Total Synthesis of Aegyptinones A and B

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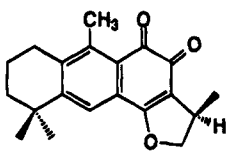
This paper describes the first total syntheses of the diterpene quinones aegyptinones A and B via an extremely direct route which should easily accommodate the production of gram quantities of each compound. The key step in the synthetic strategy involves the application of a recently developed "second-generation" photochemical aromatic annulation method for the construction of highly substituted aromatic systems. The synthesis of one of the annulation components, the diazo ketone **5**, was achieved using a Diels–Alder-based benzannulation strategy employing cyanoallene and the dienamine **13**. Cyanoallene proved to be uniquely effective for this cycloaddition, which either failed or proceeded in poor yield using several substituted acetylenes as dienophiles. The pivotal aromatic annulation reaction was accomplished by irradiating a solution of the diazo ketone **5** and the readily available siloxyalkyne **4** in a Pyrex vessel with a 450-W medium-pressure Hanovia lamp at room temperature for 17–20 h. The desired tricyclic phenol **3** was produced in 58–70% yield and was then converted to aegyptinone B (**2**) by treatment with tetra-*n*-butylammonium fluoride in the presence of oxygen. Finally, cyclization to generate aegyptinone A was accomplished in high yield by brief exposure of **2** to an ethanolic solution of concentrated sulfuric acid at room temperature. Overall, this strategy provides efficient routes (six and seven steps, respectively) to aegyptinones A and B which should facilitate the systematic investigation of the pharmacological activity of these novel diterpenes.

Plants of the genus *Salvia* serve in many parts of the world as the source of traditional medicines for the treatment of a wide variety of disorders. In the course of their investigation of Egyptian *Salvia* species, Sabri and co-workers found that extracts of the roots of the previously unexplored plant *Salvia aegyptiaca* possess potent antibacterial and antifungal activity. Further study led to the isolation and characterization of two structurally related diterpene quinones, aegyptinones A (**1**) and B (**2**).[1] Extensive NMR analysis identified these diterpenes as possessing novel rearranged abietane skeletons, and the structure of **1** has been confirmed by single-crystal X-ray diffraction analysis.



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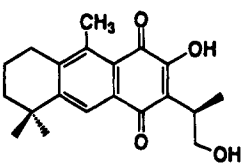

2

We have previously shown that the addition of vinylketenes to acetylenes provides the basis for an efficient annulation route to highly substituted aromatic systems.[2] In connection with our interest in testing the utility of this methodology as applied to *polycyclic* compounds, we have examined its application to the construction of the linear tricyclic system found in the aegyptinones. Herein we report the first total syntheses of these diterpenes via an extremely direct route which should easily accommodate the production of gram quantities of each compound, thus facilitating the systematic investigation of their pharmacological activity.

The pivotal step in our strategy for the synthesis of the aegyptinones involves the recently developed "second-generation" version of our aromatic annulation strategy[2d] which has expanded the scope of the method to include the synthesis of *polycyclic* compounds which were not readily available using the original cyclobutenone-based reaction. Prior experience gained in the synthesis of the Dan Shen diterpene quinones[2f] suggested that the tricyclic phenol **3** might serve as a common precursor to both aegyptinones A and B. Our retrosynthetic plan for this key intermediate called for its assembly in one step via an annulation involving the siloxyalkyne **4** and the diazo ketone **5**. Scheme 1 outlines the mechanistic course of the proposed key annulation reaction. Irradiation of the α-diazo ketone **5** triggers a photochemical Wolff rearrangement producing the arylketene **6**, which combines with acetylene **4** in a regiospecific [2 + 2] cycloaddition to form **7**. Further irradiation then induces 4π electrocyclic opening of the cyclobutenone ring, thus generating the vinylketene **8** which undergoes rapid 6π electrocyclization to afford, after tautomerization, the desired tricyclic phenol.

Our original plan for the synthesis of diazo ketone **5** envisioned generating this key tetrahydronaphthalene intermediate via a Diels–Alder-based benzannulation strategy employing 3-pentyn-2-one and the dienamine **9**.[3] Snowden has previously reported that **9** combines at room temperature with methyl propiolate to afford a dihydroaromatic cycloadduct which eliminates the elements of dimethylamine to form **10** upon warming in the presence of silica gel.[4] However, in spite of this encour-

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(1) Sabri, N. N.; Abou-Donia, A. A.; Ghazy, N. M.; Assad, A. M.; El-Lakany, A. M.; Sanson, D. R.; Gracz, H.; Barnes, C. L.; Schlemper, E. O.; Tempesta, M. S. *J. Org. Chem.* **1989**, *54*, 4097.

