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A modified Robinson annulation process to α,α-disubstituted-β,γ-unsaturated cyclohexanone system. Application to the total synthesis of nanaimoal

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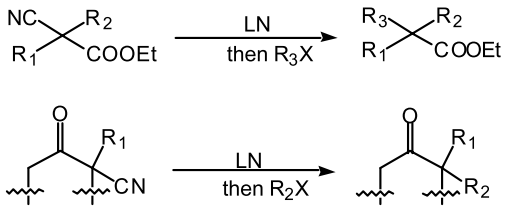
Abstract—4-Cyano-2-cyclohexenones were found to be susceptible to reductive alkylation reactions, giving the corresponding 2,2-disubstituted-3-cyclohexenone derivatives in a completely regioselective manner. This newly developed methodology has been successfully applied towards the total synthesis, in racemic form, of the marine natural product nanaimoal.

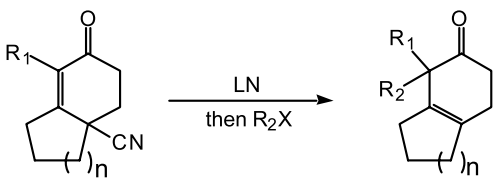
1. Introduction

Since the landmark report by Robinson[1] followed by a demonstration of its utility in organic synthesis by Woodward,[2] the Robinson annulation process has attracted extensive attention and continues to occupy a pivotal role in the construction of polycyclic systems.[3] In this report we wish to detail our investigation into a modified Robinson annulation process towards the construction of α,α-disubstituted-β,γ-unsaturated cyclohexanone systems,[4] inherently unattainable via traditional Robinson annulation methodologies, starting with readily available α-cyano activated cycloalkanone derivatives.

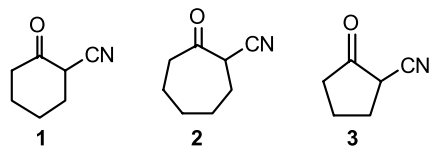
The impetus for our project was the discovery that α-cyano esters[5] and ketones[6] were easily and expeditiously converted, in a completely regioselective manner, to the corresponding α-alkylated carbonyl compounds via sequential treatement with lithium naphthalenide (LN) and an alkylating agent (Scheme 1). Extension of this reductive alkylation process to vinylogous α-cyano cycloalkanones then unveiled a highly effective process for an efficient and completely regioselective alkylation of the α-carbon with concomitant transposition of the double bond to the β,γ-position (Scheme 2).



Scheme 1.



Scheme 2.



2. Results and discussion

The starting α-cyano cycloalkanones **1**–**3** used for the present study were readily prepared by Thorpe–Ziegler

Keywords: ketones; cyano compounds; reduction; alkylation.
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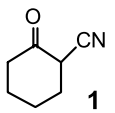
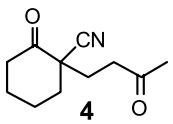
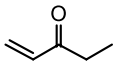
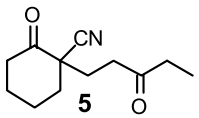
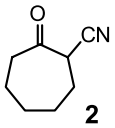
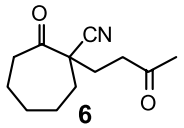
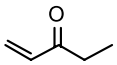
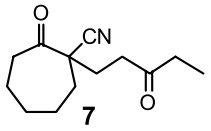
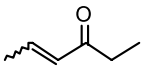
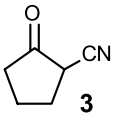
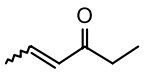
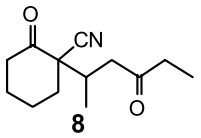
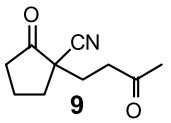
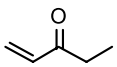
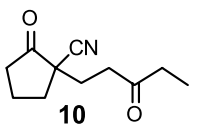
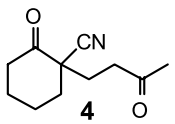
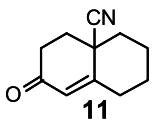
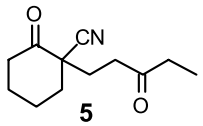
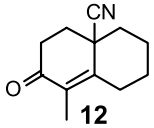
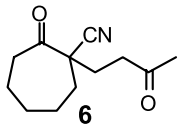
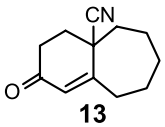
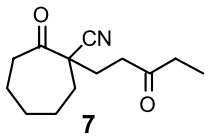
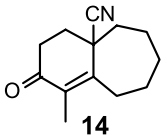
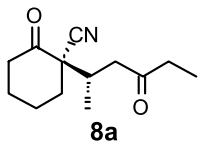
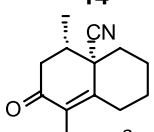
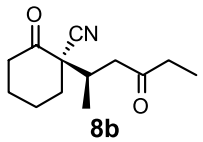
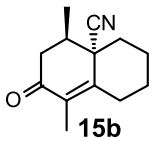
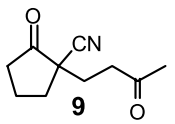
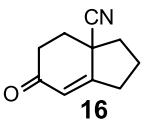
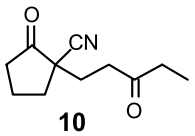
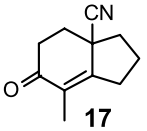
Table 1. Michael addition of 2-cyanocycloalkanones **1**–**3** to methyl vinyl ketone and derivatives

Entry	Starting ketone	Michael acceptor	Method[a]	Product	Yield (%)
1	 **1**		A	 **4**	90
2	**1**		A	 **5**	90
3	 **2**		A	 **6**	89
4	**2**		A	 **7**	87
5	**1**		A	[b]	–
6	 **3**		A	[c]	–
7	**1**		B (reflux, 25 h)	 **8**	74[d]
8	**3**		B (rt, 25 h)	 **9**	89
9	**3**		B (rt, 16 h)	 **10**	87

[a] Method A: Al_2O_3, rt, 20 min; Method B: DABCO, DME, 0°C, 30 min, then Michael acceptor, reflux or rt.
[b] No reaction was observed.
[c] Polymerization of the starting cyano ketone **3** occurred extensively.
[d] The reaction gave a 1:1 mixture of chromatographically separable diastereomers **8a** and **8b**.

condensation[7] of the corresponding alkanedicarbonitriles, using sodium *N*-methylanilide (generated in situ from sodium hydride and *N*-methylaniline) as a base,[8] followed by acid hydrolysis of the resulting enamine. 2-Cyanocycloalkanones **1**–**3** were found to undergo Robinson annulation readily. However, the vinylogous α-cyano ketone products were found to be most effectively achieved by performing the Michael addition and the aldol condensation reactions separately. The Michael addition process, greatly facilitated by the presence of the activating nitrile functionality, was achieved using one of two methods (Table 1). The first method (Method A) involved the sequential addition of the Michael donor and acceptor onto activated (100°C, 4 h) aluminum oxide.[9] This process gave the Michael adducts **4**–**7** rapidly (ca. 20 min), cleanly, and in high yields (entries 1–4). However, this method was found to be ineffective when 2-cyanocyclopentanone (**3**) or β-substituted methyl vinyl ketone derivatives were employed (entries 5 and 6). As a result, a more encompassing procedure was enlisted (Method B). Thus, using 1,2-dimethoxyethane (DME) as solvent, either at room temperature or under refluxing conditions, and 1,4-diaza[2.2.2]bicyclooctane (DABCO)[10] as base, the previously inert 2-cyanocyclopentanone (**3**) and β-substituted methyl vinyl ketone derivatives individually

Table 2. Aldol condensation of diketones **4**–**10** using *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water

Entry	Diketone	Time (h)	Product	Yield (%)
1	 **4**	22	 **11**	95
2	 **5**	22	 **12**	99
3	 **6**	22	 **13**	95
4	 **7**	22	 **14**	95
5	 **8a**	22	 **15a**[a]	99
6	 **8b**	22	 **15b**	99
7	 **9**	22	 **16**	85
8	 **10**	22	 **17**	83

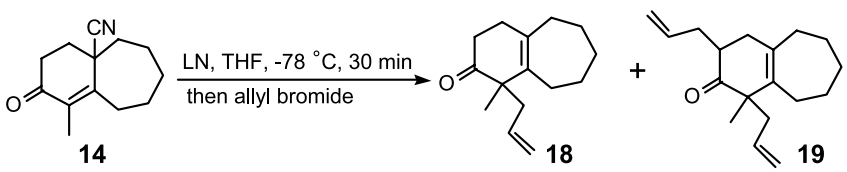
[a] The structure of this compound was confirmed by a single crystal X-ray crystallographic analysis. By inference, the relative stereochemistry of the closely related compounds **8a**, **8b**, and **15b** was deduced.

gave the desired Michael adducts **8**–**10** (entries 7–9) in good yields. With the Michael adducts **4**–**10** in hand, their respective aldol condensation reaction was achieved by treatment with *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water, giving the desired bicyclic enones **11**–**17** in good yields (Table 2).

Enone **14** was chosen as the model compound for our initial studies of the reductive alkylation process, and the results are tabulated in Table 3. Following the established precedents from our laboratories, we began the investigation using 4 equiv. of LN[11] followed by the addition of 4 equiv. of allyl bromide. The reduction process was performed at −78°C, while the mixture was warmed to room temperature after the addition of allyl bromide. As predicted, the reductive alkylation process did indeed give the α-alkylated product **18** with concomitant transposition of the double bond to the ring fusion position. However, α,α′-dialkylated product **19** was also produced in significant proportions (entry 1). A reduction in the amount of both LN and allyl bromide did not yield any significant improvement in selectivity (entry 2). Obviously a change in strategy was required.

The procedure followed for the above stated entries called for the addition of the starting enone to the LN solution (Method A). An obvious modification was to add the LN solution to that of the starting enone. This has the advantage of ensuring that, assuming the reduction process was instantaneous, the bare minimum of reducing agent was introduced simply by observing a retention of the deep blue color of the LN solution on the reaction mixture. As such, following this titrative method (Method B), an ever so slight improvement in selectivity for ketone **18** was achieved (entry 3). We next attempted increasing the amount of allyl bromide introduced while maintaining the reaction temperature at −78°C. As shown in Entry 4, the inclusion of this modification allowed for a completely chemoselective reaction, giving the α-alkylated product **18** in high yield with no indication of by-product **19**. Using this improved reductive alkylation procedure, enones **12**, **14**, **15a**, **15b**, and **17** were successfully α-alkylated to give ketones **18**, **20**–**25** in good yields (Table 4, entries 1–8). Table 4 also includes a case in which the ensuing reductive decyanation product

Table 3. Optimization study for the reductive alkylation process

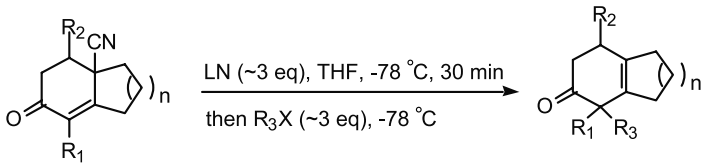


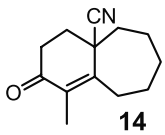
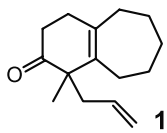
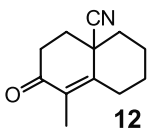
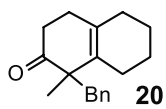
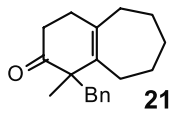
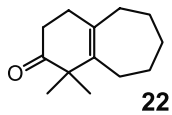
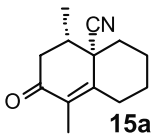
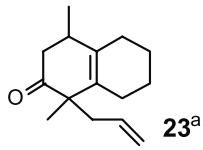
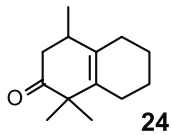
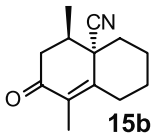
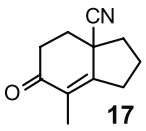
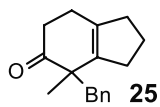
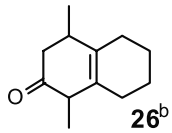
Entry	Method[a]	LN (equiv.)	Allyl bromide (equiv.)	Temperature (°C)	Time (h)	Yield (%)	
						18	**19**
1	A	4	4	rt	14	43	32
2	A	2.5	1.2	rt	15	44	33
3	B	3[b]	1.2	rt	17	46	27
4	B	3[b]	3	−78	20	87	0

[a] Method A: A solution of enone **14** in THF is introduced into the LN solution at −78°C. Method B: The LN solution is introduced dropwise into a solution of enone **14** in THF at −78°C.

[b] The LN equivalents for Method B were calculated from the amount of LN solution added, given the known concentration of the stock LN solution.

Table 4. Reductive alkylation of α-alkylated-γ-cyano-α,β-unsaturated cyclohexanones



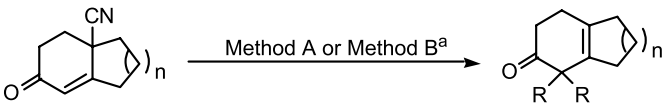
Entry	Enone	Alkylating Agent	Time	Product	Yield (%)
1	 **14**	Allyl bromide	20 h	 **18**	87
2	 **12**	Benzyl bromide	20 h	 **20**	99
3	**14**	Benzyl bromide	24 h	 **21**	99
4	**14**	Methyl iodide	24 h	 **22**	93
5	 **15a**	Allyl bromide	19 h	 **23**[a]	82
6	**15a**	Methyl iodide	19 h	 **24**	81
7	 **15b**	Allyl bromide	22 h	**23**[a]	76
8	 **17**	Benzyl bromide	22 h	 **25**	82
9	**15b**	NH_4Cl	5 min	 **26**[b]	85

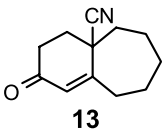
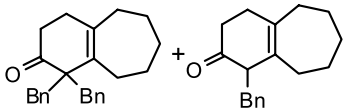
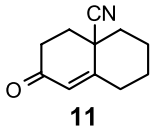
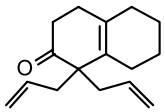
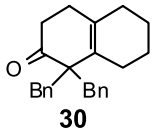
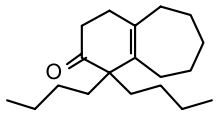
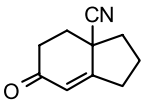
[a] An inseparable diastereomeric mixture was obtained, the ratio of which was determined by ^{1}H NMR to be ca. 9:1.
[b] A mixture of two inseparable diastereomers was produced in a ratio of ca. 1:1 as shown by the ^{1}H NMR spectrum.

was trapped with a proton source (entry 9). In this way, compound **26**, an α-monosubstituted-β,γ-unsaturated cycloalkanone, was produced from compound **15b** in high yield.

