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Metalated nitriles: stereodivergent cation-controlled cyclizations☆

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ABSTRACT

Stereodivergent cyclizations of γ-hydroxy cyclohexanecarbonitriles are controlled simply through judicious choice of cation in the alkylmetal base. Deprotonating a series of cyclic γ-hydroxy nitriles with *i*-PrMgBr generates *C*-magnesiated nitriles that cyclize under stereoelectronic control to *cis*-fused hydrindanes, decalins, and bicyclo[5.4.0]undecanes. An analogous deprotonation with BuLi triggers cyclization to *trans*-fused hydrindanes, decalins, and bicyclo[5.4.0]undecanes consistent with a sterically controlled electrophilic attack on an equatorial nitrile anion. Using cations to control the geometry of metalated nitriles provides a versatile, stereodivergent cyclization to *cis*- and *trans*-hydrindanes, decalins, and [5.4.0]undecanes, and reveals the key geometric requirements for intramolecular S_N2 and S_N2' displacements.

1. Introduction

Metalated nitriles are nucleophilic chameleons, readily adapting to the local environment by adopting different structures.[2] X-ray crystallographic analyses of metalated nitriles[3] show two main structural classes: *N*-metalated nitriles in which the metal coordinates to the nitrile nitrogen[4] and *C*-metalated nitriles[5] in which the metal is bound to the formally anionic carbon (Fig. 1, **1** and **2**, respectively). Crystallographically derived bond lengths for *N*- and *C*-metalated nitriles reveal only a slight weakening of the C≡N triple bond (1.15–1.20 Å), relative to the C≡N bond length of neutral nitriles (1.14 Å),[6] indicative of a predominant inductive stabilization[7] of the negative electron density. Consistent with the inductive stabilization are short C–CN bonds[8] stemming from an electrostatic contraction between the formal anion and the powerful electron-withdrawing nitrile group.[9]

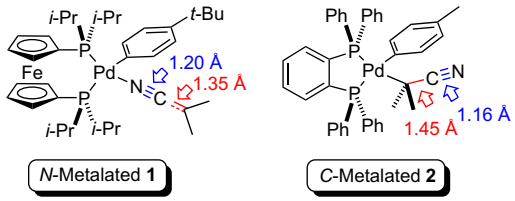
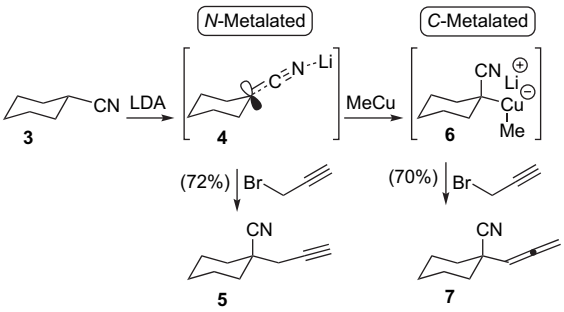


Figure 1. Structures of metalated nitriles.

Moderating the ligand or metal environment exerts a pronounced influence on the site of coordination in metalated nitriles. The solid-state *N*- and *C*-palladated nitriles **1** and **2**[10] differ rather modestly in their structural features, essentially in the nature of the phosphine ligand, but exhibit completely different coordination modes to the same nitrile! ^{7}Li NMR reveals basically the same structural trends for metalated nitriles in solution; a preference for N- or C-metalation that depends intimately on ligand and solvent,[11] and minimal delocalization of the anion into the carbon–nitrogen triple bond.[9]

Differences in the site of metal coordination relay into different reactivity modes for *N*- and *C*-metalated nitriles. For example, reductive elimination from the *N*-palladated nitrile **1** is 10 times faster than that for the analogous *C*-palladated nitrile **2**.[10] In some cases, the reactivity differences between *N*- and *C*-metalated nitriles translates into completely different reaction trajectories as illustrated in the stereodivergent alkylations of metalated cyclohexanecarbonitrile (Scheme 1). Deprotonating cylohexanecarbonitrile (**3**) with LDA



Scheme 1. Regiodivergent alkylations of *N*- and *C*-metalated nitriles.

☆ See Ref. 1.

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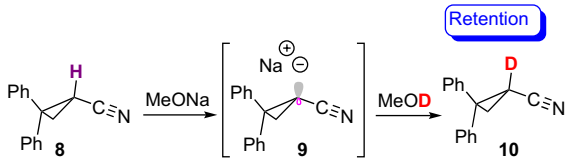
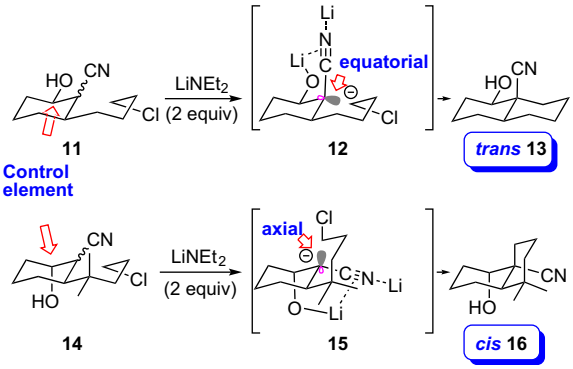
generates the planar, *N*-lithiated nitrile[12] **4**, which attacks propargyl bromide in an S_N2 displacement leading to the alkyne **5**.[13] Adding methylcopper prior to the alkylation effectively transforms the *N*-lithiated nitrile **4** into the tetrahedral *C*-cuprated nitrile **6**. Intercepting **6** with propargyl bromide affords the allene **7** in an S_N2' displacement reminiscent of cuprates.[14]

The structure and reactivity of metalated nitriles varies considerably in different solvents.[15] In general, hydrocarbon solvents favor N-metalation,[15] ethereal solvents favor N- or C-metalation depending on the metal–ligand combination,[11] and highly polar solvents favor solvent-separated nitrile anions.[16] Nitrile anions were first implicated during pioneering deprotonations to determine the configurational stability of 'chiral carbanions' (Scheme 2).[17] Under kinetic conditions the deuteration of chiral cyclopropanecarbonitrile **8** proceeds with greater than 99.9% stereochemical retention, implying the intermediacy of the pyramidal anion **9**.[18] Subsequent quests to generate chiral nitrile anions[19] have proved challenging because of the relatively low barrier for inversion of the pyramidal nitrile anion.[20]



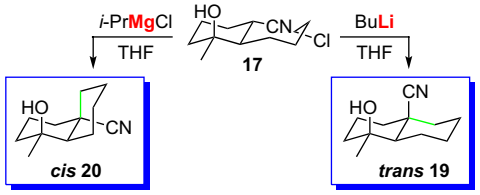
Scheme 2. Retentive deuteration of a nitrile anion.

An alternative strategy for generating chiral, nitrile-stabilized carbanions is to control the geometry of the anion through internal chelation.[21] Cyclizations of β-hydroxy nitriles have exploited this strategy by forming internally chelated nitrile anions that selectively cyclize to *trans*- and *cis*-decalin depending on the stereochemistry of the adjacent hydroxyl-bearing carbon (Scheme 3).[22] Simply deprotonating the β-hydroxy nitrile **11** at low temperatures and warming, triggers a facile, completely stereoselective cyclization to the *trans*-decalin **13** whereas the diastereomeric β-hydroxy nitrile **14** cyclizes to the *cis*-decalin **16** under identical conditions. The divergent stereoselectivity is consistent with cyclization through internal chelates simplistically viewed as pyramidal, nitrile anions **12** and **15**. Defining the geometry of these chiral carbanions through lithium coordination to the electron-rich[23] π-cloud of the metalated nitrile[24] effectively translates the stereochemistry of the carbinol methine to the chiral nucleophile.



Scheme 3. Chelation-controlled cyclizations of nitrile anions.

Tuning metalated nitriles through chelation suggested a more daring strategy for controlling the geometry simply through judicious choice of cation. The appeal stems from diverting one nitrile through two stereodivergent alkylation manifolds to two diastereomeric products, a challenging transformation that potentially explains why cation-controlled alkylations are relatively rare.[15,25] Preliminary cyclizations[26] demonstrated the viability of stereodivergent decalin and bicyclo[4.3.0]undecane cyclizations simply by using different alkylmetal bases to introduce mono- or divalent metal cations (Scheme 4).

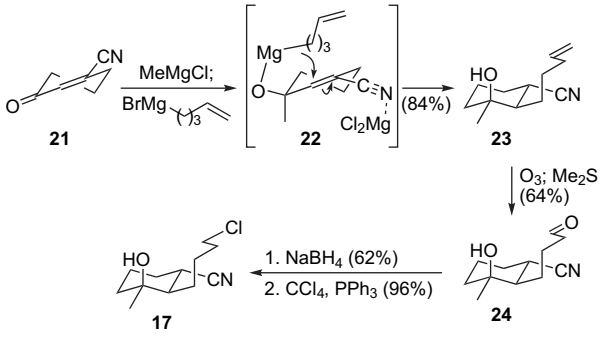


Scheme 4. Cation-controlled cyclizations.

Expanding the cation-dependent cyclization strategy, particularly for the synthesis of hydrindanes, provides critical insight into the requirements for selectively generating *cis*- and *trans*-fused bicyclic nitriles. Internal alkylations with allylic electrophiles reveal stark reactivity differences in analogous cyclizations of five-, six-, and seven-membered nitriles of direct relevance for S_Ni alkylations in general. A detailed account of these cyclizations demonstrates the dramatic influence of cation in controlling the metalated nitrile geometry, provides a versatile method for accessing *cis*- and *trans*-hydrindanes, decalins, and bicyclo[5.4.0]undecanes, and reveals the key geometric requirements for intramolecular S_N2 and S_N2' displacements.

