Oxidative DMSO Cyclization Cascade to Bicyclic Hydroxyketonitriles

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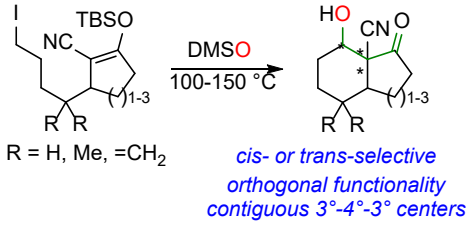


Abstract

Thermolysis of ω-iodoalkyl-β-siloxyalkenenitriles in DMSO triggers an oxidative cyclization cascade that affords highly oxygenated hydrindanones, decalones, and undecanones. The cyclization cascade is highly unusual on three counts: the cyclization installs a contiguous array of tertiary-quaternary-tertiary centers, thermolysis equilibrates a quaternary center, and the enolsilyl ether crossed-aldol proceeds without a catalyst.

Introduction

Oxygenated natural products occupy a privileged position in pharmaceutical discovery.[1] The degree of oxygenation broadly correlates with bioactivity reflecting the increased affinity of polar functionality to bind the biological machinery controlling favorable medicinal outcomes.[2] The relationship between oxidation and bioactivity is exemplified within terpenoids where increased oxygenation correlates with

higher incidences of anticancer, antiviral, antibiotic, and immunosuppressive bioactivity compared to less oxidized counterparts.[3]

Embedded within oxygenated terpenoids are an important subset of bioactive hydrindanes, decalins, and bicyclo[4.3.0]undecanes containing oxygenated, angular carbons (Fig. 1). These terpenoids vary in the size of the bicyclic core and the degree of oxidation of the angular carbon; representative terpenoids include the nitrous oxide inhibitor **1**,[4] the cytotoxic acutifolone **2**,[5] the reverse transcriptase inhibitor **3**,[6] the anti-leukemic ambrosanolide **4**,[7] and the sestertepenoid **5**, an inhibitor of *M. tubercolosis*.[8]

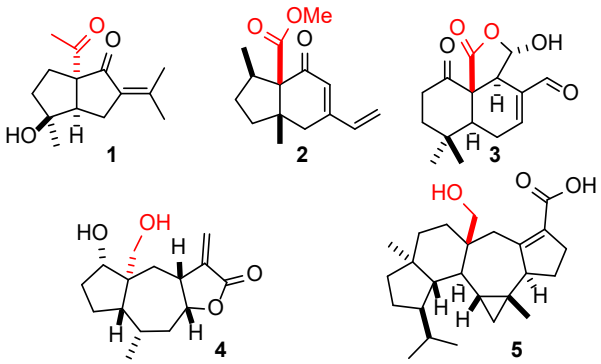
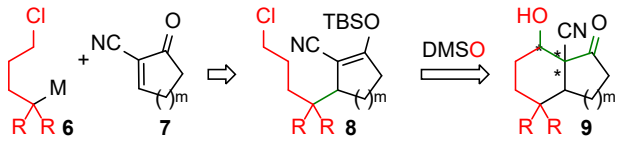


Figure. 1. Representative angularly oxygenated, bioactive terpenoids

Unified synthetic strategies to oxidized hydrindane, decalin, and undecane ring systems are rare.[9] A conceptually attractive strategy to access oxygenated terpenoid-like cores with three different oxidized carbon was envisaged through an organometallic addition-oxidative cyclization sequence (Scheme 1). The strategy benefits from the efficient conjugate addition-silylation of ω-chloroalkylorganometallics **6** to oxoalkenenitriles **7**[10] that generate chloroalkylalkenenitriles **8**.[11] Conceptually, oxidation of chloride **8** would unmask an intermediate aldehyde poised for an aldol-type condensation to form bicyclic hydroxyketonitriles **9**. The modular approach installs carbons at three different oxidation levels, three contiguous stereocenters, with access to varying ring scaffolds suited for elaboration into bioactive targets.[12] Described below is the fulfilment of this direct, stereoselective route to oxygenated hydroxyketonitriles **9**.

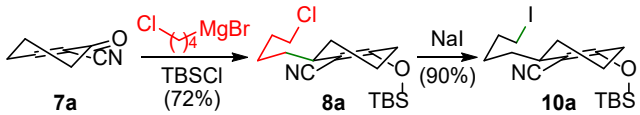
Scheme 1. DMSO oxidative cyclization strategy.



Results and Discussion

Facile conjugate addition of 4-chlorobutylmagnesium bromide[13] to oxonitrile **7a**[14] provided rapid access to the oxidative cyclization prototype **8a** (Scheme 2). Attempts to oxidize the chloride **8a** with DMSO were unsuccessful, even in the presence of Bu_4NI or $AgBF_4$. However, facile chlorine-iodine interchange[15] provided rapid access to **10a** that proved amenable to the oxidative cyclization cascade (Scheme 3).

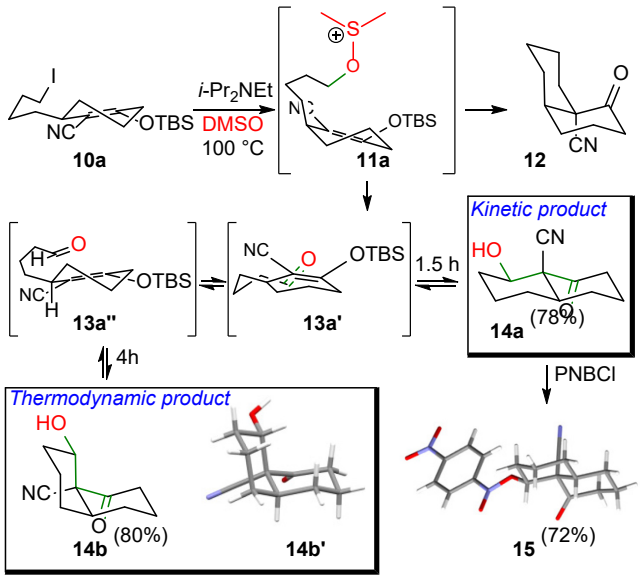
Scheme 2. Alkenenitrile prototype for oxidative cyclization.



DMSO and amine oxide[16] oxidation of alkyl iodides[17] and tosylates[18] has not been employed in bond-forming cascades.[19] The cyclization cascade of iodide **10a** (Scheme 3) requires precise timing for the oxidation (**10a** → **11a** → **13**) and cyclization steps (**13a'** → **14a** or **13a''** → **14b**) because a slow deprotonation of the sulfonium salt **11a** incurs the potential for a premature cyclization of the nucleophilic enol ether to afford decalone **12**; early oxidative explorations in DMSO with **10a** and amine oxide protocols afforded only decalone **12**. Switching to thermolysis with **10a** and *i*-Pr_2NEt revealed a thermal window between 80 and 150 °C for the efficacious oxidation.[20] Monitoring the oxidation of **10a** revealed that formation of the aldehyde-nitrile **13a** was complete after only 20 minutes at 100 °C (76% yield); at temperatures lower than 100 °C the reaction became sluggish, stalling at temperatures below 80 °C.[21] Continued thermolysis at 100 °C triggered an intramolecular aldol-type condensation to generate primarily the *trans*-decalone **14a** (78% yield after 1.5 h; the configuration was determined by conversion to the

crystalline PNB ester **15** followed by crystallographic analysis) accompanied by approximately 10% of the diastereomeric *cis*-decalone **14b**. [22]

Scheme 3. DMSO oxidative cyclization to *cis*- and *trans*-decalones **14a** and **14b**.



