylphosphoryl azide (0.036 mL, 0.17 mmol), β-(trimethylsilyl)ethanol (0.086 mL, 0.60 mmol), and $Et_3N$ (0.023 mL, 0.17 mmol) in THF (6.0 mL) was heated at reflux for 16 h. The solution was then poured into EtOAc (50 mL). The organic phase was washed with 1 N HCl (20 mL) and $H_2O$ (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of the crude product by flash chromatography (30% $Et_2O$/hexanes) provided carbamate **21** (0.087 g, 87% yield) as an approximate 1:1 mixture of atropisomers (clear oil): $[\alpha]^{25}_D$ −32.8 (*c* 1.3, $CHCl_3$); $^1H$ NMR (400 MHz, $C_6D_6$) δ 8.40 (s, 1 H), 8.37 (s, 1 H), 7.70−7.64 (m, 8 H), 7.59−7.55 (m, 4 H), 7.49−7.46 (m, 4 H), 7.27−7.17 (m, 16 H), 6.35 (dd, *J* = 9.4 Hz, *J* = 1.4 Hz, 1 H), 6.27 (dd, *J* = 9.6 Hz, *J* = 1.6 Hz, 1 H), 4.78 and 4.74 (AB quartet, $J_{AB}$ = 10.6 Hz, 4 H), 4.31 (t, *J* = 8.4 Hz, 2 H), 4.30, (t, *J* = 8.4 Hz, 2 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 3.46 (s, 3 H), 3.43 (s, 3 H), 3.43 (s, 3 H), 3.42 (s, 3 H), 3.36 and 3.29 (AB of ABX, $J_{AB}$ = 9.8 Hz, $J_{AX}$ = 5.8 Hz, $J_{BX}$ = 5.8 Hz, 4 H), 2.68 (m, 2 H), 2.35 (s, 3 H), 2.32 (s, 3 H), 2.18 (d, *J* = 1.6 Hz, 3 H), 2.17 (d, *J* = 1.6 Hz, 3 H), 1.08 (s, 9 H), 0.99 (s, 9 H), 0.98 (m, 4 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.66 (d, *J* = 6.4 Hz, 3 H), −0.071 (s, 9 H), −0.075 (s, 9 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) δ 197.2, 197.1, 153.8, 152.6, 152.4, 145.1, 144.9, 144.7, 139.4, 139.2, 138.8, 138.5, 138.4, 136.0, 135.9, 135.3, 135.2, 134.0, 133.8, 129.9, 129.8, 128.6, 128.4, 127.4, 127.2, 127.0, 126.7, 126.6, 126.1, 126.0, 121.2, 121.4, 120.8, 100.0, 99.7, 76.3, 67.7, 63.5, 62.4, 62.2, 56.1, 56.0, 36.6, 36.5, 27.0, 19.4, 19.3, 18.0, 16.6, 16.3, 12.1, 12.0, 10.3, 10.2, −1.6; IR ($CHCl_3$) 3400, 1725, 1650, 1600, 1575 $cm^{-1}$; HRMS calcd for $C_{50}H_{64}NO_8Si_2$ ($M^+$ + 1) 862.4171, found 862.4134. Anal. Calcd for $C_{50}H_{63}NO_8Si_2$: C, 69.65; H, 7.36; N, 1.62. Found: C, 69.72; H, 7.63; N, 1.59.