2. Results and discussion

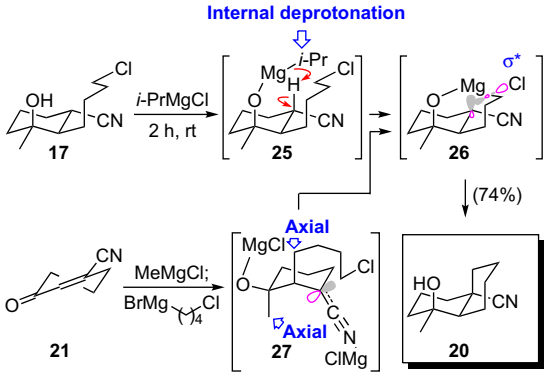
Probing the viability of a cation-dependent cyclization required a short, efficient synthesis of a cyclic nitrile prototype. The γ-hydroxy nitrile **17** admirably fulfilled this requirement (Scheme 5). Rapid assembly of the carbon scaffold was achieved by sequential addition of MeMgCl and 4-pentenylmagnesium bromide to oxonitrile **21**.[27] Key to this multiple bond-forming process is the alkylmagnesium alkoxide **22**,[28] which assists in preorganizing the stereoelectronically controlled axial[29] conjugate addition.[30] Axial addition of the pentenyl group occurs opposite the quaternary methyl leading initially to a diaxial cyclohexanecarbonitrile that subsequently equilibrates to the cyclic nitrile **23** in which both alkyl substituents are relaxed into the equatorial orientation. Ozonolysis, reduction, and chlorination[31] (**23**→**24**→**17**) readily transforms the terminal olefin into the pendant chlorobutyl electrophile required for cyclization.



Scheme 5. Synthesis of nitrile cyclization prototype **17**.

Cyclization of the hydroxy nitrile **17** exploits the hydroxyl group as an internal directing group.[32] Addition of *i*-PrMgCl to **17** leads to the isopropylmagnesium alkoxide[33] **25** (Scheme 6) in which the

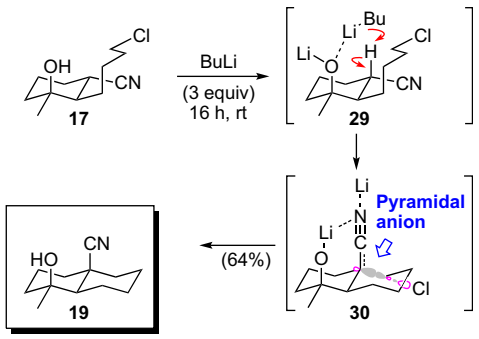
Grignard-type reagent is ideally anchored for the internal deprotonation en route to **26** and yet geometrically prevented from attack on the electrophilic nitrile group.[34] *C*-Magnesiated nitriles[35] analogous to **26** exhibit a preference for retentive alkylation with alkyl halides through a three-centered, C–Mg σ* orbital overlap.[36] Although the side-on orbital overlap is far from optimal, the alternative co-linear approach of the chloromethylene carbon to the small σ lobe of the C–Mg bond is sterically prohibited. Consistent with this established trend, magnesiated nitrile **26** delivers the *cis*-decalin **20** as the sole stereoisomer.[37]



Scheme 6. cis-Selective cyclizations of magnesiated nitriles.

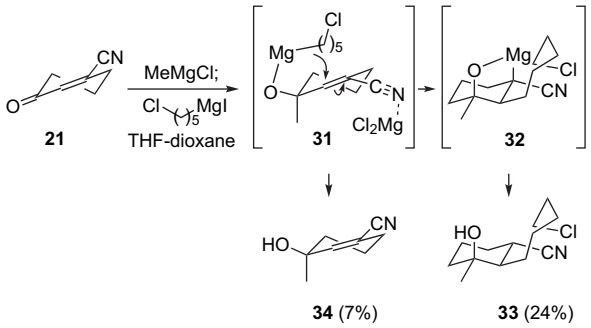
Direct formation of the *cis*-decalin **20** has previously been achieved through the sequential addition of MeMgCl and chlorobutylmagnesium bromide[38] to oxonitrile **21** (Scheme 6).[39] Mechanistic experiments performed prior to finding the electrophile-dependent alkylations of *C*-magnesiated nitriles, implied that the intermediate dimagnesiated nitrile **27**, generated immediately following the axial conjugate addition, was particularly reactive and cyclized to **20** faster than a chair-to-chair conformational inversion (**27**→**26**).[29] The preferential cyclization of the *C*-magnesiated nitrile **26** to the *cis*-decalin **20**, coupled with an anticipated steric compression imposed by the two axial substituents in **27**, strongly implies that the Grignard addition–cyclization **21**→**20** actually proceeds from the dimagnesiated nitrile **27** through the *C*-magnesiated nitrile **26** to the *cis*-decalin **20** (Scheme 6).

Cyclizing the hydroxy nitrile **17** to the diastereomeric *trans*-decalin **19** was predicated on generating a dilithiated nitrile bearing an equatorial anion. Extensive experimentation with alkyllithium and lithium amide combinations eventually identified BuLi as the optimum base for the cyclization (Scheme 7).[40] Alkyllithiums are prone to attack nitriles,[41] implying an oxygen assisted deprotonation[42] of the lithium alkoxide **29**. Exclusive cyclization to the *trans*-decalin **19** requires overlap of an equatorially oriented nucleophile with the σ* orbital of the C–Cl bond, consistent with forming the internally coordinated, pyramidal nitrile anion **30**.



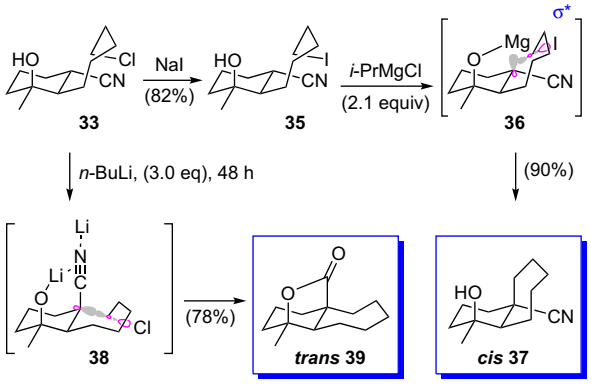
Scheme 7. trans-Selective cyclization with a dilithiated nitrile anion.

Stereodivergent cyclizations of the γ-hydroxy nitrile **17** to *cis*- and *trans*-decalin **20** and **19** stimulated homologous cyclizations to seven-membered *cis*- and *trans*-bicyclo[5.4.0]undecane. Synthesis of the requisite chloronitrile precursor **33** was achieved through the sequenced addition of MeMgCl and chloropentylmagnesium iodide[43] to oxonitrile **21** (Scheme 8). Although direct, the modest yield focused attention on increasing the nucleophilicity of chloropentylmagnesium iodide to avoid the persistent isolation of the alkenenitrile **34** resulting from 1,2- but not 1,4-addition. Increased efficiency was achieved by adding dioxane, the intention being to sequester the magnesium dihalide[44] and promote formation of the alkylmagnesium alkoxide assembly **31** required for the conjugate addition. Even under optimal conditions with excess chloropentylmagnesium iodide, 7% of the hydroxyalkene nitrile **34** was isolated. Although the yield of **33** is modest, the strategy allows direct access to the precursor required for the cation-controlled cyclization.



Scheme 8. 1,4-Additions to oxonitrile **17**.

Formation of the cyclization precursor **33** via the *C*-magnesiated nitrile **32** (Scheme 8) presaged a surprisingly difficult cyclization! Deprotonating **33** with *i*-PrMgCl at room temperature conditions, which effectively cyclize the six-membered *C*-magnesiated nitrile **26** (Scheme 6), fails to induce any cyclization. Coaxing the cyclization of **33** to *cis*-bicyclo[5.4.0]undecane **37** (Scheme 9) requires conversion of the chloride to the corresponding iodide **35** followed by deprotonation and heating of the reaction to reflux. Essentially no cyclization of the iodide **35** occurs at room temperature. The cis stereochemistry of **37**[45] is consistent with a stereoelectronically controlled $S_E2_{(ret)}$ displacement[46] via the *C*-magnesiated nitrile **36**.

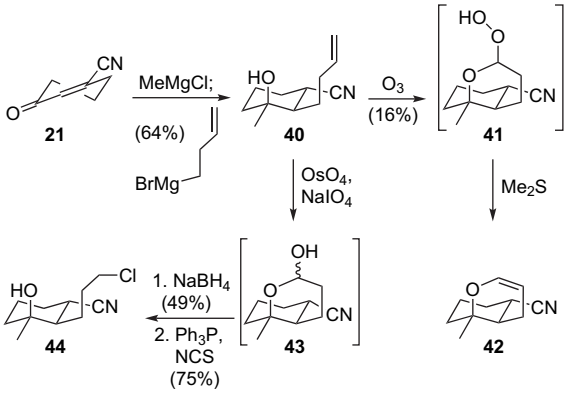


Scheme 9. Stereodivergent cyclizations to bicyclo[5.4.0]undecanes.

The stereodivergent cyclization of **33** with BuLi proved similarly challenging. Following BuLi-induced deprotonation, the lithiated nitrile **38** cyclized particularly slowly over 2 days at room temperature. The extended reaction time allows for the first-formed

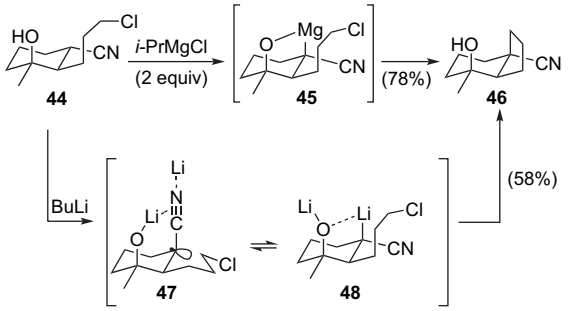
alkoxide to internally attack the proximal axial nitrile[47] leading to the *trans*-lactone **39** after an aqueous workup.[48]

Extending the cation-controlled cylization strategy to the synthesis of hydrindanes was complicated by the increased torsional strain present in *trans*-fused hydrindanes[49] and by an unanticipated proximity effect en route to the cyclization precursor. Addition of MeMgCl and 3-butenylmagnesium bromide to oxonitrile **21** afforded the hydroxy nitrile **40**, which requires excision of the terminal carbon and chlorination for conversion to **44** (Scheme 10). Ozonolysis of **40** and reduction with dimethylsulfide afforded not the anticipated lactol **43** but a low yield of the enol ether **42**. Although several mechanistic sequences can lead to **42**, the complete absence of an aldehyde or lactol suggests that the axial alcohol intercepts the intermediate carbonyl oxide to afford hydroperoxide **41** that promptly suffers elimination. Osmium tetroxide–sodium periodate cleavage of **40** circumvents enol ether formation, affording the very sensitive lactol **43**. Immediate reduction of the crude lactol affords an intermediate alcohol that was successfully chlorinated without interference of the tertiary alcohol.[50]



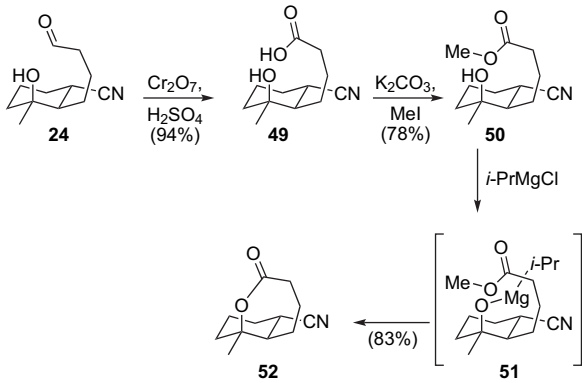
Scheme 10. Synthesis of the hydrindane cyclization precursor **44**.