We next turned our attention to the reductive alkylation of α-unsubstituted-α,β-unsaturated ketones **11**, **13**, and **16**, the results of which are presented in Table 5. Using the optimized procedure detailed above, the reductive alkylation of enone **13** was found to be lacking in selectivity, giving both α,α-dialkylated ketone **27** and α-monoalkylated ketone **28** in poor yield (entry 1). Other reaction conditions

Table 5. Reductive alkylation of α-unalkylated-γ-cyano-α,β-unsaturated cyclohexanones



Entry	Enone	Alkylating Agent	Method[a]	Time (h)	Product(s)	Yield (%)
1	 **13**	Benzyl bromide	A	23	 **27** **28**	40[b]
2	**13**	Benzyl bromide	B	21	**27**	67
3	 **11**	Allyl bromide	B	24	 **29**	51
4	**11**	Benzyl bromide	B	21	 **30**	81
5	**13**	*n*-Butyl iodide	B	19	 **31**	63
6	 **16**	Benzyl bromide	B	24	 **32**	62

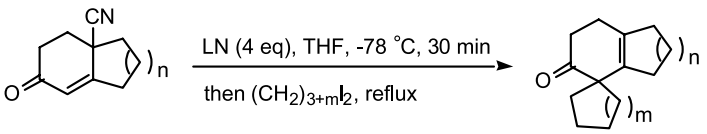
[a] Method A: LN (~3 equiv.), THF, −78°C, 30 min, then RX (4 equiv.), −78°C; Method B: LN (4 equiv.), THF, −78°C, 30 min, then RX (4 equiv.), rt.
[b] Ratio of **27/28**=2:3.

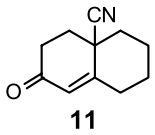
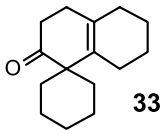
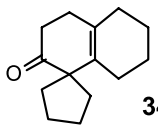
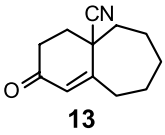
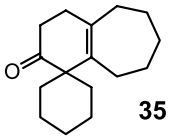
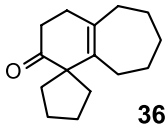
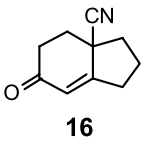
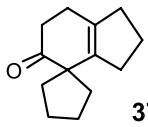
were attempted to improve the monoalkylation, including adjustment of reaction temperature and the amount of alkylating agent, but the formation of the dialkylated product could not be suppressed to a significant extent. It appears that the α-monoalkylated compounds such as **26** are best prepared via the kinetic protonation process illustrated in Table 4, entry 9. On the other hand, taking advantage of the observed ease of dialkylation, the following simple procedure could be effectively applied to facilitate the introduction of two identical substituents. Sequential treatment of enone **13** with 4 equivalents each of LN (−78°C) and benzyl bromide (rt) gave the α,α-dibenzylated ketone **27** as the sole product in good yield (Table 5, entry 2). This method of generating α,α-dialkylated-β,γ-unsaturated cyclohexanone derivatives from the parent γ-cyano-α,β-unsaturated precursors was found to be general. Under similar conditions, ketones **29**–**32** were produced in synthetically useful yields (entries 3–6).

An extrapolation of the above results obtained for dialkylation suggests that spirocyclic compounds may be procurable via reductive alkylation involving an appropriate dihaloalkane as the trapping agent. This reductive spiro-annulation process was shown experimentally to be feasible. The formation of spiro compound **33**, for instance, could be effected by treatment of cyano enone **11** with LN (4 equiv.) in THF at −78°C for 30 min, followed by adition of 1,5-diiodopentane (2 equiv.). Experimental results showed that the spiro ring formation was more effective when performed at elevated temperatures. In refluxing THF, compound **33** was produced in 51% yield after 22 h. A considerable drop of yield to 35% occurred when the reaction was carried out at room temperature. Experimental results also showed that diiodoalkanes were superior to the corresponding dibromo compounds as alkylating agents. With 1,5-dibromopentane, the spiro-annulation of **11** gave compound **33** in substantially lower yields (40% in refluxing THF; 27% at room temperature). The reductive spiro-annulation process is apparently general. Compounds **34**–**37** werer similarly prepared. Results are summarized in Table 6.

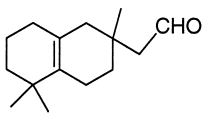
As shown above, a novel and general approach towards the generation of a quaternary center bearing a vinyl group, a common system found in natural products, via a modified Robinson annulation process has been successfully developed. The newly generated quaternary center may be symmetrical or asymmetrical depending on the specific application. This methodology is expected to be of use to synthetic organic chemists. An example is demonstrated in

Table 6. Reductive spiro-annulation of α-unalkylated-γ-cyano-α,β-unsaturated cyclohexanones



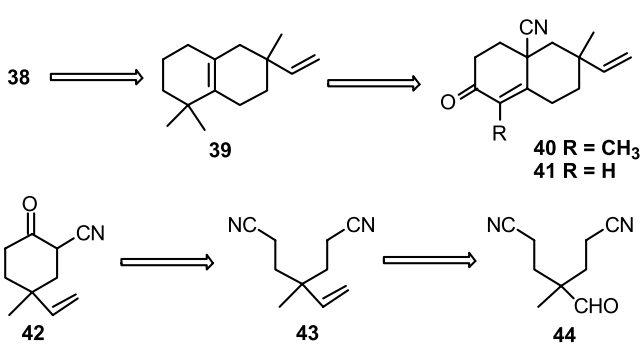
Entry	Enone	Alkylating Agent	Time (h)	Product	Yield (%)
1	 **11**	$(CH_2)_5I_2$	22	 **33**	51
2	**11**	$(CH_2)_4I_2$	19	 **34**	61
3	 **13**	$(CH_2)_5I_2$	22	 **35**	53
4	**13**	$(CH_2)_4I_2$	20	 **36**	58
5	 **16**	$(CH_2)_4I_2$	20	 **37**	58

our concise total synthesis of the marine natural product nanaimoal (**38**)[12] detailed below.



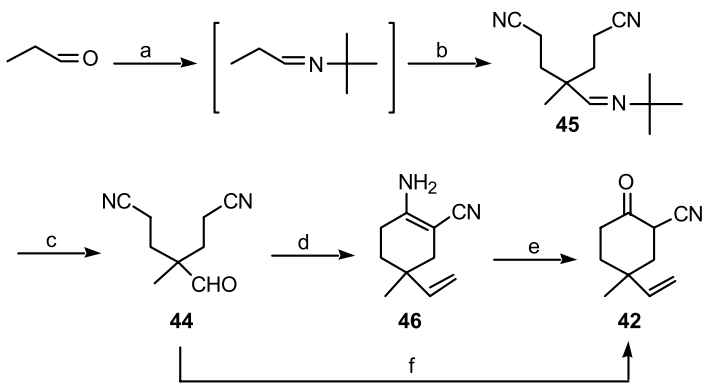
38

Nanaimoal (**38**) was first isolated and identified by Andersen et al. in 1984 as the major component in the methanol extracts of dorid nudibranch *Acanthodoris nanaimoensis*.[12] Our retrosynthesis of nanaimoal is depicted in Scheme 3. The target molecule was envisioned to be achievable from dienyl compound **39** which will result from the reductive alkylation of either enone **40** or **41** followed by deoxygenation via a Wolff–Kishner process. Enones **40** and **41** are proposed to result from a Robinson annulation process starting from cyano ketone **42**, which is proposed to be produced via the Thorpe–Ziegler condensation of dinitrile **43**. Finally, dinitrile **43** can be synthesized by subjecting known aldehyde **44**[13] to a Wittig olefination process.

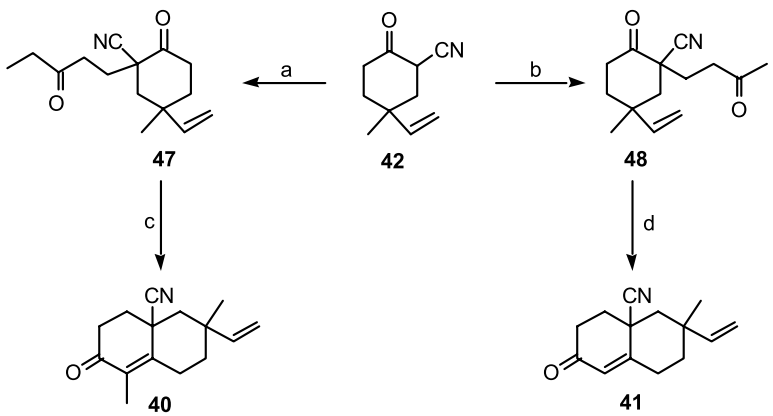


Scheme 3.

Our endeavor towards the total synthesis of nanaimoal (**38**) began with the synthesis of aldehyde **44** by following literature precedent with some modifications. Thus, starting with propionaldehyde (Scheme 4), treatment with *t*-butylamine in the presence of potassium carbonate gave the corresponding imine derivative[13] which was then treated with acrylonitrile to achieve the two-fold Michael addition product **45**. Aldehyde **44** was realized by hydrolysis of dinitrile **45** with hydrochloric acid and was subsequently subjected to Wittig olefination reaction conditions by treatment with methylenetriphenylphosphino ylid. Interestingly, the reaction did not yield the expected dinitrile **43**, but enamine **46**. Apparently, in addition to the anticipated olefination of the aldehyde, a Thorpe–Ziegler condensation also ensued, presumably as a consequence of the presence of excess ylid in the reaction mixture. Hydrolysis of enamine **46** with hydrochloric acid gave cyano ketone **42**. Given this result, the synthesis of ketone **42** from aldehyde **44** was



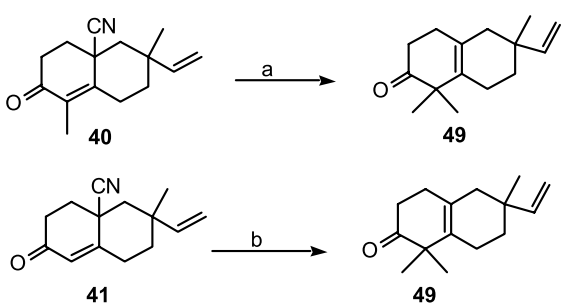
Scheme 4. *Reagents and conditions*: (a) *t*-BuNH$_2$, K_2CO_3, toluene, r.t., 16 h; (b) acrylonitrile, toluene, reflux, 48 h, 75% over 2 steps; (c) HCl, EtOH, r.t., 14 h, 96%; (d). Ph_3PCH_3Br, *n*-BuLi, THF, −78°C to rt, 30 min, 77%; (e) HCl, toluene, reflux, 1 h, 90%; (f) Ph_3PCH_3Br, *n*-BuLi, THF, −78°C to rt, 30 min, then HCl (pH ~1), 17 h, 91% over two steps.



Scheme 5. *Reagents and conditions*: (a) DABCO, EVK, DME, 0°C to rt, 23 h, 74%; (b) DABCO, MVK, DME, 0°C to rt, 23 h, 83%; (c) *p*-TsOH, toluene, reflux, −H_2O, 24 h, 88%; (d) *p*-TsOH, toluene, reflux, −H_2O, 24 h, 89%.

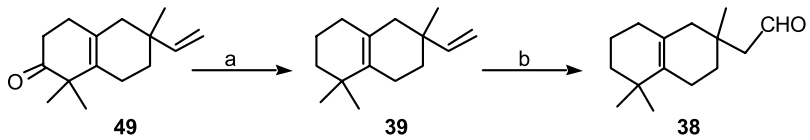
subsequently simplified into a one-pot process. Upon completion of the Wittig/Thorpe–Ziegler reaction, the reaction mixture was acidified with hydrochloric acid and stirred at room temperature until hydrolysis was complete. In this way, ketone **42** was isolated in much higher yield than the previous two-step sequence.

The Robinson annulation of ketone **42** to give enone **40** (Scheme 5) was achieved by first treating ketone **42** with ethyl vinyl ketone (EVK) in the presence of DABCO in DME. The resulting diketone **47** was then heated with *p*-toluenesulfonic acid in toluene to give enone **40**. Likewise, enone **41** was constructed starting with ketone **42** under similar conditions but using methyl vinyl ketone (MVK) as the Michael acceptor, giving diketone **48**. The key reductive alkylation step was then investigated first with enone **40** (Scheme 6). Using the procedure developed for the reductive alkylation of α-alkylated enones (vide supra), enone **40** was reduced with LN in a titrative fashion followed by the introduction of methyl iodide into the deep blue reaction mixture. Upon workup and purification, ketones **49** was isolated in 77% yield. The reductive alkylation of enone **41** was also carried out. Following the procedure delineated previously for the reductive alkylation of α-unalkylated enones (vide supra), enone **41** was reductively alkylated by sequential treatment with LN and methyl iodide. In this way, dimethyl ketone **49** was generated cleanly albeit in modest yield (41%). Efforts to modify the reaction conditions and reagent amounts in an attempt to increase the yield of the reaction met with little success.



