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β-Siloxy unsaturated nitriles: stereodivergent cyclizations to *cis*- and *trans*-decalins

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Abstract—Nitrile and enolate anions exhibit divergent intramolecular cyclization stereoselectivities. Enolates cyclize to *cis*-decalones, whereas nitrile anions are predisposed to pyramidalize, cyclizing instead through a less-congested conformation to *trans*-decalins. Conjugation of nitrile anions with adjacent sp^2 centers prevents pyramidalization, and redirects cyclization through a planar-delocalized anion to *cis*-decalins. Collectively these cyclizations allow conversion of a single β-siloxynitrile to either *cis*- or *trans*-decalins that are ideally suited for elaboration into terpenoid natural products.

1. Introduction

The decalin ring system is one of the most prevalent structural motifs contained within terpenoid natural products.[1] Decalin-containing terpenoids are broadly partitioned into two stereochemical groups reflecting different stereochemical orientations of the two sp^3 bridgehead carbons; *trans*-decalin-containing terpenoids and the less common, but numerically significant, *cis*-decalin terpenoids.[2] Highlighting the two decalin series are the diastereomeric clerodane terpenoids **1** and **2**[3] (Fig. 1) that differ at a single stereocenter and yet co-occur in the same plant!

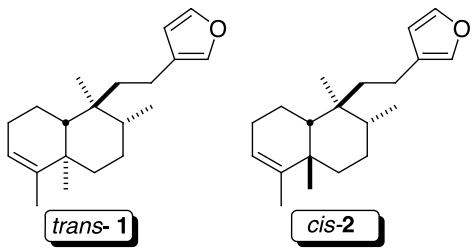


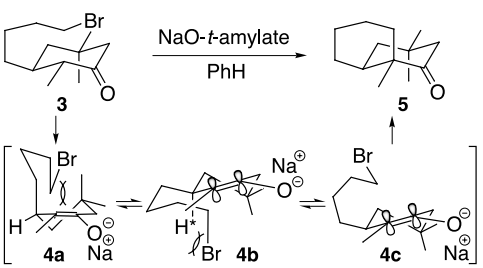
Figure 1. Diastereomeric clerodane diterpenoids.

The widespread occurrence of biologically important[4] *cis*- and *trans*-decalins has stimulated numerous syntheses of this ubiquitous ring system.[5] Conceptually, the most attractive route to diastereomeric *cis*- and *trans*-decalins is through a stereodivergent cyclization of a single intermediate to either a *cis*- or *trans*-decalin. Historically, equilibration of *cis*-decalones often furnished both stereochemical series, although the equilibration is strongly dependent on the substitution pattern[6] and necessarily requires an epimerizable ring junction. Diterpenoids **1** and **2** exemplify the challenge in devising efficient, stereodivergent syntheses of *cis*- and *trans*-decalins varying only in the non-epimerizable ring junction stereochemistry.

The prevalence of *cis*-decalone intermediates stems from the stereoselectivity of intramolecular ketone enolate alkylations. Pioneering enolate cyclizations[7] with conformationally-biased decalones demonstrates that the stereochemistry is kinetically controlled (Scheme 1).

Cyclization of the enolate **4** clearly identifies the reactive conformation as **4c** since the *gem*-dimethyl substituent causes a severe diaxial interaction that effectively precludes cyclization from conformer **4a**. Exclusive formation of the *cis*-decalone **5** therefore occurs from conformation **4c** since cyclization from **4b** would evolve to a *trans*-decalin.

Originally[2] the preference for enolate cyclizations through conformation **4c**, rather than **4b**, was presumed to stem from



Scheme 1. *cis*-Selective enolate cyclizations.

Keywords: decalin; stereoselectivity; terpenoids; nitrile anions.

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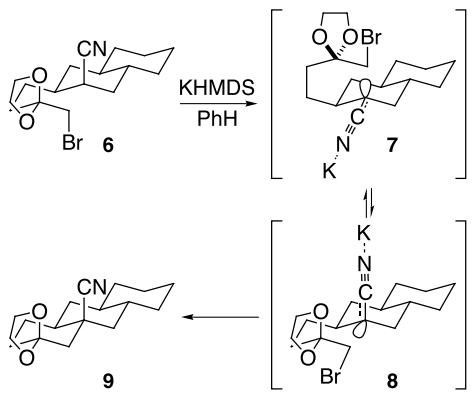
a destabilizing steric compression between the large bromine atom and the adjacent axial proton (H*) in conformer **4b**. A comparative stereoelectronic analysis of conformers **4b** and **4c** reveals a more subtle reason for the stereoselectivity—the orbital alignment between the nucleophilic and electrophilic centers. Conformations **4b** and **4c** differ primarily in the orientation of the π-electrons, with the nucleophilic enolate orbitals of **4b** being tilted away from the electrophilic carbon–bromine bond, whereas the π-orbitals of **4c** are ideally aligned for an S_N2 displacement. Formation of the *cis*-fused decalin **5** is therefore stereoelectronically controlled by the orientation of the π-orbitals in the endocyclic enolate.

Contrasting with the *cis*-selective enolate cyclizations are a seminal series of nitrile anion cyclizations to *trans*-decalins.[8] The reversed stereoselectivity stems from the propensity of nitrile anions to pyramidalize,[9] fulfilling an inherent stereoelectronic requirement for a nucleophilic orbital oriented directly towards the electrophilic carbon (Scheme 2). Cyclization therefore occurs through the least sterically congested conformation[10] **8** resulting in the predominant formation of the *trans*-decalin **9**.



Scheme 2. *trans*-Selective nitrile anion cyclizations.

2. Results and discussion

Comparative conformational analyses of the half-chair enolate **4b** and the chair nitrile anion **8** corroborate the stereoelectronic control in the stereodivergent cyclizations (Fig. 2). The pseudo-equatorial orientation of the enolate

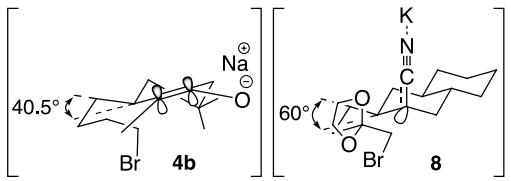
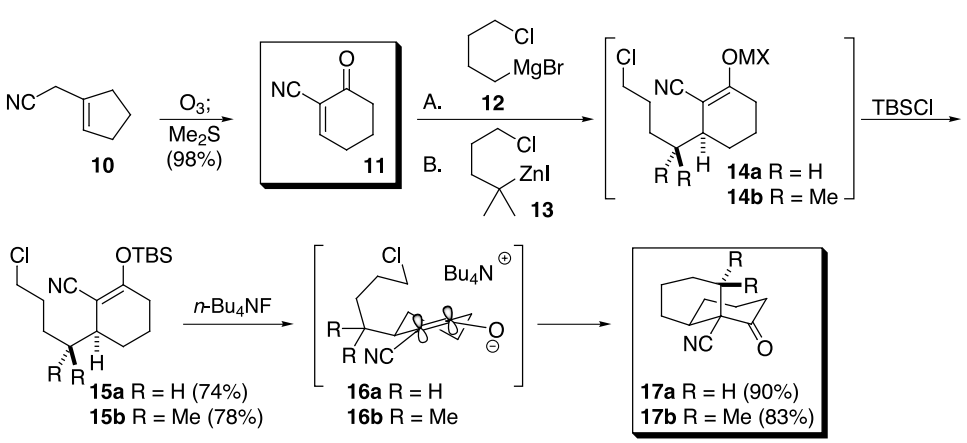


Figure 2. Stereoelectronically controlled cyclizations.