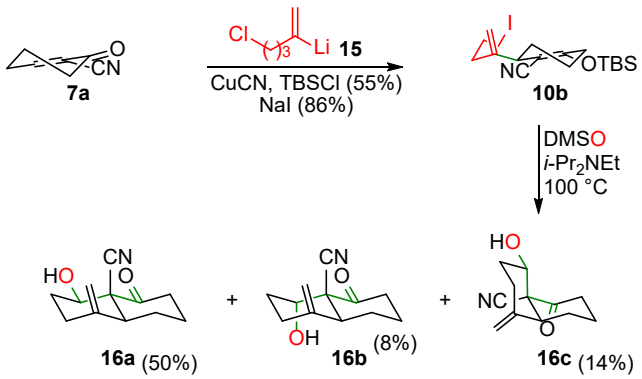
The cyclization stereoselectivity showed an intriguing concentration, time, and base dependence. Increasing the reaction concentration from 0.05 mM to a 0.2 mM decreased the efficiency providing **14a** (21%), **14b** (15%), and 10% of the methylthiomethyl ether **14c** (**14b**, HO = $MeSCH_2O$), presumably from trapping **14b** with the thionium ion derived from dehydration of DMSO.[23] Extending the thermolysis of **10a** from 1.5 to 4 h afforded the *cis*-decalone **14b** by equilibrating **14a** through a retroaldol-aldol process (**14a** to **13** to **14b**). Substituting Proton Sponge for *i*-Pr_2NEt accelerated the cyclization-equilibration process to afford **14b** in 81% yield after 4 h. The interconversion of **14a** and **14b** represents a rare example of an equilibration at a quaternary center.[24]

The crossed aldol cyclization of **13** can conceivably arise directly from the silyl enol ether or via an enol derived from *i*-Pr_2NEt.HI-induced protodesilylation.[25] Isolation of aldehyde **13** allowed thermolysis in DMSO in the absence of *i*-Pr_2NEt or *i*-Pr_2NEt.HI which gave only the *cis*-decalone **14b** (80% yield after 1 h at 100 °C); the enol silyl ether crossed-aldol is unusual in not requiring a catalyst.[26] The tentative implication is that the presence of *i*-Pr_2NEt.HI causes protodesilylation of **13** followed by a kinetically

controlled aldol cyclization to *trans*-decalone **14a**. Longer reaction times, or the use of Proton Sponge, facilitates a retro-aldol-aldol equilibration favoring conversion of **14a** to **14b**. The thermodynamic preference for the *cis*-decalone **14b** is consistent with the rather delicately tilted equilibrium in 8a-substituted 1-decalones that favors *cis*-decalones.[27]

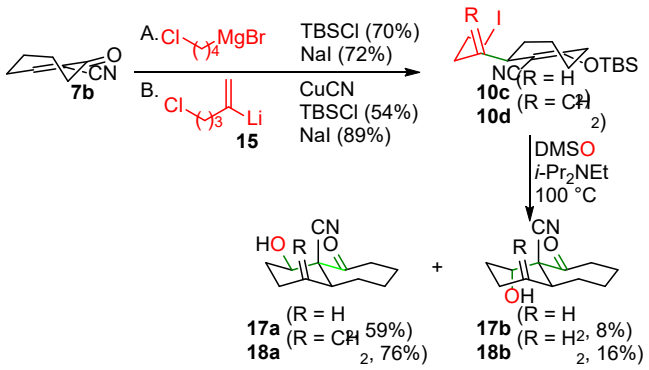
The thermal oxidative cyclization of **10a** established valuable parameters to extend the strategy to other ring systems. The prevalence of *exo*-methylene-containing terpenoids[28] stimulated cyclization of the methylene-substituted iodonitrile **10b**, prepared through a copper-catalyzed addition of alkenyllithium **15**[29] to oxonitrile **7a** followed by chloride-iodide interchange (Scheme 4). Cyclization of **10b** with DMSO and *i*-Pr_2NEt, at 100 °C provided the *trans*-decalones **16a** and **16b** (58%) accompanied by the *cis*-decalone **16c** (14%).[30]

Scheme 4. Oxidative cyclization to *exo*-methylene decalones.



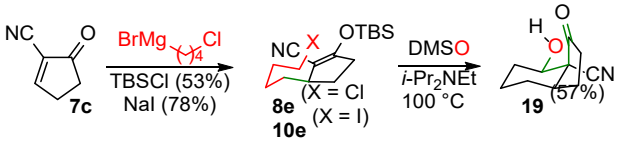
The oxidative cyclization was extended to undecanones via the seven-membered oxonitrile **7b** (Scheme 5). Addition of chlorobutylmagnesium bromide, or the alkenyllithium **15**, to **7b** generated the corresponding β-siloxyalkenenitriles that were subjected to a Finkelstein iodination to afford **10c** and **10d**, respectively. Oxidative cyclization of **10c** afforded the *trans*-undecanonenitriles **17a** and **17b** 67%), whereas **10d** afforded the *trans*-undecanonenitriles **18a** and **18b** (92%).

Scheme 5. Oxidative cyclization to *trans*-undecanones.



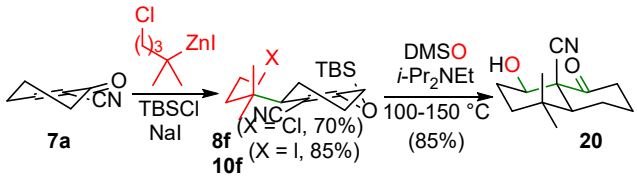
The strategy was extended to a hydrindane through an oxidative annelation with the 5-membered oxonitrile **7c** (Scheme 6). Conjugate addition of chlorobutylmagnesium bromide to **7c** followed by silylation afforded the chloride **8e** whose treatment with NaI provided iodide **10e** (Scheme 6). Oxidative cyclization of **10e** afforded the *cis*-hydrindanone **19** with the *trans* orientation between the angular nitrile and the vicinal hydroxyl group.[31]

Scheme 6. Oxidative cyclization to the *cis*-hydrindanone **19**.



The potential of the oxidative cyclization cascade is illustrated with the rapid assembly of **20**, a differentially oxidized decalin containing a *gem*-dimethylcyclohexane motif found in many terpenes (Scheme 7).[32] An uncatalyzed conjugate addition of a chloroalkylorganozinc to oxonitrile **7a** afforded chloride **8f** whose chloride-iodide interchange provided iodide **10f**. Thermolysis of **10f** at 100 °C for 2 h afforded a mixture of alcohol diastereomers that were equilibrated by heating at 150 °C for 1 h, to provide **20** in 85% yield.[33] The rapid formation of **20** illustrates the potential of the oxidative cyclization in generating complex scaffolds with differentially oxidized carbons.

Scheme 7. Assembly of an oxygenated decalone for terpene synthesis.



Conclusions

Thermolytic, oxidative cyclization of β-siloxyalkenenitriles bearing pendant ω-iodoalkyl substituents provides a mild, efficient route to bicyclic hydroxyketonitriles. The DMSO oxidation of the pendant alkyliodide to the corresponding aldehyde initiates a simple cascade that triggers an uncatalyzed, diastereoselective, aldol cyclization. The highly unusual aldol-retroaldol installs a contiguous array of tertiary-quaternary-tertiary stereocenters. The strategy is rapid and modular, and provides rapid access to oxidized hydrindanones, decalones, and undecanones richly decorated with alcohol, ketone, and nitrile groups for target-directed synthesis.