Scheme 6. *Reagents and Conditions*: (a) LN (~3 equiv.), THF, −78°C, 45 min, then CH_3I (4 equiv.), −78°C, 20 h, 77%; (b) LN (4 equiv.), THF, −78°C, 30 min, then CH_3I (4 equiv.), −78°C to rt, 4 h, 41%.

Following the above described reductive alkylation processes for the generation of ketone **49**, all that was required to complete the synthesis of nanaimoal (**38**) was to remove the ketone oxygen followed by oxidation of the terminal carbon–carbon double bond to an aldehyde. Deoxygenation of the ketone carbonyl present in **49** was achieved under standard Huang Minglon reduction conditions,[14] giving dienyl compound **39** in good yield (Scheme 7). For the



Scheme 7. *Reagents and Conditions*: H_2NNH_2, KOH, DEG, 110–120°C, 2 h, then 210–220°C, 4 h, 76%; (b) Sia_2BH, THF, 0°C to rt, 25 h, then PCC, CH_2Cl_2, reflux, 3 h, 66%.

conversion of the terminal olefin found in bicyclic diene **39** to an aldehyde, a one-pot hydroboration/oxidation process as described by Brown et al.[15] was employed. Thus, a solution of diene **39** in THF was treated with freshly prepared disiamylborane. Upon completion of the hydroboration, the solvent was removed, and the residue was treated with pyridinium chlorochromate (PCC) in refluxing methylene chloride. In this way, nanaimoal (**38**) was isolated in 66% yield after purification.[16]

3. Conclusion

We have described a modified Robinson annulation process for the regioselective generation of α,α-disubstituted-β,γ-unsaturated cyclohexanone systems, taking advantage of the facile reductive alkylation of γ-cyano-α,β-unsaturated enones by sequential treatment with LN and an alkylating agent. Both symmetrical and unsymmetrical substitution patterns can be achieved simply by suitable choice of enone precursors and reaction conditions. As well, the efficacy of this newly developed methodology has been demonstrated in a concise total synthesis of the marine natural product nanaimoal (**38**), starting from propionaldehyde. This modified Robinson annulation process is expected to experience extensive synthetic application, especially towards the synthesis of natural products containing a quaternary center bearing a vinyl group.

4. Experimental

4.1. General

Melting points (mp) were recorded on a Köfler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratories at the University of Alberta and the National Chiao Tung University. Fourier transform infrared spectra (IR) were recorded on a Nicolet Magna 750 or Bomem MB-100 FT instrument. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using the following spectrometers: Bruker AM-200 (200 MHz), Bruker AM-300 (300 MHz), Bruker AC-300 (300 MHz), Varian Inova 300 (300 MHz), Bruker AM-400 (400 MHz), and Varian Inova 600 (600 MHz). Coupling constants are reported to ±0.5 Hz, and chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on the following spectrometers: Bruker AM-200 (50 MHz), Bruker AM-300 (75 MHz), and Bruker AM-400 (100 MHz). Carbon-13 multiplicities were derived from either Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (Attached Proton Test (APT)) or distortionless enhancement by polarization transfer experiments (DEPT). In the APT experiments, methylene groups and quaternary carbons appear as in-phase (p) resonances with respect to the deuterated solvent signal, while methyl and methine carbons appear as anti-phase (a) resonances. High resolution electron impact mass spectra (HRMS (EI)) were recorded using a Kratos MS-50 mass spectrometer. Electrospray mass spectra (ESMS) were recorded using a Hewlet-Packard 1100 MSD mass spectrometer. Spectral data were recorded as *m*/*z* values. Bulb-to-bulb distillations were performed using a Kugelrohr distillation apparatus. Unless otherwise stated, all materials used were commercially available and used as supplied. All compounds synthesized are racemic. Reactions requiring anhydrous conditions were performed in flame-dried glassware, cooled under an argon or nitrogen atmosphere. Unless otherwise stated, reactions were carried out under argon or nitrogen and monitored by analytical thin layer chromatography performed on aluminum-backed plates precoated with silica gel 60 F_{254} as supplied by Merck. Visualization of the resulting chromatograms were done by looking under an ultraviolet lamp (λ=254 nm) followed by dipping in an ethanol solution of vanillin (5% w/v) containing sulfuric acid (3% v/v) and charring by heat gun. Solvents for reactions were dried and distilled under an argon or nitrogen atmosphere prior to use as follows: THF, diethyl ether (ether), and DME from a dark blue solution of sodium benzophenone ketyl; benzene, toluene, dichloromethane, and chloroform from calcium hydride. Unless stated otherwise, anhydrous magnesium sulfate was used for drying organic solutions, and solvents were removed under water aspirator vacuum using a Buchi rotoevaporator. Flash chromatography was used routinely for purification and separation of product mixtures using silica gel of 230–400 mesh size as supplied by Merck. Solvents for flash chromatography were distilled under normal atmosphere prior to use. Eluent systems are given in volume/volume concentrations.

4.2. General procedure for the preparation of 2-cyanocycloalkanones 1–3

The known compounds **1**–**3** were prepared from pimelonitrile, suberonitrile, and adiponitrile, respectively, by a modified Thorpe–Ziegler process using sodium *N*-methylanilide, generated in situ from sodium hydride and *N*-methylaniline.[8] The general procedure is illustrated immediately below with 2-cyanocyclohexanone (**1**) as an example.

4.2.1. 2-Cyanocyclohexanone (1). To a solution of sodium hydride (3.64 g, 121.4 mmol; 80% w/w) and *N*-methylaniline (13.3 mL, 121.6 mmol) in THF (60 mL), was added pimelonitrile (4.94 g, 40.43 mmol) in THF (30 mL) dropwise by an addition funnel over 30 min. The resulting

mixture was heated under reflux for 2 h and then cooled to 0°C, at which time water (15 mL) was added to quench the reaction followed by addition of concentrated HCl to acidify the solution to around pH 2. The aqueous solution was extracted with ether (3×20 mL), and the combined extracts were washed with brine, dried, filtered and concentrated. The crude residue was subjected to purification by flash chromatography on silica gel (20% ethyl acetate in *n*-hexane) to give compound **1** (4.58 g, 92% yield) as a colorless oil: IR (neat, cm^{-1}): 2250 (CN), 1724 (C═O); ^1H NMR (300 MHz, $CDCl_3$): δ 3.46 (dd, J=13, 7 Hz, 1H), 2.65 (m, 1H), 2.52–2.28 (m, 2H), 2.15–1.93 (m, 3H), 1.90–1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 200.5 (C═O), 116.6 (CN), 43.3 (CH), 40.6 (CH_2), 32.1 (CH_2), 26.8 (CH_2), 23.6 (CH_2); HRMS (EI): calcd for C_7H_9NO: 123.0685; found: 123.0682.

4.2.2. 2-Cyanocycloheptanone (2). Suberonitrile (1.23 g, 9.05 mmol) was treated with sodium hydride (0.82 g, 27.17 mmol; 80% w/w) and *N*-methylaniline (3.0 mL, 27.44 mmol) to give compound **2** (1.22 g, 98% yield) as a colorless oil: IR (neat, cm^{-1}): 2248 (CN), 1719 (C═O); ^1H NMR (300 MHz, C_6D_6): δ 2.80 (dd, J=12, 5 Hz, 1H), 2.09 (m, 1H), 1.99 (m, 1H), 1.35–1.19 (m, 4H), 1.05–0.90 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6, DEPT): δ 202.1 (C═O), 117.6 (CN), 44.4 (CH), 41.9 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 23.2 (CH_2); HRMS (EI): calcd for $C_8H_{11}NO$: 137.0849; found: 137.0842.

4.2.3. 2-Cyanocyclopentanone (3). Treatment of adiponitrile (4.82 g, 44.64 mmol) with sodium hydride (4.02 g, 134.05 mmol; 80% w/w) and *N*-methylaniline (14.6 mL, 133.89 mmol) gave compound **3** (4.78 g, 98% yield) as a colorless oil: IR (neat, cm^{-1}): 2246 (CN), 1753 (C═O); ^1H NMR (300 MHz, $CDCl_3$): δ 3.15 (dd, J=18, 8 Hz, 1H), 2.50 (m, 1H), 2.39 (m, 1H), 2.30–2.09 (m, 2H), 2.03–1.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 207.3 (C═O), 116.6 (CN), 39.0 (CH), 36.3 (CH_2), 28.1 (CH_2), 20.7 (CH_2); HRMS (EI): calcd for C_6H_7NO: 109.0517; found: 109.0514.

4.3. General procedure for the synthesis of compounds 4–7

The general procedure is illustrated immediately below with compound **4** as a specific example.

4.3.1. 2-Oxo-1-(3-oxobutyl)cyclohexanecarbonitrile (4). Al_2O_3 (3 g) was placed in a round bottom flask and heated in the oven at 100°C for 1 h. After it was cooled to room temperature under an atmosphere of nitrogen, 2-cyanocyclohexanone (**1**) (500 mg, 4.13 mmol) was added, and the resulting mixture stirred vigorously for 10 min. This was followed by addition of MVK (0.5 mL, 6.19 mmol) dropwise over 20 min. After the reaction was complete, ether was added, and the resulting mixrue filtered and concentrated. The residue thus obtained was purified by chromatography (15% ethyl acetate in *n*-hexane) to give compound **4** (720 mg, 90% yield) as a white solid: mp (ethyl acetate and *n*-hexane): 46.5–47°C; IR ($CHCl_3$ cast, cm^{-1}): 2235 (CN), 1720 (C═O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.54–2.43 (m, 3H), 2.41–2.31 (m, 1H), 2.11–2.00 (m, 2H), 1.96 (s, 3H), 1.83–1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 205.9 (C═O), 202.5 (C═O), 119.0 (CN), 50.4 (C), 38.3 (CH_2), 38.0 (CH_2), 29.3 (CH_3), 27.0 (CH_2), 26.9 (CH_2), 21.2 (CH_2×2); HRMS (EI): calcd for $C_{11}H_{15}NO_2$: 193.1103; found: 193.1098; Anal. calcd for $C_{11}H_{15}NO_2$: C 68.37, H 7.82, N 7.25; found: C 68.58, H 7.76, N 7.13.

4.3.2. 2-Oxo-1-(3-oxopentyl)cyclohexanecarbonitrile (5). Treatment of 2-cyanocyclohexanone (**1**) (500 mg, 4.13 mmol) with Al_2O_3 (3 g), and EVK (0.6 mL, 6.19 mmol) gave compound **5** (770 mg, 90% yield) as a colorless oil: IR (neat, cm^{-1}): 2235 (CN), 1716 (C═O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (ddd, J=13.5, 10, 5.5 Hz, 1H), 2.50 (dt, J=10, 6 Hz, 2H), 2.42–2.29 (m, 3H), 2.21–2.08 (m, 2H), 2.03–1.63 (m, 6H), 0.92 (t, J=7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 208.9 (C═O), 202.7 (C═O), 119.2 (CN), 50.7 (C), 38.6 (CH_2), 38.5 (CH_2), 37.3 (CH_2), 35.6 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 21.5, (CH_2), 7.4 (CH_3); HRMS (EI): calcd for $C_{12}H_{17}NO_2$: 207.1259; found: 207.1256.

4.3.3. 2-Oxo-1-(3-oxobutyl)cycloheptanecarbonitrile (6). Treatment of 2-cyanocycloheptanone (**2**) (500 mg, 3.64 mmol) with Al_2O_3 (3 g) and MVK (0.4 mL, 5.46 mmol) gave compound **6** (672 mg, 89% yield) as a colorless oil: IR (neat, cm^{-1}): 2240 (CN), 1714 (C═O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.63–2.56 (m, 4H), 2.21–2.13 (m, 2H), 2.11 (s, 3H), 1.09 (m, 4H), 1.70–1.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 206.0 (C═O), 205.2 (C═O), 119.6 (CN), 54.6 (C), 39.6 (CH_2), 38.4 (CH_2), 35.7 (CH_2), 29.8 (CH_2), 29.5 (CH_3), 28.6 (CH_2), 25.2, (CH_2), 24.8 (CH_2); HRMS (EI): calcd for $C_{12}H_{17}NO_2$: 207.1259; found: 207.1263.

4.3.4. 2-Oxo-1-(3-oxopentyl)cycloheptanecarbonitrile (7). Treatment of 2-cyanocycloheptanone (**2**) (500 mg, 3.64 mmol) with Al_2O_3 (3 g) and EVK (0.6 mL, 5.46 mmol) gave compound **7** (700 mg, 87% yield) as a colorless oil: IR (neat, cm^{-1}): 2235 (CN), 1713 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.53 (dt, J=13, 4 Hz, 1H), 2.47–2.37 (m, 3H), 2.28 (q, J=6.5 Hz, 2H), 2.10–1.99 (m, 2H), 1.85–1.74 (m, 4H), 1.60–1.15 (m, 4H), 0.86 (t, J=8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 208.7 (C═O), 205.3 (C═O), 119.6 (CN), 54.7 (C), 39.6 (CH_2), 37.1 (CH_2), 35.8 (CH_2), 35.5 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 25.2, (CH_2), 24.8 (CH_2), 7.2 (CH_3); HRMS (EI): calcd for $C_{13}H_{19}NO_2$: 221.1416; found: 221.1416.

4.4. General procedure for the synthesis of compounds 8a, 8b, 9 and 10

The general procedure is illustrated immediately below with the preparation of compounds **8a** and **8b** as a specific example.