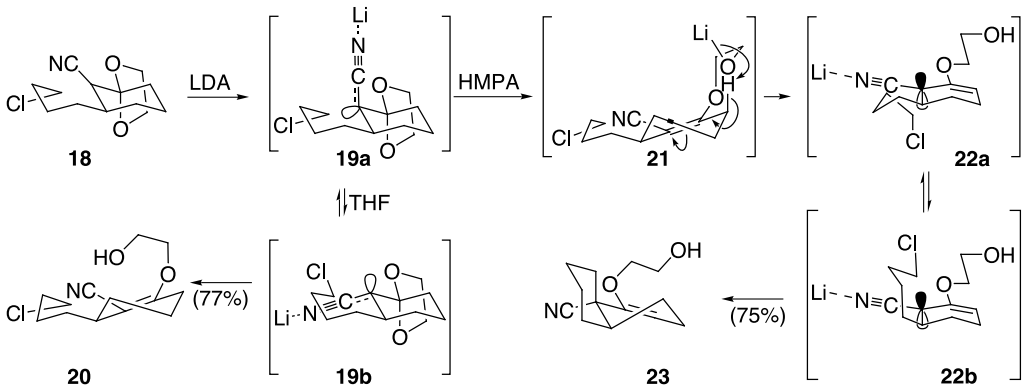
side chain in **4b** positions the electrophilic tether closer to the 'equator' of the half-chair, allowing the bromomethylene carbon to more easily approach the nucleophilic carbon than in the corresponding chair conformation of the nitrile anion **8** (40° versus 60°).[11] Despite the apparent geometric proclivity for enolate cyclization to a *trans*-decalin, **4** cyclizes exclusively to the *cis*-decalin **5** whereas the nitrile anion **8** selectively cyclizes to the *trans*-decalin **9**—consistent with orbital alignment being the determining factor rather than folding of the electrophilic side chain. The complementary orbital alignments account for the selectivity differences of endocyclic enolate and exocyclic nitrile anion cyclizations and establish the fundamental stereoelectronic requirements for a general strategy to *cis*- and *trans*-decalins.

β-Siloxy unsaturated nitriles are uniquely poised for stereodivergent cyclizations to *cis*- and *trans*-decalins through selective unmasking of the latent nitrile and enolate anion moieties.[12] The β-siloxy unsaturated nitriles **15** are ideal prototypes for developing stereodivergent cyclizations to *cis*- and *trans*-decalins since **15** are rapidly synthesized in two synthetic operations (Scheme 3). Ozonolysis of **10**, and addition of Me_2S, triggers a domino ozonolysis–aldol cyclization[13] providing ketonitrile **11** for a facile conjugate addition with 4-chlorobutylmagnesium bromide[14] (**12**) or the *gem*-dimethyl organozinc reagent **13**.[15] Intercepting the intermediate enolate **14** with TBSCl effectively prevents a premature enolate cyclization[16] and provides the unsaturated β-siloxy-nitriles **15**[17] for stereoselective cyclizations.

Unmasking the enolates **16** with *n*-Bu_4NF results in a smooth cyclization to the *cis*-decalins **17** (Scheme 3). Facile cyclization of the ammonium enolate contrasts with minimal cyclization[16] of the magnesium or zinc enolates **14**, presumably reflecting the greater enolate nucleophilicity



Scheme 3.



Scheme 4. Influence of β-alkoxy and sp^2 centers on nitrile anion cyclizations.

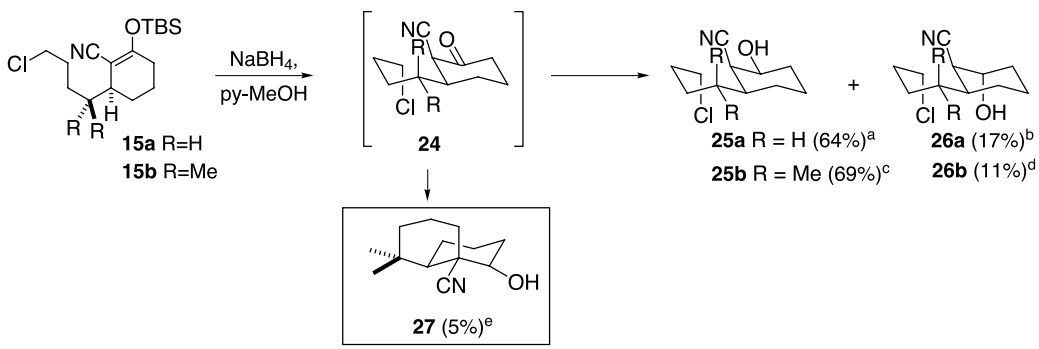
that results from minimal complexation with the tetra-*n*-butylammonium cation. NMR analysis of the crude product clearly shows only one diastereomer with the *cis*-decalin stereochemistry being unequivocally determined by X-ray diffraction.[18]

Cyclizing **15a** and **15b** to *trans*-decalins requires conversion to a pyramidalized nitrile anion.[10] Forming a pyramidalized anion from the β-siloxy nitrile requires temporary masking of the adjacent sp^2 centers since related benzylic nitrile anions favor a planar geometry, implying that delocalization overcomes the propensity of nitrile anions to pyramidalize.[9] Attempted masking of the sp^2 hybridized enol silyl ether **15a** by methanol-induced ketalization triggers sequential enol ether hydrolysis, nitrile methanolysis and retro-Claisen fragmentation,[19] whereas ethylene glycol effectively installs the cyclic acetal to afford **18** (Scheme 4).