**5-(Benzyloxy)-8-[(4′*S*,2′*E*)-5′-(*tert*-butyldiphenylsiloxy)-2′,4′-dimethyl-1′-oxopent-2′-en-1′-yl]-7-methoxy-6-methyl-3-[N-[[2″-(trimethylsilyl)ethoxy]carbonyl]amino]-1,4-naphthoquinone (22).** A solution of ceric ammonium nitrate (CAN) (0.14 g, 0.26 mmol) in 1:1 $CH_3CN/H_2O$ (1.0 mL) was added to a 0 °C solution of carbamate **21** (0.075 g, 0.087 mmol) in $CH_3CN$ (4.4 mL) and $H_2O$ (0.13 mL). The resulting solution was stirred at 0 °C for 15 min and then was poured into $H_2O$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a bright yellow oil. Purification of the crude product by flash chromatography (30% $Et_2O$/hexanes) provided the desired naphthoquinone **22** (0.062 g, 85% yield) as an approximate 1:1 mixture of atropisomers (bright yellow oil): $[\alpha]^{25}_D$ −35.7 (*c* 1.1, $CHCl_3$); $^1H$ NMR (400 MHz, $C_6D_6$) δ 7.80 (s, 1 H), 7.76 (s, 1 H), 7.69−7.57 (m, 16 H), 7.28−7.16 (m, 16 H), 6.37 (dd, *J* = 9.4 Hz, *J* = 1.4 Hz, 1 H), 6.28 (dd, *J* = 9.4 Hz *J* = 1.4 Hz, 1 H), 4.83 and 4.71 (AB quartet, $J_{AB}$ = 10.4 Hz, 2 H), 4.83 and 4.68 (A′B′ quartet, $J_{AB}$ = 10.7 Hz, 2 H), 4.09 (m, 4 H), 3.57 (s, 3 H), 3.54 (s, 3 H), 3.48 (A of ABX and A′B′X′, $J_{AB}$ = 10.4 Hz, $J_{AX}$ = 4.0 Hz, 2 H), 3.38 (m, overlap of B of ABX and A′B′X′, 2 H), 2.62 (m, 2 H), 2.32 (d, *J* = 0.8 Hz, 3 H), 2.32 (d, *J* = 1.2 Hz, 3 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.07 (s, 9 H), 1.04 (s, 9 H), 0.84 (d, *J* = 6.4 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.83 (m, 4 H), −0.12 (s, 9 H), −0.012 (s, 9 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) δ 196.3, 196.2, 183.5, 183.4, 178.3, 178.2, 162.3, 159.9, 152.2, 143.8, 143.6, 141.9, 141.1, 139.4, 139.2, 137.5, 136.0, 135.9, 133.9, 133.7, 133.6, 133.6, 133.6, 131.7, 131.5, 130.0, 129.9, 129.9, 128.7, 128.6, 128.5, 127.8, 127.5, 127.4, 127.4, 127.3, 127.2, 127.0, 120.0, 119.9, 114.3, 114.1, 75.4, 67.8, 67.7, 64.5, 62.4, 62.3, 36.2, 36.1, 27.0, 26.9, 19.4, 19.4, 17.6, 16.6, 16.3, 12.4, 10.2, 10.2, −1.7; IR ($CHCl_3$) 3360, 1735, 1700, 1655, 1565 $cm^{-1}$; HRMS calcd for $C_{48}H_{58}NO_8Si_2$ ($M^+$ + 1) 832.3702, found 832.3678.

**8-[(4′*S*,2′*E*)-5′-(*tert*-Butyldiphenylsiloxy)-2′,4′-dimethyl-1′-oxopent-2′-en-1′-yl]-5-hydroxy-7-methoxy-6-methyl-3-[*N*-[[2″-(trimethylsilyl)ethoxy]carbonyl]amino]-1,4-naphthoquinone (23).** A solution of naphthoquinone **22** (0.030 g, 0.036 mmol) in MeOH (0.36 mL) was stirred over 10% Pd/C (0.010 g) under an atmosphere of $H_2$ for 3 h. Air was then bubbled through the solution for 30 min to oxidize the dihydronaphthoquinone. The resulting solution was concentrated *in vacuo*, and the crude product was purified by flash chromatography (30% $Et_2O$/hexanes). This provided naphthoquinone **23** (0.023 g, 85% yield) as an approximate 1:1 mixture of atropisomers (orange oil): $[\alpha]^{25}_D$ −14.8 (*c* 1.2, $CHCl_3$); $^1H$ NMR (400 MHz, $C_6D_6$) δ 12.22 (s, 1 H), 12.18 (s, 1 H), 7.69−7.65 (m, 4 H), 7.61−7.58 (m, 6 H), 7.48 (s, 1 H), 7.44 (s, 1 H), 7.24−7.18 (m, 12 H), 6.38 (dd, *J* = 9.4 Hz, *J* = 1.0 Hz, 1 H), 6.33 (dd, *J* = 9.4 Hz, *J* = 1.4 Hz, 1 H), 4.10 (m, 4 H), 3.55 (s, 3 H), 3.52 (s, 3 H), 3.50−3.55 (m, overlap of ABX and A′B′X′, 4 H), 2.60 (m, 2 H), 2.28 (d, *J* = 1.2 Hz, 3 H), 2.27 (d, *J* = 1.2 Hz, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H), 1.07 (s, 9 H), 1.02 (s, 9 H), 0.84 (m, 4 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), −0.10 (s, 9 H), −0.11 (s, 9 H); $^{13}C$ NMR (100 MHz, $C_6D_6$) δ 196.3, 184.1, 184.0, 182.8, 163.4, 162.8, 162.7, 152.1, 144.1, 143.9, 140.3, 140.2, 139.3, 139.1, 136.0, 135.9, 133.8, 133.7, 129.9, 128.7, 128.6, 127.4, 127.3, 127.0, 116.2, 116.0, 110.3, 110.2, 67.8, 67.7, 64.7, 62.5, 62.4, 36.2, 36.1, 26.9, 19.4, 17.6, 16.6, 16.3, 12.3, 9.3, 9.2, −1.7; IR ($CHCl_3$) 3370, 3100 (br), 1720, 1690, 1635, 1610, 1570 $cm^{-1}$; HRMS calcd for $C_{37}H_{42}NO_8Si_2$ ($M^+$ − $C_4H_9$) 684.2449, found 684.2479.