4.4.1. 1*R-(1*S**-Methyl-3-oxopentyl)-2-oxocyclohexanecarbonitrile (8a) and 1*R**-(1*R**-methyl-3-oxopentyl)-2-oxocyclohexanecarbonitrile (8b).** To a solution of 2-cyanocyclohexanone (**1**) (1 g, 8.26 mmol) and DABCO (1.13 g, 9.91 mmol) in DME (40 mL) at 0°C, was added 4-hexen-3-one (1.9 mL, 16.53 mmol) dropwise. The resulting mixture was heated at reflux for 25 h. After the solution was cooled to room temperature, it was poured into 2N hydrochloric acid (10 mL) at 0°C. The aqueous solution was extracted

with ether (3×20 mL). The combined extracts were washed with brine, dried, filtered and concentrated. The residue thus obtained was subjected to flash chromatography on silica gel (15% ethyl acetate in *n*-hexane) to give a pair of diastereomers **8a** and **8b** (1:1, 1.35 g, 74% yield), each as a white solid: **8a**: mp (ethyl acetate and *n*-hexane): 162–163°C; IR ($CHCl_3$ cast, cm^{-1}): 2232 (CN), 1714 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.68 (dd, J=7, 7 Hz, 1H), 2.43–2.31 (m, 3H), 2.01–1.98 (m, 1H), 1.81–1.51 (m, 7H), 1.10 (d, J=6 Hz, 3H), 1.01 (t, J=7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 214.5 (C═O), 202.9 (C═O), 120.9 (CN), 51.5 (CH), 49.8 (CH_2), 46.9 (CH_2), 35.4 (CH_2), 33.1 (CH_2), 28.8 (CH_2), 22.1 (CH_2), 20.1 (CH_2), 16.4, (CH_3), 6.5 (CH_3); HRMS (EI): calcd for $C_{13}H_{19}NO_2$: 221.1416; found: 221.1413; Anal. calcd for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33; found: C 70.53, H 8.83, N 6,32; **8b**: mp (ethyl acetate and *n*-hexane): 143.5–144°C; IR (KBr, cm^{-1}): 2228 (CN), 1695 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.86 (m, 1H), 2.74 (q, J=6.5 Hz, 1H), 2.33 (dd, J=6.5, 4 Hz, 1H), 2.18–1.91 (m, 4H), 1.83–1.32 (m, 6H), 1.15 (d, J=7 Hz, 3H), 1.03 (t, J=6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 207.8 (C═O), 202.1 (C═O), 122.5 (CN), 50.8 (C), 44.9 (CH), 40.4 (CH_2), 35.0 (CH_2), 34.2 (CH_2), 24.5 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 16.7 (CH_3), 6.4 (CH_3); HRMS (EI): calcd for $C_{13}H_{19}NO_2$: 221.1416; found: 221.1412; Anal. calcd for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33; found: C 70.71, H 8.48, N 6.51.

4.4.2. 2-Oxo-1-(3-oxobutyl)cyclopentanecarbonitrile (9). Treatment of 2-cyanocyclopentanone (**3**) (500 mg, 4.58 mmol) with DABCO (625 mg, 5.49 mmol) and MVK (1.1 mL, 9.16 mmol) in DME (20 mL) at room temperature for 25 h gave comound **9** (730 mg, 89% yield) as a colorless oil: IR (neat, cm^{-1}): 2237 (CN), 1751 (C═O), 1714 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.84 (ddd, J=18, 8, 6 Hz, 1H), 2.65 (ddd, J=18, 8, 6 Hz, 1H), 2.42–2.37 (m, 3H), 2.16 (s, 3H), 2.14–2.01 (m, 4H), 1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 195.5 (C═O), 192.5 (C═O), 118.6 (CN), 47.6 (C), 38.5 (CH_2), 36.0 (CH_2), 35.0 (CH_2), 29.7 (CH_3), 27.5 (CH_2), 18.9 (CH_2); HRMS (EI): calcd for $C_{10}H_{13}NO_2$:179.0946; found: 179.0947.

4.4.3. 2-Oxo-1-(3-oxopentyl)cyclopentanecarbonitrile (10). Treatment of cyano ketone **3** (500 mg, 4.58 mmol) with DABCO (626 mg, 5.49 mmol) and EVK (1 mL, 9.16 mmol) in DME (20 mL) at room temperature for 16 h gave compound **10** (770 mg, 87% yield) as a colorless oil: IR (neat, cm^{-1}): 2236 (CN), 1752 (C═O), 1714 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.71 (ddd, J=18, 8, 5.5 Hz, 1H), 2.54 (ddd, J=18, 8, 5.5 Hz, 1H), 2.38 (q, J=7 Hz, 2H), 2.36–2.29 (m, 4H), 2.09–1.95 (m, 3H), 1.80 (m, 1H), 1.16 (t, J=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 209.1 (C═O), 209.0 (C═O), 118.7 (CN), 47.6 (C), 37.1 (CH_2), 36.0 (CH_2), 35.8 (CH_2), 34.8 (CH_2), 22.2 (CH_3), 18.9 (CH_2), 7.5 (CH_3); HRMS (EI): calcd for $C_{11}H_{15}NO_2$: 193.1103; found: 193.1111.

4.5. General procedure for the synthesis of compopunds 11–14, 15a, 15b, 16 and 17

Using compound **11** as a specific example, the general procedure is illustrated immediately below.

4.5.1. 7-Oxo-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (11). A solution of compound **4** (500 mg, 2.59 mmol) and *p*-toluenesulfonic acid (400 mg, 2.07 mmol) in toluene (30 mL) was heated under reflux for 22 h using a Dean–Stark water separator. The resulting mixture was cooled to room temperature. Saturated aqueous sodium bicarbonate (10 mL) was added, and the aqueous solution extracted with ether (3×20 mL). The organic layers were combined, washed with brine, dried, filtered and concentrated. Flash chromatography of the residue on silica gel (15% ethyl acetate in *n*-hexane) afforded compound **11** (430 mg, 95% yield) as a white solid: mp (ethyl acetate and *n*-hexan): 61–62°C; IR ($CHCl_3$ cast, cm^{-1}): 2332 (CN), 1687 (C═O), 1629 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.69 (s, 1H), 2.61–2.36 (m, 5H), 2.23 (dd, J=13.5, 1.5 Hz, 1H), 1.99–1.91 (m, 2H), 1.65–1.62 (m, 2H), 1.45–1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.5 (C═O), 157.3 (C═), 126.8 (CH═), 120.1 (CN), 38.7 (CH_2), 38.2 (C), 34.4 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 25.9 (CH_2), 22.6 (CH_2); HRMS (EI): calcd for $C_{11}H_{13}NO$: 175.0997, found: 175.0998; Anal. calcd for $C_{11}H_{13}NO$: C 75.40, H 7.48, N 7.99; found: C 75.32, H 7.74, N 7.94.

4.5.2. 8-Methyl-7-oxo-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (12). Treatment of diketone **5** (500 mg, 2.41 mmol) with *p*-TsOH (370 mg, 1.92 mmmol) gave compound **12** (450 mg, 99% yield) as a colorless oil: IR (neat, cm^{-1}): 2229 (CN), 1676 (C═O), 1622 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.77 (dt, J=14.5, 3 Hz, 1H), 2.57–2.37 (m, 2H), 2.21 (dt, J=14.5, 4 Hz, 1H), 2.16–2.06 (m, 2H), 1.90–1.71 (m, 4H), 1.69 (d, J=1.5 Hz, 3H), 1.42–1.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.0 (C═O), 150.1 (C═), 131.8 (C═), 120.6 (CN), 38.9 (CH_2), 34.0 (CH_2), 33.1 (CH_2), 28.4 (CH_2), 25.4 (CH_2), 22.3 (CH_2), 10.8 (CH_3); HRMS (EI): calcd for $C_{12}H_{15}NO$: 189.1154; found: 189.1163.

4.5.3. 2-Oxo-2,3,4,5,6,7,8,9-octahydrobenzocycloheptene-4a-carbonitrile (13). Treatment of diketone **6** (500 mg, 2.41 mmol) with *p*-TsOH (372 mg, 1.92 mmol) gave compound **13** (433 mg, 95% yield) as a white solid: mp (ethyl acetate and *n*-hexane): 77–78°C: IR ($CHCl_3$ cast, cm^{-1}): 2228, (CN), 1675 (C═O), 1621 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.94 (s, 1H), 2.66–2.62 (m, 1H), 2.52–2.41 (m, 3H), 2.22–2.10 (m, 3H), 2.01–1.97 (m, 2H), 1.84–1.6 (m, 2H), 1.54–1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.4 (C═O), 161.4 (C═), 129.8 (CH═), 120.8 (CN), 40.3 (C), 37.4 (CH_2×2), 34.6 (CH_2), 34.2 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 24.0 (CH_2); HRMS (EI): calcd for $C_{12}H_{15}NO$:189.1154; found: 189.1154; Anal. calcd for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.04; found: C 76.08, H 8.20, N 7.28.

4.5.4. 1-Methyl-2-oxo-2,3,4,5,6,7,8,9-octahydrobenzocycloheptene-4a-carbonitrile (14). Treatment of diketone **7** (500 mg, 2.26 mmol) with *p*-TsOH (350 mg, 1.81 mmol) gave compound **14** (435 mg, 95% yield) as a white solid: mp (ethyl acetate and *n*-hexane): 80–81°C; IR ($CHCl_3$ cast, cm^{-1}): 2228 (CN), 1674 (C═O), 1618 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.69–2.43 (m, 3H), 2.20–1.95 (m, 6H), 1.76 (s, 3H), 1.74–1.71 (m, 2H), 1.41–1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 195.9 (C═O), 153.6 (C═), 134.9 (C═), 121.5 (CN), 40.8 (C), 38.5 (CH_2),

34.5 (CH_2), 33.0 (CH_2), 30.5 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 23.0 (CH_2), 10.8 (CH_3); HRMS (EI): calcd for $C_{13}H_{17}NO$: 203.1310; found: 203.1310; Anal. calcd for $C_{13}H_{17}NO$: C 76.81, H 8.43, N 6.89; found: C 76.75, H 8.77, N 6.95.

4.5.5. (4a*S* *,5*S* *)-5,8-Dimethyl-7-oxo-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (15a). Treatment of diketone **8a** (500 mg, 2.26 mmol) with *p*-TsOH (347 mg, 1.8 mmol) gave compound **15a** (455 mg, 99% yield) as a white solid: mp (ethyl acetate and *n*-hexane); 96–97°C IR ($CHCl_3$ cast, cm^{-1}): 2226 (CN), 1673 (C═O), 1619 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.91–2.88 (m, 1H), 2.46–2.42 (m, 3H), 2.40–2.2 (m, 1H), 2.10–2.02 (m, 2H), 1.86–1.81 (m, 2H), 1.80 (s, 3H), 1.34–1.30 (m, 2H), 1.22 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.7 (C═O), 150.7 (C═), 132.0 (C═), 119.1 (CN), 44.6 (C), 42.5 (CH_2), 37.2 (CH), 36.6 (CH_2), 26.9 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 16.5 (CH_3), 11.1 (CH_3); HRMS (EI): calcd for $C_{13}H_{17}NO$: 203.1310; found: 203.1304; Anal. calcd for $C_{13}H_{17}NO$: C 76.81, H 8.43, N 6.89; found:.C 76.91, H 8.43, N 6.83.

4.5.6. (4a*S* *,5*R* *)-5,8-Dimethyl-7-oxo-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (15b). Treatment of diketone **8b** (500 mg, 2.26 mmol) with *p*-TsOH (347 mg, 1.8 mmol) gave compound **15b** (455 mg, 99% yield) as a colorless oil: IR ($CHCl_3$ cast, cm^{-1}): 2230, (CN), 1676 (C═O), 1626 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.81 (dd, J=16, 4 Hz, 1H), 2.55–2.42 (m, 3H), 2.26–2.16 (m, 1H), 2.06–1.87 (m, 4H), 1.79 (s, 3H), 1.66–1.58 (m, 1H), 1.34–1.30 (m, 1H), 1.11 (d, J=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.3 (C═O), 151.6 (C═), 130.4 (C═), 121.6 (CN), 45.4 (C), 41.0 (CH_2), 35.6 (CH), 32.0 (CH_2), 30.3 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 15.3 (CH_3), 11.1 (CH_3); HRMS (EI): calcd for $C_{13}H_{17}NO$: 203.1310; found: 203.1300.

4.5.7. 5-Oxo-1,2,3,4,5,7a-hexahydroindene-3a-carbonitrile (16). Treatment of diketone **9** (500 mg, 2.59 mmol) with *p*-TsOH (403 mg, 2.03 mmol) gave compound **16** (381 mg, 85% yield) as a colorless oil: IR (neat, cm^{-1}): 2230 (CN), 1673 (C═O), 1620 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (s, 1H), 2.83–2.75 (m, 1H), 2.70–2.38 (m, 6H), 2.11–1.91 (m, 1H), 1.87 (dt, J=13.5, 5 Hz, 1H), 1.61 (dt, J=12, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.5 (C═O), 165.3 (C═), 124.7 (CH═), 119.8 (CN), 43 (C), 38.2 (CH_2), 34.2 (CH_2), 32.6 (CH_2), 30.1 (CH_2), 22.2 (CH_2); HRMS (EI): calcd for $C_{10}H_{11}NO$: 161.0841; found: 161.0833.

4.5.8. 4-Methyl-5-oxo-1,2,3,4,5,7a-hexahydroindene-3a-carbonitrile (17). Treatment of diketone **10** (500 mg, 2.59 mmol) with *p*-TsOH (403 mg, 2.03 mmol) gave compound **17** (385 mg, 83% yield) as a colorless oil: IR (neat, cm^{-1}): 2228 (CN), 1668 (C═O), 1622 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.74–2.37 (m, 2H), 2.07–2.03 (m, 6H), 1.88 (dt, J=13.5, 4 Hz, 1H), 1.63 (s, 3H), 1.59 (dt, J=12.5, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 196.3 (C═O), 158.6 (C═), 131.3 (C═), 120.4 (CN), 43.8 (C), 39.1 (CH_2), 34.3 (CH_2), 32.6 (CH_2), 29.6 (CH_2), 22.8 (CH_2), 11.5 (CH_3); HRMS (EI): calcd for $C_{11}H_{13}NO$: 175.0997; found: 175.0994.