Deprotonating **18** was anticipated to trigger cyclization via the pyramidal nitrile anion **19** (Scheme 4). LDA indeed deprotonates **18** but triggers alkoxide ejection to form **20**,[20] presumably reflecting a facile anion inversion followed by a rapid anti-periplanar elimination.[21] Repeating the cyclization in neat HMPA was envisaged to render the alkoxide elimination reversible,[22] providing the requisite pyramidal nitrile anion **19** by equilibration. The dramatic effect of HMPA was immediately apparent in efficiently forming a single decalin **23** (Scheme 4), although the successful cyclization was tempered in finding the decalin stereochemistry to be *cis*.[23] Presumably, deprotonation initiates an elimination to the alkoxide **21** followed by inter- or intramolecular deprotonation[24] to generate the conjugated, planar anion **22** where cyclization to the *trans*-decalin is prevented through **22a**, redirecting the stereoelectronically controlled cyclization through **22b** to the *cis*-decalin **23**. Although undesired, the cyclization of **22** establishes that two adjacent sp^2 centers are sufficient to abrogate the propensity of the nitrile anion to pyramidalize.[9]

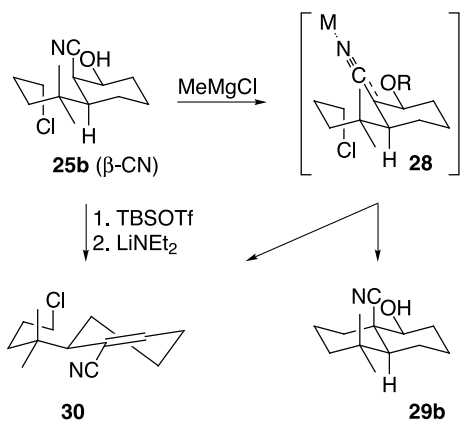
A potential solution to overcome alkoxide elimination is to install an equatorial oxygen substituent since a diaxial elimination is retarded by virtue of proceeding through a high-energy twist conformation. Selective formation of the requisite equatorial alcohols **25** occurs readily upon borohydride reduction in a pyridine–methanol solvent mixture,[25] (Scheme 5). Performing the reduction at −20°C, rather than at ambient temperature, allows identification of the keto-nitrile **24** as a transient intermediate, presumably formed through methoxide-induced[26] silyl ether cleavage, that is subsequently reduced with excess $NaBH_4$. Similarly, borohydride reduction of **15b** affords primarily the equatorial β-hydroxynitriles **25b** accompanied by the axial β-hydroxy nitrile **26b** (11%) and a small amount of the *cis*-decalins **27** (Scheme 5). Formation of *cis*-decalins **27** requires rapid cyclization of the enolate intermediate prior to protonation, that is likely facilitated by the close proximity[27] of the electrophilic side-chain induced by the *gem*-dimethyl group.[28] The *cis*-stereochemistry was determined by oxidation of **27** to *cis*-decalone **17b**.

Access to the alcohols **25a** and **25b** affords potential cyclization precursors with equatorial oxygenation.[29] Silylation of **25b** and exposure to $LiNEt_2$ generates alkenenitrile **30** despite requiring a twist conformation for



Scheme 5. (a) α:β, 1:2; (b) α:β, 1:1; (c) α:β, 1:3; (d) α:β, 0:1; (e) α:β, 1:1.

an E_2 alkoxide elimination (Scheme 6). An alternative strategy to circumvent alkoxide ejection is the double deprotonation of a β-hydroxy nitrile that, although unknown,[12] is precedented by analogous enolate alkylations[30] of aldol dianions. Initial cyclizations of **25b** (β-CN) explored MeMgCl as the base since magnesium alkoxides are highly covalent[31] thereby facilitating formal dianion formation. Surprisingly, the dimagnesiated intermediate is completely unreactive at room temperature, requiring refluxing THF to coax a modest 47% yield of the *trans*-decalin **29b** in addition to 17% of the alkenenitrile **30** (Scheme 7). The remarkable formation of **30** through the elimination of MgO stimulated the development of a general alkenenitrile synthesis by MgO ejection,[21] and provided insight for cleanly cyclizing nitrile dianions by changing the metal cation.

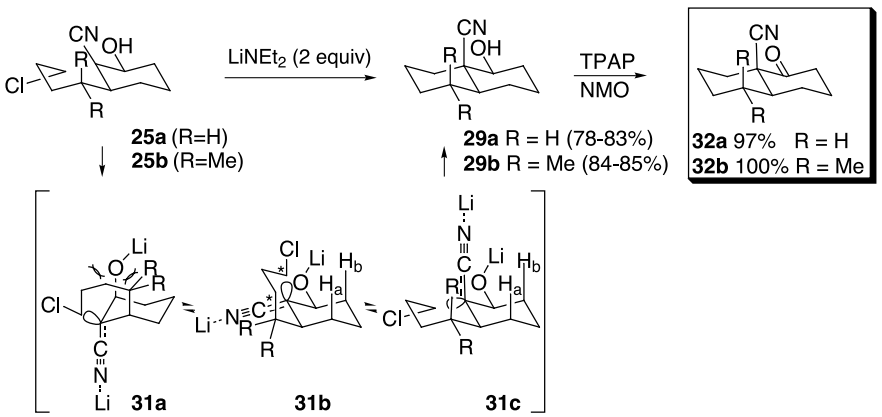


Scheme 6.

two syn-axial interactions between the axial nitrile and H_a and H_b in **31c**. The latter conformation, **31c**, avoids one *syn*-axial interaction, with a more profound stabilization (~2 kcal mol^{-1})[32] resulting from the axial orientation of the small nitrile rather than the larger ring methylene groups (the A-value for a nitrile is 0.1 kcal mol^{-1} compared to 0.85 kcal mol^{-1} for a methylene group).[33] Interestingly, the β-hydroxynitriles **25b** cyclize at −78°C, whereas the *des*-methyl analogs **25a** require warming to room temperature, suggesting a beneficial orientation of the chloroalkyl electrophile induced by buttressing of the *gem*-dimethyl substituents,[27] analogous to the effect observed on reducing **15b** with borohydride (Scheme 5). TPAP oxidation[34] of the resulting hydroxy decalins **29a** and **29b** afford single, crystalline[13] *trans*-decalones **32a** and **32b**.

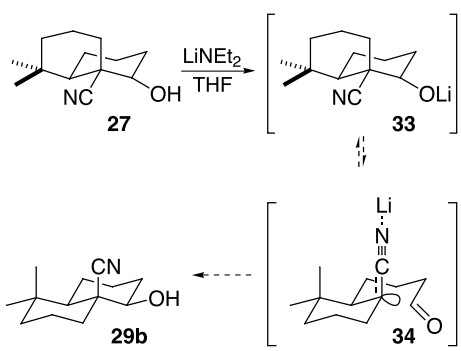
Conceivably the exquisite stereoselectivity in the cyclizations of **25** could stem from a facile 'retro-aldol' equilibration from the *cis*-decalin **27** (Scheme 8). Mechanistically, formation of the alkoxide **33**, retro-aldol fragmentation to **34**, and recyclization through conformer **34**, conceivably equilibrates **27** to the equatorially-oriented *trans*-nitrile **29b** (Scheme 8). Evidence against the equilibration was garnered by individually subjecting the *cis*-decalins **27**, α and β OH, to the same cyclization conditions with complete recovery of the *cis*-nitriles **27**.

Nitrile and enolate anions cyclize with divergent stereoselectivities. The inherent orbital alignment of sp^2-hybridized enolates favor stereoelectronically-controlled cyclizations to *cis*-decalones, whereas nitrile anions are predisposed to pyramidalize, and cyclize with complementary stereoselectivity to *trans*-decalins. Adjacent sp^2



Scheme 7. *trans*-Selective nitrile anion cyclizations.