**8-[(4′*S*,2′*E*)-5′-(*tert*-Butyldiphenylsiloxy)-2′,4′-dimethyl-1′-oxopent-2′-en-1′-yl]-5-hydroxy-7-methoxy-6-methyl-2-(methylthio)-3-[*N*-[[2″-(trimethylsilyl)ethoxy]carbonyl]-amino]-1,4-naphthoquinone (4).** To a solution of naphthoquinone **23** (0.013 g, 0.018 mmol) in MeOH (0.090 mL) under an $O_2$ atmosphere was added NaSMe (0.54 mL, 0.5 M in MeOH, 0.27 mmol). The resulting solution was stirred for 10 min and then poured into 0.5 M $NaHSO_4$ (5 mL) and $Et_2O$ (5 mL). The aqueous phase was extracted with $Et_2O$ (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude red oil. Purification of the crude product by flash chromatography (30% $Et_2O$/hexanes) afforded the methylthio substituted naphthoquinone **4** (0.010 g, 72% yield) as an approximate 1:1 mixture of atropisomers (red oil): $[\alpha]^{25}_D$ −43.1 (*c* 0.8, $CHCl_3$); $^1H$ NMR (400 MHz, $C_6D_6$) δ 12.46 (s, 1 H), 12.42 (s, 1 H), 7.68−7.60 (m, 8 H), 7.23−7.18 (m, 14 H), 6.38 (dd, *J* = 9.2 Hz, *J* = 1.2 Hz, 1 H), 6.31 (dd, *J* = 9.8 Hz, *J* = 1.4 Hz, 1 H), 4.21 (m, 4 H), 3.51 (s, 3 H), 3.47 (s, 3 H), 3.50−3.34 (m, overlap of ABX and A′B′X′, 4 H), 2.59 (m, 2 H), 2.24 (d, *J* = 1.2 Hz, 3 H), 2.22 (d, *J* = 1.6

Hz, 3 H), 2.14 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 6 H), 1.07 (s, 9 H), 1.04 (s, 9 H), 0.92 (m, 4 H), 0.90 (d, $J$ = 6.8 Hz, 3 H), 0.74 (d, $J$ = 6.4 Hz, 3 H), −0.11 (s, 18 H); $^{13}$C NMR (100 MHz, $C_6D_6$) δ 196.2, 196.0, 182.6, 179.6, 162.5, 162.4, 152.0, 144.5, 144.3, 140.0, 139.7, 139.2, 139.0, 138.8, 138.5, 136.0, 135.9, 133.8, 133.6, 131.4, 131.3, 130.0, 130.0, 129.5, 129.5, 128.6, 127.8, 127.4, 127.2, 127.0, 127.0, 126.9, 110.4, 110.3, 67.6, 67.5, 64.9, 62.4, 62.3, 36.2, 26.9, 19.4, 17.7, 17.5, 16.7, 16.3, 12.2, 9.3, 9.3, −1.6; IR ($CHCl_3$) 3360, 3100 (br), 1730, 1660, 1620, 1580, 1565, 1490 cm$^{-1}$; HRMS calcd for $C_{38}H_{44}NO_8SSi_2$ ($M^+ - C_4H_9$) 730.2327, found 730.2295. Anal. Calcd for $C_{42}H_{53}NO_8SSi_2$: C, 64.01; H, 6.78; N, 1.78. Found: C, 63.83; H, 6.64; N, 1.66.

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**Supporting Information Available:** $^1$H NMR spectra of **6**, **10**, **13**, **18b**, **20**, **22**, and **23** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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