4.6. General procedure for the synthesis of compounds 18 and 20–25 and characterization of side product 19

The general procedure applied to effect the reductive alkylation is illustrated below using compound **18** as a specific example.

4.6.1. 1-Allyl-1-methyl-1,3,4,5,6,7,8,9-octahydrobenzohepten-2-one (18) and 1,3-diallyl-1-,3,4,5,6,7,8,9-octahydrobenzohepten-2-one (19). To a solution of compound **14** (200 mg, 0.98 mmol) in THF (2 mL) at −78°C, was added dropwise a precooled (−78°C) 0.98 M solution of LN in THF until the resulting solution turned deep green (2.94 mmol of LN was used based on the volume of stock solution added). The mixture was stirred for additional 30 min, followed by rapid addition of allyl bromide (0.26 mL, 2.94 mmol) in one portion. After stirring for 20 h at -78°C, the reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture extracted with ether (4×20 mL). The combined extracts were washed with brine, dried, filtered and concentrated. The residue was subjected to flash chromatography on silica gel (0.25% ethyl acetate in *n*-hexane) to give compound **18** (186 mg, 87%) as a colorless oil: IR (neat, cm^{-1}): 1713 (C═O), 1639 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.48 (ddd, J=10, 7, 7 Hz, 1H), 4.93–4.87 (m, 2H), 2.49–2.40 (m, 3H), 2.34–2.31 (m, 2H), 2.24–2.00 (m, 5H), 1.83–1.21 (m, 6H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 214.7 (C═O), 138.2 (C═), 135.7 (C═), 134.7 (CH═), 116.8 (CH_2═), 52.0 (C), 41.3 (CH_2), 37.6 (CH_2), 35.3 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 28.6 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 22.9 (CH_3); HRMS (EI): calcd for $C_{15}H_{22}O$: 218.1671; found, 218.1663.

The above procedure which resulted in the exclusive formation of the monoalkylation product was followed for the preparation of compounds **20**–**25**. When the above alkylation step was carried out at room temperature after the initial decyanation with LN at −78°C, the oily compound **19** was invariably produced (27–33% yields) reardless of the amount of allyl bromide used (1.2–4 equiv.). Compound **19** showed the following spectral data: IR (neat, cm^{-1}): 1710 (C═O), 1640 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.74 (dddd, J=18, 6, 6, 2 Hz, 1H), 5.54 (dddd, J=9, 7, 5, 2.5 Hz, 1H), 5.02–4.88 (m, 4H), 2.72–2.64 (m, 1H), 2.51–2.44 (m, 1H), 2.38–1.93 (m, 8H), 1.79–1.2 (m, 7H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 214.6 (C═O), 139.1 (C═), 136.5 (CH═), 134.6 (C═), 134.0 (CH═), 117.3 (CH_2═), 116.0 (CH_2═), 52.2 (C), 45.7 (CH), 43.7 (CH_2), 38.9 (CH_2), 35.1 (CH_2), 33.2 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 27.3 (CH_2), 26.0 (CH_2), 20.2 (CH_3); HRMS (EI): Calcd for $C_{18}H_{26}O$: 258.1984; found: 258.1980.

4.6.2. 1-Benzyl-1-methyl-3.4.5,6,7,8-hexahydro-1*H*-naphthalen-2-one (20). Sequential treatment of cyano enone **12** (200 mg, 1.05 mmol) with LN (3.15 mmol) and benzyl bormide (0.39 mL, 3.15 mmol) for 20 h gave compound **20** (264 mg, 99% yield) as a coloress oil: IR (neat, cm^{-1}): 1708 (C═O), 1601 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.12–7.09 (m, 3H), 6.97–6.94 (m, 2H), 3.06 (d, J=13 Hz, 1H), 2.72 (d, J=13 Hz, 1H), 2.29–2.21 (m, 1H), 2.12–1.99 (m, 3H), 1.87–1.37 (m, 8H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.8 (C═O), 138.1 (C═), 131.2 (C═), 130.4 (C═), 129.8 (CH═×2), 127.5 (CH═×2),

126.1 (CH═), 53.0 (C), 43.3 (CH_2), 37.6 (CH_2), 30.7 (CH_2), 28.6 (CH_2), 24.5 (CH_2), 23.6 (CH_3), 22.6 (CH_2), 22.5 (CH_2); HRMS (EI): calcd for $C_{18}H_{22}O$: 254.1671; found: 254.1669.

4.6.3. 1-Benzyl-1-methyl-1,3,4,5,6,7,8,9-octahydrobenzocyclohepten-2-one (21). Sequential treatment of cyano ketone **14** (200 mg, 0.98 mmol) with LN (2.94 mmol) and benzyl bromide (0.36 mL, 2.94 mmol) for 24 h gave compound **21** (260 mg, 99% yield) as a white solid: mp (ethyl acetate–*n*-hexane): 97–98°C; IR ($CHCl_3$ cast, cm^{-1}): 1709 (C═O), 1600 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.23–7.09 (m, 3H), 6.95–6.93 (m, 2H), 3.03 (d, J=13.5 Hz, 1H), 2.71 (d, J=13.5 Hz, 1H), 2.30 (dt, J=13.5, 7 Hz, 1H), 2.27–2.21 (m, 4H), 2.15 (dt, J=17, 7 Hz, 1H), 2.02 (dt, J=13, 6.5 Hz, 1H), 1.91–1.56 (m, 7H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.1 (C═O), 138.2 (C═), 137.2 (C═), 136.6 (C═), 129.7 (CH═×2), 127.6 (CH═×2), 126.0 (CH═), 53.6 (C), 43.2 (CH_2), 37.9 (CH_2), 35.3 (CH_2), 32.5 (CH_2), 31.0 (CH_2), 29.3 (CH_2), 27.3 (CH_2), 25.9 (CH_2), 23.5 (CH_3); HRMS (EI): calcd for $C_{19}H_{24}O$: 268.1827; found: 268.1834; Anal. calcd for $C_{19}H_{24}O$: C 85.03, H 9.01; found: C 84.84, H 9.18.

4.6.4. 1,1-Dimethyl-1,3,4,5,6,7,8,9-octahydrobenzocyclohepten-2-one (22). Sequential treatment of cyano enone **14** (200 mg, 0.98 mmol) with LN (2.94 mmol) and methyl iodide (0.18 mL, 2.94 mmol) for 24 h gave compound **22** (175 mg, 93% yield) as a colorless oil: IR (neat, cm^{-1}): 1710 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (t, J= 6.5 Hz, 2H), 2.35 (t, J=7 Hz, 2H), 2.11–2.08 (m, 4H), 1.74–1.68 (m, 2H), 1.43–1.38 (m, 4H), 1.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.8 (C═O), 140.2 (C═), 133.6 (C═), 42.7 (C), 36.3 (CH_2), 35.0 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 28.8 (CH_2), 27.4 (CH_2), 26.0 (CH_2), 23.7 (CH_3×2); HRMS (EI): calcd for $C_{13}H_{20}O$: 192.1514; found: 192.1516.

4.6.5. 1-Allyl-1,4-dimethyl-3,4,5,6,7,8-hexahydro-1*H*-naphthalen-2-one (23). Sequential treatment of cyano enone **15a** (200 mg, 0.98 mmol) with LN (2.95 mmol) and allyl bromide (0.26 mL, 2.95 mmol) for 19 h gave a mixture of two diastereomeric ketones **23** (9:1 based on ^1H NMR analysis, 149 mg, 82% yield) as a colorless oil: IR (neat, cm^{-1}): 1711 (C═O), 1640 (C═C); ^1H NMR (400 MHz, $CDCl_3$): major isomer: δ 5.51 (ddd, J=9.5, 7.5, 6 Hz, 1H), 4.96–4.91 (m, 2H), 2.56 (dd, J=17.5, 6 Hz, 1H), 2.32–2.28 (m, 3H), 2.23 (dd, J=13.5, 3 Hz, 1H), 2.18–1.90 (m, 3H), 1.64–1.55 (m, 5H), 1.13 (s, 3H), 0.94 (d, J=7 Hz, 3H); minor isomer (distinct signals) δ 5.41 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): major isomer: δ 215.3 (C═O), 135.3 (C═), 134.5 (CH═), 131.6 (C═), 117.2 (CH_2═), 51.5 (C), 46.4 (CH_2), 42.7 (CH_2), 36.0 (CH), 28.9 (CH_2), 24.1 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 22.8 (CH_3), 20.3 (CH_3); minor isomer (distinct signals): δ 116.7 (CH_2═), 44.1 (CH_2), 39.1 (CH_2), 36.7 (CH), 31.5 (CH_2), 28.8 (CH_2), 23.9 (CH_2), 22.6 (CH_2), 20.2 (CH_3), 14.0 (CH_3); HRMS (EI): calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1664.

The same diastereomeric mixture of ketones **23** (162 mg, 76% yield) was also obtained form cyano enone **15b** (200 mg, 0.98 mmol) upon sequential treatment with LN (2.95 mmol) and allyl bromide (0.26 mL, 2.95 mmol) for 22 h.

4.6.6. 1,1,4-Trimethyl-3,4,5,6,7,8-hexahydro-1*H*-naphthalen-2-one (24). Sequential treatment of cyano enone **15a** (200 mg, 0.98 mmol) with LN (2.94 mmol) and methyl iodide (0.18 mL, 2.94 mmol) for 19 h gave compound **24** (152 mg, 81% yield) as a colorless oil: IR (neat, cm^{-1}): 1713 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.78 (dd, J=12.5, 6 Hz, 1H), 2.34 (m, 1H), 2.20 (dd, J=12.5, 4 Hz, 1H), 2.10–1.52 (m, 8H), 1.12 (s, 6H), 0.94 (d, J=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.9 (C═O), 133.6 (C═), 132.6 (C═), 47.5 (C), 43.9 (CH_2), 36.6 (CH), 28.8 (CH_2), 25.3 (CH_3), 24.1 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 22.8 (CH_3), 20.0 (CH_3); HRMS (EI): calcd for $C_{13}H_{20}O$: 192.1514; found: 192.1517.

4.6.7. 4-Benzyl-4-methyl-1,2,3,4,6,7-hexahydroinden-5-one (25). Sequential treatment of cyano enone **17** (200 mg, 1.14 mmol) with LN (3.39 mmol) and benzyl bromide (0.42 mL, 3.39 mmol) for 22 h gave compound **25** (224 mg, 82% yield) as a colorless oil: IR (neat, cm^{-1}): 1706 (C═O), 1602 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–6.93 (m, 5H), 2.99 (d, J=13 Hz, 1H), 2.74 (d, J= 13 Hz, 1H), 2.44–2.22 (m, 5H), 2.02 (d, J=6.5 Hz, 1H), 1.94 (dd, J=15, 7 Hz, 3H), 1.73–1.66 (m, 1H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.8 (C═O), 138.0 (C═), 136.4 (C═), 129.7 (CH═×2), 129.3 (C═), 127.8 (CH═×2), 126.2 (CH═), 51.2 (C), 44.2 (CH_2), 37.6 (CH_2), 36.0 (CH_2), 31.7 (CH_2), 23.7 (CH_2), 23.4 (CH_3), 22.8, (CH_2); HRMS (EI): calcd for $C_{17}H_{20}O$: 240.1514; found: 240.1511.

4.7. 1,4-Dimethyl-3,4,5,6,7,8-hexahydro-1*H*-naphthalen-2-ones (26)

To a solution of cyano enone **15b** (200 mg, 0.98 mmol) in THF (2 mL) at −78°C, was added dropwise a precooled (−78°C) 0.98*M* solution of LN in THF until the resulting solution turned deep green (2.94 mmol of LN was used based on the volume of the stock solution added). The reaction mixture was stirred for 30 min, at which time an aqueous saturated solution of ammonium chloride (5 mL) was added. After 5 min, water (20 mL) was added and the resulting solution extracted with ether (4×20 mL). The extracts were combined, dried, filter, and concentrated. Flash chromatography of the residue on silica gel (0.25% ethyl acetate in *n*-hexane) gave a 1:1 mixture of two inseparable diasteriomeric enones **26** (148 mg, 85% yield) as a colorless oil: IR (neat, cm^{-1}): 1716 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.70 (dd, J=14, 7 Hz, 1H), 2.59 (dd, J=14, 7 Hz, 1H), 2.55–2.30 (m, 3H), 2.24 (dd, J=13, 4 Hz, 1H), 2.12–1.44 (m, 18H), 1.13 (d, J=7.5 Hz, 3H), 1.12 (d, J=7.5 Hz, 3H), 0.94 (d, J=7 Hz, 3H), 0.92 (d, J=7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 213.1 (C═O), 214.0 (C═O), 133.3 (C═), 133.0 (C═), 130.1 (C═), 129.7 (C═), 48.0 (CH), 47.3 (CH), 45.8 (CH_2), 44.5 (CH_2), 37.2 (CH), 36.5 (CH), 28.3 (CH_2×2), 28.1 (CH_2), 27.5 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 20.3 (CH_3), 19.7 (CH_3), 16.7 (CH_3), 14.8 (CH_3); HRMS (EI): calcd for $C_{12}H_{18}O$: 178.1358; found: 178.1354.

4.8. General procedure for the proparation of compounds 27 and 29–32 and characterization of side product 28

The general procedure is illustrated immediately below using compound **27** as a specific example.