Lithium diethylamide-induced cyclization of the β-hydroxy nitriles **25a** and **25b** proceed with exquisite stereocontrol—with no detectable elimination (Scheme 7). Both sets of nitrile epimers (R=H and Me) cyclize in virtually identical yield, and within the same time period, indicating alkylation through a single dianion **31**. The stereoselectivity reflects an exclusive preference for cyclization through conformation **31c**. Severe 1,3-diaxial interactions in **31a** effectively prevent cyclization from this conformation whereas the primary difference between **31b** and **31c** are the three destabilizing *syn*-axial interactions between the axial methylenes (*) and H_a and H_b in **31b**, compared with



Scheme 8.

centers diminish the nitrile anion pyramidalization, redirecting cyclization through a planar-delocalized anion to *cis*-decalins, analogous to enolate cyclizations. Delineating the fundamental stereoelectronic features of nitrile anion and enolate cyclizations permits controlled, stereodivergent cyclizations of β-siloxy unsaturated nitriles to either *cis*- or *trans*-decalones through selective unmasking of the respective enolate and nitrile anion intermediates. Collectively these cyclization strategies rapidly assemble a variety of decalin precursors ideally suited for elaboration into terpenoid natural products.

3. Experimental[35]

3.1. Data for compounds

3.1.1. 2-(*tert*-Butyldimethylsilyloxy)-6-(4-chloro-butyl)-1-cyclohexenyl-1-carbonitrile (15a). A THF solution (20 mL) of 4-chlorobutylmagnesium bromide[14] (**12**) was prepared by the addition of 30 μL of 1-bromo-4-chlorobutane to magnesium metal (237 mg, 9.76 mmol) at room temperature. The solution was sonicated until cloudy, cooled to 0°C, and then neat 1-bromo-4-chlorobutane (1.0 mL, 8.94 mmol total) was slowly added. After 2 h the solution was briefly warmed to room temperature and was then added to a −78°C, THF solution (40 mL) of **11**[13] (1.00 g, 8.13 mmol). After 45 min the solution was allowed to warm to room temperature, solid TBDMSCl (1.84 g, 12.20 mmol) was added, and stirring was continued for a further 15 h. The resultant mixture was quenched by the addition of saturated, aqueous NH_4Cl, extracted with EtOAc, dried ($MgSO_4$), and concentrated. The crude product was purified by radial chromatography (4 mm plate, 1:19 EtOAc–hexanes) to afford 1.97 g (74%) of **15a** as an oil: IR (film) 2208, 1626 cm^{-1}; ^1H NMR δ: 0.21 (s, 3H), 0.22 (s, 3H), 0.96 (s, 9H), 1.26–1.81 (m, 10H), 2.10–2.31 (m, 3H), 3.53 (br t, J=7 Hz, 2H); ^{13}C NMR δ: −3.8, 18, 19.9, 23.8, 25.4, 26.5, 30.9, 32.5, 33.6, 35.1, 44.8, 95.5, 118.3, 165.6; MS *m/e* 327 (M); HRMS (ESI) calcd for (M+Na^+) $C_{17}H_{30}NOSiNa$ 350.1677, found 350.1661.

3.1.2. 6-{4-[2-Cyano-3-(1,1,2,2-tetramethyl-2-silapropoxy)cyclohex-2-enyl]butyl}-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohex-1-enecarbonitrile (i). An experiment performed as above without slow formation of **12** afforded 66% of **15a** and 14% of **i** as a crystalline, X-ray diffracting,[18] solid: IR (film) 2206, 1622 cm^{-1}; ^1H NMR δ: 0.22 (s, 6H), 0.23 (s, 6H), 0.98 (s, 18H), 1.26–1.78 (m, 16H), 2.10–2.14 (m, 4H), 2.29 (br s, 2H); ^{13}C NMR δ: −3.7, 18.1, 19.9 25.5, 26.6, 26.7, 31.0, 34.5, 35.2, 95.9, 118.5, 165.4.

3.1.3. 5-Chloro-2-iodo-2-methylpentane (iv). An ethereal solution of MeLi (41.7 mmol) was added to a −78°C, THF solution (40 mL) of 5-chloropentanone (2.28 g, 18.9 mmol) and, after 10 min, saturated aqueous NH_4Cl was added. The crude mixture was extracted with ethyl acetate to afford 2.08 g of 5-chloro-2-methyl-pentan-2-ol as a clear, analytically pure, viscous liquid (81%): IR (film) 3389 cm^{-1}; ^1H NMR δ 1.23 (s, 6H), 1.56–1.62 (m, 2H), 1.82–1.92 (m, 2H), 2.17 (br s, 1H), 3.56 (t, J=6.6 Hz, 2H); ^{13}C NMR δ 27.6, 29.1, 40.8, 45.5, 70.4; MS *m/e* 119 (M−OH). Neat 5-chloro-2-methyl-pentan-2-ol (2.08 g, 15.2 mmol) and $MeSiCl_3$ (1.37 g, 9.2 mmol) were sequentially added to a room temperature, acetonitrile solution (23 mL) of NaI (6.88 g, 45.9 mmol). After 15 min water was added and the crude product was extracted with ethyl acetate. The extracts were successively washed with saturated aqueous sodium thiosulfate, water, and brine. The crude material was purified by vacuum distillation (4 mm Hg, 60–70°C) to afford 2.79 g (74%) of **iv** as a caramel colored liquid: IR (film) 1102 cm^{-1}; ^1H NMR δ1.72–1.78 (m, 2H), 1.94 (s, 6H), 1.98–2.08 (m, 2H), 3.60 (t, J=6.3 Hz, 2H); ^{13}C NMR δ: 31.9, 38.1, 44.5, 47.6, 50.1; MS *m/e* 246 (M+H).

3.1.4. 2-(*tert*-Butyldimethylsiloxy)-6-((2-methyl-5-chloro)-2-pentyl)-1-cyclohexenyl-1-carbonitrile (15b). A THF solution (40 mL) of $ZnCl_2$ (3.32 g, 24.39 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, 48.78 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), **iv** (4.0 g, 16.26 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 cold (−78°C), THF solution (100 mL) of **11** (2.0 g, 16.26 mmol) over 30 min. After 4 h solid TBDMSCl (3.68 g, 24.39 mmol) was added and the solution was allowed to warm to room temperature over a 12 h period. Saturated, aqueous NH_4Cl was then added and the 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 **15b** as a clear, viscous liquid: IR (film) 2203, 1614 cm^{-1}; ^1H NMR δ 0.23 (s, 3H), 0.25 (s, 3H), 0.99 (s, 12H), 1.03 (s, 3H), 1.41–1.91 (m, 8H), 2.10–2.15 (m, 2H), 2.33–2.38 (m, 1H), 3.51 (ddd, J=17, 10.5, 6.9 Hz, 1H), 3.56 (ddd, J=17, 10.5, 6.4 Hz, 1H); ^{13}C NMR: δ −3.7, 18.2, 21.2, 24.0, 25.6, 25.8, 26.0, 27.6, 31.2, 37.0, 38.0, 43.1, 45.7, 92.8, 120.3, 168.8; MS *m/e* 355 (M+H).