Experimental Section

General Experimental Conditions. All nonaqueous reactions were performed in oven- or flame-dried glassware under a nitrogen atmosphere. All chemicals were purchased from commercial vendors and used as received unless otherwise specified. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone-sodium under N_2 before use, dimethylsulfoxide (DMSO) and N,N-Diisopropylethylamine were obtained from a solvent purification system (Innovative Technology Inc., model PS-MD7). Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 250 μm precoated silica gel plates. Reactions with microwave heating

were performed in microwave vials using a Biotage Initator Microwave Synthesizer (Model: Initiator). ^{1}H NMR and ^{13}C{^{1}H} high resolution nuclear magnetic resonance spectra were recorded on a Varian Inova 400 (400 MHz/101 MHz) instrument. Chemical shifts are reported relative to TMS (δ 0.00) for ^{1}H NMR and chloroform (δ 77.16) for ^{13}C{1H}. IR spectra were recorded as thin films (PerkinElmer Spectrum 100 FT-IR Spectrometer). High-resolution mass spectra were obtained on a Bruker 12.0 Tesla APEX – Qe FTICR-MS with and Apollo II ion source (positive electrospray ionization with an ion cyclotron resonance cell) and a Thermo-Finnigan LTQ-FT 7T FT-ICR spectrometer with an atmospheric pressure chemical ionization (APCI) source with direct infusion run in positive ion mode at 5 kV with an Orbitrap ion trap mass analyzer. All crystallographic data were acquired at 100 Kelvin on a Bruker KAPPA APEX II DUO equipped with a CCD area detector (8.333 pixels/mm) using molybdenum radiation (λ= 0.71073 Å) originating from a sealed fine-focus tube. COSMO (Bruker AXS) was used for collection strategy determination. All frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data was corrected for absorption effects with a multi-scan method using SADABS. All structures were solved and refined using the Bruker SHELXTL software package using full matrix least squares refinement. APEX2/APEX3 and OLEX2 were used as analysis interfaces.

General conjugate addition (Method A). A THF solution of the appropriate Grignard reagent (1.2 equiv) was slowly added to a -78 ºC, THF solution of the oxonitrile (1.0 equiv). After 45 min, the solution was allowed to warm to rt and then solid TBDMSCl (2.0 equiv) was added. After 24 h, saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4) and

concentrated. The crude product was purified on a Reveleris X2 MPLC purification system using a silica gel cartridge (hexanes:ethyl acetate).

General conjugate addition (Method B). A hexanes solution of BuLi (1.6 M, 1.1 eq.) was added to a -78 ºC, THF solution of 4-chloro-2-iodo-but-1-ene (1 equiv) or 5-chloro-2-iodo-pent-1-ene (1 equiv). After 5 min, a THF solution of CuCN (1.1 equiv) pre-fused with LiCl (1.1 equiv)[34] was added resulting in a yellow solution. Stirring was continued for an additional 15 min at-78°, followed by dropwise addition of the oxonitrile (0.8 eq.) in THF. After 45 min, the solution was allowed to warm to rt and then solid TBDMSCl (2.0 equiv) was added After 24 h, saturated, aqueous NH_4Cl was added, the phases were separated, and then the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified on a Reveleris X2 MPLC purification system using a silica gel cartridge (hexanes:ethyl acetate).

*2-((tert-Butyldimethylsilyl)oxy)-6-(4-chlorobutyl)cyclohex-1-ene-1-carbonitrile (**8a**)*. Following the general conjugate addition method A with 1-oxo-2-cyclohexenyl-2-carbonitrile **6a** (1.00 g, 8.25 mmol, in 10 mL THF),[14] chlorobutylmagnesium bromide[13] (0.43 M, 21.0 mL in THF), and TBDMSCl (2.50 g, 16.6 mmol) afforded after purification by MPLC (12 g silica cartridge, EtOAc: hexanes, 5:95 to 10:90, 10 min) 1.96 g (72%) of **8a** as a clear, light yellow oil spectrally identical to material previously isolated.[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (td, *J* = 6.6, 1.2 Hz, 2H), 2.34 – 2.26 (m, 1H), 2.13 (ddd, *J* = 7.5, 4.6, 2.4 Hz, 2H), 1.88 – 1.68 (m, 5H), 1.64 – 1.48 (m, 2H), 1.48 – 1.23 (m, 3H), 0.97 (s, 9H), 0.22 (s, 3H), 0.22 (s, 3H). $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 165.7, 118.4, 95.5, 45.0, 35.1, 33.7, 32.5, 30.9, 26.5, 25.5, 23.9, 20.0, 18.1, -3.7, -3.8.

*2-((tert-Butyldimethylsilyl)oxy)-6-(4-chlorobutyl)cyclohex-1-ene-1-carbonitrile (**8b**).* Following the general conjugate addition method B with oxonitrile **6a** (323 mg, 2.67 mmol, 5 mL THF), 5-chloro-2-iodo-pentene[35] (750 mg, 3.26 mmol, 10 mL THF), BuLi (1.60 M, 2.1 mL), a 10 mL THF solution pre-fused with CuCN (300 mg, 3.35 mmol), LiCl (150 mg, 3.54 mmol, 1.1 eq.), and TBDMSCl (1.00 g, 6.63 mmol) afforded, after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 494 mg (55%,) of **8b** as a clear oil: IR (ATR) 2210, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (br. s, 1H), 4.89 (br. s, 1H), 3.68 – 3.46 (m, 2H), 3.05 – 2.95 (m, 1H), 2.23 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.18 – 2.06 (m, 3H), 2.04 – 1.86 (m, 2H), 1.78 – 1.48 (m, 4H), 0.97 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H).$^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 166.4, 148.0, 118.4, 113.1, 93.5, 44.5, 42.5, 31.0, 30.9, 30.7, 26.6, 25.5, 18.7, 18.1, -3.76, -3.73.; HRMS (+APCI) m/z [M + H+] calcd for $C_{18}H_{31}ONClSi$ 340.1858; found 340.1864.

*2-(tert-Butyldimethylsilyl)oxy)-7-(4-chlorobutyl)cyclohept-1-ene-1-carbonitrile (**8c**).* Following the general conjugate addition method A with 1-oxo-2-cycloheptenyl-2-carbonitrile[36] (**6b**) (225 mg, 1.66 mmol, in 10 mL THF), chlorobutylmagnesium bromide[13] (0.43 M, in 5.0 mL THF) and TBDMSCl (300 mg, 1.99 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 400 mg (70%,) of **8c** as a clear, light yellow oil: IR (ATR) 2204, 1614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (t, *J* = 6.7 Hz, 2H), 2.48 (m, 1H), 2.36 – 2.23 (m, 2H), 1.93 – 1.75 (m, 3H), 1.74 – 1.37 (m, 9H), 0.98 (s, 9H), 0.24 (s, 6H).$^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 170.8, 118.9, 98.8, 44.9, 37.5, 35.5, 33.4, 32.5, 31.9, 28.3, 25.5, 25.0, 24.0, 18.1, -3.7, -3.8. HRMS (+APCI) m/z [M + H+] calcd for $C_{18}H_{33}ONClSi$ 342.2015; found 342.2024.

*2-((tert-Butyldimethylsilyl)oxy)-7-(4-chlorobutyl)cyclohept-1-ene-1-carbonitrile (**8d**).* Following the general conjugate addition method B with oxonitrile **6b** (250 mg, 1.85 mmol), 5-chloro-2-iodo-pentene[35] (500 mg, 2.17 mmol), BuLi (1.60 M, 1.50 mL, 1.1 eq.), a 10 mL THF solution pre-fused with CuCN (220 mg, 2.46 mmol), LiCl (100 mg, 2.36 mmol), and TBDMSCl (750 g, 4.98 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 353 mg (54%,) of **8d** as a clear oil: IR (ATR) 2206, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (br. s, 1H), 4.97 (br. s, 1H), 3.57 (t, *J*

= 6.5 Hz, 2H), 3.06 – 2.98 (m, 1H), 2.38 (br t, *J* = 5.6 Hz, 2H), 2.32-2.11 (m, 2H), 2.03-1.92 (m, 2H), 1.92 – 1.77 (m, 2H), 1.77 – 1.67 (m, 1H), 1.67 – 1.58 (m, 3H), 0.98 (s, 9H), 0.25 (s, 6H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 170.6, 147.2, 119.2, 112.3, 97.5, 44.6, 44.5, 35.2, 31.6, 30.7, 29.9, 26.3, 25.5, 23.7, 18.1, -3.68, -3.73; HRMS (+APCI) m/z [M + H+] calcd for $C_{19}H_{33}ONClSi$ 354.2015; found 354.2025.