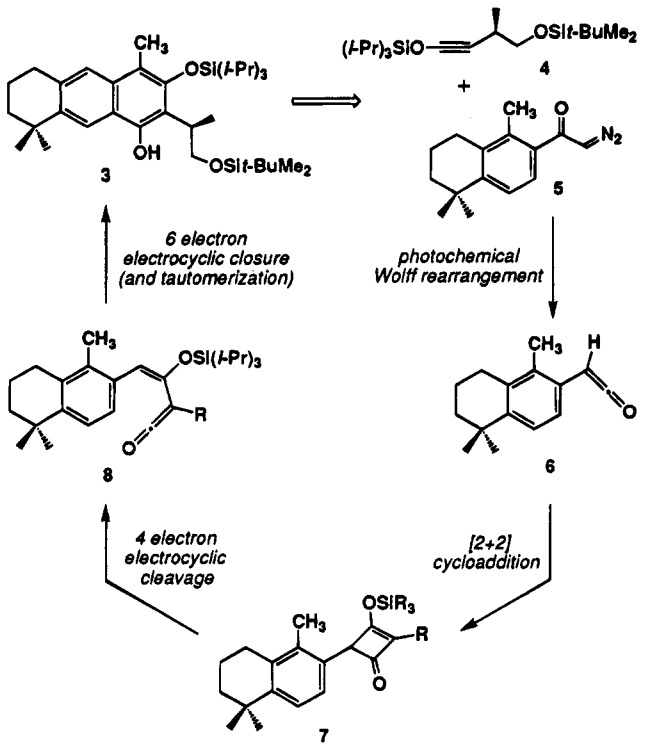
(2) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (c) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (d) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093. (e) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527. (f) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.

(3) For a review of the chemistry of dienamines, see: Hickmott, P. W. *Tetrahedron* **1984**, *40*, 2989.

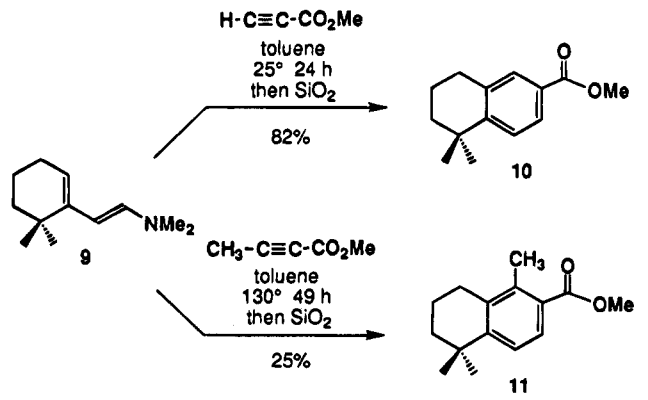
(4) Snowden, R. G.; Wust, M. *Tetrahedron Lett.* **1986**, *27*, 703.

0022-3263/94/1959-4844$04.50/0

Scheme 1

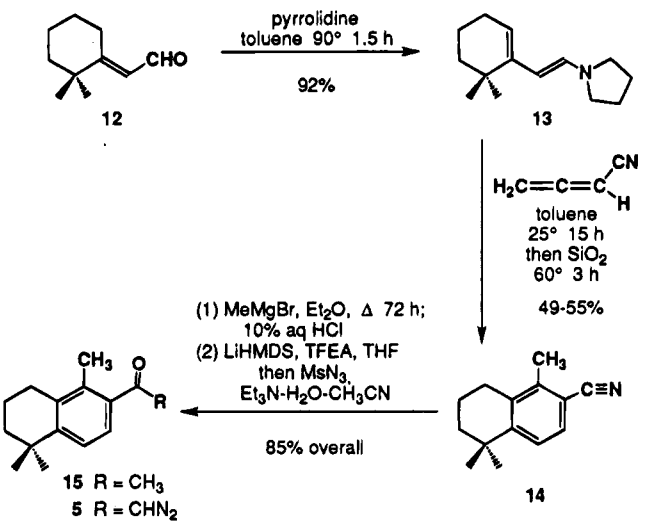


aging precedent, we were unable to achieve efficient cycloaddition with this dienamine and several *substituted* acetylenic carbonyl compounds under a variety of conditions. No cycloaddition between **9** and 3-pentyn-2-one was observed to take place upon heating and at pressures up to 7 kbar, and while methyl butynoate did add to **9** at high temperatures, the desired benzannulation product (**11**) could only be obtained in 25% yield.