Cyclizing hydroxy nitrile **44** to the *cis*-hydrindane **46** proceeded smoothly upon addition of *i*-PrMgCl (Scheme 11). In contrast, all attempts to coax the stereodivergent cyclization of **44** to the more highly strained *trans*-hydrindane[49] were frustrated by preferential cyclization to the *cis*-hydrindane **46**. For example, addition of BuLi with or without additives generated only the *cis*-hydrindane **46**.[51] Presumably the inherent angle strain required to align the electrophilic σ* orbital of the C–Cl bond with the pyramidal π-complexed anion **47** is responsible for redirecting the cyclization to the *cis*-hydrindane **46**. Although tentative, cyclization might occur through the *C*-lithiated nitrile **48**, which is structurally analogous to internally chelated organolithiums.[42]



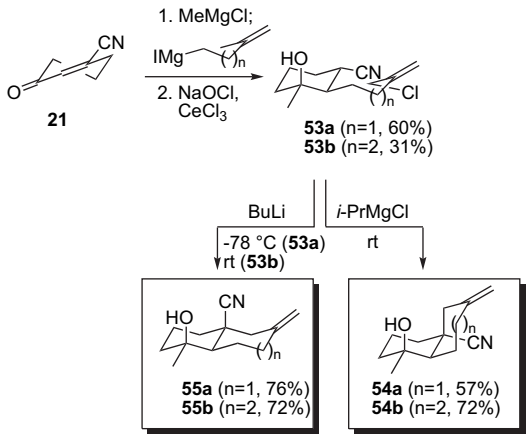
Scheme 11. Cyclizations to *cis*-hydrindane **46**.

With the aim of extending the cation-controlled cyclization strategy to functionalized bicyclic nitriles, attention was focused on the cyclization of ester nitrile **50** (Scheme 12). Facile access to the ester nitrile **50** was achieved by sequential oxidation of the aldehyde **24** (Scheme 5) and methylation of the resulting acid **49**. Addition of *i*-PrMgCl to ester nitrile **50** at −78 °C, conditions that avoid Grignard addition to esters,[52] resulted in a very smooth cyclization, not to the desired decalin, but to the lactone **52** (Scheme 11).[53] Presumably the intermediate magnesium alkoxide **51** reacts faster with the pendant ester than in the internal deprotonation. Alternative cyclization strategies with various combinations of base, the use of aldehyde electrophiles, or with protected alcohols were uniformly unsuccessful.



Scheme 12. Intramolecular lactonization with an ester nitrile.

Cyclizations of allylic chlorides provided an appealing strategy for introducing modest yet versatile functionality into the cation-controlled cyclization. Augmenting the synthetic attraction of the anticipated *exo*-methylene products was the added opportunity to investigate the inherent geometric requirements for intramolecular S_N2 and S_N2' displacements. In practice, the strategy proved particularly rewarding because of the increased electrophilicity of the allylic chlorides and the rapid access to the cyclization precursors (Scheme 13). Sequential 1,2–1,4-Grignard addition to oxonitrile **21** installed the entire carbon skeleton with direct chlorination providing the chloronitriles **53a** and **53b** without the need for protecting the tertiary hydroxyl group. Facile cyclization occurs upon addition of *i*-PrMgCl at room temperature, affording the *cis*-decalin **54a**[54] from **53a** and the *cis*-bicyclo[5.4.0]undecane **54b** from **53b** (Scheme 13).



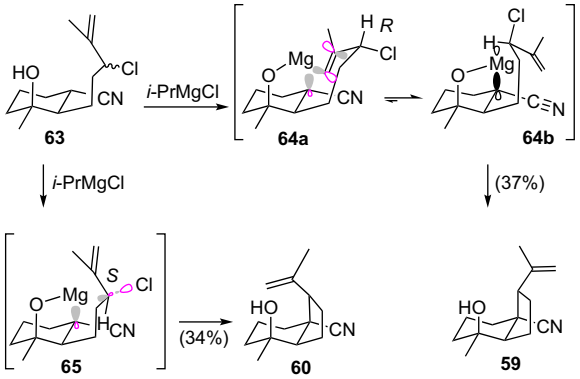
Scheme 13. Stereodivergent decalin and bicyclo[5.4.0]undecane syntheses.

Standard addition of BuLi to **53a** and **53b** triggers two facile trans-selective cyclizations. A measure of the increased reactivity is gleaned from the comparative cyclization of **53a** to **55a**, which

occurred at −78 °C (Scheme 13) whereas the *des*-methylene analog **17** (Scheme 7) required 16 h at room temperature. While optimizing the BuLi-induced cyclization of **53a**, a considerable amount of an unstable species was observed in the crude reaction mixture, which was tentatively identified as an iminolactone resulting from internal attack of the lithium alkoxide onto the nitrile. An expedient solution was to add TsOH·H_2O that effectively regenerates the nitrile without any trace of the lactone or iminolactone.[55] The increased reactivity of the allylic chloride-containing nitrile **53b** similarly facilitates closure of the seven-membered ring without any lactonization (cf. **33**→**39**, Scheme 9).[56]

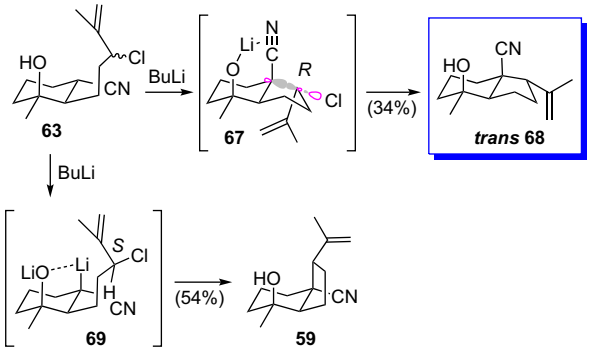
The dramatically facilitated allylic chloride displacements stimulated a revised approach to *trans*-hydrindanes. The strategy was predicated on an allylic electrophile having a larger antibonding orbital capable of overlapping an equatorially oriented nitrile anion with a reduced torsional strain (**62**, Scheme 14).[57] Exploring this stereoelectronic control strategy was achieved with nitrile **57**, obtained from sequential 1,2–1,4-additions to oxonitrile **21** followed by regioselective allylic oxidation and chlorination of the intermediate nitrile **56** (Scheme 14). Cyclizing **57** with *i*-PrMgCl efficiently generates the two *cis*-hydrindanes **59** and **60**[58] but with minimal stereocontrol over the two contiguous tertiary–quaternary stereocenters. Presumably there is only a minimal preference for cyclization via conformer **58b**, which avoids projecting the allylic methyl toward the nitrile group as in **58a**, but ultimately leads to a considerable steric interaction caused by the *endo* orientation of the isopropenyl group. Cyclizing the hydroxy nitrile **57** with BuLi provided the same two *cis*-hydrindanes **59** and **60**. By analogy to the related BuLi cyclization of **44** (Scheme 11) the cyclization is tentatively presumed to proceed from the *C*-lithiated nitrile **61a** to **60** and from **61b** to **59** (Scheme 14).

Preferential cyclization of the dilithiated nitrile **61** to the *cis*-hydrindanes **59** and **60** implies that S_N2' displacement on an allylic chloride provides insufficient orbital overlap to direct the cyclization to a *trans*-hydrindane. S_N2 displacement of the secondary allylic chloride **63** (Scheme 15), obtained by NaOCl oxidation of **56** (75%), presented an attractive solution. Although counter-intuitive, the chirality of the allylic chloride should be relayed through the alkylation to matched and mismatched transition structures because the *C*-magnesiated and dilithiated nitriles are chiral at carbon. Cyclizing **63** with *i*-PrMgCl generated the *cis*-fused hydrindanes **59** and **60** in approximately equal ratios. The stereochemical outcome is consistent with an $S_E2_{(ret)}$ cyclization[60] of the *R*-allylic chloride through conformer **64b** to the *cis*-hydrindane **59** and cyclization of the *S*-allylic chloride diastereomer to **60** via conformation **65**. Despite an effective orbital alignment for S_N2' displacement, through **64a**, none of the seven-membered ring was detected in the crude reaction mixture.



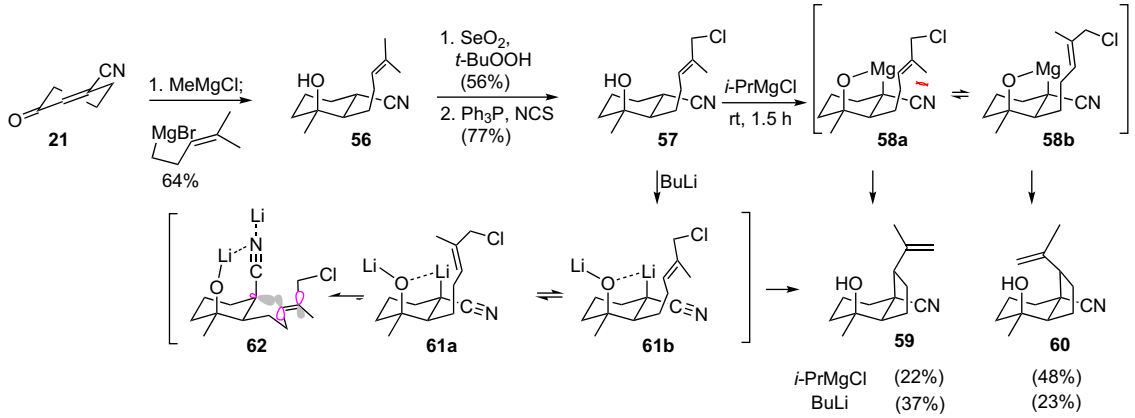
Scheme 15. Cyclizations of allylic chlorides to *cis*-hydrindanes.