*2-((tert-Butyldimethylsilyl)oxy)-5-(4-chlorobutyl)cyclopent-1-ene-1-carbonitrile (**8e**).* Following the general conjugate addition method A with oxonitrile **6c** (226 mg, 2.11 mmol, in 10mL THF),[37] chlorobutylmagnesium bromide[13] (0.43 M, in 6.0 mL THF) and TBDMSCl (706 mg, 4.68 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 350 mg (53%,) of **8e** as a clear, oil: IR (ATR) 2204, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (t, *J* = 6.6 Hz, 2H), 2.81 (m, 1H), 2.42 – 2.33 (m, 2H), 2.14 (m, *J* = 12.9, 1H), 1.88 – 1.75 (m, 2H), 1.70 (m, 1H), 1.63 – 1.53 (m, 1H), 1.53 – 1.39 (m, 2H), 1.39 – 1.26 (m, 1H), 0.96 (s, 9H), 0.24 (s, 6H).$^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 170.2, 116.6, 92.5, 44.8, 41.8, 34.3, 33.6, 32.5, 27.2, 25.3, 23.8, 18.1, -3.99, -4.01.; HRMS (+APCI) m/z [M + H+] calcd for $C_{16}H_{29}ONClSi$ 314.1703; found 314.1702

*2-(tert-Butyldimethylsiloxy)-6-((2-methyl-5-chloro)-2-pentyl)-1-cyclohexenyl-1-carbonitrile (**8f**).* A THF solution (40 mL) of $ZnCl_2$ (3.32 g, 24.4 mmol) was slowly added (45 min) to a refluxing dark green, THF solution (20 mL) formed by the addition of finely cut Li metal (339 mg, 48.8 mmol) to naphthalene (666 mg, 5.20 mmol). The solution was refluxed for an additional 1.25 h and then the Zn metal was allowed to settle overnight. The supernatant was removed by syringe and the Zn metal was washed with THF (15 mL). The Zn was suspended in THF (40 mL), 5-chloro-2-iodo-2-methylpentane (4.00 g, 16.3 mmol) was added and then the resultant mixture was heated to reflux for 2 h. The solution was allowed to cool (1.5-2 h) during which time the excess zinc metal settled on the bottom of the flask. The organozinc iodide was removed by syringe and added to a -78 °C, THF solution (100 mL) of oxonitrile **6a** (2.00 g, 16.3 mmol) over 30 min. After 4 h solid TBDMSCl (3.68 g, 24.39 mmol) was added, and then the solution was allowed to stir for 12 h. Saturated, aqueous NH_4Cl was added, and the then crude product was extracted with EtOAc. Concentration of the crude material and purification by column

chromatography (5:95 EtOAc:hexanes) gave 4.51 g (78%) of **8f** as a clear, viscous liquid: IR (film) 2947, 2203, 1614 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (ddd, *J* = 17, 10.5, 6.4 Hz, 1H), 3.51 (ddd, *J* = 17, 10.5, 6.9 Hz, 1H), 2.33-2.38 (m, 1H), 2.10-2.15 (m, 2H), 1.41-1.91 (m, 8H), 1.03 (s, 3H), 0.99 (s, 12H), 0.25 (s, 3H), 0.23 (s, 3H); ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 168.8, 120.3, 92.8, 45.7, 43.1, 38.0, 37.0, 31.2, 27.6, 26.0, 25.8, 25.6, 24.0, 21.2, 18.2, -3.7; MS m/e 355 (M+H).

General Chloride-Iodide Exchange. An anhydrous acetone solution (5-10 mL) of NaI (5 equiv) and the appropriate chloride intermediate (1 equiv) was heated in a microwave reaction vial (10-20 mL) at 100 ºC. After 2.5 h, the solution was allowed to cool to ambient temperature, and then saturated, aqueous NH_4Cl was added. The phases were separated and then the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified on a Reveleris X2 MPLC purification system using a silica gel cartridge (hexanes:ethyl acetate).

*2-((tert-Butyldimethylsilyl)oxy)-6-(4-iodobutyl)cyclohex-1-ene-1-carbonitrile (**10a**).* Following the general chloride-iodide exchange procedure with chloride **8a** (450 mg, 1.37 mmol) and NaI (1.000 g, 6.67 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 520 mg (90%,) of **10a** as a clear oil: IR (ATR) 2206, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 – 3.13 (m, 2H), 2.37-2.28 (m, 1H), 2.18-2.09 (m, 2H), 1.98 – 1.65 (m, 5H), 1.65 – 1.20 (m, 5H), 0.98 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ 165.7, 118.4, 95.5, 35.0, 33.33, 33.31, 30.9, 27.5, 26.6, 25.5, 20.0, 18.1, 7.1, -3.73, -3.72 HRMS (+APCI) m/z [M + H+] calcd for $C_{17}H_{31}ONISi$ 420.12141; found 420.1225.

*2-(tert-Butyldimethylsilyl)oxy)-6-(4-iodobutyl)cyclohex-1-ene-1-carbonitrile (**10b**).* Following the general chloride-iodide exchange with chloride **8b** (201 mg, 0.59 mmol) and NaI (450 mg, 3.00 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 219 mg (86%,) of **10b** as a clear, light yellow oil: IR (ATR) 2210, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

5.01 (s, 1H), 4.89 (s, 1H), 3.31 – 3.12 (m, 2H), 3.03-2.95 (m, 1H), 2.27 – 2.05 (m, 4H), 2.05-1.90 (m, 2H), 1.76 – 1.48 (m, 4H), 0.98 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 166.4, 147.6, 118.3, 113.3, 93.4, 42.5, 34.6, 31.5, 30.9, 26.6, 25.5, 18.7, 18.1, 6.7, -3.6, -3.7.; HRMS (+APCI) m/z [M + H+] calcd for $C_{18}H_{31}ONISi$ 432.1214; found 432.1223.

*2-((tert-Butyldimethylsilyl)oxy)-7-(4-iodobutyl)cyclohex-1-ene-1-carbonitrile (**10c**).* Following the general chloride-iodide exchange with chloride **8c** (220 mg, 0.64 mmol) and NaI (500 mg, 3.34 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 200 mg (72%,) of **10c** as a clear oil: IR (ATR) 2202, 1613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (t, *J* = 7.0 Hz, 2H), 2.47 (ddd, *J* = 15.5, 9.7, 2.4 Hz, 1H), 2.35 – 2.22 (m, 2H), 1.92 – 1.80 (m, 3H), 1.75 – 1.56 (m, 5H), 1.54 – 1.41 (m, 4H), 0.98 (s, 9H), 0.24 (s, 6H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 170.8, 118.9, 98.8, 37.4, 35.5, 33.4, 33.0, 31.9, 28.6, 28.3, 25.5, 24.0, 18.1, 6.9, -3.7, -3.8. HRMS (+APCI) m/z [M + H+] calcd for $C_{18}H_{33}ONISi$ 434.1371; found 434.1384.

*2-((tert-Butyldimethylsilyl)oxy)-7-(4-iodobutyl)cyclohept-1-ene-1-carbonitrile (**10d**).* Following the general chloride-iodide exchange with chloride **8d** (179 mg, 0.51 mmol) and NaI (450 mg, 3.00 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 200 mg (89%,) of **10d** as a clear, light yellow oil: IR (ATR) 2206, 1643, 1615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.97 (s, 1H), 3.30 – 3.15 (m, 2H), 3.05-2.98 (m, 1H), 2.49-2.35 (m, 2H), 2.27 – 2.08 (m, 2H), 2.07 – 1.94 (m, 2H), 1.94 – 1.77 (m, 2H), 1.75 – 1.56 (m, 4H), 0.98 (s, 9H), 0.25 (s, 6H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 170.9, 146.7, 119.3, 112.5, 97.4, 44.4, 35.2, 35.0, 31.4, 29.9, 26.3, 25.6, 23.7, 18.1, 6.6, -3.6, -3.7; HRMS (+APCI) m/z [M + H+] calcd for $C_{19}H_{33}ONISi$ 446.1371; found 446.1387.