4.8.1. 1,1-Dibenzyl-1,3,4,5,6,7,8,9-octahydrobenzocyclohepten-2-one (27) and 1-benzyl-1,3,4,5,6,7,8,9-octahydrobenzocyclohepten-2-one (28). To a solution of cyano enone **13** (200 mg, 1.05 mmol) in THF (2 mL) at −78°C, was added dropiwise a precooled (−78°C) 0.98 M solution of LN in THF until the color of the resulting solution remain deep green (3.05 mmol of LN was used). This was followed by the addition of an extra eq of LN (1.05 mmol). After stirring at −78°C for 30 min, benzyl bromide (0.49 mL, 4.1 mmol) was introduced, and the resulting solution stirred at room temperature for 20 h. An aqueous satruated solution of ammonium chloride (20 mL) was added. Extraction with ether (4×20 mL) followed by drying, filtration and concentration gave an oil which was purified by flash chromatography (silica gel, 0.25% ethyl acetate in *n*-hexane) to give compound **27** (242 mg. 67% yield) as a white solid: mp (ethyl acetate–*n*-hexane): 83.5–84°C; IR ($CHCl_3$ cast, cm^{-1}): 1707 (C═O), 1601 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.02 (m, 10H), 3.24 (d, J=13.5 Hz, 2H), 2.86 (d, J=13.5 Hz, 2H), 2.39 (dd, J=5, 5 Hz, 2H), 1.91 (dd, J=5, 5 Hz, 2H), 1.84 (t, J=7 Hz, 2H), 1.73–1.63 (m, 4H), 1.59–1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 214.7 (C═O), 139.3 (C═), 137.8 (C═×2), 133.8 (C═), 130.0 (CH═×4), 127.7 (CH═×4), 126.2 (CH═×2), 59.6 (C), 43.7 (CH_2×2), 39.6 (CH_2), 35.8 (CH_2), 32.1 (CH_2), 30.2 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 25.5 (CH_2); HRMS (EI): calcd for $C_{25}H_{28}O$: 344.2140; found: 344.2142; Anal. calcd for $C_{25}H_{28}O$: C 87.16, H 8.19; found: C 87.39, H 8.32.

The above procedure, which gave compound **27** as the only product, was also used to prepare compounds **29**–**32**. In a similar experiment, cyano enone **13** (200 mg, 1.05 mmol) was treated with LN (3.15 mmol) and benzyl bromide (0.51 mL, 4.2 mmol) at −78°C for 23 h. In this case, compounds **27** (58 mg, 16% yield) and **28** (64 mg, 24% yield) were isolated after chromatographic purification. The later compound, a colorless liquid, showed the following spectral data: IR (neat, cm^{-1}): 1708, (C═O), 1606 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.05 (m, 5H), 3.11 (dd, J=12, 3.5 Hz, 1H), 2.83–2.77 (m, 2H), 2.34–2.01 (m, 7H), 1.75–1.37 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 214.0 (C═O), 138.5 (C═), 136.0 (C═), 134.0 (C═), 129.2 (CH═×2), 128.1 (CH═×2), 126.3 (CH═), 56.3 (CH), 38.1 (CH_2), 37.1 (CH_2), 34.6 (CH_2), 33.5 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 26.7 (CH_2), 26.0 (CH_2); HRMS (EI): calcd for $C_{18}H_{22}O$: 254.1671; found: 254.1676.

4.8.2. 1,1-Diallyl-3,4,5,6,7,8-hexahydro-1*H*-naphthalen-2-one (29). Treatment of cyano enone **11** (200 mg, 1.14 mmol) with LN (4.56 mmol) and allyl bromide (0.41 mL, 4.64 mmol) at room temperature for 24 h gave compound **29** (134 mg, 51% yield) as a colorless liquid: IR (neat, cm^{-1}): 1712 (C═O), 1639 (C═C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.56–5.42 (m, 2H), 4.95–4.88 (m, 4H), 2.46 (dd, J=14, 8 Hz, 2H), 2.36–2.31 (m, 2H), 2.33–1.95 (m, 8H), 1.63–1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 214.4 (C═O), 134.1 (CH═×2), 132.1 (C═), 129.3 (C═), 117.1 (CH_2═×2), 55.7 (C), 41.3 (CH_2×2), 39.3 (CH_2), 30.8 (CH_2), 29.3 (CH_2), 24.0 (CH_2), 22.9 (CH_2), 22.7 (CH_2); HRMS (EI): calcd for $C_{16}H_{22}O$: 230.1671; found: 230.1671; Anal. calcd for $C_{16}H_{22}NO$: C 83.43, H 9.63; found: C 83.30, H 9.77.

4.8.3. 1,1-Dibenzyl-3,4,5,6,7,8-hexahydro-1*H*-naphthalen-1-one (30). Treatment of cyano enone **11** (200 mg. 1.14 mmol) with LN (4.56 mmol) and benzyl bromide (0.55 mL, 5.46 mmol) at room temperature for 21 h gave compound **30** (304 mg, 81% yield) as a colorless liquid: IR (neat, cm^{-1}): 1703 (C═O), 1601 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.02 (m, 10H), 3.18 (d, J=13 Hz, 2H), 2.94 (d, J=13 Hz, 2H), 2.39 (dd, J=5.5, 5.5 Hz, 2H), 1.77–1.56 (m, 8H), 1.25 (t, J=7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.6 (C═O), 137.7 (C═×2), 134.5 (C═), 129.9 (CH═×4), 127.8 (CH═×4), 127.0 (C═), 126.2 (CH═×2), 59.3 (C), 43.2 (CH_2×2), 39.7 (CH_2), 30.9 (CH_2), 37.7 (CH_2), 25.1 (CH_2), 22.8 (CH_2), 22.6 (CH_2); HRMS (EI): calcd for $C_{24}H_{26}O$: 330.1984; found: 330.1983.

4.8.4. 1,1-Dibutyl-1,3,4,5,6,7,8,9-octahydrobenzocyclohepten-2-one (31). Treatment of cyano enone **13** (200 mg, 0.98 mmol) with LN (3.92 mmol) and *n*-butyl iodide (0.45 mL, 3.92 mmol) at room temperature for 19 h gave compound **31** (170 mg, 63% yield) as a colorless liquid: IR (neat, cm^{-1}): 1708 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.40–2.29 (m, 2H), 2.18 (dd, J=5, 5 Hz, 2H), 2.08 (dd, J=5, 5 Hz, 2H), 1.76–1.66 (m, 4H), 1.50–0.84 (m, 16H), 0.79 (t, J=7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 216.5 (C═O), 137.2 (C═), 136.6 (C═), 56.3 (C), 39.8 (CH_2), 37.6 (CH_2×2), 35.9 (CH_2), 32.7 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 27.5 (CH_2×2), 27.0 (CH_2), 26.2 (CH_2), 23.1 (CH_2×2), 14.0 (CH_3×2); HRMS (EI): calcd for $C_{19}H_{32}O$: 276.2453; found: 276.2443.

4.8.5. 4,4-Dibenzyl-1,2,3,4,6,7-hexahydroinden-5-one (32). Treatment of cyano enone **16** (200 mg, 1.24 mmol) with LN (4.96 mmol) and benzyl bromide (4.96 mmol) at room temperature for 24 h gave compound **32** (242 mg, 62% yield) as a colorless liquid: IR (neat, cm^{-1}): 1705 (C═O), 1600 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.18–6.97 (m, 10H), 3.21 (d, J=13 Hz, 2H), 2.85 (d, J=13 Hz, 2H), 2.69–2.64 (m, 2H), 2.15–1.93 (m, 4H), 1.38 (t, J=7 Hz, 2H), 1.26–1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.7 (C═O), 140.4 (C═), 137.7 (C═×2), 134.6 (C═), 129.8 (CH═×4), 127.8 (CH═×4), 126.2 (CH═×2), 57.6 (C), 43.7 (CH_2×2), 39.7 (CH_2), 36.0 (CH_2), 32.3 (CH_2), 22.9 (CH_2), 22.5 (CH_2); HRMS (EI): calcd for $C_{23}H_{24}O$: 316.1827; found: 316.1819.

4.9. General procedure for the preparation of compounds 33–37

The general procedure is illustrated immediately below with compound **33** as a specific example.

4.9.1. 3,4,5,6,7,8-Hexahydrospiro[cyclohexane-1,1′-naphthalen]-2-one (33). To a solution of cyano enone **11** (200 mg, 1.14 mmol) in THF (5 mL) at −78°C, was addded dropwise a precooled 0.91 M solution of LN in THF until the color of the resulting solution remained deep green (3.41 mmol of LN was used). An additional eq of LN (1.14 mmol) was then introduced. The resulting solution was stirred for 30 min. This was followed by the addition of 1,5-diiodopentane (0.36 mL, 2.42 mmol). The reaction mixture was heated under reflux for 22 h. After cooling to room temperature, an aqueous saturated solution of

ammoninum chloride (20 mL) was added, and the resulting solution extracted with ether (4×20 mL). Drying, filtration, and concentration gave the crude product which was subjected to flash chromatography on silica gel (*n*-hexane) to give compound **33** (127 mg, 51% yield) as a colorless liquid: IR (neat, cm^{-1}): 1709 (C═O), 1642 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (t, J=8 Hz, 2H), 2.32–2.30 (m, 2H), 1.92–1.86 (m, 4H), 1.78–1.75 (m, 2H), 1.60–1.42 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 215.9 (C═O), 135.4 (C═), 128.8 (C═), 51.6 (C), 35.1 (CH_2), 33.3 (CH_2), 32.0 (CH_2×2), 30.3 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 23.1 (CH_2), 23.0 (CH_2×2), 22.4 (CH_2); HRMS (EI): calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1667.

4.9.2. 3,4,5,6,7,8-Hexahydrospiro[cyclopentane-1,1′-naphthalen]-2-one (34). Sequential treatment of cyano enone **11** (200 mg, 1.14 mmol) with LN (4.40 mmol) and 1,4-diiodobutane (0.3 mL, 2.27 mmol) for 19 h gave compound **34** (143 mg, 61% yield) as a colorless oil: IR (neat, cm^{-1}): 1709 (C═O), 1640 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.52 (t, J=7.5 Hz, 2H), 2.23 (t, J=7 Hz, 2H), 1.94–1.87 (m, 6H), 1.66–1.58 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 214.0 (C═O), 133.3 (C═), 128.1 (C═), 57.9 (C), 36.3 (CH_2), 34.5 (CH_2×2), 31.4 (CH_2), 30.3 (CH_2), 27.0 (CH_2×2), 24.8 (CH_2), 23.0 (CH_2), 22.6 (CH_2); HRMS (EI): calcd for $C_{12}H_{20}O$: 204.1514; found: 204.1514.

4.9.3. 1,3,4,5,6,7,8,9-Octahydrospiro[cyclohexane-1,1′-benzocyclohepten]-2-one (35). Sequential treatment of cyano enone **13** (200 mg, 1.06 mmol), with LN (4.28 mmol) and 1,5-diiodopentane (0.32 mL, 2.15 mmol) for 22 h gave compound **35** (130 mg, 53% yield) as a colorless liquid: IR (neat, cm^{-1}): 1709 (C═O), 1641 (C═C); ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (t, J=6.5 Hz, 2H), 2.40 (t, J=6.5 Hz, 2H), 2.15–2.06 (m, 4H), 1.72–1.60 (m, 6H), 1.57–1.54 (m, 6H), 1.49–1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 216.4 (C═O), 141.5 (C═), 135.3 (C═), 51.9 (C), 36.3 (CH_2), 34.9 (CH_2), 34.8 (CH_2), 32.5 (CH_2×2), 31.7 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 22.8 (CH_2×2); HRMS (EI): calcd for $C_{16}H_{24}O$: 232.1827; found: 232.1827.

4.9.4. 1,3,4,5,6,7,8,9-Octahydrospiro[cyclopentane-1,1′-benzocyclohepten]-2-one (36). Sequential treatment of cyano enone **13** (200 mg, 1.06 mmol) with LN (4.22 mmol) and 1,4-diiodobutane (0.28 mL, 2.12 mmol) for 20 h gave compound **36** as a colorless liquid (133 mg, 58% yield): IR (neat, cm^{-1}): 1708 (C═O), 1639 (C═C); ^1H NMR (400 MHz, $CDCl_3$); δ 2.51 (t, J=7 Hz, 2H), 2.35 (t, J=7.5 Hz, 2H), 2.10–2.05 (m, 4H), 1.87–1.84 (m, 2H), 1.74–1.68 (m, 2H), 1.66–1.53 (m, 6H), 1.46–1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 214.3 (C═O), 139.0 (C═), 134.4 (C═), 38.7 (C), 36.9 (CH_2), 35.0 (CH_2), 34.6 (CH_2×2), 33.0 (CH_2), 32.6 (CH_2), 29.9 (CH_2), 27.9 (CH_2), 26.8 (CH_2×2), 26.0 (CH_2); HRMS (EI): calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1664.

4.9.5. 1,2,3,4,6,7-Hexahydrospiro[cyclopentane-4,4′-inden]-5-one (37). Sequential treatment of cyano enone **16** (200 mg, 1.24 mmol) with LN (4.66 mmol) and 1,4-diiodobutane (0.36 mL, 2.73 mmol) for 20 h gave compound **37** (136 mg, 58% yield) as a colorless liquid: IR (neat, cm^{-1}): 1780 (C═O), 1602 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.55 (t, J=7 Hz, 2H), 2.33–2.26 (m, 6H), 1.92–1.86 (m, 4H), 1.65–1.58 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 214.6 (C═O), 140.5 (C═), 133.4 (C═), 55.9 (C), 36.3 (CH_2), 35.8 (CH_2), 34.8 (CH_2×2), 31.6 (CH_2), 26.7 (CH_2×2), 25.9 (CH_2), 22.9 (CH_2); HRMS (EI): calcd for $C_{13}H_{18}O$: 190.1358; found: 190.1358.