Exposing hydroxy nitrile **63** to BuLi did indeed provide a *trans*-hydrindane although accompanied by the *cis*-hydrindane **59** (Scheme 16). Fortunately, the configuration of the two stereocenters in the *trans*-hydrindane **68** was unambiguously secured through X-ray crystallographic analysis of the *p*-nitrobenzoate derivative **66** (Fig. 2).



Scheme 16. Nitrile cyclizations to *cis*- and *trans*-hydrindanes.

The stereochemistry of the crystalline *trans*-hydrindane **66** requires an S_N2 displacement by an equatorial anion on the *R*-allylic chloride **67** (Scheme 16). Overlap between the equatorially oriented pyramidal nitrile anion **67** and the σ* of the C–Cl bond minimizes steric compression by staggering the isopropenyl group between the cyclohexane ring carbons. In addition, the geometry permits alignment of the C–Cl bond with the adjacent olefinic π-system for a stereoelectronically assisted displacement.[61] The π-assistance must be integral for the cyclization because the analogous des-chloropropyl electrophile cyclizes exclusively to a



Scheme 14. Metalated nitrile cyclizations to *cis*-hydrindanes.

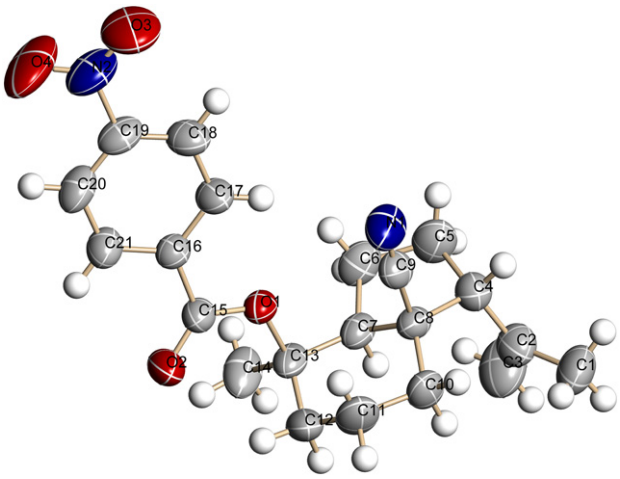


Figure 2. ORTEP of the *trans*-hydrindane **66**.

cis-hydrindane (cf. **44**→**46**, Scheme 11). Presumably the σ*–π interaction sufficiently increases the cone of accessibility[62] for a facile S_N2 displacement by the equatorial nitrile anion **67**. Cyclizing the *S*-diastereomer through an analogous conformation would thrust the isopropenyl group into the nitrile group, which potentially explains the preference for cyclization through **69** to the *cis*-hydrindane **59** (Scheme 16). Despite extensive effort, the diastereomeric chlorides were inseparable precluding their individual cyclization to test whether each selectively processes to a *cis*- or *trans*-hydrindane.

3. Conclusion

Judicious choice of cation allows the stereodivergent cyclizations of β-hydroxy cyclohexenecarbonitriles to *cis*- and *trans*-hydrindanes, decalins, and [5.4.0] undecanes. Deprotonating β-hydroxy cyclohexenecarbonitriles with *i*-PrMgBr or BuLi generates two geometrically complementary metalated nitriles; divalent magnesium favors a *C*-magnesiated, whereas monovalent lithium favors an *N*-coordinated nitrile anion. Internal displacements of *C*-magnesiated nitriles trigger stereoelectronically controlled electrophilic substitutions to *cis*-fused bicyclic nitriles. In contrast, alkylations of dilithiated nitrile anions are controlled by internal bridging of lithium to the electron-rich nitrile π-electrons, which generates an equatorial nitrile anion. The equatorially oriented nucleophilic orbital is ideally aligned for cyclization to *trans*-bicyclic nitriles.

Comparative cyclizations of *C*-magnesiated and dilithiated nitriles with allylic chlorides provide key insight into the geometric requirements for intramolecular S_N2 and S_N2' displacements. Stereodivergent, cation-controlled cyclizations to *cis*- and *trans*-decalins and [5.4.0] undecanes are more facile with allylic chlorides than for the corresponding *des*-methylene analogs. Comparable cyclizations to hydrindanes depend intimately on the hybridization of the electrophilic carbon. *C*-Magnesiated nitriles cyclize to *cis*-hydrindanes in S_N2 and S_N2' displacements whereas the cyclizations of dilithiated nitriles appear to be redirected in S_N2 displacements with secondary allylic chlorides. In this case, the stereochemistry of the electrophilic carbon channels the cyclization toward the *trans*-hydrindane. Collectively, the cation-controlled cyclizations to *cis*- and *trans*-hydrindanes, decalins, and [5.4.0] undecanes demonstrate the key influence of metal coordination in controlling nitrile anion geometry and provide insight into the geometric requirements for intramolecular S_N2 and S_N2' displacements.

4. Experimental section

4.1. General methods

NMR spectra were recorded in $CDCl_3$ (300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR) and are reported in parts per million (δ) relative to TMS using $CHCl_3$ as an internal reference. All reactions were performed under a nitrogen atmosphere in glassware dried under high vacuum. Anhydrous solvents were distilled from sodium benzophenone ketyl or CaH_2. Bulk solvents for chromatography and workup of reactions were distilled through glass. Radial chromatography was performed on a Chromatotron® using individually prepared 1-, 2-, or 4-mm rotors.

4.2. General deprotonation–cyclization procedure with *i*-PrMgCl

A THF solution (3 equiv) of *i*-PrMgCl was added dropwise to a room temperature THF solution of γ-hydroxy nitrile. After 1.5 h, saturated, aqueous, NH_4Cl was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography afforded pure material for further characterization.

4.3. General deprotonation–cyclization procedure with BuLi

A hexanes solution (2.1–3.0 equiv) of BuLi was added, dropwise, to a −78 °C THF solution of γ-hydroxy nitrile. After 2 h, the mixture was allowed to warm to room temperature and after a further 1.5 h, an aqueous solution (3 equiv) of $TsOH\cdot H_2O$ was added. After 15 min, brine was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude product that was purified by radial chromatography.

4.3.1. (1S,2R*,3S*)-3-Hydroxy-3-methyl-2-(pent-4-enyl)cyclohexanecarbonitrile (**23**)*

A THF solution (2.7 mL) of MeMgCl (7.4 mmol) was added to a −20 °C THF solution (30 mL) of 3-oxo-cyclohex-1-enecarbonitrile (857.8 mg, 7.09 mmol). After 2 h at −20 °C, a THF solution (4 mL) of pent-4-enylmagnesium bromide was added. [5-Bromo-1-pentene (1.26 mL, 10.6 mmol) was slowly added to a 0 °C THF (4 mL) suspension of Mg (314.8 mg, 13.1 mmol), activated by addition of 1,2-dibromoethane (0.12 mL, 1.4 mmol) and allowed to react at 0 °C for 1 h.] After 24 h, NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (10:90, EtOAc/hexanes) afforded 1.32 g (89%) of **50** as an oil. IR (film) 3490.6, 3076.4, 2238.4, 1640.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.30–1.40 (m, 5H), 1.44–1.78 (m, 7H), 2.05–2.09 (m, 2H), 2.69 (td, *J*=11.9, 3.6 Hz, 1H), 4.93–5.03 (m, 2H), 5.76–5.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 29.0, 29.0, 29.2, 30.4, 31.4, 34.0, 39.6, 47.7, 70.8, 114.7, 122.8, 138.3.

4.3.2. (1S,2R*,3S*)-3-Hydroxy-3-methyl-2-(4-oxobutyl)-cyclohexanecarbonitrile (**24**)*

Gaseous ozone was passed through a −78 °C CH_2Cl_2 (20 mL) solution of **50** (331 mg, 1.6 mmol) until the distinctive blue color of excess ozone persisted. Ozonolysis was then terminated, the solution was allowed to warm to room temperature, and then neat Me_2S (3 mL) was added dropwise. After 16 h, the mixture was concentrated, the resulting oil was redissolved in EtOAc, and the organic phase was then washed with brine, dried ($NaSO_4$), and concentrated. The crude product was purified by radial chromatography (30:70, EtOAc/hexanes) to provide 210 mg (64%) of **51** as

an oil. IR (film) 3434.4, 2237.2, 1709.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.29–1.91 (m, 11H), 1.99–2.05 (m, 1H), 2.29–2.37 (m, 1H), 2.46 (t, J=6.6 Hz, 1H), 2.68 (br t, J=10.3 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 21.7, 28.7, 28.8, 30.2, 31.0, 39.5, 43.8, 47.5, 70.4, 122.7, 202.6; MS (EI) m/z 209 (M^+).

4.3.3. (1S*,2R*,3S*)-3-Hydroxy-2-(4-hydroxybutyl)-3-methylcyclohexanecarbonitrile (**i**)

Solid $NaBH_4$ (45.4 mg, 1.2 mmol) was added to a methanolic solution (10 mL) of aldehyde **24** (167 mg, 0.8 mmol). After 4 h, an aqueous solution of HCl (1 M, 3 mL) was added, and after 15 min, 10 mL ether was added, the layers were separated, and the aqueous phase was extracted with ether (3×10 mL). The combined organic phase was washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated under reduced pressure, and the residue was then purified by radial chromatography (30:70, EtOAc/hexanes) to afford 152 mg (90%) of **i** as an oil. IR (film) 3445, 2239 cm^{-1}; ^1H NMR δ 1.27 (s, 3H), 1.29–1.79 (m, 13H), 2.09 (d, J=10.8 Hz, 1H), 2.73 (td, J=12, 3 Hz, 1H), 3.67 (t, J=6.0 Hz, 2H); ^{13}C NMR δ 20.0, 25.7, 28.7, 29.1, 30.2, 31.3, 32.6, 39.5, 47.7, 61.9, 70.5, 123.0; HRMS (ESI) calculated for ($M+Na^+$) $C_{12}H_{21}NO_2Na^+$: 234.1464, found: 234.1456.