2-((tert-Butyldimethylsilyl)oxy)-6-(4-iodobutyl)cyclohex-1-ene-1-carbonitrile (10e). Following the general chloride-iodide exchange with chloride **8e** (204 mg, 0.65 mmol) and NaI (580 mg, 3.87 mmol) afforded after purification by MPLC (4 g silica cartridge, EtOAc: hexanes, 2:98 to 10:90, 10 min), 207 mg (78%,) of **10e** as a clear oil: IR (ATR) 2204, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (td, *J* =

6.9, 2.1 Hz, 2H), 2.86 - 2.76 (m, 1H), 2.43 - 2.35 (m, 2H), 2.23 – 2.07 (m, 1H), 2.02 – 1.76 (m, 2H), 1.76 – 1.63 (m, 1H), 1.63 – 1.54 (m, 1H), 1.53 – 1.26 (m, 3H), 0.97 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H). $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 170.2, 116.6, 92.5, 41.8, 33.9, 33.6, 33.3, 27.5, 27.3, 25.3, 18.1, 6.9, -3.97, -3.99 HRMS (+APCI) m/z [M + H+] calcd for $C_{16}H_{29}ONISi$ 406.1058; found 406.1062.

2-((tert-Butyldimethylsilyl)oxy)-6-(5-iodo-2-methylpentan-2-yl)cyclohex-1-ene-1-carbonitrile ***(10f)***. Neat chloride **8f** (2.47 g, 7.0 mmol) was added to room temperature, acetone solution (100 mL) of sodium iodide (5.21 g, 35 mmol) and then the mixture was heated to reflux. After 24 h the reaction was allowed to cool, concentrated, washed with water, extracted with CH_2Cl_2 and dried (Na_2SO_4). Concentration, and radial chromatography (1:19 EtOAc/hexanes) of the resulting yellow oil, provided 2.82 g (85 %) of **14** as a colorless oil: IR (film) 2205 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.30 -3.50 (m, 2H), 2.56-2.61 (m, 1H), 2.37-2.41 (m, 2H), 1.99-2.21 (m, 4H), 1.54-1.89 (m, 4H), 1.29 (s, 3H), 1.26 (s, 3H), 1.26 (s, 9H), 0.53 (s, 3H), 0.51 (s, 3H); $^{13}C\{^{1}H\}$ (75 MHz, C_6D_6) δ 193.5, 94.6, 44.3, 43.1, 37.8, 27.2, 26.8, 25.6, 19.2-2.5; HRMS (ESI) calcd for (M+Na) $C_{19}H_{34}INOSi$ 470.1347, found 470.1351.

General DMSO Cyclization Procedure. A dry DMSO solution (5 mL) of the iodide (1 equiv) and *i*-Pr_2NEt (5 equiv) or proton sponge (5 equiv) was heated in a microwave reaction vial (10-20 mL) at 100 ºC in a microwave reactor. After 1.5-4.0 h, the solution was allowed to cool to ambient temperature, and then deionized water was added. The phases were separated and then the aqueous phase was extracted (3 x 15 mL) with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified on a Reveleris X2 MPLC purification system using a silica gel cartridge (hexanes:ethyl acetate) or ternary (hexanes: ethyl acetate: dichloromethane) with gradient elution.

2-(tert-Butyldimethylsilyl)oxy)-6-(4-butanal)cyclohex-1-ene-1-carbonitrile ***(13a)***. Following the general DMSO cyclization, iodide **10a** (225 mg, 0.54 mmol) and *i*-Pr_2NEt (0.50 mL, 2.86 mmol) with microwave heating for 20 min at 100 ºC afforded, after purification by MPLC (4 g silica cartridge,

hexanes: ethyl acetate, 90:10), 125 mg (76%,) of **13a** as a clear oil: IR (ATR) 2206, 1723, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.5 Hz, 1H), 2.57 – 2.39 (m, 2H), 2.38 – 2.27 (m, 1H), 2.18 – 2.09 (m, 2H), 1.84 – 1.70 (m, 4H), 1.65 – 1.54 (m, 2H), 1.47 – 1.25 (m, 2H), 0.97 (s, 9H), 0.22 (s, 3H), 0.22 (s, 3H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 202.1, 165.8, 118.4, 95.2, 43.9, 35.1, 34.0, 30.9, 26.5, 25.5, 20.0, 19.1, 18.1, -3.7, -3.8. HRMS (+APCI) m/z [M + H+] calcd for $C_{17}H_{30}O_2NSi$ 308.2040; found 308.2040.

(4S, 4aS*, 8aS*)-4-hydroxy-5-oxooctahydronaphthalene-4a(2H)-carbonitrile (**14a**).* Following the general DMSO cyclization with iodide **10a** (39 mg, 0.09 mmol), *i*-Pr_2NEt (0.10 mL, 0.57 mmol), and microwave heating for 1.5 h at 100 ºC afforded, after purification by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min), 14 mg (78%) of **14a** as a clear oil: IR (ATR) 3496, 2359, 2236, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (ddd, *J* = 11.7, 4.3, 2.9 Hz, 1H), 3.29 (d, *J* = 3.2 Hz, 1H), 2.92 (td, *J* = 13.7, 6.6 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.22 – 2.13 (m, 1H), 2.05 –1.54 (m, 9H), 1.42 – 1.26 (m, 1H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 205.7, 116.6, 70.0, 60.9, 46.5, 39.1, 29.6, 29.1, 28.5, 26.4, 22.8. HRMS (+APCI) m/z [M + H+] calcd for $C_{11}H_{16}O_2N$ 194.1176; found 194.1176. **Procedure for the cyclization of 10a on a 1 mmole scale:** Following the general DMSO cyclization with iodide **10a** (421 mg, 1.00 mmol), *i*-Pr_2NEt (0.9 mL, 5.15 mmol), and heating in an oil bath for 4 h at 100 ºC afforded, after purification by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min), 142 mg (73%,) of **14a** and 23 mg (12%,) of **14b** spectroscopically identical to material previously isolated as described below. **Procedure for the cyclization of 10a at 0.2 mM:** Following the general DMSO cyclization with iodide **10a** (438 mg, 1.04 mmol), *i*-Pr_2NEt (0.9 mL, 5.15 mmol), and microwave heating 1.5 h at 100 ºC afforded, after purification by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min), 43 mg (21%,) of **14a** and 30 mg (15%,) of **14b** spectroscopically identical to material previously isolated along 25 mg (10%) of **14c** as a white solid that was recrystallized by diffusion of hexanes into a chloroform whose structure was solved by crystallographic analysis (CDC#2104386). For *(4R*, 4aS*, 8aS*)-4-((methylthio)methoxy)-5-oxooctahydronaphthalene-4a(2H)-carbonitrile (**14c**).* mp 114.2 - 116.2 ºC: IR (ATR) 2243, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.66

(ABq, Δν = 44.8 Hz, *J* = 12.0 Hz, 2H), 4.41 (dd, *J* = 8.5, 3.7 Hz, 1H), 2.81 – 2.47 (m, 3H), 2.08 (s, 3H), 2.04 – 1.58 (m, 10H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 202.3, 119.0, 72.3, 70.5, 42.9, 37.7, 27.1, 26.5, 26.4, 26.2, 24.4, 19.3, 13.9; HRMS (+APCI) m/z [M – OCH_2SCH_3] calcd for $C_{11}H_{14}NO$ 176.1070; found 176.1070.