The synthesis of the key tetrahydronaphthalene intermediate was ultimately achieved by employing *cyanoallene* as the dienophile for the crucial Diels–Alder step. Dienophiles with olefinic π bonds are often more reactive than similarly activated alkynes,[5] and as expected, we found that cyanoallene[6-8] readily engages in Diels–Alder reactions with **9** and related dienamines at

Scheme 2



25 °C. Scheme 2 outlines the synthesis of diazo ketone **5** via this approach. The requisite dienamine **13**[9] was easily prepared in 92% yield from the known aldehyde **12**[10,11] by treatment with 1.2 equiv of pyrrolidine in toluene at 90 °C for 1.5 h. Benzannulation was then achieved by the reaction of 2.5 equiv of cyanoallene with **13** in toluene at 25 °C for 15 h, followed by addition of silica gel and heating at 60 °C.[13] Chromatographic purification furnished the desired bicyclic nitrile **14** as a white solid (mp 78.5–79.5 °C) in 49–55% overall yield. As expected, none of the regioisomeric Diels–Alder adduct was produced in this reaction. Addition of methylmagnesium bromide to **14** next proceeded smoothly in refluxing ether to afford the methyl ketone **15** (mp 79.5–80.5 °C) in 90% yield. Conversion of this ketone to the α-diazo derivative **5** was achieved by employing the improved "detrifluoroacetylative" diazo transfer method recently developed in our laboratory.[14] The α-diazo ketone **5** was obtained as yellow crystals (mp 42.5–43 °C) in 94% yield in this fashion.

Siloxyalkyne **4** was selected to serve as the acetylene component for the pivotal aromatic annulation step. This acetylene was conveniently prepared from commercially available (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate using the Kowalski reaction[15] as described by us previously.[2f] The key aromatic annulation reaction was achieved by irradiating a degassed solution of the diazo ketone **5** and 3.0–3.5 equiv of **4** in a Pyrex vessel with a 450-W medium-pressure Hanovia lamp for 17–20 h (Scheme 3). The α-diazo ketone was best added in two

(5) For example, see: Samer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183.

(6) The preparation of cyanoallene in >90% yield by the reaction of propargyl bromide with KCN–CuCN has been described: Brandsma, L.;Verkruijisse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier Scientific Pub. Co.: New York, 1981; p 173.

(7) Diels–Alder reactions of this highly reactive dienophile with cyclopentadiene and 2,5-dimethylfuran have been reported previously: Kurtz, P.; Gold, H.; Disselnkötter, H. *Liebigs Ann. Chem.* **1959**, *624*, 1.

(8) Boger has reported a case of an intramolecular 1,2-diazine Diels–Alder reaction which proceeds under milder conditions using an allene dienophile than with the comparable alkyne and alkene: Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230.

(9) This dienamine could be prepared in higher yield than the dimethylamino derivative **9**.

(10) Snowden, R. G.; Linder, S. M.; Wust, M. *Helv. Chim. Acta* **1989**, *72*, 892 and references cited therein.

(11) We prepared this α,β-unsaturated aldehyde by the Peterson reaction of 2,2-dimethylcyclohexanone with the lithium derivative of 2-(trimethylsilyl)acetaldehyde *tert*-butylimine according to the general method of Corey.[12]

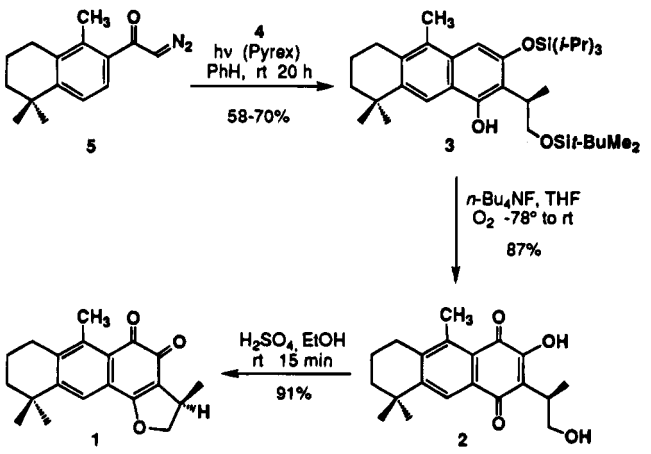
(12) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 7.

(13) In large scale runs, the Diels–Alder reaction was conducted at 25 °C for 24 h and the elimination step required 10 h.

(14) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

(15) Kowalski, C. J.; Lal, G. S.; Hague, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127.

Scheme 3



equal portions, with the second portion added after 2 h. Although previously we had found that most aromatic annulations were best carried out in 1,2-dichloroethane at concentrations of 0.3–0.7 M,[2d–f] in this case optimal results were obtained by using a more dilute (0.04 M) solution of the diazo ketone in benzene. In this fashion the desired tricyclic phenol **3** was obtained in 58–70% yield [mp 57–59 °C; $[\alpha]^{25}_D = -8.9°$ ($CHCl_3$, $c = 0.67$)] after purification by silica gel chromatography.