3.1.5. *cis*-10-Cyano-decahydro-1-naphthalenone (17a). A THF solution (6 mL) of **15a** (90 mg, 0.275 mmol) and *n*-Bu_4NF (1.0 M, 0.33 mmol) was refluxed for 3 h and then allowed to cool to room temperature, overnight. The resultant mixture was concentrated and the crude product was purified by radial chromatography (2 mm plate, 1:9 EtOAc–hexanes) to afford 44 mg (90%) of **17a** as an oil. Careful dissolution in EtOAc–hexanes afforded white crystals (mp 88–89°C) suitable for X-ray crystallography:[18] IR (film) 2237, 1714 cm^{-1}; ^1H NMR δ: 1.40–1.48 (m, 2H), 1.60–2.06 (m, 9H), 2.25–2.50 (m, 3H), 2.60–2.69 (m, 1H); ^{13}C NMR δ: 21.9, 22.6, 23.3, 26.7, 27.4, 29.5, 38.1, 42.7, 51.7, 120.4, 203.2; MS *m/e* 177 (M).

3.1.6. 8αβ-Cyano-5α,5β-dimethyl-3,4,4αβ,5,6,7,8,8α-octahydro-1(2*H*)-naphthalenone (17b). A THF solution (2 mL) of *n*-Bu_4NF (0.583 mmol) was added to a room temperature, THF solution (3 mL) of **15b** (0.10 g,

0.29 mmol). After 2 h water was added and the reaction mixture was extracted with ethyl acetate. The crude material was concentrated and was then purified by radial chromatography (1 mm plate, 3:7 EtOAc–hexanes) to afford 0.50 g (83%) of the *cis*-decalin **17b** as white, X-ray diffracting,[18] crystals (mp 57–58°C): IR (KBr) 2239, 1710 cm^{-1}; ^1H NMR δ 0.91 (s, 3H), 1.26 (s, 3H), 1.29–1.33 (m, 1H), 1.45 (ddd, J=14, 11, 3.7 Hz, 1H), 1.60–1.83 (m, 5H), 1.98–2.09 (m, 4H), 2.42–2.59 (m, 2H); ^{13}C NMR δ 19.1, 22.6, 24.0, 29.3, 29.5, 29.8, 33.6, 35.6, 37.0, 50.2, 51.9, 121.7, 204.1; HRMS (ESI) calcd for (M+Na^+) $C_{13}H_{19}NONa$ 228.1359, found 228.1364.

3.1.7. Dimethyl 3-(chlorobutyl)-heptanedioate (iii). A methanolic solution (20 mL) of **15a** (224 mg, 1.05 mmol) and *p*-TsOH (100 mg, 0.53 mmol) was heated to reflux for 5 h and then allowed to cool to room temperature. The crude mixture was filtered through a short silica column (10×10 mm), concentrated, and purified by radial chromatography (1 mm plate, 1:9–1:4 EtOAc–hexanes) to afford 170 mg (58%) of **iii** as an oil: IR (film): 1738 cm^{-1}; ^1H NMR δ: 1.25–1.81 (m, 11H), 2.28–2.40 (m, 2H), 2.31 (br t, J=7 Hz, 2H), 3.51 (t, J=6.6 Hz, 2H), 3.66 (s, 3H), 3.68 (s, 3H); ^{13}C NMR δ: 22.7, 24.4, 24.7, 31.5, 31.7, 32.4, 33.8, 44.6, 45.1, 51.5 (coincident methyl signals), 173.6, 176.2; HRMS (ESI) calcd for (M+Na^+) $C_{13}H_{23}ClO_4Na$ 301.1177, found 301.1183.

3.1.8. *trans*- and *cis*-2-Cyano-3-(4-chloro-butyl)-cyclohexanone ethylene ketal (18). A benzene solution (20 mL) of **15a** (224.0 mg, 0.68 mmol), ethylene glycol (44 μL, 0.79 mmol) and a trace of *p*-toluenesulfonic acid (5 mg) was heated to reflux for 4 h. The resultant mixture was concentrated and the crude product was then purified by radial chromatography (2 mm plate, 1:1 hexanes–CH_2Cl_2) to afford 128 mg (72%) of **18** as a 5:1 ratio of *trans* and *cis* isomers (ratio determined by ^1H NMR). Repeated chromatography gave pure samples of each isomer with the *trans*isomer being obtained as an oil: IR (film) 2243 cm^{-1}; ^1H NMR δ: 0.85 (br qd, J=13, 3 Hz, 1H), 1.22–1.93 (m, 12H), 2.47 (d, J=11.7 Hz, 1H), 3.55 (t, J=6.5 Hz, 2H), 3.93–4.07 (m, 2H), 4.18–4.28 (m, 2H); ^{13}C NMR δ: 22.1, 23.5, 29.6, 32.4, 33.7, 34.9, 38.5, 44.8, 45.8, 65.6, 65.9, 107.9, 119.3; MS *m/e* 258 (M+H). The *cis* isomer **17** was obtained as an oil: IR (film) 2239 cm^{-1}; ^1H NMR δ: 1.25–1.93 (m, 13H), 2.78 (br s, 1H), 3.55 (t, J=6.5 Hz, 2H), 3.93–4.06 (m, 4H); ^{13}C NMR δ: 22.1, 24.0, 27.5, 32.1, 32.4, 33.2, 37.1, 42.6, 44.8, 64.8, 65.0, 107.6, 118.1; MS *m/e* 258 (M+H).

3.1.9. 2-(2-Hydroxyethoxy)-6-(4-chlorobutyl)-1-cyclohexene-1-carbonitrile (20). A hexane solution (0.25 mL) of BuLi (1.06 M, 0.27 mmol) was added to a THF solution (3 mL) of *i*-Pr_2NH (32 μL, 0.23 mmol) followed by cooling to −78°C. After 10 min, a THF solution (1 mL) of **18**, as a 5:1 mixture of isomers, (26 mg, 0.10 mmol) was added. The solution was allowed to warm to room temperature, stirred for 5 h, and then aqueous HCl (10%) was added until a pH of 7. The reaction mixture was extracted with EtOAc, the combined extracts were dried ($MgSO_4$), concentrated, and the crude product purified by radial chromatography (1 mm plate, 3:7 EtOAc–hexanes) to afford 20 mg (77%) of **20** as an oil: IR (film) 3434, 2206, 1626 cm^{-1}; ^1H NMR δ: 1.30–1.88 (m, 11H), 2.26–2.30 (m, 3H), 3.56 (t, J=6 Hz, 2H), 3.85 (br t, J=4 Hz, 2H), 4.08 (t, J=4 Hz, 2H); ^{13}C NMR δ: 19.7, 23.9, 26.3, 26.5, 32.5, 33.6, 35.0, 44.9, 61.4, 69.7, 92.6, 123.2, 168.0; MS *m/e* 258 (M+H).