(4R, 4aS*, 8aS*)-4-hydroxy-5-oxooctahydronaphthalene-4a(2H)-carbonitrile (**14b**).* Following the general DMSO cyclization with iodide **10a** (40 mg, 0.10 mmol), *i*-Pr_2NEt (0.1 mL, 0.57 mmol), and microwave heating for 4 h at 100 ºC afforded after purification by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min) 15 mg (81%) of **14b** as a white solid that was recrystallized by diffusion of hexanes into a chloroform solution of **14b** to give a white crystalline solid (mp 145.0-146.1 ºC) whose structure was solved by crystallographic analysis (CDC# 2104380); IR (ATR) 3456, 2359, 2243, 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, *J* = 8.5 Hz, 1H), 2.68 – 2.48 (m, 3H), 2.16 – 1.98 (m, 2H), 1.95 (s, 1H), 1.92 – 1.62 (m, 7H), 1.58 – 1.49 (m, 1H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 202.7, 118.0, 68.1, 42.4, 37.7, 31.5, 29.7, 27.0, 26.1, 24.4, 19.4; HRMS (+APCI) m/z [M + H+] calcd for $C_{11}H_{16}O_2N$ 194.1176; found 194.1176. **Procedure for the oxidative cyclization of 10a with Proton Sponge as the base:** Following the general DMSO cyclization with iodide **10a** (31 mg, 0.07 mmol), Proton Sponge (94 mg, 0.44 mmol), and microwave heating for 4 h at 100 ºC afforded after purification by flash chromatography (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min) 15 mg (81 %) of **14b** spectroscopically identical to material previously isolated. **Procedure for the formation of 14b by thermolysis of aldehyde 13a:** Thermolysis of a DMSO solution (5 mL) of aldehyde **13a** (30 mg, 0.10 mmol) at 100 ºC (microwave heating) for 1 h afforded, after purification by flash chromatography (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min), 15 mg (80 %,) of **14b** spectroscopically identical to material previously isolated. **Preparation from 14b by equilibration:** A methanolic solution (5 mL) of **14b** (20 mg, 0.10 mmol) and K_2CO_3 (117 mg, 0.85 mmol) was maintained at rt for 4 days. Water was added and the resulting mixture was then extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), concentrated, and purified by MPLC (4 g silica

cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 50:50, 10 min) to afford 15 mg (75 %) of **14a** spectroscopically identical to material previously isolated.

(1R, 4aR*, 8aS*)-8a-cyano-8-oxodecahydronaphthalen-1-yl-4-nitrobenzoate* ***(15)***. Dimethylaminopyridine (19 mg, 0.16 mmol), *p*-nitrobenzoylchloride (29 mg, 0.16 mmol) and *i*-Pr_2NEt (0.05 mL, 0.29 mmol) were added to a dry CH_2Cl_2 solution (2 mL) of 1**4a** (25 mg, 0.13 mmol). After 24 h the solution was quenched with water, extracted with ethyl actetate, concentrated and purified by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 50:50, 10 min) to afford 32 mg (72 %) of **15** as a white crystalline solid, recrystallized from EtOAc/hexanes by evaporation, whose structure was determined by crystallographic analysis (CDC#2104384), mp: 165.5-168.5 ºC: IR (ATR) cm^{-1} 2357, 1731, 1529, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.23 (m, 2H), 8.23 – 8.15 (m, 2H), 5.39 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.01 (ddd, *J* = 13.8, 13.0, 6.5 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.30 – 2.15 (m, 2H), 2.12 –1.96 (m, 1H), 1.94 –1.62 (m, 7H), 1.56 – 1.40 (m, 1H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 200.7, 163.1, 150.6, 135.0, 130.9, 123.5, 116.5, 71.1, 58.5, 47.8, 38.9, 29.0, 28.8, 28.3, 26.9, 22.6. HRMS (+APCI) m/z [M + H+] calcd for $C_{18}H_{19}N_2O_5$ 343.1289, found 343.1290.

(4R, 4aS*, 8aS*)-4-hydroxy-1-methylene-5-oxooctahydronaphthalene-4a(2H)-carbonitrile* ***(16a)***. Following the general DMSO cyclization with iodide **10b** (406 mg, 0.94 mmol) and *i*-Pr_2NEt (1.0 mL, 5.73 mmol) and microwave heating for 1.5 h at 100 ºC afforded a crude mixture of alcohols that were purified by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min) to afford 98 mg (50%,) of **16a,** 16 mg (8%,) of **16b** and 24 mg (14%,) of **16c**. For **16a**: recrystallization from by evaporation EtOAc/hexanes provided a crystalline material whose structure was solved by crystallographic analysis (CDC# 2104378): mp 90.5-92.0 ºC; IR (ATR) cm^{-1} 3529, 2234, 1718; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.14 (s, 1H), 4.14 (dt, J = 12.0, 3.7 Hz, 1H), 3.34 (d, *J* = 3.3 Hz, 1H), 2.92 (td, *J* = 13.8, 6.5 Hz, 1H), 2.57 – 2.39 (m, 2H), 2.30 – 2.19 (m, 2H), 2.19 – 1.97 (m, 4H), 1.84 – 1.63 (m, 2H).$^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 205.5, 143.1, 115.9, 111.8, 70.0, 61.1, 49.0, 38.9, 32.6, 30.8, 25.7, 24.5; HRMS (+APCI) m/z [M + H+] calcd for $C_{12}H_{16}O_2N$ 206.1176, found 206.1176. **Procedure for**

cyclization at 0.2 mM: Following the general DMSO cyclization with iodide **10b** (472 mg, 1.09 mmol) and *i*-Pr_2NEt (0.9 mL, 5.15 mmol) and microwave heating for 3 h at 100 ºC afforded a crude mixture of alcohols that were purified by MPLC (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 5:95, 10 min) to afford 55 mg (24%,) of **16a,** 16 mg (7%,) of **16b** and 56 mg (25%,) of **16c**. **For 16b**: recrystallization by evaporation from EtOAc/hexanes provided a crystalline material whose structure was solved by crystallographic analysis (CDC# 2104379): mp: 86.0-87.5 ºC: IR (ATR) cm^{-1} 3532, 2233, 1721; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (br. s, 1H), 4.90 (br. s, 1H), 4.52 (q, *J* = 3.0 Hz, 1H), 3.26 (dd, *J* = 3.2, 2.2 Hz, 1H), 2.99 – 2.83 (m, 2H), 2.55-2.39 (m, 2H), 2.30 – 2.15 (m, 2H), 2.11 – 1.96 (m, 3H), 1.94 – 1.83 (m, 1H), 1.78 – 1.69 (m, 1H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 205.4, 145.1, 116.6, 110.4, 66.7, 58.4, 44.5, 39.2, 30.3, 29.2, 25.4, 24.6; HRMS (+APCI) m/z [M + H+] calcd for $C_{12}H_{16}O_2N$ 206.1176, found 206.1178. For **16c**: recrystallization by evaporation from EtOAc/hexanes provided a crystalline material whose structure was solved by crystallographic analysis whose structure was solved by crystallographic analysis (CDC# 2104375): mp: 165.5-168.0 ºC: IR (ATR) 3545, 2360, 2339, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (br. s, 1H), 4.97 (br. s, 1H), 4.45 (dd, *J* = 11.2, 4.2 Hz, 1H), 2.98 (dd, *J* = 12.6, 4.3 Hz, 1H), 2.67 – 2.56 (m, 2H), 2.49 – 2.35 (m, 2H), 2.25 – 2.13 (m, 2H), 2.12 – 1.96 (m, 1H), 1.88 – 1.71 (m, 4H). $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 201.4, 142.7, 116.9, 114.1, 68.56, 63.5, 51.8, 37.2, 33.2, 28.7, 26.8, 25.0; HRMS (+APCI) m/z [M + H+] calcd for $C_{12}H_{16}O_2N$ 206.1176; found 206.1176.