4.3.4. (1S*,2R*,3S*)-2-(4-Chlorobutyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**17**)

Solid PPh_3 (360 mg, 1.38 mmol) and CCl_4 (636 mg, 4.14 mmol) were sequentially added to a room temperature CH_2Cl_2 solution (10 mL) of **i** (145 mg, 0.69 mmol). After stirring overnight, the solvent was removed and the crude product purified by radial chromatography (1:4, EtOAc/hexane) to afford 150 mg (96%) of **17** as an oil. IR (film) 3491, 2237 cm^{-1}; ^1H NMR δ 1.04 (br s, 1H), 1.28 (s, 3H), 1.33–1.84 (m, 12H), 2.11 (br d, J=11.2 Hz, 1H), 2.72 (td, J=12, 3 Hz, 1H), 3.67 (t, J=6.0 Hz, 2H); ^{13}C NMR δ 20.2, 26.9, 28.9, 29.1, 30.4, 31.4, 32.8, 39.8, 44.6, 47.7, 70.8, 122.8; MS 230 (M+H); HRMS (ESI) calculated for ($M+Na^+$) $C_{12}H_{20}ClNONa^+$: 252.1126, found: 252.1127.

4.3.5. (1R*,5S*,6S*)-5-Hydroxy-5-methylbicyclo[4.4.0]-decanecarbonitrile (**20**)

Employing the general deprotonation–cyclization procedure with *i*-PrMgCl (0.7 M, 0.2 mL) and chloronitrile **17** (16 mg, 0.07 $mmol^{-1}$) afforded 10.0 mg (74%) of the nitrile **19** spectrally identical to material previously synthesized.[63]

4.3.6. (1S*,6S*,5R*)-5-Hydroxy-5-methylbicyclo[4.4.0]-decanecarbonitrile (**27**)

Employing the general deprotonation–cyclization procedure with BuLi (0.55 mL, 1.1 mmol) and chloronitrile **17** (115 mg, 0.5 mmol) afforded 62 mg (64%) of the nitrile **19** spectrally identical to material previously synthesized.[63]

4.3.7. (1S*,2R*,3S*)-2-(5-Chloropentyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**33**)

A THF solution (1.3 mL) of MeMgCl (4.0 mmol) was added to a −20 °C THF solution (8 mL) of 3-oxo-cyclohex-1-enecarbonitrile (456.8 mg, 3.8 mmol). After 2 h at −20 °C, the THF solution was added to a 0 °C THF solution (5 mL) of 5-chloropentyl-4-enylmagnesium bromide. [5-Chloro-1-iodopentane (1.6 mL, 11.3 mmol) was slowly added to a 0 °C THF (5 mL) suspension of Mg (380.5 mg, 15.9 mmol), activated by addition of 1,2-dibromoethane (0.1 mL, 1.5 mmol) and allowed to react at 0 °C for 1 h.] Dry dioxane (1.5 mL) was added to the mixture and the solution was then allowed to warm to room temperature. After 24 h, saturated, aqueous, NH_4Cl (5 mL) was added, the mixture was extracted with EtOAc, and the combined organic extracts were then washed with brine, dried (Na_2SO_4), and concentrated. Purification of the resulting crude product by radial chromatography (10:90, EtOAc/hexanes) afforded 218.6 mg (24%) of **33** as an oil and 118.4 mg (13%) of **34** spectrally identical to material previously isolated.[64] For **33**: IR (film) 3482.2, 2236.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.38–1.82 (m, 15H), 2.07–2.08 (m, 1H), 2.69 (td, J=11.7, 3.4 Hz, 1H), 3.53 (t, J=6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 27.2, 29.0, 29.0, 29.5, 30.4, 31.4, 32.2, 39.7, 45.0, 47.7, 70.8, 122.9.; HRMS (ESI) m/z calculated for ($M+Na)^+$ ($C_{14}H_{22}ClNONa^+$): 278.1288, found: 278.1278.

4.3.8. (1S*,2R*,3S*)-3-Hydroxy-2-(5-iodopentyl)-3-methylcyclohexanecarbonitrile (**36**)

An acetone solution (10 mL) of chloro **33** (62.6 mg, 0.3 mmol) and NaI (771.2 mg, 5.1 mmol) was refluxed for 3 days. The mixture was allowed to cool to room temperature, washed with saturated $NaHCO_3$, and then extracted with ether. The combined organic extracts were dried (Na_2SO_4) and concentrated, and then the crude product was purified by radial chromatography (8:92, EtOAc/hexanes) to afford 70.5 mg (82%) of **36** as an oil. IR (film) 3482.0, 2237.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.32–1.78 (m, 13H), 1.86 (p, J=7.1 Hz, 2H), 2.09–2.11 (m, 1H), 2.70 (td, J=11.7, 3.7 Hz, 1H), 3.20 (t, J=7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.0, 20.2, 28.7, 29.2, 29.5, 30.5, 30.9, 31.5, 33.1, 39.8, 47.8, 70.9, 122.9; HRMS (ESI) m/z calculated for ($M+Na)^+$ ($C_{13}H_{22}INONa^+$): 358.0644, found: 358.0620.

4.3.9. (1S*,4aS*,9aR*)-1-Hydroxy-1-methyldecahydro-1H-benzo[7]annulene-4a-carbonitrile (**37**)

A THF solution (0.2 mL) of *i*-PrMgCl (0.3 mmol) was added, dropwise, to a room temperature THF (3 mL) solution of **36** (35.5 mg, 0.1 mmol). After refluxing for 6 h, the solution was allowed to cool and then saturated, aqueous, NH_4Cl (2 mL) was added. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude product was purified by radial chromatography (30:70, EtOAc/hexanes) to afford 19.8 mg (90%) of **37** as an oil. IR (film) 3419.8, 2227.7 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26–1.97 (m, 16H), 1.50 (s, 3H), 2.08–2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 23.0, 23.2, 29.0, 30.1, 34.7, 36.3, 40.1, 40.2, 51.7, 72.2, 127.0; HRMS (ESI) m/z calculated for ($M+Na)^+$ ($C_{13}H_{21}ONa^+$): 230.1521, found: 230.1509.

4.3.10. trans-8-Methyl-13-oxa-tricyclo[6.3.2.0^{1,7}]tridecan-12-one (**39**)

A hexanes solution (0.1 mL) of BuLi (0.3 mmol) was added, dropwise, to a −78 °C THF solution (2 mL) of **33** (28.7 mg, 0.1 mmol). After 2 h, the mixture was allowed to warm to room temperature and after 2 days, an aqueous, saturated, solution (2 mL) of NH_4Cl was added. The aqueous phase was extracted with EtOAc and then the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude product was purified by radial chromatography (10:90, EtOAc/hexanes) to afford 15.5 mg (78%) of **39** as an oil. IR (film) 1768.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21–1.26 (m, 2H), 1.35 (s, 3H), 1.53–1.98 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 24.8, 25.6, 27.1, 30.8, 32.3, 36.5, 38.6, 39.3, 56.1, 61.1, 87.7, 183.5; HRMS (ESI) m/z calculated for ($M+H)^+$ ($C_{13}H_{22}O_2^+$): 209.1542, found: 209.1554.

4.3.11. (1S*,2R*,3S*)-2-(But-3-enyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**40**)

A THF solution (1.4 mL) of MeMgCl (3.7 mmol) was added to a −20 °C THF solution (15 mL) of 3-oxo-cyclohex-1-enecarbonitrile (427.3 mg, 3.5 mmol). After 2 h at −20 °C, the intermediate magnesium alkoxide was added to a 0 °C THF solution (4 mL) of butenylmagnesium bromide. [4-Bromo-1-butene (0.5 mL, 5.3 mmol) was slowly added to a 0 °C THF (4 mL) suspension of Mg (156.8 mg, 6.5 mmol), activated by addition of 1,2-dibromoethane (0.1 mL, 0.7 mmol) and allowed to react at 0 °C for 1 h.] The resulting mixture was allowed to warm to room temperature and after

24 h, an aqueous, saturated solution (1.5 mL) of NH_4Cl was added. The aqueous phase was separated and then extracted with EtOAc and the combined organic extracts were then washed with brine, dried (Na_2SO_4), and concentrated. Purification of the resulting crude product by radial chromatography (20:80, EtOAc/hexanes) afforded 438.3 mg (64%) of **40** as an oil. IR (film) 3493.2, 2238.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.37–1.68 (m, 8H), 1.82–1.89 (m, 1H), 2.09–2.41 (m, 3H), 2.73 (td, J=11.7, 3.9 Hz, 1H), 4.99–5.09 (m, 2H), 5.79–5.87 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.3, 28.9, 29.2, 30.5, 31.5, 33.7, 39.8, 46.8, 70.9, 115.2, 122.8, 138.2; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{12}H_{19}NONa^+$): 216.1359, found: 216.1357.

4.3.12. (4aR*,5S*,8aS*)-8a-Methyl-4a,5,6,7,8,8a-hexahydro-4H-chromene-5-carbonitrile (**42**)

Gaseous ozone was passed through a −78 °C CH_2Cl_2 solution (25 mL) of **40** (397.9 mg, 2.1 mmol) until the distinctive blue color of excess ozone persisted. Ozonolysis was then terminated, the solution was allowed to warm to room temperature, and then neat Me_2S (4 mL) was added. After 16 h, the mixture was concentrated, the resulting oil was redissolved in EtOAc, and then washed with brine, dried ($NaSO_4$), and concentrated. The crude product was then purified by radial chromatography (8:92, EtOAc/hexanes) to provide 59.3 mg (16%) of **42** as a solid. IR (film) 3062.5, 2236.3, 1649.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.35 (td, J=11.8, 4.4 Hz, 1H), 1.56–1.75 (m, 3H), 1.85 (br d, J=11.7 Hz, 1H), 2.11–2.14 (m, 1H), 2.20 (br d, J=5.8 Hz, 1H), 2.38–2.46 (m, 1H), 2.58 (td, J=11.7, 2.9 Hz, 1H), 4.62 (t, J=5.9 Hz, 1H), 6.23–6.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 22.3, 24.3, 29.5, 29.6, 37.4, 39.2, 72.9, 96.3, 122.1, 141.2; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{11}H_{15}NONa^+$): 200.1051, found: 200.1035.