3.1.10. *cis*-1-(2-Hydroxyethoxy)-10-cyano-3,4,5,6,7,8-octahydronaphthalene (23). A hexane solution (0.19 mL) of *n*-BuLi (1.06 M, 0.20 mmol) was added to a −40°C, HMPA solution (6 mL) of *i*-Pr_2NH (28 μL, 0.20 mmol). After 30 min a THF solution (1 mL) of **18**, as a 5:1 ratio of epimers, (20 mg, 0.1 mmol) was added. After 1.5 h at −40°C, the solution was allowed to warm to room temperature and stirred for a further 3.5 h. Aqueous HCl (10%) was added until a pH of 7, the reaction mixture was extracted with EtOAc, and then the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by radial chromatography (2 mm plate, 1:4–3:7 EtOAc–hexanes) to afford 15 mg (75%) of **23** as an oil: IR (film) 3439, 2234, 1664 cm^{-1}; ^1H NMR δ: 1.48–1.98 (m, 11H), 2.09–2.18 (m, 3H), 3.73–3.88 (m, 4H), 4.76 (t, J=4.0 Hz, 1H); MS *m/e* 222 (M+H). Upon standing **22** (20 mg, 0.1 mmol) in $CDCl_3$ at room temperature for 2 days *cis*-9-cyano-1-naphthalenone ethyl ketal was obtained 20 mg (100%) as an oil: IR (film) 2866, 2236 cm^{-1}; ^1H NMR δ: 1.37–1.94 (m, 14H), 2.21–2.23 (br s, 1H), 3.95–4.03 (m, 2H), 4.17–4.26 (m, 2H); ^{13}C NMR δ: 19.7, 21.9, 23.0, 24.3, 25.5, 28.3, 30.2, 37.2, 49.4, 65.5, 65.6, 109.8, 122.6; MS *m/e* 221 (M). Acid hydrolysis (10% aqueous HCl in THF, 1:1) afforded **17a** spectrally identical to material isolated previously.

3.1.11. 6-(4-Chlorobutyl)-2-hydroxycyclohexanecarbonitrile (25a,26a). Incremental portions of solid $NaBH_4$ (195 mg 5.16 mmol) were added over 25 min to a stirred, room temperature, solution (16 mL, 3:1 pyridine–methanol) of the β-siloxy nitrile **15a** (1.53 g 4.30 mmol). After 10 h saturated, aqueous NH_4Cl was added and the aqueous phase extracted with EtOAc (3×50 mL). The organic extracts were combined, washed succesively with 10% aqueous HCl, and brine, dried ($MgSO_4$), and concentrated. The crude mixture of alcohols were separated by radial chromatography (4 mm plate, 3:7 EtOAc–hexanes) to afford 431 mg (43%) of **25a** (β-CN), 210 mg (21%) of **25a** (α-CN), 90 mg (9%) of **26a** (β-CN) and 80 mg (8%) of **26a** (α-CN) as clear oils. For **25a** (α-CN): IR (film) 3426, 2240 cm^{-1}; ^1H NMR δ 0.77–0.92 (m, 1H), 1.15–1.68 (m, 6H), 1.71–1.89 (m, 5H), 2.05–2.18 (m, 2H), 2.48 (d, J=4.4 Hz, 1H), 3.55 (t, J=6.4 Hz, 2H), 3.71 (ddd, J=14.6, 10, 4 Hz, 1H); ^{13}C NMR δ 23.0, 23.6, 29.7, 32.4, 33.7, 33.9, 39.0, 44.8, 44.9, 71.3, 120.7; MS *m/e* 216 (M+H). For **25a** (β-CN): IR (film) 3426, 2240 cm^{-1}; ^1H NMR δ 1.18–1.37 (m, 2H), 1.49–1.68 (m, 7H), 1.73–1.88 (m, 3H), 1.94–2.00 (m, 2H), 3.16 (br s, 1H), 3.55 (t, J=6.5 Hz, 2H), 3.66 (dt, J=11.5, 4.4 Hz, 1H); ^{13}C NMR δ 23.3, 24.0, 27.7, 31.6, 32.3, 33.4, 38.0, 42.2, 44.7, 70.0, 118.1; MS *m/e* 216 (M+H). For **26a** (α-CN): IR (film) 3452, 2242 cm^{-1}; ^1H NMR δ 0.85–0.98 (m, 2H), 1.25–2.04 (m, 12H), 2.86 (br t, J=4.1 Hz, 1H), 3.55 (t, J=6.6 Hz, 2H), 4.23 (br s, 1H); ^{13}C NMR δ 19.0, 24.0, 28.0, 30.0, 32.4, 32.6, 32.8, 39.6, 44.8, 67.1, 119.0; MS *m/e* 216 (M+H). For **26a** (β-CN): IR (film) 3452, 2242 cm^{-1}; ^1H NMR δ 0.88–1.05 (m, 2H), 1.22–2.06 (m, 12H), 2.44 (dd, J=10.3, 2.5 Hz, 1H), 3.55 (t, J=6.4 Hz, 2H), 4.21 (br s, 1H); ^{13}C NMR δ 18.9, 23.6, 29.5,

31.7, 32.4, 33.4, 34.2, 41.7, 44.8, 66.5, 120.7; MS *m/e* 216 (M+H).