(4R, 4aS*, 9aS*)-4-hydroxy-5-oxodecahydro-4aH-benzo[7]annulene-4a-carbonitrile (**17a**) and (4S*, 4aS*, 9aS*)-4-hydroxy-5-oxodecahydro-4aH-benzo[7]annulene-4a-carbonitrile (**17b**).* Following the general DMSO cyclization with iodide **10c** (125 mg, 0.29 mmol), *i*-Pr_2NEt (0.25 mL, 1.43 mmol) and microwave heating for 1.5 h at 100 ºC afforded a 3.1:1 ratio (as determined by ^1H NMR analysis of the crude reaction mixture) of an inseparable mixture of alcohols **17a** and **17b** that were purified by MPLC (4 g silica cartridge, hexanes: ethyl acetate, 95:5 to 5:95) to afford 35 mg (59%) of **17a** and 5 mg (8%) of **17b** as colorless oils: IR (ATR) cm^{-1} 3447, 2239, 1709; HRMS (+APCI) m/z [M + H+] calcd for $C_{12}H_{18}O_2N$ 208.1332, found 208.1332. For **17a** ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 - 4.21 (m, 1H), 3.15

– 3.04 (m, 1H), 2.76-2.58 (m, 1H), 2.20 (br. s, 1H), 2.12 – 1.28 (m, 12H), 2.23 – 1.06 (m, 1H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 205.2, 117.7, 71.3, 63.7, 43.3, 42.6, 35.5, 30.3, 30.1, 25.6, 22.9, 21.8. For **17b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, *J* = 2.7 Hz, 1H), 2.87 – 2.78 (m, 2H), 2.76 – 2.58 (m, 1H), 2.32 – 2.23 (m, 1H), 2.12 – 1.28 (m, 12H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 209.4, 118.1, 71.7, 59.3, 43.2, 35.9, 35.0, 31.0, 29.7, 27.8, 24.0, 18.9.

(1R, 4aS*, 9aS*)-9a-cyano-9-oxodecahydro-1H-benzo[7]annulen-1-yl 4-nitrobenzoate (**17a'**)* and *(4aS*, 5R*, 9aR*)-4a-cyano-4-oxodecahydro-1H-benzo[7]annulen-5-yl 4-nitrobenzoate (**17b'**).* Dimethylaminopyridine (102 mg, 0.83 mmol), *p*-nitrobenzoyl chloride (150 mg, 0.81 mmol), and *i*-Pr_2NEt (1.0 mL, 5.73 mmol) were added to a CH_2Cl_2 solution (5 mL) of a 1:4 mixture of alcohols **17a** and **17b** (75mg, 0.36 mmol). After 24 h the solution was concentrated and purified to afford after purification by flash chromatography (4 g silica cartridge, hexanes: (ethyl acetate: CH_2Cl_2, 95:5 to 50:50, 10 min) 84 mg (65 %,) of **17a'** and 28 mg (22%) of **17b'** as white crystalline solids. **For 17a'**: recrystallization by evaporation from a CH_2Cl_2-hexanes solution afforded crystalline **17a'** whose structure was determined by crystallographic analysis (CDC# 2104382): mp 185.0-187.0 ºC; IR (ATR) cm^{-1} 2239, 1777; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.25 (m, 2H), 8.25 – 8.10 (m, 2H), 5.57 (dd, *J* = 11.9, 4.4 Hz, 1H), 3.10 – 2.99 (m, 1H), 2.72 – 2.58 (m, 1H), 2.30 – 2.19 (m, 1H), 2.05 (m, 2H), 1.97 – 1.38 (m, 9H), 1.28 – 1.13 (m, 1H); (101 MHz, $CDCl_3$) δ 202.5, 162.9, 150.7, 134.8, 130.8, 123.6, 117.2, 74.1, 61.0, 43.8, 42.0, 35.3, 30.1, 27.3, 25.6, 22.6, 22.0; HRMS (+APCI) m/z [M + H+] calcd for $C_{19}H_{21}N_2O_5$ 357.1445; found 357.1450. **For 17b'**: recrystallization by evaporation from a CH_2Cl_2-hexanes solution afforded crystalline **17b'** whose structure was determined by crystallographic analysis (CDC# 2104381)**:** mp 142.0-145.0 ºC; IR (ATR) cm^{-1} 2237, 1732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.28 (m, 2H), 8.17 – 8.10 (m, 2H), 5.70 (t, *J* = 2.9 Hz, 1H), 2.70 – 2.55 (m, 2H), 2.53 – 2.42 (m, 1H), 2.21 – 2.10 (m, 1H), 2.10 - 1.94 (m, 3H), 1.93 – 1.51 (m, 8H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 205.3, 162.4, 150.8, 134.6, 130.5, 123.9, 116.8, 75.7, 59.1, 43.4, 37.0, 34.9, 30.9, 29.1, 26.8, 25.2, 19.8; HRMS (+APCI) m/z [M + H+] calcd for $C_{19}H_{21}N_2O_5$ 357.1445; found 357.1447.

(4R, 4aS*, 9aS*)-4-hydroxy-1-methylene-5-oxodecahydro-4aH-benzo[7]annulene-4a-carbonitrile* ***(18a)*** *and (4S*, 4aS*, 9aS*)-4-hydroxy-1-methylene-5-oxodecahydro-4aH-benzo[7]annulene-4a-carbonitrile* ***(18b)***. Following the general DMSO cyclization with iodide **10d** (65 mg, 0.15 mmol), *i*-Pr_2NEt (0.1 mL, 0.57 mmol) and microwave heating for 1.5 h at 100 ºC afforded a 2.0:1.0 ratio (determined by ^1H NMR analysis of the crude reaction mixture) of a mixture of alcohols **18a** and **18b** that were purified by MPLC (4 g silica cartridge, hexanes: ethyl acetate, 95:5 to 5:95) to afford 24 mg (76%) of **18a** and **18b** as an inseparable mixture of colorless oils: IR (ATR) cm^{-1} 3445, 2244, 1713; HRMS (+APCI) m/z [M + H+] calcd for $C_{13}H_{18}NO_2$ 220.1332, found 220.1332. **For (18a):** ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.96 (s, 1H), 4.42 (ddd, *J* = 12.2, 6.0, 4.1 Hz, 1H), 3.20 – 3.09 (m, 1H), 2.66 (dt, *J* = 13.7, 8.9 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.17 – 1.90 (m, 8H), 1.89 – 1.65 (m, 2H), 1.30 – 1.11 (m, 1H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 204.4, 144.0, 117.3, 112.1, 71.6, 64.8, 45.8, 41.5, 33.5, 32.0, 30.6, 25.1, 21.9. **For 18b:** ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.88 (s, 1H), 4.43 – 4.34 (m, 1H), 3.04 – 2.94 (m, 1H), 2.31 – 2.14 (m, 2H), 2.17 – 1.89 (m, 11H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 208.5, 146.3, 117.6, 110.5, 72.3, 62.4, 42.8, 40.6, 32.6, 30.1, 29.2, 28.0, 24.7.

(1S, 4aR*, 9aR*)-9a-cyano-4-methylene-9-oxodecahydro-1H-benzo[7]annulen-1-yl 4-nitrobenzoate* ***(18a')*** *and (1S*, 4aR*, 9aR*)-9a-cyano-4-methylene-9-oxodecahydro-1H-benzo[7]annulen-1-yl 4-nitrobenzoate* ***(18b')***. Dimethylaminopyridine (27 mg, 0.22 mmol), *p*-nitrobenzoyl chloride (47 mg, 0.25 mmol), and *i*-Pr_2NEt (0.25 mL, 1.43 mmol) were added to a CH_2Cl_2 solution (5 mL) of a 2:1 mixture of alcohols **18a** and **18b** (31mg, 0.14 mmol). After 24 h the solution was concentrated and purified to afford after purification by flash chromatography (4 g silica cartridge, hexanes: (ethyl acetate: CH_2Cl_2), linear gradient 95:5 to 50:50, 10 min) 27 mg (51 %,) of **18a'** and 13 mg (26%) of **18b'** as white, crystalline solids. **For 18a':** recrystallization by evaporation from a CH_2Cl_2-hexanes solution afforded crystalline **18a'** whose structure was determined by crystallographic analysis whose structure was determined by crystallographic analysis (CDC# 2104377)**:** mp 186.0-187.7 ºC; IR (ATR) cm^{-1} 2239, 1721; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.27 (m, 2H), 8.19 – 8.15 (m, 2H), 5.75 (dd, *J* = 11.9, 4.5 Hz, 1H), 5.14 (br.