Cleavage of the silyl ether protective groups and oxidation to produce aegyptinone B was achieved in a single operation by exposure of **3** to the action of 2.5 equiv of tetra-*n*-butylammonium fluoride in THF (−78 °C to rt, 14 h) in the presence of oxygen. Column chromatography on silica gel (gradient elution with 10–20% ethyl acetate–hexanes) provided aegyptinone B (**2**) in 87% yield with spectroscopic properties consistent with those previously reported.[1,16] Finally, cyclization of **2** to generate the tetracyclic *o*-quinone system of aegyptinone A was accomplished in high yield by brief exposure of **2** to an ethanolic solution of concentrated sulfuric acid at room temperature. Synthetic aegyptinone A [mp 137–138.5 °C; $[\alpha]^{25}_D = -102°$ ($CHCl_3$, $c = 0.13$)] was indistinguishable from an authentic sample[17] of the natural product by comparison of NMR, IR, TLC, optical rotation, and melting point characteristics.

Experimental Section

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated using a Büchi rotary evaporator at ca. 20 mmHg unless otherwise indicated. Column chromatography was performed on Baker silica gel (230–400 mesh). Melting points are corrected.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Tetrahydrofuran, diethyl ether, and benzene were distilled from sodium benzophenone ketyl. Methylene chloride, acetonitrile, triethylamine, diisopropylamine and 1,1,1,3,3,3-hexamethyldisilylazane were distilled from calcium hydride. 2,2-Dimethylcyclohexanone, 2-(trimethylsilyl)acetaldehyde *tert*-butylimine and cyanoallene were prepared according to published literature procedures (*vide infra*).

2′,2′-Dimethylcyclohexylideneacetaldehyde (12). A three-necked, 250-mL, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a glass stopper was charged with a solution of diisopropylamine (7.39 g, 10.2 mL, 73 mmol) in 100 mL of THF and cooled at 0 °C while *n*-butyllithium solution (2.56 M in hexanes, 25 mL, 64 mmol) was added dropwise by syringe over 10 min. After 5 min, 2-(trimethylsilyl)acetaldehyde *tert*-butylimine[12] (11.0 g, 64 mmol) was added dropwise at 0 °C over 10 min to the straw-colored solution. The reaction mixture was stirred at 0 °C for 30 min and then cooled with a dry ice-acetone bath (−78 °C) while a solution of 2,2-dimethylcyclohexanone[18] (6.5 g, 52 mmol) in 15 mL of THF was added dropwise over 10 min. The resulting mixture was allowed to warm to 25 °C, stirred for 12 h at that temperature, and then diluted with 10 mL of water and acidified to pH 4.5 by the addition of oxalic acid (ca. 5 g). After 1 h, the aqueous phase was separated and extracted with two 100-mL portions of ether. The combined organic phases were washed with 200 mL of saturated aqueous $NaHCO_3$ solution and 200 mL of saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 7.92 g of a viscous oil. Column chromatography on silica gel (elution with 1% EtOAc–petroleum ether) gave 7.25 g (92%) of aldehyde **12** as a colorless oil, with spectral data consistent with that previously reported for this compound.[4] The product could also be purified by Kugelrohr distillation (bath temperature 38 °C, 1.2 mmHg). Distillation at higher temperatures produced a mixture of both the α,β and the β,γ isomers which was also suitable for use in the next reaction: IR (film) 2950, 2760, 1720, 1680, 1460, and 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.97 (d, $J = 8$ Hz, 1 H), 5.80 (d, $J = 8$ Hz, 1 H), 2.69 (m, 2 H), 1.57 (m, 4 H), 1.43 (m, 2 H), and 1.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 174.3, 123.2, 41.4, 38.0, 28.0, 27.2, 25.4, and 21.5.

(*E*)-[2-[(6′,6′-Dimethylcyclohex-1′-enyl)]ethenyl]pyrrolidine (13). A 100-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with aldehyde **12** (4.44 g, 29.2 mmol, ca. 4:1 mixture of the α,β and the β,γ isomers), pyrrolidine (3.0 mL, 2.6 g, 36 mmol), and 40 mL of toluene. The resulting solution was heated to 90 °C for 1.5 h and then concentrated under reduced pressure. The remaining solvent and starting material were removed by Kugelrohr distillation (bath temperature 65 °C, 0.25 mmHg), and Kugelrohr distillation of the residual brown oil (bath temperature 110 °C, 0.25 mmHg) afforded 5.47 g (91%) of dienamine **13** as a yellow oil: IR ($CHCl_3$) 2929, 1629, 1459, and 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, J = 13.5 Hz, 1 H), 5.43 (t, $J = 4$ Hz, 1 H), 4.67 (d, J = 13.5 Hz), 3.06–3.11 (m, 4 H), 2.01 (dt, $J = 4$, 6 Hz, 2 H), 1.83–1.87 (m, 4 H), 1.45–1.61 (m, 4 H), and 1.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 134.7, 114.4, 97.3, 48.9, 39.5, 33.7, 28.8, 26.3, 25.0, and 19.5; HRMS *m/e* calcd for $C_{14}H_{23}N$ 205.1831, found 205.1829.