3.1.12. 6-(4-Chloro-1,1-dimethylbutyl)-2-hydroxycyclohexanecarbonitrile (25b), (26b), and (27). Following the procedure for the reduction of **15a** the β-siloxy nitrile **15b** (2.49 g, 6.99 mmol) was reduced with $NaBH_4$ to afford 934 mg (55%) of **25b** (β-CN), 238 mg (14%) of **25b** (α-CN), 187 mg (11%) of **26b** (β-CN), 43 mg (3%) of **27** (α-CN), and 29 mg (2%) of **27** (β-CN)as oils. For **25b** (β-CN): IR (film) 3432, 2235 cm^{-1}; ^1H NMR δ 1.00 (s, 3H), 1.09 (s, 3H), 1.15–1.29 (m, 2H), 1.50–1.92 (m, 8H), 2.04–2.11 (m, 2H), 2.25 (dd, *J*=11, 9.8 Hz, 1H), 3.49 (dt, *J*=13, 6 Hz, 1H), 3.58 (dt, *J*=13, 7 Hz, 1H) 3.68–3.75 (dt, *J*=10, 4 Hz, 1H); ^{13}C NMR δ 23.0, 25.9, 26.0, 27.3, 33.6, 35.7, 38.1, 38.4, 40.3, 45.5, 60.4, 72.7, 122.4; MS *m/e* 244 (M+H). For **25b** (α-CN): IR (film) 3415, 2235 cm^{-1}; ^1H NMR δ 0.99 (s, 3H), 1.00 (s, 3H), 1.06–1.76 (m, 10H), 1.87–2.04 (m, 2H), 3.21 (br s, 1H), 3.52 (t, *J*=6.6 Hz, 2H), 3.65 (br dt, *J*=11, 4 Hz, 1H); ^{13}C NMR δ 22.7, 23.9, 24.7, 25.2, 27.3, 31.7, 35.1, 38.1, 45.5, 46.9, 71.5, 119.6; MS *m/e* 244 (M+H). For **26b**: IR (film) 3439, 2235 cm^{-1}; ^1H NMR δ 0.94 (s, 3H), 0.95 (s, 3H), 1.23–1.59 (m, 4H), 1.61–1.88 (m, 8H), 2.92 (br s, 1H), 3.51 (br t, *J*=6.6 Hz, 2H), 4.24 (br dd, *J*=5.6, 2.8 Hz, 1H); ^{13}C NMR δ 20.4, 23.5, 24.5, 25.2, 25.8, 27.2, 29.2, 34.7, 38.0, 40.1, 45.7, 68.5, 120.5; MS *m/e* 244 (M+H). For **27** (α-CN): (mp 88–90°C); IR (KBr) 3435, 2959, 2930, 2242 cm^{-1}; ^1H NMR δ 0.91 (s, 3H), 1.04 (s, 3H), 1.15–1.28 (m, 2H), 1.33–1.52 (m, 3H), 1.54–1.92 (m, 8H), 1.98–2.10 (m, 1H), 3.83 (t, *J*=2.8 Hz, 1H); ^{13}C NMR δ 19.4, 20.2, 20.4, 23.8, 30.6, 31.7, 33.2, 33.2, 41.2, 43.9, 44.0, 71.9, 123.7; MS *m/e* 208 (M+H); HRMS (ESI) calcd for (M+Na^+) $C_{13}H_{21}NONa$ 230.1515, found 230.1523. Oxidation of **27** (α-CN)(6 mg, 29 μmol), following the procedure for **31a**, afforded, after radial chromatography (1 mm plate, 1:9 EtOAc–hexanes), 5 mg (83%) of **17b** as a white crystalline solid. For **27** (β-CN): (mp 94–96°C); IR (KBr) 3450, 2952, 2872, 2235 cm^{-1}; ^1H NMR δ 0.89 (s, 3H), 1.20–1.98 (m, 13H), 1.36 (s, 3H), 2.21 (br s, 1H), 3.80 (dd, *J*=11, 4 Hz, 1H); ^{13}C NMR δ 19.6, 22.0, 22.3, 23.0, 27.9, 28.7, 31.4, 34.2, 34.3, 44.4, 47.4, 75.6, 126.7; MS *m/e* 208 (M+H). Oxidation of **27** (β-CN) (7 mg, 34 μmol), following the procedure for **31a**, afforded, after radial chromatography (1 mm plate, 1:9 EtOAc–hexanes), 6 mg (86%) of **17b** as a white crystalline solid.

3.1.13. 6-(4-Chloro-1,1-dimethylbutyl)cyclohex-1-enisocyanide (30). Neat TBSOTf (24 μL, 0.103 mmol) was added to a CH_2Cl_2 solution (1.5 mL) of **25b** (β-CN) (20 mg, 0.082 mmol) and pyridine (13 μL, 0.164 mmol). After 3 h water was added and the aqueous phase extracted with EtOAc. The extracts were combined, washed successively with $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1 mm plate, 1:19 EtOAc–hexanes) to afford 27 mg (92%) of (1*R**,2*R**)-6-(4-chloro-1,1-dimethylbutyl)-2-(1,1,2,2-tetramethyl-1-silapropoxy)cyclohexanecarbonitrile (**v**) as a colorless oil: IR (film) 2237 cm^{-1}; ^1H NMR δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 0.98 (s, 3H), 0.99 (s, 3H), 1.10–1.88 (m, 12H), 2.99 (br s, 1H), 3.51(td, *J*=6, 2.3 Hz, 2H), 3.54–3.61 (m, 1H); ^{13}C NMR δ −4.8, 18.0, 22.7, 23.8, 24.7, 25.2, 25.7, 27.3, 32.1, 34.9, 38.1, 38.6, 45.5, 46.7, 72.0, 119.6; MS *m/e* 300 (M− *t*-Bu). Cyclization of the silyl ether **v** following the general procedure afforded only **30**, spectrally identical to a previously characterized sample.[16]

3.1.14. (1*R,2*R**)-2-Hydroxy-7,7-dimethylbicyclo-[4.4.0]decanecarbonitrile (29b) by cyclization with MeMgCl.** A THF solution (3 M) of MeMgCl (55 μL, 0.163 mmol) was added to a cold, −78°C, THF solution (1 mL) of **25b** (β-CN) (18 mg, 0.074 mmol). After 3 h at −78°C only starting material was observed by TLC and consequently the reaction was allowed to warm to room temperature overnight. TLC analysis showed only starting material and therefore the reaction was heated to reflux. After 5 h the reaction mixture was allowed to cool to room temperature, saturated aqueous NH_4Cl was added and the aqueous phase was extracted with EtOAc. The combined organics were washed with water and brine, dried (Na_2SO_4), concentrated, and purified via radial chromatography (1 mm plate, 1:9–3:10 EtOAc–hexanes) to give 7 mg (47%) of **29b** and 3 mg (17%) of **30**.

3.2. General procedure for cyclizing β-hydroxy nitriles

A THF solution of $LiNEt_2$ (2.5 equiv.) was prepared by addition of a BuLi solution (hexanes, 2.5 equiv.) to a −78°C, THF solution (1 M) of Et_2NH (2.7 equiv.). The resulting pale yellow solution was allowed to stir at −78°C for 15 min. A THF solution (1 M) of the β-hydroxy nitrile (1 equiv.) was added and the resulting mixture allowed to warm slowly (~4 h) to room temperature and stirred an additional 8 h at room temperature. Saturated, aqueous NH_4Cl was added and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The resulting material was purified by radial chromatography to yield the hydroxy nitrile.

3.2.1. (1*R,2*R**)-2-Hydroxybicyclo[4.4.0]decanecarbonitrile (29a).** The general procedure was employed with **25a** (β-CN) (22 mg, 0.102 mmol) to afford, after radial chromatography (1 mm plate, 3:7 EtOAc–hexanes), 15 mg (78%) of **29a** as a white crystalline solid (mp 87–89°C): IR (KBr) 3434, 2234 cm^{-1}; ^1H NMR δ1.16–1.49 (m, 7H), 1.57–2.03 (m, 8H), 2.41–2.46 (m, 1H), 3.31 (br dd, *J*=11, 3 Hz, 1H); ^{13}C NMR δ 22.9, 23.5, 25.5, 29.6, 29.7, 32.6, 33.0, 43.0, 50.2, 75.2, 120.5; MS *m/e* 180 (M+H). The general procedure was employed with **25a** (α-CN) (20 mg, 0.093 mmol) to afford, after radial chromatography (1 mm plate, 3:7 EtOAc–hexanes), 13 mg (83%) of **29a** as a white crystalline solid.