s, 1H), 5.02 (br. s, 1H), 3.11 – 3.00 (m, 1H), 2.77 – 2.64 (m, 1H), 2.61 – 2.50 (m, 1H), 2.41 –2.14 (m, 4H), 2.11 –1.81 (m, 5H), 1.29 – 1.22 (m, 1H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 201.9, 163.0, 150.8, 143.1, 134.6, 130.9, 123.6, 116.7, 112.8, 73.9, 62.4, 46.3, 41.0, 33.0, 30.4, 29.0, 25.3, 22.3; HRMS (+APCI) m/z [M + H+] calcd for $C_{20}H_{21}N_2O_5$, 369.1445; found 369.1451. **For 18b'**: recrystallization by evaporation from a CH_2Cl_2-hexanes solution afforded crystalline **18b'** whose structure was determined by crystallographic analysis whose structure was determined by crystallographic analysis (CDC# 2125103) mp 142.0-144.5 ºC: IR (ATR) cm^{-1} 1737, 1520; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.32 (m, 2H), 8.20 – 8.16 (m, 2H), 5.71 (t, *J* = 2.8 Hz, 1H), 5.19 (s, 1H), 5.05 (s, 1H), 3.15 (d, *J* = 10.6 Hz, 1H), 2.74 – 2.57 (m, 2H), 2.45 – 1.98 (m, 7H), 1.83 – 1.55 (m, 3H); $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 204.6, 162.4, 150.9, 144.5, 134.4, 130.6, 123.9, 116.1, 112.0, 75.8, 61.7, 43.3, 42.0, 30.8, 29.6, 29.4, 29.0, 25.6; HRMS (+APCI) m/z [M + H+] calcd for $C_{20}H_{21}N_2O_5$, 369.1445; found 369.1447.

(3aR, 4R*, 7aR*)-4-Hydroxy-3-oxooctahydro-3aH-indene-3a-carbonitrile* ***(19)*** Following the general DMSO cyclization with iodide **10e** (52 mg, 0.13 mmol), *i*-Pr_2NEt (0.10 mL, 0.57 mmol) and microwave heating for 1.5 h at 100 ºC afforded after purification by flash chromatography (4 g silica cartridge, hexanes: ethyl acetate, 95:5 to 5:95) 13 mg (57 %,) of **19** as an off-white solid (mp 153.5 to 156.2 ºC): IR (ATR) cm^{-1} 3480, 2241, 1745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (dd, *J* = 10.2, 3.8 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.70 – 2.45 (m, 2H), 2.41 (br. s, 1H), 2.10 – 1.74 (m, 5H), 1.70 – 1.60 (m, 3H); δ $^{13}C\{^{1}H\}$ (101 MHz, $CDCl_3$) δ 208.5, 116.9, 66.5, 55.9, 42.0, 36.4, 30.2, 24.1, 23.4, 19.2; HRMS (+APCI) m/z [M + H+] calcd for $C_{10}H_{14}O_2N$ 180.1019, found 180.1021.

(3aS, 4R*, 7aS*)-3a-Cyano-3-oxooctahydro-1H-inden-4-yl 4-nitrobenzoate* ***(19')*** Dimethylaminopyridine (18 mg, 0.15 mmol), *p*-nitrobenzoyl chloride (33 mg, 0.18 mmol), and *i*-Pr_2NEt (0.10 mL, 0.57 mmol) were added to a rt, CH_2Cl_2 solution (2 mL) of **19** (14 mg, 0.08 mmol). After 24 h the solution was concentrated and purified by flash chromatography (4 g silica cartridge, hexanes: ethyl acetate, linear gradient 95:5 to 50:50, 10 min) to afford 20 mg (77 %,) of **19'** that was recrystallized from EtOAc/hexanes by evaporation to afford crystalline **19'** whose structure was determined by

crystallographic analysis (CDC# 2125104)**:** as a white crystalline solid, 117-120 ºC: IR (ATR) cm^{-1} 2243, 1745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.21 (m, 4H), 5.31 (dd, *J* = 10.3, 4.0 Hz, 1H), 2.94 – 2.82 (m, 1H), 2.72 (ddd, *J* = 20.1, 8.7, 3.6 Hz, 1H), 2.52 (dt, *J* = 20.1, 9.4 Hz, 1H), 2.18 – 1.66 (m, 8H). $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 205.3, 163.7, 150.9, 134.4, 131.1, 123.7, 116.5, 68.4, 54.2, 42.4, 35.4, 28.1, 23.8, 23.0, 19.1. (+APCI) m/z [M + H+] calcd for $C_{17}H_{17}O_5N_2$ 329.1132, found 329.1135.

(4R, 4aS*, 8aS*)-4-Hydroxy-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (**20**).* A DMSO solution (1 mL) of **10f** (24 mg, 0.054 mmol) and neat *i*-Pr_2NEt (0.05 mL, 0.27 mmol) was added to a DMSO solution (5 mL) heated to 100 °C in a microwave. After 2 h the temperature was increased to 150 °C for 30 min and then the flask was immediately cooled in an ice-water bath. Water was added, the mixture was extracted with EtOAc, and then the organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a yellow oil. Radial chromatography (2:3 EtOAc/hexanes) yielded 9.5 mg (85 %) of the *trans*-decalin **20** as a colorless oil: IR (film) 3524, 2233, 1724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (br t, *J* = 8 Hz, 1H), 3.10 (s, 1H), 2.97 (td, *J*= 13.8, 6.9 Hz, 2H), 2.45-2.51 (m, 1H), 2.18-2.25 (m, 1H), 1.23-2.01 (m, 7H), 1.18 (s, 3H), 0.95 (s, 3H); $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$) δ 205.3, 117.8, 70.4, 59.1, 53.6, 38.8, 34.4, 31.5, 26.3, 23.2, 20.4; HRMS (ESI) calcd for (M+Na) $C_{13}H_{19}NO_2$ 244.1308, found 244.1300.

(4R, 4aS*, 8aS*)-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-5-oxo-octahydro-naphthalene-4a-carbonitrile (**21**).* Neat pyridine (2.2 µL, 0.028 mmol) and TBS-triflate (3.8 µL, 0.017 mmol) were added sequentially to a rt, CH_2Cl_2 solution (1 mL) of **20** (2.5 mg, 0.011 mmol). After 12 h the reaction was poured into a saturated, aqueous, solution of sodium bicarbonate, the aqueous phase was extracted with CH_2Cl_2 and then the combined extracts were washed with brine and dried (Na_2SO_4). Concentration of the organic extract followed by radial chromatography (19:1 EtOAc / hexanes) gave 3.1 mg (90 %) of **21** as a white crystalline solid that was recrystallized from EtOAc/hexanes by evaporation to afford crystalline **21** (mp. 273-275 °C) whose structure was

determined by crystallographic analysis (CDC# 2032226): IR (film) 2232, 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (dd, *J* = 11, 5 Hz, 1H), 3.07 (ddd, *J* = 19, 13, 7 Hz, 1H), 2.36-2.39 (m, 1H), 2.17-2.24 (m, 1H), 1.18-2.05 (m, 8H), 1.15 (s, 3H), 0.91 (s, 3H), 0.85 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 202.5, 118.8, 69.1, 60.3, 55.1, 39.0, 38.6, 34.0, 31.4, 28.7, 27.4, 25.7, 23.7, 20.2, 17.93, -4.22, -4.94; HRMS (ESI) calcd for M+Na $C_{19}H_{33}NO_2SiNa$ 358.2173 found 358.2155.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/

^{1}H and ^{13}C spectra and CIF files for **14b**, **14c**, **15**, **16a**, **16b**, **16c**, **17a'**, **17b'**, **18a'**, **19'** and **21** (PDF).

FAIR data, including the primary NMR FID files, for compounds **8a**-**8e**, **10a**-**10e**, **13a**, **14a**-**14c**, **15**, **16a**-**16c**, **17a**, **17b**, **17a'**, **17b'**, **18a**, **18a'**, **18b**, **18b'**, **19**, **19'** (ZIP)

Notes

The authors declare no competing financial interest.

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