2-Cyano-1,5,5-trimethyl-5,6,7,8-tetrahydronaphthalene (14). A 50-mL, round-bottomed flask fitted with a rubber septum was charged with dienamine **13** (0.500 g, 2.43 mmol), 10 mL of toluene, and cyanoallene[6] (0.400 g, 6.15 mmol). The septum was replaced with an argon inlet adapter, and the reaction mixture was stirred at 25 °C for 15 h after which time 1.5 g of silica gel (TLC grade, E. Merck PF-254) was added. The resulting slurry was heated at 60 °C for 3 h, allowed to cool to room temperature, and then filtered using ca. 50 mL of hexane to wash the silica gel (until a colorless filtrate was obtained). Concentration and purification by column chromatography on silica gel (gradient elution with 0–1% ethyl acetate–hexanes) afforded 0.238 g (49%) of nitrile **14** as an off-white solid, mp 78.5–79.5 °C. This reaction was carried out on a scale using up to 5.7 g of dienamine, with yields ranging from 49 to 55% in different runs: IR ($CHCl_3$) 2930,

(16) We obtained aegyptinone B as yellow crystals with mp 118–119 °C (corrected) and $[\alpha]^{25}_D = +8.7°$ ($CHCl_3$, $c = 2.09$). Sabri and coworkers reported mp 101–102 °C (uncorrected) and did not measure the optical rotation of this substance. We were unable to obtain an authentic sample of aegyptinone B for direct comparison with our synthetic material.

(17) We are grateful to Professor Nawal Sabri for providing us with an authentic sample of aegyptinone A.

(18) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.

2215, 1585, and 1475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8 Hz, 1 H), 7.28 (d, J = 8 Hz, 1 H), 2.63 (t, J = 6 Hz, 2 H), 2.42 (s, 3 H), 1.82–1.91 (m, 2 H), 1.62–1.66 (m, 2 H), and 1.29 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 140.2, 136.1, 129.3, 124.9, 119.1, 109.9, 38.0, 34.4, 31.5, 27.8, 18.9, and 18.0. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.47; H, 8.66; N, 7.06.

1-(1,5,5-Trimethyl-5,6,7,8-tetrahydro-2-naphthyl)ethanone (15). A 10-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with a solution of nitrile **14** (0.523 g, 2.62 mmol) in 3.5 mL of diethyl ether. Methylmagnesium bromide (3.0 M in ether, 1.4 mL, 4.2 mmol) was added rapidly by syringe, and the resulting solution was heated at reflux for 72 h. The reaction mixture was then cooled to room temperature and poured into a mixture of 60 mL of ether, 50 mL of ice–water, and 50 mL of 10% aqueous HCl. The aqueous layer (together with the insoluble material suspended at the interface of the two phases) was separated and transferred to a 250-mL, round-bottomed flask equipped with a reflux condenser. This mixture was heated at reflux for 1 h, allowed to cool to room temperature, and then extracted with four 25-mL portions of ether. The combined organic phases were washed with 25 mL of saturated aqueous $NaHCO_3$ and 25 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.609 g of a light brown solid. Column chromatography on silica gel (gradient elution with 0–50% benzene–hexanes) furnished 0.549 g of a cream-colored solid. Recrystallization from hot aqueous methanol (15:1 MeOH–H_2O) yielded (in two crops) 0.510 g (90%) of ketone **15** as colorless plates, mp 79.5–80.5 °C. This reaction was carried out on a scale using up to 2.3 g of **15**, with yields ranging from 89 to 90% in different runs: IR (film) 2930, 1675, 1585, and 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8 Hz, 1 H), 7.25 (d, J = 8 Hz, 1 H), 2.65 (t, J = 6 Hz, 2 H), 2.54 (s, 3 H), 2.31 (s, 3 H), 1.80–1.88 (m, 2 H), 1.60–1.66 (m, 2 H), and 1.29 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 149.2, 137.1, 136.3, 135.3, 125.3, 123.8, 38.2, 34.3, 31.7, 30.3, 28.0, 19.4, and 16.4. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.43; H, 9.12.