4.3.13. (1S*,2R*,3S*)-3-Hydroxy-2-(3-hydroxypropyl)-3-methylcyclohexanecarbonitrile (**ii**)

A *t*-BuOH solution (0.2 mL) of OsO_4 (0.01 mmol) was added to a THF, H_2O solution (3.0 mL) and (2.0 mL) of **40** (20.8 mg, 0.1 mmol). After 15 min, an aqueous solution (1.0 mL) of $NaIO_4$ (115.3 mg, 0.5 mmol) was added dropwise. After 3 h, aqueous, saturated, $Na_2S_2O_3$ solution (4.0 mL) was added, the aqueous phase was extracted with ether, and the combined organic extracts were dried ($NaSO_4$) and concentrated, affording 18.5 mg of the crude lactol **43**. This compound was directly reduced without further purification. The lactol **43** was dissolved in MeOH (2 mL) and then solid $NaBH_4$ (28.6 mg, mmol) was added portionwise. After 3 h, HCl 1.5 mL was added, the aqueous phase was extracted with ether, and the combined organic extracts were washed with brine, dried ($NaSO_4$), and concentrated. Purification of the resulting crude alcohol by radial chromatography (EtOA/hexanes, 25:85) afforded 10.3 mg (48%, two steps) of alcohol (**ii**) as an oil. IR (film) 3414.3, 2238.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.38–1.74 (m, 9H), 1.85–1.92 (m, 2H), 2.10–2.12 (m, 1H), 2.75 (td, J=11.7, 3.7 Hz, 1H), 3.69 (t, J=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 25.7, 29.1, 30.4, 31.4, 32.3, 39.8, 47.4, 62.7, 70.9, 123.1; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{11}H_{19}NO_2Na^+$): 220.1313, found: 220.1296.

4.3.14. (1S*,2R*,3S*)-2-(3-Chloropropyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**44**)

A THF solution (2.0 mL) of alcohol (**ii**) (60.2 mg, 0.3 mmol) was added dropwise to a THF solution (10.0 mL) of Ph_3P (383.3 mg, 1.5 mmol) and NCS (203.0 mg, 1.5 mmol). After 16 h, the solution cleared and then the mixture was diluted with ether. Saturated, aqueous, $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated, and then the crude product was purified by radial chromatography (15:85, EtOAc/hexanes) to afford 55 mg (75%) of **44** as an oil. IR (film) 3492.0, 2238.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.37–1.46 (m, 2H), 1.50–1.71 (m, 5H), 1.85–2.03 (m, 2H), 2.11–2.22 (m, 1H), 2.75 (td, J=11.7, 3.4 Hz, 1H), 3.54–3.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 27.0, 29.1, 30.5, 31.3, 32.2, 39.9, 45.2, 47.2, 70.9, 122.7; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{11}H_{18}ClNONa^+$): 238.0975, found: 238.0959.

4.3.15. (3aS*,7S*,7aR*)-7-Hydroxy-7-methyloctahydro-1H-indene-3a-carbonitrile (**46**)

A THF solution (0.1 mL) of *i*-PrMgCl (3.0 M, 0.2 mmol) was added, dropwise, to a room temperature THF (1 mL) solution of **44** (11.8 mg, 0.05 mmol). After stirring overnight, saturated, aqueous, NH_4Cl (2 mL) was added. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4), and concentrated. The resulting crude product was purified by radial chromatography (15:85, EtOAc/hexanes) to afford 9.8 mg (78%) of **46** as an oil. IR (film) 3454.2, 2232.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25–1.27 (m, 1H), 1.49 (s, 3H), 1.50–1.84 (m, 9H), 1.96–2.03 (m, 2H), 2.08–2.14 (m, 1H), 2.22–2.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.7, 25.2, 29.4, 30.3, 35.1, 38.2, 41.2, 54.0, 71.2, 125.7.

4.3.16. 4-((1R*,2S*,6S*)-6-Cyano-2-hydroxy-2-methylcyclohexyl)-butanoic acid (**49**)

An aqueous solution (1.5 mL) of Jones reagent [prepared by mixing 3 N H_2SO_4 (2 mL) with $NaCr_2O_3\cdot 2H_2O$ (2.0 g)] was added dropwise to a 0 °C acetone solution (6 mL) of **24** After 15 min, *i*-PrOH was added dropwise until the solution turned green. The mixture was extracted with EtOAc, the combined organic extracts were washed with H_2O, dried ($NaSO_4$), and then concentrated. Purification of the crude product by radial chromatography (60:40:3, EtOAc/hexanes/Et_3N), afforded 403.4 mg (94%) of acid (**49**) as an oil. IR (film) 3453.9, 2237.2, 1710.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.32–1.94 (m, 11H), 2.10 (d, J=12.7 Hz, 1H), 2.38 (br s, 2H), 2.74 (td, J=11.7, 3.6 Hz, 1H), 3.09–3.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 24.3, 28.9, 29.0, 30.4, 31.1, 39.8, 45.1, 47.6, 70.9, 122.8, 178.6.

4.3.17. Methyl 4-((1R*,2S*,6S*)-6-cyano-2-hydroxy-2-methylcyclohexyl)butanoate (**50**)

Neat MeI (0.3 mL, 4.7 mmol) was added to a room temperature DMF solution (10 mL) of acid (**49**) (70.5 mg, 0.3 mmol) and K_2CO_3 (216.5 mg, 1.6 mmol). After 16 h, the mixture was washed with brine and extracted with EtOAc. The combined organic extracts were washed with saturated NaCl, dried ($NaSO_4$), concentrated, and purified by radial chromatography (40:60, EtOAc/hexanes) to provide 74.9 mg (78%) of **50** as an oil. IR (film) 3504.3, 2236.8, 1736.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.33–1.98 (m, 10H), 2.06–2.10 (m, 2H), 2.35 (br t, J=6.6 Hz, 2H), 2.72 (td, J=11.8, 3.4 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 24.4, 28.9, 30.3, 31.1, 34.1, 39.7, 47.5, 51.5, 70.7, 122.7, 173.9.

4.3.18. (5aR*,6S*,9aS*)-9a-Methyl-2-oxodecahydrobenzo[b]-oxepine-6-carbonitrile (**52**)

A THF solution (0.5 mL) of *i*-PrMgBr (0.6 mmol) was added dropwise to a −78 °C THF solution (5 mL) of **52** (37.8 mg, 0.2 mmol). After 0.5 h, the solution was allowed to warm to room temperature and after a further 2 h, aqueous saturated NH_4Cl was added. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($NaSO_4$), and concentrated to afford the crude product. Purification by radial chromatography (30:70, EtOAc/hexanes) afforded 27.3 mg (83%) of **52** as a solid, whose structure was solved by X-ray crystallography. IR (film) 3498.1, 2236.8, 1713.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (td, J=13.7, 4.0 Hz, 1H), 1.59 (s, 3H), 1.65–1.90 (m, 7H), 1.97 (br t, J=12.9 Hz, 2H), 2.10–2.28 (m, 3H), 2.64 (td, J=14.8, 2.7 Hz, 1H),

2.79–2.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 20.0, 25.6, 27.2, 28.0, 30.2, 37.2, 40.9, 45.2, 80.4, 120.9, 173.9.

4.3.19. (1S*,2R*,3S*)-3-Hydroxy-3-methyl-2-(3-methylbut-3-enyl)cyclohexanecarbonitrile (**iii**)

A THF solution (2.2 mL) of MeMgCl (5.4 mmol) was added to a −20 °C THF solution (15 mL) of 3-oxo-cyclohex-1-enecarbonitrile (626.8 mg, 5.2 mmol). After 2 h at −20 °C, a THF solution (5 mL) of 3-methylbut-3-enylmagnesium iodide was added. [4-Iodo-2-methybut-1-ene (1.4 g, 7.3 mmol) was slowly added to a 0 °C THF (5 mL) suspension of Mg (273.5 mg, 11.4 mmol), activated by addition of 1,2-dibromoethane (0.2 mL, 2.1 mmol) and allowed to react at 0 °C for 1 h.] After 24 h, aqueous, saturated, NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (10:90, EtOAc/hexanes) afforded 770.4 mg (72%) of **iii** as an oil. IR (film) 3499.7, 3073.3, 2238.4, 1650.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.37–1.66 (m, 6H), 1.77 (s, 3H), 1.86–1.93 (m, 1H), 2.10–2.17 (m, 2H), 2.32–2.38 (m, 1H), 2.74 (td, J=11.7, 3.8 Hz, 1H), 4.74 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 22.2, 27.8, 28.9, 30.4, 31.3, 37.7, 39.6, 47.2, 70.7, 110.3, 122.8, 145.3; HRMS (ESI) m/z calculated for $(M+H)^+$ ($C_{13}H_{22}NO^+$): 208.1657, found: 208.1686.

4.3.20. (1S*,2R*,3S*)-3-Hydroxy-3-methyl-2-(4-methylpent-4-enyl)cyclohexanecarbonitrile (**iv**)

A THF solution (0.5 mL) of MeMgCl (1.4 mmol) was added to a −20 °C THF solution (6.0 mL) of 3-oxo-cyclohex-1-enecarbonitrile (**21**)[65] (159.4 mg, 1.3 mmol). After 2 h at −20 °C, the intermediate magnesium alkoxide was added to a 0 °C THF solution (6.0 mL) of 4-methylpent-4-enylmagnesium iodide. [5-Iodo-2-methylpent-1-ene (414.9 mg, 2.0 mmol) was slowly added to a 0 °C THF (6.0 mL) suspension of Mg (79.0 mg, 3.3 mmol), activated by addition of 1,2-dibromoethane (0.05 mL, 0.5 mmol) and allowed to react at 0 °C for 1 h.] The resulting mixture was allowed to warm to room temperature and after 24 h, an aqueous, saturated solution (1.5 mL) of NH_4Cl was added. The aqueous phase was separated, extracted with EtOAc, and the combined organic extracts were then washed with brine, dried (Na_2SO_4), and concentrated. Purification of the resulting crude product by radial chromatography (10:90, EtOAc/hexanes) afforded 149.2 mg (51%) of **iv** as an oil. IR (film) 3490.7, 3073.8, 2236.7, 1444.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.34–1.43 (m, 3H), 1.73 (s, 3H), 1.52–1.81 (m, 8H), 2.04–2.11 (m, 3H), 2.71 (td, J=11.7, 3.4 Hz, 1H), 4.70 (s, 1H), 4.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 22.3, 27.6, 29.1, 29.3, 30.5, 31.5, 38.1, 39.7, 47.8, 70.9, 110.2, 122.9, 145.3; HRMS (ESI) m/z calculated for $(M+H)^+$ ($C_{14}H_{24}NO^+$): 222.1813, found: 222.1794.