4.10. 3-(*tert*-Butyliminomethylidenyl)-3-methyl-1,5-pentanedicarbonitrile (45)

To a suspension of *tert*-butylamine (42 mL, 0.42 mol) and potassium carbonate (29 g, 0.21 mol) in toluene (40 mL), was added propionaldehyde (15 mL, 0.21 mol). The light yellow suspension was stirred at room temperature for 45 min and then filtered. The residue was washed with toluene (3×20 mL) and additional potassium carbonate (29 g, 0.21 mol) was added to the combined filtrate. The resulting light yellow suspension was then stirred at room temperature for 16 h. The suspension was filtered into a 500 mL round bottom flask and acrylo-nitrile (70 mL, 1.06 mol) was added to the clear yellow filtrate. The solution was heated to reflux and maintained at refluxing temperature for 48 h, at which time it was cooled to room temperature and filtered over a pad of Celite. The residue was washed with copious amounts of toluene and the solvent was removed in vacuo to give a clear light yellow oil which was distilled under reduced presure (178°C/0.5 Torr) to give the desired product as a clear light yellow oil (34.508 g, 75% yield): IR (CH_2Cl_2 cast, cm^{-1}) 2246 (CN), 1666 (CH═N); ^1H NMR (200 MHz, CD_2Cl_2) δ 7.30 (s, 1H), 2.13 (m, 4H), 1.84–2.03 (m, 2H), 1.71 (ddd, J=16, 10, 10 Hz, 1H), 1.15 (s, 9H), 1.06 (s, 3H); ^{13}C NMR (50 MHz, CD_2Cl_2, APT) δ 159.8 (a), 120.4 (p), 57.5 (p), 41.3 (p), 33.9 (p), 29.5 (a), 21.3 (a), 12.5 (p); HRMS (EI) $[M-CH_3]^+$: calcd for $C_{12}H_{18}N_3$: 204.1501; found: 204.1505; ESMS (*m/z*) $[M+H]^+$: 220.1.

4.11. 3-Formyl-3-methyl-1,5-pentanedicarbonitrile (44)

To a solution of bis-cyano imine **45** (34.508 g, 0.157 mol) in ethanol (50 mL), was added aqueous hydrochloric acid (2.48N, 50 mL). The resulting homogeneous solution was stirred at room temperature for 14 h, at which time chloroform (100 mL) was added and the resulting solution stirred for an additional 5 min at room temperature. The aqueous layer was separated and extracted with chloroform (3×100 mL). The combined organic extracts were washed sequentially with water (100 mL), saturated sodium bicarbonate (100 mL), and brine (100 mL), and then dried. After filtration and evaporation of solvent in vacuo, the crude product was isolated as a opaque yellow oil. Vacuum distillation (177°C/0.1 Torr) of the crude oil then gave the desired bis-cyano aldehyde **44** as a clear viscous light yellow oil (24.789 g, 96% yield); IR (neat, cm^{-1}): 2247 (CN), 1725 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 9.30 (d, J=3.5 Hz, 1H), 2.12–2.17 (m, 4H), 1.86–1.71 (m, 4H), 1.01 (d, J=1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 202.7 (C═O), 118.9 (CN×2), 47.5 (C), 29.4 (CH_2×2), 17.3 (CH_3), 11.7 (CH_2×2); HRMS (EI): calcd for $C_9H_{13}NO_2$ (M+1): 165.1028; found 165.1021.

4.12. 2-Amino-5-methyl-5-vinyl-1-cyclohexene-carbonitrile (46)

To a suspension of methyltriphenylphosphonium bromide (48.07 g, 0.132 mol) in THF (150 mL) cooled to 0°C, was added dropwise *n*-butyllithium (2.5 M in hexane, 50 mL, 0.125 mol). The resulting clear reddish orange colored solution was then stirred at 0°C for 1 h before cooling to −78°C, at which time the clear solution became a colored suspension. A solution of the starting bis-cyano aldehyde **44** (10.013 g, 0.061 mol) in THF (50 mL) was then added dropwise via a dropping funnel to the suspension at −78°C. After the addition was completed, the cooling bath was removed and the reaction suspension allowed to warm to room temperature. After 30 min, saturated aqueous ammonium chloride was added dropwise until no more precipitate was present and the aqueous layer was extracted with ether (4×100 mL). The combined organic extracts were then washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL). After drying, filtration, and evaporation of solvent in vacuo, the crude product was obtained as a clear colorless oil. The crude product was purified by flash chromatography using 20% EtOAc/hexane as eluent to furnish the desired cyano enamine **46** as a white solid (7.640 g, 77% yield); mp (ethyl acetate and *n*-hexane): 89–90°C; IR ($CHCl_3$ cast, cm^{-1}): 3443, 3355 (NH_2), 2181 (CN), 1641, 1611 (C═C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.69 (dd, J=17.5, 13 Hz, 1H), 4.97–4.91 (m, 2H), 4.25 (s, 2H), 2.18–1.94 (m, 4H), 1.59–1.41 (m, 2H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 155.4 (C═), 145.0 (CH═), 120.6 (CN), 111.8 (CH_2═), 72.4 (C═), 34.9 (CH_2), 34.7 (C), 32.3 (CH_2), 25.9 (CH_3), 25.5 (CH_2); HRMS (EI): calcd for $C_{10}H_{14}N_2$: 162.1157; found: 162.1154; Anal. calcd for $C_{10}H_{14}N_2$: C 74.03, H 8.70, N 17.27; found: C 74.09, H 8.82, N 17.23.

4.13. 5-Methyl-2-oxo-5-vinylcyclohexanecarbonitrile (42)

To a suspension of methyltriphenylphosphonium bromide (15.59 g, 44 mmol) in THF (50 mL) cooled to 0°C, was added *n*-butyllithium (2.5 M in hexane, 16.3 mL, 41 mmol) dropwise. The resulting clear red solution was stirred at 0°C for 1 h followed by cooling to −78°C, at which time the solution became an orange colored suspension. A solution of the bis-cyano aldehyde **44** (3.19 g, 20 mmol) in THF (30 mL) was then introduced dropwise via a dropping funnel. When addition was complete, the reaction mixture was stirred at −78°C for 15 min before the cooling bath was removed. After 1 h, a 2.48N hydrochloric acid was carefully added dropwise until precipitate had dissolved. Additional hydrochloric acid was then added until the pH was approximately 1. The orange colored mixture was stirred vigorously at room temperature for 17 h before the aqueous layer was seperated and extracted with ether (3×400 mL). The combined organic layers were washed sequentially with water, saturated sodium bicarbonate, and brine, dried, filtered, and concentrated in vacuo. The crude product thus obtained was subjected to vacuum distillation (123–130°C/0.7 torr) to yield the title compound as a clear viscous oil (2.91 g, 91% yield): IR ($CDCl_3$ cast, cm^{-1}): 3361 (OH), 2251 (CN), 2210 (═C–CN), 1728 (C═O); ^1H NMR (400 MHz, $CDCl_3$, three isomers consisting of an enol tautomer and two keto diastereomers in a respective ratio of 1:2:7): δ 5.87 (dd, J=18, 11 Hz, 0.7H), 5.82 (dd, J=18, 11 Hz, 0.2H), 5.74 (dd, J=18, 11 Hz, 0.1H), 5.35 (d, J=11 Hz, 0.7H), 5.25 (d, J=18 Hz, 0.7H), 5.08 (d, J=18 Hz, 0.2H), 5.07 (d, J=11 Hz, 0.2H), 5.03 (dd, J=11, 1 Hz, 0.1H), 5.00 (dd, J=18, 1 Hz, 0.1H), 3.69 (dd, J=13, 6 Hz, 0.2H), 3.63 (dd, J=14, 6 Hz, 0.7H), 2.29–2.55 (m, 2.5H), 2.08–2.18 (m, 0.6H), 1.99–2.07 (m, 0.9H), 1.95 (dd, J=14, 14 Hz, 0.7H), 1.74–1.81 (m, 0.5H), 1.70 (ddd, J=14, 14, 6 Hz, 0.7H), 1.30 (s, 0.6H), 1.12 (s, 2.1H), 1.05 (s, 0.3H); ^{13}C NMR (50 MHz, $CDCl_3$, APT) δ 200.4 (p), 200.3 (p), 166.1 (p), 145.4 (a), 144.7 (a), 142.2 (a), 118.7 (p), 116.4 (p), 115.0 (p), 112.0 (p), 111.9 (p), 79.4 (p), 41.2 (p), 41.0 (p), 40.1 (a), 39.8 (a), 37.2 (p), 36.6 (p), 36.5 (p), 36.2 (p), 35.5 (p), 35.4 (p), 32.4 (p), 29.3 (a), 25.8 (p), 25.6 (a), 21.3 (a); HRMS (EI): calcd for $C_{10}H_{13}NO$: 163.0997; found: 163.0996.

4.14. 5-Methyl-2-oxo-1-(3-oxopentyl)-5-vinylcyclo-hexanecarbonitrile (47)

To a solution of starting α-cyano ketone **42** (706 mg, 4 mmol) in DME (15 mL) was added DABCO (615 mg, 5 mmol) and the resulting clear solution was cooled to 0°C. After stirring at 0°C for 15 min, EVK (0.7 mL, 7 mmol) was added dropwise and the resulting clear colorless reaction solution was allowed to warm to room temperature. After stirring at room temperature for 23 h, the clear light yellow reaction solution was poured into ice-cold dilute hydrochloric acid solution and the slightly acidic aqueous layer was then extracted with ethyl acetate (4×50 mL). The combined organic extracts were washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried, filtered, and concentrated in vacuo to give the crude product as a clear light yellow oil. Flash chromatography using 20% EtOAc/ hexane as eluent then gave the title Michael adduct **47** as a clear oil (7:3 inseparable mixture of diastereomers, 522 mg, 49% yield): IR ($CHCl_3$ cast, cm^{-1}): 2233 (CN), 1718 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 6.16 (ddd, J=18, 11, 1 Hz, 0.7H), 5.82 (dd, J=18, 11 Hz, 0.3H), 5.31 (d, J= 11 Hz, 0.7H), 5.26 (d, J=18 Hz, 0.7H), 5.10 (d, J=11 Hz, 0.3H), 5.08 (d, J=18 Hz, 0.3H), 3.02 (ddd, J=14, 14, 6 Hz, 0.7H), 2.70–2.80 (m, 1.1H), 2.51–2.68 (m, 1.8H), 2.25–2.51 (m, 4H), 2.15–2.25 (m, 1H), 1.94–2.08 (m, 0.7H), 1.64–1.92 (m, 2.7H), 1.36 (s, 0.9H), 1.08 (s, 2.1H), 1.07 (dd, J=7, 7 Hz, 2.1H), 1.05 (dd, J=7, 7 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 209.4 (p), 209.1 (p), 203.5 (p), 145.7 (a), 143.0 (a), 119.8 (p), 119.1 (p), 114.3 (p), 112.3 (p), 49.8 (p), 48.8 (p), 48.3 (p), 47.2 (p), 37.8 (p), 37.6 (p), 36.9 (p), 36.3 (p), 36.0 (p), 35.9 (p), 35.1 (p), 30.3 (a), 29.3 (p), 26.6 (a), 7.8 (a); HRMS (EI): calcd for $C_{15}H_{21}NO_2$: 247.1572; found: 247.1562; Anal. calcd for $C_{15}H_{21}NO_2$: C 72.83, H 8.56, N 5.67; found: C 72.80, H 8.76, N 5.60.

4.15. 5-Methyl-2-oxo-1-(3-oxobutyl)-5-vinylcyclo-hexanecarbonitrile (48)

To a solution of α-cyano ketone **42** (254 mg, 1.56 mmol) in DME (5 mL) was added DABCO (209 mg, 1.86 mmol) and the resulting clear solution was cooled to 0°C. After stirring at 0°C for 30 min, MVK (0.28 mL, 3.36 mmol) was added

dropwise and the cooling bath was removed. The slightly cloudy reaction mixture was allowed to stir at room temperature for 24 h, at which time it was poured into ice-cold dilute hydrochloric acid solution. The aqueous layer was extracted with ether (4×30 mL) and the combined organic extracts were washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried, filtered, and concentrated in vacuo. The resulting light yellow oil was purified by flash chromatography using 15% EtOAc/hexane as eluent to furnish, after evaporation of solvent, the desired Michael adduct **48** as a light yellow oil in a 2:1 mixture of diastereomers (284 mg, 78% yield): IR ($CDCl_3$ cast, cm^{-1}): 2232 (CN), 1727 (C═O); HRMS (EI): calcd for $C_{14}H_{19}NO_2$: 233.1416; found: 233.1408; Anal. calcd for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00; found C 72.15, H 8.47, N 5.68. An aliquot of the mixture was subjected to extensive flash chromatography using 10% EtOAc/hexane as eluent to furnish the individual diastereomers for further characterization. Isomer **1** (minor product): ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dd, J=18, 11 Hz, 1H), 5.09 (d, J=11 Hz, 1H), 5.08 (d, J=18 Hz, 1H), 2.56–2.82 (m, 4H), 2.30–2.50 (m, 2H), 2.20 (dd, J=14, 2 Hz, 1H), 2.16 (s, 3H), 1.96 (d, J=14 Hz, 1H), 1.80–1.92 (m, 2H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 206.3 (p), 203.5 (p), 145.8 (a), 119.7 (p), 112.3 (p), 48.3 (p), 42.7 (p), 39.1 (p), 37.4 (p), 36.3 (p), 35.1 (p), 29.9 (a), 29.2 (p), 26.4 (a); HRMS (EI): calcd for $C_{14}H_{19}NO_2$: 233.1416; found: 233.1405; Isomer **2** (major product): ^1H NMR (600 MHz, $CDCl_3$) δ 6.12 (ddd, J=18, 11, 1 Hz, 1H), 5.29 (d, J=11 Hz, 1H), 5.24 (d, J=18 Hz, 1H), 3.00 (ddd, J=13, 13, 5 Hz, 1H), 2.77 (ddd, J=18, 1, 5 Hz, 1H), 2.58 (ddd, J= 18, 10, 5 Hz, 1H), 2.37 (ddd, J=14, 4, 4 Hz, 1H), 2.24–2.33 (m, 2H), 2.13–2.19 (m, 1H), 2.15 (s, 3H), 1.78 (ddd, J=14, 10, 5 Hz, 1H), 1.70 (dddd, J=13, 13, 4, 1 Hz, 1H), 1.66 (d, J=14 Hz, 1H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 206.6 (p), 203.5 (p), 143.0 (a), 119.1 (p), 114.4 (p), 49.8 (p), 47.2 (p), 39.0 (p), 36.9 (p), 36.3 (p), 35.9 (p), 30.3 (a), 30.0 (a), 29.2 (p); HRMS (EI): calcd for $C_{14}H_{19}NO_2$: 233.1416; found: 233.1416.