(*S*)-(+)-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropionate. A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (11.81 g, 100 mmol) in 60 mL of methylene chloride. This solution was cooled with an ice bath (0 °C) while imidazole (16.34 g, 240 mmol) and *tert*-butyldimethylsilyl chloride (18.09 g, 120 mmol) were added alternately in portions. The reaction mixture was stirred at 25 °C for 24 h and then poured into 100 mL of ether and 150 mL of saturated aqueous NaCl solution. The aqueous phase was separated and extracted with three 100-mL portions of ether, and the combined organic phases were washed with four 200-mL portions of water and 200 mL of saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Filtration of the resulting colorless liquid through a 3-cm plug (150 g) of silica gel (elution with 5% EtOAc–petroleum ether) afforded 22.68 g (98%) of the ester as a colorless liquid: $[\alpha]^{25}_D$ = +17.44° ($CHCl_3$, c = 1.25); IR ($CHCl_3$) 3950, 1750, 1470, and 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.59–3.77 (m, 2 H), 3.62 (s, 3 H), 2.63 (m, J = 7 Hz, 1 H), 1.11 (d, J = 7 Hz, 3 H), 0.82 (s, 9 H), and 0.00 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 65.2, 51.3, 42.4, 25.5, 17.9, 13.2, and −5.9; HRMS m/e calcd for $C_{10}H_{21}O_2Si$ 201.1311 (M^+ − OMe), found 201.1310.

2-[(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2-propyl]-1-[(triisopropylsilyl)oxy]acetylene (4). A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with a solution of dibromomethane (5.34 g, 2.17 mL, 30.9 mmol) in 45 mL of THF and then cooled to −78 °C with a dry ice–acetone bath. A 100-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and rubber septum was charged with a solution of 2,2,6,6-tetramethylpiperidine (5.04 g, 6.03 mL, 35.7 mmol) in 45 mL of THF and then cooled with an ice bath while a *n*-butyllithium solution (2.58 M in hexane, 13.0 mL, 33.6 mmol) was added dropwise over ca. 5 min. The resulting lithium tetramethylpiperidide solution was stirred at 0 °C for 15 min, cooled to −78 °C, and transferred via cannula into the dibromomethane solution over 10 min. The resulting bright yellow solution was stirred at −78 °C for 15 min. A precooled (−78 °C) solution of (*S*)-(+)-methyl-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropionate (3.12 g, 14.4 mmol) in 45 mL of THF was next added dropwise via cannula over 15 min, and the orange reaction mixture was then stirred for 10 min at −78 °C. *n*-Butyllithium solution (2.58 M in hexanes, 26.7 mL, 69.0 mmol) was added via syringe over 10 min, and the reaction mixture was stirred at −78 °C for 10 min, the cooling bath was then removed, and the mixture was stirred further at 25 °C for 45 min. The orange-brown solution was next cooled at −78 °C while a precooled (−78 °C) solution of triisopropylsilyl chloride (13.9 g, 15.6 mL, 72 mmol) in 45 mL of THF was added via cannula over 20 min. The dry ice–acetone bath was replaced with an ice bath, and the reaction mixture was stirred at 0 °C for 5 h. The resulting mixture was diluted with 100 mL of pentane and 100 mL of saturated aqueous $NaHCO_3$ solution, and the aqueous layer was separated and extracted with two 100-mL portions of pentane. The combined organic phases were washed with 200 mL of saturated aqueous $NaHCO_3$ solution, 200 mL of water, and 200 mL of saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated initially at 20 mmHg and then at ≤0.005 mmHg for 48 h to give 5.72 g of an orange oil. Column chromatography on silica gel (elution with hexanes) afforded 2.86 g (52%) of the silyloxy acetylene **4** as a colorless oil: $[\alpha]^{25}_D$ = −2.64° ($CHCl_3$, c = 0.65); IR (film) 2950, 2280, 1460, and 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (dd, J = 5, 10 Hz, 1 H), 3.31 (app t, J = 10 Hz, 1 H), 2.44 (m, 1 H), 1.25 (m, 3 H), 1.11 (d, J = 6 Hz, 18 H), 1.10 (d, 3 H), 0.89 (s, 9 H), and 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.0, 68.4, 32.5, 27.7, 25.7, 18.5, 18.1, 17.1, 11.6, and −5.7; HRMS m/e calcd for $C_{16}H_{33}O_2Si_2$ 313.2017 (M^+ − C_4H_9), found 313.2019.