4.3.21. (1S*,2R*,3S*)-2-(3-(Chloromethyl)but-3-enyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**53a**)

An aqueous solution (0.9 mL) of NaOCl (1.3 mmol) was added, dropwise, to a room temperature H_2O/CH_2Cl_2 (1:1, 7.0 mL) biphasic mixture containing **iii** (146.2 mg, 0.7 mmol) and $CeCl_3\cdot 7H_2O$ (494.7 mg, 1.3 mmol). After 50 min, saturated, aqueous, $Na_2S_2O_3$ (3 mL) was added and the aqueous phase was then extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (20:80, EtOAc/hexanes) afforded 141.6 mg (83%) of **53a** as an oil. IR (film) 3484.5, 2237.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.39–1.66 (m, 6H), 1.93–2.01 (m, 1H), 2.10–2.13 (m, 1H), 2.29–2.35 (m, 3H), 2.46–2.52 (m, 1H), 2.75 (td, J=11.7, 3.6 Hz, 1H), 4.05–4.12 (m, 2H), 5.04 (s, 1H), 5.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 27.8, 29.2, 30.4, 31.3, 32.9, 39.9, 47.3, 48.2, 70.9, 114.9, 122.7, 144.8; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{14}H_{23}NaNOCl^+$): 264.1131, found: 264.1136.

4.3.22. (1S*,2R*,3S*)-2-(4-(Chloromethyl)pent-4-enyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**53b**)

An aqueous solution (0.4 mL) of NaOCl (0.6 mmol) was added, dropwise, to a room temperature H_2O/CH_2Cl_2 (1:1, 6 mL) biphasic mixture containing **iv** (68.1 mg, 0.3 mmol) and $CeCl_3\cdot 7H_2O$ (218.1 mg, 0.6 mmol). After 50 min, saturated, aqueous, $Na_2S_2O_3$ (3 mL) was added and the aqueous phase was then extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (8:96 to 20:80, EtOAc/hexanes) afforded 131.7 mg (60%) of **53b** as an oil. IR (film) 3491.5, 3082.4, 2237.8, 1642.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.36–1.45 (m, 3H), 1.54–1.88 (m, 7H), 2.08–2.13 (m, 1H), 2.20–2.26 (m, 2H), 2.72 (td, J=11.7, 3.4 Hz, 1H), 4.06 (d, J=3.9 Hz, 2H), 5.00 (s, 1H), 5.15 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 24.1, 27.3, 29.2, 29.3, 30.5, 31.5, 33.4, 39.8, 47.8, 48.3, 70.9, 114.8, 122.9, 144.6; HRMS (ESI) m/z calculated for $(M+H)^+$ ($C_{14}H_{22}NOCl^+$): 256.1424, found: 256.1411.

4.3.23. (1S*,4aR*,8aR*)-1-Hydroxy-1-methyl-6-methylenedecahydronaphthalene-4a-carbonitrile (**54a**)

A THF solution (0.3 mL) of *i*-PrMgCl (0.6 mmol) was added dropwise to a room temperature THF solution (12 mL) of **53a** (51.8 mg, 0.2 mmol). After 1.5 h, saturated, aqueous, NH_4Cl (5 mL) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (60:40 to 100:0, CH_2Cl_2/hexanes) afforded 24.8 mg (57%) of **54a** as a solid, whose structure was unequivocally determined by X-ray diffraction. IR (film) 3481.2, 2233.4, 1652.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.55–1.88 (m, 9H), 2.03–2.09 (m, 2H), 2.37 (br d, J=13.2 Hz, 1H), 2.49 (p, J=5.9 Hz, 1H), 2.78 (br d, J=13.2 Hz, 1H), 4.76 (s, 1H), 4.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 24.1, 30.2, 32.2, 37.2, 39.6, 43.0, 46.4, 72.4, 110.9, 125.6, 143.3; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{13}H_{19}NO^+$): 228.1364, found: 228.1375.

4.3.24. (1S*,4aR*,9aR*)-1-Hydroxy-1-methyl-6-methylenedecahydro-1H-benzo[7]annulene-4a-carbonitrile (**54b**)

A THF solution (0.05 mL) of *i*-PrMgCl (3.0 M, 0.1 mmol) was added dropwise to a room temperature THF solution (1 mL) of **53b** (8.1 mg, 0.03 mmol). After 4 h, saturated, aqueous, NH_4Cl (1 mL) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (10:90 to 30:70, EtOAc/hexanes) afforded 5.0 mg (72%) of **54b** as an oil. IR (film) 3477.8, 3074.1, 2230.7, 1643.2 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.28 (m, 2H), 1.52 (s, 3H), 1.40–2.00 (m, 9H), 2.08–2.23 (m, 2H), 2.43–2.48 (m, 1H), 2.51 (d, J=13.6 Hz, 1H), 2.61 (d, J=13.6 Hz, 1H), 4.97 (s, 1H), 5.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 22.9, 27.9, 30.0, 34.3, 36.6, 37.7, 40.6, 45.9, 51.5, 72.3, 115.0, 126.2, 143.9; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{14}H_{21}ONNa^+$): 242.1521, found: 242.1948.

4.3.25. (1S*,4aS*,8aR*)-1-Hydroxy-1-methyl-6-methylenedecahydro-naphthalene-4a-carbonitrile (**55a**)

A hexanes solution (0.1 mL) of BuLi (0.2 mmol) was added, dropwise, to a −78 °C THF solution (2 mL) of **53a** (24.8 mg, 0.1 mmol). After 2 h, the mixture was allowed to warm to room temperature and after a further 1.5 h, a THF solution (1 mL) of $TsOH\cdot H_2O$ (58.5 mg, 0.3 mmol) was added. After 15 min, brine (2 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude product that was purified by radial chromatography (10:90, EtOAc/hexanes) to afford 15.9 mg (76%) of **55a** as an oil. IR (film) 3477.7, 3074.3, 2231.4, 1649.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.23–1.33 (m, 1H), 1.37 (td,

J=12.5, 3.7 Hz, 2H), 1.45 (td, J=13.7, 4.3 Hz, 2H), 1.62–1.69 (m, 3H), 1.83 (br d, J=13.6 Hz, 1H), 2.02–2.08 (m, 3H), 2.46–2.53 (m, 2H), 4.85 (s, 1H), 4.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 24.2, 29.0, 34.2, 37.5, 40.2, 41.0, 47.1, 51.4, 70.3, 111.9, 122.7, 142.6; HRMS (ESI) m/z calculated for $(M+H)^+$ ($C_{13}H_{20}NO^+$): 206.1500, found: 280.1490.

4.3.26. *(1S*,4aS*,9aR*)-1-Hydroxy-1-methyl-6-methylenedecahydro-1H-benzo[7]annulene-4a-carbonitrile (**55b**)*

A hexanes solution (0.05 mL) of BuLi (0.2 mmol) was added, dropwise, to a −78 °C THF solution (2 mL) of **53b** (18.5 mg, 0.1 mmol). After 2 h, the mixture was allowed to warm to room temperature and after a further 1.5 h, a THF solution (1 mL) of $TsOH\cdot H_2O$ (58.5 mg, 0.3 mmol) was added. After 15 min, brine (2 mL) was added and the mixture was then extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude product that was purified by radial chromatography (8:92, EtOAc/hexanes) to afford 11.4 mg (72%) of **55b** as an oil. IR (film) 3491.9, 3073.8, 2232.4, 1641.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.20–1.68 (m, 4H), 1.77–2.13 (m, 5H), 2.30 (d, J=13.7 Hz, 1H), 2.41 (t, J=6.8 Hz, 1H), 2.53 (d, J=13.7 Hz, 1H), 4.96 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 25.7, 25.9, 29.4, 34.7, 38.9, 40.0, 41.8, 49.0, 54.0, 71.7, 116.0, 123.5, 143.7; HRMS (ESI) m/z calculated for $(M+K)^+$ ($C_{14}H_{21}NOK^+$): 258.1260, found: 258.1279.

4.3.27. *(1S*,2R*,3S*)-3-Hydroxy-3-methyl-2-(4-methylpent-3-enyl)cyclohexanecarbonitrile (**56**)*

A THF solution (0.3 mL) of MeMgCl (0.8 mmol) was added to a −20 °C THF solution (2.5 mL) of 3-oxo-cyclohex-1-enecarbonitrile (**21**)[65] (87.6 mg, 0.7 mmol). After 2 h at −20 °C, a THF solution (2.5 mL) of 4-methylpent-3-enylmagnesium bromide was added. [5-Bromo-2-methyl-2-pentene (0.2 mL, 1.3 mmol) was slowly added to a 0 °C THF (2.5 mL) suspension of Mg (46.9 mg, 2.0 mmol), activated by addition of 1,2-dibromoethane (0.03 mL, 0.3 mmol) and allowed to react at 0 °C for 1 h.] After 24 h, saturated, aqueous, NH_4Cl (2 mL) was added, the mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the resulting crude by radial chromatography (10:90, EtOAc/hexanes) afforded 102.9 mg (64%) of **56** as an oil. IR (film) 3492.3, 2237.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.32–1.42 (m, 4H), 1.52–1.57 (m, 3H), 1.63 (s, 3H), 1.69 (s, 3H), 1.73–1.80 (m, 2H), 2.07–2.09 (m, 2H), 2.27 (m, 1H), 2.70 (td, J=11.7, 3.4 Hz, 1H), 5.14 (br t, J=1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 25.6, 28.0, 29.0, 29.0, 29.7, 30.5, 31.5, 39.6, 47.1, 70.8, 122.9, 123.9, 132.3; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{14}H_{23}NONa^+$): 244.1677, found: 244.1659.

4.3.28. *(1S*,2R*,3S*)-3-Hydroxy-2-((E)-5-hydroxy-4-methylpent-3-enyl)-3-methylcyclohexanecarbonitrile (**v**)*

A CH_2Cl_2 solution (0.5 mL) of **56** (39.4 mg, 0.2 mmol) and t-BuOOH (0.1 mL, 0.4 mmol) was added to a 0 °C CH_2Cl_2 solution (0.5 mL) of SeO_2 (9.9 mg, 0.1 mmol). After 3.5 h, the mixture was diluted with ether (1.5 mL), aqueous, saturated, $NaHCO_3$ was added, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated, and the resulting crude product was then purified by radial chromatography (40:60 to 55:45, EtOAc/hexanes) to afford 23.6 mg (56%) of alcohol (**v**) as an oil. IR (film) 3425.4, 2238.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.32–1.63 (m, 9H), 1.67 (s, 3H), 1.80–1.87 (m, 1H), 2.07 (br d, J=10.8 Hz, 1H), 2.16 (sextet, J=7.3 Hz, 1H), 2.26–2.34 (m, 1H), 2.69 (td, J=11.7, 3.2 Hz, 1H), 3.97 (s, 2H), 5.44 (t, J=7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 20.1, 27.6, 28.9, 29.4, 30.4, 31.6, 39.7, 47.1, 68.5, 70.7, 123.1, 125.1, 135.5.