4.16. 3,8-Methyl-7-oxo-3-vinyl-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (40)

To a 100 mL round bottom flask mounted with a Dean–Stark apparatus, was added *p*-toluenesulfonic acid hydrate (0.32 g, 1.6 mmol) and benzene (50 mL). The clear solution was heated to reflux, and the water–benzene azeotrope was drained. After no more water was evident in the distillate (~30 mL was drained), the solution was cooled to room temperature, and a solution of the starting diketone **47** (520 mg, 2.0 mmol) in anhydrous benzene (30 mL) was quickly introduced. The resulting solution was heated to reflux, and the water–benzene azeotrope was drained. After refluxing for 2 h, the solution was then cooled to room temperature, and ether was added (20 mL). Saturated sodium bicarbonate was added, and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed sequentially with water and brine, dried, filtered, and concentrated in vacuo to give the crude product. Flash chromatographic purification of the crude product (20% ethyl acetate in *n*-hexane) gave the title compound as a light yellow oil in a 1:1 mixture of diastereomers (420 mg, 86% yield): IR (neat, cm^{-1}): 2228 (CN), 1674 (C═O), 1622 (C═C); HRMS (EI): calcd for $C_{15}H_{19}NO$: 229.1467; found: 229.1472. A portion of the mixture was then subjected to extensive flash chromatography using 10% ethyl acetate/ *n*-hexane as eluent to give the individual diastereomers for further characterization. ^1H NMR (400 MHz, $CDCl_3$): Isomer **1**: δ 5.75 (dd, J=18. 11, Hz, 1H), 4.99 (d, J= 18 Hz, 1H), 4.98 (d, J=11 Hz, 1H), 2.72–2.84 (m, 2H), 2.47–2.61 (m, 2H), 2.34 (ddd, J=14, 5, 3 Hz, 1H), 2.06 (dd, J=14, 3 Hz, 1H), 1.94 (ddd, J=15, 14, 4 Hz, 1H), 1.84 (s, 3H), 1.78 (dddd, J=14, 4, 4, 3 Hz, 1H), 1.53 (ddd, J=14, 13, 4 Hz, 1H), 1.52 (d, J=14 Hz, 1H), 1.45 (s, 3H); Isomer **2**: 6.16 (ddd, J=18, 11, 1 Hz, 1H), 5.26 (dd, J=11, 1 Hz, 1H), 5.21 (dd, J=18, 1 Hz, 1H), 2.68–2.81 (m, 2H), 2.48–2.60 (m, 2H), 2.33 (ddd, J=14, 5, 3 Hz, 1H), 2.21 (dd, J=14, 3 Hz, 1H), 2.14 (ddd, J=14, 7, 3 Hz, 1H), 1.92 (ddd, J=15, 14, 4 Hz, 1H), 1.83 (s, 3H), 1.43 (d, J=14 Hz, 1H), 1.39 (dddd, J=14, 14, 4, 1 Hz, 1H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, APT): Isormer **1**: δ 196.4 (p), 150.1 (p), 148.0 (a), 132.7 (p), 121.8 (p), 111.0 (p), 47.9 (p), 36.1 (p), 36.0 (p), 35.6 (p), 35.4 (p), 34.3 (p), 25.2 (p), 22.7 (a), 11.3 (a); Isomer **2**: 196.4 (p), 150.4 (p), 143.1 (a), 132.3 (p), 120.9 (p), 114.0 (p), 50.0 (p), 36.7 (p), 36.3 (p), 35.3 (p), 34.8 (p), 34.1 (p), 31.1 (a), 25.5 (p), 11.2 (a). HRMS (EI): Isomer **1**: calcd for $C_{15}H_{19}NO$: 229.1467; found: 229.1464; Isomer **2**: calcd for $C_{15}H_{19}NO$: 229.1467; found: 229.1467. Isomer **1**: Anal. calcd for $C_{15}H_{19}NO$: C 78.56, H 8.35, N 6.11; found: C 78.56, H 8.32, N 5.82; Isomer **2**: Anal. calcd for $C_{15}H_{19}NO$: C 78.56, H 8.35, N 6.11; found: C 78.13, H 8.36, N 5.72.

4.17. 3-Methyl-7-oxo-3-vinyl-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (41)

This compound was prepared from **48** following a similar method to that described for **40**. The desired cyano enone **41** was obtained as a white solid in a 2:1 mixture of diastereomers (623 mg, 55% yield): mp 54–58°C; IR ($CHCl_3$ cast, cm^{-1}): 2228 (CN) and 1684 cm^{-1} (C═O); HRMS (EI): calcd for $C_{14}H_{17}NO$: 215.1310; found: 215.1312; Anal. calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 78.14, H 8.11, N 6.19; A portion of the mixture was subjected to extensive flash chromatographic separation using 10% EtOAc/hexane as eluent to give the individual diastereomers for further characterization. Isomer **1** (minor product): ^1H NMR (300 MHz, $CDCl_3$): δ 5.98 (d, J=2 Hz, 1H), 5.74 (dd, J=18, 11 Hz, 1H), 5.01 (dd, J=18, 1 Hz, 1H), 4.98 (dd, J=11, 1 Hz, 1H), 2.69–2.85 (m, 2H), 2.36–2.58 (m, 3H), 2.12 (dd, J=14, 3 Hz, 1H), 1.98 (ddd, J=15, 14, 4 Hz, 1H), 1.74 (ddd, J=14, 5, 5 Hz, 1H), 1.74 (dd, J=14, 5 Hz, 1H), 1.55 (d, J=15 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, APT): δ 196.6 (p), 156.9 (p), 147.8 (a), 127.3 (a), 120.9 (p), 111.2 (p), 47.5 (p), 36.5 (p), 36.2 (p), 35.9 (p), 34.4 (p), 31.6 (p), 29.3 (p), 21.9 (a); HRMS (EI): calcd for $C_{14}H_{17}NO$: 215.1310; found: 215.1310; Isomer **2** (major product): ^1H NMR (300 MHz, $CDCl_3$): δ 6.14 (ddd, J=18, 11, 1 Hz, 1H), 5.95 (d, J=2 Hz, 1H), 5.28 (d, J=11 Hz, 1H), 5.21 (d, J=18 Hz, 1H), 2.65–2.86 (m, 2H), 2.49 (dddd, J=17, 4, 4, 1 Hz, 1H), 2.31–2.44 (m, 2H), 2.26 (dd, J=14, 3 Hz, 1H), 2.12 (ddd, J=14, 5, 5 Hz, 1H), 2.12 (dd, J=14, 5 Hz, 1H), 1.96 (ddd, J=15, 14, 4 Hz, 1H), 1.44 (d, J=14 Hz, 1H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, APT): 195.8 (p), 156.5 (p), 141.5 (a),

126.0 (a), 119.1 (p), 113.5 (p), 48.5 (p), 35.9 (p), 34.9 (p), 34.2 (p), 33.3 (p), 30.6 (p), 30.4 (a), 28.7 (p); HRMS (EI): calcd for $C_{14}H_{17}NO$: 215.1310; found: 215.1311.

4.18. 1,1,6-Trimethyl-6-vinyl-3,4,5,6,7,8-hexahydro-1*H*-naphthalen-2-one (49)

To a solution of the starting cyano enone **40** (960 mg, 0.419 mmol) in THF (5 mL) cooled to −78°C, was added dropwise a 0.54 M solution of LN in THF (2.4 mL, 1.25 mmol). The resulting blue solution was stirred at −78°C for 45 min, followed by rapid addition of methyl iodide (0.11 mL, 251 mg, 1.77 mmol). The clear light yellow reaction mixture was stirred at −78°C for 20 h. Solid ammonium chloride (~100 mg) was added, and the suspension was allowed to warm to room temperature. Water was introduced dropwise to dissolve all precipitate, and the aqueous layer was separated and extracted with ether (4×30 mL). The combined organic extracts were washed sequentially with water (30 mL) and brine (30 mL), dried, filtered, and concentrated in vacuo. The light yellow oil thus obtained was subjected to flash chromatography using 0.4% EtOAc/hexane as eluent to give the desired bicyclic ketone **49** as a colorless oil (70 mg, 77% yield): IR ($CHCl_3$ cast, cm^{-1}): 1716 (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.77(dd, J=18, 11 Hz, 1H), 4.92 (dd, J=11, 2 Hz, 1H), 4.89 (dd, J=18, 2 Hz, 1H), 2.49–2.60 (m, 2H), 2.28 (mt, J=8 Hz, 2H), 2.00 (m, 3H), 1.81 (md, J=18 Hz, 1H), 1.52 (dddd, J=13, 6, 6, 1 Hz, 1H), 1.44 (dddd, J=13, 6, 6, 1 Hz, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, APT): δ 215.8 (p), 146.9 (a), 133.0 (p), 126.2 (p), 110.6 (p), 47.0 (p), 41.7 (p), 35.9 (p), 34.9 (p), 33.8 (p), 30.9 (p), 29.7 (p), 25.8 (a), 24.1 (a), 23.8 (a); HRMS (EI): calcd for $C_{15}H_{22}O$: 218.1671; found: 218.1671; Anal. calcd for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.22, H 9.91.

Alternatively, the desired bicyclic ketone **49** may also be synthesized from bicyclic ketone **41** in the following manner. To a slution of ketone **41** (82 mg, 0.381 mmol) in THF cooled to −78°C, was added a preformed LN solution (1.0 M in THF, 1.6 mL, 1.6 mmol) dropwise. The resulting blue solution was stirred at −78°C for 30 min, followed by the rapid introduction of methyl iodide (0.085 mL, 1.4 mmol). The clear light yellow solution was warmed to room temperature. After stirring for 4 h, saturated aqueous ammonium chloride was added (10 mL). The aqueous layer was extracted with ether (4×20 mL), and the combined organic extracts were washed with water (20 mL) and brine (20 mL), dried, filtered, and concentrated in vacuo. Flash chromatography of the resulting light yellow oil using 0.25% EtOAc/hexane as eluent gave bicyclic ketone **49** (34 mg, 41% yield).

4.19. 1,1,6-Trimethyl-6-vinyl-1,2,3,4,5,6,7,8-octahydronaphthalene (39)

To a solution of the starting bicyclic ketone **49** (110 mg, 0.51 mmol) in diethylene glycol (8 mL), were added potassium hydroxide pellets (80% w/w, 190 mg, 2.72 mmol) and anhydrous hydrazine (0.15 mL, 4.78 mmol). A Dean-Stark apparatus containing 4 Å molecular sieves was then fitted onto the round bottom flask, and the clear light yellow reaction mixture was heated to 110–120°C. After 2 h at 110–120°C, the temperature was gradually raised to 210°C and maintained there for an additional 4 h. The clear solution was then cooled to room temperature, diluted with water, and extracted with petroleum ether (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated under reduced pressure. Flash chromatograpgh through a short column using petroleum ether as eluent furnished the desired deoxygenated product **39** (78 mg, 76% yield) as a colorless oil: IR (neat, cm^{-1}): 1638 (C═C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 (dd, J=17.5, 10.5 Hz, 1H), 4.88–4.84 (m, 2H), 1.94–1.78 (m, 5H), 1.33–1.67 (m, 7H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,DEPT): δ 147.3 (CH═), 133.6 (C═), 125.4 (C═), 110.0 (CH_2═), 42.3 (CH_2), 39.8 (CH_2), 35.0 (C), 34.4 (CH_2), 33.5 (C), 31.6 (CH_2), 27.8 (CH_3×2), 25.6 (CH_3), 21.7 (CH_2), 19.4 (CH_2); HRMS (EI): calcd for $C_{15}H_{24}$: 204.1878; found: 204.1873.

4.20. (±)-Nanaimoal (38)

To a solution of the starting diene **39** (21 mg, 0.103 mmol) in THF (3 mL) cooled to 0°C, was added dropwise a preformed solution of disiamyborane in THF (0.5 M, 0.82 mL, 0.41 mmol). The resulting clear colorless solution was allowed to warm to room temperature and stirred for 25 h. The solvent was removed in vacuo, and the residue redissolved in dichloromethane (2 mL). This clear colorless solution was then added to a bright orange solution of pyridinium dichlorochromate (443 mg. 2.06 mmol) in dichloromethane (3 mL), and the resulting dark brown suspension was then heated to reflux. After refluxing for 3 h, the dark suspension was cooled to room temperature, and diluted with ether (20 mL). The resulting dark suspension was filtered over a pad of Celite. The residue was rinsed with copious amount of ether, and the filtrate was concentrated in vacuo. Flash chromatography of the resulting clear oil using 5% Et_2O/hexane as eluent yielded the desired aldehyde **38** as a fragrant clear colorless oil (12 mg, 66% yield): IR ($CHCl_3$ cast, cm^{-1}): 2849, 2730, 1721 (CHO); ^1H NMR (400 MHz, $CDCl_3$): 9.86 (t, J=3 Hz, 1H), 2.29 (dd, J=14, 3 Hz, 1H), 2.22 (dd, J=14, 3 Hz, 1H), 2.01 (m, 2H), 1.84 (d, J=17 Hz, 1H), 1.79 (m, 2H), 1.76 (d, J=17 Hz, 1H), 1.59 (m. 4H), 1.44 (m, 4H), 1.05 (s, 3H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, APT): δ 203.9 (a), 133.8 (p), 125.3 (p), 53.7 (p), 43.7 (p), 39.7 (p), 34.8 (p), 33.6 (p), 32.2 (p),31.6 (p), 27.9 (a×2), 26.0 (a), 21.3 (p), 19.4 (p); HRMS (EI): calcd for $C_{15}H_{24}O$: 220.1827; found: 220.1823.

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