2-Diazo-1-(1,5,5-trimethyl-5,6,7,8-tetrahydro-2-naphthyl)-1-ethanone (5). A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.43 mL, 1.09 g, 6.78 mmol) in 6 mL of THF and then cooled at 0 °C while a *n*-butyllithium solution (2.62 M in hexanes, 2.52 mL, 6.60 mmol) was added rapidly dropwise by syringe. After 10 min, the resulting solution was cooled in a dry ice–acetone bath (−78 °C), and a solution of methyl ketone **15** (1.298 g, 6.00 mmol) in 8 mL of THF was added dropwise via cannula over 5 min. The reaction mixture was stirred at −78 °C for 30 min, and then 2,2,2-trifluoroethyl trifluoroacetate (0.96 mL, 1.4 g, 7.2 mmol) was added rapidly by syringe in one portion. After 10 min the reaction mixture was poured into a separatory funnel containing 40 mL of 5% HCl solution and 40 mL of ether. The aqueous phase was extracted with 40 mL of ether, and the combined organic phases were washed with 25 mL of saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated to provide a light brown oil which was immediately dissolved in 6 mL of CH_3CN and transferred to a 25-mL round-bottomed flask fitted with a rubber septum. Water (0.105 mL, 0.105 g, 6.0 mmol) and triethylamine (1.25 mL, 0.91 g, 9.0 mmol) were added, and a solution of methanesulfonyl azide (1.10 g, 9.00 mmol) in 2 mL of CH_3CN was added dropwise via cannula over 1 min. The resulting yellow solution was stirred at 25 °C for 3.25 h and then poured into a separatory funnel containing 25 mL of 5% NaOH solution and 70 mL of ether. The organic phase was separated and washed with two 25-mL portions of 5% NaOH solution, three 25-mL portions of water, and 25 mL of saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Column chromatography on silica gel (elution with 5% ethyl acetate–hexanes) furnished 1.363 g (94%) of diazo ketone **5** as a yellow solid: mp 42.5–43 °C; IR (film) 3090, 2930, 2100, 1620, and 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H), 5.42 (br s, 1 H), 2.63 (t, J = 7 Hz, 2 H), 2.31 (s, 3 H), 1.80–1.86 (m, 2 H), 1.61–1.65 (m, 2 H), and 1.28 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 148.8, 136.3, 136.0, 134.3, 124.1, 124.0, 56.2, 37.9, 33.9, 31.3, 27.6, 18.9, and 15.7; UV λ_{max} (CCl_4)

262 (ϵ = 12 300) and 285 (sh). Anal. Calcd for $C_{15}H_{18}ON_2$: C, 74.60; H, 7.41; N, 11.42. Found: C, 74.35; H, 7.49; N, 11.56.

2-[(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-propyl]-3-(triisopropylsiloxy)-5,9,9-trimethyl-6,7,8,9-tetrahydroanthran-1-ol (3). A solution of diazo ketone **5** (0.200 g, 0.825 mmol) and silyloxy acetylene **4** (1.84 g, 4.96 mmol) in 40 mL of benzene was divided into four portions of equal volume and transferred into four Pyrex tubes (15-mm i.d. × 25 cm) fitted with a rubber septum. Each solution was degassed by three freeze–pump–thaw cycles at −196 °C (≤0.5 mmHg), and the reaction tubes were then placed around a 450-W Hanovia lamp in a water bath. The reaction tubes were irradiated for 2 h while keeping the temperature at ca. 20 °C. A second portion of diazo ketone (0.050 g, 0.21 mmol per tube, for a total of 0.400 g, 1.65 mmol) was then added (effervescence!), and the reaction flasks were again degassed (one freeze–pump–thaw cycle at −196 °C, ≤0.5 mmHg) and irradiated for another 15 h. The contents of the tubes were combined and concentrated to afford a brown oil. Column chromatography on silica gel (gradient elution with 0–5% $CHCl_3$–hexanes) gave 0.540 g of unreacted silyloxy acetylene **4** and 0.617 g (64%) of the aromatic annulation product **3** as a white solid: mp 55–57 °C; $[\alpha]^{25}_D$ = −8.9° ($CHCl_3$, c = 0.67); IR ($CHCl_3$) 3190, 2940, 1625, 1590, and 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 8.15 (s, 1 H), 6.81 (s, 1 H), 4.01 (d, J = 2.5 Hz, 2 H), 3.91 (m, 1 H), 2.86 (t, J = 6 Hz, 2 H), 2.40 (s, 3 H), 1.84–1.93 (m, 2 H), 1.65–1.70 (m, 2 H), 1.40 (s, 6 H), 1.39 (d, J = 7 Hz, 3 H), 1.37 (m, 3 H), 1.13 (d, J = 7 Hz, 18 H), 0.98 (s, 9 H), 0.19 (s, 3 H), and 0.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 151.7, 141.1, 132.9, 130.8, 128.1, 120.7, 117.9, 116.6, 100.8, 69.4, 39.1, 34.5, 32.8, 32.7, 31.6, 29.0, 25.9, 19.8, 18.5, 18.3, 15.1, 14.6, 13.1, and two peaks at −5.6. Anal. Calcd for $C_{35}H_{60}O_3Si_2$: C, 71.86; H, 10.34. Found: C, 71.81; H, 10.21.