4.3.29. *(1S*,2R*,3S*)-2-((E)-5-Chloro-4-methylpent-3-enyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**57**)*

A THF solution (1.0 mL) of alcohol (**v**) (72.4 mg, 0.3 mmol) was added dropwise to a THF solution (2.5 mL) of Ph_3P (100.2 mg, 0.4 mmol) and NCS (51.0 mg, 0.4 mmol). After approximately 1.5 h, the solution cleared and then the mixture was diluted with ether. Saturated, aqueous, $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated, and then the crude product was purified by radial chromatography (15:85, EtOAc/hexanes) to afford 67.1 mg (86%) of **57** as an oil. IR (film) 3491.3, 2239.2 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.31–1.67 (m, 8H), 1.76 (s, 3H), 1.80–1.85 (m, 1H), 2.07 (br d, J=13.6 Hz, 1H), 2.13–2.21 (m, 1H), 2.31–2.38 (m, 1H), 2.71 (td, J=11.7, 3.4 Hz, 1H), 4.01 (s, 2H), 5.55 (t, J=7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.1, 27.9, 29.0, 29.0, 30.4, 31.4, 39.7, 47.0, 52.2, 70.7, 122.8, 130.0, 132.4; HRMS (ESI) m/z calculated for $(M+H)^+$ ($C_{13}H_{20}NONa^+$): 264.1131, found: 264.1136.

4.3.30. *(3S*,3aR*,7S*,7aR*)-7-Hydroxy-7-methyl-3-(prop-1-en-2-yl)octahydro-1H-indene-3a-carbonitrile (**59**) and (3R*,3aR*,7S*,7aR*)-7-hydroxy-7-methyl-3-(prop-1-en-2-yl)-octahydro-1H-indene-3a-carbonitrile (**60**)*

A THF solution (0.09 mL) of i-PrMgCl (1.6 M) was added, dropwise, to a room temperature THF solution (1.5 mL) of **57** (12.2 mg, 0.048 mmol). After 1.5 h, saturated, aqueous, NH_4Cl (2 mL) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (10:90, EtOAc/hexanes) afforded 2.5 mg (22%) of **59** as a solid, whose structure was unequivocally determined by X-ray diffraction and 5.6 mg (48%) of **60** as an oil. For **59** as an oil: IR (film) 3475.5, 3076.0, 2229.4, 1641.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.57–2.09 (m, 14H), 2.30 (t, J=7.7 Hz, 1H), 2.85 (t, J=8.1 Hz, 1H), 4.88–4.88 (m, 1H), 4.98 (p, J=1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 21.8, 24.4, 27.5, 30.0, 31.4, 36.2, 46.2, 53.2, 53.9, 70.9, 113.9, 124.5, 144.6. For **60** as a solid: IR (film) 3486.1, 3088.2, 2231.8, 1642.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.58–1.89 (m, 10H), 1.93 (s, 3H), 1.95–1.98 (m, 1H), 2.43 (t, J=10.0 Hz, 1H), 2.93 (t, J=10.0 Hz, 1H), 4.90 (s, 1H), 5.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 23.3, 23.7, 24.1, 25.4, 29.1, 34.4, 43.7, 55.2, 55.5, 71.5, 113.8, 125.4, 141.7; HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{14}H_{21}NONa^+$): 242.1521, found: 242.1499. *Cyclization of **57** with BuLi*. A hexanes solution (0.05 mL) of BuLi (2.5 M) was added, dropwise, to a −78 °C THF solution (2.5 mL) of **57** (14.7 mg, 0.056 mmol). After 1.5 h, the mixture was allowed to warm to room temperature and after a further 1.5 h, a THF solution (1 mL) of $TsOH\cdot H_2O$ (32.8 mg) was added. After 15 min, brine (2 mL) was added and the mixture was then extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude product that was purified by radial chromatography (12:88 to 1:4 to 3:7, EtOAc/hexanes) to afford 4.6 mg (37%) of **59** as an oil and 2.8 mg of **60** as a crystalline solid. *Cyclization of **63** with i-PrMgCl*. A THF solution (0.15 mL) of i-PrMgCl (0.3 mmol) was added, dropwise, to a room temperature THF solution (2 mL) of **63** (25.4 mg, 0.1 mmol). After 1.5 h, saturated, aqueous, NH_4Cl (2 mL) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (5:95 to 20:80, CH_2Cl_2/hexanes) afforded 7.4 mg (34%) of **60** as a solid and 8 mg (37%) of **59** as an oil.

4.3.31. *7a-Cyano-octahydro-4-methyl-1-(prop-1-en-2-yl)-1-1H-inden-4-yl 4-nitrobenzoate (**vi**)*

A hexanes solution (0.03 mL) of BuLi (0.08 mmol) was added, dropwise, to a −78 °C THF solution (0.75 mL) of **71** (17.5 mg, 0.08 mmol). After 10 min, a THF solution (0.75 mL) of PNBCl

(16.3 mg, 0.09 mmol) was added dropwise. The mixture was refluxed for 6 h, cooled to room temperature, and then saturated aqueous NH_4Cl (2 mL) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (8:92 to 40:60, EtOAc/hexanes) afforded 14.2 mg (70%) of **vi** as a solid (mp 187–188 °C), whose structure was unequivocally determined by X-ray diffraction. IR (film) 2233.1, 1713.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.61–1.67 (m, 1H), 1.92 (s, 3H), 1.94 (s, 3H), 1.74–2.14 (m, 9H), 2.72–2.75 (m, 1H), 3.16 (t, J=9.1 Hz, 1H), 4.88 (s, 1H), 5.00 (s, 1H), 8.12 (d, J=8.8 Hz, 2H), 8.28 (d, J=8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 21.9, 24.7, 25.8, 27.2, 32.2, 32.8, 46.0, 51.6, 56.8, 114.3, 123.4, 123.5, 130.5, 136.7, 145.1, 150.4, 163.3.

4.3.32. (1S,2R*,3S*)-2-(3-Chloro-4-methylpent-4-enyl)-3-hydroxy-3-methylcyclohexanecarbonitrile (**63**)*

An aqueous solution (0.2 mL) of NaOCl (0.3 mmol) was added, dropwise, to a room temperature H_2O/CH_2Cl_2 (1:1, 4.0 mL) biphasic mixture containing **56** (40.0 mg, 0.2 mmol) and $CeCl_3\cdot 7H_2O$ (123.3 mg, 0.3 mmol). After 50 min, saturated, aqueous, $Na_2S_2O_3$ (1 mL) was added and the aqueous phase was then extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by radial chromatography (15:85, EtOAc/hexanes) afforded 61.3 mg (75%) of a 1:1 mixture of diastereomeric **63** as an oil. IR (film) 3470.2, 3081.1, 2238.2, 1643.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.36–1.95 (m, 7H), 1.81 (s, 3H), and 1.82 (s, 3H), 2.07–2.28 (m, 2H), 2.68–2.76 (m, 1H), 4.34 (t, J=7.2 Hz, 1H), and 4.35 (t, J=7.2 Hz, 1H), 4.89 (s, 1H), and 4.90 (s, 1H), 5.02 (s, 1H) and 5.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, (17.1), 20.1, (20.1), 26.6, (27.2), 28.9, (29.0), 30.3, (31.3), 35.3, (36.5), 39.7, (39.9), 47.0, (47.4), 66.8, (66.9), 70.7, (70.8), 114.4, (114.4), 122.5, (122.7), 128.1, (128.3), 143.8, (143.9); HRMS (ESI) m/z calculated for $(M+Na)^+$ ($C_{14}H_{22}NOClNa^+$): 278.1282, found: 278.1299.

4.3.33. (3S,3aS*,7S*,7aR*)-7-Hydroxy-7-methyl-3-(prop-1-en-2-yl)octahydro-1H-indene-3a-carbonitrile (**68**)*

A hexanes solution (0.1 mL) of BuLi (0.3 mmol) was added, dropwise, to a −78 °C THF solution (2 mL) of **63** (25.2 mg, 0.1 mmol). After 2 h, saturated, aqueous, NH_4Cl was added. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude product that was purified by radial chromatography (8:92 to 40:60, EtOAc/hexanes) to afford 11.6 mg (54%) of **59** spectrally identical to material isolated previously and 7.4 mg (34%) of **68** as an oil. IR (film) 3476.0, 3077.4, 2228.2, 1641.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, J=2.0 Hz, 3H), 1.26–1.33 (m, 2H), 1.58 (d, J=2.0 Hz, 1H), 1.68–2.02 (m, 7H), 1.78 (s, 3H), 2.09–2.12 (m, 1H), 2.26–2.30 (m, 1H), 2.98 (d, J=8.7 Hz, 1H), 4.69 (s, 1H), 5.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 21.7, 25.3, 27.0, 29.5, 31.9, 39.2, 46.6, 51.5, 53.8, 70.6, 113.7, 125.3, 146.0.

*4.3.34. 7a-Cyano-octahydro-4-methyl-1-(prop-1-en-2-yl)-1H-inden-4-yl 4-nitrobenzoate (**66**)*

A hexanes solution (0.04 mL) of BuLi (0.1 mmol) was added, dropwise, to a −78 °C THF solution (1.0 mL) of **68** (21.2 mg, 0.1 mmol). After 10 min, a THF solution (1.0 mL) of PNBCl (19.8 mg, 0.1 mmol) was added dropwise. The mixture was refluxed for 5 h, cooled to room temperature, and then saturated aqueous NH_4Cl (2 mL) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Purification by radial chromatography (8:92, EtOAc/hexanes) afforded 21.8 mg (61%) of **66** as a solid (mp 103–105 °C), whose structure was unequivocally determined by X-ray diffraction. IR (film) 2227.9, 1714.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84–0.89 (m, 1H), 1.24–1.35 (m, 3H), 1.69 (s, 3H), 1.75–1.93 (m, 3H), 1.82 (s, 3H), 1.98–2.17 (m, 2H), 2.36–2.44 (m, 1H), 3.07–3.13 (m, 2H), 4.73 (s, 1H), 5.07 (s, 1H), 8.28 (d, J=8.8 Hz, 2H), 8.39 (d, J=8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 21.9, 24.7, 25.4, 26.9, 31.9, 33.8, 46.4, 53.2, 53.9, 83.1, 114.0, 123.3, 125.3, 131.3, 136.5, 145.9, 150.4, 164.0.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.110.

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