3.2.2. (1*R)-2-Oxobicyclo[4.4.0]decanecarbonitrile (32a).** Solid TPAP (0.05 equiv.) was added in one portion to a room temperature, CH_2Cl_2 solution (0.05 M) of **29a** (23 mg, 0.128 mmol, 1 equiv.), NMO (1.5 equiv.) and powdered 4 Å molecular sieves (500 mg/mmol). After 8 h the suspension was filtered through a short pad of silica, eluting with CH_2Cl_2, the filtrate was concentrated and then purified by radial chromatography (1 mm plate 1:9, EtOAc–hexanes) to afford 22 mg (97%) of **32a** as a white crystalline, X-ray diffracting,[18] solid (mp 55–56°C): IR (KBr) 2227, 1731 cm^{-1}; ^1H NMR δ 1.54–1.64 (m, 2H), 1.74–2.34 (m, 10H), 2.41–2.52 (m, 1H), 2.63–2.73 (m, 1H), 3.19 (ddd, *J*=14, 7, 2 Hz, 1H); ^{13}C NMR δ 23.8, 26.9,

28.2, 30.8, 31.1, 31.6, 39.7, 49.0, 54.3, 118.7, 201.6; MS *m/e* 178 (M+H).

3.2.3. (1*R,2*R**)-2-Hydroxy-7,7-dimethylbicyclo[4.4.0]-decanecarbonitrile (29b).** The general cyclization procedure was employed with **25b** (β-CN) (261 mg, 1.074 mmol), with the modification of maintaining the solution at −78°C for 4 h before adding saturated, aqueous NH_4Cl. Radial chromatography (1 mm plate, 3:7 EtOAc–hexanes) afforded 189 mg (85%) of **29b** as a white, crystalline, X-ray diffracting,[18] solid (mp 104–106°C): IR (KBr) 3460, 2238 cm^{-1}; ^1H NMR δ 0.90 (s, 3H), 0.97 (dd, J=12, 3 Hz, 1H) 1.05 (s, 3H), 1.11–1.44 (m, 5H), 1.50 (ddd, J=13, 5, 3 Hz, 1H), 1.59–2.00 (m, 5H), 2.48 (ddd, J=13.4, 5, 3 Hz, 2H), 3.28 (dd, J=11.4, 4.2 Hz, 1H); ^{13}C NMR δ 19.2, 20.5, 23.2, 23.7, 32.0, 32.5, 33.2, 34.3, 41.2, 47.2, 50.8, 76.6, 122.2; MS *m/e* 207 (M^+). Repeating the general procedure with **25b** (α-CN) (22 mg, 0.091 mmol), with the modification of maintaining the solution at −78°C for 4 h before adding saturated, aqueous NH_4Cl. Radial chromatography (1 mm plate, 3:7 EtOAc–hexanes) afforded 16 mg (84%) of **29b** as a white crystalline solid.

3.2.4. (1*R)-7,7-Dimethyl-2-oxobicyclo[4.4.0]decane-carbonitrile (32b).** Oxidation of **29b** (87 mg, 0.420 mmol), following the procedure for **29a**, afforded, after radial chromatography (1 mm plate, 1:9 EtOAc–hexanes), 86 mg (100%) of **32b** as a white, X-ray diffracting,[13] crystalline solid (mp 59–61°C): IR (KBr) 2224, 1723 cm^{-1}; ^1H NMR δ 0.91 (s, 3H), 1.12 (s, 3H), 1.13–1.24 (m, 2H), 1.43–2.06 (m, 8H), 2.17 (dddd, J=13, 7, 6, 3 Hz, 1H), 2.37–2.44 (m, 1H), 2.93 (dt, J=13.6, 6.8 Hz, 1H); ^{13}C NMR δ 18.4, 20.3, 23.5, 26.4, 30.3, 31.9, 34.5, 38.6, 40.5, 51.6, 54.8, 120.4, 203.1; MS *m/e* 205 (M).

3.3. Attempted equilibration of 27

Employing the general cyclization procedure with 1.5 equiv. of $LiNEt_2$, the *cis*-decalin **27** (α-OH, 14 mg, 0.068 mmol) for 3 h at −78°C, followed by the addition of saturated aqueous NH_4Cl and extractive isolation gave 12 mg (86%) of recovered *cis*-decalin **27** (α-OH). An analogous deprotonation of **27** (β-OH) (11 mg, 0.053 mmol) afforded 8 mg (73%) of recovered **27** (β-OH).

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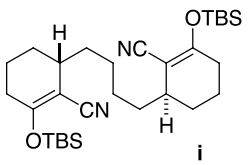
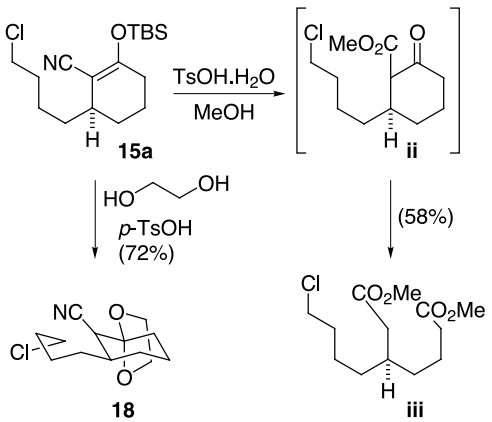
16. Cyclization of the intermediate enolate **14a** occurs on warming, affording decalone **17a** and an epimeric mixture of monocyclic ketones in equilibrium with the enol tautomer.
17. Optimization experiments revealed the need for slow formation of **12** at −10°C to minimize formation of the corresponding bis-Grignard reagent that otherwise generates the bis-addition product **i**. The stereochemical assignment was determined by X-ray crystallography[18] of the sole diastereomer isolated in 14% yield.



i

18. The supplementary crystallographic data for all of the crystal structures (i CCDC# 183551, 17b CCDC# 183548, 29b CCDC# 183549, 32b CCDC# 183550) can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

19.



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23. Facile ketalization of **23** occurs in $CDCl_3^a$ which, followed by acid hydrolysis, converges **23** to the *cis*-decalone **17a**. Lu, T. J.; Cheng, S. M.; Sheu, L. J. *J. Org. Chem.* **1998**, *63*, 2738.
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28. No decalins were detected from the borohydride reduction of the corresponding *des*-methyl nitrile **15a**.
29. Probing the role of the proximal hydroxyl group led to an extensive series of cyclizations with the *des*-hydroxy analog of **25a**.[10]
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32. Assuming a full *syn*-axial interaction between the CH_2Cl and H_a and H_b, the steric interactions present in **31b** are 3×0.85 kcal mol^{-1}, compared to 2×0.1 kcal mol^{-1} for the axially oriented nitrile in **31c**.
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35. For general experimental procedures see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. All ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.