2-((*S*)-1-Hydroxy-2-propyl)-3-hydroxy-5,9,9-trimethyl-6,7,8,9-tetrahydro-1,4-anthracenedione (2, (−)-Aegyptinone B). A 25-mL, pear-shaped flask fitted with a rubber septum was charged with a solution of the aromatic anulation product **3** (0.700 g, 1.20 mmol) in 12 mL of THF and cooled to −78 °C. Oxygen was bubbled through the reaction mixture via a needle inlet while a tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 3.0 mL, 3.0 mmol) was added dropwise by syringe over 1 min. The cold bath was then removed (the orange solution turned red), and oxygen was bubbled through the reaction mixture for 14 h at 25 °C. The resulting blood-red solution was poured into a mixture of 25 mL of saturated aqueous NH_4Cl solution, 50 mL of ether, and 20 mL of THF. The aqueous layer was separated and extracted with three 50-mL portions of ether, and the combined organic phases were washed with two 25-mL portions of 10% aqueous HCl solution and 50 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated to yield an orange-brown oil. Column chromatography on silica gel (gradient elution with 10–20% ethyl acetate–hexanes) provided 0.340 g of a yellow-orange solid which was taken up in pentane and then concentrated under reduced pressure to afford 0.340 g (87%) of aegyptinone B (**2**) as a yellow solid: mp 118–119 °C (lit.[1] red crystals from MeOH mp 101–102 °C); $[\alpha]^{25}_D$ = +8.7° ($CHCl_3$, c = 2.09); IR (KBr) 3460, 3330, 2970, 2940, 2880, 1650, 1580, 1460, 1420, 1380, 1350, 1335, 1270, 1230, 1120, 1070, 1030, 1010, 990, 960, 920, 900, and 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 3.95 (dd, J = 7, 11 Hz, 1 H), 3.84 (dd, J = 5, 11 Hz, 1 H), 3.46 (m, 1 H), 2.75 (t, J = 6 Hz, 2 H), 2.67 (s, 3 H), 1.83–1.91 (m, 2 H), 1.68–1.64 (m, 2 H), 1.34 (s, 6 H), and 1.29 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 183.0, 154.7, 153.6, 142.1, 141.5, 132.0, 124.5, 124.1, 123.2, 65.4, 37.6, 34.9, 32.7, 31.0, 28.3, 18.8, 16.4, and 14.3; UV λ_{max} (MeOH) 203 (ϵ = 53 700), 268 (25 100), 280 (24 500), and 352 (3630); HRMS m/e calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1672. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.17; H, 7.27.

1-Oxo-2,3-dihydro-3(*S*)-methylcyclopenta-7,11,11-trimethyl-8,9,10,11-tetrahydroanthracene-5,6-dione (1, (−)-Aegyptinone A). A 25-mL, pear-shaped flask fitted with a rubber septum was charged with a solution of aegyptinone B **2** (0.250 g, 0.761 mmol) in 6 mL of ethanol. Concentrated sulfuric acid (3 mL, CAUTION! EXOTHERMIC REACTION) was added dropwise over 5 min. The resultant dark red solution was stirred at 25 °C for 15 min and then poured into 100 mL of water and extracted with two 100-mL portions of ether. The combined organic phases were washed twice with 100 mL of 5% HCl solution and once with 100 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.268 g of a dark red oil. Column chromatography on silica gel (gradient elution with 5–10% ethyl acetate–petroleum ether) provided 0.215 g (91%) of aegyptinone A (**1**) as red-orange crystals: mp 137–138.5 °C (lit.[1] mp 136 °C); $[\alpha]^{25}_D$ = −102° ($CHCl_3$, c = 0.13); IR (KBr) 2970, 2950, 2940, 2880, 1690, 1655, 1645, 1620, 1580, 1555, 1470, 1410, 1395, 1375, 1350, 1290, 1260, 1215, 1195, 1185, 1160, 1135, 1110, 1055, 1000, 970, 945, 920, 905, 810, and 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 4.87 (t, J = 9.5 Hz, 1 H), 4.35 (dd, J = 6.0, 9.3 Hz, 1 H), 3.58 (m, 1 H), 2.70 (t, J = 6.4, 2 H), 2.57 (s, 3 H), 1.79–1.88 (m, 2 H), 1.61–1.66 (m, 2 H), 1.34 (d, J = 6.8 Hz, 3 H), and 1.30 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 176.1, 170.8, 152.1, 143.8, 141.1, 126.1, 125.5, 121.6, 118.1, 81.2, 37.6, 34.8, 34.5, 31.2, 28.4, 19.0, 18.7, and 16.4; UV λ_{max} (MeOH) 268 (ϵ = 31 600), 276 (30 900), 305 (7900), and 370 (3300). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.28; H, 7.11.

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